IN THIS ISSUE

Migalastat treatment benefits Fabry disease patients with amenable variants

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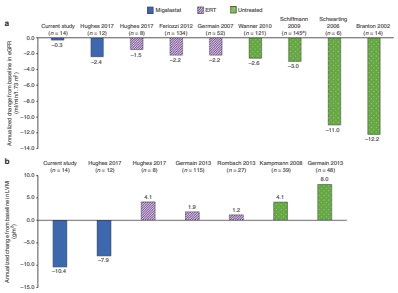

Fabry disease is a rare progressive X-linked lysosomal storage disorder. Pathogenic variants in the *GLA* gene that lead to functional deficiency of α-galactosidase A (α-Gal A) underpin the disease causing globotriaosylceramide (GL-3 or Gb_3) to accumulate in lysosomes. Untreated patients with the condition show a wide range of symptoms, including peripheral neuropathy, cardiovascular disease, stroke, end-stage renal disease, gastrointestinal disorders, and premature death. Currently, enzyme replacement therapy is the standard treatment, but lifelong biweekly infusions can be burdensome to patients and reduce adherence. However, migalastat, a first-in-class small-molecule chaperone, is an alternative therapeutic option for patients with amenable *GLA* variants. In a phase III placebo-controlled clinical trial called the FACETS study, migalastat improved symptoms in Fabry disease patients with such variants. As reported in this issue, Germain et al. gauged the clinical benefit of migalastat for males in the FACETS study with classic Fabry disease. Patients in the study received 150 mg migalastat every other day. The researchers assessed changes in measurements of disease severity, including glomerular filtration rate, left ventricular mass index, number of GL-3 inclusions per renal peritubular capillary (PTC), plasma lyso-Gb_3 levels, peripheral blood mononuclear cell (PBMC) α-Gal A activity, and diarrhea symptoms from baseline through 24 months. Patients who received migalastat showed improved measures. For example, at month 24, the mean annualized change in glomerular filtration rate was -0.3 mL/min/1.73 m^2 and the average annualized change in left ventricular mass index was -16.7 g/m^2. The results indicate that patients taking migalastat showed improved renal and cardiac status. Likewise, diarrhea symptoms improved (mean annualized change -0.9) and lyso-Gb_3 levels (-36.8 nmol/L) and PTC GL-3 inclusions (-0.7) decreased. Additionally, α-Gal A activity increased 8.2-fold above baseline. The authors conclude that migalastat provides beneficial clinical outcomes for male patients with the most severe form of Fabry disease, and they support treatment with migalastat in patients with amenable variants. —*V. L. Dengler, News Editor*

Genetic analyses reveal how primary and secondary microcephaly differ

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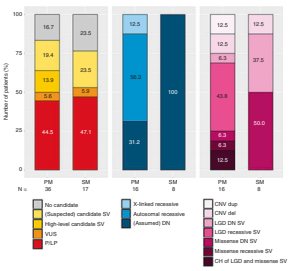

Microcephaly, an abnormally small head for age, sex, and ethnicity, affects 2–3% of the global population. Although microcephaly presents as a feature of many genetic syndromes, systematic evaluation of the condition itself is rare. Only two previous studies were identified that used sequencing to find disease-causing or candidate genes in microcephaly cohorts. Neither study distinguished between primary microcephaly, which presents at birth, and secondary microcephaly, which develops after birth. Boonsawat et al. combined high-resolution chromosomal microarray analysis and exome sequencing to illuminate the genetic landscape of primary and secondary microcephaly in a cohort of 62 patients. Following recruitment to the study, patients underwent detailed clinical and genetic assessments. The researchers determined that 58% of patients (36/62) in the cohort had primary microcephaly (PM) and 27% (17/36) had secondary microcephaly (SM). Sequencing analysis identified pathogenic or likely pathogenic causative variants in 48% of the total cohort and variants of uncertain significance in 5% of patients. Diagnostic yield was similar for the PM (44%) and SM (47%) subcohorts, yet Boonsawat and colleagues noted that the subcohorts displayed different modes of inheritance. The researchers saw predominantly autosomal recessive inheritance and biallelic likely gene-disrupting (LGD) variants in PM patients, suggesting that complete lack of protein may be the most common cause of the condition. In contrast, dominant de novo LGD or assumed loss-of-function missense variants were frequently seen in the SM subcohort, implicating haploinsufficiency as a mechanism. Additionally, the researchers identified 22 candidate genes plus 26 suspected candidate genes in the cohort. Five of the identified genes are novel: four (*SPAG5*, *TEDC1*, *VPS26A*, and *DDX1*) with biallelic variants and one (*ZNFR3*) with a de novo variant. Unexpectedly, the researchers also found likely pathogenic variants in mitochondria-related genes in three patients, highlighting the role of mitochondrial disorders in microcephaly. The authors conclude that PM and SM are heterogeneous conditions and that furthering the understanding of differences between the two, including genetic underpinnings, may ultimately aid patient management. —*V. L. Dengler, News Editor*

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