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ORIGINAL ARTICLE

Molecular characterization of autosomal recessive Glycogen storage disease type Ib in a Pakistani family

Zeeshan Nazir [1,2], Musharraf Jelani [2], Naveed Wasif [3], Fakhar Alam [4]

ABSTRACT

Objective: To investigate Glycogen storage disease GSD type Ib in a Pakistani family through whole exome sequencing (WES) and Sanger sequencing to identify the genetic mutation and confirm its autosomal recessive inheritance.

Methods: This case-control and observational study was conducted at Islamia College University Peshawar, Pakistan, in the laboratory of Center for Omic Sciences in collaboration with Ulm University, Germany within a period of one year. Comprehensive clinical evaluations, comprising radiological examinations and liver function tests, established the diagnosis of GSD in the index patient, who presented with hepatomegaly, oral ulcerations, night tremors, short stature and delayed speech development as compared to her normal age controls and laboratory results indicated hypoglycemia and hyperuricemia. Whole exome sequencing (WES) was performed on the index patient to identify mutations in the SLC37A4 gene, followed by Sanger sequencing of family members to confirm the autosomal recessive inheritance of the recognized mutation.

Results: It is estimated that 80% of GSD-I patients have type I-a and only 20% are affected with type I-b. The analysis revealed a previously reported alteration (c.92-94del; p.Phe31del) in the SLC37A4 gene, found in a homozygous state in the affected sibling, while obligate carriers were heterozygous. The variant was absent in fifty healthy controls from the same ethnic background.

Conclusion: The study highlights the role of WES and Sanger sequencing in the diagnosis of rare diseases like GSD-Ib and recommends genetic testing of close relatives to assess carrier status and guide informed reproductive and clinical decisions in order to prevent recurrence.

Keywords: Glycogen Storage Disease IB [Supplementary Concept] (MeSH); GSD Ib (MeSH); G6PT1 (Non-MeSH); Irritable Bowel Syndrome (MeSH); Neutropenia (MeSH); Consanguineous (MeSH); Consanguineous Marriage (MeSH); Hepatomegaly (MeSH).

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1: Department of Allied Health Sciences, CECOS University, Peshawar, Pakistan
2: Rare Diseases Genetics and Genomics, Centre for Omic Sciences, Islamia College Peshawar, Pakistan
3: Institute of Human Genetics, Ulm University and Ulm University Medical Center, 89081, Ulm, Germany; Institute of Human Genetics, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany
4: Medical Officer, District Head Quarter Hospital, Karak, Pakistan

Email ✉ : zeeshanktk123464@gmail.com
Contact #: +92-347-5129831

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INTRODUCTION

Glycogen metabolism plays a critical role in maintaining blood glucose levels during physical activity and under normal physiological conditions. During eating, insulin triggers glycogen storage in muscle and hepatocytes while hindering glycogenolysis. Similarly, between fasting periods, molecules like Glucagon and catechol amines stimulate glycogenolysis and impede glycogenesis.[1] It is essential to acknowledge that hepatic glycogen storage disorders (GSDs) are metabolic disorders that are primarily caused by the imbalance of endogenous glucose production (EGP) and metabolic clearance rate, with disturbances in gluconeogenesis and glycogenolysis being key contributors.[2] Most GSDs are inherited in an autosomal recessive pattern,[3] except for Danon disease which follows an X-linked recessive pattern. The prime hallmark of most GSDs is abnormal glycogen storage.[4]

The concept of Glycogen storage disease type I (GSD-I) was introduced in 1929 by Edgar von Gierk and was described as anomalous accretion of Glycogen in tissues from that time onward it is famously known as von Gierk disease.[5] Von Gierk named it "Hepatonephromegalia glycogenica".[6] GSD is a complex of multi-disorders with 14 different types that are primarily caused by defects in the metabolism of Gycogen, which ultimately proceeds to improper accretion of glycogen in various body tissues and organs. The von Gierk disease i.e. also famously known as (GSD-I) is a set of autosomal recessive disorders initiated by deficits in the functioning of glucose-6-phosphatase (G6Pase i.e.Ia)/glucose-6-phosphate transporter (G6PT i.e. Ib) complexes.[7]

Patients with Glycogen Storage Disease Type I (GSD-I) typically experience hypoglycemia due to the inability to break down glycogen into glucose, leading to low blood sugar levels. They may also exhibit hyperlactatemia, characterized by elevated levels of lactic acid in the blood, which can occur due to impaired gluconeogenesis. Additionally, some patients may display a round, doll-like face, which can be indicative of fat deposition, although this is not a universal symptom. The disease primarily affects the liver's ability to release glucose from Glycogen, leading to various metabolic complications.[1]

Differential feature of GSD type Ib is that these patients present neutrophil dysfunction and develop inflammatory bowel syndrome.[8]

The SLC37A4 gene, also known as G6PT, is responsible for Glycogen storage disease type Ib (GSD-Ib), as indicated by its OMIM number 602671. This gene is located on chromosome 11q23.3 and spans approximately 5.3

kb, consisting of nine exons. It has been observed that around 80% of patients with Glycogen Storage Disease type I have type Ia, while only about 20% are diagnosed with type Ib.[8] To date, 126 mutations have been attributed to the SLC37A4 gene. These mutations are categorized into different classes based on the mode of variation and their impact on protein structure (https://www.hgmd.cf.ac.uk/).

Pakistan has a diverse population with a high incidence of consanguineous marriages, which increases the likelihood of recessive genetic disorders like Glycogen Storage Disease Type Ib (GSD Ib). Similarly, there is a lack of molecular characterization studies on GSD Ib in Pakistani populations, making this research essential for understanding the genetic basis of the disease in this region.

GSD Ib is a severe metabolic disorder that affects Glycogen metabolism, leading to hypoglycemia, hepatomegaly, and other complications. Accurate diagnosis and characterization are crucial for proper management and treatment.[4] Identifying the molecular basis of GSD Ib in Pakistani families can facilitate genetic counseling and allow for informed family planning.

There is a scarcity of molecular data on GSD Ib in Pakistani populations, making it challenging to understand the genetic epidemiology of the disease. Subsequently, the relationship between specific genetic mutations and the clinical presentation of GSD Ib in Pakistani patients is not well understood which hinders the development of effective treatments.

METHODS

Ethical endorsement and participants' consensus: Ethical approval was acquired from the Institutional Bioethical Committee of Islamia College University Peshawar (letter # 529/ORIC/ICP dated 21-08-2019), before the commencement of the study, written informed consent was voluntarily provided by all the participants and the legal guardian after a detailed briefing. The family was fully informed about the study's objectives, adhering to the principles outlined in the Declaration of Helsinki.

Particulars about the research study: This observational case-control study was conducted at the Center for Omic Sciences, Islamia College University, Peshawar, Pakistan. The subject was a consanguineous family from District Karak, Khyber Pakhtunkhwa, referred by a clinician for suspected metabolic disorder and subsequently investigated through molecular analysis.

Blood samples were collected from the family members for DNA analysis, to investigate the genetic basis of the condition. Family pedigree, clinical information, and proband's history were provided to Macrogen, South Korea, for whole exome sequencing, followed by Sanger sequencing validation at the Institute of Human Genetics, Ulm University Medical Center, Ulm University, 89081 Ulm, Germany.

Clinical evaluation and investigations: Radiological investigations including x-rays and ultrasound reports were analyzed by a radiologist at Lady Reading Hospital Peshawar Pakistan, and a pediatrician at North West General Hospital Peshawar subsequently cross-examined the data. Comprehensive laboratory investigations, including chemistry immunology, and hematological tests were conducted and thoroughly assessed the proband's medical condition. Hematological parameters including complete blood count (CBC) and differential leukocyte count (DLC) were assessed using cobas m 511 (Roche Diagnostics), similarly, biochemical profiles including liver function tests (LFTs) and lipid profiles performed through cobas C-701 (Roche Diagnostics).

Ultrasound-guided needle biopsy: Ultrasound-guided (U/D) biopsy is one of the precise and most reliable tools for analyzing soft tissue anomalies. This technique provides real-time imagining which is primarily due to ultrasound technology. Leveraging ultrasound technology to ensure accuracy and prevent damage to nearby nerves, arteries, and veins. Its non-ionizing radiation property makes it safer for patients. The U/D biopsy is favored for its efficiency, reproducibility, and minimal invasiveness, making it the preferred choice for soft tissue sampling.[9] An ultrasound-guided needle biopsy of the liver was performed using an 18-gauge semiautomatic side-notch Tru-Cut biopsy needle, under real-time imaging guidance by an ultrasound machine. The procedure of sample collection was carried out by a trained radiologist at Lady Reading Hospital (Medical Teaching Institution) Peshawar, Pakistan. And the subsequent examination of the sample was performed at Agha Khan Hospital Karachi, Pakistan.

Periodic acid-schiff staining with diastase (PAS-D): Periodic Acid-Schiff staining with Diastase PAS-D staining, a combination of periodic Acid-Schiff with diastase enzyme, is employed to specifically differentiate Glycogen from other PAS-positive substances in tissue samples. The diastase enzyme digests Glycogen into smaller components like maltose and glucose, which are then removed from the tissue, enabling clear identification of Glycogen deposits in the sample.[10]

Criteria for sample collection: Blood samples were collected from participants based on proband's phenotypic observations, medical history, the inheritance pattern of the disorder and consanguinity. Detailed family investigations were carried out to provide a comprehensive understanding of the disorder.

Inclusion criteria

• The family must have at least one of the unaffected parents alive.

Exclusion criteria

• The samples with below criteria were rejected.

• The family that showed non-genetic causes, showed a history of narcotics drug use or the presence of any infectious disease, and whose blood samples had already been taken by someone else for genetic analysis were excluded from the study.

Blood sample collection: Peripheral blood samples (4-5 ml) were collected in EDTA tubes from five family members including proband, parents, and unaffected siblings suspected of GSD Ib. To avoid any cross confusion family pedigree and blood samples were properly labeled and documented.

Genomic DNA extraction: Genomic DNA was extracted using the QIAGEN, Germany midi genomic DNA extraction kit at the Center for Omic Sciences laboratory. The obtained DNA was

stored at 3-4°C till further processing.

Qualitative and quantitative analysis of DNA: To confirm the presence of DNA, samples were analyzed through gel electrophoresis by following day. Similarly, the quantitative analysis was performed through a Nanodrop spectrophotometer (Thermo Fisher Scientific USA).

Qualitative analysis: To ensure the quality of DNA samples, gel electrophoresis was performed on 1% agarose, and a trans-illuminator (Cleaver Scientific Ltd, Model: OMNIDOC, Serial No.: 170221007) was used for visualization.

Quantitative analysis of DNA: Nanodrop (Thermo Fisher Scientific USA) was used for the quantitative examination of gDNA. Refined gDNA with the concentration of 50ng/µL was used for subsequent investigation.

Whole exome sequencing: According to pedigree analysis and phenotypic observations, DNA from the peripheral blood of three candidates i.e. two parents and one proband was sent to a commercial rare disease diagnostics laboratory Macrogene South Korea (https://3billion.io/) for whole exome sequencing. All exons of all human genes (~22,000) were captured by xGen Exome Research Panel v2 (Integrated DNA Technologies, Coralville, Iowa, USA). The captured genomic regions were sequenced using the NovaSeq platform (Illumina, San Diego, CA). The variant calling was performed using CoNIFER (https://conifer.sourceforge.net/)

Sanger sequencing analysis: The variant identified and shortlisted through whole exome sequencing was validated through Sanger sequencing at the Institute of Human Genetics, Ulm University Medical Center, Ulm University, 89081 Ulm, Germany, (ABI PRISM® 3700 Genetic Analyzer) for its homozygous segregation in autosomal recessive mode. Sequence alignment and editing of the Sanger sequenced data was performed using BioEdit software (version x.x, Tom Hall, Ibis Biosciences, Carlsbad, CA, USA), to ensure the difference between wild type and pathogenic variants among members of the affected family which confirmed the mode of inheritance in the family as well.

Primer designing for Sanger sequencing: Primers for the Sanger study were arranged using Primer3Plus input(https://www.bioinformatics.nl/primer3plus) and the sequence of SLC37A4 exon 3 was obtained from Ensemble Genome Browser (www.ensembel.org) correspondingly.

RESULTS

Clinical report: The index patient (IV-1), was a four-years-girl. She was the first offspring of a consanguineous marriage and was born through normal vaginal delivery without complications. Both the parents were unaffected. The pedigree scrutiny showed an autosomal recessive pattern of inheritance (Figure 1). The family had no history of similar phenotypes. No prenatal abnormalities were recorded. In early infancy, she had recurrent oral ulcerations and had started episodic hypoglycemia with sleep breaks in the night with tremors. She was treated on lactose-free formula in addition to her normal breastfeeding. She had been reported for short stature i.e. at the age of 80 months her height was 97 cm which is less than normal ranges (109-130 centimeters), with a Z-score of -4.73 and 0.1% as per CDC growth charts (https://www.cdc.gov/growthcharts/cdc-growth-charts.htm) failure to thrive, and delayed speech development as compared to her normal age controls. The patient also had observed irritable bowel syndrome (IBS) i.e. recurrent episodes of diarrhea and constipation, recurrent respiratory infection, tonsillitis, and vomiting due to improper digestion.

She had one healthy younger brother two years of age and no abnormality had been observed till the time of this study. The variant was also listed in the ClinVar database(https://www.ncbi.nlm.nih.gov/clinvar/variation/973538/).

Phenotypic observations: The proband's phenotypic observation showed protruded cheeks compared to age/gender-matched controls. Similarly, there is a prominent abdominal distention which is usually observed in GSD patients due to severe hepatomegaly.

Radiological examinations: As per the radiologist's comments X-ray image of the proband showed slight abdominal dilatation (88 mm), which endorses that the patient has having enlarged liver which is a prime hallmark of GSD. Abdominal ultrasound of the proband shows hypertrophied liver (137mm)

Table I: Primers used for PCR amplification of SLC37A4 exon 3

Primer	Sequence	Length	TM
SLC37A4_2F	5'-TGGCGCTCAGTAATCTCTTG-3'	20bp	59.2°
SLC37A4_1R	5'-GGGATTTCCCACCTCACTCT-3'	20bp	60.3°

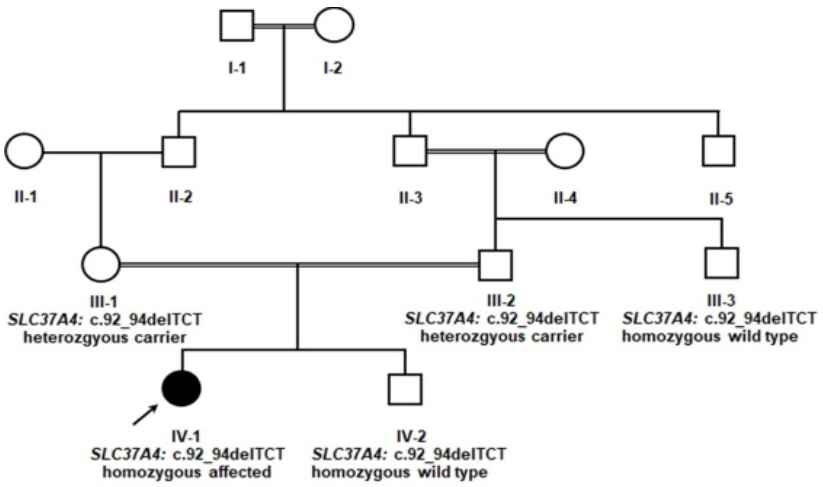

Figure 1: Pedigree structure and segregation analysis of the family with SLC37A4 mutation (c.92_94delTCT). Filled symbols show the affected, the arrow indicates the proband and the double line highlights consanguineous union.

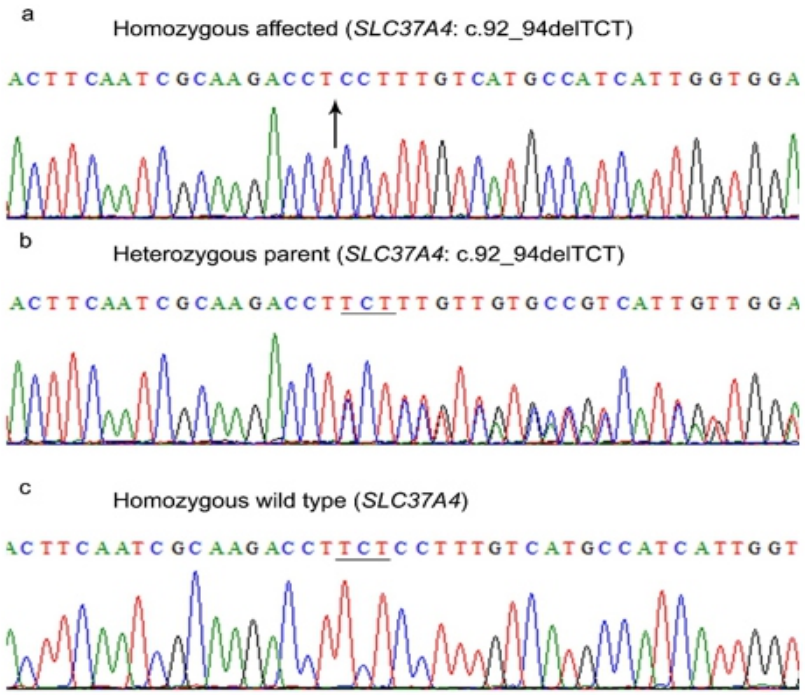

Figure 2: Sanger sequencing chromatograms results of exon 3 SLC37A4 gene depicting (a) affected index patient presenting homozygous deletion of three nucleotides (b) heterozygous variation in obligate carriers and (c) wild type or unaffected healthy controls.

which is (130.9mm) in normal individuals.

Laboratory tests and investigations: Laboratory investigations including hematological parameters revealed anemia; decreased mean corpuscular volume and decreased red blood cell count. Similarly, the biochemical parameters elevated alkaline phosphatase, hypercalcemia increased C-reactive protein level, and hypertriglyceridemia, hypoglycemia, and infantile lymphocytosis were also observed. Neutropenia which leads to recurrent episodes of infection was also observed.

Biopsy examinations: The microscopic examinations of the biopsy report showed enlarged hepatocytes with cytoplasmic clearing. Intervening areas of steatosis were also identified. Special stain i.e. Periodic Acid-Schiff stain (PAS+/-) highlights intracytoplasmic Glycogen which was lost on the Periodic Acid-Schiff staining with Diastase (PASD) special stain. Immunohistochemical stain CD68 was also negative. The mentioned features favor Glycogen Storage Disease.

In this report through sequencing data analysis, we confirmed a previously reported variant (c.92_94del; p.Phe31del) of the SLC37A4 gene, segregating in the homozygous condition in the affected sibling. The obligate carriers were heterozygous for the identified variant; however, it was not detected in fifty healthy controls of the same ethnic group.

Interpretation of SLC37A4 variant: Whole exome sequencing data analysis shortlisted a homozygous three bases deletion (c.92_94delTTC) in exon 3 of solute carrier family 37 member 4 (SLC37A4 OMIM 602671) gene located on chromosome 11q23.3. The three-base deletion could result in an in-frame deletion of phenylalanine at amino acid position 31 (p.Phe31del). Thus, the altered protein did not contain one amino acid at position 31 of the SLC37A4 protein (Figure 2). This variant had not been reported in Pakhtun or Pakistani population before; however, was not a novel and had previously been reported in other populations with Glycogen storage disease type 1b.[6]

DISCUSSION

The prime utility of the SLC37A4 gene is to translocate G6P from the cytosol into the lumen of the endoplasmic reticulum.[11] A diagnostic approach for Glycogen Storage Disease type I (GSD I) relies on its clinical presentation like abnormal levels of glucose, triglycerides, lipids, lactate, and uric acid in the blood, liver biopsy to measure enzymatic functionality and genetic testing via sequencing.[12]

Modern molecular diagnostic concepts are grounded on mutation analyses of disease-causing genes known in each clinical type of GSD. It reduces the chance of false or overlapping phenotyping and is very helpful in differential diagnoses.[13] In this regard, direct Sanger sequencing of the candidate gene or Whole exome sequencing (WES) could be an effective approach for precise molecular diagnosis of GSD Ib.[14]

The prime hallmark of GSD Ib is that patients often experience neutropenia due to a compromised glycogenolytic pathway,[15,12,14] the same condition has been observed in our study proband. Similarly one of the Korean patients showed inflammatory bowel disease known as irritable bowel syndrome (IBS) [15] "is" common to our study patient as well. An individual who has a history of recurrent oral ulceration and peripheral neutropenia is strongly suspected of GSD Ib and should subsequently go for mutational analysis of DNA to clarify its ambiguity with other sub-classifications like GSD Ia/Ib.[16]

Whole exome sequencing analysis identified a homozygous deletion of three bases (c.92_94delTTC) in exon 3 of the SLC37A4 gene (OMIM 602671), located on chromosome 11q23.3. This variant was subsequently confirmed through Sanger sequencing, demonstrating its homozygous inheritance consistent with an autosomal recessive pattern. The deletion leads to an in-frame loss of phenylalanine at amino acid position 31 (p.Phe31del), resulting in the absence of this specific amino acid in the SLC37A4 protein.

It is essential to declare that our kind of identical mutation was reported for the first time in Brazilian patients in that particular cohort study twenty seven novel mutations were identified including c.92_94delTCT a three-base deletion which resulted in p.Phe31_Ser32del but that was declared as an uncertain mutation in

terms of pathogenicity.[13] Similarly, a study conducted in England reported the same type of mutation in the SLC37A4 gene which presented anemia, low mean corpuscular volume (MCV), and neutropenia that are commonly shared with the present study mutation.[17]

It is important to mention that we simply cannot diagnose an individual with GSD Ib based on clinical or laboratory investigations. In a study conducted on a German patient, it was established that an individual had having normal neutrophil count but was diagnosed with GSD Ib after the genetic screening, this confirmed that a decrease in neutrophil number is not a prime hallmark of GSD Ib rather it can also be observed in GSD Ia patients.[17]

The mentioned study comprises five members of a single family and due to limited genetic diversity, the study may not represent a large population. Which needs to be analyzed at a broader level to get a clear depiction of the condition. Similarly, this study was limited to the level of genetic sequencing a clearer picture could be drawn through proteomics understanding

This study highlights the use and significance of the latest molecular-based diagnostic approach i.e. Whole Exome Sequencing (WES) followed by Sanger sequencing in the given population. It is recommended to use the same type of diagnostic method as it helps in identifying and validating genetic conditions that are with rare frequency.

CONCLUSION

This study aimed to identify the causative genetic variant in an affected sibling and conduct carrier testing within a consanguineous family. WES proved effective in pinpointing the responsible mutation in a suspected single-gene disorder. While clinical diagnosis of Glycogen Storage Disease is often complicated by overlapping phenotypes among the nine known subtypes, WES offers a precise approach by evaluating all possible pathogenic variants simultaneously. In this case, WES followed by Sanger sequencing confirmed a homozygous three-base pair deletion (c.92_94delTTC) in exon 3 of the SLC37A4 gene (OMIM 602671), located on chromosome 11q23.3. Carrier analysis revealed both parents were heterozygous, while the affected sibling was homozygous for the deletion. Two other family members were found to be wild-type and not at risk of transmitting the disorder, indicating that future consanguineous unions involving these individuals may not pose a genetic risk.

REFERENCES

1. Ellingwood SS, Cheng A. Biochemical and clinical aspects of Glycogen Storage Disease. J Endocrinol 2018;238(3):R131-41. https://doi.org/10.1530/joe-18-0120
2. Derks TGJ, Rijn M Van. Lipids in hepatic Glycogen Storage Disease : pathophysiology , monitoring of dietary management and future directions. J Inherit Metab Dis 2015;38(3):537-43. https://doi.org/10.1007/s10545-015-9811-2
3. D'souza RS, Levandowski C, Slavov D, Graw SL, Allen LA, Adler E, et al. Danon disease clinical features, evaluation, and management. Circ Hear Fail 2014;7(5):843-9. https://doi.org/10.1161/circheartfailure.114.001105
4. Saudubray JM, Van Den Berghe G, Walter JH. Inborn metabolic diseases diagnosis and treatment. Inborn Metab Dis Diagnosis Treat 2012;1.https://doi.org/10.1007/978-3-642-15720-2
5. Ballavenuto JMA, de Oliveira JDD, Alves RJ. Glycogen Storage Disease type i (Von gierke disease): Report of two cases with severe dyslipidemia. Arq Bras Cardiol 2020;114(4):23-6. https://doi.org/10.36660/abc.20190037
6. Chou J, Matern D, Mansfield B, Chen YT. Type I Glycogen Storage Diseases: Disorders of the Glucose-6- Phosphatase Complex. Curr Mol Med 2002;2(2):121-43. https://doi.org/10.2174/1566524024605798
7. Wang DQ, Fiske LM, Carreras CT, Weinstein DA. Natural history of hepatocellular adenoma formation in Glycogen Storage Disease type i. J Pediatr 2011;159(3):442-6. http://dx.doi.org/10.1016/j.jpeds.2011.02.031
8. Kishnani PS, Austin SL, Abdenur JE, Arn P, Bali DS, Boney A, et al. Diagnosis and management of Glycogen Storage Disease type I: A practice guideline of the American College of Medical Genetics and Genomics. Genet Med 2014;16(11):1-29. https://doi.org/10.1038/gim.2014.128
9. Battaglia M, Pollastri P, Ferraro A, Betoni F. The role of ultrasound-guided needle biopsy in the diagnosis of soft-tissue tumors. J Ultrasound 2007;10(2):59-62. https://doi.org/10.1016/j.jus.2007.03.001
10. Borel F, Mueller C. Alpha-1 Antitrypsin Deciency. Humana New York, NY: Humana Press; 2017. pp-278.https://doi.org/10.1007/978-1-4939-7163
11. Chou JY, Mansfield BC. The SLC37 Family of Sugar- Phosphate / Phosphate Exchangers. 1st ed. Vol. 73, Exchangers. Elsevier Inc.; 2014. pp:357–82.https://dx.doi.org/10.1016/B978-0-12-800223-0.00010-4
12. Dissanayake VH, Jayasinghe JD, Tilakaratna V. A novel mutation in SLC37A4 gene in a Sri Lankan boy with Glycogen Storage Disease type Ib associated with very early onset neutropenia. J Mol Genet Med 2011;05(01):262-3. https://doi.org/10.4172/1747-0862.1000046
13. Sperb-Ludwig F, Pinheiro FC, Bettio Soares M, Nalin T, Ribeiro EM, Steiner CE, et al. Glycogen storage diseases: Twenty-seven new variants in a cohort of 125 patients. Mol Genet Genomic Med 2019;7(11):1-10. https://doi.org/10.1002/mgg3.877
14. Choi R, Park H doo, Ko JM, Lee J, Lee DH, Hong SJ, et al. Novel SLC37A4 Mutations in Korean Patients With Glycogen Storage Disease Ib. Ann Lab Med 2017;37(3):261-6. https://doi.org/10.3343/alm.2017.37.3.261
15. Han SH, Ki CS, Lee JE, Hong YJ, Son BK, Lee KH, et al. A novel mutation (A148V) in the glucose 6-phosphate translocase (SLC37A4) gene in a Korean patient with Glycogen Storage Disease type 1b. J Korean

Med Sci 2005;20(3):499-501. https://doi.org/10.3346/jkms.2005.20.3.499

16. Zhang Y, Sun H, Wan N. Mutation analysis of SLC37A4 in a patient with Glycogen Storage Disease-type Ib. J Int Med Res 2019;47(12):5996-6003.https://doi.org/10.1177/0300060519867819

17. Veiga-da-cunha M, Gerin I, Chen Y tsong, Lee PJ, Leonard J V, Schaftingen E Van. The Putative glucose 6-phosphate translocase gene is mutated in essentially all cases of Glycogen Storage Disease type I non-a. Eur J Hum Genet 1999;7(6):71723.https://doi.org/10.1038/sj.ejhg.5200366

AUTHORS' CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

ZN: Acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

MJ: Conception and study design, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

NW & FA: Acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

KMUJ web address: www.kmuj.kmu.edu.pk
Email address: kmuj@kmu.edu.pk