Table 1 Overview of glycogen storage diseases

GSD type (eponym)	OMIM#	Defective enzyme or transporter	Gene/inheritance	Gene location	Primary tissue involvement	Distinctive features
GSD-0	GSD-0a: 240600	Liver glycogen synthase	GYS2/AR	12p12.1	Liver	No hepatomegaly. Postprandial hyperglycemia, glycosuria, and hyperlactatemia. Extremely low amount of glycogen in liver tissue
	GSD-0b: 611556	Muscle glycogen synthase	GYS1/AR	19q13.33	Muscle	Cardiac involvement, risk of sudden cardiac arrest
GSD-I (von Gierke)	GSD-Ia: 232200	Glucose-6-phosphatase	G6PC/AR	17q.21	Liver	Coagulopathy, anemia, osteopenia, osteoporosis, renal dysfunction, HA, HCC
	GSD-Ib: 232220	Glucose-6-phosphatase transporter	SLC37A4/AR	11q23.3	Liver	Neutropenia, neutrophil dysfunction, recurrent infections, oral and intestinal mucosal ulcers, IBD, autoimmunity
GSD-II (Pompe)	232300	Acid α-glucosidase	GAA/AR	17q25.3	Muscle	Cardiomyopathy, infantile-onset form. Muscle weakness, late-onset form
Danon disease (formerly GSD-IIb)	300257	Lysosome-associated membrane protein-2	LAMP2/XLD	Xq24	Muscle	Skeletal and cardiac myopathy, arrhythmia, intellectual disability
GSD of heart	600858	AMP-activated protein kinase, γ-2 regulatory subunit	PRKAG2/AD	7q36.1	Muscle	Severe ventricular hypertrophy. Electrocardiographic preexcitation and conduction system disease. Premature sudden cardiac death (< 40 yr)
GSD of heart, lethal congenital	261740	AMP-activated protein kinase, γ-2 noncatalytic subunit	PRKAG2/AD	7q36.1	Muscle	Some mutations (R531Q, R384T) cause more severe phenotype. Fetal onset, extreme cardiomegaly, death in infancy
GSD-III (Cori/Forbes)	IIIa/IIIb: 232400	Glycogen debrancher enzyme	AGL/AR	1p21.2	IIIa: Liver + muscle; IIIb: Liver	Liver fibrosis, cirrhosis, HA, HCC (as a complication of cirrhosis). IIIa: Elevated CK, motor developmental delay, myopathy, cardiomyopathy
GSD-IV (Andersen)	232500	Glycogen branching enzyme	GBE1/AR	3p12.2	Liver	Classical hepatic form (rapidly progressive liver disease, HSM, cirrhosis, HCC). Non-progressive hepatic form. Neuromuscular presentation (perinatal, congenital, childhood and adult forms). Myopathy, cardiomyopathy, neuropathy, CNS involvement, APBD. Amylopectin aggregations in liver
GSD-V (McArdle)	232600	Muscle glycogen phosphorylase	PYGM/AR	11q13.1	Muscle	Exercise intolerance, muscle cramps, rhabdomyolysis, myoglobinuria, "second wind" phenomenon
GSD-VI (Hers)	232700	Liver glycogen phosphorylase	PYGL/AR	14q22.1	Liver	Phenotypic variability (overlap with GSD-IX). Severe hepatic involvement reported. Mild hypotonia and cardiopathy reported. Excessive glycogen accumulation with structurally normal glycogen in liver tissue. Enzyme deficiency in erythrocytes, leukocytes
GSD-VII (Tarui)	232800	Muscle phosphofructokinase	PFKM/AR	12q13.11	Muscle	Exertional myopathy, exercise intolerance, muscle cramps, hemolytic anemia. Rapidly progressive infantile form (multisystem involvement, seizures, cardiomyopathy)
GSD-IX	GSD-IXa1 (XLG-1): 306000	Phosphorylase kinase, α-subunit, liver	PHKA2/XLR	Xp22.13	Liver	The most common subtype. Symptomatic female carriers due to X chromosome inactivation. Clinical symptoms and laboratory abnormalities gradually disappear with age. Severe phenotypes reported
	GSD-IXb: 261750	Phosphorylase kinase, β-subunit	PHKB/AR	16q12.1	Liver	Marked accumulation of glycogen in both liver and muscle. Muscle symptoms are generally mild or absent
	GSD-IXc: 613027	Phosphorylase kinase, γ-subunit	PHKG2/AR	16p11.2	Liver	More severe phenotype with increased risk for liver fibrosis and cirrhosis
	GSD-IXd: 300559	Phosphorylase kinase, α-subunit, muscle	PHKA1/XLR	Xq13.1	Muscle	Muscle weakness and muscle cramps during exercise. Mostly in adults

GSD-X	261670	Muscle phosphoglycerate mutase	PGAM2/AR	7p13	Muscle	Exercise intolerance, muscle cramps and pain, rhabdomyolysis, myoglobinuria
Fanconi-Bickel syndrome (formerly GSD-XI)	227810	Glucose transporter 2	SLC2A2/AR	3q26.2	Liver	Hepatorenal involvement. Proximal renal tubular dysfunction. Osteoporosis/rickets. Different patterns of dysglycemia. Postprandial hyperglycemia and hypergalactosemia
GSD-XI	612933	Lactate dehydrogenase A	LDHA/AR	11p15.1	Muscle	Exertional myoglobinuria, easy fatigability, exercise induced myalgia, erythematosquamous skin lesions on the extensor surfaces of the extremities
GSD-XII	611881	Fructose-1,6-bisphosphate aldolase A	ALDOA/AR	16p11.2	Muscle	Rhabdomyolysis induced by fever and/or exercise, hemolytic anemia with or without myopathy or cognitive dysfunction
GSD-XIII	612932	Enolase 3 (β-enolase)	ENO3/AR	17p13.2	Muscle	Exercise intolerance, exercise induced myalgia, muscle weakness
GSD-XV	613507	Glycogenin-1	GYG1/AR	3q24	Muscle	Ventricular arrhythmogenic cardiomyopathy, progressive muscle weakness

GSD: Glycogen storage disease; HA: Hepatic adenoma; HCC: Hepatocellular carcinoma; AR: Autosomal recessive; XLR: X-linked recessive; XLD: X-linked dominant; CK: Creatinine kinase; CNS: Central nervous system; APBD: Adult polyglucosan body disease: IBD: Inflammatory bowel disease.

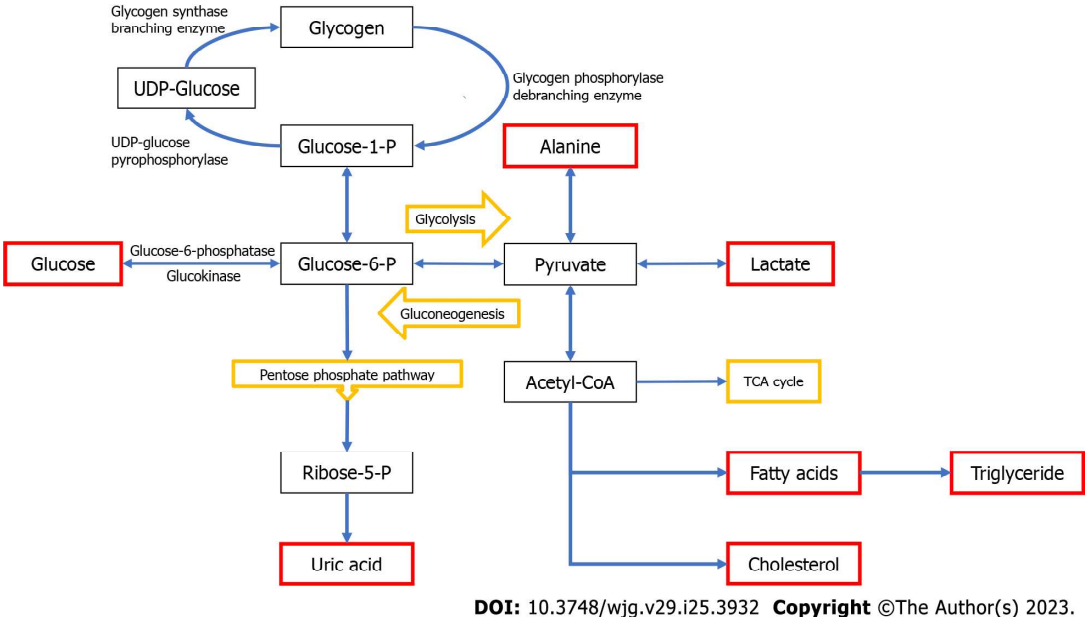

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Figure 1 Simplified pathway of glycogen synthesis and degradation in hepatocytes. Glucose and glycogen convert into one another *via* synthesis or degradation (glycogenolysis) through various steps. The liver plays a central role in maintaining normoglycemia. During the fasting state, the liver maintains glucose homeostasis *via* a metabolic shift from synthesizing glycogen to endogenous glucose production by glycogenolysis and gluconeogenesis. Specific enzyme or transporter defects in these pathways are associated with clinical and biochemical manifestations including hepatomegaly, hypoglycemia, hyperlipidemia, hypertriglyceridemia, hyperlactatemia, and hyperuricemia. GSD: Glycogen storage disease; UDP-Glucose: Uridine diphosphate glucose; Glucose-1-P: Glucose 1-phosphate; Glucose-6-P: Glucose-6-phosphate; Acetyl-CoA: Acetyl coenzyme A; TCA: Tricarboxylic acid.

rate-limiting step in hepatic glycogen synthesis. GYS deficiency in liver leads to a marked reduction in hepatic glycogen stores. The inability to synthase glycogen inevitably leads to conversion of dietary carbohydrate to lactate rather than being stored as glycogen in the liver. Postprandial hyperglycemia, glycosuria, and lactic acidemia are replaced by ketotic hypoglycemia during fasting[12]. There is often ketosis after a routine overnight fast.

There are wide phenotypical variations[13]. Fasting hypoglycemia usually manifests in late infancy when overnight feedings are discontinued. Hypoglycemia typically occurs early in the morning prior to having breakfast. Hypoglycemia is responsible for the symptoms observed in GSD-0, which encompasses lethargy, pallor, nausea, vomiting, and, in some cases, seizures. Although some children may display developmental delay, most are neurologically normal. Some patients may remain asymptomatic or experience only mild symptoms[14]. Notably, liver enlargement is not a feature of GSD-0. GSD-0 is the only hepatic GSD that is not typically associated with hepatomegaly[15]. Short