Genetics of neurodegenerative diseases

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 frontal-temporal 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.

Amue 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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REFERENCES

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