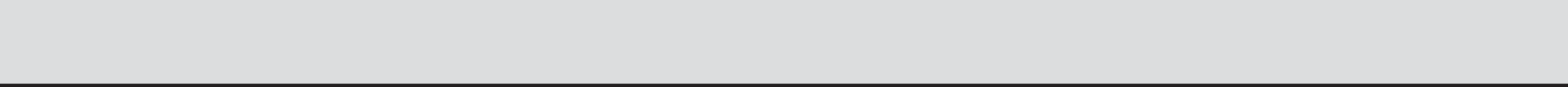


Tuesday October 30
Oral Presenters Abstracts



**NEUROSCIENCE/BEHAVIOR
ORAL PRESENTATION****Tuesday October, 30****9.00 – 9.15am****O4-1****A MISSENSE MUTATION IN THE MOUSE GENE ENCODING HERC1 UBIQUITIN LIGASE RESULTS IN PURKINJE CELLS DEGENERATION WITH SEVERE ATAXIA**Tomoji Mashimo^{1,2}, Toshiko Tsurumi¹, Tadao Serikawa¹, Jean-Louis Guénet²¹Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University, Kyoto, Japan, ²Unité de Génétique des Mammifères, Institut Pasteur, Paris, France

Mice homozygous for the autosomal recessive mutation *tambaleante* (*tbl*) exhibit degeneration of cerebellar Purkinje cells starting approximately two months after birth. We mapped the *tbl* locus on mouse chromosome 9, and identified the *tbl* mutation as resulting from a Gly483Glu substitution in the highly conserved domain of the guanine nucleotide exchange factor, the RCC1-like domain (RLD) 1, of the HERC1 protein. *Herc1* encodes a giant polypeptide of 4861 amino acid residues, containing two regions of the RLD, and a carboxy-terminal HECT domain characteristic of E3 ubiquitin-protein ligases. Transgenic complementation using BAC clones containing the full length of the wild type *Herc1* gene restored a normal phenotype in mutant mice. Our observations indicate that the *Herc1* is critical for postnatal survival of Purkinje cells, and suggest that this gene might be involved in temporal and spatial dynamic regulations of protein trafficking essential for the maintenance of Purkinje cells.

**NEUROSCIENCE/BEHAVIOR
ORAL PRESENTATION****Tuesday October, 30****9.15 – 9.30am****O4-2****ANALYSIS OF THE FANTOM TRANSCRIPTOME DATABASE: IDENTIFICATION OF A NOVEL
MODULATOR OF NICOTINIC ACETYLCHOLINE RECEPTORS**Martin Darvas¹, Marco Morsch², Ildiko Racz¹, Seifollah Ahmadi², Dieter Swandulla², and Andreas Zimmer¹¹University of Bonn, ¹Institute of Molecular Psychiatry, ²Department of Physiology

Nicotinic acetylcholine receptors (nAChRs) are pentameric ion-channels gated by the neurotransmitter acetylcholine and also by nicotine. Their functional properties can be allosterically modulated by snake venom neurotoxins and by related endogenous small proteins of the u-PAR/Ly-6 family. Here we identify Lypd6, a distantly related novel member of the u-PAR/Ly-6 family expressed in neurons as a novel modulator of nAChRs. Transgenic mice over-expressing Lypd6, displayed behaviors that were indicative of an enhanced cholinergic tone, such as a higher locomotor arousal, increased prepulse-inhibition, improved working memory and hypoalgesia. These mice were also more sensitive to the analgesic effects of nicotine. Single cell recordings from isolated trigeminal neurons demonstrated that Lypd6 selectively enhanced the calcium-component of nicotine-evoked currents. Lypd6 seemed to be essential for embryo development, because transgenic mice expressing siRNAs directed against Lypd6 were unable to procreate. Thus, Lypd6 is a critical modulator of nAChR signaling in vivo.

**NEUROSCIENCE/BEHAVIOR
ORAL PRESENTATION****Tuesday October, 30****9.30 – 9.45am****O4-3****EXPLORING THE FUNCTION OF FBXL3 IN MAMMALIAN CIRCADIAN RHYTHMS**

Patrick M Nolan¹, Alun R Barnard¹, Lydia Teboul¹, Inna Johnson¹, Luca Busino², Michele Pagano², Elizabeth Maywood³, Michael H Hastings³, Sofia Godinho¹

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Progeny of *N*-ethyl-*N*-nitrosourea (ENU) mutagenized mice were used in a screen for mutations affecting circadian rhythms. An abnormal mouse with a circadian period significantly longer than the population mean was identified. Test-matings confirmed semi-dominant inheritance of the phenotype (wildtype period ~23.6 hrs, heterozygous period ~24 hrs, homozygous period ~26.5 hrs). The mutation, named “after hours” (*Afh*), results in a C358S substitution in the F-box protein FBXL3. FBXL3 is part of a large family of mammalian F-box proteins, which act as ubiquitin E3 ligases. Molecular analysis established that FBXL3 binds to the products of two molecular circadian clock genes in mammals (*Cry1* and *Cry2*). The *Afh* mutation reduces the affinity of FBXL3 for CRY proteins. This prolongs the phase of CRY-mediated negative feedback and reduces peak levels of additional members of the core circadian oscillator (*Per*, *Cry* and *Bmal1*). Thus, using an unbiased genetic screen, it has been firmly established that FBXL3 is an important regulator of the molecular circadian oscillator in mammals. To further explore the role of *Fbxl3* in circadian rhythms we identified a gene-trap line with vector integration between exons 1 and 2 of *Fbxl3*. Heterozygous null mutants (*Fbxl3*^{+/Δ}) have a similar lengthened circadian period (~24 hr) to heterozygous *Afh* mutants (*Fbxl3Afh*^{+/+}). The behavioural and molecular analysis of homozygous null mutants (*Fbxl3*^{-/-}) and compound heterozygotes (*Fbxl3*^{Afh/-}) is ongoing. This work will offer definitive proof that the *Afh* phenotype results from a mutation in *Fbxl3* and also provides evidence regarding possible functional redundancy in the CRY degradation pathway.

**NEUROSCIENCE/BEHAVIOR
ORAL PRESENTATION****Tuesday October, 30****10.00 – 10.15am****O4-4****MITOCHONDRIAL RESPIRATION DEFICIENCIES ALTER SOCIAL BEHAVIOR AND SPATIAL MEMORY IN MICE**

Atsuko Kasahara^{1,2}, Kazuto Nakada^{1,2}, Akitsugu Sato¹, Keizo Takao^{3,4}, Tsuyoshi Miyakawa^{3,4}, Jun-Ichi Hayashi¹
¹Grad. Life and Environ. Science, Univ. of Tsukuba, ²TARA, Univ. of Tsukuba, ³Grad. Sch. Med., Kyoto Univ.,
⁴ICMS, Fujita Health Univ

Mitochondria possess multiple copies of own genome, mitochondrial DNA (mtDNA), and the mtDNA encodes 13 subunits essential for mitochondrial respiratory function. It has been known that mtDNAs with pathogenic mutations are associated with mitochondrial diseases. Moreover, it has been reported that mutated mtDNAs was detected in patients with psychiatric disorders. These forward genetic studies suggested the possibility that the mutated mtDNA is responsible for psychiatric disorders. To test this possibility, we evaluated behavior and spatial memory using a reverse genetic mouse model carrying homoplasmic mtDNA with a missense mutation in COXI gene (mito-miceCOXI), which is one of the subunits of cytochrome c oxidase (Complex IV in respiratory chain: COX). The mito-miceCOXI showed mitochondria respiration deficiencies, because of the homoplasmic mutation in COXI, and exhibited lactic acidosis slightly, because of the resultant up-regulation of glycolysis to compensate the mitochondrial respiration deficiencies. However, they did not show other clinical phenotypes for mitochondrial diseases, that is, these mice apparently healthy. Then, social behavior was estimated by sociability and preference for social novelty, and spatial memory was evaluated by Barnes circular maze. Surprisingly, we observed a selective impairment in response to social novelty, while spatial memory was elevated in mito-miceCOXI. These results show that mitochondria respiration deficiencies due to mutated mtDNA are associated with social behavior and spatial memory, and the mito-miceCOXI are the useful model for elucidating molecular mechanisms of psychiatric disorders from mitochondrial causes.

**NEUROSCIENCE/BEHAVIOR
ORAL PRESENTATION****Tuesday October, 30****10.15 – 10.30am****O4-5****FOUR-DIMENSIONAL QUANTITATIVE ANALYSIS ON THE GAIT OF MUTANT MICE BY USING THE MOTION CAPTURE TECHNOLOGY**

Satoshi Oota, Kazuyuki Mekada, Fujimi Arai, Yuichi Obata, Kaoru Fukami-Kobayashi and Atsushi Yoshiki
RIKEN BRC

By using the motion capture technology, we analyzed a sequence of motion data of abnormal gait of hugger (hug) mutant mice. Homozygous (hug/hug) mutant mice exhibited an awkward gait pattern, while their heterozygous (hug/+) siblings walked normally. We used six infrared cameras to capture positions of retroreflective markers placed at nine points on the body of each mouse. Each camera recorded two-dimensional trajectories of the markers, and the trajectories were integrated by Eva-RT (4.0-4.2) software to reconstruct a set of three-dimensional trajectories for each mouse. The gait patterns estimated from the sets of trajectories of homozygous and heterozygous mutant mice were compared to detect mutant-specific gait patterns in four-dimension. We could detect high-resolution mutant-specific gait patterns from the data, in terms of time and space (1/120 sec and approximately 0.3 mm, respectively). Since this approach has originally been developed for analyzing human complex motion and behavior, abundant information correlating genes and phenotypes has already been accumulated in this field. Therefore, quantitative analysis of the motion capture data of the mouse will potentially fill gaps between mouse and human behavioral phenotypes, especially in terms of neuroscience.