

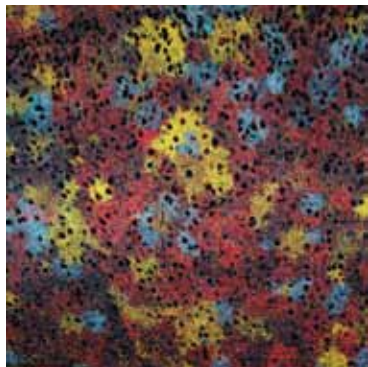
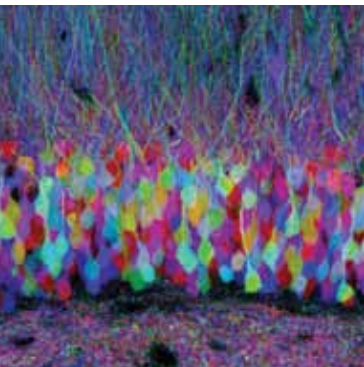
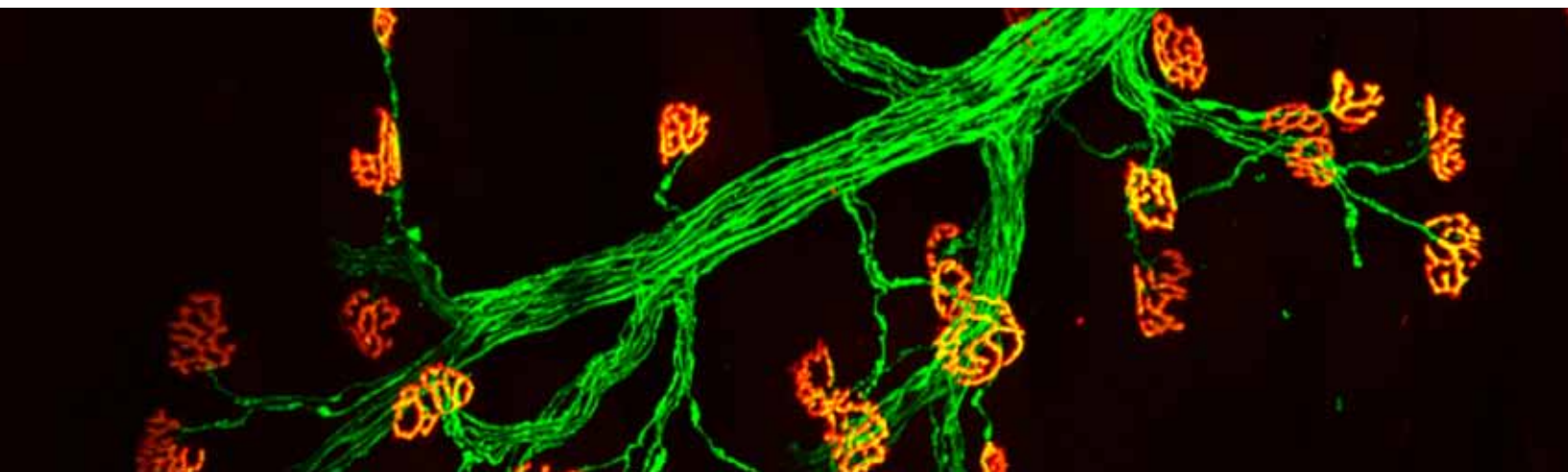


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Mouse Models for Huntington's Disease Research

October 2009



Leading the Search for Tomorrow's Cures

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Huntington's Disease Mouse Model Resource

One of the more common genetic disorders, Huntington's disease is a devastating, degenerative brain disorder for which there is neither treatment nor cure. It slowly diminishes an individual's ability to walk, think, talk, and reason. More than a quarter of a million Americans either have Huntington's or are at risk of inheriting it. Huntington's typically begins in mid-life, between the ages of 30 and 45, though onset may occur as early as the age of two (Huntington's Disease Society of America, www.hdsa.org).

Huntington's Disease Models

For a current list of all strains, go to www.jax.org/jaxmice/list/ra1625.html

Gene/Allele/Name		
Page	Stock No.	Strain Name
<i>Dld</i>, dihydrolipoamide dehydrogenase		
	008333	B6;129P2- <i>Dld</i> ^{tm1Ptl} /J
<i>Gt(ROSA)26Sor</i>, gene trap ROSA 26, Philippe Soriano		
4	007708	B6.129- <i>Gt(ROSA)26Sor</i> ^{tm1(HD*103Q)Xwy} /J
<i>Hap1</i>, huntingtin-associated protein 1		
4	007749	STOCK <i>Hap1</i> ^{tm1Xjl} /J
<i>Htt</i> (formerly HD), huntingtin		
5	004595	B6.129P2- <i>Htt</i> ^{tm2Detl} /J
5	003597	B6.129- <i>Htt</i> ^{tm4Mem} /J
5	003598	B6.129- <i>Htt</i> ^{tm5Mem} /J
	003454	B6.129- <i>Htt</i> ^{tm3Mem} /J
	004595	B6.129P2- <i>Htt</i> ^{tm2Detl} /J
	002688	B6.129S4- <i>Htt</i> ^{tm1Mem} /J
	003453	STOCK <i>Htt</i> ^{tm2Mem} /J
	003455	STOCK <i>Htt</i> ^{tm4Mem} /J
	003456	STOCK <i>Htt</i> ^{tm5Mem} /J

Gene/Allele/Name		
Page	Stock No.	Strain Name
<i>HTT</i> (formerly HD), huntingtin, human		
6	004360	B6;SJL-Tg(HD)63Aron/J
6	003627	B6C3-Tg(HD82Gln)81Dbo/J
7	002809	B6CBA-Tg(HDexon1)61Gpb/1J
7	007578	CBy.Cg-Tg(HDexon1)61Gpb/J
8	002810	B6CBA-Tg(HDexon1)62Gpb/1J
8	008197	FVB/N-Tg(HTT*97Q)IXwy/J
8	003640	FVB/NJ-Tg(YAC72)2511Hay/J
8	004938	FVB-Tg(YAC128)53Hay/J
9	007247	FVB/N-Tg(YAC353G6)W7Hay/J
	006494	B6CBA-Tg(HDexon1)62Gpb/3J
	006471	B6.Cg-Tg(HDexon1)61Gpb/J
<i>UBB</i>, ubiquitin B, human		
9	008833	C57BL/6-Tg(Camk2a-UBB)3413-1Fwvl/J

Phenotypes Displayed by Genetic Models

Strain Name (Stock Number)	Developed by	Molecular Mutation	Phenotype
B6.129S4- <i>Htt^{tm1Mem}</i> /J (002688)	M. MacDonald	KO of exons 4-5	homozygotes die ~ E8
STOCK <i>Htt^{tm2Mem}</i> /J (003453)	M. MacDonald	20 CAG repeats	normal
B6.129- <i>Htt^{tm3Mem}</i> /J (003454)	M. MacDonald	50 CAG repeats	normal
B6.129- <i>Htt^{tm4Mem}</i> /J (003597)	M. MacDonald	92 CAG repeats	nuclear inclusions detected by 12 months
B6.129- <i>Htt^{tm5Mem}</i> /J (003598)	M. MacDonald	111 CAG repeats	nuclear inclusions detected by 10 months
B6.129P2- <i>Htt^{tm2Detl}</i> /J (004595)	G. Bates	150 CAG repeats	nuclear inclusions detected at about 10 months
B6C3-Tg(HD82Gln)81Dbo/J (003627)	D. Borchelt	82 CAG repeats	Intranuclear inclusions and neuritic aggregates in various regions; animals die at five to six months
FVB/N-Tg(HTT*97Q)IXwy/J (008197)	W. Yang	97 CAA-CAG repeats	progressive motor impairment by two months of age, brain atrophy by 12 months
B6.129- <i>Gt(ROSA)26Sor^{tm1(HD*103Q)Xwy}</i> /J (007708)	W. Yang	98 CAG repeats	polyQ HD protein is floxed, so expression of neuropathogenic protein is cre-dependent
B6;SJL-Tg(HD)63Aron/J (004360)	N. Aronin	100 CAG repeats	cortical and striatal neuropathology by five months
CBy.Cg-Tg(HDexon1)61Gpb/J (007578)	G. Bates	100 CAG repeats	onset of progressive HD phenotype by 15-21 weeks of age
B6CBA-Tg(HDexon1)61Gpb/1J (002809)	G. Bates	115 CAG repeats	progressive neurological phenotype with later onset than line 62 (below)
B6CBA-Tg(HDexon1)62Gpb/1J (002810)	G. Bates	144 CAG repeats	R6/2 line exhibits an early-onset (nine to 11 weeks) progressive neurological phenotype including choreiform-like movements, involuntary stereotypic movements, tremor, and epileptic seizures and neuronal intranuclear inclusions which contain both the huntingtin and ubiquitin proteins
FVB/NJ-Tg(YAC72)2511Hay/J (003640)	M. Hayden	72 CAG repeats	By 12 months of age selective degeneration of medium spiny neurons in the lateral striatum is observed
FVB-Tg(YAC128)53Hay/J (004938)	M. Hayden	128 CAG repeats	progressive motor impairment appears at six months of age, followed by progressive neurodegeneration, starting at nine months of age, and hypokinesia at 12 months
FVB/N-Tg(YAC353G6)W7Hay/J (007247)	M. Hayden	133 CAG repeats	contains a mutation conferring resistance to caspase-6 cleavage; serves as control for strain 004938

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Gene/Marker Gt(ROSA)26Sor	Name gene trap ROSA 26, Philippe Soriano Common Name(s) Gtrgeo26; Gtrosa26; R26; ROSA26; beta geo
Allele Symbol/Name Common Name(s)	Gt(ROSA)26Sor^{tm1(HD*103Q)Xwy}, targeted mutation 1, X William Yang mhtt-exon1 (103Q); RosaHD
Strain Name	B6.129-Gt(ROSA)26Sor^{tm1(HD*103Q)Xwy/J}
Stock Number	007708
Additional Research Areas	Neurobiology Research; Mouse/Human Gene Homologs; Research Tools: Cre-lox System
General Terms	Use of MICE by companies or for-profit entities requires a license prior to shipping. (www.jax.org/jaxmice/licensing/UCLA_2.htm)
Phenotype	Mice heterozygous for the RosaHD mutant allele are viable and fertile. These mice have the neuropathogenic polyQ-mutant variant of the human Huntingtin protein (mhtt-exon1; 103Q) inserted into the <i>Gt(ROSA)26Sor</i> locus. Expression of mhtt-exon1 is blocked by an upstream <i>loxP</i> -flanked transcriptional STOP sequence. When bred to mice with a Cre recombinase gene under the control of a promoter of interest, the STOP sequence is deleted in the tissue of interest, and mhtt-exon1 expression is observed. As these RosaHD mutant mice allow <i>cre</i> -conditional expression of the neuropathogenic mhtt-exon1 protein, they may be useful in studying Huntington's disease (HD) or other polyQ disorders. Of note, sequencing of the polyQ region (using mice from the 11th backcross) indicate the actual number of repeats to be 98. For example, when bred to strains expressing cre in brain tissues (such as Nestin-Cre (see Stock No. 003771) or Emx1-Cre (see Stock No. 005628), bi-transgenic offspring show pathological cell-cell interactions critically contribute to cortical pathogenesis of HD.
Selected Reference(s)	Gu X, Li C, Wei W, Lo V, Gong S, Li SH, Iwasato T, Itoharu S, Li XJ, Mody I, Heintz N, Yang XW. 2005. Pathological cell-cell interactions elicited by a neuropathogenic form of mutant Huntingtin contribute to cortical pathogenesis in HD mice. <i>Neuron</i> 46:433-44.
Gene/Marker Hap1	Name huntingtin-associated protein 1 Common Name(s) HAP-1; HAP2; HIP5; HLP; hHLP1
Allele Symbol/Name Common Name(s)	Hap1^{tm1Xjl}, targeted mutation 1, Xiao-Jiang Li HAP1-
Strain Name	STOCK Hap1^{tm1Xjl/J}
Stock Number	007749
General Terms	Strain(s) not available to companies or for-profit entities. (www.jax.org/jaxmice/licensing/EMORYNOFP.htm)
Additional Research Areas	Cell Biology Research; Developmental Biology Research; Neurobiology Research; Mouse/Human Gene Homologs; Research Tools: Cell Biology Research, Neurobiology Research
Phenotype	Mice homozygous for this Huntingtin Associated Protein (HAP1)-deficient allele have neurodegeneration in areas of the hypothalamus that control feeding behavior, resulting in decreased feeding behavior, dehydration, hypoactivity, and death between two and 15 days after birth. No protein expression from the targeted gene is observed in brain tissue from homozygous mice. Hypothalamus tissue from HAP1-deficient homozygotes exhibit reduced levels of gamma-aminobutyric acid-A (GABA _A ; a neurotransmitter associated with feeding) and tropomyosin-related kinase A receptor tyrosine kinase (TrkA; a nerve growth factor receptor associated with neurite outgrowth). Heterozygous mice are viable and fertile with no abnormalities in HAP1 expression levels, life span, behavior, and body weight. These huntingtin-associated protein-1 (HAP1) mutant mice may be useful in studying the hypothalamic neurodegeneration and loss of body weight in Huntington's disease (HD), neurotransmitters, microtubule-dependent transporters, intracellular trafficking, receptor tyrosine kinase and neurite function, and feeding. <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. These mice were originally published on a mixed Black Swiss and 129S6/SvEvTac genetic background. It should be noted that the phenotype could vary from that originally described. We will modify the strain description if necessary as published results become available.</i>
Selected Reference(s)	Li SH, Yu ZX, Li CL, Nguyen HP, Zhou YX, Deng C, Li XJ. 2003. Lack of huntingtin-associated protein-1 causes neuronal death resembling hypothalamic degeneration in Huntington's disease. <i>J Neurosci</i> 23:6956-64. Rong J, McGuire JR, Fang ZH, Sheng G, Shin JY, Li SH, Li XJ. 2006. Regulation of intracellular trafficking of huntingtin-associated protein-1 is critical for TrkA protein levels and neurite outgrowth. <i>J Neurosci</i> 26:6019-30. Sheng G, Chang GQ, Lin JY, Yu ZX, Fang ZH, Rong J, Lipton SA, Li SH, Tong G, Leibowitz SF, Li XJ. 2006. Hypothalamic huntingtin-associated protein 1 as a mediator of feeding behavior. <i>Nat Med</i> 12:526-33.

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Gene/Marker Htt	Name huntingtin Common Name(s) C430023I11Rik; HD; Hdh; IT15
Allele Symbol/Name Common Name(s)	Htt^{tm2Detl}, targeted mutation 2, Peter J Detloff CHL2; Hdh(CAG)150; HdhQ150; HdhCAG150
Strain Name Stock Number Former & Common Name(s) General Terms	B6.129P2-Htt^{tm2Detl}/J 004595 B6.129P2-Hd ^{tm2Detl} /J; B6.129P2-Hdh ^{tm2Detl} /J; STOCK Hdh ^{tm2Detl} /J Use of MICE by companies or for-profit entities requires a license prior to shipping. (www.jax.org/jaxmice/licensing/UAB.htm).
Additional Research Areas Phenotype	Mouse/Human Gene Homologs; Neurobiology Research Mice homozygous for the targeted allele are viable and fertile. At 15-40 weeks of age mice carrying this allele on a segregating C57BL/6 and 129P2 background exhibit an abnormal gait, clasping behavior and diminished exploratory activity. Infrequent tonic-clonic like seizures may also be observed. Mice with a higher percentage of C57BL/6 in their genetic background develop behavioral and neurological phenotypes at a much later age (70-100 weeks). (Heng MY <i>et al.</i> 2007) Mutant mice may be noticeably smaller than wild-type littermates. Increased glial fibrillary acidic protein immunoreactivity is present in the striatum and ubiquitin- and huntingtin-positive neuronal intranuclear inclusions (NIIs) are detected throughout the dorsal striatum, nucleus accumbens and to a lesser extent other regions of the brain. Onset of symptoms occurs earlier for homozygotes than for heterozygotes. This mutant mouse strain represents a model that may be useful in studies related to Huntington's disease.
Selected Reference(s)	Lin CH, Tallaksen-Greene S, Chien WM, Cearley JA, Jackson WS, Crouse AB, Ren S, Li XJ, Albin RL, Detloff PJ. 2001. Neurological abnormalities in a knock-in mouse model of Huntington's disease. <i>Hum Mol Genet</i> 10:137-44. Heng MY, Tallaksen-Greene SJ, Detloff PJ, Albin RL. 2007. Longitudinal evaluation of the Hdh(CAG)150 knock-in murine model of Huntington's disease. <i>J Neurosci</i> 27:8989-98.
Allele Symbol/Name Common Name(s)	Htt^{tm4Mem}, targeted mutation 4, Marcy E MacDonald Hdh ^{Q92}
Strain Name Stock Number Former & Common Name(s) Additional Research Areas Phenotype	B6.129-Htt^{tm4Mem}/J 003597 B6.129-Hd ^{tm4Mem} /J; B6.129-Hdh ^{tm4Mem} /J Mouse/Human Gene Homologs; Neurobiology Research This strain carries 92 CAG repeat units in the first exon of the endogenous <i>Htt</i> gene. Huntington's-like pathology is seen in the striatum, including nuclear localization of the protein, N-terminal inclusions, and insoluble aggregate formation. Instability of the length of the CAG repeat between generations is seen. Expression of this phenotype is delayed relative to <i>Htt^{tm5}</i> (Stock No. 003456). <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. This is the case for the strain above. It should be noted that the phenotype could vary from that originally described. We will modify the strain description if necessary as published results become available.</i>
Selected Reference(s)	White JK, Auerbach W, Duyao MP, Vonsattel JP, Gusella JF, Joyner AL, MacDonald ME. 1997. Huntingtin is required for neurogenesis and is not impaired by the Huntington's disease CAG expansion. <i>Nat Genet</i> 17:404-10.
Allele Symbol/Name Common Name(s)	Htt^{tm5Mem}, targeted mutation 5, Marcy E MacDonald Hdh ^{Q111}
Strain Name Stock Number Former & Common Name(s) Additional Research Areas Phenotype	B6.129-Htt^{tm5Mem}/J 003598 B6.129-Hd ^{tm5Mem} /J; B6.129-Hdh ^{tm5Mem} /J Mouse/Human Gene Homologs; Neurobiology Research This strain carries 111 CAG repeat units in the first exon of the endogenous <i>Htt</i> gene. Huntington's-like pathology is seen in the striatum, including nuclear localization of the protein, N-terminal inclusions, and insoluble aggregate formation. Instability of the length of the CAG repeat between generations is seen. Expression of the phenotype occurs earlier than in <i>Htt^{tm4}</i> (Stock No. 003455). <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. This is the case for the strain above. It should be noted that the phenotype could vary from that originally described. We will modify the strain description if necessary as published results become available.</i>

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Selected Reference(s)	Wheeler VC, Auerbach W, White JK, Srinidhi J, Auerbach A, Ryan A, Duyao MP, Vrbanac V, Weaver M, Gusella JF, Joyner AL, MacDonald ME. 1999. Length-dependent gametic CAG repeat instability in the Huntington's disease knock-in mouse. <i>Hum Mol Genet</i> 8:115-22.
Gene/Marker HTT	Name huntingtin Common Name(s) Tg(HDexon1)62nGpb; R6/2
Allele Symbol/Name Common Name(s) Promoter	Tg(HD)63Aron, transgene insertion 63, Neil Aronin HD100L63; TgCAG100 <i>HTT</i> , huntingtin
Strain Name Stock Number Former & Common Name(s) General Terms	B6;SJL-Tg(HD)63Aron/J 004360 B6;J-Tg(HD)63Aron/J; B6;SJL-Tg(HD)63Aron Use of MICE by companies or for-profit entities requires a license prior to shipping. (www.jax.org/jaxmice/licensing/UMASS.htm)
Additional Research Areas Phenotype	Developmental Biology Research; Mouse/Human Gene Homologs; Neurobiology Research These transgenic mice express the initial N-terminal third of the mutant human huntingtin gene (IT15) under the direction of the rat neuron-specific enolase promoter. Expected transgene expression was confirmed by Northern blot, RT-PCR and Western blot analysis. Mice heterozygous for the transgene have a phenotype mimicking much of the morphological and subcellular neuropathology that occurs in the striatum and cortex in human Huntington's disease. Behavioral abnormalities are variable in onset and intensity, beginning between three to six months of age. Transgenic mice exhibit increased levels of nuclear and cytoplasmic huntingtin and dysmorphic dendrites in the striatum and cortex. Electron microscopic analysis of nuclear inclusions of cortical and striatal neurons detects granular and filamentous structures that appear to be similar to structures seen in brain affected by Huntington's disease. Cortical stimulation and N-methyl-D-aspartate (NMDA) receptor activation produces abnormal electrophysiological responses from striatal neurons.
Selected Reference(s)	Laforet GA, Sapp E, Chase K, McIntyre C, Boyce FM, Campbell M, Cadigan BA, Warzecki L, Tagle DA, Reddy PH, Cepeda C, Calvert CR, Jokel ES, Klapstein GJ, Ariano MA, Levine MS, DiFiglia M, Aronin N. 2001. Changes in cortical and striatal neurons predict behavioral and electrophysiological abnormalities in a transgenic murine model of Huntington's disease. <i>J Neurosci</i> 21:9112-23.
Allele Symbol/Name Common Name(s) Promoter	Tg(HD82Gln)81Dbo, transgene insertion 81, David R Borchelt N171-82Q; TGN(HD82Gln)81Dbo <i>HTT</i> , huntingtin
Strain Name Stock Number Former & Common Name(s) General Terms	B6C3-Tg(HD82Gln)81Dbo/J 003627 B6C3F1/J-Tg(HD82Gln)81Dbo/J Use of MICE by companies or for-profit entities requires a license prior to shipping. (www.jax.org/jaxmice/licensing/JHU2FPLIC.htm)
Additional Research Areas Phenotype	Developmental Biology Research; Mouse/Human Gene Homologs; Neurobiology Research Mice expressing this transgene appear normal at birth through one to two months. Mice fail to gain weight, develop tremors, hypokinesia and lack coordination. They exhibit an abnormal gait and frequent hind limb clasping. Life expectancy is five to six months. Studies using huntingtin antibodies indicated numerous immunoreactive nuclear inclusions in multiple neuron populations. Neuritic damage is evident.
Selected Reference(s)	Schilling G, Becher MW, Sharp AH, Jinnah HA, Duan K, Kotzok JA, Slunt HH, Ratovitski T, Cooper JK, Jenkins NA, Copeland NG, Price DL, Ross CA, Borchelt DR. 1999. Intracellular inclusions and neuritic aggregates in transgenic mice expressing a mutant N-terminal fragment of huntingtin [published erratum appears in <i>Hum Mol Genet</i> 1999 May;8(5):943]. <i>Hum Mol Genet</i> 8:397-407.
Allele Symbol/Name Common Name(s) Promoter	Tg(HDexon1)61Gpb, transgene insertion 61, Gillian Bates R6/1; htt tm ; HD R6/1 <i>HTT</i> , huntingtin
Strain Name Stock Number Former & Common Name(s) General Terms	B6CBA-Tg(HDexon1)61Gpb/1J 002809 B6CBA-Tg(HDexon1)61Gpb/J Use of MICE by companies or for-profit entities requires a license prior to shipping. (www.jax.org/jaxmice/licensing/UMDSKCL.htm)
Additional Research Areas Phenotype	Developmental Biology Research; Mouse/Human Gene Homologs; Neurobiology Research Mice have been generated that are transgenic for the 5' end of the human HD gene carrying (CAG)115-

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(CAG)150 repeat expansions. In both the 61Gpb and 62Gpb founder lines, the transgene is ubiquitously expressed. Transgenic mice exhibit a progressive neurological phenotype that mimics many of the features of HD, including choreiform-like movements, involuntary stereotypic movements, tremor, and epileptic seizures, as well as nonmovement disorder components, including unusual vocalization. They urinate frequently and exhibit loss of body weight and muscle bulk through the course of the disease. Neurologically they develop Neuronal Intranuclear Inclusions (NII) which contain both the huntingtin and ubiquitin proteins. These NII have also been identified in human HD patients. The age of onset of HD symptoms is reported to occur between 15 and 21 weeks for the 61Gpb line and between nine and 11 weeks for the 62Gpb line.

<i>Selected Reference(s)</i>	Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, Lawton M, Trotter Y, Levrach H, Davies SW, Bates GP. 1996. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. <i>Cell</i> 87:493-506.
<i>Strain Name</i>	CBy.Cg-Tg(HDexon1)61Gpb/J
<i>Stock Number</i>	007578
<i>General Terms</i>	Use of MICE by companies or for-profit entities requires a license prior to shipping. (www.jax.org/jaxmice/licensing/UMDSKCL.htm)
<i>Additional Research Areas</i>	Developmental Biology Research; Mouse/Human Gene Homologs; Neurobiology Research; Research Tools: Neurobiology Research
<i>Phenotype</i>	Mice have been generated that are transgenic for the 5' end of the human HD gene carrying approximately 100 CAG repeat expansions. In this founder line (61Gpb), the transgene is ubiquitously expressed. Transgenic mice exhibit a progressive neurological phenotype that mimics many of the features of HD, including choreiform-like movements, involuntary stereotypic movements, tremor, and epileptic seizures, as well as nonmovement disorder components, including unusual vocalization. They urinate frequently and exhibit loss of body weight and muscle bulk through the course of the disease. Neurologically they develop Neuronal Intranuclear Inclusions (NII) which contain both the huntingtin and ubiquitin proteins. These NII have also been identified in human HD patients. The age of onset of HD symptoms is reported to occur between 15 and 21 weeks for this 61Gpb line. On the BALB/cByJ genetic background, the CAG tract remains somatically stable throughout the life span of the mouse but may contract over generations (even with male transmission). These HDexon1 mice may be useful in Huntington's Disease research. <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. Mice with this mutation were originally published on a mixed CBA x C57BL6 genetic background. It should be noted that the phenotype could vary from that originally described. We will modify the strain description as published results become available.</i>
<i>Selected Reference(s)</i>	Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, Lawton M, Trotter Y, Levrach H, Davies SW, Bates GP. 1996. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. <i>Cell</i> 87:493-506.
<i>Allele Symbol/Name</i>	Tg(HDexon1)62Gpb, transgene insertion 62, Gillian Bates
<i>Common Name(s)</i>	Tg(HDexon1)62nGpb; R6/2
<i>Promoter</i>	HTT, huntingtin
<i>Strain Name</i>	B6CBA-Tg(HDexon1)62Gpb/1J
<i>Stock Number</i>	002810
<i>Former & Common Name(s)</i>	B6CBA-Tg(HDexon1)62oGpb/J; B6CBA-TgN(HDexon1)62Gpb
<i>Important Note</i>	January 2007: alteration in strain name and phenotype.
<i>General Terms</i>	Use of MICE by companies or for-profit entities requires a license prior to shipping. (www.jax.org/jaxmice/licensing/UMDSKCL.htm)
<i>Additional Research Areas</i>	Cardiovascular Research; Developmental Biology Research; Diabetes and Obesity Research; Mouse/Human Gene Homologs; Neurobiology Research
<i>Phenotype</i>	This line is transgenic for the 5' end of the human HD gene carrying (CAG)115-(CAG)150 repeat expansions. The transgene is ubiquitously expressed. Transgenic mice exhibit a progressive neurological phenotype that mimics many of the features of HD, including choreiform-like movements, involuntary stereotypic movements, tremor, and epileptic seizures, as well as nonmovement disorder components, including unusual vocalization. They urinate frequently and exhibit loss of body weight and muscle bulk through the course of the disease. Neurologically they develop Neuronal Intranuclear Inclusions (NII) which contain both the huntingtin and ubiquitin proteins. Previously unknown, these NII have subsequently been identified in human HD patients. The age of onset of HD symptoms is reported to occur between nine and 11 weeks. Commonly known as the "R6/2" strain. Transgenic mice develop hyperglycemia by 12 weeks of age with a corresponding decrease in insulin levels. Pancreatic beta cells develop huntingtin inclusions as early as seven weeks of age, by 12 weeks more than 95% of beta cells have inclusions. Pancreatic alpha and delta cells also exhibit some inclusions (24% and 6% of cells, respectively) by 12 weeks. Pancreatic islets become hypotonic and beta cells are dramatically reduced in number by 12 weeks. Beta cells contain very few insulin secretory vesicles. (Bjorkqvist M <i>et al.</i> 2005)

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<i>Selected Reference(s)</i>	Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, Lawton M, Trotter Y, Leach H, Davies SW, Bates GP. 1996. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. <i>Cell</i> 87:493-506.
<i>Allele Symbol/Name</i>	Tg(HTT*97Q)IXwy, transgene insertion I, X William Yang
<i>Common Name(s)</i>	BACHD-I
<i>Promoter</i>	HTT, huntingtin
<i>Strain Name</i>	FVB/N-Tg(HTT*97Q)IXwy/J
<i>Stock Number</i>	008197
<i>General Terms</i>	Use of MICE by companies or for-profit entities requires a license prior to shipping. (www.jax.org/jaxmice/licensing/UCLA_2.htm)
<i>Additional Research Areas</i>	Developmental Biology Research; Mouse/Human Gene Homologs; Neurobiology Research; Research Tools: Cre-lox System
<i>Phenotype</i>	Mice hemizygous for the BACHD transgene are viable and fertile. Under the control of endogenous human <i>htt</i> regulatory machinery, BACHD mice have relatively high expression levels of a neuropathogenic, full-length human mutant Huntingtin (fl-mhtt) modified to harbor a <i>loxP</i> -flanked human mutant <i>htt</i> exon 1 sequence (containing 97 mixed CAA-CAG repeats encoding a continuous polyglutamine (polyQ) stretch). Prior to Cre recombinase exposure, BACHD mice exhibit progressive motor deficits, neuronal synaptic dysfunction, and selective late-onset neuropathology without somatic polyQ repeat instability in the aged brain. Moreover, BACHD mice reproduce a mhtt aggregation pattern reminiscent of that in adult-onset Huntington's disease (HD). Importantly, a relatively steady-state level of predominantly fl-mhtt and a small amount of mhtt N-terminal fragments present in both the nucleus and cytoplasm, are responsible for the onset and progression of neuropathology. Upon exposure to Cre recombinase, the floxed mhtt-exon1 portion of the transgene is removed and fl-mhtt expression is terminated. These BACHD mice represent a robust <i>in vivo</i> paradigm for studying the HD pathogenesis elicited by fl-mhtt. These mice may be useful in the testing of candidate therapeutics and in studies examining the contribution of mhtt expression in individual neuronal and non-neuronal cell types in the pathogenesis of HD-like phenotypes <i>in vivo</i> .
<i>Selected Reference(s)</i>	Gray M, Shirasaki DI, Cepeda C, Andre VM, Wilburn B, Lu XH, Tao J, Yamazaki I, Li SH, Sun YE, Li XJ, Levine MS, Yang XW. 2008. Full-length human mutant huntingtin with a stable polyglutamine repeat can elicit progressive and selective neuropathogenesis in BACHD mice. <i>J Neurosci</i> 28:6182-95.
<i>Allele Symbol/Name</i>	Tg(YAC72)2511Hay, transgene insertion 2511, Michael Hayden
<i>Common Name(s)</i>	YAC72
<i>Promoter</i>	HTT, huntingtin
<i>Strain Name</i>	FVB/NJ-Tg(YAC72)2511Hay/J
<i>Stock Number</i>	003640
<i>General Terms</i>	Use of MICE by companies or for-profit entities requires a license prior to shipping. (www.jax.org/jaxmice/licensing/UBC.htm)
<i>Additional Research Areas</i>	Developmental Biology Research; Mouse/Human Gene Homologs; Neurobiology Research
<i>Phenotype</i>	Mice homozygous for this transgene are viable and fertile. The human huntingtin transgenic protein is expressed widely in many tissues (identical to the endogenous huntingtin protein), but has highest levels of expression in the brain and testes. Electrophysiological abnormalities can be measured by six months. A behavioral phenotype is first detected at seven months when evidence of mild hyperkinetic movement disorder is noticeable. This disorder is characterized by progressive spontaneous hyperactivity during the dark phase of open field-testing. By 12 months of age selective degeneration of medium spiny neurons in the lateral striatum is observed. This degeneration is associated with the translocation of N-terminal huntingtin fragments to the nucleus. This strain represents a Huntington's Disease mouse model where a mutant full-length human huntingtin is expressed under control of its endogenous promoter.
<i>Selected Reference(s)</i>	Hodgson JG, Agopyan N, Gutekunst CA, Leavitt BR, LePiane F, Singaraja R, Smith DJ, Bissada N, McCutcheon K, Nasir J, Jamot L, Li XJ, Stevens ME, Rosemond E, Roder JC, Phillips AG, Rubin EM, Hersch SM, Hayden MR. 1999. A YAC mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration. <i>Neuron</i> 23:181-92.
<i>Allele Symbol/Name</i>	Tg(YAC128)53Hay, transgene insertion 53, Michael Hayden
<i>Common Name(s)</i>	HD53; YAC128
<i>Promoter</i>	HTT, huntingtin
<i>Strain Name</i>	FVB-Tg(YAC128)53Hay/J
<i>Stock Number</i>	004938

Select Models for Huntington's Disease Research

<i>General Terms</i>	Use of MICE by companies or for-profit entities requires a license prior to shipping. (www.jax.org/jaxmice/licensing/UBC.htm)
<i>Additional Research Areas Phenotype</i>	Developmental Biology Research; Mouse/Human Gene Homologs; Neurobiology Research These transgenic mice express the human huntingtin protein containing a 128 CAG repeat expansion. Human huntingtin mRNA and protein is detected. Hyperkinesia begins at three months of age with progressive motor impairment appearing at six months of age. This is followed by progressive neurodegeneration, starting at nine months of age, and hypokinesia at 12 months. The motor dysfunction, Rotorod deficit, is correlated with neuronal loss. Mutants exhibit decreased brain weight and reduced striatal and cortical volumes. 18% shrinkage of striatal neurons is observed in 12 month old mutants. A significant decrease (15%) in the number of striatal neurons occurs by 12 months of age. Nuclear huntingtin aggregate inclusions of striatal neurons from 18 month old mutant mice are detected at the light microscopy level. This mutant mouse strain represents a model that may be useful in studies of Huntington's disease.
<i>Selected Reference(s)</i>	Slow EJ, van Raamsdonk J, Rogers D, Coleman SH, Graham RK, Deng Y, Oh R, Bissada N, Hossain SM; Yang YZ, Li XJ, Simpson EM, Gutekunst CA, Leavitt BR, Hayden MR. 2003. Selective striatal neuronal loss in a YAC128 mouse model of Huntington disease. <i>Hum Mol Genet</i> 12:1555-67.
<i>Allele Symbol/Name</i>	Tg(YAC353G6)W7Hay, transgene insertion W7, Michael Hayden
<i>Common Name(s)</i>	C6R7; YAC353G6
<i>Promoter</i>	HTT, huntingtin
<i>Strain Name</i>	FVB/N-Tg(YAC353G6)W7Hay/J
<i>Stock Number</i>	007247
<i>Additional Research Areas Phenotype</i>	Developmental Biology Research; Mouse/Human Gene Homologs; Neurobiology Research These transgenic mice express the human huntingtin protein containing a 133 CAG repeat expansion and a mutation in exon 13 conferring resistance to caspase-6 cleavage to the gene product. Expected caspase-6 cleaved fragments are not detected in brain lysates by Western blot analysis. Transgenic mice have brain weight and striatal volume similar to wildtype controls and do not exhibit neuronal loss at 12 months of age when compared to transgenic mice that express human huntingtin protein containing a 128 CAG repeat (FVB-Tg(YAC128)53Hay/J Stock No. 004938). These transgenic mice have activity levels and motor function similar to wildtype controls, and are resistant to neuron excitotoxicity. Immunohistochemical analysis of striatal brain sections reveals delayed nuclear localization of mutant huntingtin protein in these transgenic mice at nine months of age. Between nine and 12 months of age, an increase of nuclear huntingtin is observed. Homozygotes are viable, fertile, normal in size and do not display any gross physical or behavioral abnormalities. This mutant mouse strain represents a model that may be useful in studies of Huntington's disease. This strain can serve as the control for the FVB-Tg(YAC128)53Hay/J (Stock No. 004938).
<i>Selected Reference(s)</i>	Graham RK, Deng Y, Slow EJ, Haigh B, Bissada N, Lu G, Pearson J, Shehadeh J, Bertram L, Murphy Z, Warby SC, Doty CN, Roy S, Wellington CL, Leavitt BR, Raymond LA, Nicholson DW, Hayden MR. 2006. Cleavage at the caspase-6 site is required for neuronal dysfunction and degeneration due to mutant huntingtin. <i>Cell</i> 125:1179-91.

Gene/Marker **UBB**

Name **ubiquitin B**

Allele Symbol/Name
Common Name(s)
Promoter

Tg(Camk2a-UBB*)3413-1Fwvl, transgene insertion 3413-1, FW van Leeuwen
UBB⁺¹ 3413; UBB^{<+1>} 3413
Camk2a, calcium/calmodulin-dependent protein kinase II alpha

Strain Name
Stock Number
Phenotype

C57BL/6-Tg(Camk2a-UBB)3413-1Fwvl/J
008833
These transgenic mice express the mutant human ubiquitin B, *UBB⁺¹*, under the direction of the mouse *Camk2a*, calcium/calmodulin-dependent protein kinase II alpha, promoter. In hemizygotes, mutant transcript is expressed at 49% of the endogenous levels. The transgene is expressed in neurons of the cortex, hippocampus, amygdala and striatum. Hemizygous transgenic mice exhibit diminished ubiquitin-proteasome system activity with a resulting increase in ubiquitinated proteins in the cortex. Transgenic mice display a reduced synaptic plasticity in the hippocampus and impaired spatial learning. Mice homozygous for the transgenic insert are viable, fertile, normal in size and do not display any gross physical abnormalities. This mutant mouse strain may be useful in studies of neurodegenerative diseases such as Alzheimer's and Huntington disease.

Selected Reference(s)

Fischer DF, van Dijk R, van Tijn P, Hobo B, Verhage MC, van der Schors RC, Li KW, van Minnen J, Hol EM, van Leeuwen FW 2009. Long-term proteasome dysfunction in the mouse brain by expression of aberrant ubiquitin. *Neurobiol Aging* 30 :847-63.

Research Models for Huntington's Disease

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

Links to research models for Huntington's Disease.

Neurobiology Research Tools

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

View database generated lists for research tools for neurobiology strains either by strain name, including strain description or by promoter, including site of expression.

Other Related Mouse Model Areas

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Links to the following research areas under Neurobiology Research: Alzheimer's Disease, Amyotrophic lateral sclerosis (ALS) Disease, Parkinson's Disease, and Spinal Muscular Atrophy (SMA) Disease.

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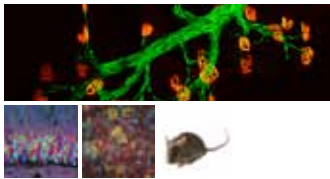
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1. Top: Motor neurons in the lateral gastrocnemius of B6.Cg-Tg(Thy1-YFP)16Jrs/J (Stock Number 003709) are seen as green, acetylcholine receptors on the muscle are labeled with bungarotoxin in red. Courtesy of Dr. Rob Burgess, The Jackson Laboratory.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