**Mouse Models of Dysferlin Deficiency**

## SJL/J (SJL-*Dysf*)

**Availability:** The Jackson Laboratory
**Stock number:** 000686
**Strain information:** http://jaxmice.jax.org/strain/000686.html
**Contact:** 800-422-MICE (800-422-6423)
610 Main Street, Bar Harbor, Maine 04609 USA
Mice are shipped at a specific age in weeks.
**Mutation:** Exon 45 (171 base pairs, aa1628-1685) is deleted in dysferlin mRNA, due to a mutation in the 3' splice junction. This deletion removes part of the fifth C2 domain (C2E) of the protein. The mice are homozygous for this mutation.
**Symptoms:** Mild myopathic lesions can be detected histologically by around 1 month of age. These mice develop active myopathy in striated muscle by 6-8 months, primarily in the proximal muscle groups, and have progressive muscle weakness. Muscular atrophy begins around 10 months, and by 16 months there is approximately 50% replacement of muscle fibers by fat. There is dispute about whether young SJL mice (1-2 months) are stronger or weaker than control mice. The mice also have other symptoms, including a high incidence of lymphoma around 10-14 months, increased susceptibility to autoimmune diseases and viral infections, and extreme aggression in males. They are homozygous for a retinal degeneration allele (*Pde6b* gene).
**Comparison:** Disease progression is similar to Dysf-/- (Campbell), Dysf-/- (Brown), and C57BL/10.SJL mice, and faster than in A/J mice. As in both A/J and Dysf-/- (Brown) mice, proximal muscles are more severely affected than distal muscles. The other symptoms, however, are not shared with the other dysferlin-deficient mice and are likely due to complicating genetic features of this strain.
**References:** Weller AH, et al. 1997. Spontaneous myopathy in the SJL/J mouse: pathology and strength loss. *Muscle & Nerve* 20:72-80.
Bittner RE, et al. 1999. Dysferlin deletion in SJL mice (SJL-*Dysf*) defines a natural model for limb girdle muscular dystrophy 2B. *Nature Genetics* 23:141-142.
Vafiadaki E, et al. 2001. Cloning of the mouse *dysferlin* gene and genomic characterization of the SJL-Dysf mutation. *Neuroreport* 12:625-629.

## A/J

**Availability:** The Jackson Laboratory
**Stock number:** 000646
**Strain information:** http://jaxmice.jax.org/strain/000646.html
**Contact:** 800-422-MICE (800-422-6423)
610 Main Street, Bar Harbor, Maine 04609 USA

Mice are shipped at a specific age in weeks.
**Mutation:** An ETn retrotransposon (5-6kb) is inserted in Intron 4 of the dysferlin gene. The mice are homozygous for this insertion.
**Symptoms:** Histological evidence of dystrophy is not seen until 4-5 months of age and muscle weakness progresses slowly. Abdominal muscles are most severely affected, followed by proximal muscles and then distal muscles. The mice also have other symptoms, including a high incidence of lung adenomas and mammary adenocarcenomas. They are homozygous for an age related hearing loss allele (*Cdh23* gene) and for hemolytic complement deficiency (C5, *Hc*gene).
**Comparison:** Disease progression is slower than in SJL/J, Dysf-/- (Campbell), Dysf-/- (Brown), and C57BL/10.SJL mice. Non-dysferlin-related genetic differences in this strain are probably responsible for the slow progression. As in both SJL/J and Dysf-/- (Brown) mice, proximal muscles are more severely affected than distal muscles. As in Dysf-/- (Brown) mice, abdominal muscles are also affected.
**Control(s):** A/HeJ, A/WySnJ
**References:** Ho M, et al. 2004. Disruption of muscle membrane and phenotype divergence in two novel mouse models of dysferlin deficiency. *Human Molecular Genetics* 13:1999-2010.

## Dysf-/- (B6.129-*Dysf*tm1Kcam/Mmmh)

**Kevin Campbell**
**Availability:** Mutant Mouse Regional Resource Centers (MMRRC)
**Stock number:** 010317-MU/H
**Strain information:** http://www.mmrrc.org/strains/10317/010317.html
**Contact:** 800-910-2291 or 207-288-6009
Breeder mice are available from a cryoarchive after 3-4 months.
**Mutation:** A 12-kb region of the genome, containing the last three exons (Exons 53-55, aa1983-2080) of dysferlin, is deleted. This deletion removes the transmembrane domain of the protein. The mice are of a mixed 129SvJ and C57BL/6 background and are homozygous for this deletion.
**Symptoms:** Individual necrotic muscle fibers can be detected histologically by around 2 months of age. Active myopathy is evident by 8 months of age.
**Comparison:** Disease progression is similar to SJL/J, Dysf-/- (Brown), and C57BL/10.SJL mice, and faster than in A/J mice.
**Control(s):** C57BL/6 (for homozygotes); littermates (for heterozygotes)
**References:** Bansel D, et al. 2003. Defective membrane repair in dysferlin-deficient muscular dystrophy. *Nature* 432:168-172.

## Dysf-/-

**Robert Brown**
**Availability:** Dr. Mengatt Ho
**Email:** dmshmf@nccs.com.sg
**Contact:** +65 62221920
Division of Medical Sciences, National Cancer Centre, 11 Hospital Drive, Singapore 169610

**Mutation:** A 1.8-kb region of the genome, containing Exon 45 (aa1628-1685) of dysferlin, is deleted. This deletion removes part of the fifth C2 domain (C2E) of the protein. The mice are of a mixed 129SvJ and C57BL/6 background and are homozygous for this deletion.
**Symptoms:** Degenerating muscle fibers can be detected histologically by around 2 months of age, primarily in the proximal and abdominal muscles. Active myopathy is evident in all skeletal muscles by 6 months of age. At 8 months of age some mice show muscle weakness in their hind limbs.
**Comparison:** Disease progression is similar to SJL/J, Dysf-/- (Campbell), and C57BL/10.SJL mice, and faster than in A/J mice. As in both SJL/J and A/J mice, proximal muscles are more severely affected than distal muscles. As in A/J mice, abdominal muscles are also affected.
**References:** Ho M, et al. 2004. Disruption of muscle membrane and phenotype divergence in two novel mouse models of dysferlin deficiency. *Human Molecular Genetics* 13:1999-2010.

## C57BL/10.SJL-*Dysf*

**Availability:** Dr. Reginald Bittner
**Email:** reginald.bittner@univie.ac.at
**Contact:** +43 1 4277 61182
Medical University of Vienna, Währingerstrasse 13, A-1090 Vienna, Austria
**Mutation:** Same as the mutation in SJL/6 mice. This mutation was transferred to the C57BL/10 background by repeated backcrossing. The strain should be more than 99.5% homozygous for the dysferlin mutation.
**Symptoms:** Histological changes in muscle, including a few inflammatory infiltrates, can be detected by around 3 weeks of age. Different mice have different distributions of muscle weakness: either proximal or distal muscles are more severely affected.
**Comparison:** Disease progression is similar to SJL/J, Dysf-/- (Campbell), and Dysf-/- (Brown) mice, and faster than in A/J mice.
**Control(s):** C57BL/10
**References:** von der Hagen M, et al. 2005. The differential gene expression profiles of proximal and distal muscle groups are altered in pre-pathological dysferlindeficient mice. *Neuromuscular Disorders* 15:863-877

## C57BL/6J-Chr $6^{A/J}$/NaJ

**Availability:** The Jackson Laboratory
**Stock Number:** 004384
**Strain information:** http://jaxmice.jax.org/strain/004384.html
**Contact:** 800-422-MICE (800-422-6423)
610 Main Street, Bar Harbor, Maine 04609 USA
Mice are shipped at a specific age in weeks.
**Mutation:** As this strain carries chr6 from the A/J mice, they should have the same dysferlin mutation as the A/J strain - ETn retrotransposon (5-6kb) is inserted in Intron 4 of the dysferlin gene.

The mice should be tested for the presence of the insertion.

**Description**: A chromosome substitution or consomic strain is an inbred strain with one of its chromosomes replaced by the homologous chromosome of another inbred strain. The C57BL/6J and A/J strains in this set were chosen because they differ in their susceptibility to diseases such as arthritis, asthma, atherosclerosis, cancer, several infectious diseases, inflammatory responses, and physiological, behavioral and sensory phenotypes. Chromosome substitution strain nomenclature is designated as Host Strain - Chromosome #<Donor Strain>/Laboratory code. For example, C57BL/6J-Chr1$^{A}$/NaJ carries chromosome 1 for strain A/J (A) on a C57BL/6J background, was constructed in the laboratory of Joseph Nadeau (Na) and is maintained at The Jackson Laboratory (J). Chromosome substitution strains or consomic strains can accelerate quantitative trait loci identification and mapping.

**Development:** Dr. Joseph Nadeau from Case Western Reserve University developed the C57BL/6J-Chr #A/NaJ strain set by replacing individual chromosomes from the A/J donor strain into the C57BL/6J host strain using a marker-assisted series of backcrosses (Nadeau et al., 2000). The set was donated to The Jackson Laboratory in 2004.

**Symptoms:** Not characterized

**Comparison:** Not characterized

**Control:** C57Bl/6J

**References:** None relating to dysferlin or muscle pathology.