SPG10 in German families with hereditary spastic paraplegia

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Hereditary spastic paraplegia (HSP) comprises a clinically and genetically heterogeneous group of neurodegenerative disorders of the spinal cord. At present 31 SPG loci and 11 genes have been characterized including 12 loci and 6 genes for autosomal dominant HSP, 14 loci and 3 genes for autosomal recessive disease and 4 loci and 2 genes for X-linked forms. HSP presents clinically as “pure” spastic paraplegia with signs and symptoms restricted to pyramidal tracts or as “complicated” form in which spasticity is accompanied by additional signs like mental retardation, dysarthria, ataxia or distal amyotrophy. Mutations in the spastin gene (SPG4) and the atlastin gene (SPG3) are responsible for about 45% and 10% of autosomal dominant HSP in Germany.
SPG10 is caused by mutations in the neuronal kinesin heavy chain gene KIF5A. Kinesin motors power anterograde transport of membranous organelles and a variety of other cargoes along axonal microtubule tracts. Two KIF5A mutations have been identified in spastic paraplegia so far, both affecting the highly conserved motor domain and thus most likely disabling axonal transport.
We identified a large German family with autosomal dominant spastic paraplegia in which the polymorphic markers D12S1586, D12S1691, D12S355 and D12S83 demonstrated linkage to the SPG10 locus whereas haplotype analysis excluded linkage to other dominant HSP loci. Direct sequencing of the motor domain of KIF5A (exons 1-10) revealed a heterozygous missense mutation G759T in exon 9 leading to the exchange of an evolutionary highly conserved lysine residue by asparagine (K253N). This mutation is cosegregating with the disease in our family and is absent in 100 control chromosomes.
To determine the frequency of SPG10 in German, Dutch and Austrian families we presently screen the motor domain of KIF5A in index patients of 85 families with autosomal dominant HSP in which SPG4 and SPg3 mutations were previously excluded.
Whereas onset in previously reported SPG10 families is early (mean: 10 years of age) we observed onset of spastic gait disturbance in our family between 15 and 33 years. The most severely affected patients became wheelchair-bound after 30 – 40 years disease duration at the age of 60 – 65 years. Clinically the disease presented as pure spastic paraplegia. Electrophysiology revealed subclinical mild to moderate peripheral neuropathy of sensory-motor type with axonal and demyelinating characteristics.