

Twisted legs and extra digits (*Tsed*): a new dominant skeletal mutation that maps to Chromosome 5

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Mutation (allele) symbol: *Tsed*

Mutation (allele) name: twisted legs and extra digits

Strain of origin: mixed stock of C57BL/6J, 129, and CAST/EiJ

Current strain name: STOCK-*Tsed*/GrsrJ

Stock #006425 (jaxmice.jax.org)

Phenotype categories: skeletal

### **Origin and Description**

In 2005 Norman Hawes in the Mouse Mutant Eye Resource of The Jackson Laboratory discovered a mouse with unusual legs in a mixed stock that contained C57BL/6J, 129, and CAST/EiJ. These mutants have noteworthy polydactyly on all four feet and many display twisted hind legs. The twisted hind legs are often oriented inward toward the body with varying degrees of severity, and in an individual mutant one, both or neither hind leg can display this phenotype. Homozygotes of both sexes are viable and fertile and the *Tsed* stock is maintained by crossing two homozygotes together, thus all progeny born are affected. We have named this new, spontaneous mouse mutation twisted legs and extra digits (*Tsed*).



*Tsed* homozygote has polydactyly on all 4 feet

## **Genetic Analysis**

This mutation has been maintained by continuously inbreeding sibling mutants for many generations and in this way a homozygous line was generated. To confirm the pattern of inheritance a male mutant was outcrossed to two BALB/cByJ females yielding 14 progeny. Twelve of these were phenotypically affected with polydactyly on all feet and variably twisted hind legs, and two, one male and one female, were phenotypically normal. When these two phenotypically normal animals were bred together all of their offspring were phenotypically affected. Thus, this mutation is dominant and there is incomplete penetrance when bred to BALB/cByJ.

Using a mapping population generated by crossing to CAST/EiJ and then backcrossing the affected F1 hybrids to C57BL/6J, *Tsed* was mapped to Chromosome 5 between *D5Mit349* and *D5Mit106*. This segment includes the gene sonic hedgehog (*Shh*), for which mutants have a phenotype that includes polydactyly and twisted hind legs.

## **Pathology**

Hearing assessment by brainstem auditory evoked potential on one homozygote at 73 days of age and two homozygotes at 140 days of age showed normal hearing. Eye examinations on three female and two male homozygotes at approximately 4 months of age showed normal eyes in all cases. Examination of x-rays, one magnified 3X and two magnified 4X, of female homozygotes at four weeks of age showed bowed long bones in the hind-legs of two of these three mutants. One displayed a severe curvature of the left tibia and fibula and another displayed a slight bowing of the right tibia and fibula with exaggerated curvature of the distal lower limb at the junction of the tibia and fibula and the right femur appeared slightly shorter than normal. The axial skeleton and forelimbs appear normal in all three x-rays. Our routine pathological screen was performed on a five-week old homozygous male and no further lesions were found.

## **Discussion**

We report a new dominant skeletal mutation, which maps to Chromosome 5, that causes significant polydactyly on all four paws and variable twisting of the hind legs. This mutation has incomplete penetrance when heterozygous on a background that includes BALB/cByJ. The gene sonic hedgehog is a good candidate based on map location and phenotype.

## **Acknowledgements**

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