

**Monday November, 13**  
**10.30am – 12.30pm**  
**Poster Session 1**  
**Neuroscience/Behavior Pages**  
**Posters P15 – P27**

- P15 MUTATION IN INOSITOL 1,4,5-TRIPHOSPHATE RECEPTOR TYPE 1 GENE UNDERLIES A SEVERE MOVEMENT DISORDER IN MICE**  
J van de Leemput<sup>1</sup>, J Chandran<sup>1</sup>, J Hardy<sup>1</sup>, E Fisher<sup>2</sup>, H Cai<sup>1</sup>, A Singleton<sup>1</sup>  
<sup>1</sup>National Institutes of Health, National Institute on Aging, Bethesda, MD, United States, <sup>2</sup>University College London, Department of Neurodegenerative Disease, London, United Kingdom
- P16 A NETWORK OF CO-REGULATED TRANS-GENES WITH COMMON LINKAGE TO DISTAL CHROMOSOME 1**  
K Mozhui, L Lu, R Williams  
University of Tennessee Health Science Center, Memphis, TN, United States
- P17 A MOLECULAR CIRCUITRY CONTROLLING REGIONAL GENE EXPRESSION IN THE BRAIN**  
Z Zhou<sup>1</sup>, R Hart<sup>2</sup>, R Jornsten<sup>3</sup>, D Richardson<sup>3</sup>, D Moore<sup>4</sup>, NL Hayes<sup>5</sup>, RS Nowakowski<sup>5</sup>  
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- S18/ P18 CANDIDATE GENE ASSOCIATION STUDIES FOR ANXIETY AND ACTIVITY IN HETEROGENOUS STOCK AND RECOMBINANT INBRED (BXD) MICE**  
MJ Parsons, L Liu, C Fernandes, JL Paya-Cano, LC Schalkwyk  
Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, United Kingdom
- P19 THE TRANSMEMBRANE AMPA RECEPTOR REGULATORY PROTEIN (TARP) GAMMA SUBUNITS AND ABSENCE EPILEPSY**  
VA Letts, WN Frankel  
The Jackson Laboratory, Bar Harbor, ME, United States
- P20 IDENTIFICATION AND CONFIRMATION OF QUANTITATIVE TRAIT LOCI INFLUENCING ALCOHOL CONSUMPTION IN AN F2 INTERCROSS BETWEEN INBRED C57BL/6BYJ AND CONGENIC 129.B6-TAS1R3 STRAINS**  
C Lin, N Bosak, X Li, M Theodorides, D Reed, M Tordoff, A Bachmanov  
Monell Chemical Senses Center, Philadelphia, PA, United States
- P21 TOWARDS DEFINING MOLECULAR SIGNATURES OF CELL TYPES IN THE MOUSE CNS: GENOME-WIDE HIGH RESOLUTION EXPRESSION MAPPING IN THE ADULT MOUSE BRAIN**  
S Sunkin, C Dang, M Hawrylycz, J Hohmann, E Lein, P Wohnoutka, A Jones  
Allen Institute for Brain Science, Seattle, WA, United States
- P22 QTL MAPPING FOR ALCOHOL INTAKE AND RELATED PHENOTYPES IN FH/WJD X ACI/N CROSS**  
A Parsian<sup>1</sup>, AH Rezvani<sup>2</sup>, B Patra<sup>1</sup>, AJ Parsian<sup>1</sup>, DH Overstreet<sup>3</sup>  
<sup>1</sup>University of Arkansas for Medical Sciences, Little Rock, AR, United States, <sup>2</sup>Duke University, Durham, NC, United States, <sup>3</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, United States
- P23 NADPH OXIDASE COMPONENTS ARE REQUIRED FOR NORMAL VESTIBULAR DEVELOPMENT AND FUNCTION**  
DE Bergstrom  
The Jackson Laboratory, Bar Harbor, ME, United States
- P24 GENETIC DISSECTION OF TRANSCRIPTIONAL REGULATORY NETWORK IN MOUSE HIPPOCAMPUS**  
L Lu<sup>1</sup>, Hippocampus Consortium<sup>2</sup>  
<sup>1</sup>University of Tennessee, Memphis, Memphis, TN, United States, <sup>2</sup>[http://www.genenetwork.org/dbdoc/HC\\_M2\\_0606\\_P.html](http://www.genenetwork.org/dbdoc/HC_M2_0606_P.html), United States

**P25 HAPLOTYPE-ASSOCIATED MAPPING OF BEHAVIOR ACROSS INBRED STRAINS: IDENTIFICATION OF LOCI ASSOCIATED WITH LOCOMOTOR ACTIVITY IN A NOVEL ENVIRONMENT**

JS Bailey, L Grabowski, JR Walker, T Wiltshire, LM Tarantino  
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**P26 MISSENSE MUTATION IN THE VOLTAGE SENSOR OF THE P/Q-TYPE  $Ca^{2+}$  CHANNEL RESULTS IN DOMINANT CEREBELLAR ATROPHY AND ATAXIA IN WOBBLY MICE**

G Xie<sup>1</sup>, S Clapcote<sup>1</sup>, B Nieman<sup>2</sup>, T Tallero<sup>3</sup>, Y Huang<sup>3</sup>, I Vukobradovic<sup>1</sup>, S Cordes<sup>1</sup>, L Osborne<sup>3</sup>, J Rossant<sup>2</sup>, J Sled<sup>2</sup>, J Henderson<sup>3</sup>, J Roder<sup>1</sup>

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**P27 QUANTITATIVE TRAIT LOCUS MAP OF INTENSITY INDEPENDENT NOISE RESISTANCE IN 129S6 MICE**

BL Tempel<sup>1</sup>, VA Street<sup>1</sup>, DJ Shilling<sup>1</sup>, CM Liberman<sup>2</sup>, KW Broman<sup>3</sup>, SG Kujawa<sup>2</sup>

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**P15****MUTATION IN INOSITOL 1,4,5-TRIPHOSPHATE RECEPTOR TYPE 1 GENE UNDERLIES A SEVERE MOVEMENT DISORDER IN MICE**

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A mutation arose spontaneously while generating a transgenic knock-out mouse using 129x1/SvJ ES cells (129x1/PJ5) on a C57BL/6J background. Non-specific integration of the construct was ruled out using vector-specific PCR. Affected mice display a phenotype characterized by touch-induced seizures, marked by severe truncal, upper and lower limb contractions into unusual, twisting postures. Age of onset is around P21, after which the mice rapidly deteriorate and often die at four weeks due to dehydration. Heterozygote mice do not display any of the disease features. Heritability studies demonstrated an autosomal recessive inheritance of the mutation. To map the location of the disease causing mutation, genome wide linkage analysis using strain specific SNPs (single nucleotide polymorphisms) and RFLPs (restriction fragment length polymorphisms) was applied. A region of high linkage was assigned to chromosome 6 on the 129x1/SvJ background. Genes within this region included inositol 1,4,5-triphosphate receptor type 1 (IP3R1); *opisthotonos* mice display a phenotype similar to that observed in our mouse and has been attributed to a deletion in *IP3R1*. Sequencing the gene encoding IP3R1 revealed a novel mutation located in the carbonic anhydrase-related protein (CARP) binding site of IP3R1. Although a member of the carbonic anhydrase (CA) family, due to its high similarity in sequence, the function of CARP is unknown. Currently, we are studying expression at RNA as well as protein level. Moreover, calcium-release imaging in cerebellar Purkinje cells will be conducted to study any alterations in electrophysiological properties of mutant versus wild type IP3R1.

**P16****ANETWORK OF CO-REGULATED TRANS-GENES WITH COMMON LINKAGE TO DISTAL CHROMOSOME 1**

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We carried out a QTL analysis of a recently generated mouse hippocampus gene expression microarray data. The genome-wide QTL transcriptome maps revealed a distinct column of *trans*-acting genes with a common linkage to an interval on distal chromosome 1 (Chr1), between 170-175 Mb. Similar analysis of the forebrain and cerebellum microarray data confirmed a *trans*-band in the same locus. With this 5 Mb interval as the common factor, ~244 co-regulated *trans*-genes with LRS greater than 15 were selected out of the population of hippocampus transcripts. Gene ontology analysis generated a GO tree with highly enriched categories of genes that can be largely grouped into—(1) nucleic acid binding factors involved in gene expression and protein synthesis; and (2) ubiquitin-protein ligases involved in protein degradation mechanisms. The 5Mb Chr1 interval harbours several *cis*-acting genes for transmembrane proteins implicated in signal transduction and development, especially of the nervous system (e.g. *Ltap*, *Igsf8*, *Igsf9*). Two diseases are also linked to genes in this interval—*Ltap* linked to neural tube defects, and *Ncstn*, associated with Alzheimer's disease. The 1Mb interval in the vicinity of *Ltap* is known to have a highly conserved synteny with its homologous region on distal human Chr1, 1q21-23. Migraine, diabetes, and tumorigenesis are some of the disorders linked to 1q21-23, and this may explain the high density of complex traits QTLs mapped to mouse mid-distal Chr1.

Acknowledgement: We thank members of the Hippocampus Consortium for excess to the data.

**P17****A MOLECULAR CIRCUITRY CONTROLLING REGIONAL GENE EXPRESSION IN THE BRAIN**Z Zhou<sup>1</sup>, R Hart<sup>2</sup>, R Jornsten<sup>3</sup>, D Richardson<sup>3</sup>, D Moore<sup>4</sup>, NL Hayes<sup>5</sup>, RS Nowakowski<sup>5</sup><sup>1</sup>UMDNJ-Graduate School of Biomedical Sciences, Piscataway, NJ, United States, <sup>2</sup>Department of Cell Biology and Neuroscience, Rutgers University, Piscataway, NJ, United States, <sup>3</sup>Department of Statistics, Rutgers University, Piscataway, NJ, United States, <sup>4</sup>Department of Biostatistics, UMDNJ-School of Public Health, Piscataway, NJ, United States, <sup>5</sup>Department of Neuroscience and Cell Biology, UMDNJ-Robert Wood Johnson Medical School, Piscataway, NJ, United States

Regions of the brain differ in morphology, cellular composition, function, and gene expression. To investigate the molecular controls on these properties, we analyzed differential gene expression using tissue from 6 regions of normal adult mouse brain: hippocampus, striatum, neocortex, cerebellum, olfactory bulb and retina using Affymetrix MOE430 2.0 and mirMAX miRNA microarray chips. We found 92 genes expressed predominantly in hippocampus, including about 60 genes with known or predicted functions. These include transcription factors, ion channel subunits, neurotransmitter receptor subunits, adhesion molecules, enzymes, and transporters. A clustering and cross-correlation analysis between mRNA and miRNA expression level revealed a few clusters in which miRNA expression level is highly negatively correlated with one or more mRNAs. In one cluster, for example, miR-132 is highly negatively correlated with 20 mRNAs. This cluster was further analyzed to establish a possible basis for co-regulation. First, using the Genomatix common transcription factor analysis tool, we found 18 identified promoter regions and one statistically significant common transcription factor binding site which was for the LIM homeodomain factors, including Lhx3 and Lmx1B. Second, the LIM mRNAs are targets of miR-132, as predicted by PicTar. Third, Lhx3 and Lmx1B mRNAs are present in our tissue. Taken together, this suggests that increased miR-132 may downregulate the mRNAs of Lhx3 and/or Lmx1b, leading in turn to decreased Lhx3 and/or Lmx1b protein levels and decreased mRNA levels for the genes of this cluster. We suggest that this and other miRNA → Transcription Factor → mRNA molecular circuits could play a major role in controlling regional gene expression in the brain.

*See Page 32 for S18/P18***P19****THE TRANSMEMBRANE AMPA RECEPTOR REGULATORY PROTEIN (TARP) GAMMA SUBUNITS AND ABSENCE EPILEPSY**VA Letts, WN Frankel

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Our studies have focused on the stargazer mouse with its mutation in the TARP gamma2 subunit gene, Cacng2. The stargazer mouse has a pleiotropic phenotype, including absence seizures. These absence seizures are generalized over the cortex and can be detected by a distinctive EEG profile showing repetitive spike-wave discharges.

Absence seizures arise from perturbations within the cortex and thalamus of the brain. Interconnecting neurons between these two regions, and interneurons from the reticular thalamic nuclei, form the thalamocortical loop. A balance of excitatory and inhibitory currents through this loop is maintained in the normal brain. Disruptions of this balance are believed to underlie the seizure phenotype, but it is unclear whether this imbalance initiates from within the cortex, the thalamus or from both regions.

The gamma3 and gamma4 proteins are most closely related to gamma2 and all are predominantly expressed in the brain. We have previously constructed a gamma4 targeted mutant. Although this single mutant has no abnormal phenotype, we have shown, using double homozygous gamma4, gamma2 mutants, that the targeted gamma4 disruption results in absence seizures when gamma2 expression is also compromised.

We are following up on these studies with the gamma3 targeted mutation. As with the gamma4 mutant, the gamma3 targeted mouse has no overt phenotype. Double mutants between these gamma3 mutants with the gamma2 and gamma4 mutants will help to elucidate the role of these gamma subunits in suppressing absence seizures. Furthermore, gamma4 is highly expressed in the thalamus, but has relatively low expression in the cortex. Conversely, gamma3 expression is high in the cortex and low in the thalamus. Therefore studies of these mutants will also reveal the contribution of each brain region to the generation of absence seizures in these targeted mice.

**P20****IDENTIFICATION AND CONFIRMATION OF QUANTITATIVE TRAIT LOCI INFLUENCING ALCOHOL CONSUMPTION IN AN F2 INTERCROSS BETWEEN INBRED C57BL/6BYJ AND CONGENIC 129.B6-TAS1R3 STRAINS**

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Alcohol consumption by mice is a complex trait, which is consistent with a multigenic inheritance of ethanol consumption by humans. In our previous study using F2 hybrids between the C57BL/6ByJ (B6) and 129P3/J (129) strains, we conducted a genome screen of quantitative trait loci (QTL) for consumption of 3% and 10% ethanol solutions given in two-bottle tests (Genome Res., 2002, 12:1257). One of the QTL affecting consumption of both ethanol solutions was mapped to distal chromosome 4 and corresponds to the *Tas1r3* gene (formerly *Sac*, saccharin preference locus) encoding a sweet taste receptor, T1R3. In addition to the *Tas1r3* gene, several other QTL polymorphic between the B6 and 129 strains affect ethanol consumption. To confirm these other QTL and refine their linkages, we have produced and analyzed an F2 intercross between the inbred B6 and congenic 129.B6-*Tas1r3* strains. Because B6 and 129.B6-*Tas1r3* mice have the same allele of the *Tas1r3* gene, its contribution to phenotypic variation is eliminated in this cross. As a result, using B6 × 129.B6-*Tas1r3* F2 compared with B6 × 129 F2 allowed us to improve mapping of previously detected QTL and identify new QTL. For example, the LOD score for the *Ap7q* locus on proximal chromosome 7 increased from 5.66 to 9.41 for 10% ethanol intake and from 2.99 to 8.04 for 10% ethanol preference. New significant linkages were identified on chromosome 9 (3% ethanol intake, LOD=5.89; 3% ethanol preference, LOD=5.44; 10% ethanol intake, LOD=2.86) and chromosome 2 (10% ethanol intake, LOD=3.31; 10% ethanol preference, LOD=4.40). This approach utilizing the cross between inbred and congenic strains simplifies the genetic architecture of quantitative traits and thus facilitates positional cloning of QTL.

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**P21****TOWARDS DEFINING MOLECULAR SIGNATURES OF CELL TYPES IN THE MOUSE CNS: GENOME-WIDE HIGH RESOLUTION EXPRESSION MAPPING IN THE ADULT MOUSE BRAIN**

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Several techniques to study gene expression (DNA microarrays and serial analysis of gene expression) on a genomic-scale have been applied to large brain regions; however, these techniques lack spatial specificity in the resulting expression profile. A high-throughput colorimetric *in situ* hybridization platform has been developed to generate cellular resolution gene expression maps of the adult mouse brain. The goal of the Allen Brain Atlas (ABA) is to map the expression of ~20,000 genes in C57BL/6J. Currently, over half a million high resolution images of expression patterns are in the ABA database ([www.brain-map.org](http://www.brain-map.org)), which contains ~500 terabytes of data. To assist in the search, visualization, and analysis of expression patterns, informatics tools allow the user to query the database by anatomic structure in combination with expression level, density, and pattern as well as to view the expression data in Brain Explorer, a 3D mapping application.

Approximately 80% of the genes assayed are expressed in the brain. The major cell types, such as neurons, astrocytes, and oligodendrocytes, are defined by gene expression. Gene ontology analysis of these genes reflects the different functionality of these cell classes. While many of the expressed genes have widespread or non-restricted expression, only ~25% display regional and/or cell type specificity. Of these genes, it is extremely rare to find highly localized expression or expression in only one structure. Another remarkable finding is that gene expression is heterogeneous in known anatomical regions, such as the dorsal and ventral subregions of the hippocampus, suggesting further functional divisions within defined cytoarchitectural units. In the cortex, gene expression subdivides both the laminar and functional organization. Major cell types in each brain region can be defined by panels of genes. Overall, the expression patterns show a tremendous diversity of cell types. It has been estimated that there are ~1,000 cell types in the brain; however, few of these cell types have been defined transcriptionally. The ABA database is a freely available resource that will assist in more global approaches to redefine functional cellular neuroanatomy in the mouse central nervous system.

**P22****QTL MAPPING FOR ALCOHOL INTAKE AND RELATED PHENOTYPES IN FH/WJD X ACI/N CROSS**

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A handicap with previous QTL studies of alcohol intake in rats is a lack of information about the heritability of alcohol intake. However, recent detailed studies of the behaviour of the inbred Fawn-Hooded (FH/Wjd) and ACI/N rats and their intercrosses have revealed heritability in the range of 0.6-0.7 for alcohol intake. In the production of F2 progeny for the determination of QTL, which will be reported at the meeting, we decided to carry out an extensive behavioural characterization of the parents, F1s and F2s. We have found, for example, that alcohol intake and preference are very highly correlated, as expected. However, unexpected was that alcohol intake was not at all related to swim test immobility, since alcoholism and depression are commonly associated in humans. Another finding that supports previous literature was a small positive association between alcohol intake and saccharin intake. Sample DNA has been prepared from rats comprising the upper and lower 15 percentile of the alcohol intake distribution and QTL analyses on these samples will be reported at the meeting. Further studies will determine whether QTL for alcohol intake overlap with those for related measures like saccharin intake or unrelated measures like swim test immobility.

**P23****NADPH OXIDASE COMPONENTS ARE REQUIRED FOR NORMAL VESTIBULAR DEVELOPMENT AND FUNCTION**

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The ability of the mammalian inner ear to detect linear acceleration and gravity is dependent upon the proper formation, localization, and maintenance of crystalline deposits known as otoconia. Otoconia act as inertial masses affixed to stereocilia of the saccular and utricular maculae. Deflection of otoconia/stereocilia in response to linear acceleration and/or gravity generates vestibular-evoked potentials that are transmitted to the brain. In humans, aging, trauma, and ototoxic drugs can interfere with normal otoconial localization and maintenance, resulting in vestibular dysfunction. To better understand the development of the macular/otoconial system, we have been studying the head tilt (*het*) and head slant (*hslt*) loci of mice. Both *het* and *hslt* mutant mice display a complete absence of saccular and utricular otoconia and display several behaviors consistent with vestibular impairment. Recombination- and deletion-based positional cloning strategies have identified *Nox3* and *Noxo1* as the causative genes underlying the *het* and *hslt* phenotypes, respectively. Sequence analysis shows that *Nox3* is paralogous to *gp91phox* (*Nox2*), an NADPH oxidase of immune cells that generates reactive oxygen species as a bacteriocidal weapon against invading microorganisms. Similarly, *Noxo1* is paralogous to *p47phox* (*Ncf1*), a cytosolic component of the same oxidase complex. Based on these results, we have hypothesized that a novel NADPH oxidase complex, composed of immune complex paralogs, is present in the vestibular system and acts to initiate otoconial development from components in the endolymph including otoconin 90, calcium, otopetrin 1, and bicarbonate. Current experiments are directed at identifying additional components of the vestibular NADPH oxidase complex.

**P24**

**GENETIC DISSECTION OF TRANSCRIPTIONAL REGULATORY NETWORK IN MOUSE HIPPOCAMPUS**

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The hippocampus is a critical component of the CNS that governs learning, memory, and navigational skills. Marked differences in hippocampal structure and function have been characterized in rodents and human. This variation is generated by differences in gene sequence, transcriptional activity, and environmental factors. This study aimed to dissect gene expression networks in the hippocampus of 68 BXD strains, both parental strains and reciprocal F1 progeny. Hippocampii were dissected and mRNA levels were measured using Affymetrix M430 2.0 arrays. Data were used to map QTLs associated with variation in expression of ~45,000 transcripts. Differences in the expression of ~6000 transcripts are linked to one or more loci at a genome-wide significance level ( $P < 0.05$ ), distributed across almost all chromosomes. Approximately 2600 of these transcripts are modulated by strong cis-acting QTLs that are tightly linked to the chromosomal location of the transcript itself, indicating that genetic variations within these transcript genes or the nearby promoter/regulatory regions affect the transcription level. Another large group of transcripts are modulated by trans-acting QTLs. Hundreds of transcripts often share a common trans-acting QTL and presumably these groups often share common molecular networks and genetic control. The data is available through public web-based resource (<http://www.genenetwork.org>) that allows custom genetic linkage analysis, co-regulated transcripts identification, and correlation analysis.

**P25**

**HAPLOTYPE-ASSOCIATED MAPPING OF BEHAVIOR ACROSS INBRED STRAINS: IDENTIFICATION OF LOCI ASSOCIATED WITH LOCOMOTOR ACTIVITY IN A NOVEL ENVIRONMENT**

JS Bailey, L Grabowski, JR Walker, T Wiltshire, LM Tarantino

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The search for genes involved in quantitative traits has employed both forward and reverse genetic approaches. In the area of behavior, both strategies have met with some success. The search for quantitative trait loci (QTL) for behavioral phenotypes has yielded hundreds of loci and studies are ongoing to narrow the chromosomal locations and identify the underlying polymorphisms.

More recently, large-scale efforts have been initiated to genotype SNPs across 48 inbred strains and to develop a haplotype map based on the SNP genotypes. This map, along with phenotypic analysis of the inbred strains, has already been used to identify QTLs for a number of clinical phenotypes including lung tumor and atherosclerosis susceptibility.

We are currently using this approach to identify genes involved in modulating behavior. We have developed a set of behavioral assays that model anxiety, depression, stress response and sensorimotor gating and have completed data collection for 29 inbred mouse strains. .

As expected, we see significant strain differences in all assays. Interestingly, we also see strain-specific sex differences for many of the behaviors we have examined. In addition, the use of several assays believed to model different aspects of the same behavioral trait has allowed us to make interesting comparisons both between assays and between strains.

Finally, using haplotype associated mapping analysis, we have identified a locus involved in locomotor response to a novel environment. Studies are currently underway to investigate the role of a candidate gene in the region that has previously been linked with locomotor activity.

**P26****MISSENSE MUTATION IN THE VOLTAGE SENSOR OF THE P/Q-TYPE  $Ca^{2+}$  CHANNEL RESULTS IN DOMINANT CEREBELLAR ATROPHY AND ATAXIA IN WOBBLY MICE**

G Xie<sup>1</sup>, S Clapcote<sup>1</sup>, B Nieman<sup>2</sup>, T Tallerico<sup>3</sup>, Y Huang<sup>3</sup>, I Vukobradovic<sup>1</sup>, S Cordes<sup>1</sup>, L Osborne<sup>3</sup>, J Rossant<sup>2</sup>, J Sled<sup>2</sup>, J Henderson<sup>3</sup>, J Roder<sup>1</sup>

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Dominant mutations of the P/Q type  $Ca^{2+}$  channel (CACNA1A) underlie several human neurological disorders, including FHM1, EA2 and SCA6. The previously described mouse *Cacna1a* mutants (*tottering*, *leaner*, *rolling Nagoya* and *rocker*) are recessive mutations. Here we report a novel dominant mutation of mouse *Cacna1a*. This *wobbly* mutant was identified in an ENU mutagenesis dominant behavioral screen. Cerebellar ataxia was the predominant neurological phenotype observed in *wobbly* mice. Heterozygotes exhibit ataxia from 3 weeks of age and have a normal lifespan, while homozygotes exhibit more severe ataxia from postnatal day 8, later develop involuntary twisting body movements and die prematurely. Both heterozygotes and homozygotes exhibit cerebellar atrophy with focal reduction of the molecular layer. No obvious loss of Purkinje cells or decrease in size of the granule cell layer was observed. Real-time PCR revealed altered expression levels of *Cacna1g*, *Calb2* and *Th* in *wobbly* cerebella, but *Cacna1a* mRNA and protein levels were unchanged. Positional cloning revealed that *wobbly* mice have a missense mutation leading to an arginine to leucine (R1255L) substitution, resulting in neutralization of a positively charged amino acid in repeat III of voltage sensor segment S4. Electrophysiological measurements of Purkinje cells in *wobbly* mice are in progress. Positive charge neutralization in S4 has been shown to underlie several cases of human dominant FHM1 with ataxia. The dominant *wobbly* mutant thus highlights the importance of the voltage sensor and provides a starting point to unravel the neuropathological mechanisms of this disease.

**P27****QUANTITATIVE TRAIT LOCUS MAP OF INTENSITY INDEPENDENT NOISE RESISTANCE IN 129S6 MICE**

BL Tempel<sup>1</sup>, VA Street<sup>1</sup>, DJ Shilling<sup>1</sup>, CM Liberman<sup>2</sup>, KW Broman<sup>3</sup>, SG Kujawa<sup>2</sup>

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Noise-induced hearing loss (NIHL) is a widespread and growing health problem. Estimates suggest that 30 million persons in the USA are exposed to dangerous sound levels each day; long-playing digital music devices may increase this number dramatically. Toward understanding how the ear might be made resistant to noise exposure, we have used a quantitative trait locus (QTL) approach in mice, comparing CBA/CaJ, a good hearing strain, and 129S6, a strain that shows intensity-independent noise resistance (IINR) (Yoshida et al., 2000). To test for noise resistance 4-week old mice are exposed to noise (103 dB SPL, octave band 8-16 kHz, 2 hr.), held for 2 weeks, then tested for hearing thresholds at 8, 12, 16, 24 and 32 kHz using auditory brain response (ABR) measures. Testing of 234 N2 backcross animals revealed approximately 1 in 10 of the N2s with noise resistance similar to the 129S6 parental strain, suggesting 3-4 contributing loci. Whole genome scans at 15 cM resolution were performed using dinucleotide repeat markers on all N2 mice. Analysis with R/qtl using data for each of the ABR frequencies as independent phenotypes identified QTLs on Chrs. 4, 11, 14, 17 and 18 with maximal LOD scores of 3.8, 2.3, 3.8, 6.0 and 2.4, respectively. We identify the intensity independent noise resistance QTLs on Chrs. 17, 4 and 14 as *iinr1*, *iinr2* and *iinr3*, respectively. No evidence was found for genetic interactions between the QTLs in this cross.

Current work is focused on narrowing the QTL intervals using additional dinucleotide markers to scan N2 individuals and strain-specific single nucleotide polymorphism (SNP) data. An integrative genomics approach using microarray expression analysis, quantitative PCR analysis, parental haplotype analysis, candidate hearing loss gene and pathway analysis has identified 6 candidate genes of interest within the *iinr1* QTL on Chr. 17. These genes are being sequenced in each of the parental strains to identify potential SNP differences. Gene transfer between strains, combined with functional testing for noise resistance will help identify genes that contribute to intensity independent noise resistance.

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