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Review article

Genetics of channelopathies associated with sudden cardiac death

Oscar Campuzano[1,2,#], Georgia Sarquella-Brugada[3,#], Ramon Brugada[1,2], Josep Brugada[3,4,*]

[1]Cardiovascular Genetics Center, University of Girona – IDIBGI, Spain
[2]Department of Medical Sciences, School of Medicine, University of Girona, Spain
[3]Unit of Arrhythmias, Hospital Sant Joan de Deu, University of Barcelona, Spain
[4]Unit of Arrhythmias, Hospital Clinic de Barcelona, University of Barcelona, Spain
*Email: josep@brugada.org
[#]Both authors contributed equally

ABSTRACT
Recent technological advances in cardiology have resulted in new guidelines for the diagnosis, treatment and prevention of diseases. Despite these improvements, sudden death remains one of the main challenges to clinicians because the majority of diseases associated with sudden cardiac death are characterized by incomplete penetrance and variable expressivity. Hence, patients may be unaware of their illness, and physical activity can be the trigger for syncope as first symptom of the disease. Most common causes of sudden cardiac death are congenital alterations and structural heart diseases, although a significant number remain unexplained after comprehensive autopsy. In these unresolved cases, channelopathies are considered the first potential cause of death. Since all these diseases are of genetic origin, family members could be at risk, despite being asymptomatic. Genetics has also benefited from technological advances, and genetic testing has been incorporated into the sudden death field, identifying the cause in clinically affected patients, asymptomatic family members and post-mortem cases without conclusive diagnosis. This review focuses on recent advances in the genetics of channelopathies associated with sudden cardiac death.

Keywords: Sudden cardiac death, arrhythmias, channelopathies, genetics

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INTRODUCTION

Sudden death (SD) is defined as a "*natural and unexpected event that occurs within the first hour after onset of symptoms in an apparently healthy subject or whose disease was not severe enough to predict a fatal outcome, and in which a thorough postmortem examination fails to demonstrate an adequate cause of death*".[1] Nearly 85% of all SD are of cardiac origin, called sudden cardiac death (SCD). SCD is a leading cause of death in Western countries, and despite a huge number of deaths it remains without a definitive diagnosis.[2]

In the last 50 years, technological advances in biomedicine have improved diagnosis. Genetics has been one of the main fields to take advantage of this technological progress. Cardiology has incorporated these advances in genetics, identifying several new genes responsible for disease associated with SCD. As a consequence, genetic testing has been progressively incorporated into clinical diagnoses, identifying the cause of the disease in clinically affected patients, unresolved post-mortem cases and even in asymptomatic individuals who - despite being asymptomatic - are at risk of SCD because they carry the genetic alteration responsible for the disease.[3] Therefore, genetics has been incorporated into current clinical guidelines on SCD.

There are many types of heart disease in which genetic factors - with or without accompanying structural heart disease - may predispose an individual to arrhythmias or SCD. Examples include coronary heart disease, heart failure, congenital cardiac channelopathies, cardiomyopathies, coronary artery anomalies and/or aortic root dissection.[4] Currently, nearly 80% of SCD cases in individuals over 55 years old are a consequence of coronary heart disease. However, SD in the young-adult population ($<$ 35 years old) is often caused by arrhythmic syndromes without structural heart disease.[5] In addition, in young population ($<$ 15 years old), nearly 40% of SD have a potential arrhythmogenic origin.[6]

CHANNELOPATHIES

Channelopathies are a group of cardiac diseases characterized by a structurally normal heart leading to arrhythmogenesis, syncope and SCD.[7] These diseases are of genetic origin and within affected families, variable expressivity and incomplete phenotype of several members are frequent. Some of these diseases are not accompanied by changes in the electrocardiogram (ECG), which makes them more difficult to diagnose. Given that these diseases are caused by a genetic alteration, genetic testing can contribute substantially both to the diagnosis of affected patients and to prevention, with the identification of asymptomatic individuals at risk.[8] Recent advances in the field of genetics have identified several genetic alterations in genes encoding ion channel proteins or associated proteins.[9]

Ion channels are proteins located in the membrane of the myocyte, which allow the movement of ions in and out, in order to maintain ion balance. A complex coordination of open/close channels in response to the electric gradient gives rise to the cardiac action potential. Currently, most of the aspects of genetic alteration associated with SCD have been identified in sodium, potassium and calcium channels. Several other elements are also necessary to achieve a coordinated cardiac activity,[10] but these are less well understood. If ion channel proteins or associated proteins are defective, cardiac activity is altered inducing arrhythmogenesis that may lead to SCD.

In general, depending on which ion channel is affected, different syndromes will be present. Nevertheless, the same syndrome may show a certain degree of overlap with different types of channel being affected. In addition, the interaction of genetic factors and environment as a phenotype modifier[11] is well documented. Finally, and despite the tremendous advances in genetics of channelopathies associated with SCD, a large proportion of families remain without a genetic diagnosis after comprehensive genetic analysis.[12] Integration of knowledge of all these facts will lead to key information for stratifying risk of SCD.

SODIUM CHANNEL AND ASSOCIATED PROTEINS

Several genetic alterations in sodium channels have been identified as causative of diseases associated with SCD (Table 1). Different genetic defects in the same gene can give rise to different phenotypes, and even combinations of phenotypes.[13] Among the diseases identified, there are two main ion channel diseases: Long QT syndrome (LQT) and Brugada Syndrome (BrS).

Table 1. Overview of ion channel diseases.

Channel	Disease	Inheritance	Gene	Protein
Sodium	LQT 3	AD	*SCN5A*	Nav1.5
	LQT 10	AD	*SCN4B*	Navβ4
	LQT 17	AD	*SCN1B*	Navβ1
	BrS 1	AD	*SCN5A*	Nav1.5
	BrS 2	AD	*GPD1-L*	Glycerol-3-P-DH-1
	BrS 5	AD	*SCN1B*	Navβ1
	BrS 7	AD	*SCN3B*	Navβ3
	BrS 16	AD	*SCN2B*	Navβ2
	Br S 17	AD	*SCN10A*	Navβ
	BrS 19	AD	*PKP2*	Plakophilin-2
Sodium-associated	LQT 9	AD	*CAV3*	M-Caveolin
	LQT 12	AD	*SNTA1*	α-Syntrophin
	BrS 10	AD	*RANGRF*	RAN-G-release factor (MOG1)
	BrS 14	AD	*SLMAP*	Sarcolemma associated protein
Potassium	LQT 1	AD/AR	*KCNQ1*	Kv7.1 hERG/Kv11.1
	LQT 2	AD	*KCNQ2*	MinK
	LQT 5	AD/AR	*KCNE1*	MiRP1
	LQT 6	AD	*KCNE2*	Kv2.1/Kir2.1
	LQT 7	AD	*KCNJ5*	Kv3.4/Kir3.4
	LQT 13	AD	*KCNH2*	hERG/Kv11.1
	SQT 2	AD	*KCNQ1*	Kv7.1
	SQT 3	AD	*KCNJ2*	Kv2.1/Kir2.1
	BrS 6	AD	*KCNE3*	MiRP2
	BrS 8	AD	*KCNJ8*	Kv6.1/Kir6.1
	BrS 9	AD	*HCN4*	Hyperpolarization cyclic nucleotide-gated 4
	BrS 11	AD	*KCNE5*	Potassium voltage-gated channel subfamily E member1 like
	BrS 12	AD	*KCND3*	Kv4.3/Kir4.3
	CPVT 3	Sex-related	*KCNJ2*	Kv2.1/Kir2.1
Potassium-associated	LQT 11	AD	*AKAP9*	Yotiao
	BrS 18	AD	*ABCC9*	ATP-binding cassette transporter of IK-ATP (SUR2A)
Calcium	BrS 3/shorter QT (SQT 4)	AD	*CACNA1C*	Cav1.2
	BrS 4/shorter QT (SQT 5)	AD	*CACNB2B*	Voltage-dependent β-2
	BrS 13	AD	*CACNA2D1*	Voltage-dependent α2/δ1
	BrS 15	AD	*TRPM4*	Transient receptor potential M4
	SQT 6	AD	*CACNA2D1*	Voltage-dependent α2/δ1
	LQT 8	AD	*CACNA1C*	Cav1.2
	LQT 14	AD	*RYR2*	Ryanodine Receptor 2
	LQT 15	AD	*CALM1*	Calmodulin 1
	LQT 16	AD	*CALM2*	Calmodulin 2
	CPVT 1	AD	*RYR2*	Ryanodine Receptor 2
	CPVT 2	AR	*CASQ2*	Calsequestrin 2
Calcium-associated	LQT 4	AD	*ANK2*	Ank-B
	CPVT 4	AR	*TRDN*	Triadin
	CPVT 5	AD	*CALM1*	Calmodulin 1

AD, Autosomic Dominant; AR, Autosomic Recessive; AF, Atrial Fibrillation; BrS, Brugada Syndrome; CPVT, Catecholaminergic Polymorphic Ventricular Tachycardia; LQT, Long QT Syndrome; SQT, Short QT Syndrome.

Long QT syndrome

Long QT syndrome characterized by prolongation of the QT interval in the ECG (Figure 1). The clinical presentation can be variable, ranging from asymptomatic patients to syncope, ventricular arrhythmias, typically *torsade de pointes*, and SCD. LQT is one of the leading causes of sudden death among young people.[14] So far, more than 600 genetic alterations have been reported as pathogenic. Some of these are localized in 3 sodium genes (*SCN5A*, *SCN4B* and *SCN1B*) and 2 associated-proteins (Caveolin3 and Syntrophin)[15] (Figure 2).

Pathogenic variance in *SCN5A* (LQT syndrome type 3) causes a functional defect based on incomplete inactivation of the channel, thereby allowing continued entry of sodium ions into the cell during repolarization and leading to enhanced function. Usually, arrhythmias occur at rest.[13] In the case of the *SCN4B* sodium gene, the beta sub-unit ($Na_v\beta4$) of the sodium channel causes a negative change in the sodium dependent voltage in the activation channel.[16] Recently, a pathogenic variant has also been identified in the *SCN1B* gene as responsible of LQT syndrome. It encodes two $Na_v\beta1$ sub-unit cardiac isoforms: $Na_v\beta1$ isoform a, and $Na_v\beta1$ isoform b.[17] If we look at sodium associated proteins, the

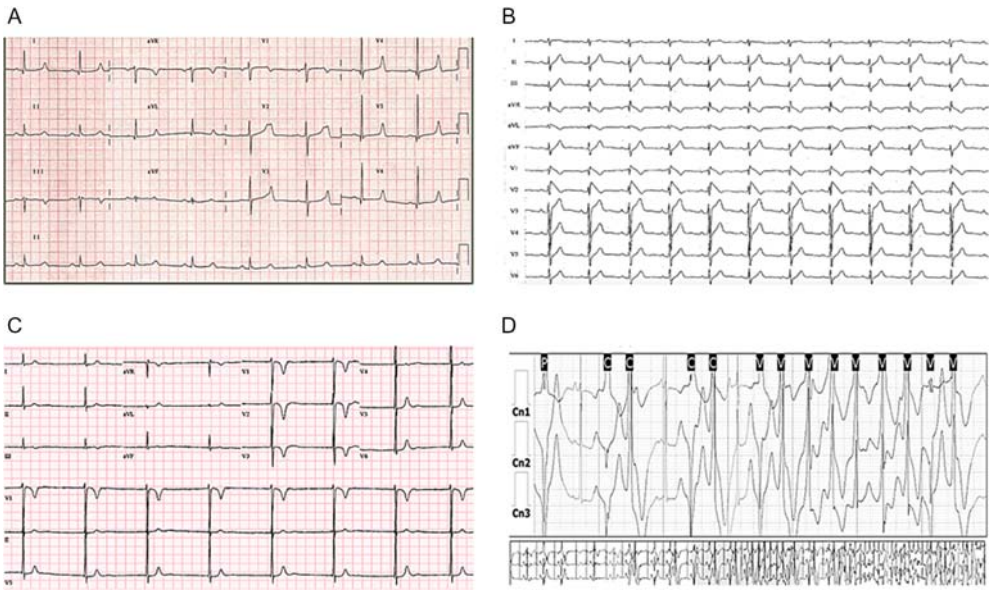

Figure 1. Electrocardiograms showing A. Long QT Syndrome B. Brugada Syndrome C. Short QT Syndrome, and D. Catecholaminergic Polymorphic Ventricular Tachycardia.

CAV3 gene encodes for caveolin-3, which is the main protein that forms the caveolae in cardiac and skeletal muscle. Pathogenic variants in the *CAV3* gene have been associated with LQT Syndrome due to caveolin-3 interacting with Kir2.1, and genetic alterations decreasing I_{K1} density.[18] The other sodium-associated protein is α1-Syntrophin, encoded by the *SNTA1* gene. α1-Syntrophin is one of the dystrophin-associated proteins, and contains multiple protein interacting motifs. A total of 3 pathogenic variants of *SNTA*$_1$ associated with LQT syndrome have been reported.[19]

Brugada syndrome

This cardiac entity is characterized by ST elevation at leads V1-3 in the ECG, leading to ventricular arrhythmias and SCD (Figure 1). The mean age of onset of events is around 40 years, mainly in men.[20] Most of the pathogenic variants have been identified in sodium genes, although potassium and calcium genes have also been also associated with BrS (*SCN1B, SCN2B, SCN3B, SCN10A, GPD1-L, RANGRF, SLMAP, PKP2, KCNE3, KCNJ8, KCND3, KCNE5, HCN4, ABCC9, CACNA1C, CACNB2b, CACNA2D1*, and

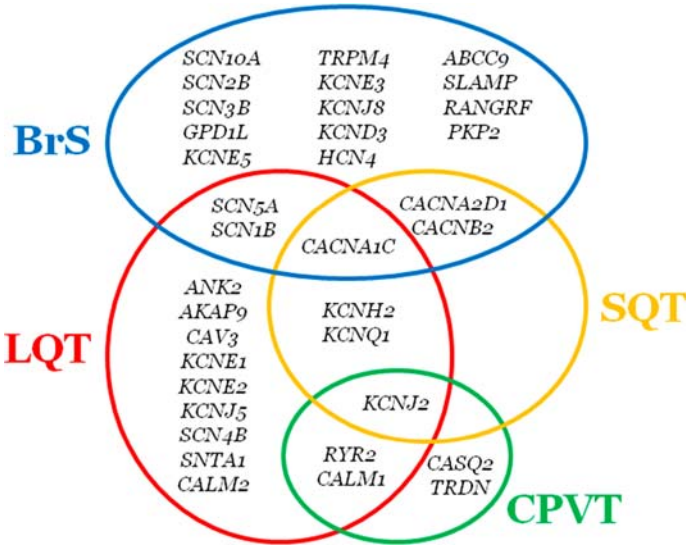

Figure 2. Diagram of overlapping genes associated with main cardiac channelopathies. Short QT Syndrome (SQT), Long QT Syndrome (LQT), Brugada Syndrome (BrS), and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT).

TRPM4) (Figure 2). All these genes together are responsible for nearly 35% of BrS cases.[21] Regarding sodium channels and associated proteins (*SCN5A*, *GPD1-L*, *SCN1B*, *SCN3B*, *SCN2B*, *SCN10A*, *PKP2*, *RANGRF*, and *SLMAP*), the *SCN5A* gene alone is responsible for nearly 25% of BrS cases. This gene encodes the cardiac sodium channel Nav1.5, and is responsible for phase 0 of the cardiac action potential. Pathogenic variations in the *SCN5A* gene induce a loss of function.[22] Other pathogenic variations have been published in *SCN1B*, *SCN2B*, and *SCN3B* encoding beta subunits that modify Nav1.5 (increasing or decreasing I_{Na}). The *SCN1B* gene encodes the β1 subunit of the cardiac sodium channel conducting the INa current. In the heart, the biophysical function of β1 subunits and of β1b splicing variants is to modify the function of Nav1.5, by increasing the I_{Na}.[23] The *SCN2B* gene encodes the β2 sodium channel subunit,[24] and the *SCN3B* gene encodes the β3 subunit of the cardiac sodium channel conducting the I_{Na} current. In the heart the function of the β3 subunit is to modify the function of Nav1.5 by increasing the Ina, similarly to the β1 subunit, but with different kinetics.[25] Recently, the *SCN10A* gene, a neuronal sodium channel gene encoding Nav1.8, has also been found to modulate *SCN5A* expression and the electrical function of the heart,[26] and pathogenic variants of the *GPD1-L* gene have been implicated in reducing both the surface membrane expression and the inward sodium current.[27] Other studies have shown the *RANGRF* gene to impair the trafficking of Nav1.5 to the membrane, leading to I_{Na} reduction and clinical manifestation of BrS.[28] In 2012, a pathogenic variant was identified in *SLMAP*. This gene encodes the sarcolemmal membrane-associated protein which is localized at the T-tubules and sarcoplasmic reticulum, and it causes BrS by modulating the intracellular trafficking of the Nav1.5 channel.[29] Finally, a pathogenic variant has been identified in *PKP2* (plakophilin-2 protein). This is a desmosomal gene and correlation between the loss of expression of plakophilin-2 and reduced I_{Na} has been identified in BrS patients.[30]

POTASSIUM CHANNEL AND ASSOCIATED PROTEINS

Potassium channels are key participants in the cardiac action potential, and genetic alterations in these channels or associated proteins may lead to dysfunction and potassium imbalance[31] (Table 1). There are 4 main channelopathies associated with SCD: LQT syndrome, short QT syndrome (SQT), BrS and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT).

Long QT Syndrome

As already mentioned, LQT syndrome is usually caused by repolarization abnormalities with implication of the potassium channels (Iks, Ikr, Iki). Pathogenic genetic variants identified in potassium genes lead to a loss of function; this in turn gives rise to a decrease in the release of potassium, inducing the channels to remain open for longer and the QT interval to be prolonged due to a longer ventricular repolarization time.[32]

Currently, several pathogenic genetic alterations have been reported in 6 different potassium channel genes (*KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2*, *KCNJ2*, and *KCNJ5*), and one associated protein (*AKAP9*), accounting for 50% to 60% of the clinically diagnosed LQT syndrome cases[15] (Figure 2). The main gene associated with LQT syndrome is *KCNQ1*, with pathogenic variants responsible for 40% to 50% of cases of prolonged QT interval, giving rise to type 1 long QT syndrome.[33] This protein binds to the protein encoded by the *KCNE1* gene (*minK*) to form the Iks functional complex.[34] Around 10 different pathogenic variants have been identified in *KCNE1*. Another disease-associated gene is *KCNH2*, which encodes a subunit of the Ikr complex; This Ikr complex is the most important inducer of fast repolarization in phase 3 of Cardiac Action Potential. Pathogenic variants in *KCNH2* lead to loss of function in the Ikr channel, and account for 35% to 45% of LQT syndrome cases.[35] Pathogenic variants of *KCNE2* similarly lead to loss of channel function, as do those in the *KCNJ2* gene, which encodes Ik1 (Kir2.1) protein (Tawil-Anderson syndrome).[36] However, the incidence of this latter gene variant in the population is very low and rarely associated with SCD. Other potassium genes associated with LQT syndrome include *KCNJ5*, which encodes for Kir3.4 channel (also called GIRK4). *KCNJ5* forms homomeric channels or functional heteromeric channels with other Kir3.x, channels responsible for G protein-coupled inwardly rectifying potassium channel current (IKACh), mainly expressed in the sinoatrial node, sinoventricular node and atria.[37] Finally, a potassium-associated protein identified in LQT syndrome patients is A-kinase-anchoring proteins (AKAPs) 9, which is a scaffolding protein that determines the localization of protein kinase A (PKA) and other proteins that regulate the PKA (phosphatases or other kinases). It is encoded by the *AKAP9* gene. Few pathogenic variants have been

reported in this gene, the AP duration is prolonged due to a reduction of the cAMP-dependent phosphorylation of Kv7.1, and reduction in cAMP stimulation response occurs.[38]

Short QT syndrome

Short QT syndrome (SQT) is a rare and lethal cardiac entity characterized by no structural heart alterations and a short QT interval in the ECG (< 330 ms). It also shows absent or minimal ST segments, an interval from J point to T wave peak (Jp-Tp) measured in the precordial lead with the T wave of greatest amplitude < 120 ms, and possible tall T waves with narrow base similar to the T wave of moderate hyperkalemia ("desert tent T waves"). In addition, you have a frequent early repolarization pattern, prolongation of T peak-T end interval, and a possible presence of prominent U waves (Figure 1). All these events may lead to ventricular arrhythmias, syncope and SCD at an early age, although asymptomatic patients have also been reported.[39]

Currently, these genetic alterations have been identified in 6 different genes (*KCNQ1*, *KCNJ2*, *KCNH2*, *CACNA1C*, *CACNB2*, and *CACNA2D1*) (Figure 2), which follow an autosomal dominant pattern of inheritance, demonstrate high penetrance and are responsible for nearly 60% of clinically diagnosed cases.[40] Type 1 short QT syndrome has been associated with genetic variants in *KCNH2* that induce a fast activation of potassium currents, with enhanced Ikr function and shortened ventricular action potentials. In this type, cardiac events are generally associated with adrenergic situations (noise or exercise), although cases of cardiac events at rest have also been published.[41] Type 2 short QT syndrome has been linked to genetic variant in *KCNQ1*, which enhances the function of the potassium channel, leading to a shortening of the action potential. In this gene, a particularly highly malignant entity characterized by bradycardia *in uterus* and SQT and Atrial Fibrillation (AF) in the neonatal period has been reported.[42] Type 3 short QT syndrome is caused by genetic variants in *KCNJ2*, leading to an acceleration of the phase 3 action potential.[43]

Brugada syndrome

Several pathogenic variants have been identified in potassium channels in BrS families (*KCNE3*, *KCNJ8*, *KCND3*, *KCNE5*, *HCN4* and *ABCC9*). In 2011, the first evidence implicating a novel gain-of-function pathogenic variant in *KCND3* associated with BrS was published. This gene encodes a voltage-gated potassium channel which is prominent in the repolarization phase of the action potential.[44] Pathogenic variants associated with BrS have been also identified in the *KCNE3* gene. This gene encodes MiRP2, a regulatory β subunit of the transient outward potassium channel I_{to}, which is one of five homologous auxiliary β subunits (KCNE peptides) of voltage-gated potassium ion channels.[45] It is well-known that BrS follows an autosomal dominant pattern of inheritance. However, so far, only a few pathogenic variants associated with BrS have been reported in these potassium genes.[47]

One pathogenic variant associated with BrS patients has been located in the *KCNE1L* gene (*KCNE5*) – X-linked gene.[46] Recently, a BrS family carrying a pathogenic variant in the *KCNJ8* gene was also reported. In addition, BrS has also been associated with *HCN4*, which encodes the hyperpolarization-activated cyclic nucleotide-gated potassium channel 4. This is expressed in the sinus node and cells of cardiac conduction system, thus loss of function of HCN_4 protein is associated with sinus nodal dysfunction.[48] Finally, the *ABCC9* gene encodes the sulfonylurea receptor subunits SUR2A.[49] Pathogenic variants in this gene induce a gain-of-function in I(K-ATP), and when coupled with a loss-of-function in *SCN5A*, may underlie a severe arrhythmic phenotype.

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare cardiac disorder characterized by adrenergic-induced bi-directional and polymorphic ventricular arrhythmias leading to SCD, mainly in the juvenile population, without structural heart alterations (Figure 1). The baseline ECG is usually normal, and unfortunately the first presentation can also be SCD.[50]

Currently, CPVT is known to be caused by impaired intracellular calcium handling due to nearly 200 pathogenic genetic variations in 5 different genes (*RyR2*, *CASQ2*, *KCNJ2*, *CALM1* and *TRDN*) (Figure 2). Focusing on *KCNJ2*, only 3 genetic variants have been associated with CPVT (CM045295, CM066888, and CM066889) to date, but a further variation (CM111211) has been reported in a patient showing Andersen-Tawil syndrome and CPVT mimicry.[51]

CALCIUM CHANNELS AND ASSOCIATED PROTEINS

Calcium channels have been implicated in an increasing number of inherited cardiac arrhythmias allowing activation of the contraction of the heart[52] (Table 1). Among these, a combination of BrS and shorter QT, LQT syndrome, BrS, SQT syndrome, and CPVT are the main diseases associated with SCD.

Combination of Brugada syndrome and shorter QT interval

Genetic variants in *CACNA1C* are responsible for a defective functioning of the type-L calcium channels, inducing a loss of channel function linked to the combination of BrS with shorter QT.[53] Other genetic variants in *CACNB2b* lead to the same ECG traces (combination of BrS and shorter QT).[53]

Short QT syndrome

The third calcium gene is *CACNA2D1* and only 1 pathogenic variant has been associated with SQTS (CM111612).[54] However, this variant is currently discussed as pathogenic due to its identification in a control population.

Long QT syndrome

Some genetic variants in calcium genes associated with LQT syndrome (*CACNA1C*, *RYR2*, *CALM1*, *CALM2* and *ANK2*) have been reported.[15] Pathogenic variants in *CACNA1C* cause LQT syndrome Type 8 (Timothy syndrome). This type of long QT syndrome is uncommon, but has the highest associated mortality. The genetic variation induces an enhanced function with I_{Ca} abnormality, and loss of the channel dependent voltage, leading to a prolongation of the action potential. This gives rise to an ECG with an extremely long QT interval.[55] Recently, a few cases of LQT syndrome have been identified in two genes: *CALM1* and *CALM2*. *CALM1* and *CALM2*, together with *CALM3*, encode for calmodulin protein. Their products have identical amino acid sequences, and all three are expressed in the human heart left ventricle. Calmodulin is a multifunctional Ca^{+2} binding protein essential for transduction of Ca^{+2} signals to influence the activity of cardiac ion channels, kinases, and other target proteins in heart.[56] However, association of both these genes with LQT syndrome should be further studied. Finally, LQT syndrome has been associated with *ANK2*, an associated calcium protein.[57] This gene encodes for the Ankyrin-B protein. Ankyrins are adaptor proteins that link membrane proteins, transporters, and cell adhesion molecules to cytoskeleton, including Nav1.5, Na+/Ca+2 exchanger, Na+/K+ ATPase, Kir6.2, and the inositol trisphosphate (IP_3) receptor. Variations in ANK2 result in a dysfunctional ankyrin-B, causing a Na+/Ca+2 exchanger and Na+/K+ ATPase dysfunction. This dysfunction leads to an increment of intracellular Na+ and Ca+2 ions, producing cellular early and delayed afterdepolarizations (EADs and DADs, respectively) in response to catecholamine.[58] So far, nearly 20 variations have been identified in the *ANK2* gene.

BrugadasSyndrome

In 2010, the *CACNA2D1* gene was associated with BrS.[54] So far, no more than 5 genetic variants have been reported. In addition, pathogenic genetic variants have also been reported in the *TRPM4* gene which encodes the transient receptor potential melastatin protein number 4, a calcium-activated nonselective cation channel, and a member of a large family of transient receptor potential genes.[59] Few genetic variants have been published as causative of BrS in this gene, so far.

Catecholaminergic polymorphic ventricular tachycardia

As previously mentioned, nearly 200 pathogenic genetic variations in 5 different genes (*RyR2*, *CASQ2*, *KCNJ2*, *CALM1* and *TRDN*) have been identified to date. Calcium-related genes are implicated in regulating intracellular calcium, and both types of defect lead to increased function of these proteins, and to an increased outflow of calcium from the sarcoplasmatic reticulum. This excess of calcium is associated with alterations in the sarcolemmal membrane potential leading to late depolarization, which predispose to lethal arrhythmias.[60]

The main gene associated with CPVT is *RyR2*.[61] The ryanodine receptor is an intracellular calcium channel that is located in the sarcoplasmatic reticulum and activated by the influx of small amounts of calcium, thereby allowing the outflow of stored calcium. This is crucial in triggering heart muscle contraction. One other gene associated with CPVT is *CASQ2* which encodes the cardiac muscle family member of the calsequestrin family that acts as an internal calcium store in muscle cells.[62] Nearly 25 genetic variants have been associated with CPVT showing mainly an autosomal recessive inheritance

pattern. Two calcium associated proteins have also been reported in CPVT cases, Calmodulin (*CALM1*)[63] and Triadin (*TRDN*).[64] To date, only two genetic variants have been linked to CPVT (CM128791 and CM128792) in *CALM1*. Recently, a potential association of the *CALM2* gene in overlapping clinical features of LQTS and CPVT has been published, but its pathogenic role remains to be clarified.[56] Finally, Triadin is an integral membrane protein that contains a single transmembrane domain, involved in anchoring Calsequestrin (*CASQ2*) to the junctional sarcoplasmic reticulum and allowing its functional coupling with the Ryanodine receptor (*RyR2*) that regulates sarcoplasmic reticulum calcium release. Currently, 3 genetic variants have been associated with CPVT (CM124195, CM124194, and CD124196).

CONCLUSIONS

Cardiology has greatly benefited from the recent progress in genetics, which has helped both to unravel the origin of several cardiac diseases, and to understand their mechanistic pathways. A proportion of this improved genetic understanding has been applied to the diagnosis and prevention of channelopathies associated with SCD. Genetic test have been incorporated into clinical practice to diagnose clinically affected patients, to identify individuals who despite asymptomatic are at risk of SCD, and to unravel the genetic alterations responsible for death in post-mortem cases with no-conclusive cause of death after autopsy. Despite several genes have been reported in ion channel diseases, a large proportion of clinically diagnosed families remain without a recognized genetic cause of disease. Continuing efforts in researching the genetics of SCD will allow us to identify new genetic alterations associated with SCD, improving current diagnostic tests, early prevention, and risk stratification. Finally, all these genetic advances in conjunction with families, clinicians, and basic researchers will be crucial to the advancement of biomedicine towards personalized treatments.

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