The spectrum of axonopathies

From CMT2 to HSP

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Hereditary spastic paraplegias (HSP) are characterized by the presence of lower extremity spasticity and weakness. They are genetically heterogeneous and are classified as pure or complicated, depending on the presence of other clinical features, one of which is peripheral neuropathy. Charcot-Marie-Tooth type 2 (CMT2) refers to the axonal form of hereditary motor sensory neuropathy. While HSP and CMT2 have historically been viewed as distinct entities, divided by their predilection for central vs peripheral nerve axons, their clinical and genetic overlap is becoming increasingly recognized. Multiple HSP-associated genes, including *BSCL2* (SPG17), *atlastin-1* (SPG3A), *NIPA1* (SPG6), *spastin* (SPG4), and *KIF5A* (SPG10), cause substantial involvement of peripheral nerves.[1] Mutations in a single gene may cause either HSP or CMT2. Furthermore, HSP and CMT2 share several pathomechanisms, with causative mutations in both diseases occurring in genes involved in myelination, axonal transport, membrane trafficking, cytoskeletal organization, and mitochondrial function.[1]

Spastic paraplegia type 10 (SPG10) is a rare form of autosomal dominant HSP caused by mutations in the *kinesin family member 5A* (*KIF5A*) gene. SPG10 is frequently associated with neuropathy, and *KIF5A* mutations can also cause a pure CMT2 phenotype without upper motor neuron signs.[2,3] In this issue of *Neurology*®, Liu et al.[4] confirm the varied phenotypes associated with *KIF5A* mutations by screening the gene in a large number of patients with HSP and CMT2 using a combination of genetic methodologies. Sanger sequencing was used to screen the exons encoding the motor domain (in which the majority of mutations occur) in 186 patients with HSP and 215 patients with CMT2, and whole-exome sequencing (WES) was used in one patient. In addition, the authors used targeted resequencing covering all exons of *KIF5A* to screen 66 patients with either HSP or CMT2 with pyramidal signs.

The authors identify 2 novel and 3 previously reported heterozygous missense mutations in 6 unrelated patients. Detailed clinical and electrophysiologic data reveal that 3 patients had CMT2 with or without pyramidal signs, while 3 patients presented with a HSP phenotype with or without axonal neuropathy. HSP with neuropathy was more common than CMT2 with pyramidal signs. Two families also had associated cognitive dysfunction and one patient had HSP with cerebellar ataxia, a feature not previously described in SPG10. Both the HSP and CMT2 phenotypes occurred within the same family, confirming the allelic nature of the 2 disorders. As discussed by the authors, a phenotype–genotype correlation of *KIF5A* mutations cannot be established based on their results.

Liu et al.[4] used a combination of traditional and time-consuming Sanger sequencing as well as more modern next-generation sequencing (NGS) methods in order to expand the phenotypic spectrum of a known gene. WES is increasingly being used in genetic research and has made possible the rapid expansion in the numbers of known disease-associated genes. (In CMT, there are now over 70 causative genes described, half of which were described in the last 4 years.) However, WES is expensive and requires complex data analysis in order to filter out nonpathogenic or irrelevant variants. In addition, some regions of the genome are not well-covered by current technology; thus use of WES remains limited in clinical practice.[5] Targeted resequencing of a single gene is an attractive method of single gene analysis as it is quicker and more cost-effective than Sanger sequencing or WES. The authors demonstrate effective use of all 3 methods to comprehensively evaluate mutations in a large gene.

KIF5A encodes a kinesin motor protein, which binds microtubules and allows for effective axonal transport and intracellular trafficking.[1,4] The long length of peripheral nerve and corticospinal tract axons makes them highly dependent on the effective delivery of necessary cargo. The authors also discuss several other genes involved in axonal transport, mutations in which may cause axonal neuropathy, spasticity, or both, thereby highlighting axonal transport as a common theme in the pathogenesis of both axonal neuropathy and spastic paraplegia.

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Liu et al.[4] firmly establish that *KIF5A* should be included in the growing list of genes causing overlap syndromes of HSP and CMT2. Mutations in *KIF5A* are rare, however, and it is impractical to sequence this large gene in all patients. Targeted resequencing or focused genetic panels may therefore be preferable. As WES and whole-genome sequencing become more efficient and affordable, their use will become more widespread in clinical practice, particularly when evaluating patients with complex phenotypes. However, increasing use of NGS will inevitably lead to variants of unclear relevance being found in individual patients. For this reason, genotype–phenotype studies remain essential to help guide the clinician in interpretation.

The broadening phenotypic spectrum associated with specific genes is not unique to CMT and HSP, but is increasingly recognized in virtually every area of neurology. The neurologic community is therefore faced with the challenge of reconsidering historical classification schemes of disease, which are proving too rigid in the genetic era. Should SPG10, for example, be referred to as a *KIF5A*-associated axonopathy instead? The number of genes resulting in a broad phenotypic spectrum will inevitably increase as genetic techniques become more efficient. At this time of rapid genetic discovery, it is especially important to continue careful clinical phenotyping of patients at the bedside.

A critical question that remains is what determines the site of axonal injury (upper motor neuron vs peripheral nerve) in a particular patient with a *KIF5A* mutation. Further work clearly needs to be to be done in order to identify both environmental and genetic modifiers that may be playing a role. Determining the mechanism for selective vulnerability of axons in *KIF5A*-associated disorders will be crucial to understanding this complex spectrum of disease.

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