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, Misumoto 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 colleagues⁵ 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 colleagues⁶ address the genetic heterogeneity of epilepsy with auditory features (EAF). From a large cohort of patients with EAF, they identified 15 probands without LGII 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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No targeted funding reported.

DISCLOSURE
Stefan M. Pulst has served on the editorial boards of Journal of Cerebellum, NeuroMolecular Medicine, Continuum, Experimental Neurology, Neurogenetics, 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 Prognimor 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 Livingston (The Ataxias), AAN Press (Genetics in Neurology and Molecular Neurology.org/ng © 2015 American Academy of Neurology
Genetic Testing in Neurology, 2nd–5th editions), Academic Press (Genetics of Movement Disorders), and Oxford University Press (Neurogenetics).

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


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Stefan M. Pulst
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