

Cardiology Clinics

Volume 18 • Number 2 • May 2000

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VENTRICULAR ARRHYTHMIAS**LONG QT SYNDROME****G. Michael Vincent MD**

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The long QT syndrome (LQTS) is a disorder of cardiac ion channels that affect repolarization. The characteristic manifestations are prolongation of the QT interval and T-wave abnormalities on the ECG and exercise or emotion precipitation of syncope and sudden death, resulting from the ventricular tachyarrhythmia torsade de pointes (TDP) (Fig. 1). The ion-channel dysfunction may be acquired or inherited. The acquired form is more common, usually caused by administration of QT-prolonging drugs (Tables 1 and 2), which for the most part impair the function of the I_{Kr} delayed rectifier channel. The inherited form is caused by mutations of genes that encode for cardiac ion channels, principally the I_{Kr} and I_{Ks} delayed rectifier potassium channels, with a minority of cases caused by mutations of the gene that encodes for the cardiac sodium channel.

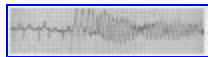


Figure 1. An ECG strip from a 15-year-old boy with LQT1, undergoing an exercise ECG examination, showing the onset of torsades de pointes.

TABLE 1 -- DRUGS THAT PROLONG THE QT INTERVAL OR INDUCE TORSADES DE POINTES

Drug (Brand Names)	Drug Class (Clinical Usage)
Amiodarone (Cordarone)	Antiarrhythmic (heart rhythm)
Amitriptyline (Elavil, Endep)	Antidepressant (depression, pain, others)
Amoxapine (Asendin)	Antidepressant (depression, pain, others)
Ampicillin (Omnipen, Principen, Polycillin)	Antibiotic
Astemizole (Hismanal)	Antihistamine (allergy)

Bepridil (Vasocor)	Antianginal (heart pain)
Chlorpromazine (Thorazine)	Mental illness and nausea/vomiting
Cisapride (Propulsid)	Stimulates intestinal motility
Clarithromycin (Biaxin)	Antibiotic
Clemastine (Tavist)	Antihistamine
Clomipramine (Anafranil)	Mental illness
Desipramine (Norpramin)	Antidepressant (depression and others)
Diphenhydramine (Benadryl)	Antihistamine
Disopyramide (Norpace)	Antiarrhythmic (heart rhythm)
Doxepin (Sinequan, Zonalon)	Antidepressant (depression, pain, others)
Erythromycin (Akne-Mycin, EES, EryDerm, Erygel, Ery-Tab, Erythrocin, Erythromycin Base Filmtab, Erythrostatin, Ilotycin, PCE, Staticin)	Antibiotic and intestinal stimulant
Flecainide (Tambocor)	Antiarrhythmic
Fludrocortisone (Florinef)	Maintain blood pressure/retain sodium
Fluphenazine (Prolixin)	Mental illness, Parkinson's disease
Haloperidol (Haldol)	Mental illness, agitation
Ibutilide (Corvert)	Antiarrhythmic
Imipramine (Tofranil)	Antidepressant (depression, pain, others)
Indapamide (Lozol)	Diuretic (stimulates water and salt loss)
Ipecac	Stimulates vomiting in poisoning
Maprotiline (Ludiomil)	Antidepressant (depression)
Moricizine (Ethmozine)	Antiarrhythmic
Nortriptyline (Pamelor)	Antidepressant (depression and others)
Pentamidine (Pentacarinat, Pentam, NebuPent)	Antiinfective (pneumonia and others)
Perphenazine (Trilafon)	Mental illness
Pimozide (Orap)	Tourette's syndrome, seizures
Probucol (Lorelco)	Lowers cholesterol
Procainamide (Procan, Procanbid, Pronestyl)	Antiarrhythmic
Prochlorperazine (Compazine)	Nausea
Protriptyline (Vivactil)	Antiarrhythmic
Quinidine (Cardioquin, Duraquin, Quinidex, Quinaglute)	Antiarrhythmic
Ipecac Risperidone (Risperdal)	Mental illness
Sotalol (Betapace)	Antiarrhythmic
Tamoxifen (Nolvadex)	Breast cancer treatment
Terfenadine (Seldane)	Antihistamine (allergy)
Thioridazine (Mellaril)	Mental illness
Thiothixene (Navane)	Mental illness

Tocainide (Tonocard)	Antiarrhythmic
Trifluoperazine (Stelazine)	Mental illness
Trimethoprim Sulfamethoxazole (Bactrim, Septra)	Antibiotic

TABLE 2 -- ADDITIONAL DRUGS TO BE AVOIDED IN PATIENTS WITH THE LONG QT SYNDROME

Asthma/Allergy Medications	Asthma Medications
Ephedrine (Adrenaline), Bronchaid, Epifin, Epinal, Epipen, Epiteate, Eppy/N, Medihaler, Epi, S-2, Isoproterenol (Isuprel, Medihaler-Iso)	Albuterol (Proventil, Ventolin, Ventolin Rotahaler, orsyrup, Volmax, Xopenex)
Epinephrine	Metaproterenol (Alupent, Metaprel, Metaproterenol)
	Salmeterol (Serevent)
	Terbutaline (Brethaire, Brethine, Brethine-SC, Bricnyl)
Decongestants	Diet Pills
Phenylldrine, Propagest Phindecon)	Fenfluramine (Pondimin)
Phenylpropanolamine (Acutrim, Dexatrim, Phenoxine, Pseudoephedrine	Phentermine (Adipex, Fastin, Ionamin, Obenix, Obephen, Obermine Obestin, T-Diet)
Phenylephrine (Neosynephrine) (Novafed, Pedia-CareDecongestant, Sudafed)	Sibutramine (Meridia)
Drugs to Prevent Low Blood Pressure	Medication to Prevent Premature Labor
Midodrine (ProAmatine)	Ritodrine (Yutopar)
Nor-epinephrine (Levophed)	

The drugs presented in this table have the potential to stimulate the sympathetic nervous system and therefore would best be avoided by patients with the long QT syndrome. If these drugs must be given, careful monitoring of the heart rhythm is essential.

Inherited LQTS has become a particularly important entity for several reasons. It is estimated to be present in 1 in 7000 persons in the United States and thus is not a rare disorder. It may cause as many as 3000 unexpected deaths in children and young adults per year. Further, recent discoveries concerning the molecular genetics and pathophysiology of LQTS have provided important insights into the mechanisms of arrhythmias, not only in LQTS but in general. These findings may provide molecular strategies for arrhythmia prevention in some of the estimated 300,000 to 400,000 sudden cardiac deaths [100] that occur annually in the United States, including an estimated 7000 to 8000 in young persons.

MOLECULAR GENETICS OF LQTS

Inherited LQTS is an autosomal dominant genetic disorder caused by mutations of genes that encode for

cardiac ion channels. Five genes have been discovered as of this time. Four encode for potassium ion channels and one for the cardiac sodium channel. An additional locus has been discovered on chromosome 4, but the gene has not yet been identified. The currently known genes are listed in [Table 3](#).

TABLE 3 -- GENES CAUSING LONG QT SYNDROME

Designation	Gene	Gene Product	Ion Channel	Chromosome Locus
LQT1	<i>KvLQT1</i>	I _{Ks} alpha-subunit	I _{Ks}	11p15.5
LQT2	<i>HERG</i>	I _{Kr} alpha-subunit	I _{Kr}	7q35-36
LQT3	<i>SCN5A</i>	Na ⁺ channel unit	I _{Na}	3q21-24
LQT4	Unknown	Unknown	Unknown	4q25-27
LQT5	<i>MinK</i>	I _{Ks} beta-subunit	I _{Ks}	21q22.1-2
LQT6	<i>MiRP1</i>	I _{Kr} beta-subunit	I _{Kr}	21q22.1

Over 180 different mutations of the five known genes have been described. LQTS, therefore, shows a large degree of genetic heterogeneity. Nearly every family manifests a different mutation, and no real genetic "hot spots" have been identified. Importantly, only about 50% of clinically apparent LQTS patients can be genotyped to one of these genes. This suggests that additional LQTS genes must exist that cause the disorder in the other families. The inability to identify a genetic mutation in some LQTS patients limits the utility of genetic testing for LQTS, because a negative result does not exclude the disease.

The first genetic locus for LQTS was mapped in 1991 to chromosome 11p15.5 ^[31] in a large family of Danish origin. The author had identified the proband of this family in 1973 following an unexpected sudden death. Over a number of years, we expanded the pedigree to over 1300 members and prospectively obtained ECGs for more than 500, identifying about 100 clinically affected individuals. ^[23] An ECG from an affected family member is shown in [Figure 2](#). The cardiac events in this family were precipitated by exercise and emotion, and eight sudden deaths probably caused by LQTS, prior to the proband's, were identified from family records. The large number of clearly affected persons allowed successful application of the newly described linkage analysis technique, localizing the position to the Harvey ras-1 locus on chromosome 11. ^[31] In 1996, the gene was identified by positional cloning ^[89] and named *KvLQT1*, because it appeared to encode a novel voltage gated potassium channel with a putative shaker-like potassium channel topology ([Fig. 3](#)), with six transmembrane-spanning domains, a pore region, and intracellular amino and carboxy terminals. The functional potassium ion channels are formed by the assembly of four of these units, a tetramer.



Figure 2. A 12-lead ECG from a symptomatic 18-year-old female LQT1 patient. The T-wave morphology is common for the LQT1 genotype. The QT is 0.45 seconds and QTc is 0.52 seconds.



Figure 3. Molecular topology of the *KvLQT1* gene. (Courtesy of Don Atkinson, Salt Lake City, UT.)

The discovery of the gene mutations and their physiologic consequences has expanded markedly the understanding of the molecular basis of arrhythmias. Therefore, a brief discussion of the findings in each genotype follows.

KvLQT1 (LQT1) and MinK (LQT5)

KvLQT1 coassembles with the small gene *MinK* to form the I_{Ks} delayed rectifier potassium channel. [8] [28] *KvLQT1* encodes for the larger alpha subunit and *MinK* the small beta subunit of I_{Ks} . *KvLQT1* consists of 16 exons, spans 400 kb, has relatively small amino and carboxy termini, and encodes a protein of 676 amino acids. [61] At least 78, mostly missense, mutations of *KvLQT1* have been reported, accounting for approximately 45% of the currently known LQTS mutations. They primarily occur in the intracellular, transmembrane-spanning, and pore domains, with a few in the extracellular region. *MinK* (also known as *KCNE1* or *IsK*) has just three exons, spans approximately 40 kb, and encodes a protein of 129 amino acids. It has a single transmembrane spanning domain with small intra- and extracellular components (Fig. 4). Only a few mutations of this gene have been identified, accounting for about 2% of known LQTS mutations. [61] The *stoichiometry* of the alpha-beta subunit complexes is not clear. Four alpha subunits (*KvLQT1*) are thought to form a tetramer to make a functional channel unit. The number of beta subunits (*MinK*) that are involved in the assembly of the channel protein, however, is not certain. [61]



Figure 4. Molecular topology of the *MinK* gene. (Courtesy of Don Atkinson, Salt Lake City, UT.)

HERG (LQT2) and MiRP1 (LQT6)

HERG, the "human ether-a-go-go related" gene, is the *LQT2* gene, mutations of which cause chromosome 7-linked LQTS. [13] *MinK*-related peptide 1 (*MiRP1*) is a small protein similar in size and function to *MinK* and sits adjacent to *MinK* on chromosome 21. [4] *HERG* and *MiRP1* coassemble to form the channel conducting the rapidly activating delayed rectifier current I_{Kr} . *HERG* encodes for the alpha subunit, and *MiRP1* the beta subunit, in a fashion similar to *KvLQT1* and *MinK*. *HERG* has a putative shaker-like structure (Fig. 5) similar to *KvLQT1*, but has more extensive amino and carboxyl termini than does *KvLQT1*. *HERG* consists of 16 exons, spans 55 kb, and encodes a protein of 1159 amino acids. More than 81 mutations of the gene have been identified thus far, representing approximately 46% of the known LQTS gene mutations. [61] Most mutations are in the spanning domains and the pore region, but unlike *KvLQT1* there are also many mutations in the amino and carboxyl termini. *MiRP1*, similar to *MinK*, has one spanning domain with small intra- and extracellular components. It encodes a protein of 127 amino acids. Three missense mutations have been identified. Two were associated with only modest QT prolongation. The third was associated with a borderline QT interval, and the disorder was only recognized during clarithromycin administration, giving rise to an apparent drug-induced LQTS. This observation in addition to others [42] provides additional evidence for the concept that drug-induced LQTS may occur in the setting of an underlying abnormal I_{Kr} (or other) channel.

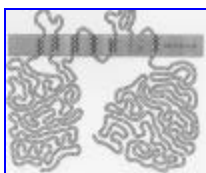


Figure 5. Molecular topology of the *HERG* gene, showing the more extensive intracellular amino and carboxy termini. (Courtesy of Don Atkinson, Salt Lake City, UT.)

SCN5A (LQT3)

The cardiac Na⁺ channel gene *SCN5A* is the LQT3 gene. [9] [13] [90] [91] [92] Mutations cause chromosome 3-linked LQTS. The gene consists of 28 exons spanning 80 kb. *SCN5A* appears to encode a complete ion channel (without complexing with a beta subunit) with 2016 amino acids. *SCN5A* consists of four homologous domains, DI through DIV, each of which consists of a protein with six transmembrane-spanning domains, a voltage sensor in the S4 domain, and a pore region between the S5 and S6 domains (Fig. 6). At least 13 mutations of this gene have been described, making up approximately 6% of known LQTS mutations.



Figure 6. Molecular topology of the *SCN5A* gene. (Courtesy of Don Atkinson, Salt Lake City, UT.)

LQT4

This locus was identified by linkage analysis in one French family, [48] but even several years later the gene has not been reported. It is probable that this is a very rare genotype, and it may be present only in this single family. The phenotype in LQT4 is unique among the LQTS genotypes, with a high incidence of atrial fibrillation and unusual T-wave morphology.

RELATIVE FREQUENCY OF THE LQTS GENOTYPES

In genotyped patients, the *KvLQT1* gene is the most common, being found in about 50% of patients. *HERG* accounts for about 45% of cases. Thus, mutations of the potassium genes *KvLQT1* and *HERG* together cause about 95% of cases. The *SCN5A* gene accounts for about 3% to 5% of the cases. The *MinK* and *MiRP1* genes each account for 1% or less. The LQT4 genotype is very rare. As noted previously, approximately 50% of families who appear to have LQTS by clinical criteria cannot be genotyped to one of these genes. Some of these families probably have mutations of as yet unidentified genes. In others, however, the limitations of linkage analysis and genotyping technology may prevent successful genotyping. The author suggests this because the phenotypes (symptoms and ECG findings) in many families are very much like LQT1 and LQT2. One possible explanation is that there are other beta subunits in the *MinK* family (in addition to *MinK* and *MiRP1*) that coassemble with *KvLQT1* and/or *HERG*. Mutations in such genes could account for some of the genotyping failures with the ECG and other phenotypic features similar to LQT1 or LQT2.

CLINICAL GENETICS

Historically, two forms of LQTS have been recognized. Jervell and Lange-Nielsen syndrome is characterized by severe LQTS with a high incidence of sudden death, severe congenital deafness, and autosomal recessive inheritance. [26] [27] Romano-Ward syndrome shows autosomal dominant inheritance and normal hearing. The molecular findings have clarified the genetics of Jervell and Lange-Nielsen syndrome and have demonstrated all LQTS to be autosomal dominant, but with reduced penetrance and variable expression of the phenotypic features. [35] [38] [22] [81] The deafness in the patient with Jervell and Lange-Nielsen syndrome is inherited as an autosomal recessive trait.

A mutation of one *KvLQT1*, *MinK*, *HERG*, *MiRP1*, or *SCN5A* allele, the heterozygous condition, causes the Romano-Ward syndrome. Because these are autosomal genes, men and women inherit the mutant genes equally. Each offspring of an affected parent has a 50% chance of inheriting the mutant allele, because the affected parent has a 50% chance of contributing the mutant allele to each child. In a very large family, it would be expected that 50% of children would have LQTS. In a family of usual size, however, all, none, or any combination may be affected. The risk is similar to flipping a coin. Flipped three of four times, the result may be all heads, all tails, or any combination.

Jervell and Lange-Nielsen syndrome occurs if a child inherits two mutant *KvLQT1* or *MinK* alleles, one from each parent. They may be either two mutant *KvLQT1* or two *MinK* alleles (the homozygous condition) or one mutant allele of *KvLQT1* and one of *MinK* (the compound heterozygous condition). [36] [49] [50] [63] This inheritance usually occurs in a consanguineous marriage, such as between cousins, in which both have a mutant *KvLQT1* or *MinK* gene. The homozygous or compound heterozygous child has a "double dose" of dysfunctional ion channels, thereby producing the more severe LQTS, with longer QT intervals, earlier and more severe symptoms, and a higher rate of sudden death than seen in the heterozygotes with Romano-Ward syndrome. The deafness of the patient with Jervell and Lange-Nielsen results from the absence of the *KvLQT1* gene. *KvLQT1* is expressed in the inner ear, lung, and kidney in addition to the heart. [71] One normal *KvLQT1* allele is necessary for production of the potassium rich endolymph and organ of Corti in the ear. The heterozygous Romano-Ward patient has one normal allele and, therefore, has normal hearing, but the homozygote or compound heterozygote Jervell and Lange-Nielsen syndrome patient has no endolymph production or organ of Corti formation, resulting in severe, bilateral, congenital deafness along with LQTS. Each child in a Jervell and Lange-Nielsen syndrome family has a 25% chance of being homozygous and having the syndrome, a 50% chance of being heterozygous and having Romano-Ward syndrome, and a 25% chance of being normal. Previously it was thought that the members of a Jervell and Lange-Nielsen syndrome family with normal hearing were unaffected with LQTS. The recognition that the heterozygotes in the Jervell and Lange-Nielsen syndrome families have autosomal dominant Romano-Ward LQTS has important implications for screening and treatment of family members. The mutations causing Jervell and Lange-Nielsen syndrome so far reported produce a less severe I_{Ks} channel defect than those causing the more typical, and obvious, Romano-Ward syndrome. [36] [49] [62] [70] Therefore, the heterozygotes had lesser degrees of QT prolongation, averaging about 0.46 seconds or less, and fewer symptoms than the typical Romano-Ward patients. With this phenotype, they were not detected prior to the genetic analyses. The heterozygotes are not without risk of cardiac events, however, and all potentially affected family members need to be carefully screened by ECG for heterozygous LQTS. These genetic findings in Jervell and Lange-Nielsen syndrome represent a new paradigm of inheritance, namely a combination of a recessive trait, the deafness, and a dominant trait, the LQTS, both existing in members of the same family, caused by the same genetic defect.

CLINICAL MANIFESTATIONS

LQTS occurs in all races and ethnic groups, although the relative frequency in each group is as yet unknown, because no systematic screening of different groups has been attempted. The principal symptoms are syncope and sudden death, from TDP (Fig. 1). Most often, TDP is self-terminating and causes a syncopal episode from which the patient quickly recovers. Cardiac arrest occurs if the TDP is more persistent, and sudden death results if the rhythm does not return to normal spontaneously and the patient is not resuscitated.

Acquired LQTS is usually a result of the administration of drugs (Table 2) that block cardiac ion

channels, most commonly the I_{Kr} potassium channel, which is the channel affected by mutations of the *HERG* and *MiRP1* genes. [32] [46] Drug-induced LQTS is an idiosyncratic response, occurring in just a few percent of patients given these drugs, and the mechanisms rendering one person vulnerable to TDP upon administration of the drug but not most others is unknown. The recognition that both drug-induced and the LQT2 form of inherited LQTS are caused by dysfunction of the I_{Kr} channel has suggested that patients who have drug-induced LQTS may have an underlying genetic predisposition. We, and many others, have identified patients with apparent acquired LQTS who, upon further investigation, turn out to have inherited LQTS. Some had prolonged QT intervals on prior ECGs but had been overlooked as asymptomatic LQTS patients. Some, however, have normal to borderline QT intervals. The recognition that some LQTS gene carriers have normal to borderline QT intervals, which we first reported in 1992, [84] certainly supports the hypothesis that patients with acquired LQTS may have an underlying genetic predisposition, which would render the patients vulnerable to TDP if exposed to QT-prolonging drugs. [4] [14] [35] [42] [81] Acquired LQTS also occurs as a consequence of a number of acute and chronic neurologic disorders, such as subarachnoid hemorrhage and diabetic autonomic neuropathy, [18] [22] [29] presumably because of effects of these diseases on the autonomic nervous system center [2] [3] [95] with resultant alterations of cardiac repolarization. An association between LQTS and sudden infant death syndrome also has been suggested. [51] [55] As is well known, electrolyte disturbances such as hypokalemia and hypomagnesemia also can cause QT prolongation, T-wave abnormalities, and arrhythmias.

Syncope, caused by TDP, is the primary symptom in inherited LQTS. Patients may have one to hundreds of episodes. The symptoms commonly occur within the first few years of life in patients with Jervell and Lange-Nielsen syndrome patients, and the mortality rate with this form is higher than in patients with Romano-Ward. In Romano-Ward syndrome, the median ages at symptom onset and sudden death are in the pre- to midteenaged years. Of interest, at least one-third of gene carriers never develop symptoms, lead completely normal lifestyles, and have normal lifespans. Approximately one third has just one to a few syncopal spells as children, then none thereafter. [81] At present, it is not possible to determine accurately which course any given patient will follow. The risk of cardiac events (syncope, aborted sudden death, sudden death) varies somewhat by genotype. [98] The cumulative mortality rate is similar in all three genotypes, but the risk of having a cardiac event appears to be higher in LQT1 and LQT2 patients than in the LQT3 patients. In this study, 62% of LQT1, 46% of LQT2, and 18% of LQT3 patients had symptoms between birth and age 40 years. Although the cardiac events were less frequent in LQT3 patients, the percentage of cardiac events that were lethal was higher (20%) than in LQT1 or LQT2 (4%).

A number of publications have suggested that seizures are a feature of LQTS. Certainly, the syncopal episodes of many LQTS patients mistakenly have been labeled seizures. It is not clear that LQTS patients actually have seizures as part of the phenotype. Uncommonly, a protracted syncope leads to an hypoxic seizure. Otherwise, it is my belief that seizures are not a part of LQTS. The history of the event usually allows differentiation between a seizure and a cardiac syncope if a careful accounting of the circumstances surrounding the event is available to the physician. With a sketchy history, the differentiation is often difficult.

Syncope and sudden death often occur most during exercise or emotion, with an important minority occurring during sleep. Events are uncommon while patients are awake and at rest and without apparent provocation. The precipitating processes vary by genotype. [53] [69] [94] Patients with mutations affecting the I_{Ks} channel (LQT1, LQT5, Jervell and Lange-Nielsen; the *KvLQT1* and *MinK* genes) have events almost exclusively during exercise or emotion (for example, startle, fright, and anger). Those with mutations affecting I_{Na} (LQT3; the *SCN5A* gene) have the large majority of their events during sleep. It is unknown whether dreams, stages of sleep, or bradyarrhythmias play a role in these events. In patients with mutations affecting the I_{Kr} channel (LQT2; the *HERG* and *MiRP1* genes), the events are about equally

divided between exercise or emotion and sleep. Auditory stimuli more frequently precipitate events in LQT2 patients than LQT1 patients. ^[94]

It is not entirely clear just how often sudden death occurs in LQTS patients. Most reports have included primarily highly symptomatic patients and small family groups. If the asymptomatic and briefly symptomatic patients and the 40% of gene carriers with normal to borderline QT intervals are included, sudden death appears to occur in as many as 30% of untreated, actively symptomatic patients, and about 5% of all gene carriers. ^[98] Importantly, sudden death may be the first manifestation of the disease, ^[43] ^[81] and thus our recommendation is that asymptomatic patients should be treated prophylactically with beta-blockers, as one cannot accurately predict the risk in a given patient, and a "second chance" may not be available.

ECG MANIFESTATIONS

The predominant feature is, of course, QT prolongation. The QTc averages 0.49 seconds ^[82] ^[83] ^[98] in both LQT1 and LQT2 genotypes. In the modest number of LQT3 patients available for study, the values appear to be somewhat longer, with a mean value around 0.51 seconds. ^[98] The range of QTc intervals extends from about 0.41 seconds to more than 0.60 seconds. Although QT-interval prolongation is the characteristic feature of LQTS, it is not always present. We first demonstrated this finding in 1992 in the family we initially genotyped to the Harvey-ras-1 locus on chromosome 11. Using the genetic results to identify LQTS patients rather than the ECG allowed us to determine the spectrum of QT intervals in 68 LQTS patients. ^[82] Five percent of the gene carriers had a QTc of no more than 0.44 seconds, commonly considered to be normal, and another 30% had a QTc between 0.45 and 0.47 seconds, values that overlapped those of a nongene carrier normal cohort. Thus, 35% of these LQTS gene carriers had normal to nondiagnostic QT intervals. The disease gene in this family was subsequently identified as the *KvLQT1* gene. ^[89] We have expanded that family progressively and added many others, including LQT2 and LQT3 families, in order to further the evaluation of QTc intervals in gene carriers. [Figure 7](#) shows the QTc distribution in 301 gene carriers with the LQT1, LQT2, and LQT3 genotypes. The wide range of QTc intervals in LQTS patients is evident. This wide range is evident in all genotypes and within all sizeable families of each genotype. ^[84] The factors responsible for such a wide range of values, even among members of a single family with the same gene and same mutation, are not known. In these 301 carriers, 12% had a normal QTc (no more than 0.44 seconds) and 30% had a QTc between 0.45 and 0.47 seconds. By genotype, 12% of LQT1, 17% of LQT2, and 5% of LQT3 patients had QTc values no more than 0.44 seconds. ^[83] Similar percentages have been reported from the International Long QT Syndrome Registry in a smaller number of gene carriers, with 11% of LQT2, and 8% of LQT3 patients having QTc no more than 0.44 seconds. ^[98] Thus, LQTS has reduced penetrance of the prolonged QT phenotype, and diagnosis by ECG may be difficult, because the QTc is neither completely sensitive nor specific. Obviously, LQTS cannot be excluded by a normal QTc interval on the resting ECG. A sensitivity and specificity analysis of diagnostic utility of the QTc was performed on the 301 gene carriers and a similar sized group of genotyped noncarriers. The analysis showed that a QTc interval of 0.47 seconds in men and a QTc of 0.48 seconds in women was 100% sensitive for LQTS, and a QTc no more than 0.40 seconds in men and no more than 0.42 seconds in women was 100% specific for excluding LQTS. The best overall diagnostic discrimination was present at a QTc of 0.46 seconds, with overall predictive accuracy at about 93%. Exercise testing is often of help in clarifying the situation in those 40% of patients with QTc values in the nondiagnostic range of 0.41 to 0.47 seconds. ^[24] ^[30] ^[65] ^[75] ^[93] An abnormal QT response to exercise, with failure to decrease appropriately, that is, in proportion to the decrement in cycle length, seems to be characteristic of the LQT1 genotype, ^[75] to be variable in the LQT2 genotype (about 50% of the time in our experience), and not to occur in the LQT3 genotype, in which the QT shortening even may be exaggerated. ^[54] The abnormal QT dynamicity is best demonstrated by a

comparison of the QT interval with the QS2 interval (a measure of mechanical systole) ([Fig. 8](#)).^[26] In normal subjects, the QT and QS2 intervals are essentially the same, and the ratio of QT:QS2 approximates 1.0, both at rest and during exercise. In contrast, in LQT1 and many LQT2 patients, the QT and QS2 responses to exercise are disparate. The QS2 is normal, but the QT is longer than QS2 at rest and becomes proportionately even more abnormal during exercise and especially early recovery. The physiologic mechanisms responsible for this response in the LQT1 patients are related to the previously mentioned kinetics of I_{Ks} , including the very slow inactivation,^[66] which allows the channels to remain open accumulatively at fast heart rates, thus increasing the repolarizing current at higher heart rates and the amplification of current by beta-adrenergic stimulation.^{[28] [42] [64]} These factors are thought to be responsible for the shortening of the action potential duration (APD) with exercise and increasing heart rate in normal subjects.^{[87] [88]} In LQT1 patients, both of these mechanisms are impaired, the I_{Ks} current presumably does not increase during exercise or adrenergic stimulation, and the QT shortening response is decreased to absent, as manifest in [Figure 8](#). The mechanism for an abnormal QT dynamic response in some of the LQT2 patients is not yet clear.

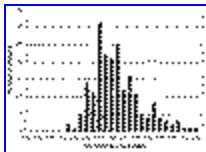


Figure 7. Distribution of QTc intervals in 301 LQTS gene carriers. The very broad range of QTc intervals is evident as is the presence of gene carriers with normal to borderline QTc intervals of 0.41 to 0.47 seconds.

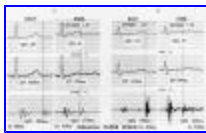


Figure 8. Electrocardiographic and phonocardiographic recordings at rest and exercise in a normal subject (A) and a patient with the *KvLQT1* genotype of LQTS (B). The relationship between the QT interval and the QS2 interval is shown in both patients. The relationship is quantitated by calculating the QT/QS2 interval. In the normal subject, the QT and QS2 intervals are similar during both rest and exercise, whereas in the LQTS patient, the QT shortens minimally during exercise in spite of a reduction of cycle length from 855 to 520 msec. The QS2 interval shortened normally (compare the QS2 in the LQTS patient to that of the normal, at essentially the same cycle length). The abnormal relationship between QT and QS2 is demonstrated by the marked increment in QT/QS2 ratio to 1.52.

Abnormalities of T-wave morphology also have been described commonly in LQTS patients. Data from the International Registry suggested that specific morphologies might be present in each genotype.^[34] More recently, 10 T-wave patterns that may be relatively genotype-specific have been described.^[23] Examples of common T-wave patterns in LQT1 and LQT2 patients are shown in [Figures 2](#) and [9](#). These patterns may be useful for predicting the molecular genotype of LQTS patients. At present, molecular genotyping is expensive and time-consuming, and not available for most patients. Genotype prediction by ECG pattern could be useful for limiting the initial genetic search strategy to the predicted gene, which would reduce search time and cost. Further, as molecular-based treatments become available, ECG prediction of genotype could be helpful in identifying patients suitable for treatment.

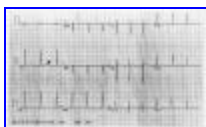


Figure 9. A 12-lead ECG from a 16-year-old LQT2 patient with a mutation of the *HERG* gene. This genotype is characterized by bifid T waves (*arrow*), particularly present in inferior and lateral precordial leads. The QT interval is 0.43 seconds and the QTc is 0.47 seconds.

PATHOPHYSIOLOGY

Although the physiologic defects in the different LQTS genotypes are diverse, all cause prolongation of

the APD. The APD prolongation renders the myocytes vulnerable to early afterdepolarizations (EADs), which are the initiating mechanism for the TDP arrhythmia. APD prolongation produces a baseline propensity to EADs by activation of L-type Ca^{++} channels, ^[25] providing the inward depolarizing current necessary for generating the EAD. It would appear, though, that additional physiologic perturbation must be present in LQTS patients in order to develop EADs and TDP, because most patients have years, sometimes lifetimes as noted previously, with prolonged QT intervals yet no TDP or symptoms. The recognized perturbations (triggers) seem to vary by genotype as discussed earlier in text. The prolongation of APD is not homogeneous in all myocytes, which causes both transmural and regional heterogeneity of repolarization, with particular variability being demonstrated between the epicardial, endocardial, and midmyocardial (M-cell) myocytes. It is proposed that the dispersion of recovery provides the substrate for a reentry **ventricular tachycardia**, which is responsible for the maintenance of the TDP. To further our understanding of the arrhythmias of LQTS, we first look at the unique physiologic characteristics of each genotype and then discuss the TDP arrhythmia from the viewpoint of new and important experimental models of LQTS.

HERG encodes a voltage-dependent K channel that is responsible for the rapidly activating, rapidly inactivating outward current I_{Kr} , ^[43] ^[46] one of the two major currents responsible for repolarization of the myocyte, the other being I_{Ks} . The mutations of *HERG* or *MiRP1* cause a reduction of the magnitude of the I_{Kr} current and, thus, prolong the APD. Variable degrees of channel impairment occur depending upon the specific mutation. ^[45] In most cases, the current reduction is severe. Depending upon the tetramer assembly process, one or all four of the units could be mutant types, or normal ("wild") types. The mutant units are nonfunctional and do not contribute to repolarization. This by itself decreases the current. The current reduction is usually more severe than would be predicted from the effect of the mutant proteins, however, because of the presence of a dominant-negative or "poison pill" effect in which the mutant units adversely affect the wild-type units, thus causing more dysfunction than would be expected from just the mutant units. In the *HERG* (LQT2) genotype, TDP and symptoms occur both during sleep and during stress and exercise. The mechanism of TDP during sleep, seen in LQT3 as well as LQT2, is not well understood. The mean QT duration and range of QT values are the same in LQT2 patients as in LQT1 patients, yet LQT1 patients do not have sleep-related TDP. Thus, the QTc duration is not the difference. A potential mechanism for the TDP during sleep in LQT2 patients may be related to the unique inactivation kinetics of *HERG*. ^[60] ^[96] *HERG* demonstrates strong inward rectification and large outward current if reactivated quickly after repolarization has occurred. *HERG* would be particularly active, therefore, in the presence of afterdepolarizations, and *HERG* is reported to be specifically involved in suppression of afterdepolarizations. A reduction of *HERG* current in LQT2 patients may encourage the development of TDP during sleep-related bradycardia, for example, if the APD prolongs further and EADs develop and are not suppressed by *HERG* reactivation. A further mechanism that may contribute to TDP at rest or in sleep is suggested by experimental models of LQT2. An arterially perfused wedge of canine left ventricle ^[52] was developed to model the LQTS genotypes. Using the I_{Kr} blocker d-sotalol, a model of LQT2 was created. The d-sotalol increased transmural dispersion of recovery at baseline, because of greater prolongation of APD in M-cells compared with epi- or endocardial cells, and spontaneous and stimulation-induced TDP-like activity was produced. Because M-cells show excessive APD prolongation at longer cycle lengths, ^[4] ^[5] ^[6] it could be that even greater propensity to EADs and TDP occurs at night during bradycardia. The physiology of LQT2 must involve other factors in addition to these speculations, of course, in order to explain TDP during exercise and emotion, and also the absence of any symptoms in many patients with LQT2 whose ECG and QT intervals look no different from those with symptoms.

KvLQT1 and *MinK* encode for the I_{Ks} channels. Similar to the situation with *HERG*, mutations of these genes produce a variable reduction in current. The mechanism is usually, but not always, a dominant-negative effect. Reduction of the I_{Ks} current causes prolongation of the APD and predisposition to

EADs. In contrast to I_{Kr} , the I_{Ks} current is slowly activating and inactivates very slowly. [66] As noted previously, the very slow inactivation of I_{Ks} causes current increases at fast heart rates, and also, I_{Ks} is activated by beta-adrenergic stimulation. These features appear to be the principal mechanisms by which APD shortens with exercise and increasing heart rate. In studies using the perfused canine wedge preparation referred to previously, a model of LQT1 was produced by the I_{Ks} blocker chromanol 293B. [56] The APD of all cell types was increased, but similarly, so there was no increment in transmural dispersion of recovery. This could correlate with the near complete absence of sleep- or rest-related cardiac events in LQT1. The administration of isoproterenol abbreviated the epi- and endocardial APD but not that of the M cells, causing an increase in transmural dispersion and spontaneous and stimulation-induced TDP like activity. These changes are concordant with the exercise or emotion precipitation of cardiac events in LQT1 patients.

LQT3 is caused by mutations of the cardiac sodium-channel gene *SCN5A*. The normal sodium channel opens briefly to allow a large influx of sodium ions, which depolarizes the cell. The channel quickly inactivates, leaving just a small persistent inward current. In contrast to the effect of mutations on the K genes, which produce a "loss of function" abnormality, the *SCN5A* gene mutations cause an unusual abnormality, a "gain of function" abnormality. The mutations of *SCN5A* interfere with inactivation of the channel, allowing short or longer repetitive reopenings of the channel throughout the action potential. [20] [90] [92] Variable degrees of dysfunction have been reported with different mutations. As with *KvLQT1* and *HERG*, it is not clear that the phenotype or risk of cardiac events correlates with the degree of channel dysfunction. The persistent inward current, the "gain of function," causes prolongation of the APD and predisposition to EADs. In general, the degree of QT prolongation is greater in LQT3 than in LQT1 and LQT2 patients. Also, in the canine wedge model of LQT3 produced by administration of the sodium-channel blocker ATX-II, [52] there was preferential and marked prolongation of M-cell APD, producing a much greater degree of transmural dispersion of recovery than seen in the LQT1 and LQT2 models. These findings might suggest that LQT3 patients have a higher risk of cardiac events than the other genotypes. The risk of events, however, has been reported to be actually lower in LQT3 compared with LQT1 and LQT2, although the percentage of events that were lethal was higher in LQT3, [98] as discussed previously.

If EADs are the initiating mechanism for Tdp, [5] [11] [17] [32] [37] [44] [59] [68] [92] what mechanism is responsible for the sustained arrhythmia? Sustained triggering and reentry both have been considered. Recently, animal models of the LQT2 and LQT3 genotypes have supported a reentry mechanism. [2] [15] [16] [17] A complex reentrant arrhythmia initiated by EADs was responsible for the polymorphic VT in these models. The unique morphology of TDP was caused by a complex, scroll-like activation pattern through both ventricles, with the activation pattern, and ultimately termination, determined by functional conduction block.

Most cardiac events in LQTS are syncope, caused by self-terminating TDP. In some patients, however, the TDP degenerates into ventricular fibrillation, and the patient has sudden death. This may occur with the first syncope or after many syncopal episodes. It is not known why TDP degenerates to ventricular fibrillation in some cases and not most others, but it seems reasonable to suspect that the degree of dispersion of repolarization at the time of the TDP plays an important role. Measurements of repolarization at rest such as QT duration or QT dispersion do not provide accurate predictions of risk. Measures during exercise or sleep, for example, might be more predictive. TDP usually follows a short-long-short cycle sequence in which the complex completing the last (short) cycle is a premature ventricular contraction (PVC). [21] [85] [86] It is not known yet if the cycle-length changes are different by genotype. The effect of cycle length recently has been reported from an animal model of LQT3. [45] In some cases the immediate precipitator of arrhythmia was the occurrence of a second EAD, arising from a different site than the first, infringing upon the recovery pattern of the first EAD. In other cases a slight

lengthening of the "long-cycle" cycle length resulted in increased dispersion of repolarization at key sites, particularly in M-cell areas. This resulted in new areas of functional conduction block and slowed conduction, which facilitated reentry. These animal studies suggest that a variety of physiologic changes, some quite subtle, play a role in determining when TDP develops. These types of studies ultimately may help to explain why some patients with LQTS never have symptoms, others have many syncopal spells but never sudden death, and yet others die with their first episode.

MANAGEMENT OF LQTS

The gold-standard therapy for LQTS remains beta-blocker administration, which is effective in the large majority of patients. Like virtually all treatments, there are treatment failures and partial responders, but it is estimated that beta-blocker treatment is effective in 80% to 90% of patients with a significant reduction in rate of sudden death. ^{[10] [19] [33] [52] [74] [80] [97]} Our long-term follow-up of a number of LQT1 patients suggest that beta-blockers are particularly effective in this genotype. ^{[72] [79]} It is very important that patients on beta-blockers are compliant and take their medication regularly. In LQT2 patients, one half or more of events are triggered by exercise or stress, and beta-blockers are a likely to be effective, but the remainder have sleep or rest precipitation, and the physiology and therapeutic needs in these events may be different. Clinical experience in the proportionately few LQT3 patients precludes an accurate assessment of beta-blocker efficacy, but some clinical observations and results in experimental models suggest the possibility of lower efficacy or even adverse effect. ^[57] The implantable cardiac defibrillator (ICD) is being employed with increasing frequency, especially in apparently high-risk patients such as those experiencing TDP while on beta-blockers and those who have had cardiac arrest. Pacemakers and left stellatectomy also have been shown to be of benefit, particularly in those with bradycardia and failure on antiadrenergic therapy, respectively. Asymptomatic children and young persons should be treated prophylactically with beta-blockers upon diagnosis. It is not possible to predict whether they will have symptoms subsequently; approximately two thirds will, and some will have sudden death as their first event, as noted previously.

The molecular findings have raised the possibility of genotype-specific and molecular-directed therapy. ^{[39] [40]} The first suggestion came from the initial studies on *HERG* channel function. It was discovered that the I_{Kr} current was inversely proportional to the extracellular potassium ion concentration. ^[46] This paradoxical effect suggested that increased serum potassium might have therapeutic benefit in patients with the *HERG* genotype. An acute trial of potassium loading in a small number of patients with chromosome 7 LQTS demonstrated impressive shortening of the QT interval and normalization of T-wave morphology. ^[42] Longer-term trials to determine the therapeutic effectiveness of this regimen are underway. Another study reported the difficulty of maintaining elevated serum potassium over time, ^[67] and it may be difficult to achieve effective therapy over the many years required for protection from syncope and sudden death in a typical patient with LQTS detected during childhood. It is not yet known if potassium loading can prevent TDP and sudden death.

In LQT3, both experimental and clinical observations indicate that sodium-channel blockers, such as mexiletine, can prevent the repetitive, inappropriate openings and shorten the QT interval. ^{[41] [54]} It is as yet unknown if this treatment prevents TDP, syncope, and sudden death, and clinical trials are underway in LQT3 patients.

In LQT1, potassium-channel openers have theoretic potential for treatment, and there is some evidence of potential therapeutic efficacy. ^[58] They have more effect, however, on vascular than on cardiac channels, and it may be difficult to give doses which are cardioeffective, because they may be associated

with unacceptable side effects. [24]

SUMMARY

In conclusion, much has been learned in the past several years regarding the molecular biology of LQTS, and this information has been directly applicable to the clinical care of patients with this syndrome. The knowledge also has been of considerable importance for understanding the molecular basis of arrhythmias in general and is providing insights into potential molecular-based therapies for arrhythmias.

ACKNOWLEDGMENTS

Sincere appreciation is expressed to Don Atkinson in Dr Mark Keating's laboratory at the University of Utah, who kindly provided the graphic representations of the LQTS gene morphologies, [Figs. 3](#) through [6](#). Also, great appreciation to Raymond Wosley, MD, PhD, of Georgetown University, who compiled the list of drugs to avoid, shown in [Table 1](#), for the sudden arrhythmia death syndromes (SADS Foundation, Salt Lake City, UT), and to the SADS Foundation for permission to reproduce the list for this article. Many thanks also to Katherine Timothy and Jeanette Buenger for their help in preparation of the article.

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