Clinical and genetic spectrum of hereditary cardiac arrhythmia syndromes

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General Introduction

Title: Familial Primary Arrhythmias: Genes, Mechanisms and Treatment: Present Perspective (Authors: Z. A. Bhuiyan and A. A. M. Wilde)
The Heart is a specialised organ that contracts synchronously, pumping blood to the body and to the lungs. The upper two chambers of the heart are called atria (right and left), the bottom two chambers are called ventricles (right and left). Right atrium receives deoxygenated blood from all parts of the body except for the lungs and transports them to right ventricle. The left atrium receives oxygenated blood from the lungs and transports them to the left ventricle and then to rest of the body. Cardiac excitation originates in the sinoatrial (SA) node and propagates through the atria into the atrial-ventricular (AV) node. The impulse then propagates through the Purkinje conduction system to the ventricles which then contract. The synchronized pumping action of the heart is caused by a flow of electricity through the heart that repeats itself in a cycle.

**Heart muscle, Gap junction, Desmosome and Ion channel**

Three layers of tissues, epicardium, myocardium and the endocardium forms the outer to inner layers of the heart. Cardiac myocytes are the major functioning cells in the heart and are extensively coupled so that impulses propagate rapidly and uniformly. Individual cardiomyocytes are separated from each other by a specialised boundary called the intercalated disc (ICD), where gap junction proteins, desmosomes, macula adherens and ion channels are located.\(^1\) Gap junctions consist of tightly packed connexins which permits intercellular exchange of small molecules and excitatory current flow between neighbouring cells. Desmosomes alongwith adherens junctions are responsible for the mechanical attachments of individual cardiomyocytes. All these components of the intercalated disc are topologically segregated and serve distinct functions, disruption of one affects the function of others, predisposing the heart to arrhythmias.\(^1,3\)

**Cardiac Action Potential**

The cardiac action potential (AP) is generated by orchestrated interactions between various ion channels (Figure 1). The standard model used to describe the cardiac action potential is the action potential of the ventricular myocyte. This action potential has 5 phases (numbered 0-4).

Phase 4 (Figure 1) is the resting membrane potential, and during this phase the cell is not being stimulated. Phase 4 corresponds with the diastole during which the heart is both electrically and mechanically quiescent and atria and ventricles are filled with blood. In this phase, atrial and ventricular myocytes have a stable, negative resting membrane potential of about -85 mV.

Phase 0 (Figure 1) is the rapid depolarization phase, dominated by the sodium channel, which generates a large and fast inward current, \(I_{Na}\), to depolarize the membrane. Upon activation,
channels enter into an inactivated stage which is non-conducting and refractory. The ability of the cell to open the fast Na⁺ channels during phase 0 is related to the membrane potential at the moment of excitation. If the membrane potential is at its baseline (about -85 mV), all the fast Na⁺ channels are closed, and excitation will open them all, causing a large influx of Na⁺ ions into the cell. If, however, the membrane potential is less negative, the cell may not be excitable, and conduction through the heart may be hampered, increasing the risk for arrhythmias. Phase 0 of the cardiac action potential is the trigger for the initiation of the contraction of the atria and ventricles.³

Phase 1 (Figure 1) is the early repolarization phase. Repolarization results from the rapid activation and inactivation of the outward, repolarizing, transient K⁺ current Ito against the background of a decrease in sodium channel permeability and an increase in calcium channel permeability.⁴ This influx of calcium ions (Ca²⁺) into the cell signals Ryanodine receptors (RyR2s) on the sarcoplasmic reticulum to release of Ca²⁺ into the cytosol. This Ca²⁺ induced release of Ca²⁺ leads to tropomyosin translocation and myofilament contraction.

A delicate balance between inward and outward currents results in the plateau phase of the repolarization phases 2 and 3 (Figure 1). The repolarization phase is mediated by the orchestrated activities of the delayed rectifier K⁺ currents (Ikr and Iks), the inward rectifier K⁺ current (IK1) along with a gradual decrease in net depolarizing currents. The resting membrane potential of the myocytes is maintained by the background I_{K1} (phase 4), which is linked to the next cycle of AP initiated by new influx of INa.

Summation of these action potentials can be detected on the body surface electrocardiogram (ECG) (Figure 1). Atrial depolarization manifest on the ECG as P waves, while ventricular depolarization and repolarizations are seen as QRS and T waves, respectively (Figure 1).

**Arrhythmia Mechanism and Types**

Abnormalities in impulse generation, during propagation, or the duration and configuration of individual cardiac action potentials form the basis of disorders of cardiac rhythm. Cardiac arrhythmias are responsible for an estimated one million cases of syncope and sudden cardiac death (SCD), only among Europeans and Americans each year.⁵ Familial arrhythmias comprise a significant percentage in this population. Genetics and pathophysiology of the familial arrhythmias are quite complex and we have just begun to understand the intricate and complex processes behind the mechanism of arrhythmogenesis.

First reports linking genetic mutations to primary arrhythmias were published between 1995 and 1997 from the laboratory of Dr. Mark T. Keating and Dr. Pascal Guicheney.⁶⁻¹¹ Thereafter, during the last 13 years, we have observed potential discoveries linking mutations in cardiac ion channels, gap junction protein encoding genes with a wide variety of inherited arrhythmia syndromes.¹² Well coordinated crosstalks between the structural and electrical
components of the heart are required for proper cardiac function.\textsuperscript{2,13} Disruption/distortion in this communication could predispose the heart to arrhythmias with or without any structural defects in the heart.\textsuperscript{1,13}

Arrhythmias are classified into two main categories: bradycardia and tachycardia. Tachycardia is subclassified into supraventricular and ventricular tachycardia. In bradycardia, the heart rate is less than 60 beats per minute. A heart rate faster than 100 beats per minute is called tachycardia. Supraventricular arrhythmias originate from the atria. As named, ventricular arrhythmias originate from the ventricles. A fast uncoordinated heart rate is called fibrillation. Ventricular fibrillation (VF) is one of the most serious forms of all arrhythmias. General mechanisms of tachyarrhythmias include reentry, triggered activity (early after depolarizations, EAD; delayed after depolarizations, DAD), and abnormal automaticity.\textsuperscript{4}

**Supraventricular Arrhythmia**
A very common supraventricular arrhythmia is atrial fibrillation. A normal heart beats between 60 and 100 times a minute. During atrial fibrillation, the atria beat at 400 to 600 times per minute. In response to this, the ventricles usually beat irregularly with variable heart rate, depending on the refractoriness of the AV node. Atrial fibrillation is usually seen in patients with cardiovascular diseases, but could also be due to a genetic pathology. Once AF is developed, it is well possible that it might last lifetime.

**Ventricular Arrhythmias**
Tachyarrhythmias that originate in the ventricles are more debilitating than those that originate in the atria. In sustained ventricular tachycardia (VT), consecutive impulses arise from the ventricles at a heart rate of 100 beats or more per minute, which stops sometimes automatically without any intervention. But prolonged sustained VTs need to be intervened by drug treatment or electrical conversion. Prolonged sustained VTs might degenerate further into a totally disorganized electrical activity known as VF. VF also can many times present as the first manifestation of arrhythmia, which could be lethal in many occasions.

**Cardiac Channelopathies**
Ion channels are pore-forming protein complexes that provide controlled inward and outward ionic currents across the cell membranes, which is critical for cardiac contractility, rhythm generation and propagation. Channelopathies could be either congenital (often resulting from mutation/s in various genes) or acquired (resulting from autoimmune attack or drug effect on an ion channel). A large number of dysfunctions are caused by mutations in genes coding for cardiac ion channels. Long QT syndrome (LQTS), Short QT syndrome (SQTS), Sick sinus syndrome (SSS), Isolated Cardiac Conduction defect (ICCD), Brugada syndrome
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(BrS), Atrial Fibrillation (AF) and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) are the presently known cardiac channelopathies.

**Long QT syndrome (LQTS)**

Congenital LQTS is an inherited disorder defined by prolongation of the QT interval. Patients with all forms of LQTS are predisposed to the ventricular tachyarrhythmia torsade de pointes (TdP) leading to recurrent syncope or sudden cardiac death. In many cases, syncope or sudden death could be the first and the only manifestation. LQTS affects an estimated 1 in 2,000 people worldwide.\(^{14}\)

The ECG hallmark of the LQTS is, as its name suggests, prolongation of the QT interval (corrected for heart rate i.e. QTc). Normal values of QTc are 440ms in males and 450 ms in females. In children age-dependent (and gender dependent) values are relevant. Values above 480ms in the absence of an identified cause are generally considered highly suspect for LQTS. The molecular basis of LQTS is heterogeneous and to date, mutations in at least 12 different genes have been reported in LQTS patients (Table 1). Up to 70% of LQTS patients are reported to have a mutation in one of the 12 reported genes. Among the presently known 12 types of LQTs, the most common are LQT1, LQT2 and LQT3, caused by mutations in cardiac ion channel genes \(\text{KCNQ1}, \text{KCNH2}\) and \(\text{SCN5A}\), respectively. Mutations in these three genes constitute more than 90% of genotyped patients.\(^{6-11,15}\) Among the remaining nine genes implicated in LQTS, \(\text{ANK2}, \text{CAV3}\), and \(\text{AKAP9}\) are regulatory/chaperone genes,
KCNE1, KCNE2, KCNJ2 and SCN4B are ancillary subunits of major ion channel genes and CACNA1C is the pore forming α-subunit of the cardiac L-type calcium channel gene (Table 1). Mutations in these genes, combined, comprise the remaining 10% of the presently genotyped LQTS.

Among all reported mutations in LQT1 to LQT3, missense mutations are most common (72%), followed by frameshift mutations (10%), in-frame deletions, and nonsense and splice-site mutations (5% to 7% each) (15). Around 8% of the LQTS patients carry mutations in two LQTS causing genes and had longer QTc and also 3.5 fold more risk of cardiac arrest. Early after depolarization (EAD) is considered as the initiating arrhythmogenic mechanism in LQTS.4

LQT1: Mutations in the KCNQ1 gene cause the commonest form of LQTS referred to as LQT1, comprising around 50% of the total genotyped LQTS patients. KvLQT1 (coded by KCNQ1) along with its β-subunit minK (coded by KCNE1) co-assemble to form the cardiac K+ channel (Figure 4), which is responsible for the slowly activating delayed rectifier outward K+ current (I\textsubscript{Ks}). In this form of the disease, syncope or sudden death is triggered by adrenergic drives e.g. emotional stress, physical exertion, diving, swimming etc.17 Schwartz et al. (2001) reported that LQT1 patients experienced the majority of their events (62%) during exercise and only 3% during rest/sleep.18 Swimming is a typical trigger for cardiac events in these patients. Mutation/s (mostly missense) in KCNQ1 cause loss-of-function of the mutant allele but this non-functional allele still could exert a dominant negative effect on the normal/wild type allele, which is the pathologic basis of autosomal dominant LQT1 (Figure 2). Truncating mutations in the KCNQ1 are also non-functional and are not able (mostly) to exert dominant negative effect on the normal allele and hence the mono-allelic truncating KCNQ1 mutation carriers usually lack any significant phenotypes, neither on ECG nor clinically.

Pathogenic mutations in the KCNQ1 could be located all over the coding exons (including their intronic junctions). Among all the mutations, patients with mutations at the transmembrane domains are at higher risk of LQTS-related cardiac events and have greater sensitivity to sympathetic stimulation.19-20 Homozygous or compound heterozygous mutations in the KCNQ1 gene are rare, but when present, cause the recessive type of the disease, Jervell and Lange-Nielsen syndrome (JLNS). Clinical phenotype in JLNS patients are severer (also longer QTc) than the dominant LQT1, and the cardiac manifestations appear more frequently during the early childhood.21 Patients with JLNS suffer additionally from bilateral sensorineural deafness. JLNS causing homozygous KCNQ1 mutations are predominantly truncating (except several missense mutations), leading to complete loss/absence of the functional K\textsubscript{LQT1} protein and I\textsubscript{Ks} channel. This I\textsubscript{Ks} is also present in the inner ear and is required
to maintain normal hearing. In some cases, homozygous/compound heterozygous KCNQ1 mutations could still have some residual IKs function left, these patients suffer only from arrhythmia but not from deafness (please see chapter-8 of this thesis).

**LQT2:** LQT2 is equally prevalent as LQT1, accounting for 35-40% of genotyped LQTS patients. Mutations in the *KCNH2* gene are responsible for the LQT2 form of LQTS. *KCNH2* encodes for the HERG protein, and mutations could cause reduction in the rapid component of the delayed rectifier repolarizing current (I\text{Kr}). This reduction of the I\text{Kr} contributes to lengthening of the QT interval (Figures 1 and 2). Molecular mechanisms that account for reduced I\text{Kr} current in these patients are disruption of I\text{Kr} channel synthesis, membrane trafficking, gating, or permeation. 29% of the syncopal attacks in LQT2 occur during rest/sleep and only 13% of the syncopal attacks were reported during exercise. Sudden startling noises e.g. alarm clock noise, telephone ringing often trigger syncopal events in these patients. Patients with mutations in the pore region of the *KCNH2* gene are at markedly increased risk for arrhythmia-related cardiac events compared with patients with nonpore mutations. In neonates, 2:1 Atrioventricular block (AVB) is preferentially associated with *KCNH2* mutations. Complete AV block complicated by LQTS were also found in 17% of adult patients with a mutation in the *KCNH2* gene. Homozygous mutations in *KCNH2* are rare and when present, patients suffer from a severe form of LQT, with 2:1 AV block and severe ventricular arrhythmias, well before and immediately after birth.

**LQT-3:** LQT3 accounts for \(\leq 10\%\) of genotyped LQT patients. LQT3 is caused by gain of function mutations that disrupt fast inactivation of the α-subunit (Na\textsubscript{v} 1.5) of the voltage-gated sodium channels encoded by *SCN5A* (Figures 1 and 2). Normally, wild-type (WT) Na\textsuperscript{+} channels open in response to membrane depolarization, then enter into an inactivation state that prevents reopening during sustained depolarization. LQT-3 causing mutations in *SCN5A* exert their deleterious effects by disrupting the inactivation process either by reducing the rate of channel inactivation or by increasing the likelihood of recovery from inactivation. As a result, the inward sodium current persists abnormally during the plateau phase of the cardiac action potential (Figure 2). This persistent entry of positive electrical currents prolong the duration of the action potential. LQT3 patients experience the majority of their events (39%) during during sleep/rest, and about 13% of the events were reported to occur during rest/sleep. Genotype and phenotype relationship in *SCN5A* mutations is intricate and complex. In several instances single *SCN5A* mutation were shown to exert two or even three distinct phenotypes of arrhythmias in the same family. Male patients with a mutation at the LQT3 locus could develop symptoms much earlier than the female patients. Homozygous *SCN5A* mutations have been described
in Long-QT syndrome with functional 2:1 AV block.\(^3\)

**LQT-4:** LQT-4 represents the first non-channel form of LQTS. A mutation in \(\text{ANK2}\), a member of a family of versatile membrane adapters, leads to intracellular calcium overload which contributes to the LQT4 syndrome (Table 1). In addition to QT prolongation, this syndrome is associated with sinus bradycardia and paroxysmal atrial fibrillation.\(^3\)

\(\text{ANK2}\) is required for the localization and post-translational stability of \(\text{Na}^+/\text{Ca}^{2+}\) exchanger in cardiomyocytes.\(^4\) Pathogenic effect of the \(\text{ANK2}\) mutations could be severe and the clinical expressions depend on the severity of the mutation. All mutations (<10) till date described are missense mutations.

**LQT-5:** The MinK protein is a cardiac K\(^+\) channel accessory subunit encoded by the \(\text{KCNE1}\) gene. Mutations in \(\text{KCNE1}\) are associated with the LQT5 form of LQTS (Figure 1 and 2).\(^4\)\(^2\)\(^3\) \(\text{KCNE1}\) mutations reduce \(I_{\text{Kr}}\) and also exert dominant-negative effect on the wild type normal allele, which causes delayed cardiac repolarization (Figures 1 and 2), leading to an increased risk of arrhythmia in the heterozygous carriers.\(^9\) To date, <20 LQT5-related \(\text{KCNE1}\) mutations (all missense) have been reported, but this number and the incidence of mutations are very small compared with the principal LQTS mutations (LQT1-3). Heterozygous \(\text{KCNE1}\) mutation carriers were observed to have milder LQTS phenotypes in a study from Japan.\(^44\) Homozygous \(\text{KCNE1}\) mutation carriers were reported to suffer from JLNS.\(^45\)\(^46\)

**LQT-6:** \(\text{KCNE2}\) gene encodes MinK-related peptide 1 (MiRP1), a \(\beta\)-subunit of the cardiac potassium channel \(I_{\text{Kr}}\) (Figures 1 and 2). Mutations in \(\text{KCNE2}\) cause defects in the rapidly activating component of the delayed rectifier potassium current (\(I_{\text{Kr}}\)), responsible for the LQT6.\(^47\) Reported mutations in \(\text{KCNE2}\) gene till date are <15, all are missense. Auditory/aesthetic stimulus like alarm clock noise, door ringing bell etc. could provoke syncopal attacks in \(\text{KCNE2}\) mutation carriers similar to \(\text{KCNH2}\) mutation carriers.\(^48\)

**LQT-7:** This syndrome is also known as Andersen-Tawil syndrome (ATS). ATS is a rare disorder, manifested by occasional syncope and cardiac arrest. ECG features include mild QT interval prolongation, abnormal U waves, frequent ventricular ectopy, bidirectional ventricular tachycardia (VT) and polymorphic VT. This syndrome also exhibits extracardiac features which include skeletal muscle periodic paralysis and developmental problems, such as cleft palate, low set ears, short stature, and developmental features in the limbs.\(^5\)\(^9\) Majority of clinically diagnosed ATS patients are reported to have a mutation in \(\text{KCNJ2}\).\(^49\) \(\text{KCNJ2}\) encodes a pore-forming subunit of inwardly rectifying potassium channels (\(I_{\text{k1}}\)), which maintains normal resting membrane potentials (Figures 1 and 2).\(^50\)\(^51\) To date, ≥35 heterozygous
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LONG QT SYNDROME MECHANISM

SHORT QT SYNDROME MECHANISM

ECG

Normal ECG
Long QT ECG

Normal ECG
Short QT ECG

ACTION POTENTIAL

Prolonged AP duration in Long QT Syndrome

Shortened AP duration in Short QT Syndrome

ELECTROPHYSIOLOGICAL MECHANISM

LQT1 (SCN5A)
LQT2 (KCNE2)
LQT5 (HCN4)
LQT6 (KCNE1)
LQT7 (KCNE2)
LQT8 (SCN8A)
LQT10 (SCN5A)
LQT12 (SCN5A)

I_{Ks} decrease
I_{Ks}
I_{Kf} decrease
I_{Kf}
I_{K1} decrease
I_{K1}
I_{Na} increase
I_{Na}
I_{Ca-L} increase
I_{Ca-L}
KCNJ2 mutations are reported in ATS, and ATS causing mutations in KCNJ2 showed loss-of-function and dominant negative suppression effects.\(^5^2\) The clinical severity of ventricular arrhythmias are usually milder in ATS than in other types of LQTS,\(^4^9\) however, there are reports of aborted sudden death in unrelated ATS patients in several studies.\(^5^3-^5^4\)

**LQT-8:** Also known as Timothy syndrome (TS), combines severe QT prolongation with syndactyly, baldness at birth, and small teeth in 100% of cases and less penetrant cardiac structural malformations, autism, mental retardation, and facial dysmorphic features.\(^5^5\) There are two subtypes: TS1 and TS2. Mutations in the α-1 subunit of the L-type calcium current (\(I_{\text{Ca,L}}\)) encoding gene \(CACNA1C\) lead to LQT-8 (both subtypes). To date 13 cases of TS1 were reported and all occurred due to a single de novo missense G406R mutation in the exon 8A of \(CACNA1C\) gene.\(^5^5\) All TS1 individuals have syndactyly (webbing of fingers and toes).\(^5^6\) Comparatively severer variant, TS2, arises due to mutations in exon 8. None of the two reported TS2 patients had syndactyly. TS1 and TS2 mutations in \(CACNA1C\) lead to a gain of function defect, augmenting the depolarising \(\text{Ca}^{2+}\) current during the plateau phase of the action potential (fig 2), thereby prolongs the action potential duration (Figures 1 and 2).

**LQT-9 and LQT-10:** Fairly recent genes associated with LQTS are \(CAV3\), which encodes Caveolin-3, and \(SCN4B\), which encodes \(\text{Na}_\beta\), an auxiliary β-subunit of the cardiac sodium channel.

Mutations in \(CAV3\) and \(SCN4B\) produce gain of function in late \(I_{\text{Na}}\), causing an LQT3-like phenotype (Figure 1 and 2).\(^5^7-^5^9\) They are named as LQT-9 (associated with \(CAV3\) mutation) and LQT-10 (associated with \(SCN4B\) mutation).

**LQT-11:** In the heart, sympathetic nervous system (SNS) regulation of cardiac action potential duration (APD) is mediated by β-adrenergic receptor (β-AR) activation, which requires assembly of AKAP9 (Yotiao) with the α-subunit (KvLQT1) of the \(I_{\text{Ks}}\) channel.

Mutation in \(AKAP9\) causes LQT-11 (Figures 1 and 2).\(^6^0\) To date only one mutation (S1570L) has been reported in \(AKAP9\) with a detection rate of 2%.\(^6^0\) Mutation in \(AKAP9\) negatively affects the interaction between KvLQT1 and AKAP9 (Yotiao) and prolongs the action potential.
### Clinical and Genetic Spectrum of Hereditary Cardiac Arrhythmia Syndromes

<table>
<thead>
<tr>
<th>Disease name</th>
<th>Disease causing gene (encoded protein)</th>
<th>Functional effect</th>
<th>Arrhythmia onset</th>
<th>Resting ECG</th>
<th>ECG at onset of arrhythmia</th>
<th>QT change with exercise</th>
<th>Response to β-blockers</th>
<th>Extracardiac features</th>
</tr>
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<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1 (K, LQT1)</td>
<td>decreased I(_{Ks})</td>
<td>emotional or physical stress, swimming, diving</td>
<td>broad based T wave</td>
<td>tachycardia</td>
<td>relative increase</td>
<td>yes</td>
<td>no</td>
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<tr>
<td>LQT2</td>
<td>KCNH2 (HERC1)</td>
<td>decreased I(_{Ks})</td>
<td>emotional or physical stress, sudden loud noise</td>
<td>low-amplitude T wave with notching</td>
<td>with pause</td>
<td>some shortening</td>
<td>yes, less than LQT1 response</td>
<td>no</td>
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<tr>
<td>LQT3</td>
<td>SCN5A (α-subunit of sodium channel, α1,2)</td>
<td>increased late sodium current</td>
<td>rest, sleep</td>
<td>long isoelectric ST segment</td>
<td>pause?</td>
<td>bradycardia</td>
<td>adequate shortening</td>
<td>ns</td>
</tr>
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<td>LQT4</td>
<td>ANK-BN1NL2 (ANK2)</td>
<td>disruption of localization and post-translational stability of Na(^+/Ca(^{2+}) exchanger</td>
<td>ns</td>
<td>bradycardia, atrial arrhythmia</td>
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<td>ns</td>
<td>ns</td>
<td>ns</td>
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<td>KCNE1 (minK)</td>
<td>decreased I(_{Ks})</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>LQT6</td>
<td>KCNE2 (mRP1)</td>
<td>decreased I(_{Ks})</td>
<td>auditory/aerodynamic stimuli like alarm clock noise, door ringing bell</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>no</td>
</tr>
<tr>
<td>LQT7</td>
<td>KCNJ2 (Kol2,1)</td>
<td>decreased I(_{Ks})</td>
<td>exercise</td>
<td>large U-wave, extrasystoles</td>
<td>ns</td>
<td>ns</td>
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<td>yes**</td>
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<td>LQT8</td>
<td>CACNA1C (α-1 subunit of TCA(_{Ca}))</td>
<td>increased L-type calcium current</td>
<td>ns</td>
<td>very long QT interval</td>
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<td>ns</td>
<td>ns</td>
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<td>LQT9</td>
<td>CAV3 (CAV3)</td>
<td>increased late sodium current</td>
<td>ns</td>
<td>ns</td>
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<td>ns</td>
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<td>LQT10</td>
<td>SCN4B (Na(_{v})4)</td>
<td>increased late sodium current</td>
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<td>AKAP9</td>
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<td>LQT12</td>
<td>SNT1/N (SNT1)</td>
<td>Increased late sodium current</td>
<td>ns</td>
<td>ns</td>
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<td>ns</td>
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<tr>
<td>JNNS</td>
<td>biallelic mutations in KCNQ or KCNE1</td>
<td>loss of I(_{Ks})</td>
<td>see LQT1</td>
<td>ns</td>
<td>ns</td>
<td>no</td>
<td>yes</td>
<td>bilateral deafness</td>
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<tr>
<td>LQT1</td>
<td>(transient) biallelic mutations in KCNQ</td>
<td>near absence of I(_{Ks})</td>
<td>see LQT1</td>
<td>ns</td>
<td>ns</td>
<td>no</td>
<td>yes</td>
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ns: not specified

*skeletal muscle periodic paralysis, cleft palate, low set ears, short stature.

** syndactyly, baldness at birth, small teeth, and occasionally cardiac structural malformations, autism, mental retardation, facial dysmorphic features.

**Table 1:** Summary of genes and chromosomal loci (where genes are not known) for LQTS.
duration.

**LQT-12:** The most recent gene reported to cause LQTS is α-1-Syntrophin (SNTN1). SNTN-1 mutation causes gain of function of the cardiac sodium channel Na,1.5, pathophysiologic basis of LQT-12 (figure 2).

**Acquired LQTS**

Acquired LQTS is caused by factors and substances that decreases potassium flux and impair the ability of the myocardium to repolarize. Well-recognized conditions that negatively influence the “repolarization reserve” are female gender, hypokalemia, and drugs that inhibit cardiac potassium channels. A number of commonly prescribed drugs could preferentially bind and block the HERG channel (encoded by KCNH2) due to its unique structure and increases predisposition to drug-induced arrhythmia. Mutations or polymorphisms in HERG may facilitate this binding.

Certain variants of MiRP1 (encoded by KCNE2) also contribute to a significant fraction of cases of drug-induced LQTS. One example is T8A-MiRP1 is a common SNP in the MiRP1, reported in about 1.6% of healthy individuals. Individuals harbouring this SNP had a normal electrocardiogram at rest but developed a very long QT interval on Bactrim (trimethoprim/sulfamethoxazole (TMP/SMX)) therapy due to the fact that the channels formed with T8A-MiRP1 are inhibited by SMX.

S1103Y and L1825P in SCN5A has also been associated with acquired LQT3. Drugs affecting the intracellular calcium overload also could cause acquired variant LQT in otherwise normal individuals. Procainamide and Quinidine induces LQT and torsades de pointes in otherwise normal individuals who carried a SNP E1813K in the ANK2. These drugs suppress the ANK2 function in individuals harbouring the SNP E1813K and prolong the QT interval inducing intracellular calcium load. Autoimmune mediated LQTS has also been described in a patient with IgG containing anti-HERG antibodies.

**Electrocardiographic (ECG) features in the three common forms of Long QT syndrome:**

Typical ST-T-wave patterns are present in the majority of genotyped LQTS patients and can be used to identify LQT1, LQT2, and possibly LQT3 genotypes.

The LQT1 form of the long-QT syndrome is associated with a broad T wave without shortening of the QT interval at exercise (figure 3a). LQT2 is associated with low-amplitude, often bifid, T waves (Figure 3b). LQT3 is associated with a long isoelectric segment and a narrow-based, tall T wave (Figure 3c). Pause dependence of TdP onset in congenital LQTS is genotype specific, being predominant in LQT2 but almost absent in LQT1. Although patterns
Figure 3: ECG recordings from patients with LQT1, LQT2 and LQT3 and LQT8.

A) 12 lead ECG of a 18 year old male with a KCNQ1 mutation. The QT interval is prolonged (QTc = + 500ms). The ST segment has a broad base and relatively large amplitude. Conduction interval is normal (standard calibration).

B) 12 lead ECG of a 14 year old girl with a KCNH2 mutation. The QT interval is prolonged (QTc, +520ms). The ST segment is notched in lead V3 and has relatively low amplitude in the extremity leads. Conduction interval is normal (standard calibration).

C) 12 lead ECG of a 12 year old boy with a SCN5A mutation. The QT interval is prolonged (QTc = 600 ms). The ST segment has a long (almost) isoelectric segment with a large, sharp and narrow T wave. Conduction interval is normal (standard calibration).

D) 12 lead ECG of a 2 year old boy with a CACNA1C mutation. The QT interval is very prolonged (620 ms; QTc= 911 ms) with upright T wave. The ST segment shows T wave alternans which are most evident in leads V3-V5.

E) Two lead ECG (lead II and III) from a 14 year old girl with KCNH2 mutation. In the middle part of ECG a TdP episode is seen that lasts a few seconds and terminates spontaneously. Prior to the TdP episode, ventricular extrasystoles disturb a regular sinus rhythm. Note the prolonged QTc particularly after the arrhythmia.
may suggest a specific genotype of the long-QT syndrome, exceptions have been described. Mutation list and their carrier patients are still inadequate in number to perform such genotype specific ECG analysis in LQT4-LQT12 patients.

**Genotype-Phenotype**
Clinical expression of LQTS is not uniform, variation in penetrance and expression are influenced by age, gender, genotype, environmental factors, therapy, and possibly by not yet identified modifier genes. The genotype-phenotype correlation in heterozygous carriers has been investigated in detail in the LQT1, LQT2 and LQT3 syndrome patients, as these 3 forms constitute more than 90% of genotyped LQTS patients. During childhood, the risk of cardiac events is significantly higher in LQT1 males than in LQT1 females, whereas no significant gender-related differences were seen in the risk of cardiac events among LQT2 and LQT3 carriers. During adulthood (also after age 40) LQT2 and LQT1 patients had a significantly higher risk of cardiac events in females than respective males. In general, lethality of cardiac events seem to be more predominant in LQT3 patients than in LQT1 and LQT2 patients. Women with LQTS have a reduced risk for cardiac events during pregnancy, but an increased risk during the 9-month postpartum period, especially among women with the LQT2 genotype. The QTc is an independent predictor of risk among patients with a mutation at the LQT1 locus and those with a mutation at the LQT2 locus but not among those with a mutation at the LQT3 locus.

**Intrauterine Death, Sudden Deaths in Infants, Children and Adults: role of mutations in Ion channel genes**
Recurrent third-trimester fetal loss was reported in heterozygous R1623Q SCN5A mutation carriers in a single report. Intrauterine fetal death at 36 weeks of gestation was also reported in a homozygous KCNHI2 mutation carrier. Sudden cardiac death (SCD) in children could often be caused by a mutation in the cardiac ion channel gene. In a report, >50% of the children with an unexplained SCD was shown to have a mutation in one of the known cardiac ion channel genes. Though, mutations in SCN5A seem to be predominant in SIDS, mutations in KCNQ1 were also reported. New additions to this list are mutations in KCNH2, KCNE2 and CAV3, SCN4B and SCN3B. In 12% of the Sudden Arrhythmic Death Syndrome between 16-64 yrs of age were found to have LQTS.

**Diagnosis**
Most common clinical features of LQT patients are palpitations, presyncope, syncope and sudden death. These clinical features also could be seen in patients with other arrhythmia
syndromes e.g. catecholaminergic polymorphic ventricular tachycardia and secondary arrhythmia syndromes (due to various cardiomyopathies).

A proper history taking relevant to the disease is required, which in many occasions lead to the specific subtype of LQTS. This history taking includes the proband him/herself and also of any family members with similar history. History also should be focused on precipitating factors which provoked the symptoms e.g. swimming, alarm noise, door ringing bell etc. Physical examinations and Echocardiography (or MRI/CT) are required to exclude the presence of any structural abnormality in index patients with LQTS. An ECG exhibiting prolonged QTc at rest in a structurally normal heart is the sine qua non to the diagnosis. To rule out the acquired cases of LQTS (occurs in 5 to 20% of cases) patients should be screened for serum electrolytes (K⁺, Ca²⁺, Mg²⁺), hypothyroidism and other eliciting factors. Patients should be inquired about the use of drugs that can prolong the QT interval, which includes several antiarrhythmic drugs (www.torsades.org).

A great percentage (30-40%) of individuals with LQT1 has a non-diagnostic QTc at rest, and concealed LQT1, therefore unmasking LQT1 is clinically important as LQT1 represents one of the two most common subtypes of LQTS.89 Exercise or epinephrine QT stress test could sometime (not always) help in differentiating between a rare but functionally irrelevant “mutation” in KCNQ1 versus a pathogenic, LQT1-causing mutation.89-91 Sotalol also could help in unmasking the concealed LQT.92 Similarly, identification of occult LQT2 patients remains an unresolved problem. Shimizu et al. demonstrated that epinephrine bolus (but not steady state epinephrine) increased Tpe in LQT2 patients.93 Erythromycin was also found prolong the Tpe in LQT2 patients.94

Single Nucleotide Polymorphism (SNP), Ethnicity and LQTS predisposition

The term Single nucleotide polymorphism (SNP) refers to single nucleotide DNA sequence variations within the genome, and which seems to exert no pathogenic effect. SNPs are present all over the genome (exons, introns, gene regulatory regions) and can change the amino acid codon (non-synonymous changes) and can also be silent (synonymous changes). Some SNPs are found in equal frequency in all populations and some of them can be seen prevalently in specific ethnic/regional populations. For a nucleotide variation to be considered an SNP, generally accepted criteria are that this variant should be present in at least 1% of the population (Human Genome data base, NCBI). SNPs are usually considered harmless, but there are SNPs which can enhance the risk of a disease in specific populations. For example, S1103Y is a common SNP in SCN5A, about 13.2% of African Americans carry the Y1103 allele. Heterozygous carriers for this genotype seem to be associated with increased risk for arrhythmia in adults with 8-fold increased risk of arrhythmias without marked channel dys-
function in vitro. Infants with African-Americans origin with 2 copies of the common synonymous SNP S1103Y in SCN5A are predisposed to 24-fold increased risk for SIDS. Similarly, R1193Q comprises 12% of the alleles in Han Chinese compared to <0.2% in other populations, considerably increasing the risk for LQTs (and some times Brugada Syndrome) in the Han Chinese population. L1622I codon in ANK2 is conserved across species, and about 4% of the Africans share this allele. Effect of this SNP on arrhythmia susceptibility in the African populations remain to be studied.

Clinical Management of LQTS
Cessation of all drugs known to prolong the QT interval and the correction of electrolyte imbalances and/or precipitating metabolic conditions should be the primary focus while treating LQTS patients. Because syncpe or death in the LQTS is often adrenergically mediated, restriction of patients’ participation in athletic activities is generally recommended. It is not known whether this restriction should be extended to patients with forms of the disease in which adrenergic stressors are not prominent. Silent mutation carriers should be counselled about the characteristics of the disorder and also need to be properly informed about the risk of mutation transmission to offspring, also mentioning the fact that that offspring of a silent mutation carrier could express the disease phenotype when carried the mutation unlike his/her silent mutation carrier parent.

The mainstay of therapy for the long-QT syndrome is and has been β-blockade. Long-acting preparations such as nadolol and metoprolol are usually used, and the efficacy of β-blockade is assessed by blunting of the exercise heart rate (e.g., by >20%). The percentages of patients who were free of recurrence with β-blocker therapy was reported to be higher and the death rate was lower among LQT1 patients (81% and 4%, respectively) than the LQT2 (59% and 4%, respectively) and LQT3 (50% and 17%, respectively) patients. Furthermore β-blockade can be used as a prophylactic treatment in silent mutation carriers to reduce SCD. Since, women with LQTS (especially LQT2) have an increased risk during the 9-month postpartum period, β-blockers should be prescribed to reduce any cardiac events during this high-risk period.

An implantable cardioverter–defibrillators (ICDs) can be considered for patients with recurrent syncope despite β-blocker therapy or in patients with high risk for cardiac arrest (e.g. symptomatic LQT2 and LQT3 with a documented QTc prolongation). β-blockers have limited efficacy in JLNS in which and early therapy with implanted cardioverter-defibrillators were recommended. Another effective anti-adrenergic therapy is ablation of the left stellate ganglion. This therapy, also called left cardiac sympathetic denervation (LCSD), has been shown to be effective alike β-blockers, particularly in LQT1 patients. LCSD should be considered in patients with recurrent syncope despite beta-blockade and in patients who experience arrhythmia storms with an implanted defibrillator.
blockers such as mexiletine and flecainide may normalize the QTc interval in patients with the LQT3 subtype, but they may also increase the risk of sudden death in patients with overlapping Brugada syndrome; their role as primary therapy in LQT3 thus remains uncertain. In vitro analysis was performed to check the efficacy of mexiletine showed some mutations are responsive to mexiletine and some are not.\textsuperscript{100} Low-dose flecainide was reported as a promising therapeutic agent for LQTS patients with DeltaKPQ mutation carriers in the SCN5A.\textsuperscript{101} These findings should be carefully addressed in the clinical setting in patient cure. LCSD should also be considered in all forms of LQTS patients with recurrent syncope despite β-blockade and in patients who experience arrhythmia storms with an implanted defibrillator.\textsuperscript{99} Pacing has limited value in the treatment of LQTS but might be used to allow full dose β-blocker therapy or in young infants to postpone ICD implantation. A pause-dependent arrhythmias (LQT2) may be prevented by pacing and pacing protocols that favor relatively fast heart rates can prove useful in patients as they may prevent electrical storm.\textsuperscript{102} Several compounds (Nicorandil, NS3623) act as potassium channel openers and correct the QTc interval, are still in the experimental stage.\textsuperscript{103-104} Though they seem to work as potassium channel activator, further functional and clinical research studies are required before they could be brought to the clinic.

**Short QT syndrome**

The short QT syndrome (SQTS) has been recognized recently as a new entity characterized by ion channel mutations, leading to sudden cardiac death due to VF associated with short refractory periods. The short QT syndrome has been characterized by major and minor cardiac events, or symptoms. The major events include syncope, ventricular fibrillation and sudden cardiac death. The minor events include palpitations, light headedness/ dizziness, and paroxysmal atrial fibrillation. Sudden cardiac death could be frequent first symptom and first clinical presentation. Most patients have a significant family history of sudden cardiac death of relatives with a variable age distribution, ranging from 3 months to 70 years of age. The mean age of SQTS diagnosis is 30 years.\textsuperscript{105} It has been suggested that sudden infant death syndrome may in some cases be attributed to SQTS.\textsuperscript{106}

ECG is characterized by a short QT interval of typically less than 300 ms with tall peaked, narrow symmetrical T waves. Short refractory periods lead to a propensity to develop atrial or ventricular fibrillation at electrophysiology study. SQTS is a genetically heterogeneous disease characterized by at least three different gene mutations of potassium channels involved in cardiac repolarization. Three forms of SQTS have been diagnosed due to mutations in three different genes (Table 2), which are as follows:

- **SQTT-1:** A mutation in \textit{KCNH2} which causes gain of function (contrary to loss of function...
mutations) is responsible for SQT-1 (figures 1 and 2). To date, only one missense mutation in KCNH2 encoded HERG (N588K) have been described in SQT-1, that lead to gain of function and shortening of the action potential duration.107-108

SQT-2: Mutation in the KCNQ1 gene could also result in accelerated activation kinetics consistent with a gain of function in the outward current and is considered the pathophysiology of short QT syndrome (SQT-2) (Figures 1 and 2).109-110

SQT-3: KCNJ2 encodes the pore-forming subunit of inwardly rectifying potassium channel ($I_{K1}$). Mutation in this gene which causes gain of function of the $I_{K1}$ channel, and the generated current do not decrease to the extent of normal potassium channels, shortens the action potential (Figures 1 and 2). ECG shows unique features of asymmetric tall T waves with a rapid descending portion.111 The QT-interval in the described patients are in the 320 ms range. The clinical syndrome is extremely heterogeneous with variation in symptoms and risk of sudden cardiac death within an individual genotype. At this point in time, it is difficult to link genotypes with definite phenotypic expression.112 Given the high incidence of sudden cardiac death in SQTS, an ICD is recommended unless there is an absolute contraindication to implantation. Pharmacologic therapy is a potential alternative to ICDs in patients in whom ICD implant is not feasible. Hydroquinidine so far has been as the only agent to revert short QT interval to normal.113-114

**Brugada syndrome**

Brugada syndrome (BrS) is a leading cause of death due to ventricular arrhythmias among young men in Southeast Asia, and also responsible for a considerable numbers of sudden cardiac deaths worldwide. Among patients presenting with the syndrome, 20-50% are reported with a family history of sudden cardiac death.

Heterozygous mutations in the cardiac Na+ channel encoding SCN5A gene cause approximately 20% of the cases of BrS. Heterozygous mutations in the α-1 (CACNA1C) and the β-2b subunits (CACNB2) of the cardiac L-type calcium channel genes (figure 1 and table 2) were recently reported in BrS patients (8%) in combination with short QT interval.115 Mutation in GPDL-L and SCNIB gene has also been implicated in BrS comprising <2 % of BrS patients.116-118

All these BrS causing mutations, either by trafficking deficiency or abrogation in the electrical property, or affecting its binding to the adaptor molecule ankyrin-G prevents accumulation of SCN5A encoded Na, 1.5 at cell surface sites in ventricular cardiomyocytes,118,119 which results in premature closing of the sodium channel or less available channels during phase 1 of the action potential (Figure 1).

This loss or deficient sodium channel function manifests the BrS specific ECG in these pa-
tients (Figure 4). Sodium channel blockers, cocaine, antidepressants and antihistamines are also known to facilitate the Brugada-type ECG by reducing the inward sodium current.\textsuperscript{120-121} Actually, sodium channel blockers are clinically in use to unmask BrS in those cases in which there is a strong suspicion of the disease but no electrocardiographic proof. Reentry is considered the dominant mechanism in Brugada syndrome based on conduction slowing, easy VT/VF induction during electrophysiological study and the polymorphic nature of the arrhythmias.\textsuperscript{122}

The main ECG findings in BrS are ST-segment elevation in the right precordial leads (V1-V3), with or without the presence of incomplete or complete right bundle branch block (Figure 4). Occasionally, like in a French family with BrS, ST segment elevation and prominent J wave were observed in the inferior and also in right precordial leads. But, some family members showed classic ECG pattern of ST segment elevation in the right precordial and not in the inferior leads.\textsuperscript{123} Among the two major types of ST segment elevations in BrS, coved-type morphology is required for the diagnosis, while the saddle-back type is an intermediate form that requires confirmation using pharmacological challenge (conversion into coved-type) or genetic analysis.\textsuperscript{122} A large majority of BrS patients goes undetected without a mutation. ECG characteristics indicative for \textit{SCN5A} mutations are longer conduction intervals and higher ST amplitude.\textsuperscript{124}

In the largest population of children affected by BrS described to date, fever represented the most important precipitating factor for arrhythmic events.\textsuperscript{125} Patients with a spontaneously appearing Brugada ECG have a high risk for sudden arrhythmic death secondary to ventricular tachycardia/fibrillation.\textsuperscript{120-121} In the adult population, the risk of arrhythmic events is higher in previously symptomatic patients.\textsuperscript{120}

Controversy exists in the management of asymptomatic patients with the classic ECG pattern. Therapeutic intervention with antipyretics or termination of the culprit medication (e.g. antidepressants and antihistamines) is warranted and carrier family members should be informed that some medications and disease states (fever) might increase their risk of arrhythmias.\textsuperscript{120-121} In patients with previous symptoms (most likely) related to the occurrence of ventricular arrhythmias, there is general agreement that they should be protected with an implantable defibrillator. Longer follow-up in well-controlled clinical trials will be needed to better understand how to manage asymptomatic patients.

**Cardiac Conduction Defect or Lev-Lenègre syndrome**

Progressive cardiac conduction defect (PCCD) is a frequent disease commonly attributed to degeneration and fibrosis of the His bundle and its branches. Cardiac conduction disease (CCD) is mostly encountered as a consequence of cardiac injury (caused by ischaemia or surgery), as the major cardiac manifestation of neuromuscular diseases, or in association
with congenital cardiac abnormalities. However, isolated cardiac conduction disease (ICCD), with a progressive nature in some instances (also known as Lenegre and Lev disease) has also been described.

Three distinct genetic forms have been distinguished in families displaying an autosomal dominant inheritance (Table 2). One form involves mutations in \textit{SCN5A}. Mutations in \textit{SCN5A} cause (progressive) cardiac conduction defect, also called hereditary Lenegre disease, characterized by an age-related alteration in the conduction of the cardiac impulse through the His-Purkinje system, ultimately leading to a pacemaker implantation but no ST-segment elevation.

An intriguing overlap exists between Lenegre disease and BrS: decreased availability of the sodium channel accounts for both clinical entities. Linkage to chromosome 19q13.2–q13.3 and chromosome 16q23–24 has respectively been identified in two kindreds with the disorder (Table 2). The causative genes at each of these loci are yet to be identified. Patients with CCD or Lev-Lenègre disease are usually treated with conventional pacemaker therapy. Dual chamber pacing (DDD pace makers) or VVI PM’s are mostly used in patients without or with atrial fibrillation.

**Sick Sinus Syndrome**

Sick sinus syndrome (SSS) encompasses a broad array of disturbances involving sinus node dysfunction. Common clinical manifestations are syncope, presyncope, dizziness, and fatigue. ECG typically manifests sinus Bradycardia, sinus arrest, and/or sinoatrial block. Epi-
sodes of atrial tachycardias coexisting with sinus bradycardia ('tachycardia-bradycardia syndrome') are also common in this disorder. SSS occurs most often in the elderly associated with underlying heart disease or previous cardiac surgery, but can also occur in the fetus, infant, or child without heart disease or other contributing factors, in which case it is considered to be a congenital disorder (also see Table 2). In a significant portion of patients, however, this disease appears in the absence of an identifiable cardiac abnormality or other

Table 2: Summary of genes and chromosomal loci (where genes are not known) for SQTs, BrS, CCD, SSS, CPVT and FAF.

<table>
<thead>
<tr>
<th>Disease name</th>
<th>Disease causing gene (encoded protein)</th>
<th>Functional effect of disease causing mutation</th>
<th>ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQT-1</td>
<td>KCNQ1 (HERG)</td>
<td>increased I{sub}_K_C</td>
<td>short QT interval of typically less than 300 ms with tall peaked, narrow symmetric T waves.</td>
</tr>
<tr>
<td>SQT-2</td>
<td>KCNQ1 (IK, 1.1)</td>
<td>increased I{sub}_K_C</td>
<td></td>
</tr>
<tr>
<td>SQT-3</td>
<td>KCNQ2 (IK, 2.1)</td>
<td>increased I{sub}_K_C</td>
<td></td>
</tr>
<tr>
<td>BrS-1</td>
<td>SCN5A (r-subunit of sodium channel Na_l, 1.5)</td>
<td>reduced surface Na_l, 1.5</td>
<td>ST-segment elevation in the right precordial leads (V1-V3), with or without the presence of nonspecific or complete right bundle branch block.</td>
</tr>
<tr>
<td>BrS-2</td>
<td>GPD1-L (glycerol-3-phosphate dehydrogenase 1-like)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BrS-3</td>
<td>CACNA1C (a-1 subunit of L{sub}_Ca)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BrS-4</td>
<td>CACNB2 (b-2b subunit of L{sub}_Ca)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BrS-5</td>
<td>CACNB1 (b-1 subunit of sodium channel)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCD-1</td>
<td>unknown (19q13.2-q13.3)</td>
<td>unknown</td>
<td>cardiac conduction defect at all cardiac levels.</td>
</tr>
<tr>
<td>CCD-2</td>
<td>SCN5A (r-subunit of sodium channel Na_l, 1.5)</td>
<td>reduced surface Na_l, 1.5</td>
<td></td>
</tr>
<tr>
<td>CCD-3</td>
<td>unknown (chr16q23-q24)</td>
<td>unknown</td>
<td></td>
</tr>
<tr>
<td>SSS-1</td>
<td>HCN4 (Hyperpolarization activated cyclic nucleotide gated channel-4)</td>
<td>unknown</td>
<td>sinus bradycardia, sinus arrest, and/or nonsustained block. Episodes of atrial tachycardia coexisting with sinus bradycardia.</td>
</tr>
<tr>
<td>SSS-2</td>
<td>SCN5A (r-subunit of sodium channel Na_l, 1.5)</td>
<td>reduced surface Na_l, 1.5</td>
<td>cardiac conduction defect.</td>
</tr>
<tr>
<td>CPVT-1</td>
<td>RYR2 (RyR2)</td>
<td>premature cytosolic release of Ca{sup}_2{sup}^+</td>
<td>Ventricular premature complexes, later in bigeminy, followed by bidirectional or polymorphic ventricular tachycardia</td>
</tr>
<tr>
<td>CPVT-2</td>
<td>CASQ2 (CASQ2)</td>
<td>premature cytosolic release of Ca{sup}_2{sup}^+</td>
<td></td>
</tr>
<tr>
<td>CPVT-3</td>
<td>gene unknown (chr1p44-21)</td>
<td>unknown</td>
<td>same same</td>
</tr>
<tr>
<td>FAF-1</td>
<td>gene unknown (chr17q22-q24)</td>
<td>unknown</td>
<td>atrial fibrillation, no specific features</td>
</tr>
<tr>
<td>FAF-2</td>
<td>gene unknown (chr6q14-q16)</td>
<td>unknown</td>
<td>atrial fibrillation, no specific features</td>
</tr>
<tr>
<td>FAF-3</td>
<td>KCNQ1 (I{sub}_K_C)</td>
<td>unknown</td>
<td>atrial fibrillation, no specific features</td>
</tr>
<tr>
<td>FAF-4</td>
<td>KCNE2 (mRP1)</td>
<td>unknown</td>
<td>atrial fibrillation, no specific features</td>
</tr>
<tr>
<td>FAF-5</td>
<td>GLUL (Connexin-40)</td>
<td>unknown</td>
<td>atrial fibrillation, no specific features</td>
</tr>
<tr>
<td>FAF-6</td>
<td>KCNJ5 (I{sub}_K_C)</td>
<td>unknown</td>
<td>atrial fibrillation, no specific features</td>
</tr>
<tr>
<td>FAF-7</td>
<td>gene unknown (chr5q5)</td>
<td>unknown</td>
<td>prolonged AP wave.</td>
</tr>
</tbody>
</table>

SQT: Short QT syndrome; BrS: Brugada syndrome; CCD: Cardiac Conduction Disease; SSS: Sick Sinus Syndrome; CPVT: Catecholaminergic Polymorphic Ventricular Tachycardia; FAF: Familial Atrial Fibrillation.
associated conditions. Compound heterozygous mutations in \textit{SCN5A} gene have been described in five individuals between 2 years to 9 years with SSS.\textsuperscript{129} Schulze-Bahr et al. (2003) first reported a frameshift mutation (1631delC) in the pace-maker gene \textit{HCN4}, in a 66 yr old woman of idiopathic sick sinus syndrome (also see Table 2).\textsuperscript{130} One year later, Ueda et al. (2004) reported a missense D553N mutation in a 43-year-old woman who experienced first syncope at her 20 yrs followed by recurrent syncope at 34 yrs.\textsuperscript{131} Co-segregation of D553N with the phenotype being found in her family in two other affected individuals. These sporadic two cases were followed by two reports where the authors reported missense mutations (S672R and G480R) in the critical regions of \textit{HCN4} gene segregating in a large family with sinus bradycardia.\textsuperscript{132-133} The heart rate varied from 43 to 60 beats per minute in persons with the mutated gene in both families. Sporadic \textit{HCN4} mutation carriers had complex array of rhythm disturbances,\textsuperscript{130-131} which seems in contrast with the bradycardia as the only clinical abnormality in the familial patients.\textsuperscript{132-133} Additionally, sinus node dysfunction was also observed in combination with other cardiac arrhythmias, including LQTS, BrS, idiopathic ventricular fibrillation and PCCD.\textsuperscript{134}

Regarding therapy of SSS, pacemaker therapy may be appropriate in some cases, drug suppression of arrhythmias in others, and both strategies may be required in many individuals. Anticoagulation is critical for treatment of many individuals with SND, particularly those with paroxysmal or persistent atrial fibrillation. In general, pacemaker therapy is indicated and has proven to be highly effective in patients with SND when bradyarrhythmia has been demonstrated to account for symptoms.\textsuperscript{135}

**Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)**

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is an arrhythmogenic disorder of the heart characterized by a reproducible form of polymorphic ventricular tachycardia, inducible by physical activity, stress or catecholamine infusion, which can deteriorate into ventricular fibrillation. Patients present with recurrent syncope, seizures or sudden death following physical activity or emotional stress. CPVT can be inherited as an autosomal dominant or recessive trait. ECG parameters, including the QTc interval are generally normal or borderline prolonged, however sinus bradycardia is frequently observed. The hallmark of the disease comprises ventricular arrhythmias of varying morphology that do not exist under resting conditions but appear only upon physical exercise, excitement or catecholamine administration (Figure 5). These arrhythmias are first seen as ventricular premature complexes, later in bigeminy, followed by bidirectional or polymorphic ventricular tachycardia eventually leading to ventricular fibrillation. Clinical penetrance in this disease ranges from 25 to 100\%, with an average of 70 to 80\%. Syncope appears to be the first symptom in more than half of the patients. When untreated, the mortality to CPVT is high,
reaching 30-50% by the age of 30 years.
The gene locus corresponding for autosomal dominantly inherited CPVT(1) was initially mapped to chromosome 1q42-43, with eventual identification of missense mutations in the RYR2 gene in 50-60% of the patients (figure 1 and table 2).136-140 In a recent report 2% of SIDS cases have been linked to CPVT causing mutations in RYR2.141 Mutations in RYR2 are mostly missense mutations (only few are deletion of an amino acid), mutations are clustered in the N-terminal, Central and C-terminal domains of RYR2 (our observation).142 Genomic rearrangements (large deletions/insertions) or copy number variations in RYR2 has not been reported, so far. Clinical phenotypes of the RYR2 mutation carriers are solely adrenergic driven CPVT, a single report suggests that RYR2 mutation could also be causal to ARVD, which is still debated.137 To date, this is the only report of the co-occurrence of a second disease entity (ARVD) reported in conjunction with familial CPVT patients.137 Second variant of CPVT (2) is caused by homozygous or compound heterozygous null mutation in the CASQ2 gene.143-145 The cardiac ryanodine receptor (RYR2) and CASQ2 governs the release of Ca²⁺ from the sarcoplasmic reticulum, which initiates muscle contraction (Figure 1). Mutations in these genes lead to premature release of calcium from the intracellular stores, thereby causes increased cytosolic Ca²⁺ concentration, which causes arrhythmia. Delayed after depolarizations (DAD) is considered the dominant mechanism for arrhythmogenesis in CPVT.146

Mutations in RYR2 or CASQ2 do not comprise all the CPVT patients, still 50% of the CPVT patients go undetected without a genetic pathology, necessitating the identification of other variants of CPVTs and their pathophysiology. β-blockers without sympathomimetic activity are clinically effective in reducing syncope in CPVT patients, but implantation of an automatic internal defibrillator is occasionally needed in these patients. But, there remain still a small percentage of patients who are ill controlled with the present modalities of treatments.

**Atrial fibrillation**

Atrial fibrillation is a rhythm disorder characterized by chaotic electrical activity of cardiac atria and is the most common type of sustained cardiac arrhythmias. AF is a leading cause of cardiovascular morbidity, and stroke. Most cases of AF are seen in association with other cardiac or systemic conditions, but, 10% to 30% of patients were reported to have lone AF.147 Though, our basic understanding about the ionic and molecular mechanisms of AF is still at the initial stage, increased inward rectifier K⁺ current and altered Ca²⁺ handling are presently thought to be the pathophysiologic basis of AF.148 Gain of function mutations in KCNQ1, KCNE2, KCNE3 and KCNE5 has been reported in AF (table 2).149-152 Loss of function mutation (E375X) in KCNA5 gene has also been reported in a family with lone AF.
Mutations in cardiac gap-junction protein connexin 40 (\textit{GJA5}) have been found in 25% of patients of idiopathic atrial fibrillation.\textsuperscript{153} Among the total 4-reported \textit{GJA5} mutations, three are somatic, one is a germline mutation. The cardiac gap-junction protein connexin 40 (\textit{GJA5}) is expressed selectively in atrial myocytes and mediates the coordinated electrical activation of the atria. A recent report suggests that mutations in \textit{SCN5A} may predispose patients with or without underlying heart disease to AF accounting for 6% of the AF cases.\textsuperscript{155} AF can also present in 2% of patients with genetically proven LQTS, BrS and SQT, but the association of AF with genetically confirmed CPVT cases are not reported.\textsuperscript{156-158} Darbar et al. (2008) recently reported a novel AF locus on chromosome 5p15, where the causative gene remains to be identified (table 2).\textsuperscript{159} Mutations in \textit{SCN1B} and \textit{SCN2B} have also been recently reported in AF (Table 2).\textsuperscript{160}

\textbf{Overlap syndromes}

LQTS causing \textit{SCN5A} mutations are associated with gain-of-function defect of the encod-
ing Na\(^+\) channel, while BrS and ICCD causing mutations are typically associated with loss-of-function defects. Hence, two opposite functional pathophysiologies are responsible for LQT and BrS.

There are several reports of where LQTS and BrS were observed in patients due to single identical mutation in the \textit{SCN5A} gene. An insertion of an aspartic acid residue (1795insD) in the C-terminus of \textit{SCN5A} can result in BrS, LQTS and ICCD features in the same patients.\(^{34,161}\) Also conduction at all cardiac levels is hampered in these patients. The deletion of a lysine (K1500) was found to be associated with BrS, LQTS, and ICCD.\(^{162}\) A French study in several families with BrS or ICCD identified a missense mutation G1406R pathogenic to both phenotypes.\(^{35}\) E1784K mutation in \textit{SCN5A} was recently described in a family with LQT3, BrS and SND.\(^{36}\)

How can a single mutation cause both phenotypes in the same patient (and also in mice) with the opposite effect on the channel function? Electrophysiologic analysis, \textit{in vitro} and also with 1795insD transgenic mice provided an answer. Drastic reduction of peak sodium current (causing BrS phenotype), delayed time course of fast inactivation and small persistent sodium current pathogenic to LQT3 were observed in heterologous expression system and also in mice.\(^{161,163}\)

\begin{figure}
\centering
\includegraphics[width=\textwidth]{desmosomes}
\caption{Schematic representation of the molecular organization of cardiac desmosomes. Cardiac desmosomes are multiprotein structures in the cell membrane and consist of three protein families: (1) transmembrane proteins (cadherins): desmogleins (DSG-2) and desmocollins (DSC-2); (2) linker-(armadillo-repeat) proteins: plakoglobin (JUP) and plakophilin (PKP-2); and (3) plakins: desmoplakin (DSP). DSG-2 and DSC-2 comprise the transmembrane component of the desmosomal complex. Extracellular domains of the DSG2 and DSC2 interface directly with their counterparts on adjacent cells. The intracellular domains of the DSG2 and DSC2 interact with plakoglobin JUP and PKP-2. PKP2 and JUP bind to the N-terminal domain of DSP. The C-terminus of DSP anchors intermediate filaments, mainly desmin (figure modified and adapted from the review article of Sen-Chowdhry et al. J Am Coll Cardiol. 2007 ;50:1813-21).\(^{172}\)}
\end{figure}
V1516D mutation in ANK2 was reported both in LQT and BrS patients. Very recently Darbar et al. (2008) elaborated that BrS and/or LQT3 causing mutations could also cause lone AF (155). AV block, DCM, Right ventricular fibrosis and conduction delay, sinus node dysfunction) were also observed with mutations in LQT/Brugada causing SCN5A gene. Mutations in the CAV3 gene were originally described in the autosomal-dominant limb-Mutation in this gene also recently has been described in LQTS patients. Despite no phenotype overlap, diverse diseases are observed due to mutations in the same gene. This could be due to the fact that functional aberration due to mutation/s in CAV3, an adapter molecule for ion channel, could be mild to severe depending on the location of the mutation and could also be the fact that pathological consequences of certain mutations are organ specific. No phenotypic overlap or additional phenotype was reported in CPVT patients (excepting a report of ARVD association). Variability in clinical penetrance and sometimes with additional phenotypes due to identical cardiac ion channel mutations is likely to be modified, synergized (or attenuated) by environmental factors, gender and individual genetic back up. This individual variation in disease susceptibility could be due to SNPs located inside the pathogenic gene or could be located in a place far from the primary disease locus, and which might directly or indirectly be involved in the functional circuit of the pathogenetic gene. K897T is an otherwise harmless, frequently observed SNP in the KCNH2 gene, which was described to unmask the subclinical LQT2 phenotype in a patient who carried both A1116V mutation and the K897T SNP in the KCNH2 gene. Other family members who harboured the A1116V mutation (but not K897T) were devoid of any clinical symptoms. Though, in this study conclusion was drawn from the findings of a single symptomatic carrier, the approach of this study was quite novel. We recommend to perform similar study with more patients. Severity in clinical phenotype and longer QT intervals were also reported in patients who co-harboured a common SNP D85N in minK (encoded by KCNE1) along with the pathogenic LQT1 causing mutation in KCNQ1 gene. A block of 6-SNPs in the promoter region of SCN5A modulates the phenotypes in Brugada patients (Bezzina et al. 2006), being prevalent among the South Asians, and was shown to be associated with cardiac conduction disease prevalence/preponderance among South Asians. Another intragenic SNP H558R in SCN5A encoded Na_1.5 was also described as a modulator in BrS patients, where R558 carriers had attenuated BrS phenotype. Similar extensive studies (including replication studies) with both intragenic and extragenic SNP markers are required, which might answer about the interindividual variability, also ethnic variability in disease vulnerability and progression.
Diseases of Cardiac Desmosomes

Contractile function of the heart is dependent on the highly coordinated electrical and mechanical activation of the cardiac myocytes. Adherens junctions and desmosomes are responsible for mechanically coupling cardiac myocytes. Adherens junctions, consisting of classical N-cadherins, and its cytoplasmic binding partners, the catenins link the intercalated disc to the actin cytoskeleton intracellularly (Figure 6). In contrast to adherens junctions, desmosomes are not linked to the actin cytoskeleton; rather, they are associated with intermediate filaments, mainly desmin (Figure 6). Desmosomes are located in tissues that are exposed to frictional and shear stress, especially abundant in myocardium and in skin epidermis. Defects in components of cardiac desmosomes could compromise their functional properties leading to myocyte detachment and death. During the recent few years mutations in various cardiac desmosomal genes has been linked to Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) (Table 3). Desmosome impairment is believed to predispose to tissue damage under conditions of mechanical stress, leading to the disruption and subsequent degeneration of cardiomyocytes. ARVD/C is a familial disease characterized by progressive fibrofatty replacement of the right ventricular (RV) myocardium. The main histologic feature is progressive loss of right ventricular
myocardium, which becomes replaced with adipose and fibrous tissue. These changes may be localized and in early disease are often confined to the so-called “triangle of dysplasia”: the inflow, outflow, and apical regions of the right ventricle. Aneurysm formation is typical. Diffuse myocardial involvement leads to global right ventricular dilation. Fibrofatty substitution of the left ventricle is common in advanced disease; the posterolateral wall is preferentially affected, with relative sparing of the septum. Patchy inflammatory infiltrates may be present in areas of myocardial damage. Left ventricular (LV) involvement occurs with disease progression and was present on histology in >75% of cases in a multicenter pathological study. ARVD/C is a genetically heterogeneous disease, most commonly inherited in an autosomal-dominant fashion with incomplete penetrance and variable expression. The estimated prevalence of ARVD/C in the general population ranges from 1 in 2000 to 1 in 5000. The disease affects men more frequently than women, with an approximate ratio of 3:1.

The major clinical features of ARVD/C are different types of arrhythmias with a left branch block pattern pointing to a RV origin of the arrhythmias. The most important electrocardiographic abnormalities are T-wave inversion in the right precordial leads and the presence of late potentials in signal averaging ECG (Figure 7). The diagnosis of right ventricular cardiomyopathy is based on echocardiographic and angiographic documentation of localized or widespread structural and dynamic abnormalities involving mainly or exclusively the right ventricle, in the absence of valve disease, shunts, active myocarditis, and coronary disease. Endomyocardial biopsy is useful in the differential diagnosis.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Diseases causing gene (encoded protein)</th>
<th>Functional effect</th>
<th>Resting ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVD/C-1</td>
<td>TGFRI (TGFRI)</td>
<td>unknown</td>
<td>T-wave inversion in the right precordial leads and the presence of late potentials in signal averaging ECG, occasionally epsilon waves in the right precordial leads. Right precardial conduction delay, often low amplitude extremity leads.</td>
</tr>
<tr>
<td>ARVD/C-2</td>
<td>RYR2 (RYR2)</td>
<td>altered Ca²⁺ handling?</td>
<td></td>
</tr>
<tr>
<td>ARVD/C-3</td>
<td>gene unknown (chr 14q12-q22)</td>
<td>unknown</td>
<td></td>
</tr>
<tr>
<td>ARVD/C-4</td>
<td>gene unknown (chr 2q32.1-2q32.3)</td>
<td>unknown</td>
<td></td>
</tr>
<tr>
<td>ARVD/C-5</td>
<td>TMEM43 (TMEM43)</td>
<td>putative element for adipogenic transcription factor</td>
<td></td>
</tr>
<tr>
<td>ARVD/C-6</td>
<td>gene unknown (chr 19q13-p12)</td>
<td>unknown</td>
<td></td>
</tr>
<tr>
<td>ARVD/C-7</td>
<td>gene unknown (chr 18q22.3)</td>
<td>unknown</td>
<td></td>
</tr>
<tr>
<td>ARVD/C-8</td>
<td>DSP (Desmoplakin)</td>
<td>Adiposis, fatty cell infiltration, fibrosis in RV myocardium</td>
<td></td>
</tr>
<tr>
<td>ARVD/C-9</td>
<td>PKP2 (Plakophilin-2)</td>
<td>Adiposis, fatty cell infiltration, fibrosis in RV myocardium</td>
<td></td>
</tr>
<tr>
<td>ARVD/C-10</td>
<td>DSP2 (Desmoglein-2)</td>
<td>Adiposis, fatty cell infiltration, fibrosis in RV myocardium</td>
<td></td>
</tr>
<tr>
<td>ARVD/C-11</td>
<td>DSP2 (Desmocollin-2)</td>
<td>Adiposis, fatty cell infiltration, fibrosis in RV myocardium</td>
<td></td>
</tr>
<tr>
<td>ARVD/C-12</td>
<td>JUP (Plakoglobin-2)</td>
<td>Adiposis, fatty cell infiltration, fibrosis in RV myocardium</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Summary of genes and chromosomal loci (where genes are not known) for ARVD/C.
Clinical and Genetic Spectrum of Hereditary Cardiac Arrhythmia Syndromes

of ARVD/C is recommended on the diagnostic criteria of the Task Force of the European Society of Cardiology/International Society and Federation of Cardiology. The Task Force Criterias are mentioned in Table 4. Clinical diagnosis requires either: two major criteria; one major plus two minor criteria; or four minor criteria; in each case with criteria from different categories. A prolonged S-wave upstroke in V1 through V3 on ECG was also frequently found in ARVD/C patients in a study and were recommended as a diagnostic ECG marker.179

The majority of disease-causing mutations have so far been identified in genes encoding proteins of specialized adhesive junctions between cells also known as desmosomes. Mutations in genes encoding Plakophilin-2 (PKP2) and Desmoplakin (DSP) were reported in unrelated ARVD/C index patients.180-183 Recently, mutations in Desmoglein (DSG2) and Desmocollin-2 (DSC2) genes have been found in up to 12% and 5% respectively of ARVD/C patients in whom PKP2 and some other genes encoding desmosomal proteins were excluded.184-186

Among the non-desmosomal genes reported to be linked to ARVD/C, are the cardiac ryanodine receptor gene RYR2 and the TGF-B3.137,187 Role of RyR2 and TGF-B3 mutations in ARVD/C pathogenesis are still a debated issue, more studies are required to elucidate their role, if there is any, on ARVD/C pathogenesis. A very recent addition to this list of genes in ARVD/C pathogenesis, is TMEM43, mutation of which causes ARVD/C-5.188-189 TMEM43 is a putative response element for adipogenic transcription factor and mutation in TMEM43 caused lethal, fully penetrant, sex influenced morbid disorder.189 We lack datas about the

Table 4: Diagnostic criteria for Arrhythmogenic Right Ventricular Cardiomyopathy

<table>
<thead>
<tr>
<th>Diagnostic criteria for Arrhythmogenic Right Ventricular Cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global and/or Regional Dysfunction and Structural Alterations</strong></td>
</tr>
<tr>
<td><strong>Tissue Characterization of Walls</strong></td>
</tr>
<tr>
<td><strong>Regionalized Abnormalities</strong></td>
</tr>
<tr>
<td><strong>Depolarization Abnormalities</strong></td>
</tr>
<tr>
<td><strong>Arrhythmias</strong></td>
</tr>
<tr>
<td><strong>Family History</strong></td>
</tr>
<tr>
<td><strong>Major</strong></td>
</tr>
<tr>
<td>Severe dilation and reduction of RV EF with no (or only mild) LV involvement. Localized RV aneurysms. Severe segmental RV dilatation.</td>
</tr>
<tr>
<td>Fibrofatty replacement of myocardium or endomyocardial biopsy</td>
</tr>
<tr>
<td>Ejection fraction localized prolongation (&gt;100ms) of the QRS complex in right precordial leads.</td>
</tr>
<tr>
<td>Familial disease confirmed at necropsy or surgery.</td>
</tr>
<tr>
<td><strong>Minor</strong></td>
</tr>
<tr>
<td>Global RV dilatation and reduced EF with normal left ventricle. Regional right ventricular hypertrophy.</td>
</tr>
<tr>
<td>Inverted T waves in V2 and V3</td>
</tr>
<tr>
<td>Late potentials on SAECG</td>
</tr>
<tr>
<td>LBBB VT on ECG, Holter, exercise testing. Frequent ventricular extrasystoles (&gt;100/24 hours) (Holter).</td>
</tr>
<tr>
<td>Familial history of premature sudden death due to suspected ARVC. Familial history (clinical diagnosis based on present criteria).</td>
</tr>
</tbody>
</table>

RV indicates right ventricle; EF, ejection fraction; LV, left ventricle; SAECG, signal-averaged electrocardiogram; LBBB, left bundle branch block; VT, ventricular tachycardia; ECG, electrocardiogram; ARVC, Arrhythmogenic right ventricular cardiomyopathy

Table 4: Diagnostic criteria for Arrhythmogenic Right Ventricular Cardiomyopathy
predisposition of the various mutations in Dutch ARVD/C patients, their familial occurrence, disease penetrance etc.

In resuscitated and symptomatic (syncopal) patients an ICD is recommended. More difficult is the treatment of asymptomatic isolated patients or asymptomatic individuals from a symptomatic family. Risk stratification, including programmed electrical stimulation seem not very successful in ARVD/C. Whether all these patients need to be treated pharmacologically (e.g. with sotalolol) or with devices is unclear. Often the family history, mostly based on emotional arguments, leads the way.

References


Clinical and Genetic Spectrum of Hereditary Cardiac Arrhythmia Syndromes


96. Van Norstrand DW, Tester DJ, Ackerman MJ. Overrepresentation of the proarrhythmic, sudden death predisposing sodium channel polymorphism S1103Y in a population-
Clinical and Genetic Spectrum of Hereditary Cardiac Arrhythmia Syndromes


Clinical and Genetic Spectrum of Hereditary Cardiac Arrhythmia Syndromes


Aims and Outline

Cardiac arrhythmias are responsible for an estimated one million cases of syncope and sudden cardiac death (SCD) among Europeans and Americans each year (Priori SG et al. Task Force on Sudden Cardiac Death, European Society of Cardiology. Europace. 2002;4: 3-18). Arrhythmias due to genetic causes comprise a significant percentage in this population. This frequency is speculated to be even higher in some populations where consanguineous marriages are quite often. Mechanism of these familial or genetic arrhythmias are quite complex and we have just begun to understand the intricate and complex process of the mechanisms of arrhythmogenesis.

This project was subdivided in 14 different studies with the aim of identifying novel familial arrhythmias, the genes involved and the pathogenic mutation/s. In depth clinical analysis was performed in elaborating new variants of familial arrhythmias. Studies were also aimed at elucidating the pathophysiology of arrhythmogenesis due to genetic mutation/s. We have also aimed at discovering new modalities of treatment in drug resistant arrhythmia patients.

Chapter-1: This introductory chapter describes the basic known facts about the genetics and pathophysiology of various familial arrhythmias. Types and prevalence of presently known familial arrhythmias, phenotypes, and their clinical management has been described.

Chapter-2: We have identified two families from the northern part of the Netherlands, where 16-members suffered from clinical phenotypes of catecholaminergic polymorphic ventricular tachycardia (CPVT), combined with atrial fibrillation, atrial standstill and dilated cardiomyopathy. The observed clinical phenotypes are novel and familial. We have performed genome wide linkage analysis in this family. Eventually, we have identified the pathogenic genetic locus, gene and mutation in this family. We have discussed the functional consequence of the mutation. Additionally, we have also elaborated how the mutation evolved in these two unlinked families due to replication infidelity in chromosomes.

Chapter-3: In the second chapter we have elucidated a new variant of CPVT identified in a consanguineous family from Sudan. Clinical manifestation of arrhythmias appeared at early age and was often associated with sudden cardiac death. We have identified a new locus pathogenic to this fatal variant of CPVT, which we named CPVT-3, as previously two variants of CPVT (1 and 2) have been discovered and molecularly characterized. We have also investigated plausible candidate genes in the linked locus with the aim to explore the pathophysiology of this novel and fatal variant of CPVT-3.
Chapter 4-5: In the 3rd and 4th chapter, we have mentioned the development of a new screening method for effective diagnostic screening of the RyR2 gene in CPVT-1 patients. Mutation/s in this gene have been reported in ~50% of CPVT patients. With this newly developed method we have performed a pilot scanning study to identify the region of interest for effective screening of CPVT patients. CPVT cohorts (44 of Northern European descent, and 1 of Turkish origin) were included in this study. Findings in this study identified most mutation prone exons in the RYR2 gene, which are currently being used in patient care.

Chapter-6: Currently β-blocker is the first line of therapy in CPVT. But, there are instances where this therapy does not sufficiently protect the patient from fatal arrhythmias. We describe the remarkable long term efficacy of left stellate ganglion ablation in the drug resistant CPVT patients.

Chapter-7: We have identified a family from Saudi Arabia with a history of repeated early miscarriages and intrauterine fetal losses due to intrauterine persistent arrhythmias. We sought to identify the molecular mechanism of intrauterine arrhythmogenesis in this consanguineous family. Clinical, molecular and functional investigation was performed. By candidate gene mapping we have identified the gene and the pathogenic mutation causative to the fatal arrhythmias. We also characterized the biological and clinical consequences of the mutation.

Chapter-8: Clinical, molecular and functional investigations were performed in two consanguineous Arabian families with the history of sudden cardiac death of several children. By candidate gene mapping we have identified the gene and the mutation pathogenic to the fatal arrhythmias. We have functionally characterized the mutation. We have analysed and discussed their possible founder origin in the tribal community. We have also discussed the functional aspect of a novel molecular observation in restoring hearing phenotype in the affected children sparing the arrhythmia phenotype.

Chapter-9 to 10: This is an extension study mentioned in chapter 7 and 8. We have performed clinical and genetic analysis in 6 children probands and their family members from supposedly unrelated 6-Saudi Arabian families, who had unexplained complex arrhythmias with history of unexplained sudden cardiac deaths (SCD) of siblings or family members. In chapter-10, we have performed clinical and genetic analysis of two children with long QT syndrome, patients originated from the Kelantan province of Malaysia.

Chapter-11 to 14: Mutations in cardiac desmosomal genes have been recently reported in
relation to the pathogenicity of familial Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C).
We have recruited 116-ARVD/C and ARVD/C like (with some features of ARVD/C, not fulling the task force criteria) patients in the Netherlands to elucidate the molecular pathogenesis of ARVD/C in the Dutch population. We have screened the cardiac desmosomal genes in these cohorts. We have also performed genotype-phenotype analysis in the mutation carriers. In a similar study, we have identified and screened a Caucasian family from the USA, afflicted with ARVD/C. We have elucidated and discussed the inconsistent nature of the desmosomal gene mutations in disease penetrance and progression.

**In conclusion (chapter -15),** this study was aimed at isolating new variants of genetic arrhythmias, elucidating their pathophysiology in arrhythmogenesis and finding new modalities in drug resistant life threatening arrhythmia syndromes.