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Cases in Precision Medicine: Genetic Assessment After a Sudden Cardiac Death in the Family

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Abstract

Sudden death in a family is associated with serious anxiety among family members. Assessing the cause of death may help determine the risk for other family members, thus alleviating some anxiety. In some cases, the cause of death may be evident on autopsy; however, in cases of arrhythmias, standard autopsy will not reveal the cause of death. Evaluation of the circumstances of death, medical history of the deceased, and results of genetic testing may reveal a diagnosis. Once a diagnosis is made, relatives should receive genetic testing and clinical assessment to stratify their risk. Depending on their risk, various interventions are available, including medication, defibrillators, and lifestyle modifications.

ToC Summary

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After a sudden death in a family, assessing the cause of death may help determine the risk for other family members. In cases of arrhythmias, standard autopsy will not reveal the cause of death. Evaluation of the circumstances of death, medical history of the deceased, and results of genetic testing may reveal a diagnosis. This article discusses the current clinical utility of genetic testing in the context of advising patients with a family member who has died suddenly.

Case Presentation

The following case is a composite of several clinical scenarios.

Your patient is a 22-year-old woman who, after the recent death of her brother, is anxious about her risk for early death. Her brother, a 13-year-old boy with a history of syncope, died suddenly during a soccer game. Two hours before his death, the brother took diphenhydramine for an insect bite. The boy's autopsy was unremarkable. The heart was grossly normal, with an interventricular septal thickness of 8 mm (normal, 6 to 10 mm) and a left ventricular mass of 143 g (normal, 67 to 162 g). Histologic examination of all organs was nondiagnostic. Review of the decedent's medical records showed a mildly prolonged rate-corrected QT interval (QTc) of 450 ms (normal, ≤440 ms) on a routine, resting electrocardiogram (ECG). On another ECG, the QTc was 465 ms (normal, ≤440 ms). Your patient has a father, a mother, and an adolescent sister who are still living.

When Should You Consider a Molecular Autopsy?

When evaluating a case of sudden death, the anatomical autopsy, medical history, and circumstances of death provide complementary information. If the anatomical autopsy is unremarkable and the heart is structurally normal, the death may be classified as sudden arrhythmic death syndrome. To support this conclusion, the medical history and circumstances surrounding the death should be concordant (Table 1). Focused assessment of the medical history should include symptoms (syncope, presyncope, and palpitations), medications (including those that may prolong the QT interval), intercurrent illnesses, and history of fever (trigger for Brugada syndrome). Evaluation of the family history should include known cardiac diseases (including arrhythmias), cardiac arrest, syncope and presyncope, and epilepsy. The place, time, and circumstances of death (especially suspicious incidents of single-vehicle motor accidents or unexplained drowning) may be associated with fatal arrhythmias.

A molecular autopsy or postmortem genetic analysis should be considered if the anatomical autopsy is unremarkable and the other evidence suggests sudden arrhythmic death syndrome (1). Autopsy specimens that may be used for genetic testing include 5 to 10 mL of blood preserved with K_2EDTA (purple-top tube), blood spot cards, frozen tissue, and extracted DNA. Paraffin-embedded samples cannot be used for genetic testing; the DNA is difficult to extract and damage occurs with this type of specimen processing. Refrigerating specimens at 4 °C will preserve them only for approximately 2 weeks, but freezing and maintaining samples at −20 °C to −70 °C will preserve them for genetic testing indefinitely (2).

Because postmortem genetic testing is often the last attempt to determine a cause of death, more comprehensive genetic testing is recommended. If sudden arrhythmic death syndrome

is suspected, a genetic test panel for arrhythmias should be performed (Table 2). At this time, most medical examiners do not perform postmortem genetic testing and most insurance companies do not cover it. Thus, the deceased person's family members incur the cost of genetic testing, although some clinical laboratories offer a discounted rate for families paying out of pocket. The cost of a genetic test panel is policy dependent but usually varies between $1000 and $1500. With an adequate sample, results of genetic testing generally are available in 4 weeks. What Genetic Tests Are Used When Evaluating a Family in a Case of Sudden Death?

Not only does a molecular autopsy help make a diagnosis for the deceased person, it also can help in the identification and treatment of at-risk family members. If a mutation is identified, all first-degree family members, such as parents, siblings, and children, should have targeted testing for the familial mutation (3). Targeted testing for a specific mutation is typically faster (with results in about 2 weeks) and less expensive than comprehensive gene panel testing (about $400). Insurance companies often cover genetic testing for insured family members. Family members identified as carriers of the familial mutation should have relevant clinical screening. For an arrhythmogenic mutation, this would include a physical examination, ECG, exercise ECG, and echocardiogram (3). In addition, family members who are identified as noncarriers of the familial mutation are considered "true negatives."

Although usually informative, clinical interpretation of genetic data may be inconclusive when a variant of uncertain significance (VUS) is identified. The frequency of VUS varies by ethnic group and is lowest for whites and highest for Africans, African Americans, and Asians. If a VUS is identified, follow-up of family members is necessary to further assess pathogenicity. This evaluation includes clinical assessment of relatives for features of the condition and genetic assessment to determine which family members carry the variant. Consistent cosegregation of the genetic variant with features of the clinical condition might indicate that the genetic variant is disease causing. In addition, if the variant is found for the first time in the affected person—a de novo mutation—it is more likely to be disease causing. A cardiovascular genetic professional can help coordinate family member testing and assess the pathogenicity of variants. What Clinical Evaluation and Testing Should a Relative Receive in a Case of Sudden Death?

Because of your patient's family history of sudden death, you perform a thorough physical examination and a cardiac evaluation (resting ECG, exercise ECG, and echocardiogram). On physical examination, the patient is normotensive (no orthostatic hypotension), with a regular heart rate and rhythm. No specific murmurs are heard on auscultation. The resting ECG shows normal sinus rhythm, with a resting heart rate of 65 bpm and a QTc of 438 ms (normal, ≤450 ms). The exercise ECG reveals no arrhythmias or QT prolongation. An echocardiogram shows normal systolic function and cardiac dimensions, with an interventricular septal thickness of 7 mm (normal, 6 to 10 mm).

You encourage your patient to urge her sister to have a physical examination and cardiac evaluation also. On examination, her sister is normotensive (no orthostatic hypotension), with a regular heart rate and rhythm. No specific murmurs are heard on auscultation. Her resting ECG reveals a QTc of 490 ms (normal, ≤450 ms), with a normal heart rate and

rhythm. An echocardiogram is unremarkable. Given the family history and her ECG, your patient's sister probably has long QT syndrome (LQTS). She has a score of 3.5 by the Schwartz criteria for LQTS, which corresponds to a high probability of LQTS (Table 3). She begins treatment with nadolol, and the potential risks and benefits of an implantable cardioverter-defibrillator (ICD) are discussed. She decides to pursue genetic testing for LQTS to make a more informed decision about an ICD and to provide genetic information to the rest of her family.

How Do You Diagnose LQTS?

Long QT syndrome has a frequency of about 1 in 2000 persons and is characterized by a prolongation of the QT interval (4). Persons with this condition are predisposed to fatal ventricular tachyarrhythmias, particularly torsade de pointes. The diagnosis of LQTS includes a history of syncopal events without neurologic cause, a family history of sudden cardiac death, characteristic T-wave abnormalities, and prolongation of the QTc on ECG. (Normal QTc is ≤440 ms in males and ≤450 ms in females.) Because 25% of patients with LQTS have normal-range QTc on resting ECG (concealed LQTS), genetic testing is the most effective means for diagnosing LQTS when a familial mutation has been identified (5). An early diagnosis is particularly important, because death is the first symptom of disease in 10% to 15% of persons with LQTS, and a family history of sudden death is often associated with significant anxiety (5).

Long QT syndrome has different subtypes, each with its own set of triggers and treatments. Precise management of LQTS requires diagnosis of a specific subtype through genetic testing to inform lifestyle recommendations and treatment. The LQT1 subtype (which comprises 35% of all LQTS cases) is associated with mutations in an ion channel that is responsive to adrenergic stimulus (5). Because of this relationship, approximately 88% of cardiac events in LQT1 occur during exercise or stimulated emotional states (4). Subtype LQT2, the second most common, is triggered by auditory stimuli, emotion, exercise, and sleep. The LQT3 subtype is less common and is associated with infrequent cardiac events triggered by sleep (5).

How Should Positive Results of a Genetic Test Be Used?

Genetic testing of your patient's sister shows that she has a heterozygous G289D missense mutation in the transmembrane region of *KCNQ1* (potassium voltage-gated channel subfamily Q member 1), a known mutation present in LQT1 (6). A preserved tissue sample from the deceased brother is tested for the G289D mutation in *KCNQ1*, revealing the same mutation. Because the pathogenicity of this variant is well documented, the cause of death is probably an LQTS-related fatal ventricular arrhythmia. The use of diphenhydramine, a QT-prolonging drug, may have triggered the lethal event (7). Genetic testing of your patient and her parents reveals that the father is a carrier of the G289D mutation, but neither your patient nor her mother have the mutation. Your patient has an informative negative result from genetic testing and a normal cardiac evaluation. She is not at increased risk for sudden death. In addition, her results from genetic testing indicate that her future children are not at increased risk for LQTS.

You inform your patient's father about his genetic test results. On the basis of these results alone, a diagnosis of LQT1 can be made. You order a cardiac evaluation, which reveals a normal heart rate and rhythm. No specific murmurs are present on auscultation. Resting ECG shows a QTc of 448 ms (normal, ≤440 ms). Prolongation of the QTc to 465 ms (normal, ≤445 ms) occurs during the recovery phase of an exercise ECG. Because first cardiac events are less likely in this age group, you begin treatment with propranolol or nadolol, ensure that he is not taking any QT-prolonging medications, and advise him against ICD placement. You instruct him to warn his other health care providers not to prescribe QT-prolonging drugs.

What Can Be Done to Mitigate the Risk for LQTS?

Although the risk for arrhythmia depends on the specific gene mutation, age, sex, and physical activity, most patients with LQT1 can lead normal lives with appropriate medical management. Management begins with lifestyle modifications and avoidance of drugs that prolong the QT interval. Patients with LQT1, who have impaired I_{KS} channels, do not shorten their QT intervals during tachycardia effectively. Therefore, major catecholamine release, as happens during exercise, triggers early afterdepolarizations, which may result in torsade de pointes. Because of this risk, patients with LQT1 should avoid strenuous exercise, especially swimming and diving without supervision, because of the increased risk for drowning. Debate continues regarding participation in competitive sports, particularly for asymptomatic patients (8, 9). Consensus guidelines from the Heart Rhythm Society, European Heart Rhythm Association, and Asia Pacific Heart Rhythm Society state that some low-risk patients with genetically confirmed LQTS, only borderline QTc prolongation, no history of cardiac symptoms, and no family history of sudden cardiac death may be allowed to participate in competitive sports (3). These patients still require appropriate LQTS medications at all times, and external defibrillators with trained personnel are required during competitive activity. In addition, medications with QT-prolonging effects should be avoided in all patients with LQTS: An updated database may be found at https://crediblemeds.org.

Most patients with LQT1 require medical treatment. The therapeutic approach begins with medical interruption of the sympathetic input to the myocardium with β-blockers. β-Blockers are the mainstay of treatment, because they blunt the catecholaminergic response, interrupt the trigger for torsade de pointes, and may even shorten the QT interval (10). They are clinically indicated in all young patients with LQT1, even those who have no symptoms (11). However, 2 exceptions exist: patients who cannot tolerate β-blockers and older patients (those aged ≥20 years) with a normal QTc and no history of cardiac symptoms (first cardiac events are rare in this subgroup) (12). In contrast, β-blockers are used in asymptomatic adults with LQT2 and LQT3; in these subtypes, first-time events occur more frequently in adulthood.

Not all β-blockers have the same anti arrhythmic effects on LQTS (12). Nadolol and propranolol are more effective than metoprolol in reducing cardiac events; thus, they are the preferred β-antagonists in LQTS (12). Long-acting β-blockers are preferred over short-acting formulations, because these medications may be given once or twice a day and have

more consistent blood concentrations. For symptomatic patients, long-acting β-blockers in maximally tolerated doses are recommended and abrupt discontinuation should be avoided.

Automated ICD placement represents an important management option for patients with LQTS but should be used judiciously (13). In general, ICDs are not indicated for persons with LQTS who have no symptoms and have not received β-blocker treatment. Prophylactic ICD therapy should be considered for persons with LQTS who have survived a cardiac arrest, symptomatic patients with syncope despite receiving appropriate β-blocker therapy, or asymptomatic patients with a significantly prolonged QTc (>550 ms). Before placing an ICD, especially in young patients, one should consider adverse sequelae, such as infection, malfunction, inappropriate shocks, and subsequent anxiety. In the pediatric population, ICD placement is constrained further because of patient size and age (14).

Although surgical left cervicothoracic sympathectomy denervation is rarely performed, it is another effective method for decreasing cardiac events in patients with LQTS (15). The procedure involves high thoracic left sympathectomy and ablation of the lower two thirds of the stellate ganglion along with thoracic ganglia T2 to T4. It works by reducing norepinephrine release at the ventricles, thereby increasing the threshold for ventricular fibrillation without reducing heart rate or contractility. Left cervicothoracic sympathectomy should be considered for patients with β-blocker-resistant symptoms, those unable to tolerate β-blockers, those unwilling or unable to receive an ICD, and those with a history of cardiac arrest. The most common side effects of the procedure are dry skin in the left arm and face and profuse sweating on the right side (16).

Summary

A thorough autopsy of your patient’s brother, including molecular genetic testing, gave the family closure regarding the likely cause of death. Cardiac evaluations and genetic testing of the family determined that your patient is not at increased risk for sudden death, relieving a great deal of anxiety and preventing additional medical evaluation. Lastly, your patient’s sister and father can now be appropriately treated, in a “gene-specific” way, to decrease their risk for sudden death.

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Table 1.

Elements of History That Point Toward or Away From a Classification of Arrhythmic Sudden Cardiac Death

Element	Likely SADS	Unlikely SADS
Symptoms	Syncope, presyncope, palpitations	Syncope with aura, postictal findings, unilateral tongue bite
Medical history	QT-prolonging medications, exercise-related events	Vasovagal syncope
Family history	Sudden cardiac death (or aborted sudden cardiac death), arrhythmias, syncope	Epilepsy

SADS = sudden arrhythmic death syndrome.

Table 2.

Conditions Associated With Genetic Causes of Sudden Cardiac Death

Condition	Clinical Presentation	Physical Examination Findings	Diagnostic Testing	ECG Patterns	Associated Genes (Frequency in Patient Population)	Age of Onset	Penetrance*	Clinical Management
Arrhythmogenic RV cardiomyopathy	Palpitations, syncope, dyspnea, RV failure	None	12-lead ECG, SAECG, TTE, CMR, Holter monitoring, EP study, endomyocardial biopsy, genetic testing	Inverted T waves in the right precordial leads, epsilon wave	*PKP2* (34%–74%) *DSP* (2%–39%) *DSG2* (5%–26%) *DSC2* (1%–2%) *JUP* (0.5%–2%) *TMEM43* (rare)	Age at diagnosis generally in adulthood	Low and age dependent	Sport restriction, antiarrhythmic drugs, ICD, radiofrequency ablation
Brugada Syndrome	Syncope, nocturnal agonal respiration, sudden death	None	12-lead ECG, drug challenge, EP study, genetic testing	Right precordial elevated ST segment (≥2 mm) descending with an upward convexity to an inverted T wave	*SCN5A* (15%–30%)	Age at diagnosis generally in adulthood. Mean age of sudden death is 40 y.	Low for persons with an *SCN5A* pathogenic variant	ICD, quinidine, (amiodarone), radiofrequency ablation (RVOT epicardium), avoidance of drugs
Catecholaminergic polymorphic VT	Exercise-related syncope, palpitations, sudden death	None	12-lead ECG, stress ECG, TTE, Holter monitoring, EP study, genetic testing	During exercise, increasing complexity of ventricular arrhythmias; bidirectional VT	*RYR2* (50%–55%) *CASQ2* (2%–5%) *TRDN* (1%–2%) *CALM1* (<1%) Unknown (35%–45%)	Mean age of onset, 7-12 y	High	Sport restriction, β-blocker, flecainide, ICD, LCSD
Long QT syndrome	Syncope, palpitations, sudden death	None	12-lead ECG, stress ECG, Holter monitoring, genetic testing	Prolonged QTc	*KCNQ1* (30%–35%) *KCNH2* (25%–30%) *SCN5A* (5%–10%) *AKAP9, ANK2, CACNA1C, CALM1, CALM2, CAV3, KCNE1, KCNE2, KCNJ2, KCNJ5, SNTA1* (<1% each)	Mean age of diagnosis is before age 30 y	Gene-specific lifetime penetrance: *KCNQ1*: 63% *KCNH2*: 46% *SCN5A*: 18%	Depending on genotype: sport restriction, β-blocker, mexiletine, ICD, LCSD, avoidance of QT-prolonging drugs
Short QT Syndrome	Syncope, palpitations, sudden death	None	12-lead ECG, Holter monitoring, genetic testing	Shortened QTc	*KCNH2, KCNQ1, KCNJ2, CACNA1C, CACNB2, CACNA2D1* (unknown)	Mean age at diagnosis, 23 y	Low	Quinidine, ICD
Hypertrophic cardiomyopathy	Syncope, chest pain, dyspnea, fatigue,	Systolic murmur, worsened with standing	12-lead ECG, TTE, CMR, Holter monitoring,	Prominent voltages with repolarization abnormality,	*MYH7* (40%) *MYBPC3* (40%)	Diagnosis in adolescents and adults	Moderate	β-Blockers, nondihydropyridine calcium channel blockers,

Condition	Clinical Presentation	Physical Examination Findings	Diagnostic Testing	ECG Patterns	Associated Genes (Frequency in Patient Population)	Age of Onset	Penetrance*	Clinical Management
	palpitations, sudden death	or Valsalva, decreased with squatting	genetic testing, cardiac catheterization, EP study	inferolateral q waves, giant negative T waves mid-precordial, left atrial dilatation	*TNNT2* (5%) *TNNI3* (5%) *TPM1* (2%) *MYL3* (1%) *MYL2, ACTC1, CSRP3, ACTN2, MYH6, TCAP, TNNC1, PLN, MYOZ2, NEXN* (unknown)			disopyramide, ICD, myectomy
Dilated cardiomyopathy	Dyspnea, fatigue, palpitations	None, unless the patient has heart failure	12-lead ECG, blood tests, TTE, CMR, Holter monitoring, genetic testing, cardiac catheterization	Atrial or ventricular hypertrophy, microvoltages	*TTN* (10%–20%) *LMNA* (6%) *MYH7* (4.2%) *MYH6* (3%–4%) *TNNT2* (2.9%) *BAG3* (2.5%) *ANKRD1* (2.2%) *SCN5A* (2%–4%) *MYBPC3* (2%–4%) *RBM20* (1.9%) *TPM1* (<1%–1.9%) *TNNI3* (1.3% AD, <1% AR) *TNNC1* (<1%–1.3%) *TMPO* (1.1%) *LDB3* (1%) *TCAP* (1%) *VCL* (1%) *SGCD, PSEN1, PSEN2, NEXN, DES, CSRP3, ACTC1, ACTN2* (<1%) *TAZ, PLN, EYA4, DSG2, DMD* (unknown)	Age at diagnosis generally in adulthood	Moderate	β-Blockers, ACEIs/ARBs, diuretics, antiarrhythmic drugs, ICD (CRT)
Aortic aneurysm	Pain, no symptoms	Difference in blood pressure between left and right arm.	CT, MRI, TTE	None	*ACTA2* (12%–21%) *TGFBR2* (5%) *FBN1* (3%) *TGFBR1* (3%) *SMAD3*	Adult onset	Moderate	β-Blockers, ACEIs/ARBs, surgery

Condition	Clinical Presentation	Physical Examination Findings	Diagnostic Testing	ECG Patterns	Associated Genes (Frequency in Patient Population)	Age of Onset	Penetrance*	Clinical Management
					(2%) *LOX* (1.5%) *BGN, COL3A1* (rare) *FOXE3* (1.4%) *MAT2A, MYH11, MYLK, PRKG1, TGFB2* (1%) *MFAP5* (0.25%) *TGFB3* (2 cases)			

ACEI = angiotensin-converting enzyme inhibitor; *ACTA2* = actin, α_2, smooth muscle, aorta; *ACTC1* = actin, α, cardiac muscle 1; *ACTN2* = actinin α_2; AD = autosomal dominant; *AKAP9* = A-kinase anchoring protein 9; *ANK2* = protein ankyrin B; *ANKRD1* = ankyrin repeat domain 1; AR = autosomal recessive; ARB = angiotensin-receptor blocker; *BAG3* = BCL2-associated athanogene 3; *BGN* = biglycan; *CACNA1C* = calcium voltage-gated channel subunit α_{1C}; *CACNA2D1* = calcium voltage-gated channel auxiliary subunit $\alpha_2\delta_1$; *CACNB2* = calcium voltage-gated channel auxiliary subunit β_2; *CALM1* = calmodulin 1; *CALM2* = calmodulin 2; *CASQ2* = calsequestrin 2 protein; *CAV3* = caveolin 3; CMR = cardiac magnetic resonance; *COL3A1* = collagen type III α_1 chain; CRT = cardiac resynchronization therapy; *CSRP3* = cysteine and glycine-rich protein 3; CT = computed tomography; *DES* = desmin; *DMD* = dystrophin; *DSC2* = desmocollin 2; *DSG2* = desmoglein 2; *DSP* = desmoplakin; ECG = electrocardiogram; EP = electrophysiology; *EYA4* = EYA (eyes absent) transcriptional coactivator and phosphatase 4; *FBN1* = fibrillin 1; *FOXE3* = forkhead box E3; ICD = implantable cardioverter-defibrillator; *JUP* = plakoglobin; *KCNE1* = potassium voltage-gated channel Isk-related family member 1; *KCNE2* = potassium voltage-gated channel Isk-related family member 2; *KCNH2* = potassium voltage-gated channel subfamily H member 2; *KCNJ2* = potassium inwardly rectifying channel subfamily J member 2; *KCNJ5* = potassium inwardly rectifying channel subfamily J member 5; *KCNQ1* = potassium voltage-gated channel subfamily Q member 1; LCSD = left cardiac sympathetic denervation; *LDB3* = LIM domain binding 3; *LMNA* = lamin A/C; *LOX* = lysyl oxidase; *MAT2A* = methionine adenosyltransferase 2A; *MFAP5* = microfibril-associated protein 5; MRI = magnetic resonance imaging; *MYBPC3* = protein myosin-binding protein C, cardiac-type; *MYH6* = myosin heavy chain 6; *MYH7* = myosin heavy chain 7; *MYH11* = myosin heavy chain 11; *MYL2* = myosin light chain 2; *MYL3* = myosin light chain 3; *MYLK* = myosin light chain kinase; *MYOZ2* = myozenin 2; *NEXN* = nexilin F-actin binding protein; *PKP2* = protein plakophilin 2; *PLN* = phospholamban; *PRKG1* = protein kinase cGMP-dependent 1; *PSEN1* = presenilin 1; *PSEN2* = presenilin 2; QTc = rate-corrected QT interval; *RBM20* = RNA binding motif protein 20; RV = right ventricular; RVOT = RV outflow tract; *RYR2* = ryanodine receptor 2; SAECG = signal-averaged ECG; *SCN5A* = sodium channel protein type 5; *SGCD* = sarcoglycan 5; *SMAD3* = SMAD family member 3; *SNTA1* = syntrophin TAZ = tafazzin; *TCAP* = titin-cap; *TGFB2* = transforming growth factor β_2; *TGFB3* = transforming growth factor β_3; *TGFBR1* = transforming growth factor β-receptor 1; *TGFBR2* = transforming growth factor p-receptor 2; *TMEM43* = transmembrane protein 43; *TMPO* = thymopoietin; *TNNC1* = troponin C1, slow skeletal and cardiac type; *TNNI3* = cardiac muscle protein troponin I, cardiac muscle; *TNNT2* = protein troponin T, cardiac muscle; *TPM1* = tropomyosin a1 chain; *TRDN* = triadin; TTE = transthoracic echocardiogram; *TTN* = titin; *VCL* = vinculin; VT = ventricular tachycardia.

*Penetrance: low, <30%; moderate, 30%–60%; high, >60%. Some variability exists in each disease category by gene and specific variant.

Table 3.

Schwartz Criteria

Findings	Points*
ECG	
QTc ≥ 480 ms	3
QTc 460–479 ms	2
QTc 450–459 ms (in males)	1
QTc ≥ 480 ms during fourth minute of recovery from exercise stress test	1
Torsade de pointes	2
T-wave alternans	1
Notched T wave in 3 leads	1
Low heart rate for age (< second percentile)	0.5
Clinical history	
Syncope with stress	2
Syncope without stress	1
Family history†	
Family member(s) with definite LQTS	1
Unexplained sudden cardiac death in an immediate family member aged <30 y	0.5

ECG = electrocardiogram; LQTS = long QT syndrome; QTc = rate-corrected QT interval.

*Points are assigned to each finding in the patien's ECG, clinical history, and family history: ≤1.0 point, low probability of LQTS; 1.5–3.0 points, intermediate probability of LQTS; ≥3.5 points, high probability of LQTS.

†The same family member cannot be counted twice under the family history category.