Hereditary Spastic Paraplegia (HSP) genetics in the exome era: data on 123 HSP exomes

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Hereditary spastic paraplegias (HSP) comprise a group of clinically and genetically heterogeneous neurodegenerative disorders that share the common clinical feature of lower limb spasticity and weakness. At least 10 genes causing autosomal dominant HSP are known today, together explaining about two third of cases. Proportional contribution oft he additional 17 genes causing autosomal recessive and X-linked HSP are less clear.
We have screened a large cohort of HSP patients for mutations in the most common HSP genes. Mutation negative index cases (n=100) and additional family members (n=23) were examined by exome sequencing with a coverage of 98.6% for the coding sequence of known HSP genes.
In the 78 dominant families included in the study we identified mutations in SPG3, SPG8, SPG10 and SPG31. We even identified several SPG4 mutations that had been previously overlooked in diagnostic labs. Taken together the molecular diagnosis was established in an additional third of families with previously unknown disease causes. Even after exome sequencing about 30% of autosomal dominant cases remain unsolved, indicating that there are still more autosomal dominant HSP genes to find.
The sheer number of variants we identified in whole exomes further emphasizes the need for standardized criteria to determine pathogenicity of variants. We have weighed several factors to make consistent evaluations of disease relevance of a variant, including co-segregation with the phenotype, rarity in a large control cohort, previous reports of a change and functional considerations.
This study provides an HSP-focused preview on the challenges we are going to face when taking genetic diagnostic testing to a genomic approach.