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The Author Reply: Genotypic and Phenotypic Heterogeneity of LGMD1D due to *DNAJB6* Mutations

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Dear Editor,

Limb-girdle muscular dystrophies type 1D (LGMD1D) is generally known as an adult-onset musculoskeletal disease. However, according to reports, there are cases of onset in children, including Nam, et al.'s study.[1] Although most patients with LGMD1D are characterized by an onset in adulthood, some develop at an early age, and as noted, the age of disease onset can vary. Our patients also presented with various clinical manifestations. In our patients, there was no significant evidence of cardiac involvement based on past history, clinical symptoms and signs, findings on physical examination, laboratory data, and chest X-ray. The possibility of subclinical cardiac abnormality in our patients cannot be ruled out completely, however, alhough we believe that our patients did not have cardiac abnormalities at that time.

In addition, serum creatine kinase (CK) levels (our normal range: 35–232 IU/L) are a useful clinical biomarker, but fluctuate and vary, even at low levels in a muscle atrophy state. The serum CK levels of our patients were normal to mildly elevated. The first patient had a CK level of 175 IU/L, and the second patient had levels of 504 IU/L and 673 IU/L on two tests. The last patient had a level of 301 IU/L.

We also agree that the phenotype of LGMD1D may appear more heterogeneous than we thought. This has been confirmed from the paper published by Ruggieri, et al.[2] According to the paper, patients with proximal G/F domain mutations (Phe89, Phe91, and Phe93) in *DNAJB6* show proximal limb-girdle weakness, whereas patients with distal G/F domain mutations (Pro96 and Phe100) expereience distal leg weakness.

We stated more than nine mutations in the *DNAJB6* gene have been reported, including p.Phe89Ile, p.Phe91Ile, pPhe-91Leu, p.Phe93Ile, p.Phe93Leu, p.Pro96Arg, p.Pro96Leu, p.Phe-100Val, and p.Phe100Ile. Recently, two mutations (c.284A>T, p.Asn95Ile, two families; and c.293_295delATG, p.Asp98del, one family) were reported.[3] Thus, at least 11 different mutations have been identified so far (Table 1). As next generation sequencing becomes more wildly used, additional novel mutations will be identified.

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Table 1. Clinical Features and Genetic Findings for *DNAJB6* Mutations

Genotype	References	Region of study	Onset age	Distribution of weakness	Serum CK	Muscle pathology	Bulbar symptoms
p.Phe89Ile	Kim, et al.[4]	Asia	30–40	Proximal	NL	N/A	None
	Couthouis, et al.[5]	America	8–18	Proximal	NL	RV	-
	Sarparanta, et al.[6]	America	20–55	Proximal	NL–10×	Myopathic, RV	Yes
p.Phe91Ile	Palmio, et al.[7]	Europe	6–13	Proximal	NL–2×	RV, fibrosis, atrophy, myofibrillar aggregations	None
	Ruggieri, et al.[2]	Europe	16	Proximal	NL	Dystrophic, RV	None
p.Phe91Leu	Nam, et al.[1]	Asia	8–11	Proximal	NL–2×	RV	None
	Palmio, et al.[7]	Europe	15	Proximal and distal	NL	RV, Fibrosis, atrophy, myofibrillar aggregations	Yes
	Ruggieri, et al.[2]	Europe	11	Proximal	NL	Myopathic, RV	Yes
p.Phe93Ile	Sato, et al.[8]	Asia	30s	Proximal	1.5–5×	Myopathic, RV	None
p.Phe93Leu	Harm, et al.[9]	America	30–40	Proximal	3–6×	Myopathic, RV	None
	Ruggieri, et al.[2]	Europe	45	Proximal	NL	Myopathic, RV	None
p.Ans95Ile	Jonson, et al.[3]	Europe	36–55	Distal	NL–2×	RV	Yes
p.Pro96Arg	Harm, et al.[9]	African American	18–35	Distal	2×	N/A	None
p.Pro96Leu	Tsai, et al.[10]	Asia	30–40	Proximal	NL	Fatty change	Yes
p.Asp98del	Jonson, et al.[3]	Europe	16, 20	Proximal and distal	2×	RV	None
p.Phe100Val	Ruggieri, et al.[2]	Europe	10–50	Proximal and distal	1.5–4×	RV	Yes
p.Phe100Ile	Kim, et al.[4]	Asia	17, 27	Proximal and distal	3×	RV	Yes

N/A, not available; NL, normal; RV, rimmed vacuole.

one DNAJB6 cause limb-girdle muscular dystrophy. Nat Genet 2012;44:450-5.
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