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Genetic Neurodegenerative Diseases: The Human Illness and Transgenic Models

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REVIEW

The neurodegenerative disorders, a heterogeneous group of chronic progressive diseases, are among the most puzzling and devastating illnesses in medicine. Some of these disorders, such as Alzheimer's disease, amyotrophic lateral sclerosis, the prion diseases, and Parkinson's disease, can occur sporadically and, in some instances, are caused by inheritance of gene mutations. Huntington's disease is acquired in an entirely genetic manner. Transgenic mice that express disease-causing genes recapitulate many features of these diseases. This review provides an overview of transgenic mouse models of familial amyotrophic lateral sclerosis, familial Alzheimer's disease, and Huntington's disease and the emerging insights relevant to the underlying molecular mechanisms of these diseases.

The majority of the autosomal dominant neurodegenerative diseases are characterized by onset in adult life, chronic progressive course, distinct clinical phenotypes, specific cellular abnormalities involving subsets of neurons, and eventually, fatal outcomes. For the most part, there are no specific therapies. The identification of mutant genes has allowed investigators to establish in vitro and in vivo systems to examine the cellular abnormalities associated with mutant gene products in a number of these diseases.

Motor Neuron Disease

Amyotrophic lateral sclerosis (ALS), the most common adult onset motor neuron disease, manifests as weakness and muscle atrophy with occasional spastic paralysis, reflecting the selective involvement of lower, and in some cases, upper motor neurons (*1*). The neuropathological features of lower motor neurons include the hyperaccumulation of phosphorylated neurofilaments, intracellular inclusions that stain with antibodies to ubiquitin, intracytoplasmic inclusions resembling Lewy bodies, fragmented Golgi, attenuated dendrites, and swellings in proximal axonal segments filled with neurofilaments.

About 10% of ALS cases are familial (FALS), and in almost all cases, inheritance exhibits an autosomal dominant pattern (*2*). A subset (15 to 20%) of patients with autosomal dominant FALS have missense mutations in the gene encoding cytosolic Cu/Zn superoxide dismutase 1 (SOD1) (*3*, *4*), which catalyzes the conversion of the radical $\cdot O_2$ to O_2 and H_2O_2. Multiple lines of evidence from cell culture and transgenic models indicate that FALS-linked mutations cause SOD1 to acquire toxic properties. First, some FALS mutations retain near normal levels of enzyme activity or stability (*5*), and mutant SOD1 subunits do not alter the metabolism or activities of wild-type SOD1 in a dominant negative fashion (*6*). Second, SOD1 null mice do not develop a FALS-like syndrome (*7*). Moreover, transgenic mice expressing a variety of mutant human or mouse SOD1 develop weakness and muscle atrophy with pathological changes similar to those occurring in human disease (Fig. 1). For example, in mice expressing the G37R variant of SOD1 (in which Gly^{37} has been mutated to Arg), spinal motor neurons are the most profoundly affected cells, showing axonal and dendritic abnormalities that include SOD1 accumulations in irregularly swollen portions of motor axons, abnormal axonal cytoskeleton architecture, and small vacuoles (derived from damaged mitochondria) in both axons and dendrites (*8*, *9*). Interestingly, different SOD1 mutations are associated with different cellular phenotypes. For example, in mice expressing human G85R SOD1, astrocytes contain SOD1 and ubiquitin-immunoreactive Lewy body–like inclusions before clinical signs appear (*10*); at later stages, motor neurons also contain SOD1- and ubiquitin-positive aggregates. Thus, although the different SOD1 mutants selectively damage motor neurons (presumably, by means of a common mechanism), the different mutations can be associated with different types of cellular pathology in mice.

Although the pathogenic process or processes by which mutant SOD1 causes degeneration of motor neurons are not fully understood, an emerging view is that the mutations induce conformational changes in SOD1 that promote the ability of bound copper to engage in chemical reactions that produce hydroxyl radicals (*11*), reactive nitrogen species (*12*), or other perturbations of the biology of motor neurons. Transgenic mice expressing G93A SOD1 (Gly^{93}→Ala mutation) have been used to test a variety of therapeutic agents relevant to these potential mechanisms. Administration of vitamin E (an antioxidant) and selenium (which raises concentrations of the antioxidant enzyme glutathione peroxidase) modestly delays both the onset and progression of disease without affecting survival; in contrast, riluzole and gabapentin (antiexcitotoxins) do not influence the onset or progression of disease (*13*). Oral administration of D-penicillamine (a copper chelator) delays the onset of disease (*14*).

Genetic strategies have also been used to gain insight into mechanisms of disease. Coexpression of Bcl-2 (an anti-apoptotic protein) and mutant SOD1 extends survival but has no effect on disease progression (*15*). In G93A SOD1 mice overexpressing a dominant negative inhibitor of the apoptosis-associated protease, interleukin-1B converting enzyme, there was a modest slowing of disease progres-

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sion (*16*). Thus, experimental, therapeutic, and genetic manipulations have been interpreted to support the idea that oxidative damage, excitotoxicity, and apoptotic processes may play roles in the pathogenesis of disease. However, it should be emphasized that none of these processes appears to be the primary mechanism of SOD1-mediated injury.

Previous studies of ALS and a variety of animal models have suggested significant roles for abnormalities of neurofilament biology in motor neuron disease (*17*). The role of neurofilaments in disease was examined by crossbreeding G37R SOD1 transgenic mice to transgenic mice that express a neurofilament H–β-galactosidase fusion protein (NF-H–lacZ), which is poorly transported in axons (*18*). In G37R SOD1 mice coexpressing NF-H–lacZ, neurofilaments are retained within the cell bodies of neurons, but the disease progresses in a manner identical to the disease in mice that express G37R SOD1 alone (*19*), implying that axonal NF may not be involved in the initiation or progression of disease.

Future studies of motor neuron disease will be greatly aided by the identification of other genes linked to FALS. Over the coming years, investigators will clarify the ways in which mutant gene products compromise the functions of motor neurons, to determine the biochemical participants in the pathogenic pathways (some of which represent therapeutic targets) and to design and test novel treatment approaches.

Alzheimer's Disease

Alzheimer's disease (AD), the most common cause of dementia in adult life (*20*), is associated with the selective damage of brain regions and neural circuits critical for cognition and memory (*21*), including neurons in the neocortex, hippocampus, amygdala, basal forebrain cholinergic system, and brainstem monoaminergic nuclei (Fig. 2). Dysfunction and death of neurons in these neural circuits leads to reduced numbers of generic synaptic, as well as transmitter-specific, markers in target fields (*22*). Affected neurons accumulate tau and ubiquitin immunoreactivities within neurofibrillary tangles (NFTs), in cell bodies and dendrites, and in dystrophic neurites. The NFTs, aggregations of poorly soluble filaments, are composed principally of hyperphosphorylated isoforms of tau, a microtubule-binding protein (*23*).

In addition to neurofibrillary pathology, AD patients show numerous senile plaques which are composed of dystrophic neurites displayed around extracellular deposits of ~4-kD Aβ (*24*) derived from β-amyloid precursor proteins (APPs) (*25*). APPs are type-1 integral membrane glycoproteins that are subject to alternative proteolytic pathways (*26*). Some APP molecules are cleaved endoproteolytically within the Aβ sequence by a plasma membrane protease termed α-secretase to release the ectodomain of APP ($APP^{s\alpha}$) (*26, 27*). Aβ peptides are generated by endoproteolytic cleavage of APP by activities, termed β- and γ-secretase (Fig. 3) (*26*). About 90% of secreted Aβ peptides are Aβ40, a soluble form of the peptide, whereas about 10% of secreted Aβ peptides are Aβ42 and Aβ43—species that are highly fibrillogenic, readily aggregated, and neurotoxic (*28*). Aβ42 and Aβ43 peptides are deposited early and selectively in plaques (*29, 30*). Presenilin 1 (PS1) and PS2 are highly homologous ~43- to 50-kD proteins with eight transmembrane domains. With a single exception, which involves an in-frame deletion of exon 9 in PS1, the genetic abnormalities in presenilin are missense mutations that result in single amino acid substitutions. The presenilin polypeptides accumulate as ~27- to 28-kD NH_2-terminal and ~16- to 17-kD COOH-terminal derivatives in vivo (*31*); the absolute amounts of these fragments are tightly regulated and saturable, and the presenilin fragments are stably associated with each other (*32*).

Most cases of early onset AD are familial (FAD) autosomal dominant disorders caused by mutations in APP, PS1, and PS2 [for reviews, see (*33, 34*)]. In the late-onset forms of AD, there are no specific gene mutations that are associated with the inheritance of disease; however, specific alleles of apolipoprotein E4 (apoE) [for review, see (*35*)] and α2 macroglobulin (A2M) are associated with increased risk for AD (*36*). The first FAD mutation to be identified was APP-V717I (Fig. 3) (*37*); cells expressing APP with substitutions of the Val residue at position 717 secrete a higher fraction of Aβ42 peptides relative to cells that express wild-type APP (*38*). Additional FAD-linked APP mutations have been reported (Fig. 3) (*39*). In one case, APP harboring a double mutation at codons 670 and 671 that results in a Lys-Met to Asn-Leu substitution proximal to the β-secretase site is subject to processing in a manner that results in elevated secretion of Aβ40 and Aβ42 peptides (*40*). Hence, all the FAD mutations influence APP processing in a manner that elevates production of the Aβ42 and Aβ43 peptides. Surprisingly, FAD-linked PS1 and PS2 variants appear to influence APP processing at the γ-secretase site, leading to increased secretion of highly amyloidogenic Aβ42 and Aβ43 species (*41*).

Several groups have created transgenic mouse models of amyloidogenesis and Aβ-associated abnormalities (*42*). We highlight some of these efforts below.

The first successful transgenic-derived model of Aβ amyloid deposition was generated with a platelet-derived growth factor–β promoter to drive the expression of a human APP minigene that encodes the FAD-linked APP-V717F substitution. The brains of mice showed diffuse Aβ deposits and mature plaques (dystrophic neurites displayed around Aβ cores) associated with astrocytes (*43, 44*).

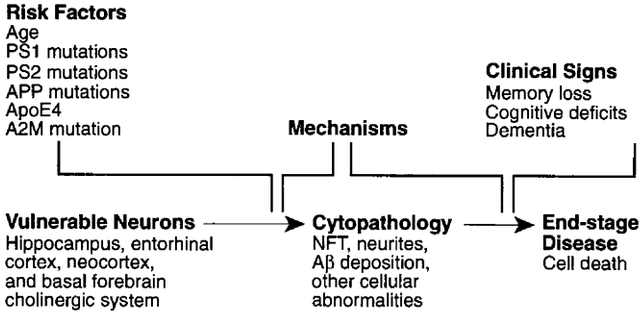


Fig. 2. Alzheimer's diseases. Schematic showing the relations between clinical or pathological phenotypes and mutant genes, other risk factors, and vulnerable populations of neurons. Genetically engineered mice can reproduce some of the clinical, biochemical, and pathological features of AD.

Fig. 1. (**A**) G37R HuSOD1 transgenic mouse with paralysis of the limbs. (**B**) Motor neuron from a case of A4V ($Ala^4 \rightarrow Val$ mutation) SOD1-linked FALS showing SOD1-immunoreactive aggregates in a motor neuron. Similar aggregates occur in some lines of SOD1 mutant transgenic mice.

Increased numbers of microglia were clustered in and around plaques, but NFTs were not evident. Assessments of the performance of these mice on behavioral tasks have not been published. Hsiao and colleagues used the hamster prion protein promoter to overexpress human APP with Lys-Met to Asn-Leu mutations (Hu-APP695swe) in the brains of transgenic mice. The brains of one of these lines (Tg2576) of transgenic mice showed elevated levels of Aβ40 and Aβ42; dystrophic neurites; and Aβ deposits in amygdala, hippocampus, and cortex (*45*). The Tg2576 mice have shown impairments at a young age on several memory tests including the Morris water maze, a spatial reference memory task, and the Y-maze alternation tasks (*45*, *46*).

In view of the earlier studies showing that mutant PS1 influences production of amyloidogenic Aβ42 and Aβ43 peptides, transgenic mice were generated that express either wild-type PS1 or A246E PS1 (Ala^{246}→Glu mutation), and these were mated with mice that express a murine APP transgene with a "humanized" Aβ domain (Mo/Hu-APPswe mice) (*47*) (Fig. 4). Similarly, Holcomb *et al.* (*46*) mated PS1 transgenic mice with APPswe transgenic mice (line Tg2576). Both studies demonstrated that mice coexpressing mutant PS1 with APPswe developed Aβ deposits much earlier than age-matched animals that express APPswe alone, mutant PS1 alone, or wild-type PS1 with APPswe. Thus, coexpression of FAD-linked PS1 variants accelerates the deposition of Aβ. It should be noted that the transgenic models of Aβ amyloidogenesis do not fully recapitulate the entire spectrum of neuropathological alterations seen in human AD cases. For example, although phosphorylated tau epitopes are present in dystrophic neurites, NFTs have not been described. Moreover, neuronal loss is only observed in mice with extremely high amyloid burdens.

ApoE, the major serum protein involved with cholesterol storage, transport, and metabolism (*48*), is polymorphic and encoded by three alleles (apoE2, -3, and -4). The presence of one or two E4 alleles is associated with earlier onset of disease and an enhanced amyloid burden in brain but has little effect on the rate of progression of dementia (*49*). Thus, it appears that the apoE allele type is not causative, but rather influences the age of onset of AD.

The effects of apoE on amyloid deposition have been tested by mating $apoE^{-/-}$ mice with APP-V717F transgenic mice (*50*). At 6 months of age, APP-V717F:$apoE^{+/+}$ mice showed robust amyloid deposition, whereas APP-V717F:$apoE^{-/-}$ mice exhibited only sparse, diffuse Aβ deposits that were not in a β-pleated sheet arrangement. These studies suggest that apoE may influence the aggregation or influence the clearance of Aβ peptides.

In summary, multiple studies in transgenic mice provide strong evidence to support the view that Aβ42 formation is an early and critical pathogenic event: mice expressing APP with mutations linked to disease develop Aβ deposits at an accelerated pace, coexpression of PS variants linked to FAD accelerates the rate of Aβ deposition, and ApoE plays a role in modulating the rate of Aβ deposition. Thus, three known genetic causes or risk factors for FAD and AD effect Aβ deposition. Whether therapeutic agents that effect the concentration, deposition, aggregation, degradation, clearance, or toxicity of Aβ will influence the clinical and pathological features of AD is unclear. Nevertheless, it seems likely that approaches that reduce the concentration of Aβ or the rate of amyloid aggregation and deposition in proximity to synapses and neuronal cell bodies could be beneficial for patients with AD. Clearly, as brain penetrant agents with these activities are developed, the aforementioned transgenic models will be indispensable for validating the in vivo efficacy of these agents.

Trinucleotide Repeat Diseases

The neurological diseases that are associated with autosomal dominant trinucleotide-repeat mutations include Huntington's disease (HD), several spinal cerebellar ataxias (SCA), and dentatorubral

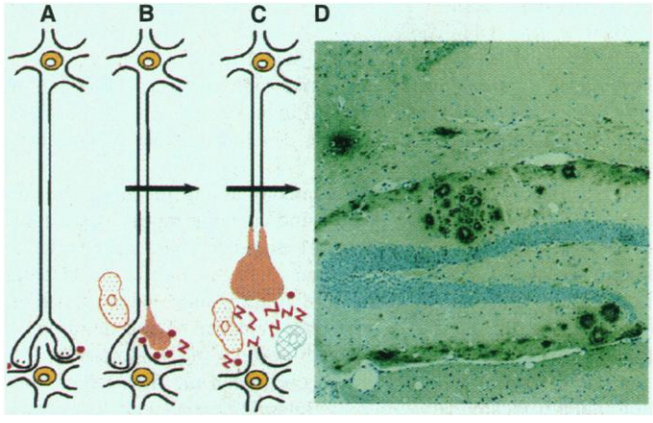
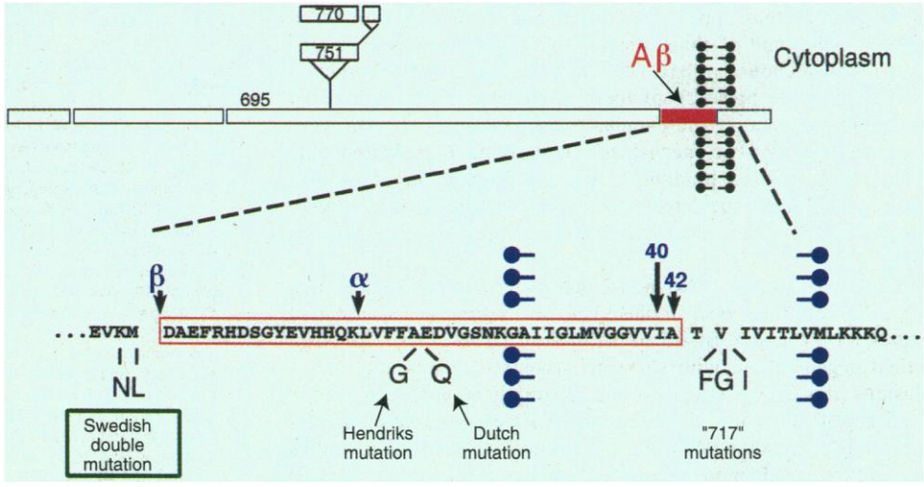


Fig. 4. Postulated evolution of structural abnormalities in APPswe transgenic mice and evidence of Aβ deposits in the hippocampus. (**A**) This two-neuron circuit is intact, but amounts of Aβ (red dots) are increased near the synapse. (**B**) Large APP-containing neurite associated with elevated amounts of Aβ and early Aβ deposits (red Z's). (**C**) Neuritic plaques with APP-enriched neurites, Aβ deposits, astrocytes, and microglia. Synaptic interactions are increasingly compromised progressing from (A) to (C). (**D**) Aβ42 deposits (brown) in the hippocampus of a 24-month-old Mo/Hu-APPswe transgenic mouse.

Fig. 3. Schematic showing APP-695, -751, and -770 isoforms (Aβ resides partially in the transmembrane domain and partially in the ectodomain). Note the α- and β-secretase–cleavage sites and the positions of APP mutations linked to FAD. Cleavage at residues 40 and 42 is thought to be the result of an endoproteinase, putatively termed γ-secretase. A subset of γ-secretase cleavages occurs at residues 39, 41, and 43. Modified from (*33*). Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.



pallidoluysian atrophy (DRPLA). HD and DRPLA are manifest by unusual movements and dementia; SCA-1 and SCA-3 or Machado-Joseph disease are characterized by ataxia and lack of coordination. In all of these illnesses, the clinical signs are associated with dysfunction and death of specific populations of neurons (*51*). In HD, the chorea and dementia are related to degeneration of subsets of striatal and cortical neurons, respectively [for review, see (*52*)]; apoptosis is thought to play a role in the degeneration of these nerve cells (*53*). In SCA-1, SCA-3, and DRPLA, a variety of cell populations, particularly those in the cerebellum, undergo degeneration (*51*). As described below, each of these diseases is associated with the presence of misfolded protein aggregates that contain all or part of the mutant protein and ubiquitin. These aggregates are usually present in the nucleus but can also be seen in the cytoplasm of affected neurons.

The first neurological disease to be identified as caused by expansions in polyglutamine repeats was spinal bulbar muscular atrophy, an X-linked illness caused by expanded CAG repeats in the coding region of the androgen receptor gene (*54*). Similarly, HD, SCA-I, SCA-3, and DRPLA are caused by expanded polyglutamine tracts in the coding region of huntingtin (HD) (*55*), ataxin-1 (SCA-I) (*56*), ataxin-3 (SCA-3) (*57*), and atrophin-1 (DRPLA) (*58*).

To create a transgenic model of SCA-I (*56*), researchers used a Purkinje cell–specific promoter to drive high levels of expression of either the wild-type or mutant ataxin-1 in the cerebellum. Several lines of mice expressing mutant transgenes developed ataxia and degeneration of Purkinje cells (*56*).

Mice that express a transgene encompassing the first exon of the human huntingtin (Htt) protein and carrying repeat expansions develop a progressive neurological disorder characterized by a tremor, abnormal movements, and, in some cases, mild ataxia (*59*). The brains of affected animals were slightly smaller than those of normal littermates, but there was little evidence of degeneration of specific cell types in the striatum or cortex (*59*). Importantly, the analysis of these transgenic animals provided the first demonstration that a truncated Htt with polyglutamine expansions was prone to form intranuclear and cytoplasmic inclusions that are immunoreactive with antibodies raised to ubiquitin and to the NH_2-terminus of Htt. Similar inclusions, containing ataxin-1 and ubiquitin, were recognized subsequently in transgenic mice expressing mutant SCA1 (*60*). To date, nuclear inclusions have been detected in tissues from patients with HD, SCA-1, SCA-3, and DRPLA (*60*, *61*).

On the basis of these findings in transgenic mice and humans, it is now thought that expanded CAG repeats in the coding sequences alter protein folding in ways that lead to the formation of aggregates that appear in both the nucleus and cytoplasm. Although in some of these models the degeneration of neurons is not conspicuous, it has been hypothesized that the mutant proteins and the presence of these aggregates can be toxic and cause the dysfunction and eventual degeneration of specific populations of cells. The mechanisms underlying these pathogenic events may involve binding of mutant proteins to other proteins, which are sequestered, inactivated, or otherwise damaged, that play important roles in the biology of these specific neurons (*62*).

In addition to transgenic mouse models, one of the trinucleotide repeat diseases has been modeled in invertebrates. The targeted expression of mutant SCA3 in the eyes of *Drosophila* resulted in retinal degeneration, with some cells containing intranuclear inclusions (*63*). These model systems are highly amenable to genetic studies that allow the identification of suppressors or enhancers that modify phenotype or cellular pathology. In the future, studies of these transgenic models, both mammalian and invertebrate, will provide significant new information about the molecular events by which polyglutamine expanded proteins elicit toxicity to specific populations of neurons.

Conclusions

Transgenic strategies have allowed investigators to produce mice that recapitulate some, if not all, of the features of SOD1-linked FALS, APP- and PS1-linked FAD, and trinucleotide repeat disorders. These models are proving to be very useful in investigations of the nature of biochemical alterations in neural tissue, the character and evolution of pathologies, and the pathogenic mechanisms by which the mutant proteins cause damage to specific circuits leading to distinct clinical signs. The emerging view is that each of these diseases results because the presence of the mutant proteins, in some instances improperly folded or aggregated, directly or indirectly triggers pathogenic biochemical cascades that eventually effect the physiology of subsets of neural cells. Ultimately, some of the affected nerve cells die. Complemented by in vitro investigations, the studies of transgenic animals have begun to define some of the in vivo events occurring in these illnesses. Moreover, new technologies including structural biophysical methods and differential gene display approaches will help to define the conformational changes in mutant proteins and the variety of genes that are regulated in pathogenic cascades, respectively. In turn, these studies will provide critical information concerning potential pharmacological targets and approaches for therapy that can be tested in transgenic models. The demonstration of therapeutic efficacies in these model systems should then be rapidly translated into new treatments for these devastating human neurodegenerative disorders.

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