Spectrum of Mutations in Long-QT Syndrome Genes

KVLQT1, HERG, SCN5A, KCNE1, and KCNE2

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Background—Long-QT Syndrome (LQTS) is a cardiovascular disorder characterized by prolongation of the QT interval on ECG and presence of syncope, seizures, and sudden death. Five genes have been implicated in Romano-Ward syndrome, the autosomal dominant form of LQTS: KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. Mutations in KVLQT1 and KCNE1 also cause the Jervell and Lange-Nielsen syndrome, a form of LQTS associated with deafness, a phenotypic abnormality inherited in an autosomal recessive fashion.

Methods and Results—We used mutational analyses to screen a pool of 262 unrelated individuals with LQTS for mutations in the 5 defined genes. We identified 134 mutations in addition to the 43 that we previously reported. Eighty of the mutations were novel. The total number of mutations in this population is now 177 (68% of individuals).

Conclusions—KVLQT1 (42%) and HERG (45%) accounted for 87% of identified mutations, and SCN5A (8%), KCNE1 (3%), and KCNE2 (2%) accounted for the other 13%. Missense mutations were most common (72%), followed by frameshift mutations (10%), in-frame deletions, and nonsense and splice-site mutations (5% to 7% each). Most mutations resided in intracellular (52%) and transmembrane (30%) domains; 12% were found in pore and 6% in extracellular segments. In most cases (78%), a mutation was found in a single family or an individual.

Key Words: long-QT syndrome ■ arrhythmia ■ death, sudden ■ torsade de pointes ■ genetics

Long-QT syndrome (LQTS) is a cardiovascular disorder characterized by an abnormality in cardiac repolarization leading to a prolonged QT interval on the surface ECG. LQTS causes syncope, seizures, and sudden death, usually in young, otherwise healthy individuals.1–3 The clinical features of LQTS result from episodic ventricular tachyarrhythmias, such as torsade de pointes and ventricular fibrillation.4,5 Two inherited forms of LQTS exist. The more common form, Romano-Ward syndrome, is not associated with other phenotypic abnormalities and is inherited as an autosomal dominant trait with variable penetrance.2,3 Jervell and Lange-Nielsen syndrome is characterized by the presence of deafness, a phenotypic abnormality inherited as an autosomal recessive trait.1 LQTS can also be acquired, usually as a result of pharmacological therapy.

In previous studies, we mapped LQTS loci to chromosomes 11p15.5 (LQT1),6 7q35-36 (LQT2),7 and 3p21-24 (LQT3).8 A fourth locus (LQT4) was mapped to 4q25-27.8 Our molecular genetic studies identified 5 genes: KVLQT1 (LQT1),9 HERG (LQT2),10 SCN5A (LQT3),11 and 2 genes located at 21q22, KCNE1 (LQT5)12 and KCNE2 (LQT6).13 KVLQT1, HERG, KCNE1, and KCNE2 encode potassium channel subunits. Four KVLQT1 α-subunits assemble with minK (β-subunits encoded by KCNE1, stoichiometry is unknown) to form Ik, channels underlying the slowly activating delayed rectifier potassium current in the heart.14,15 Four HERG α-subunits assemble with MiRP1 (encoded by KCNE2, stoichiometry unknown) to form Ik, channels, which underlie the rapidly activating, delayed rectifier potassium current.13 Mutant subunits lead to reduction of Ik, or Ip, by a loss-of-function mechanism, often with a dominant-negative effect.16–19 SCN5A encodes the cardiac sodium channel that is responsible for Ina, the sodium current in the heart.20 LQTS-associated mutations
in SCN5A cause a gain of function.\textsuperscript{21,22} In the heart, reduced \(I_{\text{Ks}}\) or \(I_{\text{Kr}}\) or increased \(I_{\text{Na}}\) leads to prolongation of the cardiac action potential, lengthening of the QT interval, and increased risk of arrhythmia. KVLQT1 and KCNE1 are also expressed in the inner ear.\textsuperscript{23,24} We and others have demonstrated that complete loss of \(I_{\text{Ks}}\) causes the severe cardiac phenotype and deafness in Jervell and Lange-Nielsen syndrome.\textsuperscript{23,25–27}

Presymptomatic diagnosis of LQTS is currently based on prolongation of the QT interval on ECG. Genetic studies, however, have shown that diagnosis based solely on ECG is neither sensitive nor specific.\textsuperscript{28,29} Genetic screening using mutational analysis can improve presymptomatic diagnosis. However, no comprehensive study identifying and cataloging all LQTS-associated mutations in all 5 genes has been done. To determine the relative frequency of mutations in each gene, facilitate presymptomatic diagnosis, and allow genotype-phenotype studies, we screened a pool of 262 unrelated individuals with LQTS for mutations in the 5 defined genes.

**Methods**

**Ascertainment and Phenotyping**

Individuals were ascertained in clinics from North America and Europe. They were evaluated for LQTS on the basis of QTc (the QT interval corrected for heart rate) and the presence of symptoms. In this study, we focused on the probands. Individuals show prolongation of the QT interval (QTc \(\geq 460\) ms) and/or documented torsade de pointes, ventricular fibrillation, cardiac arrest, or aborted sudden death. Informed consent was obtained in accordance with local institutional review board guidelines. Phenotypic data were interpreted without knowledge of genotype. Sequence changes altering coding regions or predicted to affect splicing that were not detected in \(\geq 400\) control chromosomes were defined as mutations. No changes except known polymorphisms were detected in any of the genes in the control population. This does not exclude the possibility that some mutations are rare variants not associated with disease.

**Mutational Analyses**

To determine the spectrum of LQTS mutations, we used single strand conformation polymorphism (SSCP) and DNA sequence analyses to screen 262 unrelated individuals with LQTS. Seventeen primer pairs were used to screen KVLQT1,\textsuperscript{30} 21 primer pairs were used for HERG,\textsuperscript{30} and 3 primer pairs were used for KCNE1 and KCNE2.\textsuperscript{12} Thirty-three primer pairs\textsuperscript{31} were used in SSCP analysis to screen all SCN5A exons in 50 individuals with suspected abnormalities in \(I_{\text{Na}}\). Exons 23 to 28, in which mutations were previously identified, were screened in all 262 individuals.

**Results**

We ascertained and phenotyped 262 individuals with LQTS. Sex, age, QTc, and presence of symptoms are summarized in Table 1. The average age at ascertainment was 29 years, and the corrected QT interval was 492 ms. Seventy-five percent had a history of symptoms, and females predominated, with an \(\approx 2:1\) ratio. Although the numbers were small, corrected QT intervals for individuals harboring KCNE1 and KCNE2 mutations were shorter, at 457 ms.

To determine the spectrum of mutations in these individuals, we performed SSCP analyses. KVLQT1 mutations associated with LQTS were identified in 52 individuals (Figure 1, Table 2). Twenty of the mutations were novel.

**Table 1. Age, QTc, Sex, and Presence of Symptoms**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Age, y (mean ± SD)</th>
<th>Sex, F/M</th>
<th>QTc, ms (mean ± SD)</th>
<th>Symptoms, † %</th>
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<td>52/23</td>
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<td>51/29</td>
<td>498±48</td>
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<td>5/26</td>
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<td>55</td>
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<td>40</td>
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<tr>
<td>All</td>
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<td>173/89</td>
<td>492±47</td>
<td>75</td>
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</table>

\*Age at ascertainment.
†Symptoms include syncope, cardiac arrest, and sudden death.

**Figure 1. Schematic of predicted topology of KVLQT1 and locations of LQTS-associated mutations. KVLQT1 consists of 6 putative transmembrane segments (S1 to S6) and a pore (P) region. Each circle represents an amino acid. ● Approximate locations of LQT-associated mutations identified in our laboratory.**

**Figure 2. Schematic of HERG mutations. HERG consists of 6 putative transmembrane segments (S1 to S6) and a pore (P) region. ● Locations of LQT-associated mutations.**
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<th>Position</th>
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<td>60</td>
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<tr>
<td>G477 + 1A</td>
<td>M159sp</td>
<td>S2</td>
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<td>1 JLN, 1 UK</td>
<td>This, 36</td>
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<td>1</td>
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<td>3</td>
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<td>3</td>
<td>36, 38</td>
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</table>
HERG mutations were identified in 68 LQTS individuals (Figure 2, Table 3). Fifty-two of these mutations were novel. SCN5A mutations were identified in 8 cases (Figure 3, Table 4). Five of the mutations were novel. Three novel KCNE1 mutations were identified (Figure 4, Table 5), and 3 mutations were identified in KCNE2 (Figure 5, Table 6). None of the KVLQT1, HERG, SCN5A, KCNE1, or KCNE2 mutations were observed in 400 control chromosomes.

**Discussion**

Previous studies had defined 126 distinct disease-causing mutations in the LQTS genes **KVLQT1**, **HERG**, **SCN5A**, **KCNE1**, and **KCNE2**. The spectrum of mutations in LQTS includes a wide range of genetic variations, with HERG being the most commonly mutated gene, followed by SCN5A. The identification of novel mutations in KCNE1 and KCNE2 further expands our understanding of the genetic basis of LQTS.

<table>
<thead>
<tr>
<th>Nucleotide Change</th>
<th>Coding Effect</th>
<th>Position</th>
<th>Exon</th>
<th>No. of Families†</th>
<th>Study</th>
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Ins indicates insertion; del, deletion; sp, last unaffected amino acid before predicted splice mutation; fs, last amino acid unaffected by a frameshift (number after fs is number of amino acids before termination); JLN, Jervell and Lange-Nielsen syndrome; RW, Romano-Ward syndrome; and UK, unknown.

*Novel mutation.
†Number of Romano-Ward families unless otherwise indicated.
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<td>This</td>
</tr>
</tbody>
</table>

Abbreviations and symbols as in Table 2.
KCNE1, and KCNE2 (Tables 3 to 7).* Most of them were found in KVLQT1 (n=66) and HERG (n=41), and fewer in SCN5A (n=9), KCNE1 (n=7), and KCNE2 (n=3). These mutations were identified in regions with known intron/exon structure, primarily the transmembrane and pore domains. In this study, we screened 262 individuals with LQTS for mutations in all known arrhythmia genes. We identified 134 mutations, 80 of which were novel (Tables 2 to 6). Together with 43 mutations reported in our previous studies, we have now identified 177 mutations in these 262 LQTS individuals (68%). The failure to identify mutations in 32% of the individuals may result from phenotypic errors, incomplete sensitivity of SSCP, or presence of mutations in regulatory sequences. However, it is also clear that additional LQTS genes await discovery.7,8

Missense mutations were most common (72%), followed by frameshift mutations (10%), in-frame deletions, and nonsense and splice-site mutations (5% to 7% each, Table 7). Most mutations resided in intracellular (52%) and transmembrane (30%) domains; 12% were found in pore and 6% in extracellular segments (Table 8). One hundred one of the 129 distinct LQTS mutations (78%) were identified in single families or individuals. Most of the 177 mutations were found in KVLQT1 (n=75; 42%) and HERG (n=80; 45%). These 2 genes accounted for 87% of the identified mutations, and mutations in SCN5A (n=14; 8%), KCNE1 (n=5; 3%), and KCNE2 (n=3; 2%) accounted for the other 13%.

**TABLE 4. Summary of All SCN5A Mutations**

<table>
<thead>
<tr>
<th>Nucleotide Change</th>
<th>Coding Effect</th>
<th>Position</th>
<th>Exon</th>
<th>No. of RW Families</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>G3340A*</td>
<td>D1114N</td>
<td>DII/DIII</td>
<td>18</td>
<td>1</td>
<td>This</td>
</tr>
<tr>
<td>C5911T</td>
<td>T1304M</td>
<td>DIII/S4</td>
<td>22</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>A3974G</td>
<td>N1325S</td>
<td>DIII/S4/S5</td>
<td>23</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>C4501G*</td>
<td>L1501V</td>
<td>DIII/DIV</td>
<td>26</td>
<td>1</td>
<td>This</td>
</tr>
<tr>
<td>del4511–4519</td>
<td>del1505–1507</td>
<td>DIII/DIV</td>
<td>26</td>
<td>4</td>
<td>11, 32</td>
</tr>
<tr>
<td>del4850–4852*</td>
<td>delF1617</td>
<td>DIV/S3/S4</td>
<td>28</td>
<td>1</td>
<td>This</td>
</tr>
<tr>
<td>G4868A</td>
<td>R1623Q</td>
<td>DIV/S4</td>
<td>28</td>
<td>2</td>
<td>This, 53</td>
</tr>
<tr>
<td>G4868T*</td>
<td>R1623L</td>
<td>DIV/S4</td>
<td>28</td>
<td>1</td>
<td>This</td>
</tr>
<tr>
<td>G4931A</td>
<td>R1644H</td>
<td>DIV/S4</td>
<td>28</td>
<td>2</td>
<td>This, 32</td>
</tr>
<tr>
<td>G4934T</td>
<td>T1645M</td>
<td>DIV/S4</td>
<td>28</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>G5349A</td>
<td>E1784K</td>
<td>C-terminal</td>
<td>28</td>
<td>2</td>
<td>This, 59</td>
</tr>
<tr>
<td>G5360A*</td>
<td>S1787N</td>
<td>C-terminal</td>
<td>28</td>
<td>1</td>
<td>This</td>
</tr>
<tr>
<td>A5369G</td>
<td>D1790G</td>
<td>C-terminal</td>
<td>28</td>
<td>1</td>
<td>54</td>
</tr>
<tr>
<td>insTGA5385–86</td>
<td>insD1795–96</td>
<td>C-terminal</td>
<td>28</td>
<td>1</td>
<td>68</td>
</tr>
</tbody>
</table>

Abbreviations and symbols as in Table 2. Fifty individuals with suspected abnormalities in \( I_{Na} \) were screened for all SCN5A exons. All individuals were screened for exons 23–28.

**TABLE 5. Summary of All KCNE1 Mutations**

<table>
<thead>
<tr>
<th>Nucleotide Change</th>
<th>Coding Effect</th>
<th>Position</th>
<th>Exon</th>
<th>No. of RW Families†</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>C20T</td>
<td>T7I</td>
<td>N-terminal</td>
<td>3</td>
<td>1</td>
<td>JLN</td>
</tr>
<tr>
<td>G95A*</td>
<td>R32H</td>
<td>N-terminal</td>
<td>3</td>
<td>1</td>
<td>This</td>
</tr>
<tr>
<td>G139T</td>
<td>V47F</td>
<td>S1</td>
<td>3</td>
<td>1</td>
<td>JLN</td>
</tr>
<tr>
<td>TG151, 152AT</td>
<td>L51H</td>
<td>S1</td>
<td>3</td>
<td>1</td>
<td>JLN</td>
</tr>
<tr>
<td>A172C/</td>
<td>TL58–59</td>
<td>S1</td>
<td>3</td>
<td>1</td>
<td>JLN</td>
</tr>
<tr>
<td>TG176–177CT</td>
<td>PP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C221T</td>
<td>S74L</td>
<td>C-terminal</td>
<td>3</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>G226A</td>
<td>D76N</td>
<td>C-terminal</td>
<td>3</td>
<td>1, 1 RW, 1</td>
<td>26, 1, 56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(JLN + RW)</td>
<td></td>
</tr>
<tr>
<td>T259C</td>
<td>W87R</td>
<td>C-terminal</td>
<td>3</td>
<td>1</td>
<td>61</td>
</tr>
<tr>
<td>C292T*</td>
<td>R98W</td>
<td>C-terminal</td>
<td>3</td>
<td>1</td>
<td>This</td>
</tr>
<tr>
<td>C379A*</td>
<td>P127T</td>
<td>C-terminal</td>
<td>3</td>
<td>1</td>
<td>This</td>
</tr>
</tbody>
</table>

Abbreviations and symbols as in Table 2.
Multiple mutations were found in regions encoding S5, S5/P, P, and S6 of KVLQT1 and HERG. The P region of potassium channels forms the outer pore and contains the selectivity filter. Transmembrane segment 6, corresponding to the inner helix of KcsA, forms the inner two thirds of the pore. This structure is supported by the S5 transmembrane segment, corresponding to the outer helix of KcsA, and is conserved from prokaryotes to eukaryotes.

Mutations in these regions will most likely disrupt potassium transport. Many mutations were identified in the C-terminus of KVLQT1 and HERG. Changes in the C-terminus of HERG could lead to anomalies in tetramerization, because it has been proposed that the C-terminus of eag, which is related to HERG, is involved in this process.

Multiple mutations were also identified in regions that were different for KVLQT1 and HERG. In KVLQT1, multiple mutations were found in the sequences coding for the S2/S3 and S4/S5 linkers. Coexpression of S2/S3 mutants with wild-type KVLQT1 in Xenopus oocytes led to simple loss of function or dominant-negative effect without significantly changing the biophysical properties of \( I_{K_b} \) channels. Conversely, S4/S5 mutations altered the gating properties of the channels and modified KV-LQT1 interactions with minK subunits. In HERG, more than 20 mutations were identified in the N-terminus. HERG channels lacking this region deactivate faster, and mutations in the region had a similar effect.

Mutations in KCNE1 and KCNE2, encoding minK and MiRP1, the respective \( I_{K_b} \) and \( I_{K_c} \) subunits, altered the biophysical properties of the channels. An MiRP1 mutant involved in clarithromycin-induced arrhythmia increased channel blockade by the antibiotic. Mutations in SCN5A, the sodium channel \( a \)-subunit responsible for cardiac \( I_{Na} \), destabilized the inactivation gate, causing delayed channel inactivation and dispersed reopenings. One SCN5A mutant affected the interactions with the sodium channel \( \beta \)-subunit.

It is interesting to note that probands with KCNE1 and KCNE2 mutations were older and had shorter QTc than probands with the other genotypes. The significance of these differences is unknown, however, because the number of probands with KCNE1 and KCNE2 genotypes was small.

This catalogue of mutations will facilitate genotype-phenotype analyses. It also has clinical implications for presymptomatic diagnosis and, in some cases, for therapy. Patients with mutations in KVLQT1, HERG, KCNE1, and KCNE2, for example, may benefit from potassium therapy. Conversely, sodium channel blockers might be helpful in patients with SCN5A mutations. The identification of mutations is of importance for ion channel studies as well. The expression of mutant channels in heterologous systems can reveal how structural changes influence the behavior of the channel or how mutations affect processing. These studies improve our understanding of channel function and provide insights into mechanisms of disease. Finally, mutation identification will contribute to the development of genetic screening for arrhythmia susceptibility.

Acknowledgments

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Spectrum of Mutations in Long-QT Syndrome Genes: KVLQT1, HERG, SCN5A, KCNE1, and KCNE2


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