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Glycogen Storage Disease: Clinical, Biochemical, and Molecular Heterogeneity

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Glycogen storage diseases (GSDs) are characterized by abnormal inherited glycogen metabolism in the liver, muscle, and brain and divided into types 0 to X. GSD type I, glucose 6-phosphatase system, has types Ia, Ib, Ic, and Id, glucose 6-phosphatase, glucose 6-phosphate translocase, pyrophosphate translocase, and glucose translocase deficiencies, respectively. GSD type II is caused by defective lysosomal α-glucosidase (*GAA*), subdivided into 4 onset forms. GSD type III, amylo-1,6-glucosidase deficiency, is subdivided into 6 forms. GSD type IV, Andersen disease or amylopectinosis, is caused by deficiency of the glycogen-branching enzyme in numerous forms. GSD type V, McArdle disease or muscle phosphorylase deficiency, is divided into 2 forms. GSD type VI is characterized by liver phosphorylase deficiency. GSD type VII, phosphofructokinase deficiency, has 2 subtypes. GSD types VIa, VIII, IX, or X are supposedly caused by tissue-specific phosphorylase kinase deficiency. GSD type 0, glycogen synthase deficiency, is divided into 2 subtypes.
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Glycogen storage disease (GSD), inborn errors of glycogen metabolism, has been known to mainly be a liver disease with the exception of Pompe (GSD type II), McArdle (GSD type V), or Tarui (GSD type VII) diseases. Recently, however, various muscular disorders involving different types of muscles have been described to be caused by defective glycogen metabolism. The respective deficient enzymes and the responsible genes of various GSD types are comprised in Tables 1 and 2.

GSD Type I (von Gierke Disease)

Glucose 6-phosphatase (G6Pase), the key enzyme in the homeostatic regulation of blood glucose levels, catalyzes the terminal step in both glycogenolysis and gluconeogenesis.[1] Deficiency of G6Pase, the most severe form of hepatic GSDs, is characterized by hepatomegaly, nephromegaly, obesity, tachypnea, and short stature. Chronic complications are hepatic adenomas, gout, osteoporosis, renal failure, pulmonary hypertension, and platelet dysfunction. The microsomal G6Pase system consists of membrane-bound phosphohydrolase and various translocases for G6P (T1), phosphate (T2), and glucose (T3).[2,3] Deficiency of T1, namely GSD type Ib, shows systemic infections like stomatitis, Crohn-like enteritis as a result of neutropenia, neutrophil, and monocyte dysfunction. Common laboratory findings of GSD Ia and Ib are hypoglycemia, hyperlipidemia, hyperuricemia, and lactic acidemia. Deficiencies of T2 (GSD Ic) or T3 (GSD Id) have not yet been completely elucidated; however, the patients are supposed to have milder clinical courses.[3,4] As an initial diagnostic step for GSD I, the glucagon and epinephrine loading test can support the clinical suspicion. Through the observation of a significant elevation of plasma biotinidase among patients with GSD Ia,[5] we have developed a 2-step diagnostic procedure without liver biopsy to confirm the clinical diagnosis of GSD Ia: the plasma biotinidase assay followed by the molecular analysis of the G6Pase gene.[6] According to our data of over 50 GSD type Ia patients, R83C and Q347X account for approximately 60% among the white population. For the diagnosis of GSD Ib, the analysis of a fresh liver sample is necessary.[4] However, this can be spared by the analysis of the glucose transport in polymorphonuclear cells[7,8] followed by the G6PT gene analysis.[9] According to our experience and other reports, mutations c1211 to 1212 delCT, G339C, and 1 bp insertion account for approximately 33%, 20%, and 10%

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Table 1 Various Types of Glycogen Storage Disease Types I-IV

Type	Deficient enzyme	Gene symbol	Literature
I (von Gierke)			
Ia	Glucose 6-phophatase	G6PC	6
Ib	G6P tranlocase (T1)	SLC37A4	9
Ic	Phophotranslocase (T2)	NPT4(?)	10,11
Id	Glucose translocase (T3)	?	
II			
Infantile (Pompe disease)	Lysosomal α-glucosidase	*GAA*	17
Childhood	〃	〃	〃
Juvenile	〃	〃	〃
Adult	〃	〃	〃
III (Cori disease)			
IIIa (Liver & muscle form)	Amylo-1,6-glucosidase	*AGL*	24
IIIb (liver form)	〃	〃	〃
IIIc (muscle form)	〃	〃	〃
IV (Andersen disease)			
Infantile form	Branching enzyme	GBE1	37,38
(Liver)	Branching enzyme	〃	〃
(Neuomuscular)	〃	〃	〃
Juvenile or adult form (Liver, muscle)	〃	〃	〃
Polyglucosan body disease (APBD)	〃	〃	〃

alleles, respectively, among white GSD Ib patients.[10] The molecular defect of GSD Ic has not yet been clearly elucidated.[11,12]

GSD Type II

Patients with the infantile form of lysosomal 1,4-α-glucosidase deficiency or Pompe disease start to show clinical symptoms at a median age of 1.6 months. They usually present within 6 months of life with severe axial hypotonia, hypertrophic cardiomyopathy, respiratory insufficiency, frequent respiratory infections, delayed motor milestones, hepatomegaly, and macroglossia. The symptoms of the childhood forms are severely progressive with predominantly proximal muscular weakness involving also respiratory muscles, but cardiac muscle is rarely involved. The late-onset form shows slower progression of myopathy than the infantile onset form and seldom cardiomegaly. The juvenile/adult forms reveal predominant slowly progressing proximal muscular weakness in lower extremities with truncal involvement and sometimes respiratory insufficiency.[13,14] The *GAA* activity in muscle or in fibroblasts correlates inversely with clinical subtypes, the infantile form having less than 2%, childhood 1% to 5%, and juvenile and adult up to 22% residual enzyme activities. According to the Rotterdam group, the *GAA* activity in fibroblasts is significantly influenced by culture techniques such as culture duration.[15] Thus, special caution is necessary for detecting late-onset forms with this kind of cell type.[15] Even though the early-onset forms can easily be diagnosed in leukocytes,[16] a secure diagnosis of the late-onset forms can be

Table 2 Various Types of Glycogen Storage Disease Types V-X and 0

Type	Deficient enzyme	Gene symbol	Literature
V (McArdle disease)			
Adult form	Muscle phosphorylase	PYGM	40
Infantile form	〃	〃	〃
VI (Hers disease)	Liver phosphorylase	PYGL	41
VII (Tarui disease)			
Severe form	Phosphofructokinase	PFKM	42
Mild form	〃	〃	〃
Phosphorylase activation system defects			
VIII (VIa/IXA)	Phosphorylase kinase (liver PBK)		
(XLG I/II)	α-subunit of PBK	PHKA2	46-48
Autosomal recessive	β subunit of PBK	PHKB	47,49
IXB	γ or δ subunit of PBK (?)	PHKG2	50,52
IXC	Cardiac muscle PBK	?	
IXD (adult form)	Muscle PBK	PHKA1	51
(Severe muscle form)		PHKA1(?), PHKG1(?)	51,52
X (multisystem)	Protein kinase(?)	?	
GSD 0	Glycogen synthase (liver)	GYS2	53
	〃 (muscle)	GYS1	54