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REVIEW ARTICLE
Complex Genetics of Amyotrophic Lateral Sclerosis

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Introduction

Amyotrophic lateral sclerosis (ALS) is a common adult-onset neurodegenerative disease leading to paralysis and death typically within 2–5 years of diagnosis. Approximately 10% of ALS cases are inherited, with the remainder of cases being sporadic in origin. This distribution of familial and sporadic disease is similar to other adult-onset neurodegenerative diseases, such as Parkinson disease and Alzheimer disease (see, e.g., Przedborski et al. 2003). The annual incidence of ALS is 1–2 per 100,000, leading to a lifetime risk of developing ALS of 1 per 800 (Cleveland and Rothstein 2001). Except for atypical variants of ALS, the familial form of disease is clinically indistinguishable from the sporadic cases (see, e.g., Hand and Rouleau 2002). There is a slight male-to-female preponderance (1.3:1–1.6:1) that appears to be decreasing (Nelson 1995). Similarly, some epidemiologic studies suggest that the overall incidence of ALS is rising (Riggs and Schochet 1992).

Pathologic features of ALS include loss of motor neurons in the spinal ventral horns, most brainstem motor nuclei, and motor cortex. Interestingly, Onuf's nucleus, which controls urethral and sphincter function, and motor neurons in the oculomotor, trochlear, and abducens cranial nerve nuclei are spared. Histopathological features include ubiquitinated inclusions in lower motor neurons and axonal swellings that are thought to contain disarrayed neurofilaments (Ince 2000). It is thought that the process of ALS begins with an initiation or triggering event, followed by the propagation of motor neuron demise up and down the spinal cord (see Armon [2003] for a detailed description of this hypothesis). The exact mechanisms underlying the selective motor neuron degeneration in ALS remain elusive, but experimental evidence implicates many potential factors, including oxidative damage, excitotoxicity, apoptosis, abnormal neurofilament function, defects in axonal transport, aberrant protein processing and degradation, increased inflammation, and mitochondrial dysfunction (Cleveland and Rothstein 2001; Bruijn et al. 2004). Although hypotheses abound, it is difficult to determine which of these processes is most important in triggering cell dysfunction and death and what determines the selective vulnerability of motor neurons.

The World Federation of Neurology diagnostic criteria for ALS include the presence of upper and lower motor neuron degeneration with a progressive phenotype in the absence of evidence that indicates other diseases (Revised Criteria for the Diagnosis of ALS Web site). Typically, there is no cognitive impairment or loss of sensory nerve function, although there are ALS variants that include these symptoms. Upper motor neuron signs include clonus and hyperreflexia, and lower motor neuron signs include atrophy, weakness, and fasciculations. ALS diagnoses are categorized as "clinically definite," "clinically probable," and "clinically possible," on the basis of the number and location of the cardinal signs. The diagnosis of ALS is often one of excluding other diseases and waiting for the disease to progress to meet the full diagnostic criteria. A variety of studies are often performed to exclude syndromes that have symptoms that mimic ALS, including postpoliomyelitis syndrome; multifocal motor neuropathy; endocrinopathies, especially hyperparathyroid or hyperthyroid states; lead intoxication; infections; and paraneoplastic syndromes (Motor Syndromes Web site; Revised Criteria for the Diagnosis of ALS Web site).

Genetics of ALS

There is an obvious genetic component in only ~10% of ALS cases; these cases exhibit significant phenotypic and genetic heterogeneity. At least 12 genetic loci, with dominant, recessive, and X-linked patterns of inheritance, have been associated with familial ALS and related ALS syndromes (table 1). Although specific genetic alterations do not appear to cause sporadic ALS, a number of potential susceptibility and modifier loci have been identified (table 2). I will discuss the genes and loci that have been implicated in the causation and/or susceptibility of both sporadic and familial ALS.

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Adult-Onset ALS Genes

There are at least six dominantly inherited, adult-onset ALS genes (table 1); however, only the gene for ALS1 (MIM 105400)—copper-zinc superoxide dismutase (*SOD1* [MIM 147450]), on chromosome 21q22.1—has been identified. Mutations in *SOD1* account for ~20% of familial ALS (Rosen et al. 1993). Identifying the genes causing the remaining 80% of familial ALS cases will be challenging, since many of the remaining loci appear to segregate in individual families.

Cytoplasmic Copper-Zinc Superoxide Dismutase

The first ALS-associated gene to be identified was the *SOD1* gene, on human chromosome 21 (Rosen et al. 1993). SOD1 is a 153–amino acid protein, containing one copper and one zinc, that is predominantly located in the cytoplasm as a homodimer. SOD1 detoxifies superoxide, creating oxygen and hydrogen peroxide, which can then be cleared by catalase and glutathione peroxidase. Copper is required for SOD1 activity, whereas zinc is thought to stabilize the protein structure. To date, >100 unique mutations in *SOD1* have been identified (Andersen et al. 2003; alsod.org Web site). The majority of mutations in *SOD1* are missense mutations, with a small percentage of deletion and insertion mutations that result in prematurely terminated SOD1 polypeptides. The expression of a mutant SOD1 polypeptide, with or without residual SOD1 activity, is necessary to cause the ALS phenotype, suggesting a dominant negative mechanism rather than one of haploinsufficiency. Even after >10 years of investigation, the exact mechanism of *SOD1*-mediated pathogenesis remains uncertain.

There is considerable phenotypic variation in *SOD1*-mediated ALS, including age at onset and severity and rate of decline; however, this can only partly be explained by the spectrum of mutations. Because clinical variation occurs among patients of the same *SOD1* genotype and members of the same family (Andersen et al. 1997), it is apparent that the phenotype is modified by other genetic and/or environmental factors. One example is the D90A *SOD1* mutation, which is recessive in some genetic backgrounds but dominant in others (Al-Chalabi et al. 1998). The recessive D90A *SOD1* mutations share a common founder haplotype, suggesting that there is a linked *cis*-acting protective factor that makes this mutation recessive in this specific genetic background (Parton et al. 2002). Genetic background also affects other forms of *SOD1*-mediated ALS. Although it causes one of the most severe forms of the disease, with death typically occurring <18 mo after diagnosis, the penetrance of the A4V *SOD1* mutation is only 91% (Cudkowicz et al. 1997). Similarly, the A89V *SOD1* mutation shows incomplete penetrance and variable age at onset (Rezania et al. 2003). The variable penetrance and age at onset caused by *SOD1* mutations can be mimicked in transgenic mouse models of ALS, by varying the mouse strain on which a mutation is carried (Kunst et al. 2000).

Transgenic mice that develop ALS-like phenotypes have been constructed with at least nine forms of mutant human *SOD1*: A4V, G93A, G85R, G37R, D90A, L126Z, H46R/H48Q, H46R/H48Q/H63G/H120G, and G127insTGGG (Dal Canto and Gurney 1995; Wong et al. 1995; Bruijn et al. 1997*b*; Brannstrom et al. 1998; Deng et al. 1999; Wang et al. 2002, 2003; Jonsson et al. 2004). Another mouse model of ALS was generated using the mouse gene with a G86R mutation that corresponds to the human G85R mutation (Ripps et al. 1995). Transgenic rats, carrying G93A or H46R *SOD1,* also develop ALS-like phenotypes (Nagai et al. 2001; Howland et al. 2002). Although each model of ALS is phenotypically consistent for a given mutation, they vary in their age at onset, disease progression, and certain histopathological features, mimicking the diversity of phenotypes observed in human ALS. In the mouse and rat models of ALS, the mutant *SOD1* allele is expressed in the presence of the two endogenous copies of the wild-type *SOD1* gene; thus, the mice and rats have either normal or increased SOD1 activity levels, depending on the activity of the *SOD1* mutant expressed. However, *SOD1* overexpression is not the cause of ALS, since mice overexpressing wild-type human *SOD1* do not develop an ALS-like phenotype (Dal Canto and Gurney 1995; Wong et al. 1995). In G93A *SOD1* mice (Jaarsma et al. 2000) but not in G85R *SOD1* mice (Bruijn et al. 1998), overexpression of wild-type *SOD1* accelerates disease onset and progression. Lack of *SOD1* is also not sufficient to cause ALS in mice. Mice with *SOD1* null alleles have a number of interesting phenotypes but do not develop symptoms of ALS (Reaume et al. 1996). Together, these results suggest that mutations in *SOD1* cause a novel toxic gain of function that is lethal to motor neurons.

Although ALS is predominantly a disease of motor neuron loss, neuronal expression of mutant *SOD1* is not sufficient to cause ALS. Overexpression of mutant *SOD1* in neurons or astrocytes alone does not cause ALS or motor neuron death in transgenic mice (Gong et al. 2000; Pramatarova et al. 2001; Lino et al. 2002). Studies in chimeric mice, created from mixtures of normal and mutant *SOD1*-expressing cells, reveal that toxicity to motor neurons requires damage from mutant SOD1 acting from within nonneuronal cells (Clement et al. 2003). In the chimeras, motor neurons expressing only wild-type *SOD1* develop ALS pathology when adjacent nonneuronal cells express mutant *SOD1*. Furthermore, nonneuronal cells expressing only wild-type *SOD1* delay degeneration and extend survival of nearby

Table 1

Familial ALS Loci

Disease	Type(s) of Inheritance	MIM Number		Gene	Onset	Chromosome	Interval	Size (Mb)	Reference(s)
		Disease	Gene						
ALS1	Dominant and recessive (D90A)	105400	147450	*SOD1*	Adult	21q22.1			Rosen et al. 1993; Al-Chalabi et al. 1998
ALS2	Recessive	205100	606352	Alsin *(ALS2)*	Juvenile	2q33			Hadano et al. 2001; Yang et al. 2001
ALS3	Dominant	606640			Adult	18q21	D18S846–D18S1109	8	Hand et al. 2002; Sapp et al. 2003
ALS4	Dominant	602433	608465	*SETX*	Juvenile	9q34			Chen et al. 2004
ALS5	Recessive	602099			Juvenile	15q15.1-q21.1			Hentati et al. 1998
ALS6	Dominant	608030			Adult	16q12	D16S339–D16S3032	4.2	Abalkhail et al. 2003; Ruddy et al. 2003; Sapp et al. 2003
ALS7	Dominant	608031			Adult	20ptel-p13	Telomere–D20S199	1	Sapp et al. 2003
ALS8	Dominant	608627	605704	*VAPB*	Adult	20q13.33			Nishimura et al. 2004*a*, 2004*b*
ALS-FTD	Dominant	105550			Adult	9q21-22	D9S301–D9S167	17	Hosler et al. 2000
ALS X	Dominant				Adult	Xp11-q12			Siddique et al. 1998*a*
ALS with dementia, Parkinsonism	Dominant	600274	157140	*MAPT*	Adult	17q21			Clark et al. 1998; Hutton et al. 1998
Progressive LMN disease	Dominant	601143	607641	*DCTN1*	Adult	2p13			Puls et al. 2003

motor neurons expressing mutant *SOD1* in these chimeric mice (Clement et al. 2003). Because ALS pathology is seen in the chimeras but not in the mice with mutant *SOD1* overexpression in the neurons or astrocytes alone, it appears that expression of mutant *SOD1* in both cell types is necessary to initiate the disease process. From there, *SOD1* expression from nonneuronal cells modulates disease progression, with the effect being dependent on the form of *SOD1* expressed.

Although the toxic gain of function of mutant SOD1 has not yet been elucidated, there are numerous hypotheses of SOD1-mediated toxicity. These have been recently and expertly reviewed by others (e.g., Cleveland and Rothstein 2001; Hand and Rouleau 2002; Heath and Shaw 2002; McGeer and McGeer 2002; Ischiropoulos and Beckman 2003; Bruijn et al. 2004); however, several major hypotheses, including oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammation, and aggregation, will be summarized here. These mechanisms are not mutually exclusive, and the complicated pathogenic process of ALS may include features of all of them.

Because of its role of preventing cellular damage from superoxide, one of the first hypotheses of SOD1-mediated toxicity was copper-mediated oxidative and peroxidative damage by a promiscuous mutant SOD1 enzyme. In support of this, there is evidence of lipid peroxidation and nitrotyrosine formation in both transgenic models and human patients with ALS (Dal Canto and Gurney 1995; Beal et al. 1997). Some mutations in SOD1 make the protein more susceptible to forming a zinc-deficient variant (Crow et al. 1997; Estévez et al. 1999). The copper in the zinc-deficient SOD1 becomes more accessible, allowing SOD1 to participate in a number of deleterious reactions, including oxidizing endogenous antioxidants such as ascorbate, transferring electrons to oxygen to produce superoxide, and creating peroxynitrite from nitric oxide (Estévez et al. 1998, 1999). In vitro experiments by Estévez et al. (1999) have shown that zinc-deficient SOD1 kills motor neurons through a peroxynitrite dependent mechanism. In support of this mechanism acting in vivo, a specific inhibitor of neuronal nitric oxide synthase (AR-R 17,477) was able to delay onset in the G93A *SOD1* mice (Facchinetti et al. 1999). However, G93A *SOD1* mice that also lack the neuronal nitric oxide synthase gene develop ALS without a delay in disease onset (Facchinetti et al. 1999), making the role of neuronal nitric oxide and its by-products uncertain.

Additional experiments raise questions about the copper-dependent hypothesis of SOD1-mediated toxicity. SOD1 that has been engineered not to bind copper by mutating the histidine residues required for copper binding (H46R/H48Q/H63G/H120G) causes ALS in transgenic mice (Wang et al. 2003). Furthermore, knocking out the gene for the copper chaperone (*CCS* [MIM 603864]) that inserts copper into SOD1 has no effect on the development of ALS in transgenic mice (Subramaniam et al. 2002). However, even in the *CCS* null mice, there is residual SOD1 activity; therefore, this mechanism cannot be ruled out entirely.

Substantial evidence links mutations in *SOD1* to mitochondrial dysfunction. Previously, SOD1 was considered an exclusively cytoplasmic protein; however, recent studies show that ~1%–2% of SOD1 is located in the intermembrane space of mitochondria (Mattiazzi et al. 2002). Some researchers postulate that it is this mitochondrial pool of mutant SOD1 that triggers disease. One of the first pathological changes in G93A and G37R *SOD1* transgenic mice is the development of large membrane-bound vacuoles derived from degenerating mitochondria in motor neurons (Dal Canto and Gurney 1995; Wong et al. 1995). G93A *SOD1* mice also develop metabolic defects in mitochondrial energy generation, in both spinal cord and motor regions of the brain (Browne et al. 1998; Jung et al. 2002; Mattiazzi et al. 2002). Kong and Xu (1998) found evidence of a burst of degenerating mitochondria within motor neurons immediately prior to symptom onset in G93A *SOD1* mice. Recently, Liu et al. (2004) found that mutant SOD1—but not wild-type SOD1—is selectively and aberrantly recruited to the cytoplasmic face of mitochondria only in tissues affected by ALS. This recruitment was independent of enzymatic activity and the copper chaperone for SOD1. Although some mutant SOD1 was correctly imported into the intermembrane space, covalently damaged adducts of mutant SOD1 accumulated on the cytoplasmic face of mitochondria in spinal cord. This tissue-specific recruitment suggests that mitochondrial abnormalities may be involved in disease initiation.

One observation in both sporadic and familial ALS is the selective loss of the glial glutamate transporter EAAT2 (MIM 600300) (Rothstein et al. 1995; Howland et al. 2002) in some but not all patients and animal models. EAAT2 (GLT1 in rodents) is responsible for clearing 90% of the glutamate near motor neurons (Cleveland and Rothstein 2001). Glutamate-mediated excitotoxicity is thought to occur from the repetitive firing or elevation of intracellular calcium by calcium-permeable glutamate receptors. A role of glutamate-mediated excitotoxicity in both sporadic and familial disease is bolstered by the efficacy of riluzole, a compound that antagonizes glutamate excitotoxicity, which is effective in slowing disease in both mice and humans (Gurney et al. 1998; Miller et al. 2003).

There is growing evidence that inflammation and microglial activation play a role in the pathogenesis of ALS (McGeer and McGeer 2002). Reactive microglia and astrocytes accumulate in the areas surrounding degenerating motor neurons (reviewed by McGeer and McGeer 2002). Obal et al. (2001) demonstrated that intra-

peritoneal injections of immunoglobulin G from human patients with ALS caused the recruitment of activated microglia to the ventral horn of the spinal cord of mice. Numerous biochemical markers of inflammation are observed in ALS spinal cord tissue. Both caspase 1 and cyclooxygenase 2 are increased in spinal cord of mutant *SOD1* transgenic mice (McGeer and McGeer 2002; Bruijn et al. 2004). These enzymes generate mature interleukin-1β and prostaglandin E2, respectively. Both of these diffusible compounds are proinflammatory and can activate cell death. Supporting their role in ALS, inhibitors of caspases and cyclooxygenase 2 have been shown to prolong survival in G93A *SOD1* transgenic mice (Li et al. 2000; Klivenyi et al. 2004). Other markers of inflammation are also increased in ALS. For example, tumor necrosis factor α, which can activate apoptosis, is up-regulated in the spinal cord of mutant G93A *SOD1* mice (Elliott 2001). Taken together, these data suggest that mutations in *SOD1* directly or indirectly induce a variety of inflammatory responses that may play a role in the selective death of motor neurons.

A final, and perhaps favored, potential mechanism of SOD1-mediated toxicity is aggregation of mutant SOD1. Aggregates of misfolded mutant SOD1 protein in affected motor regions are a common pathologic feature of mutant *SOD1* mouse models of ALS (Dal Canto and Gurney 1995; Bruijn et al. 1997*a,* 1998; Wang et al. 2002; Jonsson et al. 2004). The effect of SOD1 aggregation may be analogous to the effects of aggregates of mutant proteins in other neurodegenerative diseases, such as Alzheimer disease, Huntington disease, and Parkinson disease, in which aggregation of mutated proteins causes oxidative stress, depletes important cellular proteins, and disrupts proteasome and chaperone function. In vitro experiments have linked SOD1 aggregation to apoptotic cell death (Durham et al. 1997; Roy et al. 1998). Watanabe et al. (2001) found additional proteins in SOD1 aggregates, including CCS; ubiquitin; neurofilaments; glial fibrillary acidic protein (GFAP [MIM 137780]); two neuronal glutamate transporters, GLAST (MIM 600111) and EAAC1 (MIM 133550); and proteins involved in chaperone and proteasome functions. Overexpression of chaperones can suppress mutant SOD1 aggregation, protect neuronal function, and enhance survival of motor neurons in culture (Takeuchi et al. 2002). Arimoclomol, an inducer of heat shock proteins, increased life span by 22% in the G93A *SOD1* mice (Kieran et al. 2004), further supporting the hypothesis that aggregated SOD1 is toxic to motor neurons.

Although SOD1 is ubiquitously expressed, aggregates of mutant SOD1 are found only within the nervous system of mutant *SOD1* transgenic mice, despite the very high concentrations of mutant SOD1 in other organs, higher in liver or kidney than in spinal cord (Wang et al. 2002; Puttaparthi et al. 2003). Puttaparthi et al. (2003) used an organotypic spinal cord slice culture system from G93A *SOD1* mice to show that proteasome-mediated protein degradation represents the major clearance mechanism for SOD1 aggregates in spinal cord. It is interesting that proteasome activity decreases most prominently in spinal cord during aging, and this decrease correlates with accumulation and aggregation of mutant SOD1 in vivo (Puttaparthi et al. 2003). These observations may help to explain the selective vulnerability of motor neurons to mutant SOD1 with increased age.

Juvenile-Onset ALS Genes

There are three loci for juvenile onset ALS (table 1): one is autosomal dominant, on chromosome 9q34 (*ALS4* [MIM 602433]) (Chen et al. 2004); and two are autosomal recessive, on chromosomes 2q33 (*ALS2* [MIM 205100]) (Hadano et al. 2001; Yang et al. 2001) and 15q15.1-q21.1 (*ALS5* [MIM 602099]) (Hentati et al. 1998). In general, survival time from diagnosis is longer and disease progression slower in the juvenile-onset cases. The chromosome 2 and chromosome 9 genes have been identified, whereas the chromosome 15 locus remains to be identified.

ALS2: Alsin

Two groups (Hadano et al. 2001; Yang et al. 2001) identified the chromosome 2 recessive ALS gene known as "alsin" or *ALS2* (MIM 606352). Alsin/*ALS2* is alternatively spliced to produce a long and a short transcript. It was originally hypothesized that deletions affecting both transcripts result in ALS2, whereas homozygous deletions affecting just the long transcript cause a related disease, juvenile primary lateral sclerosis (Hadano et al. 2001; Yang et al. 2001). However, Eymard-Pierre et al. (2002) found that mutations in alsin/*ALS2* could also cause infantile-onset ascending hereditary spastic paralysis (IAHSP), with no overt genotype-phenotype correlation.

Alsin/ALS2 is an 184-kDa protein with three putative guanine-nucleotide-exchange factor (GEF) domains. The function of alsin/ALS2 is not yet well understood. Alsin/ALS2, which has Rab5 activity (Otomo et al. 2003), can act as a guanine nucleotide exchange factor for Rac1 (Topp et al. 2004) and appears to be important for endosomal dynamics (Kunita et al. 2004). At least two groups have created *alsin/ALS2* knockout mice (Kriz et al. 2003; Cai et al. 2003); however, no major phenotypes consistent with ALS or other motor neuron disease have yet been described. It is interesting that Kanekura et al. (2004) recently discovered that the long isoform of alsin/ALS2 specifically binds to mutant—but not to wild-type—SOD1, via its RhoGEF domain. Expression of the

long isoform of alsin/ALS2 protected motor neurons in vitro from mutant SOD1-mediated toxicity. The physical interactions between mutant SOD1 and alsin/ALS2 may link the motor neuron-specific pathways of pathogenesis in these two forms of familial ALS.

ALS4: Senataxin

The *ALS4* locus, mapped to chromosome 9q34, was originally identified in a single large family with autosomal dominant juvenile ALS. This family was unusual, because life expectancy was normal, although the clinical criteria were sufficient to diagnose ALS. Other motor neuron disorders, including distal spinal muscular atrophy or spinal Charcot-Marie-Tooth syndrome, have also been linked to this locus (De Jonghe et al. 2002), but later clinical re-examination of these families resulted in ALS diagnoses (Chen et al. 2004). Chen et al. (2004) identified missense mutations in the senataxin (*SETX* [MIM 608465]) gene in three families with autosomal dominant juvenile ALS. Each family had a distinct mutation—L389S, R2136H, and T3I—in the *SETX* gene. Senataxin is a large protein with a superfamily I DNA/RNA helicase domain (Chen et al. 2004). The majority of the protein appears novel, with no domain conservation or homology to other proteins for much of its length (Chen et al. 2004). The exact function of senataxin is not known, but DNA/RNA helicases are involved in DNA repair, replication, recombination, transcription, RNA processing, transcript stability, and the initiation of translation. Recessive loss-of-function mutations in *SETX* are associated with ataxia-oculomotor apraxia type 2 (Moreira et al. 2004). Ataxia-oculomotor apraxia is a heterogeneous disorder characterized by cerebellar ataxia/atrophy, oculomotor apraxia, loss of reflexes, late peripheral neuropathy, and immunodeficiency. The phenotypic differences between these disorders and their distinct patterns of inheritance suggest that the dominant *ALS4* mutations cause a toxic gain of function, resulting in a motor neuron–specific phenotype, whereas the recessive loss-of-function mutations cause a pleiotropic phenotype.

Atypical ALS

The symptoms of ALS can occasionally occur together with Parkinson disease and dementia or frontotemporal dementia (FTD [MIM 600274]) alone. FTD is a neurodegenerative disorder involving degeneration of the frontal and temporal cortices, accompanied by dementia. Hosler et al. (2000) identified five families with autosomal dominant ALS and FTD (ALS-FTD [MIM 105550]). The causative gene was mapped to a 17-cM interval between D9S301 and D9S167 on chromosome 9q21 (Hosler et al. 2000). The ALS-FTD locus is associated with a range of phenotypes, and not all patients develop all symptoms of ALS and FTD, suggesting that the phenotype can be modulated by other genetic or environmental influences. Although Hosler et al. (2000) did not find any evidence for ALS-FTD genes on other chromosomes, Ostojic et al. (2003) recently identified a Swedish family with ALS-FTD without linkage to this locus, suggesting that additional ALS-FTD loci remain to be identified. Prudlo et al. (2004) identified a single patient with ALS-FTD and a chromosomal translocation, t(18;21)(q23;q22), that may be associated with the disease. Because this is an isolated case, it is difficult to predict whether this balanced translocation is incidental or associated with disease. In similar studies, Meyer et al. (2003) demonstrated that patients with sporadic ALS have, in general, a higher rate of constitutional chromosomal rearrangement than does the general population, but these studies have not been verified with a larger patient population. If causally related to disease, these unique translocations would provide a valuable resource for the identification of additional ALS causative genes.

As described above, the symptoms of ALS can occasionally occur together with Parkinson disease and dementia. Mutations in the microtubule-associated protein tau (*MAPT* [MIM 157140]) gene are associated with FTD with Parkinson disease, with ALS symptoms sometimes associated with the phenotype (Clark et al. 1998; Hutton et al. 1998). The mutant tau, which is encoded by the *MAPT* gene, forms insoluble aggregates and filamentous inclusions that are associated with neurodegeneration. Not all individuals with symptoms of familial ALS with FTD and Parkinson disease have *MAPT* mutations (Kowalska et al. 2003; Wilhelmsen et al. 2004), suggesting that, as with ALS and ALS-FTD, additional genes causing this constellation of symptoms remain to be identified.

Puls et al. (2003) characterized a family with a disorder related to ALS that had a progressive, autosomal dominant form of lower motor neuron disease without sensory symptoms (MIM 607641). A single base-pair change in the dynactin (*DCTN1* [MIM 601143]) gene, causing a G59S mutation in a single North American family, was identified. The G59S mutation is located in a highly conserved domain that binds to microtubules. The interaction of dynactin with dynein is thought to be required for the retrograde axonal transport of vesicles and organelles. Impaired axonal transport in motor neurons has been proposed as a mechanism for neuronal degeneration in motor neuron disease.

Genetics of Sporadic ALS

Glutamate Transporters and Receptors

As described above, suppressed expression of the glial glutamate transporter *EAAT2* occurs in ~60% of patients with sporadic ALS (Rothstein et al. 1995), implicating

Table 2

Human Susceptibility and Modifier Loci

Gene	MIM Number	Chromosome	Variant	Association	Reference
NEFH	162230	22q12.1-q13.1	KSP deletions	Sporadic	Al-Chalabi et al. 1999
VEGF	192240	6p12	Promoter SNPs	Sporadic	Lambrechts et al. 2003
SMN1	600354	5q12.2-q13.3	Copy number	Sporadic	Corcia et al. 2002
SMN2	601627	5q12.2-q13.3	Copy number	Sporadic	Veldink et al. 2001
CNTF	118945	11q12.2	Null allele	Familial	Giess et al. 2002
ApoE ε4	107741	19q13.2	ε4 genotype	Sporadic	Drory et al. 2001
EAAT2	600300	11p13-p12	Decreased expression	Familial, sporadic	Rothstein et al. 1995
GluR2	138247	4q32-q33	Altered RNA editing	Sporadic	Kawahara et al. 2004

glutamate excitotoxicity in the pathogenesis of sporadic ALS. The mechanism of the selective loss of EAAT2 in affected spinal cord regions may be the aberrant processing of the *EAAT2* transcript (Lin et al. 1998), but ALS-specific aberrant splicing events have not been observed by all investigators (e.g., Flowers et al. 2001). Additional evidence for a role of glutamate excitotoxicity in ALS comes from recent work by Kawahara et al. (2004). They investigated the RNA editing of the *GluR2* (MIM 138247) subunit of the glutamate AMPA receptor in patients with sporadic ALS and in controls. Under normal conditions, RNA editing changes a glutamine to arginine in virtually 100% of transcripts, rendering the channel impermeable to calcium. In RNA-specific adenosine deaminase (*ADAR2* [MIM 601218]) null mice, defects in the *GluR2* editing process lead to premature neuronal death that can be rescued by restoring normal RNA editing function (Higuchi et al. 2000). *GluR2* editing was observed to be defective in spinal motor neurons from patients with sporadic ALS but not in Purkinje cells, which were isolated by laser capture microdissection. Control samples showed 100% editing in all analyzed cells, suggesting that there is an ALS-specific motor neuron defect in *GluR2* RNA editing that may be involved in the process of motor neuron death (Kawahara et al. 2004).

Neurofilaments

The abnormal accumulation of neurofilaments in the cell bodies and proximal axons of motor neurons is a hallmark of the pathogenesis of ALS (Rouleau et al. 1996). There is evidence that mutations in the neurofilament heavy (*NF-H,* or *NEFH* [MIM 162230]) gene are associated with a small fraction of ALS in a subset of cases and may predispose to disease development (Al-Chalabi et al. 1999). These mutations do not segregate with disease in familial ALS (Cleveland 1999) and, thus, are either not directly causative or act at low penetrance. However, genetic manipulations of neurofilament subunit expression in transgenic mice have confirmed the importance of neurofilaments in motor neuron integrity. First, the overexpression of NF-H, NF-L, and peripherin, as well as the disrupted activity of the microtubule-motor dynein, all cause development of paralytic phenotypes associated with motor neuron degeneration and muscle denervation (reviewed by Lariviere and Julien [2004]). Other alterations in neurofilament gene expression are beneficial in the mutant *SOD1* mouse models of ALS. For example, disease development in the G85R *SOD1* mice is delayed on an *NF-L* null background (Williamson et al. 1998). NF-L is the major neurofilament subunit required for filament assembly; thus, in *NF-L* null mice, NF-M and NF-H are not assembled and transported correctly, resulting in reduced levels in axons but increased levels in motor neuron cell bodies. This may explain why the overexpression of human NF-H increased the mean life span of the G37R *SOD1* mice by 65% (Couillard-Després et al. 1998).

Vascular Endothelial Growth Factor

Lambrechts et al. (2003) have shown that vascular endothelial growth factor (*VEGF* [MIM 192240]) is a modifier of ALS in both mice and humans. When the hypoxia-responsive element was deleted from the *VEGF* promoter, mice developed a late-onset motor neuron disease reminiscent of ALS (Oosthuyse et al. 2001). When these *VEGF* mice were bred to G93A SOD1 mice, ALS onset was accelerated, reducing the mean age at death from 124 to 107 d ($P = .001$ [Lambrechts et al. 2003]). Further studies revealed that certain SNPs in the human *VEGF* gene were associated with both reduced *VEGF* expression and increased ALS risk (Lambrechts et al. 2003), suggesting a link between VEGF expression levels and ALS susceptibility.

Survival of Motor Neuron

Homozygous deletions of the survival of motor neuron gene (*SMN1* [MIM 600354]) on chromosome 5 cause spinal muscular atrophy (SMA [MIM 253300]), a fatal childhood-onset neuromuscular disease characterized by the death of spinal motor neurons and subsequent muscle paralysis. A second highly conserved gene, *SMN2* (MIM 601627), has five nucleotide differences between intron 6 and exon 8 that distinguish it from *SMN1*. One of these polymorphisms causes frequent skipping of exon 7 and very low levels of intact SMN2 protein as a result. One study of 110 patients

with ALS and 100 controls found that *SMN2* gene deletions were overrepresented in patients with sporadic ALS (16%) when compared with controls (4%) and may be risk factors for motor neuron disease development (Veldink et al. 2001). In a similar study, Corcia et al. (2002) investigated 167 patients with ALS and their unaffected spouses for *SMN1* and *SMN2* copy number. Surprisingly, 16% of patients with ALS had an abnormal copy number of *SMN1* (one or three copies), versus 4% of controls. In contrast to the results of Veldink et al. (2001), no differences in *SMN2* copy number were observed between the groups. Although the *SMN* gene involved differs between the studies, both implicate a role for *SMN* copy number in the risk of developing ALS. Further studies are needed to clarify the role of the *SMN1* and *SMN2* genes in sporadic ALS.

Ciliary Neurotrophic Factor

Although there is considerable phenotypic heterogeneity within families with mutant *SOD1*–mediated ALS, Giess et al. (2002) searched for modifier loci in an unusual family with ALS. A 25-year-old man carrying a V148G *SOD1* mutation died from ALS 11 mo after disease onset. His mother and three other family members developed ALS between the ages of 43 and 62 years. His 35-year-old carrier sister remained asymptomatic. Because of the early onset and rapid progression of disease in this individual, several candidate modifier loci were analyzed. A homozygous null mutation in his ciliary neurotrophic factor (*CNTF* [MIM 118945]) gene, a potent survival factor for motor neurons, was identified. The other patients with ALS and the unaffected sister were either wild-type or heterozygous at the *CNTF* locus. Because of this result, Giess et al. (2002) bred *CNTF* null mice to G93A *SOD1* transgenic mice to create $CNTF^{-/-}$/G93A *SOD1* mice. In these mice, ALS developed significantly earlier ($P < .001$), although disease duration was unaffected. Similarly, ALS onset occurred ~10 years earlier (48.6 ± 15 versus 58.4 ± 9 years) in 8 people with the $CNTF^{-/-}$ genotype compared with 30 $CNTF^{+/+}$ controls. As with the mouse model, disease duration was not affected, suggesting that *CNTF* genotype affects susceptibility to disease initiation but not disease progression.

Apolipoprotein E

The apolipoprotein E (*ApoE* [MIM 107741]) ε4 genotype is known to be associated with a lowered age at Alzheimer disease onset; therefore, Drory et al. (2001) genotyped 100 consecutive patients with ALS and 133 controls for the *ApoE* ε4 allele. Although the frequency of the *ApoE* ε4 allele was slightly higher in patients with ALS (15.1%) versus controls (10.9%), there was no association between *ApoE* genotype and age at ALS onset. However, Kaplan Meier survival analysis demonstrated that the *ApoE* ε4 genotype correlated with a shortened survival (32 mo; $P = .03$) after diagnosis compared with other *ApoE* genotypes, suggesting that *ApoE* ε4 can effect disease progression but not onset. This result is somewhat controversial, since it has not been observed by all groups (e.g., Siddique et al. 1998*b*).

Gene-Environment Interactions

Many genes that play a role in the pathogenesis of ALS have been identified or mapped; however, because ALS is predominantly sporadic in origin, environmental triggers are clearly involved in disease initiation. Very few ALS environmental risks have been identified, perhaps because the triggers act only in a genetically susceptible individual. There is an unusual ALS variant in Guam and other regions of the Western Pacific called "ALS-PDC" (parkinsonism-dementia complex) that appears to result from eating toxins from the cycad nut that have been concentrated in flying foxes (Banack and Cox 2003). This diet-induced disease can be recapitulated in mice by feeding them washed cycad flour (Wilson et al. 2002). The mouse model shares many of the features of traditional ALS, including reduced expression of the glial glutamate transporter *EAAT2/GLT-1* (Wilson et al. 2003). The identification of other environmental risk factors for ALS has been difficult, but a number of potential disease triggers have been identified, including smoking, BMI, a glutamate-rich diet, heavy-metal exposure, and military service including the first Gulf War (Kamel et al. 1999, 2003; Nelson et al. 2000*a*, 2000*b*; Scarmeas et al. 2002; Armon 2003; Haley 2003; Weisskopf et al. 2004).

ALS Therapy Development

Riluzole, the only FDA-approved treatment for ALS, works as well in the *SOD1* mouse model as it does in people with sporadic ALS (e.g., Gurney et al. 1998). Therefore, the mutant SOD1 models are used extensively for drug screening. However, these model organisms have several significant limitations. Because of the rapid disease progression in these mice, treatment typically begins presymptomatically, something that is currently not possible in human sporadic ALS. Furthermore, therapies that work presymptomatically may target disease initiation from mutant SOD1 rather than disease propagation, which is ultimately the necessary target for human ALS treatment and which may be a process distinct from disease initiation. In spite of these weaknesses, the SOD1 mutant mice and rats remain the best animal models for ALS. Drugs tested for efficacy in ALS have targeted many of the pathways implicated in disease pathogenesis, including protein aggregation, apoptosis, cell cycle regulation, excitotoxicity, immune system regulation, inflam-

mation, mitochondrial function, and oxidative stress (fig. 1). Treatment regimens including vitamins, antibiotics, pain medication, carboxyfullerenes, bone marrow transplantation, and stem cells have been tried as therapeutics in the mice (fig. 1) (see, e.g., Bruijn 2002). While many trials are carried out in academic laboratories, the ALS Therapy Development Foundation initiates four to six drug-screening studies each month in the G93A *SOD1* mouse model, with ~12 drug studies ongoing at any given time (ALS Therapy Development Foundation Treatment Targets Web site). A number of compounds, such as creatine and coenzymeQ10, extend life span, delay the onset of motor impairment, protect against motor neuron loss, and decrease the evidence of oxidative stress in mouse models of disease (Matthews et al. 1998; Klivenyi et al. 1999). However, not all compounds that are efficacious in mice are effective in patients with ALS. For example, Groeneveld et al. (2003) demonstrated that, although creatine is effective in the G93A *SOD1* mouse model of ALS, it did not effect survival or disease progression in patients with ALS in a recent clinical trial.

Because of their striking neuroprotective effects in vitro, a variety of neurotrophic factors, such as CNTF, glial cell–derived neurotrophic factor (GDNF [MIM 600837]), brain-derived neurotrophic factor (BDNF [MIM 113505]), and insulin growth factor 1 (IGF-1 [MIM 113505]), have been largely unsuccessful in human clinical trials for the treatment of ALS (see, e.g., Bruijn 2002). Only IGF-1 has had marginal success in one of two clinical trials (Mitchell et al. 2002). Although these agents are strongly neuroprotective in vitro, their limited efficacy in vivo may be due to the limited ability of these compounds to cross the blood-brain barrier. Two recent studies exploited the retrograde transport ability of some recombinant viral vectors to deliver IGF-1, GDNF, and VEGF to motor neurons and surrounding cells in ALS mouse models (Kaspar et al. 2003; Azzouz et al. 2004). Retrograde transport from motor neurons that innervate muscles requires the virus to bind to re-

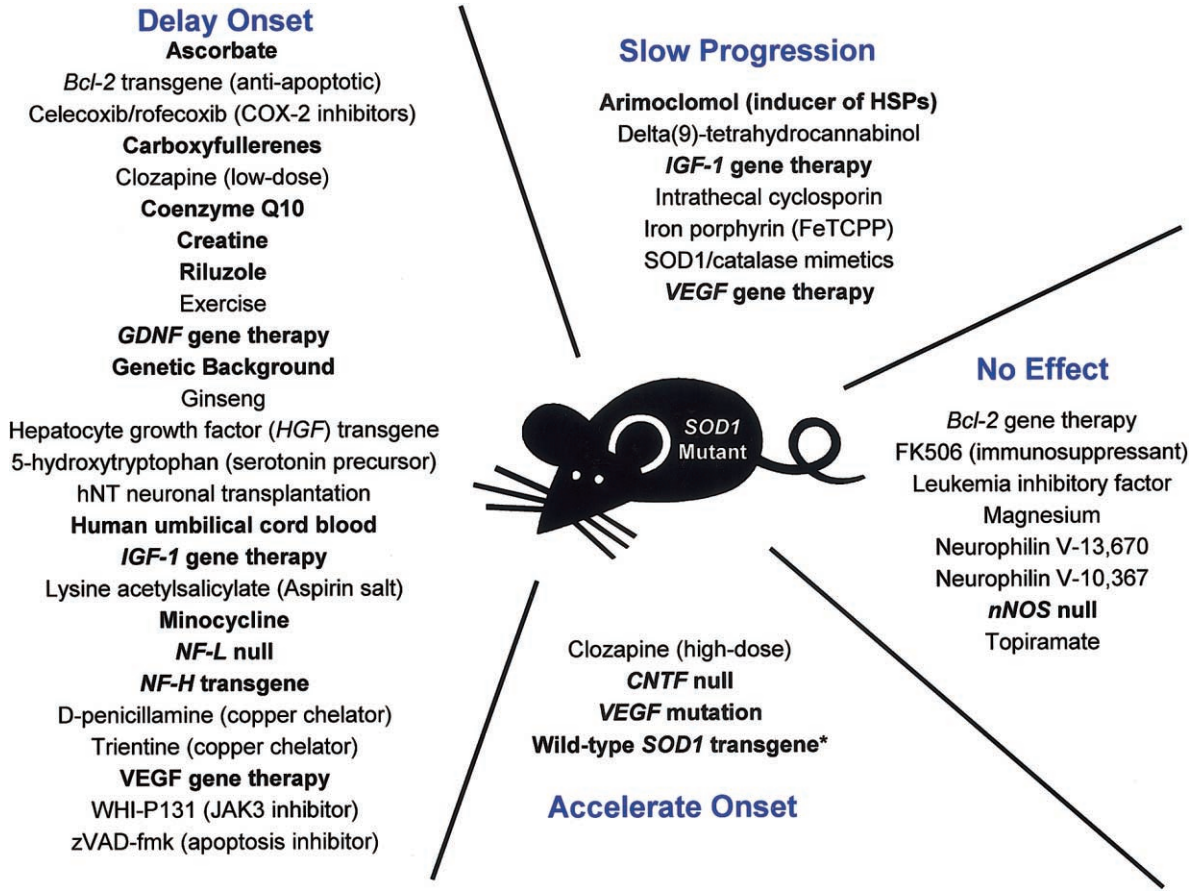

Figure 1 Therapeutic approaches utilized in the mutant *SOD1* trangenic mice. A variety of therapeutic genes and agents have been tested in the mutant *SOD1* transgenic mice. Treatments discussed in the text are in boldface type. The asterisk (*) reflects a result that was observed in G93A but not G85R SOD1 mice.

ceptors on the axon terminal, with subsequent transport to the motor neuron nucleus, allowing sustained gene expression. These studies are extraordinarily promising, since the treatment regimens not only delayed disease onset but could slow disease progression when initiated after onset of symptoms.

Kaspar et al. (2003) used the retrograde transport ability of adeno-associated virus (AAV) to directly target affected motor neurons, to test the efficacy of IGF-1 and GDNF in the G93A *SOD1* mouse model of ALS. In injections into the quadriceps muscle, as much as 1.1% of the virus injected at a dose of 1×10^{10} viral particles was transported to the lumbar region of the spinal cord, as assessed by quantitative PCR. The AAV vectors expressing GDNF or IGF-1 were bilaterally injected into the hindlimb quadriceps and intercostal muscles of G93A *SOD1* animals before disease onset at 60 d of age, with a dosage of 1×10^{10} particles per injection (Kaspar et al. 2003). IGF-1 and GDNF treatment delayed ALS onset by 31 and 16 d and increased median survival by 37 and 16 d, respectively, compared with GFP-treated controls. Injections of IGF-1 not only delayed the onset but also slowed the rate of disease progression in some mice. In contrast, GDNF delayed the onset of symptoms but did not alter disease progression.

To test the ability of the IGF-1 and GDNF treatments to affect disease after it had begun, Kaspar et al. (2003) used the same treatment protocol on mice that were 90 d old, the age at which symptoms begin. In this treatment regimen, GDNF treatment caused a 7-d extension in survival ($P < .0001$). In contrast, IGF-1 treatment extended the median life span by 22 d and slowed progression of the disease, as assessed by body mass loss, rotarod performance, and grip strength. These combined results suggest that treatment with IGF-1 after the onset of overt motor dysfunction results not only in an extension of life but also in a delay in the functional decline associated with the disease.

In similar studies, Azzouz et al. (2004) used a recombinant lentiviral vector (rabies-G pseudotyped equine infectious anemia virus), which also exhibits retrograde transport, to test the effect of human VEGF expression on ALS onset in the G93A *SOD1* mice. This experiment was based on the previous observation that low levels of VEGF expression correlate with ALS susceptibility (Lambrechts et al. 2003). Bilateral injections of VEGF viral vectors into hindlimb gastrocnemius, diaphragm, intercostal, facial, and tongue muscles at 3 wk of age significantly ($P < .0001$) delayed ALS onset (95–123 d) and increased the average life span (125–163 d) (Azzouz et al. 2004). Like Kaspar et al. (2003), Azzouz et al. (2004) also treated the symptomatic 90-d-old G93A *SOD1* mice, increasing survival from 127 d to 146 d ($P < .0001$). Like IGF-1, VEGF is an effective treatment after disease onset and appears to both delay initiation and slow propagation of disease in the G93A *SOD1* mice.

Future Directions

It is difficult to predict the future, but the identification of both additional ALS genes and ALS modifier genes will allow the creation of new models for study. The utility of such models for understanding the pathogenesis of ALS has been demonstrated in the mutant *SOD1* mice. Mechanistic insights gleaned from new ALS genes and mouse models will uncover new targets for therapy development. The testing of synergistic combinations of therapeutics targeting multiple pathogenic mechanisms has already begun, and such studies will likely be expanded. If safety issues with gene therapy vectors can be ameliorated, clinical trials with IGF-1 or VEGF would be worth pursuing, since they are effective in model organisms after symptomatic onset of disease. One potential approach to ALS therapy, not discussed in detail above, is treatment with stem cells. Human safety studies for intraspinal cord implantation of autologous mesenchymal stem cells have already begun in patients with ALS (Mazzini et al. 2003), and clinical trials with stem cells, perhaps as delivery vehicles for neurotrophic factors, may be conducted in the future. Therapy development has unfortunately lagged behind the elucidation of the genetic and pathogenic mechanisms involved in ALS. The future, however, is bright. Because it is possible to slow disease progression in mouse models of familial ALS after symptomatic onset of disease, the creation of effective therapies for ALS is likely an achievable task.

Note added in proof.—The ALS8 locus (table 1) was recently identified. A missense mutation in the vesicle-associated membrane protein/synaptobrevin-associated membrane protein B (*VAPB* [MIM 605704]) was discovered in several families with ALS and related motor neuron diseases (Nishimura et al. 2004*b*).

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Electronic-Database Information

The URLs for data presented herein are as follows:

alsod.org: The ALS Online Database, http://www.alsod.org/
ALS Therapy Development Foundation, http://www.als.net/
ALS Therapy Development Foundation Treatment Targets, http://www.als.net/research/treatments/targetClasses.asp
Motor Syndromes, http://www.neuro.wustl.edu/neuromuscular/motor.html

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for ALS1, *SOD1,* CCS, EAAT2, GFAP, GLAST, EAAC1, *ALS4, ALS2, ALS5,* alsin, *SETX,* ALS-FTD, *MAPT,* FTD, progressive motor neuron disease without sensory symptoms, *DCTN1,* GluR2, *ADAR2, NF-H,* VEGF, *SMN1,* SMA, *SMN2, CNTF, ApoE,* GDNF, BDNF, IGF-1, ALS3, ALS6, ALS7, ALS8, *VAPB,* and ALS X)

Revised Criteria for the Diagnosis of Amyotrophic Lateral Sclerosis (El Escorial Revisited), http://www.wfnals.org/guidelines/1998elescorial/elescorial1998.htm

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