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The clinical and electrocardiographic phenotype of patients with genotype-negative long QT syndrome

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ABSTRACT

BACKGROUND Long QT syndrome (LQTS) is a genetic heart disease that increases the risk of ventricular arrhythmias and sudden cardia arrest. Despite advances in genetic testing, a small subset of patients with LQTS remain genetically elusive.

OBJECTIVE This study aimed to determine the prevalence and clinical characteristics of patients with a phenotype of LQTS but without a genotype.

METHODS This study aimed to identify phenotype-positive, genotype-negative patients with LQTS seen at Mayo Clinic (2000–2024). Retrospective data included demographics, clinical evaluations, electrocardiograms, and genetic results. Diagnosis adhered to established criteria, and genotype-negative LQTS was defined by the absence of pathogenic variants despite clinical presentation.

RESULTS The study included 1829 patients with LQTS. Of these, 1706 (93%) had pathogenic or likely pathogenic variants, and 95 patients (5%) had upgraded clinical variants of uncertain significance, leaving 32 (1.7%) with negative genetic tests. Among the genotype-negative patients, 17 underwent next-generation sequencing, identifying a genetic cause in 6 cases (0.3% of the total). The mean age at diagnosis for the remaining 26 patients was 25 ± 15 years, with 76% being women and an average initial corrected QT of 498 ± 41 ms. Fourteen patients (53%) experienced cardiac events prior to diagnosis, and 11 (44%) received an implantable cardioverter-defibrillator. The mean follow-up period was 8 ± 7 years.

CONCLUSION Genotype-negative LQTS accounted for < 2% of our cohort, highlighting diagnostic and management challenges. Comprehensive clinical evaluation and advanced genetic testing remain essential for accurate diagnosis and care.

KEYWORDS Long QT syndrome; Genotype negative; Sudden cardiac death; Genetic heart disease; Next-generation sequencing

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Introduction

Long QT syndrome (LQTS) is a genetic heart disease characterized by prolongation of the cardiac action potential, as evidenced clinically by a prolonged QT interval on a 12-lead electrocardiogram (ECG).[1,2] This condition predisposes at-risk individuals to a heightened risk of torsades de pointes (TdP), the characteristic form of polymorphic ventricular tachycardia (VT) observed in LQTS; subsequent LQTS/TdP-triggered sudden cardiac arrest (SCA); and sudden cardiac death (SCD).[3] The clinical expressivity of LQTS is broad, encompassing asymptomatic individuals to those highly symptomatic and experiencing recurrent syncope, seizures, and SCA/SCD, underscoring the imperative for precise diagnosis and risk stratification.[4,5]

The diagnostic approach for LQTS integrates careful phenotypic assessment with genetic testing. Phenotypic

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assessment involves a thorough clinical evaluation, including symptomatology, family history, identification of characteristic ECG findings, and exercise stress testing. Genetic testing aims to identify pathogenic variants in genes associated with LQTS, thereby providing genetic confirmatory evidence for diagnosis and directing therapeutic interventions and follow-up assessment.[6,7] Three main LQTS-causative genes, *KCNQ1, KCNH2*, and *SCN5A*, encoding cardiac ion channels account for most genetically proven cases. However, minor genes have been implicated in a smaller proportion of cases, with varying levels of supporting evidence. A recent study by Adler and colleagues[8] has reclassified 6 previously accepted LQTS genes as disputed, emphasizing the need for continuous reassessment of genetic data.

Recent advancements in genetic sequencing technologies, particularly next-generation sequencing (NGS), have markedly enhanced the detection of causative variants implicated in LQTS.[9] In addition, the dynamic reclassification of variants of uncertain significance (VUSs) to likely pathogenic or pathogenic (LP/P) variants and the importance of phenotyping in this designation have further refined the diagnostic accuracy.[10,11]

Despite significant advancements in genetic testing and the discovery of 13+ minor LQTS-susceptibility genes, a subset of patients remains genotype negative, posing a significant challenge for clinicians, given that some may still exhibit symptoms, leading to potential misdiagnosis, undertreatment, or underestimation of the severity of their condition.[12] Notably, recent studies, including one by Lahrouchi and colleagues,[13] have suggested that the genotype-negative remnant may be polygenic while carrying the same risk as those with a monogenic form of the disease. This ambiguity underscores the need for a comprehensive understanding of this population and guidance for providers facing such diagnostic uncertainties. This study aimed to determine the prevalence and spectrum of patients with a clinical diagnosis of LQTS who remain genotype negative after comprehensive genetic testing, thereby providing deeper insights into the phenotype, management, and outcomes for this unique subset of patients with LQTS.

Abbreviations

ECG: electrocardiogram

ICD: implantable cardioverter-defibrillator

LP/P: likely pathogenic/pathogenic

LQTS: long QT syndrome

NGS: next-generation sequencing

PRS: polygenic risk score

QTc: corrected QT

SCA: sudden cardiac arrest

SCD: sudden cardiac death

TdP: torsades de pointes

VUS: variant of uncertain significance

VT: ventricular tachycardia

Methods

This study, approved by the Mayo Clinic Institutional Review Board (#10-008515 and 16-008436), involved a retrospective analysis of all patients seen at Mayo Clinic's Windland Smith Rice Genetic Heart Rhythm Clinic in Rochester, Minnesota, between July 2000 and May 2024. Our objective was to identify the prevalence of phenotype-positive, but genotype-negative patients with LQTS and assess their clinical characteristics and risk of cardiac events.

Study population and data collection

Patients included in the study underwent clinical evaluation and risk stratification by a multidisciplinary team of genetic cardiologists and LQTS specialists (M.J.A. and J.R.G.). Data collection involved a review of the electronic health records for patient demographics, clinical characteristics, cardiologic evaluations, genetic test results, ECG records (with manually calculated corrected QT [QTc] values), results from exercise or epinephrine stress tests, family history of SCA/SCD or LQTS, treatments, and outcomes.

Clinical criteria for LQTS diagnosis

Diagnosis of LQTS was based on established clinical criteria, including a prolonged QT on ECG, characteristic T-wave morphology, clinical history, family history of LQTS or SCA, or cardiac-related events. Secondary causes of acquired QT prolongation, such as concomitant use of QT-prolonging medications, electrolyte abnormalities, and systemic conditions known to affect repolarization, were systematically assessed to ensure an accurate diagnosis. In certain cases, although concomitant exogenous QT-prolonging factors might have been present, careful evaluation showed that a diagnosis of LQTS was still warranted.[14]

Definition of genotype-negative LQTS

Genotype-negative LQTS was defined as the absence of identifiable pathogenic variants in known LQTS major genes (*KCNQ1, KCNH2, and SCN5A*) and comprehensive evaluation of minor genes (*ALG10B, CACNA1C, CALM1-3, CAV3, KCNE1, KCNJ2, and TRDN*) despite a clinical presentation consistent with a LQTS phenotype. Patients whose LQTS genetic testing (1) was negative, (2) had only a VUS that could not be upgraded to LP/P based on phenotype, or (3) had a positive variant but in a gene not related to LQTS were included in this category for further evaluation. In addition, patients with a previous clinical diagnosis of genotype-positive LQTS by variants in a disputed gene, such as *AKAP9, ANK2, KCNE2, KCNJ5, SCN4B*, and *SNTA*, were reassessed.[8] In these cases, genotype positive referred to the presence of a variant in one of these disputed genes, but the significance of these variants required reassessment. These cases were considered for further evaluation of whether the clinical phenotype was present or dismissed as normal if no supporting evidence was found. Selected patients displaying specific characteristics indicative of gene-related phenotypes, such as distinct T-wave morphology or unique responses to stress tests, were subjected to a broader genetic test evaluation or NGS testing in a research context.

Statistical analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study cohort.

Continuous variables were reported as mean ± standard deviation, whereas categorical variables were expressed as frequencies and percentages.

Ethical considerations

The study was conducted following the principles of the Declaration of Helsinki and approved by the Mayo Clinic Institutional Review Board. Informed consent was waived owing to the retrospective nature of the study, and patient data were anonymized to maintain confidentiality.

Results

Between July 2000 and May 2024, 2206 patients were evaluated for LQTS at Mayo Clinic's Windland Smith Rice Genetic Heart Rhythm Clinic. Of these, 329 patients (15%) were dismissed as normal with the removal of their previously rendered diagnosis of LQTS. In addition, 13 patients were excluded owing to a lack of genetic testing, and 35 patients owing to a lack of follow-up data (Figure 1).

Among the remaining cohort of 1829 patients, thorough evaluations were conducted including clinical history, ECGs, physical examinations, exercise tests, and genetic testing. Of these, for 1706 patients (93.2%), an LP/P variant in an established LQTS-associated gene was identified as classified following the American College of Medical Genetics and Genomics guidelines.[15] In addition, 95 patients (5.2%) with variants previously classified as a VUS were upgraded to LP/P based on clinical phenotype and genetic evaluation. Variants that remained classified as VUS, along with the rationale for nonupgrade, are presented in Supplemental Table 1. The distribution of patients by gene and variant classification (LP/P and upgraded VUS) across major and minor genes is presented in Table 1. After these exclusions, 32 patients (1.7%) remained identified as genotype negative for further assessment. The cohort selection process is summarized in Figure 1.

Table 1 Genotypic characteristics of the LQTS cohort

Genes	Number of patients, n (%)	P/LP variant, n (%)	VUS upgraded, n (%)
Total cohort	1829 (100)	1709 (93.4)	95 (5.2)
Major genes	1681 (91.6)	1598 (95.1)	83 (4.9)
KCNQ1	918 (50.2)	868 (94.5)	50 (5.5)
KCNH2	584 (31.9)	557 (95.3)	27 (4.7)
SCN5A	179 (9.8)	173 (96.6)	6 (3.4)
Minor genes	123 (6.7)	111 (90.2)	12 (9.8)
ALG10B	6 (0.3)	6 (100)	0 (0)
CACNA1C	37 (2)	35 (94.5)	2 (5.5)
CALM1	7 (0.3)	7 (100)	0 (0)
CALM2	8 (0.4)	5 (62.5)	3 (37.5)
CALM3	1 (0.05)	1 (100)	0 (0)
CAV3	2 (0.1)	0 (0)	2 (100)
KCNE1	43 (2.3)	38 (88.3)	5 (11.7)
KCNJ2	12 (0.6)	12 (100)	0 (0)
TRDN	7 (0.3)	7 (100)	0 (0)
Genotype negative	26 (1.4)	-	-

Values are presented as n (%).
LQTS = long QT syndrome; P/LP = pathogenic/likely pathogenic; VUS = variant of uncertain significance.

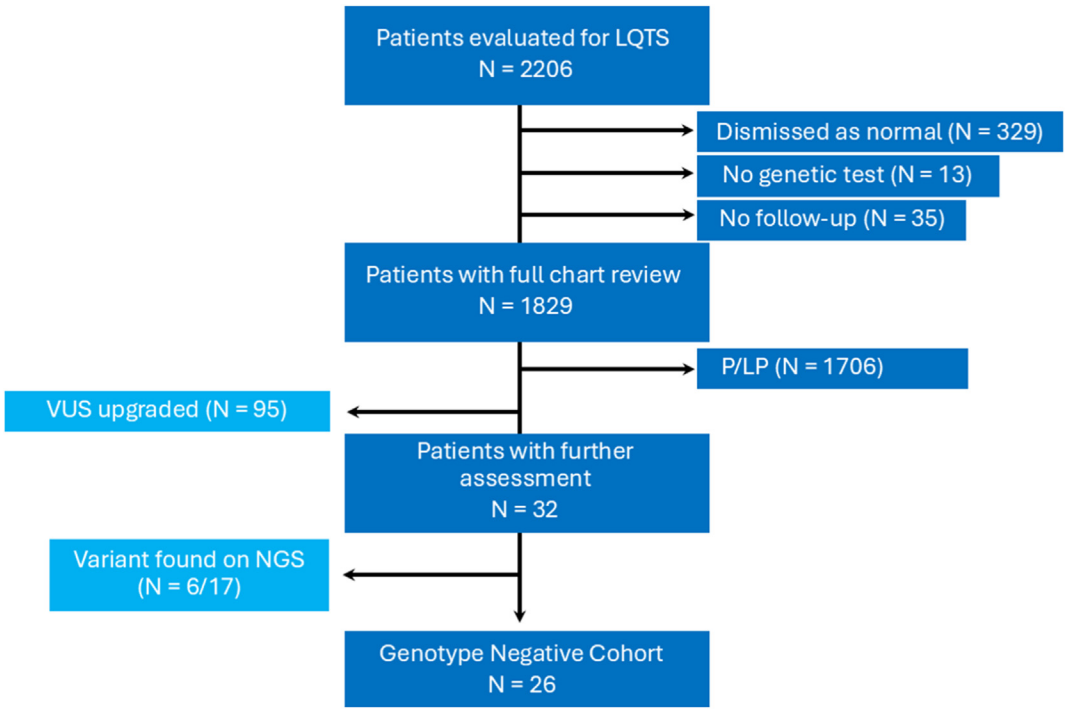


Figure 1
Study cohort flowchart. LQTS = long QT syndrome; NGS = next-generation sequencing; P/LP = pathogenic/likely pathogenic; VUS = variant of uncertain significance.

Of the 32 genotype-negative patients, 17 had enrolled in and completed research-based NGS (either exome or genome). Among these, a genetic cause was identified in 6 of 17 patients (35%; 0.3% of all patients), as summarized in Table 2.[16–20] Notably, these involved 2 patients, with deep intronic variants in the *KCNH2*-encoded Kv11.1 alpha subunit (ie, the LQT2-causative gene), whose ECG phenotypes had generated an index of suspicion for LQT2. In addition, 2 patients had homozygous variants in *TRDN* leading to the subsequent first description of triadin knockout syndrome.[20,21] Similarly, an *ALG10B* variant, found in 1 patient, led to the description of *ALG10B* as a novel LQTS-susceptibility gene.[16] Among the remaining cohort, 7 patients were enrolled in a broader comprehensive genetic test (> 150 cardiac channelopathy genes), a further laboratory deletion duplication test was performed for 5 other patients, and 3 patients received only the commercial genetic test (13 LQTS genes evaluated).

In total, 26 patients (1.4%) remained and were considered true genotype negative for the final study cohort (Figure 1). The patients had all undergone genetic testing for the 13 LQTS-associated genes through LQTS gene panels, broad arrhythmia panels, or, for some, research-based NGS. Demographic and clinical characteristics of these patients are presented in Table 3, and the clinical demographics between the genotype-negative patients and the major gene phenotypes (LQT1, LQT2, and LQT3) are presented in Table 4.

These patients (20 women; 76%) had a mean age at diagnosis of 25 ± 15 years and a mean QTc at first evaluation of 498 ± 41 ms. Among these, 10 (38%) were considered athletes at the time of diagnosis. A thorough evaluation was conducted to determine whether their QT prolongation could be attributed to athletic training rather than LQTS,[19] and all were found to have at least 1 of following: persistent QT prolongation after deconditioning, abnormal stress test results, documented cardiac events, or ECG abnormalities such as T-wave notching, findings inconsistent with the benign QT remodeling previously described in athletes.

Among the 26 unrelated patients in our genotype-negative LQTS cohort, 24 (92%) were considered probands, whereas 2 (8%) were nonprobands. The prevalence of genotype-negative LQTS among all probands in our cohort was 24 of 732 (3%). Notably, 8 of 26 individuals (31%) had a reported family history of LQTS; however, these affected relatives were not evaluated at our institution. The 2 nonprobands included 1 patient with at least 5 affected family members and another whose only affected relative was a sister who survived an SCA. Both underwent comprehensive genetic testing, including deep intronic variant analysis, but no pathogenic variants were identified. Notably, the affected relatives of these 2 nonprobands were not evaluated at our clinic.

In this cohort, clinical assessments suggest specific LQTS subtypes based on the phenotypes, ECG findings, and stress test results. Five patients (19%) were suspicious of LQT1 secondary to their LQT1-like maladaptive QT reactivity during stress testing. Seven patients (26%) were LQT2-like owing to the presence of flat and notched T waves on their ECGs. In

Table 3 Clinical characteristics of genotype-negative patients

Clinical characteristics	Total Cohort (N = 26)
Age at diagnosis, y	25 ± 15
Gender, n (% women)	20 (76)
Proband, n (%)	23 (88)
Family history of SCA at <45 y old, n (%)	7 (26)
First QTc, ms	498 ± 41
Treatment modalities, n (%)	
Beta-blockers	20 (76)
ICD	11 (42)
LCSD	4 (15)
INT	3 (11)
Sodium channel blocker	2 (7)
Symptomatology, n (%)	
First event	
Syncope	7 (26)
Seizure	4 (15)
SCA	1 (4)
Torsades de pointes	1 (4)
VT/VF	1 (4)
Follow-up events, n	
Syncope	12
ICD shock	2
NSVT	2
SCA	2
Torsades de pointes	2
Arrhythmia-related death	1
Follow-up time, y	8 ± 7

Continuous variables are expressed as mean ± standard deviation.
ICD = implantable cardioverter-defibrillator; INT = intentional nontreatment; LCSD = left sympathetic chain denervation; NSVT = nonsustained ventricular tachycardia; QTc = corrected QT; SCA = sudden cardiac arrest; VT/VF = ventricular tachycardia/ventricular fibrillation.

Table 2 Next-generation sequencing results

Patient	Exome/genome	Gene	Variant	QTc (ms)	Age at diagnosis (y)	Symptoms before diagnosis
1	Genome	*ALG10B*	p.G6S[16]	505	2	Asymptomatic
2	Exome	*CACNA1C*	p.G402S[17]	550	1	SCA
3	Genome	*KCNH2*	(deep intronic) c.3331-316G>T[18]	492	29	Multiple syncope
4	Genome	*KCNH2*	(deep intronic) c.2399-28A>T[19]	570	12	Syncope
5	Exome	*TRDN*	p.K147fs (homozygous)[20]	500	2	SCA
6	Exome	*TRDN*	p.K147fs (homozygous)[20]	480	2	Syncope

QTc = corrected QT; SCA = sudden cardiac arrest.

Table 4 LQTS cohort demographic characteristics between genotypes

Characteristics	Entire LQTS cohort	LQT1	LQT2	LQT3	Genotype negative
Cohort totals, n	1829	918	584	179	26
Women, n (%)	1089 (59)	543 (59)	338 (58)	109 (61)	20 (76)
Age at diagnosis, y	20 ± 18	21 ± 19	18 ± 17	19 ± 18	25 ± 15
First QTc, ms	466 ± 41	466 ± 39	471 ± 46	470 ± 39	498 ± 41
Cardiac events before diagnosis					
Patients with 1 or more events, n (%)	641 (35)	294 (32)	222 (38)	53 (29)	14 (53)
SCA, n (%)	69 (4)	15 (2)	25 (4)	8 (4.5)	1 (4)
Seizure, n (%)	64 (3.5)	24 (3)	32 (5.5)	2 (1)	4 (16)
Cardiac syncope, n (%)	258 (14)	134 (15)	94 (16)	12 (7)	7 (26)
Cardiac events after diagnosis and during treatment					
Patients with 1 or more BCEs, n (%)	188 (10)	81 (9)	75 (12)	20 (11)	9 (34)

Values are presented as mean ± standard deviation or n (%).
BCE = breakthrough cardiac event (eg, cardiac syncope, seizure, ICD shock, cardiac arrest); ICD = implantable cardioverter-defibrillator; LQT1, 2, or 3 = long QT syndrome type 1, 2, or 3; LQTS = long QT syndrome; QTc = corrected QT; SCA = sudden cardiac arrest.

addition, 1 patient (4%) had been predicted clinically to be LQT3.

Overall, 14 patients (53%) experienced at least 1 cardiac event, including syncope in 7 (26%), seizures in 4 (15%), TdP or VT in 2 (8%), and SCA in 1 (4%). Of these, 12 patients had their first event before diagnosis (46% of 26). Regarding treatment modalities, 11 patients received an implantable cardioverter-defibrillator (ICD), and 4 had left cardiac sympathetic denervation surgery.

Figure 2A illustrates the case of a female patient diagnosed clinically as having LQTS at 28 years of age. The initial clinical suspicion was LQT1, based on phenotypic presentation and exercise testing. Her first cardiac event, a syncopal event requiring cardiopulmonary resuscitation without the need for external defibrillation, occurred during exercise. At the time of initial evaluation, her resting ECG demonstrated a QTc of 550 ms. After the discontinuation of QT-prolonging medications, her QTc decreased to 505 ms, and further electrolyte optimization led to a reduction to 495 ms. Treadmill stress testing revealed maladaptive QT prolongation during the recovery phase (Figure 2A). Comprehensive genetic analysis, including NGS, did not identify a possible disease-associated variant. The patient was initially managed with nadolol but underwent left sympathetic chain denervation (LCSD) in 2021 because of beta-blocker intolerance. Over 3 years of follow-up, she has remained event free, with resting QTc's stabilizing between 450 and 460 ms. However, stress testing continued to demonstrate the QT maladaptation characteristic of LQT1. Reanalysis of the KCNQ1 introns remains negative.

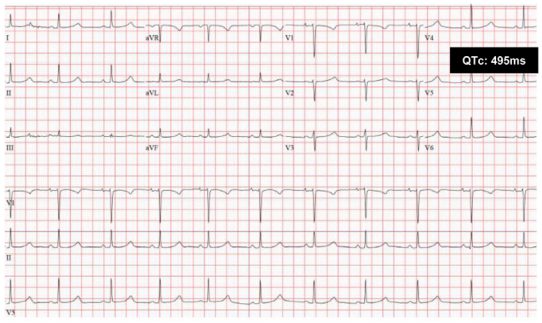
Figure 2B illustrates the case of a 10-year-old man with persistent QT prolongation. The patient, an index case with no family history of SCD or cardiac events, was initially diagnosed after an incidental ECG finding of a prolonged QT (508 ms). Serial ECGs confirmed persistently increased QTc's (549 ms, 540 ms, and 540 ms). A stress test revealed further increases in QTc at peak exercise (540 ms) and inadequate adaptation during recovery (QTc 529 ms at 3 minutes). A comprehensive genetic evaluation, including NGS, was performed and returned negative for variants associated with LQTS. Given his extreme QT prolongation, nadolol was initiated to mitigate arrhythmic risk, and subsequently, LCSD was performed as an additional protective measure. Because of repeated instances of extreme QT prolongation of ECG follow-up (QTc >600 ms), a primary prevention ICD was placed.

The mean follow-up period since diagnosis was 8 ± 7 years. One patient experienced the first event after the diagnosis was made. Nine patients (34% of 26 and 64% of 14) developed subsequent events, totaling 20 additional events, including 2 SCA, 2 TdP, 1 ventricular fibrillation with appropriate ventricular fibrillation–terminating shock, 2 nonsustained VT, and 12 syncopal episodes.

Figure 3 illustrates the case of a 39-year-old woman with a confirmed diagnosis of LQTS, based on recurrent syncope, QT prolongation, and documented nonsustained polymorphic VT (Figure 3A). Her symptoms began postpartum, and a comprehensive evaluation ruled out ischemic and secondary causes of QT prolongation. While awaiting genetic results, she developed TdP deteriorating to SCA (Figure 3B) during an episode of persistent vomiting, requiring multiple shocks for successful defibrillation. Given her high-risk profile, a secondary prevention ICD was placed. Despite therapy with nadolol and avoidance of QT-prolonging medications, she continued to experience recurrent TdP episodes, often in the setting of concomitant systemic stressors, with QTc's exceeding 600 ms during these events. Genetic testing did not identify pathogenic variants in known LQTS-associated genes. She had no known family history of LQTS; her mother's uncle died suddenly at the age of 24 years.

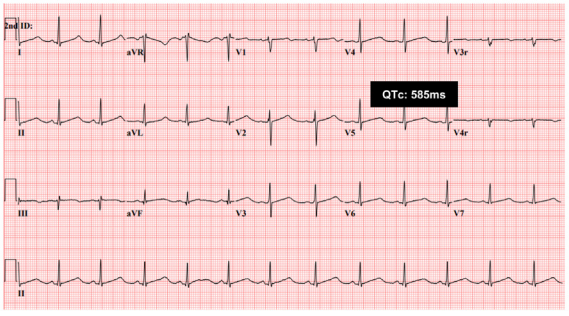
Figure 3 presents the case of a 65-year-old woman who met LQTS diagnostic criteria, with prolonged QTc and documented TdP. She developed malignant arrhythmias in the context of a systemic stressor and severe vomiting leading to hypokalemia (Figure 3C). However, even after correcting all reversible factors, QT prolongation persisted, and she continued to experience recurrent nonsustained TdP

A



	QT	HR	QTc
Sitting	480	60	480
Supine	480	58	472
Standing	480	59	476
Exercise - 1 minute	450	73	496
Exercise - 3 minutes	430	81	500
Peak	320	142	492
Recovery - 1 minute	360	120	509
Recovery - 3 minutes	420	105	556
Recovery - 5 minutes	420	90	514

B



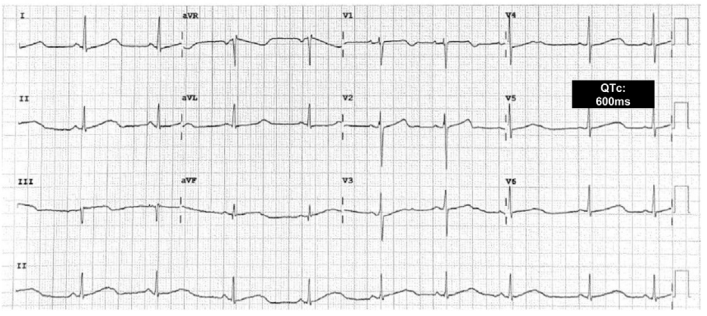
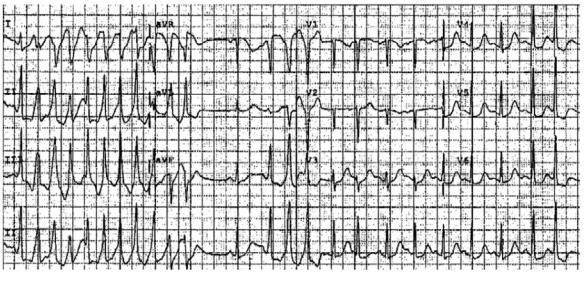


Figure 2

A: Electrocardiographic (ECG) and stress test findings of a female patient diagnosed as having long QT syndrome. The resting ECG demonstrates a QTc of 495 ms. Treadmill stress testing reveals maladaptive QT prolongation, with QTc values of 509 ms, 556 ms, and 514 ms at sequential time points at 1, 3, and 5 minutes of recovery, respectively. **B:** ECGs of a 10-year-old asymptomatic male with extreme QT prolongation before and after left sympathetic chain denervation (LCSD). Pre-LCSD ECG demonstrates a markedly increased QTc of 585 ms with a QTc of 600 ms after LCSD. HR = heart rate; QTc = corrected QT.

A



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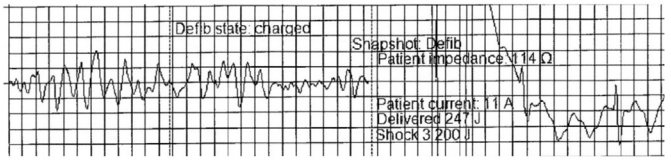

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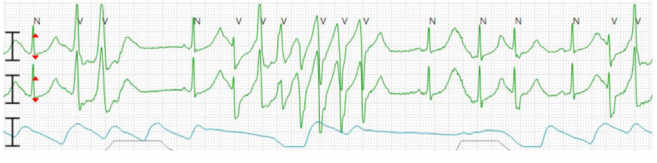

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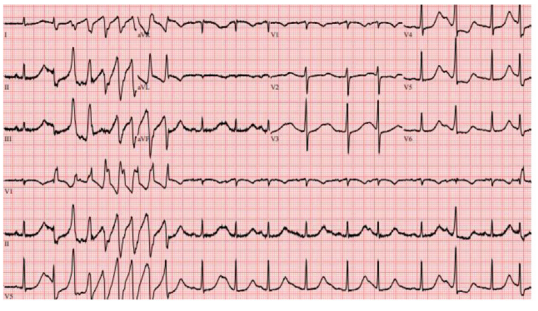

Figure 3

Examples of arrhythmias in patients with genotype-negative long QT syndrome. **A:** Electrocardiogram (ECG) after 1 of the syncope events demonstrating nonsustained polymorphic ventricular tachycardia in a 39-year-old female patient. **B:** ECG of this patient capturing torsades de pointes (TdP) during sudden cardiac arrest with subsequent shock delivery. **C:** ECG capturing TdP in the setting of hypokalemia secondary to prolonged vomiting in a 65-year-old female patient. **D:** ECG demonstrating persistent QT prolongation with recurrent nonsustained TdP despite correction of electrolyte abnormalities.

(Figure 3D). Further evaluation ruled out structural heart disease, and genetic testing was negative except for a truncating VUS in ALPK3. While on beta-blocker therapy, her QTc improved, stabilizing at 450–460 ms, and she has remained arrhythmia free. She had no family history of LQTS or SCD.

In our cohort, 1 female patient passed away after an arrhythmic event during follow-up. She was diagnosed initially as having LQTS at the age of 30 years after experiencing a seizure and a baseline QTc of 520 ms. She had a long-standing history of psychiatric illness, requiring multiple psychotropic medications that were managed carefully to minimize their impact on her QT interval. Despite thorough medication adjustments, she exhibited persistent QT prolongation and ECG abnormalities, suggesting an underlying diagnosis of congenital LQTS. Before genetic testing, her ECG, with its flat T waves in the limb leads and notched T waves in the lateral precordial leads, generated a clinical index of suspicion for LQT2 but her *KCNH2* gene was normal. During follow-up, she experienced 2 significant cardiac events, both syncopal episodes occurring during pregnancy and the postpartum period. Later, she underwent ICD removal owing to superior vena cava thrombosis. She was found deceased at home at the age of 37 years while undergoing treatment for pneumonia, which included azithromycin, doxycycline, and over-the-counter cough suppressants. Her death was presumed to be arrhythmic in nature.

Discussion

Our retrospective observational analysis of 2206 patients assessed for LQTS revealed that although the majority had identifiable LP/P variants, a small but clinically significant subset of patients with LQTS (1.4%) remained genotype negative after comprehensive genetic testing across known LQTS-related genes. In addition, some patients presented variants in recently updated disputed genes, which required careful diagnosis and phenotype reassessment.[8] This cohort highlights the ongoing challenges in diagnosing and managing LQTS without definitive genetic markers, underscoring the complexity of this condition and the changing landscape of genetic testing and variant adjudication.

The significant proportion of patients previously dismissed as normal (15% of the patients evaluated for LQTS) based on clinical evaluation underscores the critical role of comprehensive phenotype reassessment for the accurate diagnosis of LQTS, particularly in determining a true diagnosis of genotype-negative LQTS. Previous studies from our institution, including those by Taggart and colleagues[22] and Bains and colleagues,[23] have demonstrated the complexities and frequent pitfalls in diagnosing LQTS, especially in distinguishing true disease from borderline or transient QT prolongation. Misinterpretations of ECG findings—such as incorrect QTc measurements, inclusion of U waves, and transient QTc prolongation after vasovagal syncope—remain common sources of misdiagnosis.[7,22,23] Before labeling a patient as genotype-negative LQTS, acquired contributors must be ruled out, careful evaluation should be performed, and borderline cases should undergo reassessment to prevent overdiagnosis.

Genetic testing plays a central role in the diagnosis, risk stratification, and management of LQTS and should be guided by clinical suspicion and current guidelines. When appropriately applied, it can identify a causative variant and inform tailored treatment strategies in most patients, improving care precision.[7,24] However, test results must be interpreted with caution, particularly in the presence of VUS, to avoid overdiagnosis and unnecessary interventions. In patients with a clear clinical phenotype but negative genetic results, it is essential to ensure that advanced testing methods, such as NGS, have been used to cover the full spectrum of LQTS-associated genes. If not, continued reevaluation is recommended and updated genetic testing, if indicated, should be pursued given that older and limited panels may miss relevant variants. This approach helps avoid premature classification as genotype negative and ensures that high-risk patients continue to receive appropriate follow-up and care.[23,25]

Our specialized center's comprehensive evaluations revealed (likely) pathogenic variants in 98% of cases, contrasting with the 25% genotype-negative rate reported previously.[26] Advancements in genetic testing, particularly NGS, have significantly enhanced our ability to identify novel genetic variants associated with LQTS.[27] In this study, NGS was used for research purposes in select cases, enabling the detection of deep intronic variants in *KCNH2* and novel LQTS-susceptibility genes such as *ALG10B*.[16,28] Furthermore, the continuous reclassification of VUS to more accurately reflect their pathogenicity underscores the importance of ongoing genetic research.[11]

Despite these advancements, 2 nonproband cases in our cohort, both with strong family histories of clinically diagnosed LQTS, remained without an identifiable genetic cause, even after comprehensive intronic variant analysis. This highlights the potential existence of yet-undiscovered genetic contributors, including novel gene associations, polygenic influences, or epigenetic mechanisms. Finally, the absence of a family history of LQTS in 69% of genotype-negative cases may reflect a lower likelihood of a monogenetic substrate. Although these individuals met clinical criteria for LQTS, their genotype-negative status suggests that alternative mechanisms may contribute to their phenotype.[13,29]

Polygenic risk scores (PRSs) have emerged as a tool to quantify the cumulative contribution of common genetic variants to LQTS susceptibility.[13] Studies have demonstrated that genotype-negative patients with LQTS tend to have higher PRS than genotype-positive individuals, suggesting a possible polygenic contribution to disease risk. Lahrouchi and colleagues[13] highlighted that approximately 15% of LQTS-susceptibility variance can be attributed to common genetic variation, reinforcing the overlap between QT regulation in the general population and in monogenic congenital LQTS 12. In addition, a QTc-PRS incorporating multiple QT-associated variants explains a modest but significant portion of QT interval variability. Although a PRS may provide insight into the overarching genetic architecture of LQTS, its clinical

utility remains uncertain, given that no established thresholds exist to guide diagnosis or risk stratification.[30,31] Further studies are still needed to determine the exact role of a patient's PRS in management and how it may integrate with the current standard of care.

In a recent study published by Shimamoto and colleagues[17] (2024), the prevalence of genotype-negative patients was reported to be significantly higher in Japanese and Italian cohorts than in ours, with rates of 12% and 20%, compared with our 1.4%. This discrepancy could be attributed to differences in genetic evaluation but mostly in different genetic backgrounds across populations. Their cohort primarily comprised individuals of Asian and European descent, whereas ours includes a predominantly American patient population. Previous studies already proved that ethnicity affects the types and frequencies of genetic variants in LQTS, suggesting that genetic testing and interpretation should be adapted to improve accuracy across diverse populations.[18,19,32] In addition, referral biases and the limited inclusion of family members in our cohort may contribute to the observed differences, because these factors can affect the detection rate of genotype-negative cases.

As a quaternary referral center specializing in inherited arrhythmias, our institution receives a high volume of complex and high-risk cases, leading to an inherent referral bias. In addition, all patients initially classified as genotype-negative LQTS in general clinical practice have undergone rigorous reevaluation at our center. This process refines our genotype-negative cohort with individuals with a more definitive and, as a result, severe phenotype, distinguishing them from those in less specialized settings, which may include a broader spectrum of cases with milder disease.

Furthermore, the relationship between LQTS and athletic participation remains complex, requiring careful differentiation between physiological adaptations and pathologic QT prolongation.[33] Although recent studies support a more individualized approach to allow most athletes with LQTS to safely participate in sports under appropriate medical management, distinguishing true congenital LQTS from exercise-induced repolarization changes remains challenging. Recently, Dagradi and colleagues[34] demonstrated that intensive training can lead to transient QT prolongation that mimics congenital LQTS but often normalizes after a period of detraining, suggesting an acquired, adaptive response to exercise that we refer to as QT remodeling rather than genetic origin. In our cohort, 10 of 26 genotype-negative patients (38%) were considered athletes at the time of diagnosis. However, in contrast to the findings from Dagradi and colleagues,[34] thorough evaluation confirmed that their QT prolongation persisted even after deconditioning or was associated with abnormal stress tests, cardiac events, and ECG abnormalities such as T-wave notching, all features inconsistent with this component of the "athlete's heart." These findings highlight the importance of comprehensive clinical assessment beyond genetic testing to accurately distinguish true LQTS from exercise-induced changes.

It must be recognized that, in our study, such rigorous evaluation and exclusion of borderline cases have resulted in a small cohort of patients with an ostensibly malignant phenotype. Nonetheless, clinical management of genotype-negative LQTS should be dictated by phenotype rather than simply the absence of a genetic diagnosis. Risk stratification must remain grounded in established clinical markers, including QTc duration, symptom burden, and arrhythmic risk factors, rather than a blanket assumption of high risk.[5] Standardized protocols emphasizing phenotype-driven management and careful reassessment of suspected cases remain essential to ensure appropriate therapeutic decisions and avoid overaggressive treatment in all patients with LQTS where no definitive mutation is identified.[10,24]

Recent investigations have begun to assess the phenotype of genotype-negative patients with LQTS, addressing previous gaps in understanding their clinical presentation. Our findings challenge the notion that genotype-negative patients may represent a milder form of LQTS or that a diagnosis of LQTS can be excluded by a negative genetic test alone. However, for a diagnosis of LQTS to persist after a negative genetic test, a clear clinical phenotype must be evident. In our cohort, more than half of the genotype-negative patients experienced significant cardiac events, including syncope, TdP, VT, and SCA, with most being index cases. This underscores the importance of vigilant clinical assessment and management of genotype-negative patients. Consideration of interventions such as ICDs and LCSD is essential to mitigate the risk of adverse outcomes. Clinicians must remain vigilant in assessing and managing this population to ensure appropriate treatment and follow-up, emphasizing the need for ongoing monitoring and comprehensive care.

Limitations

This study faced some inherent limitations. Both referral and selection bias of our center as a quaternary center for evaluation of LQTS likely influenced the prevalence and phenotype of this remnant cohort of true phenotype-positive LQTS who have remained genetically elusive (ie, genotype-negative LQTS), given that patients evaluated in this setting are possibly more complex and on top of that undergo rigorous phenotype reassessment, leading to the higher exclusion rate among borderline or misdiagnosed cases as previously discussed.

In this retrospective cohort study, comprehensive NGS, including deep intronic variant analysis, was not performed in all patients but only in selected cases as part of research protocols. Despite attempts to include all patients, this was not always possible owing to patient preference or loss to follow-up, low likelihood of identifying a genetic cause after previous expanded genetic panels, and cost-related barriers. As such, considering a 35% genotype-positive rate among those who did undergo NGS, this should be considered in the overall genotype-negative rate in this cohort.

Furthermore, reclassification of variants and the adjudication of disputed genes remain dependent on the expertise of the genetic cardiologist and access to genetic counseling. These factors underscore the challenges in diagnosing and managing genotype-negative LQTS and highlight the need for continued advancements in genetic testing, genetic reevaluation and retesting if needed, and standardized variant interpretation. In addition, although all cases were evaluated meticulously, the impact of potential confounders such as diabetes and athletic status on the phenotype remains uncertain. These influences require further investigation not only in larger and more diverse clinical cohorts but also at the translational and cellular levels to elucidate their potential role in modifying electrophysiological properties and arrhythmic risk.

Conclusion

Genotype-negative LQTS accounts for < 2% of our cohort of LQTS, substantially lower than previous estimates. Our study highlights the challenges and complexities in diagnosing and managing genotype-negative patients with LQTS. Comprehensive clinical assessment and advanced genetic testing are both critical for accurate diagnosis and effective management, underscoring the need for ongoing research and vigilance in clinical practice.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2025.05.053.

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