Meta-analysis of age at onset in spastin-associated hereditary spastic paraplegia provides no evidence for a correlation with mutational class

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Key points

- The hereditary spastic paraplegias (HSPs) are a group of single gene disorders in which the corticospinal tracts fail to develop normally, or degenerate after initially normal development. The HSPs all share the principal clinical feature of progressive lower limb spastic paralysis, and are subdivided into pure and complicated forms, depending on the presence of additional neurological or non-neurological features.1 2

- The pure HSPs tend to be associated with neurodegeneration, rather than abnormal development, and histopathological studies in pure HSP show a length-dependent “dying back” of the terminal ends of the corticospinal tract axons, with the longest axons being involved first.1 The SPG4 gene, spastin, is the most important pure HSP gene, being responsible for approximately 40% of definite autosomal dominant pure HSP and a smaller proportion of sporadic cases and cases with uncertain family history.3 4 The 616 amino acid spastin protein is a widely expressed AAA (ATPases associated with diverse cellular activities) protein.5

- More than 100 different spastin mutations have been described, including numerous missense, nonsense, frameshift, and splice site mutations, as well as less frequent whole exon deletions. With only a few possible exceptions, the missense mutations are located in the AAA cassette, from amino acids 342–599. Splice site mutations almost exclusively involve exons 5–16. Nonsense and frameshift mutations are scattered across the gene, with the smallest predicted protein consisting of fewer than 40 amino acids, the largest 562 amino acids.5

- It is likely that the molecular pathological mechanism of truncating and splice site spastin mutations is loss of function. The associated abnormal transcripts may be unstable, and recent data show that mutant spastin protein is absent in fibroblasts from patients with nonsense and frameshift spastin mutations.6 7 These classes of spastin mutation are probably associated with haploinsufficiency, with disease occurring once functioning spastin levels fall below a critical threshold level. Tolerance for reduced dosage of functioning spastin may be very low, as some “leaky” (that is, creating both wild-type and aberrant splice variants) splice site mutations result in only slight reductions in wild-type mRNA expression.9 On the other hand, spastin missense mutations may act via a different mechanism. It has been suggested that spastin has a microtubule severing function and that spastin missense mutants bind constitutively to microtubules, perhaps acting in a dominant negative fashion to block the normal function of spastin or unidentified spastin-related proteins.5

- One approach to resolve the issue of whether spastin missense mutations have a different molecular pathological mechanism to other mutational types is to examine whether mutational class is correlated with clinical features. We therefore carried out a meta-analysis of age at onset vs mutational class correlations in HSP caused by spastin mutations, in order to test the null hypothesis that there is no difference in age at onset between groups of families with different classes of spastin mutation.

- Data gathered on 75 families revealed no significant difference in age at onset between HSP patients with missense vs other spastin mutational classes, providing no evidence for a genotype-phenotype correlation.

Abbreviations: HSP, hereditary spastic paraplegia

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data for individual affected patients directly from the relevant papers, or from unpublished data. Asymptomatic individuals were excluded from the analysis.

Within each study, we compared age at onset across different mutational classes and then estimated, as the summary “effect”, a hazard ratio of non-missense relative to missense mutation families using conditional Cox regression. We then pooled the resultant hazard ratios and variances using standard methods of meta-analysis as implemented in Stata 7.0 (Stata Corp., TX, USA). The hazard ratio was homogenous across studies and there was no significant difference in age at onset in families with missense mutations and the mean age at onset weighted by family membership. Individual study and pooled hazard ratios for missense mutations relative to all other classes of mutations are shown in table 2. The hazard ratio was calculated as the ratio of the weighted mean ages at onset between groups, and secondly, it was feasible that similar ages at onset may arise from different molecular pathological mechanisms. It is likely that direct experimental work or further meta-analyses with very large sample sizes will be required to resolve this issue.

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