Maternal PCB Exposure Reprogrammed the Drug-processing Transcriptome of Testis in Mouse Offspring Over a Time Course

Elijah M Jung

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Science

University of Washington

2023

Committee:

Julia Yue Cui

Elaine M Faustman

Program Authorized to Offer Degree:

Department of Environmental and Occupational Health Sciences

University of Washington

Abstract

Maternal PCB Exposure Reprogrammed the Drug-processing Transcriptome of Testis in Mouse Offspring Over a Time Course

Elijah M Jung

Chair of the Supervisory Committee:

Julia Yue Cui

Department of Environmental and Occupational Health Sciences

Polychlorinated Biphenyls (PCBs) are persistent environmental contaminants that pose a significant public health risk including reproductive toxicity partly because they are endocrine disruptors. The lipophilic nature of PCBs increases the risk of developmental exposure due to placenta and breast milk transfer. While liver is the major site for PCB metabolism, testis is known to express various drug-metabolizing enzymes, transporters, and transcription factors including nuclear receptors (together called drug-processing genes) that may serve as additional defense system. However, very little is known regarding the developmental regulation of the testicular drug-processing genes by maternal PCB exposure. Therefore, the goal of this study was to determine how maternal PCB exposure regulate drug-processing genes in testis of pups over a time course. Dams were orally exposed to the Fox River PCB mixture via peanut butter/oil at 0.1 mg/kg or 1 mg/kg body weight, or vehicle, throughout pregnancy and lactation period. RNA-Seq was conducted in testis of pups at postnatal day (PND) 28 and PND 35 (n=3/exposure group). Genes involved in spermatogenesis were differentially regulated by PCBs at both doses and at both ages. The PCB-mediated transcriptome response was weakened over time, with more dysregulated genes observed at PND 28 than PND 35. At PND 28, most of the differentially

regulated drug-processing genes were up-regulated by maternal PCB exposure in a dose-response manner. This was associated with a dose-dependent increase in the mRNA expression of estrogen receptor beta (Esr2) and aryl hydrocarbon receptor. At PND 35, the PCB dose-response pattern was less prevalent. In conclusion, maternal exposure to the Fox River PCB mixture dose-dependently up-regulated various drug-processing genes in testis of the mouse offspring, but its effect appeared to be weakened over time.

Table of Contents

INTRODUCTION

Maternal exposure to various environmental toxicants is a significant route of exposure for the developing testis in male pups and may lead to compromised capacity of chemical detoxification and delayed onset of reproductive diseases later in life (Henriksen *et al.*, 2023). Therefore, it is important to unveil the developmental regulatory patterns of important testicular drug-processing genes, including various phase-I and -II drug metabolizing enzymes and transporters. The goal of this study is to determine the developmental reprogramming of the drug-processing genes by maternal exposure to a class of human health relevant persistent organic pollutants, namely polychlorinated biphenyls (PCBs) in testis of male pups over a time course.

I. PCBs

Environmental contamination of PCBs (polychlorinated biphenyls) is a significant public health concern and their bioaccumulation along the food chain can have detrimental effects on human health and the ecosystem. Human exposures can occur through dietary consumption via freshwater fish species and in some Indigenous population, through eating whale meat
Tee *et al*., 2003; Weintraub and Birnbaum, 2008). Consumption of fish contaminated with fish has been observed with ranges as low as 0.4 ng/g to 1.8 ng/g, whereas consumption of whale meat ranging as high as 10,000 ng/g (Chukmasov *et al*., 2019; Xue *et al.*, 2014). Most notably, cetaceans, dolphins and whales, are highly exposed to PCBs due to the lipophilic nature of PCBs and the cetacean's proximity near human sources (Jepson *et al*., 2016; Andvik *et al*., 2021). PCB metabolism is dependent on chlorine substituents (Kania-Korwel and Lehmler, 2016). Mice studies have shown a relatively wide range of half-lives, being as short as 0.54 days to 15.8 days for female mice (Kania-Korwel and Lehmler, 2016). Among human studies, these values can range from 6-7 months to 33-34 months for more chlorinated compounds (Steele *et al.*, 1986). Children observations of PCBs half-lives range from 3-9 years depending on the chlorination, indicating similar half-life to adults. Data on testicular damage have been mixed. Human exposure studies have been consistent with the relationship between PCB exposure and reduced

sperm motility across varying levels of exposures ranging from 0.31 ng/g to 2.3 ng/g (Meeker and Hauser, 2010; Dallinga *et al*., 2002; Bush *et al*., 1986). Developmental toxicity of PCBs have been of particular concern due to high reading of PCBs in placental materials (Pocar *et al*., 2012; Guvenius *et al*., 2003). Outside of placental exposure, infants can be exposed to PCBs from breast milk with studies from monkeys deriving an minimal risk level (MRL) of 0.02 mg/kg/day (Safe, 1990, PCB CONTAMINATED SEDIMENT IN THE LOWER FOX RIVER AND GREEN BAY, n.d.; *ATSDR's Toxicological Profiles: Web Version*, 2002). Studies on lactating mothers found significant correlation between lactational PCB exposure and infant development resulting in decreased head circumference and weight within the first six months (Ellsworth *et al*., 2020; Lancz *et al*., 2015). The range of exposure observed in these studies was 41.5 to 365.1 ng/mL and included PCB congeners 132, 138, 153, 163, and 180. The present study utilized a PCB mixture that mimics the PCB contamination in the Fox River. Between 1950s and 1960s, paper mills in the Lower Fox River incorporated polychlorinated biphenyls (FOX RIVER NRDA/PCB RELEASES Site Profile, n.d.). Over 270,000 people in the river system were potentially exposed to the compound due to contamination of sediment and fish, followed by bio-magnification along the food chain (FOX RIVER NRDA/PCB RELEASES Site Profile, n.d.). One of the biggest concerns of contamination to human population in the area is notable fishing activities (PCB CONTAMINATED SEDIMENT IN THE LOWER FOX RIVER AND GREEN BAY, n.d.). The formulation of PCBs found in the specific Fox River has been approximated to contain 35% of Aroclor 1242, 35% of Aroclor 1248, 15% of Aroclor 1254, and 15% of Aroclor 1260 (Kostyniak *et al*., 2005). Pregnant women and children in particular are sensitive to the effects of PCBs, marking the consumption of contaminated fish of high concern to the population living near the Fox River (PCB CONTAMINATED SEDIMENT IN THE LOWER FOX RIVER AND GREEN BAY, n.d.).

PCBs are known reproductive toxicants (Carlsen *et al*., 1992; Swan *et al*., 2000; Travison *et al*., 2007; Andersson *et al*., 2007; Paulozzi, 1999; Huyghe *et al*., 2003; Andersen *et al*., 2000).

Difficulties arise when studying reproductive pathways due to their unique late stage developmental period during puberty resulting in developmental exposure apparent after puberty (Pocar *et al.*, 2012; Heindel *et al.*, 2017). There is evidence from both *in vitro* and *in vivo* studies suggesting that PCBs directly impact testicular development. The reported reproductive effects of PCB exposure include an increased anogenital distance, increased prostate size, and decreased epididymal weight at 50 ng/g (Gupta, 2000). PCB-exposed rat offspring had smaller testes, epididymides, and seminal vesicles, and they also had decreased numbers of sperm and spermatid as well as impaired daily sperm production exposed to 275 ug/kg body weight of PCB 118 (Kuriyama and Chahoud, 2004). PCB-exposed adult male rats had a decrease in the cauda epididymal weight, epididymal sperm count, and motile epididymal sperm count. The spermatozoa of PCB 132–exposed offspring produced higher levels of reactive oxygen species (ROS) than the control group. In the 1 mg/kg dose group, p53, a tumor suppressant gene, was induced, and caspase 3 was inhibited. While in the 10 mg/kg dose group, activation of caspases 3 and 9 was increased. In addition, the expression of other tumor suppressing genes such as Fas, Bax, bcl-2, and p53 were down-regulated (Hsu *et al.*, 2007). Germ cell proliferation was inhibited and the apoptosis of the germ cell was induced in a dose-dependent manner after exposure to Aroclor 1254 ranging from 0.5 to 500 ug/kg (Cai *et al.*, 2011). PCB 153 affect neonatal Sertoli and gonocyte cells (precursor germ cells). ROS and cytoskeleton changes were found for both while PCB 153 produced apoptosis (Zhang *et al.*, 2013).

II. Testis

Reproductive toxicity may have long-lasting effects from behavioral changes to physical malformities (European Agency for Safety and Health at Work, 2016). The male testicular organ is essential for two major functions: spermatogenesis (creation of germ cells) and as part of the endocrine system producing steroid hormones (Soloyan *et al.*, 2019). The internal structure of the testis contains seminiferous tubules, coiled tubes contained within the scrotum. Three major cell types are observed in testicular cells consisting of Sertoli cell secreting inhibin, Leydig cells

associated with androgen production, and germ cells that develop sperm cells (Soloyan *et al.*, 2019).

III. Drug-processing genes

III-1. Phase-I and -II Drug-Metabolizing Enzymes

Exogenous and endogenous substances can be bio-transformed in the body through several metabolic processes traditionally associated with the liver and intestines (Döring and Petzinger, 2014, p. 0). Phase-I enzymes are associated with one of three reactions, oxidation, reduction, and hydrolysis to assist the absorption of compounds within the tissues (Phang-Lyn and Llerena, 2022). Phase-II enzymes are associated with a wider variety of reactions namely, methylation, glucuronidation, acetylation, sulfation, adding charged species to allow excretion of endogenous compounds. Compared to phase-I enzymes, the resulting reaction is typically less active. Research have tied phase-II reactions catalyzing phase-I reactions resulting in closer ties between the two biotransformation (Zhang, 2011). It is our goal to determine how testicular drug-processing genes are developmentally reprogrammed following maternal PCB exposure over a time course.

III-2. Transporters

Transporters membrane proteins are some of the largest family of membrane protein essential for the their role in the shuffling of xenobiotics and endogenous molecules(Liang *et al.*, 2015). Current research has focused on transporters as important targets for drug development (Liang *et al.*, 2015). Two families of transporters are of particular concern, namely the ATP binding cassette (ABC) and solute carrier (SLC) transporters. ABC family of transporters are efflux transporters, while SLC family of transporters are involved in either uptake or efflux of chemicals depending on the specific SLC family members(Stieger and Gao, 2015). ABC transporters are active transporters utilizing ATP with 48 members categorized into seven families in humans (Chaves *et al*., 2014). Often, these transporters are responsible for the efflux of drugs and other xenobiotics (Strazielle and Ghersi-Egea, 2015). SLC transporters have a variety of

transport mechanisms consisting of 395 individual human genes (Morris *et al.*, 2017). These families of transporters expressed in various tissues and known for transporting a number of organic ions/cations, peptides, drugs, drug conjugates, steroids, and other substrates (Morris *et al.*, 2017). The testis-blood barrier plays an important role in the protecting the developing gametes from toxic insults (Hau *et al.*, 2023). Most transporters express themselves within the Sertoli Cells, however select Abc transporters have limited expression in Leydig cells (Hau *et al.*, 2023). My hypothesis is that efflux transporters sensitive to transportation of environmental toxicants would have increased expression, whereas uptake transporters would have decreased expression, as a compensatory mechanism to reduce the toxicity of reproductive toxicants.

III-3. Xenobiotic-sensing transcription factors including nuclear receptors

Nuclear receptors are a family of transcription factors essential for sensing stimuli (Forman and Evans, 1995). A number of nuclear receptors have come under study due to their ability to respond to foreign compounds, xenobiotic receptors (Mackowiak *et al.*, 2018). Constitutive androstane receptor (CAR), peroxisome proliferator-activated receptor (PXR), and aryl hydrocarbon receptor (Ahr) are major xenobiotic receptors noted for their control of disposition and detoxification through activation of phase I/II enzymes and transporters (Mackowiak *et al.*, 2018). Among xenobiotic receptors, PCB specificity has been noted between coplanar ('dioxinlike') and noncoplanar ('non-dioxinlike') molecules. Both CAR and PXR have been studied to have a major role in noncoplanar PCBs while Ahr have been observed in activation of coplanar PCBs

; Al-Salman and Plant, 2012; Bemis *et al.*, 2005; Kaminski, n.d.). Previous investigation into xenobiotic nuclear receptors on male reproductive systems indicated regulatory function by both CAR and PXR (Whyte-Allman *et al.*, 2017). Thus it is our hypothesis, upregulation of xenobiotic-sensing transcription factors would have increased expression from maternal exposure to PCBs.

III-IV. Known Expression of Drug Processing Genes

Drug-processing genes have been extensively studied in the liver, intestines, and kidneys, which are notable for their xenobiotic biotransformation capacities (Meyer, 1996, Zhang *et al.*, 2012). Recently studies in the literature have also characterized the expression and regulation of the drug-processing genes in brain, because these genes together with the blood brain barrier can determine the sensitivity to environmental toxicant induced neurotoxicity (Stieger and Gao, 2015; Strazielle and Ghersi-Egea, 2015; Chaves *et al.*, 2014; Sethi *et al.*, 2021). However, relatively less is known regarding the regulation of the drug-processing genes in reproductive organs. While the testis is not a typical drug-processing organ, there have been some literature reports that characterized certain genes involved in xenobiotic removal. Many drug-processing genes are expressed in Sertoli cells, whereas several drug processing genes have also been observed in other cell types within the testis (Su *et al.*, 2011). ABC superfamily of transporters are expressed highly in the Sertoli cells, and have also been reported in Leydig cells and peritubular myeloid cells (Su *et al.*, 2011). Mdr3 has been detected in Sertoli cells, Leydig cells, peritubular myoid cells, and late spermatids in rodent models (Croop *et al.*, 1989; Melaine *et al.*, 2002). Abcc1 (Mrp1) is found in the basal compartment of Sertoli and Leydig cells of mice and rats (Wijnholds *et al.*, 1998; Bart *et al.*, 2004). Abcg2 (BCRP) have been detected in peritubular myoid cells in human testicular tumors (Bart *et al.*, 2004). Among the Slc transporters, Slc21a14 was only found in Leydig cells of humans and mice (Pizzagalli *et al.*, 2002). Slco6b1 and Slco6c1 were found in Sertoli cells, spermatogonia, and Leydig cells of humans and rats (Suzuki *et al.*, 2003). Slc21a7 is found in Sertoli cells in rodent models (Augustine *et al.*, 2005). Slc22a1 (OCT1), Slc22a3 (OCT3), Slc22a4 (OCTN1), and Slc22a5 (OCTN2) have been identified in Sertoli cells of mice and humans testis (Klaassen and Aleksunes, 2010). Both Slc22a5 and Slc22a3 have also been identified in the sperm tail and epididymal spermatozoa indicating potential roles in sperm maturation and metabolism (Kobayashi *et al.*, 2007; Jeulin and Lewin, 1996).

IV. RNA-sequencing

RNA-sequencing of testis-specific transporter genes is an avenue to better understanding and predict the pathway a particular compound is affecting male reproductive organs. RNA-seq utilizes deep-sequencing techniques that is more precise than other forms of transcriptomic readings (Wang *et al.*, 2009). Microarrays offer high throughput and precise readings but are held back by requiring genome sequences and are difficult to compare between experiments (Wang *et al*., 2009). RT-qPCR offers similar levels of precision with significant cost reductions, but does not have the scalability or discovery RNA-seq provides (Nonis *et al.*, 2014). Northern blot is another more visual technique but like RT-qPCR does not scale well with an increasing number of gene targets (Taniguchi *et al.*, 2001). With our hypothesis seeking to understand a large number of potential gene targets, RNA-seq provides the highest level of precision that also enables our comparison with a number of different studies.

In summary, the unique biological and developmental composition of testes provides an avenue of research that is unexplored with regards to PCB mixtures. Increasing evidence has shown while the male reproductive organs are not primary areas of xenobiotic transformations, their unique responses have an impact on the health of an organism. The physical properties of PCBs and their dioxin like make-up make them more susceptible by absorption within the testes, potentially by-passing the traditional xenobiotic transformation by other organs, namely the liver and intestines. Very little is known regarding the developmental regulation of the drug-processing genes in testis of offspring following *in utero* and lactational exposure to PCBs. The biotransformation of PCBs has been characterized in previous studies (Cai *et al.*, 2011; Hau *et al.*, 2023; Han *et al.*, 2019; Nixon *et al.*, 2014). However, for many of these studies, they have focused on effects by specific PCB congeners with little research on mixtures (Zhang *et al*., 2014). Therefore, the goal of my thesis is to characterize the regulation of the drug-processing genes following maternal exposure to the Fox River PCB mixture. My central hypothesis that distinct

drug-processing genes are persistently programmed during postnatal development by maternal PCB exposure in a dose-dependent manner.

MATERIALS AND METHODS

Identifying testis-enriched drug-processing genes using the ENCODE datasets.

FASTQ files were mapped to the mouse reference genome (GRCm39 – release date: 07/22/2020) and counts were generated using STAR v2.7.10a (Dobin *et al.*, 2013) following the pipeline from ENCODE (https://www.encodeproject.org/microrna/microrna-seq/). STAR was recompiled with sse2neon (https://github.com/DLTcollab/sse2neon). Code was injected using Xcode 14 (https://developer.apple.com/xcode/). FASTQ files from 16 metabolic organs (BioProject Accession Number: PRJNA66167, n=3/organ) were retrieved from the NCBI GEO database and were mapped to the mouse reference genome. The sequencing map files were converted to count files/map (SAM) files were converted and sorted to binary alignment/map (BAM) format using SAMtools version 1.8(Li *et al.*, 2009). Transcript abundance was estimated using the integrated Quantmode (STAR v2.7.10a). Genes were considered expressed if the average raw count was > 1 for at least one group. Differential analysis was performed using EdgeR v3.38.4 (Robinson *et al.*, 2010) between testis and all other organs. A gene is considered testis-enriched if its average mRNA in testis is greater than 10-fold of the average mRNA in 16 other organs. A likelihood ratio testing, upper quartile LRT FC 1.5 FDR <0.05, and potential outliers were removed using RUVSeq v.1.34.0 (Risso *et al.*, 2014). Differential expression analysis was performed using edgeR v.3.42.2 (Robinson *et al.*, 2010). Heatmaps were generated using the R package ComplexHeatmap v.2.16.0 (Gu, 2022). String Analysis was performed using STRING (https://string-db.org).

Chemicals. The Fox River PCB mixture was prepared as described before (Cheng *et al.*, 2018; Lim *et al.*, 2020). Briefly, the Fox River PCB mixture is composed of 4 Aroclors: Aroclor 1242, Aroclor 1248, Aroclor 1254, and Aroclor 1260, all provided from Dr. Hans Lehmler's group from Iowa University. Solutions of each Aroclor (50 mg/ml in acetone) were combined in a ratio of 35:25:15:15% by weight for Aroclor 1242, Aroclor 1248, Aroclor 1254, and Aroclor 1260, respectively (Kostyniak *et al.*, 2005). Organic Peanut Butter vehicle was purchased from Trader Joe's (Seattle, Washington).

Animals. Female C57BL/6J mouse dams (Jackson Laboratory, Bar Harbor, Maine) were exposed to PCBs at 0.1, 1, or 6 mg/kg body weight two week prior to mating via peanut butter mixed with PCBs. Exposure to PCBs continued throughout pregnancy and lactation until the pups were weaned at PND 28. Pups were never directly exposed to PCBs. Testis from male pups was collected at postnatal day (PND) 28 and 35, immediately frozen in liquid nitrogen, and stored at −80°C until further analysis.

RNA Isolation. Total RNA was isolated from frozen testis using the RNA- Bee reagent (Tel-Test Inc, Friendswood, Texas) according to the manufacturer's protocol. RNA concentrations were quantified using a NanoDrop 1000 Spectrophotometer (Thermo Scientific, Waltham, Massachusetts) at 260 nm. The integrity of total RNA samples was evaluated by formaldehyde-agarose gel electrophoresis with visualization of 18S and 28S rRNA bands under UV light and confirmed by an Agilent 2100 Bioanalyzer (Agilent Technologies Inc, Santa Clara, California). Testis RNA samples with RNA integrity (RIN) values above 8.0 were used for RNA- Seq.

RNA Sequencing of testis Samples and Data Processing. In triplicates, RNA sequencing was performed in male testis at PND 28 and 35. The cDNA library was constructed using an Illumina TruSeq Stranded mRNA kit (Illumina, San Diego, CA) using the poly-A tail selection strategy. The RNA fragmentation, first- and second-strand cDNA syntheses, end repair, adaptor ligation, and

PCR amplification were performed according to the manufacturer's protocol. The cDNA libraries were then validated for quantity and integrity using an Agilent 2100 Bioanalyzer (Agilent Technologies, Inc., Santa Clara, CA) before sequencing. Reads were sequenced using a 50 bp paired-end sequencing per the Illumina manufacturer's protocol. The FASTQ files were de-multiplexed and concatenated for each sample. Quality control of the FASTQ files was performed using FastQC (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/). Reads were mapped to the mouse reference genome (GRCm39) and counts were generated using STAR v2.7.10a (Dobin *et al.*, 2013). Transcript abundance was estimated using the integrated Quantmode (STAR v2.7.10a). For RNA-Seq, samples were categorized by age, sex, and exposure. Analysis was performed in the same manner in the ENCODE dataset.

Results

Drug Processing Genes Identified in Testes in ENCODE Database.

The foundation of understanding the role of drug processing genes started with analyzing the ENCODE database comparing our testicular models with other organs. Sixteen metabolic organs (BioProject Accession Number: PRJNA66167, n=3/organ) were retrieved from the NCBI GEO database and were mapped to the mouse reference genome, GRCm39 comparing the vehicle controls using the ENCODE database to provide information on RNA expression (Figure 1). Heatmaps were used to visualize the range of expression to determine the biological significance of drug-processing genes within the testes. In general, the major drug-processing organs, liver, and small intestines, had the highest relative expression of drug processing genes (Figure 2). Specifically, among the Phase I enzymes, the cytochrome p450s had high upregulation relative to other organs (Figure 2A). Among the Phase II enzymes, the liver had high upregulation of glucuronosyltransferase (Figure 2B). Despite these expected results, some Phase I and II genes observe expression similar to liver and/or intestinal data indicating potential routes of drug metabolism within testicular organs indicating potential

functions as minor drug processing organs (Figure 2). Specifically, for phase I enzymes, some of the cytochrome p450 cyp2 genes had comparable expressions found in the liver (Figure 2A). Among phase II enzymes, glutathione S-transferase, N-acetyltransferases, uridine diphosphate-glycosyltransferases, and sulfotransferases saw upregulations similar or higher than other organs (Figure 2B). This provided our first indication the testes had the ability to potentially metabolize and/or process toxicants with localized expression of drug-processing genes.

Effect of Fox River PCB Mixture on Testis Transcriptome.

Assessment of Fox River PCB mixture on testicular transcriptome was determined using bulk RNA-seq of whole mice testis (n = 3 per exposure) across two time points, PND 28 and 35 (Figure 3) to determine early life exposure to an environmentally relevant PCB mixture. As shown in Figure 4A-B, principal component analysis (PCA) was performed on normalized, filtered gene expression. Exposure to PCBs on earlier time points (PND 28) had similar genetic variation in low and high doses (Figure 4A) compared to control mice. The genetic variation during later timepoint of the exposures were more similar to the controls (Figure 4B), suggesting greater transcriptomic differences when exposed at PND 28. The number of differentially regulated genes vary significantly by both dose and age (Figure 4A). Specifically in the male testis in PND 28 male mice, the low dose exposure had 193 genes while the higher dose differentially regulated 1488 genes. This pattern does not hold in the later PND 35 with 216 differentially expressed genes in the low dose and only 118 genes in the higher dose. The later time point show higher resistance towards PCB exposure with the high dose exposure seeing even less gene regulation than the low dose exposure. This trends in differentially expressed genes match similarly with the previous PCA plot (Figure 4A-B). Venn Diagrams (Figure 7B) were used to visualize differentially regulated genes both common and uniquely regulated following exposure to Fox River PCBs. Among the different exposure groups, the earlier time point of PND 28 consistently had higher number of uniquely regulated genes. Specifically, the high PCB dose at PND 28 had the highest number of uniquely regulated genes with 1161 genes expressed. In contrast, the same dosage at PND 35,

only 24 genes were uniquely expressed. PCB effect weaken over time, comparing the number of differentially regulated genes observed in PND 28. The dose response originally seen in PND 28 is lost in PND 35 with gene counts showing the high dose at PND 35 having less genes than low dose equivalent. Twenty nine genes were found to be differentially regulated among all exposure groups. Using STRING analysis, these 29 genes were analyzed for protein interactions using a confidence interval of 0.700 (Figure 7C). This pathway analysis found that four genes (Rnase10, C4bp, Crisp1, and Adam7) from the 29 differentially regulated genes by PCBs which were correlated with spermatogenesis function. Rnase10 has been previously found to be secrete proximal epididymal protein required for post-testicular sperm maturation and male fertility(RNASE10 GeneCards, n.d.). C4bp control the classical pathway of complement activation (Mus musculus complement component 4 binding protein (C4bp), mRNA, 2022). Crisp1 is suggested to help spermatozoa undergo functional maturation while they move from the testis to the ductus deferens. Adam7 is a disintegrin and metalloproteinase domain-containing protein that may play an important role in sperm maturation and gonadotropic function (ADAM7 GeneCards, n.d.). In all exposure shared genes, a dose response was recorded in PND 28 while suppression of this response was observed in PND 35. Altogether, the commonly differentially regulated genes by all exposure groups suggest that spermatogenesis is a common target by PCBs at both doses and at both developmental ages.

Drug Processing Genes alternations following Fox River PCB Mixture exposure

To determine the overall scope of transcriptomic change regarding testicular action, differentially regulated genes were sorted into categories associated with drug processing, including phase-I and -II metabolism, transporters, and nuclear receptors as described in MATERIALS AND METHODS (Figure 5). Investigation of transcriptomic changes to testis suggest potential effects on earlier timepoints following a compensatory mechanism. In general, the earlier time point of PND 28 had induction of differentially regulated genes following a dose response pattern (Figure 5A). This pattern was lost in the later time point with suppression of

genes previously found to be induced (Figure 5B). This may indicate a compensatory response due to xenobiotic (PCB) exposure. At PND28, PCBs up-regulated the uptake transporters Slc34a3 and Slc36a3 (Figure 5A). Slc34a3 has been associated with expression in testicular cancers (Genecards.org). Slc36a3 is predicted as an amino acid transporter (Genecards.org). The same genes in PND 35 see induced expression with exposure to PCBs while most genes pivot closer to their control state.

RNA-seq provides accurate measurements compared to relative quantifications techniques, i.e., mRNA methodologies. Comparisons of abundance between targeted drug processing genes were made after observing their general expression patterns in heatmaps (Figure 5). Transporters were observed across timepoints to compare their absolute transcript counts under non-exposure and PCB-exposed conditions. Targets were segregated into phase I and -II drug-metabolizing enzymes as well as transporters with further break down into their specific functions.

Phase I enzymes are known for their oxidase activity by cytochrome enzymes. Several groups were noted for their significance in expression. Up-regulation of alcohol metabolism related genes (e.g., Adh1, Adh7, Adhfe1, Aldh1a7, and Aldh6a1) all followed similar patterns of increased expression of genes with higher doses in PND 28 but with loss of this response in PND 35 (Figure 8). Among the Cytochrome P450s, three of them (e.g., Cyp2e1, Cyp2j6, and Cyp4f16) were noted and followed the same trend observed in previous Phase I enzymes with a dose response at PDN 28 with loss of response in PND 35 (Figure 8A). Cyp2e1 (Figure 8A) was unusual for having overall decreasing response in PND 35. This cytochrome P450 enzymes is specifically known for its responsibility in breaking down foreign compounds (Genecards.org). In addition, flavin-containing monooxygenases found trends aligning with other Phase I enzymes, seeing an increasing dose response from low to high dose in PND 28 with the response weakened in PND 35 (Figure 8B). Phase I enzymes also include classes of reducing agents as well. Phase I enzymes from these families are associated with preventing oxidative stress. Aldo-Keto

Reductase 1b7 and 1c19 (Akr1b7 and Akr1c19) and Glutathione peroxidase 3 (Gpx3) were upregulated in PND 28 with minor reductions in PND 35 specifically in the enzymes, Akr1c19 predicted in its involvement in steroid metabolic process (NCBI.gov), and Gpx3 (Figure 9A). Hydrolysis reactions are the final, major group of Phase I enzymes. Carboxylesterase and epoxide hydrolases (Carboxylesterase 1D, Carboxylesterase 5a, and Epoxide hydrolase 2 respectively) also followed similar responses to the Aldo-keto reductases having an increasing dose response in PND 28. Carboxylesterase 5a (Ces5a), known for its role in fatty acid metabolism and hydrolysis with various xenobiotics (Genecards.org), were down regulated in PND 35 that mimic the results found in other Phase I enzymes namely, Akr1c19 and Gpx3 (Figure 10B).

Overall, Phase II enzymes exhibited less pronounced transcriptomic alterations compared to Phase I enzymes. However, certain methylated Phase II enzymes had changes correlated with those observed with Phase I enzymes. Three methylation Phase II enzymes (Catechol-O-methyltransferase, Glutathione S-transferase, and Thiopurine S-methyltransferase) had significant dose response changes from low to high dose of PCB in PND 28 (Figure 11A). This effect in PND 35 was not retained. 3'-phosphoadenosine 5'-phosphosulfate synthase 1 (Papss1), known for mediating the sulfate activation pathway (Genecards.org), showed a dose response in PND 28 (Figure 11A). PND 35 did not see any significant changes for Papss1.

Transcription factors similarly were limited in their transcriptomic response however a couple of transcription factors stood out. Two transcription factors, Ahr and Esr1, had increasing expression with response to increasing dose in PDN 28 (Figure 11B). Both transcription factors had no effect from vehicle control in PND 35. Ahr is well known for response to planar aromatic hydrocarbons and has been shown to regulate xenobiotic response (Genecards.org). Esr1 is an estrogen receptor response for regulating estrogen-inducible genes essential for reproductive function and development (Genecards.org).

Uptake Solute Carrier transporters (SLC) contain a number of important facilitative or secondary-active pumps to transport various substrates. Seven known uptake solute carrier transporters, namely Slc2a4, Slc38a1, Slc44a1, Slc7a11, Slc34a3, Slc38a4, Slc38a5, with statistical significance found in the high dose during PND 28 for all of them following an increasing dose response. The majority of SLC transporter upregulated in PND 28 were found to have amino acid substrates indicating movement of micromodules during PCB exposure. Despite this bias toward amino acid transport, a wide variety of endogenous molecules in PCB-dosed mice suggest a large response in resource allocation to address the addition of the PCB chemical. One Slco transporter, Slco2a1, had statistically significant changes in expression at PND 28 (Figure 12A). Slco transporters, more commonly known as organic anion transporting peptides (OATP), are better associated with xenobiotic transformation within the larger Solute carrier proteins.

Solute Carrier transporters also can efflux substrates. A number of Slc transporters with nucleotide substrates (Slc17a5, Slc17a6, and Slc17a9) were recognized for their statistical significance increasing gene expression during PND 28 (Figure 14). Once again, this pattern does not hold in PND 35 with all exposure showing similar levels of expression regardless of their initial pattern in PND 28. Slc1a5, Slc50a1 (better known as SWEET1), and Slc9a6 show clear increasing trends at PND 28 but offering little change at the later developmental timepoint, PND 35. In addition, a number of Slc transporters were predicted for their transportation due to the lack of literature. Slc16a11 and Slc16a13 are a class of transporters with a monocarboxylic acid as its defining substrate had significant increase in gene expression at the high dose of PCB on PND 28 (Figure 14 A). Unusually, these predicted efflux transporters see a decreased trend in the high dose at PND 35, but this was not noted as statistically significant.

Bidirectional solute carriers were also noted, containing a wide variety of different substrates. Fox River PCB upregulated genes for a number of endogenous substrates in PND 28 including Slc16a10, an amino acid bidirectional transporter, Slc16a2, a thyroid hormone bidirectional transporter, Slc26a7, a sodium bidirectional transporter, Slc28a3, a nucleotide sugar

bidirectional transporter, and Slc4a4, a bicarbonate bidirectional transporter (Genecards.org) (Figure 15).

Abc transporters are a class of efflux ATPases known for their movement of xenobiotics and endogenous metabolites. Four Abc transporters had significant changes in PND 28 (Figure 13A). Abca2 and Abcb7 see similar range in trends only finding an increasing expression in PND 28 with no effect in PND 35. The general efflux transporter Abcb5 uniquely had increasing expression correspond with PCB levels in both PND 28 and 35. Abcc4, more commonly known as Mrp4 or multidrug resistance protein 4, had increases in expression at PND 28 in the high dose of PCBs.

In conclusion, the present study investigated the effect of an environmentally relevant mixture of PCBs of relevant concentrations involved in a potential mother-child transformation in the male reproductive systems. Our study suggests the Fox River PCB mixture has potential early developmental effects on rodent models activating a number of inflammatory and xenobiotic transporters as a compensatory response. A general trend in observed transcriptomic data had persistent effect from PCB exposure expression responses where less between snapshot assessments over the timescale of PND 28 to PND 35. Basal testicular functions were noted also for aligning with the compensatory response seen in drug-processing genes.

DISCUSSION

Xenobiotic metabolism is highly conserved among different organism, organs, and life stages especially between mammalian species (Pinne *et al.*, 2016; Kliewer *et al.*, 2002). PCBs have been previously found to induce xenobiotic metabolism (Gährs *et al.*, 2013; Takeuchi *et al.*, 2017; Al-Salman and Plant, 2012; Bemis *et al.*, 2005; Kaminski, n.d.). The process of detoxification are attributed to two well established xenobiotic sensors, pregnane X receptor (PXR) and constitutive androstane receptor (CAR) (Wang *et al.*, 2012). Both rely on a number of drug-metabolism enzymes and transporters in order to detoxify or eliminate endogenous compounds. Evidence of activation of these pathways can indicate adverse effects from exposure

to toxicants. Previous studies have identified the presence of organochlorine compounds may exhibit endocrine disruptor activities altering PXR-regulated steroid hormone metabolism (Jacobs *et al.*, 2005). Exposure of non-coplanar polychlorinated biphenyls were found to activate both the PXR and CAR pathways in human liver cell models (Al-Salman and Plant, 2012). An in-vivo study found altercations in retinoid homeostasis resulting from PCB exposure (Shmarakov *et al.*, 2019). Using *Car*-null mice, Shmarakov et al., 2019 found no significant decline in retinoic acid during administration of PCBs, with the same administration to non-modified mice had significant declines providing strong evidence linking disruption of retinoid homeostasis by PCBs through a CAR-dependent manner (Shmarakov *et al.*, 2019).

Our study found several Phase I enzymes enriched in PCB-exposed mice. Many these genes consist of alcohol dehydrogenases, which have previously been found to implicated in retinoic acid synthesis during spermatogenesis specifically those classified as class I and class IV (Deltour *et al.*, 1997). Retinoic acid has been found to have an essential role in spermatogenesis, with studies disrupting retinoic acid nuclear receptor resulting in postnatal lethality and reproductive dysfunction (Lufkin *et al.*, 1993). Six alcohol dehydrogenase enzymes were recognized to be upregulated by PCBs on PND 28, namely Adh1, Adh7, Aldh1a7, Aldh6a1, and Adhfe1. Adh1 is a phase I enzymes enriched in the Sertoli cells of testicular organs, disruption in this process can lead to decreased function of spermatogenesis (Deltour *et al.*, 1997). As a component of the alcohol metabolism pathways, Adh1 plays an important role in the oxidation of retinol into retinaldehyde as a part of the retinoic acid metabolism (Vernet *et al.*, 2006). The increased expression of Adh1 during PND 28 in our current study indicates that maternal exposure to PCBs may be implicated in the disruption of retinoid homeostasis due to increased CAR activation (Shmarakov *et al.*, 2019). Adh7 is another phase I enzyme and very little information is available regarding its function in testis. However, as a member of the alcohol dehydrogenase class IV family, it has been previously linked to roles in regulating retinoic acid (Deltour *et al.*, 1997; Rajendram *et al.*, 2016). Our study found Adh7 to be upregulated by PCB

during PND 28 following the trend seen by Adh1. Adhfe1 another alcohol dehydrogenase upregulated by PCB exposure is a relatively newer recognized alcohol dehydrogenase enzyme with evidence to suggest a role in regulating retinoic acid in early development (Deltour *et al.*, 1997; Shabtai *et al.*, 2016). The Aldh1a family of enzymes are required to oxidize retinal to retinoic acid with many of the recognized family noted for their presence in Sertoli cells or spermatogonia (Arnold *et al.*, 2015). Both Aldh1a7 and Aldh6a1 were up regulated by maternal exposure to the high PCB dose at PND 28. Because these Aldh enzymes are essential in the metabolism of retinoic acids (Arnold *et al.*, 2015), it is possible that maternal PCB exposure at the high dose may disturb retinoic acids metabolism in the offspring (Alarcón *et al.*, 2021). In conclusion, the alcohol/aldehyde oxidizing enzymes effect on maternal PCB exposure was much weaker at PND 35 as compared to PND 28. This rapid normalization of the gene expression pattern indicates that there may be a compensatory or adaptive mechanism to mitigate the toxicity of PCBs.

Cytochrome P450s are the quintessential Phase I enzymes, with several of them in our study showing increased expression when exposed to PCBs. Cyp2e1 is a phase I drug-metabolizing enzymes found to be enriched in liver; however, it is also expressed in Leydig cells and Spermatocytes. Within testis, Cyp2e1 is notable for metabolizing acrylamide, a known testis toxicant that can transmit the testis barrier (Shipp *et al.*, 2006). Acrylamide has been previously known to decrease copulatory behavior and loss of spermatogenesis (Nixon *et al.*, 2014). This increased expression of Cyp2e1 may suggest PCBs are metabolized as a toxicant within the testis. Nixon et al., 2014 found exposure to acrylamide was correlated with increased expression of Cyp2e1 in the germ cells of testis. Cyp2e1, along with other cytochrome P450s, had decreased expression by at PND 35 during PCB exposure. Inflammatory response was also recorded through the expression of Cyp4f16. Cyp4f16 is a ω-hydroxylases, a subfamily of enzymes noted for their hydroxylation of medium- and long-chain fatty acids along with their derivatives (Ni and Liu, 2021) with evidence suggesting these P450s are influential in the role of inflammation (Ni and

Liu, 2021). Decreased expression of cytochrome P450s after previously increased expression in due to toxicant exposure often occurs after metabolism of the toxicant (Zhao *et al.*, 2021). The decreased expression of cytochrome P450s in PND 35 may indicate clearance of PCBs through specific enzymes.

Fmo1 showed little evidence within the literature for testicular function. However one study linking exposure to estrogen was found to significantly down-regulate Fmo2 expression in-utero affecting male gonad development, impairing fertility and masculinization (Cr *et al.*, 2007). Gpx3 has been correlated with seminiferous tubules and recent literature has correlated Gpx3 with higher levels to address oxidative stress in sheep studies (Yao *et al.*, 2023). Expression of Glutathione peroxidases indicate protection from reactive oxygen species, implicating oxidative stress from PCB exposure. Seeing levels of this enzyme decrease in PND 35 are findings consistent with a prediction that the amount of PCB does not persist long after initial exposure in early development. This aligns with previous studies observing half-lives of PCB in mice with numbers ranging from 0.54 days in PCB 176 12.9 days in PCB 91 (Kania-Korwel and Lehmler, 2016). The Ces genes have been implicated in the metabolism of xenobiotics and of natural substrates. Prior studies of carboxylesterases in humans show PCBs inhibit the role of these transporters (Sun *et al.*, 2020). Ces5a has been found to be involved in rat spermatogonia and play role in sperm deformation (Han *et al.*, 2019). Prior literature on this particular carboxylesterase has been sparse due to the lack expression in organs typically noted for drug metabolism i.e. liver (Zhang *et al.*, 2012). Nonetheless, many carboxylesterase are induced by CAR activators indicating the increased expression found in PND 28 may be similar to other phase I enzymes (Zhang *et al.*, 2012).

In addition to Phase I enzymes, Phase II had enriched specificity in the testes. Among recognized phase II enzymes, Comt has previously been studied as a potential target for male infertility. Epidemiological studies on infertile males showed that there is an association between increased Comt expression and Sertoli cell-only syndrome (Parada-Bustamante *et al.*, 2017).

Comt in our study had increased expression levels with increasing levels of PCB on PND 28, mimicking the Phase I enzymes in our study, suggesting PCB at an early stage of development, could be indicative of dysregulation in spermatogenesis. The lack of literature on phase II enzymes in general indicate a need for characterization of these targets, specifically in a reproductive setting.

Transporters have attained increasing attention in their role of detoxification with consideration of potential drug metabolism within cells (Döring and Petzinger, 2014). A number of uptake transporters up regulated by maternal PCB exposure in testis of male pups at PND 28. Uptake transporters have traditionally been of interest in the effect of PCB congeners on neurotoxicity (Caudle *et al.*, 2006). Previous studies have shown PCBs activate the CAR and PXR pathways inducing increased activity of transporters (Hernandez *et al.*, 2009). Many of these transporters have been characterized in their specific organ however, their role in terms of xenobiotic transformation has been poor (Lin *et al.*, 2015). Further investigation of uptake Slc transporter may provide insight towards the induction of PCBs in testicular organ and potentially provide therapeutic targets to help prevent absorption.

Efflux transporters are recognized for their detoxifying roles especially among Abc family of transporters (EPEL *et al.*, 2008). Abcc4, or more commonly known as Multidrug Resistance Protein 4, are active in blood barrier to efflux unmodified toxicants out of systems (EPEL *et al.*, 2008). Abc transporters have been previously known to be essential to efflux estrogen metabolites with high affinity (Järvinen *et al.*, 2018). PCB's estrogen-like similarly can target Abc transporters providing additional avenues within biological systems. However, this does not explain all the transporters observed to see increased expression due to PCB exposure. Several transporters mentioned in previous studies have been found to have counterparts in other investigations, particularly in studies involving zebrafish models (Romersi and Nicklisch, 2022). However, these characterizations are focus on aquatic models not to mention utilize difference vertebrate systems allowing the extrapolation of PCB model to mice or humans difficult. This

suggests another avenue of investigation to determine the extent and role of Slc transporters not only in PCB exposure but also those specific to organs like the male testicular organs of mammals at very specific times and locations during development. Some of these observations suggest refinement of exposures i.e. defining the dose response at the lower levels and earlier timepoints, that seemed to be more potent than observed in our current study. Fundamentally, Abc and Slc transporters observed here display a compensatory mechanism observed in both Phase I and Phase II enzymes suggesting correlations with retinol metabolism and CAR pathways in PND 28. Further investigation would look further into what role Slc transporter have in the xenobiotic acquisition of PCBs in the context of inflammatory models.

We have observed mRNA levels of two transcription factors to show significant upregulated expression in PND 28 in a dose-dependent manner that was lost in PDN 35. Aryl hydrocarbon receptor (Ahr) is a ligand dependent transcription factor responsible in its role of xenobiotic response with evidence to show control over genes associated with phase I and II enzymes (Rothhammer and Quintana, 2019;

Tijet *et al.*, 2006). PCBs has been previously identified to show agonist activity against Ahr, inducing dioxin-like activity and potentially disrupting the endocrine system (Takeuchi *et al.*, 2017; Tijet *et al.*, 2006). In addition, Ahr has been implicated in the formation of seminiferous tubules and sperm development with rodent models (Hansen *et al.*, 2014; Wajda *et al.*, 2017). Human testicular studies have shown Ahr activation between 7 and 19 weeks of gestation indicating the importance in early reproductive development (Coutts *et al.*, 2007). While the Ahr response observed in our study is consistent with other dioxin-like studies in the literature, we did not do a longer-term evaluation to determine if this resulted in dysregulated sperm function. Estrogen receptor 1 (Esr1 or estrogen receptor alpha) had a similar response to Ahr. Esr1 is a ligand-dependent transcription factor regulated by estrogen (Welboren *et al.*, 2009). Esr1 has been previously observed expression in the adult Sertoli and Leydig cells of human male

reproductive organs (Filipiak *et al.*, 2013). ER knockout mice have provided evidence Esr1 and estrogen are necessary for spermatogenesis (Filipiak *et al.*, 2013). Previous studies on Esr1 on PCB exposure in rodent models observed similar trends of gene expression levels at lower dose regiments that match our relatively higher dose values suggesting a similar mode of action may be at play (Ceccatelli *et al.*, 2006). As PCB's have been noted for their estrogenic similarities, this effect by Fox River PCBs indicates a potential disruptive role in spermatogenesis that can lead to infertility in later stages of development.

CONCLUSION

Taken together, the expression of both drug-metabolizing enzymes and transporters indicates an early developmental response to maternal exposure that is reflected in developing pups after birth (Figure 16). An altered transcriptome response to PCB was observed with persistent effects that weaken between PND 28 and 35. Spermatogenesis was observed to be a common target in both dose and development. At PND 28, differentially regulated genes were induced in a dose-response manner by PCB exposure. A compensatory mechanism may be at play due to the decreased levels of drug-processing genes at PND 35 however, the long-term physiological effects of exposure are still under question. Additional investigation to determine the effects of Fox River PCB at puberty would provide additional answers towards understanding if the compensatory mechanism observed was successful in preventing long term damage by maternal PCB exposure.

Our current study has certain limitations, including small sample sizes (n = 3 per exposure group) for testes transcriptomics and inability to determine PCB metabolite from maternal exposure. Prior epidemiological studies have measured lactational concentrations of PCBs from anywhere between 0.5 and 4 mg/kg of fat in humans (Egusquiza *et al.*, 2020). describe in utero PCB transfer and lactation transfer and ultimately what that means]. The dose of Fox River PCB mixture at 0.1 and 1 mg/kg body weight in laboratory mice resulted from exposure assessment

that is close to human ingestion and inhalation and are similar to doses that have been used to investigate maternal exposure (Ampleman *et al.*, 2015; Keil Stietz *et al.*, 2021; Sethi *et al.*, 2021). In addition, the doses chosen lead to levels of PCBs that recapitulate the observations found in animal and human studies (Yang *et al.*, 2009; Chu *et al.*, 2003; Li *et al.*, 2019; Covaci *et al.*, 2002). Despite these limitations, our study provides the first evidence of early-life exposure through maternal exposure by Fox River Mixture of PCBs can alter the male reproductive transcriptome. With many of the core mechanisms and genes evolutionarily conserved, our findings provide novel insight early life exposure maternally can have impacts on the genetic expression, thus the expression of proteins.

ACKNOWLEDGMENT:

The authors would like to thank members of the Cui Laboratory for help in tissue collection and editing the manuscript.

AUTHORSHIP CONTRIBUTIONS:

Participated in research design: Suh and Cui.

Conducted experiments: Jung.

Contributed new reagents or analytic tools: N/A.

Performed data analysis: Jung and Cui.

Wrote and/or edited the manuscript: Jung, Faustman, and Cui.

Figure 1.

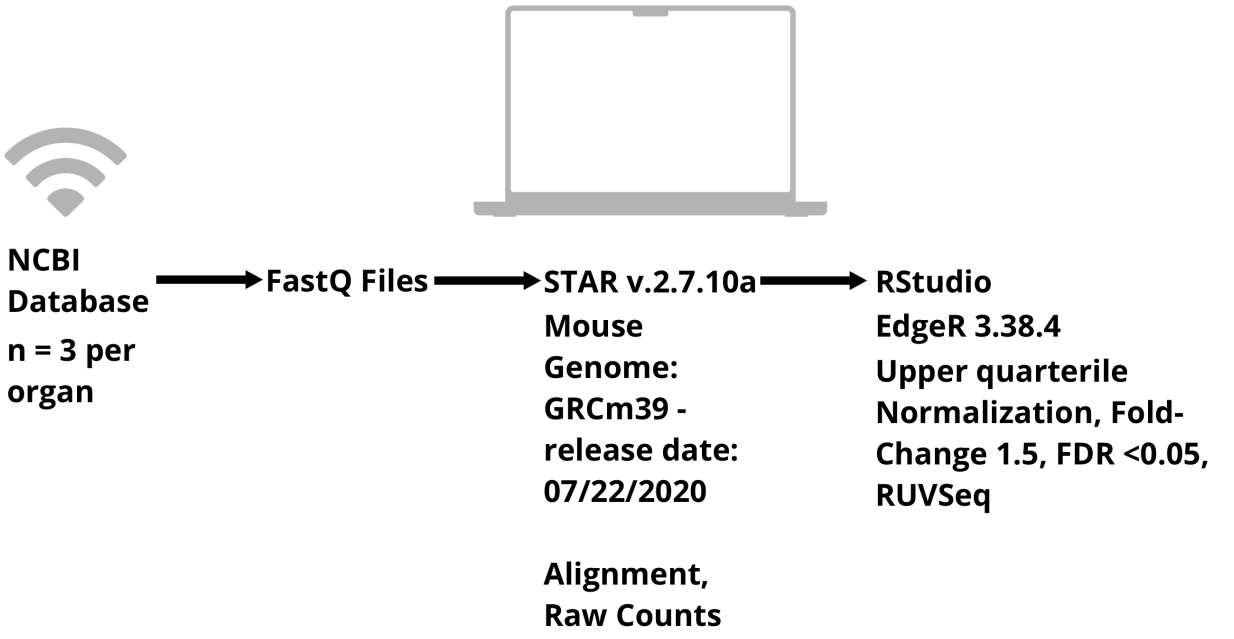


Figure 1.
ENCODE database was mined to identify drug-processing genes enriched within testes. STAR was recompiled using sse2neon to work on modern ARM devices. Genome compilation, mapping, and counts were all obtained through STAR. The reference genome used for compilation was the GRCm39. Differential analysis utilized EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.

Figure 2.

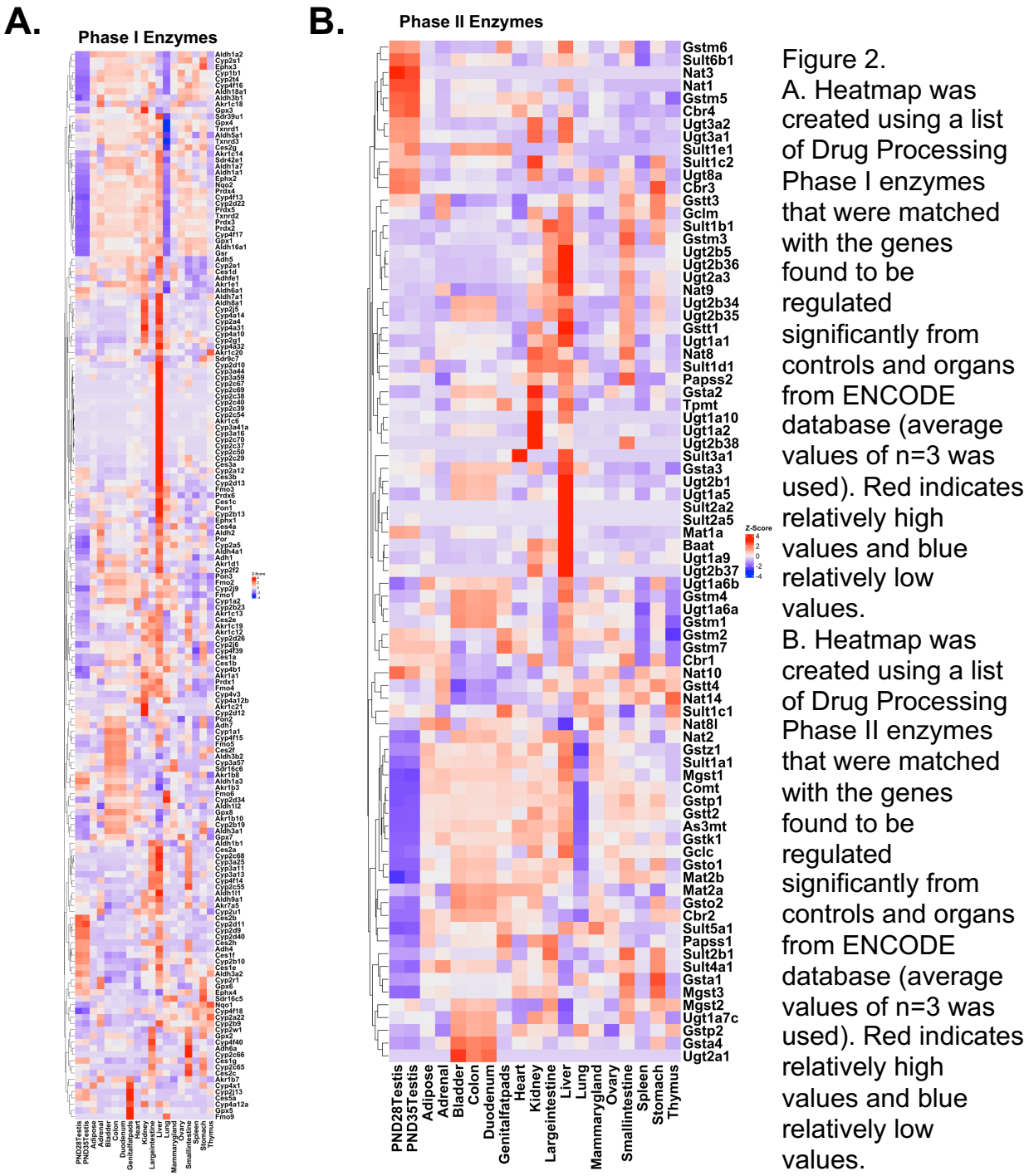
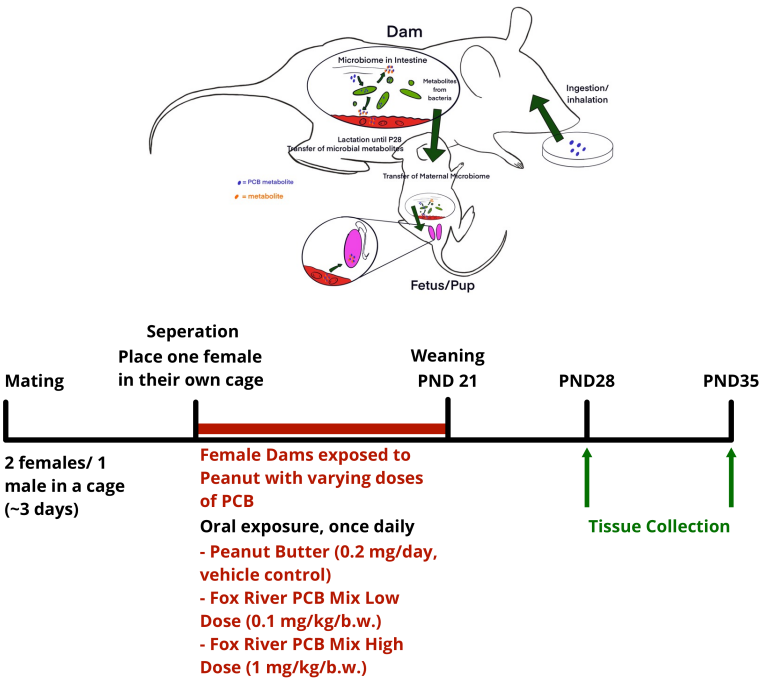


Figure 2.
A. Heatmap was created using a list of Drug Processing Phase I enzymes that were matched with the genes found to be regulated significantly from controls and organs from ENCODE database (average values of n=3 was used). Red indicates relatively high values and blue relatively low values.
B. Heatmap was created using a list of Drug Processing Phase II enzymes that were matched with the genes found to be regulated significantly from controls and organs from ENCODE database (average values of n=3 was used). Red indicates relatively high values and blue relatively low values.

Figure 3.

A.



B.

Collected Testis Tissue Samples → RNA Processing → FastQ Files → STAR v.2.7.10a → RStudio

n = 3 per Exposure

Mouse Genome: GRCm39 - release date: 07/22/2020

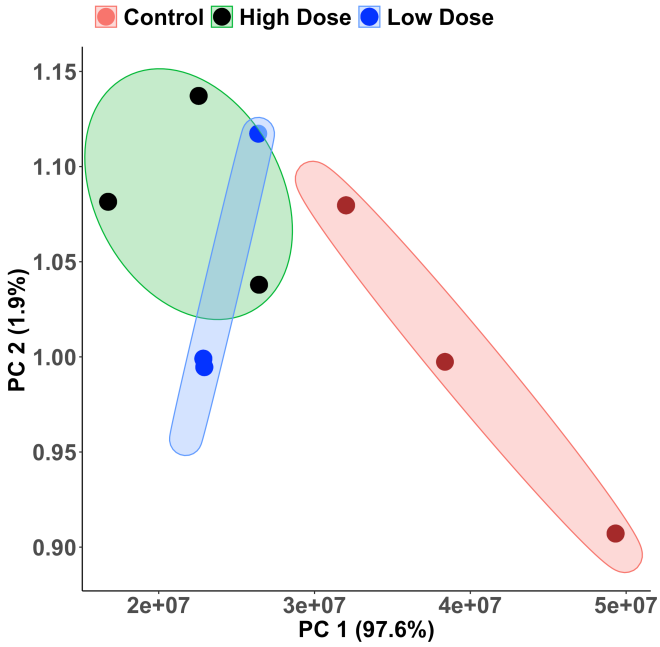
Alignment, Raw Counts

EdgeR 3.38.4
Upper quarterile Normalization, Fold-Change 1.5, FDR <0.05, RUVSeq

Figure 3.
A. Samples were obtained from Post-natal day (PND) 28 and 35 pups maternally exposed to PCBs in either 0, 0.1, or 1 mg/kg b.w. doses.
B. STAR was recompiled using sse2neon to work on modern ARM devices. Genome compilation, mapping, and counts were all obtained through STAR. The reference genome used for compilation was the GRCm39. Differential analysis utilized EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.

Figure 4.

A. PND 28



B. PND 35

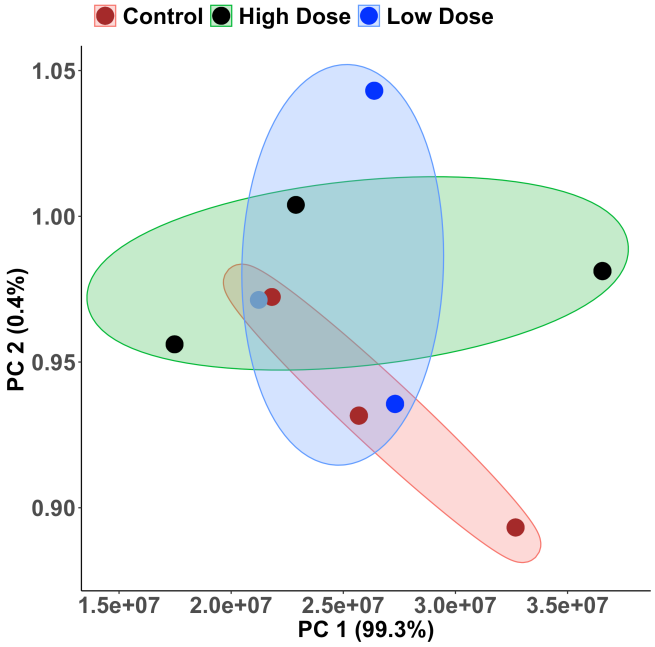


Figure 4.
A. PCA plot showing the distribution of testis tissue in PND 28. Both exposed low and high dose tissues see clustering while the non-exposed mice were visually detached.
B. PCA plot of tissue distribution in PND 35 mice showing a convergence of tissue distribution between exposed and unexposed mice suggesting our first hint at a compensatory mechanism.

Figure 5.

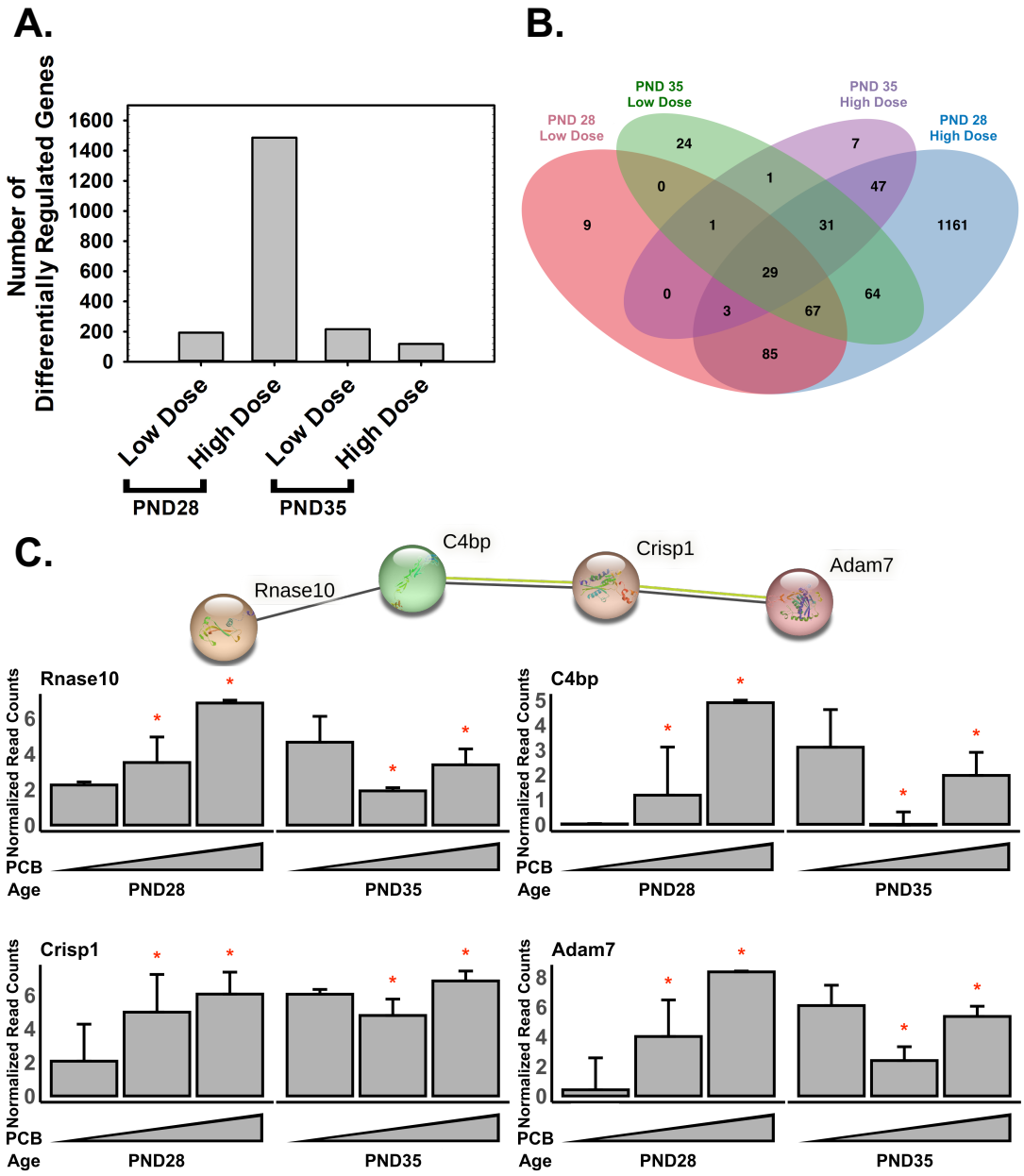


Figure 5.
A. Total number of genes found to be significantly regulated in male control mice.
B. Venn Diagram displaying genes found with significant regulation between Post Natal 28 and Post Natal 35 mice.
C. String Analysis (0.700 confidence interval) of 29 expressed genes shared in all treatments. Genes associated here are consistent with sperm development and maturation. (No GO analysis, 0.900 confidence saw no results). To further investigate, the four visually shown genes are provided with their transcriptome data all showing a increasing dose-response in PND 28. PND 35 sees a mild induction in the exposed mice.

Figure 6.

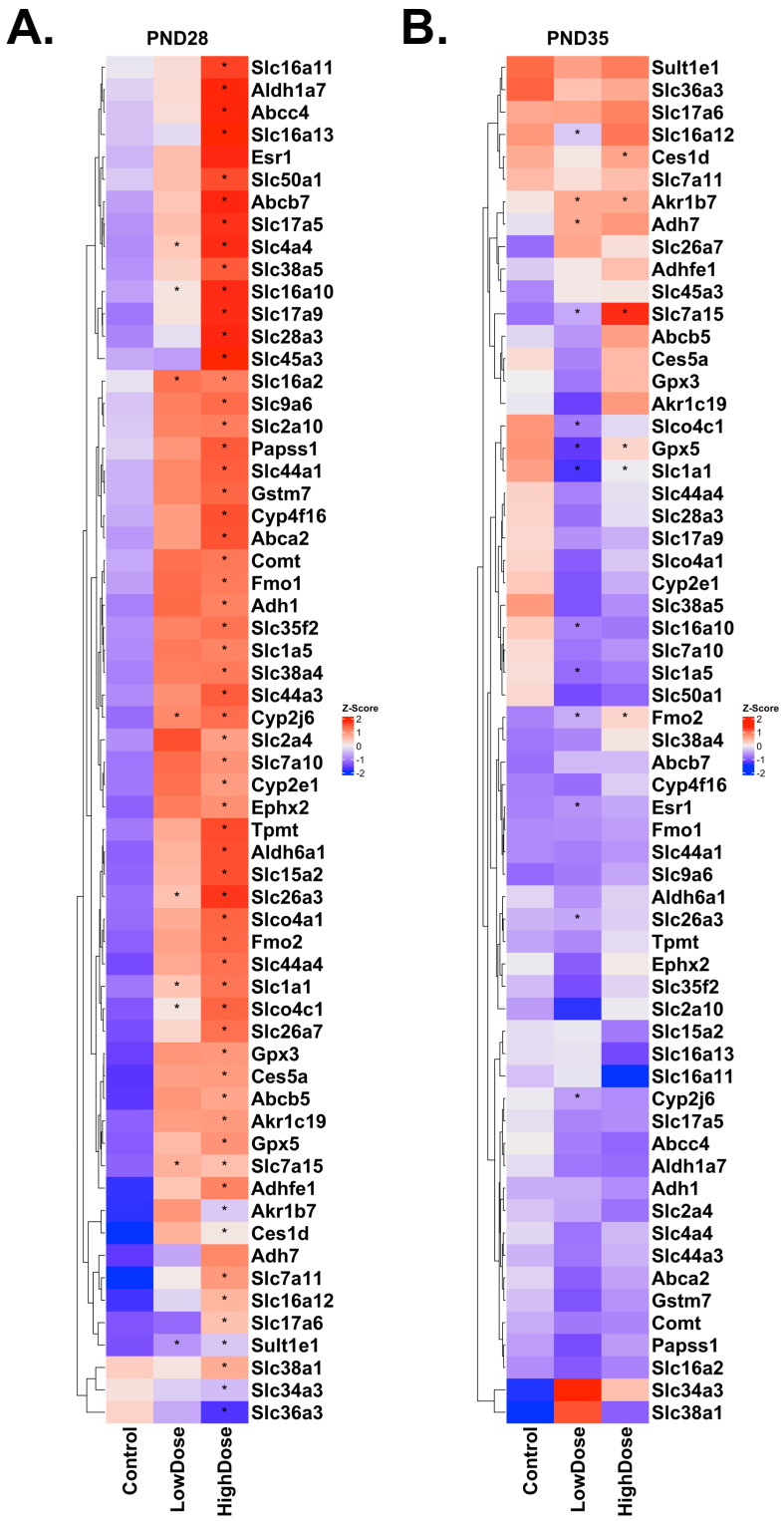


Figure 6.
Heatmap was created using a list of Drug Processing genes (Transporters, Phase I, Phase II, and Nuclear receptors) that were matched with the genes found to be regulated significantly from controls (average values of n=3 was used). Red indicates relatively high values and blue relatively low values. Significance was determined using likelihood ratio testing, upper quartile LRT RUVSeq FC 1.5 FDR <0.05. A. Heatmap comparing Control and Low Dose in PND 28 mice. B. Heatmap comparing Control and High Dose in PND 28 mice. C. Heatmap comparing Control and Low Dose in PND 35 mice. D. Heatmap comparing Control and High Dose in PND 35 mice.

Figure 7.

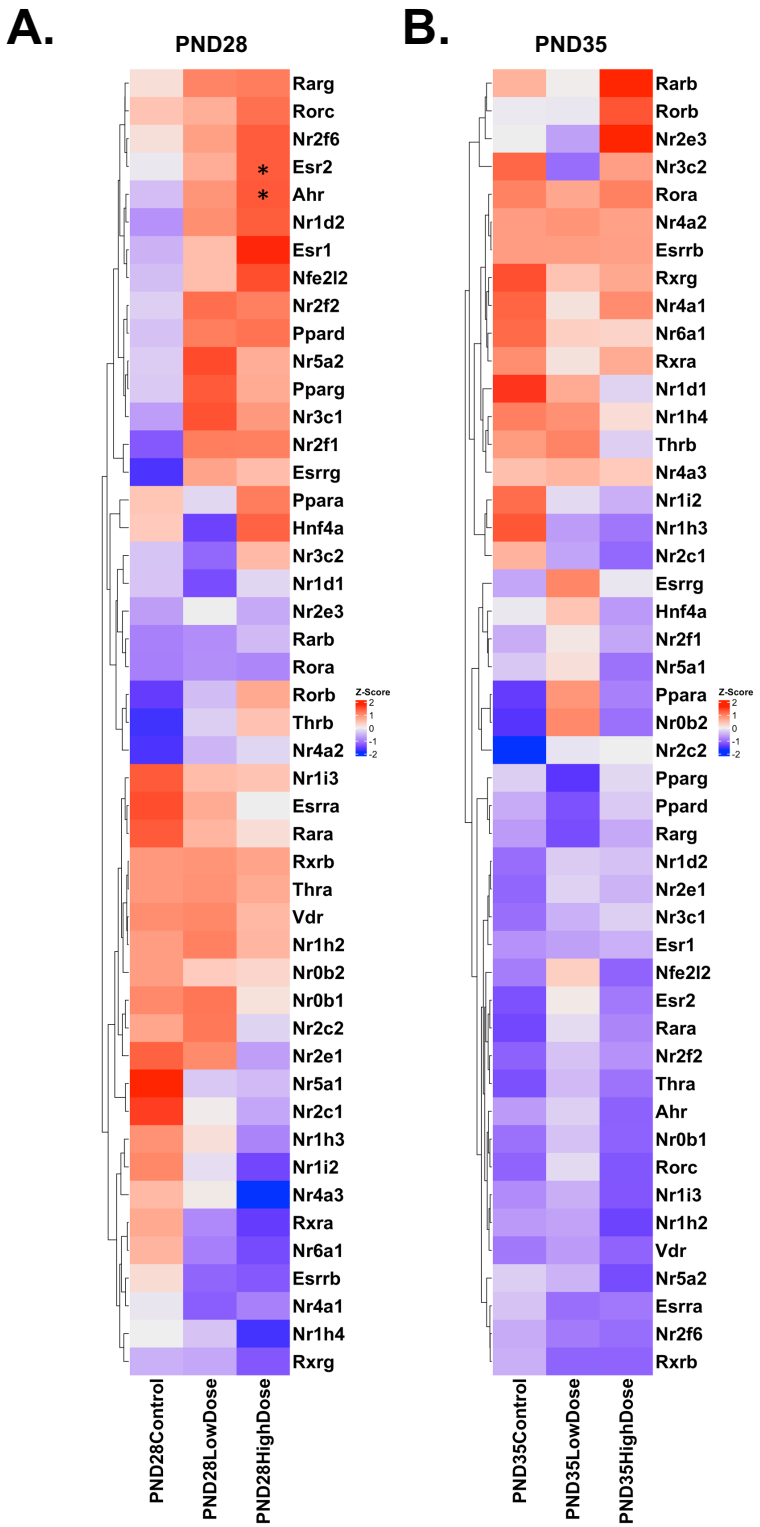


Figure 7.
Using the same list of Drug Processing genes matched previously, nuclear receptors were separated for better visualization, with genes found to be regulated significantly from controls (average values of n=3 was used). Red indicates relatively high values and blue relatively low values. Significance was determined using likelihood ratio testing, upper quartile LRT RUVSeq FC 1.5 FDR <0.05. A. Heatmap comparing Control and Low Dose in PND 28 mice. B. Heatmap comparing Control and High Dose in PND 28 mice. C. Heatmap comparing Control and Low Dose in PND 35 mice. D. Heatmap comparing Control and High Dose in PND 35 mice.

Figure 8. Phase I Enzymes (Oxidation)

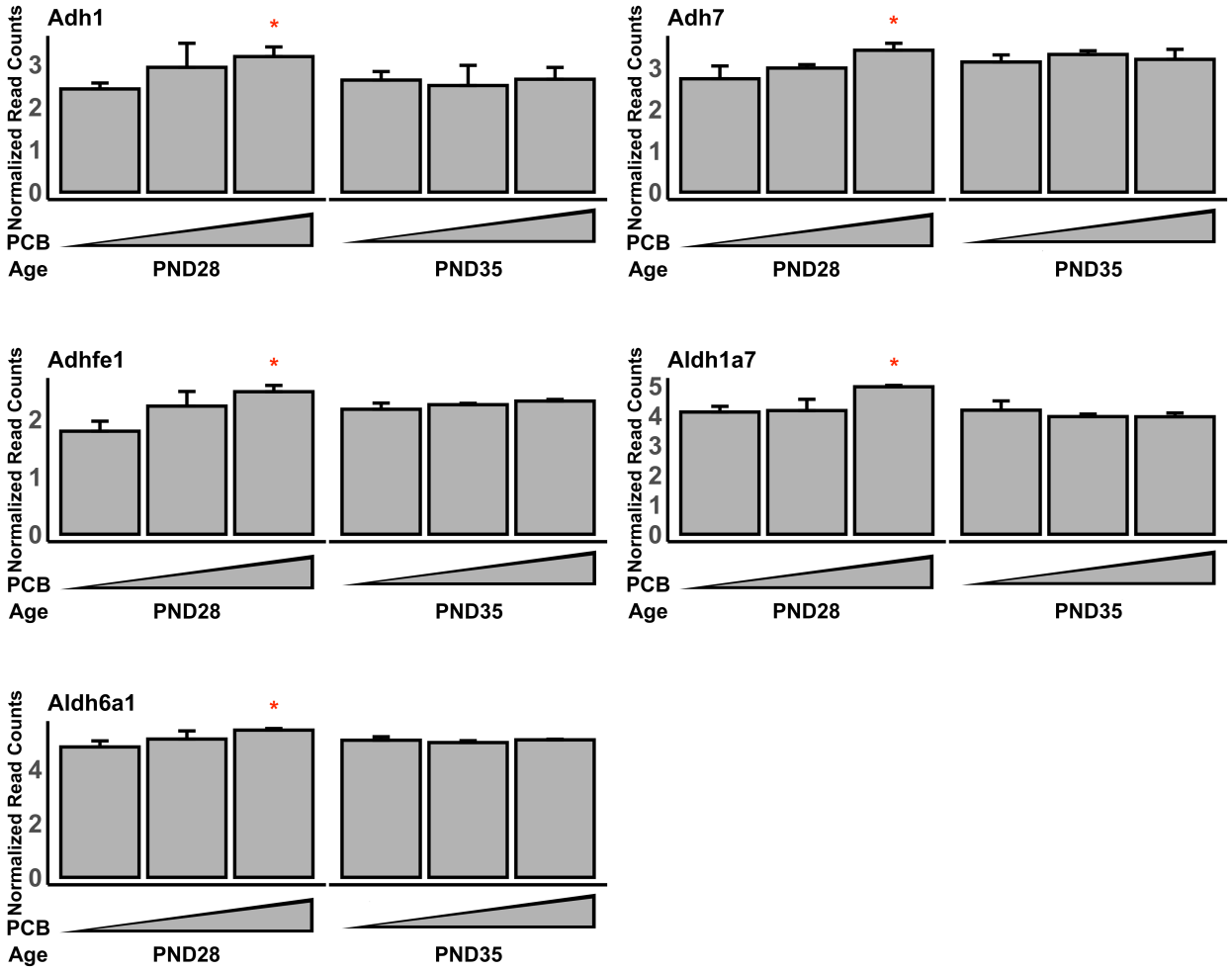


Figure 8.
The mRNA expression of differentially regulated aldehyde dehydrogenase Phase I enzymes in testes of PND 28 and 35 mice (n = 3/group, RNA-seq). * indicate statistical significance by EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.

Figure 9. Phase I Enzymes (Oxidation)

A.

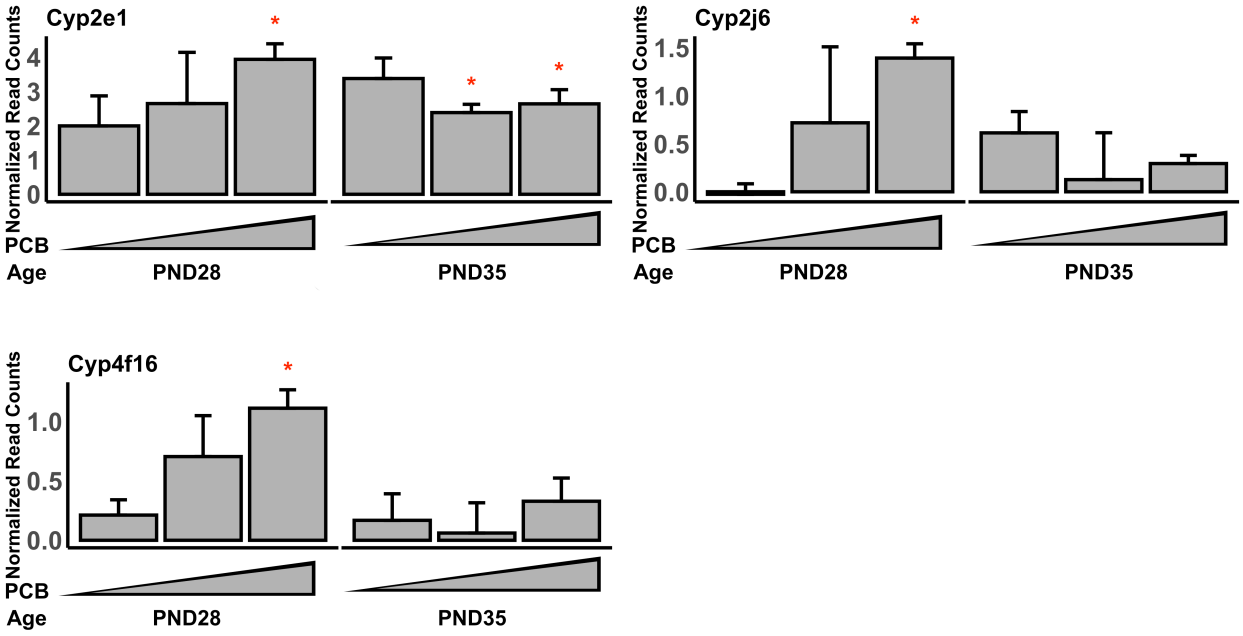


Figure 9.

A. The mRNA expression of differentially regulated cytochrome P450 Phase I enzymes in testes of PND 28 and 35 mice (n = 3/group, RNA-seq). * indicate statistical significance by EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.
B. The mRNA expression of differentially regulated Flavin containing monooxygenase Phase I enzymes in testes of PND 28 and 35 mice (n = 3/group, RNA-seq). * indicate statistical significance by EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.

B.

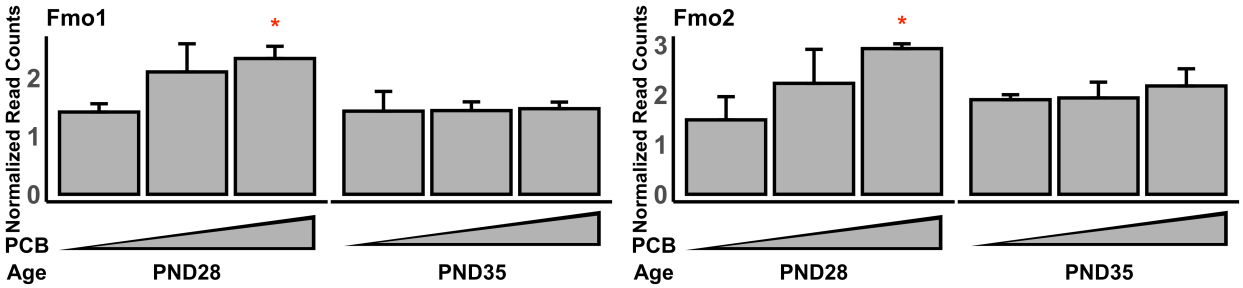
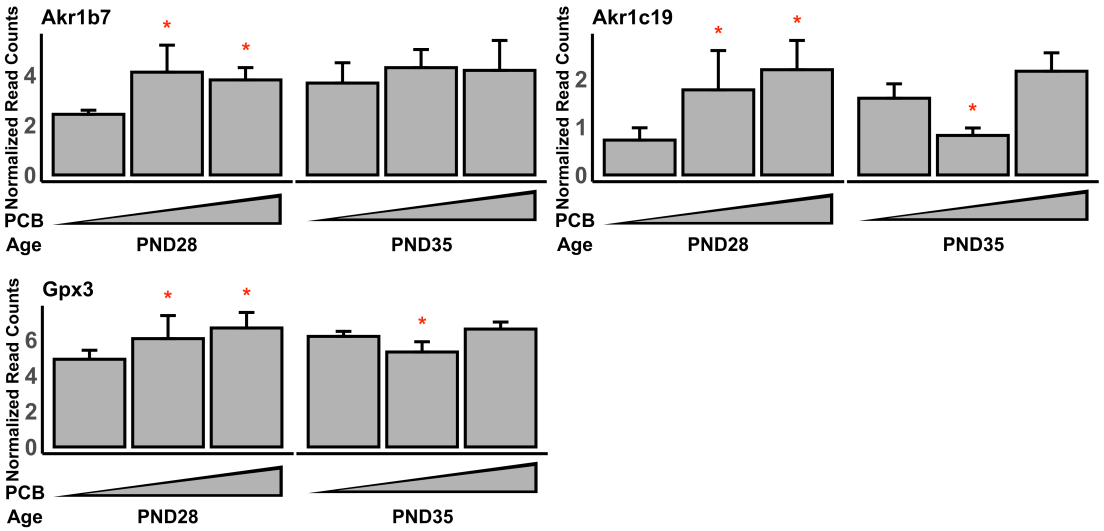


Figure 10. Phase I Enzymes

A. Reduction



B. Hydrolysis

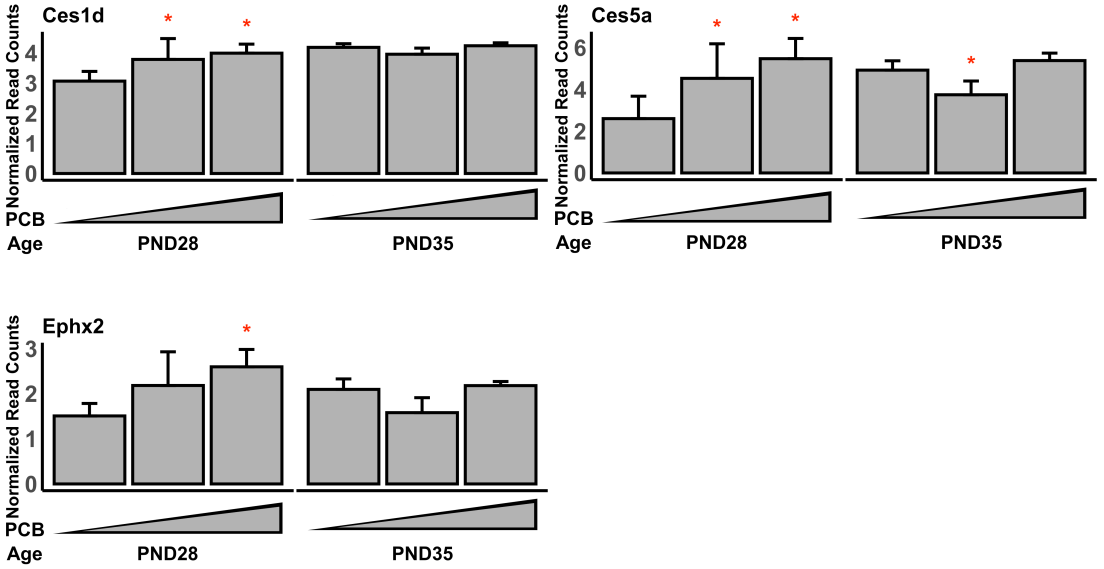


Figure 10.

A. The mRNA expression of differentially regulated reducing Phase I enzymes in testes of PND 28 and 35 mice (n = 3/group, RNA-seq). * indicate statistical significance by EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.
B. The mRNA expression of differentially regulated hydrolyzing Phase I enzymes in testes of PND 28 and 35 mice (n = 3/group, RNA-seq). * indicate statistical significance by EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.

Figure 11. Phase II Enzymes & Nuclear Receptors

A. Phase II Enzymes

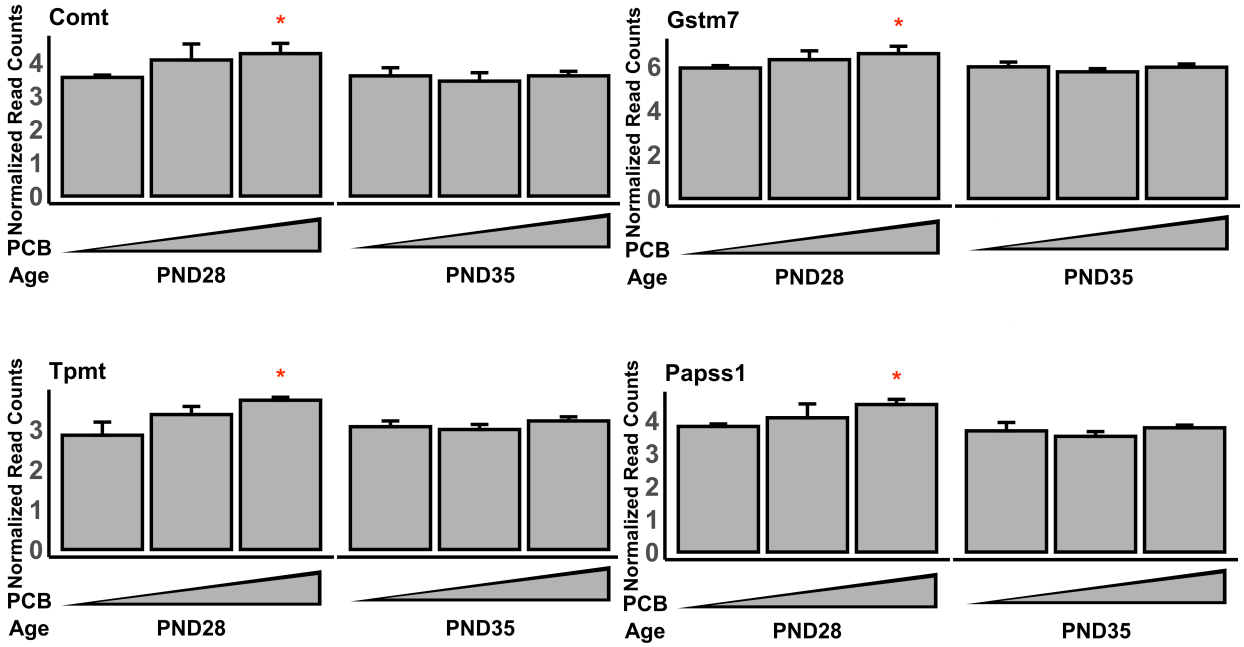


Figure 11.

A. The mRNA expression of differentially Phase II enzymes in testes of PND 28 and 35 mice (n = 3/group, RNA-seq). * indicate statistical significance by EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.
B. The mRNA expression of differentially regulated nuclear receptors in testes of PND 28 and 35 mice (n = 3/group, RNA-seq). * indicate statistical significance by EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.

B. Nuclear Receptors

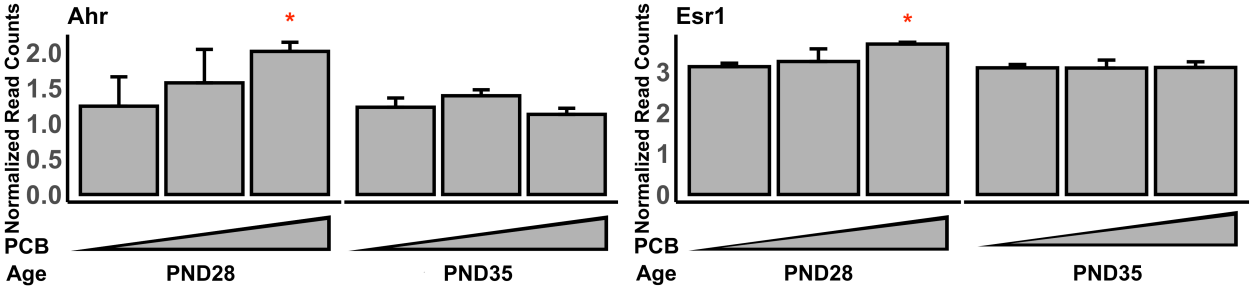


Figure 12. Transporters (Uptake)

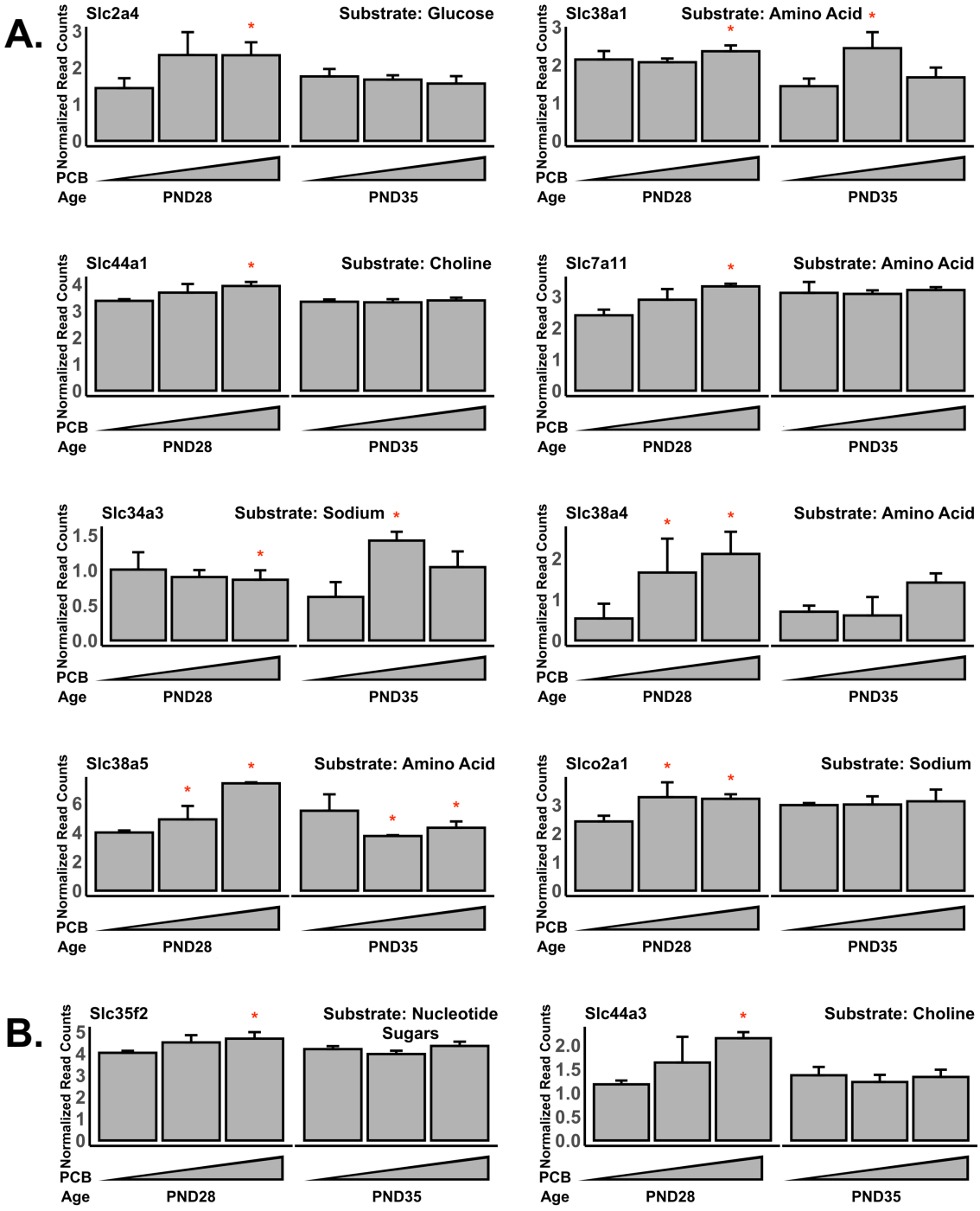


Figure 12.
The mRNA expression of differentially regulated drug processing uptake transporters in testes of PND 28 and 35 mice (n = 3/group, RNA-seq). * indicate statistical significance by EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.

Figure 13. Transporters (Efflux)

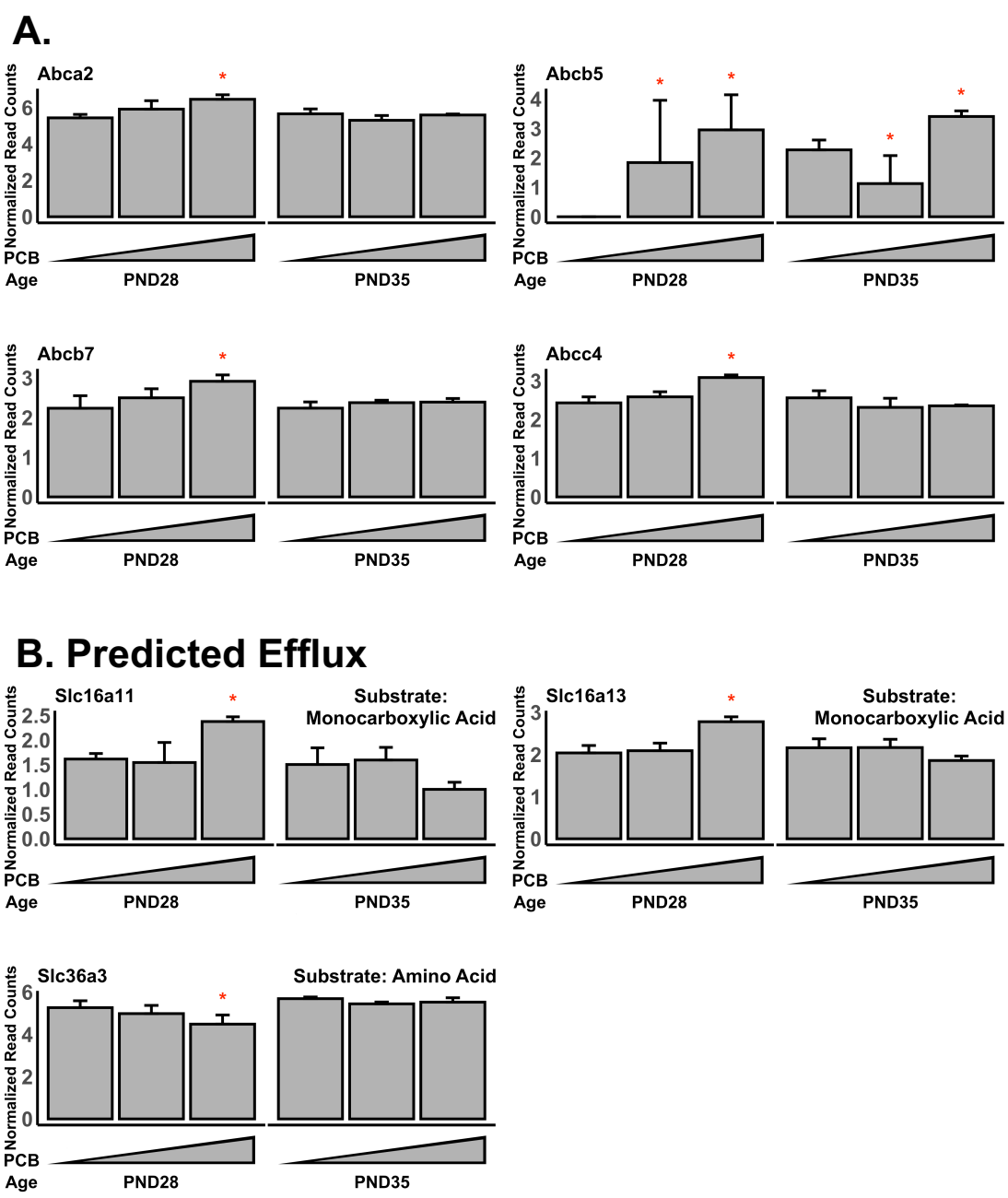


Figure 13.

A. The mRNA expression of differentially regulated drug processing efflux ATP-binding cassette transporters in testes of PND 28 and 35 mice (n = 3/group, RNA-seq). * indicate statistical significance by EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.
B. The mRNA expression of differentially regulated drug processing predicted efflux transporters in testes of PND 28 and 35 mice (n = 3/group, RNA-seq). * indicate statistical significance by EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.

Figure 14. Transporters (Efflux)

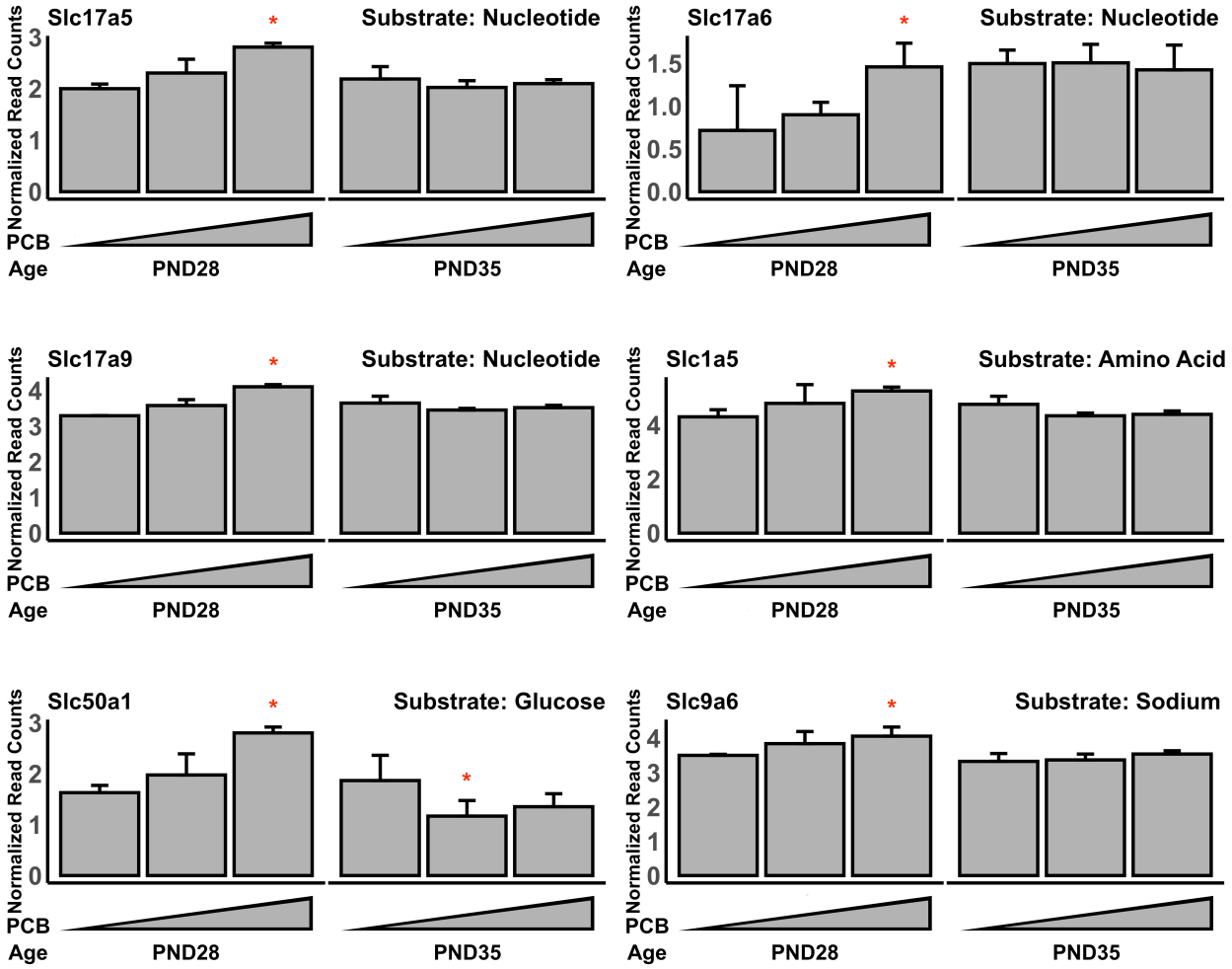


Figure 14.
The mRNA expression of differentially regulated drug processing efflux solute carrier transporters in testes of PND 28 and 35 mice (n = 3/group, RNA-seq). * indicate statistical significance by EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.

Figure 15. Transporters (Bidirectional)

A.

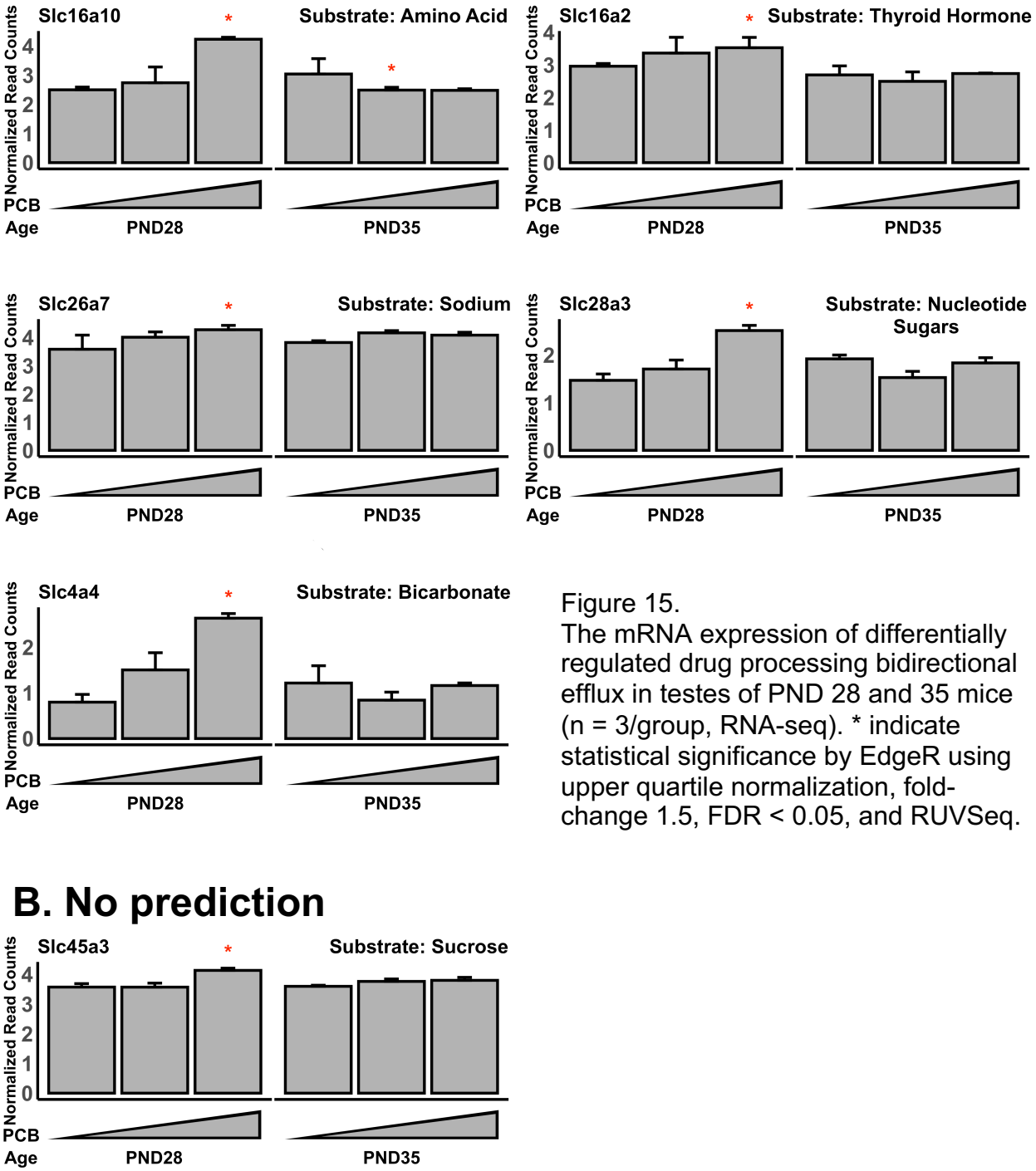


Figure 15.
The mRNA expression of differentially regulated drug processing bidirectional efflux in testes of PND 28 and 35 mice (n = 3/group, RNA-seq). * indicate statistical significance by EdgeR using upper quartile normalization, fold-change 1.5, FDR < 0.05, and RUVSeq.

B. No prediction

Figure 16. Summary Figure

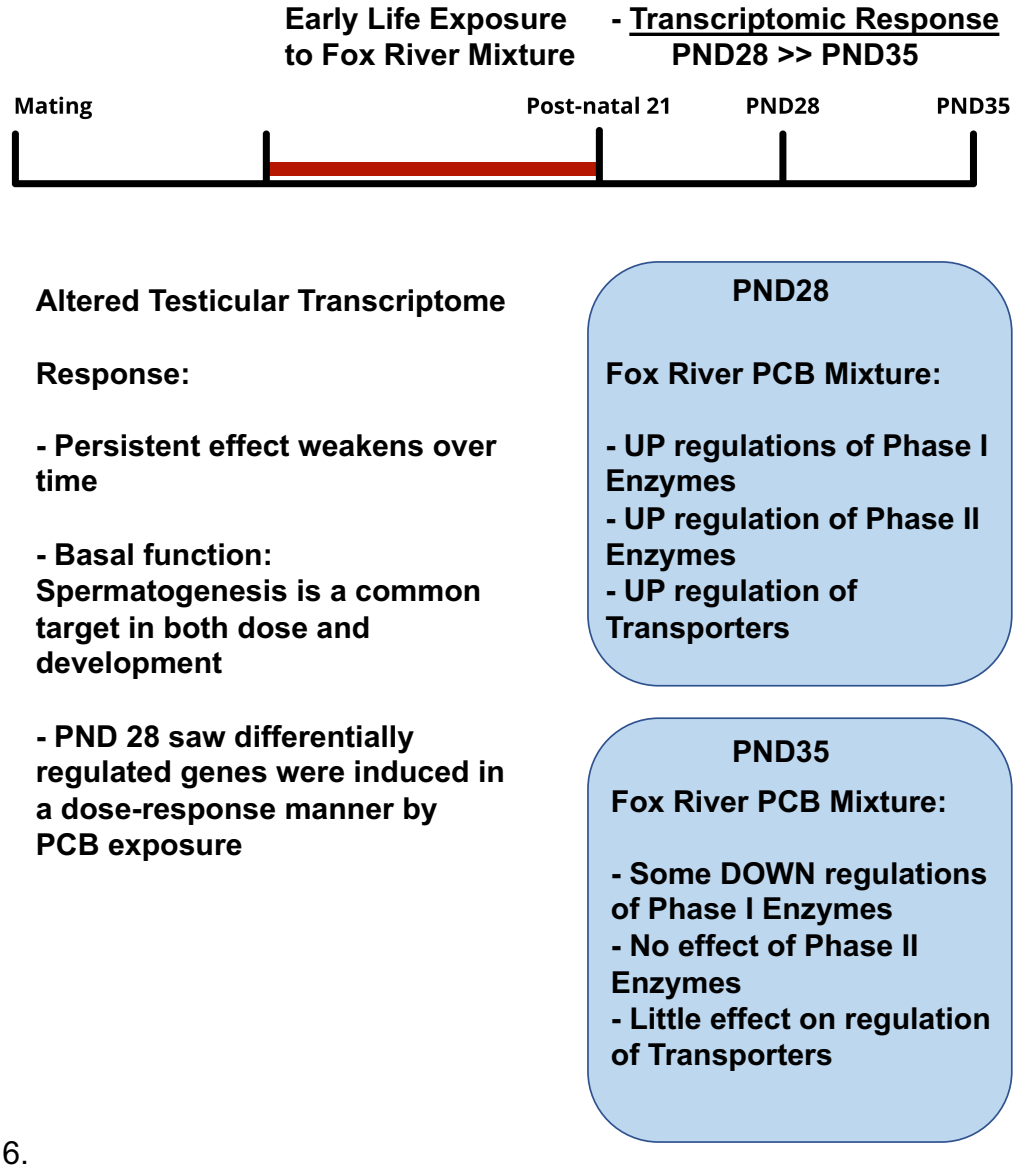


Figure 16.
Summary figure of results. Exposure lasted throughout pregnancy and lactation to mimic the conditions individuals would experience in the contaminated Fox River. An altered transcriptome response to PCB was observed with persistent effects that weaken between PND 28 and 35. Spermatogenesis was observed to be a common target in both dose and development with both Ahr and Esr1 nuclear receptors to be activated, both known xenobiotic receptors. At PND 28, differentially regulated genes were induced in a dose-response manner by PCB exposure. Genes related to CAR and retinol pathways were activated indicating a compensatory mechanism may be at play due to the decreased levels of drug-processing genes at PND 35. In conclusion, the Fox River PCB mixture upregulate drug-processing genes within the testis indicating xenobiotic transformation to limit exposure to PCBs.

SUPPLEMENTAL FIGURE LEGENDS

Figure S1. Mapping statistics from RNA alignment data

Figure S2. Box plots of differentially abundant metabolites in liver and serum. Data are shown as relative abundance. The pound signs and asterisks represent differential abundance in the CV and GF groups, respectively.

Figure S1. String Analysis was performed on differentially expressed genes with significance calculated using likelihood ratio testing, upper quartile LRT RUVSeq FC 1.5 FDR <0.05. Only edge confidence of the highest value (0.900) is shown with colored nodes indicating query proteins and first shell of interactors unless otherwise noted. Each network nodes represents proteins produced by a single, protein-coding gene locus. A. 193 differentially expressed genes in PND 28 Low Dose. Developmental pathways and bacterial response was noted. B. 1487 differentially expressed genes in PND 28 High Dose. C. 216 differentially expressed genes in PND 35 Low Dose. D. 118 differentially expressed genes in PND 35 High Dose. . String Analysis (0.900 confidence interval) of 9 uniquely expressed genes in PND 28 Low Dose. GTPases and skeletal muscular contractions were highly expressed in this dosage. String Analysis (0.700 confidence interval) of 29 expressed genes shared in all treatments. Genes associated here are consistent with sperm development and maturation

Table S1. Mapping Statistics

Table S1. Mapping Statistics		
K1	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	48462817 44977582 92.81%
K6	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	34474728 31745255 92.08%
K7	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	27250743 25259977 92.69%
K15	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	28069002 25914837 92.33%
K16	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	47117892 43565435 92.46%
K19	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	41914223 38575120 92.03%
K20	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	33935327 31417522 92.58%
K21	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	28932738 26811209 92.67%
K24	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	29500049 27546835 93.38%
K26	Number of input reads |	59853058

	Uniquely mapped reads number | Uniquely mapped reads % |	55754587 93.15%
K27	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	28907811 26796192 92.70%
K28	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	21686910 19983180 92.14%
K30	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	32039236 29678990 92.63%
K32	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	22191104 20520419 92.47%
K35	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	28825031 26781280 92.91%
K36	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	34178872 31529187 92.25%
K38	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	40747832 37815817 92.80%
K39	Number of input reads | Uniquely mapped reads number | Uniquely mapped reads % |	34432020 31969192 92.85%

Table S2A. String GO Biological Process PND 28 Low

String GO Biological Process P28 Low						
#term ID	term description	observed gene count	background gene count	strength	false discovery rate	matching proteins in your network (labels)
GO:0009888	Tissue development	38	1720	0.42	0.00046	Cav2,Cdh1,Pax2,Slc44a4,Stc1,Tbx3,Ros1,Rnase10,Tfap2b,Pax8,Lrp4,Pck1,Bmpr1b,Sema3c,Ces1d,St14,Pgm5,Fhod3,Rbm24,Akap9,Pou3f3,Ly6e,Dsg2,Ptgs1,Cbs,Postn,Lrp2,Erbb3,Bmpr2,Myh11,Ehf,Gata3,Enpp1,Vcan,Cfh,Ap1s2,Atrx,Odam
GO:0048513	Animal organ development	56	3230	0.32	0.00046	Cav2,Cdh1,Pax2,Slc44a4,Krt19,Stc1,Tbx3,Perp,Rnase10,Krt8,Kif5b,Tfap2b,Des,Pax8,Lrp4,Pck1,Ptpn22,Enpep,Bmpr1b,Sema3c,Npy,Pls3,Got2,St14,Ltf,Scd1,Hoxb7,Fhod3,Rbm24,Akap9,Abcb5,Cdo1,Hoxd4,Srd5a2,Pou3f3,Hoxb8,Ly6e,Dsg2,Nipbl,Ptgs1,Cbs,Lrp2,Erbb3,Bmpr2,Myh11,Hba-a1,B2m,Gata3,Enpp1,Vcan,Arhgap5,Cfh,Ap1s2,Atrx,Odam,Hoxb6
GO:0009617	Response to bacterium	21	660	0.58	0.001	Cd52,Lpl,Pck1,Ptpn22,Npy,Iigp1,Ltf,Scd1,Kiaa1551,Defb11,Lcn2,Defb37,Defb42,Wfdc13,Hba-a1,Defb43,B2m,Ptges,Wfdc15b,Gbp2,Psmb9
GO:0042742	Defense response to bacterium	13	260	0.78	0.0016	Npy,Iigp1,Ltf,Scd1,Defb11,Lcn2,Defb37,Defb42,Wfdc13,Defb43,B2m,Wfdc15b,Gbp2
GO:0050896	Response to stimulus	89	6908	0.19	0.0031	Cav2,Cdh1,Cd52,Pax2,Crip1,Krt19,Stc1,Ptgds,Lpl,Foxred2,Cldn7,Tbx3,Perp,Ros1,Smc6,Rab15,Nol8,Chrna2,Ly6f,Retnla,Krt18,Krt8,Kif5b,Gldc,Tfap2b,C4bp,Pax8,Lrp4,Pck1,Bche,Ptpn22,Bmpr1b,Casp8ap2,Sema3c,Npy,Iigp1,Atp2a1,Asb11,Got2,Ces1d,Ltf,Vipr1,Scd1,Cuzd1,Kiaa1551,Rbm24,Dpp4,Kcnk1,Akap9,Cdo1,Srd5a2,Defb11,Lcn2,Ly6e,Dsg2,Tmem150c,Blnk,Nipbl,Ptgs1,Gprc5c,Gpr82,Cbs,Defb37,Trim2,Defb42,Postn,Lrp2,Erbb3,Gpx3,Bmpr2,Wfdc13,Hba-a1,S100a16,Defb43,B2m,Ptges,Gata3,Enpp1,Wfdc15b,Arhgap5,Cfh,Ap1s2,Atrx,Zbtb20,Cth,Odam,Frk,Gbp2,Psmb9
GO:0052547	Regulation of peptidase activity	16	443	0.64	0.0032	Cdh1,Pax2,Perp,Serpina1f,Tfap2b,Casp8ap2,Ltf,Spink8,BC048546,Spink10,Wfdc13,Pi15,Wfdc6b,Wfdc8,Wfdc15b,Psmb9
GO:0044419	Interspecies interaction between organisms	29	1309	0.42	0.0034	Cav2,Cd52,Lpl,Krt8,Kif5b,C4bp,Pck1,Ptpn22,Npy,Iigp1,Ltf,Scd1,Kiaa1551,Dpp4,Thoc2,Defb11,Lcn2,Defb37,Defb42,Wfdc13,Hba-a1,Defb43,B2m,Ptges,Gata3,Wfdc15b,Cfh,Gbp2,Psmb9
GO:0010033	Response to organic substance	46	2742	0.3	0.0041	Cav2,Cdh1,Pax2,Krt19,Stc1,Ptgds,Lpl,Foxred2,Cldn7,Nol8,Ly6f,Krt18,Krt8,Kif5b,Gldc,Pax8,Pck1,Bche,Ptpn22,Bmpr1b,Iigp1,Atp2a1,Got2,Ces1d,Scd1,Cuzd1,Cdo1,Srd5a2,Lcn2,Ly6e,Dsg2,Cbs,Trim2,Postn,Lrp2,Bmpr2,Hba-a1,B2m,Ptges,Gata3,Enpp1,Cfh,Atrx,Zbtb20,Cth,Gbp2
GO:0010466	Negative regulation of peptidase activity	12	256	0.75	0.0041	Pax2,Serpina1f,Tfap2b,Ltf,Spink8,BC048546,Spink10,Wfdc13,Pi15,Wfdc6b,Wfdc8,Wfdc15b
GO:0052548	Regulation of endopeptidase activity	15	415	0.64	0.0041	Cdh1,Pax2,Perp,Serpina1f,Tfap2b,Casp8ap2,Ltf,Spink8,BC048546,Spink10,Wfdc13,Wfdc6b,Wfdc8,Wfdc15b,Psmb9

Table S2B. String GO Biological Process PND 28 High

#term ID	term description	observed gene count	background gene count	strength	false discovery rate	matching proteins in your network (labels)
GO:0009888	Tissue development	195	1720	0.28	1.42E-12	Cav2,Tbx2,Cdh1,Itga3,Shh,Elf3,Hlf,Pax2,Aqp1,Prkacb,Igf1r,Slc44a4,Krt14,Cav1,Rab25,Bmp7,Stc1,Lama5,Celsr1,Etv4,Tbx3,Ros1,Agr2,Rock2,Sdc1,Id2,Fam101b,Arg2,Gpld1,Aspn,Marveld2,F2rl1,Plau,Rnase10,Bmp1,Spry2,Cldn1,Cxadr,Ets2,Runx1,Lbh,Anxa1,Vwa2,Itgb8,Nrp1,Tfap2b,Casp8,Epha4,Serpine2,Lamc2,Prrx1,Pax8,Itgav,Lrp4,Pck1,Ccdc39,Slc7a11,Efna1,Bmpr1b,Ift74,Sema3c,Gpnmb,Mgp,Cd9,Nupr1,Sfrp1,Ces1d,Mmp15,St14,Ctsh,Hoxb5,Pgm5,Ppl,Npnt,Ccno,Creb3l2,Lum,Egr2,Fhod3,Rbm24,Tgfb2,Sh3pxd2b,Fgf1,Akap9,Myf6,Inhba,Hoxb4,Spry1,Sfn,Axin2,Pou3f3,Upk1b,Ar,Nfib,Ppp3ca,Myo3b,Igf1,Ly6e,Dsg2,Cd24a,Hoxd9,Atp7a,Ptgs1,Tmtc3,Ezr,Gpc3,Jak2,Gas1,Junb,Wnt5a,Cbs,Wls,Rock1,Egr1,Cebpb,Esr1,Pla2g4a,Postn,Cxcl12,Myom1,Bglap3,Ptpro,Hhip,Apc,Cdh3,Dab2,Lrp2,Dysf,Erbb3,Speg,Kif20b,Bmpr2,Dnase1l2,Myh11,Dlg5,Ehf,Lama3,Stat6,Zfp750,Hoxb3,Ccnd1,Cldn3,Crb3,Mbnl1,Hoxc4,Llgl2,Aldoc,Sema3b,Itga4,Gata3,Kitl,Enpp1,Camk2d,Hpn,Esrp1,Wnt7b,Vcan,Tfap2a,Arid4b,Tagln2,Tnfrsf19,Cfh,Hoxd3,Col7a1,Pbrm1,Ap1s2,Bcl2,Atrx,Trp63,Met,Esrp2,Ahr,Fgfr2,Erbb4,Aire,Dsp,Vegfa,Satb1,Odam,Apod,Sorbs2,Nebl,Prlr,Kif26b,Matn2,Lox,Trps1,Gcnt4,Cep290,Jmjd1c,Gcnt1,Edaradd,Pou3f1,Agrn,Ash1l

GO:0030154	Cell differentiation	344	3674	0.19	1.42E-12	Cav2,Tbx2,Cdh1,Egfl6,Slc26a3,Itga3,Hoxc8,Shh,Elf3,Hlf,G6pdx,Pax2,Igf1r,Slc44a4,Neu1,Krt14,Krt19,Cav1,Rab25,Bmp7,Tex15,Dazl,Stc1,Lama5,Celsr1,Nkap,Top2b,Suz12,Etv4,Slc2a4,Tbx3,Nrbp2,Ros1,Dusp6,Sycp3,Srebf1,Bzw2,Agr2,Rock2,Sdc1,Id2,Fam101b,Gpld1,Marveld2,Hexb,F2rl1,Emb,Rnase10,Esco2,Bmp1,Spry2,Cldn1,Alcam,Cxadr,Ets2,Runx1,Faim2,Mospd1,Krt8,Tnfrsf21,Lbh,Kif5b,Impact,Atp8b1,Gnaq,Anxa1,Fas,Vwa2,Gfra1,Itgb8,Farp1,Nptx1,Sclt1,Nrp1,Cplx2,Prex2,Tfap2b,Casp8,Zap70,Epha4,Serpine2,Mlph,Slc45a3,Lamc2,Prrx1,Fcgr2b,Acvr1c,Phf19,Pax8,Itgav,Lrp4,Pck1,Fabp4,Slc7a11,P2ry1,Bche,Mme,Ptpn22,Sycp1,Efna1,Cd1d1,Hormad1,Bmpr1b,Ift74,Tnfrsf1b,Mycl,Sema3c,Smarcd3,Cd38,Gabrb1,Stap1,Plac8,Tmem106b,Gpnmb,Npy,Bhlhe40,Mgp,Bhlhe41,Cd9,Nav3,Nupr1,Parva,Ptpn5,Dock11,Acsl4,Mecp2,Sfrp1,Ces1d,Mmp15,St14,Mpzl2,Plekha1,Six6os1,Hoxb5,Pgm5,Scd1,Nexn,Lepr,Brca2,Ppl,Syne1,Pcm1,Npnt,Ccno,Hoxb7,Creb3l2,Egr2,Ss18l1,Fhod3,Zbtb1,Gpr126,Rbm24,Tgfb2,Mfhas1,Sh3pxd2b,Thoc2,Myof,Fgf1,Six5,Akap9,Abcb5,Zfp503,Hook3,Mylip,Myf6,Zdhhc15,Inhba,Hoxd4,Hoxb4,Ptger4,Srd5a2,Ccdc88a,Spry1,Sfn,Axin2,Pou3f3,Upk1b,Ccdc66,Ar,Nfib,Ppp3ca,Emx2,Erbb2,Myo3b,Igf1,Pik3r1,Frmd7,Cd24a,Hoxd9,Foxi1,Atp7a,Lingo1,C1galt1c1,Nipbl,Adra2c,Ptgs1,Tmtc3,C77080,Ezr,Gpc3,Jak2,Gas1,Junb,Wnt5a,Rnase9,Nav1,Tmem120b,Rock1,Egr1,Cebpb,Esr1,Slco4c1,Yes1,Postn,Cxcl12,Myom1,Epha1,Chrdl1,Bglap3,Tubb2b,Ptpro,Hhip,Ablim1,Apc,Etv5,Cdh3,Dab2,Lrp2,Adrb3,Dysf,Erbb3,Aldh6a1,Nin,Rnasel,Speg,Kif20b,Bmpr2,Notch3,C77370,Zfx,Hdac7,Dnase1l2,Mybl1,Dgkg,Myh11,Dlg5,Ehf,Ddx3y,Lama3,Stat6,Zfp750,Plscr1,Hoxb3,Ccnd1,Cldn3,Tpd52,Lig4,Tmf1,Crb3,Zcchc11,Omp,Cebpa,Tet2,Mbnl1,B2m,Aldoc,Sema3b,Itga4,Ptbp3,Abca2,Gata3,Kitl,Enpp1,Camk2d,Idh2,Ube3a,Esrp1,Wnt7b,Arhgef28,Vcan,Camk2b,Tfap2a,Arid4b,Tagln2,Ildr2,Cfh,Hoxd3,Zfp281,Col7a1,Pbrm1,Ap1s2,Zfp932,Bcl2,Amot,Atrx,Gpr116,Klf7,Rbm11,Tead3,Thy1,Tcf4,Trp63,Steap4,Met,Ahr,Fgfr2,Syt2,Samd9l,Syk,Erbb4,Aire,Dsp,Vegfa,Satb1,Apod,Fsip2,Sorbs2,Nebl,Prlr,Stau2,Cdhr5,Vldlr,Matn2,Tbx22,Gdf10,Lox,Trps1,Frk,Cep290,Ccr2,Enpp2,Nedd4l,Retn,Tet1,Apoe,Jmjd1c,H2-D1,Apobec3,Edaradd,Topaz1,Pou3f1,Agrn,Kirrel3,Spock1

GO:0032502	Developmental process	477	5629	0.15	1.42E-12	Hoxb9,Cav2,Tbx2,Cdh1,Alox12,Egfl6,Ocrl,Slc26a3,Itga3,Hoxc8,Shh,Elf3,St8sia6,Gys1,Hlf,G6pdx,Pax2,Aqp1,Prkacb,Igf1r,Rcn1,Ggt1,Slc44a4,Neu1,Krt14,Krt19,Cav1,Rab25,Rpl10,Bmp7,Kcnq1,Tex15,Dazl,Cad,Stc1,Lama5,Celsr1,Nkap,Rbfox3,Top2b,Suz12,Atad5,Etv4,Slc2a4,Tbx3,Nrbp2,Perp,Ros1,Lims1,Atp2b1,Dusp6,Sycp3,Ccng1,Srebf1,Bzw2,Agr2,Rock2,Sdc1,Rgs9,Smc6,Id2,Fam101b,Arg2,Gpld1,Aspn,Cxcl14,Marveld2,Hexb,F2rl1,Emb,Plau,Rnase10,Esco2,Bmp1,Spry2,Rrm2b,Hrsp12,Cldn1,Alcam,Cxadr,Ets2,Runx1,Faim2,Mospd1,Krt8,Tnfrsf21,Lbh,Kif5b,Impact,Atp8b1,Gnaq,Anxa1,Pcsk5,Fas,Slc1a1,Capn1,Smc3,Vwa2,Gfra1,Sat1,Itgb8,Chm,Farp1,Nptx1,Sclt1,Nrp1,Cplx2,Rb1cc1,Prex2,Tfap2b,Casp8,Zap70,Des,Epha4,Serpine2,Mlph,Slc45a3,Lamc2,Prrx1,Fcgr2b,Acvr1c,Phf19,Pax8,Itgav,Kif18a,Meis2,Lrp4,Mal,Pck1,Fabp4,Ccdc39,Slc7a11,P2ry1,Bche,Mme,Ptpn22,Sycp1,Efna1,Enpep,Cd1d1,Hormad1,Bmpr1b,Ift74,Tnfrsf1b,Mycl,Sema3c,Smarcd3,Angptl7,Cd38,Gabrb1,Stap1,Plac8,Tmem106b,Tspan12,Gpnmb,Npy,Bhlhe40,Mgp,Kcnj8,Bhlhe41,Cd9,Slc17a6,Nav3,Mfge8,Nupr1,Parva,Dkk3,Ptpn5,Mki67,Dock11,Pls3,Cox7b,Acsl4,Rps4x,Mecp2,Sfrp1,Got2,Ces1d,Mmp15,St14,Mpzl2,Hcn4,Ctsh,Ltf,Plekha1,Six6os1,Plvap,Hoxb5,Pgm5,Galnt11,Scd1,Nexn,Lepr,Brca2,Ppl,Syne1,Ptchd1,Pcm1,Npnt,Ccno,Hoxb7,Creb3l2,Lum,Hs3st6,Egr2,Ss18l1,Fhod3,Ofd1,Zbtb1,Lpar6,Gpr126,Rbm24,Tgfb2,Mfhas1,Sh3pxd2b,Thoc2,Myof,Fgf1,Six5,Rab26,Akap9,Abcb5,Cdo1,Zfp503,Gjb3,Hook3,Mylip,Ramp3,Myf6,Zdhhc15,Inhba,Hoxd4,Hoxb4,Wfs1,Serpinf2,Ptger4,Srd5a2,Ccdc88a,Spry1,Sfn,Axin2,Nrip1,Pou3f3,Upk1b,Hoxb8,Ccdc66,Ar,Nfib,Ppp3ca,Emx2,Cldn4,Erbb2,Myo3b,Igf1,Ly6e,Pik3r1,Dsg2,Frmd7,Cenpe,Cd24a,Upf2,Hoxd9,Foxi1,Atp7a,Lingo1,C1galt1c1,Nipbl,Shisa2,Adra2c,Ptgs1,Tmtc3,C77080,Gjb1,Ezr,Gpc3,Jak2,Pdlim1,Gas1,Junb,Wnt5a,Rnase9,Cbs,Nav1,Wls,Tmem120b,Vps13a,Rock1,Egr1,Cebpb,Uty,Esr1,Pla2g4a,Dach1,Slco4c1,Yes1,Postn,Cxcl12,Myom1,Epha1,Calcrl,Chrdl1,Hp,Bglap3,Ptpn3,Tubb2b,Mup4,Ptpro,Emp2,Hhip,Ablim1,Apc,Etv5,Cdh3,Dab2,Lrp2,Sycp2,Adrb3,Ltbp3,Dysf,Erbb3,Arnt2,Aldh6a1,Nin,Rnasel,Speg,Kif20b,Bmpr2,Notch3,Uprt,C77370,Zfx,Hdac7,Pi15,Dnase1l2,Mybl1,Dgkg,Myh11,Dlg5,Ehf,Ddx3y,Lama3,Stat6,Zfp750,Plscr1,Hoxb3,Ccnd1,Cldn3,Tpd52,Lig4,Tmf1,Crb3,Ramp1,Pgap1,Zcchc11,Omp,Cebpa,Tet2,Mbnl1,Fjx1,Hoxc4,Shroom2,Llgl2,B2m,Aldoc,Sema3b,Itga4,Ptbp3,Abca2,Aco1,Gata3,Kitl,Enpp1,Camk2d,Idh2,Ube3a,Hpn,Esrp1,Shroom1,Wnt7b,Arhgef28,Top1,Nnat,Vcan,Camk2b,Tfap2a,Arid4b,Sstr1,Arhgap5,Tagln2,Tnfrsf19,Ildr2,Cfh,Hoxd3,Zfp281,Col7a1,Pbrm1,Ap1s2,Cryba4,Pla2r1,Zfp932,Rif1,Bcl2,Amot,Atrx,Gpr116,Capg,Klf7,Rbm11,Ephb6,Tead3,Thy1,Mbnl3,Tcf4,Trp63,Steap4,Met,Comt,Esrp2,Ahr,Fgfr2,Syt2,Ano1,Samd9l,Syk,Fzd10,Erbb4,Aire,Dsp,Vegfa,Satb1,Lcp1,Odam,Sri,Apod,Fsip2,Sorbs2,Nebl,Prlr,Kif26b,Stau2,Wars,Trove2,Cdhr5,Vldlr,Fam3c,Prickle3,Matn2,Tbx22,Gdf10,Lox,Trps1,Phc3,Frk,Gcnt4,Rnf43,Cep290,Nrg4,Ccr2,Enpp2,Nedd4l,Retn,Lrrc32,Tet1,Hoxb6,Apoe,Jmjd1c,Gcnt1,H2-D1,Apobec3,Zbed6,Edaradd,Topaz1,Pou3f1,Agrn,Kirrel3,Ash1l,Spock1

GO:0048869	Cellular developmental process	347	3731	0.19	1.42E-12	Cav2,Tbx2,Cdh1,Egfl6,Slc26a3,Itga3,Hoxc8,Shh,Elf3,Hlf,G6pdx,Pax2,Igf1r,Slc44a4,Neu1,Krt14,Krt19,Cav1,Rab25,Bmp7,Tex15,Dazl,Stc1,Lama5,Celsr1,Nkap,Top2b,Suz12,Etv4,Slc2a4,Tbx3,Nrbp2,Ros1,Dusp6,Sycp3,Srebf1,Bzw2,Agr2,Rock2,Sdc1,Smc6,Id2,Fam101b,Gpld1,Marveld2,Hexb,F2rl1,Emb,Rnase10,Esco2,Bmp1,Spry2,Cldn1,Alcam,Cxadr,Ets2,Runx1,Faim2,Mospd1,Krt8,Tnfrsf21,Lbh,Kif5b,Impact,Atp8b1,Gnaq,Anxa1,Fas,Vwa2,Gfra1,Itgb8,Farp1,Nptx1,Sclt1,Nrp1,Cplx2,Prex2,Tfap2b,Casp8,Zap70,Epha4,Serpine2,Mlph,Slc45a3,Lamc2,Prrx1,Fcgr2b,Acvr1c,Phf19,Pax8,Itgav,Lrp4,Pck1,Fabp4,Slc7a11,P2ry1,Bche,Mme,Ptpn22,Sycp1,Efna1,Cd1d1,Hormad1,Bmpr1b,Ift74,Tnfrsf1b,Mycl,Sema3c,Smarcd3,Cd38,Gabrb1,Stap1,Plac8,Tmem106b,Gpnmb,Npy,Bhlhe40,Mgp,Bhlhe41,Cd9,Nav3,Nupr1,Parva,Ptpn5,Dock11,Acsl4,Mecp2,Sfrp1,Ces1d,Mmp15,St14,Mpzl2,Plekha1,Six6os1,Hoxb5,Pgm5,Scd1,Nexn,Lepr,Brca2,Ppl,Syne1,Pcm1,Npnt,Ccno,Hoxb7,Creb3l2,Egr2,Ss18l1,Fhod3,Zbtb1,Gpr126,Rbm24,Tgfb2,Mfhas1,Sh3pxd2b,Thoc2,Myof,Fgf1,Six5,Akap9,Abcb5,Zfp503,Hook3,Mylip,Myf6,Zdhhc15,Inhba,Hoxd4,Hoxb4,Ptger4,Srd5a2,Ccdc88a,Spry1,Sfn,Axin2,Pou3f3,Upk1b,Ccdc66,Ar,Nfib,Ppp3ca,Emx2,Erbb2,Myo3b,Igf1,Pik3r1,Frmd7,Cd24a,Hoxd9,Foxi1,Atp7a,Lingo1,C1galt1c1,Nipbl,Adra2c,Ptgs1,Tmtc3,C77080,Ezr,Gpc3,Jak2,Gas1,Junb,Wnt5a,Rnase9,Nav1,Tmem120b,Rock1,Egr1,Cebpb,Esr1,Slco4c1,Yes1,Postn,Cxcl12,Myom1,Epha1,Chrdl1,Bglap3,Tubb2b,Mup4,Ptpro,Hhip,Ablim1,Apc,Etv5,Cdh3,Dab2,Lrp2,Adrb3,Dysf,Erbb3,Aldh6a1,Nin,Rnasel,Speg,Kif20b,Bmpr2,Notch3,C77370,Zfx,Hdac7,Dnase1l2,Mybl1,Dgkg,Myh11,Dlg5,Ehf,Ddx3y,Lama3,Stat6,Zfp750,Plscr1,Hoxb3,Ccnd1,Cldn3,Tpd52,Lig4,Tmf1,Crb3,Zcchc11,Omp,Cebpa,Tet2,Mbnl1,B2m,Aldoc,Sema3b,Itga4,Ptbp3,Abca2,Gata3,Kitl,Enpp1,Camk2d,Idh2,Ube3a,Esrp1,Wnt7b,Arhgef28,Vcan,Camk2b,Tfap2a,Arid4b,Tagln2,Ildr2,Cfh,Hoxd3,Zfp281,Col7a1,Pbrm1,Ap1s2,Pla2r1,Zfp932,Bcl2,Amot,Atrx,Gpr116,Klf7,Rbm11,Tead3,Thy1,Tcf4,Trp63,Stea p4,Met,Ahr,Fgfr2,Syt2,Samd9l,Syk,Erbb4,Aire,Dsp,Vegfa,Satb1,Apod,Fsip2,Sorbs2,Nebl,Prlr,Stau2,Cdhr5,Vldlr,Matn2,Tbx22,Gdf10,Lox,Trps1,Frk,Cep290,Ccr2,Enpp2,Nedd4l,Retn,Tet1,Apoe,Jmjd1c,H2-D1,Apobec3,Edaradd,Topaz1,Pou3f1,Agrn,Kirrel3,Spock1

GO:0048731	System development	387	4350	0.17	2.96E-12	Hoxb9,Cav2,Tbx2,Cdh1,Alox12,Itga3,Hoxc8,Shh,Elf3,Gys1,Hlf,G6pdx,Pax2,Aqp1,Prkacb,Igf1r,Rcn1,Slc44a4,Neu1,Krt19,Cav1,Rpl10,Bmp7,Kcnq1,Tex15,Cad,Stc1,Lama5,Celsr1,Nkap,Rbfox3,Top2b,Suz12,Atad5,Etv4,Tbx3,Nrbp2,Perp,Atp2b1,Srebf1,Bzw2,Agr2,Rock2,Sdc1,Rgs9,Id2,Fam101b,Arg2,Gpld1,Aspn,Cxcl14,Hexb,F2rl1,Emb,Plau,Rnase10,Esco2,Bmp1,Spry2,Rrm2b,Hrsp12,Cldn1,Alcam,Cxadr,Runx1,Faim2,Krt8,Tnfrsf21,Lbh,Kif5b,Impact,Atp8b1,Gnaq,Anxa1,Pcsk5,Fas,Slc1a1,Capn1,Vwa2,Gfra1,Sat1,Itgb8,Chm,Farp1,Nptx1,Sclt1,Nrp1,Cplx2,Rb1cc1,Prex2,Tfap2b,Casp8,Zap70,Des,Epha4,Serpine2,Slc45a3,Lamc2,Prrx1,Fcgr2b,Acvr1c,Pax8,Itgav,Kif18a,Meis2,Lrp4,Mal,Pck1,Ccdc39,Slc7a11,P2ry1,Bche,Mme,Ptpn22,Efna1,Enpep,Cd1d1,Bmpr1b,Ift74,Tnfrsf1b,Mycl,Sema3c,Smarcd3,Angptl7,Cd38,Gabrb1,Stap1,Tmem106b,Tspan12,Gpnmb,Npy,Bhlhe40,Mgp,Kcnj8,Bhlhe41,Cd9,Slc17a6,Nav3,Mfge8,Nupr1,Parva,Ptpn5,Mki67,Dock11,Pls3,Cox7b,Acsl4,Mecp2,Sfrp1,Got2,St14,Mpzl2,Ctsh,Ltf,Plekha1,Hoxb5,Galnt11,Scd1,Nexn,Lepr,Brca2,Ppl,Syne1,Ptchd1,Pcm1,Npnt,Hoxb7,Creb3l2,Lum,Egr2,Ss18l1,Fhod3,Zbtb1,Gpr126,Rbm24,Tgfb2,Mfhas1,Sh3pxd2b,Thoc2,Fgf1,Six5,Rab26,Akap9,Abcb5,Cdo1,Gjb3,Hook3,Mylip,Ramp3,Myf6,Zdhhc15,Inhba,Hoxd4,Hoxb4,Wfs1,Serpinf2,Ptger4,Srd5a2,Ccdc88a,Spry1,Sfn,Axin2,Nrip1,Pou3f3,Hoxb8,Ccdc66,Ar,Nfib,Ppp3ca,Emx2,Cldn4,Erbb2,Myo3b,Igf1,Ly6e,Pik3r1,Dsg2,Frmd7,Cd24a,Upf2,Hoxd9,Foxi1,Atp7a,Lingo1,Nipbl,Adra2c,Ptgs1,Tmtc3,Gjb1,Gpc3,Jak2,Pdlim1,Gas1,Junb,Wnt5a,Cbs,Nav1,Wls,Vps13a,Rock1,Egr1,Cebpb,Uty,Esr1,Pla2g4a,Postn,Cxcl12,Myom1,Epha1,Calcrl,Chrdl1,Hp,Bglap3,Ptpn3,Tubb2b,Ptpro,Hhip,Ablim1,Apc,Etv5,Cdh3,Dab2,Lrp2,Sycp2,Ltbp3,Dysf,Erbb3,Arnt2,Nin,Speg,Kif20b,Bmpr2,Notch3,Uprt,C77370,Zfx,Hdac7,Dnase1l2,Dgkg,Myh11,Dlg5,Lama3,Stat6,Plscr1,Hoxb3,Ccnd1,Cldn3,Tpd52,Lig4,Tmf1,Ramp1,Pgap1,Omp,Cebpa,Tet2,Mbnl1,Fjx1,Hoxc4,Shroom2,Llgl2,B2m,Sema3b,Itga4,Ptbp3,Abca2,Gata3,Kitl,Enpp1,Camk2d,Idh2,Ube3a,Hpn,Esrp1,Wnt7b,Arhgef28,Nnat,Vcan,Camk2b,Tfap2a,Arid4b,Sstr1,Arhgap5,Tnfrsf19,Ildr2,Cfh,Hoxd3,Col7a1,Pbrm1,Ap1s2,Cryba4,Bcl2,Amot,Atrx,Gpr116,Capg,Klf7,Tead3,Thy1,Tcf4,Trp63,Met,Esrp2,Ahr,Fgfr2,Syt2,Ano1,Samd9l,Syk,Erbb4,Aire,Dsp,Vegfa,Satb1,Lcp1,Odam,Sri,Apod,Sorbs2,Nebl,Prlr,Kif26b,Stau2,Wars,Trove2,Vldlr,Matn2,Lox,Trps1,Gcnt4,Cep290,Nrg4,Ccr2,Enpp2,Nedd4l,Tet1,Hoxb6,Apoe,Jmjd1c,Gcnt1,H2-D1,Apobec3,Edaradd,Pou3f1,Agrn,Kirrel3,Ash1l,Spock1

GO:0065007	Biological regulation	786	10591	0.09	2.96E-12	Hoxb9,Cav2,Tbx2,Cdh1,Alox12,Mcts1,Rem1,Egfl6,Ovgp1,Cd52,Araf,Ocrl,Slc26a3,Cnn1,Itga3,Acap1,Hoxc8,Hltf,Shh,Elf3,Ranbp2,Ier3,Hlf,Gstm7,Adh1,G6pdx,Pax2,Mospd2,Aqp1,Mapk13,Nfe2l3,Prkacb,Igf1r,Atp4a,Ggt1,Crip1,Slc44a4,Neu1,Krt19,Cav1,Rab25,Rpl10,Bmp7,Kcnc4,Kcnq1,Tex15,Kcnd1,Dazl,Cad,Birc3,Stc1,Ptgds,Prrt1,Hivep2,Lpl,Lama5,Il17rb,Celsr1,Nkap,Scube1,Mpp2,Rbfox3,Top2b,Suz12,Atad5,Etv4,Slc2a4,Cldn7,Tbx3,Wwc1,Nrbp2,Perp,Abracl,Ros1,Lims1,Atp2b1,Dusp6,Ccar1,Pcbd1,Ccng1,Rad50,Smek2,Srebf1,Atp6v1c2,Agr2,Rock2,Sdc1,Rgs9,Smc6,Ubxn2a,Id2,Fam101b,Nemf,Rab15,Serpina1f,Plek2,Arg2,Npc2,Gpld1,Aspn,Ogn,Nol8,Cxcl14,Slc28a3,Hexb,F2rl1,Plau,Rnase10,Fam208a,Tkt,Esco2,Chrna2,Bmp1,Itm2b,Spry2,Rrm2b,Hrsp12,Kcnv1,Fbxo32,Adcy8,Cldn1,Gpihbp1,Ly6f,Retnla,Gpr128,Btg3,Cxadr,St6gal1,Ets2,Runx1,Faim2,Krt18,Sncg,Mospd1,Krt8,Tnfrsf21,Cd2ap,Lbh,Ehd3,Rhoq,Clpsl2,Kif5b,Esco1,Impact,Pggt1b,Atp8b1,Tmx3,Gnaq,Anxa1,Pcsk5,Fas,Slc1a1,Capn1,Smc3,C1qtnf9,Vwa2,Gfra1,Lztfl1,Sat1,Itgb8,Sp4,Cnpy2,Chm,Farp1,Nptx1,Cnksr2,Sclt1,Nrp1,Cplx2,Rb1cc1,Prex2,Tfap2b,Tmem14a,Ikzf2,Casp8,Sgol2,Eif5b,Zap70,Ogfrl1,Epha4,Serpine2,C4bp,Slc45a3,Lamc2,Dpt,Prrx1,Fcgr2b,Rgs5,Fam129b,Acvr1c,Phf19,Lcn5,Arrdc1,Pax8,Itgav,Kif18a,Depdc7,Meis2,Lrp4,Casc5,Mal,Prom2,Cst11,Pck1,Fabp4,Ccdc39,Slc7a11,P2ry1,Bche,Mme,Veph1,Ptpn22,Sycp1,S100a11,Efna1,Enpep,Cd1d1,Hormad1,Cpne3,Atp6v0d2,Bmpr1b,Casp8ap2,Epb4.1l4b,Tpm2,Cyp2j6,Ift74,Tnfrsf1b,Mycl,Tspan1,Sema3c,Padi2,Smarcd3,Angptl7,Arhgef16,Cd38,Hgfac,Gabrb1,Stap1,Sult1e1,Plac8,Tpst2,Tmem106b,Rasl11a,Tspan12,Arhgef5,Gpnmb,Npy,Smarcad1,Bhlhe40,Clec2d,Mgp,Kcnj8,Bhlhe41,Cidec,Vamp1,Cd9,Slc17a6,Nav3,Mfge8,Rab30,Nucb2,Nupr1,Prss8,Il4ra,Parva,Dkk3,Pycard,Ptpn5,Mki67,Il13ra1,Dock11,Dynlt3,F8,Mtcp1,Brcc3,Pls3,Hmgn5,Sytl4,Acsl4,Rps6ka3,Rps4x,Abcb7,Asb11,Irak1,Mecp2,Dkc1,Sfrp1,Ido1,Got2,Ces1d,Ifi30,Rrad,Trim29,Phip,Clk1,Hcn4,Ctsh,Plscr2,Ltf,Vipr1,Rab6b,Plekha1,Six6os1,Plvap,Hoxb5,Phf20l1,Rgl3,Arhgef4,Galnt11,Tjp3,Cilp,Scd1,Hspb8,Nexn,Cuzd1,Scai,Zfp292,B4galnt2,Lepr,Tmem30b,Slc16a2,Plcl1,Bdp1,Brca2,Txlng,Paf,Arhgap27,Syne1,Ptchd1,Pcm1,Pmepa1,Cblc,Npnt,Ccno,Hoxb7,Creb3l2,Kcnh3,Maob,Lum,Egr2,Kiaa1551,Ss18l1,Fhod3,Ofd1,Egln3,Eltd1,Zbtb1,Lpar6,Dsc2,Thrsp,Gpr126,Rbm24,Setd7,Pnpla3,Tgfb2,Dpp4,Mfhas1,Sh3pxd2b,Thoc2,Arhgap18,Prkcdbp,Slco4a1,Myof,Ryden,Ogt,Dmxl1,Zbtb41,Fgf1,Six5,Rab26,Kcnk1,Akap9,Abcb5,Asb13,Cdo1,Zfp503,Hook3,Tspan15,Zfp458,Dock4,Mylip,Ramp3,Myf6,Zdhhc15,Fermt1,Inhba,Hoxd4,Hoxb4,Wfs1,Rasl10a,Rbm25,Serpinf2,Ptger4,Srd5a2,Ccdc88a,Spry1,Cacna2d1,Slk,Sfn,Rnf149,Pyurf,Axin2,Nrip1,Rasd1,Pou3f3,Bcl2l15,Hoxb8,Spink8,Ccdc66,Ar,Nfib,Fut4,Ppp3ca,Emx2,Cldn4,Erbb2,Lcn2,Gcc2,Syt12,Myo3b,Taok1,Trim16,Sdpr,Zfp445,Secisbp2l,Zfp518a,Igf1,Ly6e,Pik3r1,Cfd,Zfp697,Dsg2,Frmd7,Tmem150c,Blnk,Cenpe,Cd24a,Fbxo10,S100a1,Upf2,Ccdc125,Hoxd9,Bod1l,Tcim,Foxi1,Atp7a,Ddit4l,Lingo1,C1galt1c1,Nipbl,Shisa2,Eif2s3x,BC048546,Spin2c,Adra2c,Aff1,Rbp1,Acpp,Ulk3,Ptgs1,Kdm5d,Tmtc3,Gprc5c,Gpr82,Lurap1l,Spink10,Asap2,Dram2,Ezr,Gpc3,Jak2,Pdlim1,Gas1,Rnf180,Junb,Wnt5a,Socs6,Ppp1r3b,Socs4,Rnase9,Cbs,Wls,Vps13a,Trib1,Ephx2,Ghr,Rock1,Egr1,Ppap2c,Cebpb,Trim2,Uty,Esr1,Pla2g4a,Pygl,Elovl6,Dach1,Ifitm2,Car12,Yes1,Postn,Cxcl12,Myom1,Epha1,Calcrl,Chrdl1,Hp,Kcnh7,Gria2,Bglap3,Ptpn3,Tubb2b,Mysm1,Mup4,Ackr4,Zfp280c,Ptpro,Caml3,Osbpl6,Emp2,Hhip,Ablim1,Apc,Etv5,Klk1b27,Cdh3,Dab2,Lrp2,Sycp2,Spink12,Adrb3,Scnn1a,Ltbp3,Armcx3,Dysf,Erbb3,Plch1,Arnt2,Nin,Klk1b21,Susd4,Rnasel,Bicd1,Asb18,Guf1,Kif20b,Bmpr2,Notch3,Uprt,C77370,Zfx,Wf

						dc13,Hdac7,Mbnl2,Pi15,Mybl1,Dok1,Dgkg,Adh7,Bmf,Dlg5,Ehf,Ssb,Map9,Cp,Wnk2,Lama3,Stat6,Piezo1,Zfp750,Slc16a10,Plscr1,Arhgef40,Hoxb3,Ccnd1,Cldn3,Wfdc6b,Tpd52,Cited4,Il1rl2,Lig4,Tmf1,Moxd1,Tbc1d8b,Map3k2,Spink11,Ramp1,Zcchc11,Omp,Cebpa,Zfp280d,Tet2,Lrif1,Mbnl1,Defb25,Lgals12,Rprm,Hoxc4,Larp4,Bmyc,Cldn10,Lrcol1,Shroom2,Mdfic,Llgl2,Itga2b,Car4,Trpm7,B2m,Sema3b,Itga4,Ptges,Ptbp3,Abca2,Aco1,Gata3,Chml,Kitl,Lilrb4,Enpp1,Serinc2,Camk2d,Synpo2,Kcnj16,Arap1,Idh2,Ube3a,Kcnc3,Hpn,Esrp1,Apoc1,Zfp62,Wfdc9,Wfdc8,Wfdc15b,Wnt7b,Arhgef28,Top1,Nnat,Vcan,Tox3,Camk2b,Tfap2a,Zscan26,Arid4b,Sstr1,Arhgap5,Ntsr2,Tnfrsf19,Ildr2,Afap1l2,Rbms3,Dclk3,Cfh,Hoxd3,Zfp281,Col7a1,Pbrm1,Tmsb4x,Gpr64,Crim1,Pla2r1,Zfp932,Rif1,Bcl2,Ankrd26,Amot,Rnf128,Zfp711,Atrx,Gpr116,Ssh3,Kcnj15,Arhgef9,Capg,Klf7,Rbm11,Clic3,Zbtb20,Rbmx,Ephb6,Tead3,Thy1,Mbnl3,Tcf4,Muc20,Zbtb33,Trp63,Zfp182,Steap4,Met,Mid1ip1,Comt,Mpp7,Esrp2,Rnf186,Ahr,Mphosph8,Renbp,Fgfr2,Syt2,Ildr1,Ano1,Samd9l,Cth,Syk,Csnk1e,Mia,Fzd10,Erbb4,Arhgef38,Aire,Dsp,Vegfa,Satb1,Tril,Lcp1,Rgs17,Tpr,Odam,Rell1,Sri,Ankrd32,Tnfaip8,Apod,Gpc6,Plgrkt,Tle2,Sorbs2,Slc4a4,Prlr,Ifi203,Dlgap1,Brwd3,Kif26b,Stau2,Wars,Fgd4,Trove2,Acot1,Cdhr5,Vldlr,Fam3c,Tbx22,Gdf10,Lox,Klf3,Trps1,Phc3,Frk,Gcnt4,Rnf43,Cep290,Nrg4,Cd36,Arhgap8,Ccr2,Enpp2,Phlda1,Nedd4l,Dos,Retn,Lrrc32,Tet1,Hoxb6,Apoe,Pear1,Jmjd1c,Klrb1c,H2-D1,Apobec3,Kcnj11,Zbed6,Edaradd,Topaz1,Pou3f1,Agrn,Dennd2d,Atp13a4,Ism1,Ash1l,Ly6a,Ncf2,Spock1,Erbb2ip,Mndal

GO:0048856	Anatomical structure development	447	5258	0.15	5.52E-12	Hoxb9,Cav2,Tbx2,Cdh1,Alox12,Egfl6,Ocrl,Slc26a3,Itga3,Hoxc8,Shh,Elf3,St8sia6,Gys1,Hlf,G6pdx,Pax2,Aqp1,Prkacb,Igf1r,Rcn1,Slc44a4,Neu1,Krt14,Krt19,Cav1,Rab25,Rpl10,Bmp7,Kcnq1,Tex15,Dazl,Cad,Stc1,Lama5,Celsr1,Nkap,Rbfox3,Top2b,Suz12,Atad5,Etv4,Tbx3,Nrbp2,Perp,Ros1,Lims1,Atp2b1,Sycp3,Ccng1,Srebf1,Bzw2,Agr2,Rock2,Sdc1,Rgs9,Id2,Fam101b,Arg2,Gpld1,Aspn,Cxcl14,Marveld2,Hexb,F2rl1,Emb,Plau,Rnase10,Esco2,Bmp1,Spry2,Rrm2b,Hrsp12,Cldn1,Alcam,Cxadr,Ets2,Runx1,Faim2,Krt8,Tnfrsf21,Lbh,Kif5b,Impact,Atp8b1,Gnaq,Anxa1,Pcsk5,Fas,Slc1a1,Capn1,Vwa2,Gfra1,Sat1,Itgb8,Chm,Farp1,Nptx1,Sclt1,Nrp1,Cplx2,Rb1cc1,Prex2,Tfap2b,Casp8,Zap70,Des,Epha4,Serpine2,Slc45a3,Lamc2,Prrx1,Fcgr2b,Acvr1c,Pax8,Itgav,Kif18a,Meis2,Lrp4,Mal,Pck1,Ccdc39,Slc7a11,P2ry1,Bche,Mme,Ptpn22,Sycp1,Efna1,Enpep,Cd1d1,Hormad1,Bmpr1b,Ift74,Tnfrsf1b,Mycl,Sema3c,Smarcd3,Angptl7,Cd38,Gabrb1,Stap1,Tmem106b,Tspan12,Gpnmb,Npy,Bhlhe40,Mgp,Kcnj8,Bhlhe41,Cd9,Slc17a6,Nav3,Mfge8,Nupr1,Parva,Dkk3,Ptpn5,Mki67,Dock11,Pls3,Cox7b,Acsl4,Rps4x,Mecp2,Sfrp1,Got2,Ces1d,Mmp15,St14,Mpzl2,Hcn4,Ctsh,Ltf,Plekha1,Six6os1,Hoxb5,Pgm5,Galnt11,Scd1,Nexn,Lepr,Brca2,Ppl,Syne1,Ptchd1,Pcm1,Npnt,Ccno,Hoxb7,Creb3l2,Lum,Hs3st6,Egr2,Ss18l1,Fhod3,Ofd1,Zbtb1,Lpar6,Gpr126,Rbm24,Tgfb2,Mfhas1,Sh3pxd2b,Thoc2,Myof,Fgf1,Six5,Rab26,Akap9,Abcb5,Cdo1,Gjb3,Hook3,Mylip,Ramp3,Myf6,Zdhhc15,Inhba,Hoxd4,Hoxb4,Wfs1,Serpinf2,Ptger4,Srd5a2,Ccdc88a,Spry1,Sfn,Axin2,Nrip1,Pou3f3,Upk1b,Hoxb8,Ccdc66,Ar,Nfib,Ppp3ca,Emx2,Cldn4,Erbb2,Myo3b,Igf1,Ly6e,Pik3r1,Dsg2,Frmd7,Cenpe,Cd24a,Upf2,Hoxd9,Foxi1,Atp7a,Lingo1,C1galt1c1,Nipbl,Shisa2,Adra2c,Ptgs1,Tmtc3,Gjb1,Ezr,Gpc3,Jak2,Pdlim1,Gas1,Junb,Wnt5a,Rnase9,Cbs,Nav1,Wls,Vps13a,Rock1,Egr1,Cebpb,Uty,Esr1,Pla2g4a,Dach1,Slco4c1,Postn,Cxcl12,Myom1,Epha1,Calcrl,Chrdl1,Hp,Bglap3,Ptpn3,Tubb2b,Mup4,Ptpro,Emp2,Hhip,Ablim1,Apc,Etv5,Cdh3,Dab2,Lrp2,Sycp2,Ltbp3,Dysf,Erbb3,Arnt2,Nin,Speg,Kif20b,Bmpr2,Notch3,Uprt,C77370,Zfx,Hdac7,Pi15,Dnase1l2,Dgkg,Myh11,Dlg5,Ehf,Lama3,Stat6,Zfp750,Plscr1,Hoxb3,Ccnd1,Cldn3,Tpd52,Lig4,Tmf1,Crb3,Ramp1,Pgap1,Zcchc11,Omp,Cebpa,Tet2,Mbnl1,Fjx1,Hoxc4,Shroom2,Llgl2,B2m,Aldoc,Sema3b,Itga4,Ptbp3,Abca2,Aco1,Gata3,Kitl,Enpp1,Camk2d,Idh2,Ube3a,Hpn,Esrp1,Shroom1,Wnt7b,Arhgef28,Top1,Nnat,Vcan,Camk2b,Tfap2a,Arid4b,Sstr1,Arhgap5,Tagln2,Tnfrsf19,Ildr2,Cfh,Hoxd3,Zfp281,Col7a1,Pbrm1,Ap1s2,Cryba4,Bcl2,Amot,Atrx,Gpr116,Capg,Klf7,Rbm11,Ephb6,Tead3,Thy1,Mbnl3,Tcf4,Trp63,Met,Esrp2,Ahr,Fgfr2,Syt2,Ano1,Samd9l,Syk,Fzd10,Erbb4,Aire,Dsp,Vegfa,Satb1,Lcp1,Odam,Sri,Apod,Fsip2,Sorbs2,Nebl,Prlr,Kif26b,Stau2,Wars,Trove2,Vldlr,Fam3c,Prickle3,Matn2,Lox,Trps1,Phc3,Gcnt4,Rnf43,Cep290,Nrg4,Ccr2,Enpp2,Nedd4l,Lrrc32,Tet1,Hoxb6,Apoe,Jmjd1c,Gcnt1,H2-D1,Apobec3,Zbed6,Edaradd,Topaz1,Pou3f1,Agrn,Kirrel3,Ash1l,Spock1

GO:0007275	Multicellular organism development	421	4921	0.15	2.12E-11	Hoxb9,Cav2,Tbx2,Cdh1,Alox12,Egfl6,Ocrl,Itga3,Hoxc8,Shh,Elf3,St8sia6,Gys1,Hlf,G6pdx,Pax2,Aqp1,Prkacb,Igf1r,Rcn1,Slc44a4,Neu1,Krt19,Cav1,Rpl10,Bmp7,Kcnq1,Tex15,Dazl,Cad,Stc1,Lama5,Celsr1,Nkap,Rbfox3,Top2b,Suz12,Atad5,Etv4,Tbx3,Nrbp2,Perp,Ros1,Lims1,Atp2b1,Srebf1,Bzw2,Agr2,Rock2,Sdc1,Rgs9,Id2,Fam101b,Arg2,Gpld1,Aspn,Cxcl14,Hexb,F2rl1,Emb,Plau,Rnase10,Esco2,Bmp1,Spry2,Rrm2b,Hrsp12,Cldn1,Alcam,Cxadr,Ets2,Runx1,Faim2,Krt8,Tnfrsf21,Lbh,Kif5b,Impact,Atp8b1,Gnaq,Anxa1,Pcsk5,Fas,Slc1a1,Capn1,Vwa2,Gfra1,Sat1,Itgb8,Chm,Farp1,Nptx1,Sclt1,Nrp1,Cplx2,Rb1cc1,Prex2,Tfap2b,Casp8,Zap70,Des,Epha4,Serpine2,Slc45a3,Lamc2,Prrx1,Fcgr2b,Acvr1c,Pax8,Itgav,Kif18a,Meis2,Lrp4,Mal,Pck1,Ccdc39,Slc7a11,P2ry1,Bche,Mme,Ptpn22,Efna1,Enpep,Cd1d1,Hormad1,Bmpr1b,Ift74,Tnfrsf1b,Mycl,Sema3c,Smarcd3,Angptl7,Cd38,Gabrb1,Stap1,Tmem106b,Tspan12,Gpnmb,Npy,Bhlhe40,Mgp,Kcnj8,Bhlhe41,Cd9,Slc17a6,Nav3,Mfge8,Nupr1,Parva,Dkk3,Ptpn5,Mki67,Dock11,Pls3,Cox7b,Acsl4,Rps4x,Mecp2,Sfrp1,Got2,Mmp15,St14,Mpzl2,Hcn4,Ctsh,Ltf,Plekha1,Six6os1,Hoxb5,Galnt11,Scd1,Nexn,Lepr,Brca2,Ppl,Syne1,Ptchd1,Pcm1,Npnt,Hoxb7,Creb3l2,Lum,Hs3st6,Egr2,Ss18l1,Fhod3,Ofd1,Zbtb1,Lpar6,Gpr126,Rbm24,Tgfb2,Mfhas1,Sh3pxd2b,Thoc2,Fgf1,Six5,Rab26,Akap9,Abcb5,Cdo1,Gjb3,Hook3,Mylip,Ramp3,Myf6,Zdhhc15,Inhba,Hoxd4,Hoxb4,Wfs1,Serpinf2,Ptger4,Srd5a2,Ccdc88a,Spry1,Sfn,Axin2,Nrip1,Pou3f3,Hoxb8,Ccdc66,Ar,Nfib,Ppp3ca,Emx2,Cldn4,Erbb2,Myo3b,Igf1,Ly6e,Pik3r1,Dsg2,Frmd7,Cenpe,Cd24a,Upf2,Hoxd9,Foxi1,Atp7a,Lingo1,Nipbl,Shisa2,Adra2c,Ptgs1,Tmtc3,Gjb1,Gpc3,Jak2,Pdlim1,Gas1,Junb,Wnt5a,Cbs,Nav1,Wls,Vps13a,Rock1,Egr1,Cebpb,Uty,Esr1,Pla2g4a,Dach1,Slco4c1,Postn,Cxcl12,Myom1,Epha1,Calcrl,Chrdl1,Hp,Bglap3,Ptpn3,Tubb2b,Ptpro,Emp2,Hhip,Ablim1,Apc,Etv5,Cdh3,Dab2,Lrp2,Sycp2,Ltbp3,Dysf,Erbb3,Arnt2,Nin,Speg,Kif20b,Bmpr2,Notch3,Uprt,C77370,Zfx,Hdac7,Pi15,Dnase1l2,Dgkg,Myh11,Dlg5,Lama3,Stat6,Plscr1,Hoxb3,Ccnd1,Cldn3,Tpd52,Lig4,Tmf1,Ramp1,Pgap1,Omp,Cebpa,Tet2,Mbnl1,Fjx1,Hoxc4,Shroom2,Llgl2,B2m,Sema3b,Itga4,Ptbp3,Abca2,Aco1,Gata3,Kitl,Enpp1,Camk2d,Idh2,Ube3a,Hpn,Esrp1,Wnt7b,Arhgef28,Top1,Nnat,Vcan,Camk2b,Tfap2a,Arid4b,Sstr1,Arhgap5,Tnfrsf19,Ildr2,Cfh,Hoxd3,Zfp281,Col7a1,Pbrm1,Ap1s2,Cryba4,Bcl2,Amot,Atrx,Gpr116,Capg,Klf7,Rbm11,Ephb6,Tead3,Thy1,Mbnl3,Tcf4,Trp63,Met,Esrp2,Ahr,Fgfr2,Syt2,Ano1,Samd9l,Syk,Fzd10,Erbb4,Aire,Dsp,Vegfa,Satb1,Lcp1,Odam,Sri,Apod,Sorbs2,Nebl,Prlr,Kif26b,Stau2,Wars,Trove2,Vldlr,Fam3c,Prickle3,Matn2,Lox,Trps1,Phc3,Gcnt4,Rnf43,Cep290,Nrg4,Ccr2,Enpp2,Nedd4l,Tet1,Hoxb6,Apoe,Jmjd1c,Gcnt1,H2-D1,Apobec3,Zbed6,Edaradd,Pou3f1,Agrn,Kirrel3,Ash1l,Spock1

GO:0048513	Animal organ development	302	3230	0.19	3.02E-11	Hoxb9,Cav2,Tbx2,Cdh1,Alox12,Itga3,Hoxc8,Shh,Elf3,Gys1,Hlf,G6pdx,Pax2,Aqp1,Igf1r,Rcn1,Slc44a4,Krt19,Cav1,Rpl10,Bmp7,Kcnq1,Tex15,Cad,Stc1,Lama5,Celsr1,Nkap,Top2b,Etv4,Tbx3,Perp,Atp2b1,Srebf1,Agr2,Sdc1,Id2,Fam101b,Arg2,Gpld1,Aspn,Cxcl14,F2rl1,Rnase10,Esco2,Bmp1,Spry2,Rrm2b,Hrsp12,Cldn1,Cxadr,Runx1,Faim2,Krt8,Lbh,Kif5b,Atp8b1,Gnaq,Anxa1,Pcsk5,Fas,Capn1,Vwa2,Itgb8,Nrp1,Rb1cc1,Tfap2b,Casp8,Zap70,Des,Epha4,Serpine2,Lamc2,Prrx1,Fcgr2b,Pax8,Itgav,Kif18a,Meis2,Lrp4,Pck1,Ccdc39,Slc7a11,Mme,Ptpn22,Efna1,Enpep,Cd1d1,Bmpr1b,Ift74,Tnfrsf1b,Sema3c,Smarcd3,Angptl7,Stap1,Tspan12,Gpnmb,Npy,Mgp,Kcnj8,Cd9,Slc17a6,Nupr1,Parva,Mki67,Dock11,Pls3,Mecp2,Sfrp1,Got2,St14,Mpzl2,Ctsh,Ltf,Plekha1,Hoxb5,Galnt11,Scd1,Lepr,Brca2,Ppl,Ptchd1,Pcm1,Npnt,Hoxb7,Creb3l2,Lum,Egr2,Fhod3,Zbtb1,Gpr126,Rbm24,Tgfb2,Mfhas1,Sh3pxd2b,Fgf1,Six5,Akap9,Abcb5,Cdo1,Gjb3,Hook3,Myf6,Inhba,Hoxd4,Hoxb4,Wfs1,Ptger4,Srd5a2,Spry1,Sfn,Axin2,Nrip1,Pou3f3,Hoxb8,Ccdc66,Ar,Nfib,Ppp3ca,Emx2,Cldn4,Erbb2,Myo3b,Igf1,Ly6e,Pik3r1,Dsg2,Cd24a,Upf2,Hoxd9,Foxi1,Atp7a,Nipbl,Ptgs1,Tmtc3,Gpc3,Jak2,Pdlim1,Gas1,Junb,Wnt5a,Cbs,Wls,Egr1,Cebpb,Uty,Esr1,Pla2g4a,Cxcl12,Myom1,Calcrl,Chrdl1,Hp,Bglap3,Ptpn3,Tubb2b,Ptpro,Hhip,Apc,Cdh3,Dab2,Lrp2,Sycp2,Ltbp3,Erbb3,Arnt2,Nin,Speg,Bmpr2,Notch3,Uprt,Zfx,Hdac7,Dnase1l2,Myh11,Dlg5,Lama3,Stat6,Plscr1,Hoxb3,Ccnd1,Tpd52,Lig4,Tmf1,Pgap1,Cebpa,Tet2,Mbnl1,Fjx1,Hoxc4,Shroom2,Llgl2,B2m,Sema3b,Itga4,Ptbp3,Gata3,Kitl,Enpp1,Camk2d,Ube3a,Hpn,Esrp1,Wnt7b,Nnat,Vcan,Tfap2a,Arid4b,Sstr1,Arhgap5,Tnfrsf19,Ildr2,Cfh,Hoxd3,Col7a1,Pbrm1,Ap1s2,Cryba4,Bcl2,Atrx,Gpr116,Tead3,Thy1,Trp63,Met,Esrp2,Ahr,Fgfr2,Ano1,Samd9l,Syk,Erbb4,Aire,Dsp,Vegfa,Satb1,Lcp1,Odam,Sri,Apod,Sorbs2,Nebl,Prlr,Kif26b,Stau2,Vldlr,Matn2,Lox,Trps1,Gcnt4,Cep290,Nrg4,Ccr2,Hoxb6,Jmjd1c,Gcnt1,Apobec3,Edaradd,Pou3f1,Agrn,Kirrel3,Ash1l

GO:0050794	Regulation of cellular process	715	9541	0.1	4.11E-11	Hoxb9,Cav2,Tbx2,Cdh1,Alox12,Mcts1,Rem1,Egfl6,Ovgp1,Araf,Ocrl,Cnn1,Itga3,Acap1,Hoxc8,Hltf,Shh,Elf3,Ranbp2,Ier3,Hlf,Gstm7,G6pdx,Pax2,Mospd2,Aqp1,Mapk13,Nfe2l3,Prkacb,Igf1r,Atp4a,Crip1,Slc44a4,Neu1,Krt19,Cav1,Rab25,Rpl10,Bmp7,Kcnc4,Kcnq1,Tex15,Kcnd1,Dazl,Birc3,Stc1,Ptgds,Prrt1,Hivep2,Lpl,Lama5,Il17rb,Celsr1,Nkap,Scube1,Mpp2,Rbfox3,Top2b,Suz12,Atad5,Etv4,Slc2a4,Cldn7,Tbx3,Wwc1,Nrbp2,Perp,Abracl,Ros1,Lims1,Atp2b1,Dusp6,Ccar1,Pcbd1,Ccng1,Rad50,Smek2,Srebf1,Atp6v1c2,Agr2,Rock2,Sdc1,Rgs9,Smc6,Ubxn2a,Id2,Fam101b,Nemf,Rab15,Serpina1f,Plek2,Arg2,Gpld1,Aspn,Ogn,Nol8,Cxcl14,Hexb,F2rl1,Plau,Rnase10,Fam208a,Esco2,Chrna2,Bmp1,Itm2b,Spry2,Rrm2b,Hrsp12,Kcnv1,Fbxo32,Adcy8,Cldn1,Gpihbp1,Ly6f,Retnla,Gpr128,Btg3,Cxadr,St6gal1,Ets2,Runx1,Faim2,Krt18,Sncg,Mospd1,Krt8,Tnfrsf21,Cd2ap,Lbh,Ehd3,Rhoq,Kif5b,Esco1,Impact,Pggt1b,Atp8b1,Tmx3,Gnaq,Anxa1,Pcsk5,Fas,Capn1,Smc3,C1qtnf9,Vwa2,Gfra1,Lztfl1,Sat1,Itgb8,Sp4,Cnpy2,Chm,Farp1,Nptx1,Cnksr2,Nrp1,Cplx2,Rb1cc1,Prex2,Tfap2b,Tmem14a,Ikzf2,Casp8,Sgol2,Eif5b,Zap70,Ogfrl1,Epha4,Serpine2,Slc45a3,Lamc2,Dpt,Prrx1,Fcgr2b,Rgs5,Fam129b,Acvr1c,Phf19,Arrdc1,Pax8,Itgav,Kif18a,Depdc7,Meis2,Lrp4,Casc5,Mal,Prom2,Cst11,Pck1,Fabp4,Ccdc39,Slc7a11,P2ry1,Bche,Mme,Veph1,Ptpn22,S100a11,Efna1,Cd1d1,Hormad1,Cpne3,Bmpr1b,Casp8ap2,Epb4.1l4b,Cyp2j6,Ift74,Tnfrsf1b,Mycl,Sema3c,Padi2,Smarcd3,Angptl7,Arhgef16,Cd38,Gabrb1,Stap1,Sult1e1,Plac8,Tmem106b,Rasl11a,Tspan12,Arhgef5,Gpnmb,Npy,Smarcad1,Bhlhe40,Clec2d,Kcnj8,Bhlhe41,Cidec,Vamp1,Cd9,Nav3,Mfge8,Rab30,Nucb2,Nupr1,Prss8,Il4ra,Dkk3,Pycard,Ptpn5,Mki67,Il13ra1,Dock11,Dynlt3,Mtcp1,Brcc3,Pls3,Hmgn5,Sytl4,Acsl4,Rps6ka3,Rps4x,Asb11,Irak1,Mecp2,Dkc1,Sfrp1,Ido1,Ifi30,Rrad,Trim29,Phip,Clk1,Hcn4,Ctsh,Ltf,Vipr1,Rab6b,Plekha1,Six6os1,Plvap,Hoxb5,Phf20l1,Rgl3,Arhgef4,Galnt11,Tjp3,Cilp,Scd1,Hspb8,Nexn,Cuzd1,Scai,Zfp292,B4galnt2,Lepr,Tmem30b,Plcl1,Bdp1,Brca2,Txlng,Paf,Arhgap27,Syne1,Ptchd1,Pcm1,Pmepa1,Cblc,Npnt,Ccno,Hoxb7,Creb3l2,Kcnh3,Maob,Lum,Egr2,Kiaa1551,Ss18l1,Fhod3,Ofd1,Egln3,Eltd1,Zbtb1,Lpar6,Dsc2,Thrsp,Gpr126,Rbm24,Setd7,Tgfb2,Dpp4,Mfhas1,Sh3pxd2b,Thoc2,Arhgap18,Prkcdbp,Myof,Ryden,Ogt,Zbtb41,Fgf1,Six5,Rab26,Akap9,Asb13,Zfp503,Hook3,Tspan15,Zfp458,Dock4,Mylip,Ramp3,Myf6,Zdhhc15,Fermt1,Inhba,Hoxd4,Hoxb4,Wfs1,Rasl10a,Rbm25,Serpinf2,Ptger4,Ccdc88a,Spry1,Cacna2d1,Slk,Sfn,Rnf149,Axin2,Nrip1,Rasd1,Pou3f3,Bcl2l15,Hoxb8,Spink8,Ccdc66,Ar,Nfib,Fut4,Ppp3ca,Emx2,Cldn4,Erbb2,Lcn2,Gcc2,Syt12,Myo3b,Taok1,Trim16,Sdpr,Zfp445,Secisbp2l,Zfp518a,Igf1,Ly6e,Pik3r1,Cfd,Zfp697,Dsg2,Frmd7,Tmem150c,Blnk,Cenpe,Cd24a,Fbxo10,S100a1,Ccdc125,Hoxd9,Bod1l,Tcim,Foxi1,Atp7a,Ddit4l,Lingo1,Nipbl,Shisa2,Eif2s3x,BC048546,Spin2c,Adra2c,Aff1,Rbp1,Acpp,Ulk3,Ptgs1,Kdm5d,Tmtc3,Gprc5c,Gpr82,Lurap1l,Spink10,Dram2,Ezr,Gpc3,Jak2,Pdlim1,Gas1,Rnf180,Junb,Wnt5a,Socs6,Ppp1r3b,Socs4,Rnase9,Cbs,Wls,Trib1,Ghr,Rock1,Egr1,Ppap2c,Cebpb,Trim2,Uty,Esr1,Pla2g4a,Dach1,Ifitm2,Yes1,Postn,Cxcl12,Myom1,Epha1,Calcrl,Chrdl1,Hp,Kcnh7,Gria2,Bglap3,Ptpn3,Tubb2b,Mysm1,Mup4,Ackr4,Zfp280c,Ptpro,Calml3,Emp2,Hhip,Ablim1,Apc,Etv5,Cdh3,Dab2,Lrp2,Sycp2,Spink12,Adrb3,Ltbp3,Armcx3,Dysf,Erbb3,Plch1,Arnt2,Nin,Rnasel,Bicd1,Asb18,Guf1,Kif20b,Bmpr2,Notch3,C77370,Zfx,Wfdc13,Hdac7,Mbnl2,Pi15,Mybl1,Dok1,Dgkg,Adh7,Bmf,Dlg5,Ehf,Map9,Wnk2,Lama3,Stat6,Piezo1,Zfp750,Plscr1,Hoxb3,Ccnd1,Cldn3,Wfdc6b,Tpd52,Cited4,Il1rl2,Lig4,Tmf1,Map3k2,Spink11,Ramp1,Zcchc11,Omp,Cebpa,Zfp280d,Tet2,Lrif1,Mbnl1,Defb25,Lgals12,Rprm,Hoxc4,Larp4,Bmyc,Shroom2,Mdfic,Llgl2,Itga2b,Trpm7,B2m,Sema3b,Itga4,Pt

						ges,Ptbp3,Abca2,Aco1,Gata3,Chml,Kitl,Enpp1,Camk2d,Synpo2,Kcnj16,Arap1,Idh2,Ube3a,Kcnc3,Hpn,Esrp1,Apoc1,Zfp62,Wfdc9,Wfdc8,Wfdc15b,Wnt7b,Arhgef28,Nnat,Vcan,Tox3,Camk2b,Tfap2a,Zscan26,Arid4b,Sstr1,Arhgap5,Ntsr2,Tnfrsf19,Afap1l2,Rbms3,Dclk3,Cfh,Hoxd3,Zfp281,Col7a1,Pbrm1,Tmsb4x,Gpr64,Crim1,Pla2r1,Zfp932,Rif1,Bcl2,Ankrd26,Amot,Rnf128,Zfp711,Atrx,Gpr116,Ssh3,Kcnj15,Arhgef9,Capg,Klf7,Rbm11,Clic3,Zbtb20,Rbmx,Ephb6,Tead3,Thy1,Mbnl3,Tcf4,Muc20,Zbtb33,Trp63,Zfp182,Met,Mid1ip1,Comt,Mpp7,Esrp2,Rnf186,Ahr,Mphosph8,Renbp,Fgfr2,Syt2,Ildr1,Ano1,Cth,Syk,Csnk1e,Mia,Fzd10,Erbb4,Aire,Dsp,Vegfa,Satb1,Tril,Lcp1,Rgs17,Tpr,Odam,Rell1,Sri,Ankrd32,Tnfaip8,Apod,Gpc6,Plgrkt,Tle2,Sorbs2,Slc4a4,Prlr,Ifi203,Dlgap1,Brwd3,Kif26b,Stau2,Wars,Fgd4,Trove2,Acot1,Cdhr5,Vldlr,Fam3c,Tbx22,Gdf10,Lox,Klf3,Trps1,Phc3,Frk,Rnf43,Cep290,Nrg4,Cd36,Arhgap8,Ccr2,Enpp2,Phlda1,Nedd4l,Dos,Retn,Lrrc32,Tet1,Hoxb6,Apoe,Pear1,Jmjd1c,Klrb1c,H2-D1,Apobec3,Kcnj11,Zbed6,Edaradd,Topaz1,Pou3f1,Agrn,Ash1l,Ly6a,Ncf2,Spock1,Erbb2ip,Mndal

Table S2C. String GO Biological Process PND 35 Low

String GO Biological Process P35 Low						
#term ID	term description	observed gene count	background gene count	strength	false discovery rate	matching proteins in your network (labels)
GO:0009617	Response to bacterium	24	660	0.61	0.00014	Cd52,Ggt1,Lpl,Cldn1,Cyp2e1,Pck1,Fabp4,Car3,Npy,Star,Scd1,Thrsp,Lcn2,Cfd,Defb15,Defb42,Hp,Wfdc13,Ass1,Lypd8,Wfdc15b,Defb30,Syk,Ncf2
GO:0098609	Cell-cell adhesion	17	398	0.68	0.0013	Cdh1,Bmp7,Cldn7,Perp,Rnase10,Cldn1,Cldn8,Cldn2,Dsg2,Ezr,Cdh3,Igsf5,Syk,Dsp,Cdhr5,Cdh16,Gcnt1
GO:0007155	Cell adhesion	23	744	0.54	0.0017	Cdh1,Bmp7,Cldn7,Perp,Rnase10,Cldn1,Gpnmb,Cd9,Mfge8,Pgm5,Cuzd1,Dpp4,Cldn8,Cldn2,Dsg2,Ezr,Cdh3,Igsf5,Syk,Dsp,Cdhr5,Cdh16,Gcnt1
GO:0065007	Biological regulation	129	10591	0.13	0.0026	Hoxb9,Cdh1,Cd52,Elf3,Nfe2l3,Ggt1,Crip1,Slc34a3,Slc44a4,Krt19,Bmp7,Ptgds,Lpl,Scube1,Mpp2,Etv4,Cldn7,Tbx3,Perp,Ros1,Sdc1,Serpina1f,Rnase10,Itm2b,Cldn1,Ly6f,St6gal1,Runx1,Aqp2,Krt18,Lhcgr,Tmem132a,Slc1a1,Capn1,Cyp17a1,Gfra1,Sat1,Cnksr2,Tfap2b,C4bp,Pax8,Depdc7,Lrp4,Mal,Prom2,Pck1,Fabp4,Tspan1,Tpst2,Gpnmb,Npy,Bhlhe41,Cidec,Cd9,Mfge8,Prss8,Pls3,Asb11,Star,Got2,Fam115a,Scd1,Cuzd1,B4galnt2,Tmem30b,Hoxb7,Serpina3g,Thrsp,Gpr126,Pnpla3,Dpp4,Kcnk1,Abcb5,Cdo1,Zfp503,Tspan15,Hoxb4,Srd5a2,Pou3f3,Hoxb8,Spink8,Lcn2,Myo3b,Cfd,Dsg2,Tmem150c,Lingo1,Ptgs1,Gprc5c,Spink10,Ezr,Rnase9,Hp,Calml3,Cdh3,Adrb3,Scnn1a,Erbb3,Susd4,Wfdc13,Ehf,Slc16a10,Wfdc6b,Bmyc,Ass1,Enpp1,Serinc2,Wfdc8,Wfdc15b,Camk2b,Mid1,Gpr64,Rnf128,Kcnj15,Capg,Rbm11,Clic3,Esrp2,Syk,Dsp,Lcp1,Apod,Cdhr5,Gcnt4,Phlda1,Retn,Hoxb6,Ism1,Ncf2
GO:0045216	Cell-cell junction organization	10	157	0.85	0.0056	Cdh1,Cldn7,Perp,Cldn1,Cd9,Cldn8,Cldn2,Dsg2,Cdh3,Dsp
GO:0048732	Gland development	17	493	0.58	0.0063	Hoxb9,Cdh1,Elf3,Bmp7,Etv4,Tbx3,Cldn1,Runx1,Capn1,Pax8,Pck1,Got2,Scd1,Cdo1,Hp,Ass1,Esrp2
GO:0009888	Tissue development	35	1720	0.36	0.0084	Cdh1,Elf3,Slc44a4,Bmp7,Etv4,Tbx3,Ros1,Sdc1,Rnase10,Cldn1,Runx1,Tfap2b,Pax8,Lrp4,Pck1,Gpnmb,Cd9,St14,Pgm5,Hoxb4,Pou3f3,Myo3b,Dsg2,Ptgs1,Ezr,Cdh3,Erbb3,Ehf,Enpp1,Ap1s2,Esrp2,Dsp,Apod,Gcnt4,Gcnt1
GO:0048513	Animal organ development	53	3230	0.26	0.0084	Hoxb9,Cdh1,Elf3,Slc44a4,Krt19,Bmp7,Etv4,Tbx3,Perp,Sdc1,Rnase10,Cldn1,Runx1,Aqp2,Lhcgr,Capn1,Tfap2b,Pax8,Lrp4,Pck1,Gpnmb,Npy,Cd9,Pls3,Star,Got2,St14,Scd1,Hoxb7,Gpr126,Abcb5,Cdo1,Hoxb4,Srd5a2,Pou3f3,Hoxb8,Myo3b,Dsg2,Ptgs1,Hp,Cdh3,Erbb3,Ass1,Enpp1,Ap1s2,Esrp2,Syk,Dsp,Lcp1,Apod,Gcnt4,Hoxb6,Gcnt1
GO:0050896	Response to stimulus	92	6908	0.17	0.0084	Hoxb9,Cdh1,Cd52,Elf3,Inmt,Ggt1,Crip1,Krt19,Bmp7,Ptgds,Lpl,Mpp2,Etv4,Cldn7,Tbx3,Perp,Ros1,Sdc1,Cldn1,Ly6f,Runx1,Aqp2,Krt18,Lhcgr,Slc1a1,Capn1,Gfra1,Cyp2e1,Cnksr2,Tfap2b,C4bp,Pax8,Depdc7,Lrp4,Defb22,Pck1,Fabp4,Car3,Gpnmb,Npy,Cd9,Asb11,Star,Got2,Scd1,Cuzd1,Serpina3g,Thrsp,Gpr126,Pnpla3,Dpp4,Kcnk1,Cdo1,Srd5a2,Lcn2,Myo3b,Cfd,Dsg2,Tmem150c,Lingo1,Defb15,Ptgs1,Gprc5c,Ezr,Defb42,Hp,Calml3,Cdh3,Adrb3,Scnn1a,Erbb3,Gpx3,Wfdc13,S100a16,Ass1,Enpp1,Lypd8,Wfdc15b,Camk2b,Gpx5,Defb30,Ap1s2,Gpr64,Capg,Rbm11,Syk,Dsp,Lcp1,Apod,Retn,Gcnt1,Ncf2
GO:0051707	Response to other organism	27	1145	0.42	0.0084	Cd52,Ggt1,Lpl,Cldn1,Cyp2e1,C4bp,Defb22,Pck1,Fabp4,Car3,Npy,Star,Scd1,Thrsp,Lcn2,Cfd,Defb15,Defb42,Hp,Wfdc13,Ass1,Lypd8,Wfdc15b,Defb30,Capg,Syk,Ncf2

Table S2D. String GO Biological Process PND 35 High

String GO Biological Process P35 High						
#term ID	term description	observed gene count	background gene count	strength	false discovery rate	matching proteins in your network (labels)
GO:0009617	Response to bacterium	21	660	0.8	2.87E-07	Cd52,Cyp2e1,Cst11,Fabp4,Car3,Ido1,Star,Ltf,Scd1,Spag11b,Lcn2,Cfd,Defb15,Defb12,Defb42,Defb41,Defb25,Lypd8,Defb20,Defb30,Ncf2
GO:0042742	Defense response to bacterium	13	260	1	7.49E-06	Cst11,Ltf,Scd1,Spag11b,Lcn2,Defb15,Defb12,Defb42,Defb41,Defb25,Lypd8,Defb20,Defb30
GO:0051707	Response to other organism	23	1145	0.6	5.95E-05	Cd52,Cyp2e1,C4bp,Cst11,Fabp4,Car3,Ido1,Star,Ltf,Scd1,Spag11b,Lcn2,Cfd,Defb15,Defb12,Defb42,Il34,Defb41,Defb25,Lypd8,Defb20,Defb30,Ncf2
GO:0009605	Response to external stimulus	32	2199	0.46	5.98E-05	Cd52,Etv4,Clpsl2,Cyp2e1,C4bp,Cst11,Fabp4,Car3,Rho,Ido1,Star,Ltf,Scd1,Egr2,Spag11b,Srd5a2,Lcn2,Cfd,Tmem150c,Defb15,Defb12,Cbs,Defb42,Il34,Adrb3,Defb41,Defb25,Lrcol1,Lypd8,Defb20,Defb30,Ncf2
GO:0098542	Defense response to other organism	17	775	0.64	0.00068	C4bp,Cst11,Star,Ltf,Scd1,Spag11b,Lcn2,Cfd,Defb15,Defb12,Defb42,Il34,Defb41,Defb25,Lypd8,Defb20,Defb30
GO:0006952	Defense response	18	1133	0.5	0.023	C4bp,Cst11,Ido1,Star,Ltf,Scd1,Spag11b,Lcn2,Cfd,Defb15,Defb12,Defb42,Il34,Defb41,Defb25,Lypd8,Defb20,Defb30
GO:0045087	Innate immune response	12	558	0.63	0.0376	C4bp,Star,Ltf,Lcn2,Cfd,Defb15,Defb12,Il34,Defb41,Defb25,Defb20,Defb30

Table S3A. String Interaction PND28 Low Dose

String Interaction PND28 Low Dose												
#node1	node2	node1_string	node2_string	neighborhoo	gene_fusion	phylogenetic	homology	coexpression	experimenta	database_ar	automated_	combined_sc
Ap1s2	Ap1s3	10090.ENSM	10090.ENSM	0	0	0	0.973	0	0	0.9	0.59	0.901
Ap1s3	Ap1s2	10090.ENSM	10090.ENSM	0	0	0	0.973	0	0	0.9	0.59	0.901
Atp2a1	Myh1	10090.ENSM	10090.ENSM	0	0	0	0	0.728	0.701	0	0.5	0.955
Bmpr1b	Bmpr2	10090.ENSM	10090.ENSM	0	0	0	0.765	0.077	0.258	0.932	0.99	0.961
Bmpr2	Bmpr1b	10090.ENSM	10090.ENSM	0	0	0	0.765	0.077	0.258	0.932	0.99	0.961
Cbs	Cth	10090.ENSM	10090.ENSM	0.193	0.222	0.33	0	0.183	0.612	0.9	0.96	0.999
Cdo1	Got2	10090.ENSM	10090.ENSM	0	0	0	0	0.062	0	0.9	0.054	0.903
Cdo1	Cth	10090.ENSM	10090.ENSM	0	0	0	0	0.089	0	0.9	0.285	0.929
Cnn1	Myh11	10090.ENSM	10090.ENSM	0	0	0	0	0.47	0.046	0	0.819	0.9
Cth	Got2	10090.ENSM	10090.ENSM	0	0	0	0	0.064	0	0.9	0.368	0.935
Cth	Cdo1	10090.ENSM	10090.ENSM	0	0	0	0	0.089	0	0.9	0.285	0.929
Cth	Cbs	10090.ENSM	10090.ENSM	0.193	0.222	0.33	0	0.183	0.612	0.9	0.96	0.999
Gbp2	Iigp1	10090.ENSM	10090.ENSM	0	0	0	0	0.705	0.375	0	0.714	0.942
Gbp2	Igtp	10090.ENSM	10090.ENSM	0	0	0	0	0.848	0	0	0.696	0.952
Gbp7	Igtp	10090.ENSM	10090.ENSM	0	0	0	0	0.8	0	0	0.55	0.906
Got2	Cdo1	10090.ENSM	10090.ENSM	0	0	0	0	0.062	0	0.9	0.054	0.903
Got2	Cth	10090.ENSM	10090.ENSM	0	0	0	0	0.064	0	0.9	0.368	0.935
Hba-a1	Hbb-bs	10090.ENSM	10090.ENSM	0	0	0	0.891	0.28	0.938	0.8	0.748	0.991
Hbb-bs	Hba-a1	10090.ENSM	10090.ENSM	0	0	0	0.891	0.28	0.938	0.8	0.748	0.991
Igtp	Gbp7	10090.ENSM	10090.ENSM	0	0	0	0	0.8	0	0	0.55	0.906
Igtp	Gbp2	10090.ENSM	10090.ENSM	0	0	0	0	0.848	0	0	0.696	0.952
Iigp1	Gbp2	10090.ENSM	10090.ENSM	0	0	0	0	0.705	0.375	0	0.714	0.942
Krt18	Krt8	10090.ENSM	10090.ENSM	0	0	0	0.763	0.964	0.811	0.6	0.975	0.997
Krt19	Krt8	10090.ENSM	10090.ENSM	0	0	0	0.782	0.602	0.272	0.72	0.878	0.928
Krt8	Krt19	10090.ENSM	10090.ENSM	0	0	0	0.782	0.602	0.272	0.72	0.878	0.928
Krt8	Krt18	10090.ENSM	10090.ENSM	0	0	0	0.763	0.964	0.811	0.6	0.975	0.997
Lcn2	Lrp2	10090.ENSM	10090.ENSM	0	0	0	0	0	0.087	0	0.953	0.955
Lrp2	Lcn2	10090.ENSM	10090.ENSM	0	0	0	0	0	0.087	0	0.953	0.955
Myh1	Atp2a1	10090.ENSM	10090.ENSM	0	0	0	0	0.728	0.701	0	0.5	0.955
Myh11	Cnn1	10090.ENSM	10090.ENSM	0	0	0	0	0.47	0.046	0	0.819	0.9
Ptgds	Ptgs1	10090.ENSM	10090.ENSM	0	0	0	0	0	0	0.9	0.551	0.953
Ptgds	Ptges	10090.ENSM	10090.ENSM	0	0	0	0	0	0	0.9	0.615	0.959
Ptges	Ptgds	10090.ENSM	10090.ENSM	0	0	0	0	0	0	0.9	0.615	0.959
Ptges	Ptgs1	10090.ENSM	10090.ENSM	0	0	0	0	0	0	0.9	0.759	0.974
Ptgs1	Ptgds	10090.ENSM	10090.ENSM	0	0	0	0	0	0	0.9	0.551	0.953
Ptgs1	Ptges	10090.ENSM	10090.ENSM	0	0	0	0	0	0	0.9	0.759	0.974

Table S3B. String Interaction PND28 High Dose

String Interaction PND28 High Dose												
#node1	node2	node1_string_id	node2_string_id	neighborhood_on_chromosome	gene_fusion	phylogenetic_cooccurrence	homology	coexpression	experimentally_determined_interaction	database_annotated	automated_textmining	combined_score
Acadsb	Aldh6a1	10090.ENSMUSP00000015829	10090.ENSMUSP00000082288	0	0	0	0	0.76	0	0	0.663	0.916
Acadsb	Acsl4	10090.ENSMUSP00000015829	10090.ENSMUSP00000033634	0.053	0	0	0	0.138	0.057	0.9	0.286	0.935
Acadsb	Ehhadh	10090.ENSMUSP00000015829	10090.ENSMUSP00000023559	0.047	0	0	0	0.13	0.161	0.922	0.593	0.974
Acap1	Slc2a4	10090.ENSMUSP00000001631	10090.ENSMUSP00000018710	0	0	0	0	0.063	0.049	0.676	0.728	0.911
Acbd5	Gdap1	10090.ENSMUSP00000110172	10090.ENSMUSP00000026879	0	0	0	0	0.061	0	0.9	0.398	0.938
Aco1	Idh2	10090.ENSMUSP00000100038	10090.ENSMUSP00000103007	0.139	0	0	0	0.158	0.047	0.9	0.463	0.956
Acss3	Aldh1a7	10090.ENSMUSP00000040823	10090.ENSMUSP00000025656	0.043	0	0	0	0.146	0.065	0.9	0.197	0.927
Acss3	Aldh6a1	10090.ENSMUSP00000040823	10090.ENSMUSP00000082288	0	0	0	0	0.123	0	0.9	0.206	0.924
Acvr1c	Inhba	10090.ENSMUSP00000028178	10090.ENSMUSP00000047894	0	0	0	0	0	0.24	0.745	0.625	0.921
Adh1	Comt	10090.ENSMUSP00000004232	10090.ENSMUSP00000111272	0	0	0	0	0.068	0	0.9	0.211	0.92
Adh1	Maob	10090.ENSMUSP00000004232	10090.ENSMUSP00000040550	0	0	0	0	0.184	0	0.9	0.102	0.92

Adh1	Aldh1a7	10090.ENSMUSP00000042312	10090.ENSMUSP00000025656	0.048	0	0	0	0.221	0.066	0.9	0.51	0.959
Adh1	Cyp2e1	10090.ENSMUSP00000042312	10090.ENSMUSP00000026552	0.042	0	0	0	0.407	0	0.9	0.687	0.979
Adh7	Aldh1a7	10090.ENSMUSP00000087633	10090.ENSMUSP00000025656	0.048	0	0	0	0.159	0.066	0.9	0.366	0.944
Adh7	Cyp2e1	10090.ENSMUSP00000087633	10090.ENSMUSP00000026552	0.042	0	0	0	0.106	0	0.9	0.563	0.957
Adh7	Maob	10090.ENSMUSP00000087633	10090.ENSMUSP00000040550	0	0	0	0	0.069	0	0.9	0.143	0.913
Adh7	Comt	10090.ENSMUSP00000087633	10090.ENSMUSP00000111272	0	0	0	0	0.066	0	0.9	0.318	0.93
Adhfe1	Aldh6a1	10090.ENSMUSP00000116627	10090.ENSMUSP00000082288	0	0	0	0	0.421	0.91	0	0.629	0.979
Agrn	Hs3st6	10090.ENSMUSP00000137931	10090.ENSMUSP00000040919	0	0	0	0	0.051	0	0.9	0.078	0.904
Agrn	Hs3st3a1	10090.ENSMUSP00000137931	10090.ENSMUSP00000055930	0	0	0	0	0.051	0	0.9	0.068	0.903
Agrn	Lrp2	10090.ENSMUSP00000137931	10090.ENSMUSP00000079752	0	0	0	0	0.052	0	0.9	0.265	0.924
Agrn	Hs3st3b1	10090.ENSMUSP00000137931	10090.ENSMUSP00000091647	0	0	0	0	0.051	0	0.9	0.137	0.911
Agrn	Vcan	10090.ENSMUSP00000137931	10090.ENSMUSP00000105173	0	0	0	0	0.061	0.146	0.9	0.472	0.952
Ahr	Cav1	10090.ENSMUSP00000112137	10090.ENSMUSP00000007799	0	0	0	0	0.061	0	0	0.919	0.921

Ahr	Esr1	10090.ENSMUSP0000011213 7	10090.ENSMUSP0000007007 0	0	0	0	0	0	0.761	0	0.989	0.997
Ahr	Arnt2	10090.ENSMUSP0000011213 7	10090.ENSMUSP0000008215 4	0	0	0	0.549	0.061	0.725	0.803	0.892	0.966
Akap9	Kcnq1	10090.ENSMUSP0000004612 9	10090.ENSMUSP0000000968 9	0	0	0	0	0	0.402	0.8	0.788	0.972
Akr1b7	Dcxr	10090.ENSMUSP0000000744 9	10090.ENSMUSP0000002614 4	0	0	0	0	0	0	0.9	0.338	0.93
Aldh1a7	Comt	10090.ENSMUSP0000002565 6	10090.ENSMUSP0000011127 2	0	0	0	0	0.062	0	0.9	0.145	0.912
Aldh1a7	Maob	10090.ENSMUSP0000002565 6	10090.ENSMUSP0000004055 0	0	0	0	0	0.169	0	0.9	0.126	0.921
Aldh6a1	Ehhadh	10090.ENSMUSP0000008228 8	10090.ENSMUSP0000002355 9	0	0	0	0	0.282	0.043	0.9	0.309	0.946
Alox12	Cyp2e1	10090.ENSMUSP0000000032 9	10090.ENSMUSP0000002655 2	0	0	0	0	0	0	0.9	0.128	0.909
Alox12	Ptgs1	10090.ENSMUSP0000000032 9	10090.ENSMUSP0000005997 7	0	0	0	0	0.062	0	0.9	0.49	0.948
Amot	Wwc1	10090.ENSMUSP0000010845 5	10090.ENSMUSP0000001899 3	0	0	0	0	0.063	0.807	0	0.792	0.959
Ano1	Ezr	10090.ENSMUSP0000011261 6	10090.ENSMUSP0000006373 4	0	0	0	0	0	0	0	0.968	0.968
Anxa1	Dysf	10090.ENSMUSP0000002556 1	10090.ENSMUSP0000008057 9	0	0	0	0	0.065	0.436	0.6	0.867	0.968
Anxa1	S100a11	10090.ENSMUSP0000002556 1	10090.ENSMUSP0000002951 5	0	0	0	0	0.519	0.402	0	0.987	0.996

Ap1m2	Ap1s2	10090.ENSMUSP00000111093	10090.ENSMUSP00000107913	0	0	0	0	0.119	0.582	0.8	0.517	0.959
Ap1m2	Ap1s3	10090.ENSMUSP00000111093	10090.ENSMUSP00000125268	0	0	0	0	0.119	0.56	0.8	0.465	0.953
Ap1s2	Ap1s3	10090.ENSMUSP00000107913	10090.ENSMUSP00000125268	0	0	0	0.973	0	0	0.9	0.59	0.901
Apc	Arhgef4	10090.ENSMUSP00000078337	10090.ENSMUSP00000035980	0	0	0	0	0.063	0.927	0.932	0.463	0.997
Apc	Axin2	10090.ENSMUSP00000078337	10090.ENSMUSP00000051331	0	0	0	0	0.066	0.783	0.932	0.812	0.997
Apc	Csnk1e	10090.ENSMUSP00000078337	10090.ENSMUSP00000113975	0	0	0	0	0.063	0.62	0.676	0.241	0.901
Apc	Tle2	10090.ENSMUSP00000078337	10090.ENSMUSP00000121125	0	0	0	0	0.066	0	0.9	0.08	0.906
Apoc1	Apoe	10090.ENSMUSP00000104091	10090.ENSMUSP00000133302	0	0	0	0	0.732	0	0.54	0.873	0.983
Apoe	Lpl	10090.ENSMUSP00000133302	10090.ENSMUSP00000015712	0	0	0	0	0.062	0	0.9	0.827	0.982
Apoe	Gpihbp1	10090.ENSMUSP00000133302	10090.ENSMUSP00000023243	0	0	0	0	0.103	0	0.9	0.476	0.949
Apoe	Lrp2	10090.ENSMUSP00000133302	10090.ENSMUSP00000079752	0	0	0	0	0.08	0.305	0.9	0.777	0.983
Apoe	Vldlr	10090.ENSMUSP00000133302	10090.ENSMUSP00000127329	0	0	0	0	0.059	0.478	0.54	0.984	0.996
Ar	Prkacb	10090.ENSMUSP00000052648	10090.ENSMUSP00000005164	0	0	0	0	0	0.047	0.914	0.083	0.918

Ar	Cav1	10090.ENSMUSP00000052648	10090.ENSMUSP00000007799	0	0	0	0	0	0.102	0	0.942	0.947
Ar	Atrx	10090.ENSMUSP00000052648	10090.ENSMUSP00000109203	0	0	0	0	0	0.461	0.132	0.892	0.945
Ar	Pik3r1	10090.ENSMUSP00000052648	10090.ENSMUSP00000056774	0	0	0	0	0	0.081	0.676	0.917	0.973
Ar	Ccnd1	10090.ENSMUSP00000052648	10090.ENSMUSP00000091495	0	0	0	0	0.061	0.743	0.676	0.875	0.989
Arhgef28	Gnaq	10090.ENSMUSP00000105053	10090.ENSMUSP00000025541	0	0	0	0	0.051	0.087	0.86	0.579	0.942
Atp4a	Atp6v0d2	10090.ENSMUSP00000005692	10090.ENSMUSP00000029900	0	0	0	0	0	0.131	0	0.943	0.948
Atp6v0d2	Atp6v1c2	10090.ENSMUSP00000029900	10090.ENSMUSP00000020884	0	0	0	0	0.469	0.653	0.6	0.658	0.971
Atrx	Mecp2	10090.ENSMUSP00000109203	10090.ENSMUSP00000033770	0	0	0	0	0.088	0.73	0.2	0.989	0.997
Axin2	Csnk1e	10090.ENSMUSP00000051331	10090.ENSMUSP00000113975	0	0	0	0	0	0.241	0.876	0.471	0.946
B2m	Cd1d1	10090.ENSMUSP00000099534	10090.ENSMUSP00000029717	0	0	0	0	0.094	0.966	0.8	0.988	0.999
B2m	H2-D1	10090.ENSMUSP00000099534	10090.ENSMUSP00000134570	0	0	0	0	0.59	0.999	0.847	0.793	0.999
B3galt2	B4galt4	10090.ENSMUSP00000046118	10090.ENSMUSP00000023482	0	0	0	0	0	0	0.9	0.36	0.933
B3galt2	Ggta1	10090.ENSMUSP00000046118	10090.ENSMUSP00000099858	0	0	0	0	0	0	0.9	0.088	0.904

B4galt4	Ogn	10090.ENSMUSP0000002348 2	10090.ENSMUSP0000002182 2	0	0	0	0	0	0	0.9	0.148	0.911
B4galt4	Ggta1	10090.ENSMUSP0000002348 2	10090.ENSMUSP0000009985 8	0	0	0	0	0	0	0.9	0	0.9
B4galt4	Fut4	10090.ENSMUSP0000002348 2	10090.ENSMUSP0000005302 7	0	0	0	0	0	0	0.9	0.242	0.92
B4galt4	Lum	10090.ENSMUSP0000002348 2	10090.ENSMUSP0000004087 7	0	0	0	0	0.062	0	0.9	0.24	0.922
Bhlhe40	Bhlhe41	10090.ENSMUSP0000003219 4	10090.ENSMUSP0000003238 6	0	0	0	0.875	0.373	0.209	0.8	0.813	0.903
Bhlhe41	Csnk1e	10090.ENSMUSP0000003238 6	10090.ENSMUSP0000011397 5	0	0	0	0	0.062	0.865	0	0.534	0.936
Birc3	Tnfrsf1b	10090.ENSMUSP0000001394 9	10090.ENSMUSP0000003033 6	0	0	0	0	0.1	0.13	0.864	0.478	0.937
Birc3	Casp8	10090.ENSMUSP0000001394 9	10090.ENSMUSP0000002718 9	0	0	0	0	0.099	0.475	0.676	0.815	0.968
Blnk	Zap70	10090.ENSMUSP0000005784 4	10090.ENSMUSP0000002729 1	0	0	0	0	0.064	0.501	0.676	0.695	0.947
Blnk	Syk	10090.ENSMUSP0000005784 4	10090.ENSMUSP0000011385 2	0	0	0	0	0.152	0.756	0.932	0.984	0.999
Bmp1	Col5a3	10090.ENSMUSP0000002269 3	10090.ENSMUSP0000000420 1	0	0	0	0	0.104	0.042	0.9	0.149	0.917
Bmp1	Col7a1	10090.ENSMUSP0000002269 3	10090.ENSMUSP0000010770 1	0	0	0	0	0.099	0.087	0.9	0.256	0.93
Bmp1	Lox	10090.ENSMUSP0000002269 3	10090.ENSMUSP0000012924 7	0	0	0	0	0.114	0	0.9	0.659	0.967

Bmp1	Postn	10090.ENSMUSP0000002269 3	10090.ENSMUSP0000007277 3	0	0	0	0	0.122	0	0	0.976	0.979
Bmp7	Bmpr1b	10090.ENSMUSP0000000914 3	10090.ENSMUSP0000002994 8	0	0	0	0	0	0.402	0.932	0.908	0.996
Bmp7	Bmpr2	10090.ENSMUSP0000000914 3	10090.ENSMUSP0000008470 1	0	0	0	0	0	0.227	0.932	0.976	0.998
Bmpr1b	Bmpr2	10090.ENSMUSP0000002994 8	10090.ENSMUSP0000008470 1	0	0	0	0.765	0.077	0.258	0.932	0.99	0.961
Bmpr2	Cav1	10090.ENSMUSP0000008470 1	10090.ENSMUSP0000000779 9	0	0	0	0	0	0.102	0.378	0.967	0.98
C1galt1c1	St3gal2	10090.ENSMUSP0000005922 4	10090.ENSMUSP0000003419 7	0	0	0	0	0	0.047	0.9	0.399	0.937
C1galt1c1	Muc16	10090.ENSMUSP0000005922 4	10090.ENSMUSP0000003465 3	0	0	0	0	0	0	0.9	0.479	0.945
C1galt1c1	Muc15	10090.ENSMUSP0000005922 4	10090.ENSMUSP0000010664 5	0	0	0	0	0	0	0.9	0.058	0.901
C1galt1c1	Muc20	10090.ENSMUSP0000005922 4	10090.ENSMUSP0000011076 9	0	0	0	0	0	0	0.9	0.069	0.902
C1galt1c1	Muc5b	10090.ENSMUSP0000005922 4	10090.ENSMUSP0000012827 6	0	0	0	0	0	0.064	0.9	0.104	0.908
C1galt1c1	Gcnt4	10090.ENSMUSP0000005922 4	10090.ENSMUSP0000013049 6	0	0	0	0	0	0	0.9	0.507	0.948
C1galt1c1	Gcnt1	10090.ENSMUSP0000005922 4	10090.ENSMUSP0000013393 5	0	0	0	0	0	0	0.9	0.581	0.956
Cad	Got2	10090.ENSMUSP0000001377 3	10090.ENSMUSP0000003409 7	0.056	0	0	0	0.162	0.048	0.9	0.217	0.93

Calcrl	Ramp3	10090.ENSMUSP00000073875	10090.ENSMUSP00000047518	0	0	0	0	0.061	0.778	0.8	0.949	0.997
Calcrl	Ramp1	10090.ENSMUSP00000073875	10090.ENSMUSP00000095253	0	0	0	0	0	0.933	0.8	0.991	0.999
Camk2b	Mecp2	10090.ENSMUSP00000105438	10090.ENSMUSP00000033770	0	0	0	0	0.058	0	0.9	0.096	0.907
Camk2b	Camk2d	10090.ENSMUSP00000105438	10090.ENSMUSP00000102009	0	0	0.444	0.983	0	0.928	0.905	0.161	0.992
Camk2d	Mecp2	10090.ENSMUSP00000102009	10090.ENSMUSP00000033770	0	0	0	0	0	0	0.9	0.094	0.905
Car4	Slc4a4	10090.ENSMUSP00000099483	10090.ENSMUSP00000121744	0	0	0	0	0.062	0.46	0	0.839	0.911
Casc5	Cenpf	10090.ENSMUSP00000028822	10090.ENSMUSP00000129738	0	0	0	0	0.747	0	0	0.648	0.907
Casc5	Mis18bp1	10090.ENSMUSP00000028822	10090.ENSMUSP00000052109	0	0	0	0	0.717	0	0.6	0.312	0.915
Casc5	Cenpe	10090.ENSMUSP00000028822	10090.ENSMUSP00000057938	0	0	0	0	0.817	0.047	0	0.8	0.962
Casp8	Fas	10090.ENSMUSP00000027189	10090.ENSMUSP00000025691	0	0	0	0	0.106	0.899	0.905	0.981	0.999
Casp8	Pycard	10090.ENSMUSP00000027189	10090.ENSMUSP00000033056	0	0	0	0	0.062	0.402	0.8	0.585	0.947
Casp8	Pik3r1	10090.ENSMUSP00000027189	10090.ENSMUSP00000056774	0	0	0	0	0	0.041	0	0.952	0.953
Casp8	Casp8ap2	10090.ENSMUSP00000027189	10090.ENSMUSP00000029950	0	0	0	0	0	0.728	0	0.934	0.981

Casp8ap2	Phc3	10090.ENSMUSP00002995	10090.ENSMUSP00000130142	0	0	0	0	0.065	0	0.9	0	0.902
Cav1	Cav2	10090.ENSMUSP00000077799	10090.ENSMUSP00000000058	0	0	0	0.848	0.782	0.769	0.9	0.994	0.995
Cav1	Igf1r	10090.ENSMUSP00000077799	10090.ENSMUSP00000005671	0	0	0	0	0	0.058	0.457	0.874	0.93
Cav1	Prkcdbp	10090.ENSMUSP00000077799	10090.ENSMUSP00000044979	0	0	0	0	0.171	0.208	0	0.912	0.937
Cav1	Dsg2	10090.ENSMUSP00000077799	10090.ENSMUSP00000057096	0	0	0	0	0	0.199	0	0.976	0.981
Cav1	Dpp4	10090.ENSMUSP00000077799	10090.ENSMUSP00000044050	0	0	0	0	0.061	0.08	0	0.988	0.989
Cav1	Esr1	10090.ENSMUSP00000077799	10090.ENSMUSP00000070070	0	0	0	0	0	0.367	0.6	0.989	0.997
Cbs	Cth	10090.ENSMUSP00000066878	10090.ENSMUSP00000113672	0.193	0.222	0.33	0	0.183	0.612	0.9	0.96	0.999
Ccnd1	Jak2	10090.ENSMUSP00000091495	10090.ENSMUSP00000064394	0	0	0	0	0	0.058	0.909	0.672	0.969
Ccnd1	Esr1	10090.ENSMUSP00000091495	10090.ENSMUSP00000070070	0	0	0	0	0	0.756	0.176	0.982	0.996
Ccr2	Cxcl12	10090.ENSMUSP00000132453	10090.ENSMUSP00000072800	0	0	0	0	0	0.153	0.669	0.749	0.923
Cd38	Enpp1	10090.ENSMUSP00000030964	10090.ENSMUSP00000101159	0	0	0	0	0.061	0	0.9	0.244	0.922
Cd9	Itga3	10090.ENSMUSP00000032492	10090.ENSMUSP00000001548	0	0	0	0	0.062	0.402	0.43	0.889	0.959

Cdh1	Zbtb33	10090.ENSMUSP00000003312	10090.ENSMUSP00000110795	0	0	0	0	0	0	0.676	0.744	0.913
Cdh1	Erbb2	10090.ENSMUSP00000003312	10090.ENSMUSP00000053897	0	0	0	0	0.09	0.27	0.493	0.831	0.935
Cdh1	Igf1r	10090.ENSMUSP00000003312	10090.ENSMUSP00000005671	0	0	0	0	0	0.09	0.676	0.963	0.988
Cdh1	Met	10090.ENSMUSP00000003312	10090.ENSMUSP00000111103	0	0	0	0	0.062	0.13	0.676	0.982	0.994
Cdo1	Csad	10090.ENSMUSP00000046517	10090.ENSMUSP00000023805	0	0	0	0	0.089	0	0.9	0.68	0.968
Cdo1	Got2	10090.ENSMUSP00000046517	10090.ENSMUSP00000034097	0	0	0	0	0.062	0	0.9	0.054	0.903
Cdo1	Cth	10090.ENSMUSP00000046517	10090.ENSMUSP00000113672	0	0	0	0	0.089	0	0.9	0.285	0.929
Cebpa	Runx1	10090.ENSMUSP00000096129	10090.ENSMUSP00000023673	0	0	0	0	0.057	0.274	0.8	0.552	0.93
Cebpa	Trib1	10090.ENSMUSP00000096129	10090.ENSMUSP00000068834	0	0	0	0	0.078	0.862	0	0.709	0.959
Cebpa	Cebpb	10090.ENSMUSP00000096129	10090.ENSMUSP00000069850	0	0	0	0.791	0.141	0.556	0.905	0.953	0.968
Cebpa	Esr1	10090.ENSMUSP00000096129	10090.ENSMUSP00000070070	0	0	0	0	0.077	0.405	0.476	0.813	0.939
Cebpb	Egr2	10090.ENSMUSP00000069850	10090.ENSMUSP00000041053	0	0	0	0	0.067	0.058	0.909	0.5	0.955
Cebpb	Esr1	10090.ENSMUSP00000069850	10090.ENSMUSP00000070070	0	0	0	0	0	0.734	0.676	0.813	0.982

Cenpe	Kif18a	10090.ENSMUSP0000005793 8	10090.ENSMUSP0000002852 7	0	0	0	0.646	0.666	0.091	0.8	0.807	0.952
Cenpe	Mki67	10090.ENSMUSP0000005793 8	10090.ENSMUSP0000003331 0	0	0	0	0	0.945	0.666	0	0.331	0.986
Cenpe	Smc4	10090.ENSMUSP0000005793 8	10090.ENSMUSP0000004787 2	0	0	0	0	0.915	0.082	0	0.425	0.951
Cenpe	Mis18bp1	10090.ENSMUSP0000005793 8	10090.ENSMUSP0000005210 9	0	0	0	0	0.898	0.05	0	0.292	0.925
Cenpe	Kif20b	10090.ENSMUSP0000005793 8	10090.ENSMUSP0000008459 9	0	0	0	0.548	0.811	0.088	0.5	0.524	0.927
Cenpe	Smc2	10090.ENSMUSP0000005793 8	10090.ENSMUSP0000009997 9	0	0	0	0	0.918	0.655	0	0.264	0.977
Cenpe	Cenpf	10090.ENSMUSP0000005793 8	10090.ENSMUSP0000012973 8	0	0	0	0	0.937	0.079	0	0.891	0.993
Cenpf	Mki67	10090.ENSMUSP0000012973 8	10090.ENSMUSP0000003331 0	0	0	0	0	0.938	0.13	0	0.435	0.967
Cenpf	Mis18bp1	10090.ENSMUSP0000012973 8	10090.ENSMUSP0000005210 9	0	0	0	0	0.891	0	0	0.193	0.909
Cep83	Sclt1	10090.ENSMUSP0000002021 2	10090.ENSMUSP0000002686 6	0	0	0	0	0.098	0	0.72	0.97	0.991
Cers4	Ppap2c	10090.ENSMUSP0000000835 0	10090.ENSMUSP0000006967 0	0	0	0	0	0.051	0.089	0.9	0.373	0.938
Cers4	Kdsr	10090.ENSMUSP0000000835 0	10090.ENSMUSP0000001004 9	0	0	0	0	0.062	0	0.9	0.658	0.965
Ces1d	Cyp2e1	10090.ENSMUSP0000003417 2	10090.ENSMUSP0000002655 2	0	0	0	0	0.247	0	0.9	0.294	0.942

Chm	Chml	10090.ENSMUSP00000026607	10090.ENSMUSP00000100600	0	0	0	0.968	0	0	0.9	0.903	0.902
Chm	Dennd2d	10090.ENSMUSP00000026607	10090.ENSMUSP00000138462	0	0	0	0	0	0	0.9	0.088	0.904
Chml	Dennd2d	10090.ENSMUSP00000100600	10090.ENSMUSP00000138462	0	0	0	0	0	0	0.9	0.088	0.904
Cilp	Igf1r	10090.ENSMUSP00000036631	10090.ENSMUSP00000005671	0	0	0	0	0	0	0.9	0.05	0.901
Cilp	Igf1	10090.ENSMUSP00000036631	10090.ENSMUSP00000056668	0	0	0	0	0.063	0	0.9	0.11	0.909
Cldn1	Tjp3	10090.ENSMUSP00000023154	10090.ENSMUSP00000036438	0	0	0	0	0.079	0.439	0.6	0.718	0.934
Cldn3	Tjp3	10090.ENSMUSP00000091799	10090.ENSMUSP00000036438	0	0	0	0	0.42	0.058	0.6	0.71	0.928
Cmah	Nans	10090.ENSMUSP00000129007	10090.ENSMUSP00000030018	0	0	0	0	0	0	0.9	0.494	0.947
Cnn1	Myh11	10090.ENSMUSP00000001384	10090.ENSMUSP00000087756	0	0	0	0	0.47	0.046	0	0.819	0.9
Col4a6	P4ha2	10090.ENSMUSP00000098765	10090.ENSMUSP00000019050	0	0	0	0	0.062	0.047	0.9	0.106	0.909
Col5a3	P4ha2	10090.ENSMUSP00000004201	10090.ENSMUSP00000019050	0	0	0	0	0.052	0.047	0.9	0.105	0.908
Col7a1	P4ha2	10090.ENSMUSP00000107701	10090.ENSMUSP00000019050	0	0	0	0	0.062	0.047	0.9	0.103	0.909
Col7a1	Lamc2	10090.ENSMUSP00000107701	10090.ENSMUSP00000027753	0	0	0	0	0.084	0.13	0.686	0.663	0.904

Comt	Maob	10090.ENSMUSP00000111272	10090.ENSMUSP00000040550	0	0	0	0	0	0	0.9	0.839	0.983
Csad	Ggt1	10090.ENSMUSP00000023805	10090.ENSMUSP00000006508	0.041	0	0	0	0.062	0	0.9	0.092	0.907
Cst11	Lcn9	10090.ENSMUSP00000028934	10090.ENSMUSP00000023978	0	0	0	0	0.7	0	0	0.69	0.903
Cth	Got2	10090.ENSMUSP00000113672	10090.ENSMUSP00000034097	0	0	0	0	0.064	0	0.9	0.368	0.935
Cyp2e1	Cyp2j6	10090.ENSMUSP00000026552	10090.ENSMUSP00000030303	0	0	0.426	0.9	0.063	0	0.9	0.371	0.909
Cyp2e1	Ptgs1	10090.ENSMUSP00000026552	10090.ENSMUSP00000059977	0	0	0	0	0.05	0.046	0.9	0.198	0.917
Dab2	Lrp2	10090.ENSMUSP00000079689	10090.ENSMUSP00000079752	0	0	0	0	0.062	0.489	0.835	0.909	0.991
Dao	Gldc	10090.ENSMUSP00000107911	10090.ENSMUSP00000025778	0	0	0	0	0.066	0	0.9	0.384	0.937
Dao	Sardh	10090.ENSMUSP00000107911	10090.ENSMUSP00000099950	0.095	0	0	0	0.062	0.241	0.9	0.204	0.939
Ddx3y	Kdm5d	10090.ENSMUSP00000088729	10090.ENSMUSP00000061095	0	0	0	0	0.928	0.058	0	0.846	0.988
Ddx3y	Uty	10090.ENSMUSP00000088729	10090.ENSMUSP00000070012	0.042	0	0	0	0.721	0.089	0	0.861	0.962
Ddx3y	Usp9y	10090.ENSMUSP00000088729	10090.ENSMUSP00000088727	0	0	0	0	0.097	0.188	0	0.892	0.914
Defb18	Defb48	10090.ENSMUSP00000095427	10090.ENSMUSP00000098062	0	0	0	0	0.177	0	0.9	0.498	0.955

Defb21	Defb48	10090.ENSMUSP00000065102	10090.ENSMUSP00000098062	0	0	0	0	0.112	0	0.9	0.622	0.963
Defb25	Defb48	10090.ENSMUSP00000096809	10090.ENSMUSP00000098062	0	0	0	0	0	0	0.9	0.4	0.937
Defb30	Defb48	10090.ENSMUSP00000106838	10090.ENSMUSP00000098062	0	0	0	0	0.082	0	0.9	0.719	0.971
Defb42	Defb48	10090.ENSMUSP00000070629	10090.ENSMUSP00000098062	0	0	0	0	0	0	0.9	0.699	0.968
Defb43	Defb48	10090.ENSMUSP00000098060	10090.ENSMUSP00000098062	0	0	0	0	0.086	0	0.9	0.553	0.955
Defb47	Defb48	10090.ENSMUSP00000098061	10090.ENSMUSP00000098062	0	0	0	0.87	0.079	0	0.9	0.768	0.913
Dkc1	Ssb	10090.ENSMUSP00000033776	10090.ENSMUSP00000088365	0	0	0	0	0.847	0.436	0	0.055	0.911
Dkc1	Esf1	10090.ENSMUSP00000033776	10090.ENSMUSP00000036523	0	0	0	0	0.89	0.406	0	0.201	0.943
Dpp4	Mme	10090.ENSMUSP00000044050	10090.ENSMUSP00000029400	0	0	0	0	0.061	0	0.8	0.603	0.918
Dsc2	Dsg2	10090.ENSMUSP00000042905	10090.ENSMUSP00000057096	0	0	0	0.739	0.23	0.227	0.8	0.969	0.903
Dsc2	Dsp	10090.ENSMUSP00000042905	10090.ENSMUSP00000115062	0	0	0	0	0.257	0.13	0.635	0.889	0.97
Dsg2	Dsp	10090.ENSMUSP00000057096	10090.ENSMUSP00000115062	0	0	0	0	0.393	0.084	0.635	0.892	0.975
Dynlt3	Tpr	10090.ENSMUSP00000033519	10090.ENSMUSP00000117616	0	0	0	0	0	0.667	0.72	0	0.902

Efna1	Epha4	10090.ENSMUSP00002956	10090.ENSMUSP00002745	0	0	0	0	0.185	0.437	0.864	0.985	0.998
Efna1	Ephb6	10090.ENSMUSP00002956	10090.ENSMUSP00001103	0	0	0	0	0.185	0.153	0.654	0.711	0.922
Efna1	Epha1	10090.ENSMUSP00002956	10090.ENSMUSP00000730	0	0	0	0	0.208	0.153	0.864	0.986	0.998
Egr1	Junb	10090.ENSMUSP00000696	10090.ENSMUSP00000646	0	0	0	0	0.751	0.404	0.144	0.617	0.945
Ehd3	Myof	10090.ENSMUSP00002486	10090.ENSMUSP00000450	0	0	0	0	0.063	0.042	0	0.91	0.912
Eif2s3x	Rps4x	10090.ENSMUSP00005939	10090.ENSMUSP00003368	0	0	0.328	0	0.503	0.462	0.6	0.482	0.956
Elovl6	Scd1	10090.ENSMUSP00007135	10090.ENSMUSP00003693	0	0	0	0	0.349	0.144	0.8	0.842	0.98
Enpp1	Gys1	10090.ENSMUSP00001011	10090.ENSMUSP00000039	0	0	0	0	0.064	0	0.9	0.088	0.907
Enpp1	Pygl	10090.ENSMUSP00001011	10090.ENSMUSP00000712	0	0	0	0	0.061	0	0.9	0.159	0.914
Enpp1	Uprt	10090.ENSMUSP00001011	10090.ENSMUSP00000851	0	0	0	0	0	0	0.9	0	0.9
Erbb2	Vegfa	10090.ENSMUSP00000538	10090.ENSMUSP00001158	0	0	0	0	0.061	0	0.6	0.756	0.9
Erbb2	Igf1	10090.ENSMUSP00000538	10090.ENSMUSP00000566	0	0	0	0	0	0	0.6	0.769	0.903
Erbb2	Esr1	10090.ENSMUSP00000538	10090.ENSMUSP00000700	0	0	0	0	0	0.283	0	0.885	0.914

Erbb2	Jak2	10090.ENSMUSP00000053897	10090.ENSMUSP00000064394	0	0	0	0.571	0	0.147	0.932	0.687	0.957
Erbb2	Yes1	10090.ENSMUSP00000053897	10090.ENSMUSP00000072154	0	0	0	0.674	0.061	0.599	0.946	0.402	0.98
Erbb2	Erbb4	10090.ENSMUSP00000053897	10090.ENSMUSP00000114123	0	0	0	0.927	0.051	0.761	0.932	0.989	0.984
Erbb2	Erbb3	10090.ENSMUSP00000053897	10090.ENSMUSP00000080716	0	0	0	0.892	0.088	0.859	0.932	0.989	0.991
Erbb2	Pik3r1	10090.ENSMUSP00000053897	10090.ENSMUSP00000056774	0	0	0	0	0	0.807	0.932	0.62	0.994
Erbb2	Erbb2ip	10090.ENSMUSP00000053897	10090.ENSMUSP00000140536	0	0	0	0	0	0.831	0.817	0.983	0.999
Erbb2ip	Erbb3	10090.ENSMUSP00000140536	10090.ENSMUSP00000080716	0	0	0	0	0.062	0.268	0.908	0.311	0.951
Erbb2ip	Erbb4	10090.ENSMUSP00000140536	10090.ENSMUSP00000114123	0	0	0	0	0	0.268	0.908	0.187	0.941
Erbb3	Pik3r1	10090.ENSMUSP00000080716	10090.ENSMUSP00000056774	0	0	0	0	0	0.817	0.932	0.749	0.996
Erbb3	Jak2	10090.ENSMUSP00000080716	10090.ENSMUSP00000064394	0	0	0	0.568	0	0.14	0.932	0.457	0.95
Erbb3	Yes1	10090.ENSMUSP00000080716	10090.ENSMUSP00000072154	0	0	0	0.638	0	0.331	0.941	0.409	0.964
Erbb3	Nrg4	10090.ENSMUSP00000080716	10090.ENSMUSP00000130929	0	0	0	0	0	0.071	0.537	0.806	0.909
Erbb3	Met	10090.ENSMUSP00000080716	10090.ENSMUSP00000111103	0	0	0	0.564	0.082	0.227	0.818	0.917	0.915

Erbb3	Erbb4	10090.ENSMUSP00000808716	10090.ENSMUSP00000114123	0	0	0	0.931	0	0.498	0.922	0.99	0.962
Erbb4	Pik3r1	10090.ENSMUSP00000114123	10090.ENSMUSP00000056774	0	0	0	0	0	0.589	0.864	0.504	0.97
Erbb4	Esr1	10090.ENSMUSP00000114123	10090.ENSMUSP00000070070	0	0	0	0	0	0.232	0.6	0.927	0.975
Erbb4	Yes1	10090.ENSMUSP00000114123	10090.ENSMUSP00000072154	0	0	0	0.683	0	0.331	0.941	0.357	0.963
Erbb4	Nrg4	10090.ENSMUSP00000114123	10090.ENSMUSP00000130929	0	0	0	0	0	0.087	0.932	0.979	0.998
Esco1	Smc3	10090.ENSMUSP00000025142	10090.ENSMUSP00000025930	0	0	0	0	0.177	0.752	0.9	0.842	0.996
Esco2	Smc2	10090.ENSMUSP00000022613	10090.ENSMUSP00000099979	0	0	0	0	0.858	0.33	0	0.343	0.932
Esco2	Smc4	10090.ENSMUSP00000022613	10090.ENSMUSP00000047872	0	0	0	0	0.774	0.33	0	0.588	0.932
Esco2	Smc3	10090.ENSMUSP00000022613	10090.ENSMUSP00000025930	0	0	0	0	0.178	0.752	0.9	0.91	0.997
Esr1	Igf1r	10090.ENSMUSP00000070070	10090.ENSMUSP00000005671	0	0	0	0	0	0.578	0.864	0.979	0.998
Esr1	Nrip1	10090.ENSMUSP00000070070	10090.ENSMUSP00000051726	0	0	0	0	0.061	0.761	0.695	0.879	0.99
Esr1	Igf1	10090.ENSMUSP00000070070	10090.ENSMUSP00000056668	0	0	0	0	0.079	0	0.676	0.985	0.995
Esr1	Pik3r1	10090.ENSMUSP00000070070	10090.ENSMUSP00000056774	0	0	0	0	0.063	0.512	0.864	0.977	0.998

Esr1	Gata3	10090.ENSMUSP00000070070	10090.ENSMUSP00000100041	0	0	0	0	0.062	0.225	0.6	0.794	0.932
Esr1	Hdac7	10090.ENSMUSP00000070070	10090.ENSMUSP00000085744	0	0	0	0	0	0.148	0.423	0.901	0.947
Esr1	Greb1	10090.ENSMUSP00000070070	10090.ENSMUSP00000124348	0	0	0	0	0	0.057	0.845	0.736	0.958
Ezr	Prkacb	10090.ENSMUSP00000063734	10090.ENSMUSP00000005164	0	0	0	0	0	0	0.922	0.074	0.925
Ezr	Rock2	10090.ENSMUSP00000063734	10090.ENSMUSP00000020904	0	0	0	0	0	0.148	0.676	0.675	0.902
Ezr	Muc16	10090.ENSMUSP00000063734	10090.ENSMUSP00000034653	0	0	0	0	0	0	0	0.946	0.947
Ezr	Ppl	10090.ENSMUSP00000063734	10090.ENSMUSP00000039360	0	0	0	0	0	0.13	0.191	0.935	0.95
F2rl1	Gnaq	10090.ENSMUSP00000022185	10090.ENSMUSP00000025541	0	0	0	0	0	0	0.8	0.963	0.992
F8	Serpine2	10090.ENSMUSP00000033539	10090.ENSMUSP00000027467	0	0	0	0	0	0	0.9	0.398	0.937
F8	Tpst2	10090.ENSMUSP00000033539	10090.ENSMUSP00000031287	0	0	0	0	0	0	0.9	0.142	0.91
Fabp4	Lpl	10090.ENSMUSP00000029041	10090.ENSMUSP00000015712	0	0	0	0	0.238	0	0.453	0.798	0.908
Fam208a	Mphosph8	10090.ENSMUSP00000022450	10090.ENSMUSP00000112170	0	0	0	0	0.097	0.396	0	0.929	0.958
Fcgr2b	Yes1	10090.ENSMUSP00000027966	10090.ENSMUSP00000072154	0	0	0	0	0	0.134	0.917	0	0.925

Fcgr2b	Syk	10090.ENSMUSP00000027966	10090.ENSMUSP00000113852	0	0	0	0	0.176	0.539	0.636	0.7	0.953
Fgf1	Fgfr2	10090.ENSMUSP00000045710	10090.ENSMUSP00000112430	0	0	0	0	0.075	0.968	0.86	0.989	0.999
Fgfr2	Pik3r1	10090.ENSMUSP00000112430	10090.ENSMUSP00000056774	0	0	0	0	0	0.255	0.86	0.529	0.946
Fut4	Ggta1	10090.ENSMUSP00000053027	10090.ENSMUSP00000099858	0	0	0	0	0.062	0	0.9	0.042	0.902
Fzd10	Wnt7b	10090.ENSMUSP00000114114	10090.ENSMUSP00000105051	0	0	0	0	0.068	0.504	0.864	0.557	0.968
Galnt11	Muc16	10090.ENSMUSP00000036240	10090.ENSMUSP00000034653	0	0	0	0	0	0	0.9	0.061	0.902
Galnt11	Muc20	10090.ENSMUSP00000036240	10090.ENSMUSP00000110769	0	0	0	0	0	0	0.9	0.051	0.901
Galnt11	Muc5b	10090.ENSMUSP00000036240	10090.ENSMUSP00000128276	0	0	0	0	0	0.047	0.9	0.064	0.903
Galnt11	Muc15	10090.ENSMUSP00000036240	10090.ENSMUSP00000106645	0	0	0	0	0	0	0.9	0.074	0.903
Galnt12	Muc16	10090.ENSMUSP00000045721	10090.ENSMUSP00000034653	0	0	0	0	0	0	0.9	0.204	0.917
Galnt12	Muc20	10090.ENSMUSP00000045721	10090.ENSMUSP00000110769	0	0	0	0	0.062	0	0.9	0.105	0.908
Galnt12	Muc15	10090.ENSMUSP00000045721	10090.ENSMUSP00000106645	0	0	0	0	0	0	0.9	0.184	0.914
Galnt12	Muc5b	10090.ENSMUSP00000045721	10090.ENSMUSP00000128276	0	0	0	0	0	0.09	0.9	0.146	0.915

Galnt4	Muc16	10090.ENSMUSP00000125315	10090.ENSMUSP00000034653	0	0	0	0	0	0	0.9	0.44	0.941
Galnt4	Muc15	10090.ENSMUSP00000125315	10090.ENSMUSP00000106645	0	0	0	0	0	0	0.9	0.502	0.948
Galnt4	Muc20	10090.ENSMUSP00000125315	10090.ENSMUSP00000110769	0	0	0	0	0.061	0	0.9	0.081	0.906
Galnt4	Muc5b	10090.ENSMUSP00000125315	10090.ENSMUSP00000128276	0	0	0	0	0	0.07	0.9	0.191	0.918
Gas1	Shh	10090.ENSMUSP00000064555	10090.ENSMUSP00000002708	0	0	0	0	0	0.683	0.759	0.932	0.994
Gcc2	Rab6b	10090.ENSMUSP00000054033	10090.ENSMUSP00000035155	0	0	0	0	0	0.592	0.6	0.487	0.908
Gcnt1	St3gal2	10090.ENSMUSP00000133935	10090.ENSMUSP00000034197	0	0	0	0	0.048	0	0.9	0.389	0.936
Gcnt1	Muc16	10090.ENSMUSP00000133935	10090.ENSMUSP00000034653	0	0	0	0	0	0	0.9	0.272	0.924
Gcnt1	Muc15	10090.ENSMUSP00000133935	10090.ENSMUSP00000106645	0	0	0	0	0	0	0.9	0.233	0.92
Gcnt1	Muc20	10090.ENSMUSP00000133935	10090.ENSMUSP00000110769	0	0	0	0	0.061	0	0.9	0.317	0.93
Gcnt1	Muc5b	10090.ENSMUSP00000133935	10090.ENSMUSP00000128276	0	0	0	0	0	0	0.9	0.17	0.913
Gcnt4	St3gal2	10090.ENSMUSP00000130496	10090.ENSMUSP00000034197	0	0	0	0	0.061	0	0.9	0.088	0.906
Gcnt4	Muc16	10090.ENSMUSP00000130496	10090.ENSMUSP00000034653	0	0	0	0	0	0	0.9	0.16	0.912

Gcnt4	Muc15	10090.ENSMUSP0000013049 6	10090.ENSMUSP0000010664 5	0	0	0	0	0	0	0.9	0.204	0.917
Gcnt4	Muc20	10090.ENSMUSP0000013049 6	10090.ENSMUSP0000011076 9	0	0	0	0	0	0	0.9	0.557	0.953
Gcnt4	Muc5b	10090.ENSMUSP0000013049 6	10090.ENSMUSP0000012827 6	0	0	0	0	0	0	0.9	0.307	0.927
Gfra1	Prkacb	10090.ENSMUSP0000002607 6	10090.ENSMUSP0000000516 4	0	0	0	0	0	0	0.95	0	0.95
Ggt1	Lap3	10090.ENSMUSP0000000650 8	10090.ENSMUSP0000004022 2	0	0	0	0	0.062	0	0.9	0.147	0.913
Ghr	Jak2	10090.ENSMUSP0000006945 7	10090.ENSMUSP0000006439 4	0	0	0	0	0	0.629	0.922	0.755	0.992
Gldc	Sardh	10090.ENSMUSP0000002577 8	10090.ENSMUSP0000009995 0	0.164	0	0	0	0.504	0.216	0.9	0.49	0.98
Gnaq	P2ry1	10090.ENSMUSP0000002554 1	10090.ENSMUSP0000002933 1	0	0	0	0	0	0	0.8	0.953	0.99
Gne	Nans	10090.ENSMUSP0000003020 1	10090.ENSMUSP0000003001 8	0	0.649	0	0	0	0	0.9	0.697	0.988
Gne	Renbp	10090.ENSMUSP0000003020 1	10090.ENSMUSP0000011227 7	0.192	0	0	0	0	0	0.9	0.432	0.95
Got2	Lap3	10090.ENSMUSP0000003409 7	10090.ENSMUSP0000004022 2	0	0	0	0	0.135	0.429	0.8	0.405	0.933
Got2	Idh2	10090.ENSMUSP0000003409 7	10090.ENSMUSP0000010300 7	0	0	0	0	0.576	0.056	0.8	0.426	0.948
Gpc3	Shh	10090.ENSMUSP0000006413 1	10090.ENSMUSP0000000270 8	0	0	0	0	0.052	0.239	0.932	0.949	0.997

Gpc3	Hs3st6	10090.ENSMUSP00006413 1	10090.ENSMUSP00004091 9	0	0	0	0	0	0.067	0.9	0.105	0.909
Gpc3	Hs3st3a1	10090.ENSMUSP00006413 1	10090.ENSMUSP00005593 0	0	0	0	0	0	0.067	0.9	0.129	0.911
Gpc3	Lrp2	10090.ENSMUSP00006413 1	10090.ENSMUSP00007975 2	0	0	0	0	0	0	0.9	0.127	0.909
Gpc3	Hs3st3b1	10090.ENSMUSP00006413 1	10090.ENSMUSP00009164 7	0	0	0	0	0	0.067	0.9	0.244	0.923
Gpc6	Hs3st6	10090.ENSMUSP00012036 2	10090.ENSMUSP00004091 9	0	0	0	0	0	0.067	0.9	0.207	0.919
Gpc6	Hs3st3a1	10090.ENSMUSP00012036 2	10090.ENSMUSP00005593 0	0	0	0	0	0.062	0.067	0.9	0.207	0.921
Gpc6	Lrp2	10090.ENSMUSP00012036 2	10090.ENSMUSP00007975 2	0	0	0	0	0	0	0.9	0.058	0.901
Gpc6	Hs3st3b1	10090.ENSMUSP00012036 2	10090.ENSMUSP00009164 7	0	0	0	0	0	0.067	0.9	0.381	0.937
Gpc6	Vcan	10090.ENSMUSP00012036 2	10090.ENSMUSP00010517 3	0	0	0	0	0.062	0	0.9	0.313	0.929
Gpihbp1	Lpl	10090.ENSMUSP00002324 3	10090.ENSMUSP00001571 2	0	0	0	0	0.098	0.927	0.6	0.981	0.999
Gpihbp1	Pcsk5	10090.ENSMUSP00002324 3	10090.ENSMUSP00002561 8	0	0	0	0	0.068	0	0.9	0.054	0.904
Hexb	Renbp	10090.ENSMUSP00002216 9	10090.ENSMUSP00011227 7	0.168	0	0	0	0.089	0	0.9	0	0.917
Hhip	Shh	10090.ENSMUSP00007804 7	10090.ENSMUSP00000270 8	0	0	0	0	0	0.887	0.932	0.984	0.999

Hs3st3a1	Sdc1	10090.ENSMUSP00000055930	10090.ENSMUSP00000020911	0	0	0	0	0.061	0	0.9	0.082	0.906
Hs3st3b1	Sdc1	10090.ENSMUSP00000091647	10090.ENSMUSP00000020911	0	0	0	0	0.068	0	0.9	0.183	0.917
Hs3st6	Sdc1	10090.ENSMUSP00000040919	10090.ENSMUSP00000020911	0	0	0	0	0.058	0	0.9	0.1	0.907
Id2	Tcf4	10090.ENSMUSP00000020974	10090.ENSMUSP00000110636	0	0	0	0	0.06	0.803	0	0.706	0.94
Ido1	Inmt	10090.ENSMUSP00000033956	10090.ENSMUSP00000003569	0	0	0	0	0	0	0.9	0.133	0.909
Ido1	Maob	10090.ENSMUSP00000033956	10090.ENSMUSP00000040550	0	0	0	0	0	0	0.9	0.092	0.905
Ido2	Inmt	10090.ENSMUSP00000113979	10090.ENSMUSP00000003569	0	0	0	0	0.157	0	0.9	0.162	0.923
Ido2	Maob	10090.ENSMUSP00000113979	10090.ENSMUSP00000040550	0	0	0	0	0.085	0	0.9	0	0.904
Igf1	Igf1r	10090.ENSMUSP00000056668	10090.ENSMUSP00000005671	0	0	0	0	0	0.927	0.932	0.992	0.999
Igf1	Itgav	10090.ENSMUSP00000056668	10090.ENSMUSP00000028499	0	0	0	0	0	0	0.905	0.301	0.931
Igf1r	Prkacb	10090.ENSMUSP00000005671	10090.ENSMUSP00000005164	0	0	0	0.565	0.063	0.13	0.909	0.195	0.925
Igf1r	Jak2	10090.ENSMUSP00000005671	10090.ENSMUSP00000064394	0	0	0	0.564	0	0.209	0.832	0.798	0.909
Igf1r	Itgav	10090.ENSMUSP00000005671	10090.ENSMUSP00000028499	0	0	0	0	0	0.064	0.905	0.284	0.931

Igf1r	Pik3r1	10090.ENSMUSP00000005671	10090.ENSMUSP00000056774	0	0	0	0	0	0.566	0.932	0.606	0.987
Il13ra1	Il4ra	10090.ENSMUSP00000033418	10090.ENSMUSP00000033004	0	0	0	0	0.105	0.901	0.932	0.987	0.999
Il13ra1	Stat6	10090.ENSMUSP00000033418	10090.ENSMUSP00000089708	0	0	0	0	0.089	0	0.864	0.765	0.968
Il13ra1	Jak2	10090.ENSMUSP00000033418	10090.ENSMUSP00000064394	0	0	0	0	0.096	0.058	0.864	0.971	0.996
Il4ra	Jak2	10090.ENSMUSP00000033004	10090.ENSMUSP00000064394	0	0	0	0	0.065	0.242	0.932	0.424	0.968
Il4ra	Stat6	10090.ENSMUSP00000033004	10090.ENSMUSP00000089708	0	0	0	0	0.131	0.632	0.932	0.873	0.996
Inmt	Maob	10090.ENSMUSP00000035609	10090.ENSMUSP00000040550	0	0	0	0	0.163	0	0.9	0.22	0.929
Itga2b	Itgb8	10090.ENSMUSP00000099375	10090.ENSMUSP00000026360	0	0	0	0	0.063	0.214	0.84	0.452	0.927
Itga3	Lamc2	10090.ENSMUSP00000001548	10090.ENSMUSP00000027753	0	0	0	0	0.089	0.131	0.864	0.414	0.929
Itga3	Itgb8	10090.ENSMUSP00000001548	10090.ENSMUSP00000026360	0	0	0	0	0.063	0.306	0.864	0.462	0.946
Itga3	Lama3	10090.ENSMUSP00000001548	10090.ENSMUSP00000089703	0	0	0	0	0.099	0.221	0.864	0.528	0.949
Itga3	Met	10090.ENSMUSP00000001548	10090.ENSMUSP00000111103	0	0	0	0	0.078	0.133	0.934	0.303	0.958
Itga3	Lama5	10090.ENSMUSP00000001548	10090.ENSMUSP00000015791	0	0	0	0	0.176	0.221	0.864	0.676	0.968

Itga4	Itgb8	10090.ENSMUSP0000009971 8	10090.ENSMUSP0000002636 0	0	0	0	0	0.063	0.306	0.864	0.454	0.945
Itgav	Sdc1	10090.ENSMUSP0000002849 9	10090.ENSMUSP0000002091 1	0	0	0	0	0.061	0	0.932	0.287	0.95
Itgav	Itgb8	10090.ENSMUSP0000002849 9	10090.ENSMUSP0000002636 0	0	0	0	0	0.078	0.923	0.932	0.872	0.999
Itgav	Vegfa	10090.ENSMUSP0000002849 9	10090.ENSMUSP0000011588 3	0	0	0	0	0.061	0	0.864	0.404	0.917
Itgav	Postn	10090.ENSMUSP0000002849 9	10090.ENSMUSP0000007277 3	0	0	0	0	0.077	0	0.402	0.945	0.967
Itgav	Mfge8	10090.ENSMUSP0000002849 9	10090.ENSMUSP0000003282 5	0	0	0	0	0.062	0	0.676	0.968	0.989
Jak2	Lepr	10090.ENSMUSP0000006439 4	10090.ENSMUSP0000003738 5	0	0	0	0	0	0.842	0.932	0.984	0.999
Jak2	Pik3r1	10090.ENSMUSP0000006439 4	10090.ENSMUSP0000005677 4	0	0	0	0	0.072	0.721	0.932	0.376	0.987
Jak2	Kitl	10090.ENSMUSP0000006439 4	10090.ENSMUSP0000010092 0	0	0	0	0	0	0	0.831	0.468	0.906
Jak2	Socs4	10090.ENSMUSP0000006439 4	10090.ENSMUSP0000006603 1	0	0	0	0	0.062	0.091	0.832	0.515	0.921
Jak2	Socs6	10090.ENSMUSP0000006439 4	10090.ENSMUSP0000006492 9	0	0	0	0	0	0.272	0.832	0.641	0.952
Jak2	Stat6	10090.ENSMUSP0000006439 4	10090.ENSMUSP0000008970 8	0	0	0	0	0.055	0.147	0.932	0.837	0.989
Jak2	Prlr	10090.ENSMUSP0000006439 4	10090.ENSMUSP0000012221 9	0	0	0	0	0	0.713	0.932	0.953	0.999

Kcnj11	Prkacb	10090.ENSMUSP00000136002	10090.ENSMUSP00000005164	0	0	0	0	0.072	0.048	0.9	0	0.904
Kdm5d	Uty	10090.ENSMUSP00000061095	10090.ENSMUSP00000070012	0	0	0	0	0.716	0.071	0	0.881	0.966
Kdsr	Ppap2c	10090.ENSMUSP00000010049	10090.ENSMUSP00000069670	0	0	0	0	0.052	0.059	0.9	0.06	0.904
Kif5b	Ranbp2	10090.ENSMUSP00000025083	10090.ENSMUSP00000033310	0	0	0	0	0.325	0.227	0	0.977	0.987
Kitl	Pik3r1	10090.ENSMUSP00000100920	10090.ENSMUSP00000056774	0	0	0	0	0	0	0.864	0.381	0.912
Krt14	Krt5	10090.ENSMUSP00000007272	10090.ENSMUSP00000023709	0	0	0	0.753	0.652	0.927	0.6	0.975	0.991
Krt18	Tnfrsf1b	10090.ENSMUSP00000023803	10090.ENSMUSP00000030336	0	0	0	0	0	0.13	0	0.892	0.902
Krt18	Krt8	10090.ENSMUSP00000023803	10090.ENSMUSP00000023952	0	0	0	0.763	0.964	0.811	0.6	0.975	0.997
Krt19	Krt8	10090.ENSMUSP00000007317	10090.ENSMUSP00000023952	0	0	0	0.782	0.602	0.272	0.72	0.878	0.928
Lama3	Lama5	10090.ENSMUSP00000089703	10090.ENSMUSP00000015791	0	0	0	0.897	0.1	0	0.891	0.581	0.904
Lama3	Lamc2	10090.ENSMUSP00000089703	10090.ENSMUSP00000027753	0	0	0	0.595	0.095	0.701	0.966	0.886	0.993
Lama3	Met	10090.ENSMUSP00000089703	10090.ENSMUSP00000111103	0	0	0	0	0.064	0.047	0.907	0.062	0.912
Lama5	Met	10090.ENSMUSP00000015791	10090.ENSMUSP00000111103	0	0	0	0	0.062	0.047	0.907	0.061	0.912

Lama5	Lamc2	10090.ENSMUSP00000015791	10090.ENSMUSP00000027753	0	0	0	0.616	0.101	0	0.932	0.601	0.95
Lamc2	Met	10090.ENSMUSP00000027753	10090.ENSMUSP00000111103	0	0	0	0	0.063	0.047	0.907	0.113	0.917
Lap3	Prodh	10090.ENSMUSP00000040222	10090.ENSMUSP00000003620	0.042	0	0	0	0.049	0	0.9	0	0.9
Lap3	P4ha2	10090.ENSMUSP00000040222	10090.ENSMUSP00000019050	0	0	0	0	0	0	0.9	0.061	0.902
Lcn2	Lrp2	10090.ENSMUSP00000053962	10090.ENSMUSP00000079752	0	0	0	0	0	0.087	0	0.953	0.955
Lcn8	Lcn9	10090.ENSMUSP00000043902	10090.ENSMUSP00000023978	0	0	0	0	0.699	0	0	0.741	0.918
Lcn9	mCG_18947	10090.ENSMUSP00000023978	10090.ENSMUSP00000028937	0	0	0	0	0.701	0	0	0.696	0.905
Ldhd	Pdha1	10090.ENSMUSP00000068086	10090.ENSMUSP00000033662	0	0	0	0	0.061	0	0.9	0.164	0.914
Lims1	Tmsb4x	10090.ENSMUSP00000020078	10090.ENSMUSP00000107795	0	0	0	0	0	0.436	0	0.968	0.981
Lims1	Parva	10090.ENSMUSP00000020078	10090.ENSMUSP00000033030	0	0	0	0	0.067	0.819	0.864	0.993	0.999
Lingo1	Tnfrsf19	10090.ENSMUSP00000059050	10090.ENSMUSP00000106865	0	0	0	0	0.062	0	0	0.973	0.974
Lpl	Ppap2c	10090.ENSMUSP00000015712	10090.ENSMUSP00000069670	0	0	0	0	0	0	0.9	0	0.9
Lpl	Pcsk5	10090.ENSMUSP00000015712	10090.ENSMUSP00000025618	0	0	0	0	0	0	0.9	0.143	0.91

Lpl	Pnpla3	10090.ENSMUSP00000015712	10090.ENSMUSP00000043826	0	0	0	0	0.051	0	0.9	0.466	0.944
Lrp2	Shh	10090.ENSMUSP00000079752	10090.ENSMUSP00000002708	0	0	0	0	0.061	0	0.864	0.931	0.99
Lrp2	Sdc1	10090.ENSMUSP00000079752	10090.ENSMUSP00000020911	0	0	0	0	0	0	0.9	0.071	0.903
Lum	Ogn	10090.ENSMUSP00000040877	10090.ENSMUSP00000021822	0	0	0	0.641	0.444	0	0.9	0.849	0.959
Lum	St3gal2	10090.ENSMUSP00000040877	10090.ENSMUSP00000034197	0	0	0	0	0	0.049	0.9	0	0.9
Lum	Tgfb2	10090.ENSMUSP00000040877	10090.ENSMUSP00000043849	0	0	0	0	0.063	0.083	0.8	0.553	0.912
Maob	Sat1	10090.ENSMUSP00000040550	10090.ENSMUSP00000026318	0	0	0	0	0.063	0	0.9	0.063	0.904
Mapk13	Vegfa	10090.ENSMUSP00000004986	10090.ENSMUSP00000115883	0	0	0	0	0.05	0	0.9	0.108	0.907
Met	Pik3r1	10090.ENSMUSP00000111103	10090.ENSMUSP00000056774	0	0	0	0	0	0.141	0.864	0.503	0.937
Met	Muc20	10090.ENSMUSP00000111103	10090.ENSMUSP00000110769	0	0	0	0	0	0.436	0.864	0.069	0.922
Mid1ip1	Thrsp	10090.ENSMUSP00000111186	10090.ENSMUSP00000042988	0	0	0	0.803	0	0.682	0.8	0.689	0.942
Mki67	Smc4	10090.ENSMUSP00000033310	10090.ENSMUSP00000047872	0	0	0	0	0.92	0.041	0	0.149	0.929
Mki67	Smc2	10090.ENSMUSP00000033310	10090.ENSMUSP00000099979	0	0	0	0	0.819	0.699	0	0.186	0.951

Muc15	St6gal1	10090.ENSMUSP00000106645	10090.ENSMUSP00000023601	0	0	0	0	0	0	0.9	0.05	0.9
Muc15	St3gal2	10090.ENSMUSP00000106645	10090.ENSMUSP00000034197	0	0	0	0	0	0	0.9	0.102	0.906
Muc15	Muc16	10090.ENSMUSP00000106645	10090.ENSMUSP00000034653	0	0	0	0	0	0	0.9	0.78	0.977
Muc15	St6galnac4	10090.ENSMUSP00000106645	10090.ENSMUSP00000099882	0	0	0	0	0	0	0.9	0.05	0.9
Muc15	Muc5b	10090.ENSMUSP00000106645	10090.ENSMUSP00000128276	0	0	0	0	0.364	0	0.9	0.732	0.981
Muc15	Muc20	10090.ENSMUSP00000106645	10090.ENSMUSP00000110769	0	0	0	0	0	0	0.9	0.857	0.985
Muc16	St6gal1	10090.ENSMUSP00000034653	10090.ENSMUSP00000023601	0	0	0	0	0	0	0.9	0.197	0.916
Muc16	St3gal2	10090.ENSMUSP00000034653	10090.ENSMUSP00000034197	0	0	0	0	0	0	0.9	0.173	0.913
Muc16	St6galnac4	10090.ENSMUSP00000034653	10090.ENSMUSP00000099882	0	0	0	0	0	0	0.9	0.089	0.905
Muc16	Muc5b	10090.ENSMUSP00000034653	10090.ENSMUSP00000128276	0	0	0	0	0.079	0	0.9	0.783	0.978
Muc16	Muc20	10090.ENSMUSP00000034653	10090.ENSMUSP00000110769	0	0	0	0	0.058	0	0.9	0.796	0.979
Muc20	St6gal1	10090.ENSMUSP00000110769	10090.ENSMUSP00000023601	0	0	0	0	0	0	0.9	0.107	0.906
Muc20	St3gal2	10090.ENSMUSP00000110769	10090.ENSMUSP00000034197	0	0	0	0	0	0	0.9	0.142	0.91

Muc20	St6galnac4	10090.ENSMUSP0000011076 9	10090.ENSMUSP0000009988 2	0	0	0	0	0	0	0.9	0.105	0.906
Muc20	Muc5b	10090.ENSMUSP0000011076 9	10090.ENSMUSP0000012827 6	0	0	0	0	0.062	0	0.9	0.738	0.973
Muc5b	St6gal1	10090.ENSMUSP0000012827 6	10090.ENSMUSP0000002360 1	0	0	0	0	0.063	0	0.9	0.075	0.905
Muc5b	St3gal2	10090.ENSMUSP0000012827 6	10090.ENSMUSP0000003419 7	0	0	0	0	0	0	0.9	0.074	0.903
Muc5b	St6galnac4	10090.ENSMUSP0000012827 6	10090.ENSMUSP0000009988 2	0	0	0	0	0	0	0.9	0.06	0.901
Mylip	Vldlr	10090.ENSMUSP0000004740 3	10090.ENSMUSP0000012732 9	0	0	0	0	0.064	0.732	0.9	0.55	0.987
Nans	Renbp	10090.ENSMUSP0000003001 8	10090.ENSMUSP0000011227 7	0	0	0	0	0.061	0	0.9	0.197	0.918
Neb	Tpm2	10090.ENSMUSP0000004776 3	10090.ENSMUSP0000003018 4	0	0	0	0	0.139	0.086	0.6	0.757	0.913
Nedd4l	Sfn	10090.ENSMUSP0000013283 8	10090.ENSMUSP0000005037 4	0	0	0	0	0	0.516	0.8	0.055	0.9
Nedd4l	Scnn1a	10090.ENSMUSP0000013283 8	10090.ENSMUSP0000008016 4	0	0	0	0	0	0.88	0.9	0.988	0.999
Nipbl	Smc1b	10090.ENSMUSP0000005938 5	10090.ENSMUSP0000002306 8	0	0	0	0	0.287	0.754	0	0.659	0.935
Nipbl	Smc3	10090.ENSMUSP0000005938 5	10090.ENSMUSP0000002593 0	0	0	0	0	0.698	0.946	0.6	0.937	0.999
Nipbl	Smc4	10090.ENSMUSP0000005938 5	10090.ENSMUSP0000004787 2	0	0	0	0	0.543	0.401	0	0.743	0.923

Nrp1	Sema 3b	10090. ENSMU SP0000 0026917	10090. ENSMU SP0000 0099591	0	0	0	0	0	0.437	0.86	0.933	0.994
Nrp1	Vegfa	10090. ENSMU SP0000 0026917	10090. ENSMU SP0000 0115883	0	0	0	0	0.061	0.856	0.676	0.99	0.999
Nrp1	Sema 3c	10090. ENSMU SP0000 0026917	10090. ENSMU SP0000 0030568	0	0	0	0	0.081	0.437	0.932	0.98	0.999
Ogn	St3gal 2	10090. ENSMU SP0000 0021822	10090. ENSMU SP0000 0034197	0	0	0	0	0.076	0.049	0.9	0	0.904
Ogt	Tet2	10090. ENSMU SP0000 0045409	10090. ENSMU SP0000 0096203	0	0	0	0	0.134	0.699	0	0.916	0.976
Ogt	Tet1	10090. ENSMU SP0000 0045409	10090. ENSMU SP0000 0133279	0	0	0	0	0.062	0.406	0	0.976	0.985
P4ha2	Prodh	10090. ENSMU SP0000 0019050	10090. ENSMU SP0000 0003620	0	0	0	0	0	0	0.9	0.049	0.9
Papss1	Suox	10090. ENSMU SP0000 0029666	10090. ENSMU SP0000 0056195	0	0	0	0	0.061	0	0.9	0.147	0.912
Pbrm1	Smarc d3	10090. ENSMU SP0000 0107727	10090. ENSMU SP0000 0030791	0	0	0	0	0.097	0.711	0.842	0.758	0.988
Pgm5	Pygl	10090. ENSMU SP0000 0036025	10090. ENSMU SP0000 0071231	0.139	0	0	0	0.553	0.041	0.9	0.36	0.972
Phc3	Suz12	10090. ENSMU SP0000 0130142	10090. ENSMU SP0000 0017692	0	0	0	0	0.063	0	0.9	0.223	0.92
Phf19	Suz12	10090. ENSMU SP0000 0028232	10090. ENSMU SP0000 0017692	0	0	0	0	0.077	0.912	0.6	0.796	0.992
Pik3r1	Zap70	10090. ENSMU SP0000 0056774	10090. ENSMU SP0000 0027291	0	0	0	0	0	0.164	0.898	0.298	0.935

Pik3r1	Yes1	10090.ENSMUSP00000056774	10090.ENSMUSP00000072154	0	0	0	0	0	0.58	0.811	0.172	0.928
Pik3r1	Syk	10090.ENSMUSP00000056774	10090.ENSMUSP00000113852	0	0	0	0	0	0.227	0.932	0.588	0.976
Plau	Serpine2	10090.ENSMUSP00000022368	10090.ENSMUSP00000027467	0	0	0	0	0	0.318	0.926	0.974	0.998
Pnisr	Prpf39	10090.ENSMUSP00000029911	10090.ENSMUSP00000112953	0	0	0	0	0.78	0	0	0.641	0.917
Ppp3ca	Smek2	10090.ENSMUSP00000053101	10090.ENSMUSP00000020755	0	0	0	0	0.117	0.259	0.9	0.105	0.933
Prkacb	Vegfa	10090.ENSMUSP00000005164	10090.ENSMUSP00000115883	0	0	0	0	0	0	0.95	0.074	0.951
Prpf39	Rbm25	10090.ENSMUSP00000112953	10090.ENSMUSP00000048470	0	0	0	0	0.434	0.737	0	0.622	0.938
Prpf4b	Rbm25	10090.ENSMUSP00000077019	10090.ENSMUSP00000048470	0	0	0	0	0.688	0.694	0	0.225	0.919
Ptgds	Ptgs1	10090.ENSMUSP00000015234	10090.ENSMUSP00000059977	0	0	0	0	0	0	0.9	0.551	0.953
Ptgds	Ptges	10090.ENSMUSP00000015234	10090.ENSMUSP00000099916	0	0	0	0	0	0	0.9	0.615	0.959
Ptges	Ptgs1	10090.ENSMUSP00000099916	10090.ENSMUSP00000059977	0	0	0	0	0	0	0.9	0.759	0.974
Ptpn22	Zap70	10090.ENSMUSP00000029433	10090.ENSMUSP00000027291	0	0	0	0	0.535	0.13	0.907	0.692	0.986
Rab6b	Tmf1	10090.ENSMUSP00000035155	10090.ENSMUSP00000093325	0	0	0	0	0.08	0.57	0.6	0.446	0.9

Rad50	Smc3	10090.ENSMUSP00002064 9	10090.ENSMUSP00002593 0	0.123	0	0	0	0.789	0.107	0.676	0.393	0.961
Ranbp2	Tpr	10090.ENSMUSP00000033 10	10090.ENSMUSP00000117616	0	0	0	0	0.657	0.162	0.8	0.525	0.969
Rgs17	Rgs9	10090.ENSMUSP00000116291	10090.ENSMUSP00000209 20	0	0	0	0.764	0.079	0	0.9	0.536	0.915
Rgs17	Rgs5	10090.ENSMUSP00000116291	10090.ENSMUSP00000279 97	0	0	0	0.873	0	0	0.9	0.244	0.902
Rgs5	Rgs9	10090.ENSMUSP00000279 97	10090.ENSMUSP00000209 20	0	0	0	0.819	0.06	0	0.9	0.572	0.911
Rock1	Rock2	10090.ENSMUSP00000069 549	10090.ENSMUSP00000209 04	0	0	0	0.968	0.208	0.41	0.9	0.905	0.95
Rock1	Vegfa	10090.ENSMUSP00000069 549	10090.ENSMUSP00000115883	0	0	0	0	0	0.043	0.966	0.301	0.975
Rock2	Vegfa	10090.ENSMUSP00000209 04	10090.ENSMUSP00000115883	0	0	0	0	0	0.043	0.949	0.43	0.97
Rpl10	Rpl3l	10090.ENSMUSP00000088 26	10090.ENSMUSP00000129325	0.08	0	0	0	0.589	0.617	0	0.461	0.911
Rpl10	Rps4x	10090.ENSMUSP00000088 26	10090.ENSMUSP00000033683	0	0	0	0	0.7	0.847	0	0.543	0.977
Rpl10	Rpl36a	10090.ENSMUSP00000088 26	10090.ENSMUSP00000108837	0	0	0	0	0.832	0.919	0	0.64	0.994
Rpl10	Rpl39	10090.ENSMUSP00000088 26	10090.ENSMUSP00000110886	0.043	0	0	0	0.822	0.944	0	0.69	0.996
Rpl36a	Rps4x	10090.ENSMUSP00000108837	10090.ENSMUSP00000033683	0	0	0	0	0.766	0.621	0	0.627	0.964

Rpl36a	Rpl3l	10090.ENSMUSP00000108837	10090.ENSMUSP00000129325	0	0	0	0	0.641	0.693	0	0.672	0.96
Rpl36a	Rpl39	10090.ENSMUSP00000108837	10090.ENSMUSP00000110886	0	0	0	0	0.864	0.951	0	0.849	0.998
Rpl39	Rps4x	10090.ENSMUSP00000110886	10090.ENSMUSP00000033683	0	0	0	0	0.815	0.897	0	0.682	0.993
Rpl39	Rpl3l	10090.ENSMUSP00000110886	10090.ENSMUSP00000129325	0.057	0	0	0	0.589	0.766	0.6	0.349	0.972
Rpl3l	Rps4x	10090.ENSMUSP00000129325	10090.ENSMUSP00000033683	0.111	0	0.342	0	0.637	0.621	0	0.522	0.954
Runx1	Socs4	10090.ENSMUSP00000023673	10090.ENSMUSP00000066031	0	0	0	0	0	0	0.9	0	0.9
Scd1	Srebf1	10090.ENSMUSP00000036936	10090.ENSMUSP00000020846	0	0	0	0	0.119	0	0	0.917	0.923
Scnn1a	Wnk2	10090.ENSMUSP00000080164	10090.ENSMUSP00000089212	0	0	0	0	0	0	0.9	0.307	0.927
Sdc1	Vcan	10090.ENSMUSP00000020911	10090.ENSMUSP00000105173	0	0	0	0	0	0	0.918	0.445	0.952
Sfrp1	Wnt5a	10090.ENSMUSP00000033952	10090.ENSMUSP00000064878	0	0	0	0	0.064	0.504	0.677	0.738	0.955
Smarcd3	Ss18l1	10090.ENSMUSP00000030791	10090.ENSMUSP00000041288	0	0	0	0	0.062	0.464	0.9	0.396	0.965
Smc1b	Sycp3	10090.ENSMUSP00000023068	10090.ENSMUSP00000020252	0	0	0	0	0.101	0.082	0.6	0.75	0.906
Smc1b	Smc2	10090.ENSMUSP00000023068	10090.ENSMUSP00000099979	0	0	0.224	0.562	0.698	0.75	0	0.509	0.943

Smc1b	Smc3	10090.ENSMUSP00002306 8	10090.ENSMUSP00002593 0	0	0	0.364	0.555	0.76	0.992	0.9	0.984	0.999
Smc2	Smc6	10090.ENSMUSP00009997 9	10090.ENSMUSP00002093 1	0	0	0	0	0.737	0.128	0	0.697	0.924
Smc2	Smc3	10090.ENSMUSP00009997 9	10090.ENSMUSP00002593 0	0	0	0.242	0.62	0.828	0.786	0	0.725	0.974
Smc2	Smc4	10090.ENSMUSP00009997 9	10090.ENSMUSP00004787 2	0	0	0.351	0.565	0.969	0.994	0.966	0.938	0.999
Smc3	Smc6	10090.ENSMUSP00002593 0	10090.ENSMUSP00002093 1	0	0	0	0	0.834	0.139	0.9	0.839	0.997
Smc3	Sycp2	10090.ENSMUSP00002593 0	10090.ENSMUSP00007990 9	0	0	0	0	0	0.433	0.6	0.718	0.93
Smc3	Smc4	10090.ENSMUSP00002593 0	10090.ENSMUSP00004787 2	0	0	0.337	0.56	0.873	0.2	0	0.884	0.943
Smc4	Top2b	10090.ENSMUSP00004787 2	10090.ENSMUSP00001762 9	0.043	0	0	0	0.785	0.239	0	0.607	0.93
Smc4	Smc6	10090.ENSMUSP00004787 2	10090.ENSMUSP00002093 1	0	0	0	0	0.809	0	0	0.831	0.966
Spry1	Spry2	10090.ENSMUSP00004929 2	10090.ENSMUSP00002270 9	0	0	0	0.923	0.062	0.447	0.961	0.861	0.979
St3gal2	St6galnac4	10090.ENSMUSP00003419 7	10090.ENSMUSP00009988 2	0	0	0	0.654	0.061	0	0.9	0.478	0.917
Sycp1	Sycp3	10090.ENSMUSP00002944 8	10090.ENSMUSP00002025 2	0	0	0	0	0	0	0.6	0.93	0.971
Sycp1	Sycp2	10090.ENSMUSP00002944 8	10090.ENSMUSP00007990 9	0	0	0	0	0.065	0	0.6	0.951	0.98

Sycp2	Sycp3	10090.ENSMUSP00000079909	10090.ENSMUSP00000020252	0	0	0	0	0.086	0.683	0.8	0.987	0.999
Syk	Zap70	10090.ENSMUSP00000113852	10090.ENSMUSP00000027291	0	0	0	0.954	0.061	0	0.905	0.882	0.911
Syk	Yes1	10090.ENSMUSP00000113852	10090.ENSMUSP00000072154	0	0	0	0.725	0.052	0.289	0.966	0.331	0.977
Syt2	Vamp1	10090.ENSMUSP00000112438	10090.ENSMUSP00000032487	0	0	0	0	0.136	0.345	0.5	0.723	0.911
Tbc1d8b	Tpd52	10090.ENSMUSP00000094036	10090.ENSMUSP00000091943	0	0	0	0	0	0	0.9	0	0.9
Tmed5	Wnt5a	10090.ENSMUSP00000002837	10090.ENSMUSP00000064878	0	0	0	0	0	0.091	0.9	0	0.905
Tmed5	Wnt7b	10090.ENSMUSP00000002837	10090.ENSMUSP00000105051	0	0	0	0	0	0.091	0.9	0.043	0.905
Top1	Top2b	10090.ENSMUSP00000105094	10090.ENSMUSP00000017629	0	0	0	0	0.164	0.656	0	0.873	0.96
Tuba8	Tubb2b	10090.ENSMUSP00000032233	10090.ENSMUSP00000075178	0	0	0	0.914	0.23	0.3	0.857	0.748	0.921
Upf2	Upf3b	10090.ENSMUSP00000058375	10090.ENSMUSP00000075614	0	0	0	0	0.127	0.975	0.8	0.984	0.999
Wls	Wnt5a	10090.ENSMUSP00000067898	10090.ENSMUSP00000064878	0	0	0	0	0.087	0.599	0.6	0.698	0.949
Wnt5a	Wnt7b	10090.ENSMUSP00000064878	10090.ENSMUSP00000105051	0	0	0	0.929	0	0.151	0.9	0.746	0.916

Table S3C. String Interaction PND35 Low Dose

String Interaction PND35 Low Dose												
#node1	node2	node1_string	node2_string	neighborhoo	gene_fusion	phylogenetic	homology	coexpression	experimenta	database_ar	automated_	combined_sc
Ap1m2	Ap1s2	10090.ENSM	10090.ENSM	0	0	0	0	0.119	0.582	0.8	0.517	0.959
Ass1	Got2	10090.ENSM	10090.ENSM	0	0	0	0	0.122	0	0.9	0.22	0.925
Cdo1	Got2	10090.ENSM	10090.ENSM	0	0	0	0	0.062	0	0.9	0.054	0.903
Cyp17a1	Cyp2e1	10090.ENSM	10090.ENSM	0	0	0.408	0.723	0.106	0	0.9	0.327	0.923
Cyp17a1	Star	10090.ENSM	10090.ENSM	0	0	0	0	0.066	0	0	0.938	0.94
Cyp17a1	Srd5a2	10090.ENSM	10090.ENSM	0	0	0	0	0.088	0	0.9	0.711	0.971
Cyp2e1	Ptgs1	10090.ENSM	10090.ENSM	0	0	0	0	0.05	0.046	0.9	0.198	0.917
Dsg2	Dsp	10090.ENSM	10090.ENSM	0	0	0	0	0.393	0.084	0.635	0.892	0.975
Fabp4	Lpl	10090.ENSM	10090.ENSM	0	0	0	0	0.238	0	0.453	0.798	0.908
Gcnt1	Muc5b	10090.ENSM	10090.ENSM	0	0	0	0	0	0	0.9	0.17	0.913
Gcnt4	Muc5b	10090.ENSM	10090.ENSM	0	0	0	0	0	0	0.9	0.307	0.927
Hs3st3b1	Sdc1	10090.ENSM	10090.ENSM	0	0	0	0	0.068	0	0.9	0.183	0.917
Hs6st2	Sdc1	10090.ENSM	10090.ENSM	0	0	0	0	0.062	0	0.9	0.26	0.924
Lpl	Pnpla3	10090.ENSM	10090.ENSM	0	0	0	0	0.051	0	0.9	0.466	0.944
Muc5b	St6gal1	10090.ENSM	10090.ENSM	0	0	0	0	0.063	0	0.9	0.075	0.905
Ptgds	Ptgs1	10090.ENSM	10090.ENSM	0	0	0	0	0	0	0.9	0.551	0.953

Table S3D. String Interaction PND35 High Dose

String Interaction PND35 HIgh Dose												
#node1	node2	node1_string	node2_string	neighborhoo	gene_fusion	phylogenetic	homology	coexpression	experimenta	database_ar	automated_t	combined_sc
Cst11	Lcn9	10090.ENSM	10090.ENSM	0	0	0	0	0.7	0	0	0.69	0.903
Defb21	Defb48	10090.ENSM	10090.ENSM	0	0	0	0	0.112	0	0.9	0.622	0.963
Defb25	Defb48	10090.ENSM	10090.ENSM	0	0	0	0	0	0	0.9	0.4	0.937
Defb30	Defb48	10090.ENSM	10090.ENSM	0	0	0	0	0.082	0	0.9	0.719	0.971
Defb42	Defb48	10090.ENSM	10090.ENSM	0	0	0	0	0	0	0.9	0.699	0.968
Defb47	Defb48	10090.ENSM	10090.ENSM	0	0	0	0.87	0.079	0	0.9	0.768	0.913
Lcn8	Lcn9	10090.ENSM	10090.ENSM	0	0	0	0	0.699	0	0	0.741	0.918
Lcn9	mCG_18947	10090.ENSM	10090.ENSM	0	0	0	0	0.701	0	0	0.696	0.905
Muc15	Muc5b	10090.ENSM	10090.ENSM	0	0	0	0	0.364	0	0.9	0.732	0.981

Table S3E. String Interaction Shared

String Interaction All Shared												
#node1	node2	node1_string	node2_string	neighborhood	gene_fusion	phylogenetic	homology	coexpression	experimenta	database_an	automated_	combined_sc
Adam7	Crisp1	10090.ENSM	10090.ENSM	0	0	0	0	0.688	0	0	0.399	0.804
C4bp	Rnase10	10090.ENSM	10090.ENSM	0	0	0	0	0.701	0	0	0	0.701
C4bp	Crisp1	10090.ENSM	10090.ENSM	0	0	0	0	0.7	0	0	0.048	0.702

References

ADAM7 GeneCards (n.d.).

Alarcón S, Esteban J, Roos R, Heikkinen P, Sánchez-Pérez I, Adamsson A, Toppari J, Koskela A, Finnilä MAJ, Tuukkanen J, Herlin M, Hamscher G, Leslie HA, Korkalainen M, Halldin K, Schrenk D, Håkansson H, and Viluksela M (2021) Endocrine, metabolic and apical effects of in utero and lactational exposure to non-dioxin-like 2,2′,3,4,4′,5,5′-heptachlorobiphenyl (PCB 180): A postnatal follow-up study in rats. *Reproductive Toxicology* **102**:109–127.

Al-Salman F, and Plant N (2012) Non-coplanar polychlorinated biphenyls (PCBs) are direct agonists for the human pregnane-X receptor and constitutive androstane receptor, and activate target gene expression in a tissue-specific manner. *Toxicol Appl Pharmacol* **263**:7–13.

Ampleman MD, Martinez A, DeWall J, Rawn DFK, Hornbuckle KC, and Thorne PS (2015) Inhalation and Dietary Exposure to PCBs in Urban and Rural Cohorts via Congener-Specific Measurements. *Environ Sci Technol* **49**:1156–1164.

Andersen AG, Jensen TK, Carlsen E, Jørgensen N, Andersson AM, Krarup T, Keiding N, and Skakkebaek NE (2000) High frequency of sub-optimal semen quality in an unselected population of young men. *Hum Reprod* **15**:366–372.

Andersson A-M, Jensen TK, Juul A, Petersen JH, Jørgensen T, and Skakkebaek NE (2007) Secular decline in male testosterone and sex hormone binding globulin serum levels in Danish population surveys. *J Clin Endocrinol Metab* **92**:4696–4705.

Andvik C, Jourdain E, Lyche JL, Karoliussen R, and Borgå K (2021) High Levels of Legacy and Emerging Contaminants in Killer Whales (Orcinus orca) from Norway, 2015 to 2017. *Environmental Toxicology and Chemistry* **40**:1848–1858.

Arnold SL, Kent T, Hogarth CA, Schlatt S, Prasad B, Haenisch M, Walsh T, Muller CH, Griswold MD, Amory JK, and Isoherranen N (2015) Importance of ALDH1A enzymes in determining human testicular retinoic acid concentrations. *J Lipid Res* **56**:342–357.

ATSDR's Toxicological Profiles: Web Version (2002) , CRC Press.

Augustine LM, Markelewicz RJ, Boekelheide K, and Cherrington NJ (2005) Xenobiotic and endobiotic transporter mRNA expression in the blood-testis barrier. *Drug Metab Dispos* **33**:182–189.

Bart J, Hollema H, Groen HJM, de Vries EGE, Hendrikse NH, Sleijfer DT, Wegman TD, Vaalburg W, and van der Graaf WTA (2004) The distribution of drug-efflux pumps, P-gp, BCRP, MRP1 and MRP2, in the normal blood-testis barrier and in primary testicular tumours. *Eur J Cancer* **40**:2064–2070.

Bemis JC, Nazarenko DA, and Gasiewicz TA (2005) Coplanar polychlorinated biphenyls activate the aryl hydrocarbon receptor in developing tissues of two TCDD-responsive lacZ mouse lines. *Toxicol Sci* **87**:529–536.

Bush B, Bennett AH, and Snow JT (1986) Polychlorobiphenyl congeners,p,p′-DDE, and sperm function in humans. *Arch Environ Contam Toxicol* **15**:333–341.

Cai J, Wang C, Wu T, Moreno JML, Zhong Y, Huang X, Chen Y, and Zuo Z (2011) Disruption of spermatogenesis and differential regulation of testicular estrogen receptor expression in mice after polychlorinated biphenyl exposure. *Toxicology* **287**:21–28.

Carlsen E, Giwercman A, Keiding N, and Skakkebaek NE (1992) Evidence for decreasing quality of semen during past 50 years. *BMJ* **305**:609–613.

Caudle WM, Richardson JR, Delea KC, Guillot TS, Wang M, Pennell KD, and Miller GW (2006) Polychlorinated Biphenyl–Induced Reduction of Dopamine Transporter Expression as a Precursor to Parkinson's Disease–Associated Dopamine Toxicity. *Toxicological Sciences* **92**:490–499.

Ceccatelli R, Faass O, Schlumpf M, and Lichtensteiger W (2006) Gene expression and estrogen sensitivity in rat uterus after developmental exposure to the polybrominated diphenylether PBDE 99 and PCB. *Toxicology* **220**:104–116.

Chaves C, Shawahna R, Jacob A, Scherrmann J-M, and Declèves X (2014) Human ABC transporters at blood-CNS interfaces as determinants of CNS drug penetration. *Curr Pharm Des* **20**:1450–1462.

Cheng SL, Li X, Lehmler H-J, Phillips B, Shen D, and Cui JY (2018) Gut Microbiota Modulates Interactions Between Polychlorinated Biphenyls and Bile Acid Homeostasis. *Toxicol Sci* **166**:269–287.

Chu S, Covaci A, and Schepens P (2003) Levels and chiral signatures of persistent organochlorine pollutants in human tissues from Belgium. *Environ Res* **93**:167–176.

Chukmasov P, Aksenov A, Sorokina T, Varakina Y, Sobolev N, and Nieboer E (2019) North Pacific Baleen Whales as a Potential Source of Persistent Organic Pollutants (POPs) in the Diet of the Indigenous Peoples of the Eastern Arctic Coasts. *Toxics* **7**:65.

Coutts SM, Fulton N, and Anderson RA (2007) Environmental toxicant-induced germ cell apoptosis in the human fetal testis. *Hum Reprod* **22**:2912–2918.

Covaci A, de Boer J, Ryan JJ, Voorspoels S, and Schepens P (2002) Distribution of organobrominated and organochlorinated contaminants in Belgian human adipose tissue. *Environ Res* **88**:210–218.

Cr C, O S, P D, P C, Jd V, and S N (2007) Estrogen receptor alpha is a major contributor to estrogen-mediated fetal testis dysgenesis and cryptorchidism. *Endocrinology* **148**, Endocrinology.

Croop JM, Raymond M, Haber D, Devault A, Arceci RJ, Gros P, and Housman DE (1989) The three mouse multidrug resistance (mdr) genes are expressed in a tissue-specific manner in normal mouse tissues. *Mol Cell Biol* **9**:1346–1350.

Dallinga JW, Moonen EJC, Dumoulin JCM, Evers JLH, Geraedts JPM, and Kleinjans JCS (2002) Decreased human semen quality and organochlorine compounds in blood. *Human Reproduction* **17**:1973–1979.

Deltour L, Haselbeck RJ, Ang HL, and Duester G (1997) Localization of class I and class IV alcohol dehydrogenases in mouse testis and epididymis: potential retinol dehydrogenases for endogenous retinoic acid synthesis. *Biol Reprod* **56**:102–109.

Dobin A, Davis CA, Schlesinger F, Drenkow J, Zaleski C, Jha S, Batut P, Chaisson M, and Gingeras TR (2013) STAR: ultrafast universal RNA-seq aligner. *Bioinformatics* **29**:15–21.

Döring B, and Petzinger E (2014) Phase 0 and phase III transport in various organs: combined concept of phases in xenobiotic transport and metabolism. *Drug Metab Rev* **46**:261–282.

Egusquiza RJ, Ambrosio ME, Wang SG, Kay KM, Zhang C, Lehmler H-J, and Blumberg B (2020) Evaluating the Role of the Steroid and Xenobiotic Receptor (SXR/PXR) in PCB-153 Metabolism and Protection against Associated Adverse Effects during Perinatal and Chronic Exposure in Mice. *Environ Health Perspect* **128**:047011.

Ellsworth L, McCaffery H, Chernyak S, Lam S, Sargis RM, Padmanabhan V, and Gregg B (2020) Lactational exposure to polychlorinated biphenyls is higher in overweight /obese women and associated with altered infant growth trajectory: A pilot study. *Current Research in Toxicology* **1**:133–140.

EPEL D, LUCKENBACH T, STEVENSON CN, MACMANUS-SPENCER LA, HAMDOUN A, and SMITAL T (2008) EFFLUX TRANSPORTERS: Newly Appreciated Roles in Protection against Pollutants. *Environ Sci Technol* **42**:3914–3920.

European Agency for Safety and Health at Work (2016) *State of the art report on reproductive toxicants: summary*, Publications Office of the European Union, LU.

Filipiak E, Suliborska D, Laszczynska M, Walczak-Jedrzejowska R, Oszukowska E, Marchlewska K, Kula K, and Slowikowska-Hilczer J (2013) Estrogen receptor alpha localization in the testes of men with normal spermatogenesis. *Folia Histochem Cytobiol* **50**:340–345.

Forman BM, and Evans RM (1995) Nuclear hormone receptors activate direct, inverted, and everted repeats. *Ann N Y Acad Sci* **761**:29–37.

FOX RIVER NRDA/PCB RELEASES Site Profile (n.d.).

Gährs M, Roos R, Andersson PL, and Schrenk D (2013) Role of the nuclear xenobiotic receptors CAR and PXR in induction of cytochromes P450 by non-dioxinlike polychlorinated biphenyls in cultured rat hepatocytes. *Toxicol Appl Pharmacol* **272**:77–85.

Gu Z (2022) Complex heatmap visualization. *iMeta* **1**:e43.

Gupta C (2000) Reproductive Malformation of the Male Offspring Following Maternal Exposure to Estrogenic Chemicals. *Proceedings of the Society for Experimental Biology and Medicine* **224**:61–68.

Guvenius DM, Aronsson A, Ekman-Ordeberg G, Bergman A, and Norén K (2003) Human prenatal and postnatal exposure to polybrominated diphenyl ethers, polychlorinated biphenyls, polychlorobiphenylols, and pentachlorophenol. *Environ Health Perspect* **111**:1235–1241.

Han L, Yang Z, Wang L-J, Yan H-Y, Zhang Y, Han X-Y, Yao Y-P, Dang X, Zhang Y-H, Guo X-M, Zhang H-L, and Liu T (2019) [Expression of the Ces5a gene in the rat testis]. *Zhonghua Nan Ke Xue* **25**:867–873.

Hansen DA, Esakky P, Drury A, Lamb L, and Moley KH (2014) The aryl hydrocarbon receptor is important for proper seminiferous tubule architecture and sperm development in mice. *Biol Reprod* **90**:8.

Hau RK, Wright SH, and Cherrington NJ (2023) Drug Transporters at the Human Blood-Testis Barrier. *Drug Metab Dispos*, doi: 10.1124/dmd.122.001186, American Society for Pharmacology and Experimental Therapeutics.

Heindel JJ, Skalla LA, Joubert BR, Dilworth CH, and Gray KA (2017) Review of developmental origins of health and disease publications in environmental epidemiology. *Reprod Toxicol* **68**:34–48.

Henriksen LS, Frederiksen H, Jørgensen N, Juul A, Skakkebæk NE, Toppari J, Petersen JH, and Main KM (2023) Maternal phthalate exposure during pregnancy and testis function of young adult sons. *Sci Total Environ* **871**:161914.

Hernandez JP, Mota LC, and Baldwin WS (2009) Activation of CAR and PXR by Dietary, Environmental and Occupational Chemicals Alters Drug Metabolism, Intermediary Metabolism, and Cell Proliferation. *Curr Pharmacogenomics Person Med* **7**:81–105.

Hsu P-C, Pan M-H, Li L-A, Chen C-J, Tsai S-S, and Guo YL (2007) Exposure in utero to 2,2′,3,3′,4,6′-hexachlorobiphenyl (PCB 132) impairs sperm function and alters

testicular apoptosis-related gene expression in rat offspring. *Toxicology and Applied Pharmacology* **221**:68–75.

Huyghe E, Matsuda T, and Thonneau P (2003) Increasing incidence of testicular cancer worldwide: a review. *J Urol* **170**:5–11.

Jacobs MN, Nolan GT, and Hood SR (2005) Lignans, bacteriocides and organochlorine compounds activate the human pregnane X receptor (PXR). *Toxicol Appl Pharmacol* **209**:123–133.

Järvinen E, Deng F, Kidron H, and Finel M (2018) Efflux transport of estrogen glucuronides by human MRP2, MRP3, MRP4 and BCRP. *J Steroid Biochem Mol Biol* **178**:99–107.

Jepson PD, Deaville R, Barber JL, Aguilar À, Borrell A, Murphy S, Barry J, Brownlow A, Barnett J, Berrow S, Cunningham AA, Davison NJ, ten Doeschate M, Esteban R, Ferreira M, Foote AD, Genov T, Giménez J, Loveridge J, Llavona Á, Martin V, Maxwell DL, Papachlimitzou A, Penrose R, Perkins MW, Smith B, de Stephanis R, Tregenza N, Verborgh P, Fernandez A, and Law RJ (2016) PCB pollution continues to impact populations of orcas and other dolphins in European waters. *Sci Rep* **6**:18573, Nature Publishing Group.

Jeulin C, and Lewin LM (1996) Role of free L-carnitine and acetyl-L-carnitine in post-gonadal maturation of mammalian spermatozoa. *Hum Reprod Update* **2**:87–102.

Kaminski N (n.d.) Activation of AhR signaling cascades in PCB induced immune dysfunction.

Kania-Korwel I, and Lehmler H-J (2016) Toxicokinetics of chiral polychlorinated biphenyls across different species--a review. *Environ Sci Pollut Res Int* **23**:2058–2080.

Keil Stietz KP, Kennedy CL, Sethi S, Valenzuela A, Nunez A, Wang K, Wang Z, Wang P, Spiegelhoff A, Puschner B, Bjorling DE, and Lein PJ (2021) In utero and lactational PCB exposure drives anatomic changes in the juvenile mouse bladder. *Curr Res Toxicol* **2**:1–18.

Klaassen CD, and Aleksunes LM (2010) Xenobiotic, bile acid, and cholesterol transporters: function and regulation. *Pharmacol Rev* **62**:1–96.

Kliewer SA, Goodwin B, and Willson TM (2002) The Nuclear Pregnane X Receptor: A Key Regulator of Xenobiotic Metabolism. *Endocrine Reviews* **23**:687–702.

Kobayashi D, Tamai I, Sai Y, Yoshida K, Wakayama T, Kido Y, Nezu J-I, Iseki S, and Tsuji A (2007) Transport of carnitine and acetylcarnitine by carnitine/organic cation transporter (OCTN) 2 and OCTN3 into epididymal spermatozoa. *Reproduction* **134**:651–658.

Kostyniak PJ, Hansen LG, Widholm JJ, Fitzpatrick RD, Olson JR, Helferich JL, Kim KH, Sable HJK, Seegal RF, Pessah IN, and Schantz SL (2005) Formulation and Characterization of an Experimental PCB Mixture Designed to Mimic Human Exposure from Contaminated Fish. *Toxicological Sciences* **88**:400–411.

Kuriyama SN, and Chahoud I (2004) In utero exposure to low-dose 2,3′,4,4′,5-pentachlorobiphenyl (PCB 118) impairs male fertility and alters neurobehavior in rat offspring. *Toxicology* **202**:185–197.

Lancz K, Hertz-Picciotto I, Jusko TA, Murínová Ľ, Wimmerová S, Šovčíková E, Dedík L, Strémy M, Drobná B, Farkašová D, and Trnovec T (2015) Duration of breastfeeding and serum PCB 153 concentrations in children. *Environ Res* **136**:35–39.

Li AJ, Feldman SM, McNally RK, and Kannan K (2019) Distribution of Organohalogen and Synthetic Musk Compounds in Breast Adipose Tissue of Breast Cancer Patients in Ulster County, New York, USA. *Arch Environ Contam Toxicol* **77**:68–78.

Li H, Handsaker B, Wysoker A, Fennell T, Ruan J, Homer N, Marth G, Abecasis G, and Durbin R (2009) The Sequence Alignment/Map format and SAMtools. *Bioinformatics* **25**:2078–2079.

Liang Y, Li S, and Chen L (2015) The physiological role of drug transporters. *Protein Cell* **6**:334–350.

Lim JJ, Li X, Lehmler H-J, Wang D, Gu H, and Cui JY (2020) Gut Microbiome Critically Impacts PCB-induced Changes in Metabolic Fingerprints and the Hepatic Transcriptome in Mice. *Toxicol Sci* **177**:168–187.

Lin L, Yee SW, Kim RB, and Giacomini KM (2015) SLC Transporters as Therapeutic Targets: Emerging Opportunities. *Nat Rev Drug Discov* **14**:543–560.

Lufkin T, Lohnes D, Mark M, Dierich A, Gorry P, Gaub MP, LeMeur M, and Chambon P (1993) High postnatal lethality and testis degeneration in retinoic acid receptor alpha mutant mice. *Proc Natl Acad Sci U S A* **90**:7225–7229.

Mackowiak B, Hodge J, Stern S, and Wang H (2018) The Roles of Xenobiotic Receptors: Beyond Chemical Disposition. *Drug Metab Dispos* **46**:1361–1371, American Society for Pharmacology and Experimental Therapeutics.

Meeker JD, and Hauser R (2010) Exposure to Polychlorinated Biphenyls (PCBs) and Male Reproduction. *Systems Biology in Reproductive Medicine* **56**:122–131, Taylor & Francis.

Melaine N, Liénard M-O, Dorval I, Le Goascogne C, Lejeune H, and Jégou B (2002) Multidrug resistance genes and p-glycoprotein in the testis of the rat, mouse, Guinea pig, and human. *Biol Reprod* **67**:1699–1707.

Meyer UA (1996) Overview of enzymes of drug metabolism. *J Pharmacokinet Biopharm* **24**:449–459.

Morris ME, Rodriguez-Cruz V, and Felmlee MA (2017) SLC and ABC Transporters: Expression, Localization, and Species Differences at the Blood-Brain and the Blood-Cerebrospinal Fluid Barriers. *AAPS J* **19**:1317–1331.

Mus musculus complement component 4 binding protein (C4bp), mRNA (2022).

Ni K-D, and Liu J-Y (2021) The Functions of Cytochrome P450 ω-hydroxylases and the Associated Eicosanoids in Inflammation-Related Diseases. *Front Pharmacol* **12**:716801.

Nixon BJ, Katen AL, Stanger SJ, Schjenken JE, Nixon B, and Roman SD (2014) Mouse spermatocytes express CYP2E1 and respond to acrylamide exposure. *PLoS One* **9**:e94904.

Nonis Alberto, De Nardi B, and Nonis Alessandro (2014) Choosing between RT-qPCR and RNA-seq: a back-of-the-envelope estimate towards the definition of the break-even-point. *Anal Bioanal Chem* **406**:3533–3536.

Parada-Bustamante A, Molina C, Valencia C, Flórez M, Lardone MC, Argandoña F, Piottante A, Ebensperguer M, Orihuela PA, and Castro A (2017) Disturbed testicular expression of the estrogen-metabolizing enzymes CYP1A1 and COMT in infertile men with primary spermatogenic failure: possible negative implications on Sertoli cells. *Andrology* **5**:486–494.

Paulozzi LJ (1999) International trends in rates of hypospadias and cryptorchidism. *Environ Health Perspect* **107**:297–302.

PCB CONTAMINATED SEDIMENT IN THE LOWER FOX RIVER AND GREEN BAY (n.d.).

Phang-Lyn S, and Llerena VA (2022) Biochemistry, Biotransformation, in *StatPearls [Internet]* p, StatPearls Publishing.

Pinne M, Ponce E, and Raucy JL (2016) Transactivation Assays to Assess Canine and Rodent Pregnane X Receptor (PXR) and Constitutive Androstane Receptor (CAR) Activation. *PLOS ONE* **11**:e0164642, Public Library of Science.

Pizzagalli F, Hagenbuch B, Stieger B, Klenk U, Folkers G, and Meier PJ (2002) Identification of a novel human organic anion transporting polypeptide as a high affinity thyroxine transporter. *Mol Endocrinol* **16**:2283–2296.

Pocar P, Fiandanese N, Secchi C, Berrini A, Fischer B, Schmidt J-S, Schaedlich K, Rhind SM, Zhang Z, and Borromeo V (2012) Effects of Polychlorinated Biphenyls in CD-1 Mice: Reproductive Toxicity and Intergenerational Transmission. *Toxicological Sciences* **126**:213–226.

Rajendram Roshanna, Rajendram Rajkumar, and Preedy VR (2016) Chapter 35 - Ethanol Metabolism and Implications for Disease, in *Neuropathology of Drug Addictions and Substance Misuse* (Preedy VR ed) pp 377–388, Academic Press, San Diego.

Risso D, Ngai J, Speed TP, and Dudoit S (2014) Normalization of RNA-seq data using factor analysis of control genes or samples. *Nat Biotechnol* **32**:896–902, Nature Publishing Group.

RNASE10 GeneCards (n.d.).

Robinson MD, McCarthy DJ, and Smyth GK (2010) edgeR: a Bioconductor package for differential expression analysis of digital gene expression data. *Bioinformatics* **26**:139–140.

Romersi RF, and Nicklisch SCT (2022) Interactions of Environmental Chemicals and Natural Products With ABC and SLC Transporters in the Digestive System of Aquatic Organisms. *Frontiers in Physiology* **12**.

Rothhammer V, and Quintana FJ (2019) The aryl hydrocarbon receptor: an environmental sensor integrating immune responses in health and disease. *Nat Rev Immunol* **19**:184–197, Nature Publishing Group.

Safe S (1990) Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs). *Crit Rev Toxicol* **21**:51–88.

Sethi S, Keil Stietz KP, Valenzuela AE, Klocke CR, Silverman JL, Puschner B, Pessah IN, and Lein PJ (2021) Developmental Exposure to a Human-Relevant Polychlorinated Biphenyl Mixture Causes Behavioral Phenotypes That Vary by Sex and Genotype in Juvenile Mice Expressing Human Mutations That Modulate Neuronal Calcium. *Front Neurosci* **15**:766826.

Shabtai Y, Shukrun N, and Fainsod A (2016) ADHFe1: a novel enzyme involved in retinoic acid-dependent <I>Hox</I> activation. *The International Journal of Developmental Biology* **61**:303–310, UPV/EHU Press.

Shipp A, Lawrence G, Gentry R, McDonald T, Bartow H, Bounds J, Macdonald N, Clewell H, Allen B, and Van Landingham C (2006) Acrylamide: review of toxicity data and dose-response analyses for cancer and noncancer effects. *Crit Rev Toxicol* **36**:481–608.

Shmarakov IO, Lee YJ, Jiang H, and Blaner WS (2019) CONSTITUTIVE ANDROSTANE RECEPTOR MEDIATES PCB-INDUCED DISRUPTION OF RETINOID HOMEOSTASIS. *Toxicol Appl Pharmacol* **381**:114731.

Soloyan H, De Filippo RE, and Sedrakyan S (2019) Tissue Engineering of the Reproductive System, in *Encyclopedia of Tissue Engineering and Regenerative Medicine* (Reis RL ed) pp 393–403, Academic Press, Oxford.

Steele G, Stehr-Green P, and Welty E (1986) Estimates of the biologic half-life of polychlorinated biphenyls in human serum. *New England journal of medicine (USA)*.

Stieger B, and Gao B (2015) Drug Transporters in the Central Nervous System. *Clin Pharmacokinet* **54**:225–242.

Strazielle N, and Ghersi-Egea J-F (2015) Efflux transporters in blood-brain interfaces of the developing brain. *Front Neurosci* **9**:21.

Su L, Mruk DD, and Cheng CY (2011) Drug transporters, the blood-testis barrier, and spermatogenesis. *J Endocrinol* **208**:207–223.

Sun H-Z, Qin G-Q, Wang F-G, Bai Y, Zhang Z, and Fang Z-Z (2020) Hydroxylated polychlorinated biphenyls (OH-PCBs) exert strong inhibitory effects towards human carboxylesterases (CESs). *Science of The Total Environment* **745**:141140.

Suzuki T, Onogawa T, Asano N, Mizutamari H, Mikkaichi T, Tanemoto M, Abe M, Satoh F, Unno M, Nunoki K, Suzuki M, Hishinuma T, Goto J, Shimosegawa T, Matsuno S, Ito S, and Abe T (2003) Identification and characterization of novel rat and human gonad-specific organic anion transporters. *Mol Endocrinol* **17**:1203–1215.

Swan SH, Elkin EP, and Fenster L (2000) The question of declining sperm density revisited: an analysis of 101 studies published 1934-1996. *Environ Health Perspect* **108**:961–966.

Takeuchi S, Anezaki K, and Kojima H (2017) Effects of unintentional PCBs in pigments and chemical products on transcriptional activity via aryl hydrocarbon and nuclear hormone receptors. *Environmental Pollution* **227**:306–313.

Taniguchi M, Miura K, Iwao H, and Yamanaka S (2001) Quantitative assessment of DNA microarrays--comparison with Northern blot analyses. *Genomics* **71**:34–39.

Tee PG, Sweeney AM, Symanski E, Gardiner JC, Gasior DM, and Schantz SL (2003) A longitudinal examination of factors related to changes in serum polychlorinated biphenyl levels. *Environmental Health Perspectives* **111**:702–707, Environmental Health Perspectives.

Tijet N, Boutros PC, Moffat ID, Okey AB, Tuomisto J, and Pohjanvirta R (2006) Aryl Hydrocarbon Receptor Regulates Distinct Dioxin-Dependent and Dioxin-Independent Gene Batteries. *Mol Pharmacol* **69**:140–153, American Society for Pharmacology and Experimental Therapeutics.

Travison TG, Araujo AB, O'Donnell AB, Kupelian V, and McKinlay JB (2007) A population-level decline in serum testosterone levels in American men. *J Clin Endocrinol Metab* **92**:196–202.

Vernet N, Dennefeld C, Rochette-Egly C, Oulad-Abdelghani M, Chambon P, Ghyselinck NB, and Mark M (2006) Retinoic Acid Metabolism and Signaling Pathways in the Adult and Developing Mouse Testis. *Endocrinology* **147**:96–110.

Wajda A, Łapczuk J, Grabowska M, Pius-Sadowska E, Słojewski M, Laszczynska M, Urasinska E, Machalinski B, and Drozdzik M (2017) Cell and region specificity of Aryl hydrocarbon Receptor (AhR) system in the testis and the epididymis. *Reproductive Toxicology* **69**:286–296.

Wang Y-M, Ong SS, Chai SC, and Chen T (2012) Role of CAR and PXR in Xenobiotic Sensing and Metabolism. *Expert Opin Drug Metab Toxicol* **8**:803–817.

Wang Z, Gerstein M, and Snyder M (2009) RNA-Seq: a revolutionary tool for transcriptomics. *Nat Rev Genet* **10**:57–63.

Weintraub M, and Birnbaum LS (2008) Catfish consumption as a contributor to elevated PCB levels in a non-Hispanic black subpopulation. *Environmental Research* **107**:412–417.

Welboren W-J, Sweep FCGJ, Span PN, and Stunnenberg HG (2009) Genomic actions of estrogen receptor alpha: what are the targets and how are they regulated? *Endocr Relat Cancer* **16**:1073–1089.

Whyte-Allman S-K, Hoque MT, Jenabian M-A, Routy J-P, and Bendayan R (2017) Xenobiotic Nuclear Receptors Pregnane X Receptor and Constitutive Androstane Receptor Regulate Antiretroviral Drug Efflux Transporters at the Blood-Testis Barrier. *J Pharmacol Exp Ther* **363**:324–335, American Society for Pharmacology and Experimental Therapeutics.

Wijnholds J, Scheffer GL, van der Valk M, van der Valk P, Beijnen JH, Scheper RJ, and Borst P (1998) Multidrug resistance protein 1 protects the oropharyngeal mucosal layer and the testicular tubules against drug-induced damage. *J Exp Med* **188**:797–808.

Xue J, Liu SV, Zartarian VG, Geller AM, and Schultz BD (2014) Analysis of NHANES measured blood PCBs in the general US population and application of SHEDS model to identify key exposure factors. *J Expo Sci Environ Epidemiol* **24**:615–621, Nature Publishing Group.

Yang D, Kim KH, Phimister A, Bachstetter AD, Ward TR, Stackman RW, Mervis RF, Wisniewski AB, Klein SL, Kodavanti PRS, Anderson KA, Wayman G, Pessah IN, and Lein PJ (2009) Developmental Exposure to Polychlorinated Biphenyls Interferes with Experience-Dependent Dendritic Plasticity and Ryanodine Receptor Expression in Weanling Rats. *Environ Health Perspect* **117**:426–435.

Yao T, Weng X, Liang W, Li W, Wu W, and Li F (2023) Differences of the anti-oxidative capability, GPX3, and Cu/ZnSOD expression in Hu sheep testis with different size at six-month-old. *Anim Biotechnol* 1–9.

Zhang J, Liang J, Zhu H, Li C, and Wu Q (2013) PFOS and PCB 153 have direct adverse effects on neonatal testis modeled using a coculture of primary gonocyte and sertoli cells. *Environmental Toxicology* **28**:322–331.

Zhang Q, Lu M, Wang C, Du J, Zhou P, and Zhao M (2014) Characterization of estrogen receptor α activities in polychlorinated biphenyls by in vitro dual-luciferase reporter gene assay. *Environmental Pollution* **189**:169–175.

Zhang Y (2011) Phase II Enzymes, in *Encyclopedia of Cancer* (Schwab M ed) pp 2853–2855, Springer, Berlin, Heidelberg.

Zhang Y, Cheng X, Aleksunes L, and Klaassen CD (2012) Transcription Factor-Mediated Regulation of Carboxylesterase Enzymes in Livers of Mice. *Drug Metab Dispos* **40**:1191–1197.

Zhao M, Ma J, Li M, Zhang Y, Jiang B, Zhao X, Huai C, Shen L, Zhang N, He L, and Qin S (2021) Cytochrome P450 Enzymes and Drug Metabolism in Humans. *Int J Mol Sci* **22**:12808.