Genetic Classification of Primary Neurodegenerative Disease

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Genetic Classification of Primary Neurodegenerative Disease

John Hardy* and Katrina Gwinn-Hardy

REVIEW

During the past 10 years (the "decade of the brain"), some of the genetic causes of many of the primary neurodegenerative diseases, which include Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, prion disease, and many ataxic syndromes, have been found. These breakthroughs mean that for many of these diseases we now know the initiating trigger as well as the final outcome. These diseases have many pathological mechanisms in common, and there may be relatively few pathways to neuronal death seen in these disorders. Thus, treatment strategies developed for a particular disease may be found to have efficacy in more than one disorder.

The first golden age in the study of neurodegenerative disease occurred in the early years of this century and was largely centered in Germany. Technological advances in that era made it possible to characterize diseases that until that time had not been defined. Alzheimer (1907), Pick (1906), Lewy (1912), and their colleagues (*1*), making use of the microscope and of tissue staining procedures developed by Nissl (1892), Bielchovsky (1903), and their colleagues (*2*), classified neurodegenerative diseases as clinicopathological entities. This rigorous intellectual approach to neurodegenerative diseases has dominated thought about such diseases ever since. The clinicopathological approach has served us well. Its major weakness is that, although the clinician can see a disease progressing, the pathologist can see (with rare exceptions) only the final outcome—a still photograph at the end of a long process or an ephemeral glimpse during its course.

We are fortunate to be in the second golden age of study of neurodegenerative disease. This, too, is being driven by technological progress, now through the application of molecular genetics and molecular biology and what can loosely be described as the human genome project. This approach has allowed us to define the genetic bases of many of these diseases. Defining these starting points, and knowing the endpoints, is forcing us to think of neurodegenerative diseases as processes that start with certain biochemical changes, which in turn lead to others, ultimately resulting in a clinically and pathologically recognizable phenotype. In parallel with these molecular advances, progress in imaging techniques is allowing the sequential anatomic and functional imaging of individuals in the preclinical and early stages of neurodegenerative processes (*3*). It is hoped that this reductionist approach—that is, thinking of neurodegenerative diseases as pathological biochemical pathways—will lead to effective intervention and treatment or avoidance of these devastating diseases. The advances in imaging techniques should allow better descriptions of the natural history of a given disorder as well as evaluation of interventions.

The landmark events in our current molecular era include identification of the chromosome linkage for Huntington's disease (*4*), cloning of the prion and amyloid precursor protein (APP) genes (*5*), identification of pathogenic prion mutations (*6*) and of triplet repeat mutations in neurodegenerative disease (*7*), construction of mice with prion mutations that developed pathology (*8*), and elucidation of pathogenic processes that underlie neurodegeneration in transgenic mice (*9*). The above-referenced papers define the technical strategy as follows: identify pathogenic genes by positional cloning, by cloning genes that encode proteins involved in the disease, or by combining the two approaches; find pathogenic mutations; and then model and study the disease in cells by transfection and in mice by transgenesis (*10*). This breathtakingly simple though arduous approach has now been successfully applied to an impressive number of autosomal-dominant neurodegenerative diseases (see Table 1).

Redefining and Reclassifying Neurodegenerative Diseases

An unexpected consequence of this approach to neurodegenerative disease is that the phenotype of a given mutation may not clearly predict a single expected clinicopathological entity. In the ataxias, abnormalities occur in any one of a number of different genes, yet the clinical syndromes from the varied mutations are strikingly similar to each other. Although there are certainly clinical differences, they occur inconsistently, and the clinical classifications do not fit well with the genetic classifications (Table 1) (*11*). Quite different from this is the situation with prion diseases, which have a very wide

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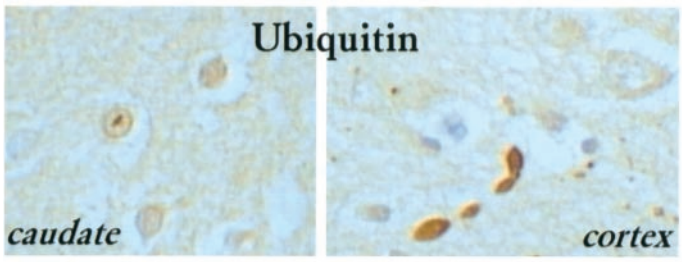

Fig. 1. Ubiquitin immunostaining of Huntington's disease neurons reveals intranuclear inclusion bodies in select neurons in the caudate nucleus and dystrophic neuronal processes in the neocortex. These lesions have been shown to contain huntingtin.

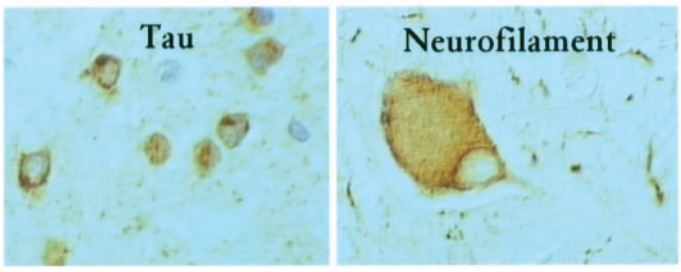

Fig. 2. FTDP-17 has characteristic neuronal (and glial) tau immunoreactivity, such as perinuclear filamentous aggregates in small nonpyramidal neurons in layer II of the cortex. Ballooned neurons, which are best demonstrated with antibodies to phosphorylated neurofilament epitopes, are commonly found in lower layers of cortex in FTDP-17.

phenotype and include cases without spongiform change or with fatal familial insomnia rather than the classic phenotypes (*12*). Similarly, the identification of genetic linkages for frontotemporal dementias has shown that the phenotypes of these diseases are more varied than was suspected (*13*). Even Alzheimer's disease, defined by genetic means, has a wider phenotype than was expected on clinicopathological grounds and includes cases that present with spastic paraparesis and without neuritic plaques (*14*).

In some of these cases, we understand part of the reasons behind the phenotypic variability. Some of the variability in the pathological phenotype of *tau*-encoded frontotemporal dementia depends on the precise *tau* mutation (*15*). The polymorphism at codon 129 in the prion gene can alter the phenotype of prion disease when it is in either the cis or the trans configuration with the pathogenic mutation; thus, the expressivity of prion mutations is extremely variable (*16*). Much of the variability in phenotype among individuals with mutations in the same gene, or even among individuals with the same mutation, remains unexplained. A particular type of unexplained variability in the phenotype of mutations is the occurrence of individuals who carry mutations but do not develop disease; in this case, the term "nonpenetrant" is used to label our lack of understanding. The variability observed with apolipoprotein E as a risk modifier for Alzheimer's disease has been germane not only to our understanding of the modifying factors for risk of that disease but also to our concept of how penetrance in general may arise (*17*). In families where APP-encoded Alzheimer's disease is common, the genetic variability in apolipoprotein E modifies the age of onset of disease (*18*). This is a clear demonstration that genetic variability at loci other than the pathogenic locus can epistatically alter disease expressivity. It is likely that other examples of these epistatic interactions will be found to be responsible for both age-at-onset effects and other variations in the phenotypes of neurodegenerative disease. Efforts to influence not only the fundamental genetic abnormality but also the modifying factors will be key for future treatment of neurodegenerative disease, as some of these modifying factors may lead to a delay in onset or to reduced severity of disease.

The Revealing Illusion of Selective Vulnerability

A key issue in the current research in neurodegenerative disease is that of selective vulnerability. Selective vulnerability guides us in our journey to understand neurodegenerative disease from a research standpoint, and it is the major clue for solving the diagnostic puzzle which a patient presents in the clinical setting. Only by considering this selectivity can we compare and contrast the biological mechanisms of these diseases. Each strikes a seemingly select group of neurons. Huntington's disease causes cell death in the caudate and results in chaotic movement. Parkinson's disease destroys cells in the substantia nigra, resulting in rigidity and tremor and preventing initiation of movement. Amyotrophic lateral sclerosis damages the lower motor and pyramidal neurons and causes weakness and spasticity. Alzheimer's disease isolates the hippocampus and parietal lobes and prevents formation of new memory. However, closer inspection reveals that the selective vulnerability is not as absolute as it might appear at first. Patients with Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis can develop dementia, reflecting cortical pathology late in the disease. Patients with Alzheimer's disease frequently develop parkinsonism. Thus, selective vulnerability is not an absolute but reflects the interplay of two characteristics: the first is that each disease process affects populations of neurons to varying degrees along a time line; the second is that the remarkable plasticity of the nervous system allows functional compensation until a large amount of damage has been sustained, after which there may be an apparent catastrophic failure. The result of this interplay of factors is that diseases often give the illusion of striking a single clinical domain at a time, when in fact they have a more global effect that exposes functional systems at different times along that disease's natural history. Much of the disease—in fact, the period in the disease when treatment will ultimately prove critical—probably occurs well before symptoms or signs are manifest. Many examples of this notion of "presymptomatic and preclinical" loss could be given, but two will suffice: individuals carrying the huntingtin mutation have abnormal brain scans years before they exhibit symptoms (*19*), and Parkinson's patients do not manifest movement abnormalities until greater than an estimated 70% of their nigral cells are lost (*20*). This latter fact underlies the asymmetry of the early stages of Parkinson's disease, as first one nigra and then the other loses cells until there are not enough in reserve to cover the loss and the threshold for compensation is overstepped (*21*). However, although the notion of selective vulnerability is oversimplified, it is valuable, not least because the different pathogeneses have distinctive selectivities. For example, many of the polyglutamine diseases share a predilection for the cerebellum (*22*) and lead to ataxia, the α-synucleinopathies have a predilection for the substantia nigra (*23*), and many of the tauopathies involve cortical pyramidal neurons and thus manifest as dementia (*24*). Thus, the apparent selectivities give imperfect but nonetheless valuable insights into the

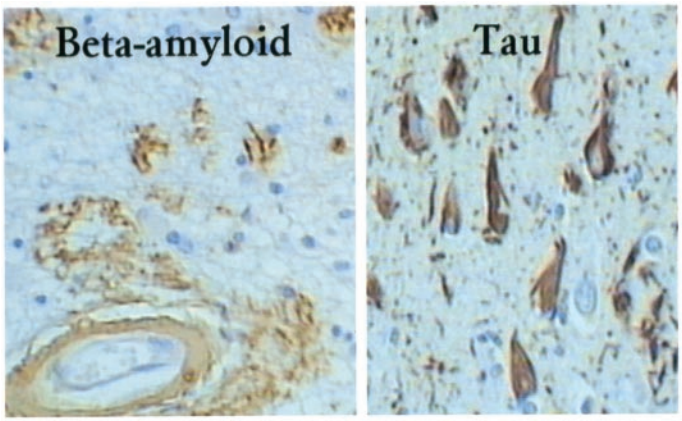

Fig. 3. The major histopathologic hallmarks of Alzheimer's disease include β-amyloid deposits around and within the walls of blood vessels (cerebral amyloid angiopathy) and in brain parenchyma (senile plaques). Neurofibrillary lesions that are immunoreactive for the microtubule-associated protein tau are found within neuronal cell bodies (neurofibrillary tangles) and neuronal processes (neuropil threads).

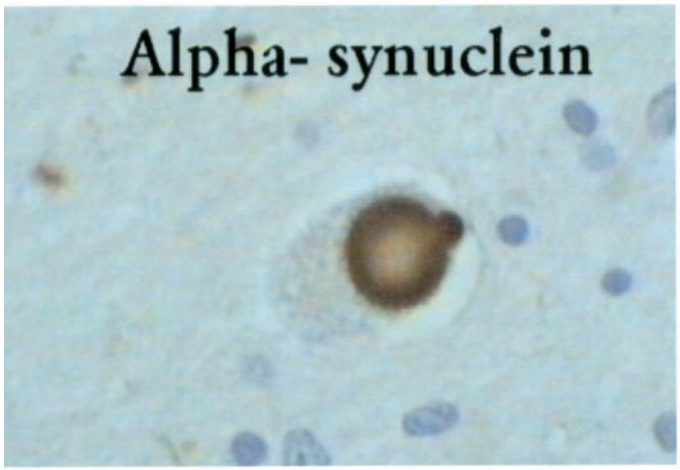

Fig. 4. The hallmark of Parkinson's disease is the Lewy body, an intraneuronal hyaline inclusion that is immunoreactive with antibodies to α-synuclein.

underlying pathogeneses. It will be instructive to study why many polyglutamine diseases primarily strike the cerebellum and why huntingtin mutations are an exception to this rule.

General Categories of Neurodegenerative Disease

A surprising finding is that most autosomal-dominant neurodegenerative diseases fall into two categories and that within these there are pathogenic relationships between different diseases. These two categories are the polyglutamine diseases and the tau- and synucleinopathies. Amyotrophic lateral sclerosis, caused by superoxide dismutase mutations in a few families (*25*), does not obviously fit into this imperfect classification scheme, which we offer as a simple rubric.

Polyglutamine Diseases

The identification of unstable triplet repeat mutations is one of the great discoveries of human genetics. A number of triplet repeat mutations have been shown to be unstable: first, an expanded CGG repeat at the fragile-X chromosome site (*26*), followed by expanded CTG repeats in the myotonic dystrophy gene, which encodes myotonin kinase (*27*), and expanded GAA repeats in frataxin, the gene for Friedreich's ataxia (*28*). These triplet repeat expansion mutations all appear to cause instability in the corresponding mRNA and are thus "loss-of-function" mutations. However, expanded CAG repeat mutations, encoding polyglutamine, have a particular relevance in neurodegeneration in that all cause disease through dominant gain-of-function mechanisms (Table 1). The mechanism of toxicity of the polyglutamine diseases was not clear until transgenic mice bearing a polyglutamine huntingtin-derived construct were shown to have intranuclear polyglutamine inclusions (*9*) (Fig. 1). Examination of pathological tissues subsequently revealed that these intranuclear inclusions, often occurring in the vulnerable neurons, appear to be a constant feature of the many polyglutamine diseases (*29*). The mechanism of pathogenesis of these inclusion bodies is not yet clear; what is clear is that, although the gene containing the mutation may vary, this is largely irrelevant to the disease process. Many of these diseases show a distinct predilection for the cerebellum, and some also affect sensory neurons (see Table 1 for exceptions).

Historically, the dominant ataxias have been extremely difficult to differentially diagnose (*11*). We can now see that the reason for the difficulty is that they are largely caused by similar mutations in different genes. Identification of the CAG repeat mutations allows these diseases to be straightforwardly diagnosed by molecular means. Once treatments for these diseases are developed, it is likely that similar strategies will work for all of them, which makes differentiation between them less important than was believed in the premolecular era.

Tauopathies and Synucleinopathies

Tangles (largely consisting of the protein tau) and Lewy bodies (largely consisting of the protein α-synuclein) are found in many neurodegenerative diseases. Tangles are found in frontotemporal dementia with parkinsonism (Fig. 2), Alzheimer's disease (Fig. 3), progressive supranuclear palsy, Guam disease, and some forms of prion disease (*30*). Lewy bodies are found in Parkinson's disease (Fig. 4), some forms of Alzheimer's disease, some forms of prion disease, and Lewy body dementia (*31*). These inclusion bodies are usually found in neurons, although both may be found in glia (*32*). The relationship between diagnostic category and types of inclusions is variable from disease to disease and, in the absence of an understanding of these diseases, can appear as a list of arbitrary diagnoses. However, with the advent of molecular genetics we are beginning to understand these pathologies as processes with initiating lesions. For example, autosomal-dominant Alzheimer's disease can be caused by mutations in the APP, presenilin 1 (PS1), or presenilin 2 (PS2) gene. Mutations at all three of these loci lead to

Table 1. Autosomal dominant primary neurodegenerative diseases. Ch, chromosome; PrP, prion protein; T, tangles; LB, Lewy bodies; +, is present or exists; AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; SOD, superoxide dismutase.

Disease	Linkage	Gene	Mutations	Pathology	Transgenic (comment)	Ref.
Prion	Ch20	Prion	Mainly missense	PrP plaques, sometimes T or LB; classically associated with spongiform changes	+ (no T or LB)	(*36*)
AD	Ch21	APP	Missense around Aβ, increase Aβ42	Amyloid plaques and T, may see LB	+ (no T or LB)	(*37*)
	Ch14	PS1	Mainly missense, increase Aβ42	Amyloid plaques and T	+ (no plaques T or LB)	(*38*)
	Ch1	PS2	Missense, increase Aβ42	Amyloid plaques and T	+ (no plaques T or LB)	(*39*)
PD	Ch4q	α-synuclein	Missense	LB	Not reported	(*33*)
	Ch2	Not identified	Not known	LB (and T?)	Not reported	(*40*)
	Ch4p	Not identified	Not known	LB	Not reported	(*41*)
FTD	Ch17	Tau	Missense and splice	T, sometimes with "unusual periodicity"	Not reported	(*15*)
	Ch3	Not identified	Not known	Not reported	Not reported	(*42*)
ALS	Ch21	SOD	Mainly missense	Lewy-like bodies	+ (motor neuron disease, inclusions, cell loss)	(*43*)
SBMA*	X	AR	Polyglutamine	Nuclear inclusions	+ (no phenotype)	(*44*)
HD	Ch4	Huntingtin	Polyglutamine	Nuclear inclusions	+ (inclusions, movement disorder, cell loss)	(*45*)
DRPLA	Ch12	Atrophin 1	Polyglutamine	Nuclear inclusions	Not reported	(*46*)
SCA1	Ch6	Ataxin 1	Polyglutamine	Nuclear inclusions	+ (ataxic, inclusions, cell loss)	(*47*)
SCA2	Ch12	Ataxin 2	Polyglutamine	Not reported	Not reported	(*48*)
SCA3/MJD	Ch14	Ataxin 3	Polyglutamine	Nuclear inclusions	+ (ataxic, cerebellar atrophy)	(*49*)
SCA4	Ch16	Not identified	Not known	Not reported	Not reported	(*50*)
SCA5	Ch11	Not identified	Not known	Not reported	Not reported	(*51*)
SCA6	Ch19	CACNL1A4	Polyglutamine	Not reported	Not reported	(*52*)
SCA7	Ch3	SCA7	Polyglutamine	Nuclear inclusions	Not reported	(*53*)

*SBMA is technically not autosomal dominant but it is probably dominant in its cellular mode of action.

increased production of the amyloidogenic peptide Aβ42. Thus, this peptide is likely to be the initiating factor in these cases of Alzheimer's disease. Although familial cases of Alzheimer's disease are rare, the molecular basis of the disease has important lessons about the etiology of other types of Alzheimer's disease. It is parsimonious to suppose that Aβ is involved in the initiation of all cases of this disorder. Tangles are an invariant pathology and Lewy bodies are a frequent pathology in Alzheimer's disease. Both lesions occur in cases of disease with APP mutations (*31*). Thus, when these lesions occur in Alzheimer's disease, it must be a consequence of the production of Aβ. Similarly, in the Indiana prion kindred, the pathogenic mutation is in the prion gene, yet both tangles and Lewy bodies occur (*32*). In this case also, therefore, the tau and α-synuclein pathologies are secondary events to prion abnormalities. Mutations in tau lead to tangles and dementia in frontotemporal dementia (*15*); mutations in α-synuclein lead to the occurrence of Lewy bodies and Parkinson's disease (*33*). The fact that mutations in either tau or α-synuclein can lead to their cognate pathologies as primary events suggests that, when these pathologies occur as secondary events, they are close to the pathway to cell death.

It is tempting to speculate, but by no means certain, that there are relatively few ways a neuron can respond to chronic stress brought about, for example, by increased quantities of Aβ: tangles or Lewy bodies may represent two of the hallmarks of cellular reaction. It is clear that some neurons are more tangle-prone and others are more Lewy body–prone. This is an important clue as we attempt to unveil the meaning of apparent selective vulnerability discussed above. Finally, it is interesting that the function of tau relates to microtubule assembly, and synucleins may be involved with neurofilaments because they co-localize in both Lewy bodies and transfected cells (*34*). Thus, it is possible that both pathologies relate to alternative responses of the cytoskeleton to chronic stress. It is not clear whether tangles or Lewy bodies represent a cellular attempt to maintain function or to repair damage or whether they simply represent the appearance of a neuron as it is dying slowly. Are tangles or Lewy bodies an attempt at buttressing the cell to keep it from losing morphology related to function? Or are they damaging the neuron? In any case, they certainly represent an intermediary between a normal and a dead neuron. Mutations in tau and synuclein can be regarded as revealing the neuronal populations that are most susceptible to these pathways to cell death. Further understanding of these proteins will be germane to teaching us the meaning of apparent selective vulnerability as discussed in the previous sections. In Alzheimer's disease or in prion disease, this underlying anatomy of vulnerability is overlaid and distorted by the anatomy of the primary pathology.

Conclusions

The past 10 years have seen much progress toward understanding the etiologies of neurodegeneration. The classifications of diseases and disease mechanisms suggested here are intended to aid understanding and not to mask the profound deficits in our knowledge. We still have little understanding of how or why neurons die, and this remains a fundamentally difficult area of study. The genetic models of disease now available offer the first hope in our current golden era of neuroscience in which we strive to address this issue. So far, the progress we have made in understanding has not yielded any lasting benefits in terms of treatment or avoidance of these diseases except through the unsatisfactory means of genetic counseling. Pharmacologic treatments for these diseases remain based on neurotransmitter strategies—on palliative rather than curative therapy. Hopefully, the understanding that molecular biology has brought, and the accompanying tools, particularly animal models of these diseases, will soon influence their treatment (*35*). Only by considering neurodegeneration as a biological process will we be able to intervene.

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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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