GMPPB-Associated Dystroglycanopathy: Emerging Common Variants with Phenotype Correlation.

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Abstract

Mutations in GDP-mannose pyrophosphorylase B (GMPPB), a catalyst for the formation of the sugar donor GDP-mannose, were recently identified as a cause of muscular dystrophy resulting from abnormal glycosylation of α-dystroglycan. In this series, we report nine unrelated individuals with GMPPB-associated dystroglycanopathy. The most mildly affected subject has normal strength at 25 years, whereas three severely affected children presented in infancy with intellectual disability and epilepsy. Muscle biopsies of all subjects are dystrophic with abnormal immunostaining for glycosylated α-dystroglycan. This cohort, together with previously published cases, allows preliminary genotype-phenotype correlations to be made for the emerging GMPPB common variants c.79G>C (p.D27H) and c.860G>A (p.R287Q). We observe that c.79G>C (p.D27H) is associated with a mild limb-girdle muscular dystrophy phenotype, whereas c.860G>A (p.R287Q) is associated with a relatively severe congenital muscular dystrophy typically involving brain development. Sixty-six percent of GMPPB families to date have one of these common variants.

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