Skimpy: A new mutation on Chromosome 7 causing impaired balance and reduced lifespan.

Authors: Belinda S. Harris, Patricia F. Ward-Bailey, Kenneth R. Johnson, Roderick T. Bronson

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

Mutation (allele) symbol: *skp*

Mutation (allele) name: skimpy

Gene symbol: *skp*

Strain of origin: CXB5/By

Current strain name: CXB5/ByJ-*skp*/GrsrJ

Stock #009156 (jaxmice.jax.org)

Phenotype categories: gait, size, fertility, lethal

Abstract
A mouse carrying the skimpy mutation was discovered in 2002 in a Mouse Mutant Resource colony of CXB5/By mice at the Jackson Laboratory and was first recognized by its small body size as compared to its littermates. The skimpy mutation has been mapped to Chromosome 7.

A mouse affected by the skimpy mutation is shown on the left and a littermate control on the right. Both are 16 days of age.

Origin and Description
We have identified a new recessive mouse mutation that causes affected mice to walk on their toes, have impaired balance, and have a smaller body size than their littermate controls. Homozygotes do not live long enough to breed and have a shortened lifespan,

usually dying by four weeks of age. The colony is maintained by progeny testing; most heterozygous pairs produce less than the expected 25% homozygotes.

Genetic Analysis
Using standard PCR mapping protocols, a cross was set up by mating an affected *sk*p mouse to a CAST/Ei mouse to produce F1s. The F1s were then intercrossed and produced 21 affected progeny that were utilized for linkage analysis. The *skp* mutation was found on Chromosome 7, maps between *D7Mit31* (NCBI 37 position 94.6 Mb)and *D7Mit9* (NCBI 37 position 130.6 Mb), and is non-recombinant with *D7Mit353* (NCBI 37 position 106.6 Mb). Based on map location and phenotypic similarities, the *Smpd1* (sphingomyelin phosphodiesterase1, acid lysomal) gene is thought to be a good candidate.

Pathology
Our standard pathology screen[1] on 5 *skp* homozygotes at one month of age showed atrophic thymus glands, underdeveloped myelin, and aspermiogenesis indicative of a developmental delay. One male homozygote and one male untested +/? control at three weeks of age had delayed myelin development. The same male homozygote had deficient zymogen (a proenzyme that is transformed by proteolysis into an enzyme when activated by another enzyme).

Hearing assessments by auditory brainstem response on individual animals were not done as no affected animals survived long enough to have the test accurately performed.

The eyes of 3 three-week old *skp* homozygotes were examined with an ophthalmoscope and all showed poor retinal vessels and a cortical cataract. Eye histology showed that the lens capsule was ruptured and there was lens extrusion with a wavy abnormal retina. A five-month old heterozygous female also showed abnormal retinal vessels. This retinal eye phenotype is characteristic of the CXB5/By background strain and likely not to be caused by the new *skp* mutation.

Discussion
Skimpy is located near *Smpd1* (sphingomyelin phosphodiesterase 1, acid lysomal). Although this gene has a similar phenotype, it has not been proven to be the gene responsible for the skimpy phenotype.

Acknowledgements
The authors thank Norman Hawes for eye 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.