Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 36, No. 1, 2000
ISSN 0735-1097/00/$20.00
PII S0735-1097(00)00716-6

REVIEW ARTICLES

The Long QT Syndromes: Genetic Basis and Clinical Implications

Chern-En Chiang, MD, PHD,* Dan M. Roden, MD, FACC†
Taipei, Taiwan and Nashville, Tennessee

It is becoming clear that mutations in the KVLQT1, human "ether-a-go-go" related gene, cardiac voltage-dependent sodium channel gene, minK and MiRP1 genes, respectively, are responsible for the LQT1, LQT2, LQT3, LQT5 and LQT6 variants of the Romano-Ward syndrome, characterized by autosomal dominant transmission and no deafness. The much rarer Jervell-Lange-Nielsen syndrome (with marked QT prolongation and sensorineural deafness) arises when a child inherits mutant KVLQT1 or minK alleles from both parents. In addition, some families are not linked to the known genetic loci. Cardiac voltage-dependent sodium channel gene encodes the cardiac sodium channel, and long QT syndrome (LQTS) mutations prolong action potentials by increasing inward plateau sodium current. The other mutations cause a decrease in net repolarizing current by reducing potassium currents through "dominant negative" or "loss of function" mechanisms. Polymorphic ventricular tachycardia (torsade de pointes) is thought to be initiated by early after-depolarizations in the Purkinje system and maintained by reentry in the myocardium. Clinical presentations vary with the specific gene affected and the specific mutation. Nevertheless, patients with identical mutations can also present differently, and some patients with LQTS mutations may have no manifest baseline phenotype. The question of whether the latter situation is one of high risk for administration of QT prolonging drugs or during myocardial ischemia is under active investigation. More generally, the identification of LQTS genes has provided tremendous new insights for our understanding of normal cardiac electrophysiology and its perturbation in a wide range of conditions associated with sudden death. It seems likely that the approach of applying information from the genetics of uncommon congenital syndromes to the study of common acquired diseases will be an increasingly important one in the next millennium. (J Am Coll Cardiol 2000;36:1–12) © 2000 by the American College of Cardiology

The Long QT Syndrome (LQTS) is an uncommon and fascinating disorder. Jervell and Lange-Nielsen (1) reported the first case with prolonged QT interval, congenital deafness and sudden death in children; they speculated that death was due to asystole. Since that initial report, LQTS has drawn tremendous interest from clinicians and basic scientists. An initial mechanism proposed was the "sympathetic imbalance" theory, while later workers suggested the concept that a defect in a specific membrane ionic channel would prove responsible. The identification of mutations in genes encoding ionic channel proteins supports the latter view. The identification of LQTS genes and developing correlations between specific mutations and clinical presentations not only will contribute to improved therapy for patients with this intriguing disorder but will also provide a good model for further studies of the way that specific genetic abnormalities can alter cardiac electrophysiology and, eventually, how they may be treated.

From the *Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital and National Yang-Ming University School of Medicine, Taipei, Taiwan; and the †Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee. This work was supported, in part, by grants from the National Science Council, Taiwan (NSC 88-2314-B-075-065 and NSC 89-2314-B-075-023) and Taipei Veterans General Hospital (Taipei VGH 89-59, 89-253) and the United States Public Health Service (HL46681, HL49989). Dr. Roden is the holder of the William Stokes chair in Experimental Therapeutics, a gift of the Dai-ichi Corporation.

Manuscript received October 28, 1999; revised manuscript received January 18, 2000, accepted March 27, 2000.

BACKGROUND

Jervell and Lange-Nielsen (1) provided the first formal description of the disease in 1957 in a family with four children who suffered from congenital deafness, syncope and QT prolongation in electrocardiogram (ECG). Three children died suddenly; the parents, who were not consanguineous, and two other children had normal QT interval and hearing and led a normal life. In the early 1960s, Romano et al. (2) and Ward (3) independently described a similar disease entity but without deafness. Thus, the Romano-Ward (RW) syndrome is an autosomal dominant disorder without congenital deafness while Jervell-Lange-Nielsen (JLN) syndrome has been viewed as an autosomal recessive disease with congenital deafness.

Yanowitz et al. (4) found that the QT interval could be prolonged by right stellectomy or left stellate ganglion stimulation. Subsequently, Schwartz et al. (5) were able to induce T wave alternans (often seen in LQTS patients) by left stellate ganglion stimulation. They further successfully treated a medically refractory young patient by left stellec-

Abbreviations and Acronyms

ECG = electrocardiogram
HERG = human "ether-a-go-go" related gene
I_{Kr} = rapidly activating component of delayed rectifier potassium current
I_{Ks} = slowly activating component of delayed rectifier potassium current
JLN = Jervell-Lange-Nielsen
LQTS = long QT syndrome
MiRP1 = minK related peptide 1
QTc = corrected QT interval
RW = Romano-Ward
SCN5A = cardiac voltage-dependent sodium channel gene

tomy. It was at that time that "sympathetic imbalance" theory prevailed: the syncopal episodes were thought to be due to sudden sympathetic discharges from the left stellate ganglion.

The first comprehensive report on the beneficial effects of beta-adrenergic blocking agents appeared in 1975 (6) and was further substantiated a decade later (7). The reported 10-year mortality rate was reduced from 71% in untreated patients to 6% by beta-blockers or left cardiac sympathetic denervation.

In 1979, Cramptom et al. (8) initiated the International Registry for LQTS, which, in the intervening years, has enrolled over 2,000 families. As described below, the Registry is providing a rich source of clinical and family data, which can now be interpreted in a modern genetic context.

In 1991, Keating et al. (9) reported very tight linkage to the Harvey ras-1 locus on the short arm of chromosome 11 (11p15.5) in a large LQTS kindred. Harvey ras-1 was ruled out as the disease gene (10), and the actual gene at this locus (LQT1) remained unidentified for another five years. In the nine months between March 1995 and January 1996, three LQTS genes were identified (11–13), and two further genes have been implicated since (14,15). Families unlinked to any known locus have been reported (16), and mechanisms underlying the JLN syndrome have been identified (17–19). Importantly, clinical differences among affected patients (depending on the specific gene and perhaps the specific mutations) have now been observed (20–23), and genotype-specific therapy has now been proposed (24,25). As well, it is becoming clear that the clinical manifestations of LQTS vary among individuals carrying the same mutations (26), with some affected patients even displaying normal QT intervals (27).

INCIDENCE

The incidence of RW syndrome is unknown, estimated to be about one gene carrier in 10,000 population (20,28). But increasing identification of apparently asymptomatic gene carriers with normal QT intervals may make this an underestimate. The JLN syndrome is much rarer. Fraser et al. (29) estimated that the prevalence of JLN syndrome in children aged 4 to 15 years in England, Wales and Ireland at between 1.6 and 6 per million.

Table 1. Current Genetic Information in LQTS

	Chromosome Locus	Gene	Current
Autosomal dominant (Romano-Ward)			
LQT1	11p15.5	KVLQT1 (KCNQ1)	$\downarrow I_{Ks}$
LQT2	7q35–36	HERG	$\downarrow I_{Kr}$
LQT3	3p21–24	SCN5A	$\uparrow I_{Na}$
LQT4	4q25–27	Unknown	Unknown
LQT5	21q22.1–22.2	MinK (KCNE1)	$\downarrow I_{Ks}$
LQT6	21q22.1–22.2	MiRP1 (KCNE2)	$\downarrow I_{Kr}$
LQT7	Unknown	Unknown	Unknown
Autosomal recessive (Jervell-Lange-Nielsen)			
JLN1	11p15.5	KVLQT1 (KCNQ1)	$\downarrow\downarrow I_{Ks}$
JLN2	21q22.1–22.2	MinK (KCNE1)	$\downarrow\downarrow I_{Ks}$
JLN3	Unknown	Unknown	Unknown

HERG = human "ether-a-go-go" related gene; I_{Kr} = rapidly activating component of delayed rectifier potassium current; I_{Ks} = slowly activating component of delayed rectifier potassium current; I_{Na} = sodium current; JLN = Jervell-Lange-Nielsen syndrome; MiRP1 = minK related peptide 1; SCN5A = cardiac voltage-dependent sodium channel gene.

MOLECULAR BIOLOGY (TABLE 1)

Keating et al. (9), using genome-wide linkage analysis, mapped the first gene for LQTS to chromosome 11p15.5 in a single large kindred. However, LQT locus heterogeneity was subsequently demonstrated (30,31).

KVLQT1 (KCNQ1). In 1996, Wang et al. (13), using positional cloning, found the chromosome 11-linked LQTS gene (LQT1) to be KVLQT1 at 11p15.5. KVLQT1 is strongly expressed in the heart and encodes a protein with structural features of a voltage-gated potassium channel. Multiple mutations, giving rise to amino acid substitutions or truncated proteins, have now been described in KVLQT1-linked LQTS (32–43) (Fig. 1).

KVLQT1 has the six membrane spanning segment topology typical of a voltage-gated potassium channel (13), and protein subunits are thought to co-assemble with minK (see below) to form the channel responsible for slowly activating component of delayed rectifier potassium current (I_{Ks}). KVLQT1 is expressed not only in the heart but also in other human tissues such as pancreas, kidney, placenta and lung but not in liver, skeletal muscle or brain (13). It has also been shown by in situ hybridization that KVLQT1 is expressed in the stria vascularis of mouse inner ear (17), which is important in understanding the deafness seen in JLN syndrome.

In individuals with LQT1, normal and mutant KVLQT1 alleles are coexpressed in myocytes. In some cases, the mutant form of KVLQT1 interferes with the function of the normal wild-type form through a dominant-negative ("poison pill") mechanism. In other cases, the mutant protein shows no function. In either case, I_{Ks} is decreased, resulting in prolongation of cardiac repolarization and an increased risk of arrhythmias (34). Recently, recessive forms

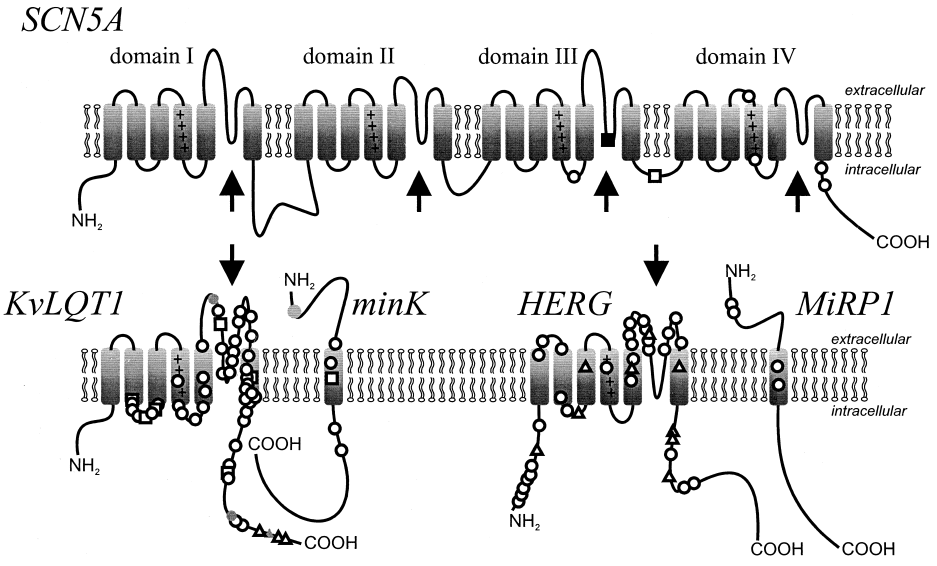

Figure 1. Mutations causing the long QT syndrome in the sodium channel protein (SCN5A, **top**) and potassium channel protein complexes I_{Ks}, encoded by KvLQT1 and minK and I_{Kr}, encoded by HERG and MiRP1. The **arrows** show the locations of the pores through which sodium or potassium ions permeate. The **unfilled symbols** show the location of mutations reported in the autosomal dominant Romano-Ward form of the syndrome and the **gray symbols** are those associated with the autosomal recessive form (Jervell-Lange-Nielsen). Point mutations are shown by **circles**, insertion/deletion events or splice events that leave the open reading frame intact are shown by **squares** and truncations are shown by **triangles** (adapted from reference [44] with permission). HERG = human "ether-a-go-go" related gene; MiRP1 = minK related peptide 1; SCN5A = cardiac voltage-dependent sodium channel gene.

of RW syndrome without deafness have been described in patients homozygous for KVLQT1 mutations (45,46). Since these parents, like JLN parents, are heterozygous for a KVLQT1 mutation but have a normal QT interval, it is thought that not all KVLQT1 mutations are clinically manifest or there is variable penetrance. Thus, phenotypically mild (subclinical) mutations in LQTS genes may be present among the general population, and it has been suggested that these patients may be predisposed to drug- or stress-induced arrhythmias (33,45).

In 1997, Neyroud et al. (17) linked JLN to chromosome 11p15.5 by analyzing four consanguineous families. They then identified a homozygous deletion-insertion event in the C-terminal domain of KVLQT1 in three affected children of two families. Thereafter, Splawski et al. (18) also described a patient homozygous for a KVLQT1 mutation from a family with an autosomal dominant LQTS. This patient had marked corrected QT interval (QTc) prolongation and congenital deafness while the parents were phenotypically normal. Severe QT prolongation and deafness presumably reflect marked decreases in I_{Ks} channels. The finding that KVLQT1 is expressed in the stria vascularis of mouse inner ear provides further evidence that KVLQT1 plays a pivotal role in normal hearing, probably through maintaining the endolymph homeostasis (17). Thus, it is now accepted that homozygous mutations of KVLQT1 cause JLN syndrome (JLN1) (19,47,48) (Fig. 1), and consanguinity is frequent in these families. The deafness requires the presence of two mutant alleles. Jervell-Lange-Nielsen syndrome patients are also thought to be highly susceptible to arrhythmias although even a single mutant allele (as in the parents) appears to increase arrhythmia risk; thus, arrhythmia risk seems dependent on "gene dosage."

Human "ether-a-go-go" related gene (HERG). The LQT2 locus was mapped in affected families to 7q35–36 (49), and the gene was then identified by a candidate gene approach, that is, screening for genes at the identified locus yielded mutations in affected individuals. The LQT2 disease gene is HERG, which also encodes a potassium channel (50). Curran et al. (12) identified six LQTS-associated mutations in HERG and concluded that the latter is the gene responsible for chromosome 7-linked LQTS (LQT2). As with KVLQT1, multiple mutations in HERG have been identified (35,51–59) (Fig. 1).

The HERG is highly expressed in the heart (12), and, like other potassium channels, the encoded protein has six transmembrane segments. The HERG encodes the major subunit of the rapidly activating component of the delayed rectifier potassium current (I_{Kr}) (50). This outward current is the major contributor to the rapid repolarization of phase 3 of the action potential recorded from human myocytes. As with KVLQT1, mutations of the gene cause loss-of-function or dominant-negative I_{Kr} suppression to decrease the repolarizing currents (60). Defects in biosynthetic processing of mutant HERG channel protein have also been reported (56,61). In vitro minK has been reported to be able to co-assemble with HERG to modulate the amplitude of the repolarizing current (62). More recently, minK-related peptide 1 (MiRP1) has been identified as a protein partner for HERG, and MiRP1 mutations have been implicated in drug-associated LQTS (15) (see below). The I_{Kr} is also the primary molecular target for methanesulfonanilide (63) and

most other blocking drugs known to cause torsade de pointes (64), thus linking the congenital and acquired syndromes. A recent report has described a child homozygous for a HERG mutation, who presented with marked QT prolongation and arrhythmias but no deafness at birth (59).

Cardiac voltage-dependent sodium channel gene (SCN5A). The candidate gene approach was undertaken by Jiang et al. (49) and Wang et al. (11) who discovered that the gene responsible for chromosome 3-linked LQTS (LQT3) is the cardiac sodium channel gene SCN5A (3p21–24). The initially described mutation was an intragenic deletion of nine nucleotides (three amino acids) in a region that is important for channel inactivation. Thereafter, other investigators (65–70) reported other mutations, further confirming SCN5A to be the gene for LQT3 (Fig. 1).

Cardiac voltage-dependent sodium channel gene encodes a protein with four homologous domains (DI–DIV), each of which contains six transmembrane segments (S1–S6) (71). Thus, unlike the case with potassium channels, expression of a single sodium channel protein is sufficient to recapitulate sodium current. It is highly expressed in human heart, but not in brain, liver or skeletal muscle (where other genes are required for sodium current) (72). Whereas the KVLQT1- and HERG-encoded gene defects represent a loss of channel function, the SCN5A-encoded defects result in a "gain of function" abnormality. The LQT3 mutations produce a persistent noninactivating, mexiletine- and tetrodotoxin-sensitive sodium inward current in the plateau phase of cardiac action potential through several mechanisms (65–67,69,73). Another recently reported mechanism was that a point mutation in the alpha-subunit of the human sodium channel induced a change in alpha- and beta-interaction with resulting change in inactivation of the heteromeric channels (66). The end result is a prolongation of cardiac action potential and an increased risk of torsade de pointes. One large kindred with a single SCN5A mutation causing LQT3 and the Brugada syndrome has also been reported (74).

MinK (KCNE1). MinK was first cloned by Takumi et al. (75) from rat kidney cDNA library and mapped to chromosome 21q22.1–q22.2 (76). The cloned cDNA encodes a membrane protein that consists of 130 amino acids with a single putative transmembrane domain. It can induce a slowly activating, voltage-dependent potassium current by co-assembling with oocyte-endogenous KVLQT1 transcripts in *Xenopus* oocytes (75). It is now generally accepted that minK coassembles with KVLQT1 to form I_{Ks} (77,78).

Splawski et al. (14) defined minK missense mutations in affected members of two LQT families. Both mutations (S74L, D76N) reduced I_{Ks} by shifting the voltage dependence of activation and accelerating channel deactivation. It has also been shown that mutant I_{Ks} channels formed with D76N and S74L minK subunits have lower unitary currents and diminished open probabilities (79). Thus, these functional studies support the idea that minK represents a fifth LQTS locus (LQT5) (80) (Fig. 1). Interpretation of the clinical manifestations of LQT5 may be complicated by differing effects of minK mutations on KVLQT1 and HERG (81). The functional consequences of these mutations would be delayed cardiac repolarization and an increased risk of arrhythmia.

As with KVLQT1, homozygotes for minK mutations have been identified among JLN patients. Schulze-Bahr et al. (19) studied a Lebanese family with JLN syndrome, in which three of six children had prolonged QTc intervals and congenital bilateral deafness or deaf-mutism (19). Two of the three had suffered from recurrent syncope since early childhood. Both parents and the three other children showed normal hearing and normal QTc. In this family, mutations in minK (KCNE1), with one mutant allele from the father and a different mutant allele from the mother, were found in all affected children; this is termed compound heterozygosity. Unaffected individuals had only one mutant allele. One mutation, Asp76Asn mutation, corresponded to a mutation in rat minK (Asp77Asn), which showed a severe reduction of the I_{Ks}-channel activity upon expression in *Xenopus* oocytes (82). Duggal et al. (80) found the same mutation (Asp76Asn) in minK in a patient with JLN syndrome. The proband's mother and half-sister were both heterozygous for this mutation. Interestingly, both these family members had prolonged QTc intervals, thereby showing that not all JLN "carriers" have a normal phenotype. Like KVLQT1, the minK gene is expressed in the inner ear. Genetically modified mice in which the minK locus is disrupted (minK –/–) exhibit a movement disorder (shaker/waltzer behavior) (83) typical of an inner ear defect. In the inner ear of knockout animals, hair cells degenerate, and the strial marginal cells and the vestibular dark cells are unable to generate an equivalent short circuit current in vitro, indicating a lack of transepithelial potassium secretion. The mice also have blunted QT adaptation to heart rate variation, which may reflect greater susceptibility to arrhythmias (83). Kupershmidt et al. (84) have observed a similar movement disorder in their minK-knockout/LacZ-knockin mice. These findings provide convincing evidence that minK is one of the JLN genes (JLN2) (Fig. 1).

MiRP1. Recently, a novel potassium channel gene encoding MiRP1 has been cloned (15). This small membrane protein is thought to assemble with HERG to alter its function. Unlike channels formed only with HERG, mixed complexes resemble native cardiac I_{Kr} channels in their gating, unitary conductance, regulation by potassium and distinctive biphasic inhibition by the class III antiarrhythmic E-4031. Three missense mutations associated with LQTS and ventricular fibrillation were identified in MiRP1. Mutants form channels that open slowly and close rapidly, thereby diminishing potassium currents. These findings support the idea that MiRP1 is one of the LQT genes (LQT6) (Fig. 1). Although MiRP1 mutations have been described in drug-associated LQTS, and co-expression of HERG with MiRP1 does appear to modulate drug

Table 2. Genotype-Specific Clinical Features*

	LQT1	LQT2	LQT3
Arrhythmia onset	Physical exercise	Auditory stimuli	Rest, sleep
T wave abnormality	Prolonged T wave duration	Small or notched T wave	Delayed onset of T wave
Cardiac events through age of 40			
≥1 event (%)†	62	46	18
≥2 event (%)†	37	36	5
Lethality of cardiac events (%)†	4	4	20
Median age at first event (yr)‡	9	12	16

*Data are gathered from Vincent et al. (20), Zareba et al. (22), Ackerman (28), Wilde et al. (23), Schwartz et al. (88) and Locati et al. (90); †$p < 0.001$ for the comparison of all three groups; ‡$P < 0.05$ for the comparison of all three groups.

sensitivity of I_{Kr}, the exact role of MiRP1 expression in the heart is still an open question, especially considering that it has been difficult to detect in cardiac tissue.

Unidentified genes. The LQT4 locus has been linked to chromosome 4q25-27 in a 65-member family (16). The responsible gene has not yet been found. Patients in this family are characterized by severe bradycardia, a bizarre T wave and atrial fibrillation.

At most, 50% to 75% of families with RW syndrome are linked to LQT1 through LQT6 genotypes. Marks et al. (85) identified three boys with LQTS, atrioventricular block and simple syndactyly. The QT intervals were extremely prolonged (QTc > 600 ms). Two of the three children died suddenly despite treatment with beta-adrenergic blocking agents and permanent pacing. Syndactyly and LQTS have also been reported in women patients (86). The responsible genes for these patients and those in whom the RW syndrome has not been linked remain to be determined.

There are still some patients with JLN syndrome in whom disease genes have not been found (87), indicating further genetic heterogeneity in JLN syndrome, as in RW syndrome.

SYMPTOMATOLOGY

Most data on clinical presentations were gathered before it was understood that multiple mutations, on multiple genes, can cause LQTS and that patients may display highly variable phenotypes including even no phenotype. Most clinical data relate to LQT1 and LQT2, the most common subtypes, and may not apply to rarer forms. It has been stated that no more than 60% of patients are symptomatic (20,28). Syncope, seizure-like activity and cardiac arrest are the common clinical presentations. Eighty-five percent of events are related to physical activity and emotional stress. Sometimes auditory stimuli, such as a telephone ringing or an alarm clock sounding, will trigger the syncopal episodes, especially in patients with LQT2 (23). A higher incidence of syncope was found to occur during menstruation (88) and in the postpartum period (89). Fifteen percent of the symptoms occurred during rest or sleep, and this is thought to occur more commonly in LQT3 patients (20,21). Thirty percent of patients have no family history; these cases have de novo mutations or reflect reduced penetrance. In LQT1 (the most common), the risk of cardiac events is higher in men until puberty and higher in women during adulthood (90). These genotype-specific clinical features are shown in Table 2.

ECG PATTERNS

QT prolongation. A widely accepted method for correcting QT interval for rate is Bazett's formula (91): $QTc = QT \div (RR)^{1/2}$. Lead II is generally the best single lead for measuring QT interval (28) because the T wave ending is usually discrete and the QT interval obtained from lead II has a good correlation with the maximal QT measured from the 12-lead ECG. A QTc interval longer than 440 ms has been considered prolonged. However, data from the International Registry for LQTS show that 68 (5%) of 1,345 family members who have a QTc < 440 ms had a cardiac arrest (88), suggesting affected patients may (sometimes or always) have normal QT intervals. Garson et al. (92) similarly reported that 6% of 287 patients with LQTS had a normal QTc interval. An analysis of 199 members from LQT1-genotyped families demonstrated that, with a QTc cutoff value of 440 ms, 11% of family members were misclassified (20). No affected gene carriers had a QTc of 410 ms or less, and no normal persons had a QTc of 470 ms or more (men) or 480 ms or more (women) (20). If a QTc of 460 ms was used as a cutoff point, the positive predictive value was 92%, and the negative predictive value was 94% (28). Since 6% of gene carriers have a first normal QTc, and QTc can vary on repeated tracings, repeat ECGs are indicated to identify disease carriers if the suspicion is high. Eventually, genotyping will be available to address molecular diagnosis.

During an exercise test, an abnormal QT cycle-length relationship with failure of the QTc to shorten normally with increasing heart rate and persistent prolongation in the recovery stage have been reported in some subjects, especially those with LQT1 (93).

In the normal population, women have longer QT intervals, probably due to QT shortening in men after puberty, rather than QT prolongation in women during reproductive years (94). In LQTS, men exhibit shorter mean QTc values than both women and children (90,95), for both genotype-positive and -negative blood relatives. Thus, it has been postulated that adult gender differences in the propensity toward torsade de pointes reflect the rela-

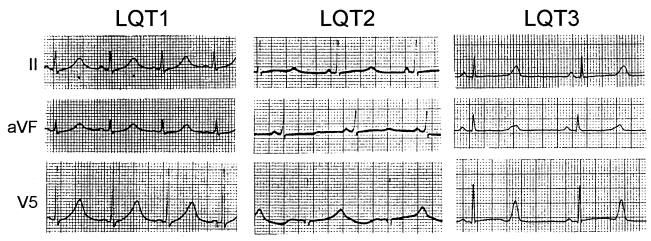

Figure 2. Different patterns of ST-T wave complex in patients with long QT syndrome. Please see text for detail (adapted from reference [99] with permission).

tively greater presence in men of a factor that blunts QT prolongation responses (21).

QT dispersion. In addition to the temporal heterogeneity described above (i.e., the ECG can sporadically be normal), repolarization in LQTS also displays substantial spatial (96) and transmural (97) heterogeneity. Spatial dispersion of QT and QTc have been calculated using two indexes: the difference between the longest and the shortest value measured in each of the 12 ECG leads (QTmax-QTmin, QTcmax-QTcmin) and the relative dispersion of QT and QTc (standard deviation of QT/QT average × 100, standard deviation of QTc/QTc average × 100). Both indexes of dispersion of repolarization are increased in LQTS patients compared with control subjects (96).

T-U wave abnormalities and T wave alternance. It has been proposed that the degree of transmural heterogeneity can be determined by the duration of the second half (post-peak) of the T wave (97). Repolarization of the epicardial action potential, the earliest to repolarize, was found to coincide with the peak of the T wave in vitro; repolarization of the midmyocardial cells (M cells), the last to repolarize, coincided with the end of the T wave. Thus, it was proposed that the action potential duration of the longest M cells determines the QT interval and the Tpeak-Tend interval serves as an index of transmural heterogeneity of repolarization.

Patients with LQTS may present with multiple morphological abnormalities of T wave, such as broad-based, biphasic, bifid or notched T waves. These T wave abnormalities can be observed in normal subjects but much less commonly than in patients with LQTS (15% vs. 62%) (98). Among LQTS patients, these T wave abnormalities were more common in those with a history of cardiac arrest or syncope (81% vs. 19%) (98). A notched T wave observed during the recovery phase of exercise tests is reported to be highly suggestive of LQTS (98).

Different patterns of the ST-T wave complex have also been suggested in patients with LQTS (Fig. 2). T wave duration is particularly long in patients with LQT1. Patients with LQT2 usually have small T and/or notched T waves. T wave onset is unusually prolonged in patients with LQT3 (99). In a preliminary report (100), genotypes were correctly predicted in 98% of families with typical patterns. Overall, 80% of families were correctly predicted based on ECG ST-T wave pattern (100).

Temporal heterogeneity of the repolarization in LQTS can also be observed in beat-to-beat alternation of T wave polarity or amplitude (T wave alternans). It may be observed briefly at rest but most commonly appears during emotional or physical stress and may herald torsade de pointes and is a marker for high-risk patients (5).

Bradycardia. Some reports suggest that the average resting heart rate is lower in LQTS patients, especially in children, compared with normal control subjects (6). In addition, patients with LQTS have a mean heart rate lower than normal controls during moderate and maximal exercise, but there is considerable overlap with the normal distribution. Sinus node dysfunction has been reported in patients with LQTS (93). Some patients have sinus arrest and a notched T wave in the first beat after a pause. Repetitive ventricular beats and torsade de pointes usually take off from the second peak after the notch (101). It has been reported that after successful left cardiac sympathetic denervation, the notched T wave will disappear after a pause (101). An especially malignant form of LQTS presents with 2:1 atrioventricular block and/or intraventricular conduction disturbances likely arising because of very marked action potential prolongation in the conducting system (102).

The extent of sinus bradycardia is highly variable, which suggests that either certain gene defects are more likely to be associated with this manifestation of the disease than others or expression of other genes determines whether an individual subject develops sinus bradycardia (21).

CARDIAC ARRHYTHMIAS

Monophasic action potential recordings have shown that action potential durations are prolonged in ventricular muscle in LQTS (97). Early afterdepolarizations are thought to arise during prolonged phase 2 or phase 3 of the action potential as a result of reactivation of L-type calcium currents or possibly other inward currents, such as sodium-calcium exchange current or sodium current (103). Typically, torsade de pointes starts with a premature ventricular depolarization, followed by a compensatory pause. The next sinus beat often has a markedly prolonged QT interval and an even more bizarre T wave. This is then followed by a train of polymorphic ventricular tachycardia (torsade de pointes) (Fig. 3) (104) whose first beat may represent triggering from an early afterdepolarization. The "short-long-short" sequence heralding torsade de pointes is a hallmark of LQTS. Torsade de pointes may stop spontaneously, accounting for syncopal attacks, or may degenerate into ventricular fibrillation with sudden death as a terminal event.

El-Sherif and his associates (105) found that by analysis of tridimensional activation patterns in an animal model of LQTS, the initial beat of polymorphic ventricular tachycardia consistently arose as focal activity from a subendocardial

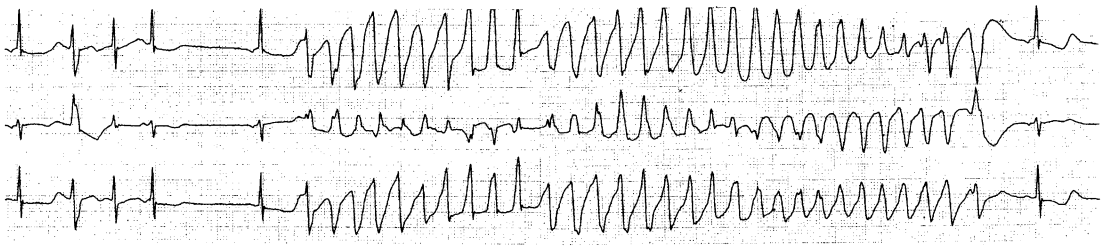

Figure 3. The short-long-short sequence before the onset of torsade de pointes in a patient with long QT syndrome.

site, whereas subsequent beats were due to successive subendocardial focal activity, reentrant excitation or a combination of both mechanisms (105). They further showed that an apparent shift in QRS axis in torsade de pointes was due to a predominantly single localized circuit that varied its location and orientation from beat to beat, with the majority of ventricular myocardium being activated in a centrifugal pattern (106). This suggests early afterdepolarization-related initiation in the Purkinje system (subendocardium) with maintenance by reentry.

DIAGNOSIS

A history of unexplained syncope or sudden death in a child or young adult, especially during physical exertion or emotional agitation, and a history of unexplained drowning or near-drowning, should provoke a suspicion of the possibility of LQTS (28,43). Seizure or syncope seemingly precipitated by "fight, flight or fright" has been said to indicate LQTS until proven otherwise (28). More than one half of the 8,000 sudden unexpected deaths in children may be attributable to LQTS (28), and the 10-year mortality rate of untreated LQTS may be as high as 50%, making consideration of the diagnosis mandatory in some clinical situations. Despite advances in the understanding of the molecular mechanisms underlying the cellular electrophysiologic defects found in patients with LQTS, the diagnosis is still based on the clinical characteristics of the patient and the family. In those with characteristic features of LQTS, the typical cases present no diagnostic difficulty, assuming the physician is aware of the disease. However, borderline cases are more complex and require integration of multiple clinical variables including ECG findings at rest and with exercise, clinical history and family history.

Schwartz et al. (7) proposed the first diagnostic criteria for LQTS in 1985, providing a quantitative approach to the diagnosis of LQTS by giving different weights to major and minor criteria. Subsequent developments in understanding LQTS, including the findings that women have longer QTc than men, that there is a large overlap of QTc values between gene carriers and noncarriers and that there are a number of clinical parameters found to be significantly different between patients with and without LQTS, led to the formulation of new criteria published in 1993 (107).

These new criteria are shown in Table 3 (107). They are based on findings from the ECG, clinical history and family history. The point total ranges from 0 to 9. Three probability categories have been defined: <1 point = low probability; 2 to 3 points = intermediate probability; >4 points = high probability. In patients with a score of 2 to 3 points, serial ECGs should be obtained since the QTc value in patients with LQTS may vary from time to time. Furthermore, screening ECGs from other family members will be needed.

Exercise testing and Holter monitoring should be performed on all suspected LQTS patients, although the positive predictive accuracy is small. Corrected QT interval shortening or lengthening during or after exercise testing has not been very useful, because there are few normal standards and prospective studies on the accuracy of these QTc changes in risk stratification have not been performed. Invasive electrophysiologic testing, with and without catecholamine infusion, is not useful.

In borderline cases, genetic testing to identify new mutations may eventually be used but has not yet matured to

Table 3. Diagnostic Criteria in LQTS (107)

	Points
Electrocardiographic findings*	
QTc†	
>480 ms	3
460–470 ms	2
450 (men) ms	1
Torsade de pointes‡	2
T wave alternans	1
Notched T wave in three leads	1
Low heart rate for age§	0.5
Clinical history	
Syncope‡	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history‖	
Family members with definite LQTS¶	1
Unexplained sudden cardiac death before age 30 among immediate family members	0.5

Scoring: < 1 point = low probability; 2 to 3 points = intermediate probability; >4 points = high probability.

*In the absence of medications or disorders known to affect these ECG features; †QTc calculated by Bazett's formula, where QTc = QT/$\sqrt{RR}$; ‡mutually exclusive; §resting heart rate below the second percentile for age; ‖the same family member cannot be counted twice; ¶definite LQTS is defined by an LQT score >4.

LQTS = long QT syndrome; QTc = corrected QT interval.

become a routinely available clinical tool. In a recent report of nine families with sporadic cases of LQTS (26), that is, families in which, besides the proband, none of the family members had clinical signs of the disease, 33% of the 46 family members were found to be gene carriers by molecular diagnosis, with an estimated penetrance of only 25%. It seems appropriate to perform molecular screening in all family members of genotyped patients, when available.

Contemporary molecular approaches can be used to analyze genomic DNA (e.g., from peripheral lymphocytes) and to detect LQTS-associated mutations. This approach is particularly useful for members in a family in which the causative mutant gene and specific mutations have been identified from a proband. At least one case of mutations in both HERG and KVLQT1 have been found in two severely affected sisters from a large LQTS family (double heterozygosity), suggesting that genetic analysis of severely affected young patients should include an investigation for >1 mutation in the LQT genes (58). Otherwise, screening for disease-associated mutations is not yet widely performed, because it is costly and time-consuming and because some unknown LQTS genes remained to be determined. The genomic structure of all five known human LQTS genes is now known, an important step in making presymptomatic diagnosis for the mutations in these gene loci more widely available (15,71,108).

MANAGEMENT

For asymptomatic patients there are differing opinions with regard to the need for treatment. Schwartz et al. (109) initially recommended treatment for patients without symptoms in six conditions:

1) in those with congenital deafness because the risk of cardiac events is particularly high;
2) in neonates and infants because the risk is especially high during the first months of life;
3) in affected siblings of children who have died suddenly, because of the emotional stress present in the family;
4) in patients with documented T wave alternans because this is a sign of enhanced electrical instability;
5) in patients with very long QTc (>600 ms), a group thought to be more symptomatic;
6) when there is anxiety and an explicit request for treatment in a family after thorough explanation.

Vincent et al. (20) and Garson et al. (92) have recommended treatment for all asymptomatic patients if under age 40 at the time of diagnosis since it is sometimes impossible to predict which asymptomatic patient will become symptomatic, and 30% to 40% of sudden deaths occur at the first event. In a recent analysis done by Priori et al. (110), death as the first symptom was found to be common, suggesting all young asymptomatic patients should be treated.

There is no disagreement that symptomatic patients need treatment. There are five modalities of treatment for patients with LQTS at the present time: 1) beta-blockers, 2) pacemakers, 3) left cardiac sympathetic denervation, 4) implantable cardioverter-defibrillator, and 5) gene-based therapy. The goal of therapy is to prevent malignant ventricular tachyarrhythmias (ventricular tachycardia, torsade de pointes and ventricular fibrillation).

Beta-blockers. Beta-blockers remain first-line treatment for LQTS. Initially described in 1975 (6) and then substantiated by the beneficial effect reported in 1985 (7), the reported effect of beta-blocker therapy is to decrease mortality from 71% in historical controls to 6% in a treated group (109). Syncope or other events recur in patients on beta-blockers in about 25% of cases, and the chance of sudden death at five years has been estimated to be 10% despite therapy (111).

The dose of beta-blockers should be maximized, ascertained by a reduced heart rate response to treadmill exercise testing, aiming for a maximal heart rate of 130 beats/min or less. All beta-blockers appear to be effective, and no prospective comparative studies have been performed. Propranolol is widely used, at a daily dose of 2 to 3 mg/kg. Nadolol is also widely used because of its longer half-life (so missing a dose may not be catastrophic). Noncompliance exposes patients to their baseline risk of cardiac events and probably accounts for a percentage of treatment failure, especially in adolescents. In patients who develop severe bradycardia or profound sinus arrest (e.g., >2.0 s), concomitant pacemaker therapy is indicated.

The precise mechanism of the efficacy of beta-blockers in LQTS remains unknown. The QTc remains prolonged after effective treatment with beta-blockers, but QTc dispersion, measured as (QTc maximum minus QTc minimum), decreases in the responders (112). A cutoff value of 100 ms for QTmax minus QTmin had an 80% sensitivity and 82% specificity in discriminating between responders and nonresponders. In one series, LQTS patients who did not respond to beta-blockade underwent left cardiac sympathetic denervation and, thereafter, remained asymptomatic (mean follow-up, 5 ± 4 years). In this group, dispersion of repolarization was significantly reduced by the surgical denervation to values similar to that of the responders to beta-blockade (112). Thus, the persistence of excessive QT dispersion after the institution of therapy with beta-blockers is one possible marker that may allow the early identification of patients likely to remain at high risk and may, therefore, suggest the need to proceed to alternate therapies.

Recently, Shimizu et al. (113) showed in a canine model that chromanol 293B (an I_{Ks} blocker) was not sufficient to induce torsade de pointes but that the addition of a beta-agonist was highly arrhythmogenic, likely by increasing transmural dispersion of repolarization. They postulated that this was a result of a large augmentation of residual I_{Ks} in epicardial and endocardial cells but not in M cells, in which I_{Ks} is intrinsically less prominent. This study provides a mechanistic understanding of the cellular basis for the therapeutic actions of beta-blockers in LQT1. In a human

study, Shimizu et al. (114) also demonstrated that the addition of propranolol completely reversed the effect of epinephrine in prolonging the QT interval and increasing the dispersion in LQT1 patients. A possibly related mechanism for beta-blocker efficacy is inhibition of reactivated inward calcium current, an effect that would apply to all forms of LQTS. Verapamil, an L-type calcium channel blocker, has been demonstrated to eliminate or reduce early afterdepolarizations and suppress torsade de pointes in patients with LQTS who underwent challenge with epinephrine infusion (103). Verapamil may be an effective alternative for patients unable to tolerate beta-blockers, such as patients with asthma, although long-term safety and efficacy data are not available.

Cardiac pacing. The beneficial effects of pacing in high-risk LQTS patients probably relate to the prevention of bradycardia and pauses and the shortening of long QT interval, factors that are known to be arrhythmogenic (111). However, pacemakers should not be regarded as a sole therapy for LQTS and should be used as an adjunct to beta-blockers to prevent the occurrence of severe bradycardia, or pauses, in patients with pre-existing atrioventricular block or when there is evidence of pause-dependent arrhythmias.

Left cardiac sympathetic denervation. Left cardiac sympathetic denervation should be reserved as a back-up therapy when repeated syncopal attacks are not controlled by beta-blockers and pacing. The largest series, reported by Schwartz et al. (109), enrolled 123 patients and was claimed to be representative because it encompassed 90% of the entire LQTS population who underwent left cardiac sympathetic denervation and had a long follow-up period (mean = 10 years). All these patients were unresponsive to or did not tolerate the full-dose of beta-blockers. Left cardiac sympathetic denervation produced a marked decrease in the number of patients with cardiac events (from 99% to 45%) and in the number of cardiac events per patient (from 21 ± 31 to 1 ± 3). Most of the patients who still had cardiac events after surgery had only one, usually during the first six months. The total incidence of sudden death was 8% in 10 years, and the five-year survival rate was 94%.

In order to achieve adequate left cardiac sympathetic denervation in humans, it is necessary to remove the first four to five of the left thoracic ganglia together with the lower half of the left stellate ganglion. Preservation of the upper half of the left stellate ganglion will avoid iatrogenic Horner's syndrome.

Implantable cardioverter-defibrillator. An implantable cardioverter-defibrillator is currently used when the combination of beta-blockers, left cardiac sympathetic denervation and/or pacing fails to prevent the syncopal attacks. It is also proposed as first-line therapy when the presenting event is a resuscitated cardiac arrest. While the implantation of an implantable cardioverter-defibrillator truly appears to decrease the incidence of sudden death in patients with LQTS (115), implantable cardioverter-defibrillators can also produce emotional distress that can trigger arrhythmias and shocks. To avoid shocks for episodes of short, self-terminating torsade de pointes, a revised detection and treatment algorithm has been incorporated into some devices.

Gene-based therapy. In LQT3 patients, experimental (116) and clinical studies (24) have suggested that the sodium channel blockers, mexiletine and lidocaine, may prevent the repetitive opening of the channel, shorten the QT interval and normalize the morphology of the T wave. Thus, they have been viewed as "gene-specific" LQT3 therapies. However, in both LQT2 and LQT3 models, mexiletine has also been shown to be effective in reducing dispersion and preventing torsade de pointes (117). As well, in a canine model of LQT1, mexiletine abbreviated the action potential duration of M cells more than that of epicardium and endocardium, thus diminishing transmural dispersion and the effect of isoproterenol to induce torsade de pointes (113). Currently, these therapies can be regarded only as adjuncts to beta-blockers, and their usefulness as sole therapy for LQTS needs further studies. Importantly, QT shortening cannot be equated with reduced risks. Thus, while molecular genetic studies may raise the possibility of genotype-specific therapies targeting ion channels, any intervention that decreases net inward current or increases net outward current will decrease QT interval and may protect LQTS patients from arrhythmias. Increasing the patient's serum potassium level to about 1.5 mEq/L above baseline with spironolactone, potassium chloride intravenous infusion and oral potassium chloride supplementation resulted in a 24% reduction in the QTc in seven patients with LQT2, compared with 4% in five healthy control subjects, and resolved the notched T wave abnormality (25). This is thought to reflect increased I_{Kr} and should be effective in all forms of LQTS. On the other hand, although raising serum potassium reverses the ECG abnormalities in LQT2, a long-lasting rise of serum potassium may be only partially achievable because of normal renal function (118). Nicorandil, an opener of the ATP-sensitive potassium channel, has been shown to improve the repolarization abnormalities during epinephrine infusion in LQT1 patients (114), and nicorandil has been reported to be effective in a patient with LQTS whose syncopal attacks were refractory to beta-blockade (119). The long-term effect of potassium channel openers in patients with LQTS needs to be determined.

FUTURE DIRECTIONS

The history of LQTS began with single cases and has progressed to a firm understanding of basic genetic and molecular mechanisms. There is now a prospect for specific therapy, based on genotype and, conceivably, actual gene therapy. Most importantly, the identification of LQTS genes has provided tremendous new insights for our understanding of normal cardiac electrophysiology and its perturbation in a wide range of conditions associated with sudden

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death. It seems likely that this paradigm, using new genetic approaches in congenital and acquired diseases, will be an increasingly important one in the next millennium.

Reprint requests and correspondence: Chern-En Chiang, Division of Cardiology, Veterans General Hospital-Taipei, 201, Sec 2, Shih-Pai Road, Taipei, Taiwan. E-mail: cechiang@vghtpe.gov.tw.

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