Molecular genetic studies in Bulgarian patients with hereditary spastic paraplegia

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Hereditary spastic paraplegia (HSP) is a group of neurogenerative disorders of the upper motor neurons characterized with extreme clinical and genetic heterogeneity. We have established an HSP biobank containing extended genealogical and clinical information and genetic material of more than 120 patients and families with this disorder. The mode of disease inheritance is AD/D in about 22% of the cases, AR - in 19%, while in the other patients there is no reported positive family history. Importantly, our patient cohort includes several extended Gypsy families with both pure and complicated HSP forms.

So far, mutation analysis of the two most common genes associated with autosomal-dominant HSP forms identified genetic defects in 47% of the AD cases. *Spastin* gene mutations were associated with predominantly pure forms of the disease with substantial differences in onset age. Affected individuals with *atlastin* mutations presented with severe neurological deficit starting within the first decade of life, rapid invalidation and signs of axonal type of peripheral neuropathy in some cases. Further screening of *KIF5A*, *HSPD1* and *PLP1* in mutation negative patients revealed no pathogenic variations in these genes.

In the families with AR-HSP forms, one novel c.241T>A substitution, leading to a premature stop codon (L78X) was indentified in the *paraplegin* gene. This mutation was found in a large Gypsy family with five affected individuals and AR mode of HSP inheritance. The proband has a complicated HSP form with onset in the second decade and carry this mutation in a homozygous state. Interestingly, two other patients are L78X heterozygotes and present with pure HSP starting in the fifth decade of life. The L78X mutation was absent in additional Gypsy AR-HSP families tested, as well as in population matched control chromosomes. The results suggest that there is no single founder mutation in the *paraplegin* gene accounting for the majority of recessive HSP cases in this community and additional genetic causes must exists. So far, genetic linkage studies performed in two extended Gypsy pedigrees excluded the known AR-HSP loci. Homozygosity mapping and haplotype sharing analyzes are under way.