A Remutation to Dilute Lethal, *Myo5a*$^{d\text{-}l32J}$

Son Yong Karst, Patricia F. Ward-Bailey, David E. Bergstrom, Leah Rae Donahue and Muriel T. Davisson-Fahey

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Mutation Symbol: *Myo5a*$^{d\text{-}l32J}$

Mutation Name: dilute lethal 32 Jackson

Gene symbol: *Myo5a*

Strain of origin: B6.V-*Lep*^{ob}/J

Current strain name: B6.Cg-*Myo5a*$^{d\text{-}l32J}$/GrsrJ

Stock #01404 (jaxmice.jax.org)

Phenotype categories: pigmentation, neurological

Abstract
A recessive mutation that arose spontaneously causes a diluted coat color and a severe neuromuscular disorder. Through phenotypic analysis, SNP genotyping, and non-complementation with the dilute allele of DBA/2J, this mutation was determined to be a mutation of myosin VA and has been designated *Myo5a*$^{d\text{-}l32J.}$

Origin and Description
In 2008 Henri Loiselle identified mutants in a production colony of B6.V-*Lep*^{ob}/J mice at The Jackson Laboratory. Homozygotes can be recognized by approximately 7 to 8 days of age, when their first coat of hair comes in, because they have a gray coat color while unaffected siblings on the nonagouti background are black. This dilution appears similar to that of DBA/2J mice, which are homozygous for *Myo5a*^{d}. In addition to the coat color defect, these mutants have difficulty in walking such that they lose balance and fall over displaying extreme backward arching of the spine and backward arching upward of the head and tail. This severe neuromuscular disorder characterized by convulsions and opisthotonus is identical to that described for dilute lethal (*Myo5a*$^{d\text{-}l}$) homozygotes[1,2]. Mutant mice are kept with their parents beyond the standard wean age and, although most die by 3 weeks of age, some are occasionally found to live longer than 3 weeks of age.

The new mutation has been maintained by crossing hosts of homozygous ovary transplants with C57BL/6J males and intercrossing the obligate heterozygous offspring to generate homozygotes. Through this repeated backcross-intercross breeding scheme the *Lep*^{ob} mutation was bred out of the mutant subline. A DNA sample has been preserved with the Jackson Laboratory DNA Resource, but the strain will not be maintained long term or cryopreserved.

Genetic Analysis
This new mutation was shown to have recessive inheritance by mating a host of a homozygous ovarian transplant to an unrelated CAST/EiJ male. The F1 hybrids were all unaffected. These unaffected F1 hybrids were intercrossed, and affected F2 mice were generated for linkage analysis. Using standard SNP protocols, linkage analysis for this mutation was completed in the Fine Mapping Laboratory at The Jackson Laboratory. This mutation maps to Chromosome 9, between NCBI 37 position 074179540 Mb and NCBI 37 position 088834868 Mb, consistent with it being a mutation of *Myo5a*.

A test for allelism with a *Myo5a* mutant was performed by breeding an obligate heterozygote to DBA/2J, which is carrying the $Myo5a^{d}$ allele. This mating produced 14 offspring in two litters in which 10 progeny were born with diluted coat color proving the new mutation allelic with $Myo5a^{d}$. While this failed complementation proves this new mutation to be an allele of *Myo5a*, this mutant displays the severe neurological defects found in dilute lethal mutants and absent in the dilute mutant so this new mutation has been assigned the next allele designation in the dilute lethal series to arise at The Jackson Laboratory, $Myo5a^{d\text{-}l32J}$.

Pathology
A routine pathological screen of a homozygote at 46 days of age showed clumps of melanin in the dermis, probably from atrophy of follicles. There were few sperm and focal mild pyelonephritis was found.

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References
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2. Searle AG, A lethal allele of dilute in the house mouse. *Heredity* 1952; **6**:395-401

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