In this review, the up-to-date understanding of the molecular basis of primary ventricular arrhythmias will be outlined. Two disorders have recently been well described at the molecular level, the long QT syndromes and Brugada syndrome, and in this paper we review the current scientific knowledge of each disease. Curr Opin Cardiol 2000, 15:12–22 © 2000 Lippincott Williams & Wilkins, Inc.

Abbreviations

ARVD arrhythmogenic right ventricular dysplasia
ECG electrocardiograph
JLNS Jervell and Lange-Nielsen syndrome
LQTS long QT syndrome
QT corrected QT interval
RBBB right bundle branch block
SUDS sudden and unexpected death syndrome
SUNDS sudden unexpected nocturnal death syndrome

Sudden cardiac death occurs in the United States with a reported incidence of greater than 300,000 persons per year [1••]. Although coronary heart disease is a major cause of death, other causes contribute to this problem. In many of these non–ischemia related cases, autopsies are unrevealing. Interest in identifying the underlying cause of the death in these instances has been focused on cases of unexpected arrhythmogenic death, which is estimated to represent 5% of all sudden deaths. In cases in which no structural heart disease can be identified, the long QT syndrome (LQTS), ventricular preexcitation, and idiopathic ventricular fibrillation or Brugada syndrome [2] (characterized by ST segment elevation in the right precordial leads with or without right bundle branch block [RBBB]) are most commonly considered as likely causes. The purpose of this paper is to describe the current understanding of the clinical and molecular genetic aspects of inherited diseases in which arrhythmias are prominent features, specifically LQTS and Brugada syndrome.

The long QT syndromes

Clinical description

The LQTSs are inherited or acquired disorders of repolarization identified by the electrocardiographic (ECG) abnormalities of prolongation of the QT interval corrected for heart rate (QTc) above 460 to 480 ms, relative bradycardia, T-wave abnormalities (Fig. 1), and episodic ventricular tachyarrhythmias [3], particularly torsades de pointes (Fig. 2). The inherited form of LQTS is transmitted as an autosomal dominant or autosomal recessive trait. Acquired LQTS may be seen as a complication of various drug therapies such as macrolide antibiotics (ie, erythromycin), antihistamines (ie, terfenadine), antiarrhythmia agents (ie, quinidine), tricyclic antidepressants, and antifungal agents (ie, ketoconazole). In addition, electrolyte abnormalities such as hypokalemia can result in LQTS. Whether the abnormality is genetically based or acquired, the clinical presentation is similar. In many cases, the initial presentation is syncope, whereas in other instances, recurrent seizures may trigger an evaluation that includes an ECG, leading to the diagnosis. Tragically, some individuals have sudden death as their initial presenting feature and this has been reported to occur in families in some cases.

Clinical genetics

Two differently inherited forms of familial LQTS have been reported. The Romano-Ward syndrome is the most...
common of the inherited forms of LQTS and appears to be transmitted as an autosomal dominant trait [4,5]. In this disorder, the disease gene is transmitted to 50% of the offspring of an affected individual. However, low penetrance has been described and therefore gene carriers may, in fact, have no clinical features of disease [6••]. Individuals with Romano-Ward syndrome have the pure syndrome of prolonged QT interval on ECG with the associated symptom complex of syncope, sudden death, and in some patients, seizures [7,8]. Occasionally, other noncardiac abnormalities such as diabetes mellitus [9,10], asthma [11], or syndactyly [12] may be associated with QT prolongation. LQTS may also be involved in some cases of sudden infant death syndrome [13,14••,15].

The Jervell and Lange-Nielsen Syndrome (JLNS) is a relatively uncommon inherited form of LQTS. Classically, this disease has been described as having apparent autosomal recessive transmission [16,17]. These patients have a clinical presentation identical to those with Romano-Ward syndrome but also have associated sensorineural deafness [16–18]. Clinically, patients

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**Figure 1. Torsades de pointes in long QT syndrome**

Electrocardiograms demonstrating prolonged QT intervals and onset of torsades de pointes in inherited long QT syndrome (LQTS). This rhythm abnormality is responsible for the clinical features of LQTS.

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**Figure 2. Ideograms of chromosome 11, 7, 3, 4, and 21**

Approximate locations of LQT1 (KVLQT1), LQT2 (HERG), LQT3 (SCN5A), LQT4, and LQT5 (minK), respectively. LQT6 (MiRP1) is located at the same chromosomal position as LQT5.
with JLNS usually have longer QT intervals as compared with individuals with Romano-Ward syndrome and in these patients the disease also has a more malignant course. Recently, Priori et al. [19] reported autosomal recessive cases of Romano-Ward syndrome, thus changing one of the sine qua non conditions of JLNS.

Gene mapping in Romano-Ward syndrome

The first gene for autosomal dominant LQTS was mapped by Keating et al. [20] to chromosome 11p15.5 (LQT1) using genome-wide linkage analysis in a large Utah family. Soon afterwards, Keating et al. [21] reported consistent linkage of several other LQTS families to chromosome 11p15.5. However, LQTS locus heterogeneity was subsequently reported by Towbin et al. [22] and others [23–25] and confirmed by the mapping of the second LQTS locus to chromosome 7q35-36 (LQT2) and the third LQTS locus to chromosome 3p21-24 (LQT3) [26]. Schott et al. [27] mapped the fourth LQTS locus to chromosome 4q25-27 (LQT4), and a fifth gene (minK) located on chromosome 21q22 was shown to be LQT5 (Fig. 3). More recently, a sixth gene, the minK-related peptide 1 (MiRP1), localized to 21q22 as well, was identified [30••]. In several other families with autosomal dominant LQTS the condition is not linked to any known LQTS loci, indicating the existence of additional LQTS-causing genes.

Gene identification in Romano-Ward syndrome

KVLQT1 or KCNQ1: the LQT1 gene

The first of the genes mapped for LQTS, termed LQT1, required 5 years from the time that mapping to chromosome 11p15.5 was first reported to gene cloning. This gene, originally named KVLQT1, but more recently called KCNQ1, is a novel potassium channel gene that consists of 16 exons, spans approximately 400 kb, and is widely expressed in human tissues including heart, inner ear, kidney, lung, placenta, and pancreas, but not in skeletal muscle, liver, or brain [31]. In the original report, 11 different mutations (deletion and missense mutations) were identified in 16 LQTS families, establishing KVLQT1 as LQT1. To date, more than 100 families with KVLQT1 mutations have been described. Although most of the mutations are “private” (i.e., only seen in one family), there is at least one frequently mutated region (called a “hot spot”) of KVLQT1 [31–33].

Analysis of the predicted amino acid sequence of KVLQT1 suggests that it encodes a potassium channel α-subunit with a conserved potassium-selective pore-signature sequence flanked by six membrane-spanning segments similar to shaker-type channels (Fig. 4). A putative voltage sensor is found in the fourth membrane-spanning domain (S4) and the selective pore loop is between the fifth and sixth membrane-spanning domains (S5,S6). Biophysical characterization of the KVLQT1 protein confirmed that KVLQT1 is a voltage-gated potassium channel protein subunit that requires coassembly with a β-subunit called minK to function properly (Fig. 4) [28,29]. Expression of either KVLQT1 or minK alone results in inefficient (or no) current development. When minK and KVLQT1 are coexpressed in either mammalian cell lines or Xenopus oocytes, however, the slowly activating potassium current (IKs) is developed in cardiac myocytes [28,29]. Combination of normal and mutant KVLQT1 subunits forms abnormal IKs channels and these mutations are believed to act through a dominant-negative mechanism (the mutant form of KVLQT1 interferes with the function of the normal wild-type form through a “poison pill”-type mechanism) or a
loss-of-function mechanism (only the mutant form loses activity) [34].

Because KVLQT1 and minK form a unit, mutations in minK could also be expected to cause LQTS, and this fact was subsequently demonstrated (see “minK: the LQT5 gene”) [35].

HERG: the LQT2 gene

After the initial localization of LQT2 to chromosome 7q35-36 by Jiang et al. [26], candidate genes (i.e., genes encoding proteins that could cause repolarization abnormalities if mutated, such as ion channels, modulators of ion channels, members of the sympathetic nervous system) in this region were analyzed. HERG (human ether-a-go-go-related gene), a cardiac potassium channel gene that was originally cloned from a brain cDNA library [36] and found to be expressed in neural crest-derived neurons [37], microglia [38], a wide variety of tumor cell lines [39], and the heart [40], was one of the candidates evaluated and found to be mutated in patients with clinical evidence of LQTS [40]. Six LQTS-associated mutations were identified in HERG, including missense mutations, intragenic deletions, and a splicing mutation. Later, Schulze-Bahr et al. [41] reported a single-basepair deletion and a stop codon mutation in HERG, confirming this to be LQT2. Currently, this gene is thought to be the second most common gene mutated in LQTS (second to KVLQT1). As with KVLQT1, “private” mutations that are scattered throughout the entire gene without clustering preferentially are seen.

The HERG gene consists of 16 exons and spans 55 kb of genomic sequence [40]. The predicted topology of HERG is shown in Figure 5 and is similar to KVLQT1. Unlike KVLQT1, HERG has extensive intracellular amino- and carboxyl-termini, with a region in the carboxyl-terminal domain having sequence similarity to nucleotide binding domains.

Electrophysiologic and biophysical characterization of expressed HERG in Xenopus oocytes established that HERG encodes the rapidly activating delayed-rectifier potassium current IKr [42,43]. Electrophysiologic studies of LQTS-associated mutations showed that they act through either a loss-of-function or a dominant-negative mechanism [44]. In addition, protein trafficking abnormalities have been shown to occur [45,46]. This channel has been shown to coassemble with β-subunits for normal function, similar to that seen in Iks. McDonald et al. [47] initially suggested that the complexing of HERG with minK is needed to regulate the Ikr potassium current. Bianchi et al. [48] provided confirmatory evidence that minK is involved in regulation of both Iks and Ikr. Recently, Abbott et al. [30••] identified MiRP1 as a β-subunit for HERG (see “MiRP1: the LQT6 gene”).

SCN5A: the LQT3 gene

The positional candidate gene approach was also used to establish that the gene responsible for chromosome 3–linked LQTS (LQT3) is the cardiac sodium channel gene SCN5A [49,50]. SCN5A is highly expressed in human myocardium, but not in skeletal muscle, liver, or uterus [51,52]. Recently, it has been found to be expressed in brain [53]. It consists of 28 exons that span 80 kb and encodes a protein of 2016 amino acids with a putative structure that consists of four homologous domains (DI to DIV), each of which contains six membrane-spanning cysteines.

**Figure 5. The molecular architecture of the cardiac INa sodium channel encoded by SCN5A**

Four mutations are shown.
segments (S1 to S6) similar to the structure of the potassium channel α-subunits (Fig. 6) [41–43]. Linkage studies with LQT3 families and SCN5A initially demonstrated linkage to the LQT3 locus on chromosome 3p21-24 [51,52] and three mutations, one 9-basepair intragenic deletion (DK1505_P1506_Q1507), and two missense mutations (R1644H and N1325S), were also identified in six LQTS families [51,52]. All three mutations were expressed in Xenopus oocytes and it was found that all mutations generated a late phase of inactivation-resistant, mexiletine- and tetrodotoxin-sensitive whole-cell currents through multiple mechanisms [54,55]. Two of the three mutations showed dispersed reopening after the initial transient, but the other mutation showed both dispersed reopening and long-lasting bursts [55]. These results suggested that SCN5A mutations act through a gain-of-function mechanism (the mutant channel functions normally, but with altered properties such as delayed inactivation) and that the mechanism of chromosome 3–linked LQTS is persistent noninactivated sodium current in the plateau phase of the action potential. Later, An et al. [56] showed that not all mutations in SCN5A are associated with persistent current and demonstrated that SCN5A interacted with β-subunits. Furthermore, mutations in SCN5A have been shown to result in widely different clinical phenotypes. Novel mutations in SCN5A were identified by our laboratory in patients with Brugada syndrome and idiopathic ventricular fibrillation [57••], disorders with normal QTc, but ST segment elevation in the right precordial leads. Electrophysiologically, these mutations result in more rapid recovery from inactivation of the mutant channels or loss of function, causing the Brugada syndrome–type phenotype.

minK: the LQT5 gene

The minK (lsK or KCNE1) gene was initially localized to chromosome 21 (21q22.1) and found to consist of three exons that span approximately 40 kb. It encodes a short protein consisting of 130 amino acids and has only one transmembrane-spanning segment with small extracellular and intercellular regions [34,35,58]. When expressed in Xenopus oocytes, it produces potassium current that closely resembles the slowly activating delayed-rectifier potassium current I_{Ks} in cardiac cells [58,59]. The fact that the minK clone was expressed only in Xenopus oocytes and not in mammalian cell lines raised the question whether minK is a human channel protein. With the cloning of KVLQT1 and coexpression of KVLQT1 and minK in both mammalian cell lines and Xenopus oocytes, it became clear that KVLQT1 interacts with minK to form the cardiac slowly activating delayed-rectifier potassium current I_{Ks} in cardiac cells [58,59]. The fact that the minK clone was expressed only in Xenopus oocytes and not in mammalian cell lines raised the question whether minK is a human channel protein. With the cloning of KVLQT1 and coexpression of KVLQT1 and minK in both mammalian cell lines and Xenopus oocytes, it became clear that KVLQT1 interacts with minK to form the cardiac slowly activating delayed-rectifier potassium current I_{Ks} in cardiac cells [58,59]. The fact that the minK clone was expressed only in Xenopus oocytes and not in mammalian cell lines raised the question whether minK is a human channel protein. With the cloning of KVLQT1 and coexpression of KVLQT1 and minK in both mammalian cell lines and Xenopus oocytes, it became clear that KVLQT1 interacts with minK to form the cardiac slowly activating delayed-rectifier potassium current I_{Ks} in cardiac cells [58,59]. The fact that the minK clone was expressed only in Xenopus oocytes and not in mammalian cell lines raised the question whether minK is a human channel protein.
defective LQTS was also created [60]. The functional consequences of these mutations include delayed cardiac repolarization and, hence, an increased risk of arrhythmias.

**MiRP1: the LQT6 gene**

The *MiRP1* gene (the *minK*-related peptide 1 or *KCNE2* gene) is a novel potassium channel gene recently cloned and characterized by Abbott et al. [30••]. This small integral membrane subunit protein assembles with *HERG (LQT2)* to alter its function and enable full development of the *I_K_1* current (Fig. 4). *MiRP1* is a 123-amino-acid channel protein with a single predicted transmembrane segment similar to that described for *minK* [58]. Chromosomal localization studies mapped this *KCNE2* gene to chromosome 21q22.1, within 79 kb of *KCNE1 (minK)* and arrayed in opposite orientation [30••]. The open reading frames of these two genes share 34% identity and both are contained in a single exon, suggesting that they are related through gene duplication and divergent evolution.

Three missense mutations associated with LQTS and ventricular fibrillation were identified in *KCNE2* by Abbott et al. [30••], and biophysical analysis demonstrated that these mutants form channels that open slowly and close rapidly, thus diminishing potassium currents. In one case, the missense mutation, a C-to-G transversion at nucleotide 25 that produced a glutamine (Q) to glutamic acid (E) substitution at codon 9 (Q9E) in the putative extracellular domain of *MiRP1*, led to the development of torsades de pointes and ventricular fibrillation after intravenous clarithromycin infusion (ie, drug induced).

Therefore, like *minK*, this channel protein acts as a β-subunit but, by itself, leads to risk of ventricular arrhythmia when mutated. These similar channel proteins (ie, *minK* and *MiRP1*) suggest that a family of channels exist that regulate ion channel α-subunits. The specific role of this subunit and its stoichiometry remain unclear and are currently being hotly debated.

**Genetics and physiology of autosomal recessive long QT syndrome (Jervell and Lange-Nielsen syndrome)**

Neyroud et al. [61] reported the first molecular abnormality in patients with JLNS when they reported on two families in which three children were affected by JLNS and in whom a novel homozygous deletion-insertion mutation of *KVLQT1* in three patients was found. A deletion of 7 bp and an insertion of 8 bp at the same location led to premature termination at the C-terminal end of the *KVLQT1* channel. At the same time, Splawski et al. [62] identified a homozygous insertion of a single nucleotide that caused a frameshift in the coding sequence after the second putative transmembrane domain (S2) of *KVLQT1*. Together, these data strongly suggested that at least one form of JLNS is caused by homozygous mutations in *KVLQT1*. This has been confirmed by others [34,63••,64].

As a general rule, heterozygous mutations in *KVLQT1* cause Romano-Ward syndrome (LQTS only), whereas homozygous (or compound heterozygous) mutations in *KVLQT1* cause JLNS (LQTS and deafness). The hypothetical explanation suggests that although heterozygous *KVLQT1* mutations act by a dominant-negative mechanism, some functional *KVLQT1* potassium channels still exist in the stria vascularis of the inner ear. Therefore congenital deafness is averted in patients with heterozygous *KVLQT1* mutations. For patients with homozygous *KVLQT1* mutations, no functional *KVLQT1* potassium channels can be formed. It has been shown by in situ hybridization that *KVLQT1* is expressed in the inner ear [61], suggesting that homozygous *KVLQT1* mutations can cause the dysfunction of potassium secretion in the inner ear and lead to deafness. However, it should be noted that incomplete penetrance exists and not all heterozygous or homozygous mutations follow this rule [7,19].

As with Romano-Ward syndrome, if *KVLQT1* mutations can cause the phenotype, it could be expected that *minK* mutations could also be causative of the phenotype (JLNS). Schulze-Bahr et al. [65], in fact, showed that mutations in *minK* result in JLNS syndrome as well, and this was confirmed subsequently [62]. Hence, abnormal *I_K_s* current, whether it occurs due to homozygous or compound heterozygous mutations in *KVLQT1* or *minK*, results in LQTS and deafness.

**Genotype-phenotype correlations**

Moss et al. [66] showed several years ago that the ECG manifestations of LQTS were in great part determined by the channel mutated. Different T-wave patterns were clearly evident when comparing tracings from patients with mutations in *LQT1*, *LQT2*, and *LQT3*. More recently, Zareba et al. [67] showed that the mutated gene may result in a specific clinical phenotype with different triggers and may predict outcome. For instance, these authors suggested that mutations in *LQT1* and *LQT2* result in early symptoms (ie, syncope) but the risk of sudden death was relatively low for any event. In contrast, mutations in *LQT3* resulted in a paucity of symptoms but when symptoms occurred they were associated with a high likelihood of sudden death. In addition, mutations in *LQT1* and *LQT2* appeared to be associated with stress-induced symptoms, including response to auditory triggers (ie, alarm clock). *LQT3*, on the other hand, appeared to be associated with sleep-associated symptoms. Coupled with the findings by Moss et al. [66], it could be suggested that understand-
ing the underlying cause of LQTS in any individual could be used to improve survival.

**Genetic testing**

As described, six LQTS-causing genes have been identified and more than 100 mutations have been described to date. This genetic heterogeneity makes genetic testing more difficult than if a single gene were responsible for the disease. In large families in which linkage analysis may be performed, identification of the gene of interest (if the linkage is to one of the known genes) can be accomplished relatively rapidly and screening of mutations undertaken. Once a mutation is identified in one affected family member (usually the proband), focused screening of the remaining family members for this mutation can be undertaken. In small families or sporadic cases, analysis is much more difficult because mutation screening for all known genes must be initiated. In our laboratory, KVLQTI (LQTI) mutations are screened initially because this appears to be the most common disease-causing gene [68]. If no mutation is uncovered in KVLQTI, HERG (the next most common gene mutated) is screened before SCN5A, KCNE1, and KCNE2 [30••,33,51,69]. If no mutation is found in any of these genes, however, it cannot be concluded that the individual does not have LQTS because other disease-causing genes remain to be discovered.

Other causes of sudden cardiac death in individuals with structurally normal hearts have been studied as well [70–72]. In many instances, the underlying cause is never identified. However, one cause of syncope and sudden death, the Brugada syndrome, has recently been intensively studied [2].

**Brugada syndrome**

**Clinical aspects**

The first identification of the ECG pattern of RBBB with ST elevation in leads V1 to V3 was reported by Osher and Wolff [73]. Shortly thereafter, Edeiken [74] identified persistent ST elevation without RBBB in 10 asymptomatic men, and Levine et al. [75] described ST elevation in the right-sided chest leads and conduction block in the right ventricle in patients with severe hyperkalemia. The first association of this ECG pattern with sudden death was described by Martini et al. [76] and later by Aihara et al. [77]. This association was further confirmed in 1991 by Brugada and Brugada [78], who described four patients with sudden and aborted sudden death with ECGs demonstrating RBBB and persistent ST elevation in leads V1 to V3. In 1992, these authors characterized what they believed to be a distinct clinical and ECG syndrome [2].

The finding of ST elevation in the right-sided chest leads has been observed in a variety of clinical and experimental settings and is not unique or diagnostic of Brugada syndrome by itself. Situations in which these ECG findings occur include electrolyte or metabolic disorders, pulmonary or inflammatory diseases, and abnormalities of the central or peripheral nervous system. In the absence of these abnormalities, the term idiopathic ST elevation is often used and may identify Brugada syndrome patients.

The ECG findings and associated sudden and unexpected death have been reported as common problems in Japan and Southeast Asia, where the syndrome most commonly affects men during sleep [79]. This disorder, known as sudden and unexpected death syndrome (SUDS) or sudden unexpected nocturnal death syndrome (SUND), has many names in Southeast Asia, including hangungut (to rise and moan in sleep) in the Philippines; non-laïtai (sleep-death) in Laos; laï-tai (died during sleep in Thailand); and pokkuri (sudden and unexpectedly ceased phenomenon) in Japan. Generally, SUDS victims are young, healthy men in whom death occurs suddenly with a groan, usually during sleep late at night. No precipitating factors are identified and autopsy findings are generally negative [80]. Life-threatening ventricular tachyarrhythmias as a primary cause of SUDS have been demonstrated, with ventricular fibrillation occurring in most cases [81].

**Brugada syndrome and arrhythmogenic right ventricular dysplasia**

Controversy exists concerning the possible association of Brugada syndrome and arrhythmogenic right ventricular dysplasia (ARVD), with some investigators arguing that these are the same disorder or that at least one is a forme fruste of the other [82–87]. However, the classic echocardiographic, angiographic, and magnetic resonance imaging findings of ARVD are not seen in Brugada syndrome patients. In addition, Brugada syndrome patients typically are without the histopathologic findings of ARVD. Further, the morphology of ventricular tachycardia/ventricular fibrillation differs [88].

**Clinical genetics**

Like ARVD, most of the families thus far identified with Brugada syndrome apparently have autosomal dominant inheritance [84,88,89,90••]. In these families, approximately 50% of offspring of affected patients develop the disease. Although the number of families reported has been small, it is likely that this is due to underrecognition as well as premature and unexpected death [90••,91].

**Molecular genetics**

In animal studies, blockade of the calcium-independent 4-aminopyridine-sensitive transient outward potassium current (Ito) results in surface ECG findings of elevated, downsloping ST segments [91,92] due to greater abbrevi-
ation in the epicardial action potential compared with the endocardium (which lacks a plateau phase) [93]. Loss of the action potential plateau (or dome) in the epicardium but not endocardium would be expected to cause ST segment elevation and, because loss of the dome is caused by an outward shift in the balance of currents active at the end of phase 1 of the action potential (principally \( I_{\text{Ca}} \) and \( I_{\text{Kt}} \)), autonomic neurotransmitters such as acetylcholine facilitate loss of the action potential dome by suppressing calcium current and augmenting potassium current, whereas \( \beta \)-adrenergic agonists (ie, isoproterenol, dobutamine) restore the dome by augmenting \( I_{\text{Ca}} \) [94–96]. Sodium channel blockers also facilitate loss of the canine right ventricular action potential dome as a result of a negative shift in the voltage at which phase 1 begins [97,98]. Based on this information, candidate genes \((I_{\text{to}}, I_{\text{Ca}}, \text{and } I_{\text{Na}})\) could be selected for study.

In 1998, our laboratory reported the findings on six families and several sporadic cases of Brugada syndrome [57••]. The families were initially studied by linkage analysis using markers to the known ARVD loci and linkage was excluded. Candidate gene screening using the mutation analysis approach of single-strand conformation polymorphism analysis and DNA sequencing was performed and \( SCN5A \) was chosen for study, based on the suggestions of Gussak and Antzelevitch [90••], Antzelevitch [91], Lukas and Antzelevitch [93], Antzelevitch et al. [94], Litovsky and Antzelevitch [95], Antzelevitch [96], and Krishnan and Antzelevitch [97,98]. In three families, mutations in \( SCN5A \) were identified [57••] including a missense mutation (G-to-T base substitution) causing a substitution of a highly conserved threonine by methionine at codon 1620 (T1620M) in the extracellular loop between transmembrane segments S3 and S4 of domain IV (DIV3 to DIV4), an area important for coupling of channel activation to fast inactivation; a two-nucleotide insertion (AA) that disrupts the splice-donor sequence of intron 7 of \( SCN5A \); and a single-nucleotide deletion (A) at codon 1397 that results in an inframe stop codon that eliminates DIIS6, DIVS1 to DIVS6, and the carboxyterminus of \( SCN5A \) (Fig. 6).

Biophysical analysis of the mutants in \( Xenopus \) oocytes demonstrated a reduction in the number of functional sodium channels in both the splicing mutation and one-nucleotide deletion mutation, which should promote development of reentrant arrhythmias. In the missense mutation, sodium channels recover from inactivation more rapidly than normal. In this case, the presence of both normal and mutant channels in the same tissue would promote heterogeneity of the refractory period, a well-established mechanism of arrhythmogenesis. Inhibition of the sodium channel \( I_{\text{Na}} \) current causes heterogeneous loss of the action potential dome in the right ventricular epicardium, leading to a marked dispersion of depolarization and refractoriness, an ideal substrate for development of reentrant arrhythmias. Phase 2 reentry produced by the same substrate is believed to provide the premature beat necessary for initiation of the ventricular tachycardia and ventricular fibrillation responsible for symptoms in these patients. Interestingly, however, Kambouris et al. [99] identified a mutation in essentially the same region of \( SCN5A \) as the T1620M mutation (R1623H), but the clinical and biophysical features of this mutation were found to be consistent with LQT3 and not Brugada syndrome. Hence, there clearly remains a gap in our understanding of these entities.

### Conclusions

Ion channel abnormalities result in cardiac arrhythmias that define LQTS and Brugada syndrome. This consistent type of protein alteration causing ventricular arrhythmias supports our concept of a “final common pathway” of cardiovascular disease [100,101••]. In this instance, it appears that ion channelopathies result in ventricular arrhythmias. A similar view of other cardiac disorders can also be considered. For instance, alterations in sarcomeric proteins have been shown to result in hypertrophic cardiomyopathy whereas altered cytoskeletal proteins have been shown to cause dilated cardiomyopathy. It is possible that definition of these “common pathways” can lead to a better understanding of a variety of diseases, as it has for LQTS and Brugada syndrome, and can ultimately lead to better therapies and improved longevity.

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**Table 1. Diagnostic criteria long QT syndrome**

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<tr>
<th>Clinical finding</th>
<th>Points</th>
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<tr>
<td>ECG Finding</td>
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<td>QT, ( t )</td>
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<tr>
<td>&gt; 480 ms(^{1/2})</td>
<td>3</td>
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<td>460–470 ms(^{1/2})</td>
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<tr>
<td>Torsades de pointes(^{3} )</td>
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<td>T-wave alternans</td>
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<td>Notched T wave in 3 leads</td>
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<td>Family history(^{11} )</td>
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<tr>
<td>Family members with definite LQTS(^{9} )</td>
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<tr>
<td>Unexplained sudden cardiac death ( &lt; 30 ) among immediate family members</td>
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*Scoring: < 1 point = low probability of LQTS; 2–3 points = immediate probability of LQTS; > 4 points = high probability of LQTS. In the absence of medications or disorders known to affect these ECG features, \( QT_{\text{c}} \), calculated by Bazett’s formula, where \( QT_{\text{c}} = QT\sqrt{RR} \), is preferred. **Resting heart rate \( < \) the second percentile for age. \(^{1} \)The same family member cannot be counted twice. \(^{3} \)Definite LQTS is defined by an LQTS score \( > 4 \). ECG, electrocardiographic; LQTS, long QT syndrome; \( QT_{\text{c}} \), QT interval corrected for heart rate. From Schwartz et al. [3]."
References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
**Of outstanding interest


Arrhythmias


Recent update of the electrophysiology at play in Brugada syndrome.


Description of the “final common pathway” hypothesis.