Hereditary Spastic Paraplegia Genetics in the Exome Era: Data on 123 HSP Exomes

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Abstract

Hereditary spastic paraplegias (HSP) comprise a group of clinically and genetically heterogeneous neurodegenerative disorders that share the common clinical feature of lower limb spastic paraplegia. At least ten genes causing autosomal dominant HSP are known to date, together explaining approximately 60% of cases. An additional 17 genes cause recessive and X-linked forms, with less certain proportional contribution. Knowledge of frequency of HSP subtypes and genotype-phenotype correlation is limited thus far due to phenotypic pre-selection of most study cohorts and incomplete testing of known, especially rare, genes. We have screened a large cohort of 300 autosomal dominant and other familial and sporadic HSP patients for mutations in the most common HSP genes, including SPG3, SPG4 and SPG31. Mutation negative families (n=100) were examined by whole exome sequencing, which sufficiently covered 98.6% of the coding area of all HSP genes. Several dozen rare conserved coding variants were identified across known HSP genes and we describe a number of unusual phenotypes in affected patients. All variants were evaluated for pathogenicity. Applying whole exome analysis we were able to narrow the number or index patients without genetic diagnosis for autosomal dominant HSP genes from 44% to approximately 30%. Our in depth analysis of the exome results demonstrate that whole exome sequencing is a mature tool for mutational screening studies in HSP and beyond. In addition we begin to face new challenges of interpretation of data from single patients caused by the identification of variants in multiple HSP genes or in known genes of related disorders, including CMT2 and ALS.