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Congenital disorder of glycosylation type 1T with a novel truncated homozygous mutation in PGM1 gene and literature review

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Abstract

The congenital disorders of glycosylation are a group of clinically and biochemically heterogeneous diseases characterized by multisystem involvement due to glycosylation defect of protein and lipid. Here we report a 49-year-old man with exercise-induced fatigue and pain of muscle, tachypnea, cleft palate and bifid uvula. Exercise induced elevation of serum creatine kinase (CK), ammonia and lactic acid was recorded. The abnormal levels of myoglobin, CK-MB and LDH as well as S-T elevation in electrocardiogram were observed in repeated hospitalization recordings. Electromyography showed myopathic damage. Repetitive nerve stimulation test of low rates showed decrement in the left deltoid muscle. He was identified with a novel homozygous frameshift variant in Phosphoglucomutase type 1 gene (c.405delT p.N135Kfs*9) by whole exome sequencing. Muscle biopsy exhibited minimal variation in fiber size without abnormal glycogen accumulation. Compared with controls', the patient's sample showed no signal at ~61 kDa using N- or C-terminus antibody of Phosphoglucomutase type 1 in western blotting. A signal at ~20 kDa was detected in patient using N-terminus antibody. Immunofluorescence revealed trace expression of C-terminus and a much lower expression of N-terminus on the sarcolemma than normal. Our findings indicate that c.405delT encodes a truncated protein with abnormal distribution and expression in skeletal muscle. In conclusion, genes associated with congenital disorders of glycosylation should be analyzed in patients with maxillofacial dysplasia, exertional weakness, cardiac involvement and exercise-induced-ammoniemia, without glycogen storage in skeletal muscle.

Keywords: Congenital disorder of glycosylation; Glycogen storage disease; PGM1; Whole exome sequencing.

1. Introduction

The congenital disorders of glycosylation (CDG) are a group of clinically and biochemically heterogeneous diseases characterized by multisystem involvement due to glycosylation defect of protein and lipid [1,2]. The protein glycosylation in human cells is classified into N- and O-linked glycosylation [3]. Phosphoglucomutase type 1 (PGM1) is the predominant isoform of PGM in skeletal muscle and most other tissues, which is critical for catalyzing the reversible conversion between glucose 1-phosphate (G-1-P) and glucose 6-phosphate (G-6-P), as well as glycogenesis and glycogenolysis [4,5]. The enzyme activity of PGM1 provides the necessary precursor G-1-P, which is also crucial for protein N-linked glycosylation reactions.

PGM1 related CDG (MIM 612941) is characterized as oral-facial malformation, myopathy, cardiomyopathy, hepatopathy, hypoglycemia attack, growth retardation and endocrinopathy, which is also known as glycogen storage disease type XIV (GSD XIV) [6–10]. The block of the final step of glycogenolytic capacity in skeletal muscle is the predominant reason for severe exercise intolerance [11]. Recent studies have shown D-galactose supplementation could

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improve the protein glycosylation of skin fibroblast cell lines from patients, as well as ameliorate the patients' ability to use carbohydrate in skeletal muscle during exercise [7,11,12]. However, whether galactose supplementation could improve peak exercise tolerance or muscle strength still remains unclear. Furthermore, the galactose therapy does not seem to be able to fully alleviate all clinical symptoms [11,13].

In this work, we performed detailed clinical and genetic assessment as well as pathological study in a patient with PGM1 deficiency and prominent muscle symptoms due to novel homozygous frameshift mutation of PGM1.

2. Methods

2.1. Ethical approval

The Ethics Committee of Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, approved the study. All participants provided written informed consent.

2.2. Patient

This study enrolled a non-consanguineous family. The patient and his parents were clinically examined.

2.3. Mutation analysis

Blood samples were taken from the proband and his parents. Unaffected individuals ($n = 200$) of matched geographic ancestry were also included as healthy controls. Genomic DNA was extracted from 3 ml peripheral blood samples by a standard protocol using QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany). We then performed whole exome sequencing on the patient's genomic DNA. The identified sequence variant was further interpreted and classified according to the American College of Medical Genetics and Genomics (ACMG) Standards and Guidelines [14]. During this session, two neurogeneticists further analyzed the allele frequency (1000 g, ESP6500, dbSNP, ExAC and 200 in-house ethnically matched healthy controls), pathogenicity prediction [Mutationtaster (http://www.mutationtaster.org)], relation of the gene to disease, and inheritance pattern. Putative pathogenic variant was further confirmed by Sanger sequencing both the forward and reverse strands.

2.4. Muscle biopsy

An open muscle biopsy was performed on the right biceps brachii muscle of the patient. The tissue was frozen and then cut at 7-μm sections. These sections were stained according to standard histological and enzyme histochemical procedures with hematoxylin and eosin (HE), modified Gomori Trichrome, periodic acidic Schiff (PAS), oil red O (ORO), nicotinamide adenine dinucleo-tide tetrazolium reductase, succinate dehydrogenease, cytochrome C oxidase, and esterase. Immunofluorescence was applied using antibodies against PGM1-N-terminus (1:250, ab192876, abcam) and PGM1-C-terminus (1:500, ab192876, abcam) respectively. Anti-β-Spectrin (1:100, NCL-SPEC1, Novocastra) was exploited as sarcolemma marker.

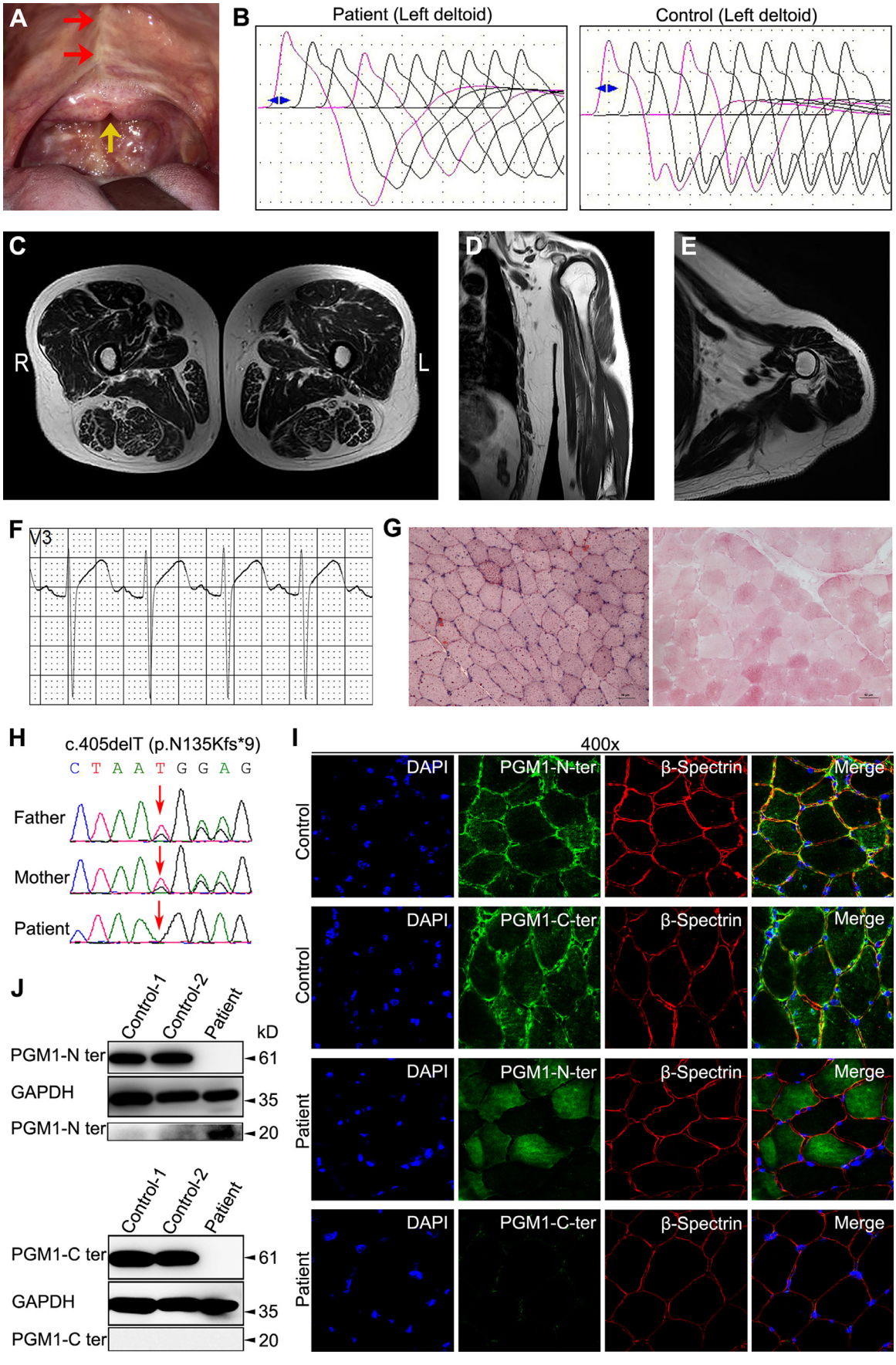
2.5. Western blotting

Protein of muscle tissue lysate was extracted and the expression level of PGM1 was detected by western blotting with anti-PGM1-N-terminus antibody (1:1000, ab192876, abcam) and anti-PGM1-C-terminus antibody (1:5000, ab192876, abcam) respectively.

3. Results

3.1. Clinical findings

The patient from the eastern part of China was a 49-year-old man who had lifelong recurrent exertional muscle fatigue, muscle pain, exercise-induced bosom frowsty and tachypnea. He was born of full term spontaneous vaginal delivery with normal birth weight (3.1 kg). Cleft palate and bifid uvula were observed when he was born, which interfered with feeding and pronunciation. The age of achieving sitting, standing and walking alone was 8, 10 and 14 months old, respectively. At the age of 4 and 10–33, he had undergone one cleft palate repair surgery and two repair surgeries for postoperative perforation respectively. Initially, muscle weakness was more severe in lower limbs than in upper limbs, which could be aggravated after physical exercise or labor. During school days, poor performances of physical education examinations were recorded, such as running, rope skipping, playing basketball and so on. Upon evaluation, dysarthria was evident which was characterized as difficulty in making plosives and retroflex sounds. Bifid uvula and central palate scar after surgery (Fig. 1A) were noticed. At the age of 49, the physical examination showed normal strength in neck flexion (5/5 on a medical research council scale graded 0–5), reduced strength of four limbs (4^+/5 and 4/5 in proximal upper and proximal lower limbs, respectively, 5/5 and 5^-/5 in distal upper and distal lower limbs, respectively) and reduced tendon reflexes in lower limbs. In general, the weakness had proximal maximum with lower limbs even worse than upper ones. Muscle tone in four limbs was almost normal. Ptosis, nystagmus, ataxia and myokymia were not noted. He walked slowly with mild waddling gait. Psychomotor and cognitive function tests were normal. Resting serum creatine kinase (CK) was 117–304 IU/L (normal 22–269 IU/L). After continued exercise, the patient felt muscle pain and swelling and the CK was elevated with 2 to 128 folds of the upper limit of normal range. Once after strenuous exercise, the CK was up to 34,636 IU/L and pigmenturia was also observed. Blood lactate was 3.11 and 3.53 mmol/L before and after exercise, respectively (normal 0.7–2.7 mmol/L). Blood ammonia


A
B
Patient (Left deltoid)
Control (Left deltoid)
C
R
L
D
E
F
V3
G
H
c.405delT (p.N135Kfs*9)
C T A A T G G A G
Father
Mother
Patient
I
400x
DAPI
PGM1-N-ter
β-Spectrin
Merge
Control
DAPI
PGM1-C-ter
β-Spectrin
Merge
Control
DAPI
PGM1-N-ter
β-Spectrin
Merge
Patient
DAPI
PGM1-C-ter
β-Spectrin
Merge
Patient
J
Control-1
Control-2
Patient
kD
PGM1-N ter
61
GAPDH
35
PGM1-N ter
20
Control-1
Control-2
Patient
PGM1-C ter
61
GAPDH
35
PGM1-C ter
20

was 44 and 127 mmol/L before and after exercise, respectively (normal 9–47 mmol/L). His vital capacity was 3000 ml (3500–4000 ml for normal adult male) at the age of 49. The cardiac involvement was suggested by myoglobin at 200.8–615.7 ng/ml (normal < 70 ng/ml), CK-MB at 5.1–36.1 ng/ml (normal 0.3–4 ng/ml) and LDH at 107–477 IU/L (normal 98–192 IU/L). The patient's AST was 74–169 IU/L (normal 8–40 IU/L) and ALT was 87 IU/L (normal 10–64 IU/L). His BMI was 25.10 (height = 167 cm, weight = 70 kg). An electromyogram showed motor unit potential (MUP) spontaneous activity with small, short and multi-phase in tibialis anterior muscle, gastrocnemius, and biceps. Decrements on low rates (3–5 Hz) of repetitive nerve stimulation (RNS) of left deltoid at baseline were recorded (Fig. 1B). Muscle MRI showed mild to moderate increased signal intensity mainly involving the posterior muscle in lower limbs (Fig. 1C), the trapezius muscle and deltoid muscle of the left side (Fig. 1D,E) on the T1-weighted MR sequences. The degree of muscle fatty infiltration was quantified as semimembranosus = 2 points, semitendinosus = 2 points, biceps = 2 points, gracilis = 1 point, left sartorius = 1 point, left trapezius = 2 points and left deltoid = 1 point [15,16]. Nerve conduction studies (NCS) were normal. Electrocardiogram (ECG) hinted elevation of S-T (Fig. 1F) in II, III, aVF and V3-V6. However, both cardiac and hepatic ultrasonographic examinations showed normal organ size with normal echogenity.

3.2. Myopathological finding

Muscle biopsy showed minimal change of fiber size by HE, mild increase of lipid by ORO (Fig. 1G, left panel) without abnormal glycogen storage by PAS (Fig. 1G, right panel).

3.3. Genetic findings

The patient was identified with one homozygous variant c.405delT (p.N135Kfs*9) in PGM1 gene. Both of his parents were heterozygous carriers of the same variant (Fig. 1H), which was not identified in 200 healthy controls, 1000 Genome Project (http://browser.1000 genomes.org), NHLBI Exome Sequencing Project (ESP) Exome Variant Server (http://evs.gs.washington.edu/EVS), Exome Aggregation Consortium (ExAC) or dbSNP (http://www.ncbi.nlm.nih.gov/snp). c.459delT was predicted to be 'disease causing' by Mutationtaster (probability score: 1.0, range: 0–1.0). The variant was classified as 'pathogenic variant' according to the ACMG standards and guidelines [14].

3.4. Mutant protein detection

Immunofluorescence revealed normal distribution mode of PGM1 both in fiber and on sarcolemma in healthy control. For the patient, mutant PGM1 on sarcolemma could be hardly detected using either N-terminus or C-terminus antibody. However, remarkable lower fluorescence intensity was indeed detected in the patient's muscle fiber by PGM1 N-terminus antibody (Fig. 1I). The results of western blotting showed that protein extracts from muscle of normal controls exhibited a strong signal at ~61 kDa, while there was no signal detected from the patient using either N-terminus or C-terminus antibody. However, a signal at ~20 kDa was indeed detected in the patient but not in controls by using N-terminus antibody (Fig. 1J).

4. Discussion

We described a Chinese patient presenting oral-facial malformations and exercise intolerance due to a PGM1 mutation (c.405delT). His parents each carrying one heterozygous variant were not clinically affected. The results of western blotting disclosed that a truncated type of protein might exist due to frameshift sequence and premature stop codon, leading to PGM1 deficiency in protein length which was also confirmed by immunofluorescence.

To date, 32 PGM1 mutations were identified among 32 patients from 29 families (including this study) diagnosed as PGM1-related CDG 1T or GSD XIV (Fig. 2) [7–9,11,17–22], of which one half were caused by homozygous mutations and the other were due to compound heterozygous ones. Thirty-one mutations (c.55A > G, c.112A > T, c.122A > G, c.157_158delinsG, c.184G > C, c.343A > G, c.361G > C, c.551delT, c.661delC, c.661C > T, c.689G > A, c.771delT, c.787G > T, c.788A > G, c.871G > A, c.988G > C, c.1010C > T, c.1129G > A, c.1144 + 3A > T, c.1145–222G > T, c.1145–1G > C, c.1162G > A, c.1258T > C, c.1264C > T, c.1495C > T, c.1507C > T, c.1508G > A, c.1547T > C, c.1551C > A, c.1588C > T, c.1600–523G > A) have been reported, while our mutation (c.405delT) was undocumented before. In this paper, we reviewed both clinical and genetic characteristics of these 32 patients from various origins (Table 1). The male to female ratio of 1.91 (21:11) might suggest a male predilection. However, the concrete mechanism should be further explored with more patients studied and the function of PGM1 enzyme or pathway investigated. Symptoms were characterized by oral-facial malformation (26/32), myopathy (21/30), glycometabolism

Fig. 1. A. The bifid uvula (vertical arrow) and the central palate scar left postoperatively (horizontal arrows). B. Low rates (3–5 Hz) of repetitive nerve stimulation of left deltoid at baseline in patient (left panel) and healthy control (right panel). C–E. Muscle MRI in lower limbs and left upper limb. Mild to moderate increased signal intensity, and trapezius atrophy on the T1-weighted MR sequences. F. Elevated S-T in electrocardiogram. G. Muscle biopsy revealed mild change of fiber size (left panel) without abnormal glycogen storage by PAS (right panel). Bar = 50 μm. H. The segregation of PGM1 c.405delT (p.N135Kfs*9) was confirmed by Sanger sequencing showing the patient to be homozygous and his parents as heterozygous carriers. I. Detection of PGM1 protein in muscle frozen-section from normal control (top two) and the patient (bottom 2) by using N-terminus or C-terminus antibody via immunofluorescence microscopy. J. Western blotting showed a strong signal at ~61 kDa of muscle tissues from control samples. There was no signal detected in the patient's protein using either N- terminus or C- terminus antibody. A signal at relative smaller molecular weight (~20 kDa) was detected in the patient but not in control using N- terminus antibody.

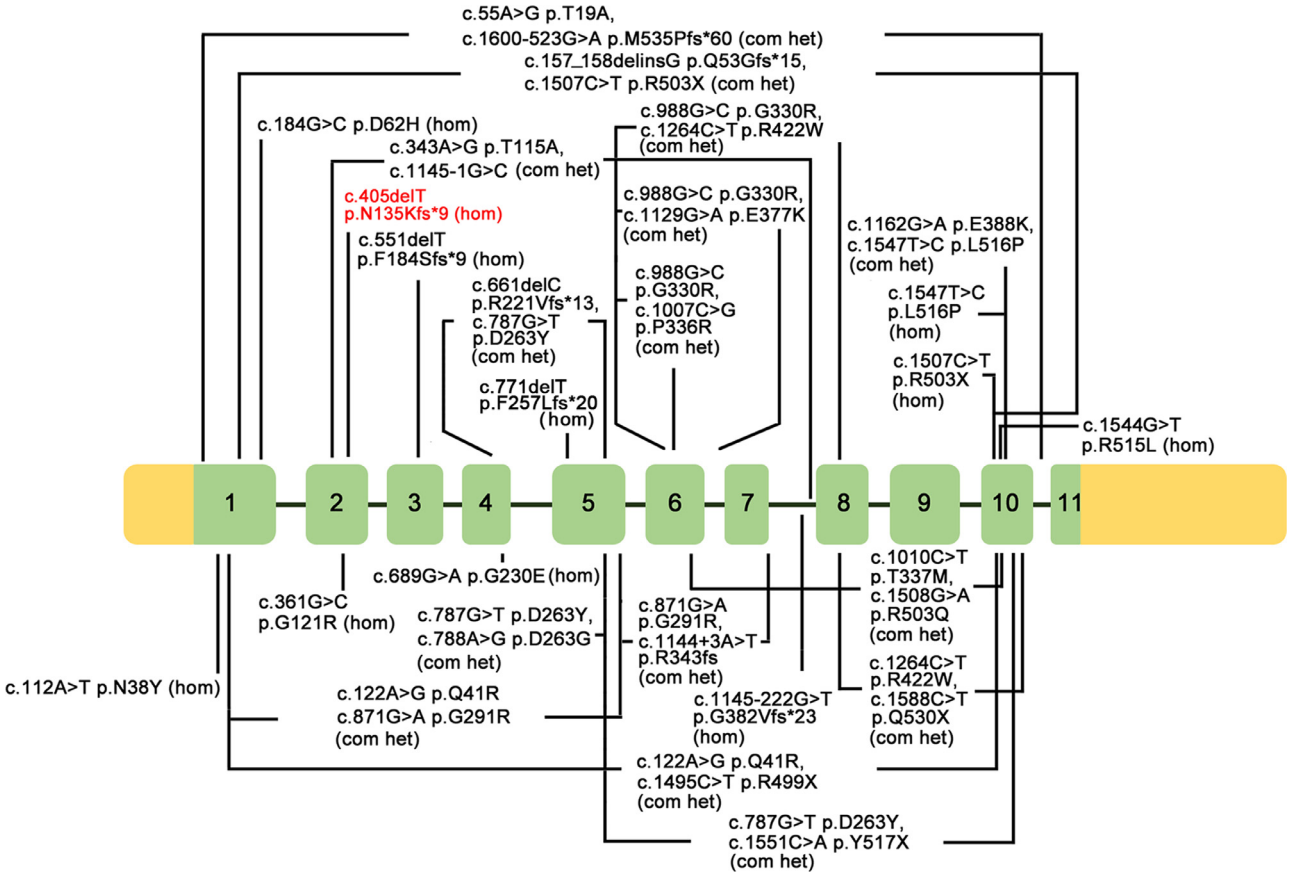


Fig. 2. Gene structure of PGM1 gene and PGM1 mutations in 29 CDG 1T families investigated here and documented previously.

disorder (29/32), short stature (26/32), as well as abnormal elevation of blood ammonia and lactate (4/5 and 5/7, respectively). Patients with and without abnormal cardiac function took almost equal share of the totality (15/32 vs 17/32). The elevation of liver enzyme index was also recorded (30/30). Oral-facial malformation, one of the most common abnormalities, included cleft palate (24/32) and bifid uvula (21/31), or Pierre-Robin sequence. PGM1 deficiency manifests its glucose metabolism disorder as exertional fatigue, episodes of hypoglycemia, ammoniemia, and lactic acidosis [7]. Skeletal muscles not being able to quickly use glycogen to produce energy in anaerobic conditions, results in exercise intolerance and potential rhabdomyolysis. Similarly, hepatic glycogen could not be successfully decomposed into glucose via G-6-P when fasting, may lead to hypoglycemia occurrence. Since G-6-P cannot be successfully converted to glycogen, large amounts of G-6-P are diverted to lactate after a carbohydrate-rich meal [23]. The characteristics mentioned above are also observed in GSD Ia, which also harbors G-6-P defect [24].

Electrophysiologically, it is interesting that our patient had unilateral positive decrement during RNS test of low rates, demonstrating potential involvement of the neuro-muscular junction. Considering none of the patients documented before had undergone RNS tests, the interpretation of the RNS examinations should be further explored with more patients studied. Among the patients undergoing muscle biopsy, only 1/24 exhibited abnormal glycogen accumulation in PAS staining, which may illustrate pathological heterogeneity linked to different impacts of various mutations on the enzyme [23]. The mild increase of lipid in ORO staining in this case could be nonspecific.

PGM1 gene (NM_002633) contains a total of 11 exons (Fig. 2), which encodes a PGM1 protein with 562 amino acids. PGM1 protein includes a total of 4 domains, namely alpha-D-phosphohexomutase alpha/beta/alpha domain I (residues 15–157), alpha-D-phosphohexomutase alpha/beta/alpha domain II (residues 194–300), alpha-D-phosphohexomutase alpha/beta/alpha domain III (residues 306–420) and C-terminal domain (residues 464–525) [25]. Among all of the 32 mutations, 19 mutations were missense and 10 mutations were truncating ones with premature stop codon. The other three were intronic mutations. There are 8 mutations located in exon 10, which is suggested to be a functional conservative sequence. Exon 10 of PGM1 gene encodes the protein residual 489 to residue 533, among which residual 515 is one of the key substrate binding sites of PGM1 enzyme. The PGM1 c.405delT (p.N135Kfs*9) mutation is located in the first alpha/beta/alpha domain of PGM1 protein. The frameshift results in changes of a series of amino acids downstream and introduces a premature stop codon, leading to 420 missing amino acids (74.6% of the whole length).

Table 1
Genetic and clinical characteristics of PGM1-related CDG.

Family ID	Gender	PGM1 mutation	Oral-facial		Heart	Skeletal muscle		
			Cleft palate	Bifid uvula		Myopathy	CK (U/L)	Biopsy
1	M	c.405delT (p.N135Kfs*9)	+	+	ST elevation	Exercise intolerance	1000–34,626, R (NM 22–269)	Fiber size variation; PAS(-), ORO↑
2 [7]	2/2: M	c.1547T > C (p.L516P)	2/2: +	2/2: +	2/2: -	2/2: Exercise intolerance	789 and 380	1/2: enzymatic activity ↓ (4.4% of control), 1/2: NR
3 [7]	F	c.988G > C (p.G330R), c.1129G > A (p.E377K)	+	+	Sever FS 5%	Exercise intolerance	50,000, R	Enzymatic activity ↓ (1.3% of control)
4 [7]	M	c.787G > T (p.D263Y), c.788A > G (p.D263G)	–	+	Cardiac arrest	NR	NR	Enzymatic activity ↓ (2.4% of control)
5 [7]	M	c.122A > G (p.Q41R), c.1495C > T (p.R499X)	–	–	–	–	<300	Enzymatic activity ↓ (2.5% of control)
6 [7]	1/2: M, 1/2: F	c.1145–222G > T (p.G382Vfs*23)	2/2:+	2/2:+	1/2: LV slightly enlarged; 1/2: severe FS 7% & cardiac arrest	2/2: Exercise intolerance	10,000 (R), 7942	2/2: Enzymatic activity ↓ (2.2% and 2.8%)
7 [7]	F	c.1507C > T (p.R503X)	+	+	Severe FS 5%	–	10,000, R	Enzymatic activity ↓(7.7% of control)
8 [7]	M	c.361G > C (p.G121R)	+	+	Severe FS 5%, cardiac arrest	Muscle weakness	250	Enzymatic activity ↓ (6.6% of control)
9 [7,9]	M	c.343A > G (p. T115A), c.1145–1G > C	–	–	–	Exercise intolerance	10,000, R	Glycogen accumulation, enzymatic activity ↓ (1.2% of control)
10 [7]	F	c.122A > G (p.Q41R), c.871G > A (p.G291R)	–	–	–	–	<300	Enzymatic activity ↓ (12% of control)
11 [7]	F	c.112A > T (p.N38Y)	+	+	–	–	3000	Enzymatic activity ↓ (3.1% of control)
12 [7]	M	c.787G > T (p.D263Y), c.1551C > A (p.Y517X)	+	+	–	Muscle weakness	<300	Enzymatic activity ↓ (2.8% of control)
13 [7]	M	c.55A > G (p.T19A), c.1600–523G > A (p.M535Pfs*60)	+	+	–	Exercise intolerance	2000	Enzymatic activity ↓ (3.3% of control)
14 [7]	2/2: M	c.184G > C (p.D62H)	2/2:+	2/2:+	2/2:-	2/2:-	2/2:-	2/2: Enzymatic activity ↓ (2.1% and 2.8% of control)
15 [7]	M	c.1162G > A (p.E388K), c.1547T > C (p.L516P)	+	+	Severe FS < 10%, cardiac arrest	–	NA	Enzymatic activity ↓ (1.2% of control)
16 [7]	F	c.551delT (p.F184Sfs*9)	+	+	–	–	NA	NR
17 [7]	F	c.661delC (p.R221Vfs*13), c.787G > T (p.D263Y)	+	+	–	Exercise intolerance	10,000, R	Enzymatic activity ↓ (0.3% of control)
18 [8,21]	F	c.1264C > T (p.R422W), c.1588C > T (p.Q530X)	+	–	Dilated cardiomyopathy	+	NR	Biopsy IHC:-, enzymatic activity in cells: 0% of control
19 [8]	F	c.689G > A (p.G230E)	+	–	+	+	NR	NA
20 [8]	F	c.1544G > T (p.R515L)	+	–	+	+	NR	Enzymatic activity in cells: 0% of control
21 [8]	M	c.157–158delinsG (p.Q53Gfs*15), c.1507C > T (p.R503X)	+	+	–	+	NR	NA
22 [8]	M	c.988G > C (p.G330R), c.1007C > G (p.P336R)	–	+	–	+	NR	Enzymatic activity in cells: 5% of control
23 [8]	M	c.112A > T (p.N38Y)	–	–	–	–	NR	NA
24 [17]	M	c.871G > A (p.G291R), c.1144 + 3A > T (p.R343fs)	–	–	–	Exercise intolerance	500–1000	Enzymatic activity in cells: 0.2% of control
25 [18]	M	c.1010C > T (p.T337M), c.1508G > A (p.R503Q)	+	–	–	+	1.69 μkat/L (NM < 0.69)	Enzymatic activity in cells: 5% of control
26 [19]	F	c.551delT (p.F184Sfs*9)	+	+	Cardiomyopathy	NR	NR	NR
27 [11]	M	c.988G > C (p.G330R), c.1264C > T (p.R422W)	–	–	Dilated cardiomyopathy	Exercise intolerance	2500–13,600 (R)	+ mild change (increase of internal nuclei)
28 [20]	M	c.1162G > A (p.E388K), c.1547T > C (p.L516P)	+	+	Dilated cardiomyopathy	Exercise intolerance	+	NR
29 [22]	M	c.771delT (p.F257Lfs*20)	+	NR	Long QT syndrome, enlarged LV	Exercise intolerance	NR	NR
Total	M: 21, F: 11	Hom: 13 Com het: 16	24/32	21/31	15/32	21/30	19/21	24/24

(*continued on next page*)

Table 1 (*continued*)

Family ID	Liver	Glycometabolism	Ammonia	Lactate	Short stature
1	AST & ALT ↑	LBG 3.89 mmol/L, urine ketone (+++)	BE: 44, AE: 127↑ (NM 9–47 μmol/L)	BE: 3.11↑, AE: 3.53↑ (NM 0.7–2.7 mmol/L)	–
2 [7]	2/2: AST & ALT ↑. 1/2: steatosis, fibrosis	LBG 2.6 mmol/L & 2.8 mmol/L	NR	NR	2/2: +
3 [7]	AST & ALT ↑. Increased glycogen, steatosis	LBG 1 mmol/L	NR	NR	+
4 [7]	AST & ALT ↑.	LBG 1.9 mmol/L	NR	NR	+
5 [7]	AST & ALT ↑. Cholestasis, fibrosis, steatosis	LBG 1.8 mmol/L	NR	NR	–
6 [7]	2/2: AST & ALT ↑	2.8, 3.2 mmol/L	NR	NR	2/2: +
7 [7]	AST & ALT ↑. Increased glycogen, steatosis	1.8 mmol/L	NR	NR	+
8 [7]	AST & ALT ↑	2.6	NR	NR	+
9 [7,9]	AST & ALT ↑	–	+ (BE < 50 μmol/L, AE > 350 μmol/L)	–	–
10 [7]	AST & ALT ↑	1.6	NR	NR	–
11 [7]	AST & ALT ↑	<2.7	NR	NR	–
12 [7]	AST & ALT ↑	2.4	NR	NR	+
13 [7]	AST & ALT ↑	1.4	NR	NR	+
14 [7]	2/2: AST & ALT ↑	2.1, 2.4	NR	NR	+
15 [7]	AST & ALT ↑	2.6	NR	NR	+
16 [7]	NR	2.4	NR	NR	+
17 [7]	AST & ALT ↑	3.6	NR	NR	+
18 [8,21]	+	+	NR	NR	+
19 [8]	+	+	NR	NR	+
20 [8]	+	+	NR	NR	+
21 [8]	+	+	NR	NR	+
22 [8]	+	+	NR	NR	+
23 [8]	+	+	NR	NR	–
24 [17]	+	–	+ (↑after exercise) 380 μmol/L	+ (↑after intravenous glucose) 4.9 mmol/L	+
25 [18]	+	LBG 2.4 mmol/L	NR	5 mmol/L (NM < 2.3)	+
26 [19]	AST, ALT: ↑, enlarged liver	+ (hypoinsulinemic hypoglycemia)	–	–	+
27 [11]	NR	–	BE: 30, AE: 347↑ μmol/L	BE: -, AE: 0.8↑ mmol/L	+
28 [20]	AST, ALT: ↑	Low fasting hypoglycaemia	NR	BE: -, AE: 7↑ mmol/L	+
29 [22]	AST, ALT: ↑	Hypoglycemic episodes	NR	NR	+
Total	30/30	29/32	4/5	5/7	26/32

PGM1 = Phosphoglucomutase type 1, CDG = congenital disorder of glycosylation, CK = creatine kinase, F = female, M = male, "+" = present, "−" = absent, NR = not reported, NA = not available, PAS = periodic acidic Schiff (PAS), ORO = oil red O, AST = aspartate transaminase, ALT = alanine aminotransferase, LBG = lowest blood glucose, BE = before exercise, AE = after exercise, NM = normal range, R = rhabdomyolysis, FS = fractional shortening, LV = left ventricle, IHC = immunohistochemistry, Hom = Homozygous, Het = Heterozygous.

In this case, we did not observe evidence of liver fibrosis, dilated cardiomyopathy or congenital malformation, which were reported before as severe phenotypes among PGM1 deficiency patients [4,8], suggesting the residual enzymatic activity of a truncated protein according to the results of western blotting and immunofluorescence. The relatively milder phenotype could also be associated with his timely repair of cleft palate in a very young age, early pronunciation training, good medical care and appropriate nutrition supply. However, we did not discover clear genotype-phenotype correlations, indicating clinical heterogeneity existed in this group of patients.

5. Conclusion

The present study identified the first Chinese patient with CDG 1T caused by novel homozygous frameshift mutation in the PGM1 gene, which encodes a truncated protein with abnormal distribution and reduced expression without abnormal glycogen storage in skeletal muscle. This study further emphasized the importance of PGM1 screening for the patients manifesting as inborn oral-facial malformation, exercise intolerance, glycometabolism disorder as well as short stature.

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