Unsteady small lethal: A new spontaneous mouse mutation on Chromosome 15

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Mutation (allele) symbol: *usl*

Mutation (allele) name: unsteady small lethal

Strain of origin: MRL/MpJ-*Fas*^{lpr}/J

Current strain name: B6.MRL-*usl*/GrsrJ

Stock #023062 (jaxmice.jax.org)

Phenotype categories: neurological, size, developmental

Abstract:
We have identified a new, recessive mouse mutation that causes runted body size, lack of vitality, splayed hind legs, circling, ataxia, and pre-wean death. We have mapped this mutation to Chromosome 15 and named it unsteady small lethal, with the mutation symbol *usl*.

Origin and Description:
A spontaneous phenotypic mutation was discovered in 2003 in the MRL/MpJ-*Fas*^{lpr}/J colony at The Jackson Laboratory. Mutants were first recognized by their small, runted size and lack of vitality. Affected mice splay their back legs, stagger from side-to-side, and usually die by three weeks of age. A few lean their head or display a slow circling phenotype. When intercrossed, some unaffected siblings produce mutants, proving that this is a recessive mutation. Homozygotes do not live long enough to breed, but this mutation can be maintained by intercrossing progeny tested heterozygotes. Heterozygotes live a normal lifespan and are fertile with litter sizes normal for this genetic background. We named this mutation unsteady small lethal, with the mutation symbol *usl*.

Homozygotes are produced in less than a Mendelian ratio, indicative of reduced penetrance or embryonic/perinatal lethality. Five intercrossed heterozygous pairs on an MRL/MpJ-*Fas*^{lpr}/J genetic background, produced seven affected animals from among thirty-seven born (18.9%). Given the severity of the phenotype we do not attribute this deviation to reduced penetrance.

The *usl* mutation was backcrossed onto C57BL/6J by breeding a progeny tested heterozygote to C57BL/6J at each generation, alternating between male and female heterozygous breeders at different generations in a manner that ensured that both sex

chromosomes came from C57BL/6J. At generation N5 homozygotes displayed the same phenotype of small size, ataxia, and pre-wean lethality that was seen on the original MRL/MpJ-*Fas*^{lpr}/J background.

Genetic Analysis:
Using the Mouse Mutant Resource standard mapping protocol, a heterozygote was outcrossed to CAST/EiJ. None of the F1 hybrid offspring expressed the mutation. The F1 hybrids were progeny tested and the proven heterozygotes were intercrossed and 20 of their F2 offspring, representing 40 meioses, were used for linkage analysis. The *usl* mutation maps to Chromosome 15 between *D15Mit167* (at 59.9 Mbp) and *D15Mit3* (at 68.9 Mbp).

Pathology:
A routine pathological screen on one three-week-old male homozygote revealed an atrophic thymus, small spleen, immature testis, colitis with dilation of crypts and sloughed epithelium. One homozygous female at two weeks of age showed a mineralized area of necrosis in the liver, irregular nodular cartilage in the growth plate of the knee, hyperkeratosis of squamous epithelium of the stomach, and marked gliosis of white matter of the spinal cord. A second homozygous female at two weeks of age also displayed hyperkeratosis of the squamous epithelium of the stomach and thymic atrophy, as well as a few apoptotic granule cells in the cerebellum. Eye examinations of one female mutant at 13 days of age and one female and one male mutant at 16 days of age revealed no abnormalities, nor were any eye abnormalities found in unaffected siblings at 13 days, 16 days, 4 months, or 6 months of age.

Discussion:
We have identified and performed preliminary characterization on a spontaneous, recessive mouse mutation that causes diminished body size, fragile health, ataxia and a variety of neurological phenotypes until death by approximately three weeks of age. Initial screening shows an array of variable lesions in three pre-wean mice including epithelial defects in the digestive tract, thymic atrophy, and, more consistent with a neurological mutant, gliosis of white matter of the spinal cord, and a few apoptotic granule cells in the cerebellum of one mouse. We have mapped this mutation to distal Chromosome 15 and have begun efforts to identify the underlying molecular defect through exome sequencing.

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