Article:
Pinós, T., Cubbon, R.M. orcid.org/0000-0001-7844-3600, Santalla, A. et al. (7 more authors) (2025) Cardiovascular involvement in glycogen storage diseases. Nature Reviews Cardiology. ISSN 1759-5002

https://doi.org/10.1038/s41569-025-01171-w

Cardiovascular involvement in glycogen storage diseases

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Abstract

Glycogen storage diseases (GSDs) are rare conditions affecting both sexes that are caused by inherited deficiencies of enzymes involved in glycogen synthesis or breakdown, or in glycolysis. The liver and skeletal muscle are usually the most affected tissues. Yet, because glycogen has an important role in cardiac development and function, several GSDs are associated, at least indirectly, with cardiac disorders some of which have severe consequences from the first months of life. Early identification of these conditions is, therefore, an important issue, and implementation of strategies to prevent fatal outcomes due to cardiovascular disease is vital. In this Review, we discuss the pathophysiological mechanisms and the preclinical, clinical and epidemiological evidence for cardiovascular involvement in various GSDs. We also discuss interventions that can help preserve heart function, including changes in nutrition and exercise, as well as the few available molecular therapies to address the underlying metabolic anomalies.

[H1] Introduction

In mammals, carbohydrates are stored in the form of intracellular glycogen. Glycogen storage disorders (GSDs; each type classified by a Roman numeral) are rare conditions, affecting both sexes, with an overall prevalence at birth of 1:20,000–1:43,000[1]. GSDs are caused by inherited (usually autosomal recessive) deficiencies of enzymes involved in glycogen synthesis or breakdown, or in glycolysis (Box 1; Fig. 1). Because GSDs mainly affect skeletal muscle and the liver, the two tissues with the highest capacity for glycogen storage, the resulting phenotype often includes exercise intolerance, alterations in glucose homeostasis or both. Glycogen also has an important role in cardiac development and function[2] (Fig. 2; Box 2). Therefore, some GSDs can affect the cardiovascular system, often

from infancy, unless an isoenzyme is present that can replicate the function of the deficient enzyme. Disease manifestations are caused either by energy deficiency or by the toxic effects of accumulated glycogen, which induce organomegaly, disrupt the cellular architecture, affect cellular biophysical properties and impair organelle (e.g. lysosomes, mitochondria) function[3]. In GSDs, cardiac injury generally evokes a non-specific hypertrophic response, and contractile dysfunction might be an early sign or develop later in life. Conduction disturbances are also found in affected individuals, including enhanced conduction at the early stage of disease, followed by arrhythmia and conduction block[3].

In this Review, we address the evidence for cardiovascular involvement in various GSDs (types 0b, I, II, IIIa, IV, V, VII and XV) and in two related conditions — protein kinase AMP-activated non-catalytic subunit gamma 2 (PRKAG2) syndrome and Danon disease. To the best of our knowledge, these are essentially the GSDs that can affect the cardiovascular system. As such, discussing other GSDs with a less clear cardiovascular involvement would fall outside the scope of this Review. On the other hand, we believe this topic is timely because, except mainly for the infantile form of GSDII, the clinical focus of GSD-related affectations is frequently put on the liver and/or skeletal muscle tissue. Yet, the overall success of enzyme replacement therapy in children with GSDII or recent tantalizing findings on gene therapy for Danon disease (as discussed later) might be followed in the foreseeable future by other trials, supporting the importance of early awareness of cardiovascular affectation in the context of these conditions. In addition to emphasizing the need for early identification of potential cardiac abnormalities, we discuss strategies aimed at preserving cardiac function, including the few available molecular therapies, as well as lifestyle interventions.

[H1] Glycogen storage diseases

[H2] Glycogen storage disease type 0b

GSD0b (Lewis' disease; prevalence <1:1,000,000) is caused by a deficiency in the muscle (skeletal and cardiac) isoform of glycogen synthase, which is encoded by the *GYS1* gene. This enzyme catalyses the addition of glucose monomers to the growing glycogen molecule through the formation of α-1,4-glycosidic linkages[4] (Fig. 1). Most (90%) *Gys1*$^{-/-}$ mice die shortly after birth due to abnormal cardiac growth (smaller ventricles and dilated atria compared with wild-type controls)[2], confirming that cardiac glycogen synthesis is critical for the normal development of the heart in mice and, presumably, in humans.

[H3] ***Case reports*****.** GSD0b was first described in 2007 in three siblings of Syrian origin[5]. The oldest brother died from sudden cardiac arrest (SCA) at the age of 10 years. The cause of his death was listed as (echocardiography-determined) hypertrophic cardiomyopathy (HCM). No glycogen was detected in cardiomyocytes (which showed hypertrophy with enlarged nuclei, but no myocyte disarray or fibrosis) on post-mortem biopsy. Two years later, the second patient (male; aged 11 years) also showed HCM, together with very poor performance and a decrease in blood pressure (BP) during exercise testing. By contrast, the third sibling (female; aged 2 years) was asymptomatic and had normal cardiac dimensions, although glycogen deficiency was noted on skeletal muscle biopsy[5].

Another case of genetically diagnosed GSD0b was described in a Japanese girl, who experienced recurrent exertional syncopal episodes (after running as little as 50 meters) accompanied by muscle weakness and pain from the age of 5 years until she died from SCA 7 years later[4]. Cardiac assessments (including ECG, echocardiography, stress cardiac catheterization and stress myocardial scintigraphy) revealed no abnormalities, except for mild ischaemic findings on exercise ECG[4]. No cardiac biopsy results were reported, but skeletal-

muscle biopsies showed depletion of glycogen in all muscle fibres. One hypothesis to explain the episodes of syncope and SCA was intermittent arrhythmia, although no ECG recordings were obtained during these events. However, because losses of consciousness were gradual and lasted for hours, these episodes might have been caused by metabolic distress rather than being cardiac in origin[4].

Cameron et al. reported a case of an 8-year-old South Indian boy with genetically diagnosed GSD0b who died from SCA while exercising with his classmates at school[6]. He had no history of exercise intolerance. Family history revealed that his parents were consanguineous and that a female sibling had died aged 6 days of an undetermined cause. The boy's autopsy showed that the heart was structurally normal, with appropriate size, weight and ventricular wall thickness. Skeletal-muscle glycogen stores were depleted, but whether this deficiency also occurred in the heart was not reported. Mitochondrial ultrastructure was abnormal (especially in the skeletal muscle tissue and to a lesser degree in the heart), suggesting undue proliferation to counteract the glycogen deficiency and provide more ATP by oxidation[6].

In 2022, two unrelated cases (women aged 47 years and 57 years) of adult-onset skeletal myopathy with no heart involvement on Holter monitoring, echocardiography or cardiac MRI (CMR) were reported[7]. *GYS1* molecular genetic analysis confirmed a diagnosis of GSD0b in both patients, and muscle biopsy revealed marked glycogen depletion in nearly all myofibers[7].

[H3] ***Management.*** Genetic testing for GSD0b is advisable in children with abnormal cardiac responses to increased workloads, as well as those with defined myocardial disease, owing to the potentially lethal nature of this condition in childhood[6]. No specific guidelines have been published for the management of cardiac problems in GSD0b, although early cardioverter-

defibrillator implantation can be considered on a case-by-case basis in patients with high-risk features, such as ventricular arrhythmia or likely cardiogenic syncope. Selective β_1-receptor blockade was used in the surviving Syrian siblings discussed above (bisoprolol in the male with HCM and metoprolol in the asymptomatic female)[5].

[H2] Glycogen storage disease type I

The two major subtypes of GSDI (von Gierke disease, prevalence ~1:100,000[8]) are GSDIa and GSDIb. These conditions are caused by deficiencies in glucose 6-phosphatase (encoded by the *G6PC* gene) and glucose-6-phosphate exchanger (also known as G6PT; encoded by the *SLC37A4* gene), respectively. Both result in excessive accumulation of glycogen and fat in the liver, kidney and intestinal mucosa[8,9]. The complications of GSDI are multisystemic in untreated, or inadequately treated, patients and can include systemic arterial hypertension and pulmonary hypertension (PH)[8,9].

[H3] ***Systemic hypertension***. High BP is the most common cardiovascular abnormality in patients with GSDI, and usually occurs in the context of renal disease[8]. Hypertension is caused by activation of the renin–angiotensin system (RAS) leading to increased production of angiotensin II — a multifunctional cytokine that stimulates the proliferation of mesangial cells, glomerular endothelial cells and fibroblasts, and acts as a profibrogenic factor. In mice with GSDIa, components of the RAS were upregulated, and these animals had comparable renal biopsy findings to patients with GSDIa[10]. Systemic hypertension in the context of GSDI does not usually develop until the second decade of life or later. However, in two unrelated cases of GSDI — a 2-year-old girl (with mild HCM on echocardiographic evaluation)[11] and a 6-month-old boy (with normal echocardiographic findings)[12] — early kidney dysfunction (hyperfiltration) and damage (increased mesangial proliferation and focal basement

membrane thickening on renal biopsy) were reported. In a cohort of 38 (39% female) patients with GSDIa (n = 32) or GSDIb (n = 6), 18 children under the age of 10 years had normal renal function, whereas 14 of the 20 older patients (aged 13–47 years) had altered renal function (persistent proteinuria), and 10 of these patients developed hypertension[13]. Renal biopsies in three of the patients with proteinuria showed focal segmental glomerulosclerosis[13]. In another study, a multi-ethnic cohort of patients with GSDIa and GSDIb (n = 231 and n = 57, respectively), hypertension requiring treatment was detected in 6% of all patients at a median age of 17 years (range 4–42 years)[14].

[H3] ***Pulmonary hypertension*****.** PH has also been reported as complication of GSDI, often with a fatal outcome. At the mechanistic level, pulmonary vasoconstrictor stimuli (severe, persistent metabolic acidosis or hypoxia) can induce or accelerate primary PH in patients with GSDI[15]. Another potential mechanism is impaired metabolism of circulating vasoconstrictive agents that are normally removed or altered by the liver (epinephrine, norepinephrine, histamine and serotonin) due to hepatic damage[15], a condition prevalent in adults with GSDI who often develop liver adenomas[8]. Notably, plasma levels of serotonin (a vasoconstrictor acting on pulmonary vascular smooth muscle cells) were substantially elevated in a patient with both GSDIa and PH compared with healthy control individuals or patients with either GSDI or severe PH alone[16].

A case of GSDI was reported in 1980 of a 16-year-old female who suffered a fatal SCA[17]. Post-mortem examination showed that the heart weighed 250 g (approximately twice the normal weight for her body size). The lungs were focally haemorrhagic and, at the microscopic level, showed the changes of primary PH — muscular hypertrophy and intimal fibrosis of small and medium-sized arteries, as well as numerous plexiform lesions[17]. In 1990, Hamaoka et al. reported on a 12-year-old girl and a 16-year-old boy from Japan, both of

whom had GSDI and died of progressive heart failure (HF) due to PH[15]. Echocardiography revealed dilatation of the right atrium (RA), right ventricle (RV) and main pulmonary artery (mPA), and chest x-ray revealed pulmonary oedema[15]. Another 12-year-old girl from Japan with GSDI died after unsuccessful treatment for right HF[18]. Autopsy revealed marked dilatation and hypertrophy of the RA and RV, with no evidence of cardiac shunt or valvular disease, and cardiomyocytes of these chambers were hypertrophied. Microscopic images revealed muscular pulmonary arteries with advanced pathological changes involving almost complete fibrous occlusion, aneurysm-like dilatation and plexiform lesions. Another case of fatal outcome due to PH was reported in a 21-year-old Japanese woman with GSDI[19]. Echocardiography showed dilatation of the RA, RV and mPA, but no intracardiac anomaly. Treatment with various drugs was ineffective, and the patient died on day 7 after admission, with no autopsy performed[19]. Authors from Switzerland reported on an 8-year-old girl previously diagnosed with GSDI who died from intractable HF[20]. The autopsy showed an enlarged RA with an atrial septal defect (secundum type) and a hypertrophic RV with normal outflow tract. The mPA was extremely dilated, whereas the small peripheral pulmonary arteries showed fibrosis, together indicating severe obstructive pulmonary vascular disease. The left heart and the arteries of the systemic circulation were normal. The authors suggested that the coexistence of GSDI with a congenital cardiac malformation caused pulmonary vascular obstruction, leading to rapid deterioration[20]. Another case of fatal PH with death due to progressive HF in association with GSDI was described in a woman aged 24 years[21]. Cardiac catheterization showed a PA pressure (PAP) of 116/79 mmHg (normal 15–30/4–12 mmHg) with normal systemic BP and no systemic–pulmonary shunt or other causes of PH, such as liver cirrhosis, portal hypertension or thromboembolic phenomena[21].

In a prospective study of 22 patients (50% female) with GSDI (21 GSDIa, 1 GSDIb; age range 5–44 years), six patients had an abnormal RV-to-RA gradient (>20 mmHg),

suggesting an elevation in RV pressure and PAP in the absence of RV outflow tract obstruction[21]. None of the patients had an alternate identifiable cause of PH[21]. In another study, 54 Korean patients (39% female) with GSDIa (median age at diagnosis 3.9 years) were followed for up to 8 years[22]. Two patients (one male, one female) were diagnosed with PH at the ages of 27 years and 22 years, respectively. The male patient was treated with the prostacyclin analogue, beraprost sodium, but he died at the age of 41 years. The female patient's initial echocardiogram showed a systolic PAP of 81 mmHg and a D-shaped left ventricle (LV), typical in the context of RV dilatation. Follow-up echocardiography after treatment with sildenafil showed a moderate decrease in PAP to 64 mmHg[22]. Sildenafil was also effective in attenuating PH progression secondary to GSDI in two boys, aged 17 years[23] and 14 years[24]. Primary PH in the setting of GSDI has been detected on echocardiography as early as 10 days of age[25]. However, no cases of PH or relevant cardiac abnormality were found on routine echocardiography in 28 patients (14 female; age range 3–51 years) with GSDI (24 GSDIa, 4 GSDIb)[24], illustrating the wide spectrum of PH presentation in GSDI.

[H3] ***Management*****.** Management of hypoglycaemia is the primary concern in infants and young children with GSDI, as it permeates all aspects of their diet and lifestyle[8]. Disease-specific guidelines include the following recommendations for the prevention of cardiovascular sequelae[8]:

- BP monitoring from infancy to detect systemic hypertension.
- Maintaining lipid levels within the normal range to prevent atherosclerosis.
- Echocardiography performed every 3 years (or shorter intervals, if clinical symptoms are present) from the age of 10 years, with attention to PAP by tricuspid regurgitation jet velocity to detect PH.

- Regular diagnostic studies for kidney damage (renal ultrasound, urinalysis, serum electrolytes), with angiotensin-converting-enzyme inhibitor (ACE) or angiotensin II receptor blocker therapy if kidney dysfunction develops.

The diagnosis, monitoring and treatment of systemic hypertension and PH in patients with GSDI should follow that of affected individuals without GSDI[8]. As most patients with PH also have metabolic abnormalities, achieving good metabolic control might help to prevent this condition[8]. If PH is detected, treatment with medications such as bosentan and sildenafil is recommended, in consultation with a clinician experienced in managing PH[8].

A trial has been recently published showing the safety of 52-week gene therapy with DTX401(an investigational adeno-associated virus serotype 8 vector expressing the human *G6PC* gene) in 12 adults with GSDIa[26]. Further research might determine the efficacy of gene therapy to improve cardiovascular outcomes in this condition.

[H2] Glycogen storage disease type II

GSDII (Pompe disease) is caused by pathogenic mutations in the gene encoding lysosomal α-glucosidase (*GAA*)[27]. Deficiency of this enzyme leads to pathological accumulation of glycogen inside and outside lysosomes (*i.e.* released into the cytoplasm) in the myocytes of smooth, skeletal and cardiac muscle, where it causes lysosomal rupture and cell hypertrophy, impairing cell function[28-30]. Clinical severity is inversely related to the amount of residual enzyme activity[29], which varies depending on the hundreds of pathogenic mutations identified in the *GAA* gene[31]. GSDII is classified into two major subtypes — infantile onset (GSDIIa; prevalence 1:126,118[32]) and late onset (GSDIIb; prevalence 1:21,902[32]).

[H3] ***Infantile onset.*** Infants with GSDIIa show minimal (<1%) lysosomal α-glucosidase activity[33] and rapidly progressive HCM (sometimes before birth[34,35]). Early-onset HCM and

abnormal cardiac glycogen accumulation, but not early death, has been reported in *Gaa*$^{c.1826dupA}$ (p.Y609*) mouse model causing infantile-onset GSDII[36]. In another study, *Gaa*$^{-/-}$ mice showed enlarged aortic diameter and numerous vacuoles containing fine granular or amorphous material inside the aortic wall[37]. Cardiomyocytes differentiated from the induced pluripotential stem cells of a 5-month-old patient with GSDIIa were hypertrophied and had decreased levels of lysosomal α-glucosidase, abnormal glycogen accumulation in lysosomes, as well as remarkably reduced numbers of mitochondrial and elevated reactive oxygen species derived from dysfunctional mitochondria[38]. The link between profound mitochondrial dysregulation with increased cellular apoptosis and GSDIIa pathogenesis has been corroborated in *Gaa*$^{-/-}$ mouse models and in patients, albeit with experiments confined to the skeletal-muscle[39].

A study of 20 patients (30% female) from centres in the Netherlands and 133 cases (42% female) from the literature showed that median age of GSDIIa symptom onset was 1.6 months[40]. Survival without treatment beyond the first year of life was rare (5–8%)[40]. Post-mortem examination indicates cardiac enlargement (with a globoid heart shape), thickening of the ventricular walls and interventricular septum and chamber dilatation[33]. Histological images indicate loss of striations and microvacuolated sarcoplasm in cardiomyocytes, and lysosomes containing β-glycogen, on electron microscopy[33]. The cardiac conduction system can also be affected. A post-mortem report of four infants (four male, one female) who died within the first year of life showed enlarged and vacuolated cells with marked glycogen infiltration, similar to the myocardium, in the sinoatrial and atrioventricular nodes and atrioventricular bundles[41]. Ante-mortem electrocardiographic studies were available for one patient, and showed high conduction speeds reflected by short PR-intervals[41].

[H3] ***Late onset.*** The typical presentation of GSDIIb includes proximal muscle weakness and respiratory insufficiency. Symptoms commonly begin in the third decade of life, but sometimes in childhood or adolescence[42]. Evidence also exists for cardiac abnormalities in the absence of muscle manifestations[43]. In a Dutch cohort of 46 patients with GSDIIb (24 female; age range 25–71 years), only two individuals had cardiac abnormalities on echocardiography — a 57-year-old man with HCM phenotype (normal LV mass) and a 67-year-old man with decreased LV ejection fraction (LVEF, 48%) and atrial fibrillation (AF)[44]. However, in another study of 17 patients with genetically proven late-onset GSDII (six females; mean age 50 years) cardiac pathology was investigated using comprehensive CMR[45]. Three patients showed a non-ischaemic late gadolinium enhancement (LGE) pattern in the LV basal inferolateral wall, and three demonstrated elevated global extracellular volume (ECV) values indicative of interstitial myocardial fibrosis[45]. Non-specific abnormalities, such as left atrial (LA) dilatation, were present in two patients, and an HCM phenotype was seen in one patient. Two of the three LGE-positive patients also had hypertension and global ECV values >30% in addition to LA dilatation. At the end of the follow-up period (median 25 months), only one cardiovascular event occurred (acute coronary syndrome in one of the LGE-positive patients with a high cardiovascular risk profile)[45]. Mori et al. reported a case of GSDIIb complicated by primary hyperparathyroidism in a 35-year-old woman who was free of muscle symptoms[43]. She he presented 1-week post-partum with CMR-ascertained LV enlargement, pronounced wall motion abnormalities and reduced systolic function (LVEF 34%). Endomyocardial biopsy showed striking sarcoplasmic vacuolization, excess glycogen staining and frequent membrane-bound glycogen on electron microscopy, consistent with lysosomal glycogen deposition[43]. In a study from France, four of 131 patients (one female; age range 32–45 years) with GSDIIb and apparently free of cardiovascular risk factors required pacemaker implantation due to severe

atrioventricular block[46]. By contrast, in another study, there were no structural or functional cardiac differences on CMR or 2D speckle-tracking echocardiography assessments between 12 patients with GSDIIb (six female; mean age 38 years) and 187 healthy controls[47]. Similarly, LVEF (~64%) was comparable between 10 patients with late-onset GSDII (four female; mean age 57 years) and seven aged-matched controls[48]. In a systematic review of 48 studies, van Kooten et al. found that severe cardiovascular abnormalities in patients with GSDIIb carrying the most common *GAA* mutation (c.-32T>G (IVS1-13 T>G)) are rare and not significantly different from the general population[49]. In addition, no overall differences were found in case–control comparisons of electrocardiographic findings. However, patient numbers were small and various conduction abnormalities have been described in cohort studies of patients with GSDIIb, with short PR-interval, right bundle branch block and Wolff–Parkinson–White (WPW) syndrome being the most common[49]. WPW syndrome was reported in 2.3–9.4% of patients across four cohorts, which is higher than the prevalence in the general population (<0.25%)[49]. The cause of these conduction abnormalities could be glycogen accumulation in the myocardium, the conduction system or both[50,51].

The most frequently reported vascular abnormality in patients with GSDIIb is the elongation and distention of arteries (dolichoectasia), with a predisposition for the vertebrobasilar arteries (VBA), which serve the cervical spinal cord, brainstem, cerebellum, thalamus and occipital lobe[49]. A case–control study showed that cerebral arterial diameter was higher in ten adult patients with GSDIIb (five female; mean age 46 years) than in age and sex-matched controls[52]. In cohort studies, the prevalence of VBA dolichoectasias was 2–72%, which is above reported estimates for the general population (0.8–6.5%)[49]. Focal aneurysms are another important vascular abnormality reported in cohort studies of patients with GSDIIb, affecting not only the anterior cerebral circulation (2–14% of patients) and VBA (3–6% of patients), but also the aorta (2–10% of patients)[49]. Notably, a 48-year-old man

with GSDIIb receiving enzyme replacement therapy (ERT; see later section) was reported as presenting with massive annuloaortic dilatation (maximum diameter 96 mm)[53]. Arteriopathy primarily involving the ascending thoracic aorta (diameters of 35–44 mm) has also been described in five female patients aged 33–64 years[54]. The pathophysiology of all these vascular abnormalities is likely to be multifactorial, as both GSDIIb-related factors (e.g. degeneration of arterial wall smooth muscle cells caused by glycogen accumulation) and established cardiovascular risk factors are associated with dolichoectasia and aneurysm formation[49].

GSDIIb has also been linked to PH. The potential causative mechanisms are unclear, although respiratory muscle weakness and reduced pulmonary function could be contributing factors[55]. A 29-year-old Japanese man with GSDIIb died 21 months after starting ERT[56]. The autopsy showed pulmonary veno-occlusive disease, with severe occlusive endothelial hypertrophy in the small pulmonary veins, resulting in severe PH[56]. PH has also been described in two 16-year-old female patients with late-onset GSDII[55,57]. Systolic PAP was 65 mmHg in one patient (severe PH)[55,] and 35 mmHg in the other patient (mild PH) who had been receiving ERT for 5 years[57].

[H3] ***Diagnosis and follow-up.*** Numerous guidelines or consensus documents from various countries are available for the diagnosis and management of both forms of GSDII[58-63]. Despite wide clinical heterogeneity, presentation within the first few months of life, hypotonia, failure to thrive, generalized muscle weakness and severe non-obstructive HCM with a concentric distribution of LV hypertrophy followed by hypokinetic end-stage cardiomyopathy, usually within the first year of life are typical of GSDIIa[64]. Moreover, infants with biventricular hypertrophy, who often present with signs of HF and systolic dysfunction and one or more indicators of metabolic disease (e.g. muscle hypotonia or increased levels of creatine kinase and transaminases, consanguinity or matrilineal pattern of

inheritance) should be investigated for GSDIIa in consultation with a metabolic disease specialist[64]. In addition to genetic testing, measurement of lysosomal α-glucosidase in leukocytes can facilitate diagnosis[3].

Life-threatening arrhythmias can occur in patients with ventricular pre-excitation (VPE), especially in the context of cardiomyopathy. Therefore, electrocardiography should be conducted at least once in all patients with newly diagnosed GSDIIb[49]. Furthermore, because ERT does not prevent rhythm disorders, some authors have recommended periodic Holter monitoring in patients with GSDIIb[49]. Given that thoracic aortic aneurysm is an under reported vascular complication of GSDIIb, chest X-ray and echocardiography should be performed in patients with this condition[54]. When dolichoectasia is suspected, or the ascending aorta is not visualized, contrast enhanced CT of the chest or magnetic resonance angiography might be necessary[54].

[H3] ***Enzyme replacement therapy.*** In the absence of therapeutic intervention, GSDII (especially GSDIIa) has a poor prognosis, mainly due to end-stage HF[64]. However, in infants with GSDIIa, ERT has been shown to reverse LV hypertrophy[27]. ERT for GSDII involves human enzyme forms produced by recombinant DNA technology — alglucosidase alfa, avalglucosidase alfa-ngpt, or cipaglucosidase alfa co-administered with an enzyme stabilizer, miglustat[65-73]. Despite heterogeneity between studies, a 2024 meta-analysis showed that, when compared with placebo or no treatment, ERT was associated with significant reductions in LV mass (mean decrease 131.3 g/m^2) in 49 infants with GSDIIa (therapy onset age 0.4–14.6 months; follow-up 27.6–63.0 months) with no major adverse events[27]. A reduction in mortality (HR 0.10, 95% CI 0.05–0.19) was also reported for ERT in 39 infants (follow-up 27.6–30.0 months, respectively)[27]. However, other studies have shown that, after 30 months, infants with GSDIIa who are receiving ERT still show disease progression with various severe manifestations[73]. Concerns have been raised about potential ERT-associated sequelae,

such as a high incidence of arrhythmias (18% of 38 children), but a causal relationship cannot be inferred[74]. Nevertheless, regular screening for arrhythmias in children receiving ERT is warranted[71].

Patients who do not produce any endogenous (even non-functional) lysosomal α-glucosidase (cross-reactive immunologic material (CRIM) negative) are prone to develop high sustained antibody titres to ERT[72] and have a poor response to therapy[76,77]. Thus, prophylactic immune tolerance induction (ITI, consisting of rituximab, methotrexate and intravenous immunoglobulin) in combination with ERT can decrease, or prevent, the formation of antidrug antibodies and can be lifesaving[78]. Early (≤4 weeks) ERT and ITI in five neonates with CRIM-negative GSDIIa elicited significant reductions in LV mass compared with infants who were treated later[79]. Additionally, the use of plasma cell-targeting agents, such as the proteasome inhibitor bortezomib, in combination with immunomodulatory regimens has been successful in eliminating high-sustained antibody titres against ERT in patients with GSa[79]. Remarkably, a fetus with CRIM-negative GSDIIa who had two affected siblings (deceased at 8 and 29 months, one of whom received ERT) received in utero ERT in addition to standard postnatal ERT[35]. All prenatal and postnatal electrocardiographic and echocardiographic studies were normal throughout follow-up (up to age 13 months)[35].

For patients with GSDIIb, the 2024 European consensus statement[62] outlines the criteria for starting and stopping ERT. Therapy should commence when diagnosis is confirmed by enzyme activity testing in leukocytes, fibroblasts or skeletal muscle and/or when pathogenic mutations are present in both alleles of the *GAA* gene, the patients is symptomatic and has residual skeletal and respiratory muscle function. Therapy should be stopped if the patient develops infusion-associated reactions or high antidrug antibody titres. However, no recommendations were made regarding cardiac outcomes[62].

[H3] ***Other molecular therapies.*** Several preclinical studies demonstrated that genetic reduction of glycogen synthesis via suppression of glycogen synthase 1 (GYS1), ameliorates glycogen pathology in GSDII mice[81-83]. Findings include a profound reduction in glycogen accumulation in the heart, together with significant decreases in lysosomal swelling and autophagic build-up as well as a complete correction of cardiomegaly[82]. A small molecule that potently inhibits GYS1, MZ-101, has been reported to reduce glycogen accumulation in skeletal muscle with comparable efficacy to ERT in GSDII mice[84] and in healthy humans[85]. However, glycogen measurements from cardiac biopsies are needed. Gene therapy might also represent a new alternative treatment for GSDII, with research performed in murine models[86] and ongoing trials in humans (Table 1).

[H3] ***Nutrition and exercise.*** A consortium of European experts has recommended that, in addition to treatment with ERT, patients with GSDIIb might benefit from concomitant diet and aerobic exercise therapy[63]. Nutritional assessment is important in patients with motor disability, because the relative lack of exercise limits energy expenditure and so calorie intake must be reduced to avoid obesity[63]. However, a reduced total energy intake often leads to a decrease in protein and micronutrient intake[63]. Therefore, ensuring that patients with GSDIIb are tested and treated for nutritional deficiencies is an important aspect of care[63].

Evidence from 29 adult patients showed that a combination of aerobic (30 min of cycling) and strength (either body weight, free weights or exercise machines) training three times per week for 12–20 weeks improved peak oxygen uptake (VO_{2peak}) by 9–10%[87]. These findings are promising, given that cardiorespiratory fitness is a robust, independent prognostic factor of morbidity and mortality from all causes, particularly cardiovascular conditions[88-92]. The AHA advocates for the routine assessment of VO_{2peak} as a clinical vital sign[93].

[H2] Glycogen storage disease type IIIa

GSDIII (Cori disease; prevalence~1:100,000[94]) is caused by mutations in the gene encoding glycogen debranching enzyme (*AGL*) with subsequent deficiency of this enzyme and tissue accumulation of limit dextrins **[G]**[95,96]. Two disease subtypes have been identified: GSDIIIa, which affects the liver, skeletal muscle and heart[95,96] and accounts for 85% of cases, and GSDIIIb, which mainly affects the liver[97] with common manifestations including hepatomegaly, ketosis, hypoglycaemia, muscle weakness and growth delay[94]. Here, we focus on GSDIIIa.

In a survey of patients with GSDIII from nine countries, cardiac conditions were reported by 66% of 29 adults and 46% of 46 caregivers of affected children[95]. HCM is the most common cardiac manifestation. In a study from the USA, 12 of 23 patients with GSDIIIa (mean age 16.5 years, range 1 month to 55.5 years) had HCM, although most were asymptomatic and had preserved LVEF[98]. Age of onset of cardiac manifestations is variable[3], and HCM can manifest in the first decade of life. In two different cohorts of patients with GSDIIIa, 32% of 28 children (mean age 6.6 years)[99] and 48% of 23 children (median age 10 years)[100] had signs of HCM. This condition can also occur later in life, and has been reported in 33–45% of adults (aged 18–68 years) with GSDIIIa across several studies[95,98,100]. However, in one of the reports, only 10% of patients with HCM were symptomatic with reduced LVEF[95].

Cardiac manifestations of GSDIIIa can have fatal consequences, and cases of early heart transplantation have been reported [95,101,102]. A 36-year-old woman was reported to have died from SCA attributable to glycogen accumulation in the conduction system (similar to that seen in GSDII[41]), which might have predisposed the patient to a lethal arrhythmia[101]. GSDIIIa has also been linked to recurrent ventricular tachycardia, as described in a 23-year-

old Japanese man[102]. Other cases of sudden cardiac death in patients with GSDIIIa have been reported. For example, a 4-year-old boy[103] and an 11-year-old girl, whose autopsies both showed marked cardiomegaly[104], and a 38-year-old woman with moderate HCM and patchy fibrosis on autopsy[105]. Other post-mortem heart biopsies have revealed mild-to-moderate vacuolation due to cytosolic limit dextrin accumulation in the cardiomyocytes of both ventricles and of the RA, as well as in specialized cells of the sinoatrial and atrioventricular nodes and in the cardiac conduction system[101]. Smooth muscle cells can also be affected, with both sinoatrial and atrioventricular node arteries showing mild vacuolation or hyperplasia[101]. In explanted hearts, numerous foci of myocardial scarring throughout both ventricles, as well as subendocardial fibrosis, have been observed[101].

PH can also develop in association with GSDIII. Two female patients (aged 13 and 16 years) of Latin American descent (diagnosed with GSDIIIa and GSDIIIb, respectively) developed PH, one of whom (with GSDIIIb, systolic PAP 88 mmHg) died aged 18 years[106]. Lee et al. hypothesized that PH could be caused by the over-production or reduced clearance of a diffusible substance by the diseased liver, or that glycogen accumulation in the underlying pulmonary vasculature could be involved[106].

[H3] ***Diagnosis of HCM and follow-up.*** The main aim of cardiovascular investigations in patients with GSDIIIa is to screen for HCM, for which conventional treatments and dietary modifications (see below) are indicated[107]. Echocardiography and electrocardiography should be performed annually[95,107]. CMR can be considered when echocardiography is suspicious for HCM in older children and adults, and repeated every 5 years[107]. Blood assays for N-terminal pro B-type natriuretic peptide (NT-proBNP) can be used in patients presenting with HCM, even when asymptomatic, to identify early myocardial stress and to monitor progress[107]. As PH can be a rare complication in patients with GSDIIIa, echocardiography with a focus on

PAP should be performed if patients present with symptoms of right-sided HF, such as shortness of breath or oedema[106].

[H3] ***Nutrition.*** No specific therapy for GSDIIIa is available[3] and management is largely limited to dietary measures. Traditionally, frequent feeding, ingestion of corn starch or both were recommended to prevent fasting hypoglycaemia. However this approach can worsen cardiac damage by increasing tissue accumulation of limit dextrins[107]. The 2010 GSDIII consensus guidelines[108] recommend that adolescent and adult patients adopt a high-protein, low-complex-carbohydrate diet (25% and <50% of total calories, respectively) and to avoid simple sugars and fasting. Several case reports, with a range of dietary approaches, have been published. All share the common theme of low-carbohydrate and high-protein and/or high-fat intake[109–111,112–116]. These studies have shown apparent cardiac benefits for these diets. For example, reductions in LV mass[111–113], interventricular septal thickness[109,110, 114,115], NT-proBNP level[114], LV outflow tract gradient and improvements in LVEF[116]. Importantly, these improvements contrasted with the deleterious effects, such as LV hypertrophy, associated with earlier high-protein, high-carbohydrate diets involving frequent corn starch meals. Interestingly, a 32-year-old woman with GSDIIIa and HCM was denied a heart transplant due to obesity[117]. She subsequently followed a low-calorie (900 kcal per day), high-protein (37% of total energy) diet that resulted in weight loss of 10kg, improvements in electrocardiographic and echocardiographic LV parameters, ultimately reversing the need for transplantation[117].

[H3] ***Gene therapy.*** Preclinical research on gene therapy has been conducted in GSDIII mice, with decreases in cardiac glycogen levels[118,119]. Treatment with rapamycin for 12–16 months[120], or RNA interference therapy through silencing of the glycogen synthase 2 (liver)

gene (*Gys2*) [121], have demonstrated reductions in the glycogen content of the muscle, liver or both in GSDIII canine[120] and mouse[121] models, respectively, but no analyses were performed on cardiac tissue. Further research is needed to determine whether these preclinical findings can be translated to clinical practice.

[H2] Glycogen storage disease type IV

GSDIV (Andersen disease; prevalence 1:600,000–800,000[122]) is caused by deficiency in 1,4-α-glucan-branching enzyme 1 (encoded by the *GBE1* gene), which catalyses the formation of α-1,6 branch points during glycogen synthesis[123,124]. Shortage of this protein leads to the accumulation of amylopectin-like polyglucosan bodies **[G]**, mainly in the liver, skeletal muscle, heart and nervous system, with subsequent cellular damage due to foreign body reaction or osmotic swelling[124].

A mouse model of GSDIV (*Gbe1*$^{-/-}$) showed reduced glycogen accumulation in the developing hearts of embryos, together with abnormal cardiac development, including ventricular hypertrabeculation and poor function in late gestation that ultimately led to HF and embryonic lethality[125]. In addition, the cell-cycle regulators G1/S-specific cyclin-D1 and Myc proto-oncogene protein were highly expressed in cardiomyocytes and likely contributed to cardiomyocyte proliferation and trabeculation of the ventricular walls[125]. Cardiac biopsies from patients with GSDIV show hypertrophic cardiomyocytes, interstitial fibrosis and numerous intrasarcoplasmic inclusions which, when seen on electron microscopy, are consistent with amylopectin-like polyglucosan bodies[126].

Clinical manifestations of GSDIV are highly heterogeneous, ranging from prenatal death (usually unrelated, at least directly, to cardiac causes) to mild, adult-onset disease[124,127]. The majority (~92%) of attributable deaths are reported before the age of 4 years[124]. GSDIV can be divided into the ‘classic’ (progressive liver dysfunction leading to death or liver

transplantation within 5 years) or 'non-progressive' (no severe liver failure) hepatic forms and the 'neuromuscular' form, which is divided into various subtypes. Cardiac involvement, mostly in the form of dilated cardiomyopathy (DCM)[3] affects ~28% of patients with GSDIV, either in association with systemic manifestations (~26%) or alone (~2%)[124].

H3] ***Case reports*****.** A case was reported of a 19-year-old man with GSDIV who was free of neuromuscular manifestations, but diagnosed with severe non-ischaemic DCM (LVEF 10–15%)[126]. CMR showed transmural LGE in the lateral, anterolateral and inferolateral walls from the apex to the base[126]. He received an implantable cardioverter defibrillator (ICD) and LV assist device, before undergoing heart transplantation[126]. When present, cardiac manifestations can vary[124], even between affected siblings. For example, an 18-year-old patient developed progressive DCM and severe HF and died from SCA 1-year later[128,129]; however, his 14-year-old exhibited only mild cardiomyopathy. Other presentations include DCM within the first year of life[130,131], during childhood[132,133] or manifestations in adulthood (e.g. DCM with reduced LVEF[134,135], or DCM with absent LGE[136] and increased RV trabeculation[137]). Electrocardiographic abnormalities can also occur, including first-degree atrioventricular block in the first decade of life[132], and multiform ventricular arrhythmia with paroxysmal AF in the third decade of life[135]. Severe HF has been reported as the cause of death in young patients (aged 2–19 years) with GSDIV[128,129,132,138,139].

[H3] ***Management.*** Recommendations for the diagnosis and management of all clinical phenotypes of GSDIV were published in 2023[140]. Patients should receive a comprehensive cardiac evaluation at the time of diagnosis and longitudinal follow-up by a cardiologist[140]. Baseline testing should include measurement of NT-proBNP level, electrocardiography, Holter monitoring and CMR with contrast and echocardiography[140]. Investigations should be

repeated annually (or sooner with clinical worsening), with the exception of CMR, which should be repeated every 3–5 years[140].

A multidisciplinary team, including specialists in medical genetics, cardiology and cardiac surgery, should be consulted when considering whether to proceed with mechanical circulatory support or cardiac transplantation[140]. For patients with cardiomyopathy refractory to medical management, surgical intervention, including mechanical support and cardiac transplantation, can be considered[140]. Monitoring the progression of heart disease and comorbidities of liver and neurological disease is critical to determine the timing of cardiac transplantation[140]. Evaluation of cardiac function with CMR and echocardiography should be performed before liver transplantation, even in the absence of clinical decompensation[140]. Combined heart and liver transplantation has not yet been documented in a patient with GSDIV, but is an option for those with both HF and liver failure[140].

[H2] Glycogen storage disease type V

GSDV (McArdle disease; prevalence ~1:140,000[141]) is caused by a deficiency in the skeletal muscle-specific isoform of glycogen phosphorylase (encoded by the *PYGM* gene), which catalyses the breakdown of glycogen into glucose-1-phosphate[142]. GSDV is characterized by exercise intolerance, including early exertional fatigue, muscle weakness, myalgia and contractures[143]. These effects are often accompanied by rhabdomyolysis that, when severe, can induce life-threatening arrhythmias through hyperkalaemia due to the abrupt, excess release of potassium from muscle fibres into the bloodstream[143]. Two cases have been reported of severe rhabdomyolysis, with successful resuscitation of cardiac arrest, in patients with GSDV [144,145]. GSDV is traditionally considered to be a 'pure myopathy'[146]. Cardiac glycogen deposits and cellular histological structure were normal in a mouse model of GSDV[147], in contrast to the massive glycogen deposits found in the skeletal-muscle tissue of

these animals[148]. In addition, a study published in 2024 showed that the human adult heart expresses glycogen phosphorylase, muscle form (~11% of total glycogen phosphorylase), together with the liver and brain isoforms of this enzyme[147]. Thus, theoretically, this physiology allows for preservation of cardiac glycogen breakdown in GSDV, and is consistent with a report of normal myocardial histology in a patient with this condition[149], as well as in GSDV mice[147].

[H3] ***Case reports and cohort studies*****.** A few reports of cardiac comorbidity in patients (mostly men) with GSDV have been published[150]. For example, a 19-year-old man presented with impaired atrioventricular nodal conduction, which was initially attributed to impaired glycogen metabolism within the conduction system[151]. In addition, HCM in the setting of GSDV was reported in two men aged 33 years[152] and 69 years[153]. Although these comorbidities were unlikely to have been caused by GSDV per se (since as mentioned above glycogen breakdown and cardiac histology are thought to be essentially preserved in this condition), it is possible that severe muscular symptoms mask cardiovascular symptoms, leading to a delay in diagnosis of an eventual coexistent cardiac condition. A marked improvement in early myalgia and tachycardia after ~10 min of exercise is hallmark of GSDV[154,155]. This so-called 'second wind' occurs due to increased availability of blood-borne substrates, such as free fatty acids and glucose, which can be metabolised by skeletal myocytes, because the metabolic block occurs upstream of glucose uptake in these cells[156,157]. One unanswered question is whether the tachycardia that occurs before the second wind reflects some degree of transient cardiac dysfunction, with some patients initially referred to a cardiologist before GSDV is diagnosed. A study of eight (three female) middle-aged patients with GSDV showed lower values of LV global longitudinal strain (GLS) after moderate-intensity cycle-ergometer exercise, eliciting the second wind phenomenon, compared with

healthy age-matched and sex-matched controls[147]. Nevertheless, no between-group differences were noted in GLS at rest or immediately after maximal exertion, or in echocardiography-determined cardiac dimensions[147].

[H3] ***Management*****.** CMR or echocardiography every 5–10 years is recommended in patients with GSDV, even if a causal relationship between GSDV and cardiac involvement has not been shown[147]. Basal plasma creatine kinase level should be established as a reference point, and can be monitored to aid assessment of rhabdomyolysis[143]. Notably, an elevated creatine kinase level is not an immediate alert for a cardiac event and more-specific cardiac biomarkers should also be assed[143].

Tailored exercise is also beneficial in patients with GSDV. A systematic review of seven non-randomized studies (*n* = 34 adults) indicated that 3–5 sessions of moderate intensity (60–85% of peak heart rate) aerobic exercise per week over 4–32 weeks increased VO_{2peak} by 14–111%[87]. Other studies have shown that tailored, moderate-intensity aerobic training increases mean peak cardiac output (from 13.1 l/min to 15.0 l/min in eight patients (four female; aged 33–61 years)[158], and from 15.2 l/min to 18.9 l/min in seven patients (four female; mean age 41 years[159]). Additionally, physically active patients with GSDV experience slower disease progression, with less frequent episodes of rhabdomyolysis than their inactive peers[145]. Oral sucrose (37–150 g) 15–30 minutes pre-exercise blunts the tachycardia that precedes the second wind[156,157,160], and current clinical guidelines recommend that patients with GSDV consume carbohydrates (e.g. one can of soda or sports drink) before strenuous exercise, although not on daily basis to prevent weight gain and related health issues[143].

[H2] Glycogen storage disease type VII

GSDVII (Tarui disease) is an exceptionally rare condition with fewer than 200 cases described worldwide. The highest prevalence occurs in people of Ashkenazi Jewish descent. GSDVII is caused by deficiency in the skeletal-muscle isoform of ATP-dependent 6-phosphofructokinase (PFK-M; encoded by the *PFKM* gene), which catalyses the phosphorylation of fructose-6-phosphate to fructose-1,6-bisphosphate[143]. A *Pfkm*$^{-/-}$ mouse model showed severe respiratory muscle dysfunction and cardiomegaly, with high levels of glycogen in cardiac muscle[161]. Patients with GSDVII have severe and partial reductions in PFK-M in skeletal muscle and erythrocytes, respectively. The main disease manifestations are exercise intolerance and rhabdomyolysis, often associated with haemolytic anaemia and hyperuricaemia[143,162]. Progression of GSDVII can lead to thickening of the heart valves, potentially attributed to excess glycogen storage[163].

[H3] ***Case reports*****.** A severe, infantile disease form of GSDVII, with cardiopathy and respiratory failure leading to death in childhood, has been reported. The older of two Bedouin siblings showed 'cardiomegaly' and died at the age of 21 months[164]. However, the electrocardiographic and radiographic findings suggestive of cardiomegaly were not specified and a cardiac biopsy was not performed[164]. The patient's younger sister presented with progressive generalized muscle weakness with no cardiac manifestations on electrocardiography or chest radiography. She also died at the age of 21 months. Her heart showed a high glycogen content and a lack of PFK-M activity[164].

[H3] ***Management*****.** No specific recommendations are available for the management of cardiac sequelae in patients with GSDVII, largely due to the rarity of the disease[143]. However, as for GSDV, the basal plasma creatine kinase level should be established as a reference point and sequentially tested to identify rhabdomyolysis[143].

[H2] Glycogen storage disease type XV

GSDXV (prevalence <1:1,000,000) is caused by a deficiency in the glycosyl-transferase, glycogenin-1 (encoded by the *GYG1* gene), which catalyses the first step in glycogen synthesis[165,166]. In most patients, disease onset is late (age 20–50 years), with progressive widespread muscle weakness and wasting, but no cardiac manifestations[167-169]. A form with isolated cardiac involvement has also been reported (five male patients, aged 27–52 years) [167-169]. A histopathological hallmark of GSDXV is the presence of amylopectin-like polyglucosan bodies[165,167,168] with severe associated conditions, as summarized below. In a *Gyg1*$^{-/-}$ mouse model, most animals died shortly after birth due to cardiorespiratory failure, but no cardiac functional assessment was performed[170].

[H3] ***Case reports*****.** The first report of GSDXV was published in 2010[167]. A 27-year-old man with a history of muscle weakness presented with ventricular fibrillation and several short bursts of non-sustained ventricular tachycardia after defibrillation. He had a mild increase in LV volume and mass and a slightly decreased LVEF on CMR. The patient received an ICD and medical therapy with a β-blocker and an ACE inhibitor[167]. In a later case series of three patients with *GYG1* mutations, cardiomyopathy was described in two middle-aged men (LVEF 25-35%, with extensive LGE and regional LV wall thinning), both of whom underwent heart transplantation, and another 34-year old man with HCM and extensive LGE, but preserved LVEF who received an ICD and was under treatment with bisoprolol, spironolactone and warfarin.[168] In addition, severe LV epimyocardial and intramyocardial oedema and scarring, albeit with only slightly impaired LVEF and GLS, and cerebellar stroke has been reported in a young adult with GSDXV, who was initially diagnosed with myocarditis[169].

[H3] ***Management*****.** There is currently no specific treatment available for GSDXV[3] and no disease-specific guidelines have been published, given that only five cases of cardiac involvement have been characterized[167-169]. If GSDXV is suspected, cardiologists should ensure that *GYG1* is included in the panel selected for the genetic study[169]. Arrhythmias and HF should be managed symptomatically[169]. An ICD and pharmacological treatment with a β-blocker and an ACE inhibitor were prescribed in the index case described above[167]. ICDs have also been used in three other patients, two of whom later received heart transplants at the ages of 48 and 52 years[168].

[H1] Related diseases

Two other conditions associated with altered glycogen metabolism, but not always considered within the list of GSDs (since they are not directly due to genetic deficits in enzymes of glycogen synthesis or breakdown, or of glycolysis), can present with severe myocardial involvement — PRKAG2 cardiac syndrome and Danon disease. Of note, although there are other conditions not considered as GSDs that are also characterised by glycogen alterations, cardiac involvement is particularly remarkable (and potentially life-threatening) in PRKAG2 cardiac syndrome or Danon disease.

[H2] PRKAG2 syndrome

PRKAG2 syndrome is a rare autosomal dominant disorder caused by genetic variants in the gene encoding 5'-AMP-activated protein kinase subunit γ-2 (PRKAG2), a regulatory subunit of AMP-activated protein kinase (AMPK), which senses cellular metabolic state and regulates carbohydrate and lipid metabolism[171]. These mutations result in myocardial glycogen accumulation leading to HCM[3], progressive conduction abnormalities, such as VPE (WPW syndrome)[172-176]. Hypokinetic HCM can also be caused by the detrimental effect of

long-term RV pacing therapy[3]. The onset of cardiac manifestations usually occurs during adolescence or adulthood[3]. The true prevalence PRKAG2 syndrome is unknown, but could be present in 0.5–1.0% of patients with HCM[175,177]. Despite the rarity of this condition, patients benefit from early identification, due to the high risk of complete atrioventricular block[177,178] and SCD caused by AF and rapid antegrade conduction through an accessory pathway[179]. In this regard, HCM in patients with PRKAG2 syndrome has a similar natural history to HCM caused by sarcomere protein mutations[3]. However, PRKAG2 syndrome is often characterized by an eccentric distribution of LV hypertrophy, with CMR showing a focal mid-inferolateral pattern in the early stage of disease, and more diffuse pattern focused on the interventricular septum in advanced cases[180]. Myocardial biopsy reveals marked cardiomyocyte hypertrophy and large vacuoles with glycogen[3,181].

[H3] ***Cohort studies*****.** Several cohorts of patients with PRKAG2 syndrome from various geographical regions have been studied[182–186]. In a multicentre European cohort of 90 patients (47% female; median age 37 years), HCM was present in 67%[183]. The percentage of HCM-affected patients was higher in two other studies — 86% in 22 patients from South Asia (32% female; mean age 39)[184] and 100% in an international cohort of 25 patients (42% female; median age 37 years)[185]. VPE or accessory pathway ablation, or SCD, respectively, occurred in 33% and 8% of the multicentre European cohort[183], 67% and 17% of the international cohort[185] and 77% and 27% of the South Asian group[184]. Moreover, the incidence of SCD was 26% in a study of 66 patients (31% female) from Brazil[186]. In a French cohort of 34 patients (62% female), the probability of HCM, VPE or SCD occurring by 40 years of age was 61%, 70% and 20%, respectively[182].

[H3] ***Screening and follow-up.*** The combination of HCM and VPE, or a familial history of VPE, is highly suggestive of PRKAG2 syndrome[3,182] and should prompt next-generation sequencing or target testing for *PRKAG2* mutations. Importantly, if fasciculoventricular pathways **[G]** are detected on electrocardiography, the patient should be tested for *PRKAG2* mutations, because the long-term prognosis is much worse (possible development of complete atrioventricular block, atrial flutter or AF) than when this conduction abnormality is not linked to PRKAG2 syndrome[187]. Follow-up of patients with PRKAG2 syndrome should include annual electrocardiography, echocardiography at baseline and every 1–2 years (depending on phenotype and clinical progression), exercise stress testing to determine VO_{2peak} and the presence of arrhythmias, serum NT-proBNP measurement and Holter monitoring to stratify the risk of SCD[188].

[H3] ***Management.*** No specific treatment exists for PRKAG2 syndrome[3,64]. Standard therapy for HF is recommended where relevant, including appropriate fluid management (especially when HCM is severe), standard antiarrhythmic treatment, early consideration of pacemaker or cardioverter-defibrillator implantation and ablation of accessory atrioventricular pathways and prompt referral for heart transplantation in patients with clinical progression or end-stage HF[188].

[H2] Danon disease

Danon disease is a rare (prevalence <1:1,000,000), X-linked dominant disorder[189,190], first described in 1981 in two unrelated 16-year-old boys presenting with intellectual disability (at the time referred to as 'mental retardation'), cardiomegaly and proximal myopathy[191]. Histological findings of glycogen build-up in muscle tissue, similar to those seen in GSDII, meant that Danon disease was originally classified as a lysosomal storage disease and was

termed 'GSDIIb'[190]. However, in 2000, mutations in gene encoding the lysosome-associated membrane glycoprotein 2 (LAMP2) were identified as the cause of Danon disease[192] — the first example of human cardiomyopathy syndrome caused by alterations in a lysosomal structural protein rather than an enzyme[192].

LAMP2 is a critical component of lysosomal membranes that participate in the fusion of autophagosomes — key structures in macroautophagy. Therefore, LAMP2 deficiency leads to failure of cellular autophagy and accumulation of glycogen granules and intracytoplasmic vacuoles containing autophagic material, mainly in myocytes and cardiomyocytes[192-194]. In addition, failure to remove aged mitochondria via autophagy (also known as 'mitophagy') leads to mitochondrial dysfunction, energy deficiency and oxidative stress[3]. In advanced myocardial disease, interstitial or focal fibrosis is the most prominent feature[3].

[H3] ***Case reports and cohort studies*****.** Danon cardiomyopathy manifests as a lethal condition in the first two decades of life, characterized by marked HCM (in one 14-year-old boy, ventricular septal thickness was 65 mm, exceeding all previously reported values) and VPE, with progressive clinical deterioration leading rapidly to cardiac death before the age of 25 years[195]. Post-mortem examination of hearts from two patients with Danon disease showed massive cardiac hypertrophy (1.27 kg and 1.43 kg) with asymmetric LV wall thickening, prominent clusters of cardiomyocytes with distinctive and extensive sarcoplasmic vacuolation and inclusions of amorphous granular material in some cells within areas of scarring[195]. In 44 patients (41% female) from various geographical locations, the respective prevalence of HCM, DCM, conduction abnormalities and WPW was 33.3%, 27.3%, 80.0% and 26.7% in women, and 88.0%, 12.0%, 86.4%, 68.2% in men[196]. In general, men were more severely affected than women, being unlikely to reach the age of 25 years without heart

transplantation[196]. Combining these data with 63 other Danon disease case reports in the literature[197-209], the respective average ages of first symptom, heart transplant and death were 27 years, 33 years and 34 years in women and 12 years, 17 years and 19 years in male patients[196]. A study of 38 Japanese patients (47% female) showed that HCM was highly prevalent in young male patients (84%; mean age 17 years), whereas DCM was more prevalent in older female patients (71%; mean age 38 years)[209]. A systematic review, including 56 female and 90 male patients, demonstrated that cardiac abnormalities were present in 92.5% of patients[210]. Women tended to present with isolated cardiac disease (73% of patients) whereas Danon disease was frequently multisystemic in men (presenting as a triad of cognitive impairment, skeletal myopathy and HCM in 42% of patients) [210].

[H3] ***Screening, diagnosis and follow-up.*** Danon disease is present in a small proportion of patients included in historical HCM cohorts and has a very distinct clinical profile. Therefore, strict application of the 2014 ESC guidelines[211] or 2020 AHA/ACC guidelines[212] on HCM is unlikely to be appropriate. Neither document contain specific recommendations for the evaluation and treatment of patients with Danon disease. However, both sets of guidelines highlight the importance of clinical 'red flags' in patients with HCM that should prompt genetic testing for *LAMP2* variants (Table 2)[213].

Given that sex is a major determinant of age at disease onset, surveillance of at-risk individuals (healthy carriers of *LAMP2* mutations) differs for male and female patients[214]. Although both sexes should be screened during the first year of life, yearly multidisciplinary follow-up care is recommended thereafter in boys, whereas annual follow-up visits do not need to commence until the age of 6 years in girls[214].

An international consensus on the differential diagnosis and management of patients diagnosed with Danon disease was published in 2023[214]. The initial examination should

include assessment of both cardiac and extracardiac features[214], preferably at specialist centres where a multidisciplinary team can provide a comprehensive management strategy[214]. The following assessments should be performed at baseline evaluation and during follow-up: blood tests (creatine kinase, transaminases, NT-proBNP, troponin), electrocardiography and Holter monitoring, echocardiography and CMR[214].

[H3] ***Medical therapy.*** No therapies specific for Danon disease are currently available, although novel gene therapies are being investigated, as discussed below. A multidisciplinary approach, including cardiology, neurology, genetics, ophthalmology, rehabilitation medicine and physical therapy, should be used to alleviate the multisystem effects of the disease[214]. Clinical signs and symptoms should guide the use of medications for HF and arrhythmias, such as diuretics and antiarrhythmics, with β-blockers as first-line therapy[214]. Because cardiomyopathy in Danon disease is characterized by progressive myocardial fibrosis and eventual systolic dysfunction, therapies to attenuate cardiac remodelling (RAS inhibition and β-blockers) are often used[214]. Cardiotoxic medications and stimulants should be avoided[214].

[H3] ***Device therapy*****.** Currently available data support a low threshold for ICD use in patients with Danon disease who have severe HCM, unexplained syncope or non-sustained ventricular tachycardia[214]. A subcutaneous device should be considered in young patients who do not require pacing, to minimize the long-term risk of infection and vascular complications[214]. Patients should be advised against strenuous physical activity and competitive sports to decrease the risk of stress-provoked arrhythmia (in those without an ICD) or arrhythmic storm (in those with an ICD)[214]. A 2022 position statement from the Italian Society of Cardiology and the Italian Society of Paediatric Cardiology provides further specific recommendations for the treatment of patients with Danon disease and HCM,

specifically in relation to primary preventive implantation of an ICD, catheter ablation of atrioventricular re-entry tachycardia and consideration for cardiac transplantation[215].

[H3] ***Heart transplantation.*** A transplant might be required in patients with end-stage cardiomyopathy. Post-transplantation survival in patients with Danon disease seems to be similar to that of patients with other cardiomyopathies[216]. In the largest cohort of patients with Danon disease who underwent transplantation (n = 38, 50% female), 5-year survival was 87.1%, which supports the allocation of donor organs to this population[216]. The prognosis is particularly favourable in women[216].

[H3] ***Gene therapy.*** Cardiotropic vectors, such as adeno-associated viruses (AAV), are under investigation for GSDs and have been shown to deliver genetic material to the heart while minimizing uptake in other organs[217]. A preclinical study, in which a recombinant AAV serotype 9 vector was used to deliver a *LAMP2B* transgene (an isoform of *LAMP2*) to a mouse model of Danon disease (*Lamp2*$^{-/-}$), showed dose-dependent restoration of human LAMP2B protein in the heart, liver and skeletal muscle together with improvements cardiac function[218]. A phase 1 clinical trial has been conducted to evaluate the safety and efficacy of a single infusion of RP-A501 (an AAV serotype 9 vector containing the transgene *LAMP2B,* with a transient immunomodulatory regimen) in seven men with Danon disease[219]. In the six patients with normal baseline LVEF, cardiac LAMP2 protein expression was found, with a reduction or stabilization of LV mass, preservation of LVEF and reduction or stabilization in serum cardiac troponin I and NT-proBNP levels. At 24–54 months, all patients were alive, with complete resolution of any adverse effects[219].

[H2] Awareness of glycogen storage diseases

Early identification of disease is required for the management of cardiac sequelae in all types of GSD. However, diagnosis is often not made until many years after symptom onset. For example, the median age at diagnosis in a European registry of patients with GSDV (n = 269; 47% female) was 30 years (range 5–79, with no between-sex differences) despite symptom onset typically occurring during the first decade of life[220]. Early genetic testing, preferably with next-generation sequencing of a panel of genes associated with the various GSDs, rather than single gene testing[221], could improve diagnosis. Whole genome sequencing is increasingly available, and variant interpretation should follow expert guidelines[222]. Early cardiac assessment can also help in GSD diagnosis. Notably, HCM affects most infants with GSDII and could serve as a marker for antenatal diagnosis through fetal echocardiography[34]. HCM was detected in 0.39% of 1,268 fetuses in pregnant women referred for fetal echocardiography; three of these babies (0.24%) had postnatal confirmation of GSDII, prompting early initiation of ERT[34]. Several clues, or 'red flags', should be considered during clinical assessment to identify GSDs or related conditions (PRKAG2 syndrome and Danon disease) associated with severe cardiac disease (Table 2)[64].

Unfortunately, socioeconomic disparities present a problem in the diagnosis of GSDs, which are rarely reported in low-income countries due to a lack of genetic testing and diagnostic infrastructure. In societies where combating poverty and childhood infection is an unresolved priority, many rare conditions, even the most severe, are likely to remain unnoticed.

[H1] Conclusions

Glycogen has an important role in cardiac development and function. Therefore, some GSDs resulting in excess glycogen that cannot be metabolized (GSDII, GSDIII), in a deficit of

glycogen synthesis (GSD0b), or in the accumulation of amylopectin-like polyglucosan bodies (GSDIV, GSDXV) can have fatal cardiac consequences from early life. These disorders have diverse cardiac manifestations and outcome that reflect their differing pathophysiologies. Unfortunately, at present, little can be done to prevent infant death in the most severe forms of GSD, other than heart transplantation or ERT, with the latter only available for GSDII. Many uncertainties remain about how best to prevent or mitigate the increased risk of cardiac comorbidities, in GSDs. Early identification of these rare conditions is important, yet diagnosis is often delayed and cardiologists specializing in inherited cardiac conditions, such as HCM, should remain vigilant for undiagnosed GSDs[174]. The rarity of many of these diseases means that robust therapies are lacking, and more clinical trials are needed to address this issue. However, hope is emerging from gene therapy trials, which may help to mitigate the primary diseases, rather than manage the complications.

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Acknowledgements

R.M.C. is supported in part by the National Institute for Health and Care Research (NIHR) Leeds Biomedical Research Centre (BRC) (NIHR203331). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. Research by T.P., C.F.L. and M.A.M. is funded by the Spanish Ministry of Economy and Competitiveness and Fondos Feder (grants PI22/00201, PI21/00381, and FORT23/00023, respectively). Research by A.L. and C.F.L. is funded by Wereld Kanker Onderzoek Fonds (WKOF) as part of the World Cancer Research Fund International grant programme [IIG_FULL_2021_007]. A.L. is also affiliated to the CIBER of Frailty and Healthy Aging (CIBERFES), Instituto de Salud Carlos III, Madrid, Spain.

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T.P., R.M.C., C.F.-L., A.S.-L., J.N., N.Ø. and A.L. researched data for the article. T.P., R.M.C., A.S., C.F.-L., A.S.-L., J.N., N.Ø. and A.L. contributed to discussions of content. T.P., J.N., N.Ø. and A.L. wrote the manuscript. T.P., R.M.C., A.S., C.F.-L., M.A.M., J.A., J.N., N.Ø. and A.L. reviewed/edited the manuscript before submission.

Competing interests

R.M.C. has received speaker's fees from Janssen Oncology. The other authors declare no competing interests.

Key points

- Glycogen is needed for normal cardiac development and metabolism, but the precise expression and role of the many enzymes involved glycogen metabolism remains to be elucidated.
- Glycogen storage diseases (GSDs) are rare genetic conditions affecting both sexes caused by deficiencies of enzymes involved in glycogen synthesis or breakdown, or in glycolysis.
- Many GSDs are directly or indirectly associated with increased risk of cardiovascular disease, with a broad spectrum of clinical presentations and outcomes.
- Some GSDs manifest early in life with stereotypical features; others present later and can be confused with other disorders. Cardiologists should be vigilant for 'red flags' suggesting undiagnosed GSDs.
- Supportive cardiovascular care, ranging from routine medication to heart transplantation, is required in patients with GSDI; enzyme replacement therapy (which is available only for GSDII) can improve cardiac outcomes.
- Novel therapies are needed to improve cardiac outcomes in GSDs; gene therapies addressing underlying genetic abnormalities have shown promise in early-phase clinical trials.

Table 2 | Diagnostic features[1] and management of GSDs and related conditions

Disease; inheritance pattern	Manifestations ('red flags')	Timing of presentation	Electrocardiographic signs[2]	Echocardiographic/ CMR signs	Cardiac biopsy	SCD risk	Assessment	Treatment
GSD0b (Lewis' disease); AR	Poor exercise capacity and abnormal cardiac response to increased exercise workload in children	Childhood	NR	HCM	Glycogen depletion	Increased in children during physical exertion	No disease-specific guidelines available	No disease-specific therapy available; early consideration for an ICD
GSDI (von Gierke disease); AR	Hepatomegaly, hypoglycaemia, lactic acidaemia, hyperlipidaemia, hyperuricaemia, growth restriction, systemic arterial hypertension, PH	Childhood	NR	Signs of PH (resting mPAP >20 mmHg, but often much higher)	NR	NR	Monitoring of BP, PH, kidney function and lipid levels	No disease-specific therapy available, metabolic control (hypoglycaemia), standard management of cardiac complications
GSDIIa (Pompe disease, infantile form); AR	Hepatomegaly, increased liver enzymes, delayed motor development within the first few months of life, hypotonia, failure to thrive, generalized muscle weakness	First year of life	Possible conduction system abnormalities, short PR interval, VPE, electrocardiographic criteria for increased LV hypertrophy (usually within the first year of life) with concentric pattern followed by hypokinetic end-stage cardiomyopathy	Severe HCM (extreme concentric pattern; wall thickness >30 mm)	Microvacuolated sarcoplasm and lysosomes containing β-glycogen in in cardiomyocytes	Increased if not treated	In-depth cardiovascular follow-up	ERT, standard management of cardiac complications
GSDIIb (Pompe disease, late-onset form); AR	Severe arrhythmias, proximal muscle weakness, respiratory insufficiency, dolichoectasias in	Adolescence, adulthood	Possible increased prevalence of WPW syndrome	NR	Same as infantile form, but potentially less marked	Same risk as in the general population	Electrocardiography, chest X-ray, contrast-enhanced chest CT or MR angiography (if suspicion of dolichoectasia or the	ERT, standard management of cardiac complications, nutritional assessment, combined aerobic

	VBA, aortic aneurism, PH (rare)						ascending aorta is not visualized)	and strength training
GSDIII (Cori disease); AR	Hepatomegaly, hypoglycaemia, muscle weakness, growth restriction in children, PH (but rare)	Variable	Possibility of ventricular arrhythmias	HCM (concentric pattern),	Accumulation of 'abnormal' glycogen (limit dextrin) in cardiomyocytes	Possible increase	Echocardiography every 5 years (CMR if HCM is identified), NT-proBNP measurement to detect early HF, PH screening	No disease-specific therapy available, high-protein low carbohydrate diet
GSDIV (Andersen disease); AR	Cirrhosis, encephalopathy, myopathy	Variable	NR	DCM	Amylopectin-like polyglucosan bodies in cardiomyocytes	Possible increase	NT-proBNP measurement, electrocardiography, Holter monitoring, CMR with contrast and/or echocardiography	No disease-specific therapy available, multidisciplinary team to consider mechanical support or heart transplantation
GSDV (McArdle disease); AR	Exercise intolerance with 'second wind', increased serum creatine kinase level, episodes of severe rhabdomyolysis (dark urine)	Variable	Normal	Normal	Normal	Same risk as in the general population, severe rhabdomyolysis should be avoided due to potential risk of hyperkalaemia	Echocardiography or CMR every 5–10 years	No disease-specific therapy available, combined aerobic and strength treating, carbohydrate drink before strenuous exercise
GSDVII (Tarui disease); AR	Exercise intolerance (no 'second wind'), rhabdomyolysis, often associated with haemolytic anaemia and hyperuricaemia	Variable	NR	NR	Increased glycogen levels (more evidence is needed), no PFK-M activity	NR	NR	No disease-specific therapy available, avoid carbohydrates before strenuous exercise
GSDXV; AR	Progressive widespread muscle weakness and wasting	Adolescence, adulthood	NR	DCM or hypokinetic HCM	Deposits of amylopectin-like polyglucosan bodies	NR	NR	No disease-specific therapy available, standard management of

								cardiac complications
PRKAG2 syndrome; AD	No (or minor) myopathy, early-onset AF, high creatine kinase levels	Adolescence, adulthood	Short PR-interval, AV block	HCM (concentric pattern), global LV hypokinesia in some cases (with or without LV dilatation)	Cytosolic glycogen deposits	Increased risk	Electrocardiography (at least annually), echocardiography (every 1–2 years), exercise stress testing, NT-proBNP measurement, Holter monitoring	No disease-specific therapy available, standard treatment for HF and arrhythmias, ablation of accessory AV pathway, early consideration for pacemaker or ICD, heart transplant in the most severe cases
Danon disease; X-linked dominant	Skeletal myopathy, intellectual disability, high creatine kinase level, greater extracardiac manifestation in male than in female patients	First two decades of life	Short PR-interval/VPE, AV block, voltage criteria for extreme LV hypertrophy	HCM (extreme concentric pattern, wall thickness >30 mm), possible hypokinetic HCM, extensive LGE	Accumulation of glycogen granules and intracytoplasmic vacuoles containing autophagic material	Increased risk	Measurement of creatine kinase, transaminases, NT-Pro-BNP and cTnI (annually), electrocardiography, Holter monitoring (every 6–12 months), echocardiography (annually), CMR (every 2–3 years).	No disease-specific therapy available (gene therapy trials are ongoing), ICD in severely affected patients, subcutaneous device in young individuals not requiring pacing

[1]The described phenotypes are not seen in all patients; the table reflects the most commonly reported findings. [2]In general, a short PR-interval or VPE should raise suspicion for a 'classic' GSD, whereas AV block suggests PRKAG2 syndrome or Danon disease. AD, autosomal dominant; AF, atrial fibrillation; AR, autosomal recessive; AV, atrioventricular; BP, blood pressure; CMR, cardiac MRI; cTnI, cardiac troponin I; DCM, dilated cardiomyopathy; ERT, enzyme replacement therapy; GSD, glycogen storage disease; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LV, left ventricle; mPAP, mean pulmonary arterial pressure; NR, not reported; NT-proBNP, N-terminal pro B-type natriuretic peptide; PFK-M, ATP-dependent 6-phosphofructokinase, muscle type; PH

pulmonary hypertension; PRKAG2, 5'-AMP-activated protein kinase subunit γ-2; SCD, sudden cardiac death; VBA, vertebrobasilar arteries; VPE; ventricular pre-excitation.

Table 1 | Ongoing clinical trials targeting cardiac outcomes in GSDs and related conditions.

ClinicalTrials ID; Title (country)	Design	Participants age and sex	Main study aim(s)	Cardiac outcome(s)	Follow-up
GSDII (Pompe disease)					
NCT00701701; Immune tolerance induction study (USA)	Non-randomized, open label	≥1 month (children and adults); female and male	Efficacy, safety and clinical benefit of two ITI regimens (cyclophosphamide or rituximab + methotrexate) in combination with myozyme[1] (alglucosidase alfa)	LVM (Z-score), LVMI	18 months
NCT05793307; Evaluation of the safety and efficacy of infantile-onset Pompe disease gene therapy drug (China)	Non-randomized, open label	<6 months; female and male	Safety and effectiveness of GC301, an AVV expressing codon-optimized human *GAA*	BNP, CK-MB, cTnI, LVM, LVMI	26 and 52 weeks
NCT05567627; Clinical exploration of AAV expressing human *GAA* gene therapy for patients with infantile-onset Pompe disease (China)	Non-randomized, open label	≤6 months; female and male	Safety and effectiveness of GC301, an AAV expressing codon-optimized human *GAA*	LVM	26 and 52 weeks
NCT04848779; A prospective study to observe and describe clinical outcomes of alglucosidase alfa treatment in patients ≤6 months of age with infantile-onset Pompe disease (USA)	Prospective	≤6 months; female and male	Effect of routine treatment with alglucosidase alfa in patients with infantile-form GSDII on invasive, ventilation-free survival	LVM (Z-score), number of participants with electrocardiographic abnormalities	52 and 104 weeks
NCT05164055; Avalglucosidase alfa French post-trial access for participants with Pompe disease (PTA avalglucosidase) (France)	Single group, open label	≥6 months (children and adults); female and male	To follow up, and provide post-trial access to ERT with avalglucosidase alfa to patients with GSDII	LVMI (Z-score) in infant patients	Every 6 months up to 2.5 years
NCT06666413; China post-approval	Single group, open label	<18 years; female and male	Safety and efficacy of avalglucosidase alfa intravenous	LV mass (Z-score)	52 weeks

commitment (PAC) study of avalglucosidase alfa in participants with IOPD (China)			infusion in participants with infantile-onset GSDII		
NCT04910776; Clinical study for treatment-naïve IOPD babies to evaluate efficacy and safety of ERT with avalglucosidase alfa (Baby-COMET) (USA)	Single group, open label	≤12 months; female and male	Efficacy, safety, pharmacokinetics and pharmacodynamics of avalglucosidase alfa in treatment-naïve patients with infantile-onset GSDII	LVM (Z-score), number of participants with clinically significant electrocardiographic abnormalities	52 and 208 weeks
Danon disease					
NCT06092034; A gene therapy study of RP-A501 in male patients with Danon disease (USA)	Single group, open label	≥8 years; male	Efficacy and safety of RP-A501, a recombinant AAV9 containing the human *LAMP2* isoform B transgene	LVMI, hs-cTnI and NT-proBNP levels, event-free survival (events include heart transplant and HF hospitalization)	12 and 60 months

[1]Sanofi S. A. (Genzyme Corporation). AAV, adeno-associated virus; BNP, brain natriuretic peptide; CK-MB, creatine phosphokinase MB; cTnI, cardiac troponin I; GAA, lysosomal alpha-glucosidase; GSD, glycogen storage disease; ERT, enzyme replacement therapy; HF, heart failure; hs-cTnI, high-sensitivity cardiac troponin I; ITI, immune tolerance induction; LAMP2, lysosome-associated membrane glycoprotein 2; LVM, left ventricle mass; LVMI, left ventricular mass index; NT-ProBNP, N-terminal pro B-type natriuretic peptide.

Fig. 1 | Glycogen storage diseases and related conditions. The deficiencies (or alterations in activity) of enzymes or structural proteins in glycogen storage diseases (GSD) and related conditions are shown. Genetic variations lead to glycogen deficiency in the heart (GSD0b) or to excess accumulation of normal glycogen (GSDII, GSDV, GSDVII, PRKAG2 and Danon disease) or 'abnormal' glycogen (limit dextrin (GSDIIIa), amylopectin-like polyglucosan bodies (GSDIV and GSDXV)). Glycogen accumulation can occur in cardiac cells (infantile-onset GSDII, GSDIIIa, GSDIV, possibly GSDVII and GSXV) and in extracardiac cells (liver, kidney, intestinal mucosa (GSDI) or skeletal-muscle (GSDV)). Extracardiac glycogen deposits can indirectly affect the cardiovascular system (e.g. the pulmonary vessels (GSDI) or rhabdomyolysis-induced hyperkalaemia (GSDV)). AMPK, AMP-activated protein kinase; G6Pc, glucose-6-phosphatase, catalytic subunit; LAMP2, lysosome-associated membrane glycoprotein 2; P, phosphorylation; PFKM, ATP-dependent 6-phosphofructokinase, muscle type; PPi, pyrophosphate; PRKAG2, 5'-AMP-activated protein kinase subunit γ-2; SLC37A4, glucose-6-phosphate exchanger SLC37A4 (also known as G6PT); UDP, uridine diphosphate; UTP, uridine triphosphate.

Fig. 2 | The structure and functions of glycogen in the heart. In healthy cardiomyocytes, glycogen granules (glucose polymers with hundreds of α-1,4 and α1–6 glycoside linkages, with the latter creating a more compact, branched structure) are stored in the subsarcolemmal, perinuclear, intermyofibrillar and intramyofibrillar areas of the cytosol. An alternative to cytosolic storage of glycogen, glycopaghy, involves the lysosomes. Glycophagy is upregulated in some glycogen storage diseases (GSD), such as the infantile-onset form of GSDII (Pompe disease). In the cytosol, glycogen is degraded by glycogen debranching enzyme, which hydrolyses α1–6 glycoside linkages to leave the short outer glycogen branches (also known as 'limit dextrin') and by glycogen phosphorylase, which removes 1,4-α-glucosyl units from the outer branches to release glucose 1-phosphate. In the lysosomes, lysosomal α-glucosidase catalyses the cleavage of both α-1,4 and α-1,6-glycosidic bonds. Glycogenolysis-derived ATP (especially from subsarcolemmal depots) is crucial for fuelling membrane (sarcolemma)-bound pumps (sodium–potassium and sarcoplasmic reticulum (SR) calcium-ATPases, SERCA), ensuring basic cellular functions. Additionally, glycogenolytic ATP is needed not only to break the myosin–actin cross-bridge in myofibrils (freeing the myosin for the next contraction), but also to ensure intracellular calcium homeostasis in the context of contraction–relaxation cycles. The release of calcium from the SR through ryanodine receptors triggers myofibril contractions, whereas ATP-dependent reuptake of calcium back into the SR (through SERCA) is needed during relaxation.

Box 1 | The discovery of glycogen and glycogen storage diseases

In 1857, Claude Bernard communicated the isolation of glycogen from liver tissue and the chemical/physical properties of the isolated substance[223]. The next milestone, as well as many other discoveries in the history of glycogen metabolism, was achieved by the Coris — the husband and wife Carl and Gerty. In 1929, they proposed the theoretical cycle that later won

them the Nobel Prize, the Cori cycle (wherein lactic acid released by mammalian muscles is largely reconverted into liver glycogen under the influence of hormones, including the newly discovered insulin)[224]. In that same year, the German pathologist von Gierke described the first GSD (GSDI, von Gierke disease) after reviewing the autopsy reports of two children whose livers and kidneys contained excessive glycogen amounts[225] while another researcher, Schoenheimer, demonstrated that the glycogen isolated from the liver of von Gierke's original case showed the same structural characteristics as normal glycogen but was unable to be degraded, as opposed to minced normal human liver[226]. Schoenheimer thus concluded that the enzyme/s that degrade liver glycogen to glucose is/are absent in GSDI.

In 1952, the Coris reported six patients with GSDI and discovered that it was the absence of the hepatic enzyme glucose-6-phosphatase that caused this condition[227], thereby establishing the first metabolic disorder in which an enzyme defect was identified. Furthermore, two and six patients showed essentially total enzyme deficiency or normal activity, respectively, prompting the authors to recognise the phenotype variability of GSDs[227]. Two decades before, a Dutch pathologist, Pompe, had described the case of a 7-month-old baby who died of idiopathic cardiac hypertrophy and showed generalised muscle weakness as well as massive 'vacuolar' glycogen storage in virtually all tissues at post-mortem examination[228]. Similar cases were reported by others in the same[229,230] and following years[228]. In 1954, Pompe disease was classified as GSDII by G. Gori to reflect the abnormal glycogen metabolism[231]. However, at that time, the cause of the disease, the 'vacuolar' nature of the storage, as well as the apparently normal molecular structure of the accumulated glycogen remained a mystery[228]. The connection between lysosomes, the enzyme defect, and GSDII was solved in 1963 by a Belgian biochemist, Hers, who discovered a new enzyme, maltase, which catalyses the hydrolysis of glycogen to glucose and was absent in the patients[232]. He also realised that his new enzyme resides in the lysosomes,

being the only glycogen-degrading enzyme present in these organelles[228]. In earlier years the Coris had discovered a new sugar phosphate ester, glucose 1-phosphate, the product of the glycogen breakdown by an enzyme that is present in mammalian muscle and acts in the presence of inorganic phosphate, phosphorylase (or myophosphorylase)[233]. Many other glycolytic enzymes were subsequently purified by the Coris and collaborators who came to their laboratory, and some were crystallised with the expert guidance of Arda Green, a protein chemist who joined them in 1942[224].

The potential cardiac involvement in GSDs other than GSDII has been traditionally less studied in light of the more common liver and muscle-related symptoms. Thanks to advances in genetics, in the nineties scientists became progressively able to manipulate the mouse genome, with the subsequent arrival of transgenic (knockout) mice[234]. The first GSDII knockout mouse model—which showed cardiomegaly and was developed to test gene/molecular therapies—was reported in 1998[235]. This represented an important advancement as naturally-occurring animal models of GSDII—and of GSDs in general—are less suitable for preclinical research because of the physical dimension of the animal, the long generation time and the small litter size (e.g. cattle)[236] or the evolutionary distance from humans (e.g. quail)[237].

Box 2 | Cardiac glycogen

In the adult heart under normal physiological conditions, lipids serve are the primary substrates[238], whereas glycogen becomes a more prominent fuel with increasing cardiac load (e.g. adrenergic stimulation[239] or exertion[240,241]) and is critical for cell survival during ischaemia[242,243]. Cardiomyocyte glycogen content averages 80–100 mmol·kg^{-1} dry weight in mammals[244] (~2% of the cell volume in adults[245]), and research in mice shows a much lower (~50%) content in females than in males[246]. Cardiac glycogen content is dynamic, markedly decreasing with higher workloads or physical exercise[247], and increasing after prolonged fasting[248] or in post-exercise recovery[249]. Particularly high glycogen levels are found in animals adapted to hypoxia[250], in patients with diabetic cardiomyopathy[251] and in newborn babies (30% of cardiomyocyte volume[245]). Cardiac glycogen is present at high levels during early-to-mid gestation before falling to lower levels at birth[252,253], suggesting a specific role in embryonic development.

Glycogen can be degraded both in the cytosol and in the lysosomes (see also Fig. 2)[254]. Although the cytosolic pathway is considered quantitatively the most important, the lysosomal pathway is needed for the turnover of glycogen during myocardial metabolic stress (e.g. ischaemia, diabetic cardiomyopathy)[251,255,256] or in infants with glycogen storage disease (GSD) type II (Pompe disease)[257]. Transmission electron microscopy has revealed heterogeneous intracellular localization and utilisation of the glycogen granules within mammalian (rodent) cardiomyocytes[258] (see the figure). Although glycogen concentration is comparable in mammalian heart and skeletal muscle[244], the distribution differs. For example, 60–80% of rat skeletal-muscle glycogen is stored in the intermyofibrillar region[259], whereas the glycogen content in the subsarcolemmal region of cardiomyocytes is higher than in the myofibrillar regions, correlating with higher energy delivery to active ion exchange across the sarcolemma than in skeletal-muscle fibres[260]. Indeed, during myocardial ischaemia,

glycogen depletion predominantly occurs in the subsarcolemmal region, demonstrating that various glycogen localizations serve different energy requirements[242,258]. The individual glycogen granules have autonomous metabolic machinery, with functional compartmentalization of oxidative and glycolytic metabolism[242,261,262]. Notably, in the isolated perfused rat heart, glycolytically-produced ATP preserves action potential and membrane integrity during ischaemia[263]. A clear subcellular link exists between key glycolytic enzymes and membrane-bound pumps — sarcolemmal sodium-potassium ATP-ases[264-266] and sarcoplasmic reticulum calcium-ATPases[267-270] — as well as between glycolytic intermediates and calcium release by sarcoplasmic reticulum ryanodine receptors[270].

Transmission electron micrographs of glycogen in rat cardiomyocytes and skeletal myocytes. a,b, Subsarcolemmal region of adult rat cardiomyocytes and skeletal muscle fibres, respectively, showing glycogen granules (black dots), which are more abundant in cardiomyocytes. **c,d,** Myofibrillar region of adult rat cardiomyocytes and skeletal myocytes, respectively, where glycogen granules (black dots) are less prominent in cardiomyocytes. **e,f,** Neonatal rat cardiomyocytes (subsarcolemmal and myofibrillar regions, respectively) exhibiting more extensive glycogen stores than adult cardiomyocytes (as shown in panels **a** and **c**, respectively).**g,h** Adult GSDII (*Gaa*$^{-/-}$) mouse cardiomyocytes showing extensive glycogen stores in the myofibrillar regions. Scale bar = 500 nm. ID, intercalated disc; M, mitochondrion; PM, plasma membrane (also known as the sarcolemma); SR, sarcoplasmic reticulum; Z, Z-discs. Samples for Panels **a**–**d, g and h** were prepared ad hoc for this Review, using optimal contrast of glycogen granules as previously described by the authors for cardiomyocytes[242] and skeletal myocytes[259]. Panels **e** and **f** courtesy of Dr Kimberley M. Mellor.

Glossary terms

Amylopectin-like polyglucosan bodies

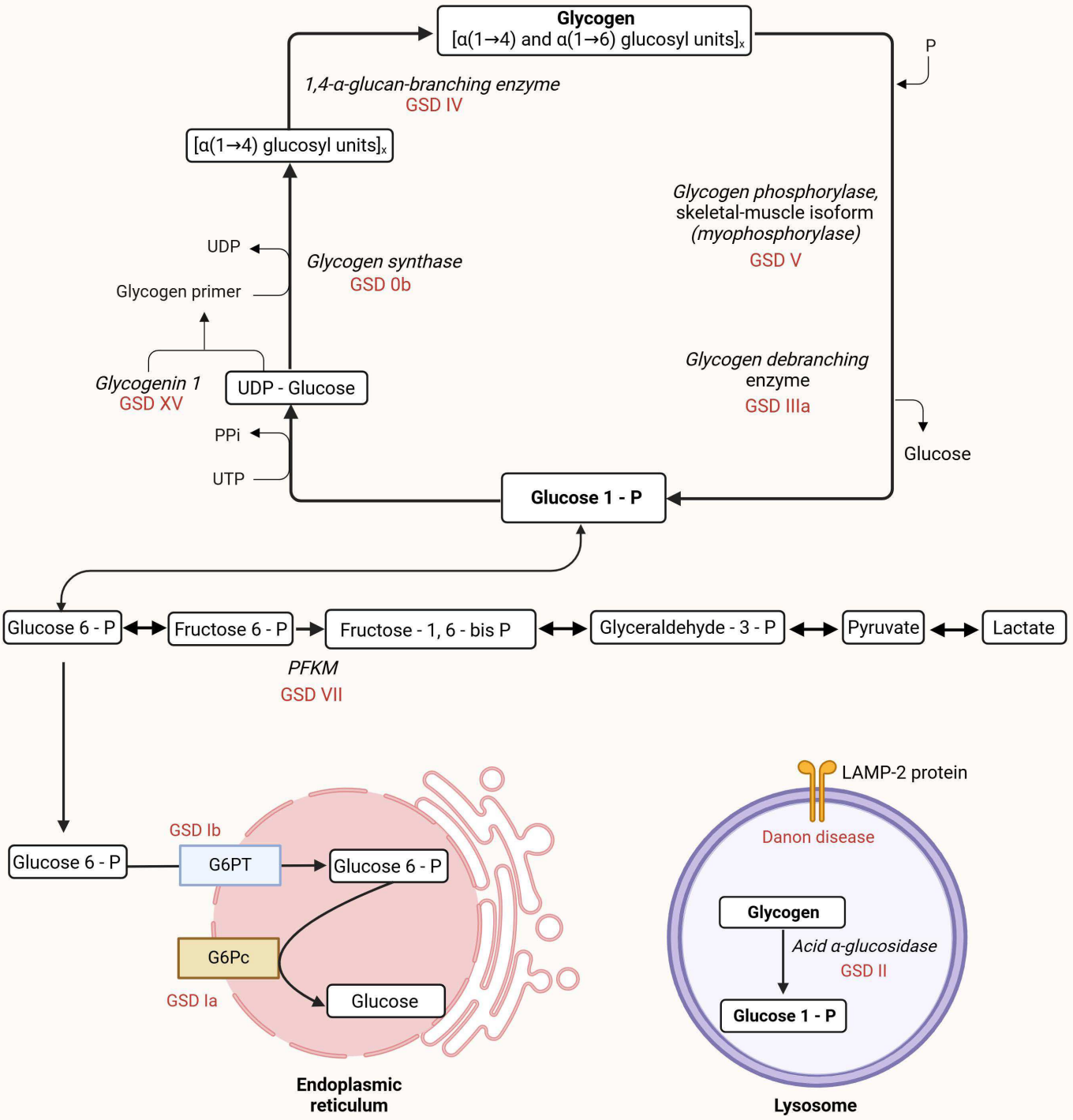
Aberrant glucose polymers that differ in structure and appearance to glycogen and are less soluble. They accumulate in tissues and are a common feature of some GSDs (IV, XV), neurodegenerative diseases and physiological aging.

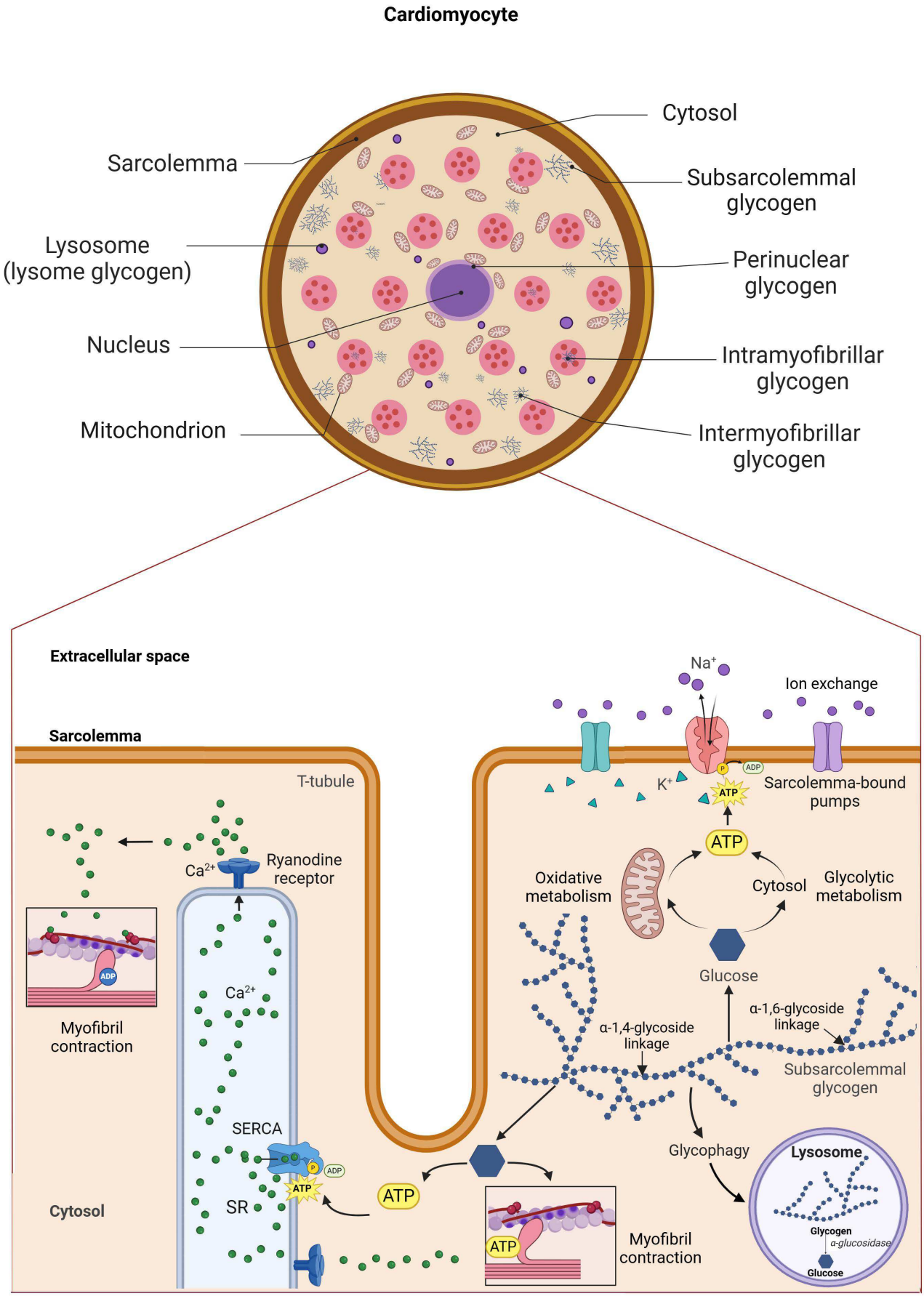
Fasciculoventricular pathways

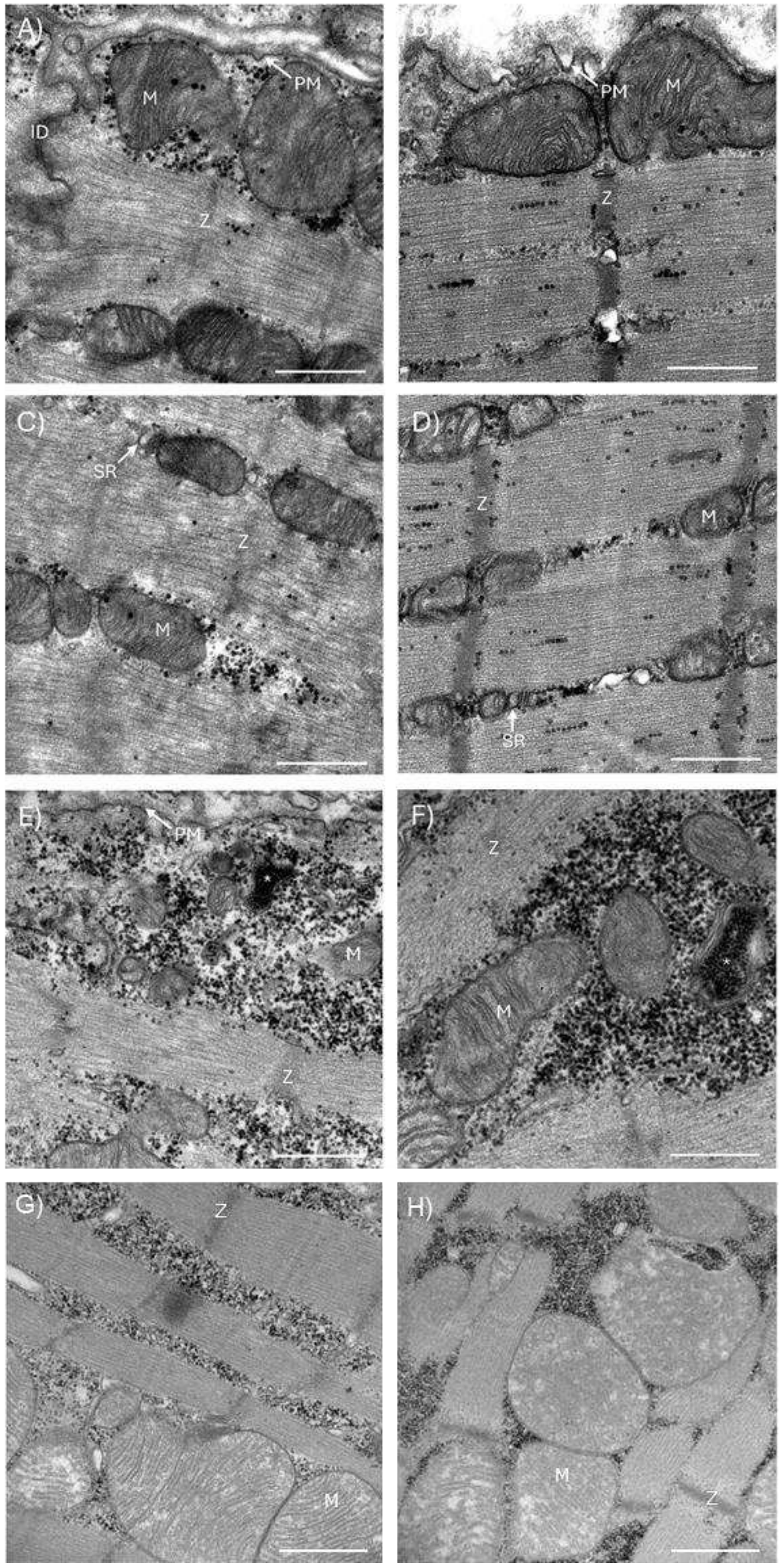
Uncommon pre-excitation variants characterized by accessory connections between the bundle of His and the ventricles.

Limit dextrins

When a branched polysaccharide (such as glycogen) is hydrolysed enzymically, glucose units are removed one at a time until a branch point (i.e. limit dextrin) is reached. Further hydrolysis requires a different enzyme, glycogen phosphorylase.


Extracellular space
Membrane
Cytosol
Glycogen
[α(1→4) and α(1→6) glucosyl units]x
P
1,4-α-glucan-branching enzyme
GSD IV
[α(1→4) glucosyl units]x
Glycogen phosphorylase, skeletal-muscle isoform (myophosphorylase)
GSD V
UDP
Glycogen synthase
GSD 0b
Glycogen primer
Glycogenin 1
GSD XV
UDP - Glucose
Glycogen debranching enzyme
GSD IIIa
PPi
UTP
Glucose
Glucose 1 - P
Glucose 6 - P
Fructose 6 - P
Fructose - 1, 6 - bis P
Glyceraldehyde - 3 - P
Pyruvate
Lactate
PFKM
GSD VII
GSD Ib
Glucose 6 - P
G6PT
Glucose 6 - P
G6Pc
GSD Ia
Glucose
Endoplasmic reticulum
LAMP-2 protein
Danon disease
Glycogen
Acid α-glucosidase
GSD II
Glucose 1 - P
Lysosome
α
γ
β
PRKAG2
Altered AMPK activity
Glycogen synthase
↑ Glycogen storage


Cardiomyocyte
Cytosol
Sarcolemma
Subsarcolemmal glycogen
Lysosome (lysome glycogen)
Perinuclear glycogen
Nucleus
Intramyofibrillar glycogen
Mitochondrion
Intermyofibrillar glycogen
Extracellular space
Sarcolemma
T-tubule
Na+
Ion exchange
K+
ADP
ATP
Sarcolemma-bound pumps
Ca2+
Ryanodine receptor
Oxidative metabolism
Cytosol
Glycolytic metabolism
Glucose
α-1,6-glycoside linkage
α-1,4-glycoside linkage
Subsarcolemmal glycogen
Myofibril contraction
SERCA
SR
Cytosol
Glycophagy
Lysosome
Glycogen
α-glucosidase
Glucose
Myofibril contraction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