



Left Ventricular Hypertrophy with Ventricular Pre-Excitation: Distinguishing Sarcomeric Hypertrophic Cardiomyopathy from Genetic and Metabolic Phenocopies

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Abstract

Left ventricular hypertrophy (LVH) accompanied by a short PR interval or ventricular pre-excitation should prompt consideration of diagnoses beyond conventional sarcomeric hypertrophic cardiomyopathy (HCM). This critical review examines the clinical, electrophysiologic, imaging, biochemical, genetic, and mechanistic features that distinguish sarcomeric HCM from PRKAG2 cardiomyopathy, Danon disease, and selected Fabry and Pompe disease phenocopies. Particular emphasis is placed on defining the electrical phenotype because a short PR interval, a true atrioventricular accessory pathway, and a fasciculoventricular pathway are not interchangeable findings. PRKAG2 cardiomyopathy combines autosomal dominant cardiac glycogenosis with variable hypertrophy, pre-excitation, atrial arrhythmias, and progressive conduction disease; emerging preclinical data also suggest early glycogen-independent AMPK γ 2-myosin and calcium-handling abnormalities. Danon disease, caused by LAMP2 deficiency, is an aggressive X-linked cardioskeletal disorder in which fasciculoventricular and true atrioventricular accessory pathways may coexist, and phase 1 AAV9-LAMP2B gene-replacement data have now been reported. Cardiovascular magnetic resonance can refine the differential, including histologically validated low native T1 as a marker of myocardial glycosphingolipid accumulation in Fabry disease. A practical diagnostic strategy integrates the ECG mechanism, pedigree, extracardiac phenotype, echocardiography, cardiovascular magnetic resonance, disease-directed biochemical testing, genetic confirmation, and electrophysiology when pathway mechanism or risk remains uncertain. Correct molecular diagnosis directly changes surveillance, family screening, treatment, and advanced heart-failure planning.

Keywords: Danon disease; Fabry disease; fasciculoventricular pathway; hypertrophic cardiomyopathy; left ventricular hypertrophy; Pompe disease; PRKAG2 cardiomyopathy; ventricular pre-excitation; Wolff-Parkinson-White syndrome.

Introduction and Clinical Significance

Hypertrophic cardiomyopathy (HCM) is a heterogeneous myocardial disorder defined by left ventricular hypertrophy (LVH) that is not solely explained by abnormal loading conditions. In many patients, HCM reflects pathogenic variation in genes encoding proteins of the cardiac sarcomere, most commonly inherited in an autosomal dominant pattern. Contemporary guidelines therefore place sarcomeric disease at the center of the diagnostic framework while emphasizing that several genetic, metabolic, and storage

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disorders can reproduce an HCM-like phenotype. These phenocopies are clinically important because their natural history, extracardiac manifestations, inheritance patterns, arrhythmic risks, and disease-specific therapies can differ substantially from those of conventional sarcomeric HCM [1,2]. Among the most useful clues to an alternative diagnosis are electrocardiographic abnormalities that appear disproportionate to, or atypical for, conventional HCM. A short PR interval, ventricular pre-excitation, progressive conduction disease, or unusual combinations of bradyarrhythmia and tachyarrhythmia should prompt consideration of a nonsarcomeric disorder. The 2023 European Society of Cardiology cardiomyopathy guideline specifically identifies short PR interval or pre-excitation as a diagnostic red flag for glycogen-storage disorders, Danon disease, PRKAG2 cardiomyopathy, Anderson-Fabry disease, and mitochondrial disease [2]. The 2024 AHA/ACC multisociety HCM guideline similarly recommends consideration of phenocopy genes, including PRKAG2, LAMP2, and GLA, when the clinical phenotype suggests a systemic or nonsarcomeric disorder [1]. The association between LVH and pre-excitation is particularly relevant because it enriches the differential diagnosis for glycogen-storage and lysosomal disorders. In a selected series of 24 patients with increased LV wall thickness and electrocardiograms suggestive of ventricular pre-excitation, Arad and colleagues identified pathogenic variants in PRKAG2 in 7 patients and LAMP2 in 4 patients [3]. In contrast, neither gene was identified in a separate group selected for massive hypertrophy without electrophysiologic abnormalities. In this enriched cohort, ventricular pre-excitation substantially increased the yield of LAMP2 and PRKAG2 testing, supporting its use as a phenotypic red flag rather than a diagnostic endpoint [3].

Recent clinical reports continue to illustrate this diagnostic challenge. Patients with PRKAG2 cardiomyopathy may present with an apparent HCM phenotype, ventricular pre-excitation, conduction disease, and even dynamic left ventricular outflow tract obstruction, closely resembling conventional HCM [4]. Conversely, not every patient with PRKAG2 or Danon disease demonstrates classic pre-excitation, and not every short PR interval reflects a conventional atrioventricular accessory pathway. The clinician must therefore distinguish the myocardial phenotype from the electrophysiologic mechanism rather than treating “LVH with pre-excitation” as a single diagnosis.

This review critically examines LVH accompanied by ventricular pre-excitation or related conduction abnormalities, with emphasis on distinguishing sarcomeric HCM from PRKAG2 cardiomyopathy, Danon disease, and selected metabolic or storage phenocopies. We integrate clinical presentation, electrocardiography, electrophysiology, cardiac imaging, biochemical and genetic testing, natural history, and

management. A central objective is to clarify when apparent pre-excitation represents a true atrioventricular accessory pathway, a fasciculoventricular connection, or accelerated conduction without a conventional accessory pathway, because this distinction may alter both risk assessment and treatment.

Literature Search Strategy

A structured literature search was performed for this critical narrative review. PubMed and Ovid Embase were searched in October 2026 using title/abstract terms combining hypertrophic cardiomyopathy or left ventricular hypertrophy with pre-excitation, Wolff-Parkinson-White syndrome, short PR interval, PRKAG2, LAMP2/Danon disease, Fabry disease, Pompe disease, conduction disease, accessory pathways, and electrophysiology. Six formal PubMed searches yielded 1,961 raw records and 1,568 unique records after PMID deduplication. Two formal Ovid Embase searches yielded 754 raw records and 565 unique records after within-database deduplication; records were then compared with the PubMed corpus to identify Embase-unique candidates. Two Cochrane Library searches identified one CENTRAL trial record and one Cochrane Review, neither of which added core evidence for the review question. The working search window was January 2000 through October 2026; older seminal studies were retained through backward citation chasing. Studies were prioritized when they provided original genetic, natural-history, electrophysiologic, imaging, mechanistic, diagnostic, or treatment data directly relevant to LVH with pre-excitation or its major phenocopies. Guidelines and consensus statements were used for contemporary diagnostic and management context. Redundant reports, noncardiac literature, generic Wolff-Parkinson-White studies without a relevant cardiomyopathy phenotype, and case reports without a distinct mechanistic or diagnostic contribution were deprioritized. Backward and forward citation chasing was completed for 10 anchor papers. Because the review was designed as a critical narrative synthesis rather than a systematic review, no PRISMA flow diagram or formal risk-of-bias instrument was applied.

Etiologies and Differential Diagnosis

Sarcomeric hypertrophic cardiomyopathy

Sarcomeric HCM remains the principal comparator for any patient with otherwise unexplained LVH. Strong-evidence HCM genes include MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, and ACTC1, and inheritance is most often autosomal dominant [1]. The phenotype may include asymmetric or concentric hypertrophy, dynamic left ventricular outflow tract obstruction, myocardial fibrosis, atrial and ventricular arrhythmias, and sudden cardiac death risk. Ventricular pre-excitation, however, is not a characteristic

feature of sarcomeric HCM. Its presence—particularly when accompanied by marked conduction disease, an unusual pedigree, extracardiac manifestations, or very early disease onset—should lower the threshold for phenocopy evaluation rather than being automatically attributed to coincidental Wolff-Parkinson-White syndrome (Table 1).

The distinction is probabilistic rather than absolute. A patient with sarcomeric HCM may also have an accessory pathway, and a patient with a metabolic phenocopy may lack pre-excitation. The diagnostic value of pre-excitation therefore lies in how it changes the pretest probability of alternative disease, not in its ability to establish a diagnosis by itself.

PRKAG2 cardiomyopathy

PRKAG2 cardiomyopathy is an autosomal dominant disorder caused by pathogenic variants in PRKAG2, which encodes the $\gamma 2$ regulatory subunit of AMP-activated protein kinase (AMPK). Familial linkage studies first established PRKAG2 as a cause of inherited ventricular pre-excitation accompanied by cardiac hypertrophy and conduction abnormalities [5]. The disorder is now recognized as a cardiac glycogen-storage cardiomyopathy with substantial phenotypic heterogeneity (Table 1). The largest contemporary multicenter cohort demonstrates why the classic triad of LVH, pre-excitation, and conduction disease should be viewed as a suggestive pattern rather than a mandatory diagnostic combination. Among 90 PRKAG2-variant carriers, LVH was present in 67%, ventricular pre-excitation or prior accessory-pathway ablation in 33%, permanent pacing in 19%, and atrial fibrillation in 18% at baseline [6]. Earlier and complementary longitudinal cohorts likewise demonstrate high age-dependent burdens of pre-excitation, conduction disease, pacing, heart failure, and sudden death, while emphasizing substantial family- and variant-level heterogeneity [7-9]. Clinically, PRKAG2 should be considered when LVH occurs in an autosomal dominant pedigree together with ventricular pre-excitation, unexplained bradycardia, sinus-node dysfunction, atrioventricular block, or early atrial arrhythmia. Cardiac imaging may closely mimic sarcomeric HCM, including asymmetric hypertrophy and, in selected cases, dynamic outflow obstruction. This overlap reinforces the need to integrate ECG, pedigree, imaging, and genetic data rather than relying on myocardial morphology alone.

Danon disease

Danon disease is an X-linked disorder caused by pathogenic variants in LAMP2. Primary LAMP-2 deficiency was established as the molecular basis of this autophagic vacuolar cardioskeletal myopathy in foundational genetic and pathologic studies [10]. It is among the most severe inherited cardiomyopathies that can mimic HCM, particularly in younger patients.

Cardiac disease is often accompanied by skeletal myopathy, cognitive or developmental abnormalities, retinal disease, and elevated creatine kinase or transaminase levels, although women may present with predominantly cardiac disease [7,25]. The cardiac phenotype is strongly influenced by sex and age. Males commonly develop severe hypertrophic cardiomyopathy early in life with rapid progression toward advanced heart failure, whereas females tend to present later and may develop either hypertrophic or dilated remodeling. The 2025 International Danon Disease Registry, including 116 patients, confirmed earlier presentation and more progressive hypertrophy and heart failure in males while identifying a clinically important subset of females with severe early disease [25]. A small prospective male cohort subsequently provided complementary longitudinal evidence of progressive cardiac remodeling and declining function [26]. Pre-excitation is a major diagnostic clue but is electrophysiologically heterogeneous. Danon disease may involve fasciculoventricular pathways, conventional or extranodal atrioventricular accessory pathways, or both. This distinction is clinically important because fasciculoventricular pathways are generally benign, whereas atrioventricular accessory pathways may conduct rapidly and participate in reentrant tachycardia. The coexistence of both mechanisms in the same patient means that a delta wave should not be assumed to represent a benign fasciculoventricular connection (Table 1).

Other metabolic and storage phenocopies

Fabry disease and Pompe disease are useful comparators because both can produce LVH and abnormalities of atrioventricular conduction, yet the electrophysiologic substrate differs from the conventional accessory-pathway model. Fabry disease is an X-linked lysosomal disorder caused by reduced or absent α -galactosidase A activity with glycosphingolipid accumulation in multiple organs, including the myocardium [2]. Cardiac involvement may include LVH, fibrosis, conduction disease, and arrhythmia. A short PR interval can occur, but it should not automatically be interpreted as ventricular pre-excitation. Electrophysiologic observations have demonstrated accelerated atrioventricular and His-Purkinje conduction without a true accessory pathway in at least some patients [22]. CMR can provide an additional diagnostic clue because reduced native myocardial T1 may precede overt LVH, with newer biopsy-correlated data supporting an inverse relationship between native T1 and myocardial glycosphingolipid burden [21,23]. Pompe disease results from acid α -glucosidase deficiency and lysosomal glycogen accumulation. The infantile form can cause massive hypertrophic cardiomyopathy, high ECG voltages, and a short PR interval in association with skeletal myopathy and hypotonia [24]. In a cohort of infants treated with recombinant human acid α -glucosidase,

enzyme replacement was accompanied by lengthening of the PR interval and reductions in LV voltage and LV mass, supporting a relationship between metabolic substrate and the cardiac electrical phenotype [24]. The mechanism of PR shortening in Pompe disease, however, should not be assumed to be identical to a conventional atrioventricular accessory pathway. Other conditions—including mitochondrial disorders and additional syndromic cardiomyopathies — may also produce combinations of LVH and conduction abnormalities. They remain part of the broader differential diagnosis, but PRKAG2 cardiomyopathy and Danon disease warrant particular emphasis when genuine ventricular pre-excitation accompanies an HCM-like phenotype because of their strong and repeatedly observed association with this presentation (Table 1) [2,3].

Cellular and Molecular Mechanisms

Sarcomeric HCM as the mechanistic comparator

Sarcomeric HCM arises from pathogenic variation in proteins of the cardiac contractile apparatus. The resulting disturbance in sarcomere function initiates a complex remodeling program involving cardiomyocyte hypertrophy, altered energetics, myofibrillar disarray, and interstitial fibrosis. These changes can produce the familiar HCM phenotype of increased wall thickness, diastolic dysfunction, dynamic obstruction, and arrhythmogenic substrate. Importantly, this mechanism is fundamentally different from the intracellular storage and autophagic defects that characterize PRKAG2 cardiomyopathy, Danon disease, Fabry disease, and Pompe disease. The shared endpoint of increased LV wall thickness can therefore obscure very different cellular diseases.

PRKAG2: altered AMPK signaling, glycogen accumulation, and pre-excitation

PRKAG2 encodes the $\gamma 2$ regulatory subunit of AMPK, a central sensor of cellular energy status. Human genetic and pathologic studies established PRKAG2 cardiomyopathy as a glycogen-storage disease with myocyte enlargement and vacuolar glycogen accumulation distinct from conventional sarcomeric HCM [27]. Disease-associated PRKAG2 variants alter AMPK signaling and myocardial glucose/glycogen handling, producing intracellular glycogen accumulation and marked hypertrophy [28,29]. This model offers a biologically coherent explanation for the coexistence of a storage cardiomyopathy and pre-excitation, but it should not be overgeneralized. It represents one PRKAG2 variant in a transgenic overexpression system, and the anatomy of human pre-excitation may be more heterogeneous. Nevertheless, it supports an important mechanistic principle: altered myocardial substrate can change not only ventricular structure but also electrical insulation at the atrioventricular junction [28]. Subsequent experimental work challenged

the simplified view that PRKAG2-associated hypertrophy and electrical disease are merely passive consequences of glycogen accumulation. In a mouse model in which glycogen storage was genetically suppressed, ventricular pre-excitation was abolished while excess myocardial growth persisted, implicating separable growth signaling pathways [29]. More recently, a PRKAG2 R299Q zebrafish model demonstrated electrical and contractile abnormalities before detectable glycogen accumulation. Enhanced AMPK $\gamma 2$ -myosin interaction altered calcium handling, and partial rescue with myosin inhibition support a glycogen-independent early mechanism, although these findings remain preclinical and should not be interpreted as evidence for mavacamten therapy in patients with PRKAG2 cardiomyopathy [30].

Danon disease: impaired autophagy and progressive myocardial injury

Danon disease results from deficiency of lysosome-associated membrane protein 2 (LAMP-2), particularly the LAMP-2B isoform expressed in cardiac and skeletal muscle [10]. LAMP-2 deficiency impairs macroautophagy, leading to accumulation of autophagic vacuoles and glycogen, mitochondrial dysfunction, oxidative stress, cell death, and progressive myocardial fibrosis [14]. This differs fundamentally from the sarcomeric-disarray model of conventional HCM and from the primary energy-sensing abnormality in PRKAG2 cardiomyopathy. This mechanism helps explain the aggressive clinical trajectory of Danon disease. Severe hypertrophy may develop rapidly, particularly in males, while progressive cell injury and fibrosis can eventually produce systolic dysfunction or a dilated phenotype. The same diffuse disease process may also involve the conduction system. However, the mechanism of apparent pre-excitation in Danon disease should not be reduced to a single pathway. Electrophysiologic studies demonstrate both fasciculoventricular connections and extranodal atrioventricular accessory pathways, sometimes within the same patient, showing that more than one conduction substrate can underlie an apparently similar surface pre-excitation pattern [18].

Fabry and Pompe disease: different storage substrates, convergent hypertrophic phenotypes

Fabry disease and Pompe disease illustrate how different lysosomal storage defects can converge on an HCM-like phenotype while producing distinct tissue and electrophysiologic signatures. In Fabry disease, deficient α -galactosidase A activity causes lysosomal glycosphingolipid accumulation, which contributes to cellular dysfunction, hypertrophy, inflammation, and fibrosis [2,23]. The myocardial storage signature is reflected in CMR by reduced native T1, often before LVH is evident, although fibrosis and inflammation can later modify or pseudonormalize T1

Table 1: Distinguishing Features of Sarcomeric HCM and Major Genetic/Metabolic Phenocopies Associated with LVH and Pre-Excitation.

Disorder	Genetic/Clinical Clues	ECG/electrophysiology	Imaging, diagnosis and management implications
Sarcomeric HCM	Usually autosomal dominant; strong-evidence genes include MYH7 and MYBPC3 among others. Primary myocardial phenotype without a storage syndrome; LVOTO may occur [1].	LVH voltage, repolarization abnormalities, AF/VT may occur. Ventricular pre-excitation is uncommon; its presence should prompt phenocopy evaluation [1,11].	Asymmetric, concentric, or apical LVH; fibrosis by LGE may occur. Manage with HCM-specific risk stratification and family testing once sarcomeric disease is established [1].
PRKAG2 cardiomyopathy	PRKAG2; autosomal dominant. Cardiac glycogenosis with LVH, early AF, progressive bradycardia/AV block, and frequent pacing; overt extracardiac disease is uncommon [5,6].	Short PR/delta wave or prior AP ablation in about one-third; AV block, bundle-branch disease, sinus-node dysfunction, and AF are important complementary clues [6].	May closely mimic HCM. Significant LVOTO was uncommon in the largest cohort; small studies suggest bradycardia with relatively preserved GLS and evolving CMR T1/LGE patterns. No approved etiologic therapy; emphasize rhythm/conduction surveillance [4,6,12,13].
Danon disease	LAMP2; X-linked. Severe cardiomyopathy, especially in males; skeletal myopathy, cognitive/developmental abnormalities, retinal disease, and CK/transaminase elevation may occur. Women may have isolated cardiac disease [14,15,16,17].	Pre-excitation may reflect FVP, true AV/extranodal AP, or both. AV block, sinus-node dysfunction, atrial and ventricular arrhythmias also occur; potentially malignant AP conduction has been documented [14,18,19].	Males commonly show marked HCM morphology; females may show dilated or hypokinetic phenotypes. Extensive LGE and sex-specific CMR patterns are reported. Multidisciplinary care and timely transplant evaluation are central. AAV9-LAMP2B has published phase 1 human data but remains investigational [14,17,20].
Fabry disease	GLA; X-linked alpha-galactosidase A deficiency. Renal disease, neuropathic pain, angiokeratomas, gastrointestinal, cerebrovascular, and ocular manifestations may accompany LVH; late-onset cardiac-predominant disease occurs [2,21].	Short PR can occur without a conventional AP; later conduction disease and atrial/ventricular arrhythmias may develop [22].	Low native myocardial T1 is a characteristic clue and may precede LVH; biopsy-correlated data support an inverse relationship with glycosphingolipid burden. Confirm with alpha-Gal A/lyso-Gb3 testing in males and genetic testing, particularly in females. Disease-specific therapy may include ERT or chaperone therapy [2,21,23].
Pompe disease	GAA; autosomal recessive acid alpha-glucosidase deficiency. Infantile disease features hypotonia, macroglossia, weakness, and severe hypertrophy; later-onset disease is often neuromuscular-predominant [2,24].	Short PR, high LV voltage, and conduction abnormalities are characteristic in infantile disease; the substrate should not automatically be equated with a conventional AP [24].	Marked concentric LVH may regress with enzyme replacement. Diagnose with GAA activity followed by confirmatory enzymatic/genetic testing. ERT can reduce LV mass and improve associated ECG abnormalities [2,24].

Note: Abbreviations: AF, atrial fibrillation; AP, accessory pathway; AV, atrioventricular; CMR, cardiovascular magnetic resonance; ERT, enzyme replacement therapy; FVP, fasciculoventricular pathway; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction.

values [21,23]. Thus, tissue characterization can provide mechanistic information that wall thickness alone cannot. In Pompe disease, deficient acid α -glucosidase causes lysosomal glycogen accumulation in cardiac and skeletal muscle. Cardiac glycogen storage enlarges myocytes and can markedly thicken the ventricular walls in infantile disease. Short PR intervals and high QRS voltages are common, but the electrophysiologic basis appears more complex than a single discrete accessory pathway and may involve glycogen-related enlargement and remodeling of specialized conduction tissue [24]. The improvement in PR interval, ECG voltage, and LV mass observed with enzyme replacement

therapy provides clinical evidence that the electrical and structural phenotype is at least partly reversible when the underlying metabolic defect is treated [24]. Taken together, these disorders demonstrate that LVH is a final common phenotype produced by fundamentally different molecular processes. The accompanying electrical phenotype—whether true atrioventricular pre-excitation, fasciculoventricular conduction, accelerated atrioventricular conduction, or progressive conduction block—can provide mechanistic information that narrows the differential diagnosis. This concept forms the basis for the diagnostic approach developed in subsequent sections of this review.

Clinical Presentation and Natural History

PRKAG2 cardiomyopathy

The clinical expression of PRKAG2 cardiomyopathy is broader than the classic combination of LVH, ventricular pre-excitation, and conduction disease. In the largest contemporary multicenter cohort, 90 individuals from 27 centers were a median age of 33 years; LVH was present in 67%, pre-excitation or previous accessory-pathway ablation in 33%, permanent pacing in 19%, and atrial fibrillation in 18% at baseline [6]. Earlier natural-history work in 45 mutation carriers demonstrated high penetrance of characteristic ECG abnormalities by adolescence and a substantial burden of progressive conduction disease requiring pacing [9]. Thevenon and colleagues likewise reported age-dependent arrhythmic and myocardial complications in 34 patients from 9 families [7]. The disorder is also dynamic. During a median follow-up of approximately 6 years in the Lopez-Sainz cohort, atrial fibrillation became increasingly common, new pacemaker implantation occurred in 21%, heart-failure hospitalization in 14%, sudden death or an equivalent event in 8%, transplantation in 4%, and death in 13% [6]. A South Asian cohort of 22 affected individuals from 3 families showed similarly substantial conduction and arrhythmic morbidity, although all carried the same Arg302Gln variant and event rates should not be generalized across the PRKAG2 spectrum [8]. The myocardial phenotype is heterogeneous. LVH may be concentric or asymmetric, and ventricular function can remain preserved until later stages. In the Lopez-Sainz cohort, none of the patients with detailed echocardiographic assessment had a left ventricular outflow tract (LVOT) gradient greater than 30 mm Hg or systolic anterior motion of the mitral valve, suggesting that substantial dynamic obstruction is not a typical population-level feature [6]. Nevertheless, contemporary case reports document marked dynamic LVOT obstruction in genetically confirmed PRKAG2 disease, including a resting gradient of 47 mm Hg that increased to 70 mm Hg with Valsalva [4]. Thus, the presence of obstruction should not be used to exclude a metabolic phenocopy when other red flags are present. Extracardiac manifestations appear less prominent in PRKAG2 than in Danon, Fabry, or Pompe disease. Skeletal muscle symptoms were uncommon in the largest cohort [6]. Consequently, the clinical diagnosis often depends heavily on the cardiac pattern itself: unexplained LVH accompanied by pre-excitation, early AF, sinus-node dysfunction, atrioventricular block, bundle-branch disease, or a family history of similar electrical and structural abnormalities.

Danon disease

Danon disease generally follows a more aggressive course than PRKAG2 cardiomyopathy, particularly in affected males. Classic registry data established early hypertrophic

disease, skeletal muscle involvement, and high transplant/mortality burden in males [15]. In the 2020 European multicenter registry of 57 patients (30 males, 27 females), cardiac involvement occurred in 96%, LVH in 73% of males and 74% of females, and 27% underwent transplantation or received an LV assist device; men developed heart failure at a younger age [16]. The 2025 International Danon Disease Registry provides the strongest contemporary longitudinal dataset. Among 116 patients, males presented on average about a decade earlier and demonstrated more progressive hypertrophy and heart failure than females. Female trajectories were heterogeneous, including a subgroup with severe early disease resembling the male phenotype [25]. These observations argue against describing female Danon disease as uniformly mild or late onset. A complementary 2025 pediatric cohort of 29 patients found that ventricular pre-excitation increased from 36% at initial evaluation to 54% at latest follow-up and was associated with greater posterior-wall hypertrophy, although limited electrophysiology testing precluded definitive assignment of the underlying pathway mechanism [31]. Contemporary CMR data further refine the sex-specific phenotype. In a 24-patient retrospective cohort, 11 of 15 males (73.3%) predominantly had a hypertrophic phenotype, whereas 8 of 9 females (88.9%) predominantly had a dilated phenotype. Females also had lower left ventricular ejection fraction and more impaired systolic strain, with more extensive tissue abnormalities on CMR [17]. Because the female patients were older than the males, some of these differences may reflect both sex and disease stage; nonetheless, the findings support surveillance strategies that account for the possibility of transition from hypertrophy to systolic dysfunction. Advanced heart failure remains a major determinant of outcome in Danon disease. Ventricular arrhythmias, conduction abnormalities, pre-excitation, implantable cardioverter-defibrillator use, ventricular assist support, and transplantation are all encountered in clinical practice. The rapid disease trajectory in many males makes early recognition especially important, while the delayed and sometimes isolated cardiac presentation in females can make diagnosis more difficult.

Comparator phenotypes: sarcomeric HCM, Fabry disease, and Pompe disease

Sarcomeric HCM typically presents as an isolated myocardial disorder with variable age-related penetrance and does not characteristically include ventricular pre-excitation. Consequently, a young patient with LVH plus a short PR interval, delta wave, progressive conduction disease, or marked extracardiac findings warrants reassessment of the etiologic diagnosis even if the ventricular morphology appears typical for HCM [1,2]. Fabry disease often has a later and more systemic presentation, with renal, neurologic,

dermatologic, and cerebrovascular manifestations accompanying or preceding cardiac involvement. Cardiac disease may progress from glycosphingolipid storage and early functional abnormalities to LVH, conduction disease, replacement fibrosis, heart failure, and arrhythmia [2,21]. Pompe disease, by contrast, is most relevant to the differential diagnosis when severe LVH and short PR occur in infancy or early childhood together with hypotonia, skeletal muscle weakness, macroglossia, or other manifestations of lysosomal glycogen storage [24]. The very different ages of presentation and extracardiac phenotypes provide useful context when interpreting the ECG findings (Table 2).

Electrocardiographic and Electrophysiologic Differentiation

Apparent pre-excitation is not a single electrophysiologic entity

A central challenge in evaluating LVH with a short PR interval is determining whether the ECG actually represents ventricular pre-excitation and, if so, what anatomic connection is responsible. A conventional atrioventricular accessory pathway bridges the atrium and ventricle outside the

atrioventricular node and can participate in atrioventricular reentrant tachycardia or conduct atrial fibrillation rapidly to the ventricle. A fasciculoventricular pathway (FVP), in contrast, connects the His-Purkinje system to ventricular myocardium distal to the atrioventricular node. Because the atrioventricular node remains part of the antegrade conduction pathway, an isolated FVP is generally considered benign and does not itself participate in atrioventricular reentrant tachycardia [11,18]. A third situation is a short PR interval without true accessory-pathway-mediated ventricular pre-excitation. Accelerated atrioventricular or His-Purkinje conduction has been described in storage disorders such as Fabry disease, and conduction-system enlargement or remodeling has been proposed in Pompe disease [22,24]. Thus, the terms short PR, delta wave, ventricular pre-excitation, FVP, and Wolff-Parkinson-White syndrome should not be used interchangeably (Table 2).

Pre-excitation in HCM and storage/metabolic phenotypes

The diagnostic value of pre-excitation is supported by pediatric and young-adult HCM cohorts. In a single-center study of 345 patients younger than 21 years with HCM, 28 had

Table 2: Electrical Phenotypes in LVH With a Short PR Interval or Apparent Pre-Excitation.

Electrical finding	Likely mechanism	Clinical meaning / risk	Management implication
Short PR without convincing delta wave	Accelerated AV or His-Purkinje conduction; not necessarily an AP. Reported in storage disorders including Fabry and Pompe disease [22,24]	Does not by itself establish WPW or accessory-pathway-mediated risk.	Interpret with QRS morphology, clinical phenotype, and—when needed—EP data; avoid reflex labeling as WPW.
Fasciculoventricular pathway	Connection from the His-Purkinje system to ventricular myocardium distal to the AV node [11,18]	Generally benign; does not usually participate in AV reentrant tachycardia or provide rapid atrial-to-ventricular bypass of the AV node [18]	Do not ablate an isolated FVP solely because of pre-excitation. Confirm the mechanism when clinically uncertain, especially because a true AV accessory pathway can coexist with FVP in Danon disease [18,19]
True AV / extranodal accessory pathway	Atrial-to-ventricular connection bypassing the AV node [11,18,32]	Can support AVRT and, if rapidly conducting antegradely, can permit dangerous ventricular rates during AF [32]	Risk-stratify by EPS when appropriate; catheter ablation is definitive therapy for clinically important AP-mediated pre-excitation [32]
FVP plus true accessory pathway	Coexisting pathways; repeatedly described in Danon disease cohorts [18,19]	A benign FVP can mask or remain after ablation of a separate clinically important AP; surface ECG may not distinguish the two [11,18,19].	Maintain suspicion for multiple mechanisms when pre-excitation persists or changes after ablation; EPS may be required.
Progressive conduction disease	Sinus-node dysfunction, AV block, or intraventricular conduction disease related to the underlying cardiomyopathy, especially PRKAG2 and Danon [2,6,14]	May coexist with pre-excitation and can drive syncope, bradycardia, pacing need, and longitudinal risk.	Longitudinal ECG/ambulatory surveillance; pacemaker or ICD decisions should follow the clinical conduction and arrhythmic phenotype.

Note: AV nodal blocking agents are contraindicated specifically in pre-excited AF with antegrade accessory-pathway conduction because of the risk of ventricular fibrillation or hemodynamic deterioration; this contraindication should not be generalized to all patients with PRKAG2, Danon disease, or a short PR interval [32].

ventricular pre-excitation. Pre-excitation was substantially more frequent in patients with storage or metabolic etiologies than in patients with isolated HCM [11]. Among 22 patients who underwent invasive electrophysiology study (EPS), investigators identified both true atrioventricular accessory pathways and FVPs, with some patients having multiple pathways or coexistence of both mechanisms. Importantly, no surface ECG characteristic reliably distinguished benign FVP-mediated pre-excitation from potentially dangerous atrioventricular accessory-pathway conduction [11]. These findings argue against using the surface ECG alone to infer pathway risk in patients with HCM-like phenotypes. Very high QRS and delta-wave amplitudes may increase suspicion for a storage disorder, but they do not define pathway anatomy. When the distinction would alter risk assessment or ablation decisions, invasive electrophysiologic characterization may be required [11].

PRKAG2-associated electrical disease

PRKAG2 cardiomyopathy combines ventricular pre-excitation with a progressive conduction-system phenotype. In the 90-patient multicenter cohort, 39% had a PR interval shorter than 120 ms, 33% demonstrated a pre-excitation pattern, 13% had first-degree atrioventricular block, and bundle-branch abnormalities were common; 19% already had permanent pacemakers at first evaluation [6]. Importantly, invasive EP work in PRKAG2-associated FVP shows that an FVP can account for apparent pre-excitation while the underlying disease independently carries substantial risks of sinus-node dysfunction, atrioventricular block, and atrial arrhythmias [33]. The mechanistic model is also distinctive. In transgenic PRKAG2 disease, glycogen-filled myocytes disrupted the annulus fibrosus and produced microscopic atrioventricular connections rather than a single, morphologically discrete bypass tract [28]. Human pathway anatomy may be more heterogeneous, but the model provides a biologic explanation for why structural storage disease and abnormal atrioventricular activation can coexist. It also suggests why conventional assumptions about a single accessory pathway may not always apply in PRKAG2 cardiomyopathy.

Danon disease: coexistence of FVP and clinically important accessory pathways

Danon disease provides the clearest evidence that apparently similar ECG pre-excitation can arise from different pathways in the same disease. In a multicenter registry of 40 genetically confirmed patients, 13 (32.5%) had pre-excitation on resting ECG [18]. Nine underwent EPS: FVP was identified in 7 of 9, an extranodal accessory pathway in 7 of 9, and both mechanisms coexisted in 5; two patients had accessory pathways with malignant conduction properties [18]. An independent 16-patient Danon cohort subsequently

found FVP in all 4 patients undergoing EPS, with true left-sided atrioventricular accessory pathways coexisting in 2 [19]. These observations have direct clinical implications. An isolated FVP is generally benign and should not be ablated simply because pre-excitation is present, yet FVP does not exclude a second atrioventricular accessory pathway capable of rapid antegrade conduction [18,19]. EPS should therefore be considered when symptoms, syncope, documented tachyarrhythmia, concerning pathway behavior, persistent or changing pre-excitation after ablation, or diagnostic uncertainty would change risk assessment or management. Because available studies are small and selectively referred, routine invasive EPS for every asymptomatic Danon patient with a delta wave cannot be justified from current evidence.

Implications for interpretation and subsequent management

A practical ECG approach begins by asking three separate questions: Is the PR interval truly short for age? Is there convincing early ventricular activation with a delta wave and QRS widening? If pre-excitation is present, does the clinical phenotype suggest a conventional atrioventricular accessory pathway, an FVP, or a storage-related conduction abnormality? The answer should then be integrated with age, inheritance pattern, extracardiac findings, ambulatory rhythm monitoring, imaging, and genetic testing. This layered approach avoids two common errors: dismissing pre-excitation as incidental WPW in a patient with a phenocopy, and labeling every short PR interval in a storage disorder as WPW.

Echocardiographic and Cardiovascular Magnetic Resonance Differentiation

Echocardiography: overlapping morphology, different clinical context

Echocardiography establishes the presence, distribution, and hemodynamic consequences of LVH but rarely identifies the molecular diagnosis by itself. Sarcomeric HCM may show asymmetric septal hypertrophy, apical hypertrophy, concentric remodeling, systolic anterior motion of the mitral valve, and dynamic LVOT obstruction. PRKAG2, Danon, Fabry, and Pompe disease can reproduce portions of this spectrum, so morphology must be interpreted together with electrical and systemic clues [1,2]. Direct comparative data are limited but informative. Tang and colleagues compared 9 PRKAG2 patients with LVH, 41 genetically confirmed sarcomeric HCM patients, and 202 healthy volunteers. Wall thickness was similar between the PRKAG2 and sarcomeric HCM groups, whereas PRKAG2 patients had a substantially lower resting heart rate and relatively preserved global longitudinal strain (GLS). Mean GLS was -18.9% in PRKAG2 versus -13.4% in sarcomeric HCM, and a model

combining heart rate with GLS showed high discriminatory performance in this small cohort [17]. These findings are hypothesis-generating rather than diagnostic thresholds, because the PRKAG2 sample was very small and included only patients with established LVH.

Dynamic obstruction deserves particular caution. In the large PRKAG2 natural-history cohort, none of the patients with detailed echocardiographic data had an LVOT gradient greater than 30 mm Hg or systolic anterior motion [6]. Yet the 2026 index case that prompted this review had severe PRKAG2-related LVH with a resting LVOT gradient of 47 mm Hg that increased to 70 mm Hg with Valsalva [4]. Thus, LVOTO may favor conventional HCM statistically, but it cannot exclude PRKAG2 disease when the ECG, pedigree, or conduction phenotype is atypical.

CMR in PRKAG2 cardiomyopathy

CMR can add tissue characterization to morphology, but the PRKAG2 evidence base remains small. In a study of 6 mutation carriers from two families, all had LVH in at least one segment. Younger affected individuals could show focal mid-inferolateral or inferior hypertrophy with reduced native T1 and no late gadolinium enhancement (LGE), whereas an older patient with extensive hypertrophy had LGE and higher native T1 values consistent with increasing fibrosis [12]. The authors proposed that PRKAG2 morphology and tissue characteristics may evolve with disease stage, from glycogen-dominant hypertrophy toward a more fibrotic phenotype. These observations are clinically appealing but require cautious interpretation because of the very small sample size, family clustering, and technical limitations of early T1 mapping. CMR should therefore be used to identify patterns that strengthen or weaken a phenotypic hypothesis rather than as a stand-alone test for PRKAG2 cardiomyopathy.

CMR in Danon disease

Danon disease frequently produces striking structural abnormalities, and CMR can reveal fibrosis and sex-specific ventricular remodeling. In an earlier series of 6 male patients, 5 had a hypertrophic phenotype and 1 a dilated phenotype; LGE was present in all patients, and the subset undergoing mapping showed increased native T1 and extracellular volume (ECV) [34]. Although the cohort was small, these findings suggested substantial myocardial injury beyond simple hypertrophy. The larger 2026 study of 24 patients provides a more contemporary view. Males predominantly exhibited HCM morphology, whereas females predominantly exhibited DCM morphology and had lower ejection fraction and more impaired systolic strain [17]. LGE commonly involved the apical and free-wall myocardium, while relative sparing of the mid-basal septum was more prominent in males. ECV and mapping abnormalities supported diffuse

tissue injury, with females showing more advanced fibrotic remodeling in this cohort [17]. No single LGE distribution is sufficiently specific to diagnose Danon disease, and sex comparisons are confounded by differences in age and disease stage. Nevertheless, severe early LVH, extensive LGE, progressive systolic dysfunction, and the characteristic clinical or electrical phenotype should heighten suspicion for LAMP2 disease and prompt genetic evaluation.

Fabry disease and the diagnostic value of native T1

Fabry disease provides one of the most useful tissue-characterization contrasts in the LVH differential. In 63 genotyped Fabry patients compared with 63 matched healthy volunteers, native myocardial T1 was lower in Fabry patients both with and without LVH, supporting detection of sphingolipid storage before overt hypertrophy [21]. More recently, a 40-patient study paired CMR with endomyocardial biopsy and demonstrated an inverse relationship between native T1 and histologically measured myocardial glycosphingolipid burden; midventricular septal measurements showed the strongest agreement and high discrimination for severe storage [23]. Low native T1 is therefore a useful clue when Fabry disease is clinically plausible, and the newer biopsy-correlated data strengthen its biologic validity [23]. However, absolute thresholds remain scanner-, field-strength-, sequence-, site-, age-, sex-, and phenotype-dependent. Fibrosis and inflammation can also increase T1 and lead to pseudonormalization in advanced disease. CMR interpretation should therefore incorporate LGE distribution, ventricular morphology, disease stage, renal function, and biochemical/genetic confirmation rather than relying on a universal T1 cutoff [21,23].

Pompe disease and integrated imaging interpretation

In infantile Pompe disease, echocardiography typically demonstrates marked concentric hypertrophy and increased LV mass, often in conjunction with the characteristic ECG pattern of high voltage and short PR. Enzyme replacement therapy can produce substantial regression of LV mass, and the parallel improvement in ECG voltage and PR interval provides a useful example of a reversible metabolic cardiomyopathy phenotype [24]. CMR is less central to the classic infantile diagnostic presentation than in Fabry, PRKAG2, or Danon disease, but the broader principle is the same: imaging abnormalities should be interpreted as manifestations of an underlying cellular process, not as a disease label by themselves. An integrated imaging strategy is therefore preferable. Echocardiography defines wall thickness, geometry, function, and obstruction; CMR refines hypertrophy distribution and identifies fibrosis or storage-related tissue characteristics; and the ECG determines whether accompanying electrical abnormalities make a phenocopy more likely. The combination of these modalities, together with pedigree, extracardiac findings, and genetic testing, is

more informative than any individual imaging feature and helps prevent morphology alone from driving the etiologic diagnosis.

Biochemical and Genetic Differentiation

When to broaden the genetic evaluation beyond sarcomeric HCM

Genetic testing is not merely confirmatory when LVH is accompanied by pre-excitation, conduction disease, an unusual age at presentation, or extracardiac findings. The 2024 AHA/ACC multisociety HCM guideline recommends evaluation for HCM and other genetic causes of unexplained hypertrophy when the presentation is atypical or another genetic condition is suspected [1]. The ESC cardiomyopathy guideline similarly identifies short PR/pre-excitation, atrioventricular block, and extreme LVH as red flags for glycogen-storage, lysosomal, and related disorders [2]. Contemporary multicenter data further support a structured multiparametric red-flag approach integrating family history, examination, ECG, echocardiography, and laboratory findings rather than relying on a single feature [35]. The practical implication is that the diagnostic process should be phenotype driven rather than panel driven. A patient with otherwise typical isolated HCM may reasonably begin with validated sarcomeric genes, whereas a patient with LVH plus a delta wave, progressive bradycardia, skeletal myopathy, renal disease, cognitive findings, or a distinctive inheritance pattern should undergo testing that captures the relevant phenocopies from the outset. This strategy reduces the risk of a technically 'negative' sarcomeric panel being misinterpreted as evidence that the hypertrophy is nongenetic.

PRKAG2 cardiomyopathy

PRKAG2 cardiomyopathy is established by identification of a pathogenic or likely pathogenic PRKAG2 variant in the appropriate clinical context. The autosomal dominant inheritance pattern can be highly informative, particularly when hypertrophy co-segregates with ventricular pre-excitation, atrial fibrillation, sinus-node dysfunction, or atrioventricular block [2,5,6]. Unlike several systemic storage disorders, PRKAG2 disease often lacks striking extracardiac manifestations. In the largest contemporary cohort, skeletal muscle symptoms were uncommon, although mild creatine kinase elevation was reported in a minority of patients [6]. Thus, the absence of overt myopathy should not lower clinical suspicion when the cardiac phenotype is characteristic. No single biochemical marker is sufficiently specific to diagnose PRKAG2 cardiomyopathy. Variant interpretation therefore requires attention to phenotype, segregation, population frequency, and established gene-disease relationships, especially when a variant of uncertain significance is encountered. Once a pathogenic familial

variant is identified, cascade testing can identify relatives who require longitudinal cardiac surveillance and those who did not inherit the familial variant [1].

Danon disease

Danon disease requires a different diagnostic framework because of its X-linked inheritance and multisystem expression. The international Danon consensus integrates LAMP2 genotype with objective cardiovascular, skeletal muscle, and neurocognitive abnormalities [14]. Cardiovascular findings include LVH, reduced ejection fraction, arrhythmias, atrioventricular block, ventricular pre-excitation due to Wolff-Parkinson-White or fasciculoventricular pathways, and late gadolinium enhancement. Skeletal muscle evaluation may reveal weakness or abnormalities on functional testing, while creatine phosphokinase, AST, and ALT can be elevated. Cognitive or developmental abnormalities provide an additional clue, particularly in affected males [14]. Sex materially alters the diagnostic presentation. Male patients often have early multisystem disease, whereas female patients may present with apparently isolated cardiomyopathy and few extracardiac clues [14,15,16,17]. Consequently, absence of skeletal or cognitive abnormalities does not exclude Danon disease in a woman with otherwise unexplained cardiomyopathy. For a LAMP2 variant of uncertain significance, the consensus document describes additional supportive approaches, including demonstration of abnormal LAMP2 expression or characteristic autophagic vacuolar pathology in an appropriate clinical and familial context [14].

Fabry and Pompe disease

Fabry disease is particularly important because establishing the diagnosis can alter treatment. The ESC guideline recommends assessment of alpha-galactosidase A activity and lyso-Gb3 in male patients with suspected Fabry disease, whereas genetic testing is usually required for confirmation in female patients [2]. Cardiac magnetic resonance may strengthen suspicion: reduced native myocardial T1 is common in Fabry disease and can precede overt LVH, but it is a phenotypic biomarker rather than a substitute for biochemical and molecular confirmation [21]. Pompe disease should be considered especially in infants with severe concentric hypertrophy, short PR interval, high ECG voltage, hypotonia, delayed motor milestones, or other neuromuscular features. The ESC guideline describes screening with GAA activity followed by confirmatory acid alpha-glucosidase testing in fibroblasts or muscle when appropriate [2]. In the enzyme-replacement cohort reviewed in this article, all participants had marked endogenous GAA deficiency documented before treatment [24]. The diagnostic lesson is that the same ECG-hypertrophy combination can arise from disorders that require very different confirmatory tests.

A Practical Diagnostic Approach to LVH With Apparent Pre-Excitation

Confirm the myocardial phenotype before assigning an HCM label

Evaluation should begin by confirming that increased LV wall thickness is not adequately explained by loading conditions such as systemic hypertension, aortic stenosis, or physiologic remodeling. Echocardiography should define the distribution and severity of hypertrophy, ventricular function, mitral-valve anatomy, and resting or provoked LV outflow tract obstruction. CMR is useful when morphology is uncertain or when tissue characterization may reveal fibrosis or a storage-related signature. The purpose of this first step is not yet to identify the gene, but to establish that the patient truly has an unexplained cardiomyopathic phenotype.

Define the electrical phenotype precisely

The ECG should then be interrogated as a mechanistic test rather than simply labeled 'WPW.' A short PR interval should be distinguished from convincing ventricular pre-excitation with a delta wave and QRS widening. Coexisting findings such as marked QRS voltage, repolarization abnormalities, sinus bradycardia, atrioventricular block, bundle branch block, or atrial arrhythmia may provide additional clues. This distinction matters because a short PR interval can reflect accelerated atrioventricular or His-Purkinje conduction, whereas a delta wave can arise from a true atrioventricular accessory pathway or a fasciculoventricular pathway. Surface ECG cannot reliably separate a benign fasciculoventricular pathway from a potentially dangerous atrioventricular accessory pathway in patients with HCM-like phenotypes [11]. In Danon disease, both pathway types may coexist in the same patient, and malignant accessory-pathway conduction has been documented [18]. Therefore, when pathway mechanism or risk is clinically important, electrophysiologic testing should be considered rather than inferring anatomy from the surface ECG alone.

Use inheritance and extracardiac findings to prioritize the differential

The pedigree is a high-yield discriminator. Autosomal dominant transmission with hypertrophy, pre-excitation, and progressive conduction disease favors PRKAG2 cardiomyopathy; an X-linked pattern with severe early cardiomyopathy and skeletal, cognitive, or retinal manifestations favors Danon disease [2,6,14]. Renal disease, neuropathic symptoms, angiokeratomas, cerebrovascular manifestations, or low native T1 increase suspicion for Fabry disease, whereas infantile hypotonia, macroglossia, weakness, and massive hypertrophy favor Pompe disease [2]. Importantly, female Danon or Fabry patients may

have attenuated extracardiac disease, so the absence of a multisystem phenotype is not reassuring when the cardiac clues are strong.

Integrate imaging, laboratory testing, genetics, and electrophysiology

The final diagnostic step is integrative. Imaging should define phenotype and tissue characteristics; biochemical testing should be ordered when a treatable metabolic disorder is plausible; and genetic testing should match the clinical red flags rather than being restricted reflexively to sarcomeric genes. A practical sequence is: unexplained LVH → precise ECG characterization → pedigree and extracardiac review → echocardiography and CMR → phenotype-directed biochemical and genetic testing → EPS when the mechanism or risk of pre-excitation remains uncertain. This multiparametric strategy is consistent with contemporary guideline and cohort-based red-flag frameworks [1,2,35]. Figure 1 summarizes this approach.

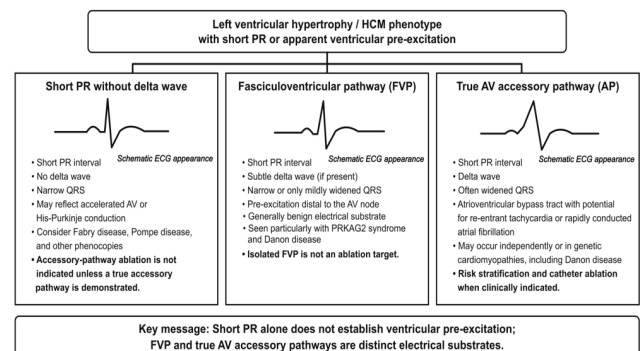


Figure 1: Distinguishing electrical phenotypes in left ventricular hypertrophy with short PR or pre-excitation. The figure shows a phenotype-driven diagnostic algorithm for unexplained LVH with apparent pre-excitation. A short PR interval without convincing ventricular pre-excitation should be distinguished from a delta-wave pattern caused by a true atrioventricular accessory pathway or a fasciculoventricular pathway. Clinical phenotype, inheritance, extracardiac findings, imaging, biochemical testing, and molecular diagnosis should be integrated before electrophysiology study is used when pathway mechanism or risk remains uncertain. AD, autosomal dominant; AP, accessory pathway; CMR, cardiovascular magnetic resonance; EPS, electrophysiology study; FVP, fasciculoventricular pathway; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy.

This algorithm (Figure 1) intentionally avoids treating 'LVH with pre-excitation' as a diagnosis. Similar surface patterns can arise from disorders with different inheritance, cellular biology, arrhythmic substrates, prognosis, and therapy. The goal is to identify both the myocardial disease and, when clinically relevant, the mechanism of the electrical abnormality.

Management, Electrophysiologic Risk, and Treatment Challenges

Management should follow the molecular diagnosis, not the morphology alone

Once the underlying disorder is identified, management should no longer default automatically to conventional sarcomeric HCM pathways. Standard treatment of symptoms, heart failure, and arrhythmias remains important across phenotypes, but the molecular diagnosis changes surveillance, family screening, expectations for disease progression, and access to disease-specific therapy. This is particularly relevant for Fabry and Pompe disease, in which targeted metabolic therapy is available, and for Danon and PRKAG2 disease, in which progressive conduction or advanced heart-failure phenotypes may dominate the clinical course [1,2].

PRKAG2 cardiomyopathy

There is currently no approved etiologic therapy for PRKAG2 cardiomyopathy [2]. Management is therefore directed at the major clinical manifestations: ventricular hypertrophy and heart failure, atrial and ventricular arrhythmias, progressive sinus-node or atrioventricular conduction disease, and accessory pathways when present. The high frequency of atrial fibrillation and pacemaker implantation in longitudinal cohorts supports regular rhythm and conduction surveillance [6]. Pacemaker or defibrillator therapy should be based on the patient's conduction disease and arrhythmic risk rather than on the presence of a PRKAG2 variant alone. Dynamic LV outflow obstruction deserves individualized interpretation. Significant obstruction appears uncommon in larger PRKAG2 cohorts, although well-documented obstructive cases exist [4,6]. Accordingly, obstruction should be treated according to its hemodynamic and symptomatic significance while recognizing that evidence derived from sarcomeric obstructive HCM may not fully address the underlying glycogen-storage cardiomyopathy.

Danon disease

Danon disease requires early multidisciplinary management because progression can be rapid and extracardiac disease may affect functional status and treatment decisions. No approved therapy currently corrects the underlying LAMP2 defect in routine clinical care [2,14]. However, human phase 1 AAV9-LAMP2B gene-replacement data have now been published, so gene therapy should be described as investigational clinical therapy rather than only a preclinical concept [20]. Consensus-based care still emphasizes coordinated cardiology, electrophysiology, genetics, neurology, ophthalmology, rehabilitation, and advanced heart-failure management [18]. Sudden-death

risk stratification remains difficult because conventional HCM models have not been validated in Danon disease. The international consensus supports a low threshold for considering ICD therapy in patients with severe LVH, unexplained syncope, or nonsustained ventricular tachycardia while acknowledging the limited evidence base [14]. Advanced heart failure should prompt timely transplant evaluation. In the largest transplant cohort summarized in the consensus document, 5-year post-transplant survival was approximately 87%, supporting transplantation as a viable strategy despite the multisystem nature of the disease [14].

Management of ventricular pre-excitation and pre-excited atrial fibrillation

The management of pre-excitation depends on whether a true atrioventricular accessory pathway is present. A fasciculoventricular pathway is generally considered benign because it does not participate in atrioventricular reentrant tachycardia or independently confer the same risk of rapid atrial-to-ventricular conduction; however, its presence does not exclude a second clinically important accessory pathway, particularly in Danon disease [11,18]. Electrophysiologic evaluation is therefore valuable when symptoms, pathway behavior, or surface ECG findings raise concern. Pre-excited atrial fibrillation is a distinct emergency because rapid antegrade conduction over an accessory pathway can precipitate ventricular fibrillation. The 2023 ACC/AHA/ACCP/HRS atrial fibrillation guideline recommends electrical cardioversion for hemodynamic instability, catheter ablation of the accessory pathway as definitive therapy, and intravenous procainamide or ibutilide as pharmacologic options in hemodynamically stable pre-excited AF [32]. Drugs that predominantly block atrioventricular nodal conduction - including verapamil, diltiazem, amiodarone, digoxin, adenosine, and beta blockers - are contraindicated in this specific setting because they may facilitate rapid accessory-pathway conduction and hemodynamic deterioration [32]. This contraindication should be stated precisely. It applies to atrial fibrillation with antegrade accessory-pathway conduction; it does not mean that atrioventricular nodal blockers are universally contraindicated in all patients with PRKAG2 cardiomyopathy, Danon disease, a short PR interval, or an HCM phenotype. Misapplying the rule outside pre-excited AF can create unnecessary therapeutic restrictions.

Disease-specific treatment and family management

A molecular diagnosis can open treatment pathways unavailable for sarcomeric HCM. Fabry disease may be treated with enzyme replacement or, in selected genotypes, pharmacologic chaperone therapy; the timing and choice of therapy require disease-specific expertise [2]. Enzyme

replacement therapy is recommended for Pompe disease, and clinical data demonstrate improvement in LV mass and associated ECG abnormalities during treatment of infantile disease [2,24]. These examples underscore why diagnosing a phenocopy is not an academic exercise: treatment of the underlying metabolic defect can alter the cardiac phenotype. Genetic counseling and cascade testing are integral to management. Once a pathogenic familial variant is identified, relatives can receive genotype-directed surveillance rather than indefinite nonspecific screening. The inheritance pattern also changes counseling: PRKAG2 and most sarcomeric HCM are usually autosomal dominant, Danon and Fabry disease are X-linked, and Pompe disease is autosomal recessive [1,2,14].

Emerging Concepts, Knowledge Gaps, and Future Directions

Moving from morphology to mechanism

The principal conceptual shift is from classifying patients by wall thickness alone to classifying them by mechanism. Sarcomeric dysfunction, AMPK dysregulation, defective autophagy, sphingolipid storage, and lysosomal glycogen accumulation can all produce LVH, yet they differ substantially in conduction-system involvement, extracardiac disease, inheritance, and response to therapy. Future diagnostic frameworks should therefore treat LVH as a phenotype that triggers mechanistic investigation rather than as a final disease label.

The electrophysiologic substrate remains incompletely defined

The anatomy and clinical significance of pre-excitation in storage cardiomyopathies remain incompletely resolved. The PRKAG2 transgenic model supports disruption of the annulus fibrosus by glycogen-filled myocytes as one mechanism of microscopic atrioventricular connections [28]. In contrast, human Danon studies demonstrate fasciculoventricular and extranodal atrioventricular pathways, sometimes coexisting [18]. Surface ECG cannot reliably distinguish these mechanisms [11]. Larger genotype-linked electrophysiologic cohorts are needed to determine how pathway anatomy, variant type, and disease stage interact and whether the electrical substrate evolves as myocardial disease progresses.

Imaging biomarkers require prospective validation

CMR offers promising disease-specific clues, but most available studies remain small and retrospective. PRKAG2 T1 and LGE observations derive from very small cohorts, while Danon CMR studies are limited by sample size, age and sex differences, and heterogeneous disease stage [12,17,34]. Fabry native T1 has the strongest tissue validation among the selected phenocopies: it is sensitive to storage before

overt hypertrophy and now correlates with biopsy-defined glycosphingolipid burden [21,23]. Even so, absolute T1 values remain sequence-, scanner-, and field-strength-dependent and can pseudonormalize with fibrosis. Prospective multicenter harmonization is required before quantitative thresholds can serve as stand-alone diagnostic or prognostic criteria.

Risk stratification is a major unmet need

Rare-disease cohorts consistently demonstrate clinically important arrhythmia, conduction disease, heart failure, and transplantation, but they remain underpowered for robust individualized risk models. PRKAG2 cohorts are subject to referral and selection bias, and Danon disease lacks validated sudden-death prediction algorithms [6,14]. As a result, device decisions often rely on extrapolation from general cardiomyopathy practice plus disease-specific expert judgment. International registries with standardized phenotyping and longitudinal outcomes are essential to define predictors of sudden death, advanced conduction disease, and transition to end-stage heart failure.

Targeted molecular therapy may redefine the field

A major practical reason to pursue mechanism is that some phenocopies have disease-specific therapy, as illustrated by Fabry and Pompe disease. Danon disease has now progressed from preclinical gene replacement to early human clinical investigation: AAV9-LAMP2B improved molecular and physiologic phenotypes in a murine model [36], and a phase 1 open-label study of seven male patients demonstrated myocardial LAMP2 expression with encouraging LV-mass and cardiac-biomarker signals in the six patients with preserved baseline ejection fraction [20]. Serious treatment-associated complications occurred, one patient with baseline LV dysfunction required transplantation, and the uncontrolled sample is far too small to establish efficacy. PRKAG2 cardiomyopathy still lacks an approved etiologic treatment, but experimental evidence that early electrical and hypertrophic abnormalities may arise through both glycogen-dependent and glycogen-independent mechanisms suggests future targets beyond simple reduction of glycogen storage [29,30].

Priority questions for future research

- Can standardized ECG or noninvasive mapping features reliably distinguish atrioventricular accessory pathways from fasciculoventricular pathways before EPS?
- Which PRKAG2 variants predict predominant pre-excitation, conduction disease, hypertrophy, or heart-failure phenotypes?
- How should sex, age, genotype, LGE burden, and ventricular function be integrated into Danon sudden-death and transplant risk assessment?

- Can quantitative CMR mapping differentiate PRKAG2, Danon, Fabry, and sarcomeric HCM with sufficient accuracy for routine clinical use?
- Does early molecular diagnosis and treatment alter the development of pre-excitation or conduction disease, in addition to reversing or preventing hypertrophy?
- What surveillance intervals are optimal for genotype-positive patients before overt hypertrophy or arrhythmia develops?

Key Points

- LVH accompanied by a short PR interval, ventricular pre-excitation, or progressive conduction disease should trigger evaluation for an HCM phenocopy rather than being assumed to represent conventional sarcomeric HCM.
- Sarcomeric HCM remains the principal comparator, but ventricular pre-excitation is uncommon and should lower the threshold for considering PRKAG2 cardiomyopathy, Danon disease, and other storage or metabolic disorders.
- PRKAG2 cardiomyopathy is an autosomal dominant cardiac glycogen-storage disorder in which LVH, pre-excitation, atrial arrhythmias, and conduction disease are variably expressed; the classic triad is not required for diagnosis.
- Danon disease is an X-linked LAMP2 cardiomyopathy with important sex-related differences, aggressive disease particularly in males, and frequent extracardiac manifestations, although women may present with isolated cardiac disease.
- A short PR interval, a delta wave, a fasciculoventricular pathway, and a true atrioventricular accessory pathway are not interchangeable findings and may reflect different mechanisms and different risks.
- In Danon disease, fasciculoventricular and extranodal atrioventricular accessory pathways can coexist, so surface ECG alone may be insufficient to define pathway anatomy or risk.
- Imaging can narrow the differential: low native T1 is a characteristic Fabry clue with histologic validation of its relationship to myocardial glycosphingolipid burden, Danon disease may show extensive and sex-specific fibrosis/remodeling, and PRKAG2 cardiomyopathy may mimic sarcomeric HCM while showing stage-dependent CMR abnormalities [12,17,21,23].
- Biochemical and genetic testing should be phenotype directed; PRKAG2, LAMP2, GLA, and GAA require different confirmatory strategies and different family-counseling approaches.

- The prohibition against atrioventricular nodal blocking agents applies specifically to atrial fibrillation with rapid antegrade accessory-pathway conduction; it should not be generalized to every patient with PRKAG2, Danon disease, or a short PR interval.
- Correct molecular diagnosis changes management by guiding rhythm and conduction surveillance, cascade testing, disease-specific therapy in Fabry and Pompe disease, timely advanced heart-failure planning in aggressive phenocopies, and eligibility for emerging investigational therapies such as LAMP2 gene replacement in Danon disease [2,14,20,24].

Conclusion

Left ventricular hypertrophy with apparent ventricular pre-excitation is best approached as a diagnostic pattern rather than a diagnosis. The combination should prompt a structured reassessment of both the myocardial phenotype and the electrical mechanism. Sarcomeric HCM, PRKAG2 cardiomyopathy, Danon disease, Fabry disease, Pompe disease, and other metabolic disorders can converge on an HCM-like morphology, but they differ substantially in inheritance, cellular pathobiology, conduction-system involvement, extracardiac disease, prognosis, and therapy. A practical evaluation integrates ECG and electrophysiology with pedigree analysis, echocardiography, CMR, disease-directed biochemical testing, and genetic confirmation. This approach is clinically consequential: it can identify benign fasciculoventricular conduction versus a potentially malignant atrioventricular accessory pathway, reveal a treatable storage disorder, refine family screening, and prompt earlier rhythm, device, or advanced heart-failure management. Future multicenter studies should move beyond morphology toward genotype-linked electrical and imaging phenotypes that support disease-specific risk prediction and targeted therapy.

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References

1. Ommen SR, Ho CY, Asif IM, et al. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation* 149 (2024): e1239-e1311.
2. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J* 44 (2023): 3503-3626.
3. Arad M, Maron BJ, Gorham JM, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med* 352 (2005): 362-372.
4. Bukhari S, Barth AS, Rivers B, Madrazo J, Carrick RT. Left Ventricular Hypertrophy With Pre-Excitation: Thinking Beyond the Usual Hypertrophic Cardiomyopathy Diagnosis. *JACC Case Rep* 31 (2026): 108232.
5. Gollob MH, Green MS, Tang AS, et al. Identification of a gene responsible for familial Wolff-Parkinson-White syndrome. *N Engl J Med* 344 (2001): 1823-1831.
6. Lopez-Sainz A, Dominguez F, Lopes LR, et al. Clinical Features and Natural History of PRKAG2 Variant Cardiac Glycogenesis. *J Am Coll Cardiol* 76 (2020): 186-197.
7. Thevenon J, Laurent G, Ader F, et al. High prevalence of arrhythmic and myocardial complications in patients with cardiac glycogenesis due to PRKAG2 mutations. *Europace* 19 (2017): 651-659.
8. Ahamed H, Balegadde AV, Menon S, et al. Phenotypic expression and clinical outcomes in a South Asian PRKAG2 cardiomyopathy cohort. *Sci Rep* 10 (2020): 20610.
9. Murphy RT, Mogensen J, McGarry K, et al. Adenosine monophosphate-activated protein kinase disease mimicks hypertrophic cardiomyopathy and Wolff-Parkinson-White syndrome: natural history. *J Am Coll Cardiol* 45 (2005): 922-930.
10. Nishino I, Fu J, Tanji K, et al. Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). *Nature* 406 (2000): 906-910.
11. Przybylski R, Saravu Vijayashankar S, O'Leary ET, et al. Hypertrophic Cardiomyopathy and Ventricular Preexcitation in the Young: Cause and Accessory Pathway Characteristics. *Circ Arrhythm Electrophysiol* 16 (2023): e012191.
12. Poyhonen P, Hiippala A, Ollila L, et al. Cardiovascular magnetic resonance findings in patients with PRKAG2 gene mutations. *J Cardiovasc Magn Reson* 17 (2015): 89.
13. Tang L, Li X, Zhou N, Jiang Y, Pan C, Shu X. Echocardiographic characteristics of PRKAG2 syndrome: a research using three-dimensional speckle tracking echocardiography compared with sarcomeric hypertrophic cardiomyopathy. *Cardiovasc Ultrasound* 20 (2022): 14.
14. Hong KN, Eshraghian EA, Arad M, et al. International Consensus on Differential Diagnosis and Management of Patients With Danon Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol* 82 (2023): 1628-1647.
15. Boucek D, Jirikowic J, Taylor M. Natural history of Danon disease. *Genet Med* 13 (2011): 563-568.
16. Lotan D, Salazar-Mendiguchia J, Mogensen J, et al. Clinical Profile of Cardiac Involvement in Danon Disease: A Multicenter European Registry. *Circ Genom Precis Med* 13 (2020): e003117.
17. Liu N, Yang K, Cao G, et al. Sex-Specific Cardiac Magnetic Resonance Phenotypes in Danon Disease: A Retrospective Cohort Study. *J Magn Reson Imaging* 63 (2026): 403-414.
18. Darden D, Hsu JC, Tzou WS, et al. Fasciculoventricular and atrioventricular accessory pathways in patients with Danon disease and preexcitation: A multicenter experience. *Heart Rhythm* 18 (2021): 1194-1202.
19. Chen X, Fu L, He J, et al. A Frequent Observation of Wolff-Parkinson-White Syndrome and Fasciculoventricular Pathways in Patients With Danon Disease. *Circ J* 86 (2022): 309-318.
20. Greenberg B, Taylor M, Adler E, et al. Phase 1 Study of AAV9.LAMP2B Gene Therapy in Danon Disease. *N Engl J Med* 392 (2025): 972-983.
21. Pica S, Sado DM, Maestrini V, et al. Reproducibility of native myocardial T1 mapping in the assessment of Fabry disease and its role in early detection of cardiac involvement by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 16 (2014): 99.
22. Aryana A, Fifer MA, Ruskin JN, Mela T. Short PR interval

- in the absence of preexcitation: a characteristic finding in a patient with Fabry disease. *Pacing Clin Electrophysiol* 31 (2008): 782-783.
23. Galea N, Marchitelli L, Pambianchi G, et al. Diagnostic performance of native T1 in grading histologically proven myocardial glycosphingolipid accumulation in Fabry disease. *Insights Imaging* 17 (2026): 114.
 24. Ansong AK, Li JS, Nozik-Grayck E, et al. Electrocardiographic response to enzyme replacement therapy for Pompe disease. *Genet Med* 8 (2006): 297-301.
 25. Hong KN, Eshraghian E, Khedro T, et al. An International Longitudinal Natural History Study of Patients With Danon Disease: Unique Cardiac Trajectories Identified Based on Sex and Heart Failure Outcomes. *J Am Heart Assoc* 14 (2025): e038394.
 26. Khedro T, Attias J, Eshraghian E, et al. Danon disease in male patients: a prospective natural history study to augment understanding of the phenotype. *Orphanet J Rare Dis* 20 (2025): 530.
 27. Arad M, Benson DW, Perez-Atayde AR, et al. Constitutively active AMP kinase mutations cause glycogen storage disease mimicking hypertrophic cardiomyopathy. *J Clin Invest* 109 (2002): 357-362.
 28. Arad M, Moskowitz IP, Patel VV, et al. Transgenic mice overexpressing mutant PRKAG2 define the cause of Wolff-Parkinson-White syndrome in glycogen storage cardiomyopathy. *Circulation* 107 (2003): 2850-2856.
 29. Kim M, Hunter RW, Garcia-Menendez L, et al. Mutation in the gamma2-subunit of AMP-activated protein kinase stimulates cardiomyocyte proliferation and hypertrophy independent of glycogen storage. *Circ Res* 114 (2014): 966-975.
 30. Ge Q, Saha K, Burch ML, et al. AMPK γ 2 Regulates Cardiac Hypertrophy and Arrhythmias via Interacting With Myosin. *Circ Res* 139 (2026): e328910.
 31. Zhang Q, Chan W, Chen Y, et al. Clinical and Genetic Profile of Chinese Children With Danon Disease: A Single-Center Retrospective Cohort Study. *Can J Cardiol* 41 (2025): 89-101.
 32. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 83 (2024): 109-279.
 33. Sternick EB, Oliva A, Gerken LM, et al. Clinical, electrocardiographic, and electrophysiologic characteristics of patients with a fasciculoventricular pathway: the role of PRKAG2 mutation. *Heart Rhythm* 8 (2011): 58-64.
 34. He J, Xu J, Chen L, Ji K, Fan X, Zhao S, Lu M. Clinical features and cardiovascular magnetic resonance characteristics in Danon disease. *Clin Radiol* 75 (2020): 712.e1-712.e11.
 35. Maurizi N, Monda E, Biagini E, et al. Hypertrophic cardiomyopathy: prevalence of disease-specific red flags. *Eur Heart J* 46 (2025): 3082-3094.
 36. Manso AM, Hashem SI, Nelson BC, et al. Systemic AAV9.LAMP2B injection reverses metabolic and physiologic multiorgan dysfunction in a murine model of Danon disease. *Sci Transl Med* 12 (2020): eaax1744.



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