# HSP IN BULGARIAN GYPSIES - CLINICAL AND GENETIC STUDIES

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Hereditary spastic paraplegias (HSP) are a group of rare neurodegenerative disorders of the upper motor neurons characterized by extreme clinical and genetic heterogeneity. The HSP disease is currently untreatable and poorly understood, warranting research on its etiology and potential targets for intervention.

We aim at clarifying the biological complexity underlying this condition focusing on the identification of novel genes and disease-causing mutations involved in HSP pathogenesis. To this end, we initiated a study of Bulgarian HSP patients from Gypsy/Roma ethnic origin. Research on HSP in this unique founder population provides a substantial and yet unexplored potential, as limited genetic diversity, large traditional families and shared ancestral mutations facilitate gene discovery and genotype-phenotype correlations.

So far, we have collected extended genealogical and clinical information, and DNA material of 22 Gypsy familial (predominantly recessive) and sporadic HSP cases. Geographical clustering of the patients was observed and distant relationship was established between several families. In two extended pedigrees segregation of two or more different HSP clinical subtypes was documented. Mutation screening of the spastin gene identified a previously reported c.415+1G>T mutation to segregate with a pure HSP form in one dominant family. Analysis of the paraplegin gene revealed a common nonsense mutation (L78X) in three patients from different presumably unrelated pedigrees. Preliminary genotype-phenotype correlations suggest substantial clinical variability to be associated with this genetic defect. In two consanguineous nuclear families with three or more affected and unaffected individuals linkage to known autosomal recessive HSP loci was excluded by homozygosity mapping. Exome sequencing of the probands is underway.