Spastin mutations in sporadic cases of spastic paraplegia.

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SPG4 encodes spastin, a member of the AAA protein family, and is the major gene responsible for autosomal dominant spastic paraplegia. It accounts for 10-40% of families with pure (or eventually complicated) hereditary spastic paraparesis (HSP). SPG4 mutations in patients without a family history has not been systematically studied.
Our objectives were to assess the frequency of *SPG4* mutation in a large series of patients with spastic paraplegia without family histories. We selected 146 mostly European probands with progressive spastic paraplegia for which major neurological causes were excluded and without familial history of the disease. One hundred and three probands presented pure spastic paraplegia while 43 had additional features. DNA was screened by DHPLC for mutations in the 17 coding exons of the *SPG4* gene. Sequence variants were characterized by direct sequencing. A panel of 600 control chromosomes was used to rule out polymorphisms.
The overall rate of mutations was 12%. We identified 19 different mutations, 13 of which were novel, in 18 different patients. In one family, where both parents were examined and found to be normal, the mutation was shown to be transmitted by the asymptomatic mother, indicating reduced penetrance. The parents of other patients were not available for analysis but were reported to be normal on history. There was no evidence for *de novo* mutations. The mutations found in these apparently isolated patients were mostly of the missense type and tended to be associated with a less severe phenotype than in previously described patients with inherited mutations.The unexpected presence of *SPG4* gene mutations in patients with sporadic spastic paraplegia argues in favour of gene testing in patients with pure or complicated spastic paraplegia without family histories.