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Recent progress in congenital long QT syndrome

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Abstract

Purpose of review—As genetic testing for long QT syndrome (LQTS) has become readily available, important advances are being made in understanding the exact link between ion channel mutation and observed phenotype. This paper reviews recent findings in the literature.

Recent findings—Congenital LQTS is an important cause of sudden cardiac death. To date, 12 genes have been identified as the cause of congenital LQTS. With increasing availability of genetic testing, subtype-specific management of LQTS has become the standard of care. Detailed correlative studies between LQTS mutations and clinical phenotypes are leading the field towards 'mutation-specific' management within LQTS subtypes. A clear link between the distinct functional/biophysical defect in each LQT mutation and disease phenotype is complicated by the variable penetrance and pleiotropic expression of clinical phenotype. This is especially evident with the overlap syndrome now documented for several sodium channel (*SCN5A*) mutations.

Summary—The management of LQTS has become subtype-specific due to the availability of genotype information. Review of recent literature suggests that 'mutation-specific' management is possible based upon distinct functional/biophysical characteristics of mutations within each LQT gene. Further research is required to clearly delineate the molecular and cellular mechanisms underlying variable penetrance, and pleiotropic expression of LQTS mutations.

Keywords

genetics; ion channels; long QT syndrome; mutation-specific management; sudden cardiac death

Introduction

Long QT syndrome (LQTS) is a rare (1:2500–1:10000) inherited disorder that is associated with an increased propensity to arrhythmogenic syncope, polymorphous ventricular tachycardia, and sudden cardiac death [1]. LQTS was probably first reported in 1856 by Meissner [2], who described a deaf girl who collapsed and died while being publicly reprimanded at school. Jervell and Lange-Nielsen [3] provided the first complete description of congenital LQTS in 1957; they reported a family with four deaf-mute children with fainting spells, sudden death, and prolonged QT intervals (Jervell Lange-Nielsen syndrome or JLN). Romano *et al*. [4] and Ward [5] independently reported patients with autosomal dominant cardiac disorder identical to JLN, but without the deafness (Romano–Ward syndrome or RWS). In the contemporary literature, RWS is used interchangeably with

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LQTS. Our understanding of this disorder changed dramatically in the 1990s, when three genes were identified to be linked to autosomal dominant forms of LQTS: *KvLQT1* (*KCNQ1*), human ether-à-go-go related gene (*hERG*) (*KCNH2*), and *SCN5A* [6]. Consistently with the autosomal recessive inheritance, JLN was subsequently found to be a homozygous mutation of *KvLQT1* and subsequently *KCNE1* [7].

These and subsequent findings established LQTS as a heterogeneous congenital cardiac channelopathy, a disease caused by mutations in genes coding for cardiac ion channel subunits or channel-associated proteins [1]. In this manuscript, we will provide an overview of congenital LQTS as well as reviewing the major advances over recent years. Acquired LQTS will not be extensively discussed.

LQTS is associated with delayed repolarization of ventricular cells in the heart detected as abnormally long QTc [heart rate (HR) corrected QT] intervals on ECG. The details of the ionic currents responsible for cellular cardiac action potentials have been reviewed elsewhere [8]. QTc/action potential duration prolongation can arise from either a decrease in repolarizing current (potassium channel current) or an increase in excitatory membrane current (sodium or calcium channel currents or both) during the action potentials plateau phase. Most commonly, QTc prolongation is produced by delayed repolarization due to loss of function of cardiac potassium (K^+) currents, I_{Kr} or I_{Ks} [9]. Less commonly, QT prolongation results from prolonged depolarization due to an increase in inward current (via inactivation disruption), carried by either the principal cardiac sodium channel (Nav1.5, I_{Na}) or L-type calcium (Ca^{2+}) channels (Cav1.2, $I_{Ca,L}$) [10,11].

Long QT syndrome genetics

Congenital LQTS currently is associated with mutations in 12 different genes, with the majority of the known mutations located in the first three: LQT1 (*KCNQ1*) mutations account for 42–45% of genetically positive LQTS, LQT2 (*KCNH2*) for 35–45%, and LQT3 (*SCN5A*) for 8–10% [12,13]. All of the LQT genes except LQT4, LQT9, LQT11, and LQT12 code for ion channel subunits. LQT4 (*ANKB* or *ANK2*) encodes a structural protein, ankyrin-B, which anchors ion channels to specific domains in the plasma membrane [14]. LQT9 (*CAV3*) is a gene encoding caveolin 3, a membrane scaffolding protein that interacts with a variety of signaling proteins including sodium channels [15]. LQT11 (*AKAP9* or yotiao) encodes an A-kinase anchoring protein, shown to be an integral part of the I_{Ks} macromolecular complex, whose presence is necessary for the physiological response of the I_{Ks} channel to β-adrenergic stimulation [16,17]. LQT12 (*SNTA1*) codes for α-1 syntrophin, known to associate with the Nav1.5 cardiac sodium channel as part of the neuronal nitric oxide synthase complex that appears to regulate ion channel function [18••]. Other than LQT7 and LQT8, which are part of multisystemic disorders, Andersen–Tawil (periodic paralysis, dysmorphic features, and long QTU) [19,20] and Timothy syndromes (autism, syndactyly, and LQT) [21], all LQTS genes appear to be functionally related to three cardiac ion currents: I_{Ks}, I_{Kr}, and I_{Na}. Dysfunction of these three ionic currents, caused by either channel subunit or accessory protein mutations, appears to be the ‘final common pathways’ for LQTS (Table 1).

Depending on the stringency of clinical phenotype assessment, the yield for positive genetic results in LQTS ranges from 50 to 78% [12,13]. The cohorts with longer average QTc intervals and more symptoms have a higher yield of clinical testing [22]. Interestingly, about 10% of gene-positive LQTS had multiple mutations in the tested genes [13]. This leaves at least 22% of clinically positive LQTS without a genetic explanation. We believe that studies of phenotypically robust, but genotype-negative, LQTS patients will yield additional LQTS genes and novel insights into the fundamental mechanism of cardiac ion channel physiology.

However, additional LQTS subtypes will likely each account for only a minute percentage of the total congenital LQTS population, and point to interacting proteins and modifiers that affect the final common pathways: I_{Ks}, I_{Kr}, and I_{Na} (Fig. 1).

Gene/mutation-specific arrhythmia risk factors and management

The discovery that distinct LQTS variants are associated with genes coding for different ion channel subunits has had a major impact on the diagnosis, analysis, and treatment of LQTS patients. Clinical data have revealed distinct risk factors associated with the different LQTS genotypes, and that genotypic information must be taken into account during patient evaluation, diagnosis, and management. Current prophylactic and preventive therapy for LQTS to reduce the incidence of syncope and sudden death include β-blockers, implanted defibrillators, and, less frequently, left cervicothoracic sympathetic ganglionectomy [23]. The utility of sodium channel blockers such as flecainide, mexilitine, and more recently ranolazine in LQT3 is being actively investigated [24,25•]. It is becoming clear that the efficacies of the therapies are variable according to the LQTS genotype [26]. With the increasing availability of LQTS genetic testing, gene-specific patient management is now generally considered standard of care and information regarding mutation-specific risk stratification and therapy is rapidly evolving [23]. Given the rarity of patients with LQT4–12, extensive genotype–phenotype correlation studies have not been performed. Until such data become available, it is logical to manage patients according to their affected currents. This review is thus organized according to the affected final common pathway currents I_{Ks}, I_{Kr}, and I_{Na}.

I_{Ks}

The LQT variants where I_{Ks} is dysfunctional include LQT1, LQT5, and LQT11; the majority are of the LQT1 variant. Homozygous mutations of *KCNQ1* and *KCNE1* are the genetic basis for JLN, where affected patients are also deaf [7]. LQT1 patients are at greatest risk for cardiac events during exercise or conditions associated with elevated sympathetic nerve activity [26]. β-Blocking drugs, despite minimal effects on the QTc interval, are associated with a significant reduction in cardiac events and are considered the first-line treatment in LQTS. Critical evaluation of genotyped LQTS patients treated with β-blockers has made it clear that patients with LQT1 subtype derive the most significant benefit, whereas this treatment is less effective for LQT2 and neutral for LQT3 patients [27].

Most insights into the causal effects of mutations affecting I_{Ks} have generally revealed mutation-dependent loss of function and loss of responsiveness to adrenergic regulation. However, two studies also have addressed ‘mutation–phenotype’ correlation in *KCNQ1* mutations. In a first study by Zareba *et al*. [28] mutations were classified by structural localization within the ion channel (prepore, pore, and postpore); however, no significant difference was found in ECG characteristics, cardiac events, and response to β-blockade according to the location of the mutations. In a second, larger study by Moss *et al*. [29] in which LQT1 mutations were classified by location (N-terminus, C-terminus, and transmembrane), mutation type (missense vs. nonmissense), and biophysical function (haploinsufficiency vs. dominant negative), the transmembrane location, missense mutation, and dominant negative biophysical profiles were found to be independent predictors of higher frequency of cardiac events. This study contributes to building clinical predictors of disease severity based on mutation and biophysical properties, thus representing an important step towards mutation-specific management of LQTS.

I_{Kr}

The LQT variants where I_{Kr} is dysfunctional include LQT2 and LQT6; the majority are of LQT2. It is worth noting that unintended inhibition of I_{Kr} accounts for the majority of the drug-induced LQTS [30]. Cardiac events in LQT2 are associated with arousal, conditions in which patients are startled, or both [26]. More than 200 putative disease-causing mutations have been identified for *KCNH2;* most appear to disrupt the maturation and trafficking process, thereby reducing the number of functional ion channels at the cell surface membrane [31]. In a report from the International LQTS Registry [32], *KCNH2* mutations were classified according to pore vs. nonpore localization; patients with pore mutations experienced a higher frequency of arrhythmia-related cardiac events at an earlier age than did patients with nonpore mutations. A larger, more recent study [33••], which combined *KCNH2* patients and mutations from three LQTS registries, found that in missense mutations the location of mutation significantly influenced the clinical phenotype, whereas the risk of nonsense mutations did not appear to be modulated by the location of the mutation. This was the first demonstration of the location–type interaction for the production of clinical phenotype.

Despite structural similarities between the two six-transmembrane spanning potassium ion channels *KCNQ1* and *KCNH2*, the level of risk conferred by mutation location-type appears to be highly specific and cannot be extrapolated from one potassium channel to another. These studies tell us that LQT mutations are not created equal, and it is necessary to go beyond the simple classification of LQT subtypes for more accurate risk stratification and treatment.

I_{Na}

LQT variants with dysfunctional I_{Na} include LQT3, LQT9, LQT10, and LQT12, with the majority of patients having LQT3 (*SCN5A*) mutations. The greatest contrast in LQT subtype risk factors can be seen by comparing LQT3 with LQT1 patients. In *SCN5A* mutation carriers, risk of cardiac events is highest during rest (bradycardia) when sympathetic activity is low. As might be expected, treatment with β-blockers does not appear to afford LQT3 patients much benefit [26]. In fact, it is surprising that mimicking the LQT3 risk condition by β-blockade is not more harmful. It is now clear that genotype–phenotype correlation studies of *SCN5A* mutations are complicated by the fact that *SCN5A* mutations are thought to be causal in other arrhythmia syndromes, including Brugada syndrome, sinus node dysfunction, and conduction disease [34–36]. Previously, the *SCN5A* arrhythmia syndromes have been considered clinical entities distinguishable by the biophysical profiles of the mutated channels. In general, most LQT3 mutations disrupt channel inactivation and cause abnormal sustained sodium current (I_{NaL}) during the action potential plateau phase, referred to as a ‘gain of function’ [10]. In contrast, Brugada and conduction disease *SCN5A* mutations diminish sodium current, resulting in a ‘loss of function’ [35]. Recent studies have demonstrated that the clinical and biophysical overlap among the various types of *SCN5A* mutations is greater than previously appreciated [37]. The *SCN5A* ‘overlap’ syndrome was first reported in a family with *SCN5A* 1795insD mutation, an insertion mutation in the c-terminus. The large multigenerational family presented with the full spectrum of arrhythmic syndromes, including sinus node dysfunction, conduction disease, Brugada syndrome, and LQT3 [38,39]. This mutation was shown to have a dual effect with inappropriate sodium entry at slow HRs (LQTS ECG pattern), and reduced sodium entry at fast HRs (Brugada ECG pattern) [38], and distinct mutations of the same residue (Y1795) cause either Brugada syndrome (Y1795H) or LQT3 (Y1795C) [40]. Interestingly, transgenic mice expressing the murine equivalent of *SCN5A* 1795insD mutation revealed a full spectrum of LQTS, conduction disorder, and right ventricle conduction delay (Brugada) syndrome, but the severity, as well as the magnitude, of sodium current reduction was greatly modulated by the

background strain of mice [41•,42]. There are now two reports [43,44••] of families with ΔKPQ mutations (deletion of lysine, proline, and glutamine in residues 1505–1507; first LQT3 mutation described and considered the prototype for gain-of-function mutation) that manifest as LQT3, conduction disease, and possibly cardiomyopathy.

The *SCN5A* overlap syndrome presents a management conundrum for LQT3 patients. Na^+ channel blockers such as lidocaine, mexiletine, and flecainide with local anesthetic properties are currently believed to be the most promising treatment for LQT3 patients due to preferential inhibition of I_{NaL} [1,12,13]. Ranolazine, a drug developed as an antianginal agent and affecting a number of cardiac ion channels, has also been found to be highly selective for blocking I_{NaL} [45,46]. Accumulating knowledge of the overlap syndrome raises concern over use of these sodium channel blockers for LQT3, which may unintentionally unmask Brugada and other *SCN5A* arrhythmia syndromes.

It is intriguing that the effect of treatment with β-blockers for LQT3 patients appears to be clinically neutral despite simulation of risk conditions by reducing HR and adrenergic input. This paradox may be explained by a recent study [47••] that showed that β-blockers such as propranolol, metoprolol, and carvedilol also inhibit I_{NaL}. These studies may have implications beyond LQT3. Given that I_{NaL} is present in myocytes of failing heart, it is possible that the local anesthetic-like effect may be an underappreciated mechanism that contributes to the clinical benefit of β-blockers.

Conclusion

Despite LQTS being a relatively rare disease, insights derived from the investigations of LQT ion channel mutations have markedly advanced our understanding of human cardiac electrophysiology. Through LQTS studies, for example, it is now absolutely clear that the same clinical phenotype (delayed ventricular repolarization) can be caused by alterations in any one of a growing number of genes. Further, it is clear from the work described above that it is now possible to manage LQTS patients utilizing a subtype-specific strategy. As our ability to understand the link from genotype to phenotype in LQTS increases, so does our potential to pharmacologically treat these disorders based primarily on genotype rather than phenotype. Ongoing investigations are laying the foundation for the novel paradigm for mutationspecific risk stratification and management based on the biophysical, topographical, and structural characteristics of the mutation.

What are the major obstacles to achieving the goal of mutation-specific or personalized management of patients with congenital LQTS? One major hurdle is the variable expression of LQT mutations in individual patients. This is particularly problematic for LQT3/ *SCN5A* mutations, in which it is becoming increasingly clear that multiple arrhythmic syndromes called overlap syndrome can occur even with mutations (ΔKPQ) that were previously identified to have biophysical profiles consistent with only LQT3. There is evidence that, for some mutations, the variable phenotypic expression of the *SCN5A* mutation is not only a consequence of the specific mutation but also due to modifiers that may be present in the patients [41•,42]. Without more complete understanding of the link between mutation and pheno-type in LQTS patients, we will be limited in our ability to risk stratify and derive pharmacologic treatment based upon the mutation and modifiers.

Current advances in stem cell technology have developed the breakthrough technology to allow us to manipulate the pluripotency of differentiated somatic cells by widely available molecular and cell culture techniques. It is possible to derive induced pluripotent stem cells (iPSCs) from patient skin biopsies [48]. This technology, combined with our ability to differentiate iPSCs into cardiomyocyte lineage, empowers us with unprecedented

opportunities to directly examine patient-specific cardiomyocytes. We believe this will be a particularly powerful technique because cardiac myocytes derived from patient-specific iPSCs will have the full complement of individual genetic variations, including modifiers of LQTS phenotypes. By performing functional studies of patient-specific cardiomyocytes, we will have the opportunity to record and examine the effect of a given mutation in the native cardiomyocyte environment. We believe these studies are the novel paradigm that will allow us to reach mutation-specific, and ultimately patient-specific, management of LQTS.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 286).

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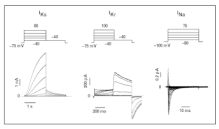

Figure 1. Long QT syndrome common final pathway current traces I_{Ks}, I_{Kr}, and I_{Na} recorded using patch clamp studies

Stimulation protocols are indicated above the current traces.

Table 1

Long QT subtypes classified by final common pathways

Current	Long QT subtype	Genes	Protein	Function
I_{Ks}	LQT1	*KCNQ1*	Kv7.1	α-Subunit I_{Ks}
	LQT5	*KCNE1*	minK	β-Subunit I_{Ks}
	LQT11	*AKAP9*	Yotiao	Regulatory adaptor I_{Ks}
I_{Kr}	LQT2	*KCNH2*	Kv11.1	α-Subunit I_{Kr}
	LQT6	*KCNE2*	MiRP1	β-Subunit I_{Kr}
I_{Na}	LQT3	*SCN5A*	Nav1.5	α-Subunit I_{Na}
	LQT4	*ANK2*	Ankyrin B	Adaptor I_{NaK} INa–Ca, INa
	LQT9	*CAV3*	M-Caveolin	Adaptor I_{Na}
	LQT10	*SCN4B*	Navb4	β-Subunit I_{Na}
	LQT12	*SNTA1*	a-1-Syntrophin	Scaffolding protein I_{Na}
I_{k1}	LQT7	*KCNJ2*	Kir2.1	α-Subunit I_{K1}
I_{CaL}	LQT8	*CACNA1C*	Cav1.2	α-Subunit I_{CaL}