

**NEUROSCIENCE/BEHAVIOR
ORAL PRESENTATION****TUESDAY NOVEMBER, 14****9.15AM - 9.30AM****O12****USE OF MOUSE INBRED STRAIN GENOMICS TO IDENTIFY GENES INVOLVED IN TAIL SUSPENSION AND OPEN FIELD PERFORMANCE**

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Haplotype association mapping (HAM) represents a relatively new attempt at identifying genes underlying complex behaviors and biologies. This approach exploits natural phenotypic and genetic differences among inbred laboratory mouse strains, using high density single nucleotide polymorphism (SNP) maps to identify ancestral genomic regions (haplotypes) shared by strains that also segregate phenotypically. We selected 30 inbred laboratory mouse strains based on the Mouse Phenome Database priority list and used the Tail Suspension Test (TST) to measure behavioral despair and the Open Field (OF) test to measure anxiety and general locomotor activity. In both tests, we found a large strain-dependent distribution in the duration of immobility (TST), thigmotaxis (OF), and total distance traveled (OF). We then performed in silico haplotype association mapping to link TST and OFA performance to highly resolved genomic regions. Finally, we performed microarray analysis of hippocampi from the highest and lowest immobility strains from the TST. By comparing the gene expression patterns across the inbred strains with the variation in TST performance, we identified a small set of genes as potential candidates for the control of the assayed behavior.

**NEUROSCIENCE/BEHAVIOR
ORAL PRESENTATION****TUESDAY NOVEMBER, 14****9.30AM - 9.45AM****O13****ROLE OF GENES THAT ESCAPE X INACTIVATION IN NEURAL DIFFERENTIATION**J Xu, CM Disteche

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In humans, 15 to 25% of X-linked genes escape X inactivation and are transcribed from both X chromosomes in females. Deficiency in these X escapee genes plays a role in phenotypic abnormalities of Turner syndrome (monosomy X), including impaired social cognitive ability. We examined the expression of five mouse X-linked escapees including *Usp9x*, *Utx*, and *Ddx3x*, which map into the critical region for Turner neurocognitive phenotype. These X escapees have Y paralogues. To test the expression of the X-Y paralogues during neural differentiation, we measured gene expression of each X-Y pair in pluripotent P19 embryonic carcinoma cells, which were differentiated into neurons by retinoic acid induction. Expression of the X paralogues was uniformly higher than the Y paralogues for all five X/Y pairs in undifferentiated and differentiated cells. There was an increase in expression of X-Y genes in differentiated neurons, consistent with a role for these genes in neural function. Histone H3 acetylation and H4 lysine 20 tri-methylation were analyzed at the promoter sequences of *Usp9x* and *Usp9y*. H3 acetylation was higher on *Usp9x* promoter than *Usp9y* before and after differentiation; consistent with the higher expression of *Usp9x*. The difference between the two paralogues in expression and H3 modifications implies discordance in regulation which may lead to sex differences in brain development. In contrast, H4 lysine 20 trimethylation at both genes was enhanced in neurons, suggesting it is a marker for differentiated neurons. Our results suggest a role for X escapee genes in neuronal development associated with specific histone modifications.

**NEUROSCIENCE/BEHAVIOR
ORAL PRESENTATION****TUESDAY NOVEMBER, 14****9.45AM - 10.00AM****O14****POSITIONAL CLONING OF A NEW NEUROLOGICAL MOUSE MUTANT: PALE TREMOR**C.Y. Chow¹, Y Zhang², L.S. Weisman², M.H. Meisler¹¹University of Michigan, Department of Human Genetics, Ann Arbor, MI, United States, ²University of Michigan, Life Sciences Institute, Ann Arbor, MI, United States

pale tremor (plt) was recently identified in our mouse colony as a new, autosomal recessive neurological mutant. *plt* is characterized by pigment dilution, a lethal movement disorder, and selective loss of neurons in sensory ganglia, motor cortex, deep cerebellar nuclei, and other specific brain regions. Affected neurons and fibroblasts contain enlarged vesicles that fill the cytoplasm and stain positively for the lysosomal marker LAMP2. The number of pigmented cells in hair follicles was greatly reduced and the few remaining pigmented cells contain clumped melanosomes characteristic of mutants with vesicle disorders. *plt* arose on a mixed genetic background. To map and clone the mutant gene, we carried out a mapping cross with the wild-derived strain, CAST/Ei. We mapped *plt* to a 2 Mb region on mouse chromosome 10 by analysis of 532 F2 offspring. An Etn2b element insertion into an intron of the pale-tremor gene results in loss of function. The severity of the phenotype is exacerbated by modifier(s) from the CAST background. The identity and function of the pale tremor gene will be discussed.

**NEUROSCIENCE/BEHAVIOR
ORAL PRESENTATION****TUESDAY NOVEMBER, 14****10.00AM - 10.15AM****O15****PITX2 IS REQUIRED FOR NORMAL MIGRATION AND DIFFERENTIATION IN DISTINCT POPULATIONS OF NEURONS IN THE DEVELOPING MOUSE MIDBRAIN AND HYPOTHALAMUS**DM Martin, JM Skidmore

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Transcriptional regulation of neuronal differentiation is a central topic in developmental neurobiology. *Pitx2*, a paired-like transcription factor, is expressed in postmitotic neurons of the developing mammalian brain. In humans, *PITX2* mutations result in Rieger syndrome, a haploinsufficiency disorder with malformations of the teeth and craniofacial structures, cerebellar defects, and impaired cognition. Prior studies demonstrated a requirement for *Pitx2* in mouse subthalamic nucleus and superior colliculus development, but the mechanisms and affected stages of neuronal development were unknown. These studies were also limited by lack of reporter tagged alleles for tracing *Pitx2* lineage neurons and their projections. Here we report (1) a novel fate mapping strategy using *Pitx2cre* knock-in mice and a nuclear localized *lacZ* reporter for tracking *Pitx2* lineage neurons, and (2) a new loss of function *Pitx2* knock-in allele, *Pitx2TauLacZ*, for marking neuronal projections. Analysis of *Pitx2cre* and *Pitx2TauLacZ* alleles, in combination with a previously characterized *Pitx2null* allele, demonstrates significant defects in neuronal location and projections with loss of *Pitx2*. *Pitx2* deficient neurons are mislocalized in the developing hypothalamus and midbrain, consistent with brain region-specific roles for *Pitx2* in neuronal migration and differentiation. Neurons expressing LMX1B, a LIM-homeodomain transcription factor, are absent in the subthalamic nucleus of *Pitx2* mutants, yet *Pitx2* expression is normal in *Lmx1b* mutant embryos. Thus, *Lmx1b* neuronal lineages depend on PITX2 for normal migration or survival but *Pitx2* is not a direct target of LMX1B. Ongoing studies will identify transcriptional targets and signalling molecules disrupted by *Pitx2* deficiency in these brain regions.

**NEUROSCIENCE/BEHAVIOR
ORAL PRESENTATION****TUESDAY NOVEMBER, 14****10.15AM - 10.30AM****O16****AXONAL PATHOLOGY PRECEDES CELL BODY DAMAGE IN A MOTOR NEURON SYNUCLEINOPATHY**DE Cabin¹, RL Nussbaum²¹McLaughlin Research Institute, Great Falls, MT, United States, ²UCSF, San Francisco, CA, United States

Alpha-synuclein (SNCA) is associated with genetic and sporadic forms of Parkinson disease (PD). Transgenic mice expressing a prion promoter-driven mutant form of SNCA develop a lethal motor neuron disease. As human synucleinopathies such as PD and multiple system atrophy likely have commonalities in pathogenesis, understanding the basis of the motor neuron disease may provide insights into early stages of human synucleinopathies, including PD.

In the transgenics, SNCA-positive inclusions develop in some motor neurons. These are not the mature Lewy bodies characteristic of PD. Additional pathology includes gliosis, and ventral root Wallerian degeneration. No TUNEL-positive neuronal nuclei were detected, nor cells positive for activated caspase-3. A small number of motor neurons are positive for Fluoro-Jade B and thus are undergoing a non-apoptotic form of neurodegeneration. Examination of neuromuscular junctions indicates that axonal degeneration precedes withdrawal from synapses.

Spinal cord motor neurons are not affected in PD, but the pathology seen in the transgenics may reflect an early stage that is difficult to study in humans. Motor neuron function is necessary for mouse viability; the transgenic mice die before formation of Lewy bodies and neuronal death. Humans do not develop symptoms required for diagnosis of PD until the function of most nigral dopaminergic neurons is lost. We predict that an early stage of PD will be axonal malfunction and degeneration, with Lewy body formation and nigral cell death occurring late in the disease course. Microarray analysis of spinal cord transcripts is underway to better understand early stages of this synucleinopathy.