

Clinical and molecular characterization of autosomal recessive forms of hereditary spastic paraplegia with cognitive deficits

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Aims: Hereditary spastic paraplegias (HSPs) comprise a clinically and genetically heterogeneous group of neurodegenerative disorders, resulting in progressive spasticity of the lower limbs. In contrast to “pure HSP”, additional clinical features are present in patients with complicated HSP. Based on the mode of inheritance (autosomal recessive, autosomal dominant and X-linked) and the linkage data, to date, 36 distinct genetic loci have been described, 15 genes could be identified. We have recently characterized in detail the phenotype of two German pedigrees with AR-HSP with thin corpus callosum (TCC; Winner et al. 2004 and 2006). For 4 large consanguineous Turkish families we could narrow down the SPG11 minimal critical region to a 2.93 cM interval with a maximum LOD score of 11.84 (Oelmez et al., 2006). Mutations in the human spatacsin gene (SPG11) could recently been identified as one major cause of complicated AR-HSP (Stevanin et al., 2007). The aim of this study is the further clinical and molecular genetic characterization of families with autosomal recessive complicated HSP (AR-HSP) with thin corpus callosum (TCC) and/or cognitive deficits.

Methods: Neurological examination, evaluation of a clinical questionnaire and the HSP rating scale (SPRS) for a total of 32 families with AR-HSP plus TCC and/or cognitive deficits. Linkage analysis using QF-PCR for informative markers in close vicinity of SPG7, 11, 14, 15, 20, 21 and 26. Sequence analysis of 24 genes from the SPG11 candidate region.

Results: 4 consanguineous families from Turkey were compatible with linkage to SPG11 and together with additional families and sporadic cases subjected to a candidate gene analysis to identify the SPG11 gene. So far, we could identify causal spatacsin mutations in 5 families previously linked to SPG11 and in one well characterized German sporadic patient.

In 3 families data were compatible with linkage to SPG7, SPG20 or SPG21, respectively. A subgroup of 10 families with AR-HSP and TCC and/or cognitive deficits, not linked to either SPG7, SPG11, SPG20 or SPG21, were further characterized. Clinical evaluation revealed mean age at the time of first signs of spasticity around 1-4 years of age. Linkage analysis was compatible with linkage of one large Turkish family to SPG14 with a LOD score of 2.2 at D3S1601. So far, only one family with linkage to SPG14 had been reported in the literature (Vaza et al., 2000). In the remaining 9 families no clear evidence for linkage to any of the analyzed 6 loci was observed. These 9 families will now be tested for linkage to the remaining autosomal recessive SPG loci and/or implemented in the identification of new genes associated with complicated AR-HSP.

Conclusion: The subgroup of AR-HSP with thin corpus callosum and/or cognitive deficits is genetically heterogeneous. Further neurological and genetic evaluation of these families might reveal,

if certain loci are associated with distinct clinical features and contribute to our understanding of the molecular mechanisms underlying hereditary spastic paraplegia.