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J Neural Transm. Author manuscript; available in PMC 2012 January 1.

Published in final edited form as:
J Neural Transm. 2011 January ; 118(1): 27–45. doi:10.1007/s00702-010-0476-6.

Transgenic animal models of neurodegeneration based on human genetic studies

Brandon K. Harvey, **Christopher T. Richie**, **Barry J. Hoffer**, and **Mikko Airavaara**
Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD 21224, USA

Brandon K. Harvey: bharvey@intra.nida.nih.gov

Abstract

The identification of genes linked to neurodegenerative diseases such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and Parkinson's disease (PD) has led to the development of animal models for studying mechanism and evaluating potential therapies. None of the transgenic models developed based on disease-associated genes have been able to fully recapitulate the behavioral and pathological features of the corresponding disease. However, there has been enormous progress made in identifying potential therapeutic targets and understanding some of the common mechanisms of neurodegeneration. In this review, we will discuss transgenic animal models for AD, ALS, HD and PD that are based on human genetic studies. All of the diseases discussed have active or complete clinical trials for experimental treatments that benefited from transgenic models of the disease.

Keywords

ALS; PD; AD; HD; Huntington's disease; Parkinson's disease; Amyotrophic lateral sclerosis; Alzheimer's disease; Transgenic; Animal model; Neurodegeneration; Genetic linkage

Introduction

Genes have been identified as risk factors for the cause of neurodegenerative diseases through studies of families and populations with patterns of inherited neurodegenerative diseases. Once a pedigree analysis has identified a pattern of inheritance, linkage studies can identify chromosomal loci where putative disease genes may be located. Sequencing of putative genes from members of an established disease pedigree can potentially identify a specific mutation that follows the disease inheritance pattern. Once a gene and mutation have been identified, transgenic animals can be generated to model the human disease or provide insight into the gene's function (see Fig. 1 for overview). In this review, we discuss transgenic animal models of several prominent neurodegenerative diseases that are based on genes identified through human gene linkage studies. The common symptoms and pathological changes of Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and Parkinson's disease (PD) and their associated loci and genes are summarized in Table 1.

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Alzheimer's disease

Alzheimer's disease is the most prevalent of neurodegenerative diseases that causes progressive memory loss and dementia in affected patients. Diagnosis of AD occurs post-mortem by confirming the presence of neurofibrillary tangles (NFT) and amyloid plaques which are found in the several brain regions including the subiculum and entorhinal cortex. The NFT are intraneuronal microtubule bundles comprised hyperphosphorylated forms of microtubule associated protein tau (MAPT). The amyloid plaques are extracellular deposits primarily consisting of the amyloid β peptide. To date, 16 genes or loci have been identified for AD (OMIM 104300). In this review, we will briefly describe several genes that have been used to generate transgenic models of AD.

Amyloid beta A4 precursor protein (*APP; AD1*)

Pedigree analysis of a family with early onset autosomal dominant AD identified a mutation (V717F) in the *APP* gene (Murrell et al. 1991). Using the APP V717F mutation, the first transgenic mouse model of AD (PDAPP) was developed (Games et al. 1995). The PDAPP mouse exhibited plaque pathology by 6–9 months of age but did not show NFT pathology or substantial cell loss. Analysis of Swedish families with early onset AD identified a double mutation (K670N and M671L) in the *APP* gene (Mullan et al. 1992). A transgenic mouse (Tg2576) was generated based on the double mutation in APP and these mice had plaque pathology at 9 months of age and cognitive deficits. No NFT pathology or cell loss was observed (Hsiao et al. 1996). A second laboratory generated a transgenic mouse (APP23) based on the Swedish double-mutant but used a different promoter to express the transgene (Sturchler-Pierrat et al. 1997). Similar to Tg2576, the APP23 developed plaques, around 6 months of age, and had cerebrovascular amyloid and some neuronal loss (Sturchler-Pierrat et al. 1997; Calhoun et al. 1998, 1999). A mutation in APP (E693Q) was identified in patients with hereditary cerebral hemorrhage with amyloidosis of Dutch type (HCHWA-D), an autosomal dominant form of amyloidosis (Levy et al. 1990). The E693Q mutant form of APP was used to generate the APP-Dutch transgenic mouse which developed congophilic amyloid angiopathy, but did not show other phenotypes consistent with AD (Herzig et al. 2004).

Additional APP mutant-based transgenic mice and genetic crosses with other AD gene-based mutants (some described below) have been studied and these models have allowed hundreds of studies evaluating therapeutics and investigating the mechanisms of Alzheimer's disease (Dodart and May 2005; McGowan et al. 2006; Duyckaerts et al. 2008; Woodruff-Pak 2008; Howlett and Richardson 2009). In addition to mouse models based on mutations found in human genes, there are non-transgenic models of AD in the rat, rabbit, dog and primate that offer the ability to conduct complementary studies for the evaluation of therapeutics and the understanding of disease mechanisms (Woodruff-Pak 2008). However, mouse models of AD based on human mutations in APP and other AD genes remain the most widely used for evaluating potential therapeutics.

Apoliprotein E (*APOE; AD2*)

The epsilon 4 allele of apolipoprotein E (*APOE-E4*) gene was detected at a high frequency in a population of patients with late-onset familial AD compared to spousal controls (Saunders et al. 1993). Another study identified APOE-E4 as a highly significant risk factor for AD (Corder et al. 1993). Although APOE-E4 remains the highest risk factor identified for sporadic AD (Bertram and Tanzi 2005), no transgenic animals based on *APOE-E4* allele have produced an AD phenotype. However, replacement of the mouse *APOE* gene with human APOE4 allele causes cognitive impairments (Raber et al. 1998), decreased excitatory synaptic transmission and reduction in dendritic density and complexity (Wang et al. 2005a; Dumanis et al. 2009), There is also strong evidence that APOE-E4 increases deposition of

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Aβ peptide in amyloid plaques and evidence that APOE can influence tau phosphorylation (Small and Duff 2008). Mice expressing human *APOE4* allele in a mouse *APOE4* null background exhibited increased insoluble APOE protein in parallel with an increased Aβ burden as they aged (Bales et al. 2009). Overall, the identification of APOE as a risk factor for AD may be most useful for diagnostic purposes to identify patients who may benefit from a therapy aimed at reducing Aβ (Lambert and Amouyel 2007; Bird 2008). As more studies unravel the mechanistic actions of APOE in AD and other diseases, better therapeutic strategies may be developed.

Presenilin 1 (*PSEN1; AD3*)

Mutations in the presenilin 1 gene on chromosome 14 (Sherrington et al. 1995) is the most common cause of autosomal dominant forms of familial AD. To date, 175 mutations in *PSEN1* have been identified (AD and FTD Mutation Database; http://www.molgen.ua.ac.be/ADMutations). The *PSEN1* gene encodes a protein component of the proteolytic gamma-secretase complex whose activity in combination with beta-secretase generates Aβ from APP. Using two mutations, M146L (Sherrington et al. 1995) and M146V (Haltia et al. 1994), identified in PSEN1, two transgenic mouse strains were generated (Duff et al. 1996). Both strains exhibited increased Aβ peptide in the brain but no obvious plaque pathology was reported. Additional mutations in *PSEN1* can influence Aβ processing (Brouwers et al. 2008) but, to date, no mutant of *PSEN1* alone provides a suitable phenocopy of AD.

Presenilin 2 (*PSEN2; AD4*)

Through linkage studies of autosomal dominant forms of early-onset AD, the gene encoding presenilin 2 on chromosome 1 was identified (Levy-Lahad et al. 1995a, b). To date, 14 mutations in *PSEN2* have been identified (AD and FTD Mutation Database; http://www.molgen.ua.ac.be/ADMutations). Similar to PSEN1, PSEN2 is a protein component of the proteolytic gamma secretase complex important for processing APP (Brouwers et al. 2008). Unlike mice lacking PSEN1, *PSEN2* null mice are viable with no obvious defects and no significant differences in processing APP (Donoviel et al. 1999; Herreman et al. 1999). Using the N141I mutation in PSEN2, transgenic mice were generated and found to have higher levels of insoluble Aβ peptide compared to control mice (Sawamura et al. 2000). Although PSEN2 can influence Aβ peptide processing, no transgenic animals based on PSEN2 alone recapitulate AD phenotype. The relevance of presenilin-based transgenics is discussed in a recent review (Elder et al. 2010).

Microtubule-associated protein tau (*MAPT*)

The presence of NFTs in post-mortem brain is one of the defining pathologies of AD. A major component of the NFTs is MAPT and changes in its phosphorylation, cellular distribution, and structure can lead to tau pathologies or “tauopathies” such as that seen in AD (Brunden et al. 2008; Garcia-Sierra et al. 2008; Honson and Kuret 2008; Takashima 2008). Linkage studies identified mutations in human chromosome 17q21.1 that are correlated to frontotemporal dementia. To date, 44 mutations in MAPT have been identified (AD and FTD Mutation Database; http://www.molgen.ua.ac.be/ADMutations). There have been several transgenic mice generated based on mutations in the human *MAPT* gene that have provided clear evidence for mutant tau in NFT pathology and dementia (McGowan et al. 2006). Although the mechanism by which mutations in MAPT lead to neurodegeneration remains unknown, therapeutic strategies targeting the phosphorylation status of tau are being developed (Gong and Iqbal 2008).

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Combined transgenic models

Although none of the transgenic rodent models based on single gene mutations have been able to fully recapitulate the features of AD, combinations of transgenes have provided novel transgenic models that have a progressive pathology with behavioral deficits. For example, mice containing the P301L mutation in MAPT were crossed with the amyloid precursor protein mutant Tg2576 to generate “TAPP” mice. The TAPP mice exhibited increased NFTs in the limbic system and olfactory cortex (Lewis et al. 2001). Using an alternative approach, Oddo et al. (2003a, b) microinjected the transgenes for APP (Swe) and Tau (P301L) into single-cell embryos from homozygous PS1 (M146V) mice to create a triple transgenic mouse (3xTg-AD). The 3xTg-AD mice progressively develop synaptic dysfunction, APP-containing plaques and NFTs (Oddo et al. 2003a, b). The 3xTg-AD mouse has thus been the most widely used model of AD for evaluating potential therapies, examining environmental vulnerabilities and studying disease mechanism (Gimenez-Llort et al. 2007; Foy et al. 2008). Overall, there has been significant progress in understanding disease mechanisms for AD using transgenic rodent models that are based on mutated human genes in AD patients.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is a neurodegenerative disease that results from the progressive loss of motor neurons in brain and spinal cord. Onset of disease typically occurs in middle adulthood but forms with juvenile onset also occur. Symptoms include asymmetrical muscle weakness and muscle fasciculations. The disease progresses rapidly after onset leading to paralysis and eventually death within 5 years. Most cases of ALS are sporadic with an estimated 10% of cases exhibiting a pattern of inheritance. To date, molecular genetic studies have identified the corresponding genes for nine of the twelve ALS loci defined by linkage studies (Table 1).

Superoxide dismutase (*SOD1; ALS1*)

The first gene associated with ALS was the superoxide dismutase-1 (*SOD1*) gene encoding an enzyme capable of inactivating superoxide radicals (Rosen et al. 1993). Approximately 20% of the familial forms of ALS can be attributed to mutations in the *SOD1* gene, many of which follow an autosomal dominant inheritance pattern. The identification of *SOD1* as a genetic factor for ALS led to the development of *SOD1* transgenic animals. Gurney et al. (1994) reported that mice over-expressing a human *SOD1* allele containing a G93A substitution developed spinal cord motor neuron loss and related paralysis. Following that initial study with the G93A variant, 13 additional transgenic mice have been made that produced a broad range of outcomes but all exhibit some characteristics of the disease (Ripps et al. 1995; Wong et al. 1995; Bruijn et al. 1997; Wang et al. 2002, 2003, 2005b; Tobisawa et al. 2003; Jonsson et al. 2004, 2006; Chang-Hong et al. 2005; Watanabe et al. 2005; Deng et al. 2006). A recent publication has extensively reviewed and summarized the numerous studies related to *SOD1* transgenic mice including therapeutic testing with these models (Turner and Talbot 2008). For the current review, we will focus on the remaining genes that have been implicated in ALS.

Alsin (*ALS2*)

Two deletion mutations in the *ALS2* gene were identified from pedigree analysis of an autosomal recessive inherited form of juvenile onset ALS (Yang et al. 2001). Alsin, the protein encoded by the *ALS2* gene, has been shown to be important for the survival and growth of neurons, as well as neurite outgrowth (Tudor et al. 2005; Jacquier et al. 2006). Although the primary sequence contains several functional domains implicating a role in guanine nucleotide exchange, the precise structural or enzymatic function of this protein

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remains unknown. To date, at least five independently generated *ALS2* knockout mice have been characterized (Cai et al. 2005; Devon et al. 2006; Hadano et al. 2006; Yamanaka et al. 2006; Deng et al. 2007) Although each of these knockout alleles produced viable homozygous mice, the resulting animals failed to show any neuropathological features consistent with motor neuron degeneration. However, subsequent studies with these variants did provide several insights into the function of alsin. These insights will be discussed here only briefly, since a recent review by Cai et al. (2008) provides an in-depth comparison of their construction and phenotypic characterization. The first report demonstrated that *ALS2* null mice or neurons derived from *ALS2* null mice were more vulnerable to oxidative stress. Interestingly, this allele did not enhance the spinal cord degeneration or paralysis phenotype of SOD1 (G93A) mice (Lin et al. 2007). Age-related loss of Purkinje cells and disturbance of spinal motor neurons was detected by electrophysiological and immunohistochemical analyses in a second variant (Hadano et al. 2006). Devon et al. (2006) showed that their *ALS2* null mice were hypoactive, had smaller than normal cortical motor neurons and disrupted endosomal fusion activity. Lai et al. (2006) discovered that AMPA receptor trafficking was disrupted in *ALS2* null mice and this rendered neurons more vulnerable to glutamate-mediated excitotoxicity. Finally, several groups have shown that ALS2 is required for proper axonal development and function (Yamanaka et al. 2006; Deng et al. 2007; Otomo et al. 2008).

Although each variant has provided some insight into the functions of ALS2 in motor neurons, no single *ALS2* null allele has completely reproduced the behavioral and pathological features of ALS. While it is difficult to speculate on the precise reason for this shortfall, it is possibly due to nuances in the *ALS2* genomic sequence (i.e. alternate splicing) as it spans eighty kilobases, but ultimately produces a three kilobase transcript. Recreating such structural complexity is difficult with current techniques. Nonetheless, future studies may benefit from the development of transgenic mice harboring human mutant forms of *ALS2* in an *ALS2* null background either alone or in conjunction with other predisposing genes.

Senataxin (*SETX; ALS4*)

Senataxin is the affected gene that causes the autosomal dominant familial form of juvenile ALS associated with the *ALS4* locus (Chance et al. 1998; Chen et al. 2004). Mutations in *SETX* have been previously linked to the autosomal recessive disease ataxia with oculomotor apraxia type 2 (AOA2). SETX contains a conserved superfamily I DNA/RNA helicase domain that suggests this protein has a nuclear function related to nucleic acid processing (Chen et al. 2004). Although in vitro studies have demonstrated that cells carrying the AOA2 type mutations have increased sensitivity to oxidative DNA damage, similar studies with *ALS4*-related alleles have not been reported (Suraweera et al. 2007). The development of *ALS4/SETX* transgenic animals is needed to understand the role of *ALS4* mutants in motor neuron disease.

Vesicle-associated membrane protein-associated protein B (*VAPB; ALS8*)

The gene encoding vesicle-associated membrane protein-associated protein B (VAPB), corresponds to *ALS8*, an autosomal dominant adult-onset form of ALS. The *VAPB* gene was identified as a putative ALS gene from a pedigree analysis of a large Brazilian family (Nishimura et al. 2004) and a specific mutation, P56S, was linked to 200 diseased individuals out of 1500 in the 8 pedigrees studied (Nishimura et al. 2005). A study of post-mortem spinal cord tissue from ALS patients determined that *VAPB* mRNA expression was decreased compared to control tissue (Anagnostou et al. 2008). Transgenic flies expressing the corresponding mutation in *Drosophila* VAPB produced hallmarks of human ALS including locomotion defects, neuronal death and aggregate formation (Chai et al. 2008). In

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yeast and neuronal cells, expression of the P56S mutant increased ER stress and vulnerability to ER stress, respectively (Suzuki et al. 2009). Although the development of a transgenic rodent model has yet to be reported, the ability to study the *ALS8* phenotypes in flies and yeast should prove to be powerful tools when screening for genetic modifiers of disease or therapeutic drugs.

Angiogenin (*ANG; ALS9*)

Based on an association between the *ANG* gene and a frequently occurring single nucleotide polymorphism in a population of ALS patients (Greenway et al. 2004), a more comprehensive study was conducted which identified seven missense mutations in patients with both sporadic ALS and familial autosomal dominant *ALS9* (Greenway et al. 2006). Additional mutations in *ANG* have been identified in various populations with ALS (Wu et al. 2007; Conforti et al. 2008; Gellera et al. 2008; Paubel et al. 2008). Similar to activities described above for ALS2/alsin, cell culture studies have shown that mutant forms of human ANG impeded neurite extension and promoted degeneration (Subramanian et al. 2008). ANG promotes survival of motor neurons in vitro and in vivo and angiogenin delivery to SOD1 (G93A) mice increased lifespan and motor neuron survival (Kieran et al. 2008). Collectively, angiogenin affects motor neuron survival and neuritic growth, and the presence of angiogenin in serum may be a useful biomarker for ALS. The development of animal models based on human mutant forms of *ANG* may provide a means to evaluate therapeutic and diagnostic approaches to ALS.

TAR DNA binding protein (*TARDBP; ALS10*)

Several studies have confirmed that mutations in the *TARDBP* gene are associated with familial *ALS10*-type forms of ALS (Kabashi et al. 2008; Kuhnlein et al. 2008; Rutherford et al. 2008; Sreedharan et al. 2008; Van Deerlin et al. 2008; Corrado et al. 2009) and sporadic ALS (Daoud et al. 2009). The TARDBP protein contains two RNA-binding motifs which are involved in alternative mRNA splicing (Bose et al. 2008). A recent publication by Kraemer et al. reported that while homozygous *TARDBP*-null mice (−/−) die as embryos around day 7.5, heterozygous (+/−) mice exhibit signs of motor defects and muscle weakness (Kraemer et al. 2010). Another report by Kabashi et al. (2010) employs a zebrafish model to express the mutant alleles associated with the human disease state. These transgenic fish displayed swimming deficits and defects in axonal elongation and branching. The ability of the zebrafish model to phenocopy the human disease state and its feasibility as a high throughput system makes it an ideal platform for experimental therapeutics.

In conclusion, the available repertoire of transgenic animals modeling non-*SOD1*-based ALS has only begun to develop, and new genes and loci are still being added. While this manuscript was in preparation, the causative gene was identified for *ALS6* and two new loci, *ALS11* and *ALS12*, have been identified (Chow et al. 2009; Vance et al. 2009; Maruyama et al. 2010). With continued growth and characterization of the *ALS* loci and associated genes, these tools may prove to be as powerful as the *SOD1* animal collection, which has produced several therapeutic strategies (e.g. arimoclomal, ceftriaxone, IGF-1, HDAC inhibitors) that are now in clinical trials (http://www.clinicaltrials.gov). Future studies will no doubt lead to the identification of more ALS loci and give rise to even more transgenic animal models to be used in our effort to understand this complicated degenerative disease.

Huntington's disease

Huntington's disease is an autosomal dominant progressive neurodegenerative disorder. HD was found to be an inherited disease already in nineteenth century and it was named after George Huntington who characterized the disease (Huntington 1872). Distinctive symptoms

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for HD are chorea, dystonia, incoordination, weight loss, cognitive difficulties and psychiatric problems. The onset of symptoms is usually midlife, but it can vary from early childhood to old age. HD is fatal usually within 15–20 years after the onset. Pathologically, HD is characterized by neuronal cell loss and atrophy most prominently in caudate and putamen (Vonsattel et al. 1985). Within the striatum neurodegeneration occurs in medium spiny neurons. Enkephalin containing striatal medium spiny neurons projecting to the external globus pallidus are more vulnerable than those containing substance P projecting to the internal globus pallidus (Reiner et al. 1988).

Huntingtin (*IT15*)

Unlike the other neurodegenerative disorders described in this review, HD is linked to a specific genetic deficit found on chromosome 4 (Gusella et al. 1983) and the gene, *IT15*, was found to have a CAG repeat longer than normal (HDCRG 1993). The expansion of the CAG/polyglutamine repeat is at the N-terminus of huntingtin protein; the normal allele sizes are 6–37 CAG repeats and expanded HD allele sizes are 35–121 repeats. The length of the repeat correlates with age of onset and the longest repeats are detected in juvenile cases (HDCRG 1993). Patients having CAG repeats 30–40 are rare, and individuals without symptoms have been found to have 36, 37, 38 and 39 repeats (Rubinsztein et al. 1996).

Huntingtin is a 350 kDa protein and is expressed at high levels in neurons of the brain and in testis of adults (Bennett et al. 2009). Huntingtin is necessary for development since homozygous knock-out embryos are not viable (Nasir et al. 1995; Zeitlin et al. 1995). Huntingtin also has an important role in postnatal development. Elimination of HD gene in postnatal development leads to neuronal degeneration, a motor abnormality phenotype and early mortality (Dragatsis et al. 2000). Furthermore, mutated huntingtin can rescue the knockout mice (White et al. 1997; Leavitt et al. 2001).

The first transgenic mouse model for HD was generated, carrying 5′ end of the human *HD* gene (CAG)115-150 (Mangiarini et al. 1996). They established three mouse lines with CAG repeat expansions that had an HD phenotype: R6/1 with 116 repeat units, R6/2 with 144 repeat units, R6/5 with wider spectrum of repeats: 128, 132, 135, 137 and 156. R6/2 mice have been studied most and show choreiform-like movements, involuntary stereotypic movements, tremor, epileptic seizures and premature death (Mangiarini et al. 1996). The age of onset is 9–11 weeks and the age of death is 10–13 weeks in R6/2 mice. R6/2 mice have huntingtin aggregates in the nucleus of neurons seen prior to developing a neurological phenotype (Davies et al. 1997). Also, the mRNA for type 1 metabotropic glutamate receptors and for D1 dopamine receptors is already reduced at the age of 4 weeks (Cha et al. 1998).

Several additional transgenic mouse models of HD have been generated with different lengths of CAG repeats and progressive HD phenotype (White et al. 1997; Reddy et al. 1998; Schilling et al. 1999; Shelbourne et al. 1999; Wheeler et al. 2000; Laforet et al. 2001; Lin et al. 2001; Menalled et al. 2002; Gray et al. 2008). A series of studies has been reported based on a yeast artificial chromosome (YAC) mouse model with full-length form of huntingtin under the endogenous promoter. These mice show CAG repeat- and age-dependent behavioral deficits which correlate to striatal atrophy and neuronal loss (Hodgson et al. 1999; Slow et al. 2003).

A conditional mouse model of HD in which mutant *huntingtin* gene is turned off via tetracycline-induced activation (Yamamoto et al. 2000), expresses mutated huntingtin containing 94 CAG repeats. The mice have neuronal inclusions and characteristic neuropathology when they are studied at the age of 18 weeks. Also, they show progressive motor dysfunction starting at the age of 4 weeks (Yamamoto et al. 2000). When the mutated

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huntingtin protein expression was blocked at the age of 18 weeks, it led to reduction of neuronal inclusions and a decrease in behavioral phenotype when mice were analyzed 16 weeks later (Yamamoto et al, 2000). The area and density of dopamine D1 receptors in caudate putamen increased significantly and striatal GFAP density decreased 16 weeks after inactivation of mutated huntingtin protein synthesis. Yamamoto (2000) thus indicate that continued synthesis of mutated huntingtin protein is needed to maintain inclusions and symptoms of HD.

A transgenic rat model of HD, with a mutated *huntingtin* gene containing 51 CAG repeats, expresses adult-onset neurological phenotypes, cognitive impairments, progressive motor dysfunction and neuronal nuclear inclusions in the brain (von Horsten et al. 2003). The transgenic rats have a late onset of phenotype and they die between 15 and 24 months. Transgenic HD rats have an age- and genotype-dependent deterioration of psychomotor performance and choreiform symptoms (Cao et al. 2006).

Recently, HD was modeled in rhesus macaque with a lentiviral vector (Cai et al. 2008). Yang et al. (2008) injected rhesus oocytes with lentivirus expressing exon 2 of the human *huntingtin* gene with 84 CAG repeats and five transgenic monkeys carrying mutant huntingtin were produced. The monkeys showed the main features of HD disease including nuclear inclusions, neuropil aggregates and a behavioral phenotype but all of them died at early stage of life.

In the HD model in Drosophila the N-terminal fragment of the human mutant protein containing 2, 75 and 120 CAG repeats were expressed in the photoreceptor neurons of the fly eye (Jackson et al. 1998). Jackson et al. found that neuronal differentiation is normal and the onset of degeneration is correlated with the length of CAG repeats. The expanded repeats are initially cytoplasmic but relocalization to the nucleus occurs before neuronal death.

C. elegans does not have huntingtin homolog, but worms are an efficient way to study cellular mechanisms. Faber et al. found CAG repeats of 2, 23, 95 and 150 in *C. elegans* sensory neurons and that the CAG_{150} repeat led to protein aggregates and degeneration of sensory neuron terminals but did not lead to cell death (Faber et al. 1999). The CAG_{150} repeat increased the vulnerability of sensory neurons to toxic OSM-10 green fluorescent protein. In another study, *C. elegans* over-expressing 128 CAG repeats led to neuronal dysfunction but did not lead to neuronal cell death (Parker et al. 2005).

Unlike the other neurodegenerative disorders described in this review, HD is linked to a single gene, *huntingtin*. Animal models based mutant forms of the *huntingtin* gene have been generated from worms to primates and have been used to study the disease mechanism and test potential therapeutics. Over 500 clinical trials are active or have been completed for HD (http://www.clinicaltrials.gov) and the animal models described above have been indispensable to the corresponding preclinical studies.

Parkinson's disease

Parkinson's disease is a slow, progressive neurodegenerative disorder that is characterized pathologically by the loss of dopaminergic neurons in the pars compacta of the substantia nigra. The cardinal symptoms of PD are resting tremor, rigidity, bradykinesia and occasionally dementia. PD is primarily idiopathic resulting from a complex interaction of genetics and environment. A subset (<15% of cases) of patients have a family history of PD and pedigree analyses have identified 13 *PARK* loci to date (OMIM 168600). Molecular genetics studies have identified genes associated with 11 of 16 *PARK* loci and transgenic

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animal models for six of these genes (i.e. *α-synuclein, parkin, DJ-1, PINK1, UCH-L1* and *LRRK2*) will be discussed below.

α-Synuclein (*PARK1* and *PARK4*)

The first gene linked to PD was the *α*-synuclein gene and the first mutation, A53T, was found in a large family with an autosomal dominant pattern of inherited PD (Polymeropoulos et al. 1997). Two additional mutants A30P and E46K were subsequently identified in independent linkage studies (Ueda et al. 1993; Zarranz et al. 2004). Alpha-synuclein is found in presynaptic nerve terminals and originally was identified as a non-*β* amyloid component of Alzheimer's disease-related amyloid plaques (Ueda et al. 1993). In post-mortem brains of PD patients, *α*-synuclein was detected in Lewy bodies which are pathological hallmarks of PD (Spillantini et al. 1997). Normal *α*-synuclein is important for physiologic function of dopamine neurons as deletion of *α*-synuclein leads to reduction in striatal dopamine and reduction in TH-positive fibers but does not affect number of TH-positive neurons in aging mice (Abeliovich et al. 2000; Al-Wandi et al. 2008).

Transgenic mice over-expressing human *α*-synuclein showed an accumulation of *α*-synuclein in neuronal inclusion bodies found in several brain regions including the substantia nigra (Masliah et al. 2000). The formation of inclusion bodies correlated with loss of striatal dopaminergic terminals and motor impairment. Transgenic mice expressing human *α*-synuclein with the A30P mutation exhibited increased accumulation of the mutant *α*-synuclein in the neuronal cell bodies and neurites (Kahle et al. 2000). In a recent study the A30P mutation in mice led to development of motor performance deficits at the age of 13 months and reduced levels of dopamine in striatum at the age of 15 months (Plaas et al. 2008). Similarly, transgenic mice expressing human *α*-synuclein with both the A53T mutation or “wild-type” human *α*-synuclein exhibited Lewy body-like pathology, evidence of neurodegeneration and motor deficits; however, the transgenic protein was not expressed in nigral neurons (Kahle et al. 2000). Using a different promoter, transgenic mice expressing the A53T mutant, but not the human “wild type” *α*-synuclein, developed severe motor deficits that led to death, paralleled by the accumulation of cytoplasmic filamentous inclusions in neurons (Giasson et al. 2002). In the Giasson et al. (2002) study, the mouse prion protein promoter was used, compared to Thy-1 promoter used in the studies by Kahle et al. (2000) and van der Putten et al. (2000) indicating that the temporal and spatial expression of the human synuclein forms is important for the manifestation of neurodegenerative effects (Kahle et al. 2000; van der Putten et al. 2000). A study comparing transgenic mice expressing human *α* -synuclein, A53T mutant and A30P mutant from the mouse prion promoter, found that the A53T mutant caused more neurodegeneration associated with abnormal accumulation of detergent-insoluble aggregates of *α*-synuclein (Giasson et al. 2002). Mice overexpressing human *α*-synuclein with both A53T and A30P mutations had accumulation of *α*-synuclein in neurons, decreased dopamine concentrations in striatum and motor impairment (Ikeda et al. 2009). Although the aforementioned studies are models of *α*-synucleopathies, the lack of selective expression in nigral neurons or nigral degeneration thus fails to generate a full phenocopy of PD.

Selective expression of the wild-type, A53T or A30P mutants in dopaminergic neurons using the tyrosine hydroxylase promoter did not cause selective loss of nigral neurons or striatal dopamine, or the development of inclusions in dopaminergic neurons (Matsuoka et al. 2001). A separate study by Rathke-Hartlieb et al. (2001) showed similar findings and reported no change in sensitivity to the dopaminergic toxin, MPTP. Richfield et al. (2002) used the rat tyrosine hydroxylase 9.0 kb promoter to express a transgenic double mutant (A53T and A30P) form of *α*-synuclein in dopaminergic neurons. Expression of the double mutant led to age-related declines in motor coordination, striatal dopamine and integrity of dopaminergic terminals but no inclusion bodies were reported (Richfield et al. 2002). In

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contrast to a previous study (Rathke-Hartlieb et al. 2001), mice expressing wild-type or double-mutant human α-synuclein were more susceptible to MPTP toxicity (Richfield et al. 2002). A communication by Tofaris et al. (2006) used the rat TH promoter to express a truncated form of human α-synuclein in a mouse α-synuclein null background. Unlike previous reports, inclusion bodies were observed in the substantia nigra. An age-related decline in striatal dopamine and locomotor activity was also observed in these animals (Tofaris et al. 2006). This study indicated that the C-terminal portion of α-synuclein is important for the formation of inclusions. To summarize, overexpressing human α-synuclein or its mutated forms in transgenic mice is not sufficient to cause a complete Parkinsonian phenotype. However, this approach is valuable for understanding synucleopathies and for studying vulnerability to environmental toxins and possible therapies aimed at preventing synucleopathies. Despite numerous studies indicating that α-synuclein is involved in synaptic turnover/function and synaptic trafficking, its endogenous function and pathological role as a component of Lewy bodies remains to be determined.

Recent studies indicate transgenic mice with both the double-mutant human form of α-synuclein and the exon 3 knockout of *parkin* have combined age- and tissue-related effects on mitochondrial morphology and integrity (Stichel et al. 2007). Further studies on the relationship of α-synuclein and parkin may provide insights into the molecular mechanisms of mitochondrial dysfunction in PD.

Parkin (*parkin; PARK2*)

Studies of autosomal recessive inheritance pattern of early-onset PD in a group of Japanese families led to the identification of the *parkin* gene at the *PARK2* locus (Kitada et al. 1998). Since the study by Kitada and colleagues, multiple studies have shown that mutations in Parkin are linked to autosomal recessively inherited PD. Unlike α-synuclein that has few identified mutations, more than a 100 mutations have been identified in the *parkin* gene (Abbas et al. 1999; Lucking et al. 2000; Hedrich et al. 2001, 2004; Itier et al. 2003; Oliveira et al. 2003; Klein et al. 2007). Parkin has an E3 ubiquitin-protein ligase activity (Shimura et al. 2000) and targets proteins for degradation by the proteosome (Zhang et al. 2000; Chung et al. 2001; Imai et al. 2001).

Several laboratories have generated *parkin* knockout mice by targeting different exons of the *parkin* gene (Bonifati et al. 2003; Goldberg et al. 2003; Palacino et al. 2004; Von Coelln et al. 2004; Perez et al. 2005; Sato et al. 2006). The phenotype of the mice varies and overall they fail to develop a Parkinsonian phenotype, but the different knockout models may provide a means to examine the role of parkin in protein turnover, oxidative stress and mitochondrial dysfunction.

DJ-1 (*PARK7*)

The DJ-1 gene was identified at the *PARK7* locus (van Duijn et al. 2001) with a point mutation (L166P) that cosegregated with the disease allele in an Italian family (Bonifati et al. 2003). Mutations in DJ-1 are autosomal recessive and are associated with early onset of PD (Abou-Sleiman et al. 2003; Bonifati et al. 2003; Hague et al. 2003; Hedrich et al. 2004; Annesi et al. 2005). DJ-1 is a member of the THiJ/pfpI family and exhibits a redox-dependent chaperone function which may be important for combating oxidative-stress (Shenk et al. 2009).

Studies of DJ-1 knockout animals demonstrated that absence of DJ-1 expression (1) decreases motor function and (2) alters dopamine function in the nigrostriatal pathway (Chen et al. 2005; Goldberg et al. 2005; Kim et al. 2005). A recent study demonstrated that upregulation of DJ-1 can compensate for defects in *pink1* mutant flies (Hao et al. 2010).

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Development of transgenic animals based on other mutations in DJ-1 as well as further studies on DJ-1 knockout mice may provide a useful platform for testing gene therapeutic strategies for patients carrying DJ-1 mutations and offer opportunities to further understand the role of DJ-1 in oxidative stress.

PTEN-induced kinase 1 (*PINK1; PARK6*)

Point mutations in the PTEN-induced kinase or *PINK1* gene, a putative mitochondrial kinase at the *PARK6* locus, are the second most frequently occurring cause of autosomal recessively inherited early-onset PD (Valente et al. 2001,2004; Hatano et al. 2004; Rogaeva et al. 2004; Rohe et al. 2004; Bonifati et al. 2005; Bender et al. 2006; Ibanez et al. 2006). PINK1 is present throughout the brain and localizes to mitochondria where it is thought to protect against mitochondrial dysfunction (Gandhi et al. 2006).

Studies examining knockdown or knockout of the *PINK1* gene failed to produce a PD phenotype (Kitada et al. 2007; Zhou et al. 2007). However, a transgenic mouse created by targeting the human G309D-PINK1 mutation into mice created a knockout mouse that exhibited mitochondrial dysfunction in brain, impaired spontaneous locomotor activity, weight loss and dopaminergic synapse dysfunction in aged mice (Gispert et al. 2009). Although there was no signs of neurodegeneration in the mice described by Gispert et al., the observed changes in dopamine, α-synuclein and locomotion in older animals suggests that this mouse model may recapitulate certain features of early PD. Consistent with this model, mutations in both DJ-1 and *PINK1* genes have been identified in subset of patients with early onset PD. Biochemical studies suggest DJ-1 stabilizes PINK1 and works cooperatively with it to protect cells against oxidative stress (Gandhi et al. 2006). Studies in *Drosophilia* have found that PINK1 and Parkin are involved in a common pathway important for mitochondrial function and morphology (Clark et al. 2006; Park et al. 2006, 2009; Deng et al. 2008; Kim et al. 2008; Yang et al. 2008). Future studies examining the role of PINK1 and parkin in mitochondrial function in mammalian models may lead to the development of a mouse model that more closely resembles the pathology of PD.

Ubiquitin carboxy-terminal hydrolase-L1 (*UCH-L1; PARK5*)

A missense mutation (I93M) in the ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1) gene was identified in a sibling pair affected by PD (Leroy et al. 1998). Although no additional mutations in UCH-L1 have been linked to PD, a variant (S18Y) has been identified that correlates with lowered risk of developing PD (Lincoln et al. 1999; Maraganore et al. 1999, 2004). The gracile axonal dystrophy (gad) mouse has a deletion in the *UCH-L1* gene, but the mice do not exhibit behavioral and pathological characteristics of PD (Saigoh et al. 1999). Recently, Setsuie et al. (2007) generated a transgenic mouse expressing the I93M mutant form of UCH-L1 under expression of the PDGF-beta promoter. Mice over-expressing UCH-L1 (I93M) had fewer dopaminergic neurons in the substantia nigra and decreased striatal dopamine levels compared to wild-type mice. The transgenic mice also exhibited increased levels of insoluble UCH-L1 in the midbrain, increased sensitivity to MPTP (Setsuie et al. 2007) and over-expression of α-synuclein (Yasuda et al. 2009). Overall, the occurrence of the UCH-L1 mutation in PD patients is rare, but a transgenic mouse study using the I93M mutations, suggests that UCH-L1 function may contribute to dopaminergic degeneration. Additional genetic analysis studies in PD patients or studies on the effects of expressing the S18Y mutation in mice are needed to explore the relevance of UCH-L1 in PD.

Leucine-rich repeat kinase 2 (*LRRK2; PARK8*)

The leucine-rich repeat kinase 2 (*LRRK2*) gene at the *PARK8* locus (Funayama et al. 2002) was initially identified from a pedigree of autosomal dominantly inherited PD (Paisan-Ruiz

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et al. 2004; Zimprich et al. 2004). The LRRK2 protein, approximately 286 kD, has multiple predicted domains. In rodent basal ganglia LRRK2 is found in lysosomes, endosomes, transport vesicles and mitochondria (Biskup et al. 2006) and overexpression or knockdown of LRRK2 has been shown to impair synaptic vesicle endocytosis (Shin et al. 2008). Nearly 50 mutations in LRRK2 have been identified and currently constitute the most common cause of inherited PD. The common G2019S mutation is found in idiopathic cases of PD (Lesage et al. 2007) and has been shown to increase kinase activity in vitro (Chen et al. 2005). West and colleagues also described altered kinase activity of the R1441C/G mutation in the GTPase domain of LRRK2 (West et al. 2005).

Recently, a transgenic mouse was generated by introducing a BAC containing a FLAG-tagged LRRK2 expressed from 35 kb of the LRRK2 promoter and 60 kb of the *LRRK2* 3′ non-coding region (Li et al. 2007). The FLAG-LRRK2 was expressed in several brain regions including the dopaminergic neurons of the substantia nigra. Affinity-purified FLAG-LRRK2 from brains of transgenic mice had higher kinase and GTPase activity compared to FLAG-LRRK2 from lung or from FLAG-LRRK2 transfected into HEK-293T cells. HEK-293T cells transfected with the R1441C/G mutant of LRRK2 had decreased GTPase activity compared to non-mutant LRRK2 (Ekstrand et al. 2007). Although these in vivo results support previous in vitro reports of kinase and GTPase activity of LRRK2 and its possible role in PD, the effects of overexpressing the FLAG-LRRK2 on the dopaminergic nigrostriatal neurons or locomotor activity was not described.

The loss of LRRK2 expression in Drosophila leads to dopaminergic neuron degeneration and altered locomotor activity (Lee et al. 2007). Recent studies on mice containing LRRK2 WT, LRRK2 G2019S or LRRK2 R1441G mutations do not result in a PD phenotype (Li et al. 2009, 2010; Lin et al. 2009; Tong et al. 2009). Given there is no obvious neurodegeneration, these models do not currently provide an opportunity to evaluate therapeutic strategies. Further studies examining how environmental stressors combined with LRRK2 mutations may lead to PD-like phenotype may provide a better phenocopy of PD.

Although the loss of dopaminergic neurons in the SN is the primary “mechanism” that causes PD, the molecular changes that lead to the loss of this specific cell type is unknown. Several genes described above are linked to PD but the majority of patients (80–85%) do not appear to have an inherited genetic link. The disease likely results from the complex interplay of genetic predisposition seeded in the genes described above and related genes in common cellular pathways, the chemical properties of dopamine and its metabolism, and environmental factors known to affect the dopaminergic system. The use of transgenic models for PD has been valuable in our understanding of disease mechanism. Future studies utilizing these models to understand the complex interplay of genes, dopamine metabolism and the environment may lead to therapies tailored to halt progression of disease or prevent the disease from occurring.

Concluding remarks

Transgenic animal models based on mutations in human genes enable researchers to dissect the function of a mutant gene or combination of mutant genes in the pathophysiology of the disease. More importantly, once a transgenic model has been established to have characteristics of a disease, it can be used as a platform for evaluating potential genetic and pharmacological therapies. As we gain more understanding of how the genes identified in human pedigree analyses and gene linkage studies fit into cellular pathways that contribute to disease, we can use transgenic animals to examine how the combination of multiple “mutations” leads to neurodegeneration.

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Acknowledgments

The authors thank Dr. Marc Halterman for his recommendations on the table. This work was supported by the Intramural Research Program at the National Institute on Drug Abuse.

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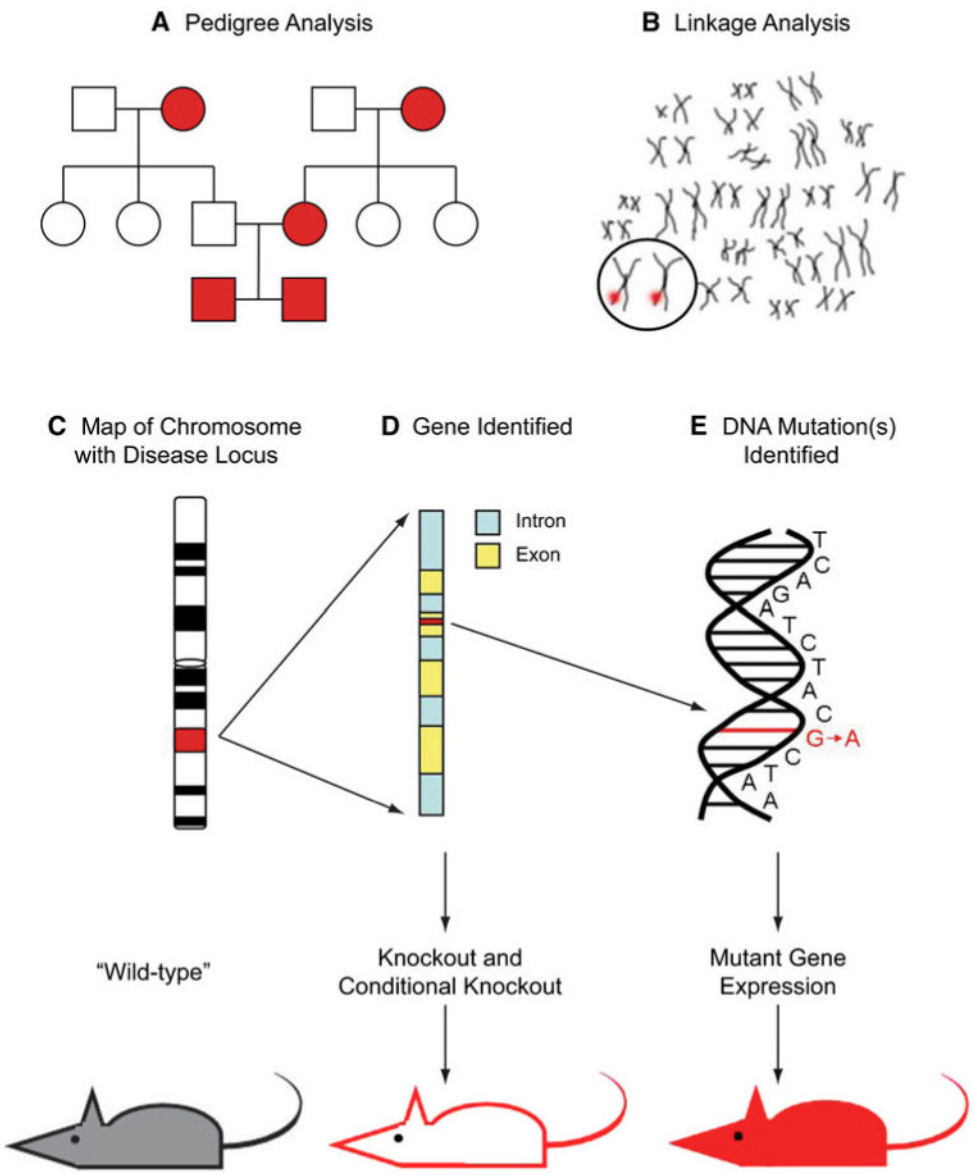

Fig. 1.

Generation of transgenic mouse models based on inheritance patterns of human disease. Families or populations with traceable lineages of a disease are subjected to pedigree analysis (**a**) and individuals are subjected to gene linkage studies to identify associated chromosomes (**b**). Further molecular analyses link genetic markers to specific region of chromosome, or locus (**c**) and potentially identify a disease-related gene (**d**). Sequence analysis of putative gene(s) from diseased and non-diseased members of the pedigree can reveal inherited mutation(s) in the gene (**e**). Once the gene and mutation have been identified in affected pedigree members, the mouse ortholog of the human gene can be knocked out completely or conditionally (**d** *arrows*). Also, the mutated human gene can be introduced into the mouse as a replacement for, or in addition to the mouse ortholog (**e** *arrows*). Transgenic mice generated based on the identified gene and its mutants are an important tool when studying behavioral and pathological phenocopy of human disease and when evaluating potential therapeutics for disease

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Table 1

Neurodegenerative diseases: symptoms, pathology and associated genetic linkage

Disease	Symptoms	Pathology	Gene map locus	Locus name	Associated gene
Alzheimer's disease (AD)	Dementia	Amyloid-containing plaques in cortex	21q21	AD1	Amyloid precursor protein
	Apraxia	Neurofibrillary tangles	19q13.2	AD2	Apolipoprotein E (APOE)
	Aphasia		14q24.3	AD3	Presenilin-1 (PSEN1)
	Depression, anxiety and delusions		1q31–q42	AD4	Presenilin-2 (PSEN2)
	Short attention span		12p11.23– q13.12	AD5	Not yet determined
	Visuospatial navigation deficits		10q24	AD6	Not yet determined
			10p13	AD7	Not yet determined
			20p	AD8	Not yet determined
			19p13.2	AD9	Not yet determined
			7q36	AD10	Not yet determined
			9q22.1	AD11	Not yet determined
			8p12–q22	AD12	Not yet determined
			1q21	AD13	Not yet determined
			1q25	AD14	Not yet determined
			3q22–q24	AD15	Not yet determined
			Xq21.3	AD16	Not yet determined
Amyotrophic lateral sclerosis (ALS)	Muscle weakness and wasting	Loss of lower motor neurons in ventral horn of spinal cord	21q22.1	ALS1	Superoxide dismutase-1 (SOD1)
	Muscle fasciculations and cramping	Degeneration of corticospinal tracts	2q33	ALS2	Alsin
	Impaired limb dexterity	Neurodegeneration in primary motor cortex	18q21	ALS3	Not yet determined
	Respiratory failure	Reactive astrocytes in motor cortex and spinal cord	9q34	ALS4	Senataxin (SETX)
	Dysphagia and aspiration	Cytoplasmic inclusions in degenerating neurons	15q15.1–q21.1	ALS5	Not yet determined
	Hypophonic speech		16q12	ALS6	Fused in sarcoma (FUS)
			20p13	ALS7	Not yet determined
			20q13.3	ALS8	Vesicle-associated membrane protein-associated protein B (VAPB)
			14q11.2	ALS9	Angiogenin (ANG)

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Disease	Symptoms	Pathology	Gene map locus	Locus name	Associated gene
			1p36.2	ALS10	TAR DNA Binding protein (TARDBP)
			6q21	ALS11	Homolog of yeast FIG 4
			10p15–p14	ALS12	Optineurin
Huntington's disease (HD)	Choreiform movements	Loss of neurons in caudate and putamen	4pl6.3	ITI5	Huntingtin
	Depression	Gliosis in striatum			
	Dementia				
	Emotional incontinence				
Parkinson's disease (PD)	Resting tremor	Loss of neurons in substantia nigra	4q21	PARK1	Synuclein (SNCA)
	Muscle rigidity	Cytoplasmic inclusions in degeneration neurons (Lewy bodies)	6q25.2–q27	PARK2	Parkin
	Bradykinesia		2p13	PARK3	Not yet determined
	Postural instability		4q21	PARK4	Synuclein (SNCA)
	Cognitive decline		4p14	PARK5	Ubiquitin C-ternubak esterase L1 (UCHL1)
	Depression		1p36	PARK6	PTEN-induced putative kinase1 (PINK1)
	Physical discomfort		1p36	PARK7	DJ1
			12q12	PARK8	Leucine-rich repeat 2 (LRRK2)
			1p36	PARK9	ATP13A2
			1p32	PARK10	Not yet determined
			2q37.1	PARK11	GRB10-interacting GYF protein (GIGYF2)
			Xq21–q25	PARK12	Not yet determined
			2p12	PARK13	HTRA serine peptidase 2 (HTRA2)
			18q11	PARK14	Not yet determined
			22q12–q13	PARK15	FBX07
			1q32	PARK16	Not yet determined

Gene map locus, locus name and associated gene information based on Online Mendelian Inheritance in Man (OMIM) database at http://www.ncbi.nlm.nih.gov/omim/