Co-dominant spastin mutations cause severe HSP

It is not known why members of the same family with hereditary spastic paraparesis vary in clinical presentation. Chinnery et al. show that severe infantile spastic paraplegia can be due to co-dominant mutations in the spastin gene, demonstrating that additional genetic factors can modify the phenotype.

Cerebral palsy, assortative mating, and compound heterozygous SPG4/spastin mutations

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The hereditary spastic paraplegias (HSPs) are emerging as a large group of inherited disorders in which the predominant syndrome is lower extremity spastic weakness.1 The HSPs are genetically heterogeneous and clinically diverse. There is often major clinical variability within a given genetic type of HSP and indeed within a family in which all affected subjects share precisely the same HSP gene mutation. Most of our evolving concepts of HSP clinical syndromes and pathogenesis are influenced by our experience with SPG4 HSP since it represents approximately 40% of dominantly inherited HSP and may be the most common type (or most frequently ascertained type) of HSP.

In the Chinnery et al. family, infantile-onset lower extremity spasticity was associated with compound heterozygous SPG4/spastin mutations. In this family, the grandfather had mild gait disturbance in childhood that progressed in adulthood to marked lower extremity spasticity associated with urinary urgency. Molecular analysis showed that he was heterozygous for a novel SPG4 missense mutation (P361L). This mutation was transmitted to his daughter, who at age 34 is asymptomatic and has a normal neurological examination. This woman’s 38-year-old husband has hyperreflexia, sustained ankle clonus, extensor plantar responses and was shown to be heterozygous for a different SPG4 missense mutation (S44L); homozygosity of this mutation has been associated previously with adult onset spastic paraplegia.2 This couple’s child had infantile onset lower extremity spasticity and was shown to have inherited both the SPG4 P361L mutation (from her mother) and the SPG4 S44L mutation (from her father).

Although the theoretical role of placenta previa in the child’s spastic gait must also be considered, this report illustrates important emerging HSP concepts. First, the severity and age-of-onset of HSP symptoms may be highly variable within a family and the parents of affected children may be asymptomatic. Second, the occurrence of early-onset HSP reinforces the importance of considering HSP in the differential diagnosis of individuals with infantile onset spastic diplegia suspected of having cerebral palsy. Third, although the association of earlier onset and more severe symptoms with compound heterozygous SPG4 mutations does not resolve debate about whether SPG4 mutations are pathogenic through haploinsufficiency or through dominant negative mechanisms, it does support the findings of Svenson et al.3 that co-inherited variation in the SPG4 coding sequence itself influences the phenotype of subjects with SPG4 HSP. Finally, the occurrence of an individual whose parent had spastic gait marrying someone with sustained ankle clonus could be viewed as an example of assortative mating (for example, in which mate selection is influenced by the phenotypic similarity or dissimilarity between potential spouses) and reminds us that such matings can potentially influence (positively or negatively) the phenotype of HSP and other inherited disorders.

References
