Next-generation-sequencing facilitates genotyping of hereditary spastic paraplegias

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Hereditary spastic paraplegia (HSP) is a neurodegenerative disorder defined clinically by progressive lower limb spasticity and weakness. HSP is a highly heterogeneous condition with at least 48 loci identified so far, involving X-linked (XL), autosomal recessive (AR) and autosomal dominant (AD) inheritance. For correct diagnosis molecular testing is essential since clinical parameters by themselves are not reliable to differentiate HSP forms. Thus, the purpose of this study was to establish amplicon based high throughput genotyping for AR-HSP. A sample of 187 index cases with sporadic or recessive spastic paraplegia were analyzed by applying an array based amplification strategy to generate amplicon libraries followed by a pooled next-generation sequencing (NGS) approach to investigate the *CYP7B1*-(SPG5) and *Paraplegin*-gene (SPG7). We identified one SPG5 and four SPG7 patients. All of them were compound heterozygous for two mutations. In total, three known *CYP7B1* mutations and eleven mutations in *Paraplegin*, including five novel mutations (p.W29X, p.R139X, p.R247X, p.G344D and p.R398X), were detected through amplicon-based next generation sequencing. Discovering the molecular basis of the neurodegenerative disorder HSP is challenging given the increasing number of subtypes. Our study illustrates how amplicon based NGS can be used as a suitable platform to provide data on molecular mutations at a necessary throughput and accuracy.