

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

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## 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

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## INTRODUCTION

Dystroglycanopathies are a group of clinically heterogeneous inherited neuromuscular disorders caused by reduced glycosylation of  $\alpha$ -dystroglycan ( $\alpha$ -DG) [1]. Mutations in the guanosine diphosphate mannose (GDP-mannose) pyrophosphorylase B (*GMPPB*) gene resulting in reduced  $\alpha$ -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  $\alpha$ -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,

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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 *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 185<sup>th</sup> 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 (116<sup>th</sup> 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.

## ACKNOWLEDGMENTS

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## DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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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.Val370Ile	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.