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Diagnostic Accuracy of Screening Electrocardiograms in Long QT Syndrome I

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ABSTRACT. *Objective.* **Inherited long QT syndrome (LQTS) may present with syncope, seizures, and/or sudden death as a result of ventricular tachyarrhythmias. Identification of family members who are at risk because they harbor the genetic substrate for LQTS is critical. Presently, such identification relies on the 12-lead electrocardiogram (ECG). The purpose of this study was to evaluate the efficacy of the automated ECG as a screening tool for LQTS.**

Method. **Molecular testing of a proband and 22 additional family members for the KVLQT1 mutation and symptomatic status facilitated the classification of each family member into the following patient groups: noncarriers (13), asymptomatic carriers (5), and symptomatic carriers (5). Each individual had a standard 12-lead ECG from which the computer and manual (lead II) corrected QT interval were determined. In addition, we determined the accuracy of the computer ECG diagnostic interpretation for each patient group.**

Results. **With the use of a corrected QT interval of ≥460 ms as a diagnostic cutoff, the positive and negative predictive values for identifying at-risk individuals were 100%. Despite this, the computer-generated ECG diagnostic interpretation erroneously classified 6 of 23 family members. Moreover, half of the family members, proved to have the ion channel defect, received the diagnostic interpretation "normal ECG."**

Conclusion. **Reliance on the computer-generated ECG diagnostic interpretation alone will fail to identify many at-risk family members. It is suggested that all first-degree relatives of an identified LQTS proband have a 12-lead ECG that is reviewed independently by a physician who is familiar with LQTS in an effort to improve screening for this potentially lethal syndrome.** *Pediatrics* **2001;108:8–12;** ***electrocardiogram, long QT syndrome, QT interval, sudden death.***

ABBREVIATIONS. LQTS, long QT syndrome; QTc, corrected QT interval; ECG, electrocardiogram; SIDS, sudden infant death syndrome.

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The inherited long QT syndrome (LQTS) is characterized by QT interval prolongation and its trademark ventricular tachyarrhythmia, *torsade de pointes*.[1–4] With symptoms ranging from relatively benign syncopal spells to seizures and sudden death, it is imperative that affected individuals be identified. Because the first manifestation of the disease occasionally can be fatal, it is critical to identify asymptomatic family members who possess the genetic substrate. Although the cardiac ion channel mutations that are responsible for LQTS continue to be unveiled, diagnostic genetic testing remains unavailable clinically.[5] Thus, the diagnosis of LQTS continues to rely primarily on the presence of symptoms, family history, and determination of the corrected QT interval (QTc) from a 12-lead electrocardiogram (ECG).

Before the molecular breakthroughs in LQTS, a QTc of ≥440 ms was considered prolonged.[6,7] In 1992, Vincent et al[8] examined the QTc distribution in 3 families that were genotyped for the chromosome 11p15.5 locus for LQTS (LQT1). Having categorized each patient as a carrier or noncarrier of this LQTS locus, this study demonstrated substantial patient misclassification on the basis of the QTc cutoff value of 440 ms. These results led to the present practice of assigning a QTc of ≥460 ms as prolonged and a QTc between 420 ms and 460 ms as borderline or equivocal.[3]

Many physicians, however, are not aware of what constitutes abnormal QT prolongation and are not able to corroborate independently the computer-generated QTc using Bazett's rate-correction formula.[9] Rather, many physicians rely on the computer-generated diagnostic interpretation that accompanies each ECG before thoroughly reviewing the ECG.[10,11] Therefore, it is critical to investigate the diagnostic accuracy of such automated algorithms. Incorrectly assigning the diagnosis of LQTS to an unaffected patient could result in unnecessary stress, anxiety, and possibly unwarranted therapy. Conversely, failure to identify at-risk individuals could prove to be a fatal mistake.

METHODS

Study Participants

Study participants consisted of a 10-year-old proband who presented with a near drowning and was defibrillated poolside from *torsade de pointes*[12] and 22 of his first-degree relatives in whom molecular testing had confirmed a △F339–KVLQT1 mutation in 9 additional family members.[13] Regarding nomenclature, the designation △F339–KVLQT1 indicates that the defect is

present in the gene KVLQT1, which encodes the potassium channel that is responsible for 1 of the principal phase 3 repolarizing currents in the heart. Mutations in KVLQT1 compose approximately 25% of all LQTS. The specific mutation △F339 denotes that there is a deletion of the 339th amino acid, phenylalanine (F). Of the 10 △F339–KVLQT1-positive individuals, 5 were "symptomatic" carriers and 5 were "asymptomatic" carriers. The remaining 13 family members were "noncarriers." Informed consent was obtained from all participants before their enrollment in this study, which was approved by the Mayo Foundation Institutional Review Board.

Screening 12-Lead ECG and Manual Calculation of the QTc

The screening ECGs were performed in the ECG laboratory at Mayo Clinic Rochester, where approximately 600 ECGs are analyzed each day. Four ECG technicians, 1 adult cardiologist, and 1 pediatric cardiologist staff the ECG reading room. Each ECG technician reviews approximately 150 ECGs and the corresponding computer-generated diagnostic interpretations daily. After "overreading" the computer's diagnostic interpretation, the technician/physician generates a final ECG diagnostic interpretation.

Each individual had a standard 12-lead ECG recorded at a paper speed of 25 mm/s (Fig 1). None of the participants was on any cardiac rate- or rhythm-altering medications. One of the authors (M.D.M.), blinded to the patient's genotype, measured the R-R and QT intervals for every beat in all 12 leads. With the use of calipers, each QT interval was measured from the onset of the QRS complex to the termination of the T wave (the point at which the descending limb of the T wave intersects with the isoelectric line). Any U waves that occurred after the T wave returned to the isoelectric line were not included in the QT interval measurement. Next, each QT interval was corrected for heart rate with the use of Bazett's formula ($QTc = QT/RR^{1/2}$). [9] Lead II is the conventional lead used to identify QT prolongation.[6] Thus, a mean QTc manually derived from lead II was compared between genetically unaffected and affected individuals (noncarriers and carriers).

Computer Algorithm for QTc and Diagnostic Interpretation "Prolonged QT"

The automated, computer-generated QT interval measurements and diagnostic interpretation were obtained with the use of the 12SL ECG Analysis Program (Marquette Electronics, Milwaukee, WI).[14] The computer QTc (Fig 1) is not based on inspection of lead II alone. Rather, the algorithm derives a median QTc, correcting for heart rate with the use of Bazett's formula, after inspection of all 12 leads.

In addition, the diagnostic interpretation "prolonged QT" is generated by the computer when the following conditions are satisfied: 1) ventricular rate of ≤100 bpm, 2) QRS duration of ≤120 ms with no evidence of bundle branch block, and 3) QTc of ≥460 ms without evidence of abnormal T-wave morphology.[14] When the QTc is between 480 and 499 ms, the interpretation "prolonged QT" is rendered as long as myocardial ischemia/infarction algorithms are not satisfied. When the QTc exceeds 500 ms, the interpretation "prolonged QT" is rendered independent of T-wave repolarization abnormalities and/or myocardial infarction/ischemia.

Statistical Methods

Comparisons between groups were accomplished with the use of the unpaired 2-tailed student's *t* test for unequal variance. All values are given in tabulated form as the mean ± 1 SD along with range of values. The original data points and the mean values are displayed in the figures. We elected to express QTc in its commonly used units, milliseconds.

RESULTS

Screening 12-Lead ECG

Table 1 summarizes demographic and ECG data for the 10 △F339–KVLQT1 carriers and 13 noncarriers. The computer QTc was significantly greater ($P \leq .0001$) in △F339–KVLQT1 carriers (496 ± 42 ms) than in noncarriers (418 ± 24 ms). A comparison between the computer QTc and the mean QTc derived manually from inspection of lead II is shown in Fig 2. There was no statistical difference between the computer QTc (12-lead median composite) and the manual QTc (lead II average) for noncarriers, asymptomatic carriers, and symptomatic carriers. In addition, there was excellent individual patient correlation between the computer and the manual QTc (average difference <10 ms, data not shown). Six (46%) of 13 of the noncarriers had a computer QTc between 420 and 460 ms. With the use of only a QTc of ≥460 ms

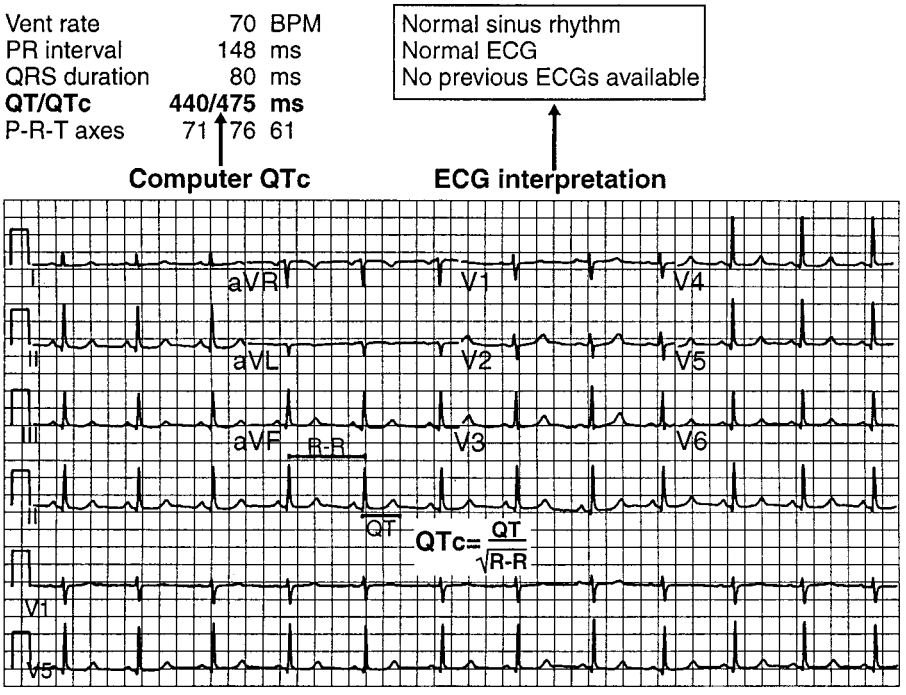

Fig 1. Twelve-lead ECG from an asymptomatic △F339–KVLQT1 carrier. Standard screening ECG recorded at a paper speed of 25 mm/s. QT and R-R intervals are highlighted in lead II for manual calculation of Bazett's QTc. Computer-generated QTc and diagnostic interpretation are shown in bold.

TABLE 1. Demographic and Electrocardiographic Comparison Between Noncarriers and ΔF339-KVLQT1 Carriers

	Noncarriers	ΔF339-KVLQT1	*P* Value
Number of subjects	13	10	
Mean age (yr)	21 ± 25	37 ± 15	NS
Range	2–85	10–57	
Men/women	4/9	5/5	NS
Mean resting heart rate (min^{-1})	86 ± 19	71 ± 20	<.01
Range (min^{-1})	63–111	53–89	
Computer QTc (ms)	418 ± 24	496 ± 42	<.0001
Range	384–456	460–590	
Manual QTc (ms), mean lead II	421 ± 25	498 ± 42	<.0001
Range	392–462	449–554	

NS indicates not significant.

as cutoff, the computer QTc discriminated each individual's genetic status correctly.[3,8]

Accuracy of ECG Diagnostic Interpretation

The accuracy of the ECG diagnostic interpretation was evaluated for all 3 patient subsets (Fig 3). Overall, 6 (27%) of 22 of the proband's relatives would have been misclassified on the basis of the computer's diagnostic interpretation even after overreading by the technician/cardiologist. For noncarriers, 1 of the 13 individuals (computer QTc = 456 ms) received the diagnostic interpretation "prolonged QT interval" after physician/technician overreading. All noncarriers had a QTc of ≤460 ms.

The accuracy rate of the diagnostic interpretation for asymptomatic △F339–KVLQT1-positive individuals was only 20% (1 "prolonged QT" and 4 "normal ECG" interpretations, example shown in Fig 1). The overreading process did not change any of these interpretations despite that the 4 "normal ECGs" had a computer QTc of 460, 470, 472, and 475 ms. The computer QTc from the single correct interpretation in this subset was 488 ms.

Last, the diagnostic interpretation for symptomatic carriers identified correctly 3 of the 5 individuals. Three "prolonged QT," 1 "borderline QT," and 1 "normal ECG" interpretations were reported. The "borderline QT" diagnosis was changed to "prolonged QT" during overreading. All symptomatic carriers had a QTc of ≥480 ms, except for the ECG that was interpreted as normal (QTc = 479 ms). Thus, the overall diagnostic accuracy of the final diagnostic interpretation in those with the △F339–KVLQT1 mutation was only 50%.

DISCUSSION

The stakes are high in LQTS. The need to identify correctly family members who may harbor the genetic substrate for potentially fatal arrhythmias requires that the syndrome's principal screening modality, the ECG, be scrutinized carefully. This study evaluated the electrocardiographic profile of a single ion channel perturbation in a single LQTS family. Despite this obvious limitation, the findings raise profound concerns regarding the accuracy of the diagnostic interpretation associated with the 12-lead ECG.

Disturbing is that the computer-generated diagnostic interpretation, even with a safeguard technician/physician overreading process in place, failed to identify half of the △F339–KVLQT1-positive individuals despite displaying QT prolongation (ie, QTc of ≥460 ms). Because individuals with prolongation of the QT interval may present with sudden cardiac death, it is most important to detect by any screening program the subset of family members who are asymptomatic carriers. Unfortunately, only 1 of the 5 asymptomatic carriers was diagnosed correctly and received a "prolonged QT" automated diagnostic interpretation. In the absence of molecular testing, these individuals may have been dismissed as normal. They would not have been privy to proper genetic counseling, to warnings about swimming and strenuous exertion, to the list of contraindicated medications, or to possible β-blocker therapy.

This study reinforces several important caveats for the electrocardiographic screening of LQTS. First, individuals with a QTc of ≥460 ms must be considered carefully regardless of the computer's diagnostic interpretation. In this study, with the use of a QTc of ≥460 ms as a diagnostic cutoff, the computer-derived QTc completely distinguished the noncarriers from the △F339–KVLQT1-positive individuals. It would be interesting to see what the diagnostic accuracy would have been for other automated ECG analysis systems. As a retrospective study, we were constrained to the 12SL ECG Analysis Program from Marquette Electronics that is used in the clinical practice at Mayo Clinic Rochester.[14] It is noteworthy that all 5 of the false-negative diagnostic interpretations occurred when the QTc was between 460 and 479 ms. Perhaps the test for T-wave abnormalities that must be satisfied in this algorithm is too restrictive when the QTc is in this range. To be sure, a computer QTc of ≥460 ms warrants critical scrutiny even in the face of an interpretive summary statement of "normal ECG."

Second, although there was excellent agreement between the computer QTc and the manual QTc in this study, we continue to recommend strongly that the QTc be calculated independently. With clearly delineated T-wave inscriptions, this particular family likely posed a best-case scenario to the automated system. Errors in the automated measurement of the QT interval increase when the precise end of the T wave cannot be detected easily.[15] In addition, Moss et al[16] demonstrated that T-wave morphologies can vary significantly from the pristine T waves displayed uniformly by this family. Therefore, screening ECGs in an LQTS evaluation should be scrutinized carefully for subtle but potentially genotype-specific T-wave profiles. Furthermore, when determining a patient's QTc manually, it is essential to derive a mean QTc from lead II. Simply identifying and measuring the longest QT interval in the 12-lead ECG will produce a substantial number of false-positive results. Here, 6 of the 13 noncarriers possessed a maximum QTc greater than 460 ms (data not shown).

Third, the findings of this study sound a cautionary note to the use of the 12-lead ECG as part of a

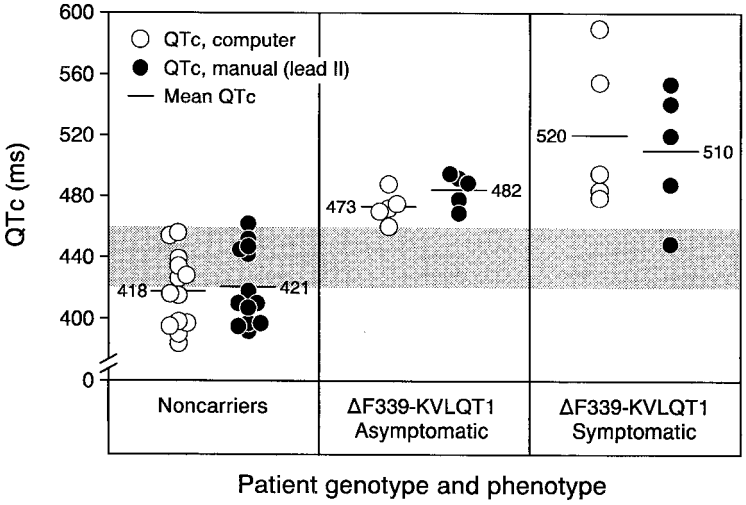

Fig 2. Computer QTc and manual QTc (lead II) in a genotyped △F339–KVLQT1 family. QTc = ($QT/RR^{1/2}$), shaded area from 420 to 460 ms indicates the range for a "borderline/equivocal" QTc. Note that QTc is displayed in milliseconds by convention.

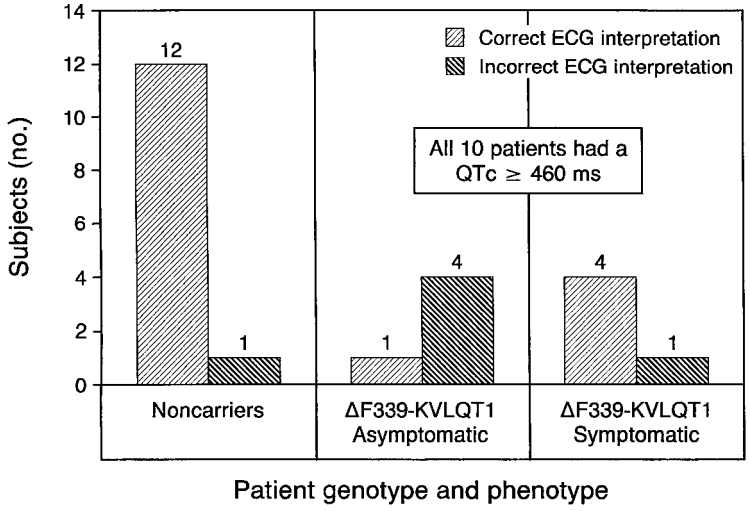

Fig 3. Accuracy of ECG diagnostic interpretation. For noncarriers, a "correct" assignment was considered if the statement "normal ECG" appeared, whereas an accurate classification in the △F339–KVLQT1 patients occurred if the statement "prolonged QT" appeared in the diagnostic interpretation.

universal newborn screen for the identification of infants who are at risk for sudden infant death syndrome (SIDS) secondary to LQTS. Schwartz et al[17] performed an impressive 18-year study of ECGs taken on the third of fourth day of life from more than 34 000 infants and demonstrated a strong association between ECG evidence of QT prolongation and SIDS. More recently, they provided direct molecular evidence of a sporadic (infant affected, mother and father both normal) sodium channel defect in a single case of near-SIDS.[18] This case report provided additional proof-of-principle to support the notion that cardiac channelopathies may provide the substrate for some cases of SIDS. Whether these findings warrant an ECG as part of any state's newborn screen has been debated intensely with concerns raised about the screening ECG's poor positive predictive value (1%–2%) and the cost of such a universal ECG screening program.[19–21] In this study, the diagnostic interpretation of the screening ECG in a known, genotyped LQTS family displayed a negative predictive value (70%) that is unacceptable for a screening tool.

Finally, the identification of a family member as having "wrong QT syndrome" or "concealed" LQTS (long QT genetic defect with a borderline or equivocal QT interval) remains problematic and awaits advances in molecular genetic testing. In this study, the mutation was completely penetrant with every carrier having a QTc that exceeded 460 ms. Other studies that investigated QTc parameters in genotyped LQTS families reported normal individuals with QTc exceeding 460 ms as well as LQT1 patients having disease-causing mutations despite a QTc as low as 400 ms.[8,22–25] The present borderline zone, 420 to 460 ms, likely contains a preponderance of false-positive results. Whether the lower limit for borderline QT prolongation should be 420 ms or 440 ms is debatable. Here, 6 of the 13 noncarriers had an equivocal QTc between 420 and 460 ms. As illustrated in this study and others, molecular genetic testing plays a vital role in establishing a definitive diagnosis in such family members with an equivocal/borderline QTc on their screening 12-lead ECG.[24,25]

CONCLUSION

LQTS is a genetically based arrhythmogenic disorder that may manifest, without warning, with sudden death. Once an LQTS proband is identified, it is necessary to identify other family members who are

at-risk for this potentially fatal disease. Until routine molecular testing becomes available to screen for these ion channelopathies, the screening ECG will remain the cornerstone in the evaluation of the family with LQTS. Despite a family's having "ideal T-wave morphology," the diagnostic interpretation provided by the automated analysis system accompanied by direct physician/technician overreading misdiagnosed half of the family members who were shown to possess the genetic defect. Therefore, we recommend that all screening ECGs for LQTS be reviewed by a physician who is familiar with LQTS to examine carefully the T-wave morphology and determine independently the QTc and the ECG diagnostic interpretation.

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NOBODY IS THINKING ABOUT YOU

Yes, I know, you are certain that your friends are becoming your enemies; that your grocer, garbageman, clergyman, sister-in-law, and your dog are all of the opinion that you have put on weight, that you have lost your touch, that you have lost your mind; furthermore, you are convinced that everyone spends two-thirds of every day commenting on your disintegration, denigrating your work, plotting your assassination. I promise you: nobody is thinking about you. They are thinking about themselves—just like you.

Rosenblatt R. *Rules for Aging: Resist Normal Impulses, Live Longer, Attain Perfection*. New York, NY: Harcourt, Inc; 2000

Noted by JFL, MD

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