Small roller: A new recessive neurological mutation that maps to Chromosome 8

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Mutation (allele) symbol: *smrl*

Mutation (allele) name: small roller

Gene symbol: *smrl*

Strain of origin: CXB10/HiAJ

Current strain name: CXB10/HiAJ-*smrl*/GrsrJ

Stock #016887 (jaxmice.jax.org)

Phenotype categories: neurological, growth/size

Abstract
We have identified a new, spontaneous, recessive mouse mutation that causes severe ataxia with diminished righting capability, reduced body size, and increased prenatal lethality. We have named this mutant small roller (*smrl*) and have mapped it to Chromosome 8 between genetic markers 08-061195953-M and 08-90088021-M.

Ten month old heterozygous control on the left and small roller homozygote on the right showing smaller body size and rolling on its side when walking

Origin and Description
A spontaneous mutation was identified in the CXB10/HiAJ colony at The Jackson Laboratory. This mutant was first identified by weakness and difficulty in locomotion. The phenotype can usually be identified by 2 weeks of age. The hind legs are often splayed and the ataxia includes a severe side-to-side gait with swaying hindquarters and the body held close to the ground. The severe swaying often results in rolling onto one side, and these mutants have difficulty returning to their feet. These mutants also have trouble righting when placed on their backs. Although they roll onto their sides, they then struggle to get to their feet, often pawing at the shavings. Younger mutants appear to have an increased respiration rate when trying to right themselves. The phenotype seems to decrease somewhat in severity as the mutants age. These mutants are distinctly smaller than unaffected littermates, about half the normal size at wean age and three quarters normal size as adults. To nurture the survival of mutant pups, meal should be placed within easy reach and they should be left with their mothers beyond the usual three week wean age. We have named this mutant small roller, with the mutation symbol *smrl*.

This mutation was proved recessive by the generation of mutant offspring from intercrosses of some, but not all, phenotypically wild-type siblings of mutants. This colony is maintained by breeding homozygous females to unaffected sibling males and then intercrossing their obligate heterozygous offspring. Litters from homozygous females do best when fostered. Homozygous females are fertile, but have reduced litter sizes, averaging less than 3 pups per litter, and their pups have decreased survival rates. Of 59 pups in 21 litters born from homozygous females bred to heterozygous males 35 were heterozygous (normal phenotype); 7 were homozygous by phenotype; 5 were born dead; and, in the first week after birth, before phenotypic classification, 4 were found dead and 8 were missing entirely. If all born dead, found dead, and missing pups were homozygotes the yield is still less than 41% homozygotes, short of the 50% homozygotes expected. This suggests there is prenatal death at least of homozygous embryos in homozygous mothers. Of 22 litters from homozygous females bred with +/? males (from which no mutants were ever sired and thus they were presumed +/+) there were 50 normal looking (heterozygous) pups, 15 born dead, and 6 found dead and 13 missing in the first week after birth, before phenotypic classification. This is an average litter size of (84/22) 3.8, slightly higher than pairs producing homozygotes but still a small litter size.

Two homozygous males, one housed with one heterozygous female and one housed with two heterozygous females, failed to produce offspring. Cryopreservation of sperm from one homozygous male failed because the recovered sperm was not viable. Sperm from heterozygous males can be recovered successfully from cryopreservation. It remains to be determined whether homozygotes have some sort of deficiency in spermatogenesis or sperm quality.

Heterozygous intercrosses also have a noticeable number of pups born dead or missing in the first week after birth. Of 329 pups from heterozygous intercrosses 66 (20%) had the homozygous phenotype, 252 (76.6%) had a normal phenotype, 5 were born dead, 1 was found dead and 5 were missing sometime after birth and before phenotypic assessment, at approximately 1 week of age. Thus, if the born dead, found dead and missing are all assumed homozygous this would raise the percent mutant to 23.4%, near the Mendelian

expectation.

Genetic Analysis
Using the standard mapping protocols of The Mouse Mutant Resource, an outcross of a heterozygous male to a CAST/EiJ female was established and the F1 hybrid offspring, of which none had a mutant phenotype, were intercrossed. Of three intercross pairs that produced mutants there were a total of 330 pups of which 70 were mutant (21%). Linkage analysis using SNP typing mapped *smrl* to Chromosome 8 between genetic markers 08-061195953-M and 08-90088021-M.

Pathology
Routine pathology screens showed no lesions in two male homozygotes at 25 weeks of age or two female heterozygotes at 20 weeks of age. Eye examinations of these same mice showed normal eyes for all tested. Auditory brainstem response testing of two heterozygotes and two homozygous mutants showed moderate hearing loss in all mice tested, consistent with anticipated results for this mixed genetic background. Thus, no hearing loss could be attributed to the *smrl* mutation.

Discussion
We report a new, recessive mutation that we have named small roller, and which we have mapped to Chromosome 8. This spontaneous mutation causes severe ataxia and difficulty righting, which involves difficulty coordinating and controlling the limbs. This appears to be a neurological mutant, but an initial histological screen revealed no clear neurologic defect.

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