



Review

The Genetic Architecture of Sudden Cardiac Death: A State-of-the-Art Review

Sabrina Montuoro ^{1,†}, Emanuele Monda ^{2,*,†}, Gaetano Diana ², Emanuele Bobbio ², Vera Fico ², Marta Rubino ², Martina Caiazza ², Adelaide Fusco ², Annapaola Cirillo ², Federica Verrillo ², Francesca Dongiglio ², Giuseppe Palmiero ², Federica Barra ², Giulia Frisso ³, Maria Giovanna Russo ², Paolo Calabrò ² and Giuseppe Limongelli ²

- ¹ Health Science Interdisciplinary Center, Scuola Superiore Sant'Anna, Piazza Martiri della Libertà 33, 56127 Pisa, Italy; sabrina.montuoro@santannapisa.it
- ² Inherited and Rare Cardiovascular Diseases, Department of Translational Medical Sciences, University of Campania 'Luigi Vanvitelli', Monaldi Hospital, Via Leonardo Bianchi 1, c/o Monaldi Hospital, AORN Colli, 80131 Naples, Italy; verafico94@gmail.com (V.F.); g.palmiero@hotmail.it (G.P.)
- ³ Department of Advanced Biomedical Sciences, Università degli Studi di Napoli Federico II, Via Pansini, 80131 Naples, Italy
- * Correspondence: emanuelemonda@me.com; Tel.: +39-3348607935
- † These authors contributed equally to this work.

Abstract

Sudden cardiac death (SCD) is a major global health issue, defined as sudden natural death presumed to be of cardiac cause. While in the elderly SCD is commonly associated with coronary artery disease, in the younger population it is linked to inherited cardiomyopathies or channelopathies, even though SCD can remain unexplained even after a comprehensive autopsy in a substantial proportion of cases. In this context, genetic testing has gained importance, supported by the widespread availability of techniques such as next-generation and whole-exome/genome sequencing and their reduced costs. This state-of-the-art review summarizes the genetic bases of sudden cardiac death among cardiomyopathies, channelopathies and in sudden unexplained death presumed to be of arrhythmic cause. Among the structural causes, inherited cardiomyopathies such as hypertrophic, dilated, non-dilated left ventricular, arrhythmogenic right ventricular and restrictive ones represent major substrates for malignant ventricular arrhythmias mostly arising from variants in sarcomeric or desmosomal genes. Channelopathies (long or short QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia) are caused by variants in genes encoding cardiac ion channels and/or regulatory proteins, which equally predispose to high risk of life-threatening ventricular arrhythmias. In sudden arrhythmic death syndrome, with a structurally normal heart, post-mortem genetic testing (molecular autopsy) can uncover an underlying inherited condition. However, variants of uncertain significance are detected in more than half of the cases, underscoring the need for a multidisciplinary approach. Genetic testing also plays a key role in cascade screening of first-degree relatives. While monogenic variants drive risk in inherited cardiac disorders, emerging evidence suggests that polygenic contributions may modulate SCD susceptibility, highlighting future roles for polygenic risk scores in risk stratification.

Keywords: sudden cardiac death; genetic testing; cardiomyopathy; channelopathy



Academic Editor: Bo Gregers Winkel

Received: 26 January 2026

Revised: 10 March 2026

Accepted: 12 March 2026

Published: 19 March 2026

Copyright: © 2026 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and

conditions of the [Creative Commons](https://creativecommons.org/licenses/by/4.0/)

[Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

1. Introduction

Sudden cardiac death (SCD) is defined as a sudden natural death presumed to be of cardiac cause, occurring within 1 h of symptom onset in witnessed cases and within 24 h of last being seen alive in unwitnessed cases [1]. In older individuals, SCD is predominantly caused by coronary artery disease (CAD), whereas in younger populations it is more frequently associated with cardiomyopathies or channelopathies [2].

For this reason and owing to the increased availability of clinical data and reduced costs, the 2022 European Society of Cardiology (ESC) guidelines on SCD and ventricular arrhythmias expanded the role of genetic testing compared with the 2015 guidelines. Previously, genetic testing was considered only during the initial diagnostic work-up of patients with suspected inherited arrhythmogenic disease or when the proband had a first-degree relative who experienced SCD. In contrast, in the latest guidelines, genetic testing is considered a priority in SCD prevention, made possible by the introduction of extensive gene panel sequencing and improved methodologies, such as next-generation sequencing (NGS) or the whole-exome sequencing (WES).

Genetic testing should be performed in conditions predisposing to VA or when SCD is suspected to have a genetic basis, both in living and deceased individuals. This includes patients with cardiomyopathies such as hypertrophic (HCM, OMIM phenotypic series number: 192600), dilated (DCM, OMIM phenotypic series number: 115200), non-dilated left ventricular (NDLVC, OMIM phenotypic series number: 604169), arrhythmogenic right ventricular (ARVC, OMIM phenotypic series number: 107970) and restrictive cardiomyopathy (RCM, OMIM phenotypic series number: 115210) [1]. Genetic testing is equally recommended in patients with channelopathies, such as long QT syndrome (LQTS, OMIM phenotypic series number: 192500), Brugada syndrome (BrS, OMIM phenotypic series number: 601144), catecholaminergic polymorphic ventricular tachycardia (CPVT, OMIM phenotypic series number: 604772), and short QT syndrome (SQTS, OMIM phenotypic series number: 609620) [1]. Additionally, the role of post-mortem genetic testing (i.e., molecular autopsy) has been underscored, given its ability to identify underlying inherited cardiac conditions in deceased people with negative autopsy, therefore enabling relatives to undergo complete cascade screening and appropriate risk stratification.

This state-of-the-art review addresses the clinical relevance of genetic variants in SCD, highlighting the role of genetics in cardiomyopathies, channelopathies, and unexplained death. It also explores the clinical implications of a positive genetic test and discusses future perspectives in this rapidly evolving field.

2. Epidemiology and Mechanisms of Sudden Cardiac Death

SCD represents a major global health issue, accounting for approximately 15–20% of all deaths and 50% of deaths attributable to cardiovascular disease [3,4]. Despite substantial advances in both preventive strategies and therapeutic interventions, SCD remains a leading cause of mortality, with survival rates after cardiac arrest still below 5% [3].

The incidence of SCD increases markedly with advancing age, independently of sex or race. However, the proportion of deaths classified as sudden is greater among younger populations [4]. At any age, females have a lower incidence of SCD than males, although most events occur in structurally normal hearts in the female population [5]. Racial differences have also been reported, although not fully understood, with a higher prevalence in Black populations [6].

Sudden cardiac arrest, the clinical event underlying most SCDs, typically occurs without warning and presents with abrupt loss of consciousness, collapse, and absence of breathing due to cerebral hypoperfusion [7]. Following sudden death, a comprehensive premorbid evaluation and autopsy (including macroscopic, histological, and toxicological

analyses) are essential to determine whether the cause is non-cardiac, cardiac, or unexplained [8]. In the latter scenario, or when a genetic etiology is suspected, molecular autopsy and subsequent cascade genetic testing in first-degree relatives are recommended (Figure 1) [8].

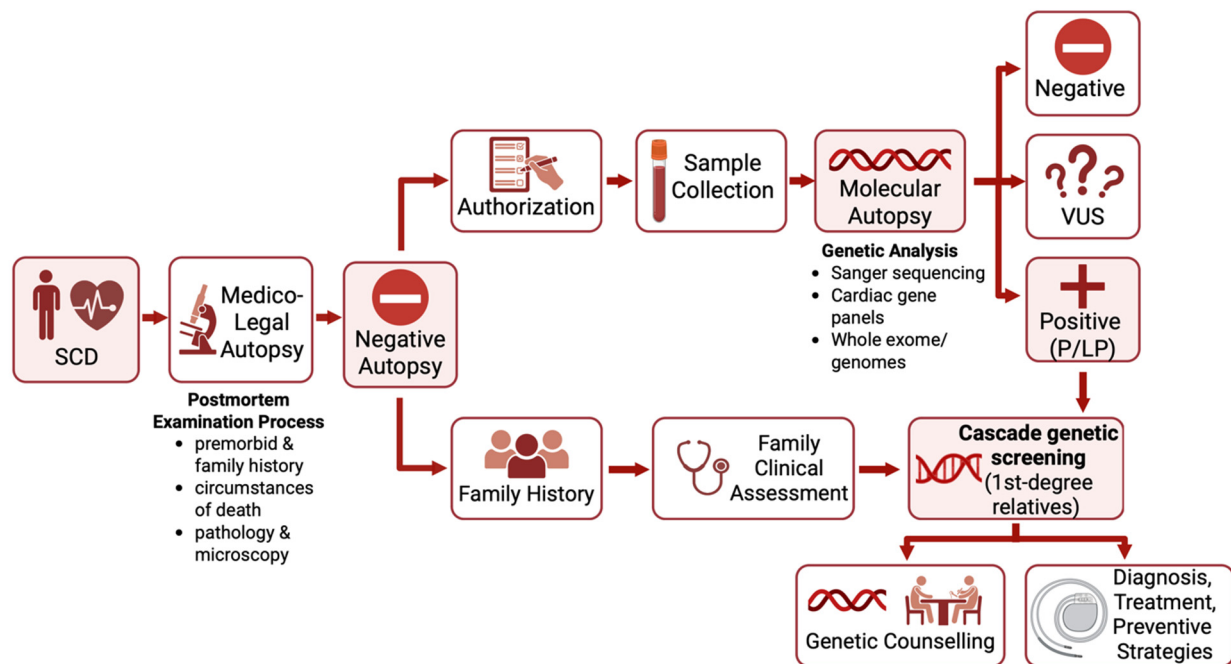


Figure 1. Post-mortem diagnostic pathway and familial evaluation after sudden arrhythmic death. This figure illustrates the diagnostic pathway following sudden cardiac death, integrating medico-legal autopsy findings with molecular autopsy, genetic analysis, and subsequent cascade screening of first-degree relatives.

Undetected cardiovascular diseases may predispose to SCD: most cases indeed result from arrhythmic events, such as ventricular fibrillation (VF) or ventricular tachycardia [9]. The causes of SCD can be broadly categorized into structural and arrhythmogenic etiologies. In individuals under 35 years, SCD is most often due to congenital or inherited cardiac conditions, whereas CAD accounts for approximately 80% of SCD cases in those over 35 years [7].

Among the structural causes in young individuals, HCM remains the most common, followed by DCM, ARVC and NDLVC [10]. In cardiomyopathies, post-mortem examination typically identifies a clear pathological substrate. In contrast, this is not the case for inherited arrhythmogenic disorders, such as LQTS, SQTS, BrS, and CPVT. These disorders result from pathogenic variants affecting cardiac ion channel genes, predisposing individuals to ventricular arrhythmias and VF [11]. Because these conditions rarely produce structural cardiac abnormalities, post-mortem examinations are often unremarkable (“negative autopsy”), with normal histology and toxicology. These unexplained sudden deaths, which may account for up to 40% of SCD cases in the young (1–40 years), are referred to as sudden arrhythmic death syndrome (SADS) [10].

In this context, genetic testing has become a key diagnostic and preventive tool, particularly in SADS among children and young adults. As many of these disorders follow an autosomal dominant inheritance pattern, identifying a pathogenic variant enables post-mortem diagnosis, family risk stratification, and implementation of targeted preventive measures.

3. Genetic Basis of Sudden Cardiac Death in Cardiomyopathies

The main group of inherited arrhythmogenic syndromes responsible for SCD in the young are cardiomyopathies, characterized by progressive structural abnormalities that predispose to malignant arrhythmias. Although structural changes can be detected at forensic autopsy, the major arrhythmic event may eventually occur before overt structural changes become apparent in the heart [12]. This is the so-called “concealed cardiomyopathy” [13].

A wide range of genes have been implied in inherited cardiomyopathies, reflecting the marked genetic heterogeneity underlying these disorders (Table 1) [14]. Most of them encode sarcomere proteins, which are responsible for force generation in the myocardium [15]. Other genes implied are desmosomal ones, whose variation leads to impaired cell-cell adhesion and myocardial fibrofatty replacement, and cytoskeletal and Z-disc genes, which play structural and signaling roles [16]. Finally, genes related to calcium handling and various metabolic or storage disorders can also be involved.

Table 1. Genes associated with major monogenic cardiomyopathies, inheritance patterns, and characteristic ECG/CMR features.

Cardiomyopathy	Common Associated Genes	Inheritance	Other: Typical ECG/CMR Patterns (When Relevant)
HCM	Sarcomeric: <i>ACTC1</i> [17], <i>MYBPC3</i> [18], <i>MYH7</i> [19], <i>MYL2</i> [20], <i>MYL3</i> [21], <i>TNNI3</i> [22], <i>TNNT2</i> [22]	AD: Predominantly sarcomeric, RASopathy	ECG: Low-voltage QRS, Q waves/pseudo-infarct pattern (amyloidosis).
	Others: <i>ABCC9</i> [23], <i>ALPK3</i> [24], <i>BAG3</i> [25], <i>CACNA1C</i> [26], <i>CAV3</i> [26], <i>COX15</i> [27], <i>CRYAB</i> [28], <i>DES</i> [29], <i>FHL1</i> [30], <i>FLNC</i> [31], <i>FXN</i> [32], <i>GAA</i> [33], <i>GLA</i> [34], <i>LAMP2</i> [35], <i>LDB3</i> [36], <i>PLN</i> [36], <i>PRKAG2</i> [37], <i>PTPN11</i> [38], <i>RAF1</i> [39], <i>RIT1</i> [40], <i>SLC25A4</i> [41], <i>TPM1</i> [42], <i>TTR</i> [43]	X-linked: Anderson–Fabry (<i>GLA</i>), Danon disease (<i>LAMP2</i>) AR: Friedreich’s ataxia (<i>FXN</i>)	CMR: Patchy mid-wall LGE in hypertrophied segments (sarcomeric HCM).
DCM	Titin: <i>TTN</i> [44]	AD: <i>LMNA</i> , <i>RBM20</i> , sarcomeric	ECG: AV block/conduction disease (<i>LMNA</i> , <i>DES</i>). Low peripheral QRS voltages (<i>PLN</i>). Pseudo-infarct posterolateral pattern (<i>DMD</i>).
	Nuclear envelope: <i>LMNA</i> [45] Others: <i>BAG3</i> [45], <i>DES</i> [46,47], <i>DMD</i> [48], <i>DSP</i> [49], <i>FLNC</i> [50], <i>MYH7</i> [51], <i>PLN</i> [52], <i>RBM20</i> [53], <i>SCN5A</i> [54], <i>TNNC1</i> [55], <i>TNNT2</i> [56]	X-linked: Dystrophinopathy (<i>DMD</i>), Emery–Dreifuss disease (emerin) AR: <i>DES</i>	CMR: Mid-wall septal LGE (<i>LMNA</i>). Extensive inferolateral LGE (dystrophinopathies). Ring-like/subepicardial LGE (<i>DSP</i> , truncating <i>FLNC</i>).

Table 1. Cont.

Cardiomyopathy	Common Associated Genes	Inheritance	Other: Typical ECG/CMR Patterns (When Relevant)
NDLVC	Frequent: <i>DSP</i> [57], <i>FLNC</i> [57], <i>LMNA</i> [58], <i>PLN</i> [14], <i>RBM20</i> [59], <i>TMEM43</i> [14]	AD: <i>LMNA</i> , <i>DES</i> , <i>FLNC</i> , <i>PLN</i> , <i>TMEM43</i> , <i>RBM20</i> AR: <i>DES</i>	ECG: AV block/conduction disease (<i>LMNA</i> , <i>DES</i>). Low QRS voltages (<i>DSP</i> , <i>PLN</i>).
	Others [60]: <i>ACTC1</i> , <i>ACTN2</i> , <i>DES</i> , <i>DMD</i> , <i>DMPK</i> , <i>GATA4</i> , <i>ILK</i> , <i>LDB3</i> , <i>MIB1</i> , <i>MYBPC3</i> , <i>MYH7</i> , <i>MYL2</i> , <i>MYL3</i> , <i>NKX2-5</i> , <i>NNT</i> , <i>NONO</i> , <i>OBSCN</i> , <i>PRDM16</i> , <i>SCN5A</i> , <i>TAZ</i> , <i>TBX5</i> , <i>TBX20</i> , <i>TCAP</i> , <i>TNNT2</i> , <i>TPM1</i> , <i>TTN</i>		CMR: Presence of non-ischemic scar (LGE) or fatty replacement, often essential for diagnosis. Ring-like/subepicardial pattern (<i>DSP</i> , <i>FLNC</i> , <i>PLN</i> , <i>TMEM43</i>). Mid-wall septal fibrosis (<i>LMNA</i>).
ARVC	Desmosomal: <i>PKP2</i> [61], <i>DSP</i> [62], <i>DSG2</i> [63], <i>DSC2</i> [63], <i>JUP</i> [64]	AD: <i>PLN</i> , Desmosomal, <i>TMEM43</i> AR: Desmosomal	ECG: T-wave inversion in V1–V3; terminal activation delay.
	Others: <i>DES</i> [65], <i>PLN</i> [66], <i>TMEM43</i> [67]		CMR: Structural/functional RV abnormalities; fibrofatty replacement, often biventricular. CMR is recommended as a first-line imaging modality for RV assessment.
RCM	Sarcomeric: <i>TNNI3</i> [68], <i>MYBPC3</i> [69], <i>MYH7</i> [70], <i>MYL2</i> [71], <i>MYL3</i> [72], <i>MYPN</i> [73], <i>TNNT2</i> [74], <i>TMP1</i> [42], <i>TTN</i> [75]	AD: Sarcomeric, <i>DES</i> , <i>FLNC</i> , <i>BAG3</i> , <i>RASopathy</i> AR: <i>DES</i>	ECG: AV block (desminopathy, amyloidosis).
	Other: <i>ACTN2</i> [76], <i>BAG3</i> [77], <i>DES</i> [78], <i>FHL1</i> [30], <i>FLNC</i> [79]		CMR: Partial LV or RV apical obliteration + LGE at endocardial level.

AD = autosomal dominant; AR = autosomal recessive; ARVC = arrhythmogenic right ventricular cardiomyopathy; AV = atrioventricular; CMR = cardiac magnetic resonance; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LGE = late gadolinium enhancement; NDLVC = non-dilated left ventricular cardiomyopathy; RCM = restrictive cardiomyopathy; RV = right ventricular.

3.1. Hypertrophic Cardiomyopathy

HCM is a genetically heterogeneous disease with variable expressivity and incomplete penetrance, characterized by left ventricle hypertrophy not entirely explained by cardiac overload [60].

The most recent American Heart Association (AHA) classification subdivides HCM into primary HCM, caused by variants in sarcomeric genes, and secondary HCM, due to non-sarcomeric mutation (e.g., metabolic disorders, neuromuscular diseases, malformative syndromes or mitochondrial disorders) [80]. Pathogenic variants in sarcomeric genes can be detected in 40% of sporadic and 60% of familial HCM cases [81]. The most commonly involved genes encode cardiac myosin-binding protein C (*MYBPC3*, accounting for approximately 30–40% of cases), β -myosin heavy chain (*MYH7*, accounting for approximately 10–30%) and cardiac troponin T and I (*TNNT2* and *TNNI3*, each accounting for 3–10%) [82,83].

In pediatric patients and young athletes [84], HCM is associated with an increased arrhythmic risk due to myocyte disarray, cardiac fibrosis and small-vessel disease, resulting in higher SCD risk. Currently, both pediatric and adult SCD risk scores do not include genetic testing as a predictive factor [85–88], because its prognostic role remains uncertain and therefore not clinically useful [12]. Nevertheless, in patients with a family history of HCM, identifying a pathogenic variant may identify patients at risk of developing HCM during follow-up and potentially introduce personalized management [89,90].

3.2. Dilated Cardiomyopathy

DCM is defined as the presence of LV dilatation and global or regional systolic dysfunction unexplained solely by abnormal loading conditions or CAD [91]. Despite improvements in DCM management, the incidence of SCD remains approximately 0.15% per year, mainly due to ventricular arrhythmias and electromechanical dissociation [92].

In pediatric patients, an inherited cause is the most common etiology, with genetic variants accounting for up to 50% of idiopathic DCM cases [93]. Genetic testing is recommended in patients with idiopathic DCM, particularly in young individuals and in those with conduction delay or a positive family history [94]. As an inherited cardiomyopathy, DCM is usually transmitted in an autosomal dominant pattern, with more than 40 implicated genes, mostly encoding sarcomeric or structural proteins. Among these, *TTN* truncating variants are the most frequent, accounting for more than 25% of hereditary DCM [95]. The association between *TTN* variants and SCD is not limited to a higher burden of high-risk non-sustained ventricular tachycardia; rather, it appears to be primarily driven by severe left ventricular dysfunction and myocardial fibrosis [44].

Recent studies indicate that pathogenic variants in *PLN* [52], *DSP* [49], *LMNA* [45], *FLNC* [96], *DES* [46,47], and *RBM20* [53] confer significantly higher arrhythmic risk than other causes of DCM, independent of systolic function [92]. In *LMNA* pathogenic variant carriers, the arrhythmic substrate for ventricular arrhythmias coexists with an elevated risk of brady-arrhythmias due to atrioventricular block, together predisposing to SCD and supporting ICD-based preventive strategies [97]. In the *DES* gene, the coil 1 domain is a mutational hotspot. The p.L136P and p.A120D variants impair filament assembly: the former is associated with DCM, whereas the latter disrupts desmin localization at the intercalated disc, increasing arrhythmic risk [46,47].

The growing evidence linking specific phenotypes with variants in genes encoding nuclear envelope proteins (*LMNA*, *EMD*, and *TMEM43*), desmosomal proteins (*DSP*, *DSG2*, *DSC2* and *PKP2*), and certain cytoskeleton proteins has led to the development of risk-estimation scores to identify individuals with an increased risk for SCD [98]. Particularly, specific risk scores for *PLN* R14del [99], *FLNC* truncating variant [100], *LMNA* [98] and *DSP* [101] variants are available.

3.3. Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC is a genetically determined heart muscle disorder characterized by fibrofatty replacement of the myocardium [60]. This pathological remodeling creates an anatomical substrate for electrical instability, which predisposes affected individuals (particularly young patients and athletes) to SCD, with an incidence of approximately 7% per year as shown in a meta-analysis of 5845 ARVC patients without ICD [102].

ARVC is typically inherited in an autosomal dominant pattern with incomplete penetrance, or it may arise from de novo pathogenic variants. The involved genes include desmosomal genes, such as *PKP2* (plakophilin-2), *DSP* (desmoplakin), *DSG2* (desmoglein-2), *DSC2* (desmocollin-2), and *JUP* (plakoglobin) [103]. Carriers of multiple pathogenic variants often exhibit an earlier onset of sustained ventricular arrhythmias.

Although most desmosomal variants confer comparable risk, *DSP* variants are particularly associated with increased susceptibility to SCD [104], while *PKP2* variants have been linked to earlier arrhythmic onset [105]. Non-desmosomal genes such as *TMEM43*, *LMNA*, and *PLN* also contribute to arrhythmogenic phenotypes, increasing SCD risk [106].

3.4. Non-Dilated Left Ventricular Cardiomyopathy

According to the latest ESC guidelines, NDLVC is a recently defined entity characterized by left ventricular non-ischemic scarring, with or without global or regional systolic dysfunction, without evidence of left ventricular dilation [60]. Among the diagnostic criteria, global isolated hypokinesia without scarring not explained by loading conditions is included [60]. It shares a genetic continuum with DCM and ARVC, and SCD risk and ICD indications largely mirror those of DCM, with myocardial fibrosis representing an additional arrhythmic substrate.

Although the etiology is heterogenous, a recent study involving 42 NDLVC patients displayed positive genetic testing in more than one-third of them. Particularly, a genetic cause was more frequent in patients with LV fibrosis at CMR [107]. As with other cardiomyopathies, genetic predisposition is a key determinant of SCD risk [60]. Among high-risk genotypes, *LMNA* pathogenic variants are notable for their high penetrance, often leading to early-onset ventricular arrhythmias or advanced atrioventricular blocks [108]. Similarly, the *DSP* [104], *RBM20* and *PLN* pathogenic variants are associated with a higher incidence risk of life-threatening arrhythmias. The genetic overlap among DCM, NDLVC, and ARVC, particularly involving desmosomal genes (*DSP*, *DSG2*, *DSC2*, *PKP2*), emphasizes the need for etiology-based diagnosis to guide management [14].

High-risk genotypes, myocardial inflammation, male sex, non-sustained VTs, left ventricular ejection fraction <45%, and septal or ring-like late gadolinium enhancement have been recently identified as independent predictors of a first major arrhythmic event within 60 months, leading to the development of a validated risk prediction score [108].

3.5. Restrictive Cardiomyopathy

RCM is the least common form of cardiomyopathy and is characterized by restrictive left or right ventricular pathophysiology due to myocardial dysfunction, interstitial fibrosis or endomyocardial disorders. The disease often progresses rapidly, leading to heart failure and frequently requiring heart transplantation. Both metabolic (i.e., Anderson–Fabry disease) and infiltrative disorders, such as cardiac amyloidosis, may present with a restrictive phenotype [92].

Evidence regarding SCD risk stratification in RCM is limited for most etiologies. Nevertheless, arrhythmias are highly prevalent, with a great incidence of atrial fibrillation and approximately 10% of VTs, contributing to an increase risk of intracardiac thrombosis and death [109].

From a genetic perspective, variants encoding for cardiac troponin I (*TNNI3*) represent the major identified genetic cause of primary RCM. Particularly, in a large Chinese pediatric RCM cohort (n = 185), *TNNI3* variants were identified in 61% of patients, followed by *MYH7* and *TTNT2* [110]. In a pediatric RCM case, a pathogenic variant in encoded cardiac troponin T (*TNNT2-R94C*) was shown to cause dysfunction of calcium-dependent regulation of myocardial contraction, probably leading to malignant arrhythmias [74]. However, the genetic RCM background partially overlaps with other cardiomyopathies, including variants in *DES* or *FLNC* genes [111]. Given the short event-free survival, often less than two years, management strategies such as low thresholds for ICD or early referral for heart transplant should be considered to reduce SCD risk.

4. Genetic Basis of Sudden Cardiac Death in Channelopathies

Approximately 5% of SCD occur in patients without structural heart disease or CAD and are therefore attributed to primary electric disorders [112]. Cardiac channelopathies alter the cardiac action potential and the electrical conduction system and are predominantly caused by pathogenic variants in ion channel genes (Figure 2). Variants affecting sodium channels (*SCN5A*), potassium channels (*KCNQ1*, *KCNH2*, *KCNJ2*), and calcium channels or calcium-regulating proteins (*CACNA1C*, *CALM1*, *CALM2*, *CALM3*), as well as genes involved in calcium release from the sarcoplasmic reticulum (*RYR2*, *CASQ2*, *TRDN*, *TECLRL*), have been implicated in these disorders [113].

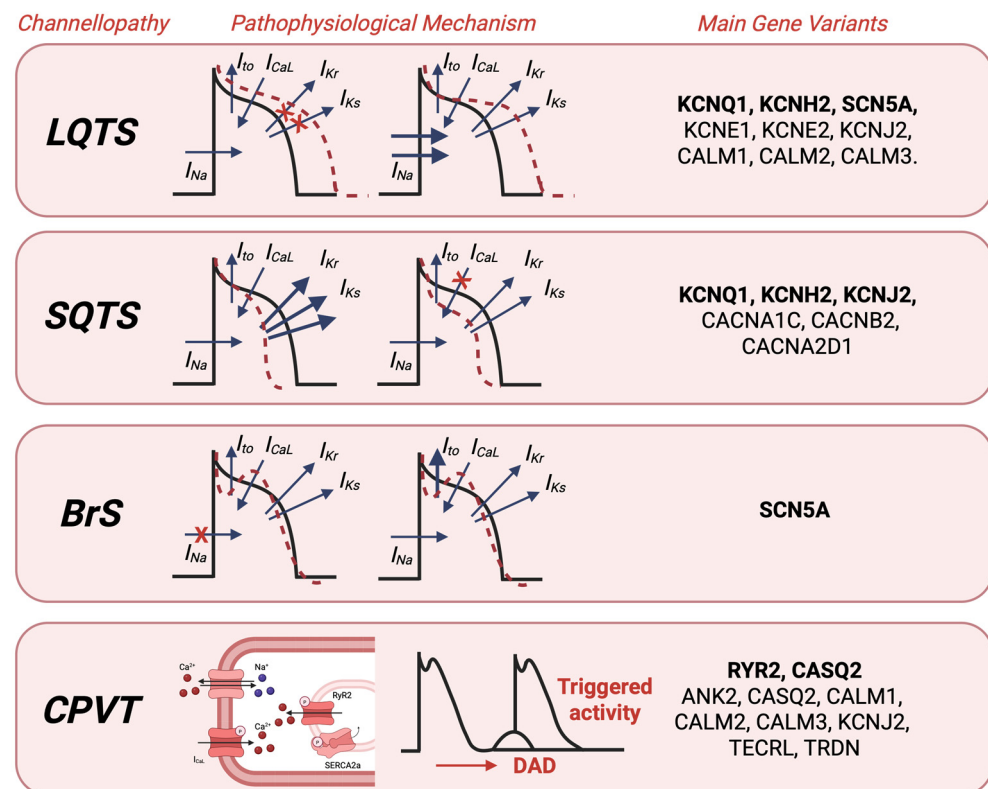


Figure 2. Channelopathies: Main pathophysiological mechanisms and main genes variants. Schematic overview of the key pathophysiological mechanisms and major gene variants associated with the main cardiac channelopathies. For LQTS, prolonged repolarization is caused by reduced outward K⁺ currents or increased inward Na⁺/Ca²⁺ currents. SQTs results from accelerated repolarization due to increased K⁺ currents or, in some cases, Ca²⁺-channel loss of function. Brugada syndrome is characterized by early repolarization abnormalities mainly due to reduced Na⁺ current or increased I_{to}. CPVT arises from abnormal sarcoplasmic reticulum Ca²⁺ handling leading to delayed after depolarizations (DADs) and triggered activity. Genes shown in bold are those with definitive or strong evidence for pathogenic involvement. Dotted lines illustrate the modifications of the cardiac action potential associated with each channelopathy. Red crosses indicate ion currents that are abolished, while thicker arrows represent enhancement of the corresponding currents.

Genetic testing plays a key role in diagnosis and risk stratification. Early identification of affected individuals through recognition of specific electrocardiographic abnormalities at rest or arrhythmogenic responses during exercise or pharmacological testing is essential for timely management [95].

4.1. Long QT Syndrome

LQTS is an inherited channelopathy characterized by a delayed ventricular repolarization, manifesting as a prolonged corrected QT interval (>450 ms in men and >470 ms in

women) [1]. It represents the most frequent genetic channelopathy, with an estimated prevalence of 1 in 2000/2500 individuals in the general population. The disorder most commonly results from loss-of-function variants in the voltage-gated potassium channel, leading to a prolonged action potential duration [114].

According to the gene variant implied, we can distinguish three main genotypes, accounting 75–90% of diagnosed cases [115]. LQT1 is caused by pathogenic variants in the *KCNQ1* gene, encoding the alpha-subunit of the slow delayed rectifier potassium current. LQT2 is associated with *KCNH2* variants, affecting the rapid delayed rectifier current, while LQT3 is caused by gain-of-function variants in *SCN5A*, which enhance the late sodium current [116,117]. LQTS exhibits incomplete penetrance and variable expressivity, even within the same family [118]. The presence of modifier genes partially explains this variability. For instance, *NOS1AP* or *KCHN2* polymorphism can modulate arrhythmic risk [118].

A prolonged QTc reflects an increased action potential duration and increased cardiomyocyte refractoriness, responsible for an electrical substrate that can result in frequent early afterdepolarizations [106]. This electrical heterogeneity can generate the substrate for polymorphic ventricular arrhythmias, particularly torsades de pointes, and consequently to SCD [117]. Nevertheless, the arrhythmic risk is highly heterogeneous and depends on the interplay of clinical, electrophysiological and genetic factors. Genotype-specific triggers have been described: arrhythmias typically occur during sport in LQT1 patients; during emotional or auditory stress in LQT2 patients; and during sleep or at rest in LQT3 individuals [119].

In LQTS, lifestyle modification is essential, including avoidance of QT-prolonging drugs, correction of electrolyte imbalances, and prevention of genotype-specific triggers [120]. From a pharmacological standpoint, non-selective β -blockers, such as nadolol or propranolol, are the most effective in reducing arrhythmic risk and are recommended even for genotype-positive, phenotype-negative individuals [121]. Genotype-specific therapies, such as mexiletine for LQT3, may be beneficial [122]. ICD implantation is indicated in symptomatic or high-risk patients [1], while left cardiac sympathetic denervation can be considered for recurrent or refractory ventricular arrhythmias [123].

4.2. Short QT Syndrome

SQTS is a rare inherited channelopathy characterized by an abnormally short QT interval on the ECG (<350 ms) and an increased susceptibility to supraventricular and ventricular arrhythmias, including SCD [106]. Despite its severity, SQTS remains poorly understood and underdiagnosed.

From a genetic standpoint, pathogenic variants in potassium channel genes, most commonly *KCNH2*, *KCNQ1*, and *KCNJ2*, account for a proportion of cases. Interestingly, although these are the same genes implicated in LQTS, the variants in SQTS are gain-of-function, leading to accelerated cardiac repolarization rather than its delay. In addition, variants in genes encoding the $\text{Ca}_v1.2$ L-type calcium channel subunits (*CACNA1C* and *CACNB2*) have been described. These variants abbreviate the ventricular action potential and may produce an overlapping Brugada ECG phenotype.

The arrhythmogenic mechanism of SQTS remains incompletely defined, even if it is thought to involve an increased transmural dispersion of repolarization, resulting from heterogeneity in the action potential duration across the ventricular wall. Notably, despite the presence of a positive family history in approximately half of patients, only a minority ($\approx 14\%$) of clinically diagnosed cases have an identifiable genetic variant, underscoring the genetic heterogeneity and current limitations of molecular diagnosis [124]. SQTS is

considered a highly lethal condition, emphasizing the need for early recognition and tailored management.

4.3. Brugada Syndrome

BrS, first described as an inherited arrhythmia syndrome by Pedro and Josep Brugada, is a polygenic cardiac channelopathy characterized by a predisposition to syncope, ventricular arrhythmias, and SCD, most commonly occurring during sleep [125]. The global prevalence is estimated at approximately 0.5 per 1000 individuals, with a male predominance [125]. However, its true prevalence is likely underestimated, as many affected individuals remain asymptomatic or may present with SCD as the first manifestation.

BrS reflects abnormalities in ion channel function, particularly involving the right ventricular outflow tract, leading to both repolarization and depolarization disturbances. These electrical alterations manifest as the characteristic “coved-type” ST-segment elevation in the right precordial ECG leads (i.e., V1–V3), known as the Brugada type 1 pattern. In certain cases, the ECG abnormalities are latent and require pharmacological provocation (e.g., with ajmaline or flecainide) to unmask the diagnostic pattern [1].

BrS accounts for up to 28% of SCD cases in individuals with structurally normal hearts, most often due to VF, triggered by premature ventricular complexes with a short coupling interval [126,127]. Two main hypotheses have been proposed to explain its arrhythmogenic mechanism: the repolarization and the depolarization ones [120]. The repolarization hypothesis suggests that accentuated transmural gradients in repolarization, driven by enhanced outward potassium currents, produce both the ECG features and the propensity for re-entry [128]. The depolarization hypothesis posits that conduction slowing, particularly in the RVOT, leads to delayed activation and truncation of the action potential upstroke, facilitating re-entrant arrhythmias [129].

Only variants in the *SCN5A* gene are currently recognized as definitively disease-causing for BrS, although the majority of cases are not attributable to a single pathogenic variant [130]. *SCN5A* encodes the α -subunit of the cardiac sodium channel $Na_v1.5$, and loss-of-function variants lead to impaired sodium current due to delayed channel activation and premature inactivation, ultimately resulting in abbreviation of the cardiac action potential [131]. Beyond *SCN5A*, more than 20 additional genes have been proposed to contribute to BrS pathogenesis. However, using an evidence-based semiquantitative scoring system integrating genetic and experimental data, independent curation teams demonstrated that, to date, only *SCN5A* shows definitive evidence for disease causation, while the causal role of the other genes remains disputed [130]. These include genes encoding other sodium channel subunits (*SCN1B*, *SCN2B*, *SCN3B*, *SCN10A*), potassium channel components (*KCNAB2*, *KCNE3*, *KCND3*, *SEMA3A*), and L-type calcium channel subunits (*CACNA1C*, *CACNB2b*) [127]. Moreover, variants in non-channel proteins, such as *GPD1L* (which regulates $Na_v1.5$ phosphorylation) [132] and *PKP2* (a desmosomal protein) [133], have also been implicated.

The current evidence supports a polygenic or multifactorial inheritance model, with multiple variants and modifier genes contributing to disease expression, as demonstrated from genome-wide association studies [134]. Notably, three single-nucleotide polymorphisms (SNPs, *rs11708996* in *SCN5A*, *rs10428132* in *SCN10A*, and *rs9388451* near *HEY2*) were identified to be associated with increased BrS risk, leading to the development of a BrS polygenic risk score. While *SCN5A* remains a key genetic determinant for BrS SCD risk stratification as demonstrated by a recent meta-analysis [135], polygenic and electrophysiological studies support a multifactorial risk model [136].

ICD implantation represents the cornerstone of BrS management and remains the most effective method for SCD prevention [125]. Given that BrS diagnosis is mostly done in

young individuals, accurate risk stratification is crucial [94]. In patients at high risk for SCD but also at increased risk of device-related infection, a subcutaneous ICD may represent an effective alternative. Conversely, in lower-risk patients, such as asymptomatic patients with a drug-provoked type 1 ECG pattern, the use of an implantable loop recorder should be preferred for long-term rhythm monitoring [137].

4.4. Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is a rare inherited arrhythmia with an estimated prevalence of approximately 1 in 10,000 individuals. It typically manifests in childhood, between 4 and 12 years, with exercise- or emotion-induced syncope or cardiac arrest [138]. The baseline ECG is usually normal, and diagnosis relies on exercise testing, after the exclusion of structural heart disease. During exertion, premature ventricular contractions usually appears at heart rates over 100 beats per minute and may progress to polymorphic VT or to the pathognomonic “bidirectional VT” [139]. Although many patients remain asymptomatic, symptomatic individuals usually experience stress-induced syncope, making athletes a particularly vulnerable population [140]. Despite being less frequent than LQTS, CPVT accounts for a significant proportion of SADS, with an untreated mortality rate approaching 30% before the age of 40 years [141].

Pathogenic variants in *RYR2* (encoding the cardiac ryanodine receptor) cause approximately 60% of cases and are inherited in an autosomal dominant manner, whereas *CASQ2* (encoding calsequestrin-2) variants account for about 5% and follow an autosomal recessive pattern [142]. Rare variants in other calcium-handling genes, such as *CALM1* and *TRDN*, have also been described [139]. CPVT results from an abnormal calcium release from the sarcoplasmic reticulum, leading to cytosolic Ca^{2+} overload and activation of the $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger. The consequent transient inward current produces delayed afterdepolarizations that can trigger ventricular arrhythmias [106].

The role of genetic testing in CPVT is evolving, as benign variants in *RYR2* are a relatively common finding in these patients. Nevertheless, *RYR2* variants affecting the C-terminal region are associated with a high risk of life-threatening arrhythmias [143,144], while *CASQ2* variants are linked to a more severe phenotype [145]. The overall diagnostic yield of genetic testing remains modest, with approximately 40% of clinically diagnosed cases testing negative [119].

Management focuses on reducing adrenergic stimulation through lifestyle modification (avoidance of emotional stress and competitive sports), and non-selective β -blockers, which represent first-line therapy and are also recommended for asymptomatic carriers [146]. Flecainide may be added in symptomatic or refractory patients. In high-risk individuals, left cardiac sympathetic denervation or ICD implantation can be considered, although ICD use remains controversial due to the risk of catecholamine-mediated electrical storms [147].

5. Genetic Basis of Sudden Unexplained Death

While autopsy may identify a structural cardiac abnormality, up to 40% of sudden deaths remain unexplained even after comprehensive pathological and toxicological assessment, warranting a more in-depth search for underlying genetic causes [148]. This scenario is particularly common in the young, where a fatal arrhythmia is often presumed. In such cases, post-mortem genetic testing enhances diagnostic accuracy, as cardiomyopathies and channelopathies [149] represent major inherited causes of SCD in the absence of structural heart disease [150].

The so-called “molecular autopsy” is typically performed on fresh-frozen tissue or EDTA-preserved blood, and the current guidelines recommend retaining formalin-fixed,

paraffin-embedded samples to enable subsequent DNA analysis [151]. Over the past two decades, molecular autopsy has evolved from Sanger sequencing of selected candidate genes to NGS and WES [152], expanding analysis to both channelopathy- and cardiomyopathy-related genes.

Traditional genetic testing targeted only four major genes (*KCNQ1*, *KCNH2*, *SCN5A*, and *RYR2*), yielding putatively pathogenic variants in $\leq 30\%$ of autopsy-negative SUD cases. The use of WES increases this yield, reaching up to 44% in a study of 32 SUD cases [153], although results across large cohorts remain heterogeneous (13–44%) [149,154]. The diagnostic utility of molecular autopsy alone is significantly improved when combined with clinical and genetic evaluation of relatives (cascade screening), achieving an overall diagnostic yield up to 39% [149].

The diagnostic utility of molecular autopsy alone ($\approx 13\text{--}22\%$) is significantly enhanced when combined with comprehensive clinical and genetic evaluation of surviving relatives (cascade screening), reaching an overall diagnostic yield of up to 39% [149]. Genetic contributors to sudden unexplained death are mainly variants in channelopathy genes [155] (such as *SCN5A*, *KCNQ1*, *KCNH2*, and *RYR2*) and in cardiomyopathy genes (e.g., *MYBPC3*, *MYH7*, *PKP2*, *DSP*, *TTN*), supporting the concept of concealed cardiomyopathy [150]. An extended approach using WES, a broadened virtual gene panel, and multidisciplinary variant prioritization has achieved a 69% diagnostic yield, including 80% in structurally normal hearts, outperforming standard genetic strategies in a cohort of 39 cases [156].

Beside the identification of putative or causative pathogenic or likely pathogenic variants, variants of uncertain significance (VUS) are identified in up to 50–80% of cases, underscoring the need for a multidisciplinary approach to classify their probability of being pathogenic or benign [156]. When the heart appears structurally normal, a broader genomic approach, extending beyond targeted panels and incorporating polygenic risk assessment, may further enhance diagnostic yield [157].

6. Genetics for Prediction of Sudden Cardiac Death

In addition to demographic and environmental determinants, familial aggregation and heritable factors substantially contribute to the overall risk of SCD [2]. Furthermore, familial predisposition plays a significant role in the susceptibility to SCD. A family history of SCD in a first-degree relative has been shown to be independently associated with an increased risk of SCD [4]. The risk is further amplified within the framework of parental early-onset SCD, particularly when both parents are affected [2]. Nevertheless, especially in DCM patients, a negative family history does not exclude familial disease [158].

For Mendelian cardiovascular disorders, the role of genetic testing is well established, enabling the identification of pathogenic variants and the implementation of gene-specific preventive and therapeutic strategies, as well as a cascade screening of relatives [159]. Conversely, the contribution of genetic testing to the prediction of CAD-associated SCD remains scarce, with the notable exception of familial hypercholesterolemia [160].

It has been hypothesized that SCD in the setting of common and complex disease does not result from a single mutation but rather from the cumulative effect of multiple SNPs [9], each conferring a modest increase in risk. GWASs have therefore compared the genomes of individuals who experienced sudden cardiac arrest to those of healthy controls, identifying common variants associated with SCD risk [161], some of them overlapping with loci influencing established risk factors such as QT interval duration [162].

In parallel, polygenic risk scores, which aggregate the effects of numerous SNPs into a single estimate of genetic susceptibility, are emerging as a potential tool for identifying individuals at high risk of SCD [9], especially CAD-associated SCD [163]. However, their

clinical translation remains limited, largely due to challenges in demonstrating strong and specific associations between genetic profiles and SCD occurrence.

Importantly, the traditional dichotomy between monogenic and polygenic diseases is increasingly being reconsidered. Evidence suggests that, in classical monogenic disorders, such as BrS and inherited cardiomyopathies, common genetic variants may act as modifiers of disease penetrance and severity, thereby blurring the boundary between monogenic and polygenic inheritance [9].

7. Clinical Consequences of Positive Genetic Testing

The risk of SCD is dynamic and influenced by multifactorial drivers and may vary over time, requiring continuous and individualized monitoring. Genotype-positive individuals should undergo periodic assessment through ECG, Holter monitoring, imaging and stress testing, and other non-invasive tools [1,60]. While genetic analysis cannot replace clinical assessment due to its variable yield, it complements it by identifying pathogenic or sporadic variants that direct the targeted evaluation of relatives.

In families with a proband carrying pathogenic variants associated with cardiomyopathies or channelopathies, first-degree relatives should initially undergo ECG and echocardiography [89], as up to 60% may show latent phenotypes [2]. Early detection allows timely preventive measures such as ICD implantation, pharmacologic therapy, or lifestyle adjustments [92].

Genetic counselling is crucial to ensure accurate interpretation of results and informed decision-making [164], also because up to 50% of first-degree relatives display a positive genetic testing for genes associated with SCD [13]. Variant misclassification can lead to inappropriate management and significant psychological distress; thus, evaluation should occur within expert multidisciplinary teams [156]. National registries, such as ToRSADe, are instrumental for harmonizing diagnostic criteria and improving genotype–phenotype correlations [165].

Given that disease expression and arrhythmic risk evolve, periodic re-evaluation is essential, reflecting the shift toward precision medicine. Moreover, comprehensive post-cardiac arrest care, including psychological support and rehabilitation, is fundamental for survivors and their families to restore quality of life [166].

8. Future Perspectives

Advances in NGS technologies have made large-scale genetic testing increasingly accessible and affordable. WES and whole-genome sequencing (WGS) now represent key tools for identifying novel variants and expanding the spectrum of genes associated with SCD [136,167]. When clinical testing fails to reveal a causative variant in patients with a strong suspicion of inherited disease, genomic research focused on novel gene discovery should be prioritized [9].

Although genetic testing has proven effective in monogenic conditions, our understanding remains incomplete [151]. A comprehensive view of SCD susceptibility will emerge only by integrating genetic, epigenetic, and environmental determinants. Artificial intelligence and machine learning will be pivotal in managing the expanding volume of genomic and clinical data, refining variant classification, and improving diagnostic accuracy through large, publicly available genotype–phenotype databases [94].

Emerging therapeutic strategies, including gene therapy, hold promise for directly correcting pathogenic variants and restoring normal protein function [95]. In CPVT, for instance, adeno-associated viral vectors expressing the *CASQ2* gene have shown antiarrhythmic effects in preclinical models, proportional to protein restoration levels [168].

Finally, ensuring equitable access to genetic testing, counselling, and post-mortem molecular analysis remains a global priority. The implementation of standardized and widely available genetic screening is essential to translate genomic advances into effective prevention and care.

9. Conclusions

SCD remains a major global health challenge, particularly in such cases that remain unexplained. While in older people established cardiovascular diseases are the most frequent causes of SCD, inherited cardiomyopathies and channelopathies are the predominant etiology in the young. Pathogenic or likely pathogenic variants in sarcomeric and ion channel genes are the most common findings, with each cardiomyopathy or channelopathy associated with specific gene variants and molecular mechanisms.

In this setting, the increased accessibility to low-cost NGS and the new multidisciplinary genetic approach have substantially improved diagnostic accuracy and familiar risk assessment. Therefore, genetic testing has become part of the clinical practice and post-mortem examination as well, enabling precision in diagnosis, prevention, and patient-tailored therapy. Nevertheless, the full translation of genetic discoveries into clinical benefit requires continuous refinement of variant interpretation, integration with other “omics” approaches, and incorporation of artificial intelligence tools. Moving forward, equitable access to genetic testing and expert interpretation will be essential to ensure that genomic medicine effectively contributes to reducing the burden of sudden cardiac death worldwide.

Author Contributions: Conceptualization, S.M., E.M. and G.L.; writing—original draft preparation, S.M., E.M., G.D., E.B., V.F., M.R., M.C., A.F., A.C., F.V., F.D., G.P. and F.B.; writing—review and editing, G.F., M.G.R., P.C. and G.L.; visualization, S.M.; supervision, G.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were generated or analyzed in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Zeppenfeld, K.; Tfelt-Hansen, J.; de Riva, M.; Winkel, B.G.; Behr, E.R.; Blom, N.A.; Charron, P.; Corrado, D.; Dagres, N.; de Chillou, C.; et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur. Heart J.* **2022**, *43*, 3997–4126. [[CrossRef](#)] [[PubMed](#)]
2. Scrocco, C.; Bezzina, C.R.; Ackerman, M.J.; Behr, E.R. Genetics and genomics of arrhythmic risk: Current and future strategies to prevent sudden cardiac death. *Nat. Rev. Cardiol.* **2021**, *18*, 774–784. [[CrossRef](#)]
3. Hayashi, M.; Shimizu, W.; Albert, C.M. The Spectrum of Epidemiology Underlying Sudden Cardiac Death. *Circ. Res.* **2015**, *116*, 1887–1906. [[CrossRef](#)] [[PubMed](#)]
4. Deo, R.; Albert, C.M. Epidemiology and Genetics of Sudden Cardiac Death. *Circulation* **2012**, *125*, 620–637. [[CrossRef](#)]
5. Chugh, S.S.; Uy-Evanado, A.; Teodorescu, C.; Reinier, K.; Mariani, R.; Gunson, K.; Jui, J. Women have a lower prevalence of structural heart disease as a precursor to sudden cardiac arrest: The Ore-SUDS (Oregon Sudden Unexpected Death Study). *J. Am. Coll. Cardiol.* **2009**, *54*, 2006–2011. [[CrossRef](#)]
6. Becker, L.B.; Han, B.H.; Meyer, P.M.; Wright, F.A.; Rhodes, K.V.; Smith, D.W.; Barrett, J. Racial Differences in the Incidence of Cardiac Arrest and Subsequent Survival. *N. Engl. J. Med.* **1993**, *329*, 600–606. [[CrossRef](#)]
7. Kumar, A.; Avishay, D.M.; Jones, C.R.; Shaikh, J.D.; Kaur, R.; Aljadah, M.; Kichloo, A.; Shiwalkar, N.; Keshavamurthy, S. Sudden cardiac death: Epidemiology, pathogenesis and management. *Rev. Cardiovasc. Med.* **2021**, *22*, 147. [[CrossRef](#)]

8. Basso, C.; Aguilera, B.; Banner, J.; Cohle, S.; d'Amati, G.; de Gouveia, R.H.; di Gioia, C.; Fabre, A.; Gallagher, P.J.; Leone, O.; et al. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. *Virchows Arch.* **2017**, *471*, 691–705. [\[CrossRef\]](#)
9. Marijon, E.; Narayanan, K.; Smith, K.; Barra, S.; Basso, C.; Blom, M.T.; Crotti, L.; D'Avila, A.; Deo, R.; Dumas, F.; et al. The Lancet Commission to reduce the global burden of sudden cardiac death: A call for multidisciplinary action. *Lancet* **2023**, *402*, 883–936. [\[CrossRef\]](#)
10. Semsarian, C.; Ingles, J. Molecular autopsy in victims of inherited arrhythmias. *J. Arrhythmia* **2016**, *32*, 359–365. [\[CrossRef\]](#)
11. Sarquella-Brugada, G.; Campuzano, O.; Iglesias, A.; Sánchez-Malagón, J.; Guerra-Balic, M.; Brugada, J.; Brugada, R. Genetics of sudden cardiac death in children and young athletes. *Cardiol. Young* **2013**, *23*, 159–173. [\[CrossRef\]](#)
12. Martínez-Barrios, E.; Grassi, S.; Brión, M.; Toro, R.; Cesar, S.; Cruzalegui, J.; Coll, M.; Alcalde, M.; Brugada, R.; Greco, A.; et al. Molecular autopsy: Twenty years of post-mortem diagnosis in sudden cardiac death. *Front. Med.* **2023**, *10*, 1118585. [\[CrossRef\]](#)
13. Isbister, J.C.; Nowak, N.; Yeates, L.; Singer, E.S.; Sy, R.W.; Ingles, J.; Raju, H.; Bagnall, R.D.; Semsarian, C. Concealed Cardiomyopathy in Autopsy-Inconclusive Cases of Sudden Cardiac Death and Implications for Families. *J. Am. Coll. Cardiol.* **2022**, *80*, 2057–2068. [\[CrossRef\]](#)
14. Mistrulli, R.; Ferrera, A.; Salerno, L.; Vannini, F.; Guida, L.; Corradetti, S.; Addeo, L.; Valcher, S.; Di Gioia, G.; Spera, F.R.; et al. Cardiomyopathy and Sudden Cardiac Death: Bridging Clinical Practice with Cutting-Edge Research. *Biomedicines* **2024**, *12*, 1602. [\[CrossRef\]](#)
15. Žebrauskienė, D.; Sadauskienė, E.; Puronaitė, R.; Masiulienė, R.; Vaišnorė, R.; Bratčikovienė, N.; Valevičienė, N.; Barysienė, J.; Jakaitienė, A.; Preikšaitienė, E. Genotype-Phenotype Relationship in Hypertrophic Cardiomyopathy. *Genes* **2025**, *16*, 1090. [\[CrossRef\]](#)
16. Eldemire, R.; Mestroni, L.; Taylor, M.R.G. Genetics of Dilated Cardiomyopathy. *Annu. Rev. Med.* **2024**, *75*, 417–426. [\[CrossRef\]](#)
17. Zarate, Y.A.; Abdelmoti, L.M.; Oh, S.; White, A.; Starks, C.; Au, M.G.; Chen, J.; Weaver, N.K.; Korotkov, K.V.; Galperin, E. ACTC1 Variants Result in Isolated and Syndromic Cardiac Phenotypes. *Clin. Genet.* **2025**, *108*, 713–719. [\[CrossRef\]](#)
18. Adalsteinsdottir, B.; Burke, M.; Maron, B.J.; Danielsen, R.; Lopez, B.; Diez, J.; Jarolim, P.; Seidman, J.; Seidman, C.E.; Ho, C.Y.; et al. Hypertrophic cardiomyopathy in myosin-binding protein C (MYBPC3) Icelandic founder mutation carriers. *Open Heart* **2020**, *7*, e001220. [\[CrossRef\]](#)
19. Kelly, M.A.; Caleshu, C.; Morales, A.; Buchan, J.; Wolf, Z.; Harrison, S.M.; Cook, S.; Dillon, M.W.; Garcia, J.; Haverfield, E.; et al. Adaptation and validation of the ACMG/AMP variant classification framework for MYH7-associated inherited cardiomyopathies: Recommendations by ClinGen's Inherited Cardiomyopathy Expert Panel. *Genet. Med.* **2018**, *20*, 351–359. [\[CrossRef\]](#)
20. Manivannan, S.N.; Darouch, S.; Masmoudi, A.; Gordon, D.; Zender, G.; Han, Z.; Fitzgerald-Butt, S.; White, P.; McBride, K.L.; Kharrat, M.; et al. Novel frameshift variant in MYL2 reveals molecular differences between dominant and recessive forms of hypertrophic cardiomyopathy. *PLoS Genet.* **2020**, *16*, e1008639. [\[CrossRef\]](#)
21. Osborn, D.P.S.; Emrahi, L.; Clayton, J.; Tabrizi, M.T.; Wan, A.Y.B.; Maroofian, R.; Yazdchi, M.; Garcia, M.L.E.; Galehdari, H.; Hesse, C.; et al. Autosomal recessive cardiomyopathy and sudden cardiac death associated with variants in MYL3. *Genet. Med.* **2021**, *23*, 787–792. [\[CrossRef\]](#)
22. Pua, C.J.; Tham, N.; Chin, C.W.L.; Walsh, R.; Khor, C.C.; Toepfer, C.N.; Repetti, G.G.; Garfinkel, A.C.; Ewoldt, J.F.; Cloonan, P.; et al. Genetic Studies of Hypertrophic Cardiomyopathy in Singaporeans Identify Variants in *TNNI3* and *TNNT2* That Are Common in Chinese Patients. *Circ. Genom. Precis. Med.* **2020**, *13*, 424–434. [\[CrossRef\]](#)
23. Fernlund, E.; Kissopoulou, A.; Green, H.; Karlsson, J.E.; Ellegård, R.; Årstrand, H.K.; Jonasson, J.; Gunnarsson, C. Hereditary Hypertrophic Cardiomyopathy in Children and Young Adults—The Value of Reevaluating and Expanding Gene Panel Analyses. *Genes* **2020**, *11*, 1472. [\[CrossRef\]](#)
24. Lopes, L.R.; Garcia-Hernández, S.; Lorenzini, M.; Futema, M.; Chumakova, O.; Zateyshchikov, D.; Isidoro-Garcia, M.; Villacorta, E.; Escobar-Lopez, L.; Garcia-Pavia, P.; et al. Alpha-protein kinase 3 (ALPK3) truncating variants are a cause of autosomal dominant hypertrophic cardiomyopathy. *Eur. Heart J.* **2021**, *42*, 3063–3073. [\[CrossRef\]](#)
25. Park, J.; Levin, M.G.; Zhang, D.; Reza, N.; Mead, J.O.; Carruth, E.D.; Kelly, M.A.; Winters, A.; Kripke, C.M.; Judy, R.L.; et al. Bidirectional Risk Modulator and Modifier Variant of Dilated and Hypertrophic Cardiomyopathy in *BAG3*. *JAMA Cardiol.* **2024**, *9*, 1124–1133. [\[CrossRef\]](#)
26. Rubattu, S.; Bozzao, C.; Pennacchini, E.; Pagannone, E.; Musumeci, B.M.; Pian, M.; Germani, A.; Savio, C.; Francia, P.; Volpe, M. A Next-Generation Sequencing Approach to Identify Gene Mutations in Early- and Late-Onset Hypertrophic Cardiomyopathy Patients of an Italian Cohort. *Int. J. Mol. Sci.* **2016**, *17*, 1239. [\[CrossRef\]](#)
27. Antonicka, H.; Mattman, A.; Carlson, C.G.; Glerum, D.M.; Hoffbuhr, K.C.; Leary, S.C.; Kennaway, N.G.; Shoubbridge, E.A. Mutations in COX15 Produce a Defect in the Mitochondrial Heme Biosynthetic Pathway, Causing Early-Onset Fatal Hypertrophic Cardiomyopathy. *Am. J. Hum. Genet.* **2003**, *72*, 101–114. [\[CrossRef\]](#)

28. Thorkelsson, A.; Chou, C.; Tripp, A.; Ali, S.A.; Galper, J.; Chin, M.T. Hypertrophic Cardiomyopathy-Associated CRYABR123W Activates Calcineurin, Reduces Calcium Sequestration, and Alters the CRYAB Interactome and the Proteomic Response to Pathological Hypertrophy. *Int. J. Mol. Sci.* **2025**, *26*, 2383. [\[CrossRef\]](#)
29. Tadros, R.; Francis, C.; Xu, X.; Vermeer, A.M.C.; Harper, A.R.; Huurman, R.; Kelu Bisabu, K.; Walsh, R.; Hoorntje, E.T.; Te Rijdt, W.P.; et al. Shared genetic pathways contribute to risk of hypertrophic and dilated cardiomyopathies with opposite directions of effect. *Nat. Genet.* **2021**, *53*, 128–134. [\[CrossRef\]](#)
30. Binder, M.S.; Brown, E.; Aversano, T.; Wagner, K.R.; Calkins, H.; Barth, A.S. Novel FHL1 Mutation Associated with Hypertrophic Cardiomyopathy, Sudden Cardiac Death, and Myopathy. *JACC Case Rep.* **2020**, *2*, 372–377. [\[CrossRef\]](#)
31. Walsh, R.; Offerhaus, J.A.; Tadros, R.; Bezzina, C.R. Minor hypertrophic cardiomyopathy genes, major insights into the genetics of cardiomyopathies. *Nat. Rev. Cardiol.* **2022**, *19*, 151–167. [\[CrossRef\]](#)
32. Payne, R.M.; Wagner, G.R. Cardiomyopathy in Friedreich Ataxia: Clinical Findings and Research. *J. Child Neurol.* **2012**, *27*, 1179–1186. [\[CrossRef\]](#)
33. Rupp, S.; Felimban, M.; Schänzer, A.; Schranz, D.; Marschall, C.; Zenker, M.; Logeswaran, T.; Neuhäuser, C.; Thul, J.; Jux, C.; et al. Genetic basis of hypertrophic cardiomyopathy in children. *Clin. Res. Cardiol.* **2019**, *108*, 282–289. [\[CrossRef\]](#)
34. Chaves-Markman, A.V.; Markman, M.; Calado, E.B.; Pires, R.F.; Santos-Veloso, M.A.O.; Pereira, C.M.F.; Lordsleem, A.B.M.D.S.; Lima, S.G.; Markman Filho, B.; Oliveira, D.C. GLA Gene Mutation in Hypertrophic Cardiomyopathy with a New Variant Description: Is it Fabry's Disease? *Arq. Bras. Cardiol.* **2019**, *113*, 77–84. [\[CrossRef\]](#)
35. Meinert, M.; Englund, E.; Hedberg-Oldfors, C.; Oldfors, A.; Kornhall, B.; Lundin, C.; Wittström, E. Danon disease presenting with early onset of hypertrophic cardiomyopathy and peripheral pigmentary retinal dystrophy in a female with a de novo novel mosaic mutation in the LAMP2 gene. *Ophthalmic Genet.* **2019**, *40*, 227–236. [\[CrossRef\]](#)
36. Zheng, J.; Huang, Z.; Hou, S.; Jiang, X.; Zhang, Y.; Liu, W.; Jia, J.; Li, Y.; Sun, X.; Xie, L. Case Report: Novel LIM domain-binding protein 3 (LDB3) mutations associated with hypertrophic cardiomyopathy family. *Front. Pediatr.* **2022**, *10*, 947963. [\[CrossRef\]](#)
37. Ahamed, H.; Balegadde, A.V.; Menon, S.; Menon, R.; Ramachandran, A.; Mathew, N.; Natarajan, K.U.; Nair, I.R.; Kannan, R.; Shankar, M.; et al. Phenotypic expression and clinical outcomes in a South Asian PRKAG2 cardiomyopathy cohort. *Sci. Rep.* **2020**, *10*, 20610. [\[CrossRef\]](#)
38. Tartaglia, M.; Kalidas, K.; Shaw, A.; Song, X.; Musat, D.L.; van der Burgt, I.; Brunner, H.G.; Bertola, D.R.; Crosby, A.; Ion, A.; et al. PTPN11 Mutations in Noonan Syndrome: Molecular Spectrum, Genotype-Phenotype Correlation, and Phenotypic Heterogeneity. *Am. J. Hum. Genet.* **2002**, *70*, 1555–1563. [\[CrossRef\]](#)
39. Thompson, D.; Patrick-Esteve, J.; Surcouf, J.W.; Rivera, D.; Castellanos, B.; Desai, P.; Lilje, C.; Lacassie, Y.; Marble, M.; Zambrano, R. RAF1 variants causing biventricular hypertrophic cardiomyopathy in two preterm infants: Further phenotypic delineation and review of literature. *Clin. Dysmorphol.* **2017**, *26*, 195–199. [\[CrossRef\]](#)
40. Leegaard, A.; Gregersen, P.A.; Nielsen, T.Ø.; Bjerre, J.V.; Handrup, M.M. Successful MEK-inhibition of severe hypertrophic cardiomyopathy in RIT1-related Noonan Syndrome. *Eur. J. Med. Genet.* **2022**, *65*, 104630. [\[CrossRef\]](#)
41. Von Renesse, A.; Morales-Gonzalez, S.; Gill, E.; Salomons, G.S.; Stenzel, W.; Schuelke, M. Muscle Weakness, Cardiomyopathy, and L-2-Hydroxyglutaric Aciduria Associated with a Novel Recessive SLC25A4 Mutation. In *JIMD Reports*; Morava, E., Baumgartner, M., Patterson, M., Rahman, S., Zschocke, J., Peters, V., Eds.; Springer: Berlin/Heidelberg, Germany, 2018; Volume 43, pp. 27–35. [\[CrossRef\]](#)
42. Carlus, S.J.; Almuzaini, I.S.; Karthikeyan, M.; Loganathan, L.; Al-Harbi, G.S.; Carlus, F.H.; Al-Mazroea, A.H.; Morsy, M.M.; Abo-Haded, H.M.; Abdallah, A.M.; et al. A novel homozygous TPM1 mutation in familial pediatric hypertrophic cardiomyopathy and in silico screening of potential targeting drugs. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 7732–7744. [\[CrossRef\]](#)
43. Lopes, L.R.; Futema, M.; Akhtar, M.M.; Lorenzini, M.; Pittman, A.; Syrris, P.; Elliott, P.M. Prevalence of TTR variants detected by whole-exome sequencing in hypertrophic cardiomyopathy. *Amyloid* **2019**, *26*, 243–247. [\[CrossRef\]](#)
44. Akhtar, M.M.; Lorenzini, M.; Cicerchia, M.; Ochoa, J.P.; Hey, T.M.; Sabater Molina, M.; Restrepo-Cordoba, M.A.; Dal Ferro, M.; Stolfo, D.; Johnson, R.; et al. Clinical Phenotypes and Prognosis of Dilated Cardiomyopathy Caused by Truncating Variants in the TTN Gene. *Circ. Heart Fail.* **2020**, *13*, e006832. [\[CrossRef\]](#)
45. Wang, Z.; Wu, J.; Lv, Z.; Liang, P.; Li, Q.; Li, Y.; Guo, Y. LMNA-related cardiomyopathy: From molecular pathology to cardiac gene therapy. *J. Adv. Res.* **2025**, *77*, 443–464. [\[CrossRef\]](#)
46. Asatryan, B.; Rieder, M.; Murray, B.; Muller, S.A.; Tichnell, C.; Gasperetti, A.; Carrick, R.T.; Joseph, E.; Leung, D.G.; Te Riele, A.S.J.M.; et al. Natural History, Phenotype Spectrum, and Clinical Outcomes of Desmin (DES)-Associated Cardiomyopathy. *Circ. Genom. Precis. Med.* **2025**, *18*, e004878. [\[CrossRef\]](#)
47. Brodehl, A.; Diedingm, M.; Biere, N.; Unger, A.; Klauke, B.; Walhorn, V.; Gummert, J.; Schulz, U.; Linke, W.A.; Gerull, B.; et al. Functional characterization of the novel DES mutation p.L136P associated with dilated cardiomyopathy reveals a dominant filament assembly defect. *J. Mol. Cell. Cardiol.* **2016**, *91*, 207–214. [\[CrossRef\]](#)

48. Johnson, R.; Otway, R.; Chin, E.; Horvat, C.; Ohanian, M.; Wilcox, J.A.L.; Su, Z.; Prestes, P.; Smolnikov, A.; Soka, M.; et al. DMD-Associated Dilated Cardiomyopathy: Genotypes, Phenotypes, and Phenocopies. *Circ. Genom. Precis. Med.* **2023**, *16*, 421–430. [[CrossRef](#)]
49. Augusto, J.B.; Eiros, R.; Nakou, E.; Moura-Ferreira, S.; Treibel, T.A.; Captur, G.; Akhtar, M.M.; Protonotarios, A.; Gossios, T.D.; Savvatis, K.; et al. Dilated cardiomyopathy and arrhythmogenic left ventricular cardiomyopathy: A comprehensive genotype-imaging phenotype study. *Eur. Heart J.-Cardiovasc. Imaging* **2019**, *21*, 326–336. [[CrossRef](#)]
50. Ortiz-Genga, M.F.; Cuenca, S.; Dal Ferro, M.; Zorio, E.; Salgado-Aranda, R.; Climent, V.; Padrón-Barthe, L.; Duro-Aguado, I.; Jiménez-Jáimez, J.; Hidalgo-Olivares, V.M.; et al. Truncating FLNC Mutations Are Associated with High-Risk Dilated and Arrhythmogenic Cardiomyopathies. *J. Am. Coll. Cardiol.* **2016**, *68*, 2440–2451. [[CrossRef](#)]
51. De Frutos, F.; Ochoa, J.P.; Navarro-Peñalver, M.; Baas, A.; Bjerre, J.V.; Zorio, E.; Méndez, I.; Lorca, R.; Verdonshot, J.A.J.; García-Granja, P.E.; et al. Natural History of MYH7-Related Dilated Cardiomyopathy. *J. Am. Coll. Cardiol.* **2022**, *80*, 1447–1461. [[CrossRef](#)]
52. Feyen, D.A.M.; Perea-Gil, I.; Maas, R.G.C.; Harakalova, M.; Gavidia, A.A.; Arthur Ataam, J.; Wu, T.H.; Vink, A.; Pei, J.; Vadgama, N.; et al. Unfolded Protein Response as a Compensatory Mechanism and Potential Therapeutic Target in PLN R14del Cardiomyopathy. *Circulation* **2021**, *144*, 382–392. [[CrossRef](#)] [[PubMed](#)]
53. Gregorich, Z.R.; Zhang, Y.; Kamp, T.J.; Granzier, H.L.; Guo, W. Mechanisms of RBM20 Cardiomyopathy: Insights from Model Systems. *Circ. Genom. Precis. Med.* **2024**, *17*, e004355. [[CrossRef](#)] [[PubMed](#)]
54. Wilde, A.A.M.; Amin, A.S. Clinical Spectrum of SCN5A Mutations. *JACC Clin. Electrophysiol.* **2018**, *4*, 569–579. [[CrossRef](#)]
55. Mazzarotto, F.; Tayal, U.; Buchan, R.J.; Midwinter, W.; Wilk, A.; Whiffin, N.; Govind, R.; Mazaika, E.; de Marvao, A.; Dawes, T.J.W.; et al. Reevaluating the Genetic Contribution of Monogenic Dilated Cardiomyopathy. *Circulation* **2020**, *141*, 387–398. [[CrossRef](#)]
56. Hershberger, R.E.; Pinto, J.R.; Parks, S.B.; Kushner, J.D.; Li, D.; Ludwigsen, S.; Cowan, J.; Morales, A.; Parvatiyar, M.S.; Potter, J.D. Clinical and Functional Characterization of TNNT2 Mutations Identified in Patients with Dilated Cardiomyopathy. *Circ. Cardiovasc. Genet.* **2009**, *2*, 306–313. [[CrossRef](#)]
57. Vodnjov, N.; Zupan Mežnar, A.; Maver, A.; Dolinšek, A.; Peterlin, B.; Writzl, K. Non-dilated left ventricular cardiomyopathy with arrhythmias is commonly caused by the nonsense variant *DSP: c. 3793G >T* in Slovenian patients. *Clin. Genet.* **2024**, *106*, 500–504. [[CrossRef](#)]
58. Setti, M.; Iseppi, M.; Verdonshot, J.A.J.; Rizzi, J.G.; Paldino, A.; Pio Loco Detto Gava, C.; Barbati, G.; Dal Ferro, M.; Venner, M.F.G.H.M.; Raafs, A.G.; et al. Integrated Role of Cardiac Magnetic Resonance and Genetics in Predicting Left Ventricular Reverse Remodelling in Dilated and Non-Dilated Cardiomyopathy. *Eur. J. Heart Fail.* **2025**, *27*, 2571–2581. [[CrossRef](#)]
59. Gaertner, A.; Klauke, B.; Brodehl, A.; Milting, H. *RBM20* mutations in left ventricular non-compaction cardiomyopathy. *Pediatr. Investig.* **2020**, *4*, 61–63. [[CrossRef](#)]
60. Arbelo, E.; Protonotarios, A.; Gimeno, J.R.; Arbustini, E.; Barriales-Villa, R.; Basso, C.; Bezzina, C.R.; Biagini, E.; Blom, N.A.; de Boer, R.A.; et al. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur. Heart J.* **2023**, *44*, 3503–3626. [[CrossRef](#)]
61. Smith, E.D.; Lakdawala, N.K.; Papoutsidakis, N.; Aubert, G.; Mazzanti, A.; McCanta, A.C.; Agarwal, P.P.; Arscott, P.; Dellefave-Castillo, L.M.; Vorovich, E.E.; et al. Desmoplakin Cardiomyopathy, a Fibrotic and Inflammatory Form of Cardiomyopathy Distinct from Typical Dilated or Arrhythmogenic Right Ventricular Cardiomyopathy. *Circulation* **2020**, *141*, 1872–1884. [[CrossRef](#)] [[PubMed](#)]
62. Giannoni, A.; Modena, M.; Montuoro, S.; Bonanni, F.; Grigoratos, C.; Barison, A.; Todiere, G.; Rossi, A.; Vittorini, S.; Emdin, M.; et al. A Novel Homozygous Mutation of the Desmoplakin Gene with Biventricular Arrhythmogenic Cardiomyopathy. *JACC Case Rep.* **2025**, *30*, 103688. [[CrossRef](#)] [[PubMed](#)]
63. Chen, L.; Hu, Y.; Saguner, A.M.; Bause, B.; Liu, Y.; Shi, A.; Guan, F.; Chen, Z.; Bueno Marinas, M.; Wu, L.; et al. Natural History and Clinical Outcomes of Patients with *DSG2/DSC2* Variant-Related Arrhythmogenic Right Ventricular Cardiomyopathy. *Circulation* **2025**, *151*, 1213–1230. [[CrossRef](#)]
64. Vahidnezhad, H.; Vahidnezhad, H.; Youssefian, L.; Faghankhani, M.; Mozafari, N.; Saeidian, A.H.; Niaziarimi, F.; Abdollahimajd, F.; Sotoudeh, S.; Rajabi, F.; et al. Arrhythmogenic right ventricular cardiomyopathy in patients with biallelic JUP-associated skin fragility. *Sci. Rep.* **2020**, *10*, 21622. [[CrossRef](#)]
65. Hedberg, C.; Melberg, A.; Kuhl, A.; Jenne, D.; Oldfors, A. Autosomal dominant myofibrillar myopathy with arrhythmogenic right ventricular cardiomyopathy 7 is caused by a DES mutation. *Eur. J. Hum. Genet.* **2012**, *20*, 984–985. [[CrossRef](#)]
66. Li, Z.; Chen, P.; Xu, J.; Yu, B.; Li, X.; Wang, D.W.; Wang, D.W. A PLN nonsense variant causes severe dilated cardiomyopathy in a novel autosomal recessive inheritance mode. *Int. J. Cardiol.* **2019**, *279*, 122–125. [[CrossRef](#)]
67. Bariani, R.; Rigato, I.; Cason, M.; Marinas, M.B.; Celeghin, R.; Pilichou, K.; Bause, B. Genetic Background and Clinical Features in Arrhythmogenic Left Ventricular Cardiomyopathy: A Systematic Review. *J. Clin. Med.* **2022**, *11*, 4313. [[CrossRef](#)] [[PubMed](#)]
68. Mouton, J.; Pellizzon, A.S.; Goosen, A.; Kinnear, C.J.; Herbst, P.G.; Brink, P.A.; Moolman-Smook, J.C. Diagnostic disparity and identification of two TNNI3 gene mutations, one novel and one arising de novo, in South African patients with restrictive cardiomyopathy and focal ventricular hypertrophy. *Cardiovasc. J. Afr.* **2015**, *26*, 63–69. [[CrossRef](#)]

69. Blagova, O.; Pavlenko, E.; Sedov, V.; Kogan, E.; Polyak, M.; Zaklyazminskaya, E.; Lutokhina, Y. Different Phenotypes of Sarcomeric MyBPC3-Cardiomyopathy in the Same Family: Hypertrophic, Left Ventricular Noncompaction and Restrictive Phenotypes (in Association with Sarcoidosis). *Genes* **2022**, *13*, 1344. [\[CrossRef\]](#)
70. Zhao, Y.; Liu, S.; Mo, H.; Hua, X.; Chen, X.; Zhang, Y.; Wang, W.; Zhao, Q.; Song, J. MYH7 Mutations in Restrictive Cardiomyopathy. *JACC Adv.* **2025**, *4*, 101693. [\[CrossRef\]](#) [\[PubMed\]](#)
71. De Bortoli, M.; Vio, R.; Basso, C.; Calore, M.; Minervini, G.; Angelini, A.; Melacini, P.; Vitiello, L.; Vazza, G.; Thiene, G.; et al. Novel Missense Variant in MYL2 Gene Associated with Hypertrophic Cardiomyopathy Showing High Incidence of Restrictive Physiology. *Circ. Genom. Precis. Med.* **2020**, *13*, e002824. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Kazmierczak, K.; Liang, J.; Maura, L.G.; Scott, N.K.; Szczesna-Cordary, D. Phosphorylation Mimetic of Myosin Regulatory Light Chain Mitigates Cardiomyopathy-Induced Myofilament Impairment in Mouse Models of RCM and DCM. *Life* **2023**, *13*, 1463. [\[CrossRef\]](#)
73. Filomena, M.C.; Yamamoto, D.L.; Caremani, M.; Kadarla, V.K.; Mastrototaro, G.; Serio, S.; Vydyanath, A.; Mutarelli, M.; Garofalo, A.; Pertici, I.; et al. Myopalladin promotes muscle growth through modulation of the serum response factor pathway. *J. Cachexia Sarcopenia Muscle* **2020**, *11*, 169–194. [\[CrossRef\]](#)
74. Ezekian, J.E.; Clippinger, S.R.; Garcia, J.M.; Yang, Q.; Denfield, S.; Jeewa, A.; Dreyer, W.J.; Zou, W.; Fan, Y.; Allen, H.D.; et al. Variant R94C in TNNT2-Encoded Troponin T Predisposes to Pediatric Restrictive Cardiomyopathy and Sudden Death Through Impaired Thin Filament Relaxation Resulting in Myocardial Diastolic Dysfunction. *J. Am. Heart Assoc.* **2020**, *9*, e015111. [\[CrossRef\]](#) [\[PubMed\]](#)
75. Wacker, J.; Di Bernardo, S.; Lobrinus, J.A.; Jungbluth, H.; Gautel, M.; Beghetti, M.; Fluss, J. Successful heart transplant in a child with congenital core myopathy and delayed-onset restrictive cardiomyopathy due to recessive mutations in the titin (TTN) gene. *Pediatr. Transplant.* **2023**, *27*, e14561. [\[CrossRef\]](#) [\[PubMed\]](#)
76. Lan, B.; Liu, Z.; Bai, J.; Tang, J.; Zhang, J. Restrictive cardiomyopathy due to new mutation in the ACTN2 gene: A case report. *Eur. Heart J.-Case Rep.* **2025**, *9*, ytaf421. [\[CrossRef\]](#)
77. Schänzer, A.; Rupp, S.; Gräf, S.; Zengeler, D.; Jux, C.; Akintürk, H.; Gulatz, L.; Mazhari, N.; Acker, T.; Van Coster, R.; et al. Dysregulated autophagy in restrictive cardiomyopathy due to Pro209Leu mutation in BAG3. *Mol. Genet. Metab.* **2018**, *123*, 388–399. [\[CrossRef\]](#)
78. Tuoliken, S.; Li, J.-H.; Lu, M. Restrictive cardiomyopathy with unique fibrosis pattern and familial atrial arrhythmia associated with DES mutation. *Eur. Heart J.* **2025**, *46*, 2031. [\[CrossRef\]](#)
79. Aristizabal, A.M.; Guzmán-Serrano, C.A.; Lizcano, M.I.; Mosquera, W.; Lores, J.; Pachajoa, H.; Cely, C. FLNC Associada a Cardiomiopatia Restritiva e Hipertrabeculação, uma Associação Rara. *Arq. Bras. Cardiol.* **2024**, *121*, e20230790. [\[CrossRef\]](#)
80. Ommen, S.R.; Ho, C.Y.; Asif, I.M.; Balaji, S.; Burke, M.A.; Day, S.M.; Dearani, J.A.; Epps, K.C.; Evanovich, L.; Ferrari, V.A.; 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* **2024**, *149*, e1239–e1311. [\[CrossRef\]](#) [\[PubMed\]](#)
81. Finocchiaro, G.; Bhatia, R.T.; Westaby, J.; Behr, E.R.; Papadakis, M.; Sharma, S.; Sheppard, M.N. Sudden Cardiac Death During Exercise in Young Individuals with Hypertrophic Cardiomyopathy. *JACC Clin. Electrophysiol.* **2023**, *9*, 865–867. [\[CrossRef\]](#)
82. Del Duca, F.; Ghamlouch, A.; Manetti, A.C.; Napoletano, G.; Sonnini, E.; Treves, B.; De Matteis, A.; La Russa, R.; Sheppard, M.N.; Fineschi, V.; et al. Sudden Cardiac Death, Post-Mortem Investigation: A Proposing Panel of First Line and Second Line Genetic Tests. *J. Pers. Med.* **2024**, *14*, 544. [\[CrossRef\]](#)
83. Topriceanu, C.-C.; Pereira, A.C.; Moon, J.C.; Captur, G.; Ho, C.Y. Meta-Analysis of Penetrance and Systematic Review on Transition to Disease in Genetic Hypertrophic Cardiomyopathy. *Circulation* **2024**, *149*, 107–123. [\[CrossRef\]](#)
84. Finocchiaro, G.; Westaby, J.; Sheppard, M.N.; Papadakis, M.; Sharma, S. Sudden Cardiac Death in Young Athletes. *J. Am. Coll. Cardiol.* **2024**, *83*, 350–370. [\[CrossRef\]](#)
85. O'Mahony, C.; Jichi, F.; Pavlou, M.; Monserrat, L.; Anastasakis, A.; Rapezzi, C.; Biagini, E.; Gimeno, J.R.; Limongelli, G.; McKenna, W.J.; et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). *Eur. Heart J.* **2014**, *35*, 2010–2020. [\[CrossRef\]](#) [\[PubMed\]](#)
86. Norrish, G.; Ding, T.; Field, E.; Ziolkowska, L.; Olivotto, I.; Limongelli, G.; Anastasakis, A.; Weintraub, R.; Biagini, E.; Ragni, L.; et al. Development of a Novel Risk Prediction Model for Sudden Cardiac Death in Childhood Hypertrophic Cardiomyopathy (HCM Risk-Kids). *JAMA Cardiol.* **2019**, *4*, 918–927. [\[CrossRef\]](#)
87. Monda, E.; Limongelli, G. Integrated Sudden Cardiac Death Risk Prediction Model For Patients with Hypertrophic Cardiomyopathy. *Circulation* **2023**, *147*, 281–283. [\[CrossRef\]](#) [\[PubMed\]](#)
88. Montuoro, S.; Monda, E.; Limongelli, G. Risk Models for Sudden Cardiac Death in Hypertrophic Cardiomyopathy. *J. Am. Coll. Cardiol.* **2025**, *86*, 67–70. [\[CrossRef\]](#)
89. Teekakirikul, P.; Zhu, W.; Huang, H.C.; Fung, E. Hypertrophic Cardiomyopathy: An Overview of Genetics and Management. *Biomolecules* **2019**, *9*, 878. [\[CrossRef\]](#) [\[PubMed\]](#)

90. Bakalakos, A.; Monda, E.; Elliott, P.M. Tailored therapeutics for cardiomyopathies. *Nat. Rev. Cardiol.* **2025**, *22*, 814–831. [\[CrossRef\]](#)
91. Elliott, P.; Andersson, B.; Arbustini, E.; Bilinska, Z.; Cecchi, F.; Charron, P.; Dubourg, O.; Kühn, U.; Maisch, B.; McKenna, W.J.; et al. Classification of the cardiomyopathies: A position statement from the european society of cardiology working group on myocardial and pericardial diseases. *Eur. Heart J.* **2007**, *29*, 270–276. [\[CrossRef\]](#)
92. Polovina, M.; Tschöpe, C.; Rosano, G.; Metra, M.; Crea, F.; Mullens, W.; Bauersachs, J.; Sliwa, K.; de Boer, R.A.; Farmakis, D.; et al. Incidence, risk assessment and prevention of sudden cardiac death in cardiomyopathies. *Eur. J. Heart Fail.* **2023**, *25*, 2144–2163. [\[CrossRef\]](#)
93. Gigli, M.; Merlo, M.; Graw, S.L.; Barbati, G.; Rowland, T.J.; Slavov, D.B.; Stolfo, D.; Haywood, M.E.; Dal Ferro, M.; Altinier, A.; et al. Genetic Risk of Arrhythmic Phenotypes in Patients with Dilated Cardiomyopathy. *J. Am. Coll. Cardiol.* **2019**, *74*, 1480–1490. [\[CrossRef\]](#)
94. Tfelt-Hansen, J.; Garcia, R.; Albert, C.; Merino, J.; Krahn, A.; Marijon, E.; Basso, C.; Wilde, A.A.M.; Haugaa, K.H. Risk stratification of sudden cardiac death: A review. *EP Eur.* **2023**, *25*, eua203. [\[CrossRef\]](#) [\[PubMed\]](#)
95. Dewars, E.R.; Landstrom, A.P. The Genetic Basis of Sudden Cardiac Death: From Diagnosis to Emerging Genetic Therapies. *Annu. Rev. Med.* **2025**, *76*, 283–299. [\[CrossRef\]](#)
96. Verdonchot, J.A.J.; Vanhoutte, E.K.; Claes, G.R.F.; Helderma-van den Enden, A.T.J.M.; Hoeijmakers, J.G.J.; Hellebrekers, D.M.E.I.; de Haan, A.; Christiaans, I.; Lekanne Deprez, R.H.; Boen, H.M.; et al. A mutation update for the *FLNC* gene in myopathies and cardiomyopathies. *Hum. Mutat.* **2020**, *41*, 1091–1111. [\[CrossRef\]](#) [\[PubMed\]](#)
97. Van Rijsingen, I.A.W.; Arbustini, E.; Elliott, P.M.; Mogensen, J.; Hermans-van Ast, J.F.; van der Kooi, A.J.; van Tintelen, J.P.; van den Berg, M.P.; Pilotto, A.; Pasotti, M.; et al. Risk Factors for Malignant Ventricular Arrhythmias in Lamin A/C Mutation Carriers. *J. Am. Coll. Cardiol.* **2012**, *59*, 493–500. [\[CrossRef\]](#) [\[PubMed\]](#)
98. Wahbi, K.; Ben Yaou, R.; Gandjbakhch, E.; Anselme, F.; Gossios, T.; Lakdawala, N.K.; Stalens, C.; Sacher, F.; Babuty, D.; Trochu, J.N.; et al. Development and Validation of a New Risk Prediction Score for Life-Threatening Ventricular Tachyarrhythmias in Laminopathies. *Circulation* **2019**, *140*, 293–302. [\[CrossRef\]](#)
99. Van Der Heide, M.Y.C.; Verstraeten, T.E.; van Lint, F.H.M.; Bosman, L.P.; de Brouwer, R.; Proost, V.M.; van Drie, E.; Taha, K.; Zwinderman, A.H.; Dickhoff, C.; et al. Long-term reliability of the phospholamban (PLN) p.(Arg14del) risk model in predicting major ventricular arrhythmia: A landmark study. *EP Eur.* **2024**, *26*, euae069. [\[CrossRef\]](#)
100. Filamin C Registry Consortium; Gigli, M.; Stolfo, D.; Barbati, G.; Graw, S.; Chen, S.N.; Merlo, M.; Medo, K.; Gregorio, C.; Dal Ferro, M.; et al. Arrhythmic Risk Stratification of Carriers of Filamin C Truncating Variants. *JAMA Cardiol.* **2025**, *10*, 359–369. [\[CrossRef\]](#)
101. Carrick, R.T.; Gasperetti, A.; Protonotarios, A.; Murray, B.; Laredo, M.; van der Schaaf, I.; Dooijes, D.; Syrris, P.; Cannie, D.; Tichnell, C.; et al. A novel tool for arrhythmic risk stratification in desmoplakin gene variant carriers. *Eur. Heart J.* **2024**, *45*, 2968–2979. [\[CrossRef\]](#)
102. Bosman, L.P.; Sammani, A.; James, C.A.; Cadrin-Tourigny, J.; Calkins, H.; van Tintelen, J.P.; Hauer, R.N.W.; Asselbergs, F.W.; Te Riele, A.S.J.M. Predicting arrhythmic risk in arrhythmogenic right ventricular cardiomyopathy: A systematic review and meta-analysis. *Heart Rhythm* **2018**, *15*, 1097–1107. [\[CrossRef\]](#) [\[PubMed\]](#)
103. Bermudez-Jimenez, F.J.; Protonotarios, A.; García-Hernández, S.; Pérez Asensio, A.; Rampazzo, A.; Zorio, E.; Brodehl, A.; Arias, M.A.; Macías-Ruiz, R.; Fernández-Armenta, J.; et al. Phenotype and Clinical Outcomes in Desmin-Related Arrhythmogenic Cardiomyopathy. *JACC Clin. Electrophysiol.* **2024**, *10*, 1178–1190. [\[CrossRef\]](#)
104. Di Lorenzo, F.; Marchionni, E.; Ferradini, V.; Latini, A.; Pezzoli, L.; Martino, A.; Romeo, F.; Iorio, A.; Bianchi, S.; Iascone, M.; et al. DSP-Related Cardiomyopathy as a Distinct Clinical Entity? Emerging Evidence from an Italian Cohort. *Int. J. Mol. Sci.* **2023**, *24*, 2490. [\[CrossRef\]](#) [\[PubMed\]](#)
105. Bhonsale, A.; Groeneweg, J.A.; James, C.A.; Dooijes, D.; Tichnell, C.; Jongbloed, J.D.; Murray, B.; te Riele, A.S.; van den Berg, M.P.; Bikker, H.; et al. Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers. *Eur. Heart J.* **2015**, *36*, 847–855. [\[CrossRef\]](#)
106. Bezzina, C.R.; Lahrouchi, N.; Priori, S.G. Genetics of Sudden Cardiac Death. *Circ. Res.* **2015**, *116*, 1919–1936. [\[CrossRef\]](#)
107. Monda, E.; Murredda, A.; Rubino, M.; Diana, G.; Palmiero, G.; Verrillo, F.; Cirillo, C.; Cirillo, A.; Fusco, A.; Frisso, G.; et al. Aetiology and clinical manifestations of patients with non-dilated left ventricular cardiomyopathy. *Eur. J. Heart Fail.* **2024**, *26*, 2579–2581. [\[CrossRef\]](#)
108. Peretto, G.; Merlo, M.; Ambrosi, A.; Bacigalupi, E.; Villatore, A.; Molinari, L.; Anguera, I.; Claver, E.; Dal Ferro, M.; Suwalski, P.; et al. Major arrhythmias in non-dilated left ventricular cardiomyopathy: A novel prediction score. *Eur. Heart J.* **2025**, *47*, 94–106. [\[CrossRef\]](#)
109. Wang, H.; Liu, S.; Zhang, X.; Zheng, J.; Lu, F.; Lip, G.Y.; Bai, Y. Prevalence and Impact of Arrhythmia on Outcomes in Restrictive Cardiomyopathy—A Report from the Beijing Municipal Health Commission Information Center (BMHCIC) Database. *J. Clin. Med.* **2023**, *12*, 1236. [\[CrossRef\]](#)

110. Chen, H.; Liu, S.; Zhang, X.; Zheng, J.; Lu, F.; Lip, G.Y.H.; Bai, Y. Clinical-genetic profiles and risk prediction model in childhood restrictive cardiomyopathy: A national cohort study of China. *BMC Med.* **2025**, *23*, 630. [[CrossRef](#)]
111. Brodehl, A.; Gerull, B. Genetic Insights into Primary Restrictive Cardiomyopathy. *J. Clin. Med.* **2022**, *11*, 2094. [[CrossRef](#)] [[PubMed](#)]
112. Tan, S.M.L.; Lim, S.L.; Ong, M.E.; Leong, K.M. Genetics of Sudden Cardiac Arrest: Overview of Genetic Risk Factors and Aetiologies. *Arrhythmia Electrophysiol. Rev.* **2025**, *14*, e18. [[CrossRef](#)] [[PubMed](#)]
113. Fan, L.; Yin, P.; Xu, Z. The genetic basis of sudden death in young people—Cardiac and non-cardiac. *Gene* **2022**, *810*, 146067. [[CrossRef](#)]
114. Krahn, A.D.; Laksman, Z.; Sy, R.W.; Postema, P.G.; Ackerman, M.J.; Wilde, A.A.M.; Han, H.-C. Congenital Long QT Syndrome. *JACC Clin. Electrophysiol.* **2022**, *8*, 687–706. [[CrossRef](#)]
115. Ackerman, M.J.; Tester, D.J.; Jones, G.S.; Will, M.L.; Burrow, C.R.; Curran, M.E. Ethnic Differences in Cardiac Potassium Channel Variants: Implications for Genetic Susceptibility to Sudden Cardiac Death and Genetic Testing for Congenital Long QT Syndrome. *Mayo Clin. Proc.* **2003**, *78*, 1479–1487. [[CrossRef](#)]
116. Tobert, K.E.; Bos, J.M.; Garmany, R.; Ackerman, M.J. Return-to-Play for Athletes with Long QT Syndrome or Genetic Heart Diseases Predisposing to Sudden Death. *J. Am. Coll. Cardiol.* **2021**, *78*, 594–604. [[CrossRef](#)]
117. Giudicessi, J.R.; Wilde, A.A.M.; Ackerman, M.J. The genetic architecture of long QT syndrome: A critical reappraisal. *Trends Cardiovasc. Med.* **2018**, *28*, 453–464. [[CrossRef](#)]
118. Schwartz, P.J.; Crotti, L.; George, A.L. Modifier genes for sudden cardiac death. *Eur. Heart J.* **2018**, *39*, 3925–3931. [[CrossRef](#)]
119. Garcia-Elias, A.; Benito, B. Ion Channel Disorders and Sudden Cardiac Death. *Int. J. Mol. Sci.* **2018**, *19*, 692. [[CrossRef](#)] [[PubMed](#)]
120. Schwartz, P.J.; Ackerman, M.J.; Wilde, A.A.M. Channelopathies as Causes of Sudden Cardiac Death. *Card. Electrophysiol. Clin.* **2017**, *9*, 537–549. [[CrossRef](#)] [[PubMed](#)]
121. Specterman, M.J.; Behr, E.R. Cardiogenetics: The role of genetic testing for inherited arrhythmia syndromes and sudden death. *Heart* **2023**, *109*, 434–441. [[CrossRef](#)]
122. Mazzanti, A.; Maragna, R.; Faragli, A.; Monteforte, N.; Bloise, R.; Memmi, M.; Novelli, V.; Baiardi, P.; Bagnardi, V.; Etheridge, S.P.; et al. Gene-Specific Therapy with Mexiletine Reduces Arrhythmic Events in Patients with Long QT Syndrome Type 3. *J. Am. Coll. Cardiol.* **2016**, *67*, 1053–1058. [[CrossRef](#)]
123. Fudim, M.; Boortz-Marx, R.; Ganesh, A.; Waldron, N.H.; Qadri, Y.J.; Patel, C.B.; Milano, C.A.; Sun, A.Y.; Mathew, J.P.; Piccini, J.P. Stellate ganglion blockade for the treatment of refractory ventricular arrhythmias: A systematic review and meta-analysis. *J. Cardiovasc. Electrophysiol.* **2017**, *28*, 1460–1467. [[CrossRef](#)]
124. Mazzanti, A.; Kanthan, A.; Monteforte, N.; Memmi, M.; Bloise, R.; Novelli, V.; Miceli, C.; O'Rourke, S.; Borio, G.; Ziencuk-Krajka, A.; et al. Novel Insight Into the Natural History of Short QT Syndrome. *J. Am. Coll. Cardiol.* **2014**, *63*, 1300–1308. [[CrossRef](#)]
125. Narasimhan, B.; Na, J.; Monasky, M.M.; Brugada, R.; Miyasaka, Y.; Brugada, J.; Brugada, P.; Krittawong, C. Brugada syndrome. *Nat. Rev. Dis. Primer* **2025**, *11*, 38. [[CrossRef](#)]
126. Krahn, A.D.; Behr, E.R.; Hamilton, R.; Probst, V.; Laksman, Z.; Han, H.-C. Brugada Syndrome. *JACC Clin. Electrophysiol.* **2022**, *8*, 386–405. [[CrossRef](#)]
127. Kapplinger, J.D.; Tester, D.J.; Alders, M.; Benito, B.; Berthet, M.; Brugada, J.; Brugada, P.; Fressart, V.; Guerchicoff, A.; Harris-Kerr, C.; et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. *Heart Rhythm* **2010**, *7*, 33–46. [[CrossRef](#)]
128. Yan, G.-X.; Antzelevitch, C. Cellular Basis for the Brugada Syndrome and Other Mechanisms of Arrhythmogenesis Associated with ST-Segment Elevation. *Circulation* **1999**, *100*, 1660–1666. [[CrossRef](#)] [[PubMed](#)]
129. Behr, E.R.; Ben-Haim, Y.; Ackerman, M.J.; Krahn, A.D.; Wilde, A.A.M. Brugada syndrome and reduced right ventricular outflow tract conduction reserve: A final common pathway? *Eur. Heart J.* **2021**, *42*, 1073–1081. [[CrossRef](#)] [[PubMed](#)]
130. Hosseini, S.M.; Kim, R.; Udupa, S.; Costain, G.; Jobling, R.; Liston, E.; Jamal, S.M.; Szybowska, M.; Morel, C.F.; Bowdin, S. Reappraisal of Reported Genes for Sudden Arrhythmic Death: Evidence-Based Evaluation of Gene Validity for Brugada Syndrome. *Circulation* **2018**, *138*, 1195–1205. [[CrossRef](#)]
131. Asatryan, B.; Medeiros-Domingo, A. Molecular and genetic insights into progressive cardiac conduction disease. *EP Eur.* **2019**, *21*, 1145–1158. [[CrossRef](#)] [[PubMed](#)]
132. Valdivia, C.R.; Ueda, K.; Ackerman, M.J.; Makielski, J.C. GPD1L links redox state to cardiac excitability by PKC-dependent phosphorylation of the sodium channel SCN5A. *Am. J. Physiol.-Heart Circ. Physiol.* **2009**, *297*, H1446–H1452. [[CrossRef](#)]
133. Cerrone, M.; Lin, X.; Zhang, M.; Agullo-Pascual, E.; Pfenniger, A.; Chkourko Gusk, H.; Novelli, V.; Kim, C.; Tirasawadichai, T.; Judge, D.P.; et al. Missense Mutations in Plakophilin-2 Cause Sodium Current Deficit and Associate with a Brugada Syndrome Phenotype. *Circulation* **2014**, *129*, 1092–1103. [[CrossRef](#)] [[PubMed](#)]
134. Barc, J.; Tadros, R.; Glinge, C.; Chiang, D.Y.; Jouni, M.; Simonet, F.; Jurgens, S.J.; Baudic, M.; Nicastro, M.; Potet, F.; et al. Genome-wide association analyses identify new Brugada syndrome risk loci and highlight a new mechanism of sodium channel regulation in disease susceptibility. *Nat. Genet.* **2022**, *54*, 232–239. [[CrossRef](#)]

135. Doundoulakis, I.; Pannone, L.; Chiotis, S.; Della Rocca, D.G.; Sorgente, A.; Tsioufis, P.; Del Monte, A.; Vetta, G.; Piperis, C.; Overeinder, I.; et al. SCN5A gene variants and arrhythmic risk in Brugada syndrome: An updated systematic review and meta-analysis. *Heart Rhythm* **2024**, *21*, 1987–1997. [[CrossRef](#)] [[PubMed](#)]
136. Jimmy Juang, J.-M.; Liu, Y.B.; Chen, C.Y.; Yu, Q.Y.; Chattopadhyay, A.; Lin, L.Y.; Chen, W.J.; Yu, C.C.; Huang, H.C.; Ho, L.T.; et al. Validation and Disease Risk Assessment of Previously Reported Genome-Wide Genetic Variants Associated with Brugada Syndrome: SADS-TW BrS Registry. *Circ. Genom. Precis. Med.* **2020**, *13*, e002797. [[CrossRef](#)]
137. García-Izquierdo, E.; Scrocco, C.; Palacios-Rubio, J.; Assaf, A.; Ripoll-Vera, T.; Hernandez-Betancor, I.; Ramos-Ruiz, P.; Melero-Pita, A.; Segura-Domínguez, M.; Jiménez-Sánchez, D.; et al. Arrhythmia detection using an implantable loop recorder after a negative electrophysiology study in Brugada syndrome: Observations from a multicenter international registry. *Heart Rhythm* **2024**, *21*, 1317–1324. [[CrossRef](#)] [[PubMed](#)]
138. Roston, T.M.; Kannankeril, P.J.; Hathaway, J.; Vinocur, J.M.; Etheridge, S.P.; Potts, J.E.; Maginot, K.R.; Salerno, J.C.; Cohen, M.I.; Hamilton, R.M.; et al. The clinical and genetic spectrum of catecholaminergic polymorphic ventricular tachycardia: Findings from an international multicentre registry. *EP Eur.* **2018**, *20*, 541–547. [[CrossRef](#)]
139. Skinner, J.R.; Winbo, A.; Abrams, D.; Vohra, J.; Wilde, A.A. Channelopathies That Lead to Sudden Cardiac Death: Clinical and Genetic Aspects. *Heart Lung Circ.* **2019**, *28*, 22–30. [[CrossRef](#)]
140. Mascia, G.; Brugada, J.; Arbelo, E.; Porto, I. Athletes and suspected catecholaminergic polymorphic ventricular tachycardia: Awareness and current knowledge. *J. Cardiovasc. Electrophysiol.* **2023**, *34*, 2095–2101. [[CrossRef](#)]
141. Priori, S.G.; Napolitano, C.; Memmi, M.; Colombi, B.; Drago, F.; Gasparini, M.; DeSimone, L.; Coltorti, F.; Bloise, R.; Keegan, R.; et al. Clinical and Molecular Characterization of Patients with Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation* **2002**, *106*, 69–74. [[CrossRef](#)]
142. Abbas, M.; Miles, C.; Behr, E. Catecholaminergic Polymorphic Ventricular Tachycardia. *Arrhythmia Electrophysiol. Rev.* **2022**, *11*, e20. [[CrossRef](#)] [[PubMed](#)]
143. Shimamoto, K.; Ohno, S.; Kato, K.; Takayama, K.; Sonoda, K.; Fukuyama, M.; Makiyama, T.; Okamura, S.; Asakura, K.; Imanishi, N.; et al. Impact of cascade screening for catecholaminergic polymorphic ventricular tachycardia type 1. *Heart* **2022**, *108*, 840–847. [[CrossRef](#)]
144. Mazzanti, A.; Kukavica, D.; Trancuccio, A.; Memmi, M.; Bloise, R.; Gambelli, P.; Marino, M.; Ortíz-Genga, M.; Morini, M.; Monteforte, N.; et al. Outcomes of Patients with Catecholaminergic Polymorphic Ventricular Tachycardia Treated with β -Blockers. *JAMA Cardiol.* **2022**, *7*, 504–512. [[CrossRef](#)] [[PubMed](#)]
145. Di Barletta, M.R.; Viatchenko-Karpinski, S.; Nori, A.; Memmi, M.; Terentyev, D.; Turcato, F.; Valle, G.; Rizzi, N.; Napolitano, C.; Gyorke, S.; et al. Clinical Phenotype and Functional Characterization of CASQ2 Mutations Associated with Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation* **2006**, *114*, 1012–1019. [[CrossRef](#)] [[PubMed](#)]
146. Heidbuchel, H.; Arbelo, E.; D’Ascenzi, F.; Borjesson, M.; Boveda, S.; Castelletti, S.; Miljoen, H.; Mont, L.; Niebauer, J.; Papadakis, M.; et al. Recommendations for participation in leisure-time physical activity and competitive sports of patients with arrhythmias and potentially arrhythmogenic conditions. Part 2: Ventricular arrhythmias, channelopathies, and implantable defibrillators. *EP Eur.* **2021**, *23*, 147–148. [[CrossRef](#)]
147. Bergeman, A.T.; Wilde, A.A.M.; Van Der Werf, C. Catecholaminergic Polymorphic Ventricular Tachycardia. *Card. Electrophysiol. Clin.* **2023**, *15*, 293–305. [[CrossRef](#)]
148. Winkel, B.G.; Holst, A.G.; Theilade, J.; Kristensen, I.B.; Thomsen, J.L.; Ottesen, G.L.; Bundgaard, H.; Svendsen, J.H.; Haunsø, S.; Tfelt-Hansen, J. Nationwide study of sudden cardiac death in persons aged 1–35 years. *Eur. Heart J.* **2011**, *32*, 983–990. [[CrossRef](#)]
149. Lahrouchi, N.; Raju, H.; Lodder, E.M.; Papatheodorou, E.; Ware, J.S.; Papadakis, M.; Tadros, R.; Cole, D.; Skinner, J.R.; Crawford, J.; et al. Utility of Post-Mortem Genetic Testing in Cases of Sudden Arrhythmic Death Syndrome. *J. Am. Coll. Cardiol.* **2017**, *69*, 2134–2145. [[CrossRef](#)]
150. Guo, L.; Torii, S.; Fernandez, R.; Braumann, R.E.; Fuller, D.T.; Paek, K.H.; Gadhoke, N.V.; Maloney, K.A.; Harris, K.; Mayhew, C.M.; et al. Genetic Variants Associated with Unexplained Sudden Cardiac Death in Adult White and African American Individuals. *JAMA Cardiol.* **2021**, *6*, 1013–1022. [[CrossRef](#)]
151. Miles, C.J.; Behr, E.R. The role of genetic testing in unexplained sudden death. *Transl. Res.* **2016**, *168*, 59–73. [[CrossRef](#)]
152. Nunn, L.M.; Lopes, L.R.; Syrris, P.; Murphy, C.; Plagnol, V.; Firman, E.; Dalageorgou, C.; Zorio, E.; Domingo, D.; Murday, V.; et al. Diagnostic yield of molecular autopsy in patients with sudden arrhythmic death syndrome using targeted exome sequencing. *EP Eur.* **2016**, *18*, 888–896. [[CrossRef](#)]
153. Anderson, J.H.; Tester, D.J.; Will, M.L.; Ackerman, M.J. Whole-Exome Molecular Autopsy After Exertion-Related Sudden Unexplained Death in the Young. *Circ. Cardiovasc. Genet.* **2016**, *9*, 259–265. [[CrossRef](#)]
154. Ripoll-Vera, T.; Pérez Luengo, C.; Borondo Alcázar, J.C.; García Ruiz, A.B.; Sánchez Del Valle, N.; Barceló Martín, B.; Poncela García, J.L.; Gutiérrez Buitrago, G.; Dasi Martínez, C.; Canós Villena, J.C.; et al. Sudden cardiac death in persons aged 50 years or younger: Diagnostic yield of a regional molecular autopsy program using massive sequencing. *Rev. Esp. Cardiol. Engl. Ed.* **2021**, *74*, 402–413. [[CrossRef](#)] [[PubMed](#)]

155. Monda, E.; Lioncino, M.; Rubino, M.; Caiazza, M.; Cirillo, A.; Fusco, A.; Pacileo, R.; Fimiani, F.; Amodio, F.; Borrelli, N. The Risk of Sudden Unexpected Cardiac Death in Children. *Heart Fail. Clin.* **2022**, *18*, 115–123. [[CrossRef](#)] [[PubMed](#)]
156. Modena, M.; Giannoni, A.; Aimo, A.; Aretini, P.; Botto, N.; Vittorini, S.; Scatena, A.; Bonuccelli, D.; Di Paolo, M.; Emdin, M.; et al. Whole-exome sequencing to identify causative variants in juvenile sudden cardiac death. *Hum. Genom.* **2024**, *18*, 102. [[CrossRef](#)]
157. Behr, E.R. Explaining the unexplained: Applying genetic testing after cardiac arrest and sudden death. *Eur. Heart J.* **2022**, *43*, 3082–3084. [[CrossRef](#)] [[PubMed](#)]
158. Orphanou, N.; Papatheodorou, E.; Anastasakis, A. Dilated cardiomyopathy in the era of precision medicine: Latest concepts and developments. *Heart Fail. Rev.* **2022**, *27*, 1173–1191. [[CrossRef](#)]
159. Wilde, A.A.M.; Semsarian, C.; Márquez, M.F.; Shamloo, A.S.; Ackerman, M.J.; Ashley, E.A.; Sternick, E.B.; Barajas-Martinez, H.; Behr, E.R.; Bezzina, C.R.; et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. *EP Eur.* **2022**, *24*, 1307–1367. [[CrossRef](#)]
160. Beheshti, S.O.; Madsen, C.M.; Varbo, A.; Nordestgaard, B.G. Worldwide Prevalence of Familial Hypercholesterolemia. *J. Am. Coll. Cardiol.* **2020**, *75*, 2553–2566. [[CrossRef](#)]
161. Glinge, C.; Lahrouchi, N.; Jabbari, R.; Tfelt-Hansen, J.; Bezzina, C.R. Genome-wide association studies of cardiac electrical phenotypes. *Cardiovasc. Res.* **2020**, *116*, 1620–1634. [[CrossRef](#)]
162. Chugh, S.S.; Reinier, K.; Singh, T.; Uy-Evanado, A.; Socoteanu, C.; Peters, D.; Mariani, R.; Gunson, K.; Jui, J. Determinants of Prolonged QT Interval and Their Contribution to Sudden Death Risk in Coronary Artery Disease: The Oregon Sudden Unexpected Death Study. *Circulation* **2009**, *119*, 663–670. [[CrossRef](#)] [[PubMed](#)]
163. Sandhu, R.K.; Dron, J.S.; Liu, Y.; Moorthy, M.V.; Chatterjee, N.A.; Ellinor, P.T.; Chasman, D.I.; Cook, N.R.; Khera, A.V.; Albert, C.M. Polygenic Risk Score Predicts Sudden Death in Patients with Coronary Disease and Preserved Systolic Function. *J. Am. Coll. Cardiol.* **2022**, *80*, 873–883. [[CrossRef](#)]
164. Könnemann, H.; Dagres, N.; Merino, J.L.; Sticherling, C.; Zeppenfeld, K.; Tfelt-Hansen, J.; Eckardt, L. Spotlight on the 2022 ESC guideline management of ventricular arrhythmias and prevention of sudden cardiac death: 10 novel key aspects. *EP Eur.* **2023**, *25*, euad091. [[CrossRef](#)] [[PubMed](#)]
165. Girolami, F.; Spinelli, V.; Maurizi, N.; Focardi, M.; Nesi, G.; Maio, V.; Grifoni, R.; Albora, G.; Bertaccini, B.; Targetti, M.; et al. Genetic characterization of juvenile sudden cardiac arrest and death in Tuscany: The ToRSADE registry. *Front. Cardiovasc. Med.* **2022**, *9*, 1080608. [[CrossRef](#)] [[PubMed](#)]
166. Van Den Heuvel, L.; Do, J.; Yeates, L.; Burns, C.; Semsarian, C.; Ingles, J. Sudden cardiac death in the young: A qualitative study of experiences of family members with cardiogenetic evaluation. *J. Genet. Couns.* **2024**, *33*, 361–369. [[CrossRef](#)]
167. Andersen, J.D.; Jacobsen, S.B.; Trudsø, L.C.; Kampmann, M.-L.; Banner, J.; Morling, N. Whole genome and transcriptome sequencing of post-mortem cardiac tissues from sudden cardiac death victims identifies a gene regulatory variant in NEXN. *Int. J. Legal Med.* **2019**, *133*, 1699–1709. [[CrossRef](#)]
168. Henriquez, E.; Hernandez, E.A.; Mundla, S.R.; Wankhade, D.H.; Saad, M.; Ketha, S.S.; Penke, Y.; Martinez, G.C.; Ahmed, F.S.; Hussain, M.S. Catecholaminergic Polymorphic Ventricular Tachycardia and Gene Therapy: A Comprehensive Review of the Literature. *Cureus* **2023**, *15*, e47974. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.