Review

Genetics of Sudden Cardiac Death

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Review

Genetics of Sudden Cardiac Death

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Abstract

Introduction: Cardiomyopathies (DCM, HCM and ACM) and primary arrhythmogenic disorders (BrS, LQTS and CPVT) are the most common causes of sudden cardiac death (SCD) in young people. Systematic investigations of genome wide SNP, GWAS have enabled the identification of many genetic variants associated with cardiovascular diseases. **Body:** Genetic testing for cardiomyopathies and inherited channelopathies primarily includes panel testing for genes with definitive and strong evidence, and genes with moderate evidence can be considered. Cardiomyocyte exhibiting proteins, involved in the pathogenesis of the genetic cardiomyopathies, include sarcomeric, cytoskeletal, desmosomal and nuclear envelope proteins. Inherited cardiac channelopathies are caused by mutations in genes encoding cellular structures that affect calcium ion availability or membrane ion channels (sodium, potassium or calcium channels). Common variants associated with SCD included those in genes encoding cardiac ion channels (e.g., SCN5A, KCNQ1, KCNH2), calmodulin (CALM2), sarcomeric proteins (MYH7, MYBPC3, TNN, TNNI3), and desmosomal proteins (RyR2, DES).**Conclusions**: This review provides evidence that specific genetic variants are associated with an increased risk of SCD. The data emphasizes the importance of genetic screening and early intervention in individuals with a family history of SCD or risk factors for inherited cardiac conditions causing SCD. Gene-specific management of familial cardiomyopathies and inherited cardiac channelopathies causing SCD should be emphasized for further research with the improvement of targeted genetic disorders treatment.

Keywords: sudden cardiac death; genetics; sudden arrhythmic death; genetic cardiomyopathy

1. Introduction

The introduction should briefly place the study in a broad context and highlight why it is important. It should define the purpose of the work and its significance. The current state of the research field should be carefully reviewed and key publications cited. Please highlight controversial and diverging hypotheses when necessary. Finally, briefly mention the main aim of the work and highlight the principal conclusions. As far as possible, please keep the introduction comprehensible to scientists outside your particular field of research. References should be numbered in order of appearance and indicated by a numeral or numerals in square brackets—e.g., [1] or [2,3], or [4–6]. See the end of the document for further details on references. Sudden cardiac death (SCD) is defined as sudden natural death of cardiac cause that occurs within 1 h of onset of symptoms in witnessed cases, and within 24 h of last being seen alive when it is unwitnessed, it is also reported by autopsy as the natural unexpected death of unknown or cardiac cause [1]. Cardiomyopathies (dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM) and arrhythmogenic cardiomyopathy (ACM)) are the most common cause of sudden cardiac death in people under 40 years of age, however, in the pediatric population and in adolescents, primary arrhythmogenic disorders (Brugada Syndrome (BrS), Long-QT-Syndrom (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) are more common cause of sudden cardiac death [2]. The incidence

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of sudden cardiac death increases with age; in the 40s, the most common cause is coronary artery disease, and later structural heart disease predominates [3,4]. For all age groups, the incidence of sudden cardiac death is higher in men than in women [5]. Atherosclerosis Risk in Communities Study (ARIC) investigated racial differences in the cumulative risk of SCD and confirmed that ethnic background has large effect, blacks have a higher risk of sudden cardiac death than whites [6]. In a prospective study of children and young adults (Australia and New Zealand) 490 cases of SCD were identified, annual incidence was 1.3 cases per 100,000 persons (1-35 y; 72% M). The most common found cause of sudden cardiac death was coronary artery disease (24%), second were inherited cardiomyopathies (16%). 40% of cases died of unexplained sudden cardiac death, it was the most common cause of death in those under 31y and clinically relevant cardiac gene mutation was identified in 27% of unexplained sudden cardiac death in which genetic testing was performed and after the follow-up, a clinical diagnosis of an inherited cardiovascular disease was identified in 13% of family members of victims of sudden cardiac death [7]. The Cardiac Arrest Registry to Enhance Survival (CARES) has evaluated out of hospital cardiac arrest (OHCA) events of presumed cardiac etiology that involve persons who received resuscitative effort, it includes 40 274 OHCA records, of which 31 689 OHCA events were presumed to be of cardiac etiology (myocardial infarction or arrhythmia) that received resuscitation efforts in the prehospital setting, the survival rate to hospital admission was only 26.3%, and the overall survival rate from cardiac arrest to hospital discharge was 9.6% [8]. SCD can have a clear monogenic component (autosomal dominant (AD), autosomal recessive (AR), and sex-linked inheritance) due to the presence of an inherited arrhythmia syndrome or cardiomyopathy (young adults), but it can also be caused by polygenic conditions [9]. Mendelian disease variants are ultra-rare in the population but are often not sufficient in isolation to cause a disease phenotype. Common variants can contribute to disease burden or modulate the effects of Mendelian variants. Diseases such as HCM and LQTS are often Mendelian or near-Mendelian where Mendelian variants of large effect sizes can cause of act as protective or regulatory modifiers. Other diseases such as DCM and BrS have a complex etiology (substantial non Mendelian genetic and non-genetic factors) [10] There are 4000 discovered genes causing hereditary cardiomyopathies, hereditary arrhythmias and cardiac conduction defects [11,12]. Most of the single nucleotide polymorphisms (SNP) are located in intergenic regions of the human genome and affect gene expression and gene regulation that was confirmed by the ENCODE (ENCyclopedia Of DNA Elements) Project [13]. Mutations (MUT) are very rare (1:1000), non-synonymous amino acid exchanges that are neither an SNP nor a MUT are classified as variants of unknown significance (VUS) (0.1 – 0.5%) and do not co-segregate with a certain phenotype [14]. Systematic investigations of genome wide SNP, genome-wide association studies (GWAS) tend to focus on SNPs and widespread diseases, also cardiovascular diseases (myocardial infarction, arterial hypertension, atrial fibrillation, or quantitative trait loci (QTL) for distinct ECG parameters) [15–19]. GWAS have enabled the identification of many genetic variants associated with cardiovascular diseases, therefore, genomic risk scores or polygenic risk scores (PRS) were formed to assess an individual's genetic predisposition to developing hereditary cardiovascular diseases [20–22].

This systematic review aimed to investigate genetic variants associated with SCD to further raise awareness of the need for genetic testing in survivors of sudden cardiac arrest and the segregation of families of victims of sudden cardiac death for further genetic testing. The review is based on the literature collected form PubMed, Scopus and Web of Science. Databases were investigated using keywords; sudden cardiac death, genetics, sudden arrhythmic death and genetic cardiomyopathy. The inclusion criteria were: studies published in English and studies that include data on adults who died of sudden cardiac death. The exclusion criteria were: letters, case reports and non-peer-reviewed articles. This research included the literature form April 2004 to May 2025 with focus on clinically relevant studies.

The structure of this review is as follows: Section 2 Genetic cardiomyopathies (2.1. Hypertrophic cardiomyopathy, 2.2. Dilated cardiomyopathy, 2.3. Arrhythmogenic cardiomyopathy), Section 3

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Inherited channelopathies (3.1. Brugada syndrome, 3.2. Long QT syndrome, 3.3. Short QT syndrome, 3.4. Catecholaminergic polymorphic ventricular tachycardia)

2. Genetic Cardiomyopathies

The genetic cardiomyopathies are classified based on morphological and functional features as; hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and arrhythmogenic cardiomyopathy (ACM) [23]. Cardiomyocyte exhibiting proteins, involved in the pathogenesis of the genetic cardiomyopathies, include sarcomeric, cytoskeletal, desmosomal and nuclear envelope proteins [24].

2.1. Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by asymmetric left ventricular hypertrophy, often with involvement of the interventricular septum; other variations include involvement of the left ventricular (LV) apex or mid wall with myocyte hypertrophy and fibrosis [25]. The annual mortality from SCD alone is low (≤1%) in most HCM patients but in some the risk is significantly higher (≥4% to <6%)**;** patients with ≥ 15% LV mass with LGE at MR, left ventricular ejection fraction (LVEF)<50%, LV apical aneurysm or patients with sarcomeric pathogenic mutation, who then have an indication for cardioverter defibrillator (ICD) implantation [1]. 50% to 60% of the HCM cases have sarcomere gene mutation, with the MYBPC3 or MYH7 gene being the most common [26]. Genetic testing primarily includes panel testing for genes with strong evidence of causing familial HCM; MYBPC3 (locus 11p11.2, myosin-binding protein C3), MYH7 (locus 14q11.2-q12, beta myosin heavy chain), TNNI3 (locus 19q13.49, troponin I, cardiac type), TNNC1 (locus 3p21.1, troponin C, cardiac type), TPM1 (locus 15q22.2, alpha tropomyosin), ACTC1 (locus 15q.14, alpha cardiac actin), MYL2 (locus 12q24.11, regulatory myosin light chain), MYL3 (locus 3p21.31, essential myosin light chain), PM1 (locus 15q22.2, alpha tropomyosin), FHOD3 (locus 18q12.2, formin homology 2 domain containing 3), FLNC (locus 7q32.1, filamin C), ALPK3 (locus 15q25.3, alpha kinase 3), PRKAG2 (locus 7q36.1, protein kinase AMP-activated non-catalytic subunit gamma 2), CACNA1C (locus 12p13.33, calcium voltage-gated channel subunit alpha1 C), ACTN2 (locus 1q43, actinin alpha 2), CSRP3 (locus 11p15.1, cysteine- and glycine-rich protein 3) [27–32]. TNNT2 (locus 1q32.1, troponin T, cardiac type), and subsequent genetic testing for genes with moderate level of evidence for the development of hypertrophic cardiomyopathy; KLHL24 (locus 3q27.1, Kelch-like family member), TRIM63 (locus 1p36.11, tripartite motif containing), and JPH2 (locus 20q13.12, junctophilin). (according to ClinGen). Genetic testing for HCM can be done if there is clinical suspicion in patients with certain syndromes such as LAMP2 (Danon disease), GLA (Fabry disease), PRKAG2 (glycogen storage disease), TTR (Transthyretin amyloidosis), GAA (Pompe disease) and others, the results of which could modify the treatment approach, for example, to a more aggressive approach in some of these conditions, such as more aggressive clinical management of patients with Danon disease or enzyme replacement therapy in patients with Fabry disease [33–37]. Likely-pathogenic or pathogenic (LP/P) result after genetic testing in the proband should be an indication for cascade genetic testing of first-degree relatives [13]. Carriers of a LP/P sarcomere variants have a worse prognosis compared to sarcomere variant negative patients, such as earlier onset of disease, higher incidence of atrial fibrillation and ventricular arrhythmias, heart failure and higher incidence of SCD [38–40].

2.2. Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is defined by left ventricular or biventricular dilatation and systolic dysfunction in the absence of coronary artery disease, sufficient to cause global systolic impairment, or abnormal loading conditions (hypertension, valve disease) [41]. Familial DCM is in general inherited as an autosomal dominant trait, while autosomal recessive, mitochondrial (maternal transmission), or X-linked inheritance are less common [42,43]. In patients with newly

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discovered cardiomyopathy, the diagnosis of idiopathic dilated cardiomyopathy was confirmed in 20% to 35% of cases [44]. Genetic testing primarily includes panel testing for genes with strong evidence of causing familial DCM; BAG3 (locus 10q26.11, myopathy BAG family molecular chaperone regulator 3), DES (locus 2q35, desmin), FLNC (locus 7q32.1, filamin-C), LMNA (locus 1q22, lamin A/C), MYH7 (locus 14q11.2, β myosin heavy chain), RBM20 (locus 10q25.2, RNA-binding motif protein 20), SCN5A (locus 3p22.2, sodium channel protein type 5 subunit alpha), TNNC1 (locus 3p21.1, cardiac troponin C), TTN (locus 2q31.2, titin), TNNT2 (locus 1q32.1, troponin T), JPH2 (locus 20q13.12, junctophilin 2), LDB3, NRAP, PPA2, TNNI3 (locus 19q13.4, cardiac troponin I), VCL (locus 10q22.2, metavinculin), and for genes with moderate level of evidence for the development of dilated cardiomyopathy; ACTC1 (locus 15q11q14, cardiac alpha-actin), BAG5 (myopathy BAG family molecular chaperone regulator 3), FLII, RPL3L (ribosomal protein L3-like), MYLK3 and MYZAP. (according to ClinGen). LMNA, RBM20, and FLNC gene mutations are associated with a higher risk of ventricular arrhythmias and SCD [45–47]. Desmosomal and LMNA variants are the most strongly associated with a higher frequency of sudden cardiac death and ventricular arrhythmias regardless of LVEF (left ventricular ejection fraction) [48]. Truncating variants in titin gene (TTN) are the most frequent in DCM (20% of cases) [49]. Some DCM mutated genes, egz. genes coding desmosomal proteins and ion flux, overlap with other cardiomyopathy subtypes; ACM but also with channelopathies [50]. Identification of pathogenic variants in possible in up to 50% of DCM patients [50]. A complex polygenic inheritance pattern combined with environmental influences can also be hypothesized in DCM [51,52]. Genetic testing is recommended in DCM patients with the highest yield of pathogenic variant screening and should be considered even in the absence of familial context or associated clinical features (<60 years of age). The most common genes associated with DCM (TTN, LMNA, FLNC) should be included in the panel [13]. LP/P result after genetic testing in the proband should be an indication for cascade genetic testing of first-degree relatives [13]. ICD therapy should be considered early in LMNA carriers (truncating vs. missense variant), higher risk of SCD is also associated with pathogenic variants (truncated variants) in FLNC, DES, RBM20, and PLN genes FLNC, DES, RBM20, and PLN genes [13,53,54]. According to 2022 ESC guidelines ICD implantation should be considered in DCM patients with a pathogenic mutation in LMNA gene, if the estimated 5-year risk of life-threatening VA is ≥10% and in the presence of NSVT or LVEF <50% or AV conduction delay, but also in patients with a LVEF <50% and ≥2 risk factors (syncope, LGE on CMR, inducible SMVT at PES, pathogenic mutations in LMNA, PLN, FLNC, and RBM20 genes) [1].

2.3. Arrhythmogenic Cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM) or arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart muscle disease characterized by progressive fibro and fibrofatty myocardial replacement which may act as a substrate for ventricular arrhythmias and SCD. ARVC phenotype can bez classic with isolated right ventricular (RV) involvement, also there are other forms; the biventricular disease variants (BiVACM), dominant-right (ARVC) or dominant-left (ALVC) [55]. The most common pattern of inheritance is autosomal dominant, however, the form of ACM associated with syndromes (Naxos disease, Carvajal syndrome) is inherited in an autosomal recessive pattern [56]. In up to 50% of patients with ACM, a mutation is found in one of the 5 genes encoding desmosomal proteins: desmoplakin (DSP), plakophillin (PKP2), plakoglobin (JUP), desmoglein-2 (DSG2), and desmocollin-2 (DSC2), non-desmosomal genes are also linked to the ACD onset, but their function is incompletely elucidated [57,58]. Genes that are most likely associated with the development of ACM are; DSC2 (locus 18q12.1, desmocollin 2 (desmosome), causing ARVC, less frequent BiVACM and ALVC), DSG2 (locus 18q12.1, desmoglein 2 (desmosome), causing frequent BiVACM and ALVC), DSP (locus 6p24.3, desmoplakin (desmosome), causing frequent BiVACM and ALVC), PKP2 (locus 12p11.21, plakophilin 2 (desmosome), causing classic ARVC, BiVACM and ALVC in a minority of cases), TMEM43 (locus 3p25.1, transmembrane protein 43 (nuclear envelope), causing ARVC and BiVACM, and genes with moderate level of evidence for the development of the disease; PLN (locus 6q22.31, phospholamban (sarcoplasmic reticulum; calcium handling), frequent

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ALVC/DCM) and DES (locus 2q35, desmin (cytoskeleton), frequent ALVC with conduction system abnormalities). (according to ClinGen). Many cohort studies on large numbers of subjects with ACM report some carriers with multiple desmosomal gene mutations with the prevalence of individuals with >1 desmosome mutation from 4% to 16%, as expected patients with >1 desmosome gene mutation were at higher risk of arrhythmia and SCD [59,60]. Genetic testing is indicated and identification of a mutation is possible in 2/3 of cases [61]. ACM disease penetrance in first-degree relatives is 28–58% [62]. The incidence and predictors of ICD therapy in patients with ARVD were investigated in a study on 86 patients after placement of an ICD for primary prevention and appropriate ICD therapy was seen in 48% [63]. ICD implantation should be considered in primary prevention in patients with definite ARVC and an arrhythmic syncope, or severe RV or LV systolic dysfunction or moderate right or left ventricular dysfunction, and either NSVT [1]. Genetic testing is recommended for all patients with phenotypic features of ACM, it referes to definitive disease-associated genes (currently PKP2, DSP, DSG2, DSC2, TMEM43, PLN, FLNC, DES, LMNA), variant-specific genetic testing is recommended for family members [13].

3. Inherited Channelopathies

Inherited cardiac channelopathies are caused by mutations in genes encoding cellular structures that affect calcium ion availability or membrane ion channels (sodium, potassium or calcium channels) [64]. The balance between the transmembrane transport of potassium, sodium and calcium in cardiac myocyte enables the cardiac cycle. Mutations in genes encoding these specific ion channels can impair ionic conduction, leading to channelopathies and ventricular arrhythmias and can cause SCD [64]. The most important hereditary channelopathies include the following disorders: long-QT syndrome (LQTS), short-QT syndrome (SQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT), they are often characterized by specific ECG abnormalities either at baseline or during particular conditions, such as exercise (CPVT and LQTS), fever (BrS), or pharmacological challenge (BrS) [64–66].

3.1. Brugada Syndrome

Brugada syndrome is an inherited arrhythmogenic disorder characterized by specific electrocardiogram pattern (ST-segment elevation in the right precordial leads) and malignant ventricular arrhythmias (ventricular fibrillation) and an increased risk of SCD, infrequently with conduction diseases and atrial arrhythmias [1,13]. BrS type I morphology is characterized by ST-segment elevation ≥ 2mm in ≥1 lead among the right precordial leads V1, V2 positioned in the 4th intercostal space, spontaneously or after provocative drug testing with a class I antiarrhythmic drug [13]. Multiple sodium channels isoforms have been isolated (INa 1.1-1.9), isoform NaV1.5 has been isolated in the human heart and consists of an α and an auxiliary β-subunit [67]. The SCN5A gene α subunit is sufficient to express a functional channel and β subunit increases the level of channel expression therefore it can affect voltage dependent inactivation. Mutations of the sodium channel genes can cause a decrease in the level of channel expression or acceleration of inactivation or incomplete inactivation during maintained depolarization, which favors a proarrhythmic state and LQTS, BrS and conduction disorders [67,68]. BrS causing rare genetic variants in SCN5A (locus 3p22.2, loss of INa1.5 channel function) are identified in 15-30% of cases, it is the only definite genetic variant causing the disease. (according to ClinGen) In a study on 13 large families composed of 115 mutation carriers the function of a SCN5A mutation to cause a BrS phenotype was investigated and proved the incomplete penetrance; noncarriers of the SCN5A variant can show a positive provocative drug challenge [69]. Tadros et al. investigated genetic factors as predictors of ajmaline-induced PR and QRS changes and Type I BrS, and proved that genetic factors that effect sodium channel function combined with polygenic risk scores for Brugada syndrome (PRSBrS) derived from published genome-wide association studies, family history, and a baseline electrocardiogram can predict the development of a diagnostic drug-induced Type I BrS [70]. ICD implantation is recommended in patients with BrS who survived cardiac arrest, had documented malignant arrhythmia or arrhythmic

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syncope, with the recommendation to avoid potentiating factors [1]. The presence of a LP/P SCN5A variant confirms the diagnosis of BrS in patients with a type I BrS ECG, but the absence of variant does not exclude the diagnosis [13]. Genetic testing of all family members of patients with Brugada syndrome is recommended [71].

3.2. Long QT Syndrome

The congenital long QT syndrome (LQTS) is a hereditary channelopathy and is associated with cardiac repolarization dysfunction. It is detectable on the baseline ECG by the prolongation of the QT interval (QTc ≥480 ms or a LQTS risk score >3) that can be associated with T-wave abnormalities (biphasic T waves, notched T waves) [1,72–74]. Genetic testing primarily includes panel testing for genes with definitive and strong evidence of causing familial LQTS; CALM1 (locus 14q32.11, L-type calcium channel), CALM2 (locus 2p21, L-type calcium channel), CALM3 (locus 19q13.32, L-type calcium channel), KCNQ1 (locus 11p15.5, loss-of-IKs channel function 40–55%), KCNH2 (locus 7q35-36, loss-of-IKr channel function 30–45%), SCN5A (locus 3p21-p24, increase in INa1.5 channel function 5–10%), TRDN (locus 6q22.31, L-type calcium channel), and gene with moderate level of evidence for the development of the disease; CACNA1C (locus 12p13.3, L-type calcium channel). (according to ClinGen) Genetic testing can detect gene mutations in 75% of LQTS and 90% of positive genotypes include genes with definitive evidence of causing the disease [75]. The subtypes of LQTS based on the mode of inheritance: (1) autosomal-dominant LQTS without extra-cardiac manifestation. (2) autosomal-dominant LQTS with extra-cardiac manifestation, including: Andersen–Tawil Syndrome (LQT7), characterized by frequent ventricular arrhythmia, facial dysmorphologies and periodic paralysis) and Timothy Syndrome (LQT8), characterized by prolonged QT, cardiac malformations, syndactyly, autism spectrum disorder and dysmorphism. (3) Autosomal recessive LQTS, including Jervell and Lange–Nielsen Syndrome, combining extreme QT prolongation with congenital deafness [76–78]. Based on the mechanism of action, LQTS genes can be divided into the following groups: those that reduce potassium outward current (KCNQ1, KCNH2; 80% of all genetically confirmed LQTS, KCNE1 and KCNE2 causing mild phenotype), increase sodium inward current (SNC5A causing overlapping syndromes; LQTS, BrS and cardiac conduction abnormalities) and increase calcium inward current (CALM1, CALM2, CALM3) [79–81]. Mutations in CALM genes have a high incidence of malignant arrhythmias, according to the International Calmodulinopathy Registry lifethreatening arrhythmias appeared in 78% of the cases, mean QTc was almost 600 ms [82]. Genotype–phenotype studies have found that in most cases LQTS is secondary to loss-of-function mutations on KCNQ1 (LQTS Type 1 - LQT1) and KCNH2 (LQTS Type 2 - LQT2) or gain-of-functions SCN5A mutations (LQTS Type 3 - LQT3) that predisposes young and otherwise healthy individuals to life-threatening arrhythmias [83–87]. Mazzanti et al. present the 1-2-3-LQTS-Risk model, validated 5-year risk score model for patients with LQTS, and suggest ICD implantation in a 5-year risk ≥5% (number needed to treat (NNT) is 9) [87]. ECG characteristics for LQT1 cases are broad-based T waves (experience cardiac events during exercise), for LQT2, T waves are low amplitude or notched (auditory stimuli are a specific trigger of arrhythmia, for LQT3 cases often have a long isoelectric ST-segment (experience cardiac events during sleep). LQT1 patients have a better response to β blockers, LQT2 and LQT3 are more malignant form of the disease [1,87]. Cascade screening of family members of patients with LQTS is necessary even if they do not meet ECG criteria [88]. Molecular genetic testing is recommended for definitive disease associated genes to be performed on all patients who meet the following criteria; acquired LQTS who experienced drug-induced TdP, aged < 40 years and have a QTc >440 ms (M) and >450 ms (W) [13]. Gene-specific management of LQTS has become feasible in clinical practice; egz. patients with KCNQ1 variant are at higher risk during sympathetic and can benefit from antiadrenergic intervention (betablockers and left cardiac sympathetic denervation (LCSD)), in patients with KCNH2-LQTS is important to preserve adequate potassium level, mexiletine treatment has been shown to be effective in patients with SCN5A and KCNH2 variants [89–93].

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3.3. Short QT Syndrome

Short QT syndrome (SQTS) is a channelopathy that is characterized by a short QT interval on the basal ECG and carries an increased risk of atrial fibrillation and ventricular arrhythmias. SQTS diagnostic criteria are: QTc ≤320 ms alone, or QTc ≤360 ms combined with a family history of SQTS, aborted cardiac arrest in the absence of heart disease or pathogenic mutation [1]. Genetic testing primarily includes panel testing for genes with definitive and strong evidence for SQTS; KCNH2 (locus 7q35-36, increase in IKr channel function) and KCNQ1 (locus 11p15.5, increase in IKs channel function), and moderate evidence; KCNJ2 (locus 17q23, increase in IK1 channel function) and SLC4A3 (locus 2q35). (according to ClinGen) Autosomal recessive primary systemic carnitine deficiency syndrome, characterized by progressive cardiomyopathy, skeletal myopathy, hypoglycaemia and hyperammonaemia and is caused by variants in SLC22A5, is also associated with SQTS and SCD and it has been proven that QT interval in this syndrome is responsive to carnitine supplementation treatment [95]. Quinidine is currently the best results in treating SQTS and QT interval prolongation [1]. ICD implantation is recommended in patients with SQTS after cardiac arrest event or documented spontaneous sustained VT, an ICD implantation should be considered in SQTS patients with arrhythmic syncope [1]. Variant-specific genetic testing of family members of patients with LQTS is recommended [13].

3.4. Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare malignant heritable arrhythmia syndrome characterized by polymorphic or bidirectional ventricular tachycardia in young people that occurs during physical or emotional stress. Individuals can have a normal baseline electrocardiogram (ECG), and diagnosis is based on the occurrence of arrhythmia during exercise stress test or in Holter ECG recording [1,13,97]. Genetic testing primarily includes panel testing for genes with definitive and strong evidence for CPVT; RyR2 (locus 1q43, inappropriate Ca2+ release from the SR), CASQ2 (locus 1p13.1, inappropriate Ca2+ release from the SR), TECRLa (locus 4q13.1, altered Ca2+ homeostasis, possibly linked to fatty acid/lipid metabolism), TRDNa (locus 6q22.31, expression leading to remodeling of the cardiac dyad/calcium release unit), KCNJ2 (locus 17q24.3, loss-of-IK1 channel function), and moderate evidence CALM 1–3 (locus 14q32.11, 2p21, 19q13.32, RyR2 binding affinity resulting in inappropriate Ca2+ release from the SR). RyR2 gene mutation (RyR2 gene encodes the sarcoplasmic reticulum (SR) Ca2+ channel called RyR), as autosomal dominant trait, is found in almost 60% of patients with CPVT [98–100]. Mutations of CASQ2 are less common as autosomal recessive trait. The CASQ2 gene encodes calsequestrin-2 (protein that binds free calcium in the sarcoplasmic reticulum) [101]. Mutations in KCNJ2 gene that also cause the Andersen–Tawil syndrome have been described in a few patients with normal QTc-interval and a CPVT phenotype [102]. In phenotype-positive CPVT patients who are negative for CPVT definitive genes, genetic testing may be considered for CPVT phenocopies resulting from pathogenic variants in the KCNJ2, SCN5A, and PKP2 genes [103,104]. Variant-specific genetic testing is recommended for family members of CPVT patients and the identification of the disease-causative variant [13]. While ICD implantation is certainly indicated in the secondary prevention of sudden cardiac death, some studies and a systematic review of 53 studies highlight possible harmful consequences of ICD implantation in primary prevention, for example, a fatal ICD-related electrical storm (4/1429 patients) and numerous possible complications unrelated to frequent device activation have been reported [105].

4. Conclusions

This review provides evidence that specific genetic variants are associated with an increased risk of SCD. The data emphasizes the importance of genetic screening and early intervention in individuals with a family history of SCD or risk factors for inherited cardiac conditions causing SCD. Gene-specific management of familial cardiomyopathies and inherited cardiac channelopathies

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causing SCD should be emphasized for further re-search with the improvement of targeted genetic disorders treatment.

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Abbreviations

The following abbreviations are used in this manuscript:

sudden cardiac death SCD
dilated cardiomyopathy DCM
hypertrophic cardiomyopathy HCM
arrhythmogenic cardiomyopathy ACM
Brugada Syndrome BrS
Long-QT-Syndrom LQTS
catecholaminergic polymorphic ventricular tachycardia CPVT
Atherosclerosis Risk in Communities Study ARIC
Cardiac Arrest Registry to Enhance Survival CARES
out of hospital cardiac arrest OHCA
autosomal dominant AD
autosomal recessive AR
single nucleotide polymorphisms SNP
ENCyclopedia Of DNA Elements ENCODE
Mutations MUT
genome-wide association studies GWAS
quantitative trait loci QTL
electrocardiogram ECG
polygenic risk scores PRS
left ventricular LV
Late Gadolinium Enhancement LGE
Magnetic resonance MR
left ventricular ejection fraction LVEF
cardioverter defibrillator ICD
myosin-binding protein C3 MYBPC3
beta myosin heavy chain MYH7
troponin I, cardiac type TNNI3
troponin C, cardiac type TNNC1
alpha tropomyosin TPM1
alpha cardiac actin ACTC1
regulatory myosin light chain MYL2
essential myosin light chain MYL3
alpha tropomyosin PM1
formin homology 2 domain containing 3 FHOD3
filamin C FLNC
alpha kinase 3 ALPK3

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protein kinase AMP-activated non-catalytic subunit gamma 2 PRKAG2
calcium voltage-gated channel subunit alpha1 C CACNA1C
actinin alpha 2 ACTN2
cysteine- and glycine-rich protein 3 CSRP3
Kelch-like family member KLHL24
tripartite motif containing TRIM63
junctophilin JPH2
Likely-pathogenic or pathogenic LP/P
desmin DES
filamin-C FLNC
lamin A/C LMNA
β myosin heavy chain MYH7
RNA-binding motif protein 20 RBM20
sodium channel protein type 5 subunit alpha SCN5A
metavinculin VCL
ribosomal protein L3-like RPL3L
arrhythmogenic right ventricular cardiomyopathy ARVC
right ventricular RV
biventricular disease variants BiVACM
dominant-right arrhythmogenic cardiomyopathy ARVC
dominant-left arrhythmogenic cardiomyopathy ALVC
desmoplakin DSP
plakophillin PKP2
plakoglobin JUP
desmoglein-2 DSG2
desmocollin-2 DSC2
transmembrane protein 43 TMEM43
phospholamban PLN
polygenic risk scores for Brugada syndrome PRSBrS
calmodulin 1-3 CALM1, CALM2, CALM3
Torsades de Pointes TdP
left cardiac sympathetic denervation LCSD
Short QT syndrome SQTS
Ryanodine RyR

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