Brief report

Genetic Testing of Patients With Long QT Syndrome

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ABSTRACT

Congenital long QT syndrome is mainly caused by mutations in the KCNQ1, KCNH2 and SCN5A genes. The aim of this study was to investigate the prevalence of mutations in these three genes in patients with long QT syndrome or idiopathic ventricular fibrillation seen at our center. The study included nine patients with long QT syndrome and four with idiopathic ventricular fibrillation. Overall, 71.4% of mutations were in KCNH2 and 28.6% were in SCN5A. No mutations were found in KCNQ1. Only two mutations had been previously observed. Mutations were also found in six of the 19 relatives studied. In conclusion, our initial experience shows that genetic testing had a high sensitivity for diagnosing long QT syndrome. Mutations were found most frequently in the KCNH2 gene.

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Estudio genético en el síndrome de QT largo en nuestro medio

RÉSUMÉ

Le syndrome de QT long congénitо са se caractérise par des mutations des gènes KCNQ1, KCNH2 et SCN5A. Nous avons évalué la prévalence des mutations dans ces gènes dans notre série de patients, soit pour le syndrome de QT long et fibrillation ventriculaire idiopathique. Il s'agissait de 9 patients avec le syndrome de QT long et 4 avec fibrillation ventriculaire idiopathique. Les mutations étaient dans 71,4% dans KCNH2 et dans 28,6% dans SCN5A. Nous n'avons pas trouvé de mutations dans le KCNQ1. Seulement deux mutations avaient été précédemment signalées. Les mutations étaient aussi trouvées chez 6 des 19 proches étudiés. En conclusion, notre expérience initiale montre que le test génétique a une grande sensibilité pour le diagnostic de syndrome de QT long. Mutations étaient le plus fréquemment trouvées dans la KCNH2.

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INTRODUCTION

Long QT syndrome (LQTS) is a cardiac channelopathy that can lead to sudden death caused by ventricular arrhythmias. Hundreds of mutations associated with this condition have been described in 12 different genes, mainly encoding sodium and potassium channels. 1,2,3 Approximately 75% of the mutations described in LQTS are located in 3 genes: KCNQ1 (potassium channel), KCNH2 (potassium channel), and SCN5A (sodium channel). In 25%–30% of patients with LQTS, complete sequencing of all the genes with known mutations fails to yield a genetic diagnosis. 3

Since LQTS has a penetrance of between 25% and 90%, patients with the disease may nevertheless have a normal electrocardiogram (ECG). In the event of cardiac arrest, these patients may be classified as having idiopathic ventricular fibrillation (IVF). Although the etiology of LQTS is not restricted to channelopathies, the potential usefulness of testing for mutations in the genes implicated in LQTS has recently been highlighted. 4

The aim of this study was to describe the main genotypic characteristics of a group of patients with LQTS and assess the usefulness of genetic testing in patients with IVF.

METHODS

The study included 9 patients who met the diagnostic criteria for LQTS (mean (SD) age, 22.6 (21.6) years; 66.7% women) and 4 patients with IVF (age, 26 (22.1) years; 50% women) who were assessed in our arrhythmias unit. The study included family history, laboratory workup, echocardiogram, and Holter monitoring. In the 4 patients with IVF and a normal corrected QT (QTC)
interval, an electrophysiology study was carried out, along with coronary angiography, flecainide and epinephrine challenge. Genetic testing was carried out in 19 relatives of the probands with abnormal genotypes. All patients or their legal guardians provided signed informed consent.

A 5 mL sample of peripheral blood was obtained for use as a sequencing template and the genes were sequenced by polymerase chain reaction. Only missense mutations that were not present in controls were considered pathologic.

RESULTS

The clinical characteristics of the patients are shown in Table 1. The results of the clinical and genetic study are shown in Table 2. Of the 9 patients with LQTS, 7 (77.7%) had mutations: 71.4% in KCNH2 and 28.6% in SCN5A. No mutations were identified in KCNQ1. Only 2 of the mutations had previously been reported as associated with LQTS.2,5 Two patients (50%) with IVF had mutations, one in KCNH2 and the other in SCN5A; neither mutation had been described previously.

KCNH2

Mutations were most commonly found in KCNH2. The mean age of the affected patients was 17.3 (16) years and the mean QTc interval was 511 ms. We found 8 mutations (Table 2), only 2 of which had been previously described as associated with LQTS (G1882S and G1714R).2,5 Both are located between the P (pore) region and the fifth transmembrane domain, an essential region that acts as a selectivity filter for potassium.9

SCN5A

Of the patients with LQTS in whom a mutation was identified, 28.6% had previously undescribed missense mutations in SCN5A. However, the clinical course supported a diagnosis of type 3 LQTS; there was evidence of a direct causal relationship with LQTS. Previous studies showed that genetic alterations are found in 65%–70% of cases and that the most frequently mutated gene is SCN5A.1,8 We observed a slightly higher frequency of mutations (77.7%), and in our patients KCNH2 was the most commonly affected gene. These results cannot be extrapolated, however, given the small sample size.

DISCUSSION

Although isolated mutations have been reported,7 no data are available from Spanish patient series addressing the genetic characteristics of LQTS. Our study provides preliminary data on the genotype profile of a small group of Spanish patients with LQTS and IVF. A multicenter study will be necessary to obtain larger groups and draw conclusions that can be extrapolated to the general population. Previous studies showed that genetic alterations are found in 65%–70% of cases and that the most frequently mutated gene is KCNQ1.1,8 We observed a slightly higher frequency of mutations (77.7%), and in our patients KCNH2 was the most commonly affected gene. These results cannot be extrapolated, however, given the small sample size.
Table 2
Mutations Associated With Long QT Syndrome in Our Patient Series

<table>
<thead>
<tr>
<th>QTc</th>
<th>Pharmacological stress test (adrenaline/flecainide)</th>
<th>Phenotypic diagnosis</th>
<th>Diagnostic score</th>
<th>Treatment</th>
<th>Genetic study</th>
<th>Final diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>555</td>
<td>No</td>
<td>LQTS</td>
<td>8</td>
<td>ICD</td>
<td>KCNH2 + (1910 A&gt;G; Glu&gt;Gly)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>478</td>
<td>No</td>
<td>LQTS</td>
<td>4</td>
<td>ICD</td>
<td>SCN5A + (3985 G&gt;R Gly&gt;Ser)</td>
</tr>
<tr>
<td>Patient 3</td>
<td>442</td>
<td>+</td>
<td>LQTS</td>
<td>4</td>
<td>ICD</td>
<td>SCN5A + (1673 A&gt;R His&gt;Arg)</td>
</tr>
<tr>
<td>Patient 4</td>
<td>367</td>
<td>–</td>
<td>IVF</td>
<td>1</td>
<td>ICD</td>
<td>Negative</td>
</tr>
<tr>
<td>Patient 5</td>
<td>405</td>
<td>–</td>
<td>IVF</td>
<td>2</td>
<td>ICD</td>
<td>KCNH2 + (541 C&gt;G Arg&gt;Trp) (577 G&gt;R Al-Thr) (62 G&gt;R Gly&gt;Arg)</td>
</tr>
<tr>
<td>Patient 6</td>
<td>631</td>
<td>No</td>
<td>LQTS</td>
<td>8</td>
<td>ICD</td>
<td>KCNH2 + (1714 G&gt;R Gly&gt;Ser)</td>
</tr>
<tr>
<td>Patient 7</td>
<td>413</td>
<td>–</td>
<td>IVF</td>
<td>2</td>
<td>ICD</td>
<td>SCN5A + (1673 A&gt;R His&gt;Arg)</td>
</tr>
<tr>
<td>Patient 8</td>
<td>720</td>
<td>No</td>
<td>LQTS</td>
<td>7.5</td>
<td>ICD</td>
<td>Negative</td>
</tr>
<tr>
<td>Patient 9</td>
<td>577</td>
<td>No</td>
<td>LQTS</td>
<td>4</td>
<td>BB</td>
<td>Negative</td>
</tr>
<tr>
<td>Patient 10</td>
<td>–</td>
<td>No</td>
<td>LQTS</td>
<td>4</td>
<td>ICD</td>
<td>KCNH2 + (343G&gt;R Val&gt;Met)</td>
</tr>
<tr>
<td>Patient 11</td>
<td>488</td>
<td>+</td>
<td>LQTS</td>
<td>5</td>
<td>ICD</td>
<td>KCNH2 + (1882 G&gt;S Gly&gt;Arg)</td>
</tr>
<tr>
<td>Patient 12</td>
<td>400</td>
<td>–</td>
<td>IVF</td>
<td>1</td>
<td>ICD</td>
<td>Negative</td>
</tr>
<tr>
<td>Patient 13</td>
<td>476</td>
<td>No</td>
<td>LQTS</td>
<td>3.5</td>
<td>No</td>
<td>KCNH2 + (del 3079–3124)</td>
</tr>
</tbody>
</table>

Abbreviations: A, homozygous adenine; Al, alanine; Arg, arginine; Asp, aspartic acid; BB, beta blockers; C, homozygous cytosine; ICD, implantable cardioverter defibrillator; IVF, idiopathic ventricular fibrillation; G, homozygous guanine; Gly, glycine; Glu, glutamic acid; His, histidine; Met, methionine; R, heterozygous guanine/adenine; S, heterozygous guanine/cytosine; Ser, serine; LQTS, long QT syndrome; Thr, threonine; Trp, tryptophan; Val, valine.

Of the 9 missense mutations found, only 2 had previously been described as having a causal relationship with LQTS. Although the disease could be ruled out in asymptomatic relatives of these patients, analysis of the biophysical properties of the mutated ion channels would be necessary to unequivocally establish pathogenicity. However, data such as the region of the channel that is affected, the resulting amino acid change, and the absence of this protein in control subjects can help to assess the potential pathogenicity of the mutation.

In our case series, 22.2% of the patients with LQTS and 50% of those with IVF had a negative genotype. This finding highlights the need to perform more extensive genetic testing in negative cases to include all other genes that have been described, along with the importance of exploring new candidate genes to explain the etiology of LQTS.

The proportion of patients with arrhythmic events following treatment with beta blockers, which are more frequent in LQTS3 etiology of LQTS. Importantly, exploring new candidate genes to explain the need to perform more extensive genetic testing in negative cases to include all other genes that have been described, along with the importance of exploring new candidate genes to explain the etiology of LQTS.

CONFLICTS OF INTEREST

The authors state that they have no conflicts of interest.

REFERENCES


