HeartRhythm

The Official Journal of the Heart Rhythm Society, The Cardiac Electrophysiology Society, and The Pediatric & Congenital Electrophysiology Society

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Prevalence, spectrum, and outcomes in patients with nonpenetrant long QT syndrome

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ABSTARCT

BACKGROUND Congenital long QT syndrome (LQTS) is characterized by prolongation of the QT interval and risk of syncope/seizures, sudden cardiac arrest, and sudden cardiac death. Despite being genotype positive, some patients have nonpenetrant LQTS, defined as the absence of any objective electrocardiographic (ECG)/cardiac evidence for abnormal cardiac repolarization.

OBJECTIVE This study aimed to determine the prevalence of nonpenetrant LQTS type 1 (LQT1) and LQTS type 2 (LQT2), assess penetrance over time, and evaluate clinical management and outcomes at a single specialty center.

METHODS A retrospective review was performed on patients with LQT1 or LQT2 to identify those with "nonpenetrant LQTS," defined as asymptomatic status plus nondiagnostic heart rate–corrected QT interval at baseline ECG and absence of maladaptive exercise stress test. Demographics, ECG phenotype, symptomatic status, and therapy over at least 12 months of follow-up were abstracted for each patient.

RESULTS Between July 1, 2000, and May 1, 2024, 57 of 719 asymptomatic patients (8%; 37% female; mean age at first evaluation 17 ± 15 years) with either LQT1 (37%) or LQT2 (63%) met the inclusion criteria for nonpenetrant LQTS. Mean heart rate–corrected QT interval at first evaluation was 434 ± 18 ms. Over 7 ± 6 years of follow-up, all patients remained asymptomatic; 37 (65%) remained ECG nonpenetrant. Most recently, 32 (56%) were on beta-blocker therapy and 25 (44%) were monitored with intentional nontherapy.

CONCLUSION The estimated prevalence of nonpenetrant LQT1 and LQT2 is approximately 8%. Two-thirds of patients remained ECG nonpenetrant, and all remained phenotypically nonexpressive during follow-up. Patients with nonpenetrant LQT1 or LQT2 may be treated with an intentional nontherapy strategy devoid of drugs, denervation, or devices.

KEYWORDS Arrhythmia; Concealed; Long QT syndrome; Nonpenetrant; Sudden cardiac death

(Heart Rhythm 2026;23:e436–e441)

Long QT syndrome (LQTS) is a heritable arrhythmogenic disorder caused by abnormalities in the repolarization phase of the cardiac action potential. Approximately 80%–90% of cases are caused by pathogenic variants in 3 different ion channel encoding genes, *KCNQ1*, *KCNH2*, and *SCN5A*, which are associated with the LQTS subtypes LQTS type 1 (LQT1), LQTS type 2 (LQT2), and LQTS type 3 (LQT3), respectively.[1–3] Present in approximately 1 in 2000 Caucasian individuals, LQTS can manifest as syncope, seizure, sudden cardiac arrest (SCA), and, in some tragic cases, sudden cardiac death.[4] However, when properly treated, the risk of cardiac events is extremely low.[5]

Approximately 40% of cases are considered concealed LQTS presenting with a nondiagnostic heart rate–corrected QT interval (QTc) at baseline ECG, defined at the 99th percentile as 480 ms for adult women, 470 ms for adult

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https://doi.org/10.1016/j.hrthm.2025.11.040
1547-5271/$-see front matter

men, and 460 ms for males and females during the prepubertal phase.[6–8] An important diagnostic tool, exercise stress testing can unmask initially nondiagnostic LQTS by revealing genotype-specific, maladaptive repolarization responses in patients with LQT1 or LQT2.[9,10] Approximately 70% of initially concealed patients are revealed to be electrocardiographically (ECG) penetrant after demonstration of maladaptive QT response on exercise stress testing.[8,11] In addition, a maladaptive QTc response during the stress test is used in the calculation of the Schwartz score for the diagnosis of LQTS.[8–10,12,13] Nonetheless, after both a resting ECG and an exercise stress test evaluation, a subset of patients with either LQT1 or LQT2 remain nonpenetrant with a nondiagnostic ECG and normal stress test and are asymptomatic at the time of first evaluation. Herein, we set out to identify the prevalence of nonpenetrant LQTS and evaluate the management, outcomes, and conversion rates in this group of patients.

Methods

A retrospective analysis of 1372 patients with either LQT1 or LQT2 was performed to identify the cohort of patients considered nonpenetrant at the first visit to Mayo Clinic's Windland Smith Rice Genetic Heart Rhythm Clinic between July 1, 2000, and May 1, 2024. Although there may be a small number of patients at other institutions who were initially diagnosed as nonpenetrant and subsequently converted to penetrant status before arriving at Mayo Clinic, these patients were not included in our cohort in an effort to ensure that guideline-directed therapy, nonpenetrant diagnosis criteria, and overall follow-up were consistent in our analysis of patients with nonpenetrant LQTS.

Of note, unlike LQT1 and LQT2, LQT3 cannot be unmasked by adrenergic stimulation through exercise stress testing, which makes it difficult to label a patient with LQT3 as nonpenetrant. Therefore, LQT3 was excluded from this study. Nonpenetrance was defined as patients with a (likely) pathogenic KCNQ1 (LQT1) or KCNH2 (LQT2) disease-causing variant who were asymptomatic (no history of cardiac-induced syncope/seizure or SCA) at evaluation, had a nondiagnostic resting diagnostic ECG, and did not demonstrate evidence of a maladaptive QT response to exercise on treadmill stress testing. Of note, if we implemented beta-blocker (BB) therapy as part of a patient's LQTS-directed treatment program, we never transiently pause or wash out their BB prior to stress testing. The definitions and important distinctions among asymptomatic, concealed, and nonpenetrant LQTS are presented in Figure 1. For further study of asymptomatic patients with LQTS, including both penetrant and nonpenetrant patients, please see our previous 2025 study.[14] For the purposes of this study, the resting QTc was considered nondiagnostic if QTc was less than the 99th percentile for age and sex, defined as ≤480 ms for adult females, ≤470 ms for adult males, and ≤460 ms for males or females younger than 13 years. These values have been widely used in clinical practice and research and are reflected in current guidelines of the European Society of Cardiology, which defines a diagnostic prolonged QTc of >480 ms, and were adopted in the 2023 guidelines from the Canadian Cardiovascular Society.[15–17] It is worth noting that other recent work identified slightly different values for the 99th percentile. In 2018, Vink et al[18] defined the 99th percentile as being ≤460 ms for adult females, ≤450 ms for adult males, and ≤480 ms for children younger than 13 years. Had we used these cutoff values to select our concealed cohort, 57 children would have been added, whereas 80 women and 33 men would have been excluded, totaling 352 concealed patients rather than 408. Using these alternate values would have resulted in 2 male patients being excluded from our final nonpenetrant cohort, both of whom remained nonpenetrant during follow-up. Therefore, the use of alternate 99th percentile QTc values may have slightly altered the cohort selection but would not have altered the final conclusions of our study.

The exercise stress test was considered to show a maladaptive QTc response suggestive of LQT1 if the QTc exceeded 480 ms at peak exercise or 3 or 5 minutes of recovery. For LQT2, a $\triangle$QTc, defined as the absolute difference in QTc measurements at 1 and 5 minutes of recovery, was considered maladaptive if greater than 30 ms.[8] Any abnormal T-wave morphology such as the LQT2-suggested notched T waves on a baseline ECG, stress test, or Holter monitor if available disqualified a patient from nonpenetrant status. Demographics, clinical and electrophysiological phenotype, symptomatic status, and therapy over the course of at least 12 months of follow-up were abstracted for each patient. Guideline-directed therapy included pharmacologic therapy, left-sided cardiac denervation, or an implantable cardioverter-defibrillator. Intentional nontherapy (INT) was defined as preventive measures only such as avoidance of QT-prolonging medications, fever reduction when present, and maintenance of proper hydration and electrolyte balance accompanied by continued clinical follow-up. The online genetic and structural protein database *UniProt* was used to evaluate the location and frequency of variants in the *KCNQ1*-encoded Kv7.1 channel (protein ID: P51787) and the *KCNH2*-encoded Kv11.1 channel (protein ID: Q12809).[19]

Abbreviations

BB: beta-blocker

ECG: electrocardiogram

INT: intentional nontherapy

LQTS: long QT syndrome

QTc: heart rate–corrected QT interval

SCA: sudden cardiac arrest

Results

Overall, 1007 of 1372 patients with either LQT1 or LQT2 (73%) were asymptomatic at the time of their first Mayo Clinic evaluation. Of these, 719 patients had at least 1 ECG, 1 stress test, and 1 follow-up visit available to permit inclusion in this study. After careful review, 408 patients (57%) were classified as ECG concealed with a nondiagnostic ECG (Figure 2). Of these, 323 (79%) were identified via cascade genetic testing after a family member was diagnosed as having LQTS, whereas 85 patients (21%) were the index case themselves, discovered incidentally via routine screening or testing after other medical concerns. After exercise stress testing, 351 of

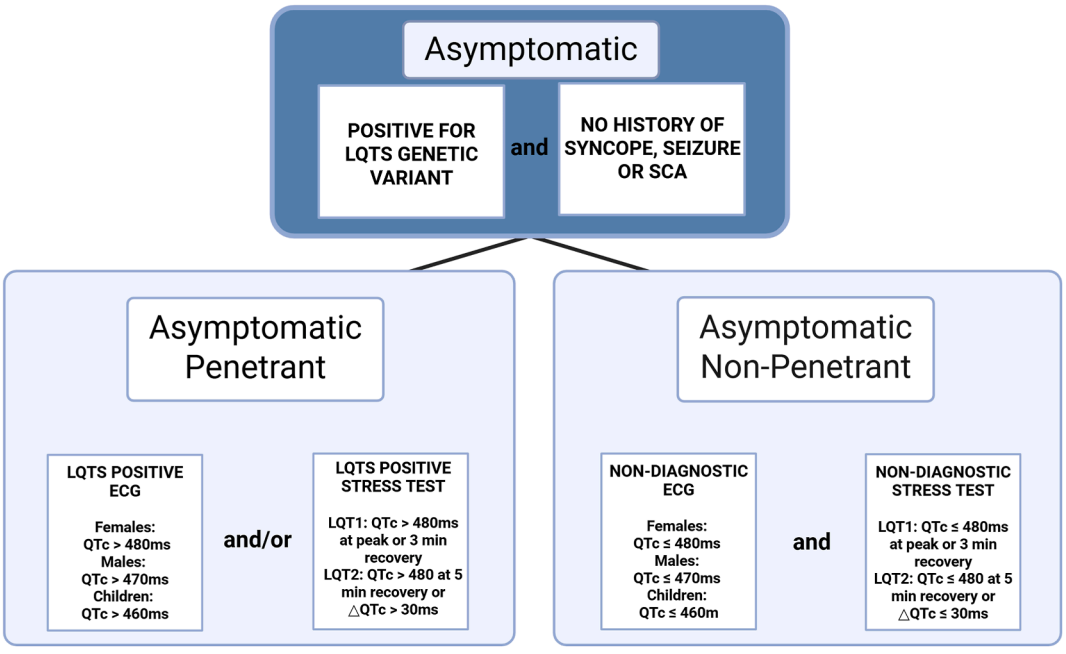

Figure 1
Inclusion criteria for nonpenetrant LQTS. Diagram showing definitions and inclusion criteria for concealed and nonpenetrant LQTS. True nonpenetrance is defined as nondiagnostic ECG and exercise stress test, whereas concealed LQTS requires only a nondiagnostic ECG. ECG and stress test values based on the first visit to Mayo Clinic or the first ECG reviewed and confirmed by Mayo Clinic heart rhythm specialists. ECG = electrocardiogram; LQTS = long QT syndrome; QTc = heart rate–corrected QT interval; SCA = sudden cardiac arrest.

408 patients (86%; 216 LQT1 [62%], 135 LQT2 [38%]) were unmasked after evidence of a maladaptive QTc response despite a resting QTc below the 99th percentile values in health.

The remaining 57 patients (14%) were considered nonpenetrant, meeting all inclusion criteria as described earlier (Figure 2). As such, 8% of patients with LQT1 and LQT2 (57 of 719) were considered nonpenetrant, 21 female (37%) had a mean age at diagnosis of 17 ± 15 years, and the mean QTc at first Mayo Clinic evaluation was 434 ± 18 ms. Mean follow-up was 7 ± 6 years. 21 patients were LQT1 (37%) and 36 were LQT2 (63%) (Table 1). During the diagnostic exercise stress test at Mayo Clinic, peak exercise QTc for patients with LQT1 was 430 ± 24 and recovery QTc at the third minute was 437 ± 27 ms. For patients with LQT2, QTc at the fifth minute of recovery was 437 ± 21 ms and △QTc was 14 ± 10 ms.

As shown in Table 1, most of initially nonpenetrant patients (52 of 57 [91%]) were, as expected, not the index case but relatives of LQTS probands that were identified subsequently by cascade genetic testing. Among the index cases in these families, 23 (44%) presented with SCA or sudden cardiac death, 16 (31%) had seizure/syncope, and 13 (25%) were asymptomatic but were discovered after an incidental ECG finding of idiopathic QT prolongation. In total, 37 of 57 initially nonpenetrant patients (65%) had at least 1 relative with LQTS-related symptoms. There was no significant difference in phenotype status of probands or symptom status of LQTS-positive relatives between patients who remained nonpenetrant through follow-up and those who converted to penetrant status.

Variant evaluation showed 41 unique variants were represented in these 57 patients, 13 in *KCNQ1* (LQT1) and 28 in *KCNH2* (LQT2). The specific variants, location, and totals are presented in Supplemental Table 1. More than half of variants (65%) were located in the cytoplasmic regions of the channel and 23% in the transmembrane region of the ion channel. The specific p.Ile235Asn-KCNQ1 variant was found in 29% of 57 nonpenetrant patients with LQTS and all patients with LQT1 who converted to penetrant. In the LQT2 subgroup, 11% of patients had the p.Arg176Trp-KCNH2 variant. Close review of the family histories of the initially nonpenetrant patients revealed that 4 of the variants in *KCNQ1* and 6 in *KCNH2* were observed exclusively in asymptomatic LQTS individuals and were not seen in any symptomatic relatives. The remaining 31 variants, including both of the overrepresented variants, were present in at least 1 symptomatic patient. The association of each variant with symptomatic or asymptomatic status in the LQTS family members of these initially nonpenetrant patients is presented in Supplemental Table 1.

Initial treatment consisted of BB monotherapy for 42 patients (74%) and INT for 15 (26%) (Table 1). During follow-up, several patients who had previously elected to be on BBs for extra protection switched to INT because of unwanted BB side effects.

During follow-up, all 57 initially nonpenetrant patients remained asymptomatic with no instances of a sentinel LQTS-related breakthrough cardiac event. In total, 20 of 57 patients (35%) converted to ECG penetrance. The mean age for penetrance to emerge was 21 ± 13 years.

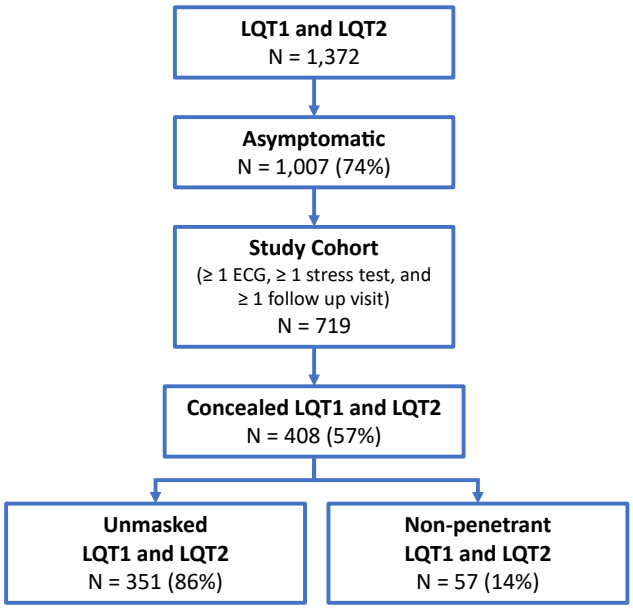

Figure 2
Selection of study cohort and unmasking of LQT1 and LQT2. Flowchart showing study cohort identification with eventual cohorts identified as those unmasked by exercise stress testing (left) and nonpenetrant LQTS (right). ECG = electrocardiogram; LQT1 = LQTS type 1; LQT2 = LQTS type 2; LQTS = long QT syndrome.

Table 1 Demographics of patients with electrocardiographically nonpenetrant LQTS

Clinical characteristics	Total	Nonpenetrant at follow-up	Converted to penetrant LQTS during follow-up
Total (n)	57	37 (65)	20 (35)
Women, n (%)	21 (37)	11 (30)	10 (50)
Age at diagnosis (mean y ± SD)	17 ± 15	18 ± 17	15 ± 12
Age at penetrance (mean y ± SD)	n/a	n/a	21 ± 13
Mean resting QTc (ms ± SD)	434 ± 18	432 ± 20	437 ± 15
LQTS subtypes, n (%)			
LQT1	21 (37)	18 (49)	3 (15)
LQT2	36 (63)	19 (51)	17 (85)
Proband, n (%)	5 (9)	3 (8)	2 (10)
Related to affected family member, n (%)	52 (91)	34 (92)	18 (85)
Initial therapy, n (%)			
BB	42 (74)	30 (81)	12 (40)
INT	15 (26)	7 (19)	8 (60)
Therapy during follow-up, n (%)			
BB	32 (56)	22 (59)	10 (50)
INT	25 (44)	15 (41)	10 (50)

BB = beta-blocker; INT = intentional nontherapy; LQT1 = LQTS type 1; LQT2 = LQTS type 2; LQTS = long QT syndrome; n/a = not applicable; QTc = heart rate–corrected QT interval; SD = standard deviation.

Mean time to conversion was 6 ± 5 years after initial diagnosis with 4 of 20 patients (25%), all female, converting to penetrant disease during puberty (defined as 13–17 years). Of converted patients, 11 (55%) showed genotype-specific penetrance on exercise stress test, 6 (30%) exhibited a resting QTc beyond the aforementioned thresholds on their follow-up ECG, and 3 (15%) showed both an LQTS-positive ECG and exercise stress test. Most patients (85%) who converted were relatives of index cases. ECG conversion was most common in patients with LQT2 (16; 80%) (Table 1). Conversion did not alter management for most patients (18 of 20 [90%]). In the most recent evaluation, 10 converted patients (50%) were on BB monotherapy and 10 (50%) on INT (Table 1); 2 patients (10%) had opted to remove a daily BB in favor of the INT strategy owing to BB intolerance.

Discussion

Outcomes and proper identification

Continued knowledge growth and increased uptake of variant-specific cascade genetic testing will continue to result in more individuals being diagnosed as having concealed or ECG nonpenetrant LQTS. Such a diagnosis, defined as phenotypically mild according to Schwartz score criteria, raises the question of the most appropriate treatment strategy for these patients. Herein, we studied the prevalence and management of nonpenetrant LQT1 and LQT2 and described the clinical outcomes of these patients. Although any LQTS diagnosis is never a 0 risk of sudden cardiac events, our data indicate that, with close monitoring and proper treatment, the chance of a life-threatening arrhythmia in our nonpenetrant patient population is extremely low, with all 57 initially diagnosed, nonpenetrant patients remaining completely symptom free. These results are even more positive than the low risk previously described in all asymptomatic patients. Furthermore, patients who are genotype−/phenotype+ (the clinical opposite of our current cohort) have a much higher risk of cardiac events with all patients shown to have at least 1 cardiac event, typically prior to diagnosis.[20]

In addition, our data highlight other important clinical and genetic factors to consider when diagnosing and treating this nonpenetrant population. Previous studies have demonstrated that approximately 30%–40% of patients with LQTS present as concealed with a nondiagnostic QTc on their resting ECG.[21,22] With such a substantial number of genotype-positive patients presenting with nondiagnostic ECG results (concealed LQTS), we must look a bit beyond diagnostic resting QTc values. Thus, in many patients with LQTS, ECG penetrance must be unmasked through exercise stress testing expressed as a maladaptive QTc response for patients with LQT1 and LQT2, particularly during the recovery phase.[6,23] In our cohort, close to 90% of patients with previously named "non-diagnostic QT interval LQTS" had maladaptive QTc responses on exercise stress test, emphasizing the key role for stress testing in the proper evaluation and diagnosis of LQT1 and LQT2. Patients who do not receive a stress test as part of their risk assessment workup may be misclassified in penetrance and thereby risk status.[8,11,12] In 2011, Goldenberg et al[24] highlighted the prevalence of concealed LQTS and found

that patients with genotype-positive LQTS with a nondiagnostic ECG made up at least 25% of the at-risk LQTS population carrying a 4% risk of LQTS-associated cardiac events. Starting with a cohort of 408 patients with a normal resting QTc LQTS (ie, concealed LQTS), our current study focused on 57 patients with nonpenetrant LQTS (which required both a nondiagnostic ECG and a normal exercise stress test for diagnosis). Importantly, these patients with nonpenetrant LQTS had a significantly lower risk of cardiac events than patients with concealed LQTS. Thus, every effort should be made to ensure that all eligible patients complete stress testing before completing the diagnosis of concealed vs nonpenetrant. However, as seen in our cohort, there will always be a subset of patients who are unable to complete stress testing for various reasons such as physical immobility, unrelated health complications, or, most commonly, being younger than 6 years. The need for alternative testing in those who cannot undergo stress testing may eventually be met via other means of evaluation. For example, QTc values derived from Holter monitor recordings may be a potential surrogate for exercise stress testing in certain low-risk individuals.[25] However, until such a testing substitute is proven more reliable across multiple groups, guidelines indicate that patients who are unable to complete exercise stress testing are therefore unable to truly be classified as fully nonpenetrant and therefore will remain in a higher risk bracket even if all other clinical classifications indicate potential nonpenetrance. After careful evaluation and diagnostic testing, 8% of our patients were classified as truly nonpenetrant, with approximately a third of patients showing evidence for ECG penetrance subsequently.

Suggested treatment for nonpenetrant patients

Given that the risk of cardiac events is estimated to be low, treatment selection for nonpenetrant patients should incorporate the use of precision medicine, careful risk stratification, and shared decision making. Although BBs such as nadolol or propranolol are the cornerstone treatment for LQTS, they are not free of side effects. BB-induced reduction in quality of life can influence the provider's decision to prescribe them and the patient's ability to be treatment compliant. This often leads to a desire to stop BB use over time.[26] Alternatively, previous studies show that, when patients are properly diagnosed and risk stratified, INT can be an excellent choice for specific low-risk asymptomatic patients with LQTS. The general criteria required for consideration of INT are outlined in our 2020 paper and include asymptomatic status, diagnosis at an older age, and a resting QTc of <470 ms.[27] As such, per recommendation guidelines, most nonpenetrant patients were started on BB therapy, but a switch to INT during follow-up was observed for a subset of patients. Although this means that active treatment is not initiated, patients remain under routine monitoring and regular, periodic clinical follow-up, even with a low probability of penetrance, and are urged to follow the simple QT-preventive measures to minimize even further the risk of QT-associated events. This treatment recommendation slightly differs from our observations in our asymptomatic cohort where we found that some patients (24%) qualified for INT and a large proportion of patients (66%) were still recommended for continued BB therapy.[14] Frequency of follow-up evaluation and risk reassessment for all initially nonpenetrant patients typically ranges from every 1 to 5 years and depends on multiple factors including age, sex, patient/family anxiety, current life circumstances or transitions, and presence or absence of other health concerns. At follow-up, the balance between BB and INT in patients who converted to penetrant status was evenly split, as presented in Table 1. A slightly larger percentage of converted patients (50%) are on INT than those who remained nonpenetrant (41%), a difference attributed to patients' preference for INT owing to BB intolerance. As a note, although the diagnosis of nonpenetrance encouraged some patients to switch to INT, others, even those who remained nonpenetrant during follow-up, personally felt more comfortable with a BB-based treatment plan. This is presented in Table 1, which shows both patients on INT and those on BB during follow-up. This highlights the reality that although a patient may qualify for INT, not every shared decision-making outcome will result in the patient selecting INT. In fact, BB remains an important treatment option for our nonpenetrant patients.

Variant location and penetrance

In addition to the phenotypic presentation, genotype plays a critical role in guiding treatment decisions for patients with LQTS.[28] Interestingly, 7 of 21 of our patients with initially nonpenetrant LQT1 (33%) had transmembrane domain variants that are known to alter protein kinase A (PKA) phosphorylation in the ion channel, none of which were near the main phosphorylation site of KCNQ1, p.Ser27.[29] Notably, every patient with LQT1 who converted to penetrant status during follow-up shared the transmembrane variant: p.Ile235Asn-KCNQ1. A 2014 study of a concealed LQT1 family found that KCNQ1: p.Ile235Asn limited PKA phosphorylation and induced conformational changes in the ion channel.[21] Another patient with LQT1 also had a transmembrane variant known to affect PKA phosphorylation of the ion channel, KCNQ1; p.Gly269Ser.[30,31] Other studies have shown that transmembrane variants in Kv7.1 have unique properties and various levels of electrophysiological dysfunction.[17,19,20]

For LQT2, variants located in the pore region of KCNH2 are usually more phenotypic than those in the transmembrane domains owing to greater disruption of the rapid component of the delayed rectifier potassium channel current.[32,33] In the LQT2 group, only 2 of 34 patients (6%) had a variant in the pore region, whereas the remaining 32 of 34 patients (94%) had variants outside of the pore region of KCNH2.

Limitations

All patient data described were derived from a tertiary LQTS specialty center. Patients seen at other centers may have slightly different outcomes. In addition, the use of INT therapy is continuously evolving, and all patients including those on INT are regularly evaluated for potential treatment changes that may be needed.

Conclusion

In our study, the estimated prevalence of ECG nonpenetrance in LQT1 and LQT2 is <10%. During follow-up, most patients (65%) remain nonpenetrant, never showing any evidence of ECG- or stress test–positive LQTS with the remaining patients converting to an ECG-detectable substrate. Patients with nonpenetrant LQT1 and LQT2 may be treated with an INT strategy devoid of drugs, denervation, or devices.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2025.11.040.

Funding Sources: This work was supported by the Mayo Clinic Windland Smith Rice Comprehensive Sudden Cardiac Death Program (M.J.A.) and the Mayo Clinic Center for Translational Science Activities through grant number UL1TR002377 from the National Center for Advancing Translational Sciences, a component of the National Institutes of Health. E.R. was also supported by the National Institutes of Health Training Grant T32 5T32GM145408 from the National Institute of General Medical Sciences.

Disclosures: Dr Ackerman is a consultant for Abbott, Boston Scientific, Bristol Myers Squibb, Illumina, Invitae, Medtronic, Tenaya Therapeutics, and UpToDate. M.J.A. and Mayo Clinic have license agreements with AliveCor, Anumana, ARMGO Pharma, Prolaio, Solid Biosciences, and Thryv Therapeutics. However, none of these entities were involved in this study. Other authors declare no conflicts.

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