

## SPG5 und SPG6 – zwei seltene Formen der HSP

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### SPG5:

Autosomal recessive spastic paraplegias (ARHSPs) usually have clinically complex phenotypes but the SPG5, SPG24 and SPG28 loci are considered to be associated with pure forms of the disease.

We performed a genome-wide scan in a large French family. Fine mapping of the refined SPG5 region on chromosome 8q12 was performed in another 17 ARHSP families with additional microsatellite markers.

After exclusion of known ARHSP loci the genome-wide screen provided evidence of linkage with a maximal multipoint lod score of 2.6 in the *D8S1113-D8S1699* interval. This interval partially overlapped *SPG5* and reduced it to a 5.9 megabase (Mb)-region between *D8S1113* and *D8S544*. In a family of Algerian origin from a series of 17 other ARHSP kindreds, linkage to the SPG5 locus was supported by a multipoint lod score of 2.3.

The direct sequencing of the coding exons of seven candidate genes did not detect mutations/polymorphisms in the index cases of both linked families.

The phenotype of the two *SPG5*-linked families consisted of spastic paraparesis associated with deep sensory loss. In several patients with long disease durations, there were also mild cerebellar signs.

The frequency of SPG5 was ~10% (2/18) in our series of ARHSP families with pure or complex forms. We have refined the *SPG5* locus to a 3.8 cM interval and extended the phenotype of this form of ARHSP to include slight cerebellar signs.

### SPG6:

Recently, 3 different missense mutations in the *NIPAI* gene (T45R, A100T and G106R), responsible for *SPG6*, were identified in ADHSP families. The phenotype was pure in all patients in the seven known SPG6 families of Chinese, Iraqi, Irish, English, Brazilian/Portuguese and Japanese origin. In the present study, we established the frequency of *NIPAI* mutations in a large cohort of 110 Caucasian ADHSP index cases. All index patients were excluded for known mutations in the spastin gene (*SPG4*) or in the atlastin gene (*SPG3A*) when onset occurred before the age of 10. We found the G106R mutation in only one French family, in which 6 patients had a pure form of HSP with onset between the age of 8 to 60 years associated, in 3 patients with memory deficits. Nucleotide 316, where this mutation occurred, appears to be a hot spot for recurrent mutations in *SPG6*. However, this form of ADHSP was found in less than 1% of our families.