A remutation to *Scn8a*$^{med\text{-}jo}$ named jolting 2 Jackson

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Mutation (allele) symbol: *Scn8a*$^{med\text{-}jo2J}$

Mutation (allele) name: jolting 2 Jackson

Gene symbol: *Scn8a*

Strain of origin: B6.129S7-*Ldlr*^{tm1Her} */J*

Current strain name: B6(129S7)-*Scn8a*$^{med\text{-}jo2J}$/GrsrJ

Stock #004073 (jaxmice.jax.org)

Phenotype categories: neuromuscular

Abstract
A neuromuscular remutation to jolting (a mutation in the *Scn8a* gene) has been identified. Mice homozygous for this recessive mutation can be recognized at 15 days of age by their unsteady gait and tremor of the head and trunk. Mutant mice often survive to adulthood and some have bred.

Origin and Description
Mice carrying this mutation were found by Jay Young in August 1997, in the B6.129S7-*Ldlr*^{tm1Her}/J strain in a production colony at The Jackson Laboratory and were brought to the Mouse Mutant Resource (MMR). Homozygous mutants are easily recognized at 15 days of age by their shaky, unsteady gait. Weaning must be delayed for homozygotes until at least 6 weeks of age. The strain is maintained by ovarian transplantation; the host female is mated to a non-mutant sibling (+/?) of the homozygous mutant ovary donor. Then heterozygous progeny are mated together and the cycle is repeated. The targeted mutation (*Ldlr*^{tm1Her}) in the strain of origin has been bred out of the jolting 2 Jackson strain.

Genetic Analysis
Tests for Allelism:
A test for allelism with *Unc5c*^{rcm} produced 0 *rcm*/19 born.
A test for allelism with *Agtpbp1*^{pcd} produced 0 *pcd*/29 born.
A test for allelism with jolting (*Scn8a*$^{med\text{-}jo}$) produced 12 *med-jo*/29 born.

Pathology

A pathological screen[1] of 12 mutants from 6 to 9 months of age revealed Purkinje cell loss, dystrophic axons in the cerebellar white matter, and apoptotic spermatids in the testes. At 34 weeks of age there was degeneration of cervical joints, while at 27 weeks there was slightly elevated degeneration of cervical joints.

Hearing was assessed by ABR[2] testing of 4 mutants and 2 controls at 51 days of age. The mutants showed elevated ABR thresholds (~ 30 dB above controls), long latencies and abnormal waveforms. The mutant animal cochlear function is normal, but mutants suffer from a deficit in central auditory processing.

Discussion

A test for allelism between C57BL/6J-*Scn8a*$^{med\text{-}jo}$ and B6(129S7)-*Scn8a*$^{med\text{-}jo2J}$ confirmed that the two mutations are allelic. The Mouse Genome Database (MGD) places the *Scn8a* gene on Chromosome 15 at 60 cM.

Acknowledgements

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References

Mouse Genome Database (MGD) Mouse Genome Informatics Project, The Jackson Laboratory, Bar Harbor, Maine. World Wide Web (informatics.jax.org)

[1]**Standard Histology Protocol used in the Mouse Mutant Resource:** For fixation of tissues, mice were deeply anesthetized with tribromoethanol (avertin) until they no longer displayed a withdrawal reflex in the hind limbs and then perfused intracardially with Bouin's fixative following a flush of the vasculature with saline solution. After soaking in Bouin's for one week to demineralize bones, tissues were dissected. Six segments of spine with axial muscles and spinal cord in situ, representing cervical, thoracic and lumbar spinal segments, were dissected. The brain was removed and sliced into 6 cross sectional pieces at the levels of olfactory lobes, frontal cortex, striatum, thalamus, midbrain, rostral and caudal medulla with cerebellum. Midsagittal slices of hind leg through the knees were prepared. Slices of basal skull through the pituitary and inner ears were taken. Both eyes, salivary glands and submandibular lymph node, trachea plus thyroid and sometimes parathyroid were removed and cassetted. A longitudinal slice of skin from the back was removed. The thymus, slices of lung, and a longitudinal slice of heart were cassetted. Similarly slices of liver through gall bladder, kidney with adrenal attached, pancreas and spleen were prepared. The stomach was sliced longitudinally to include both squamous and glandular portions. Loops of small intestine from 3 levels and slices of large intestine and cecum were removed, as were slices of urinary bladder. The whole uterus, with ovaries attached, was taken. In males testes were sliced longitudinally. The accessory male organs including seminal vesicles, coagulating gland and prostate were removed en block. Altogether in most cases all tissue fit into a total of 10 cassettes. The cassettes were processed in an automatic tissue processor to dehydrate tissues which were then embedded in paraffin. Six micron sections were cut and stained with hematoxylin and eosin (H&E). Sections of brain and spinal cord in vertebral bones also were stained with luxol fast blue (LFB) for myelin and cresylecht violet (CV) for cellular detail.

[2]**ABR thresholds** in mice are determined using a semi-automated computer system (Intelligent Hearing Systems, Miami, Florida). Subdermal needle electrodes are inserted at the vertex and ventrolaterally to both ears of anesthetized mice. Specific auditory stimuli from 10-100 dB SPL are delivered binaurally through plastic tubes from high frequency transducers. ABR thresholds are obtained, in an acoustic chamber, for clicks and for 8, 16, and 32 kHz pure-tone pips.