Review Paper

Frequency of *G6PC1* and *SLC37A4* Genetic Variants in Asian Patients With Glycogen Storage Disease Type I: A Systematic Review

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ABSTRACT

Background: Glycogen storage disease type I (GSD I), or Von Gierke disease, is a rare autosomal recessive disorder caused by mutations in the *G6PC1* (GSD Ia) or *SLC37A4* (GSD Ib) genes. Early genetic diagnosis is essential to prevent complications.

Objectives: This study aimed to systematically review reported *G6PC1* and *SLC37A4* variants in Asian patients and to identify region-specific mutation patterns.

Methods: A systematic search of Web of Science, PubMed, Embase, Scopus, ProQuest, and Google Scholar was performed through June 4, 2023, using appropriate MeSH terms and keywords. Eligible studies included cross-sectional studies, cohorts, case reports/series, and case-control designs that reported the type and frequency of pathogenic or likely pathogenic *G6PC1* or *SLC37A4* variants in Asian patients with GSD I. Two reviewers independently extracted data, with discrepancies resolved by a third reviewer. Variant pathogenicity was assessed using the American College of Medical Genetics and Genomics (ACMG) criteria and cross-validated with ClinVar and HGMD. Regional variant frequencies were summarized using descriptive methods.

Results: Seventy studies from 14 Asian countries, comprising 680 patients, were included. Distinct regional mutation patterns were identified. In East Asia, the *G6PC1* c.648G>T and *SLC37A4* c.572C>T/c.521C>T variants predominated. In West Asia, *G6PC1* c.247C>T and *SLC37A4* c.1042_1043delCT were most frequent. In South Asia, G6PC1 c.648G>T/c.150_151delGT and *SLC37A4* c.796_797del/c.898C>T were common. These patterns highlight both shared and region-specific variants.

Conclusions: The study reveals diverse, region-specific *G6PC1* and *SLC37A4* mutations in Asian patients with GSD I, supporting targeted genetic screening and personalized diagnostics.

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Introduction

Glycogen storage diseases are a group of rare metabolic disorders characterized by defects in glycogen metabolism, leading to glycogen accumulation in tissues, particularly the liver and muscles [1-3]. Among more than 20 subtypes, glycogen storage disease type I (GSD I), or von Gierke disease, is the most common [4]. It results from deficiencies in the glucose-6-phosphatase complex (*G6PC1*), which plays a critical role in the final step of both glycogenolysis and gluconeogenesis by catalyzing the conversion of glucose-6-phosphate to free glucose. This reaction is essential for maintaining normal blood glucose levels during fasting. Deficiency of this complex prevents the release of glucose into the circulation, leading to severe fasting hypoglycemia and intracellular accumulation of glycogen and lipids, particularly in hepatocytes and renal tubular cells. Based on the affected component of the G6Pase complex, GSD I is classified into two major subtypes: GSD Ia, due to *G6PC1* deficiency, and GSD Ib, caused by glucose-6-phosphate transporter (*SLC37A4*) deficiency. GSD I follows an autosomal recessive inheritance pattern and is more prevalent in populations with high rates of consanguinity [3]. Clinically, GSD I presents in infancy with hypoglycemia, lactic acidemia, hyperlipidemia, hyperuricemia, and hepatomegaly. Chronic metabolic imbalance may lead to long-term complications, including growth retardation, hepatic adenomas with a potential risk of malignant transformation, progressive renal dysfunction, osteoporosis, and delayed puberty. GSD Ib also features neutropenia and inflammatory bowel disease, which predispose affected individuals to recurrent bacterial infections, oral ulcers, and inflammatory bowel disease, thereby contributing to increased morbidity and reduced quality of life [1, 3, 5-7].

Accurate and early diagnosis is essential to prevent complications. While clinical features and biochemical tests are informative, overlapping symptoms with other GSD types, such as GSD III, can complicate diagnosis. Thus, molecular genetic testing, particularly gene mutation analysis, provides a reliable, noninvasive diagnostic tool [5, 8]. Numerous mutations in *G6PC1* and *SLC37A4* have been reported across various ethnicities. However, the mutation spectrum and frequencies can differ significantly by region [3]. Despite this genetic diversity, the overall incidence of GSD I does not appear to differ significantly among populations [3].

Although numerous mutations of *G6PC1* and *SLC37A4* have been reported in various ethnic groups, there is limited systematic data on their prevalence and regional patterns in Asian populations, which hinders optimal genetic counseling and the development of effective diagnostic strategies. This study aims to systematically review reported variants of *G6PC1* and *SLC37A4* in Asian patients with GSD I. Specifically, we sought to identify prevalent mutations in different Asian regions (participants), compare mutation distributions across regions (comparisons), summarize variant frequencies and patterns (outcomes), and synthesize data from observational studies including case reports, case series, and cohort studies (study design). Identifying prevalent mutations and regional patterns can enhance genetic counseling and streamline diagnostic approaches. These findings may also improve patient outcomes through targeted treatment strategies.

Materials and Methods

Information sources and search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) guidelines. A detailed review protocol was developed a priori and prospectively registered in the international prospective register of systematic reviews (PROSPERO) under the registration number CRD42023475081. The registered protocol is publicly available in the PROSPERO database [1]. A comprehensive literature search was conducted in the following electronic databases: Web of Science, PubMed/MEDLINE, Embase, Scopus, and ProQuest, covering studies published from January 1995 to June 4, 2023. The final search was performed on June 4, 2023. In addition, Google Scholar was searched to identify potentially relevant gray literature.

Reference lists of all included articles and relevant reviews were manually screened to identify additional eligible studies. No direct contact with study authors was undertaken to obtain unpublished data. The full electronic search strategies for all databases, including search terms, Boolean operators, and applied limits (language), are provided in Supplementary File S1 to ensure search reproducibility.

Eligibility criteria

Eligible studies were selected based on the PICOS framework.

Participants (P): Asian patients with a confirmed diagnosis of GSD Ia or GSD Ib.

Intervention/Exposure (I): Genetic analysis of *G6PC1* and/or *SLC37A4* variants.

Comparison (C): Comparison of variant distribution across different Asian regions and populations, where applicable.

Outcomes (O): Type, frequency, and distribution of pathogenic or likely pathogenic variants.

Study design (S): Observational studies, including case reports, case series, cross-sectional, case–control, and cohort studies.

Studies published between 1995 and 2023 in English and available as full-text peer-reviewed articles were included. Conference abstracts, reviews, editorials, non-English publications, and duplicate reports were excluded to ensure data completeness and methodological quality.

Study selection

All records identified through database searching were imported into reference management software, and duplicate records were removed. Two reviewers independently screened the titles and abstracts of all retrieved studies to identify potentially eligible articles. Full texts of the selected studies were then assessed for eligibility based on the predefined inclusion and exclusion criteria. Any disagreements between reviewers at any stage were resolved through discussion or consultation with a third reviewer. Studies meeting the eligibility criteria were included in the final systematic review. As no meta-analysis was conducted, all eligible studies were synthesized narratively.

Data collection process

Data were independently extracted by two reviewers using a predefined data extraction form. Extracted information included publication year, country, sample size, disease subtype, gene variant details, and consanguinity. Any discrepancies between reviewers were resolved through discussion or consultation with a third reviewer. For studies with missing or unclear information, attempts were made to clarify data from the original reports. This process ensured consistency, accuracy, and reliability of the extracted data.

Data items

The following variables were extracted from each included study:

- Study characteristics: authors, publication year, and country;

- Participants: number of patients, disease subtype (GSD Ia or Ib), consanguinity;

- Gene variants: gene name, nucleotide and protein changes, exon location, type of mutation (missense, nonsense, frameshift, splice-site, deletion).

PICOS elements:

- Participants: Asian patients with GSD I;

- Intervention: molecular genetic testing (gene mutation analysis);

- Comparison: variant distribution across regions;

- Outcome: variant frequencies and patterns;

- Study design: observational studies including case reports, case series, and cohort studies;

Only pathogenic or likely pathogenic variants were included; benign variants and polymorphisms were excluded. No additional assumptions or simplifications were applied beyond the predefined criteria.

Data extraction and regional classification

Two reviewers independently screened and extracted data, with discrepancies resolved by a third reviewer. Extracted data included publication year, country, number of patients, disease subtype, mutation details, and consanguinity. To assess geographic variation, studies were grouped into three Asian regions: East Asia, South Asia, and West Asia, following standard United Nations regional definitions.

Only pathogenic or likely pathogenic mutations were included; benign variants and polymorphisms were excluded from the analysis. Pathogenicity classification was performed based on the American College of Medical Genetics and Genomics (ACMG) guidelines, with ClinVar and VarSome used as reference tools to support and validate variant interpretation. In this systematic review, only variants classified as pathogenic or likely pathogenic were included, while benign variants and polymorphisms were excluded.

Risk of bias within studies

Given the descriptive and genetic nature of the included studies—most of which consisted of case reports, case series, cross-sectional studies, and observational cohorts without comparative interventions or outcome measures—a formal quantitative risk-of-bias assessment was considered of limited applicability. Therefore, study quality was evaluated qualitatively at the study level by assessing the clarity of GSD I diagnosis, confirmation of molecular genetic testing, completeness of variant reporting, and transparency of methodological descriptions. Only studies reporting pathogenic or likely pathogenic variants were included to enhance data reliability. These quality considerations were considered during the narrative synthesis and interpretation of variant distribution and frequency patterns.

Risk of bias across studies

As no meta-analysis was performed, statistical assessments of bias across studies, such as publication bias or heterogeneity measures, were not applicable. Nevertheless, potential sources of bias across studies were considered qualitatively, including uneven geographic representation of Asian countries, small sample sizes in some regions, and selective reporting of variants in individual studies. These limitations are acknowledged and discussed in the Discussion section to provide context for interpreting the overall findings.

Data synthesis and summary measures

As this systematic review did not perform a meta-analysis, results were synthesized narratively and using descriptive statistics. Data from individual studies were extracted and grouped by gene (*G6PC1* or *SLC37A4*), country, and Asian region. Principal summary measures included the number of patients with each variant, allele frequencies, and percentage ranges. Frequencies were presented in tables and summarized narratively to compare variant distributions across Asian regions, highlighting prevalent mutations and geographic differences. This descriptive approach ensures clarity and allows assessment of regional patterns and prevalence without statistical pooling or use of consistency measures, such as I^2.

Given the descriptive nature of the included studies and the focus on genetic variant reporting, no effect estimates, confidence intervals, or meta-analytic measures were calculated. Study-level variant data are presented in detail in tables to allow assessment of variant frequencies and regional patterns.

Results

Search results and study selection

A total of 1,706 records were identified across the Web of Science, PubMed, Embase, Scopus, and ProQuest databases. After removing duplicates, 853 unique records remained. Screening of titles and abstracts excluded 641 studies that did not meet the inclusion criteria. The full texts of 211 articles were subsequently assessed for eligibility, resulting in the exclusion of 140 studies that did not focus on Asian populations, one study lacking a full text, and 29 studies for other reasons (e.g. non-human studies or insufficient data). An updated search and manual review added two additional studies, yielding a total of 70 studies included in this systematic review.

These included studies, published between 1995 and 2023, encompassed 680 patients from 14 countries and represented diverse ethnic groups and physiographic regions across Asia. The characteristics of the included studies, including country, patient numbers, disease subtypes, and mutation details, are summarized in Tables 1 [5-7, 9-11, 22, 26-58], 2 [3, 13-17, 60-65], 3 [63, 67-71], categorized by region and ethnicity. A PRISMA flow diagram (Figure 1) illustrates the detailed study selection process, including screening, eligibility assessment, and reasons for exclusion at each stage.

Study characteristics

The included studies comprised a total of 70 publications, including case reports, case series, cross-sectional studies, and cohort studies, published between 1995 and 2023. Sample sizes varied widely, ranging from single-patient case reports to multicenter studies involving more than 100 patients. Overall, the studies included 680 patients diagnosed with glycogen storage disease type I, encompassing both GSD Ia (*G6PC1*-related) and GSD Ib (*SLC37A4*-related) subtypes.

Participants were patients of Asian origin from 14 countries across East Asia, West Asia, and South Asia. The primary outcomes assessed in all studies were the identification and frequency of pathogenic or likely pathogenic variants in the *G6PC1* and/or *SLC37A4* genes. Most studies employed molecular genetic techniques such as Sanger sequencing, next-generation sequencing, or whole-exome sequencing for variant detection. Funding sources and risk-of-bias assessments were not consistently reported across studies and were therefore not analyzed at the individual study level.

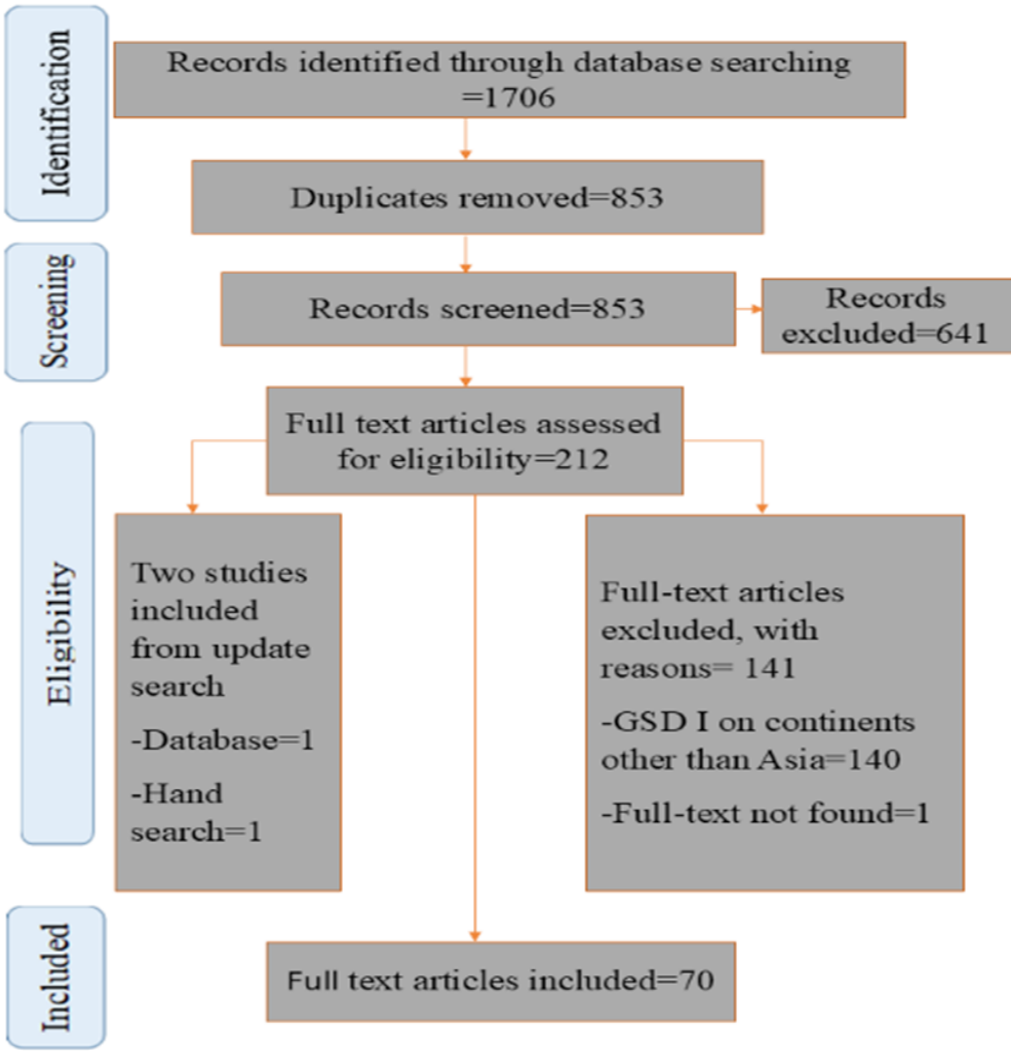

Figure 1. The PRISMA flow diagram outlining the search

Due to the descriptive and genetic nature of the included studies, no interventions, comparators, or follow-up periods were applicable. Detailed characteristics of each study, including country, study design, sample size, disease subtype, and identified variants, are summarized in Tables 1 [5-7, 9-11, 22, 26-58], 2 [3, 13-17, 60-65], 3 [63, 67-73].

Across the 70 included studies, qualitative assessment indicated that most studies employed validated molecular genetic methods for variant detection. However, smaller case reports or series from underrepresented regions may have introduced selection bias, and some studies lacked complete details on consanguinity or patient characteristics. These considerations were accounted for in the interpretation of variant distribution and frequency patterns.

Distribution and relative frequencies of *G6PC* and *SLC37A4* gene variants

Tables 4, 5, and 6 present a comprehensive summary of the various *G6PC* gene variants and their distribution across different regions of Asia, while Tables 7, 8, and 9 present *SLC37A4* gene variants. These tables detail the frequency of each variant type by country and ethnic group, based on individual study data. The total variant frequency for each gene was calculated by dividing the number of occurrences of each variant by the total number of reported variants associated with *G6PC* or *SLC37A4*. The column titled "variant frequency related to each study (%)" incorporates data from Tables 1, 2, and 3 for each respective country or ethnicity. The reported values reflect a range of variant frequencies observed in various populations, excluding those derived from case reports.

Table 1. Types and relative frequencies of gene mutations in male and female patients with GSD1a/b in East Asia by country

No	Ref.	Country	Sample size	GSD1 type (Ia/Ib)	Gene	Location (Exon/Intron)	Genetic Variant			No. (%)	Consanguinity (Yes/NO/ Not Mentioned)
							Nucleotide change	Amino acid Change	Mutation Type	Mutations	
1	[11]	China	3	Ib	*SLC37A4*	Exon 4	c.351delC	p.G117fs*28	Frameshift	1(16.67)	Not mentioned
						Exon 6	c.572C>T	p. P191L	Missense	2(33.33)	
						Exon 9	c.935_937delCTG	P.T312Sfs*13	Frameshift	1(16.67)	
						Exon 10	c.1042_1043delCT	p.L348Vfs*5	Frameshift	1(16.67)	
						Exon 11	c.1145_1163del	p.382_388del	Missense	1(16.67)	
2	[26]	China	1	Ia	*G6PC*	Exon 2	c.248G>A	p.R83H	Missense	1(50)	Not mentioned
						Exon 5	c.648G>T	p.L216L	Synonymous	1(50)	
3	[27]	China	3	Ib	*SLC37A4*	Exon 6	c.572C>T	p.P191L	Missense	2(33.33)	Not mentioned
						Exon 7	c.870+5G>A	-	Intron Variant	1(16.67)	
						Exon 7	c.680G>A	p.W227*	Nonsense	1(16.67)	
						Exon 10	c.1016G>A	p.G339D	Missense	1(16.67)	
						Exon 10	c.343G>A	p.G115R	Missense	1(16.67)	
4	[28]	China	1	Ib	*SLC37A4*	Exon 6	c.572C>T	p.P191L	Missense	1(33.33)	No
					SLC37A4	Exon 10	c.1043T>C	p.L348P	Missense	1(33.33)	
					Lipoprotein lipase (LPL)	Exon 4	c.483delA	p.A162Pfs*10	Frameshift	1(33.33)	
5	[29]	China	1	Ib	*SLC37A4*	Exon 4	c.356C>T	p.P119L	Missense	2(100)	Yes
6	[12]	China	32	Ia	*G6PC*	Exon 1	c.113A>T	p.D38V	Missense	1(4.54)	No
						Exon 2	c.238T>A	p.F80I	Missense	1(4.54)	
						Exon 2	c.248G>A	p.R83H	Missense	3(13.64)	
						Exon 2	c.262delG	p.V88fs	Frameshift	4(18.18)	
						Exon 3	c.353G>A	p.G118D	Missense	1(4.54)	
						Exon 4	c.518T>C	p.L173P	Missense	1(4.54)	
						Exon 5	c.648G>T	p.L216=	Synonymous	8(36.36)	
						Exon 5	c.821C>T	p.A274V	Missense	1(4.54)	
						Exon 5	c.1022T>A	p.I341N	Missense	2(9.09)	
						Exon 5	c.572C>T	p.P191L	Missense	1(25)	
				Ib	*SLC37A4*	Exon 5	c.576_577insT	p.D193*	Nonsense	1(25)	No
						-	g.5700_5703delAAGT	-	Frameshift	1(25)	
						Exon 10	c.1042_1043delCT	p.L348fs	Frameshift	1(25)	

No	Ref.	Country	Sample size	GSD1 type (Ia/Ib)	Gene	Location (Exon/Intron)	Genetic Variant			No. (%)	Consanguinity (Yes/NO/ Not Mentioned)
							Nucleotide change	Amino acid Change	Mutation Type	Mutations	
7	[30]	China	1	Ib	*SLC37A4*	Exon 4	c.359C>T	p.P120L	missense	1(50)	No
						Exon 5	c.572C>T	p.P191L	missense	1(50)	
8	[31]	China	1	Ia	*G6PC*	5′ regulatory sequence as well as exon 1, intron 1, exon 2 and partial intron 2 of the *G6PC* gene	chr17 g.41049904 _ 41057049del7125 starts from the first intron of the *LINC00671* gene to intron 2 of the *G6PC* gene	7.1 kb deletion covering two exons	Large deletion (chr17 g.41049879 _ 41057003del7125) was thus 7125 bp in length	1(50)	No
						Exon 2	c.326G>A	p.C109Y	Missense	1(50%0	
9	[32]	China	1	Ia	*G6PC*	Exon 4	c.518T>C	p.L173P	Missense	2(100)	Yes
10	[8]	China	5	Ia	*G6PC*	Exon 2	c.238T>A	p.F80I	Missense	2(10)	No
						Exon 2	c.248G>A	p.R83H	Missense	2(10)	
						Exon 2	c.262delG	p.V88FfsX14	Frameshift	7(35)	
						Exon 2	c.353G>A	p.G118D	Missense	2(10)	
						Exon 3	c.821C>T	p.A274V	Missense	3(15)	
						Exon 5	c.1022T>A	p.I341N	Missense	2(10)	
						Exon 5	c.648G>T	p.L216=	Synonymous	2(10)	
11	[33]	China	1	Ia	*G6PC*	Exon 2	c.311A> T	p.L104Q	Missense	1(50)	No
						Exon 5	c.648G>T	p.L216=	Synonymous	1(50)	
12	[34]	China	1	Ia	*G6PC*	Exon 2	c.327G>A	p.R83H	Missense	1(50)	No
						Exon 4	c. 597T >C	p.L173P	Missense	1(50)	
13	[35]	China	26	Ia	*G6PC*	Exon 2	c.310C>T	p.Q104X	Nonsense	1(1.96)	Not mentioned
						Exon 4	c.508C>T	p.R170X	Nonsense	1(1.96)	
						Exon 2	c.341delG	p.I101*	Deletion	1(1.96)	
						-	c.248G>A	p.R83H	Missense	7(13.72)	
						Exon 5	c.727G>T	-	Splicing	41(80.39)	
14	[36]	China	1	Ib	*SLC37A4*	Exon 4	c.572C>T	p.P191L	Missense	1(50)	No
						Exon 2	g.70T>C	p.Y24H	Missense	1(50)	
15	[37]	China	5	Ia	*G6PC*	Exon 2	c.326C >T	p.R83C	Missense	1(10)	Not mentioned
						Exon 2	c.327G>A	p.R83H	Missense	7(70)	
						-	-	Unidentified	-	2(20)	
16	[38]	Taiwan	1	Ia	*G6PC*	Exon 2	c.248G>A	p.R83H	Missense	1(50)	Not mentioned
						Exon 5	c.814G >T	p.G272W	Missense	1(50)	

No	Ref.	Country	Sample size	GSD1 type (Ia/Ib)	Gene	Location (Exon/Intron)	Genetic Variant			No. (%)	Consanguinity (Yes/NO/ Not Mentioned)
							Nucleotide change	Amino acid Change	Mutation Type	Mutations	
17	[39]	Taiwan	1	Ia	*G6PC*	Exon 5	c.1074A>C	p.*358Yext*43	Stoploss	2(100)	Yes
18	[40]	Taiwan	1	Ib	*SLC37A4*	Exon 3	c.354_355insC	p. W118fsX12	Insertion	2(50)	No
						-	c.736T>C	p.W246R	Missense	2(50)	
19	[41]	Chinese patients of Taiwan	18	Ia	*G6PC*	Exon 2	c.327G>A	p.R83H	Missense	13(37.14)	Not mentioned
						Exon 2	c.341delG	p.I101*	Frameshift	1(2.86)	
						Exon 2	c.389C>T	p.Q104X	Nonsense	1(2.86)	
						Exon 3	c.435A>T	p.H119L	Missense	1(2.86)	
						Exon 5	c.933insAA	-	Frameshift	1(2.86)	
						Exon 5	c.727G>T	-	-	16(45.71)	
						Exon 5	c.1101T>A	p.I341N	-	2(5.71)	
20	[42, 43]	Taiwan	18	Ia	*G6PC*	Exon 2	c.327G>T	p.R83H	Missense	13(36.11)	Yes
						Exon 5	c.727G >T	-	-	16(44.44)	
						-	c.793G>T	p.L238=	Synonymous	1(2.78)	
						Exon 2	c.341delG	p.I101*	Deletion	1(2.78)	
						-	c.933insAA	polypeptide stops 16 amino acids after lysine 285-	Frame-Shift	1(2.78)	
						Exon 2	c.327G>A	p.R83I	Missense	4(11.11)	
21	[44]	Taiwan	1	Ia	*G6PC*	Exon 1	c.46A>G	p.T16A	Missense	1(50)	Not mentioned
						Exon 2	c.248G>A	p.R83H	Missense	1(50)	
22	[45]	Taiwan	1	Ia	*G6PC*	Exon 3	c.356A>T	p.H119L	Missense	1(50)	Not mentioned
						Exon 5	c.648G>T	p.L216=	Synonymous	1(50)	
23	[46]	Taiwan	1	Ia	*G6PC*	Exon 2	c.341delG	p.I101*	Deletion	2(100)	Not mentioned
24	[47]	Taiwan	1	Ia	*G6PC*	Exon 2	c.327G>A	p.R83H	Missense	1(50)	Not mentioned
						Exon 2	c.341delG	p.I101*	Deletion	1(50)	
25	[47]	Taiwan	1	Ia	*G6PC*	Exon 2	c.327G>A	p.R83H	-	1(50)	Not mentioned
						Exon 3	c.341delG	p.Ser115Alafs*15	Deletion	1(50)	
26	[48]	Taiwan	2	Ia	*G6PC*	Exon 2	c.327G>A	p.R83H	Missense	2(50)	Not mentioned
						Exon 5	c.1101T>A	p.I341N	Missense	2(50)	
27	[18]	Hong Kong	3	Ib	*SLC37A4*	Exon 3	g.1689C>T	p.P191L	Missense	3(50)	Not mentioned
						Exon 3	g.1563G>A	p.G149E	Missense	3(50)	

No	Ref.	Country	Sample size	GSD1 type (Ia/Ib)	Gene	Location (Exon/Intron)	Genetic Variant			No. (%)	Consanguinity (Yes/NO/ Not Mentioned)
							Nucleotide change	Amino acid Change	Mutation Type	Mutations	
28	[20]	Hong Kong	3	Ia	*G6PC*	Exon 5	c.727G>T	changes codon 216 from CTG --r CTT, both encoding leucine	Synonymous	5(83.33)	No
						Exon 2	c.341delG	p.I101*	Nonsense	1(16.66)	
29	[7]	korean	54	Ia	*G6PC*	Exon 1	c.152T>C	p.F51S	Missense	1(1.06)	7 families were related and 47 families were unrelated
						Exon 2	c.248G>T	p.R83H	Missense	1(1.06)	
						Exon 3	c.384C>A	p.Y128*	Nonsense	2(2.13)	
						Exon 3	c.365G>A	p.G122D	Missense	4(4.25)	
						Exon 5	c.648G>T	p.Phe217Serfs*16	Synonymous	81(86.17)	
						Exon 5	c.664G>A	p.G222R	Missense	3(3.19)	
						Exon 5	c.763A>G	p.T255A	Missense	1(1.06)	
						Exon 5	c.976T>C	p.S326P	Missense	1(1.06)	
30	[49]	korean	13	Ia	*G6PC*	Exon 3	c.384C>A	p.Y128X	Nonsense	1(3.85)	No
						Exon 3	c.365G>A	p.G122D	Missense	2(7.69)	
						Exon 4	c.532C>G	p.P178A	Missense	1(3.85)	
						Exon 5	c.648G>T(c.727G>T)	p.L216=	Synonymous	21(80.77)	
						Exon 5	c.764C>T	p.T255I	Missense	1(3.85)	
31	[50]	korean	2	Ia	*G6PC*	-	c.444G>A	p.G122D	-	2(50)	No
						Exon 5	c.616delT	p.Leu206Serfs*27	Frameshift	2(50)	
32	[22]	korean	1	Ib	*SLC37A4*	Exon 3	c.443C>T	p.A148V	Subsititation	1(50)	No
						Exon 8	c.1042_1043delCT	P.L348fsX400	Frameshift	1(50)	
33	[51]	Japan	20	Ia	*G6PC*	Exon 5a	c.727G>T	-	Subsititation	39(97.5)	No
						Exon 2	c.327G >A	-	-	1(2.5)	
34	[6]	Japan	4	Ia	*G6PC*	Exon 2	c.327G>A	p.R83H	Missense	1(12.5)	Parents of patients 1, 2, and 4 were not related, whereas those of patient 3 were first cousins.
						Exon 4	c.588C>T	p.R170X	Nonsense	3(37.5)	
						Exon 5	c.849C>T	p.P257L	Missense	2(25)	
						Exon 5	c.727G>T	-	Subsititation	2(25)	

No	Ref.	Country	Sample size	GSD1 type (Ia/Ib)	Gene	Location (Exon/Intron)	Genetic Variant			No. (%)	Consanguinity (Yes/NO/ Not Mentioned)
							Nucleotide change	Amino acid Change	Mutation Type	Mutations	
35	[52]	Japan	51	Ia	*G6PC*	Intron 1	c.IVS1-1g<a	-	-	1(0.99)	Consanguinity was present in 4 families and The parents of the rest of the patients did not have a Consanguinity marriage
						Exon 2	c.327G>A	p.R83H	Missense	3(2.97)	
						Exon 3	c.444G>A	p.G122D	Subsititation	1(0.99)	
						Exon 4	c.588C>T	p.R170X	Nonsense	6(5.94)	
						Exon 4	c.615A>C	p.H179P	Subsititation	1(0.99)	
						Exon 5	c.849C>T	p.P257L	Missense	2(1.98)	
						Exon 5	c.727G>T	-	Splicing	88(87.13)	
36	[53]	Japan	3	Ia	*G6PC*	Exon 5	c.727G>T	-	Splicing	6(50)	Yes
						Exon 5	c.653A>G	p.Thr192Ala	Subsititation	6(50)	
37	[5]	Japan	9	Ia	*G6PC*	Exon 5	c.727G>T	-	Splicing	18(100)	No
38	[9]	Japan	127	Ia	*G6PC*	Exon 4	c.352T>C	p. W118R	Nonsense	(2)	Not mentioned
						Exon 5	c.727G>T	-	Splicing	(98)	
				Ib	*SLC37A4*	Exon 4	c.352T>C	p. W118R	Nonsense	(83)	
						Exon 5	c.727G>T	-	Splicing	(17)	
39	[10]	Japan	6	Ib	*SLC37A4*	Exon 1	c.202delT	-	Deletion	1(8.33)	Not mentioned
						Exon 2	c.217C>T	p.Q73X	Subsititation	2(16.66)	
						Exon 3	c.679delCCTA	-	Deletion	2(16.66)	
						Exon 3	c.497G>T	p.R166L	Missense	1(8.33)	
						Exon 4	c.352T>C	p. W118R	Nonsense	3(25)	
						Exon 5	c.841G>C	p.G281R	Missense	1(8.33)	
						Exon 8	c.1211_1212delCT	-	Deletion	1(8.33)	
						Exon 8	c.1243C>T	p.R415X	Stopgain	1(8.33)	
40	[54]	Japan	1	Ib	*SLC37A4*	Intron 1	[22]* site of intron 1, at the position –2 IVS1	-	Subsititation	1(50)	No
						Exon 2	c.521C>T	p.W118R	Missense	1(50)	
41	[55]	Japan	4	Ib	*SLC37A4*	Exon 9	c.1094delGCTGinsTC	The mutation caused a frameshift and generated a truncated 323 residue protein with an abnormal carboxyl-terminal peptide of NH2-SHDSVHVPLP-GNSDQ-COOH. / p.Ser366Argfs*3	Frameshift	4(50)	Parents of patient 1, but not patient 2 or 3 or 4, were consanguineous
						Exon 2	c.521C>T	p.W118R	Missense	4(50)	

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*The eastern region of Asia consists of the Asian nations of China (including the special administrative regions of Hong Kong, Macau, and Tibet), Japan, Mongolia, North Korea (Democratic People's Republic of Korea), South Korea (Republic of Korea), and Taiwan (Republic of China).)

Table 2. Types and relative frequencies of gene mutations in male and female patients with GSD1a/b in Western Asia by Country

No	Author.(s), Year	Country	Sample Size	GSDI type (Ia/Ib)	Gene	Location (Exon/ Intron)	Genetic variant			No. (%)	Consanguinity (Yes/No/Not Mentioned)
							Nucleotide change	Amino acid Change	Mutation type	Mutations	
1	[14]	Iran	37	Ia	*G6PC*	Exon 1	c.84C>T (rs758804611)	p.D28=	Synonymous	1(8.33)	Consanguineous marriage was observed in the families of 74% patients.
						Exon 1	c.18T>C (rs144652516)	p.N6=	Synonymous	1(8.33)	
						Exon 2	c.326C>T	p.R83C	Substitution	6(50)	
						Exon 2	c.233C>A	p.Y85X	Nonsense	2(16.66)	
						Exon 2	c.340 + 10C>A (rs368450665)	-	Non coding (SNV)	1(8.33)	
						Exon 5	c.*23T>C (rs2229611)	-	Non coding (SNV)	1(8.33)	
2	[20]	Iran	1	Ib	*SLC37A4*	Exon 12	c.1245G>A	p.Trp415Ter	Nonsense	2(100)	Yes
3	[57]	Iran	20	Ib	*SLC37A4*	Exon 4	c.365G>A	p.G122E	Missense	2(16.66)	Yes
						Exon 8	c.1042_1043delCT	p.Leu348Valfs*53	(Frameshift)	6(50)	
						Whole SLC37A4 deletion	g.118895235_ 118901	946del	Deletion 4	(33.33)	
4	[58]	Israel	3	Ia	*G6PC*	Exon 5	c.888G>T	p.G270V	Missense	6(100)	Yes
5	[15]	Israel	12	Ia	*G6PC*	Exon 2	c.326C>T	p.R83C	Missense	20(83.33)	Not mentioned
						Exon 4	c.576T>G	p.V166G	Missense	4(16.66)	
6	[21]	Israel	9	Ia	*G6PC*	Exon 2	c.326C>T	p.R83C	Missense	12(85.71)	Not mentioned
						Exon 4	c.576T>G	p.V166G	Missense	2(14.28)	
7	[19]	Turkey	2	Ib	*SLC37A4*	Exon 8	c.1211/1212 delCT	-	Deletion	4(100)	Yes
8	[61]	Turkey	26	5 Ia	G6PC	Exon 2	c.247C>T	p.R83C	Missense	8(80)	Not mentioned
						Exon 4	c.562+1G>A	(p.?)	Splicing	2(20)	
				1 Ib	SLC37A4	Exon 5	c.1043_1044delCT	p.Pro348ArgfsTer5	Deletion	2(100)	

No	Author.(s), Year	Country	Sample Size	GSDI type (Ia/Ib)	Gene	Location (Exon/ Intron)	Genetic variant			No. (%)	Consanguinity (Yes/No/Not Mentioned)
							Nucleotide change	Amino acid Change	Mutation type	Mutations	
9	[13]	Turkey	38	12	Ia	G6PC	Exon 1	c.44C>G	p.Ser15Ter	Nonsense	2(8.33)	7 GSDIa patients and 1 GSDIb patient were consanguineous marriages
							Exon 2	c.247C>T	p.Arg83Cys	Missense	20(83.33)	
							Exon 5	c.927delT	p.Phe309LeufsTer4	Frameshift	2(8.33)	
				2	Ib	SLC37A4	Exon 3	c.1042_1043del	p.Leu348fs	Deletion	1(50)	
							Exon 4	c.1004G>A	p.Gly335Glu	Missense	1(50)	
10	[60]	Turkey	1		Ia	G6PC	Exon 1	c.137T>G	p.Leu46Arg	Missense	2(100)	Yes
11	[3]	Turkey	1		Ib	SLC37A4	Intron 4	c.381+1G>C	-	Splicing	2(100)	Yes
12	[16]	Turkey	27		Ia	G6PC	Exon 1	c.113A>T	p.D38V	Substitution	-	Not mentioned
							Exon 1	c.189G>A	p.W63X	Substitution	-	
							Exon 1	c.229T>C	p.W77R	Substitution	2(3.7)	
							Exon 1	c.79delC	p.Gln27Argfs	Deletion		
							Exon 2	c.247C>T	p.R83C	Substitution	37(68.5)	
							Exon 3	c.380_381insTA	p.Tyr127delinsTyrThrfs	Insertion	-	
							Exon 4	c.508G>A	p.R170Q	Substitution	-	
							Exon 5	c.562G>C	p.G188R	Substitution	2(3.7)	
							Exon 5	c.809G>T	p.G270V	Substitution	4(7.4)	
							Exon 5	c.1039C>T	p.Q347X	Substitution	-	
							Exon 5	c.979_981delTTC	p.Phe327del	Deletion	-	
							Exon 5	c.648G>T	p.Leu216Leu	Splicing	-	
13	[17]	Turkey	12		Ib	G6PC	Exon 1	c.229T>C	p.W77R	Substitution	10(41.66)	Yes
							Exon 2	c.247C>T	p.R83C	Substitution	14(58.33)	

Table 3. Types And Relative Frequencies Of Gene Mutations In Male And Female Patients With Gsdia/B In South Asia By Country

No	Ref.	Country	Sample Size	GSDI Type (xa/Ib)	Gene	Location (Exon/ Intron)	Genetic Variant			No. (%)	Consanguinity (Yes/No/Not Mentioned)
							Nucleotide Change	Amino Acid Change	Mutation Type	Mutations	
1	[62]	Pakistan	1	Ia	*G6PC*	Exon 1	c.193G>C	p.A65P	missense	2 (100)	Not mentioned
			7	Ib	*SLC37A4*	Exon 3	c.169175 del	p.S57Lfs*16	frameshift	2 (14.28)	
						Exon 7	c.796_797del	p.M266Efs*59	frameshift	8 (57.14)	
						Exon 8	c.898C>T	p.R300C	missense	4 (28.57)	
2	[19]	Pakistan	1	Ib	*SLC37A4(G6PT)*	Exon 2	c.338 _ 344delAGTCGGC	-	deletion	2 (100)	Not mentioned
3	[63]	India	6	Ia	*G6PC*	Exon 1	c.227A>T	p.Lys76Met		2 (16.66)	5 yes & 1 Not known
						Exon 2	c.208del	p.Trp70fs	deletion	2 (16.66)	
						Exon 3	c.355C>G	p.His119Asp	missense	2 (16.66)	
						Exon 4	c.468G>A	p.Trp156Ter	nonsense	2 (16.66)	
						Exon 4	c.550G>T	p.Gly184Ter		2 (16.66)	
						Exon 5	c.664G>A	p.Gly222Arg	missense	2 (16.66)	
			4	Ib	*G6PT/ SLC37A4*	Exon 1	c.139 _ 148+5delinsCA	-	deletion	1 (12.5)	2
						Exon 2	c.139G>C	p.Asp47His	missense	2 (25)	
						Exon 6	c.945_964del	p.Met315Ilefs*4	deletion	1 (12.5)	
						Exon 8	c.898C>T	p.Arg300Cys	missense	2 (25)	
						Exon 10	c.1287 _ 1290del	p.*430Gluext*52	deletion	2 (25)	

No	Ref.	Country	Sample Size	GSDI Type (xa/Ib)	Gene	Location (Exon/ Intron)	Genetic Variant			No. (%)	Consanguinity (Yes/No/Not Mentioned)
							Nucleotide Change	Amino Acid Change	Mutation Type	Mutations	
4	[64]	India	6	Ia	*G6PC*	Exon 2	c.293delC/ter101	p.V99Cfs*3	Deletion	3 (25)	No
						Exon 5	c.992C>T	p.A331V	Substitution	1 (8.33)	
						Exon 3	c.373G>C	p.G125R	Splicing	1 (8.33)	
						Exon 3	c.446G>A	P.R149Q	Missense	1 (8.33)	
						Exon 3	c.353G>A	P.G118D	Substitution (mis-sense)	2 (16.66)	
						Intron 1 Exon 2	IVS1-2A>T	p.I78fs166X	Deletion (frame-shift)	2 (16.66)	
						Intron 3	IVS3+39G>A	-	Splicing	1 (8.33)	
						Intron 3	IVS3+42G>A	-	Missense	1 (8.33)	
5	[65]	India	13	Ia	*G6PC*	5'-UTR of G6PC1 (promoter)	c.-225C>G	-	Substitution	4 (100)	Not mentioned
6	[66]	India	10	Ia	*G6PC*	3	c.355C>G	p.H119D	Missense	4 (100)	No
7	[62]	India	17	Ia	*G6PC*	Exon 2	c.247C>T	p.R83C	-	0	Seven children were born of second-degree Consanguineous marriages.
						Exon 5	c.727G>T	-	-	0	
						Exon 5	c.1039C>T	p.Q347X	-	0	
8	[67]	India	5	Ia	*G6PC*	Intron 1	c.150_151delGT	p.Trp50Cysfs*10	Frameshift	10 (100)	No
9	[19]	India	1	Ib	*SLC37A4*	Exon 2	c.152-154 deletion TCA	p.I52del	Inframe deletion	2 (100)	Yes

No	Ref.	Country	Sample Size	GSDI Type (xa/Ib)	Gene	Location (Exon/ Intron)	Genetic Variant			No. (%) Mutations	Consanguinity (Yes/No/Not Mentioned)
							Nucleotide Change	Amino Acid Change	Mutation Type		
10	[68]	Sri Lankan	1	Ib	*SLC37A4*	Exon 1	Guanine to Adenine substitution at codon 50	p.G50E	Missense	2 (100)	Yes
11	[69]	Vietnamese	1	Ia	*G6PC*	Exon 3	c.356A>T	p.H119L	Missense	2 (100)	Not mentioned
12	[70]	Thailand	2	Ia	*G6PC*	Exon 2	c.248G>A	p.R83H	Missense	3 (75)	Not mentioned
						Exon 5	c.648G>T	p.L216=	Synonymous	1 (25)	
13	[71]	Malaysia	30	Ia	*G6PC*	Exon 1	c.226A>T	p.K76X	Nonsense	3 (7.14)	Not mentioned
						Exon 1	c.155A>T	p.H52L	Missense	4 (9.52)	
						Exon 2	c.337C>T	p.P113S	Missense	2 (4.76)	
						Exon 2	c.248G>A	p.R83H	Missense	7 (16.66)	
						Exon 4	c.518T>C	p.L173P	Missense	2 (4.76)	
						Exon 5	c.648G>T	p.L216L	Synonymous	21 (50)	
						Exon 5	c.664G>A	p.G222R	Missense	1 (2.38)	
						Exon 5	c.1036G>C	p.A346P	Missense	1 (2.38)	
						Exon 5	c.706T>A	p.W236R	Missense	1 (2.38)	

Note: The region of South Asia, or Southern Asia, includes Afghanistan, Bangladesh, Bhutan, India, Thailand, the Maldives, Nepal, Pakistan, and Sri Lanka

Table 4. Types and relative frequencies of gene mutations in male and female patients with GSDIa in East Asia by country

Ref.	Name of the Country or Ethnicity	No. (%) Mutations	Amino Acid Change	Nucleotide Change	Molecular Consequence	Exon(E)/ Intron(I)	The Range of Mutation frequency Related to Each Variant	No. (%) Allele
[33]*	China	1(50)	p.L216=		Synonymous			
[45]*	Taiwan	1(50)			Synonymous/abnormal Splicing			
[49]	Korea	21(80.77)			Splicing			
[8]	China	2(10)			Synonymous			
[41]	Chinese patients of Taiwan	16(45.71)	-		-			
[42, 43]	Taiwan	16(44.44)	-		-	E5		
[20]	Hong Kong	5(83.33)	changes codon 216 from CTG --r CTT, both encoding leucine		Synonymous			
[12]	China	8(36.36)	p.L216=	c.648G>T (c.727G>T)	synonymous		100 to 10	348(67.96)
[35]	China	41(80.39)	-		Splicing			
[7]	korean	81(86.17)	p.F217Sfs*16		Synonymous			
[51]	Japan	39(97.5)	-		Subsititation	E5a		
[6]	Japan	2(25)			Subsititation			
[52]	Japan	88(87.3)			Splicing			
[53]	Japan	6(50)			Splicing	E5		
[5]	Japan	18(100)			Splicing			
[9]	Japan	(98)			Splicing			
[42, 43]	Taiwan	4(11.11)	p.R83I					
[47]*	Taiwan	2(50)						
[34]*	China	1(50)			Missense			
[37]	China	7(70)	p.R83H	c.327G>A		E2	70 to 11.11	29(5.66)
[48]	Taiwan	2(50)						
[47]*	Taiwan	1(50)			-			
[41]	Chinese patients of Taiwan	13(37.4)			Missense			
[8]	China	2(10)						
[35]	China	7(13.72)						
[44]*	Taiwan	1(50)	p.R83H	c.248G>A	Missense	E2	13.72 to 10	14(2.73)
[12]	China	3(13.64)						
[38]*	Taiwan	1(50)						
[42, 43]	Taiwan	13(36.11)	p.R83H	c.327G>T	Missense	E2	36.11	13(2.53)

Ref.	Name of the Country or Ethnicity	No. (%) Mutations	Amino Acid Change	Nucleotide Change	Molecular Consequence	Exon(E)/ Intron(I)	The Range of Mutation frequency Related to Each Variant	No. (%) Allele
[6]	Japan	3(37.5)	p.R170X	c.588C>T	Nonsense	E4	37.5 to 5.94	9(1.75)
[54]		6(5.94)						
[35]	China	1(1.96)			Deletion			
[41]	Chinese patients of Taiwan	1(2.86)			Frameshift			
[42, 43]	Taiwan	1(2.78)	p.I101*		Deletion	E2		
[46]*	Taiwan	2(100)		c.341delG	Deletion		16.66 to 1.96	(1.56)
[47]*	Taiwan	1(50)			Deletion			
[20]	Hong Kong	1(16.66)			Nonsense			
[47]*	Taiwan	1(50)	p.S115Afs*15		Deletion	E3		
[8]	China	7(35)	p.V88FfsX1	c.262delG	Frameshift	E2	35	7(1.36)
[53]	Japan	6(50)	p.T192A	c.653A>G	Subsititation	E5	50	6(1.17)
[49]	korean	2(7.69)	p.G122D	c.365G>A	Missense	E3	7.69 to 4.25	6(1.17)
[7]		4(4.25)						
[51]		1(2.5)	-		-			
[6]	Japan	1(12.5)	p.R83H	c.327G>A	Missense	E2	12.5 to 2.5	5(0.97)
[52]		3(2.97)						
[12]	China	2(9.09)	p.I341N	c.1022T>A	Missense	E5	10 to 9.09	4(0.78)
[8]	China	2(10)						
[8]	China	1(4.54)	p.A274V	c.821C>T	Missense	E5	15 to 4.54	4(0.78)
[8]	China	3(15)				E3		
[8]	China	4(18.18)	p.V88fs	c.262_262delG	Frameshift	E2	18.18	4(0.78)
[6]	Japan	2(25)	p.P257L	c.849C>T	Missense	E5	25 to 1.98	4(0.78)
[52]		2(1.98)						
[48]	Taiwan	2(50)	p.I341N	c.1101T>A	Missense	E5	50 to 5.71	4(0.78)
[41]	Chinese patients of Taiwan	2(5.71)			-			
[8]	China	2(10)	p.F80I	c.238T>A	Missense	E2	10 to 4.54	3(0.58)
[12]	China	1(4.54)						
[49]	Korea	1(3.85)	p.Y128X	c.384C>A	Nonsense	E3	3.85 to 2.13	3(0.58)
[7]		2(2.13)	p.Y128*					
[8]	China	1(4.54)	p.L173P	c.518T>C	Missense	E4	4.54	3(0.58)
[32]*		2(100)						

Ref.	Name of the Country or Ethnicity	No. (%) Mutations	Amino Acid Change	Nucleotide Change	Molecular Consequence	Exon(E)/ Intron(I)	The Range of Mutation frequency Related to Each Variant	No. (%) Allele
[12]	China	1(4.54)	p.G118D	c.353G>A	Missense	E3	10 to 4.54	3(0.58)
[8]	China	2(10)				E2		
[7]	Korea	3(3.19)	p.G222R	c.664G>A	Missense	E5	3.19	3(0.58)
[42, 43]	Taiwan	1(2.78)	polypeptide stops 16 amino acids after lysine 285-	c.933insAA	Frameshift	-	2.86 to 2.78	2(0.39)
[41]	Chinese patients of Taiwan	1(2.86)	-			E5		
[37]	China	2(20)	Unidentified	-	-	-	20	2(0.39)
[50]	Korea	2(50)	p.G122D	c.444G>A	-	-	50	2(0.39)
[39]*	Taiwan	2(100)	p.*358Yext*43	c.1074A>C	Stoploss	E5	-	2(0.39)
[50]	Korea	2(50)	p.Leu206Serfs * 27	c.616delT	Frameshift	E5	50	2(0.39)
[49]	Korea	1(3.85)	p.T255I	c.764C>T	Missense	E5	3.85	1(0.19)
[45]*	Taiwan	1(50)	p.H119L	c.356A>T	Missense	E3		1(0.19)
[44]*	Taiwan	1(50)	p.T16A	c.46A>G	Missense	E1		1(0.19)
[52]	Japan	1(0.99)	p.H179P	c.615A>C	Subsititation	E4	0.99	1(0.19)
[52]	Japan	1(0.99)	p.G122D	c.444G>A	Subsititation	E3	0.99	1(0.19)
[7]	Korea	1(1.06)	p.S326P	c.976T>C	Missense	E5	1.06	1(0.19)
[7]	Korea	1(1.06)	p.T255A	c.763A>G	Missense	E5	1.06	1(0.19)
[7]	Korea	1(1.06)	p.F51S	c.152T>C	Missense	E1	1.06	1(0.19)
[7]	Korea	1(1.06)	p.R83H	c.248G>T	Missense	E2	1.06	1(0.19)
[12]	China	1(4.54)	p.D38V	c.113A>T	Missense	E1	4.54	1(0.19)
[26]*	China	1(50)	p.R83H	c.G248A	Missense	E2	-	1(0.19)
[26]*	China	1(50)	p.L216L	c.G648T	Synonymous	E5	-	1(0.19)
[31]*	China	1(50)	p.C109Y	c.326G>A	Missense	E2	-	1(0.19)
[31]*	China	1(50)	7.1 kb deletion covering two exon	chr17 g.41049904 _ 41057049del7125 starts from the first intron of the *LINC00671* gene to intron 2 of the *G6PC* gene	Large deletion (chr17 g.41049879 _ 41057003del7125) was thus 7125 bp in length	5′ regulatory sequence as well as exon 1, intron 1, exon 2 and partial intron 2 of the *G6PC* gene	-	1(0.19)
[33]*	China	1(50)	p.L104Q	c.311A>T	Missense	E2	-	1(0.19)
[35]	China	1(1.96)	p.Q104X	c.310C>T	Nonsense	E2	1.96	1(0.19)
[35]	China	1(1.96)	p.R170X	c.508C>T	Nonsense	E4	1.96	1(0.19)

Ref.	Name of the Country or Ethnicity	No. (%) Mutations	Amino Acid Change	Nucleotide Change	Molecular Consequence	Exon(E)/ Intron(I)	The Range of Mutation frequency Related to Each Variant	No. (%) Allele
[34]*	China	1(50)	p.L173P	c.597T>C	Missense	E4	-	1(0.19)
[37]	China	1(10)	p.R83C	c.326C>T	Missense	E2	10	1(0.19)
[38]*	Taiwan	1(50)	p.G272W	c.814G>T	Missense	E5	-	1(0.19)
[42, 43]	Taiwan	1(2.78)	p.L238=	c.793G>T	Synonymous	-	2.78	1(0.19)
[49]	korean	1(3.85)	p.P178A	c.532C>G	Missense	E4	3.85	1(0.19)
[41]	Chinese patients of Taiwan	1(2.86)	p.Q104X	c.389C>T	Nonsense	E2	2.86	1(0.19)
[41]	Chinese patients of Taiwan	1(2.86)	p.H119L	c.435A>T	Missense	E3	2.86	1(0.19)
[9]	Japan	(2)	p. W118R	c.352T>C	Nonsense	E4	2	-
				Total =512				

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*Case-control studies and studies with a sample size of 1 weren't included in the calculation of the reported mutation rate range.

East Asia

East Asia includes China (with Hong Kong, Macau, and Tibet), Japan, Mongolia, North Korea, South Korea, and Taiwan. From 41 studies, 860 alleles were analyzed, identifying 571 mutated alleles and 83 unique mutations. Of these, 33 unique mutations were associated with the *SLC37A4* gene and 50 with the *G6PC* gene, yielding an overall mutation detection rate of 66.39% (Table 1).

G6Pase gene variants in East Asia

A total of 27 studies across China, Japan, Taiwan, Korea, and Hong Kong investigated *G6PC* mutations in 245 patients. In total, 50 different mutations were found among 512 mutant alleles. The majority were missense (45), followed by nonsense (9), splice site (7), frameshift (5), and other types. Mutations clustered mostly in exons 2, 3, 4, and 5 (Table 1).

The most prevalent mutation was c.648G>T, representing 67.96% of mutant alleles, and it was widely observed in Japan (153 alleles), Korea (102), China (68), Taiwan (17), and Hong Kong (5). This was followed by c.327G>A (p.R83H) with 5.66% frequency, especially in Chinese and Taiwanese patients. Other notable variants included c.248G>A, c.327G>T, and c.588T>G (p.R170X), each ranging from approximately 1.7% to 2.7% (Table 4).

SLC37A4 gene variants in East Asia

Twelve studies documented 33 *SLC37A4* mutations across 59 alleles. The most common were in exons 4, 3, 5, and 10. A splice-site mutation in intron 1 (IVS1 -2 A>C) was also identified. The most frequent variant in China was c.572C>T (p.P191L) (13.55%), while c.521C>T (p.W118R) dominated in Japan (8.62%).

Another significant mutation, c.1094delGCTG/insTC (p.Ser366Argfs*3), produced a truncated protein and accounted for 6.77% of mutations. c.1042_1043delCT, a frameshift mutation in exon 8, was particularly common in China and Korea (5.08%).

Other recurrent variants included c.352T>C, g.1689C>T, c.679delCCTA, and c.935_936delCTG, all found at low to moderate frequencies across regional studies (Tables 1 and 3).

West Asia

Thirteen studies from Turkey, Iran, and Israel reported data on 190 patients, including 118 with GSD Ia and 28 with GSD Ib. Across these, 33 distinct variants were identified in 145 patients (Table 2).

Table 5. Types and relative frequencies of gene mutations in male and female patients with GSDIa in Western Asia by country

Ref.	Name of The Country or Ethnicity	No. (%) Mutations	Amino Acid Change	Nucleotide Change	Molecular Consequence	Exon(E)/ Intron (I)	The range of Mutation frequency related to each Variant	No. (%) Allele
[59]	Turkey	8(80)	p. R83C	c.247C>T (previously c.326C>T)	Missense	E2	85.71 to 50	117(72.67)
[13]		20(83.33)						
[17]		14(58.33)						
[16]		37(68.5)			Substitution			
[14]	Iran	6(50)						
[15]	Israel	20(83.33)			Missense			
[21]	Israel	12(85.71)			Missense			
[16]	Turkey	2(3.7)	p.W77R	c.229T>C	Substitution	E1	41.66 to 3.7	12(7.45)
[17]		10(41.66)						
[58]	Israel	6(100)	p.G270V	c.888G>T (c.809G>T)	Missense	E5	100 to 7.4	10(6.21)
[16]	Turkey	4(7.4)			Substitution			
[15]	Israel	4(16.66)	p.V166G	c.576T>G	Missense	E4	16.66 to 14.28	6(3.72)
[21]		2(14.28)						
[14]	Iran	2(16.66)	p.Y85X	c.233C>A	Nonsense	E2	16.66	2(1.24)
[60]*	Turkey	2(100)	p.L46R	c.137T>G	Missense	E1	-	2(1.24)
[59]	Turkey	2(20)	-	c.562+1G>A	Splicing	E4	20	2(1.24)
[13]	Turkey	2(8.33)	p.S15T	c.44C>G	Nonsense	E1	8.33	2(1.24)
[16]	Turkey	2(3.7)	p.G188R	c.562G>C	Substitution	E5	3.7	2(1.24)
[13]	Turkey	2(8.33)	p.F309LfsT4	c.927delT	Frameshift	E5	8.33	2(1.24)
[14]	Iran	1(8.33)	-	c.340+10C>A (rs368450665)	Non coding(SNV)	E2	8.33	1(0.62)
[14]	Iran	1(8.33)	-	c.*23T>C (rs2229611)	Non coding(SNV)	E5	8.33	1(0.62)
[14]	Iran	1(8.33)	p.D28=	c.84C>T (rs758804611)	Synonymous	E1	8.33	1(0.62)
[14]	Iran	1(8.33)	p.N6=	c.18T>C (rs144652516)	Missense	E1	8.33	1(0.62)
[16]	Turkey	-	p.D38V	c.113A>T	Substitution	E1	-	-
[16]	Turkey	-	p.W63X	c.189G>A	Substitution	E1	-	-
[16]	Turkey	-	p.Q27Rfs	c.79delC	Deletion	E1	-	-
[16]	Turkey	-	p.Y127delinsYTfs	c.380_381insTA	Insertion	E3	-	-
[16]	Turkey	-	p.R170Q	c.508G>A	Substitution	E4	-	-
[16]	Turkey	-	p.Q347X	c.1039C>T	Substitution	E5	-	-
[16]	Turkey	-	p.F327del	c.979_981delTTC	Deletion	E5	-	-

Ref.	Name of The Country or Ethnicity	No. (%) Mutations	Amino Acid Change	Nucleotide Change	Molecular Consequence	Exon(E)/ Intron (I)	The range of Mutation frequency related to each Variant	No. (%) Allele
[16]	Turkey	-	p.L216L	c.648G>T	Splicing	E5	-	-
		Total:161						

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Table 6. Types and relative frequencies of gene mutations in male and female patients with GSDIa in South Asia by country

Ref.	Name of the Country or Ethnicity	No. (%) Mutations	Amino Acid Change	Nucleotide Change	Molecular Consequence	Exon(E)/ Intron(I)	The range of Mutation Frequency related to Each Variant	No. (%) Allele
[70] [71]	Thailand Malaysia	1(25) 21(50)	p.L216=	c.648G>T	Synonymous	E5	25 to 50	22(23.91)
[67]	India	10(100)	p.W50Cfs*10	c.150_151delGT	Frameshift	I1	100	10(10.86)
[70] [71]	Thailand Malaysia	3(75) 7(16.66)	p.R83H	c.248G>A	Missense	E2	75 to 16.66	10(10.86)
[63] [66]	India	2(16.66) 4(100)	p.H119D	c.355C>G	Missense	E3	100 to 16.66	6(6.52)
[65]	India	4(100)	-	c.-225C>G	Substitution	5'-UTR of G6PC1 (promoter)	100	4(4.34)
[71]	Malaysia	4(9.52)	p.H52L	c.155A>T	Missense	E1	9.52	4(4.34)
[64]	India	3(25)	p.V99Cfs*3	c.293delC/ter101	Deletion	E2	25	3(3.26)
[71]	Malaysia	3(7.14)	p.K76X	c.226A>T	Nonsense	E1	7.14	3(3.26)
[63] [71]	India Malaysia	2(16.66) 1(2.38)	p.G222R	c.664G>A	Missense	E5	16.66 to 2.38	3(3.26)
[62]*	Pakistan	2(100)	p.A65P	c.193G>C	Missense	E1	-	2(2.17)
[63]	India	2(16.66)	p.K76M	c.227A>T	-	E1	16.66	2(2.17)
[63]	India	2(16.66)	p.W70fs	c.208del	Deletion	E2	16.66	2(2.17)
[63]	India	2(16.66)	p.W156T	c.468G>A	Nonsense	E4	16.66	2(2.17)
[64]	India	2(16.66)	p.G118D	c.353G>A	Missense	E3	16.66	2(2.17)
[63]	India	2(16.66)	p.G184T	c.550G>T	-	E4	16.66	2(2.17)
[69]*	Vietnamese	2(100)	p.H119L	c.356A>T	Missense	E3	-	2(2.17)
[71]	Malaysia	2(4.76)	p.P113S	c.337C>T	Missense	E2	4.76	2(2.17)
[71]	Malaysia	2(4.76)	p.L173P	c.518T>C	Missense	E4	4.76	2(2.17)
[64]	India	2(16.66)	p.I78fs166X	IVS1-2A>T	Deletion (frameshift)	I1 E2	16.66	2(2.17)
[71]	Malaysia	1(2.38)	p.A346P	c.1036G>C	Missense	E5	2.38	1(1.08)

Ref.	Name of the Country or Ethnicity	No. (%) Mutations	Amino Acid Change	Nucleotide Change	Molecular Consequence	Exon(E)/ Intron(I)	The range of Mutation Frequency related to Each Variant	No. (%) Allele
[71]	Malaysia	1(2.38)	p.W236R	c.706T>A	Missense	E5	2.38	1(1.08)
[64]	India	1(8.33)	p.A331V	c.992C>T	Substitution	E5	8.33	1(1.08)
[64]	India	1(8.33)	p.G125R	c.373G>C	Splicing	E3	8.33	1(1.08)
[64]	India	1(8.33)	p.R149Q	c.446G>A	Missense	E3	8.33	1(1.08)
[64]	India	1(8.33)	-	IVS3+39G>A	Splicing	I3	8.33	1(1.08)
[64]	India	1(8.33)	-	IVS3+42G>A	Missense	I3	8.33	1(1.08)
[62]	India	0	p.R83C	c.247C>T	-	E2	0	0
[62]	India	0	-	c.727G>T	-	E5	0	0
[62]	India	0	p.Q347X	c.1039C>T	-	E5	0	0
Total: 92								

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G6PC gene variants in West Asia

Research on *G6PC* gene variants in West Asia has been limited to three countries: Turkey, Iran, and Israel, despite the region comprising 20 countries, including Armenia, Azerbaijan, and Saudi Arabia.

Nine studies focused on G6PC mutations, reporting 24 distinct variants across 236 alleles, of which 161 were mutated (mutation rate: 68.22%). Israel showed the highest mutation detection rate (100%), followed by Turkey (92.1%) and Iran (16.21%). The most common mutation was c.247C>T (p.R83C), observed in 72.67% of cases and across all three countries. p.W77R (c.229T>C) was the second most frequent (7.45%), especially in Turkish cohorts. c.888G>T (p.G270V) ranked third (6.21%) and was also reported from both Turkey and Israel. Additional low-frequency variants included c.576T>G, c.809G>T, and several private or rare substitutions (Table 5).

SLC37A4 gene variants in West Asia

The mutation spectrum of the *SLC37A4* gene has been documented in only two West Asian countries: Turkey and Iran. Six studies from Turkey and Iran reported 9 unique *SLC37A4* variants in 27 patients. The overall mutation detection rate was 50%. Most patients (92.6%) came from consanguineous families.

The most frequent variant was c.1042_1043delCT (p.L348Vfs*53), found in 41.66% of cases, with 50–100% frequency across studies. In Iran, notable variants included g.118895235_118901del (946del) (16.66%) and c.1245G>A (p.W415T) (8.33%). In Turkey, c.381+1G>C and c.1043_1044delCT (p.P348Rfs*5) were found in smaller proportions (8.33% each) (Table 8).

South Asia

South Asia encompasses Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka. Thirteen studies involving 105 patients identified 39 distinct variants across 120 alleles—29 related to GSD Ia and 10 to GSD Ib. Consanguinity was reported in only 15 families (Table 3).

G6PC gene variants in South Asia

Between 2001 and 2022, 29 G6PC mutations were identified in Malaysia, Thailand, India, Pakistan, and Vietnam. India contributed the most data (57 patients, 19 variants). Malaysia reported 42 mutated alleles in 30 patients. Shared mutations included c.648G>T and c.248G>A in Malaysia and Thailand.

The most frequent mutation was c.648G>T (p.L216=), especially in Thailand and Malaysia (23.91%). In India, c.150_151delGT (p.W50Cfs*10) was most common (10.86%), followed by c.355C>G (p.H119D) (6.52%) and c.-225C>G (4.34%). c.248G>A was the third most common overall (10.86%). Mutations mainly clustered in exons 2, 3, and 5 (Table 6).

Table 7. Types and relative frequencies of gene mutations in male and female patients with GSDIb in East Asia by country

Ref.	Name of the Country or Ethnicity	No. (%) Mutations	Amino Acid Change	Nucleotide Change	Molecular Consequence	Exon (E)/ Intron (I)	The Range of Mutation Frequency Related to Each Variant	No. (%) Allele
[11]	China	2(33.33)	p.P191L	c.572C>T	Missense	E6	33.33 to 25	8(13.55)
[27]	China	2(33.33)						
[28]	China	1(33.33)				E5		
[12]	China	1(25)						
[30]*	China	1(50)						
[36]*	China	1(50)				E4		
[54]*	Japan	1(50)	p.W118R	c.352T>C (Previously c.521T>C)	Missense	E2	98 to 25	8(13.55)
[55]		4(50)						
[9]		-(98)			Nonsense	E4		
[10]		3(25)						
[55]	Japan	4(50)	The mutation caused a frameshift and generated a truncated 323 residue protein with an abnormal carboxyl-terminal peptide of NH2-SHDSVHVPLPGNSDQ-COOH. / p.Ser366Argfs*3	c.1094delGCTG/ insTC	Frameshift	E9	50	4(6.77)
[11]	China	1(16.67)	p.L348Vfs*5	c.1042_1043delCT	Frameshift	E10	25 to 16.67	3(5.08)
[12]		1(25)	p.L348fs					
[22]*	Korea	1(50)	P.L348fsX400			E8		
[18]	Hong Kong	3(50)	p.P191L	g.1689C>T	Missense	E3	50	3(5.08)
[18]	Hong Kong	3(50)	p.G149E	g.1563G>A	Missense	E3	50	3(5.08)
[40]*	Taiwan	2(50)	p.W118fsX12	c.354_355insC	Insertion	E3	-	2(3.38)
[40]*	Taiwan	2(50)	p.W246R	c.736T>C	Missense	-	-	2(3.38)
[29]*	China	2(100)	p.P119L	c.356C>T	Missense	E4	-	2(3.38)
[10]	Japan	2(16.66)	p.Q73X	c.217C>T	Subsititation	E2	16.66	2(3.38)
[10]	Japan	2(16.66)	-	c.679delCCTA	Deletion	E3	16.66	2(3.38)
[11]	China	1(16.67)	p.382_388del	c.1145_1163del	Missense	E11	16.67	1(1.69)
[11]	China	1(16.67)	p.G117fs*28	c.351delC	Frameshift	E4	16.67	1(1.69)
[11]	China	1(16.67)	P.T312Sfs*13	c.935_936delCTG	Frameshift	E9	16.67	1(1.69)
[27]	China	1(16.67)	-	c.870 + 5G>A	Intron variant	E7	16.67	1(1.69)
[27]	China	1(16.67)	p.W227*	c.680G>A	Nonsense	E7	16.67	1(1.69)

Ref.	Name of the Country or Ethnicity	No. (%) Mutations	Amino Acid Change	Nucleotide Change	Molecular Consequence	Exon (E)/ Intron (I)	The Range of Mutation Frequency Related to Each Variant	No. (%) Allele
[27]	China	1(16.67)	p.G339D	c.1016G>A	Missense	E10	16.67	1(1.69)
[27]	China	1(16.67)	p.G115R	c.343G>A	Missense	E10	16.67	1(1.69)
[28]	China	1(33.33)	p.L348P	c.1043T>C	Missense	E10	-	1(1.69)
[28]	China	1(33.33)	p.A162Pfs∗10	c.483delA	Frameshift	E4	-	1(1.69)
[12]	China	1(25)	p.D193*	c.576_577insT	Nonsense	E5	25	1(1.69)
[12]	China	1(25)	-	g.5700_5703 delAAGT	Frameshift	-	25	1(1.69)
[30]*	China	1(50)	p.P120L	c.359C>T	Missense	E4	-	1(1.69)
[36]*	China	1(50)	p.Y24H	g.70T> C	Missense	E2	-	1(1.69)
[22]*	Korea	1(50)	p.A148V	c.443C>T	Subsititation	E3	-	1(1.69)
[9]	Japan	-(17)	-	c.727G>T	Splicing	E5	17	-
[10]	Japan	1(8.33)	-	c.202delT	Deletion	E1	8.33	1(1.69)
[10]	Japan	1(8.33)	p.R166L	c.497G>T	Missense	E3	8.33	1(1.69)
[10]	Japan	1(8.33)	p.G281R	c.841G>C	Missense	E5	8.33	1(1.69)
[10]	Japan	1(8.33)	-	c.1211-1212delCT	Deletion	E8	8.33	1 (1.69)
[10]	Japan	1(8.33)	p.R415X	c.1243C>T	Stopgain	E8	8.33	1(1.69)
[54]*	Japan	1(50)	-	A to C transversion at the –2 splicing acceptor site of intron 1, at the position –2 IVS1	Subsititation	I1	-	1(1.69)
				Total: 59				

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* Case-control studies and studies with a sample size of 1 weren't included in the calculation of the reported mutation rate range.

SLC37A4 gene variants in South Asia

From 2000 to 2022, five studies (14 patients) identified 10 *SLC37A4* mutations across India, Pakistan, and Sri Lanka. A total of 28 alleles were analyzed with a 100% detection rate. Four patients were from consanguineous families.

Variants included 4 missense mutations, 2 frameshifts, 4 deletions, and 1 in-frame deletion. Most mutations were located in exons 1 and 2. The most common variant was c.796_797del (p.M266Efs*59) in Pakistan (28.57%), followed by c.898C>T (p.R300C) in India (21.42%). Other less frequent variants included c.169_175del (p.S57Lfs*16) and c.150G>A (p.G50E) (Table 9).

Discussion

This systematic review analyzed 70 studies, including 680 patients from 14 Asian countries, examining mutations in the *G6PC1* and *SLC37A4* genes among patients with GSD Ia and Ib. By organizing variants geographically across East, West, and South Asia, we identified both shared and region-specific mutation patterns. Key prevalent mutations included c.648G>T in East and South Asia, R83C and p.W77R in West Asia, and c.572C>T in China, providing strong evidence for regionally tailored genetic screening strategies.

Table 8. Types and relative frequencies of gene mutations in male and female patients with GSDIb in Western Asia by country

Ref.	Name of the Country or Ethnicity	No. (%) Mutations	Amino Acid Change	Nucleotide Change	Molecular Consequence	Exon (E)/ Intron (I)	The Range of Mutation frequency Related to each Variant	No. (%) Allele
[57]	Iran	6(50)	p.L348Vfs*53	c.1042_1043delCT (previously c.1211_1212delCT)	Deletion (Frameshift)	E8	100 to 50	10(38.46)
[19]	Turkey	4(100)	-		Deletion			
[57]	Iran	4(33.33)	p.946del	g.118895235_118901	Deletion	whole SLC37A4 deletion	33.33	4(15.38)
[56]*	Iran	2(100)	p.W415T	c.1245G>A	Nonsense	E12	-	2(7.69)
[61]*	Iran	2(100)	-	c.1124-2A>G	Missense	E9	-	2(7.69)
[57]	Iran	2(16.66)	p.G122E	c.365G>A	Missense	E4	16.66	2(7.69)
[3]*	Turkey	2(100)	-	c.381+1G>C	Splicing	I4	-	2(7.69)
[59]*	Turkey	2(100)	p.P348RfsT5	c.1043_1044delCT	Deletion	E5	-	2(7.69)
[13]	Turkey	1(50)	p.G335E	c.1004G>A	Missense		50	1(3.84)
[13]	Turkey	1(50)	p.L348fs	c.1042_1043del	Deletion		50	1(3.84)
Total: 26								

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Table 9. Types and relative frequencies of gene mutations in male and female patients with GSDIb in South Asia by country

Ref.	Name of the Country or Ethnicity	No. (%) Mutations	Amino Acid Change	Nucleotide Change	Molecular Consequence	Exon(E)/ Intron(I)	The range of Mutation frequency related to each Variant	No. (%) Allele
[62]	Pakistan	8(57.14)	p.M266Efs*59	c.796_797del	Frameshift	E7	57.14	8(28.57)
[62]	Pakistan	4(28.57)	p.R300C	c.898C>T	Missense	E8	28.57 to 25	6(21.42)
[63]	India	2(25)						
[62]	Pakistan	2(14.28)	p.S57Lfs*16	c.169175 del	Frameshift	E3	14.28	2(7.14)
[63]	India	2(25)	p.D47H	c.139G>C	Missense	E2	25	2(7.14)
[19]*	Pakistan	2(100)	-	c.338_344delAGTCGGC	Deletion	E2	-	2(7.14)
[63]	India	2(25)	p.*430Eext*52	c.1287_1290del	Deletion	E10	25	2(7.14)
[72]*	India	2(100)	p.I52del	c.152-154 deletion TCA	Inframe deletion	E2	-	2(7.14)
[68]*	Sri Lankan	2(100)	p.G50E	Guanine to Adenine substitution at codon 50	Missense	E1	-	2(7.14)
[63]	India	1(12.5)	p.M315Ifs*4	c.945_964del	Deletion	E6	12.5	1(3.57)
[63]	India	1(12.5)	--	c.139_148+5delinsCA	Deletion	E1	12.5	1(3.57)
Total:28								

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These findings have clear clinical relevance: they guide healthcare providers and genetic counselors in accurate diagnosis, targeted molecular testing, and informed counseling, particularly in populations with high consanguinity and founder effects. The data from East Asia are particularly robust, while evidence from other regions remains limited, highlighting the need for further research in underrepresented populations. Overall, this review establishes a comprehensive genetic landscape of GSD I in Asia, supporting both clinical decision-making and future investigations into variant prevalence, regional distribution, and population-specific founder effects.

East Asia showed the highest mutation reporting, particularly from Japan, Korea, China, and Taiwan. The most frequent *G6PC1* variant was c.648G>T (c.727G>T), representing 67.96% of all mutations in the region and reaching up to 92% in Korean patients and 81% in Japanese cohorts [5, 7, 9]. This variant causes a splicing error, resulting in a truncated G6Pase protein with approximately 18% enzymatic activity [5]. It appears to be a founder mutation, especially in Japanese populations. Other frequent East Asian mutations included c.327G>A (R83H) and c.248G>A, both missense mutations within exon 2, accounting for 5.6% and 3.1% of mutations respectively, especially among Chinese and Taiwanese populations [6]. These mutations were less common in Korea and Japan (Table 4).

In *SLC37A4*, East Asian patients commonly exhibited c.572C>T (P191L) and c.352T>C (W118R) (Table 7) [9, 10]. The former represented 23% of mutations in Chinese studies, while the latter was dominant in Japanese GSD Ib patients (17%) [6]. The c.1042_1043delCT deletion also appeared in 4.6% of alleles across Korean and Chinese patients [11, 12]. West Asia showed dominance of the c.247C>T (R83C) mutation in *G6PC1*, found in 72.67% of cases in studies from Turkey, Iran, and Israel [13-15]. In Iranian cohorts alone, it was reported in over 80% of patients. The p.W77R mutation followed with 11.3% frequency in Turkish patients, while c.888G>T (G270V) made up 6.2% of reported variants [16, 17].

For *SLC37A4*, the c.1042_1043delCT deletion was the most frequent in Iranian GSD Ib patients (64%), followed by g.118895235_118901del (10.5%) and c.1245G>A (W415T) (7.9%) [18-20].

South Asia displayed a broader mutation spectrum. The c.648G>T mutation appeared again, particularly in Malaysia (31%) and Thailand (27%). In India, the most frequent *G6PC1* mutation was c.150_151delGT (W50Cfs*10), comprising 39.5% of cases [21]. Other regionally shared variants were c.248G>A (13%) and c.355C>G (H119D, 8.5%).

In *SLC37A4*, Pakistani and Indian patients showed frequent c.796_797del (M266Efs*59) and c.898C>T (R300C) mutations, accounting for 44.6% and 28.7% respectively in localized studies [22]. These mutations were rarely identified in other Asian regions.

Comparative data from Europe indicates that R83C, the dominant West Asian variant, is also prevalent in Mediterranean populations but nearly absent in East Asia. Conversely, c.648G>T, common in East and South Asia, is largely undetected in European cohorts. The c.327G>A variant, although present in Asia, occurs at significantly lower frequencies in Europe [23-25].

These findings support the design of regionally customized genetic screening panels. Including prevalent variants such as c.648G>T, R83H, and c.572C>T for East/South Asia and R83C, p.W77R for West Asia can significantly improve diagnostic yield. High consanguinity rates and population-specific founder effects further emphasize the value of population-based genetic approaches in GSD I diagnosis and counseling.

Conclusion

This systematic review highlights substantial genetic diversity in *G6PC1* and *SLC37A4* mutations among Asian patients with GSD I. Distinct mutation patterns across East, West, and South Asia underscore the necessity for region-specific genetic screening and tailored diagnostic strategies. Key prevalent variants, such as c.648G>T in East/South Asia and c.572C>T in China, enhance diagnostic accuracy and can guide targeted patient management.

These findings provide a comprehensive overview of the genetic landscape of GSD I in Asia, supporting clinical decision-making, informed genetic counseling, and public health planning, particularly in populations with high consanguinity or founder effects. Furthermore, the study highlights gaps in data from underrepresented regions and emphasizes the need for future research employing advanced sequencing approaches, larger cohorts, and inclusive population sampling to better characterize variant frequencies and regional patterns.

Overall, this review underscores the critical role of genetic testing in improving patient outcomes and lays a foundation for personalized medicine approaches in GSD I across diverse Asian populations.

Limitations

This study provides valuable insights into GSD I mutations by analyzing genetic variations across different geographic regions in Asia, the largest continent with a population of approximately 4.7 billion. However, several limitations should be acknowledged. At the study and outcome levels, many included studies had small sample sizes and limited representation from certain countries, which may affect the accuracy and generalizability of variant frequency estimates. At the review level, despite conducting a comprehensive systematic search across multiple databases, some studies may have been missed due to language restrictions, incomplete reporting, or limited accessibility, potentially introducing reporting bias. Furthermore, our analysis included only 32 of 48 Asian countries, encompassing 680 individuals, which may not fully capture the continent's ethnic and geographic diversity. These limitations highlight the need for broader analyses, particularly in underrepresented populations, and suggest that future studies could benefit from using whole-exome sequencing or other high-throughput genetic approaches to provide a more complete picture of genetic variation in GSD I across Asia.

Ethical Considerations

Compliance with ethical guidelines

The study protocol was approved by the Research Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran (Code: IR.ARI.MUI.REC.1403.155).

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Authors contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflicts of interest

The authors declared no conflict of interest.

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Supplementary Material S1

PubMed

PICo

Population= ("Glycogen storage disease type Ia"[tiab] OR "Glycogen storage disease type Ib"[tiab] OR "Von Gierke disease"[tiab] OR "Type I Glycogen storage disease"[tiab] OR "Type Ia Glycogen storage disease"[tiab] OR "Type Ib Glycogen storage disease"[tiab] OR "Glycogen storage disease type 1"[tiab] OR "Glycogen storage disease type 1a"[tiab] OR "Glycogen storage disease type 1b"[tiab] OR "Type 1 Glycogen storage disease"[tiab] OR "Type 1a Glycogen storage disease"[tiab] OR "Type 1b Glycogen storage disease"[tiab] OR "Glycogen storage disorder type I"[tiab] OR "Glycogen storage disorder type Ia"[tiab] OR "Glycogen storage disorder type Ib"[tiab] OR "Glycogen storage disorder type 1"[tiab] OR "Glycogen storage disorder type 1a"[tiab] OR "Glycogen storage disorder type 1b"[tiab] OR "Type I Glycogen storage disorder"[tiab] OR "Type Ia Glycogen storage disorder"[tiab] OR "Type Ib Glycogen storage disorder"[tiab] OR "Type 1 Glycogen storage disorder"[tiab] OR "Type 1a Glycogen storage disorder"[tiab] OR "Type 1b Glycogen storage disorder"[tiab] OR "Gierke Disease"[tiab] OR (Disease[tiab] AND Gierke[tiab]) OR "Gierke's Disease"[tiab] OR (Disease[tiab] AND Gierke's[tiab]) OR "Gierkes Disease"[tiab] OR "Glucose-6-Phosphatase Deficiency"[tiab] OR (Deficienc*[tiab] AND "Glucose-6-Phosphatase"[tiab]) OR "Glucose 6 Phosphatase Deficiency"[tiab] OR "Glucose-6-Phosphatase Deficienc*"[tiab] OR "Glycogen Storage Disease 1"[tiab] OR "GSD I"[tiab] OR "Glycogenosis 1"[tiab] OR "Hepatorenal Glycogen Storage Disease"[tiab] OR "von Gierke Disease"[tiab] OR (Disease[tiab] AND "von Gierke"[tiab]) OR "von Gierke's Disease"[tiab] OR (Disease[tiab] AND "von Gierke's"[tiab]) OR "von Gierkes Disease"[tiab] OR (Deficiency[tiab] AND Glucosephosphatase[tiab]) OR (Deficiencies[tiab] AND Glucosephosphatase[tiab]) OR "Glucosephosphatase Deficienc*"[tiab])

Phenomenon of interest= ("Next-generation sequencing"[tiab] OR NGS[tiab] OR "Whole exome sequencing"[tiab] OR WES[tiab] OR (Sequencing[tiab] AND Exome[tiab]) OR "Whole Transcriptome Sequencing"[tiab] OR (Sequencing[tiab] AND "Whole Transcriptome"[tiab]) OR ("Transcriptome Sequencing"[tiab] AND Whole[tiab]) OR "Complete Transcriptome Sequencing"[tiab] OR (Sequencing[tiab] AND "Complete Transcriptome"[tiab]) OR ("Transcriptome Sequencing*"[tiab] AND Complete[tiab]) OR "Whole Exome Sequencing"[tiab] OR ("Exome Sequencing"[tiab] AND Whole[tiab]) OR (Sequencing[tiab] AND "Whole Exome"[tiab]) OR "Complete Exome Sequencing*"[tiab] OR ("Exome Sequencing*"[tiab] AND Complete[tiab]) OR (Sequencing[tiab] AND "Complete Exome"[tiab]) OR variants[tiab] OR "variants types"[tiab] OR "variants Abundance"[tiab] OR "variants frequency"[tiab] OR Variation[tiab] OR Mutation*[tiab])

Context=-

("Glycogen storage disease type Ia"[tiab] OR "Glycogen storage disease type Ib"[tiab] OR "Von Gierke disease"[tiab] OR "Type I Glycogen storage disease"[tiab] OR "Type Ia Glycogen storage disease"[tiab] OR "Type Ib Glycogen storage disease"[tiab] OR "Glycogen storage disease type 1"[tiab] OR "Glycogen storage disease type 1a"[tiab] OR "Glycogen storage disease type 1b"[tiab] OR "Type 1 Glycogen storage disease"[tiab] OR "Type 1a Glycogen storage disease"[tiab] OR "Type 1b Glycogen storage disease"[tiab] OR "Glycogen storage disorder type I"[tiab] OR "Glycogen storage disorder type Ia"[tiab] OR "Glycogen storage disorder type Ib"[tiab] OR "Glycogen storage disorder type 1"[tiab] OR "Glycogen storage disorder type 1a"[tiab] OR "Glycogen storage disorder type 1b"[tiab] OR "Type I Glycogen storage disorder"[tiab] OR "Type Ia Glycogen storage disorder"[tiab] OR "Type Ib Glycogen storage disorder"[tiab] OR "Type 1 Glycogen storage disorder"[tiab] OR "Type 1a Glycogen storage disorder"[tiab] OR "Type 1b Glycogen storage disorder"[tiab] OR "Gierke Disease"[tiab] OR (Disease[tiab] AND Gierke[tiab]) OR "Gierke's Disease"[tiab] OR (Disease[tiab] AND Gierke's[tiab]) OR "Gierkes Disease"[tiab] OR "Glucose-6-Phosphatase Deficiency"[tiab] OR (Deficienc*[tiab] AND "Glucose-6-Phosphatase"[tiab]) OR "Glucose 6 Phosphatase Deficiency"[tiab] OR "Glucose-6-Phosphatase Deficienc*"[tiab] OR "Glycogen Storage Disease 1"[tiab] OR "GSD I"[tiab] OR "Glycogenosis 1"[tiab] OR "Hepatorenal Glycogen Storage Disease"[tiab] OR "von Gierke Disease"[tiab] OR (Disease[tiab] AND "von Gierke"[tiab]) OR "von Gierke's Disease"[tiab] OR (Disease[tiab] AND "von Gierke's"[tiab]) OR "von Gierkes Disease"[tiab] OR (Deficiency[tiab] AND Glucosephosphatase[tiab]) OR (Deficiencies[tiab] AND Glucosephosphatase[tiab]) OR "Glucosephosphatase Deficienc*"[tiab]) AND ("Next-generation sequencing"[tiab] OR NGS[tiab] OR "Whole exome sequencing"[tiab] OR WES[tiab] OR (Sequencing[tiab] AND Exome[tiab]) OR "Whole Transcriptome Sequencing"[tiab] OR (Sequencing[tiab] AND "Whole Transcriptome"[tiab]) OR ("Transcriptome Sequencing"[tiab] AND Whole[tiab]) OR "Complete Transcriptome Sequencing"[tiab] OR (Sequencing[tiab] AND

"Complete Transcriptome"[tiab]) OR ("Transcriptome Sequencing*"[tiab] AND Complete[tiab]) OR "Whole Exome Sequencing"[tiab] OR ("Exome Sequencing"[tiab] AND Whole[tiab]) OR (Sequencing[tiab] AND "Whole Exome"[tiab]) OR "Complete Exome Sequencing*"[tiab] OR ("Exome Sequencing*"[tiab] AND Complete[tiab]) OR (Sequencing[tiab] AND "Complete Exome"[tiab]) OR variants[tiab] OR "variants types"[tiab] OR "variants Abundance"[tiab] OR "variants frequency"[tiab] OR Variation[tiab] OR Mutation*[tiab])

Embase

("Glycogen storage disease type Ia":ti,ab OR "Glycogen storage disease type Ib":ti,ab OR "Von Gierke disease":ti,ab OR "Type I Glycogen storage disease":ti,ab OR "Type Ia Glycogen storage disease":ti,ab OR "Type Ib Glycogen storage disease":ti,ab OR "Glycogen storage disease type 1":ti,ab OR "Glycogen storage disease type 1a":ti,ab OR "Glycogen storage disease type 1b":ti,ab OR "Type 1 Glycogen storage disease":ti,ab OR "Type 1a Glycogen storage disease":ti,ab OR "Type 1b Glycogen storage disease":ti,ab OR "Glycogen storage disorder type I":ti,ab OR "Glycogen storage disorder type Ia":ti,ab OR "Glycogen storage disorder type Ib":ti,ab OR "Glycogen storage disorder type 1":ti,ab OR "Glycogen storage disorder type 1a":ti,ab OR "Glycogen storage disorder type 1b":ti,ab OR "Type I Glycogen storage disorder":ti,ab OR "Type Ia Glycogen storage disorder":ti,ab OR "Type Ib Glycogen storage disorder":ti,ab OR "Type 1 Glycogen storage disorder":ti,ab OR "Type 1a Glycogen storage disorder":ti,ab OR "Type 1b Glycogen storage disorder":ti,ab OR "Gierke Disease":ti,ab OR (Disease:ti,ab AND Gierke:ti,ab) OR "Gierkes Disease":ti,ab OR "Glucose-6-Phosphatase Deficiency":ti,ab OR (Deficienc*:ti,ab AND "Glucose-6-Phosphatase":ti,ab) OR "Glucose 6 Phosphatase Deficiency":ti,ab OR "Glucose-6-Phosphatase Deficienc*":ti,ab OR "Glycogen Storage Disease 1":ti,ab OR "GSD I":ti,ab OR "Glycogenosis 1":ti,ab OR "Hepatorenal Glycogen Storage Disease":ti,ab OR "von Gierke Disease":ti,ab OR (Disease:ti,ab AND "von Gierke":ti,ab) OR "von Gierkes Disease":ti,ab OR (Deficiency:ti,ab AND Glucosephosphatase:ti,ab) OR (Deficiencies:ti,ab AND Glucosephosphatase:ti,ab) OR "Glucosephosphatase Deficienc*":ti,ab) AND ("Next-generation sequencing":ti,ab OR NGS:ti,ab OR "Whole exome sequencing":ti,ab OR WES:ti,ab OR (Sequencing:ti,ab AND Exome:ti,ab) OR "Whole Transcriptome Sequencing":ti,ab OR (Sequencing:ti,ab AND "Whole Transcriptome":ti,ab) OR ("Transcriptome Sequencing":ti,ab AND Whole:ti,ab) OR "Complete Transcriptome Sequencing":ti,ab OR (Sequencing:ti,ab AND "Complete Transcriptome":ti,ab) OR ("Transcriptome Sequencing*":ti,ab AND Complete:ti,ab) OR "Whole Exome Sequencing":ti,ab OR ("Exome Sequencing":ti,ab AND Whole:ti,ab) OR (Sequencing:ti,ab AND "Whole Exome":ti,ab) OR "Complete Exome Sequencing*":ti,ab OR ("Exome Sequencing*":ti,ab AND Complete:ti,ab) OR (Sequencing:ti,ab AND "Complete Exome":ti,ab) OR variants:ti,ab OR "variants types":ti,ab OR "variants Abundance":ti,ab OR "variants frequency":ti,ab OR Variation:ti,ab OR Mutation*:ti,ab)

Scopus

TITLE-ABS-KEY("Glycogen storage disease type Ia" OR "Glycogen storage disease type Ib" OR "Von Gierke disease" OR "Type I Glycogen storage disease" OR "Type Ia Glycogen storage disease" OR "Type Ib Glycogen storage disease" OR "Glycogen storage disease type 1" OR "Glycogen storage disease type 1a" OR "Glycogen storage disease type 1b" OR "Type 1 Glycogen storage disease" OR "Type 1a Glycogen storage disease" OR "Type 1b Glycogen storage disease" OR "Glycogen storage disorder type I" OR "Glycogen storage disorder type Ia" OR "Glycogen storage disorder type Ib" OR "Glycogen storage disorder type 1" OR "Glycogen storage disorder type 1a" OR "Glycogen storage disorder type 1b" OR "Type I Glycogen storage disorder" OR "Type Ia Glycogen storage disorder" OR "Type Ib Glycogen storage disorder" OR "Type 1 Glycogen storage disorder" OR "Type 1a Glycogen storage disorder" OR "Type 1b Glycogen storage disorder" OR "Gierke Disease" OR (Disease AND Gierke) OR "Gierke's Disease" OR (Disease AND Gierke's) OR "Gierkes Disease" OR "Glucose-6-Phosphatase Deficiency" OR (Deficienc* AND "Glucose-6-Phosphatase") OR "Glucose 6 Phosphatase Deficiency" OR "Glucose-6-Phosphatase Deficienc*" OR "Glycogen Storage Disease 1" OR "GSD I" OR "Glycogenosis 1" OR "Hepatorenal Glycogen Storage Disease" OR "von Gierke Disease" OR (Disease AND "von Gierke") OR "von Gierke's Disease" OR (Disease AND "von Gierke's") OR "von Gierkes Disease" OR (Deficiency AND Glucosephosphatase) OR (Deficiencies AND Glucosephosphatase) OR "Glucosephosphatase Deficienc*") AND TITLE-ABS-KEY("Next-generation sequencing" OR NGS OR "Whole exome sequencing" OR WES OR (Sequencing AND Exome) OR "Whole Transcriptome Sequencing" OR (Sequencing AND "Whole Transcriptome") OR ("Transcriptome Sequencing" AND Whole) OR "Complete Transcriptome Sequencing" OR (Sequencing AND "Complete Transcriptome") OR ("Transcriptome Sequencing*" AND Complete) OR "Whole Exome Sequencing" OR ("Exome Sequencing" AND Whole) OR (Sequencing AND "Whole Exome") OR "Complete Exome Sequencing*" OR

("Exome Sequencing*" AND Complete) OR (Sequencing AND "Complete Exome") OR variants OR "variants types" OR "variants Abundance" OR "variants frequency" OR Variation OR Mutation*)

Web of Science

TS=("Glycogen storage disease type Ia" OR "Glycogen storage disease type Ib" OR "Von Gierke disease" OR "Type I Glycogen storage disease" OR "Type Ia Glycogen storage disease" OR "Type Ib Glycogen storage disease" OR "Glycogen storage disease type 1" OR "Glycogen storage disease type 1a" OR "Glycogen storage disease type 1b" OR "Type 1 Glycogen storage disease" OR "Type 1a Glycogen storage disease" OR "Type 1b Glycogen storage disease" OR "Glycogen storage disorder type I" OR "Glycogen storage disorder type Ia" OR "Glycogen storage disorder type Ib" OR "Glycogen storage disorder type 1" OR "Glycogen storage disorder type 1a" OR "Glycogen storage disorder type 1b" OR "Type I Glycogen storage disorder" OR "Type Ia Glycogen storage disorder" OR "Type Ib Glycogen storage disorder" OR "Type 1 Glycogen storage disorder" OR "Type 1a Glycogen storage disorder" OR "Type 1b Glycogen storage disorder" OR "Gierke Disease" OR (Disease AND Gierke) OR "Gierke's Disease" OR (Disease AND Gierke's) OR "Gierkes Disease" OR "Glucose-6-Phosphatase Deficiency" OR (Deficienc* AND "Glucose-6-Phosphatase") OR "Glucose 6 Phosphatase Deficiency" OR "Glucose-6-Phosphatase Deficienc*" OR "Glycogen Storage Disease 1" OR "GSD I" OR "Glycogenosis 1" OR "Hepatorenal Glycogen Storage Disease" OR "von Gierke Disease" OR (Disease AND "von Gierke") OR "von Gierke's Disease" OR (Disease AND "von Gierke's") OR "von Gierkes Disease" OR (Deficiency AND Glucosephosphatase) OR (Deficiencies AND Glucosephosphatase) OR "Glucosephosphatase Deficienc*") AND TS=("Next-generation sequencing" OR NGS OR "Whole exome sequencing" OR WES OR (Sequencing AND Exome) OR "Whole Transcriptome Sequencing" OR (Sequencing AND "Whole Transcriptome") OR ("Transcriptome Sequencing" AND Whole) OR "Complete Transcriptome Sequencing" OR (Sequencing AND "Complete Transcriptome") OR ("Transcriptome Sequencing*" AND Complete) OR "Whole Exome Sequencing" OR ("Exome Sequencing" AND Whole) OR (Sequencing AND "Whole Exome") OR "Complete Exome Sequencing*" OR ("Exome Sequencing*" AND Complete) OR (Sequencing AND "Complete Exome") OR variants OR "variants types" OR "variants Abundance" OR "variants frequency" OR Variation OR Mutation*)

Proquest

TI,AB,SU("Glycogen storage disease type Ia" OR "Glycogen storage disease type Ib" OR "Von Gierke disease" OR "Type I Glycogen storage disease" OR "Type Ia Glycogen storage disease" OR "Type Ib Glycogen storage disease" OR "Glycogen storage disease type 1" OR "Glycogen storage disease type 1a" OR "Glycogen storage disease type 1b" OR "Type 1 Glycogen storage disease" OR "Type 1a Glycogen storage disease" OR "Type 1b Glycogen storage disease" OR "Glycogen storage disorder type I" OR "Glycogen storage disorder type Ia" OR "Glycogen storage disorder type Ib" OR "Glycogen storage disorder type 1" OR "Glycogen storage disorder type 1a" OR "Glycogen storage disorder type 1b" OR "Type I Glycogen storage disorder" OR "Type Ia Glycogen storage disorder" OR "Type Ib Glycogen storage disorder" OR "Type 1 Glycogen storage disorder" OR "Type 1a Glycogen storage disorder" OR "Type 1b Glycogen storage disorder" OR "Gierke Disease" OR (Disease AND Gierke) OR "Gierke's Disease" OR (Disease AND Gierke's) OR "Gierkes Disease" OR "Glucose-6-Phosphatase Deficiency" OR (Deficienc* AND "Glucose-6-Phosphatase") OR "Glucose 6 Phosphatase Deficiency" OR "Glucose-6-Phosphatase Deficienc*" OR "Glycogen Storage Disease 1" OR "GSD I" OR "Glycogenosis 1" OR "Hepatorenal Glycogen Storage Disease" OR "von Gierke Disease" OR (Disease AND "von Gierke") OR "von Gierke's Disease" OR (Disease AND "von Gierke's") OR "von Gierkes Disease" OR (Deficiency AND Glucosephosphatase) OR (Deficiencies AND Glucosephosphatase) OR "Glucosephosphatase Deficienc*") AND TI,AB,SU("Next-generation sequencing" OR NGS OR "Whole exome sequencing" OR WES OR (Sequencing AND Exome) OR "Whole Transcriptome Sequencing" OR (Sequencing AND "Whole Transcriptome") OR ("Transcriptome Sequencing" AND Whole) OR "Complete Transcriptome Sequencing" OR (Sequencing AND "Complete Transcriptome") OR ("Transcriptome Sequencing*" AND Complete) OR "Whole Exome Sequencing" OR ("Exome Sequencing" AND Whole) OR (Sequencing AND "Whole Exome") OR "Complete Exome Sequencing*" OR ("Exome Sequencing*" AND Complete) OR (Sequencing AND "Complete Exome") OR variants OR "variants types" OR "variants Abundance" OR "variants frequency" OR Variation OR Mutation*)

Google scholar

("Glycogen storage disease type Ia" OR "Glycogen storage disease type Ib" OR "Von Gierke disease" OR "Type I Glycogen storage disease" OR "Type Ia Glycogen storage disease" OR "Type Ib Glycogen storage disease" OR

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All records=1706

Pubmed=288

Scopus=580

Web of science=327

Embase=384

Proquest=53

Google scholar=74

4, 5 june 2023

An updated search was conducted on 21 May 2025.