Spotlight on the June 2015 issue

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Neurol Genet
2015;1:e11; doi: 10.1212/NXG.0000000000000011

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 studies[1] 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 colleagues[2] 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 colleagues[6] 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 colleagues[3] 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 colleagues[5] 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 colleagues[7] 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*.

STUDY FUNDING

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 Progenitor 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*

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Funding information and disclosures are provided at the end of the editorial. Go to Neurology.org/ng for full disclosure forms.

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

1. Winsvold BS, Nelson CP, Malik R, et al. Genetic analysis for a shared biological basis between migraine and coronary artery disease. Neurol Genet 2015;1:e10. doi: 10.1212/NXG.0000000000000010.
2. Mitsumoto H, Nagy PL, Gennings C, et al; for the PLS COSMOS Study Group. Phenotypic and molecular analyses of primary lateral sclerosis. Neurol Genet 2015;1:e3. doi: 10.1212/01.NXG.0000464294.88607.dd.
3. Pyle A, Nightingale HJ, Griffin H, et al. Respiratory chain deficiency in nonmitochondrial disease. Neurol Genet 2015;1:e6. doi: 10.1212/NXG.0000000000000006.
4. Auranen M, Palmio J, Ylikallio E, et al. *PFKM* gene defect and glycogen storage disease GSDVII with misleading enzyme histochemistry. Neurol Genet 2015;1:e7. doi: 10.1212/NXG.0000000000000007.
5. Pippucci T, Licchetta L, Baldassari S, et al. Epilepsy with auditory features: a heterogeneous clinic-molecular disorder. Neurol Genet 2015;1:e5. doi: 10.1212/NXG.0000000000000005.
6. Auranen M, Ylikallio E, Shcherbii M, et al. *CHCHD10* variant p.(Gly66Val) causes axonal Charcot-Marie-Tooth disease. Neurol Genet 2015;1:e1. doi: 10.1212/NXG.0000000000000003.
7. Dhindsa R, Bradrick SS, Yao X, et al. Epileptic encephalopathy–causing mutations in *DNM1* impair synaptic vesicle endocytosis. Neurol Genet 2015;1:e4. doi: 10.1212/01.NXG.0000464295.65736.da.
8. Ducros A. Are migraineurs naturally born "well-hearted"? Neurol Genet 2015;1:e8. doi: 10.1212/NXG.0000000000000008.
9. Lesage S, Bras J, Cormier-Dequaire F, et al. Loss-of-function mutations in *RAB39B* are associated with typical early-onset Parkinson disease. Neurol Genet 2015;1:e9. doi: 10.1212/NXG.0000000000000009.