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Diagnosis of Congenital Long-QT Syndrome

Nathaniel W. Taggart, MD; Carla M. Haglund; David J. Tester, BS; Michael J. Ackerman, MD, PhD

Background—Long-QT syndrome (LQTS) is a potentially lethal cardiac channelopathy that can be mistaken for palpitations, neurocardiogenic syncope, and epilepsy. Because of increased physician and public awareness of warning signs suggestive of LQTS, there is the potential for LQTS to be overdiagnosed. We sought to determine the agreement between the dismissal diagnosis from an LQTS subspecialty clinic and the original referral diagnosis.

Methods and Results—Data from the medical record were compared with data from the outside evaluation for 176 consecutive patients (121 females, median age 16 years, average referral corrected QT interval [QTc] of 481 ms) referred with a diagnosis of LQTS. After evaluation at Mayo Clinic’s LQTS Clinic, patients were categorized as having definite LQTS (D-LQTS), possible LQTS (P-LQTS), or no LQTS (No-LQTS). Seventy-three patients (41%) were categorized as No-LQTS, 56 (32%) as P-LQTS, and only 47 (27%) as D-LQTS. The yield of genetic testing among D-LQTS patients was 78% compared with 34% for P-LQTS and 0% among No-LQTS patients (P<0.0001). The average QTc was greater in either D-LQTS or P-LQTS than in No-LQTS (461 versus 424 ms, P<0.0001). Vasovagal syncope was more common among the No-LQTS subset (28%) than the P-LQTS/D-LQTS group (8%; P=0.04). Determinants for discordance (ie, positive outside diagnosis versus No-LQTS) included overestimation of QTc, diagnosing LQTS on the basis of “borderline” QTc values, and interpretation of a vasovagal fainting episode as an LQTS-precipitated cardiac event.

Conclusions—Diagnostic concordance was present for less than one third of the patients who sought a second opinion. Two of every 5 patients referred with the diagnosis of LQTS departed without such a diagnosis. Miscalculation of the QTc, misinterpretation of the normal distribution of QTc values, and misinterpretation of symptoms appear to be responsible for most of the diagnostic miscues. (Circulation. 2007;115:2613-2620.)

Key Words: long-QT syndrome ■ syncope ■ genetic screening ■ ion channels ■ electrocardiography

Congenital long-QT syndrome (LQTS) affects approximately 1 in 3000 persons, is one of the most common cardiac channelopathies, and is characterized by delayed ventricular repolarization often associated with a prolonged QT interval on a 12-lead surface ECG. Under certain physiological stresses, LQTS may degenerate into its trademark dysrhythmia of torsade de pointes and manifest as syncope, seizures, or sudden death.1–3 In a small proportion of individuals, sudden death is the sentinel event.4 However, LQTS may never show its hallmark feature of QT-interval prolongation, and patients may have a lifelong asymptomatic course.5

Given this phenotypic variability, LQTS continues to pose a significant diagnostic challenge. Despite tremendous advances in our knowledge about LQTS and a general increased awareness of this condition and its potential lethality, the difficulty of recognizing subtle and unusual presentations of this potentially lethal channelopathy continues, which results in tragic misses of an LQTS-affected individual. At the same time, increased awareness of the broad phenotypic variability in LQTS creates the potential for overdiagnosis of LQTS. Although failure to recognize its warning signs can culminate in sudden cardiac death, increased awareness can also lead to overdiagnosis and result in unnecessary and burdensome treatments and interventions.

The diagnosis of LQTS has relied historically on a set of scored clinical criteria known as the Schwartz score.6 Central to the Schwartz score is the calculated heart rate–corrected QT interval (QTc) from the 12-lead ECG. In addition, the score considers findings from both a clinical and family history (Table 1). A Schwartz score equal to or exceeding 4 indicates high probability or definite LQTS (D-LQTS), whereas lower scores are associated with either possible-LQTS (P-LQTS), also called borderline LQTS, or low-probability LQTS.

More recently, additional clinical tests have shown some value in assisting in the diagnosis of inherited LQTS. The

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epinephrine QT stress test, in particular, may be useful in unmasking some types of LQTS, particularly concealed type 1 LQTS (LQT1).6,7 Because of the limited availability of more definitive tests, the ECG remains one of the most important clinical tests in the evaluation of LQTS. In the occasional case (for example, when the QTc is 760 ms), the ECG alone may be sufficient to diagnose LQTS. Likewise, a QTc of 350 ms in an individual with no family history of LQTS essentially excludes LQTS.

However, QTc measurements that fall between these extremes pose a greater diagnostic challenge. Figure 1 shows a distribution of QTc values seen among healthy postpubertal males and females,8 as well as the distribution of QTc values of patients with genetically proven LQTS from Mayo Clinic’s Long QT Syndrome Clinic. Among our genotype-positive patients, the average QTc is 482±57 ms. Considering a QTc of 440 ms as “borderline” creates a substantial overlap zone where differentiating individuals with LQTS from their normal counterparts becomes quite difficult. A significant number of individuals with LQTS have concealed LQTS, with QTc values that cross well into the normal range. In one study, for example, 27% of subjects shown to carry a known LQTS genetic defect had a QTc interval <440 ms.10 These cases of so-called “concealed” LQTS would be missed by relying too heavily on the ECG. On the other hand, many patients could be diagnosed erroneously with congenital LQTS if the diagnosis were rendered principally because of a borderline QTc measurement.

Furthermore, physicians’ ability to accurately measure QTc has been called into question. Viskin and colleagues11 recently published a survey of 902 physicians, each of whom were asked to measure the QTc based on ECGs from 2 adults with LQTS and 2 healthy adults. Here, cardiologists were no more likely to accurately measure the QTc than noncardiologist physicians, and both groups correctly measured the QTc only half the time. Although overestimating the QTc of an individual with LQTS or underestimating the QTc of an individual without LQTS would potentially lead to significant distress in the patient and his or her family,12 errors of this type may result in misdiagnosis. Not diagnosing LQTS in a patient who indeed has the disorder may place that person at risk of sudden death for an otherwise highly treatable condition, whereas incorrectly diagnosing healthy individuals as having LQTS would potentially lead to significant distress in the patient and his or her family.12

Restriction from physical activity and competitive sports can be emotionally devastating to the young athlete. In addition, β-blockers, the mainstay of prophylactic medical therapy for LQTS, may result in significant adverse effects, including decreased energy and depression.

It becomes important, then, that the clinician render the diagnosis of this serious disorder with as much certainty as possible. Given these complex issues, we sought to answer the question: Is LQTS being overdiagnosed?

Methods

Study Cohort and Study Design

In the present institutional review board–approved study, we conducted a retrospective chart review of 509 consecutive patients seen

TABLE 1. LQTS Clinical Probability Score Card

<table>
<thead>
<tr>
<th>Finding</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td></td>
</tr>
<tr>
<td>Clinical history of syncope*</td>
<td>1</td>
</tr>
<tr>
<td>Without stress</td>
<td>2</td>
</tr>
<tr>
<td>With stress</td>
<td>3</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td>0.5</td>
</tr>
<tr>
<td>Family history of LQTS†</td>
<td>1</td>
</tr>
<tr>
<td>Unexplained sudden death in a first-degree family member &lt;30 y old†</td>
<td>0.5</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
</tr>
<tr>
<td>Corrected QT interval (QTc by Bazett's formula)</td>
<td></td>
</tr>
<tr>
<td>450 ms (in males)</td>
<td>1</td>
</tr>
<tr>
<td>460–470 ms</td>
<td>2</td>
</tr>
<tr>
<td>&gt;480 ms</td>
<td>3</td>
</tr>
<tr>
<td>Torsade de pointes*</td>
<td>2</td>
</tr>
<tr>
<td>T-wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>&gt;3 Leads with notched T waves</td>
<td>1</td>
</tr>
<tr>
<td>Bradycardia (&lt;second percentile for age)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

A score <1 = low probability; 1 to <4 = intermediate probability; ≥4 = high probability.

*Syncope and torsade de pointes are mutually exclusive.

†Cannot count the same family member for both criteria.

Adapted from Schwartz et al6 with permission from the American Heart Association. Copyright 1993.
at the Mayo Clinic Long QT Syndrome Clinic in Rochester, Minn, from May 1999 to October 2005. To be included in the present study, patients must have received previously a formal diagnosis of LQTS by an adult or pediatric cardiologist. Patients were excluded from the study if they had been seen previously at the Mayo LQTs clinic, had previously undergone genetic testing for LQTS, or were referred for evaluation without a formal diagnosis of LQTS. Of the 509 charts reviewed, 176 patients satisfied the criteria for inclusion in the present study.

A detailed review of these 176 patients’ records was then conducted. Data were abstracted from the electronic medical record and paper charts by a single investigator (NWT). Results from genetic testing were collected separately (CMH). For 161 patients, the QTc was calculated manually by the attending physician (MJA) at the time of the initial Mayo evaluation, and both the computer and manual calculated QTc were documented in the medical record. The QTc was calculated manually by averaging the QTc from either the rhythm strip for limb lead II or precordial lead V5. For the remaining 15 patients, the ECGs from their original visits were obtained, and the QTc was calculated by an investigator (NWT) at the time of the study. Bazet’s formula, in which the QT interval is divided by the square root of the R-R interval, was used to calculate the QTc.

Schwartz scores (Table 1) were calculated for patients based on their outside records (outside Schwartz score) and based on data obtained at their second-opinion Mayo evaluation (Mayo Schwartz score). In both cases, the attending clinician’s interpretation of the QTc, rather than the computer measurement, was used when the Schwartz score was calculated. If QTc measurements from >1 previous ECG were referred to in the electronic record, the longest QTc was used to tabulate a Schwartz score. Because the QTc is a key component in the derived Schwartz score, 45 subjects did not have a documented QTc from an outside ECG and were therefore excluded from calculation of the average outside Schwartz score for the cohort.

After clinical evaluation, patients were diagnosed by a single LQTS specialist (MJA) according to their perceived risk of having LQTS. This diagnosis was expressed in the clinical notes at the time of the referral evaluation and was based on symptoms, family history, ECG findings, and results from exercise or epinephrine stress testing in some cases. Schwartz scores were considered in diagnosing an individual as having definite, possible, or no evidence of LQTS, but the derived score itself was not considered definitive of the diagnosis. For individuals with a first-degree relative with genetically proven LQTS, baseline risk of having LQTS was considered to be 50%. For the purpose of the present study, patients were assigned to 1 of 3 classifications: insufficient evidence to warrant the diagnosis of LQTS (No-LQTS), possible or “borderline” LQTS (P-LQTS), or definite LQTS (D-LQTS). Assignment to one of these clinical diagnoses preceded LQTS genetic testing and was therefore independent of any genetic test results.

After evaluation in the Long QT Syndrome Clinic, some patients underwent genetic testing to identify an LQTS-causing gene mutation. The decision to undergo genetic testing was ultimately determined by the patients and family, although individuals believed to be at high risk of LQTS were encouraged to undergo genetic testing at the time of their second-opinion evaluation. LQTS genetic testing was performed with either denaturing high-performance liquid chromatography or direct DNA sequencing in either Mayo Clinic’s Sudden Death Genomics Laboratory or with the commercially available LQTS-D (D-LQTS). Assignment to one of these clinical diagnoses preceded LQTS genetic testing and was therefore independent of any genetic test results.

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Table 2 summarizes the demographics of the 176 patients who were previously diagnosed elsewhere with LQTS and who met the study’s outlined inclusion criteria. Females outnumbered males by more than 2 to 1. The range of age at time of referral was newborn to 73 years. The mean age was 22 years, with a median age of 16 years. This cohort included 15 sets of first-degree relatives, totaling 34 individuals. One hundred twenty-eight patients (73%) described a history of potential cardiac symptoms. One hundred fourteen patients (65%) had a history of syncope or presyncope, 15 (8%) had a history of palpitations, and 8 (4%) had a history of chest pain. Only 9 patients (5%) had a personal history of aborted cardiac arrest. With regard to family history, 18 individuals (10%) reported a history of a parent, sibling, or offspring (ie, first-degree relative) who was diagnosed with LQTS. Nine (5%) had a family history of sudden death before the age of 30 years in a first-degree relative.

Nearly three fourths of patients had been recommended to receive or had initiated specific intervention for LQTS. Almost two thirds of patients had begun β-blocker therapy, and 17 patients (~10%) had been implanted already with an implantable cardiac defibrillator. In addition, 8% were advised to avoid strenuous physical activity, with no other intervention.

### Table 2. Demographics*

| Age at referral, y, mean±SD | 22±14 |
| Sex, M/F | 55/121 |
| Average referral QTc, ms, mean±SD | 481±54 |
| Average outside Schwartz score | 2.7 |
| Family history, % | |
| LQTS in first-degree relative | 10 |
| Sudden unexplained death | 5 |
| Symptoms, % | |
| Syncope/presyncope | 65 |
| Vasovagal | 21 |
| Other | 44 |
| Palpitations | 8 |
| Chest pain | 4 |
| Aborted cardiac arrest | 5 |
| Treatment, % | |
| Activity restriction alone | 8 |
| β-Blocker | 61 |
| ICD | 10 |

*N=176.

Variables that were statistically significant in univariate models were included in a multivariate logistic regression model to determine whether they remained significant after adjustment for potential confounders. All analyses were conducted with JMP version 5.0 (SAS Institute, Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Results

**Population Characteristics**

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### Statistical Analysis

Average QTc readings reported by referring physicians were compared with readings of the same ECGs by the Mayo physicians using paired t tests. Characteristics of patients with either P-LQTS or D-LQTS were compared with characteristics of patients classified as No-LQTS with univariate logistic regression. Probability values of <0.05 were considered statistically significant.
Clinical Evaluation and Diagnosis

After their second-opinion evaluation, only 27% of patients were dismissed as having D-LQTS, 32% were diagnosed with P-LQTS, and 41% were dismissed with No-LQTS ($P<0.0001$; Figure 2). Most of the subset classified here as No-LQTS were dismissed, in fact, as normal. Only 4 of these patients were diagnosed with other significant conditions, which included type 1 Andersen-Tawil syndrome, dilated cardiomyopathy, drug-induced QT prolongation, and pheochromocytoma. In addition, 4 individuals clinically designated as P-LQTS were subsequently found to have $RyR2$-gene–positive catecholaminergic polymorphic ventricular tachycardia. These 8 patients were excluded from further statistical analysis.

Next, we sought to elucidate the factors that contributed to the substantial discordance between the initial diagnosis and the second-opinion diagnosis. We found that the most common explanation involved errors with respect to the signature ECG feature of LQTS, namely, the QTc. During their primary evaluation, the average reported QTc was 481 ± 54 ms. The average outside Schwartz score of those patients with sufficient clinical data to calculate a score ($n=131$) was 2.7. In contrast, the mean Mayo-derived Schwartz score for these patients was significantly less at 1.5 ($P<0.001$). The average Mayo-derived Schwartz score of all referred patients was 1.8.

During their Mayo LQTS Clinic evaluation, the patients’ available outside ECGs were reanalyzed. A revised QTc was documented for 113 patients. The

![Mayo LQTS Referral Cohort](image)

**Figure 2.** Diagnostic outcome of LQTS referral cohort. CPVT indicates catecholaminergic polymorphic ventricular tachycardia; ATS1, type 1 Andersen-Tawil syndrome; and DCM, dilated cardiomyopathy.

was much lower (0.8 versus 2.4; $P<0.0001$), and the prevalence of vasovagal syncope or presyncope was much higher (35% versus 13%; $P=0.001$) than among the P-LQTS/D-LQTS subset. In multivariate analysis, a QTc < 460 ms was significantly more common in the No-LQTS cohort than in the P-LQTS/D-LQTS cohort based on either the referring physician’s ECG interpretation (45% versus 24%; $P=0.02$) or interpretation of the ECG obtained at the time of the second-opinion evaluation (94% versus 55%; $P<0.0001$).

Next, we sought to determine the phenotypic differences between the subset ($n=99$) classified here as either P-LQTS or D-LQTS compared with the 69 patients who were dismissed as No-LQTS ($P=0.0001$). Except for similarities in sex distribution and age at initial diagnosis, the 2 subsets were strikingly different (Table 3). For the No-LQTS subset, the QTc was much lower (424 versus 461 ms; $P<0.0001$), the presence of a family history of LQTS was much lower (3% versus 16%; $P=0.02$), the mean clinically assessed Mayo Schwartz score was much lower (0.8 versus 2.4; $P<0.0001$), and the prevalence of vasovagal syncope or presyncope was much higher (35% versus 13%; $P=0.001$) than among the P-LQTS/D-LQTS subset. In multivariate analysis, a QTc < 460 ms was significantly more common in the No-LQTS cohort than in the P-LQTS/D-LQTS cohort based on either the referring physician’s ECG interpretation (45% versus 24%; $P=0.02$) or interpretation of the ECG obtained at the time of the second-opinion evaluation (94% versus 55%; $P<0.0001$).

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During their Mayo LQTS Clinic evaluation, the patients’ available outside ECGs were reanalyzed. A revised QTc based on these ECGs was documented for 113 patients. The

| TABLE 3. Comparison of Patients With P-LQTS or D-LQTS Versus No-LQTS |
|---|---|---|---|---|---|
| Age at referral, y | P-LQTS (n=52) | D-LQTS (n=47) | P-/D-LQTS (n=99) | No-LQTS (n=69) | $P$ (P-LQTS/D-LQTS vs No-LQTS) |
| % Female | 73 | 72 | 72 | 65 | NS |
| % With vasovagal syncope | 12 | 4 | 8 | 28 | 0.001 |
| % With reported family history of LQTS | 10 | 23 | 16 | 3 | 0.02 |
| % With family history of SCD | 8 | 6 | 7 | 1 | NS |
| Average Mayo QTc, ms | 441 | 484 | 461 ± 42 | 424 ± 22 | <0.0001 |
| % With Mayo QTc < 460 ms | 75 | 32 | 55 | 94 | <0.0001 |
| Average Mayo Schwartz score | 1.7 | 3.2 | 2.4 | 0.8 | <0.0001 |

SCD indicates sudden cardiac death.
average QTc reported by the referring physician for these patients was 479±55 ms, whereas the average revised QTc was 465±43 ms, a difference of 14 ms (P=0.002). The significance of this apparent overestimation was supported by the average QTc from the repeat ECGs performed at the time of the Mayo evaluation for the same cohort (446±42 ms).

Furthermore, nearly one third (31%) of the patients who were dismissed from our clinic as having insufficient evidence of LQTS (No-LQTS) had a significantly overestimated QTc at the time of their original ECG, compared with only 12% of subjects diagnosed as D-LQTS or P-LQTS (P=0.02). For this calculation, a significantly overestimated QTc was defined as an outside calculated QTc at least 20 ms greater than the revised QTc. The overestimate ranged from 21 ms to as high as 182 ms, with an average QTc overestimation of 63 ms (Figure 3). The most dramatic example involved a referred QTc of 592 ms that was examined and revised to 410 ms, which more closely approximated the repeat QTc of 427 ms. We noted that the discrepancy between the originally assessed QTc value and our recalculated QTc was most often attributable to erroneous U-wave inclusion in calculating the QTc (Figure 4A).

Besides issues with the QTc, attaching particular significance to the patient’s episode of syncope/presyncope may have led to a premature diagnosis of LQTS. Specifically, patients with a final clinical diagnosis of No-LQTS were significantly more likely to have a history of vasovagally mediated syncope than those with a final diagnosis of D-LQTS or P-LQTS (28% versus 8%; OR=3.40; P=0.001). This misinterpretation of vasovagal symptoms as being consistent with congenital LQTS was particularly accentuated for patients with “borderline” findings on ECG. More than one third (35%) of patients found in our clinic to have No-LQTS had a history of a vasovagal “spell” (including near-syncpe) and a QTc <460 ms.

**LQTS Genetic Testing**
Subsequent to the rendered second-opinion diagnosis, genetic testing was conducted for a significant portion of these patients (Figure 5). An LQTS-causing mutation was identified in 78% of the D-LQTS patients who underwent genetic testing, with LQT1 and LQT2 genotypes being most common (Figure 6). This yield is consistent with the reported yield of genetic testing in the setting of clinically definite LQTS. Among the 38 P-LQTS patients who were genetically tested, a disease-causing mutation was established in 34%, thus allowing one third of patients with P-LQTS to be upgraded subsequently to D-LQTS and to be treated with genotype-specific recommendations in mind. For those dismissed with a clinical diagnosis of P-LQTS subsequently accompanied with either a negative genetic test or for whom genetic testing was not performed, treatment recommendations generally consisted of prophylactic β-blocker therapy and QT drug avoidance. Importantly, among the 22 individuals who were classified as No-LQTS and went on to have genetic testing, none of them hosted LQTS-causing mutations (P<0.0001 comparing yield in D-LQTS versus No-LQTS). This independent objective evidence further corroborated the second-opinion clinical impression of No-LQTS.

**Discussion**
Over the past decade, there have been significant efforts to increase both physician and public awareness regarding the highly treatable but potentially lethal syndrome, LQTS. The present study suggests that the pendulum may have swung toward the proverbial “dark side” of increased awareness, namely, overdiagnosis. Of the entire cohort of patients referred to Mayo Clinic’s Long QT Syndrome clinic having been diagnosed previously with and treated for LQTS, 2 of every 5 patients left without the diagnosis of LQTS. In fact, the vast majority of these were dismissed as otherwise healthy individuals without any significant cardiovascular disease. Only a small percentage of patients were found to have other cardiac conditions, such as catecholaminergic polymorphic ventricular tachycardia, Andersen-Tawil syndrome, and dilated cardiomyopathy.

This diagnostic reversal had a profound impact on these patients, because 80% had their lives directly affected by some clinical intervention that stemmed from this presumed diagnosis. Overall, 17 patients (~10%) in the present cohort had been implanted already with an implantable cardioverter defibrillator, including 12 (12%) of 99 patients dismissed with either P-LQTS or D-LQTS and 5 (7%) of 69 patients dismissed from Mayo Clinic without a diagnosis of LQTS (ie, No-LQTS). Focusing on the 5 patients with potentially unnecessary implants, 3 had a history of syncpe, 2 were completely asymptomatic, and none had a family history of either LQTS or premature sudden death. Their average referral QTc was 522 ms, whereas the average QTc at the time of their Mayo evaluation was 433 ms.

The most dramatic case included a 46-year-old female with syncpe and referral QTc of 592 ms who received an implantable cardioverter defibrillator, a reasonable strategy for the management of a patient with extreme QT prolongation; however, her QTc was a gross overestimate. On remeasurement, her QTc was only 410 ms. Her repeat ECG again demonstrated a normal QTc (427 ms). In addition, her genetic test (a test that captures at least 75% of LQTS) was negative. Erroneous inclusion of normal U waves, as shown in Figure 4A, was the apparent culprit for the QTc discrepancy. Thus, we see the potential harm...
associated with overestimation of the QTc, particularly in the context of syncope.

Indeed, the present study shows that an erroneous QTc calculation was one of the primary reasons for individuals being misdiagnosed as having LQTS. Most of these errors involved overestimation of the QTc. In particular, our observations suggest that caution be exercised with respect to inclusion of the U wave in the calculation of the QT interval. One may surmise that those overestimating the QTc were general adult or pediatric cardiologists, rather than arrhythmia specialists; however, among the subset of patients dismissed as No-LQTS, more than half had been given the diagnosis of LQTS by an electrophysiologist. It is noteworthy that the vast majority of patients seeking a second opinion in the present study were “self-referred.”

Figure 4. Erroneous U-wave inclusion in the QTc calculation. A, Shown is an example of one of the sources of erroneous QTc calculations. These U waves are extremely common, particularly among adolescents and particularly in the precordial leads V2 and V3. One can easily see that its inclusion as part of the T wave can yield a grossly overestimated QTc. B, Two rhythm strips with magnified insets are shown that depict how the normal U waves shown in Figure 4A can and should be distinguished from pathological U waves (top) seen in type 1 Andersen-Tawil syndrome and from the notched T waves (bottom) that can be seen in type 2 LQTS.
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specific medical management of their syndrome. 

nosis, which facilitated appropriate and sometimes genotype- 
gene positive D-LQTS. For those patients, genetic test-
patients who were dismissed initially with possible LQTS to 
study, genetic testing permitted an upgrade of one third of 
whom the diagnostic certainty is less robust. In the present 
LQTS and their family members but also for patients in 
stratification in patients with clinically diagnosed definite 
to the evaluation of LQTS, is evident, not only for risk 
scrutiny of the T and U waves are critical to the LQTS 
Figure 4, careful calculation of the QTc and meticulous 
morbidity, both physical and emotional. As depicted in 
we demonstrate that such QTc miscalculations contributed to 
overdiagnosis, inappropriate interventions, and significant 
morbidly, both physical and emotional. As depicted in 
Figure 4, careful calculation of the QTc and meticulous 
scrutiny of the T and U waves are critical to the LQTS 
evaluation.

Finally, the role of genetic testing, as an important adjunct 
to the evaluation of LQTS, is evident, not only for risk 
stratification in patients with clinically diagnosed definite 
LQTS and their family members but also for patients in 
whom the diagnostic certainty is less robust. In the present 
study, genetic testing permitted an upgrade of one third of 
patients who were dismissed initially with possible LQTS to 
genotype-positive D-LQTS. For those patients, genetic testing 
erased any doubts and uncertainty regarding their diagnos-
which facilitated appropriate and sometimes genotype-
pecific medical management of their syndrome.

Study Limitations
As with any retrospective study, there are several potential 
limitations. First, the reviewed data are only as good as the 
source material. Even with meticulous documentation during 
their evaluation, the quantity and quality of records we had 
available from the outside evaluations varied greatly. We 
attempted to minimize these potential confounders by excluding 
from some data analyses those subjects whose outside 
medical data were incomplete. For example, patients were not 
included in the calculation of the mean outside Schwartz score if there was no documentation of a QTc calculated by 
the physician who rendered the initial diagnosis of congenital 
LQTS.

Second, comprehensive LQTS genetic testing was not 
performed in every patient in the present study. Although 
>80% of those with either definite or possible LQTS sought 
genetic testing, less than one third of patients dismissed as normal pursued genetic testing. There are several cogent 
explanations for the decreased frequency of genetic testing 
among the patients in the No-LQTS subset. Until May 2004, 
genetic testing was only available to our patients as an 
institutional review board–approved free research test in 
Mayo Clinic’s Sudden Death Genomics Laboratory. Nearly 
all of the tested No-LQTS patients were evaluated before this 
time and were enrolled in the research study. The majority of 
the nontested patients were seen after this time. Given the 
rendered opinion that there was insufficient clinical and ECG 
evidence to merit a diagnosis of LQTS, most patients chose not to pursue the commercially available test. Consequently, 
without genetic testing of every patient dismissed as normal, 
we cannot be absolutely certain that there were no "silent" 
carriers of a known LQTS gene mutation in this cohort. 
Nevertheless, every one of the 22 genetically tested patients 
dismissed as normal had a negative genetic test, and the 
phenotype of these tested patients was identical to the 
phenotype of the rest of the No-LQTS subset who chose not 
to pursue genetic testing (data not shown).

Finally, it is unclear whether or not these patients reflect 
the population of patients at large who have been diagnosed 
with LQTS. It is conceivable that patients with lesser support 
for their diagnosis may have been more likely to seek a 
second opinion, whereas patients with obvious LQTS were 
not referred, effectively producing an apparent “epidemic” of 
overdiagnosed LQTS. An important caveat to that assump-
tion, however, is that the majority of patients who sought a 
second opinion in the present study were “self-referred,” 
which suggests that the physician rendering the diagnosis of 
LQTS was comfortable with his/her rendered label and 
subsequent treatment plan. Consequently, we may be seeing 
a glimpse of the proverbial dark side of increased awareness, 
namely, overdiagnosis of LQTS. On the other hand, failure to 
recognize LQTS in a timely fashion continues to exist. In 
fact, approximately half of autopsy-negative sudden death 
victims with postmortem evidence for LQTS-causing muta-
tions had strong personal or family history warning signs that 
seemingly were unrecognized or unheeded.12

Conclusions
Congenital LQTS appears to be significantly overdiagnosed. 
Diagnostic concordance was present for less than one third of 
the patients seeking a second opinion. Two of every 5 patients 
who arrived with the diagnosis of LQTS departed without
that diagnosis. Miscalculation of the QTc, misinterpretation of the normal distribution of QTc values, and misinterpretation of symptoms appear responsible for most of the diagnostic miscues. Although the consequences of failing to properly identify the patient who truly has LQTS can be tragic, the overdiagnosis of LQTS also has significant consequences, which include morbidity associated with unnecessary medical intervention (including implantable cardioverter defibrillators, as seen in the present study), dramatic lifestyle changes, and the profound anxiety that stems from the perception that these individuals have a potentially life-threatening heart condition.

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References


**CLINICAL PERSPECTIVE**

Once viewed as a rare, highly lethal sudden death syndrome, congenital long-QT syndrome (LQTS) is now recognized as the most common cardiac channelopathy, with an estimated incidence of 1 in 3000. Underscored by genotypic and phenotypic heterogeneity, LQTS is generally highly treatable, and when diagnosed, sudden death should be the exception. Despite tremendous advances in our knowledge about LQTS and a general increased awareness of this condition and its potential lethality, the difficulty of recognizing subtle and unusual presentations of this potentially lethal channelopathy continues, which results in tragic misdiagnoses of an LQTS-affected individual. At the same time, increased awareness of the broad phenotypic variability in LQTS creates the potential for overdiagnosis of LQTS. In the present study of 176 consecutive patients diagnosed elsewhere with LQTS and seeking a second opinion, we sought to determine whether or not this increased awareness and tendency for overdiagnosis was occurring. We found that 40% of the patients who came with a diagnosis of LQTS left without this diagnosis, with the vast majority dismissed as normal. This included 5 patients who were implanted with an implantable cardioverter defibrillator, potentially unnecessarily. Miscalculation of the corrected QT interval, misinterpretation of the normal distribution of corrected QT interval values, and misinterpretation of symptoms appear to be responsible for most of the diagnostic miscues. Although failure to recognize the warning signs of LQTS can culminate in sudden cardiac death, increased awareness can also lead to overdiagnosis and result in unnecessary and burdensome treatments and interventions.
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