TABLE 452-3 GENETIC MOTOR NEURON DISEASES (*CONTINUED*)

Disease	Locus	Gene	Inheritance	Usual Onset	Gene Function	Unusual Features
SPG20	13q	Spartin	AR	Childhood	Endosomal trafficking protein	
SPG21	15q	Maspardin	AR	Childhood	Endosomal trafficking protein	
SPG35	16q	Fatty acid 2 hydrolase	AR	Childhood	Membrane protein	Multiple CNS features
SPG39	19p	Neuropathy target esterase	AR	Early childhood	Esterase	
SPG44	1q	Connexin 47	AR	Childhood	Gap junction protein	Possible mild CNS features
SPG46	9p	β-Glucosidase 2	AR	Childhood	Glycoside hydrolase	Thin corpus callosum, mental retardation
SPG2	Xq	Proteolipid protein	XR	Early childhood	Myelin protein	Sometimes multiple CNS features
SPG1	Xq	L1-CAM	XR	Infancy	Cell adhesion molecule	
SPG22	Xq	SLC16A2	XR	Infancy	Monocarboxylic acid transporter	
	Xq	Adrenoleukodystrophy	XR	Early adulthood	ATP binding transporter protein	Possible adrenal insufficiency, CNS inflammation
IV. ALS-Plus Syndromes						
ALS with fronto-temporal dementia, Parkinson's disease	9p	C9orf72				
Amyotrophy with behavioral disorders	17q	Tau protein				
Parkinsonism						

Abbreviations: ALS, amyotrophic lateral sclerosis; BSCL2, Bernadelli-Seip congenital lipodystrophy 2B; AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; FSP, familial spastic paraplegia; FUS/TLS, fused in sarcoma/translocated in liposarcoma; TDP43, Tar DNA binding protein 43 kd; XR, X-linked recessive.

and gene translation, both in the cytoplasm and locally in dendritic spines in response to electrical activity. How mutations in FUS/TLS provoke motor neuron cell death is not clear, although this may represent loss of function of FUS/TLS in the nucleus or an acquired, toxic function of the mutant proteins in the cytosol. In the third group of ALS genes, the primary problem is defective axonal cytoskeleton and transport (dynactin, profilin-1). It is striking that variants in other genes (e.g., EphA4) influence survival in ALS but not ALS susceptibility. Beyond the upstream, primary defects, it is also evident that the ultimate neuronal cell death process is complex involving multiple cellular processes that accelerate cell death. These include but are not limited to excitotoxicity, impairment of axonal transport, oxidative stress, activation of endoplasmic reticulum stress and the unfolded protein response, and mitochondrial dysfunction.

Multiple recent studies have convincingly demonstrated that nonneuronal cells importantly influence the disease course, at least in ALS transgenic mice. A striking additional finding in neurodegenerative disorders is that miscreant proteins arising from gene defects in familial forms of these diseases are often implicated in sporadic forms of the same disorder. For example, germline mutations in the genes encoding β-amyloid and α-synuclein cause familial forms of Alzheimer's and Parkinson's diseases, and posttranslational, noninherited abnormalities in these proteins are also central to sporadic Alzheimer's and Parkinson's diseases. Analogously, recent reports propose that nonheritable, posttranslational modifications in SOD1 are pathogenic in sporadic ALS.

TREATMENT AMYOTROPHIC LATERAL SCLEROSIS

No treatment arrests the underlying pathologic process in ALS. The drug riluzole (100 mg/d) was approved for ALS because it produces a modest lengthening of survival. In one trial, the survival rate at 18 months with riluzole was similar to placebo at 15 months. The mechanism of this effect is not known with certainty; riluzole may reduce excitotoxicity by diminishing glutamate release. Riluzole is generally well tolerated; nausea, dizziness, weight loss, and elevated liver enzymes occur occasionally. Pathophysiologic studies of mutant SOD1–related ALS in mice have disclosed diverse targets for therapy; consequently, multiple therapies are presently in clinical trials for ALS including experimental trials of small molecules, mesenchymal stem cells, and immunosuppression. Interventions such as antisense oligonucleotides (ASO) that diminish expression of mutant SOD1 protein prolong survival in transgenic ALS mice and rats and are also nearing trial now for SOD1-mediated ALS.

In the absence of a primary therapy for ALS, a variety of rehabilitative aids may substantially assist ALS patients. Foot-drop splints facilitate ambulation by obviating the need for excessive hip flexion and by preventing tripping on a floppy foot. Finger extension splints can potentiate grip. Respiratory support may be life-sustaining. For patients electing against long-term ventilation by tracheostomy, positive-pressure ventilation by mouth or nose provides transient (several weeks) relief from hypercarbia and hypoxia. Also extremely beneficial for some patients is a respiratory device (Cough Assist Device) that produces an artificial cough. This is highly effective in clearing airways and preventing aspiration pneumonia. When bulbar disease prevents normal chewing and swallowing, gastrostomy is uniformly helpful, restoring normal nutrition and hydration. Fortunately, an increasing variety of speech synthesizers are now available to augment speech when there is advanced bulbar palsy. These facilitate oral communication and may be effective for telephone use.

In contrast to ALS, several of the disorders (Tables 452-1 and 452-3) that bear some clinical resemblance to ALS are treatable. For this reason, a careful search for causes of secondary motor neuron disease is warranted.

OTHER MOTOR NEURON DISEASES

SELECTED LOWER MOTOR NEURON DISORDERS

In these motor neuron diseases, the peripheral motor neurons are affected without evidence of involvement of the corticospinal motor system (Tables 452-1, 452-2, and 452-3).