Genotype- and Phenotype-Guided Management of Congenital Long QT Syndrome

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Abstract: Congenital long QT syndrome (LQTS) is a genetically heterogeneous group of heritable disorders of myocardial repolarization linked by the shared clinical phenotype of QT prolongation on electrocardiogram and an increased risk of potentially life-threatening cardiac arrhythmias. At the molecular level, mutations in 15 distinct LQTS-susceptibility genes that encode ion channel pore-forming α-subunits and accessory β-subunits central to the electromechanical function of the heart have been implicated in its pathogenesis. Over the past 2 decades, our evolving understanding of the electrophysiological mechanisms by which specific genetic substrates perturb the cardiac action potential has translated into vastly improved approaches to the diagnosis, risk stratification, and treatment of patients with LQTS. In this review, we describe how our understanding of the molecular underpinnings of LQTS has yielded numerous clinically meaningful genotype-phenotype correlations and how these insights have translated into genotype- and phenotype-guided approaches to the clinical management of LQTS. (Curr Probl Cardiol 2013;38:417–455.)

O ver the last 2 decades, advances at the bench and bedside have broadened our understanding of the pathogenesis and clinical management of congenital long QT syndrome (LQTS), a potentially lethal genetic disorder of cardiac repolarization that represents a leading cause of sudden cardiac death (SCD), particularly autopsy-negative SCD, in the young. Clinically, LQTS is characterized by a prolonged heart rate–corrected QT interval (QTc) on electrocardiogram (ECG) and a predilection for LQTS-triggered cardiac events including syncope, seizures, and sudden cardiac arrest, often during times of emotional or physical duress.[1,2]

Classically, LQTS follows 2 distinct patterns of inheritance: the autosomal dominant Romano-Ward syndrome,[3,4] which affects between 1:2000 and 1:5000 individuals[5] and presents with an isolated cardiac phenotype, and the autosomal recessive Jervell and Lange-Nielsen syndrome (JLNS),[6,7] which affects between 1:1,000,000 and 1:4,000,000 individuals and presents with bilateral sensorineural deafness in addition to a malignant LQTS cardiac phenotype. In reality, LQTS represents a genetically and phenotypically heterogeneous group of disorders, which also includes rare multisystem disorders, such as Timothy syndrome (TS), characterized by a host of physical or developmental abnormalities, or both, in addition to the classic phenotype of QT prolongation and an increased risk of SCD.[8] Furthermore, as our understanding of the genetic basis of LQTS continues to expand, it has become clear that LQTS, like many monogenic disorders, is subject to the genetic phenomena of incomplete penetrance and variable expressivity, whereby genotype-positive family members display a spectrum of clinical phenotypes ranging from a lifelong asymptomatic state to sudden death in infancy.[9] As such, the interplay between genotype and phenotype in LQTS is likely far more complex than previously envisioned.

Although only a small minority of the number of annual sudden deaths in the United States, which is $>250,000$, are attributable to LQTS and other heritable arrhythmia syndromes,[10,11] for several reasons, it remains important for all practicing cardiologists to develop or maintain a working knowledge of the pathogenic basis, diagnostic approaches, and phenotype- and genotype-guided clinical management of patients with LQTS. Firstly, LQTS represents a potentially life-threatening, yet highly treatable genetic disorder. Given the marked reduction in mortality observed with proper treatment, there is simply no excuse for clearly symptomatic patients to go undiagnosed, untreated, or improperly managed. Secondly, the level of effort and scrutiny dedicated to the elucidation of genotype-phenotype correlations in LQTS is virtually unrivaled within the realm of cardiovascular disease. As such, the

translation of our understanding of the molecular mechanisms underlying LQTS pathogenesis to the development of novel and clinically meaningful genotype- and phenotype-specific approaches to LQTS diagnosis and treatment serves as a prototype or paradigm that could be broadly applicable to the study of other inherited and acquired forms of SCD-predisposing cardiovascular disorders in the postgenomic era.

In this review, we describe our current understanding of the electrophysiological and genetic basis of LQTS, the standard diagnostic approaches used to glean important genotypic and phenotypic information, and lastly how our growing mechanistic understanding of LQTS pathogenesis has led to the development of clinically meaningful approaches to the genotype- and phenotype-guided clinical management of LQTS.

Genetic and Electrophysiological Basis of LQTS

The electromechanical function of the heart, which is reflected by electrocardiographic parameters such as the QT interval, is dependent on the coordinated activation and inactivation of inward depolarizing and outward repolarization currents that underlie the major phases of the cardiac action potential (Fig 1).[12,13] Genetic defects in the ion channel's pore-forming (α) and auxiliary subunits responsible for conducting these currents, which enhance depolarizing Na^+ and Ca^{2+} currents (I_{Na} and $I_{Ca,L}$) or diminish repolarizing potassium currents (I_{Ks}, I_{Kr}, and I_{K1}), can prolong the ventricular cardiac action potential (Fig 1A), resulting in prolongation of the heart rate–corrected QT interval (QTc) on surface ECG. By no means equivalent to a diagnosis of LQTS, a guidelines-based definition of "prolonged QTc" is met by men with a QTc ≥ 450 ms and by women with a QTc ≥ 460 ms, although, practically, a QTc ≥ 470 for men and a QTc ≥ 480 for women are used for screening purposes (Fig 1A and C).[9,14] In the setting of QT prolongation, increased cardiomyocyte refractoriness and enhancement of the Na^+-Ca^{2+} current leads to the abnormal spontaneous activation of the L-type Ca^{2+} channel, which may provide the pathogenic substrate for early afterdepolarization–triggered *torsades de pointes* (TdP), the hallmark and sudden death–predisposing form of polymorphic ventricular fibrillation observed in LQTS.[15]

Over the past 2 decades, 15 distinct LQTS-susceptibility genes, each encoding a critical pore-forming α- or auxiliary subunit of key cardiac ion channels, have been identified through a combination of classical linkage analysis or mutational analysis of biologically plausible, candidate genes, or both (Fig 2). Following the identification of the 3 major LQTS-susceptibility genes responsible for most LQTS cases,[16-18] 12 minor LQTS-susceptibility
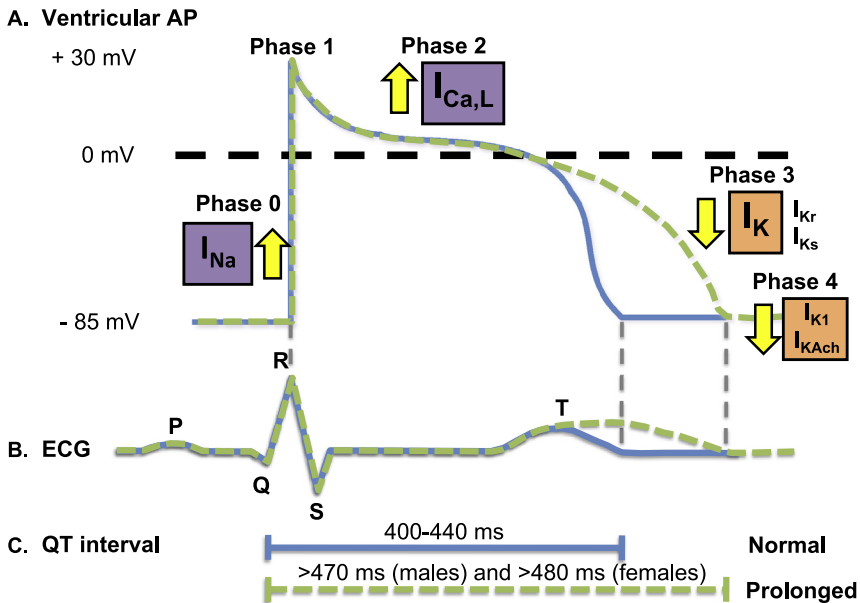
FIG 1. Electrophysiological basis of LQTS. (A) Tracings of the normal cardiac ventricular action potential (blue) observed in healthy cases and prolonged cardiac ventricular action potential (green) observed in long QT syndrome. (B) Schematic representation of a normal ECG (blue) and QT interval prolongation (green). (C) Schematic depiction of normal (blue) and prolonged (green) QT intervals.

genes were described subsequently (Table 1). The following sections briefly review the genetic basis of LQTS, including pertinent aspects of the major, minor, and multisystem LQTS genotypes as well as so-called modifier genetic loci associated with the modulation of LQTS disease severity.

Major LQTS–Susceptibility Genes

Mutations in *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3) represent the most common causes of LQTS and collectively account for an estimated 60%-75% of genotype-positive LQTS cases (Table 1).[19,20] *KCNQ1* encodes the Kv7.1 pore-forming α-subunit that generates the slowly activating component of the delayed rectifier potassium current (I_{Ks}) essential for maintaining the physiological QT shortening observed with increased sympathetic tone or heart rates[21] and endocochlear potassium cycling required for normal hearing.[22] Heterozygous loss-of-function mutations in *KCNQ1* cause autosomal dominant (AD) type 1 LQTS (LQT1), the most prevalent LQTS subtype, and create an arrhythmogenic substrate that predisposes affected individuals to cardiac
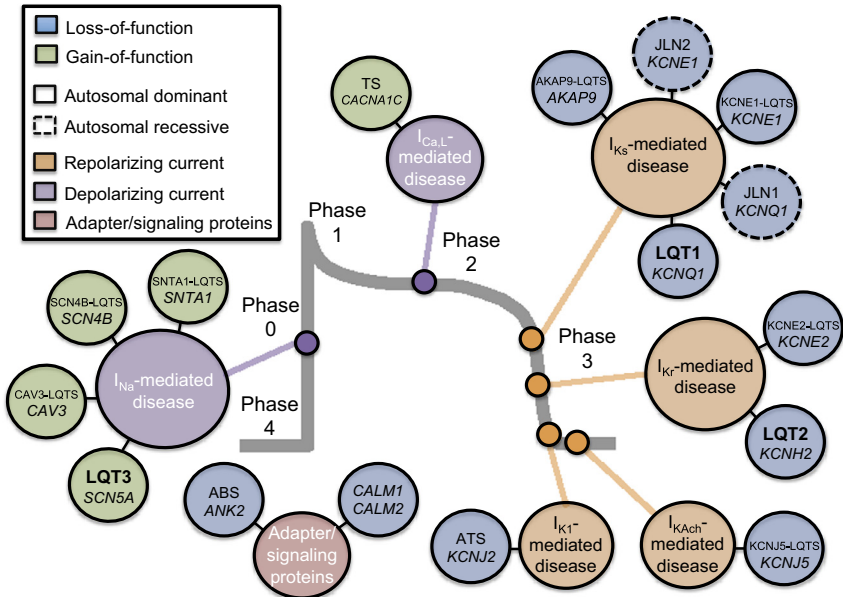
FIG 2. Current-centric classification of LQTS–susceptibility genes. Perturbation of ventricular cardiac action potential depolarization (purple), repolarization (orange), or adaptor or signaling proteins that influence depolarization or repolarization (maroon) by mutations in LQTS–susceptibility genes are grouped according to the specific current perturbed by the underlying genetic defect. Blue circles represent loss-of-function mutations to the specified current, whereas green circles represent a gain-of-function mutation. Solid lines indicate disorders that are autosomal dominant, whereas dashed lines indicate those that are autosomal recessive. Adapted from Giudicessi and Ackerman.[9]

events during times of physical and emotional duress owing to the inability of the defective I_{Ks} current to adequately adapt to β-adrenergic stimulation.[16,19,20,23] Classically, homozygous or compound heterozygous mutations in *KCNQ1* cause the extremely rare autosomal recessive (AR) JLNS (JLNS1), which is characterized by extreme QT prolongation, high risk of cardiac events, and bilateral sensorineural hearing loss or deafness secondary to the near abolishment of I_{Ks} function in the heart and inner ear.[6,24] However, emerging evidence suggests that malignant LQT1 cardiac manifestations, akin to those observed in JLNS, without any discernible evidence of sensorineural deafness or hearing loss (so-called AR LQT1), may be a more commonly observed phenotype in individuals with homozygous or compound heterozygous mutations in *KCNQ1* than JLNS1, at least in countries such as the United States with relatively genetically heterogeneous populations.[25]

The second most prevalent LQTS subtype (LQT2) is caused by heterozygous loss-of-function mutations in the *KCNH2*-encoded

TABLE 1. Genetic basis of long QT syndrome and multisystem syndromes associated with QT prolongation

Gene (Genotype)	Locus	Protein	Functional effect	Mode of inheritance	Frequency	References
LQTS (Major)						
KCNQ1 (LQT1)	11p15.5	Kv7.1	Reduced I_{Ks}	AD; AR	30%-35%	16,25
KCNH2 (LQT2)	7q35-46	Kv11.1	Reduced I_{Kr}	AD	25%-30%	17
SCN5A (LQT3)	3p21-p24	Nav1.5	Increased I_{Na}	AD	5%-10%	18
LQTS (Minor)						
AKAP9 (AKAP9-LQTS)	7q21-q22	Yotiao	Reduced I_{Ks}	AD	<1%	38
CACNA1C (CACNA1C-LQTS)	12p13.3	Cav1.2	Increased $I_{Ca,L}$	AD	<1%	132
CAV3 (CAV3-LQTS)	3p25	Caveolin 3	Increased I_{Na}	AD	<1%	45
KCNE1 (KCNE1-LQTS)	21q22.1	MinK	Reduced I_{Ks}	AD	<1%	37
KCNE2 (KCNE2-LQTS)	21q22.1	MiRP1	Reduced I_{Kr}	AD	<1%	40
KCNJ5 (KCNJ5-LQTS)	11q24	Kir3.4	Reduced $I_{K,ACh}$	AD	<1%	48
SCN4B (SCN4B-LQTS)	11q23.3	Nav1.5 β4-subunit	Increased I_{Na}	AD	<1%	46
SNTA1 (SNTA-LQTS)	20q11.2	Syntrophin-α1	Increased I_{Na}	AD	<1%	47
JLNS						
KCNQ1 (JLNS1)	11p15.5	Kv7.1	Reduced I_{Ks}	AR	Very rare	24
KCNE1 (JLNS2)	21q22.1	MinK	Reduced I_{Ks}	AR	Very rare	39
ABS						
ANKB (ABS)	4q25-q27	Ankyrin B	Aberrant ion channel or transporter localization	AD	<1%	51
ATS						
KCNJ2 (ATS)	17q23	Kir2.1	Reduced I_{K1}	AD	<1%	56
TS						
CACNA1C (TS)	12p13.3	Cav1.2	Increased $I_{Ca,L}$	Sporadic	Very rare	8
Recurrent infantile cardiac arrest syndrome						
CALM1	14q24-q31	Calmodulin 1	Dysfunctional Ca^{2+} signaling	Sporadic	<1%	63
CALM2	2p21	Calmodulin 2	Dysfunctional Ca^{2+} signaling	Sporadic	<1%	63

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

human-ether-a-go-go–related gene potassium channel 1 (hERG1 or Kv11.1) that conducts the rapidly activating component of the delayed rectifier potassium current (I_{Kr}), which along with I_{Ks} is responsible for phase 3 repolarization of the cardiac action potential (Fig 1A).[13,17,19,20] Although most LQT1-causative *KCNQ1* mutations appear to form functional Kv7.1 α-subunits capable of coassembling with wild-type Kv7.1 α-subunits and thereby exerting a dominant-negative effect on the I_{Ks} current ($\geq 50\%$ reduction), most LQT2-causative *KCNH2* mutations produce mutant Kv11.1 α-subunits that are improperly folded, retained in the endoplasmic reticulum, or otherwise fail to make it to the cell surface, resulting in haploinsufficiency and $\leq 50\%$ reduction in the I_{Kr} current. Similar to LQT1, a small percentage of LQT2 cases may harbor homozygous or compound heterozygous mutations in *KCNH2* (or another major LQTS-susceptibility gene) and not surprisingly, are associated typically with a more severe cardiac phenotype.[26-28] In addition to causing LQT2, the unique structural features of the tetrameric hERG/Kv11.1 channel make it particularly susceptible to blockade by an array of pharmacologic agents resulting in acquired or drug-induced LQTS, which has been reviewed in detail elsewhere.[29]

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Melvin Scheinman: One other clinical situation that draws attention to the possibility of the presence of a forme fruste of LQTS is the presence of a drug-induced torsades. Virtually all such drugs involve block in the I_{Kr} channel, thus mimicking LQTS2. A number of drugs have been removed because of this complication (ie seldane, cisapride, and grepafloxacin) while a wide variety of drugs have been implicated including antiarrhythmic agents (sotalol and dofetilide), antibiotics (erythromycin and floxacin), and antipsychotics (thorazine). Torsades may be due to drug-drug interactions which interfere with drug metabolism (Seldane and ketoconazole CYP450 3A4 substrates) or due to "concealed LQTS" brought out by exposure to QT-prolonging agents. Studies by Roden et al. show that patients with drug-induced torsades will frequently have an underlying genetic mutation associated with LQTS. (Roden DM. Novel rare variants in congenital cardiac arrhythmia genes. *Pharmacogenomics*, 2012.)

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Heterozygous gain-of-function mutations in the *SCN5A*-encoded Nav1.5 cardiac sodium channel, which conducts the inward sodium current (I_{Na}) responsible for phase 0 depolarization, cause LQT3, the third most common cause of congenital LQTS (Fig 1A).[18-20] Mechanistically, LQT3-causative mutations in *SCN5A* prolong the QT interval via small net increases in the I_{Na} current, which are commonly secondary to an abnormal persistent or sustained late sodium current or to impaired Nav1.5 inactivation observed across the entire voltage range and time course of action potential plateau that perturb the

delicate balance between inward and outward currents.[30,31] Unlike LQT1 (and to an extent LQT2), the QT interval of patients with LQT3 adequately shortens at higher heart rates, but it tends to prolong excessively at slower heart rates. As a result, patients with LQT3 are at greater risk of having an LQTS-triggered cardiac event while at rest, particularly during sleep.[23,32] Although the precise electrophysiological mechanism underlying this phenomena are still poorly understood, it is has been long speculated,[33] and recently demonstrated in a murine model,[34] that diurnal variation in cardiac repolarization patterns may underlie the time-dependent vulnerability to ventricular arrhythmias observed in LQT3 and other heritable cardiac arrhythmia syndromes.

Minor LQTS–Susceptibility Genes

Following the discovery of the 3 major LQTS-susceptibility genes, at least 10 additional minor LQTS-susceptibility genes, collectively accounting for $<5\%$ of LQTSs, have been described. Given that ion channel pore-forming α-subunits typically function in concert with a number of auxiliary subunits, it is not surprising that most of the minor LQTS-susceptibility genes are components of the ion channel macromolecular complexes that function to conduct the I_{Na}, I_{Kr}, and I_{Ks} currents in vivo. As such, an easy way to recall both the genetic and electrophysiological basis of the minor LQTS-susceptibility genes is through the use of a current-centric model similar to that depicted in Figure 2. The 7 minor genes that present with a "pure" LQTS phenotype are described briefly in the following section using a current-centric model, whereas the minor genes that present with QT prolongation in the setting of prominent extracardiac manifestations are covered in the ensuing section.

At the least, the in vitro recapitulation of the native I_{Ks} current requires the assembly of Kv7.1 with the *KCNE1*-encoded minK β-subunit.[21,35] Furthermore, minK and the *AKAP9*-encoded A kinase anchor protein 9 (yotiao) mediate critical Kv7.1 phosphorylation events required for the physiological enhancement of the I_{Ks} current during times of β-adrenergic stimulation.[36] Not surprisingly, loss-of-function mutations in both *KCNE1* (KCNE1-LQT2)[37] and *AKAP9* (AKAP9-LQTS)[38] generate defective I_{Ks} currents that fail to adequately respond to β-adrenergic stimulation and represent rare causes of I_{Ks}-mediated LQTS (Fig 2). Lastly, as minK also functions as a primary molecular constituent of I_{Ks} in the heart and the inner ear, homozygous or compound mutations in *KCNE1* or digenic compound heterozygous mutations in *KCNQ1* and *KCNE1* represent a rare cause of JLNS (Table 1).[39]

Although the in vivo role of the *KCNE2*-encoded MiRP1 β-subunit in the recapitulation of the native I_{Kr} current conducted by hERG/Kv11.1

remains at the center of much debate,[40-43] loss-of-function mutations in *KCNE2* have been associated with both congenital (KCNE2-LQTS) and acquired forms of LQTS.[40,44] Currently, KCNE2/MiRP1 remains the only hERG-interacting protein linked to LQTS (Fig 2).

To date, mutations in 3 β-subunit (*SCNB4*-encoded β4 subunit or SCNB4-LQTS) or accessory (*CAV3*-encoded caveolin 3 or CAV3-LQTS and *SNTA1*-encoded syntrophin α1 or SNTA1-LQTS) proteins that comprise the larger Nav1.5 macromolecular complex are rare causes of LQTS via the induction of an abnormal persistent or sustained late sodium current that mimics the electrophysiological perturbations associated with many LQT3-causative *SCN5A* mutations (Fig 2).[45-47] Details of the precise molecular roles of these and other Nav1.5-interacting proteins are reviewed in detail elsewhere.[31]

Lastly, in 2010, Yang et al.[48] identified a single loss-of-function mutation in the *KCNJ5*-encoded Kir3.4 pore-forming α-subunit that conducts the G protein-coupled, inwardly rectifying protein current (I_{KAch}) that cosegregated with an LQTS phenotype in a large multigenerational pedigree (Fig 1). Although the I_{Kr}, I_{Ks}, and I_{K1} currents are primarily responsible for ventricular repolarization, at least in murine models, there is emerging evidence that I_{KAch} is active, but masked by the constitutively active I_{K1} current, during repolarization phases of the cardiac action potential.[49] Although no additional mutations in *KCNJ5* have been described to date, the I_{KAch} current does appear to play a limited but biologically plausible role in the pathogenesis of LQTS.

Genetics of Multisystem Long-QT Syndrome: Ankyrin-B, Anderson-Tawil, Timothy, and Recurrent Infantile Cardiac Arrest Syndromes

In addition to JLNS, 4 other LQTS genotypes or subtypes characterized by QT prolongation and an increased risk of syncope, seizures, and sudden cardiac death in the setting of a variety of extracardiac manifestations have been described in the literature and thus are best described as "multisystem" forms of LQTS. The genetic and electrophysiological basis of these multisystem forms of LQTS are summarized in chronological order within Table 1 and discussed briefly in the ensuing paragraphs.

In 1995, Schott et al.[50] identified a novel genetic locus (4q25-27) that segregated in a large French kindred with the unique clinical phenotype of QT prolongation, sinus node dysfunction, and episodic atrial fibrillation. Nearly a decade later, the causal gene within the 4q25-27 locus was determined to be *ANK2*-encoded ankyrin-B, a specialized adaptor protein required for the

establishment of membrane microdomains, and loss-of-function mutations in *ANK2* caused a multisystem form of LQTS, now termed sick sinus syndrome with bradycardia or simply ankyrin-B syndrome (ABS).[51,52] Functionally, ABS arises secondary to the disruption of cellular microdomains involving a number of cardiac ion channels and transporters including the Na^+-K^+ ATPase, the Na^+-Ca^{2+} exchanger, and the inositol-3-phosphate receptor and the generation of aberrant cytoplasmic Ca^{2+} release.[53]

Initially described clinically in 1971, Andersen-Tawil syndrome (ATS) is a rare multisystem form of LQTS characterized by the clinical triad of dysmorphic physical features (low-set ears, micrognathia, and clinodactyly), periodic paralysis, and nonsustained ventricular arrhythmia.[54,55] At the molecular level, heterozygous loss-of-function mutations in the *KCNJ2*-encoded Kir2.1 inward rectifier potassium channel result in a reduction of the I_{K1} current that contributes to phase 3 repolarization and prolongation of action potential duration that generates the substrate for re-entrant arrhythmias in ATS.[56,57] In comparison with the "classical" forms of LQTS (eg, LQT1-3), patients with ATS typically exhibit milder QT prolongation, presence of characteristic broad, high-amplitude U-waves, and decreased risk of life-threatening EAD-triggered ventricular arrhythmias.[58]

TS is an extremely rare multisystem form of LQTS caused by gain-of-function mutations that impair the voltage-dependent inactivation of the *CACNA1C*-encoded Cav1.2 channel, thereby resulting in an increased L-type Ca^{2+} current ($I_{Ca,L}$) during the plateau phase of the cardiac action potential (Fig 1), which leads to a complex phenotype that includes variable degrees of autism spectrum disorder, syndactyly, and severe cardiac arrhythmias.[8,59] Unlike most forms of LQTS, which usually follow Mendelian inheritance patterns, the two TS-causative mutations identified to date G402S and G406R, in the mutually exclusive exon 8 and exon 8a *CACNA1C* splice variants, respectively, are inherited invariably in a sporadic fashion.[8,60] As such, it appears that either de novo mutagenesis or parental mosaicism is the primary inheritance patterns of TS.[61,62]

Most recently, the exome sequencing of 2 parent-child trios revealed that heterozygous sporadic or de novo mutations in 2 of the 3 genes that collectively encode calmodulin (*CALM1* and *CALM2*), a ubiquitous Ca^{2+}-binding protein responsible for a plethora of intracellular signaling processes, cause a multisystem disorder with features of severe LQTS (QTc > 600 ms, 2:1 atrioventricular block, and macroscopic T-wave alternans) characterized by neurodevelopmental delays, seizures, and recurrent cardiac arrest during early infancy.[63] Although the precise electrophysiological mechanism(s) by which mutant calmodulin severely disrupts myocardial repolarization in this newly described

recurrent infantile cardiac arrest syndrome remains unknown, this intriguing discovery hints at a greater role for intracellular Ca^{2+} signaling in the pathogenesis of LQTS and possibly sudden infant death syndrome (SIDS).

Genetic Modifiers of Long QT Syndrome Disease Severity

Interestingly, most of the LQTS subtypes described earlier are subjected to incomplete penetrance and variable expressivity, that is to say affected individuals within the same multigenerational pedigree, who harbor the same LQTS-causative mutation, paradoxically display variable degrees of disease expression causing them to assume vastly different clinical courses.[9] It is now understood that a complex combination of genetic and environmental factors modulates the symptom onset, degree of QTc prolongation, and risk of having LQTS-triggered cardiac events that collectively encompass objective measures of LQTS disease severity. Here, we summarize several recently discovered genetic determinants of LQTS disease severity, commonly referred to as modifier genes, which may modulate the phenotype of patients with a primary LQTS-causative mutation.

To date, the bulk of LQTS genetic modifiers described in the literature represent common genetic variants within known LQTS-susceptibility genes that impart a modest, but discernible functional phenotype or effect (Table 2). For example, common amino acid–altering single nucleotide polymorphisms (SNPs) in *KCNE1* (D85N),[64] *KCNH2* (K897T),[65] and *SCN5A* (H558R)[66,67] exert modest electrophysiological effects that can modulate the in vivo or in vitro phenotypic expression of certain LQT1-, LQT2-, and LQT3-causative mutations, respectively. Furthermore, recent studies have also identified a role for noncoding SNPs within critical genomic regions, such as the promoter or 3' untranslated regions, known to regulate the expression of established LQTS-susceptibility genes (Table 2).[68,69] As SNPs in the promoter or 3′ untranslated region can theoretically enhance or diminish the expression of either wild-type or mutant alleles through the differential binding of critical transcription factors or microRNAs, respectively, these SNPs are referred to as allele-specific modifiers and add an additional layer of complexity to our understanding of the genetic architecture of LQTS.

In addition to SNPs within established LQTS-susceptibility genes, several studies have illustrated that SNPs within genes that modulate cardiac ion channel function through posttranslation-level or transcription-level events can serve as genetic modifiers of LQTS disease severity

TABLE 2. Common variants shown to modify long QT syndrome disease severity

Locus	SNP ID	MAF	Amino acid change[*]	Function	QTc/ Adrenergic effect	References
Coding variants within LQTS-susceptibility genes						
21q *KCNE1*	rs1805128	0.01	D85N	MinK β-subunit (I_{Ks})	↑ QTc	64
7q *KCNH2*	rs1805123	0.24	K897T	Kv11.1 α-subunit (I_{Kr})	↑ QTc	65
3p *SCN5A*	rs1805124	0.18	H558R	Nav1.5 α-subunit (I_{Na})	↑ QTc	66,67
Noncoding variants within LQTS-susceptibility genes						
11p *KCNQ1*	rs2519184	0.09	None	3′UTR of Kv7.1 α-subunit (I_{Ks})	Allele- specific QTc effect	68
	rs8234	0.49	None	3′UTR of Kv7.1 α-subunit (I_{Ks})	Allele- specific QTc effect	68
	rs10798	0.49	None	3′UTR of Kv7.1 α-subunit (I_{Ks})	Allele- specific QTc effect	68
Variants outside of LQTS-susceptibility genes						
4p *ADRA2C*	rs61767072	0.06	Del322-325	α2-Adrenergic receptor	↑ Adrenergic response[*]	73
10q *ADRB1*	rs1801253	0.3	G389R	β1-Adrenergic receptor	↑ Adrenergic response[*]	72,73
1q *NOS1AP*	rs16857031	0.14	None	Nitric oxide synthetase 1 adaptor protein (nNOS signaling)	↑ QTc	74,75
	rs4657139	0.41	None	Nitric oxide synthetase 1 adaptor protein (nNOS signaling)	↑ QTc	74,75

Abbreviations: 3′UTR, 3′untranslated region and nNOS, neuronal nitric oxide synthetase.
*Increased adrenergic response as assessed by higher baroreflex sensitivity values has been associated with an increased risk of cardiac events in LQT1, but does not appear to be mediated by QTc interval.

(Table 2). Firstly, LQT1 disease severity or expressivity can be modified by common amino acid–altering SNPs in the genes encoding the α2 and β1 adrenergic receptors secondary to a loss of α2 autoinhibitory feedback or increased presynaptic epinephrine release (ADRA2C-del322-325)[70] or by enhanced β1 activity secondary to improved coupling to adenylyl cyclase (ADRB1-G389R)[71] resulting in increased baroreceptor or autonomic responsiveness.[72,73] Secondly, common noncoding SNPs (rs4657139

and rs16847548) in *NOS1AP*-encoded nitric oxide synthetase 1 adaptor protein, previously associated with QT interval duration in the general population, have been associated with modest QT prolongation and risk of SCD in a large South African KCNQ1-A341V LQT1 kindred,[74] as well a prospective registry of patients with LQTS.[75]

Clinical Presentation and Diagnosis of LQTS

Prevalence and Clinical Presentation

In 2009, Schwartz et al.[5] used population-based ECG and molecular screening of 44,456 Italian infants to place the estimated prevalence of congenital LQTS at ∼1 in 2000 persons. Although this study provided the first data-driven estimate of infants with the phenotype of an abnormally long QTc, it did not take into account those individuals who may harbor a disease-causative mutation but fail to display objective evidence of QTc prolongation. Interestingly, recent analysis of population-scale exome sequencing from the National Heart Lung and Blood Institute Exome Sequencing Project database placed the prevalence of a potentially pathogenic LQTS genotype, defined as a variant previously shown to cosegregate with disease or that features a functionally perturbed electrophysiological phenotype, at ∼1 in 80.[76] Although incomplete penetrance and variable expressivity certainly contribute to the discordance observed between the population-based estimates of "pathogenic" LQTS genotype (1:80) and an expressed QTc clinical phenotype (1:2000) prevalence, the precise mechanism(s) that underlie this discordance are not fully understood and are worthy of future investigations.

Phenotypically, LQTS is characterized objectively by the presence of QTc prolongation on 12-lead ECG (with QTc values >470 ms for men and >480 ms for women, representing approximate 99th percentile values) in the absence of structural heart disease or secondary causes of a QTc prolongation and an increased risk of syncope, seizures, and tragically sudden death secondary to TdP, the characteristic form of polymorphic ventricular tachycardia observed in LQTS (Fig 3).[14] However, just as QTc values beyond the 99th percentile do not necessarily equal a diagnosis of LQTS, normal QTc values do not exclude LQTS. In fact, an estimated 10%-40% of genotype-positive individuals do not display any objective evidence of a QT abnormality and are classified as "normal QT interval" LQTS or "concealed" LQTS.[77,78]

Although QT interval prolongation serves as the key electrocardiographic hallmark of LQTS, careful analysis of T-wave morphology can also provide useful diagnostic information. For instance, specific ST-T wave patterns correlate with each of the major LQTS genotypes (broad-based
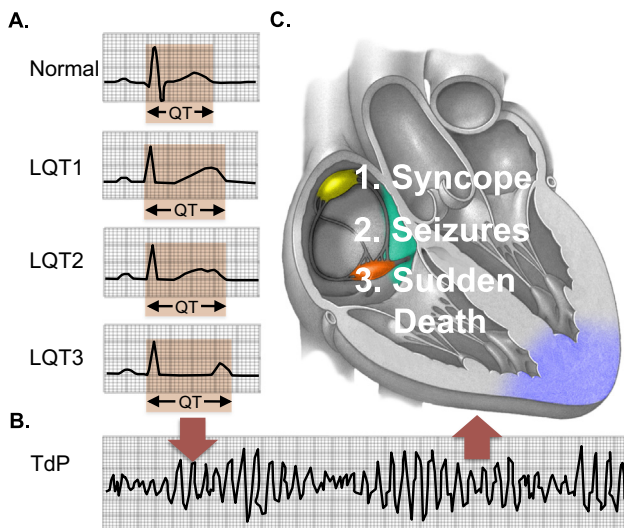
FIG 3. Electrocardiographic and clinical hallmarks of LQTS. (A) Schematic ECGs displaying the broad-based T-wave pattern associated with long QT syndrome type 1 (LQT1), notched T-wave pattern associated with long QT syndrome type 2 (LQT2), and long isoelectric segment with normal symmetrical T-wave pattern associated with long QT syndrome type 3 (LQT3) and QT prolongation observed in LQT1-LQT3 compared with normal. (B) Triggers such as strenuous exercise (LQT1), sudden noises (LQT2), or sleep or rest (LQT3) can cause the stable but prolonged myocardial repolarization to degenerate into TdP, the characteristic form of polymorphic ventricular fibrillation observed in LQTS, depicted in this schematic ECG. (C) The clinical manifestations of TdP in LQTS are dependent on the restoration of cardiac rhythm (syncope/seizures) or the failure to do so (sudden death), either spontaneously or by a defibrillator.

T waves in LQT1, low-amplitude notched T waves in LQT2, and late-onset peaked or biphasic T waves in LQT3; Fig 3A); thereby providing the astute clinician with the ability to anticipate the possible genotype before the initiation of genetic testing.[79,80] Furthermore, T-wave alternans, in either polarity or amplitude, is as a marker of cardiac electrical instability that identifies a higher risk subset.[81]

Standard Diagnostic Approaches

Despite the plethora of advanced imaging, diagnostic, and genetic tests available today, the most important factor needed to establish a diagnosis of LQTS still remains the patient's overall clinical picture. In fact, attempts to interpret a patient's 12-lead ECG, commercial genetic testing, or other adjunct test results without first obtaining a meticulous personal and family history (eg, insufficient evidence) represent some of the most common diagnostic miscues leading to premature or incorrect diagnosis of LQTS.[82]

Accordingly, the first step toward establishing a diagnosis of LQTS should always be to carefully assess the patient's overall clinical picture by obtaining a meticulous personal and family history. Here, the primary goal is to ascertain if the patient had any LQTS-triggered episodes of syncope, seizure, or aborted sudden cardiac arrest and if a history of similar LQTS-triggered cardiac events, sudden unexplained deaths or accidents or drownings, or long-standing diagnosis of a seizure disorder is present amongst first-, second-, and third-degree relatives. Given that the rate of reflex vasovagal syncope is similar between patients with LQTS and the general population,[83] any personal or family history of fainting merits further scrutiny before the initiation of additional testing (eg, 12-lead ECG) as the misinterpretation of vasovagal symptoms in the setting of a borderline QTc is the most common cause of a premature or incorrect LQTS diagnosis.[82] Although syncope upon standing or preceding nausea is suggestive of a vasovagal origin, syncope while supine (eg, rest or sleep), during times of emotional or physical duress, or preceding palpitations or auditory stimuli is reported more frequently by patients with LQTS than otherwise healthy individuals and therefore should increase suspicion for arrhythmic syncope.[84]

As a rule, any individual with a personal or family history suspicious for LQTS should undergo a thorough cardiac evaluation including but not limited to a 12-lead ECG. As mentioned previously, the primary diagnostic characteristic of LQTS is a prolonged QTc on 12-lead ECG (Fig 3), defined by the latest AHA-ACC-HRS guidelines as a QTc ≥ 450 ms in men and ≥ 460 ms in women.[85] However, the use of these $\sim$95th percentile values, without corroborating clinical data that raise the index of clinical suspicion, would result in an unacceptable number of diagnostic mishaps given the known overlap in QTc values between patients with LQTS and healthy individuals (Fig 4).[82] Thus, employing the 99th percentile of the QTc value distribution (>470 in adult males and >480 in adult females) would improve the positive predictive value for LQTS, especially when a clinical picture suggestive of LQTS accompanies a QTc that exceeds the 99th percentile for sex and age.

At this point in the evaluation, the "Schwartz score," a diagnostic scorecard that takes into account elements of the ECG, personal history, and family history can be helpful to quantitatively assess the clinical probability of LQTS for a given index case (Table 3).[86,87] Although not a strict cutoff value, a Schwartz score ≥ 3.5 (high probability of LQTS) is a useful metric for determining which patients and families would benefit most from further assessment so as to solidify the diagnosis of LQTS, namely the judicious use of provocation or stress tests and genetic tests, as described later.
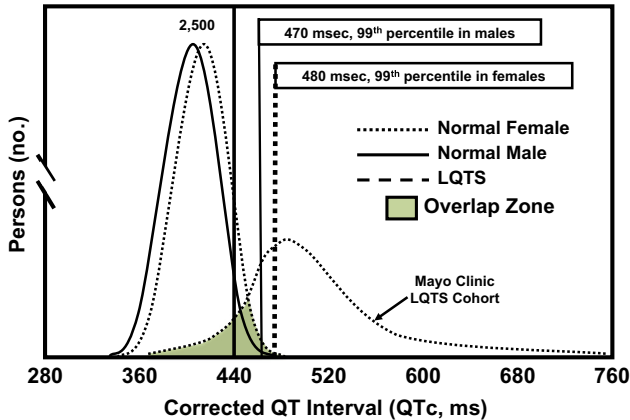
FIG 4. QTc distribution in health and disease. The distribution of QTc values in health was derived from nearly 80,000 healthy adult males and females.[81] The distribution of QTc values in LQTS were derived from all patients with genetically proven LQTS evaluated in the Mayo Clinic's Long QT Syndrome Clinic. Adapted with permission from Taggart et al.[82]

Provocation or Stress Tests and Genetic Testing

Although provocation or stress tests and clinical genetic testing are not needed to establish the diagnosis of LQTS in the setting of a robust clinical phenotype, unmasking or identifying a specific LQTS genotype (eg, LQT1, LQT2, and LQT3) has assumed an increasingly important role when it comes to assessing the risk of SCD, selecting appropriate therapeutic interventions, and identifying potentially at-risk relatives.[88]

In general, the usefulness of catecholamine provocation and exercise stress tests in the diagnosis of LQTS is confined to unmasking an LQT1 genotype. Paradoxical QTc prolongation during the recovery phase of the Bruce treadmill stress test protocol (ie, >470 ms at 2-4 minutes of recovery) or paradoxical lengthening of the absolute QT interval by >30 ms following low-dose epinephrine administration (≤0.1 mcg/kg/minute) can be indicative of the blunted physiological response of the defective I_{Ks} current to β-adrenergic stimulation seen in LQT1.[79,89,90] Although a positive result of the treadmill stress and epinephrine provocation tests certainly increases the pretest probability of LQT1, paradoxical QT lengthening does not equal a diagnosis of LQT1 or LQTS in general, nor can the presence of normal QTc shortening rule out other types of LQTS.[32]

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Melvin Scheinman: The authors point out the importance of provocative stress testing in order to better define the cause of the LQTS. In addition to standard exercise stress testing and epinephrine infusions, one other simple test

(proposed by Viskin) is of value. This test involves measurement of the QTc both supine and in the erect position. Standing will result in mild increases in heart rate and abnormal prolongation of the QTc in affected individuals. It should be emphasized that QTc measurement during exercise may be misleading when using the Bazett correction since the QT interval will shorten much less than the exercise heart rate, hence resulting in overcorrection. The most meaningful measurements are made 4-5 minutes into recovery. In addition, while the epinephrine challenge is an important provocateur of abnormal QTc, this medication results in augmentation of the U waves in normals and hence care must be taken to measure the QT interval alone without the confounding influence of the U wave. According to Lepeshkin, the interval from peak of T wave to peak of the U wave is $\geq$150 ms. This is helpful in distinguishing notched T waves from T-U waves. (JACC 55:1955, 2010.)

Finally, some important considerations regarding genetic testing in the diagnostic evaluation of patients with suspected LQTS are necessary. Given that approximately 4% of ostensibly healthy white individuals and 6%-8% of black individuals harbor a rare, amino acid–altering genetic variant in 1 of the 3 major LQTS-susceptibility genes (*KCNQ1*, *KCNH2*, or *SCN5A*),[91] beginning

TABLE 3. Diagnostic criteria and score for LQTS

	Points[*]
Electrocardiographic findings[†]	
QTc[§] interval	
$\geq$480 ms	3
460-479 ms	2
450-459 ms (men)	1
QTc[‡] $\geq$480 ms during 2nd-4th minute of recovery from exercise stress test	1
Documented TdP[§]	2
T-wave alternans	1
Notched T wave in 3 leads	1
Resting heart rate below second percentile for age	0.5
Clinical history	
Syncope[§]	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history	
Relatives with clinically definitive LQTS[‖]	1
Unexplained sudden cardiac death in immediate relative <30 y of age[‖]	0.5

[*]Total score indicates probability of LQTS: $\leq$1 point (low), 2-3 points (intermediate), $\geq$3.5 points (high).
[†]In the absence of medications, electrolyte abnormalities, or disorders known to influence these electrocardiographic parameters.
[‡]QTc calculated using Bazett formula (QTc = QT/$\sqrt{RR}$).
[§]Mutually exclusive.
[‖]Same family member cannot be counted twice.

any LQTS evaluation with genetic testing is downright dangerous and represents a fundamental failure to recognize the probabilistic, rather than deterministic or binary, nature of clinical genetic testing. That said, current Heart Rhythm Society (HRS)-European Heart Rhythm Association (EHRA) guidelines recommend the judicious use of comprehensive (major and minor LQTS genes listed in Table 1) or targeted (major LQTS genes listed in Table 1) LQTS genetic testing for (1) any individual with a strong clinical suspicion of LQTS based on clinical or family history and electrocardiographic phenotype, (2) any asymptomatic individual with unexplained QTc prolongation (>480 ms before puberty and >500 ms after puberty), and (3) appropriate relatives, regardless of clinical or electrocardiographic phenotype, when a *bona fide* LQTS-causative mutation has been identified in the index case.[92]

As with any clinical test, the proper interpretation of LQTS genetic testing results requires a firm understanding of all potential sources of false-positive (eg, frequency of rare but innocuous genetic variants within a particular gene in healthy individuals) and false-negative (eg, prevalence of a concealed LQTS phenotype secondary to incomplete penetrance or variable expressivity) results that contribute to the test's collective "signal-to-noise" ratio.[93] Importantly, whenever ordering or attempting to interpret genetic test results, it is paramount to remember that as the strength of LQTS clinical phenotype decreases (ie, the pretest probability of disease), the possibility of a false-positive genetic test result increases significantly. Unfortunately, even when LQTS genetic testing is used in an appropriate and judicious manner, rare "Variants of Uncertain Significance" (VUS), alterations in the normal sequence of a gene whose association with disease risk is uncertain because of insufficient or inconclusive evidence (commonly used criteria are listed in Table 4) to confidently label the variant as "pathogenic or disease causative," can still be encountered in LQTS-susceptibility genes.

Fortunately, studies coupling the established rate of rare and presumably innocuous background genetic variation in healthy individuals with a large compendia of mutations identified in clinically definite LQTS cases have yielded a number of clinically meaningful observations that have enhanced the interpretation of indeterminant variant (ie, a VUS) in major LQTS-susceptibility genes[91,94] Specifically, certain mutation types (eg, radical or truncating) and missense mutations localizing to particular topological structure-function domains of the Kv11.1/hERG, Kv7.1, and Nav1.5 channels (eg, pore or transmembrane regions) are associated with a high ($>90\%$) estimated predictive value (EPV). When identified in a case with high clinical probability for LQTS, these variants are more likely to be the

TABLE 4. Principles of rare variant interpretation

Major pathogenicity criteria
Cosegregation of variant with disease in a multigenerational pedigree
Absence or extreme rarity of variant in healthy controls and public exomes or genomes
Radical (eg, nonsense, frameshift, or insertion or deletion) mutation
Amino acid–altering variants localizing to key structure-function domain[*]
Minor pathogenicity criteria
Perturbed electrophysiological phenotype observed during in vitro functional studies
Agreement of multiple in silico phenotype prediction tools on variant pathogenicity

[*]For example, the transmembrane and pore regions of *KCNQ1*, *KCNH2*, or *SCN5A*. Additional key structure-function domains in the major LQTS-susceptibility genes are detailed in Figure 5.

disease-causative mutations.[91,93] Furthermore, coupling ion channel topology with the synergistic use of multiple independent in silico phenotype prediction tools such as "Sorting Intolerant From Tolerant" (SIFT) and "Polymorphism Phenotyping" (PolyPhen) have displayed the ability to enhance the interpretation of genetic variants localizing to regions where the topology-driven EPVs are suboptimal.[94] Collectively, these insights have enabled an algorithm to aid in the probabilistic interpretation of an LQTS genetic testing result (Fig 5).

Genotype- and Phenotype-Guided Risk Stratification and Management of LQTS

Genotype- and Phenotype-Driven Risk Stratification

At present, both genotypic (eg, LQTS genetic, intragenic, and mutation-specific subtype) and phenotypic (eg, gender, QTc, and history of cardiac events) characteristics are used to guide the risk stratification, and ultimately the clinical management, of patients with LQTS (Fig 6). Those patients who harbor *bona fide* LQT1-causative mutations on >1 *KCNQ1* allele (eg, JLNS and AR-LQT1),[25,95,96] who have experienced ≥ 10 cardiac events before the age of 18 years,[97] or who have TS are at highest risk ($\geq 80\%$) of having 1 or more LQTS-associated cardiac events before the age of 40, including a high rate of sudden cardiac arrest or death, and thus require aggressive clinical management, which often involves more invasive approaches such as left cardiac sympathetic denervation (LCSD) and or use of an implantable cardioverter-defibrillator (ICD).

Similarly, individuals with a QTc ≥ 550 ms, regardless of LQTS genotype[97]; a QTc ≥ 500 ms with an LQT1, LQT2, or males with an LQT3 genotype[88]; non-JLNS patients with *bona fide* LQTS-causative mutations on >1 major LQTS-susceptibility allele (eg, compound

FIG 5. Evidence-based algorithm designed to aid in the interpretation of a LQTS genetic test result. Algorithm for interpreting a "positive" LQTS genetic test. Radical mutations that significantly alter or truncate Kv7.1 or Kv11.1, such as insertions or deletions, alteration of intronic or exonic splice site boundaries, and nonsense mutations, are probably associated with LQTS. Those rare missense mutations that localize to Kv7.1 (TM or pore, SA, or C terminal domains), Kv11.1 (C terminal when ≥3 tools are in agreement, TM or Pore, PAS or PAC, or cNBD), or Nav1.5 (TM or pore or linker, or C terminus) are probably or possibly pathogenic. Variants outside these topological structure-function domains are truly ambiguous variants or variants of uncertain significance (VUS) without the aid of additional evidence (cosegregation with disease, LQTS-like electrophysiological phenotype, etc.). Abbreviations: cNBD, cyclic nucleotide–binding domain; EPV, estimated predictive value; IDL, interdomain linker; PAC, per-ARNT-sim C terminal associated; PAS, per-ARNT-sim; SA, subunit assembly; TM, transmembrane. Adapted from Giudicessi and Ackerman.[93]

Extremely High Risk (≥ 80%)

TS
JLNS
AR-LQT1
≥ 10 cardiac events before age 18

High Risk (≥ 50%)

Compound or digenic heterozygosity
QTc ≥ 500 ms
LQT1
LQT2
Male sex, LQT3
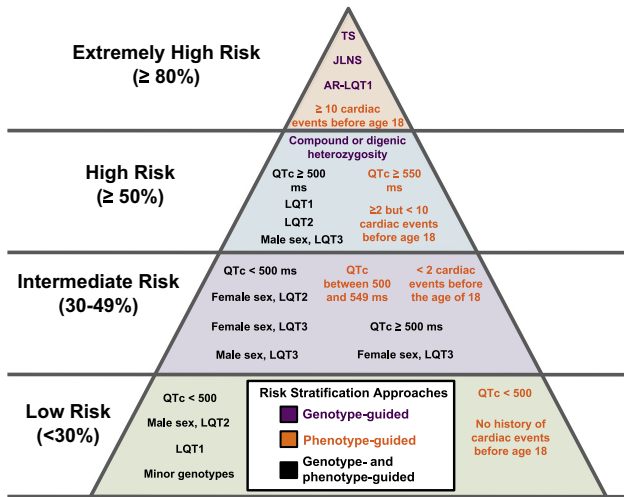QTc ≥ 550 ms
≥2 but < 10 cardiac events before age 18

Intermediate Risk (30-49%)

QTc < 500 ms
Female sex, LQT2
Female sex, LQT3
Male sex, LQT3
QTc between 500 and 549 ms
QTc ≥ 500 ms
Female sex, LQT3
< 2 cardiac events before the age of 18

Low Risk (<30%)

QTc < 500
Male sex, LQT2
LQT1
Minor genotypes
QTc < 500
No history of cardiac events before age 18

Risk Stratification Approaches
Genotype-guided
Phenotype-guided
Genotype- and phenotype-guided

FIG 6. Genotype- and phenotype-guided risk classification of patients with LQTS. Risk groups have been defined based on the previously published probability of experiencing a first or recurrent cardiac event (syncope, seizure, sudden cardiac arrest, or sudden cardiac death) before 40 years of age without appropriate therapeutic interventions. A probability of experiencing a first cardiac event >80% defines the extremely high-risk group, >50% the high-risk group, between 30% and 49% as the intermediate-risk group, and below 30% as the lowest-risk group. Genotype-guided recommendations are indicated by purple text, phenotype-guided recommendations are indicated by orange text, and a combination of genotype- and phenotype-guided recommendations is indicated by black text within the figure.

heterozygosity or digenic heterozygosity),[27,98] or individuals who have had ≥2 but <10 cardiac events before the age of 18 years[97] are at higher risk (≥50%) for experiencing an LQTS-associated cardiac event(s) before the age of 40 years and often require a combination of medical, surgical, or device-related management.

Individuals with a QTc between 500 and 549 ms, regardless of genotype; females with major genotype-positive LQTS; male LQT3 patients with a QTc < 500 ms; and any individual who has experienced <2 cardiac events before the age of 18 years are at intermediate risk for experiencing an LQTS-associated cardiac event(s) before the age of 40 years and require some form of treatment, typically β-adrenergic blockers.[88,97]

All other patients with LQTS (eg, asymptomatic patients with a QTc < 500 ms aside from certain high-risk gender or genotype combinations such as postpubertal females with LQT2; Fig 6) are at lower risk and the selection of appropriate therapy, if any, is performed on an individualized basis.

Medical, Surgical, and Device-Related Management

In general, regardless of symptomatic status, all patients with LQTS should avoid QT-prolonging medications whenever possible and maintain adequate hydration and thereby normal electrolyte levels, especially in the setting of emesis, diarrhea, or other medical conditions known to cause hypokalemia. Furthermore, given that sudden cardiac arrest or death can be the sentinel event, appropriate tailored therapeutic interventions should be initiated in most patients with LQTS, with the possible exception of some patients with asymptomatic, concealed (QTc < 460 ms) LQTS.[2] Currently, LQTS therapy targets the following 2 distinct strategies: (1) reduction in sympathetic or adrenergic tone, and therefore arrhythmia risk, via the use of β-adrenergic receptor antagonists and or LCSD and (2) correction or cessation of life-threatening arrhythmias via the timely delivery of electrical impulses by an ICD. The medical, surgical, and device-related interventions commonly used to fulfill these principles in the clinical management of patients with LQTS are reviewed briefly in the following section.

Since the 1970s, β-adrenergic receptor antagonists (β-blockers) have been first-line therapy for the prevention of life-threatening arrhythmias in LQTS, which are often triggered by sudden increases in sympathetic activity.[99] Although the efficacy of β-blockers in the reduction of LQTS-associated cardiac events, particularly in LQT1 and LQT2, is undisputable,[100,101] the observation that 20%-30% of previously symptomatic patients with LQTS experience breakthrough cardiac events[102,103] and that different β-blockers have variable effects (eg, blockade) on the late or sustained cardiac Na^+ current (propranolol > nadolol >> metoprolol)[104] has led to widespread concern that not all β-blockers share an equivalent level of antiarrhythmic efficacy.[105] For this purpose, a multicenter study of symptomatic patients with LQTS receiving β-blockers recently demonstrated that propranolol and nadolol are significantly more effective than metoprolol at preventing breakthrough cardiac events.[106] Previously, concerns regarding the efficacy of atenolol, were raised based on a smaller observational study.[105] Among the largest LQTS specialty centers throughout the world, propranolol (2-4 mg/kg/day; half-life 4-5 hours) and nadolol (1-2 mg/kg/day; half-life 14-24 hours) are recommended for the initial treatment of all forms of LQTS. Propranolol may be the preferred β-blocker for LQT3.

Unfortunately, in some cases, particularly those with malignant forms of LQTS such as TS and JLNS, β-blocker monotherapy may not provide adequate protection against life-threatening ventricular arrhythmias, which

could result in breakthrough events, or the dosage needed to achieve adequate protection is poorly tolerated. In these patients, an extrapleural[107] or video-assisted thoracoscopic[108,109] LCSD, which involves the removal of the lower half the stellate ganglion (T1) and thoracic ganglia (T2-T4) of the left sympathetic chain with preservation of the upper half of the stellate ganglion (T1) to avoid iatrogenic Horner syndrome (Fig 7), often provides a strong antifibrillatory and QTc-attenuating effect via the localized attenuation of norepinephrine release in the left ventricular myocardium.[110,111] In a large series of 147 high-risk patients with LQTS (average QTc 563 ± 65 ms; 99% symptomatic), Schwartz et al.[111] demonstrated a >90% overall reduction in cardiac events postdenervation with a mean follow-up of 8 years. Importantly, the 5 patients in this larger study who underwent LCSD secondary to multiple ICD shocks or electrical storms displayed a 95% reduction in the number of shocks during a 4 year follow-up.[111] Similar observations have been seen for patients with medically

FIG 7. Left cardiac sympathetic denervation. (A) Anatomical drawing depicting the extrapleural exposure of the left cardiac sympathetic chain during video-assisted thoracic surgery left cardiac sympathetic denervation (VATS-LCSD). The stellate ganglion is located under the superior edge of the incision. The dashed line indicates the resection of the lower half of the left stellate ganglion occurring just above the major lower branches. (B) Videoscopic still-frame from a VATS-LCSD depicting the left cardiac sympathetic chain before dissection of the pleura. (C) Videoscopic still-frame from a VATS-LCSD depicting the left cardiac sympathetic chain after dissection of the pleura. Adapted with permission from Collura et al.[109]

refractory LQTS and malignant LQTS subtypes such as JLNS.[112,113] As such, LCSD should be considered for patients with LQTS who (1) experience LQTS-triggered breakthrough cardiac events despite adequate β-blockade, (2) cannot tolerate β-blocker therapy secondary to undesirable side effects or absolute contraindications such as asthma, (3) experience ≥1 appropriate ventricular fibrillation–terminating ICD shock(s) or electrical storms, or (4) require a so-called bridge to ICD owing to young age and particularly malignant or high-risk LQTS genotype or phenotype.[109]

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Melvin Scheinman: The authors emphasize the role of left cardiac sympathetic denervation (LCSD) for high-risk LQTS patients and treatment of patients with LQTS refractory to -blocker therapy. It should be emphasized that there are no randomized control trials which systematically evaluate the results of this treatment. The current data relative to LCSD comes largely from a small number of centers. In a comprehensive review by Schwartz et al the incidence of syncope and sudden cardiac death was halved but clearly LCSD cannot be used in lieu of ICS insertion in the very high-risk LQTS group. (Zipes and Jallife. *Cardiac EP From Cell to Bedside*. Philadelphia: WB Anders; 2000:597-610.)

Our own experience is less sanguine. In a long-term study of 10 patients who underwent left stellate (one) or cervicothoracic sympathectomy (nine) followed for a mean of 38.6 ± 19 months, 8 patients experienced recurrent symptoms and 3 experienced cardiac arrest (fatal in one). We also found evidence of re-enervation of the left sympathetics in patients who originally developed Horner syndrome. The work of Shiuknman and colleagues emphasizes that both stellata and T1-T4 activate the heart and clinically for patients with ventricular tachycardia storm bilateral denervation is more effective than unilateral denervation. (Bhandari AK, Scheinman MM, Morady F, et al. Circulation: efficacy of left cardiac sympathectomy. 1984;70(6):1018-1023; Ajijola. *Am J Physiol*. 2013; JACC, 2015.)

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Finally, as the awareness and diagnosis of heritable cardiac arrhythmia syndromes such as LQTS increases, the number of young individuals receiving implantable cardioverter-defibrillators (ICDs) has also increased precipitously. Although few would argue against immediate ICD implantation following a documented LQTS-triggered cardiac arrest, the long-term complications and quality-of-life issues associated with early ICD implantation make the decision to implant an ICD in those who have not experienced a cardiac arrest more tenuous.

Interestingly, an examination of the largest series of LQTS patients with ICDs ($n = 233$) confirmed the reality that most patients with LQTS receiving an ICD had not experienced a cardiac arrest and many had not even failed initial β-blocker therapy, suggesting that the practice of

"defensive medicine" influences clinical decision making.[114] Furthermore, during an average follow-up of <5 years, 28% of LQTS patients with an ICD received an appropriate shock, whereas 31% of patients experienced at least one adverse event including but not limited to device-related infections, lead-related complications, ICD revisions, and inappropriate shocks.[114] As a result, a clinical scorecard (M-FACT; Table 5), based on simple clinical variables, was developed to identify those patients where ICD implantation may be most appropriate. Partly based on M-FACT criteria (Table 5) and that single-center studies indicate that most patients with LQTS can be treated effectively without an ICD,[115] an ICD should be considered for those patients with LQTS who (1) survived a cardiac arrest despite adequate β-blockade or LCSD, (2) survived a cardiac arrest off therapy, except when a reversible or preventable cause such as QT-prolonging medications or electrolyte abnormalities are identified, (3) have recurrent LQTS-triggered syncope despite adequate β-blockade when LCSD is not a viable option, (4) have recurrent LQTS-triggered syncope despite adequate β-blockade and LCSD, and (5) in rare extenuating circumstances, such as asymptomatic patients with a QTc ≥ 550 ms with overt signs of electrical instability (eg, T-wave alternans) on ECG or additional objective evidence of being high risk (eg, postpubertal women with LQT2) despite adequate β-blockade and LCSD, or both.[2]

Genotype-Guided Management

Over the past 2 decades, the progressive unraveling of the numerous genetic, electrophysiological, and clinical underpinnings of LQTS described earlier has led to the enumeration of multiple clinically meaningful genotype-phenotype correlations that have unlocked previously unforeseen management strategies and enabled genotype-guided management of LQTS to become a reality. Genotype-specific recommendations

TABLE 5. 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 aborted cardiac arrest		No	Yes	
Events on therapy		No	Yes	
Age at ICD implantation, y		<20	≤ 20	

The acronym M-FACT denotes M for Minus 1 point for being free of cardiac events while on therapy for > 10 years; F for five hundred and fifty millisecond QTc; A for age ≤ 20 years at time of ICD implantation; C for cardiac arrest; and T for events on therapy.

for the clinical management of the major LQTS subtypes (LQT1-LQT3), minor LQTS subtypes, and malignant forms of LQTS (TS, JLNS, AR LQT1, etc.) are further described.

Given that patients with LQT1 have an increased risk of LQTS-triggered cardiac events in the setting of increased sympathetic tone,[23] often secondary to emotional or physical duress, not surprisingly, the use of antiadrenergic interventions (β-blockers and or LCSD) has proven extremely effective. In fact, the β-blocker noncompliance or the concomitant use of QT-prolonging medications or both are responsible for most of the life-threatening breakthrough cardiac events in patients with single-mutation LQT1 who have come to clinical attention.[116] Although strenuous exercise, particularly swimming,[117] has long been recognized as a "trigger" for cardiac events in patients with LQT1, recently, our group decided to respectfully reevaluate the strict competitive sports participation ban previously recommended by the 2005 36th Bethesda Conference[118] and European Society for Cardiology (ESC)[119] guidelines. Although most patients with LQT1 (108/182, 59.3%) and those with LQT1-LQT3 in general (223/353, 63.2%) followed up at the Mayo Clinic were not involved or elected to discontinue involvement in sports at the time of diagnosis, no difference in mortality or the rate of cardiac events was observed between nonathletes and the 60 patients with LQT1-LQT3 (33 LQT1) who elected to continue sports participation in contradiction of both the Bethesda and ESC guidelines.[120,121] In light of the low rate of LQTS-triggered cardiac events during sports and rising obesity rates in the United States' pediatric population, the Mayo Clinic Long QT Syndrome Clinic has elected to adopt a patient or family centered approach that embraces patient or family autonomy when athletes with LQTS have been evaluated meticulously, accurately risk stratified, treated robustly, and thoroughly counseled regarding the potential risks or dangers before returning to the playing field.

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Melvin Scheinman: The data from the national sports registry conducted by Rachel Lampert supports relaxation in allowing LQTS patients with defibrillators to participate in vigorous sporting activity. This includes the patients with LQTS who were formerly (Bethesdal guidelines) restricted from vigorous activities. My own clinical experience is on accord with the more relaxed approach to exercise in those with defibrillators. (Lampert R, Olshansky B. Sports participation in patients with implantable cardio-defibrillators. *Herzschrittmacherther Elektrophysiol*. 2012;23(2):87-93.)

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Compared with LQT1, individuals with LQT2 are more susceptible to LQTS-triggered cardiac events when serum potassium levels fall[2]; when

aroused from sleep or rest by sudden noises such as alarm clocks, telephones, or crying babies[23,122]; and during the postpartum period.[123,124] As such, LQT2-specific management recommendations include (1) careful maintenance of serum potassium levels with a combination of diet, oral potassium supplementation, and if necessary, use of potassium-sparing diuretics such as spironolactone, (2) blunting or removal of causes of sudden noise from the bedroom and education of family members and other individuals sharing the home to avoid yelling or otherwise startling the patient, and (3) counseling women with LQT2 and their partners on the necessity of β-blocker compliance, adequate rest, and avoidance of QT-prolonging medications during the postpartum period. Although β-blockers remain first-line therapy for the treatment of LQT2, given the higher rate of life-threatening breakthrough cardiac events (6%-7%),[102] specifically resuscitated SCAs, ultimately, many high-risk patients with LQT2 require LCSD or, if clinically indicated, an ICD.

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Melvin Scheinman: Another very important genotype-phenotype interaction was described by Barsheshet et al. They studied 860 patients with mutations in the KCNQ1 channel. Patients were divided into those with missense mutations in the membrane-spanning domain (44%), cytoplasmic loops (15%), C/N terminus (20%) or nonmissense mutations. The patients were followed from birth to age 40. They recorded 27 aborted and 78 sudden death events. They concluded that missense mutations in the C loops (intra-cytoplasmic loops) exhibited the highest risk for sudden death and -blocker therapy was more beneficial for those with C loop abnormalities and attenuated for the others. Finally, expression studies showed impaired regulation of PKA activity as the mechanism of these findings. (*Circulation*, 2012;125:1988.)

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Of the major LQTS subtypes, patients with LQT3 tend to experience the highest rate of breakthrough cardiac events while on β-blocker therapy (10%-15%). As a result, there has been increasing interest in targeting the pathogenic late sodium current produced by LQT3-causative *SCN5A* "gain-of-function" mutations with a combination of a β-blocker, preferably propranolol, and an adjuvant sodium channel blocker such as mexiletine or ranolazine as an LQT3-specific management strategy.[125,126] However, despite the successful use of a combination of propranolol and mexiletine to treat isolated cases of malignant perinatal LQT3 caused by the unique SCN5A-G1631D mutations,[127] the effect of mexiletine appears to be largely mutation-specific,[126] thereby necessitating a cumbersome drug challenge under continuous ECG monitoring to assess both therapeutic efficacy and the potential of eliciting an unwanted type 1 Brugada

syndrome–like ECG pattern (PR prolongation and ST-segment elevation in the right precordial leads), given the pleiotropic nature of some *SCN5A* mutations.[128] Although ranolazine has shown great promise as a direct late sodium current blocker in experimental systems[129] and small case series,[130] the widespread clinical efficacy of ranolazine in the treatment of LQT3 remains unknown.

Similarly to LQT2, given the higher rate of breakthrough cardiac events while on β-blocker therapy, ultimately more patients with LQT3 may require LCSD or ICD implantation or both. However, contrary to popular belief, the mere presence of an LQT3-causative mutation should not be viewed as a clinical indication for an ICD. Instead, it should be one factor that is considered in the context of the patient's entire clinical picture.

Given the rare nature of the minor LQTS subtypes and multisystem forms of LQTS (Table 1), no specific genotype-phenotype correlations exist, nor are there any true evidence-based guidelines for the management of these patients. That said, as most of the minor genotypes perturb the I_{Ks} (AKAP9-LQTS and KCNE1-LQTS), I_{Kr} (KCNE2-LQTS), or I_{Na} (CAV3-LQTS, SCN4B-LQTS, and SNTA1-LQTS) currents in an analogous fashion to what is observed in LQT1, LQT2, and LQT3, respectively, practically, minor LQTS subtypes can be managed in the same way as the corresponding major LQTS subtype (eg, AKAP9-LQTS and KCNE1-LQTS can be managed like LQT1). However, this rule does not hold for the more malignant or multisystem forms of LQTS, such as TS and JLNS, where β-blocker therapy alone is often insufficient and early initiation of individualized combination therapy consisting of β-blockers, adjunct antiarrhythmic agents, LCSD, and ICD therapy should be strongly considered.

Management of "Concealed or Low-Risk" LQTS

Owing to incomplete penetrance and variable expressivity, roughly 25% of patients with genotype-positive LQTS (relatives > index cases) fail to manifest any overt clinical hallmark of the disease (ie asymptomatic with a QTc ≤ 440 ms). Although individuals with "concealed" LQTS have a markedly reduced risk of sudden cardiac death or aborted cardiac arrest (4%) compared with those with "expressive" phenotypes (15%), they still carry a >10-fold higher relative risk than their genotype-negative or phenotype-negative relatives (0.4%).[131] This creates a clinical management conundrum where overtreatment would likely continue as some genotype-positive or phenotype-negative individuals might need prophylactic β-blocker therapy. Although individuals with a concealed LQTS

phenotype who harbor LQT1- and LQT3-causative missense mutations in the Kv7.1 and Nav1.5 transmembrane domains appear to be at the highest risk for life-threatening cardiac events,[131] the inability to more accurately risk stratify genotype-positive or phenotype-negative individuals highlights the need to deepen our understanding of the complex interplay between genetic and environmental determinants that modulate the penetrance or expressivity of the primary LQTS-causative mutation as well as to develop further genotype-, intragenic-, and mutation-specific approaches to risk stratification and, eventually, to the treatment of LQTS.

Summary

In conclusion, over the past 2 decades, tireless work from bench to bedside has unraveled many of the electrophysiological and genetic underpinnings of LQTS, allowing for the elucidation of meaningful genotype-phenotype correlations that have advanced how individuals with this potentially life-threatening disorder are diagnosed, risk stratified, and clinically managed. For the visually inclined, the various clinically meaningful genotype-phenotype correlations, diagnostic approaches, risk stratification strategies, and therapeutic interventions discussed in the preceding sections have been synthesized into a single evidence-based algorithm designed to provide practicing cardiologists, who likely only rarely encounter patients with LQTS, with a quick reference that outlines the most pertinent aspects of the genotype- and phenotype-guided management of congenital LQTS (Fig 8).

Concluding Remarks

It seems that as quickly as one set of puzzles is solved, new and inherently more complex ones emerge. Although this is certainly the case for LQTS in the postgenomic era, the rise of new technologies, such as whole-exome and genome sequencing, and recent generation of patient-specific, LQTS-induced pluripotent stem cell models seem poised to address complex lingering issues such as (1) the genetic substrates responsible for the ∼20% of LQTS cases that remain currently genetically elusive, (2) the novel genetic determinants that contribute to phenotypic expressivity or the lack thereof with concealed LQTS, (3) the discrepancy observed between the public domain prevalence of a possible LQTS genotype (∼1:80) and LQTS phenotype (∼1:2000), and (4) the development of therapeutic interventions with less undesirable side effects and

Suspected LQTS Case

Assess LQTS Clinical Picture
• Personal History (syncope, ACA, etc.)
• Family History (SCD, seizure disorder, etc.)
• Cardiac evaluation (QTc, T-wave morphology, etc.)

Modified Schwartz Score ≥ 3.5?
(For full criteria see table 3)

Yes → **High Index of Clinical Suspicion**

No → **Intermediate/Low Index of Clinical Suspicion**

Clinical Picture Remains Suspicious Despite Borderline/ Concealed Phenotype?
(Genotype-positive relatives, positive stress test, etc.)

Yes → **Initiate Clinical Genetic Testing**

No → **Likelihood of LQTS is Low**

High Probability LQTS-Causative Mutation Identified?
(Co-segregation with disease, absent in controls, radical mutation, localizes to key structure-function domain, etc.)

No → **Low Probability VUS or Genotype-Negative**

Yes → **Genotype-Guided Management**

LQT1
• Assure anti-adrenergic therapy compliance.
• Avoid situations associated with emotional or physical duress.
• Assess sports participation on individualized basis.

LQT2
• Maintain serum K+ levels.
• Avoid sudden noises during sleep/rest.
• Exercise caution during postpartum period.
• β-blockers (propranolol or nadolol)

LQT3
• Propranolol
• Consider use of adjuvant sodium channel blocker (mexiletine or ranolazine)
• Lower threshold for LCSD/ICD implantation due to breakthrough events.

Minor
• No evidence-based guidelines.
• AKAP9- and KCNE1-LQTS manage as LQT1.
• KCNE2-LQTS manage as LQT2.
• CAV3-, SCN3B, and SNTA1-LQTS manage as LQT3.

Malignant/ Multisystem
(TS, JLNS, AR LQT1, etc.)
• Manage with combination of β-blockers, adjuvant anti-arrhythmic agents, LCSD, and/ or ICD implantation early on.

Phenotype-Guided Management

Syncope, seizures, or asymptomatic

Prophylactic β-blockers (propranolol or nadolol)

Breakthrough events, poorly tolerated, or contraindicated?

Yes → **LCSD**

No

Aborted Cardiac Arrest or M-FACT score ≥ 4
(For full criteria see table 4)

Consider ICD
(in addition to other interventions)

Yes ←

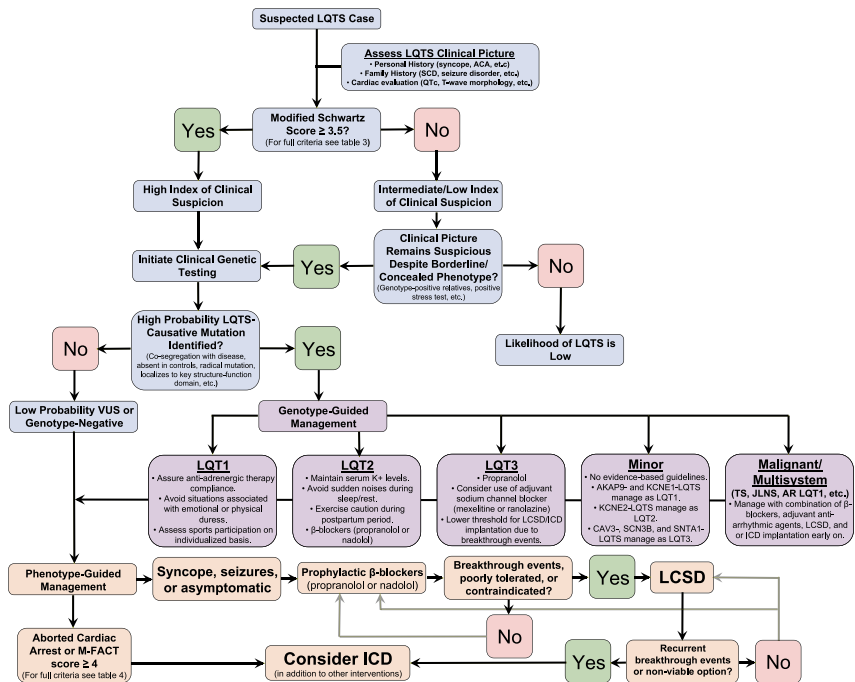**Recurrent breakthrough events or non-viable option?**

Yes / No

FIG 8. An integrated approach to the diagnosis, risk stratification, and genotype- and phenotype-guided management of patients with LQTS. Blue boxes denote the recommended steps in assessing the index of clinical suspicion for LQTS based on personal and family history, thorough cardiac evaluation including a 12-lead electrocardiogram, and if appropriate, clinical LQTS genetic testing. For those individuals in whom a *bona fide* LQTS-causative mutation is identified, purple boxes indicate the recommended genotype-guided management of specific LQTS genetic substrates based in part on established genotype-phenotype correlations and our current understanding of the pathogenesis or electrophysiological mechanisms of these disorders. Lastly, orange boxes indicate the recommended phenotype-guided management of individuals in whom a specific LQTS genotype remains elusive or cannot be established as well as genotype-positive individuals already receiving gene-specific treatment. Importantly, it should be noted that for genotype-positive individuals, both genotype- and phenotype-guided management strategies are utilized concurrently.

better safety profiles than those in use today. Hopefully, insights into the pathophysiological mechanisms, clinical manifestations, and therapeutic responses gained from these efforts will pave the way for the development of refined and novel approaches to the genotype- and phenotype-guided clinical management of patients afflicted by this potentially lethal, yet highly treatable, genetic disorder.

■

Melvin Scheinman: The authors are to be congratulated on a splendid and authoritative review of the LQTS. They offer a superb review of both the

genetics and basic electrophysiology of this syndrome. The authors take advantage of extensive database from the Mayo Clinic and formulate an eminently reasonable approach to the clinical diagnoses and treatment of these patients. The manuscript is replete with superb figures and is a valuable read not only for the general cardiologist but for cardiac electrophysiologists as well.

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