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【 CASE REPORT 】

A Mild Clinical Phenotype with Myopathic and Hemolytic Forms of Phosphoglycerate Kinase Deficiency (PGK Osaka): A Case Report and Literature Review

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Abstract:

Phosphoglycerate kinase (PGK) deficiency is an X-linked disorder characterized by a combination of hemolytic anemia, myopathy, and brain involvement. We herein report a Japanese man who had several episodes of rhabdomyolysis but was training strenuously to be a professional boxer. Mild hemolytic anemia was noted. The enzymatic activity of PGK was significantly reduced, and a novel missense mutation, p.S62N, was identified in the *PGK1* gene. A literature review revealed only one case with a mixed hemolytic and myopathic phenotype like ours. This mild phenotype indicates the complex pathophysiology of PGK deficiency and suggests the benefits of dietary control and exercise.

Key words: glycogen storage disease, myopathy, hemolysis, ischemic exercise test, dietary intake, PGK Osaka

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Introduction

Phosphoglycerate kinase (PGK) deficiency (OMIM #300653) is a glycogen storage disease with X-linked inheritance. PGK is a key enzyme catalyzing an important ATP-generating step in glycolysis (1, 2). PGK1 is expressed ubiquitously, but patients with PGK deficiency exhibit various combinations of three major symptoms: hemolytic anemia, myopathy (rhabdomyolysis), and mental retardation and various other neurological disorders. A simple form, either myopathic or hemolytic alone, and a mixed form with brain involvement are commonly reported (1). However, a mixed form with myopathic and hemolytic symptoms has rarely been reported.

We herein report a patient carrying a novel *PGK1* mutation showing a mixed hemolytic and myopathic phenotype and mild exercise intolerance, enabling him to perform boxing.

Case Report

The proband was a 23-year-old Japanese man with no family history of neuromuscular or hematological disorders. However, a detailed maternal family history was unavailable because of estrangement (Figure A). His developmental milestones were normal. However, he had had attacks of exertional myalgia starting at three years old. He had been hospitalized at 14 and 16 years old for rhabdomyolysis, with an up to 100-fold increase in creatine kinase (CK). He was able to perform sports activities normally and had been training strenuously to be a professional boxer. However, he stopped boxing because he was unable to pass the professional test due to his medical history. Even after stopping boxing, he still suffered attacks provoked by exercise with varying degrees and durations, and each attack was unpre-

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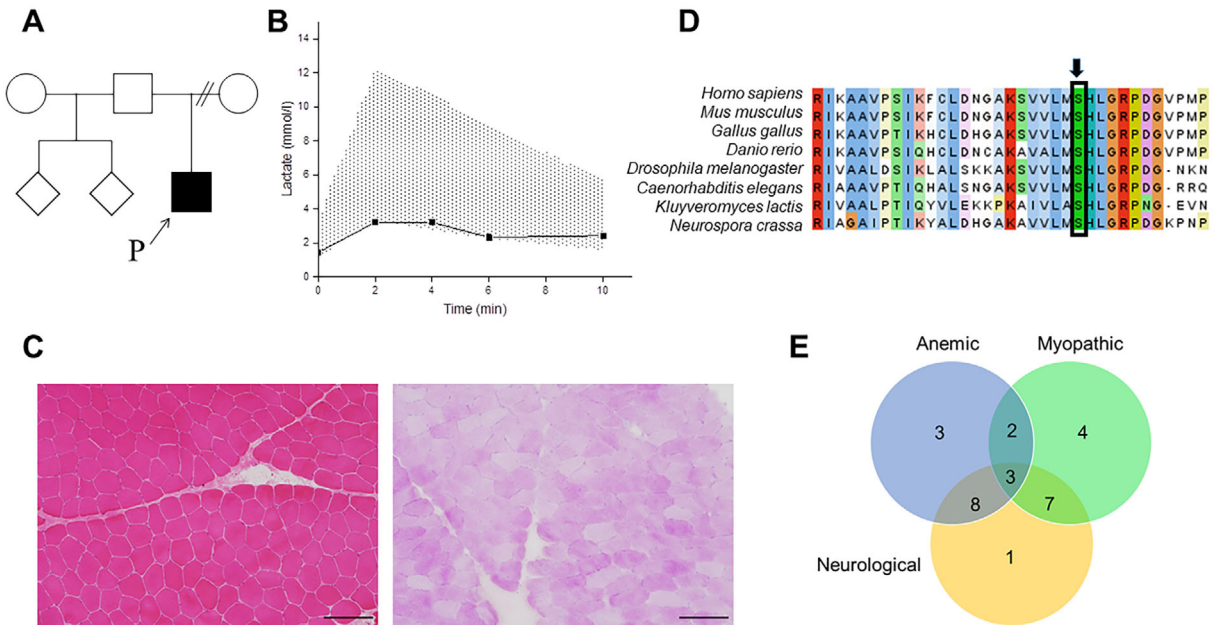

Figure. **Case description and clinical features of PGK deficiency in the literature. (A) Family tree. The arrow indicates the proband, and the black symbol indicates the affected individual. The diamonds indicate persons of unknown sex. (B) Forearm semi-ischemic exercise test elicited a subnormal elevation of lactate in the proband. The shaded area indicates a normal response. (C) Muscle histopathology with Hematoxylin and Eosin staining (left) and periodic acid-Schiff staining (right) is unremarkable. The scale bars indicate 100 μm. (D) The S62 residue in PGK1 is conserved across species. (E) The number of reported *PGK1* mutations is shown with a Venn diagram of phenotypic presentations.**

Table 1. **Glycolytic Enzyme Activities in the Skeletal Muscle.**

Enzymes	Our case	Control
Phosphorylase (+AMP)	53.0	58.9±17.5 (1.9-8.2)
Phosphorylase b kinase	40.0	39.5±10.8 (33.3-89.3)
Phosphoglucomutase	397.9	351.1±81.1 (221.1-562.0)
Phosphohexose isomerase	1,237.6	929.0±213.8 (669.1-1,204.0)
Phosphofructokinase	74.4	62.3±17.7 (33.7-88.5)
Aldolase	306.3	395.3±119.8 (246.7-580.0)
Glyceraldehyde-3P-dehydrogenase	2,577.1	2,508.1±749.6 (1,577.8-3,107.2)
Phosphoglycerate kinase	37.3	1,133.9±302.2 (658.3-1,470.2)
Phosphoglycerate mutase	954.3	1,086.6±300.4 (687.7-1,491.5)
Enolase	229.9	514.5±109.6 (224.6-692.5)
Pyruvate kinase	1,630.7	1,337.4±390.2 (1,029.3-2,734.4)
Lactate dehydrogenase	1,153.7	1,876.4±759.3 (1,029.3-2,734.4)
Debranching enzyme*	79.7	106.7±24.7 (57.8-176.1)

Activities are expressed as nmoles of substrate utilized/min/mg protein: mean±standard deviation. *nmoles of glucose released/hr/mg protein (spectrophotometric assay; substrate: PLD)

dictable.

At his first visit to our clinic, neurological examinations, including muscle strength and intelligence, were normal, and dysmorphic features were not noted. The CK and liver enzyme levels were normal during attack-free intervals, but mild hemolytic anemia with a hemoglobin value of 11.2 to 13.0 g/dL was persistent. Reticulocytes were elevated to 10.3%, and HbA1c was remarkably decreased to 2.4%. The total bilirubin level was slightly elevated (1.2 to 1.9 mg/dL). There were no abnormalities in blood cell morphology, and direct and indirect Coombs tests were normal. Lactate and pyruvate values were normal at rest (1.3 and 0.12 mmol/L, respectively). A semi-ischemic forearm exercise test evoked only a modest or sub-normal lactate increase (Figure B), while NH_3 showed a normal increase. No abnormalities were found by an electrocardiogram, ultrasound cardiography, or needle electromyography. A muscle biopsy from the biceps brachii was unremarkable, including periodic acid-Schiff

Table 2. PGK1 Mutations and Clinical Features in Patients with PGK1 Deficiency.

Nucleotide change	Amino acid change	Variant name	Number of patients	Age of diagnosis (years)	RBC PGK activity (%)	Muscle PGK activity (%)	Hb (g/dL)	Reticulocytes (%)	A	M	N	References
c.140 T>A	p.I47N	Barcelona	1	3	8	N.A.	6-6-7.3	N.A.	+	-	+	3
c.185 G>A	p.S62N	Osaka	1	23	2.9	3.3	11.2-13.0	10.3	+	+	-	Present case
c.263 T>C	p.L88P	Matsue	1	9	5	N.A.	N.A.	N.A.	+	-	+	4
c.323 G>A	p.C108Y		1	32	2.6	1.9	N.A.	N.A.	-	-	+	5
c.358 G>A	p.E120K		3	13	N.A.	N.A.	N.A.	N.A.	+	+	+	6
c.417+1 G>T	IVS4+1 G>T	North Caroline	1	12	3	2	N.A.	2.7	-	+	+	7
c.461 T>C	p.L154P		1	19	<M.L.	N.A.	N.A.	N.A.	+	-	+	8
c.473 G>T	p.G158V	Shizuoka	1	27	1	N.A.	12.8	2.5	+	+	-	9
c.491 A>T	p.D164V	Amiens/ New York	7	2-19	5	N.A.	2.0-10.0	5.0-26.0	+	-	+	5, 10-13
c.571_573 delAAG	p.K191del	Alabama	1	36	4	N.A.	14.I	6.4	-	-	-	14
c.617 G>C	p.R206P	Uppsala	1	26	10	N.A.	5.6-13.7	5.6-13.7	+/-	-	+	15,16
c.637_640 delGGCG	p.G213E fs*21	Fukui	1	36	6	3	N.A.	N.A.	-	+	-	17
c.639 C>T	p.G213= splicing alteration		2	16, 21	5	N.A.	N.A.	N.A.	-	+	-	18,19
c.649 G>A	p.V217I		1	16	78-91	N.A.	N.A.	N.A.	-	+	+	20
c.755 A>C	p.E252A	Antwerp	1	25	6	8	13.2	N.A.	-	+	-	21
c.756+3 A>G	IVS7+3A>G		2	14, 16	15	N.A.	13.3, 16.1	N.A.	-	+	+	22
c.756+5 G>A	IVS7+5G>A	Fukuroi	1	33	14	9	N.A.	N.A.	-	+	+	23
c.758 T>C	p.I253T	Hamamatsu	1	11	8	4	N.A.	N.A.	-	+	+	24
c.796_798 delinsATG	p.V266M	Tokyo	1	6	10	N.A.	9.3	12.5	+	-	+	25
c.802 G>A	p.D268N	München	Population survey		21	N.A.	N.A.	0.4-1.3	-	-	-	26
c.854 A>T	p.D285V	Herlev	1	68	49	N.A.	9-10	10-45	+	-	-	27
c.943 G>A	p.D315N	Creteil	1	31	3	5	14.3	N.A.	-	+	-	5, 10
c.946 T>C	p.C316R	Michigan	1	9	10	N.A.	7.5-13.0	1.5-5.0	*+I-*	-	+	28
c.959 G>A	p.S320N	Murcia	1	6	36	N.A.	7.6	9.0	+	-	+	3
c.1060 G>C	p.A354P	Kyoto	1	3	6	N.A.	4.9-9.0	24.0	+	+	+	29
c.1105 A>C	p.T369P	Detroit	1	N.A.	N.A.	N.A.	5.4	37.3	+	-	-	30
c.1112 T>A	p.I371K		1	4	12	N.A.	8.6-14.1	5-17	+	+	+	31
c.1114 G>A	p.G372S		1	38	19.7	N.A.	N.A.	N.A.	-	+	+	32
c.1132 A>C	p.T378P	Afula	4	18-30	2	1	13.4-14.5	N.A.	-	+	*+I-*	33-35
c.1180 A>G	p.T394A	Aoto	1	3	11.2-13.9	N.A.	6.7	11.5	+	-	-	36

Adopted and modified from (32, 39). A: anemia, M: muscular disorders after physical exercises, N: neurological disorders, N.A.: not available, <M.L.: below mesurable level

staining (Figure C).

His clinical presentation suggested glycogen storage diseases, although a partial deficiency pattern with the ischemic test. Analysis of glycolytic enzymes revealed a decrease in the PGK activity, namely, 37.3 nmol/min/mg for the muscle (normal 831.7-1,436.1) and 0.7 μmol/min/gHb for erythrocytes (normal 21.6-27.4) (Table 1). A kinetic study of PGK revealed Km and Kcat for 3-phosphoglycerate of 0.83 mmol/L (normal 0.24-0.34) and 31.2/s (normal 661.2-766.6), respectively. The activities of other glycolytic enzymes (Table 1) and carnitine/beta-oxidation and mitochondrial respiratory chain enzymes (data not shown) were within normal ranges.

After obtaining informed consent under the approval of the institutional review board, a confirmatory genetic analysis, using an exome sequencing platform, was performed to analyze the following genes: *HADHA, HADHB, PFKM, PYGM, PHKA1, PHKB, PGK1, PGAM2, LDHA, LDHB, ALDOA, ENO3, PGM1, CPT2, ACADVL, ETFA, ETFB, ETFDH, and LPIN1*. After eliminating high-frequency variants, one novel mutation, *PGK1* (NM_000291): c.G185A, p.S62N, was identified, which was not listed in a database (gnomAD; https://gnomad.broadinstitute.org/). The S62 residue in PGK1 is highly conserved across species, highlighting the functional importance (Figure D).

Literature review

We summarized 29 mutations of PGK deficiency previously reported in the English literature (Table 2) (3-36). The clinical presentation varied significantly among reported cases. Two-thirds showed neurological symptoms, and around half showed anemia or myological symptoms (Figure E). The patients showing only neurological manifestations were rare, and those with neurological manifestations usually also showed hemolytic anemia or myopathic symptoms. Notably, mutations presenting as a mixed form with myopathic and hemolytic symptoms were described only in one report of PGK Shizuoka, aside from our case (Figure E) (9).

Discussion

We encountered a case with a relatively mild clinical phenotype of a mixed form of PGK deficiency without brain symptoms, harboring a novel missense mutation, p. S62N (PGK Osaka). In addition, the presence of a modest lactate increase with a semi-ischemic exercise test was consistent with a low residual capacity of glycogenolysis, such as PGK deficiency (37). The patient had had several instances of rhabdomyolysis, but exercise intolerance was mild, which allowed him to box.

The identified variant has not previously been reported as responsible for PGK deficiency, but several lines of evidence support its pathogenicity. The variant is not listed in the databases of the general population, such as gnomAD or Japanese Multi Omics Reference Panel (ToMMo8.3KJPN https://jmorp.megabank.tohoku.ac.jp). The S62 residue in PGK1 is highly conserved across species from bacteria to mammals (Figure D). Prediction using *in silico* tools suggests pathogenicity, as follows: CADD_phred score=23.4, PROVEAN=-2.892, deleterious (Combined Annotation Dependent Depletion (CADD) https://cadd.gs.washington.edu/, PROVEAN http://provean.jcvi.org/index.php). Furthermore, the mutated residue is located next to a substrate-binding site (residues 63-66) (https://www.uniprot.org/uniprot/P00558). Therefore, the mutation likely causes a conformational change in the protein structure and deleterious effects on enzyme activity.

Our case is the second case of PGK deficiency to show only myopathy and anemia, following the PGK Shizuoka case (9). However, no increase in reticulocytes was observed in the PGK Shizuoka case. Reticulocyte counts and other measurements have been conducted in only limited cases to investigate hemolysis. Thus, mild hemolytic anemia may have been overlooked. Indeed, the Hb concentration in our case was in the normal range, but the extremely low HbA1c value led to the diagnosis of hemolytic anemia. Our case underscores the importance of suspecting and testing for hemolysis for the clinical diagnosis of glycogenosis.

A previous study indicated that patients with a higher residual PGK activity (4-9% in erythrocytes and 5-10% in muscles) only show myopathy, while those with a lower residual PGK activity (2.6% in erythrocytes and muscles) show multisystem involvement (38). However, the milder phenotype of our case does not seem to be explained by the residual PGK activity (2.9% in erythrocytes and 3.3% in muscles). An *in vitro* enzymatic analysis contrarily showed that mutations causing only myopathy affected both the catalytic properties and protein stability of PGK (39). There seem to be complex molecular characteristics that link PGK and the clinical phenotypes.

Other factors that may modify the phenotype are diet and exercise. In phosphofructokinase deficiency, another downstream defect in glycolysis, a glucose-rich diet is not helpful as an energy source. Instead, it suppresses fatty acid usage due to insulin secretion and leads to decreased exercise capacity (40). The beneficial effect of a low carbohydrate diet has recently been reported for several types of glycogen storage diseases (41, 42). Furthermore, it has been postulated that increased serum ketone bodies due to a low-carbohydrate diet or intermittent fasting and exercise can lead to positive adaptation and improved physical activity tolerance in patients with glycogen storage diseases (43). Our patient strenuously exercised to be a professional boxer while monitoring his body weight. This diet control and exercise might have led to the induction of fatty acid metabolism and possibly residual glycolytic activity. Despite the low residual enzyme activity, *in vivo* metabolic conversion may have contributed to symptom relief.

We believe that our case further highlights the complex pathophysiology of PGK deficiency and may suggest the benefits of proper control of dietary intake and exercise.

The authors state that they have no Conflict of Interest (COI).

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References

1. DiMauro S, Spiegel R. Progress and problems in muscle glycogenoses. Acta Myol **30**: 96-102, 2011.
2. Beutler E. PGK deficiency. Br J Haematol **136**: 3-11, 2007.
3. Noel N, Flanagan J, Kalko SG, et al. Two new phosphoglycerate kinase mutations associated with chronic haemolytic anaemia and neurological dysfunction in two patients from Spain. Br J Haematol **132**: 523-529, 2006.
4. Maeda M, Yoshida A. Molecular defect of a phosphoglycerate kinase variant (PGK-Matsue) associated with hemolytic anemia: Leu → pro substitution caused by T/A → C/G transition in exon 3. Blood **77**: 1348-1352, 1991.
5. Echaniz-Laguna A, Nadjar Y, Béhin A, et al. Phosphoglycerate

kinase deficiency: a nationwide multicenter retrospective study. J Inherit Metab Dis **42**: 803-808, 2019.

6. David D, Almeida LS, Maggi M, et al. Clinical severity of PGK1 deficiency due to a novel p.E120k substitution is exacerbated by co-inheritance of a subclinical translocation t(3;14)(q26.33;q12), disrupting NUBPL gene. JIMD Rep **23**: 55-65, 2015.

7. Tsujino S, Tonin P, Shanske S, et al. A splice junction mutation in a new myopathic variant of phosphoglycerate kinase deficiency (PGK North Carolina). Ann Neurol **35**: 349-353, 1994.

8. Ward SK, Stevens CA, Keates-Baleeiro J, Bhakta M. Therapeutic benefit of blood transfusion in a patient with novel PGK1 mutation (c.461T>C [p.L154P]). J Pediatr Hematol Oncol **42**: e228-e230, 2019.

9. Fujii H, Kanno H, Hirono A, Shiomura T, Miwa S. A single amino acid substitution (157 Gly→Val) in a phosphoglycerate kinase variant (PGK Shizuoka) associated with chronic hemolysis and myoglobinuria. Blood **79**: 1582-1585, 1992.

10. Cohen-Solal M, Valentin C, Plassa F, et al. Identification of new mutations in two phosphoglycerate kinase (PGK) variants expressing different clinical syndromes: PGK Créteil and PGK Amiens. Blood **84**: 898-903, 1994.

11. Turner G, Fletcher J, Elber J, Yanagawa Y, Dave V, Yoshida A. Molecular defect of a phosphoglycerate kinase variant associated with haemolytic anaemia and neurological disorders in a large kindred. Br J Haematol **91**: 60-65, 1995.

12. Flanagan JM, Rhodes M, Wilson M, Beutler E. The identification of a recurrent phosphoglycerate kinase mutation associated with chronic haemolytic anaemia and neurological dysfunction in a family from USA. Br J Haematol **134**: 233-237, 2006.

13. Rhodes M, Ashford L, Manes B, Calder C, Domm J, Frangoul H. Bone marrow transplantation in phosphoglycerate kinase (PGK) deficiency. Br J Haematol **152**: 500-502, 2011.

14. Yoshida A, Twele TW, Davé V, Beutler E. Molecular abnormality of a phosphoglycerate kinase variant (PGK-Alabama). Blood Cells Mol Dis **21**: 179-181, 1995.

15. Hjelm M, Wadam B, Yoshida A. A phosphoglycerate kinase variant, PGK Uppsala, associated with hemolytic anemia. J Lab Clin Med **96**: 1015-1021, 1980.

16. Fujii H, Yoshida A. Molecular abnormality of phosphoglycerate kinase-Uppsala associated with chronic nonspherocytic hemolytic anemia. Proc Natl Acad Sci U S A **77**: 5461-5465, 1980.

17. Hamano T, Mutoh T, Sugie H, Koga H, Kuriyama M. Phosphoglycerate kinase deficiency: an adult myopathic form with a novel mutation. Neurology **54**: 1188-1190, 2000.

18. Aasly J, Van Diggelen OP, Boer AM, Brønstad G. Phosphoglycerate kinase deficiency in two brothers with McArdle-like clinical symptoms. Eur J Neurol **7**: 111-113, 2000.

19. Svaasand EK, Aasly J, Landsem VM, Klungland H. Altered expression of PGK1 in a family with phosphoglycerate kinase deficiency. Muscle Nerve **36**: 679-684, 2007.

20. Matsumaru S, Oguni H, Ogura H, et al. A novel *PGK1* mutation associated with neurological dysfunction and the absence of episodes of hemolytic anemia or myoglobinuria. Intractable Rare Dis Res **6**: 132-136, 2017.

21. Ookawara T, Davé V, Willems P, et al. Retarded and aberrant splicings caused by single exon mutation in a phosphoglycerate kinase variant. Arch Biochem Biophys **327**: 35-40, 1996.

22. Coppens S, Koralkova P, Aeby A, et al. Recurrent episodes of myoglobinuria, mental retardation and seizures but no hemolysis in two brothers with phosphoglycerate kinase deficiency. Neuromuscul Disord **26**: 207-210, 2016.

23. Shirakawa K, Takahashi Y, Miyajima H. Intronic mutation in the *PGK1* gene may cause recurrent myoglobinuria by aberrant splicing. Neurology **66**: 925-927, 2006.

24. Sugie H, Sugie Y, Ito M, Fukuda T. A novel missense mutation (837T→C) in the phosphoglycerate kinase gene of a patient with a myopathic form of phosphoglycerate kinase deficiency. J Child Neurol **13**: 95-97, 1998.

25. Fujii H, Chen SH, Akatsuka J, Miwa S, Yoshida A. Use of cultured lymphoblastoid cells for the study of abnormal enzymes: molecular abnormality of a phosphoglycerate kinase variant associated with hemolytic anemia. Proc Natl Acad Sci U S A **78**: 2587-2590, 1981.

26. Fujii H, Krietsch WKG, Yoshida A. A single amino acid substitution Asp→Asn) in a phosphoglycerate kinase variant (PGK Munchen) associated with enzyme deficiency. J Biol Chem **255**: 6421-6423, 1980.

27. Valentin C, Birgens H, Craescu CT, Brødum-Nielsen K, Cohen-Solal M. A phosphoglycerate kinase mutant (PGK Herlev; D285V) in a Danish patient with isolated chronic hemolytic anemia: mechanism of mutation and structure-function relationships. Hum Mutat **12**: 280-287, 1998.

28. Maeda M, Bawle EV, Kulkarni R, Beutler E, Yoshida A. Molecular abnormalities of a phosphoglycerate kinase variant generated by spontaneous mutation. Blood **79**: 2759-2762, 1992.

29. Morimoto A, Ueda I, Hirashima Y, et al. A novel missense mutation (1060G → C) in the phosphoglycerate kinase gene in a Japanese boy with chronic haemolytic anaemia, developmental delay and rhabdomyolysis. Br J Haematol **122**: 1009-1013, 2003.

30. Zaidi AU, Bagla S, Ravindranath Y. Identification of a novel variant in phosphoglycerate kinase-1 (PGK1) in an African-American child (PGK1 Detroit). Pediatr Hematol Oncol **36**: 302-308, 2019.

31. Fermo E, Bianchi P, Chiarelli LR, et al. A new variant of phosphoglycerate kinase deficiency (p.I371K) with multiple tissue involvement: molecular and functional characterization. Mol Genet Metab **106**: 455-461, 2012.

32. Garcia-Solaesa V, Serrano-Lorenzo P, Ramos-Arroyo MA, et al. A novel missense variant associated with a splicing defect in a myopathic form of PGK1 deficiency in the Spanish population. Genes (Basel) **10**: 785, 2019.

33. Spiegel R, Gomez EA, Akman HO, Krishna S, Horovitz Y, DiMauro S. Myopathic form of phosphoglycerate kinase (PGK) deficiency: a new case and pathogenic considerations. Neuromuscul Disord **19**: 207-211, 2009.

34. Sotiriou E, Greene P, Krishna S, Hirano M, DiMauro S. Myopathy and parkinsonism in phosphoglycerate kinase deficiency. Muscle Nerve **41**: 707-710, 2010.

35. Virmani T, Rotstein M, Spiegel R, Akman HO, DiMauro S, Greene PE. Levodopa responsive parkinsonism in two patients with phosphoglycerate kinase deficiency. Mov Disord Clin Pract **1**: 240-242, 2014.

36. Tamai M, Kawano T, Saito R, et al. Phosphoglycerate kinase deficiency due to a novel mutation (c. 1180A>G) manifesting as chronic hemolytic anemia in a Japanese boy. Int J Hematol **100**: 393-397, 2014.

37. Haller R, Vissing J. Functional evaluation of metabolic myopathies. In: Myology. 3rd ed. Engel A, Franzini-Armstrong C, Eds. McGraw-Hill, New York, 2004: 665-679.

38. Vissing J, Akman HO, Aasly J, et al. Level of residual enzyme activity modulates the phenotype in phosphoglycerate kinase deficiency. Neurology **91**: e1077-e1082, 2018.

39. Chiarelli LR, Morera SM, Bianchi P, et al. Molecular insights on pathogenic effects of mutations causing phosphoglycerate kinase deficiency. PLoS One **7**: e32065, 2012.

40. Haller RG, Lewis SF. Glucose-induced exertional fatigue in muscle phosphofructokinase deficiency. N Engl J Med **324**: 364-369, 1991.

41. Olgac A, İnci A, Okur İ, et al. Beneficial effects of modified Atkins diet in glycogen storage disease type IIIa. Ann Nutr Metab **76**: 233-241, 2020.

42. Similä ME, Auranen M, Piirilä PL. Beneficial effects of ketogenic diet on phosphofructokinase deficiency (glycogen storage disease

type VII). Front Neurol **11**: 57, 2020.

43. Reason SL, Godfrey RJ. The potential of a ketogenic diet to minimize effects of the metabolic fault in glycogen storage disease V and VII. Curr Opin Endocrinol Diabetes Obes **27**: 283-290, 2020.