Challenges and Controversies in the Genetic Diagnosis of HSP

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There are many challenges for an accurate genetic diagnosis for hereditary spastic paraplegia which were reviewed in this talk. Difficulties include a high level of genetic heterogeneity, with multiple genes and a rapidly expanding gene list (over 81 distinct genetic forms have been identified so far). Furthermore, there is a genetic and phenotype overlap with other inherited disorders such as the hereditary cerebellar ataxias, familial amyotrophic lateral sclerosis, hereditary neuropathies, and monogenic Parkinson's disease. It is important to be alert for HSP 'mimics' including adrenoleukodystrophy and cerebrotendinous xanthomatosis. HSP may also be difficult to distinguish from disorders without a clear Mendelian inheritance, including primary lateral sclerosis, cerebral palsy, and multiple sclerosis. When the phenotype is complex, it can be difficult to determine whether the condition should be labelled as a form of HSP. Further adding to the complexity is that certain HSP genes may have different modes of transmission; for example, *KIF1A*, *REEP2*, and *ATL1*. Additionally, cases of HSP have been described with concurrent independent genetic diagnoses, such as a family with both a *REEP1* mutation and a 15q duplication. There are now several different strategies for pursuing a genetic diagnosis in HSP, such as a targeted gene panels, whole exome sequencing, and whole genome sequencing, and each has advantages and disadvantages. Moreover, it is worth considering dedicated tests for copy number variants, structural variants, and repeat expansion disorders. New approaches including long read sequencing and RNA diagnostics may help improve the diagnostic rate for HSP well above 50%.