

Genetics of Sudden Cardiac Death, the Channelopathies: Today's Perspective and the Future

Abdullah Alabdulgader*

Senior Congenital Cardiologist and Invasive Electrophysiologist, Prince Sultan Cardiac Center (Founder & Chief Physician), Alhasa, Saudi Arabia.

*Correspondence:

Abdullah Alabdulgader, Senior Congenital Cardiologist, Invasive Electrophysiologist and Cardiac Astrophysicist, Prince Sultan Cardiac Center (Founder and Chief Physician), Alhofuf, Alhasa, Saudi Arabia.

Received: 10 July 2021; Accepted: 20 August 2021

Citation: Alabdulgader Abdullah. Genetics of Sudden Cardiac Death, the Channelopathies: Today's Perspective and the Future. *Cardiol Vasc Res.* 2021; 5(4): 1-13.

ABSTRACT

Channelopathy constitute significant proportion of SCD worldwide (around 10% or 370000 deaths annually). Besides LQTS, the channelopathies include Brugada syndrome (BrS), short QT syndrome, Early Repolarization Syndrome (ERS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and congenital sick sinus syndrome. It was constituting a mysterious group of disease until the second half of the last century when Anton Jervell and Fred Lange-Nielsen described Jervell Lange-Nielsen syndrome in 1957. It was late until 1995 where genetic characterization commenced. Later on, the massive genetic information obtained in the field with discovery of genetic heterogeneity and allelic heterogeneity were all part of our new understanding and clues to solve the historical conundrum of channelopathies. Here, we review the genetic basis of sudden cardiac death with a focus on the current knowledge on the genetics of the primary electric disorders caused primarily by mutations in genes encoding ion channels. Diving deep into the genetic details of those syndromes enable us to improve our knowledge and decode the pathophysiology of those malignant arrhythmias. The ultimate ambition is prevention of channelopathy based sudden cardiac death and associated disorders in human.

Keywords

Arrhythmia, BrS: Brugada syndrome, CPVT: Catecholaminergic Polymorphic ventricular Tachycardia, ERS: early repolarization syndrome, Heart Rate Variability, LQTS: Long QT Syndrome, PCCD: Progressive Cardiac Conduction Disease, SCD: Sudden Cardiac Death.

Introduction

One of the most devastating life moments, that may impact the whole life of a person, families and societies is sudden death experience of close relative or beloved. The whole medical provision is dedicated to prevent or delay death while maintaining good quality of life (QOL). For this reason, sudden loss of human life is creating the most serious challenge for medical professionals and decision makers. Sudden Cardiac Death (SCD) is defined as death occurring unexpectedly in the first hour after

symptoms commence. In the United States around 300000 death is occurring every year because of SCD. It is conspicuous that this huge loss in the world communities is creating major social impact. This impact is undoubtedly more destructive with the loss of young member of the family. Ion channels in the myocardial cellular membrane are responsible for creating the basic unit of the electromagnetic foundation in humans known as cardiac action potential (AP). This is the result of an elegant interplay of ions at the cellular level. Genetic mutations in these channels can predispose to wide spectrum of clinical presentations and syndromes referred collectively to channelopathies. The basic pathology is genetic mutations creating disturbance in the process of critical ions traffic (Na⁺, Ca⁺⁺, K⁺) across the cell membrane. The delicate miraculous balance in this ion traffic is the basic unit of the normal action potential. Disturbance of this balance in terms of loss or gain of function is the source of the fatal heart rhythm.

Sadly, life-threatening arrhythmias and Sudden Cardiac Death can be the first presenting symptom. Scientists and clinicians are racing in the last two decades in a unique complementary scientific effort to reconcile the rapidly growing body of knowledge of the molecular mechanisms and clinical correlates of SCD. In this chapter we will discuss up to date clinical syndromes and their genetic and molecular correlates, and the new perspectives to improve our skills and laboratory diagnostic modalities as well as risk stratification to cherry pic the effected individuals before fatal strike deprive us from our lovers.

The Channelopathies, Genetics and clinical correlates

Channelopathies Historical land marks

In the last 25 years, the sudden cardiac death science witnessed revolutionary developments derived mainly from the genetic discoveries of mutant genes and associated subunits controlling the trans-membrane traffic of ions. Connie R. Bezzina, et al elaborates extensively in genetics of sudden death with focus on cardiac channelopathies and its clinical as well as electrocardiographic implications [1]. The complexity of the genetic mutations as etiological factor of channelopathies can be simplified knowing that without exception the various cardiac primary electric disorders are genetically heterogeneous, that is mutations in different genes can lead to the same clinical disease manifestation. Furthermore, considerable allelic heterogeneity exists in that many different mutations within each gene cause the disease. Genetic heterogeneity and allelic heterogeneity are two very important observations for us in the field of channelopathy to fulfill missing chains that we must unravel to reach to the dream of aborting

the pathology of channelopathy and the fatal cardiac rhythms in humans and mammals. In 1856, Meissner from Germany provided what is thought to be the first description of LQTS [2]. Meissner was able to describe three members from a single family who experienced sudden death. The proband was a girl who was deaf and was reported to die suddenly after being reprimanded by school director. Family history discloses the death of two siblings during emotional experience. This report was before the Dutch physician and physiologist Willem Einthoven invented the ECG in 1895. This means there was no QT interval measured in this family. It was about one hundred years later, in 1957 when Anton Jervell and Fred Lange- Nielsen described Jervell Lange- Nielsen syndrome which described autosomal inheritance of emotion based recurrent syncopal attacks and deafness. The disease was first described in 4 out of 10 of Norwegian family members. Three of the four died suddenly at ages 4,5 and 9 [3]. Six years later, in 1963, Cesarino Romano Italian pediatrician, and in 1964 Owen Conor Ward Irish pediatrician described Romano Ward Syndrome which was similar familial disease but dominantly inherited and without sensorineural deafness. Keating and coworkers in the early to mid-1990 s made much progress in the understanding of inherited predisposition to SCD [4-7]. Other Channelopathies where introduced in the next years with better understanding of the Schematic representation of a cardiomyocyte protein that is involved in the pathogenesis of the primary electric disorders (Figure 1). Brugada syndrome is named after the Spanish brothers cardiologists Pedro and Josep Brugada who described the condition in 1992, although the association between the characteristic ECG pattern and sudden cardiac death had been reported in 1989. Ramon Brugada, their

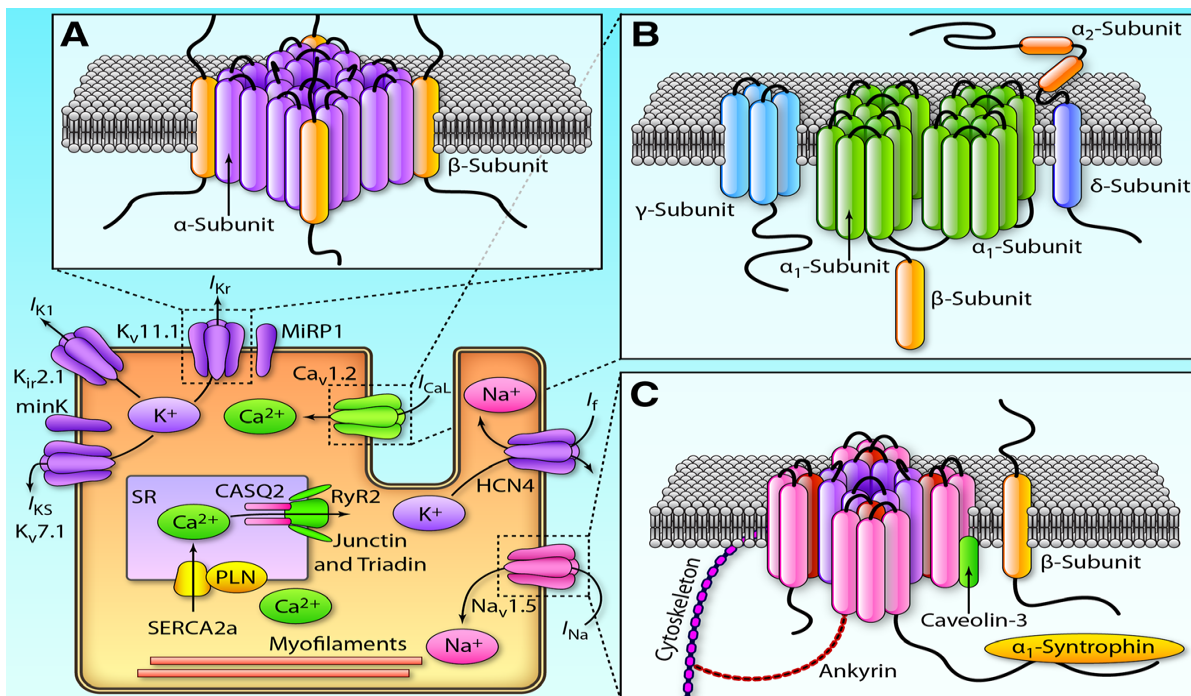


Figure 1: Proteins of cardiac cell that are involved in inherited ventricular arrhythmias which was defined from 1995 until 2020. SERCA2a denotes sarcoplasmic/endoplasmic reticulum calcium ATPase 2a; and SR denotes sarcoplasmic reticulum (Illustration credit: Ben Smith) [1].

Table 1A: Long QT Syndrome Genes and Mutations.

Clinical name	Chromosomal locus Gene name		Current Affected Non cardiac effects	
LQT1	11p15.5	KCNQ1 (KVLQT1)	K+ (Iks)	Deafness with recessive form (JLNS)
LQT2	7q35-36	HERG (KCNH2)	K+ (Ikr)	
LQT3	3p21-24	SCN5A	Na+ (INA)	
LQT4	4q25-27	Ankyrin B	Na+ (INA)	
LQT5	21q22. 1-22.2	KCNE1 (minK)	K+ (Iks)	Deafness with recessive form (JLNS)
LQT6	21q22. 1-22.3	KCNE2 (MiRP1)	K+ (Ikr)	
LQT7 (Anderson)	17q23	KCNJ2	K+ (Kir2.1)	Anderson-Tahwil syndrome with some mutations
LQT8 (Timothy)	12p13.3	CACNA1C	Ca ++ (Ica-L)	Timothy syndrome with some mutations
LQT9	3p25	CAV3 (Caveolin)	Na+ (INA)	
LQT10	11q23.3	SCN4B	Na+ (INA)	
LQT11	7q21-q22	AKAP9 (A - anchor protein 9)	K+ (I) Ks	
LQT12	20q11.2	SNTA1 (alpha-1 syntrophin)	Na+ (INA)	
LQT13	11q24.3	KCNJ5	K+ (Kir)	
LQT14	14q24-q31	Calmodulin1	Many #	Seizures, developmental delay
LQT15	2p21.1-p21.3	Calmodulin2	Many #	Seizures, developmental delay
LQT16	19q13.2-q13.3	Calmodulin3	Many #	Seizures, developmental delay
LQT17		Triadin		

Table 1B: Brugada Syndrome Genes and Mutations.

	Locus	Gene	Ion Channel	
BrS1	3p21	SCN5A, Na _v 1.5	↓ I _{Na}	11%-28%
BrS2	3p24	GPD1L	↓ I _{Na}	Rare
BrS3	12p13.3	CACNA1C, Ca _v 1.2	↓ I _{Ca}	6.6%
BrS4	10p12.33	CACNB2b, Ca _v β2b	↓ I _{Ca}	4.8%
BrS5	19q13.1	SCN1B, Na _v β1	↓ I _{Na}	1.1%
BrS6	11q13-14	KCNE3, MiRP2	↑ I _{to}	Rare
BrS7	11q23.3	SCN3B, Na _v β3	↓ I _{Na}	Rare
BrS8	12p11.23	KCNJ8, Kir6.1	↑ I _{KATP}	2%
BrS9	7q21.11	CACNA2D1, Ca _v α2δ	↓ I _{Ca}	1.8%
BrS10	1p13.2	KCND3, K _v 4.3	↑ I _{to}	Rare
BrS11	17p13.1	RANGRF, M0G1	↓ I _{Na}	Rare
BrS12	3p21.2-p14.3	SLMAP	↓ I _{Na}	Rare
BrS13	12p12.1	ABCC9, SUR2A	↑ I _{KATP}	Rare
BrS14	11q23	SCN2B, Na _v β2	↓ I _{Na}	Rare
BrS15	12p11	PKP2, Plakophilin-2	↓ I _{Na}	Rare
BrS16	3q28	FGF12, FHAF-1	↓ I _{Na}	Rare
BrS17	3p22.2	SCN10A, Na _v 1.8	↓ I _{Na}	16.7%
BrS18	6q	HEY2 (transcriptional factor)	↑ I _{Na}	Rare
BrS19	7p12.1	SEMA3A, Semaphorin	↑ I _{to}	Rare

youngest brother was encouraged to be specialized in cardiac genetics where he completed the chain and discovered in 1998 the first genetic mutation linked to BrS, the SCN5A gene. SCN5A is a highly conserved gene located on human chromosome 3. This gene encodes the alpha subunit of the cardiac sodium channel. Since then, more than 350 pathogenic mutations in several genes have been published. These genes encode subunits of cardiac sodium, potassium, and calcium channels as well as genes involved in the trafficking or regulation of these channels. LQTS and BrS discovery stories became like pro-story which enlighten more progressive channelopathy discoveries. Channelopathy associated genes to the best of what we know until 2020 are illustrated in (Table 1 A&B).

The first description of Catecholaminergic Polymorphic VT was published in 1960 by Kent Burge. He was a Norwegian cardiologist who described three sisters who suffered from syncopal attacks induced by exercise or emotion. The bidirectional tachycardia itself was described in 1975. The term Catecholaminergic Polymorphic VT was used for the first time in 1978. The first genetic mutation was described in 1999, in chromosome 1q42-q43 which was found to be in the RYR2 gene in 2001. The first description of short QT syndrome was in 2000. The association of short QT interval to SCD was described in 2003 and the first genetic mutation was identified in 2004.

The LQTS genetics and clinical correlates

LQT1 is the most frequent between all LQTSs, accounting for approximately 35% of all. The underlying genetic mutation is in KCNQ1 gene giving rise to loss of function of the slowly activating delayed rectifier current (IKs) [8]. LQT2 constitute about 30% of all LQTSs population. The underlying genetic mutation is loss-of-function mutations in KCNH2 (also known as HERG). The rapidly activated delayed rectifier current (IKr) is encoded in this protein [9]. In contrast the least frequent but more lethal type, LQT3 found in 10% of LQTS population, is due to gain of function mutation in SCN5A. This will lead to increase of the late sodium current (INa) [10]. Between 90% of genotype positive LQTS patients, LQT1, LQT2 and LQT3 accounts for 90% of all [11,12]. Other rare types of LQTSs accounts for less than 1% and are attributed to mutations encoding ion channel subunits like; KCNJ5, KCNE1, KCNE2 and SCN4B or proteins that regulate ion channels function like: AKAP9, CAV3, ANKB, SNT1, CALM1, and CALM2. The minor allele frequency in the general population renders its genetic interpretation and correlation to the clinical practice of more complex nature. As part of the huge number of reported alleles of the different diseases in medicine the clinical value of those rare alleles in terms of management of LQTSs is minimal as its exact pathogenic role is not certain. Up to the moment, all LQTSs are confined to the heart except three important clinical variants which present with extracardiac manifestations creating an important distinguishing phenotype.

First is Jervell and Lange-Nielsen syndrome which is inherited in autosomal recessive manner due to homozygous or compound heterozygous mutations in KCNQ [13] or KCNE [14]. It is corrected QT Interval (QTc) is characterized by severe prolongation. Life threatening arrhythmias and SCD with deafness (sensorineural) can be elucidated from history in the different generations of the affected family members. Recessive variant of Jervell Lange-Nielsen syndrome with homozygous or compound heterozygous mutations with no deafness has been described [15,16]. Second is Anderson-Tawil syndrome (LQT7). This syndrome is very rare (1:1,000,000) characterized by triad of clinical presentation with facial dysmorphism in the form of low-set ears and a small lower jaw, periodic paralysis as well as long QT interval. The underlying genetic disorder in most cases are mutation in the potassium channel gene KCNJ2 gene which encodes an ion channel that transports potassium out of cardiac muscle cells causing loss of function [17].

Third is Timothy syndrome (LQT8). It is an important LQTS for clinicians because of two major reasons: being highly lethal and being the only QT syndrome where death is caused by extra cardiac phenotype. The most striking manifestation of Timothy syndrome (LQT8) is the finding of two truly rare signs: syndactyly (frequency of 0.03% of births) and long QT syndrome (1:2500) in the same child. Arrhythmias present in 94% of affected children as well as congenital heart defects and AV block (60%) and (if they live enough) autism (in 80%). About half of them will show facial dimorphism in the form of flattened nose. They tend to have small teeth due to poor enamel coating and accordingly they develop dental caries easily Episodes

of malignant hypoglycemia as well as weakened immune system are also important manifestation of Timothy syndrome.



Figure 2: Syndactyly in two patients with Timothy syndrome [18].

Heterozygous mutation G406R of heterozygous nature in CACNA1C is the primary cause [18]. Minority of patients will reach the age for reproduction. For this reason, way of transmission is deduced from mosaicism of germinal cells. It is very important for the whole medical communities to understand the fact that within a family with LQTS patient, the presence of normal QT interval in the other family members (less than 440ms) who do not have related symptoms; the search for genetic mutation carriers is a must. The risk of cardiac events is 10 folds more in mutation carriers compared to non-carriers [19,20]. For proper risk stratification of LQTS patients we need always to know the true predictors and the heaviness of each in contribution to the outcome. The most important indicators to predict cardiac events in LQTS patients are aborted SCD, torsades de pointes, previous syncopal attack, or QTc more than 500ms [21,22-25].

In addition to age as prepubertal female and adult male. Sex and hormonal related risk contributions for cardiac events include female especially pubertal and postpartum (mainly in LQT2), and post-menopausal period [26,27]. Genotype related degree of QT interval prolongation is proven with more severe QT interval prolongation is seen with Jervell and Lang-Nielsen [28] and Timothy Anderson syndrome (LQT8). This severe spectrum of the LQTSs carries more severe arrhythmic events occurring at younger age with poor outcome to therapy compared to other genetic subtypes of LQTSs. Statistical management with computing of the risk factors from the mega data from LQT data bases of the most common three types (LQT1, LQT2 and LQT3) with genotype-phenotype correlation indicates the most important determinants of SCD and response to therapy are: genotype, sex and duration of QTc interval [21,29]. The clinical and electrocardiographic features of those three subtypes were unveiled with more advanced genotype-phenotype studies [30-31]. LQT1 patients are well known to have cardiac events precipitated by exercise, particularly swimming or diving. The ECG appearance in LQT1 is typically showing broad based T wave. LQT2 auditory stimuli has been known to be highly specific trigger. The ECG appearance in LQT2 is typically showing T wave of low amplitude or notched [32]. The LQT3 are devastating as they occur predominantly during rest periods or sleep. The ECG appearance in LQT3 is typically showing a long isoelectric ST-segment. LQT syndromes natural

history revealed more benign course of LQT1 as well as more favorable response to beta blockers compared to LQT2 and LQT3 [21]. The severity of the biological and physical defect is expected to be affected by the type of mutation and its location inside the channel subdomain. Type and location of the mutation is also expected to affect the abundance of the respective ion channel on the sarcolemma. Consequently, those two factors will be reflected on disease severity. This genetic defect in type and location of the ion channel are supported by clinical correlates. Mutations of KCNQ1 subtype when it occurs at transmembrane regions or mutations of dominant negative effect are associated with higher risk category of cardiac events compared to C-terminal mutations and haplo insufficiency respectively [33].

In LQT2 when a point mutation in which a single nucleotide change results in a codon that codes for a different amino acid (missense mutation) if happens in the pore region of the channel, seems to be associated with higher risk of fatal arrhythmias [34]. LQT2 are of better outcome in male patients unless the missense mutation is in the pore loop regions where men will carry worse prognosis. This illustrates clearly the necessity of performing functional characterization of mutant genes (which is still research but not clinical tool) as critical component of risk stratification and management plans in clinical practice. More than one mutation in more than one LQTS genes might be inherited in the same individual. This was reported in 10%-15% of probands and may explain variation in disease severity between LQTS carriers [17].

The QT interval is longer in those individuals as well as their propensity to cardiac arrhythmias. Single-nucleotide polymorphism (SNPs) is a DNA sequence variation occurring when a single nucleotide in the genome differs between members of a species or paired chromosomes in an individual. The contribution of SNPs on QTc modulation is the target of new scientific efforts nowadays. SNPs studies when carried in large families descended from the same founder mutation is attractive research option as it eliminates the confounding effect seen in diverse families [35-37]. SNPs were shown to be a modulator of QTc by Genome Wide Studies conducted in general population [38-41]. SNPs at NOS1AP [42,43] and KCNQ1 [44] identified by GWAS have been shown to modulate the QT-interval and the risk of cardiac arrhythmia in patients with LQTS.

Brugada Syndrome genetics and clinical correlates

BrS death events are known to be at rest periods or sleep [45]. This type of channelopathies is characterized by tendency for genetic expression in male more than female and age after fourth decade of life [46]. In the Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes, BrS criteria for diagnosis consist of coved ST segment elevation ≥ 0.2 mV in one or more of the three mid precordial leads (2nd, 3rd or 4th ICS) that happen spontaneously or secondary to pharmaceutical agent administration (class 1 medications) [47]. Dynamicity of ECG findings of BrS with intermittent presentation is not infrequent finding. BrS ECG findings can be induced pharmaceutically using sodium blockers or with febrile illnesses

[47]. Historically, the SCN5A mutations encoding the α -subunit were the first to be described [48]. An overlapping phenotype of BrS and SQTs can be seen with gene mutations in the CaV1.2 L-type calcium channel subunits, CACNA1C or CACNB2 [49]. Those three mutations of BrS impair channel trafficking or alter its biophysical properties ending up with decreasing inward current. Other uncommon genes are SCN1B, SCN3B, and GPD1L which affects sodium channel and calcium channel-associated proteins [50,51]. Rarely reported gene mutations which lack cause effect relationship with BrS are outward K⁺ channels mutations (KCND3, KCNE3, and KCNJ8) as well as the pacemaker current gene HCN4 [52]. In spite of all those reports around 80% of BrS remains genetically unknown. Comprehensive analysis of 12 BrS susceptibility genes in diverse unrelated families disclose SCN5A mutations in 16. The other 11 gene mutations were associated with less than 5% of the cohort [53]. Mutations in the calcium-activated nonselective cation channel encoded by the transient receptor potential melastatin protein number 4 or TRPM4 gene was reported in $\approx 6\%$ of BrS cases [54].

Another study reported 150 typical BrS patients document SCN5A mutations in 16% of the cohort [55]. Those findings were challenged by two recent studies, authors of which could not reproduce similar findings [56,57]. Genetic testing carries paramount importance to diagnose the index case and to risk stratify relatives as well as to introduce preventive measures (avoiding certain drugs and being more aggressive with febrile illnesses management) [46,56]. Detailed genetic testing can play significant risk stratification role. It was seen that SCN5A mutation with resultant prematurely truncated protein (stop codon or frame shift), if compared to patients with missense mutations carries more likelihood for prolonged PR and QRS intervals as well as higher risk for syncopal attacks [57].

Short-QT Syndrome (SQTs) genetics and clinical correlates

QTc interval < 350 ms is accepted to establish the diagnosis of SQTs [58,59]. In 2000 when SQTs was described it was clear for medical communities that both extremes of QT, either with prolongation or shortening are arrhythmogenic. SQTs gene mutations KCNH2, KCNQ1, and KCNJ2 (all are K⁺ channels) are in common also with LQTSs [60-62]. Other gene mutations are CACNA1C and CACNB2 encoding the L-type calcium channel subunits which can cause either SQTs or overlapping phenotype with short QT interval and Brugada electrocardiographic phenotype [63]. SQTs mutations in K⁺ channels results in gain of function which will be reflected electrocardiographically as short repolarization [63-68]. On the other hand, mutations involving Ca⁺⁺ channels are causing similar shortening of AP but through loss of function mechanism. SQTs mutations biophysical effect can be looked at as the opposite of LQTSs in the same genes. Paucity of positive genetic testing in affected individuals similar to BrS, is also a feature of SQTs. Mutation search in familial disease presenting in nearly 50%, showed positive mutations in only 14% [69]. Reviewing the data of the same publication revealed high fatality of SQTs in 73 affected individuals. Unfortunately, SCD is often the first presenting symptom.

Catecholaminergic Polymorphic VT genetics and clinical correlates

CPVT is inherited group of rhythm disorder with classical polymorphic or bidirectional behavior occurring during stress either physical or emotional [70]. Electrocardiographic diagnosis is usually absent in routine ECG, as CPVT is mainly diagnosed during the arrhythmic events while doing exercise testing or recording a Holter. The hidden ECG changes of CPVT is creating major management difficulty as the disease is highly lethal with mortality rate around 30% in affected victims before the age of 40 years [71,72]. When CPVT is diagnosed, ryanodine receptor 2 (RyR2) mutations which is of autosomal dominant inheritance is the culprit in 60% of individuals [73-75]. RyR2 mutations clustered most of time around three specified positions of the RR2 protein, (Figure 6) while in $\approx 10\%$ to 15% of cases, mutations are outside those regions [76,77]. The other most common CPVT mutations are occurring in the Calsequestrin-2 (CASQ2) protein. It is inherited as autosomal recessive and known to be more severe [78]. When the inheritance of CASQ2 mutations result in homozygous or heterozygous of the compound type, the disease is more severe. On the other hand, in case of heterozygous inheritance the clinical picture will be either without symptoms or present with mild form of the disease [79-81] the sarcoplasmic reticulum (SR) Ca^{2+} channel named (RyR) are encoded in the RYR2 gene. The ryanodine receptor is a large protein (size is 560-kDa) positioned within cell membrane facing the L- Ca^{++} channel (within the T-tubules) as seen in Figure 3.

The protein that binds free Ca^{++} inside Sarcoplasmic Reticulum (SR) is encoded within CASQ2 gene. Recently it was shown that cardiac cell calsequestrin through acting as luminal sensor

of calcium acts to modulate the ryanodine receptor 2 function [82]. SR diastolic release of Ca^{++} is caused by RYR2 and CASQ2 mutations. This will result in triggered activity. In recent publication, another two Ca^{++} regulation genes were described and were implicated in CPVT development: CALM1 and TRDN [83,84]. Registry of more cases is needed to know the clinical impact of those two genes in CPVT. Mutation in ANKB (LQT4) and KCNJ2(LQT8) were seen in patients with normal QTc interval and CPVT phenotype [85,86]. In RYR2 mutations, the site of the mutation does matter. Mutation in the C terminal portion if compared to mutations with N terminal domain mutation carries higher risk of nonsustained VT [87]. Again, such important findings lack higher statistical significance in medical literature, as reporting more cases are needed. In view of the high lethality of CPVT, genetic search for mutation is a must for relatives of the index case [13].

Channelopathy genetics of other syndromes Early repolarization Syndrome (ERS)

ERS can be diagnosed with relative ease in the presence of ventricular arrhythmias and sudden death associated with early repolarization pattern in ECG. The whole mark of ECG manifestations is J point elevation with prominent T wave. The precise mechanism is unknown. Canine studies demonstrated increased trans mural gradients as possible mechanism [88]. While most cases do not prove presence of any mutation, rarely gene mutations affecting either reduction of Ca^{++} inward current, or increased K^{+} outward current have been documented [89,90]. In the presence of high frequency of the genetic bases of ESR, epigenetic and environmental factors must play an important polygenic factor in ERS and associated arrhythmias. Medical literature before 2016

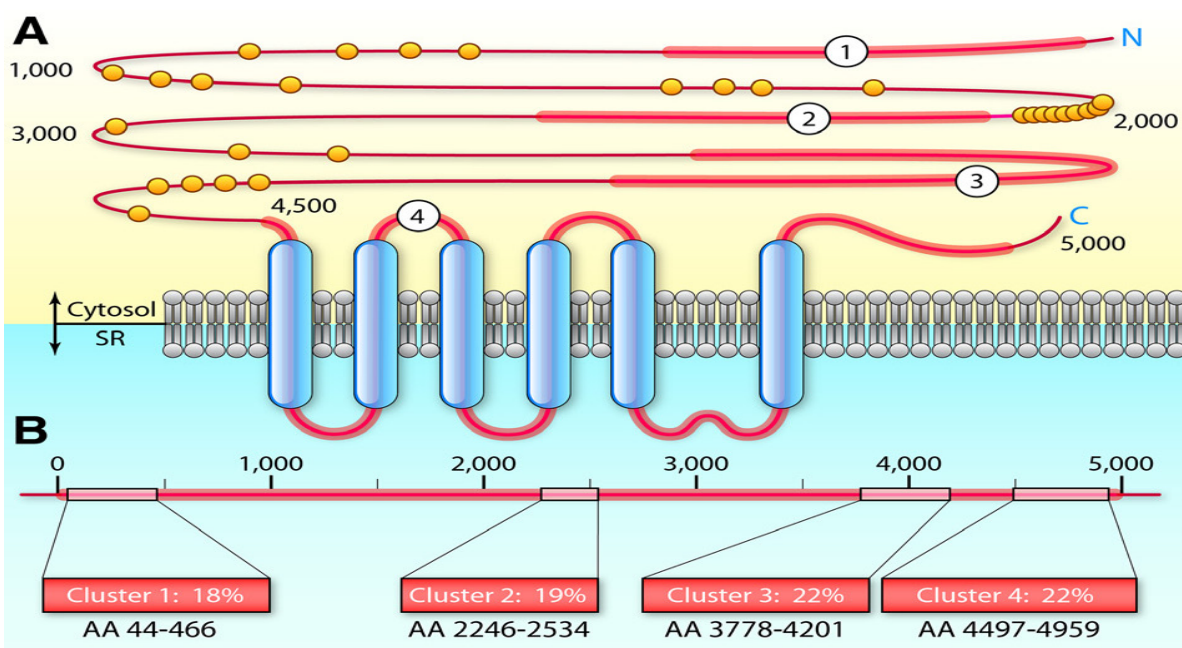


Figure 3: Ryanodine Receptor2 (RyR2) mutational clusters: A: frequent mutations clusters represented by red lines, Individual mutations outside the clusters seen in yellow. B: Clusters seen as amino acid range and percentage of published mutations. Numbers in A refer to cluster in B. (Illustration credit: Ben Smith) [1].

did not distinguish clearly between Brugada syndrome and ERS, while after 2016 they are discussed as two distinct disease entities with ECG and clinical overlapping manifestations. Significant number of proved Brugada genetic mutations individuals have been diagnosed with ERS. **Allelic heterogeneity** is prominent feature in Brugada syndrome and ER syndrome. Different mutations within each gene as well as different gene mutations can lead to the same clinical picture. Beside allelic heterogeneity, **genetic heterogeneity** is also clear where different gene mutations and variants can present simultaneously, exerting its effect on more subunit of K⁺, Ca⁺⁺ and Na⁺ structures [2]. KCNJ8 is the first gene mutation described for ERS. It encodes for Kir6.1-IkATP which is a pore forming subunit of the ATP sensitive K⁺ channel. A variant of this gene (KCNJ8-S422L) was demonstrated in a young female with ESR pattern and episodic VF [91]. Loss of function mutations in the SCN5A gene and L-type calcium channel genes were described afterward in a set of patients with idiopathic VF and ER (LTCC, CACNA1C, CACNB2, CACNA2D1) [92,93]. Another genetic variant was described in the ABCC9 gene which encode the ATP binding cassette transporter channel of the ATP sensitive K⁺ channel [94]. All those gene mutations present as ERS could work through disturbing the balance of the inward outward currents leading to acceleration process of epicardial repolarization and VF.

Progressive cardiac conduction disease (PCCD)

PCCD is a progressive pathological deterioration of the cardiac conduction system that usually present with bradycardia but may present as SCD. SCN5A was the first gene associated with PCCD.

As a matter of fact, some SCN5A mutations might represent more complex phenotypes referred to as "Overlap Syndromes" compromising PCCD with BrS and LQT3 [95]. Altered expression of genes responsible of impulse transmission including Ca⁺⁺ channels and cytoskeletal components might present as PCCD. The resulting phenotype might be a complex process of environmental factors in genetically predisposed affected individuals in addition to degenerative process of ageing [1].

Inherited Sinus Node Dysfunction

Sinus node is the true pace maker of the human heart. Sophisticated ion channels interplay will result in sinus node AP. Most of times sinus node dysfunction is acquired degenerative process but could be genetically inherited. The predominant ion channel currents affected are hyperpolarization-activated, cyclic nucleotide-gated (HCN 4) channels, L- type Ca, T- type Ca, delayed rectifier K, and acetylcholine (ACh)-activated channels. [185] loss of function mutations of the SCN5A gene may lead to bradycardia due to defective formation of the action potential upstroke in the periphery of the SA node but not in the center of the SA node.

Idiopathic Ventricular Fibrillation (IVF)

Patients with IVF present with a sudden onset of ventricular fibrillation (VF) of unknown origin that is not identified even after extensive diagnostic testing. Most primary arrhythmia disorders

were regarded as IVF before they were discovered. For example, BrS was described as IVF in Nature article in 1998 [96]. For this reason Idiopathic ventricular fibrillation (IVF) is a rare cause of SCD now a days. In the era of explosive genetic discoveries and system wide biology approach for diseases evaluation, the diagnosis of IVF should be a diagnosis of exclusion of other SCD diseases including structural cardiac disease (ie, myocarditis, cardiac sarcoidosis, arrhythmogenic right ventricular dysplasia, hypertrophic, and dilated cardiomyopathy) and primary arrhythmia syndromes (ie, LQTS, BrS, CPVT, short-QT syndrome, and ERS). In addition, exclusion of respiratory, metabolic, and toxicological causes is a must. Studies in which careful phenotypic and genetic analysis had been performed showed that these primary arrhythmia syndromes are actually separate disease entities, with a separate pathophysiology [97,98]. The differentiation between IVF and other primary arrhythmic syndromes has been facilitated by the advance in genetic testing, for example in CPVT and LQTS patients where the yield of genetic testing is 60% and 75%, respectively [99]. In addition, genetic testing has facilitated the detection of causative mutations for IVF, such as the Dutch DPP6-haplotype and CALM1 [100,101].

Future speculations towards revolutionary solutions in genetics of channelopathies

Future speculations in the genetic arena

Tremendous progress has been made in the discovery of putative mutations and genes responsible for different channelopathies [102]. In the way of advances to scrutinize the pathogenic mutations comes the growing number of variants of unknown significance (VUS). It is an allele, or variant form of a gene, that has been identified through genetic testing but whose significance to the function or health of an organism is not identified. Researchers continue to work on better understanding how to stratify the risk of life-threatening arrhythmia based on the genotype and phenotype of the individual. Recently discovered channelopathies like SQTS are not exemption from the role with relative paucity of positive mutations, which renders proper treatment plans not conclusive. The selective effect of certain pharmaceutical agents in specific genetic subgroups should acts as decoder for the mystery of channelopathies. For example patients with SQTS and HERG mutation had shorter QTc at baseline and a greater QTc prolongation after treatment with hydroquinidine (HQ) [103]. The delta T50 is a measure of the variability of ventricular repolarization (at 50% of the T-wave downslope). It has been used to identify patients with LQTS in combination with QT interval cutoffs, as well as to identify patients at higher risk for cardiac events [104]. Rest and exercise QT interval measurements have been used to create a validated algorithm for diagnosing LQTS [105]. End-recovery QT interval measurements have also been used and, in combination with clinical history and mutation-specific information, can aid in understanding the pathogenicity of VUS [106]. Copy number variations (CNV) defined as DNA segment of one kilobase (kb) or larger that is present at a variable copy number in comparison with a reference genome, are a form of genetic abnormality that may explain the genetic basis of channelopathies in cases where there is

no identifiable point mutation [107]. Some CNVs have no apparent influence on phenotype, while as many as 40 others have been definitively linked with disease. It is conceivable that in the future CNV may be added to genetic screens. Despite our increasingly sophisticated knowledge of the underlying pathophysiology, novel medical therapies tailored specifically for these syndromes have yet emerged in the clinical setting. Novel forms of treatment that specifically address the aberrant molecular pathophysiology defining these conditions will be our immediate priority step in order to effectively suppress arrhythmic events and to ultimately obviate the need for ICD implants.

Decoding the channelopathies' mysteries using induced pluripotent stem cell-derived cardiomyocyte research

The available platforms, shaping the future, to develop and investigate pharmaceutical therapeutic mechanisms for successful channelopathies treatment can be classified into different levels. First is at the organism level including clinical as well as animal models. Second is at the tissue and organ level (Purkinje fibers). Third is at cellular and molecular level (cardiac ions, induced pluripotent stem cells) [108]. Since the first report in 2006, bench researchers have made use of "induced pluripotent stem cell" (iPS) systems to study the electrophysiological and pharmacological characteristics of cardiomyocyte cells that are specific to an individual patient and his/her mutation and channelopathy. This

technology has huge potential to promote our understanding of individual channelopathies and further steer the management of channelopathies in an individualistic, genotype-specific manner in the future [109,110]. It provides a robust platform to advance the science and clinical care of sudden cardiac death. Major ion channels of the human heart are expressed in the human induced pluripotent stem cell-derived cardiomyocyte (iPSC-CM). The iPSC-CMs are created by somatic cells reprogramming into pluripotent stem cells using viral transduction or non-viral transfection or soluble proteins to introduce transcriptional factors to the somatic cell [111]. The resulting induced pluripotent stem cell can be differentiated specifically to induced pluripotent stem cell-derived cardiomyocyte (iPSC-CM) [112]. The iPSC-CMs can express encoded genes of the heart that might be absent in the original donor somatic cell. An ion channel disease can be expressed and recapitulated electro physiologically so clinical diagnosis can be identified as well as genetic screening in the family. Variant of uncertain significance (VUS) can be developed where electrophysiological testing can be examined in the produced iPSC-CMs. Then comparison to the index case can be done. As the case in genetic testing, iPSC-CM may miss identifying the arrhythmia. In this situation, we will rely on clinical evaluation and family screening. Induced pluripotent stem of human cardiomyocyte (iPSC-CM) is superior to animal models or heterologous transfection models for channelopathies research (Figure 4) [113]. Its capabilities to create specific

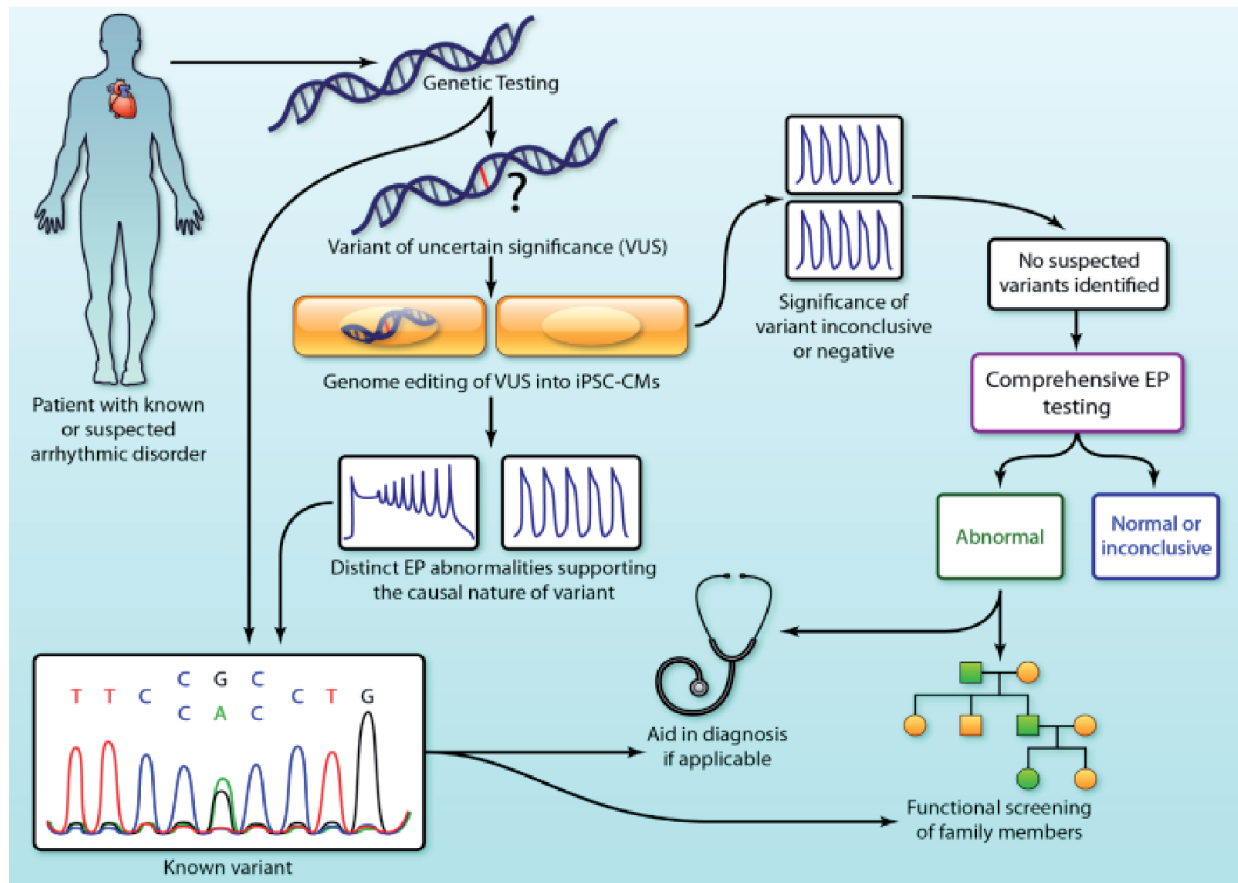


Figure 4: Potential role for iPSC-CMs in the evaluation of patients with known or at risk for arrhythmic disorders. Clinical genetic testing attempts to identify a rare variant in genes commonly associated with arrhythmic disorders. (Illustration credit: Ben smith) [113].

therapeutic options and its abilities to define disease-specific drug toxicity are unique.

This level of research in conjunction with proper understanding of the basic electrophysiology of channelopathies [114] is expected to illuminate our understanding of the true pathophysiology of channelopathies and their targeted therapies in the near future.

Summary

Genetic heterogeneity and allelic heterogeneity are two prominent features of channelopathies. In LQT1 the underlying genetic mutation is in *KCNQ1* gene giving rise to loss of function of the slowly activating delayed rectifier current (IKs). In LQT2 the underlying genetic mutation is loss-of-function mutations in *KCNH2* (also known as *HERG*). The rapidly activated delayed rectifier current (IKr) is encoded in this protein. LQT3 is due to gain of function mutation in *SCN5A*. This will lead to increase of the late sodium current (INa). All LQTSs are confined to the heart except three important clinical syndromes: Jervell Lange-Nielsen syndrome, Anderson-Tawil syndrome (LQT7) and Timothy syndrome (LQT8). The most important risk stratifiers to predict cardiac events in LQTS patients are: aborted SCD, torsade's de pointes, or previous syncopal attack, QTc more than 500ms in addition to age. Genotype related degree of QT interval prolongation is proven with more severe QT interval prolongation is seen with Jervell and Lange-Nielsen and Timothy Anderson syndrome (LQT8). This severe spectrum of the LQTSs carries potential for more severe arrhythmic events occurring at younger age with poor outcome to therapy compared to other genetic subtypes of LQTSs. Genotype-phenotype correlation indicates the most important determinants of SCD and response to therapy are: genotype, sex and duration of QTc interval. LQT1 patients are well known to have cardiac events precipitated by exercise, particularly swimming or diving. The ECG appearance in LQT1 is typically showing broad based T wave. In LQT2 patients, auditory stimuli have been known to be highly specific trigger. The ECG appearance in LQT2 is typically showing T wave of low amplitude or notched. The LQT3 patient's natural history is devastating as they occur predominantly during rest periods or sleep. The ECG appearance in LQT3 is typically showing a long isoelectric ST-segment. LQT syndromes natural history revealed more benign course of LQT1 as well as more favorable response to beta blockers compared to LQT2 and LQT3. In addition, the type of mutation and its location inside the channel subdomain is affecting disease severity. Functional characterization of mutant gene must be part of mutation risk stratification plans in the near future. Variability in severity of LQTSs can be also explained by multiple mutations occurring in the same person (seen in 10-15% of cases). In spite of *SCN5A* mutations encoding the α -subunit is famous for Brugada syndrome (BrS), 80% of BrS lack proven mutation. Paucity of positive genetic mutations is also a feature of Short QT syndrome (SQTS). If positive, its mutations biophysical effect can be looked at as the opposite of LQTSs in the same genes. In CPVT, the protein *RYR2* mutations occurs in 60% of affected population. The second most common genetic mutations occur in *CASQ2* protein and tends to be more severe. Most cases of ERS do not prove presence of any mutation.

The first gene mutation of Progressive cardiac conduction disease PCCD described was *SCN5A*. This mutation can be associated with complex phenotype of PCCD, Brs, and LQT3, sometimes referred as (overlap syndrome). The list of idiopathic VF is getting shorter with more progressive discoveries of new disease entities. Tremendous progress has been made in the discovery of putative mutations and genes responsible for different channelopathies including incorporation of new techniques and measurements. This includes variants of unknown significance (VUS), The delta T50 measurement, rest and exercise QT interval measurements, end-recovery QT interval measurements, and Copy number variations (CNV). The platforms, shaping the future, to develop and investigate pharmaceutical therapeutic mechanisms for successful channelopathies treatment at the three levels: organism, tissue and cellular levels are promising. In specific, induced pluripotent stem cell" (iPS) systems to study the electrophysiological and pharmacological characteristics of channelopathy are promising. This technology has huge potential to promote our understanding of individual channelopathies and further steer the management of channelopathies in an individualistic, genotype-specific manner for better future of humans.

References

1. Bezzina CR, Lahrouchi N, Priori SG. Genetics of Sudden Cardiac Death. *Circulation Research*. 2015; 116: 1919-1936.
2. Vincent GM. The long QT syndrome. *Indian Pacing Electrophysiology Journal*. 2002; 2: 127-142.
3. Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval, and sudden death. *American Heart Journal*. 1957; 54: 59-68.
4. Romano C, Gemme G, Pongiglione R. Rare Cardiac Arrhythmias of the Pediatric Age. II. Syncopal Attacks due to Paroxysmal Ventricular Fibrillation. (Presentation of 1st Case in Italian Pediatric Literature). *La Clinica Pediatrica (Bologna)*. 1963; 45: 656-683.
5. Ward OC. A New Familial Cardiac Syndrome in Children. *Journal of the Irish Medical Association*. 1964; 54: 103-106.
6. Wang Q, Shen J, Splawski I, et al. *SCN5A* mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell*. 1995; 80: 805-811.
7. Wang Q, Curran M, Splawski I, et al. Positional cloning of a novel potassium channel gene: *KVLQT1* mutations cause cardiac arrhythmias. *Nature Genetics*. 1996; 12: 17-23.
8. Curran ME, Splawski I, Timothy KW, et al. A molecular basis for cardiac arrhythmia: *HERG* mutations cause long QT syndrome. *Cell*. 1995; 80: 795-803.
9. Curran ME, Splawski I, Timothy KW, et al. A molecular basis for cardiac arrhythmia: *HERG* mutations cause long QT syndrome. *Cell*. 1995; 80: 795-803.
10. Wang Q, Shen J, Li Z, et al. Cardiac sodium channel mutations in patients with long QT syndrome, an inherited cardiac arrhythmia. *Human Molecular Genetics*. 1995; 4: 1603-1607.
11. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA Expert

- Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies: This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace*. 2011; 13: 1077-1079.
12. Hedley PL, Jørgensen P, Schlamowitz S, et al. The genetic basis of long QT and short QT syndromes: A mutation update. *Human Mutation*. 2009; 30: 1486-1511.
 13. Neyroud N, Tesson F, Denjoy I, et al. A novel mutation in the potassium channel gene KVLQT1 causes the Jervell and Lange-Nielsen cardio auditory syndrome. *Nature Genetics*. 1997; 15: 186-189.
 14. Schulze-Bahr E, Wang Q, Wede kind H, et al. KCNE1 mutations cause Jervell and Lange-Nielsen syndrome. *Nature Genetics*. 1997; 17: 267-268.
 15. Westenskow P, Splawski I, Timothy KW, et al. Compound Mutations. *Circulation*. 2004; 109: 1834-1841.
 16. Priori SG, Schwartz PJ, Napolitano C, et al. A Recessive Variant of the Romano-Ward Long-QT Syndrome? *Circulation*. 1998; 97: 2420-2425.
 17. Plaster NM, Tawil R, Tristani-Firouzi M, et al. Mutations in Kir2.1 Cause the Developmental and Episodic Electrical Phenotypes of Andersens Syndrome. *Cell*. 2001; 105: 511-519.
 18. Splawski I, Timothy KW, Sharpe LM, et al. CaV1.2 Calcium Channel Dysfunction Causes a Multisystem Disorder Including Arrhythmia and Autism. *Cell*. 2004; 119: 19-31.
 19. Priori SG, Schwartz PJ, Napolitano C, et al. Risk Stratification in the Long-QT Syndrome. *New England Journal of Medicine*. 2003; 348: 1866-1874.
 20. Goldenberg I, Horr S, Moss AJ, et al. Risk for Life-Threatening Cardiac Events in Patients with Genotype-Confirmed Long-QT Syndrome and Normal-Range Corrected QT Intervals. *Journal of the American College of Cardiology*. 2011; 57: 51-59.
 21. Kimbrough J, Moss AJ, Zareba W, et al. Clinical Implications for Affected Parents and Siblings of Proband with Long-QT Syndrome. *Circulation*. 2001; 104: 557-562.
 22. Hobbs JB, Peterson DR, Moss AJ, et al. Risk of Aborted Cardiac Arrest or Sudden Cardiac Death During Adolescence in the Long-QT Syndrome. *Jama*. 2006; 296: 1249.
 23. Sauer AJ, Moss AJ, McNitt S, et al. Long QT syndrome in adults. *Journal of the American College of Cardiology*. 2007; 49: 329-337.
 24. Seth R, Moss AJ, McNitt S, et al. Long QT syndrome and pregnancy. *Journal of the American College of Cardiology*. 2007; 49: 1092-1098.
 25. Buber J, Mathew J, Moss AJ, et al. Risk of Recurrent Cardiac Events After Onset of Menopause in Women with Congenital Long-QT Syndrome Types 1 and 2. *Circulation*. 2011; 123: 2784-2791.
 26. Schwartz PJ, Spazzolini C, Crotti L, et al. The Jervell and Lange-Nielsen Syndrome. *Circulation*. 2006; 113: 783-790.
 27. Priori SG. Association of Long QT Syndrome Loci and Cardiac Events Among Patients Treated with β -Blockers. *Jama*. 2004; 292: 1341.
 28. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-Phenotype Correlation in the Long-QT Syndrome. *Circulation*. 2001; 103: 89-95.
 29. Zhang L, Timothy KW, Vincent GM, et al. Spectrum of ST-T-Wave Patterns and Repolarization Parameters in Congenital Long-QT Syndrome. *Circulation*. 2000; 102: 2849-2855.
 30. Wilde AA, Jongbloed RJ, Doevendans PA, et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). *Journal of the American College of Cardiology*. 1999; 33: 327-332.
 31. Moss AJ, Shimizu W, Wilde AA, et al. Clinical Aspects of Type-1 Long-QT Syndrome by Location, Coding Type, and Biophysical Function of Mutations Involving the KCNQ1 Gene. *Circulation*. 2007; 115: 2481-2489.
 32. Shimizu W, Moss AJ, Wilde AA, et al. Genotype-phenotype aspects of type 2 long QT syndrome. *Journal of the American College of Cardiology*. 2009; 54: 2052-2062.
 33. Priori SG, Napolitano C, Schwartz PJ. Low Penetrance in the Long-QT Syndrome. *Circulation*. 1999; 99: 529-533.
 34. Lahtinen AM, Marjamaa A, Swan H, et al. KCNE1D85N polymorphism - a sex-specific modifier in type 1 long QT syndrome? *BMC Medical Genetics*. 2011; 12.
 35. Amin AS, Giudicessi JR, Tijssen AJ, et al. Variants in the 3' untranslated region of the KCNQ1-encoded Kv7.1 potassium channel modify disease severity in patients with type 1 long QT syndrome in an allele-specific manner. *European Heart Journal*. 2011; 33: 714-723.
 36. Villiers CPD, Merwe LVD, Crotti L, et al. AKAP9 Is a Genetic Modifier of Congenital Long-QT Syndrome Type 1. *Circulation: Cardiovascular Genetics*. 2014; 7: 599-606.
 37. Arking DE, Pulit SL, Crotti L, et al. CARE Consortium; COGENT Consortium; DCCT/EDIC; eMERGE Consortium; HRGEN Consortium. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. *Nature genetics*. 2014; 46: 826-836.
 38. Arking DE, Pfeufer A, Post W, et al. A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. *Nature Genetics*. 2006; 38: 644-651.
 39. Pfeufer A, Sanna S, Arking DE, et al. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nature Genetics*. 2009; 41: 407-414.
 40. Newton-Cheh C, Eijgelsheim M, Rice KM, et al. Common variants at ten loci influence QT interval duration in the QTGEN Study. *Nature Genetics*. 2009; 41: 399-406.
 41. Crotti L, Monti MC, Insolia R, et al. NOS1AP Is a Genetic Modifier of the Long-QT Syndrome. *Circulation*. 2009; 120: 1657-1663.

42. Tomás M, Napolitano C, Giuli LD, et al. Polymorphisms in the NOS1AP Gene Modulate QT Interval Duration and Risk of Arrhythmias in the Long QT Syndrome. *Journal of the American College of Cardiology*. 2010; 55: 2745-2752.
43. Duchatelet S, Crotti L, Peat RA, et al. Identification of a KCNQ1 Polymorphism Acting as a Protective Modifier Against Arrhythmic Risk in Long-QT Syndrome. *Circulation: Cardiovascular Genetics*. 2013; 6: 354-361.
44. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes. *Heart Rhythm*. 2013; 10: 1932-1963.
45. Antzelevich C, Brugada P, Borggrefe M. Brugada Syndrome. Report of the Second Consensus Conference. *ACC Current Journal Review*. 2005; 14: 31.
46. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature*. 1998; 392: 293-296.
47. Antzelevitch C, Pollevick GD, Cordeiro JM, et al. Loss-of-Function Mutations in the Cardiac Calcium Channel Underlie a New Clinical Entity Characterized by ST-Segment Elevation, Short QT Intervals, and Sudden Cardiac Death. *Circulation*. 2007; 115: 442-449.
48. Watanabe H, Koopmann TT, Scouarnec SL, et al. Sodium channel β 1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. *Journal of Clinical Investigation*. 2008; 118: 2260-2268.
49. Norstrand DWV, Valdivia CR, Tester DJ, et al. Molecular and Functional Characterization of Novel Glycerol-3-Phosphate Dehydrogenase 1-Like Gene (GPD1-L) Mutations in Sudden Infant Death Syndrome. *Circulation*. 2007; 116: 2253-2259.
50. Wilde AAM, Behr ER. Genetic testing for inherited cardiac disease. *Nature Reviews Cardiology*. 2013; 10: 571-583.
51. Crotti L, Marcou CA, Tester DJ, et al. Spectrum and Prevalence of Mutations Involving BrS1- Through BrS12-Susceptibility Genes in a Cohort of Unrelated Patients Referred for Brugada Syndrome Genetic Testing. *Journal of the American College of Cardiology*. 2012; 60: 1410-1418.
52. Behr ER, Savio-Galimberti E, Barc J, et al. Role of common and rare variants in SCN10A: results from the Brugada syndrome QRS locus gene discovery collaborative study. *Cardiovascular Research*. 2015; 106: 520-529.
53. Bhuiyan ZA, Berg MPVD, Tintelen JPV, et al. Expanding Spectrum of Human RYR2 -Related Disease. *Circulation*. 2007; 116: 1569-1576.
54. Tang Y, Tian X, Wang R, et al. Abnormal Termination of Ca²⁺ Release Is a Common Defect of RyR2 Mutations Associated with Cardiomyopathies. *Circulation Research*. 2012; 110: 968-977.
55. Scouarnec SL, Karakachoff M, Gourraud JB, et al. Testing the burden of rare variation in arrhythmia-susceptibility genes provides new insights into molecular diagnosis for Brugada syndrome. *Human Molecular Genetics*. 2015; 24: 2757-2763.
56. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies: This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace*. 2011; 13: 1077-1079.
57. Meregalli PG, Tan HL, Probst V, et al. Type of SCN5A mutation determines clinical severity and degree of conduction slowing in loss-of-function sodium channelopathies. *Heart Rhythm*. 2009; 6: 341-348.
58. Gussak I, Brugada P, Brugada J, et al. Idiopathic Short QT Interval: A New Clinical Syndrome? *Cardiology*. 2000; 94: 99-102.
59. Yan GX, Antzelevitch C. Cellular Basis for the Brugada Syndrome and Other Mechanisms of Arrhythmogenesis Associated with ST-Segment Elevation. *Circulation*. 1999; 100: 1660-1666.
60. Gaita F, Giustetto C, Bianchi F, et al. Short QT Syndrome. *Circulation*. 2003; 108: 965-970.
61. Brugada R, Hong K, Dumaine R, et al. Sudden Death Associated with Short-QT Syndrome Linked to Mutations in HERG. *Circulation*. 2004; 109: 30-35.
62. Shimizu W, Aiba T, Kurita T, et al. Paradoxical Abbreviation of Repolarization in Epicardium of the Right Ventricular Outflow Tract During Augmentation of Brugada-Type ST Segment Elevation. *Journal of Cardiovascular Electrophysiology*. 2001; 12: 1418-1421.
63. Bellocq Chloé, Ginneken ACV, Bezzina CR, et al. Mutation in the KCNQ1 Gene Leading to the Short QT-Interval Syndrome. *Circulation*. 2004; 109: 2394-2397.
64. Deo M, Ruan Y, Pandit SV, et al. KCNJ2 mutation in short QT syndrome 3 results in atrial fibrillation and ventricular proarrhythmic. *Proceedings of the National Academy of Sciences*. 2013; 110: 4291-4296.
65. Cordeiro J, Brugada R, Wu Y, et al. Modulation of inactivation by mutation N588K in KCNH2: A link to arrhythmogenesis in short QT syndrome. *Cardiovascular Research*. 2005; 67: 498-509.
66. Mazzanti A, Kanthan A, Monteforte N, et al. Novel Insight into the Natural History of Short QT Syndrome. *Journal of the American College of Cardiology*. 2014; 63: 1300-1308.
67. Leenhardt A, Lucet V, Denjoy I, et al. Catecholaminergic Polymorphic Ventricular Tachycardia in Children. *Circulation*. 1995; 91: 1512-1519.
68. Martin CA, Matthews GDK, Huang CLH. Sudden cardiac death and inherited channelopathy: the basic electrophysiology of the myocyte and myocardium in ion channel disease. *Heart*. 2012; 98: 536-543.
69. Priori SG, Napolitano C, Memmi M, et al. Clinical and Molecular Characterization of Patients with Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation*. 2002; 106: 69-74.
70. January CT, Riddle JM, Salata JJ. A model for early afterdepolarizations: induction with the Ca²⁺ channel agonist Bay K 8644. *Circulation Research*. 1988; 62: 563-571.
71. Jiang D, Wang R, Xiao B, et al. Enhanced Store Overload-

- Induced Ca²⁺ Release and Channel Sensitivity to Luminal Ca²⁺ Activation Are Common Defects of RyR2 Mutations Linked to Ventricular Tachycardia and Sudden Death. *Circulation Research*. 2005; 97: 1173-1181.
72. Hayashi M, Denjoy I, Extramiana F, et al. Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation*. 2009; 119: 2426-2434.
 73. Priori S, Napolitano C, Tiso N. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *ACC Current Journal Review*. 2001; 10: 69.
 74. Laitinen P, Brown K, Piippo K. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. *ACC Current Journal Review*. 2001; 10: 69.
 75. Medeiros-Domingo A, Bhuiyan ZA, Tester DJ, et al. The RYR2-Encoded Ryanodine Receptor/Calcium Release Channel in Patients Diagnosed Previously with Either Catecholaminergic Polymorphic Ventricular Tachycardia or Genotype Negative, Exercise-Induced Long QT Syndrome. *Journal of the American College of Cardiology*. 2009; 54: 2065-2074.
 76. Priori SG, Chen SW. Inherited Dysfunction of Sarcoplasmic Reticulum Ca²⁺ Handling and Arrhythmogenesis. *Circulation Research*. 2011; 108: 871-883.
 77. Lahat H, Pras E, Olender T, et al. A Missense Mutation in a Highly Conserved Region of CASQ2 Is Associated with Autosomal Recessive Catecholamine-Induced Polymorphic Ventricular Tachycardia in Bedouin Families from Israel. *The American Journal of Human Genetics*. 2001; 69: 1378-1384.
 78. Barletta MRD, Viatchenko-Karpinski S, Nori A, et al. Clinical Phenotype and Functional Characterization of CASQ2 Mutations Associated with Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation*. 2006; 114: 1012-1019.
 79. Postma AV, Denjoy I, Hoorntje TM, et al. Absence of Calsequestrin 2 Causes Severe Forms of Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation Research*. 2002; 91: e21-e26.
 80. Sam de la Fuente, Irene M Van Langen, Alex V Postma, et al. A case of catecholaminergic polymorphic ventricular tachycardia caused by two calsequestrin 2 mutations. *Pacing Clin Electrophysiol*. 2008; 31: 916-919.
 81. Nyegaard M, Overgaard MT, Søndergaard MT, et al. Mutations in Calmodulin Cause Ventricular Tachycardia and Sudden Cardiac Death. *The American Journal of Human Genetics*. 2012; 91: 703-712.
 82. Roux-Buisson N, Cacheux M, Fourest-Lieuvain A, et al. Absence of triadin, a protein of the calcium release complex, is responsible for cardiac arrhythmia with sudden death in human. *Human Molecular Genetics*. 2012; 21: 2759-2767.
 83. Tester DJ, Arya P, Will M, et al. Genotypic heterogeneity and phenotypic mimicry among unrelated patients referred for catecholaminergic polymorphic ventricular tachycardia genetic testing. *Heart Rhythm*. 2006; 3: 800-805.
 84. Mohler PJ, Splawski I, Napolitano C, et al. A cardiac arrhythmia syndrome caused by loss of ankyrin-B function. *Proceedings of the National Academy of Sciences*. 2004; 101: 9137-9142.
 85. Werf CVD, Nederend I, Hofman N, et al. Familial Evaluation in Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation: Arrhythmia and Electrophysiology*. 2012; 5: 748-756.
 86. Yan GX, Antzelevitch C. Cellular Basis for the Electrocardiographic J Wave. *Circulation*. 1996; 93: 372-379.
 87. Burashnikov E, Pfeiffer R, Barajas-Martinez H, et al. Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death. *Heart Rhythm*. 2010; 7: 1872-1882.
 88. Haïssaguerre M, Chatel S, Sacher F, et al. Ventricular Fibrillation with Prominent Early Repolarization Associated with a Rare Variant of KCNJ8/KATPChannel. *Journal of Cardiovascular Electrophysiology*. 2009; 20: 93-98.
 89. Watanabe H, Nogami A, Ohkubo K, et al. Response to Letter Regarding Article, "Electrocardiographic Characteristics and SCN5A Mutations in Idiopathic Ventricular Fibrillation Associated with Early Repolarization." *Circulation: Arrhythmia and Electrophysiology*. 2012; 5: 60-61.
 90. Burashnikov E, Pfeiffer R, Barajas-Martinez H, et al. Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death. *Heart Rhythm*. 2010; 7: 1872-1882.
 91. Hu D, Barajas-Martínez H, Terzić A, et al. ABCC9 is a novel Brugada and early repolarization syndrome susceptibility gene. *International Journal of Cardiology*. 2014; 171: 431-442.
 92. Milanese R, Bucchi A, Baruscotti M. The genetic basis for inherited forms of sinoatrial dysfunction and atrioventricular node dysfunction. *Journal of Interventional Cardiac Electrophysiology*. 2015; 43: 121-134.
 93. Grant AO, Carboni MP, Neplioueva V, et al. Long QT syndrome, Brugada syndrome, and conduction system disease are linked to a single sodium channel mutation. *Journal of Clinical Investigation*. 2002; 110: 1201-1209.
 94. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature*. 1998; 392: 293-296.
 95. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. *Journal of the American College of Cardiology*. 1992; 20: 1391-1396.
 96. Priori SG, Napolitano C, Memmi M, et al. Clinical and Molecular Characterization of Patients with Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation*. 2002; 106: 69-74.

97. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies: This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Euro pace*. 2011; 13: 1077-1097.
98. Alders M, Koopmann TT, Christiaans I, et al. Haplotype-Sharing Analysis Implicates Chromosome 7q36 Harboring DPP6 in Familial Idiopathic Ventricular Fibrillation. *The American Journal of Human Genetics*. 2009; 84: 468-476.
99. Marsman RF, Barc J, Beekman L, et al. A Mutation in CALM1 Encoding Calmodulin in Familial Idiopathic Ventricular Fibrillation in Childhood and Adolescence. *Journal of the American College of Cardiology*. 2014; 63: 259-266.
100. Chockalingam P, Rammeloo LA, Postema PG, et al. Fever-Induced Life-Threatening Arrhythmias in Children Harboring an SCN5A Mutation. *Pediatrics*. 2011; 127: e239-e244.
101. Schwartz PJ, Moss AJ, Vincent GM, et al. Diagnostic criteria for the long QT syndrome. An update. *Circulation*. 1993; 88: 782-784.
102. <https://www.intechopen.com/online-first/inherited-ventricular-arrhythmias-the-channelopathies-and-scd-current-knowledge-and-future-speculation>.
103. Giustetto C, Schimpf R, Mazzanti A, et al. Long-term follow-up of patients with short QT syndrome. *Journal of the American College of Cardiology*. 2011; 58: 587-595.
104. Chockalingam P, Wilde A. The multifaceted cardiac sodium channel and its clinical implications. *Heart*. 2012; 98: 1318-1324.
105. Amin AS, Asghari-Roodsari A, Tan HL. Cardiac sodium channelopathies. *Pflügers Archiv - European Journal of Physiology*. 2010; 460: 223-237.
106. Obeyesekere MN, Sy RW, Klein GJ, et al. End-recovery QTc: A useful metric for assessing genetic variants of unknown significance in long-QT syndrome. *Journal of Cardiovascular Electrophysiology*. 2012; 23: 637-642.
107. Barc J, Briec F, Schmitt S, et al. Screening for copy number variation in genes associated with the long QT syndrome. *Journal of the American College of Cardiology*. 2011; 57: 40-47.
108. Sallam K, Li Y, Sager PT, et al. Finding the rhythm of sudden cardiac death. *Circulation research*. 2015; 116: 1989-2004.
109. Noseworthy P, Porthan K, Tikkanen J, et al. The early repolarization pattern: Clinical correlates and heritability. *Journal of the American College of Cardiology*. 2011; 57: 2284-2289.
110. Tikkanen JT, Anttonen O, Junttila MJ, et al. Long-term outcome associated with early repolarization on electrocardiography. *New England Journal of Medicine*. 2009; 361: 2529-2537.
111. Kui C, Congxin H, Xi W, et al. Characteristic of the prevalence of J wave in apparently healthy Chinese adults. *Archives of Medical Research*. 2008; 39: 232-235.
112. Rice KS, Dickson G, Lane M, et al. Elevated serum gastrin levels in Jervell and Lange-Nielsen syndrome: A marker of severe KCNQ1 dysfunction? *Heart Rhythm*. 2011; 8: 551-554.
113. Terrenoire C, Wang K, Tung KWC, et al. Induced pluripotent stem cells used to reveal drug actions in a long QT syndrome family with complex genetics. *J Gen Physiol*. 2013; 141: 61-72.
114. Abdullah Abdulrhman Al Abdulgader. Inherited Ventricular Arrhythmias, the Channelopathies and SCD; Current Knowledge and Future Speculation – Epidemiology and Basic Electrophysiology. *Intech Open*. 2020.