SPG7 HSP more common in Australia

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Genetic testing providing insight

The explosion of new knowledge about HSP in this decade is painting a more complex picture of:

- **the relationships between neurodegenerative conditions**
- **a wider range of symptom profiles for individual HSP types**
- **an ever-increasing number of both genes and mutations being associated with HSP, and**
- **greater diversity in the rates that different HSP genes show up in different countries.**

Fundamental to all this new knowledge is the increasing sophistication, availability and affordability of new and better ways of doing genetic testing.

Dr Mark Davis

The PathWest lab in Perth, Western Australia is highly regarded nationally for its HSP genetic testing service. The lab is headed up by Dr Mark Davis, who shares below an emerging picture of the HSP landscape in Australia, based on the results of hundreds of tests where neurologists suspected HSP. Here is what Mark has to say:

Positive HSP gene tests occur at a rate of just over one in three

When the first Next Generation Sequencing (NGS) gene panel was set up in this laboratory in 2012, there were 26 genes known to be associated with HSP. In 2016, when the panel was redesigned to incorporate recent literature on the subject, the number of genes had grown to 92. Somewhat disappointingly, this huge increase in the number of HSP-associated genes has not resulted in a significant increase in the diagnostic rate – the usual suspects are still the usual suspects.

Overall our gene panel screening has resulted in answers for 115 of 315 cases tested, a diagnostic rate of 36.5%. This may seem like quite a low rate, however it may well be that a significant percentage of the people tested for suspected HSP may, in fact, have a different neurodegenerative condition. It should not be assumed that all 315 likely have HSP and the testing available today can pick up only around 37%, so the real figure is likely somewhat higher, but not known at this point.

SPG4 most common closely followed by SPG7

As with most published studies globally, the SPAST gene associated with SPG4 type HSP accounts for the largest proportion of cases (35/115 – 30%), however the next most frequently identified gene in our laboratory is SPG7 (25/115 – 22%). This compares to recent studies in which SPG11 is the most common positive diagnosis after SPAST (Morais et al European Journal of Human Genetics (2017) 25, 1217–1228; Ishiura et al Journal of Human Genetics (2014) 59, 163–172). In our population, SPG11 accounts for just 4/115 (3%) of cases.

The difference is due in part to a specific SPG7 mutation that occurs with higher frequency in people of British ancestry than those of mainland European background – p.Ala510Val (Roxburgh et al, J Neurol 2013; 260:1286–1294). This variant accounts for about half of the SPG7 disease-associated alleles* that we see, and interestingly is also the most common pathogenic variant identified in our sporadic ataxia population. Despite this difference, however, the overall pick-up rate in published population studies is similar to ours (35.7% – 42%).

Genetic overlap between neurodegenerative conditions

The introduction of NGS gene panels that include genes for ataxia, HSP and motor neurone disease (MND) together in the one analysis has highlighted the genetic overlap in these phenotypes (physical characteristics or symptom profile). Mutations in SPAST and SPG11 have being identified in a small subset of MND patients and MFN2 mutations, normally associated with Charcot-Marie-Tooth disease (CMT) have been identified in several HSP cases, as well as the earlier mentioned association between SPG7 and ataxia.

Question mark hangs over genetics of undiagnosed cases

The question arises as to the cause of the nearly two thirds of cases still undiagnosed. Some cases may be due to variants in known genes that are of a type that is difficult to detect or interpret using current methods, such as non-coding variants. Others may be solved by adding newly-discovered disease genes to the analysis, and to the elucidation of novel inheritance patterns in known genes (such as dominant HSP mutations in KIF1A). Improved knowledge about the role of as yet poorly understood genetic regions such as non-coding RNAs may also help, however it is unlikely that any of these factors will result in substantial improvements to the overall diagnostic rate.

*Allele: Alleles are different variations of the same gene. For each gene, we have two alleles – one from each parent (like blue eyes or brown eyes).