Congenital long QT syndrome: genetic architecture, risk stratification and treatment approaches

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This review article discusses current and controversial issues related to the diagnosis, risk stratification, and management of patients with congenital long QT syndrome (LQTS). Recent data on the genetic architecture of LQTS are presented, a risk stratification model is analyzed, and new potential cardiovascular prognostic factors are characterized. Much attention is given to the description of genotype-phenotype correlations of LQTS and molecular genetic mechanisms of cardiac transmembrane ion channel abnormalities that are key in the arrhythmogenesis of LQTS. The main methods of management of patients with LQTS, especially those at high risk of cardiac events, including a genotype-specific approach to management, are also presented.

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Introduction

Congenital long QT syndrome (LQTS) is the most common inherited arrhythmia in the absence of structural heart disease [1–3]. LQTS is characterized by a genetically and phenotypically heterogeneous cardiac repolarization disorder manifested by an increased risk of polymorphic ventricular tachycardia (VT) and sudden cardiac death (SCD) [4, 5].

The prevalence of congenital LQTS in the population is not well known, but is thought to be between 1:2500 and 1:5000 [6]. Considering that it is undetectable in up to ⅔ of patients and 10 % to 35 % of patients have a normal QTc, it is likely that the true prevalence of LQTS is much higher [6, 7]. In general, the clinical penetrance of LQTS for all genetic types ranges from 25 % to 100 %, with an average of about 40 % [8, 9]. However, the penetrance is significantly increased by additional factors, especially by drugs that prolong the QT interval [10].

The molecular/genetic (cellular) mechanism of LQTS is based on ion channel dysfunction caused by mutations in LQTS susceptibility genes, which contributes to a decrease in the currents of inward-rectifier potassium channels (I_{Ks}, I_{Kr}, I_{K1}) and/or an increase in the depolarizing inward sodium or calcium currents (I_{Na} and I_{CaL}), resulting in prolongation of the action potential (AP) and QT interval [2, 4, 11]. In the presence of significant slowing of ventricular repolarization and increased transmural dispersion of repolarization, early postdepolarizations (electrical substrate) occur that act as trigger activity from the Purkinje network and initiate the development of polymorphic VT, especially the pirouette-type *torsades de pointes* (TdP) that is a distinctive feature of LQTS [1, 10, 12].

The aim of this review article is to detail the current genetic architecture of congenital LQTS, describe new potential risk factor (RF) stratification and current therapeutic strategies, including a genotype-specific approach in the management of patients with LQTS.

Current genetic architecture of congenital LQTS

Congenital LQTS is a polygenic disease and currently about 17 LQTS genotypes (referred to as LQT — long QT) and more than 760 mutations have been identified, leading to a revision of the LQTS classification [3, 13]. LQTS is known to be associated with mutations in 6 potassium channel genes (*KCNQ1, KCNH2, KCNE1, KCNE2, KCNJ2, KCNJ5*), 2 sodium channel genes (*SCN5A, SCN4B*), 1 calcium channel gene (*CACNA1C*) and 4 specific binding and assembly protein genes (*AKAP9, ANK9, CAV3, SNTA1*) [13, 14]. The contribution of genes involved in cellular calcium homeostasis, such as calmodulin (*CALM1, CALM2, CALM3*) and triadin (TRDN), which cause malignant variants of LQTS, is also increasingly recognized [1, 3, 13].

It should be noted that 6 LQTS susceptibility genes are classified as "defined" or definitive (*KCNQ1, KCNH2, SCN5A, CALM1, CALM2, CALM3*), 1 gene is *TRDN,* with strong evidence and 1 gene is *CACNA1C* with moderate evidence [8]. Therefore, genetic testing for these genes should be considered in patients with LQTS whose clinical manifestations correspond to a specific phenotypic expression. These extremely rare, pathogenic or probable pathogenic variants that significantly reduce repolarization reserve define the penetrant monogenic variants of congenital LQTS [13].

According to ClinGen, most of the identified LQTS susceptibility genes (*ANK2, KCNE1, KCNE2, KCNJ2, KCNJ5, SNTA1, AKAP9, SCN4B, CAV3*) have controversial or limited evidence [8] and should not be routinely tested in the evaluation of patients and families with LQTS. These genes are associated with potentially proarrhythmic "functional risk alleles" and poorly penetrant functional genetic variants in congenital LQTS [13].

Over the past two decades, the accumulated clinical experience has set the stage for a revision of the genetic architecture of LQTS with a possible downregulation of about 40 % of LQTS susceptibility genes. Taking into account the syndromic approach, a new classification of LQTS has been proposed, distinguishing the following genotype-phenotype correlations 1) non-syndromal variants of LQTS with canonical or "major" genes non-syndromal variants of LQTS with "minor" genes syndromal variants of LQTS with multisystem involvment (in 5–10 % of LQTS cases). Syndromal LQTS (Ankyrin-B, Andersen-Tawil, Timothy, and Jervell and Lange-Nielsen syndromes),

in which QT interval prolongation is possible, are associated with a pathogenic variant in one of the additional minor LQTS susceptibility genes [13, 15].

The 3 most common LQTS genotypes are caused by mutations in canonical genes — *KCNQ1, KCNH2, and SCN5A*, which are designated LQT1, LQT2, and LQT3, respectively (Table 1). These genes account for 85–95 % of all gene-positive LQTS cases [1, 6, 16]. The LQT1 genotype is the most common, occurring in 35–50 % of all LQTS variants and causing the development of Jervell and Lange-Nielsen syndrome in 90 % of cases [2, 17]. The LQT2 genotype is detected in 25–40 % and the LQT3 genotype in 5–10 % of cases. The other LQTS genotypes are found in less than 1.5 % of cases [13].

The *KCNQ1* gene responsible for the development of LQT1 encodes the α-subunit of the potassium channel that regulates slow delayed rectifier potassium currents (I_{Ks}). Loss-of-function mutations in *KCNQ1* cause a decrease in I_{Ks}, contributing to prolonged repolarization and QT interval, particularly during exercise [1, 2, 16]. The LQT2-related *KCNH2* gene encodes the α-subunit of the voltage-gated potassium channel and mediates the fast delayed rectifier potassium current (I_{Kr}) [4]. Loss-of-function mutations of the *KCNH2* gene result in decreased I_{Kr} current and are more likely to be associated with cardiac events. The *SCN5A* gene, responsible for LQT3, encodes a voltage-gated sodium channel (NaV1.5). *SCN5A* gain-of-function mutations result in increased late sodium depolarizing current (I_{NaL}) and AP prolongation [13].

It should be noted that genetic variants of minor LQTS susceptibility genes, the population frequency of which significantly exceeds the prevalence of congenital LQTS with canonical genes, may cause proarrhythmic state in the background of QT prolonging drugs, electrolyte abnormalities, structural heart disease and genetic background with repolarization

Table 1. **Characteristics of LQTS susceptibility genes [13]**

Gene	Locus	Protein	Mutation effect	Frequency (%)
Non-syndromal LQTS with canonical genes				
KCNQ1 (LQT1)	11p15.5	K_V7.1	Decrease of I_{Ks}	30–35
KCNH2 (LQT2)	7q35-36	K_V11.1	Decrease of I_{Kr}	25–30
SCN5A (LQT3)	3p21-p24	Na_V1.5	Increase of I_{Na}	5–10
Non-syndromal LQTS with minor genes				
AKAP9	7q21-q22	Yotiao	Decrease of I_{Ks}	< 1
CACNA1C	12p13.3	Ca_V1.2	Increase of I_{CaL}	~ 1-2
CALM1	14q32.11	Calmodulin-1	Increase of I_{CaL} (Ca^{2+}-dependent inactivation)	~ 1-2
CALM2	2p21.3	Calmodulin-2		~ 1
CALM3	19q13.32	Calmodulin-3		< 1
CAV3	3p25	Caveolin-3	Increase of I_{Na}	< 1
KCNE1	21q22.1	MinK	Decrease of I_{Ks}	< 1
KCNE2	21q22.1	MiRP1	Decrease of I_{Kr}	< 1
KCNJ5	11q24.3	Kir3.4	Decrease of $I_{K, Ach}$	< 1
SCN4B	11q23.3	β4-subunit/ Na_V1.5	Increase of I_{Na}	< 1
SNTA1	20q11.2	α1-syntrophin	Increase of I_{Na}	< 1
Cardiac phenotype of Timothy syndrome (type II)				
CACNA1C	12p13.3	Ca_V1.2	Increase of I_{CaL}	~ 1
Syndromal LQTS with multisystem involvement				
Jervell and Lange-Nielsen syndrome (JLNS).				
KCNQ1 (JLNS 1)	11p15.5	K_V7.1	Decrease of I_{Ks}	Very rare
KCNE1 (JLNS 2)	21q22.1-q22	MinK	Decrease of I_{Ks}	
Ankyrin-B syndrome				
ANKB	4q25-q27	Ankyrin-B	Decrease of Ankyrin-B	< 1
Andersen-Tawil syndrome				
KCNJ2	17q23	Kir2.1	Decrease of I_{K1}	< 1
Timothy syndrome (type I)				
CACNA1C	12p13.33	Ca_V1.2	Increase of I_{CaL}	Very rare
Triadin knockout syndrome				
TRDN	6q22.31	Triadin	Increase of I_{CaL}	~ 2

reserve deficiency [10, 13]. These variants result in a moderate decrease in cardiac repolarization reserve and rarely cause syncope or SCD due to LQTS. Therefore, these variants may serve as major drivers of so-called oligogenic variants of congenital LQTS when present in genetic backgrounds containing other QT-related genetic modifiers, such as common variants in *NOS1AP* [11].

The involvement of calmodulin (*CALM*) and triadin (*TRDN*) genes in LQTS has been linked to their connection to calcium signaling mechanisms, including regulation of cardiac ion channels [3, 13]. Three *CALM1-3* genes located on different chromosomes encode the same calmodulin protein, and their rare genetic variants are associated with *LQT14, LQT15, and LQT16*. The phenotypic features of these variants are manifestation of symptoms in infancy or early childhood, with marked sinus bradycardia or atrioventricular block, prolongation of the QT interval, seizures, and developmental delay. The *TRDN* gene, which encodes L-type calcium channels (triadin protein), has been classified as having strong evidence for causation of atypical LQTS, a triadin knockout syndrome. Atypical features include autosomal recessive inheritance, onset in infancy or early childhood, and negative T-peaks in the precordial leads of the ECG.

Homozygous or compound heterozygous mutations in the *KCNQ1* (type I) and *KCNE1* (type II) genes, which encode the α- and β-subunits of the potassium channel I_{Ks}, respectively, have been shown to be associated with different types of Jervell and Lange-Nielsen syndrome [2, 17]. This syndrome is characterized by bilateral sensorineural deafness, QTc prolongation usually greater than 550 m/s, and the occurrence of VT or ventricular fibrillation (VF) [15]. Cardiac features are most commonly inherited as an autosomal dominant trait, and sensorineural deafness is inherited as an autosomal recessive trait [13]. Pathogenic variants in the *KCNE1* gene have been shown to be relatively benign compared to pathogenic variants in the *KCNQ1* gene. In addition, expression of the *KCNQ1* gene in nervous tissue may contribute to the combination of channelopathy and epilepsy [16].

Loss-of-function variants of ankyrin-B encoded by *ANK2* have been shown to be associated with ankyrin-B syndrome (LQT4, according to the traditional classification), which is manifested by different phenotypes of arrhythmias resulting from impaired cellular calcium homeostasis [13]. The *ANK2* gene has an extremely low mutation frequency and functional features uncharacteristic of LQTS: atrial fibrillation, complete atrioventricular block or sinus node dysfunction.

KCNJ2 gene variants are usually associated with Andersen-Tawil syndrome, which is characterized by a triad of features: 1) hypokalemic periodic paralysis craniofacial and skeletal dysmorphism; and 3) QT interval prolongation with a high risk of polymorphic VT [15]. Mutations in the *KCNJ2* gene (type I), which encodes the Kir2.1 protein of the abnormal potassium rectifier channel (I_{K1} current), an important regulator of resting membrane potential, are detected in 80–90 % of cases. In 10–20 % of cases, Andersen-Tawil syndrome is associated with a mutation in the *KCNJ5* gene (type II), which encodes the G protein-coupled Kir3.4 potassium channels that conduct the $I_{K,Ach}$ current. It should be noted that in Ankyrin-B and Andersen-Tawil syndromes, QT interval prolongation is not a permanent feature of the cardiac phenotype.

Mutations in the *CACNA1C* gene, encoding the L-type calcium channel (CaV1.2), are associated with Timothy syndrome, which has two molecular genetic variants: the "classical" variant (type I) with a multisystem phenotype and the "atypical" variant (type II) — an isolated cardiac phenotype [13, 15]. The "classical" variant (LQT8, according to the traditional classification) is caused by a mutation in exon 8a of the *CACNA1C* gene and polymorphism of clinical manifestations: facial dysmorphism, autism, syndactyly, congenital heart defects, immunodeficiency states and early family history of SCD before the age of 30 years. In addition to possible QT interval prolongation, the ECG shows notable sinus bradycardia, macroalternation of the T-wave, conduction abnormalities, and ventricular arrhythmias, often drug-induced.

Risk stratification for cardiac events in congenital LQTS

Despite its rarity, congenital LQTS is the leading cause of SCD in otherwise healthy young adults, highlighting the importance of robust risk stratification to reduce the burden of SCD [5, 18, 19]. Genetic testing can identify the molecular substrate and thus genotype-specific proarrhythmic conditions [9, 10, 14]. However, the risk of arrhythmia in individual patients varies widely even within families carrying the same variant. This makes individual risk stratification

a challenging task, especially when antiarrhythmic treatment or cardioverter-defibrillator implantation is indicated [20, 21].

The developed system for risk stratification of cardiac events in patients with congenital LQTS under 40 years of age includes such markers as resting QTc interval value, sex, and the 3 main genotypes of the disease — LQT1, LQT2, and LQT3 (Table 2) [16, 18, 21]. Based on these markers, 3 risk levels or groups of patients have been identified: low risk (<30 %), intermediate risk (30–40 %), and high risk (>50 %).

Thus, a baseline QTc ⩾500 m/s at rest is considered definitely abnormal when observed in the absence of QT-prolonging RF. It is an independent predictor of cardiac events and serves as a class I recommendation for genetic testing for LQTS [21]. Of note, numerous prospective studies have demonstrated the high predictive value of prognostic stratification in patients with LQTS [1, 22, 23].

Table 2. **Risk stratification in patients with congenital LQTS [14]**

Risk of cardiac events by the age of 40	Resting QTc	Genotype	Gender
High risk (>50 %)	⩾ 500 m/s	LQT1	male/female
		LQT2	male/female
		LQT3	male
Intermediate risk (30–49 %)	< 500 m/s	LQT2	female
		LQT3	female
		LQT3	male
	⩾ 500 m/s	LQT3	female
Low risk (<30 %)	< 500 m/s	LQT2	male
		LQT1	male/female

Determination of LQTS genotype is a determinant of RF of SCD along with QT interval duration [21, 24]. Women with LQT2 and men with LQT3 who have a QTc interval >500 m/s fall into a higher risk category for SCD independent of other RF [12, 15]. In addition, women with LQT2 are at highest risk for cardiac events in the peripartum period, especially in the first 9 months after delivery [25]. The onset of arrhythmic events in childhood has been shown to be an important predictor of their recurrence in later life [5, 18]. However, in individuals with a positive genotype, a family history of SCD in a first-degree relative is not associated with an increased risk of SCD in LQTS [19].

In recent years, new markers for prognostic stratification in LQTS have been proposed to differentiate risk groups among patients with LQTS. In addition, new risk stratifiers for LQTS have demonstrated a high predictive value in the prediction of cardiac events, superior to the resting QTc interval [26-28]. In particular, the $T_{peak} - T_{end}$ interval has been shown to be an indicator of cardiac proarrhythmic potential due to transmural and local repolarization dispersion in patients with LQTS [27]. It has also been demonstrated that QT interval dispersion (QTd) — the variability of the QT interval between the leads of a standard ECG — reflects the heterogeneity of ventricular repolarization and may therefore serve as a marker of cardiac electrical instability [29].

The assessment of exercise repolarization reserve is of practical interest, although genotype-specific proarrhythmic triggers, particularly QTc response, are not included in risk stratification schemes for patients with LQTS. This is particularly important given that approximately 40 % of patients with genetically confirmed LQTS have a normal resting QTc interval. It is known that the QTc interval is prolonged during exercise in LQT1 (impaired adaptation of QT interval to HR), shortened in LQT2, and significantly shortened in LQT3 [2, 16].

It has also been shown that in LQTS, heterogeneously prolonged ventricular repolarization and impaired regional repolarization lead to changes in myocardial mechanical function, creating an electromechanical substrate capable of causing pathological myocardial excitability and triggers the *re-entry mechanism* [26, 28]. In this context, a new criterion of electromechanical dispersion has been proposed — the "electromechanical window", an indicator determined by tissue Doppler cardiac imaging.

Importantly, these potential markers of cardiac event risk have been shown to be strongly correlated with outcomes of BAB therapy and sympathetic denervation, to have genotypic risk differences, and to allow differentiation between symptomatic and asymptomatic patients with LQTS [27].

In addition, the correct diagnosis of LQTS in patients with a normal resting QTc interval but genetically confirmed LQTS is important for risk stratification. Recently, the use of artificial intelligence in the interpretation of standard ECGs has allowed the identification of patients with electrocardiographically hidden LQTS and provides almost 80 % accurate pretest assessment of LQTS genotype in patients with normal resting QTc interval [30].

Role of genetic risk in the prediction of cardiac events in LQTS

Given that LQTS is the most common channelopathy in which SCD is often the first manifestation of the disease, the clinical importance of genetic type identification is high [12, 18, 21].

The impact of genotype, sex and age on the prognosis of LQTS has been described in detail by the International LQTS Registry study group in patients with LQT1-3 variants [16]. Mortality from cardiac events was highest in men and women with LQT3 (19 % and 18 %, respectively), followed by men with LQT1 and LQT2 (5 % and 6 %, respectively), and finally women (2 % for both types). In addition, affected males have an increased incidence of cardiac events in childhood, but the trend is reversed in adolescence and early adulthood [12]. The risk of cardiac events in childhood has been shown to be significantly higher in men with LQT1 than in women with LQT1 (OR 1.72), whereas there were no significant gender differences in patients with LQT2 and LQT3. In adulthood, women with LQT1 and LQT2 had a higher risk of cardiac events than men. Earlier symptom manifestation was associated with a more severe LQTS outcome.

Goldenberg I. et al. [25] evaluated the individual risk of cardiac events in 767 women with LQT1 and LQT2 types aged 15–60 years based on the developed prognostic model. The risk prediction model included the following variables: genotype/mutation position, specific QTc thresholds, history of syncope, and beta blockers (BAB) therapy. The predicted 10-year cardiac event rate was shown to be 2 % at low risk, 5 % at intermediate risk, and 14 % at high risk. The authors believe that the model developed to estimate prognosis in LQTS may help to improve gender-specific risk stratification and therapeutic decision making.

Carriers of LQTS mutations are shown to have an increased risk of cardiac events even in the absence of QTc prolongation. At the same time, the penetrance of mutations in patients with normal QTc may be reflected in the abnormal shape of the T-wave [16, 19]. Cortez D. et al [31] demonstrated the predictive value of the three-dimensional vector of the T wave as a quantitative indicator of repolarization in *KCNH2* (LQT2) mutation carriers with normal QTc at high risk for cardiac events.

In addition, the prognostic significance of assessing the effect of BAB therapy on the incidence of cardiac events depending on the LQTS genotype has been demonstrated [32]. Thus, in patients younger than 40 years, the incidence of cardiac events during BAB therapy was significantly higher in LQT2 (46 %) and LQT3 (42 %) types than in patients with LQT1 type (30 %) [12]. Arrhythmic events in LQT3 have been shown to be more likely to be fatal.

Mutations that result in amino acid substitutions in specific regions of the ion channel also increase the risk of arrhythmias [12, 23]. For example, in LQT1 type, mutations in the cytoplasmic loops of the *KCNQ1* protein or mutations with dominant negative ion current effects are associated with a worse prognosis, especially when compared to mutations affecting the C-terminal regions of the protein. It is also known that single nucleotide polymorphisms in *NOS1AP* and *KCNQ1* are associated with an increased risk of cardiac events in patients with LQTS and can therefore be used in clinical risk stratification [12, 18].

Treatment tactics for congenital LQTS

When choosing management tactics for patients with LQTS, it should be considered that specific manifestations of the disease are syncope and SCD caused by polymorphic VT or VF, often provoked by acute adrenergic activation. Patients diagnosed with LQTS are advised to make lifestyle changes and refrain from taking drugs that prolong the QT interval (Class I; Level of Evidence B) [21, 33]. It is important to note that the choice of therapeutic tactics should be determined by the phenotype, but knowledge of the LQTS genotype may help in prescribing genotype-specific therapy [1, 14].

Genotype-specific pharmacotherapy for LQTS. Currently BAB, especially nadolol and propranolol remain the main drugs used for the treatment of LQTS [32, 34, 35]. According to clinical guidelines, prescription of BAB is indicated in patients with LQT1 and LQT5 diagnosed by genetic testing (class IIa; level of evidence B). In patients with LQT3, the prevailing opinion for a long time was that there was no effect or contraindication to BAB [32]. However, recent studies have shown that BAB significantly reduce the risk of cardiac events in patients with LQT3, especially in women [25].

From the point of view of genotype-specific treatment of LQTS, not all BAB are equivalent [35]. Four BABs studied — nadolol, metoprolol, propranolol, bisoprolol — showed similar efficacy in preventing arrhythmic events in LQT1, but in LQT2, nadolol proved

to be the only BAB that caused a significant reduction in risk. In pregnant women diagnosed with LQTS, nadolol is also recommended because it is the most effective BAB for LQTS and is well tolerated [25].

For LQT2 and LQT6, additional therapy may include long-term potassium supplements and/or spironolactone (class IIa; level of evidence B), and calcium channel blockers are recommended (class IIb; level of evidence B). Because LQT3 is caused by an excess of I_{Na} sodium current entry, mexiletine, which has antiarrhythmic effects (class IIa; level of evidence B), is recommended [21, 36]. In addition, mexiletine significantly shortened the QTc interval in ⅔ of patients with potassium channel-mediated LQT2 [37]. The drug is effective both as monotherapy and in combination with BAB [37].

Long-term treatment with amiodarone has been shown to prolong the QT interval, but TdP is very rare [1, 21]. This is because amiodarone slows repolarization uniformly in all layers of the cardiac wall and therefore does not cause an increase in transmural dispersion of repolarization, which is a substrate for TdP [1, 4, 9]. In addition, the low risk of developing TdP with amiodarone is related to the drug's additional effect of inhibiting I_{NaL}, which reduces the arrhythmogenic potential.

Ranolazine has also been successfully used to treat ventricular arrhythmias in patients with LQT3. The drug blocks late sodium and fast potassium currents (I_{NaL}, I_{Kr}) and therefore has the effects of class IC and III antiarrhythmic drugs [38]. During long-term therapy with ranolazine, the degree of QT interval prolongation is limited, which is explained by the drug's effect of blocking the I_{NaL} current. In addition, like flecainide, ranolazine counters TdP inducers and can therefore be used in patients with LQT3, especially when flecainide is contraindicated [37]. In Andersen-Tawil syndrome, calcium channel blockers (verapamil) and fast sodium channel blockers (flecainide) are recommended to control ventricular arrhythmias [21, 33].

Non-pharmacologic treatment options for LQTS

Implantation of a cardioverter-defibrillator (ICD) is an integral part of the current therapeutic options for LQTS [33, 39, 40]. This is because the recurrent episodes of sudden cardiac arrest are often observed despite optimal medical therapy. Therefore, the use of ICD is recommended for the primary prevention of SCD in patients diagnosed with LQT3 by molecular genetic testing and for the secondary prevention of SCD in patients diagnosed with LQTS: LQT1, LQT2, LQT5 and LQT6 (Class I, Level of Evidence B). The ICD is also indicated in patients with a clinical diagnosis of LQTS in the presence of significant RF of SCD in the background of BAB administration (Class IIa, Level of Evidence B). The ICD may be recommended in patients with recurrent VT or SCD who have contraindications for BAB [21, 34].

Independent RF that closely correlate with motivated ICD discharges in the setting of adequate BAB therapy have been identified [39, 40]: previous sudden cardiac arrest; long (>500 m/s) or very long QTc interval (>550 m/s); LQT2 genotype and multiple mutations associated with LQTS (mainly patients with Jervell and Lange-Nielsen syndrome).

The artificial cardiac pacemaker (ACP) implantation remains one of the most effective methods of VT prevention in patients with LQTS, especially in those with "pause-dependent" arrhythmias [2, 18]. Indications for ACP are: absence of BAB effect or their intolerance; presence of spontaneous atrioventricular or sinoatrial block; "jagged rhythm" in AF [1, 2, 16]. To optimize the effectiveness of ACP, it is necessary to meet the requirements for programming the electrostimulation parameters: 1) set a sufficiently high lower frequency limit of electrostimulation disable ACP algorithms that allow HR deceleration below the lower frequency limit or can cause pauses (hysteresis function) use the "rhythm frequency smoothing" algorithm to prevent pause-dependent TdP.

The beneficial effects of ACP may be related to the shortening of the QTc interval and the elimination of the pause-dependent TdP trigger. It should be noted that a relatively frequent imposed resting rhythm and/or absence of pauses after extrasystoles (without ACP hysteresis function) prevents TdP. ACP implantation combined with BAB is probably an effective method in patients with LQTS by preventing episodes of TdP and/or reducing the effects of BAB-induced bradycardia [34]. An ICD with integrated anti-bradycardia electrical stimulation function may provide more benefit by preventing bradycardia-dependent TdP and/or managing VT/VF episodes [39, 40].

Cardiac sympathetic denervation (CSD) has been proposed as an effective therapy for LQTS in addition to antiarrhythmic drugs and ICD [21, 39]. Removal of the left stellate ganglion has been shown to elimi-

nate the asymmetric sympathetic innervation of the heart, which is an arrhythmogenic factor, leading to a shortening of the QT interval and the reduced risk of SCD [20]. Current clinical guidelines consider the use of left-sided CSD in patients diagnosed with LQTS who have underlying RF for SCD despite receiving BAB (class IIa recommendation, level of evidence B) [21]. (Complete) surgical removal of the ganglia and bilateral sympathectomy compared to video thoracoscopic (partial) sympathectomy has been shown to significantly shorten the QTc interval and reduce the incidence of cardiac events in patients with LQTS [11].

Dusi V. et al. [41] found in 125 patients with LQTS, including those with ICD, a reduction in the mean annual cardiac event rate of 86 % ($p<0.0001$) after CSD. Patients with QTc ⩾500 m/s had a 50 % chance of achieving a mean QTc shortening of 60 m/s. For primary prevention of SCD, the CSD procedure was effective in 97 % of cases. Thus, there is a compelling evidence for the long-term benefit of left-sided CSD in LQTS complicated by arrhythmic events. At the same time, antiarrhythmic protection depends on the phenotype of LQTS and the degree of QTc shortening after CSD.

Conclusion

As demonstrated, the high frequency of background genetic variability observed in recent years, particularly in minor LQTS susceptibility genes, is changing paradigms about the genetic architecture of congenital LQTS. As a result, a number of minor LQTS susceptibility genes previously thought to be responsible for 5–10 % of non-syndromal LQTS variants may be downgraded to the status of gene with limited or controversial evidence or categorized as oligogenic/polygenic variants.

Given these issues, there is a need for ongoing reassessment (reclassification) of functional risk alleles and poorly penetrant LQTS genetic variants that may contribute to the pathogenesis of LQTS and therefore reflect the true genetic risk of the disease. Despite advances in the management of patients with LQTS, including effective genotype-specific pharmacotherapy and the widespread use of implantable antiarrhythmic devices, congenital LQTS remains a dangerous disease with potentially fatal consequences. Therefore, further large prospective clinical trials are urgently needed, especially to improve risk stratification for cardiac events and early detection of patients and their family members with LQTS.

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References

1. Wilde AAM, Amin AS, Postema PG. Diagnosis, management, and therapeutic strategies for congenital long QT syndrome. Heart. 2022; 108:332–8. DOI: 10.1136/heartjnl-2020-318259
2. Lankaputhra M, Voskoboinik A. Congenital long QT syndrome: a clinician's guide. Intern Med J. 2021; 51(12):1999–2011. DOI: 10.1111/imj.15437
3. Schwartz PJ. 1970–2020: 50 years of research on the long QT syndrome-from almost zero knowledge to precision medicine. Eur Heart J. 2021; 42(11):1063–72. DOI: 10.1093/eurheartj/ehaa769
4. Li C, Gao Y, Liu W. Advances in molecular genetics of long QT syndrome and summary of gene variants in Chinese. J Clin Cardiol. 2023; 39(3):176–81. DOI: 10.13201/j.issn.1001–1439.2023.03.004
5. Ahn KJ, Song MK, Lee SY, et al. The Outcome of Long QT Syndrome, a Korean Single Center Study. Korean Circ J. 2022; 52(10):771–81. DOI: 10.4070/kcj.2022.0081
6. Offerhaus JA, Bezzina CR, Wilde AAM. Epidemiology of inherited arrhythmias. Nat Rev Cardiol. 2020; 17(4):205–15. DOI: 10.1038/s41569-019-0266-2
7. Li K, Zhang P. Clinical advances in congenital long QT syndrome. Cardiology Discovery. 2021; 1(3):195–201. DOI: 10.1097/CD9.0000000000000017
8. Santen GWE, Leitch HG, Cobben J. Gene-disease relationship evidence: A clinical perspective focusing on ultra-rare diseases Human Mutation. 2022; 43:1082–8. DOI: 10.1002/humu.24367
9. Krahn A, Laksman Z, Sy R, et al. Congenital long QT syndrome. JACC Clin Electrophysiol. 2022; 8(5):687–706. DOI: 10.1016/j.jacep.2022.02.017
10. Lopez-Medina AI, Campos-Staffico AM, Chahal CA, et al. Genetic risk factors for drug-induced long QT syndrome: findings from a large real-world case-control study. Pharmacogenomics. 2024; 25(3):117–31. DOI: 10.2217/pgs-2023-0229
11. Shah SR, Park K, Alweis R. Long QT syndrome: a comprehensive review of the literature and current evidence. Curr Probl Cardiol. 2019; 44(3):92–106. DOI: 10.1016/j.cpcardiol.2018.04.002
12. Tedeev TG, Cherkashin DV, Kutelev GG, et al. The modern state of the problem of congenital long QT syndrome. Doctor.Ru.

2024;23(1):38–45. DOI: 10.31550/1727-2378-2024-23-1-38-45. Russian. DOI: 10.31550/1727-2378-2024-23-1-38-45

13. Adler A, Novelli V, Amin AS, et al. An international, multicentered, evidence-based reappraisal of genes reported to cause congenital long QT syndrome. Circulation. 2020; 141:418–28. DOI: 10.1161/CIRCULATIONAHA.119.043132
14. Wilde AAM, Semsarian C, Márquez MF, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. J Arrhythmia. 2022; 38(4):491–553. DOI: 10.1093/europace/euac030
15. Wallace E, Howard L, Liu M, et al. Long QT Syndrome: genetics and future perspective. Pediatric Cardiology. 2019; 40(7):1419–30. DOI: 10.1007/s00246-019-02151-x
16. Shimizu W, Makimoto H, Yamagata K, et al. Association of genetic and clinical aspects of congenital long QT syndrome with life-threatening arrhythmias in Japanese patients. JAMA Cardiol. 2019; 4(3):246–54. DOI: 10.1001/jamacardio.2018.4925
17. Il'darova RA, Sherbakova NV, Bereznitskaya VV, Shkolnikova MA. Cardiac and non-cardiac characteristics of Jervell-Lange-Nielsen syndrome. Vestnik aritmologii. 2021;28(3):37–44. Russian. DOI: 10.35336/VA-2021-3-37-44
18. Wang M, Peterson DR, Pagan E, et al. Absolute risk of life-threatening cardiac events in long QT syndrome patients. Front Cardiovasc Med. 2022; 9:988951. DOI: 10.3389/fcvm.2022.988951
19. Rieder M, Kreifels P, Stuplich J, et al. Genotype-specific ECG-based risk stratification approaches in patients with long-QT syndrome. Front Cardiovasc Med. 2022; 9:916036. DOI: 10.3389/fcvm.2022.916036
20. Etheridge SP, Asaki SY, Niu MC. A personalized approach to long QT syndrome. Curr Opin Cardiol. 2019; 34(1):46–56. DOI: 10.1097/HCO.0000000000000587
21. Shlyakhto EV, Arutyunov GP, Belenkov YuN, Boytsov SA. National guidelines for risk identification and prevention of sudden cardiac death. (2nd ed.). M.: Medpraktika-M, 2018. 247 p. Russian.
22. Tardo DT, Peck M, Subbiah RN, et al. The diagnostic role of T wave morphology biomarkers in congenital and acquired long QT syndrome: a systematic review. Ann Noninvasive Electrocardiol. 2023; 28(1):e13015. DOI: 10.1111/anec.13015
23. Crotti L. From gene-specific to function-specific risk stratification in long QT syndrome type 2: implications for clinical management. Europace. 2023; 25(4):1320–2. DOI: 10.1093/europace/euad035
24. Vaykhanskaya TG, Sivitskaya LN, Persidskikh YuA, et al. Long QT Syndrome: Clinical and Genetic Diagnostic Complications. Kardiologiya v Belarusi. 2020;12(5):747–66. Russian. DOI: 10.34883/PI.2020.12.5.012
25. Goldenberg I, Bos JM, Yoruk A, et al. Risk prediction in women with congenital long QT syndrome. JAHA. 2021; 10(14):e021088. DOI: 10.1161/JAHA.121.021088
26. Odening KE, van der Linde HJ, Ackerman MJ, et al. Electromechanical reciprocity and arrhythmogenesis in long QT syndrome and beyond. Eur Heart J. 2022; 43(32):3018–28. DOI: 10.1093/eurheartj/ehac135
27. Sugrue A, van Zyl M, Enger N, et al. Echocardiography-guided risk stratification for long QT syndrome. JACC. 2020; 76:2834–43. DOI: 10.1016/j.jacc.2020.10.024
28. Charisopoulou D, Koulaouzidis G, Rydberg A, Henein MY. Reversed apico-basal myocardial relaxation sequence during exercise in long QT syndrome mutations carriers with history of previous cardiac events. Front Physiol. 2021; 12:780448. DOI: 10.3389/fphys.2021.780448
29. Rudy Y. Noninvasive mapping of repolarization with electrocardiographic imaging. JAHA. 2021; 10: e021396. DOI: 10.1161/JAHA.121.021396
30. Bos JM, Attia ZI, Albert DE, Noseworthy PA, et al. Use of artificial intelligence and deep neural Networks in evaluation of patients with electrocardiographically concealed long QT syndrome from the surface 12-lead electrocardiogram. JAMA Cardiol. 2021; 6(5):532–8. DOI: 10.1001/jamacardio.2020.7422
31. Cortez D, Zareba W, McNitt S, et al. Quantitative T-wave morphology assessment from surface ECG is linked with cardiac events risk in genotype-positive KCNH2 mutation carriers with normal QTc values. J Cardiovasc Electrophysiol. 2019; 30(12):2907–13. DOI: 10.1111/jce.14210
32. Han L, Liu F, Li Q, et al. The efficacy of beta-blockers in patients with long QT syndrome 1–3 according to individuals' gender, age, and QTc intervals: A Network Meta-analysis. Front Pharmacol. 2020; 11:579525. DOI: 10.3389/fphar.2020.579525
33. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. JACC. 2018;72(14):1677–749. DOI: 10.1161/CIR.0000000000000548
34. Went TR, Sultan W, Sapkota A et al. A systematic review on the role of beta-blockers in reducing cardiac arrhythmias in long QT syndrome subtypes 1–3. Cureus. 2021; 13(9): e17632. DOI: 10.7759/cureus.17632
35. Wang G, Chu H, Zhao N. The clinical diagnosis and management of long QT syndrome: insights from the 2022 ESC Guidelines. Rev Cardiovasc Med. 2023; 24(6):170–74. DOI: 10.31083/j.rcm2406170

36. Bos JM, Crotti L, Rohatgi RK et al. Mexiletine shortens the QT interval in patients with potassium channel-mediated type 2 long QT syndrome. Circ Arrhythm Electrophysiol. 2019; 12(5):e007280. DOI: 10.1161/CIRCEP.118.007280
37. Yang Y, Lv TT, Li SY, Zhang P. Sodium channel blockers in the management of long QT syndrome types 3 and 2: A system review and meta-analysis. J Cardiovasc Electrophysiol. 2021; 32(11):3057–67. DOI: 10.1111/jce.15223
38. Cano J, Zorio E, Mazzanti A et al. Ranolazine as an alternative therapy to Flecainide for SCN5A V411M long QT syndrome type 3 patients. Front Pharmacol. 2020; 11:580481. DOI: 10.3389/fphar.2020.580481
39. Wang M, Peterson DR, Rosero S et al. Effectiveness of implantable cardioverter-defibrillators to reduce mortality in patients with long QT syndrome. JACC. 2021; 78(21):2076–88. DOI: 10.1016/j.jacc.2021.09.017
40. Biton Y, Rosero S, Moss AJ et al. Primary prevention with the implantable cardioverter-defibrillator in high-risk long-QT syndrome patients. Europace. 2019; 21:339–46. DOI: 10.1093/europace/euy149
41. Dusi V, Pugliese L, De Ferrari GM et al. Left cardiac sympathetic denervation for long QT syndrome: 50 years' experience provides guidance for management. JACC: Clinical Electrophysiology. 2022; 8(3):281–94. DOI: 10.1016/j.jacep.2021.09.002