The Evaluation of a Borderline Long QT Interval in an Asymptomatic Patient

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KEYWORDS

• Long QT syndrome • Epinephrine • Exercise testing • Asymptomatic

KEY POINTS

- The incidence of long QT syndrome (LQTS) is approximately 1 in 2500, but 25% to 50% of patients may demonstrate a normal or borderline long QT interval.
- The rate of life-threatening arrhythmias in patients with LQTS with normal corrected QT intervals is very low (approximately 0.13% per year) but higher (>10-fold) than that in unaffected family members.
- Avoidance of QT-prolonging medications and routine therapy with highly efficacious β-blockers significantly reduce life-threatening arrhythmia.
- Therefore, identification of the index case and affected family members is critical.
- Comprehensive clinical history taking, rest and provocative electrocardiographic testing, and targeted genetic testing assists in diagnosing patients with LQTS with normal or borderline QT intervals.

CLINICAL CASE

A 42-year-old man with a history of depression and seasonal allergic disorder treated with the antidepressant fluoxetine daily and the antihistamine cetirizine as required presents to his family physician with signs of lower limb cellulites. Before commencement of antibiotics, the physician performs an electrocardiography (ECG) to evaluate the QT interval (**Fig. 1**). The patient denies a history of syncope. A family history taking was done because of the borderline nature of the QT interval. The patient admits to an unfortunate family history of an uncle's sudden death at the age of 27 years at his own surprise birthday party, who also had a history of syncopal episodes during thunderstorms.

Questions

1. What elements of this history are suggestive of long QT syndrome (LQTS) and what type of congenital LQTS?
2. How prevalent is a normal or borderline long QT interval in patents with congenital LQTS?
3. What percentage of patients with drug-induced long QT are subsequently diagnosed with congenital LQTS?
4. What nongenetic tests can be performed to assist in the diagnosis of LQTS?
5. What is the sensitivity of genetic testing to diagnose congenital LQTS?
6. When should genetic testing be offered to asymptomatic patients?

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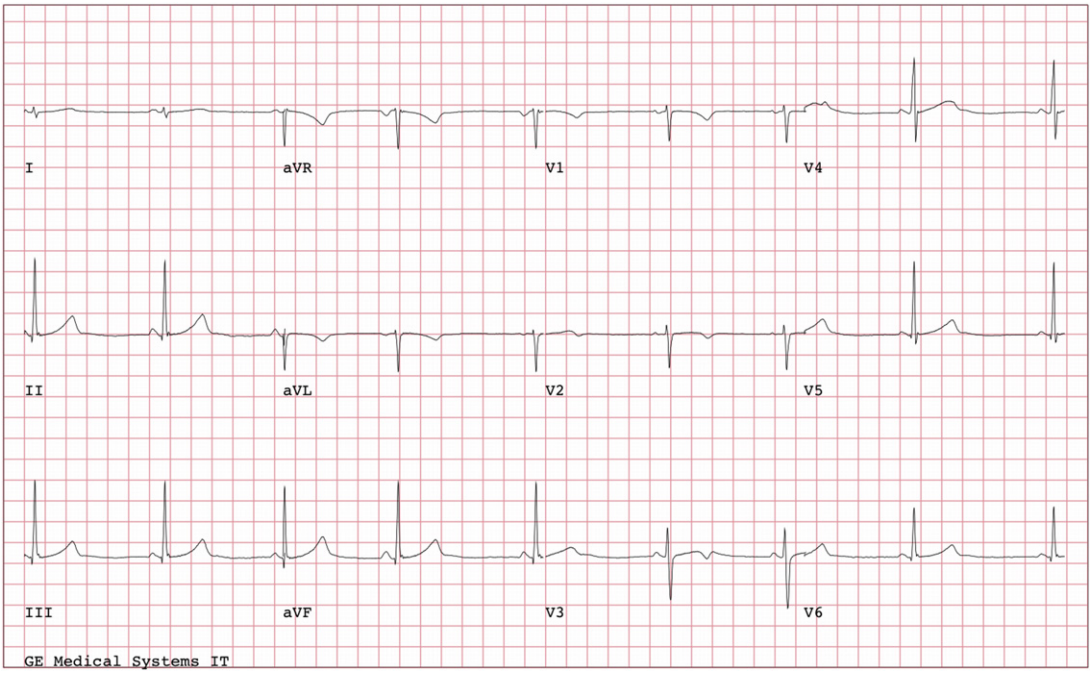

Fig. 1. Clinical case, borderline QT and QTc intervals at rest. Resting ECG, heart rate = 54 beats per minute, QT = 480 ms, and QTc = 455 ms.

Diagnosis

Exercise stress testing was undertaken by a cardiologist (**Fig. 2**). The exercise stress test revealed paradoxical QT prolongation. After weaning and discontinuation of both medications, QT findings at rest and with exercise were unchanged. Subsequent genetic testing revealed a disease-causing mutation involving the KCNH2 gene (type 2 LQTS [LQT2]). Cascade family screening was subsequently performed, starting with immediate relatives. β-Blocker therapy was begun in all mutation carriers.

DISCUSSION

The Challenges of Diagnosing LQTS in Asymptomatic Patients with Borderline Long QT Intervals

Population-based studies reporting the distribution of QTc intervals in healthy individuals report that, in the adult population, normal QTc values are 350 to 450 milliseconds (ms) for men and 360 to 460 ms for women.[1,2] Genetic studies reporting the QTc intervals of individuals who are not genetically affected define a normal QT range that is similar to that in these population-based studies.[3] However, there is considerable overlap of QTc intervals between truly healthy individuals and patients affected by LQTS. For instance, a QTc cutoff of more than 450 ms fails to identify 10% of patients who carry an LQTS mutation and incorrectly classifies 10% of healthy controls as having LQTS.[4] Alternatively, selecting a QTc cutoff of more than 430 ms has 100% sensitivity but lacks specificity and results in the overdiagnosis of 40% of healthy controls as affected.[4]

Genetic testing is not the panacea to resolve this dilemma. Genetic testing is not universally feasible and remains expensive. Genetic testing may be definitive but can often show a variant of unknown significance (VUS), and only detects a mutation in approximately 75% of patients with a clear LQTS phenotype.

Clinical criteria such as the Schwartz criteria (**Table 1**) identify patients with a high probability of LQTS (score>4) but have a low sensitivity of only 19% (specificity of 99%).[5] Nevertheless, these criteria remain very useful in the evaluation of patients suspected of having LQTS (**Fig. 3**).

In the absence of rigorous cutoff values, patients with a very long QT interval (QTc >480 ms) may be diagnosed to have LQTS, even in the absence of symptoms. Patients with a lesser degrees of QT prolongation require additional testing to clarify the diagnosis. QTc prolongation may be distinguished into 3 categories. For men, a cutoff of less than 440 ms is considered normal, 440 to

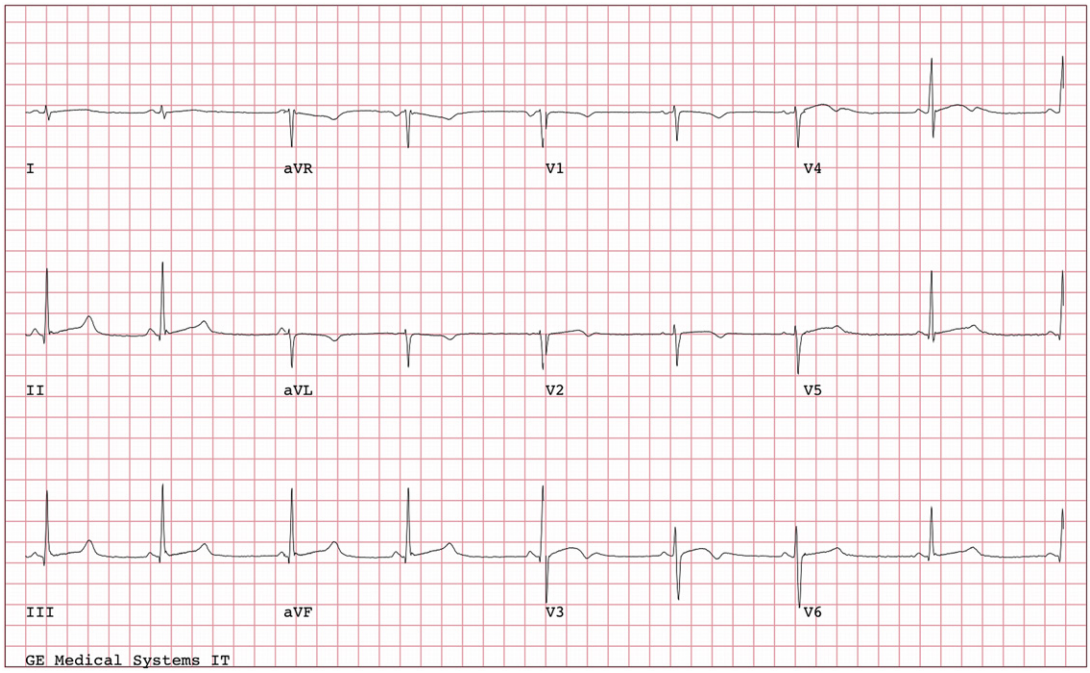

Fig. 2. Clinical case, stress exercise test QT and QTc intervals. Four minutes into recovery following exercise, heart rate = 52 beats per minute, QT = 520 ms, and QTc = 485 ms.

470 ms is considered borderline, and more than 470 ms is considered prolonged (**Fig. 4**). For women, a cutoff of less than 450 ms is considered normal, 450 to 480 ms is considered borderline, and more than 480 ms is considered prolonged.[6]

Provocative testing can enhance the diagnostic accuracy in patients with borderline long QT intervals; however, interpretation can be hindered by inaccurate measurement[7] and varied test accuracies (**Fig. 5**, **Table 2**).[8–10] Despite these challenges, the diagnosis of LQTS is critical in the index case and for extended family screening, with the intent to initiate highly efficacious β-blocker therapy to reduce the risk of sudden cardiac death (SCD) associated with torsades de pointes (TdP) (**Fig. 6**).

Measuring the QT Interval

It is critical to accurately measure and calculate the QT and QTc intervals. Most physicians cannot accurately calculate a QTc interval.[7] In a study assessing 4 standardized ECGs, the correct QTc interpretation was returned by 96% of QT experts and 80% of arrhythmia experts but only by 50% of cardiologists and 40% of noncardiologists. It is also noteworthy that manual measurements have greater reliability than automated measuring techniques.[11] The longest QT intervals are generally measured in the precordial leads. The standard leads to measure the QT are V_5 and lead II. U waves are conventionally not included in the measurement. However, differentiating U waves from bifid T waves can be challenging when prominent (>1.5–2 mV). A large U wave (>2 mV) starting before the termination of the T wave may be included in the measurement (this alternatively may be interpreted as the terminal portion of a bifid T wave). The QT interval should be measured as the time interval from the beginning of the QRS complex to the end of the T wave. The end of the T wave is defined as the intersection point between the isoelectric baseline and the tangent line representing the maximal downward/upward slope of a positive/negative T wave, respectively (see **Fig. 4**).[12,13] In addition to measuring an absolute QT interval, a rate-corrected QT (QTc) interval should also be calculated. Several methods are available for correcting the heart rate. The Bazett formula (QT divided by the square root of the R-R interval) remains widely used.[14] QT and QTc measurement during atrial fibrillation should be averaged over 10 consecutive beats.

T wave morphology is often abnormal in LQTS; patients with type 1 LQTS (LQT1) classically have a broad-based T wave and tend to have syncope or SCD during physical exercise. Patients with

Table 1
Schwartz diagnostic criteria for LQTS

ECG findings[a]	
A. QTc	
≥480 ms	3
460–480 ms	2
>450 m (in men)	1
B. Torsades de pointes	2
C. T wave alternans	1
D. Notched T wave in 3 leads	1
E. Low heart rate for age[b]	0.5
Clinical history	
A. Syncope	
With stress[c]	2
Without stress[c]	1
B. Congenital deafness	0.5
Family history[d]	
A. Family members with definite LQTS[e]	1
B. Unexplained sudden cardiac death below age 30 years among immediate family members	0.5

QTc calculated by Bazett formula.
[a] In the absence of medications or disorders known to affect these ECG features.
[b] Resting heart rate below the second percentile for age.
[c] Mutually exclusive.
[d] The same family member cannot be counted in A and B.
[e] Definite LOTS is defined by an LQTS score >4. <1 point, low probability of LQTS; 2 to 3 points, intermediate probability of LOTS; >4 points, high probability of LOTS.

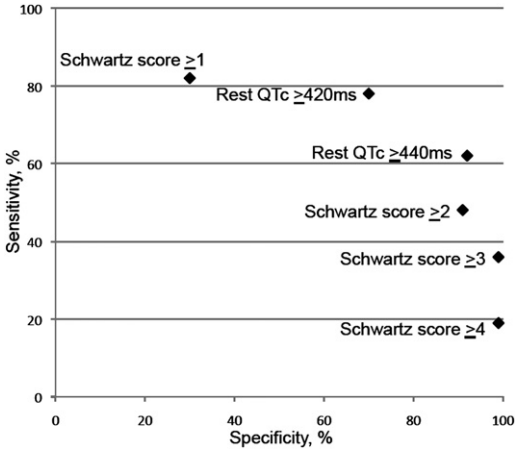

Fig. 3. Sensitivity and specificity of QTc cutoff values and Schwartz score to diagnose LQTS. (*Data from* Hofman N, Wilde AA, Tan HL. Diagnostic criteria for congenital long QT syndrome in the era of molecular genetics: do we need a scoring system? Eur Heart J 2007;28:1399.)

type 2 LQTS (LQT2) tend to have a notched or low-amplitude T wave and symptoms with sudden auditory stimuli or strong emotion. Patients with LQT3 have a long flat ST segment, a tendency toward sinus bradycardia, and a higher incidence of SCD during sleep (see **Fig. 5**).[15]

Acquired LQTS

QT prolongation can be due to common genetic variants or can be acquired. The incidence of acquired LQTS is much higher than the incidence of congenital LQTS. Many factors predispose to QT prolongation, including, age, female gender, left ventricular hypertrophy, heart failure, myocardial ischemia, hypertension, diabetes mellitus, hyperthyroidism, bradycardia, and electrolyte abnormalities (including hypokalemia and hypomagnesaemia).[16,17] However, one of the most common causes of acquired QTc prolongation is the use of QT-prolonging drugs.[17] Virtually all QT-prolonging drugs act by blocking the rapid component of the delayed rectifier potassium channel (I_{Kr}). Some drugs associated with QT prolongation are devoid of a recognized risk of arrhythmia, whereas others seem to be associated with cardiac arrhythmia without QTc prolongation.[17] Several lists have been published of drugs associated with QTc prolongation and cardiac arrhythmias. The authors favor www.qtdrugs.org.

Pharmacodynamic and pharmacokinetic drug-drug interactions may lead to QTc prolongation. Pharmacodynamic interactions of concomitantly used drugs can lead to a prolonged QTc interval if the individual QTc-prolonging drugs have an additive effect. Pharmacokinetic effects may occur if a drug reduces the clearance of a concomitantly used QTc-prolonging drug. Pharmacokinetic interactions often involve drugs which are both metabolized by cytochrome P450 (CYP) isoenzymes.

Single nucleotide polymorphisms in drug-metabolizing enzyme genes, such as CYP2D6, can lead to an altered function of the enzyme. Subjects with 2 nonfunctional CYP2D6 alleles are classified as poor metabolizers. Approximately 5% to 10% of the Caucasian population are poor metabolizers.[18] These patients using QTc-prolonging drugs metabolized by CYP2D6 have an increased risk of developing QTc prolongation and/or TdP. Altered activity of drug transporters due to genetic polymorphisms can also lead to a change in drug clearance or intracellular drug concentrations and consequently influence the QTc interval.[19]

Previously unrecognized LQTS disease-causing mutations or VUS can be identified in 5% to 20% of patients with drug-induced TdP,[20,21] compared

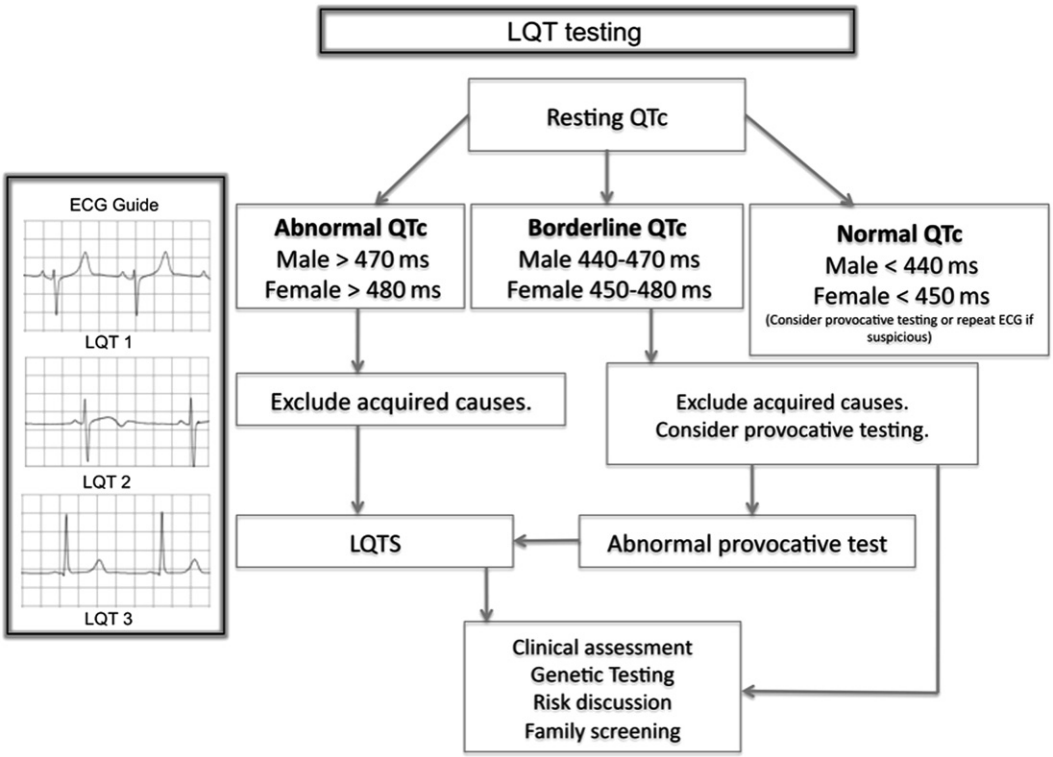

Fig. 4. An algorithmic approach for the diagnosis of LQTS.

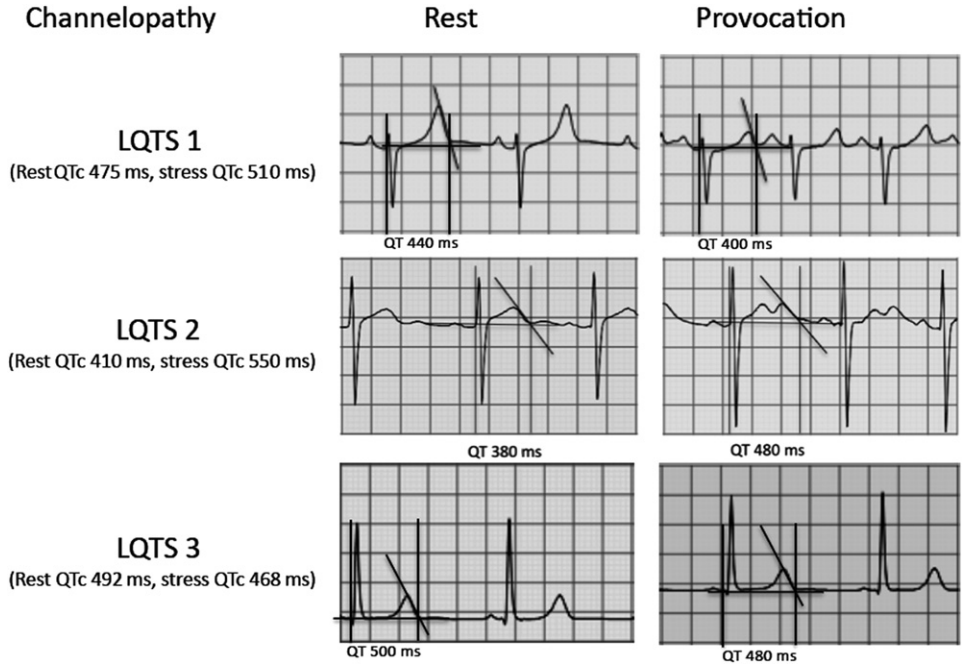

Fig. 5. Examples of QT prolongation with provocation. Patients with LQT1 classically have a broad-based T wave. Patients with LQT2 tend to have a notched or low-amplitude T wave. Patients with LQT3 have a long flat ST segment. LQT1 (rest QTc of 475 ms; 4 minutes into recovery following exercise QTc of 510 ms). LQT2 (rest QTc of 410 ms, which fails to shorten on standing QTc of 550 ms). LQT3 (rest QTc of 492 ms, with shorter recovery QTc of 468 ms following exercise).

Table 2
Definitions of a positive provocative test for diagnosing Long QT syndrome

Adrenaline	Exercise	QT Increase	QTc Increase or Absolute QTc
0.10 μg/kg/min[10]		≥30 ms	
0.10 μg/kg/min[53]			≥30 ms
Anytime up to 0.4 μg/kg/min			≥65 ms[54] or ≥600 ms[55]
	1 min into recovery[8]		≥460 ms
	4 min into recovery[8,39]		≥455 ms
	Any time in recovery[9]		≥460 ms
	Recovery - rest[9]		≥30 ms

with a VUS rate of 4% to 8% in controls.[20–23] Several genetic variations have been identified in patients with drug-induced severe QTc prolongation, TdP, aborted cardiac arrest (ACA), or SCD.[20,21]

The role of genetic testing in the isolated setting of drug-induced QT prolongation requires individual consideration, taking into account the individual's clinical and extended family history. Genetic testing is generally discouraged until further data regarding clinical implications emerge. Exercise and/or adrenaline provocative testing can be used to guide clinical decisions (including whether to offer genetic testing) in the index case and subsequently in family members (see later). LQTS genetic testing in the setting of drug-induced TdP should be considered for that index case, and subsequent family screening may be guided by the genetic result (or in the absence of a casual mutation in the index case, comprehensive clinical assessment and provocative testing should be considered starting with first-degree relatives).

Congenital LQTS

Most patients with LQTS are asymptomatic, and the condition is discovered incidentally on an ECG, by family history taking (eg, relative of an individual with SCD or ACA), or after an episode of syncope or severe ventricular arrhythmia. LQTS affects 1 in 2500 individuals.[24] Patients with LQTS are at increased risk of developing TdP. Certain triggers such as intense adrenergic or auditory stimulation seem to be particularly arrhythmogenic in LQTS. Swimming has been shown to trigger symptoms in nearly 15% of patients with LQT1.[25] Numerous

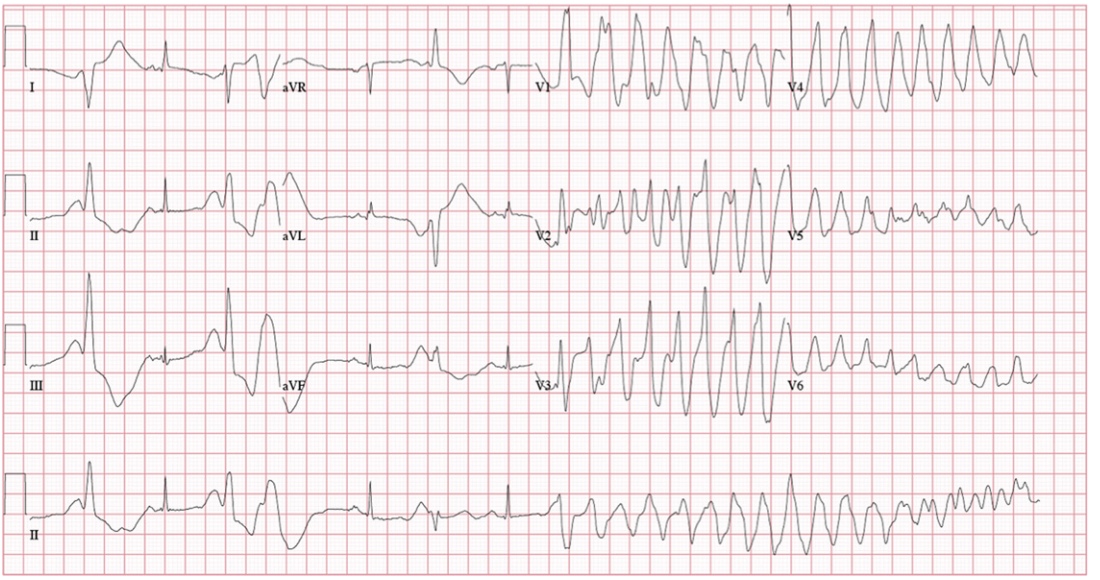

Fig. 6. Torsades de pointes.

LQTS-causing mutations have been identified (**Table 3**), summarized in http://www.fsm.it/cardmoc. LQT1 to LQT3 account for an estimated 85% to 95% of LQTS cases.[26]

Natural History of Patients with Congenital LQTS with a Normal QT Interval

The rate of ACA or SCD in patients with LQTS with normal QTc intervals (<440 ms) is reported to be very low (4% from birth through age 40 years, corresponding to an approximate event rate of 0.13% per year).[27] This risk is significantly lower than that in those with prolonged QTc intervals (15%). However, this very low risk is still a more than 10-fold increase in the risk for life-threatening events compared with unaffected family members, which highlights the need to identify asymptomatic patients with LQTS. Patients with LQTS with normal QTc intervals should be carefully followed up and should receive a similar management strategy as overtly phenotype-positive patients with LQTS, including avoidance of QT-prolonging medications and routine therapy with highly efficacious β-blockers.[28]

Mechanism of Congenital LQTS

QT prolongation results from ion channel dysfunction that prolongs cellular repolarization.[29,30] Myocardial repolarization is primarily mediated by potassium ions. Decreased outward potassium current mediated by a loss-of-function mutation in I_{Ks} (slowly activating delayed rectifier potassium channel) leads to LQT1. Decreased outward potassium current mediated by a loss-of-function mutation in I_{Kr} (rapid) leads to LQT2. I_{Kr} channels represent a smaller fraction of the potassium channels responsible for repolarization and are not as sympathetically responsive as I_{Ks} channels. I_{Kr} is activated in low adrenergic circumstances and I_{Ks} in higher adrenergic states. A gain-of-function mutation of I_{Na} leads to enhanced activity of inward sodium current and failed inactivation leading to LQT3.

These channel dysfunctions that result in prolonged repolarization may cause early afterdepolarizations due to activation of inward depolarizing currents, which reach a threshold causing ventricular extrasystoles with resultant TdP.

Diagnosing LQTS in Asymptomatic Patients

Patients with idiopathic borderline QT prolongation (ie, QT prolongation that cannot be attributed to acquired or reversible conditions) require additional tests to clarify the diagnosis because clinical criteria alone lack sensitivity. Clinical criteria such as the Schwartz criteria[31] that have been used for identifying disease-causing LQTS mutations (score $\geq$4) have high specificity but low sensitivity and are typically very low in the absence of significant QT prolongation (one of the scoring criteria, see **Table 1**).

Because the ion channel defects (primarily I_{Ks} and to a lesser extent I_{Kr}) are stressed under sympathetic stimulation, exercise stress testing and/or pharmacologic adrenergic provocation can enhance the diagnostic accuracy in patients with borderline long QTc intervals.[32–35] Adrenergic provocation may reveal a paradoxical QT response characterized by QT lengthening rather than expected shortening that is pathognomonic for LQT1 or failed shortening with increase in heart

Table 3
LQTS genotypes and affected channels

Channelopathy	Channel Defect	Gene	Protein	Frequency
LQTS 1	Loss of I_{Ks}	KCNQ1	K_v7.1	Approximately 45%
LQTS 2	Loss of I_{Kr}	KCNH2	K_v11.1	Approximately 30%
LQTS 3	Gain of I_{Na}	SCN5A	Na_v1.5	Approximately 10%
LQTS 4	Loss of $I_{Na,K}$	ANK2	Ankyrin-B	Approximately 1%
LQTS 5	Loss of I_{Ks}	KCNE1	Mink	Approximately 1%
LQTS 6	Loss of I_{Kr}	KCNE2	MiRP1	Rare
LQTS 7	Loss of I_{K1}	KCNJ2	Kir2.1	Rare
LQTS 8	Gain $I_{Ca,\ L}$	CACNA1	Ca_v1.2	Rare
LQTS 9	Gain of I_{Na}	CAV3	Caveolin-3	Rare
LQTS 10	Gain of I_{Na}	SCN4B	β4	Rare
LQTS 11	Loss of I_{Ks}	AKAP9	Yotiao	Rare
LQTS 12	Gain of I_{Na}	SNTA1	α1-syntrophin	Rare

rate. In patients with LQT2, there may be a transient prolongation of the QTc interval followed by shortening because of the presence of intact I_{Ks} channels.[36,37] The LQT3 phenotype is characterized by a constant reduction of the action potential duration with adrenergic stimulation because of stimulation of the intact I_{Kr} and I_{Ks} channel (see **Fig. 5**).

Evaluation of the QT response to the brisk tachycardia induced by standing provides important information that aids in the diagnosis of LQTS.[38] Despite similar heart rate acceleration in response to brisk standing in patients and controls, the QT interval of controls shortened by 21 ± 19 ms, whereas the QT interval of patients with LQTS increased by 4 ± 34 ms ($P<.001$). In addition, the QTc interval increased by 50 ± 30 ms in the control group and by 89 ± 47 ms in the LQTS group ($P<.001$). Receiver operating characteristic curves showed that the test added diagnostic value and the response was particularly impaired in patients with LQT2.

Exercise stress testing has been used for differentiating patients with LQTS from unaffected individuals (see **Table 2**). The end of recovery QTc (defined as 4 minutes into recovery after exercise stress testing) has been reported to have clinical use in distinguishing patients with LQTS from healthy individuals. A QTc less than 445 ms at the end of recovery had a sensitivity of 92% and a specificity of 88% at identifying healthy individuals.[8] An algorithm incorporating the resting and end recovery QTc at identifying disease-causing LQT mutations has also been reported.[39] This validated algorithm reported a rest QTc greater than 470 ms in men or greater than 480 ms in women or a postexercise end recovery QTc greater than 445 ms as a sensitive means of detecting LQT disease-causing mutation carriers with sensitivity, specificity, and accuracy of 0.94, 0.82, and 0.91, respectively. An insufficient number of patients with borderline or normal QT has been classified with these cutoff values to be conclusive, but this is clearly an advisable strategy to risk stratify this patient population. Exercise testing is readily accessible and easily performed. Another recent study reported that either an absolute QTc of 460 ms or greater during any time in the recovery phase or a maladaptive paradoxic increase in QTc (defined as QTc recovery minus QTc baseline≥30 ms, see **Table 2**) distinguished patients with either manifest or concealed LQT1 from healthy individuals.[9]

Increased QT hysteresis may be a unique feature of LQT2 syndrome. QT hysteresis is calculated as the QT interval difference between exercise and 1 to 2 minutes into recovery at similar heart rates (within 10 beats per minute) at heart rates of approximately 100 beats per minute.[40] In patients with LQT2 with impaired I_{Kr}, the QT fails to shorten at intermediate heart rates in early exercise. However, recruitment of I_{Ks} at higher heart rates is associated with appropriate QT shortening, which persists into the recovery phase. This consequently leads to an exaggerated QT difference between exercise and recovery, which manifests as increased QT hysteresis. QT hysteresis greater than 25 ms has a sensitivity and specificity of 73% and 68%, respectively, in identifying patients with LQT2 over LQT1.[41]

Adrenaline infusion is another means to unmask LQTS. Two major protocols have evolved for adrenaline infusion: the bolus and brief infusion (Shimizu protocol)[42] and the escalating dose protocol (Mayo protocol).[43] Gradually increasing the dose of adrenaline from 0.05, 0.1, 0.2, and 0.3 μg/kg/min can distinguish healthy controls from patients with concealed LQT1 (see **Table 2**). In one study[10] of 147 genotyped patients, the median change in QT interval during low dose adrenaline infusion was −23 ms in the gene-negative group, +78 ms in the LQT1 group, −4 ms in the LQT2 group, and −58 ms in the LQT3 group. A paradoxic QT response (**Table 4**) had a sensitivity of 92.5%, specificity of 86%, positive predictive value of 76%, and negative predictive value of 96% for identifying patients with LQT1. Provocative test accuracy was highest for LQT1 and modest for LQT2. This study reported that patients on β-blocker therapy at the time of testing are also likely to have lower diagnostic accuracy (see **Figs. 2** and **5**, see **Table 2**). It is noteworthy that graded infusion of adrenaline or isoproterenol in normal subjects is associated with QTc prolongation. However, an absolute QT prolongation by more than 20 to 30 ms is not typically seen at any dose level of adrenaline or isoproterenol.

These studies should be performed with appropriate medical supervision. Both the Shimizu and

Table 4
Drug infusions for diagnosis of LQTS

Drug	Infusion
Epinephrine	Infusion started at 0.05 μg/kg/min and increased every 5 min to 0.1 and 0.2 μg/kg/min for 5 min at each dose
Isoproterenol	Infusion started at 1 μg/min and increased every 5 min to a maximum of 5 μg/min

Mayo protocol are well tolerated with a low incidence of adverse events. However, drugs for resuscitation, including intravenous β-blockers, should be available by the bedside.

Data on the utility of Holter monitoring for the diagnosis and prognosis of LQTS is unclear. Some studies have reported the minimal diagnostic and prognostic utility of Holter monitoring in evaluating LQTS.[44,45] However, studies have also reported the value of Holter monitoring in diagnosing LQTS and, in particular, the utility of diurnal repolarization dynamics.[46] Holter monitoring may be more useful in LQT2 and LQT3 because of the more pronounced QT prolongation observed compared with LQT1 at slow heart rates in these patients (particularly at night).

w?>Provocative testing may be considered to assess QT response (1) in patients with a suspicion of LQT1 or LQT2 who have not been genotyped (including in first-degree relatives with genotype-negative LQTS), (2) in those with a genetic diagnosis of LQT1 or LQT2 but with a resting xxxthat is normal, and (3) if the LQT1-associated mutation is novel. The test is not recommended for patients with LQT3.

Clinical decision making can be challenged because of varied test accuracies associated with exercise stress testing and catecholamine infusion testing. The absence of QTc prolongation or the presence of borderline changes should not supplant clinical evidence. Even clearly abnormal QT intervals must be carefully reviewed within the clinical context. QT intervals should be viewed as another part of the diagnostic workup and in the context of the pretest probability, not as a binary positive or negative test (similar to genetic test results). When testing yields borderline changes despite high clinical suspicion (high pretest probability; eg, Schwartz score >3), an alternative provocative test may be used if necessary (eg, catecholamine infusion).

Genetic Testing of the Index Case

Genetic test result must be interpreted with great caution because all genetic tests are probabilistic tests rather than binary ones and need to be viewed in the overall clinical context.[23] Genetic testing yields possible causative mutations for 75% to 80% of patients with a clear LQTS phenotype. Therefore a negative genetic test result cannot exclude the diagnosis of LQTS by itself. Copy number variants, large deletions and duplications in KCNQ1 and KCNH2 genes explain around 3% of LQTS in patients with no point mutation in these genes.[47] Therefore, screening for CNVs in the KCNQ1 and KCNH2 genes should be considered in patients with negative conventional testing, only if they have a compelling phenotype and have other affected family members. This is a dynamic area with rapid evolution in capability and cost, so communication with a local or regional expert is advised.

Clinical LQTS genetic testing is recommended for any index case in which LQTS is suspected based on the patient's clinical history, family history, QT interval duration, inspection of T wave morphology, and response to either exercise or catecholamine stress testing (see **Table 3**).[48,49] LQTS genetic testing should not be performed solely in response to a borderline long QT interval or even in a patient with a past history of syncope with a borderline long QT interval. The significant rate of rare VUS (4%–8%)[23] in the LQT genes complicates correct interpretation of the variants and mandates that LQTS genetic testing be sought based on clinical suspicion rather than ordered indiscriminately. Therefore before genetic testing, a comprehensive clinical assessment is warranted that usually includes clinical assessment (Schwartz score) and provocative testing (abrupt standing and exercise stress testing and/or catecholamine infusion testing).

In asymptomatic patients, LQTS genetic testing is recommended for patients with unequivocal and idiopathic serial QT prolongation (QTc>480 ms in prepubertal children and QTc>500 ms in adults). The Heart Rhythm Society[48] proposed that QTc/genetic testing cutoff values found in asymptomatic patients during screening are higher than the American Heart Association guidelines–based designations of a QTc greater than 450 ms in adult men and greater than 460 ms in adult women as prolonged.[50]

When genetic testing is negative, several conditions should be considered that mimic LQTS. If a patient has exercise-triggered cardiac events, a mildly prolonged or normal resting QTc (usually <460 ms), and exercise-induced ventricular ectopy, a diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT) or Andersen-Tawil syndrome (LQT7) may be considered. In one study, a CPVT disease-causing mutation in the ryanodine gene (RyR2) was identified in approximately 6% of 269 patients suspected to have LQTS.[51] Conversely, amongst 11 unrelated patients with suspected CPVT, 4 possessed LQTS-associated mutations.[52] Therefore, screening for CPVT genes may be considered when bidirectional/polymorphic ventricular tachycardia is demonstrated in patients without an LQT mutation. Additional screening for LQT mutations may be appropriate when a clinical diagnosis of CPVT is suspected with atypical or borderline QT intervals.[51]

Interpreting Genetic Test Results

Genetic testing may yield results that are difficult to interpret. Genetic variants can represent benign single nucleotide polymorphisms, VUS, or disease-causing mutations. Many mutations in LQTS represent novel and rare variants. Therefore genetic test results should be viewed in the complete clinical context. When a VUS is encountered with a high pretest probability (eg, Schwartz score >3), it is likely disease causing. When a VUS is associated with less than conclusive evidence that it is disease causing (despite availability of comprehensive clinical information, including clinical assessment from first-degree relatives), a cautious diagnosis of a benign variant maybe reached, given the relatively high incidence of VUS in controls (4%–8%)[23] compared with the low incidence of LQTS (1 in 2500).[24] However, ongoing patient follow-up is prudent. However, the degree of pretest probability that indicated genetic testing may be adequate to diagnose LQTS despite the presence of a VUS or despite the absence of a disease-causing LQT mutation. In other words, given the poor sensitivity of genetic testing (approximately 75%), the lack of a clearly disease-causing mutation in the context of a high pretest probability (clinical criteria) does not exclude LQTS.

Cascade Family Screening

When a causative mutation is identified, mutation-specific genetic testing of all first-degree relatives should be undertaken. A normal resting ECG with a normal QTc is not sufficient to rule out LQTS in asymptomatic relatives. If the results of genetic test, history taking, and 12-lead ECG are negative, LQTS is ruled out. However, if the mutation-specific genetic test result is negative but prolonged QTc intervals are present, a genetic reevaluation that could include repeated testing or proceeding with independent comprehensive LQTS genetic testing should be considered. Clinical and genetic evaluation of distant relatives should extend in concentric circles of first-degree relatives depending on where the LQTS-associated mutation tracks.[48] When a causative mutation is not identified in the index case despite a clinical diagnosis of LQTS, family screening should incorporate clinical history taking and assessment of rest and provocative QTc intervals.

SUMMARY

When a patient with borderline QT prolongation is encountered, a thorough clinical evaluation should be performed. Reversible causes should be identified and remedied. If QT prolongation persists or the history is suspicious, postural response and exercise testing should be performed. The results of this testing should inform the role of genetic testing or further provocation with adrenaline in equivocal patients. When LQTS is diagnosed, cascade family screening should be undertaken and therapy with β-blockers initiated.

REFERENCES

1. Wu J, Kors JA, Rijnbeek PR, et al. Normal limits of the electrocardiogram in Chinese subjects. Int J Cardiol 2003;87:37–51.
2. Anttonen O, Junttila MJ, Rissanen H, et al. Prevalence and prognostic significance of short QT interval in a middle-aged Finnish population. Circulation 2007; 116:714–20.
3. Vincent GM, Timothy KW, Leppert M, et al. The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. N Engl J Med 1992;327:846–52.
4. Allan WC, Timothy K, Vincent GM, et al. Long QT syndrome in children: the value of rate corrected QT interval and DNA analysis as screening tests in the general population. J Med Screen 2001;8:173–7.
5. Hofman N, Wilde AA, Kaab S, et al. Diagnostic criteria for congenital long QT syndrome in the era of molecular genetics: do we need a scoring system? Eur Heart J 2007;28:575–80.
6. Viskin S. The QT interval: too long, too short or just right. Heart Rhythm 2009;6:711–5.
7. Viskin S, Rosovski U, Sands AJ, et al. Inaccurate electrocardiographic interpretation of long QT: the majority of physicians cannot recognize a long QT when they see one. Heart Rhythm 2005;2:569–74.
8. Chattha IS, Sy RW, Yee R, et al. Utility of the recovery electrocardiogram after exercise: a novel indicator for the diagnosis and genotyping of long QT syndrome? Heart Rhythm 2010;7:906–11.
9. Horner JM, Horner MM, Ackerman MJ. The diagnostic utility of recovery phase QTc during treadmill exercise stress testing in the evaluation of long QT syndrome. Heart Rhythm 2011;8(11):1698–704.
10. Vyas H, Hejlik J, Ackerman MJ. Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: diagnostic accuracy of the paradoxical QT response. Circulation 2006;113:1385–92.
11. McLaughlin NB, Campbell RW, Murray A. Comparison of automatic QT measurement techniques in the normal 12 lead electrocardiogram. Br Heart J 1995;74:84–9.
12. Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal". J Cardiovasc Electrophysiol 2006;17:333–6.
13. Postema PG, De Jong JS, Van der Bilt IA, et al. Accurate electrocardiographic assessment of the QT interval: teach the tangent. Heart Rhythm 2008;5:1015–8.

14. Bazett HC. The time relations of the blood-pressure changes after excision of the adrenal glands, with some observations on blood volume changes. J Physiol 1920;53:320–39.
15. Moss AJ, Zareba W, Benhorin J, et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation 1995;92: 2929–34.
16. Gaudron P, Kugler I, Hu K, et al. Time course of cardiac structural, functional and electrical changes in asymptomatic patients after myocardial infarction: their inter-relation and prognostic impact. J Am Coll Cardiol 2001;38:33–40.
17. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004;350:1013–22.
18. Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics 2002;3:229–43.
19. McBride BF, Yang T, Liu K, et al. The organic cation transporter, OCTN1, expressed in the human heart, potentiates antagonism of the HERG potassium channel. J Cardiovasc Pharmacol 2009;54:63–71.
20. Lehtonen A, Fodstad H, Laitinen-Forsblom P, et al. Further evidence of inherited long QT syndrome gene mutations in antiarrhythmic drug-associated torsades de pointes. Heart Rhythm 2007;4:603–7.
21. Yang P, Kanki H, Drolet B, et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. Circulation 2002; 105:1943–8.
22. Paulussen AD, Gilissen RA, Armstrong M, et al. Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. J Mol Med (Berl) 2004;82:182–8.
23. Kapa S, Tester DJ, Salisbury BA, et al. Genetic testing for long-QT syndrome: distinguishing pathogenic mutations from benign variants. Circulation 2009;120:1752–60.
24. Schwartz PJ, Stramba-Badiale M, Crotti L, et al. Prevalence of the congenital long-QT syndrome. Circulation 2009;120:1761–7.
25. Moss AJ, Robinson JL, Gessman L, et al. Comparison of clinical and genetic variables of cardiac events associated with loud noise versus swimming among subjects with the long QT syndrome. Am J Cardiol 1999;84:876–9.
26. Splawski I, Shen J, Timothy KW, et al. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. Circulation 2000;102: 1178–85.
27. Goldenberg I, Horr S, Moss AJ, et al. Risk for life-threatening cardiac events in patients with genotype-confirmed long-QT syndrome and normal-range corrected QT intervals. J Am Coll Cardiol 2011;57:51–9.
28. Vincent GM, Schwartz PJ, Denjoy I, et al. High efficacy of beta-blockers in long-QT syndrome type 1: contribution of noncompliance and QT-prolonging drugs to the occurrence of beta-blocker treatment "failures". Circulation 2009;119:215–21.
29. Keating MT, Sanguinetti MC. Molecular genetic insights into cardiovascular disease. Science 1996; 272:681–5.
30. Chiang CE, Roden DM. The long QT syndromes: genetic basis and clinical implications. J Am Coll Cardiol 2000;36:1–12.
31. Schwartz PJ, Moss AJ, Vincent GM, et al. Diagnostic criteria for the long QT syndrome. An update. Circulation 1993;88:782–4.
32. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 2001;103:89–95.
33. Vincent GM, Jaiswal D, Timothy KW. Effects of exercise on heart rate, QT, QTc and QT/QS2 in the Romano-Ward inherited long QT syndrome. Am J Cardiol 1991;68:498–503.
34. Jackman WM, Friday KJ, Anderson JL, et al. The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. Prog Cardiovasc Dis 1988;31:115–72.
35. Shimizu W, Ohe T, Kurita T, et al. Epinephrine-induced ventricular premature complexes due to early afterdepolarizations and effects of verapamil and propranolol in a patient with congenital long QT syndrome. J Cardiovasc Electrophysiol 1994;5:438–44.
36. Dumaine R, Antzelevitch C. Molecular mechanisms underlying the long QT syndrome. Curr Opin Cardiol 2002;17:36–42.
37. Kass RS, Moss AJ. Long QT syndrome: novel insights into the mechanisms of cardiac arrhythmias. J Clin Invest 2003;112:810–5.
38. Viskin S, Postema PG, Bhuiyan ZA, et al. The response of the QT interval to the brief tachycardia provoked by standing: a bedside test for diagnosing long QT syndrome. J Am Coll Cardiol 2010;55:1955–61.
39. Sy RW, van der Werf C, Chattha IS, et al. Derivation and validation of a simple exercise-based algorithm for prediction of genetic testing in relatives of LQTS probands. Circulation 2011;124:2187–94.
40. Krahn AD, Klein GJ, Yee R. Hysteresis of the RT interval with exercise: a new marker for the long-QT syndrome? Circulation 1997;96:1551–6.
41. Wong JA, Gula LJ, Klein GJ, et al. Utility of treadmill testing in identification and genotype prediction in long-QT syndrome. Circ Arrhythm Electrophysiol 2010;3:120–5.
42. Shimizu W, Noda T, Takaki H, et al. Diagnostic value of epinephrine test for genotyping LQT1, LQT2, and LQT3 forms of congenital long QT syndrome. Heart Rhythm 2004;1:276–83.
43. Ackerman MJ, Khositseth A, Tester DJ, et al. Epinephrine-induced QT interval prolongation: a gene-specific paradoxical response in congenital long QT syndrome. Mayo Clin Proc 2002;77:413–21.

44. Kaufman ES, Priori SG, Napolitano C, et al. Electrocardiographic prediction of abnormal genotype in congenital long QT syndrome: experience in 101 related family members. J Cardiovasc Electrophysiol 2001;12:455–61.
45. Mauriello DA, Johnson JN, Ackerman MJ. Holter monitoring in the evaluation of congenital long QTsyndrome. Pacing Clin Electrophysiol 2011;34(9):1100–4.
46. Neyroud N, Maison-Blanche P, Denjoy I, et al. Diagnostic performance of QT interval variables from 24-h electrocardiography in the long QT syndrome. Eur Heart J 1998;19:158–65.
47. Barc J, Briec F, Schmitt S, et al. Screening for copy number variation in genes associated with the long QT syndrome: clinical relevance. J Am Coll Cardiol 2011;57:40–7.
48. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace 2011;13:1077–109.
49. Gollob MH, Blier L, Brugada R, et al. Recommendations for the use of genetic testing in the clinical evaluation of inherited cardiac arrhythmias associated with sudden cardiac death: Canadian Cardiovascular Society/Canadian Heart Rhythm Society joint position paper. Can J Cardiol 2011;27:232–45.
50. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. Circulation 2009;119:e241–50.
51. Tester DJ, Kopplin LJ, Will ML, et al. Spectrum and prevalence of cardiac ryanodine receptor (RyR2) mutations in a cohort of unrelated patients referred explicitly for long QT syndrome genetic testing. Heart Rhythm 2005;2:1099–105.
52. Tester DJ, Arya P, Will M, et al. Genotypic heterogeneity and phenotypic mimicry among unrelated patients referred for catecholaminergic polymorphic ventricular tachycardia genetic testing. Heart Rhythm 2006;3:800–5.
53. Shimizu W, Noda T, Takaki H, et al. Epinephrine unmasks latent mutation carriers with LQT1 form of congenital long-QT syndrome. J Am Coll Cardiol 2003;41:633–42.
54. Krahn AD, Gollob M, Yee R, et al. Diagnosis of unexplained cardiac arrest: role of adrenaline and procainamide infusion. Circulation 2005;112:2228–34.
55. Kaufman ES, Gorodeski EZ, Dettmer MM, et al. Use of autonomic maneuvers to probe phenotype/genotype discordance in congenital long QT syndrome. Am J Cardiol 2005;96:1425–30.