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REVIEW

Genetics of long-QT syndrome

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Congenital long QT syndrome (LQTS) is an inherited arrhythmia syndrome characterized by a prolonged QT interval in the 12-lead ECG, torsades de pointes and not negligible prevalence of sudden cardiac death. The genetic testing plays an important role in the diagnosis of LQTS. A total of 15 genes have been reported for autosomal-dominant forms of Romano–Ward-type congenital LQTS and 2 genes for autosomal-recessive forms of the Jervell and Lange–Nielsen syndrome. In this review, we summarize the recent advances in genetics of LQTS and briefly describe forward perspectives of LQTS investigation.
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INTRODUCTION

Long-QT syndrome (LQTS) is characterized by a prolonged QT interval on 12-lead electrocardiograms (ECGs) that can progress to a polymorphic ventricular tachycardia (VT) known as torsades de pointes. Clinically, torsades de pointes can produce syncope, ventricular fibrillation or even sudden cardiac death. The prevalence of congenital LQTS is reportedly 1 in 2000.[1] In this review, we focus on the advances in our understanding of the genetics of LQTS.

CRITERIA FOR DIAGNOSIS

The Schwartz score[2] is used to diagnose congenital LQTS (Table 1). Patients with a Schwartz score $\geqslant 3.5$ points in the absence of a secondary cause for QT prolongation are diagnosed with LQTS. Recently, in 2013, an expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes was published by the Heart Rhythm Society, the European Heart Rhythm Association and the Asia Pacific Heart Rhythm Society.[3] They reported that congenital LQTS should be diagnosed when the following criteria are fulfilled:

(1) An LQTS risk score $\geqslant 3.5$ without a secondary cause for QT prolongation.
(2) An unequivocally pathogenic mutation in one of the LQTS genes.
(3) In the presence of a corrected QT interval (QTc) $\geqslant 500$ ms on repeated 12-lead ECGs using Bazett's formula in the absence of a secondary cause for QT prolongation.

They adjunctively mentioned that LQTS can be diagnosed when the QTc is between 480 and 499 ms on repeated 12-lead ECGs in patients with unexplained syncope, without a secondary cause for QT prolongation, and in the absence of a pathogenic mutation.

As just described, the genetic testing is included in the diagnosis criteria and has an important role in the diagnosis of LQTS.

GENETICS

The three main types of LQTS and genetic testing

A total of 15 genes have been reported in autosomal dominant forms of Romano–Ward-type congenital LQTS (Table 2). Moreover, most of the genetic abnormalities identified thus far appear to prolong the duration of action potentials by decreasing the potassium current (loss-of-function mutation) or increasing the sodium or calcium current (gain-of-function mutation), resulting in clinical QT prolongation on the ECG.

Between 1995 and 1996,[4–6] three major causative genes were recognized for LQTS and associated with LQTS types 1–3: *KCNQ1*-encoding Kv7.1 (for LQT1), *KCNH2* encoding Kv11.1 (for LQT2) and *SCN5A* encoding Nav1.5. Napolitano *et al.*[7] reported that they identified 235 different mutations in 310 (72%) of 430 probands (49% KCNQ1, 39% KCNH2 and 10% SCN5A). In Japan, Shimizu *et al.*[8] reported the three major genes constituted more than 80% of total genotyped patients with LQTS. According to the Heart Rhythm Society/European Heart Rhythm Association Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies, abnormalities of the three LQTS-associated genes are detected in ~75% of clinically definite LQTS, with rates of 30%–35%, 25%–40% and 5%–10% for LQTS types LQT1, LQT2 and LQT3, respectively.[9] LQTS genetic testing contributes to not only diagnosis but also gene-specific and mutation-specific risk stratification and patient management. They recommended that comprehensive or specific genetic testing for *KCNQ1*, *KCNH2* and *SCN5A* be performed for any patient who fulfills the following criteria:[9]

(1) where a cardiologist has established a strong suspicion for LQTS based on clinical examination,
(2) where a patient has asymptomatic QT prolongation in the absence of other clinical conditions that may prolong the QT interval,

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Table 1 Diagnosis of long QT syndrome

Parameters	*Points*
Electrocardiographic findings[a]	
A) QTc time[b]	
⩾480 ms	3
460–479 ms	2
450–459 ms (male)	1
B) Four-minute recovery QTc after exercise test ⩾480 ms	1
C) Torsade de pointes[c]	2
D) T-wave alternance	1
E) Notched T wave	1
F) Low heart rate for age[d]	0.5
Clinical manifestations	
A) Syncope[c]	
With stress	2
Without stress	1
B) Congenital deafness	0.5
Family history	
A) Family members with definite LQTS[e]	1
B) Unexpected sudden cardiac death at age <30 years in family members	0.5

Abbreviation: LQTS, long QT syndrome.
⩾3.5 points, diagnosed as LQTs; 1.5–3 points, suspect of LQTs; ⩽1 point, unlikely LQTS.
[a]In the absence of medications or disorders known to affect these electrocardiographic features.
[b]QTc calculated by Bazett's formula where $QTc = QT/\sqrt{RR}$.
[c]Mutually exclusive.
[d]Resting heart rate below the second percentile for age.
[e]The same family member cannot be counted in A and B.

(3) where a patient is asymptomatic, with QTc values >460 ms (prepuberty) or >480 ms (adults) on serial 12-lead ECGs and
(4) when an LQTS-causative mutation is identified in an index case, mutation-specific genetic testing is recommended for the family members.

Risk stratification of LQTS using the genetic information

In 600 patients with LQT1, Moss *et al.*[10] demonstrated that those with mutations in the transmembrane region of Kv7.1, those with missense mutations and those with mutations resulting in dominant-negative ion currents had greater risk of arrhythmic events than those with other mutations. In a Japanese multicenter study, Shimizu *et al.*[11] also reported that patients with LQT1 and transmembrane mutations are at a higher risk of cardiac events and had a greater sensitivity to sympathetic stimulation than those with C-terminal mutations. Subsequently, Barsheshet *et al.*[12] demonstrated that patients with C-loop missense mutations in the *KCNQ1* gene exhibited a high risk for life-threatening events, and that β-blocker therapy was effective for them.

Regarding LQT2, Shimizu *et al.*[13] demonstrated in 858 patients that missense mutations in the transmembrane pore region are associated with significantly higher rates of cardiac events than are other missense mutations. Recently, Liu *et al.*[14] also reported that a trafficking-deficient mutation in the transmembrane non-pore region of Kv11.1 causes a dominant-negative effect and a severe clinical course.

Patients with LQTS having both the pathogenic variants and a QTc>500 ms are also at high risk, in particular when they are symptomatic. In contrast, the asymptomatic genetically diagnosed LQTS patients are evaluated at lower risk. An important risk factor for these patients comes from drugs that block the I_{Kr} current and conditions that lower their plasma potassium level.[3]

Table 2 Genes associated with the long QT syndrome

LQTS type	*Gene*	*Protain*	*Current*
Romano–Ward syndrome			
LQT1	*KCNQ1*	Kv7.1	I_{Ks} ↓
LQT2	*KCNH2*	KV11.1	I_{Kr} ↓
LQT3	*SCN5A*	Nav1.5	I_{Na} ↑
LQT4	*Ankyrin-B*	Ankyrin	Na+/K+ ATPase and so on
LQT5	*KCNE1*	MinK	I_{Ks} ↓
LQT6	*KCNE2*	MiRP1	I_{Kr} ↓
LQT7	*KCNJ2*	Kir2.1	I_{K1} ↓
LQT8	*CACNA1C*	CaV1.2	$I_{Ca\text{-}L}$ ↑
LQT9	*CAV3*	Caveolin3	I_{Na} ↑
LQT10	*SCN4B*	SCNβ4subunit	I_{Na} ↑
LQT11	*AKAP-9*	Yotiao	I_{ks} ↓
LQT12	*SNTA1*	Syntrophin-α1	I_{Na} ↓
LQT13	*KCNJ5*	Kir3.4	I_{KACh} ↓
LQT14	*CALM1*	Calmodulin1	Disorder of calcium signaling
LQT15	*CALM2*	Calmodulin2	
Jervell and Lange–Nielsen syndrome			
JLN1	*KCNQ1*	Kv7.1	I_{Ks} ↓
JLN2	*KCNE1*	MinK	I_{Ks} ↓

Genome-wide association study about QT times

In 2009, two genome-wide association studies of QT intervals, the QTGEN and QTSCD, have been reported in *Nature Genetics*.[15,16] Common single-nucleotide polymorphisms in *NOS1AP*, *KCNQ1*, *KCNH2*, *SCN5A*, *KCNJ2* and *RNF207* were detected and the genes were reported as candidates for ventricular arrhythmias and sudden cardiac death. Earle *et al.*[17] demonstrated that the single-nucleotide polymorphisms reported in *NOS1AP* and *KCNQ1*, which affect the QT interval, were also associated with an increased risk of cardiac events in patients with LQTS. Recently, they reported that single-nucleotide polymorphisms of *NOS1AP* increased the risk of cardiac events in patients with LQT2 and they also reported regarding the link between the *KCNQ1* single-nucleotide polymorphism and the *KCNH2* mutations.[18] Other researchers have tried to clarify the drug–gene interactions that influence the QT interval, but numerous problems remain unresolved.[19]

The other genes beyond the three common LQTs

Beyond the three common LQTS gene variants, several mutations encoding ion-channel subunits, except for those associated with LQT4, LQT9, LQT11, LQT12, LQT14 and LQT15, have also been found. Notably, mutations in *KCNQ1* (that is, JLN1, also associated with LQT1) and *KCNE1* (that is, JLN2, also associated with LQT5) have also been found to be causal in autosomal-recessive forms of the Jervell and Lange–Nielsen syndrome attributable to a decrease in the *Iks*. They are accompanied by neurosensorial deafness and a markedly prolonged QT interval[19] (Table 2).

Mutations in the potassium channel genes

The LQTS types associated with slowly activating delayed rectifier potassium current (I_{Ks}) dysfunction include LQT1, LQT5, LQT11, JLN1 and JLN2 (Table 2), although most are associated with LQT1. Mutations in *KCNE1*, which are associated with LQT5, cause defective trafficking of the I_{Ks} channel, reduce amplitude of the I_{Ks} current and influence disease pathogenesis.[20] A mutation in *AKAP9*, which is associated with LQT11, has been shown to reduce the interaction

between Kv7.1 and A-kinase anchor protein 9, reduce the cyclic AMP-induced phosphorylation of the channel, eliminate the functional response of the I_{Ks} channel to cyclic AMP and prolong the action potential in a computational model of the ventricular cardiomyocyte.[21]

The LQTS types associated with rapidly activating delayed rectifier potassium current (I_{Kr}) dysfunction include LQT2 and LQT6, with the former accounting for the majority of cases. Most of the mutations in *KCNH2* disrupt the maturation and trafficking process before reducing the number of functional ion channels at the cell surface membrane.[22] However, mutations of *KCNE2* (the β-subunit of Kv11.1), which are associated with LQT6, have been reported to modulate Kv11.1 channel gating and currents, and to be proarrhythmic.[23]

Mutations in the sodium channel genes

The LQTS types with dysfunctional late-activating sodium channels (I_{Na}) include LQT3, LQT9, LQT10 and LQT12, although most are LQT3. Notably, numerous mutations have been characterized as leading to or predisposing to LQT3. In addition, mutations of Nav1.5 have been linked to a variety of cardiac diseases such as LQTS, Brugada syndrome, cardiac conduction defects, atrial fibrillation and dilated cardiomyopathy.[24,25] Phenotypic overlap of LQT3 with Brugada syndrome is also observed in some carriers of *SCN5A* mutations.[26] For example, the α-subunit of Nav1.5 interacts with several regulatory proteins and the mutations of these genes cause disease related to sodium-channel dysfunction.[27] *SCN4B* encodes the β-subunit of the sodium channel that is critical to the regulation of sarcolemmal expression and the gating of Nav1.5. An *SCN4B* mutation associated with LQT10 has been shown to increase the persistence of the I_{Na} with a positive shift toward inactivation.[28] Caveolin-3 acts in conjunction to increase peak I_{Na} through a cyclic AMP-independent pathway; a *CAV3* mutation associated with LQT9 subsequently results in QT prolongation only during β-blocker therapy.[29] *SNTA1* is associated with LQT12, which encodes α-1-syntrophin, and is associated with the Nav1.5 channel as part of the neuronal nitric oxide synthesis complex. A mutation in *SNTA1* is associated with an increase in both the peak and the persistence of the I_{Na} due to a change in the binding of the PDZ domain.[30]

Mutations in other genes

A type of LQTS that is associated with a mutation in *KCNJ2* is LQT7, which creates a condition known as Andersen–Tawil syndrome. This is characterized by a triad of periodic paralysis, a long QU interval associated with ventricular arrhythmias and skeletal development anomalies. In this condition, a reduction in Kir2.1 due to the *KCNJ2* mutation prolongs the terminal phase of the cardiac action potential. Because of the reduced extracellular potassium levels, sodium/calcium exchanger-dependent delays after depolarization are induced, resulting in spontaneous arrhythmias.[31] The common clinical characteristics of LQT7 and cathecolaminergic polymorphic VT (CPVT), such as biphasic premature ventricular contractions, make diagnosis difficult. Several factors can assist in the differential diagnosis: T-U patterns (i.e. prolonged terminal T downslope, wide T-U junction, and biphasic and enlarged U waves), relatively slow polymorphic or biphasic VT and frequent ventricular ectopic beats at rest may be useful in distinguishing LQT7 from CPVT. After KCNJ2 mutations were identified in patients with CPVT phenotype, differential diagnosis between LQT7 and CPVT by genotyping became more challenging.[32]

The most severe phenotypic form of LQTS is Timothy syndrome (LQT8). This is associated with point mutations in *CACNA1C*, which cause slowed inactivation of CaV1.2 that increase the influx of calcium, prolong the cardiac action potential and promote lethal arrhythmias. Timothy syndrome is quite rare because of the fatal phenotype and multisystem manifestations, including congenital heart disease, syndactyly, immunodeficiency, cognitive abnormalities and autism.[33] Recently, mild LQT8 cases with *CACNA1C* mutation without phenotype of Timothy syndrome were reported.[34,35]

Crotti *et al.*[36] performed exome sequencing in infants with recurrent cardiac arrest and dramatically prolonged QTc intervals, discovering heterozygous *de novo* mutations in *CALM1* and *CALM2* encoding calmodulin (that is, LQT14 and LQT15, respectively). In addition, Makita *et al.*[37] reported the presence of *CALM1* and *CALM2* mutations in LQTS probands by next-generation sequencing approaches. They revealed that these calmodulin mutations disrupted calcium-ion binding to the protein and were associated with LQTS and with overlapping features of LQTS and CPVT.

FUTURE PERSPECTIVES

Numerous ion-channel mutations have been reported and various approaches have been used to confirm the associated functional change, including expression models (using human embryonic kidney cells, Chinese hamster ovary cells or *Xenopus* oocytes), experimental mouse models, computational approaches, neonatal mouse cardiomyocytes and induced pluripotent stem cells.[38,39] The assessment of gene expression with induced pluripotent stem cells is useful when confirming drug efficacy, in particular in cases with complex genotypes.[40,41]

Furthermore, gene analysis techniques have advanced remarkably. As previously mentioned, we can obtain significant amount of data using next-generation sequencing approaches, exome analysis[42] and genome-wide association studies. Next-generation sequencing technology allows a comprehensive genetic analysis of LQTS such as a copy number variation.[43] Whole-exome sequencing is efficient to elucidate the underlying genetic mechanism of diseases. However, an investigator often faces difficulties to identify the possible disease causative variant among hundreds of variants per patient DNA sample and it takes up a lot of energy. We have to identify potential candidate genes by considering genotype–phenotype association, the relationship between genotype and disease development of each family member, publicly available internet-based gene-prioritization tools, *in silico* variant annotation prediction and functional studies.[44,45]

In addition, we can use the large bioinformatics data registries of genome browsers, such as HapMap (http://hapmap.ncbi.nlm.nih.gov/), NCBI (http://www.ncbi.nlm.nih.gov/), UCSC (https://genome.ucsc.edu/), 1000 genome data (http://www.1000genomes.org/) and recently publicly available database, the ExAC browser, which contains exome sequencing data on up to 60 000 individuals (http://exac.broadinstitute.org/).

A recent epochal report demonstrated that rapid whole-genome sequencing could be performed with a speed-optimized bioinformatics platform in LQTS patients that could provide comprehensive diagnostic information at 10 days of life. Their approach was certified by the Clinical Laboratory Improvement Amendments.[46] The goal of identifying the genetic basis of the disease is to individualize and optimize treatment strategies. Finally, it is important to identify and profile the relatives of LQTS probands to identify their risk. In a review article reported by Semsarian *et al.*[47], in sudden cardiac death cases where no cause of death is identified at post mortem, genetic testing of post-mortem blood in a specialized multidisciplinary clinic setting may identify a cause of death in up to 30%. The ultimate goal is

to prevent future adverse clinical outcomes and sudden cardiac death (SCD) events in surviving relatives.

Porta *et al.*[48] reported that patients with higher sympathetic control of the QT interval and reduced vagal control of the heart rate were at lower risk of complications than other patients with LQT1 carrying the same mutation. Myerburg[49] has also stated that gene expression was modulated by physiological fluctuations, drug and electrolytes, and environmental factors, and that we must consider the role of epistasis with other modifying gene variants.

Thus, both genomic and non-genomic factors are important when diagnosing congenital ion-channel diseases and the need to advance genetic analysis is therefore apparent.

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