New Mutations in the KVLQT1 Potassium Channel That Cause Long-QT Syndrome

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Background—Long-QT syndrome (LQTS) is an inherited cardiac arrhythmia that causes sudden death in young, otherwise healthy people. Four genes for LQTS have been mapped to chromosome 11p15.5 (LQT1), 7q35–36 (LQT2), 3p21–24 (LQT3), and 4q25–27 (LQT4). Genes responsible for LQT1, LQT2, and LQT3 have been identified as cardiac potassium channel genes (KVLQT1, HERG) and the cardiac sodium channel gene (SCN5A).

Methods and Results—After studying 115 families with LQTS, we used single-strand conformation polymorphism (SSCP) and DNA sequence analysis to identify mutations in the cardiac potassium channel gene, KVLQT1. Affected members of seven LQTS families were found to have new, previously unidentified mutations, including two identical missense mutations, four identical splicing mutations, and one 3-bp deletion. An identical splicing mutation was identified in affected members of four unrelated families (one Italian, one Irish, and two American), leading to an alternatively spliced form of KVLQT1. The 3-bp deletion arose de novo and occurs at an exon-intron boundary. This results in a single base deletion in the KVLQT1 cDNA sequence and alters splicing, leading to the truncation of KVLQT1 protein.

Conclusions—We have identified LQTS-causing mutations of KVLQT1 in seven families. Five KVLQT1 mutations cause the truncation of KVLQT1 protein. These data further confirm that KVLQT1 mutations cause LQTS. The location and character of these mutations expand the types of mutation, confirm a mutational hot spot, and suggest that they act through a loss-of-function mechanism or a dominant-negative mechanism. (Circulation. 1998;97:1264-1269.)

Key Words: arrhythmias ■ long-QT syndrome ■ potassium ■ death, sudden ■ KVLQT1

Sudden death from cardiac arrhythmias is thought to account for 11% of all natural deaths.1,2 LQTS is an inherited cardiac disorder that causes syncope, seizures, and sudden death, usually in young and otherwise healthy individuals.3–5 In many cases, the first symptom is sudden death. Individuals with LQTS usually have prolongation of the QT interval on electrocardiograms, an indication of abnormal repolarization.5,8 The clinical features of LQTS result from episodic ventricular tachyarrhythmias, specifically torsade de points and ventricular fibrillation.5–11

Inherited LQTS can result from at least five different genes. Four genes were mapped to chromosome 11p15.5 (LQT1),12,13 7q35–36 (LQT2),14 3p21–24 (LQT3),14 and 4q25–27 (LQT4).15 Several other families with autosomal dominant LQTS are not linked to any known LQTS loci (unpublished data), indicating that additional LQTS locus heterogeneity exists. Three LQTS genes (LQT1, LQT2, and LQT3) were identified either by the candidate gene approach or positional cloning. These include the cardiac potassium channel genes KVLQT1 (LQT1),16 HERG (LQT2),17 and the cardiac sodium channel gene SCN5A (LQT3).18,19 In addition, mutations in KVLQT1 were shown to result in both Romano-Ward syndrome (heterozygous mutations) and Jervell and Lange-Nielsen syndrome (homozygous mutations).16,20 Wang et al16 identified 11 different types of KVLQT1 mutations (one 3-bp deletion and 10 missense mutations) in 16 LQTS families with Romano-Ward syndrome and, more recently, Neyroud et al20 identified a homozygous insertion-deletion mutation in Jervell and Lange-Nielsen syndrome.16,20 Here, we report identification of new KVLQT1 mutations in affected members of seven families with Romano-Ward syndrome. We identified two identical missense mutations (one in a
white kindred and the other in a Japanese family), four identical splicing mutations, and a 3-bp deletion that truncates the KVLQT1 channel; the latter mutation arose de novo.

**Methods**

**Identification of LQTS Patients**

LQTS patients were identified throughout North America, Europe, and Asia, with the majority of patients being identified from the International LQTS Registry established by the National Institutes of Health at the University of Rochester, NY. Informed consent was obtained from participants in 115 families in accordance with standards established by local institutional review boards. For each individual, historical data (the presence of syncope, the number of syncopal episodes, the presence of seizures, the age of onset of symptoms, and the occurrence of sudden death) and the length of the QT, \( t \) were obtained. Phenotypic criteria used were as follows: (1) Individuals without any symptoms and with a QT of \( \leq 0.41 \) second were classified as unaffected, (2) symptomatic individuals with a QT of \( \geq 0.45 \) second and asymptomatic individuals with a QT of \( \geq 0.47 \) seconds were considered affected, and (3) symptomatic individuals with a QT of \( \leq 0.44 \) second and asymptomatic individuals with a QT between 0.41 and 0.47 second were classified as uncertain. 12,14,16,18

**Genomic DNA Samples and Linkage Analysis**

Genomic DNA was prepared from peripheral blood lymphocytes or cell lines derived from Epstein-Barr virus–transformed lymphocytes by standard procedures. 22 Genotypic analysis for paternity evaluation was performed with 15 short-tandem-repeat polymorphisms that were previously mapped to 15 different chromosomes (Genome Data Base). Amplification of each short tandem repeat was carried out as previously described. 14,16

**SSCP Analysis**

SSCP and DNA sequence analyses were used to screen for KVLQT1 mutations with DNA samples from 115 LQTS families. The partial genomic structure of KVLQT1 was previously determined. 16 Primers (intronic sequences) that can PCR-amplify exons encoding trans-membrane domains S2-S6 were defined previously from the partial genomic structure and used in this study for SSCP analysis. 16 PCR was carried out in a 10-\( \mu \)L volume containing 50 ng genomic DNA, 0.52 \( \mu \)mol/L of each primer, 75 \( \mu \)mol/L of each dNTP, 1 \( \mu \)Ci [\( ^{32}P \)]dCTP, 0.24 mmol/L spermidine, 1.5 mmol/L MgCl\(_2\), 10 mmol/L Tris (pH 8.3), 50 mmol/L KCl, and 1 U Taq DNA polymerase (Promega and Gibco-BRL). PCR amplification was carried out in a Perkin-Elmer System 9600 thermocycler using the following profile: 1 cycle of denaturation at 94°C for 5 minutes; 5 cycles at 94°C for 20 seconds, 64°C for 20 seconds, 72°C for 30 seconds; and 25 cycles of 94°C for 20 seconds, 62°C for 20 seconds, 72°C for 30 seconds; followed by a 5-minute extension at 72°C. Amplified samples were diluted fivefold with 50 \( \mu \)mol of formamide buffer (95% formamide, 10 mmol/L EDTA, 0.1% bromphenol blue, 0.1% xylene cyanol) and 50 \( \mu \)L of 0.1% SDS/10 mmol/L EDTA. The mixture was denatured at 94°C for 5 minutes, then cooled rapidly on ice and held for 5 minutes. For each sample, 3 to 5 \( \mu \)L was loaded onto 10% nondenaturing polyacrylamide gels (acylamide to bisacrylamide ratio ≈ 45:1) and run at 8 W overnight at room temperature. Gels were dried on Schleicher and Schuell filter paper and exposed to x-ray film.

**DNA Sequencing**

Both normal and aberrant SSCP bands were cut out of the gel and rehydrated in 100 \( \mu \)L water for 30 minutes at 65°C. Ten microliters of the eluted DNA was reamplified with the original PCR primers in a total volume of 100 \( \mu \)L. Amplified products were purified through 2% low-melting agarose. These products were sequenced directly with an ABI Sequencer or subcloned into PBLeuScript-SK\(^{11}\) (Stratagen) by use of the T-vector method as described, 23 and several colonies were sequenced by the dideoxy chain termination method with Sequenase Version 2.0 (United States Biochemicals, Inc).

**Results**

**KVLQT1 Splicing Mutations Associated With LQTS in Four Families**

Aberrant SSCP conformers were identified in affected members of four families (F1002, F1003, F1004, and F1005). Pedigree structures are shown. Individuals with characteristic features of LQT, including prolongation of QT interval on ECG and history of syncope or aborted sudden death are indicated by solid circles (females) or squares (males). Unaffected individuals are indicated by open symbols, and individuals with an equivocal phenotype by hatched symbols. Deceased individuals are indicated by a slash. Results of SSCP analyses are shown below each pedigree. Aberrant SSCP conformers are indicated by arrows. Sequence analyses of normal (left) and aberrant (right) conformers revealed that all four families had an identical change, a G to A substitution (SP/A249/g-a). This mutation occurs in splice-donor sequence of exon in S6 domain. PCR primers 9 and 10 in Wang et al\(^{13}\) were used: 9, CCCCAGGACCCCAGCTGTCCAA; and 10, AGGCTGACCACGTGTCCTCT.

**Figure 1.** KVLQT1 splicing mutation cosegregating with LQT in families F1002, F1003, F1004, and F1005. Pedigree structures are shown. Individuals with characteristic features of LQT, including prolongation of QT interval on ECG and history of syncope or aborted sudden death are indicated by solid circles (females) or squares (males). Unaffected individuals are indicated by open symbols, and individuals with an equivocal phenotype by hatched symbols. Deceased individuals are indicated by a slash. Results of SSCP analyses are shown below each pedigree. Aberrant SSCP conformers are indicated by arrows. Sequence analyses of normal (left) and aberrant (right) conformers revealed that all four families had an identical change, a G to A substitution (SP/A249/g-a). This mutation occurs in splice-donor sequence of exon in S6 domain. PCR primers 9 and 10 in Wang et al\(^{13}\) were used: 9, CCCCAGGACCCCAGCTGTCCAA; and 10, AGGCTGACCACGTGTCCTCT.

**Selected Abbreviations and Acronyms**

LQTS = long-QT syndrome

PCR = polymerase chain reaction

QT = QT interval on ECG corrected for heart rate

SSCP = single-strand conformation polymorphism
disrupts the splice-donor sequence within the S6 transmembrane domain. The fact that the same substitution cosegregated with the disease status in four unrelated LQTS families (one Italian, one Irish, and two American) strongly suggests this variant to be a mutation.

**KVLQT1 Missense Mutations Associated With LQTS in Two Families**

SSCP analysis with a pair of primers in the S6 domain revealed aberrant bands in affected members of families F1006 and F1007 (Fig 2). These abnormal SSCP bands were not seen in DNA samples from unaffected members of these families (Fig 2) or from more than 150 control individuals (data not shown). DNA sequence analysis of the normal and aberrant conformers revealed that both F1006 and F1007 had a white family. The same mutation was previously reported in six other families. PCR primers 9 and 10 in Wang et al16 were used (see Fig 1).

**De Novo Intragenic Deletion of KVLQT1 in a Sporadic Case of LQTS**

SSCP analysis with a pair of primers within the pore region of KVLQT1 identified an aberrant conformer in an affected individual in F1008 (Fig 3). This SSCP anomaly was not observed in DNA samples from either parent, from the patient’s unaffected brother (Fig 3), or from more than 150 control subjects (data not shown). Direct sequencing of the abnormal SSCP band identified a 3-bp deletion (SP/V212/ΔGGT) spanning an exon-intron boundary in the pore region. This deletion results in a frame shift in KVLQT1 cDNA sequence, leading to a nonfunctional protein. Genotypic analysis of this kindred using more than 15 polymorphic markers confirmed paternity. QTc intervals for proband, proband’s father, and proband’s mother are 0.50, 0.39, and 0.36 second, respectively. PCR primers 7 and 8 in Wang et al16 were used: 7, TCCTGGAGCCCGAACTGTGTGT; and 8, AGGCTGACCAGACTGTCCCTCT.

**Phenotype-Genotype Correlation**

Despite the genotypic differences found in these seven families, the phenotype was fairly similar in all affected individuals (Table 1). In six of seven families, the QTc was >0.500 second; the seventh family had QTc measured in the range of 0.490 to 0.493. In addition, six of seven families were symptomatic, with episodes of syncope. Only the family in which the QTc was <0.500 second was without symptoms (Table 1). T-wave alternans, ventricular tachycardia, and torsade de pointes were uncommon; only one family had evidence of T-wave alternans, and two families were noted to have episodes of torsade de pointes (Table 1).

**Discussion**

The potassium channel gene KVLQT1 was initially identified by positional cloning,16 and 11 different types of missense mutations of KVLQT1 were identified in 16 LQTS families in the original report (Table 2). Later, Tanaka et al24 reported...
four missense mutations, and Russell et al\textsuperscript{25} reported two additional missense mutations in three LQTS families, including a previously reported mutation, A246V (previously named A212V) (Table 2). In this report, we found the same A246V mutation in affected members of two more LQTS families, including one Japanese family (Table 2 and Fig 4). To date, of 30 families with \textit{KVLQT1} mutations, alanine at position 246 was mutated 10 times (33\%) (Table 2). The

### TABLE 1. Phenotype-Genotype Correlation

<table>
<thead>
<tr>
<th>Family No.</th>
<th>Affected</th>
<th>Mutation</th>
<th>QT, Average, s (Range)</th>
<th>T-Wave Alternans</th>
<th>Symptoms</th>
<th>VT/TdP</th>
<th>SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1002</td>
<td>7</td>
<td>SP/A249/g-a</td>
<td>0.510 (0.505–0.515)</td>
<td>No Syncope</td>
<td>TdP</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>F1003</td>
<td>6</td>
<td>SP/A249/g-a</td>
<td>0.537 (0.500–0.613)</td>
<td>No Syncope</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>F1004</td>
<td>1</td>
<td>SP/A249/g-a</td>
<td>0.493</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>F1005</td>
<td>2</td>
<td>SP/A249/g-a</td>
<td>0.520 (0.510–0.530)</td>
<td>No Syncope</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>F1006</td>
<td>9</td>
<td>A246V</td>
<td>0.550 (0.500–0.570)</td>
<td>No Syncope</td>
<td>Yes; n=2</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>F1007</td>
<td>2</td>
<td>A246V</td>
<td>0.623</td>
<td>Yes Syncope</td>
<td>TdP Yes; n=1</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>F1008</td>
<td>4</td>
<td>SP/V212/ΔGGT</td>
<td>0.502 (0.500–0.505)</td>
<td>No Syncope</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

QT\textsubscript{c} indicates corrected QT interval for heart rate by Bazzett’s formula: QT = V\sqrt{R – R}; VT, ventricular tachycardia; TdP, torsade de pointes; and SCD, sudden cardiac death.

### TABLE 2. Summary of KVLQT1 Mutations

<table>
<thead>
<tr>
<th>Nucleotide Change</th>
<th>Coding Effect</th>
<th>Mutation Denotation (Old)</th>
<th>Region</th>
<th>Mutation Denotation (New)*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆TCG</td>
<td>Missense</td>
<td>F38W/G39Δ</td>
<td>S2</td>
<td>F72W/G73Δ</td>
<td>Wang et al\textsuperscript{16}</td>
</tr>
<tr>
<td>GCC to CCC</td>
<td>Missense</td>
<td>A49P</td>
<td>S2-S3</td>
<td>A83P</td>
<td>Wang et al\textsuperscript{16}</td>
</tr>
<tr>
<td>GCC to ACC</td>
<td>Missense</td>
<td>A49T</td>
<td>S2-S3</td>
<td>A83T</td>
<td>Tanaka et al\textsuperscript{24}</td>
</tr>
<tr>
<td>GGG to AGG</td>
<td>Missense</td>
<td>G60R</td>
<td>S2-S3</td>
<td>G94R</td>
<td>Wang et al\textsuperscript{16}</td>
</tr>
<tr>
<td>CGG to CAG</td>
<td>Missense</td>
<td>R61Q</td>
<td>S2-S3</td>
<td>R95Q</td>
<td>Wang et al\textsuperscript{16}</td>
</tr>
<tr>
<td>GTG to ATG</td>
<td>Missense</td>
<td>V125M</td>
<td>S4-S5</td>
<td>V159M</td>
<td>Wang et al\textsuperscript{16}</td>
</tr>
<tr>
<td>CTC to TTC</td>
<td>Missense</td>
<td>L144F</td>
<td>S5</td>
<td>L178F</td>
<td>Wang et al\textsuperscript{16}</td>
</tr>
<tr>
<td>GGG to AGG</td>
<td>Missense</td>
<td>G177R</td>
<td>D pore</td>
<td>G211R</td>
<td>Wang et al\textsuperscript{16}</td>
</tr>
<tr>
<td>∆GGT</td>
<td>Deletion</td>
<td>SP/V212(∆GGT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACC to AIC</td>
<td>Missense</td>
<td>T183I</td>
<td>S pore</td>
<td>T2171</td>
<td>Wang et al\textsuperscript{16}</td>
</tr>
<tr>
<td>ATC to ATG</td>
<td>Missense</td>
<td>I184M</td>
<td>S pore</td>
<td>I218M</td>
<td>Tanaka et al\textsuperscript{24}</td>
</tr>
<tr>
<td>GGC to ACC</td>
<td>Missense</td>
<td>G185S</td>
<td>S pore</td>
<td>G219S</td>
<td>Russel et al\textsuperscript{23}</td>
</tr>
<tr>
<td>GGG to AGG</td>
<td>Missense</td>
<td>G185S</td>
<td>S pore</td>
<td>G219S</td>
<td>Russel et al\textsuperscript{23}</td>
</tr>
<tr>
<td>GTG to ATG</td>
<td>Missense</td>
<td>G185R</td>
<td>S6</td>
<td>G230R</td>
<td>Tanaka et al\textsuperscript{24}</td>
</tr>
<tr>
<td>GGT to GAG</td>
<td>Missense</td>
<td>A212E</td>
<td>S6</td>
<td>A246E</td>
<td>Wang et al\textsuperscript{16}</td>
</tr>
<tr>
<td>GGC to GAG</td>
<td>Missense</td>
<td>A212E</td>
<td>S6</td>
<td>A246E</td>
<td>Wang et al\textsuperscript{16}</td>
</tr>
<tr>
<td>GGC to GTG</td>
<td>Missense</td>
<td>A212V</td>
<td>S6</td>
<td>A246V</td>
<td>Wang et al\textsuperscript{16}</td>
</tr>
<tr>
<td>GGG to GTG</td>
<td>Missense</td>
<td>A212V</td>
<td>S6</td>
<td>A246V</td>
<td>Wang et al\textsuperscript{16}</td>
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<td>A246V</td>
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<td>Missense</td>
<td>A212V</td>
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</tr>
<tr>
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<td>Missense</td>
<td>A212V</td>
<td>S6</td>
<td>A246V</td>
<td>Wang et al\textsuperscript{16}</td>
</tr>
<tr>
<td>CAGTACT to GTTGAGAT</td>
<td>Deletion and Insertion</td>
<td>C-terminal</td>
<td>G\textsubscript{114} V\textsubscript{116} S\textsubscript{117} G\textsubscript{119} G\textsubscript{119} X\textsubscript{122} to V\textsubscript{116} E\textsubscript{117} A\textsubscript{118} G\textsubscript{119} X\textsubscript{122}</td>
<td>Neya et al\textsuperscript{20}</td>
<td></td>
</tr>
</tbody>
</table>

*The previously reported KVLQT1 sequence by Wang et al\textsuperscript{16} lacked 34 amino acids at the N-terminal end, which has been cloned recently.\textsuperscript{32} The new mutation denotation system is based on the complete amino acid sequence of KVLQT1.
frequent occurrence of A246 mutations and its presence in both white and Japanese populations indicate that the alanine residue at position 246 is a mutational hot spot in KVLQT1.

An identical splicing mutation was identified in affected members of four unrelated families (one Italian, one Irish, and two American); no unaffected individuals from these families or from more than 150 normal control subjects demonstrate the splicing mutation. In addition, the mutation occurs in a highly conserved region of the gene. Together, these data strongly suggest that the splicing change we identified is the disease-causing mutation. We also identified a 3-bp deletion that arose de novo. The 3-bp deletion, spanning an exon-intron boundary in the pore region, not only alters splicing but also leads to a 1-bp deletion in the coding region, causing a frame shift and truncation of the KVLQT1 protein. These data strongly support the notion that mutations in KVLQT1 cause the chromosome 11-linked LQTS.

Since the original identification of genes for chromosome 3-linked LQTS (SCN5A) and chromosome 7-linked LQTS (HERG), electrophysiological studies have established that the molecular mechanism for chromosome 3-linked LQTS is the presence of a late phase of inactivation-resistant sodium current in the plateau phase of the action potential (a gain-of-function mechanism), whereas HERG mutations cause the loss of IKs, the late potassium current, through dominant-negative mechanisms or loss-of-function mechanisms. Molecular mechanisms of KVLQT1 mutations are currently unknown. Analysis of the predicted amino acid sequence of KVLQT1 suggests that it encodes a potassium channel subunit. Recent electrophysiological characterization of the KVLQT1 protein in various heterologous systems has confirmed that KVLQT1 is a voltage-gated potassium channel protein. When coexpressed with minK, KVLQT1 forms the slowly activating potassium current (IKs) in cardiac myocytes. A combination of normal and mutant KVLQT1 subunits could therefore form abnormal IKs channels. Thus, LQTS-associated mutations of KVLQT1 could act through a dominant-negative mechanism. The type and location of KVLQT1 mutations described here are consistent with this hypothesis. The missense mutation, A246V, was identified in two families and affects the S6 domain. Two mutations lead to premature termination and truncated proteins (one splicing mutation identified in four unrelated families and one 3-bp deletion that arose de novo). In the first case, the S6 domain and the carboxyl end of the protein are truncated, leaving intact the amino end of the protein and S1 domain to the pore. In the second case, a frame shift and altered splicing cause truncation of the protein in the pore. Alternatively, the latter two mutations could act through a loss-of-function mechanism. In general, these patients had moderate symptomatology, with relatively frequent episodes of syncope and long QT intervals (>0.500 second). It is unclear whether mutations in certain regions of the KVLQT1 gene will cause more malignant disease than mutations in other regions of the gene. Electrophysiological characterization of KVLQT1 mutations will shed light on the molecular mechanisms of these mutations and possibly allow for predictions of clinical outcome.

Neyroud et al demonstrated a homozygous insertion-deletion mutation in the 3′ end of KVLQT1 leading to Jervell and Lange-Nielsen syndrome, which includes LQT and deafness. They show that the hearing abnormality occurs in three individuals because of the loss of function of the channel, which is the result of mutation on both alleles (ie, homozygous mutation). When a heterozygous mutation occurs, no matter at which end of the gene, it appears that Romano-Ward syndrome (ie, no deafness) results. Despite the possibility that heterozygous mutations in KVLQT1 act in a dominant-negative mechanism, some functional KVLQT1 potassium channels exist in the stria vasilaris of the inner ear. Therefore, deafness is averted.

Identification of SCN5A and HERG as LQTS genes has led to potential new rational gene-specific therapy to prevent life-threatening arrhythmias. Mexiletine, a sodium channel blocking agent, has been shown to markedly shorten the QTc interval, and R01-HL-51618 (Dr Moss), and The Texas Children’s Hospital Foundation Endowed Chair in Pediatric Cardiac Research (Dr Towbin). Dr Wang is also a Visiting Professor of the China National Rice Research Institute.


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