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This issue contains a wide variety of articles covering new genes and mutations, unusual phenotypes, and a reminder that novel genetic technologies need to be paired with the appropriate mechanisms to inform patients of new results or annotations of DNA variants.

In an impressive combination of physiologic, morphologic, and genomic methods, Engel and coworkers[1] identify truncating homozygous mutation in *MUNC13-1* as the cause of microcephaly, cortical hyperexcitability, and fatal myasthenia. A likely common pathway for the patient's distinct aspects of the phenotype is the functional interaction of MUNC13-1 and syntaxin 1B.

The relatively new method of mendelian randomization (MR) is used by Rhead and colleagues[2] to study the relationship of vitamin D levels and multiple sclerosis. With the caveats inherent in MR analysis, they conclude that 25-hydroxyvitamin D levels are causally related to multiple sclerosis. For readers unfamiliar with MR, the authors' introduction and discussion provide a concise summary of the promises and limitations of MR to detect causal relationships.

Hirst and colleagues[3] analyze patients with biallelic mutations in *AP5Z1* usually associated with a spastic paraplegia phenotype (SPG48). They find a much wider phenotypic spectrum including a variety of movement disorders. Consistent with these phenotypic observations, electron microscopy of skin fibroblasts detected PAS-positive multilamellar storage material consistent with a role for AP5 in endolysosomal processing.

KCNQ2 encodes a potassium channel subunit that forms a homotetramer or heterotetramer for proper channel function. Millichap and colleagues[4] further characterize the epileptic encephalopathy associated with *KCNQ2* mutation and improvements of seizures with ezogabine in a subgroup of patients. The study also emphasizes the severity of dominant-negative mutations as compared to other *KCNQ2* mutation types usually associated with benign familial neonatal epilepsy.

A novel cause for late-onset autosomal dominant ataxia with neuropathy in a 5-generation Belgian family is described by Depondt et al.[5] The mutation occurred in the *MME* gene and was a C143Y amino acid substitution. Of note, recessive mutations in this gene have been described in Japanese patients with axonal neuropathy.

Van der Zee and colleagues[6] describe a homozygous mutation in the *CTSF* (cathepsin F) gene as the cause for autosomal recessive neuronal ceroid lipofuscinosis (Kufs disease). As some members of this family showed marked frontal lobe dysfunction without seizures, the authors screened a large panel of patients with frontotemporal dementia. Two unrelated individuals carried a heterozygous variant and later developed a progressive supranuclear palsy–like phenotype. The role of *CTSF* in frontotemporal dementia will need further analysis in other populations.

These full-length articles are complemented by 6 Clinical/Scientific Notes on late-onset Lafora disease due to *EPM2a* mutation,[7] the analysis of a glucocerebrosidase variant in Parkinson disease (Mallet et al.[8]), the causation of Leigh syndrome by a mutation in *MT-TL2*,[9] a novel de novo missense mutation in *GNB1* causing dystonia and intellectual disability,[10] and novel *TK2* mutations as a cause of delayed muscle maturation.[11]

Finally, the medical and ethical mandates to offer carrier testing to women at risk of being carriers of a Duchenne muscular dystrophy mutation are presented by Bogue and Ramchandren.[12] The evolving landscape of improved genetic technologies and the "duty to reassess" and recontact family members is further discussed in the accompanying editorial by Newcomb and Flanigan.[13]

NOTE ADDED IN PROOF After publication of the identification of *MME* mutations as the cause of SCA43 by Depondt et al.[5] in this issue, Auer-Grumbach et al.[14] identified dominant *MME* mutations in patients with late-onset axonal neuropathies.

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