ABSTRACT

ARAMBULA, SHERYL ELIZABETH. Sex-Specific Impact of Early-Life Bisphenol A (BPA) Exposure on Brain Development. (Under the direction of Dr. Heather B. Patisaul).

Bisphenol A (BPA) is a well-recognized endocrine disruptor that is commonly used as a component of polycarbonate plastics and epoxy resins, and found in a variety of household products. Thus, human exposure to BPA is widespread, with levels higher in children than adults. Extensive experimental and epidemiological evidence supports associations between developmental BPA exposure and sex-specific socioemotional behavioral outcomes including hyperactivity, anxiety, aggression, and cognitive deficits. However, the molecular underpinnings of these behavioral outcomes remain poorly understood. The studies within this dissertation were conducted as part of the CLARITY-BPA (Consortium Linking Academic and Regulatory Insights on BPA Toxicity) research program and examined the impact of early-life BPA exposure on the hippocampal, hypothalamic, and amygdalar transcriptomes of neonates and the sexually dimorphic brain nuclei of juveniles. NCTR-Sprague Dawley rats (NCTR-SD) were exposed to wide range of BPA doses (2.5 - 25,000 μg/kg body weight (bw)/day) pre- and/or postnatally. The hippocampus, hypothalamus, and amygdala were microdissected from postnatal day 1 (PND 1) brains and RNA-sequencing and qRT-PCR were used to assess gene expression. In addition, unbiased stereology was used to quantify the volume of the sexually dimorphic nucleus (SDN), the anteroventral periventricular nucleus (AVPV), the posterodorsal portion of the medial amygdala (MePD), and the locus coeruleus (LC) at PND 28. Overall, early-life BPA exposure induced sex-, brain region-, and dose-specific effects. In the neonate brain, gene expression analysis revealed further evidence for disruption of estrogen receptor expression (*Esr1* and *Esr2*) and oxytocin (*Oxt* and *Oxtr*) and vasopressin (*Avpr1a*) systems in

the hippocampus, hypothalamus, and amygdala. Evidence for disruption of signaling pathways critical for synaptic organization and synaptic transmission were also observed in the female neonate amygdala. In the prepubertal brain, no appreciable effects of BPA were observed on the volume of the SDN or the LC. However, AVPV volume was enlarged in both sexes. Collectively, these results show the developing nervous system is sensitive to BPA exposure and add to a growing body of literature showing neurodevelopmental effects of BPA, at levels below the current FDA No Observed Adverse Effect Level (NOAEL) of 5 mg/kg bw/day. Furthermore, they provide insight into the mechanistic changes that precede and underlie the neurobehavioral effects associated with developmental BPA exposure.

Sex-Specific Impact of Early-Life Bisphenol A (BPA) Exposure on Brain Development

by
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DEDICATION

To my mom for teaching me that anything is possible and to face the future with curiosity and optimism. To my sister and father, for making me stubborn, hardheaded, and determined. To my nephew, Parker J. Light, for reminding me to slow down and enjoy the moments that count. To my friends, family, mentors, and Russell Mick for keeping me sane and providing endless support.

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"Biography is a system in which the contradictions of a human life are unified."

- José Ortega y Gasset

(1883 - 1955)

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CHAPTER 1

Endocrine Disrupting Chemicals and Behavior

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ABSTRACT

Endocrine disrupting chemicals (EDCs) are a diverse group of compounds that interfere with the organizational or activational effects of hormones. There is growing concern that early-life exposure to EDCs may be contributing to the increasing prevalence of sex-biased neurodevelopmental disorders by multiple mechanisms. While it is difficult to make causal links, extensive experimental and epidemiological evidence supports associations between early-life exposure to environmental contaminants and sex-specific neurobehavioral outcomes. This review provides an overview of the neurobiological and behavioral consequences of developmental exposure to EDCs with an emphasis on bisphenol A, high volume production chemical found in a variety of commonly used products.

KEYWORDS

affective**,** anxiety, behavior, bisphenol, BPA, brain, development, EDC, endocrine disrupting chemicals, environmental contaminant, exploratory, learning, memory sex differences, sexually dimorphic, social

1. INTRODUCTION

Inexorably connected, the endocrine system and nervous system work in tandem to regulate the development and expression of behavior. This relationship is best exemplified by the early actions of steroid hormones on the mammalian brain, which induce enduring changes in the brain that impact sexually dimorphic behavior [31, 36, 65, 81]. Although brain development is a tightly regulated and orchestrated process, it is vulnerable to exogenous substances that interfere with the action of natural hormones.

Endocrine disrupting chemicals (EDCs) are a diverse group of exogenous compounds that have been found to interfere with the endocrine system and produce adverse health effects in exposed individuals or their offspring. Numerous classes of chemicals including plasticizers, flame-retardants, fungicides, pesticides, pharmaceuticals, heavy metals, and even naturally occurring compounds such as phytoestrogens are endocrine disrupting **(Table 1)**. These and other EDCs dampen, block, or potentiate the action of endogenous hormones through a variety of direct and indirect mechanisms. For example, they may agonize or antagonize hormone receptors, interfere with hormone biosynthesis, or alter the number of hormone receptors [48]. The long-term consequences of EDCs depend on a variety of factors including the genetic susceptibility of the organism and the dose, duration, and developmental window of exposure.

Since the term was first coined nearly three decades ago, EDCs have received considerable attention from both the scientific community and the public [58, 84]. While highly debated, endocrine disruption provides a plausible explanation for the global increase

in the prevalence of sex-biased neurodevelopmental disorders, most notably attention-deficit hyperactivity disorder and autism spectrum disorder, which cannot be fully explained by genetic factors alone. Although the etiology of these disorders are not well understood, there is increasing concern that developmental exposure to EDCs may enhance risk by disrupting sexual differentiation of the brain. Indeed, extensive experimental and epidemiological evidence supports associations between early-life exposure to environmental contaminants and sex-specific neurobehavioral outcomes.

The goal of the current review is to examine the evidence for altered behavior as a consequence of EDC exposure. Although hundreds of suspected EDCs have been identified, bisphenol A (BPA) is arguably one of the most widely used and extensively studied. Thus for illustrative purposes, we will concentrate on the effects of early exposure to this notorious chemical.

2. BPA: A LANDMARK ENDOCRINE DISRUPTING CHEMICAL

Our focus on BPA is significant because this well recognized EDC is widely used as a component of polycarbonate plastics and epoxy resins and commonly incorporated into numerous household products. Human exposure occurs primarily from contaminated food and beverages [125], and in industrialized countries, more than 90% of individuals are estimated to have detectable amounts of BPA in their bodies [18-20, 25, 73]. Early-life exposure is of major concern because this period is characterized by rapid growth and has long been recognized as a critical window of vulnerability to the effects of neurotoxic and

neuroendocrine disrupting agents. In humans, BPA has been detected in fetal plasma [59], amniotic fluid [40], fetal liver [87] and placenta tissue [109], demonstrating the capacity for significant gestational exposure. Moreover, the fetal brain is particularly susceptible to environmental exposures because the blood-brain barrier is not fully formed, and thus provides limited protection [3, 96]. Accordingly, levels of chemical exposures that have no obvious effects on the adult nervous system can pose a significant risk when exposure occurs developmentally.

A litany of studies provide evidence that developmental exposure to BPA results in neurobiological and mood-related behavioral consequences, even at doses below the current U.S. Food and Drug Administration No Observed Adverse Effect Level (NOAEL) of 5 mg/kg body weight (bw)/day. It should be emphasized that despite an abundance of literature, there is a general lack of understanding concerning the specific cellular mechanisms by which BPA alters human neurodevelopment**.** Initially developed as a synthetic estrogen [38], BPA has long been considered weakly estrogenic. Until recently, BPA was primarily believed to exert its effects by engaging estrogen receptors (ERs). However, the binding affinity of BPA for both ERα and ERβ in cell culture assays is 10,000 – 100,000 fold lower than the endogenous estrogen [7, 67, 126], making it improbable that BPA mediates its effects solely through classical ER-dependent nuclear pathways. In fact, BPA has also been demonstrated to have a low binding affinity for other steroid receptors [105, 133] and to have rapid, non-genomic actions via membrane-bound ERs [5, 117, 124]. Most recently, studies have shown developmental BPA exposure can induce sex- and region-

specific changes in DNA methylation patterns in the brain that are accompanied by decreased expression of ERs [69, 70]. These alternative modes of action emphasize the complex, multi-modal routes by which EDCs can impact brain and behavior across the lifespan.

3. SEXUALLY DIMORPHIC BEHAVIORS AS INDICATORS OF ENDOCRINE DISRUPTION

Sexual differentiation is the process by which the brain becomes structurally and functionally different between males and females. Sexual differentiation of the brain was once thought to hinge almost entirely upon gonadal hormones: generally, the brain develops as male in the presence of these hormones, and as female in their absence. However, recent evidence indicates this process is more nuanced and involves multiple sex-specific hormonal, genetic, and epigenetic factors that influence sexually dimorphic physiology and behavior thorough a variety of mechanisms [82, 83, 110].

Disruption of sexually dimorphic behavior is a common outcome of developmental exposure to EDCs, particularly BPA. Indeed, sex-specific behavioral impacts of BPA have been demonstrated in numerous animal models and human epidemiological studies. Considering their complex, multifactorial origin, it is not surprising that BPA has been found to decrease, eliminate, and even reverse behavioral sex differences. It is unclear, however, whether the differential effects of BPA in males and females are due to disruption of already existing behavioral dimorphisms or whether they reflect sex-specific vulnerability.

4. EVIDENCE FROM ANIMAL MODELS

The majority of experimental studies on neurobiological and behavioral consequences of developmental BPA exposure (gestational and/or neonatal) employ rodent models. Here we provide a summary of these findings and limit our discussion to studies that use BPA doses at or lower than the current FDA NOAEL (5 mg/kg bw/day).

4.1 Exploratory and Affective Behaviors

Experimental animal studies in rodents provide compelling evidence that developmental BPA exposure can increase the expression of anxiety-related and exploratory behaviors. However, effects vary across sex, animal model, and age at testing. Studies examining developmental BPA exposure in juveniles typically demonstrate sex-specific effects, but results are inconsistent. For example, two studies on juvenile C57BL/6J mice conclude that gestational and/or neonatal BPA exposure increased anxiety in males but had no effect in females [33, 80], while another study with CD-1 mice reported the opposite [45]. Additionally, a recent study in juvenile Sprague Dawley rats found no effects of perinatal BPA exposure on exploratory or anxiety activity, in either sex [101].

Studies in adults are more consistent and in general, females display more robust anxiogenic effects following early-life BPA exposure compared to males [46, 54, 106, 114]. For example, neonatal exposure to 10 μg/kg of BPA was found to decrease exploratory-behavior and increase anxiety-like behavior in adult female CD-1 mice, resulting in a behavioral phenotype similar to that of adult control males [46]. This is consistent with other

studies that show developmental BPA exposure can decrease or eliminate sex differences typically observed in adult rodents, on a number of behavioral paradigms used to assess anxiety [45, 54, 62, 66, 69]. Experiments using other animal models (including zebrafish, voles and other alternative rodent species, and non-human primates) provide further evidence that developmental BPA exposure induces anxiety-related behaviors [64, 69, 88, 93, 114]. This consistency across studies and varying animal models prompted the World Health Organization to conclude that there is some concern about impacts of developmental BPA exposure on brain and behavior [43]. While the underlying mechanisms remain unclear, this behavioral disruption is commonly associated with perturbation of ER-related gene expression in the hypothalamus and the amygdala [4, 21-23, 69, 93, 100, 102]. Moreover, a recent study found that prenatal BPA exposure induced sex-specific effects on anxiety-like behaviors in adult BALB/c mice that corresponded to changes in DNA methylation and mRNA levels of ERα in the hypothalamus [69]. These data provide intriguing evidence that BPA-induced disruption of anxiety behavior may be mediated through an epigenetic mechanism.

Other EDCs shown to alter anxiety-related and exploratory behaviors include phthalates (1,2), polychlorinated biphenyls (thyroid disrupting) (3,4), some flame-retardants (thyroid disrupting) (5), and vinclozolin (androgen disrupting) (6,7). Perhaps best characterized is the spectrum of adverse neurobehavioral outcomes associated with developmental lead exposure. Considerable and consistent research, in a variety of animal models including rodents, cats, and non-human primates, shows that developmental lead exposure can induce hyperactivity,

impulsivity, and aggression [17, 27, 37, 51, 56, 74, 77]. While not an EDC in the classic sense, lead and other metals can be endocrine disrupting in some circumstances [28, 53, 55, 85].

4.2 Learning and Memory

Impairments in cognitive abilities have also been observed following developmental exposure to BPA. Under normal conditions, male rodents typically perform significantly better than females on spatial learning and memory tasks and, interestingly, early-life BPA exposure has repeatedly been shown to reduce this sex difference [24, 62, 130]. Several studies in rats and mice suggest that gestational and/or neonatal exposure to BPA can negatively impact spatial memory in both juvenile and adult males [68, 71, 78, 118, 130-132]. As an example, exposure to BPA (0.5 and 5 mg/kg bw/day) during the perinatal period significantly impaired spatial memory in juvenile and adult male ICR mice [132]. In contrast, data on the effects of BPA on spatial learning and memory in females is sparse and mixed results have been reported [24, 78, 130]. Notably, the described changes in spatial memory were associated with BPA-induced alterations in dendritic spine density and morphology, as well as reduced expression of N-methyl-d-aspartic acid (NMDA) glutamatergic receptors and ERβ [39, 78, 118, 131] in the hippocampus.

Experimental research also shows that dioxin [63, 111], polychlorinated biphenyls [41, 108], polybrominated diphenyl ethers (PBDEs) [32, 121], chlorpyrifos [47, 76], and other EDCs can result in altered learning and memory behaviors. As an example, perinatal

exposure to PDBE slowed motor skill development in adolescent and adult CD-1 mice [10]. Similarly, a series of experiments in mice found neonatal exposure to multiple PBDE congeners caused significant adult learning and memory deficits that corresponded to inhibition of the hippocampal cholinergic system [122, 123].

4.3 Paternal, Social, and Sexual Behaviors

In rodents, changes in parental, social, and sexual behaviors have been reported after developmental exposure to BPA, but evidence is sparse and inconsistent [1, 2, 44, 54, 61, 86, 98, 99, 107, 114, 129]. To date only two studies have examined the relationship between developmental BPA exposure and subsequent maternal behavior. One of these found that prenatal exposure to BPA 10 μg/kg bw/day decreased the amount of time female CD-1 mice spent huddling over or nursing their offspring [90]. The second study, which was conducted in Wistar rats, reported similar effects of gestational and lifelong BPA exposure to 5 μg/kg bw [9]. The impact of developmental BPA exposure on paternal behavior is unknown. This is likely due to the fact that traditional rodent models used in toxicology do not display bi-parental care.

Evidence that developmental BPA exposure can alter behaviors related to sociality is limited and highly discordant, but existing literature suggests that female social behavior may be more sensitive to disruption than males. For example, exposure to 1.25 mg of BPA during the prenatal period increased male and female juvenile social play in C57Bl6J mice [129]. In contrast, another report perinatal exposure to 40 μg/kg BPA reduced social play in female

juvenile Sprague-Dawley rats (males were not assessed) [99]. A study in prairie voles, a more prosocial animal model than laboratory rats or mice, found sex- and age-specific effects on social behavior. Neonatal exposure to 5 and 50 μg/kg bw/day decreased social investigation in juvenile males and slightly inhibited partner preference formation in adult females. These behavioral outcomes were accompanied by sex-dependent changes in the number of dopaminergic-, oxytocin-, and vasopressin neurons in the paraventricular nucleus of the hypothalamus and dopaminergic neurons in the bed nucleus of stria terminals [114].

Some published data suggests early-life BPA exposure can induce subtle changes in adult sexual behavior, but supporting evidence is mixed [1, 2, 44, 61, 86, 98, 107]. Two studies in rodents have found a slight impairment in male sexual performance in terms of latency, intromission, and ejaculation [44, 61], where others have found none [98]. Female data is similarly mixed but generally indicates female sexual behavior is unaffected by developmental BPA exposure. In rodents, female proceptive and receptive behaviors are often determined by hopping and darting and the lordosis response. Exposure to 0.05 mg/kg of BPA during the neonatal period decreased hopping and darting rate in adult female Wistar rats, while lordosis behavior was unaffected [86]. Another study, conducted in Sprague-Dawley rats, observed a modest increase in lordosis behavior in adult females following perinatal exposure to 40 μg/kg of BPA [44]. Other studies have observed no effects of developmental exposure on proceptive or receptive behaviors in females [1, 2, 107].

Animal data also indicates effects of developmental exposure to other EDCs including methoxychlor [50, 89, 115], polychlorinated biphenyls [112, 113, 127], phthalates [34, 75],

phytoestrogens [91, 92, 94], and chlorpyrifos [35, 119, 120] on parental, social, and sexual behaviors. For instance, a number of studies in rodents provide evidence that PCBs can adversely impact sociosexual behavior and, in general, suggest that females may be more vulnerable to disruption than males. In rats gestational and neonatal exposure reduces receptive and proceptive sexual behaviors such as lordosis and likelihood to mate [29, 113, 115].

5. EVIDENCE FROM EPIDEMIOLOGICAL STUDIES

Although the health impacts of developmental BPA exposure remain controversial, during the last decade several epidemiological studies have reported adverse behavior in children developmentally exposed to BPA [6, 11, 12, 16, 26, 42, 52, 57, 79, 97, 104].

The first was a longitudinal cohort study (the Health Outcomes and Measures of the Environment Study; HOMES) included 249 mothers and their children and measured maternal BPA urine concentrations during pregnancy (gestational weeks 16 and 24) and around the time of birth. When the children were 2 years old, their behavior was evaluated using a questionnaire designed to assess adaptive and problem behaviors in community and home settings. In girls, but not boys, significant associations were found between higher levels of maternal BPA during gestation and increased externalizing behaviors, specifically hyperactivity and aggression [11]. In a follow-up study on the HOMES cohort, behavior and executive function were examined at 3 years of age. Higher levels of maternal BPA during gestation were correlated with increased anxiety, hyperactivity, and depressive behavior,

particularly in girls [12]. Of note, two subsequent studies on the HOMES cohort found no associations between maternal levels of gestational BPA and autistic behaviors in children 4 to 5 years old [14] or visual spatial ability in children 7 years old [15]. This outcome highlights that while chemical exposures can produce measureable and meaningful decrements in behavior and cognition that can have life-long implications, manifestation of a clinically defined disorder, such as autism, is highly unlikely and would be notoriously difficult to prove.

Other longitudinal cohort studies have found stronger associations between prenatal urinary BPA levels and adverse childhood behavior in boys than in girls. In cohort of African-American and Dominican women and their children (Center for Children's Environmental Health Cohort; CCCEH), higher maternal urinary BPA concentration was associated with increased aggression and emotionally reactive behavior in boys at 3–5 years of age [97]. A follow-up study on the CCCEH cohort, found 7 to 9 year old boys exposed to higher concentrations of BPA during gestation had increased internalizing (symptoms of anxiety and depression) and externalizing (aggression and rule-breaking) problems [104]. Similarly, three additional cohort studies have reported positive correlations between higher gestational BPA concentrations and behavioral problems in boys at 6 - 10 years of age including increased symptoms of anxiety, depression, and inattention [26, 42, 52]. Lastly, the most recent epidemiological study found a relationship between maternal urinary BPA concentration during pregnancy and poorer working memory and increased internalizing behavior in boys at 3 years of age [16].

Collectively these epidemiological studies strongly suggest that developmental BPA exposure may have adverse neurobehavioral effects in children, which may differ between boys and girls. This conclusion is concordant with the abundant animal data although the mechanisms of action remain poorly understood. In general, the conclusions from the described studies are strengthened by their use of large mother-child cohorts, BPA measurements across several gestational time points, and multiple observed behavioral outcomes. However, it is important to recognize the limitations inherent to longitudinal cohort studies that may have contributed to the discrepant results, particularly demographic differences across cohorts. Additionally, differences in neuropsychological assessments and substantial within-person variation in urinary BPA concentrations may also contribute to the heterogeneity in the literature [13, 116].

Robust evidence from epidemiological studies support a relationship between early-life EDC exposure and neurobehavioral outcomes. Behavioral deficits, including impairments in learning, memory, and social skills, have been linked with developmental exposure to PCBs, numerous flame retardants, and other persistent organic pollutants (POPs). Of these, the evidence for PCB-related effects on neurodevelopment is particularly compelling. Several longitudinal cohort studies have observed associations between developmental PCB exposure and impairments in measures of executive functioning such as processing speed, verbal abilities, and visual recognition memory [8, 60, 72, 103]. Similar impairments in executive functioning are also linked to developmental lead and methylmercury exposure [49, 128]. Because humans are exposed to a complex cocktail of EDCs and other toxicants

continuously, combined effects of multiple exposures are a significant and growing concern.

6. CONCLUSIONS

The experimental evidence summarized above supports the hypothesis that developmental exposure to BPA, even at doses below the current NOAEL, may interfere with some aspect of sexual differentiation of the nervous system, thereby resulting in disruption of both reproductive and non-reproductive behaviors. During fetal and child development, the brain is particularly susceptible to environmental stressors such as EDCs. A recent study found that children of parents who were concerned about EDCs had decreased urinary concentrations of BPA, which suggests that by exercising precaution we may be able to reduce our exposure to chemicals [95]. While developmental exposure to BPA and other EDCs may contribute to neural disorders in children, it should be emphasized that available literature does not provide direct causal evidence. Further mechanistic and epidemiological studies are needed to clarify the relationship between EDC exposure and human health. Greater information is also needed about the effect of mixtures and repeated exposures over multiple critical periods.

7. REMAINING CHALLENGES AND FUTURE DIRECTIONS

Accumulating evidence suggests that developmental EDC exposure is contributing to the rising rate of neurobehavioral disorders. However, there are many obstacles that make it difficult to establish direct causal relationships. First, the intervening period between

neurodevelopmental insult and the manifestation of a resulting behavioral dysfunction can be very long. During this period, which may take years or decades in humans, behavior is concomitantly influenced by other factors including genetics, experience, and lifestyle. Consequently, ascertaining the contribution of single chemical exposure is extraordinarily difficult. Moreover, humans are exposed to varying amounts and mixtures of EDCs throughout their lifetime. Already an area of increased interest, modeling "real world" human exposure (i.e., chronic, low-dose mixtures) will greatly enhance the translational value of animal studies in the EDC field.

In humans, studies on the neurobehavioral changes following early-life EDC exposure are constrained by practical and ethical limitations. An obvious limitation is the relative inaccessibility of the human brain. Both *in vivo* and *in vitro* models can be used to identify peripheral biomarkers of EDC exposure and associated diseases, which can be incorporated into new and existing epidemiological studies. Reliable biomarkers could also have important implications for identifying at-risk populations.

Since the advent of the endocrine disruption concept nearly 30 years ago [30], the field has made substantial progress in identifying several unique mechanisms of EDC action on the brain but gaps remain in establishing direct relationships between changes in neuronal substrate and consequential changes in behavior. Improved understanding will require deeper investigation into the basic neural and molecular mechanisms underlying complex behaviors such as activity, sociability, and executive function. As understanding their

biological origins grows, so does the capacity to more reliably predict and prevent injury from EDCs and other developmental neurotoxicants.

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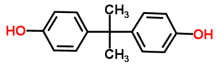
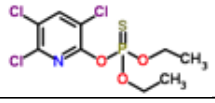
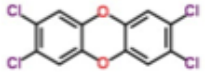
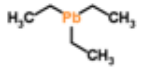
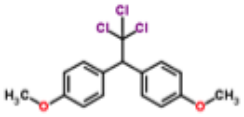
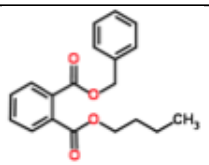
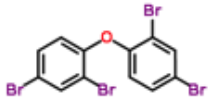
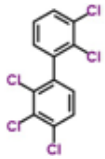
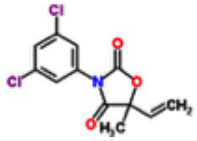
CHAPTER 1 TABLES

Table 1

Table 1. Structures and potential sources of endocrine disrupting chemicals with published behavioral effects.

EDC	Structure	Potential Sources of Human Exposure
Bisphenol A (BPA)		•Food packaging •Medical devices •Thermal receipt paper •Epoxy resins and polycarbonate plastics
Chlorpyrifos		•Insecticide in agricultural and commercial settings •Reside on fruits and vegetables
Dioxins	 *Tetrachlorodibenzo-p-dioxin*	•High fat food (e.g., dairy products, animal fat, and eggs) •Industrial processes (e.g., municipal waste incineration)
Lead	 *Triethyl lead*	•Paint •Lead-based gasoline •Dust •Drinking water •Children's jewelry and toys
Methoxychlor (MXC)		•Insecticide used on pets, home gardens, crops, and livestock •Air, soil, water contaminant
Phthalates	 *Benzyl butyl phthalate*	•Plastics •Food packaging •Personal care products and pharmaceuticals •Vinyl flooring, wall covering, and carpet backing •High-fat foods (e.g., dairy products animal fat, and eggs)
Polybrominated Diphenyl Ethers (PBDEs)	 *Pentabromodiphenyl ether*	•Flame retardants •House dust contaminant •Fish, meat, and dairy products •Soil and sediments •Outdoor air
Polychlorinated Biphenyls (PCBs)	 *2,2',3,3',4-PCB*	•High-fat foods (e.g., dairy products animal fat, and eggs) •Ground water contaminant •Electrical transformers, capacitors, and other industrial waste •Outdoor air
Vinclozolin		•Fungicide •Food and drinking water contaminant •Ground water •Outdoor air

CHAPTER 2

ORIGINAL RESEARCH

Impact of Low Dose Oral Exposure to Bisphenol A (BPA) on the Neonatal Rat Hypothalamic and Hippocampal Transcriptome: A CLARITY-BPA Consortium Study

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Bisphenol A (BPA) is an endocrine disrupting, high volume production chemical found in a variety of products. Evidence of prenatal exposure has raised concerns that developmental BPA may disrupt sex-specific brain organization and, consequently, induce lasting changes on neurophysiology and behavior. We and others have shown that exposure to BPA at doses below the no-observed-adverse-effect level can disrupt the sex-specific expression of estrogen-responsive genes in the neonatal rat brain including estrogen receptors (ERs). The present studies, conducted as part of the Consortium Linking Academic and Regulatory Insights of BPA Toxicity program, expanded this work by examining the hippocampal and hypothalamic transcriptome on postnatal day 1 with the hypothesis that genes sensitive to estrogen and/or sexually dimorphic in expression would be altered by prenatal BPA exposure. NCTR Sprague-Dawley dams were gavaged from gestational day 6 until parturition with BPA (0-, 2.5-, 25-, 250-, 2500-, or 25 000-μg/kg body weight [bw]/d). Ethinyl estradiol was used as a reference estrogen (0.05- or 0.5-μg/kg bw/d). Postnatal day 1 brains were microdissected and gene expression was assessed with RNA-sequencing (0-, 2.5-, and 2500-μg/kg bw BPA groups only) and/or quantitative real-time PCR (all exposure groups). BPA-related transcriptional changes were mainly confined to the hypothalamus. Consistent with prior observations, BPA induced sex-specific effects on hypothalamic ERα and ERβ (*Esr1* and *Esr2*) expression and hippocampal and hypothalamic oxytocin (*Oxt*) expression. These data demonstrate prenatal BPA exposure, even at doses below the current no-observed-adverse-effect level, can alter gene expression in the developing brain. (***Endocrinology*** **157: 3856–3872, 2016)**

Bisphenol A (BPA) is a well-known endocrine-disrupting compound (EDC) used in a wide range of products, including food and beverage containers, medical equipment, plastic water pipes, and thermal receipts, from which it can leach, thereby resulting in human exposure (1–3). BPA has been found in human fetal plasma and in placental tissue (1, 2), indicating that maternal BPA is able to cross the placenta. Evidence of prenatal exposure has raised concern that subtle effects of developmental BPA exposure on brain organization and sexual differentiation may have long-term impacts on neurophysiology and behavior (3–5). Over the past decade, the National Toxicology Program (NTP), World Health Organization, Food and Agricultural Organization, and others have expressed concern for effects on the brain and behavior (6–10). The Food and Drug Administration (FDA), however, subsequently departed from this view and in 2014 stated that

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Abbreviations: BPA, bisphenol A; bw, body weight; CLARITY-BPA, Consortium Linking Academic and Regulatory Insights on BPA Toxicity; Ct, cycle threshold; EDC, endocrine-disrupting compound; EE, ethinyl estradiol; ER, estrogen receptor; FDA, Food and Drug Administration; GABA, γ-aminobutyric acid; GD, gestational day; *Lepr*, leptin receptor; NCSU, North Carolina State University; NCTR, National Center for Toxicological Research; NCTR-SD, NCTR Sprague-Dawley; NOAEL, no-observed-adverse-effect level; NTP, National Toxicology Program; OT, oxytocin; padj, *P* value was adjusted for multiple testing using the Benjamini-Hochberg false discovery rate; PND, postnatal day; *Ptgds*, prostaglandin D2 synthase; qRT-PCR, quantitative real-time PCR; RNA-seq, RNA-sequencing.

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the "FDA's current perspective, based on its most recent safety assessment, is that BPA is safe at the current levels occurring in foods. Based on FDA's ongoing safety review of scientific evidence, the available information continues to support the safety of BPA for the currently approved uses in food containers and packaging." Historically, hazard characterization studies used to inform regulatory decision making have not investigated neural endpoints or included human-relevant doses (11, 12), limitations which have contributed to the lack of consensus on the potential health effects of developmental BPA exposure.

The experiments here were conducted as part of the Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) program (11–13), a collaborative effort coordinated by the National Institute of Environmental Health Sciences (NIEHS)/NTP and the FDA's National Center for Toxicological Research (NCTR) and specifically designed to address these information gaps and validate prior findings. CLARITY-BPA studies incorporate research recommendations from the World Health Organization and others (6–9, 14, 15), including comparing effects in both sexes, testing at multiple ages, use of a low phytoestrogen diet, inclusion of a reference estrogen, and evaluation of multiple BPA doses, particularly doses at or below the no-observed-adverse-effect level (NOAEL) of 5 mg/kg per day. The present study was specifically designed to focus on the neonatal brain and tested the hypothesis that gestational BPA exposure can have sex-specific effects on the brain transcriptome.

It is well established that even transient alterations in gene expression during perinatal brain development can cause irreversible changes in brain organization and, consequently, neuroendocrine physiology and behavior (16–19). Work by us and others has revealed that exposure to low doses (defined here as doses at or below the NOAEL of 50-mg/kg body weight [bw]/d) of BPA early in life impairs spatial memory (20) and alters sociosexual (21, 22) and anxiogenic behaviors in a variety of animal models (23, 24). Although the mechanisms by which BPA induces these and related behavioral outcomes remain unclear (3), developmental BPA exposure induces structural and molecular changes within brain regions essential for the coordination of these behaviors, most notably the hippocampus (25–28) and hypothalamus (29–32). For example, prenatal low-dose exposure has been demonstrated to alter dendritic (26) and synaptic structure and decrease mRNA expression of synaptophysin, spinophilin, and other genes critical for synapse formation and plasticity in the hippocampus of juvenile rodents (25, 26). In the hypothalamus, we and others have found age, region and sex-specific evidence for disrupted estrogen receptor (ER) expression or immunoreactivity after perinatal BPA exposure at or below the NOAEL (27, 29, 32–36).

Although the developing hippocampus and the hypothalamus appear to be vulnerable to BPA and other endocrine disruptors, surprisingly few studies have focused on prenatal exposure specifically, or assessed neural outcomes in the immature brain, particularly during the neonatal period (37). Albeit a relatively small literature, available studies suggest that prenatal BPA exposure can alter ER density in the developing brain, especially the hypothalamus. For example, in utero exposure to low doses of BPA disrupted sexually dimorphic gene expression patterns of ERα and ERβ (*Esr1* and *Esr2*) and estrogen-related receptor-γ (*Esrrg*) in juvenile mice (27). In a prior study using similar dosing methods and the same strain of rat as the present study, we found expression of *Esr1* and *Esr2* to be up-regulated by BPA in multiple subregions of the hypothalamus and amygdala in a sex-dependent manner on the day after birth (postnatal day [PND]1) (38). In other prior rat studies, we have also observed evidence of disruption on the expression of the neuropeptide oxytocin (*Oxt*) (23, 29). The present studies extend this prior work by examining the full transcriptome in the hypothalamus and hippocampus on PND1 with the hypothesis that, in addition to *Esr1* and *Esr2*, gene families sensitive to estrogen and/or sexually dimorphic in expression would be altered by prenatal BPA exposure, including *Oxt*.

That low doses of BPA have an estrogenic mode of action in vivo has been questioned because BPA has relatively low binding affinities for nuclear ERs (10 000- to 100 000-fold lower than estradiol) (39–41). Disruption of ER expression, particularly during critical windows of hormone-dependent sexual differentiation, may be an alternative mechanism by which BPA alters estrogen-mediated brain organization. Thus, the transcriptomic approach was undertaken to look for evidence that BPA might be active via other modes of action. Quantitative real-time PCR (qRT-PCR) was used to verify prior findings related to ER expression and compare expression of a predetermined set of genes across all available exposure groups and follow-up on applicable RNA-sequencing (RNA-seq) findings (Table 1).

Pregnant NCTR Sprague-Dawley (NCTR-SD) rats were treated orally by gavage with vehicle, 5 doses of BPA (2.5-, 25-, 250-, 2500-, and 25 000-μg/kg bw/d), or ethinyl estradiol (EE) (0.05- or 0.5-μg/kg bw/d) from gestational day (GD)6 through parturition. Because it was not economically feasible to assess the transcriptome from all available groups, 3 (vehicle, BPA 2.5, and BPA 2500) were selected for this purpose, and qRT-PCR was used to assess expression levels of candidate genes (*Esr1*, *Esr2*, and *Oxt*) and novel genes of interest identified by RNA-seq in all

Table 1. Candidate and Novel Genes Assessed With qRT-PCR

ABI Assay Number	Gene	Description	NCBI Accession Number	Region of Interest	Rationale for Analysis	References
Rn03928990_g1	*18s*	*R. norvegicus* 18S ribosomal RNA	NR_046237	Both	Endogenous control	
Rn01640372_m1	*Esr1*	*R. norvegicus* estrogen receptor1 (ERα)	NM_012689.1	Both	Coordinate estrogen signaling, can be nuclear or membrane bound, bind BPA	42–44
Rn00562610_m1	*Esr2*	*R. norvegicus* estrogen receptor2 (ERβ)	NM_012754.1	Both	Coordinate estrogen signaling, can be nuclear or membrane bound, bind BPA	42–44
Rn00564446_g1	*Oxt*	*R. norvegicus* oxytocin/ neurophysin 1 prepropeptide	NM_012996.3	Both	Mediates affiliation, social behavior, and mood, responsive to estrogen, altered by perinatal BPA	29, 45
Rn00564605_m1	*Ptgds*	*R. norvegicus* prostaglandin D2 synthase (brain)	NM_013015.2	Both	Plays role in neuroprotection; sexually dimorphic expression in neonates; differential expression observed in RNA-seq	46–48
Rn00691548_m1	*Slc1a2*	*R. norvegicus* solute carrier family 1 member 2, transcript variant 2	NM_001035233.1	Both	Represents primary excitatory pathway; differential expression observed in RNA-seq	49
Rn00824654_m1	*Slc32a1*	*R. norvegicus* solute carrier family 32, member 1	NM_031782.1	Both	Represents primary inhibitory signaling pathway; differential expression observed in RNA-seq	50
Rn01433205_m1	*Lepr*	*R. norvegicus* leptin receptor	NM_012596.1	Hypothalamus	Signaling altered by BPA in vitro; differential expression observed in RNA-seq	51

exposure groups. Data on other endpoints, at other ages, are forthcoming from other CLARITY studies but are beyond the scope of this specific subproject.

Materials and Methods

Animal husbandry and dosing

PND1 pups were obtained from litters generated for the CLARITY-BPA consortium program (11, 12). Detailed descriptions of animal husbandry, diet, breeding, and dose preparation and administration have been published elsewhere (13); therefore, only relevant methods are summarized here. All elements of the experimental design including doses, timing of exposure, and day of euthanizing were developed and agreed upon by the consortium. The program uses sibling NCTR-SD rats from an ongoing guideline-compliant chronic 2-year study, which follows standard protocols and contains classical endpoints typically considered by regulatory agencies in hazard identification and risk assessment (11, 12). Two other CLARITY-BPA studies (one by our own lab and both focused on behavior) have been published before this one (52, 53). Animals were maintained in an Association for Assessment and Accreditation of Laboratory Animal Care-accredited facility, and the NCTR Institutional Animal Care and Use Committee approved all procedures in advance.

Dams were housed in rooms maintained on a 12-hour light, 12-hour dark cycle (6 AM to 6 PM) at 23 ± 3°C with a relative humidity level of 50 ± 20%. A soy- and alfalfa-free (5K96 verified casein diet 10 IF, round pellets, γ-irradiated; catalog 1810069, Purina Mills) diet and Millipore-filtered water in glass water bottles with silicone stoppers (7721 clear; Plasticoid Co) were provided ad libitum. Extracts of diet and other study materials were monitored for BPA and myco/phytoestrogens (genistein, daidzein, zearalenone, and coumestrol) by liquid chromatography and mass spectrometry (54). Each diet lot assayed contained less BPA than the protocol-specified limit of 5 parts per billion (54) and less than 1 parts per million genistein and daidzein and less than 0.5 parts per million zearalenone and coumestrol. Similarly, drinking water, polysulfone cage leachates, and bedding extracts were found to have BPA levels below the level of the average analytical method blanks (13).

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Approximately 2 weeks before mating, female Sprague-Dawley rats from the NCTR colony (NCTR-SD) were randomized to 8 exposure groups stratified by bw to produce approximately equal mean bws in each group. Eight dose groups were included in this study (vehicle and BPA 2.5-, 25-, 250-, 2500-, and 25 000-μg/kw bw/d and EE 0.05- and 0.5-μg/kw bw/d). The 2 EE groups were incorporated into the CLARITY design for the purposes of serving as a reference estrogen and to provide directional guidance to establish whether BPA-related effects were consistent with an "estrogenic" effect. Mating pairs were assigned randomly, subject to the constraint that no sibling or first cousin mating was permitted. Aside from mating occurring in solid-bottomed polysulfone caging with hardwood chip bedding, mating was conducted as previously described (54).

Beginning on GD6, dams were gavaged daily with 0.3% carboxymethyl cellulose/kg bw/d (vehicle control group), 2.5-μg BPA/kg bw/d (BPA 2.5 group), 25.0-μg BPA/kg bw/d (BPA 25 group), 250-μg BPA/kg bw/d (BPA 250 group), 2500-μg BPA/kg bw/d (BPA 2500 group), 25 000-μg BPA/kg bw/d (BPA 25 000 group), 0.05-μg EE/kg bw/d (EE 0.05 group), or 0.5-μg EE/kg bw/d (EE 0.5 group). Dose volume was determined immediately after daily bw collection and dosing continued until the day of parturition (PND0). Internal dose levels were not assessed, but information regarding BPA pharmacokinetics in this strain is published elsewhere (55, 56). Dams and pups were left undisturbed during PND0. On PND1, terminal pup weights were collected and pups (no more than 1 per sex per litter) were euthanized by decapitation. Within sex, there were no significant effects of exposure on pup terminal bw (data not shown). Heads were rapidly frozen in dry ice and shipped to the Patisaul laboratory at North Carolina State University (NCSU), where they were archived and stored at −80°C until processing. All tissues were coded, and all testing was done blinded to exposure group.

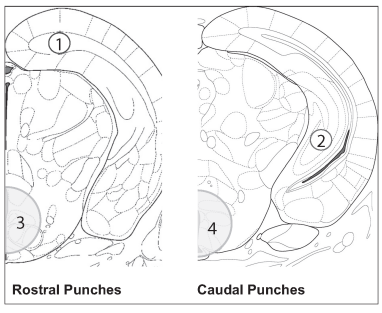
Tissue collection

Each whole head was coronally cryosectioned (Leica CM1900) from the caudal end until the caudal borders of the hypothalamus and hippocampus were identified. Anatomical landmarks were located with the assistance of a rat and mouse brain atlas (57, 58). Tissue samples were obtained using a sterilized stainless steel punch that was briefly cooled on dry ice, as previously described (23). For each animal, 2 hypothalamic punches and 4 hippocampal punches were obtained (Figure 1A). The hypothalamic tissue collected consisted of 2 sequential punches, 1 taken anteromedially and 1 caudomedially, with a micropunch 1.25 mm in diameter and 1.00 mm in depth. These punches were combined and collectively comprised the entire hypothalamus sample. Because the hippocampus is irregular in shape, a series of smaller punches were made to obtain sufficient material but also ensure anatomical specificity. For each animal, 4 punches were made, each 0.5 mm in diameter and 1.00 mm in depth: 1 pair of bilateral anterodorsal punches and 1 pair of bilateral caudoventral punches. All 4 samples were combined and collectively comprised the entire hippocampus sample. Each punch sample was expelled out of the stainless steel punch directly into a BPA-free Eppendorf tube on dry ice and stored at −80°C.

RNA-sequencing

The experimental design for transcriptome sequencing was developed in consultation with the NCSU Genomic Sciences Laboratory and the Bioinformatics Research Core. Transcriptome sequencing was performed by the Genomic Sciences Laboratory on 24 hippocampal (n = 4 per sex per group) and 24 hypothalamic (n = 4 per sex per group) samples (Figure 1B). Three experimental groups were examined: control, BPA 2.5, and BPA 2500. These doses were selected in consultation with other consortium members based on effects observed in other subprojects (52, 53) and prior results in analogous studies using NCTR-SD rats (34, 38). Because the DNA needed to be sent to another CLARITY member for subsequent studies (to be published elsewhere), DNA and RNA were coextracted from frozen tissue samples using the ZR-duet DNA/RNA miniprep copurification kit and treated with an on-column DNase I digestion, per the manufacturer's protocol (Zymo Research). RNA quality was assessed with the Agilent 2100 Bioanalyzer. All hippocampal samples had an RNA integrity number more than or equal to 9 and all hypothalamic samples had an RNA integrity number of 10. To optimize library complexity, all samples used as input material for library preparation had greater than 100 ng of total RNA. Sequencing libraries were prepared with the NEBNext Ultra Directional RNA Library Prep kit for Illumina and the NEBNext Poly (A) mRNA Magnetic Isolation Module (catalogs E7420 and E7490; New England Biolabs). Per manufacturer's instructions, mRNA was isolated, heat fragmented, and primed with random primers. First strand cDNA synthesis was performed with actinomycin D and Protoscript II Reverse Transcriptase. Second strand cDNA synthesis was performed with second strand synthesis reaction buffer containing dUTP, which replaces dTTPs and preserves strand orientation information. After cDNA

A



B

Groups	RNAseq	qRT-PCR
Vehicle	4♂, 4♀	6♂, 6♀ hyp 5♂, 6♀ hipp
2.5 BPA	4♂, 4♀	6♂, 6♀
25 BPA	0	5♂, 5♀
250 BPA	0	5♂, 5♀
2500 BPA	4♂, 4♀	6♂, 6♀hyp 6♂, 5♀ hipp
25000 BPA	0	5♂, 5♀
0.05 EE	0	5♂, 5♀
0.5 EE	0	5♂, 5♀

Figure 1. A, Anatomical representation of regions extracted via micropunch (obtained by approaching the regions of interest caudally and punching rostrally) and used for gene expression analysis. For each animal, 1 pair of bilateral anterodorsal hippocampal punches (1, unshaded) and 1 pair of bilateral caudoventral hippocampal punches (2, unshaded) were made, each 0.5 mm in diameter and 1.00 mm in depth. All 4 punches were combined, collectively comprising the whole hippocampus. Hypothalamic tissue consisted of 2 sequential punches (1.25 mm in diameter and 1.00 mm in depth): 1 anteromedial (3, shaded) and 1 caudomedial (4, shaded). B, Sample sizes for RNA-seq and qRT-PCR.

synthesis, the fragments were purified and size selected using AMPure XP beads (catalog A63881; Beckman Coulter Genomics). The cDNA library fragments were then treated with an End Repair enzyme mix and ligated onto adaptors specifically designed for the Illumina platform. PCR was used to replace the dUTPs in the adaptor sequence and the second strand of the cDNA fragments, enrich adaptor-ligated cDNA, and add 6-nucleotide barcode sequences that allow for pooling of multiple samples for sequencing and sorting of data during analysis. Library clean-up was performed with AMPure XP beads and quality was confirmed on the Agilent 2100 Bioanalyzer. For both experiments (hippocampus and hypothalamus), cDNA libraries were combined into 2 pools of equal molar amounts. Following a balanced block design (59), both pools were multiplexed and run across 3 lanes. Libraries were sequenced using the 125-bp single-end protocol on an Illumina HiSeq2500 sequencer. Approximately 29.9 million reads were generated per hippocampal library and 29.2 million reads per hypothalamic library.

RNA-seq data processing

RNA-seq data analysis was performed by the Bioinformatics Core at the University of Virginia. Quality control of read data was assessed with FastQC before and after adaptor trimming and filtering. The STAR alignment tool (60) was used to align reads to the *Rattus norvegicus* (rn5) reference genomic sequence, downloaded from UCSC's Genome Browser. After aligning data, the number of reads mapping to GENCODE was calculated using the featureCounts software in the Subread package (61). Count data were normalized for sequencing depth and distortion, and dispersion was estimated using the DESeq2 Bioconductor (62, 63) package in the R statistical computing environment.

Quantitative real-time PCR

Gene expression analysis by qRT-PCR was performed on 8 treatment groups (n = 5–6; sample numbers indicated in Supplemental Figure 1B): vehicle and BPA 2.5-, 25-, 250-, 2500-, and 25 000-μg/kg bw/d and EE 0.05- and 0.5-μg/kg bw/d. A DNA/RNA miniprep copurification kit (catalog D7001; Zymo Research) with the addition of an on-column DNase I digestion (catalog E1007; Zymo Research) was used to extract RNA. Extracted DNA was sent to another CLARITY consortium member for independent analysis. mRNA was reverse transcribed to single-strand complementary cDNA with the high capacity RNA-to-cDNA kit (catalog 4387406; Applied Biosystems). Each RT reaction was incubated for 60 minutes at 37°C, 5 minutes at 95°C, and stored at −20°C until use. Real-time PCR was performed with an ABI StepOnePlus Real-Time PCR System. A TaqMan probe-based protocol was used to detect gene expression, and primers and probes were included in these predesigned assays (Table 1). The PCRs were incubated in 96-well plates and run using the manufacturer's recommended cycling parameters of 50°C for 2 minutes, 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. All reactions consisted of 1-μL hypothalamic RT product or 2-μL hippocampal RT product, 1-μL of 20× TaqMan gene expression assay mix, 10 μL of TaqMan Universal PCR Master Mix, and nuclease-free H_2O in a quantity sufficient to make a 20-μL total reaction volume. No-template controls were run for each TaqMan gene expression assay and each PCR was run in triplicate. An inter-run calibrator and the sample maximization approach was followed to avoid technical and run-to-run variation (64). To correct for variation in starting cDNA concentrations, cycle threshold (Ct) values for the gene of interest for each sample were normalized to the Ct for 18s rRNA for each sample. 18s was selected as the normalizing transcript based on preliminary work for these experiments with other candidates showing that 18s was the most reliable and robust. Quantitative mRNA expression data were acquired and analyzed by the Livak ΔΔ-Ct (ΔΔ-Ct) method (65).

Data decoding

All testing and data collection for the RNA-seq was conducted blind to exposure. All individuals had a unique identifier and the samples belonging to each experimental group (grouped by exposure and sex) were designated with a letter (A, B, C, etc). The blinded raw data were submitted to the NTP Chemical Effects in Biological Systems database. It was then independently verified to account for all expected datasets and data points, and "locked" such that data could not be altered. The NCSU researchers were then provided with the exposure code for data analysis. The qRT-PCR experimental design depended, in part, on the RNA-seq results. Thus, the qRT-PCR phase was performed after the RNA-seq data was decoded but blind to the other, remaining, groups.

Genes for the qRT-PCR analyses were selected either a priori, because they were previously shown to be altered by developmental BPA exposure in brain (*Esr1*, *Esr2*, and *Oxt*), sexually dimorphic in PND1 hypothalamus (prostaglandin D2 synthase [*Ptgds*]) (66), or identified from the RNA-seq results (*Lepr*, *Slc32a1*, and *Slc1a2*). Additionally, *Slc32a1* and *Slc1a2* were considered gross indicators of altered inhibitory and excitatory neurotransmission. The blinded raw data were then submitted to Chemical Effects in Biological Systems and locked as described for the RNA-seq experiments and analyzed once the data were decoded.

Statistical analysis

The statistical approach was developed to be consistent with previously published transcriptome projects of similar scale (equivalent sample size or smaller) in rat brain (48) and guidelines for low-dose EDC studies with sample sizes in this range (67). Within each exposure group, no same-sex litter mates were included, so potential litter effects did not need to be statistically accounted for.

RNA-seq analysis

For all data, the hippocampus and the hypothalamus were analyzed separately. The DEseq2 package was used to fit a negative binomial model for each gene using an extended model matrix. To identify sex differences in gene expression, the male and female controls were compared independent of other exposure groups. With that exception, all other data were compared within sex. For each comparison, the *P* value was adjusted for multiple testing using the Benjamini-Hochberg false discovery rate (padj) (68). Some genes could not be corrected because their abundance was too low to justify analysis (padj = N/A). Thus, for all comparisons, statistical significance was defined as padj ≤ .05. The group for which the greatest numbers of genes were significantly altered by BPA was the hypothalamic male BPA

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2500 group. Thus, to further query the sex-specificity of these effects, an interaction term in the negative binomial model was fit to examine the nonlinear effect of sex-by-exposure compared with unexposed controls. This approach considerably narrowed the prospective list of significantly altered genes.

qRT-PCR analysis

Statistical analyses were performed and graphed using Prism v6 software (GraphPad Software, Inc). Two samples (1 for hypothalamic *Oxt* and 1 for hypothalamic *Esr2*) were excluded due to technical error. Outliers (no more than 1 per group) were identified using a Grubb's test. Final sample sizes are listed in table 3 below. Data from the hippocampus and hypothalamus were analyzed independently and, because gene expression was anticipated to be sexually dimorphic in some cases, analyzed within sex. The study had multiple related but independent hypotheses, each of which was tested independently and included only the relevant groups for addressing that specific hypothesis. Using a 2-tailed Mann-Whitney *U* test, it was first established whether expected sex differences in gene expression between the male and female controls were present. Also using a 2-tailed Mann-Whitney *U* test, we next addressed the primary goal of the study: establish whether BPA impacts gene expression in either region of interest at any of the doses employed, in either sex. When BPA-related effects were found, qualitative comparisons with the EE groups were made to see whether directionality was consistent with an estrogenic effect. Finally, EE was used as a reference estrogen and thus expected to masculinize sexually dimorphic gene expression in females. Within sex, differences in mean expression values between the controls and each of the 2 EE groups were identified using a 2-tailed Mann-Whitney *U* test. In all cases, effects were considered significant at $P \leq .05$.

Results

Expression assessment by RNA-seq

Effect of prenatal BPA exposure on hippocampal gene expression

Effects of BPA on the PND1 hippocampal transcriptome were minimal. Expression of 13 genes was altered in the BPA 2.5 exposed females. Of these, endoglin (*Eng*) and Centers for Disease Control-like kinase 4 (*Clk4*) exhibited the largest fold change (−1.52 and 1.65, respectively) (Supplemental Table 1a). No significant effects of BPA were observed in the BPA 2500 exposed females. In BPA 2.5 exposed males, only expression of RuvB-like AAA ATPase 2 (*Ruvbl2*) was decreased (Supplemental Table 1b). In the BPA 2500 exposed males, 10 genes were differentially expressed. Of these, neurotrophin receptor associated death domain (*Nradd*) and ER degradation enhancing α-mannosidase-like protein 1 (*Edem1*) showed the largest fold change (−1.75 and 1.70, respectively).

Effect of prenatal BPA exposure on hypothalamic gene expression

BPA-related transcriptional changes were more numerous in the hypothalamus than in the hippocampus but only in males. In the BPA 2.5 exposed females only one gene was altered and only 2 were altered in the BPA 2500 group. Common salivary protein 1 (*Csap1*) was down-regulated in both the BPA 2.5 and BPA 2500 females (fold changes were −1.31 and −1.32, respectively). In addition, SPARC-like 1 (*Sparcl1*) was down-regulated in the BPA 2500 females (Supplemental Table 2a). In males, there was a robust effect of prenatal exposure to BPA at both doses (Supplemental Table 2b). In the BPA 2.5 exposed males, 639 genes were affected by BPA compared with same-sex controls. Of these, 360 were down-regulated and 279 were up-regulated. In males exposed to BPA 2500, 1107 genes were significantly altered. Of these, 553 were down-regulated and 554 were up-regulated. A total of 371 genes were significantly altered by BPA in both dose groups (Supplemental Table 3). Because so many more genes were affected in males than females in the BPA 2500 group, a two-way ANOVA with sex and exposure as factors was used to specifically identify genes for which there was a significant sex by exposure interaction. This approach identified 32 differentially expressed genes (28 up-regulated and 4 down-regulated) (Table 2). Of these, aquaporin 1 (*Aqp1*) exhibited the largest fold change (1.62); 13 of these genes were also significantly affected at the 2.5 dose (*Ap5M1*, *Atad5*, *Atm*, *Cd2Ap*, *Dennd4C*, *Dusp26*, *Mat2A*, *Scn9A*, *Setx*, *Slc32A1*, *Tia1*, *Ythdc2*, and *Zdhhc15*).

Sex differences in gene expression levels

For each brain region, the male and female controls were compared independent of other exposure groups to identify genes for which expression differed by sex. This was done to both confirm that our procedures were robust enough to detect known sex differences and to potentially identify novel genes for which expression varies by sex on PND1. As anticipated, the hippocampus had fewer sexually dimorphic transcripts than the hypothalamus. In the hippocampus, 29 genes were expressed at significantly different levels in males and females, with 23 (79.3%) being more highly expressed in males and 6 (20.7%) being more highly expressed in females (Supplemental Table 4a). In the hypothalamus, 210 genes with sexually dimorphic expression patterns were identified, with 147 (74.6%) having higher expression levels in females (Supplemental Table 4b). Of these, hypothetical protein LOC680227 (*LOC680227*) and pro-α-1 collagen, type 1 (*Col1a1*) exhibited the largest fold changes (6.98 and 4.94, respectively). Consistent with previous reports, expression of

Table 2. Differentially Expressed Genes for Which There Was a Significant Sex by Exposure Interaction at 2500-μg BPA/kg bw/d in Males

Gene	Gene Name	Fold Change	log2 (Fold Change)	padj Value
Atm	Ataxia telangiectasia mutated homolog	1.318	0.398	.019
Ddx26b	DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 26B	1.431	0.517	.019
Prp2l1	Proline-rich protein 2-like 1	1.471	0.557	.019
Scn9a	Sodium channel, voltage-gated, type IX, α	1.389	0.474	.019
Tbc1d4	TBC1 domain family, member 4	1.432	0.518	.019
Tgds	TDP-glucose 4,6-dehydratase	1.331	0.413	.019
Tia1	TIA1 cytotoxic granule-associated RNA-binding protein	1.253	0.325	.019
Ythdc2	YTH domain containing 2	1.290	0.367	.019
Aqp1	Aquaporin 1	1.616	0.692	.020
Cd2ap	CD2-associated protein	1.320	0.400	.022
Fancd2	Fanconi anemia, complementation group D2	1.331	0.413	.022
Slc32a1	Solute carrier family 32 (GABA vesicular transporter), member 1	−1.449	−0.535	.022
Trpm3	Transient receptor potential cation channel, subfamily M, member 3	1.253	0.325	.022
Vstm2b	V-set and transmembrane domain containing 2B	−1.316	−0.396	.022
Ap5m1	Adaptor-related protein complex 5, μ-1 subunit	1.373	0.457	.025
Sparcl1	SPARC-like 1 (hevin)	1.366	0.450	.025
Arhgap29	ρ-GTPase activating protein 29	1.388	0.473	.027
Itsn2	Intersectin 2	1.254	0.327	.027
Atad5	ATPase family, AAA domain containing 5	1.282	0.358	.027
Lepr	Leptin receptor	1.497	0.582	.027
Mrs2	Magnesium homeostasis factor homolog	1.330	0.411	.035
Tnc	Tenascin C	1.365	0.449	.041
Ralgapa2	Ral GTPase-activating protein, α-subunit 2	1.281	0.357	.043
Mat2a	Methionine adenosyltransferase II, α	1.237	0.307	.044
Supt20	Suppressor of Ty 20	1.266	0.340	.044
Dennd4c	DENN/MADD domain containing 4C	1.300	0.378	.044
Pycrl	Pyrroline-5-carboxylate reductase like	−1.198	−0.261	.044
Cep295	Centrosomal protein 295	1.359	0.443	.046
Adamts12	ADAM metallopeptidase with thrombospondin type 1 motif, 12	1.447	0.533	.047
Dusp26	Dual specificity phosphatase 26 (putative)	−1.251	−0.323	.047
Setx	Senataxin	1.240	0.310	.047
Zdhhc15	Zinc finger, DHHC-type containing 15	1.312	0.392	.047

Ptgds and cAMP-regulated phosphoprotein 21 (*Arpp21*) was higher in females (47, 48). Similarly, as anticipated, *Oxt*, nuclear receptor subfamily 2, group F, member 2 (*Nr2f2*), and ribosomal protein L30 (*Rpl30*) were expressed at higher levels in males (48, 66).

Expression assessment by qRT-PCR

A summary of the significant outcomes in both hippocampus and hypothalamus are listed in Table 3. Data for genes in which there was no significant effect of BPA in either sex are not listed. A full summary of the RNA-seq (including raw and adjusted *P* values) and qRT-PCR data for all genes assessed by qRT-PCR is provided in Supplemental Table 5. For the RNA-seq data, only comparisons where padj ≤ .05 were considered biologically meaningful and statistically significant.

Effect of prenatal BPA or EE exposure on hippocampal gene expression

Esr1 expression levels in the hippocampus were not affected by BPA or EE in either sex (Figure 2, A and B). In males, *Esr2* expression levels were significantly increased in the BPA 25 000 and EE 0.05 groups (Figure 2D). Within females, however, there were no significant effects of exposure on *Esr2* expression (Figure 2C). In males, *Oxt* expression was significantly decreased in the BPA 2500 and BPA 25 000 groups (Figure 3B), whereas in females, *Oxt* expression was higher in the BPA 25 group (Figure 3A). No significant effects of BPA or EE on the expression of *Ptgds*, *Slc1a2*, or *Slc32a1* were identified in either sex (Figure 3, C–H).

Effect of prenatal BPA or EE exposure on hypothalamic gene expression

Higher expression of *Esr1* was identified in the female BPA 2.5, BPA 250, and BPA 25 000 groups (Figure 4A), but BPA had no significant effect on *Esr1* expression in the male hypothalamus (Figure 4B). Similarly, expression levels of *Esr2* were significantly higher in the female BPA 2.5, BPA 250, and BPA 25 000 groups, but there were no significant effects of BPA or EE on *Esr2* in males (Figure 4, C

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Table 3. qRT-PCR Outcomes and Descriptive Statistics for Genes Found to be Significantly Altered by BPA Exposure

Gene	Comparison (n)	Relative Abundance	*U*	*P* Value
Hippocampus				
ERβ (*Esr2*)	♂ BPA 25 000 (5) to ♂ Control (4)	9.451	0	.016
	♂ EE 0.05 (5) to ♂ Control (4)	8.209	0	.016
Oxytocin (*Oxt*)	♀ BPA 25 (5) to ♀ Control (5)	3.729	2	.032
	♂ BPA 2500 (6) to ♂ Control (5)	0.438	3	.030
	♂ BPA 25 000 (4) to ♂ Control (5)	0.434	1	.032
Hypothalamus				
ERα (*Esr1*)	♀ BPA 2.5 (6) to ♀ Control (5)	6.055	0	.004
	♀ BPA 250 (5) to ♀ Control (5)	5.254	1	.016
	♀ BPA 25 000 (5) to ♀ Control (5)	3.514	0	.008
ERβ (*Esr2*)	♀ BPA 2.5 (6) to ♀ Control (5)	5.507	1	.009
	♀ BPA 250 (5) to ♀ Control (5)	3.534	2	.032
	♀ BPA 25 000 (5) to ♀ Control (5)	2.810	2	.032
	♀ Control (4) to ♂ Control (6)	0.230	2	.038
Oxytocin (*Oxt*)	♀ BPA 2.5 (6) to ♀ Control (5)	8.795	3	.030
	♀ BPA 250 (5) to ♀ Control (5)	6.200	1	.016
	♀ EE 0.05 (5) to ♀ Control (5)	16.245	2	.032
	♂ BPA 25 (5) to ♂ Control (5)	20.757	2	.032
	♂ Control (5) to ♂ EE 0.5 (5)	11.965	0	.008
Prostaglandin D2 synthase (*Ptgds*)	♀ EE 0.5 (5) to ♀ Control (6)	5.927	1	.009
	♂ EE 0.5 (5) to ♂ Control (6)	7.365	2	.017
GABA vesicular transporter (*Slc32a1*)	♀ BPA 2.5 (6) to ♀ Control (6)	5.247	0	.004
	♀ BPA 250 (5) to ♀ Control (5)	4.398	0	.008
	♀ BPA 25 000 (5) to ♀ Control (5)	3.761	2	.032
	♀ EE 0.05 (5) to ♀ Control (5)	4.329	1	.016
	♂ EE 0.5 (5) to ♂ Control (5)	1.878	3	.030
	♀ Control (4) to ♂ Control (6)	0.210	0	.010

For each group, the sample size is listed in parentheses.

and D). *Oxt* expression was elevated in the female BPA 2.5, BPA 250, and EE 0.05 groups (Figure 5A) and the male BPA 25 and EE 0.05 groups (Figure 5B). For both males and females, *Ptgds* expression in the EE 0.5 groups was increased compared with the same-sex control (Figure 5, C and D). In females (Figure 5G), *Slc32a1* expression was elevated in the BPA 2.5, BPA 250, BPA 25 000, and EE 0.5 groups. By contrast, within males, elevated levels were only observed in the EE 0.05 group (Figure 5H). For both males and females, there were no significant effects of prenatal BPA or EE on the expression of *Slc1a2* or leptin receptor (*Lepr*) (Figure 5, E, F, I, and J).

Sex differences in gene expression levels

No significant sex differences were observed between control animals in the hippocampus (Figure 6A). In the hypothalamus, *Esr2* and *Slc32a1* were expressed at higher levels in males (Figure 6B). EE masculinized hypothalamic *Slc32a1* expression but only at the lower dose. In males, the highest dose of EE exhibited a hypermasculinizing effect on *Slc32a1*, upregulating expression (Figure 5G). EE did not significantly affect hypothalamic *Esr2* expression in either sex (Figure 4, C and D).

Discussion

The present study represents the most comprehensive evaluation of gestational BPA exposure on gene expression levels in the neonatal rat hippocampus and hypothalamus to date. Additionally, to our knowledge, this is the only study that has analyzed the full hippocampal transcriptome at PND1 and looked for possible sex differences. Thus, the present studies contribute fundamental new knowledge about sex-specific gene expression in the newborn rat hypothalamus and hippocampus as well as sex-specific sensitivity to gestational BPA exposure at what is generally accepted as a low-dose range.

As anticipated, expression changes induced by BPA were primarily confined to the hypothalamus, a region that coordinates a wide range of neuroendocrine activities including growth, feeding, and reproductive behavior. Hypothalamic transcription changes identified by RNA-seq were overwhelmingly male specific with robust overlap between the 2 dose groups examined (2.5 and 2500). The single gene found by RNA-seq to be altered by BPA at both doses in the female hypothalamus is most abundant

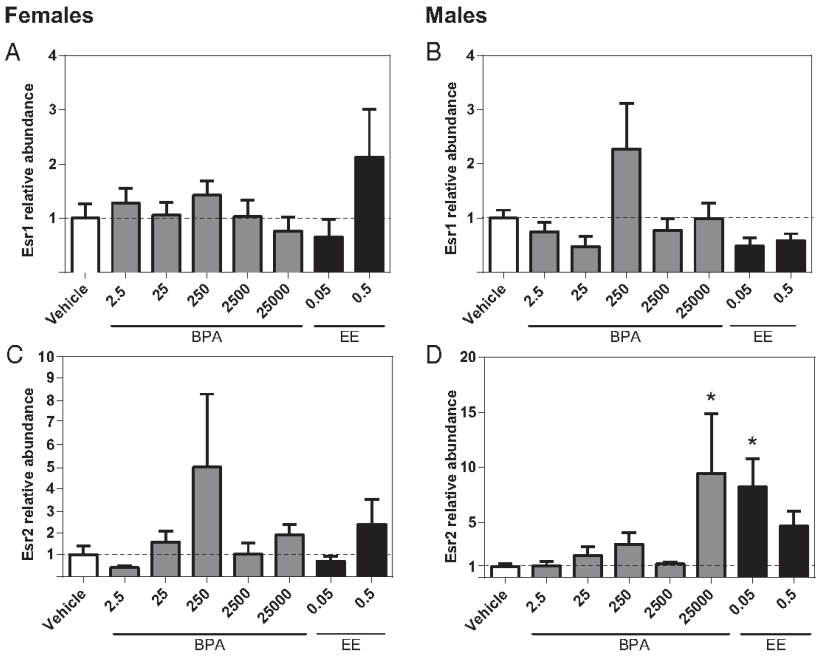

Figure 2. Effects of gestational BPA and EE on neonatal hippocampal ER expression. BPA or EE did not affect *Esr1* expression in females (A) or males (B). In females, there was no effect of BPA or EE on *Esr2* expression (C). In males, exposure to the highest BPA dose and lowest EE dose resulted in significantly increased *Esr2* expression (D). Graphs depict mean ± SEM; *, $P \leq .05$.

in respiratory epithelium but is also in pituitary and has previously been identified as being sensitive to BPA in a seminiferous tubule culture model (69). It is unclear what the functional significance of this might be and was thus not followed up. Detection may indicate that the micropunches contained at least some material from the pituitary, which is not unexpected given that the pituitary is physically connected to the hypothalamus.

Gene Ontology analysis using the functional annotation tool of DAVID 6.7 (70) for the 371 genes found to be altered in the hypothalamus of both the BPA 2.5 and 2500 male groups revealed "regulation of transcription" as the only significantly (adjusted $P \leq .05$) enriched pathway (45 genes). Deeper analysis of specific cellular pathways within this general term identified none for which more than only a handful of genes were altered, an outcome interpreted to indicate that BPA is unlikely to be acting in the developing brain via a mode of action not previously identified. A caveat of this conclusion is that the vast majority of available gene annotations (available in DAVID and similar annotation tools) were made in tissues outside of the brain and not in neonatal tissues (or both sexes). Thus, the annotations may not be reasonably applicable to this specific data set. A follow-up analysis was then performed using Ingenuity Pathway Analysis (QIAGEN) with a stringent preanalysis filter restricting input to only neural tissues/cell lines. This revealed the "nervous system development and function" as a significantly enriched physiological system (26 genes) with BPA-sensitive genes identified for 37 subfunctions, but, again, all subfunctions were enriched with only a handful of genes (with significance ranging from $P \leq .05$ to $P \leq .002$). Interestingly, the single function with the most BPA-sensitive genes (*Fox06*, *Limk1*, *Mark4*, *Rhob*, and *Scn1a*; $P \leq .02$) was "morphology of dendritic spines." Disruption of spine morphology has previously been associated with BPA exposure in rodents and nonhuman primates of both sexes (71–73). Annotation analysis for the subset of 32 transcripts identified as significantly affected in BPA 2500 males also identified no significantly enriched pathways (via DAVID or Ingenuity Pathway Analysis).

A limitation of the RNA-seq analysis is that an unsupervised principle components analysis did not clearly delineate RNA-seq data by exposure group or sex in either the hippocampus or the hypothalamus (Supplemental Figure 1B). This outcome is not entirely unexpected for the

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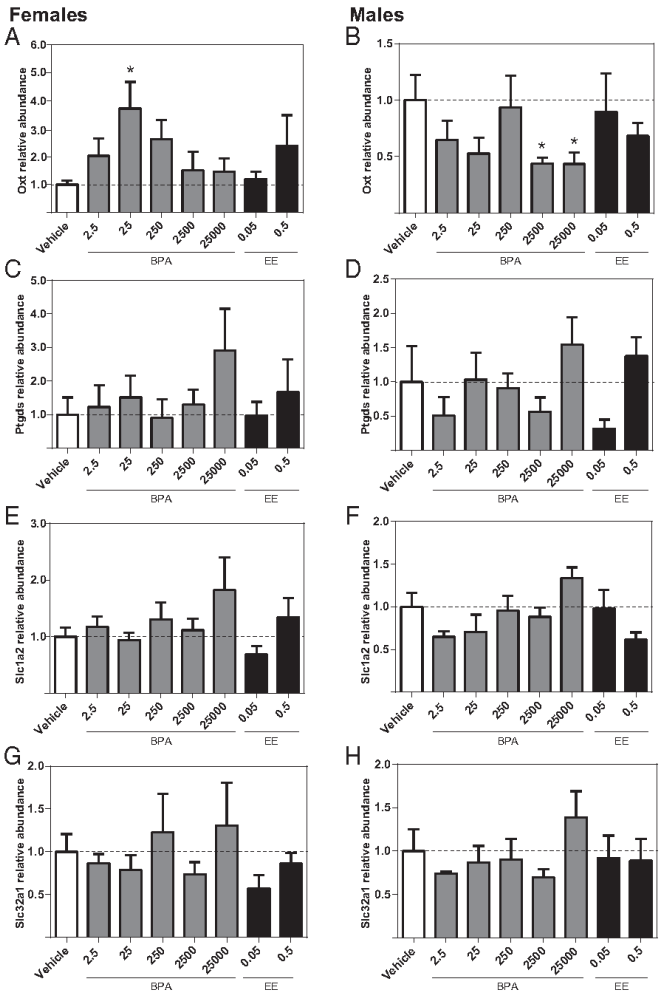

Figure 3. Effects of gestational BPA and EE exposure on neonatal hippocampal expression of selected genes. In females, exposure to 25-μg BPA/kg bw/d significantly increased *Oxt* expression (A). In males, exposure to 2500- and 25 000-μg BPA/kg bw/d decreased expression of *Oxt* (B). BPA and EE had no significant effect on *Ptgds* (C and D), *Slc1a2* (E and F), or *Slc32a1* (G and H) expression in either females or males. Graphs depict mean ± SEM; *, $P \leq .05$.

hippocampus, because there were few effects of BPA and only minimal evidence for sexually dimorphic neonatal gene expression (74). In the neonatal hypothalamus, however, many genes are known to be sexually dimorphic, and BPA-related effects were male biased at both doses examined, thus we expected this data to cluster more robustly. Despite this caveat, the analysis successfully detected transcripts known to be sexually dimorphic. For example, a study analyzing sexually dimorphic gene expression in the rat preoptic area of the hypothalamus at PND2 detected higher expression of *Ptgds* and *Arpp21* in females and higher expression of *Oxt* (found in the present study to be sensitive to BPA) and *Nr2f2* in males (66). Similarly, a microarray analysis of the whole hypothalamus of male and female mice detected female-biased expression of *Ptgds* on the day of birth (47). Detection of these and other transcriptional sex differences by RNA-seq in the present study was interpreted to signify that our RNA-seq approach had sufficient resolution and statistical power (Supplemental Table 4) to detect group differences (sex and exposure).

Specific genes of interest (selected both a priori based on prior work showing they are sensitive to BPA exposure, and from the RNA-seq analysis) were further assessed by qRT-PCR on all 8 of exposure groups (summarized in Supplemental Table 5). The directionality of the results generally confirmed the RNA-seq data, including the small number of BPA-related effects in the hippocampus. That the highest BPA dose up-regulated of *Esr2* in PND1 male hippocampus is consistent with a prior study in BALB/c mice investigating the effects of in utero exposure to 2-μg/kg BPA on juveniles (27). As early as embryonic day 17, ERβ is abundantly expressed in the developing rodent hippocampus (75), but the specific functional role it plays in the organization of the hippocampus has not been fully characterized. Hippocampal *Oxt* was down-regulated in males exposed to 2500- and 25 000-μg/kg bw/d and up-regulated in females exposed to 25-μg/kg bw/d. Oxytocin (OT) is primarily synthesized in the paraventricular and supraoptic nuclei of the hypothalamus (PVN and SON, respectively) and axonal projections from a subset of these neurons transport OT to the hippocampus and other regions (76–78). OT is normally translated in the perikarya of neurons; however, mRNA has been found in hypothalamic axons, suggesting it may also be locally synthesized in nerve terminals (79, 80).

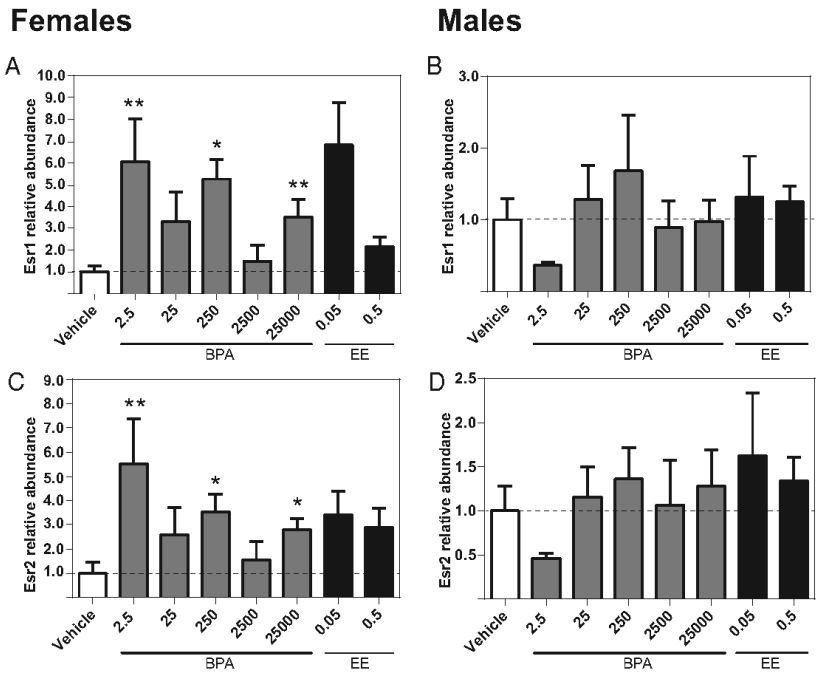

Figure 4. Effects of gestational BPA and EE exposure on neonatal hypothalamic ER expression. Exposure to 2.5-, 250-, and 25 000-μg BPA/kg bw/d increased female expression of *Esr1* and *Esr2* (A and C). Expression in males was unaffected (B and D). EE had no effect on ER expression in either sex. Graphs depict mean ± SEM; *, $P \leq .05$ and **, $P \leq .01$.

Emerging evidence in adult rodents now indicates OT may play a neuroprotective role in the hippocampus by buffering neuroendocrine and behavioral responses to stress and stimulating neurogenesis (81, 82). We and others have previously reported effects of BPA on OT signaling pathways in the hypothalamus and the amygdala (3, 23, 24, 29, 83), but the present study is the first to suggest gestational exposure to BPA may alter *Oxt* expression in the hippocampus. Subsequent investigation will be necessary to confirm this observation and delineate its functional significance.

To date, only 4 other animal studies have investigated the effects of gestational BPA exposure on hippocampal gene expression, and, in all of these, the analysis was conducted in juveniles or adults (25–27, 84). A paper published as this study was in preparation found prenatal (GD0–GD19) exposure to 200-μg/kg BPA per day induced sex-specific changes in juvenile and adult mouse expression of brain-derived neurotrophic factor (*Bdnf*), a gene known to be epigenetically regulated in response to environmental exposures (84). In the present study, differential expression of *Bdnf* was not detected with RNA-seq, and we had insufficient amounts of RNA to evaluate expression with qRT-PCR.

The hippocampus was selected as a region of interest because it is critically involved in learning and memory and sensitive to stress (85). Some published data suggest BPA-related effects on these behaviors, including a related study conducted as part of the CLARITY-BPA consortium, which reported that females perinatally exposed to 2500-μg/kg BPA completed the Barnes maze, a spatial learning and memory task, more slowly than unexposed controls, but no other decrements (53). Others have not found memory-related effects (eg, Refs. 3, 87). It is possible that few hippocampal effects were detected here because exposure was entirely prenatal, and we looked for effects so early in postnatal development. Rodent hippocampal development begins in midembryogenesis (approximately embryonic d 8.5) but undergoes radical changes in cell acquisition and gross morphology during the first 2 weeks of postnatal life (88–92), making it possible that the critical period of hippocampal susceptibility to endocrine disruption is postnatal (93). Subsequent

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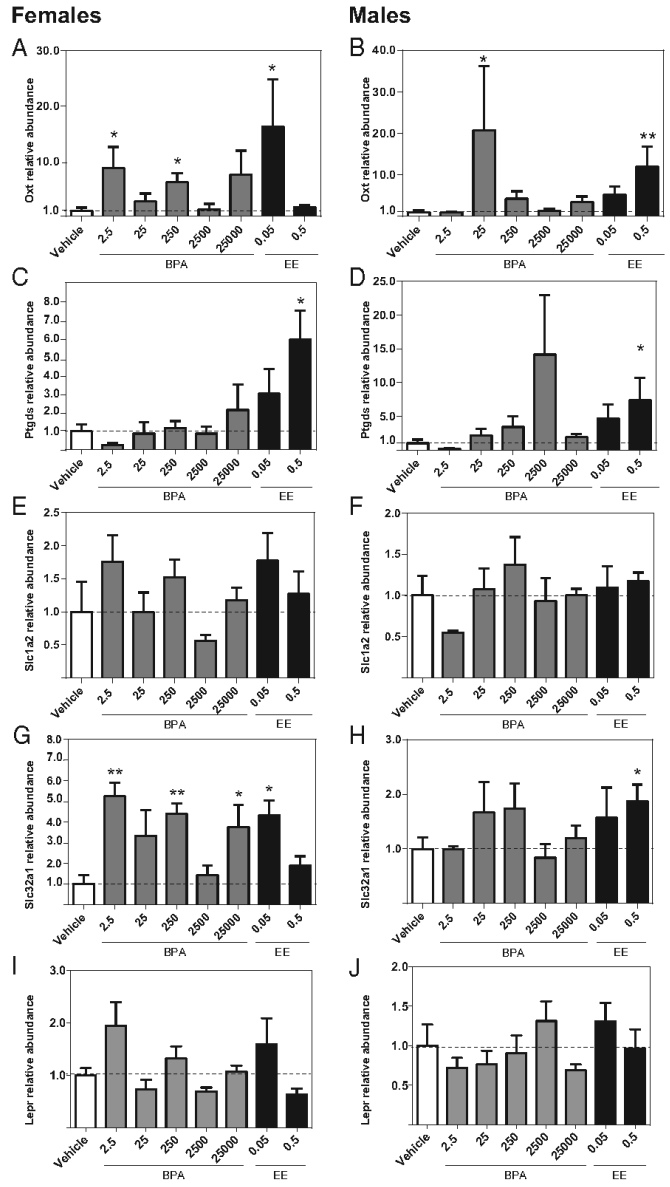

Figure 5. Effects of gestational BPA or EE on neonatal hypothalamic expression of selected genes. Exposure to 2.5- and 250-μg BPA/kg bw/d and 0.05-μg EE/kg bw/d increased female expression of *Oxt*. A, In males, 25-μg BPA/kg bw/d and the highest dose of EE increased *Oxt* expression (B). Only the highest dose of EE affected *Ptgds*, increasing expression in both females and males (C and D). *Slc1a2* expression levels were not affected by BPA or EE in either sex (E and F). The low dose of EE and 2.5-, 250-, and 25 000-μg BPA/kg bw/d masculinized (increased) female expression of *Slc32a1* (G). The high dose of EE increased male expression of *Slc32a1* (H). BPA or EE did not affect Lepr expression in either females (I) or males (J). Graphs depict mean ± SEM; *, $P \leq .05$ and **, $P \leq .01$.

studies in the CLARITY-BPA program will examine hippocampal endpoints at later ages.

By contrast, the critical period of hypothalamic hormone-mediated sexual differentiation spans perinatal development and peaks a few days after birth (94) and EDC sensitivity during this time is well characterized (95, 96), including age, sex, and subregional impacts of BPA on ER expression (37). A prior study by our group, using a similar exposure paradigm and rats of the same strain and age, detected BPA- and EE-related effects on ER gene transcription across the hypothalamus (38). These effects, as well as sex differences in expression, varied by subregion. Here, expected sex differences were only detected for *Esr2*. This effect is likely attributable to sex-specific *Esr2* expression differences in the anteroventral periventricular nucleus of the hypothalamus (32, 97, 98). Similarly, although evidence of BPA-related impacts on ER expression is consistent with prior work by us and others, the outcomes reported here do not completely recapitulate the observations made in our previous study using the same rat strain (including a sex difference in *Esr1* expression in unexposed animals) (38). This result is not entirely unexpected, however, because in the present study, we examined the whole hypothalamus, rather than its individual subregions. Thus, region-specific differences in ER expression (between sexes and/or exposure groups) are homogenized and, consequently, not fully detectable. Additionally, we have previously shown that gestational gavage of the dam can potentially minimize or obfuscate sex differences in newborn rats (32). That gestational BPA exposure increased *Esr1* and *Esr2* expression in females but not in proportion to the dose administered suggests a possible nonmonotonic

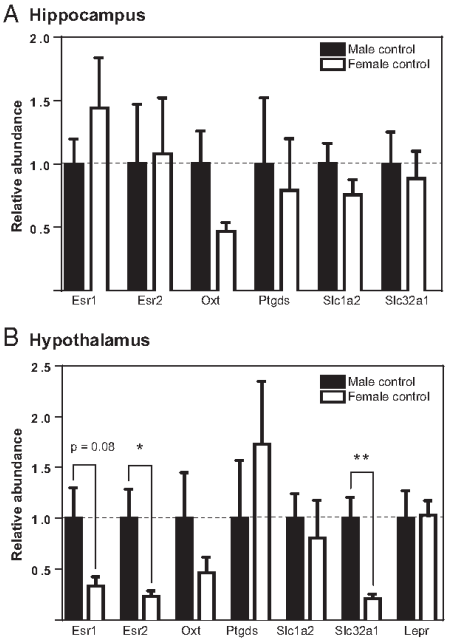

Figure 6. Sex differences in hippocampal and hypothalamic expression of selected genes. Relative differences in gene expression between male and female control (unexposed) groups with male gene expression set as baseline. A, No genes were sexually dimorphic in the neonatal hippocampus. B, *Esr2* and *Slc32a1* exhibited male biased expression. Graphs depict mean ± SEM; *, $P \leq .05$ and **, $P \leq .01$.

dose response worthy of follow-up study. Finally, effects of BPA and EE exposure were not concordant. Although BPA masculinized expression of *Esr2*, EE had no effect. This result was unexpected as endogenous estrogens are well established to induce brain masculinization in rodents (95, 96).

Evidence of disrupted *Oxt* was also found in the hypothalamus. Sexually dimorphic expression of *Oxt* has previously been reported in the preoptic area of the prenatal hypothalamus (66), and both the RNA-seq and qRT-PCR analyses in the present study indicated a similar pattern of expression (higher in males than females), but the difference failed to reach statistical significance. Increased *Oxt* expression in females at 2.5- and 250-μg/kg BPA, is indicative of masculinization and concordant with prior work from our lab demonstrating the ability of neonatal BPA to increase the number of OT neurons in the PVN of adult females (29). OT has been shown to regulate and induce ERα expression during development, and manipulations of OT can alter the expression of ERα in both juveniles and adults (99). Thus, evidence for concomitant disruption of *Esr1* and OT by BPA in females of the present study suggests these outcomes may be related. EE masculinized expression in females but only at the lower dose suggesting some sort of compensation for endocrine disruption at higher doses (of EE or BPA).

The RNA-seq analysis revealed possible effects on hypothalamic *Lepr*. Identified changes in *Lepr* expression did not survive false discovery rate correction for any comparisons except the BPA 2500 male exposure group in the exposure by sex analysis (up-regulated by BPA). We thus followed up with qRT-PCR across all exposure groups, but *Lepr* was not found to be significantly altered in any group. Thus, it remains unclear whether *Lepr* is vulnerable to gestational BPA exposure. A more robustly powered analysis of the arcuate nucleus, where *Lepr* is most heavily concentrated, would likely be more revealing.

Prenatal BPA (2.5, 250, and 25 000 μg/kg·d) exposure enhanced expression of the sexually dimorphic gene *Slc32a1* in the female hypothalamus. *Slc32a1* encodes the vesicular inhibitory amino acid transporter, which is essential for inhibitory synaptic transmission (100) and responsible for the reuptake and storage of glycine and γ-aminobutyric acid (GABA) into synaptic vesicles. Data related to BPA effects on neurotransmitters are sparse, but evidence for heightened GABA levels in the female adult mouse brain after perinatal exposure to 500-μg/kg bw/d BPA by gavage of the dam has been reported (101). Similarly, GABA release from hypothalamic fragments collected from perinatally exposed rats was elevated, as were serum GABA levels (102). Disruption of inhibitory signaling in the hypothalamus could be a mechanism by which BPA and other EDCs impact the developing brain but further studies are necessary to fully explore this possibility.

Notably, it is not unexpected that qRT-PCR, which is more targeted and sensitive, identified effects of BPA that were not identified as statistically significant with RNA-seq, particularly after accounting for false discovery rate (hypothalamic *Slc32a1* is a notable example for some dose levels; see Supplemental Table 5). Imperfect quantitative concordance between different methodologies, particularly for low abundance transcripts such as the ERs, is not unexpected given that these approaches have different levels of sensitivity and different technical limitations (103). The capacity for RNA-seq to detect expression differences is contingent on both the number of read counts per gene and the magnitude of expression change. For low expression genes, RNA-seq may not achieve sufficient transcript sampling to adequately resolve group differences in mRNA abundance (104, 105). Additionally, a critical goal of the present study was to maximize anatomical specificity while simultaneously ensuring we obtained enough tissue to extract sufficient quantities of RNA for sequenc-

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ing. Incorporating a preamplification step before RNA-seq could have allowed us to use less tissue and/or increase our capacity to detect rare transcripts but doing so can result in the preferential amplification of some transcripts (typically the most abundant) resulting in decreased representation of the remaining transcripts. Thus, we opted not to take this approach.

Summary and Conclusions

The present studies found limited effects of BPA on the PND1 rat hypothalamus and hippocampus but provide further evidence that developmental BPA exposure, at levels below the NOAEL, can alter brain mRNA levels of ERs and OT. Altered *Slc32a1* levels in the hypothalamus suggest that BPA may also alter aspects of GABA signaling. These data are consistent with the 2 CLARITY-BPA studies published to date, both of which found some but minimal evidence of BPA-related effects on hypothalamic and hippocampal-mediated behaviors (52, 53). That EE was not consistently masculinizing for all sexually dimorphic endpoints is inconsistent with decades of prior literature showing that estradiol is masculinizing in the rodent hypothalamus (95, 96), possibly indicating that EE does not fully recapitulate the neural actions of endogenous estrogen. Most basic neuroendocrine research into ER-mediated brain development has historically used either 17β-estradiol or estradiol benzoate via injection, because it is rapidly converted to estradiol (106). By contrast, toxicological studies preferentially use EE, because it can be orally administered and thus mimics human exposure routes to BPA and other EDCs. Alternatively, the lack of EE effects could be interpreted to indicate that neither dose was sufficient to induce full masculinization, or that the SD rat is insensitive to exogenously administered estrogens (as has been purported but debated for decades) (86, 107–109). Emerging data from the CLARITY-BPA studies will be informative for distinguishing between these possibilities and establishing the degree to which BPA impacts the development of other tissue targets and organ systems. Collectively, these data support prior conclusions that prenatal BPA exposure, even at doses below the current NOAEL, alters ER and OT gene expression in the developing brain.

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CHAPTER 3

Prenatal bisphenol A (BPA) exposure alters the transcriptome of the neonate rat amygdala in a sex-specific manner: a CLARITY-BPA consortium study

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HIGHLIGHTS

- Epidemiological data links prenatal BPA exposure to adverse behavior in children.
- Prenatal BPA exposure was hypothesized to alter the PND 1 amygdalar transcriptome.
- Female amygdala appears more sensitive to BPA during fetal development.
- *Oxt*, *Avpr1a*, *Esr2*, *Ar*, *Camk4*, and *Grm5* were altered in sex-specific manner.
- Prenatal BPA may alter pathways for synaptic transmission and neurodevelopment.

KEYWORDS: bisphenol A, brain, amygdala, gene expression

ABSTRACT

Bisphenol A (BPA) is a widely recognized endocrine disruptor prevalent in many household items. Because experimental and epidemiological data suggest links between prenatal BPA exposure and altered affective behaviors in children, even at levels below the current US FDA No Observed Adverse Effect Level (NOAEL) of 5 mg/kg body weight (bw)/day, there is concern that early life exposure may alter neurodevelopment. The current study was conducted as part of the CLARITY-BPA (Consortium Linking Academic and Regulatory Insights on BPA Toxicity) program and examined the full amygdalar transcriptome on postnatal day (PND) 1, with the hypothesis that prenatal BPA exposure would alter the expression of genes and pathways fundamental to sex-specific affective behaviors. NCTR Sprague-Dawley dams were gavaged from gestational day 6 until parturition with BPA (2.5, 25, 250, 2500, or 25000 µg/kg bw /day), a reference estrogen (0.05 or 0.5 µg ethinyl estradiol (EE_2)/kg bw/day), or vehicle. PND 1 amygdalae were microdissected and gene expression was assessed with qRT-PCR (all exposure groups) and RNAseq (vehicle, 25 and 250 µg BPA, and 0.5 µg EE_2 groups only). Our results demonstrate that that prenatal BPA exposure can disrupt the transcriptome of the neonate amygdala, at doses below the FDA NOAEL, in a sex-specific manner and indicate that the female amygdala may be more sensitive to BPA exposure during fetal development. We also provide additional evidence that developmental BPA exposure can interfere with estrogen, oxytocin, and vasopressin signaling pathways in the developing brain and alter signaling pathways critical for synaptic organization and transmission.

1. INTRODUCTION

Bisphenol A (BPA) is a widely recognized endocrine disruptor and ubiquitous environmental contaminant prevalent in many household items including food and beverage containers, medical equipment, plastic water pipes, and thermal receipt paper. In industrialized countries greater than 90% of individuals have detectable levels of BPA in their bodies, with exposure occurring primarily through diet [1-5]. Additionally, levels of BPA have been detected in placental tissue, amniotic fluid, and maternal and fetal plasma [6-8], which is of particular concern because it is well-established that exposure to chemicals during the critical period of fetal brain development can cause long-term impairments to brain function [9]. Moreover, throughout this period of rapid growth, the blood-brain barrier is immature and provides limited protection against neurotoxic and neuroendocrine disrupting agents [10, 11]. Here we extended on prior work in the hypothalamus and hippocampus [12], conduced as part of a uniquely constructed research consortium, to test the hypothesis that prenatal BPA exposure produces sex-specific transcriptomic changes in the neonatal rat amygdala.

Animal and human data suggest that early-life BPA exposure may disrupt neurodevelopmental processes and contribute to, at least in part, the increasing incidence of sex-biased neurobehavioral and mood disorders [13, 14]. Extensive experimental and epidemiological evidence supports associations between developmental BPA exposure and sex-specific socioemotional behavioral outcomes including hyperactivity, anxiety, aggression, and cognitive deficits, even at doses below the current US Food and Drug

Administration No Observed Adverse Effect Level (NOAEL) of 5 mg/kg body weight (bw)/day [13, 15-21]. Furthermore, a published report by the Food and Agriculture Organization of the United Nations and the World Health Organization identified "changes in anxiety and convergence of anatomical brain sex differences" as a potential human-relevant health risk of developmental BPA exposure [22]. The mammalian amygdala plays an integral part in the regulation of socioemotional behaviors, particularly those related to anxiety and fear [23-27], and is thus a conceivable target of prenatal BPA exposure.

Previous work has revealed that early-life exposure to low doses of BPA can induce structural, molecular and functional changes in the amygdala that are associated with altered behaviors [28]. For example, perinatal BPA exposure was found to alter synaptic transmission and plasticity in the basolateral amygdala of juvenile rats [29]. An additional study found that prenatal and lactational exposure to BPA disrupted levels of the neurotransmitters GABA and glutamate in the amygdala of adult mice in a sex-specific manner [30]. Moreover, studies from our group and others have observed modified expression of genes encoding DNA methyltransferase 1 [31], estrogen receptors (ERs) [15], AMPA and NMDA receptor subunits [32], and vasopressin [33], in juvenile and adult rats and mice developmentally exposed to BPA.

Although available literature suggests the developing amygdala is vulnerable to BPA disruption, very little is known regarding the impact of exclusively prenatal exposure on gene expression in the amygdala and, to our knowledge, no one has assessed the effects on BPA on the amygdalar transcriptome. The present studies extend prior work by examining the full

transcriptome in the amygdala on postnatal day (PND) 1, with the hypothesis that prenatal BPA exposure alters the expression of genes and pathways fundamental to sex-specific socioemotional behaviors including anxiety.

Because few published studies are designed for the specific purpose of informing human risk assessment and thus fail to meet the strict criteria for inclusion, recent reviews of the BPA literature by regulatory agencies exclude most studies from consideration and maintain the position that BPA is safe at current exposure levels (documents available for download here: https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm064437.htm). As part of a collaborative research program known as the consortium linking academic and regulatory insights on BPA toxicity (CLARITY-BPA), the present study, and the other published and forthcoming studies encompassed in the program, fill a critical data communication gap because they were specifically designed to resolve controversies surrounding the design and interpretation of BPA toxicity studies and to be informative for risk assessment [34-37]. CLARITY-BPA studies incorporate research recommendations published by the WHO and others for enhancing robustness and reproducibility of endocrine disrupting chemical (EDC) studies [22, 38-41]. This includes strict use of blinding, controlling for potential litter effects, minimizing exogenous EDC exposures, oral dosing, use of a reference estrogen, and evaluation of multiple BPA doses, particularly levels at or below the FDA NOAEL. Additionally, we have ensured that our methodological and data reporting adhere to ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines as published by the National Centre for the Replacement Refinement and

Reduction of Animals in Research (NC3Rs) to maximize reproducibility and utility for systematic review.

Using tissues from a complementary, previously published study [12], a transcriptome-wide approach was used for the first time to identify genes and pathways targeted by low levels of BPA during fetal development in the amygdala. Pregnant NCTR Sprague Dawley rats (NCTR-SD) were exposed to a wide range of BPA doses (2.5, 25, 250, 2500, and 25,000 μg/kg bw/day), ethinyl estradiol (EE_2; 0.05- or 0.5-μg/kg bw/day), or vehicle from gestational day (GD) 6 to parturition through oral gavage. Quantitative real-time PCR (qRT-PCR) was used to evaluate the expression of six candidate genes pre-selected because of their (1) role in socioemotional behaviors, (2) sex-biased expression pattern in the amygdala, (3) sensitivity to BPA or estrogen and/or, (4) importance in sexual differentiation of the amygdala (Table 1). Additionally, RNA sequencing (RNAseq) and enrichment analysis were used to characterize the neonatal amygdala transcriptome of four exposure groups (vehicle, BPA 25, BPA 250, and 0.05 EE_2) and to probe for evidence of previously unidentified modes of action. Additional genes were also subsequently analyzed by qRT-PCR to validate the RNAseq analysis.

2. MATERIALS AND METHODS

2.1 Animal Care:

Study animals were housed in an Association for Assessment and Accreditation of Laboratory Animal Care (AALAC) accredited facility. All procedures were approved in

advance by the National Center for Toxicological Research Institutional Animal Care and Use Committee (NCTR-IACUC). PND 1 pups were obtained from litters produced for the CLARITY-BPA program [35, 37]. Methods for animal husbandry, diet, breeding, dose preparation and administration, and necropsy are described in detail elsewhere [34]; therefore, only relevant methods are reviewed below.

Sprague-Dawley rats from the NCTR colony (NCTR-SD strain code 23) were housed in solid-bottomed polysulfone caging with hardwood chip bedding at 23 ± 3°C with a relative humidity level of 50 ± 20% on a 12:12h light/dark cycle (0600-1800). Food (soy- and alfalfa-free diet verified casein diet 10 IF 5K96; Cat. 1810069; Purina Mills, Richmond, IN) and Millipore-filtered water in glass water bottles with silicone stoppers (#7721 clear, The Plasticoid Co., Elkton, MD) were provided for *ad libitum* consumption. Extracts of each diet lot were analyzed for BPA and myco/phytoestrogens (genistein, daidzein, zearalenone, and coumestrol) by liquid chromatography and mass spectrometry [42] and all had levels below the average analytical method blanks [34]. Drinking water, polysulfone cage leachates, and bedding extracts were also found to have BPA levels below the level of the average analytical method blanks [34].

2.2 Reagents and Dosing:

The BPA (CAS # 80-05-7, catalog # B0494, TCI America, Portland, OR) and EE_2 (CAS # 57-63-6, catalog #E4876, Sigma-Aldrich, St. Louis, MO) were more than 99% pure and administered in 0.3% aqueous carboxymethyl cellulose (CMC; catalog # C5013, Sigma-

Aldrich, St. Louis, MO). The EE_2 groups were included to serve as the "reference estrogen" and to determine if BPA-related effects were consistent with an estrogenic mode of action.

Two weeks before mating, dams were randomized to one of eight exposure groups stratified by body weight to produce approximately equal mean body weights in each group. Sires were randomly assigned subject to the constraint that no sibling or first cousin mating was permitted, as previously described [42]. Mating was confirmed by the presence of a sperm plug or sperm-positive vaginal cytology [defined as GD 0]. To model the exposure route used to establish the NOAEL, dams were gavaged daily with vehicle (0.3% CMC/kg bw/day), BPA (2.5, 25, 250, 2500, or 25000 μg BPA/kg bw/day), or EE_2 (0.05 or 0.5 μg EE_2/kg bw/day) from GD6 until the day of parturition [postnatal day (PND) 0]. Dams and pups were left undisturbed on PND0. On PND 1, pups (one per sex per litter) were weighed and euthanized by rapid decapitation. Heads were collected, snap frozen, and shipped coded (blinded) to the Patisaul lab where they were stored at -80°C until processing.

2.3 Tissue Collection and Preparation:

Each whole head was coronally cryosectioned (Leica CM1900, Nussloch, Germany) from the caudal end until the caudal borders of the amygdala were identified. Two sequential bilateral punches, each 1.00 mm in diameter and 1.00 mm in depth, were collected caudally to rostrally; this corresponded with plates 69-75 of the Atlas of the Developing Mouse Brain [43] (Supplemental Fig. 1). All four punches, which collectively comprised the entire amygdala, were combined and stored in BPA-free Eppendorf tubes at -80°C. These punches

were collected at the same time we collected hypothalamic and hippocampal studies for a prior, published study [12] with the intention of performing the amygdalar assessment as a follow-up (secondary analysis) if any significant observations were found in the other brain regions. The outcomes of that prior study informed the selection of the dose groups and primary genes of interest for the present study.

2.4 Quantitative real-time PCR:

Analysis was performed on eight exposure groups (n = 5-7 for the predetermined genes, n = 3-7 for the validation genes; sample size based on availability of cDNA): vehicle, BPA 2.5, 25, 250, 2500, and 25000 and EE_2 0.05 and 0.5. Total RNA was extracted with the Qiagen RNEasy Miniprep kit. An Agilent 2100 Bioanalyzer with an RNA 6000 Nano Chip was used to determine RNA purity and concentration and each sample had a RIN of 10. Single-stranded cDNA synthesis was performed with 350 ng of RNA input using the high capacity RNA-to-cDNA kit (Applied Biosystems, Cat. 4387406) and samples were stored at -20°C until use. qRT-PCR was performed as previously published [12] using a TaqMan probe-based protocol and detected on a StepOnePlus™ Real-Time PCR System (Applied Biosystems, Life Technologies, Grand Island, NY) with the following cycling parameters: 50°C for 2 min, 95°C for 10 min, followed by 40 cycles of 95°C for 15 sec and 60°C for 1 min. Each sample was run in triplicates the sample maximization approach was followed to avoid technical and run-to-run variation [44]. Cycle threshold (Ct) values for the gene of

interest were normalized to the Ct for 18s rRNA and relative data were determined by the Livak ΔΔ cycle threshold (ΔΔ-Ct) method [45].

2.5 RNAseq Data Analysis:

The experimental design for transcriptome sequencing was developed in consultation with the NCSU Genomic Sciences Laboratory (GSL). Transcriptome sequencing was performed by the GSL on 24 amygdala samples (n = 3 per sex per group). Four experimental groups were examined: vehicle, 25 BPA, 250 BPA, and 0.5EE_2. RNA extraction was performed with the Qiagen RNEasy Miniprep kit according to the manufacturer protocol (Qiagen, Cat. 74134). Total RNA samples were submitted to the North Carolina State Genomic Sciences Laboratory for Illumina RNA library construction and sequencing. Prior to library construction, RNA integrity, purity, and concentration were assessed using an Agilent 2100 Bioanalyzer with an RNA 6000 Nano Chip (Agilent Technologies, USA). All samples had an RNA integrity number (RIN) of 10. To optimize library complexity, only samples that had greater than 300 ng of total RNA were used as input material for library preparation.

As previously described [12], messenger RNA (mRNA) was purified using the oligo-dT beads provided in the NEBNext Poly (A) mRNA Magnetic Isolation Module (New England Biolabs, Cat. E7490). Complementary DNA (cDNA) libraries for Illumina sequencing were prepared with the NEBNext Ultra Directional RNA Library Prep Kit and the NEBNext Mulitplex Oligos (New England Biolabs, Cat. E7420 and E7335). Briefly,

mRNA was isolated, heat fragmented, and primed with random oligos for first strand cDNA synthesis. Second strand cDNA synthesis was performed with dUTPs to preserve strand orientation information. Next, the double-stranded cDNA fragments were purified using AMPure XP beads (Beckman Coulter Genomics, Cat. A63881), end-repaired, and ligated onto adaptors specifically designed for the Illumina platform. Following ligation, the samples were size-selected to a final library size of 400-550 bp (adapters included) using sequential AMPure XP bead isolation. Protocol-specified PCR amplification was performed to enrich adaptor-ligated cDNA and add specific indexes for each sample. The amplified library fragments were purified and quality and final concentration was assessed using an Agilent 2200 Tapestation. The final quantified cDNA libraries were pooled into equimolar amounts for clustering and sequencing on an Illumina HiSeq 2500 DNA sequencer (4 lanes), utilizing a 125 bp single end sequencing reagent kit (Illumina, USA). Approximately 37.5 million reads were generated per sample. The software package Real Time Analysis (RTA), was used to generate raw bcl, or base call files, which were then de-multiplexed by sample into fastq files for data submission.

Data analysis for RNAseq was performed in consultation with the Bioinformatics Core of the NCSU Center for Human Health and Environment. Sequence data was evaluated with FastQC and 12 poor quality bases were trimmed from the 5'-end. The good quality reads were aligned to the *Rattus norvegicus* (rn6) reference genome (downloaded from UCSC) using the STAR software package [46]. For each replicate, per-gene counts of uniquely mapped reads were calculated using htseq-count script from the HTSeq python

package [47]. Count data were normalized for sequencing depth and distortion, and dispersion was estimated using the DESeq2 Bioconductor [48, 49] package in the R statistical computing environment. We fit a leaner model using treatment levels and differentially expressed genes were identified after applying multiple testing corrections using the Benjamini-Hochberg procedure (padj<0.05) [46]. Lastly, canonical pathway-based functional analyses of transcriptomic datasets, with an adjusted p-value (padj) less than 0.05, were performed with Ingenuity Pathway Analysis (IPA; QIAGEN). To identify relevant pathways, IPA core analysis was initially filtered to only include annotations made in neurons, astrocytes, or the amygdala. Then the analysis was then re-run to evaluate the robustness and relevance of the main findings in the context of a more global analysis by including annotations made in all tissues types and cell-lines. Associated canonical pathways were generated with the negative log probability of a particular network being enriched due to random chance [-log (p-value)] and the p-values were calculated using a right-tailed Fisher's exact tests.

2.6 Data Blinding and Statistical Analysis:

All dosing and related work conducted at NCTR was conducted by investigators blinded to exposure as described in detail in Heindel et al. (2015). The brains were then given a unique identifier and grouped by letter (group A, B, C etc.) and sent to NCSU so that analysis could be done blinded to exposure group and sex. All tissue micropunching was conducted blinded and the samples stored at -80°C until the prior, related study was

completed and published [12] (which necessitated unblinding). Because the present study was considered a secondary, follow-up study, data from the prior study was critically necessary to inform the present one but the experimental design was conceived and developed under unblinded conditions. Once the groups for RNAseq were selected, the individual samples were selected at random by an investigator blinded to individual and group ID, and all RNAseq work and bioinformatics was conducted blinded. Because qRT-PCR used all remaining samples (not all samples had sufficient cDNA for analysis), that work could not be done fully blinded, but to minimize risk of bias all of the individual samples were randomized across plates.

The statistical approach was developed to be consistent with previously published transcriptome projects of similar scale (equivalent sample size or smaller) in rat brain [12, 47] and guidelines for low dose endocrine disrupting chemical (EDC) studies [48]. Within each exposure group, no same-sex littermates were included, so potential litter effects did not need to be statistically accounted for.

qRT-PCR: Statistical analysis for all of the data was performed and graphed using Prism version 7 (GraphPad Software, Inc., La Jolla, CA). For each gene of interest, a Grubb's test for outliers ($\alpha = 0.05$) was conducted and up to one outlier per group was removed. In total, only two outliers were removed from all of the qRT-PCR data: a 2.5 BPA male and a vehicle female from the vasopressin receptor (*Avpr1a*) analysis. Next, a two-tailed Mann-Whitney U test was used to determine if any sex differences in gene expression were detected in the unexposed controls. Finally, a two-tailed Mann-Whitney U test was

used to compare each exposure group to the same-sex vehicle control. When BPA-related effects were found, qualitative comparisons to the EE_2 groups were made to see if directionality was consistent with an "estrogenic" effect. In all cases, effects were considered significant at $p \leq 0.05$.

RNAseq: The DEseq2 package was used to fit a negative binomial model for each gene using an extended model matrix. To identify baseline sex differences in gene expression, the male and female controls were compared independent of other exposure groups. With that exception, all other data were compared within sex. For each comparison, the p-value was adjusted for multiple testing using the Benjamini-Hochberg method at a false discovery rate of 5% [46]. A cutoff of $padj \leq 0.05$ was used to select differentially expressed transcripts and genes.

3. RESULTS

3.1 Impact of prenatal BPA or EE_2 exposure on specific genes of interest in the PND 1 amygdala:

Based on our a priori hypotheses and prior publications [12], specific genes of interest were selected for analysis by qRT-PCR because of their (1) importance in socioemotional behaviors; (2) role in sexual differentiation; (3) sensitivity to BPA or estrogen; and/or (4) sex-biased expression pattern in the PND 1 amygdala (Table 1). Five of the six genes were significantly altered by prenatal BPA or EE_2 exposure and a summary of the descriptive statistics for significant outcomes is listed in Table 2.

ERα (*Esr1*) expression levels in the amygdala were not affected by BPA or EE_2 in either sex (Fig. 1A). In males, ERβ (*Esr2*) expression was significantly upregulated in the BPA 25 groups, whereas in females, *Esr2* expression was upregulated in BPA 250 group (Fig. 1B). In males, oxytocin receptor (*Oxtr)* expression levels were significantly increased in the BPA 25 and BPA 250 groups. In females, higher *Oxtr* expression was observed in the BPA 2.5, BPA 25, BPA 250, BPA 25000, and EE_2 0.5 groups (Fig. 1C). Prenatal BPA exposure had sex-specific effects on *Avpr1a*. In males, expression was downregulated in the BPA 2.5 groups and upregulated in the BPA 25 and BPA 250 groups. Male *Avpr1a* expression was also increased in the EE_2 0.5 group. Conversely, no significant effects of prenatal BPA or EE_2 were observed on *Avpr1a* among females (Fig. 1D). Androgen receptor (*Ar*) expression was significantly upregulated in the BPA 25 groups in males, whereas in females, *Ar* expression in the BPA 250 and EE_2 0.5 groups was upregulated (Fig. 1E). There were no significant effects of BPA on growth arrest and DNA damage-inducible beta (*Gadd45b*) expression in either males or females. In females, *Gadd45b* expression was upregulated in the EE_2 0.5 group (Fig. 1F).

3.2 Impact of prenatal BPA or EE_2 exposure on the PND 1 amygdalar transcriptome:

RNAseq transcriptome profiling was evaluated in animals exposed to vehicle, 25 or 250 μg BPA/kg bw/day, and 0.5 μg EE_2/kg bw/day. These doses were selected because they cover the lower range of exposures at which BPA-induced effects have been reported in the scientific literature, including other CLARITY-BPA studies, and are below the current FDA

NOAEL of 5 mg/kg bw/day. Unsupervised principal component analysis of all gene expression profiles did not reveal a clear separation between exposure groups (Supplementary Fig. 2A). When PCA was performed within sex, female exposure groups clustered more distinctly than males (Supplementary Fig. 2B). Thus all subsequent analyses were conducted within sex. With the exception of one female 0.5 EE_2 replicate, samples treated with BPA and EE_2 clustered together and were clearly distinct from the female vehicle control samples (Supplementary Fig. 2C).

When compared to the same-sex vehicle group, males exposed to 25 μg BPA showed more significant transcript changes than males exposed to 250 μg BPA (89 genes and 1 gene, respectively; Supplementary Table 1A-B). IPA identified (1) STAT activation (3 genes, $p \leq 0.01$); (2) Wnt/β-catenin signaling (4 genes, $p \leq 0.01$); (3) RAR activation (4 genes, $p = 0.01$); (4) corticotrophin releasing hormone (CRH) signaling (3 genes, $p = 0.01$); and PTEN signaling (3 genes, $p = 0.01$) as the top five most significantly enriched canonical pathways by the male 25 BPA dataset (Fig. 2A). Only 52 genes were significantly altered by 0.5 μg EE_2 in the male amygdala (Supplementary Table 1C), however a large portion of these genes (35/52) overlapped with the set of genes significantly altered in the male BPA 25 group (Fig. 3A). (1) GABA receptor signaling (2 genes, $p = 0.01$); (2) protein ubiquitination pathway (3 genes, $p = 0.02$); (3) CRH signaling (2 genes, $p = 0.04$); and (4) DNA methylation and transcriptional repression signaling (1 gene, $p = 0.045$) were the only pathways significantly enriched by the differentially expressed genes in the male 0.05 EE_2 dataset (Fig. 2A).

BPA- and EE_2- related transcriptional changes were more numerous in females than males. In total 251 and 341 genes were differentially expressed in the 25 BPA and 250 BPA groups, respectively, with robust overlap between the two dose groups (174 genes) (Supplementary Table 2A-B and Fig. 3B). The top scoring canonical pathways enriched with genes perturbed by 25 μg BPA were: (1) G protein coupled receptor (GPCR) signaling (17 genes, $p \leq 0.001$); (2) GABA signaling (8 genes, $p \leq 0.001$); (3) CREB signaling in neurons (12 genes, $p \leq 0.001$); (4) dopamine-DARPP32 feedback in cAMP signaling (11 genes, $p \leq 0.001$); and (5) CRH signaling (9 genes, $p \leq 0.001$). IPA identified (1) GPCR signaling (17 genes, $p \leq 0.001$); (2) neuregulin signaling (10 genes, $p \leq 0.001$); (3) synaptic long term potentiation (11 genes, $p \leq 0.001$); (4) GABA receptor signaling (8 genes, $p \leq 0.001$); and (5) bone morphogenetic protein (BMP) signaling (9 genes, $p \leq 0.001$) as the top scoring pathways enriched by the differentially expressed genes in the female 250 BPA dataset (Fig. 2B). Finally, the most robust effects of prenatal exposure were observed in the 0.5 EE_2 group in which 629 genes were significantly altered (Fig. 3B and Supplementary Table 2C). The five top scoring results from the IPA pathway analysis were (1) GPCR signaling (24 genes, $p \leq 0.001$); (2) synaptic long term potentiation (15 genes, $p \leq 0.001$); (3) dopamine-DARPP32 feedback in cAMP signaling (17 genes, $p \leq 0.001$); (4) neuregulin signaling (12 genes, $p \leq 0.001$); and (5) CRH signaling (13 genes, $p \leq 0.001$) (Fig. 2B).

3.3 Validation of differentially expressed genes of interest identified by transcriptomics in the PND 1 amygdala:

qRT-PCR was used to follow up, in all exposure groups, on two differentially expressed genes identified by RNAseq. We focused on metabotropic glutamate receptor mGluR 5 (*Grm5*) and calmodulin-dependent protein kinase type IV (*Camk4*) because they modulate neurodevelopment [70], synaptic transmission, glutamate receptor signaling, CREB signaling, cAMP-mediated signaling, and other canonical pathways identified as significantly enriched in the female 25 and 250 BPA groups (Table 3). In males, *Camk4* was upregulated in the 25 BPA group. In females, higher *Camk4* expression was observed in the BPA 2.5, BPA 25, BPA 250, BPA 25000, EE_2 0.05 and EE_2 0.5 groups and there was a trend for upregulation in the BPA 2500 group (Fig. 1G and Table 2). *Grm5* expression was significantly increased in the male BPA 25 BPA. In females, *Grm5* expression was increased in the BPA 250, BPA 2500, BPA 25000, EE_2 0.05, and EE_2 0.05 groups and there was a trend for upregulation observed in the BPA 25 group (Fig. 1H and Table 2).

3.4 Sex differences in PND 1 amygdala gene expression:

RNAseq identified relatively few sex differences in overall gene expression in the PND 1 amygdala and no genes were expressed exclusively in one sex or the other (Supplementary Table 3). Only nine genes had sex differences in expression, with four being more highly expressed in males and five being more highly expressed in females. Three of the four genes that were more highly expressed in males were Y-linked: eukaryotic

translation initiation factor 2 subunit 3 (*Eif2s3y*), lysine demethylase 5D (*Kdm5d*), and DEAD (Asp-Glu-Ala-Asp) box polypeptide 3 (*Ddx3*). Among all of the genes identified as differentially expressed between unexposed males and females, *Eif2s3y* exhibited the largest fold change (-11.27). As shown in Fig. 4A-F, qRT-PCR identified no sex differences in genes of interest selected a priori (*Esr1*, *Esr2*, *Oxtr*, *Avpr1a*, *Ar*, and *Gadd45b*) or *Grm5* (Fig. 4H), although there was a nonsignificant trend for lower female expression of *Oxtr* ($p = 0.08$; Table 2). Expression of Camk4, however, was significantly higher in males than females (Fig. 4G and Table 2).

4. DISCUSSION

The results from the present study demonstrate for the first time that prenatal BPA exposure, at doses below the current FDA NOAEL, can alter the transcriptome of the neonate amygdala. Additionally, these data are consistent with, and provide further evidence that developmental BPA exposure can interfere with estrogen, oxytocin and vasopressin signaling pathways in the developing brain. Transcriptome profiling revealed sex-specific effects of prenatal BPA exposure with evidence of altered GPCR-signaling, CREB-signaling, synaptic plasticity, and pathways related to nervous system growth and development in the female amygdala. While the functional and physiological significance of these gene expression changes within the neonate amygdala remain unclear, the present data yield further insight into the mechanisms by which BPA may influence socioemotional behaviors in a sex-specific manner. In addition, the present data contribute important fundamental information

regarding sex-specific gene expression patterns in the developing brain as, to our knowledge, this is the first report of sex differences in the full amygdala transcriptome at PND 1.

In the PND 1 amygdala, expression of *Oxtr* and *Avpr1a* was disrupted by prenatal BPA exposure in a sex- and dose- dependent manner. In females, *Oxtr* expression was significantly upregulated by prenatal BPA exposure (2.5, 25, 250, and 25,000 µg) and there was a trend ($p = 0.08$) for upregulation at the 2,500 µg dose. In males, *Oxtr* was also significantly upregulated by prenatal exposure to 25 and 250 µg BPA. Amygdalar *Avpr1a* expression was downregulated by the lowest dose of BPA (2.5 µg) and upregulated by 25 and 250 µg BPA in males but female levels were unaffected. These data are consistent with prior studies reporting BPA-related disruption of oxytocin (OXT) and vasopressin (AVP) systems in the brains of juvenile and adult rodents ([12, 15, 20, 71, 72]; reviewed in [58]). For example, perinatal BPA exposure to BPA via drinking water (1 mg/L) resulted in heightened anxiety-related behaviors in juvenile Wistar rats that were concomitant with decreased amygdalar expression of genes, including *Esr2*, crucial for the production and release of OXT and AVP in the paraventricular nucleus of the hypothalamus [20]. The neuropeptides OXT and AVP are powerful mediators of social behaviors including affiliation, anxiety, and stress regulation [56, 73-75]. In adult rodents, *Oxtr* and *Avpr1a,* are robustly expressed throughout the brain and have been found in several amygdalar subnuclei, including the central nucleus and medial amygdala [57]. Their receptors are also present during development and both can be detected in the fetal rat brain as early as embryonic day 12 [76]. Numerous studies in rodents and non-human primates clearly demonstrate that

changes in the OXT or AVP system during early life can permanently alter the brain and behavior [69, 77-79]. This converging evidence points to a possible organizational role of OXT and AVP, where their activity during critical periods of brain development may program later social behavior. Overall, our data adds to the growing body of literature indicating BPA-related disruption of the organization of OXT and AVP systems in the brain. While the functional significance of the transcriptional data reported here remains to be established, sex-specific disruption of *Oxtr* and *Avpr1a* in the developing amygdala likely contribute to the sex-specific behavioral changes attributed to early-life BPA exposure, including anxiety-related behaviors.

A surprising outcome of this study was the minimal effect of prenatal BPA exposure on ER expression. *Esr2* expression was increased in males and females prenatally exposed to 25 and 250 μg of BPA, respectively, but *Esr1* expression was unaffected by prenatal BPA exposure in both sexes. Early-life BPA exposure has repeatedly been shown to disrupt levels of ER expression in the hypothalamus and limbic nuclei of neonatal and older rodents [12, 21, 61, 62, 65]. To our knowledge, however, only two studies to date have explored the impact of early-life BPA exposure on ER mRNA in the developing amygdala and both found sex-specific increases in *Esr1* and *Esr2* expression, with effects on *Esr2* being more robust [21, 65]. Notably, the magnitude of effects varied among amygdalar subnuclei, suggesting that discrepancies between these prior studies and the present one are likely due to methodological differences. By examining the entire amygdala as a whole, it is plausible that subnuclei specific differences in ER expression (between exposure groups and/or sexes) were

homogenized and, consequently, not fully detectable. Additionally, in a prior study conducted in collaboration with NCTR we found differences in amygdalar ER expression, particularly *Esr2* expression, between gavaged vehicle and ungavaged naïve controls suggesting a possible effect of gavage itself [21].

Prenatal exposure to 25 and 250 μg of BPA enhanced *Ar* expression in males and females, respectively. Information regarding the impact of developmental BPA exposure on *Ar* expression is sparse but one study reported increased levels of *Ar* in the cerebrum of PND 2 ICR mice exposed to 50 mg/kg of BPA on gestational days 6 and 15 [80]. In addition, embryonic exposure of zebrafish to BPA (1.6 μg/L) resulted in precocious hypothalamic neurogenesis that was dependent on androgen receptor (AR) mediated upregulation of aromatase [18]. Studies using rats and mice that lack ARs (i.e., rodents with the testicular feminization mutation) demonstrate that ARs are required for the full masculinization of many brain regions, especially the amygdala [81]. For example, the volume of the posterdorsal portion of the medial amygdala (MePD) is larger in males than females and the male MePD has more neurons with larger soma, more astrocytes, greater dendritic length, and higher spine density [52, 82-84]. All of these sex differences are heavily dependent on the presence of ARs during perinatal development. *Ar* expression in the rat forebrain is regulated by estrogen, not androgen, during the early postnatal period [53]. Therefore, upregulation of *Ar* by BPA in the neonate amygdala is consistent with an estrogenic mode of action that may disrupt sexual differentiation of the developing amygdala. In a prior CLARITY-BPA study, we reported that perinatal exposure to 2,500 μg BPA/kg bw/day

enlarged the volume of the right MePD in juvenile males [28]. While this singular effect may be due to disruption of *Ar* expression, causality cannot be established because the as the exposure paradigms and the doses at which BPA-related effects were observed differed from the current study. Thus, further investigation would be required to confirm this putative mechanism and characterize the functional implications of heightened *Ar* expression.

We found no effect of prenatal BPA exposure on *Gadd45b* expression in the developing amygdala, and also failed to find the expected sex difference in *Gadd45b* expression. A prior study, also in the Sprague-Dawley rat and examining the amygdala as a whole, observed a female biased expression pattern of *Gadd45b* at PND 1 [67]. Diet may be one factor contributing to our inability to replicate the finding. In the previous experiment, the diet was not described in detail, but rather described as "standard." Prior literature has demonstrated that "standard laboratory chow" is typically soy-based and thus contains significant amounts of hormonally active phytoestrogens [85-87]. We and others have shown that this source of background of EDC exposure can obfuscate or alter sex differences [15, 88]. Amygdalar *Gadd45b* expression was of interest because it is implicated in the regulation of "rough and tumble play," a juvenile social play behavior that occurs more frequently in males than females [68], but also because Gadd45b facilitates activity-induced DNA demethylation [89, 90]. While a number of studies provide evidence of BPA-related effects on epigenetic marks [13, 60, 91-93], no studies have examined whether prenatal BPA exposure can perturb epigenetic 'erasers' in the developing brain. Our observation does not rule out the possibly that early-life BPA exposure may be interfering with other epigenetic

regulators. For instance, prenatal BPA exposure has been shown to induce sex-specific effects on social and anxiety-like behaviors in adult BALB/c mice that were associated with changes in DNA methylation and mRNA levels of ERα in the hypothalamus and hippocampus [60].

In addition to targeted qRT-PCR, we used an unbiased discovery-based approach to profile differential gene expression changes within the neonate amygdalar transcriptome to further investigate potential mechanisms underlying the sex-specific effects of early-life BPA exposure on the brain. One caveat of this approach is that prior work by us and others has demonstrated that RNAseq may not be capable of sufficient transcript sampling to adequately resolve group differences in expression because most genes of interest have low abundance and effect size between differentially expressed genes is low compared to other organs [12, 94, 95]. Amygdalar transcription changes identified by RNAseq were overwhelmingly female specific, with substantial overlap between the two BPA groups examined (25 and 250 μg). In contrast, extremely few differentially expressed genes were detected in males exposed to 25 and 250 μg BPA (89 genes and 1 gene, respectively) and there was no overlap between these genes suggesting they are not biologically meaningful. We conclude that the amygdala transcriptome is sex-specifically vulnerable to gestational BPA exposure with females more sensitive than males. By contrast, transcriptional effects in the PND 1 hypothalamus and hippocampus of these same animals was more pronounced in males than females, with disruption more robust in the hypothalamus [12]. Collectively, these data indicate that early-life BPA exposure can have sex-specific and region-specific effects on the

transcriptome of the developing brain and highlight the importance of sex and region as biological variables in neurodevelopmental EDC studies.

qRT-PCR was used to assess expression levels of two differentially expressed genes of interest identified by RNAseq in all exposure groups: *Camk4* and *Grm5*. The magnitude and directionality of the results generally confirmed the RNAseq data. A sex differences in *Camk4* expression was also detected in the unexposed controls by RNAseq but the statistical significance of that difference did not survive FDR. Females prenatally exposed to BPA and EE_2 displayed robust enhancement of *Camk4* at every dose with the exception of 2500 μg of BPA, although there was a modest trend for enhancement ($p = 0.08$). In the nervous system, Ca^{2+}/CaM dependent kinase IV (CaMKIV) is a well-known mediator of calcium dependent gene expression, and emerging evidence indicates that CaMKIV is essential for neurodevelopment, synaptic plasticity, and the consolidation of behavioral memory [70, 96, 97]. Furthermore, consistent with our pathway analyses, overexpression of CAMKIV in transgenic C57BL/6 mice was shown to significantly increase long-term potentiation in the juvenile anterior cingulate cortex [98]. *Grm5* expression was also increased by BPA (250, 2500, and 25000 μg) and EE_2 (0.05 μg) exposure in females and a trend towards upregulation was observed for 25 μg BPA and 0.05 μg EE_2 ($p = 0.07$ and 0.06, respectively). Group I metabotropic glutamate receptors (MGluRs), which include glutamate metabotropic receptor 5 (GRM5), mediate a diverse variety of neuronal functions and are critical modulators of activity-dependent synaptic plasticity in a variety of brain regions, including

the amygdala [99, 100]. Notably, disregulation of group I MGluRs mediated signaling has been implicated in a range of childhood neurodevelopmental disorders [101-103].

IPA analyses of the female transcriptomic data revealed a number of canonical pathways significantly activated by both 25 and 250 μg of BPA, many of which are associated with neuronal development and synaptic transmission. Deeper analysis of specific genes within each of these pathways revealed BPA and EE_2 had a number of overlapping and directionally similar effects on expression (Table 3). Available data regarding the impact of BPA exposure on neuronal development and synaptic transmission is sparse but effects on juvenile and adult synaptogenesis, neuronal differentiation/migration, and synaptic plasticity have been reported following prenatal and neonatal exposure to BPA [29, 104-106]. The impact of BPA on the developing brain, however, remains largely unknown because research to date has focused almost exclusively on juvenile or adult animals. In the current study, pathways involved in synaptic plasticity, CREB signaling in neurons, and cAMP-mediated signaling displayed predicted increases in the amygdala of females exposed to 25 and 250 μg of BPA prenatally. Consistent with these findings, accelerated neuronal differentiation and migration was found in the neocortex of ICR/Jcl mice on embryonic days 12.5 and 16.5 following daily exposure to 20 μg/kg of BPA via maternal injection; however, sex was not considered a factor in this study [105]. In vivo, doses of BPA ranging from 1 to 100 nM of BPA induced rapid effects on LTP and increased spine density in the CA1 and CA3 regions of hippocampal slice cultures of rats [107]. In rodents, perinatal brain development is associated with activity-dependent synaptic refinement and extensive remodeling that

contributes to growth and stabilization of connections [108, 109]. Although many of these processes are hormonally modulated by estradiol during development [110, 111], our current understanding of amygdala physiology is limited and based almost exclusively on research conducted in adult animals [112, 113]. Numerous experimental studies on early-life stress, however, have demonstrated that environmental insult can alter synaptic patterning in the amygdala and lead to impaired affective behavior later in life, including anxiety and social behavior [114-118]. Although beyond the scope of this paper, these studies suggest that disruption of neuronal development and synaptic transmission may potentially underlie the behavioral effects associated with early-life BPA exposure in females. However, this is a purely speculative and further studies are needed to definitively demonstrate that relationship.

5. CONCLUSIONS

These data reveal that prenatal BPA exposure disrupts the transcriptome of the neonate amygdala at doses below the FDA NOAEL, with females appearing to be more sensitive than males. Within females, BPA-related transcriptional changes were reasonably concordant with EE_2-related changes suggesting that at least some outcomes were consistent with an "estrogenic" mode of action. However, the pathway analysis supports the hypothesis that other mechanisms are also likely involved. That conclusion is consistent with our prior CLARITY-BPA studies, which also reported discordant effects of EE_2 and BPA on the volume of sexually dimorphic brain regions and the PND 1 hippocampal and hypothalamic

transcriptome [12, 28]. We also provide additional evidence that BPA can disrupt the organization of AVP and OT pathways in the developing brain and alter signaling pathways critical for synaptic organization and transmission. That some responses appear to be non-linear is consistent with a wealth of prior literature showing that BPA and other EDCs can have non-monotonic dose response curves [62, 119-121], the mechanism(s) by which these occur remains unresolved. The observation of effects at the lower end of the dose curve is also consistent with prior CLARITY-BPA studies by us on behavioral endpoints and also in brain, ovary and heart [12, 28, 36, 122-124].

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CHAPTER 3 TABLES

Table 1

Table 1. Rationale for genes of interest selected a priori

Preselected Genes of Interest	Rationale				Selected References
Androgen receptor (*Ar*)	**A**		**C**	**D**	[49-55]
Arginine vasopressin (*Avpr1a*)	**A**		**C**		[56-59]
Estrogen receptor α (*Esr1*)	**A**	**B**		**D**	[12, 21, 49, 50, 60-64]
Estrogen receptor β (*Esr2*)	**A**	**B**		**D**	[12, 21, 49, 50, 61-66]
Growth arrest and DNA damage inducible β (*Gadd4b*)		**B**			[67, 68]
Oxytocin receptor (*Oxtr*)	**A**		**C**		[56-58, 69]

Legend

A Previously shown to be influenced by BPA
B Sex biased expression in amygdala
C Estrogen-dependent expression
D Important for sexual differentiation of the amygdala

Table 2

Table 2. qRT-PCR outcomes and descriptive statistics for genes found to be significantly altered by BPA or EE_2 exposure. Sample sizes for each group are in parentheses.

Gene Symbol	Comparison (n)	Relative Abundance	U	*p*-value
Preselected genes of interest				
Esr2	♂ 25 BPA (7) to ♂ Veh (6)	2.38	3	≤ 0.01
	♀ 250 BPA (6) to ♀ Veh (7)	1.67	6	0.04
Oxtr	♂ Veh (7) to ♂ Veh (6)	0.70	8	0.08
	♂ 25 BPA (7) to ♂ Veh (6)	1.95	2	≤ 0.01
	♂ 250 BPA (7) to ♂ Veh (6)	1.37	6	0.04
	♀ 2.5 BPA (6) to ♀ Veh (7)	1.37	8	0.04
	♀ 25 BPA (6) to ♀ Veh (7)	1.90	4	≤ 0.01
	♀ 250 BPA (6) to ♀ Veh (7)	1.97	5	0.02
	♀ 25000 BPA (6) to ♀ Veh (7)	1.58	4	≤ 0.01
	♀ 0.5 EE2 (5) to ♀ Veh (7)	2.01	0	≤ 0.01
Avpr1a	♂ 2.5 BPA (4) to ♂ Veh (6)	0.75	2	0.04
	♂ 25 BPA (7) to ♂ Veh (6)	2.27	0	≤ 0.01
	♂ 250 BPA (7) to ♂ Veh (6)	1.56	4	≤ 0.01
	♂ 0.5 EE2 (7) to ♂ Veh (6)	1.41	6	0.04
Ar	♂ 25 BPA (7) to ♂ Veh (6)	2.43	3	≤ 0.01
	♀ 250 BPA (6) to ♀ Veh (7)	1.84	6	0.04
Gadd45b	♀ 0.5 EE2 to (5) ♀ Veh (7)	1.77	5	0.05
Genes selected from RNAseq analysis				
Camk4	♀ Veh (5) to ♂ Veh (5)	0.54	0	≤ 0.01
	♂ 25 BPA (7) to ♂ Veh (5)	1.75	3	≤ 0.01
	♀ 2.5 BPA (6) to ♀ Veh (5)	2.54	0	≤ 0.01
	♀ 25 BPA (6) to ♀ Veh (5)	2.02	0	≤ 0.01
	♀ 250 BPA (6) to ♀ Veh (5)	2.24	0	≤ 0.01
	♀ 2500 BPA (6) to ♀ Veh (5)	1.68	5	0.08
	♀ 25000 BPA (6) to ♀ Veh (5)	2.48	0	≤ 0.01
	♀ 00.5 EE2 (6) to ♀ Veh (5)	1.83	0	≤ 0.01
	♀ 0.5 EE2 (5) to ♀ Veh (5)	2.52	0	≤ 0.01
Grm5	♂ 25 BPA (7) to ♂ Veh (6)	1.54	4	≤ 0.01
	♀ 25 BPA (6) to ♀ Veh (4)	1.62	3	0.07
	♀ 250 BPA (6) to ♀ Veh (4)	1.89	0	≤ 0.01
	♀ 2500 BPA (5) to ♀ Veh (4)	1.71	0	0.02
	♀ 25000 BPA (6) to ♀ Veh (4)	2.01	2	0.04
	♀ 0.05 EE2 (6) to ♀ Veh (4)	1.46	1	0.02
	♀ 0.5 EE2 (3) to ♀ Veh (4)	2.14	0	0.06

Table 3

Table 3. Differentially expressed genes identified by RNAseq within selected canonical pathways identified by IPA analysis in exposed females (normalized to ♀ vehicle; adjusted p-value ≤ 0.05).

Gene Symbol	Gene Name	♀ 25 µg BPA		♀ 250 µg BPA		♀ 0.5 µg EE_2		IPA Canonical Pathway(s)
		Padj	FC	Padj	FC	Padj	FC	
Adcy1	Adenylate Cyclase 1	2.34E-08	1.91	5.92E-09	1.94	8.09E-10	2.01	cAMP-Mediated Signaling CREB Signaling in Neurons GABA Receptor Signaling Synaptic Long Term Potentiation
Adcy5	Adenylate Cyclase 5	3.97E-02	1.30	NS	NS	NS	NS	cAMP-Mediated Signaling CREB Signaling in Neurons GABA Receptor Signaling
Adcy9	Adenylate Cyclase 9	4.81E-02	1.43	NS	NS	3.94E-02	1.41	cAMP-Mediated Signaling CREB Signaling in Neurons GABA Receptor Signaling
Akap11	A-Kinase Anchoring Protein 11	5.97E-03	1.30	2.11E-03	1.31	NS	NS	cAMP-Mediated Signaling
Atf2	Activating Transcription Factor 2	NS	NS	NS	NS	2.62E-04	1.35	cAMP-Mediated Signaling CREB Signaling in Neurons Synaptic Long Term Potentiation
Braf	B-Raf Proto-Oncogene, Serine/Threonine Kinase	NS	NS	NS	NS	4.13E-03	1.44	cAMP-Mediated Signaling
Camk2A	Calcium/Calmodulin-Dependent Protein Kinase Ii Alpha	3.99E-03	1.33	2.62E-03	1.33	NS	NS	cAMP-Mediated Signaling CREB Signaling in Neurons Synaptic Long Term Potentiation
Camk4	Calcium/Calmodulin-Dependent Protein Kinase Iv	NS	NS	1.72E-02	1.41	NS	NS	cAMP-Mediated Signaling CREB Signaling in Neurons Glutamate Receptor Signaling Synaptic Long Term Potentiation
Chrm3	Cholinergic Receptor, Muscarinic 3	9.57E-03	1.41	4.56E-02	1.32	9.64E-03	1.37	cAMP-Mediated Signaling
Creb1	Camp Responsive Element Binding Protein 1	NS	NS	NS	NS	2.82E-02	1.43	cAMP-Mediated Signaling CREB Signaling in Neurons Synaptic Long Term Potentiation
Gabrb1	Gamma-Aminobutyric Acid Type A Receptor Beta 1 Subunit	NS	NS	2.16E-02	1.35	3.31E-03	1.40	GABA Receptor Signaling
Gabrb2	Gamma-Aminobutyric Acid Type A Receptor Beta 2 Subunit	4.22E-03	1.51	6.11E-05	1.67	9.03E-05	1.64	GABA Receptor Signaling
Gabrb3	Gamma-Aminobutyric Acid Type A Receptor Beta 3 Subunit	NS	NS	1.07E-02	1.37	1.64E-02	1.33	GABA Receptor Signaling
Gabrg1	Gamma-Aminobutyric Acid Type A Receptor Gamma 1 Subunit	4.96E-02	1.26	1.26E-04	1.42	3.66E-03	1.32	GABA Receptor Signaling
Gabrg2	Gamma-Aminobutyric Acid Type A Receptor Gamma 2 Subunit	2.40E-02	1.32	4.16E-03	1.37	1.45E-02	1.32	GABA Receptor Signaling
Gnaq	G Protein Subunit Alpha Q	1.57E-02	1.30	4.56E-04	1.40	8.22E-04	1.37	CREB Signaling in Neurons Synaptic Long Term Depression Synaptic Long Term Potentiation
Grik3	Glutamate Ionotropic Receptor Kainate Type Subunit 3	1.43E+00	0.04	4.45E-02	1.41	NS	NS	CREB Signaling in Neurons Glutamate Receptor Signaling

Table 3 (continued)

Grin2B	Glutamate Ionotropic Receptor Nmda Type Subunit 2B	NS	NS	NS	NS	2.71E-02	1.38	CREB Signaling in Neurons Glutamate Receptor Signaling Synaptic Long Term Potentiation
Grin3A	Glutamate Ionotropic Receptor Nmda Type Subunit 3A	NS	NS	NS	NS	2.34E-02	1.37	Glutamate Receptor Signaling Synaptic Long Term Potentiation
Grm3	Glutamate Metabotropic Receptor 3	NS	NS	2.83E-02	1.43	2.34E-02	1.42	CREB Signaling in Neurons Glutamate Receptor Signaling Synaptic Long Term Depression Synaptic Long Term Potentiation
Grm5	Glutamate Metabotropic Receptor 5	1.11E-02	1.41	2.66E-03	1.44	2.83E-04	1.51	CREB Signaling in Neurons Glutamate Receptor Signaling Synaptic Long Term Depression Synaptic Long Term Potentiation
Gucy1a 2	Guanylate Cyclase 1 Soluble Subunit Alpha 2	NS	NS	3.25E-02	1.41	3.15E-02	1.39	Synaptic Long Term Depression
Htr1A	5-Hydroxytryptamine Receptor 1A	NS	NS	NS	NS	2.34E-02	1.44	cAMP-Mediated Signaling
Htr1B	5-Hydroxytryptamine Receptor 1B	1.29E-02	1.44	1.13E-02	1.43	2.14E-04	1.58	cAMP-Mediated Signaling
Irs1	Insulin Receptor Substrate 1	NS	NS	NS	NS	1.45E-03	1.54	CREB Signaling in Neurons
Kcnq2	Potassium Voltage-Gated Channel Subfamily Q Member 2	2.88E-02	1.35	2.16E-02	1.35	2.84E-02	1.32	GABA Receptor Signaling
Kcnq3	Potassium Voltage-Gated Channel Subfamily Q Member 3	2.98E-02	1.40	4.48E-03	1.48	2.66E-03	1.49	GABA Receptor Signaling
Kl	Klotho	2.58E-02	-1.34	NS	NS	3.54E-02	-1.30	CREB Signaling in Neurons
Kras	Kras Proto-Oncogene, Gtpase	NS	NS	8.34E-03	1.33	2.18E-03	1.36	CREB Signaling in Neurons Synaptic Long Term Depression Synaptic Long Term Potentiation
Mapk1	Mitogen Activated Protein Kinase 1	NS	NS	NS	NS	2.24E-02	1.26	cAMP-Mediated Signaling CREB Signaling in Neurons Synaptic Long Term Potentiation
Oprl1	Opioid Related Nociceptin Receptor 1	NS	NS	2.28E-02	1.32	9.63E-05	1.48	cAMP-Mediated Signaling
Pde4D	Phosphodiesterase 4D	NS	NS	NS	NS	3.16E-02	1.36	cAMP-Mediated Signaling
Pde9A	Phosphodiesterase 9A	2.46E-02	-1.39	4.20E-02	-1.35	4.20E-03	-1.44	cAMP-Mediated Signaling
Pde10A	Phosphodiesterase 10A	2.80E-02	1.39	1.18E-02	1.42	3.22E-03	1.46	cAMP-Mediated Signaling
Plcl1	Phospholipase C-Like 1	NS	NS	NS	NS	2.23E-03	1.41	CREB Signaling in Neurons Synaptic Long Term Potentiation
Ppm1l	Protein Phosphatase, Mg2+/Mn2+ Dependent, 1L	1.75E-02	1.27	1.18E-02	1.27	3.80E-02	1.22	Synaptic Long Term Depression
Prkacb	Protein Kinase Camp-Activated Catalytic Subunit Beta	2.55E-02	1.36	5.61E-04	1.50	2.24E-03	1.43	cAMP-Mediated Signaling CREB Signaling in Neurons Synaptic Long Term Potentiation

Table 3 (continued)

Prkar2A	Protein Kinase Camp-Dependent Type 2 Regulatory Subunit Alpha	NS	NS	3.12E-03	1.49	1.48E-02	1.40	cAMP-Mediated Signaling CREB Signaling in Neurons Synaptic Long Term Potentiation
Prkca	Protein Kinase C, Alpha	9.91E-03	1.49	1.12E-02	1.46	2.08E-03	1.52	Synaptic Long Term Depression Synaptic Long Term Potentiation
Prkce	Protein Kinase C, Epsilon	1.26E-03	1.51	8.43E-04	1.50	5.35E-03	1.41	CREB Signaling in Neurons Synaptic Long Term Depression Synaptic Long Term Potentiation
Slc1A2	Solute Carrier Family 1 Member 2	3.20E-05	1.74	2.73E-05	1.72	4.72E-06	1.76	Glutamate Receptor Signaling
Slc38A1	Solute Carrier Family 38, Member 1	2.92E-03	1.40	1.35E-04	1.47	2.48E-04	1.44	Glutamate Receptor Signaling

CHAPTER 3 FIGURES

Figure 1

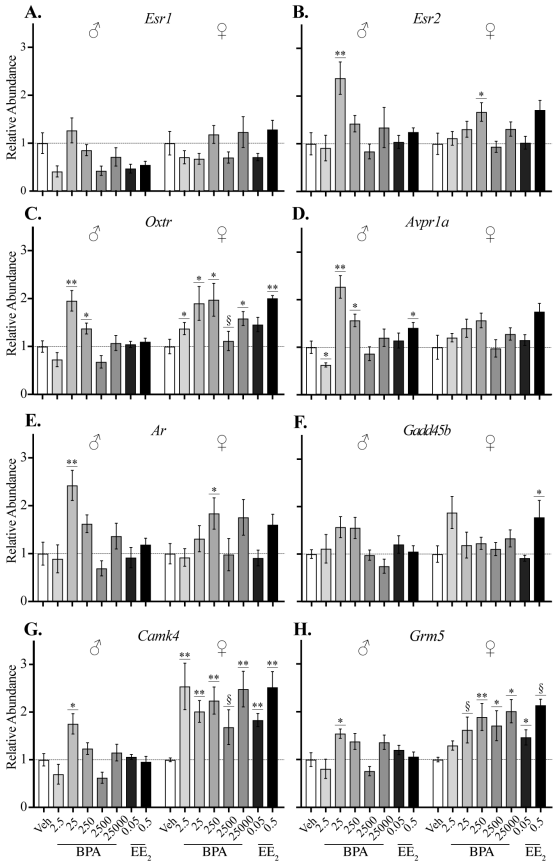

Fig. 1: Effects of gestational BPA or EE_2 on neonatal amygdalar expression of selected genes. *Esr1* was unaffected by BPA or EE_2 (A). Esr2 was increased by 2.5 µg BPA in males and 250 µg BPA in females (B). *Oxtr* was increased by 250 and 250 µg BPA in males and 2.5, 25, 250, and 25,000 µg BPA and 0.5 µg EE_2 in females (C). Male *Avpr1a* was decreased by 2.5 µg BPA and increased by 25 and 250 µg BPA (D). *Ar* was increased by 25 µg BPA in males and 250 µg BPA and 0.5 µg EE_2 in females (E). Female *Gadd45b* was increased by 0.5 µg EE_2 (F). *Camk4* was upregulated in males by 25 µg BPA and in females by 2.5, 25, 250, and 25000 µg BPA and 0.05 and 0.5 µg EE_2 (G). *Grm5* was increased by 25 µg BPA in males and 250, 2500, 25000 µg BPA and 0.05 µg EE_2 in females (H). Graphs depict mean ± SEM (*$p \leq 0.05$, **$p \leq 0.01$, and §$p \leq 0.08$).

Figure 2

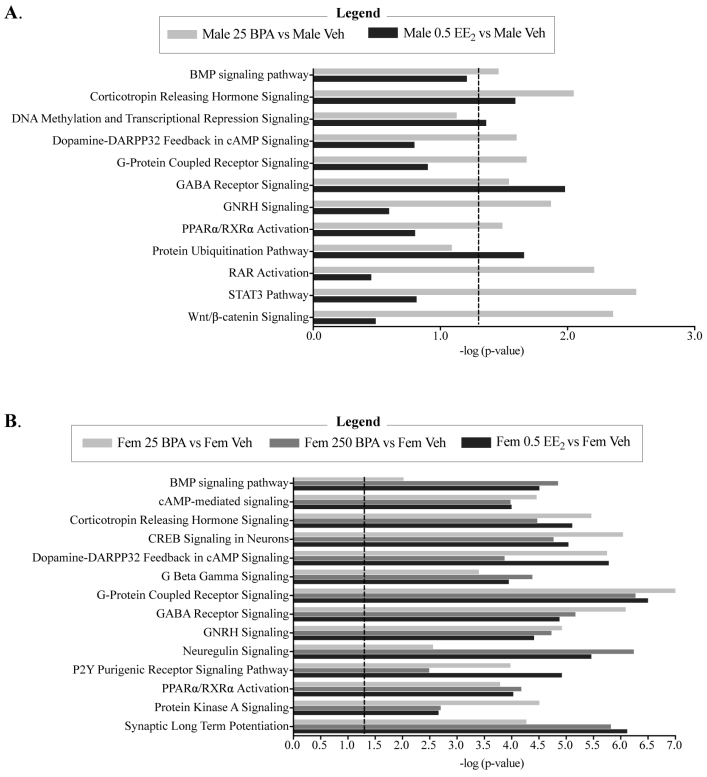

Fig. 2: Top canonical pathways enriched by differentially expressed genes. The x-axis represents negative log p values based on the probability that molecules in the uploaded dataset were included in the predefined IPA canonical pathways by true association as opposed to inclusion of molecules based on chance alone. For each male (A) and female (B) exposure group, only the top 10 pathways with the largest negative log *p* values are shown. The dashed line indicates the threshold of significance for a p-adjusted value of 0.05.

Figure 3

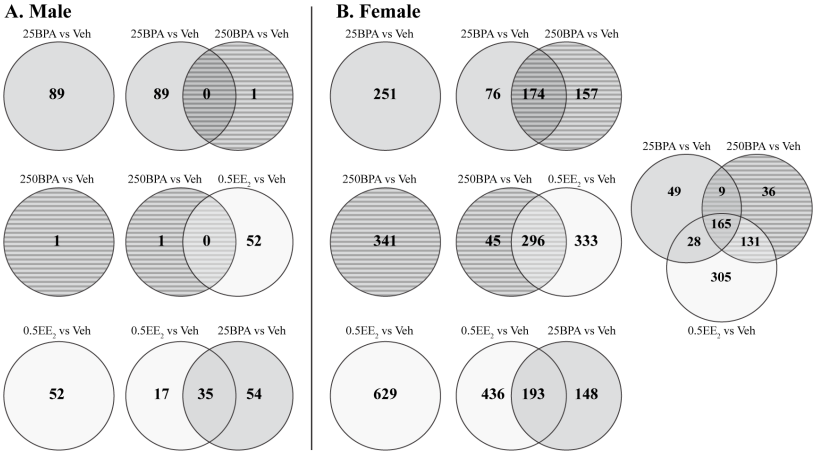

Fig. 3: Prenatal exposure to BPA and EE_2 result in common and unique differently expressed genes. Differentially expressed genes (padj ≤ 0.05) were identified in males (A) and females (B) prenatally exposed to 25 and 250µg BPA and 0.5 µg EE_2. Venn diagrams were created using Venny (http://bioinfogp.cnb.csic.es/tools/venny/).

Figure 4

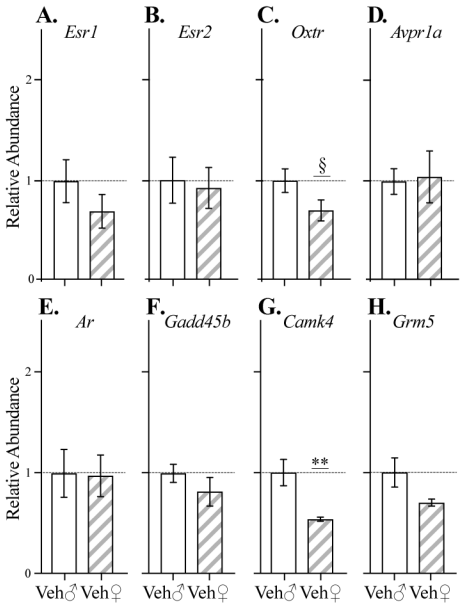

Fig. 4: Sex differences in amygdala expression of selected genes. Relative differences in gene expression between male and female control (unexposed) groups with male gene expression set as baseline. No a priori selected genes were sexually dimorphic in the neonate amygdala. (A-F). Expression of *Camk4* was significantly higher in males than females (G). No sex difference in *Grm5* was detected (H). Graphs depict mean ± SEM (**$p \leq 0.01$ and §$p \leq 0.08$).

CHAPTER 4

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Full Length Article

Effects of perinatal bisphenol A exposure on the volume of sexually-dimorphic nuclei of juvenile rats: A CLARITY-BPA consortium study

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ABSTRACT

Bisphenol A (BPA) is a high volume endocrine disrupting chemical found in a wide variety of products including plastics and epoxy resins. Human exposure is nearly ubiquitous, and higher in children than adults. Because BPA has been reported to interfere with sex steroid hormone signaling, there is concern that developmental exposure, even at levels below the current FDA No Observed Adverse Effect Level (NOAEL) of 5 mg/kg body weight (bw)/day, can disrupt brain sexual differentiation. The current studies were conducted as part of the CLARITY-BPA (Consortium Linking Academic and Regulatory Insights on BPA Toxicity) program and tested the hypothesis that perinatal BPA exposure would induce morphological changes in hormone sensitive, sexually dimorphic brain regions. Sprague-Dawley rats were randomly assigned to 5 groups: BPA (2.5, 25, or 2500 μg/kg bw/day), a reference estrogen (0.5 μg ethinylestradiol (EE_2)/kg bw/day), or vehicle. Exposure occurred by gavage to the dam from gestational day 6 until parturition, and then to the offspring from birth through weaning. Unbiased stereology was used to quantify the volume of the sexually dimorphic nucleus (SDN), the anteroventral periventricular nucleus (AVPV), the posterodorsal portion of the medial amygdala (MePD), and the locus coeruleus (LC) at postnatal day 28. No appreciable effects of BPA were observed on the volume of the SDN or LC. However, AVPV volume was enlarged in both sexes, even at levels below the FDA NOAEL. Collectively, these data suggest the developing brain is vulnerable to endocrine disruption by BPA at exposure levels below previous estimates by regulatory agencies.

1. Introduction

Perhaps one of the best-known and most intensely studied endocrine disrupting chemicals (EDCs) is bisphenol A (BPA). A high production volume chemical, BPA is used as a monomer in the production of polyvinyl chloride and polycarbonate plastics, epoxy resins, and a multitude of other commercial and consumer products (FAO/WHO, 2011). Human exposure to BPA is virtually unavoidable and occurs primarily from contaminated food and beverages. In industrialized countries, well over 90% of individuals are estimated to have detectable amounts of BPA in their bodies, albeit in small amounts (serum levels are typically in the range of 4 ng/ml or lower) (Bushnik et al., 2010; Calafat et al., 2005, 2008; Casas et al., 2013; LaKind and Naiman, 2015). The most significant route of human exposure is thought to be ingestion, with dietary intake estimated to range from 0.1–1.4 μg/kg body weight (bw)/day, but exposure can also occur from other sources (FAO/WHO, 2011). BPA can cross the placenta and there is some evidence that it may accumulate in the fetus after repeated exposures (Ikezuki et al., 2002; Schonfelder et al., 2002; Taylor et al., 2008). In fetal rodents, BPA has been shown to preferentially accumulate in brain, in some cases to a greater degree in males than females (Negri-Cesi, 2015). In its 2014 updated safety assessment of Bisphenol A (BPA) for use in food contact applications, the US Food and Drug Administration defined the No Observed Adverse Effect Level (NOAEL) as 5 mg/kg bw/day based largely on two multigenerational rodent studies (documents available for download here: https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm064437.htm).

BPA has been reported to interfere with the metabolism and signaling of endogenous steroid hormones, particularly estrogen,

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and numerous studies, including our own, have repeatedly shown in multiple species that developmental exposure to BPA can perturb sexually dimorphic brain development and behavior, even at exposures below the current FDA NOAEL (representative examples include (Braun et al., 2011; Jasarevic et al., 2013; Kinch et al., 2015; Patisaul et al., 2012b; Rebuli and Patisaul, 2016; Sullivan et al., 2014; Wolstenholme et al., 2011)). Although this compounding evidence is compelling, because few published studies are evaluated to be of high utility for human risk assessment, there remains a lack of consensus on the potential risks BPA pose to the developing brain in humans. The studies herein were specifically designed and conducted in response to that informational limitation under the CLARITY-BPA research program (Consortium Linking Academic and Regulatory Insights on BPA Toxicity) (Birnbaum et al., 2012; Heindel et al., 2015; Johnson et al., 2016; Schug et al., 2013), a multi-investigator effort coordinated and supported by the National Toxicology Program (NTP), National Institute of Environmental Health Sciences (NIEHS), and U.S. Food and Drug Administration (FDA) to help provide clarifying evidence. The present study tested the hypothesis that early-life BPA exposure can alter the volume of sexually dimorphic structures in the brain, and serves as a follow-up to our prior CLARITY-BPA paper describing non-reproductive behavioral outcomes in the same animals (Rebuli et al., 2015).

Designed to draw upon the strengths of academic and guideline-compliant studies in order to address research gaps and confirm prior findings, this and all other CLARITY-BPA studies are uniquely powerful because they incorporate research recommendations published by the WHO and others (Beronius et al., 2010, 2009; Chapin et al., 2008; FAO/WHO, 2011; FDA, 2012; NTP, 2008) for enhancing robustness and reproducibility, including complete data blinding, use of only one animal per sex per litter (with the litter as the experimental unit), oral dosing, inclusion of a reference estrogen, and evaluation of multiple BPA doses, particularly levels at or below the FDA NOAEL. Additionally, as in our prior, published CLARITY-BPA studies (Arambula et al., 2016; Rebuli et al., 2015), sex was considered as a biological variable. Exposure levels and endpoints examined were established via consortium consensus and selected to maximize utility in risk assessment. The animals used for the present study were tested as juveniles for effects on sexually dimorphic, non-reproductive behaviors prior to sacrifice (Rebuli et al., 2015). Only limited and inconsistent evidence for heightened anxiety and exploratory behavior were observed, leading us to conclude that there were no systematic effects of BPA on the behavioral endpoints tested. Here we focused on exposure-related effects on the volume of sexually dimorphic brain nuclei in these animals with the hypothesis that perinatal exposure would abrogate volumetric sex differences. Sprague-Dawley rats from an existing colony at the National Center for Toxicological Research (NCTR-SD) were perinatally exposed to vehicle, BPA (2.5, 25, or 2500 μg/kg bw/day), or a reference estrogen (0.5 μg/kg bw/day 17α-ethinylestradiol (EE_2)). To ensure precise oral dosing, dams were gavaged from gestational day 6 (GD 6) until parturition and offspring were directly gavaged from postnatal day 1 (PND 1) to weaning (PND 21). PND 28 brains were coronally sectioned, thionin-stained for Nissl substance, and unbiased stereology was used to quantify the volume of sexually dimorphic brain regions.

Throughout the mammalian brain, several morphological and functional brain sex differences arise during the fetal and postnatal period in response to the organizational effects of steroid hormones (De Vries, 2004; McCarthy, 2008; Simerly, 2002). The two regions most classically associated with morphological sex differences in rodents are the aptly named sexually dimorphic nucleus (SDN) of the preoptic area and the anteroventral periventricular nucleus (AVPV). Both of these morphometric sex differences are mediated by estradiol but effects on apoptosis are opposite, resulting in the SDN being 5–7 times larger in males (Gorski, 1978) and the AVPV being nearly 1.6 times larger in females (Davis et al., 1996; Simerly et al., 1997). Volumetric sex differences of the SDN and AVPV emerge perinatally and during adolescence, respectively, and increase in magnitude until adulthood (Ahmed et al., 2008; Davis et al., 1996; Gorski, 1978; Simerly et al., 1997). The mechanisms by which the SDN and AVPV are sexually differentiated are well described, require estrogen receptor alpha (ERα), and can be predictably manipulated by exogenous hormones (Lenz and McCarthy, 2010; Schwarz and McCarthy, 2008; Simerly, 2002). Thus, they are considered particularly useful targets for assessing the endocrine disrupting properties of chemicals such as BPA.

The posterodorsal portion of the medial amygdala (MePD) was also selected for assessment because ERs are known to play a role in the sexual differentiation process (Cooke et al., 2003), and we have previously demonstrated that prenatal BPA exposure can alter sex-specific patterns of MePD ERβ expression (Cao et al., 2013). Although anatomical sex differences in the prepubescent rodent amygdala are not as great as in the preoptic area of the hypothalamus, the volume of the rat MePD is roughly 15–20% larger in prepubertal males than females (Cooke et al., 2007; Cooke and Woolley, 2005). Circulating levels of gonadal steroids maintain and enhance the MePD volumetric sex difference throughout puberty (Ahmed et al., 2008) and adulthood (Cooke et al., 2003), resulting in the adult male MePD being approximately 2 times larger than females (Cooke et al., 1999; Hines et al., 1992).

Lastly, we explored the effects of BPA on the volume of the locus coeruleus (LC), a nucleus located in the pons and selected because one laboratory has generated data suggesting perinatal BPA exposure can have sex-specific effects on LC volume in Wistar rats (Kubo et al., 2001, 2003). A female biased sexual dimorphism in rodent LC volume has been reported, however, this appears to be strain- and species- dependent (Babstock et al., 1997; Garcia-Falgueras et al., 2005). Thus, whether or not a sex difference exists, and might be vulnerable to BPA, was of interest in our animal model. As the principal site of norepinephrine synthesis in the central nervous system, the LC plays a critical role in modulating behavioral, autonomic, and endocrine responses to stress.

2. Materials and methods

The study is a component of the CLARITY-BPA program and used the same animals for which behavioral data are already published (Rebuli et al., 2015). Because the comprehensive study design details are described in that prior publication, only the most directly relevant methods are summarized here.

2.1. Animal husbandry

Sprague-Dawley rats from the National Center for Toxicological Research colony (NCTR-SD rats) were housed in an Association for Assessment and Accreditation of Laboratory Animal Care- (AALAC) accredited facility at NCTR (23 ± 3 °C, 50 ± 20% relative humidity, and 12:12 h light dark cycle, lights off at 0600 h). All aspects of this study were approved by the NCTR Institutional Animal Care and Use Committee (IACUC). Rats were housed in conditions designed to minimize unintentional exposure to BPA and other EDCs (use of glass water bottles with filtered water, thoroughly washed polysulfone caging and woodchip bedding) and a soy- and alfalfa-free diet (5K96 verified casein diet 10 IF, round pellets, γ-irradiated; Cat. 1810069, Purina Mills, Richmond IN) and Millipore-filtered water were provided ad libitum. Extracts of diet and other study materials were monitored for BPA and myco/phytoestrogens by liquid chromatography/mass spectrometry

(Delclos et al., 2014) and all had levels below the average analytical method blanks (Heindel et al., 2015). Because these rats were bred for behavioral testing and thus required special housing, they were generated from the same colony as the CLARITY-BPA studies but not obtained from the mainline study and housed separately (in a different building) after weaning (Rebuli et al., 2015). The study was designed and executed with the litter as the statistical unit.

2.2. Reagents and dosing

The BPA (CAS # 80-05-7, catalog # B0494, TCI America, Portland, OR) and ethinylestradiol (EE_2; CAS # 57-63-6, catalog #E4876, Sigma-Aldrich, St. Louis, MO) were more than 99% pure and administered in 0.3% aqueous carboxymethyl cellulose (CMC; catalog # C5013, Sigma- Aldrich, St. Louis, MO) by gavage daily at a volume of 5 ml/kg bw using a modified Hamilton Microlab ML511C programmable 115 V pump (Hamilton Co., Reno, NV) (Lewis et al., 2010).

Two weeks prior to mating, female NCTR-SD rats were randomly assigned to exposure groups stratified by body weight to ensure body weights were equivalent across all groups. Male breeders were assigned such that no sibling or first cousin mating occurred and mating was conducted as previously described (Delclos et al., 2014). To model the exposure route used to establish the FDA NOAEL, dams were orally gavaged daily with vehicle (0.3% CMC), 2.5, 25, or 2500 μg BPA/kg bw/day, or 0.5 μg EE_2/kg bw/day from GD 6 until the onset of labor (note: the full CLARITY-BPA study has additional exposure groups, see (Heindel et al., 2015)). Neither the dams nor the pups were dosed on the day of birth (PND 0). On PND 1, litters were randomly culled to a maximum litter size of 10 (minimum size of 6) to achieve equal numbers of males and females. After the litter was culled, the pups were directly gavaged daily through weaning (PND 21). For pups younger than PND 5, the gavage needle was not inserted past the pharynx.

The 3 doses of BPA used in this study cover the lower range of exposures at which BPA-induced effects have been reported in scientific literature and include levels of BPA below the current FDA NOAEL of 5 mg/kg bw/day. Because many of the reported effects of BPA are hypothesized to be due to an estrogenic mode of action a reference estrogen group (0.5 μg EE_2/kg bw/day) was included.

2.3. Weaning and tissue collection

Offspring were weaned on PND 21 after their last daily gavage and identified by a tail tattoo with a unique identification number. As described previously, only offspring from litters with at least 9 pups and a reasonably balanced sex ratio at birth (no litter had more than a 4 pup sex difference except for 2 litters in load 5, which had a 5 pup sex difference: 9 males and 4 females) were used in this study (Rebuli et al., 2015). Animals were transferred to new rooms and housed in groups of 2–3 (same-exposure group, same-sex, same-age, non-siblings) under conditions identical to the preweaning rooms described above, apart from the light cycle (23:00–11:00), which was adjusted to accommodate behavior testing. To ensure no test animals were housed alone, a same sex and age treatment-naïve "companion" animal was provided when needed. Twelve animals per sex per group were assigned to the current study (1/sex/litter). Behavioral testing occurred before puberty on PNDs 25–27 using a battery of behavioral tests predictive of anxiety (open-field and elevated plus maze), the outcomes of which are published (Rebuli et al., 2015). The animals (n = 120) were then sacrificed on PND 28 by CO_2 asphyxiation followed by rapid decapitation. Brains were collected, flash frozen on crushed dry ice and shipped from NCTR to North Carolina State University (NCSU) where they were stored at −80 °C.

2.4. Tissue processing and Nissl staining

The brain of each animal was cryosectioned (Leica CM1900, Nußloch, Germany) into three serial sets of 20 μm coronal sections, mounted onto Superfrost plus slides (Fisher Scientific, Pittsburgh, PA) and stored at −80 °C. On the day prior to staining, one set of sections was thawed and dried at room temperature overnight. The sections were then defatted in 100% xylene, rehydrated in a series of descending ethanols and Milli-Q water (Merck Group, Darmstadt, Germany), and stained for Nissl substance with thionin (0.2%) to visualize anatomical structures. The slides were then dehydrated in ascending ethanols, cleared in 100% xylene, and cover-slipped with DPX mounting medium (VWR International Inc., Poole, England).

2.5. Stereological quantification

Unbiased stereology was performed using the Stereologer™ software (Stereology Resource Center, Inc., MD) on a Leica DM2500P microscope (Leica Microsystems, Wetzlar, Germany) equipped with a motorized stage (Applied Scientific Instrumentation, Eugene, OR) and a video camera (IMI Technology Co., Seoul, Korea). Procedures for volumetric assessment were similar to those we have used for prior studies (McCaffrey et al., 2013; Patisaul et al., 2007).

Unilateral contours of the AVPV, SDN, and LC and bilateral contours of the MePD were drawn at low magnification (5×) from the live image with the assistance of a rat and mouse brain atlas (Paxinos, 1991, 2007). Bilateral measurements of the MePD were taken because there are subtle volumetric differences between the left and the right MePD as well as between the sexes (Cooke et al., 2007; Johnson et al., 2008). A uniform grid of points with an area per point of 2000 μm^2 was randomly superimposed over each section and all of the points lying within the region of interest were selected. Based on these counts, volume was estimated using the Cavalieri method (Gundersen and Jensen, 1987) and coefficient of error for individual volume estimates was less than 10% (CE < 0.10).

The volume of the AVPV and SDN were independently defined and measured by two blinded investigators to confirm that the measurement methodology was reproducible. For the analysis, the data from both investigators was averaged. A single investigator, blinded to exposure groups, then quantified the volume of the LC and MePD. Only animals for which every section within regions of interest were perfectly intact were examined. Thus, because of tissue damage or uneven staining, some material could not be analyzed: 2 brains were excluded for the SDN, 3 for the AVPV, 24 for the left MePD, 20 for the right MePD, and 13 for the LC. The number of animals excluded was higher for the MePD because this region is volumetrically larger than the others and thus requires more sections to fully measure. If even a single section was damaged or missing, then the animal was excluded to prevent measurement error. Sample sizes for all endpoints are indicated in the figures.

2.6. Data decoding

To ensure that all investigators remained blinded during data collection, all tissue samples provided by NCTR were given a unique identifier and designated with a letter (A–C, etc.) to denote each experimental group (grouped by exposure and sex) but blind the NCSU team to exposure. Coded raw data were submitted to the NTP Chemical Effects in Biological Systems (CEBS) repository after all volumetric measurements were complete. After a CEBS administrator performed a quality control analysis, the raw data was archived, and the NCSU investigators were then unblinded and began the statistical analysis. This code was not the same as the

one used for these animals while they underwent behavioral testing. Thus, all information obtained from these animals was collected under blinded conditions.

2.7. Statistical analysis

Statistical analysis for all of the data was performed and graphed using Prism version 7 (GraphPad Software, Inc., La Jolla, CA). The statistical approach was designed to be consistent with published guidelines for low dose EDC studies (Haseman et al., 2001) and previously published stereological studies of similar scale (equivalent or smaller sample sizes) in the rat brain (Adewale et al., 2011; McCaffrey et al., 2013). Within each exposure group, no same-sex littermates were included, so potential litter effects did not need to be statistically accounted for. Because it can differ, the volume of the left and right MePDs were first analyzed individually. Significant differences in size were not observed, thus a combined data set was generated by calculating an average (of left and right) MePD size (for animals in which both could be measured) or by using the single available value (from the left or the right). This produced a single, representative MePD volume for each animal.

Prior to all statistical analysis, data were assessed within each region using the Shapiro-Wilk normality test ($\alpha = 0.05$) and violations were only found for residual groups within the MePD and SDN. In some cases this was due to the presence of statistical outliers, which we ultimately chose not to remove in order to ensure a full accounting of all data. Violations of normality may increase the chance of type I error, but are not uncommon with sample sizes of 9–12/sex/group (Cohen et al., 2002). Because occurrences of non-normality or outliers did not meaningfully impact the statistical outcome or interpretation of the data, rather than differentially perform non-parametric tests in cases where deviation from normality occurred, we applied a constant modeling approach to all endpoints in each region of interest.

For each region of interest, all data were first analyzed by a two-way analysis of variance (ANOVA) with sex and exposure as factors to identify significant main effects and their interactions. To maximize resolution regarding potential sex-specific effects, the data were then analyzed within sex by a one-way ANOVA and the Dunnett's Multiple Comparison post hoc test was used to compare each exposure group to the same-sex vehicle control group. Lastly, *t*-tests were used to identify sex differences and, most importantly, to ensure known sex differences were detected in the unexposed control groups. Confirmation of known sex differences in the vehicle controls was considered to be an indication that the measurements were robust, sufficiently powered to detect a difference in the range of that effect size, and properly conducted. All analyses were two-tailed and the level of significance for all data was set at $p \leq 0.05$.

3. Results

All results are summarized in Table 1. As expected, the volumes of the SDN, AVPV, and MePD were sexually dimorphic in the vehicle control groups. Overall, BPA and EE_2 had minimal effects on these volumetric sex differences.

3.1. SDN volume

There was a main effect of sex [$F(1, 108) = 279.60$, $p \leq 0.001$] on the volume of the SDN but no effect of exposure and no significant interaction. In all exposure groups SDN volume was significantly larger in males than females (Fig. 1B and Table 1). When exposure was examined within sex, there were no significant effects of BPA or EE_2 observed.

Table 1
Effect of Sex and Perinatal BPA or EE_2 Exposure on the Volume of Juvenile Rat Brain Nuclei.

Endpoint	Group	Effect of Sex	
SDN Volume	Vehicle	F < M	$p \leq 0.001$
	2.5 BPA	F < M	$p \leq 0.001$
	25 BPA	F < M	$p \leq 0.001$
	2500 BPA	F < M	$p \leq 0.001$
	0.5 EE_2	F < M	$p \leq 0.001$
AVPV Volume	Vehicle	F > M	$p \leq 0.003$
	2.5 BPA	↑F > M	$p \leq 0.001$
	25 BPA	↑F > M↑	$p \leq 0.023$
	2500 BPA	↑F > M↑	$p \leq 0.001$
	0.5 EE_2	F > M	$p \leq 0.001$
Left MePD Volume	Vehicle	F < M	$p \leq 0.001$
	2.5 BPA	F < M	$p \leq 0.001$
	25 BPA	F < M	$p \leq 0.008$
	2500 BPA	F < M	$p \leq 0.001$
	0.5 EE_2	F <vM	$p \leq 0.010$
Right MePD Volume	Vehicle	F < M	$p \leq 0.001$
	2.5 BPA	F < M	$p \leq 0.001$
	25 BPA	F < M	$p \leq 0.001$
	2500 BPA	↑F < M	$p \leq 0.001$
	0.5 EE_2	F < M	$p \leq 0.006$
Averaged MePD Volume	Vehicle	F < M	$p \leq 0.001$
	2.5 BPA	F < M	$p \leq 0.001$
	25 BPA	F < M	$p \leq 0.001$
	2500 BPA	F < M	$p \leq 0.001$
	0.5 EE_2	F < M	$p \leq 0.001$
LC Volume	Vehicle	F = M	ns
	2.5 BPA	F = M	ns
	25 BPA	F = M	ns
	2500 BPA	F = M	ns
	0.5 EE_2	F = M↑	$p = 0.02$

Notes: All brain nuclei except the LC were sexually dimorphic in size and there was no instance where exposure eliminated that difference. "↑" represents a significant increase in volume compared with the same-sex vehicle control."ns" represents a p-value which was not significant.

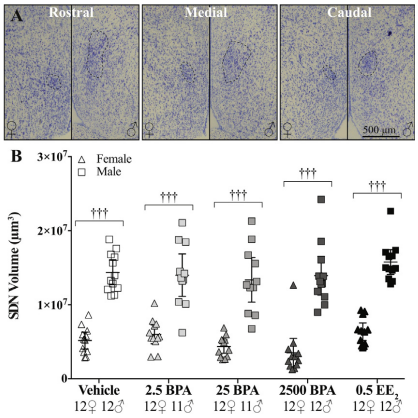

Fig. 1. (A) Representative thionin stained coronal sections showing the sexually dimorphic nucleus (SDN). Sections are arranged from rostral to caudal and the dotted line indicates the boundaries of the area measured. Perinatal exposure to BPA or EE_2 had no significant effects on SDN volume in either sex (B). As expected, SDN volume was significantly larger in males than females in all exposure groups. Significant sex differences in volume are represented by $^{\dagger\dagger\dagger}p \leq 0.001$. Error bars represent the 95% confidence interval and sample size is provided at the bottom.

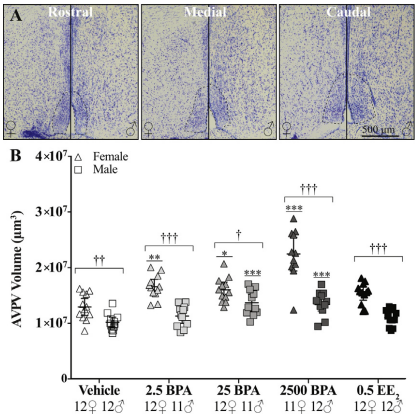

Fig. 2. (A) Representative thionin-stained coronal sections showing the anteroventral periventricular nucleus (AVPV). Sections are arranged from rostral to caudal and the dotted line indicates the boundaries of the area measured. In females, perinatal exposure to 2.5, 25, and 2500 µg BPA/kg bw/day increased AVPV volume (B). In males, perinatal exposure to 25 and 2500 µg BPA/kg bw/day increased AVPV volume. As expected, AVPV volume was found to be significantly larger in females than males in all exposure groups. Exposure to 0.5 µg EE_2/kg bw/day had no significant effects on AVPV volume. Significant differences in volume compared to the same-sex vehicle group are represented by $^{***}p \leq 0.001$, $^{**}p \leq 0.01$, and $^{*}p \leq 0.05$. Significant sex differences in volume are represented by $^{\dagger\dagger}p \leq 0.01$, and $^{\dagger}p \leq 0.05$. Error bars represent the 95% confidence interval and sample size is provided at the bottom.

3.2. AVPV volume

Two-way ANOVA revealed a main effect of sex [F (1, 107) = 115.40, $p \leq 0.001$] and exposure group [F (4107) = 23.79, $p \leq 0.001$], plus a significant interaction [F (4, 107) = 6.97, $p \leq 0.001$] on AVPV volume. Within females, perinatal exposure to 2.5, 25, and 2500 µg BPA/kg bw/day increased the volume of the AVPV ($p = 0.008$, $p = 0.031$, and $p \leq 0.001$, respectively; Fig. 2B). In males, perinatal exposure to 25 and 2500 µg BPA/kg bw/day increased AVPV volume when compared to the same sex vehicle control group ($p \leq 0.001$ for both). In all exposure groups, AVPV volume was found to be significantly larger in females than males (Fig. 2B and Table 1). Perinatal exposure to 0.5 µg EE_2/kg bw/day did not significantly affect AVPV volume in either sex.

3.3. MePD volume

In the left MePD, two-way ANOVA revealed a main effect of sex [F (1, 90) = 80.98, $p \leq 0.001$] and exposure [F (4, 90) = 2.98, $p = 0.02$], plus a significant interaction [F (4, 90) = 3.34, $p = 0.01$]. When exposure was examined within sex, however, no significant effects of BPA or EE_2 on left MePD volume were identified in either sex. As expected, left MePD volume was significantly larger in males than females in all exposure groups (Fig. 3 and Table 1).

In the right MePD, there were significant main effects of sex [F (1, 86) = 91.31, $p \leq 0.001$] and exposure [F (4, 86) = 4.91, $p = 0.001$] on volume. Compared to the same-sex vehicle control, right MePD volume was significantly increased in females perinatally exposed to 2500 µg BPA/kg bw/day ($p = 0.001$). Right MePD volume was significantly larger in males than females for all exposure groups (Fig. 3 and Table 1).

Using the data set in which the right and left MePD measurements were combined, there was a main effect of sex [F (1, 99) = 140.30, $p \leq 0.001$] and a significant interaction of sex and exposure [F (4, 99) = 3.06, $p = 0.02$] on MePD volume. Within sex, however, perinatal exposure to BPA or EE_2 had no significant effects on MePD volume in either males or females (Fig. 4B). Male MePD volume was significantly larger than females in all exposure groups (Fig. 4B and Table 1).

3.4. LC volume

Two-way ANOVA revealed a significant main effect of exposure [F (4, 97) = 2.73, $p = 0.034$] but not sex on the LC volume. Compared to the same sex vehicle control animals, LC volume was

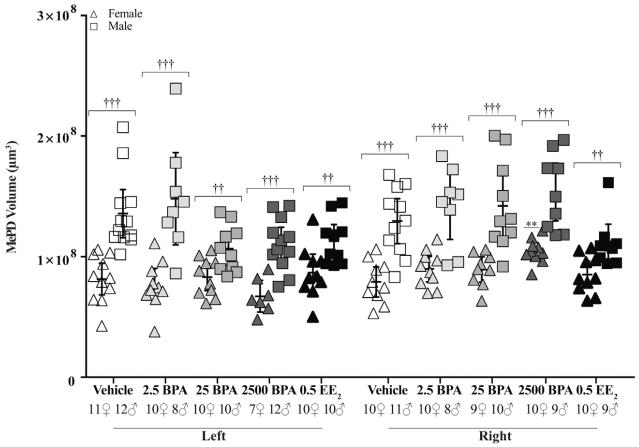

Fig. 3. In the right medial posterodorsal amygdala (MePD), perinatal exposure to 2500 µg BPA/kg bw/day increased MePD volume compared to the same sex vehicle controls. However, overall evidence for BPA- and EE_2- related effects were minimal and inconsistent on both the volume of the left and right MePD. In both the left and right MePD, volume was found to be significantly larger in males than females in all exposure groups. Significant differences in volume compared the same-sex vehicle group are represented by $^{**}p \leq 0.01$. Significant sex differences in volume are represented by $\dagger\dagger\dagger p \leq 0.001$, $\dagger\dagger p \leq 0.01$, and $\dagger p \leq 0.05$. Error bars represent the 95% confidence interval and sample size is provided at the bottom.

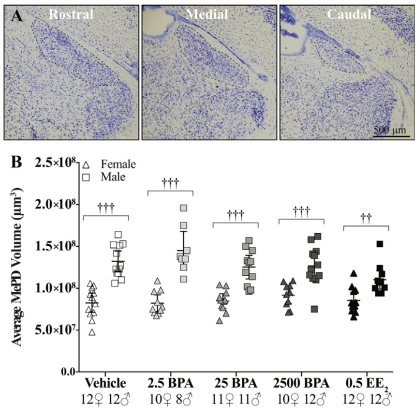

Fig. 4. (A) Representative thionin-stained coronal sections showing the posterodorsal subnucleus of the medial amygdala (MePD). Sections are arranged from rostral to caudal. The dotted line indicates the boundaries of the area measured. Perinatal exposure to BPA or EE_2 had no significant effects on MePD volume (B). MePD volume was larger in males than females in all exposure groups. Significant sex differences in volume are represented by $^{\dagger\dagger\dagger}p \leq 0.001$, and $^{\dagger\dagger}p \leq 0.01$. Error bars represent the 95% confidence interval and sample size is provided at the bottom.

significantly increased in males perinatally exposed to 0.5 µg EE_2/kg bw/day ($p = 0.02$) (Fig. 5B and Table 1). In all exposure groups, LC volume was not found to be significantly different between males and females (Fig. 5B and Table 1). No significant effects of BPA on LC volume were identified in either sex.

4. Discussion

BPA effects were mainly confined to the AVPV, which was increased by perinatal exposure in both sexes at multiple dose levels. Perinatal exposure to 2.5 µg/kg bw/day BPA increased AVPV volume in females and exposure to 25 and 2500 µg BPA/kg bw/day increased volume in both males and females. Because endogenous estradiol, acting through ERα and ERβ, is masculinizing in the AVPV (Bodo et al., 2006; Patchev et al., 2004), these effects suggest that BPA is functionally acting as an estrogen antagonist (McCarthy, 2008). Within the MePD, an effect of BPA on volume was detected only in the right MePD in males exposed to the 2500 µg BPA/kg bw/day exposure group. Because the left and right MePD nucleus have numerous structural and functional differences, an effect on only one side is biologically plausible. LC volume was not found to be sexually dimorphic in this animal model, and slightly but statistically increased by EE_2 but not BPA. EE_2 did not, however, masculinize any of the sexually dimorphic nuclei, demonstrating that it was not effective as a positive control. These data show that perinatal BPA exposure, at an oral exposure range well below the current FDA NOAEL, is capable of disrupting brain sexual differentiation in rats.

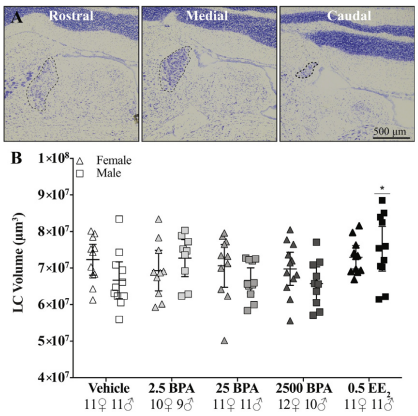

Fig. 5. (A) Representative thionin-stained coronal sections showing the locus coeruleus (LC). Sections are arranged from rostral to caudal. The dotted line indicates the boundaries of the area measured. LC volume was significantly increased in males perinatally exposed to 0.5 µg EE_2/kg bw/day (B). BPA had no effects on LC volume. Significant differences in volume compared the same-sex vehicle group are represented by $^{*}p \leq 0.05$. Error bars represent the 95% confidence interval and sample size is provided at the bottom.

Well-characterized as sexually dimorphic, the rat AVPV contains several robust sex differences critical to the sex-specific neuroendocrine and reproductive functions of this region, including the capacity to coordinate steroid positive feedback in females (Simerly, 2002). Identification of the AVPV as a sensitive target for BPA is a consistent finding across the literature, with a couple of prior studies reporting volumetric effects. Some evidence for disruption of AVPV volume was observed in prepubertal female offspring of CD-1 mice exposed to 250 ng BPA kg/day delivered by osmotic pump from GD 8 to lactational day 16. An important distinction, however, is the direction of the effect. While total AVPV volume was not actually quantified, perinatal BPA exposure led to a significant decline in the number of tissue sections spanning the rostral-caudal extent of the AVPV in prepubertal females (Rubin et al., 2006). In contrast, a prior experiment from our lab group found neonatal exposure to 250 µg of BPA by subcutaneous injection every 12 h during the first two days of life (approximately 42 mg BPA/kg bw/day) had no effect on the AVPV volume of adult male Sprague-Dawley rats (females not examined) (Patisaul et al., 2007). The directional disparity in volumetric outcomes may at least partially result from experimental design differences (dose, route of administration, timing of exposure) and variation in the neural structure of rats and mice (Bonthuis et al., 2010).

BPA-related disruption of sexually dimorphic endpoints within the AVPV has also been reported. The AVPV contains a sexually dimorphic population of dopaminergic neurons that are more abundant in females than males and differentiate under the influence of ERα and ERβ (Bodo et al., 2006; Simerly et al., 1985, 1997). Of the three studies examining the effect of developmental BPA exposure on this population in the prepubertal rodent AVPV, two found sex- and dose-specific effects. Neonatal exposure to 250 µg of BPA by subcutaneous injection every 12 h during the first two days of life increased the number of dopaminergic neurons in the male rat prepubertal AVPV but had no effect in females (Patisaul et al., 2006). In CD-1 mice, transplacental and lactational exposure, spanning GD 8 to PND 16 to much lower BPA exposures (25 and 250 ng/kg bw/day) decreased the number of dopaminergic neurons in the prepubertal female AVPV but had no effect on males (Rubin et al., 2006). Conversely, the third experiment, which used the same route and timing of exposure as the present study, found no effects of perinatal BPA exposure to 2.5 or 25 µg/kg bw/day on AVPV dopaminergic cell numbers in PND 21 male and female NCTR-SD rats (Ferguson et al., 2015). Notably, while a female-biased sexual dimorphism in dopaminergic cells was reported, the expected sex difference in total AVPV volume was not found. Although we were able to detect a volumetric sex difference in the present study, it was smaller than has been reported in prior studies, suggesting that AVPV sex differences may be smaller in the NCTR-SD strain. Alternatively, this discrepancy may simply be a

result of age. While this sex difference emerges pre-pubertally, the differential cell death that enhances the sex difference is not complete until the late perinatal period (Ahmed et al., 2008; Davis et al., 1996; Gorski, 1978; Simerly et al., 1997). Notably, the sensitive window for AVPV differentiation occurs earlier, just after birth, suggesting that any action of BPA or EE_2 on AVPV volume most likely occurred perinatally.

Kisspeptin neurons in the AVPV are also sexually dimorphic, with adult females possessing many more kisspeptin neurons than males (Kauffman et al., 2007) and the ontogeny of this sex difference is primarily mediated by estrogen activity on ERα (Patisaul et al., 2012a, 2009). Moreover, kisspeptin is the principal regulator of gonadotropin secretion and crucial for the timing of pubertal onset and ovulation (Oakley et al., 2009; Pineda et al., 2010; Pinilla et al., 2012). Prior rodent studies provide compelling evidence that developmental BPA exposure can alter levels of kisspeptin mRNA expression (*Kiss1*) and the number of kisspeptin immunoreactive (kisspeptin-ir) neurons in the AVPV in a sex- and age- specific manner. For instance, in the rat, perinatal exposure to 2 μg BPA/kg bw/day increased the number of kisspeptin-ir neurons at PND 30, 50, and 90 in males (Bai et al., 2011) and neonatal exposure to 50 mg BPA/kg bw/day was found to downregulate *Kiss1* expression in adult females (Patisaul et al., 2009). Due to the nature of the study design and other logistical constraints, we were not able to examine kisspeptin or other AVPV-related endpoints other than volume.

BPA-related effects in the AVPV appear complex, as reported outcomes vary by dose, sex, age, and species/strain of rodent model. Nevertheless, results from prior experiments, together with the observations reported herein, indicate that BPA disrupts sexual differentiation of the AVPV, most likely by interfering with endogenous estrogen. Previous studies demonstrate that developmental BPA exposure can alter the expression of ERα and ERβ in the AVPV (Cao et al., 2014; Monje et al., 2009; Rebuli et al., 2014). This disruption may occur via an epigenetic mechanism, as BPA has been shown to induce lasting changes in DNA methylation of genes encoding estrogen receptors (Kundakovic et al., 2013; Nugent et al., 2010). Thus, BPA may be interfering with sexual differentiation by acting directly on ERs, or indirectly by altering ER levels. The observed impacts on AVPV sexual differentiation contribute to, and are consistent with a large body of literature reporting BPA-related effects on reproductive behavior and physiology (Peretz et al., 2014; Ziv-Gal and Flaws, 2016).

In contrast to the AVPV, no effects of perinatal BPA exposure on SDN volume were observed in either sex. Available literature regarding BPA-related effects on SDN volume has yielded contradictory results that have been attributed to inconsistencies in key study design elements, including methodological differences for SDN-volume measurements and defining the borders of the SDN. Generally, studies using levels of BPA above the FDA NOAEL have found SDN volume to be unaffected by prenatal and/or postnatal exposure (Kwon et al., 2000; Nagao et al., 1999; Patisaul et al., 2007; Takagi et al., 2004). The one exception to this found perinatal BPA exposure ranging from 10,000 to 10,000,000 μg/kg bw/day orally administered to dams through cookie treats, diminished SDN volume in adult male Long Evans rats (McCaffrey et al., 2013). Notably, calbindin-ir was used to delineate the anatomical boundaries of the SDN. Calbindin is a calcium-binding protein expressed in a subdivision of sexually dimorphic SDN neurons (Sickel and McCarthy, 2000). It is possible that calbindin-ir reveals the border of the SDN more precisely than classical histological staining methods, including Nissl. This may contribute to the contradictory results reported for doses of BPA equivalent to or below the FDA NOAEL. For example, SDN volume evaluated by cresyl violet stain was unaltered in adult Wistar rats perinatally exposed to 30, 300 and 1500 μg BPA/kg bw/day (Kubo et al., 2001, 2003). In contrast, a study that delineated the SDN with calbindin-ir, and employed the same animal model and exposure paradigm as the present study, found SDN volume was increased in males perinatally exposed to 2.5 and 25.0 μg BPA/kg bw/day (He et al., 2012). That outcome supports our general conclusion that disruption of sexually dimorphic brain volumetrics can occur at doses well below the FDA NOAEL.

To our knowledge, this is the only study to examine the effects of BPA exposure on the volume of the MePD. Right MePD volume in males exposed to the 2500 μg BPA/kg bw/day was increased, but it is difficult to interpret the significance of this singular finding. Prior studies from our lab group have found that developmental BPA exposure, at levels below the FDA NOAEL, can alter ERβ expression in the amygdala (Patisaul et al., 2012b), and the MePD expression of ERs α and β in a sex- and dose- dependent manner (Cao et al., 2014, 2013). ERβ expression appears to be particularly sensitive to disruption by BPA in this region. Because both androgen and estrogen receptors mediate MePD sexual differentiation (Johansen et al., 2004), it is at least conceivable that BPA-induced alterations in ER expression underlie the morphometric change reported here but subsequent work will be needed to comprehensively explore that possibility. The sex-biased outcome may also reflect sex-biased exposure as at least one prior study has found that BPA accumulates to a higher degree in the fetal brain of males compared to females in BALB/c mice (Mita et al., 2012). Brain levels were not directly measured in the present study. Additionally, because the endocrine system contains multiple feedback loops, it is possible that brain effects could result from BPA-related actions extramural to the brain.

One lab has previously explored the effects BPA on LC volume and both studies from that group used Wistar rats (Kubo et al., 2001, 2003). Perinatal exposure to levels of BPA below the FDA NOAEL increased male LC volume and decreased female LC volume, thereby reversing the sex difference. In Wistar rats the female LC contains more neurons and has a greater overall volume than the male LC. This, however, appears to be strain-specific, as sex differences have not been observed in Long Evans or Sprague-Dawley rats (Babstock et al., 1997; Garcia-Falgueras et al., 2005, 2006; Guillamon et al., 1988; Pinos et al., 2001). Here we found no sex difference in LC and no effect of BPA exposure at any of the exposure levels examined. Considered collectively, these results highlight the importance of strain when designing and interpreting rodent EDC studies.

0.5 μg/kg bw/day EE_2 was not masculinizing for any of the sexually dimorphic endpoints examined and thus not an effective positive control. Notably, our two prior CLARITY-BPA studies on the brain and behavior also failed to consistently find any effects of EE_2 on sexually dimorphic endpoints (Arambula et al., 2016; Rebuli et al., 2015). Historically, the vast majority of studies establishing the mechanisms by which brain nuclei are sexually differentiated by steroid hormones have used 17β-estradiol itself or estradiol benzoate via injection at doses typically ranging from 2 to 50 μg (estimating that a female rat pup weighs ~6 g this dose range would be comparable to 333–8333 μg/kg bw) (Arnold and Gorski, 1984; Gorski, 1978; Gorski and Wagner, 1965; Gurney and Konishi, 1980). For the CLARITY-BPA program and other toxicological studies, oral dosing is preferable because it models the typical human exposure route, thus EE_2 was used as the reference estrogen. Failure to produce measurable effects on SDN or AVPV volume could indicate that the dose was insufficient, dosing was improperly conducted, EE_2 does not reach the brain, EE_2 is not masculinizing in brain, or the this strain of rat is resistant to estrogen. Of these, the first possibility is considered most likely. While there is considerable historical toxicological data on EE_2 and uterine weight, only a paucity of studies have examined the impact of EE_2 on sexually dimorphic neuroendocrine or behavioral

endpoints. One, using exposures ranging from 0.05 to 50 μg/kg bw/day demonstrated doses above 5 μg/kg bw/day were most effective at masculinizing sexually dimorphic behaviors related to reproduction in the Wistar rat (Ryan et al., 2010). Most relevant to the present study, work from a different lab group that used the same SD-NCTR strain found perinatal oral exposure to 5.0 and 10.0 μg/kg/day successfully masculinized the SDN volume in females (He et al., 2012). These data support the conclusion that the dose of EE_2 used here was likely insufficient, and also emphasize the need to establish a dose-response relationship for EE_2 and hypothalamic masculinization across this and other toxicologically valued strains.

Finally, the data reported herein are consistent with the other studies from the CLARITY-BPA consortium published to date. Collectively all have shown sporadic and generally modest effects of BPA on the brain and behavior, cardiac endpoints, and female ovarian follicle numbers and sex steroid levels (Arambula et al., 2016; Gear et al., 2017; Johnson et al., 2016; Patel et al., 2017; Rebuli et al., 2015). Significantly, the observed increase in female AVPV volume occurred at the same doses reported to cause effects in other CLARITY-BPA studies. We previously reported, for example, that prenatal exposure to 2.5 μg BPA/kg bw/day upregulated hypothalamic expression of ERα in neonate females (Arambula et al., 2016). Continuous exposure to 2.5 μg/kg bw/day from GD 6 to PND 21 also reduced the numbers of primordial, primary, preantral, and total healthy follicles in the ovary of PND 21 females (Patel et al., 2017). These consistencies support concerns that BPA can produce effects below the FDA NOAEL in multiple systems.

5. Conclusions

This study provides evidence that developmental BPA exposure, at levels below the FDA NOAEL, can impact sexual differentiation of the AVPV. Neither BPA nor EE_2 impacted the volume of the SDN or the MePD, and EE_2 had a minimal effect on LC volume. Limitations of this study include potential stress-related effects of gavage (Cao et al., 2013) and the failure of the reference estrogen to masculinize any of the sexually dimorphic endpoints, an outcome which likely reflects insufficient dose. Emerging data from ongoing CLARITY-BPA projects will establish the degree to which BPA impacts the development of other tissue types and organ systems. Comprehensive approaches that simultaneously assess molecular and functional phenotypes, as well the size of specific brain regions, are needed to fully characterize the neurodevelopmental effects of BPA exposure, but collectively, these data support prior conclusions that prenatal BPA exposure, even at exposure levels below the current FDA NOAEL, alters sexual differentiation of the brain.

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Disclosure statement

The authors have no conflicts of interest to disclose.

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CHAPTER 5

Conclusions

Since the late 1990s, an enormous amount of data has amassed linking bisphenol A (BPA) exposure to a spectrum of health problems in hormone-sensitive tissues, including early-onset puberty, prostate and mammary gland cancers, and sex-biased neurodevelopmental disorders, among others. The results reported in my dissertation contribute to this body of evidence by demonstrating that the adverse effects of fetal BPA exposure on the brain are apparent as early as postnatal day 1 (PND 1). Moreover, they provide mechanistic insight into how early-life BPA exposure alters neurodevelopment and results in later-life behavioral outcomes including anxiety and deficits in sociality.

Despite strong evidence of BPA's endocrine disrupting properties, the human health risks associated with BPA exposure continue to be debated among the scientific community, regulatory agencies, and the public at large. Some of this controversy undoubtedly stems from discrepancies in the literature (Figure 1), which may simply arise from methodological differences, yet provide ample opportunity to manufacture doubt on the studies that do show harm. A more significant area of contention, however, surrounds the process by which the US Food and Drug Administration (FDA) and other regulatory agencies review and assess available evidence on BPA and evaluate the risk of exposure. For example, the FDA's 2014 Updated Review of Literature and Data on BPA (CAS RN 80-05-7) found no "information in the evaluated studies to prompt a revision of FDA's safety assessment of BPA in food packaging at this time." Yet, a majority of the studies reviewed were dismissed from

consideration and deemed inadequate because they didn't adhere to Good Laboratory Practice (GLP) standards (guidelines that govern the process by which laboratory studies are planned, performed, monitored, and archived) and weren't specifically designed for risk assessment purposes. Accordingly, the FDA maintains the position that current exposure levels are not likely to be harmful. In some cases, this strict method of review has eliminated all of the published literature from evaluation and left only industry-contracted studies in the risk assessment, which overwhelmingly conclude BPA is benign. This has frustrated academic scientists and exacerbated the highly divisive debate about BPA regulation.

To address these controversies, the National Institutes of Environmental Health Sciences (NIEHS), the National Toxicology Program (NTP), and the FDA National Center for Toxicological research (NCTR) developed an unprecedented research model known as the Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA). CLARITY-BPA aimed to expand a 2-year chronic toxicity study by examining a wide range of BPA doses and incorporating hypothesis-driven mechanistic studies conducted by academic researchers [8-10]. The chronic toxicity study was conducted under GLP regulations at NCTR and biological tissue samples from that study were shared and assessed blindly by academic researchers. Although the university-based research is still ongoing, data from the chronic guideline toxicity study is scheduled to be publicly available in 2018.

CLARITY-BPA offers a novel model for integrating guideline-compliant and academic studies, enhancing quality control, and incorporating new methods and/or endpoints in risk assessment by regulatory agencies. As the first study of its kind, this

collaborative effort was not without pitfalls and controversy. For instance, the animal model (NCTR Sprague-Dawley rat) and the use of direct gavage dosing generated considerable debate among a large number of consortium participants because of concerns about stress to the animals. Frequent in-person meetings and conference calls among consortium participants were critical to facilitate open communication and address research issues. Overall, by participating in this collaborative program, the FDA is showing a willingness to work towards a comprehensive, integrated assessment of the health effects of BPA and to be more inclusive about the data it uses for regulatory decision-making.

The studies presented in Chapters 2 - 4 of this dissertation represent a portion of the data obtained under the CLARITY-BPA program and explore the impact of early-life BPA exposure on sex-specific brain organization and gene expression in the neonate and juvenile NCTR-SD. As a whole, the literature clearly shows an association between developmental BPA exposure and disruption of sexually dimorphic social and anxiety behaviors, but the molecular underpinnings of these behavioral outcomes remain poorly understood. Classically, BPA is considered estrogenic and thought to disrupt genomic actions mediated by nuclear estrogen receptors (ERα and β). However, the binding affinity of BPA for ERα and ERβ is approximately 10,000 - 100,000 fold lower than endogenous estradiol [11-13], which suggests that BPA may target signaling pathways upstream or downstream of estradiol to produce effects consistent with an estrogenic mode of action. Recent evidence demonstrates that early-life BPA exposure can alter the expression of ER mRNA in the brain by modifying DNA methylation patterns [14, 15]. In addition, BPA has a low binding

affinity for other steroid receptors, including thyroid and androgen receptors [16, 17], and has been shown to have rapid, non-genomic actions via membrane-bound ERs [18-20]. These diverse modes of action emphasize the multiple and complex mechanisms by which BPA can affect the brain and behavior across the lifespan.

In order to identify mechanistic changes that precede and underlie the neurobehavioral effects associated with developmental BPA exposure, the studies in Chapters 2 and 3 examined the impact of prenatal BPA exposure on the transcriptomes of the hippocampus, hypothalamus, and the amygdala at postnatal day 1(PND 1). An economically feasible approach, qRT-PCR, was used to assess the expression levels of *a priori*-selected candidate genes in males and females prenatally exposed to a wide range of BPA doses (2.5, 25, 250, 2500, and 25000 μg/kg body weight (bw)/day). Non-linear, dose-dependent effects on gene expression were observed, a finding consistent with what is frequently observed for many endocrine endpoints. Although the molecular and biochemical mechanisms underlying this type of dose-response remain poorly understood, they are not unexpected and likely reflect the intersection of multiple responses across several levels of biological organization [21-23].

Consistent with prior literature and my hypothesis that BPA would alter genes and pathways fundamental to sex-specific affective behaviors, the results from Chapters 2 and 3 provide further evidence that developmental BPA exposure disrupts the organization of oxytocin and vasopressin systems and mRNA expression of ERα and ERβ. Effects of prenatal BPA exposure on the PND 1 hippocampal transcriptome were limited but more

pronounced in males. In contrast, BPA-induced alterations in gene expression detected by RNAseq were most robust and extensive in the male hypothalamus and female amygdala. Within the female amygdala, BPA-related transcriptional changes were moderately concordant with the effects of the reference estrogen (17α-ethinyl-estradiol), suggesting that at least some outcomes were consistent with an "estrogenic" mode of action; however, other mechanisms are likely involved (see Chapter 3 for discussion). Additionally, pathway-based analysis of the female amygdalar transcriptomic data revealed activation of a number of pathways involved in neuronal development and synaptic transmission by both the 25 and 250 μg BPA/kg bw/day doses. As demonstrated in early-life stress literature, environmental insult can alter activity-dependent synaptic refinement in the amygdala and result in impaired affective behaviors later in life [24-28]. Thus, this novel action of BPA in the amygdala may be one mechanism by which BPA can disrupt behavioral outcomes in a sex-specific manner, a possibility that should be followed up in future studies. Lastly, to my knowledge, the studies described in Chapters 2 and 3 are the first to characterize sex-differences in the full amygdalar and hippocampal transcriptomes at PND 1 and so they provide fundamental, new information about sex-specific gene expression patterns in the neonate amygdala and hippocampus.

Findings presented in Chapter 4 confirmed that perinatal BPA exposure could disrupt sexual differentiation of the anteroventral periventricular nucleus (AVPV) by enhancing AVPV volume in males and females. Presumably, these effects resulted from BPA action on ERs. Numerous studies, including my own, indicate that developmental BPA exposure

disrupts expression of ER mRNA, and data suggests this may be mediated by epigenetic mechanisms [14, 15]. Future studies that examine the sex-specific effects of BPA on a broad range of epigenetic writers, readers, and erasers within the AVPV will provide insight on the mechanistic basis of this outcome. The results from Chapter 4 are largely concordant with a body of literature showing BPA-related effects on reproductive behavior and physiology [29, 30]; however, these endpoints were not assessed in the CLARITY-BPA consortium. While the expected sex-differences in volume were detected in the sexually dimorphic nucleus and the posterodorsal portion of the medial amygdala, no appreciable effects of perinatal BPA exposure were found (see Chapter 4 for discussion).

Early-life BPA exposure induced sex-, brain region-, and dose-specific effects on gene expression in neonates and the volume of sexually dimorphic nuclei in juveniles. While the functional and physiological significance of these outcomes were not assessed, they provide further insight into the mechanisms by which developmental BPA exposure may impair affective behaviors in a sex-specific manner. A deeper understanding of the basic neural and molecular mechanisms underlying complex behaviors, such as activity, sociability, and executive function, is required to fully comprehend the effects of BPA on neurodevelopment and the mechanisms by which developmental BPA exposure can result in adverse behavioral outcomes later in life. Moreover, it should be emphasized that sexual differentiation is complex, multifaceted, and occurs independently in different brain regions, such that the downstream effects of a single steroid hormone can vary markedly in different regions and at different times throughout development [31-33]. This highlights the

importance of sex, brain region, and age as biological variables that should be incorporated into all subsequent endocrine disrupting chemical research on neurobehavioral endpoints.

Overall, my data show that the developing nervous system is sensitive to BPA exposure and add to a growing body of literature showing neurodevelopmental effects of BPA, at levels below the current FDA No Observed Adverse Effect Level (NOAEL) of 5 mg/kg bw/day. The CLARITY-BPA research program confirmed what we already knew: BPA is a neuroendocrine disruptor. Although a lot remains to be discovered in terms of mechanisms, there is more than enough data to make sound conclusions about the threat developmental BPA exposure poses to human health. Because of public concern about the risks of BPA exposure, especially for pregnant women and children, several US states have already banned the use of BPA in multiple products such as baby bottles, sippy cups, and reusable food containers, and some companies have voluntarily removed BPA from their products. However, BPA remains a common component of the epoxy resin that lines the interior of canned foods, such as soup and vegetables (information available at http://ipen.org/documents/introduction-endocrine-disrupting-chemicals-edcs). In order to mitigate the risks of BPA exposure, the federal government has enough information to take immediate action and ban BPA from all food packaging. There will never be unequivocal evidence that BPA causes neurobehavioral disorders, nor should there be if corrective actions are precautionary and preventative. Nevertheless, establishing a precise relationship between developmental BPA exposure and changes in the brain in behavior remains a scientific endeavor worth pursing. Future BPA studies will create a foundation on which to explore

how exposure to other EDCs alters socioemotional behaviors and related, coordinating, pathways.

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CHAPTER 5 FIGURE

Figure 1

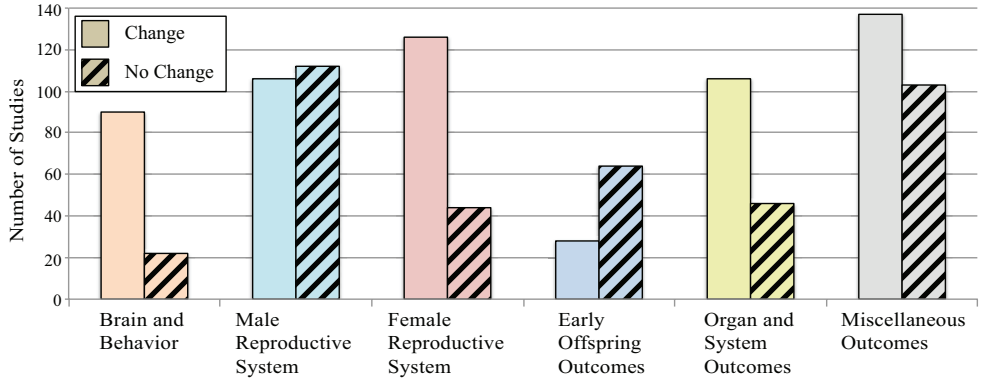


Figure 1: Variability of BPA data across organ systems. Graph was generated using data from The Endocrine Disruption Exchange (TEDX) Low-Dose Bisphenol A project, which compared 391 in vitro and in vivo studies published prior to 2009 that evaluated BPA exposure at ≤ 1 mg/kg/day. Notably, while data was less consistent for other organ systems and outcomes the majority of studies reported BPA-related impacts on the brain and behavior.

APPENDIX 1

Chapter 2 Supplementary Figures and Tables

Supplemental Table 1. RNA-seq analysis of differentially expressed hippocampal genes

Supplemental Table 1. RNA-seq analysis of differentially expressed hippocampal genes

Supplemental Table 1a. BPA exposed females vs control females

Significantly (padj ≤ 0.05) altered genes in 2.5BPA ♀ vs. Control ♀

Gene Symbol	Description	Fold Change	log2FC	p value	padj
Hdlbp	high density lipoprotein binding protein	-1.332	-0.414	1.500E-06	0.013
Clk4	CDC-like kinase 4	1.646	0.719	1.600E-05	0.036
Plrg1	pleiotropic regulator 1	1.359	0.443	2.080E-05	0.036
Thoc1	THO complex 1	1.581	0.661	2.380E-05	0.036
Rmnd1	required for meiotic nuclear division 1 homolog	1.342	0.424	2.820E-05	0.036
Rsrc2	arginine and serine rich coiled-coil 2	1.452	0.538	2.970E-05	0.036
Krr1	small subunit processome component homolog	1.362	0.446	3.550E-05	0.036
Slc25a36l1	solute carrier family 25 (pyrimidine nucleotide carrier), member 36-like 1	1.490	0.575	4.030E-05	0.036
Exosc7	exosome component 7	1.410	0.496	4.080E-05	0.036
Eng	endoglin	-1.520	-0.604	4.300E-05	0.036
Trappc9	trafficking protein particle complex 9	-1.358	-0.441	4.950E-05	0.038
Luc7l3	LUC7-like 3 pre-mRNA splicing factor	1.590	0.669	6.700E-05	0.047
ENSRNOG00000017758	similar to NICE-3	1.331	0.412	7.450E-05	0.048

Significantly (padj ≤ 0.05) altered genes in 2500BPA ♀ vs. Control ♀

None

Supplemental Table 1b. BPA exposed males vs control males

Significantly (padj ≤ 0.05) altered genes in 2.5BPA ♂ vs. Control ♂

Gene Symbol	Description	Fold Change	log2FC	p value	padj
Ruvbl2	RuvB-like AAA ATPase 2	-1.285	-0.362	6.65E-07	0.014

Significantly (padj ≤ 0.05) altered genes in 2500BPA ♂ vs. Control ♂

Gene Symbol	Description	Fold Change	log2FC	p value	padj
Nradd	neurotrophin receptor associated death domain	-1.754	-0.811	1.760E-06	0.012
Edem1	ER degradation enhancing alpha-mannosidase like protein 1	1.695	0.761	1.800E-06	0.012
Cchcr1	coiled-coil alpha-helical rod protein 1	-1.591	-0.670	4.610E-06	0.019
Ppp2r5c	protein phosphatase 2, regulatory subunit B', gamma	1.320	0.400	6.000E-06	0.019
Elovl1	ELOVL fatty acid elongase 1	-1.538	-0.621	1.860E-05	0.047
Actr2	ARP2 actin-related protein 2 homolog	1.506	0.591	2.700E-05	0.048
Lrrc71	leucine rich repeat containing 71	-1.494	-0.579	3.280E-05	0.048
Opcml	Opcml	1.583	0.663	3.390E-05	0.048
Cyb5b	Cyb5b	1.352	0.435	3.430E-05	0.048
Sfxn1	Sfxn1	1.348	0.431	3.760E-05	0.048

Supplemental Table 2. RNA-seq analysis of differentially expressed hypothalamic genes

Supplemental Table 2. RNA-seq analysis of differentially expressed hypothalamic genes

Supplemental Table 2a. BPA exposed females vs control females

Significantly (padj ≤ 0.05) altered genes in 2.5BPA ♀ vs. Control ♀

Gene Symbol	Description	Fold Change	log2FC	p value	padj
Csap1	common salivary protein 1	-1.308	-0.387	1.550E-06	0.033

Significantly (padj ≤ 0.05) altered genes in 2500BPA ♀ vs. Control ♀

Sparcl1	SPARC like 1	-1.622	-0.698	5.130E-08	1.080E-03
Csap1	common salivary protein 1	-1.321	-0.402	6.460E-07	6.800E-03

Supplemental Table 2b. BPA exposed males vs control males

Significantly (padj ≤ 0.05) altered genes in 2.5BPA ♂ vs. Control ♂

Gene Symbol	Description	Fold Change	log2FC	p value	padj
Ythdc2	YTH domain containing 2	1.501	0.586	5.300E-09	5.820E-05
Ipo4	importin 4	-1.303	-0.382	3.450E-08	1.900E-04
Mat2a	methionine adenosyltransferase II, alpha	1.446	0.532	1.260E-07	4.600E-04
Akap10	A kinase (PRKA) anchor protein 10	1.389	0.474	3.510E-07	8.470E-04
Zfp317	zinc finger protein 317	1.494	0.579	3.850E-07	8.470E-04
Rictor	rapamycin-insensitive companion of mTOR	1.416	0.502	1.740E-06	3.190E-03
Agap3	ArfGAP with GTPase domain, ankyrin repeat and PH domain 3	-1.318	-0.398	5.410E-06	3.500E-03
C1galt1	core 1 synthase, glycoprotein-N-acetylgalactosamine 3-beta-galactosyltransferase, 1	1.488	0.573	5.030E-06	3.500E-03
Dpy19l4	dpy-19-like 4 (C. elegans)	1.461	0.547	5.300E-06	3.500E-03
Drap1	Dr1 associated protein 1 (negative cofactor 2 alpha)	-1.302	-0.381	3.660E-06	3.500E-03
Lcor	ligand dependent nuclear receptor corepressor	1.544	0.627	3.530E-06	3.500E-03
Mtmr10	myotubularin related protein 10	1.387	0.472	5.180E-06	3.500E-03
Ndufb10	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 10	-1.373	-0.457	3.820E-06	3.500E-03
Rnf170	ring finger protein 170	1.376	0.460	5.210E-06	3.500E-03
Sp1	Sp1 transcription factor	1.417	0.503	5.090E-06	3.500E-03
Ttc39b	Fras1 related extracellular matrix 1	1.494	0.579	4.440E-06	3.500E-03
Uhmk1	U2AF homology motif (UHM) kinase 1	1.422	0.508	5.210E-06	3.500E-03
Atad5	ATPase family, AAA domain containing 5	1.402	0.487	9.630E-06	4.660E-03
Carf	calcium response factor	1.424	0.510	7.810E-06	4.660E-03
Csk	c-src tyrosine kinase	-1.169	-0.225	1.020E-05	4.660E-03
DMD	dystrophin, muscular dystrophy	1.386	0.471	9.800E-06	4.660E-03
Eml2	echinoderm microtubule associated protein like 2	-1.347	-0.430	9.710E-06	4.660E-03
Esyt2	extended synaptotagmin 2	1.386	0.471	9.160E-06	4.660E-03
Fam35a	family with sequence similarity 35, member A	1.472	0.558	8.280E-06	4.660E-03
RGD1562390	similar to RGD, leucine-rich repeat, tropomodulin and proline-rich containing protein	-1.355	-0.438	1.100E-05	4.840E-03
Evi5l	ecotropic viral integration site 5-like	-1.235	-0.305	1.260E-05	5.150E-03
Foxp4	forkhead box P4	-1.370	-0.454	1.310E-05	5.150E-03
Gpr162	G protein-coupled receptor 162	-1.286	-0.363	1.270E-05	5.150E-03
Lrrc4b	leucine rich repeat containing 4B	-1.342	-0.424	1.420E-05	5.180E-03
Tmem132e	transmembrane protein 132E	-1.432	-0.518	1.410E-05	5.180E-03
Dennd4c	DENN domain containing 4C	1.420	0.506	1.990E-05	7.060E-03
Has2	hyaluronan synthase 2	1.456	0.542	2.250E-05	7.720E-03

Supplemental Table 2 (continued)

Atm	ataxia telangiectasia mutated homolog (human)	1.383	0.468	2.710E-05	8.770E-03
Slc32a1	solute carrier family 32 (GABA vesicular transporter), member 1	-1.501	-0.586	2.650E-05	8.770E-03
ATP11B	ATPase, class VI, type 11B	1.421	0.507	2.880E-05	8.900E-03
Gtf3c3	general transcription factor IIIC, polypeptide 3	1.344	0.426	3.000E-05	8.900E-03
Srrd	SRR1 domain containing	-1.408	-0.494	2.980E-05	8.900E-03
Aatk	apoptosis-associated tyrosine kinase	-1.275	-0.350	3.370E-05	9.490E-03
Rbm15b	RNA binding motif protein 15B	-1.247	-0.319	3.360E-05	9.490E-03
Scn9a	sodium channel, voltage-gated, type IX, alpha	1.445	0.531	3.500E-05	9.610E-03
Yipf6	Yip1 domain family, member 6	1.452	0.538	3.910E-05	1.050E-02
Adrm1	adhesion regulating molecule 1	-1.263	-0.337	4.070E-05	1.060E-02
Tubg1	tubulin, gamma 1	-1.307	-0.386	4.170E-05	1.060E-02
Cacnb2	calcium channel, voltage-dependent, beta 2 subunit	1.271	0.346	4.380E-05	1.090E-02
Fam179b	family with sequence similarity 179, member B	1.345	0.428	4.720E-05	1.150E-02
Ppp1r9b	protein phosphatase 1, regulatory subunit 9B	-1.204	-0.268	4.880E-05	1.170E-02
Poglut1	protein O-glucosyltransferase 1	1.322	0.403	5.050E-05	1.180E-02
Nufip2	FMR1 interacting protein 2	1.414	0.500	5.470E-05	1.190E-02
Hdac5	histone deacetylase 5	-1.337	-0.419	5.310E-05	1.190E-02
Ssbp3	single stranded DNA binding protein 3	-1.222	-0.289	5.520E-05	1.190E-02
Zdhhc15	zinc finger, DHHC-type containing 15	1.410	0.496	5.290E-05	1.190E-02
Dph6	diphthamine biosynthesis 6	1.361	0.445	6.070E-05	1.280E-02
Foxo6	forkhead box O6	-1.347	-0.430	6.160E-05	1.280E-02
RGD1307365	similar to KIAA1009 protein	1.428	0.514	6.380E-05	1.300E-02
Cacnb1	calcium channel, voltage-dependent, beta 1 subunit	-1.290	-0.367	6.860E-05	1.310E-02
Grik2	glutamate receptor, ionotropic, kainate 2	1.337	0.419	6.910E-05	1.310E-02
Irf2bp1	interferon regulatory factor 2 binding protein 1	-1.282	-0.358	6.930E-05	1.310E-02
Lrrn2	leucine rich repeat neuronal 2	-1.283	-0.359	6.540E-05	1.310E-02
Pianp	PILR alpha associated neural protein	-1.330	-0.411	7.050E-05	1.310E-02
Cilp2	cartilage intermediate layer protein 2	-1.439	-0.525	7.250E-05	1.330E-02
ATG101	autophagy related 101	-1.207	-0.271	7.870E-05	1.370E-02
Mta1	metastasis associated 1	-1.207	-0.271	7.830E-05	1.370E-02
Oaz1	ornithine decarboxylase antizyme 1	-1.231	-0.300	8.160E-05	1.370E-02
Setx	senataxin	1.324	0.405	8.240E-05	1.370E-02
Trappc8	trafficking protein particle complex 8	1.318	0.398	7.730E-05	1.370E-02
Wdr18	WD repeat domain 18	-1.299	-0.377	8.070E-05	1.370E-02
Lmtk3	lemur tyrosine kinase 3	-1.366	-0.450	8.400E-05	1.380E-02
Rnf208	ring finger protein 208	-1.347	-0.430	8.680E-05	1.380E-02
Zfp575	zinc finger protein 575	-1.391	-0.476	8.570E-05	1.380E-02
Bmyc	brain expressed myelocytomatosis oncogene	-1.354	-0.437	9.540E-05	1.500E-02
Cd2ap	CD2-associated protein	1.371	0.455	1.000E-04	1.530E-02
RGD1309995	similar to CG13957-PA	1.404	0.490	9.880E-05	1.530E-02
Clcc1	chloride channel CLIC-like 1	1.245	0.316	1.080E-04	1.540E-02
Cotl1	coactosin-like 1 (Dictyostelium)	-1.388	-0.473	1.060E-04	1.540E-02
Fzr1	fizzy/cell division cycle 20 related 1 (Drosophila)	-1.317	-0.397	1.070E-04	1.540E-02
Ndufs7	NADH dehydrogenase (ubiquinone) Fe-S protein 7	-1.293	-0.371	1.060E-04	1.540E-02
Pls3	plastin 3 (T-isoform)	1.360	0.444	1.030E-04	1.540E-02
Polr2e	polymerase (RNA) II (DNA directed) polypeptide E, 25kDa	-1.254	-0.326	1.090E-04	1.540E-02
Hcn2	hyperpolarization activated cyclic nucleotide-gated potassium channel 2	-1.308	-0.387	1.160E-04	1.560E-02
Katnbl1	katanin regulatory subunit B1 like 1	1.428	0.514	1.120E-04	1.560E-02
Lrfn3	leucine rich repeat and fibronectin type III domain containing 3	-1.337	-0.419	1.170E-04	1.560E-02
RGD1562608	similar to KIAA1328 protein	1.262	0.336	1.150E-04	1.560E-02

Supplemental Table 2 (continued)

Atxn3	ataxin 3	1.445	0.531	1.190E-04	1.580E-02
Cdk7	cyclin-dependent kinase 7	1.359	0.443	1.210E-04	1.580E-02
Zbtb25	zinc finger and BTB domain containing 25	1.395	0.480	1.250E-04	1.620E-02
Cdc37	cell division cycle 37 homolog (S. cerevisiae)	-1.246	-0.317	1.280E-04	1.630E-02
Ergic3	ERGIC and golgi 3	-1.234	-0.303	1.300E-04	1.630E-02
Krit1	KRIT1, ankyrin repeat containing	1.433	0.519	1.290E-04	1.630E-02
Uba52	ubiquitin A-52 residue ribosomal protein fusion product 1	-1.329	-0.410	1.390E-04	1.710E-02
Atad2	ATPase family, AAA domain containing 2	1.461	0.547	1.430E-04	1.740E-02
Tnk2	tyrosine kinase, non-receptor, 2	-1.283	-0.359	1.450E-04	1.750E-02
Casp8ap2	caspase 8 associated protein 2	1.414	0.500	1.510E-04	1.800E-02
Zfp483	zinc finger protein 483	1.430	0.516	1.550E-04	1.830E-02
Akap17a	A-kinase anchoring protein 17A	-1.204	-0.268	1.590E-04	1.860E-02
Zfp157	zinc finger protein 157	1.380	0.465	1.690E-04	1.950E-02
Pick1	protein interacting with PRKCA 1	-1.255	-0.328	1.740E-04	1.990E-02
Acot7	acyl-CoA thioesterase 7	-1.296	-0.374	2.630E-04	2.020E-02
Actr5	ARP5 actin-related protein 5 homolog (yeast)	-1.274	-0.349	2.430E-04	2.020E-02
Aip	aryl-hydrocarbon receptor-interacting protein	-1.271	-0.346	1.960E-04	2.020E-02
Atl3	atlastin GTPase 3	1.402	0.488	2.100E-04	2.020E-02
BC005561	cDNA sequence BC005561	1.411	0.497	1.950E-04	2.020E-02
Clip2	CAP-GLY domain containing linker protein 2	-1.202	-0.266	1.960E-04	2.020E-02
Ctdspl2	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase like 2	1.364	0.448	2.160E-04	2.020E-02
Dact3	diacylglycerol lipase, beta	-1.310	-0.390	2.330E-04	2.020E-02
Dlgap4	discs, large homolog-associated protein 4 (Drosophila)	-1.259	-0.332	1.800E-04	2.020E-02
Dtx1	deltex E3 ubiquitin ligase 1	-1.259	-0.332	2.720E-04	2.020E-02
Eid2	EP300 interacting inhibitor of differentiation 2	-1.383	-0.468	2.450E-04	2.020E-02
Eml5	echinoderm microtubule associated protein like 5	1.344	0.427	2.560E-04	2.020E-02
Fbxl15	F-box and leucine-rich repeat protein 15	-1.352	-0.435	2.230E-04	2.020E-02
Gas2	growth arrest-specific 2	1.370	0.454	2.700E-04	2.020E-02
Ints2	integrator complex subunit 2	1.358	0.442	2.710E-04	2.020E-02
Itch	itchy E3 ubiquitin protein ligase homolog (mouse)	1.366	0.450	2.540E-04	2.020E-02
Lcorl	ligand dependent nuclear receptor corepressor-like	1.370	0.454	2.190E-04	2.020E-02
Map7d1	MAP7 domain containing 1	-1.223	-0.291	2.150E-04	2.020E-02
Mdm4	Mdm4 p53 binding protein homolog (mouse)	1.398	0.483	1.920E-04	2.020E-02
Med13	mediator complex subunit 13	1.333	0.415	2.390E-04	2.020E-02
Mitd1	MIT, microtubule interacting and transport, domain containing 1	1.415	0.501	2.750E-04	2.020E-02
Mrpl52	mitochondrial ribosomal protein L52	-1.320	-0.401	2.320E-04	2.020E-02
Ndufa13	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13	-1.240	-0.310	1.980E-04	2.020E-02
Nlgn2	neuroligin 2	-1.341	-0.423	2.620E-04	2.020E-02
Nomo1	nodal modulator 1	-1.176	-0.234	2.250E-04	2.020E-02
Nsmaf	neutral sphingomyelinase (N-SMase) activation associated factor	1.290	0.367	2.400E-04	2.020E-02
Numbl	numb homolog (Drosophila)-like	-1.330	-0.411	2.220E-04	2.020E-02
Osgin2	oxidative stress induced growth inhibitor family member 2	1.334	0.416	2.230E-04	2.020E-02
PCBP2	poly(rC) binding protein 2	-1.176	-0.234	2.130E-04	2.020E-02
PHF20L1	PHD finger protein 20-like 1	1.317	0.397	2.500E-04	2.020E-02
Plod2	procollagen lysine, 2-oxoglutarate 5-dioxygenase 2	1.423	0.509	2.550E-04	2.020E-02
Podxl2	podocalyxin-like 2	-1.266	-0.340	2.320E-04	2.020E-02
Ppp2r5d	protein phosphatase 2, regulatory subunit B', delta isoform	-1.162	-0.217	2.750E-04	2.020E-02
Ppwd1	peptidylprolyl isomerase domain and WD repeat	1.385	0.470	2.540E-04	2.020E-02

Supplemental Table 2 (continued)

	containing 1				
Prr3	proline rich 3	-1.207	-0.271	2.410E-04	2.020E-02
Psme4	proteasome (prosome, macropain) activator subunit 4	1.363	0.447	2.750E-04	2.020E-02
Pvrl1	poliovirus receptor-related 1	-1.342	-0.424	2.680E-04	2.020E-02
Rnaseh2a	ribonuclease H2, subunit A	-1.278	-0.354	2.430E-04	2.020E-02
Rnf10	ring finger protein 10	-1.218	-0.284	2.440E-04	2.020E-02
Scand1	SCAN domain-containing 1	-1.359	-0.443	2.370E-04	2.020E-02
Scn1a	sodium channel, voltage-gated, type I, alpha	1.309	0.388	2.120E-04	2.020E-02
Sez6l2	seizure related 6 homolog (mouse)-like 2	-1.301	-0.380	2.440E-04	2.020E-02
Slc25a16	solute carrier family 25 (mitochondrial carrier, Graves disease autoantigen), member 16	1.333	0.415	2.580E-04	2.020E-02
Snx13	sorting nexin 13	1.376	0.460	2.460E-04	2.020E-02
Syt4	synaptotagmin IV	1.367	0.451	2.100E-04	2.020E-02
Tesk1	testis-specific kinase 1	-1.271	-0.346	2.630E-04	2.020E-02
Trak1	trafficking kinesin protein 1	-1.188	-0.248	1.830E-04	2.020E-02
Vstm2l	V-set and transmembrane domain containing 2 like	-1.364	-0.448	1.890E-04	2.020E-02
Wdtc1	WD and tetratricopeptide repeats 1	-1.246	-0.317	2.520E-04	2.020E-02
Zfp579	zinc finger protein 579	-1.275	-0.350	2.760E-04	2.020E-02
Zfp871	zinc finger protein 871	1.407	0.493	1.790E-04	2.020E-02
Zfp9	zinc finger protein 9	1.373	0.457	2.510E-04	2.020E-02
Zmat1	zinc finger, matrin-type 1	1.362	0.446	2.710E-04	2.020E-02
Zufsp	zinc finger with UFM1-specific peptidase domain	1.313	0.393	2.420E-04	2.020E-02
Kcnt2	potassium channel, subfamily T, member 2	1.316	0.396	2.820E-04	2.050E-02
Bok	BCL2-related ovarian killer	-1.260	-0.333	2.890E-04	2.080E-02
Btaf1	BTAF1 RNA polymerase II, B-TFIID transcription factor-associated, (Mot1 homolog, S. cerevisiae)	1.363	0.447	2.930E-04	2.080E-02
Cntfr	ciliary neurotrophic factor receptor	-1.370	-0.454	2.900E-04	2.080E-02
MBD3	methyl-CpG binding domain protein 3	-1.299	-0.377	2.910E-04	2.080E-02
Eif6	eukaryotic translation initiation factor 6, pseudogene 1	-1.173	-0.230	3.010E-04	2.120E-02
Tmem87b	transmembrane protein 87B	1.329	0.410	3.080E-04	2.150E-02
Ahctf1	AT hook containing transcription factor 1	1.340	0.422	3.260E-04	2.200E-02
Arid4a	AT rich interactive domain 4A (Rbp1 like)	1.356	0.439	3.220E-04	2.200E-02
Mios	missing oocyte, meiosis regulator, homolog (Drosophila)	1.374	0.458	3.160E-04	2.200E-02
Prpf39	PRP39 pre-mRNA processing factor 39 homolog (S. cerevisiae)	1.423	0.509	3.180E-04	2.200E-02
Ranbp2	RAN binding protein 2	1.418	0.504	3.270E-04	2.200E-02
Smarcb1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	-1.220	-0.287	3.230E-04	2.200E-02
Tmem168	transmembrane protein 168	1.399	0.484	3.300E-04	2.200E-02
Trim28	tripartite motif-containing 28	-1.157	-0.211	3.310E-04	2.200E-02
Fam127b	family with sequence similarity 127, member B	-1.261	-0.334	3.380E-04	2.230E-02
Hmx3	H6 family homeobox 3	-1.429	-0.515	3.380E-04	2.230E-02
Zfp715	protein Zfp715 (Fragment)	1.282	0.358	3.470E-04	2.240E-02
Ncapg	non-SMC condensin I complex, subunit G	1.433	0.519	3.430E-04	2.240E-02
Phc3	polyhomeotic homolog 3 (Drosophila)	1.327	0.408	3.470E-04	2.240E-02
Ctbp1	C-terminal binding protein 1	-1.190	-0.251	3.530E-04	2.250E-02
Mvb12b	multivesicular body subunit 12B	-1.267	-0.341	3.570E-04	2.250E-02
Nvl	nuclear VCP-like	1.392	0.477	3.570E-04	2.250E-02
Slc10a4	solute carrier family 10 (sodium/bile acid cotransporter family), member 4	-1.426	-0.512	3.510E-04	2.250E-02
Cpne3	copine III	1.354	0.437	3.650E-04	2.260E-02
Ttf1	transcription termination factor, RNA polymerase I	1.361	0.445	3.600E-04	2.260E-02

Supplemental Table 2 (continued)

Zfp449	zinc finger protein 449	1.345	0.428	3.650E-04	2.260E-02
Atl2	atlastin GTPase 2	1.330	0.411	3.800E-04	2.300E-02
Hcfc1r1	host cell factor C1 regulator 1 (XPO1-dependent)	-1.429	-0.515	3.760E-04	2.300E-02
Hectd2	HECT domain containing 2	1.369	0.453	3.840E-04	2.300E-02
Rfc1	replication factor C (activator 1) 1	1.220	0.287	3.840E-04	2.300E-02
Samd10	sterile alpha motif domain containing 10	-1.241	-0.312	3.760E-04	2.300E-02
Secisbp2l	SECIS binding protein 2-like	1.257	0.330	3.860E-04	2.300E-02
Stub1	STIP1 homology and U-Box containing protein 1	-1.275	-0.350	3.790E-04	2.300E-02
Gnaz	guanine nucleotide binding protein (G protein), alpha z polypeptide	-1.261	-0.334	3.880E-04	2.310E-02
Fam76a	family with sequence similarity 76, member A	1.329	0.410	3.920E-04	2.320E-02
Fam19a5	family with sequence similarity 19 (chemokine (C-C motif)-like), member A5	-1.229	-0.298	3.960E-04	2.330E-02
Zfp560	zinc finger protein 560	1.343	0.425	3.980E-04	2.330E-02
Nr2f6	nuclear receptor subfamily 2, group F, member 6	-1.295	-0.373	4.140E-04	2.380E-02
Rhob	ras homolog gene family, member B	-1.325	-0.406	4.130E-04	2.380E-02
Zfp192	zinc finger protein 192	1.417	0.503	4.120E-04	2.380E-02
Rps6kb1	ribosomal protein S6 kinase, 70kDa, polypeptide 1	1.326	0.407	4.180E-04	2.390E-02
AABR07054370.1	AABR07054370.1	-1.234	-0.303	4.320E-04	2.430E-02
Lmna	lamin A	-1.261	-0.334	4.300E-04	2.430E-02
Papolg	poly(A) polymerase gamma	1.374	0.458	4.290E-04	2.430E-02
Dzip3	DAZ interacting zinc finger protein 3	1.317	0.397	4.600E-04	2.470E-02
ENSRNOG00000017708	uncharacterized protein	-1.301	-0.380	4.410E-04	2.470E-02
Npat	nuclear protein, ataxia-telangiectasia locus	1.376	0.460	4.640E-04	2.470E-02
Ogdhl	oxoglutarate dehydrogenase-like	-1.305	-0.384	4.590E-04	2.470E-02
Pik3c2a	phosphoinositide-3-kinase, class 2, alpha polypeptide	1.399	0.484	4.480E-04	2.470E-02
Rbm28	RNA binding motif protein 28	1.293	0.371	4.550E-04	2.470E-02
Sf3b4	splicing factor 3b, subunit 4	-1.246	-0.317	4.470E-04	2.470E-02
Thra	thyroid hormone receptor alpha	-1.257	-0.330	4.610E-04	2.470E-02
Ubxn6	UBX domain protein 6	-1.234	-0.303	4.500E-04	2.470E-02
Vegfb	vascular endothelial growth factor B	-1.388	-0.473	4.620E-04	2.470E-02
Xpo4	exportin 4	1.363	0.447	4.520E-04	2.470E-02
Scyl2	SCY1-like 2 (S. cerevisiae)	1.302	0.381	4.690E-04	2.480E-02
Usp37	ubiquitin specific protease 37	1.363	0.447	4.730E-04	2.480E-02
Zfp949	zinc finger protein 949	1.347	0.430	4.710E-04	2.480E-02
Cdk2ap2	CDK2-associated protein 2	-1.361	-0.445	4.760E-04	2.490E-02
Luc7l3	cisplatin resistance-associated overexpressed protein	1.384	0.469	4.870E-04	2.520E-02
Orc3	origin recognition complex, subunit 3	1.295	0.373	4.870E-04	2.520E-02
Prcc	papillary renal cell carcinoma (translocation-associated)	-1.157	-0.210	4.970E-04	2.550E-02
Zfp580	zinc finger protein 580	-1.405	-0.491	4.960E-04	2.550E-02
Ap2a1	adaptor-related protein complex 2, alpha 1 subunit	-1.254	-0.327	5.020E-04	2.560E-02
Pot1	protection of telomeres 1	1.345	0.428	5.110E-04	2.600E-02
Asic1	acid sensing ion channel subunit 1	-1.220	-0.287	5.170E-04	2.620E-02
Cactin	spliceosome C complex subunit	-1.240	-0.310	5.560E-04	2.680E-02
Capn5	calpain 5	-1.254	-0.326	5.510E-04	2.680E-02
Cox5b	cytochrome c oxidase subunit Vb	-1.246	-0.317	5.720E-04	2.680E-02
DAGLB	death-associated protein kinase 3	-1.222	-0.289	5.550E-04	2.680E-02
Fam57b	family with sequence similarity 57, member B	-1.265	-0.339	5.700E-04	2.680E-02
Hdgfrp2	hepatoma-derived growth factor, related protein 2	-1.189	-0.250	5.320E-04	2.680E-02
Hmga1	high mobility group AT-hook 1	-1.340	-0.422	5.640E-04	2.680E-02
Kcnc4	potassium voltage gated channel, Shaw-related subfamily, member 4	-1.318	-0.398	5.360E-04	2.680E-02

Supplemental Table 2 (continued)

Lrfn1	leucine rich repeat and fibronectin type III domain containing 1	-1.322	-0.403	5.560E-04	2.680E-02
Mef2a	myocyte enhancer factor 2a	1.322	0.403	5.610E-04	2.680E-02
Mospd2	motile sperm domain containing 2	1.367	0.451	5.670E-04	2.680E-02
Neurl1a	neuralized E3 ubiquitin protein ligase 1	-1.384	-0.469	5.530E-04	2.680E-02
Sys1	Sys1 golgi trafficking protein	-1.311	-0.391	5.390E-04	2.680E-02
Tia1	TIA1 cytotoxic granule-associated RNA binding protein	1.246	0.317	5.340E-04	2.680E-02
Zfp131	zinc finger protein 131	1.325	0.406	5.640E-04	2.680E-02
ZFP87	zinc finger protein 87	1.407	0.493	5.530E-04	2.680E-02
Zfyve16	zinc finger, FYVE domain containing 16	1.371	0.455	5.490E-04	2.680E-02
Bin1	bridging integrator 1	-1.190	-0.251	5.820E-04	2.710E-02
Irf2bpl	interferon regulatory factor 2 binding protein-like	-1.293	-0.371	5.890E-04	2.710E-02
Klhdc3	kelch domain containing 3	-1.211	-0.276	5.860E-04	2.710E-02
Mrps18a	mitochondrial ribosomal protein S18A	-1.247	-0.319	5.880E-04	2.710E-02
Ubl7	ubiquitin-like 7 (bone marrow stromal cell-derived)	-1.214	-0.280	5.900E-04	2.710E-02
Ptpn4	protein tyrosine phosphatase, non-receptor type 4	1.382	0.467	5.970E-04	2.730E-02
Eif2ak2	eukaryotic translation initiation factor 2-alpha kinase 2	1.371	0.455	6.140E-04	2.740E-02
Gnpda2	glucosamine-6-phosphate deaminase 2	1.376	0.460	6.130E-04	2.740E-02
Pebp1	phosphatidylethanolamine binding protein 1	-1.261	-0.334	6.090E-04	2.740E-02
Stk11	serine/threonine kinase 11	-1.223	-0.290	6.110E-04	2.740E-02
Trim8	tripartite motif-containing 8	-1.208	-0.273	6.070E-04	2.740E-02
Zkscan2	zinc finger with KRAB and SCAN domains 2	1.301	0.380	6.100E-04	2.740E-02
Cacna2d1	calcium channel, voltage-dependent, alpha2/delta subunit 1	1.399	0.484	6.190E-04	2.750E-02
Edf1	endothelial differentiation-related factor 1	-1.323	-0.404	6.230E-04	2.750E-02
Homer1	homer homolog 1 (Drosophila)	1.382	0.467	6.260E-04	2.750E-02
Smc5	structural maintenance of chromosomes 5	1.376	0.460	6.230E-04	2.750E-02
Ap5m1	adaptor-related protein complex 5, mu 1 subunit	1.358	0.442	6.340E-04	2.770E-02
Ankfy1	ankyrin repeat and FYVE domain containing 1	1.296	0.374	6.430E-04	2.800E-02
Exosc5	exosome component 5	-1.283	-0.360	6.470E-04	2.800E-02
Fmnl1	formin-like 1	-1.249	-0.321	6.510E-04	2.800E-02
Rps4y2	ribosomal protein S4, Y-linked 2	-1.406	-0.492	6.540E-04	2.800E-02
Trim3	tripartite motif-containing 3	-1.188	-0.248	6.550E-04	2.800E-02
Wwc3	WWC family member 3	1.340	0.422	6.460E-04	2.800E-02
Eif3h	eukaryotic translation initiation factor 3, subunit H	-1.230	-0.299	6.620E-04	2.810E-02
Elp5	elongator acetyltransferase complex subunit 5	-1.209	-0.274	6.630E-04	2.810E-02
40971	40971	-1.234	-0.303	6.750E-04	2.820E-02
Aspscr1	alveolar soft part sarcoma chromosome region, candidate 1 (human)	-1.240	-0.310	6.750E-04	2.820E-02
Magel2	MAGE-like 2	-1.295	-0.373	6.710E-04	2.820E-02
Suv420h1	suppressor of variegation 4-20 homolog 1 (Drosophila)	1.289	0.366	6.750E-04	2.820E-02
Kbtbd8	kelch repeat and BTB (POZ) domain containing 8	1.404	0.490	6.830E-04	2.840E-02
Strip1	striatin interacting protein 1	-1.164	-0.219	6.870E-04	2.850E-02
Bop1	block of proliferation 1	-1.203	-0.267	7.010E-04	2.890E-02
Chek1	CHK1 checkpoint homolog (S. pombe)	1.377	0.462	7.080E-04	2.910E-02
Paf1	Paf1, RNA polymerase II associated factor, homolog (S. cerevisiae)	-1.170	-0.226	7.100E-04	2.910E-02
Cep95	centrosomal protein 95	1.315	0.395	7.650E-04	2.980E-02
Chm	choroideremia (Rab escort protein 1)	1.370	0.454	7.500E-04	2.980E-02
Clk4	CDC like kinase 4	1.384	0.469	7.530E-04	2.980E-02
Ctdnep1	CTD nuclear envelope phosphatase 1	-1.181	-0.240	7.630E-04	2.980E-02
Jund	Jun D proto-oncogene	-1.382	-0.467	7.620E-04	2.980E-02

Supplemental Table 2 (continued)

Mif	macrophage migration inhibitory factor	-1.371	-0.455	7.410E-04	2.980E-02
Mrpl37	mitochondrial ribosomal protein L37	-1.239	-0.309	7.590E-04	2.980E-02
Phactr3	phosphatase and actin regulator 3	-1.269	-0.344	7.500E-04	2.980E-02
Tnip1	TNFAIP3 interacting protein 1	-1.297	-0.375	7.540E-04	2.980E-02
Tubg2	tubulin, gamma 2	-1.264	-0.338	7.460E-04	2.980E-02
Zfp451	zinc finger protein 451	1.310	0.390	7.480E-04	2.980E-02
Zfp954	zinc finger protein 954	1.301	0.380	7.400E-04	2.980E-02
Zmynd19	zinc finger, MYND-type containing 19	-1.201	-0.264	7.400E-04	2.980E-02
Zzz3	zinc finger, ZZ-type containing 3	1.320	0.400	7.630E-04	2.980E-02
Agap2	ArfGAP with GTPase domain, ankyrin repeat and PH domain 2	-1.247	-0.319	7.830E-04	2.990E-02
Gipc1	GIPC PDZ domain containing family, member 1	-1.229	-0.297	7.900E-04	2.990E-02
Hiatl1	hippocampus abundant transcript-like 1	1.344	0.426	7.960E-04	2.990E-02
Mad2l2	MAD2 mitotic arrest deficient-like 2 (yeast)	-1.255	-0.328	7.980E-04	2.990E-02
Ndufv1	NADH dehydrogenase (ubiquinone) flavoprotein 1	-1.159	-0.213	7.920E-04	2.990E-02
Nup62	nucleoporin 62	-1.159	-0.213	7.870E-04	2.990E-02
Phldb2	pleckstrin homology-like domain, family B, member 2	1.313	0.393	7.910E-04	2.990E-02
Ptms	parathymosin	-1.213	-0.279	7.770E-04	2.990E-02
R3hdm2	R3H domain containing 2	-1.205	-0.269	7.860E-04	2.990E-02
Tmed5	transmembrane emp24 protein transport domain containing 5	1.370	0.454	7.690E-04	2.990E-02
TVP23A	trans-golgi network vesicle protein 23A	-1.194	-0.256	7.870E-04	2.990E-02
Fam135a	family with sequence similarity 135, member A	1.344	0.427	8.060E-04	3.010E-02
Abhd16a	abhydrolase domain containing 16A	-1.259	-0.332	8.280E-04	3.020E-02
Apbb1	amyloid beta (A4) precursor protein-binding, family B, member 1 (Fe65)	-1.171	-0.228	8.350E-04	3.020E-02
Ckb	creatine kinase, brain	-1.289	-0.366	8.360E-04	3.020E-02
Flywch2	FLYWCH family member 2	-1.241	-0.312	8.350E-04	3.020E-02
Mtf2	metal response element binding transcription factor 2	1.358	0.441	8.360E-04	3.020E-02
Noc4l	nucleolar complex associated 4 homolog (S. cerevisiae)	-1.253	-0.325	8.240E-04	3.020E-02
Pcmtd1	protein-L-isoaspartate (D-aspartate) O-methyltransferase domain containing 1	1.323	0.404	8.170E-04	3.020E-02
Prmt2	protein arginine methyltransferase 2	-1.214	-0.280	8.220E-04	3.020E-02
Psmd3	proteasome (prosome, macropain) 26S subunit, non-ATPase, 3	-1.220	-0.287	8.400E-04	3.020E-02
RGD1559904	similar to mKIAA1429 protein	1.331	0.413	8.200E-04	3.020E-02
Zfp853	zinc finger protein 853	-1.291	-0.368	8.340E-04	3.020E-02
Fuz	fuzzy homolog (Drosophila)	-1.260	-0.333	8.450E-04	3.030E-02
B3gat1	beta-1,3-glucuronyltransferase 1 (glucuronosyltransferase P)	-1.214	-0.280	8.670E-04	3.060E-02
Csmd3	CUB and Sushi multiple domains 3	1.317	0.397	8.700E-04	3.060E-02
Glce	glucuronic acid epimerase	1.306	0.385	8.720E-04	3.060E-02
GPX4	glutathione peroxidase 4	-1.217	-0.283	8.580E-04	3.060E-02
Plekhm2	pleckstrin homology domain containing, family M (with RUN domain) member 2	-1.254	-0.326	8.630E-04	3.060E-02
Rock1	Rho-associated coiled-coil containing protein kinase 1	1.351	0.434	8.670E-04	3.060E-02
Uqcr10	ubiquinol-cytochrome c reductase, complex III subunit X	-1.370	-0.454	8.550E-04	3.060E-02
Birc6	tetratricopeptide repeat domain 27	1.305	0.384	8.990E-04	3.080E-02
Gpr149	G protein-coupled receptor 149	1.390	0.475	8.980E-04	3.080E-02
Osgepl1	O-sialoglycoprotein endopeptidase-like 1	1.320	0.401	9.010E-04	3.080E-02
Rc3h2	ring finger and CCCH-type zinc finger domains 2	1.314	0.394	8.870E-04	3.080E-02
Slx4	SLX4 structure-specific endonuclease subunit	-1.221	-0.288	8.800E-04	3.080E-02
Srek1ip1	SREK1-interacting protein 1	1.387	0.472	8.920E-04	3.080E-02

Supplemental Table 2 (continued)

Tacc2	transforming, acidic coiled-coil containing protein 2	-1.182	-0.241	8.990E-04	3.080E-02
Ypel3	yippee-like 3	-1.230	-0.299	8.960E-04	3.080E-02
Hcrtr2	hypocretin (orexin) receptor 2	1.362	0.446	9.210E-04	3.140E-02
Smarcd3	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 3	-1.240	-0.310	9.220E-04	3.140E-02
Ndufb11	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 11	-1.250	-0.322	9.330E-04	3.160E-02
Cox6a1	cytochrome c oxidase, subunit VIa, polypeptide 1	-1.313	-0.393	9.380E-04	3.170E-02
Ap4e1	adaptor-related protein complex 4, epsilon 1 subunit	1.319	0.399	9.510E-04	3.180E-02
Sox12	SRY (sex determining region Y)-box 12	-1.284	-0.361	9.530E-04	3.180E-02
Tbc1d15	TBC1 domain family, member 15	1.323	0.404	9.540E-04	3.180E-02
Wash	WAS protein family homolog 1	-1.211	-0.276	9.480E-04	3.180E-02
Aamp	angio-associated, migratory cell protein	-1.146	-0.197	9.650E-04	3.200E-02
Itgb1	integrin beta 1 (fibronectin receptor beta)	1.264	0.338	9.610E-04	3.200E-02
Palm	paralemmin	-1.296	-0.374	9.660E-04	3.200E-02
Mospd3	motile sperm domain containing 3	-1.202	-0.265	9.760E-04	3.210E-02
Zfp706	zinc finger protein 706	-1.306	-0.385	9.770E-04	3.210E-02
Asic2	acid sensing ion channel subunit 2	-1.308	-0.387	9.920E-04	3.250E-02
Fam131c	family with sequence similarity 131, member C	-1.382	-0.467	1.000E-03	3.260E-02
Sf3b1	splicing factor 3b, subunit 1	1.287	0.364	9.990E-04	3.260E-02
Unc119	UNC-119 homolog (C. elegans)	-1.240	-0.310	9.960E-04	3.260E-02
Diras1	DIRAS family, GTP-binding RAS-like 1	-1.265	-0.339	1.020E-03	3.290E-02
Pdxp	pyridoxal (pyridoxine, vitamin B6) phosphatase	-1.270	-0.345	1.010E-03	3.290E-02
Entpd6	ectonucleoside triphosphate diphosphohydrolase 6	-1.242	-0.313	1.020E-03	3.300E-02
Nup155	nucleoporin 155	1.283	0.360	1.030E-03	3.300E-02
Pkig	protein kinase inhibitor, gamma	-1.241	-0.312	1.030E-03	3.300E-02
Smc2	structural maintenance of chromosomes 2	1.356	0.439	1.030E-03	3.300E-02
Kdm5a	lysine demethylase 5A	1.360	0.444	1.040E-03	3.310E-02
Cntn3	contactin 3 (plasmacytoma associated)	1.392	0.477	1.050E-03	3.330E-02
Cc2d1a	coiled-coil and C2 domain containing 1A	-1.227	-0.295	1.080E-03	3.340E-02
M0R9T0	uncharacterized protein	-1.321	-0.402	1.080E-03	3.340E-02
Fam189a1	similar to Protein KIAA0574	-1.339	-0.421	1.060E-03	3.340E-02
H1fx	H1 histone family, member X	-1.378	-0.463	1.050E-03	3.340E-02
Prelid1	PRELI domain containing 1	-1.251	-0.323	1.060E-03	3.340E-02
Prrc2a	proline-rich coiled-coil 2A	-1.254	-0.326	1.060E-03	3.340E-02
Rnpc3	RNA-binding region (RNP1, RRM) containing 3	1.342	0.424	1.070E-03	3.340E-02
Slit1	slit homolog 1 (Drosophila)	-1.247	-0.319	1.070E-03	3.340E-02
Tram1	translocation associated membrane protein 1	1.298	0.376	1.080E-03	3.340E-02
Ndst3	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 3	1.371	0.455	1.090E-03	3.350E-02
NOL6	nucleolar protein family 6 (RNA-associated)	-1.188	-0.248	1.090E-03	3.350E-02
Rbfa	ribosome binding factor A	-1.233	-0.302	1.090E-03	3.350E-02
Cdc27	cell division cycle 27 homolog (S. cerevisiae)	1.316	0.396	1.100E-03	3.360E-02
Papd4	PAP associated domain containing 4	1.335	0.417	1.100E-03	3.360E-02
Manea	mannosidase, endo-alpha	1.342	0.424	1.120E-03	3.390E-02
TAOK2	TAO kinase 2	-1.152	-0.204	1.110E-03	3.390E-02
Gzf1	GDNF-inducible zinc finger protein 1	1.296	0.374	1.130E-03	3.410E-02
Trdmt1	tRNA aspartic acid methyltransferase 1	1.352	0.435	1.130E-03	3.410E-02
Vps54	vacuolar protein sorting 54 homolog (S. cerevisiae)	1.331	0.413	1.130E-03	3.410E-02
Ehmt2	euchromatic histone lysine N-methyltransferase 2	-1.229	-0.297	1.170E-03	3.450E-02
Ercc6l2	ERCC excision repair 6 like 2	1.274	0.349	1.150E-03	3.450E-02
Hid1	HID1 domain containing	-1.268	-0.343	1.170E-03	3.450E-02
Lrfn4	leucine rich repeat and fibronectin type III domain containing 4	-1.275	-0.350	1.150E-03	3.450E-02

Supplemental Table 2 (continued)

Map3k11	mitogen-activated protein kinase kinase kinase 11	-1.372	-0.456	1.180E-03	3.450E-02
Pnpt1	polyribonucleotide nucleotidyltransferase 1	1.334	0.416	1.150E-03	3.450E-02
Ptov1	prostate tumor overexpressed 1	-1.271	-0.346	1.180E-03	3.450E-02
Sacs	spastic ataxia of Charlevoix-Saguenay (sacsin)	1.326	0.407	1.180E-03	3.450E-02
Sgta	small glutamine-rich tetratricopeptide repeat (TPR)-containing, alpha	-1.263	-0.337	1.170E-03	3.450E-02
Tmub1	transmembrane and ubiquitin-like domain containing 1	-1.280	-0.356	1.170E-03	3.450E-02
Fam69b	family with sequence similarity 69, member B	-1.207	-0.271	1.190E-03	3.470E-02
Tomm40	translocase of outer mitochondrial membrane 40 homolog (yeast)	-1.268	-0.343	1.190E-03	3.470E-02
Agpat1	1-acylglycerol-3-phosphate O-acyltransferase 1 (lysophosphatidic acid acyltransferase, alpha)	-1.305	-0.384	1.220E-03	3.490E-02
Atp5d	ATP synthase, H+ transporting, mitochondrial F1 complex, delta subunit	-1.308	-0.387	1.220E-03	3.490E-02
Fbxl19	F-box and leucine-rich repeat protein 19	-1.200	-0.263	1.210E-03	3.490E-02
Hspbp1	HSPA (heat shock 70kDa) binding protein, cytoplasmic cochaperone 1	-1.236	-0.306	1.200E-03	3.490E-02
Mat2b	methionine adenosyltransferase II, beta	1.326	0.407	1.220E-03	3.490E-02
Snrpd2	small nuclear ribonucleoprotein D2-like	-1.231	-0.300	1.210E-03	3.490E-02
Vsig10l	V-set and immunoglobulin domain containing 10 like	-1.278	-0.354	1.200E-03	3.490E-02
Gmcl1	germ cell-less homolog 1 (Drosophila)	1.319	0.399	1.240E-03	3.520E-02
Papss1	3'-phosphoadenosine 5'-phosphosulfate synthase 1	-1.139	-0.188	1.240E-03	3.520E-02
RGD1306502	similar to hypothetical protein FLJ11193	1.274	0.349	1.230E-03	3.520E-02
Trmt13	tRNA methyltransferase 13 homolog	1.373	0.457	1.240E-03	3.520E-02
Prrt4	similar to hypothetical gene supported by BC063892	-1.287	-0.364	1.250E-03	3.530E-02
Zc3h6	zinc finger CCCH type containing 6	1.339	0.421	1.250E-03	3.530E-02
Sema6b	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6B	-1.261	-0.335	1.260E-03	3.540E-02
Gk	glycerol kinase	1.332	0.414	1.270E-03	3.560E-02
Bcar1	breast cancer anti-estrogen resistance 1	-1.231	-0.300	1.280E-03	3.570E-02
Eef1g	eukaryotic translation elongation factor 1 gamma	-1.138	-0.187	1.310E-03	3.590E-02
LOC257650	hippyragranin	1.355	0.438	1.310E-03	3.590E-02
AABR07043823.2	AABR07043823.2	1.310	0.390	1.290E-03	3.590E-02
Itpk1	inositol 1,3,4-triphosphate 5/6 kinase	-1.247	-0.319	1.310E-03	3.590E-02
Pcbp4	poly(rC) binding protein 4	-1.236	-0.306	1.310E-03	3.590E-02
Rnd3	Rho family GTPase 3	1.319	0.399	1.300E-03	3.590E-02
Slc4a7	solute carrier family 4, sodium bicarbonate cotransporter, member 7	1.296	0.374	1.300E-03	3.590E-02
Ufl1	Ufm1-specific ligase 1	1.268	0.342	1.300E-03	3.590E-02
F8a1	coagulation factor VIII-associated (intronic transcript) 1	-1.239	-0.309	1.320E-03	3.600E-02
Gpr98	G protein-coupled receptor 98	1.375	0.459	1.320E-03	3.600E-02
Nfat5	nuclear factor of activated T-cells 5	1.334	0.416	1.320E-03	3.600E-02
Tdp2	tyrosyl-DNA phosphodiesterase 2	1.352	0.435	1.330E-03	3.610E-02
Acsf3	acyl-CoA synthetase family member 3	-1.241	-0.312	1.340E-03	3.630E-02
Dmxl1	Dmx-like 1	1.327	0.408	1.340E-03	3.630E-02
Zfp382	zinc finger protein 382	1.179	0.238	1.350E-03	3.630E-02
Api5	apoptosis inhibitor 5	1.324	0.405	1.400E-03	3.640E-02
Bai2	brain-specific angiogenesis inhibitor 2	-1.267	-0.341	1.390E-03	3.640E-02
Ccdc97	coiled-coil domain containing 97	-1.241	-0.311	1.390E-03	3.640E-02
Dusp26	dual specificity phosphatase 26 (putative)	-1.266	-0.340	1.380E-03	3.640E-02
Fam178a	family with sequence similarity 178, member A	1.324	0.405	1.380E-03	3.640E-02
Hap1	huntingtin-associated protein 1	-1.227	-0.295	1.400E-03	3.640E-02
Ipp	intracisternal A particle-promoted polypeptide	1.313	0.393	1.370E-03	3.640E-02

Supplemental Table 2 (continued)

Maz	MYC-associated zinc finger protein (purine-binding transcription factor)	-1.306	-0.385	1.360E-03	3.640E-02
Meaf6	MYST/Esa1-associated factor 6	-1.254	-0.327	1.370E-03	3.640E-02
Med25	mediator complex subunit 25	-1.285	-0.362	1.410E-03	3.640E-02
Ndufb7	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7	-1.217	-0.283	1.400E-03	3.640E-02
Ppp1r37	protein phosphatase 1, regulatory subunit 37	-1.268	-0.343	1.410E-03	3.640E-02
RGD1311863	similar to RIKEN cDNA 2410127L17	1.315	0.395	1.390E-03	3.640E-02
Rnf126	ring finger protein 126	-1.312	-0.392	1.360E-03	3.640E-02
Rundc3a	RUN domain containing 3A	-1.281	-0.357	1.400E-03	3.640E-02
Tgfb1i1	transforming growth factor beta 1 induced transcript 1	-1.303	-0.382	1.410E-03	3.640E-02
Wiz	widely-interspaced zinc finger motifs	-1.240	-0.310	1.400E-03	3.640E-02
Zfp386	zinc finger protein 386 (Kruppel-like)	1.348	0.431	1.360E-03	3.640E-02
Angel2	angel homolog 2 (Drosophila)	1.245	0.316	1.460E-03	3.660E-02
C1qtnf4	C1q and tumor necrosis factor related protein 4	-1.349	-0.432	1.440E-03	3.660E-02
Chuk	conserved helix-loop-helix ubiquitous kinase	1.353	0.436	1.450E-03	3.660E-02
Evi5l	protein Evi5l	-1.249	-0.321	1.450E-03	3.660E-02
Epn1	Epsin 1	-1.231	-0.300	1.450E-03	3.660E-02
Lpxn	leupaxin	1.273	0.348	1.440E-03	3.660E-02
Mt3	metallothionein 3	-1.318	-0.398	1.430E-03	3.660E-02
Pelp1	proline, glutamic acid and leucine rich protein 1	-1.149	-0.201	1.450E-03	3.660E-02
Rac3	ras-related C3 botulinum toxin substrate	-1.303	-0.382	1.440E-03	3.660E-02
Sh3rf1	SH3 domain containing ring finger 1	-1.234	-0.303	1.420E-03	3.660E-02
UBE2M	ubiquitin-conjugating enzyme E2M (UBC12 homolog, yeast)	-1.255	-0.328	1.430E-03	3.660E-02
Dnajb2	DnaJ (Hsp40) homolog, subfamily B, member 2	-1.146	-0.196	1.460E-03	3.670E-02
Limk1	LIM domain kinase 1	-1.193	-0.254	1.470E-03	3.690E-02
Btd	biotinidase	-1.314	-0.394	1.480E-03	3.700E-02
Cpne5	copine V	-1.296	-0.374	1.490E-03	3.700E-02
Puf60	poly-U binding splicing factor 60	-1.173	-0.230	1.480E-03	3.700E-02
RGD1560394	RGD1560394	-1.350	-0.433	1.490E-03	3.700E-02
Cnot6l	CCR4-NOT transcription complex, subunit 6-like	1.367	0.451	1.510E-03	3.710E-02
Polr2b	polymerase (RNA) II (DNA directed) polypeptide B, 140kDa	1.219	0.286	1.510E-03	3.710E-02
Thoc1	THO complex 1	1.350	0.433	1.500E-03	3.710E-02
Caly	calcyon neuron-specific vesicular protein	-1.330	-0.411	1.520E-03	3.720E-02
Ccdc106	coiled-coil domain containing 106	-1.209	-0.274	1.530E-03	3.720E-02
ERCC5	excision repair cross-complementing rodent repair deficiency, complementation group 5	1.261	0.334	1.530E-03	3.720E-02
Madd	MAP-kinase activating death domain	-1.125	-0.170	1.530E-03	3.720E-02
Pigw	phosphatidylinositol glycan anchor biosynthesis, class W	1.324	0.405	1.540E-03	3.720E-02
Samd1	sterile alpha motif domain containing 1	-1.236	-0.306	1.530E-03	3.720E-02
Zmym2	zinc finger, MYM-type 2	1.320	0.400	1.530E-03	3.720E-02
Grina	glutamate receptor, ionotropic, N-methyl D-aspartate-associated protein 1 (glutamate binding)	-1.268	-0.342	1.550E-03	3.730E-02
Pdgfa	platelet-derived growth factor alpha polypeptide	-1.258	-0.331	1.550E-03	3.730E-02
Cic	capicua homolog (Drosophila)	-1.246	-0.317	1.570E-03	3.750E-02
Fsd1	fibronectin type III and SPRY domain containing 1	-1.230	-0.299	1.560E-03	3.750E-02
Gadd45gip1	growth arrest and DNA-damage-inducible, gamma interacting protein 1	-1.258	-0.331	1.570E-03	3.750E-02
Gpaa1	glycosylphosphatidylinositol anchor attachment protein 1 homolog (yeast)	-1.239	-0.309	1.570E-03	3.750E-02
HRAS1	Harvey rat sarcoma virus oncogene	-1.250	-0.322	1.560E-03	3.750E-02
Hfm1	HFM1, ATP-dependent DNA helicase homolog (S. cerevisiae)	1.331	0.413	1.580E-03	3.760E-02

Supplemental Table 2 (continued)

Fam208a	family with sequence similarity 208, member A	1.326	0.407	1.590E-03	3.770E-02
Bag6	BCL2-associated athanogene 6	-1.185	-0.245	1.600E-03	3.790E-02
Csnk1g2	casein kinase 1, gamma 2	-1.251	-0.323	1.620E-03	3.810E-02
Nhlrc2	NHL repeat containing 2	1.339	0.421	1.610E-03	3.810E-02
SCAI	suppressor of cancer cell invasion	1.292	0.370	1.620E-03	3.810E-02
Atp13a2	ATPase type 13A2	-1.254	-0.327	1.640E-03	3.830E-02
Fam20c	family with sequence similarity 20, member C	-1.220	-0.287	1.640E-03	3.830E-02
Fnip1	folliculin interacting protein 1	1.325	0.406	1.640E-03	3.830E-02
Mgat3	mannosyl (beta-1,4-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase	-1.167	-0.223	1.640E-03	3.830E-02
RGD1308134	similar to RIKEN cDNA 1110020A23	-1.250	-0.322	1.650E-03	3.830E-02
Zfp397	zinc finger protein 397	1.364	0.448	1.640E-03	3.830E-02
Glt8d1	glycosyltransferase 8 domain containing 1	1.223	0.290	1.660E-03	3.860E-02
Bcl9l	B-cell CLL/lymphoma 9-like	-1.241	-0.312	1.670E-03	3.870E-02
Chmp4bl1	chromatin modifying protein 4B-like 1	-1.203	-0.267	1.690E-03	3.870E-02
Fam214a	family with sequence similarity 214, member A	1.229	0.297	1.680E-03	3.870E-02
Gsk3a	glycogen synthase kinase 3 alpha	-1.232	-0.301	1.700E-03	3.870E-02
Myl12b	myosin light chain 12B	-1.261	-0.334	1.670E-03	3.870E-02
Nefh	neurofilament, heavy polypeptide	-1.318	-0.398	1.700E-03	3.870E-02
Pard6a	par-6 (partitioning defective 6,) homolog alpha (C. elegans)	-1.324	-0.405	1.680E-03	3.870E-02
Slc17a6	solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 6	1.335	0.417	1.700E-03	3.870E-02
Smpdl3a	sphingomyelin phosphodiesterase, acid-like 3A	1.286	0.363	1.690E-03	3.870E-02
Ash1l	ash1 (absent, small, or homeotic)-like (Drosophila)	1.210	0.275	1.730E-03	3.910E-02
Atp11c	Atpase, class VI, type 11C	1.363	0.447	1.740E-03	3.910E-02
Frs3	fibroblast growth factor receptor substrate 3	-1.264	-0.338	1.740E-03	3.910E-02
Kif5b	kinesin family member 5B	1.245	0.316	1.730E-03	3.910E-02
Sirt2	sirtuin (silent mating type information regulation 2 homolog) 2 (S. cerevisiae)	-1.240	-0.310	1.730E-03	3.910E-02
Zfp26	zinc finger protein 26	1.359	0.443	1.730E-03	3.910E-02
Zmiz2	zinc finger, MIZ-type containing 2	-1.241	-0.312	1.730E-03	3.910E-02
Dlgap3	discs, large (Drosophila) homolog-associated protein 3	-1.268	-0.342	1.750E-03	3.920E-02
Rpl13	ribosomal protein L13	-1.265	-0.339	1.750E-03	3.920E-02
G2E3	G2/M-phase specific E3 ubiquitin ligase	1.348	0.431	1.780E-03	3.960E-02
Git1	G protein-coupled receptor kinase interacting ArfGAP 1	-1.264	-0.338	1.780E-03	3.960E-02
Chst7	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 7	-1.311	-0.391	1.800E-03	3.990E-02
Pigm	phosphatidylinositol glycan anchor biosynthesis, class M	1.340	0.422	1.800E-03	3.990E-02
Mga	MAX gene associated	1.289	0.366	1.810E-03	4.010E-02
Slc25a39	solute carrier family 25, member 39	-1.302	-0.381	1.820E-03	4.020E-02
Msh3	mutS homolog 3 (E. coli)	1.289	0.366	1.850E-03	4.030E-02
Nrsn2	neurensin 2	-1.270	-0.345	1.830E-03	4.030E-02
Nup160	nucleoporin 160	1.281	0.357	1.840E-03	4.030E-02
Phip	pleckstrin homology domain interacting protein	1.318	0.398	1.840E-03	4.030E-02
Vps37d	VPS37D, ESCRT-I subunit	-1.240	-0.310	1.830E-03	4.030E-02
Zfp286a	zinc finger protein 286A	1.290	0.367	1.830E-03	4.030E-02
Fam171a2	family with sequence similarity 171, member A2	-1.308	-0.387	1.860E-03	4.040E-02
Orc5	origin recognition complex, subunit 5	1.249	0.321	1.860E-03	4.040E-02
Aes	amino-terminal enhancer of split	-1.278	-0.354	1.870E-03	4.060E-02
Baz2b	bromodomain adjacent to zinc finger domain, 2B	1.300	0.378	1.880E-03	4.060E-02
Kif15	kinesin family member 15	1.329	0.410	1.880E-03	4.060E-02
Ppp6r3	protein phosphatase 6, regulatory subunit 3	1.218	0.285	1.880E-03	4.060E-02

Supplemental Table 2 (continued)

Ints1	integrator complex subunit 1	-1.237	-0.307	1.900E-03	4.080E-02
RGD1565183	similar to ribosomal protein L28	-1.272	-0.347	1.890E-03	4.080E-02
Adrbk1	adrenergic, beta, receptor kinase 1	-1.129	-0.175	1.910E-03	4.100E-02
Cacng8	calcium channel, voltage-dependent, gamma subunit 8	-1.329	-0.410	1.930E-03	4.120E-02
Fam76b	family with sequence similarity 76, member B	1.355	0.438	1.930E-03	4.120E-02
Rell2	RELT-like 2	-1.320	-0.401	1.930E-03	4.120E-02
Bri3	brain protein I3	-1.298	-0.376	1.940E-03	4.130E-02
Abca5	ATP-binding cassette, sub-family A (ABC1), member 5	1.326	0.407	2.000E-03	4.150E-02
Camk2n2	calcium/calmodulin-dependent protein kinase II inhibitor 2	-1.352	-0.435	2.000E-03	4.150E-02
Ccnt2	cyclin T2	1.303	0.382	1.970E-03	4.150E-02
Fam126b	family with sequence similarity 126, member B	1.341	0.423	1.980E-03	4.150E-02
Htr2a	5-hydroxytryptamine (serotonin) receptor 2A	1.351	0.434	1.990E-03	4.150E-02
Map2k2	mitogen activated protein kinase kinase 2	-1.271	-0.346	2.000E-03	4.150E-02
Mapk8ip1	mitogen-activated protein kinase 8 interacting protein 1	-1.232	-0.301	1.990E-03	4.150E-02
Morc3	microrchidia 3	1.301	0.380	1.980E-03	4.150E-02
Per1	period homolog 1 (Drosophila)	-1.323	-0.404	1.980E-03	4.150E-02
Rhoq	ras homolog gene family, member Q	1.251	0.323	2.000E-03	4.150E-02
Rnf152	ring finger protein 152	1.304	0.383	1.950E-03	4.150E-02
Sgsm1	small G protein signaling modulator 1	-1.231	-0.300	2.000E-03	4.150E-02
Sipa1l3	signal-induced proliferation-associated 1 like 3	-1.239	-0.309	1.980E-03	4.150E-02
Smarca4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4	-1.173	-0.230	1.980E-03	4.150E-02
Ubald2	UBA-like domain containing 2	-1.309	-0.388	2.010E-03	4.150E-02
Alkbh8	alkB, alkylation repair homolog 8 (E. coli)	1.337	0.419	2.070E-03	4.240E-02
Hcfc2	host cell factor C2	1.226	0.294	2.070E-03	4.240E-02
Lypla2	lysophospholipase 2	-1.187	-0.247	2.060E-03	4.240E-02
Maf1	MAF1 homolog (S. cerevisiae)	-1.131	-0.178	2.060E-03	4.240E-02
Pnmal2	PNMA-like 2	-1.179	-0.237	2.070E-03	4.240E-02
Sf3a2	splicing factor 3a, subunit 2	-1.263	-0.337	2.070E-03	4.240E-02
Atp5g2	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit C2 (subunit 9)	-1.186	-0.246	2.090E-03	4.260E-02
Lmbrd2	LMBR1 domain containing 2	1.340	0.422	2.090E-03	4.270E-02
Mbtd1	mbt domain containing 1	1.293	0.371	2.110E-03	4.300E-02
Ampd2	adenosine monophosphate deaminase 2 (isoform L)	-1.212	-0.277	2.140E-03	4.320E-02
Myo9a	myosin IXA	1.275	0.350	2.140E-03	4.320E-02
Rpl36	ribosomal protein L36	-1.315	-0.395	2.130E-03	4.320E-02
Slc25a38	solute carrier family 25, member 38	-1.200	-0.263	2.130E-03	4.320E-02
Csnk2b	casein kinase 2, beta subunit	-1.207	-0.271	2.170E-03	4.370E-02
Mast3	microtubule associated serine/threonine kinase 3	-1.272	-0.347	2.170E-03	4.370E-02
Atp13a1	ATPase type 13A1	-1.222	-0.289	2.190E-03	4.410E-02
Ckmt1b	creatine kinase, mitochondrial 1B	-1.268	-0.342	2.230E-03	4.450E-02
Il12rb2	interleukin 12 receptor, beta 2	1.314	0.394	2.220E-03	4.450E-02
Psmb5	proteasome (prosome, macropain) subunit, beta type 5	-1.221	-0.288	2.220E-03	4.450E-02
Klhl20	kelch-like 20 (Drosophila)	1.201	0.264	2.240E-03	4.460E-02
Slc35a3	solute carrier family 35 (UDP-N-acetylglucosamine (UDP-GlcNAc) transporter), member A3	1.341	0.423	2.240E-03	4.460E-02
Dapk3	death-associated protein kinase 3	-1.312	-0.392	2.250E-03	4.470E-02
Dusp8	dual specificity phosphatase 8	-1.211	-0.276	2.260E-03	4.480E-02
Pcm1	pericentriolar material 1	1.288	0.365	2.270E-03	4.480E-02
Zfp882	zinc finger protein 882	1.328	0.409	2.270E-03	4.480E-02
Sf1	splicing factor 1	-1.145	-0.195	2.300E-03	4.540E-02

Supplemental Table 2 (continued)

Med16	mediator complex subunit 16	-1.260	-0.333	2.320E-03	4.560E-02
Lgals3bp	lectin, galactoside-binding, soluble, 3 binding protein	-1.337	-0.419	2.340E-03	4.580E-02
Pkd2	polycystic kidney disease 2 homolog (human)	1.275	0.350	2.340E-03	4.580E-02
Rapgef6	Rap guanine nucleotide exchange factor (GEF) 6	1.274	0.349	2.340E-03	4.580E-02
ENSRNOG00000024507	ENSRNOG00000024507	1.299	0.377	2.360E-03	4.600E-02
Fbxo31	F-box protein 31	-1.227	-0.295	2.360E-03	4.600E-02
Lrif1	ligand dependent nuclear receptor interacting factor 1	1.359	0.443	2.360E-03	4.600E-02
Blzf1	basic leucine zipper nuclear factor 1	1.288	0.365	2.380E-03	4.620E-02
Ccdc92	coiled-coil domain containing 92	-1.225	-0.293	2.380E-03	4.620E-02
Maea	macrophage erythroblast attacher	-1.126	-0.171	2.390E-03	4.630E-02
Mri1	methylthioribose-1-phosphate isomerase homolog (S. cerevisiae)	-1.269	-0.344	2.400E-03	4.630E-02
Otub1	OTU domain, ubiquitin aldehyde binding 1	-1.188	-0.249	2.400E-03	4.630E-02
Vps72	vacuolar protein sorting 72 homolog (S. cerevisiae)	-1.199	-0.262	2.400E-03	4.630E-02
RGD1566386	similar to Hypothetical protein A430033K04	1.337	0.419	2.420E-03	4.640E-02
Tmtc3	transmembrane and tetratricopeptide repeat containing 3	1.357	0.440	2.420E-03	4.640E-02
Zfp644	zinc finger protein 644	1.242	0.313	2.420E-03	4.640E-02
Prkdc	protein kinase, DNA activated, catalytic polypeptide	1.292	0.370	2.470E-03	4.730E-02
RGD1359634	similar to RIKEN cDNA 1700088E04	-1.213	-0.279	2.480E-03	4.740E-02
MGC114464	similar to expressed sequence AI836003	-1.246	-0.317	2.500E-03	4.760E-02
Mrpl39	mitochondrial ribosomal protein L39	1.227	0.295	2.500E-03	4.760E-02
Yipf3	Yip1 domain family, member 3	-1.210	-0.275	2.490E-03	4.760E-02
Actb	actin, beta	-1.258	-0.331	2.520E-03	4.770E-02
Edem3	ER degradation enhancer, mannosidase alpha-like 3	1.242	0.313	2.520E-03	4.770E-02
Klhl28	kelch-like 28 (Drosophila)	1.316	0.396	2.520E-03	4.770E-02
Mbnl1	muscleblind-like 1 (Drosophila)	1.238	0.308	2.530E-03	4.770E-02
Arl6ip6	ADP-ribosylation-like factor 6 interacting protein 6	1.340	0.422	2.600E-03	4.810E-02
Bad	Bcl2-antagonist of cell death	-1.217	-0.283	2.590E-03	4.810E-02
C2cd2l	transmembrane protein 24	-1.200	-0.263	2.610E-03	4.810E-02
Csnk1e	casein kinase 1, epsilon	-1.229	-0.298	2.570E-03	4.810E-02
Mydgf	myeloid derived growth factor	-1.157	-0.211	2.570E-03	4.810E-02
Fam208b	family with sequence similarity 208, member B	1.289	0.366	2.590E-03	4.810E-02
H2afy2	H2A histone family, member Y2	-1.169	-0.225	2.580E-03	4.810E-02
Psmc4	proteasome (prosome, macropain) 26S subunit, ATPase, 4	-1.138	-0.186	2.600E-03	4.810E-02
RGD1309594	similar to RIKEN cDNA 1810043G02	-1.244	-0.315	2.560E-03	4.810E-02
Slc5a6	solute carrier family 5 (sodium-dependent vitamin transporter), member 6	-1.215	-0.281	2.600E-03	4.810E-02
Smarcad1	SWI/SNF-related, matrix-associated actin-dependent regulator of chromatin, subfamily a, containing DEAD/H box 1	1.332	0.414	2.600E-03	4.810E-02
Snx17	sorting nexin 17	-1.188	-0.248	2.600E-03	4.810E-02
Ube2d1	ubiquitin-conjugating enzyme E2D 1, UBC4/5 homolog (yeast)	-1.326	-0.407	2.580E-03	4.810E-02
Zfp248	zinc finger protein 248	1.333	0.415	2.550E-03	4.810E-02
Csnk1g3	casein kinase 1, gamma 3	1.300	0.378	2.640E-03	4.820E-02
E2f3	E2F transcription factor 3	1.268	0.342	2.640E-03	4.820E-02
Efcab14	EF-hand calcium binding domain 14	1.261	0.335	2.650E-03	4.820E-02
Fam89b	family with sequence similarity 89, member B	-1.247	-0.318	2.650E-03	4.820E-02
Prrt1	proline-rich transmembrane protein 1	-1.353	-0.436	2.650E-03	4.820E-02
Rbm42	RNA binding motif protein 42	-1.258	-0.331	2.640E-03	4.820E-02
Sh2d3c	SH2 domain containing 3C	-1.289	-0.366	2.630E-03	4.820E-02
Sncb	synuclein, beta	-1.297	-0.375	2.620E-03	4.820E-02
Tceal6	transcription elongation factor A (SII)-like 6	-1.235	-0.305	2.640E-03	4.820E-02

Supplemental Table 2 (continued)

Rabac1	Rab acceptor 1 (prenylated)	-1.224	-0.292	2.680E-03	4.840E-02
Traf4	Tnf receptor associated factor 4	-1.185	-0.245	2.670E-03	4.840E-02
Adcy5	adenylate cyclase 5	-1.222	-0.289	2.740E-03	4.890E-02
Chchd10	coiled-coil-helix-coiled-coil-helix domain containing 10	-1.342	-0.424	2.710E-03	4.890E-02
Eefsec	eukaryotic elongation factor, selenocysteine-tRNA-specific	-1.226	-0.294	2.740E-03	4.890E-02
Esf1	ESF1, nucleolar pre-rRNA processing protein, homolog (S. cerevisiae)	1.326	0.407	2.730E-03	4.890E-02
Fgd1	FYVE, RhoGEF and PH domain containing 1	-1.188	-0.249	2.710E-03	4.890E-02
Rpl27a	ribosomal protein L27a	-1.292	-0.370	2.740E-03	4.890E-02
Rpl35	ribosomal protein L35	-1.278	-0.354	2.740E-03	4.890E-02
Serpinc1	serine (or cysteine) peptidase inhibitor, clade C (antithrombin), member 1	1.317	0.397	2.730E-03	4.890E-02
Zfp59	zinc finger protein 59	1.327	0.408	2.710E-03	4.890E-02
Tmem18	transmembrane protein 18	1.213	0.278	2.760E-03	4.910E-02
Vprbp	Vpr (HIV-1) binding protein	1.242	0.313	2.760E-03	4.910E-02
Vcam1	vascular cell adhesion molecule 1	1.175	0.233	2.780E-03	4.930E-02
Fastkd3	FAST kinase domains 3	1.310	0.390	2.840E-03	4.940E-02
Gdap1l1	ganglioside-induced differentiation-associated protein 1-like 1	-1.227	-0.295	2.840E-03	4.940E-02
Glrx5	glutaredoxin 5	-1.299	-0.377	2.840E-03	4.940E-02
Ly6h	lymphocyte antigen 6 complex, locus H	-1.256	-0.329	2.810E-03	4.940E-02
Mark4	MAP/microtubule affinity-regulating kinase 4	-1.265	-0.339	2.810E-03	4.940E-02
Pacsin2	protein kinase C and casein kinase substrate in neurons 2	-1.170	-0.227	2.830E-03	4.940E-02
Pank3	pantothenate kinase 3	1.311	0.391	2.790E-03	4.940E-02
Prr7	proline rich 7 (synaptic)	-1.312	-0.392	2.830E-03	4.940E-02
Slitrk6	SLIT and NTRK-like family, member 6	1.349	0.432	2.830E-03	4.940E-02
Tceal3	transcription elongation factor A (SII)-like 3	-1.249	-0.321	2.830E-03	4.940E-02
Wbp4	WW domain binding protein 4 (formin binding protein 21)	1.256	0.329	2.790E-03	4.940E-02
Ythdf3	YTH domain family, member 3	1.314	0.394	2.820E-03	4.940E-02
Dscam	Down syndrome cell adhesion molecule	-1.235	-0.305	2.860E-03	4.970E-02
Arrb2	arrestin, beta 2	-1.213	-0.278	2.870E-03	4.980E-02
Zfp445	zinc finger protein 445	1.286	0.363	2.870E-03	4.980E-02
Atp1a3	ATPase, Na+/K+ transporting, alpha 3 polypeptide	-1.272	-0.347	2.910E-03	5.000E-02
Fktn	fukutin	1.265	0.339	2.900E-03	5.000E-02
Nanp	N-acetylneuraminic acid phosphatase	1.270	0.345	2.910E-03	5.000E-02
Pnisr	PNN interacting serine and arginine rich protein	1.308	0.387	2.910E-03	5.000E-02
Wbp2	WW domain binding protein 2	-1.197	-0.259	2.900E-03	5.000E-02
Significantly (padj ≤ 0.05) altered genes in 2500BPA ♂ vs. Control ♂					
Gene Symbol	**Description**	**Fold Change**	**log2FC**	**p value**	**padj**
Ythdc2	YTH domain containing 2	1.640	0.714	1.010E-12	1.400E-08
Tia1	cytotoxic granule-associated RNA binding protein 1	1.530	0.614	1.760E-11	1.210E-07
Rictor	RPTOR independent companion of MTOR, complex 2	1.545	0.628	2.060E-09	9.480E-06
Atm	ataxia telangiectasia mutated homolog (human)	1.571	0.652	4.740E-09	1.520E-05
Nsmaf	neutral sphingomyelinase (N-SMase) activation associated factor	1.497	0.582	5.490E-09	1.520E-05
Ankhd1	ankyrin repeat and KH domain containing 1	1.532	0.615	7.790E-09	1.790E-05
Cep295	centrosomal protein 295	1.675	0.744	1.840E-08	2.310E-05
Cep95	centrosomal protein 95	1.587	0.666	1.330E-08	2.310E-05
Ints2	integrator complex subunit 2	1.609	0.686	1.420E-08	2.310E-05
Mat2a	methionine adenosyltransferase II, alpha	1.481	0.567	1.710E-08	2.310E-05

Supplemental Table 2 (continued)

Prp2l1	proline rich protein 2-like 1	1.722	0.784	1.770E-08	2.310E-05
Oaz1	ornithine decarboxylase antizyme 1	-1.343	-0.425	2.260E-08	2.440E-05
Eml5	echinoderm microtubule associated protein like 5	1.570	0.651	2.470E-08	2.440E-05
Sacs	sacsin	1.625	0.700	2.460E-08	2.440E-05
Ap5m1	adaptor-related protein complex 5, mu 1 subunit	1.639	0.713	3.280E-08	3.020E-05
Atad5	ATPase family, AAA domain containing 5	1.521	0.605	3.790E-08	3.080E-05
Mdm4	transformed mouse 3T3 cell double minute 4	1.638	0.712	3.730E-08	3.080E-05
Dna2	DNA replication helicase 2 homolog (yeast)	1.614	0.691	5.510E-08	4.230E-05
Slc25a36l1	solute carrier family 25 (pyrimidine nucleotide carrier), member 36-like 1	1.367	0.451	6.210E-08	4.510E-05
Esyt2	family with sequence similarity 62 (C2 domain containing), member B	1.485	0.570	7.730E-08	5.340E-05
Tgds	TDP-glucose 4,6-dehydratase	1.533	0.616	8.820E-08	5.800E-05
Nktr	natural killer tumor recognition sequence	1.476	0.562	9.280E-08	5.830E-05
Drap1	Dr1 associated protein 1 (negative cofactor 2 alpha)	-1.356	-0.439	9.830E-08	5.910E-05
Scn9a	sodium channel, voltage-gated, type IX, alpha	1.597	0.675	1.410E-07	8.140E-05
Cep162	centrosomal protein 162	1.582	0.662	2.550E-07	1.410E-04
Srek1	splicing regulatory glutamic acid and lysine rich protein 1	1.594	0.673	3.190E-07	1.630E-04
Zfp483	zinc finger protein 483	1.622	0.698	3.100E-07	1.630E-04
Cd2ap	CD2-associated protein	1.510	0.595	3.480E-07	1.720E-04
Rbm5	RNA binding motif protein 5	1.564	0.645	4.190E-07	1.990E-04
Itsn2	intersectin 2	1.424	0.510	5.080E-07	2.340E-04
RPL12	ribosomal protein L12	-1.329	-0.410	5.770E-07	2.410E-04
Arr3	arrestin 3, retinal	1.651	0.723	5.660E-07	2.410E-04
Birc6	baculoviral IAP repeat-containing 6	1.493	0.578	5.770E-07	2.410E-04
Gtf3c3	general transcription factor IIIC, polypeptide 3	1.423	0.509	6.120E-07	2.480E-04
Mrs2	MRS2 magnesium homeostasis factor homolog (S. cerevisiae)	1.529	0.613	6.370E-07	2.510E-04
Fam19a5	family with sequence similarity 19, member A5	-1.337	-0.419	6.570E-07	2.520E-04
Ash1l	ash1 (absent, small, or homeotic)-like (Drosophila)	1.352	0.435	7.030E-07	2.570E-04
Dennd4c	DENN/MADD domain containing 4C	1.503	0.588	7.070E-07	2.570E-04
Trdmt1	tRNA aspartic acid methyltransferase 1	1.580	0.660	7.550E-07	2.680E-04
Rps21	ribosomal protein S21	-1.508	-0.593	1.090E-06	3.630E-04
Ccdc62	coiled-coil domain containing 62	1.565	0.646	1.100E-06	3.630E-04
Mfn1	mitofusin 1	1.400	0.485	1.050E-06	3.630E-04
Tnrc6a	trinucleotide repeat containing 6a	1.390	0.475	1.400E-06	4.400E-04
Tubgcp3	tubulin, gamma complex associated protein 3	1.288	0.365	1.400E-06	4.400E-04
PHF20L1	PHD finger protein 20-like 1	1.436	0.522	1.510E-06	4.620E-04
Rplp1	ribosomal protein, large, P1	-1.563	-0.644	1.560E-06	4.700E-04
Setx	senataxin	1.408	0.494	1.600E-06	4.710E-04
Ccnt2	cyclin T2	1.504	0.589	1.850E-06	5.330E-04
Rasl10b	RAS-like, family 10, member B	-1.616	-0.692	1.920E-06	5.420E-04
Arnt	aryl hydrocarbon receptor nuclear translocator	1.424	0.510	2.540E-06	6.890E-04
Arhgef6	Rac/Cdc42 guanine nucleotide exchange factor (GEF) 6	1.538	0.621	2.540E-06	6.890E-04
Ddx26b	DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 26B	1.540	0.623	2.870E-06	7.300E-04
Fam179b	family with sequence similarity 179, member B	1.406	0.492	2.870E-06	7.300E-04
Fam214a	family with sequence similarity 214, member A	1.358	0.442	2.890E-06	7.300E-04
Golgb1	golgi autoantigen, golgin subfamily b, macrogolgin 1	1.286	0.363	2.910E-06	7.300E-04
Mir770	microRNA 770	1.597	0.675	3.000E-06	7.390E-04
Chuk	conserved helix-loop-helix ubiquitous kinase	1.556	0.638	3.070E-06	7.450E-04
ATP11B	ATPase, class VI, type 11B	1.479	0.565	3.150E-06	7.500E-04
Lcor	ligand dependent nuclear receptor corepressor	1.544	0.627	3.550E-06	8.320E-04

Supplemental Table 2 (continued)

Nfat5	nuclear factor of activated T-cells 5	1.515	0.599	3.740E-06	8.610E-04
Leng8	leukocyte receptor cluster (LRC) member 8	1.506	0.591	3.890E-06	8.800E-04
Supt20	suppressor of Ty 20	1.417	0.503	4.020E-06	8.950E-04
Bri3	brain protein I3	-1.471	-0.557	4.470E-06	9.350E-04
Nf1	neurofibromatosis 1	1.292	0.370	4.290E-06	9.350E-04
Smg1	SMG1 homolog, phosphatidylinositol 3-kinase-related kinase (C. elegans)	1.494	0.579	4.380E-06	9.350E-04
Sys1	SYS1 Golgi-localized integral membrane protein homolog (S. cerevisiae)	-1.434	-0.520	4.470E-06	9.350E-04
Psmd3	proteasome (prosome, macropain) 26S subunit, non-ATPase, 3	-1.314	-0.394	4.630E-06	9.550E-04
Ttc39b	tetratricopeptide repeat domain 39B	1.493	0.578	4.730E-06	9.620E-04
Adrm1	adhesion regulating molecule 1	-1.298	-0.376	4.820E-06	9.640E-04
Akap10	A kinase (PRKA) anchor protein 10	1.344	0.426	4.910E-06	9.690E-04
AABR07030590.1	AABR07030590.1	1.580	0.660	5.620E-06	1.090E-03
Utp20	UTP20, small subunit (SSU) processome component, homolog (yeast)	1.431	0.517	5.770E-06	1.110E-03
Cdc37	cell division cycle 37 homolog (S. cerevisiae)	-1.296	-0.374	6.470E-06	1.220E-03
Eid2	EP300 interacting inhibitor of differentiation 2	-1.491	-0.576	6.720E-06	1.250E-03
Agap3	ArfGAP with GTPase domain, ankyrin repeat and PH domain 3	-1.313	-0.393	6.880E-06	1.260E-03
Pnisr	PNN-interacting serine/arginine-rich protein	1.499	0.584	6.920E-06	1.260E-03
Ahctf1	AT hook containing transcription factor 1	1.440	0.526	7.710E-06	1.380E-03
Atxn3	ataxin 3	1.533	0.616	7.980E-06	1.380E-03
Cc2d2a	coiled-coil and C2 domain containing 2A	1.465	0.551	7.880E-06	1.380E-03
Dopey1	dopey family member 1	1.417	0.503	7.890E-06	1.380E-03
Rpl32	ribosomal protein L32	-1.495	-0.580	8.340E-06	1.400E-03
Trpm7	transient receptor potential cation channel, subfamily M, member 7	1.528	0.612	8.190E-06	1.400E-03
Tmem121	transmembrane protein 121	-1.357	-0.440	1.010E-05	1.640E-03
Mex3d	mex3 homolog D (C. elegans)	-1.425	-0.511	1.000E-05	1.640E-03
Zfp382	zinc finger protein 382	1.254	0.327	1.000E-05	1.640E-03
Usp40	ubiquitin specific peptidase 40	1.498	0.583	1.030E-05	1.660E-03
Rpl27a	ribosomal protein L27a	-1.458	-0.544	1.070E-05	1.690E-03
Rpl31	ribosomal protein L31	-1.306	-0.385	1.120E-05	1.750E-03
H2afz	H2A histone family, member Z	-1.366	-0.450	1.200E-05	1.860E-03
Uqcr10	ubiquinol-cytochrome c reductase, complex III subunit X	-1.513	-0.597	1.210E-05	1.860E-03
Bmyc	brain expressed myelocytomatosis oncogene	-1.404	-0.490	1.260E-05	1.900E-03
Med13	mediator complex subunit 13	1.407	0.493	1.260E-05	1.900E-03
Kpna5	karyopherin subunit alpha 5	1.470	0.556	1.310E-05	1.920E-03
Snrpd2	predicted gene 5449	-1.324	-0.405	1.300E-05	1.920E-03
BC005561	THO complex 2	1.496	0.581	1.350E-05	1.960E-03
Prpf39	PRP39 pre-mRNA processing factor 39 homolog (yeast)	1.532	0.615	1.380E-05	1.980E-03
Cep350	centrosomal protein 350	1.402	0.488	1.400E-05	1.990E-03
Prcc	papillary renal cell carcinoma (translocation-associated)	-1.199	-0.262	1.440E-05	2.040E-03
Rps27a	similar to ribosomal protein S27a	-1.416	-0.502	1.510E-05	2.070E-03
Edrf1	erythroid differentiation regulatory factor 1	1.455	0.541	1.580E-05	2.070E-03
Hfm1	HFM1, ATP-dependent DNA helicase homolog (S. cerevisiae)	1.479	0.565	1.510E-05	2.070E-03
Ppip5k2	histidine acid phosphatase domain containing 1	1.397	0.482	1.570E-05	2.070E-03
Ndufa13	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13	-1.283	-0.360	1.560E-05	2.070E-03
Rock1	Rho-associated coiled-coil containing protein kinase 1	1.476	0.562	1.560E-05	2.070E-03

Supplemental Table 2 (continued)

Sf3b1	splicing factor 3b, subunit 1	1.393	0.478	1.530E-05	2.070E-03
Jhdm1d	jumonji C domain-containing histone demethylase 1 homolog D (S. cerevisiae)	1.539	0.622	1.590E-05	2.080E-03
Pkig	protein kinase inhibitor, gamma	-1.329	-0.410	1.670E-05	2.090E-03
RGD1309995	similar to CG13957-PA	1.456	0.542	1.630E-05	2.090E-03
Vps13c	vacuolar protein sorting 13C (yeast)	1.418	0.504	1.650E-05	2.090E-03
AABR07054370.1	AABR07054370.1	-1.293	-0.371	1.660E-05	2.090E-03
GPX4	glutathione peroxidase 4	-1.288	-0.365	1.760E-05	2.170E-03
Arfgef2	ADP-ribosylation factor guanine nucleotide-exchange factor 2 (brefeldin A-inhibited)	1.276	0.352	1.800E-05	2.170E-03
Ctnnal1	catenin (cadherin associated protein), alpha-like 1	1.429	0.515	1.830E-05	2.170E-03
Fastkd1	FAST kinase domains 1	1.408	0.494	1.750E-05	2.170E-03
Pan3	PAN3 polyA specific ribonuclease subunit homolog (S. cerevisiae)	1.285	0.362	1.790E-05	2.170E-03
Usp37	ubiquitin specific peptidase 37	1.461	0.547	1.820E-05	2.170E-03
Trmt13	tRNA methyltransferase 13 homolog	1.522	0.606	1.850E-05	2.180E-03
Alkbh7	alkB, alkylation repair homolog 7 (E. coli)	-1.402	-0.487	1.940E-05	2.260E-03
Sgk494	uncharacterized serine/threonine-protein kinase SgK494	1.515	0.599	1.940E-05	2.260E-03
Vstm2l	V-set and transmembrane domain containing 2-like	-1.423	-0.509	2.220E-05	2.530E-03
Irf2bp1	interferon regulatory factor 2 binding protein 1	-1.303	-0.382	2.210E-05	2.530E-03
Zfyve16	zinc finger, FYVE domain containing 16	1.472	0.558	2.230E-05	2.530E-03
Btaf1	BTAF1 RNA polymerase II, B-TFIID transcription factor-associated, (Mot1 homolog, S. cerevisiae)	1.438	0.524	2.260E-05	2.540E-03
Ctbp1	C-terminal binding protein 1	-1.228	-0.296	2.420E-05	2.620E-03
Rps2	similar to 40S ribosomal protein S2	-1.326	-0.407	2.440E-05	2.620E-03
Ankfy1	ankyrin repeat and FYVE domain containing 1	1.376	0.461	2.490E-05	2.620E-03
D17Wsu104e	DNA segment, Chr 17, Wayne State University 104, expressed	-1.228	-0.296	2.450E-05	2.620E-03
RGD1562608	similar to KIAA1328 protein	1.291	0.368	2.370E-05	2.620E-03
Scn3a	sodium channel, voltage-gated, type III, alpha	1.320	0.401	2.470E-05	2.620E-03
Strn	striatin, calmodulin binding protein	1.272	0.347	2.480E-05	2.620E-03
Tada2a	transcriptional adaptor 2 (ADA2 homolog, yeast)-like	1.300	0.378	2.420E-05	2.620E-03
Paxbp1	PAX3 and PAX7 binding protein 1	1.447	0.533	2.550E-05	2.640E-03
Thoc1	THO complex 1	1.489	0.574	2.540E-05	2.640E-03
Hes5	hairy and enhancer of split 5 (Drosophila)	-1.478	-0.564	2.620E-05	2.660E-03
Ssbp3	single-stranded DNA binding protein 3	-1.232	-0.301	2.620E-05	2.660E-03
Scn1a	sodium channel, voltage-gated, type I, alpha	1.357	0.440	2.640E-05	2.660E-03
Zc3h7a	zinc finger CCCH type containing 7 A	1.424	0.510	2.590E-05	2.660E-03
Ero1lb	ERO1-like beta (S. cerevisiae)	1.434	0.520	2.680E-05	2.680E-03
Cilp2	cartilage intermediate layer protein 2	-1.469	-0.555	2.800E-05	2.790E-03
Pycrl	pyrroline-5-carboxylate reductase-like	-1.289	-0.366	2.920E-05	2.880E-03
Zufsp	zinc finger with UFM1-specific peptidase domain	1.363	0.447	3.000E-05	2.940E-03
Rpl36	ribosomal protein L36	-1.450	-0.536	3.090E-05	2.960E-03
Brca2	breast cancer 2	1.363	0.447	3.070E-05	2.960E-03
Timm8b	translocase of inner mitochondrial membrane 8 homolog b (yeast)	-1.360	-0.444	3.040E-05	2.960E-03
Atp5j2	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit f, isoform 2	-1.329	-0.410	3.270E-05	2.990E-03
Dock3	dedicator of cyto-kinesis 3	1.336	0.418	3.190E-05	2.990E-03
Dennd4a	DENN/MADD domain containing 4A	1.433	0.519	3.210E-05	2.990E-03
Lmna	lamin A	-1.315	-0.395	3.180E-05	2.990E-03
Nudt3	nudix (nucleotide diphosphate linked moiety X)-type motif 3	-1.196	-0.258	3.270E-05	2.990E-03
Rab12	RAB12, member RAS oncogene family	-1.376	-0.461	3.150E-05	2.990E-03

Supplemental Table 2 (continued)

PCBP1	Poly(RC) Binding Protein 1	-1.366	-0.450	3.260E-05	2.990E-03
Ndufb4	NADH dehydrogenase (ubiquinone) 1 beta subcomplex 4	-1.443	-0.529	3.350E-05	3.040E-03
Prkdc	protein kinase, DNA activated, catalytic polypeptide	1.420	0.506	3.390E-05	3.060E-03
Zfc3h1	zinc finger, C3H1-type containing	1.476	0.562	3.450E-05	3.090E-03
Psme4	proteasome (prosome, macropain) activator subunit 4	1.423	0.509	3.480E-05	3.100E-03
Tubg1	tubulin, gamma 1	-1.310	-0.390	3.540E-05	3.130E-03
Zkscan2	zinc finger with KRAB and SCAN domains 2	1.374	0.458	3.710E-05	3.260E-03
Abca5	ATP-binding cassette, sub-family A (ABC1), member 5	1.456	0.542	3.880E-05	3.390E-03
Slc4a7	solute carrier family 4, sodium bicarbonate cotransporter, member 7	1.392	0.477	3.980E-05	3.450E-03
Rnf10	ring finger protein 10	-1.246	-0.317	4.080E-05	3.520E-03
Nfxl1	nuclear transcription factor, X-box binding-like 1	1.433	0.519	4.310E-05	3.700E-03
Rpl18a	ribosomal protein L18A	-1.287	-0.364	4.380E-05	3.730E-03
Carf	calcium response factor	1.381	0.466	4.540E-05	3.820E-03
F8a1	coagulation factor VIII-associated 1	-1.313	-0.393	4.530E-05	3.820E-03
Clip2	CAP-GLY domain containing linker protein 2	-1.224	-0.292	4.630E-05	3.870E-03
Zfp407	zinc finger protein 407	1.346	0.429	4.650E-05	3.870E-03
Naa16	NMDA receptor regulated 1-like	1.492	0.577	4.760E-05	3.890E-03
Pot1	protection of telomeres 1	1.415	0.501	4.730E-05	3.890E-03
Shfm1	split hand/foot malformation (ectrodactyly) type 1	-1.359	-0.443	4.750E-05	3.890E-03
Vstm2b	V-set and transmembrane domain containing 2B	-1.378	-0.463	4.850E-05	3.940E-03
Rps7	ribosomal protein S7	-1.299	-0.377	4.940E-05	3.980E-03
Ttc37	tetratricopeptide repeat domain 37	1.404	0.490	4.960E-05	3.980E-03
Nsd1	nuclear receptor-binding SET-domain protein 1	1.268	0.343	5.000E-05	3.990E-03
Dnajc13	DnaJ (Hsp40) homolog, subfamily C, member 13	1.332	0.414	5.030E-05	4.000E-03
Mss51	MSS51 mitochondrial translational activator	1.504	0.589	5.130E-05	4.050E-03
AABR07067506.1	AABR07067506.1	-1.429	-0.515	5.160E-05	4.050E-03
Igsf6	immunoglobulin superfamily, member 6	1.502	0.587	5.230E-05	4.080E-03
Secisbp2l	SECIS binding protein 2-like	1.298	0.376	5.260E-05	4.080E-03
Mga	MAX gene associated	1.389	0.474	5.450E-05	4.200E-03
Phip	pleckstrin homology domain interacting protein	1.430	0.516	5.500E-05	4.220E-03
Arf5	ADP-ribosylation factor 5	-1.355	-0.438	5.750E-05	4.240E-03
Rps17	ribosomal protein S17	-1.412	-0.498	5.560E-05	4.240E-03
Atad2	ATPase family, AAA domain containing 2	1.494	0.579	5.710E-05	4.240E-03
Cacnb1	calcium channel, voltage-dependent, beta 1 subunit	-1.293	-0.371	5.720E-05	4.240E-03
Cnot2	CCR4-NOT transcription complex, subunit 2	1.213	0.278	5.810E-05	4.240E-03
Htt	huntingtin	1.259	0.332	5.810E-05	4.240E-03
Itch	itchy, E3 ubiquitin protein ligase	1.408	0.494	5.730E-05	4.240E-03
Ndufb10	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 10	-1.318	-0.398	5.580E-05	4.240E-03
Nfatc3	nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 3	1.345	0.428	5.810E-05	4.240E-03
Rpl41	ribosomal protein L41	-1.305	-0.384	5.830E-05	4.240E-03
Rhob	ras homolog gene family, member B	-1.376	-0.461	5.980E-05	4.320E-03
Osbpl6	oxysterol binding protein-like 6	1.320	0.401	6.320E-05	4.540E-03
Tmem87b	transmembrane protein 87B	1.371	0.455	6.350E-05	4.540E-03
Rplp2	WD repeat domain 89	-1.494	-0.579	6.670E-05	4.750E-03
Scand1	SCAN domain-containing 1	-1.396	-0.481	6.730E-05	4.770E-03
UBE2M	ubiquitin-conjugating enzyme E2M (UBC12 homolog, yeast)	-1.328	-0.409	6.830E-05	4.810E-03
Atpif1	ATPase inhibitory factor 1	-1.327	-0.408	6.980E-05	4.840E-03
Fbxl15	F-box and leucine-rich repeat protein 15	-1.384	-0.469	7.000E-05	4.840E-03

Supplemental Table 2 (continued)

Lvrn	laeverin	1.487	0.572	6.960E-05	4.840E-03
Mphosph9	M-phase phosphoprotein 9	1.378	0.463	6.960E-05	4.840E-03
Ddhd2	DDHD domain containing 2	1.437	0.523	7.200E-05	4.950E-03
Brwd1	bromodomain and WD repeat domain containing 1	1.354	0.437	7.420E-05	5.050E-03
Dclre1c	DNA cross-link repair 1C, PSO2 homolog (S. cerevisiae)	1.477	0.563	7.460E-05	5.050E-03
Phldb2	pleckstrin homology-like domain, family B, member 2	1.379	0.464	7.410E-05	5.050E-03
Orc2	origin recognition complex, subunit 2	1.408	0.494	7.550E-05	5.060E-03
Prr7	proline rich 7 (synaptic)	-1.434	-0.520	7.530E-05	5.060E-03
TAF9	predicted gene 12372	-1.291	-0.368	7.820E-05	5.220E-03
DMD	dystrophin, muscular dystrophy	1.339	0.421	7.920E-05	5.260E-03
Vps37d	vacuolar protein sorting 37D (yeast)	-1.312	-0.392	8.140E-05	5.380E-03
Edf1	endothelial differentiation-related factor 1	-1.380	-0.465	8.420E-05	5.470E-03
Abhd8	abhydrolase domain containing 8	-1.309	-0.389	8.350E-05	5.470E-03
Dync2h1	dynein cytoplasmic 2 heavy chain 1	1.413	0.499	8.440E-05	5.470E-03
Pikfyve	phosphoinositide kinase, FYVE finger containing	1.361	0.445	8.380E-05	5.470E-03
Zmynd19	zinc finger, MYND domain containing 19	-1.239	-0.309	8.550E-05	5.520E-03
Kif20a	kinesin family member 20A	1.366	0.450	8.690E-05	5.580E-03
Pycr2	pyrroline-5-carboxylate reductase family, member 2	-1.268	-0.343	9.040E-05	5.780E-03
Luc7l3	LUC7-like 3 pre-mRNA splicing facto	1.439	0.525	9.290E-05	5.880E-03
Unc119	unc-119 homolog (C. elegans)	-1.291	-0.368	9.260E-05	5.880E-03
Chchd10	coiled-coil-helix-coiled-coil-helix domain containing 10	-1.466	-0.552	9.440E-05	5.940E-03
Basp1	brain abundant, membrane attached signal protein 1	-1.406	-0.492	9.460E-05	5.940E-03
Papss1	3'-phosphoadenosine 5'-phosphosulfate synthase 1	-1.170	-0.227	9.620E-05	6.010E-03
Ndufa3	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 3	-1.413	-0.499	9.760E-05	6.070E-03
Rps28	ribosomal protein S28	-1.459	-0.545	9.870E-05	6.110E-03
Apc	adenomatosis polyposis coli	1.265	0.339	1.010E-04	6.200E-03
Arf6	ADP-ribosylation factor 6	-1.236	-0.306	1.020E-04	6.220E-03
Clk4	CDC like kinase 4	1.455	0.541	1.030E-04	6.220E-03
Seh1l	SEH1-like (S. cerevisiae	1.245	0.316	1.020E-04	6.220E-03
Zmym6	zinc finger, MYM-type 6	1.423	0.509	1.030E-04	6.220E-03
Ppdpf	ancreatic progenitor cell differentiation and proliferation factor homolog (zebrafish)	-1.333	-0.415	1.050E-04	6.240E-03
Cfp	complement factor properdin	1.439	0.525	1.040E-04	6.240E-03
Epb4.1l5	erythrocyte protein band 4.1-like 5	1.397	0.482	1.070E-04	6.240E-03
Hnrnpa0	heterogeneous nuclear ribonucleoprotein A0	-1.343	-0.425	1.050E-04	6.240E-03
Hint1	histidine triad nucleotide binding protein 1	-1.405	-0.491	1.070E-04	6.240E-03
Phc3	polyhomeotic-like 3 (Drosophila)	1.358	0.442	1.060E-04	6.240E-03
RPL37A	ribosomal protein L37a	-1.438	-0.524	1.070E-04	6.240E-03
RGD1564420	similar to Hypothetical protein MGC31278	1.178	0.236	1.070E-04	6.240E-03
Ypel3	yippee-like 3 (Drosophila)	-1.275	-0.350	1.050E-04	6.240E-03
Rps10	ribosomal protein S10	-1.346	-0.429	1.110E-04	6.450E-03
Bnip2	BCL2/adenovirus E1B interacting protein 2	1.371	0.455	1.130E-04	6.510E-03
Zdhhc15	zinc finger, DHHC domain containing 15	1.390	0.475	1.150E-04	6.610E-03
Cox6c	cytochrome c oxidase, subunit VIc	-1.312	-0.392	1.190E-04	6.840E-03
Abca8b	ATP-binding cassette, sub-family A (ABC1), member 8b	1.399	0.484	1.230E-04	6.950E-03
Phlpp2	PH domain and leucine rich repeat protein phosphatase 2	1.328	0.409	1.230E-04	6.950E-03
Ttc14	tetratricopeptide repeat domain 14	1.466	0.552	1.220E-04	6.950E-03
H2afy2	H2A histone family, member Y2	-1.220	-0.287	1.240E-04	6.970E-03
LOC680233	hypothetical protein LOC688095	-1.382	-0.467	1.240E-04	6.970E-03
Nfrkb	nuclear factor related to kappa B binding protein	1.306	0.385	1.270E-04	7.080E-03

Supplemental Table 2 (continued)

Cox5b	cytochrome c oxidase, subunit Vb	-1.277	-0.353	1.290E-04	7.160E-03
Rps9	ribosomal protein S9	-1.464	-0.550	1.320E-04	7.300E-03
Wdr18	WD repeat domain 18	-1.289	-0.366	1.320E-04	7.300E-03
Cebpb	CCAAT/enhancer binding protein (C/EBP), beta	-1.469	-0.555	1.340E-04	7.360E-03
Nudc	nuclear distribution gene C homolog (Aspergillus), pseudogene 1	-1.434	-0.520	1.340E-04	7.360E-03
Rbbp8	retinoblastoma binding protein 8	1.332	0.414	1.370E-04	7.400E-03
Rnf208	ring finger protein 208	-1.336	-0.418	1.360E-04	7.400E-03
Sap30l	SAP30-like	-1.345	-0.428	1.350E-04	7.400E-03
H1fx	H1 histone family, member X	-1.453	-0.539	1.380E-04	7.420E-03
Fbll1	fibrillarin-like 1	-1.391	-0.476	1.390E-04	7.470E-03
Gadd45gip1	growth arrest and DNA-damage-inducible, gamma interacting protein 1	-1.319	-0.399	1.390E-04	7.470E-03
ENSRNOG00000045588	ENSRNOG00000045588	-1.306	-0.385	1.410E-04	7.520E-03
Ubald2	UBA-like domain containing 2	-1.394	-0.479	1.430E-04	7.580E-03
Sepsecs	Sep (O-phosphoserine) tRNA:Sec (selenocysteine) tRNA synthase	1.350	0.433	1.440E-04	7.610E-03
Baz2b	bromodomain adjacent to zinc finger domain, 2B	1.376	0.461	1.450E-04	7.630E-03
Rn60_14_0792.1	ENSRNOG00000029723	-1.465	-0.551	1.480E-04	7.780E-03
Hmx3	H6 homeo box 3	-1.459	-0.545	1.500E-04	7.840E-03
RPS6	ribosomal protein S6	-1.461	-0.547	1.520E-04	7.870E-03
Xpo4	exportin 4	1.398	0.483	1.510E-04	7.870E-03
ENSRNOG00000039654	ENSRNOG00000039654	-1.465	-0.551	1.530E-04	7.930E-03
Myo9a	myosin IXa	1.348	0.431	1.550E-04	7.980E-03
Mt3	metallothionein 3	-1.387	-0.472	1.580E-04	8.060E-03
Phb2	prohibitin 2	-1.235	-0.305	1.570E-04	8.060E-03
Dmc1	DMC1 dosage suppressor of mck1 homolog, meiosis-specific homologous recombination (yeast)	1.464	0.550	1.590E-04	8.120E-03
Slc28a2	solute carrier family 28 (sodium-coupled nucleoside transporter), member 2	1.463	0.549	1.620E-04	8.210E-03
Rps16	ribosomal protein S16	-1.364	-0.448	1.670E-04	8.350E-03
Ap4e1	adaptor-related protein complex AP-4, epsilon 1	1.370	0.454	1.670E-04	8.350E-03
Etfdh	electron transferring flavoprotein, dehydrogenase	1.265	0.339	1.660E-04	8.350E-03
Rpgrip1l	Rpgrip1-like	1.359	0.443	1.670E-04	8.350E-03
Rnf126	ring finger protein 126	-1.376	-0.460	1.710E-04	8.360E-03
Btbd7	BTB (POZ) domain containing 7	1.389	0.474	1.690E-04	8.360E-03
Evi5l	ecotropic viral integration site 5-like	-1.199	-0.262	1.710E-04	8.360E-03
PCBP2	poly(rC) binding protein 2	-1.179	-0.238	1.690E-04	8.360E-03
Ppp5c	protein phosphatase 5, catalytic subunit	-1.228	-0.296	1.710E-04	8.360E-03
RGD1311899	similar to RIKEN cDNA 2210016L21 gene	-1.272	-0.347	1.720E-04	8.360E-03
Slc32a1	solute carrier family 32 (GABA vesicular transporter), member 1	-1.439	-0.525	1.680E-04	8.360E-03
Zcchc7	zinc finger, CCHC domain containing 7	1.373	0.457	1.700E-04	8.360E-03
Papolg	poly(A) polymerase gamma	1.402	0.488	1.730E-04	8.390E-03
Cspp1	centrosome and spindle pole associated protein 1	1.370	0.454	1.750E-04	8.410E-03
Eif4h	eukaryotic translation initiation factor 4H	-1.218	-0.284	1.750E-04	8.410E-03
CCNL2	cyclin L2	1.376	0.461	1.760E-04	8.420E-03
Atp5i	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit E	-1.409	-0.495	1.780E-04	8.490E-03
Fam227a	family with sequence similarity 227, member A	1.456	0.542	1.780E-04	8.490E-03
Nup205	nucleoporin 205	1.357	0.440	1.840E-04	8.750E-03
Aip	aryl-hydrocarbon receptor-interacting protein	-1.273	-0.348	1.870E-04	8.860E-03
Gramd1c	GRAM domain containing 1C	1.431	0.517	1.890E-04	8.890E-03
Qtrtd1	queuine tRNA-ribosyltransferase domain containing 1	1.365	0.449	1.890E-04	8.890E-03

Supplemental Table 2 (continued)

Ankle2	ankyrin repeat and LEM domain containing 2	1.324	0.405	1.900E-04	8.900E-03
Glt8d1	glycosyltransferase 8 domain containing 1	1.270	0.345	1.920E-04	8.970E-03
Aqr	aquarius	1.229	0.297	1.960E-04	9.090E-03
Fastkd3	FAST kinase domains 3	1.401	0.486	1.970E-04	9.090E-03
Lrrk2	leucine-rich repeat kinase 2	1.431	0.517	1.960E-04	9.090E-03
Cdc34	cell division cycle 34 homolog (S. cerevisiae)	-1.354	-0.437	1.990E-04	9.110E-03
Narg2	NMDA receptor-regulated gene 2	1.442	0.528	1.980E-04	9.110E-03
Cotl1	coactosin-like 1 (Dictyostelium)	-1.370	-0.454	2.010E-04	9.180E-03
Rnpc3	RNA-binding region (RNP1, RRM) containing 3	1.397	0.482	2.020E-04	9.190E-03
Smarcb1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	-1.229	-0.297	2.020E-04	9.190E-03
Rbl1	retinoblastoma-like 1 (p107)	1.423	0.509	2.030E-04	9.210E-03
Abcc5	ATP-binding cassette, sub-family C (CFTR/MRP), member 5	1.355	0.438	2.060E-04	9.240E-03
Agbl3	ATP/GTP binding protein-like 3	1.445	0.531	2.060E-04	9.240E-03
Fuz	fuzzy homolog (Drosophila)	-1.293	-0.371	2.060E-04	9.240E-03
Snx17	sorting nexin 17	-1.236	-0.306	2.070E-04	9.240E-03
Tceal6	transcription elongation factor A (SII)-like 6	-1.299	-0.377	2.070E-04	9.240E-03
Csmd3	CUB and Sushi multiple domains 3	1.358	0.442	2.110E-04	9.360E-03
Lage3	L antigen family, member 3	-1.309	-0.389	2.110E-04	9.360E-03
Rsrp1	arginine and serine rich protein 1	1.332	0.414	2.140E-04	9.400E-03
Ndufa2	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2	-1.319	-0.399	2.130E-04	9.400E-03
Dzf17	zinc finger protein 17	1.292	0.370	2.140E-04	9.400E-03
MBD3	methyl-CpG binding domain protein 3	-1.306	-0.385	2.150E-04	9.420E-03
Mta1	metastasis associated 1	-1.193	-0.254	2.170E-04	9.430E-03
Tbc1d4	TBC1 domain family, member 4	1.412	0.498	2.170E-04	9.430E-03
Ergic3	ERGIC and golgi 3	-1.225	-0.293	2.190E-04	9.440E-03
Osgin2	oxidative stress induced growth inhibitor family member 2	1.336	0.418	2.180E-04	9.440E-03
Pcbp4	poly(rC) binding protein 4	-1.276	-0.352	2.210E-04	9.490E-03
Irf2bpl	interferon regulatory factor 2 binding protein-like	-1.318	-0.398	2.230E-04	9.570E-03
Slc25a27	solute carrier family 25, member 27	1.237	0.307	2.250E-04	9.620E-03
Rps15	ribosomal protein S15	-1.235	-0.305	2.310E-04	9.720E-03
Rps27	ribosomal protein S27	-1.393	-0.478	2.300E-04	9.720E-03
Crebrf	CREB3 regulatory factor	1.404	0.490	2.300E-04	9.720E-03
Ercc6l2	ERCC excision repair 6 like 2	1.315	0.395	2.310E-04	9.720E-03
Ipo4	importin 4	-1.193	-0.255	2.300E-04	9.720E-03
Dact3	dapper homolog 3, antagonist of beta-catenin (xenopus)	-1.310	-0.390	2.330E-04	9.730E-03
Gpr27	G protein-coupled receptor 27	-1.391	-0.476	2.320E-04	9.730E-03
Cntrl	centriolin	1.363	0.447	2.340E-04	9.740E-03
Grik2	glutamate receptor, ionotropic, kainate 2 (beta 2)	1.309	0.388	2.340E-04	9.740E-03
HRAS1	Harvey rat sarcoma virus oncogene 1	-1.297	-0.375	2.370E-04	9.770E-03
Sf3b5	splicing factor 3b, subunit 5	-1.308	-0.387	2.370E-04	9.770E-03
Thra	thyroid hormone receptor alpha	-1.271	-0.346	2.360E-04	9.770E-03
Maf1	MAF1 homolog (S. cerevisiae)	-1.158	-0.212	2.440E-04	1.000E-02
Emc6	elastin microfibril interfacer 2	-1.377	-0.462	2.500E-04	1.020E-02
Ralgapa1	GTPase activating RANGAP domain-like 1	1.293	0.371	2.520E-04	1.030E-02
Lrch3	leucine-rich repeats and calponin homology (CH) domain containing 3	1.264	0.338	2.530E-04	1.030E-02
Rnf170	ring finger protein 170	1.293	0.371	2.530E-04	1.030E-02
ENSRNOG00000029723	uncharacterized protein	1.410	0.496	2.510E-04	1.030E-02
Rnf7	ring finger protein 7	-1.392	-0.477	2.610E-04	1.040E-02
Epg5	ectopic P-granules autophagy protein 5 homolog (C.	1.366	0.450	2.610E-04	1.040E-02

Supplemental Table 2 (continued)

	elegans)				
ERCC5	excision repair cross-complementing rodent repair deficiency, complementation group 5	1.306	0.385	2.570E-04	1.040E-02
Gcfc2	GC-rich sequence DNA-binding factor 2	1.404	0.490	2.590E-04	1.040E-02
Tet1	tet oncogene 1	1.431	0.517	2.590E-04	1.040E-02
Mif	macrophage migration inhibitory factor-like	-1.406	-0.492	2.650E-04	1.050E-02
Greb1l	cDNA sequence AK220484	1.424	0.510	2.660E-04	1.050E-02
Nufip2	NUFIP2, FMR1 interacting protein 2	1.369	0.453	2.650E-04	1.050E-02
Rps29	ribosomal protein S29	-1.365	-0.449	2.670E-04	1.060E-02
RPL26	ribosomal protein L26	-1.394	-0.479	2.700E-04	1.060E-02
Rpl10a	ribosomal protein L10A	-1.355	-0.438	2.760E-04	1.070E-02
C1qtnf4	C1q and tumor necrosis factor related protein 4	-1.407	-0.493	2.780E-04	1.070E-02
Eif1b	eukaryotic translation initiation factor 1B	-1.223	-0.290	2.770E-04	1.070E-02
Gpr98	G protein-coupled receptor 98	1.434	0.520	2.720E-04	1.070E-02
Lrrc4b	leucine rich repeat containing 4B	-1.279	-0.355	2.750E-04	1.070E-02
Map7d1	MAP7 domain containing 1	-1.219	-0.286	2.730E-04	1.070E-02
Pdxp	pyridoxal (pyridoxine, vitamin B6) phosphatase	-1.303	-0.382	2.740E-04	1.070E-02
Jund	Jun proto-oncogene related gene d	-1.417	-0.503	2.820E-04	1.090E-02
Ndufv1	NADH dehydrogenase (ubiquinone) flavoprotein 1	-1.174	-0.231	2.850E-04	1.090E-02
Rpl19	ribosomal protein L19	-1.230	-0.299	2.920E-04	1.100E-02
Sf3b4	splicing factor 3b, subunit 4	-1.254	-0.327	2.930E-04	1.100E-02
Csnk1g2	casein kinase 1, gamma 2	-1.294	-0.372	2.890E-04	1.100E-02
Fam89b	family with sequence similarity 89, member B	-1.304	-0.383	2.920E-04	1.100E-02
Foxp4	forkhead box P4	-1.300	-0.378	2.900E-04	1.100E-02
Gdap2	ganglioside-induced differentiation-associated-protein 2	1.335	0.417	2.930E-04	1.100E-02
Ibtk	inhibitor of Bruton agammaglobulinemia tyrosine kinase	1.343	0.425	2.870E-04	1.100E-02
Mtus1	mitochondrial tumor suppressor 1	1.307	0.386	2.890E-04	1.100E-02
Zfp187	zinc finger protein 187	1.367	0.451	2.900E-04	1.100E-02
Cacnb2	calcium channel, voltage-dependent, beta 2 subunit	1.236	0.306	2.970E-04	1.110E-02
Mid1ip1	Mid1 interacting protein 1 (gastrulation specific G12-like (zebrafish))	-1.211	-0.276	3.020E-04	1.120E-02
Wdfy2	WD repeat and FYVE domain containing 2	1.325	0.406	3.040E-04	1.130E-02
Ccser2	coiled-coil serine-rich protein 2	1.251	0.323	3.100E-04	1.140E-02
Ubn2	ubinuclein 2	1.327	0.408	3.070E-04	1.140E-02
Zfp575	zinc finger protein 575	-1.354	-0.437	3.090E-04	1.140E-02
Scn8a	sodium channel, voltage-gated, type VIII, alpha	1.289	0.366	3.130E-04	1.150E-02
Eif4ebp3	ankyrin repeat and KH domain containing 1	1.318	0.398	3.150E-04	1.160E-02
Eml4	echinoderm microtubule associated protein like 4	1.364	0.448	3.190E-04	1.170E-02
Ssr4	signal sequence receptor, delta	-1.247	-0.318	3.240E-04	1.180E-02
Atp5e	ATP synthase, H+ transporting, mitochondrial F1 complex, epsilon subunit	-1.347	-0.430	3.280E-04	1.190E-02
KDELC1	KDEL (Lys-Asp-Glu-Leu) containing 1	1.363	0.447	3.300E-04	1.190E-02
Lrrc10b	predicted gene 705	-1.422	-0.508	3.300E-04	1.190E-02
Ptov1	prostate tumor over expressed gene 1	-1.304	-0.383	3.330E-04	1.190E-02
Poglut1	protein O-glucosyltransferase 1	1.281	0.357	3.300E-04	1.190E-02
RGD1565363	similar to RIKEN cDNA 1110025L05	-1.371	-0.455	3.340E-04	1.190E-02
Zfp192	zinc finger protein 192	1.425	0.511	3.330E-04	1.190E-02
Cox6a1	cytochrome c oxidase, subunit VI a, polypeptide 1	-1.343	-0.425	3.440E-04	1.200E-02
Lrfn4	leucine rich repeat and fibronectin type III domain containing 4	-1.307	-0.386	3.370E-04	1.200E-02
Sec61b	Sec61 beta subunit	-1.290	-0.367	3.370E-04	1.200E-02
Ssbp4	single stranded DNA binding protein 4	-1.370	-0.454	3.420E-04	1.200E-02
Slc20a1	solute carrier family 20, member 1	1.249	0.321	3.410E-04	1.200E-02

Supplemental Table 2 (continued)

Cactin	spliceosome C complex subunit	-1.251	-0.323	3.380E-04	1.200E-02
Sox12	SRY-box containing gene 12	-1.311	-0.391	3.440E-04	1.200E-02
Zfp202	zinc finger protein 202	1.336	0.418	3.440E-04	1.200E-02
Zfp428	zinc finger protein 428	-1.292	-0.370	3.410E-04	1.200E-02
Cadm4	cell adhesion molecule 4	-1.333	-0.415	3.480E-04	1.210E-02
Ddx20	DEAD (Asp-Glu-Ala-Asp) box polypeptide 20	1.281	0.357	3.480E-04	1.210E-02
Nup160	nucleoporin 160	1.329	0.410	3.530E-04	1.220E-02
Ubqln1	ubiquilin 1	-1.199	-0.262	3.540E-04	1.220E-02
Efcab14	EF-hand calcium binding domain 14	1.317	0.397	3.620E-04	1.230E-02
Flywch2	FLYWCH family member 2	-1.261	-0.334	3.580E-04	1.230E-02
Gnaz	guanine nucleotide binding protein, alpha z subunit	-1.263	-0.337	3.550E-04	1.230E-02
Npat	nuclear protein in the AT region	1.385	0.470	3.570E-04	1.230E-02
Stx3	syntaxin 3	1.343	0.425	3.560E-04	1.230E-02
ENSRNOG00000046381	ENSRNOG00000046381	-1.356	-0.439	3.600E-04	1.230E-02
Rac3	RAS-related C3 botulinum substrate 3	-1.344	-0.427	3.630E-04	1.240E-02
Rps12	ribosomal protein S12	-1.341	-0.423	3.670E-04	1.250E-02
Cd46	CD46 antigen, complement regulatory protein	1.432	0.518	3.720E-04	1.250E-02
Cdt1	chromatin licensing and DNA replication factor 1	-1.414	-0.500	3.760E-04	1.250E-02
Mdn1	midasin homolog (yeast)	1.431	0.517	3.680E-04	1.250E-02
Ncapg2	non-SMC condensin II complex, subunit G2	1.414	0.500	3.710E-04	1.250E-02
Sgpl1	sphingosine phosphate lyase 1	1.312	0.392	3.750E-04	1.250E-02
Ubr2	ubiquitin protein ligase E3 component n-recognin 2	1.241	0.312	3.700E-04	1.250E-02
Wsb1	WD repeat and SOCS box-containing 1	1.388	0.473	3.750E-04	1.250E-02
Uhrf2	ubiquitin-like, containing PHD and RING finger domains 2	1.334	0.416	3.800E-04	1.260E-02
Zfand3	zinc finger, AN1-type domain 3	-1.193	-0.254	3.790E-04	1.260E-02
Rps3a	ribosomal protein S3A	-1.268	-0.343	3.840E-04	1.270E-02
Bcl7c	B-cell CLL/lymphoma 7C	-1.304	-0.383	3.890E-04	1.270E-02
Hps5	Hermansky-Pudlak syndrome 5 homolog (human)	1.395	0.480	3.890E-04	1.270E-02
Hmga1	high mobility group AT-hook I, related sequence 1	-1.352	-0.435	3.900E-04	1.270E-02
Podxl2	podocalyxin-like 2	-1.255	-0.328	3.880E-04	1.270E-02
Trim5	predicted gene 4992	1.408	0.494	3.840E-04	1.270E-02
Ptprd	protein tyrosine phosphatase, receptor type, D	1.273	0.348	3.870E-04	1.270E-02
Serpinc1	serine (or cysteine) peptidase inhibitor, clade C (antithrombin), member 1	1.385	0.470	3.860E-04	1.270E-02
AABR07054456.3	AABR07054456.3	-1.430	-0.516	3.840E-04	1.270E-02
Fntb	farnesyltransferase, CAAX box, beta	-1.216	-0.282	3.960E-04	1.280E-02
Mysm1	myb-like, SWIRM and MPN domains 1	1.379	0.464	3.970E-04	1.280E-02
Rpl36al	ribosomal protein L36A-like	-1.290	-0.367	3.990E-04	1.280E-02
Cisd1	CDGSH iron sulfur domain 1	-1.229	-0.297	3.970E-04	1.280E-02
Cramp1l	Crm, cramped-like (Drosophila)	1.326	0.407	4.000E-04	1.280E-02
Nog	noggin	-1.393	-0.478	4.000E-04	1.280E-02
Nr2f6	nuclear receptor subfamily 2, group F, member 6	-1.296	-0.374	3.990E-04	1.280E-02
Ist1	ESCRT-III associated factor	1.171	0.228	4.030E-04	1.290E-02
Cdon	cell adhesion molecule-related/down-regulated by oncogenes	1.376	0.460	4.110E-04	1.300E-02
Chd8	chromodomain helicase DNA binding protein 8	1.169	0.225	4.150E-04	1.300E-02
Map3k2	mitogen-activated protein kinase kinase kinase 2	1.352	0.435	4.150E-04	1.300E-02
Pclo	piccolo (presynaptic cytomatrix protein)	1.271	0.346	4.080E-04	1.300E-02
Ralgapa2	Ral GTPase activating protein catalytic alpha subunit 2	1.318	0.398	4.120E-04	1.300E-02
Slc7a6	solute carrier family 7 (cationic amino acid transporter, y+ system), member 6	1.238	0.308	4.130E-04	1.300E-02
Tceal3	transcription elongation factor A (SII)-like 3	-1.301	-0.380	4.130E-04	1.300E-02

Supplemental Table 2 (continued)

Tnrc6b	trinucleotide repeat containing 6b	1.327	0.408	4.150E-04	1.300E-02
Ubqln2	ubiquilin 2	-1.200	-0.263	4.090E-04	1.300E-02
Baz2a	bromodomain adjacent to zinc finger domain, 2A	1.308	0.387	4.190E-04	1.310E-02
C1qbp	complement component 1, q subcomponent binding protein	-1.246	-0.317	4.230E-04	1.310E-02
Foxo6	forkhead box O6	-1.300	-0.378	4.250E-04	1.310E-02
Ptms	parathymosin	-1.225	-0.293	4.210E-04	1.310E-02
Phex	phosphate regulating gene with homologies to endopeptidases on the X chromosome (hypophosphatemia, vitamin D resistant rickets)	1.419	0.505	4.260E-04	1.310E-02
Zfp787	zinc finger protein 787	-1.327	-0.408	4.240E-04	1.310E-02
Gpatch8	G patch domain containing 8	1.283	0.360	4.320E-04	1.320E-02
Secisbp2	SECIS binding protein 2	1.318	0.398	4.300E-04	1.320E-02
Stard9	START domain containing 9	1.397	0.482	4.290E-04	1.320E-02
Heximl	hexamethylene bis-acetamide inducible 1	-1.194	-0.256	4.340E-04	1.330E-02
Rps25	ribosomal protein S25	-1.328	-0.409	4.430E-04	1.350E-02
Atr	ataxia telangiectasia and Rad3 related	1.411	0.497	4.470E-04	1.350E-02
Ncapd3	non-SMC condensin II complex, subunit D3	1.281	0.357	4.440E-04	1.350E-02
Prpf4b	PRP4 pre-mRNA processing factor 4 homolog B (yeast)	1.397	0.482	4.470E-04	1.350E-02
Gpr162	G protein-coupled receptor 162	-1.223	-0.291	4.540E-04	1.360E-02
Med23	mediator complex subunit 23	1.279	0.355	4.530E-04	1.360E-02
Rnf213	ring finger protein 213	1.344	0.426	4.490E-04	1.360E-02
Akt1s1	AKT1 substrate 1 (proline-rich)	-1.232	-0.301	4.580E-04	1.370E-02
Csrp2	cysteine and glycine-rich protein 2	-1.274	-0.349	4.590E-04	1.370E-02
Kansl1l	KAT8 regulatory NSL complex subunit 1-like	1.393	0.478	4.560E-04	1.370E-02
Pggt1b	protein geranylgeranyltransferase type I, beta subunit	1.336	0.418	4.570E-04	1.370E-02
Vps13d	vacuolar protein sorting 13 D (yeast)	1.239	0.309	4.600E-04	1.370E-02
ENSRNOG00000049713	ENSRNOG00000049713	1.423	0.509	4.650E-04	1.380E-02
Carmil2	capping protein regulator and myosin 1 linker 2	-1.273	-0.348	4.690E-04	1.390E-02
RGD1307752	similar to RIKEN cDNA 1110008F13	-1.186	-0.246	4.750E-04	1.400E-02
Cox5a	cytochrome c oxidase, subunit Va	-1.316	-0.396	4.850E-04	1.410E-02
Kcna2	potassium voltage-gated channel, shaker-related subfamily, member 2	1.402	0.488	4.830E-04	1.410E-02
Pfn1	profilin 1	-1.283	-0.359	4.830E-04	1.410E-02
Phb	prohibitin	-1.202	-0.266	4.780E-04	1.410E-02
Prmt2	protein arginine N-methyltransferase 2	-1.225	-0.293	4.780E-04	1.410E-02
TRAPPC2	similar to Chain A, The Crystal Structure Of The Bet3-Trs31-Sedlin Complex	-1.422	-0.508	4.780E-04	1.410E-02
Zfp706	zinc finger protein 706	-1.327	-0.408	4.840E-04	1.410E-02
Mpc2	mitochondrial pyruvate carrier 2	-1.235	-0.304	4.930E-04	1.430E-02
Phactr3	phosphatase and actin regulator 3	-1.280	-0.356	4.910E-04	1.430E-02
Socs1	suppressor of cytokine signaling 1	-1.415	-0.501	4.930E-04	1.430E-02
ATG101	autophagy related 101	-1.180	-0.239	5.050E-04	1.450E-02
Rell2	RELT-like 2	-1.366	-0.450	5.010E-04	1.450E-02
Usp24	ubiquitin specific peptidase 24	1.347	0.430	5.050E-04	1.450E-02
Nek9	NIMA (never in mitosis gene a)-related expressed kinase 9	1.238	0.308	5.110E-04	1.460E-02
Prpf19	PRP19/PSO4 pre-mRNA processing factor 19 homolog (S. cerevisiae)	-1.227	-0.295	5.070E-04	1.460E-02
Sumo2l	small ubiquitin-like modifier 4	-1.412	-0.498	5.080E-04	1.460E-02
Slc1a2	solute carrier family 1 (glial high affinity glutamate transporter), member 2	1.319	0.399	5.130E-04	1.460E-02
Qser1	glutamine and serine rich 1	1.356	0.439	5.150E-04	1.470E-02
Mir186	microRNA 186	1.406	0.492	5.190E-04	1.470E-02

Supplemental Table 2 (continued)

Fam69b	family with sequence similarity 69, member B	-1.223	-0.290	5.210E-04	1.480E-02
U2surp	U2 snRNP-associated SURP domain containing	1.343	0.425	5.240E-04	1.480E-02
ATP5G3	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c (subunit 9), isoform 3	-1.231	-0.300	5.280E-04	1.490E-02
Cygb	cytoglobin	-1.310	-0.390	5.330E-04	1.490E-02
Dock7	dedicator of cytokinesis 7	1.225	0.293	5.280E-04	1.490E-02
Ninl	ninein-like	1.329	0.410	5.330E-04	1.490E-02
Plag1	pleiomorphic adenoma gene 1	1.385	0.470	5.290E-04	1.490E-02
Psmb5	predicted gene 3375	-1.254	-0.327	5.300E-04	1.490E-02
Gfm2	G elongation factor, mitochondrial 2	1.294	0.372	5.430E-04	1.500E-02
Luzp1	leucine zipper protein 1	1.308	0.387	5.440E-04	1.500E-02
Lrp1b	low density lipoprotein-related protein 1B (deleted in tumors)	1.363	0.447	5.430E-04	1.500E-02
Nenf	neuron derived neurotrophic factor	-1.340	-0.422	5.440E-04	1.500E-02
Pgap1	post-GPI attachment to proteins 1	1.319	0.399	5.360E-04	1.500E-02
Ppp6r3	protein phosphatase 6, regulatory subunit 3	1.246	0.317	5.410E-04	1.500E-02
Ptpn9	protein tyrosine phosphatase, non-receptor type 9	1.184	0.244	5.470E-04	1.500E-02
Phtf1	putative homeodomain transcription factor 1	1.385	0.470	5.470E-04	1.500E-02
Wwc3	WWC family member 3	1.345	0.428	5.450E-04	1.500E-02
Lrrn2	leucine rich repeat protein 2, neuronal	-1.241	-0.311	5.560E-04	1.510E-02
Ranbp17	RAN binding protein 17	1.358	0.442	5.510E-04	1.510E-02
Setdb2	SET domain, bifurcated 2	1.382	0.467	5.500E-04	1.510E-02
RGD1305587	similar to RIKEN cDNA 2010107G23	-1.257	-0.330	5.550E-04	1.510E-02
Ubr5	ubiquitin protein ligase E3 component n-recognin 5	1.248	0.320	5.580E-04	1.510E-02
Zzz3	zinc finger, ZZ domain containing 3	1.330	0.411	5.520E-04	1.510E-02
Ccdc92	coiled-coil domain containing 92	-1.260	-0.333	5.700E-04	1.530E-02
Exosc5	exosome component 5	-1.288	-0.365	5.690E-04	1.530E-02
Hcfc2	host cell factor C2	1.256	0.329	5.640E-04	1.530E-02
Prr14l	proline rich 14-like	1.322	0.403	5.710E-04	1.530E-02
Serp2	stress-associated endoplasmic reticulum protein family member 2	-1.339	-0.421	5.700E-04	1.530E-02
Mff	mitochondrial fission factor	-1.415	-0.501	5.760E-04	1.540E-02
Ppp1r1a	protein phosphatase 1, regulatory (inhibitor) subunit 1A	-1.296	-0.374	5.730E-04	1.540E-02
Zfp612	zinc finger protein 612	1.356	0.439	5.780E-04	1.540E-02
Ddit4	DNA-damage-inducible transcript 4	-1.245	-0.316	5.800E-04	1.550E-02
Capzb	capping protein (actin filament) muscle Z-line, beta	-1.170	-0.227	5.890E-04	1.570E-02
Gpsm1	G-protein signalling modulator 1 (AGS3-like, C. elegans)	-1.177	-0.235	5.930E-04	1.570E-02
Tmem26	transmembrane protein 26	1.398	0.483	5.910E-04	1.570E-02
UBB	ubiquitin B	-1.242	-0.313	5.980E-04	1.580E-02
Acot7	acyl-CoA thioesterase 7	-1.275	-0.351	6.010E-04	1.580E-02
Acbd6	acyl-Coenzyme A binding domain containing 6	-1.251	-0.323	6.010E-04	1.580E-02
YBX1	similar to nuclease sensitive element binding protein 1	-1.283	-0.359	6.050E-04	1.590E-02
Krit1	KRIT1, ankyrin repeat containing	1.380	0.465	6.070E-04	1.590E-02
Sycp3	synaptonemal complex protein 3	1.413	0.499	6.030E-04	1.590E-02
Zfp451	zinc finger protein 451	1.317	0.397	6.100E-04	1.590E-02
Cep290	centrosomal protein 290	1.387	0.472	6.140E-04	1.600E-02
DPF1	D4, zinc and double PHD fingers family 1	-1.228	-0.296	6.110E-04	1.600E-02
Otud4	OTU domain containing 4	1.335	0.417	6.120E-04	1.600E-02
Rab23	RAB23, member RAS oncogene family	1.180	0.239	6.240E-04	1.620E-02
Emd	echinoderm microtubule associated protein like 4	-1.231	-0.300	6.360E-04	1.650E-02
Ganc	glucosidase, alpha	1.345	0.428	6.420E-04	1.660E-02
Exosc4	exosome component 4	-1.300	-0.378	6.470E-04	1.670E-02

Supplemental Table 2 (continued)

Hcfc1r1	host cell factor C1 regulator 1 (XPO1-dependent)	-1.408	-0.494	6.490E-04	1.670E-02
Hypk	Huntingtin interacting protein K	-1.268	-0.343	6.480E-04	1.670E-02
Mbnl1	muscleblind-like 1 (Drosophila)	1.273	0.348	6.520E-04	1.670E-02
RGD1565775	similar to RIKEN cDNA 2810403A07	1.334	0.416	6.520E-04	1.670E-02
Fam178a	family with sequence similarity 178, member A	1.348	0.431	6.580E-04	1.680E-02
Cntfr	ciliary neurotrophic factor receptor	-1.344	-0.427	6.610E-04	1.690E-02
Bms1	BMS1 homolog, ribosome assembly protein (yeast)	1.322	0.403	6.660E-04	1.700E-02
Ppia	peptidylprolyl isomerase A	-1.268	-0.342	6.740E-04	1.710E-02
Bok	BCL2-related ovarian killer protein	-1.241	-0.312	6.730E-04	1.710E-02
Cds2	CDP-diacylglycerol synthase (phosphatidate cytidylyltransferase) 2	1.291	0.368	6.830E-04	1.720E-02
Gsk3a	glycogen synthase kinase 3 alpha	-1.253	-0.325	6.830E-04	1.720E-02
Pam16	presequence translocase-associated motor 16 homolog (S. cerevisiae)	-1.304	-0.383	6.800E-04	1.720E-02
Rc3h2	ring finger and CCCH-type zinc finger domains 2	1.322	0.403	6.810E-04	1.720E-02
Ndufa6	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6 (B14)	-1.253	-0.325	6.870E-04	1.730E-02
Med17	mediator complex subunit 17	1.355	0.438	6.960E-04	1.750E-02
Arhgap29	Rho GTPase activating protein 29	1.365	0.449	6.970E-04	1.750E-02
RGD1307100	imilar to RIKEN cDNA D630029K19	1.359	0.443	7.070E-04	1.760E-02
Ltv1	LTV1 homolog (S. cerevisiae)	1.310	0.390	7.020E-04	1.760E-02
Camk2n2	calcium/calmodulin-dependent protein kinase II inhibitor 2	-1.391	-0.476	7.160E-04	1.780E-02
RGD1308134	similar to RIKEN cDNA 1110020A23	-1.272	-0.347	7.150E-04	1.780E-02
Tomm6	translocase of outer mitochondrial membrane 6 homolog (yeast)	-1.336	-0.418	7.150E-04	1.780E-02
Dda1	DET1 and DDB1 associated 1	-1.283	-0.360	7.250E-04	1.790E-02
Fnip1	folliculin interacting protein 1	1.352	0.435	7.220E-04	1.790E-02
Snx13	sorting nexin 13	1.342	0.424	7.270E-04	1.790E-02
Wbp4	WW domain binding protein 4	1.294	0.372	7.230E-04	1.790E-02
Uba52	ubiquitin A-52 residue ribosomal protein fusion product 1	-1.286	-0.363	7.380E-04	1.810E-02
Il1rapl1	interleukin 1 receptor accessory protein-like 1	1.384	0.469	7.390E-04	1.810E-02
Rrad	Ras-related associated with diabetes	-1.380	-0.465	7.340E-04	1.810E-02
Pogz	pogo transposable element with ZNF domain	1.180	0.239	7.580E-04	1.850E-02
Zfp386	zinc finger protein 386 (Kruppel-like)	1.369	0.453	7.550E-04	1.850E-02
Star	steroidogenic acute regulatory protein	1.363	0.447	7.650E-04	1.870E-02
Eml6	echinoderm microtubule associated protein like 6	1.340	0.422	7.750E-04	1.880E-02
ENSRNOG00000046986	ENSRNOG00000046986	1.287	0.364	7.730E-04	1.880E-02
Rpl13a	ribosomal protein L13A	-1.215	-0.281	7.820E-04	1.900E-02
Ly6h	lymphocyte antigen 6 complex, locus H	-1.292	-0.370	7.950E-04	1.910E-02
Rnaseh2a	ribonuclease H2, large subunit	-1.252	-0.324	7.950E-04	1.910E-02
Smc5	structural maintenance of chromosomes 5	1.367	0.451	7.980E-04	1.910E-02
Usf2	upstream transcription factor 2	-1.240	-0.310	8.040E-04	1.910E-02
Gnl1	guanine nucleotide binding protein-like 1	-1.244	-0.315	7.930E-04	1.910E-02
Med1	mediator complex subunit 1	1.256	0.329	7.890E-04	1.910E-02
Map3k11	mitogen-activated protein kinase kinase kinase 11	-1.387	-0.472	7.890E-04	1.910E-02
Ndn	necdin	-1.229	-0.297	8.020E-04	1.910E-02
Kctd17	potassium channel tetramerisation domain containing 17	-1.239	-0.309	8.000E-04	1.910E-02
Kcnmb4	potassium large conductance calcium-activated channel, subfamily M, beta member 4	-1.274	-0.349	7.980E-04	1.910E-02
ENSRNOG00000018204	ENSRNOG00000018204	1.402	0.488	7.890E-04	1.910E-02
Cox8a	cytochrome c oxidase, subunit VIIIa	-1.346	-0.429	8.130E-04	1.920E-02
Acadsb	acyl-Coenzyme A dehydrogenase, short/branched chain	1.330	0.411	8.110E-04	1.920E-02

Supplemental Table 2 (continued)

Mrps34	mitochondrial ribosomal protein S34	-1.270	-0.345	8.160E-04	1.920E-02
Mospd2	motile sperm domain containing 2	1.355	0.438	8.110E-04	1.920E-02
Snrpg	predicted gene 8186	-1.388	-0.473	8.070E-04	1.920E-02
Vps13a	vacuolar protein sorting 13A (yeast)	1.394	0.479	8.090E-04	1.920E-02
Clip3	CAP-GLY domain containing linker protein 3	-1.398	-0.483	8.200E-04	1.930E-02
Nabp2	nucleic acid binding protein 2	-1.242	-0.313	8.200E-04	1.930E-02
Mospd3	motile sperm domain containing 3	-1.205	-0.269	8.280E-04	1.940E-02
Samd14	sterile alpha motif domain containing 14	-1.319	-0.399	8.260E-04	1.940E-02
Arid4a	AT rich interactive domain 4A (RBP1-like)	1.327	0.408	8.340E-04	1.950E-02
Mrpl34	mitochondrial ribosomal protein L34	-1.310	-0.390	8.350E-04	1.950E-02
Ahr	aryl-hydrocarbon receptor	1.376	0.460	8.460E-04	1.960E-02
Fam35a	family with sequence similarity 35, member A	1.337	0.419	8.470E-04	1.960E-02
Msh3	mutS homolog 3 (E. coli)	1.313	0.393	8.430E-04	1.960E-02
Pebp1	phosphatidylethanolamine binding protein 1	-1.253	-0.325	8.470E-04	1.960E-02
Pfn2	profilin 2	-1.281	-0.357	8.500E-04	1.960E-02
Psma7	proteasome (prosome, macropain) subunit, alpha type 7	-1.208	-0.273	8.490E-04	1.960E-02
Ube2r2	ubiquitin-conjugating enzyme E2R 2	-1.174	-0.232	8.460E-04	1.960E-02
Vps72	vacuolar protein sorting 72 (yeast)	-1.222	-0.289	8.420E-04	1.960E-02
Gls	glutaminase	1.292	0.370	8.590E-04	1.970E-02
Ndufs5	NADH dehydrogenase (ubiquinone) Fe-S protein 5	-1.364	-0.448	8.570E-04	1.970E-02
Vldlr	very low density lipoprotein receptor	1.317	0.397	8.660E-04	1.980E-02
Akap8	A kinase (PRKA) anchor protein 8	1.302	0.381	8.750E-04	1.990E-02
Fam73a	family with sequence similarity 73, member A	1.213	0.279	8.770E-04	1.990E-02
Pafah1b3	platelet-activating factor acetylhydrolase, isoform 1b, subunit 3	-1.276	-0.352	8.720E-04	1.990E-02
Slfn3	schlafen 3	1.398	0.483	8.690E-04	1.990E-02
Trpm3	transient receptor potential cation channel, subfamily M, member 3	1.255	0.328	8.790E-04	1.990E-02
Tmem158	transmembrane protein 158	-1.382	-0.467	8.750E-04	1.990E-02
Usp6nl	USP6 N-terminal like	1.245	0.316	8.940E-04	2.020E-02
Timm13	translocase of inner mitochondrial membrane 13 homolog (yeast)	-1.287	-0.364	9.070E-04	2.050E-02
Tpgs1	tubulin polyglutamylase complex subunit 1	-1.309	-0.388	9.090E-04	2.050E-02
Mitd1	MIT, microtubule interacting and transport, domain containing 1	1.373	0.457	9.200E-04	2.070E-02
Cdk9	cyclin-dependent kinase 9 (CDC2-related kinase)	-1.197	-0.260	9.280E-04	2.090E-02
Mrpl54	mitochondrial ribosomal protein L54	-1.333	-0.415	9.300E-04	2.090E-02
Samd1	sterile alpha motif domain containing 1	-1.249	-0.321	9.330E-04	2.090E-02
Ndufb7	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7	-1.225	-0.293	9.380E-04	2.100E-02
Ssna1	Sjogren's syndrome nuclear autoantigen 1	-1.324	-0.405	9.370E-04	2.100E-02
BC055324	cDNA sequence BC055324	1.381	0.466	9.530E-04	2.130E-02
RGD1563834	similar to 40S ribosomal protein S16	-1.389	-0.474	9.580E-04	2.130E-02
Ubc	ubiquitin C	-1.289	-0.366	9.700E-04	2.140E-02
Dennd5b	DENN/MADD domain containing 5B	1.286	0.363	9.680E-04	2.140E-02
Nox4	NADPH oxidase 4	1.394	0.479	9.700E-04	2.140E-02
Rev3l	REV3-like, catalytic subunit of DNA polymerase zeta RAD54 like (S. cerevisiae)	1.246	0.317	9.610E-04	2.140E-02
40971		-1.227	-0.295	9.630E-04	2.140E-02
Fam127b	family with sequence similarity 127, member B	-1.237	-0.307	9.730E-04	2.150E-02
Alkbh2	alkB, alkylation repair homolog 2 (E. coli)	-1.359	-0.443	9.790E-04	2.160E-02
Kmt2a	lysine methyltransferase 2A	1.344	0.426	9.830E-04	2.160E-02
Heatr5a	HEAT repeat containing 5A	1.280	0.356	9.870E-04	2.170E-02

Supplemental Table 2 (continued)

Plekha1	pleckstrin homology domain containing, family A (phosphoinositide binding specific) member 1	1.319	0.399	9.890E-04	2.170E-02
Ctxn1	cortexin 1	-1.326	-0.407	1.000E-03	2.180E-02
Cyb561d2	cytochrome b-561 domain containing 2	-1.299	-0.377	1.010E-03	2.180E-02
Dzip3	DAZ interacting protein 3, zinc finger	1.294	0.372	1.010E-03	2.180E-02
Fkbp8	FK506 binding protein 8	-1.254	-0.326	9.950E-04	2.180E-02
Irf2bp2	interferon regulatory factor 2 binding protein 2	-1.336	-0.418	1.010E-03	2.180E-02
Sec61g	predicted gene 11575	-1.301	-0.380	1.010E-03	2.180E-02
Sh2d3c	SH2 domain containing 3C	-1.320	-0.400	1.010E-03	2.180E-02
RGD1559896	similar to RIKEN cDNA 2310022B05	-1.223	-0.290	1.000E-03	2.180E-02
Son	Son DNA binding protein	1.207	0.272	1.000E-03	2.180E-02
Syt3	synaptotagmin III	-1.318	-0.398	1.000E-03	2.180E-02
Trappc8	trafficking protein particle complex 8	1.259	0.332	1.000E-03	2.180E-02
Scyl3	SCY1-like 3 (S. cerevisiae)	1.335	0.417	1.020E-03	2.200E-02
Clock	circadian locomoter output cycles kaput	1.365	0.449	1.040E-03	2.230E-02
Fancd2	Fanconi anemia, complementation group D2	1.309	0.389	1.040E-03	2.230E-02
Npff	neuropeptide FF-amide peptide precursor	1.381	0.466	1.040E-03	2.230E-02
Zzef1	zinc finger, ZZ-type with EF hand domain 1	1.243	0.314	1.040E-03	2.230E-02
Ap3b1	adaptor-related protein complex 3, beta 1 subunit	1.268	0.343	1.050E-03	2.240E-02
Lypla2	lysophospholipase 2	-1.199	-0.262	1.050E-03	2.240E-02
Mcrip1	MAPK regulated co-repressor interacting protein 1	-1.236	-0.306	1.050E-03	2.240E-02
Gipc1	GIPC PDZ domain containing family, member 1	-1.223	-0.290	1.070E-03	2.250E-02
Hap1	huntingtin-associated protein 1	-1.233	-0.302	1.060E-03	2.250E-02
Pacsin2	protein kinase C and casein kinase substrate in neurons 2	-1.188	-0.249	1.070E-03	2.250E-02
Rab5c	RAB5C, member RAS oncogene family	-1.184	-0.244	1.070E-03	2.250E-02
Ranbp10	RAN binding protein 10	1.259	0.332	1.070E-03	2.250E-02
RGD1559909	RGD1559909	-1.295	-0.373	1.070E-03	2.250E-02
RGD1560394	RGD1560394	-1.362	-0.446	1.060E-03	2.250E-02
Topbp1	topoisomerase (DNA) II binding protein 1	1.213	0.279	1.070E-03	2.250E-02
Ube4a	ubiquitination factor E4A, UFD2 homolog (S. cerevisiae)	1.243	0.314	1.060E-03	2.250E-02
Fzr1	fizzy/cell division cycle 20 related 1 (Drosophila)	-1.261	-0.335	1.090E-03	2.270E-02
Ngfrap1	nerve growth factor receptor (TNFRSF16) associated protein 1	-1.268	-0.343	1.090E-03	2.270E-02
Acap2	ArfGAP with coiled-coil, ankyrin repeat and PH domains 2	1.223	0.291	1.090E-03	2.280E-02
Limk1	LIM-domain containing, protein kinase	-1.198	-0.261	1.090E-03	2.280E-02
MP68	6.8 kDa mitochondrial proteolipid	-1.353	-0.436	1.100E-03	2.300E-02
Rpl13	ribosomal protein L13	-1.277	-0.353	1.120E-03	2.310E-02
Wrn	Werner syndrome homolog (human)	1.376	0.460	1.130E-03	2.310E-02
Cltb	clathrin, light polypeptide (Lcb)	-1.250	-0.322	1.120E-03	2.310E-02
Dusp14	dual specificity phosphatase 14	-1.379	-0.464	1.120E-03	2.310E-02
Herpud1	homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1	-1.244	-0.315	1.120E-03	2.310E-02
Neurl1a	neuralized homolog 1A (Drosophila)	-1.359	-0.443	1.120E-03	2.310E-02
Orc3	origin recognition complex, subunit 3	1.274	0.349	1.110E-03	2.310E-02
Pnn	pinin	1.337	0.419	1.110E-03	2.310E-02
Tbk1	TANK-binding kinase 1	1.307	0.386	1.120E-03	2.310E-02
Tmem245	transmembrane protein 245	1.331	0.412	1.130E-03	2.310E-02
Vegfb	vascular endothelial growth factor B	-1.357	-0.440	1.110E-03	2.310E-02
E2f3	E2F transcription factor 3	1.292	0.370	1.130E-03	2.320E-02
Lrig2	leucine-rich repeats and immunoglobulin-like domains 2	1.302	0.381	1.150E-03	2.350E-02
Stxbp5	syntaxin binding protein 5 (tomosyn)	1.198	0.261	1.160E-03	2.370E-02

Supplemental Table 2 (continued)

Urb2	URB2 ribosome biogenesis 2 homolog (S. cerevisiae)	1.236	0.306	1.160E-03	2.370E-02
Caly	calcyon neuron-specific vesicular protein	-1.339	-0.421	1.180E-03	2.380E-02
Plekha5	pleckstrin homology domain containing, family A member 5	1.312	0.392	1.170E-03	2.380E-02
Reck	reversion-inducing-cysteine-rich protein with kazal motifs	1.330	0.411	1.170E-03	2.380E-02
Cox17	cytochrome c oxidase, subunit XVII assembly protein homolog (yeast)	-1.317	-0.397	1.180E-03	2.390E-02
Dennd1b	DENN/MADD domain containing 1B	1.364	0.448	1.180E-03	2.390E-02
Srrd	SRR1 domain containing	-1.304	-0.383	1.190E-03	2.390E-02
Nup37	nucleoporin 37	1.365	0.449	1.190E-03	2.400E-02
Zmat1	zinc finger, matrin type 1	1.317	0.397	1.200E-03	2.420E-02
Rpl36a	similar to ribosomal protein L36a	-1.257	-0.330	1.220E-03	2.450E-02
Dpp8	dipeptidylpeptidase 8	1.203	0.267	1.220E-03	2.450E-02
Ogt	O-linked N-acetylglucosamine (GlcNAc) transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylglucosaminyl transferase)	1.368	0.452	1.230E-03	2.470E-02
Numbl	numb-like	-1.283	-0.359	1.250E-03	2.510E-02
Trmt61a	tRNA methyltransferase 61 homolog A (S. cerevisiae)	-1.237	-0.307	1.260E-03	2.520E-02
RGD1559904	similar to mKIAA1429 protein	1.318	0.398	1.260E-03	2.520E-02
Rfx7	regulatory factor X, 7	1.319	0.399	1.280E-03	2.530E-02
Fau	similar to fau	-1.272	-0.347	1.280E-03	2.530E-02
Lmtk3	emur tyrosine kinase 3	-1.291	-0.368	1.280E-03	2.530E-02
Enho	energy homeostasis associated	-1.333	-0.415	1.270E-03	2.530E-02
Gdap1l1	ganglioside-induced differentiation-associated protein 1-like 1	-1.247	-0.318	1.280E-03	2.530E-02
Mrp63	mitochondrial ribosomal protein 63	-1.320	-0.400	1.270E-03	2.530E-02
Tpst1	protein-tyrosine sulfotransferase 1	-1.174	-0.231	1.280E-03	2.530E-02
Sncb	synuclein, beta	-1.320	-0.401	1.270E-03	2.530E-02
Sp1	trans-acting transcription factor 1	1.280	0.356	1.270E-03	2.530E-02
Cecr2	cat eye syndrome chromosome region, candidate 2 homolog (human)	1.351	0.434	1.290E-03	2.540E-02
Pcm1	pericentriolar material 1	1.305	0.384	1.290E-03	2.540E-02
Wdr3	WD repeat domain 3	1.240	0.310	1.300E-03	2.540E-02
Zfp78	zinc finger protein 78	1.383	0.468	1.290E-03	2.540E-02
Cat	catalase	-1.189	-0.250	1.310E-03	2.560E-02
Xrn1	5'-3' exoribonuclease 1	1.339	0.421	1.310E-03	2.570E-02
Ogfr	opioid growth factor receptor	-1.240	-0.310	1.320E-03	2.570E-02
Jun	Jun oncogene	-1.374	-0.458	1.320E-03	2.580E-02
Chadl	chondroadherin-like	-1.356	-0.439	1.330E-03	2.590E-02
Nmral1	NmrA-like family domain containing 1	-1.256	-0.329	1.340E-03	2.590E-02
Cep85	centrosomal protein 85	1.302	0.381	1.350E-03	2.610E-02
Glb1l	galactosidase, beta 1-like	1.328	0.409	1.350E-03	2.610E-02
AABR07061902.1	AABR07061902.1	-1.322	-0.403	1.350E-03	2.610E-02
Camk2n1	calcium/calmodulin-dependent protein kinase II inhibitor 1	-1.324	-0.405	1.370E-03	2.630E-02
Zfp871	zinc finger protein 871	1.340	0.422	1.360E-03	2.630E-02
Imp3	IMP3, U3 small nucleolar ribonucleoprotein, homolog (yeast)	-1.240	-0.310	1.370E-03	2.640E-02
Trit1	tRNA isopentenyltransferase 1	1.291	0.368	1.370E-03	2.640E-02
Map3k10	mitogen-activated protein kinase kinase kinase 10	-1.292	-0.370	1.380E-03	2.650E-02
Col11a1	collagen, type XI, alpha 1	1.379	0.464	1.390E-03	2.660E-02
CYC1	cytochrome c-1	-1.226	-0.294	1.390E-03	2.660E-02
Kcnt2	potassium channel, subfamily T, member 2	1.274	0.349	1.390E-03	2.660E-02
Zfp286a	zinc finger protein 286A	1.299	0.377	1.390E-03	2.660E-02

Supplemental Table 2 (continued)

Sod1	superoxide dismutase 1, soluble	-1.235	-0.304	1.400E-03	2.670E-02
Cops6	COP9 (constitutive photomorphogenic) homolog, subunit 6 (Arabidopsis thaliana)	-1.194	-0.256	1.400E-03	2.670E-02
Pink1	PTEN induced putative kinase 1	-1.282	-0.358	1.410E-03	2.680E-02
Chd9	chromodomain helicase DNA binding protein 9	1.373	0.457	1.420E-03	2.690E-02
Gnai2	guanine nucleotide binding protein (G protein), alpha inhibiting 2	-1.214	-0.280	1.420E-03	2.690E-02
Kcnj8	potassium inwardly-rectifying channel, subfamily J, member 8	1.341	0.423	1.420E-03	2.690E-02
Wnk3	WNK lysine deficient protein kinase 3	1.301	0.380	1.420E-03	2.690E-02
Clcc1	chloride channel CLIC-like 1	1.198	0.261	1.430E-03	2.710E-02
Phf15	PHD finger protein 15	1.373	0.457	1.430E-03	2.710E-02
Eefsec	eukaryotic elongation factor, selenocysteine-tRNA-specific	-1.242	-0.313	1.440E-03	2.720E-02
Stub1	STIP1 homology and U-Box containing protein 1	-1.243	-0.314	1.450E-03	2.720E-02
Strn4	striatin, calmodulin binding protein 4	-1.215	-0.281	1.460E-03	2.750E-02
Gxylt1	glycosyltransferase 8 domain containing 3	1.338	0.420	1.480E-03	2.760E-02
Mir2985	microRNA 2985	1.376	0.460	1.480E-03	2.760E-02
Ndufs7	NADH dehydrogenase (ubiquinone) Fe-S protein 7	-1.235	-0.304	1.470E-03	2.760E-02
Pla2g12a	phospholipase A2, group XIIA	-1.247	-0.318	1.480E-03	2.760E-02
Slc35f5	solute carrier family 35, member F5	1.290	0.367	1.480E-03	2.760E-02
Sf3b3	splicing factor 3b, subunit 3	1.213	0.278	1.470E-03	2.760E-02
Bad	BCL2-associated agonist of cell death	-1.229	-0.298	1.490E-03	2.770E-02
B9d2	B9 protein domain 2	-1.301	-0.380	1.510E-03	2.810E-02
Morc3	microrchidia 3	1.309	0.389	1.520E-03	2.810E-02
Nup155	nucleoporin 155	1.273	0.348	1.520E-03	2.810E-02
Stk11	serine/threonine kinase 11	-1.205	-0.269	1.520E-03	2.810E-02
Snrpd3	small nuclear ribonucleoprotein D3	-1.171	-0.228	1.520E-03	2.810E-02
Eif2ak4	eukaryotic translation initiation factor 2 alpha kinase 4	1.248	0.320	1.540E-03	2.840E-02
Frs3	fibroblast growth factor receptor substrate 3	-1.268	-0.342	1.550E-03	2.840E-02
Higd2a	HIG1 domain family, member 2A	-1.319	-0.399	1.540E-03	2.840E-02
Hmgn2	high mobility group nucleosomal binding domain 4	-1.289	-0.366	1.550E-03	2.840E-02
Nup153	nucleoporin 153	1.276	0.352	1.550E-03	2.840E-02
Prrc2c	proline-rich coiled-coil 2C	1.192	0.253	1.550E-03	2.840E-02
Atp5l	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit g	-1.248	-0.320	1.560E-03	2.850E-02
Atp5d	ATP synthase, H+ transporting, mitochondrial F1 complex, delta subunit	-1.300	-0.378	1.570E-03	2.860E-02
Mrpl12	mitochondrial ribosomal protein L12	-1.212	-0.277	1.570E-03	2.860E-02
Zfp560	zinc finger protein 560	1.301	0.380	1.560E-03	2.860E-02
EIF3F	eukaryotic translation initiation factor 3, subunit F	-1.220	-0.287	1.580E-03	2.870E-02
Cdc40	cell division cycle 40 homolog (yeast)	1.318	0.398	1.590E-03	2.880E-02
Dusp26	dual specificity phosphatase 26 (putative)	-1.262	-0.336	1.580E-03	2.880E-02
Hcn2	hyperpolarization-activated, cyclic nucleotide-gated K+ 2	-1.246	-0.317	1.590E-03	2.880E-02
Prmt10	protein arginine methyltransferase 10 (putative)	1.223	0.290	1.590E-03	2.880E-02
Ppp1r9b	protein phosphatase 1, regulatory subunit 9B	-1.155	-0.208	1.590E-03	2.880E-02
Usp28	ubiquitin specific peptidase 28	1.218	0.285	1.580E-03	2.880E-02
Rpl34	ribosomal protein L34	-1.255	-0.328	1.600E-03	2.900E-02
Ppp2r5d	protein phosphatase 2, regulatory subunit B (B56), delta isoform	-1.139	-0.188	1.620E-03	2.930E-02
Arl13b	ADP-ribosylation factor-like 13B	1.318	0.398	1.630E-03	2.940E-02
Dusp7	dual specificity phosphatase 7	-1.222	-0.289	1.640E-03	2.940E-02
Efhb	EF hand domain family, member B	1.373	0.457	1.640E-03	2.940E-02
Fnbp4	formin binding protein 4	1.278	0.354	1.640E-03	2.940E-02

Supplemental Table 2 (continued)

Map1lc3a	microtubule-associated protein 1 light chain 3 alpha	-1.301	-0.380	1.640E-03	2.940E-02
Nbeal1	neurobeachin like 1	1.351	0.434	1.650E-03	2.940E-02
Rfc1	replication factor C (activator 1) 1	1.193	0.255	1.650E-03	2.940E-02
Ttll4	tubulin tyrosine ligase-like family, member 4	1.275	0.350	1.640E-03	2.940E-02
Wwc1	WW, C2 and coiled-coil domain containing 1	-1.239	-0.309	1.630E-03	2.940E-02
Slc25a1	solute carrier family 25 (mitochondrial carrier, citrate transporter), member 1	-1.266	-0.340	1.660E-03	2.950E-02
Bop1	block of proliferation 1	-1.188	-0.248	1.660E-03	2.960E-02
Nek10	NIMA (never in mitosis gene a)- related kinase 10	1.325	0.406	1.670E-03	2.960E-02
Asun	asunder, spermatogenesis regulator	1.295	0.373	1.680E-03	2.970E-02
Pdlim4	PDZ and LIM domain 4	-1.329	-0.410	1.680E-03	2.970E-02
Noc3l	nucleolar complex associated 3 homolog (S. cerevisiae)	1.356	0.439	1.690E-03	2.980E-02
Pianp	PILR alpha associated neural protein	-1.253	-0.325	1.690E-03	2.980E-02
Rock2	Rho-associated coiled-coil containing protein kinase 2	1.314	0.394	1.690E-03	2.980E-02
Hspbp1	HSPA (heat shock 70kDa) binding protein, cytoplasmic cochaperone 1	-1.229	-0.297	1.710E-03	3.000E-02
Zdhhc6	zinc finger, DHHC domain containing 6	1.268	0.343	1.710E-03	3.010E-02
Prelid1	PRELI domain containing 1	-1.239	-0.309	1.730E-03	3.020E-02
Pick1	protein interacting with C kinase 1	-1.209	-0.274	1.720E-03	3.020E-02
Rapgef6	Rap guanine nucleotide exchange factor (GEF) 6	1.283	0.360	1.720E-03	3.020E-02
Tmem67	transmembrane protein 67	1.284	0.361	1.730E-03	3.020E-02
Ube2d1	ubiquitin-conjugating enzyme E2D 1, UBC4/5 homolog (yeast)	-1.341	-0.423	1.730E-03	3.020E-02
Fam135a	family with sequence similarity 135, member A	1.319	0.399	1.750E-03	3.030E-02
Hecw2	HECT, C2 and WW domain containing E3 ubiquitin protein ligase 2	1.275	0.351	1.740E-03	3.030E-02
Lrrc73	leucine rich repeat containing 73	-1.333	-0.415	1.750E-03	3.030E-02
Pold2	polymerase (DNA directed), delta 2, regulatory subunit	-1.285	-0.362	1.740E-03	3.030E-02
Pcdh15	protocadherin 15	1.275	0.350	1.740E-03	3.030E-02
Csk	c-src tyrosine kinase	-1.117	-0.159	1.770E-03	3.040E-02
Dusp8	dual specificity phosphatase 8	-1.218	-0.284	1.750E-03	3.040E-02
Fsd1	fibronectin type 3 and SPRY domain-containing protein	-1.228	-0.296	1.750E-03	3.040E-02
Myl9	myosin, light polypeptide 9, regulatory	-1.300	-0.378	1.760E-03	3.040E-02
Slc27a4	solute carrier family 27 (fatty acid transporter), member 4	-1.198	-0.261	1.770E-03	3.040E-02
Trnau1ap	tRNA selenocysteine 1 associated protein 1	-1.213	-0.279	1.760E-03	3.040E-02
Uqcrq	ubiquinol-cytochrome c reductase, complex III subunit VII	-1.276	-0.352	1.770E-03	3.040E-02
Vbp1	von Hippel-Lindau binding protein 1	-1.361	-0.445	1.770E-03	3.040E-02
Rnf219	ring finger protein 219	1.275	0.350	1.780E-03	3.060E-02
Utp14a	UTP14, U3 small nucleolar ribonucleoprotein, homolog A (yeast)	1.245	0.316	1.790E-03	3.070E-02
Atp6ap1l	ATPase, H+ transporting, lysosomal accessory protein 1-like	-1.368	-0.452	1.830E-03	3.130E-02
Dnmt3b	DNA methyltransferase 3B	1.348	0.431	1.830E-03	3.130E-02
Gnb2	guanine nucleotide binding protein (G protein), beta 2	-1.269	-0.344	1.830E-03	3.130E-02
Snhg11	small nucleolar RNA host gene 11 (non-protein coding)	1.348	0.431	1.830E-03	3.130E-02
Ubac2	ubiquitin associated domain containing 2	-1.186	-0.246	1.830E-03	3.130E-02
SCN2A1	sodium channel, voltage-gated, type II, alpha 1	1.244	0.315	1.850E-03	3.140E-02
Arpc1a	actin related protein 2/3 complex, subunit 1A	-1.285	-0.362	1.850E-03	3.150E-02
Tac3	tachykinin 3	-1.338	-0.420	1.870E-03	3.170E-02
H2afy	H2A histone family, member Y	-1.151	-0.203	1.880E-03	3.180E-02
RGD1310016	RIC1 homolog, RAB6A GEF complex partner 1	1.265	0.339	1.880E-03	3.180E-02

Supplemental Table 2 (continued)

RGD1307704	similar to RIKEN cDNA 2410016O06	-1.269	-0.344	1.880E-03	3.180E-02
AC109096.1	AC109096.1	-1.294	-0.372	1.880E-03	3.180E-02
Orc5	origin recognition complex, subunit 5	1.249	0.321	1.890E-03	3.200E-02
Rassf1	Ras association (RalGDS/AF-6) domain family member 1	-1.207	-0.271	1.900E-03	3.200E-02
Ppp1ca	protein phosphatase 1, catalytic subunit, alpha isoform	-1.178	-0.236	1.910E-03	3.220E-02
Rpl37	ribosomal protein L37	-1.283	-0.360	1.910E-03	3.220E-02
Cutc	cutC copper transporter homolog (E.coli)	1.313	0.393	1.930E-03	3.230E-02
Ndufb6	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6	-1.218	-0.284	1.920E-03	3.230E-02
Pnmal2	PNMA-like 2	-1.179	-0.238	1.930E-03	3.230E-02
2510002D24Rik	RIKEN cDNA 2510002D24 gene	-1.221	-0.288	1.930E-03	3.230E-02
ENSRNOG00000049932	ENSRNOG00000049932	1.360	0.444	1.930E-03	3.230E-02
Grina	glutamate receptor, ionotropic, N-methyl D-aspartate-associated protein 1 (glutamate binding)	-1.261	-0.335	1.950E-03	3.250E-02
Angel2	angel homolog 2 (Drosophila)	1.238	0.308	1.970E-03	3.280E-02
Nkx6-2	NK6 homeobox 2	-1.333	-0.415	1.990E-03	3.310E-02
Ppfibp2	protein tyrosine phosphatase, receptor-type, F interacting protein, binding protein 2	1.365	0.449	1.990E-03	3.310E-02
Rif1	Rap1 interacting factor 1 homolog (yeast)	1.347	0.430	1.990E-03	3.310E-02
Tnrc6c	trinucleotide repeat containing 6C	1.230	0.299	2.000E-03	3.320E-02
Dgcr6	DiGeorge syndrome critical region gene 6	-1.283	-0.360	2.010E-03	3.330E-02
Nhlrc2	NHL repeat containing 2	1.331	0.413	2.010E-03	3.330E-02
Smpd3	sphingomyelin phosphodiesterase 3, neutral	-1.159	-0.213	2.040E-03	3.370E-02
Tma7	translation machinery associated 7 homolog	-1.364	-0.448	2.040E-03	3.370E-02
Tmem179	transmembrane protein 179	-1.230	-0.299	2.050E-03	3.390E-02
RGD1309594	similar to RIKEN cDNA 1810043G02	-1.250	-0.322	2.060E-03	3.390E-02
Cnih2	cornichon homolog 2 (Drosophila)	-1.271	-0.346	2.070E-03	3.400E-02
Donson	downstream neighbor of SON	1.291	0.368	2.070E-03	3.400E-02
Fam189a1	family with sequence similarity 189, member A1	-1.316	-0.396	2.070E-03	3.400E-02
Ttc21b	tetratricopeptide repeat domain 21B	1.317	0.397	2.080E-03	3.410E-02
Hnrnpl	heterogeneous nuclear ribonucleoprotein L	-1.159	-0.213	2.100E-03	3.430E-02
Maz	MYC-associated zinc finger protein (purine-binding transcription factor)	-1.292	-0.370	2.100E-03	3.430E-02
Chpf	chondroitin polymerizing factor	-1.281	-0.357	2.150E-03	3.500E-02
Masp2	mannan-binding lectin serine peptidase 2	1.285	0.362	2.150E-03	3.500E-02
Tgfb1i1	transforming growth factor beta 1 induced transcript 1	-1.291	-0.368	2.150E-03	3.500E-02
AC133270.1	Rn60_14_0792.1	1.308	0.387	2.140E-03	3.500E-02
Cttnbp2	cortactin binding protein 2	1.240	0.310	2.170E-03	3.510E-02
Rundc3a	RUN domain containing 3A	-1.268	-0.343	2.170E-03	3.510E-02
Ttc7b	tetratricopeptide repeat domain 7B	-1.212	-0.277	2.170E-03	3.510E-02
Rn50_X_0744.1	Rn50_X_0744.1	-1.276	-0.352	2.170E-03	3.510E-02
Mgat4b	mannoside acetylglucosaminyltransferase 4, isoenzyme B	-1.220	-0.287	2.180E-03	3.520E-02
Nmt2	N-myristoyltransferase 2	1.254	0.326	2.170E-03	3.520E-02
Ppwd1	peptidylprolyl isomerase domain and WD repeat containing 1	1.314	0.394	2.190E-03	3.530E-02
Dstyk	dual serine/threonine and tyrosine protein kinase	1.297	0.375	2.190E-03	3.540E-02
Limd2	LIM domain containing 2	-1.211	-0.276	2.210E-03	3.550E-02
Diras1	DIRAS family, GTP-binding RAS-like 1	-1.245	-0.316	2.200E-03	3.550E-02
Atg16l1	autophagy-related 16-like 1 (yeast)	1.173	0.230	2.230E-03	3.570E-02
Fancb	Fanconi anemia, complementation group B	1.361	0.445	2.230E-03	3.570E-02
Kif15	kinesin family member 15	1.323	0.404	2.230E-03	3.570E-02
Mon2	MON2 homolog (yeast)	1.268	0.342	2.220E-03	3.570E-02

Supplemental Table 2 (continued)

Pias1	protein inhibitor of activated STAT 1	1.263	0.337	2.230E-03	3.570E-02
Trim8	tripartite motif protein 8	-1.183	-0.243	2.230E-03	3.570E-02
Fth1	ferritin heavy chain 1	-1.254	-0.326	2.240E-03	3.580E-02
Kat2b	ysine acetyltransferase 2B	1.336	0.418	2.250E-03	3.580E-02
Tdp2	tyrosyl-DNA phosphodiesterase 2	1.331	0.413	2.290E-03	3.650E-02
Csnk1g1	casein kinase 1, gamma 1	1.317	0.397	2.310E-03	3.670E-02
Dad1	defender against cell death 1	-1.268	-0.342	2.310E-03	3.670E-02
Kif21a	kinesin family member 21A	1.146	0.197	2.310E-03	3.670E-02
2410089E03Rik	RIKEN cDNA 2410089E03 gene	1.288	0.365	2.330E-03	3.690E-02
Ipo11	importin 11	1.261	0.334	2.330E-03	3.700E-02
Tubg2	tubulin, gamma 2	-1.235	-0.305	2.350E-03	3.710E-02
Chmp4bl1	chromatin modifying protein 4B-like 1	-1.197	-0.259	2.360E-03	3.710E-02
Chd6	chromodomain helicase DNA binding protein 6	1.278	0.354	2.350E-03	3.710E-02
Glipr2	GLI pathogenesis-related 2	-1.333	-0.415	2.360E-03	3.710E-02
Rusc2	RUN and SH3 domain containing 2	-1.273	-0.348	2.360E-03	3.710E-02
Strip1	striatin interacting protein 1	-1.146	-0.197	2.350E-03	3.710E-02
Dusp1	dual specificity phosphatase 1	-1.265	-0.339	2.370E-03	3.720E-02
Adamts20	ADAM metallopeptidase with thrombospondin type 1 motif, 20	1.348	0.431	2.380E-03	3.730E-02
Dars2	aspartyl-tRNA synthetase 2 (mitochondrial)	1.235	0.305	2.380E-03	3.730E-02
Npdc1	neural proliferation, differentiation and control gene 1	-1.285	-0.362	2.390E-03	3.740E-02
Abhd17a	abhydrolase domain containing 17A	-1.271	-0.346	2.400E-03	3.750E-02
Cacng8	calcium channel, voltage-dependent, gamma subunit 8	-1.321	-0.402	2.400E-03	3.750E-02
Btf3	predicted gene 9308	-1.191	-0.252	2.400E-03	3.750E-02
Lrp6	low density lipoprotein receptor-related protein 6	1.261	0.334	2.410E-03	3.760E-02
Dnajb2	DnaJ (Hsp40) homolog, subfamily B, member 2	-1.138	-0.187	2.410E-03	3.760E-02
Rad50	RAD50 homolog (S. cerevisiae)	1.301	0.380	2.420E-03	3.760E-02
Clpp	caseinolytic peptidase, ATP-dependent, proteolytic subunit homolog (E. coli)	-1.268	-0.343	2.430E-03	3.770E-02
C2cd4c	family with sequence similarity 148, member C	-1.250	-0.322	2.440E-03	3.770E-02
Iscu	IscU iron-sulfur cluster scaffold homolog (E. coli)	-1.206	-0.270	2.430E-03	3.770E-02
Usp45	ubiquitin specific petidase 45	1.272	0.347	2.420E-03	3.770E-02
Zbtb44	zinc finger and BTB domain containing 44	1.260	0.333	2.430E-03	3.770E-02
Atp13a3	ATPase type 13A3	1.342	0.424	2.450E-03	3.780E-02
Dpy19l4	dpy-19-like 4 (C. elegans)	1.288	0.365	2.450E-03	3.780E-02
Ralgapb	Ral GTPase activating protein non-catalytic beta subunit	1.192	0.253	2.450E-03	3.780E-02
Vps54	vacuolar protein sorting 54 (yeast)	1.305	0.384	2.480E-03	3.810E-02
Mrpl20	mitochondrial ribosomal protein L20	-1.210	-0.275	2.480E-03	3.820E-02
Pvrl1	poliovirus receptor-related 1	-1.276	-0.352	2.490E-03	3.830E-02
Rasa2	RAS p21 protein activator 2	1.332	0.414	2.490E-03	3.830E-02
Emilin2	echinoderm microtubule associated protein like 5	1.322	0.403	2.510E-03	3.850E-02
St6galnac6	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 6	-1.233	-0.302	2.520E-03	3.860E-02
AABR06057713.1	AABR06057713.1	1.344	0.426	2.530E-03	3.860E-02
Setd2	SET domain containing 2	1.182	0.241	2.530E-03	3.870E-02
Nvl	nuclear VCP-like	1.322	0.403	2.550E-03	3.890E-02
Cebpd	CCAAT/enhancer binding protein (C/EBP), delta	-1.328	-0.409	2.560E-03	3.900E-02
Kdm2a	lysine (K)-specific demethylase 2A	1.221	0.288	2.570E-03	3.900E-02
Pld1	phospholipase D1	1.255	0.328	2.580E-03	3.900E-02
SEC24A	Sec24 related gene family, member A (S. cerevisiae)	1.240	0.310	2.570E-03	3.900E-02
Zfp280c	zinc finger protein 280C	1.311	0.391	2.570E-03	3.900E-02
Zfp771	zinc finger protein 771	-1.266	-0.340	2.570E-03	3.900E-02

Supplemental Table 2 (continued)

Atp5b	ATP synthase, H+ transporting mitochondrial F1 complex, beta subunit	-1.164	-0.219	2.580E-03	3.910E-02
Trip12	thyroid hormone receptor interactor 12	1.270	0.345	2.580E-03	3.910E-02
Arf1	ADP-ribosylation factor 1	-1.152	-0.204	2.590E-03	3.920E-02
Eef1g	eukaryotic translation elongation factor 1 gamma	-1.129	-0.175	2.610E-03	3.930E-02
Pot1b	protection of telomeres 1B	1.324	0.405	2.610E-03	3.930E-02
Trim28	tripartite motif-containing 28	-1.131	-0.177	2.600E-03	3.930E-02
Zc3h11a	zinc finger CCCH type containing 11A	1.217	0.283	2.600E-03	3.930E-02
Cuedc1	CUE domain containing 1	-1.207	-0.272	2.640E-03	3.940E-02
Lpxn	leupaxin	1.257	0.330	2.630E-03	3.940E-02
Nrtn	neurturin	-1.354	-0.437	2.640E-03	3.940E-02
Ranbp1	RAN binding protein 1	-1.202	-0.265	2.640E-03	3.940E-02
Thoc2	THO complex 2	1.336	0.418	2.630E-03	3.940E-02
Tbcc	tubulin-specific chaperone C	-1.232	-0.301	2.640E-03	3.940E-02
AABR07045621.1	AABR07045621.1	1.350	0.433	2.630E-03	3.940E-02
Borcs6	BLOC-1 related complex subunit 6	-1.255	-0.328	2.660E-03	3.950E-02
Glce	glucuronyl C5-epimerase	1.273	0.348	2.650E-03	3.950E-02
ENSRNOG00000047147	ENSRNOG00000047147	1.353	0.436	2.650E-03	3.950E-02
Efr3a	EFR3 homolog A (S. cerevisiae)	1.329	0.410	2.670E-03	3.960E-02
Atxn10	ataxin 10	-1.152	-0.204	2.680E-03	3.970E-02
Emc10	ER membrane protein complex subunit 10	-1.237	-0.307	2.670E-03	3.970E-02
Ppp2r1a	protein phosphatase 2 (formerly 2A), regulatory subunit A (PR 65), alpha isoform	-1.207	-0.271	2.680E-03	3.970E-02
Eif3i	eukaryotic translation initiation factor 3, subunit I	-1.204	-0.268	2.690E-03	3.980E-02
Mark4	MAP/microtubule affinity-regulating kinase 4	-1.267	-0.341	2.690E-03	3.980E-02
Ndufa7	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7 (B14.5a)	-1.213	-0.278	2.690E-03	3.980E-02
Prkd3	protein kinase D3	1.319	0.399	2.700E-03	3.980E-02
Rilpl2	Rab interacting lysosomal protein-like 2	-1.220	-0.287	2.710E-03	3.990E-02
Kat2a	K(lysine) acetyltransferase 2A	-1.193	-0.254	2.720E-03	4.000E-02
Zfp608	zinc finger protein 608	1.201	0.264	2.730E-03	4.000E-02
40976		-1.247	-0.318	2.720E-03	4.000E-02
Med16	mediator complex subunit 16	-1.254	-0.327	2.740E-03	4.020E-02
Nsun3	NOL1/NOP2/Sun domain family member 3	1.353	0.436	2.740E-03	4.020E-02
Uba6	ubiquitin-like modifier activating enzyme 6	1.319	0.399	2.740E-03	4.020E-02
Med25	mediator of RNA polymerase II transcription, subunit 25 homolog (yeast)	-1.266	-0.340	2.770E-03	4.040E-02
Mccc1	methylcrotonoyl-Coenzyme A carboxylase 1 (alpha)	1.268	0.342	2.760E-03	4.040E-02
Mrpl37	mitochondrial ribosomal protein L37	-1.210	-0.275	2.760E-03	4.040E-02
Zgrf1	zinc finger, GRF-type containing 1	1.344	0.426	2.770E-03	4.040E-02
AABR07057678.1	AABR07057678.1	1.293	0.371	2.770E-03	4.040E-02
Atp9b	ATPase, class II, type 9B	1.149	0.201	2.800E-03	4.070E-02
Nav2	neuron navigator 2	1.197	0.259	2.810E-03	4.070E-02
Pkd2	polycystic kidney disease 2	1.269	0.344	2.810E-03	4.070E-02
Tstd1	predicted gene 4848	1.351	0.434	2.800E-03	4.070E-02
Trnp1	TMF1-regulated nuclear protein 1	-1.347	-0.430	2.810E-03	4.070E-02
Tmem132e	transmembrane protein 132E	-1.280	-0.356	2.810E-03	4.070E-02
Tkt	transketolase	-1.236	-0.306	2.820E-03	4.080E-02
Nme2	similar to Nucleoside diphosphate kinase B (NDK B) (NDP kinase B) (P18)	-1.246	-0.317	2.840E-03	4.100E-02
Suv420h1	suppressor of variegation 4-20 homolog 1 (Drosophila)	1.250	0.322	2.840E-03	4.100E-02
Ubl5	predicted gene 5955	-1.197	-0.259	2.870E-03	4.130E-02
Tbc1d32	TBC1 domain family, member 32	1.292	0.370	2.860E-03	4.130E-02

Supplemental Table 2 (continued)

Hars2	histidyl-tRNA synthetase 2, mitochondrial (putative)	1.247	0.318	2.890E-03	4.150E-02
Pim3	proviral integration site 3	-1.228	-0.296	2.890E-03	4.150E-02
RGD1560775	similar to RIKEN cDNA 4930579C12 gene	1.276	0.352	2.900E-03	4.160E-02
Brcc3	BRCA1/BRCA2-containing complex, subunit 3	-1.235	-0.304	2.930E-03	4.200E-02
Xrcc6	X-ray repair complementing defective repair in Chinese hamster cells 6	1.268	0.342	2.930E-03	4.200E-02
41160		-1.210	-0.275	2.930E-03	4.200E-02
Thap7	THAP domain containing 7	-1.291	-0.369	2.960E-03	4.230E-02
Rps20	ribosomal protein S20	-1.235	-0.305	2.980E-03	4.250E-02
Dmxl1	Dmx-like 1	1.300	0.378	2.980E-03	4.250E-02
Shprh	SNF2 histone linker PHD RING helicase	1.306	0.385	2.980E-03	4.250E-02
Tnip1	TNFAIP3 interacting protein 1	-1.258	-0.331	2.970E-03	4.250E-02
RGD1304704	similar to Hypothetical protein CGI-99	-1.205	-0.269	3.000E-03	4.260E-02
Rpl29	ribosomal protein L29	-1.247	-0.319	3.010E-03	4.270E-02
40969		-1.239	-0.309	3.010E-03	4.270E-02
Aatk	apoptosis-associated tyrosine kinase	-1.189	-0.250	3.050E-03	4.280E-02
Dnajc15	DnaJ (Hsp40) homolog, subfamily C, member 15	-1.202	-0.266	3.050E-03	4.280E-02
Emc4	emerin	-1.191	-0.252	3.040E-03	4.280E-02
Fbxo31	F-box protein 31	-1.220	-0.287	3.050E-03	4.280E-02
G2E3	G2/M-phase specific E3 ubiquitin ligase	1.328	0.409	3.040E-03	4.280E-02
Mtpap	mitochondrial poly(A) polymerase	1.220	0.287	3.030E-03	4.280E-02
Rassf6	Ras association (RalGDS/AF-6) domain family member 6	1.341	0.423	3.030E-03	4.280E-02
Rps11	ribosomal protein S11	-1.143	-0.193	3.020E-03	4.280E-02
Zfp580	zinc finger protein 580	-1.336	-0.418	3.020E-03	4.280E-02
RGD1562484	RGD1562484	-1.342	-0.424	3.020E-03	4.280E-02
B3gat3	beta-1,3-glucuronyltransferase 3 (glucuronosyltransferase I)	-1.240	-0.310	3.070E-03	4.290E-02
Fam131c	family with sequence similarity 131, member C	-1.338	-0.420	3.070E-03	4.290E-02
Fam216a	family with sequence similarity 216, member A	-1.176	-0.234	3.070E-03	4.290E-02
Myo3a	myosin IIIA	1.336	0.418	3.060E-03	4.290E-02
Ckb	similar to creatine kinase, brain	-1.253	-0.325	3.070E-03	4.290E-02
Fndc10	fibronectin type III domain containing 10	-1.334	-0.416	3.060E-03	4.290E-02
Farp2	FERM, RhoGEF and pleckstrin domain protein 2	1.235	0.304	3.100E-03	4.320E-02
Dlg4	discs, large homolog 4 (Drosophila)	-1.246	-0.317	3.120E-03	4.350E-02
Arpp21	cyclic AMP-regulated phosphoprotein, 21	1.324	0.405	3.140E-03	4.360E-02
Isyna1	myo-inositol 1-phosphate synthase A1	-1.297	-0.375	3.140E-03	4.360E-02
Ranbp2	RAN binding protein 2	1.332	0.414	3.130E-03	4.360E-02
Rpl35	ribosomal protein L35	-1.274	-0.349	3.150E-03	4.360E-02
RGD1306746	similar to Hypothetical protein MGC25529	1.210	0.275	3.140E-03	4.360E-02
Zbtb25	zinc finger and BTB domain containing 25	1.292	0.370	3.130E-03	4.360E-02
Aldh1a1	aldehyde dehydrogenase family 1, subfamily A1	1.342	0.424	3.170E-03	4.390E-02
Ccdc97	coiled-coil domain containing 97	-1.220	-0.287	3.190E-03	4.400E-02
Dcun1d2	DCN1, defective in cullin neddylation 1, domain containing 2 (S. cerevisiae)	1.242	0.313	3.190E-03	4.400E-02
Tmem240	transmembrane protein 240	-1.307	-0.386	3.190E-03	4.400E-02
Zfp949	zinc finger protein 949	1.286	0.363	3.200E-03	4.410E-02
Mtx3	metaxin 3	1.319	0.399	3.220E-03	4.430E-02
Ppil1	peptidylprolyl isomerase (cyclophilin)-like 1	-1.207	-0.272	3.230E-03	4.440E-02
Eif2ak2	eukaryotic translation initiation factor 2-alpha kinase 2	1.311	0.391	3.240E-03	4.440E-02
Fbn1	fibrillin 1	1.306	0.385	3.230E-03	4.440E-02
Fyn	Fyn proto-oncogene	-1.164	-0.219	3.240E-03	4.440E-02
Kif5b	kinesin family member 5B	1.229	0.297	3.240E-03	4.440E-02

Supplemental Table 2 (continued)

Comt	catechol-O-methyltransferase	-1.245	-0.316	3.280E-03	4.450E-02
Fam171a2	family with sequence similarity 171, member A2	-1.288	-0.365	3.280E-03	4.450E-02
Gosr1	golgi SNAP receptor complex member 1	1.189	0.250	3.280E-03	4.450E-02
Mfsd8	major facilitator superfamily domain containing 8	1.300	0.378	3.290E-03	4.450E-02
Mesdc1	mesoderm development candidate 1	-1.286	-0.363	3.260E-03	4.450E-02
Rnf5	ring finger protein 5	-1.194	-0.256	3.270E-03	4.450E-02
Sh3rf3	SH3 domain containing ring finger 3	-1.300	-0.379	3.290E-03	4.450E-02
RGD1305464	similar to human chromosome 15 open reading frame 39	-1.315	-0.395	3.270E-03	4.450E-02
Sgta	small glutamine-rich tetratricopeptide repeat (TPR)-containing, alpha	-1.235	-0.305	3.270E-03	4.450E-02
Srcap	Snf2-related CREBBP activator protein	1.268	0.343	3.250E-03	4.450E-02
Sra1	steroid receptor RNA activator 1	1.170	0.226	3.260E-03	4.450E-02
Tubgcp5	tubulin, gamma complex associated protein 5	1.344	0.426	3.270E-03	4.450E-02
ATL3	atlastin GTPase 3	1.309	0.388	3.300E-03	4.470E-02
Eri3	exoribonuclease 3	-1.172	-0.229	3.320E-03	4.480E-02
Kdm5a	lysine (K)-specific demethylase 5A	1.317	0.397	3.330E-03	4.490E-02
ENSRNOG00000049316	ENSRNOG00000049316	-1.340	-0.422	3.340E-03	4.500E-02
Rbm42	RNA binding motif protein 42	-1.251	-0.323	3.370E-03	4.540E-02
Atp5g2	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c (subunit 9), isoform 2	-1.177	-0.235	3.380E-03	4.550E-02
Atf7	activating transcription factor 7	1.330	0.411	3.380E-03	4.550E-02
Arhgap17	Rho GTPase activating protein 17	1.291	0.369	3.390E-03	4.550E-02
Rnasek	ribonuclease, RNase K	-1.236	-0.306	3.380E-03	4.550E-02
Tpr	translocated promoter region	1.146	0.196	3.430E-03	4.560E-02
Ap2s1	adaptor-related protein complex 2, sigma 1 subunit	-1.272	-0.347	3.420E-03	4.560E-02
Aes	amino-terminal enhancer of split	-1.260	-0.333	3.410E-03	4.560E-02
Ccdc39	coiled-coil domain containing 39	1.296	0.374	3.430E-03	4.560E-02
Dleu7	deleted in lymphocytic leukemia, 7	-1.300	-0.379	3.410E-03	4.560E-02
Hectd2	HECT domain containing 2	1.296	0.374	3.410E-03	4.560E-02
Mapk8ip1	mitogen-activated protein kinase 8 interacting protein 1	-1.218	-0.285	3.420E-03	4.560E-02
Txndc15	thioredoxin domain containing 15	-1.174	-0.231	3.420E-03	4.560E-02
Ube2v1	ubiquitin-conjugating enzyme E2 variant 1	-1.268	-0.343	3.430E-03	4.560E-02
SCAI	suppressor of cancer cell invasion	1.269	0.344	3.440E-03	4.570E-02
Wibg	within bgcn homolog (Drosophila)	-1.241	-0.311	3.450E-03	4.580E-02
Dsn1	DSN1, MIND kinetochore complex component, homolog (S. cerevisiae)	1.324	0.405	3.460E-03	4.590E-02
Mtbp	Mdm2, transformed 3T3 cell double minute p53 binding protein	1.317	0.397	3.460E-03	4.590E-02
Ago3	argonaute 3, RISC catalytic component	1.339	0.421	3.490E-03	4.610E-02
Dhrs13	dehydrogenase/reductase 13	-1.263	-0.337	3.490E-03	4.620E-02
Mlf2	myeloid leukemia factor 2	-1.211	-0.276	3.500E-03	4.630E-02
RGD1560398	RGD1560398	-1.321	-0.402	3.520E-03	4.630E-02
Sf3b2	splicing factor 3b, subunit 2	-1.124	-0.169	3.510E-03	4.630E-02
Trmt112	tRNA methyltransferase 11-2 homolog (S. cerevisiae)	-1.241	-0.311	3.510E-03	4.630E-02
Wnk1	WNK lysine deficient protein kinase 1	1.235	0.305	3.520E-03	4.630E-02
Mir3064	microRNA 3064	1.292	0.370	3.510E-03	4.630E-02
Cited4	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 4	-1.340	-0.422	3.530E-03	4.640E-02
Tmem64	transmembrane protein 64	-1.302	-0.381	3.530E-03	4.640E-02
Asna1	arsA arsenite transporter, ATP-binding, homolog 1 (bacterial)	-1.188	-0.248	3.570E-03	4.680E-02
Eif5a	eukaryotic translation initiation factor 5A	-1.180	-0.239	3.580E-03	4.680E-02
Trip11	thyroid hormone receptor interactor 11	1.267	0.341	3.570E-03	4.680E-02

Supplemental Table 2 (continued)

Fryl	furry homolog-like (Drosophila)	1.270	0.345	3.590E-03	4.690E-02
Pcgf6	polycomb group ring finger 6	1.268	0.342	3.600E-03	4.700E-02
Rtn2	reticulon 2 (Z-band associated protein)	-1.224	-0.292	3.600E-03	4.700E-02
Tspan15	tetraspanin 15	-1.224	-0.292	3.600E-03	4.700E-02
NNAT	neuronatin	-1.233	-0.302	3.620E-03	4.710E-02
RGD1566239	similar to RIKEN cDNA 2810428I15	-1.278	-0.354	3.630E-03	4.720E-02
ANAPC11	anaphase promoting complex subunit 11	-1.200	-0.263	3.650E-03	4.730E-02
Psmb4	proteasome (prosome, macropain) subunit, beta type 4	-1.203	-0.267	3.650E-03	4.730E-02
Zfp182	zinc finger protein 182	1.300	0.379	3.640E-03	4.730E-02
Eif6	eukaryotic translation initiation factor 6	-1.137	-0.185	3.660E-03	4.740E-02
Rbm28	RNA binding motif protein 28	1.238	0.308	3.650E-03	4.740E-02
Akt1	similar to serine/threonine protein kinase	-1.200	-0.263	3.670E-03	4.750E-02
Stmn3	stathmin-like 3	-1.272	-0.347	3.670E-03	4.750E-02
Ninj1	ninjurin 1	-1.296	-0.374	3.720E-03	4.800E-02
Rttn	rotatin	1.309	0.388	3.720E-03	4.800E-02
Smim18	small integral membrane protein 18	-1.260	-0.333	3.720E-03	4.800E-02
Pram1	PML-RAR alpha-regulated adaptor molecule 1	1.333	0.415	3.740E-03	4.820E-02
Sipa1l3	signal-induced proliferation-associated 1 like 3	-1.223	-0.290	3.750E-03	4.830E-02
Trim24	tripartite motif-containing 24	1.139	0.188	3.760E-03	4.830E-02
Mef2a	myocyte enhancer factor 2A	1.265	0.339	3.780E-03	4.840E-02
Rpl11	ribosomal protein L11	-1.166	-0.221	3.790E-03	4.840E-02
Top3a	topoisomerase (DNA) III alpha	1.286	0.363	3.810E-03	4.840E-02
Bax	BCL2-associated X protein	-1.204	-0.268	3.770E-03	4.840E-02
Gzf1	GDNF-inducible zinc finger protein 1	1.260	0.333	3.780E-03	4.840E-02
Hipk3	homeodomain interacting protein kinase 3	1.188	0.249	3.770E-03	4.840E-02
Itga6	integrin alpha 6	1.217	0.283	3.790E-03	4.840E-02
Psen2	presenilin 2	-1.241	-0.312	3.780E-03	4.840E-02
Spag9	sperm associated antigen 9	1.223	0.290	3.800E-03	4.840E-02
TMEM11	transmembrane protein 11	-1.179	-0.237	3.780E-03	4.840E-02
Vcan	versican	1.254	0.327	3.800E-03	4.840E-02
Efhd2	EF hand domain containing 2	-1.215	-0.281	3.820E-03	4.860E-02
Galk1	galactokinase 1	-1.257	-0.330	3.830E-03	4.860E-02
Osbpl9	oxysterol binding protein-like 9	1.204	0.268	3.820E-03	4.860E-02
CK137956	cDNA sequence CK137956	-1.333	-0.415	3.870E-03	4.880E-02
Dolk	dolichol kinase	-1.221	-0.288	3.850E-03	4.880E-02
Fam173b	family with sequence similarity 173, member B	1.199	0.262	3.860E-03	4.880E-02
Psmc3	proteasome (prosome, macropain) 26S subunit, ATPase 3	-1.155	-0.208	3.860E-03	4.880E-02
Ssx1	SSX family member 1	1.328	0.409	3.860E-03	4.880E-02
RGD1562469	RGD1562469	-1.207	-0.271	3.860E-03	4.880E-02
Abhd17c	abhydrolase domain containing 17C	-1.177	-0.235	3.890E-03	4.900E-02
ABCC9	ATP-binding cassette, sub-family C (CFTR/MRP), member 9	1.290	0.367	3.890E-03	4.900E-02
Lrfn3	leucine rich repeat and fibronectin type III domain containing 3	-1.243	-0.314	3.890E-03	4.900E-02
Dnajb11	DnaJ (Hsp40) homolog, subfamily B, member 11	-1.175	-0.233	3.910E-03	4.910E-02
Spint2	serine protease inhibitor, Kunitz type 2	-1.247	-0.318	3.910E-03	4.910E-02
Taf2	TAF2 RNA polymerase II, TATA box binding protein (TBP)-associated factor	1.262	0.336	3.900E-03	4.910E-02
Ubn1	ubinuclein 1	1.235	0.304	3.920E-03	4.920E-02
Stx7	syntaxin 7	-1.250	-0.322	3.940E-03	4.930E-02
Vprbp	Vpr (HIV-1) binding protein	1.232	0.301	3.940E-03	4.930E-02
Dnajc30	DnaJ (Hsp40) homolog, subfamily C, member 30	-1.303	-0.382	3.960E-03	4.950E-02

Supplemental Table 2 (continued)

Kcnc4	potassium voltage gated channel, Shaw-related subfamily, member 4	-1.258	-0.331	3.960E-03	4.950E-02
Lfng	LFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase	-1.236	-0.306	4.000E-03	4.990E-02
Slc39a7	solute carrier family 39 (zinc transporter), member 7	-1.168	-0.224	3.990E-03	4.990E-02

Supplemental Table 3. Overlapping significantly (padj ≤ 0.05) altered hypothalamic genes in males exposed to BPA

Supplemental Table 3. Overlapping significantly (padj ≤ 0.05) altered hypothalamic genes in males exposed to BPA

		2.5 BPA ♂ vs control ♂				2500 BPA ♂ vs control ♂			
gene	Description	Fold Change	log2FC	pvalue	padj	Fold Change	log2FC	pvalue	padj
40971	uncharacterized protein	-1.227	-2.950E-01	9.630E-04	2.140E-02	-1.227	-0.295	9.630E-04	2.140E-02
aabr07054370.1	AABR07054370.1	-1.293	-3.710E-01	1.660E-05	2.090E-03	-1.293	-0.371	1.660E-05	2.090E-03
aatk	apoptosis-associated tyrosine kinase	-1.189	-2.500E-01	3.050E-03	4.280E-02	-1.189	-0.250	3.050E-03	4.280E-02
abca5	ATP-binding cassette, sub-family A (ABC1), member 5	1.456	5.420E-01	3.880E-05	3.390E-03	1.456	0.542	3.880E-05	3.390E-03
acot7	acyl-CoA thioesterase 7	-1.275	-3.510E-01	6.010E-04	1.580E-02	-1.275	-0.351	6.010E-04	1.580E-02
adrm1	adhesion regulating molecule 1	-1.298	-3.760E-01	4.820E-06	9.640E-04	-1.298	-0.376	4.820E-06	9.640E-04
aes	amino-terminal enhancer of split	-1.260	-3.330E-01	3.410E-03	4.560E-02	-1.260	-0.333	3.410E-03	4.560E-02
agap3	ArfGAP with GTPase domain, ankyrin repeat and PH domain 3	-1.313	-3.930E-01	6.880E-06	1.260E-03	-1.313	-0.393	6.880E-06	1.260E-03
ahctf1	AT hook containing transcription factor 1	1.440	5.260E-01	7.710E-06	1.380E-03	1.440	0.526	7.710E-06	1.380E-03
aip	aryl-hydrocarbon receptor-interacting protein	-1.273	-3.480E-01	1.870E-04	8.860E-03	-1.273	-0.348	1.870E-04	8.860E-03
akap10	A kinase (PRKA) anchor protein 10	1.344	4.260E-01	4.910E-06	9.690E-04	1.344	0.426	4.910E-06	9.690E-04
angel2	angel homolog 2 (Drosophila)	1.238	3.080E-01	1.970E-03	3.280E-02	1.238	0.308	1.970E-03	3.280E-02
ankfy1	ankyrin repeat and FYVE domain containing 1	1.376	4.610E-01	2.490E-05	2.620E-03	1.376	0.461	2.490E-05	2.620E-03
ap4e1	adaptor-related protein complex AP-4, epsilon 1	1.370	4.540E-01	1.670E-04	8.350E-03	1.370	0.454	1.670E-04	8.350E-03
ap5m1	adaptor-related protein complex 5, mu 1 subunit	1.639	7.130E-01	3.280E-08	3.020E-05	1.639	0.713	3.280E-08	3.020E-05
arid4a	AT rich interactive domain 4A (RBP1-like)	1.327	4.080E-01	8.340E-04	1.950E-02	1.327	0.408	8.340E-04	1.950E-02
ash1l	ash1 (absent, small, or homeotic)-like (Drosophila)	1.352	4.350E-01	7.030E-07	2.570E-04	1.352	0.435	7.030E-07	2.570E-04
atad2	ATPase family, AAA domain containing 2	1.494	5.790E-01	5.710E-05	4.240E-03	1.494	0.579	5.710E-05	4.240E-03
atad5	ATPase family, AAA domain containing 5	1.521	6.050E-01	3.790E-08	3.080E-05	1.521	0.605	3.790E-08	3.080E-05
atg101	autophagy related 101	-1.180	-2.390E-01	5.050E-04	1.450E-02	-1.180	-0.239	5.050E-04	1.450E-02
atl3	atlastin GTPase 3	1.309	3.880E-01	3.300E-03	4.470E-02	1.309	0.388	3.300E-03	4.470E-02
atm	ataxia telangiectasia mutated homolog (human)	1.571	6.520E-01	4.740E-09	1.520E-05	1.571	0.652	4.740E-09	1.520E-05
atp11b	ATPase, class VI, type 11B	1.479	5.650E-01	3.150E-06	7.500E-04	1.479	0.565	3.150E-06	7.500E-04
atp5d	ATP synthase, H+ transporting, mitochondrial F1 complex, delta subunit	-1.300	-3.780E-01	1.570E-03	2.860E-02	-1.300	-0.378	1.570E-03	2.860E-02
atp5g2	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c (subunit 9), isoform 2	-1.177	-2.350E-01	3.380E-03	4.550E-02	-1.177	-0.235	3.380E-03	4.550E-02
atxn3	ataxin 3	1.533	6.160E-01	7.980E-06	1.380E-03	1.533	0.616	7.980E-06	1.380E-03
bad	BCL2-associated agonist of cell death	-1.229	-2.980E-01	1.490E-03	2.770E-02	-1.229	-0.298	1.490E-03	2.770E-02
baz2b	bromodomain adjacent to zinc finger domain, 2B	1.376	4.610E-01	1.450E-04	7.630E-03	1.376	0.461	1.450E-04	7.630E-03
bc005561	THO complex 2	1.496	5.810E-01	1.350E-05	1.960E-03	1.496	0.581	1.350E-05	1.960E-03
birc6	baculoviral IAP repeat-containing 6	1.493	5.780E-01	5.770E-07	2.410E-04	1.493	0.578	5.770E-07	2.410E-04
bmyc	brain expressed myelocytomatosis oncogene	-1.404	-4.900E-01	1.260E-05	1.900E-03	-1.404	-0.490	1.260E-05	1.900E-03
bok	BCL2-related ovarian killer protein	-1.241	-3.120E-01	6.730E-04	1.710E-02	-1.241	-0.312	6.730E-04	1.710E-02
bop1	block of proliferation 1	-1.188	-2.480E-01	1.660E-03	2.960E-02	-1.188	-0.248	1.660E-03	2.960E-02
bri3	brain protein I3	-1.471	-5.570E-01	4.470E-06	9.350E-04	-1.471	-0.557	4.470E-06	9.350E-04
btaf1	BTAF1 RNA polymerase II, B-TFIID transcription factor-associated, (Mot1 homolog, S. cerevisiae)	1.438	5.240E-01	2.260E-05	2.540E-03	1.438	0.524	2.260E-05	2.540E-03
c1qtnf4	C1q and tumor necrosis factor related protein 4	-1.407	-4.930E-01	2.780E-04	1.070E-02	-1.407	-0.493	2.780E-04	1.070E-02
cacnb1	calcium channel, voltage-dependent, beta 1 subunit	-1.293	-3.710E-01	5.720E-05	4.240E-03	-1.293	-0.371	5.720E-05	4.240E-03
cacnb2	calcium channel, voltage-dependent, beta 2 subunit	1.236	3.060E-01	2.970E-04	1.110E-02	1.236	0.306	2.970E-04	1.110E-02
cacng8	calcium channel, voltage-dependent, gamma subunit 8	-1.321	-4.020E-01	2.400E-03	3.750E-02	-1.321	-0.402	2.400E-03	3.750E-02
cactin	spliceosome C complex subunit	-1.251	-3.230E-01	3.380E-04	1.200E-02	-1.251	-0.323	3.380E-04	1.200E-02
caly	calcyon neuron-specific vesicular protein	-1.339	-4.210E-01	1.180E-03	2.380E-02	-1.339	-0.421	1.180E-03	2.380E-02
camk2n2	calcium/calmodulin-dependent protein kinase II inhibitor 2	-1.391	-4.760E-01	7.160E-04	1.780E-02	-1.391	-0.476	7.160E-04	1.780E-02
carf	calcium response factor	1.381	4.660E-01	4.540E-05	3.820E-03	1.381	0.466	4.540E-05	3.820E-03
ccdc92	coiled-coil domain containing 92	-1.260	-3.330E-01	5.700E-04	1.530E-02	-1.260	-0.333	5.700E-04	1.530E-02
ccdc97	coiled-coil domain containing 97	-1.220	-2.870E-01	3.190E-03	4.400E-02	-1.220	-0.287	3.190E-03	4.400E-02
ccnt2	cyclin T2	1.504	5.890E-01	1.850E-06	5.330E-04	1.504	0.589	1.850E-06	5.330E-04
cd2ap	CD2-associated protein	1.510	5.950E-01	3.480E-07	1.720E-04	1.510	0.595	3.480E-07	1.720E-04
cdc37	cell division cycle 37 homolog (S. cerevisiae)	-1.296	-3.740E-01	6.470E-06	1.220E-03	-1.296	-0.374	6.470E-06	1.220E-03
cep162	centrosomal protein 162	1.582	6.620E-01	2.550E-07	1.410E-04	1.582	0.662	2.550E-07	1.410E-04
cep95	centrosomal protein 95	1.587	6.660E-01	1.330E-08	2.310E-05	1.587	0.666	1.330E-08	2.310E-05
chchd10	coiled-coil-helix-coiled-coil-helix domain containing 10	-1.466	-5.520E-01	9.440E-05	5.940E-03	-1.466	-0.552	9.440E-05	5.940E-03
chmp4bl1	chromatin modifying protein 4B-like 1	-1.197	-2.590E-01	2.360E-03	3.710E-02	-1.197	-0.259	2.360E-03	3.710E-02
chuk	conserved helix-loop-helix ubiquitous kinase	1.556	6.380E-01	3.070E-06	7.450E-04	1.556	0.638	3.070E-06	7.450E-04
cilp2	cartilage intermediate layer protein 2	-1.469	-5.550E-01	2.800E-05	2.790E-03	-1.469	-0.555	2.800E-05	2.790E-03
ckb	similar to creatine kinase, brain	-1.253	-3.250E-01	3.070E-03	4.290E-02	-1.253	-0.325	3.070E-03	4.290E-02
clcc1	chloride channel CLIC-like 1	1.198	2.610E-01	1.430E-03	2.710E-02	1.198	0.261	1.430E-03	2.710E-02
clip2	CAP-GLY domain containing linker protein 2	-1.224	-2.920E-01	4.630E-05	3.870E-03	-1.224	-0.292	4.630E-05	3.870E-03
clk4	CDC like kinase 4	1.455	5.410E-01	1.030E-04	6.220E-03	1.455	0.541	1.030E-04	6.220E-03
cntfr	ciliary neurotrophic factor receptor	-1.344	-4.270E-01	6.610E-04	1.690E-02	-1.344	-0.427	6.610E-04	1.690E-02
cotl1	coactosin-like 1 (Dictyostelium)	-1.370	-4.540E-01	2.010E-04	9.180E-03	-1.370	-0.454	2.010E-04	9.180E-03
cox5b	cytochrome c oxidase, subunit Vb	-1.277	-3.530E-01	1.290E-04	7.160E-03	-1.277	-0.353	1.290E-04	7.160E-03
cox6a1	cytochrome c oxidase, subunit VI a, polypeptide 1	-1.343	-4.250E-01	3.440E-04	1.200E-02	-1.343	-0.425	3.440E-04	1.200E-02
csk	c-src tyrosine kinase	-1.117	-1.590E-01	1.770E-03	3.040E-02	-1.117	-0.159	1.770E-03	3.040E-02
csmd3	CUB and Sushi multiple domains 3	1.358	4.420E-01	2.110E-04	9.360E-03	1.358	0.442	2.110E-04	9.360E-03
csnk1g2	casein kinase 1, gamma 2	-1.294	-3.720E-01	2.890E-04	1.100E-02	-1.294	-0.372	2.890E-04	1.100E-02
ctbp1	C-terminal binding protein 1	-1.228	-2.960E-01	2.420E-05	2.620E-03	-1.228	-0.296	2.420E-05	2.620E-03

Supplemental Table 3 (continued)

dact3	dapper homolog 3, antagonist of beta-catenin (xenopus)	-1.310	-3.900E-01	2.330E-04	9.730E-03	-1.310	-0.390	2.330E-04	9.730E-03
dennd4c	DENN/MADD domain containing 4C	1.503	5.880E-01	7.070E-07	2.570E-04	1.503	0.588	7.070E-07	2.570E-04
diras1	DIRAS family, GTP-binding RAS-like 1	-1.245	-3.160E-01	2.200E-03	3.550E-02	-1.245	-0.316	2.200E-03	3.550E-02
dmd	dystrophin, muscular dystrophy	1.339	4.210E-01	7.920E-05	5.260E-03	1.339	0.421	7.920E-05	5.260E-03
dmxl1	Dmx-like 1	1.300	3.780E-01	2.980E-03	4.250E-02	1.300	0.378	2.980E-03	4.250E-02
dnajb2	DnaJ (Hsp40) homolog, subfamily B, member 2	-1.138	-1.870E-01	2.410E-03	3.760E-02	-1.138	-0.187	2.410E-03	3.760E-02
dpy19l4	dpy-19-like 4 (C. elegans)	1.288	3.650E-01	2.450E-03	3.780E-02	1.288	0.365	2.450E-03	3.780E-02
drap1	Dr1 associated protein 1 (negative cofactor 2 alpha)	-1.356	-4.390E-01	9.830E-08	5.910E-05	-1.356	-0.439	9.830E-08	5.910E-05
dusp26	dual specificity phosphatase 26 (putative)	-1.262	-3.360E-01	1.580E-03	2.880E-02	-1.262	-0.336	1.580E-03	2.880E-02
dusp8	dual specificity phosphatase 8	-1.218	-2.840E-01	1.750E-03	3.040E-02	-1.218	-0.284	1.750E-03	3.040E-02
dzip3	DAZ interacting protein 3, zinc finger	1.294	3.720E-01	1.010E-03	2.180E-02	1.294	0.372	1.010E-03	2.180E-02
e2f3	E2F transcription factor 3	1.292	3.700E-01	1.130E-03	2.320E-02	1.292	0.370	1.130E-03	2.320E-02
edf1	endothelial differentiation-related factor 1	-1.380	-4.650E-01	8.420E-05	5.470E-03	-1.380	-0.465	8.420E-05	5.470E-03
eef1g	eukaryotic translation elongation factor 1 gamma	-1.129	-1.750E-01	2.610E-03	3.930E-02	-1.129	-0.175	2.610E-03	3.930E-02
eefsec	eukaryotic elongation factor, selenocysteine-tRNA-specific	-1.242	-3.130E-01	1.440E-03	2.720E-02	-1.242	-0.313	1.440E-03	2.720E-02
efcab14	EF-hand calcium binding domain 14	1.317	3.970E-01	3.620E-04	1.230E-02	1.317	0.397	3.620E-04	1.230E-02
eid2	EP300 interacting inhibitor of differentiation 2	-1.491	-5.760E-01	6.720E-06	1.250E-03	-1.491	-0.576	6.720E-06	1.250E-03
eif2ak2	eukaryotic translation initiation factor 2-alpha kinase 2	1.311	3.910E-01	3.240E-03	4.440E-02	1.311	0.391	3.240E-03	4.440E-02
eif6	eukaryotic translation initiation factor 6	-1.137	-1.850E-01	3.660E-03	4.740E-02	-1.137	-0.185	3.660E-03	4.740E-02
eml5	echinoderm microtubule associated protein like 5	1.570	6.510E-01	2.470E-08	2.440E-05	1.570	0.651	2.470E-08	2.440E-05
ensrnog0000 0045588	uncharacterized protein	-1.306	-3.850E-01	1.410E-04	7.520E-03	-1.306	-0.385	1.410E-04	7.520E-03
ensrnog0000 0046381	uncharacterized protein	-1.356	-4.390E-01	3.600E-04	1.230E-02	-1.356	-0.439	3.600E-04	1.230E-02
ercc5	excision repair cross-complementing rodent repair deficiency, complementation group 5	1.306	3.850E-01	2.570E-04	1.040E-02	1.306	0.385	2.570E-04	1.040E-02
ercc6l2	ERCC excision repair 6 like 2	1.315	3.950E-01	2.310E-04	9.720E-03	1.315	0.395	2.310E-04	9.720E-03
ergic3	ERGIC and golgi 3	-1.225	-2.930E-01	2.190E-04	9.440E-03	-1.225	-0.293	2.190E-04	9.440E-03
esyt2	family with sequence similarity 62 (C2 domain containing), member B	1.485	5.700E-01	7.730E-08	5.340E-05	1.485	0.570	7.730E-08	5.340E-05
evi5l	ecotropic viral integration site 5-like	-1.199	-2.620E-01	1.710E-04	8.360E-03	-1.199	-0.262	1.710E-04	8.360E-03
exosc5	exosome component 5	-1.288	-3.650E-01	5.690E-04	1.530E-02	-1.288	-0.365	5.690E-04	1.530E-02
f8a1	coagulation factor VIII-associated 1	-1.313	-3.930E-01	4.530E-05	3.820E-03	-1.313	-0.393	4.530E-05	3.820E-03
fam127b	family with sequence similarity 127, member B	-1.237	-3.070E-01	9.730E-04	2.150E-02	-1.237	-0.307	9.730E-04	2.150E-02
fam131c	family with sequence similarity 131, member C	-1.338	-4.200E-01	3.070E-03	4.290E-02	-1.338	-0.420	3.070E-03	4.290E-02
fam135a	family with sequence similarity 135, member A	1.319	3.990E-01	1.750E-03	3.030E-02	1.319	0.399	1.750E-03	3.030E-02
fam171a2	family with sequence similarity 171, member A2	-1.288	-3.650E-01	3.280E-03	4.450E-02	-1.288	-0.365	3.280E-03	4.450E-02
fam178a	family with sequence similarity 178, member A	1.348	4.310E-01	6.580E-04	1.680E-02	1.348	0.431	6.580E-04	1.680E-02
fam179b	family with sequence similarity 179, member B	1.406	4.920E-01	2.870E-06	7.300E-04	1.406	0.492	2.870E-06	7.300E-04
fam189a1	family with sequence similarity 189, member A1	-1.316	-3.960E-01	2.070E-03	3.400E-02	-1.316	-0.396	2.070E-03	3.400E-02
fam19a5	family with sequence similarity 19, member A5	-1.337	-4.190E-01	6.570E-07	2.520E-04	-1.337	-0.419	6.570E-07	2.520E-04
fam214a	family with sequence similarity 214, member A	1.358	4.420E-01	2.890E-06	7.300E-04	1.358	0.442	2.890E-06	7.300E-04
fam35a	family with sequence similarity 35, member A	1.337	4.190E-01	8.470E-04	1.960E-02	1.337	0.419	8.470E-04	1.960E-02
fam69b	family with sequence similarity 69, member B	-1.223	-2.900E-01	5.210E-04	1.480E-02	-1.223	-0.290	5.210E-04	1.480E-02
fam89b	family with sequence similarity 89, member B	-1.304	-3.830E-01	2.920E-04	1.100E-02	-1.304	-0.383	2.920E-04	1.100E-02
fastkd3	FAST kinase domains 3	1.401	4.860E-01	1.970E-04	9.090E-03	1.401	0.486	1.970E-04	9.090E-03
fbxl15	F-box and leucine-rich repeat protein 15	-1.384	-4.690E-01	7.000E-05	4.840E-03	-1.384	-0.469	7.000E-05	4.840E-03
fbxo31	F-box protein 31	-1.220	-2.870E-01	3.050E-03	4.280E-02	-1.220	-0.287	3.050E-03	4.280E-02
flywch2	FLYWCH family member 2	-1.261	-3.340E-01	3.580E-04	1.230E-02	-1.261	-0.334	3.580E-04	1.230E-02
fnip1	folliculin interacting protein 1	1.352	4.350E-01	7.220E-04	1.790E-02	1.352	0.435	7.220E-04	1.790E-02
foxo6	forkhead box O6	-1.300	-3.780E-01	4.250E-04	1.310E-02	-1.300	-0.378	4.250E-04	1.310E-02
foxp4	forkhead box P4	-1.300	-3.780E-01	2.900E-04	1.100E-02	-1.300	-0.378	2.900E-04	1.100E-02
frs3	fibroblast growth factor receptor substrate 3	-1.268	-3.420E-01	1.550E-03	2.840E-02	-1.268	-0.342	1.550E-03	2.840E-02
fsd1	fibronectin type 3 and SPRY domain-containing protein	-1.228	-2.960E-01	1.750E-03	3.040E-02	-1.228	-0.296	1.750E-03	3.040E-02
fuz	fuzzy homolog (Drosophila)	-1.293	-3.710E-01	2.060E-04	9.240E-03	-1.293	-0.371	2.060E-04	9.240E-03
fzr1	fizzy/cell division cycle 20 related 1 (Drosophila)	-1.261	-3.350E-01	1.090E-03	2.270E-02	-1.261	-0.335	1.090E-03	2.270E-02
g2e3	G2/M-phase specific E3 ubiquitin ligase	1.328	4.090E-01	3.040E-03	4.280E-02	1.328	0.409	3.040E-03	4.280E-02
gadd45gip1	growth arrest and DNA-damage-inducible, gamma interacting protein 1	-1.319	-3.990E-01	1.390E-04	7.470E-03	-1.319	-0.399	1.390E-04	7.470E-03
gdap1l1	ganglioside-induced differentiation-associated protein 1-like 1	-1.247	-3.180E-01	1.280E-03	2.530E-02	-1.247	-0.318	1.280E-03	2.530E-02
gipc1	GIPC PDZ domain containing family, member 1	-1.223	-2.900E-01	1.070E-03	2.250E-02	-1.223	-0.290	1.070E-03	2.250E-02
glce	glucuronyl C5-epimerase	1.273	3.480E-01	2.650E-03	3.950E-02	1.273	0.348	2.650E-03	3.950E-02
glt8d1	glycosyltransferase 8 domain containing 1	1.270	3.450E-01	1.920E-04	8.970E-03	1.270	0.345	1.920E-04	8.970E-03
gnaz	guanine nucleotide binding protein, alpha z subunit	-1.263	-3.370E-01	3.550E-04	1.230E-02	-1.263	-0.337	3.550E-04	1.230E-02
gpr162	G protein-coupled receptor 162	-1.223	-2.910E-01	4.540E-04	1.360E-02	-1.223	-0.291	4.540E-04	1.360E-02
gpr98	G protein-coupled receptor 98	1.434	5.200E-01	2.720E-04	1.070E-02	1.434	0.520	2.720E-04	1.070E-02
gpx4	glutathione peroxidase 4	-1.288	-3.650E-01	1.760E-05	2.170E-03	-1.288	-0.365	1.760E-05	2.170E-03
grik2	glutamate receptor, ionotropic, kainate 2 (beta 2)	1.309	3.880E-01	2.340E-04	9.740E-03	1.309	0.388	2.340E-04	9.740E-03
grina	glutamate receptor, ionotropic, N-methyl D-aspartate-associated protein 1 (glutamate binding)	-1.261	-3.350E-01	1.950E-03	3.250E-02	-1.261	-0.335	1.950E-03	3.250E-02
gsk3a	glycogen synthase kinase 3 alpha	-1.253	-3.250E-01	6.830E-04	1.720E-02	-1.253	-0.325	6.830E-04	1.720E-02
gtf3c3	general transcription factor IIIC, polypeptide 3	1.423	5.090E-01	6.120E-07	2.480E-04	1.423	0.509	6.120E-07	2.480E-04
gzf1	GDNF-inducible zinc finger protein 1	1.260	3.330E-01	3.780E-03	4.840E-02	1.260	0.333	3.780E-03	4.840E-02
h1fx	H1 histone family, member X	-1.453	-5.390E-01	1.380E-04	7.420E-03	-1.453	-0.539	1.380E-04	7.420E-03
h2afy2	H2A histone family, member Y2	-1.220	-2.870E-01	1.240E-04	6.970E-03	-1.220	-0.287	1.240E-04	6.970E-03
hap1	huntingtin-associated protein 1	-1.233	-3.020E-01	1.060E-03	2.250E-02	-1.233	-0.302	1.060E-03	2.250E-02
hcfc1r1	host cell factor C1 regulator 1 (XPO1-dependent)	-1.408	-4.940E-01	6.490E-04	1.670E-02	-1.408	-0.494	6.490E-04	1.670E-02
hcfc2	host cell factor C2	1.256	3.290E-01	5.640E-04	1.530E-02	1.256	0.329	5.640E-04	1.530E-02

Supplemental Table 3 (continued)

hcn2	hyperpolarization-activated, cyclic nucleotide-gated K+ 2	-1.246	-3.170E-01	1.590E-03	2.880E-02	-1.246	-0.317	1.590E-03	2.880E-02
hectd2	HECT domain containing 2	1.296	3.740E-01	3.410E-03	4.560E-02	1.296	0.374	3.410E-03	4.560E-02
hfm1	HFM1, ATP-dependent DNA helicase homolog (S. cerevisiae)	1.479	5.650E-01	1.510E-05	2.070E-03	1.479	0.565	1.510E-05	2.070E-03
hmga1	high mobility group AT-hook I, related sequence 1	-1.352	-4.350E-01	3.900E-04	1.270E-02	-1.352	-0.435	3.900E-04	1.270E-02
hmx3	H6 homeo box 3	-1.459	-5.450E-01	1.500E-04	7.840E-03	-1.459	-0.545	1.500E-04	7.840E-03
hras1	Harvey rat sarcoma virus oncogene 1	-1.297	-3.750E-01	2.370E-04	9.770E-03	-1.297	-0.375	2.370E-04	9.770E-03
hspbp1	HSPA (heat shock 70kDa) binding protein, cytoplasmic cochaperone 1	-1.229	-2.970E-01	1.710E-03	3.000E-02	-1.229	-0.297	1.710E-03	3.000E-02
ints2	integrator complex subunit 2	1.609	6.860E-01	1.420E-08	2.310E-05	1.609	0.686	1.420E-08	2.310E-05
ipo4	importin 4	-1.193	-2.550E-01	2.300E-04	9.720E-03	-1.193	-0.255	2.300E-04	9.720E-03
irf2bp1	interferon regulatory factor 2 binding protein 1	-1.303	-3.820E-01	2.210E-05	2.530E-03	-1.303	-0.382	2.210E-05	2.530E-03
irf2bpl	interferon regulatory factor 2 binding protein-like	-1.318	-3.980E-01	2.230E-04	9.570E-03	-1.318	-0.398	2.230E-04	9.570E-03
itch	itchy, E3 ubiquitin protein ligase	1.408	4.940E-01	5.730E-05	4.240E-03	1.408	0.494	5.730E-05	4.240E-03
jund	Jun proto-oncogene related gene d	-1.417	-5.030E-01	2.820E-04	1.090E-02	-1.417	-0.503	2.820E-04	1.090E-02
kcnc4	potassium voltage gated channel, Shaw-related subfamily, member 4	-1.258	-3.310E-01	3.960E-03	4.950E-02	-1.258	-0.331	3.960E-03	4.950E-02
kcnt2	potassium channel, subfamily T, member 2	1.274	3.490E-01	1.390E-03	2.660E-02	1.274	0.349	1.390E-03	2.660E-02
kdm5a	lysine (K)-specific demethylase 5A	1.317	3.970E-01	3.330E-03	4.490E-02	1.317	0.397	3.330E-03	4.490E-02
kif15	kinesin family member 15	1.323	4.040E-01	2.230E-03	3.570E-02	1.323	0.404	2.230E-03	3.570E-02
kif5b	kinesin family member 5B	1.229	2.970E-01	3.240E-03	4.440E-02	1.229	0.297	3.240E-03	4.440E-02
krit1	KRIT1, ankyrin repeat containing	1.380	4.650E-01	6.070E-04	1.590E-02	1.380	0.465	6.070E-04	1.590E-02
lcor	ligand dependent nuclear receptor corepressor	1.544	6.270E-01	3.550E-06	8.320E-04	1.544	0.627	3.550E-06	8.320E-04
limk1	LIM-domain containing, protein kinase	-1.198	-2.610E-01	1.090E-03	2.280E-02	-1.198	-0.261	1.090E-03	2.280E-02
lmna	lamin A	-1.315	-3.950E-01	3.180E-05	2.990E-03	-1.315	-0.395	3.180E-05	2.990E-03
lmtk3	emur tyrosine kinase 3	-1.291	-3.680E-01	1.280E-03	2.530E-02	-1.291	-0.368	1.280E-03	2.530E-02
lpxn	leupaxin	1.257	3.300E-01	2.630E-03	3.940E-02	1.257	0.330	2.630E-03	3.940E-02
lrfn3	leucine rich repeat and fibronectin type III domain containing 3	-1.243	-3.140E-01	3.890E-03	4.900E-02	-1.243	-0.314	3.890E-03	4.900E-02
lrfn4	leucine rich repeat and fibronectin type III domain containing 4	-1.307	-3.860E-01	3.370E-04	1.200E-02	-1.307	-0.386	3.370E-04	1.200E-02
lrrc4b	leucine rich repeat containing 4B	-1.279	-3.550E-01	2.750E-04	1.070E-02	-1.279	-0.355	2.750E-04	1.070E-02
lrrn2	leucine rich repeat protein 2, neuronal	-1.241	-3.110E-01	5.560E-04	1.510E-02	-1.241	-0.311	5.560E-04	1.510E-02
luc7l3	LUC7-like 3 pre-mRNA splicing facto	1.439	5.250E-01	9.290E-05	5.880E-03	1.439	0.525	9.290E-05	5.880E-03
ly6h	lymphocyte antigen 6 complex, locus H	-1.292	-3.700E-01	7.950E-04	1.910E-02	-1.292	-0.370	7.950E-04	1.910E-02
lypla2	lysophospholipase 2	-1.199	-2.620E-01	1.050E-03	2.240E-02	-1.199	-0.262	1.050E-03	2.240E-02
maf1	MAF1 homolog (S. cerevisiae)	-1.158	-2.120E-01	2.440E-04	1.000E-02	-1.158	-0.212	2.440E-04	1.000E-02
map3k11	mitogen-activated protein kinase kinase kinase 11	-1.387	-4.720E-01	7.890E-04	1.910E-02	-1.387	-0.472	7.890E-04	1.910E-02
map7d1	MAP7 domain containing 1	-1.219	-2.860E-01	2.730E-04	1.070E-02	-1.219	-0.286	2.730E-04	1.070E-02
mapk8ip1	mitogen-activated protein kinase 8 interacting protein 1	-1.218	-2.850E-01	3.420E-03	4.560E-02	-1.218	-0.285	3.420E-03	4.560E-02
mark4	MAP/microtubule affinity-regulating kinase 4	-1.267	-3.410E-01	2.690E-03	3.980E-02	-1.267	-0.341	2.690E-03	3.980E-02
mat2a	methionine adenosyltransferase II, alpha	1.481	5.670E-01	1.710E-08	2.310E-05	1.481	0.567	1.710E-08	2.310E-05
maz	MYC-associated zinc finger protein (purine-binding transcription factor)	-1.292	-3.700E-01	2.100E-03	3.430E-02	-1.292	-0.370	2.100E-03	3.430E-02
mbd3	methyl-CpG binding domain protein 3	-1.306	-3.850E-01	2.150E-04	9.420E-03	-1.306	-0.385	2.150E-04	9.420E-03
mbnl1	muscleblind-like 1 (Drosophila)	1.273	3.480E-01	6.520E-04	1.670E-02	1.273	0.348	6.520E-04	1.670E-02
mdm4	transformed mouse 3T3 cell double minute 4	1.638	7.120E-01	3.730E-08	3.080E-05	1.638	0.712	3.730E-08	3.080E-05
med13	mediator complex subunit 13	1.407	4.930E-01	1.260E-05	1.900E-03	1.407	0.493	1.260E-05	1.900E-03
med16	mediator complex subunit 16	-1.254	-3.270E-01	2.740E-03	4.020E-02	-1.254	-0.327	2.740E-03	4.020E-02
med25	mediator of RNA polymerase II transcription, subunit 25 homolog (yeast)	-1.266	-3.400E-01	2.770E-03	4.040E-02	-1.266	-0.340	2.770E-03	4.040E-02
mef2a	myocyte enhancer factor 2A	1.265	3.390E-01	3.780E-03	4.840E-02	1.265	0.339	3.780E-03	4.840E-02
mga	MAX gene associated	1.389	4.740E-01	5.450E-05	4.200E-03	1.389	0.474	5.450E-05	4.200E-03
mif	macrophage migration inhibitory factor-like	-1.406	-4.920E-01	2.650E-04	1.050E-02	-1.406	-0.492	2.650E-04	1.050E-02
mitd1	MIT, microtubule interacting and transport, domain containing 1	1.373	4.570E-01	9.200E-04	2.070E-02	1.373	0.457	9.200E-04	2.070E-02
morc3	microrchidia 3	1.309	3.890E-01	1.520E-03	2.810E-02	1.309	0.389	1.520E-03	2.810E-02
mospd2	motile sperm domain containing 2	1.355	4.380E-01	8.110E-04	1.920E-02	1.355	0.438	8.110E-04	1.920E-02
mospd3	motile sperm domain containing 3	-1.205	-2.690E-01	8.280E-04	1.940E-02	-1.205	-0.269	8.280E-04	1.940E-02
mrpl37	mitochondrial ribosomal protein L37	-1.210	-2.750E-01	2.760E-03	4.040E-02	-1.210	-0.275	2.760E-03	4.040E-02
msh3	mutS homolog 3 (E. coli)	1.313	3.930E-01	8.430E-04	1.960E-02	1.313	0.393	8.430E-04	1.960E-02
mt3	metallothionein 3	-1.387	-4.720E-01	1.580E-04	8.060E-03	-1.387	-0.472	1.580E-04	8.060E-03
mta1	metastasis associated 1	-1.193	-2.540E-01	2.170E-04	9.430E-03	-1.193	-0.254	2.170E-04	9.430E-03
mydgf	Myeloid derived growth factor	-1.228	-2.960E-01	2.450E-05	2.620E-03	-1.228	-0.296	2.450E-05	2.620E-03
myo9a	myosin IXa	1.348	4.310E-01	1.550E-04	7.980E-03	1.348	0.431	1.550E-04	7.980E-03
ndufa13	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13	-1.283	-3.600E-01	1.560E-05	2.070E-03	-1.283	-0.360	1.560E-05	2.070E-03
ndufb10	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 10	-1.318	-3.980E-01	5.580E-05	4.240E-03	-1.318	-0.398	5.580E-05	4.240E-03
ndufb7	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7	-1.225	-2.930E-01	9.380E-04	2.100E-02	-1.225	-0.293	9.380E-04	2.100E-02
ndufs7	NADH dehydrogenase (ubiquinone) Fe-S protein 7	-1.235	-3.040E-01	1.470E-03	2.760E-02	-1.235	-0.304	1.470E-03	2.760E-02
ndufv1	NADH dehydrogenase (ubiquinone) flavoprotein 1	-1.174	-2.310E-01	2.850E-04	1.090E-02	-1.174	-0.231	2.850E-04	1.090E-02
neurl1a	neuralized homolog 1A (Drosophila)	-1.359	-4.430E-01	1.120E-03	2.310E-02	-1.359	-0.443	1.120E-03	2.310E-02
nfat5	nuclear factor of activated T-cells 5	1.515	5.990E-01	3.740E-06	8.610E-04	1.515	0.599	3.740E-06	8.610E-04
nhlrc2	NHL repeat containing 2	1.331	4.130E-01	2.010E-03	3.330E-02	1.331	0.413	2.010E-03	3.330E-02
npat	nuclear protein in the AT region	1.385	4.700E-01	3.570E-04	1.230E-02	1.385	0.470	3.570E-04	1.230E-02
nr2f6	nuclear receptor subfamily 2, group F, member 6	-1.296	-3.740E-01	3.990E-04	1.280E-02	-1.296	-0.374	3.990E-04	1.280E-02
nsmaf	neutral sphingomyelinase (N-SMase) activation associated factor	1.497	5.820E-01	5.490E-09	1.520E-05	1.497	0.582	5.490E-09	1.520E-05
nufip2	NUFIP2, FMR1 interacting protein 2	1.369	4.530E-01	2.650E-04	1.050E-02	1.369	0.453	2.650E-04	1.050E-02
numbl	numb-like	-1.283	-3.590E-01	1.250E-03	2.510E-02	-1.283	-0.359	1.250E-03	2.510E-02
nup155	nucleoporin 155	1.273	3.480E-01	1.520E-03	2.810E-02	1.273	0.348	1.520E-03	2.810E-02
nup160	nucleoporin 160	1.329	4.100E-01	3.530E-04	1.220E-02	1.329	0.410	3.530E-04	1.220E-02
nvl	nuclear VCP-like	1.322	4.030E-01	2.550E-03	3.890E-02	1.322	0.403	2.550E-03	3.890E-02
oaz1	ornithine decarboxylase antizyme 1	-1.343	-4.250E-01	2.260E-08	2.440E-05	-1.343	-0.425	2.260E-08	2.440E-05
orc3	origin recognition complex, subunit 3	1.274	3.490E-01	1.110E-03	2.310E-02	1.274	0.349	1.110E-03	2.310E-02

Supplemental Table 3 (continued)

orc5	origin recognition complex, subunit 5	1.249	3.210E-01	1.890E-03	3.200E-02	1.249	0.321	1.890E-03	3.200E-02
osgin2	oxidative stress induced growth inhibitor family member 2	1.336	4.180E-01	2.180E-04	9.440E-03	1.336	0.418	2.180E-04	9.440E-03
pacsin2	protein kinase C and casein kinase substrate in neurons 2	-1.188	-2.490E-01	1.070E-03	2.250E-02	-1.188	-0.249	1.070E-03	2.250E-02
papolg	poly(A) polymerase gamma	1.402	4.880E-01	1.730E-04	8.390E-03	1.402	0.488	1.730E-04	8.390E-03
papss1	3'-phosphoadenosine 5'-phosphosulfate synthase 1	-1.170	-2.270E-01	9.620E-05	6.010E-03	-1.170	-0.227	9.620E-05	6.010E-03
pcbp1	Poly(RC) Binding Protein 1	-1.366	-4.500E-01	3.260E-05	2.990E-03	-1.366	-0.450	3.260E-05	2.990E-03
pcbp2	poly(rC) binding protein 2	-1.179	-2.380E-01	1.690E-04	8.360E-03	-1.179	-0.238	1.690E-04	8.360E-03
pcbp4	poly(rC) binding protein 4	-1.276	-3.520E-01	2.210E-04	9.490E-03	-1.276	-0.352	2.210E-04	9.490E-03
pcm1	pericentriolar material 1	1.305	3.840E-01	1.290E-03	2.540E-02	1.305	0.384	1.290E-03	2.540E-02
pdxp	pyridoxal (pyridoxine, vitamin B6) phosphatase	-1.303	-3.820E-01	2.740E-04	1.070E-02	-1.303	-0.382	2.740E-04	1.070E-02
pebp1	phosphatidylethanolamine binding protein 1	-1.253	-3.250E-01	8.470E-04	1.960E-02	-1.253	-0.325	8.470E-04	1.960E-02
phactr3	phosphatase and actin regulator 3	-1.280	-3.560E-01	4.910E-04	1.430E-02	-1.280	-0.356	4.910E-04	1.430E-02
phc3	polyhomeotic-like 3 (Drosophila)	1.358	4.420E-01	1.060E-04	6.240E-03	1.358	0.442	1.060E-04	6.240E-03
phf20l1	PHD finger protein 20-like 1	1.436	5.220E-01	1.510E-06	4.620E-04	1.436	0.522	1.510E-06	4.620E-04
phip	pleckstrin homology domain interacting protein	1.430	5.160E-01	5.500E-05	4.220E-03	1.430	0.516	5.500E-05	4.220E-03
phldb2	pleckstrin homology-like domain, family B, member 2	1.379	4.640E-01	7.410E-05	5.050E-03	1.379	0.464	7.410E-05	5.050E-03
pianp	PILR alpha associated neural protein	-1.253	-3.250E-01	1.690E-03	2.980E-02	-1.253	-0.325	1.690E-03	2.980E-02
pick1	protein interacting with C kinase 1	-1.209	-2.740E-01	1.720E-03	3.020E-02	-1.209	-0.274	1.720E-03	3.020E-02
pkd2	polycystic kidney disease 2	1.269	3.440E-01	2.810E-03	4.070E-02	1.269	0.344	2.810E-03	4.070E-02
pkig	protein kinase inhibitor, gamma	-1.329	-4.100E-01	1.670E-05	2.090E-03	-1.329	-0.410	1.670E-05	2.090E-03
pnisr	PNN-interacting serine/arginine-rich protein	1.499	5.840E-01	6.920E-06	1.260E-03	1.499	0.584	6.920E-06	1.260E-03
pnmal2	PNMA-like 2	-1.179	-2.380E-01	1.930E-03	3.230E-02	-1.179	-0.238	1.930E-03	3.230E-02
podxl2	podocalyxin-like 2	-1.255	-3.280E-01	3.880E-04	1.270E-02	-1.255	-0.328	3.880E-04	1.270E-02
poglut1	protein O-glucosyltransferase 1	1.281	3.570E-01	3.300E-04	1.190E-02	1.281	0.357	3.300E-04	1.190E-02
pot1	protection of telomeres 1	1.415	5.010E-01	4.730E-05	3.890E-03	1.415	0.501	4.730E-05	3.890E-03
ppp1r9b	protein phosphatase 1, regulatory subunit 9B	-1.155	-2.080E-01	1.590E-03	2.880E-02	-1.155	-0.208	1.590E-03	2.880E-02
ppp2r5d	protein phosphatase 2, regulatory subunit B (B56), delta isoform	-1.139	-1.880E-01	1.620E-03	2.930E-02	-1.139	-0.188	1.620E-03	2.930E-02
ppp6r3	protein phosphatase 6, regulatory subunit 3	1.246	3.170E-01	5.410E-04	1.500E-02	1.246	0.317	5.410E-04	1.500E-02
ppwd1	peptidylprolyl isomerase domain and WD repeat containing 1	1.314	3.940E-01	2.190E-03	3.530E-02	1.314	0.394	2.190E-03	3.530E-02
prcc	papillary renal cell carcinoma (translocation-associated)	-1.199	-2.620E-01	1.440E-05	2.040E-03	-1.199	-0.262	1.440E-05	2.040E-03
prelid1	PRELI domain containing 1	-1.239	-3.090E-01	1.730E-03	3.020E-02	-1.239	-0.309	1.730E-03	3.020E-02
prkdc	protein kinase, DNA activated, catalytic polypeptide	1.420	5.060E-01	3.390E-05	3.060E-03	1.420	0.506	3.390E-05	3.060E-03
prmt2	protein arginine N-methyltransferase 2	-1.225	-2.930E-01	4.780E-04	1.410E-02	-1.225	-0.293	4.780E-04	1.410E-02
prpf39	PRP39 pre-mRNA processing factor 39 homolog (yeast)	1.532	6.150E-01	1.380E-05	1.980E-03	1.532	0.615	1.380E-05	1.980E-03
prr7	proline rich 7 (synaptic)	-1.434	-5.200E-01	7.530E-05	5.060E-03	-1.434	-0.520	7.530E-05	5.060E-03
psmb5	predicted gene 3375	-1.254	-3.270E-01	5.300E-04	1.490E-02	-1.254	-0.327	5.300E-04	1.490E-02
psmd3	proteasome (prosome, macropain) 26S subunit, non-ATPase, 3	-1.314	-3.940E-01	4.630E-06	9.550E-04	-1.314	-0.394	4.630E-06	9.550E-04
psme4	proteasome (prosome, macropain) activator subunit 4	1.423	5.090E-01	3.480E-05	3.100E-03	1.423	0.509	3.480E-05	3.100E-03
ptms	parathymosin	-1.225	-2.930E-01	4.210E-04	1.310E-02	-1.225	-0.293	4.210E-04	1.310E-02
ptov1	prostate tumor over expressed gene 1	-1.304	-3.830E-01	3.330E-04	1.190E-02	-1.304	-0.383	3.330E-04	1.190E-02
pvrl1	poliovirus receptor-related 1	-1.276	-3.520E-01	2.490E-03	3.830E-02	-1.276	-0.352	2.490E-03	3.830E-02
rac3	RAS-related C3 botulinum substrate 3	-1.344	-4.270E-01	3.630E-04	1.240E-02	-1.344	-0.427	3.630E-04	1.240E-02
ranbp2	RAN binding protein 2	1.332	4.140E-01	3.130E-03	4.360E-02	1.332	0.414	3.130E-03	4.360E-02
rapgef6	Rap guanine nucleotide exchange factor (GEF) 6	1.283	3.600E-01	1.720E-03	3.020E-02	1.283	0.360	1.720E-03	3.020E-02
rbm28	RNA binding motif protein 28	1.238	3.080E-01	3.650E-03	4.740E-02	1.238	0.308	3.650E-03	4.740E-02
rbm42	RNA binding motif protein 42	-1.251	-3.230E-01	3.370E-03	4.540E-02	-1.251	-0.323	3.370E-03	4.540E-02
rc3h2	ring finger and CCCH-type zinc finger domains 2	1.322	4.030E-01	6.810E-04	1.720E-02	1.322	0.403	6.810E-04	1.720E-02
rell2	RELT-like 2	-1.366	-4.500E-01	5.010E-04	1.450E-02	-1.366	-0.450	5.010E-04	1.450E-02
rfc1	replication factor C (activator 1) 1	1.193	2.550E-01	1.650E-03	2.940E-02	1.193	0.255	1.650E-03	2.940E-02
rgd1308134	similar to RIKEN cDNA 1110020A23	-1.272	-3.470E-01	7.150E-04	1.780E-02	-1.272	-0.347	7.150E-04	1.780E-02
rgd1309594	similar to RIKEN cDNA 1810043G02	-1.250	-3.220E-01	2.060E-03	3.390E-02	-1.250	-0.322	2.060E-03	3.390E-02
rgd1309995	similar to CG13957-PA	1.456	5.420E-01	1.630E-05	2.090E-03	1.456	0.542	1.630E-05	2.090E-03
rgd1559904	similar to mKIAA1429 protein	1.318	3.980E-01	1.260E-03	2.520E-02	1.318	0.398	1.260E-03	2.520E-02
rgd1560394	RGD1560394	-1.362	-4.460E-01	1.060E-03	2.250E-02	-1.362	-0.446	1.060E-03	2.250E-02
rgd1562608	similar to KIAA1328 protein	1.291	3.680E-01	2.370E-05	2.620E-03	1.291	0.368	2.370E-05	2.620E-03
rhob	ras homolog gene family, member B	-1.376	-4.610E-01	5.980E-05	4.320E-03	-1.376	-0.461	5.980E-05	4.320E-03
rictor	RPTOR independent companion of MTOR, complex 2	1.545	6.280E-01	2.060E-09	9.480E-06	1.545	0.628	2.060E-09	9.480E-06
rnaseh2a	ribonuclease H2, large subunit	-1.252	-3.240E-01	7.950E-04	1.910E-02	-1.252	-0.324	7.950E-04	1.910E-02
rnf10	ring finger protein 10	-1.246	-3.170E-01	4.080E-05	3.520E-03	-1.246	-0.317	4.080E-05	3.520E-03
rnf126	ring finger protein 126	-1.376	-4.600E-01	1.710E-04	8.360E-03	-1.376	-0.460	1.710E-04	8.360E-03
rnf170	ring finger protein 170	1.293	3.710E-01	2.530E-04	1.030E-02	1.293	0.371	2.530E-04	1.030E-02
rnf208	ring finger protein 208	-1.336	-4.180E-01	1.360E-04	7.400E-03	-1.336	-0.418	1.360E-04	7.400E-03
rnpc3	RNA-binding region (RNP1, RRM) containing 3	1.397	4.820E-01	2.020E-04	9.190E-03	1.397	0.482	2.020E-04	9.190E-03
rock1	Rho-associated coiled-coil containing protein kinase 1	1.476	5.620E-01	1.560E-05	2.070E-03	1.476	0.562	1.560E-05	2.070E-03
rpl13	ribosomal protein L13	-1.277	-3.530E-01	1.120E-03	2.310E-02	-1.277	-0.353	1.120E-03	2.310E-02
rpl27a	ribosomal protein L27a	-1.458	-5.440E-01	1.070E-05	1.690E-03	-1.458	-0.544	1.070E-05	1.690E-03
rpl35	ribosomal protein L35	-1.274	-3.490E-01	3.150E-03	4.360E-02	-1.274	-0.349	3.150E-03	4.360E-02
rpl36	ribosomal protein L36	-1.450	-5.360E-01	3.090E-05	2.960E-03	-1.450	-0.536	3.090E-05	2.960E-03
rundc3a	RUN domain containing 3A	-1.268	-3.430E-01	2.170E-03	3.510E-02	-1.268	-0.343	2.170E-03	3.510E-02
sacs	sacsin	1.625	7.000E-01	2.460E-08	2.440E-05	1.625	0.700	2.460E-08	2.440E-05
samd1	sterile alpha motif domain containing 1	-1.249	-3.210E-01	9.330E-04	2.090E-02	-1.249	-0.321	9.330E-04	2.090E-02
scai	suppressor of cancer cell invasion	1.269	3.440E-01	3.440E-03	4.570E-02	1.269	0.344	3.440E-03	4.570E-02
scand1	SCAN domain-containing 1	-1.396	-4.810E-01	6.730E-05	4.770E-03	-1.396	-0.481	6.730E-05	4.770E-03
scn1a	sodium channel, voltage-gated, type I, alpha	1.357	4.400E-01	2.640E-05	2.660E-03	1.357	0.440	2.640E-05	2.660E-03
scn9a	sodium channel, voltage-gated, type IX, alpha	1.597	6.750E-01	1.410E-07	8.140E-05	1.597	0.675	1.410E-07	8.140E-05

Supplemental Table 3 (continued)

secisbp2l	SECIS binding protein 2-like	1.298	3.760E-01	5.260E-05	4.080E-03	1.298	0.376	5.260E-05	4.080E-03
serpinc1	serine (or cysteine) peptidase inhibitor, clade C (antithrombin), member 1	1.385	4.700E-01	3.860E-04	1.270E-02	1.385	0.470	3.860E-04	1.270E-02
setx	senataxin	1.408	4.940E-01	1.600E-06	4.710E-04	1.408	0.494	1.600E-06	4.710E-04
sf3b1	splicing factor 3b, subunit 1	1.393	4.780E-01	1.530E-05	2.070E-03	1.393	0.478	1.530E-05	2.070E-03
sf3b4	splicing factor 3b, subunit 4	-1.254	-3.270E-01	2.930E-04	1.100E-02	-1.254	-0.327	2.930E-04	1.100E-02
sgta	small glutamine-rich tetratricopeptide repeat (TPR)-containing, alpha	-1.235	-3.050E-01	3.270E-03	4.450E-02	-1.235	-0.305	3.270E-03	4.450E-02
sh2d3c	SH2 domain containing 3C	-1.320	-4.000E-01	1.010E-03	2.180E-02	-1.320	-0.400	1.010E-03	2.180E-02
sipa1l3	signal-induced proliferation-associated 1 like 3	-1.223	-2.900E-01	3.750E-03	4.830E-02	-1.223	-0.290	3.750E-03	4.830E-02
slc32a1	solute carrier family 32 (GABA vesicular transporter), member 1	-1.439	-5.250E-01	1.680E-04	8.360E-03	-1.439	-0.525	1.680E-04	8.360E-03
slc4a7	solute carrier family 4, sodium bicarbonate cotransporter, member 7	1.392	4.770E-01	3.980E-05	3.450E-03	1.392	0.477	3.980E-05	3.450E-03
smarcb1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	-1.229	-2.970E-01	2.020E-04	9.190E-03	-1.229	-0.297	2.020E-04	9.190E-03
smc5	structural maintenance of chromosomes 5	1.367	4.510E-01	7.980E-04	1.910E-02	1.367	0.451	7.980E-04	1.910E-02
sncb	synuclein, beta	-1.320	-4.010E-01	1.270E-03	2.530E-02	-1.320	-0.401	1.270E-03	2.530E-02
snrpd2	predicted gene 5449	-1.324	-4.050E-01	1.300E-05	1.920E-03	-1.324	-0.405	1.300E-05	1.920E-03
snx13	sorting nexin 13	1.342	4.240E-01	7.270E-04	1.790E-02	1.342	0.424	7.270E-04	1.790E-02
snx17	sorting nexin 17	-1.236	-3.060E-01	2.070E-04	9.240E-03	-1.236	-0.306	2.070E-04	9.240E-03
sox12	SRY-box containing gene 12	-1.311	-3.910E-01	3.440E-04	1.200E-02	-1.311	-0.391	3.440E-04	1.200E-02
sp1	trans-acting transcription factor 1	1.280	3.560E-01	1.270E-03	2.530E-02	1.280	0.356	1.270E-03	2.530E-02
srrd	SRR1 domain containing	-1.304	-3.830E-01	1.190E-03	2.390E-02	-1.304	-0.383	1.190E-03	2.390E-02
ssbp3	single-stranded DNA binding protein 3	-1.232	-3.010E-01	2.620E-05	2.660E-03	-1.232	-0.301	2.620E-05	2.660E-03
stk11	serine/threonine kinase 11	-1.205	-2.690E-01	1.520E-03	2.810E-02	-1.205	-0.269	1.520E-03	2.810E-02
strip1	striatin interacting protein 1	-1.146	-1.970E-01	2.350E-03	3.710E-02	-1.146	-0.197	2.350E-03	3.710E-02
stub1	STIP1 homology and U-Box containing protein 1	-1.243	-3.140E-01	1.450E-03	2.720E-02	-1.243	-0.314	1.450E-03	2.720E-02
suv420h1	suppressor of variegation 4-20 homolog 1 (Drosophila)	1.250	3.220E-01	2.840E-03	4.100E-02	1.250	0.322	2.840E-03	4.100E-02
sys1	SYS1 Golgi-localized integral membrane protein homolog (S. cerevisiae)	-1.434	-5.200E-01	4.470E-06	9.350E-04	-1.434	-0.520	4.470E-06	9.350E-04
tceal3	transcription elongation factor A (SII)-like 3	-1.301	-3.800E-01	4.130E-04	1.300E-02	-1.301	-0.380	4.130E-04	1.300E-02
tceal6	transcription elongation factor A (SII)-like 6	-1.299	-3.770E-01	2.070E-04	9.240E-03	-1.299	-0.377	2.070E-04	9.240E-03
tdp2	tyrosyl-DNA phosphodiesterase 2	1.331	4.130E-01	2.290E-03	3.650E-02	1.331	0.413	2.290E-03	3.650E-02
tgfb1i1	transforming growth factor beta 1 induced transcript 1	-1.291	-3.680E-01	2.150E-03	3.500E-02	-1.291	-0.368	2.150E-03	3.500E-02
thoc1	THO complex 1	1.489	5.740E-01	2.540E-05	2.640E-03	1.489	0.574	2.540E-05	2.640E-03
thra	thyroid hormone receptor alpha	-1.271	-3.460E-01	2.360E-04	9.770E-03	-1.271	-0.346	2.360E-04	9.770E-03
tia1	cytotoxic granule-associated RNA binding protein 1	1.530	6.140E-01	1.760E-11	1.210E-07	1.530	0.614	1.760E-11	1.210E-07
tmem132e	transmembrane protein 132E	-1.280	-3.560E-01	2.810E-03	4.070E-02	-1.280	-0.356	2.810E-03	4.070E-02
tmem87b	transmembrane protein 87B	1.371	4.550E-01	6.350E-05	4.540E-03	1.371	0.455	6.350E-05	4.540E-03
tnip1	TNFAIP3 interacting protein 1	-1.258	-3.310E-01	2.970E-03	4.250E-02	-1.258	-0.331	2.970E-03	4.250E-02
trappc8	trafficking protein particle complex 8	1.259	3.320E-01	1.000E-03	2.180E-02	1.259	0.332	1.000E-03	2.180E-02
trdmt1	tRNA aspartic acid methyltransferase 1	1.580	6.600E-01	7.550E-07	2.680E-04	1.580	0.660	7.550E-07	2.680E-04
trim28	tripartite motif-containing 28	-1.131	-1.770E-01	2.600E-03	3.930E-02	-1.131	-0.177	2.600E-03	3.930E-02
trim8	tripartite motif protein 8	-1.183	-2.430E-01	2.230E-03	3.570E-02	-1.183	-0.243	2.230E-03	3.570E-02
trmt13	tRNA methyltransferase 13 homolog	1.522	6.060E-01	1.850E-05	2.180E-03	1.522	0.606	1.850E-05	2.180E-03
ttc39b	tetratricopeptide repeat domain 39B	1.493	5.780E-01	4.730E-06	9.620E-04	1.493	0.578	4.730E-06	9.620E-04
tubg1	tubulin, gamma 1	-1.310	-3.900E-01	3.540E-05	3.130E-03	-1.310	-0.390	3.540E-05	3.130E-03
tubg2	tubulin, gamma 2	-1.235	-3.050E-01	2.350E-03	3.710E-02	-1.235	-0.305	2.350E-03	3.710E-02
uba52	ubiquitin A-52 residue ribosomal protein fusion product 1	-1.286	-3.630E-01	7.380E-04	1.810E-02	-1.286	-0.363	7.380E-04	1.810E-02
ubald2	UBA-like domain containing 2	-1.394	-4.790E-01	1.430E-04	7.580E-03	-1.394	-0.479	1.430E-04	7.580E-03
ube2d1	ubiquitin-conjugating enzyme E2D 1, UBC4/5 homolog (yeast)	-1.341	-4.230E-01	1.730E-03	3.020E-02	-1.341	-0.423	1.730E-03	3.020E-02
ube2m	ubiquitin-conjugating enzyme E2M (UBC12 homolog, yeast)	-1.328	-4.090E-01	6.830E-05	4.810E-03	-1.328	-0.409	6.830E-05	4.810E-03
unc119	unc-119 homolog (C. elegans)	-1.291	-3.680E-01	9.260E-05	5.880E-03	-1.291	-0.368	9.260E-05	5.880E-03
uqcr10	ubiquinol-cytochrome c reductase, complex III subunit X	-1.513	-5.970E-01	1.210E-05	1.860E-03	-1.513	-0.597	1.210E-05	1.860E-03
usp37	ubiquitin specific peptidase 37	1.461	5.470E-01	1.820E-05	2.170E-03	1.461	0.547	1.820E-05	2.170E-03
vegfb	vascular endothelial growth factor B	-1.357	-4.400E-01	1.110E-03	2.310E-02	-1.357	-0.440	1.110E-03	2.310E-02
vprbp	Vpr (HIV-1) binding protein	1.232	3.010E-01	3.940E-03	4.930E-02	1.232	0.301	3.940E-03	4.930E-02
vps37d	vacuolar protein sorting 37D (yeast)	-1.312	-3.920E-01	8.140E-05	5.380E-03	-1.312	-0.392	8.140E-05	5.380E-03
vps54	vacuolar protein sorting 54 (yeast)	1.305	3.840E-01	2.480E-03	3.810E-02	1.305	0.384	2.480E-03	3.810E-02
vps72	vacuolar protein sorting 72 (yeast)	-1.222	-2.890E-01	8.420E-04	1.960E-02	-1.222	-0.289	8.420E-04	1.960E-02
vstm2l	V-set and transmembrane domain containing 2-like	-1.423	-5.090E-01	2.220E-05	2.530E-03	-1.423	-0.509	2.220E-05	2.530E-03
wbp4	WW domain binding protein 4	1.294	3.720E-01	7.230E-04	1.790E-02	1.294	0.372	7.230E-04	1.790E-02
wdr18	WD repeat domain 18	-1.289	-3.660E-01	1.320E-04	7.300E-03	-1.289	-0.366	1.320E-04	7.300E-03
wwc3	WWC family member 3	1.345	4.280E-01	5.450E-04	1.500E-02	1.345	0.428	5.450E-04	1.500E-02
xpo4	exportin 4	1.398	4.830E-01	1.510E-04	7.870E-03	1.398	0.483	1.510E-04	7.870E-03
ypel3	yippee-like 3 (Drosophila)	-1.275	-3.500E-01	1.050E-04	6.240E-03	-1.275	-0.350	1.050E-04	6.240E-03
ythdc2	YTH domain containing 2	1.640	7.140E-01	1.010E-12	1.400E-08	1.640	0.714	1.010E-12	1.400E-08
zbtb25	zinc finger and BTB domain containing 25	1.292	3.700E-01	3.130E-03	4.360E-02	1.292	0.370	3.130E-03	4.360E-02
zdhhc15	zinc finger, DHHC domain containing 15	1.390	4.750E-01	1.150E-04	6.610E-03	1.390	0.475	1.150E-04	6.610E-03
zfp192	zinc finger protein 192	1.425	5.110E-01	3.330E-04	1.190E-02	1.425	0.511	3.330E-04	1.190E-02
zfp286a	zinc finger protein 286A	1.299	3.770E-01	1.390E-03	2.660E-02	1.299	0.377	1.390E-03	2.660E-02
zfp382	zinc finger protein 382	1.254	3.270E-01	1.000E-05	1.640E-03	1.254	0.327	1.000E-05	1.640E-03
zfp386	zinc finger protein 386 (Kruppel-like)	1.369	4.530E-01	7.550E-04	1.850E-02	1.369	0.453	7.550E-04	1.850E-02
zfp451	zinc finger protein 451	1.317	3.970E-01	6.100E-04	1.590E-02	1.317	0.397	6.100E-04	1.590E-02
zfp483	zinc finger protein 483	1.622	6.980E-01	3.100E-07	1.630E-04	1.622	0.698	3.100E-07	1.630E-04
zfp560	zinc finger protein 560	1.301	3.800E-01	1.560E-03	2.860E-02	1.301	0.380	1.560E-03	2.860E-02
zfp575	zinc finger protein 575	-1.354	-4.370E-01	3.090E-04	1.140E-02	-1.354	-0.437	3.090E-04	1.140E-02
zfp580	zinc finger protein 580	-1.336	-4.180E-01	3.020E-03	4.280E-02	-1.336	-0.418	3.020E-03	4.280E-02
zfp706	zinc finger protein 706	-1.327	-4.080E-01	4.840E-04	1.410E-02	-1.327	-0.408	4.840E-04	1.410E-02
zfp715	protein Zfp715 (Fragment)	1.292	3.700E-01	2.140E-04	9.400E-03	1.292	0.370	2.140E-04	9.400E-03

Supplemental Table 3 (continued)

zfp871	zinc finger protein 871	1.340	4.220E-01	1.360E-03	2.630E-02	1.340	0.422	1.360E-03	2.630E-02
zfp949	zinc finger protein 949	1.286	3.630E-01	3.200E-03	4.410E-02	1.286	0.363	3.200E-03	4.410E-02
zfyve16	zinc finger, FYVE domain containing 16	1.472	5.580E-01	2.230E-05	2.530E-03	1.472	0.558	2.230E-05	2.530E-03
zkscan2	zinc finger with KRAB and SCAN domains 2	1.374	4.580E-01	3.710E-05	3.260E-03	1.374	0.458	3.710E-05	3.260E-03
zmat1	zinc finger, matrin type 1	1.317	3.970E-01	1.200E-03	2.420E-02	1.317	0.397	1.200E-03	2.420E-02
zmynd19	zinc finger, MYND domain containing 19	-1.239	-3.090E-01	8.550E-05	5.520E-03	-1.239	-0.309	8.550E-05	5.520E-03
zufsp	zinc finger with UFM1-specific peptidase domain	1.363	4.470E-01	3.000E-05	2.940E-03	1.363	0.447	3.000E-05	2.940E-03
zzz3	zinc finger, ZZ domain containing 3	1.330	4.110E-01	5.520E-04	1.510E-02	1.330	0.411	5.520E-04	1.510E-02

Supplemental Table 4. RNA-seq analysis of sexually dimorphic hippocampal and hypothalamic gene expression

Supplemental Table 4. RNA-seq analysis of sexually dimorphic hippocampal and hypothalamic gene expression

Supplemental Table 4a. Significantly (padj ≤ 0.05) altered hippocampal genes in Control ♂ vs Control ♀

Gene Symbol	Description	Fold Change	log2FC	p value	padj
Car2	carbonic anhydrase 2	-1.861	-0.896	5.000E-05	2.481E-02
Ccnl1	cyclin L1	-1.822	-0.865	5.000E-05	2.481E-02
Ccnl2	cyclin L2	-1.953	-0.966	5.000E-05	2.481E-02
Ccnt2	cyclin T2	-1.676	-0.745	5.000E-05	2.481E-02
Cdon	cell adhesion associated, oncogene regulated	-1.925	-0.945	5.000E-05	2.481E-02
Col1a1	collagen, type I, alpha 1	-7.346	-2.877	5.000E-05	2.481E-02
Crabp1	cellular retinoic acid binding protein 1	-2.179	-1.124	5.000E-05	2.481E-02
Eif2s3y	eukaryotic translation initiation factor 2, subunit 3, structural, Y-linked	1.620	0.696	5.000E-05	2.481E-02
Fam227a	family with sequence similarity 227, member A	-2.006	-1.004	5.000E-05	2.481E-02
Lace1	lactation elevated 1	-13.851	-3.792	5.000E-05	2.481E-02
Leng8	leukocyte receptor cluster (LRC) member 8	-1.846	-0.884	5.000E-05	2.481E-02
Leprel2	leprecan-like protein 2	-1.833	-0.874	5.000E-05	2.481E-02
Luc7l3	LUC7-like 3 pre-mRNA splicing factor	-1.804	-0.851	5.000E-05	2.481E-02
Npy1r	neuropeptide Y receptor Y1	2.155	1.108	5.000E-05	2.481E-02
Nrp2	neuropilin 2	1.865	0.899	5.000E-05	2.481E-02
Nts	neurotensin	-2.024	-1.017	5.000E-05	2.481E-02
Paxbp1	PAX3 and PAX7 binding protein 1	-1.904	-0.929	5.000E-05	2.481E-02
Pdyn	prodynorphin	-3.582	-1.841	5.000E-05	2.481E-02
Pnisr	PNN-interacting serine/arginine-rich protein	-2.104	-1.073	5.000E-05	2.481E-02
RGD1561931	similar to KIAA2022 protein	1.788	0.838	5.000E-05	2.481E-02
Rock1	Rho-associated coil containing protein kinase 1	-1.791	-0.841	5.000E-05	2.481E-02
Rpl30	ribosomal protein L30	-1.783	-0.834	5.000E-05	2.481E-02
Rsrp1	arginine/serine-rich protein 1	-1.658	-0.730	5.000E-05	2.481E-02
Spp1	secreted phosphoprotein 1	2.057	1.041	5.000E-05	2.481E-02
Tac1	tachykinin, precursor 1	-3.520	-1.816	5.000E-05	2.481E-02
Uhrf2	ubiquitin-like with PHD and ring finger domains 2	-1.783	-0.834	5.000E-05	2.481E-02
Cspp1	centrosome and spindle pole associated protein 1	-1.981	-0.987	1.000E-04	4.300E-02
Fam111a	family with sequence similarity 111, member A	1.708	0.772	1.000E-04	4.300E-02
Nktr	natural killer cell triggering receptor	-1.611	-0.688	1.000E-04	4.300E-02

Supplemental Table 4b. Significantly (padj ≤ 0.05) altered hypothalamic genes in Control ♂ vs. Control ♀

Gene Symbol	Description	Fold Change	log2FC	p value	padj
AABR06042582.1	AABR06042582.1	-1.857	-0.893	5.000E-05	7.773E-03
AABR06078887.1	AABR06078887.1	-1.825	-0.868	5.000E-05	7.773E-03
Abca8a	ATP-binding cassette, subfamily A (ABC1), member 8a	2.339	1.226	5.000E-05	7.773E-03

Supplemental Table 4 (continued)

Acp5	acid phosphatase 5, tartrate resistant	7.290	2.866	5.000E-05	7.773E-03
Adamts12	ADAM metallopeptidase with thrombospondin type 1 motif, 12	1.899	0.925	5.000E-05	7.773E-03
Aebp1	AE binding protein 1	2.651	1.407	5.000E-05	7.773E-03
Ahnak	AHNAK nucleoprotein	1.840	0.879	5.000E-05	7.773E-03
Arpp21	cAMP-regulated phosphoprotein 21	1.993	0.995	5.000E-05	7.773E-03
Birc6	baculoviral IAP repeat-containing 6	1.672	0.741	5.000E-05	7.773E-03
Cdkn1c	cyclin-dependent kinase inhibitor 1C	1.940	0.956	5.000E-05	7.773E-03
Cenpf	centromere protein F	1.611	0.688	5.000E-05	7.773E-03
Cfh	complement factor H	2.376	1.248	5.000E-05	7.773E-03
Col11a1	collagen, type XI, alpha 1	2.285	1.192	5.000E-05	7.773E-03
Col12a1	collagen, type XII, alpha 1	2.987	1.579	5.000E-05	7.773E-03
Col1a1	collagen, type I, alpha 1	30.730	4.942	5.000E-05	7.773E-03
Col1a2	collagen, type I, alpha 2	5.458	2.448	5.000E-05	7.773E-03
Col3a1	collagen, type III, alpha 1	4.247	2.087	5.000E-05	7.773E-03
Col6a1	collagen, type VI, alpha 1	2.234	1.159	5.000E-05	7.773E-03
Cp	ceruloplasmin (ferroxidase)	2.106	1.074	5.000E-05	7.773E-03
Ctsk	cathepsin K	4.696	2.232	5.000E-05	7.773E-03
Dab2	disabled 2, mitogen-responsive phosphoprotein	2.144	1.100	5.000E-05	7.773E-03
Dcn	decorin	8.857	3.147	5.000E-05	7.773E-03
Dlx1	distal-less homeobox 1	-1.632	-0.707	5.000E-05	7.773E-03
Dmrta2	DMRT-like family A2	3.909	1.967	5.000E-05	7.773E-03
Ebf2	early B-cell factor 2	2.938	1.555	5.000E-05	7.773E-03
Ebf3	early B-cell factor 3	2.654	1.408	5.000E-05	7.773E-03
Fam111a	amily with sequence similarity 111, member A	2.187	1.129	5.000E-05	7.773E-03
Fam227a	family with sequence similarity 227, member A	2.072	1.051	5.000E-05	7.773E-03
Fat3	FAT atypical cadherin 3	1.894	0.922	5.000E-05	7.773E-03
Foxa1	forkhead box A1	4.423	2.145	5.000E-05	7.773E-03
Foxb1	forkhead box B1	8.063	3.011	5.000E-05	7.773E-03
Frzb	frizzled-related protein	2.528	1.338	5.000E-05	7.773E-03
Gad1	glutamate decarboxylase 1	-1.548	-0.630	5.000E-05	7.773E-03
Gfap	glial fibrillary acidic protein	2.404	1.265	5.000E-05	7.773E-03
Gjb2	gap junction protein, beta 2	3.680	1.880	5.000E-05	7.773E-03
Gjb6	gap junction protein, beta 6	4.793	2.261	5.000E-05	7.773E-03
Gpr50	G protein-coupled receptor 50	-1.856	-0.892	5.000E-05	7.773E-03
Hba2	hemoglobin alpha, adult chain 2	1.807	0.853	5.000E-05	7.773E-03
Hmgcs2	3-hydroxy-3-methylglutaryl-CoA synthase 2 (mitochondrial)	1.769	0.823	5.000E-05	7.773E-03
Hopx	HOP homeobox	2.102	1.072	5.000E-05	7.773E-03
Ibsp	integrin-binding sialoprotein	12.109	3.598	5.000E-05	7.773E-03
Id3	inhibitor of DNA binding 3	2.242	1.165	5.000E-05	7.773E-03
Igf2	insulin-like growth factor 2	3.139	1.651	5.000E-05	7.773E-03
Itgb4	integrin subunit beta 4	3.862	1.949	5.000E-05	7.773E-03
Leng8	leukocyte receptor cluster (LRC) member 8	1.724	0.786	5.000E-05	7.773E-03
Lmx1a	LIM homeobox transcription factor 1 alpha	4.842	2.276	5.000E-05	7.773E-03
LOC100360841	ribosomal protein L37-like	-1.786	-0.837	5.000E-05	7.773E-03
LOC100909555	uncharacterized LOC100909555	-2.271	-1.183	5.000E-05	7.773E-03
LOC100910017	60S ribosomal protein L31-like	-1.715	-0.778	5.000E-05	7.773E-03
LOC100910855	mimecan-like	8.758	3.131	5.000E-05	7.773E-03
LOC257642	rRNA promoter binding protein	-1.894	-0.921	5.000E-05	7.773E-03
Luc7l3	LUC7-like 3 pre-mRNA splicing factor	1.693	0.760	5.000E-05	7.773E-03
Lum	lumican	29.349	4.875	5.000E-05	7.773E-03
Meis2	Meis homeobox 2	-3.710	-1.891	5.000E-05	7.773E-03
Mki67	marker of proliferation Ki-67	1.736	0.796	5.000E-05	7.773E-03

Supplemental Table 4 (continued)

Neurod6	neuronal differentiation 6	2.958	1.565	5.000E-05	7.773E-03
Nme2-ps1	non-metastatic cells 2, protein (NM23B) expressed in, pseudogene 1	-1.890	-0.918	5.000E-05	7.773E-03
Notch2	notch 2	2.026	1.019	5.000E-05	7.773E-03
Oxt	oxytocin/neurophysin 1 prepropeptide	-8.031	-3.006	5.000E-05	7.773E-03
Pitx2	paired-like homeodomain 2	5.430	2.441	5.000E-05	7.773E-03
Pnisr	PNN-interacting serine/arginine-rich protein	1.639	0.713	5.000E-05	7.773E-03
Pomc	proopiomelanocortin	1.949	0.963	5.000E-05	7.773E-03
Postn	periostin, osteoblast specific factor	14.096	3.817	5.000E-05	7.773E-03
Prpf4b	pre-mRNA processing factor 4B	1.549	0.631	5.000E-05	7.773E-03
Ptgds	prostaglandin D2 synthase	9.303	3.218	5.000E-05	7.773E-03
Rbm5	RNA binding motif protein 5	1.627	0.702	5.000E-05	7.773E-03
RGD1311723	centrosomal protein 295	1.834	0.875	5.000E-05	7.773E-03
Rn50_10_0291.1	Rn50_10_0291.1	-1.636	-0.710	5.000E-05	7.773E-03
Rpl30	ribosomal protein L30	-2.087	-1.062	5.000E-05	7.773E-03
Rps29	ribosomal protein S29	-1.591	-0.670	5.000E-05	7.773E-03
Ryr3	ryanodine receptor 3	2.138	1.097	5.000E-05	7.773E-03
Sacs	sacsin molecular chaperone	1.718	0.781	5.000E-05	7.773E-03
Scn7a	sodium channel, voltage-gated, type VII, alpha	2.450	1.293	5.000E-05	7.773E-03
Scn9a	sodium channel, voltage-gated, type IX, alpha subunit	1.666	0.736	5.000E-05	7.773E-03
Serp2	stress-associated endoplasmic reticulum protein family member 2	-1.583	-0.662	5.000E-05	7.773E-03
Slc32a1	solute carrier family 32 (GABA vesicular transporter), member 1	-1.737	-0.797	5.000E-05	7.773E-03
Smg1	SMG1 phosphatidylinositol 3-kinase-related kinase	1.713	0.776	5.000E-05	7.773E-03
Sncb	synuclein, beta	-1.546	-0.629	5.000E-05	7.773E-03
Sned1	sushi, nidogen and EGF-like domains 1	2.354	1.235	5.000E-05	7.773E-03
Spp1	secreted phosphoprotein 1	13.844	3.791	5.000E-05	7.773E-03
Thbs2	thrombospondin 2	2.528	1.338	5.000E-05	7.773E-03
Tnc	tenascin C	2.068	1.048	5.000E-05	7.773E-03
Trpm7	transient receptor potential cation channel, subfamily M, member 7	1.638	0.712	5.000E-05	7.773E-03
Ttc14	tetratricopeptide repeat domain 14	1.772	0.825	5.000E-05	7.773E-03
Vip	vasoactive intestinal peptide	2.228	1.156	5.000E-05	7.773E-03
Wsb1	WD repeat and SOCS box-containing 1	1.506	0.591	5.000E-05	7.773E-03
Zfp192	zinc finger protein 192	1.693	0.759	5.000E-05	7.773E-03
Atr	ATR serine/threonine kinase	1.758	0.814	1.000E-04	1.416E-02
C7	complement component 7	2.864	1.518	1.000E-04	1.416E-02
Cyp7b1	cytochrome P450, family 7, subfamily b, 1	2.048	1.034	1.000E-04	1.416E-02
LOC100360154	ribosomal protein S21-like	-1.850	-0.887	1.000E-04	1.416E-02
Mbp	myelin basic protein	1.703	0.768	1.000E-04	1.416E-02
Rps27l2	ribosomal protein S27-like 2	-1.626	-0.701	1.000E-04	1.416E-02
Setx	senataxin	1.546	0.629	1.000E-04	1.416E-02
Sparcl1	SPARC like 1	1.473	0.559	1.000E-04	1.416E-02
Tbc1d4	TBC1 domain family, member 4	2.739	1.453	1.000E-04	1.416E-02
AABR06028164.1	AABR06028164.1	-2.043	-1.031	1.500E-04	1.803E-02
AABR06098740.1	AABR06098740.1	-1.490	-0.575	1.500E-04	1.803E-02
Anln1	anillin, actin binding protein-like 1	2.687	1.426	1.500E-04	1.803E-02
Bag3	Bcl2-associated athanogene 3	2.390	1.257	1.500E-04	1.803E-02
Ccnt2	cyclin T2	1.563	0.644	1.500E-04	1.803E-02
Clk1	CDC-like kinase 1	1.561	0.642	1.500E-04	1.803E-02
Col5a2	collagen, type V, alpha 2	1.646	0.719	1.500E-04	1.803E-02
Cycs	cytochrome c, somatic	-1.547	-0.629	1.500E-04	1.803E-02
Emx2	empty spiracles homeobox 2	2.308	1.206	1.500E-04	1.803E-02
Fgl2	fibrinogen-like 2	2.702	1.434	1.500E-04	1.803E-02
Lpar1	lysophosphatidic acid receptor 1	1.597	0.676	1.500E-04	1.803E-02

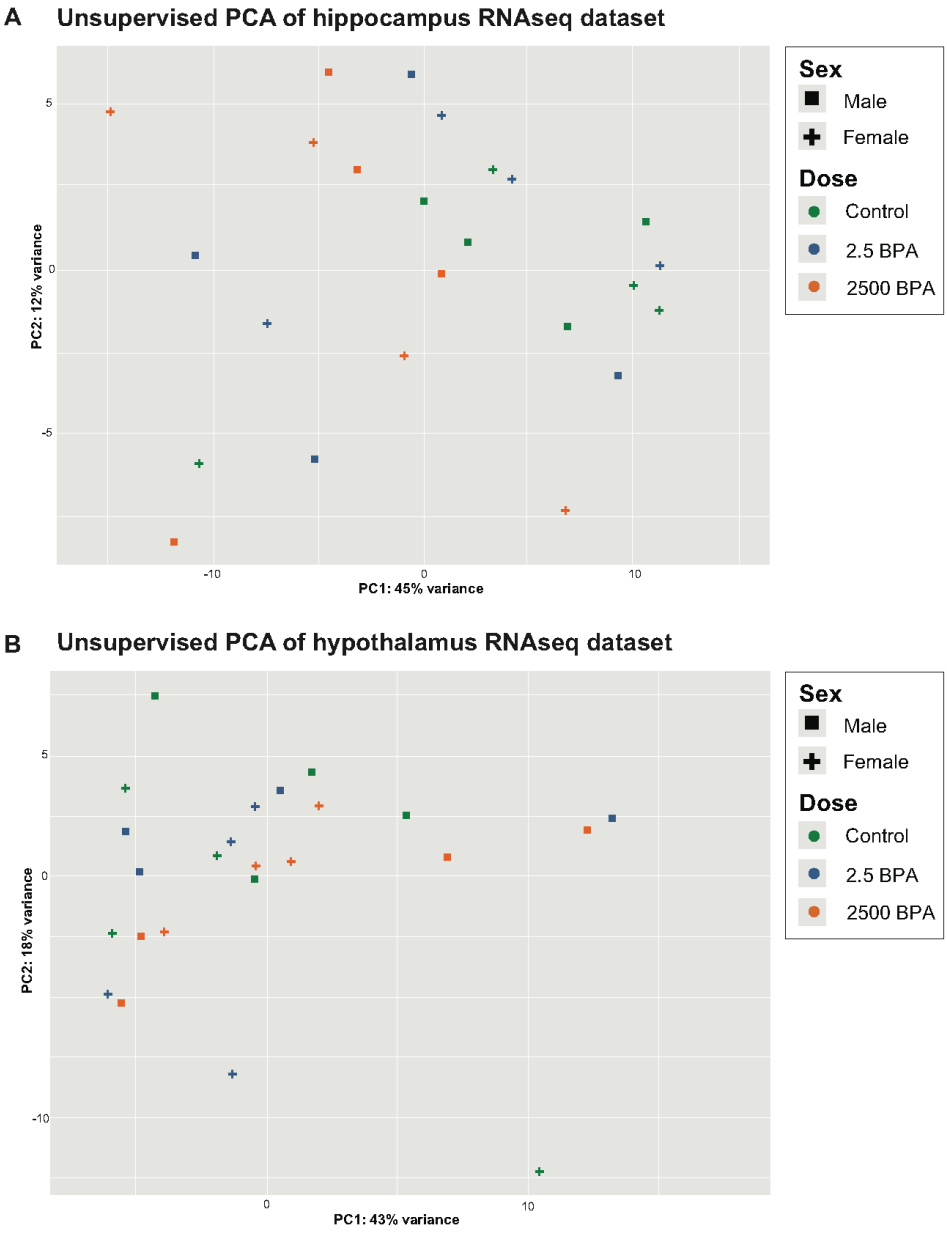
Supplemental Table 4 (continued)

Onecut3	one cut homeobox 3	-2.987	-1.579	1.500E-04	1.803E-02
Ppic	peptidylprolyl isomerase C	1.736	0.795	1.500E-04	1.803E-02
Reck	reversion-inducing-cysteine-rich protein with kazal motifs	1.826	0.868	1.500E-04	1.803E-02
Slc13a4	solute carrier family 13 (sodium/sulfate symporter), member 4	7.313	2.870	1.500E-04	1.803E-02
Sst	somatostatin	-1.569	-0.650	1.500E-04	1.803E-02
Tet1	tet methylcytosine dioxygenase 1	1.829	0.871	1.500E-04	1.803E-02
Zfp483	zinc finger protein 483	1.702	0.767	1.500E-04	1.803E-02
Aspm	abnormal spindle microtubule assembly	1.744	0.802	2.000E-04	2.270E-02
Hba1	uncharacterized protein	1.559	0.640	2.000E-04	2.270E-02
LOC688684	similar to 60S ribosomal protein L32	-1.586	-0.666	2.000E-04	2.270E-02
Mmp9	matrix metallopeptidase 9	16.267	4.024	2.000E-04	2.270E-02
Sp8	Sp8 transcription factor	-3.827	-1.936	2.000E-04	2.270E-02
Tbca	tubulin folding cofactor A	-1.599	-0.677	2.000E-04	2.270E-02
Tgds	TDP-glucose 4,6-dehydratase	1.776	0.829	2.000E-04	2.270E-02
AABR06037143.1	AABR06037143.1	-1.580	-0.660	2.500E-04	2.572E-02
AABR06057457.1	AABR06057457.1	-1.547	-0.629	2.500E-04	2.572E-02
Adamts1	ADAM metallopeptidase with thrombospondin type 1 motif, 1	2.130	1.091	2.500E-04	2.572E-02
Aldh1a2	aldehyde dehydrogenase 1 family, member A2	4.214	2.075	2.500E-04	2.572E-02
Ankhd1	ankyrin repeat and KH domain containing 1	1.548	0.631	2.500E-04	2.572E-02
Antxr1	anthrax toxin receptor 1	1.762	0.817	2.500E-04	2.572E-02
Barhl1	BarH-like homeobox 1	2.974	1.572	2.500E-04	2.572E-02
Lgals1	lectin, galactoside-binding, soluble, 1	2.239	1.163	2.500E-04	2.572E-02
LOC100363012	ribosomal protein S21, pseudogene 1	-1.492	-0.577	2.500E-04	2.572E-02
Nfat5	nuclear factor of activated T-cells 5, tonicity-responsive	1.502	0.587	2.500E-04	2.572E-02
Slc6a20	solute carrier family 6 (proline IMINO transporter), member 20	3.278	1.713	2.500E-04	2.572E-02
Trim5	tripartite motif-containing 5	1.960	0.971	2.500E-04	2.572E-02
Vps13a	vacuolar protein sorting 13 homolog A (S. cerevisiae)	1.796	0.845	2.500E-04	2.572E-02
AABR06013961.1	AABR06013961.1	-1.734	-0.794	3.000E-04	2.899E-02
Capg	capping protein (actin filament), gelsolin-like	2.108	1.076	3.000E-04	2.899E-02
Casp2	caspase 2	1.590	0.669	3.000E-04	2.899E-02
Cldn11	claudin 11	1.936	0.953	3.000E-04	2.899E-02
LOC100362583	ribosomal protein L13a-like	-1.477	-0.563	3.000E-04	2.899E-02
Lypd6b	LY6/PLAUR domain containing 6B	-1.691	-0.758	3.000E-04	2.899E-02
Mdm4	MDM4, p53 regulator	1.637	0.711	3.000E-04	2.899E-02
Nr2f2	Nr2f2	-1.515	-0.599	3.000E-04	2.899E-02
Prkd3	protein kinase D3	1.726	0.788	3.000E-04	2.899E-02
AABR06014093.1	AABR06014093.1	-1.459	-0.545	3.500E-04	3.109E-02
AABR06027146.1	AABR06027146.1	-1.672	-0.742	3.500E-04	3.109E-02
Bgn	biglycan	1.956	0.968	3.500E-04	3.109E-02
Chrm5	cholinergic receptor, muscarinic 5	1.843	0.882	3.500E-04	3.109E-02
Dopey1	dopey family member 1	1.583	0.662	3.500E-04	3.109E-02
Esyt2	extended synaptotagmin-like protein 2	1.767	0.822	3.500E-04	3.109E-02
Fam135b	family with sequence similarity 135, member B	2.086	1.061	3.500E-04	3.109E-02
Jund	jun D proto-oncogene	-1.449	-0.535	3.500E-04	3.109E-02
LOC680227	LRRGT00193	126.396	6.982	3.500E-04	3.109E-02
Panx3	pannexin 3	13.884	3.795	3.500E-04	3.109E-02
RGD1565131	similar to ribosomal protein L15	-1.684	-0.752	3.500E-04	3.109E-02
Strip2	striatin interacting protein 2	3.123	1.643	3.500E-04	3.109E-02
Vipr2	vasoactive intestinal peptide receptor 2	1.887	0.916	3.500E-04	3.109E-02
AABR06087647.1	AABR06087647.1	-1.506	-0.591	4.000E-04	3.467E-02
Ndufb2	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2	-1.886	-0.916	4.000E-04	3.467E-02
RGD2320734	cytochrome b-c1 complex subunit 9-like	-1.506	-0.591	4.000E-04	3.467E-02

Supplemental Table 4 (continued)

Vstm2l	V-set and transmembrane domain containing 2 like	-1.956	-0.968	4.000E-04	3.467E-02
Islr	immunoglobulin superfamily containing leucine-rich repeat	2.510	1.328	4.500E-04	3.786E-02
LOC679894	similar to THO complex subunit 2 (Tho2)	1.586	0.665	4.500E-04	3.786E-02
Nup62cl	Nup62cl	-1.653	-0.725	4.500E-04	3.786E-02
Rasgrf2	RAS protein-specific guanine nucleotide-releasing factor 2	1.845	0.883	4.500E-04	3.786E-02
Srek1	splicing regulatory glutamine/lysine-rich protein 1	1.593	0.672	4.500E-04	3.786E-02
AABR06009564.1	AABR06009564.1	-1.525	-0.609	5.000E-04	4.110E-02
LOC100911545	alpha-2-macroglobulin-like	2.130	1.091	5.000E-04	4.110E-02
Mrs2	MRS2 magnesium transporter	1.696	0.762	5.000E-04	4.110E-02
Timm8b	translocase of inner mitochondrial membrane 8 homolog b	-1.459	-0.545	5.000E-04	4.110E-02
Dlx2	distal-less homeobox 2	-1.685	-0.753	5.500E-04	4.346E-02
Dnah9	dynein, axonemal, heavy chain 9	1.609	0.687	5.500E-04	4.346E-02
Fam214a	family with sequence similarity 214, member A	1.516	0.600	5.500E-04	4.346E-02
LOC100362685	up-regulated during skeletal muscle growth protein 5 pseudogene	-1.620	-0.696	5.500E-04	4.346E-02
LOC100911178	uncharacterized protein	1.434	0.520	5.500E-04	4.346E-02
Prrt1	proline-rich transmembrane protein 1	-1.519	-0.603	5.500E-04	4.346E-02
Vsnl1	visinin-like 1	-1.448	-0.534	5.500E-04	4.346E-02
Cst6	cystatin E/M	-1.647	-0.720	6.000E-04	4.589E-02
Kif20b	kinesin family member 20B	2.037	1.026	6.000E-04	4.589E-02
Krit1	KRIT1, ankyrin repeat containing	1.542	0.625	6.000E-04	4.589E-02
Nktr	natural killer cell triggering receptor	1.479	0.564	6.000E-04	4.589E-02
Thoc1	THO complex 1	1.733	0.793	6.000E-04	4.589E-02
Zmym6	zinc finger, MYM-type 6	1.581	0.661	6.000E-04	4.589E-02
AABR06062966.1	AABR06062966.1	-1.472	-0.558	6.500E-04	4.602E-02
C1qc	complement component 1, q subcomponent, C chain	1.783	0.834	6.500E-04	4.602E-02
Crabp1	cellular retinoic acid binding protein 1	-2.249	-1.169	6.500E-04	4.602E-02
Dlx5	distal-less homeobox 5	-1.622	-0.698	6.500E-04	4.602E-02
Emp1	epithelial membrane protein 1	1.992	0.994	6.500E-04	4.602E-02
Fabp7	fatty acid binding protein 7, brain	-1.428	-0.514	6.500E-04	4.602E-02
LOC100911902	cellular retinoic acid-binding protein 2-like	2.034	1.025	6.500E-04	4.602E-02
LOC306079	similar to RIKEN cDNA 3100001N19	-1.526	-0.610	6.500E-04	4.602E-02
Man2a1	mannosidase, alpha, class 2A, member 1	1.584	0.664	6.500E-04	4.602E-02
Mgp	matrix Gla protein	2.823	1.497	6.500E-04	4.602E-02
Prp2l1	proline rich protein 2-like 1	1.927	0.947	6.500E-04	4.602E-02
Rpl18a	ribosomal protein L18A	-1.441	-0.527	6.500E-04	4.602E-02
Tbc1d31	TBC1 domain family, member 31	1.824	0.867	6.500E-04	4.602E-02
Top2a	topoisomerase (DNA) II alpha	1.632	0.706	6.500E-04	4.602E-02
Utrn	utrophin	1.670	0.740	6.500E-04	4.602E-02
Atad5	ATPase family, AAA domain containing 5	1.720	0.783	7.000E-04	4.836E-02
Ddr2	discoidin domain receptor tyrosine kinase 2	2.302	1.203	7.000E-04	4.836E-02
LOC100363048	rCG47273-like	-1.801	-0.849	7.000E-04	4.836E-02
Otp	orthopedia homeobox	-1.520	-0.604	7.000E-04	4.836E-02
Penk	proenkephalin	-1.549	-0.631	7.000E-04	4.836E-02
Atm	ATM serine/threonine kinase	1.696	0.762	7.500E-04	4.989E-02
Ctnnal1	catenin alpha-like 1	1.594	0.672	7.500E-04	4.989E-02
Gng2	guanine nucleotide binding protein (G protein), gamma 2	-1.620	-0.696	7.500E-04	4.989E-02
Kdm6a	lysine (K)-specific demethylase 6A	1.640	0.713	7.500E-04	4.989E-02
Kmt2c	lysine (K)-specific methyltransferase 2C	1.483	0.569	7.500E-04	4.989E-02
LOC102557074	uncharacterized LOC102557074	-1.839	-0.879	7.500E-04	4.989E-02
Psme4	proteasome activator subunit 4	1.466	0.552	7.500E-04	4.989E-02
RGD1308544	LOC361192	-1.728	-0.789	7.500E-04	4.989E-02

Supplemental Figure 1. Unsupervised principal component analyses of hippocampal and hypothalamic transcriptome data



Supplemental Figure 1: Unsupervised principal component analyses (PCA) of (A) hippocampal and (B) hypothalamic RNA-seq data did not indicate clear clustering. The data did not group by exposure or sex. PCA was run on the entire data set, not just the subset genes identified as differentially expressed (by sex or BPA exposure).

APPENDIX 2

Chapter 3 Supplementary Figures and Tables

Supplementary Table 1. Male transcriptomic datasets (normalized to male vehicle; adjusted p-value ≤ 0.05)

Supplementary Table 1a: Significantly (padj ≤ 0.05) altered genes in 25 BPA ♂ vs. Vehicle ♂

Gene Symbol	Description	log2 Fold Change	Fold Change	p-value	padj
RGD1562037	Similar To Otthump00000046255	0.59	1.51	1.43E-07	1.34E-03
St6gal2	St6 Beta-Galactoside Alpha-2,6-Sialyltransferase 2	0.58	1.49	3.23E-07	1.34E-03
Sh3pxd2b	Sh3 And Px Domains 2B	0.47	1.39	3.99E-07	1.34E-03
Ncan	Neurocan	0.41	1.33	4.45E-07	1.34E-03
Abcc9	Atp Binding Cassette Subfamily C Member 9	0.50	1.41	6.20E-07	1.35E-03
Pdgfrb	Platelet Derived Growth Factor Receptor Beta	0.43	1.35	6.72E-07	1.35E-03
Hcfc1	Host Cell Factor C1	0.57	1.49	1.20E-06	1.73E-03
Mecp2	Methyl Cpg Binding Protein 2	0.53	1.44	1.12E-06	1.73E-03
Pcdh10	Protocadherin 10	0.36	1.28	1.29E-06	1.73E-03
Adcy1	Adenylate Cyclase 1	0.60	1.51	2.76E-06	2.31E-03
Cbl	Cbl Proto-Oncogene	0.59	1.50	3.44E-06	2.31E-03
Dync1h1	Dynein Cytoplasmic 1 Heavy Chain 1	0.57	1.48	2.35E-06	2.31E-03
Birc6	Baculoviral Iap Repeat-Containing 6	0.55	1.46	2.66E-06	2.31E-03
Vwf	Von Willebrand Factor	0.53	1.45	3.25E-06	2.31E-03
Tanc2	Tetratricopeptide Repeat, Ankyrin Repeat And Coiled-Coil Containing 2	0.49	1.40	2.95E-06	2.31E-03
Fnip2	Folliculin Interacting Protein 2	0.44	1.36	2.52E-06	2.31E-03
Lamc1	Laminin Subunit Gamma 1	0.41	1.33	2.01E-06	2.31E-03
Cdc7	Cell Division Cycle 7	-0.41	-1.33	3.37E-06	2.31E-03
Hmbox1	Homeobox Containing 1	0.52	1.44	3.72E-06	2.37E-03
AABR07062799.2		0.55	1.47	4.17E-06	2.52E-03
Paqr8	Progestin And Adipoq Receptor Family Member 8	0.57	1.48	4.69E-06	2.58E-03
Chst15	Carbohydrate Sulfotransferase 15	0.56	1.47	4.65E-06	2.58E-03
Mef2a	Myocyte Enhancer Factor 2A	0.42	1.34	6.18E-06	3.24E-03
Dgkh	Diacylglycerol Kinase, Eta	0.58	1.49	8.62E-06	3.87E-03
Gpr17	G Protein-Coupled Receptor 17	0.54	1.46	8.66E-06	3.87E-03
Prkce	Protein Kinase C, Epsilon	0.47	1.39	8.32E-06	3.87E-03
Slc15a2	Solute Carrier Family 15 Member 2	0.44	1.36	7.72E-06	3.87E-03
Dleu7	Deleted In Lymphocytic Leukemia, 7	-0.53	-1.45	9.77E-06	4.21E-03
Nup214	Nucleoporin 214	0.55	1.47	1.17E-05	4.87E-03
Wdfy3	Wd Repeat And Fyve Domain Containing 3	0.48	1.40	1.46E-05	5.88E-03
Trpm4	Transient Receptor Potential Cation Channel, Subfamily M, Member 4	0.50	1.42	1.54E-05	6.01E-03
Pde10a	Phosphodiesterase 10A	0.45	1.36	1.66E-05	6.27E-03
Klhl11	Kelch-Like Family Member 11	0.51	1.42	1.76E-05	6.43E-03
Soga1	Suppressor Of Glucose, Autophagy Associated 1	0.52	1.44	1.95E-05	6.92E-03
Slc1a2	Solute Carrier Family 1 Member 2	0.55	1.46	2.23E-05	7.65E-03
Zyg11b	Zyg-11 Family Member B, Cell Cycle Regulator	0.49	1.41	2.28E-05	7.65E-03
Kcnq3	Potassium Voltage-Gated Channel Subfamily Q Member 3	0.51	1.42	2.37E-05	7.73E-03
Egflam	Egf-Like, Fibronectin Type Iii And Laminin G Domains	0.50	1.41	2.82E-05	8.96E-03
Xkr4	Xk Related 4	0.50	1.42	3.30E-05	1.02E-02
AABR07037528.1		0.52	1.44	3.55E-05	1.05E-02
Sema3a	Semaphorin 3A	0.50	1.42	3.53E-05	1.05E-02
Ubr2	Ubiquitin Protein Ligase E3 Component N-Recognin 2	0.42	1.33	3.74E-05	1.08E-02
Amer1	Apc Membrane Recruitment Protein 1	0.51	1.43	4.12E-05	1.16E-02
Dock4	Dedicator Of Cytokinesis 4	0.45	1.37	4.47E-05	1.23E-02
Sox6	Sry Box 6	0.45	1.37	4.88E-05	1.31E-02
Bmpr1b	Bone Morphogenetic Protein Receptor Type 1B	0.51	1.43	5.18E-05	1.36E-02
Plxnd1	Plexin D1	0.49	1.40	5.83E-05	1.50E-02
Plekhm3	Pleckstrin Homology Domain Containing M3	0.50	1.42	6.90E-05	1.74E-02
Xrn1	5'-3' Exoribonuclease 1	0.45	1.36	7.96E-05	1.93E-02
Srgap1	Slit-Robo Rho Gtpase Activating Protein 1	0.41	1.33	8.16E-05	1.93E-02

Supplementary Table 1 (continued)

Sox2	Sry Box 2	-0.28	-1.21	8.06E-05	1.93E-02
Ccnh	Cyclin H	-0.29	-1.22	8.44E-05	1.96E-02
Pdpr	Pyruvate Dehydrogenase Phosphatase Regulatory Subunit	0.41	1.33	8.68E-05	1.98E-02
AABR07073181.1		0.48	1.39	9.21E-05	2.02E-02
Mgat5	Mannosyl (Alpha-1,6-)-Glycoprotein Beta-1,6-N-Acetyl-Glucosaminyltransferase	0.45	1.37	9.07E-05	2.02E-02
Psd3	Pleckstrin And Sec7 Domain Containing 3	0.45	1.37	1.21E-04	2.61E-02
Tns1	Tensin 1	0.45	1.36	1.23E-04	2.61E-02
Bmpr2	Bone Morphogenetic Protein Receptor Type 2	0.43	1.35	1.32E-04	2.75E-02
Nav1	Neuron Navigator 1	0.43	1.35	1.41E-04	2.84E-02
Ldoc1l	Leucine Zipper, Down-Regulated In Cancer 1-Like	0.39	1.31	1.40E-04	2.84E-02
Vcpip1	Valosin Containing Protein Interacting Protein 1	0.39	1.31	1.46E-04	2.90E-02
Tenm4	Teneurin Transmembrane Protein 4	0.44	1.36	1.53E-04	2.90E-02
Man1a2	Mannosidase, Alpha, Class 1A, Member 2	0.35	1.27	1.50E-04	2.90E-02
Arl3	Adp Ribosylation Factor Like Gtpase 3	-0.27	-1.21	1.54E-04	2.90E-02
Tulp4	Tubby Like Protein 4	0.35	1.27	1.68E-04	3.12E-02
Apc2	Apc2, Wnt Signaling Pathway Regulator	0.31	1.24	1.75E-04	3.20E-02
AABR07041411.1		0.46	1.38	1.99E-04	3.59E-02
Itgav	Integrin Subunit Alpha V	0.46	1.37	2.05E-04	3.64E-02
Trps1	Transcriptional Repressor Gata Binding 1	0.47	1.39	2.20E-04	3.84E-02
Nsd1	Nuclear Receptor Binding Set Domain Protein 1	0.38	1.30	2.23E-04	3.84E-02
LOC100362814	Hypothetical Protein Loc100362814	0.41	1.33	2.35E-04	3.93E-02
Dlc1	Dlc1 Rho Gtpase Activating Protein	0.39	1.31	2.32E-04	3.93E-02
Smcr8	Smith-Magenis Syndrome Chromosome Region, Candidate 8	0.44	1.36	2.39E-04	3.96E-02
Cacna1e	Calcium Voltage-Gated Channel Subunit Alpha1 E	0.45	1.36	2.48E-04	4.05E-02
Hif1an	Hypoxia-Inducible Factor 1, Alpha Subunit Inhibitor	0.40	1.32	2.58E-04	4.10E-02
Map3k9	Mitogen-Activated Protein Kinase Kinase Kinase 9	0.37	1.29	2.58E-04	4.10E-02
Stox2	Storkhead Box 2	0.42	1.33	2.62E-04	4.11E-02
Trove2	Trove Domain Family, Member 2	0.38	1.30	2.72E-04	4.20E-02
Col19a1	Collagen Type Xix Alpha 1 Chain	0.47	1.39	2.79E-04	4.27E-02
Mdga1	Mam Domain Containing Glycosylphosphatidylinositol Anchor 1	0.38	1.31	2.84E-04	4.29E-02
Postn	Periostin	0.41	1.33	2.90E-04	4.33E-02
Zfp445	Zinc Finger Protein 445	0.36	1.28	2.98E-04	4.38E-02
Fbf1	Fas Binding Factor 1	0.40	1.32	3.15E-04	4.58E-02
Shc3	Shc Adaptor Protein 3	0.43	1.34	3.46E-04	4.86E-02
AABR07030603.1		0.40	1.32	3.44E-04	4.86E-02
Pcbp2	Poly(Rc) Binding Protein 2	-0.29	-1.22	3.40E-04	4.86E-02
Fam102b	Family With Sequence Similarity 102, Member B	0.44	1.36	3.52E-04	4.88E-02
Kif1a	Kinesin Family Member 1A	0.36	1.28	3.61E-04	4.96E-02
Nr2c2	Nuclear Receptor Subfamily 2, Group C, Member 2	0.42	1.34	3.68E-04	4.99E-02

Supplementary Table 1b: Significantly (padj ≤ 0.05) altered genes in 250 BPA ♂ vs. Vehicle ♂

Gene Symbol	Description	log2 Fold Change	Fold Change	p-value	padj
Itpkb	Inositol-Trisphosphate 3-Kinase B	0.61	1.52	1.15E-06	1.47E-02

Supplementary Table 1 (continued)

Supplementary Table 1c: Significantly (padj ≤ 0.05) altered genes in 0.5 EE_2 ♂ vs. Vehicle ♂

Gene Symbol	Description	log2 Fold Change	Fold Change	p-value	padj
Mef2a	Myocyte Enhancer Factor 2A	0.54	1.45	7.55E-09	8.75E-05
Hipk2	Homeodomain Interacting Protein Kinase 2	0.61	1.52	1.43E-07	6.87E-04
Ncan	Neurocan	0.42	1.34	1.78E-07	6.87E-04
Trove2	Trove Domain Family, Member 2	0.54	1.45	2.63E-07	7.62E-04
Pcdh10	Protocadherin 10	0.37	1.29	4.84E-07	1.12E-03
Pde10a	Phosphodiesterase 10A	0.50	1.42	1.23E-06	2.37E-03
Birc6	Baculoviral Iap Repeat-Containing 6	0.56	1.47	1.78E-06	2.94E-03
Adcy1	Adenylate Cyclase 1	0.59	1.50	3.87E-06	3.87E-03
Cbl	Cbl Proto-Oncogene	0.59	1.50	3.46E-06	3.87E-03
Scai	Suppressor Of Cancer Cell Invasion	0.58	1.49	3.99E-06	3.87E-03
Zyg11b	Zyg-11 Family Member B, Cell Cycle Regulator	0.54	1.45	4.27E-06	3.87E-03
Bmpr2	Bone Morphogenetic Protein Receptor Type 2	0.52	1.44	3.05E-06	3.87E-03
Dock4	Dedicator Of Cytokinesis 4	0.51	1.42	4.34E-06	3.87E-03
Pdpr	Pyruvate Dehydrogenase Phosphatase Regulatory Subunit	0.47	1.39	6.74E-06	5.58E-03
Zim1	Zinc Finger, Imprinted 1	0.57	1.49	1.01E-05	7.78E-03
Dgkh	Diacylglycerol Kinase, Eta	0.57	1.48	1.33E-05	9.65E-03
Slc1a2	Solute Carrier Family 1 Member 2	0.56	1.47	1.53E-05	9.83E-03
Itgav	Integrin Subunit Alpha V	0.53	1.44	1.51E-05	9.83E-03
Fam135b	Family With Sequence Similarity 135, Member B	0.55	1.47	1.94E-05	1.07E-02
Adam23	Adam Metallopeptidase Domain 23	0.44	1.36	1.93E-05	1.07E-02
Abcc9	Atp Binding Cassette Subfamily C Member 9	0.43	1.35	1.82E-05	1.07E-02
Psd3	Pleckstrin And Sec7 Domain Containing 3	0.49	1.41	2.43E-05	1.28E-02
Xkr4	Xk Related 4	0.50	1.41	4.27E-05	2.14E-02
Mmp17	Matrix Metallopeptidase 17	0.47	1.39	4.66E-05	2.14E-02
Hmbox1	Homeobox Containing 1	0.46	1.37	4.81E-05	2.14E-02
Vcpip1	Valosin Containing Protein Interacting Protein 1	0.42	1.34	4.54E-05	2.14E-02
Klhl11	Kelch-Like Family Member 11	0.48	1.39	5.18E-05	2.14E-02
Nob1	Nin1/Psmd8 Binding Protein 1 Homolog	-0.39	-1.31	5.02E-05	2.14E-02
Slc15a2	Solute Carrier Family 15 Member 2	0.40	1.32	5.44E-05	2.17E-02
Fem1b	Fem-1 Homolog B	0.43	1.35	5.67E-05	2.19E-02
Agps	Alkylglycerone Phosphate Synthase	0.46	1.37	6.15E-05	2.30E-02
St6gal2	St6 Beta-Galactoside Alpha-2,6-Sialyltransferase 2	0.45	1.37	6.79E-05	2.46E-02
Plekhm3	Pleckstrin Homology Domain Containing M3	0.50	1.42	7.54E-05	2.64E-02
Mob1b	Mob Kinase Activator 1B	0.43	1.35	8.29E-05	2.67E-02
Tanc2	Tetratricopeptide Repeat, Ankyrin Repeat And Coiled-Coil Containing 2	0.41	1.33	8.28E-05	2.67E-02
Tulp4	Tubby Like Protein 4	0.36	1.29	7.89E-05	2.67E-02
AABR07041411.1		0.48	1.39	1.10E-04	3.43E-02
Vwf	Von Willebrand Factor	0.44	1.36	1.33E-04	4.05E-02
Stox2	Storkhead Box 2	0.43	1.35	1.38E-04	4.05E-02
Mecp2	Methyl Cpg Binding Protein 2	0.41	1.33	1.46E-04	4.05E-02
Rnf152	Ring Finger Protein 152	0.41	1.33	1.47E-04	4.05E-02
Fnip2	Folliculin Interacting Protein 2	0.36	1.28	1.46E-04	4.05E-02
Zbtb41	Zinc Finger And Btb Domain Containing 41	0.41	1.33	1.61E-04	4.34E-02
Slc30a3	Solute Carrier Family 30 Member 3	0.49	1.40	1.67E-04	4.39E-02
Kcnq3	Potassium Voltage-Gated Channel Subfamily Q Member 3	0.45	1.36	1.78E-04	4.58E-02
Sh3pxd2b	Sh3 And Px Domains 2B	0.35	1.28	1.82E-04	4.58E-02
Man1a2	Mannosidase, Alpha, Class 1A, Member 2	0.34	1.26	2.00E-04	4.84E-02
Pip4k2b	Phosphatidylinositol-5-Phosphate 4-Kinase Type 2 Beta	0.31	1.24	2.01E-04	4.84E-02
Usp45	Ubiquitin Specific Peptidase 45	0.42	1.33	2.07E-04	4.90E-02
Amer1	Apc Membrane Recruitment Protein 1	0.46	1.38	2.21E-04	4.97E-02
Plxna4	Plexin A4	0.46	1.37	2.20E-04	4.97E-02
Radil	Rap Associating With Dil Domain	-0.40	-1.32	2.23E-04	4.97E-02

Supplementary Table 2. Female transcriptomic datasets (normalized to female vehicle; adjusted p-value ≤ 0.05)

Supplementary Table 2a: Significantly (padj ≤ 0.05) altered genes in 25 BPA ♀ vs. Vehicle ♀

Gene Symbol	Description	log2 Fold Change	Fold Change	p-value	padj
Xkr4	Xk Related 4	0.94	1.92	3.36E-13	4.22E-09
Adcy1	Adenylate Cyclase 1	0.93	1.91	3.74E-12	2.34E-08
AABR07062799.2		0.83	1.78	7.66E-11	3.20E-07
Lrrc34	Leucine Rich Repeat Containing 34	-0.94	-1.92	1.67E-09	5.23E-06
Zyg11b	Zyg-11 Family Member B, Cell Cycle Regulator	0.75	1.69	9.97E-09	2.50E-05
Slc1a2	Solute Carrier Family 1 Member 2	0.80	1.74	1.53E-08	3.20E-05
RGD1306739	Similar To Riken Cdna 1700040L02	-0.87	-1.83	2.43E-08	3.81E-05
Fhad1	Forkhead Associated Phosphopeptide Binding Domain 1	-0.88	-1.84	2.21E-08	3.81E-05
Cds2	Cdp-Diacylglycerol Synthase 2	0.71	1.63	3.28E-08	3.97E-05
Psd3	Pleckstrin And Sec7 Domain Containing 3	0.68	1.60	3.48E-08	3.97E-05
Kcne2	Potassium Voltage-Gated Channel Subfamily E Regulatory Subunit 2	-0.83	-1.77	2.91E-08	3.97E-05
Prkaa2	Protein Kinase Amp-Activated Catalytic Subunit Alpha 2	0.71	1.63	4.80E-08	5.02E-05
Wdr63	Wd Repeat Domain 63	-0.75	-1.68	6.67E-08	6.44E-05
Dync1h1	Dynein Cytoplasmic 1 Heavy Chain 1	0.69	1.61	1.71E-07	1.47E-04
Sostdc1	Sclerostin Domain Containing 1	-0.79	-1.73	1.75E-07	1.47E-04
Bmpr2	Bone Morphogenetic Protein Receptor Type 2	0.62	1.54	3.79E-07	2.97E-04
Ccdc113	Coiled-Coil Domain Containing 113	-0.79	-1.73	4.47E-07	3.30E-04
Spag6l	Sperm Associated Antigen 6-Like	-0.72	-1.65	5.12E-07	3.57E-04
Nipa1	Non Imprinted In Prader-Willi/Angelman Syndrome 1	0.56	1.48	9.86E-07	6.51E-04
Slc16a7	Solute Carrier Family 16 Member 7	0.67	1.59	1.07E-06	6.73E-04
Skil	Ski-Like Proto-Oncogene	0.65	1.57	1.25E-06	7.45E-04
Dnah6	Dynein, Axonemal, Heavy Chain 6	-0.74	-1.67	1.41E-06	8.02E-04
Birc6	Baculoviral Iap Repeat-Containing 6	0.62	1.53	1.81E-06	9.85E-04
Myo5a	Myosin Va	0.61	1.53	1.88E-06	9.85E-04
Cpeb4	Cytoplasmic Polyadenylation Element Binding Protein 4	0.47	1.38	2.15E-06	1.08E-03
Pcdha4	Protocadherin Alpha 4	0.61	1.52	2.47E-06	1.15E-03
RGD1561916	Similar To Testes Development-Related Nyd-Sp22 Isoform 1	-0.74	-1.67	2.39E-06	1.15E-03
AABR07073181.1		0.74	1.67	2.77E-06	1.16E-03
LOC500877	Ab1-152	-0.69	-1.61	2.81E-06	1.16E-03
Tekt4	Tektin 4	-0.72	-1.65	2.69E-06	1.16E-03

Supplementary Table 2 (Continued)

Iqub	Iq Motif And Ubiquitin Domain Containing	-0.74	-1.66	2.87E-06	1.16E-03
Prkce	Protein Kinase C, Epsilon	0.59	1.51	3.22E-06	1.26E-03
Nrxn1	Neurexin 1	0.46	1.38	3.64E-06	1.38E-03
Lrrc8b	Leucine Rich Repeat Containing 8 Family, Member B	0.54	1.46	4.56E-06	1.68E-03
Mlf1	Myeloid Leukemia Factor 1	-0.70	-1.62	5.27E-06	1.89E-03
Dcbld2	Discoidin, Cub And Lccl Domain Containing 2	0.54	1.45	5.59E-06	1.95E-03
41338	Membrane Associated Ring-Ch-Type Finger 6	0.48	1.40	5.99E-06	1.98E-03
Ttc21a	Tetratricopeptide Repeat Domain 21A	-0.71	-1.63	5.90E-06	1.98E-03
Slc9a7	Solute Carrier Family 9 Member A7	0.65	1.57	6.46E-06	2.07E-03
Abi2	Abl-Interactor 2	0.39	1.31	6.59E-06	2.07E-03
Nr2c2	Nuclear Receptor Subfamily 2, Group C, Member 2	0.51	1.42	7.48E-06	2.29E-03
Ak9	Adenylate Kinase 9	-0.62	-1.54	8.14E-06	2.43E-03
Lin7c	Lin-7 Homolog C, Crumbs Cell Polarity Complex Component	0.41	1.33	8.78E-06	2.56E-03
Htra1	Htra Serine Peptidase 1	0.65	1.57	1.02E-05	2.91E-03
Zfp704	Zinc Finger Protein 704	0.67	1.59	1.07E-05	2.91E-03
Wdr66	Wd Repeat Domain 66	-0.67	-1.59	1.05E-05	2.91E-03
Nav1	Neuron Navigator 1	0.59	1.51	1.11E-05	2.92E-03
Slc38a1	Solute Carrier Family 38, Member 1	0.48	1.40	1.12E-05	2.92E-03
AABR07041411.1		0.69	1.62	1.17E-05	3.00E-03
Fam183b	Family With Sequence Similarity 183, Member B	-0.61	-1.52	1.32E-05	3.31E-03
Mef2a	Myocyte Enhancer Factor 2A	0.50	1.41	1.42E-05	3.49E-03
Ttbk2	Tau Tubulin Kinase 2	0.60	1.52	1.50E-05	3.61E-03
Camk2a	Calcium/Calmodulin-Dependent Protein Kinase Ii Alpha	0.42	1.33	1.69E-05	3.99E-03
Pcdha2	Protocadherin Alpha 2	0.52	1.44	1.81E-05	4.06E-03
Cfap52	Cilia And Flagella Associated Protein 52	-0.67	-1.59	1.80E-05	4.06E-03
Enkur	Enkurin, Trpc Channel Interacting Protein	-0.68	-1.60	1.77E-05	4.06E-03
Cacna1e	Calcium Voltage-Gated Channel Subunit Alpha1 E	0.59	1.51	1.91E-05	4.13E-03
Ppm1h	Protein Phosphatase, Mg2+/Mn2+ Dependent, 1H	0.48	1.39	1.89E-05	4.13E-03
Gabrb2	Gamma-Aminobutyric Acid Type A Receptor Beta 2 Subunit	0.60	1.51	1.98E-05	4.22E-03
Tanc2	Tetratricopeptide Repeat, Ankyrin Repeat And Coiled-Coil Containing 2	0.59	1.51	2.04E-05	4.23E-03

Supplementary Table 2 (Continued)

Cfap70	Cilia And Flagella Associated Protein 70	-0.61	-1.52	2.06E-05	4.23E-03
Wdr78	Wd Repeat Domain 78	-0.59	-1.51	2.23E-05	4.52E-03
Fat3	Fat Atypical Cadherin 3	0.67	1.59	2.31E-05	4.60E-03
Lrp2	Ldl Receptor Related Protein 2	-0.63	-1.55	2.52E-05	4.94E-03
Akap11	A-Kinase Anchoring Protein 11	0.38	1.30	3.10E-05	5.97E-03
Neurl1b	Neuralized E3 Ubiquitin Protein Ligase 1B	0.52	1.44	3.42E-05	6.51E-03
Lpgat1	Lysophosphatidylglycerol Acyltransferase 1	0.50	1.41	3.59E-05	6.73E-03
AABR07044362.1		0.59	1.51	4.01E-05	7.29E-03
Pdpk1	3-Phosphoinositide Dependent Protein Kinase-1	0.48	1.39	3.96E-05	7.29E-03
Plxna4	Plexin A4	0.60	1.52	4.19E-05	7.50E-03
Flrt2	Fibronectin Leucine Rich Transmembrane Protein 2	0.59	1.51	4.24E-05	7.50E-03
Sh3pxd2a	Sh3 And Px Domains 2A	0.56	1.47	4.43E-05	7.51E-03
Hmbox1	Homeobox Containing 1	0.50	1.41	4.39E-05	7.51E-03
Mfhas1	Malignant Fibrous Histiocytoma Amplified Sequence 1	0.49	1.41	4.34E-05	7.51E-03
Pbx1	Pbx Homeobox 1	0.56	1.47	4.67E-05	7.80E-03
Klf8	Kruppel-Like Factor 8	0.62	1.53	5.32E-05	8.44E-03
Ago2	Argonaute 2, Risc Catalytic Component	0.61	1.53	5.56E-05	8.44E-03
Wnk3	Wnk Lysine Deficient Protein Kinase 3	0.54	1.45	5.34E-05	8.44E-03
Xpr1	Xenotropic And Polytropic Retrovirus Receptor 1	0.52	1.44	5.46E-05	8.44E-03
Lrp1	Ldl Receptor Related Protein 1	0.42	1.34	5.45E-05	8.44E-03
Megf9	Multiple Egf-Like-Domains 9	0.42	1.34	5.16E-05	8.44E-03
Selenoi	Selenoprotein I	0.38	1.31	5.65E-05	8.44E-03
Prmt8	Protein Arginine Methyltransferase 8	0.38	1.30	5.59E-05	8.44E-03
Cirbp	Cold Inducible Rna Binding Protein	-0.47	-1.39	5.40E-05	8.44E-03
Nsd1	Nuclear Receptor Binding Set Domain Protein 1	0.50	1.41	6.09E-05	8.99E-03
RGD1565611	Rgd1565611	-0.50	-1.41	6.18E-05	9.02E-03
Zdhhc21	Zinc Finger, Dhhc-Type Containing 21	0.55	1.46	6.27E-05	9.04E-03
Efcab1	Ef Hand Calcium Binding Domain 1	-0.60	-1.52	6.49E-05	9.26E-03
Atrnl1	Attractin Like 1	0.52	1.43	6.87E-05	9.57E-03
Chrm3	Cholinergic Receptor, Muscarinic 3	0.49	1.41	6.81E-05	9.57E-03
Ppp1r9a	Protein Phosphatase 1, Regulatory Subunit 9A	0.53	1.45	7.04E-05	9.60E-03
Pten	Phosphatase And Tensin Homolog	0.39	1.31	7.02E-05	9.60E-03
Chst15	Carbohydrate Sulfotransferase 15	0.57	1.49	7.25E-05	9.67E-03

Supplementary Table 2 (Continued)

Slc35e2b	Solute Carrier Family 35, Member E2B	0.46	1.37	7.18E-05	9.67E-03
Prkca	Protein Kinase C, Alpha	0.57	1.49	7.51E-05	9.91E-03
Tjp3	Tight Junction Protein 3	-0.61	-1.53	7.62E-05	9.96E-03
Dgkh	Diacylglycerol Kinase, Eta	0.61	1.53	7.80E-05	1.01E-02
Camk4	Calcium/Calmodulin-Dependent Protein Kinase Iv	0.54	1.45	7.87E-05	1.01E-02
Pdlim4	Pdz And Lim Domain 4	-0.57	-1.48	8.50E-05	1.08E-02
Grm5	Glutamate Metabotropic Receptor 5	0.49	1.41	8.96E-05	1.11E-02
Ropn1l	Rhophilin Associated Tail Protein 1-Like	-0.51	-1.43	8.90E-05	1.11E-02
Tmem178b	Transmembrane Protein 178B	0.45	1.36	9.22E-05	1.12E-02
Drc3	Dynein Regulatory Complex Subunit 3	-0.61	-1.52	9.16E-05	1.12E-02
Mgat5	Mannosyl (Alpha-1,6-)-Glycoprotein Beta-1,6-N-Acetyl-Glucosaminyltransferase	0.52	1.44	9.62E-05	1.13E-02
Pak3	P21 (Rac1) Activated Kinase 3	0.51	1.43	9.65E-05	1.13E-02
Cadm2	Cell Adhesion Molecule 2	0.49	1.41	9.41E-05	1.13E-02
Rsph10b	Radial Spoke Head 10 Homolog B	-0.62	-1.53	9.54E-05	1.13E-02
Tmem245	Transmembrane Protein 245	0.60	1.52	1.06E-04	1.22E-02
Man1a2	Mannosidase, Alpha, Class 1A, Member 2	0.43	1.35	1.06E-04	1.22E-02
Gas7	Growth Arrest Specific 7	0.41	1.33	1.07E-04	1.22E-02
Tekt1	Tektin 1	-0.61	-1.53	1.09E-04	1.24E-02
Rab11fip2	Rab11 Family Interacting Protein 2	0.46	1.38	1.13E-04	1.27E-02
Htr1b	5-Hydroxytryptamine Receptor 1B	0.53	1.44	1.17E-04	1.29E-02
Vamp3	Vesicle-Associated Membrane Protein 3	-0.41	-1.33	1.17E-04	1.29E-02
Erbb4	Erb-B2 Receptor Tyrosine Kinase 4	0.52	1.44	1.24E-04	1.33E-02
Mib1	Mindbomb E3 Ubiquitin Protein Ligase 1	0.47	1.38	1.24E-04	1.33E-02
Rmnd5a	Required For Meiotic Nuclear Division 5 Homolog A	0.46	1.37	1.23E-04	1.33E-02
Cfap57	Cilia And Flagella Associated Protein 57	-0.57	-1.48	1.25E-04	1.33E-02
Abr	Active Bcr-Related	0.32	1.25	1.27E-04	1.34E-02
Dgki	Diacylglycerol Kinase, Iota	0.56	1.47	1.31E-04	1.37E-02
Zim1	Zinc Finger, Imprinted 1	0.58	1.49	1.34E-04	1.38E-02
Arfgef3	Arfgef Family Member 3	0.56	1.48	1.34E-04	1.38E-02
Cpeb2	Cytoplasmic Polyadenylation Element Binding Protein 2	0.50	1.41	1.40E-04	1.43E-02
Hecw2	Hect, C2 And Ww Domain Containing E3 Ubiquitin Protein Ligase 2	0.55	1.46	1.43E-04	1.44E-02

Supplementary Table 2 (Continued)

Hecw1	Hect, C2 And Ww Domain Containing E3 Ubiquitin Protein Ligase 1	0.46	1.38	1.43E-04	1.44E-02
Krt8	Keratin 8	-0.41	-1.33	1.46E-04	1.45E-02
Tenm4	Teneurin Transmembrane Protein 4	0.55	1.47	1.47E-04	1.46E-02
P2rx6	Purinergic Receptor P2X 6	-0.43	-1.34	1.54E-04	1.51E-02
Pappa2	Pappalysin 2	0.56	1.48	1.56E-04	1.51E-02
Pifo	Primary Cilia Formation	-0.48	-1.39	1.57E-04	1.51E-02
Fbxo41	F-Box Protein 41	0.50	1.41	1.60E-04	1.53E-02
Zfp871	Zinc Finger Protein 871	0.57	1.48	1.63E-04	1.54E-02
Itga1	Integrin Subunit Alpha 1	0.56	1.47	1.63E-04	1.54E-02
AABR07037528.1		0.57	1.48	1.74E-04	1.57E-02
Kcnj4	Potassium Voltage-Gated Channel Subfamily J Member 4	0.56	1.47	1.73E-04	1.57E-02
Soga1	Suppressor Of Glucose, Autophagy Associated 1	0.56	1.47	1.72E-04	1.57E-02
Mecp2	Methyl Cpg Binding Protein 2	0.51	1.42	1.70E-04	1.57E-02
Dock3	Dedicator Of Cyto-Kinesis 3	0.50	1.41	1.73E-04	1.57E-02
Gnaq	G Protein Subunit Alpha Q	0.38	1.30	1.69E-04	1.57E-02
Gsk3b	Glycogen Synthase Kinase 3 Beta	0.43	1.34	1.85E-04	1.66E-02
Spef1	Sperm Flagellar 1	-0.48	-1.39	1.96E-04	1.75E-02
Ppm1l	Protein Phosphatase, Mg2+/Mn2+ Dependent, 1L	0.34	1.27	1.98E-04	1.75E-02
Rab3c	Rab3C, Member Ras Oncogene Family	0.55	1.47	2.02E-04	1.75E-02
Stox2	Storkhead Box 2	0.53	1.44	2.00E-04	1.75E-02
Pcnx4	Pecanex Homolog 4 (Drosophila)	0.32	1.24	2.02E-04	1.75E-02
LOC690276	Hypothetical Protein Loc690276	-0.44	-1.36	2.06E-04	1.77E-02
Cfap45	Cilia And Flagella Associated Protein 45	-0.57	-1.48	2.07E-04	1.77E-02
Itgav	Integrin Subunit Alpha V	0.55	1.46	2.32E-04	1.94E-02
Catip	Ciliogenesis Associated Ttc17 Interacting Protein	-0.56	-1.48	2.31E-04	1.94E-02
Dnah9	Dynein, Axonemal, Heavy Chain 9	-0.57	-1.49	2.31E-04	1.94E-02
Satb2	Satb Homeobox 2	0.55	1.47	2.38E-04	1.98E-02
Ccdc114	Coiled-Coil Domain Containing 114	-0.44	-1.36	2.40E-04	1.98E-02
Adgb	Androglobin	-0.42	-1.34	2.44E-04	2.00E-02
Ttc12	Tetratricopeptide Repeat Domain 12	-0.57	-1.48	2.60E-04	2.12E-02
Acan	Aggrecan	0.56	1.47	2.76E-04	2.22E-02
Uhmk1	U2Af Homology Motif Kinase 1	0.55	1.47	2.74E-04	2.22E-02
Frmpd4	Ferm And Pdz Domain Containing 4	0.50	1.41	2.88E-04	2.27E-02
Ids	Iduronate 2-Sulfatase	0.42	1.34	2.86E-04	2.27E-02
LOC654482	Hypothetical Protein Loc654482	-0.54	-1.46	2.88E-04	2.27E-02
Cfap161	Cilia And Flagella Associated Protein 161	-0.43	-1.34	2.90E-04	2.28E-02

Supplementary Table 2 (Continued)

Dok6	Docking Protein 6	0.48	1.39	2.95E-04	2.29E-02
St6gal2	St6 Beta-Galactoside Alpha-2,6-Sialyltransferase 2	0.45	1.37	2.97E-04	2.29E-02
Cfap126	Cilia And Flagella Associated Protein 126	-0.29	-1.23	2.96E-04	2.29E-02
Alg10	Alg10, Alpha-1,2-Glucosyltransferase	0.49	1.40	3.06E-04	2.34E-02
Htr2c	5-Hydroxytryptamine Receptor 2C	-0.54	-1.46	3.07E-04	2.34E-02
Gprin3	Gprin Family Member 3	0.54	1.45	3.20E-04	2.40E-02
Pgap1	Post-Gpi Attachment To Proteins 1	0.51	1.43	3.21E-04	2.40E-02
Gabrg2	Gamma-Aminobutyric Acid Type A Receptor Gamma 2 Subunit	0.40	1.32	3.19E-04	2.40E-02
Sox6	Sry Box 6	0.51	1.42	3.31E-04	2.46E-02
Pde9a	Phosphodiesterase 9A	-0.48	-1.39	3.33E-04	2.46E-02
Atp8a1	Atpase Phospholipid Transporting 8A1	0.47	1.39	3.36E-04	2.46E-02
Clcn4	Chloride Voltage-Gated Channel 4	0.35	1.27	3.41E-04	2.48E-02
Scn8a	Sodium Voltage-Gated Channel Alpha Subunit 8	0.51	1.42	3.50E-04	2.54E-02
Prkacb	Protein Kinase Camp-Activated Catalytic Subunit Beta	0.44	1.36	3.54E-04	2.55E-02
Sema3a	Semaphorin 3A	0.55	1.46	3.57E-04	2.56E-02
Plekhm3	Pleckstrin Homology Domain Containing M3	0.55	1.47	3.64E-04	2.58E-02
Kl	Klotho	-0.42	-1.34	3.66E-04	2.58E-02
Tekt2	Tektin 2	-0.43	-1.35	3.62E-04	2.58E-02
Spock2	Sparc/Osteonectin, Cwcv And Kazal Like Domains Proteoglycan 2	0.36	1.29	3.80E-04	2.65E-02
Lsm8	Lsm8 Homolog, U6 Small Nuclear Rna Associated	-0.46	-1.37	3.81E-04	2.65E-02
LOC100912373	Uncharacterized Loc100912373	-0.54	-1.46	3.86E-04	2.66E-02
Mns1	Meiosis-Specific Nuclear Structural 1	-0.55	-1.47	3.86E-04	2.66E-02
AABR07030823.1		-0.44	-1.36	3.91E-04	2.68E-02
Pcyox1	Prenylcysteine Oxidase 1	0.29	1.22	4.01E-04	2.73E-02
Plcxd2	Phosphatidylinositol-Specific Phospholipase C, X Domain Containing 2	0.45	1.37	4.08E-04	2.76E-02
Slc8a1	Solute Carrier Family 8 Member A1	0.49	1.41	4.14E-04	2.79E-02
Pde10a	Phosphodiesterase 10A	0.47	1.39	4.17E-04	2.80E-02
Kcnq2	Potassium Voltage-Gated Channel Subfamily Q Member 2	0.43	1.35	4.32E-04	2.88E-02
Fam63b	Family With Sequence Similarity 63, Member B	0.44	1.35	4.37E-04	2.90E-02
Scfd1	Sec1 Family Domain Containing 1	-0.32	-1.25	4.43E-04	2.92E-02
Cmtm4	Cklf-Like Marvel Transmembrane Domain Containing 4	0.48	1.39	4.46E-04	2.93E-02

Supplementary Table 2 (Continued)

Itgb8	Integrin Subunit Beta 8	0.50	1.42	4.53E-04	2.95E-02
Ccdc190	Coiled-Coil Domain Containing 190	-0.42	-1.34	4.53E-04	2.95E-02
Disc1	Disrupted In Schizophrenia 1	0.42	1.34	4.56E-04	2.95E-02
Kcnq3	Potassium Voltage-Gated Channel Subfamily Q Member 3	0.49	1.40	4.63E-04	2.98E-02
Ppp1r36	Protein Phosphatase 1, Regulatory Subunit 36	-0.55	-1.47	4.65E-04	2.98E-02
Kif22	Kinesin Family Member 22	-0.53	-1.45	4.70E-04	2.99E-02
Has3	Hyaluronan Synthase 3	0.50	1.41	4.76E-04	3.02E-02
Uprt	Uracil Phosphoribosyltransferase Homolog	0.49	1.40	4.84E-04	3.05E-02
Ubr3	Ubiquitin Protein Ligase E3 Component N-Recognin 3	0.41	1.33	4.87E-04	3.06E-02
Syt2	Synaptotagmin 2	0.54	1.46	4.91E-04	3.07E-02
Rnf214	Ring Finger Protein 214	0.35	1.28	5.07E-04	3.15E-02
Ubtd1	Ubiquitin Domain Containing 1	-0.49	-1.41	5.22E-04	3.23E-02
Daw1	Dynein Assembly Factor With Wd Repeats 1	-0.34	-1.27	5.32E-04	3.27E-02
Tmem212	Transmembrane Protein 212	-0.29	-1.22	5.41E-04	3.31E-02
Gpr26	G Protein-Coupled Receptor 26	0.50	1.41	5.45E-04	3.32E-02
Pdpr	Pyruvate Dehydrogenase Phosphatase Regulatory Subunit	0.46	1.38	5.51E-04	3.32E-02
Pcdh7	Protocadherin 7	0.45	1.36	5.55E-04	3.32E-02
Larp4b	La Ribonucleoprotein Domain Family, Member 4B	0.41	1.33	5.58E-04	3.32E-02
Agap1	Arfgap With Gtpase Domain, Ankyrin Repeat And Ph Domain 1	0.36	1.29	5.51E-04	3.32E-02
Efhc1	Ef-Hand Domain Containing 1	-0.52	-1.43	5.56E-04	3.32E-02
Elfn2	Extracellular Leucine-Rich Repeat And Fibronectin Type Iii Domain Containing 2	0.44	1.35	5.76E-04	3.41E-02
Dnali1	Dynein, Axonemal, Light Intermediate Chain 1	-0.36	-1.29	5.81E-04	3.42E-02
Arel1	Apoptosis Resistant E3 Ubiquitin Protein Ligase 1	0.33	1.26	6.25E-04	3.67E-02
Bach2	Btb Domain And Cnc Homolog 2	0.50	1.41	6.34E-04	3.68E-02
Mtpn	Myotrophin	0.33	1.26	6.32E-04	3.68E-02
Brinp2	Bmp/Retinoic Acid Inducible Neural Specific 2	0.48	1.40	6.45E-04	3.73E-02
Tm9sf3	Transmembrane 9 Superfamily Member 3	0.38	1.30	6.54E-04	3.76E-02
Edem1	Er Degradation Enhancing Alpha-Mannosidase Like Protein 1	0.49	1.41	6.63E-04	3.80E-02
Gstm1	Glutathione S-Transferase Mu 1	-0.41	-1.33	6.68E-04	3.81E-02
Vcpip1	Valosin Containing Protein Interacting Protein 1	0.41	1.33	6.81E-04	3.83E-02
Ablim1	Actin-Binding Lim Protein 1	0.34	1.26	6.78E-04	3.83E-02

Supplementary Table 2 (Continued)

Cfap206	Cilia And Flagella Associated Protein 206	-0.39	-1.31	6.79E-04	3.83E-02
Rap1gap2	Rap1 Gtpase Activating Protein 2	0.41	1.33	6.91E-04	3.84E-02
Calml4	Calmodulin-Like 4	-0.48	-1.39	6.87E-04	3.84E-02
Lrrc46	Leucine Rich Repeat Containing 46	-0.51	-1.42	6.88E-04	3.84E-02
Lmbrd2	Lmbr1 Domain Containing 2	0.44	1.35	6.96E-04	3.84E-02
Dnah12	Dynein, Axonemal, Heavy Chain 12	-0.46	-1.38	7.05E-04	3.88E-02
Ptbp3	Polypyrimidine Tract Binding Protein 3	0.45	1.36	7.27E-04	3.95E-02
Pcgf3	Polycomb Group Ring Finger 3	0.36	1.28	7.24E-04	3.95E-02
Nlgn3	Neuroligin 3	0.38	1.30	7.40E-04	3.97E-02
Adcy5	Adenylate Cyclase 5	0.38	1.30	7.36E-04	3.97E-02
Ralgapb	Ral Gtpase Activating Protein Non-Catalytic Beta Subunit	0.28	1.22	7.38E-04	3.97E-02
Frrs1l	Ferric-Chelate Reductase 1-Like	0.49	1.41	7.43E-04	3.97E-02
Ube3c	Ubiquitin Protein Ligase E3C	0.26	1.20	7.61E-04	4.04E-02
Tbc1d24	Tbc1 Domain Family, Member 24	0.33	1.26	7.94E-04	4.20E-02
Grik3	Glutamate Ionotropic Receptor Kainate Type Subunit 3	0.51	1.43	8.14E-04	4.24E-02
Klf12	Kruppel-Like Factor 12	0.50	1.41	8.05E-04	4.24E-02
Atp8a2	Atpase Phospholipid Transporting 8A2	0.48	1.39	8.12E-04	4.24E-02
Dusp8	Dual Specificity Phosphatase 8	0.40	1.32	8.14E-04	4.24E-02
Csrnp3	Cysteine And Serine Rich Nuclear Protein 3	0.46	1.38	8.53E-04	4.41E-02
Car2	Carbonic Anhydrase 2	-0.50	-1.41	8.53E-04	4.41E-02
Cdca3	Cell Division Cycle Associated 3	-0.52	-1.44	8.63E-04	4.44E-02
Acaca	Acetyl-Coa Carboxylase Alpha	0.40	1.32	8.69E-04	4.44E-02
Slc6a17	Solute Carrier Family 6 Member 17	0.33	1.26	8.72E-04	4.44E-02
Lnp1	Leukemia Nup98 Fusion Partner 1	0.50	1.41	8.75E-04	4.45E-02
Fam216b	Family With Sequence Similarity 216, Member B	-0.33	-1.26	8.84E-04	4.47E-02
St18	Suppression Of Tumorigenicity 18	-0.51	-1.43	8.99E-04	4.53E-02
Igsf9b	Immunoglobulin Superfamily, Member 9B	0.52	1.44	9.40E-04	4.72E-02
Adcy9	Adenylate Cyclase 9	0.52	1.43	9.63E-04	4.81E-02
Gabrg1	Gamma-Aminobutyric Acid Type A Receptor Gamma 1 Subunit	0.33	1.26	9.96E-04	4.96E-02

Supplementary Table 2 (Continued)

Supplementary Table 2b: Significantly (padj ≤ 0.05) altered genes in 250 BPA ♀ vs. Vehicle ♀

Gene Symbol	Description	log2 Fold Change	Fold Change	p-value	padj
Xkr4	Xk Related 4	0.97	1.96	5.13E-14	6.43E-10
Adcy1	Adenylate Cyclase 1	0.96	1.94	9.44E-13	5.92E-09
AABR07062799.2		0.85	1.80	4.17E-11	1.74E-07
Cds2	Cdp-Diacylglycerol Synthase 2	0.84	1.79	5.88E-11	1.84E-07
Psd3	Pleckstrin And Sec7 Domain Containing 3	0.79	1.73	1.43E-10	3.58E-07
Prkaa2	Protein Kinase Amp-Activated Catalytic Subunit Alpha 2	0.82	1.77	1.95E-10	4.08E-07
Zyg11b	Zyg-11 Family Member B, Cell Cycle Regulator	0.79	1.73	1.73E-09	3.09E-06
Nipa1	Non Imprinted In Prader-Willi/Angelman Syndrome 1	0.67	1.60	3.87E-09	6.07E-06
Lin7c	Lin-7 Homolog C, Crumbs Cell Polarity Complex Component	0.54	1.45	6.54E-09	9.11E-06
Slc35e2b	Solute Carrier Family 35, Member E2B	0.65	1.57	1.58E-08	1.69E-05
41338	Membrane Associated Ring-Ch-Type Finger 6	0.61	1.52	1.41E-08	1.69E-05
Cpeb4	Cytoplasmic Polyadenylation Element Binding Protein 4	0.56	1.47	1.62E-08	1.69E-05
Pdpk1	3-Phosphoinositide Dependent Protein Kinase-1	0.65	1.57	2.10E-08	2.03E-05
Slc1a2	Solute Carrier Family 1 Member 2	0.79	1.72	3.05E-08	2.73E-05
Birc6	Baculoviral Iap Repeat-Containing 6	0.71	1.64	4.04E-08	3.17E-05
Xpr1	Xenotropic And Polytropic Retrovirus Receptor 1	0.71	1.64	4.04E-08	3.17E-05
AABR07041411.1		0.86	1.81	5.93E-08	4.04E-05
Skil	Ski-Like Proto-Oncogene	0.72	1.65	6.44E-08	4.04E-05
Bmpr2	Bone Morphogenetic Protein Receptor Type 2	0.66	1.58	6.32E-08	4.04E-05
Mib1	Mindbomb E3 Ubiquitin Protein Ligase 1	0.66	1.58	5.91E-08	4.04E-05
Slc9a7	Solute Carrier Family 9 Member A7	0.77	1.71	8.18E-08	4.89E-05
Slc16a7	Solute Carrier Family 16 Member 7	0.73	1.66	9.23E-08	5.05E-05
Pcdha4	Protocadherin Alpha 4	0.69	1.61	9.65E-08	5.05E-05
Dcbld2	Discoidin, Cub And Lccl Domain Containing 2	0.63	1.55	9.50E-08	5.05E-05
Gabrb2	Gamma-Aminobutyric Acid Type A Receptor Beta 2 Subunit	0.74	1.67	1.27E-07	6.11E-05
Pak3	P21 (Rac1) Activated Kinase 3	0.69	1.62	1.25E-07	6.11E-05
Dync1h1	Dynein Cytoplasmic 1 Heavy Chain 1	0.69	1.61	1.67E-07	7.49E-05
Abi2	Abl-Interactor 2	0.45	1.37	1.65E-07	7.49E-05
Zfp704	Zinc Finger Protein 704	0.79	1.73	1.77E-07	7.64E-05
Pcdh7	Protocadherin 7	0.67	1.59	1.84E-07	7.71E-05
Nr2c2	Nuclear Receptor Subfamily 2, Group C, Member 2	0.59	1.50	2.69E-07	1.09E-04
Nrxn1	Neurexin 1	0.51	1.42	2.88E-07	1.13E-04
Gabrg1	Gamma-Aminobutyric Acid Type A Receptor Gamma 1 Subunit	0.51	1.42	3.31E-07	1.26E-04
Slc38a1	Solute Carrier Family 38, Member 1	0.56	1.47	3.65E-07	1.35E-04
AABR07073181.1		0.80	1.74	4.15E-07	1.42E-04
Ttbk2	Tau Tubulin Kinase 2	0.71	1.63	4.13E-07	1.42E-04
RGD1566359	Similar To Riken Cdna B230219D22	0.52	1.43	4.19E-07	1.42E-04
Pcdh19	Protocadherin 19	0.61	1.53	4.36E-07	1.44E-04
Pcnx4	Pecanex Homolog 4 (Drosophila)	0.43	1.34	5.09E-07	1.64E-04
Wnk3	Wnk Lysine Deficient Protein Kinase 3	0.66	1.58	6.61E-07	2.07E-04
Rnf152	Ring Finger Protein 152	0.67	1.59	6.94E-07	2.12E-04
Zdhhc21	Zinc Finger, Dhhc-Type Containing 21	0.67	1.59	1.15E-06	3.45E-04
Myo5a	Myosin Va	0.62	1.54	1.22E-06	3.56E-04
Rab3c	Rab3C, Member Ras Oncogene Family	0.71	1.64	1.54E-06	4.03E-04
Uprt	Uracil Phosphoribosyltransferase Homolog	0.67	1.60	1.52E-06	4.03E-04
Mfhas1	Malignant Fibrous Histiocytoma Amplified Sequence 1	0.58	1.50	1.49E-06	4.03E-04
Gtf2f1	General Transcription Factor Iif Subunit 1	-0.47	-1.38	1.52E-06	4.03E-04
RGD1306739	Similar To Riken Cdna 1700040L02	-0.75	-1.68	1.48E-06	4.03E-04
Cpeb3	Cytoplasmic Polyadenylation Element Binding Protein 3	0.69	1.62	1.65E-06	4.24E-04

Supplementary Table 2 (Continued)

Gnaq	G Protein Subunit Alpha Q	0.48	1.40	1.85E-06	4.56E-04
Clcn3	Chloride Voltage-Gated Channel 3	0.43	1.35	1.85E-06	4.56E-04
Gprin3	Gprin Family Member 3	0.71	1.63	2.05E-06	4.95E-04
Tnks	Tankyrase	0.53	1.45	2.27E-06	5.38E-04
Zim1	Zinc Finger, Imprinted 1	0.71	1.64	2.46E-06	5.61E-04
Prkacb	Protein Kinase Camp-Activated Catalytic Subunit Beta	0.58	1.50	2.46E-06	5.61E-04
Sesn3	Sestrin 3	0.61	1.52	2.61E-06	5.85E-04
LOC102553088	Collagen Alpha-1(Xxv) Chain-Like	0.74	1.67	3.38E-06	7.43E-04
Zfp871	Zinc Finger Protein 871	0.70	1.62	3.48E-06	7.43E-04
Hmbox1	Homeobox Containing 1	0.57	1.48	3.50E-06	7.43E-04
Adam23	Adam Metallopeptidase Domain 23	0.51	1.42	3.58E-06	7.48E-04
Panx1	Pannexin 1	0.54	1.46	3.85E-06	7.93E-04
Sox6	Sry Box 6	0.66	1.58	4.03E-06	8.02E-04
Erbb4	Erb-B2 Receptor Tyrosine Kinase 4	0.63	1.55	4.00E-06	8.02E-04
Prkce	Protein Kinase C, Epsilon	0.58	1.50	4.36E-06	8.43E-04
Apaf1	Apoptotic Peptidase Activating Factor 1	0.33	1.26	4.37E-06	8.43E-04
Alg10	Alg10, Alpha-1,2-Glucosyltransferase	0.62	1.54	4.83E-06	9.17E-04
Ppp1r9a	Protein Phosphatase 1, Regulatory Subunit 9A	0.61	1.53	5.14E-06	9.63E-04
Lrrc8b	Leucine Rich Repeat Containing 8 Family, Member B	0.54	1.45	5.35E-06	9.73E-04
Ccdc113	Coiled-Coil Domain Containing 113	-0.71	-1.64	5.30E-06	9.73E-04
Itgb8	Integrin Subunit Beta 8	0.65	1.57	6.05E-06	1.08E-03
Stox2	Storkhead Box 2	0.64	1.56	6.22E-06	1.09E-03
Mfap3	Microfibrillar-Associated Protein 3	0.45	1.37	6.30E-06	1.09E-03
Kcne2	Potassium Voltage-Gated Channel Subfamily E Regulatory Subunit 2	-0.67	-1.59	6.33E-06	1.09E-03
Zbtb41	Zinc Finger And Btb Domain Containing 41	0.61	1.52	7.57E-06	1.22E-03
Clvs2	Clavesin 2	0.57	1.48	7.50E-06	1.22E-03
Pcdha2	Protocadherin Alpha 2	0.55	1.46	7.40E-06	1.22E-03
Ids	Iduronate 2-Sulfatase	0.52	1.43	7.49E-06	1.22E-03
Crk	Crk Proto-Oncogene, Adaptor Protein	0.41	1.33	7.46E-06	1.22E-03
AABR07037528.1		0.68	1.60	7.68E-06	1.22E-03
Fem1b	Fem-1 Homolog B	0.55	1.47	7.86E-06	1.23E-03
Sh3pxd2a	Sh3 And Px Domains 2A	0.61	1.53	8.39E-06	1.30E-03
Flrt2	Fibronectin Leucine Rich Transmembrane Protein 2	0.64	1.56	8.85E-06	1.35E-03
Hecw1	Hect, C2 And Ww Domain Containing E3 Ubiquitin Protein Ligase 1	0.54	1.45	9.43E-06	1.43E-03
Atp8a1	Atpase Phospholipid Transporting 8A1	0.58	1.50	9.80E-06	1.46E-03
Slc8a1	Solute Carrier Family 8 Member A1	0.61	1.53	1.02E-05	1.51E-03
Uhmk1	U2Af Homology Motif Kinase 1	0.67	1.59	1.04E-05	1.52E-03
Plxna4	Plexin A4	0.64	1.56	1.14E-05	1.64E-03
Ppm1h	Protein Phosphatase, Mg2+/Mn2+ Dependent, 1H	0.49	1.40	1.16E-05	1.65E-03
Dok6	Docking Protein 6	0.58	1.49	1.18E-05	1.67E-03
Cirbp	Cold Inducible Rna Binding Protein	-0.51	-1.42	1.31E-05	1.83E-03
Lrrc34	Leucine Rich Repeat Containing 34	-0.68	-1.60	1.44E-05	1.98E-03
Neurl1b	Neuralized E3 Ubiquitin Protein Ligase 1B	0.54	1.46	1.54E-05	2.10E-03
Akap11	A-Kinase Anchoring Protein 11	0.39	1.31	1.56E-05	2.11E-03
Nes	Nestin	-0.64	-1.56	1.68E-05	2.24E-03
Ncam2	Neural Cell Adhesion Molecule 2	0.45	1.37	1.73E-05	2.28E-03
Nsd1	Nuclear Receptor Binding Set Domain Protein 1	0.53	1.45	1.76E-05	2.29E-03
Pcgf3	Polycomb Group Ring Finger 3	0.45	1.37	1.77E-05	2.29E-03
Csrnp3	Cysteine And Serine Rich Nuclear Protein 3	0.59	1.51	1.80E-05	2.31E-03
Camk2a	Calcium/Calmodulin-Dependent Protein Kinase Ii Alpha	0.41	1.33	2.07E-05	2.62E-03
Igsf9b	Immunoglobulin Superfamily, Member 9B	0.67	1.59	2.16E-05	2.63E-03

Supplementary Table 2 (Continued)

Sv2c	Synaptic Vesicle Glycoprotein 2C	0.67	1.59	2.12E-05	2.63E-03
Nav1	Neuron Navigator 1	0.57	1.48	2.16E-05	2.63E-03
Psen1	Presenilin 1	0.42	1.33	2.10E-05	2.63E-03
Pgap1	Post-Gpi Attachment To Proteins 1	0.61	1.52	2.22E-05	2.64E-03
Extl3	Exostosin-Like Glycosyltransferase 3	0.54	1.46	2.23E-05	2.64E-03
Mef2a	Myocyte Enhancer Factor 2A	0.48	1.40	2.22E-05	2.64E-03
Lmbrd2	Lmbr1 Domain Containing 2	0.55	1.46	2.29E-05	2.66E-03
Grm5	Glutamate Metabotropic Receptor 5	0.53	1.44	2.28E-05	2.66E-03
Tmem170b	Transmembrane Protein 170B	0.57	1.49	2.31E-05	2.66E-03
Lrfn5	Leucine Rich Repeat And Fibronectin Type Iii Domain Containing 5	0.41	1.33	2.47E-05	2.81E-03
Tug1	Taurine Up-Regulated 1 (Non-Protein Coding)	0.44	1.35	2.60E-05	2.94E-03
St6gal2	St6 Beta-Galactoside Alpha-2,6-Sialyltransferase 2	0.53	1.44	2.73E-05	3.06E-03
Pcdha4	Protocadherin Alpha 4	0.60	1.51	2.81E-05	3.12E-03
Prkar2a	Protein Kinase Camp-Dependent Type 2 Regulatory Subunit Alpha	0.57	1.49	2.86E-05	3.12E-03
Pnma2	Paraneoplastic Ma Antigen 2	0.47	1.39	2.86E-05	3.12E-03
Selenoi	Selenoprotein I	0.40	1.32	3.03E-05	3.28E-03
Fndc3b	Fibronectin Type Iii Domain Containing 3B	0.52	1.44	3.09E-05	3.31E-03
Ate1	Arginyltransferase 1	0.45	1.36	3.19E-05	3.39E-03
Tmod2	Tropomodulin 2	0.45	1.37	3.55E-05	3.75E-03
Mecp2	Methyl Cpg Binding Protein 2	0.56	1.47	3.63E-05	3.77E-03
Ikbkap	Inhibitor Of Kappa Light Polypeptide Gene Enhancer In B-Cells, Kinase Complex-Associated Protein	0.38	1.30	3.61E-05	3.77E-03
Mdm4	Mdm4, P53 Regulator	0.56	1.48	3.67E-05	3.78E-03
Rab11fip2	Rab11 Family Interacting Protein 2	0.50	1.41	3.76E-05	3.81E-03
Megf9	Multiple Egf-Like-Domains 9	0.43	1.34	3.76E-05	3.81E-03
Cacna1e	Calcium Voltage-Gated Channel Subunit Alpha1 E	0.57	1.49	4.03E-05	3.95E-03
Lifr	Leukemia Inhibitory Factor Receptor Alpha	0.57	1.48	4.03E-05	3.95E-03
Tmem178b	Transmembrane Protein 178B	0.47	1.38	4.03E-05	3.95E-03
Cntrl	Centriolin	-0.65	-1.57	4.03E-05	3.95E-03
Tmem56	Transmembrane Protein 56	0.54	1.45	4.26E-05	4.14E-03
Gabrg2	Gamma-Aminobutyric Acid Type A Receptor Gamma 2 Subunit	0.46	1.37	4.31E-05	4.16E-03
Tmem245	Transmembrane Protein 245	0.64	1.55	4.50E-05	4.31E-03
Fzd3	Frizzled Class Receptor 3	0.60	1.52	4.61E-05	4.33E-03
Lrrc58	Leucine Rich Repeat Containing 58	0.51	1.42	4.62E-05	4.33E-03
Fhad1	Forkhead Associated Phosphopeptide Binding Domain 1	-0.64	-1.56	4.57E-05	4.33E-03
Kcnq3	Potassium Voltage-Gated Channel Subfamily Q Member 3	0.57	1.48	4.84E-05	4.48E-03
Tbc1d24	Tbc1 Domain Family, Member 24	0.40	1.32	4.85E-05	4.48E-03
Ube3c	Ubiquitin Protein Ligase E3C	0.31	1.24	5.02E-05	4.60E-03
Cpeb2	Cytoplasmic Polyadenylation Element Binding Protein 2	0.53	1.44	5.14E-05	4.68E-03
Tanc2	Tetratricopeptide Repeat, Ankyrin Repeat And Coiled-Coil Containing 2	0.56	1.48	5.40E-05	4.84E-03
Cfap70	Cilia And Flagella Associated Protein 70	-0.58	-1.49	5.39E-05	4.84E-03
Ptbp3	Polypyrimidine Tract Binding Protein 3	0.53	1.44	5.68E-05	4.98E-03
Vcpip1	Valosin Containing Protein Interacting Protein 1	0.48	1.40	5.66E-05	4.98E-03
Gsk3b	Glycogen Synthase Kinase 3 Beta	0.46	1.37	5.63E-05	4.98E-03
Spock2	Sparc/Osteonectin, Cwcv And Kazal Like Domains Proteoglycan 2	0.41	1.33	5.74E-05	5.00E-03
Fam102b	Family With Sequence Similarity 102, Member B	0.50	1.41	6.13E-05	5.31E-03
Fstl5	Follistatin-Like 5	0.40	1.32	6.23E-05	5.36E-03
Mlf1	Myeloid Leukemia Factor 1	-0.61	-1.53	6.47E-05	5.52E-03
Zmat3	Zinc Finger, Matrin Type 3	0.57	1.48	6.62E-05	5.61E-03
Zfp597	Zinc Finger Protein 597	0.52	1.44	6.68E-05	5.62E-03
Paqr8	Progestin And Adipoq Receptor Family Member 8	0.62	1.53	6.77E-05	5.63E-03
Rgs17	Regulator Of G-Protein Signaling 17	0.56	1.48	6.77E-05	5.63E-03

Supplementary Table 2 (Continued)

Tspyl5	Tspy-Like 5	0.43	1.35	6.88E-05	5.68E-03
Arfgef3	Arfgef Family Member 3	0.59	1.50	6.98E-05	5.72E-03
Nlgn3	Neuroligin 3	0.45	1.37	7.02E-05	5.72E-03
Cadm2	Cell Adhesion Molecule 2	0.50	1.41	7.38E-05	5.97E-03
Tm9sf3	Transmembrane 9 Superfamily Member 3	0.44	1.35	7.53E-05	6.05E-03
Slc30a7	Solute Carrier Family 30 Member 7	0.51	1.42	7.66E-05	6.12E-03
Lyst	Lysosomal Trafficking Regulator	0.57	1.49	8.07E-05	6.41E-03
Plcxd3	Phosphatidylinositol-Specific Phospholipase C, X Domain Containing 3	0.62	1.54	8.21E-05	6.48E-03
Ago2	Argonaute 2, Risc Catalytic Component	0.60	1.52	8.30E-05	6.51E-03
Pten	Phosphatase And Tensin Homolog	0.39	1.31	8.56E-05	6.67E-03
Vstm2a	V-Set And Transmembrane Domain Containing 2A	0.38	1.30	8.92E-05	6.90E-03
Man1a2	Mannosidase, Alpha, Class 1A, Member 2	0.43	1.35	9.38E-05	7.22E-03
Tcp1l1	T-Complex 11 Like 1	0.60	1.51	9.62E-05	7.36E-03
Cmtm4	Cklf-Like Marvel Transmembrane Domain Containing 4	0.53	1.44	9.80E-05	7.45E-03
Rsph1	Radial Spoke Head 1 Homolog	-0.61	-1.53	1.06E-04	7.99E-03
Smcr8	Smith-Magenis Syndrome Chromosome Region, Candidate 8	0.58	1.50	1.07E-04	8.04E-03
Dnajc5	Dnaj Heat Shock Protein Family (Hsp40) Member C5	0.40	1.32	1.08E-04	8.06E-03
Kras	Kras Proto-Oncogene, Gtpase	0.41	1.33	1.12E-04	8.34E-03
Soga1	Suppressor Of Glucose, Autophagy Associated 1	0.57	1.48	1.16E-04	8.55E-03
Itga4	Integrin Subunit Alpha 4	0.61	1.52	1.22E-04	8.82E-03
Atp8a2	Atpase Phospholipid Transporting 8A2	0.55	1.46	1.21E-04	8.82E-03
Abr	Active Bcr-Related	0.32	1.25	1.21E-04	8.82E-03
Tyms	Thymidylate Synthetase	0.40	1.32	1.28E-04	9.19E-03
Timm44	Translocase Of Inner Mitochondrial Membrane 44	-0.39	-1.31	1.28E-04	9.19E-03
Adarb2	Adenosine Deaminase, Rna-Specific, B2	0.44	1.36	1.50E-04	1.07E-02
Gabrb3	Gamma-Aminobutyric Acid Type A Receptor Beta 3 Subunit	0.45	1.37	1.52E-04	1.07E-02
Pcyox1	Prenylcysteine Oxidase 1	0.31	1.24	1.52E-04	1.07E-02
Prkca	Protein Kinase C, Alpha	0.55	1.46	1.61E-04	1.12E-02
AABR07030521.1		-0.60	-1.51	1.61E-04	1.12E-02
Htr1b	5-Hydroxytryptamine Receptor 1B	0.52	1.43	1.63E-04	1.13E-02
Hcfc1	Host Cell Factor C1	0.53	1.44	1.64E-04	1.13E-02
Chl1	Cell Adhesion Molecule L1-Like	0.43	1.35	1.66E-04	1.14E-02
Plcxd2	Phosphatidylinositol-Specific Phospholipase C, X Domain Containing 2	0.48	1.40	1.72E-04	1.16E-02
Fam63b	Family With Sequence Similarity 63, Member B	0.47	1.38	1.71E-04	1.16E-02
Bicd1	Bicd Cargo Adaptor 1	0.46	1.38	1.74E-04	1.17E-02
Selenot	Selenoprotein T	0.39	1.31	1.74E-04	1.17E-02
Slc36a4	Solute Carrier Family 36 Member 4	0.56	1.47	1.81E-04	1.18E-02
Gpr26	G Protein-Coupled Receptor 26	0.54	1.45	1.78E-04	1.18E-02
Dzank1	Double Zinc Ribbon And Ankyrin Repeat Domains 1	0.51	1.43	1.79E-04	1.18E-02
Larp4b	La Ribonucleoprotein Domain Family, Member 4B	0.45	1.36	1.81E-04	1.18E-02
Clcn4	Chloride Voltage-Gated Channel 4	0.36	1.29	1.78E-04	1.18E-02
Ppm1l	Protein Phosphatase, Mg2+/Mn2+ Dependent, 1L	0.35	1.27	1.79E-04	1.18E-02
Pde10a	Phosphodiesterase 10A	0.50	1.42	1.83E-04	1.18E-02
Slc4a1ap	Solute Carrier Family 4 Member 1 Adaptor Protein	-0.44	-1.35	1.84E-04	1.18E-02
Wdr63	Wd Repeat Domain 63	-0.52	-1.43	1.85E-04	1.19E-02
Tmed8	Transmembrane P24 Trafficking Protein 8	0.53	1.45	1.89E-04	1.20E-02
Ubr3	Ubiquitin Protein Ligase E3 Component N-Recognin 3	0.44	1.35	2.01E-04	1.27E-02
Sostdc1	Sclerostin Domain Containing 1	-0.56	-1.47	2.14E-04	1.34E-02
Snx30	Sorting Nexin Family Member 30	0.48	1.40	2.16E-04	1.35E-02
Avl9	Avl9 Cell Migration Associated	0.49	1.41	2.18E-04	1.35E-02
Itgav	Integrin Subunit Alpha V	0.55	1.47	2.19E-04	1.35E-02

Supplementary Table 2 (Continued)

Lpgat1	Lysophosphatidylglycerol Acyltransferase 1	0.44	1.36	2.26E-04	1.39E-02
Dgkh	Diacylglycerol Kinase, Eta	0.57	1.49	2.30E-04	1.41E-02
Atxn1	Ataxin 1	0.57	1.49	2.33E-04	1.41E-02
Neto2	Neuropilin And Tolloid Like 2	0.34	1.27	2.32E-04	1.41E-02
Frmpd4	Ferm And Pdz Domain Containing 4	0.50	1.42	2.43E-04	1.46E-02
Cpd	Carboxypeptidase D	0.46	1.37	2.44E-04	1.46E-02
Pfdn6	Prefoldin Subunit 6	-0.36	-1.29	2.46E-04	1.47E-02
Snrk	Snf Related Kinase	0.38	1.30	2.56E-04	1.52E-02
Arel1	Apoptosis Resistant E3 Ubiquitin Protein Ligase 1	0.35	1.28	2.68E-04	1.59E-02
Kbtbd11	Kelch Repeat And Btb Domain Containing 11	0.50	1.41	2.71E-04	1.60E-02
Pdpr	Pyruvate Dehydrogenase Phosphatase Regulatory Subunit	0.49	1.40	2.79E-04	1.64E-02
Slitrk1	Slit And Ntrk-Like Family, Member 1	0.39	1.31	2.86E-04	1.67E-02
Camk4	Calcium/Calmodulin-Dependent Protein Kinase Iv	0.49	1.41	2.96E-04	1.72E-02
Cbl	Cbl Proto-Oncogene	0.54	1.45	2.98E-04	1.72E-02
Lsm11	Lsm11, U7 Small Nuclear Rna Associated	0.51	1.42	3.04E-04	1.75E-02
Ksr2	Kinase Suppressor Of Ras 2	0.56	1.47	3.08E-04	1.75E-02
Klhl11	Kelch-Like Family Member 11	0.54	1.45	3.07E-04	1.75E-02
Bace1	Beta-Secretase 1	0.38	1.30	3.06E-04	1.75E-02
Tulp4	Tubby Like Protein 4	0.50	1.42	3.18E-04	1.79E-02
Mgat3	Mannosyl (Beta-1,4-)-Glycoprotein Beta-1,4-N-Acetylglucosaminyltransferase	0.37	1.29	3.17E-04	1.79E-02
Fat3	Fat Atypical Cadherin 3	0.57	1.48	3.31E-04	1.85E-02
Ndrg3	Ndrg Family Member 3	0.34	1.27	3.34E-04	1.86E-02
Fsd1l	Fibronectin Type Iii And Spry Domain Containing 1-Like	0.51	1.43	3.37E-04	1.86E-02
Ube2j1	Ubiquitin-Conjugating Enzyme E2, J1	0.38	1.30	3.36E-04	1.86E-02
Lonrf2	Lon Peptidase N-Terminal Domain And Ring Finger 2	0.43	1.35	3.41E-04	1.88E-02
Klf12	Kruppel-Like Factor 12	0.53	1.45	3.51E-04	1.92E-02
Acvr2b	Activin A Receptor Type 2B	0.57	1.48	3.53E-04	1.92E-02
Atrnl1	Attractin Like 1	0.46	1.38	3.55E-04	1.93E-02
Frrs1l	Ferric-Chelate Reductase 1-Like	0.52	1.44	3.69E-04	1.99E-02
Sema3a	Semaphorin 3A	0.54	1.46	4.01E-04	2.16E-02
Atp8a1	Atpase Phospholipid Transporting 8A1	0.56	1.47	4.08E-04	2.16E-02
Sestd1	Sec14 And Spectrin Domain Containing 1	0.45	1.36	4.08E-04	2.16E-02
Kcnq2	Potassium Voltage-Gated Channel Subfamily Q Member 2	0.43	1.35	4.04E-04	2.16E-02
Gabrb1	Gamma-Aminobutyric Acid Type A Receptor Beta 1 Subunit	0.43	1.35	4.06E-04	2.16E-02
Amer1	Apc Membrane Recruitment Protein 1	0.54	1.45	4.11E-04	2.16E-02
Bend4	Ben Domain Containing 4	0.55	1.47	4.25E-04	2.23E-02
Clic4	Chloride Intracellular Channel 4	0.47	1.39	4.26E-04	2.23E-02
Gfod1	Glucose-Fructose Oxidoreductase Domain Containing 1	0.53	1.44	4.34E-04	2.24E-02
Ntn3	Netrin 3	0.50	1.42	4.34E-04	2.24E-02
Appl1	Adaptor Protein, Phosphotyrosine Interacting With Ph Domain And Leucine Zipper 1	0.36	1.28	4.35E-04	2.24E-02
Oprl1	Opioid Related Nociceptin Receptor 1	0.40	1.32	4.44E-04	2.28E-02
Bmpr1a	Bone Morphogenetic Protein Receptor Type 1A	0.37	1.29	4.56E-04	2.33E-02
Dgke	Diacylglycerol Kinase Epsilon	0.39	1.31	4.59E-04	2.34E-02
Fbxo41	F-Box Protein 41	0.46	1.38	4.65E-04	2.36E-02
Wdr78	Wd Repeat Domain 78	-0.49	-1.40	4.67E-04	2.36E-02
Pamr1	Peptidase Domain Containing Associated With Muscle Regeneration 1	0.53	1.45	4.78E-04	2.41E-02
Agap1	Arfgap With Gtpase Domain, Ankyrin Repeat And Ph Domain 1	0.37	1.29	4.81E-04	2.42E-02
Dnah6	Dynein, Axonemal, Heavy Chain 6	-0.53	-1.45	4.84E-04	2.42E-02
Iqub	Iq Motif And Ubiquitin Domain Containing	-0.55	-1.46	4.86E-04	2.42E-02
Chrnb2	Cholinergic Receptor Nicotinic Beta 2 Subunit	0.45	1.36	4.91E-04	2.43E-02
Ranbp6	Ran Binding Protein 6	0.45	1.37	5.08E-04	2.51E-02

Supplementary Table 2 (Continued)

Samd8	Sterile Alpha Motif Domain Containing 8	0.26	1.20	5.14E-04	2.53E-02
Rcan3	Rcan Family Member 3	0.55	1.46	5.23E-04	2.56E-02
Rbfox2	Rna Binding Protein, Fox-1 Homolog 2	0.46	1.38	5.29E-04	2.58E-02
Plekhm3	Pleckstrin Homology Domain Containing M3	0.54	1.45	5.37E-04	2.61E-02
Ak9	Adenylate Kinase 9	-0.48	-1.40	5.44E-04	2.62E-02
Spag6l	Sperm Associated Antigen 6-Like	-0.50	-1.41	5.44E-04	2.62E-02
Tekt4	Tektin 4	-0.53	-1.45	5.53E-04	2.66E-02
Dock3	Dedicator Of Cyto-Kinesis 3	0.46	1.37	5.57E-04	2.67E-02
Clasrp	Clk4-Associating Serine/Arginine Rich Protein	-0.48	-1.39	5.59E-04	2.67E-02
Pcdh11x	Protocadherin 11 X-Linked	0.54	1.45	5.67E-04	2.69E-02
Tmem181	Transmembrane Protein 181	0.37	1.29	5.76E-04	2.73E-02
Ss18l1	Ss18L1, Nbaf Chromatin Remodeling Complex Subunit	0.40	1.32	5.84E-04	2.74E-02
Myl12b	Myosin Light Chain 12B	-0.33	-1.25	5.84E-04	2.74E-02
Grm3	Glutamate Metabotropic Receptor 3	0.52	1.43	6.05E-04	2.83E-02
Mtpn	Myotrophin	0.33	1.26	6.19E-04	2.89E-02
Xiap	X-Linked Inhibitor Of Apoptosis	0.48	1.39	6.27E-04	2.90E-02
N4bp2	Nedd4 Binding Protein 2	0.46	1.37	6.26E-04	2.90E-02
Rmnd5a	Required For Meiotic Nuclear Division 5 Homolog A	0.41	1.33	6.44E-04	2.97E-02
Lgr4	Leucine-Rich Repeat-Containing G Protein-Coupled Receptor 4	0.37	1.29	6.54E-04	3.00E-02
Lrp1	Ldl Receptor Related Protein 1	0.36	1.28	6.54E-04	3.00E-02
Fam160b1	Family With Sequence Similarity 160, Member B1	0.43	1.35	6.57E-04	3.00E-02
RGD1306271	Similar To Kiaa1549 Protein	0.45	1.37	6.62E-04	3.01E-02
Gprin2	G Protein Regulated Inducer Of Neurite Outgrowth 2	0.45	1.37	6.65E-04	3.01E-02
Rsph10b	Radial Spoke Head 10 Homolog B	-0.54	-1.45	6.71E-04	3.03E-02
Fyttd1	Forty-Two-Three Domain Containing 1	0.31	1.24	6.79E-04	3.05E-02
Eps15	Epidermal Growth Factor Receptor Pathway Substrate 15	0.40	1.32	6.96E-04	3.12E-02
Ubr1	Ubiquitin Protein Ligase E3 Component N-Recognin 1	0.43	1.34	7.13E-04	3.18E-02
Gucy1a2	Guanylate Cyclase 1 Soluble Subunit Alpha 2	0.49	1.41	7.33E-04	3.25E-02
Ralgapb	Ral Gtpase Activating Protein Non-Catalytic Beta Subunit	0.29	1.22	7.33E-04	3.25E-02
Trim44	Tripartite Motif-Containing 44	0.40	1.32	7.40E-04	3.27E-02
Prmt8	Protein Arginine Methyltransferase 8	0.32	1.24	7.48E-04	3.29E-02
Caln1	Calneuron 1	0.49	1.41	7.51E-04	3.29E-02
Lhfpl4	Lipoma Hmgic Fusion Partner-Like 4	0.43	1.35	7.65E-04	3.33E-02
Ntmt1	N-Terminal Xaa-Pro-Lys N-Methyltransferase 1	-0.34	-1.27	7.63E-04	3.33E-02
Samd12	Sterile Alpha Motif Domain Containing 12	0.51	1.43	7.79E-04	3.37E-02
Rap2a	Ras Related Protein 2A	0.33	1.26	7.79E-04	3.37E-02
Has3	Hyaluronan Synthase 3	0.48	1.39	7.92E-04	3.42E-02
Mgat5	Mannosyl (Alpha-1,6-)-Glycoprotein Beta-1,6-N-Acetyl-Glucosaminyltransferase	0.45	1.37	8.01E-04	3.44E-02
Fut9	Fucosyltransferase 9	0.53	1.44	8.10E-04	3.45E-02
Sgip1	Sh3-Domain Grb2-Like (Endophilin) Interacting Protein 1	0.38	1.30	8.06E-04	3.45E-02
Purb	Purine Rich Element Binding Protein B	0.32	1.25	8.11E-04	3.45E-02
Hydin	Hydin, Axonemal Central Pair Apparatus Protein	-0.52	-1.43	8.22E-04	3.48E-02
RGD1561897	Similar To Serine/Threonine-Protein Kinase Kist (Kinase Interacting With Stathmin)	0.53	1.44	8.35E-04	3.53E-02
Kpna1	Karyopherin Subunit Alpha 1	0.25	1.19	8.44E-04	3.55E-02
Dnajc18	Dnaj Heat Shock Protein Family (Hsp40) Member C18	0.38	1.30	8.53E-04	3.58E-02
Pcdh10	Protocadherin 10	0.41	1.33	8.60E-04	3.59E-02
Nol9	Nucleolar Protein 9	0.38	1.30	8.67E-04	3.61E-02
Cnot1	Ccr4-Not Transcription Complex, Subunit 1	0.30	1.23	8.72E-04	3.62E-02
RGD1565611	Rgd1565611	-0.41	-1.33	8.77E-04	3.62E-02
Pdlim4	Pdz And Lim Domain 4	-0.48	-1.40	8.76E-04	3.62E-02
Nf1	Neurofibromin 1	0.45	1.37	9.03E-04	3.69E-02

Supplementary Table 2 (Continued)

Abhd2	Abhydrolase Domain Containing 2	0.42	1.34	9.00E-04	3.69E-02
Wdr66	Wd Repeat Domain 66	-0.51	-1.42	8.99E-04	3.69E-02
Klhl24	Kelch-Like Family Member 24	0.49	1.40	9.19E-04	3.70E-02
Dlg2	Discs Large Maguk Scaffold Protein 2	0.43	1.35	9.23E-04	3.70E-02
AABR07011697.1		0.39	1.31	9.23E-04	3.70E-02
G3bp2	G3Bp Stress Granule Assembly Factor 2	0.35	1.27	9.21E-04	3.70E-02
LOC108348250	Cullin-7	0.34	1.27	9.09E-04	3.70E-02
Sf3a3	Splicing Factor 3A, Subunit 3	-0.34	-1.27	9.26E-04	3.70E-02
Ezr	Ezrin	-0.51	-1.42	9.12E-04	3.70E-02
Ccser2	Coiled-Coil Serine-Rich Protein 2	0.43	1.35	9.82E-04	3.91E-02
Yipf6	Yip1 Domain Family, Member 6	0.35	1.28	9.89E-04	3.93E-02
Rab30	Rab30, Member Ras Oncogene Family	0.38	1.30	1.01E-03	3.97E-02
Lsm8	Lsm8 Homolog, U6 Small Nuclear Rna Associated	-0.43	-1.34	1.00E-03	3.97E-02
Cfap52	Cilia And Flagella Associated Protein 52	-0.51	-1.43	1.02E-03	4.00E-02
Cand1	Cullin-Associated And Neddylation-Dissociated 1	0.29	1.22	1.05E-03	4.13E-02
AABR07009715.1		0.46	1.37	1.06E-03	4.14E-02
AABR07019083.1		0.49	1.40	1.07E-03	4.16E-02
Cdk5r1	Cyclin-Dependent Kinase 5 Regulatory Subunit 1	0.40	1.32	1.08E-03	4.19E-02
Gmfb	Glia Maturation Factor, Beta	0.34	1.26	1.08E-03	4.19E-02
LOC100909954	Uncharacterized Loc100909954	0.40	1.32	1.09E-03	4.20E-02
Pde9a	Phosphodiesterase 9A	-0.43	-1.35	1.09E-03	4.20E-02
Disc1	Disrupted In Schizophrenia 1	0.39	1.31	1.12E-03	4.29E-02
Mdk	Midkine	-0.51	-1.43	1.12E-03	4.29E-02
Cabp7	Calcium Binding Protein 7	-0.52	-1.43	1.12E-03	4.29E-02
Enkur	Enkurin, Trpc Channel Interacting Protein	-0.51	-1.43	1.13E-03	4.29E-02
AABR07061755.1		0.50	1.41	1.16E-03	4.41E-02
Klf8	Kruppel-Like Factor 8	0.50	1.41	1.17E-03	4.42E-02
Grik3	Glutamate Ionotropic Receptor Kainate Type Subunit 3	0.50	1.41	1.18E-03	4.45E-02
St8sia3	St8 Alpha-N-Acetyl-Neuraminide Alpha-2,8-Sialyltransferase 3	0.44	1.36	1.19E-03	4.45E-02
Trove2	Trove Domain Family, Member 2	0.44	1.36	1.20E-03	4.49E-02
Chrm3	Cholinergic Receptor, Muscarinic 3	0.40	1.32	1.22E-03	4.56E-02
AABR07030603.1		0.48	1.40	1.23E-03	4.58E-02
Tmx3	Thioredoxin-Related Transmembrane Protein 3	0.33	1.26	1.23E-03	4.58E-02
Map3k2	Mitogen Activated Protein Kinase Kinase Kinase 2	0.48	1.39	1.26E-03	4.66E-02
Ift74	Intraflagellar Transport 74	-0.46	-1.37	1.28E-03	4.73E-02
Serinc1	Serine Incorporator 1	0.31	1.24	1.29E-03	4.75E-02
Bach2	Btb Domain And Cnc Homolog 2	0.47	1.38	1.32E-03	4.86E-02
Epm2aip1	Epm2A Interacting Protein 1	0.33	1.26	1.33E-03	4.87E-02
Psrc1	Proline And Serine Rich Coiled-Coil 1	-0.50	-1.42	1.35E-03	4.93E-02

Supplementary Table 2 (Continued)

Supplementary Table 2c: Significantly (padj ≤ 0.05) altered genes in 0.5 EE_2 ♀ vs. Vehicle ♀

Gene Symbol	Description	log2 Fold Change	Fold Change	p-value	padj
Adcy1	Adenylate Cyclase 1	1.01	2.01	6.45E-14	8.09E-10
Cds2	Cdp-Diacylglycerol Synthase 2	0.94	1.91	2.61E-13	1.64E-09
Xkr4	Xk Related 4	0.91	1.89	1.30E-12	5.42E-09
Zyg11b	Zyg-11 Family Member B, Cell Cycle Regulator	0.90	1.87	5.60E-12	1.76E-08
AABR07062799.2		0.86	1.81	2.38E-11	5.97E-08
Prkaa2	Protein Kinase Amp-Activated Catalytic Subunit Alpha 2	0.82	1.77	1.92E-10	3.44E-07
Pdpk1	3-Phosphoinositide Dependent Protein Kinase-1	0.74	1.67	1.76E-10	3.44E-07
Bmpr2	Bone Morphogenetic Protein Receptor Type 2	0.76	1.70	3.83E-10	6.00E-07
Psd3	Pleckstrin And Sec7 Domain Containing 3	0.75	1.68	1.19E-09	1.66E-06
Zfp704	Zinc Finger Protein 704	0.90	1.86	3.19E-09	2.86E-06
Cpeb3	Cytoplasmic Polyadenylation Element Binding Protein 3	0.85	1.81	3.42E-09	2.86E-06
Pgap1	Post-Gpi Attachment To Proteins 1	0.85	1.80	3.14E-09	2.86E-06
Dcbld2	Discoidin, Cub And Lccl Domain Containing 2	0.71	1.63	2.29E-09	2.86E-06
Slc35e2b	Solute Carrier Family 35, Member E2B	0.68	1.60	3.09E-09	2.86E-06
Pcgf3	Polycomb Group Ring Finger 3	0.62	1.54	3.25E-09	2.86E-06
Kcne2	Potassium Voltage-Gated Channel Subfamily E Regulatory Subunit 2	-0.88	-1.84	3.92E-09	3.07E-06
Zdhhc21	Zinc Finger, Dhhc-Type Containing 21	0.80	1.74	4.68E-09	3.46E-06
Fndc3b	Fibronectin Type Iii Domain Containing 3B	0.73	1.66	5.12E-09	3.57E-06
Pcdh19	Protocadherin 19	0.70	1.63	6.30E-09	4.16E-06
Ttbk2	Tau Tubulin Kinase 2	0.81	1.75	7.45E-09	4.68E-06
Slc1a2	Solute Carrier Family 1 Member 2	0.82	1.76	8.85E-09	4.72E-06
Mdm4	Mdm4, P53 Regulator	0.78	1.72	9.03E-09	4.72E-06
Birc6	Baculoviral Iap Repeat-Containing 6	0.75	1.68	8.47E-09	4.72E-06
41338	Membrane Associated Ring-Ch-Type Finger 6	0.62	1.53	8.40E-09	4.72E-06
Skil	Ski-Like Proto-Oncogene	0.76	1.70	1.04E-08	5.21E-06
Xpr1	Xenotropic And Polytropic Retrovirus Receptor 1	0.74	1.67	1.09E-08	5.26E-06
Pcdh7	Protocadherin 7	0.73	1.65	1.87E-08	8.67E-06
Zbtb41	Zinc Finger And Btb Domain Containing 41	0.76	1.69	2.15E-08	9.56E-06
Neurl1b	Neuralized E3 Ubiquitin Protein Ligase 1B	0.70	1.63	2.21E-08	9.56E-06
Nrxn1	Neurexin 1	0.56	1.47	2.36E-08	9.88E-06
Slc16a7	Solute Carrier Family 16 Member 7	0.76	1.70	2.74E-08	1.07E-05
Cpeb4	Cytoplasmic Polyadenylation Element Binding Protein 4	0.55	1.46	2.67E-08	1.07E-05
Wnk3	Wnk Lysine Deficient Protein Kinase 3	0.73	1.66	3.36E-08	1.28E-05
Gtf2f1	General Transcription Factor Iif Subunit 1	-0.53	-1.44	4.44E-08	1.64E-05
Arfgef3	Arfgef Family Member 3	0.80	1.74	6.87E-08	2.46E-05
Mecp2	Methyl Cpg Binding Protein 2	0.72	1.65	7.72E-08	2.62E-05
Mfhas1	Malignant Fibrous Histiocytoma Amplified Sequence 1	0.65	1.56	8.09E-08	2.62E-05
Pten	Phosphatase And Tensin Homolog	0.53	1.44	7.75E-08	2.62E-05
Rap2a	Ras Related Protein 2A	0.53	1.44	8.14E-08	2.62E-05
Itga4	Integrin Subunit Alpha 4	0.84	1.79	1.06E-07	3.27E-05
Lin7c	Lin-7 Homolog C, Crumbs Cell Polarity Complex Component	0.49	1.41	1.07E-07	3.27E-05
Megf9	Multiple Egf-Like-Domains 9	0.55	1.46	1.11E-07	3.33E-05
Pnma2	Paraneoplastic Ma Antigen 2	0.60	1.52	1.14E-07	3.34E-05
Sostdc1	Sclerostin Domain Containing 1	-0.80	-1.74	1.21E-07	3.45E-05
Fzd3	Frizzled Class Receptor 3	0.78	1.72	1.35E-07	3.76E-05
AABR07041411.1		0.83	1.78	1.48E-07	3.87E-05
Gpr26	G Protein-Coupled Receptor 26	0.75	1.68	1.45E-07	3.87E-05
Nr2c2	Nuclear Receptor Subfamily 2, Group C, Member 2	0.60	1.52	1.42E-07	3.87E-05
Csrnp3	Cysteine And Serine Rich Nuclear Protein 3	0.72	1.65	1.60E-07	4.08E-05
Rab3c	Rab3C, Member Ras Oncogene Family	0.77	1.70	2.43E-07	6.09E-05
Fut9	Fucosyltransferase 9	0.81	1.75	2.52E-07	6.20E-05
Slc9a7	Solute Carrier Family 9 Member A7	0.74	1.67	2.65E-07	6.39E-05
Cfap52	Cilia And Flagella Associated Protein 52	-0.80	-1.75	2.81E-07	6.66E-05

Supplementary Table 2 (Continued)

Zim1	Zinc Finger, Imprinted 1	0.77	1.71	3.11E-07	7.21E-05
Pcdh11x	Protocadherin 11 X-Linked	0.79	1.73	4.03E-07	9.03E-05
Gabrb2	Gamma-Aminobutyric Acid Type A Receptor Beta 2 Subunit	0.71	1.64	4.01E-07	9.03E-05
Pcnx4	Pecanex Homolog 4 (Drosophila)	0.43	1.35	4.14E-07	9.12E-05
Fsd1l	Fibronectin Type Iii And Spry Domain Containing 1-Like	0.72	1.65	4.31E-07	9.33E-05
Dok6	Docking Protein 6	0.67	1.59	4.40E-07	9.36E-05
Oprl1	Opioid Related Nociceptin Receptor 1	0.57	1.48	4.61E-07	9.63E-05
Nipa1	Non Imprinted In Prader-Willi/Angelman Syndrome 1	0.58	1.49	4.74E-07	9.75E-05
Ppm1h	Protein Phosphatase, Mg2+/Mn2+ Dependent, 1H	0.56	1.47	4.94E-07	1.00E-04
Ncam2	Neural Cell Adhesion Molecule 2	0.53	1.44	5.05E-07	1.01E-04
Pak3	P21 (Rac1) Activated Kinase 3	0.66	1.58	5.28E-07	1.04E-04
Flrt2	Fibronectin Leucine Rich Transmembrane Protein 2	0.72	1.65	5.44E-07	1.05E-04
Vcpip1	Valosin Containing Protein Interacting Protein 1	0.60	1.52	5.74E-07	1.09E-04
Nsd1	Nuclear Receptor Binding Set Domain Protein 1	0.62	1.53	6.15E-07	1.15E-04
Itgb8	Integrin Subunit Beta 8	0.71	1.64	6.93E-07	1.26E-04
Tnks	Tankyrase	0.56	1.47	6.94E-07	1.26E-04
Fem1b	Fem-1 Homolog B	0.61	1.53	7.40E-07	1.33E-04
Spef1	Sperm Flagellar 1	-0.63	-1.55	8.28E-07	1.46E-04
Erbb4	Erb-B2 Receptor Tyrosine Kinase 4	0.67	1.59	8.43E-07	1.47E-04
Selenoi	Selenoprotein I	0.47	1.38	8.53E-07	1.47E-04
Gprin3	Gprin Family Member 3	0.73	1.66	8.67E-07	1.47E-04
Stox2	Storkhead Box 2	0.70	1.63	8.79E-07	1.47E-04
Cmtm4	Cklf-Like Marvel Transmembrane Domain Containing 4	0.67	1.59	8.88E-07	1.47E-04
Lrrc8b	Leucine Rich Repeat Containing 8 Family, Member B	0.58	1.50	9.15E-07	1.49E-04
Dync1h1	Dynein Cytoplasmic 1 Heavy Chain 1	0.64	1.56	1.19E-06	1.91E-04
Cirbp	Cold Inducible Rna Binding Protein	-0.57	-1.48	1.24E-06	1.97E-04
Zfp871	Zinc Finger Protein 871	0.73	1.66	1.28E-06	2.01E-04
Htr1b	5-Hydroxytryptamine Receptor 1B	0.66	1.58	1.38E-06	2.14E-04
Slc38a1	Solute Carrier Family 38, Member 1	0.53	1.44	1.62E-06	2.48E-04
Mib1	Mindbomb E3 Ubiquitin Protein Ligase 1	0.58	1.50	1.65E-06	2.49E-04
Larp4b	La Ribonucleoprotein Domain Family, Member 4B	0.57	1.49	1.72E-06	2.57E-04
Tmem245	Transmembrane Protein 245	0.74	1.67	1.81E-06	2.59E-04
Cbl	Cbl Proto-Oncogene	0.71	1.64	1.82E-06	2.59E-04
Lmbrd2	Lmbr1 Domain Containing 2	0.62	1.53	1.78E-06	2.59E-04
Rmnd5a	Required For Meiotic Nuclear Division 5 Homolog A	0.57	1.48	1.80E-06	2.59E-04
Il6st	Interleukin 6 Signal Transducer	0.56	1.48	1.86E-06	2.59E-04
RGD1566359	Similar To Riken Cdna B230219D22	0.49	1.40	1.86E-06	2.59E-04
Ccdc113	Coiled-Coil Domain Containing 113	-0.74	-1.67	1.89E-06	2.60E-04
Hecw2	Hect, C2 And Ww Domain Containing E3 Ubiquitin Protein Ligase 2	0.69	1.61	1.94E-06	2.62E-04
Akap11	A-Kinase Anchoring Protein 11	0.43	1.35	1.94E-06	2.62E-04
Tmem170b	Transmembrane Protein 170B	0.64	1.56	2.05E-06	2.74E-04
Grm5	Glutamate Metabotropic Receptor 5	0.59	1.51	2.14E-06	2.83E-04
Cpeb2	Cytoplasmic Polyadenylation Element Binding Protein 2	0.62	1.53	2.46E-06	3.19E-04
Bicd1	Bicd Cargo Adaptor 1	0.58	1.49	2.44E-06	3.19E-04
Myo5a	Myosin Va	0.60	1.52	2.63E-06	3.37E-04
Ago2	Argonaute 2, Risc Catalytic Component	0.71	1.64	2.74E-06	3.47E-04
Gfod1	Glucose-Fructose Oxidoreductase Domain Containing 1	0.70	1.62	3.05E-06	3.82E-04
Atp8a1	Atpase Phospholipid Transporting 8A1	0.61	1.53	3.31E-06	4.11E-04
Slc8a1	Solute Carrier Family 8 Member A1	0.64	1.56	3.79E-06	4.67E-04
Ids	Iduronate 2-Sulfatase	0.53	1.44	4.09E-06	4.99E-04
Pank3	Pantothenate Kinase 3	0.45	1.37	4.28E-06	5.16E-04
AABR07073181.1		0.72	1.65	4.74E-06	5.57E-04
Tanc2	Tetratricopeptide Repeat, Ankyrin Repeat And Coiled-Coil Containing 2	0.64	1.56	4.75E-06	5.57E-04
Alg10	Alg10, Alpha-1,2-Glucosyltransferase	0.62	1.54	4.73E-06	5.57E-04
Man1a2	Mannosidase, Alpha, Class 1A, Member 2	0.50	1.42	5.12E-06	5.91E-04
Vstm2a	V-Set And Transmembrane Domain Containing 2A	0.44	1.36	5.14E-06	5.91E-04
Slitrk2	Slit And Ntrk-Like Family, Member 2	0.64	1.56	5.46E-06	6.22E-04

Supplementary Table 2 (Continued)

Nav1	Neuron Navigator 1	0.60	1.52	6.59E-06	7.45E-04
Cers6	Ceramide Synthase 6	0.66	1.58	6.67E-06	7.48E-04
Fgf14	Fibroblast Growth Factor 14	0.60	1.52	6.88E-06	7.57E-04
Csde1	Cold Shock Domain Containing E1	-0.57	-1.48	6.82E-06	7.57E-04
Klhl11	Kelch-Like Family Member 11	0.67	1.59	7.10E-06	7.75E-04
Igsf9b	Immunoglobulin Superfamily, Member 9B	0.71	1.63	7.69E-06	8.11E-04
Clvs2	Clavesin 2	0.56	1.48	7.68E-06	8.11E-04
Hmbox1	Homeobox Containing 1	0.55	1.46	7.50E-06	8.11E-04
Abi2	Abl-Interactor 2	0.39	1.31	7.63E-06	8.11E-04
Rnf152	Ring Finger Protein 152	0.60	1.52	7.86E-06	8.21E-04
Gnaq	G Protein Subunit Alpha Q	0.45	1.37	7.92E-06	8.22E-04
Lrrc58	Leucine Rich Repeat Containing 58	0.55	1.47	8.05E-06	8.28E-04
Fndc3a	Fibronectin Type Iii Domain Containing 3A	0.57	1.49	8.23E-06	8.40E-04
Uprt	Uracil Phosphoribosyltransferase Homolog	0.62	1.54	8.33E-06	8.43E-04
Gsk3b	Glycogen Synthase Kinase 3 Beta	0.51	1.42	8.83E-06	8.86E-04
Wdr63	Wd Repeat Domain 63	-0.61	-1.53	9.10E-06	9.06E-04
Zmat3	Zinc Finger, Matrin Type 3	0.63	1.54	9.33E-06	9.22E-04
Cpd	Carboxypeptidase D	0.55	1.46	1.07E-05	1.05E-03
Mfap3	Microfibrillar-Associated Protein 3	0.44	1.36	1.08E-05	1.05E-03
Nf1	Neurofibromin 1	0.60	1.51	1.11E-05	1.07E-03
AABR07019083.1		0.65	1.57	1.17E-05	1.11E-03
St8sia4	St8 Alpha-N-Acetyl-Neuraminide Alpha-2,8-Sialyltransferase 4	0.54	1.46	1.17E-05	1.11E-03
Plxna4	Plexin A4	0.64	1.56	1.21E-05	1.14E-03
Uhmk1	U2Af Homology Motif Kinase 1	0.66	1.59	1.28E-05	1.20E-03
Crk	Crk Proto-Oncogene, Adaptor Protein	0.40	1.32	1.30E-05	1.21E-03
Ppp1r9a	Protein Phosphatase 1, Regulatory Subunit 9A	0.58	1.50	1.38E-05	1.27E-03
Fam63b	Family With Sequence Similarity 63, Member B	0.54	1.45	1.40E-05	1.28E-03
Irs1	Insulin Receptor Substrate 1	0.63	1.54	1.60E-05	1.45E-03
Fxyd1	Fxyd Domain-Containing Ion Transport Regulator 1	-0.68	-1.61	1.60E-05	1.45E-03
Hipk2	Homeodomain Interacting Protein Kinase 2	0.65	1.57	1.65E-05	1.47E-03
Pcyox1	Prenylcysteine Oxidase 1	0.35	1.27	1.65E-05	1.47E-03
Raly	Raly Heterogeneous Nuclear Ribonucleoprotein	-0.42	-1.33	1.69E-05	1.50E-03
Sugp1	Surp And G Patch Domain Containing 1	-0.46	-1.37	1.72E-05	1.51E-03
Wdr60	Wd Repeat Domain 60	-0.52	-1.44	1.74E-05	1.52E-03
Mfap3l	Microfibrillar-Associated Protein 3-Like	0.60	1.52	1.77E-05	1.53E-03
Pdrg1	P53 And Dna Damage Regulated 1	-0.51	-1.43	1.77E-05	1.53E-03
Klf8	Kruppel-Like Factor 8	0.66	1.57	1.79E-05	1.53E-03
Cntrl	Centriolin	-0.68	-1.60	1.83E-05	1.55E-03
Clasrp	Clk4-Associating Serine/Arginine Rich Protein	-0.59	-1.51	1.97E-05	1.66E-03
Adam23	Adam Metallopeptidase Domain 23	0.47	1.38	1.99E-05	1.67E-03
Tmed8	Transmembrane P24 Trafficking Protein 8	0.61	1.52	2.06E-05	1.71E-03
Pcdha4	Protocadherin Alpha 4	0.55	1.46	2.17E-05	1.79E-03
Crim1	Cysteine Rich Transmembrane Bmp Regulator 1	0.56	1.47	2.22E-05	1.82E-03
Clcn3	Chloride Voltage-Gated Channel 3	0.38	1.30	2.27E-05	1.85E-03
Socs4	Suppressor Of Cytokine Signaling 4	0.66	1.58	2.31E-05	1.87E-03
Nes	Nestin	-0.63	-1.54	2.32E-05	1.87E-03
Lifr	Leukemia Inhibitory Factor Receptor Alpha	0.58	1.50	2.39E-05	1.87E-03
Avl9	Avl9 Cell Migration Associated	0.56	1.48	2.36E-05	1.87E-03
Nlgn3	Neuroligin 3	0.48	1.40	2.36E-05	1.87E-03
Tug1	Taurine Up-Regulated 1 (Non-Protein Coding)	0.44	1.36	2.39E-05	1.87E-03
NEWGENE_130556	Neuronal Tyrosine-Phosphorylated Phosphoinositide-3-Kinase Adaptor 2	0.64	1.55	2.47E-05	1.93E-03
Unc5d	Unc-5 Netrin Receptor D	0.61	1.53	2.52E-05	1.95E-03
Pym1	Pym Homolog 1, Exon Junction Complex Associated Factor	-0.52	-1.44	2.53E-05	1.95E-03
Rab11fip2	Rab11 Family Interacting Protein 2	0.50	1.42	2.69E-05	2.06E-03
Klhl24	Kelch-Like Family Member 24	0.62	1.54	2.74E-05	2.08E-03
Prkca	Protein Kinase C, Alpha	0.61	1.52	2.75E-05	2.08E-03
Ubr1	Ubiquitin Protein Ligase E3 Component N-Recognin 1	0.53	1.44	2.85E-05	2.14E-03

Supplementary Table 2 (Continued)

Kras	Kras Proto-Oncogene, Gtpase	0.45	1.36	2.92E-05	2.18E-03
Lyst	Lysosomal Trafficking Regulator	0.60	1.52	2.94E-05	2.18E-03
Smcr8	Smith-Magenis Syndrome Chromosome Region, Candidate 8	0.63	1.54	2.99E-05	2.21E-03
Snx13	Sorting Nexin 13	0.53	1.44	3.05E-05	2.23E-03
Plcl1	Phospholipase C-Like 1	0.49	1.41	3.06E-05	2.23E-03
Rfx3	Regulatory Factor X3	0.64	1.56	3.14E-05	2.24E-03
Extl3	Exostosin-Like Glycosyltransferase 3	0.53	1.45	3.13E-05	2.24E-03
Prkacb	Protein Kinase Camp-Activated Catalytic Subunit Beta	0.52	1.43	3.12E-05	2.24E-03
Lpgat1	Lysophosphatidylglycerol Acyltransferase 1	0.50	1.41	3.10E-05	2.24E-03
Ttc21a	Tetratricopeptide Repeat Domain 21A	-0.65	-1.56	3.48E-05	2.47E-03
Sh3bp5	Sh3-Domain Binding Protein 5	-0.35	-1.27	3.57E-05	2.52E-03
Ptbp3	Polypyrimidine Tract Binding Protein 3	0.54	1.46	3.71E-05	2.60E-03
Kcnq3	Potassium Voltage-Gated Channel Subfamily Q Member 3	0.58	1.49	3.82E-05	2.66E-03
Hecw1	Hect, C2 And Ww Domain Containing E3 Ubiquitin Protein Ligase 1	0.50	1.41	3.84E-05	2.66E-03
Timm44	Translocase Of Inner Mitochondrial Membrane 44	-0.42	-1.34	3.88E-05	2.67E-03
Sesn3	Sestrin 3	0.53	1.44	3.91E-05	2.68E-03
AABR07048211.1		0.64	1.55	4.04E-05	2.74E-03
Bach2	Btb Domain And Cnc Homolog 2	0.60	1.51	4.02E-05	2.74E-03
Abca5	Atp Binding Cassette Subfamily A Member 5	0.62	1.53	4.15E-05	2.77E-03
Zfp597	Zinc Finger Protein 597	0.54	1.45	4.14E-05	2.77E-03
Slitrk1	Slit And Ntrk-Like Family, Member 1	0.44	1.36	4.15E-05	2.77E-03
Sv2c	Synaptic Vesicle Glycoprotein 2C	0.65	1.57	4.18E-05	2.78E-03
Panx1	Pannexin 1	0.48	1.40	4.26E-05	2.82E-03
Arhgap5	Rho Gtpase Activating Protein 5	0.50	1.41	4.31E-05	2.83E-03
LOC102553088	Collagen Alpha-1(Xxv) Chain-Like	0.65	1.57	4.43E-05	2.90E-03
Chst15	Carbohydrate Sulfotransferase 15	0.59	1.50	4.50E-05	2.92E-03
Scfd1	Sec1 Family Domain Containing 1	-0.37	-1.29	4.52E-05	2.92E-03
Car2	Carbonic Anhydrase 2	-0.61	-1.52	4.57E-05	2.94E-03
Ate1	Arginyltransferase 1	0.43	1.35	4.72E-05	3.02E-03
Slc36a4	Solute Carrier Family 36 Member 4	0.61	1.52	4.77E-05	3.04E-03
Slc7a14	Solute Carrier Family 7, Member 14	0.62	1.53	4.92E-05	3.12E-03
Cacna1e	Calcium Voltage-Gated Channel Subunit Alpha1 E	0.56	1.48	5.00E-05	3.15E-03
Ranbp6	Ran Binding Protein 6	0.53	1.44	5.04E-05	3.15E-03
Clcn4	Chloride Voltage-Gated Channel 4	0.39	1.31	5.02E-05	3.15E-03
Scai	Suppressor Of Cancer Cell Invasion	0.60	1.52	5.19E-05	3.21E-03
Tspyl5	Tspy-Like 5	0.44	1.35	5.17E-05	3.21E-03
Amer1	Apc Membrane Recruitment Protein 1	0.62	1.53	5.25E-05	3.22E-03
Pde10a	Phosphodiesterase 10A	0.54	1.46	5.26E-05	3.22E-03
Unc5c	Unc-5 Netrin Receptor C	0.57	1.48	5.35E-05	3.26E-03
Gabrb1	Gamma-Aminobutyric Acid Type A Receptor Beta 1 Subunit	0.49	1.40	5.48E-05	3.31E-03
Rab30	Rab30, Member Ras Oncogene Family	0.47	1.38	5.49E-05	3.31E-03
Prdm11	Pr/Set Domain 11	0.60	1.52	5.59E-05	3.35E-03
Frmpd4	Ferm And Pdz Domain Containing 4	0.55	1.46	5.74E-05	3.41E-03
St6gal2	St6 Beta-Galactoside Alpha-2,6-Sialyltransferase 2	0.50	1.42	5.72E-05	3.41E-03
Mef2a	Myocyte Enhancer Factor 2A	0.46	1.37	5.83E-05	3.45E-03
Cnot1	Ccr4-Not Transcription Complex, Subunit 1	0.36	1.28	5.92E-05	3.48E-03
Syngr1	Synaptogyrin 1	0.49	1.40	5.96E-05	3.50E-03
Usp31	Ubiquitin Specific Peptidase 31	0.58	1.50	6.05E-05	3.53E-03
Tmem178b	Transmembrane Protein 178B	0.46	1.37	6.35E-05	3.66E-03
Gabrg1	Gamma-Aminobutyric Acid Type A Receptor Gamma 1 Subunit	0.40	1.32	6.36E-05	3.66E-03
Lrrc34	Leucine Rich Repeat Containing 34	-0.62	-1.54	6.32E-05	3.66E-03
AABR07046778.1		0.45	1.36	7.14E-05	4.09E-03
Braf	B-Raf Proto-Oncogene, Serine/Threonine Kinase	0.52	1.44	7.24E-05	4.13E-03
Pde9a	Phosphodiesterase 9A	-0.53	-1.44	7.39E-05	4.20E-03
Itga1	Integrin Subunit Alpha 1	0.59	1.50	7.70E-05	4.35E-03
Sart1	Squamous Cell Carcinoma Antigen Recognized By T Cells 1	-0.36	-1.28	7.77E-05	4.37E-03
Stam2	Signal Transducing Adaptor Molecule 2	0.46	1.37	7.88E-05	4.41E-03

Supplementary Table 2 (Continued)

Sh3pxd2a	Sh3 And Px Domains 2A	0.54	1.45	8.09E-05	4.51E-03
Cand1	Cullin-Associated And Neddylation-Dissociated 1	0.35	1.27	8.13E-05	4.52E-03
Ube3c	Ubiquitin Protein Ligase E3C	0.30	1.23	8.51E-05	4.70E-03
Dnajc18	Dnaj Heat Shock Protein Family (Hsp40) Member C18	0.45	1.36	8.60E-05	4.73E-03
Zbtb26	Zinc Finger And Btb Domain Containing 26	0.60	1.52	8.76E-05	4.80E-03
Mgat3	Mannosyl (Beta-1,4-)-Glycoprotein Beta-1,4-N-Acetylglucosaminyltransferase	0.40	1.32	9.00E-05	4.91E-03
Kctd20	Potassium Channel Tetramerization Domain Containing 20	0.48	1.40	9.40E-05	5.10E-03
Slco5a1	Solute Carrier Organic Anion Transporter Family, Member 5A1	0.61	1.53	9.67E-05	5.23E-03
Zbtb10	Zinc Finger And Btb Domain Containing 10	0.54	1.45	9.76E-05	5.26E-03
AABR07042077.1		0.51	1.42	9.84E-05	5.28E-03
Prkce	Protein Kinase C, Epsilon	0.49	1.41	1.01E-04	5.35E-03
Prpf19	Pre-Mrna Processing Factor 19	-0.31	-1.24	1.00E-04	5.35E-03
Selenot	Selenoprotein T	0.40	1.32	1.03E-04	5.47E-03
Cadm2	Cell Adhesion Molecule 2	0.49	1.40	1.07E-04	5.66E-03
Ubr3	Ubiquitin Protein Ligase E3 Component N-Recognin 3	0.45	1.37	1.08E-04	5.66E-03
Lrrtm2	Leucine Rich Repeat Transmembrane Neuronal 2	0.53	1.45	1.09E-04	5.71E-03
Dennd5b	Denn/Madd Domain Containing 5B	0.52	1.43	1.10E-04	5.72E-03
Samd8	Sterile Alpha Motif Domain Containing 8	0.29	1.22	1.11E-04	5.76E-03
Klhl9	Kelch-Like Family Member 9	0.44	1.35	1.12E-04	5.78E-03
Mmp16	Matrix Metallopeptidase 16	0.54	1.45	1.13E-04	5.80E-03
Sgip1	Sh3-Domain Grb2-Like (Endophilin) Interacting Protein 1	0.43	1.35	1.16E-04	5.96E-03
Mlf1	Myeloid Leukemia Factor 1	-0.59	-1.51	1.17E-04	5.97E-03
Soga1	Suppressor Of Glucose, Autophagy Associated 1	0.57	1.48	1.21E-04	6.12E-03
St8sia3	St8 Alpha-N-Acetyl-Neuraminide Alpha-2,8-Sialyltransferase 3	0.52	1.43	1.21E-04	6.12E-03
Dzank1	Double Zinc Ribbon And Ankyrin Repeat Domains 1	0.53	1.44	1.23E-04	6.19E-03
Glce	Glucuronic Acid Epimerase	0.45	1.37	1.25E-04	6.29E-03
Snrk	Snf Related Kinase	0.39	1.31	1.27E-04	6.35E-03
Gpr139	G Protein-Coupled Receptor 139	0.60	1.51	1.30E-04	6.46E-03
Slc4a7	Solute Carrier Family 4 Member 7	0.56	1.47	1.30E-04	6.46E-03
Krt8	Keratin 8	-0.41	-1.33	1.31E-04	6.47E-03
Tet1	Tet Methylcytosine Dioxygenase 1	0.60	1.52	1.42E-04	6.91E-03
Tcp11l1	T-Complex 11 Like 1	0.58	1.50	1.42E-04	6.91E-03
Pdpr	Pyruvate Dehydrogenase Phosphatase Regulatory Subunit	0.51	1.42	1.41E-04	6.91E-03
Sft2d1	Sft2 Domain Containing 1	-0.45	-1.36	1.42E-04	6.91E-03
RGD1561897	Similar To Serine/Threonine-Protein Kinase Kist (Kinase Interacting With Stathmin)	0.60	1.52	1.44E-04	6.96E-03
Jmy	Junction-Mediating And Regulatory Protein	0.50	1.41	1.47E-04	7.09E-03
Bend4	Ben Domain Containing 4	0.59	1.51	1.48E-04	7.12E-03
Cdh3	Cadherin 3	-0.49	-1.40	1.52E-04	7.26E-03
Fgd4	Fyve, Rhogef And Ph Domain Containing 4	0.56	1.47	1.53E-04	7.27E-03
Chn2	Chimerin 2	0.43	1.35	1.53E-04	7.27E-03
AABR07015346.1		-0.45	-1.37	1.52E-04	7.27E-03
Sh3pxd2b	Sh3 And Px Domains 2B	0.47	1.38	1.62E-04	7.65E-03
Zcchc14	Zinc Finger Cchc-Type Containing 14	0.53	1.45	1.68E-04	7.88E-03
Ikbkap	Inhibitor Of Kappa Light Polypeptide Gene Enhancer In B-Cells, Kinase Complex-Associated Protein	0.34	1.27	1.69E-04	7.91E-03
Igfbp2	Insulin-Like Growth Factor Binding Protein 2	-0.43	-1.35	1.70E-04	7.95E-03
Fstl5	Follistatin-Like 5	0.38	1.30	1.73E-04	8.04E-03
Pcdh1	Protocadherin 1	0.51	1.43	1.77E-04	8.18E-03
Ccser2	Coiled-Coil Serine-Rich Protein 2	0.49	1.40	1.81E-04	8.35E-03
Hcfc1	Host Cell Factor C1	0.53	1.44	1.82E-04	8.38E-03
Tmem151b	Transmembrane Protein 151B	0.41	1.32	1.86E-04	8.51E-03
Lamtor5	Late Endosomal/Lysosomal Adaptor, Mapk And Mtor Activator 5	-0.39	-1.31	1.87E-04	8.51E-03
Stxbp5l	Syntaxin Binding Protein 5-Like	0.56	1.48	1.88E-04	8.57E-03
RGD1565616	Rgd1565616	0.52	1.43	1.90E-04	8.58E-03

Supplementary Table 2 (Continued)

Tcerg1	Transcription Elongation Regulator 1	-0.39	-1.31	1.92E-04	8.67E-03
Plcxd2	Phosphatidylinositol-Specific Phospholipase C, X Domain Containing 2	0.48	1.39	1.96E-04	8.76E-03
Appl1	Adaptor Protein, Phosphotyrosine Interacting With Ph Domain And Leucine Zipper 1	0.38	1.30	1.95E-04	8.76E-03
Tmod2	Tropomodulin 2	0.41	1.32	1.99E-04	8.86E-03
Wdr66	Wd Repeat Domain 66	-0.57	-1.48	1.99E-04	8.86E-03
Urod	Uroporphyrinogen Decarboxylase	-0.48	-1.39	2.00E-04	8.88E-03
Gss	Glutathione Synthetase	-0.47	-1.39	2.02E-04	8.91E-03
Dnajc5	Dnaj Heat Shock Protein Family (Hsp40) Member C5	0.39	1.31	2.03E-04	8.92E-03
Sec23a	Sec23 Homolog A, Coat Complex Ii Component	0.35	1.27	2.03E-04	8.92E-03
Sox6	Sry Box 6	0.53	1.44	2.07E-04	9.05E-03
Chrna7	Cholinergic Receptor Nicotinic Alpha 7 Subunit	0.48	1.40	2.08E-04	9.05E-03
AABR07037528.1		0.56	1.48	2.08E-04	9.05E-03
Kcnj3	Potassium Voltage-Gated Channel Subfamily J Member 3	0.56	1.48	2.12E-04	9.16E-03
Disc1	Disrupted In Schizophrenia 1	0.44	1.36	2.12E-04	9.16E-03
Rsph10b	Radial Spoke Head 10 Homolog B	-0.59	-1.50	2.14E-04	9.20E-03
Taok1	Tao Kinase 1	0.52	1.44	2.17E-04	9.30E-03
Psen1	Presenilin 1	0.36	1.28	2.24E-04	9.55E-03
Chrm3	Cholinergic Receptor, Muscarinic 3	0.45	1.37	2.27E-04	9.64E-03
Tmx3	Thioredoxin-Related Transmembrane Protein 3	0.38	1.30	2.27E-04	9.64E-03
Sestd1	Sec14 And Spectrin Domain Containing 1	0.47	1.38	2.28E-04	9.64E-03
Pcnx1	Pecanex Homolog 1 (Drosophila)	0.44	1.36	2.31E-04	9.73E-03
Epg5	Ectopic P-Granules Autophagy Protein 5 Homolog	0.56	1.47	2.34E-04	9.77E-03
Yipf6	Yip1 Domain Family, Member 6	0.39	1.31	2.33E-04	9.77E-03
Slc4a1ap	Solute Carrier Family 4 Member 1 Adaptor Protein	-0.43	-1.34	2.34E-04	9.77E-03
Cox6b2	Cytochrome C Oxidase Subunit Vib Polypeptide 2	-0.50	-1.41	2.38E-04	9.90E-03
Kcns2	Potassium Voltage-Gated Channel, Modifier Subfamily S, Member 2	0.55	1.46	2.41E-04	9.99E-03
N4bp2	Nedd4 Binding Protein 2	0.49	1.41	2.45E-04	1.01E-02
Xiap	X-Linked Inhibitor Of Apoptosis	0.51	1.42	2.60E-04	1.07E-02
Anapc1	Anaphase Promoting Complex Subunit 1	0.40	1.32	2.61E-04	1.07E-02
Dgkh	Diacylglycerol Kinase, Eta	0.57	1.48	2.65E-04	1.08E-02
Serpinb1a	Serpin Family B Member 1A	-0.54	-1.45	2.69E-04	1.10E-02
Sod3	Superoxide Dismutase 3, Extracellular	-0.49	-1.40	2.72E-04	1.11E-02
Dchs1	Dachsous Cadherin-Related 1	0.43	1.35	2.75E-04	1.11E-02
Ccdc30	Coiled-Coil Domain Containing 30	-0.44	-1.36	2.76E-04	1.11E-02
RGD1306739	Similar To Riken Cdna 1700040L02	-0.57	-1.48	2.76E-04	1.11E-02
Swi5	Swi5 Homologous Recombination Repair Protein	-0.38	-1.30	2.79E-04	1.11E-02
Tulp4	Tubby Like Protein 4	0.51	1.42	2.80E-04	1.12E-02
Ak9	Adenylate Kinase 9	-0.51	-1.42	3.00E-04	1.19E-02
Gnl2	G Protein Nucleolar 2	-0.43	-1.35	3.10E-04	1.23E-02
Atp8a2	Atpase Phospholipid Transporting 8A2	0.51	1.43	3.16E-04	1.25E-02
Etnk1	Ethanolamine Kinase 1	0.35	1.27	3.17E-04	1.25E-02
Dnajb13	Dnaj Heat Shock Protein Family (Hsp40) Member B13	-0.54	-1.46	3.18E-04	1.25E-02
Ago1	Argonaute 1, Risc Catalytic Component	0.45	1.37	3.20E-04	1.25E-02
Lrp6	Ldl Receptor Related Protein 6	0.50	1.41	3.23E-04	1.26E-02
Rbbp6	Rb Binding Protein 6, Ubiquitin Ligase	-0.27	-1.20	3.27E-04	1.27E-02
Tmem56	Transmembrane Protein 56	0.47	1.39	3.31E-04	1.27E-02
Bace1	Beta-Secretase 1	0.38	1.30	3.30E-04	1.27E-02
Tbce	Tubulin Folding Cofactor E	-0.32	-1.25	3.31E-04	1.27E-02
B3galt1	Beta-1,3-Galactosyltransferase 1	0.47	1.39	3.35E-04	1.28E-02
Tbc1d24	Tbc1 Domain Family, Member 24	0.36	1.28	3.39E-04	1.30E-02
Lrp2	Ldl Receptor Related Protein 2	-0.53	-1.45	3.51E-04	1.34E-02
Mark3	Microtubule Affinity Regulating Kinase 3	-0.27	-1.21	3.60E-04	1.37E-02
Cfap70	Cilia And Flagella Associated Protein 70	-0.51	-1.42	3.61E-04	1.37E-02
Derl2	Derlin 2	0.39	1.31	3.63E-04	1.37E-02
Tnpo1	Transportin 1	0.39	1.31	3.65E-04	1.37E-02
Lonrf2	Lon Peptidase N-Terminal Domain And Ring Finger 2	0.43	1.35	3.67E-04	1.38E-02

Supplementary Table 2 (Continued)

Arpc3	Actin Related Protein 2/3 Complex, Subunit 3	-0.38	-1.30	3.70E-04	1.38E-02
Dnmt3a	Dna Methyltransferase 3 Alpha	0.48	1.39	3.79E-04	1.41E-02
Dock3	Dedicator Of Cyto-Kinesis 3	0.47	1.39	3.78E-04	1.41E-02
Adarb2	Adenosine Deaminase, Rna-Specific, B2	0.42	1.33	3.80E-04	1.41E-02
Bpgm	Bisphosphoglycerate Mutase	-0.36	-1.28	3.85E-04	1.42E-02
Lrig2	Leucine-Rich Repeats And Immunoglobulin-Like Domains 2	0.53	1.45	3.86E-04	1.42E-02
Phc3	Polyhomeotic Homolog 3	0.56	1.47	3.90E-04	1.43E-02
Samd12	Sterile Alpha Motif Domain Containing 12	0.54	1.45	3.92E-04	1.44E-02
Gabrg2	Gamma-Aminobutyric Acid Type A Receptor Gamma 2 Subunit	0.40	1.32	3.97E-04	1.45E-02
Epm2aip1	Epm2A Interacting Protein 1	0.36	1.29	3.97E-04	1.45E-02
Prkar2a	Protein Kinase Camp-Dependent Type 2 Regulatory Subunit Alpha	0.48	1.40	4.07E-04	1.48E-02
Pcdha2	Protocadherin Alpha 2	0.43	1.35	4.09E-04	1.48E-02
Ltn1	Listerin E3 Ubiquitin Protein Ligase 1	0.42	1.34	4.10E-04	1.48E-02
Arel1	Apoptosis Resistant E3 Ubiquitin Protein Ligase 1	0.34	1.27	4.07E-04	1.48E-02
Cnot6l	Ccr4-Not Transcription Complex, Subunit 6-Like	0.50	1.41	4.13E-04	1.49E-02
Frrs1l	Ferric-Chelate Reductase 1-Like	0.52	1.43	4.14E-04	1.49E-02
Prmt8	Protein Arginine Methyltransferase 8	0.33	1.26	4.16E-04	1.49E-02
Ncoa7	Nuclear Receptor Coactivator 7	0.43	1.34	4.18E-04	1.49E-02
Cbx6	Chromobox 6	0.39	1.31	4.20E-04	1.49E-02
Ccdc12	Coiled-Coil Domain Containing 12	-0.46	-1.38	4.25E-04	1.51E-02
Ppp1r36	Protein Phosphatase 1, Regulatory Subunit 36	-0.56	-1.47	4.26E-04	1.51E-02
Hs6st3	Heparan Sulfate 6-O-Sulfotransferase 3	0.54	1.45	4.29E-04	1.51E-02
Miga1	Mitoguardin 1	0.41	1.33	4.29E-04	1.51E-02
Nkrf	Nfkb Repressing Factor	0.52	1.44	4.36E-04	1.52E-02
Zfp428	Zinc Finger Protein 428	-0.39	-1.31	4.34E-04	1.52E-02
Tm9sf3	Transmembrane 9 Superfamily Member 3	0.39	1.31	4.45E-04	1.54E-02
Rbm19	Rna Binding Motif Protein 19	-0.48	-1.40	4.44E-04	1.54E-02
Usp9x	Ubiquitin Specific Peptidase 9, X-Linked	0.34	1.26	4.53E-04	1.57E-02
Cdyl2	Chromodomain Y-Like 2	0.54	1.45	4.60E-04	1.59E-02
Trove2	Trove Domain Family, Member 2	0.48	1.39	4.60E-04	1.59E-02
Elfn2	Extracellular Leucine-Rich Repeat And Fibronectin Type Iii Domain Containing 2	0.45	1.36	4.62E-04	1.59E-02
Mgat5	Mannosyl (Alpha-1,6-)-Glycoprotein Beta-1,6-N-Acetyl-Glucosaminyltransferase	0.47	1.38	4.73E-04	1.62E-02
Kcnj10	Potassium Inwardly-Rectifying Channel, Subfamily J, Member 10	0.54	1.45	4.80E-04	1.64E-02
Gabrb3	Gamma-Aminobutyric Acid Type A Receptor Beta 3 Subunit	0.42	1.33	4.80E-04	1.64E-02
Cep83	Centrosomal Protein 83	-0.51	-1.43	4.81E-04	1.64E-02
Iqub	Iq Motif And Ubiquitin Domain Containing	-0.55	-1.46	4.84E-04	1.64E-02
Hectd4	Hect Domain E3 Ubiquitin Protein Ligase 4	0.53	1.44	4.87E-04	1.64E-02
Fhad1	Forkhead Associated Phosphopeptide Binding Domain 1	-0.55	-1.47	4.86E-04	1.64E-02
Bag4	Bcl2-Associated Athanogene 4	0.40	1.32	4.90E-04	1.65E-02
Sec24a	Sec24 Homolog A, Copii Coat Complex Component	0.47	1.39	4.97E-04	1.67E-02
Paqr9	Progestin And Adipoq Receptor Family Member 9	0.51	1.43	5.06E-04	1.69E-02
Tub	Tubby Bipartite Transcription Factor	0.42	1.34	5.07E-04	1.69E-02
Anapc16	Anaphase Promoting Complex Subunit 16	-0.41	-1.33	5.09E-04	1.70E-02
Rn50_13_0829.4		0.40	1.32	5.14E-04	1.71E-02
Mob1b	Mob Kinase Activator 1B	0.49	1.41	5.24E-04	1.73E-02
Med12l	Mediator Complex Subunit 12-Like	0.54	1.45	5.25E-04	1.73E-02
Acads	Acyl-Coa Dehydrogenase, C-2 To C-3 Short Chain	-0.48	-1.40	5.30E-04	1.74E-02
Calml4	Calmodulin-Like 4	-0.49	-1.40	5.31E-04	1.74E-02
Ksr2	Kinase Suppressor Of Ras 2	0.53	1.45	5.38E-04	1.76E-02
Crtc2	Creb Regulated Transcription Coactivator 2	-0.52	-1.44	5.39E-04	1.76E-02
Hs6st2	Heparan Sulfate 6-O-Sulfotransferase 2	0.47	1.39	5.45E-04	1.77E-02
RGD1305938	Similar To Expressed Sequence Aw549877	0.36	1.29	5.44E-04	1.77E-02
Atf2	Activating Transcription Factor 2	0.37	1.29	5.51E-04	1.79E-02
AABR07025757.1		0.49	1.41	5.55E-04	1.79E-02

Supplementary Table 2 (Continued)

Coq7	Coenzyme Q7, Hydroxylase	-0.40	-1.32	5.56E-04	1.79E-02
Atp8a1	Atpase Phospholipid Transporting 8A1	0.55	1.46	5.61E-04	1.80E-02
Wdfy3	Wd Repeat And Fyve Domain Containing 3	0.52	1.44	5.61E-04	1.80E-02
Mafg	Maf Bzip Transcription Factor G	0.47	1.38	5.73E-04	1.83E-02
Cdk5r1	Cyclin-Dependent Kinase 5 Regulatory Subunit 1	0.42	1.34	5.78E-04	1.84E-02
Cfap126	Cilia And Flagella Associated Protein 126	-0.28	-1.21	5.81E-04	1.85E-02
Tacr1	Tachykinin Receptor 1	0.54	1.46	6.06E-04	1.92E-02
Dnajc8	Dnaj Heat Shock Protein Family (Hsp40) Member C8	-0.32	-1.25	6.08E-04	1.93E-02
Myl12b	Myosin Light Chain 12B	-0.33	-1.25	6.11E-04	1.93E-02
Gapvd1	Gtpase Activating Protein And Vps9 Domains 1	0.33	1.25	6.19E-04	1.95E-02
Lsm11	Lsm11, U7 Small Nuclear Rna Associated	0.48	1.39	6.21E-04	1.95E-02
Ezr	Ezrin	-0.52	-1.44	6.31E-04	1.98E-02
Rc3h1	Ring Finger And Ccch-Type Domains 1	0.48	1.40	6.37E-04	1.99E-02
Chrnb2	Cholinergic Receptor Nicotinic Beta 2 Subunit	0.44	1.35	6.37E-04	1.99E-02
Agps	Alkylglycerone Phosphate Synthase	0.48	1.39	6.39E-04	1.99E-02
Abr	Active Bcr-Related	0.28	1.22	6.57E-04	2.04E-02
G3bp2	G3Bp Stress Granule Assembly Factor 2	0.35	1.28	6.71E-04	2.08E-02
Ubxn7	Ubx Domain Protein 7	0.48	1.40	6.74E-04	2.08E-02
Snx30	Sorting Nexin Family Member 30	0.45	1.36	6.80E-04	2.09E-02
Fam8a1	Family With Sequence Similarity 8, Member A1	0.38	1.30	6.85E-04	2.11E-02
Fam160b1	Family With Sequence Similarity 160, Member B1	0.43	1.35	6.92E-04	2.12E-02
Ralgapb	Ral Gtpase Activating Protein Non-Catalytic Beta Subunit	0.29	1.22	6.96E-04	2.12E-02
Mrps25	Mitochondrial Ribosomal Protein S25	-0.40	-1.32	6.95E-04	2.12E-02
Stmn1	Stathmin 1	-0.34	-1.27	6.99E-04	2.13E-02
Gfpt1	Glutamine Fructose-6-Phosphate Transaminase 1	0.27	1.21	7.06E-04	2.15E-02
Upf3b	Upf3 Regulator Of Nonsense Transcripts Homolog B (Yeast)	-0.46	-1.37	7.10E-04	2.15E-02
Tekt1	Tektin 1	-0.53	-1.45	7.32E-04	2.21E-02
Clic4	Chloride Intracellular Channel 4	0.45	1.37	7.37E-04	2.22E-02
Hif1an	Hypoxia-Inducible Factor 1, Alpha Subunit Inhibitor	0.43	1.35	7.37E-04	2.22E-02
Mapk1	Mitogen Activated Protein Kinase 1	0.33	1.26	7.45E-04	2.24E-02
Arl5b	Adp-Ribosylation Factor Like Gtpase 5B	0.49	1.40	7.65E-04	2.29E-02
Fam107a	Family With Sequence Similarity 107, Member A	-0.53	-1.44	7.69E-04	2.30E-02
AABR07061755.1		0.51	1.43	7.71E-04	2.30E-02
Klf12	Kruppel-Like Factor 12	0.50	1.41	7.77E-04	2.31E-02
Isca2	Iron-Sulfur Cluster Assembly 2	-0.50	-1.41	7.87E-04	2.33E-02
Htr1a	5-Hydroxytryptamine Receptor 1A	0.53	1.44	7.92E-04	2.34E-02
Grm3	Glutamate Metabotropic Receptor 3	0.50	1.42	8.03E-04	2.34E-02
Dgki	Diacylglycerol Kinase, Iota	0.49	1.40	8.07E-04	2.34E-02
Mfsd8	Major Facilitator Superfamily Domain Containing 8	0.47	1.39	8.07E-04	2.34E-02
LOC100911248	Crk-Like Protein-Like	0.47	1.38	8.07E-04	2.34E-02
Grin3a	Glutamate Ionotropic Receptor Nmda Type Subunit 3A	0.45	1.37	8.04E-04	2.34E-02
Rabgap1l	Rab Gtpase Activating Protein 1-Like	0.41	1.33	8.00E-04	2.34E-02
Lrp1	Ldl Receptor Related Protein 1	0.35	1.27	8.02E-04	2.34E-02
Dnah6	Dynein, Axonemal, Heavy Chain 6	-0.51	-1.43	7.99E-04	2.34E-02
Ttc9	Tetratricopeptide Repeat Domain 9	0.30	1.23	8.20E-04	2.37E-02
Rufy1	Run And Fyve Domain Containing 1	-0.39	-1.31	8.20E-04	2.37E-02
Col9a3	Collagen Type Ix Alpha 3 Chain	-0.53	-1.44	8.20E-04	2.37E-02
Spag6l	Sperm Associated Antigen 6-Like	-0.48	-1.39	8.25E-04	2.37E-02
Rictor	Rptor Independent Companion Of Mtor, Complex 2	0.52	1.43	8.27E-04	2.37E-02
Lgr4	Leucine-Rich Repeat-Containing G Protein-Coupled Receptor 4	0.36	1.29	8.28E-04	2.37E-02
Phlpp2	Ph Domain And Leucine Rich Repeat Protein Phosphatase 2	0.50	1.41	8.34E-04	2.38E-02
Wasf3	Was Protein Family, Member 3	0.36	1.28	8.41E-04	2.39E-02
Spcs3	Signal Peptidase Complex Subunit 3	0.33	1.26	8.41E-04	2.39E-02
RGD1312005	Similar To Dd1	-0.35	-1.27	8.46E-04	2.40E-02
Col25a1	Collagen Type Xxv Alpha 1 Chain	0.53	1.44	8.53E-04	2.41E-02
Hsd11b1	Hydroxysteroid 11-Beta Dehydrogenase 1	-0.48	-1.39	8.51E-04	2.41E-02
AABR07071395.1		0.49	1.41	8.55E-04	2.41E-02
Rbfox2	Rna Binding Protein, Fox-1 Homolog 2	0.44	1.36	8.65E-04	2.43E-02

Supplementary Table 2 (Continued)

Pcdh9	Protocadherin 9	0.44	1.36	8.79E-04	2.46E-02
Wdr78	Wd Repeat Domain 78	-0.46	-1.38	8.79E-04	2.46E-02
Ss18l1	Ss18L1, Nbaf Chromatin Remodeling Complex Subunit	0.39	1.31	9.01E-04	2.52E-02
Spred1	Sprouty-Related, Evh1 Domain Containing 1	0.45	1.37	9.15E-04	2.55E-02
Lmbr1	Limb Development Membrane Protein 1	0.33	1.26	9.15E-04	2.55E-02
AABR07030521.1		-0.52	-1.44	9.20E-04	2.55E-02
Pias1	Protein Inhibitor Of Activated Stat, 1	0.45	1.36	9.23E-04	2.56E-02
Itgav	Integrin Subunit Alpha V	0.50	1.41	9.30E-04	2.57E-02
Mtpn	Myotrophin	0.32	1.25	9.37E-04	2.58E-02
Asb1	Ankyrin Repeat And Socs Box-Containing 1	0.40	1.32	9.40E-04	2.59E-02
Mgat4a	Mannosyl (Alpha-1,3-)-Glycoprotein Beta-1,4-N-Acetylglucosaminyltransferase, Isozyme A	0.47	1.39	9.53E-04	2.60E-02
Zbtb38	Zinc Finger And Btb Domain Containing 38	0.46	1.38	9.59E-04	2.60E-02
Phip	Pleckstrin Homology Domain Interacting Protein	0.46	1.37	9.58E-04	2.60E-02
Mmgt1	Membrane Magnesium Transporter 1	0.33	1.25	9.54E-04	2.60E-02
Atf6	Activating Transcription Factor 6	0.32	1.24	9.54E-04	2.60E-02
Rab14	Rab14, Member Ras Oncogene Family	0.30	1.23	9.58E-04	2.60E-02
Dpp10	Dipeptidylpeptidase 10	0.34	1.27	9.62E-04	2.61E-02
Mga	Mga, Max Dimerization Protein	0.48	1.40	9.66E-04	2.61E-02
Upf3a	Upf3 Regulator Of Nonsense Transcripts Homolog A (Yeast)	-0.38	-1.30	9.75E-04	2.63E-02
Fryl	Fry Like Transcription Coactivator	0.42	1.33	9.80E-04	2.63E-02
Csnk2a1	Casein Kinase 2 Alpha 1	0.32	1.25	9.80E-04	2.63E-02
Cbfa2t3	Cbfa2/Runx1 Translocation Partner 3	0.50	1.42	9.93E-04	2.66E-02
Shc3	Shc Adaptor Protein 3	0.49	1.41	9.99E-04	2.67E-02
RGD1306271	Similar To Kiaa1549 Protein	0.44	1.35	1.01E-03	2.70E-02
Bmpr1a	Bone Morphogenetic Protein Receptor Type 1A	0.34	1.27	1.01E-03	2.70E-02
AABR07031674.2		0.52	1.43	1.02E-03	2.70E-02
Ino80d	Ino80 Complex Subunit D	0.52	1.43	1.02E-03	2.70E-02
Mlxip	Mlx Interacting Protein	0.46	1.37	1.02E-03	2.70E-02
Kbtbd11	Kelch Repeat And Btb Domain Containing 11	0.45	1.36	1.02E-03	2.71E-02
Nceh1	Neutral Cholesterol Ester Hydrolase 1	0.48	1.40	1.03E-03	2.71E-02
Grin2b	Glutamate Ionotropic Receptor Nmda Type Subunit 2B	0.47	1.38	1.03E-03	2.71E-02
Rpf2	Ribosome Production Factor 2 Homolog	-0.42	-1.34	1.06E-03	2.79E-02
Tmem47	Transmembrane Protein 47	0.37	1.29	1.07E-03	2.79E-02
Creb1	Camp Responsive Element Binding Protein 1	0.52	1.43	1.08E-03	2.82E-02
Coa5	Cytochrome C Oxidase Assembly Factor 5	0.35	1.28	1.08E-03	2.82E-02
Stmn2	Stathmin 2	-0.29	-1.23	1.08E-03	2.82E-02
Kcnq2	Potassium Voltage-Gated Channel Subfamily Q Member 2	0.40	1.32	1.09E-03	2.84E-02
Cetn2	Centrin 2	-0.34	-1.27	1.10E-03	2.86E-02
Ddx27	Dead-Box Helicase 27	-0.38	-1.30	1.11E-03	2.87E-02
Map3k9	Mitogen-Activated Protein Kinase Kinase Kinase 9	0.41	1.33	1.12E-03	2.87E-02
Ephx1	Epoxide Hydrolase 1	-0.48	-1.39	1.12E-03	2.87E-02
Faxc	Failed Axon Connections Homolog	0.44	1.35	1.12E-03	2.89E-02
Dmxl1	Dmx-Like 1	0.46	1.37	1.13E-03	2.89E-02
Dnal1	Dynein, Axonemal, Light Chain 1	0.37	1.29	1.13E-03	2.90E-02
Pamr1	Peptidase Domain Containing Associated With Muscle Regeneration 1	0.50	1.41	1.13E-03	2.90E-02
Kdm5c	Lysine Demethylase 5C	0.38	1.30	1.14E-03	2.91E-02
Nol7	Nucleolar Protein 7	-0.33	-1.26	1.14E-03	2.91E-02
LOC100910838	Neuronal Tyrosine-Phosphorylated Phosphoinositide-3-Kinase Adapter 1-Like	-0.37	-1.30	1.17E-03	2.98E-02
AABR07043421.1		-0.32	-1.25	1.19E-03	3.02E-02
Nsmce4a	Nse4 Homolog A, Smc5-Smc6 Complex Component	-0.36	-1.28	1.19E-03	3.02E-02
Tjp3	Tight Junction Protein 3	-0.50	-1.42	1.20E-03	3.02E-02
Gpr63	G Protein-Coupled Receptor 63	0.51	1.43	1.21E-03	3.04E-02
Asb4	Ankyrin Repeat And Socs Box-Containing 4	-0.50	-1.41	1.21E-03	3.04E-02
Enah	Enabled Homolog (Drosophila)	0.36	1.28	1.21E-03	3.04E-02
Flrt1	Fibronectin Leucine Rich Transmembrane Protein 1	0.50	1.42	1.22E-03	3.05E-02
Wdr55	Wd Repeat Domain 55	-0.29	-1.22	1.23E-03	3.08E-02

Supplementary Table 2 (Continued)

Nynrin	Nyn Domain And Retroviral Integrase Containing	0.45	1.36	1.24E-03	3.08E-02
Kctd7	Potassium Channel Tetramerization Domain Containing 7	0.47	1.38	1.24E-03	3.09E-02
Exoc8	Exocyst Complex Component 8	0.38	1.30	1.24E-03	3.09E-02
Srgap1	Slit-Robo Rho Gtpase Activating Protein 1	0.45	1.37	1.26E-03	3.10E-02
Irgq	Immunity-Related Gtpase Q	0.43	1.35	1.26E-03	3.10E-02
Mturn	Maturin, Neural Progenitor Differentiation Regulator Homolog	0.37	1.29	1.26E-03	3.10E-02
Emc2	Er Membrane Protein Complex Subunit 2	-0.32	-1.25	1.26E-03	3.10E-02
Stum	Stum, Mechanosensory Transduction Mediator Homolog	0.48	1.39	1.27E-03	3.11E-02
Dock4	Dedicator Of Cytokinesis 4	0.43	1.35	1.27E-03	3.11E-02
Pcdh17	Protocadherin 17	0.48	1.40	1.28E-03	3.13E-02
Gucy1a2	Guanylate Cyclase 1 Soluble Subunit Alpha 2	0.47	1.39	1.29E-03	3.15E-02
Lamtor4	Late Endosomal/Lysosomal Adaptor, Mapk And Mtor Activator 4	-0.40	-1.32	1.29E-03	3.15E-02
Pde4d	Phosphodiesterase 4D	0.45	1.36	1.30E-03	3.16E-02
Lrrc46	Leucine Rich Repeat Containing 46	-0.48	-1.39	1.31E-03	3.18E-02
Abhd2	Abhydrolase Domain Containing 2	0.41	1.32	1.32E-03	3.21E-02
Gas7	Growth Arrest Specific 7	0.34	1.26	1.33E-03	3.21E-02
Hdac4	Histone Deacetylase 4	0.49	1.40	1.36E-03	3.29E-02
S100pbp	S100P Binding Protein	0.43	1.35	1.36E-03	3.29E-02
Rgs17	Regulator Of G-Protein Signaling 17	0.45	1.37	1.37E-03	3.30E-02
Dgke	Diacylglycerol Kinase Epsilon	0.35	1.28	1.39E-03	3.34E-02
Spin1	Spindlin 1	0.41	1.33	1.39E-03	3.35E-02
Tenm4	Teneurin Transmembrane Protein 4	0.47	1.38	1.41E-03	3.38E-02
Sema6a	Semaphorin 6A	0.37	1.29	1.41E-03	3.38E-02
Abcf1	Atp Binding Cassette Subfamily F Member 1	-0.28	-1.21	1.42E-03	3.38E-02
Pygo1	Pygopus Family Phd Finger 1	0.48	1.39	1.46E-03	3.48E-02
Kl	Klotho	-0.38	-1.30	1.49E-03	3.54E-02
Sstr1	Somatostatin Receptor 1	0.43	1.34	1.50E-03	3.56E-02
Ssh2	Slingshot Protein Phosphatase 2	0.42	1.34	1.51E-03	3.56E-02
Myl6	Myosin Light Chain 6	-0.36	-1.28	1.52E-03	3.60E-02
Eps15	Epidermal Growth Factor Receptor Pathway Substrate 15	0.38	1.30	1.53E-03	3.60E-02
Fat3	Fat Atypical Cadherin 3	0.50	1.42	1.55E-03	3.65E-02
Strn	Striatin	0.39	1.31	1.55E-03	3.65E-02
Arhgap35	Rho Gtpase Activating Protein 35	0.31	1.24	1.56E-03	3.66E-02
LOC108348250	Cullin-7	0.33	1.25	1.58E-03	3.68E-02
RGD1563812	Similar To Basic Transcription Factor 3	-0.39	-1.31	1.57E-03	3.68E-02
RGD1565611	Rgd1565611	-0.39	-1.31	1.58E-03	3.69E-02
Dnah12	Dynein, Axonemal, Heavy Chain 12	-0.43	-1.35	1.60E-03	3.72E-02
Pbx1	Pbx Homeobox 1	0.43	1.35	1.61E-03	3.75E-02
Clcn5	Chloride Voltage-Gated Channel 5	0.50	1.41	1.62E-03	3.76E-02
Yrdc	Yrdc N(6)-Threonylcarbamoyltransferase Domain Containing	-0.38	-1.30	1.63E-03	3.77E-02
Ppm1l	Protein Phosphatase, Mg2+/Mn2+ Dependent, 1L	0.29	1.22	1.65E-03	3.80E-02
Golga4	Golgin A4	-0.48	-1.39	1.66E-03	3.82E-02
Atrnl1	Attractin Like 1	0.41	1.33	1.66E-03	3.83E-02
Lrrc47	Leucine Rich Repeat Containing 47	-0.29	-1.22	1.67E-03	3.83E-02
LOC100910046	Zinc Finger Protein 60-Like	0.50	1.41	1.67E-03	3.83E-02
Pip4k2b	Phosphatidylinositol-5-Phosphate 4-Kinase Type 2 Beta	0.37	1.29	1.68E-03	3.86E-02
Tmtc1	Transmembrane And Tetratricopeptide Repeat Containing 1	0.49	1.41	1.70E-03	3.88E-02
Plxnc1	Plexin C1	0.43	1.35	1.70E-03	3.88E-02
Klhl28	Kelch-Like Family Member 28	0.47	1.39	1.71E-03	3.88E-02
Fbxo41	F-Box Protein 41	0.41	1.33	1.71E-03	3.88E-02
Plppr1	Phospholipid Phosphatase Related 1	0.27	1.20	1.71E-03	3.88E-02
Ptms	Parathymosin	-0.32	-1.24	1.71E-03	3.88E-02
Tpd52l2	Tumor Protein D52-Like 2	-0.35	-1.27	1.72E-03	3.88E-02
Adcy9	Adenylate Cyclase 9	0.49	1.41	1.75E-03	3.94E-02
Dip2a	Disco-Interacting Protein 2 Homolog A	0.36	1.28	1.74E-03	3.94E-02
Dpf3	Double Phd Fingers 3	0.50	1.41	1.76E-03	3.95E-02
Enpp2	Ectonucleotide Pyrophosphatase/Phosphodiesterase 2	-0.48	-1.39	1.76E-03	3.95E-02

Supplementary Table 2 (Continued)

Acvr2b	Activin A Receptor Type 2B	0.49	1.41	1.77E-03	3.97E-02
Ldoc1l	Leucine Zipper, Down-Regulated In Cancer 1-Like	0.43	1.35	1.78E-03	3.97E-02
Tceal3	Transcription Elongation Factor A Like 3	-0.43	-1.35	1.78E-03	3.97E-02
Eci1	Enoyl-Coa Delta Isomerase 1	-0.45	-1.37	1.78E-03	3.97E-02
Ireb2	Iron Responsive Element Binding Protein 2	0.36	1.28	1.79E-03	3.99E-02
Ctnnbl1	Catenin, Beta Like 1	-0.38	-1.30	1.81E-03	4.01E-02
Xrn1	5'-3' Exoribonuclease 1	0.42	1.34	1.81E-03	4.02E-02
Dck	Deoxycytidine Kinase	0.42	1.34	1.85E-03	4.09E-02
Zfp148	Zinc Finger Protein 148	0.35	1.27	1.86E-03	4.10E-02
Psmd12	Proteasome 26S Subunit, Non-Atpase 12	-0.27	-1.21	1.86E-03	4.10E-02
Chmp4bl1	Chromatin Modifying Protein 4B-Like 1	-0.32	-1.24	1.85E-03	4.10E-02
Snw1	Snw Domain Containing 1	-0.33	-1.26	1.86E-03	4.10E-02
Pdp2	Pyruvate Dehyrogenase Phosphatase Catalytic Subunit 2	0.46	1.37	1.87E-03	4.10E-02
Dlg2	Discs Large Maguk Scaffold Protein 2	0.40	1.32	1.89E-03	4.14E-02
Dtx3	Deltex E3 Ubiquitin Ligase 3	-0.30	-1.23	1.91E-03	4.18E-02
Hipk3	Homeodomain Interacting Protein Kinase 3	0.48	1.40	1.92E-03	4.19E-02
Paqr8	Progestin And Adipoq Receptor Family Member 8	0.48	1.39	1.94E-03	4.22E-02
Zfp319	Zinc Finger Protein 319	0.37	1.29	1.94E-03	4.22E-02
Naxd	Nad(P)Hx Dehydratase	-0.34	-1.27	1.95E-03	4.24E-02
Lrp1b	Ldl Receptor Related Protein 1B	0.48	1.39	1.96E-03	4.25E-02
Spock2	Sparc/Osteonectin, Cwcv And Kazal Like Domains Proteoglycan 2	0.32	1.24	1.98E-03	4.28E-02
Slc35e1	Solute Carrier Family 35, Member E1	0.39	1.31	2.01E-03	4.33E-02
Sidt2	Sid1 Transmembrane Family, Member 2	0.35	1.27	2.01E-03	4.33E-02
Sema3a	Semaphorin 3A	0.47	1.39	2.02E-03	4.34E-02
LOC100912373	Uncharacterized Loc100912373	-0.47	-1.39	2.03E-03	4.36E-02
Zbtb37	Zinc Finger And Btb Domain Containing 37	0.47	1.38	2.05E-03	4.38E-02
P2rx6	Purinergic Receptor P2X 6	-0.35	-1.27	2.05E-03	4.38E-02
Tchp	Trichoplein, Keratin Filament Binding	-0.46	-1.37	2.05E-03	4.38E-02
Med13	Mediator Complex Subunit 13	0.37	1.29	2.06E-03	4.39E-02
Zfp451	Zinc Finger Protein 451	0.36	1.28	2.06E-03	4.39E-02
Prr36	Proline Rich 36	0.38	1.30	2.09E-03	4.44E-02
Cc2d1b	Coiled-Coil And C2 Domain Containing 1B	-0.46	-1.37	2.09E-03	4.45E-02
Nrxn3	Neurexin 3	0.43	1.35	2.10E-03	4.45E-02
Kcnh7	Potassium Voltage-Gated Channel Subfamily H Member 7	0.42	1.34	2.11E-03	4.47E-02
Mrpl54	Mitochondrial Ribosomal Protein L54	-0.36	-1.28	2.11E-03	4.47E-02
Mmd	Monocyte To Macrophage Differentiation-Associated	0.28	1.22	2.12E-03	4.47E-02
Ubb	Ubiquitin B	-0.28	-1.22	2.12E-03	4.47E-02
Zswim6	Zinc Finger, Swim-Type Containing 6	0.39	1.31	2.17E-03	4.56E-02
LOC500877	Ab1-152	-0.45	-1.37	2.17E-03	4.56E-02
Vps13a	Vacuolar Protein Sorting 13A	0.45	1.37	2.18E-03	4.57E-02
Slc30a7	Solute Carrier Family 30 Member 7	0.39	1.31	2.19E-03	4.58E-02
Atp2b4	Atpase Plasma Membrane Ca2+ Transporting 4	0.45	1.36	2.21E-03	4.58E-02
Elavl2	Elav Like Rna Binding Protein 2	0.32	1.25	2.20E-03	4.58E-02
Mpp6	Membrane Palmitoylated Protein 6	0.32	1.25	2.21E-03	4.58E-02
Clic6	Chloride Intracellular Channel 6	-0.21	-1.16	2.21E-03	4.58E-02
Drc1	Dynein Regulatory Complex Subunit 1	-0.48	-1.40	2.20E-03	4.58E-02
Enkur	Enkurin, Trpc Channel Interacting Protein	-0.48	-1.40	2.21E-03	4.58E-02
Slc6a5	Solute Carrier Family 6 Member 5	0.48	1.40	2.25E-03	4.60E-02
Otud4	Otu Deubiquitinase 4	0.47	1.38	2.26E-03	4.60E-02
Nebl	Nebulette	0.46	1.37	2.26E-03	4.60E-02
Gatsl2	Gats Protein-Like 2	0.45	1.36	2.26E-03	4.60E-02
Kcnk10	Potassium Two Pore Domain Channel Subfamily K Member 10	0.38	1.30	2.25E-03	4.60E-02
LOC100909954	Uncharacterized Loc100909954	0.37	1.29	2.27E-03	4.60E-02
Psip1	Pc4 And Sfrs1 Interacting Protein 1	-0.27	-1.21	2.25E-03	4.60E-02
Hdgfrp2	Hepatoma-Derived Growth Factor-Related Protein 2	-0.31	-1.24	2.27E-03	4.60E-02
Brd7	Bromodomain Containing 7	-0.34	-1.26	2.26E-03	4.60E-02
Ttc27	Tetratricopeptide Repeat Domain 27	-0.35	-1.27	2.24E-03	4.60E-02

Supplementary Table 2 (Continued)

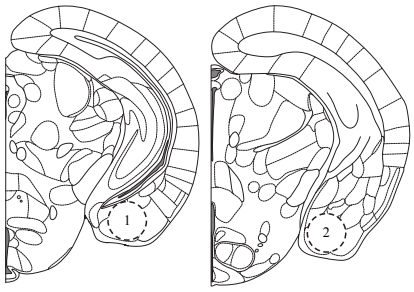
Ppie	Peptidylprolyl Isomerase E	-0.42	-1.33	2.24E-03	4.60E-02
Catip	Ciliogenesis Associated Ttc17 Interacting Protein	-0.47	-1.38	2.25E-03	4.60E-02
Ube2j1	Ubiquitin-Conjugating Enzyme E2, J1	0.32	1.25	2.28E-03	4.62E-02
Slc35a3	Solute Carrier Family 35 Member A3	0.35	1.28	2.30E-03	4.66E-02
Jade1	Jade Family Phd Finger 1	0.35	1.27	2.31E-03	4.67E-02
F5	Coagulation Factor V	-0.34	-1.26	2.33E-03	4.70E-02
Rnf169	Ring Finger Protein 169	0.48	1.39	2.38E-03	4.78E-02
Tbc1d30	Tbc1 Domain Family, Member 30	0.38	1.31	2.38E-03	4.78E-02
Msl1	Male Specific Lethal 1 Homolog	0.27	1.20	2.40E-03	4.81E-02
Cldn2	Claudin 2	-0.21	-1.16	2.43E-03	4.87E-02
Brinp2	Bmp/Retinoic Acid Inducible Neural Specific 2	0.43	1.34	2.44E-03	4.89E-02
Ttc33	Tetratricopeptide Repeat Domain 33	0.36	1.29	2.45E-03	4.90E-02
B3galt6	Beta-1,3-Galactosyltransferase 6	0.37	1.29	2.49E-03	4.96E-02
Psmc2	Proteasome 26S Subunit, Atpase 2	-0.33	-1.26	2.49E-03	4.96E-02
Ipp	Intracisternal A Particle-Promoted Polypeptide	0.36	1.28	2.50E-03	4.97E-02

Supplementary Table 3. Significant (adjusted p-value ≤ 0.05) sex-differences in gene expression identified by RNAseq (female vehicle compared to male vehicle)

Gene Symbol	Description	log2 Fold Change	Fold Change	p-value	padj
Eif2s3y	Eukaryotic Translation Initiation Factor 2, Subunit 3, Structural Gene Y-Linked	-3.49	-11.27	3.38E-196	4.12E-192
Kdm5d	Lysine Demethylase 5D	-2.53	-5.77	6.61E-100	4.03E-96
Ddx3	Dead (Asp-Glu-Ala-Asp) Box Polypeptide 3	-1.92	-3.79	5.94E-60	2.42E-56
Rn60_Y_0001.2	Pseudogene	-0.98	-1.98	3.78E-19	1.15E-15
Eif2s3	Eukaryotic Translation Initiation Factor 2 Subunit Gamma	0.51	1.43	2.40E-07	5.86E-04
Cabp7	Calcium Binding Protein 7	0.53	1.45	6.35E-06	1.29E-02
Wdr66	Wd Repeat Domain 66	0.51	1.43	9.51E-06	1.66E-02
Mlf1	Myeloid Leukemia Factor 1	0.50	1.42	1.80E-05	2.75E-02
Lrrc34	Leucine Rich Repeat Containing 34	0.49	1.40	3.61E-05	4.90E-02

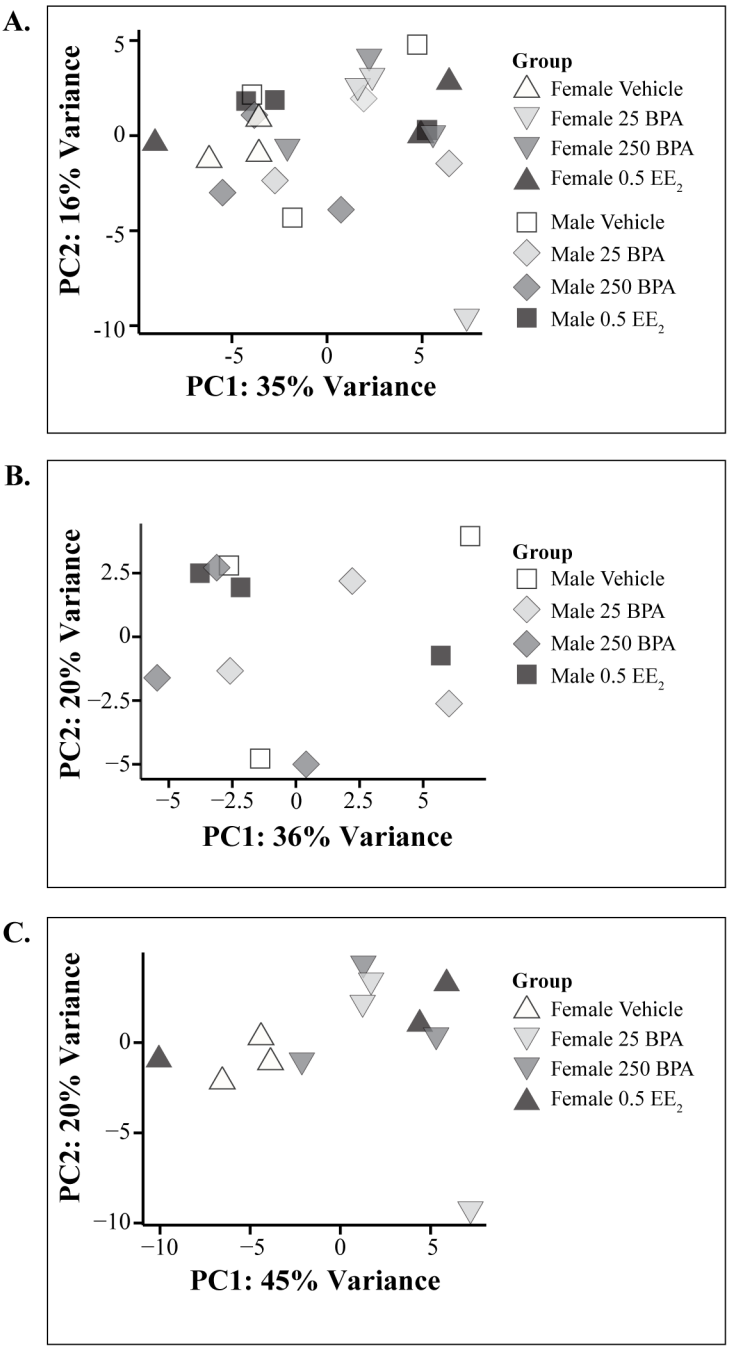
Supplementary Figures

Supplementary Figure 1. Anatomical representation of regions extracted via micropunch



Supplementary Fig. 1: Anatomical representation of regions extracted via micropunch (obtained by approaching the regions of interest caudally and punching rostrally). For each animal, one pair of bilateral caudal (1) and one pair of bilateral rostral (2) punches were made, each 1.00 mm in depth and 1.00 mm in diameter. All four punches, which collectively comprised the entire amygdala, were combined prior to RNA extraction.

Supplementary Figure 2. Unsupervised principal component analyses (PCA) for RNAseq data



Supplementary Fig. 2: Unsupervised Principal Component Analyses (PCA) for RNASeq Data. Two-dimensional representation of the first two principal components of all datasets (A), male datasets (B), and female datasets (C). Clustering by exposure was strongest in females.