Tremor and reduced lifespan (*trls*): a new neurological mutation on Chromosome 10.

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Mutation (allele) symbol: *trls*

Mutation (allele) name: tremor and reduced lifespan

Gene symbol: *trls*

Strain of origin: BKS.Cg-*m*+/+*Lepr*^{db}/J

Current strain name: BKS(Cg)-*trls/*GrsrJ

Stock #0005898 (jaxmice.jax.org)

Phenotype Categories: neurological

Abstract
A new spontaneous, recessive neurological mutation has been identified and named tremor and reduced lifespan (*trls*). This mutation, when homozygous, causes tremors in pups, a reduced body size, and a shortened lifespan. An intercross mating of this new *trls* mutation to CAST/Ei was used to map the mutation to Chromosome 10.

Origin and Description
This new recessive mutation arose in a breeding colony of BKS.Cg-*m*+/+*Lepr*^{db}/J at the Jackson Laboratory and was discovered in September of 2000 by Marianne Urquhart. Mice homozygous for the *trls* mutation can be characterized at about 14 days of age by their body size which is smaller than littermates and by a tremor in pups that is similar to that seem in the previously described shiverer (*Mbp*^{shi}) and quivering (*Spnb4*^{qv}) mutants. Most homozygous *trls*/*trls* pups die at about 3 weeks of age, although a few have lived as long as 9 weeks and one animal has survived for 10 weeks.
The BKS(Cg)-*trls*/J colony is maintained by ovarian transplant. The ovaries of a female homozygous for *trls* are transplanted into a C3SnSmn.CB17-*Prkdc*^{scid}/J (stock #001131) host, and then the host is mated to a C57BLKS/J (Stock# 000662) male. This mating has been done for 4 generations (as of 11/11/2005) without seeing any misty (*m*) or diabetic (*Lepr*^{db}*)* offspring, indicating that these mutations have been bred out of this strain.

Genetic Analysis
The *trls* mutation was first identified as a recessive mutation by crossing a BKS.Cg-*m*+/+*Lepr*^{db}-*trls* mutant to an inbred C57BL/6J mouse. In this cross no mutants were produced in the F1 generation, but mutants were produced in the F2 intercross generation. Using our standard mapping procedures[1] an intercross with CAST/Ei was set up and

generated 57 affected progeny that were used for linkage analysis. The mutation maps on mouse Chromosome 10 between *D10Mit115* (NCBIm34 position 70.3 Mb) and *D10Mit65* (NCBIm34 position 84.1 Mb) and is non-recombinant with *D10Mit7* (NCBIm34 position 81.2 Mb) and *D10Mit42* (NCBIm34 position 82.5 Mb).

Based on the phenotype and map position similarity of this new mutation to the previously described *Atcay*$^{ji\text{-}hes}$ (NCBIm34 position 81.3 Mb) mutation, a direct test for allelism was accomplished by mating two mice homozygous for *Atcay*$^{ji\text{-}hes}$ to two mice heterozygous for the new *trls* mutation. These matings produced 3 litters with a total of 18 progeny, all normal in appearance, indicating that the *trls* mutation is probably not a remutation to *Atcay*$^{ji\text{-}hes}$.

Pathology

A routine pathological screen of three mutants (two females and one male) at three weeks of age showed no lesions other than aspermiogenesis in the male. Two mutants (one female and one male) at 9 weeks of age showed clinical signs compatible with myelin deficiency, like shiverer, but both peripheral and central myelin are normal. The 9-week-old male did not show the aspermiogenesis seen in the 3-week-old male. Two controls (one female and one male) at 9 weeks of showed no lesions.

Hearing was assessed in four mutants (*trls/trls*) and three controls (+/?) at 39-45 days of age. The average ABR thresholds for high frequency stimuli (16 and 32 kHz) were 15-20 dB higher in the mutants than in the control mice, indicating a mild hearing impairment. Hearing impairment varied among mutant mice; one of the three mutants tested exhibited ABR thresholds no different from those of controls. The ABR wave pattern appeared normal in the mutant mice, in contrast to the characteristic abnormal pattern seen in myelin deficient mice. The eyes of two homozygous mutants, one male and one female, were examined with an ophthalmoscope and were determined to be normal.

Discussion

A new neurological mutation (*trls*) has been mapped to Chromosome 10 and is non-recombinant with *D10Mit7* and *D10Mit42* in the 43-44 cM position. The underlying gene for this new mutation has not been identified. The phenotype of this new mutation is tremors and shortened lifespan; however the new mutation does not show myelin deficiency. Although it maps to the same Chromosome 10 location, *trls* is not allelic with *Atcayji-hes.*

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References

The Ensembl database

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