Spectrum of ST-T–Wave Patterns and Repolarization Parameters in Congenital Long-QT Syndrome

ECG Findings Identify Genotypes

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Background—Congenital long-QT syndrome (LQTS) is caused by mutations of genes encoding the slow component of the delayed rectifier current (LQT1, LQT5), the rapid component of the delayed rectifier current (LQT2, LQT6), or the Na+ current (LQT3), resulting in ST-T–wave abnormalities on the ECG. This study evaluated the spectrum of ST–T–wave patterns and repolarization parameters by genotype and determined whether genotype could be identified by ECG.

Methods and Results—ECGs of 284 gene carriers were studied to determine ST-T–wave patterns, and repolarization parameters were quantified. Genotypes were identified by individual ECG versus family-grouped ECG analysis in separate studies using ECGs of 146 gene carriers from 29 families and 233 members of 127 families undergoing molecular genotyping, respectively. Ten typical ST-T patterns (4 LQT1, 4 LQT2, and 2 LQT3) were present in 88% of LQT1 and LQT2 carriers and in 65% of LQT3 carriers. Repolarization parameters also differed by genotype. A combination of quantified repolarization parameters identified genotype with sensitivity/specificity of 85%/70% for LQT1, 83%/94% for LQT2, and 47%/63% for LQT3. Typical patterns in family-grouped ECGs best identified the genotype, being correct in 56 of 56 (21 LQT1, 33 LQT2, and 2 LQT3) families with mutation results.

Conclusions—Typical ST–T–wave patterns are present in the majority of genotyped LQTS patients and can be used to identify LQT1, LQT2, and possibly LQT3 genotypes. Family-grouped ECG analysis improves genotype identification accuracy. This approach can simplify genetic screening by targeting the gene for initial study. The multiple ST-T patterns in each genotype raise questions regarding the pathophysiology and regulation of repolarization in LQTS.

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Key Words: genetics ■ long-QT syndrome ■ electrocardiography ■ waves
terns and hypothesized that patterns might be genotype specific and useful for identifying genotype.

Therefore, the aims of the present study were to determine (1) the spectrum of ST-T–wave patterns and quantified measures of repolarization for each genotype and (2) whether the ST-T–wave patterns and repolarization parameters could be used to identify genotypes.

Methods

Phase I: ECG Characterization of Repolarization by Genotype

The resting 12-lead ECGs of 284 gene carriers from 29 LQTS families were obtained from 5 centers of the International LQTS Registry: Salt Lake City, Utah; Rochester, NY; Detroit, Mich; Pavia, Italy; and Jerusalem, Israel. Many family members had been genotyped irrespective of phenotype, providing a study population that was international in scope and broadly representative of LQTS patients, including those with reduced penetrance and variable expressivity of phenotype. There were 131 LQT1 patients (aged 27±24 years, 62 females) from 8 families with 8 different mutations, 93 LQT2 patients (aged 31±21 years, 48 females) from 15 families with 15 different mutations, and 60 LQT3 patients (aged 23±18 years, 27 females) from 6 families with 3 different mutations. All ECGs were taken before or without β-blocker medication.

The Spectrum of ST-T–Wave Patterns and Repolarization Parameters

The 284 ECGs were jointly reviewed by Salt Lake City investigators (L.Z., K.W.T., and L.C.G.). ST-T morphology was evaluated in all 12 leads, and a representative pattern was determined. If different patterns were present in different leads, the most prevalent (present in at least 7 leads) was chosen as the representative pattern for the ECG. Patterns identified to be characteristic for each genotype were defined as typical for that genotype, and those not associated with any genotype were defined as nonspecific. The frequency of typical patterns in each genotype was determined.

Repolarization parameters were quantified to further define repolarization in each genotype. Measurements were averaged from 2 or
Statistical Analysis
Independent t tests were performed between any 2 genotypes. Because of multiple tests being applied to each measurement, a Bonferroni correction was used, and a value of P < 0.017 was considered significant. Discriminant analysis using the stepwise method was performed to determine which (if any) combination of repolarization parameters could separate the 3 genotypes. The sensitivity and specificity of this classification was determined.

Phase II: Genotype Identification by ST-T–Wave Patterns

Genotype Identification by Other Cardiologists
We evaluated whether typical ST-T–wave patterns could be used for genotype identification by cardiologists other than those who identified the characteristic patterns. ECGs from 104 newly identified LQT1 and LQT2 gene carriers from 23 families were used. Because the LQT3 genotype is uncommon, no new gene carriers were available. Thus, we randomly selected 42 of 60 LQT3 ECGs used in the pattern characterization study. The 146 ECGs included 48 LQT1 (aged 29 ± 6 years), 56 LQT2 (aged 24 ± 6 years), and 42 LQT3 (aged 27 ± 6 years) gene carriers. The ECGs available for each family was 6 ± 5.

ECG tracings were numerically coded, with name, age, sex, and source of acquisition deleted to avoid any clues as to genotype. The ECG packet plus instructions and graphical ECG templates (Figures 1 to 3) for genotype identification were reviewed by 4 cardiologists (M.H.L., S.G.P., S.J.C., and F.Y.), none of whom was involved in the pattern characterization study. Each assigned a genotype for each ECG. If the ECG pattern was not a typical pattern, it was assigned to the “uncertain” category. After receipt of their analysis, the ECGs were sent a second time, grouped by family, and the readers assigned a genotype to each family. Assignment was based on the presence of a typical pattern(s) in ≥ 1 family member. In the absence of a typical pattern, the family was labeled as uncertain. Two authors (G.M.V. and J.F.) compared assignment results with molecular genotype and calculated sensitivity/specificity of genotype identification by ECG patterns for both individual and family-grouped ECG analyses.

Prospective Genotype Identification in 127 Families Undergoing Genetic Testing
This component examined the accuracy of genotype identification by investigators experienced in the recognition of typical ECG patterns. Two investigators (L.Z. and K.W.T.) reviewed family-grouped ECGs from 233 members of 127 clinically diagnosed LQTS families, referred from many areas of the world to the Keating Laboratory at the University of Utah for molecular genetic testing. QTcs ranged from 410 to 620 ms; 10% had a normal QTc of ≤ 440 ms, and 26% had a normal to borderline QTc of ≤ 460 ms.

Genotype identification by ECG used the same written pattern descriptions and graphic templates used in Genotype Identification by Other Cardiologists. Eighty families (63%), with 129 clinically affected members, showed a typical pattern in at least 1 family member’s ECG, and a genotype was assigned to each family. The remaining 47 families, with 104 clinically affected members, had only nonspecific ST-T–wave patterns. There were 3.1 ± 2.3 ECGs

### TABLE 1. Prevalence of Typical ST-T–Wave Patterns in 3 LQTS Genotypes

<table>
<thead>
<tr>
<th>Demographics</th>
<th>LQT1 (n=179)</th>
<th>LQT2 (n=148)</th>
<th>LQT3 (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>28±23</td>
<td>29±20</td>
<td>23±18</td>
</tr>
<tr>
<td>Sex (male/female), n/n</td>
<td>85/94</td>
<td>66/82</td>
<td>33/27</td>
</tr>
<tr>
<td>Normal ST-T–wave pattern with normal QT interval (QTc&lt;440 ms), % (n)</td>
<td>1.7 (3)</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>LQT1 ST-T–wave patterns, % (n)</td>
<td>15.1 (27)</td>
<td>0</td>
<td>10 (6)</td>
</tr>
<tr>
<td>LQT2 ST-T–wave patterns, % (n)</td>
<td>20.7 (37)</td>
<td>0.7 (1)</td>
<td>8.3 (5)</td>
</tr>
<tr>
<td>LQT3 ST–wave patterns, % (n)</td>
<td>37.4 (67)</td>
<td>2 (3)</td>
<td>6.7 (4)</td>
</tr>
<tr>
<td>Late onset of normal-appearing T wave</td>
<td>14.5 (26)</td>
<td>0</td>
<td>8.3 (5)</td>
</tr>
<tr>
<td>LQT1 infantile ST-T wave</td>
<td>1.1 (2)</td>
<td>39.8 (59)</td>
<td>0</td>
</tr>
<tr>
<td>Broad-based T wave</td>
<td>2.2 (4)</td>
<td>48 (71)</td>
<td>0</td>
</tr>
<tr>
<td>Normal-appearing T wave</td>
<td>2.2 (4)</td>
<td>0.7 (1)</td>
<td>53.3 (32)</td>
</tr>
<tr>
<td>Asymmetrical peaked T wave</td>
<td>0.6 (1)</td>
<td>0</td>
<td>11.7 (7)</td>
</tr>
<tr>
<td>Nonspecific ECG patterns, % (n)</td>
<td>4.5 (8)</td>
<td>6.8 (10)</td>
<td>1.7 (1)</td>
</tr>
<tr>
<td>Overall: ECG patterns typical to genotype, %</td>
<td>87.7</td>
<td>87.8</td>
<td>65</td>
</tr>
</tbody>
</table>

### TABLE 2. Quantitative Measures of Repolarization in LQT1, LQT2, and LQT3 Gene Carriers

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n</th>
<th>Age, y</th>
<th>RR, ms</th>
<th>STc, ms</th>
<th>QTc, ms</th>
<th>T-Wave Duration, ms</th>
<th>T-Wave Amplitude, mV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>131</td>
<td>27±24</td>
<td>820±200</td>
<td>190±50</td>
<td>470±40</td>
<td>170±30</td>
<td>0.34±0.16</td>
</tr>
<tr>
<td>LQT2</td>
<td>93</td>
<td>32±22</td>
<td>900±200*</td>
<td>130±40†</td>
<td>470±30</td>
<td>230±40†</td>
<td>0.21±0.25†</td>
</tr>
<tr>
<td>LQT3</td>
<td>60</td>
<td>23±18</td>
<td>880±240</td>
<td>240±30‡</td>
<td>500±50‡</td>
<td>160±50</td>
<td>0.30±0.38</td>
</tr>
</tbody>
</table>

Values are mean±SD.
*p < 0.01 vs LQT1; †p < 0.0001 vs LQT1 or LQT3; and ‡p < 0.0001 vs LQT1 or LQT2.
per family with typical patterns versus 1.9±1.2 ECGs per family with nonspecific patterns (P<0.001). The total time spent reviewing the 233 ECGs and assigning genotype to 127 families was ~16 hours, all performed before the molecular genetic results. Single-strand conformation polymorphism analyses were performed in 1 phenotypically affected individual from each family and required 1 year for completion. The accuracy of genotype identification by ECG patterns was evaluated for the families in which mutations were identified.

Results
Phase I
Ten typical ST–T–wave patterns were identified: 4 in LQT1, 4 in LQT2, and 2 in LQT3. Representative examples of typical ECG patterns are shown in Figures 1 to 3.

LQT1 Patterns
LQT1 patterns are shown in Figure 1. The infantile ST–T–wave pattern (Figure 1a) is primarily seen in children aged 2 months to 2 years but could be seen in children aged ≤5 years. It was usually associated with other infantile ECG features, such as fast heart rate and right ventricular predominance. A short and ill-defined ST segment merged immediately with the T-wave upstroke, giving the appearance of a diagonal line to the T-wave upstroke. Bifid T waves were common, with the second component producing the peak of the T wave in most of the limb and left precordial leads. The T-wave downslope was steep. Generally, the T wave appeared broad-based, peaked, and asymmetrical. The QT interval ranged from borderline to obviously prolonged (QTc 470±30 ms).

The broad-based T wave6 (Figure 1b) is a single, smooth, broad-based T wave that is present in most leads, particularly evident in the precordial leads. The absence of a distinct T-wave onset enhanced the broad-based appearance. The QT interval ranged from normal to obviously prolonged (QTc 490±40 ms).

For the normal-appearing T wave (Figure 1c), the T-wave morphology looked normal. The QT interval ranged from normal to obviously prolonged (QTc 460±40 ms).

In the late-onset normal-appearing T wave (Figure 1d), the ST segment was prolonged, and the T-wave morphology was normal. The QTc was 490±40 ms.

LQT2 Patterns
LQT2 patterns are shown in Figure 2. Bifid T waves6,7,9 were the hallmark of the LQT2 genotype. They were usually present in most of the 12 leads. The T-wave amplitude was commonly low, and the QT interval ranged from normal to markedly prolonged (QTc 470±30 ms). Four subtypes of bifid T waves were identified: obvious bifid T waves, subtle bifid T waves of 2 types, and low-amplitude and widely split bifid T waves.

The obvious bifid T wave is shown in Figure 2a, with the second component usually occurring early on the downslope of the first component.

The subtle bifid T waves are of 2 types: (1) with the second component occurring at the top (Figure 2b) or (2) on the downslope of the T wave (Figure 2c). We emphasize the subtle nature of these bifid T waves because they can be easily missed if they are not carefully sought.

The low-amplitude and widely split bifid T wave is shown in Figure 2d). The second component often seems to merge with the U wave. This pattern tends to mimic the hypokalemic T-wave configuration.

The bifid T wave can be confused with a TU complex. It is usually distinguishable as a bifid T wave by careful observation of all 12 leads. For example, in Figure 2d, the second component of the T wave is merged with the U wave in leads II, III, aVF, and V5 to V6, but the end of the T wave can be clarified in leads I, aVL, and V1, where the U wave is absent.

Figure 4. Range of quantified repolarization parameters in LQTS genotypes, showing large overlap. This overlap prevents separation of genotypes by individual repolarization parameters.
LQT3 patterns are shown in Figure 3. In late-onset, peaked, and/or biphasic T waves, a long ST segment was present with a narrow peaked or biphasic T wave. The T-wave onset and offset were usually distinct, and the downslope was steep. The QT interval was often markedly prolonged (QTc 530–640 ms).

In the asymmetrical peaked T wave (Figure 3b), the T wave was peaked and asymmetrical with a steep downslope. The QTc was 470–630 ms.

Typical ST–T–wave patterns were seen in 88% of LQT1 and LQT2 carriers and in 65% of LQT3 carriers (Table 1). In LQT1, the normal-appearing T wave was the most common (37%), followed by the broad-based T wave (21%), and late-onset normal-appearing T wave (15%). Approximately 15% of the LQT1 gene carriers were young children, and most showed the infantile pattern. In LQT2, 88% of the gene carriers showed bifid T waves, and 7% showed a nonspecific T wave. There was a 3% overlap of typical patterns between LQT1 and LQT2. In LQT3, 53% of the carriers exhibited the late-onset peaked/biphasic T-wave pattern, 12% exhibited the asymmetrical peaked T-wave pattern, and in 33%, there was overlap with LQT1 patterns.

Quantified Repolarization Variables
Results are shown in Table 2 by genotype and in Table 3 by ST–T–wave pattern subgroup within each genotype. QTc ranged from 410 to 620 ms, with 33% (94 of 284) of the ECGs showing a QTc interval ≤460 ms. QTc was longest in LQT3 (500 ± 50 ms), with a value of P < 0.0001 compared with LQT1 (470 ± 40 ms) and LQT2 (470 ± 30 ms). STc was shortest in LQT2 (130 ± 40 ms, P < 0.0001) and longest in LQT3 (240 ± 30 ms, P < 0.0001). T-wave duration was longest in LQT2 (250 ± 40 ms) versus 190 ± 50 ms in LQT1 and 180 ± 50 ms in LQT3, P < 0.0001. T-wave amplitude was lower in LQT2 (0.21 ± 0.25 mV) than in LQT1 (0.34 ± 0.16 mV) and LQT3 (0.30 ± 0.38 mV) (P < 0.0001). However, as shown in Figure 4, a large overlap of the values between genotypes prevented genotype discrimination by any individual parameter.

Discriminant analysis, using the stepwise method, on the other hand, improved the separation of the genotypes. Two canonical discriminant functions using 3 repolarization variables resulted from this analysis (see Figure 5). The sensitivity/specificity for genotype classification were 85%/70%, 83%/94%, and 47%/63% for LQT1, LQT2, and LQT3, respectively. Low values for LQT3 and the 70% specificity value for LQT1 are concordant with the 33% of LQT3 gene carriers that had T-wave patterns similar to the pattern of LQT1 (Table 1).

Phase II
Genotype Identification by Other Cardiologists
By individual ECG analysis, the mean sensitivity/specificity for LQT1, LQT2, and LQT3 was 61%/71%, 62%/87%, and 33%/88%, respectively. With family-grouped ECG analysis, the mean sensitivity/specificity increased to 77%/81%, 79%/88%, and 54%/100%, respectively (Table 4).

Prospective Genotype Identification in 127 Families Undergoing Genetic Testing
Mutation results were obtained in 63% (80 of 127) of the families studied. The failure to identify mutations in 37% of
the families may have resulted from incomplete sensitivity of single-strand conformation polymorphism analysis, the presence of mutations in regulatory sequences, or the presence of other, currently unidentified, genes causing LQTS.

The flow chart in Figure 6 shows that in 80 families with typical ECG patterns, mutation results were obtained in 56 families. Genotypes were correctly identified by ST-T–wave patterns in all 56 families, including 21 LQT1, 33 LQT2, and 2 LQT3. The other 24 families with typical ECG patterns had no mutations detected. The assigned genotypes for these families were 3 LQT1, 19 LQT2, and 2 LQT3. Because no mutations were found, we cannot determine the accuracy of ECG identification in this group.

Forty-seven of the 127 families had nonspecific ST-T–wave patterns. A guess at a genotype was attempted. Twenty-five of these families obtained mutation results (13 LQT1, 7 LQT2, 1 LQT3, 1 LQT5, and 3 with 2 mutations). The accuracy of genotype identification was low, as expected (Table 5).

**Discussion**

The findings of the present study provide information regarding the pathophysiology of repolarization in LQTS and simple means for identifying the genotype by ECG. We presume that not all LQTS genes have been discovered; thus, other ECG patterns typical for those genotypes may be identified in the future.

**Putative Pathophysiology of Typical ST–T–Wave Patterns**

A physiological rationale exists for the different ST–T–wave morphologies and repolarization parameters, because different currents are affected. Shimizu and Antzelevitch\(^ {11,12} \) created in vitro canine LQT1, LQT2, and LQT3 models to study the electrophysiological and ECG manifestations of each genotype. Cellular electrograms from epicardial, endocardial, and M cells were recorded along with a transmural ECG.

In the LQT1 model,\(^ {11} \) the \( I_{Ks} \) blocker chromanol 293B homogeneously prolonged action potential durations (APDs) of all cell types, resulting in QT prolongation with little or no change of T-wave morphology, consistent with the normal T wave that we found to be the most common pattern in LQT1. Furthermore, they found little increase in transmural dispersion of APDs, presumably consistent with the low incidence of torsade de pointes at rest in LQT1 patients. \( \beta \)-Adrenergic stimulation with isoproterenol abbreviated the APDs of the epicardial and endocardial cells but not of the M cells, producing a broad-based T wave, an increase of transmural dispersion of repolarization, and torsade-like arrhythmia. This is consistent with the adrenergic precipitation of symptoms in LQT1. But this LQT1 model does not explain why many LQT1 patients have the broad-based T wave at rest rather than just during adrenergic stimulation, yet they generally have no symptoms at rest.

In the LQT2 model,\(^ {12} \) the \( I_{Kr} \) blocker d-sotalol produced a greater prolongation of APD in M cells than in epicardial and endocardial cells, resulting in increased transmural dispersion and bifid T waves.

The LQT3 model\(^ {12} \) was induced by sea anemone toxin, a \( \mathrm{Na}^+ \) channel inactivation blocker. It prolonged epicardial, M cell, and endocardial APDs by prolonging phase 2, producing a long-ST segment, late-onset T wave, and markedly prolonged QT interval.

Thus, the ECG recording in each model was concordant with one of the typical ST–T–wave patterns for the respective genotype.

Our results raise questions regarding the generation and regulation of repolarizing currents in LQTS. Why are there multiple ST–T–wave patterns in each genotype? What allows the occurrence in single families of all typical patterns for their genotype? Why is there no apparent relationship between ST–T–wave pattern and clinical phenotype severity to specific mutations even when different mutations produce variable degrees of channel dysfunction\(^ {13} \)? Clearly, the mech-

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**TABLE 5. Accuracy of Prospective Genotype Identification by ECG Patterns in Families With Mutation Results Obtained**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>56 Families With Typical ST–T–Wave Patterns</th>
<th>25 Families With Nonspecific Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>LQT1, %</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>LQT2, %</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>LQT3, %</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

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**Figure 6.** Results of prospective genotype identification by typical ST–T–wave patterns. In families with nonspecific patterns, genotype was assigned on basis of best-guess bases. *Three families had 2 mutations: LQT1 + LQT2, LQT1 + LQT5, and LQT3 + LQT5.
organisms regulating ST–T–wave patterns and QT duration are complex and incompletely understood, perhaps involving other factors such as additional channels, modifier genes, regulatory processes, autonomic activity, serum electrolyte levels, and regional heterogeneity of cardiac ion channel distribution within the myocardium.

**Genotype Identification by ECG**

Our results indicate that genotype can be identified by ST–T–wave patterns in the majority of LQTS patients and families. LQT1 and LQT2 account for $\approx 90\%$ of genotyped patients, and typical patterns were present in $88\%$ of patients with these genotypes. The utility of genotype identification in LQT3 remains somewhat uncertain given the small number of LQT3 patients in the study and the overlap of the LQT3 and LQT1 patterns.

Genotype identification by ECG is useful for stratifying molecular genetic studies. With 5 disease genes and >170 mutations already identified, it is very costly and time-consuming to screen all known genes and mutational sites, limiting the application of genetic studies. With a typical ECG pattern, the suspected gene can be the initial target for testing, with a higher likelihood of rapid identification of the mutation. Such a strategy will significantly reduce time and costs, allowing more families to be genotyped and enhancing genotype-phenotype correlation studies. Furthermore, if therapeutic interventions based on specific genotype$^{14,15}$ are shown to be more effective than empiric therapy, genotype identification by ECG could be helpful for therapeutic decision-making.

Some families had only nonspecific patterns. Fewer ECGs per family were available than those with typical patterns; ECG screening of additional members would probably identify some with typical patterns. Three of the 25 families with genetic results had 2 mutations. Other families may have had mutations in as-yet-unknown genes.

These findings are applicable only to patients and families with an established clinical diagnosis of LQTS. Other forms of heart disease and drugs that alter $I_{Ks}$, $I_{Kr}$, or $I_{Na}$ channel function can produce QT prolongation and similar ST–T–wave patterns. These conditions must be excluded before using these ECG patterns for genotype identification.

In summary, 10 typical ST–T–wave patterns exist in the LQT1, LQT2, and LQT3 genotypes. They are present in the majority of genotyped patients. Evaluation of several ECGs from family members increases the likelihood of finding a typical pattern. Typical patterns and quantified repolarization parameters can be used to identify LQT1, LQT2, and possibly LQT3 genotypes in the majority of LQTS patients and families. This approach can direct mutational screening strategies resulting in cost and time savings.

**Acknowledgments**

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**References**

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