Limb-girdle muscular dystrophy due to *GMPPB* mutations: A case report and comprehensive literature review

LiuQing Sun[1], DingGuo Shen[2], Ting Xiong[2], Zhibin Zhou[1], Xianghui Lu[1], Fang Cui[1]*

ABSTRACT

Mutations in the guanosine diphosphate mannose (GDP-mannose) pyrophosphorylase B (*GMPPB*) gene are rare. To date, 72 cases with *GMPPB* gene mutations have been reported. Herein, we reported a case of a 29-year-old Chinese male presenting with limb-girdle muscular dystrophy (LGMD) who was found to have two heterozygous *GMPPB* mutations. The patient had a progressive limb weakness for 19 years. His parents and elder brother were healthy. On examination he had a waddling gait and absent tendon reflexes in all four limbs. Electromyography showed myogenic damage. Muscle magnetic resonance imaging (MRI) showed fatty degeneration in the bilateral medial thigh muscles. High-throughput gene panel sequencing revealed that the patient carried compound heterozygous mutations in the *GMPPB* gene, c.553C>T (p.R185C, maternal inheritance) and c.346C>T (p.P116S, paternal inheritance). This case provides additional information regarding the phenotypic spectrum of *GMPPB* mutations in the Chinese population.

KEYWORDS: Dystroglycanopathy; limb-girdle muscular dystrophy (LGMD); guanosine diphosphate mannose (GDP-mannose) pyrophosphorylase B gene; GMPPB mutations; heterozygous mutations; high throughput gene panel sequencing

INTRODUCTION

Dystroglycanopathies are a group of clinically heterogeneous inherited neuromuscular disorders caused by reduced glycosylation of α-dystroglycan (α-DG) [1]. Mutations in the guanosine diphosphate mannose (GDP-mannose) pyrophosphorylase B (*GMPPB*) gene resulting in reduced α-DG glycosylation were first described by Carss et al. in 2013, in muscle biopsies of patients with dystroglycanopathy [2]. Subsequently, a study on zebrafish showed that *GMPPB* knockdown caused structural muscle defects with decreased motility, eye abnormalities, and reduced glycosylation of α-DG, indicating that the *GMPPB* gene is responsible for dystroglycanopathies [2]. To date, at least 72 patients with *GMPPB* gene mutations have been reported [3]. The phenotypes of *GMPPB* mutations are extremely heterogeneous, including adult-onset limb-girdle muscular dystrophy type 2T (LGMD2T), congenital muscular dystrophies (CMD), isolated rhabdomyolysis and congenital myasthenic syndrome (CMS) with/without elevated serum creatine kinase (CK) level, intellectual disability, epilepsy, eye diseases, and heart and brain abnormalities [2,4-6]. Herein, we report the case of a 29-year-old Chinese male presenting with LGMD who was found to have two heterozygous *GMPPB* mutations.

CASE REPORT

This study was approved by the Institutional Review Board of our hospital. Written informed consent was obtained from the patient for the use and publication of his data for research purposes.

A 29-year-old Chinese male arrived to our hospital with a complaint of long-term progressive limb weakness. At the age of 10, he had difficulty climbing stairs, could not run fast, and became fatigued easily. The symptoms gradually became more severe after the age of 16. He had no history of other diseases. He was the second child of his non-consanguineous parents. His parents and elder brother were without similar symptoms. On examination, he had a waddling gait and had no tendon reflexes in all four limbs. Muscle strengths were: facial (5/5), deltoid (4/5), quadriceps (4/5), iliopsoas (4/5), and gastrocnemius (5/5). His maximum serum CK level was 2.495 U/L. Holter electrocardiography (ECG) monitoring for 24 hours was normal. Electromyography studies showed myogenic damage. Muscle magnetic resonance imaging (MRI) showed fatty

[1]Department of Neurology, Hainan Branch of Chinese PLA General Hospital, Sanya, Hainan Province, China
[2]Department of Neurology, Xi'an Gaoxin Hospital, Xi'an, Shanxi Province, China

*Corresponding author: Fang Cui, Department of Neurology, Hainan Branch of Chinese PLA General Hospital, Haitang Bay, Sanya, Hainan Province 572013, China. Phone: +86-0898-37330626; Fax: +86-0898-37330626. E-mail: cuifang301@sina.cn

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degeneration in the bilateral medial thigh muscles (Figure 1). Brain MRI was normal.

High-throughput gene panel sequencing of genes related to 14 types of hereditary neuromuscular diseases (V3-panel; MyGenostics, Inc., Beijing, China) was performed. The results showed the patient carried two compound heterozygous mutations in the *GMPPB* gene. Both mutations were missense mutations: c.553C>T (p.R185C) and c.346C>T (p.P116S). In addition, both of the variants were rare and not polymorphisms. Sanger sequencing of his parents suggested that the c.553C>T mutation was maternally inherited and that the c.346C>T mutation was paternally inherited (Figure 2). Based on these data, his clinical history, and physical examination findings the patient was diagnosed with LGMD2T. He was treated with B-complex vitamins (neurotrophic therapy), but his symptoms were only minimally affected.

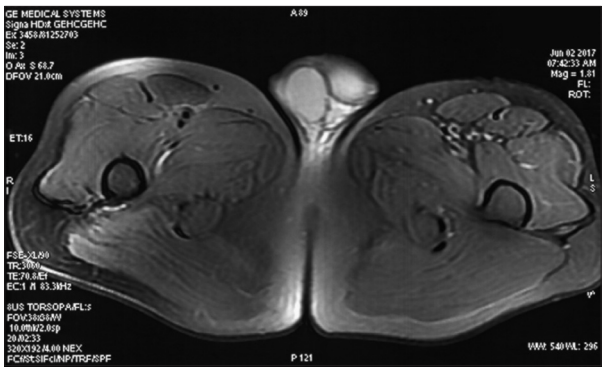

FIGURE 1. Magnetic resonance imaging (MRI) of the lower extremities. Images were acquired at the level of the upper femur. The T2WI fat suppression sequence showed slight atrophy and suspicious inflammatory changes of the left lateral femoral muscle and tensor fascia lata.

DISCUSSION

α-DG is a cell membrane protein located on muscle cells and on Schwann cells in the nervous system that undergoes extensive N-linked and O-linked glycosylation. Glycosylation is required so that α-DG can interact with other extracellular proteins. One of the results of defective α-DG glycosylation is reduced muscle contraction [7]. Thus, mutations in α-DG glycosylation-associated genes may lead to dystroglycanopathies. Currently, 18 genes involved in α-DG glycosylation have been identified, including *FKTN*, *POMGnT1*, and *FKRP* [8].

GMPPB is a cytoplasmic enzyme that catalyzes the formation of GDP-mannose, a key substrate for several glycosylation pathways, including *O*-mannosylation of α-DG [2]. Mutations in the *GMPPB* gene have recently been identified to cause α-DG glycosylation disorders [2]. Since *GMPPB* mutations causing disorders of α-DG glycosylation were first described by Carss et al. in 2013, 72 cases have been reported in the literature (Table S1) [3-6,8-15]. Most of the cases were reported in Caucasian individuals. *GMPPB* mutations are most commonly associated with LGMD2T (50% [36/72] of the cases) followed by CMS (29% [21/72] of the cases). Other phenotypes include CMD, muscular dystrophy-dystroglycanopathy (MDDG), congenital muscular dystrophy with cerebellar involvement (CMD-CRB), congenital muscular dystrophy with mental retardation (CMD-MR), and isolated rhabdomyolysis. The c.79G>C mutation is the most frequent *GMPPB* mutation. Other common *GMPPB* mutations include c.859C>T and c.860G>A [3-6,8-15].

Recently, Luo et al. reported 5 Chinese patients (belonging to 3 families) with compound heterozygous

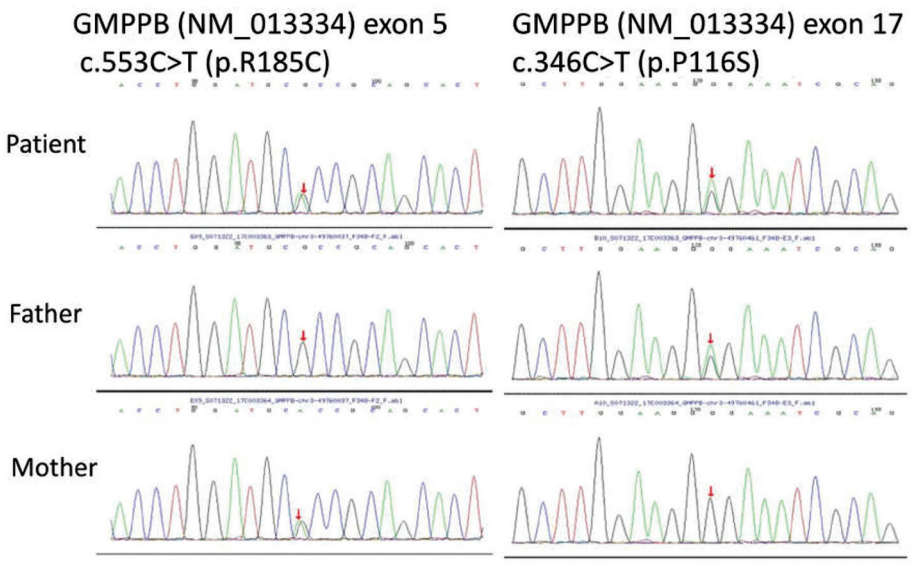

FIGURE 2. Sanger sequencing of the patient and his parents. The c.553C>T mutation was maternally inherited, and the c.346C>T mutation was paternally inherited.

GMPPB mutations, including c.1070G>A, c.1018G>A, c.C877T, and c.C966A [5]. Of them, c.1070G>A was found in all 5 patients [5]. Our patient was found to have compound heterozygous *GMPPB* mutations. The homozygous missense mutation c.553C>T has been reported in two Mexican, one Egyptian [2], and three Spanish patients [16]. The mutation changes the highly conserved arginine to cysteine (p.R185C). The 185th amino acid, arginine, is conserved throughout several species, including humans, chimpanzees, mice, zebrafish, *Drosophila*, and *Caenorhabditis elegans*, indicating its functional importance [2]. Previous studies have shown that patients homozygous for the c.553C>T mutation present with phenotypes including CMD, LGMD/CMS overlap syndromes, and LGMD (as young as 2.5 years old) [2], cataracts, mental retardation, epilepsy, and elevated serum CK levels [2,16].

The symptoms in our patient were relatively mild. The onset of LGMD was at 10 years of age, and he had no intellectual disability or eye disease. However, his serum CK level was elevated, which is consistent with previous studies [2,16]. The discrepancy in phenotypes might be attributed to the compound heterozygous mutations in our patient; however, further investigation is needed to examine this finding. The other missense mutation (c.346C>T, p.P116S) has not been reported in previous studies; this mutation changes the highly conserved proline (116th amino acid) to serine.

LGMD is the most common phenotype of *GMPPB*-associated dystroglycanopathies [3-6,8-15]. In 2015, Belaya et al. reported that some patients with *GMPPB* mutations present with CMS, defined as decreased compound muscle action potentials on repetitive nerve stimulation on electromyography [4]. This finding suggests that the neuromuscular junctions from the central to peripheral nervous system may be affected and that electromyography examination for patients with *GMPPB* mutations should include repetitive nerve stimulation tests. Even though our patient experienced severe fatigue, he did not exhibit a decrease of compound muscle action potentials on repetitive nerve stimulation.

In summary, we have reported a novel *GMPPB* mutation in a Chinese male with LGMD. This case provides additional information regarding the phenotypic spectrum of *GMPPB* mutations in the Chinese population.

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REFERENCES

[1] Taniguchi-Ikeda M, Morioko I, Iijima K, Toda T. Mechanistic aspects of the formation of alpha-dystroglycan and therapeutic research for the treatment of alpha-dystroglycanopathy: A review. Mol Aspects Med 2016;51:115-24. https://doi.org/10.1016/j.mam.2016.07.003.

[2] Carss KJ, Stevens E, Foley AR, Cirak S, Riemersma M, Torelli S, et al. Mutations in GDP-mannose pyrophosphorylase B cause congenital and limb-girdle muscular dystrophies associated with hypoglycosylation of α-dystroglycan. Am J Hum Genet 2013; 93(1):29-41. https://doi.org/10.1016/j.ajhg.2013.05.009.

[3] Sarkozy A, Torelli S, Mein R, Henderson M, Phadke R, Feng L, et al. Mobility shift of beta-dystroglycan as a marker of GMPPB gene-related muscular dystrophy. J Neurol Neurosurg Psychiatry 2018;89(7):762-8. https://doi.org/10.1136/jnnp-2017-316956.

[4] Belaya K, Rodríguez Cruz PM, Liu WW, Maxwell S, McGowan S, Farrugia ME, et al. Mutations in GMPPB cause congenital myasthenic syndrome and bridge myasthenic disorders with dystroglycanopathies. Brain 2015;138(9):2493-504. https://doi.org/10.1093/brain/awv185.

[5] Luo S, Cai S, Maxwell S, Yue D, Zhu W, Qiao K, et al. Novel mutations in the C-terminal region of GMPPB causing limb-girdle muscular dystrophy overlapping with congenital myasthenic syndrome. Neuromuscul Disord 2017;27(6):557-64. https://doi.org/10.1016/j.nmd.2017.03.004.

[6] Cabrera-Serrano M, Ghaoui R, Ravenscroft G, Johnsen RD, Davis MR, Corbett A, et al. Expanding the phenotype of GMPPB mutations. Brain 2015;138(4):836-44. https://doi.org/10.1093/brain/awv013.

[7] Adams JC, Brancaccio A. The evolution of the dystroglycan complex, a major mediator of muscle integrity. Biol Open 2015;4(9):1163-79. https://doi.org/10.1242/bio.012468.

[8] Montagnese F, Klupp E, Karampinos DC, Biskup S, Gläser D, Kirschke JS, et al. Two patients with GMPPB mutation: The overlapping phenotypes of limb-girdle myasthenic syndrome and limb-girdle muscular dystrophy dystroglycanopathy. Muscle Nerve 2017;56(2):334-40. https://doi.org/10.1002/mus.25485.

[9] Raphael AR, Couthouis J, Sakamuri S, Siskind C, Vogel H, Day JW, et al. Congenital muscular dystrophy and generalized epilepsy caused by GMPPB mutations. Brain Res 2014;1575:66-71. https://doi.org/10.1016/j.brainres.2014.04.028.

[10] Bharucha-Goebel DX, Neil E, Donkervoort S, Dastgir J, Wiggs E, Winder TL, et al. Intrafamilial variability in GMPPB-associated dystroglycanopathy: Broadening of the phenotype. Neurology 2015;84(14):1495-7. https://doi.org/10.1212/WNL.0000000000001440.

[11] Jensen BS, Willer T, Saade DN, Cox MO, Mozaffar T, Scavina M, et al. GMPPB-associated dystroglycanopathy: Emerging common variants with phenotype correlation. Hum Mutat 2015;36(12):1159-63. https://doi.org/10.1002/humu.22898.

[12] Rodríguez Cruz PM, Belaya K, Basiri K, Sedghi M, Farrugia ME, Holton JL, et al. Clinical features of the myasthenic syndrome arising from mutations in GMPPB. J Neurol Neurosurg Psychiatry 2016;87(8):802-9. https://doi.org/10.1136/jnnp-2016-313163.

[13] Oestergaard ST, Stojkovic T, Dahlqvist JR, Bouchet-Seraphin C, Nectoux J, Leturcq F, et al. Muscle involvement in limb-girdle muscular dystrophy with GMPPB deficiency (LGMD2T). Neurol Genet 2016;2(6):e112. https://doi.org/10.1212/NXG.0000000000000112.

[14] Panicucci C, Fiorillo C, Moro F, Astrea G, Brisca G, Trucco F, et al. Mutations in GMPPB presenting with pseudometabolic myopathy. JIMD Rep 2018;38:23-31.

https://doi.org/10.1007/8904_2017_25.
[15] Balcin H, Palmio J, Penttilä S, Nennesmo I, Lindfors M, Solders G, et al. Late-onset limb-girdle muscular dystrophy caused by GMPPB mutations. Neuromuscul Disord 2017;27(7):627-30. https://doi.org/10.1016/j.nmd.2017.04.006.
[16] Natera-de Benito D, Töpf A, Vilchez JJ, González-Quereda L, Domínguez-Carral J, Díaz-Manera J, et al. Molecular characterization of congenital myasthenic syndromes in Spain. Neuromuscul Disord 2017;27(12):1087-98. https://doi.org/10.1016/j.nmd.2017.08.003.

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SUPPLEMENTAL DATA

TABLE S1. Summary of 72 cases of *GMPPB* gene mutation in the literature

No.	Mutation, DNA		Mutation, protein		Sex	Onset age	Age	Phenotype	References
1	c. 79G>C	c. 859C>T	p.Asp27His	p.Arg287Trp	F	24	[1]	CMS	[4]
2	c. 781C>T	c. 130-3C>G	p.Arg261Cys	Splicing	F	15	[1]	CMS	[4]
3	c. 79G>C	c. 760G>A	p.Asp27His	p.Val254Met	F	20	[1]	CMS	[4]
4	c. 308C>T	Homozygous	p.Pro103Leu		F	16	[1]	CMS	[4]
5	c. 308C>T	Homozygous	p.Pro103Leu		F	22	[1]	CMS	[4]
6	c. 308C>T	Homozygous	p.Pro103Leu		M	31	[1]	CMS	[4]
7	c. 79G>C	c. 907C>T	p.Asp27His	p.Leu303Phe	F	25	[1]	CMS	[4]
8	c. 559C>T	c. 578T>C	p.Gln187*	p.Ile193Thr	F	1.5	[1]	MDDG	[4]
9	c. 656T>C	c. 860G>A	p.Ile219Thr	p.Arg287Gln	M	2	[1]	MDDG	[4]
10	c. 656T>C	c. 860G>A	p.Ile219Thr	p.Arg287Gln	M	2	[1]	MDDG	[4]
11	c. 64C>T	c. 1000G>A	p.Pro22Ser	p.Asp334Asn	F	2.5	[1]	MDDG	[4]
12	c. 810_813delinsTGGC	Homozygous	p.Asn271Gly		F	0	[1]	CMD-MR	[4]
13	c. 841G>A	c. 860G>A	p.Glu281Gln	p.Arg287Gln	F	1	[2]	LGMD	[3]
14	c. 810_813delinsTGGC	Homozygous	p.Asn271Gly		F	0	[2]	CMD	[3]
15	c. 810_813delinsTGGC	Homozygous	p.Asn271Gly		M	0	[2]	CMD	[3]
16	c. 727C>T	c. 754G>T	p.Arg243Trp	p.Gly252Cys	M	17	[2]	LGMD	[3]
17	c. 79G>C	c. 859C>T	p.Asp27His	p.Arg287Trp	F	20	[2]	LGMD	[3]
18	c. 1000G>A	Homozygous	p.Asp334Asn		F	4	[2]	MR	[3]
19	c. 79G>A	c. 988G>A	p.Asp27His	p.Val330Ile	M	5	[2]	-	[3]
20	c. 338G>A	c. 860G>A	p.Cys113Tyr	p.Arg287Gln	M	49	[2]	LGMD	[3]
21	c. 79G>A	c. 87C>A	p.Asp27His	p.Cys29Ter	M	48	[2]	LGMD	[3]
22	c. 79G>C	c. 95C>T	p.Asp27His	p.Pro32Leu	M	43	[2]	LGMD	[3]
23	c. 79G>A	c. 907C>T	p.Asp27His	p.Leu303Phe	F	35	[2]	LGMD	[3]
24	c. 79G>C	c. 1108G>C	p.Asp27His	p.Val370leu	F	43	[2]	LGMD	[3]
25	c. 810_813delinsTGGC	c. 810_813delinsTGGC	p.Asn271Gly	p.Asn271Gly	M	0	[2]	CMD	[3]
26	c. 1069G>A	c. 1081G>A	p.Val357Ile	p.Asp361Asn	M	0.4	[2]	CMD	[3]
27	c. 656T>C	c. 860G>A	p.Ile219Thr	p.Arg287Gln	F	-	[3]	CMD-epilepsy	[9]
28	c. 656T>C	c. 860G>A	p.Ile219Thr	p.Arg287Gln	F	-	[3]	CMD-epilepsy	[9]
29	c. 790C>T	c. 79G>C	p.Gln264*	p.Asp27His	M	2	[4]	LGMD	[10]
30	c. 790C>T	c. 79G>C	p.Gln264*	p.Asp27His	F	5	[4]	LGMD	[10]
31	c. 790C>T	c. 79G>C	p.Gln264*	p.Asp27His	F	-	[4]	LGMD	[10]
32	c. 79G>C	c. 95C>T	p.Asp27His	p.Pro32Leu	M	15	[5]	LGMD	[6]
33	c. 79G>C	c. 95C>T	p.Asp27His	p.Pro32Leu	M	26	[5]	LGMD	[6]
34	c. 79G>C	c. 797G>A	p.Asp27His	p.Cys266Tyr	M	Late 20s	[5]	LGMD	[6]
35	c. 79G>C	c. 797G>A	p.Asp27His	p.Cys266Tyr	F	35	[5]	LGMD	[6]
36	c. 79G>C	c. 1036C>A	p.Asp27His	p.Arg346Ser	M	Early 20s	[5]	LGMD	[6]
37	c. 79G>C	c. 1036C>A	p.Asp27His	p.Arg346Ser	F	Early 20s	[5]	LGMD	[6]
38	c. 860G>C	c. 458C>T	p.Arg287Gln	p.Thr153Ile	M	13	[5]	Rhabdomyolysis	[6]
39	c. 860G>C	c. 95C>T	p.Arg287Gln	p.Pro32Leu	F	0	[5]	CMD	[6]
40	c. 79G>C	c. 1069G>A	p.Asp27His	p.Val357Ile	M	17	[6]	LGMD	[11]
41	c. 79G>C	c. 1069G>A	p.Asp27His	p.Val357Ile	M	17		LGMD	[11]
42	c. 79G>C	c. 760G>A	p.Asp27His	p.V254Ma	M	15		LGMD	[11]
43	c. 79G>C	c. 402+1G>A	p.Asp27His	-	M	23		LGMD	[11]
44	c. 721C>T	c. 1034T>C	p.Pro241Sa	p.V345Aa	F	5		LGMD-MR	[11]
45	c. 860G>A	c. 656T>C	p.Arg287Gln	p.Ile219Thr	F	0.75		CMD-MR	[11]
46	c. 860G>A	c. 395C>G	p.Arg287Gln	p.Ser132Cys	F	0		CMD-MR	[11]
47	c. 860G>A	c. 859C>T	p.Arg287Gln	p.Arg287Trp	F	0.6		CMD-CRB	[11]
48	c. 94C>T	NA	p.Pro32Ser	-	M	0		CMD-CRB	[11]
49	c. 79G>C	c. 859C>T	p.Asp27His	p.Arg287Trp	F	24	[7]	CMS	[12]
50	c. 781C>T	c. 130-3C>G	p.Arg261Cys	Splicing	F	15		CMS	[12]
51	c. 79G>C	c. 760G>A	p.Asp27His	p.Val254Met	F	20		CMS	[12]
52	c. 79G>C	c. 907C>T	p.Asp27His	p.Leu303Phe	F	25		CMS	[12]
53	c. 559C>T	c. 578T>C	p.Gln187*	p.Ile193Thr	F	1.5		CMS	[12]
54	c. 308C>T	Homozygous	p.Pro103Leu		F	16		CMS	[12]
55	c. 308C>T	Homozygous	p.Pro103Leu		F	22		CMS	[12]
56	c. 308C>T	Homozygous	p.Pro103Leu		M	31		CMS	[12]
57	c. 79G>C	c. 79G>C	p.Asp27His		F	64	[8]	CMS	[8]

(Contd...)

TABLE S1. *(Continued)*

No.	Mutation, DNA		Mutation, protein		Sex	Onset age	Age	Phenotype	References
58	c. 79G>C	c. 859C>T			M	8		LGMD	[8]
59	c. 859C>T	c. 79G>C	p.Arg287Trp,	p.Asp27His	M	15	[9]	LGMD	[13]
60	c. 859C>T	c. 79G>C	p.Arg287Trp,	p.Asp27His	F	30		LGMD	[13]
61	c. 464G>A	c. 1039_1043dup	p.Arg155His,	p.Ile349Serfsa	F	12		LGMD	[13]
62	c. 79G>C	c. 760G>A	p.Asp27His,	p.Val254Met	F	18		LGMD	[13]
63	c. 859C>T	c. 79G>C	p.Arg287Trp	p.Asp27His	M	5		LGMD	[13]
64	c. 902C>G	c. 1069G>A	p.Ser301Cys,	p.Val357Ile	M	25		LGMD	[13]
65	c. 1070G>A	c. 1018G>A	p.Arg357His	p.Gly340Arg	F	26	[10]	LGMD-CMS	[5]
66	c. 1070G>A	c. 877C>T	p.Arg357His	p.Arg293Trp	F	14		LGMD-CMS	[5]
67	c. 1070G>A	c. 966C>A	p.Arg357His	p.Asn322Lys	F	23		LGMD-CMS	[5]
68	c. 1070G>A	c. 966C>A	p.Arg357His	p.Asn322Lys	M	25		LGMD-CMS	[5]
69	c. 1070G>A	c. 966C>A	p.Arg357His	p.Asn322Lys	M	20		LGMD-CMS	[5]
70	c. 79G>C	c. 943C>A	p.Asp27His	p. Gly315Ser	M	15	[11]	Pseudometabolic myopathy	[14]
71	c. 79G>C	c. 859C>T	p.Asp27His	p.Arg287Trp	F	37		LGMD	[15]
72	c. 79G>C	c. 79G>C	p.Asp27His	p.Arg287Trp	F	30s	39	LGMD	[15]

GMPPB: Guanosine diphosphate mannose (GDP-mannose) pyrophosphorylase B; CMD-CRB: Congenital muscular dystrophy with cerebellar involvement; MR: Mental retardation; CMD-MR: Congenital muscular dystrophy with mental retardation; CMD: Congenital muscular dystrophy; CMS: Congenital myasthenic syndromes; F: Female; LGMD: Limb-girdle muscular dystrophy; M: Male; MDDG: Muscular dystrophy-dystroglycanopathy