Circadian- and sex-dependent increases in intravenous cocaine self-administration in *Npas2* mutant mice

Abbreviated title: Increased cocaine intake in female *Npas2* mutants

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Abstract

Substance use disorder is associated with disruptions in circadian rhythms. The circadian transcription factor neuronal PAS domain protein 2 (NPAS2) is enriched in reward-related brain regions and regulates reward, but its role in substance use is unclear. To examine the role of NPAS2 in drug taking, we measured intravenous cocaine self-administration (acquisition, dose-response, progressive ratio, extinction, cue-induced reinstatement) in wild-type (WT) and *Npas2* mutant mice at different times of day. In the light (inactive) phase, cocaine reinforcement was increased in all *Npas2* mutants, while self-administration and motivation were affected sex-dependently. These sex differences were amplified during the dark (active) phase with *Npas2* mutation increasing self-administration, reinforcement, motivation, extinction responding and reinstatement in females, but only reinforcement in males. To determine whether circulating hormones are driving these sex differences, we ovariectomized WT and *Npas2* mutant females and confirmed that unlike sham controls, ovariectomized mutant mice showed no increase in self-administration. To identify whether striatal brain regions are activated in *Npas2* mutant females, we measured cocaine-induced ΔFosB expression. Relative to WT, ΔFosB expression was increased in D1+ neurons in the nucleus accumbens core and dorsolateral striatum in *Npas2* mutant females after dark phase self-administration. We also identified potential target genes that may underlie the behavioral responses to cocaine in *Npas2* mutant females. These results suggest NPAS2 regulates reward and activity in specific striatal regions in a sex and time of day specific manner. Striatal activation could be augmented by circulating sex hormones, leading to an increased effect of *Npas2* mutation in females.

Significance Statement

Circadian disruptions are a common symptom of substance use disorders and chronic exposure to drugs of abuse alters circadian rhythms, which may contribute to subsequent substance use. Diurnal rhythms are commonly found in behavioral responses to drugs of abuse with drug sensitivity and motivation peaking during the dark (active) phase in nocturnal rodents. Emerging evidence links disrupted circadian genes to substance use vulnerability and drug-induced alterations to these genes may augment drug-seeking. The circadian transcription factor NPAS2 is enriched in reward-related brain regions and regulates reward, but its role in substance use is unclear. To examine the role of NPAS2 in drug taking, we measured intravenous cocaine self-administration in wild-type and *Npas2* mutant mice at different times of day.

Introduction

Circadian disruptions are a common symptom of many psychiatric disorders (Kowatch et al., 1992; Morgan & Malison, 2007; Matuskey et al., 2011), including substance use disorder (SUD)(Spanagel et al., 2005; McClung, 2007; Logan et al., 2014; Lauren M DePoy et al., 2017). Diurnal rhythms in the behavioral responses to drugs of abuse are common with drug sensitivity and drug use peaking during the active compared to inactive phase, or dark and light respectively in nocturnal rodents (Baird & Gauvin, 2000; Abarca et al., 2002; Roberts et al., 2002; Sleipness et al., 2005). Chronic exposure to drugs of abuse alters circadian rhythms, which may contribute to subsequent substance use (SU)(Roberts et al., 2002; Logan et al., 2014; Lauren M DePoy et al., 2017). Emerging evidence from rodents and humans links disrupted circadian genes to SU vulnerability (Dong et al., 2011; Forbes et al., 2012; Ozburn et al., 2012, 2013; Blomeyer et al., 2013; Gamsby et al., 2013; Bi et al., 2014; Baranger et al., 2016) and drug-induced alterations to these genes may augment drug-seeking.

Almost every cell in the brain and body expresses a molecular clock, comprised of several interlocking transcriptional-translational feedback loops (Reppert & Weaver, 2002; Ko & Takahashi, 2006; Takahashi, 2016). The molecular clock is regulated by Circadian Locomotor Output Cycles Kaput (CLOCK) or its homologue, neuronal PAS domain protein 2 (NPAS2), which dimerize with Brain and Muscle ARNT-like 1 (BMAL1) to control transcription of many genes. After translation, these proteins enter the nucleus and inhibit the transcriptional activity of (CLOCK/NPAS2)/BMAL1, closing the negative feedback loop (Ko & Takahashi, 2006). Our laboratory has previously demonstrated that mutations in *Clock* lead to increased cocaine and alcohol intake in mice (McClung et al., 2005; Ozburn et al., 2012, 2013) and a loss of diurnal rhythmicity in cocaine self-administration (Roberts et al., 2002). We have also shown that while *Clock* mutation increases cocaine preference, *Npas2* mutation attenuates preference (Ozburn et al., 2015a). NPAS2 is similar to CLOCK in structure and function, yet relative to CLOCK, NPAS2 expression and promotor binding is highly rhythmic in the striatum (Garcia et al., 2000a; Ozburn et al., 2015a), including the nucleus accumbens (NAc), a major neural substrate of reward (Wise & Rompre, 1989). In fact, in the NAc rhythms in *Npas2* are more highly affected by cocaine than *Clock* (Falcon et al., 2013) and *Npas2* knockdown increases glutamatergic transmission onto dopamine *Drd1*-expressing neurons (Parekh et al., 2019). Together, these findings suggest NPAS2 might play uniquely important role in the regulation of reward within the striatum.

This study aimed to determine whether NPAS2 regulates intravenous cocaine self-administration, a translational model of drug taking, the reinforcing and motivational properties of drugs and relapse-like behavior. We investigated whether *Npas2* mutation modulates the diurnal rhythm in drug taking by measuring self-administration during both the light and dark phase. We also examined whether *Npas2* mutation differentially impacts male and female mice since sex differences are prominent in circadian rhythms (Hatcher et al., 2018) and SUD (Becker & Hu, 2008). We find that NPAS2 regulates cocaine self-administration differentially across sex and time of day (TOD). Ovarian hormones and cocaine-induced expression of striatal ΔFosB are associated with increased self-administration in *Npas2* mutant females during the dark phase. Furthermore, we identify potential target genes that might underlie the behavioral responses to cocaine in *Npas2* mutant females.

Methods and Materials

Subjects. Male and female *Npas2* mutant mice or wild-type (WT) littermates, maintained on a C57BL/6J background, were used. These mice were originally described by Garcia et al., 2000. This mutation removes the bHLH domain of NPAS2, leaving the majority of the protein intact, but incapable of binding to BMAL1 (Garcia et al., 2000b). Adult mice were maintained on a 12:12 light-dark cycle with lights on (Zeitgeber Time (ZT0)) at 0700 or 1900. Behavioral testing occurred during the light phase from ZT2-7, unless specifically indicated as a dark phase experiment (ZT14-19). Food and water were provided *ad libitum* unless otherwise indicated. Procedures were approved by the University of Pittsburgh IACUC.

Drug. Cocaine hydrochloride was provided by the National Institute on Drug Abuse. Animals were injected with 2.5, 5 or 15 mg/kg (intraperitoneal, i.p.; volume 10 ml/kg) in conditioned place preference and locomotor sensitization and 0-1 mg/kg/infusion for cocaine self-administration.

Surgery.

Jugular Catheterization. Mice were anesthetized with a 100 mg/kg ketamine / 1 mg/kg xylazine mixture. Surgery was performed under white light, during the second half of the inactive phase, regardless of light housing conditions for the mice. As previously described (Ozburn et al., 2012; Lauren M. DePoy et al., 2017), the dorsal and ventral sides were shaved and disinfected. The right jugular vein was exposed by blunt dissection and a sterile polyurethane catheter was placed and secured to the vein. The catheter is exteriorized posterior to the scapulae via a dacron mesh mount (Instech). The dorsal and ventral wounds were sutured and mice were pair housed for the duration, unless fighting or uneven sample sizes necessitated single housing. Mice recover for 6-7 days before intravenous self-administration training begins. Catheters were maintained by infusing catheters daily with 0.05 mL gentamicin (0.33 mg/mL) and heparinized saline (30 USP/mL) containing baytril (0.5 mg/kg). Catheter patency was tested approximately once per week using 0.05 mL brevital (3 mg/mL), mice that failed to lose muscle tone were excluded.

Ovariectomy. Ovariectomy (OVX) was performed as previously described (Heger et al., 2003). Female mice of at least 10 weeks of age were anesthetized with isoflurane. The ventral side was shaved and disinfected. The ovaries were located and either left intact or ligated and removed in sham and ovariectomized

groups respectively. The abdominal wall was secured with absorbable sutures and the skin stapled. Mice were allowed to recover for at least 10 days before food training began. Due to previous isoflurane treatment mice were also anesthetized with isoflurane during the jugular catheterization. Following surgery, mice were moved from a 12:12 light cycle to a reverse light cycle (1900 on) to acclimate before behavioral testing. Mice were allowed to recover for at least 10 days, ensuring reduced levels of circulating sex hormones before food training began. Hormones should be entirely ablated before cocaine self-administration.

Behavioral testing.

Conditioned place preference (CPP). As previously described (Ozburn et al., 2015a) female mice 8 weeks and older were first habituated to a testing room for 30 minutes. On day 1, a pre-conditioning test was conducted, wherein mice were placed in the center of a 3-chamber box. The outer two chambers were distinct with visual and tactile differences. Time in each chamber was recorded over the 20-minute session and any mice spending ≥50% (600 seconds) in one zone were excluded. On the subsequent 4 days mice were injected with either saline or cocaine and restricted to one side of the chamber. Saline was injected on days 2 and 4, and cocaine was injected on days 3 and 5 (2.5 or 5 mg/kg, 10 mL/kg, NIDA drug consortium). Here, a biased design was used, since ≥ 50% of mice showed a chamber bias during the pre-test, wherein the preferred chamber (>10% preference) was paired with saline or chambers were assigned pseudo-randomly if no side preference was found.

Locomotor sensitization. One cohort of animals were used to examine locomotor sensitization at least one month following CPP for cocaine. All testing was done in clear plexiglass test chambers (Kinder Scientific Smart Cage Rack System; field dimensions: 9.5” x 18.0”) equipped with infrared photobeams measuring horizontal locomotor activity. Before beginning each session, mice were allowed to acclimate to the test room for one hour. Briefly, the protocol began with 1 day of habituation to the test chamber and 2 days of 10 ml/kg saline injections (i.p.). Mice were then given 5 consecutive days of 15 mg/kg cocaine injections (i.p.). Following a 7-day withdrawal period, mice were given 2 consecutive challenge days of cocaine at the same dose. For all sessions, 60 minutes of locomotor activity was measured as distance traveled (cm), both in total and across 5-minute bins. Chambers were cleaned with 70% ethanol between animals.

Food self-administration. Mice were restricted to 85% of their free-feeding weight. Mice were trained to respond for chocolate flavored food pellets (20 mg, grain based precision pellets, Bio-Serv) in Med-Associates operant conditioning chambers. Responding on one lever was reinforced using a fixed ratio 1 (FR1) schedule. A cue light was illuminated over the active lever for the duration of the experiment. Responses on the inactive lever had no programmed consequences but were recorded. Sessions ended at 60 minutes or when the maximum of 30 pellets were acquired. Mice were trained for at least 5 sessions or until they acquired ≥25 pellets for 3 consecutive sessions.

Intravenous cocaine self-administration. After recovery from jugular catheterization, mice were trained to respond on an FR1 schedule for cocaine (0.5mg/kg/infusion, 30 µl over 1.7 seconds) on the previously inactive lever from food training (Ozburn et al., 2012). Cocaine was delivered through an armored tether connected to a swivel and syringe pump. Mice were tested 6 days/week with the last day being reserved for patency testing. Drug delivery culminated in extinction of the house light, a compound cue (auditory tone and stimulus light), and a 10-sec timeout during which no additional cocaine reinforcers can be delivered. Sessions ended when mice self-administered 60 infusions or at 60 min (first 8 sessions) or 120 min (subsequent sessions, 6 minimum). Mice were considered to have acquired the cocaine-reinforced response when mice self-administered ≥15 reinforcers across 3 sessions (with ≥ 2:1 active/inactive lever press ratio). Drug intake (infusions), discrimination of the active versus inactive and time to reach criteria were measured.

After acquisition, mice were tested on an FR1 schedule with 2 consecutive sessions of descending unit doses of cocaine (1.0, 0.5, 0.25, 0.125, 0.063, and 0 mg/kg). This dose-response analysis measured the reinforcing properties of cocaine. Next, mice self-administered cocaine at the baseline 0.5 mg/kg unit dose for two days before progressive ratio testing. The dose-response analysis is used to measure the reinforcing properties of cocaine, which will be described throughout as reinforcement. In order to measure motivation to take cocaine in the same mice, 3 counter-balanced unit doses (1.0, 0.5, and 0.25 mg/kg) were presented for 2 consecutive sessions under a progressive ratio schedule, wherein each successive infusion requires more lever press responses (1, 2, 4, 6, 9, 12, 16, 20…240). Sessions end after 4 hours or 1.5 hours without acquiring a reinforcer. This test is used to measure motivation, which will be used to describe changes to the breakpoint ratio, or the last ratio obtained for a dose of cocaine. Mice were again returned to their baseline self-administration dose (0.5 mg/kg/infusion) for two days before extinction training. Here, all lever presses had no

programmed consequences and mice were trained for 10 days or until ≤30% peak active responding at 0.5 mg/kg/infusion was reached. Following extinction, mice were tested for sensitivity to cue-induced reinstatement, a model of relapse where presentations of previously cocaine-associated cues invigorate responding on the previously cocaine-reinforced lever. Mice received one non-contingent cue presentation, followed by cues contingent upon responding on the previously active lever.

Mice used for ΔFosB quantification self-administered cocaine (0.5 mg/kg/infusion) for 14 days as above. Here, in an attempt to normalize cocaine intake between WT and *Npas2* mutant mice, infusions were limited to 25, the approximate average number of infusions acquired by WT females during self-administration. After 25 infusions were obtained the session ended and mice were removed from the chambers.

Dual RNAscope and immunohistochemistry.

RNAscope *in situ hybridization* (ISH) for *Drd1* was followed by immunohistochemistry (IHC) for ΔFosB. The percent of dopamine D1 receptor+ and D1 receptor- (D1+,D1-) neurons expressing ΔFosB were measured since these populations differentially regulate reward (Lobo et al., 2010; Yawata et al., 2012; Smith et al., 2013). Mice were trained to self-administer cocaine and brains were flash frozen 24 hr after the last self-administration session (Fig.6a). Coronal sections (14 µm) were cut on a cryostat (Leica) and serial sections between 1.54 and 0.86 mm from bregma were immediately mounted onto Super Frost Plus slides. Each resulting slide contained 4 sections ranging along the anterior-posterior extent of the striatum. Slides with frozen sections were processed using an RNAscope fluorescent multiplex kit x (Advanced Cell Diagnostics #320850). Tissue sections were fixed at 4ºC in 10% normal buffered formalin for 30 minutes and slides were rinsed three times 1X phospho-buffered saline (PBS) then dehydrated in a series of ethanol solutions at room temperature (RT)(50, 70, 100, 100% ethanol). We then hybridized the tissue sections with a *Drd1* probe (Advanced Cell Diagnostics 406491) and incubated slides at 40ºC for 2 hr in the HybEZ oven. The signal was then amplified through incubation at 40ºC with sequential amplifiers (AMP1 30 min, AMP2 15 min, AMP3 30 min) with AMP4 AltA used to detect *Drd1* in green (Alexa 488). Slides were washed twice in 1x wash buffer between incubations and then rinsed in PBS before immunohistochemical staining for ΔFosB (3 x 10 minutes).

Mounted sections were blocked for 1 hr at RT in 10% normal donkey serum and 0.3% 100x triton. Tissue was then incubated in a rabbit anti-FosB primary antibody (1:200, Cell Signaling Technology 2251) in

block overnight at 4ºC. After rinsing in PBS, sections were incubated in donkey anti-rabbit Alexa Fluor 555 secondary antibody (1:500, Thermo Fisher Scientific A-31572) in block at RT for 1.5 hr, rinsed again, counterstained with DAPI and cover-slipped with prolong gold. Throughout, sections were incubated by filling the hydrophobic barrier with approximately 150 µl of each solution. Although a pan-FosB antibody was used, full-length FosB degrades within 18-24 hr (Perrotti et al., 2008), therefore, all immunoreactivity should reflect ΔFosB.

Imaging and cell counting.

Immunofluorescence images [DAPI (blue), D1 (488 channel, green) and ΔFosB (546 channel, red)] were captured on an Olympus IX83 confocal microscope using a 20x objective at x2 magnification. Approximately 300 x 300 µm images were taken from sections along the anterior-posterior extent of the NAc core and shell, and dorsomedial (DMS) and dorsolateral (DLS) striatum. 5-6 2.5 µm z-stacks were used with an 8 µs/pixel dwell time and 1024 x 1024 pixel size. Consistent laser power, voltage and offset were used between images. Both hemispheres of 2-4 brain sections/region were imaged. Total D1+ and D1- cells as well as D1+ and D1- ΔFosB-expressing cells (see Fig.6c) were counted using ImageJ. The percentage of D1+ and D1- ΔFosB expressing cells was calculated for all conditions and brain regions. Image capture and quantification were performed by one blinded experimenter.

RNA-sequencing.

Brains were extracted and flash frozen from cocaine naïve, adult *Npas2* mutant or WT female mice in the dark phase at ~ZT16, matching time of death after self-administration when ΔFosB expression was measured (Fig.6). Bilateral 1mm punches were taken centered over the NAc, DMS or DLS. Individual animals were each used as a sample (n=4-6 per condition). Tissue was homogenized and total RNA was isolated using the RNeasy Plus Micro Kit (Qiagen). RNA quantity and quality were assessed using fluorometry (Qubit RNA Broad Range Assay Kit and Fluorometer; Invitrogen) and chromatography (Bioanalyzer and RNA 6000 Nano Kit; Agilent) respectively. Libraries were prepared using TruSeq mRNA kit for stranded mRNA. Total RNA input was enriched for mRNA and fragments. Random primers initiate first strand and second strand cDNA synthesis. Adenylation of 3' ends was followed by adapter ligation and library amplification with indexing. High

Output, 400 M clustered flowcells (75 cycles) were sequenced with the NextSeq500 platform (Illumina) in 75bp single read mode. 30 M reads per sample was targeted. Data were filtered for non- and low-expressed genes. Differential expression (DE) between genotypes, Ingenuity pathway analysis (IPA) of enriched differentially expressed genes (DEGs) and rank-rank hypergeometric overlap (RRHO) between brain regions were performed.

Statistical Analyses.

GraphPad Prism 7 and IBM SPSS statistics were used. Data are expressed as means+SEM with p=0.05 considered significant and 0.05<p<0.1 considered trending. ANOVAs were performed with significant interactions followed by Bonferroni post-hoc tests corrected for multiple comparisons. Unpaired one-tailed t-tests were used to analyze factors such as total infusions (Fig.7) since we are expecting to replicate and then reverse the increase in self-administration seen in female *Npas2* mutants.

SPSS was used for analysis when additional factors were used: TOD and/or sex. Since light phase and dark phase animals cannot be tested concurrently due to light constraints, as well as the *a priori* hypothesis that mice would self-administer more cocaine during the dark phase, each phase was measured separately. Self-administration was analyzed with 3-way repeated measure (RM) ANOVAs across session (session x sex x genotype), while criteria, total infusions and ΔFosB were analyzed with 2-way ANOVAs (sex x genotype). Data are also represented for males and females separately to highlight any relevant sex differences, although these ANOVAs were not performed (and statistics are not reported) unless significant 3-way interactions were detected. Values ≥2 standard deviations from the mean were considered outliers and excluded.

For sequencing, non-expressed genes were first removed and then the 25% low-expressed genes were filtered out. 14,270 annotated genes remaining after filtering were used as a background data set. Differential expression (DE) analysis comparing WT and mutant mice was conducted by limma-voom in each brain region separately. Genes were considered DE with a loose p-value criteria of p<0.05 without multiple comparison correction. We used rank-rank hypergeometric overlap (RRHO) as a threshold-free method to evaluate the overlap of DE patterns across pairs of brain regions (Cahill et al., 2018). RRHO identifies overlap between two ranked lists of differential gene expression. The genes are ranked by the -log10(p value) multiplied by the effect size direction. To rank the overlapping genes from RRHO by their DE significance, we

performed Adaptively-Weighted Fisher's (AW-Fisher) (Li & Tseng, 2011; Huo et al., 2020) analysis to combine the DE results for DLS and NAc. This provides a meta-analyzed p-value for each gene with increased statistical power and generates weight indicators to reflect the consistency of DE signals in the two regions [*i.e.* (1,1) DE in both regions, (1,0) DE in DLS but not NAc, and (0,1) DE in NAc but not DLS]. Overlapping genes between DLS and NAc were then ranked by their AW-Fisher meta-analyzed p-values. Fisher's exact test was used to test enrichment significance of DEGs in gene sets downloaded from http://ge-lab.org/gskb/. Pathways whose size are smaller than 3 or greater than 500 were not considered.

Results

Npas2 mutant mice have altered behavioral responses to cocaine

To expand upon evidence that NPAS2 regulates the behavioral effects of cocaine, we examined the role of NPAS2 in a translational model of drug taking, intravenous cocaine self-administration. We measured behavior in male and female *Npas2* mutant mice during the light or dark phase, since NPAS2 regulates circadian rhythms (Ko & Takahashi, 2006; Takahashi, 2016).

Animals were first trained to respond for food and discriminate between the two levers over time [day x lever interactions: light ($F_{(4,440)}$=435.04,p<0.0001), dark ($F_{(4,252)}$=114,45,p<0.0001)]. A 4-way ANOVA revealed that response rates varied by genotype and TOD (session x genotype x TOD interaction: $F_{(4,173)}$=4.19,p=0.002) and throughout, light and dark phase behavior were analyzed individually in order to identify TOD-specific effects. During the light phase, response rates tended to vary by genotype and sex (sex x genotype interaction: $F_{(1,110)}$=2.92,p=0.09)(Fig.1abc). On the other hand, only genotype differences were found during the dark phase (main effect of genotype: $F_{(1,63)}$=4.12,p=0.046)(Fig.1def) where mutants responded more on an active lever for food compared to WT mice.

After recovery from jugular catheterization, mice were trained to self-administer cocaine. As expected, self-administration was higher during the dark than light phase in all mice, as shown by a main effect of TOD ($F_{(1,95)}$=10.94,p<0.001). Overall, *Npas2* mutation differentially affects males and females (4-way ANOVA; sex x genotype: $F_{(1,95)}$=4.18,p=0.044). Subsequent 3-way ANOVAs were used to investigate the effects of *Npas2* mutation across TOD. During the light phase, male and female (Fig.2ab) *Npas2* mutant mice self-administered more cocaine than WT mice (main effect of genotype: $F_{(1,56)}$=15.98,p<0.001)(Fig.2c). On the other hand, cocaine intake varied by sex and genotype in the dark phase (sex x genotype interaction: $F_{(1,63)}$=4.65,p=0.037)(Fig.2def). To further investigate these effects, we quantified sessions required to reach criteria and total drug intake (infusions). While all *Npas2* mutant mice acquired self-administration faster and took more infusions than WT mice in the light phase [main effect of genotype: criteria ($F_{(1,53)}$=4.74,p=0.034), infusion ($F_{(1,56)}$=16.1,p=0.0002)](Fig.3ab), sex differences emerged during the dark phase where only females mutants had a higher propensity to self-administer cocaine compared to WT females [sex x genotype interaction: criteria ($F_{(1,39)}$=3.92,p=0.055), infusion ($F_{(1,39)}$=3.12,p=0.085)](Fig.3cd). This finding demonstrates

that female *Npas2* mutants indeed have increased self-administration during the dark phase, while males are unaffected.

In addition to analyzing cocaine intake directly using infusions, we also analyzed active and inactive lever pressing in order to determine whether *Npas2* mutant mice are taking more cocaine due to overall hyperactivity, which would lead to increases in both active and inactive lever pressing. A 5-way ANOVA revealed that all mice, both WT and mutant, discriminate between the active and inactive lever and respond differentially across TOD (session x lever x sex x TOD interaction: $F_{(13,1196)}$=1.99,p=0.019). Subsequently, 4-way ANOVAs were used to investigate the effects of *Npas2* mutation in the light and dark phase separately. During the light phase, active versus inactive lever pressing varied by genotype (day x lever x genotype interaction: $F_{(13,637)}$=3.75,p<0.0001), while only overall lever pressing, regardless of status, varied by sex (sex x genotype interaction: $F_{(1,49)}$=12.16,p=0.001), suggesting discriminative lever pressing doesn't vary by sex. Therefore, we excluded sex as a factor and found that similarly to cocaine intake, mutants pressed the active lever more than WT mice (session x genotype interaction: active lever pressing $F_{(13,663)}$=3.48,p<0.0001)(Fig.4c). On the other hand, inactive lever pressing was only slightly increased in *Npas2* mutants compared to WT mie (trending main effect of genotype: inactive lever pressing $F_{(1,51)}$=3.84,p=0.06). Importantly, *Npas2* mutants showed similarly significant discrimination between the active and inactive lever (session x lever interaction: $F_{(13,468)}$=35.02,p<0.0001) as WT mice (session x lever interaction: $F_{(13,858)}$=66.81,p<0.0001).

During the dark phase, a 4-way interaction further emphasizes that *Npas2* mutation differentially affects males and females (session x lever x sex x genotype interaction: $F_{(13,559)}$=2.59,p=0.002). Specifically, female mutants pressed the active lever more than WT mice (session x genotype interaction: active lever pressing $F_{(13,260)}$=2.40,p=0.0046)(Fig.4d), while male mutants show no differences (Fig.4e). Although inactive lever pressing is also changed in *Npas2* mutants females when compared to WT mice (session x genotype interaction: inactive lever pressing $F_{(13,260)}$=8.87,p<0.0001), responding is only increased on the first day of training, suggesting this increase is caused by perseveration on the inactive lever, which was previously reinforced with food and not hyperactivity. As with the light phase, all mice discriminated between the active and inactive levers [session x lever interaction: WT mice ($F_{(13,338)}$=22.4,p<0.0001), *Npas2* mutants ($F_{(13,260)}$=20.37,p<0.0001)].

To further explore the effect of *Npas2* mutation on reward, we measured CPP and locomotor sensitization. We previously found that *Npas2* mutant mice have reduced CPP compared to WT (Ozburn et al., 2015a), but only males were tested. Here we conditioned male and female mice to 2.5 or 5 mg/kg cocaine and found that sex plays a pivotal role in CPP [sex x genotype interaction: 2.5 mg/kg ($F_{(1,58)}$=4.4,p=0.04), 5 mg/kg ($F_{(1,57)}$=7.01,p=0.01)]. Although, we were able to replicate our previous finding that cocaine preference is reduced in male Npas2 mutants compared to WT controls (Ozburn et al., 2015b), we interestingly found that female mutants showed no change in preference (Fig.5a). We then confirmed that the lack of change in preference in mutant females is not due to TOD differences by measuring cocaine CPP during the dark phase. Again, cocaine preference was still unchanged in female *Npas2* mutants (Fig.5a).

During locomotor sensitization, we found that all mice sensitized to cocaine across sessions (main effect of session: $F_{(9,288)}$=136.43,p<0.001), but the locomotor-activating effects of cocaine were dependent on sex and genotype (session x sex x genotype interaction: $F_{(9,288)}$=2.54,p=0.008). When analyzed independently, female *Npas2* mutant mice showed an increase in the locomotor activating effects of cocaine compared to controls (session x genotype interaction: $F_{(9,126)}$=2.06,p=0.038)(Fig.5b), while male mice showed a sensitization effect over multiple days (main effect of session: $F_{(9,162)}$=99.76,p<0.001)(Fig.5c). These results further support the critical role of sex in how NPAS2 regulates the behavioral effects of cocaine. Importantly, hyperactivity does not appear to contribute to the differences observed in *Npas2* mutants as locomotor activity is not increased in male or female *Npas2* mutants following saline injections when compared to WT mice. These findings mirror our previous results demonstrating that locomotor response to novelty is not increased in male mutants (Ozburn et al., 2015a).

<u>Increased reinforcing and motivational properties of cocaine in *Npas2* mutant mice</u>

Following acquisition, we measured the reinforcing properties of cocaine using a dose-response analysis. Throughout, *Npas2* mutant mice took more infusions compared to controls, indicating an overall increase in the efficacy of cocaine (dose x genotype interaction: F(5,345)=10.01,p<0.0001), which did not differ regardless of TOD or sex. Similar effects were seen during light phase (dose x genotype interaction: $F_{(5,180)}$=3.98,p=0.002)(Fig.6c) and dark phase self-administration (dose x genotype interaction: $F_{(5,165)}$7.51,p<0.001)(Fig.6f). Next, a progressive ratio schedule was used to measure motivation (breakpoint

ratio), but a 4-way ANOVA only revealed a main effect of genotype ($F(1,50)=7.90, p=0.007$). This was confirmed across TOD, where *Npas2* mutant mice worked harder for each infusion of cocaine than WT controls, as shown by a higher breakpoint ratio during the light phase (main effect of genotype: $F_{(1,25)}=4.92, p=0.036$)(Fig.6i) and dark phase (main effect of genotype: $F_{(1,25)}=5.14, p=0.032$)(Fig.6l).

<u>Increased extinction responding, and cue-induced reinstatement in female *Npas2* mutant mice in the dark phase</u>

Mice then underwent extinction and cue-induced reinstatement to model relapse-like drug seeking in the absence of cocaine. All mice extinguished responding (main effect of session: $F(9,432)=28.68, p<0.0001$) and we found a trending 4-factor interaction (session x sex x genotype x TOD interaction: $F(9,432)=1.85, p=0.058$) indicating divergent effects of genotype on males and females in the light and dark phase. We found a trend for *Npas2* mutation to increase extinction responding during the light phase (main effect of genotype: $F_{(1,23)}=3.06, p=0.09$)(Fig.7c), with small increases in responding in female (Fig.7a) and male mutants (Fig.7b). However, during the dark phase, a 3-way interaction was found (session x sex x genotype interaction: $F_{(9,225)}=2.65, p=0.006$)(Fig.7f) indicating divergent effects of genotype on male and female mice. Specifically, female *Npas2* mutants showed an increase in early extinction responding in the dark phase (session x genotype interaction: $F_{(9,108)}=2.71, p=0.007$)(Fig.7d) compared to controls, while male mutants showed no differences (Fig.7e).

After extinction, contingent, previously cocaine-associated cues were presented, which reinstated responding in all mice (main effect of lever: $F_{(1,48)}=53.38, p<0.0001$). Although no TOD differences were found in a 4-way ANOVA, *Npas2* mutation differentially affected males and females (sex x genotype interaction: $F_{(1485)}=4.49, p=0.039$. In subsequent analyses, *Npas2* mutation did not affect cue-induced reinstatement during the light phase ($Fs<1$) in female or male mice (Fig.7ghi). Similar to extinction, drug seeking during reinstatement depended on sex and genotype during the dark phase (trending lever x sex x genotype interaction: $F_{(1,25)}=2.92, p=0.10$)(Fig.7l). Follow-up ANOVAs indicate that female *Npas2* mutants showed an increase in drug seeking (lever x genotype interaction: $F_{(1,12)}=4.58, p=0.05$)(Fig.7j) compared to WT mice, while male mutants showed no differences (Fig.7k). Together, these findings indicate that in the absence of cocaine,

initially or with cocaine-associated cues present, female *Npas2* mutants intensify their drug seeking, specifically in the dark phase.

Circulating sex hormones contribute to increased cocaine self-administration in female *Npas2* mutant mice

In order to determine whether ovarian hormones contribute to sex differences in self-administration in *Npas2* mutant mice, a separate cohort of females underwent an OVX or sham surgery before dark phase cocaine self-administration. As expected, we found that self-administration varied based on genotype and OVX (trending session x genotype x OVX interaction: $F_{(13,429)}$=1.62,p=0.077). While sham mutant females showed moderately increased cocaine self-administration compared to sham WT females (main effect of genotype: $F_{(1,18)}$=4.09,p=0.058)(Fig.8a), no effect was found in OVX WT and mutant mice (Fs<1)(Fig.8b). Furthermore, total drug intake was slightly increased in mutant sham compared to WT sham females ($t_{(18)}$=1.63,p=0.059)(Fig.8c), but not mutant OVX compared to WT OVX females (t<1)(Fig.8d). These findings suggest that sex hormones mediate the greater effects of *Npas2* mutation seen in female mice.

Increased ΔFosB expression in D1+ neurons in *Npas2* mutant females following dark phase cocaine self-administration

In order to determine which striatal regions might mediate increased self-administration in *Npas2* mutant females, we measured cocaine-induced expression of ΔFosB, a stable, long-lasting variant of FosB (Robison et al., 2013). Female mice self-administered cocaine during the light or dark phase. Mice were limited to 25 infusions in order to normalize acquisition [main effect of genotype: light ($F_{(1,9)}$=2.73,p=0.133), dark (F<1); genotype x session interaction: light (F<1), dark ($F_{(13,117)}$=2.23,p=0.012, no significant post-hocs)] between WT and *Npas2* mutant mice (Fig.9a). Tissue was harvested 24 hr after the last self-administration session.

We quantified the percentage of D1+ and D1- cells expressing ΔFosB in the NAc core, NAc shell, DLS and DMS (Fig.9b). No genotype differences were found in ΔFosB expression after light phase self-administration, but dark phase *Npas2* mutant females had slightly increased ΔFosB expression in the NAc shell (main effect of genotype: $F_{(1,9)}$=4.16,p=0.072) compare to WT females. In both the NAc core and DLS, this increase in ΔFosB was specific to D1+ cells [cell x genotype: NAc core ($F_{(1,8)}$=3.97,p=0.082), DLS

($F_{(1,10)}$=5.64,p=0.039)]. No effects were seen in the DMS. Throughout, ΔFosB expression was higher in D1+ compared to D1- cells [main effect of cell-type: NAc ($F_{(1,18)}$=30.47,p<0.0001), DS ($F_{(1,19)}$=27.66,p<0.0001)].

Most differentially expressed genes in *Npas2* mutant females are in the DLS and many are ΔFosB targets

We next aimed to identify possible mechanisms that could be driving increased dark phase cocaine self-administration in female *Npas2* mutant mice. Since drug taking is increased early in self-administration (Fig.2d), we believe predispositions exist in female mutants that drive this increase. Given regional differences in cocaine-induced striatal activation in female mutants, we identified DEGs in the NAc, DLS and DMS of cocaine-naïve WT and *Npas2* mutant females in the dark phase (Table.1-3). Using cut-offs of p<0.05 (uncorrected) and fold change (FC)>1.3, we found 343 DEGs in the NAc, 362 in the DMS and 922 in the DLS (Fig.9d). Due to the leniency of this p-value, some false positives are expected and fewer DEGs were found at more stringent cut-offs (Fig. 9d). Striatal regions that are similarly activated after self-administration in *Npas2* mutants show parallel changes in gene expression. The NAc and DLS, where ΔFosB expression is increased in mutant D1+ neurons, show a high level of overlap in DEGs (Fig.9e). However, the NAc and DLS show very little overlap with the DMS, where ΔFosB expression is not increased (Fig.9efg).

We used a ranked p-value meta-analysis (Huo et al., 2020) to identify DEGs specific to the DLS and NAc. Of the 463 DEGs (meta-p<0.05), many that are similarly regulated appear to modulate neurotransmission, which might contribute to increased self-administration seen here. These DEGs encode potassium channels (*e.g. Kcn1l*, *Kcnc2, Kcna4, Kcna6,* etc), GABA receptor subunits (*e.g. Gabrd*, *Gabra3,* etc)*,* matrix metallopeptidases (*Mmp14*), as well as the small rho GTPase *Rhoc* and *Snap23*, which encodes machinery necessary for vesicular fusion. Potassium channels were one of the most significant DEG categories and were primarily upregulated in both the DLS and NAc of *Npas2* mutant females.

Importantly, IPA revealed that highly significant DE pathways in *Npas2* mutant females in the DLS include CREB1 targets, G-protein signaling and ΔFosB targets (Fig.9i). This suggests that even at baseline, *Npas2* mutant females might have increased ΔFosB and CREB-mediated transcription in the DLS, which is further exacerbated in D1+ cells by cocaine self-administration (Fig.9b), but future experiments are needed to test this hypothesis directly.

As expected, the DEGs found across all 3 regions included mainly core circadian genes: *Ciart*, *Arntl* (*Bmal1*), *Nr1d1*, *Cipc*, *Bhlhe41* and *Dbp*. *Arntl* was the only upregulated circadian gene in *Npas2* mutant mice, likely to compensate for its inability to form a complex with the mutated *Npas2*. IPA also found significant enrichment in the pathway “circadian rhythms” across all regions, but especially the NAc (Fig.9ijk). Fifteen other DEGs were identified in all 3 regions suggesting they might be important target genes of *Npas2*. These include protein kinases (*Kitl*, *Camkk1*) and genes that are protective against oxidative stress (*Gpx6* and *Hebp2*). *Fabp7* was the most upregulated gene in *Npas2* mutants and plays a role in fatty acid uptake, transport and metabolism in astrocytes (Chmurzyńska, 2006).

Discussion

Overall, *Npas2* mutation increases cocaine intake and the propensity to self-administer cocaine in a sex- and circadian-dependent manner. In the light phase, cocaine taking, reinforcement and motivation are increased across sex. During the dark phase, females are more affected; reinforcement and motivation are increased across sex, while females mutants have increased drug taking, extinction responding and reinstatement. Females also appear to be driving effects on motivation, since female mutants have the highest breakpoint ratios during both TOD, although a sex difference was not found. Interestingly, while males show contradicting effects of *Npas2* mutation on light phase cocaine reward and self-administration, self-administration is uniquely affected in females. While it isn't uncommon to find opposing results for these drug-related behaviors (Larson et al., 2011), detecting a selective change in volitional drug self-administration, as with females here, is more typical.

It is well known that sex differences exist in circadian rhythms and that circulating estradiol contributes to these differences (Varnäs et al., 2003; Krizo & Mintz, 2015). Sex differences are also frequently found in the rhythmicity of peripheral circadian genes (Lu et al., 2013) and the master pacemaker, the suprachiasmatic nucleus (SCN)(Bailey & Silver, 2014). Although less is known about the extra-SCN brain, females show earlier peaks in circadian genes in the prefrontal cortex in humans (Lim et al., 2013) and the robustness of diurnal gene rhythms can vary by sex and brain region in rodents (Chun et al., 2015). These findings indicate that SCN-independent behaviors could also be affected by circulating hormones.

Despite an intersection between rhythms, hormones and extra-SCN behavior, research investigating how altered circadian rhythms, for example from circadian gene mutations, affect behavior sex-dependently is limited. One key paper found that female *Clock* mutant mice show more robust increases in exploratory and escape-seeking behavior (Easton et al., 2003). Sex differences have been examined in *Npas2* mutants, but only in the context of sleep and locomotor activity. Importantly, *Npas2* mutation doesn't affect rhythms differently in males and females at baseline (Dudley et al., 2003), only under pathological conditions, such as sleep deprivation (Franken et al., 2006), suggesting our observed sex differences are not confounded by baseline differences. Since cocaine exposure disrupts circadian rhythms and sleep (Schierenbeck et al., 2008; Angarita et al., 2016), self-administration could be inducing sex-dependent sleep and rhythm disruptions, which might lead to sex differences in cocaine intake.

To determine whether circulating hormones might contribute to increased self-administration in *Npas2* mutants, we ovariectomized female mice before dark phase cocaine self-administration. Female OVX mice with non-functional NPAS2 showed no increase in self-administration, suggesting ovarian hormones could be driving enhanced effects in *Npas2* mutant females. It is critical to continue examining how circadian genes affect behavior sex-dependently, particularly in the context of SUD since its prevalence varies by sex (Kosten et al., 1993; Robbins et al., 1999; Kennedy et al., 2013). Interestingly, our sham controls only showed a trending increase (p=0.58) in self-administration, which is likely due to these mice being older or the stress of an additional surgery. These factors are crucial to consider when investigating sex differences in future studies.

In order to further identify how mutations in *Npas2* contribute to SU in females, we measured striatal activation using ΔFosB. While other Fos proteins are transiently induced by acute drug exposure, ΔFosB is a stable, long-lasting variant induced by long-term exposure (Robison et al., 2013). This allows activation from chronic drug self-administration to be measured. Here, female WT and *Npas2* mutant mice self-administered cocaine, but drug intake was limited in order to normalize increased cocaine exposure in mutant mice.

The striatum is primarily comprised of neuron populations expressing D1 or D2 dopamine receptors (Lu et al., 1998). Activation of D1-expressing neurons in the NAc promotes cocaine preference (Lobo et al., 2010) and cocaine activates D1 and D2 neurons differently (Bertran-Gonzalez et al., 2008), inducing ΔFosB in D1 neurons (Lobo et al., 2013). NPAS2 is highly enriched in the striatum (Garcia et al., 2000a), specifically in D1 neurons (Ozburn et al., 2015a) and we recently demonstrated that *Npas2* knockdown in the NAc increases glutamatergic excitability onto D1 cells (Parekh et al., 2019). Therefore, we measured ΔFosB expression in D1+ and D1- cells throughout the striatum and found that ΔFosB expression was increased in D1+ neurons in the NAc core and DLS of *Npas2* mutant females. The NAc shell was also moderately affected, in D1+ and D1- cells, but effects in the dorsal striatum were confined to the DLS. Since the DLS mediates habitual drug seeking, and the DMS goal-directed decision making (Yin et al., 2004), *Npas2* mutant females may rely more heavily upon habitual decision-making strategies during self-administration. Future studies could use action-outcome contingency degradation or outcome devaluation to measure response strategies in *Npas2* mutant females.

Increased induction of ΔFosB in *Npas2* mutants was also specific to the dark phase when the behavioral effects of *Npas2* mutation are greatest. *Npas2* expression peaks in the NAc around ZT16 (Falcon et

al., 2013) when dark phase self-administration was conducted. It stands to reason that mutating *Npas2* would have a greater impact on behavior when mRNA expression is elevated. Higher expression suggests a functional necessity for NPAS2, however, a parallel protein rhythm has not been confirmed. Furthermore, drug intake in mice is typically higher during the dark phase, therefore, individuals could be more vulnerable to insults during periods predisposed to drug seeking. This TOD vulnerability emphasizes the importance of considering rhythms in gene expression in future studies.

In order to characterize the striatal mechanisms underlying increased dark phase self-administration in female *Npas2* mutant mice, we identified DEGs in the NAc, DLS and DMS in cocaine-naïve mice. The NAc core and shell were pooled since cocaine-induced activation was increased in the core and, to a lesser extent, shell of mutants. As expected, we found overall changes in circadian rhythm-related genes; for example, *Arntl* was upregulated, likely to compensate for its inability to form a transcriptional complex with the mutated *Npas2*. *Fabp7* was the most highly upregulated DEG in *Npas2* mutants across all regions. It regulates fatty acid uptake in astrocytes, sleep (Gerstner et al., 2017) and drug seeking under stressful conditions (Hamilton et al., 2018). *Fabp7* is rhythmically expressed throughout the brain (Schnell et al., 2014) and is similarly upregulated in *Arntl* and *Nr1d1* knockout mice (Schnell et al., 2014; Gerstner & Paschos, 2020). *Fabp7* could be upregulated in *Npas2* mutants due to the downregulation of *Nr1d1*, which represses *Fabp7* (Schnell et al., 2014).

Although some DEGs were changed throughout the striatum, patterns typically varied by subregion. The DLS and NAc had the most similar pattern of DE, while the DLS/DMS and DMS/NAc had less overlap. Less significant DE was also found in the DMS (Table.3).These findings parallel cocaine-induced activation patterns and emphasize how the DMS is differentially affected by *Npas2* mutation.

We next identified target genes in *Npas2* mutant females that might predispose increased cocaine self-administration. Using a meta-analysis (Huo et al., 2020), we identified 463 DEGs specific to the DLS and NAc where cocaine-induced activation is found in *Npas2* mutants. Many of these similarly regulated DEGs modulate neurotransmission and could therefore mediate increased glutamatergic transmission in the NAc of *Npas2* knockdown mice (Parekh et al., 2019), which could contribute to increased self-administration. These DEGs encode GABA receptor subunits, matrix metallopeptidases, small rho GTPases and synaptosomal proteins. GABAergic transmission is a promising target, since NPAS2 directly binds GABA receptor subunits (Ozburn et al., 2017). One of the most common DEG categories was potassium channels, which were

frequently upregulated and could be modulating action potential generation and short-term plasticity in the DLS and NAc of mutant females. Importantly, DEGs from the NAc could have been diluted since the shell was activated to a lesser extent than the core. Overall, the DLS is most impacted by *Npas2* mutation with additional DEGs identified that regulate neurotransmission: other GTPase-related genes (*Arhgap9,Rasal1*), scaffolding genes (*Shank1*) and glutamate receptor subunits (*Gria4*).

Interestingly, enriched pathways in the NAc, DMS and DLS are also distinct. Circadian pathways were unsurprisingly identified in all regions (Dong et al., 2011; Baranger et al., 2016), since disruptions in circadian rhythms and transcription contribute to SU vulnerability. Importantly, circadian transcription factor (CLOCK,ARNTL) pathways were particularly significant in the NAc, suggesting a critical role in linking rhythm disruptions and drug use. Meanwhile, top pathways in the DLS suggest an increase in ΔFosB and CREB signaling at baseline, which could be exacerbated following self-administration. Other DLS pathways correspond to unique DEGs that mediate neurotransmission and synaptic plasticity. Future studies could examine the role of these genes in increased self-administration in *Npas2* mutants. For example, reducing ΔFosB-mediated transcription in *Npas2* mutants in D1+ cells in the DLS might normalize cocaine self-administration.

Ultimately, these results demonstrate that decreased function in NPAS2 drives vulnerability for SU in a circadian- and sex-dependent manner. Parallel changes in striatal activation and gene expression in *Npas2* mutant females in the dark phase suggest that gene expression changes, perhaps mediated by ΔFosB signaling, underlie behavioral vulnerabilities associated with mutating the key circadian transcription factor *Npas2.*

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Figure Legends

Figure 1. No major differences were found in food self-administration. *Npas2* mutant mice were trained to self-administer food pellets. (A) In the light phase, females are unaffected by *Npas2* mutation in the light phase, while (B) *Npas2* mutant males show a slight decrease in food responding compared to WT mice. (C) This was confirmed with a sex by genotype interaction in a 3-way ANOVA. During the dark phase, *Npas2* mutants responded more for food overall. (D) While this seems to be driven primarily by female and not (E) male mutants, (F) no sex difference was found. Means+SEMs, $^{\#}p<0.1$; $*p<0.05$, *n*=16-18 dark phase; 25-36 light phase.

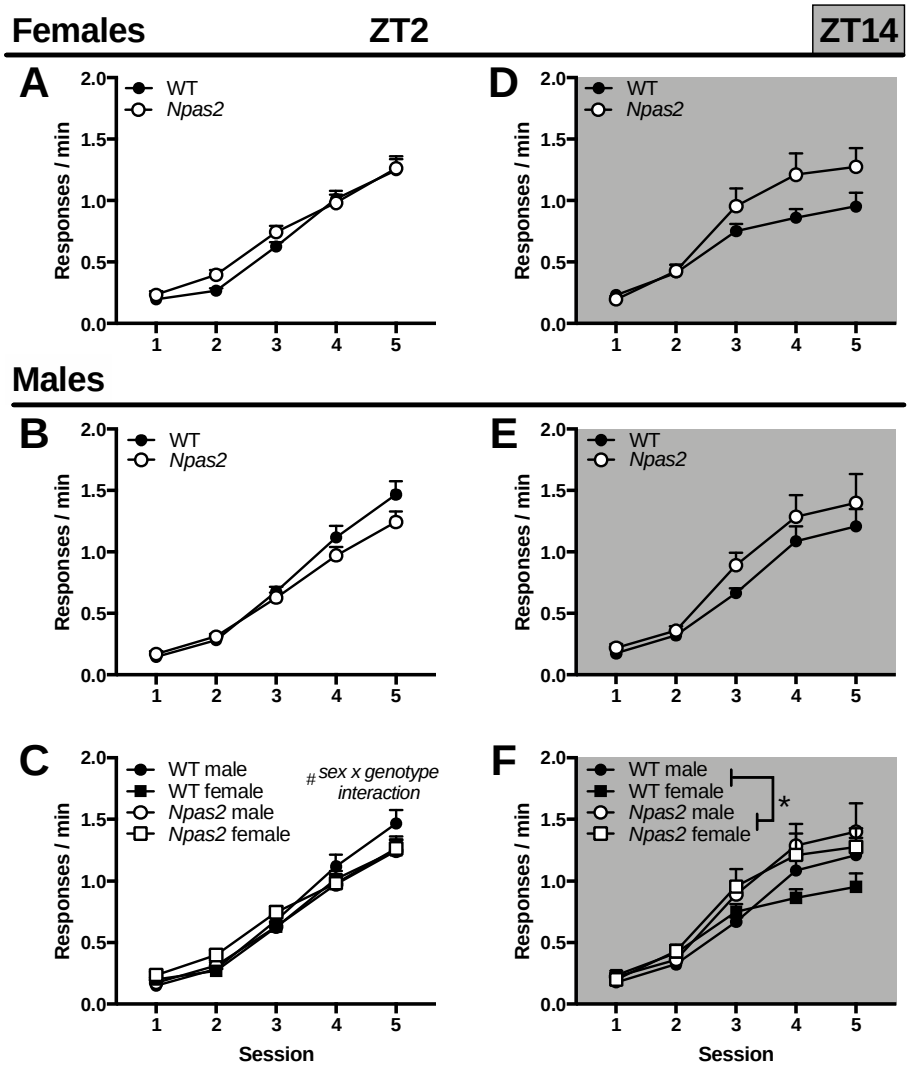

Figure 2. *Npas2* mutant mice self-administer more cocaine, particularly females in the dark phase. *Npas2* mutant mice were trained to self-administer cocaine (0.5mg/kg/infusion). (A) At ZT2, during the light phase, increased cocaine intake is seen in (A) female and (B) male *Npas2* mutant mice. (C) Although this effect seems to be particularly pronounced in female mice, overall no sex difference was found and all *Npas2* mutant mice self-administered more cocaine than WT mice. (D) In the dark, or active, phase (ZT14) cocaine intake appears to be elevated in female *Npas2* mutant mice compared to WT, (E) but not male mutants, (F) which is confirmed by a sex by genotype interaction. Means+SEMs, $^{\#}p<0.1$; $*p<0.05$; $**p<0.01$; $***p<0.001$, n=10-19.

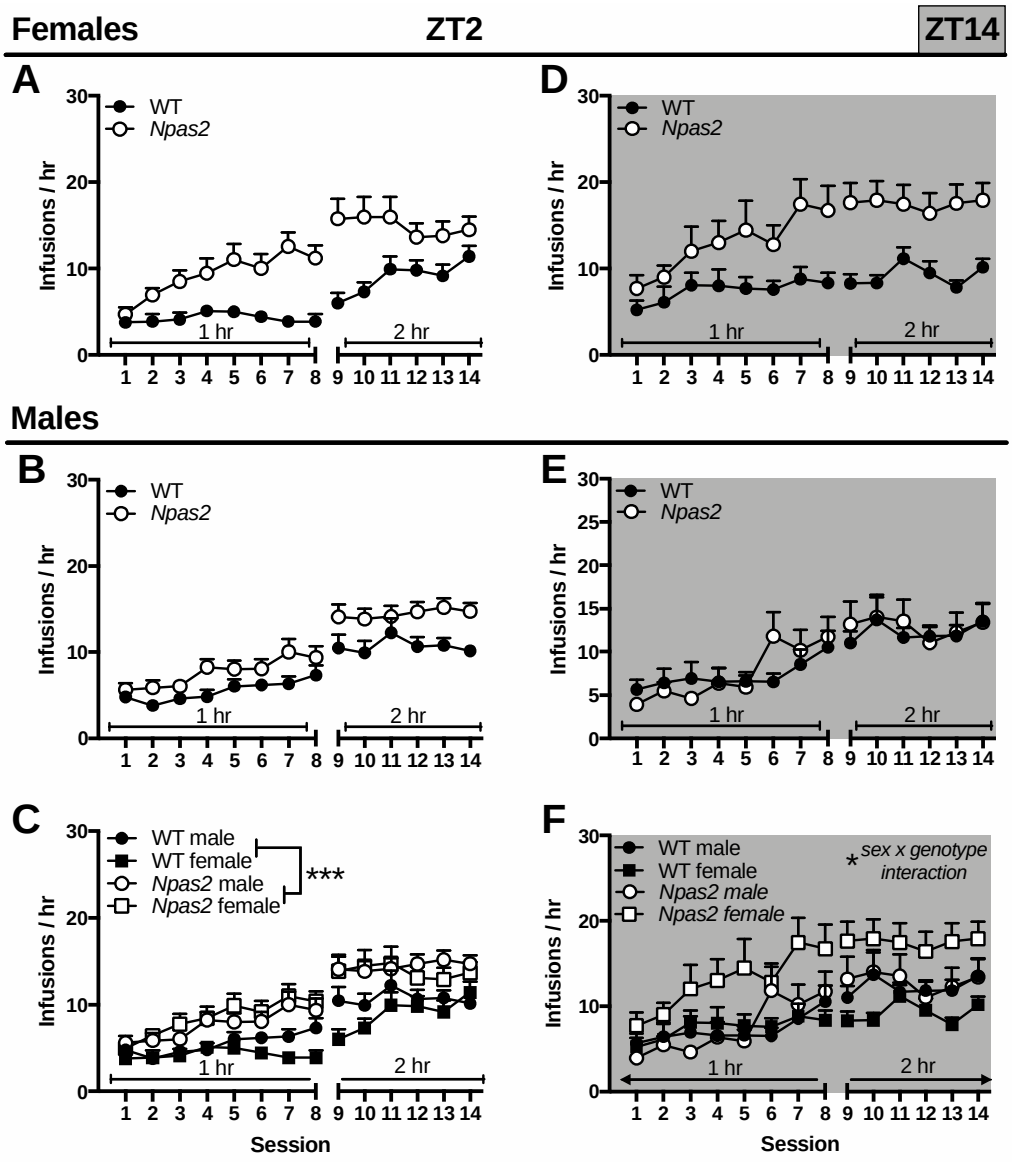

Figure 3. *Npas2* mutants have a greater propensity to self-administer cocaine. (A) An *Npas2* mutation increased the propensity to self-administer cocaine, decreasing the days required to reach acquisition criteria, during the light phase. (B) Total cocaine intake was also increased in mutant mice during the light phase. (C,D) In the dark phase, these effects were selective to females. Means+SEMs, *p<0.05; ***p<0.001, *n*=10-19.

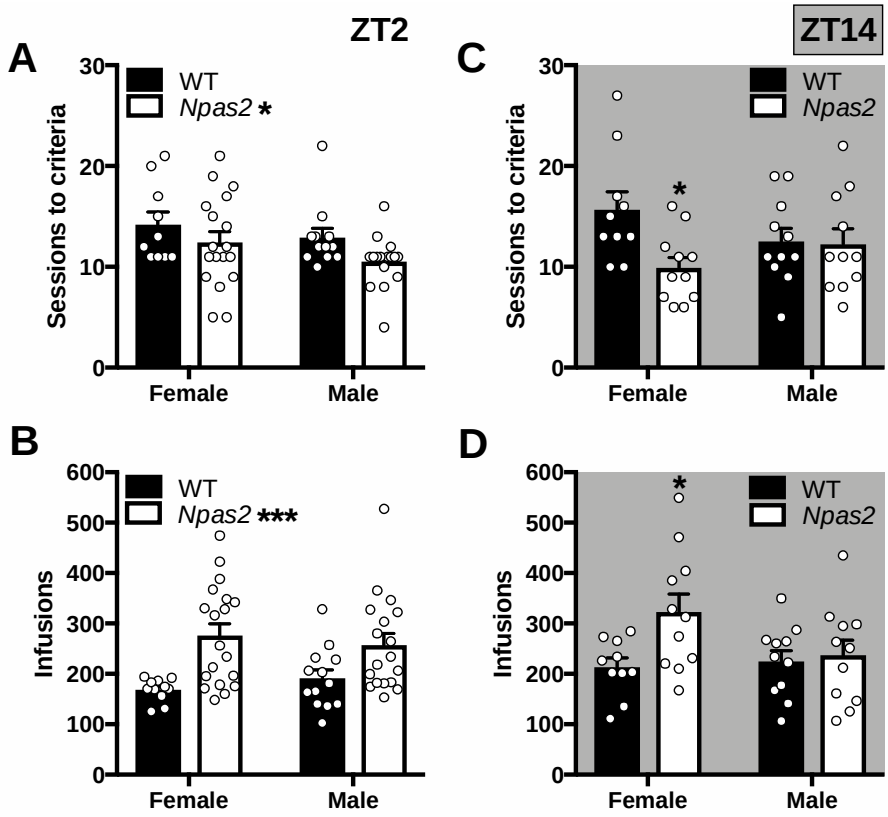

Figure 4. *Npas2* mutant mice respond more on an active lever for cocaine, particularly females in the dark phase. (A) At ZT2, during the light phase, increased active lever pressing for cocaine is seen in (A) female and (B) male *Npas2* mutant mice. (C) Although this effect seems to be greater in female mice, no sex difference was found. All *Npas2* mutant mice pressed the active lever more than WT mice (no posthocs shown), while only a trending increase in inactive lever pressing was found. Both WT and *Npas2* mutants press the active lever more than the inactive lever. (D) In the dark, or active, phase (ZT14) active lever pressing is elevated in female *Npas2* mutant mice (no posthocs shown), (E) but not male mutants. Both WT and *Npas2* mutants press the active more than the inactive lever. Means+SEMs, *n*=10-19.

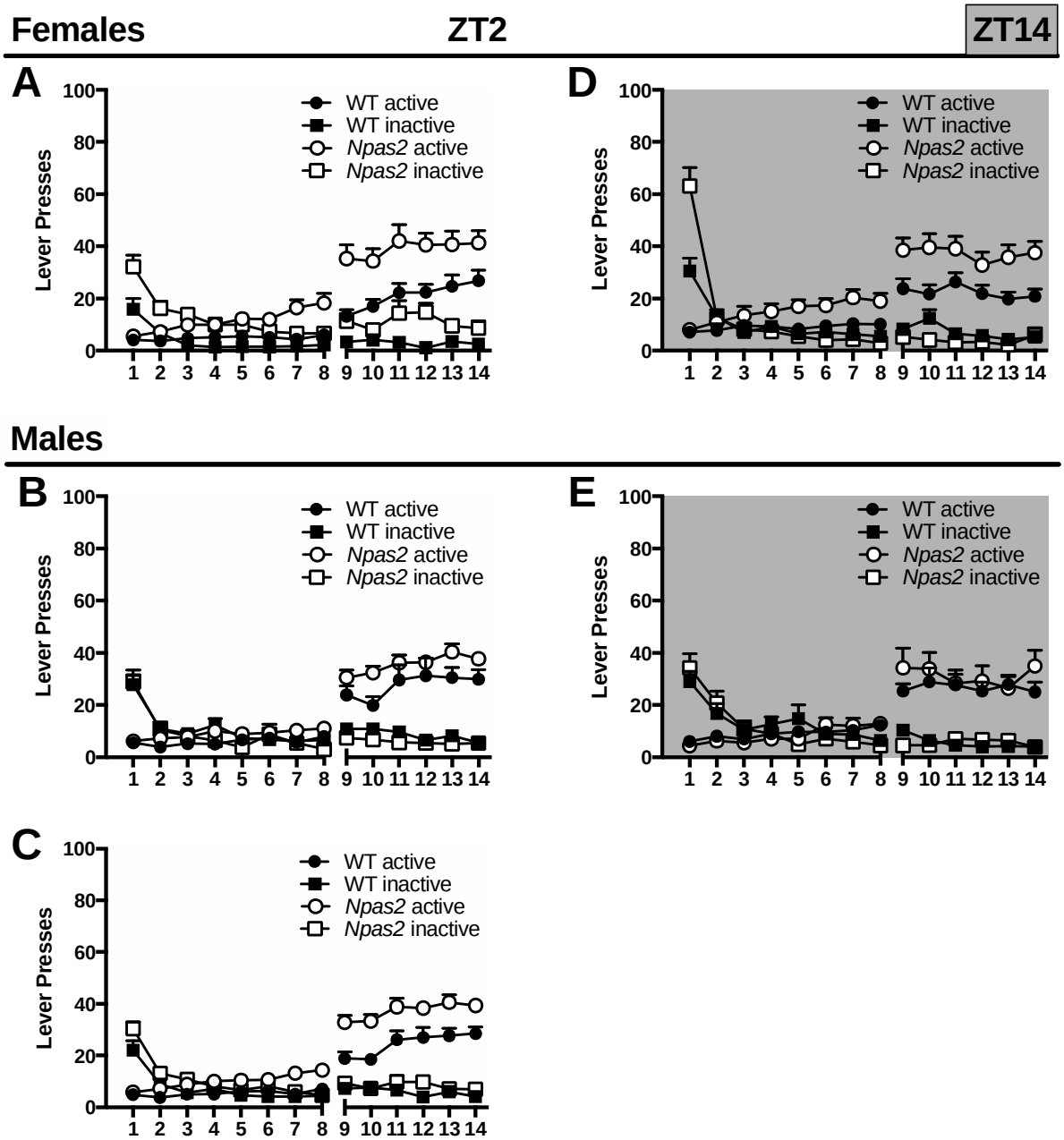

Figure 5. Sex differences in cocaine sensitization and place preference in *Npas2* mutant mice. (A) Male *Npas2* mutant mice showed a decrease in conditioned place preference to cocaine (2.5 and 5 mg/kg), whereas females showed no change. (Right) Cocaine conditioned place preference is also unchanged in the dark phase in female *Npas2* mutants. (B) One cohort of mice were then tested for locomotor sensitization. All mice showed sensitization to cocaine, but female *Npas2* mutant mice also showed elevated locomotor-activating effects of cocaine. (C) No effect of genotype was seen in male mice. Means+SEMs, #p<0.1; *p<0.05; **p<0.01, *n*=12-20.

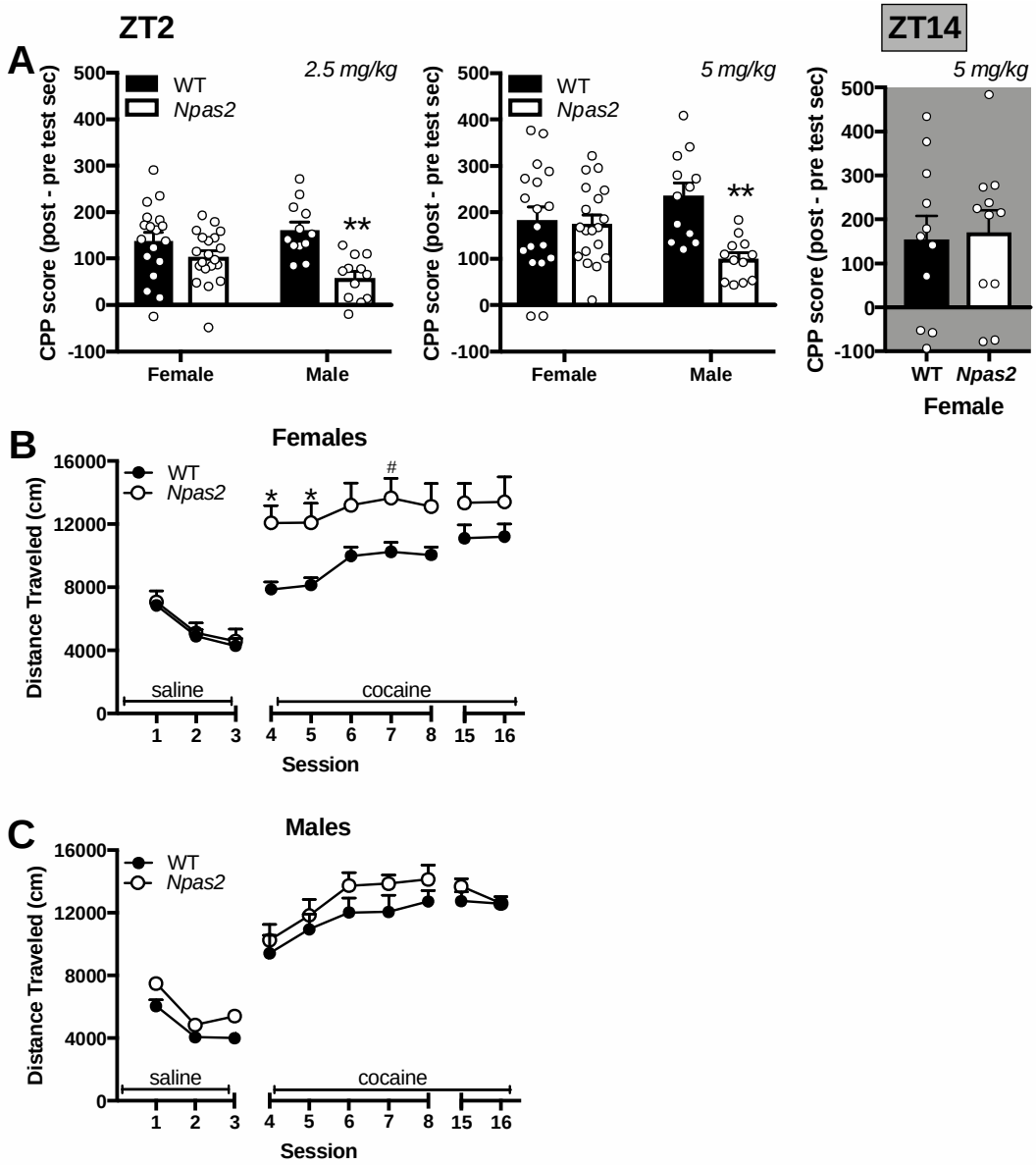

Figure 6. The reinforcing and motivational properties of cocaine were increased in *Npas2* mutant mice. During a dose-response analysis (0-1 mg/kg/infusion) at ZT 2 (light phase), *Npas2* mutant mice self-administered more infusions of cocaine across dose in both (A) female and (B) male *Npas2* mutant mice. (C) This significant increase in cocaine intake across sex suggests an increase in the reinforcing properties of cocaine. At ZT4 the reinforcing properties of cocaine were also increased in (D) female and (E) male mutant mice. Here, effects appear to be greater in female mutants, but (F) no sex effect was found. During progressive ratio testing, (G) female and (H) male *Npas2* mutant mice again worked harder for each infusion of cocaine. (I) Although a significant increase in breakpoint ratio was found across sex, this effect seems to be driven primarily by female mutant mice. Similar results are found during the dark phase, wherein breakpoint ratio was increased in (J) female and (K) male *Npas2* mutants. (L) Again, female mutants appear to be particularly affected, but no significant effect of sex was found. Means+SEMs, *p<0.05; **p<0.01; ***p<0.001, *n*=4-11.

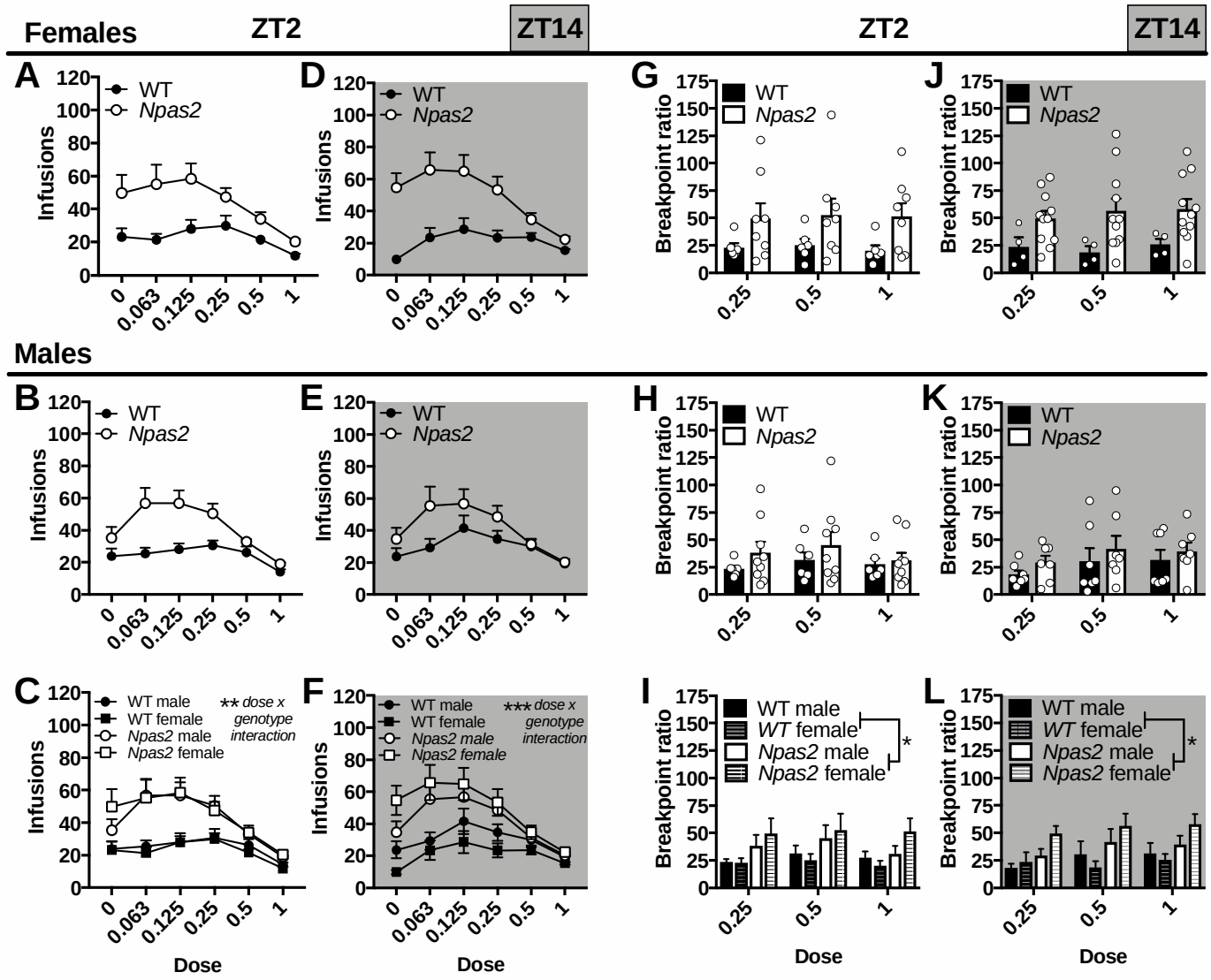

Figure 7. Increased extinction responding and cue-induced reinstatement in female *Npas2* mutant mice during the dark phase. Following progressive ratio, responding on the cocaine-associated lever was extinguished over the course of at least 10 days. Following extinction, responding on the active lever was reinstated with the presence of previously cocaine-associated cues. We found a very slight increase in extinction responding during the light phase in (A) female and (B) male mutant mice, as indicated by a (C) trending effect of genotype. On the other hand, during the dark phase, extinction responding was only increased in (D) female *Npas2* mutants, while (E) male mutants were unaffected. (F) This sex difference was confirmed by an interaction between session, sex and mutation. A similar pattern was detected for cue-induced reinstatement, wherein (G-I) no effects were found during the light phase, but (J) female and (K) male mice were differentially affected by *Npas2* mutation in the dark phase. (L) A trending interaction was found and female *Npas2* mutants responded significantly more during cue-induced reinstatement, suggesting increased drug seeking, but no differences were observed in males. Means+SEMs, #p<0.1; *p<0.05; **p<0.01, *n*=4-11.

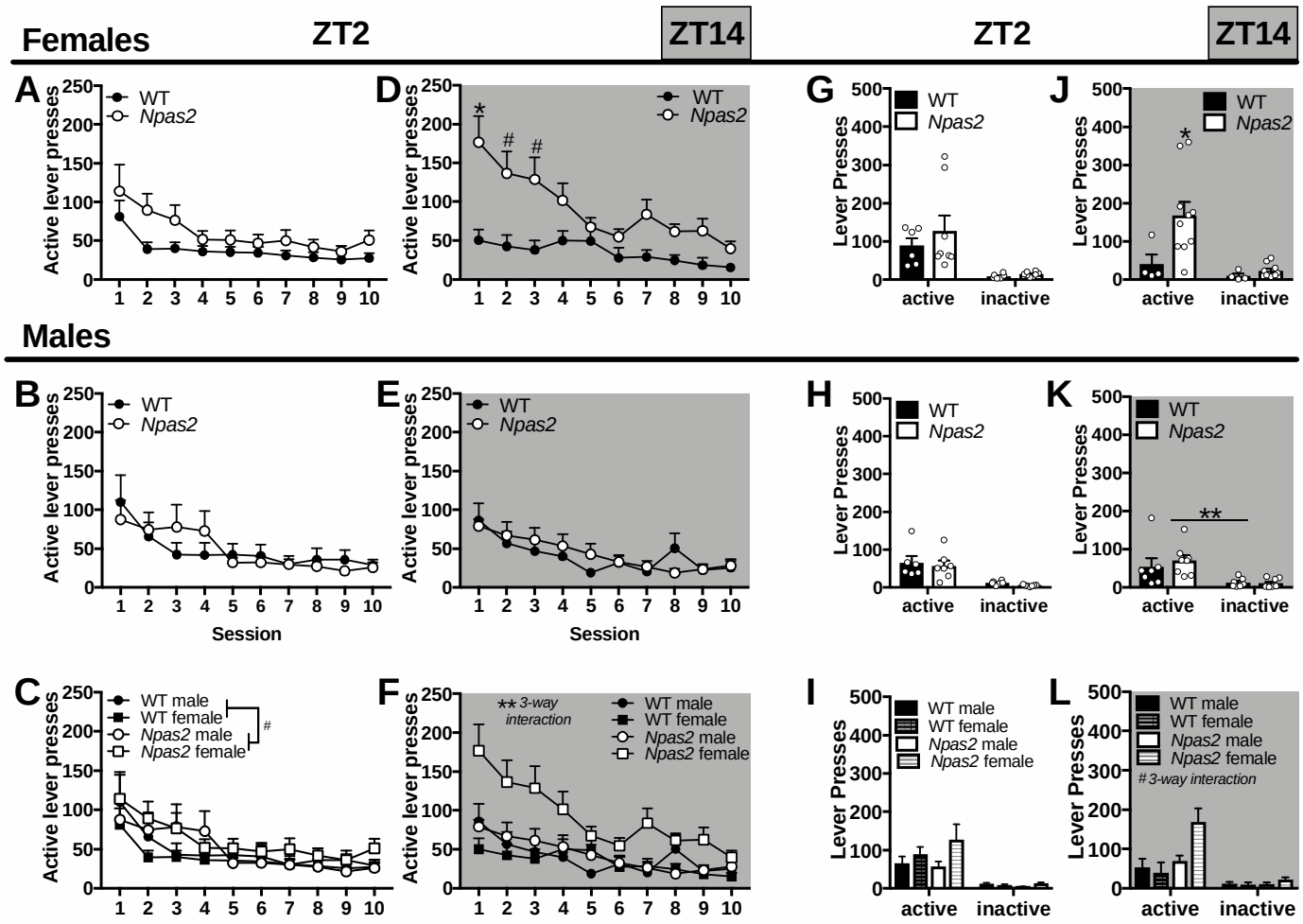

Figure 8. Ovariectomy reversed increased cocaine self-administration in *Npas2* mutant females in the dark phase. A separate cohort of female mice underwent sham surgery or ovariectomy (OVX) before being trained to self-administer intravenous cocaine. (A) Sham surgery treated mice recapitulated our original finding that *Npas2* mutant females take more cocaine than their WT counterparts during acquisition. (B) On the other hand, OVX seemed to reverse this effect with no differences seen between mutant and WT mice. These results were confirmed by total drug intake (infusions), which are (C) moderately increased in sham treated *Npas2* mutant mice, but not (D) OVX mice. Means+SEMs, $^{\#}p<0.1$; $^{*}p<0.05$, n=7-12.

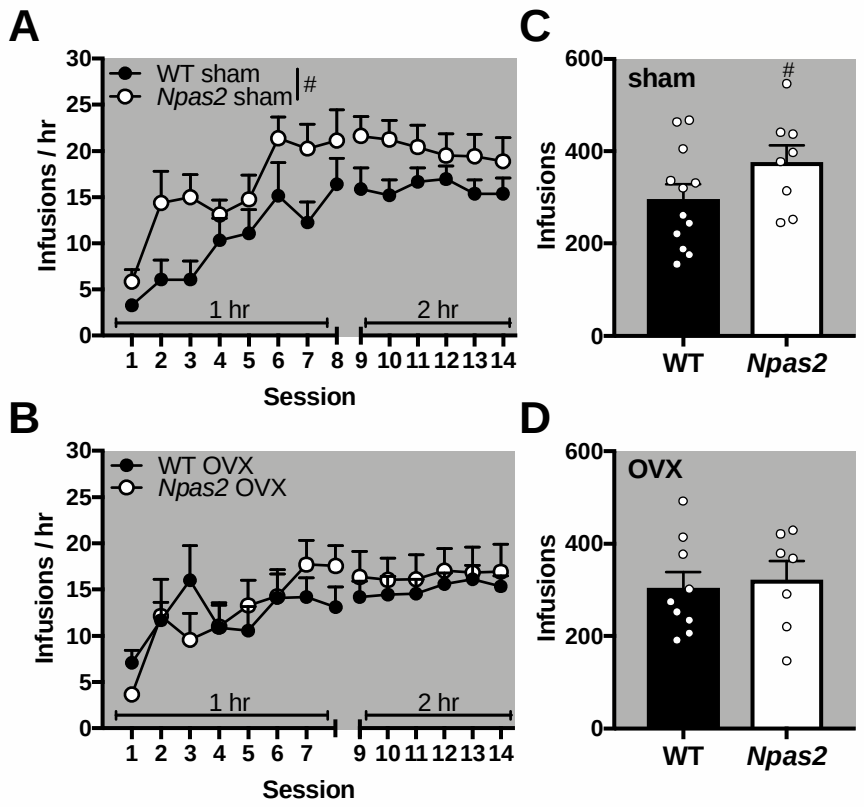

Figure 9. Striatal activation and differential gene expression in *Npas2* mutant females in the dark phase. (A) A cohort of female mice were trained to self-administer cocaine during either the light phase or dark phase. Infusions were limited to 25 in order to normalize cocaine intake between groups. (B) No differences were found between genotypes in **Δ**FosB expression following light phase cocaine self-administration. However, following dark phase self-administration **Δ**FosB expression was increased in *Npas2* mutant females in the NAc core, shell and DLS. This expression was specific to D1+ cells in the NAc core and DLS. Throughout, cocaine-induced **Δ**FosB expression was greater in D1+ compared to D1- cells. (C) Representative staining is shown with the nucleus (DAPI, blue), D1 (green) and **Δ**FosB (red) shown individually and as a composite image with 20 µm scale bar shown. (D) Table showing the cumulative number of DE genes between *Npas2* mutant and WT female mice in the dark phase with a fold change (FC) cut-off of 1.3. Various significance cutoffs are shown for the NAc, DLS and DMS. (E-G) RRHO plots showing various levels of overlap between genes that are changed with *Npas2* mutation in the NAc, DLS and DMS. (E) There is a high level of overlap between genes that are changed in the NAc and DLS, while (F) very few genes are changed in both the NAc and DMS of *Npas2* mutants. (G) Genes in the DMS and DLS are changed in opposite directions in *Npas2* mutant females. (H) Venn diagram showing unique or overlapping DEGs in the NAc, DLS and DMS with a cut-off of $p<0.05$ and FC=1.3. (I-K) Highly significant pathways altered in *Npas2* mutant females in the DLS, NAc and DMS are shown. Extended data list DEGs in the NAc (Figure 8-1), DLS (Figure 8-2) and DMS (Figure 8-3). Means+SEMs, $^{\#}p<0.1$; $^{*}p<0.05$, n=4-8.

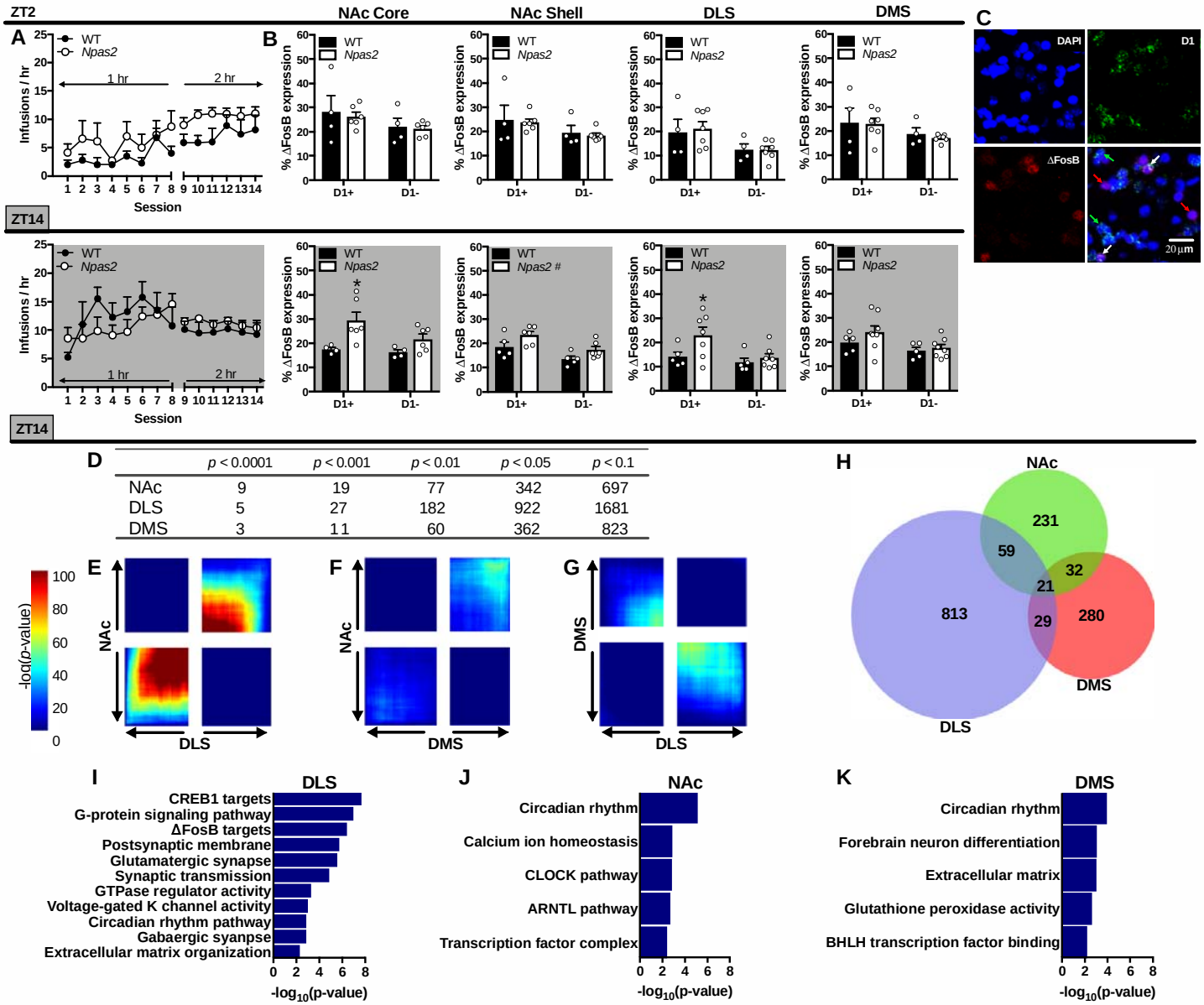

Table 1. Differential expression analysis in the NAc for WT compared to Npas2 mutant females in the dark phase.

	logFC	AveExpr	t	P.Value
Fabp7	1.1612634	6.0120551	9.3505619	0.000000373
Pantr1	1.0369289	6.8195989	7.4744017	0.000004520
Camkk1	-0.5869889	5.4926812	-7.4380299	0.000004760
Pwwp2b	-0.7097055	4.3559631	-6.7537257	0.000013200
Dbp	-0.4355640	6.6083590	-5.9270962	0.000049000
Gpx6	-1.6461238	1.7537649	-5.8168425	0.000058700
Ano2	-0.7781356	4.2878706	-5.6447926	0.000078300
Hhipl1	-1.0009787	1.0373415	-5.6018635	0.000084200

Arntl	0.5386880	5.3716454	5.5685013	0.000089100
Bhlhe41	-0.5804714	4.7851719	-5.2300369	0.000159465
Rap1gap	-0.5232239	7.2967497	-5.2075667	0.000165837
Fbxl16	-0.4766779	10.2425420	-5.1941176	0.000169778
Btg2	0.5440038	3.7381584	4.5746888	0.000513933
Nr4a1	-0.7232305	5.6791943	-4.5674539	0.000520775
Nr1d1	-0.8239104	4.7967254	-4.5522194	0.000535491
Apln	-0.3754513	5.8432032	-4.5258056	0.000562036
Fam117a	-0.5246927	3.2461452	-4.4561670	0.000638753
Camkv	-0.3635769	9.1062047	-4.3761217	0.000740469
Amz1	-0.3918705	4.4588823	-4.3266919	0.000811506
Hlf	-0.4128196	7.5582686	-4.1635782	0.001099991
Hpca	-0.2652153	9.7144101	-4.1600219	0.001107344
Hebp2	0.6029171	2.3859733	4.1462360	0.001136328
Slc25a37	-0.4287862	3.6486116	-4.0611295	0.001333390
Nt5e	0.4022720	4.4112411	4.0533665	0.001353030
Pltp	-0.3819890	6.2867688	-4.0098885	0.001468647
Ephx1	-0.4583694	5.1686625	-3.8869701	0.001853462
Slc5a11	0.9664781	-0.1342566	3.8666706	0.001926314
Mfsd9	-0.4840517	2.7155372	-3.8220107	0.002097070
Scn4b	-0.2871280	9.0405135	-3.7060719	0.002616170
Upb1	0.6309802	3.9884916	3.7020887	0.002636168
Cbs	0.4826545	4.0704008	3.7003742	0.002644823
Egfl6	1.1853001	1.6994305	3.6814056	0.002742537
St8sia2	0.6766685	3.1502105	3.6235430	0.003063892
Lonrf2	-0.4369910	7.0156844	-3.6029532	0.003187257
Cntnap5b	0.4680749	3.8323767	3.5408293	0.003590888
Fam26f	1.5262217	-0.5931345	3.5311598	0.003658217
Sypl2	-0.7958233	0.7942059	-3.5310762	0.003658805
Rdh10	0.4068653	4.5782071	3.5173595	0.003756530
Ak7	-1.3248740	-0.4177117	-3.5105390	0.003806103
Anxa7	-0.1992575	6.9286921	-3.5008639	0.003877561
4932438H23Rik	0.5940212	0.9731767	3.4978652	0.003899983
Emp2	0.3047416	5.1170321	3.4879785	0.003974842
Dbi	0.4951859	8.4058465	3.4747980	0.004076905
Csrnp1	-0.4900909	3.0629890	-3.4340028	0.004409900
Slc4a11	-0.5380027	2.3530623	-3.4313216	0.004432725
Slc20a2	0.2285171	5.9966117	3.4191967	0.004537438
Cbr2	1.1781094	-0.7945297	3.3764676	0.004926755
Ecm1	-0.5472840	2.7315067	-3.3685144	0.005002853
Tmem132e	0.3193719	4.3324199	3.3549971	0.005134915
Sntb2	-0.5934158	2.2835857	-3.3438007	0.005246956
Irak3	-0.9914885	0.1975910	-3.3147495	0.005549276
Zswim3	-0.3449034	3.4580346	-3.3127641	0.005570565
Fmo2	-0.8165182	1.8485319	-3.3015818	0.005692015
Gm266	0.4334697	2.9347581	3.2975811	0.005736110
Nlrp10	0.6316947	1.7886060	3.2679702	0.006073319

Penk	-0.3348428	11.1366609	-3.2638930	0.006121282
Dcaf12l2	1.0280698	0.5455710	3.2357941	0.006462335
Mettl13	-0.3498267	3.5683362	-3.2210640	0.006648666
Rpe65	-0.9598976	2.7554880	-3.2129470	0.006753635
Tmem215	0.7455332	1.1865126	3.2056051	0.006850009
Bhlhe40	-0.4756758	5.3160665	-3.1652603	0.007404688
Rgs16	-0.5523880	1.9663115	-3.1537567	0.007570921
Scarf2	-0.7241574	1.1105410	-3.1262431	0.007983779
Ciart	-0.5135841	3.0520688	-3.1233883	0.008027883
Gm3414	1.0506827	0.0805051	3.1100498	0.008237196
Npas4	1.2686303	0.2481480	3.1042435	0.008330001
Hmces	-0.2805592	4.1688390	-3.1039081	0.008335395
Slc25a13	-0.4508207	2.7626967	-3.0965366	0.008454799
Slc25a18	0.3392534	5.2497330	3.0905773	0.008552573
Dleu7	0.4397669	3.6083709	3.0870451	0.008611056
Prkd1	-0.2958669	3.7330145	-3.0864145	0.008621540
Edn3	-0.5174861	3.2366920	-3.0748326	0.008816349
C5ar2	1.2191614	-1.4576188	3.0460959	0.009318839
Adgrg1	0.3247911	6.2303273	3.0179281	0.009839001
Kirrel2	-0.3898798	3.6234770	-3.0167418	0.009861529
Snai3	-0.9229106	-0.9147682	-3.0149463	0.009895725
Strip2	-0.3968548	8.1036262	-3.0103072	0.009984621
Tgfb2	0.360737537	3.382782007	3.006739609	0.010053526
Lsp1	-0.872144298	1.486495112	-2.993075714	0.010321822
Lrrc10b	-0.23714746	7.086791551	-2.992170091	0.010339853
Cfap57	-0.913728967	-0.610223255	-2.991662653	0.01034997
Spata33	-0.727775036	0.082795601	-2.990051909	0.010382149
Amn	0.374828558	2.537758663	2.983176886	0.010520615
Gm2115	-0.435647885	3.085739078	-2.977607384	0.010634128
Olfm4	0.986457932	-0.250946431	2.961639928	0.010966336
Zfp593	0.36399364	3.249726469	2.955315435	0.011100744
Rapsn	0.590404642	1.040098398	2.946431801	0.011292298
S100a6	0.52464856	4.391249751	2.93983704	0.01143661
Tmem106a	-0.739333081	-0.239362301	-2.937290233	0.011492828
Zar1l	0.557112774	1.122455307	2.936868499	0.011502164
Fuz	0.35227297	3.719210268	2.926110782	0.011742856
Per3	-0.488786835	2.384851657	-2.921560648	0.011846152
Ldb2	0.28270085	5.866355409	2.914681635	0.012004027
Fam126a	0.306902435	5.935817502	2.908151706	0.012155813
Naglu	0.297989042	3.119305042	2.899978807	0.012348463
Agtr1a	0.812138355	0.294468937	2.895157767	0.012463515
Resp18	0.235615692	5.568090031	2.878200618	0.012876656
Cipc	-0.195503344	6.637698092	-2.865758845	0.01318835
Neu2	0.392688748	2.554078181	2.858377559	0.01337677
Pcdhga7	-0.335397987	3.948541539	-2.852868635	0.013519122
Hapln2	-0.430506789	2.706921497	-2.848638545	0.01362944
Klk6	-0.464584547	2.652637108	-2.848459229	0.013634136

Aldh1a1	-0.408896363	4.893260951	-2.84047306	0.013844904
Tmem154	0.874844368	-0.24472036	2.809948513	0.014680454
Tulp3	0.280340947	3.202236953	2.794577546	0.015119775
Arg2	0.270500004	3.528161024	2.792912945	0.015168119
Mctp1	0.303275149	8.798680188	2.776828733	0.015643132
Acsl5	-0.21969671	5.864722044	-2.772542577	0.015772159
Eml2	0.179669151	6.556282619	2.762053982	0.016092315
Kcnip3	-0.388966801	6.037910388	-2.759267845	0.016178425
A230065H16Rik	1.263772709	0.473440689	2.749995568	0.016468264
Pitpnm3	-0.34307734	4.681894102	-2.746329279	0.016584266
Slc26a1	-0.955935033	-0.432430337	-2.74629958	0.016585209
Mall	-0.71265938	0.470866821	-2.742385136	0.016709952
Bmp2	0.359360809	2.744468263	2.738512371	0.01683427
B230216N24Rik	0.586917784	0.845892421	2.733577949	0.016993981
Plgrkt	0.257944128	3.783583094	2.733162586	0.017007493
Zic1	0.268904749	4.192377247	2.730703588	0.017087697
Lrguk	1.197019403	-1.394854324	2.729618394	0.017123211
Fam101b	0.37226003	4.546366026	2.713243275	0.017667934
Mkln1os	0.481506731	1.903117036	2.712309027	0.017699517
C330013E15Rik	1.102235813	-1.043732706	2.693864104	0.018334493
Apold1	0.50933483	1.903193171	2.689624591	0.018483554
Mthfd1l	-0.393175593	3.335917645	-2.688821719	0.018511916
Tenm2	0.43353958	3.902455178	2.675764449	0.018979178
Pde1b	-0.206225627	9.628582146	-2.67506617	0.019004487
Ufsp1	0.393645852	3.007218859	2.673185963	0.019072801
Aldh1l1	-0.223384748	5.657753547	-2.672421047	0.019100661
Nfkb2	-0.681027135	0.40156297	-2.665501154	0.01935451
Wnt7a	-0.207631602	4.899701884	-2.659205829	0.019588301
Gpbp1l1	0.333306981	3.854194462	2.649545401	0.019952422
Shisa2	-0.299430139	3.682899488	-2.645969743	0.02008886
Gm4980	-0.373451548	3.135340171	-2.643154345	0.020196927
Skap2	-0.283138636	4.17742796	-2.639521529	0.020337206
Trf	-0.35353807	8.311339926	-2.634823661	0.020520017
Zbtb10	-0.395671998	2.302685142	-2.633341835	0.020578012
Fbxo16	0.266545767	3.308524747	2.629819186	0.020716518
Smc5	0.50243751	5.444962657	2.625258873	0.020897172
Marcksl1	0.313702185	5.949177916	2.622046594	0.021025342
Shmt1	0.634965872	0.732296334	2.621968085	0.021028484
Erf	-0.185835944	5.315483508	-2.613474886	0.021371105
Npas2	0.433225115	5.029456193	2.611563248	0.021448965
Fxyd6	0.285886121	6.790953029	2.610763735	0.021481611
Sfrp5	-0.785564559	0.986287298	-2.603424728	0.021783541
Entpd2	0.250030428	4.37521685	2.599438289	0.021949267
Cirbp	0.243912946	5.974237525	2.592952404	0.022221519
Drd3	-0.422227411	2.190674772	-2.586438826	0.022498229
Sdcbp2	-0.81570468	-0.171669491	-2.582676367	0.022659585
Tfdp2	-0.253962233	5.042330593	-2.573693438	0.023049373

Angptl3	1.304244631	-1.564272705	2.566184601	0.023380175
Sh3tc1	0.636033771	0.300070047	2.558002286	0.023745881
Lor	0.403063906	2.522560209	2.557367633	0.023774476
Prlr	1.118785634	-0.003869635	2.549226412	0.024144266
Maob	-0.189595324	5.512787789	-2.548440622	0.024180251
Fancd2	0.449260541	2.083879542	2.543670491	0.024399814
Tspan4	0.2343596	4.22138754	2.538297024	0.024649456
Zic4	0.788548886	0.207677305	2.534693009	0.024818273
Ctxn2	0.341943698	5.086152428	2.533102558	0.024893126
Apod	-0.221601811	7.896686793	-2.532056699	0.024942468
Bex4	0.272854351	4.788710758	2.52907545	0.025083637
Angpt1	0.413808064	2.256990734	2.526416723	0.025210184
Cdh15	0.345347903	3.16079533	2.523784467	0.025336078
Cxcl5	1.644740497	-2.467528	2.522883491	0.025379309
Traip	0.413544987	3.024252721	2.517202318	0.025653548
Dnaic1	0.409826928	2.712861756	2.514676407	0.025776394
Cxcl13	1.097249182	0.135450256	2.510207935	0.025995107
Inadl	0.316004887	3.686476786	2.503635624	0.026320048
Baalc	-0.206743109	8.171375619	-2.503270929	0.026338193
Cbln1	0.535367933	2.140977722	2.499350185	0.026534029
Efemp1	-0.486005657	3.114735066	-2.49766202	0.026618783
Mtmr11	0.313600629	2.662528735	2.493547336	0.026826452
Tgif2	0.767778802	0.077814665	2.493063986	0.026850949
AI662270	-1.07240865	-1.321853284	-2.490199161	0.026996586
Plb1	1.613845024	-1.518354994	2.480910248	0.02747405
Heatr5a	-0.302559157	3.743524599	-2.480167651	0.02751257
Ehbp1l1	0.251734727	5.301209121	2.478104516	0.027619861
Tctex1d1	1.037730293	-1.517920447	2.477726941	0.027639539
A330076C08Rik	-0.960922514	-0.41628479	-2.469697719	0.028061221
Tmem181b-ps	0.83126688	1.021643922	2.46740674	0.02818267
Gpr3	-0.452673859	2.308759202	-2.466993673	0.028204621
Hcfc2	-0.207333993	4.531471474	-2.464937545	0.028314132
Pde7a	0.216846659	4.169775844	2.46491699	0.028315229
5930438M14Rik	1.542492138	-3.146258898	2.463917791	0.028368596
Zfp36l2	0.323471827	4.006941619	2.458823836	0.028642172
Upp2	-0.233752861	3.870887509	-2.457052789	0.02873788
Tubb2a-ps2	0.396300824	2.364710903	2.453983038	0.0289045
Mr1	0.347628046	2.391105424	2.453217324	0.028946205
Nupr1	-0.464775258	1.828524376	-2.452788798	0.028969571
Tex9	0.463894366	1.420580058	2.443184049	0.029498047
Prex2	-0.245710039	6.389027618	-2.442700635	0.029524889
Prmt8	-0.16815624	6.989142623	-2.436266953	0.029884361
Fen1	-0.25871985	3.399534634	-2.433238204	0.030055037
Ptpn7	-0.505875025	1.52926899	-2.431740663	0.030139772
Asb4	0.951119542	0.809942051	2.428759858	0.030309115
Mbtd1	0.196110437	4.528400006	2.424867783	0.030531602
Trpv4	-1.006303631	-0.89741808	-2.422329422	0.030677548

Cpeb1	-0.214461281	4.669310334	-2.420348698	0.030791896
Vipr1	-0.449602795	2.591295582	-2.418681483	0.030888461
2810049E08Rik	1.006503928	-0.475908095	2.41854758	0.030896229
Zfp133-ps	0.418228195	1.548412152	2.416277101	0.031028234
Cd24a	0.517551397	4.377513721	2.414648458	0.031123255
Padi2	-0.388990025	3.508091378	-2.40862651	0.031477022
E2f1	-0.350604105	3.659514537	-2.406698439	0.031591101
Shf	-0.194684643	4.443725871	-2.403731252	0.031767434
Klhdc7a	-0.378838201	3.093770317	-2.402435635	0.031844725
Cish	-0.319671778	2.800604894	-2.399036716	0.032048344
1700001L19Rik	0.409869396	3.734702687	2.398602853	0.032074425
Nrtn	0.706257476	1.155251188	2.396077526	0.032226634
Magel2	0.890570996	0.674229747	2.395142003	0.032283196
Gucy2e	-0.595330366	1.299997293	-2.390040557	0.032593305
Glra3	0.58788454	2.271262322	2.388847972	0.032666209
Mb21d2	0.160947531	5.869037509	2.385618204	0.032864434
Rasd1	0.440169564	1.749255754	2.383406646	0.033000829
Gpx3	0.393167272	3.340935917	2.383060048	0.033022253
Npbwr1	0.389352356	1.816058326	2.382661522	0.033046905
Ccdc142	-0.750130312	-0.892441959	-2.381249599	0.033134382
Awat2	0.762603964	-0.646694445	2.380302094	0.03319321
Il1rapl2	-0.423168073	0.966336893	-2.378508109	0.033304867
Krt26	1.372851849	-1.618284876	2.37691668	0.033404216
P2ry2	-0.792558002	-0.931610271	-2.375907805	0.033467345
Gtf2h3	0.227749018	3.855704426	2.375734941	0.033478173
Hhatl	-0.458238736	3.384712963	-2.372582341	0.033676237
Il33	-0.453037068	6.763444913	-2.366714187	0.034047888
H2-Q2	0.576426138	1.679422622	2.366442626	0.034065182
Kazn	-0.226351906	6.671882319	-2.366388036	0.034068659
B3gat2	0.228741181	3.959036191	2.365562141	0.03412131
Wdtc1	-0.172598186	6.288272604	-2.364576449	0.034184249
Crym	0.372847043	9.386271187	2.357307584	0.034651816
Crlf1	0.852290543	-0.087950397	2.355614237	0.034761612
Tut1	-0.19955572	4.918742975	-2.355545906	0.03476605
Usp2	-0.37634829	4.374210748	-2.353708774	0.034885558
Baiap2l2	-0.689620799	-0.679496542	-2.352763352	0.034947212
1190002F15Rik	1.71765228	-2.369910497	2.347963926	0.035261801
Etaa1os	-0.70849451	-0.449721924	-2.347738898	0.035276617
Fam129a	-0.91110676	-0.016728641	-2.346347356	0.035368369
Ddx4	-0.904346769	-0.697881514	-2.343759879	0.035539579
Kcnj5	-1.040565578	-0.204874843	-2.341207118	0.035709265
Gimap8	0.355082446	2.303273398	2.338253387	0.035906566
E130008D07Rik	0.448777065	2.442427562	2.337511206	0.035956305
Dusp5	-0.496438227	1.395972864	-2.335103301	0.036118127
0610040B10Rik	0.634175746	0.880568623	2.333656563	0.036215687
Smpd2	0.202278427	3.993526956	2.332855205	0.036269834
Mllt1	-0.189749555	5.950276141	-2.327858846	0.036609174

Cd59b	-0.772535846	-0.546692876	-2.327294794	0.036647672
Trpv2	-0.247138877	3.648953103	-2.32582223	0.036748359
B3gnt7	-0.778691928	0.00101115	-2.325370871	0.036779274
Epha8	-0.438890933	1.78442549	-2.322032233	0.037008714
Sult2b1	-0.282055038	3.034551533	-2.321565146	0.037040922
A330076H08Rik	0.420039325	0.832371474	2.318231836	0.037271543
Tnnc1	0.795136892	0.548427974	2.317506866	0.037321881
Racgap1	0.191695951	4.372542477	2.315163363	0.037485046
Zfhx3	0.507580942	0.531454253	2.308705037	0.037938213
Pafah2	0.32388638	2.365978366	2.308291978	0.037967373
Tyms	0.376391582	1.699489163	2.305466635	0.038167398
Poc1b	0.299309449	2.77048685	2.305037713	0.038197852
Gm1653	0.773724941	-1.644814486	2.304246395	0.038254096
Lpar6	-0.343984882	2.068940509	-2.301734608	0.038433147
1110038F14Rik	0.215751761	3.633775026	2.292019675	0.039133177
Car13	-0.704389185	-0.016608091	-2.291218286	0.039191459
Lypd1	0.258034607	8.074739382	2.291122503	0.039198431
Ppp2r2a	-0.182243539	7.571474509	-2.290146869	0.039269508
Plk4	-0.43981841	2.562029404	-2.288457665	0.03939286
Mrgbp	0.322465114	1.72040471	2.2835009	0.039756944
Ttc38	-0.405583131	1.969174956	-2.283396068	0.039764678
Coch	0.41956318	4.109811673	2.276568878	0.040271461
Tmem114	0.750810426	-0.751066306	2.275077117	0.040383006
Il20ra	-0.42274265	1.396053411	-2.275054799	0.040384677
Smox	0.219615631	5.523294484	2.274139845	0.040453238
Nanos1	-0.191816341	6.217622984	-2.274016793	0.040462468
Nnt	-0.203819553	5.006430773	-2.269567531	0.040797517
9430015G10Rik	0.361143853	2.707991191	2.266103133	0.041060216
Hcn2	-0.276019459	6.41388045	-2.264439841	0.041186908
Urb2	-0.24869867	4.327308686	-2.264300018	0.041197575
Wwtr1	0.165581786	5.464477781	2.258546844	0.041638755
Zcchc12	0.280315772	8.361696193	2.258236593	0.041662673
Ifit1bl2	0.607039761	-0.590809969	2.256897403	0.041766063
Ikzf1	-0.321054966	2.196285551	-2.254522573	0.041950005
Fam71e1	0.440735241	1.584137273	2.254057945	0.041986082
Oxsr1	-0.201189267	5.533525058	-2.252960709	0.042071395
Mat2a	-0.15103435	7.072919997	-2.251418686	0.042191568
Plekho2	-0.251144723	4.098518788	-2.251160901	0.04221169
Casq2	0.372294351	2.431103537	2.250238593	0.042283755
Pabpc5	-0.398911944	1.028493478	-2.249336876	0.042354323
9530080O11Rik	-0.678527768	0.282273164	-2.248775277	0.04239833
Syce2	0.530592633	1.617800203	2.247512177	0.042497464
Wars2	-0.249546462	2.682254339	-2.247085675	0.042530987
Cd37	-0.359769585	1.726843679	-2.243363881	0.042824584
Casp12	0.514176255	0.592122964	2.242435185	0.042898142
Wdr6	0.300716028	7.543187566	2.242325486	0.042906839
A730017C20Rik	0.309807236	6.04406902	2.239268541	0.043149857

Rln1	-0.682982475	0.517212375	-2.239034478	0.043168517
Zbtb46	0.35804576	1.40540559	2.237566572	0.04328572
Drc1	-0.345332123	3.226316416	-2.237380327	0.043300612
Zfp652	-0.365272419	2.920734756	-2.235709263	0.043434444
Rab26	0.405675724	4.267494399	2.23549912	0.043451302
Grtp1	0.338688242	1.740676494	2.235261292	0.043470387
Apoe	0.172989538	11.06415318	2.232642236	0.043681092
Nr1d2	-0.177416478	7.794345897	-2.232518745	0.04369105
Slc1a5	-0.549150885	0.215338734	-2.232131409	0.0437223
Ccsap	-0.155799089	6.037703205	-2.231431716	0.043778803
Rftn2	0.170926341	5.345841767	2.23107903	0.04380731
Dtx4	0.242774521	3.719507792	2.230047117	0.043890819
4933439C10Rik	0.320051386	1.890986003	2.229111636	0.043966654
Fgf7	-0.876271855	-1.548713313	-2.223112792	0.044455889
Stac	0.869368819	0.148484952	2.219660446	0.044739765
2610524H06Rik	0.250973071	4.017147763	2.216502674	0.045000912
Col19a1	-0.818363725	0.148238068	-2.21432841	0.045181557
Aldh3b2	0.700931526	0.838289094	2.21395481	0.045212665
Sptssb	-0.724653219	0.04324175	-2.213689248	0.04523479
Arsj	-0.902452554	-0.029021417	-2.213536153	0.045247549
Slc6a8	-0.232845421	5.459044597	-2.213278849	0.045269001
BC005561	0.602560457	-0.313844194	2.212859838	0.045303956
A930006K02Rik	0.801396601	-0.629066723	2.208565475	0.045663665
Gca	-0.253323798	3.959885275	-2.208220338	0.045692691
Gpr137b-ps	-0.278798031	3.280460291	-2.203628194	0.046080546
Snx33	-0.285441182	3.487045404	-2.201227704	0.046284522
Ccl12	0.97625705	-0.709922176	2.200628138	0.046335601
Stk3	-0.244503052	3.495888687	-2.199399591	0.04644043
Itih2	0.739305435	-0.487113231	2.196692999	0.046672165
Tmem200a	0.346710965	3.288022887	2.196409834	0.046696472
Musk	0.340344043	3.428351744	2.196409008	0.046696543
Cyb5r1	-0.204038643	4.846325601	-2.195010051	0.046816804
Tmem63a	-0.287114919	4.655327066	-2.19397996	0.046905542
Znrd1as	-0.376046392	1.220311077	-2.193630765	0.046935659
Scrn3	-0.156786089	5.977735676	-2.192898209	0.0469989
Hspb3	-0.968489728	-0.513023791	-2.187097395	0.047502508
Tbc1d8	-0.184967357	5.279365714	-2.184586888	0.047722028
Ralyl	0.187167631	7.140948548	2.183681421	0.047801436
Kl	0.311949858	3.069161219	2.182997854	0.047861466
Kitl	0.175532822	6.989025381	2.182519444	0.047903521
Mmp14	0.270092952	3.4715433	2.178595149	0.048249802
Hexim2	0.354128864	2.509976754	2.176959516	0.048394823
Rasd2	-0.232003888	8.06466452	-2.176221739	0.04846037
Lemd1	0.701090339	0.143901917	2.175423744	0.048531361
Slc35g1	-0.471108495	0.899992977	-2.172112154	0.048827009
Fcrls	-0.183271476	6.064485811	-2.166711611	0.049312775
Agl	-0.270260914	4.932143562	-2.165395072	0.049431879

Wdr45	0.161129415	5.216480693	2.162075841	0.049733357
Trip13	0.710816855	-0.85400974	2.160583696	0.049869446
Shcbp1l	0.694373424	0.003048688	2.160420217	0.049884377
Efnb1	0.236437895	3.790855817	2.160372839	0.049888705
Mocs3	0.236043486	3.33530633	2.160222025	0.049902484
Dhrs13	0.20472897	4.166561793	2.160031651	0.049919882

Table 2. Differential expression analysis in the DLS for WT compared to Npas2 mutant females in the dark phase.

	logFC	**AveExpr**	**t**	**P.Value**
Fabp7	2.0366869	5.5077793	10.6903535	0.000000045
Arntl	0.6868789	5.6232657	7.1054508	0.000005590
Gpx6	-1.9321115	4.1990014	-6.4097117	0.000017100
Nmb	-1.8342145	1.2119899	-5.6936806	0.000057600
Neu2	0.7863056	3.6979051	5.6911691	0.000057900
Cgref1	0.6750208	4.8584254	5.3689484	0.000102445
Cntnap5b	1.1597673	3.1963773	5.3141818	0.000113043
E130012A19Rik	-1.1375825	4.7728093	-5.3092229	0.000114058
Dbi	0.7876599	8.1066647	5.0024266	0.000199490
St8sia2	1.4506944	2.2049934	4.9310197	0.000227612
Kitl	0.5063929	7.0444019	4.8838292	0.000248427
E230025N22Rik	1.5883223	1.7144461	4.8691395	0.000255301
Pdlim3	1.5368129	0.6839621	4.8389099	0.000270076
Slc7a3	-0.8770609	3.5135936	-4.6354732	0.000395514
Pantr1	1.0748149	6.9105867	4.5716438	0.000446253
Ccdc107	0.7117007	5.3985388	4.5096380	0.000501990
Smoc2	-1.9725316	1.3104666	-4.4903599	0.000520744
Ifi27l2b	2.3072288	-0.3879961	4.4488967	0.000563567
Rps6ka5	0.6822877	6.5264112	4.4449502	0.000567827
Etnppl	-0.8725167	3.4662187	-4.3690374	0.000656559
Serpinb1b	0.9324191	3.6820490	4.3498512	0.000681165
Dmp1	-1.3982462	0.4899150	-4.3211784	0.000719717
Nrde2	0.7213303	4.5148405	4.2264957	0.000863708
Egfl6	1.2875324	1.7455610	4.1849212	0.000935974
Gm266	1.0071002	2.2375231	4.1805916	0.000943847
Ehbp1l1	0.6413860	4.9514608	4.1770616	0.000950317
Ppp1r2	0.5474597	8.0742269	4.1696729	0.000964007
Rnd2	0.4526379	7.1320614	4.0837597	0.001138834
Camkk1	-0.7027273	5.7671540	-4.0159616	0.001299489
Cdo1	0.5024465	6.1958906	4.0147576	0.001302542
Zbtb18	-0.4555924	8.3400769	-3.9779652	0.001399466
Ak4	-0.5310799	5.6919302	-3.9362628	0.001518264
Bhlhe40	-0.9080103	5.4747211	-3.9167781	0.001577246

Arhgef15	0.4127668	4.6862084	3.9149633	0.001582857
Kcnip3	-0.5163964	5.9612762	-3.9084589	0.001603135
Tspan17	-0.8184361	4.2480868	-3.8873399	0.001670818
Pcsk4	-2.6349302	-0.8847428	-3.8805736	0.001693113
Elf5	1.0662190	1.3920761	3.8739926	0.001715087
Etnk2	-1.3501519	1.0493529	-3.8535740	0.001785132
Coch	0.6872598	7.2565893	3.8299280	0.001869895
Serpinb9	-0.5651658	4.3377827	-3.8295078	0.001871438
AI606473	1.0383019	0.7515510	3.7776839	0.002071973
Rilp	1.2521916	1.5357940	3.7758735	0.002079361
Ablim2	0.5491795	6.9915302	3.7684423	0.002109965
Notum	1.1507938	0.6911963	3.7608643	0.002141644
Usp3	0.6104226	5.3045330	3.7071850	0.002380304
Kcns2	0.3999860	6.6854108	3.7067812	0.002382198
Rpe65	-1.0888095	2.3735231	-3.6961315	0.002432704
Figf	-2.3498644	-0.0418443	-3.6852860	0.002485254
Upb1	0.8457280	2.9918695	3.6738128	0.002542097
Thsd7b	-1.1863125	1.7845315	-3.6674228	0.002574324
Hebp2	1.0253780	2.3664144	3.6324357	0.002758253
Ltk	-0.8068882	1.8345111	-3.6309431	0.002766389
Mpp7	0.5250200	3.4921547	3.6165408	0.002846151
Sbsn	0.8158120	4.4893841	3.6136977	0.002862169
Cbln1	-1.4155142	2.6343711	-3.6093964	0.002886576
Tnfaip2	1.2078719	0.5276231	3.5930224	0.002981427
Casq2	1.1938351	3.0022957	3.5902434	0.002997835
Yap1	0.4255597	4.5445919	3.5879631	0.003011366
Bcat1	-0.5395342	5.9179214	-3.5871018	0.003016494
Mthfs	0.7552132	1.5188168	3.5792939	0.003063376
S100a4	0.9660118	2.3748571	3.5728721	0.003102486
Tfap2d	-2.3234929	-0.6780657	-3.5680090	0.003132439
9330102E08Rik	-0.5038879	4.1162703	-3.5636394	0.003159601
Rap1gap	-0.6561368	7.2077499	-3.5535025	0.003223532
Rgs16	-1.3907089	1.0353526	-3.5479274	0.003259248
Qrfpr	-2.6858169	-0.5861207	-3.5373150	0.003328340
BB031773	1.3654354	1.2438286	3.5352283	0.003342098
Gnb4	-0.7226794	6.2139038	-3.5342058	0.003348861
Olfm3	-0.5855380	7.2730278	-3.5278703	0.003391071
Smad6	1.0347892	0.8422695	3.5258174	0.003404864
Camk1g	-0.9245237	3.6535281	-3.4965126	0.003608022
Stard4	-0.4130788	4.6740293	-3.4918122	0.003641726
Htr1d	0.8946846	3.0427924	3.4809777	0.003720626
Dmkn	0.8618949	5.1223558	3.4763764	0.003754653
Nxpe3	-0.4619876	4.4755861	-3.4610744	0.003870080
Tmem178	-0.8110643	6.0719096	-3.4600801	0.003877703
Ntng2	-1.9872770	0.7297038	-3.4551480	0.003915738
Herc3	-0.4582585	7.8601546	-3.4518680	0.003941239
Hhatl	-0.5069431	3.4117143	-3.4483912	0.003968454

Tmem44	0.4513004	5.1113475	3.4418884	0.004019863
Tex40	-1.4507403	-0.2593226	-3.4361014	0.004066175
2310075C17Rik	1.4471451	0.6425408	3.4308695	0.004108506
Sertm1	-0.7077824	3.2735924	-3.4284402	0.004128312
Gm5111	1.0455061	0.9295365	3.4194738	0.004202248
Slc17a6	-1.6483892	2.8114256	-3.4172717	0.004220609
Gm10754	0.8893562	5.6665741	3.3923524	0.004434083
Gabrd	0.4280591	7.5038740	3.3875988	0.004476020
Aqp9	0.8460523	0.8981551	3.3861517	0.004488865
Vnn1	3.0247931	-2.4505331	3.3856569	0.004493266
Etv1	0.3517916	5.9803547	3.3805512	0.004538928
Pcp4l1	0.5369287	8.5239612	3.3741031	0.004597261
Aldh1l1	-0.4716225	5.6937932	-3.3598017	0.004729338
Cbln4	-0.8859508	3.9221324	-3.3547302	0.004777083
LOC100504703	1.7056956	-0.8503222	3.3528673	0.004794742
Hbp1	0.3498823	5.2744404	3.3458714	0.004861644
Slc6a7	-0.9002217	4.3532788	-3.3426840	0.004892435
Angpt1	-1.1358737	2.1367197	-3.3403422	0.004915182
Stard10	0.3891922	6.6815378	3.3330409	0.004986783
Rgs20	0.3569202	6.4597374	3.3190703	0.005126713
Slc1a6	-0.7345433	2.2097903	-3.3181101	0.005136474
Adra2a	-1.3285184	2.8297144	-3.2960701	0.005365696
E2f1	-0.6284068	4.4101529	-3.2958154	0.005368405
Alox12b	-1.2394413	1.9251153	-3.2843755	0.005491449
Mctp1	0.4205759	8.1900332	3.2830040	0.005506389
2410006H16Rik	0.5857852	5.4183564	3.2813449	0.005524517
Elk4	-1.0109067	1.0942274	-3.2754784	0.005589091
Lipg	-1.0390702	1.7028427	-3.2748361	0.005596207
Hsbp1l1	-1.3583068	-0.6405083	-3.2726071	0.005620972
Ap1s2	0.4364937	7.3456554	3.2704603	0.005644925
Efna3	-0.3950243	4.8045380	-3.2671913	0.005681598
Slc6a15	-0.3150381	6.5904338	-3.2582973	0.005782582
Frzb	-1.0945152	3.2861534	-3.2565333	0.005802824
Adcy2	-0.5426451	7.1296775	-3.2509108	0.005867811
Faah	-0.6867553	5.2723046	-3.2464952	0.005919359
Fhl2	-0.5926378	4.7808507	-3.2344295	0.006062528
Rgs4	0.5670871	11.0830218	3.2289782	0.006128340
Wwtr1	0.3720967	5.0880254	3.2285941	0.006133004
Sesn1	0.2577169	6.6246663	3.2285085	0.006134044
Cacna1g	-1.4561929	2.1640875	-3.2221558	0.006211710
Ptgis	1.2662815	0.1141504	3.2163865	0.006283094
Pcdha10	-1.2188310	0.8848441	-3.2126230	0.006330100
Olfm4	-2.1599394	-0.9757745	-3.2107974	0.006353028
Psd4	0.8078423	1.0594556	3.2085023	0.006381970
Hsd17b7	-0.3799318	5.4334211	-3.2048402	0.006428422
Nrtn	1.0891910	2.3514587	3.2020601	0.006463911
Cipc	-0.2688051	6.6990249	-3.1969337	0.006529865

Prkaa2	-0.4372837	6.0982855	-3.1961929	0.006539451
Cd48	0.8654101	1.1448757	3.1935126	0.006574252
Mthfd1l	-0.7267703	3.3208910	-3.1826896	0.006716663
Nr1d1	-0.9962807	4.4616880	-3.1811250	0.006737503
Ankub1	0.9587640	1.6683024	3.1780820	0.006778219
Wnt10a	-1.1191345	1.7252047	-3.1776148	0.006784492
Sfxn1	0.3945693	6.9310306	3.1727963	0.006849527
Spint1	0.7489695	3.3052375	3.1693407	0.006896548
Musk	1.0229360	3.1105579	3.1567835	0.007070138
Igsf21	-0.7915715	4.9027773	-3.1489732	0.007180291
Ntsr1	-1.1582086	0.4169567	-3.1416164	0.007285610
Nt5e	0.7609688	3.9681779	3.1376853	0.007342514
Kcnk4	-1.0494915	1.9964128	-3.1374566	0.007345838
Adgrg2	-1.6090139	-1.0569294	-3.1317321	0.007429532
Hcrtr1	-1.1334159	1.3114430	-3.1295648	0.007461466
Susd2	-1.3318439	0.9027456	-3.1291053	0.007468253
Cyp4x1	-0.5920509	2.2032716	-3.1213681	0.007583474
Ppef2	1.0854500	1.0869680	3.1173663	0.007643759
Rasl11b	-0.6791235	5.0783898	-3.1156279	0.007670096
Lhx8	0.6971861	2.5649893	3.1130674	0.007709049
Ccdc61	-0.6369212	1.9869281	-3.1015447	0.007886798
Car10	-0.9400760	5.1412227	-3.1001171	0.007909102
Parp4	1.0594465	1.8939942	3.0998125	0.007913869
S100a6	0.5878116	4.7298584	3.0956808	0.007978810
Dennd3	-0.8764718	0.6866634	-3.0951856	0.007986629
Klf10	-0.6021780	5.5813614	-3.0935882	0.008011903
Gja5	1.2982219	-0.2078654	3.0909462	0.008053879
Ccdc106	0.4099046	5.6724945	3.0835399	0.008172715
Lnx1	-0.5894562	3.7330574	-3.0744310	0.008321256
Xdh	-0.6763683	2.2373832	-3.0678425	0.008430360
Wisp1	-2.0168501	0.9450324	-3.0665524	0.008451890
Qpct	0.3639057	5.9210265	3.0658644	0.008463394
Enc1	-0.5296749	8.9081917	-3.0651767	0.008474908
Trim65	-1.5897173	-1.1726533	-3.0646812	0.008483213
Mmp14	0.7202860	2.4878445	3.0573979	0.008606234
Nusap1	2.6368849	-1.7539803	3.0540691	0.008663046
Tmem158	0.5840087	8.0438812	3.0536955	0.008669447
Gpr150	-1.1352286	1.0230234	-3.0535649	0.008671684
2810468N07Rik	0.3558303	4.9120048	3.0509910	0.008715912
Vstm4	0.7222199	2.2911852	3.0508842	0.008717752
Fam26f	1.3707817	-0.8510866	3.0507346	0.008720329
Gng2	-0.8669866	7.2487392	-3.0504222	0.008725714
Kcnq1ot1	1.4898529	-0.5598562	3.0474242	0.008777569
Klhl25	-0.4085431	3.4399771	-3.0363628	0.008971539
Hsd11b1	-0.5055746	4.7035684	-3.0320163	0.009048913
Chrm3	-0.8130018	5.0644985	-3.0254514	0.009167034
Lrrc75a	-0.5963740	3.6159529	-3.0202576	0.009261563

Htr2c	0.4489931	7.0943549	3.0198116	0.009269724
4933431E20Rik	-0.2362768	6.9015363	-3.0139230	0.009378161
AI115009	-1.5784847	-0.1507895	-3.0102624	0.009446198
Sult2b1	-0.7233845	3.1348039	-3.0058901	0.009528107
Krt80	-1.6064390	0.9007339	-3.0018397	0.009604608
Cd83	-0.5403002	3.3728346	-2.9954352	0.009726816
Itga8	-0.9893483	1.9097706	-2.9948982	0.009737132
Efr3a	-0.6584383	6.9045819	-2.9893129	0.009845071
Cdc14b	-1.244448009	0.596619931	-2.977685378	0.010073586
Grip2	-1.012436713	0.970898138	-2.977041018	0.010086402
Tfeb	0.548417377	2.620478402	2.976974671	0.010087722
Fam198b	0.542124733	5.299488439	2.972479246	0.010177591
Rhoc	0.501499683	4.556880527	2.964298482	0.010343165
Gstt1	-0.456746587	3.262011223	-2.957652591	0.010479628
Sqle	-0.376642277	6.379330241	-2.957570873	0.010481317
Cds1	-0.325531006	5.805152886	-2.955927203	0.010515345
Gm11992	1.236054331	-0.150157809	2.955245599	0.010529488
Rnf152	-1.01298609	3.432585912	-2.953116717	0.010573782
Dkk3	-0.504307642	8.156814003	-2.95106918	0.010616557
Fads3	-0.461043899	3.988241713	-2.94696987	0.010702708
Zdhhc15	-0.4148846	4.057442844	-2.945615589	0.010731321
Rgs14	0.470656127	6.224145897	2.945092807	0.010742386
Uhmk1	-0.320322799	6.473544242	-2.944273474	0.010759751
Tsc22d3	-0.350484564	6.477355487	-2.940717047	0.010835446
Frrs1l	-0.279635685	7.763192676	-2.938917953	0.010873937
Pcdha9	-0.985035636	1.037423699	-2.938693125	0.010878757
1700040L02Rik	0.812239669	2.16024324	2.938491347	0.010883084
Pdlim1	-0.690850666	2.729558491	-2.938443988	0.0108841
S100a16	0.465585875	7.127548175	2.936340874	0.010929309
Mbd2	0.337237906	6.105937983	2.930717443	0.0110511
Gpsm1	0.489856915	4.863788077	2.929275062	0.011082553
Zfp953	0.680257515	1.582688291	2.928285595	0.011104181
Sfxn2	1.369269677	-0.720168617	2.925654383	0.011161897
Mtmr12	-0.32679285	5.120186472	-2.922914861	0.011222302
Prss12	-1.164700085	4.464454209	-2.922839145	0.011223976
Hist1h1c	-0.537020205	3.208715185	-2.921615997	0.011251054
1110008L16Rik	-0.496171429	2.9149092	-2.920886844	0.011267226
Kcnc4	-0.824208962	4.592806296	-2.918460013	0.011321217
Tnnt2	-1.653873024	-0.275303092	-2.916374573	0.011367816
Klk6	0.477804466	4.077756615	2.914306616	0.011414211
Angptl3	2.523179016	-1.567538198	2.914199148	0.011416627
Vamp1	-0.685980558	6.376779445	-2.909877533	0.011514206
Fbln5	0.6831683	3.216570586	2.907897371	0.01155919
Sgcz	0.612329714	2.55186309	2.905856742	0.011605729
Nr4a2	-1.586294523	4.347573008	-2.901894181	0.011696625
Pls3	-0.553249542	7.83947569	-2.899145321	0.011760092
Cd33	0.546707636	2.326412981	2.898049658	0.011785483

Mum1l1	0.577416133	3.461319245	2.897649719	0.011794765
Acap3	-0.445843118	6.787106767	-2.897278503	0.011803387
Kcne1l	0.633583447	3.186795822	2.896062767	0.011831666
1500017E21Rik	0.932221662	0.948430092	2.893655366	0.011887861
Olfm2	-0.63804251	6.007204865	-2.890883169	0.011952896
Lsp1	-0.862105383	2.122688384	-2.8881786	0.012016682
Gm11110	1.116445808	-0.031855881	2.887146415	0.012041113
Aaed1	0.477391066	2.842218996	2.886215831	0.012063182
Mapk11	-1.016931786	3.139608633	-2.886088282	0.01206621
Ankrd2	1.159021095	-0.613988485	2.882699971	0.012146918
Cxxc5	-0.534433763	5.716250115	-2.879278281	0.01222896
Faxc	-0.400414919	5.974537398	-2.877803441	0.01226449
Kcnc2	-0.896223126	5.236952893	-2.876827974	0.012288045
Emp2	0.496611735	4.600905069	2.875213788	0.012327122
Hsf4	-1.057876831	1.891096666	-2.872057822	0.012403875
Rap1gap2	-0.493986038	7.405989038	-2.8707168	0.01243663
Agbl4	-0.77574059	2.169205231	-2.864220924	0.012596502
Atp6ap1l	0.69523181	5.162913883	2.861253084	0.012670214
Pwwp2b	-0.389705487	4.781075508	-2.860491142	0.012689206
Kcna4	0.4641282	6.626389124	2.859624315	0.012710847
Car14	0.420255921	3.790889062	2.857601183	0.012761496
Pgm2l1	-0.800569928	7.3175235	-2.857576464	0.012762116
Rbp4	0.385561268	5.320261705	2.853538038	0.012863816
E030013I19Rik	-2.56147861	-1.259059167	-2.851889415	0.012905562
Bhlhe41	-0.470760741	4.548597583	-2.847707341	0.013012055
Nr2f2	-1.174925577	1.973537763	-2.844630795	0.013090946
Fzd1	-0.572502638	2.596792556	-2.843098167	0.013130422
Ehd3	-0.401373444	6.20185296	-2.842576809	0.013143877
Stk32a	0.576878103	5.025578225	2.838896377	0.013239246
Pdk1	-0.358363995	5.616521019	-2.837831692	0.013266961
Snn	0.284827899	8.646945057	2.837658082	0.013271485
6330415G19Rik	-1.292986599	-0.541284405	-2.836575542	0.013299732
Lypd6b	-1.032696036	4.224365788	-2.835306151	0.01333293
Ptpn14	1.054593955	0.731087681	2.833687221	0.013375387
Zcchc12	0.630293197	6.339240206	2.824813576	0.013610465
Glt8d2	-1.116226679	2.763280183	-2.824375819	0.013622166
Ripply3	1.178837137	-0.266859659	2.823117703	0.01365585
Hsd17b10	0.434743806	5.976533779	2.82081509	0.01371771
Ccno	0.696440863	1.942790061	2.820790572	0.01371837
Anxa5	0.267518004	6.216084668	2.819244607	0.013760058
Slc8a1	-0.870605297	6.449467138	-2.81706966	0.013818917
Ube2cbp	0.763327549	1.850204626	2.815484486	0.013861971
Cmbl	-0.596489841	4.044064062	-2.814575045	0.01388673
Tmem41a	0.365144899	4.992830409	2.81298655	0.013930081
Cadm4	-0.302329376	7.903580276	-2.811415624	0.013973083
Ctps	-0.318481185	5.726174241	-2.80908907	0.014037008
Ttc9b	-0.587524146	6.840664008	-2.808738407	0.014046668

Adrbk2	-0.765336402	4.920639561	-2.808286737	0.014059119
Fabp4	1.215645557	0.029817842	2.80775931	0.014073673
Garnl3	-0.551771467	5.875527205	-2.807239099	0.014088042
C1ql3	-0.978590564	6.505301602	-2.806905605	0.014097262
Pamr1	-0.630553305	3.513956508	-2.797151157	0.014369543
Bcl2a1b	0.815838988	0.148606523	2.794653428	0.014440086
Mpped2	0.30999454	6.802150017	2.790894109	0.014546899
Mtmr11	0.515368897	2.340584934	2.790867936	0.014547645
Tll1	-0.911012653	1.058654014	-2.785936206	0.014688948
Cbx8	0.450037507	3.441047023	2.785642114	0.014697416
Dyrk3	-0.634224123	2.41490984	-2.785055024	0.014714336
Mrpl16	0.328834295	5.756033628	2.782623529	0.014784614
Acot3	-1.050021413	0.427773726	-2.78039027	0.014849451
Dcaf4	0.419779433	4.695865606	2.780018773	0.014860263
Fam210b	0.413136115	5.182028095	2.773163758	0.015061164
Il20ra	0.765352459	1.477330957	2.771990275	0.01509582
Ltbp1	-0.897074906	1.64174471	-2.771829177	0.015100583
Lrrc2	-0.939761834	0.328268995	-2.768458459	0.015200594
Kcna6	-0.585517116	6.404570296	-2.768450889	0.015200819
Trhde	-1.106010901	5.327249075	-2.766387913	0.015262348
Thsd7a	0.724909869	5.404522685	2.75723826	0.015538182
Magohb	0.490441959	3.641803049	2.757004036	0.015545306
Gfra2	-0.92939102	4.290638912	-2.75585218	0.01558039
Isl1	0.509362353	4.075465047	2.753822545	0.015642396
Mmp9	-1.953275982	-1.660419915	-2.752811581	0.015673372
Nrn1l	1.018509473	1.868652367	2.7518235	0.015703704
Grik4	-0.816649826	3.551973772	-2.751253916	0.015721215
6530403H02Rik	0.797309423	2.025692524	2.750554988	0.015742729
Prrg3	-0.470442606	4.830162216	-2.750002618	0.015759751
Pnlip	1.210731408	0.673763	2.743481661	0.015962073
4732471J01Rik	-0.784391933	1.451012529	-2.742614235	0.015989176
Fxyd6	-0.554182845	6.404602998	-2.740575654	0.016053049
Adcy1	-0.720077131	7.17659231	-2.739314363	0.016092693
Cadps2	-1.100163987	5.660494756	-2.736997452	0.016165764
AB124611	1.27928827	-1.025599091	2.733852818	0.016265457
Tmem163	-0.619212271	4.570524337	-2.733332397	0.016282014
Lrfn2	-1.025586761	3.678200391	-2.730023967	0.016387651
Stmn1	-0.506794368	7.995758476	-2.729530369	0.016403468
Adrbk1	-0.48167535	6.877238981	-2.728546855	0.01643503
Crtac1	-0.345225216	5.557184502	-2.72853556	0.016435392
Snap23	0.489167884	4.043302716	2.727542081	0.016467334
Krt10	0.429616946	5.165938444	2.724412949	0.016568337
Ikzf3	1.365514814	1.401357377	2.722355886	0.016635063
Cck	-1.008744626	7.834012835	-2.722324423	0.016636085
Hlf	-0.325809726	7.750505549	-2.722126501	0.01664252
Zfp708	0.475689417	3.504050239	2.721143	0.016674528
Pigh	0.449736264	3.414891181	2.717633903	0.016789223

Lrfn1	-0.757578935	3.439278409	-2.717284094	0.016800699
Glp2r	-0.843969995	1.517821327	-2.716681876	0.016820473
Peg10	-0.944878248	2.309967808	-2.716348848	0.016831417
Slc23a2	-0.272112485	7.387399814	-2.714798771	0.01688245
Mvd	-0.38997982	3.65739417	-2.71014607	0.017036537
Brca1	0.761829869	2.129237047	2.709458012	0.017059439
1700052K11Rik	-0.513662729	2.313435452	-2.708448739	0.017093088
St8sia3	0.361964709	8.928332392	2.706934341	0.017143698
Dok7	-0.624891095	2.28276458	-2.705241514	0.017200444
Rpl10a	0.365523749	6.954559975	2.705234975	0.017200664
Slc26a4	-1.205412925	-0.399589651	-2.703204282	0.017268978
Rspo3	-0.824203279	2.335776005	-2.702863364	0.017280472
Cib2	-0.502892715	4.277251131	-2.702593226	0.017289585
Gls	-0.359049697	8.363012902	-2.700205109	0.017370354
Tmem215	-1.071186069	1.781096578	-2.696505002	0.017496221
Rap2a	-0.330131012	7.179295563	-2.695943909	0.017515385
Gpd2	-0.547691304	6.806249292	-2.695316947	0.017536823
Cpne7	-0.595461999	3.25334861	-2.69330893	0.017605655
Smad9	-0.851187727	1.643659508	-2.692612279	0.017629597
Sema7a	-0.356134155	7.635363007	-2.692283836	0.017640895
Papl	-1.583486254	-1.1315138	-2.689589338	0.017733852
Miip	0.666135599	1.299030061	2.689172151	0.017748287
Mllt10	0.432008136	4.664855503	2.688526287	0.017770657
Insm1	0.693793728	2.163470894	2.688153844	0.017783569
Depdc1b	1.312326034	-0.697256414	2.687733071	0.017798168
Hspb8	0.464660144	5.052130992	2.686411667	0.017844089
Sytl2	-0.600347002	5.018110165	-2.682498755	0.017980748
2900041M22Rik	-1.395143925	-0.306236003	-2.681273141	0.018023761
Syt13	-0.763650956	6.843621064	-2.676720514	0.018184414
Me1	-0.323606209	5.418819945	-2.676550767	0.01819043
Csrnp1	-0.463112065	3.531952543	-2.675723901	0.018219767
Mturn	-0.376294151	7.364991729	-2.675590375	0.018224509
Tuba8	-0.790054362	2.992881239	-2.674484188	0.018263837
Eif4e3	0.391572654	4.1477053	2.672759932	0.018325304
Olfm1	-0.630645771	8.233522116	-2.670043401	0.018422551
Rnls	0.79913105	1.109143583	2.668475135	0.018478921
AF529169	-1.514393621	-0.931784036	-2.668430889	0.018480513
Tac2	-2.326996715	0.19876494	-2.667458763	0.018515542
Rtn4r	-1.124048285	3.759133324	-2.665058385	0.018602311
Slitrk6	0.842321814	2.11362411	2.663962044	0.018642073
Syndig1	0.425760972	6.401391782	2.662570556	0.018692658
Mcm7	0.448054082	3.423596745	2.661726372	0.018723411
Gabra3	-0.619731994	7.195187603	-2.660672163	0.018761885
Gabra5	-0.502172112	6.173110469	-2.660114541	0.018782266
Frmd6	-0.464635329	3.911780399	-2.659365699	0.018809671
Rgs13	-1.527081221	-0.771525066	-2.657294024	0.018885688
Anxa7	-0.294868572	7.221559247	-2.655559104	0.018949577

Tmem25	-0.576146829	4.139529572	-2.655175308	0.018963739
Ramp3	-0.474440081	4.169533229	-2.6534417	0.019027835
Gpd1l	-0.235291196	7.681206809	-2.652728001	0.019054284
Kcnt2	-0.668859998	4.659534829	-2.650927774	0.019121156
Chia1	0.667426362	2.322670627	2.650718649	0.019128939
Smpdl3b	0.643508847	2.737080871	2.649300755	0.019181789
4933407L21Rik	0.664846971	2.03069526	2.648019496	0.019229669
Nkiras2	0.423009928	3.821866672	2.647215032	0.01925979
Neurod6	-1.134518449	6.791757558	-2.646916241	0.019270989
Ipo5	-0.391639454	6.810159725	-2.643268042	0.019408239
Slc5a11	1.389482438	-0.705598774	2.643149294	0.019412722
Cml3	-1.522328494	-1.210707395	-2.641220422	0.019485687
Lrriq3	1.716010339	-0.992088738	2.640640544	0.019507674
Obfc1	0.423941294	3.349441691	2.639449291	0.019552919
Extl1	-0.474860849	5.119969465	-2.637588131	0.01962381
Aldh3b1	0.53505979	2.343722563	2.635064145	0.019720347
Rab40b	0.343533023	6.273387848	2.634093159	0.019757607
Bdnf	-1.161256045	4.167787259	-2.633349819	0.019786177
Sulf1	-1.134390382	3.162126511	-2.631522454	0.019856583
Gucy1a2	-0.325967909	6.733698966	-2.630899856	0.019880626
Ciart	-0.561278826	3.48215714	-2.630578801	0.019893036
Clstn2	-0.656381054	4.916337429	-2.629462579	0.019936238
Hmgcs1	-0.356541955	8.326648972	-2.629418095	0.019937962
Ovol2	-1.597290119	1.613945136	-2.623105521	0.020184018
Myo1c	-0.553654964	2.726439289	-2.619915236	0.020309487
Klhl13	0.541614016	8.790981015	2.618855288	0.02035134
Dand5	0.440466019	2.873368817	2.617855284	0.020390902
Hpgd	0.317872411	4.266489595	2.617504146	0.020404811
Acadm	0.26246944	5.828886161	2.616183791	0.020457196
Khk	0.398651128	3.347085657	2.615534273	0.020483013
Hrh1	-0.763698255	3.045722842	-2.615477271	0.02048528
Satb1	-0.85789033	4.845551533	-2.613183115	0.02057673
Mns1	1.949842687	-1.450010795	2.611833767	0.020630703
Tagap1	-0.554859836	2.855397584	-2.611730004	0.020634859
Mpped1	-0.512964241	7.437232937	-2.610351773	0.020690138
Pdgfd	0.575986897	1.837021709	2.610134111	0.020698882
Apoe	0.338485449	10.46087465	2.610055243	0.020702051
Lppr1	0.461095548	5.45478696	2.609814632	0.020711721
Atg7	-0.538925761	3.404009189	-2.608576625	0.020761549
Dach1	0.539626464	5.981365451	2.606632165	0.020840044
Adra1d	-1.122604723	2.259675644	-2.605397616	0.02089003
Slc17a7	-1.007107114	10.26138464	-2.605371927	0.020891071
Itpr3	-1.207490033	-0.276601051	-2.601540454	0.02104695
Adra2b	1.08198088	0.332485473	2.60145125	0.021050593
Ppil6	0.812062257	0.995846914	2.599948653	0.021112041
Sh3gl2	-0.525726457	8.064831906	-2.599150104	0.021144767
Stx1a	-0.649467796	6.736366152	-2.598521635	0.021170558

Cbln2	-0.987452933	4.290235609	-2.597651411	0.02120632
Necab3	-0.865011321	5.201873788	-2.596226338	0.02126501
Dnaic1	0.669760704	2.035127529	2.595969649	0.021275598
Slc38a4	0.673899081	2.217397685	2.59169244	0.021452778
Mef2c	-0.511986446	8.08545984	-2.590815056	0.021489298
Isoc1	0.399068445	6.068312988	2.590001882	0.0215232
Stk36	-1.15363671	-0.169354719	-2.586505602	0.021669549
Dsel	0.262464277	6.446065428	2.586007618	0.021690472
Slc3a2	-0.2353891	7.319504705	-2.585815819	0.021698536
Gdpd2	0.895883001	1.052360532	2.57912996	0.021981441
Crym	1.080312598	6.471137477	2.578774478	0.021996582
Sumo3	0.400951003	8.733748206	2.576355014	0.022099902
3632451O06Rik	-0.527455285	4.347924534	-2.575633502	0.022130803
Jmjd6	0.302022516	4.651091934	2.572538076	0.022263851
Zkscan7	1.076126085	-0.099648836	2.572429321	0.02226854
Npnt	-0.465457703	2.560469073	-2.568819148	0.022424718
Asb11	0.531082023	3.751226276	2.56814594	0.022453958
Cd180	0.746322205	1.252267297	2.567064063	0.022501025
Asic2	-0.5542361	4.961989537	-2.564762408	0.022601475
Exog	-0.26793444	5.319545992	-2.564420443	0.022616436
Cacng1	0.954797138	0.907674019	2.564279889	0.022622588
Cds2	-0.228472381	9.332295154	-2.563135315	0.022672746
Gm15421	0.81472154	1.197065997	2.561794505	0.02273164
Kcnq3	-0.370544958	4.591794963	-2.561493502	0.022744881
Rnd1	-0.591030385	3.793978112	-2.560954414	0.022768615
Nadk2	0.288912143	6.882711006	2.560329933	0.022796138
Lag3	-0.717639886	1.020833431	-2.559872294	0.022816328
Camk2n2	-0.716296279	3.97992339	-2.557440554	0.022923901
Rpl7a	0.33637817	6.99373677	2.556536281	0.022964028
Tigar	-0.326837813	5.179508223	-2.556122617	0.022982406
Casp6	0.468756006	1.966817687	2.556080693	0.02298427
A2m	1.061266379	-0.829583576	2.554584147	0.023050884
Tcap	-1.585902099	-0.288660919	-2.554023786	0.023075874
Efcab1	0.678353063	2.466003137	2.553907034	0.023081084
Nol9	-0.362912155	4.129238003	-2.553801245	0.023085806
Il4ra	-0.582673032	1.229805158	-2.552482492	0.023144746
Zyg11b	-0.318854403	8.145979784	-2.552169103	0.023158773
Rgs12	-0.758991621	5.218608856	-2.548848713	0.023307903
Gp2	2.037996045	-1.962315525	2.547908935	0.023350279
Cpne4	-0.84979193	5.365742735	-2.546506737	0.023413644
1700028P14Rik	0.796095849	0.404079993	2.546301505	0.023422932
Slc4a10	-0.350414316	8.084130639	-2.545300779	0.023468274
Tfr2	0.83505781	1.82382205	2.542638256	0.02358932
Sgk3	0.397340276	5.537839998	2.540816978	0.023672466
Pifo	2.408610907	-1.447569902	2.540689169	0.023678312
Grm8	-0.624454742	3.864134742	-2.539682652	0.023724394
Tnfrsf19	0.279417278	7.073994455	2.539359512	0.023739207

Dclk1	-0.280420604	9.676076184	-2.538052088	0.02379923
Ppm1e	-0.808103139	6.372299601	-2.537302003	0.023833732
Cd24a	0.938818478	3.958136849	2.536770152	0.023858225
Henmt1	0.648095854	0.854873446	2.536290829	0.02388032
Slc4a8	-0.673491416	4.224501874	-2.535726797	0.023906345
Il17ra	-0.646480655	3.488205459	-2.533026117	0.024031334
Sidt1	-1.081851948	3.22984693	-2.53298858	0.024033076
Trim12a	1.189607854	-0.106331481	2.532978608	0.024033538
Kbtbd7	-0.198849409	7.030661984	-2.529182525	0.024210301
Bok	-0.623775118	5.538841034	-2.529012577	0.024218244
Rapgef4	-0.351086735	9.700375598	-2.528452729	0.024244427
Cabp1	-0.391111674	5.428783577	-2.52801804	0.024264775
Ccnb2	2.155998558	-1.941733394	2.527952387	0.02426785
Chrnb3	-1.616413218	-0.601909312	-2.526591964	0.024331647
Sord	-0.289368018	4.757894333	-2.525384686	0.024388397
Efcab12	1.871244993	-1.495579054	2.523616017	0.024471765
Tub	-0.593367534	4.869771422	-2.522779106	0.02451131
Syt16	-0.240273055	6.526628242	-2.521938618	0.024551085
Nkx2-2os	0.903953504	0.821830537	2.520896939	0.024600467
C030013G03Rik	0.812915514	3.16761153	2.519050608	0.02468823
Acad11	-0.386366384	4.410251947	-2.518509987	0.024713985
Tead2	0.591665461	1.474600757	2.515525361	0.024856634
Fam43a	-0.442267478	4.542016586	-2.514728747	0.024894841
Cdkn3	-1.42697853	-1.326091649	-2.5146247	0.024899836
1700084C01Rik	0.605792815	3.305167685	2.514462205	0.024907638
Kcng4	-1.00018451	2.594119491	-2.513572347	0.024950405
Gdf10	-0.384702491	3.279827406	-2.512090642	0.025021774
Pip4k2c	-0.264535755	7.166253117	-2.510444649	0.025101285
Entpd3	0.409898241	3.792328642	2.510290269	0.025108755
Limk1	-0.51052623	4.761023317	-2.508403669	0.025200214
Trpv2	-0.452446756	3.825548733	-2.508267529	0.025206826
Scgn	-1.829320771	-1.828626845	-2.50620382	0.025307262
Plcb4	-1.191339919	2.658877241	-2.505921092	0.025321052
Disp2	-0.859234001	5.616143354	-2.505437405	0.02534466
Syp	-0.441384209	9.988609848	-2.504605646	0.025385305
Slc13a3	0.339231663	4.006348568	2.502662148	0.025480523
Sstr2	-0.83887223	4.729846686	-2.499559312	0.025633251
Rsad1	-0.424926023	2.922846065	-2.499261222	0.02564797
Xpnpep3	-0.757927304	1.82696554	-2.498845652	0.025668503
Fam105a	0.347705977	6.295769927	2.497979878	0.025711331
Fam78a	0.558822726	1.914173416	2.495905255	0.025814237
Gng4	-0.506547023	4.995895888	-2.492941951	0.025961909
Chaf1b	2.167260831	-2.586712825	2.492768375	0.025970584
Rhbdl3	0.411495877	4.730844775	2.492165971	0.026000712
1500015L24Rik	-1.914179078	-1.36187593	-2.490534555	0.026082474
Cnih3	-0.837308415	5.600794259	-2.489340726	0.026142461
Spsb2	0.807189441	0.965843381	2.489264034	0.026146319

Klhl12	-0.217587848	5.781297956	-2.488775463	0.026170911
Ppp5c	-0.342484627	6.30919649	-2.488123126	0.026203779
Lypd1	0.384717772	6.796670688	2.487760009	0.026222092
Smyd2	-0.460249056	4.80627406	-2.486052239	0.026308385
Tbr1	-1.088324604	5.608810911	-2.485117816	0.026355716
Gpx1	0.413343309	8.254495486	2.484878627	0.026367845
Tmem74	-0.667055347	3.439830914	-2.484091589	0.026407791
C130060K24Rik	0.688664912	2.33725893	2.483662657	0.026429586
Erbb2	-1.045623246	0.010266422	-2.483089937	0.026458714
Ccnd1	-0.404226012	5.475238738	-2.482779291	0.026474526
Atp6v0e	0.376442925	5.66399775	2.481810803	0.026523881
Grm2	-1.265963391	1.469814609	-2.481400738	0.026544805
Vcam1	0.383641158	5.335945621	2.481181818	0.026555982
Cdk14	-0.624890813	6.533003804	-2.481165916	0.026556794
Fbxo2	0.24852986	6.431958048	2.480378688	0.026597024
Efhd2	-0.589807712	7.358346326	-2.480106986	0.026610923
Vsnl1	-0.712306548	9.120457964	-2.477582659	0.026740385
Cd163	0.785305616	0.956680812	2.477342758	0.026752719
Tnnc1	-1.038540785	2.680494722	-2.475577972	0.026843626
Itgb1bp1	0.461375341	6.520246376	2.47539092	0.026853278
Lsm10	0.410969745	3.311387375	2.474465115	0.026901102
Hpx	1.028173154	0.231877779	2.47383357	0.026933773
Slc25a35	-0.798958112	1.375814271	-2.472331439	0.027011632
Cyth2	-0.283216551	6.781439997	-2.470348391	0.027114748
Cldn14	1.082929898	0.980493916	2.470219442	0.027121466
Ggnbp1	-2.039513743	-1.300282183	-2.469897907	0.027138225
Dpy19l3	0.357837296	6.32617622	2.469702979	0.02714839
Ttc34	0.464614046	2.177150691	2.469634208	0.027151977
Shcbp1	0.723334074	0.905447743	2.469214806	0.027173862
Tnfrsf11b	-0.746450564	0.707029821	-2.467796935	0.027247975
Kcng2	-1.106601647	0.664134618	-2.466679399	0.027306526
Myt1	0.63453222	2.032618229	2.463945198	0.027450285
Rftn2	0.352365227	4.923068013	2.461473895	0.027580845
Acta2	0.47547753	4.068149248	2.457724144	0.02778008
Rarb	0.476640076	6.882963595	2.457631446	0.027785023
Hapln4	-0.893545843	4.93240862	-2.456142713	0.027864518
Emx1	-0.771594683	3.065661962	-2.455182947	0.027915883
Wrap53	0.293661257	4.074728803	2.454714428	0.02794099
Asb1	-0.211856275	6.328592907	-2.454325707	0.027961837
Scube3	0.823982998	2.341215706	2.454218949	0.027967566
Rsph3a	-0.645906823	1.809579481	-2.453496192	0.028006374
Mrps9	0.29083807	5.787935586	2.453448559	0.028008934
Ak5	-0.868132147	5.629911886	-2.451562049	0.028110483
Slc35f4	-0.736709388	3.94268652	-2.450983218	0.028141711
3110035E14Rik	-0.932401849	8.769197104	-2.448430047	0.028279853
Fbxl16	-0.371241439	10.15342437	-2.447503154	0.028330163
Myom3	0.822587475	1.404497764	2.445881191	0.028418407

Abcc10	0.740372524	1.992148615	2.4457314	0.02842657
Rtn4rl2	-1.4329377	1.944145972	-2.444632299	0.028486532
Net1	-0.431320044	4.690242904	-2.444436302	0.028497238
Ido1	0.7700445	6.575661922	2.444320304	0.028503576
R74862	-0.513494323	2.140678083	-2.443913435	0.028525816
Peli1	0.291896805	6.42370265	2.443890506	0.02852707
Prkar1b	-0.467222535	9.005359922	-2.441797377	0.028641754
Nudt17	-0.527255496	1.434987741	-2.440585212	0.02870837
Ncald	-0.789008237	9.976315564	-2.43946978	0.0287698
Ptpn3	-0.894381596	3.799600585	-2.435870517	0.028968882
Ptchd2	-0.552989473	3.019071491	-2.435824165	0.028971454
Gpr12	0.489120275	4.959014031	2.435064233	0.029013659
9130024F11Rik	-1.044920014	3.178705054	-2.43470988	0.029033358
Cenpu	-1.188873663	-0.67596208	-2.433949369	0.029075681
Shisa2	0.53118528	3.552372661	2.432338535	0.02916552
Coro1a	-0.377446881	6.528596853	-2.431694203	0.029201529
Retn	2.303896764	-1.84445527	2.431390941	0.029218492
Nwd2	-0.961506287	3.242306685	-2.430999348	0.029240409
Syngr1	-0.344744497	8.848204134	-2.430688248	0.029257833
Deptor	-0.620773324	3.801840837	-2.4303846	0.029274849
Ptpn23	-0.922063744	2.15290732	-2.427911577	0.029413783
Cckbr	-0.693987711	5.062365102	-2.42629448	0.029504972
Zfp58	0.401848728	3.936951123	2.425725093	0.029537144
Elmod1	0.278442983	9.689503245	2.424838083	0.029587329
Ccdc88c	0.849555159	0.587248168	2.424595923	0.029601044
Wnt9a	-0.857504405	2.312570598	-2.424096896	0.029629326
Ccl6	0.608358659	2.540165702	2.421917026	0.029753172
Ffar3	1.628571382	0.530113381	2.421573692	0.029772723
Fam163b	-0.577502051	5.232500653	-2.420732125	0.029820698
Fgf10	-1.030626105	3.056603105	-2.417935265	0.029980666
Zfp882	0.379266971	3.491123125	2.41596995	0.030093562
Dkkl1	-1.016551735	3.228861845	-2.41466391	0.03016881
Mfsd4	-0.864118827	3.990151778	-2.414496635	0.030178461
B3gat2	-0.841866006	3.605170428	-2.413661287	0.030226699
Fam216b	2.751169305	-3.927863201	2.412904274	0.030270477
Gin1	0.398176739	3.843880259	2.412317289	0.030304464
C330018D20Rik	0.361719493	5.109744702	2.411707895	0.030339787
Mre11a	0.562973178	2.924934543	2.410331446	0.030419715
Lnx2	-0.604821624	0.936733545	-2.409845605	0.030447975
Slc30a3	-0.86576196	4.703158101	-2.40916872	0.03048739
Nt5dc3	-0.47389954	6.089770954	-2.408678477	0.030515966
Syt12	-0.305510987	5.420699486	-2.408538911	0.030524106
Vip	-0.708352763	4.123337688	-2.408483608	0.030527332
Gulp1	0.557001077	4.187883261	2.40678631	0.030626502
Tmem145	-0.989120239	1.369202693	-2.405745732	0.030687452
Vcl	-0.75233281	3.322167849	-2.40552124	0.030700616
Nptxr	-1.65247979	-0.618809004	-2.40482624	0.030741406

Sprn	-0.574104208	5.441266839	-2.40339993	0.030825277
Enpp5	0.239184283	8.53879865	2.402121165	0.030900658
Pgam2	0.548856854	4.307466408	2.402037982	0.030905568
Ckap2	2.405329726	-2.333499812	2.40179909	0.030919672
4930452B06Rik	-0.492217462	2.476840682	-2.401241031	0.030952643
Nptx1	-0.90285224	7.142684037	-2.400950267	0.030969834
Acot5	-0.818712747	0.841553836	-2.400804932	0.030978431
Cdc27	-0.351761566	6.08843813	-2.400504232	0.030996225
Gprasp2	-0.252041885	6.334854829	-2.399860522	0.031034349
Sult4a1	-0.300792809	9.425075454	-2.399584062	0.031050736
Atp6v1a	-0.267628285	9.846191764	-2.398620121	0.031107937
Hfe	0.478488765	2.683058727	2.398570045	0.031110912
1190002N15Rik	-0.423061653	5.874791281	-2.398490704	0.031115625
Kcnj3	-0.600467113	6.22194666	-2.397927398	0.031149107
Tm4sf5	-1.659123777	-1.487086202	-2.396219363	0.031250838
Dgkz	-0.559056911	7.133987085	-2.39556721	0.031289764
Pgbd1	-1.179955968	0.100566504	-2.39521293	0.03131093
Apbb3	-0.304772018	4.740021399	-2.395108362	0.03131718
Bmp3	-1.400956583	2.292596943	-2.393823437	0.031394074
Pcsk9	0.781857181	2.533302079	2.393170558	0.031433214
Myl6b	-0.529129204	2.742023733	-2.3930445	0.031440776
Dnajc8	0.241874691	7.333335769	2.392895032	0.031449745
Tbc1d24	-0.492837273	5.693652994	-2.392648528	0.031464542
Nckap1	-0.261233239	9.571971541	-2.391379693	0.031540813
Zfp458	-0.425767214	2.108223756	-2.389180894	0.0316734
Ngb	-0.851209388	1.220631372	-2.388561567	0.031710841
Plxna4	-0.879028919	2.934303798	-2.388314066	0.031725815
Ywhag	-0.498018806	9.026502818	-2.388261239	0.031729012
Necab2	0.474395185	6.69536917	2.387714596	0.031762112
Me2	-0.45284045	6.512305827	-2.386212392	0.031853242
Ifi27l2a	0.974321703	2.193908145	2.386145995	0.031857275
1700007K13Rik	1.479496048	-0.406966829	2.385225311	0.031913257
6430531B16Rik	1.096095398	-1.231542551	2.384815379	0.031938213
Fkbp1b	-0.458212518	4.122293479	-2.384623412	0.031949906
Dusp6	-0.42111147	6.643086763	-2.38161878	0.032133453
2900097C17Rik	-0.23484428	8.302982088	-2.381534548	0.032138613
Prrt3	-0.573483016	4.677509482	-2.381509497	0.032140148
Lnp	-0.225728427	6.428537794	-2.381197536	0.032159266
Jdp2	-0.580562964	4.273936863	-2.38024883	0.032217473
Fdft1	-0.258204619	6.976019075	-2.377279142	0.032400323
Itgal	-1.55507431	-1.157846073	-2.377001263	0.032417483
Dleu2	0.473640734	3.771356493	2.373274895	0.032648435
Prkar2b	0.269096089	8.151187444	2.371963898	0.032730058
C630043F03Rik	0.398079285	4.614137996	2.370308599	0.032833395
Cblb	-0.565913821	2.82292434	-2.370063853	0.032848701
Ptn	0.292114735	8.43768936	2.36913074	0.032907115
Lpgat1	-0.328061167	8.113255712	-2.368504172	0.032946395

Rps23	0.456461065	9.170119853	2.364327384	0.033209379
Ap1s1	0.396391391	9.580963347	2.360731571	0.033437378
Nkx3-1	1.267138404	-0.534374501	2.360078892	0.033478921
Rit2	0.307840041	7.911066757	2.359557058	0.033512171
Cmpk2	0.255469325	5.891826643	2.358157186	0.033601522
Tubb4b	-0.271791495	8.033500688	-2.356693163	0.03369521
Krt9	0.900740109	2.650424375	2.355921166	0.033744713
Sema5b	-0.70840958	2.804502908	-2.35588978	0.033746727
Grik2	0.298743247	6.273347792	2.353705912	0.033887144
Ccdc160	-1.41204518	-0.161824962	-2.352675505	0.033953589
Slc5a6	-0.284800725	4.268885687	-2.352655188	0.0339549
St6galnac4	-0.386427359	4.209521216	-2.352638759	0.033955961
Slc11a2	-0.267336774	5.255868735	-2.35214762	0.033987677
Gfm1	-0.293544829	5.296968412	-2.352094983	0.033991078
Arhgef25	-0.412917371	5.875726366	-2.350709249	0.034080724
Pfn4	0.308600647	3.708196449	2.348933073	0.034195957
Zfp628	-0.632805624	1.355675048	-2.348889333	0.034198799
Slitrk1	-0.538604998	5.474976082	-2.348505485	0.034223752
Acer2	0.516090828	4.371639797	2.347760701	0.034272219
Npl	0.408624433	4.387605652	2.34753487	0.034286928
Angptl1	-1.008210417	-0.185569511	-2.347175158	0.034310368
Col6a4	1.173547401	0.787533255	2.346404121	0.034360665
Pttg1ip	0.269610301	6.497954138	2.344453985	0.034488188
Tppp3	0.327394998	5.708566329	2.344326373	0.034496549
Ube2ql1	-0.62909358	6.132481083	-2.34093786	0.034719249
Siglech	0.309048751	4.005443244	2.340708444	0.034734376
Arhgap9	0.884189028	0.229711768	2.340622494	0.034740045
Asb2	0.5351508	1.743527875	2.340482596	0.034749273
Rassf5	-0.822118254	3.313308485	-2.338943856	0.034850935
B9d2	0.376625128	4.79885378	2.337476518	0.034948141
Faim2	-0.454064544	8.083007779	-2.337224042	0.034964893
Prr15	-1.710838833	-0.887944299	-2.335612138	0.035072021
Fam204a	0.311702224	4.867779336	2.33394143	0.035183385
Rsl24d1	0.224749827	5.784035177	2.333078474	0.035241038
Txndc5	0.225277876	6.256107365	2.332649292	0.035269745
Btc	-1.393987356	-0.612414524	-2.331558008	0.035342836
Rplp0	0.350913433	8.990118541	2.331244024	0.035363893
Atp5g2	0.271166297	5.804278577	2.330660185	0.035403078
Mrc1	0.601254025	1.779141189	2.329198485	0.035501362
Fxyd2	0.578792604	2.789481861	2.328678042	0.035536419
C1qc	0.249008816	6.48337554	2.328346317	0.035558781
Zfpm2	-0.923193472	2.641956641	-2.327812302	0.035594807
Npas2	0.746401802	4.085549026	2.326758689	0.035665989
Dleu7	-0.469299389	2.954873962	-2.326665551	0.035672288
4931428F04Rik	-0.384570695	3.946545058	-2.324737932	0.035802887
Tmem200a	-0.775063591	3.35612873	-2.324405563	0.035825451
Gla	-0.355868235	3.774526758	-2.32344336	0.03589085

Nmi	0.514958201	2.570313615	2.322512864	0.035954202
Wnt8b	-1.620203402	0.067774841	-2.322398457	0.035961998
2610316D01Rik	0.579050271	1.94235074	2.321999077	0.035989227
Mdfic	0.496191376	2.892299534	2.3203942	0.036098842
Lonrf2	-0.561213924	6.203370251	-2.319965902	0.036128149
Wee1	-0.273926647	4.804036415	-2.319680601	0.036147683
Ccdc28b	0.439202615	4.112636807	2.318908267	0.036200615
Fam102b	0.353974328	6.808922533	2.318666354	0.036217209
Neurod2	-1.085469731	2.888481819	-2.318569759	0.036223837
Ace	-0.49770506	4.59866179	-2.317901561	0.036269718
Pdlim7	0.280937555	4.715961963	2.317834101	0.036274354
Itfg2	-0.283253895	4.034553031	-2.317534557	0.036294942
Cmya5	0.585328102	1.463638654	2.317151756	0.036321269
Pde1a	-0.797196185	7.972648602	-2.315281397	0.036450161
Col19a1	-0.874392818	0.708834413	-2.312054093	0.036673582
Fam84b	0.454810575	5.539252383	2.311980507	0.036678691
4930539E08Rik	-0.57369401	2.029527598	-2.310763989	0.036763255
Nsg2	0.31344969	10.49646255	2.310608916	0.036774048
S100a1	0.350907384	7.475824843	2.308842365	0.036897209
Esr1	-1.404571393	0.246604185	-2.308803929	0.036899893
Ptprk	-0.696751596	4.119648562	-2.307996203	0.036956339
Eef1a1	0.301782673	12.12217053	2.305553048	0.037127573
Naa25	-0.26643088	5.230393631	-2.304960695	0.037169202
Slc1a1	-0.179944832	7.57548785	-2.302967113	0.037309629
BC028528	0.601397212	2.268467575	2.302666731	0.037330831
Nsf	-0.437732315	9.005703949	-2.302191126	0.037364425
Smarcd3	0.268318484	6.837410261	2.302022149	0.037376367
Nr2f1	-0.545762208	4.338298806	-2.301910514	0.037384259
Rpl18a	0.296883	8.028888631	2.301885302	0.037386041
Gfap	0.43199854	5.249317509	2.300810483	0.037462106
Tnfrsf21	-0.436053547	5.809775687	-2.297326303	0.037709685
Prepl	-0.273415101	8.842023863	-2.296789478	0.037747968
Npsr1	-2.11562701	-1.023708358	-2.29670328	0.037754119
Olfr1344	0.713772111	1.222597813	2.291309042	0.038140901
Capn3	0.421023385	2.163225577	2.291071169	0.038158042
Gm17750	0.822812816	1.945913588	2.290972218	0.038165175
Mblac1	-0.644690474	1.463672144	-2.289586012	0.038265232
9530077C05Rik	-0.343246924	2.845339618	-2.288417468	0.03834977
Arg2	0.618838774	4.66162209	2.288132427	0.038370418
Pfkl	-0.411978312	6.6545591	-2.286530412	0.038486661
Pdp2	-0.548776754	2.049082439	-2.282940762	0.038748334
Unc13c	0.759464442	4.805240643	2.28177442	0.038833716
Dcps	0.272122897	4.475306575	2.281266448	0.038870958
Doc2a	-0.94974015	3.243998622	-2.281142145	0.038880076
Cldn12	0.275445935	7.646083015	2.280272916	0.038943895
Cluap1	0.252027491	4.676230642	2.279654814	0.038989337
Mettl9	0.357782614	7.86495664	2.279484829	0.039001843

Xkrx	0.798965838	1.832682982	2.279213563	0.039021807
Serpina9	0.530358753	5.852089265	2.277474185	0.039150051
Crocc	0.994575202	0.511369444	2.27746746	0.039150548
Gpr6	0.501545666	7.030766567	2.277308043	0.039162321
Map3k9	-0.765854754	3.083019477	-2.277168253	0.039172648
Apex2	0.431846017	2.162461196	2.276858853	0.039195514
Snap47	-0.212693578	8.800053618	-2.275713682	0.039280256
Adgrg1	0.607117136	5.013348364	2.274399268	0.039377735
Rpa2	0.333087066	3.828948345	2.27362166	0.039435511
Elac2	-0.437673111	3.279830868	-2.272364	0.039529124
Icam1	-0.694887296	0.54445951	-2.272134902	0.039546199
Slc24a4	-0.54417653	3.157354819	-2.271872198	0.039565787
D430019H16Rik	0.343608493	7.449442247	2.270726119	0.039651351
Gm5113	-0.323090252	4.159648721	-2.270495893	0.03966856
Lbp	2.225201279	-1.334423705	2.269439999	0.039747577
Utp15	-0.30669122	5.048230797	-2.268085415	0.039849164
Dab1	0.382621358	5.575103116	2.267535205	0.039890496
Vwa5b2	-0.939072167	0.85767334	-2.267361639	0.039903543
Mcemp1	1.270488318	-1.289813368	2.267210423	0.039914913
Smc5	0.366028372	4.425656386	2.266335509	0.039980759
Ccdc155	-0.977128039	1.088037363	-2.265780498	0.040022582
Rpl11	0.375345384	8.859528136	2.264910033	0.040088259
Cd9	0.328743192	7.185893259	2.264640927	0.040108584
Senp8	-0.377859529	3.29760585	-2.262724931	0.040253573
Nat8l	-0.334915517	7.790900473	-2.262595139	0.040263413
Cartpt	-1.185719522	1.350327126	-2.262519528	0.040269146
Mfng	0.50325484	2.468800889	2.260336563	0.040434999
Slc6a17	-0.484023238	7.783568773	-2.259999243	0.040460684
Kcnj6	-1.062336117	2.069030726	-2.259243644	0.040518275
Pkia	0.21360418	8.864548775	2.258989092	0.040537694
Nbeal2	-0.929571421	-0.259867174	-2.258730977	0.040557394
Fbln7	1.209646474	-0.102232868	2.257845455	0.040625048
Snap91	-0.503558928	7.479297808	-2.25731385	0.040665713
Tmprss9	1.104856452	-0.513219766	2.256359699	0.040738797
Dnajc9	0.248384952	5.342655105	2.255375531	0.04081431
Zfp365	0.20509548	10.11445538	2.255145482	0.04083198
Kif20a	1.663649782	-2.335992683	2.25482387	0.040856695
Prss23	-0.637689633	5.541304949	-2.252764252	0.041015305
Usp13	-0.565187348	3.361560179	-2.252519328	0.041034205
Aaas	-0.358196155	3.379270352	-2.250998857	0.041151717
Mbtps1	0.259925284	6.682455975	2.25091846	0.04115794
Plekha7	-1.514490186	-0.169734006	-2.250893846	0.041159845
Nxph4	-0.869218131	2.335929562	-2.249322375	0.041281654
Uqcc3	0.331566791	5.043005051	2.246609089	0.041492766
Lancl2	-0.310297603	6.987355922	-2.246104639	0.041532127
Lap3	0.256353726	6.862506499	2.245387645	0.041588133
Sncb	-0.424249293	7.369826452	-2.244815575	0.04163287

Ablim3	-0.691121975	2.520590987	-2.244681651	0.041643349
Meis2	0.340130991	8.574527381	2.244182254	0.041682449
Rnase4	0.312085982	5.403739695	2.243731822	0.041717744
Fam175a	0.539088986	2.868437574	2.243428629	0.041741518
6-Mar	-0.216419354	8.565666124	-2.243212742	0.041758454
Slc20a2	0.273663664	5.650343703	2.243008299	0.041774498
Endod1	-0.221002186	6.908219928	-2.242567459	0.041809113
Glud1	0.215311013	8.372848524	2.23985307	0.042022844
Gabra1	-0.364478038	8.926261202	-2.239236082	0.042071568
Slc36a1	-0.531449075	5.327525983	-2.237525877	0.042206903
Crhbp	-0.682820358	4.090640325	-2.236394954	0.042296622
Irs4	-2.448071871	-2.608434024	-2.23571699	0.042350492
Ptger3	-1.071027543	0.673318634	-2.235213348	0.042390552
Lnpep	-0.233755276	5.885619673	-2.235010441	0.042406702
Prss16	-1.509418353	-0.269332912	-2.234366106	0.042458023
Mbd4	-0.411500758	2.452527153	-2.233483599	0.04252841
Pmm1	0.206690081	7.718463038	2.233150226	0.042555027
Spred3	-0.361935297	4.379135376	-2.231742482	0.042667598
Laptm4b	-0.236716997	6.835242125	-2.230913147	0.042734047
Cep97	-0.360222528	3.487647485	-2.230289019	0.042784118
A930017M01Rik	-0.295144177	3.91751624	-2.229963192	0.04281028
Slc43a2	-0.447289595	4.56829795	-2.229109553	0.042878892
Pafah1b1	-0.223501449	9.358402739	-2.22847522	0.042929943
Tcte2	-0.712793699	0.118228705	-2.228231191	0.042949598
Usp14	-0.203525399	7.79123826	-2.227905343	0.042975856
Ipcef1	-0.863876145	6.97698146	-2.227836323	0.04298142
Dnali1	2.448230616	-2.919289503	2.227627514	0.042998257
Mical2	-0.84280127	4.554226284	-2.226710928	0.043072236
Klhdc10	-0.227490947	6.639354012	-2.226275313	0.043107437
Zfp78	-0.614619688	2.138017238	-2.225910097	0.04313697
Il17rc	0.545910477	3.378750842	2.225069662	0.043205003
Fgd4	-0.441688753	4.454833274	-2.224392244	0.043259913
Kcna3	-0.668857771	1.926255981	-2.224073067	0.043285808
Cacna1d	-0.788467004	2.245766621	-2.223332204	0.043345969
Rapgefl1	-0.553469868	5.13260538	-2.223219302	0.043355144
Sebox	-1.12240729	2.496612331	-2.222519262	0.043412074
Nsa2	0.261928286	6.270095807	2.221264929	0.043514256
Ccng2	0.334986672	7.501072552	2.220128513	0.043607027
BB557941	-0.958427288	-0.130956547	-2.219970115	0.043619973
Ctsc	0.319429582	3.823428795	2.219554748	0.043653937
Satb2	-1.154884272	2.981494182	-2.219183361	0.043684325
Fap	-1.249873445	1.286329061	-2.218660273	0.043727161
Kirrel2	-0.477601353	3.259867368	-2.217542444	0.043818831
Trim17	-1.29068968	-0.348646921	-2.217399263	0.043830586
Sstr1	-0.535598205	4.956047513	-2.216863298	0.043874614
Erlin1	0.271296498	5.563009922	2.215888499	0.043954797
Trpc6	-0.404344962	3.026837358	-2.215421721	0.043993241

Cdh19	-0.406311201	3.79491046	-2.214281703	0.044087266
Sestd1	-0.468002008	4.704263674	-2.213922215	0.044116954
Xpo4	-0.393389668	2.351687146	-2.213868529	0.044121389
Aldh1a1	-0.39922543	6.122904203	-2.21381574	0.044125751
Ost4	0.354887871	5.233185419	2.212916931	0.044200075
Gria4	-0.331381851	6.717575268	-2.211982026	0.044277508
Tmem132c	-1.252976184	0.657704863	-2.211805954	0.044292105
Slc15a2	0.252871014	5.362456749	2.210901966	0.044367121
Marveld1	0.506919873	2.379981215	2.21037189	0.044411164
Grb7	0.63800711	2.069368864	2.207533831	0.04464767
Ifitm10	-0.639949813	1.709348424	-2.206662234	0.04472054
Lrrtm3	0.241025595	7.219538244	2.20611896	0.044766016
Sntg2	0.616679368	2.435026304	2.205666045	0.044803962
Osbpl6	-0.525763205	3.838229518	-2.20501561	0.044858509
Oscp1	0.258039057	4.88400077	2.204316879	0.044917175
Susd4	-0.331581926	5.984120775	-2.203706532	0.04496848
Prpsap2	0.257932205	5.917750987	2.203452687	0.044989833
Carhsp1	0.316598253	6.863714898	2.202489346	0.045070957
Far2	-0.361604183	3.558078225	-2.202255088	0.045090705
Per1	-0.68623753	4.211404691	-2.200622134	0.045228586
Fam46a	-0.502457689	1.898111274	-2.200553902	0.045234356
Igf2	0.401121179	4.387201737	2.199219507	0.045347334
Ncaph	1.009233877	0.019623959	2.197909408	0.045458512
Rai14	-0.953163678	1.423521121	-2.197270382	0.045512834
Ap4e1	-0.434134224	2.701683849	-2.196753847	0.045556787
Acsl4	-0.335870842	6.399769441	-2.196169696	0.045606542
Bfsp2	0.391326525	2.788750213	2.195666301	0.045649459
Nme7	0.264039786	4.972959672	2.195017387	0.045704838
Ccm2	0.419542447	7.481640087	2.194885431	0.045716107
Tmem130	-0.43215473	6.85804434	-2.194652079	0.045736041
Bcl2l11	-0.479893264	1.491463524	-2.194312688	0.045765049
Bop1	-0.234599984	5.710950557	-2.193834195	0.045805975
Prr13	-0.282988665	4.789744009	-2.190668445	0.046077606
Adam11	-0.458235042	4.584053785	-2.18994743	0.046139681
Cysltr2	1.093650783	-0.678483374	2.189910739	0.046142842
Lingo1	-0.682927253	6.393285776	-2.189805734	0.04615189
Bnipl	1.455456316	-0.356302935	2.18917381	0.046206372
Entpd2	0.400334502	3.776210058	2.188085887	0.046300311
Snx9	-0.398327996	2.639122102	-2.187887779	0.046317436
Slc9a8	-0.354136175	3.879652269	-2.187754053	0.046329
Shank1	-0.962277852	4.016590331	-2.187043783	0.046390461
Elk3	-0.479467405	2.408417504	-2.185624671	0.046513488
Stk26	0.378750683	4.698918346	2.185288682	0.046542661
Bbc3	0.55079652	1.156216186	2.183115076	0.046731799
Casp8	0.380675031	2.221514553	2.182636408	0.046773547
Foxj1	0.663557695	1.75622223	2.17866504	0.047121263
Entpd1	0.340605159	4.597435704	2.178614435	0.047125709

B3galt2	-0.654685363	7.008414007	-2.177870124	0.047191152
Atf4	-0.360534308	6.629769858	-2.177714383	0.047204856
Acss2	-0.248109014	5.680388298	-2.177553969	0.047218975
Atp2b4	-0.835482045	5.862585539	-2.175275195	0.04741997
Fam136a	0.237783476	5.37334471	2.174460781	0.047491998
Ftx	0.828690945	0.40415437	2.17440413	0.047497012
Pparg	-0.87374232	-0.818325008	-2.173487102	0.047578245
Kif22	0.933379339	0.068911714	2.173358441	0.047589652
Vasn	-0.663644555	1.767869647	-2.173254847	0.047598839
Plscr2	0.789102099	0.823916828	2.171404365	0.047763221
Usp35	-0.635564271	2.709655428	-2.17127511	0.047774723
Gm10778	1.052704376	-1.243039486	2.170059688	0.047883003
Chrna5	-0.71502512	2.584453179	-2.169315388	0.047949425
Gm7244	0.748882686	1.350352805	2.169278516	0.047952718
Timm44	0.265243965	4.542660468	2.167893149	0.048076585
Kcnip1	-0.337424069	3.882747441	-2.16788955	0.048076907
Clmp	0.662988858	3.07439703	2.166757557	0.048178342
Mib1	-0.370923991	5.240003989	-2.165225088	0.048315981
Pfkm	-0.280299464	8.059299724	-2.164467469	0.048384162
Sun2	0.335101879	5.689238237	2.164313107	0.048398064
Rspo2	-1.06373094	4.27779772	-2.163943823	0.048431339
Coro2a	-0.810264478	2.767358251	-2.163496179	0.048471703
Usp40	0.475064706	2.028027758	2.162610918	0.048551619
Wrb	0.187497176	6.76939011	2.162522122	0.048559641
Ifit1bl1	-0.879376318	1.493016229	-2.162027268	0.048604374
Hilpda	0.484402482	3.12432114	2.161033607	0.048694313
Cenpv	0.296566538	5.06520902	2.160329111	0.048758172
Cldn1	0.71182108	2.337067551	2.15927272	0.048854076
Atxn7l3	-0.209151458	7.987905648	-2.157946459	0.048974728
Ces5a	-0.880775704	-0.24153818	-2.157696183	0.048997527
Chrna4	-0.997289504	2.802635252	-2.157688085	0.048998265
Rasal1	-0.709561722	4.497691387	-2.157642137	0.049002452
Sowahb	-0.543681157	4.086852512	-2.157107021	0.049051236
Hmgcr	-0.342758929	6.810846243	-2.154646409	0.049276144
Msra	0.317939892	5.715189662	2.154350275	0.049303276
Pcdh8	-0.923091729	2.492789516	-2.153269598	0.049402407
Adamts13	-0.802860051	0.582302662	-2.152285046	0.049492882
Sema3f	0.625710286	2.248815554	2.152133548	0.049506818
C130074G19Rik	-0.539997923	3.812862053	-2.14991663	0.049711159
Frmd3	-0.38001367	2.943098	-2.14965262	0.049735546
Cpeb1	-0.286383285	5.32393434	-2.149101956	0.049786448
Rnf34	0.268130099	7.140823226	2.148031202	0.049885563
Rab11fip4	-0.461967657	5.859023606	-2.147152487	0.04996704

Table 3. Differential expression analysis in the DMS for WT compared to Npas2 mutant females in the dark phase.

	logFC	AveExpr	t	P.Value
Fabp7	1.5198360	5.8434322	7.8598624	0.000005890
Krt12	1.9776817	2.5759939	7.1064335	0.000015600
Gpx6	-3.1581128	5.0357624	-6.3008769	0.000047900
Dbp	-0.5356117	6.9703303	-5.2624649	0.000231109
Pwwp2b	-0.7479183	4.7726895	-5.0592384	0.000320121
Bhlhe41	-0.8822748	4.6407931	-5.0113424	0.000345963
Fbxl16	-0.8018989	10.3838525	-4.9243775	0.000398659
Strip2	-0.8642462	7.1448832	-4.8926136	0.000419957
Penk	-0.8888920	11.1290147	-4.8004345	0.000488813
Dpp10	0.6033371	7.2057055	4.7409321	0.000539481
Nanos1	-0.5279408	6.5069371	-4.6116441	0.000669522
Tagln	-0.9069740	5.0067513	-4.3605552	0.001024853
Cntnap5b	1.0116087	3.5642792	4.3374315	0.001066269
Camk1g	-0.9867613	3.9453405	-4.2238799	0.001296510
Mgp	-0.8010930	4.3544018	-4.1896138	0.001375730
Iqca	2.9738646	-1.4825937	4.1260268	0.001536357
Wdhd1	1.9092475	0.7238180	4.0481028	0.001760126
Ppp2r2a	-0.4026703	8.0393064	-4.0196915	0.001849903
Gpr155	-0.4679531	7.6632481	-4.0035789	0.001902913
Adgrg1	0.6517199	5.4457128	3.9154138	0.002222167
Mfsd9	-0.8488929	2.7877310	-3.8761340	0.002381781
Egfl6	1.9893589	1.1897727	3.8101635	0.002677020
Rap1gap	-0.8978643	7.2218975	-3.8051135	0.002701122
Pantr1	0.8310085	7.4553036	3.7982723	0.002734131
Dtl	2.3561432	1.2224682	3.7721075	0.002864260
Hmga2-ps1	1.9382000	0.6356921	3.7626952	0.002912618
Wbscr27	3.5627274	-0.9927905	3.7617698	0.002917417
Ctps2	0.5714755	4.3077955	3.7115898	0.003190260
Pthlh	-0.9755732	3.0374388	-3.7050525	0.003227691
Ephx1	-0.4971560	5.4668748	-3.6904737	0.003312799
Tmprss6	1.0582919	1.6708144	3.6841497	0.003350431
Plekha2	0.5536675	4.6947826	3.6355021	0.003655012
Slc9b2	-1.3871261	1.1205542	-3.5876574	0.003982340
Pou3f1	-0.6549910	5.4875753	-3.5518505	0.004246866
Sla2	3.4573410	-2.9668325	3.5398685	0.004339349
Klhl14	1.7448436	0.1489834	3.5347815	0.004379234
BC030500	-0.5388257	3.8088489	-3.4740993	0.004884977
Ttll5	0.8193303	3.0114852	3.4702778	0.004918758
Csdc2	0.5099869	5.6910415	3.4464396	0.005134937
Arntl	0.7305508	5.6478249	3.4226660	0.005360196
F9	2.3426497	-0.9722215	3.4138091	0.005446671
Lgals9	-0.5697573	3.3536521	-3.3970755	0.005613955

Nav2	2.0437912	0.2196885	3.3687596	0.005909042
C030013G03Rik	0.9575191	2.5112294	3.3391324	0.006234728
Kif21b	1.3926974	1.4269966	3.2877556	0.006843410
Pigb	1.2452717	1.0742144	3.2854617	0.006871953
Efna3	-0.4784752	4.6560242	-3.2853274	0.006873627
Inpp4b	-0.7666218	3.4859163	-3.2490608	0.007341407
Cav1	-0.4266346	5.4417574	-3.2159890	0.007796079
Hpca	-0.3463258	10.5826248	-3.1839060	0.008264400
Ppapdc2	-0.3636709	6.1296061	-3.1567068	0.008683658
Cfh	-0.5771610	5.3277892	-3.1500488	0.008789520
Kirrel2	-0.9179092	3.2091728	-3.1490763	0.008805090
Trpc3	-0.3988284	5.3873619	-3.1393446	0.008962455
Cartpt	-1.6134962	1.4999899	-3.1310301	0.009099149
Ntrk1	-0.7634707	4.2351510	-3.1263903	0.009176341
Slc37a1	-1.0097744	1.2746680	-3.1084000	0.009481946
Mkx	2.6274319	-0.4076479	3.1076148	0.009495514
A330076C08Rik	-1.4945402	0.2838075	-3.1012672	0.009605933
Camkv	-0.5908882	9.0624408	-3.0830959	0.009929232
Adora3	3.183305122	-2.00957982	3.051750112	0.010512891
Tmem232	2.687520191	-0.758302284	3.015432664	0.011232402
Calb1	-0.678869162	8.578007848	-3.005755944	0.011432323
Wbscr16	0.647007006	2.733808965	2.991452254	0.011734396
Thbd	-0.546771442	3.960391002	-2.9882449	0.011803222
Ptpn5	-0.439092204	9.423847301	-2.983776104	0.011899792
Fibcd1	-0.60345854	4.020939637	-2.978821935	0.012007777
Camkk1	-0.712180596	5.399897806	-2.976275952	0.012063653
Sla	0.997623565	3.059450733	2.97459931	0.012100591
Slc20a2	0.381134605	5.71124374	2.970351716	0.01219468
Lrrtm3	-0.296891077	7.329830543	-2.966906074	0.012271542
Rab26	0.535585645	4.187317248	2.963010903	0.012359017
Zfp493	0.68342781	2.542288816	2.962686747	0.012366325
Postn	-1.095114552	1.989394588	-2.959802668	0.012431534
Prex2	-0.343180827	6.431605441	-2.951664849	0.012617392
Fam117a	-0.990674263	2.483234985	-2.946187772	0.012744045
Cpne6	0.741540962	4.20144874	2.941409635	0.012855574
Il12a	3.253869909	-2.299627079	2.936696012	0.012966554
Rbm38	1.87206279	0.091321813	2.936656544	0.012967487
Hs3st5	-0.49023719	4.868446676	-2.933099453	0.013051877
Fut11	0.422932178	4.567821454	2.932460472	0.013067095
Nipal2	-0.59978471	4.001270117	-2.924595146	0.01325587
Cwh43	2.878340252	-0.870141855	2.915606388	0.013474948
Zfp595	-0.781660721	2.131890948	-2.915255651	0.013483569
Med27	-0.371267226	4.954855387	-2.906266091	0.013706426
Mesdc1	-0.356014318	6.481727539	-2.902918792	0.013790345
Fam101b	0.622092873	3.816520955	2.902773912	0.013793989
Pola1	1.198926206	1.401913785	2.901851892	0.0138172
Hebp2	1.331702085	2.254195031	2.90003682	0.013863008

Tnfaip8l1	-0.592167332	3.306944526	-2.889158153	0.014140753
Mat2a	-0.30236797	7.185385069	-2.86260056	0.014842337
Gstm6	-0.857672222	3.373508806	-2.858728493	0.014947485
Stx17	0.590394025	3.765371106	2.853205441	0.015098752
Cryab	0.389731386	7.396411061	2.84996279	0.015188272
Dab1	0.407769427	5.707163826	2.8474679	0.015257508
Acta2	-0.669697173	4.459092188	-2.847194321	0.015265119
Adgrl4	-0.401345884	5.668001099	-2.842945319	0.015383816
Slc5a6	-0.401963379	4.290129813	-2.828384065	0.015797601
Cacng7	0.356561848	5.750572225	2.826639573	0.01584791
Lamc2	1.730475026	0.547161307	2.821922936	0.015984734
Fezf2	1.597658896	1.709614261	2.817402493	0.016116967
Ermap	-1.499082252	0.493350429	-2.815213061	0.016181404
Dll3	1.170135461	0.809789854	2.812043608	0.016275137
Kif23	2.199126203	-1.264368519	2.809565978	0.016348786
Adcyap1	2.892585684	-0.560798484	2.808279979	0.016387143
Krt73	2.776529138	-2.520185813	2.80792507	0.016397744
Nr1d1	-0.845502762	4.164287421	-2.807856212	0.016399802
Rttn	-1.062766083	1.062167209	-2.80520556	0.016479206
Ogn	-1.223332928	2.88417566	-2.802878491	0.016549231
Lgr6	2.970430199	-2.358708442	2.802310633	0.016566364
Nup35	-0.573765968	5.700135166	-2.791646514	0.016891397
Gng12	0.361453675	7.052847447	2.788269819	0.016995629
Zfp629	0.865641765	1.595159857	2.770533527	0.017553684
Ldb2	0.453917925	5.458062634	2.761351644	0.017849683
Zic1	-0.80537678	4.164967645	-2.757467499	0.017976381
Hist1h2be	-0.645488476	3.143224729	-2.75585321	0.0180293
Ccdc57	2.89789106	-2.203171026	2.754979934	0.018057991
Islr2	0.673104596	5.237009868	2.750676136	0.018200054
Oxld1	-0.726136802	2.643925756	-2.74617086	0.018349954
Fbxo2	0.37028666	6.503728812	2.739697855	0.018567466
Slc16a14	2.179895129	-0.851837805	2.738119376	0.018620893
Irgm2	-0.620331364	2.750745106	-2.728928424	0.018935018
Fig4	-0.407735004	6.946560485	-2.724731224	0.019080206
Rnf39	2.419319022	-0.537240322	2.722411608	0.019160917
Ifi27l2a	-0.878812847	2.523142501	-2.714706297	0.019431454
Tgtp1	2.337659546	-1.232106194	2.713325059	0.019480347
Atf3	2.032342073	-1.302375039	2.701016505	0.01992145
Il1r2	2.786573151	-2.283776568	2.696051521	0.02010216
Lrrc1	-0.498103991	4.291046526	-2.694194729	0.020170156
Ptprcap	-1.148577629	0.722723291	-2.693023648	0.020213158
Rps27	1.002344623	0.995996818	2.678973105	0.0207362
2700046G09Rik	-0.875466932	1.245998054	-2.677932079	0.02077548
Kcng3	-1.733922084	-0.605356095	-2.677407759	0.020795292
Tuba8	1.231537952	1.540397937	2.677092902	0.020807198
Mest	-0.315082393	4.898997333	-2.67698773	0.020811176
Zxdb	-0.387461402	4.700704097	-2.675527738	0.020866481

Rhoj	-0.626260795	2.366614131	-2.67111544	0.021034504
Dll1	-0.930829164	1.73442782	-2.666791758	0.021200446
Tmem169	0.613037668	3.456486921	2.663374336	0.021332518
Smyd2	0.63989539	4.228524727	2.657240982	0.021571588
Slc6a3	2.687693721	-2.325237785	2.656169992	0.021613603
Ccdc51	-0.518948014	3.733203561	-2.654143507	0.021693324
2810025M15Rik	0.541208895	3.864971601	2.653735337	0.021709416
Parvb	0.589012426	3.541390252	2.650348171	0.021843409
Cenpa	1.385488705	1.695668258	2.646980324	0.021977446
Ces5a	-1.50714927	-0.346013976	-2.645308462	0.022044284
Gpr83	-0.482991496	5.553873455	-2.644236016	0.022087264
Arhgap27	0.562298088	3.666887076	2.637551778	0.02235701
Slco5a1	0.860015128	1.35847239	2.63726769	0.022368546
Gm266	0.740050937	2.77218761	2.634780403	0.022469798
Bst2	-0.713279466	2.543367945	-2.628939282	0.022709353
Slc35d3	-0.534125691	5.861496504	-2.628897136	0.022711091
2700094K13Rik	0.54320489	3.639775544	2.625313178	0.022859328
Vat1l	-0.58134126	7.15856346	-2.623472669	0.022935823
4931414P19Rik	0.785612896	1.760890661	2.622446725	0.022978572
Myo1f	1.200758924	0.054481237	2.609614774	0.023519913
Pde1b	-0.386322317	10.13135456	-2.607477999	0.023611265
Rev3l	1.052909913	1.778131258	2.603944772	0.023763084
Tacc3	0.982204172	1.73576304	2.603184332	0.023795884
Kitl	0.321895672	7.304091653	2.602991946	0.02380419
Mapk6	0.373373686	5.959589898	2.601875017	0.023852464
Plscr2	-1.286178182	1.26458815	-2.598877038	0.023982513
Pglyrp1	-0.613075767	3.123717948	-2.594488345	0.024174145
Tinagl1	-0.536767696	3.472355772	-2.593199258	0.024230718
Amn	0.919711437	0.976259743	2.585454657	0.02457334
Rbl1	1.192914476	1.440048823	2.581216137	0.024762859
Tcfl5	-1.837030073	-0.623065137	-2.579947522	0.024819861
Rem2	-0.427803829	5.49257545	-2.571879378	0.025185404
Igsf9b	1.191122332	-0.055489292	2.570622247	0.025242833
Rabggta	-0.301198207	5.385005287	-2.569635025	0.025288023
Emp2	0.400249199	5.04312902	2.562451214	0.025619249
Slc6a15	-0.346115426	6.640735869	-2.561041999	0.025684721
Hlf	-0.485001087	7.729853562	-2.561018279	0.025685824
Snrpn	-1.283498501	0.06015049	-2.554686978	0.025982012
Crb2	0.946873342	1.428025159	2.552583744	0.026081142
Uhrf1	2.772079894	-0.961345487	2.551843522	0.026116118
A730036I17Rik	2.471484002	-0.69074278	2.548382872	0.026280246
Tceal5	0.373849231	4.806234483	2.546852575	0.026353145
Vrk1	-0.40383216	5.148749196	-2.543783228	0.026499956
Snca	0.375040549	9.312270151	2.542259219	0.026573148
Rgs2	-0.487294428	8.029156444	-2.541300926	0.026619272
Sox21	0.733579785	2.892674483	2.535791745	0.026885959
Slc5a7	-0.586863825	6.486851877	-2.531579534	0.027091621

Lrrc10b	-0.374271355	8.598321386	-2.53140043	0.0271004
Pltp	-0.402445214	6.28997825	-2.52893697	0.027221429
Itga11	2.81172019	-2.489230184	2.527105719	0.027311739
Cmc2	0.42610535	3.835566383	2.522163731	0.027556922
Slc32a1	-0.330462684	7.769920924	-2.521344513	0.027597772
Tbx18	-1.114896232	0.695489926	-2.521299572	0.027600015
Arpp19	-0.431416779	11.51886139	-2.518976361	0.027716193
Gm7120	-0.430421766	5.847654066	-2.51420213	0.027956439
Abca8b	-0.629244626	3.405621535	-2.513969079	0.027968219
Fcrls	-0.341467989	5.868766091	-2.505970025	0.02837547
Tmem39a	0.692562639	2.120817479	2.505247022	0.028412564
Gmcl1	0.383427655	4.682009555	2.504296567	0.028461399
Dmrta2	1.822970065	-0.83232745	2.503538462	0.028500409
Chrm4	-0.482067454	5.389924172	-2.503039906	0.028526092
Dlk2	-0.616523176	2.616676493	-2.501296943	0.028616058
Lum	-0.940180796	1.52729441	-2.499918734	0.028687392
D030028A08Rik	1.453701226	-0.798429358	2.499857903	0.028690545
Rps6ka4	-0.327527157	6.013397938	-2.490405639	0.029184523
3110079O15Rik	-1.620986135	-0.855661392	-2.488422611	0.029289203
Pcdhb15	0.954627953	0.951310877	2.483102078	0.029571873
Dgkb	-0.374096504	9.069189038	-2.482169105	0.029621713
Igfbp7	-0.322355879	4.777184427	-2.481723523	0.029645545
Sdk2	2.5662226	-1.297356919	2.474040673	0.03005941
Dlx6	-0.456144162	4.615711319	-2.472593201	0.03013801
Gpr88	-0.373813046	11.502939	-2.462687057	0.03068132
Nod1	0.797246759	1.160416144	2.462383274	0.030698131
Gm4013	2.84149821	-1.291940188	2.461823866	0.030729111
Tox	1.246066025	1.740005062	2.46012655	0.030823294
Bcl2l11	0.908843662	1.172666262	2.458568286	0.030910008
Alms1	2.6376972	-1.31962654	2.455531544	0.031079678
Map2k1	-0.213940631	8.744829273	-2.455480814	0.03108252
Ppp1r14c	0.386127019	3.945472449	2.454995392	0.031109728
Otud7b	0.384214369	5.429281844	2.452552483	0.031247004
Cyp39a1	0.666469249	2.883670469	2.447479636	0.031533948
Dyrk3	0.608207205	2.328959748	2.446228521	0.031605109
Lamb3	-0.965933725	1.083873581	-2.445244205	0.031661205
Atpaf1	0.30688966	4.800264939	2.444348053	0.03171236
Vwa9	0.341608202	4.718758424	2.442127787	0.031839445
Prkx	0.520443101	3.138519478	2.441397773	0.031881338
Igfbp5	0.571659921	5.781052837	2.441081779	0.031899489
Ankrd10	0.456566783	4.133065024	2.441037164	0.031902052
Zfp646	1.031323429	1.665658683	2.439621235	0.031983512
Slc18a3	-0.727287287	3.205846985	-2.43525827	0.032235786
Zfp367	0.394564263	5.049879609	2.427299154	0.032700977
Rnd1	0.83108875	2.621689516	2.423857585	0.032904137
Shmt2	0.498325658	3.381764559	2.422837084	0.032964614
Optc	2.585628214	-2.236457056	2.421082495	0.033068845

2310040G24Rik	1.487438418	-0.692935105	2.419204684	0.033180749
Jsrp1	-0.723697065	3.370696404	-2.418911416	0.033198259
Vnn1	3.019109604	-1.491945228	2.414719167	0.033449542
Arap3	-0.865117213	2.462968159	-2.413974408	0.033494375
Lpin3	2.281859517	-1.52586865	2.410831035	0.033684242
Scarf2	-1.243303871	0.590553732	-2.409537373	0.033762684
Spock3	-0.394011336	10.65607609	-2.408996328	0.033795543
Gucy2g	2.237589103	0.106520481	2.408913505	0.033800576
Pcdh11x	-0.372285519	5.244814138	-2.408581109	0.033820781
Slc10a4	-0.603870376	4.166862188	-2.408161295	0.033846318
Npy2r	-0.837911869	2.614346621	-2.406875802	0.033924627
A830019L24Rik	-2.210532192	-0.93330665	-2.405766109	0.033992368
Bves	-0.684819658	2.74089876	-2.403008902	0.034161248
Ptchd1	-0.568826622	4.167883579	-2.402896002	0.03416818
Zfp408	1.097611236	0.494640187	2.396467661	0.034565154
Klhdc8a	0.595321019	2.840884079	2.392704388	0.034799616
Htra3	-0.800887624	1.428404401	-2.392370462	0.034820494
Htr1b	-0.487017017	4.659360429	-2.389825235	0.034980032
Prrt4	-1.008031985	0.382360721	-2.38861667	0.035056033
Klf11	0.548314836	2.696804663	2.387932792	0.03509911
Prmt8	-0.254498119	7.085336116	-2.384236386	0.035332829
S100b	-0.231603057	7.233210501	-2.382443217	0.035446749
Ccdc96	2.471099074	-2.014652707	2.38054173	0.035567939
Slc38a9	-0.552836857	3.899115454	-2.379460643	0.035637019
Scn4b	-0.352238544	9.876543139	-2.378954292	0.035669419
Wdr90	0.820779239	1.088246471	2.376524953	0.035825261
Gpr101	-1.138615339	0.855306883	-2.376009666	0.035858401
Mex3b	0.430084033	3.981749621	2.375695964	0.035878591
Vav2	1.024776508	1.025445365	2.37490289	0.035929682
Ccno	-0.858979084	2.139700208	-2.371043325	0.036179325
Gm14322	-0.943097146	0.442793854	-2.3707803	0.036196399
Gpr153	0.385345532	3.751525202	2.367045621	0.036439668
Zfp213	0.408133389	3.396894929	2.359490374	0.036936631
Fam180a	-1.157415251	0.171711336	-2.35863083	0.036993582
Ypel1	0.367507924	4.729927725	2.358523432	0.037000704
Ppan	0.628784323	2.067198322	2.355856075	0.037178007
Nasp	0.41326667	3.507431793	2.355816164	0.037180666
Tnc	2.155771169	-1.006781322	2.355475356	0.03720338
Lypd6	0.445243371	5.323839732	2.352016482	0.037434668
Slc35g1	-0.639945251	1.951407001	-2.351176938	0.037491015
Stra6	-0.517041317	3.492100839	-2.350549669	0.037533168
Stmn1	0.633583911	7.156890066	2.348223248	0.037689906
Gp2	-2.56557883	-0.654674019	-2.345571449	0.037869334
Scamp1	-0.268092151	9.598964594	-2.336814507	0.038467713
Syt17	1.113734635	1.435438397	2.336029596	0.038521789
Proser2	0.712094759	1.540627323	2.33469732	0.038613744
Fbln5	-0.546584915	3.697126362	-2.333761027	0.038678494

Ep400	0.695220416	2.830454141	2.332846655	0.038741829
Hnrnpf	0.43096961	4.562422889	2.332013027	0.038799658
AW495222	0.542474217	2.481070081	2.33017993	0.038927113
Trappc6a	-0.531468474	3.738128799	-2.329081394	0.039003687
Gm694	-0.693932175	2.323225138	-2.328070446	0.039074283
Dfna5	-0.294465812	4.749867202	-2.320005015	0.039641922
Mas1	0.626695976	3.527897945	2.316032655	0.039924398
Dnajb6	0.210599578	6.458146498	2.314556891	0.040029831
Dtna	0.225455495	6.696679259	2.314527511	0.040031933
Zbtb40	1.084634612	1.264061162	2.314187688	0.04005625
Omd	-1.3991737	0.25989953	-2.30524386	0.040701379
Cib2	0.55271471	3.804712345	2.302452515	0.040904756
Grap2	-1.766409016	-1.096818146	-2.300196803	0.041069818
Amz1	-0.422852863	4.461995256	-2.296316948	0.041355223
Bub1	2.539033571	-0.482574813	2.296144471	0.041367954
C230037L18Rik	1.329363202	-0.233767807	2.294764232	0.041469974
Nelfb	0.356703786	5.042337984	2.294708567	0.041474093
Npas4	1.131017573	0.370840548	2.29236156	0.041648141
Shf	-0.461652608	4.401138237	-2.290701443	0.041771673
Anks6	-0.8382034	0.894136478	-2.288173916	0.041960425
Cdhr1	-0.744671004	2.432039926	-2.288059755	0.04196897
1700012D01Rik	-1.035155597	0.727959573	-2.286943316	0.04205262
Fam19a2	0.338072836	4.618281788	2.284924828	0.042204263
Sox2	0.337638399	5.19732978	2.284396954	0.042244007
Ppwd1	0.646036033	2.384566878	2.284083394	0.042267632
Zfp768	0.870730154	1.559445881	2.283111406	0.042340947
Scd3	0.62271427	2.293063754	2.283020718	0.042347793
Cry1	-0.343199077	6.378704595	-2.281645186	0.042451771
Tchp	1.820844926	0.133784955	2.278864992	0.042662673
2010320M18Rik	0.594595233	2.757665678	2.278614125	0.042681753
Inmt	-0.704595221	2.547375355	-2.278400093	0.042698038
Dlx2	0.987970912	1.736653045	2.277220412	0.042787902
Pcdhb8	-0.439908233	3.548071582	-2.276638399	0.042832304
Kif18a	1.877975505	0.273411121	2.275150257	0.042946036
Tns3	0.325897108	5.742139883	2.274094813	0.043026874
Rhobtb2	-0.293398587	7.303299338	-2.273424966	0.043078254
2810403D21Rik	1.277445704	-0.100299987	2.2709975	0.043264942
Etnppl	-0.5498546	3.336989739	-2.27073471	0.043285199
Anxa3	-0.379950661	4.69764941	-2.269201183	0.04340359
Upp2	-0.423334638	3.508015542	-2.268791184	0.043435295
Bbs9	-0.329246429	4.958749102	-2.264653047	0.043756536
1700037H04Rik	-0.379676703	6.743042024	-2.264231363	0.043789398
Dcdc2a	-0.468919034	3.034277551	-2.263303346	0.043861803
Glp2r	2.497154709	-1.150339169	2.26299017	0.043886263
Ticam1	-0.676691524	1.868610861	-2.261596029	0.043995308
Hdac7	-1.028038152	1.234237583	-2.2591503	0.044187231
Arx	0.378089414	3.800289226	2.258437043	0.044243353

Tmem170	0.690778804	2.198113257	2.258075672	0.044271813
Exd2	0.260680391	5.681635922	2.257602656	0.044309092
Cdh24	1.388077942	0.565293924	2.257259941	0.044336121
Slc16a3	-0.577983123	2.766452501	-2.25568454	0.04446057
Sntb1	-1.097255532	0.277897034	-2.255555119	0.044470808
Amigo3	1.983541322	-1.89605123	2.25503675	0.044511839
Vwa5b2	2.323901144	-0.810283721	2.253207231	0.04465694
Ifitm3	-0.53336337	3.630103474	-2.249458623	0.044955658
Ccdc50	0.282381627	5.943556813	2.249433387	0.044957676
Mbnl1	-0.255653879	6.704574874	-2.247068705	0.045147101
Ascl1	1.239361379	1.054713562	2.247066741	0.045147258
Hist1h2bc	-0.282257682	5.781034913	-2.246785302	0.045169854
Ccdc109b	-0.780324501	2.100132844	-2.245990517	0.045233723
A430046D13Rik	0.56258965	3.473090703	2.234594368	0.04615904
Pkib	-0.540261943	3.06816263	-2.234563702	0.046161554
Neat1	1.015035297	0.660124286	2.234304142	0.046182839
Exosc6	0.594239862	2.995306134	2.229678247	0.046563756
Ezh2	0.964126287	1.86444629	2.227207004	0.046768474
Gstt1	-0.630408496	3.398515	-2.225785829	0.046886593
Ctla2a	-0.504218052	3.875945872	-2.225211998	0.046934366
Lsr	-0.516375111	2.982717711	-2.221641962	0.047232628
Cyp2a5	-0.772739214	1.148440798	-2.216992661	0.047623763
Kcng2	1.14738841	0.025986225	2.216610601	0.047656042
Mgst3	0.334682022	6.79151066	2.215653137	0.047737026
Slc34a3	-1.817364883	-0.21508482	-2.21466554	0.047820695
4932438H23Rik	0.864893503	1.078622459	2.211382982	0.048099798
Tshz3	2.067456854	-0.361123481	2.209552508	0.048256108
P2ry1	-0.807303324	3.454528006	-2.20874914	0.048324863
Tmem175	-0.258140419	5.076057548	-2.206713745	0.048499476
Tex9	1.024898012	1.014245967	2.204388199	0.048699715
Cpne9	1.195998149	3.081812832	2.200008877	0.049078927
Ankrd40	0.196637239	7.946680133	2.19984196	0.049093436
Cbfb	0.313136078	5.412602365	2.199281068	0.04914222
C1qtnf2	-1.166268119	-0.305700865	-2.199007252	0.049166052
Dpy19l1	0.33637321	6.79249333	2.198252007	0.049231844
Pdpr	0.376388279	4.17974564	2.196255126	0.049406202
Sec14l1	-0.296760599	7.756491433	-2.193812698	0.04962026
Cipc	-0.295340871	6.675123566	-2.191464578	0.049826882