Tooth hopper: A spontaneous, dominant mouse mutation affecting gait and tooth development

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Mutation symbol: *Thpr*

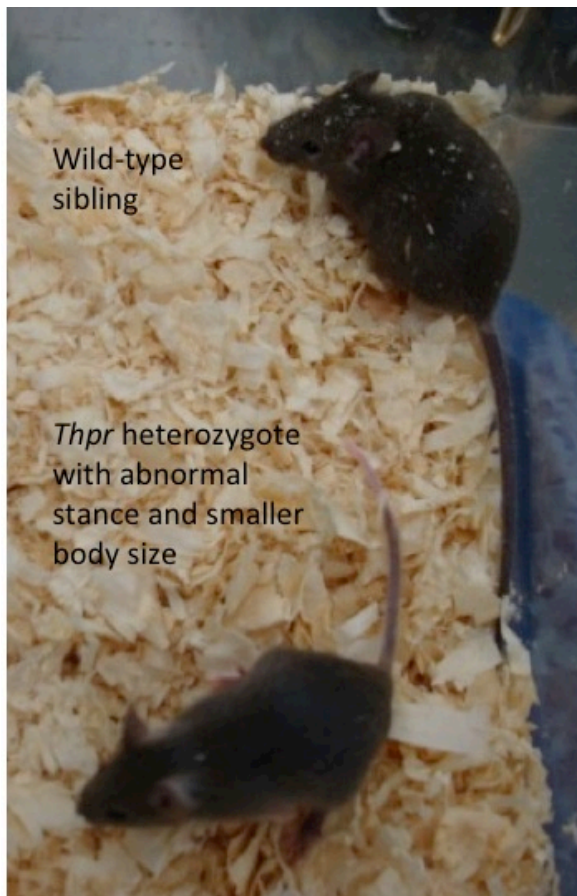
Mutation name: tooth hopper

Strain of origin: (C57BL/6J x C3H/HeJ)F1

Stock #003400 (jaxmice.jax.org)

Phenotype categories: neurological, skeletal, fertility

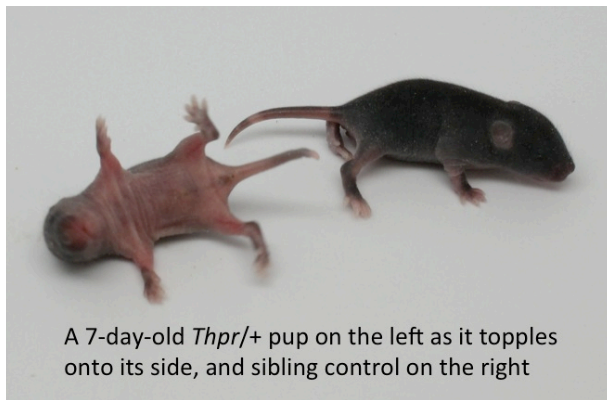
Abstract:
We have identified and characterized a spontaneous, dominant mouse mutation that we have named tooth hopper (*Thpr*). Heterozygotes hop with their back legs moving together in synchrony, develop long teeth, may lean or fall over as they try to move around the cage and are smaller in size than normal littermates. Tooth hopper has been mapped to Chromosome 2 between *D2Mit91* and *D2Mit17*.



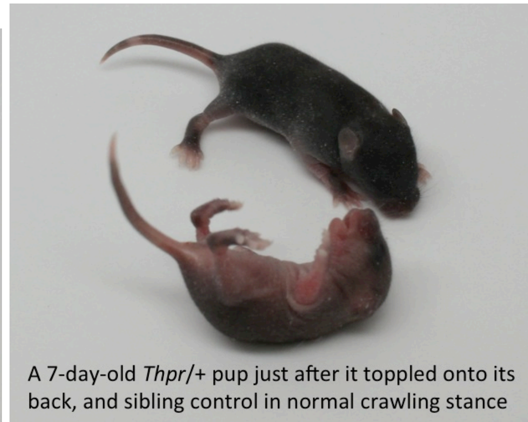
Origin and Description:

A spontaneous mutation that causes a hopping gait was identified by Pat Attanasio in a (C57BL/6J x C3H/HeJ)F1 colony at The Jackson Laboratory. Rather than the normal stride with opposing movement of front and back legs, these mutants hop with their back legs moving together in synchrony. They sometimes lean or fall over when moving. Additionally the overall body size of these mutants is smaller than normal and their teeth overgrow, usually requiring weekly trimming so that they can eat properly. A slightly longer lower jaw or growth of an additional lower tooth may cause the teeth to appear either wide set or aligned in a manner that does not juxtapose the lower and upper teeth.

Some heterozygous mutants do not live to wean age, but most are able to survive when left with their mothers for an extended week or two past the usual three-week wean age. Surviving heterozygotes seem to live well into adulthood as long as their teeth are trimmed on an as-needed basis. Crushed food (meal) should be added to their cages for an extra nutritional benefit.



A 7-day-old *Thpr*/+ pup on the left as it topples onto its side, and sibling control on the right



A 7-day-old *Thpr*/+ pup just after it toppled onto its back, and sibling control in normal crawling stance

Heterozygotes are fertile, though males breed better than females for an extended period of time. Mutant females do not care well for their young or produce very large litters. Thus, while this strain can be maintained by breeding a heterozygous female to a wild-type male, it is better to breed a wild-type female to a heterozygous male. In many cases it is advantageous to remove the male from the pregnant female so she can raise her litter alone in order to diminish the possibility of mutant pups, which are smaller than their littermates, being trampled.

Genetic Analysis:

The first indication of map position occurred early in the maintenance of this mutation when it was decided to backcross *Thpr* onto a C57BL/6J background. After a few generations of backcrossing it became clear that the carriers of this dominant mutation were also carrying the agouti allele from C3H/HeJ, thereby mapping *Thpr* to Chromosome 2. Typing SNP markers that differ between C57BL/6J and C3H/HeJ confirmed a Chromosome 2 map location between *D2Mit91* and *D2Mit17* with one recombinant at *D2Mit58* and at *D2Mit62*.

Pathology:

No noteworthy lesions were found in a full pathology screen[1] of three heterozgyotes at two months of age, two at four-and-a-half months of age, and one at six months of age.

One heterozygote had possible defects in the paraflucculus ventralis and flocculus, and a second had lost the paraflucculus ventralis and the flocculus was disorganized compared to the control. One eleven-month-old heterozygote had mild hydrocephalus and no additional lesions. One female heterozygote had inflammation around the hair follicles, an undeveloped uterus and rowing of nuclei in the leg muscle indicative of mild muscle degeneration. The spinal columns from two heterozygotes were stained for CaM Kinase II and no abnormalities were found. X-rays of one nine-month-old female, one six-month-old male and one five-month-old male did not reveal any abnormalities. Ophthalmoscopic assessment of two C57BL/6J congenic heterozygous males, one at ten weeks of age and one at twelve weeks of age, revealed no eye abnormalities. Hearing as assessed by auditory brainstem response was determined to be normal.

Acknowledgements:
We would like to thank Dr. Susan Ackerman and Linda Washburn for contributions to characterization and mapping of this mouse, Dr. Bo Chang for eye examinations, Heping Yu for ABR testing, Dr. Qing Yin Zheng for cerebellar and ear examinations, and Coleen Kane for histological preparations.

[1]**Standard Histology Protocol used in The Mouse Mutant Resource**
For fixation of tissues, mice were deeply anesthetized with tribromoethanol (avertin) until they no longer displayed a withdrawal reflex in the hind limbs and then perfused intracardially with Bouin's fixative following a flush of the vasculature with saline solution. After soaking in Bouin's for one week to demineralize bones, tissues were dissected. Six segments of spine with axial muscles and spinal cord in situ, representing cervical, thoracic and lumbar spinal segments, were dissected. The brain was removed and sliced into 6 cross sectional pieces at the levels of olfactory lobes, frontal cortex, striatum, thalamus, midbrain, rostral and caudal medulla with cerebellum. Midsagittal slices of hind leg through the knees were prepared. Slices of basal skull through the pituitary and inner ears were taken. Both eyes, salivary glands and submandibular lymph node, trachea plus thyroid and sometimes parathyroid were removed and cassetted. A longitudinal slice of skin from the back was removed. The thymus, slices of lung, and a longitudinal slice of heart were cassetted. Similarly slices of liver through gall bladder, kidney with adrenal attached, pancreas and spleen were prepared. The stomach was sliced longitudinally to include both squamous and glandular portions. Loops of small intestine from 3 levels and slices of large intestine and cecum were removed, as were slices of urinary bladder. The whole uterus, with ovaries attached, was taken. In males testes were sliced longitudinally. The accessory male organs including seminal vesicles, coagulating gland and prostate were removed en block. Altogether in most cases all tissue fit into a total of 10 cassettes. The cassettes were processed in an automatic tissue processor to dehydrate tissues which were then embedded in paraffin. Six micron sections were cut and stained with hematoxylin and eosin (H&E). Sections of brain and spinal cord in vertebral bones also were stained with luxol fast blue (LFB) for myelin and cresylecht violet (CV) for cellular detail.