CASE REPORT

Glycogen Storage Disease IXc with PHKG2 Mutation and Psoriatic-Like Lesions: A Rare Case

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Abstract

Glycogen storage diseases (GSDs) cause glycogen metabolism disorders in the human body and are genetically determined metabolic illnesses. Due to sufficient glycogen or its diseased states, glycogen is accumulated in the human body tissues due to the enzymatic defect during glycogenolysis/glycogenesis. Pathogenic transformations in the PHKG2 are related to a very unusual ailment called GSD-IXc distinguished by serious complications of the liver. Here, a case report of a patient is presented with no clinical history given but with obvious hepatomegaly and fatty infiltrations along with psoriasis-like lesions. Genetic testing revealed c.431T>C variant which is expected to cause substitution in an amino acid p.Leu144Pro. The results upturn the gene spectrum and accord with elucidating the clinical presentation of PHKG2 transformations. Special attention to this case should be given due to the sturdy link between lactose dehydrogenase-A deficiency (GSD type XI) that validates several skin wounds associated with the ailment *e.g.* pustular psoriasis-like lesions, desquamating erythematous-squamous lesions, *etc.*

Keywords: *Glycogen storage disease, PHKG2, psoriasis, glycogen metabolism, autosomal recessive.*

INTRODUCTION

GSDs are illnesses of glycogen metabolism. Cumulatively, GSDs are not unusual, but each type is considered rare. GSD incidence is predicted overall as 1 case per 20,000–43,000 live births [1]. GSDs' 19 forms are categorized by enzyme-lacking and pretentious tissues. Most GSDs are hereditary in an autosomal recessive style, except one subtype X-linked GSDIX. Maladies of glycogen degradation can mostly impact the liver, and the muscles or can be multi-organ *i.e.* mainly Pompe and Cori-Forbes disease [2]. GSD-IX is initiated due to inadequate PhK (phosphorylase b kinase) which is an essential protein kinase that regulates the lysis of glycogen to glucose. It involves four characteristic subunits encoded by distinct genes: alpha, beta, gamma and delta *i.e.* (PHKA1 and PHKA2), (PHKB), (PHKG2) and (CALM1) respectively [3]. PHKG2 is found on the 16th chromosome has 10 exons and spans 9.5 kb. PHKG2 transformations result in GSD-IXc (OMIM 613027), illustrated by cirrhosis/fibrosis of the liver, hepatomegaly, growth retardation, hypoglycemia, and increased levels of triglycerides, cholesterol and transaminases [4]. Until now, the literature has revealed 33 diverse PHKG2 transformations [5], but, an evident association between transformation severity and hepatic injury has not been established. PHKG2 mutations with allelic truncating have been identified among non-cirrhotic and cirrhotic hepatic cases [6, 7], however, the molecular process remains unidentified for such GSD-IXc liver phenotypes [8]. GSD IXc is initiated by PhK deficiency in comparison to GSD IXa, due to PHKG2 transformations being quite unusual; only 24 GSD IXc cases have been reported globally [5].

The deficiency of LDH-A (lactate dehydrogenase A) is an autosomal recessive illness due to morbific transformations in the LDHA; it is also accountable for GSD type XI. The LDH-A is a gene containing 7 exons and spans around 12 kb in 11p15.1. The LDH-A deficit is illustrated by exercise intolerance with myalgia and myoglobinuria due to rhabdomyolysis following heavy exercise [9]; acute renal failure may follow myoglobinuria [10]. Moreover, pregnant cases were reported as having uterine pain and stiffness [9], related to elevated serum pyruvate amounts [11]. Many skin lesions *e.g.* pustular psoriasis-like lesions, desquamating erythemato-squamous lesions, *etc.* have been recognized to be linked with the disease [12-14]. Such conditions occur usually in spring and settle suddenly after the fall [13-15].

This report details a case of a young male presenting GSD with hepatomegaly and the development of psoriasis-like lesions; it calls for further investigations on LDH-A deficiency of the patient because of its strong

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association with GSD and the development of pustular psoriasis-like lesions. Moreover, sequencing for the c.431T>C (p.Leu144Pro) variants in parents, if desired, would be necessary to confirm their carrier status and rule out the possibility of amplification and sequencing of only one patient allele. Testing of biological relatives can also be performed to determine their carrier status. Nevertheless, genetic counselling is also recommended.

CASE REPORT

Clinical Presentation

A 19-year-old male patient was presented for the evaluation of glycogen storage disease using genomic DNA. Through the genomic DNA of the patient, the specified gene zone was sequenced, aligned and then compared with reference sequences. The blend of Next Generation Sequencing (NGS) and Sanger sequencing analyses was used for the full coding zones of the listed genes and ~20 bases of non-coding DNA closest to each axon. The DNA was extracted from the specimen of the patient. For NGS, the DNA of the patient consistent with these zones was acquired by employing an optimized set of DNA hybridization probes. The secured DNA was sequenced by Illumina's Reversible Dye Terminator (RDT). The zones that were not covered effectively by NGS were taken up by Sanger sequencing and for that Polymerase chain reaction (PCR) was employed to expand the intended zones. After PCR product purification, cycle sequencing was done through the ABI Big Dye Terminator v.3.0 kit. Electrophoresis resolved the PCR products on an ABI 3730xl capillary sequencer. Cycle sequencing is conducted separately for approximately all cases in forward and reverse directions. For, Sanger sequencing; sequence variants are defined *via* Human Genome Variation Society (HGVS) suggestions. After sequencing, the patient sequence was aligned and a comparison was done with the reference sequences.

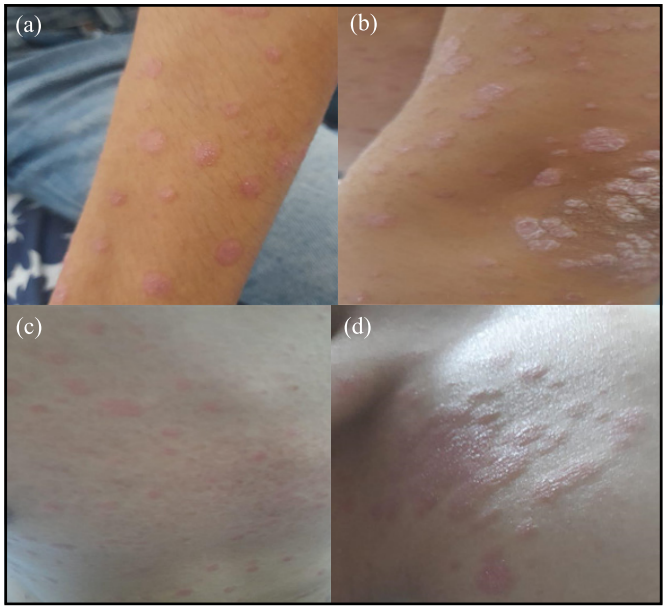

Fig. (1a-d): Images showing pustular psoriasis-like lesions on different parts of the body.

Table 1: Interpretation categories to assess differences between patients' sequences and reference sequences.

S. No.	Interpretation Categories	Results
1	Pathogenic Variants	None found
2	Likely Pathogenic Variants	Gene: PHKG2
		Transcript: NM_000294.2
		DNA variation: c.431T>C, Homozygous
		Predicted effect: p.Leu144Pro
3	Uncertain Variants	None found
4	Likely Benign Variants	None found
5	Benign Variants	Found many but not listed for the sake of brevity

Besides, another complication reported by the patient is the development of psoriasis-like lesions on the skin (**Fig. 1a-d**).

Results and Interpretation of Molecular Genetics Report

The variances from the reference sequences were allocated to one of the five elucidation categories as per American College of Medical Genetics and Genomics (ACMG) guidelines which include; pathogenic variants, likely pathogenic variants, uncertain variants, likely benign variants and benign variants (**Table 1**). The results of the NGS confirmed that the patient was glycogen storage disease-positive. The patient was homozygous in the PHKG2 gene for a variant specified as c.431T>C, which was anticipated for an amino acid substitution p.Leu144Pro. This finding was consistent with a diagnosis of glycogen storage disease type IXc.

Radiological Findings

A radiological examination of the liver was also performed to check for hepatic adenoma. The results showed hepatomegaly with fatty infiltrations and slightly coarse parenchyma.

DISCUSSION

The second very frequent reason for liver PhK deficiency is PHKG2 transformation. PhK is an intricate enzyme which consists of 4 diverse subunits. PHKG2 does encoding of the liver/ testis isoform of the catalytic gamma subunit, (which is an active position of PhK enzyme) so, PhK deficiency with PHKG2 transformation is related to a severe phenotype and has an augmented probability of hepatic cirrhosis [6, 16,

17]. In the presented case, developing hepatomegaly with fatty infiltrations and marginally coarse parenchyma were observed. c.431T>C in the PHKG2 transformation was revealed by genetic analyses. This variant has previously been reported as a cause for GSD Type IXc in the homozygous state of a Pakistani individual. Beauchamp and colleagues observed that the p.Leu 144 amino acid (highly evolutionarily conserved) was located within an α-helix in the catalytic protein domain; it is probable at this position that substitution of the native Leucine for a Proline may have a high impact on this α-helix structure [5]. As per the Human Gene Mutation Database, an amino acid alteration at an adjacent place (p.His145Tyr) was found as a causative agent [18].

The case presented by Li *et al.* detected a novel PHKG2 transformation (c.553C>T, p.Arg185X) in a family from China and confirmed it by next-generation and Sanger sequencing. The PHKG2 gene mutation field was established on 25 GSD IXc cases with PHKG2 transformations [5]. There are reports by Bali *et al.* with newly diagnosed PHKG2 transformations for three and five cases, respectively in 2014 at the same time. The PHKG2 transformation field in GSD IXc was not stated in the article, though the researchers reviewed the molecular, clinical and biochemical features linked with PHKG2 transformations. A total of 25 PHKG2 transformation cases have been reported [16]. A report of a Chinese newborn patient was presented by Shao *et al.* suffering from jaundice, hypoglycaemia, progressively elevated hepatic transaminase and obvious hepatomegaly and growth retardation, from the neonatal period. Unreported 2 novel PHKG2 transformations (F233S and R320DfsX5) were discovered by genetic tests. Functional experiments exhibited that both F223S and R320DfsX5 transformations resulted in decreased key phosphorylase b kinase enzyme actions. The two novel PHKG2 transformations were detected by whole-exome sequencing (WES) [8]. Until now, 33 diverse PHKG2 transformations have been noted through the literature survey [5], yet, a link between mutation severity and hepatic injury has not been evident. The PHKG2 transformations that are allelic truncating have been identified in both non-cirrhotic and cirrhotic hepatic cases [6, 7]. However, the molecular process remains undetermined for such separate liver phenotypes in GSD-IXc [8].

CONCLUSION

To conclude, clinical alterations in cases with PHKG2 transformations require long-term analyses with follow-up of such cases into later life. Moreover, the variants related to LDH-A deficiency must also be detected as patients present with psoriasis-like lesions (as per reported literature). The pathogenicity of the LDH isoenzymes variants must also be proven. Further guidance in diagnosis can be sought through assessments like the lactate stress test and its typical report of the pyruvate curve along with the clinical blend of myopathy and psoriatic-like lesions. This case report emphasizes the detection of unusual complications in cases of glycogen storage disease and encourages persistent research to improve the standard of patient care. Furthermore, explanations of the patient's test results were limited *via* available information. Enhanced elucidation in the future can be possible through the availability of more information and knowledge about human genetics and this specific illness. Prevention genetics also recommends that DNA sequencing of this assessment be kept in the patients' electronic medical record which will ease in automatic reinterpretation of the sequence in the future.

CONSENT FOR PUBLICATION

We took written informed consent from the patient.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

All authors equally contributed to writing.

REFERENCES

1. Özen H. Glycogen storage diseases: new perspectives. World J Gastroenterol 2007; 13(18): 2541-53.
DOI: https://doi.org/10.3748/wjg.v13.i18.2541 PMID: 17552001

2. Molares-Vila A, Corbalán-Rivas A, Carnero-Gregorio M, González-Cespón JL, Rodríguez-Cerdeira C. Biomarkers in glycogen storage diseases: an update. Int J Mol Sci2021; 22(9): 4381.
DOI: https://doi.org/10.3390/ijms22094381 PMID: 33922238

3. Choi R, Park HD, Kang B, Choi SY, Ki CS, Lee SY, *et al.* PHKA2 mutation spectrum in Korean patients with glycogen storage disease type IX: prevalence of deletion mutations. BMC Med Genet 2016; 17: 33.
DOI: https://doi.org/10.1186/s12881-016-0295-1 PMID: 27103379

4. Kishnani PS, Goldstein J, Austin SL, Arn P, Bachrach B, Bali DS, *et al.* Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2019; 21(4): 772-89.

DOI: https://doi.org/10.1038/s41436-018-0364-2 PMID: 30659246

5. Li C, Huang L, Tian L, Chen J, Li S, Yang Z. PHKG2 mutation spectrum in glycogen storage disease type IXc: a case report and review of the literature. J Pediatr Endocrinol Metab 2018; 31(3): 331-8.
DOI: https://doi.org/10.1515/jpem-2017-0170 PMID: 29360628

6. Waheed N, Saeed A, Ijaz S, Fayyaz Z, Anjum MN, Zahoor Y, *et al.* Variability of clinical and biochemical phenotype in liver phosphorylase kinase deficiency with variants in the phosphorylase kinase (PHKG2) gene. J Pediatr Endocrinol Metab 2020; 33(9): 1117-23.
DOI: https://doi.org/10.1515/jpem-2019-0603 PMID: 32697758

7. Albash B, Imtiaz F, Al-Zaidan H, Al-Manea H, Banemai M, Allam R, *et al.* Novel PHKG2 mutation causing GSD IX with prominent liver disease: report of three cases and review of literature. Eur J Pediatr 2014; 173(5): 647-53.
DOI: https://doi.org/10.1007/s00431-013-2223-0 PMID: 24326380

8. Shao Y, Li T, Jiang M, Xu J, Huang Y, Li X, *et al.* A very rare case report of glycogen storage disease type IXc with novel PHKG2 variants. 2022; 22(1): 267.
DOI: https://doi.org/10.1186/s12887-021-03055-7 PMID: 35549678

9. Tsujino S, Shanske S, Brownell AK, Haller RG, DiMauro S. Molecular genetic studies of muscle lactate dehydrogenase deficiency in white patients. Ann Neurol 1994; 36(4): 661-5.
DOI: https://doi.org/10.1002/ana.410360418 PMID: 7944300

10. Kanno T, Sudo K, Maekawa M, Nishimura Y, Ukita M, Fukutake K. Lactate dehydrogenase M-subunit deficiency: a new type of hereditary exertional myopathy. Clin Chim Acta 1988; 173(1): 89-98.
DOI: https://doi.org/10.1016/0009-8981(88)90359-2 PMID: 3383424

11. Anai T, Urata K, Tanaka Y, Miyakawa I. Pregnancy complicated with lactate dehydrogenase M-subunit deficiency: The first case report. J Obstet Gynaecol Res 2002; 28(2): 108-11.
DOI: https://doi.org/10.1046/j.1341-8076.2002.00015.x PMID: 12078970

12. Ito T, Aoshima M, Sugiura K, Fujiyama T, Ito N, Sakabe JI, *et al.* Pustular psoriasis-like lesions associated with hereditary lactate dehydrogenase M subunit deficiency without interleukin-36 receptor antagonist mutation: long-term follow-up of two cases. Br J Dermatol 2015; 172(6): 1674-6.
DOI: https://doi.org/10.1111/bjd.13590 PMID: 25640002

13. Yoshikuni K, Tagami H, Yamada M, Sudo K, Kanno T. Erythematosquamous skin lesions in hereditary lactate dehydrogenase M-subunit deficiency. Arch Dermatol 1986; 122(12): 1420-4.
DOI: https://doi:10.1001/archderm.1986.01660240084023 PMID: 3789777

14. Yue D, Zhu W, Zhao C. Exertional myalgia, contractures and annular erythema in a patient with muscle lactate dehydrogenase (LDH) deficiency. Neuromuscul Disord 2018; 28(1): 59.
DOI: https://doi.org/10.1016/j.nmd.2017.09.013 PMID: 29198466

15. Nazzari G, Crovato F. Annually recurring acroerythema and hereditary lactate dehydrogenase M-subunit deficiency. 1992; 27(2 Pt 1): 262-3.
DOI: https://doi.org/10.1016/s0190-9622(08)80735-9 PMID: 1430368

16. Bali DS, Goldstein JL, Fredrickson K, Rehder C, Boney A, Austin S, *et al.* Variability of disease spectrum in children with liver phosphorylase kinase deficiency caused by mutations in the PHKG2 gene. Mol Genet Metab 2014; 111(3): 309-13.
DOI: https://doi.org/10.1016/j.ymgme.2013.12.008 PMID: 24389071

17. Liang Y, Du C, Wei H, Zhang C, Zhang M, Hu M, *et al.* Genotypic and clinical analysis of 49 Chinese children with hepatic glycogen storage diseases. Mol Genet Genomic Med 2020; 8(10): e1444.
DOI: https://doi.org/10.1002/mgg3.1444 PMID: 32772503

18. Beauchamp N, Taybert J, Champion M, Layet V, Heinz-Erian P, Dalton A, *et al.* High frequency of missense mutations in glycogen storage disease type VI. J Inherit Metab Dis 2007; 30(5): 722-34.
DOI: https://doi.org/10.1007/s10545-007-0499-9 PMID: 17705025