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Review article

# Genotype-phenotype correlation in long QT syndrome

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## ABSTRACT

Congenital long QT syndrome, caused by a cardiac channelopathy, is a leading cause of sudden cardiac death in the young population. In total, 16 genes have been implicated in this condition, with three genes being the most commonly affected. Long QT syndrome is one of the earliest conditions for which a genotype specific treatment was designed. This genotype-phenotype correlation extends to involve the clinical presentation, electrocardiographic manifestation and treatment strategies. It is necessary for the clinician treating these patients to be cognizant of the important role played by the genotype in order to best provide counseling and treatment options to this unique population.

*Keywords:* Long QT syndrome, genotype, genotype association studies

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## INTRODUCTION

Congenital long QT syndrome (LQTS) is an inherited arrhythmic disorder with an estimated prevalence of 1:2000 and is a leading cause for sudden death in the young population.<sup>1,2</sup> Delayed repolarization of the ventricular myocardium is the central tenet of LQTS, manifesting as prolonged heart rate corrected QT interval (QTc) and resulting in torsades de pointes (TdP) mediated syncope and sudden cardiac arrest/death (SCA/SCD).<sup>3</sup> Clinical diagnosis relies not only on the presence of a prolonged QTc in the electrocardiogram (ECG), but on a comprehensive evaluation which includes attention to the personal history, family history and multiple electrocardiographic findings.<sup>4</sup> The Schwartz score which incorporates these parameters is helpful in determining the need for additional testing (Table 1).<sup>5</sup>

**Table 1. LQTS diagnostic criteria – “Schwartz score”.**

	Points
<b>Electrocardiographic findings<sup>#</sup></b>	
<b>QT interval*</b>	
≥ 480 ms	3
460–479 ms	2
450–459 ms (men)	1
<b>QTc 4th minute of recovery from EST &gt; 480 ms*</b>	1
<b>Documented TdP<sup>##</sup></b>	2
<b>T-wave alternans</b>	1
<b>Notched T-wave in 3 leads</b>	1
<b>Resting heart rate below second percentile for age</b>	0.5
<b>Clinical history</b>	
<b>Syncope<sup>##</sup></b>	
<b>With stress</b>	2
<b>Without stress</b>	1
<b>Congenital deafness</b>	0.5
<b>Family history<sup>**</sup></b>	
<b>Relatives with clinically definite LQTS</b>	1
<b>Unexplained sudden cardiac death in immediate relative &lt; 30 y of age</b>	0.5

Total score indicates probability of LQTS: ≤ 1 point: low probability; 1.5 to 3 points: intermediate probability; ≥ 3.5 points: high probability. EST: Exercise stress test.

<sup>#</sup> In the absence of medications or disorders known to affect these electrocardiographic features.

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

<sup>##</sup> Mutually exclusive.

<sup>\*\*</sup> The same family member cannot be counted twice.

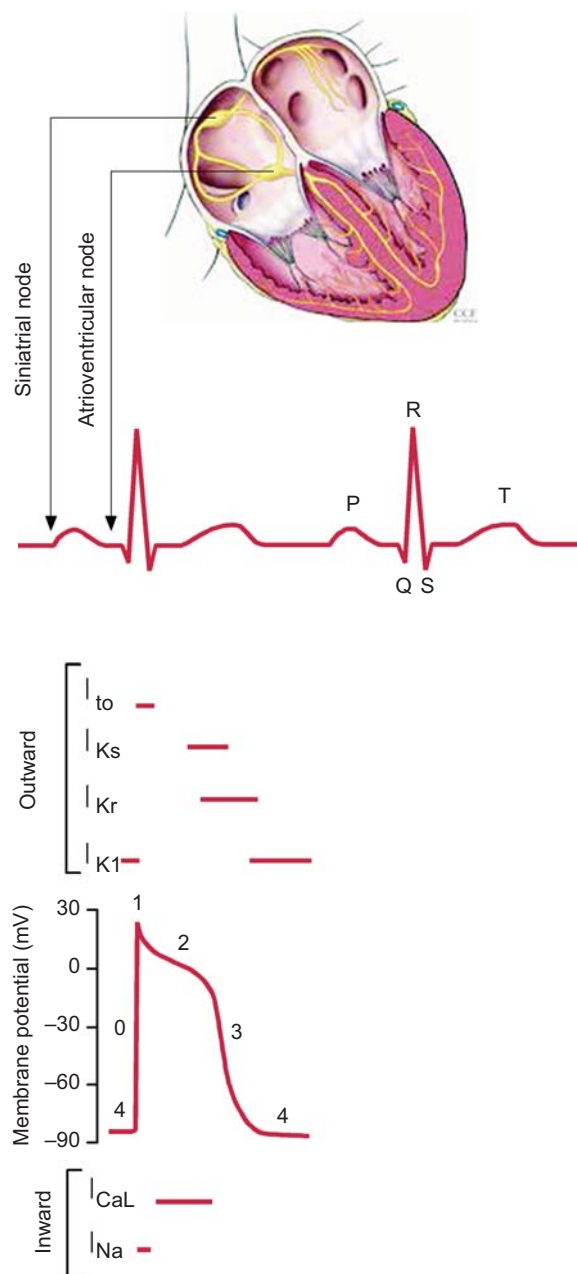
## MOLECULAR MECHANISM OF LQTS

The electrical activity that results in myocardial action potential generation and propagation is a result of cardiac ion channels that conduct either depolarizing inward current ( $Na^+$ ,  $Ca^{2+}$ ) or repolarizing outward current ( $K^+$ ). The sequential activation of these ion channels results in characteristic action potentials depending on their location (Figure 1). In the atrial and ventricular myocardium, activation of the voltage gated sodium channel ( $I_{Na}$ ) results in the initial depolarization (phase 0), followed by the transient repolarization (phase 1) that corresponds to  $I_{Na}$  inactivation and activation of transient outward potassium channel ( $I_{to}$ ). Phase 2 corresponds to a plateau as a result of the combination of depolarizing calcium channel ( $I_{Ca,L}$ ) and outward repolarizing potassium channel (delayed outward rectifying channels: ultra-rapid -  $I_{Kur}$ , rapid -  $I_{Kr}$ , slow -  $I_{Ks}$ ) activation. The continued delayed rectifying current after the closure of the  $I_{Ca,L}$ , along with the inward rectifying potassium channel ( $I_{K1}$ ) contribute to repolarization (phase 3).<sup>6</sup> The QT interval on the electrocardiogram represents the length of the ventricular depolarization and repolarization. Mutations of the aforementioned ion channels that prolong depolarization or increase repolarization currents can result in QTc prolongation. In this rapidly evolving field of channelopathies, mutations in 16 genes have so far been associated with prolonged QTc (Table 2).<sup>7</sup>

## GENOTYPE PHENOTYPE CORRELATION

### Inheritance pattern and genotype specific molecular pathology

The Romano-Ward syndrome, which occurs commonly in an autosomal dominant fashion, encompasses heterozygous mutations associated with *KCNQ1* (LQT1), *KCNH2* (LQT2), *SCN5A* (LQT3),



**Figure 1.** Ion channels involved in ventricular depolarization and repolarization.

The surface ECG corresponds to the sequential functioning of the ion channels that results in the ventricular action potential.

*KCNE1* (LQT5), *KCNE2* (LQT6), *CAV3* (LQT9), *SCN4B* (LQT10), *AKAP9* (LQT11), *SNTA1* (LQT12) and *KCNJ5* (LQT13). Homozygous or compound heterozygous mutations of *KCNQ1* or *KCNE1* occurring in autosomal recessive form underlie the relatively rare Jervell and Lange-Nielsen syndrome (JLNS). LQT1, LQT2, and LQT3 account for 75% of this condition, whereas the remainder of the identified genes are affected in 5%. About 20% of the LQTS population remain with a clinical diagnosis but as of yet unidentified genetic mutation.<sup>7</sup> LQT1 accounts for about 35% of genotype positive LQTS and results from a loss-of-function mutation of *KCNQ1*, which encodes the  $\alpha$  subunit of the  $K^+$  channel that generates  $I_{Ks}$ . Loss-of-function mutation of *KCNH2* affects the  $I_{Kr}$  resulting in LQT2, which is the second most common form of LQTS found in 30%. LQT3, the third most common form, results from a heterozygous gain-of-function mutation of the *SCN5A* affecting the inward depolarizing  $I_{Na}$ , and is found in 10% of patients with LQTS.

**Table 2. Genetic basis of conditions associated with prolonged QT interval.**

Gene	Locus	Protein
<i>KCNQ1</i> (LQT1)	11p15.5	I <sub>Ks</sub> potassium channel alpha subunit (KVLQT1, KV7.1)
<i>KCNH2</i> (LQT2)	7q35-36	I <sub>Kr</sub> potassium channel alpha subunit (HERG, KV11.1)
<i>SCN5A</i> (LQT3)	3p21-p24	Cardiac sodium channel alpha subunit (NaV1.5)
<i>AKAP9</i>	7q21-q22	Yotiao
<i>CACNA1C</i>	12p13.3	Voltage gated L-type calcium channel (CaV1.2)
<i>CALM1</i>	14q32.11	Calmodulin 1
<i>CALM2</i>	2p21.3-p21.1	Calmodulin 2
<i>CAV3</i>	3p25	Caveolin-3
<i>KCNE1</i>	21q22.1	Potassium channel beta subunit (MinK)
<i>KCNE2</i>	21q22.1	Potassium channel beta subunit (MiRP1)
<i>KCNJ5</i>	11q24.3	Kir3.4 subunit of I <sub>KACH</sub> channel
<i>SCN4B</i>	11q23.3	Sodium channel beta 4 subunit
<i>SNTA1</i>	20q11.2	Syntrophin-alpha 1
<b>Andersen-Tawil Syndrome</b>	17q23	I <sub>K1</sub> potassium channel (Kir2.1)
<i>KCNJ2</i>		
<b>Ankyrin-B Syndrome</b>	4q25-q27	Ankyrin B
<i>ANKB</i>		
<b>Timothy Syndrome</b>	12p13.3	Voltage gated L-type calcium channel (CaV1.2)
<i>CACNA1C</i>		

### Multisystem involvement

In addition to prolongation of the QT interval, multi-system involvement occurs in a minority of conditions associated with prolonged QTc. As the prototype to conditions with prolonged QT interval, JLNS results in profound congenital bilateral sensorineural hearing loss in addition to severe QT interval prolongation resulting in high risk for cardiac events. The following three multi-system conditions are associated with prolonged QTc, but might not be strictly classified as LQTS and have been considered to be "atypical LQTS".<sup>7,8</sup>

Timothy syndrome results from a de novo mutation of *CACNA1C* characterized by syndactyly, congenital heart disease, autism and other dysmorphic features in addition to significant QTc prolongation with high risk for SCD. Low set ears, micrognathia and clinodactyly along with periodic paralysis and prolonged QT interval characterize Andersen-Tawil syndrome caused by a heterozygous mutation of *KCNJ2* and carries a low risk for SCD.<sup>9</sup> Mutations of *ANK2* gene results in disruption of multiple cardiac ion channels resulting in a varying degree of sinus node dysfunction, atrial fibrillation, catecholaminergic polymorphic ventricular tachycardia and prolonged QT interval termed as ankyrin-B syndrome.<sup>10</sup>

### Genotype specific T-wave morphology

The ventricular myocardial action potential changes based on the affected ion channels along with the distributive pattern of channels in the layers of the myocardium. Although the QT interval duration has not been shown to vary with the genotype, multiple ST-segment and T-wave morphologies associated with a particular genotype have been delineated.<sup>11</sup> Due to the small available sample sizes, this association has been restricted to the most common genotypes (LQT1, LQT2 and LQT3). Presence of broad based T-waves in LQT1, low amplitude T-waves in LQT2 and late peaking T-waves in LQT3, was initially demonstrated by Moss et al.<sup>12</sup> This association was demonstrated in-vitro, based on models affecting particular ion channels.<sup>13</sup> Further delineation of the T-wave morphology was done by Zhang et al. using 284 LQTS carriers; demonstrating 10 typical patterns (4 LQT1, 4 LQT2, and 2 LQT3).<sup>14</sup> In this study, LQT1 carriers demonstrated normal or broad based T-wave pattern consistent with the homogenous action potential prolongation caused by affecting I<sub>Ks</sub>. LQT2 carriers had a bifid T-wave pattern, though to be a result of increased transmural dispersion due to greater increase in action potential duration in the M cells of the myocardium compared to the endocardium or the epicardium. Due to the delay in opening of the sodium channels and hence phase 2 of the action potential, LQT3 patients had a late-peaked T-wave (Figure 2).

### Genotype and exercise testing

LQTS demonstrates poor penetrance, with carriers in some families demonstrating a normal resting QT interval but are nevertheless at risk for TdP and for having an affected offspring.<sup>15</sup> In the absence of



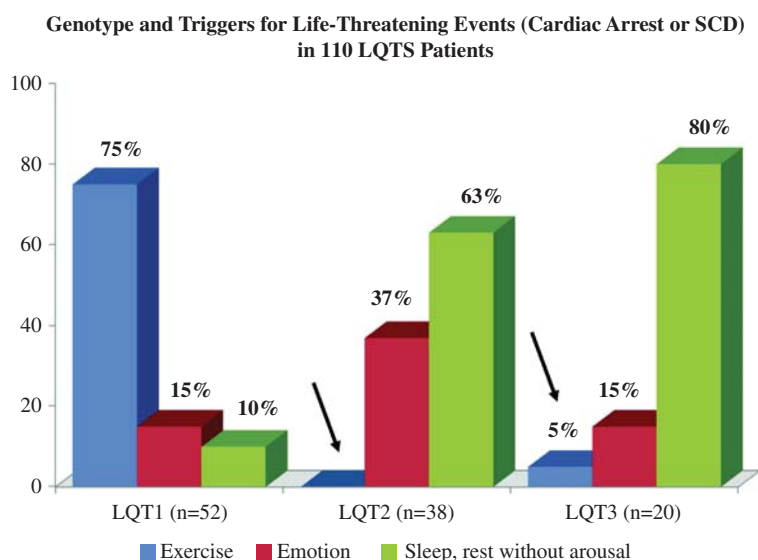
**Figure 2. Genotype specific T-wave morphology noted in LQTS patients.**

LQT1 patients typically have a broad based T-wave, while the LQT2 patients demonstrate a bifid T-wave and a late peaking T-wave characterizes LQT3.

genetic testing, these “concealed” LQTS carriers can be missed if only clinical features and resting ECG are used. QT interval prolongation during late recovery at 4 minutes after exercise stress test (EST), was found to be a sensitive screening test for LQTS when the QT interval is normal or borderline normal.<sup>16</sup> Genotype specific response to EST has been demonstrated; LQT1 patients show a significantly more prolonged QT interval at peak exercise when compared to LQT2 patients, which is persistent at early recovery phase (1 minute).<sup>16</sup> This is thought to be secondary to the duration of the exercise mediated sympathetic response and the onset of parasympathetic response at rest. In children late recovery phase at 7 minutes has been suggested to better predict the LQTS and a recovery  $\Delta$ QTc (7 min-1 min) > 30 seconds differentiated LQT2 versus LQT1.<sup>17</sup>

### Genotype specific triggers for cardiac events

Sympathetic activation caused by conditions such as physical exercise triggers the activation of  $I_{Ks}$ , which results in shorter ventricular repolarization at fast heart rates, which prevents after-depolarization caused by  $\beta$ 1-adrenergic stimulation. Hence it is not surprising that patients with LQT1, who have diminished  $I_{Ks}$  are prone to develop prolonged ventricular repolarization during exercise, whereas patients with LQT2 and LQT3 who have intact  $I_{Ks}$  are relatively protected against this phenomenon. This failure of the QT interval to adapt at faster heart rates results in a high risk for after-depolarization which can culminate in TdP. In a landmark study in 2001, involving 670 asymptomatic LQTS patients, Schwartz et al. demonstrated that the majority of LQT1 patient’s lethal and non-lethal cardiac events were triggered by exercise or stress, especially swimming (Figure 3).<sup>18</sup> It was also shown that LQT2 patients are exquisitely sensitive to sudden auditory stimuli which is thought to mimic a fright response resulting in an abrupt release of local catecholamines leading to early after



**Figure 3. Genotype specific triggers for life threatening cardiac events in LQTS patients.**

Arrows point out the rare occurrence of these events during sympathetic activation in patients without mutations affecting the  $I_{Ks}$  current. LQTS = long QT syndrome; SCD = sudden cardiac death.

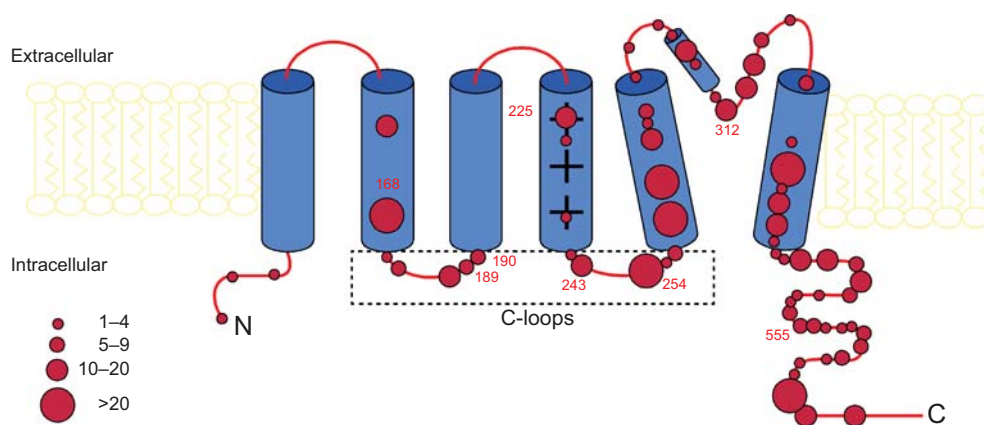
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de-polarizations and resultant TdP.<sup>18,19</sup> Due to unclear reasons, women with LQT2 are also at higher risk for cardiac events in the post-partum period. This is thought to be multifactorial which likely includes hormonal changes, sleep disruption and the sudden auditory stimuli caused by the crying neonate.<sup>20</sup> In contrast, LQT3 patients seem to be more prone for cardiac events during sleep; this is hypothesized to be secondary to amplification of the inward flow of  $\text{Na}^+$  at low heart rate when time spent at a negative potential is increased.<sup>18,21</sup>

### Genotype and risk-stratification

Risk stratification for SCD in LQTS is a daunting task given the small population of LQTS patients an even smaller subgroup who experience a cardiac event. Priori et al, in 2003, were able to complete such a task based on 647 LQTS patients from 193 families.<sup>22</sup> Overall they reported any cardiac event (syncope, SCD, cardiac arrest) before 40 years of age in 36% of their patients, and specifically SCD or cardiac arrest before 40 years of age in 13%. Males with LQT3 and females with LQT2 were found to have the highest risk for SCD or cardiac arrest at an incidence of 0.96 and 0.82/year respectively. There was a lower incidence of SCD or cardiac arrest in LQT1 without any significant gender specific differences. Patients with the autosomal recessive JLS harboring homozygous or compound heterozygous mutation of the *KCNQ1* gene are at an extremely high risk for SCD and cardiac arrest, with > 80% having these events before the age of 40.<sup>23</sup> LQTS patient who have multiple mutations ( $\geq 2$  mutations in  $\geq 1$  LQTS gene) have also been demonstrated to show longer QT interval and increased risk for serious cardiac events when compared to LQTS patients with single mutation.<sup>24</sup>

In addition to the gene affected, the location of the mutation in the gene is also useful in risk-stratification. This has been demonstrated in LQT1, caused by an abnormality in the *KCNQ1* protein. The *KCNQ1* protein comprises an intracellular N-terminus region, 6 membrane-spanning segments with 2 connecting cytoplasmic loops (C loops), and an intracellular C-terminus region. Mutations located in the C loops are associated with a high risk for serious cardiac events (Figure 4). This is thought to be secondary to the loss of protein kinase A mediated activation of  $I_{Ks}$  during periods of  $\beta_1$ -adrenergic stimulation such as exercise.<sup>25</sup>



**Figure 4.** Frequency and location of mutations in the *KCNQ1* potassium channel.

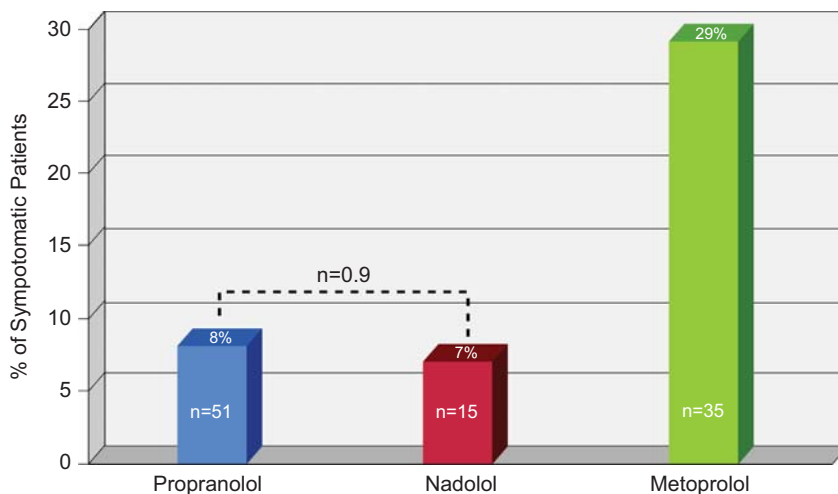
Frequency and location of mutations in the *KCNQ1* potassium channel. Diagrammatic location of 99 different mutations in the *KCNQ1* potassium channel involving 860 subjects. The  $\alpha$ -subunit involves the N-terminus (N), 6 membrane-spanning segments, 2 cytoplasmic loops (S2–S3 and S4–S5), and the C-terminus portion (C). The size of the circles reflects the number of subjects with mutations at the respective locations. Adapted from “*Circulation* 2012; 125: 1988–1996” with permission from Wolters Kluwer Health.

### Putting it all together - Genotype specific therapy

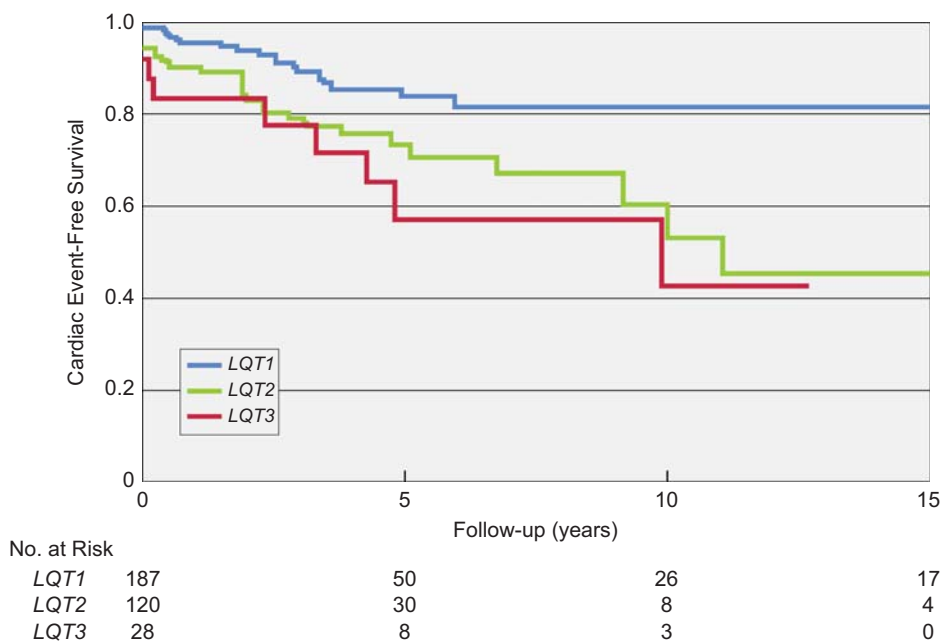
Due to the high risk for cardiac events associated with exercise, LQT1 patients are advised to refrain from competitive sports especially swimming; although some centers practice a more lenient strategy for patients who have been adequately treated and counseled.<sup>4,26</sup> Due to the association of SCD with auditory stimuli, LQT2 patients should avoid loud noises especially during arousal from sleep. This entails removal of alarm clocks and telephones from the bedroom and practicing gentle arousal of affected children by their parents. Postpartum women with LQT2 should receive adequate support for

the first 3–4 months after delivery especially with nighttime feeding of the neonate. LQT2 patients appear to be sensitive to low potassium levels and adequate potassium levels needs to be maintained.<sup>27</sup>

The mainstay of treatment for LQTS, remain  $\beta$ -blocker therapy; with the least cardiac event recurrences with propranolol and nadolol (Figure 5).<sup>28</sup> Although  $\beta$ -blocker therapy is recommended for all the genotypes of LQTS, LQT2 patients have been shown to have more breakthrough cardiac events (6–7%) in spite of adequate  $\beta$ -blockade, when compared to LQT1 patients (Figure 6).<sup>29</sup> Breakthrough events in LQT3 occur at a rate of 3% mainly in those who are at very high risk (QTc > 600 ms, events in first year of life) while on  $\beta$ -blocker therapy.<sup>3</sup> Mexiletine, a sodium channel blocker has been shown to shorten the QT interval in LQT3 patients. Given the mutation specific response to this therapy and the risk for PR interval prolongation, QRS widening and for the development of a Brugada pattern; the



**Figure 5.** Occurrence of breakthrough cardiac events in LQTS patients receiving  $\beta$ -blockers. Adapted from “*J Am Coll Cardiol* 2012; 60: 2092–2099” with permission from Elsevier.



**Figure 6.** Kaplan-Meier analysis of event-free survival of LQTS patients receiving  $\beta$ -blockers. Analysis of cumulative cardiac event-free survival in genotyped LQTS patients receiving  $\beta$ -blockers according to genotype. The definition of events includes syncope, cardiac arrest, and sudden cardiac death. y (years). Adapted with permission from “*JAMA* 2004; 292: 1341–1344.”



effect of mexiletine should be tested on individual LQT<sub>3</sub> patients under continuous ECG monitoring after the first dose.<sup>30</sup> It is important to note that mexiletine is added to  $\beta$ -blocker therapy in LQT<sub>3</sub> patients, and not commonly used in isolation. Ranolazine, a specific late sodium channel blocker has been found to be promising in the management of LQT<sub>3</sub> patients.<sup>31</sup> Patients with JLNS and Timothy syndrome continue to remain at high risk for cardiac events in spite of  $\beta$ -blocker therapy, hence the addition of prophylactic implantable cardioverter-defibrillator (ICD) and left cardiac sympathetic denervation (LCSA) has been recommended.<sup>4</sup> A scoring system (M-FACT), which takes into account QTc duration, age at implant, and cardiac events despite therapy, rather than the genotype has been developed to identify LQTS patients suitable for ICD placement.<sup>32</sup> LCSA blocks the major source of norepinephrine in the heart, and has a well-established role in the management of patients with LQTS. LCSA has been suggested for LQTS patients who are unable to take  $\beta$ -blocker therapy, remain symptomatic or at high risk for SCD on maximal  $\beta$ -blockade and, those with recurrent ICD shocks.<sup>33</sup>

## CONCLUSION

LQTS is not only the first condition for which genotype specific management was recommended, but also one in which genotype-phenotype correlations from clinical history to invasive management remains unparalleled. Tremendous advances continue to occur with the help of international and multi-centric registries along with advances in genetic technology. Looking ahead into the future, the role played by modifier genes in determining the phenotype along with studies on induced pluripotent stem cells for treatment strategies, will continue to enhance our understanding and help this unique but treatable population of LQTS patients.<sup>34,35</sup>

## Competing interests

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Aziz PF: No conflicts of interest.

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## Author contributions

Baskar S: Contributed to the conception and design of the manuscript, drafted the manuscript and has given final approval to the manuscript version submitted for publication.

Aziz PF: Contributed to the conception and design of the manuscript, revised the manuscript critically for content and has given final approval to the manuscript version submitted for publication.

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