A mutant allele of the *Cacnb4*^{lh} gene named lethargic 3 Jackson

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Mutation (allele) symbol: *Cacnb4*$^{lh\text{-}3J}$

Mutation (allele) name: lethargic 3 Jackson

Gene symbol: *Cacnb4*

Strain of origin: C3HeB/FeJ

Current strain name: C3HeB/FeJ-*Cacnb4*$^{lh\text{-}3J}$/GrsrJ

Stock #004951 (JaxMice.jax.org)

Phenotype categories: neurological

Abstract
This remutation to lethargic arose in a breeding colony of C3HeB/FeJ at The Jackson Laboratory and was discovered by Richard Sandowski and Wendy Alley. Mice homozygous for *lh-3J* have a wobbly gait and may stargaze. This neurological mutation was mapped to Chr 2 in the region where the mouse mutation lethargic (*lh*) is located at 33.9 cM. A test for allelism with lethargic was positive, confirming allelism.

Origin and Description
This remutation came to The Deviant Search Program at the Jackson Laboratory from a breeding colony of C3HeB/FeJ on May 23, 2001. Mice homozygous for lethargic 3 Jackson are recognizable at 14 days of age. They exhibit a behavior characteristic of lethargic with a wobbly gait resembling an unsteady wide legged shuffle. Some homozygotes also display occasional pauses with the head tilted upward, similar to that found in the stargazer (*Cacng2*^{stg}) mutant mice, but seizures have not been reported. The homozygotes are smaller than their littermates but live a normal lifespan. Both sexes may breed but they produce smaller litters or stop breeding earlier than heterozygous sibs.

Genetic Analysis
Using our standard mapping procedure two +/*lh* mice were crossed to two CAST/Ei mice and produced no affected progeny. F1 progeny were intercrossed and produced 45 F2 affected animals of which 35 were used to determine the chromosomal location of the *lh-3J* mutation. A genome wide scan found the *lh-3J* mutation located on Chr 2 showing 5.3 % recombination with *D2Mit241*. Individual DNAs were then typed for six additional markers. The recombination estimates with standard errors and the best gene order are: centromere-[*D2Mit320, D2Mit7*]-2.6 +/- 1.6 - *D2Mit241*- 2.9+/- 2.0 -*lh-3J*-4.3 +/- 2.5 - *D2Mit244* -7.2 +/- 3.3 - *D2Mit124-2.6* +/- 2.6-[*D2Mit182, D2Mit331*]. Gene order and recombination frequencies were calculated with the Map Manger computer program

(Manley 1993). Based on the Ensembl assembly for Chr 2, the chromosomal position for *lh-3J* is between 46098933 bp (D*2Mit241* at 30 cM) and (*D2Mit244* at 33 cM which is not mapped to the Ensembl assembly) and our next distal marker *D2Mit124at* 37cM is at 64767728 bp.

The test for allelism was done by mating a female +/*lh-3J* mouse to a male +/*lh* from an established colony. Two litters from this mated pair produced 3 affected female out of 13 progeny born. The technician in charge of the established lethargic colony compared a *lh/lh* to a similar aged *lh-3J/lh-3J* and agreed the phenotypes are similar.

Pathology

A pathological screen of 9 mutant mice showed all have *rd-1* (retinal degeneration 1) which is characteristic of the C3HeB/FeJ strain. No other consistent lesions were observed. Three of the mice had a slightly wavy hippocampus. Two mice had thyroid cysts. One mouse had mild hydrocephalus.

Acknowledgements

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References

Manley KF (1993) A MacIntosh program for storage and analysis of experimental mapping data. Mamm Genome 4, 303-313.

Mouse Genome Database (MGD) Mouse Genome Informatics Project, The Jackson Laboratory, Bar, Harbor, Maine.