Genetics of neurodegenerative diseases

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This issue contains a number of articles on neurodegenerative diseases, most of them genotypically analyzed with next-generation sequencing. Readers will find articles identifying potential mutations in new genes, articles examining different phenotypes associated with variation in the same gene, and a report showing an unusual phenotype associated with a known mutation in the *PRNP* gene. Finally, the imaging phenotypes of mutations in 2 different frontotemporal lobar dysfunction (FTLD) genes are compared.

Kohli et al.[1] used whole-exome sequencing (WES) on 11 affected individuals in an extended family with an apparent autosomal dominant pattern of late-onset Alzheimer disease (LOAD). They detected a likely damaging missense change in the tetratricopeptide repeat domain 3 (*TTC3*) gene in all affected individuals. *TTC3* is a regulator of Akt signaling, a key pathway disrupted in LOAD.

Nuytemans et al.[2] examined the overlap in the genetics of Parkinson disease (PD) and Alzheimer disease (AD) as it relates to variants in the ATP-binding cassette transporter A7 (*ABCA7*) gene. *ABCA7* is involved in clearance of aggregated proteins, and loss-of-function (LOF) variants in *ABCA7* are risk factors for AD. They therefore analyzed 396 unrelated patients with PD and 222 controls to search for *ABCA7* variants. Indeed, LOF variants were more common in patients with PD, indicating potentially shared pathways in AD and PD.

Mano et al.[3] examined 3 patients with apparent autosomal dominant PD and dementia. WES revealed a heterozygous c.314C>T (p.P105L) mutation in *PRNP*. This mutation is most commonly associated with spastic paraplegia. They then identified 2 additional families with the same mutation and a shared 7.1-Mbp haplotype among all individuals. This suggests the presence of a founder mutation and could also point to shared *cis*-acting variants (in addition to a valine at codon 129) predisposing to the parkinsonian presentation.

Ameur et al.[4] examined MRI changes in patients with behavioral variant FTLD. They showed that white matter lesions were more common in progranulin (*GRN*) mutation carriers than in individuals with *C9ORF72* repeat expansions. Many patients had extensive frontal white matter lesions in the absence of noteworthy cardiovascular risk factors.

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