

## Hereditary motor neuron disorders: genetic heterogeneity, genetic pleiotropy, and clinical overlap

Fink J.K.\*

Department of Neurology, University of Michigan; Geriatric Research Education and Clinical Center, Ann Arbor Veterans Affairs Medical Center, Ann Arbor, MI.

Hereditary motor neuron disorders (MNDs) are genetic disorders in which the major clinical syndrome arises from developmental disturbance and/or degeneration of one or more of the following: a) layer 5 pyramidal neurons in the brain motor cortex; b) descending corticospinal axons from these neurons; c) spinal motor neurons and their axons. The pattern of motor neuron disturbance (upper or lower motor neuron involvement or both) and presence or absence of other neurologic involvement yields recognizable motor neuron syndromes amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS), spinal-muscular atrophy (SMA), distal hereditary motor neuropathy (DHMN), and hereditary spastic paraplegia (HSP). In addition, motor neuron involvement is a characteristic feature of many other inherited disorders (eg. Friedreich's ataxia and Presenilin 1 and 2 mutation).

Each of these MND syndromes is clinically and genetically heterogeneous. 12 ALS loci (including Kennedy syndrome) and 10 ALS genes have been identified: SOD1, ALSIN, Senataxin, FUS, VAPB, TDP-43, Dynactin, Angiogenin, Androgen Receptor, and FIG4.

Although PLS is usually ascertained without family history, a locus for autosomal recessive PLS (due to ALSIN mutation) and autosomal dominant PLS (4p tel-4p16.1) have been identified. In addition, FIG4 mutation has been reported in two subjects with PLS.

The majority of SMA (types SMA -1, -2, and -3) is due to mutation in the survival motor neuron (SMN 1) gene, with phenotypes modified by SMN2 gene copy number. Spinal muscular atrophy with respiratory distress (SMARD type 1) results from mutations in the gene encoding immunoglobulin mu-binding protein 2 (IGHMBP2). X-linked spinal muscular atrophy is due to UBE-1 mutations. Dominantly inherited congenital spinal muscular atrophy with contractures is genetically heterogeneous with one locus identified on chromosome 12q23-q24. Dominantly inherited, late-onset, proximal SMA is caused by mutations in the vesicle associated protein VAPB (which also cause type 8 ALS).

The DHMNs are genetically heterogeneous, with both autosomal dominant and autosomal recessive forms. Among 12 clinico-genetic types of DHMN, mutations in 5 genes have been discovered: GARS; BSCL2 (subjects with BSCL2 mutations are variably classified as DHMN type V, HSMN type 5, and HSP type 17); IGHMBP2 (subjects are variably classified as DHMN type VI and SMARD-1); DCTN1; and SETX.

The HSPs show extreme clinical and genetic heterogeneity. Among the >40 genetic types, genes have been identified for dominant (Atlastin, Spastin, NIPA1, Strumpellin, Kinesin heavy chain/KIF5A, Chaperonin 60/ heat shock protein 60; BSCL2/seipin, REEP1, and ZFYVE27); recessive (CYP7B1, Paraplegin, Spatacsin, ZFYVE27, Spartin, Maspardin, Neuropathy target esterase, and epsilon subunit of the cytosolic chaperonin-containing t-complex peptide-1/Cct5); and X-linked forms (L1CAM, and Proteolipid protein).

Clinical, genetic, and anatomic overlaps between many MND syndromes blur traditional diagnostic distinctions. For example, some subjects with primary lateral sclerosis with only mild electromyographic evidence of chronic denervation meet diagnostic criteria for ALS. Subjects with BSCL2 mutations are variably diagnosed as having a form of type 2 (axonal) Charcot-Marie Tooth or Hereditary Spastic Paraplegia (SPG17). In some cases, mutations in a given gene cause more than one motor neuron disease syndrome. For example, ALSIN and FIG4 mutations are present in both ALS and PLS subjects). ALS syndrome has been reported in a subject with SPG4/spastin mutation (the single most common cause of autosomal dominant hereditary spastic paraplegia). The extent of anatomic involvement (evident by post mortem, neurophysiologic, and neuroimaging studies) often shows an even greater degree of overlap between forms of motor neuron disorders and

other degenerative conditions (particularly with spinocerebellar degenerations and hereditary motor sensory neuropathies) than predicted by clinical findings alone.

Given significant overlaps between MND syndromes, rigid use of clinical criteria for selecting genetic testing often fails to identify variant forms; and moreover, limits appreciation of the full phenotypic spectrum, an essential aspect of genetic counseling. The availability of databases that combine complete genetic information with detailed phenotypic analysis are essential for knowing what constitutes disease-causing mutation; the complete phenotypic spectrum of individual mutations; and for gaining insight into the combined effects of variation in multiple genes.