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Glycogen storage disease type I: diagnosis and phenotype/genotype correlation

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Abstract Glycogen storage disease type Ia (GSD Ia) is caused by mutations in the *G6PC* gene encoding the phosphatase of the microsomal glucose-6-phosphatase system. GSD Ia is characterized by hepatomegaly, hypoglycemia, lactic acidemia, hyperuricemia, hyperlipidemia and short stature. Other forms of GSD I (GSD I non-a) are characterized by the additional symptom of frequent infections caused by neutropenia and neutrophil dysfunction. GSD I non-a is caused by mutations in a gene encoding glucose-6-phosphatase translocase (G6PT1). We report on the molecular genetic analyses of G6PC and G6PT1 in 130 GSD Ia patients and 15 GSD I non-a patients, respectively, and provide an overview of the current literature pertaining to the molecular genetics of GSD I. Among the GSD Ia patients, 34 different mutations were identified, two of which have not been described before (A65P; F177C). Seventeen different mutations were detected in the GSD I non-a patients. True common mutations were identified neither in GSD Ia nor in GSD I non-a patients. *Conclusion:* Glycogen storage disease type Ia and and type I non-a are genetically heterogenous disorders. For the diagnosis of the various forms of glycogen storage disease type I, molecular genetic analyses are reliable and convenient alternatives to the enzyme assays in liver biopsy specimens. Some genotype-phenotype correlations exist, for example, homozygosity for one *G6PC* mutation, G188R, seems to be associated with a glycogen storage disease type I non-a phenotype and homozygosity for the 727G > T mutation may be associated with a milder phenotype but an increased risk for hepatocellular carcinoma.

Keywords Diagnosis · Glucose-6-phosphatase · Glucose-6-phosphate translocase · Glycogen storage disease type I · Molecular genetics

Abbreviations *GSD* glycogen storage disease · *G6Pase* glucose-6-phosphatase · *HCC* hepatocellular carcinoma · *SSCP* single-strand conformation polymorphism

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Introduction

In 1929, Edgar von Gierke was first to describe a glycogen storage disease (GSD), which initially was named in his honor [29, 46, 54, 59]. More than 20 years later, Cori and Cori [5] found glucose-6-phosphatase (G6Pase; EC 3.1.3.9) to be deficient in patients with von Gierke disease, followed in 1993 by Lei and coworkers' identification of the gene (*G6PC*) encoding G6Pase, which spans 12.5 kb on chromosome 17q21 [25]. Intermittently, other types of glycogen storage disease were identified and labeled chronologically from GSD type I (von Gierke disease) through GSD type XI [2].

The clinical manifestations of von Gierke disease include growth retardation, hepatomegaly, hypoglycemia, lactic acidemia, hyperuricemia, and hyperlipidemia. Long-term complications include short stature, osteoporosis, gout, renal disease, pulmonary hypertension and hepatic adenomas, which may undergo malignant transformation. In the 1960's, patients were described who also suffered from neutropenia and neutrophil dysfunction, resulting in recurrent bacterial infections and oral and intestinal mucosa ulcerations. These patients eventually were shown to have deficient G6Pase activity in intact microsomes, but normal activity in disrupted microsomes and were labeled as having GSD type Ib (OMIM 232220) as opposed to von Gierke

disease, henceforth named GSD type Ia (OMIM 232200) [47]. The biochemical defect underlying GSD Ib involves the transport of glucose-6-phosphate from the cytosol to the microsomal lumen by a glucose-6-phosphate translocase. A gene (*G6PT1*) encoding this translocase and mutations within this gene in GSD Ib patients were first described in 1997 [7]. *G6PT1* maps to chromosome 11q23 and consists of 9 exons.

Further subtypes, termed GSD IaSP, Ic, and Id, were described in a few patients until 1994. However, the elucidation of the molecular genetic basis of GSD Ia and Ib led to a further revision of the terminology. Because the patient with GSD IaSP was proven to have mutations in *G6PC* and most patients with GSD Ic and Id have mutations in the G6PT1 gene, GSD I is now divided into subtypes GSD Ia and GSD I non-a, respectively [27, 56]. The demonstration of reduced enzyme activities measured in liver biopsy specimen has so far been the gold standard for verification of the clinical diagnosis of these autosomal recessive disorders. However, in particular with regard to the diagnosis of GSD I non-a, adequate specimens with intact microsomes are not always obtained upon the first effort which often makes a repeat biopsy necessary.

In this article, we report the molecular genetic analysis of 130 GSD Ia patients and 15 GSD I non-a patients, discuss possible genotype/phenotype correlations, and outline the current approach to the differential diagnosis of patients with GSD I phenotypes.

Patients and methods

Patients

A total of 130 patients with GSD Ia and of diverse ethnic backgrounds were investigated. The diagnosis had been established prior to molecular genetic analysis by the enzyme assay in a liver biopsy specimen in 111 patients, while it was based only on the clinical presentation in the remaining 19 patients. The results on 92 of these GSD Ia patients have been reported previously [26, 31, 32, 48]. The diagnosis of GSD Ib was established by the enzyme assay following at least one liver biopsy in 14 patients. One patient's *G6PT1* gene was evaluated because the clinical presentation was suggestive of GSD I non-a.

Molecular genetic analyses

Molecular genetic analyses of the *G6PC* gene were performed in either one of our laboratories essentially as described previously [27, 31, 32, 48]. Following the purification of DNA from a minimum of 0.5 ml of blood and PCR amplification of the coding sequences using relevant primers, single-strand conformation polymorphism (SSCP) analysis was performed. Exons with abnormal SSCP band patterns were followed up by DNA sequencing, as were all exons of patients when SSCP analysis was negative for at least one mutation. This protocol can be completed within 2 weeks. Following the same principles and according to published procedures, the *G6PT1* gene of the 15 GSD I non-a patients was analyzed in one of our laboratories, but for the most part in the laboratory of Dr. Emile van Schaftingen (Brussels, Belgium) which is gratefully acknowledged [55, 56.]

Results

Glycogen storage disease type Ia

On 260 alleles we identified 34 different mutations (Table 1). The most common mutations in this ethnically diverse population were the missense mutation R83C and the nonsense mutation Q347X on 36% and 18% of alleles, respectively. However, when separating our patients according to ethnic background, truly common mutations were identified in the more homogenous populations; R83C in 92% of the 24 Jewish alleles, R83H in 58% of 12 Chinese alleles, and 130X in 54% of the 24 Hispanic alleles. No mutation was detected on 11 of the 260 alleles (4.2%); however, DNA sequencing of all exons could not be completed for the respective ten patients due to insufficient DNA material. Nineteen patients were spared a liver biopsy because the clinical diagnosis was verified by the molecular genetic analysis.

Two new missense mutations, A65P and F177C, were identified on one allele of each a Swiss and American patient, respectively. While the pathophysiologic relevance of these mutations was not proven experimentally, the nature of the A65P mutation suggests a deleterious effect on protein folding. The exchange of alanine with proline in the second transmembrane domain of G6Pase is likely to disrupt the protein's normal folding because proline's rigidity is not compatible with a smooth secondary structure [36]. The F177C mutation is also likely to be deleterious to G6Pase activity because this patient was deficient of enzyme activity as measured in a liver specimen and sequencing of the entire coding region of G6PC did not reveal any other mutations.

Glycogen storage disease type I non-a

Seventeen different mutations were identified on all alleles of the 15 patients with GSD I non-a. All except one patient's diagnosis had been established by the demonstration of reduced enzyme activity in fresh liver biopsy specimens prior to molecular genetic analysis. One patient was diagnosed on the basis of a characteristic clinical presentation and DNA analysis revealing homozygosity for the deletion 1211–1212delCT. The molecular genetic results of the other patients were reported previously, some in several publications [13, 44, 55, 56].

Discussion

Glycogen storage disease type Ia

The results of the analyses of the genes involved in GSD I of our patients compare well with other studies. With respect to GSD Ia, most studies identified mutations on all alleles investigated [1, 3, 11, 14, 17, 38, 42, 50, 62]. In a few publications, however, mutations were not iden-

Table 1. *G6PC* mutations identified to date, their incidence in patients of this study and in the literature

Mutations					Alleles (%)							
Type	Mutation	Amino acid change	Nucleotide chance	Exon	This study	This study and literature						
						Ashkenazi-Jewish	Caucasian	Chinese	Hispanic	Japanese	Turkish	Total[a]
Missense/ Nonsense	T16A	Thr16Ala	46A>G	I				1 (1.7%)				1 (0.1%)
	M5R	Met5Arg[b]	93T>G	I			2 (0.4%)					2 (0.2%)
	Q20R	Gln20Arg	138A>G	I	2 (0.8%)		2 (0.4%)					2 (0.2%)
	D38V	Asp38Val	192A>T	I	6 (2.3%)		19 (3.6%)					19 (2.2%)
	W50X	Trp50Stop	228G>A	I	1 (0.4%)		1 (0.2%)					1 (0.1%)
	Q54P	Gln50Pro	240A>C	I			2 (0.4%)					2 (0.2%)
	W63R	Trp63Arg	266T>C	I			1 (0.2%)					1 (0.1%)
	W63X	Trp63Stop	268G>A	I	6 (2.3%)		9 (1.7%)					9 (1.1%)
	A65P[c]	Ala65Pro	272G>C	I	1 (0.4%)		1 (0.2%)					1 (0.1%)
	G68R	Gly68Arg	281G>A	I	1 (0.4%)				1 (4.2%)			3 (0.4%)
	W70X	Trp70Stop	289G>A	I	1 (0.4%)		2 (0.4%)					2 (0.2%)
	K76N	Lys76Asn	307G>C	I			2 (0.4%)					2 (0.2%)
	W77R	Trp77Arg	308T>C	I	1 (0.4%)		3 (0.6%)					3 (0.4%)
	G81R	Gly81Arg	320G>A	II	1 (0.4%)		1 (0.2%)					1 (0.1%)
	R83C	Arg83Cys	326C>T	II	94 (36.2%)	42 (95.5%)	170 (32.0%)	1 (1.7%)	5 (20.8%)		22 (73.3%)	246 (29.0%)
	R83H	Arg83His	327G>A	II	12 (4.6%)		7 (1.3%)	22 (37.9%)		4 (2.9%)		33 (3.9%)
	Q104X	Gln104Stop	389C>T	II				1 (1.7%)				1 (0.1%)
	T108I	Thr108Ile	402C>T	II			1 (0.2%)					1 (0.1%)
	E110Q	Glu110Gln	407G>C	II			1 (0.2%)					1 (0.1%)
	E110K	Glu110Lys	407G>A	II	1 (0.4%)		5 (0.9%)					5 (0.6%)
	T111I	Thr111Ile	411C>T	II			1 (0.2%)					1 (0.1%)
	P113L	Pro113Leu	417C>T	II	1 (0.4%)		1 (0.2%)					1 (0.1%)
	H119L	His119Leu	435A>T	III				2 (3.4%)				2 (0.2%)
	G122D	Gly122Asp	444G>A	III						1 (0.7%)		2 (0.2%)
	A124T	Ala124Thr	449G>A	III			1 (0.2%)					1 (0.1%)
	W156L	Trp156Leu	546G>T	IV	3 (1.2%)		3 (0.6%)					3 (0.4%)
	V166A	Val166Ala	576T>C	IV			1 (0.2%)					1 (0.1%)
	V166G	Val166Gly	576T>G	IV								4 (0.5%)
	R170Q	Arg170Gln	588G>A	IV	1 (0.4%)		2 (0.4%)				2 (6.7%)	4 (0.5%)
	R170X	Arg170Stop	587C>T	IV	4 (1.5%)		11 (2.1%)			9 (6.6%)		20 (2.4%)
	Y172X	Tyr172Stop	595C>A	IV			1 (0.2%)					1 (0.1%)
	F177C[c]	Phe177Cys	609T>G	IV	1 (0.4%)		1 (0.2%)					1 (0.1%)
	P178S	Pro178Ser	611C>A	IV	1 (0.4%)				1 (4.2%)			1 (0.1%)
	H179P	His179Pro	615A>C	IV						1 (0.7%)		1 (0.1%)
	G184E	Gly184Glu	630G>A	IV			4 (0.7%)					4 (0.5%)
	G184V	Gly184Val	630G>T	IV			1 (0.2%)					1 (0.1%)
	G188R	Gly188Arg	641G>C	IV	16 (6.2%)		28 (5.2%)					28 (3.3%)
	G188S	Gly188Ser	641G>A	IV	1 (0.4%)		1 (0.2%)					1 (0.1%)
	L211P	Leu211Pro	711T>C	V			1 (0.2%)					1 (0.1%)
	G222R	Gly222Arg	743G>A	V			2 (0.4%)					2 (0.2%)
	G222R	Gly222Arg	743G>C	V			2 (0.4%)					2 (0.2%)
	W236R	Trp236Arg	785T>A	V	1 (0.4%)				1 (4.2%)			1 (0.1%)
	A241T	Ala241Thr	800G>A	V			1 (0.2%)					1 (0.1%)
	Q242X	Gln242Stop	803C>T	V	4 (1.5%)		5 (0.9%)					5 (0.6%)
	P257L	Pro257Leu	849C>T	V						4 (2.9%)		4 (0.5%)

	N264K	Asn264Lys	?	V			1 (0.2%)					1 (0.1%)
	L265P	Leu265Pro	873T > C	V	1 (0.4%)		1 (0.2%)					1 (0.1%)
	G266V	Gly266Val	876G > T	V			2 (0.4%)					2 (0.2%)
	C270R	Cys270Arg	887G > C	V			1 (0.2%)					1 (0.1%)
	G270V	Gly270Val	888G > T	V	4 (1.5%)		10 (1.9%)				1 (3.3%)	13 (1.5%)
	R295C	Arg295Cys	962C > T	V	1 (0.4%)		5 (0.9%)					5 (0.6%)
	S298P	Ser298Pro	971T > C	V			3 (0.6%)					3 (0.4%)
	F322L	Phe322Leu	1043T > C	V			1 (0.2%)					1 (0.1%)
	V338F	Val338Phe	1091G > T	V			6 (1.1%)					6 (0.7%)
	I341N	Ile341Asn	1101T > A	V				3 (5.2%)				3 (0.4%)
	L345R	Leu345Arg	1113–1114TC > GA	V	1 (0.4%)		1 (0.2%)					1 (0.1%)
	Q347X	Gln347Stop	1118C > T	V	47 (18.1%)	2 (4.5%)	115 (21.5%)		2 (8.3%)			121 (14.3%)
Splicing	IVS1–1g < a		IVS1–1g < a	I						1 (0.7%)		1 (0.1%)
	309 + 4 A > G		309 + 4 A > G	Intron 1			1 (0.2%)					1 (0.1%)
	G188D	Gly188Asp	642G > A	V	2 (0.8%)							2 (0.2%)
	727 > T	Leu216Leu	727G > T	V	4 (1.5%)			23 (39.7%)		115 (84.6%)		139 (16.4%)
Insertions	11X	11Stop	97insTGAA	I			1 (0.2%)					1 (0.1%)
	130X	130Stop	459insTA		11 (4.2%)		1 (0.2%)		13 (54.2%)			14 (1.7%)
	203X	203Stop	1 bp insertion (518delA; 518insTG)	III			1 (0.2%)					1 (0.1%)
	280X	280Stop	813insG	V			2 (0.4%)					2 (0.2%)
			933insAA	V				1 (1.7%)				1 (0.1%)
	CEQP245–248WRAA			V	1 (0.4%)		1 (0.2%)					1 (0.1%)
Deletions	35X	35Stop	158delC	I	12 (4.6%)		36 (6.7%)					36 (4.2%)
	59X	59Stop	175delGG	I			2 (0.4%)					2 (.2%)
	101X	101Stop	341delG	II	1 (0.4%)			2 (3.4%)				3 (0.4%)
	201X	201Stop	540del TTTTG	IV			1 (0.2%)					1 (0.1%)
	233X	233Stop	616delT	IV								1 (0.1%)
	300X	300Stop	793delC	V			1 (0.2%)					1 (0.1%)
	300X	300Stop	867delA	V			2 (0.4%)					2 (0.2%)
	300X	300Stop	872delC	V			1 (0.2%)					1 (0.1%)
	delF327	delPhe327	1058–1060del TTC	V	4 (1.5%)		12 (2.2%)					12 (1.4%)
Unidentified					11 (4.2%)		30 (5.6%)	2 (3.4%)	1 (4.2%)	1 (0.7%)	5 (16.7%)	39 (4.6%)
Total alleles					260	44	534	58	24	136	30	848

[a]Includes also unrelated patients of other ethnic background from the literature
[b]Only found in a patient homozygous for M5R and heterozygous for R83C, the latter not being included in this table [54]
[c]New mutations

tified on several alleles with the poorest mutation detection rate of only 75% reported by Hüner et al. [11]. While they were unsuccessful in identifying all mutations despite DNA sequencing, other studies with less than complete detection rates seem to only have used SSCP analyses without follow-up of negative results by sequencing. We also did not achieve a 100% mutation detection rate for our GSD Ia patients. However, we are confident that this is because not all relevant exons were sequenced by the time of writing due to insufficient amounts of DNA available to complete the analyses. In one of our laboratories, mutations were identified on all 98 *G6PC* alleles analyzed to date [48].

GSD Ia is a genetically heterogenous disorder with 76 different mutations detected so far among mostly compound heterozygous patients from a total of 424 different families combining our own and published data (Table 1) [1, 3, 8, 11, 14, 15, 16, 17, 19, 23, 24, 26, 33, 35, 38, 39, 41, 42, 45, 48, 50, 51, 53, 61, 62, 63, 64]. Taking all these patients together, there are no true common mutations and more than 50% appear to be private mutations. The most frequently detected mutations are R83C (29.0%) in exon II, 727G > T (16.4%) and Q347X (14.3%) in exon V, 35X (4.2%) in exon I, and R83H (3.9%) in exon II. Therefore, in order to identify at least close to 70% of mutations in the general population, three of five exons must be analyzed. This seems to translate into an unreasonably laborious effort for a diagnostic test. However, considering the relatively small size of each of the five exons, it is feasible to analyze the whole gene either as described here using SSCP analysis as a screening tool prior to DNA sequencing of relevant exons only, or by primary DNA sequencing with the latter becoming a more widely available method. Laboratories servicing more homogenous populations may, however, be able to limit their diagnostic efforts to a few mutations while still achieving an acceptable mutation detection rate. This appears to be true for patients of Ashkenazi-Jewish, Chinese, Hispanic, Japanese, and Turkish origin (Table 1).

Prior to the availability of mutation analysis, the prenatal diagnosis of GSD I depended on a fetal liver biopsy to obtain adequate material for the enzyme assay. The advent of molecular genetic analysis of the *G6PC* gene facilitated this procedure significantly. The identification of mutations within a family of an affected child has so far enabled the prenatal diagnosis of GSD Ia in a chorionic villus sample in ten fetuses, two of which were found to be affected [4, 24, 37, 41, 42, 49, 52, 61].

Glycogen storage disease type I non-a

To date, molecular genetic analyses have been performed on 121 patients with GSD I non-a (Table 2) [6, 9, 10, 12, 13, 18, 20, 21, 22, 30, 44, 55, 56]. By biochemical analyses of liver samples, 98 patients were diagnosed with GSD Ib, 15 with GSD Ic, and one patient with GSD Id. The remaining seven patients received a diagnosis of GSD I non-a based on the clinical presentation and molecular genetic analysis of the *G6PT1* gene alone, sparing them a liver biopsy. Lam and coworkers [22] reported the prenatal diagnosis of one affected fetus by molecular genetic analysis of DNA from a chorionic villus sample.

Mutations were detected on 237 of these patients' 242 alleles (97.9%). On one allele the mutation escaped detection despite DNA sequencing, while the remaining four alleles appear not to have been sequenced [30, 56]. Overall, 65 different *G6PT1* mutations have been described so far documenting significant genetic heterogeneity (Table 2). Among all of the patients with identified mutations, the five most common mutations were 1211delCT (25.2% of alleles) in exon VIII, followed by G339C (12%) in exon VIII, W118R (4.5%) in exon II, G149E (2.9%) in exon III, and Gln248X (2.9%) in exon IV, with an overall incidence of 47.5%. Separation of the patients according to their ethnic background, the largest ethnic groups were patients of either Caucasian ($n = 78$) or Japanese ($n = 15$) origin. Nevertheless, a search for the respective five most common disorders would not improve the detection rate significantly (56.4% for Caucasians, 66.8% for Japanese (Table 2). Therefore, molecular diagnostic efforts should not be limited to the search for only a few mutations but DNA sequencing should follow whenever mutations escape detection by screening methods such as SSCP analysis.

Genotype/phenotype correlation

A clear-cut genotype/phenotype correlation is not apparent for either GSD Ia or I non-a; however, among both disorders several mutations have been considered to possibly confer particular phenotypes.

Glycogen storage disease type Ia

Nakamura et al. [33] reported a GSD Ia patient who was not diagnosed until he was 40 years old, when he presented with "liver dysfunction and a liver tumour" which by 2 years later had transformed into a hepatocellular carcinoma (HCC). Several other causes of HCC but GSD Ia were excluded, such as alcohol abuse, hepatitis B and C virus infections, and loss of heterozygosity for the p53 gene. The patient was homozygous for the 727G > T splice mutation and the authors speculated whether this particular mutation may be associated with an increased risk for HCC. One of our patients, a Chinese female homozygous for 727G > T, had a similar presentation, however, was diagnosed with an incurable HCC when she was first seen by one of us at 43 years old. This common Japanese mutation (85% of alleles) may also confer a milder GSD Ia phenotype with respect to hypoglycemic events. While Kajihara et al. [14] reported a typical GSD Ia phenotype in their eight patients homozygous for 727G > T, Akanuma and col-

Table 2. *G6PT1* mutations identified to date, their incidence in patients of this study and in the literature

Mutations					Alleles (%)			
Type	Mutation	Amino acid change	Nucleotide change	Exon	This study	This study and literature		
						Caucasian	Japanese	Total
Missense/ Nonsense	M1V	Met1Val	170A > G	I	1 (3.3%)	2 (1.3%)		2 (0.8%)
	G20D	Gly20Asp	228G > A	I	2 (6.7%)	4 (2.6%)		4 (1.7%)
	N27K	Asn27Lys	250T > A	I		2 (1.3%)		2 (0.8%)
	R28C	Arg28Cys	251C > T	I		3 (1.9%)		3 (1.2%)
	R28H	Arg28His	252G > A	I				4 (1.7%)
	G50R	Gly50Arg	317G > C	II		1 (0.6%)		1 (0.4%)
	S54R	Ser54Arg	331C > A	II		1 (0.6%)		1 (0.4%)
	S55R	Ser55Arg	332A > C	II	1 (3.3%)	1 (0.6%)		1 (0.4%)
	G68R	Gly68Arg	371G > A	II		2 (1.3%)		2 (0.8%)
	W78X	Trp78Stop	403G > A	II		1 (0.6%)		1 (0.4%)
	G88D	Gly88Asp	431G > A	II				2 (0.8%)
	W96X	Trp96Stop	456G > A	II		2 (1.3%)		2 (0.8%)
	W118R	Trp118Arg	521T > C	II			11 (36.7%)	11 (4.5%)
	Q133P	Gln133Pro	567A > C	III	1 (3.3%)	1 (0.6%)		1 (0.4%)
	W137X	Trp137Stop	580G > A	III		3 (1.9%)		3 (1.2%)
	G149E	Gly149Glu	615G > A	III		2 (1.3%)	3 (10.0%)	7 (2.9%)
	G150R	Gly150Arg	617G > A	III		1 (0.6%)		1 (0.4%)
	P153L	Pro153Leu	627C > T	III	1 (3.3%)	1 (10.6%)		1 (0.4%)
	C176R	Cys176Arg	695T > C	III	1 (3.3%)	1 (0.6%)		1 (0.4%)
	C183R	Cys183Arg	716T > C	III	1 (3.3%)	5 (3.2%)		5 (2.1%)
	P191L	Pro191Leu	1689C > T	III			1 (3.3%)	1 (0.4%)
	Q218X	Gln218Stop	821C > T	IV	1 (3.3%)	1 (0.6%)		1 (0.4%)
	Y225X	Tyr225Stop	844C > A	IV		1 (0.6%)		1 (0.4%)
	W227X	Trp227Stop	850G > A	IV		1 (0.6%)		1 (0.4%)
	Q248X	Gln248Stop	911C > T	IV		5 (3.2%)		7 (2.9%)
	R300C	Arg300Cys	1067C > T	VI				2 (0.8%)
	R300H	Arg300His	1068G > A	VI		1 (0.6%)		2 (0.8%)
	H301P	His301Pro	1071A > C	VI		1 (0.6%)		1 (0.4%)
	G339C	Gly339Cys	1184G > T	VIII	3 (10%)	29 (18.6%)		29 (12.0%)
	G339D	Gly339Asp	1185G > A	VIII			1 (3.3%)	1 (0.4%)
	E355X	Glu355Stop	1232G > T	VIII		2 (1.3%)		2 (0.8%)
	A367T	Ala367Thr	1268G > A	VIII		2(1.3%)		2 (0.8%)
	G376S	Gly376Ser	1295G > A	IX	1 (3.3%)	1 (0.63%)		1 (0.4%)
	W393X	Trp393Ter	1348G > A	IX		1 (0.6%)		3 (1.2%)
	R415X	Arg415Stop	1412C > T	IX			1 (3.3%)	2 (0.8%)
Splicing	IVS1–2A > C						1 (3.3%)	1 (0.4%)
	IVS1 + 1G > A						2 (6.7%)	2 (0.8%)
	IVS1 + 1G > T				2 (6.7%)	3 (1.9%)		3 (1.2%)
	IVS2 + 1G > T					1 (0.6%)		1 (0.4%)
	IVS2 + 2T > G				2 (6.7%)	3 (1.9%)		3 (1.2%)
	IVS2 + 3delgtg							2 (0.8%)
	IVS3–1G > A					1 (0.6%)		1 (0.4%)
	IVS6–2A > G					1 (0.6%)		1 (0.4%)
	IVS7 + 1G > T						2 (6.7%)	2 (0.8%)
	IVS8 + 1G > A					1 (0.6%)		1 (0.4%)
	794G > A			III			2 (6.7%)	2 (0.8%)
	Σex8/int8			Ex8/int8				4 (1.7%)
	Σex8/int8		c.1292 + 1–1292 + 4 delGTAA	Ex8/int8				2 (0.8%)
	Σint8/ex9			Int8/ex9		2 (1.3%)		2 (0.8%)
Insertions	514insGG	128X		II		2 (1.3%)		2 (0.8%)
	528insC	130X		II	1 (3.3%)	6 (3.8%)		6 (2.5%)
	1103ins12			VI	1 (3.3%)	2 (1.3%)		2 (0.8%)
	1105insA	325X		VI		1 (0.6%)		4 (1.7%)
	1205insC	401X		VIII		1 (0.6%)		1 (0.4%)
	1041ins9	L293X		Int5/ex6	1 (3.3%)	2 (1.3%)		2 (0.8%)
In/Del	del1094 GCTG/insTC			VI			2 (6.7%)	2 (0.8%)

Table 2. (Continued)

Mutations					Alleles (%)			
Type	Mutation	Amino acid change	Nucleotide change	Exon	This study	This study and literature		
						Caucasian	Japanese	Total
Deletions	338–344del TCGGCAG	72X		II		2 (1.3%)		6 (2.5%)
	350delG	94X		II				1 (0.4%)
	629delA	211X		III		1 (0.6%)		1 (0.4%)
	653delAG	189X		III		2 (1.3%)		2 (0.8%)
	693–696del TGTG	210X		III		3 (1.9%)		3 (1.2%)
		delV235		IV			2 (6.7%)	2 (0.8%)
	1013–1029del	319X		V	1 (3.3%)	1 (0.6%)		1 (0.4%)
	1049delG	324X		VI			2 (6.7%)	3 (1.2%)
	1211delCT	400X		VIII	9 (30.0%)	43 (27.6%)		61 (25.2%)
Unidentified								5 (2.1%)
Total alleles					30	156	30	242

[a]Includes also unrelated patients of other ethnic background from the literature

leagues [1] noted that all 40 of their patients with this genotype had never suffered from severe hypoglycemia in infancy. Another patient, who was found to have significant hepatomegaly when examined for diarrhea, also did not exhibit significant fasting hypoglycemia or hyperlactacidemia [16]. She had a relatively high residual G6Pase activity (~10% of normal) in liver and was a compound heterozygote for two missense mutations, R83C and N264K. Although expression studies have not been undertaken, the N264K mutation, which has so far been described only in this patient, is likely to be responsible for the mild phenotype because the common R83C mutation is known to render G6Pase inactive [27].

Other reports noted variable phenotypes among affected siblings sharing identical *G6PC* genotypes [40, 43]. Those described by Rake et al. [43] not only differed with regard to their clinical courses, but also with respect to their residual G6Pase activities in liver (10% versus 0%). Yet another variation of the genotype/phenotype theme was noted in our four patients from three unrelated families who are homozygous for G188R [60]. While this mutation abolishes G6Pase activity and causes the typical symptoms of GSD Ia, these patients also displayed variably severe symptoms of GSD I non-a, namely neutropenia (responsive to granulocyte-colony stimulating factor) and recurrent infections. Mutations in the *G6PT1* gene were not detected in these patients and this unusual phenotype has not been encountered in compound heterozygous patients involving G188R. This observation seems to indicate a close interaction between the glucose-6-phosphate translocase and G6Pase which requires further study.

Glycogen storage disease type I non-a

In analogy to the cases with *G6PC* mutations and a GSD I non-a phenotype (see above), Kure et al. [18] described two unrelated Japanese patients who presented at 20 and 1 years old, respectively, with clinical features of GSD Ia except for the absence of fasting hypoglycemia. Neither patient had neutropenia nor recurrent bacterial infections, however, in liver biopsy specimen both patients had normal G6Pase activity in disrupted microsomes. Further evaluation by molecular genetic analysis of the *G6PT1* gene revealed mutations on both alleles of each patient indicating a diagnosis of GSD I non-a. Although both patients were compound heterozygotes their genotypes were not identical. An explanation for the association of a mild GSD Ia phenotype with different GSD I non-a genotypes is not available, but these case reports raise diagnostic issues as they underscore the necessity to evaluate both genes associated with GSD I in a few patients.

Most molecular genetic studies of the *G6PC* or the *G6PT1* gene conclude that all GSD I subtypes are associated with mutations in either gene, indicating that the terminology should undergo a change to only differentiate GSD types Ia and Ib (or I non-a) because patients that had been diagnosed biochemically with either GSD types IaSP, Ic, or Id were found to carry mutations in either the *G6PC* or *G6PT1* gene [57]. An exception is the original patient described with GSD type Ic who does not carry mutations in either gene known to be associated with GSD I [28, 34]. Although this raises the possibility of yet another gene involved in GSD I, it is remarkable that this patient's clinical presentation is unusual. This patient was diagnosed with insulin dependent diabetes mellitus at 3 years and with GSD Ic at the age of 11 years when undergoing biochemical work-up upon manifesting hepatomegaly and recurrent episodes of hypoglycemia without signs of impaired immune function. While a third subtype of GSD I cannot be excluded, the fact that this is the only "GSD Ic" patient for whom no mutations could be identified and who appears to have a unique phenotype not fully compatible with GSD I (primary insulin dependent diabetes mellitus followed by GSD Ia-like

symptoms at relatively late age), it may be postulated that this patient is affected with an altogether different disorder of glucose homeostasis.

Diagnostic approach to glycogen storage disease type I

Based on our results and the relevant available literature, it is apparent that molecular genetic analysis is a reasonable alternative to the current diagnostic gold standard as it avoids the inconvenience, potential risk, and logistical problems of an invasive liver biopsy to obtain and send fresh tissue to the few existing reference laboratories. The constellation of clinical and basic laboratory findings in most cases allows a reliable tentative diagnosis of GSD Ia or I non-a. However, because it appears that neutropenia and recurrent infections are not always encountered in GSD I non-a, and that patients who suffer from neutrophil dysfunction may actually have GSD Ia, it is advisable to analyze the other GSD I gene before considering a liver biopsy [18, 60]. An algorithm for the diagnostic work up of patients with possible GSD I reflecting these recommendations was recently published by Rake et al. [42]. However, this flowchart suggests repeated blood counts to check for neutropenia before embarking on the molecular genetic analyses because one study found that 14 of 39 (36%) GSD I non-a patients developed neutropenia not until after the 1st year of life [58]. Considering that neutropenia may be cyclic, that some patients never develop neutropenia, and that parents of infants carrying a tentative diagnosis of GSD I are usually anxious to find closure with regard to their offspring's correct diagnosis, we believe it is justified to not delay specific diagnostic efforts and to proceed early to DNA analysis.

Since first submission of this manuscript we detected two new mutations in two additional patients (D. Bali, personal communication): T255M (Thr 255 Met, 843C > T) in exon V of the G6PC gene and S356T (Ser356Thr, 1236G > C) in exon VIII of the G6PT1 gene.

The authors made their best effort to exclude errors due to redundant publications or reporting of sibships.

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