Sudden Cardiac Death and Genetic Ion Channelopathies

Long QT, Brugada, Short QT, Catecholaminergic Polymorphic Ventricular Tachycardia, and Idiopathic Ventricular Fibrillation

Carlo Napolitano, MD, PhD; Raffaella Bloise, MD; Nicola Monteforte, MD; Silvia G. Priori, MD, PhD

Sudden cardiac death is a common outcome of several cardiac disorders such as acute myocardial ischemia, myocardial infarction, and heart failure. However, ≈5% to 15% of cardiac arrest victims fail to show evidence of structural abnormalities at autopsy.1–3 In 1997, a panel of experts defined sudden death in the absence of an identifiable cause as idiopathic ventricular fibrillation (IVF): “IVF is the terminology that best acknowledges our current inability to identify a causal relationship between the clinical circumstance and the arrhythmia.”4 In the same article, the requirements for the diagnosis of IVF were identified on the basis of the clinical tools available at the time. In 1992, using the phenotypes observed in the IVF registry, we advanced the hypothesis that IVF could be the manifestation of concealed forms of arrhythmogenic disorders5 exacerbated by appropriate triggers. A few years later, the discovery of the genes of long-QT syndrome (LQTS)6–8 and the detection of incomplete penetrance9 supported this early hypothesis.

Incomplete penetrance and variable expressivity in inherited arrhythmogenic disorders imply that the distinctive ECG patterns that characterize these disorders may be concealed.10 Interestingly, however, the absence of the ECG markers of the disease is not an indicator of favorable outcome, as demonstrated by the evidence that the incidence of cardiac arrest in LQTS patients with normal QTc during the first 40 years of life is ≈4%, ie, 0.1%/y.11,12

In the last 15 years, the results of mutation screening in sudden unexplained death syndrome or sudden infant death syndrome, the so-called molecular autopsy, have been reported in several studies (Table 1).13–20 Although the yield of molecular autopsy reported by different studies is highly variable, ranging from 4% to 30%, it is sufficient to prove the concept that ion channel mutations may underlie IVF and that a positive genetic test may allow the extension of genotyping to family members of those affected to reduce additional deaths in the family.

Channelopathies Associated With Prolonged Repolarization

LQTS: Definition and Pathophysiology

LQTS is defined as an arrhythmogenic disorder in the structurally normal heart presenting with QT prolongation that is often associated with peculiar ST–T–wave morphology, syncope, and sudden death.10 Some genetic variants of the disease are associated with more complex phenotype, including extracardiac manifestations. LQTS forms with multiorgan involvement are the recessive Jervell and Lange Nielsen syndrome, characterized by QT prolongation and congenital deafness; the Andersen-Tawil syndrome, which manifests with QT prolongation associated with facial dysmorphisms and hypokalemic periodic paralysis; and the Timothy syndrome, which shows marked QT prolongation, syndactyly, paroxysmal hypoglycemia, atrioventricular block, congenital heart defects, developmental disorders/autism spectrum disorders, reduced immune response, and life-threatening arrhythmias (see Reference 10 for a review).

The number of genes known to cause LQTS has steadily increased (Table 2) over the last 15 years. However, even after extended screening, mutations in the first 3 genes identified in the early 1990s (KCNQ1, KCNH2, and SCN5A) still account for the vast majority (80%–90%) of patients. Thus, most of the recently identified genes are actually responsible for a small percentage of patients. Therefore, it is difficult to collect enough information to interpret the role of mutations identified in these minor genes.21

Interestingly, the genes associated with LQTS encode for either the macromolecular complex-forming ion channels (ie, α and β subunits) or their regulatory peptides. Mutations lead to QT interval prolongation either by impairing repolarizing currents (loss of function) or by increasing depolarizing currents (gain of function). Because different genes may participate in the same function, it turns out that multiple genetic variants may affect the same ionic current. For example, the potassium current IKs is reduced in patients who carry mutations in 3 genes: KCNQ1, KCNE1, and AKAP9, which encode the α subunit and the β subunit of the channel that conducts IKs and encodes for a regulatory protein involved in the adrenergic signaling that activates IKs (Table 2 and Figure 1).

Clinical Manifestations and Management

LQTS diagnosis should be considered in all patients presenting with QTc >440 milliseconds in male patients and...
Table 1. Molecular Autopsy in Idiopathic Ventricular Fibrillation

<table>
<thead>
<tr>
<th>Study Cohort</th>
<th>Cases, n</th>
<th>Autopsy/Toxicology Negative, n (%)</th>
<th>Genes Analyzed</th>
<th>Identified Mutations, n (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUDS (1–40 y), unselected</td>
<td>53</td>
<td>53 (100; autopsy and toxicology negative)</td>
<td>SCN5A</td>
<td>2 (2.1)</td>
<td>17</td>
</tr>
<tr>
<td>SUDS (&lt;20 y), consecutive, retrospective</td>
<td>270</td>
<td>270 (100; enrolling criteria)</td>
<td>KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2</td>
<td>2 (31 of autopsy negative)</td>
<td>14</td>
</tr>
<tr>
<td>SIDS (&lt;1 y), retrospective†</td>
<td>49</td>
<td>49 (100; enrolling criteria)</td>
<td>RyR2, selected exons</td>
<td>7 (14)</td>
<td>15</td>
</tr>
<tr>
<td>SIDS (&lt;1 y), consecutive, unselected</td>
<td>252</td>
<td>252 (55, 61 (24) borderline SIDS)</td>
<td>KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, target analysis of ANK2 (10 exons) and CACNA1C (exon 8)</td>
<td>10 (20)</td>
<td>16</td>
</tr>
<tr>
<td>SIDS (1–40 y), unselected</td>
<td>45</td>
<td>45 (252 SIDS, n = 93 (n = 48 possible SIDS))</td>
<td>SCN5A</td>
<td>2 (15 of autopsy and toxicology negative)</td>
<td>17</td>
</tr>
<tr>
<td>SIDS (&gt;45 y), consecutive, unselected</td>
<td>10 (42)</td>
<td>10 (42 (100; autopsy negative)</td>
<td>KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2</td>
<td>5 (11.9)</td>
<td>18</td>
</tr>
<tr>
<td>SIDS (1–40 y), unselected</td>
<td>14</td>
<td>14 (5)†</td>
<td>KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, target analysis of ANK2 (10 exons) and CACNA1C (exon 8)</td>
<td>10 (20)</td>
<td>16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variant</th>
<th>Gene</th>
<th>Protein</th>
<th>Effect of Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1</td>
<td>KvLQT1</td>
<td>Reduced I\textsubscript{K}</td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNH2</td>
<td>HERG</td>
<td>Reduced I\textsubscript{K}</td>
</tr>
<tr>
<td>LQT3</td>
<td>SCN5A</td>
<td>Nav1.5</td>
<td>Increased I\textsubscript{K}</td>
</tr>
<tr>
<td>LQT4</td>
<td>ANK2</td>
<td>Ankyrin B</td>
<td>Reduced membrane expression of Na\textsuperscript{+} and Ca\textsuperscript{2+} channels</td>
</tr>
<tr>
<td>LQT5</td>
<td>KCNE1</td>
<td>MinK</td>
<td>Reduced I\textsubscript{K}</td>
</tr>
<tr>
<td>LQT6</td>
<td>KCNE2</td>
<td>MI\textsubscript{RP}</td>
<td>Reduced I\textsubscript{K}</td>
</tr>
<tr>
<td>LQT7, Andersen syndrome</td>
<td>KCNJ2</td>
<td>Kir2.1</td>
<td>Reduced outward I\textsubscript{K}</td>
</tr>
<tr>
<td>LQT8, Timothy syndrome</td>
<td>CACNA1c</td>
<td>Cav1.2</td>
<td>Increased I\textsubscript{K}</td>
</tr>
<tr>
<td>LQT9</td>
<td>CAV3</td>
<td>Cardiac caveolin gene</td>
<td>Increased I\textsubscript{K} resulting from altered gating kinetic</td>
</tr>
<tr>
<td>LQT10</td>
<td>SCN4B</td>
<td>Sodium channel (\beta_4) subunit</td>
<td>Reduced subunit expression causing increased I\textsubscript{K}</td>
</tr>
<tr>
<td>LQT11</td>
<td>AKAP9</td>
<td>Yotiao</td>
<td>Impaired I\textsubscript{K} activation by catecholamines</td>
</tr>
<tr>
<td>LQT12</td>
<td>SNTA1</td>
<td>Syntrophin</td>
<td>Reduced Nav1.5 nitrosylation and increased current</td>
</tr>
<tr>
<td>LQT13</td>
<td>KCNJ5</td>
<td>Kir3.4/GIRK4</td>
<td>Reduced I\textsubscript{K} acetylcholine-dependent potassium current</td>
</tr>
</tbody>
</table>

>460 milliseconds in female patients. Except for the Timothy syndrome and rare SCN5A mutations, the presence of structural abnormalities and of acquired causes of QT prolongation should be excluded. Given the presence of incomplete penetrance and QT variability, exercise stress testing, Holter monitoring, and pharmacological challenge may be useful as diagnostic tests. Once diagnosis is established, \(\beta\)-blocker therapy is recommended. LQT1 patients respond very well to \(\beta\)-blockers; interestingly, lack of compliance is the most important cause of events occurring during antiadrenergic treatment in LQT1. Compared with LQT1 patients, LQT2 and LQT3 patients have a higher recurrence rate of arrhythmic events while on therapy. The implantation of an implantable cardioverter-defibrillator (ICD) may be considered on evidence of \(\beta\)-blocker failure and in selected high-risk individuals. Additionally, left cardiac sympathetic denervation may be an option to reduce the number of recurrences in highly symptomatic patients.

Genetic testing is useful to guide clinical management of mutation carriers in 1 of the 3 most common genes: KCNQ1, KCNH2, and SCN5A. Each of these genetic variants has a distinguishing morphology of the ST–T–wave complex, a typical trigger for arrhythmic events, and a variable response to \(\beta\)-blockers. QT interval duration is the most powerful risk factor (>500-millisecond QT threshold is considered a robust indicator of high-risk), but genotype information independently supports better clinical management. QTc is indeed modulated by genotype and sex; female patients with LQT2 and male patients with LQT3 with QTc >500 milliseconds are at highest risk of cardiac events between birth and 40 years of age in the absence of therapy. More recent evidence suggests that dissection of additional features of the mutation (such as its position and biophysical effects) might be associated with differential risk of cardiac events (Table 3).

Although genotype-phenotype correlations are useful, interindividual variability exists and must be taken into account in the assessment of any given patient or family. Incomplete penetrance and variable expressivity are indeed common in LQTS and may be explained by different causes: multiple...
mutations (compound or double heterozygosity), modulating coding single-nucleotide polymorphisms in the same gene (cis or trans) harboring the primary mutation, and different genetic combinations of subject-specific pools of single-nucleotide polymorphisms affecting the QT interval33,34 (Figure 2).

Overall, the integration of genotype information with clinical variables has produced improved risk stratification schemes. LQTS is the best example of successful genotype-supported clinical management. It is clear, however, that the identification of mutations in rare genetic variants (eg, LQT4 to LQT13) provides a marginal contribution to diagnosis and even less to risk stratification.21 We believe that this observation questions the need for screening all patients on all the

Figure 1. Cartoon illustrating the genes associated with inherited arrhythmogenic diseases grouped by ion channel/function. SR indicates sarcoplasmic reticulum; VT, ventricular tachycardia.

Table 3. Genotype-Phenotype Correlation in the Long-QT Syndrome

<table>
<thead>
<tr>
<th>ECG Pattern, Clinical Presentation</th>
<th>Risk Factors for Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>Broad T wave</td>
</tr>
<tr>
<td></td>
<td>Impaired QT adaptation during tachycardia</td>
</tr>
<tr>
<td></td>
<td>Incomplete penetrance (≈60%), especially at rest</td>
</tr>
<tr>
<td></td>
<td>High effectiveness of β-blockers</td>
</tr>
<tr>
<td>LQT2</td>
<td>Flat, notched T waves</td>
</tr>
<tr>
<td></td>
<td>Usually normal QT adaptation at fast rates</td>
</tr>
<tr>
<td></td>
<td>Reduced β-blocker effectiveness (vs LQT1)</td>
</tr>
<tr>
<td>LQT3</td>
<td>Straight ST segment, narrow T wave</td>
</tr>
<tr>
<td></td>
<td>Reduced β-blocker effectiveness (vs LQT1)</td>
</tr>
</tbody>
</table>

Figure 2. Risk stratification in long-QT syndrome (LQTS) including sex; QTc duration; LQT1, LQT2, and LQT3 genotype; and the NOS1AP genotype as a genetic modifier of the underlying main genetic defect.34
known genes, with the exception of specific malignant cases, and raises the possibility that, by limiting genetic testing to the better-characterized genes, we could reduce costs and decrease the percentage of mutations interpreted as being “variants of unknown significance.”

Pharmacological Therapy Based on Mechanisms

The evidence of incomplete effectiveness of β-blockers has stimulated the search for alternative therapeutic strategies. The so-called gene-specific therapies are centered on the idea that it is possible to counteract the biophysical effects of a mutation with the use of targeted drugs. Although bench work has suggested several plausible corrective approaches, only a few have become part of clinical management. Potassium supplements shorten QT interval by increasing the repolarizing potassium current \( I_{Kr} \) that is inversely regulated by the concentration of extracellular potassium. This approach has been proposed for LQT2, although it has the potential to shorten QT interval in all patients with at least 1 \( KCNH2 \) wild-type (functional) allele. Mexiletine was shown in cellular models of LQT3 to normalize action potential duration.\(^{35} \)

When tested in LQT3 patients, a shortening of QT interval was found in some of the mutation carriers. Of note, the effectiveness of mexiletine may be mutation specific\(^{36} \) and may even cause further QT prolongation.\(^{37} \) Thus, its use should be weighted and monitored very carefully.

Channelopathies Associated With Abbreviated Repolarization and Conduction Defects

As outlined in the previous section, LQTS is caused by a loss-of-function mutation in a channel that conducts a repolarizing current and a gain-of-function mutation in a channel that carries a depolarizing current. When the opposite effects occur, mutations cause completely different diseases such as Brugada syndrome (BrS), short-QT syndrome, early repolarization syndrome, sinus node dysfunction, and progressive conduction defects. Combinations of the above-mentioned phenotypes (eg, BrS plus conduction defect or BrS plus short QT interval) may also occur in the so-called overlap syndromes.\(^{10} \)

### BrS: Definition and Pathophysiology

BrS is characterized by ST-segment elevation with “coved” morphology in the right precordial leads and complete or incomplete right bundle-branch block. This ECG pattern is intermittent and may be unmasked by pharmacological challenge with sodium channel blockers such as procainamide, flecainide, ajmaline, or pilsicainide. The onset of ventricular arrhythmias causes the occurrence of syncope and may lead to sudden death, usually at rest. Known triggers for arrhythmic events are fever and the consumption of large meals; the latter has been related to glucose-induced insulin secretion that might enhance ST-segment elevation.\(^{38} \)

The electrophysiological mechanisms of BrS are still not completely known. It has been suggested that the arrhythmogenic substrate is due to the altered balance of inward and outward currents that is too much in favor of the latter in the early action potential phases (mainly during phase 1, loss of action potential dome), particularly in the epicardial layers. This “selective” action potential shortening increases transmural dispersion and favors reentry.\(^{39} \)

Ten different genes causally linked to BrS have been reported (Table 4). Loss-of-function mutations of \( SCN5A \) (BrS1), the gene encoding for the cardiac sodium channel, were the first to be identified, and this gene is currently the only BrS key gene.\(^{21} \) Reduced sodium current and a BrS phenotype can be also due to mutations in \( SCN5A \)-regulating genes: \( GPD1-L, SCN1B, \) and \( SCN3B \) (Table 4).\(^{40,41} \) Loss-of-
function mutations in the CACNA1c and CACNB2 genes encoding for the α and β subunits of the cardiac calcium channel can also cause BrS and may represent the second most frequent cause of the disease. Overall, no more than 30% of the genetic tests sent to genotyping facilities turn out positive for a disease-causing mutation.

Management and Role of Genetics
Management of BrS is based on the use of ICD in selected high-risk individuals. No drug has been definitely proven effective in reducing the cardiac arrest burden. It is therefore clear that risk assessment is a key issue in this condition to tailor the use of ICD therapy.

Recent data in large series of patients confirmed our initial observation that the disease is less aggressive than initially thought and showed an annual incidence of cardiac arrest between 1%/y and 2%/y (Figure 3). Of note, the event rate is time dependent with events peaking in the third to fourth decade of life (Figure 4). The presence of a spontaneous type 1 ECG (ie, no need for drug challenge to make the diagnosis) together with history of syncope consistently identifies subjects who warrant an ICD. Additional risk factors may be represented by QRS fragmentation and short ventricular refractory period, but this evidence awaits confirmation. Inducibility of ventricular tachycardia/ventricular fibrillation at programmed electric stimulation has been a matter of debate for several years, and the most recent large series and controlled studies dismiss its predictive role.

Genotype-phenotype correlation is scanty in BrS. It has been reported that SCN5A mutations are associated with a high incidence of conduction abnormalities and that those leading to truncated proteins might be more malignant; the carriers of CACNA1C mutations may have an abbreviated repolarization. At present however, there is no robust algorithm to link BrS genotype with either a specific phenotype or a distinctive risk profile. As a consequence, genetic testing cannot guide therapeutic decisions. We believe that, analogous to LQTS, the practice of unsupervised genetic screening of all known genes is a nontrivial pitfall. Indeed, adopting systematic screening of new genes before there is adequate knowledge to establish whether a mutation is truly causative for the disease may lead to the impossibility of using the results for clinical purposes. The appropriateness of this practice may require a reappraisal.

Pharmacological Therapy Based on Mechanisms
The experimental observation that agents that inhibit the transient outward current and I can restore the action potential dome in the epicardium and be antiarrhythmic by preventing the phase 2 reentry poses some rationale for the use of quinidine (a nonspecific I blocker) to treat BrS patients. Based on encouraging preliminary data, clinical trials are ongoing to test the value of quinidine to prevent sudden cardiac death in BrS (http://www.clinicaltrials.gov; identifier, NCT00789165). Several other pharmacological approaches have been proposed, but none has found clinical applicability so far.

Short-QT Syndrome
Short-QT syndrome is described as a disorder characterized by abbreviated QT interval, ventricular and atrial arrhythmias, and sudden cardiac death. There have been <70 short-QT syndrome cases reported worldwide, with the mean QTc value in the entire population of ~310 milliseconds (the upper limit set by the majority of groups is between 340 and 350 milliseconds). Symptomatic (sudden death or cardiac arrest) individuals, accounting for ~25% of the total, tend to present with shorter QTc (average, 300 milliseconds).

Mutations in 6 genes have been identified (Table 4 and Figure 1), but they account for only a few families each. The proportion of patients with short QT who are successfully genotyped is unknown, and no single gene accounts for >5% of cases. Therefore, the value of genetic testing in the syndrome is limited and does not bear prognostic implications. Data on a limited cohort of patients suggest that carriers of KCNH2 mutations may present with shorter QT interval. Risk stratification and management of short-QT syndrome are still ill defined. Analogous to other inherited channelopathies, it is likely that the severity of the ECG phenotype is related to prognosis (ie, the shorter the QT intervals, the higher the risk). Quinidine can normalize the QT interval, but its long-term efficacy is not proven. Therefore, an ICD is the only way to prevent sudden death.
Channelopathies Associated With Abnormal Calcium Handling

Catecholaminergic polymorphic ventricular tachycardia (CPVT) was described in the 1970s. Patients present unremarkable resting ECG and a peculiar pattern of ventricular arrhythmias (bidirectional or polymorphic ventricular tachycardia) reproducibly triggered by exercise or acute emotion. CPVT is characterized by a high incidence of cardiac events among untreated patients (79% in patients up to 40 years of age) and 30% incidence of sudden cardiac death.53,54

Investigations directed to disclose the molecular basis of CPVT led to the identification of mutations of 2 genes, the ryanodine receptor RyR255 and the cardiac calsequestrin CASQ2,56 which are associated with the autosomal dominant and recessive forms of CPVT, respectively (Table 4 and Figure 1). Both genes are involved in the control of calcium release from the sarcoplasmic reticulum (SR): RyR2 is the SR calcium-releasing channel, and CASQ2 is a calcium-buffering protein in the SR that may also exert a regulatory function of RyR2.

CPVT mutations lead to a loss of calcium release inhibition from the SR during diastole. As a consequence, when SR calcium content augments adrenergic activation, it drives a pathological increase in Ca\(^{2+}\) release (leak) that leads to delayed afterdepolarization and triggered activity.57

Approximately 60% of CPVT individuals carry an RyR2 mutation. Although no prognostic value is linked to specific RyR2 mutations, the value of genotyping resides in the importance of extending genetic screening to family members to identify and protect mutation carriers with antiadrenergic therapy because \(\beta\)-blockers are effective.

Pharmacological Therapy Based on Mechanisms

When a CPVT diagnosis is established, \(\beta\)-blockers should be administered. Although this approach affords protection in the majority of patients, \(\sim\)30% experience at least 1 arrhythmic event while on therapy.53,58,59 In these cases, an ICD may be indicated.

Watanabe et al\(^{60}\) recently showed that flecainide was able to suppress arrhythmias and triggered activity in a CPVT mouse model. This effect was explained by the ability of flecainide to directly modulate the ryanodine receptor. We recently performed additional investigations on the antiarrhythmic effect of flecainide\(^{61}\) in our RyR2-R4496C CPVT mouse model that support an alternative explanation. This study collected data suggesting that flecainide does not abolish delayed afterdepolarizations, ie, SR leak, but it prevents triggered activity because of its ability to block sodium current and to raise the threshold for action potential triggering by delayed afterdepolarizations (Figure 5). Despite these discordant results, data supporting the clinical value of flecainide are accumulating; therefore, the drug may be regarded as a reasonable adjunctive treatment of recurrences of arrhythmias while the patient is on \(\beta\)-blockers.

Concluding Remarks: Future Development

Thanks to the work of several groups, the community has witnessed a remarkable growth of the awareness of inherited arrhythmogenic disease. The role of these conditions as key determinants of juvenile sudden death is now largely recognized. Currently, there is a large gap between the clinically useful information that we may derive from genetic testing of the more prevalent variants and the scant insight provided by the screening of rare genetic forms that account for 1% to 5% of all cases. Accordingly, the prediction of clinical outcome based on the identification of rare DNA variants is difficult and may even be unrealistic if gathering an adequate number of patients to allow meaningful conclusions is proved to be impossible. Grouping patients under functionally homogeneous variants (eg, all patients with mutations producing a loss of sodium current) may represent a way to overcome this limitation. This approach should be flanked by high-throughput genotyping technology, providing comprehensive coverage of analyzed genes and identifying modifier single-nucleotide polymorphisms affecting outcome. The goal for the future is to fulfill the transition from a population-based management to personalized therapeutic strategies.

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References


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