High stepper: A new neurological and eye mutation mapped to Chromosome 19.

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Mutation (allele) symbol: *hstp*

Mutation (allele) name: high stepper

Gene symbol: *hstp*

Strain of origin: C57BL/6J

Current strain name: C57BL/6J-*hstp*/J

Stock #006948 (jaxmice.jax.org)

Phenotype categories: neurological/eye

Abstract
We have identified a new mouse mutation that causes an abnormal gait and eye defects in affected animals. Eyes of high stepper mice have normal fundus but histological preparations show it has rosettes and misplaced ganglion cells, which can be observed at approximately two weeks of age. The high stepper mutation (*hstp*) was mapped to Chromosome 19.

Origin and Description
A mouse carrying the high stepper mutation was discovered in 2003 by Susan Sargent at the Jackson Laboratory. The *hstp/hstp* homozygote was first recognized as having an abnormal gait as compared to its littermates. An affected mouse dramatically pulls it's rear legs, one at a time, up to its body as it walks and pulls its rear legs to its belly when picked up by the tail. High stepper is a recessive mutation in which both sexes breed and live a normal lifespan.

Genetic Analysis
Following The Mouse Mutant Resource standard mapping protocols, a female *Mus castaneus* was mated to a homozygous high stepper, and this mating produced all normal progeny. An intercross of known heterozygotes produced 48 homozygotes of which 21 were used for linkage analysis. Standard PCR analysis was performed, and the mutation was found to be located on Chromosome 19 between *D19Mit128* (NCBI 36 position 10.9Mb) and *D19Mit134* (NCBI 36 position 24.0 Mb), and is non-recombinant with *D19Mit14* NCBI 36 position 15.0 Mb). Based on phenotype and map position *Rorb* (NCBI 36 position 19.0 Mb) was thought to be a good candidate gene. Retinal RNA made from a *hstp/hstp* mutant mouse was used to sequence the coding region of *Rorb,* but a mutation was not found. Another mutation, hugger, with a similar eye phenotype was mapped to this same region, but hugger is now extinct and could not be used for a direct test for allelism. Eye histology of high stepper is almost the same as the published eye

phenotype of progressive retinal degeneration and photoreceptor cell loss seen in hugger, but is less severe. Hugger mice were reported to have fertility problems that we have not observed in high stepper mice. Phenotypical and histological similarities suggest high stepper is a possible remutation to hugger on Chromosome 19.

Pathology

Hearing as assessed by auditory brainstem response testing (ABR) on a mutant and control mouse showed normal hearing.

An eye examination by ophthalmoscope of four homozygous females and three males, as well as one female and one male control from the maintenance colony all had normal fundus. Electroretinographs (ERGs) on all homozygotes were abnormal in both the maintenance colony and the CAST mapping cross. ERGS on all control mice were normal. In high stepper mice the progression of retinal degeneration and photoreceptor cell loss is slower than in hugger. The retina, the inner nuclear layer, the inner plexiform layer and the outer plexiform layer are normal, but the outer nuclear layer is abnormal (rosettes). Misplaced ganlgion cells were observed, and where the ganglion layer is disrupted there is a loss of rods and extra cones.

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