Sunken (*sunk*): A New Skeletal Mutation on Mouse Chromosome 14

Authors: Belinda S. Harris, Patricia F. Ward-Bailey, Roderick T. Bronson, Leah Rae Donahue, Kenneth R. Johnson, and Muriel T. Davission.

Source of Support: The research was supported by NIH/NCRR grant RR01183 to the Mouse Mutant Resources (M.T. Davisson, PI) and Cancer Center Core Grant CA34196.

Mutation (allele) symbol: *sunk*

Mutation (allele) name: sunken

Strain of origin: A/J

Current strain name: A/J-*sunk*/GrsrJ

Stock #006246 (jaxmice.jax.org)

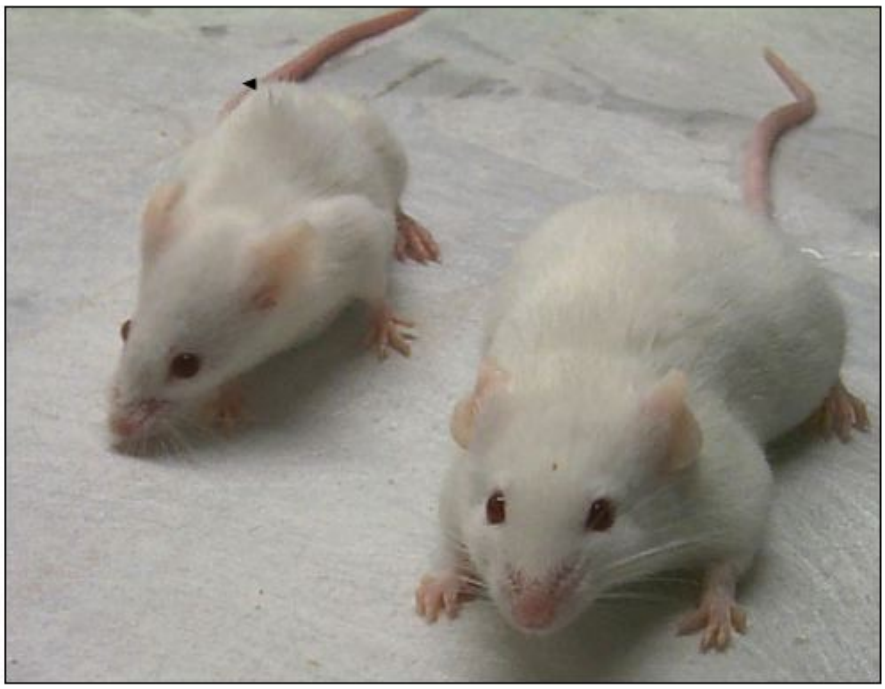
Phenotype categories: skeletal

Abstract

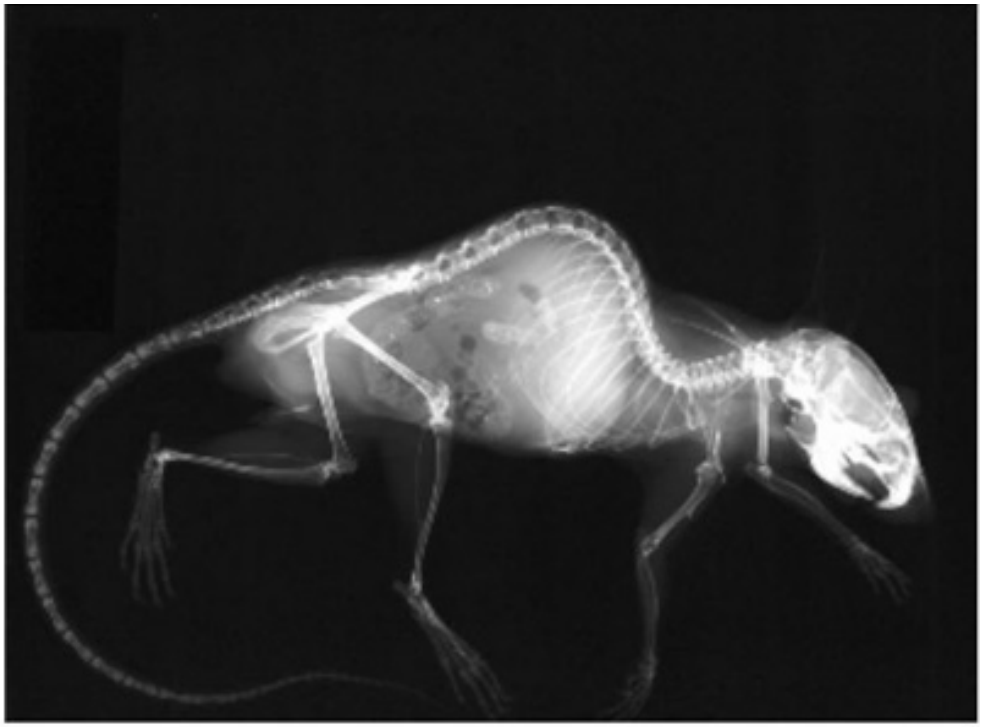
A new autosomal recessive skeletal mutation has been identified and named sunken (*sunk*). This mutation, when homozygous, causes the mice to have a smaller body size, a severe kyphosis, and the abdomen appears sunken in. An intercross of mice carrying this new mutation mated to CAST/Ei was used to map the *sunk* mutation to Chromosome 14.

Origin and Description

This new mutation arose in a breeding colony of A/J mice in the Mouse Mutant Resource at The Jackson Laboratory in 2003. Mice homozygous for the *sunk* mutation are easily characterized at two weeks of age by their smaller size, kyphosis, and a sunken appearance when lifted by its tail.



A homozygous *sunk*/*sunk* female on left and a male control littermate on right. Both at 12 weeks of age. Note the kyphosis (see arrow) on the back of the mutant.



X-ray of a 24 week old homozygous male mutant showing severe kyphosis. (mag 3X)

X-ray of the same homozygous male mutant showing the wasting in muscles in the hind end of the mouse and thinning of cortical bone. The growth plates look normal and bone length is appropriate for the size of the animal. From this ventral to dorsal view the kyphosis is not seen. (Mag. 3X)

Affected animals have an abnormal gait that makes it appear that their hips are disconnected from their body, but x-rays prove the hip bones are normal. Both sexes are viable but to date not all female homozygotes have bred. Most litters from homozygous sunken females need to be fostered, probably due to the small size of the female. The

homozygous *sunk* mice live a normal lifespan. This colony is maintained by progeny tests and by mating sunken homozygous females to non-mutant (+/?) sib males.

A *sunk*/*sunk* mutant on left and a control littermate on the right.
Note the small size and sunken in sides of the mutant.

Genetic Analysis
Using the standard mapping procedures of The Mouse Mutant Resource, an intercross was set up to map this new mutation. A female CAST/Ei mouse was mated to a male mouse homozygous for the sunken (*sunk*) mutation and also another female CAST/Ei mouse was mated to a male mouse heterozygous for the sunken (*sunk*) mutation. The unaffected heterozygous F1 progeny produced from these matings were then intercrossed and produced 33 affected F2 progeny of which 21 were used for linkage analysis. The new sunken (*sunk*) mutation was mapped to Chromosome 14, distal to *D14MIT120* (12.5 cM and NCBIm36 position 34.9 Mb) and proximal to *D14MIT20* (19.5 cM) and is non-recombinant with *D14MIT18* (16.5 cM and NCBIm36 position 46.7 Mb).

Pathology
A routine pathological screen of two male homozygous (*sunk*/*sunk*) mice at 24 weeks of age and one mutant male at 30 weeks of age showed no lesions except for the characteristic rowing of nuclei in muscle and dystrophic axons found in the A/J background strain.

Two female *sunk*/*sunk* mice and one male littermate control at 13 weeks of age, and one female *sunk*/*sunk* and a male littermate for the weeks of age, were sent for pathology for myelin staining and appeared to be normal except that all had the muscular dystrophy that is characteristic of the A/J strain.

X-Rays of two mutants at 24 weeks showed severe skeletal kyphosis, wasting of muscle in the hind quarters, and thinning of cortical bone. The growth plates appeared normal and the bone lengths were appropriate for the size of the animals. No other skeletal abnormalities were observed.

Hearing as assessed by auditory brainstem response testing (ABR) done on two homozygotes and two heterozygotes at 7 weeks of age showed severe hearing loss at high

frequency in all mutant as well as control mice tested. This hearing loss is typical of the A/J strain and not caused by this new mutation.

Acknowledgements
The authors wish to thank Heping Yu for auditory brain stem analysis, Coleen Marden for excellent skeletal and pathological preparations, and Leona Gagnon for technical photography