

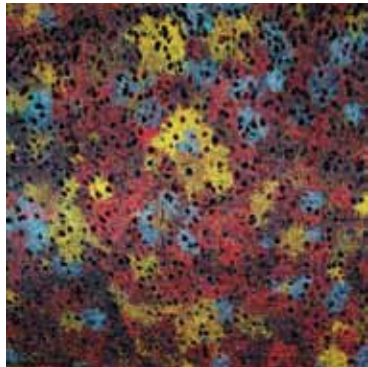
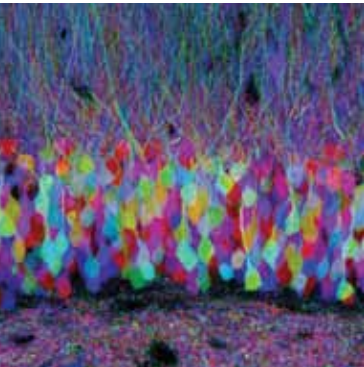
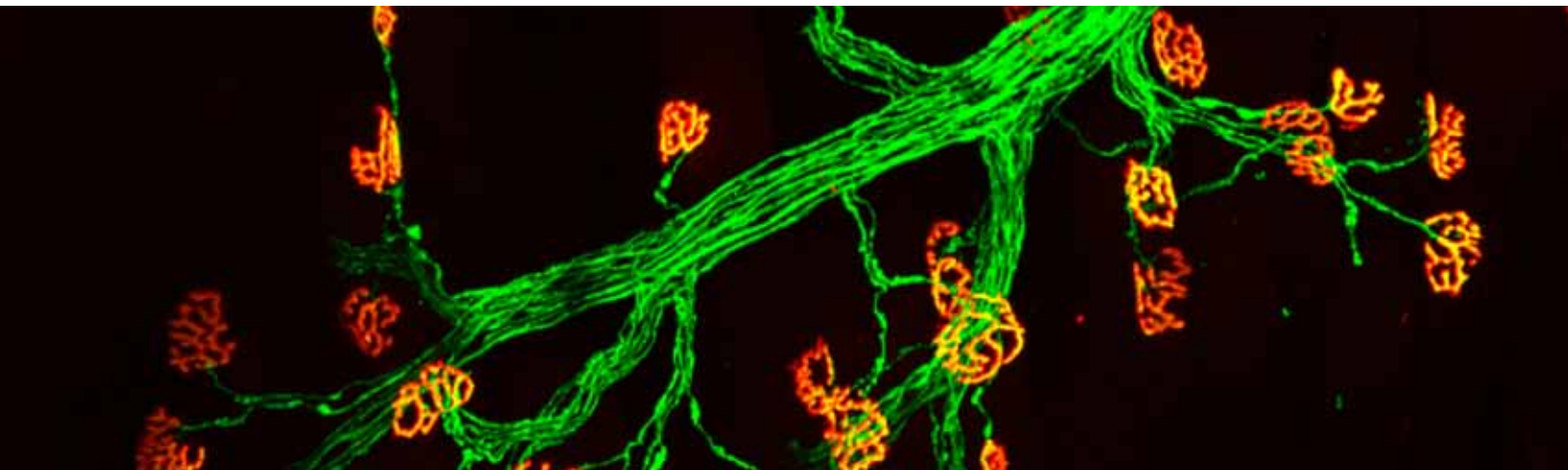


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Mouse Models for Amyotrophic Lateral Sclerosis (ALS) Disease and Spinal Muscular Atrophy (SMA) Disease

October 2009



Leading the Search for Tomorrow's Cures

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Amyotrophic Lateral Sclerosis (ALS) Disease

Amyotrophic lateral sclerosis (ALS) usually attacks both upper and lower motor neurons and causes degeneration throughout the brain and spinal cord. Early symptoms in 50% percent of affected people are a painless weakness in a hand, foot, arm, or leg. Other early symptoms include speech-swallowing and difficulty walking. ALS most commonly strikes people between 40 and 70 years old, affecting as many as 30,000 Americans at any given time. Like other neuromuscular diseases, ALS is complex, but genetically engineered mouse models are helping scientists identify the responsible genes and biochemical pathways (The ALS Association, www.alsa.org).

Visit our website for a current listing of all models

www.jax.org/jaxmice/research/neurobiology/als

* Indicates Strain is Under Development

Gene/Allele/Name		
Page	Stock No.	Strain Name
<i>Cdk5R1</i>, cyclin-dependent kinase 5, regulatory subunit (p35) 1		
<i>GFP</i>, Green Fluorescent Protein		
	005706	C57BL/6-Tg(tetO-CDK5R1/GFP)337Lht/J
<i>Sod1</i>, superoxide dismutase 1, soluble		
3	005110	FVB-Tg(Sod1*G86R)M1Jwg/J
<i>SOD1</i>, superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult)) (Human)		
3	008229*	B6.Cg-Tg(SOD1*G37R)29Dpr/J
4	008342	B6.Cg-Tg(SOD1*G37R)42Dpr/J
4	008248	B6.Cg-Tg(SOD1*G85R)148Dwc/J
5	004435	B6.Cg-Tg(SOD1*G93A)1Gur/J
5	002297	B6SJL-Tg(SOD1)2Gur/J
5	002726	B6SJL-Tg(SOD1*G93A)1Gur/J
6	008230	FVB(Cg)-Tg(Thy1-SOD1*G93A)T3Hgrd/J
	002298	B6.Cg-Tg(SOD1)2Gur/J
	002299	B6.Cg-Tg(SOD1*G93A) ^{dl1} Gur/J
	002300	B6SJL-Tg(SOD1*G93A) ^{dl1} Gur/J
	002629	C57BL/6-Tg(SOD1)3Cje/J
	002628	C57BL/6-Tg(SOD1)10Cje/J

Spinal Muscular Atrophy (SMA) Disease

SMA is the leading genetic cause of infant and toddler death. Classified in severity as Type I, II, III and adult, the disease results in a loss of motor neurons in the spinal cord and inability to control voluntary muscle movements. Affected children are weak, cry feebly, and have trouble swallowing, sucking, and breathing. From 25,000 to 55,000 people suffer from SMA in the United States, Europe and Japan (Spinal Muscular Atrophy Foundation, www.smafoundation.org). The National Institute of Neurological Disorders and Stroke selected SMA as the prototype for a \$22 million translational research project expected to yield drug candidates for Investigational New Drug Application filing within three to five years.

Most SMA cases are caused by low levels of SMN protein due to deletion of the gene Survival Motor Neuron (SMN1) on Chromosome 5. In humans, the SMN gene is duplicated. SMN1 and SMN2 are nearly identical, with a major difference being a critical transition (C to T) in exon 7. This difference results in the significant skipping of exon 7 and fewer amounts of full length SMN protein. A major strategy for treating SMA involves increasing the amount of full length transcript from the SMN2 gene. Mouse models play a critical role in deciphering the biology of the disease as well as for models of drug efficacy. The Jackson Laboratory is the husbandry and Distribution core for models of SMA.

Visit our website for a current listing of all models

www.jax.org/jaxmice/research/neurobiology/spinalmuscularatrophy

* Indicates Strain is Under Development

Gene/Allele/Name		
Page	Stock No.	Strain Name
<i>Smn1</i>, survival motor neuron 1		
<i>SMN1</i>, survival of motor neuron 1, telomeric		
<i>SMN2</i>, survival of motor neuron 2, centromeric		
7	006146	B6.129- <i>Smn1</i> ^{tm1Jme} /J
	006138	FVB.129(B6)- <i>Smn1</i> ^{tm1Jme} /J
7	006214	FVB.Cg- <i>Smn1</i> ^{tm1Msd} /J
7	007246	B6;129- <i>Smn1</i> ^{tm2Mrph} /J
7	007963	B6.Cg- <i>Smn1</i> ^{tm2Mrph} /J
7	007955	FVB.Cg- <i>Smn1</i> ^{tm2Mrph} /J
8	007249	B6;129- <i>Smn1</i> ^{tm3(SMN2/Smn1)Mrph} /J
8	007966*	B6.Cg- <i>Smn1</i> ^{tm3(SMN2/Smn1)Mrph} /J
8	007964*	FVB.Cg- <i>Smn1</i> ^{tm3(SMN2/Smn1)Mrph} /J
8	008383	B6;129- <i>Smn1</i> ^{tm4(SMN2)Mrph} /J

SMA models continued on following page

Mouse Models for Amyotrophic Lateral Sclerosis (ALS) Disease & Spinal Muscular Atrophy (SMA) Disease

SMA models continued

Gene/Allele/Name		
Page	Stock No.	Strain Name
8	008453*	B6.129- <i>Smn1</i> ^{tm4(SMN2)Mrph} /J
8	008713*	FVB.129(B6)- <i>Smn1</i> ^{tm4(SMN2)Mrph} /J
9	008714*	B6.129- <i>Smn1</i> ^{tm5(Smn1/SMN2)Mrph} /J
9	008384	B6;129- <i>Smn1</i> ^{tm5(Smn1/SMN2)Mrph} /J
9	008604*	FVB.129(B6)- <i>Smn1</i> ^{tm5(Smn1/SMN2)Mrph} /J
9	009378*	B6.129- <i>Smn1</i> ^{tm6(SMN2)Mrph} /J
9	008704	B6;129- <i>Smn1</i> ^{tm6(SMN2)Mrph} /J
9	009381*	FVB.Cg- <i>Smn1</i> ^{tm6(SMN2)Mrph} /J
10	008203	STOCK <i>Smn1</i> ^{tm1Msd} Tg(ACTA1-SMN)63Ahmb Tg(SMN2)89Ahmb/J
10	008209*	FVB.Cg- <i>Smn1</i> ^{tm1Msd} Tg(ACTA1-SMN)69Ahmb Tg(SMN2)89Ahmb/J
11	008212	STOCK <i>Smn1</i> ^{tm1Msd} Tg(Prnp-SMN)92Ahmb Tg(SMN2)89Ahmb/J
11	005026	FVB.Cg-Tg(SMN2)89Ahmb Tg(SMN1*A2G)2023Ahmb <i>Smn1</i> ^{tm1Msd} /J
12	008782*	STOCK <i>Smn1</i> ^{tm1Msd} Tg(SMN2)89Ahmb Tg(SMN2*A111G)588Ahmb/J
12	009134*	STOCK <i>Smn1</i> ^{tm1Msd} Tg(SMN2)89Ahmb Tg(SMN2*A111G)591Ahmb/J
13	007951	STOCK <i>Smn1</i> ^{tm3(SMN2/Smn1)Mrph} Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb/J
13	005025	FVB.Cg-Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb <i>Smn1</i> ^{tm1Msd} /J
14	008206	FVB.Cg- <i>Smn1</i> ^{tm1Msd} Tg(SMN2)566Ahmb/J
14	006570	STOCK <i>Smn1</i> ^{tm1Msd} Tg(Hlx9-GFP)1Timj Tg(SMN2)89Ahmb/J
15	005058	FVB.Cg-Tg(SMN2)2Hung <i>Smn1</i> ^{tm1Hung} /J
15	005024	FVB.Cg-Tg(SMN2)89Ahmb <i>Smn1</i> ^{tm1Msd} /J
16	008629*	B6.Cg-Tg(SMN2)11Tro <i>Smn1</i> ^{tm1Msd} /J
16	008630*	B6.Cg-Tg(SMN2)46Tro <i>Smn1</i> ^{tm1Msd} /J
16	008631*	B6.Cg-Tg(SMN2)11Tro Tg(SMN2)46Tro <i>Smn1</i> ^{tm1Msd} /J

Featured Amyotrophic Lateral Sclerosis (ALS) Disease Models

Gene/Marker

Sod1

Name **superoxide dismutase 1, soluble**

Common Name ALS; ALS1; Cu(2+)-Zn2+ superoxide dismutase; Cu/Zn-SOD; CuZnSOD; IPOA

Allele Symbol/Name

Common Name(s)

Promoter

Tg(Sod1*G86R)M1Jwg, transgene insertion M1, Jon W Gordon

M1; Tg(Sod1*G85R)M1Jwg; Tg(Sod1-G86R)M1Jwg

Sod1, superoxide dismutase 1, soluble

Strain Name

Stock Number

General Terms

Phenotype

FVB-Tg(Sod1*G86R)M1Jwg/J

005110

Strain(s) not available to companies or for-profit entities see www.jax.org/jaxmice/licensing/MTSNYAA.htm. These transgenic mice express the missense mutant mouse *Sod1* under the control of the endogenous promoter. The missense mutation is a point mutation in exon 4 resulting in a glycine-86 to arginine substitution, which corresponds to amino acid position 86 in the human SOD1 protein. Transgene expression is detected by RT-PCR analysis of brain, spinal cord, and other tissues. Onset of progressive loss of motor function begins at 3-4 months of age with hind limb spastic paralysis and muscle wasting. Transgenic mice do not survive beyond 4 months of age. Histological analysis of spinal cord ventral horns, brain stem and neocortex reveals neurodegeneration and abnormal neurites. Affected mice do not exhibit diminished SOD1 activity. This mutant mouse strain may be useful in studies of amyotrophic lateral sclerosis.

Selected Reference(s)

Ripps ME, Huntley GW, Hof PR, Morrison JH, Gordon JW. 1995. Transgenic mice expressing an altered murine superoxide dismutase gene provide an animal model of amyotrophic lateral sclerosis. *Proc Natl Acad Sci U S A* 92(3):689-93.

Gene/Marker

SOD1

Name **superoxide dismutase 1, soluble (Human)**

Allele Symbol/Name

Common Name(s)

Promoter

Tg(SOD1*G37R)29Dpr, transgene insertion 29, Donald L Price

G37R SOD1 (line 29), Tg(SOD1-G37R)29Dpr

SOD1, superoxide dismutase 1, soluble

Strain Name

Stock Number

Phenotype

B6.Cg-Tg(SOD1*G37R)29Dpr/J

008229

Mice hemizygous for this G37R-SOD1 transgene are viable and fertile. The expressed G37R mutant form of human *SOD1* is characterized as an enzymatically active, "gain of adverse function" mutation. Hemizygotes develop symptoms and pathology resembling human Amyotrophic Lateral Sclerosis (ALS), with paralyzation in one or more limbs attributable to the loss of motor neurons from the spinal cord. Death occurs around six to eight months of age on the original mixed genetic background from the original publication. Upon backcrossing to C57BL/6J the phenotype is significantly delayed. Transgenic mice from this founder line (line 29) express a moderate (7-fold) increase in SOD1 activity in spinal cord, with pathology restricted to motor neurons in the spinal cord and brainstem. Like wild-type SOD1, the G37R mutant SOD1 protein also forms monomer-misfolded oligomers associated with degenerating motor neurons. These G37R-SOD1 transgenic mice may be useful in studying neuromuscular disorders, including Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease).

In an attempt to offer alleles on well-characterized or multiple genetic backgrounds, alleles are frequently moved to a genetic background different from that on which an allele was first characterized. As the G37R-SOD1 transgenic mice were originally created on a mixed genetic background, it should be noted that the phenotype of the congenic mice could vary from that originally described. We will modify the strain description if necessary as published results become available.

Selected Reference(s)

Wong PC, Pardo CA, Borchelt DR, Lee MK, Copeland NG, Jenkins NA, Sisodia SS, Cleveland DW, Price DL. 1995. An adverse property of a familial ALS-linked SOD1 mutation causes motor neuron disease characterized by vacuolar degeneration of mitochondria. *Neuron* 14(6):1105-16.

Featured Amyotrophic Lateral Sclerosis (ALS) Disease Models

Allele Symbol/Name	Tg(SOD1*G37R)42Dpr, transgene insertion 42, Donald L Price
Common Name(s)	G37R SOD1 line 42; G37R(42); SOD1 G37R line 42; Tg(SOD1-G37R)42Dpr
Promoter	SOD1, superoxide dismutase 1, soluble
Strain Name	B6.Cg-Tg(SOD1*G37R)42Dpr/J
Stock Number	008342
General Terms	Strain(s) not available to companies or for-profit entities, see www.jax.org/jaxmice/licensing/UCSDNOFP.htm
Phenotype	Mice hemizygous for this G37R-SOD1 transgene are viable and fertile. The expressed G37R mutant form of human SOD1 is characterized as an enzymatically active, “gain of adverse function” mutation. Hemizygotes develop symptoms and pathology resembling human Amyotrophic Lateral Sclerosis (ALS), with paralyzation in one or more limbs attributable to the loss of motor neurons from the spinal cord. Transgenic mice from the highest expressing founder line (G37R(42) or line 42) express a 14-fold increase in SOD1 activity in spinal cord with death occurring around 3.5-4 months of age on the original mixed genetic background from the original publication. Upon backcrossing to C57BL/6J the phenotype is significantly delayed, with disease onset occurring at approximately 20 weeks of age and death occurring at approximately 24-27 weeks of age. High expression of G37R-SOD1 is associated with ALS pathology in motor neurons of the spinal cord and brainstem, widespread degenerative changes in other neuronal populations, and mild-to-moderate vacuolar changes in kidney. These high-expressing G37R(42) (or G37R-SOD1 line 42) transgenic mice may be useful in studying neuromuscular disorders, including Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig’s Disease). <i>In an attempt to offer alleles on well-characterized or multiple genetic backgrounds, alleles are frequently moved to a genetic background different from that on which an allele was first characterized. As the G37R-SOD1 transgenic mice were originally created on a mixed genetic background, it should be noted that the phenotype of the congenic mice vary from that originally described.</i>
Selected Reference(s)	Wong PC, Pardo CA, Borchelt DR, Lee MK, Copeland NG, Jenkins NA, Sisodia SS, Cleveland DW, Price DL. 1995. An adverse property of a familial ALS-linked SOD1 mutation causes motor neuron disease characterized by vacuolar degeneration of mitochondria. <i>Neuron</i> 14(6):1105-16.
Allele Symbol/Name	Tg(SOD1*G85R)148Dwc, transgene insertion 148, Don W Cleveland
Common Name(s)	148-G85R; G85R; G85R SOD1 line148; G85R line 148; SOD1 G85R line 148; Tg(SOD1-G85R)148Dwc
Promoter	SOD1, superoxide dismutase 1, soluble
Strain Name	B6.Cg-Tg(SOD1*G85R)148Dwc/J
Stock Number	008248
General Terms	Strain(s) not available to companies or for-profit entities, see www.jax.org/jaxmice/licensing/UCSDNOFP.htm
Phenotype	Mice hemizygous for this G85R-SOD1 transgene are viable and fertile, with transgenic expression of a G85R mutant form of human SOD1 associated with human familial Amyotrophic Lateral Sclerosis (ALS). Mice from this founder line (line 148) exhibit unaltered endogenous SOD1 activity; the G85R mutation is characterized as an “enzymatically inactive” mutation. Hemizygotes develop symptoms and pathology resembling human ALS; becoming paralyzed in one or more limbs due to loss of motor neurons from the spinal cord, with disease onset and rapid progression to death between 7-8 months of age. Like wild-type SOD1, the G85R mutant SOD1 protein also forms monomer-misfolded oligomers associated with degenerating motor neurons. These G85R-SOD1 transgenic mice may be useful in studying neuromuscular disorders, including Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig’s Disease). <i>In an attempt to offer alleles on well-characterized or multiple genetic backgrounds, alleles are frequently moved to a genetic background different from that on which an allele was first characterized. As the G85R-SOD1 transgenic mice were originally created on a mixed genetic background, it should be noted that the phenotype of the congenic mice could vary from that originally described. We will modify the strain description if necessary as published results become available.</i>
Selected Reference(s)	Brujin LI, Becher MW, Lee MK, Anderson KL, Jenkins NA, Copeland NG, Sisodia SS, Rothstein JD, Borchelt DR, Price DL, Cleveland DW. 1997. ALS-linked SOD1 mutant G85R mediates damage to astrocytes and promotes rapidly progressive disease with SOD1-containing inclusions. <i>Neuron</i> 18(2):327-38.

Featured Amyotrophic Lateral Sclerosis (ALS) Disease Models

Allele Symbol/Name Common Name(s)	Tg(SOD1*G93A)1Gur, transgene insertion 1, Mark E Gurney (G93A)Tg+; G1H; G93A; G93A SOD1; G93A+; G93A-SOD1; SOD1 G93A; SOD1 Tg; SOD1 ^{G93A} ; Tg(G93A-SOD1)1Gur; Tg(SOD1-G93A)1Gur; TgN(SOD1-G93A)1Gur; TgN[SOD1-G93A]1Gur; hSOD1G93A
Promoter	SOD1, superoxide dismutase 1, soluble
Strain Name	B6.Cg-Tg(SOD1*G93A)1Gur/J
Stock Number	004435
General Terms	Use of MICE by companies or for-profit entities requires a license, see www.jax.org/jaxmice/licensing/UNWSOD1.htm
Phenotype	Mice hemizygous for this SOD1-G93A (also called G93A-SOD1) transgene are viable and fertile, with transgenic expression of a G93A mutant form of human SOD1. This founder line (often referred to as G1H) is reported to have high transgene copy number. Hemizygotes exhibit a phenotype similar to amyotrophic lateral sclerosis (ALS) in humans; becoming paralyzed in one or more limbs with paralysis due to loss of motor neurons from the spinal cord. Transgenic mice have an abbreviated life span: 50% survive at 157.1+/-9.3 days (in contrast to the mixed B6SJL background where 50% survival is observed at 128.9+/-9.1 days). Female hemizygotes are poor breeders, and rarely produce more than one litter before the onset of disease. These SOD1-G93A (also called G93A-SOD1) transgenic mice may be useful in studying neuromuscular disorders, including Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease). <i>In an attempt to offer alleles on well-characterized or multiple genetic backgrounds, alleles are frequently moved to a genetic background different from that on which an allele was first characterized. As the SOD1-G93A transgenic mice were originally created on a mixed genetic background, it should be noted that the phenotype of the congenic mice could vary from that originally described. We will modify the strain description if necessary as published results become available.</i>
Selected Reference(s)	Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD, Caliando J, Hentati A, Kwon YW, Deng HX, Chen W, Zhai P, Sufit RL, Siddique T. 1994. Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation [see comments] [published erratum appears in <i>Science</i> 1995 Jul 14;269(5221):149] <i>Science</i> 264(5166):1772-5. Wooley CM, Sher RB, Kale A, Frankel WN, Cox GA, Seburn KL. 2005. Gait analysis detects early changes in transgenic SOD1(G93A) mice. <i>Muscle Nerve</i> 32(1):43-50.
Allele Symbol/Name Common Name(s)	Tg(SOD1)2Gur, transgene insertion 2, Mark E Gurney N1029; N29; WT SOD1; WTSOD1; tg-SOD1
Promoter	SOD1, superoxide dismutase 1, soluble
Strain Name	B6SJL-Tg(SOD1)2Gur/J
Stock Number	002297
General Terms	Use of MICE by companies or for-profit entities requires a license, see www.jax.org/jaxmice/licensing/UNWSOD1.htm
Phenotype	This transgenic strain carries the normal allele of the human SOD1 gene. Originally published as N1029, it has been reported that the SOD1 protein level is the same as in the transgenic strain carrying the SOD1*G93A transgene (002726), even though the copy number in the SOD1*G93A transgenic is higher. This strain serves as a control for the B6SJL-Tg(SOD1*G93A)1Gur/J (002726) and the B6SJL-Tg(SOD1*G93A) ^{dl} 1Gur/J (002300) strains.
Selected Reference(s)	Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD, Caliando J, Hentati A, Kwon YW, Deng HX, Chen W, Zhai P, Sufit RL, Siddique T. 1994. Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation [see comments] [published erratum appears in <i>Science</i> 1995 Jul 14;269(5221):149] <i>Science</i> 264(5166):1772-5.
Allele Symbol/Name Common Name(s)	Tg(SOD1*G93A)1Gur, transgene insertion 1, Mark E Gurney (G93A)Tg+; G1H; G93A; G93A SOD1; G93A+; G93A-SOD1; SOD1 G93A; SOD1 Tg; SOD1 ^{G93A} ; Tg(G93A-SOD1)1Gur; Tg(SOD1-G93A)1Gur; TgN(SOD1-G93A)1Gur; TgN[SOD1-G93A]1Gur; hSOD1G93A
Promoter	SOD1, superoxide dismutase 1, soluble
Strain Name	B6SJL-Tg(SOD1*G93A)1Gur/J
Stock Number	002726
General Terms	Use of MICE by companies or for-profit entities requires a license, see www.jax.org/jaxmice/licensing/UNWSOD1.htm
Phenotype	Mice hemizygous for this SOD1-G93A (also called G93A-SOD1) transgene are viable and fertile, with transgenic expression of a G93A mutant form of human SOD1. This founder line (often referred to as G1H) is reported

Featured Amyotrophic Lateral Sclerosis (ALS) Disease Models

<i>Selected Reference(s)</i>	<p>to have high transgene copy number. Hemizygotes exhibit a phenotype similar to amyotrophic lateral sclerosis (ALS) in humans; becoming paralyzed in one or more limbs with paralysis due to loss of motor neurons from the spinal cord. Transgenic mice have an abbreviated life span: 50% survive at 128.9+/-9.1 days (in contrast to C57BL/6J background where 50% survival is observed at 157.1+/-9.3 days). These SOD1-G93A (also called G93A-SOD1) transgenic mice may be useful in studying neuromuscular disorders, including Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease).</p> <p>Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD, Caliendo J, Hentati A, Kwon YW, Deng HX, Chen W, Zhai P, Sufit RL, Siddique T. 1994. Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation [see comments] [published erratum appears in <i>Science</i> 1995 Jul 14;269(5221):149] <i>Science</i> 264(5166):1772-5.</p>
<i>Allele Symbol/Name</i>	Tg(Thy1-SOD1*G93A)T3Hgrd, transgene insertion T3, Casper Hoogenraad
<i>Common Name(s)</i>	Thy1.2-G93A
<i>Promoter</i>	<i>Thy1</i> , thymus cell antigen 1, theta
<i>Strain Name</i>	FVB(Cg)-Tg(Thy1-SOD1*G93A)T3Hgrd/J
<i>Stock Number</i>	008230
<i>Common Name(s)</i>	FVB-T3; FVB-Thy1.2-G93A
<i>General Terms</i>	Use of MICE by companies or for-profit entities requires a license prior to shipping, see www.jax.org/jaxmice/licensing/ERASMUS.htm
<i>Phenotype</i>	<p>These Thy1.2-G93A transgenic mice have a human SOD1 cDNA harboring the G93A mutation driven by the murine Thy1.2 expression cassette. Expression of the G93A mutant SOD1 (G93A-SOD1) is directed to neurons throughout the brain and spinal cord (including spinal motor neurons). In addition, mutant SOD1 immunoreactivity is selectively distributed in axons and nerve endings at the neuromuscular junctions. While Thy1.2-G93A hemizygous mice from founder line T3 are viable and fertile with no clinical or pathological signs of motor abnormalities up to two years of age, neuronal expression of mutant SOD1 in homozygous Thy1.2-G93A mice from founder line T3 (also called T3T3 mice) develop an Amyotrophic Lateral Sclerosis (ALS)-like motor neuron disease between one to two years of age, characterized by motor neuron degeneration, muscle denervation, paralysis, and muscle weakness with cytosolic dendritic ubiquitinated SOD1 aggregates as the dominant pathological feature. Additionally, when these T3 mice are bred with N29 hSOD1 mice (see Tg(SOD1)2Gur mice; Stock No. 002297 and 002298), T3/hSOD1 double hemizygous offspring develop an ALS-like motor neuron disease between one to two years of age. These Thy1.2-G93A (or T3) transgenic mice may be useful in studying neuromuscular disorders, including Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease).</p> <p><i>In an attempt to offer alleles on well-characterized or multiple genetic backgrounds, alleles are frequently moved to a genetic background different from that on which an allele was first characterized. It should be noted that the phenotype of these mice could vary from that originally described. We will modify the strain description if necessary as published results become available.</i></p>
<i>Selected Reference(s)</i>	<p>Jaarsma D, Teuling E, Haasdijk ED, De Zeeuw CI, Hoogenraad CC. 2008. Neuron-specific expression of mutant superoxide dismutase is sufficient to induce amyotrophic lateral sclerosis in transgenic mice. <i>J Neurosci</i> 28(9):2075-88.</p>

Featured Spinal Muscular Atrophy (SMA) Disease Models

Importation of these models was supported by the Spinal Muscular Atrophy Foundation.

Gene/Marker
Smn1

Name **survival motor neuron 1**

Allele Symbol/Name
Common Name(s)

***Smn1*^{tm1.1Jme}, targeted mutation 1.1, Judith Melki**
SMN^{delta7}

Strain Name
Stock Number
General Terms

B6.129-Smn1^{tm1Jme/J}
006146

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Phenotype

Mice homozygous for this SMN^{F7} floxed allele are viable and fertile and do not display any gross physical or behavioral abnormalities. Mutant mice exhibit no transcript splicing defects. Cre-mediated recombination of the *loxP*-flanked sequences results in deletion of exon 7 of the targeted gene. As mutations of this exon are implicated in 95% of all human spinal muscular atrophy (SMA), these mice may be useful in studying SMA or other neuromuscular degenerative diseases.

When crossed to a strain expressing Cre recombinase in neurons (see Stock No. 005938, Stock No. 006297, and Stock No. 006663), this mutant mouse strain may be useful as a model of SMA.

When crossed to a strain expressing Cre recombinase in striated muscle fibers (see Stock No. 005936, Stock No. 006139, and Stock No. 006149), this mutant mouse strain may be useful as a model of SMA.

SMN^{F7} mice are available on different genetic backgrounds (see Stock No. 006138 and Stock No. 006146). In an attempt to offer alleles on well-characterized or multiple genetic backgrounds, alleles are frequently moved to a genetic background different from that on which an allele was first characterized. It should be noted that the SMN^{F7} phenotype could vary from that originally described on a mixed genetic background. We will modify the strain description if necessary as published results become available.

Creation and development was supported by the National Institute of Health and Medical Research of France (Inserm) and the Association Française contre les Myopathies (AFM). An additional help was provided by Families of SMA (U.S.A.) and Andrew's Buddies (U.S.A.).

Selected Reference(s)

Frugier T, Tiziano FD, Cifuentes-Diaz C, Miniou P, Roblot N, Dierich A, Le Meur M, Melki J. 2000. Nuclear targeting defect of SMN lacking the C-terminus in a mouse model of spinal muscular atrophy. *Hum Mol Genet* 9(5):849-58.

Allele Symbol/Name
Common Name(s)

***Smn1*^{tm1Msd}, targeted mutation 1, Michael Sendtner**
SMN-

Strain Name
Stock Number
General Terms

FVB.Cg-Smn1^{tm1Msd/J}
006214

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Phenotype

Mice that are heterozygous for the targeted mutation are viable, fertile, normal in size and do not display any gross physical or behavioral abnormalities. Beta-galactosidase staining is found in oocytes of pregnant heterozygous females. Homozygous mice have an early embryonic lethal phenotype, failing to form a blastocoel cavity and do not implant. Abnormal development is observed by 80 hours post conception. By 90 to 100 hours post conception there is massive cellular degeneration and apoptotic cell death. This mutant mouse strain may be useful in studies of spinal muscular atrophy.

Selected Reference(s)

Schrank B, Gotz R, Gunnensen JM, Ure JM, Toyka KV, Smith AG, Sendtner M. 1997. Inactivation of the survival motor neuron gene, a candidate gene for human spinal muscular atrophy, leads to massive cell death in early mouse embryos. *Proc Natl Acad Sci U S A* 94(18):9920-5.

Allele Symbol/Name
Common Name(s)

***Smn1*^{tm2Mrph}, targeted mutation 2, Andrew Murphy**
Smn1^{K1}; Smn1^{KO}; Smn1^{lacZ}

Strain Name
Stock Number
General Terms

B6;129-Smn1^{tm2Mrph/J}
007246

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This strain functions as a reporter strain for *Smn1* (survival motor neuron 1) in the heterozygous state. Exons 1 through 8 of the mouse *Smn1* gene (12.8 kb) were replaced with *lacZ* and an *FRT* site remaining from the

Featured Spinal Muscular Atrophy (SMA) Disease Models

Importation of these models was supported by the Spinal Muscular Atrophy Foundation.

Selected Reference(s)	deletion of a selection marker. This allele is a functional null and homozygous animals are embryonic lethal. Murphy A (Regeneron Pharmaceuticals, Inc.). 2008. <i>Smn1</i> deletion with <i>lacZ</i> knock in. Personal Communication.
Strain Name	B6.Cg-Smn1^{tm2Mrph}/J
Stock Number	007963
Phenotype	This strain functions as a reporter strain for <i>Smn1</i> (survival motor neuron 1) in the heterozygous state. Exons 1 through 8 of the mouse <i>Smn1</i> gene (12.8 kb) were replaced with <i>lacZ</i> and an <i>FRT</i> site remaining from the deletion of a selection marker. This allele is a functional null and homozygous animals are embryonic lethal.
Selected Reference(s)	Murphy A, Regeneron Pharmaceuticals, Inc. 2009. <i>Smn</i> allele D Personal Communication.
Strain Name	FVB.Cg-Smn1^{tm2Mrph}/J
Stock Number	007955
Phenotype	This strain functions as a reporter strain for <i>Smn1</i> (survival motor neuron 1) in the heterozygous state. Exons 1 through 8 of the mouse <i>Smn1</i> gene (12.8 kb) were replaced with <i>lacZ</i> and an <i>FRT</i> site remaining from the deletion of a selection marker. This allele is a functional null and homozygous animals are embryonic lethal.
Selected Reference(s)	Murphy A, Regeneron Pharmaceuticals, Inc. 2009. <i>Smn</i> allele D Personal Communication.
Allele Symbol/Name Common Name(s)	<i>Smn1</i>^{tm3(SMN2/Smn1)Mrph}, targeted mutation 3, Andrew Murphy <i>Smn1</i> COIN (conditional inversion)
Strain Name	B6;129-Smn1^{tm3(SMN2/Smn1)Mrph}/J
Stock Number	007249
Common Name(s)	hybrid rescue allele
General Terms	FOR-PROFIT RESEARCHERS MAY ONLY USE THESE MICE IN THE FIELD OF NEURODEGENERATIVE RESEARCH, see www.jax.org/jaxmice/licensing/REGEN_SMA.htm
Phenotype	Use of MICE by companies or for-profit entities requires a license, see www.jax.org/jaxmice/licensing/SALKFLP.htm This allele is a functional null in the non-recombined state and homozygous animals are embryonic lethal. This allele is engineered to revert to a fully functional <i>Smn1</i> allele upon Cre-mediated recombination. This mutant mouse strain may be useful in studies of Spinal Muscular Atrophy.
Selected Reference(s)	Murphy A (Regeneron Pharmaceuticals, Inc.). 2008. <i>Smn1</i> hybrid rescue allele, COIN (conditional inversion) Personal Communication.
Strain Name	B6.Cg-Smn1^{tm3(SMN2/Smn1)Mrph}/J
Stock Number	007966
Phenotype	This allele is a functional null in the non-recombined state and homozygous animals are embryonic lethal. This allele is engineered to revert to a fully functional <i>Smn1</i> allele upon Cre-mediated recombination. This mutant mouse strain may be useful in studies of Spinal Muscular Atrophy.
Selected Reference(s)	Murphy A, Regeneron Pharmaceuticals, Inc. 2009. <i>Smn</i> allele D Personal Communication.
Strain Name	FVB.Cg-Smn1^{tm3(SMN2/Smn1)Mrph}/J
Stock Number	007964
Phenotype	This allele is a functional null in the non-recombined state and homozygous animals are embryonic lethal. This allele is engineered to revert to a fully functional <i>Smn1</i> allele upon Cre-mediated recombination. This mutant mouse strain may be useful in studies of Spinal Muscular Atrophy.
Selected Reference(s)	Murphy A, Regeneron Pharmaceuticals, Inc. 2009. <i>Smn</i> allele D Personal Communication.
Allele Symbol/Name Common Name(s)	<i>Smn1</i>^{tm4(SMN2)Mrph}, targeted mutation 4, Andrew Murphy <i>Smn</i> allele B
Strain Name	B6;129-Smn1^{tm4(SMN2)Mrph}/J
Stock Number	008383
Strain Name	B6.129-Smn1^{tm4(SMN2)Mrph}/J
Stock Number	008453
Strain Name	FVB.129(B6)-Smn1^{tm4(SMN2)Mrph}/J
Stock Number	008713

Featured Spinal Muscular Atrophy (SMA) Disease Models

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General Terms	FOR-PROFIT RESEARCHERS MAY ONLY USE THESE MICE IN THE FIELD OF NEURODEGENERATIVE RESEARCH, see www.jax.org/jaxmice/licensing/REGEN_SMA.htm Use of MICE by companies or for-profit entities requires a license, see www.jax.org/jaxmice/licensing/SALKFLP.htm
Phenotype	In this hybrid allele, exon 7 of <i>Smn1</i> (survival motor neuron 1) is replaced with the equivalent exon from human <i>SMN2</i> (survival of motor neuron 2, centromeric), and is skipped in approximately 90% of the processed mRNA. Further characterization is currently in progress. This mutant mouse strain may be useful in studies of Spinal Muscular Atrophy.
Selected Reference(s)	Murphy A, Regeneron Pharmaceuticals, Inc. 2009. Smn allele D Personal Communication.
Allele Symbol/Name Common Name(s)	<i>Smn1</i>^{tm5(Smn1/SMN2)Mrph}, targeted mutation 5, Andrew Murphy Smn1 allele C
Strain Name Stock Number	B6.129-Smn1^{tm5(Smn1/SMN2)Mrph}/J 008714
Strain Name Stock Number	B6;129-Smn1^{tm5(Smn1/SMN2)Mrph}/J 008384
Strain Name Stock Number	FVB.129(B6)-Smn1^{tm5(Smn1/SMN2)Mrph}/J 008604
General Terms	FOR-PROFIT RESEARCHERS MAY ONLY USE THESE MICE IN THE FIELD OF NEURODEGENERATIVE RESEARCH, see www.jax.org/jaxmice/licensing/REGEN_SMA.htm Use of MICE by companies or for-profit entities requires a license, see www.jax.org/jaxmice/licensing/SALKFLP.htm
Phenotype	In this hybrid allele, Smn allele C, contains two tandem <i>Smn1/SMN2</i> genes. Further characterization is currently in progress. This mutant mouse strain may be useful in studies of Spinal Muscular Atrophy.
Selected Reference(s)	Murphy A (Regeneron Pharmaceuticals, Inc.). 2008. Smn allele C. Personal Communication.
Allele Symbol/Name Common Name(s)	<i>Smn1</i>^{tm6(SMN2)Mrph}, targeted mutation 6, Andrew Murphy Smn Allele D
Strain Name Stock Number	B6.129-Smn1^{tm6(SMN2)Mrph}/J 009378
Strain Name Stock Number	B6;129-Smn1^{tm6(SMN2)Mrph}/J 008704
Strain Name Stock Number	FVB.Cg-Smn1^{tm6(SMN2)Mrph}/J 009381
General Terms	FOR-PROFIT RESEARCHERS MAY ONLY USE THESE MICE IN THE FIELD OF NEURODEGENERATIVE RESEARCH, see www.jax.org/jaxmice/licensing/REGEN_SMA.htm
Phenotype	This mutant mouse carries the Smn allele D, which contains four tandem <i>Smn1/SMN2</i> genes. Further characterization is currently in progress. This mutant mouse strain may be useful in studies of Spinal Muscular Atrophy.
Selected Reference(s)	Murphy A, Regeneron Pharmaceuticals, Inc. 2009. Smn allele D Personal Communication.

Gene/Marker <i>Smn1 SMN1 SMN2</i>	Name survival motor neuron 1; survival of motor neuron 1, telomeric; survival of motor neuron 2, centromeric
Allele Symbol/Name Common Name(s)	<i>Smn1</i>^{tm1Msd}, targeted mutation 1, Michael Sendtner SMN-
Allele Symbol/Name Common Name(s) Promoter	Tg(ACTA1-SMN)63Ahmb, transgene insertion 63, Arthur H M Burghes HSA63-SMN; HSA69-SMN <i>ACTA1</i> , actin, alpha 1, skeletal muscle

Featured Spinal Muscular Atrophy (SMA) Disease Models

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Allele Symbol/Name Common Name(s) Promoter	Tg(SMN2)89Ahmb, transgene insertion 89, Arthur H M Burghes SMN2 SMN2, survival of motor neuron 2, centromeric
Strain Name Stock Number General Terms	STOCK <i>Smn1^{tm1Msd}</i> Tg(ACTA1-SMN)63Ahmb Tg(SMN2)89Ahmb/J 008203 Use of MICE by companies or for-profit entities requires a license prior to shipping, see www.jax.org/jaxmice/licensing/UOHIO.htm
Phenotype	As described for SMA mice (see Stock No. 005024), mice homozygous for <i>Smn1^{tm1Msd}</i> targeted mutation (<i>Smn</i> null allele) and human SMN2 low copy line 89 transgene exhibit symptoms, neuropathology, and early lethality similar to human type I proximal spinal muscular atrophy (SMA) patients. As an addition to that SMA model, this strain also carries the HSA-SMN transgene; with the human alpha-skeletal actin (HSA or <i>ACTA1</i>) promoter directing full-length human SMN expression at high levels in skeletal muscle. When the HSA-SMN transgene is derived from HSA69-SMN founder mice, skeletal muscle-specific SMN expression is preserved, and homozygous SMN2; <i>Smn</i> ; HSA69-SMN mutant animals (Stock No. 008209) have the same phenotype as homozygous SMA mice. In contrast, expression of the HSA-SMN transgene derived from HSA63-SMN founder mice is leaky; with high SMN expression in heart and low SMN expression in spinal cord, brain, and liver. This additional SMN expression in neural cells rescues homozygous SMN2; <i>Smn</i> ; HSA63-SMN mice (Stock No. 008203) from the severe SMA phenotype and significantly increases lifespan (average 160 days). Homozygous SMN2; <i>Smn</i> ; HSA63-SMN mice also exhibit necrotic tail development with loss of the tail giving them a “hamster” appearance. These SMN2; <i>Smn</i> ; HSA63-SMN mice may be useful for neuromuscular studies including spinal muscular atrophy (SMA).
Selected Reference(s)	Gavrilina TO, McGovern VL, Workman E, Crawford TO, Gogliotti RG, Didonato CJ, Monani UR, Morris GE, Burghes HM. 2008. Neuronal SMN expression corrects spinal muscular atrophy in severe SMA mice while muscle specific SMN expression has no phenotypic effect. <i>Hum Mol Genet</i> 2008 17(8):1063-75.
Allele Symbol/Name Common Name(s)	<i>Smn1^{tm1Msd}</i>, targeted mutation 1, Michael Sendtner SMN-
Allele Symbol/Name Common Name(s) Promoter	Tg(ACTA1-SMN)69Ahmb, transgene insertion 69, Arthur H M Burghes HSA69-SMN <i>ACTA1</i> , actin, alpha 1, skeletal muscle
Allele Symbol/Name Common Name(s) Promoter	Tg(SMN2)89Ahmb, transgene insertion 89, Arthur H M Burghes SMN2 SMN2, survival of motor neuron 2, centromeric
Strain Name Stock Number General Terms	FVB.Cg-<i>Smn1^{tm1Msd}</i> Tg(ACTA1-SMN)69Ahmb Tg(SMN2)89Ahmb/J 008209 Use of MICE by companies or for-profit entities requires a license prior to shipping, see www.jax.org/jaxmice/licensing/UOHIO.htm
Phenotype	As described for SMA mice (see Stock No. 005024), mice homozygous for <i>Smn1^{tm1Msd}</i> targeted mutation (<i>Smn</i> null allele) and human SMN2 low copy line 89 transgene exhibit symptoms, neuropathology, and early lethality similar to human type I proximal spinal muscular atrophy (SMA) patients. As an addition to that SMA model, this strain also carries the HSA-SMN transgene; with the human alpha-skeletal actin (HSA or <i>ACTA1</i>) promoter directing full-length human SMN expression at high levels in skeletal muscle. When the HSA-SMN transgene is derived from HSA69-SMN founder mice, skeletal muscle-specific SMN expression is preserved, and homozygous SMN2; <i>Smn</i> ; HSA69-SMN mutant animals (Stock No. 008209) have the same phenotype as homozygous SMA mice. In contrast, expression of the HSA-SMN transgene derived from HSA63-SMN founder mice is leaky; with high SMN expression in heart and low SMN expression in spinal cord, brain, and liver. This additional SMN expression in neural cells rescues homozygous SMN2; <i>Smn</i> ; HSA63-SMN mice (Stock No. 008203) from the severe SMA phenotype and significantly increases lifespan (average 160 days). Homozygous SMN2; <i>Smn</i> ; HSA63-SMN mice also exhibit necrotic tail development with loss of the tail giving them a “hamster” appearance. These SMN2; <i>Smn</i> ; HSA69-SMN mice may be useful for neuromuscular studies including spinal muscular atrophy (SMA).
Selected Reference(s)	Gavrilina TO; McGovern VL; Workman E; Crawford TO; Gogliotti RG; Didonato CJ; Monani UR; Morris GE; Burghes HM. 2008. Neuronal SMN expression corrects spinal muscular atrophy in severe SMA mice while muscle specific SMN expression has no phenotypic effect. <i>Hum Mol Genet</i> 2008 17(8):1063-75.

Featured Spinal Muscular Atrophy (SMA) Disease Models

Importation of these models was supported by the Spinal Muscular Atrophy Foundation.

Allele Symbol/Name Common Name(s)	<i>Smn1^{tm1Msd}</i>, targeted mutation 1, Michael Sendtner SMN-
Allele Symbol/Name Common Name(s) Promoter	Tg(Prnp-SMN)92Ahmb, transgene insertion 92, Arthur H M Burghes PrP92-SMN <i>Prnp</i> , prion protein
Allele Symbol/Name Common Name(s) Promoter	Tg(SMN2)89Ahmb, transgene insertion 89, Arthur H M Burghes SMN2 SMN2, survival of motor neuron 2, centromeric
Strain Name Stock Number General Terms	STOCK <i>Smn1^{tm1Msd}</i> Tg(Prnp-SMN)92Ahmb Tg(SMN2)89Ahmb/J 008212 Use of MICE by companies or for-profit entities requires a license prior to shipping, see www.jax.org/jaxmice/licensing/UOHIO.htm
Phenotype	As described for SMA mice (see Stock No. 005024), mice homozygous for <i>Smn1^{tm1Msd}</i> targeted mutation (<i>Smn</i> null allele) and human SMN2 transgene (SMN2 low copy line 89) exhibit symptoms, neuropathology, and early lethality similar to human type I proximal spinal muscular atrophy (SMA) patients. As an addition to that SMA model, this strain also carries the PrP-SMN transgene; with the mouse prion protein (PrP or <i>Prnp</i>) promoter directing full-length human SMN expression at high levels in neurons (with low expression in skeletal muscle and liver). When the PrP-SMN transgene is derived from PrP92-SMN founder mice, high SMN expression in spinal cord and brain is observed. Homozygous SMN2; <i>Smn</i> ; Prp92-SMN mice are rescued from the severe SMA phenotype, have significantly increased lifespan (average of 210 days) and have normal lumbar motor neuron root counts. Homozygous SMN2; <i>Smn</i> ; PrP92-SMN males are infertile, females are fertile but poor mothers, and both sexes exhibit necrotic tail development with about one-third of the normal length remaining around the time of weaning. These SMN2; <i>Smn</i> ; PrP92-SMN mutant mice may be useful in neuromuscular studies including spinal muscular atrophy (SMA).
Selected Reference(s)	Gavrilina TO, McGovern VL, Workman E, Crawford TO, Gogliotti RG, Didonato CJ, Monani UR, Morris GE, Burghes HM. 2008. Neuronal SMN expression corrects spinal muscular atrophy in severe SMA mice while muscle specific SMN expression has no phenotypic effect. <i>Hum Mol Genet</i> 2008 17(8):1063-75.
Allele Symbol/Name Common Name(s) Promoter	Tg(SMN2)89Ahmb, transgene insertion 89, Arthur H M Burghes SMN2 SMN2, survival of motor neuron 2, centromeric
Allele Symbol/Name Common Name(s) Promoter	Tg(SMN1*A2G)2023Ahmb, transgene insertion 2023, Arthur H M Burghes SMN A2G <i>SMN1</i> , survival of motor neuron 1, telomeric
Allele Symbol/Name Common Name(s)	<i>Smn1^{tm1Msd}</i>, targeted mutation 1, Michael Sendtner SMN-
Strain Name Stock Number Common Name(s) General Terms	FVB.Cg-Tg(SMN2)89Ahmb Tg(SMN1*A2G)2023Ahmb <i>Smn1^{tm1Msd}</i>/J 005026 Mild Type III SMA; SMN A2G Use of MICE by companies or for-profit entities requires a license prior to shipping, see www.jax.org/jaxmice/licensing/UOHIO.htm
Phenotype	Mice that are homozygous for the targeted mutant <i>Smn</i> allele and homozygous for the SMN2 transgene and hemizygous for the SMN1*A2G transgenes exhibit symptoms and neuropathology similar to patients afflicted with type III (mild) proximal spinal muscular atrophy (SMA). These same animals with only one copy of the SMN2 transgene are 20%-40% smaller than unaffected mice. At 3 weeks of age they become less active and show signs of muscle weakness. The mice have a shortened lifespan (less than a year) near the end of which they exhibit reduced movement, diminished grooming, shallow breathing and considerable weight loss. Immunohistochemical analysis of spinal cord tissue from 1 month-old animals indicates the presence of cytoplasmic SMN protein and intranuclear aggregates (gems) of the SMN protein. The number of gems is however, fewer than the number found in age matched control tissues. Histological analysis of muscle tissue (gastrocnemius, quadriceps, and intercostals muscles) reveals numerous angulated and atrophic fibers. This trait is more pronounced in the gastrocnemius muscle tissue. Reduced numbers of motor neurons are observed in lumbar spinal cord (29% fewer) and facial

Featured Spinal Muscular Atrophy (SMA) Disease Models

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nucleus (~19% fewer) tissues derived from 3.5-month-old triple mutant mice. Normal numbers of motor neurons are found in 5 day-old mice, indicating that motor neuron loss is a later event in SMA. Electromyograph (EMG) recordings from 4-6 month old triple mutants provide a clear indication of denervation. Associated compensatory axon sprouting is observed. Triple mutants homozygous for the SMN1 A2G transgene display a much milder phenotype, live longer and breed well. Hemizygotes can be bred, but are less efficient.

Note: In contrast to the original publication, and possibly due to inbreeding, it is the experience at The Jackson Laboratory that mice hemizygous for the SMN2 transgene do not survive.

The Jackson Laboratory is currently investigating this strain due to reports that the phenotype and lethality appear to be inconsistent with the original publication.

Creation and development was supported by the National Institutes of Health, the Deutsche Forschungsgemeinschaft to M.S., Families of SMA, the Preston fund, the Madison fund, the Mathew fund and the Muscular Dystrophy Association of America.

Selected Reference(s)	Monani UR, Pastore MT, Gavriline TO, Jablonka S, Le TT, Andreassi C, DiCocco JM, Lorson C, Androphy EJ, Sendtner M, Podell M, Burghes AH. 2003. A transgene carrying an A2G missense mutation in the SMN gene modulates phenotypic severity in mice with severe (type I) spinal muscular atrophy. <i>J Cell Biol</i> 160(1):41-52.
Allele Symbol/Name Common Name(s)	<i>Smn1^{tm1Msd}</i> , targeted mutation 1, Michael Sendtner SMN-
Allele Symbol/Name Common Name(s) Promoter	Tg(SMN2)89Ahmb, transgene insertion 89, Arthur H M Burghes SMN2 SMN2, survival of motor neuron 2, centromeric
Allele Symbol/Name Promoter	Tg(SMN2*A111G)588Ahmb SMN2, survival of motor neuron 2, centromeric
Strain Name Stock Number Phenotype	STOCK <i>Smn1^{tm1Msd}</i> Tg(SMN2)89Ahmb Tg(SMN2*A111G)588Ahmb/J 008782 Mice that are homozygous for the Tg(SMN2*A111G)588Ahmb transgene and homozygous for the <i>Smn1^{tm1Msd}</i> targeted mutation are not viable. Mice that are homozygous for the Tg(SMN2*A111G)588Ahmb transgene, homozygous for the <i>Smn1^{tm1Msd}</i> targeted mutation and hemizygous or homozygous for the Tg(SMN2)89Ahmb transgene are viable and survive for longer than one year. Expression of the Tg(SMN2*A111G)588Ahmb in founder line 588 is detected in the spinal cord, forebrain and liver by RT-PCR. This mutant mouse strain may be useful in studies of spinal muscular atrophy.
Selected Reference(s)	Workman E, Saieva L, Carrel TL, Crawford TO, Liu D, Lutz C, Beattie CE, Pellizzoni L, Burghes AH. 2009. A SMN missense mutation complements SMN2 restoring snRNPs and rescuing SMA mice. <i>Hum Mol Genet</i> 18:2215-29.

Gene/Marker
***Smn1* SMN2**

Name **survival motor neuron 1; survival of motor neuron 2, centromeric**

Allele Symbol/Name
Common Name(s)

Smn1^{tm1Msd}, targeted mutation 1, Michael Sendtner
SMN-

Allele Symbol/Name
Common Name(s)
Promoter

Tg(SMN2)89Ahmb, transgene insertion 89, Arthur H M Burghes
SMN2
SMN2, survival of motor neuron 2, centromeric

Allele Symbol/Name
Promoter

Tg(SMN2*A111G)591Ahmb
SMN2, survival of motor neuron 2, centromeric

Strain Name
Stock Number
Phenotype

STOCK *Smn1^{tm1Msd}* Tg(SMN2)89Ahmb Tg(SMN2*A111G)591Ahmb/J
009134

Mice that are homozygous for the Tg(SMN2*A111G)591Ahmb transgene and homozygous for the *Smn1^{tm1Msd}* targeted mutation are not viable. Mice that are homozygous for the Tg(SMN2*A111G)591Ahmb transgene, homozygous for the *Smn1^{tm1Msd}* targeted mutation and hemizygous or homozygous for the Tg(SMN2)89Ahmb transgene are viable and survive for longer than one year. Strong expression of the Tg(SMN2*A111G)591Ahmb transgene in founder line 591 is detected in the spinal cord, and weaker expression is detected in forebrain and

Featured Spinal Muscular Atrophy (SMA) Disease Models

Importation of these models was supported by the Spinal Muscular Atrophy Foundation.

Selected Reference(s)	<p>liver by RT-PCR. This mutant mouse strain may be useful in studies of spinal muscular atrophy Workman E, Saieva L, Carrel TL, Crawford TO, Liu D, Lutz C, Beattie CE, Pellizzoni L, Burghes AH. 2009. A SMN missense mutation complements SMN2 restoring snRNPs and rescuing SMA mice. <i>Hum Mol Genet</i> 18:2215-29.</p>
Allele Symbol/Name Common Name(s)	<p><i>Smn1</i>^{tm3(SMN2/Smn1)Mrph}, targeted mutation 3, Andrew Murphy Smn1 COIN (conditional inversion)</p>
Allele Symbol/Name Common Name(s) Promoter	<p>Tg(SMN2*delta7)4299Ahmb, transgene insertion 4299, Arthur H M Burghes SMNdelta7; Tg(SMN1*delta7)4299Ahmb SMN2, survival of motor neuron 2, centromeric</p>
Allele Symbol/Name Common Name(s) Promoter	<p>Tg(SMN2)89Ahmb, transgene insertion 89, Arthur H M Burghes SMN2 SMN2, survival of motor neuron 2, centromeric</p>
Strain Name Stock Number General Terms	<p>STOCK <i>Smn1</i>^{tm3(SMN2/Smn1)Mrph} Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb/J 007951 FOR-PROFIT RESEARCHERS MAY ONLY USE THESE MICE IN THE FIELD OF NEURODEGENERATIVE RESEARCH, see www.jax.org/jaxmice/licensing/REGEN_SMA.htm Use of MICE by companies or for-profit entities requires a license prior to shipping, see www.jax.org/jaxmice/licensing/UOHIO.htm and www.jax.org/jaxmice/licensing/SALKFLP.htm</p>
Phenotype	<p>This triple mutant mouse harbors two transgenic alleles and a single targeted mutation. The Tg(SMN2*delta7)4299Ahmb allele consists of a human <i>SMN2</i> (survival of motor neuron 2, centromeric) cDNA lacking exon 7 whereas the Tg(SMN2)89Ahmb allele consists of the entire human <i>SMN2</i> gene. Mice that are homozygous for the targeted mutant <i>Smn1</i>^{tm3(SMN2/Smn1/SMN2)Mrph} allele and homozygous for the two transgenic alleles should function similarly to SMA mutant strain FVB.Cg-Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb <i>Smn1</i>^{tm1Msd/J} (Stock No. 005025). The targeted mutant <i>Smn1</i>^{tm3(SMN2/Smn1/SMN2)Mrph} allele is engineered to revert to a fully functional <i>Smn1</i> allele upon Cre-mediated recombination. This mutant mouse strain may be useful in studies of Spinal Muscular Atrophy.</p>
Allele Symbol/Name Common Name(s) Promoter	<p>Tg(SMN2*delta7)4299Ahmb, transgene insertion 4299, Arthur H M Burghes SMNdelta7; Tg(SMN1*delta7)4299Ahmb SMN2, survival of motor neuron 2, centromeric</p>
Allele Symbol/Name Common Name(s) Promoter	<p>Tg(SMN2)89Ahmb, transgene insertion 89, Arthur H M Burghes SMN2 SMN2, survival of motor neuron 2, centromeric</p>
Strain Name Stock Number Common Name(s) General Terms	<p>FVB.Cg-Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb <i>Smn1</i>^{tm1Msd/J} 005025 Moderate Type II SMA mice; SMNdelta7;SMN2;Smn-/- Use of MICE by companies or for-profit entities requires a license prior to shipping, see www.jax.org/jaxmice/licensing/UOHIO.htm</p>
Phenotype	<p>This triple mutant mouse harbors two transgenic alleles and a single targeted mutant. The Tg(SMN2*delta7)4299Ahmb allele consists of a SMA cDNA lacking exon 7 whereas the Tg(SMN2)89Ahmb allele consists of the entire human <i>SMN2</i> gene. Mice that are homozygous for the targeted mutant <i>Smn</i> allele and homozygous for the two transgenic alleles exhibit symptoms and neuropathology similar to patients afflicted with proximal spinal muscular atrophy (SMA). At birth, triple mutants are noticeably smaller than normal littermates. By day 5, signs of muscle weakness are apparent and become progressively more pronounced over the following week as the mice display an abnormal gait, shakiness in the hind limbs and a tendency to fall over. Mean survival is approximately 13 days. Immunocytochemical analysis indicates that dystrophin expression is normal, however fibers isolated from the gastrocnemius muscle of a 14 day old triple mutant clearly show evidence of atrophy. Creation and development was supported by the National Institutes of Health, the Deutsche Forschungsgemeinschaft to M.S., Families of SMA, the Preston fund, the Madison fund, the Mathew fund and the Muscular Dystrophy Association of America.</p>
Selected Reference(s)	<p>Le TT, Pham LT, Butchbach ME, Zhang HL, Monani UR, Covert DD, Gavrilina TO, Xing L, Bassell GJ, Burghes AH. 2005. SMNDelta7, the major product of the centromeric survival motor neuron (SMN2) gene, extends survival in mice with spinal muscular atrophy and associates with full-length SMN. <i>Hum Mol Genet</i> 14(6):845-57.</p>

Featured Spinal Muscular Atrophy (SMA) Disease Models

Importation of these models was supported by the Spinal Muscular Atrophy Foundation.

Allele Symbol/Name Common Name(s)	<i>Smn1^{tm1Msd}</i>, targeted mutation 1, Michael Sendtner SMN-
Allele Symbol/Name Promoter	Tg(SMN2)566Ahmb, transgene insertion 566, Arthur H M Burghes SMN2, survival of motor neuron 2, centromeric
Strain Name Stock Number General Terms	FVB.Cg-<i>Smn1^{tm1Msd}</i> Tg(SMN2)566Ahmb/J 008206 Use of MICE by companies or for-profit entities requires a license prior to shipping, see www.jax.org/jaxmice/licensing/UOHIO.htm
Phenotype	As described for SMA mice (see Stock No. 005024), mice homozygous for <i>Smn1^{tm1Msd}</i> targeted mutation (<i>Smn</i> null allele) and single copy human SMN2 low copy line 89 exhibit symptoms, neuropathology, and early lethality similar to human type I proximal spinal muscular atrophy (SMA) patients. In contrast to that SMA model, this strain carries the high copy SMN2 (founder line 566) transgene instead of the single copy SMN2 (line 89) transgene. As a result of the high SMN2 copy number, mice homozygous for the <i>Smn1^{tm1Msd}</i> targeted mutation and high copy SMN2 line 566 (16 copies when homozygous) are rescued from all overt features of the severe SMA phenotype. Homozygous <i>Smn</i> ; SMN2 high copy line 566 mice have a shorter and thicker tail. These <i>Smn</i> ; SMN2 high copy line 566 mutant mice may be useful in neuromuscular studies including spinal muscular atrophy (SMA).
Selected Reference(s)	Piao JH, Matsuda Y, Nakamura H, Sano K. 1999. Assignment of <i>Pdnp2</i> , the gene encoding phosphodiesterase I/nucleotide pyrophosphatase 2, to mouse chromosome 15D2. <i>Cytogenet Cell Genet</i> 87(3-4):172-4. Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. 1995. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. <i>Cell</i> 80(5):795-803.
Allele Symbol/Name Common Name(s)	<i>Smn1^{tm1Msd}</i>, targeted mutation 1, Michael Sendtner SMN-
Allele Symbol/Name Common Name(s)	Tg(Hlxb9-GFP)1Tmj, transgene insertion 1, Thomas M Jessell Hb9-Gfp; Hlxb9:GFP; Hb9:GFP-1B; Gfp-HB9; Hb9::EGFP
Allele Symbol/Name Common Name(s) Promoter	Tg(SMN2)89Ahmb, transgene insertion 89, Arthur H M Burghes SMN2 SMN2, survival of motor neuron 2, centromeric
Strain Name Stock Number General Terms	STOCK <i>Smn1^{tm1Msd}</i> Tg(Hlxb9-GFP)1Tmj Tg(SMN2)89Ahmb/J 006570 Use of MICE by companies or for-profit entities requires a license prior to shipping, see www.jax.org/jaxmice/licensing/COLUMBIAAA.htm and www.jax.org/jaxmice/licensing/UOHIO.htm
Phenotype	Similar to Stock No. 005024, mice that are homozygous for the targeted mutant <i>Smn1</i> allele and carry the SMN2 transgene exhibit symptoms and neuropathology similar to patients afflicted with type I proximal spinal muscular atrophy (SMA). As an addition to Stock No. 005024, this line carries a transgene containing a Green Fluorescent Protein (<i>GFP</i>) under the direction of the mouse <i>Hlxb9</i> promoter. Transgenic mice display distinct expression of <i>GFP</i> in dendrites, axons and soma of spinal motor neurons, allowing identification, isolation and purification of spinal motor neurons by FACS. <i>GFP</i> expression mimics endogenous HLXB9 expression pattern. Fluorescence is detected in axons, dendrites and processes of spinal motor neurons at embryonic day 9.5 to postnatal day 10 aged mice. This mutant mouse strain represents a model that may be useful for purification and <i>in vivo</i> tracking of spinal motor neurons. Mice homozygous for the <i>Hlxb9-GFP</i> transgenic insert are reportedly viable, fertile, do not display any gross behavioral abnormalities, but are smaller in size than wild-type littermates. Homozygous pups born to homozygous females have a high mortality rate. In the initial characterization by the donating investigator, mice that are homozygous for the targeted mutant <i>Smn1</i> allele and carry the SMN2 transgene exhibit symptoms and mice were either stillborn or survived 4-6 days. Mice that died at or shortly after birth were slightly smaller (1.33 g. vs. 1.51 g.) than normal littermates. Mice that survive for several days are indistinguishable from normal littermates in the first 48 hours, after which they exhibit decreased suckling and movement, labored breathing and tremoring limbs. Mice succumbing at this later time point are noticeably smaller than normal littermates (1.47 g vs. 4.59). A bell-shaped trunk is also noticeable in affected mice, presumably from intercostal muscle weakness, a characteristic of type I SMA. Histological analysis indicates that affected mice that survive to day 5 exhibit a loss of motor neurons from spinal cord (35%) and facial nucleus (40%). A large number of cells with pyknotic nuclei are observed in these tissues.

Featured Spinal Muscular Atrophy (SMA) Disease Models

Importation of these models was supported by the Spinal Muscular Atrophy Foundation.

Immunohistochemical analysis indicates low-level expression of the SMN2 protein in the tissues examined (brain, liver, spinal cord) and an absence or near absence of intranuclear aggregates of the SMN protein ('gems'). Homozygous mice bearing the *Smn1* targeted mutation without a copy of the SMN2 transgene display an embryonic lethal phenotype with developmental arrest occurring prior to implantation.

Note: In contrast to the original publication, and possibly due to inbreeding, it is the experience at The Jackson Laboratory that mice hemizygous for the SMN2 transgene do not survive.

Distribution of this model is supported by the Spinal Muscular Atrophy Foundation.

Allele Symbol/Name Common Name(s) Promoter	Tg(SMN2)2Hung, transgene insertion 2, Hung Li SMN2 ⁺ SMN2, survival of motor neuron 2, centromeric
Allele Symbol/Name Common Name(s)	<i>Smn1</i>^{tm1Hung}, targeted mutation 1, Hung Li Smn-
Strain Name Stock Number Common Name(s) General Terms	FVB.Cg-Tg(SMN2)2Hung <i>Smn1</i>^{tm1Hung}/J 005058 SMA-like mice line 2 Use of MICE by non-profits requires an Material Transger Agreement (MTA) and for-profit entities require a license, see www.jax.org/jaxmice/licensing/A_SINICA.htm
Phenotype	Mice that are homozygous for the <i>Smn1</i> targeted mutation and hemizygous for the SMN2 transgene are viable, fertile and exhibit short and thickened tails. RT-PCR analysis detects alternative splicing of the transgene. Histological examination of tail tissue reveals atrophic muscles and subcutaneous edema. Skeletal muscle tissue has fewer myocytes and atrophic muscle bundles. Large motor neurons in the anterior horns of the spinal cord degenerate and are lost. There is a strong correlation between estimated copy number of the transgene and severity of the phenotype. These mice exhibit a molecular and progressive neurodegenerative phenotype similar to Type III spinal muscular atrophy. Mice that are homozygous for the targeted mutation and do not carry the transgene have an embryonic lethal phenotype, failing to survive past embryonic day 6.5.
Selected Reference(s)	Hsieh-Li HM, Chang JG, Jong YJ, Wu MH, Wang NM, Tsai CH, Li H. 2000. A mouse model for spinal muscular atrophy. <i>Nat Genet</i> 24(1):66-70.
Allele Symbol/Name Common Name(s) Promoter	Tg(SMN2)89Ahmb, transgene insertion 89, Arthur H M Burghes SMN2 SMN2, survival of motor neuron 2, centromeric
Allele Symbol/Name Common Name(s)	<i>Smn1</i>^{tm1Msd}, targeted mutation 1, Michael Sendtner SMN-
Strain Name Stock Number General Terms	FVB.Cg-Tg(SMN2)89Ahmb <i>Smn1</i>^{tm1Msd}/J 005024 Use of MICE by companies or for-profit entities requires a license prior to shipping, see www.jax.org/jaxmice/licensing/UOHIO.htm
Phenotype	Mice that are homozygous for the targeted mutant <i>Smn1</i> allele and carry the SMN2 transgene exhibit symptoms and neuropathology similar to patients afflicted with type I proximal spinal muscular atrophy (SMA). In the initial characterization by the donating investigator, mice were either stillborn or survived 4-6 days. Mice that died at or shortly after birth were slightly smaller (1.33 g. vs. 1.51 g.) than normal littermates. Mice that survive for several days are indistinguishable from normal littermates in the first 48 hours, after which they exhibit decreased suckling and movement, labored breathing and trembling limbs. Mice succumbing at this later time point are noticeably smaller than normal littermates (1.47 g vs. 4.59). A bell-shaped trunk is also noticeable in affected mice, presumably from intercostal muscle weakness, a characteristic of type I SMA. Histological analysis indicates that affected mice that survive to day 5 exhibit a loss of motor neurons from spinal cord (35%) and facial nucleus (40%). A large number of cells with pyknotic nuclei are observed in these tissues. Immunohistochemical analysis indicates low-level expression of the SMN2 protein in the tissues examined (brain, liver, spinal cord) and an absence or near absence of intranuclear aggregates of the SMN protein ('gems'). The donating investigator reports that muscle fibers (quadriceps and gastrocnemius assayed) are atrophied, a characteristic observed in SMA patients. Homozygous mice bearing the <i>Smn1</i> targeted mutation without a copy of the SMN2 transgene display an embryonic lethal phenotype with developmental arrest occurring prior to implantation.
	<i>Note: In contrast to the original publication, and possibly due to inbreeding, it is the experience at The Jackson Laboratory that mice hemizygous for the SMN2 transgene do not survive.</i>

Featured Spinal Muscular Atrophy (SMA) Disease Models

Importation of these models was supported by the Spinal Muscular Atrophy Foundation.

Creation and development was supported by the National Institutes of Health, the Deutsche Forschungsgemeinschaft to M.S., Families of SMA, the Preston fund, the Madison fund, the Mathew fund and the Muscular Dystrophy Association of America.

Selected Reference(s)	Monani UR, Sendtner M, Coover DD, Parsons DW, Andreassi C, Le TT, Jablonka S, Schrank B, Rossol W, Prior TW, Morris GE, Burghes AH. 2000. The human centromeric survival motor neuron gene (SMN2) rescues embryonic lethality in <i>Smn</i> (^{-/-}) mice and results in a mouse with spinal muscular atrophy. <i>Hum Mol Genet</i> 9(3):333-9.
Allele Symbol/Name Common Name(s)	Tg(SMN2)11Tro, transgene insertion 11, Thierry Bordet SMN2(N11)
Allele Symbol/Name Common Name(s)	<i>Smn1</i>^{tm1Msd}, targeted mutation 1, Michael Sendtner SMN-
Strain Name	B6.Cg-Tg(SMN2)11Tro <i>Smn1</i>^{tm1Msd}/J
Stock Number	008629
Common Name(s)	SMN2(N11);Smn+/-
General Terms	Strain(s) not available to companies or for-profit entities, see www.jax.org/jaxmice/licensing/TROPHOS.htm
Phenotype	Mice that are homozygous for both the <i>Smn1</i> ^{tm1Msd} allele and the Tg(SMN2)11Tro transgene (SMN2, survival of motor neuron 2, centromeric, human) exhibit a very severe phenotype with survival ranging from hours up to 7 days after birth. This mutant mouse strain may be useful in neuromuscular studies involving Spinal Muscular Atrophy (SMA).
Selected Reference(s)	Bordet T. 2009. Generation of an SMN2 transgene (line 46) MGI Direct Data Submission
Allele Symbol/Name Common Name(s)	Tg(SMN2)46Tro, transgene insertion 46, Thierry Bordet SMN2(N46)
Allele Symbol/Name Common Name(s)	<i>Smn1</i>^{tm1Msd}, targeted mutation 1, Michael Sendtner SMN-
Strain Name	B6.Cg-Tg(SMN2)46Tro <i>Smn1</i>^{tm1Msd}/J
Stock Number	008630
Common Name(s)	SMN2(N46);Smn+/-
Phenotype	Mice that are homozygous for the <i>Smn1</i> ^{tm1Msd} allele and the Tg(SMN2)46Tro (SMN2, survival of motor neuron 2, centromeric, human) transgene do not display a SMA-like phenotype. Necrotic lesions are observed on the tail, ears and teeth. This mutant mouse strain may be useful in neuromuscular studies involving Spinal Muscular Atrophy (SMA).
Selected Reference(s)	Bordet T. 2009. Generation of an SMN2 transgene (line 11) MGI Direct Data Submission
Allele Symbol/Name Common Name(s)	Tg(SMN2)46Tro, transgene insertion 46, Thierry Bordet SMN2(N46)
Allele Symbol/Name Common Name(s)	Tg(SMN2)11Tro, transgene insertion 11, Thierry Bordet SMN2(N11)
Allele Symbol/Name Common Name(s)	<i>Smn1</i>^{tm1Msd}, targeted mutation 1, Michael Sendtner SMN-
Strain Name	B6.Cg-Tg(SMN2)11Tro Tg(SMN2)46Tro <i>Smn1</i>^{tm1Msd}/J
Stock Number	008631
Common Name(s)	SMN2(N11, N46);Smn+/-
General Terms	Strain(s) not available to companies or for-profit entities, see www.jax.org/jaxmice/licensing/TROPHOS.htm
Phenotype	Triple mutant mice that are homozygous for the <i>Smn1</i> ^{tm1Msd} allele and hemizygous for the two transgenes, Tg(SMN2)11Tro and Tg(SMN2)46Tro, exhibit diminished weight gain, progressive muscle weakness, necrotic lesions and loss of neurons in the sciatic nerve. This mutant mouse strain may be useful in neuromuscular studies related to Spinal Muscular Atrophy (SMA).
Selected Reference(s)	Bordet T. 2009. Generation of an SMN2 transgene (line 11) MGI Direct Data Submission

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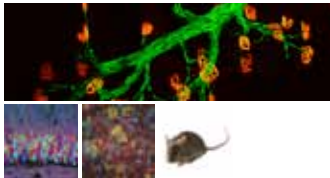
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1. Top: Motor neurons in the lateral gastrocnemus of B6.Cg-Tg(Thy1-YFP)16Jrs/J (Stock Number 003709) are seen as green, acetylcholine receptors on the muscle are labeled with bungarotoxin in red. Courtesy of Dr. Rob Burgess, The Jackson Laboratory.
2. Bottom left: B6;CBA-Tg(Thy1-Brainbow1.0)MLicH/J (Stock Number 007910) Neurons are labelled in the dentate gyrus. Courtesy of Dr. Jean Livet, Harvard University. Livet *et al.*, *Nature* 450: 56 (2007).
3. Bottom right: B6.Cg-Tg(Thy1-Brainbow1.1)MLicH/J (Stock Number 007911) Astrocytes are labelled in the cortex. Courtesy of Dr. Jean Livet, Harvard University. Livet *et al.*, *Nature* 450: 56 (2007).