

Arrhythmogenic Disorders of Genetic Origin

Long-QT Syndrome From Genetics to Management

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The congenital long-QT syndrome (LQTS) is a life-threatening cardiac arrhythmia syndrome that represents a leading cause of sudden death in the young. LQTS is typically characterized by a prolongation of the QT interval on the ECG and by the occurrence of syncope or cardiac arrest, mainly precipitated by emotional or physical stress.

Since 1975,¹ 2 hereditary variants, the Romano-Ward (RW) syndrome^{2,3} and the extremely severe Jervell and Lange-Nielsen (JLN) syndrome,^{4,5} which is associated with congenital deafness, have been included under the comprehensive name of LQTS, one of the best understood monogenic diseases. The usual mode of inheritance for RW is autosomal dominant, whereas JLN shows autosomal recessive inheritance or sporadic cases of compound heterozygosity.

Several reasons make LQTS an important disease. It can often be a lethal disorder, and symptomatic patients left without therapy have a high mortality rate, 21% within 1 year from the first syncope.⁶ However, with proper treatment, mortality is now \approx 1% during a 15-year follow-up.⁷ This makes inexcusable the existence of symptomatic but undiagnosed patients. LQTS is without doubt the cardiac disease in which molecular biology and genetics have made the greatest progress and unquestionably is the best example of genotype-phenotype correlation. In this regard, it represents a paradigm for sudden cardiac death, and its progressive unraveling helps to better understand the mechanisms underlying sudden death in more complex disorders, such as ischemic heart disease and heart failure.

This review will outline the current knowledge about the genetics of LQTS and provide essential clinical data, whereas its primary focus will be on our approach to the clinical management of these patients.

Genetics of LQTS

The electrocardiographic QT interval represents the depolarization and the repolarization phases of the cardiac action potential. The interplay of several ion channels determines the action potential duration. Decreases in repolarizing outward K^+ currents or increases in depolarizing inward sodium or calcium currents can lead to

prolongation of the QT interval, thus representing a pathophysiological substrate for LQTS. Not surprisingly, since the dawn of the molecular era in LQTS, genes encoding ion channels responsible for the timely execution of the cardiac action potential were considered plausible targets for investigation. After the identification of the first 3 genes associated with the most frequent variants,^{8–10} 10 more genes involved in fine-tuning the cardiac action potential have been associated with LQTS (Table 1).

Major LQTS Genes

By far, *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3) are the most common LQTS genes, accounting for \approx 90% of all genotype-positive cases.^{11,12} *KCNQ1* encodes the α -subunit of the K^+ channel $Kv7.1$, generating I_{Ks} , which, being physiologically increased by sympathetic activation, is essential for QT adaptation when heart rate increases. When I_{Ks} is defective, the QT interval fails to shorten appropriately during tachycardia, thus creating a highly arrhythmogenic condition. Heterozygous *KCNQ1* mutations cause the dominant RW LQT1 syndrome and account for the majority of disease-causing variants. Homozygous mutations in *KCNQ1*, or compound heterozygous mutations, cause the recessive JLN variant, characterized by deafness because of the reduced I_{Ks} in the inner ear.^{4,5}

The mutations may produce different effects in this multimeric K^+ channel. Defective and wild-type protein subunits may coassemble and exert a dominant negative effect on the current. Alternatively, some mutant subunits may not coassemble with the wild-type peptides, resulting in a loss of function that reduces the I_{Ks} current by \leq 50% (haploinsufficiency). The latter may also result as a consequence of mutations interfering with intracellular subunits trafficking, preventing the mutated peptides from reaching the cell membrane.

However, neither the localization of a mutation nor its cellular electrophysiological effect is sufficient to predict the impact on clinical manifestations.¹³ A good example is represented by a large cohort of LQT1 patients from all over the world, all carrying the A341V hot-spot mutation located in the

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Table 1. LQTS Genes

Gene	Syndrome	Frequency	Locus	Protein (Functional Effect)
<i>KCNQ1</i> (LQT1)	RWS, JLNS	40–55	11p15.5	Kv7.1 (↓)
<i>KCNH2</i> (LQT2)	RWS	30–45	7q35–36	Kv11.1 (↓)
<i>SCN5A</i> (LQT3)	RWS	5–10	3p21–p24	NaV1.5 (↑)
<i>ANKB</i> (LQT4)	RWS	<1%	4q25–q27	Ankyrin B (↓)
<i>KCNE1</i> (LQT5)	RWS, JLNS	<1%	21q22.1	MinK (↓)
<i>KCNE2</i> (LQT6)	RWS	<1%	21q22.1	MiRP1 (↓)
<i>KCNJ2</i> (LQT7)	AS	<1%	17q23	Kir2.1 (↓)
<i>CACNA1C</i> (LQT8)	TS	<1%	12p13.3	L-type calcium channel (↑)
<i>CAV3</i> (LQT9)	RWS	<1%	3p25	Caveolin 3 (↓)
<i>SCN4B</i> (LQT10)	RWS	<1%	11q23.3	Sodium channel-β4 (↓)
<i>AKAP9</i> (LQT11)	RWS	<1%	7q21–q22	Yotiao (↓)
<i>SNTA1</i> (LQT12)	RWS	<1%	20q11.2	Syntrophin α1 (↓)
<i>KCNJ5</i> (LQT13)	RWS	<1%	11q24	Kir3.4 (↓)

LQTS indicates long-QT syndrome; *KCNQ1*, potassium voltage-gated channel, KQT-like subfamily, member 1; RWS, Romano-Ward syndrome; JLNS, Jervell and Lange-Nielsen syndrome; *KCNH2*, potassium voltage-gated channel, subfamily H, member 2; *SCN5A*, sodium voltage-gated channel, type V, α subunit; *ANKB*, ankyrin B; *KCNE1*, potassium voltage-gated channel, ISK-related subfamily, member 1; MinK, minimal K⁺ ion channel; *KCNE2*, potassium voltage-gated channel, ISK-related subfamily, member 2; *MiRP*, MinK-related peptide 1; *KCNJ2*, potassium channel, inwardly rectifying, subfamily J, member 2; AS, Andersen syndrome; *CACNA1C*, calcium voltage-dependent channel, L type, α-1C subunit; TS, Timothy syndrome; *CAV3*, caveolin 3; *SCN4B*, sodium voltage-gated channel, type IV, β subunit; *AKAP9*, A-kinase anchor protein 9; *SNTA1*, syntrophin α1; *KCNJ5*, potassium channel, inwardly rectifying, subfamily J, member 5.

Functional effect: (↓) loss-of-function or (↑) gain-of-function at the cellular in vitro level.

transmembrane portion of the K⁺ channel with a mild dominant-negative functional effect; in these patients, we demonstrated a strikingly higher clinical severity among LQT1 carriers of A341V compared with LQT1 non-A341V patients, with mutations either localized to transmembrane domains or exhibiting a dominant-negative effect.¹³

The second most common gene harboring LQTS mutations is *KCNH2*, encoding the α-subunit of the K⁺ channel conducting the I_{Kr} rectifier (I_{Kr}) current. The rapid I_{Kr} (*KCNH2*) and the slow I_{Ks} (*KCNQ1*) are 2 independent components of the delayed rectifier I_K current, the major determinant of the phase 3 of the cardiac action potential. Mutations in *KCNH2* cause a reduction in I_{Kr} current, through mechanisms similar to the effects exhibited by *KCNQ1* mutations on I_{Ks} current.⁷ Up to 10% of genotyped cases may harbor compound heterozygous mutations on the same or on 2 of the main LQTS genes.^{14,15} Not surprisingly, a more severe cardiac phenotype accompanies compound mutations.^{14–16}

The third major LQTS gene, identified at the end of March 1995,⁸ is *SCN5A*, encoding the α-subunit of the cardiac sodium channel and conducting the depolarizing sodium inward current. A ground-breaking in vitro expression study by Bennett et al¹⁷ in September 1995 showed that the *SCN5A*-ΔKQP mutation produces the LQTS phenotype by increasing the delayed Na⁺ inward current and, therefore, prolonging the

action potential duration. Within a few months, in December 1995, this was followed by our report that the genetic defects in LQTS may be linked to differential responses to heart rate changes and to Na⁺ channel blockers¹⁸ and to the first evidence that mexiletine reduces the late Na⁺ current.¹⁹ This finding paved the way to the search for gene-specific therapies.

Several genetically heterogeneous disorders are also associated with alterations in the sodium current, including Brugada syndrome, atrial fibrillation, sick sinus node syndrome, and the Lev-Lenègre disease. As a further complexity, some *SCN5A* mutations show a pleiotropic behavior and are associated with >1 phenotype, the so-called overlap syndrome.²⁰ When a single mutation can have opposite functional effects (ie, increase and decrease of the Na⁺ current), what matters clinically is the phenotype.

Given the large and growing number of genetic variants identified so far, to distinguish pathogenic mutations from rare variants is critically important. Based on almost 400 definite cases and 1300 controls,²¹ the probability for a missense mutation to be pathogenic appears to depend largely on location. In general, genetic variants located in the pore and transmembrane regions are much more likely to be pathogenic. Whenever a functional study of the specific mutation has been performed, the results may help in assessing its clinical relevance. When these data are missing, as is often the case, it is important to establish whether within the family the mutation cosegregates with either symptoms or QT prolongation. An important take-home message is that the laboratory finding of an aminoacidic substitution should not be automatically taken as an indication of a disease-causing mutation.

Minor LQTS Genes

After the identification of the first 3 LQTS genes,^{8–10} several others were and are being identified; the list will continue to grow for a while.

KCNE1 and *KCNE2* encode the minimal K⁺ ion channel and the minimal K⁺ ion channel–related peptide 1, which represent the main ancillary single-transmembrane β-subunits associated with the α-subunits of *KCNQ1* and *KCNH2*. Mutations in *KCNE1* may cause either the dominant RW (LQT5) or, if present in homozygosity or compound heterozygosity, the recessive JLNS.⁷ The cases of *KCNE2* mutations associated with LQTS are few, and some of them represent acquired LQTS associated with specific drugs, almost all I_{Kr} blockers.⁷

Among the sodium channel interacting proteins, the *CAV3*, *SCN4B*, and *SNTA1* genes are regarded as additional LQTS genes (LQT9, LQT10, and LQT12).^{22–24} The *AKAP9* is involved in the phosphorylation of *KCNQ1*, and its mutations have been described in LQT11.²⁵ Two missense mutations in *CACNA1C*, encoding a voltage-gated calcium channel, are linked to Timothy syndrome (TS; LQT8), a rare and extremely malignant variant.²⁶ Finally, in a large Chinese family, a heterozygous mutation was identified in the inwardly rectifying K⁺ channel subunit Kir3.4, encoded by *KCNJ5*. The variant was present in all the 9 affected family members and was absent in >500 ethnically matched controls, suggesting a role in the pathogenesis of the novel LQT13 variant.²⁷

On the other hand, the *ANKB* and *KCNJ2* genes, often referred to as LQT4 and LQT7, are associated with complex

clinical disorders in which the prolongation of the QT interval is modest and, in our opinion, should not be strictly considered as part of LQTS.⁷

Prevalence

Even though it is customary, when dealing with any cardiac disease of genetic origin, to provide its prevalence, almost always what is presented is largely an educated guess. LQTS represents an exception. For too long, the prevalence of LQTS was assumed to be anywhere between 1/5000 and 1/20000, without any supporting data. The first data-driven indication of the prevalence of LQTS was published in 2009, on the basis of the largest prospective study of neonatal electrocardiography ever performed.²⁸ In 18 Italian maternity hospitals, an ECG was performed in 44 596 infants who were 15 to 25 days old; in this cohort, 0.07% had a QTc >470 ms, and 0.47% had a QTc between 451 and 470 ms. Molecular screening allowed the identification of a disease-causing mutation in 43% of the neonates with a QTc >470 ms and in 29% of those screened with a QTc between 461 and 470 ms. In total, 17 of 43 080 white infants were affected by LQTS, demonstrating a prevalence of at least 1:2534 apparently healthy live births (95% CI, 1:1583–1:4350).²⁸ Considerations based on the number of infants with a QTc >450 ms who were not molecularly screened actually suggest that the prevalence of LQTS is close to 1:2000. This prevalence concerns only infants with an abnormally long QTc and cannot estimate the additional incidence of silent mutations carriers (individuals who carry a disease-causing mutation but who have a normal QT interval).

Clinical Presentation

The clinical manifestations of LQTS have been described in detail too often to deserve additional repetitions here. The reader unfamiliar with LQTS can find these descriptions in previous publications.^{6,7,29} Here, we will mention only a few specific aspects that carry, in our opinion, special significance.

The ventricular tachyarrhythmia that underlies the cardiac events of LQTS is Torsades-de-Pointes, a curious type of ventricular tachycardia that most of the time is self-limiting and produces transient syncope but that can also degenerate into ventricular fibrillation and cause cardiac arrest or sudden death.⁷ It would be extremely important to know what causes Torsades-de-Pointes to stop after a limited number of seconds or to continue, with devastating consequences, but we do not.

The morphology of the T wave is often useful for the diagnosis, and the precordial leads are especially informative when they reveal biphasic or notched T waves.³⁰ T-wave alternans in polarity or amplitude (Figure 1), when observed, is diagnostic as we proposed \approx 40 years ago.³¹ T-wave alternans is a marker of major electric instability and identifies patients at particularly high risk; its presence in a patient already undergoing treatment should alert the physician to persistent high risk and warrants an immediate reassessment of therapy. Sinus pauses, unrelated to sinus arrhythmia, are an additional warning signal especially in patients with *SCN5A* mutations.^{7,32}

Diagnosis and Genetic Testing

Typical cases present no diagnostic difficulty for physicians aware of the disease. However, borderline cases are more complex and require the evaluation of multiple variables besides clinical history and ECG. The diagnostic criteria for LQTS proposed in 1985⁶ remain essentially valid for a quick assessment; however, a more quantitative approach to diagnosis became possible with the presentation of a diagnostic score in 1993 that became known as the Schwartz score, which was updated in 2006.^{33,34} The last update has just been made on the basis of the report on the diagnostic role of QT prolongation in the recovery phase of an exercise stress test^{35,36} (Table 2). The persistent use of the old scoring system by some investigators leads to an underestimation of the patients identified as probably affected and should be discontinued; a score of 3.5 points is sufficient for a high probability of LQTS.

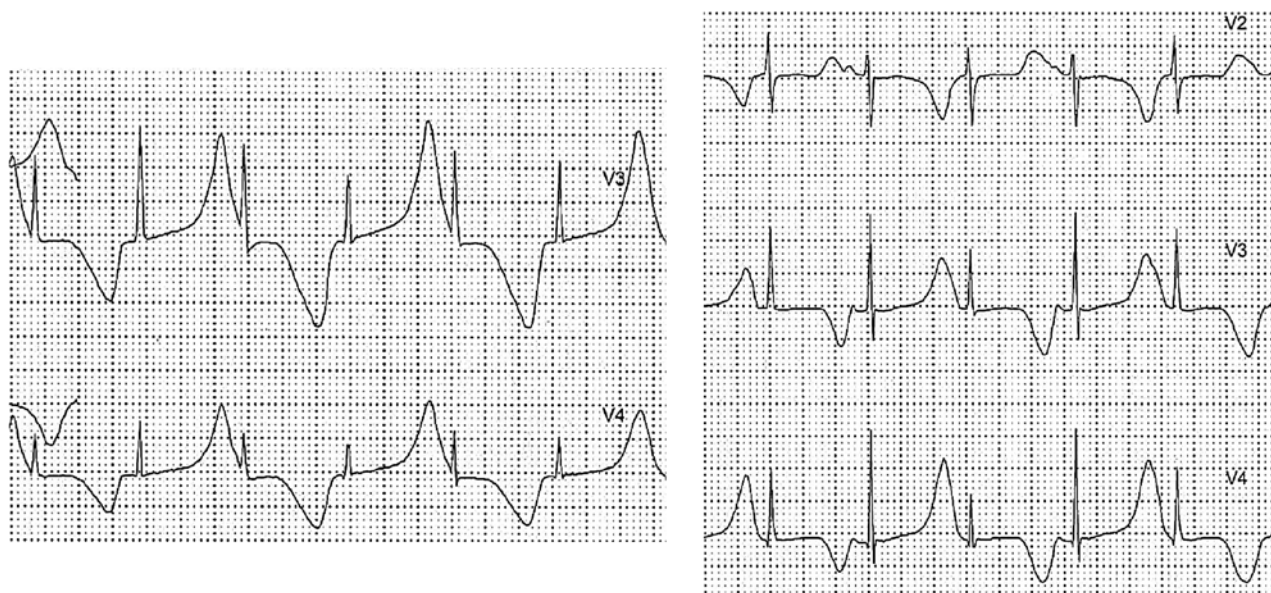


Figure 1. Examples of T-wave alternans from a 2-year-old long-QT syndrome patient with multiple episodes of cardiac arrest. Tracings are from a 24-hour Holter recording.

Table 2. LQTS Diagnostic Criteria of 1993 to 2011

		Points
Electrocardiographic findings*		
A	QTc, † ms	
	≥480	3
	460–479	2
	450–459 (men)	1
B	QTc † 4th minute of recovery from exercise stress test ≥480 ms	1
C	Torsades-de-Pointes ‡	2
D	T-wave alternans	1
E	Notched T wave in 3 leads	1
F	Low heart rate for age §	0.5
Clinical history		
A	Syncop ‡	
	With stress	2
	Without stress	1
B	Congenital deafness	0.5
Family history		
A	Family members with definite LQTS	1
B	Unexplained sudden cardiac death younger than age 30 among immediate family members	0.5

LQTS indicates long-QT syndrome.

*In absence of medications or disorders known to affect these electrocardiographic features.

†QTc calculated by Bazett formula where $QTc = QT / \sqrt{RR}$.

‡Mutually exclusive.

§Resting heart rate below the second percentile for age.

||The same family member cannot be counted in A and B.

Score: ≤1 point: low probability of LQTS; 1.5–3 points: intermediate probability of LQTS; ≥3.5 points: high probability.

Modified from Ref 36.

The importance of a correct diagnosis has assumed a new dimension in the molecular era. A new responsibility for the clinician lies in the identification of the most logical candidates for molecular screening and relates to the availability and cost of genetic testing. The best example of this situation comes from a study by Taggart et al.³⁷ In a group of 176 consecutive patients diagnosed as affected by LQTS and sent to the Mayo Clinic for management and genetic testing, they regarded 41% of them as unaffected, 32% as probably affected, and only 27% as definite cases of LQTS. Genetic testing confirmed the clinical assessment because disease-causing mutations were found in none of the unaffected, in 34% of the probably affected, and in 78% of the definitely affected. It follows that an exceedingly large number of patients incorrectly received the clinical diagnosis of LQTS by their own cardiologists.

It is indeed in the selection of patients with a suspicion of LQTS that the Schwartz score becomes especially useful. As the score gives importance to the degree of QT prolongation, it should be obvious that it cannot help in the identification of the silent mutation carriers. The smart approach consists in the use of the Schwartz score for the selection of those patients who should undergo molecular screening (everyone with a score ≥3.0) and in the use of cascade screening^{38,39} for the identification of all affected family members, including the silent mutation carriers.

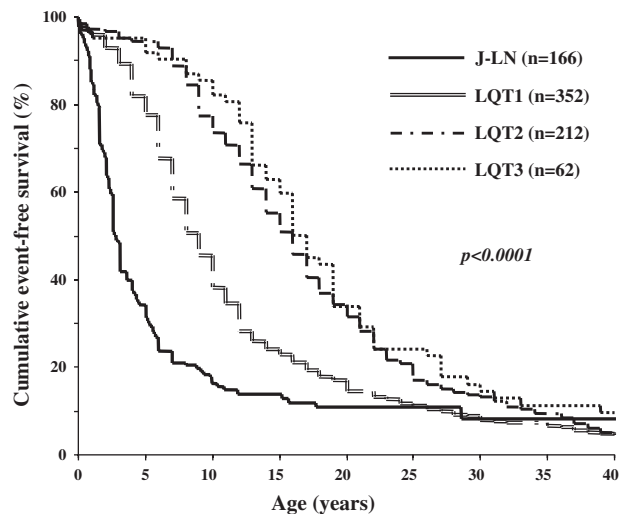


Figure 2. Kaplan-Meier curves of event-free survival comparing Jervell and Lange-Nielsen syndrome (J-LN) patients with long-QT (LQTS) syndrome type 1, LQT2, and LQT3 symptomatic patients (modified from Ref 5).

Malignant Subtypes

Two well-defined LQTS variants carry an especially high risk and are difficult to manage, the JLN syndrome^{4,5} and the TS (LQT8).²⁶

The recessive JLN has the same cardiac phenotype observed in the RW type of LQTS, complicated by a more malignant course and by congenital deafness. The largest study of JLN, based on 187 patients, did show that ≈90% of the patients have cardiac events, that they become symptomatic much earlier than in the other major genetic subgroups of LQTS (Figure 2), and that they do not respond as well to traditional therapy.⁵ Of interest, the patients whose homozygous mutations involve *KCNEL* instead of *KCNQ1* are at lower risk.⁵

The TS is an extremely rare variant characterized by marked QT prolongation associated with syndactyly and often presenting with 2:1 functional atrioventricular block and macroscopic T-wave alternans.²⁶ Congenital heart diseases, intermittent hypoglycemia, cognitive abnormalities, and autism can also be present. Of the 17 children reported by Splawski et al,²⁶ 10 (59%) died at a mean age of 2.5 years.

Genotype-Phenotype Correlation

The clinical manifestations of LQTS may vary according to the different genetic background. The disease-causing gene is the main determinant of the clinical phenotype, but also the position of the mutation in the protein and the specific disease-causing mutation can contribute to clinical severity.

Disease-Causing Gene and Phenotype

In 2003, data on 647 patients of known genotype indicated that life-threatening events were lower among LQT1 patients, higher among LQT2 women than LQT2 men, and higher among LQT3 men than LQT3 women.⁴⁰ The present study also provided the rather unexpected and important information that the number of silent mutation carriers, ie, individuals with a disease-causing mutation but with a normal QT interval, exceeds previous estimates and correlates with the

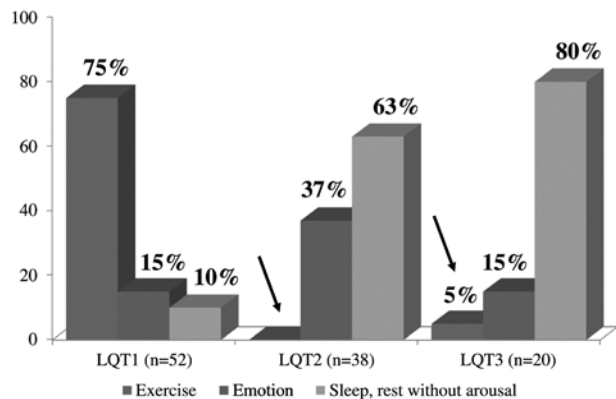


Figure 3. Triggers for all lethal and nonlethal cardiac events in the 3 genotypes (modified from Ref 41).

specific genes. Indeed, silent mutation carriers represent 36% of LQT1, 19% of LQT2, and 10% of LQT3 patients.

In 2001, Schwartz et al⁴¹ examined the possible relationship between genotype and conditions (triggers) associated with the events in 670 symptomatic patients with LQTS and known genotype. As predicted by the impairment in I_{Ks} current (essential for QT shortening during increase in heart rate), most of the events in LQT1 patients occurred during exercise or stress (Figure 3). A highly specific trigger for LQT1 is represented by swimming. Many of the events in LQT2 patients occurred during arousal, especially from auditory stimuli, such as sudden noises and telephone ringing, particularly when occurring at rest. Most of the events in LQT3 occurred while patients were asleep or at rest. LQT2 and LQT3 patients are at low risk for life-threatening arrhythmias during exercise because they have a well-preserved I_{Ks} current, allowing appropriate shortening of the QT interval whenever heart rate increases.

In a study of a uniquely large South African LQT1 founder population, we observed that faster basal heart rate and brisk autonomic responses are associated with a greater probability of being symptomatic, depending again on the gene-specific impairment of I_{Ks} .^{42,43} Relatively high values of baroreflex sensitivity imply an increased ability to change heart rate suddenly, and this could be harmful especially in LQT1 patients: sudden heart rate increases with impaired QT shortening favor the R-on-T phenomenon and initiation of ventricular tachycardia-fibrillation, whereas sudden pauses elicit early afterdepolarizations, which can trigger Torsades-de-Pointes.⁴³ Even in the postpartum period, genotype is important because arrhythmic risk is higher for LQT2 than for LQT1 patients,^{44,45} probably because of sleep disruption and sudden awakening.

Genotype-phenotype correlation exists also in rare and malignant forms of LQTS as shown by the fact that among JLN patients those with *KCNF1* mutations exhibit a markedly less severe clinical course than the majority of patients who have mutations on *KCNQ1*.⁵

Disease-Causing Mutations and Phenotype

In 2002, Moss et al⁴⁶ indicated that LQT2 patients with mutations in the pore region were at higher risk. In 2007, Moss et al⁴⁷ demonstrated that in LQT1 patients both the transmembrane

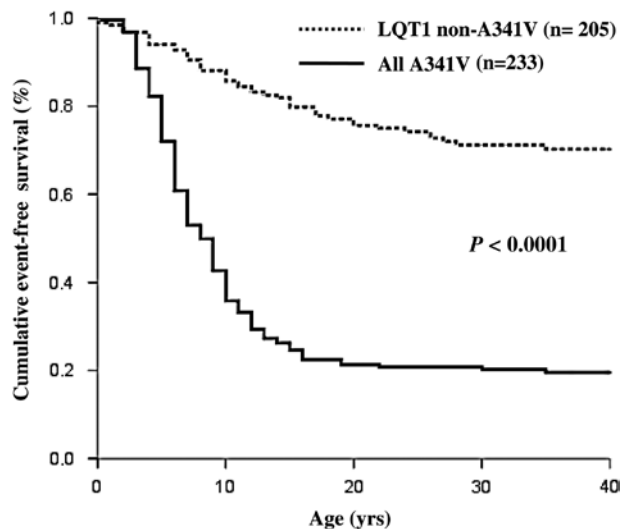


Figure 4. Unadjusted Kaplan-Meier estimate of the cumulative event-free survival (any first event) in the whole (non-South African - South African) A341V population plotted vs LQT1 non-A341V group. Any cardiac event, whichever occurred first, was considered from birth through 40 years of age and before β -blocker therapy. Numbers at risk are indicated (modified from Ref 13).

location of the mutation and their dominant-negative effect are independent risk factors for cardiac events. These studies were important because they called attention to the fact that not all mutations on the same gene produce a similar clinical phenotype and that they were the beginning of a growing number of intriguing revelations on the complexity of the genotype-phenotype correlation.

Probably, the most striking example of mutation-specific behavior comes from *KCNQ1*-A341V, a hot-spot mutation characterized by unusual clinical severity demonstrated by 80% of the patients being symptomatic, with >30% experiencing cardiac arrest or sudden death (Figure 4).^{13,42} What is puzzling is that A341V is only a mildly dominant mutation producing a relatively modest loss of I_{Ks} . The implication is that our current understanding of biophysical cellular studies is still incomplete and fails to allow a direct translation into clinical reality.

Another example of mutation-specific behavior is represented by *SCN5A*-E1784K.⁴⁸ This mutation is the most frequently described Brugada syndrome mutation, and it is also a relatively prevalent mutation among LQT3 patients. It can cause Brugada pattern, long QT, sinus node dysfunction, and life-threatening ventricular arrhythmias.⁴⁸ The management of patients with this or other pleiotropic mutations⁴⁹ should be careful, taking into account that their genetic background could favor different clinical manifestations; their management should be on the basis of the pattern manifested by multiple ECG recordings. However, even if the patient shows a pure LQT3 phenotype among sodium channel blockers, it is wise to avoid flecainide that may induce a Brugada pattern,⁵⁰ whereas mexiletine is not contraindicated. In the study of family members carrying the same mutation, physicians should be aware that they could show clinical signs of either LQTS or Brugada syndrome and should be treated accordingly.

Modifier Genes

The relationship between genotype and clinical phenotype is not necessarily linear in inherited arrhythmias. For example, in LQTS a genetic mutation may exhibit incomplete penetrance.⁵¹ Similarly, certain mutations may have variable expressivity, conferring different risk of disease expression in related individuals. Reasonably, both these aspects are linked to genetic, environmental, or developmental factors that may modulate the disease onset or its clinical severity. The genetic factors involved in this modulation, referred to as modifiers or modifier genes, are distinct from the disease-causing mutation and are the object of intense research activity.

Some common genetic variants of cardiac ion channel genes (single nucleotide polymorphisms) have detectable functional activity. These findings underlie the concept that single nucleotide polymorphisms may modulate the clinical severity of the primary mutation. By investigating a highly symptomatic LQTS proband and her relatives, Crotti et al⁵² provided the first evidence that the common polymorphism *KCNH2-K897T* (30% carrier frequency among whites) may modify the clinical expression of a latent LQT2 mutation.

The most powerful resource for studying modifier genes is represented by founder populations, in which a disease allele segregates in families descending from a common ancestor.^{53,54} In an unusually large South African LQT1 founder population,⁴² we demonstrated that 2 common variants in *NOS1AP*, encoding a nitric oxide synthase adaptor protein, were significantly associated with occurrence of symptoms, with clinical severity and QT interval.⁵⁵ Subsequently, the role of *NOS1AP* as a genetic modifier of LQTS has been confirmed in a large cohort of unrelated patients.⁵⁶ This type of study exploiting the unique features of the founder populations is likely to provide the much needed information necessary to allow a more precise custom-made risk stratification for the individual carriers of LQTS-causing mutations.

Notably, the concept of modifier genes and of modifier factors illustrates the limitations of the cellular models currently used in the assessment of a functional defect. These models allow the biophysical investigation of putative mutations in single ion channels, potentially with the coexpression of specific, a priori selected variants (eg, single nucleotide polymorphisms). However, these heterologous *in vitro* systems may not completely reproduce all the possible channel interactions, such as the complex system of *in vivo* myocardial cell. Recently, pluripotent stem cells were generated from dermal fibroblasts collected from LQTS patients.^{57–59} These cells were successfully differentiated into cardiac myocytes, exhibiting functional alterations typical of the disease. The use of induced pluripotent stem cells may represent a novel and appropriate model to better elucidate the clinical heterogeneity in LQTS.

Current Management

The most significant information concerning therapy for LQTS still comes from a 1985 study,⁶ which included 233 symptomatic patients and demonstrated the dramatic change in survival produced by pharmacological or surgical antiadrenergic therapy compared with any other therapy or no treatment. Such a large group of severely affected patients left without treatment is obviously no longer available.

β-Adrenergic Blockade

β-Adrenergic blocking agents represent the first-choice therapy in symptomatic LQTS patients, barring specific contraindications. β-Blockers seldom result in excessive bradycardia, especially if the dosage is gradually increased over several weeks.

Contrary to commonly held views, β-blockers are not all equally effective. Without question, the 2 most effective are propranolol and nadolol. Propranolol is still the most widely used drug, at 2 to 3 mg/kg per day; sometimes, the dosage is increased to 4 mg/kg, and in the more malignant cases also higher doses are justified. Nadolol is also used often because its longer half-life allows twice-a-day administration, usually at 1 to 1.5 mg/kg per day. Metoprolol is definitely less effective,⁶⁰ and the switch from propranolol or nadolol to metoprolol has been associated with tragic recurrences. It is now clear that metoprolol should not be used in the management of LQTS. Also, atenolol seems somewhat less effective, but the data available are limited.⁶¹ Even though it is unclear whether differences in Na⁺ blocking activity (what in the old days was called the membrane stabilizing effect) play a role in the clearly different clinical efficacy of various β-blockers, it is interesting to note that this blocking effect is highest for propranolol, lower but present for nadolol, and completely absent for metoprolol.⁶²

In a study of 869 LQTS patients of unknown genotype, overall mortality on β-blocker therapy was 2%, and it was 1.6% when limited to patients with syncope (no cardiac arrest) and without events in the first year of life.⁶³ There is clear evidence that β-blockers are extremely effective in LQT1 patients. Data from 2 large studies^{64,65} indicate that mortality is 0.5% and sudden death combined with cardiac arrest reaches 1%. β-Blocker noncompliance and use of QT-prolonging drugs are responsible for almost all life-threatening β-blocker failures in LQT1 patients⁶⁵; conversely, compliance and the avoidance of QT-prolonging drugs are associated with 97% reduction in the risk for cardiac events. Compared with LQT1, LQT2 patients have more life-threatening events despite β-blockers, but most of these are resuscitated cardiac arrests (6%–7%).⁶⁴ Among LQT3 patients, major events have been reported to occur more frequently (10%–15%) despite β-blockers^{41,64} and have contributed to the incorrect notion that β-blockers are of limited or no value for LQT3 patients. This misconception is the consequence of including LQT3 patients who present with events in the first year of life with those who present with events at a later time.³² Indeed, the presence of a cardiac event in the first year of life is associated with an extremely poor prognosis, independent of treatment. In patients presenting at an older age, mortality on β-blocker therapy is approximately 3% and is highest in those with markedly prolonged QTc intervals, approaching 600 ms. This information comes from the largest study ever performed in LQT3, with data on 400 patients (A. A. M. Wilde, MD, PhD, unpublished data, 2012). Left cardiac sympathetic denervation (LCSN) appears to confer significant protection from life-threatening arrhythmias in the relatively small number of LQT3 patients who received this treatment.⁶⁶ Patients with severe JLN or TS are often not adequately protected by β-blockers and require additional protection.^{5,26}

Left Cardiac Sympathetic Denervation

LCSD, ideally performed by an extrapleural approach that makes thoracotomy unnecessary, requires removal of the first 3 to 4 thoracic ganglia. The cephalic portion of the left stellate ganglion is left intact to avoid the Horner syndrome. An alternate surgical approach is represented by thoracoscopy.⁶⁷ For small infants or whenever the local surgeons do not have adequate experience, we recommend the traditional and easy approach represented by an opening in the third left intercostal space, which allows a clear visualization of the stellate ganglion with the sympathetic chain. The technical details of our favored extrapleural approach have been recently described.⁶⁸ The rationale for LCSD, largely based on its rather striking antifibrillatory effect,⁶⁹ has also been recently reviewed.⁷⁰

The latest clinical data on LCSD were published in 2004 and included 147 LQTS patients who underwent sympathectomy during the past 35 years.⁶⁶ They represented a group at high risk (99% symptomatic, with an extremely long mean QTc [563±65 ms], previous cardiac arrest in 48%, a recurrent syncope despite full-dose β -blockers in 75%). During a mean follow-up of 8 years, there was a 91% reduction in cardiac events. In 5 patients who underwent LCSD because of multiple implantable cardioverter-defibrillator (ICD) shocks and electrical storms, during a 4-year follow-up there was a 95% decrease in the number of shocks, with a dramatic improvement in the quality of life of the patients and of their families. Interestingly, LCSD produced a mean QTc shortening of 39 ms, pointing to an action on the substrate as well as on the trigger. The unavoidable conclusion is that whenever syncopal episodes recur despite a full-dose β -blocker therapy, LCSD should be considered and implemented without hesitation. Also, failure by the physician to provide the family with adequate information of the pros and cons of LCSD versus ICD implant may carry medicolegal consequences.⁷¹

Implantable Cardioverter-Defibrillator

The decision to implant an ICD is relatively easy for the clinical cardiologist. In the case of appropriate shocks, the cardiologist will have saved the life of the patient; in case of no shocks and possibly of complications, the cardiologist will have done the best for the patient's protection. On the other hand, the decision to not implant an ICD could, in the case of a tragic outcome, lead to medicolegal consequences if such a decision was not supported by a valid rationale. Even though these considerations should play no or a minimal role in medical decisions, they actually do. In light of this, physicians should analyze the current state of knowledge.

There is an overall consensus for immediately implanting an ICD in cases in which there has been a documented cardiac arrest, either on or off therapy. Some exceptions exist, such as in a clear case of a drug-induced event in an otherwise asymptomatic patient with modest QT prolongation. In contrast, opinions differ strongly regarding the use of ICDs in patients without cardiac arrest.

The current knowledge is essentially based on the largest ICD study ever published, which provided information on 233 LQTS patients.⁷² In this publication, it is disquieting that

the majority of ICDs were implanted in patients who had not had a previous cardiac arrest, and many had not even failed β -blocker therapy. Asymptomatic patients, almost absent among LQT1 and LQT2, reached the staggering number of 45% among LQT3 patients, indicating that the mere presence of an *SCN5A* mutation, even in a totally asymptomatic individual, was deemed sufficient for ICD implant. During a mean follow-up of 4.6 years, at least 1 appropriate shock was received by 28% of patients, and adverse events occurred in 25% of the study population.

Given the practical importance to identify in advance those patients with the highest probability to receive appropriate shocks, which represents the justification for the ICD implant, we developed⁷² a score (M-FACT) based on simple clinical variables available in a doctor's office during a first visit (Table 3). M-FACT considers QTc duration, age at implant, and cardiac events, despite therapy.

Appropriate ICD therapies were predicted by age <20 years, a QTc >500 ms, prior cardiac arrest, and cardiac events, despite therapy; within 7 years, appropriate shocks occurred in no patients with none of these factors and in 70% of those with all factors (Figure 5A and 5B).

Our current policy is to implant an ICD in (1) all those who survived a cardiac arrest on therapy; (2) most of those who survived a cardiac arrest off therapy, except those with a reversible/preventable cause; (3) those with syncope despite a full dose of β -blocker, whenever the option of LCSD is either not available or discarded after discussion with the patients; (4) all patients with syncope, despite a full dose of β -blocker and LCSD; and (5) exceptionally, the rare asymptomatic patients with a QTc >550 ms, who also manifest signs of high electric instability (eg, T-wave alternans) or other evidence of being at high risk (eg, long sinus pauses followed by abnormal T-wave morphologies), despite β -blockade and LCSD.

For patients with JLN or TS who appear incompletely protected by antiadrenergic therapies, we usually consider, in a case-by-case approach, the possibility of triple therapy, namely β -blockers plus LCSD plus ICD.

Gene-Specific Therapy and Management

There has been major progress in understanding the genotype-phenotype correlation, and specifically, several of the gene-specific triggers for life-threatening arrhythmias have been identified.⁴¹ This has made LQTS the first disease for

Table 3. M-FACT Risk Score

	-1 Point	0 Point	1 Point	2 Points
Event free on therapy for >10 y	Yes			
QTc, ms		≤500	>500 to ≤550	>550
Prior ACA		No	Yes	
Events on therapy		No	Yes	
Age at implant, y		>20	≤20	

M-FACT indicates M for Minus 1 point for being free of cardiac events while on therapy for >10 y; F for Five hundred and Five hundred and Fifty millisecond QTc; A for Age ≤20 y at implant; C for Cardiac arrest; T for events on Therapy; ACA, aborted cardiac arrest. Modified from Ref 72.

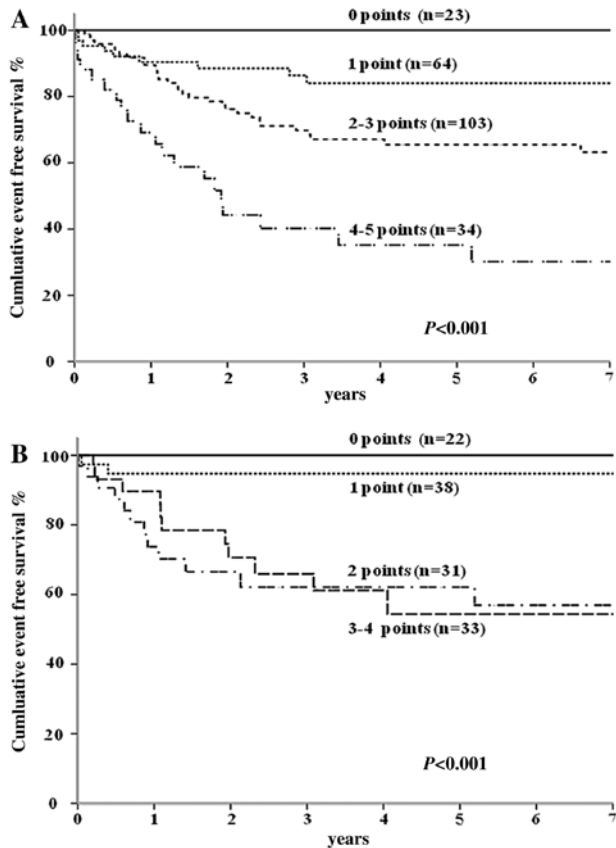


Figure 5. Cumulative event-free survival for a first appropriate implantable cardioverter-defibrillator shock according to an increasing risk score (M-FACT) in (A) all patients and (B) in patients with no prior aborted cardiac arrest (modified from Ref 72). M-FACT indicates M for Minus 1 point for being free of cardiac events while on therapy for >10 years; F for Five hundred and Five hundred and fifty millisecond QTc; A for Age \leq 20 years at implant; C for Cardiac arrest; T for events on Therapy.

which gene-specific management has become possible, and it is opening previously unforeseen preventive and therapeutic strategies.

LQT1 patients are at higher risk during sympathetic activation, such as during exercise and emotions.⁴¹ They should not participate in competitive sports. Swimming is particularly dangerous, because 99% of the arrhythmic episodes associated with swimming occur in LQT1 patients.⁴¹

LQT2 patients are exquisitely sensitive to serum K^+ levels, which should not be allowed to fall. When reasonable levels are not maintained by diet or by oral K^+ supplements, a combination with K^+ sparing agents should be considered. Because these patients are at higher risk especially when aroused from sleep or rest by a sudden noise,^{7,41} we recommend that telephones and alarm clocks are removed from their bedrooms. Also, when parents in the morning have to wake up their children, they should do it gently and without yelling. This combines good manners and gene-specific management.

The demonstration that LQT3-causing *SCN5A* mutations have a gain-of-function effect¹⁷ led to test sodium channel blockers as possible adjuvants in the management of LQT3 patients.¹⁸ Among these drugs, flecainide is seldom used by our group.⁵⁰ There is growing interest for ranolazine because

of its specific effect on the delayed current, but clinical data are still scanty, and most of the current clinical experience is with mexiletine. The effect of mexiletine is mutation-specific,⁷³ and this is why we always test its effectiveness in all LQT3 patients under continuous ECG monitoring by the acute oral drug test technique, performed in the hospital in an outpatient basis, using half of the daily dose. Within 90 minutes, the peak plasma concentration is reached, and if the QTc is shortened by >40 ms, then we add mexiletine to β -blocker therapy. Even though there is no conclusive evidence for a beneficial effect and definite failures have occurred, there is also growing evidence of significant benefit in many individual cases. We observed highly malignant forms manifesting in infancy because of mutations causing extremely severe electrophysiological dysfunctions, which were corrected by the combination of mexiletine and propranolol.⁷⁴

Independent of genotype, all LQTS patients should avoid any cardiac or noncardiac drug that blocks the I_{Kr} current. A list of such drugs is available at www.torsades.org and should be given to every patient because their family physician may not be aware of these electrophysiological actions. This is a precise responsibility of the cardiologist who follows these patients.

Asymptomatic LQTS Patients and Patients With Normal QTc

β -Blocker treatment should be initiated in all patients including those still asymptomatic because in 10% to 12% of LQTS cases the first clinical manifestation is sudden death. Among these, reasonable exceptions appear to be LQT1 men aged >40 years because they seldom have a first event after this age and possibly individuals aged >50 years with a QTc <480 ms. LQT2 women remain at risk throughout life, and it is wise to always treat them, with few exceptions.

Patients with a normal QTc (<440 ms) constitute \approx 25% of the LQTS population and have a markedly lower risk for life-threatening events compared with phenotypically affected patients but are at higher risk compared with unaffected family members.⁷⁵ We usually do not treat them, but an individual assessment, including age evaluation and family history, is appropriate. In addition, follow-up visits are recommended to monitor the stability of their condition. Finally, among LQT1 and LQT3 patients with a normal QT interval, those with missense mutations in the transmembrane regions have a nonnegligible risk of life-threatening arrhythmias⁷⁵; therefore, a mutation-specific evaluation should integrate the clinical evaluation whenever possible.

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Disclosures

None.

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