Spotlight on the June 2015 issue

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.8 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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**DISCLOSURE**

Stefan M. Pulst has served on the editorial boards of *Journal of Cerebellum, NeuroMolecular Medicine, Continuum, Experimental Neurology, Neugenetics,* and *Nature Clinical Practice Neurology* and as Editor-in-Chief of *Current Genomics.* Dr. Pulst conducts research supported by the NIH, Target ALS, and the National Ataxia Foundation. He has consulted for Ataxion Therapeutics, has received research funding from ISIS Pharmaceuticals, has served on a speakers’ bureau for Athena Diagnostics, Inc., and is a stockholder of Prognitor Life Sciences. He has received license fee payments from Cedars-Sinai Medical Center and has given expert testimony for Hall & Evans, LLC. Dr. Pulst has received publishing royalties from Churchill Livingstone (The Ataxias), AAN Press (Genetics in Neurology and Molecular Genetics in Neurology and Molecular Genetics).
REFERENCES


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