This first issue of Neurology® Genetics is out and it reflects very well the diversity of today’s genetics. The approaches employed range from genome-wide association studies1 to whole-exome sequencing (WES)2–5 and targeted resequencing of a single gene.6 One study examines the effects of disease-causing mutations on subcellular compartmentalization.7 The disease phenotypes examined are just as diverse and include episodic disorders as well as diseases of the central and peripheral nervous systems.

A multinational consortium led by Aarno Palotie found a significant overlap of genetic risk loci for migraine and coronary artery disease (CAD).1 Surprisingly, the overlap was protective and limited to migraine without aura. In the accompanying editorial, Anne Ducros discusses the complex genetic landscape for various forms of migraine and their associated risk for CAD.6 In particular, she highlights the need to look at rare genetic variation and emphasizes the role of environmental and behavioral factors that could affect migraine subtypes differentially, especially the role of medications.

In a multisite study, Mitsumoto and colleagues2 prospectively examined patients with clinically definite primary lateral sclerosis. Using cluster analysis, 2 phenotypic groups emerged. Although most patients did not have detectable mutations, well-characterized heterozygous pathogenic mutations were identified in SPG7, DCTN1, and PARK2, and 1 patient had a C9ORF72 expansion.

Auranen and colleagues6 describe a targeted resequencing effort of the CHCHD10 gene in 107 probands with Charcot-Marie-Tooth disease type 2 (CMT2), as mutations in CHCHD10 had been identified in other neurodegenerative diseases. Six of 107 families with CMT2 carried a mutation in CHCHD10.

Several articles highlight the growing importance of next-generation sequencing methods for the diagnosis of neurologic disease. Auranen et al.4 used WES in 2 siblings with exercise intolerance, cramping, and infrequent myoglobinuria. Based on normal muscle phosphofructokinase (PFK) histochemistry, glycogen storage disease type VII was thought to be excluded. However, WES revealed a causative homozygous PFKM gene defect in both siblings, which was confirmed by very low residual PFK enzyme activity in biochemical studies. Pyle and colleagues3 report 5 patients with biochemical evidence of respiratory chain deficiencies and mutations in genes not usually associated with mitochondrial dysfunction. These variants would have been missed by targeted next-generation panels or on MitoExome analysis.

Pippucci and colleagues5 address the genetic heterogeneity of epilepsy with auditory features (EAF). From a large cohort of patients with EAF, they identified 15 probands without LGI1 mutations and used WES to identify a number of variants in CNTNAP2, DEPDC5, and SCN1A. Dhindsa and colleagues7 examine the functional consequences of mutations in DNM1, a cause of epileptic encephalopathy. They show that mutant DNM1 proteins decreased endocytosis activity in a dominant-negative manner, suggesting that dysfunction of vesicle scission may lead to early-onset epilepsies.

Finally, Brice and colleagues,9 reporting for the French Parkinson’s Disease Genetics Study Group and the International Parkinson’s Disease Genomics Consortium, describe a patient with typical early-onset Parkinson disease and mild intellectual disability. Given the phenotype, the consortium data-mined exomes from a large cohort of unrelated patients for changes in the RAB39B gene and identified a single patient with a new truncating mutation in RAB39B.

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Dr. Pulst holds patents for Nucleic acids encoding ataxin-2 binding proteins, Nucleic acid encoding Schwannomin-binding proteins and products related thereto, Transgenic mouse expressing a polynucleotide encoding a human ataxin-2 polypeptide, Methods of detecting spinocerebellar ataxia-2 nucleic acids, Nucleic acid encoding spinocerebellar ataxia-2 and products related thereto, Schwannomin-binding proteins, and Compositions and methods for spinocerebellar ataxia. He receives an honorarium from the AAN as the Editor of Neurology: Genetics. Go to Neurology.org/ng for full disclosure forms.

REFERENCES


