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Novel *SLC37A4* Mutations in Korean Patients With Glycogen Storage Disease Ib

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Background: Molecular techniques are fundamental for establishing an accurate diagnosis and therapeutic approach of glycogen storage diseases (GSDs). We aimed to evaluate *SLC37A4* mutation spectrum in Korean GSD Ib patients.

Methods: Nine Korean patients from eight unrelated families with GSD Ib were included. *SLC37A4* mutations were detected in all patients with direct sequencing using a PCR method and/or whole-exome sequencing. A comprehensive review of previously reported *SLC37A4* mutations was also conducted.

Results: Nine different pathogenic *SLC37A4* mutations were identified in the nine patients with GSD Ib. Among them, four novel mutations were identified: c.148G>A (pGly50Arg), c.320G>A (p.Trp107*), c.412T>C (p.Trp138Arg), and c.818G>A (p.Gly273Asp). The most common mutation type was missense mutations (66.7%, 6/9), followed by nonsense mutations (22.2%, 2/9) and small deletion mutations (11.1%, 1/9). The most common mutation identified in the Korean population was c.443C>T (p.Ala148Val), which comprised 39.9% (7/18) of all tested alleles. This mutation has not been reported in GSD Ib patients in other ethnic populations.

Conclusions: This study expands knowledge of the *SLC37A4* mutation spectrum in Korean patients with GSD Ib.

Key Words: Glycogen storage disease, GSD Ib, Korean population, mutation, *SLC37A4*

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INTRODUCTION

Glycogen storage disease type I (GSD I) is a group of rare autosomal recessive disorders caused by deficiencies in the activities of glucose-6-phosphatase-α (G6Pase-α)/glucose-6-phosphate transporter (G6PT) complexes. The disease has an overall incidence of approximately 1 in 100,000 individuals [1, 2]. In this complex, G6Pase-α and G6PT are functionally coupled; G6PT transports G6P from the cytoplasm into the lumen of the endoplasmic reticulum, where it is hydrolyzed to glucose and inorganic phosphate by G6Pase-α [3]. A functional G6Pase-α/G6PT complex maintains interprandial glucose homeostasis. Specifically, the complex serves as a catalyst in the hydrolysis of intracellular G6P to glucose in the terminal step of gluconeogen-

esis and glycogenolysis in the liver, kidney, and intestine [2, 3]. Mutations in the *G6PC* gene, which encodes G6Pase-α, are responsible for approximately 80% of all GSD I cases, classified as GSD Ia. Mutations in the *SLC37A4* gene, which encodes G6PT, are responsible for the remaining ~20% of GSD I cases, and are classified as GSD Ib [4].

GSD is a clinically and genetically heterogeneous group of diseases that differs according to the site of abnormal glycogen metabolism (i.e., the liver, muscle, heart, or brain) [5]. Different types of GSDs can be clinically indistinguishable. For example, patients with GSD I, GSD III, GSD 0, and GSD XI present with hepatomegaly and/or hypoglycemia, and manifest as hepatic GSDs [5]. Patients with GSD Ib have symptoms similar to those of patients with GSD Ia; however, those with GSD Ib also have neutropenia and inflammatory bowel disease, which require different therapeutic options for management [4, 6]. The molecular diagnosis of GSD avoids the need for invasive liver biopsies [7]. Furthermore, the molecular diagnosis of GSD is important for establishing appropriate therapeutic and monitoring plans [8]. A recent clinical practice guideline recommended that the diagnosis of GSD I should be confirmed by using full-gene sequencing of the *G6PC* (GSD Ia) and *SLC37A4* (GSD Ib) genes [4]. The guideline also mentioned that although full-gene sequencing of both genes is available for clinical testing, targeted mutation analysis would be helpful for some ethnic groups. Testing for specific, common mutations can identify up to 100% of affected individuals, depending on the ethnic group [4]. In this context, identifying the mutation spectrum in specific ethnic populations is important for patient care [4, 8].

Since the GSD enzyme activity tests were first introduced in Korea, there have only been a few case reports of *SLC37A4* mutations in Korean patients with GSD Ib [9-12]. Therefore, the aim of this study was to evaluate the mutation spectrum in Korean patients with GSD Ib for the first time, and to further compare the spectrum to previously reported mutation spectra reported for other ethnic populations.

METHODS

1. Study population

Between April 2003 and September 2015, nine Korean children from eight unrelated families who have been identified as having *SLC37A4* variants were included in this study. Two of the patients were previously reported (cases 1 and 2 in Table 1) [9, 10]. All of these patients were identified as having *SLC37A4* mutations at Samsung Medical Center, Seoul, Korea. Written informed consent was obtained from all subjects and/or their parents. This study was conducted according to the guidelines of the Declaration of Helsinki. All procedures involving human subjects were approved by the Institutional Review Board of Samsung Medical Center.

2. *SLC37A4* mutation analysis

Human genomic DNA was prepared from peripheral blood sam-

Table 1. Clinical manifestations of Korean patients with GSD Ib with identified *SLC37A4* mutations

Case No.	Age of onset	Sex	Initial presentation	F/U period	Short stature (<3‰)	FBS <60 mg/dL	Blood lactate >2.5 mmol/L	Blood uric acid >5.0 mg/dL	TG >250 mg/dL	Cholesterol >200 mg/dL	Increased AST/ALT	HA	HCC
1	18 mo	F	Hepatomegaly, frequent asthma and pneumonia	18 mo	No	Yes	Yes	Yes	Yes	No	Yes	No	No
2	12 yr	M	Hepatomegaly, failure to thrive	NA	Yes	Yes	Yes	Yes	Yes	NA	Yes	No	No
3	11 mo	M	Hepatomegaly	16 yr	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No
4	3 mo	M	Hepatomegaly, Metabolic acidosis with respiratory compensation	2 yr	No	Yes	Yes	Yes	Yes	No	Yes	No	No
5	NA	M	Hepatomegaly	NA	NA	Yes	NA	NA	NA	NA	NA	NA	NA
6**	10 mo	M	Hepatomegaly	4 yr	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
7††	10.9 yr	F	Hepatomegaly, short stature	6 yr	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
8††	8.8 yr	M	Hepatomegaly, short stature	7 yr	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No
9‡‡	9 mo	M	Hepatomegaly, pneumonia	5 mo	No	No	Yes	Yes	Yes	Yes	Yes	NA	No

(continued to the next page)

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Table 1. Continued

Case No.	Neutropenia†	IBD/enterocolitis	Hosp.‡	G-CSF treatment	Delayed puberty	Renal disease*	Neuro-cognitive effects	Liver histology§	Liver Glycogen‖	RBC Glycogen¶	Allele 1		Allele 2		Ref.
1	Yes	No	NA	NA	N.a	NA	NA	c/w GSD	NA	NA	c.443C>T	p.Ala148Val	c.818G>A	p.Gly273Asp	[10]
2	Yes	Yes	NA	NA	NA	NA	NA	c/w GSD	12.30%	NA	c.443C>T	p.Ala148Val	c.1042_1043del	p.Leu348Valfs*53	[9]
3	Yes	No	6	Yes	No	No	Normal	c/w GSD	NA	NA	c.83G>A	p.Arg28His	c.320G>A	p.Trp107*	This study
4	Yes	Yes	6	No	N.a	Yes	Developmental delay	c/w GSD	13.20%	2.00%	c.149G>A	p.Gly50Glu	c.1042_1043del	p.Leu348Valfs*53	This study
5	NA	NA	NA	NA	NA	NA	NA	c/w GSD	NA	NA	c.148G>A	p.Gly50Arg	c.443C>T	p.Ala148Val	This study
6**	Yes	No	3	Yes	N.a	Yes	Asymmetric widening of right temporal horn on sella MRI	c/w GSD	16.72%	4.05%	c.1179G>A	p.Trp393*	c.1179G>A	p.Trp393*	This study
7††	Yes	No	1	Yes	Yes	No	Normal	c/w GSD	NA	NA	c.443C>T	p.Ala148Val	c.443C>T	p.Ala148Val	This study
8††	Yes	No	0	No	No	No	Normal	c/w GSD	NA	NA	c.443C>T	p.Ala148Val	c.443C>T	p.Ala148Val	This study
9‡‡	NA	NA	6	No	NA	Yes	Normal	c/w GSD	NA	NA	c.412T>Ci	p.Trp138Arg	c.1042_1043del	p.Leu348Valfs*53	This study

Cases 1, 2, 7, 8, and 9 were confirmed to have variant alleles located in *trans* in the family DNA analysis.
*Proteinuria, renal stones, nephrocalcinosis, or altered creatinine clearance; †Absolute neutrophil count $<1.5\times10^9$/L; ‡Infection frequency requiring hospitalization after diagnosis; §Swollen hepatocytes with periodic acid–Schiff-positivity and increased accumulation of glycogen in the cytoplasm on electron microscopy (consistent with glycogen storage disease); ‖Reference range 1–6% /wet liver weight; ¶Reference range <10%/packed red blood cell weight; **SLC37A4 mutations were identified through whole-exome sequencing and confirmed by Sanger sequencing; ††These patients are siblings. Case 7 is the proband of the family, and case 8 is her brother; ‡‡This variant was also identified in his asymptomatic female sibling, who was a heterozygote. She did not carry the other mutation of c.1042_1043del.
Abbreviations: GSD, glycogen storage disease; c/w, compatible with; FBS, fasting blood sugar (glucose); F/U, follow-up; G-CSF, granulocyte-colony stimulating factor; HA, hepatic adenoma; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; TG, triglycerides; NA, not available (the information was not submitted); N.a, not applicable because of patient's age or sex; mo, months; hosp, hospitalization; RBC, red blood cell.

ples by using a Wizard genomic DNA purification kit (Promega, Madison, WI, USA) according to the manufacturer's recommendations. All nine exons and flanking regions of the *SLC37A4* gene were amplified with PCR using primers designed by the authors (sequences available upon request). PCR was performed by using a thermal cycler (Model 970; Applied Biosystems, Foster City, CA, USA). Direct sequencing of the DNA was performed using the ABI Prism 3100 Genetic Analyzer (Applied Biosystems) with the BigDye Terminator Cycle Sequencing-Ready Reaction Kit (Applied Biosystems). The nucleotides were numbered from the first adenine of the ATG translation initiation codon in the *SLC37A4* cDNA Reference Sequence NM_001164277.1.

Whole-exome sequencing (WES) was applied for one patient (case 6 in Table 1). Exonic sequences were enriched in the DNA sample using the SureSelect Target Enrichment kit (Agilent Technologies, Santa Clara, CA, USA). Sequences were determined on a HiSeq2000 system (Illumina, San Diego, CA, USA). A total of 150–200 bp were obtained as paired-end reads. The variants of the patients that passed the quality filtering step were compared against those in public databases [National Heart, Lung, and Blood Institute Exome Sequencing Project; 1000 Genomes Project; dbSNP; Exome Aggregation Consortium (ExAC, exac.broadinstitute.org/)] with a cut-off of a global minor allele frequency <1.0%. Protein-altering variants were then selected. The variants derived from the variant filtering strategy were then prioritized on the basis of their likelihood to affect protein function, and/or to completely or partially match the patient's phenotype. The variants' effects on protein function were predicted by using public algorithms such as Sorting Intolerant from Tolerant (SIFT; http://sift.jcvi.org/).

In addition, a comprehensive review of the literature on previously reported *SLC37A4* mutations was conducted. The Human Gene Mutation Database (HGMD, http://www.hgmd.org/) was checked for previously reported sequence variants [13]. The pathogenicity of missense variants was evaluated by *in silico* analyses with SIFT and Polymorphism Phenotyping v.2 (PolyPhen-2) (http://genetics.bwh.harvard.edu/pph2/). The variants that were previously unreported with unknown pathogenicity were classified as the standards according to the American College of Medical Genetics and

Table 2. *SLC37A4* mutation spectrum in nine Korean GSD type Ib patients

Exon No.	Nucleotide change	Amino acid change	Mutation type	Location	PolyPhen-2 score	SIFT score	Allele count	Previously reported	References	Variants category*
3	c.83G>A	p.Arg28His	Missense	Luminal loop 1	1.000	0.00	1	Yes	[1, 15, 16, 18]	
3	c.148G>A	p.Gly50Arg	Missense	Luminal loop 1	1.000	0.00	1	No	[15, 16, 20]†	Pathogenic
4	c.149G>A	p.Gly50Glu	Missense	Luminal loop 1	1.000	0.00	1	Yes	[17]	
4	c.320G>A	p.Trp107*	Nonsense	Helix-2	N/A	N/A	1	No		Pathogenic
5	c.412T>C	p.Trp138Arg	Missense	Helix-3	0.741	0.00	1	No		Likely pathogenic
5	c.443C>T	p.Ala148Val	Missense	Helix-3	0.921	0.00	7	Yes	[9]	
7	c.818G>A	p.Gly273Asp	Missense	Helix-6	1.000	0.00	1	No	[21]‡	Likely pathogenic
9	c.1042_1043del	p.Leu348Valfs*53	Frameshift (small deletion)	Helix-8	N/A	N/A	3	Yes	[19, 25]	
10	c.1179G>A	p.Trp393*	Nonsense	Luminal loop 5	N/A	N/A	2	Yes	[26]	

*Previously unreported variants were classified by the American College of Medical Genetics and Genomics (ACMG) standards and guidelines for the interpretation of sequence variants [14]. †c.148G>A has not been reported previously; however, c.148G>C has been reported as a pathogenic mutation that results in the same amino acid change of p.Gly50Arg. This mutation could be categorized as a pathogenic variant by the ACMG standards and guidelines for the interpretation of sequence variants [14]. ‡c.818G>A has not been reported previously; however, c.817G>A (p.Gly273Ser) has been reported in a GSD patient [21].
Abbreviations: GSD, glycogen storage disease; N/A, not applicable.

Genomics (ACMG) guidelines for the interpretation of sequence variants [14].

RESULTS

Nine patients from eight unrelated families, including two previously reported Korean patients, were identified to have *SLC37A4* mutations. Among the nine patients, 77.8% were male. The clinical information and specific *SLC37A4* mutations identified in the nine Korean GSD Ib patients are shown in Table 1. The median age of onset was 14.5 months (range 3 months to 10.9 yr). The median age at molecular diagnostic work-up was 10.4 yr (range 6 months to 19 yr). All patients presented with hepatomegaly and elevated AST and ALT levels as the first clinical signs. All of the patients also had neutropenia (absolute neutrophil count $<1.5\times10^9$/L). Because of limited clinical information, the genotype–phenotype correlation could not be assessed.

Among 18 mutant alleles, nine different *SLC37A4* mutations were identified (Table 2). These mutations were distributed among all of the coding exons of *SLC37A4*, except for exon 11. Among the nine mutations, four were novel variants: c.148G>A (p.Gly50Arg), c.320G>A (p.Trp107*), c.412T>C (p.Trp138Arg), and c.818G>A (p.Gly273Asp). The remaining five mutations were previously reported: c.83G>A (p.Arg28His), c.149G>A (p.Gly50Glu), c.443C>T (p.Ala148Val), c.1042_1043del (p.Leu348Valfs*53), and c.1179G>A (p.Trp393*) [1, 15-21]. Two of the novel variants were classified as "pathogenic", including c.148G>A (p.Gly50Arg) and c.320G>A (p.Trp107*). The other two novel variants, c.412T>C (p.Trp138Arg) and c.818G>A (p.Gly273Asp), were classified as "likely pathogenic" according to the ACMG sequence variants interpretation guidelines [14]. Among the nine mutations, the most common were missense mutations (66.7%, 6/9) followed by nonsense mutations (22.2%, 2/9) and small deletion mutations (11.1%, 1/9).

Among the 18 tested alleles, the variants c.443C>T (p.Ala148Val), c.1042_1043del (p.Leu348Valfs*53), and c.1179G>A (p.Trp393*) were repeatedly identified in different individuals (7 times, 3 times, and 2 times, respectively). Notably, the most common mutation identified in Korean patients was c.443C>T (p.Ala148Val), accounting for 55.6% (5/9 patients) of all GSD Ib patients and 38.9% of the tested alleles (7/18 alleles). WES followed by Sanger sequencing was used to confirm that one patient (case 6) carried the known homozygous pathogenic mutation c.1179G>A (p.Trp393*). Cases 7 and 8 are siblings from the same family; case 7 is the proband of the family and case 8 is her brother.

DISCUSSION

To our knowledge, this is the first study to summarize the clinical characteristics of Korean patients with GSD Ib. The *SLC37A4* mutation spectrum is known to be distributed widely across the

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SLC37A4 gene. In this study, the most common mutations were missense mutations, which is consistent with the data in the HGMD database.

We identified four novel pathogenic [c.148G>A (p.Gly50Arg) and c.320G>A (p.Trp107*)] or likely pathogenic [c.412T>C (p.Trp138Arg) and c.818G>A (p.Gly273Asp)] *SLC37A4* mutations. Among them, c.148G>A has not been reported previously. In contrast, c.148G>C has been previously reported as a pathogenic mutation. The c.148G>C mutation results in the same amino acid change (p.Gly50Arg), abolishes the microsomal G6P uptake activity, and compromises G6PT stability [15]. The c.148G>A mutation could be categorized as a pathogenic variant according to the ACMG standards and guidelines for the interpretation of sequence variants [14].

Notably, the most common mutation identified in the Korean population was c.443C>T (p.Ala148Val), which was found in 55.6% of the GSD Ib patients and in 38.9% of the tested alleles. This mutation has not been reported in other ethnic patients with GSD Ib. It has only been reported in two alleles in East Asia, and was identified as heterozygous among 43,554 individuals (87,108 tested alleles) with an allele frequency of 2.296^{e-5} in the ExAC database. However, this site is covered in <80% of the individuals in the ExAC database, which may indicate a low-quality site. These findings suggest that this variant might be an important marker for the diagnosis of GSD Ib in the East Asian population specifically. Considering that no Japanese or Chinese patients have been reported to have c.443C>T, it is possible that this represents a recurrent mutation specific to Koreans. Although this is a very rare single nucleotide variant (SNV) in the public database, this variation was detected in most cases simultaneously with another SNV that seems to have a greater impact on protein function. Therefore, further studies are needed to confirm the pathogenicity of this recurrent SNV.

The pathogenic variant of c.1042_1043del (p.Leu348Valfs*53) was the second most frequent mutation (33.3%, 3/9 of GSD Ib patients; 16.7%, 3/18 tested alleles). This mutation has been frequently reported in mixed Caucasian (27–31%) and German (32%) populations [4]. Other mutations that have been frequently reported in other ethnic populations have not been identified in the Korean population [4]. These include c.352T>C (p.Trp118Arg) identified in 37–50% of Japanese people, and c.1015G>T (p.Gly339Cys) identified in 19–21% of mixed Caucasians and in 29% of Germans. These results suggest that Korean *SLC37A4* mutations differ from those of other ethnic populations owing to the genetic divergence of *Homo sapiens*. Furthermore, the c.443C>T mutation may be relatively new, as compared with c.1042_1043del [22], given that identification of a large proportion of rare alleles can be a signature of recent expansion, as mutations that have occurred since the expansion will not have had sufficient time to spread throughout the population [23].

In this study, cases 7 and 8, both of whom have homozygous c.443C>T mutant alleles, are siblings from the same family. These patients also showed similar clinical manifestations, including short stature and hepatic adenoma. Granulocyte-colony stimulating factor treatment was only used in case 7. However, both cases 7 and 8 tolerated dietary management (including corn starch) and only presented with minor infections (such as chronic otitis media or mucosal infection) that did not require hospitalization.

In this study, all patients with *SLC37A4* mutations had neutropenia, except for two cases whose clinical information was not available. In the literature, no correlation could be established between the presence of "leaky" mutations and the absence of neutropenia, in both, homozygous and compound heterozygous patients [24]. Further studies are needed to take into account clinical and biochemical data, which are integral for assessing genotype-phenotype correlations in the Korean population. However, recent molecular diagnostic approaches based on mutation analysis for the disease-causing genes of each type of GSD provide the advantages of avoiding invasive liver biopsies or enzymatic studies. These latter methods are historical diagnostic methods that can potentially introduce ambiguity when differentiating between several types of GSD with similar clinical findings [4]. Despite its limitations, this study is valuable to improve understanding of the *SLC37A4* mutation spectrum in the Korean population.

In conclusion, we identified four novel pathogenic and likely pathogenic *SLC37A4* variations. The c.443C>T (p.Ala148Val) variant was novel and the most common mutation identified. The *SLC37A4* mutation spectrum in Korean GSD Ib patients tends to differ from that of other ethnic populations. Direct sequence analysis of full-gene sequences is needed to provide accurate molecular diagnoses, and WES could be an effective approach in the diagnosis of GSD Ib.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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