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## INTRAFAMILIAL VARIABILITY IN GMPPB-ASSOCIATED DYSTROGLYCANOPATHY: BROADENING OF THE PHENOTYPE

Dystroglycanopathies are characterized by deficient O-mannosyl glycosylation of  $\alpha$ -dystroglycan ( $\alpha$ DG) and represent an expanding genetically, biochemically, and clinically heterogeneous group of muscular dystrophies. Currently, there are 18 known genes leading to forms of  $\alpha$ -dystroglycan-related dystrophy ( $\alpha$ DG-RD), ranging in severity from a Walker-Warburg phenotype with severe brain malformations and hypotonia to milder childhood- or adult-onset limb-girdle muscular dystrophy (LGMD) phenotypes with or without intellectual disability.<sup>1,2</sup>

We report 3 siblings with mutations in a recently identified  $\alpha$ DG gene, GDP-mannose pyrophosphorylase B (*GMPPB*),<sup>3</sup> with variable degrees of weakness and a striking spectrum of early developmental cognitive involvement in all 3 patients, as well as epilepsy in one of the 3 siblings. Ocular abnormalities and elevated creatine kinase (CK) occurred in all. These patients highlight the interfamilial and intrafamilial phenotypic variability that can exist with *GMPPB* mutations.

**Methods.** See appendix e-1 on the *Neurology*<sup>®</sup> Web site at [Neurology.org](http://Neurology.org) for a description of the Methods.

**Results.** Patients P1, P2, and P3 are siblings ages 19, 17, and 14 years old, respectively, with an LGMD pattern but variable degrees of weakness and elevated CK levels (range 3,015–18,685) (table). Patient P1 had early epilepsy and intellectual disability, and later presented with mild fatigue with exercise (at 12–13 years old) and slow running, while patient P2 had unexplained fatigue and elevated liver function tests at age 6 years, and then more notable and progressive weakness since age 12 years, with near loss of ambulation since age 16 years. Additional findings include intractable epilepsy (1/3), variable degrees of intellectual disability (3/3), ocular findings (3/3), headaches (2/3), and unexplained splenomegaly (1/3). None of the patients has known cardiac involvement.

Muscle biopsy in P2 (figure e-1) at age 11 years was dystrophic with reduced  $\alpha$ DG glycodependent immunostaining in an irregular pattern, and with normal dystrophin,  $\beta$ -dystroglycan, and sarcoglycan

staining. Laminin  $\alpha$ 2 (merosin) immunoreactivity was slightly decreased in a few fibers. Muscle imaging revealed variable degrees of myopathic changes in all 3 patients, and areas consistent with fatty infiltration in P2 and P3 (figure e-1).

Sequencing of *GMPPB* revealed compound heterozygous mutations: in exon 1 c.79G>C (p.Asp27His), previously reported,<sup>3</sup> and a maternally inherited heterozygous novel sequence variant c.790C>T (p.Gln264\*) in all 3 affected siblings. Paternal segregation testing was not available, but the c.79G>C mutation was not present in the mother.

**Discussion.** Many of the  $\alpha$ DG-RD genes encode glycosyltransferases that add O-linked mannose to  $\alpha$ DG or contribute to the synthesis of the final LARGE-dependent glycan that binds to extracellular matrix ligands or are kinases or proteins of unknown function acting along the same pathway towards this final glycoepitope.<sup>3–5</sup> In contrast, *GMPPB* function is important for the production of GDP mannose, the major mannosyl donor necessary for 4 mannosylation dependent pathways of which  $\alpha$ DG mannosylation is one. While there could thus be impairment of multiple GDP-mannose dependent pathways, *GMPPB* patients do not seem to show the extent of multisystem organ involvement often seen in patients with typical congenital disorders of glycosylation (CDG syndromes).<sup>1,3,6</sup>

The 3 siblings reported here are notable for their variable severity of weakness, intellectual disability, and ophthalmologic findings. All but 1 patient thus far described in the literature with *GMPPB* mutations has had intellectual disability, while intractable epilepsy was seen in 3/10 previously reported patients.<sup>3,6</sup> However, there has been no report of affected patients with a mild later onset motor phenotype and severe CNS findings. Carss et al.<sup>3</sup> reported patients with severe intellectual disability who had early-onset CMD phenotype with severe motor weakness. Muscle imaging, not previously reported in this disorder, reveals increased T1 hyperintensity and seems to correlate with the degree of weakness without a selective pattern (figure e-1).

There are currently no clear genotype/phenotype correlations. The degree of intrafamilial variability in our patients is striking. The p.Asp27His identified

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Table	Clinical and diagnostic summary		
	P1	P2	P3
Sex	Male	Female	Female
Current age, y	19	17	14
Presenting symptoms (age at presentation, y)	Intellectual disability (2-3); epilepsy (6)	Intellectual disability (5-6); fatigue (6-7)	Intellectual disability <sup>a</sup> ; fatigue (13)
Early gross motor development, mo	Sat, 5-6; crawled, 6-7; walked, 13	Sat, 6; crawled, 7-8; walked, 12	Sat, 5-6; crawled, 6-7; walked, 12
Maximum motor ability	Running, stair climb (no railing), jumping	Running (slowly), stair climb (with railing)	Running (slowly), stair climb (no railing), jumping
Presenting motor findings (age at presentation, y)	Fatigue with exercise (12-13)	Frequent falls and pain in arms and legs (12 <sup>b</sup> )	Early fatigue with exercise (13-14)
Severity of current motor impairment (description of function)	Minimal/mild (ambulatory, runs slowly, early fatigue, jumps)	Moderate to severe (wheelchair use, can ambulate short distance)	Mild (ambulatory, runs very slowly, early fatigue)
Current motor examination	Mild calf hypertrophy; mild proximal weakness (4-4+/5 in proximal UE and LE); normal distal strength; arise supine to stand without Gowers; runs without clearing feet well from floor	Prominent calf hypertrophy; moderate proximal weakness (4/5 UE and 3/5 LE); normal distal strength; positive Gowers maneuver on arise from supine to stand; Trendelenburg gait, unable to run	Mild calf hypertrophy; mild/moderate proximal weakness (4/5 UE and 3+ to 4-/5 LE); normal distal strength; positive Gowers maneuver on arise from supine to stand; normal walking; runs slowly
Onset of CNS findings, y	2 1/2	By 5	School age (mild) <sup>a</sup>
Main CNS features	Intellectual disability, epilepsy, ADHD, migraines	Intellectual disability, headaches	Mild intellectual disability
Neuropsychological findings, IQ <sup>c</sup>	49	58	81
GI features	Mild pharyngeal phase dysphagia	Mild pharyngeal phase dysphagia	Mild pharyngeal phase dysphagia, splenomegaly
Cardiac features	Normal EKG and echo	Normal EKG and echo	Pending evaluation
Ophthalmologic findings	Refractive amblyopia, cataracts (severe), pigmentary glaucoma	Cataracts (mild)	Polychromatic cataracts (mild), hyperopia
Brain MRI findings	Borderline bilateral cortical thinning within the posterior margins of the motor and sensory cortices; no evidence of brainstem or cerebellar atrophy	Normal	Not performed
CK level	18,685 (high)	15,511 (high)	3,015 (high)
EMG	Myopathic	Myopathic	Not performed
Muscle MRI	Normal muscle bulk, mild increase in T1 hyperintensity, normal subcutaneous fat	Normal to increased muscle bulk, moderate increase in T1 hyperintensity, <sup>d</sup> increased subcutaneous fat	Normal muscle bulk, mild increase in T1 hyperintensity, increased subcutaneous fat
Muscle ultrasound	Mild myopathic changes in a proximal pattern (leg > arm involvement)	Mild myopathic changes in a proximal pattern (leg > arm involvement)	Mild myopathic changes in a proximal pattern (leg > arm involvement)
Previous genetic testing	Not performed	Negative: <i>FKRP</i> , <i>FKTN</i> , <i>LARGE</i> , <i>POMGNT1</i> , <i>POMT1</i> , <i>POMT2</i> , <i>CAPN3</i> , <i>LMNA</i> , <i>CAV3</i> , <i>SGCA</i> , <i>SGCB</i> , <i>SGCD</i> , <i>SGCG</i> , <i>DYSF</i> , <i>ISPD</i>	Not performed

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CK = creatine kinase; LE = lower extremities; UE = upper extremities.

<sup>a</sup> Age at first cognitive concern is unclear; has required modified curriculum (not special education) in school.

<sup>b</sup> On retrospective review, the patient likely had preexisting proximal weakness as she did not ever climb stairs without the use of a railing; however, the motor impairment or weakness did not become more evident to her family and providers until closer to 12 years of age.

<sup>c</sup> Full-scale IQ based on Wechsler Scale appropriate for age—classification is as follows: 90-109 (average); 80-89 (low average); 70-79 (borderline); 69 and below (intellectual disability).

<sup>d</sup> The posterior thigh compartment (especially semitendinosus and biceps femoris muscles) shows more increased T1 signal intensity as compared to the anterior compartment in patient P2.

in our family was previously reported in a boy with LGMD who had normal cognitive function and absent eye findings. The phenotype in our patients with significant brain and lens involvement is likely due to compound heterozygosity with the loss of function mutation p.Gln264\*. Another patient

heterozygous for a null mutation (p.Arg74\*) in *GMPPB* (associated with the missense p.Asp334Asn mutation) presented with a muscle-eye-brain phenotype, while the phenotype of homozygous null or 2 different heterozygous null *GMPPB* mutations is unknown.

Our findings implicate that intellectual disability or epilepsy may be the predominant early manifestations of disease in patients with *GMPPB* mutations or other genotypic forms of  $\alpha$ -dystroglycan-related dystrophies. Our observation suggests the usefulness of early CK determination in all patients with intellectual disability, developmental delay, or otherwise unexplained epilepsy.

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