# Tremulous, a dominant spontaneous mouse mutation that causes ataxia, wasting, and premature death

Authors: Son Yong Karst, Melissa L. Berry, Heather E. Fairfield, Laura G. Reinholdt, Dave E. Bergstrom, and Leah Rae Donahue

Source of Support: This research was supported by grants RR01183 and OD010972 to the Mouse Mutant Resource (Leah Rae Donahue, PI) and Cancer Core Grant CA34196.

Mutation (allele) symbol: *Trms*

Mutation (allele) name: tremulous

Strain of origin: B6CBAF1/J

Stock numbers and strain names (jaxmice.jax.org):
#018138, B6.Cg-*Trms*/GrsrJ
#017338, STOCK *Trms*/GrsrJ

Phenotype categories: neurological

**Origin and Description:**
A spontaneous mutation that causes ataxia, wasting, and premature death was discovered by Alan Dorr in a colony of B6CBAF1/J at The Jackson Laboratory. This mutation was proven dominant by outcrossing to C57BL/6J and obtaining affected and wild-type mice in the F1 population. On a congenic C57BL/6J background no phenotype is evident at wean age, but the phenotype begins to present as early as four weeks of age and progresses rapidly to death. Heterozygotes become thinner than their wild-type littermates. These heterozygotes develop a whole body tremor that is visible when they are still, and a wobbly, increasingly labored gait. The posture becomes lower to the ground, and these mice seem cautious in their movement. The wasting and ataxia progress in severity, and on the C57BL/6J background all heterozygotes die with severe wasting before 8 weeks of age, with a few dying as early as 4 weeks of age. On a mixed STOCK background that includes CAST/EiJ and FVB/NJ in addition to CBA/J and C57BL/6J, heterozygotes have a phenotypic onset anytime between four and eight weeks of age and most live longer than 12 weeks of age with one having lived past 5 months of age. We have named this mutant tremulous (*Trms*). Because of the onset and severity of the phenotype this mutation is maintained by ovarian transplantation from heterozygous females.

**Genetic Analysis:**
Mutant animals were out crossed to FVB/NJ mice to establish heritability. Affected mice were found in the F1 generation. Backcrossing affected F1 animals to FVB/NJ produced affected N2 animals, indicating a dominant mode of inheritance. Affected N2 mice were generated for linkage analysis and fine mapping. Using standard SNP protocols, linkage analysis for this mutation was completed in the Fine Mapping Laboratory at The Jackson Laboratory. This mutation mapped to Chromosome 18, between the markers *D18Mit123* (Chr18:55,970,605 - 55,970,721 bp) and *D18Mit196* (Chr18:89,318,282 - 89,318,398 bp) (GRCm38). Whole exome sequencing was performed on a heterozygous mutant genomic DNA sample but did not reveal any candidate mutation in the critical region

with standard SNP and INDEL calling methods. Further genomic analysis is required to determine the genetic basis of this mutation; this may include whole genome sequencing of RNA sequencing methods.

**Pathology:**
A routine pathological screen of two heterozygotes at 7 weeks of age showed no significant lesions, aside from some proliferative new bone around the root of a lower incisor tooth and the suggestion of deficient otoconia in the utricle and saccule of one mouse. However, whole mount analysis of cleared inner ears revealed no otoconial deficiencies or abnormalities detected in the inner ear. Auditory brain stem response testing of one mutant at 39 days of age and one mutant and three controls at 7 weeks of age showed normal hearing. Ophthalmoscopy found no abnormalities in they eyes of two mutants and three controls at seven weeks of age. The eyes of three mutants and three controls at age 7 weeks of age, and two mutants and one control at age 6 weeks of age were tested by electroretinography and no abnormalities were found.

**Acknowledgements:**
The authors thank Alan Dorr for discovery of the mutant, Chantal Longo-Guess for hearing assessment, Leona Gagnon for ear histology, and Ron Hurd for eye examinations.