Shambling 5 Jackson: a new mutation in *Cntnap1*

Authors: Belinda S. Harris, Patricia F. Ward-Bailey, Melissa Berry, Jieping Wang, David E. Bergstrom, Roderick T. Bronson and Leah Rae Donahue

Source of Support: This research was supported by NIH/NCRR grant RR001183 to the Mouse Mutant Resource (Leah Rae Donahue, PI) and Cancer Center Core Grant CA034196.

Mutation (allele) symbol: *Cntnap1*$^{shm\text{-}5J}$

Mutation (allele) name: shambling 5 Jackson

Gene symbol: *Cntnap1*

Strain of origin: B6C3-Tg(APPswe,PSEN1dE9)85Dbo/J

Current strain name: B6.Cg-*Cntnap1*$^{shm\text{-}5J}$/GrsrJ

Stock #010823 (jaxmice.jax.org)

Phenotype categories: neuromuscular

Abstract

We have identified a new, recessive, mouse mutation, which causes an abnormal gait, reduced body size, and reduced fertility in males. This mutation was initially mapped to Chromosome 11 using an intercross with CAST/EiJ. Subsequent sequence analysis showed that this mutation is a single base pair T to C transition in exon 13 of contactin associated protein-like 1 (*Cntnap1*), which is predicted to result in a serine to proline substitution in amino acid 674. This mutation has been designated shambling 5 Jackson (*Cntnap1*$^{shm\text{-}5J}$).

Origin and Description

A mutant mouse was identified in 2005 in the B6C3-Tg(APPswe,PSEN1dE9)85Dbo/Mmjax production colony at The Jackson Laboratory by Teresa Fennelly. This mutation was initially recognized by its odd walk and the flinging about of its hind legs when picked up by the tail, for which it was initially named thrasher. By 3 weeks of age homozygotes wobble and splay their rear legs when they walk. These mice also have an overall body tremor when picked up by their tail. Shambling 5 Jackson homozygotes are first recognized by three weeks of age and live a normal lifespan. Homozygous females are fertile and raise their young, though male homozygotes are usually sterile, yet do live a normal lifespan. This colony is maintained by crossing a homozygous female to an inbred C57BL/6J male and intercrossing the resulting obligate heterozygotes. Through this backcrossing Tg(Appswe,PSEN1dE9)85Dbo has been bred out of this mutant subline but the phenotype remains the same.

Genetic Analysis

Mapping to Chromosome 11 was accomplished using an intercross with CAST/EiJ placing this mutation at marker *D11Mit360* with no recombinants. Sequence analysis performed by Jieping Wang of the murine Cntnap1 cDNA from homozygous mutants showed a single base substitution of T to C at position 2029, which is within exon 13.

This spontaneous mutation changes codon 677 from TCC to CCC, which results in an amino acid substitution from serine to proline at amino acid 674.

Pathology

Assessment of brainstem auditory evoked response and eye examinations as well as electroretinograms on two homozygotes and two heterozygotes at six weeks of age showed that all were normal. Pathology of two male homozygotes at 16 weeks and at 22 weeks of age showed no lesions.

Discussion

We report a spontaneous point mutation in exon 13 of the *Cntnap1* gene, shambling 5 Jackson (*Cntnap1*$^{shm\text{-}5J}$). This mutation differs phenotypically from published targeted mutations of *Cntnap1* and also from the original shambling mutation, which is predicted to cause a truncation deleting the c-terminal 98 amino acids, in that *Cntnap1*$^{shm\text{-}5J}$ homozygotes live past wean age and females are fertile. Thus, while this single amino acid change causes the outward neurological phenotype of the more severe *Cntnap1* mutations, this mutant is viable as an adult and offers a unique resource for the study of this gene and its role in neuromuscular function.

Acknowledgements

We would like to thank the late Norm Hawes for eye examinations, Heping Yu for ABR testing, and Coleen Kane for histological preparations.