Mutation Analysis of the Glycerol-3 Phosphate Dehydrogenase-1 Like (GPD1L) Gene in Japanese Patients With Brugada Syndrome

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Brugada syndrome is an inherited arrhythmic disorder, and mutations in the SCN5A gene, encoding cardiac sodium channels, are identified in approximately 15% of cases. A novel causative gene (glycerol-3 phosphate dehydrogenase-1 like; GPD1L) has been reported, and in the present study, 80 unrelated Japanese patients were screened for GPD1L mutations: 1 synonymous mutation was identified, as well as 1 intronic variant, both of which were absent in 220 control alleles. Additionally, a single-nucleotide polymorphism was detected in 4 patients. No non-synonymous mutations were found. GPD1L does not appear to be a major cause of Brugada syndrome in the Japanese population.

Key Words: Arrhythmia; Brugada syndrome; GPD1L

Brugada syndrome (BrS) is an inherited disorder, characterized by sudden death from ventricular tachyarrhythmias and ST-segment elevation in the right precordial leads! In approximately 15% of patients, loss-of-function mutations in the SCN5A gene, which encodes the α-subunit of the voltage-gated cardiac sodium channel, have been identified; however, other responsible genes remain to be determined.

Recently, London et al identified a new causative gene, glycerol-3 phosphate dehydrogenase-1 like (GPD1L), using linkage analysis of a large Italian-descent family. GPD1L mutations were found in patients with sudden infant death syndrome, but London’s group did not identify GPD1L mutations in the probands of 19 smaller families with BrS. Other investigators also failed to detect GPD1L mutations in 38 Dutch BrS patients.

BrS is more prevalent in Asian countries, including Japan and we previously reported genetic analysis in 38 Japanese BrS patients. We therefore screened extensively for the prevalence of GPD1L and SCN5A mutations in 80 Japanese probands with BrS in the present study, which was approved by the Institutional Ethics Committee and all patients provided informed consent.

The cohort consisted of 76 males and 4 females (mean age, 47.4±17.0 years); 39 patients (48.9%) were symptomatic and 26 (32.5%) had a family history of sudden death. The entire GPD1L coding region was amplified by each exon, and analyzed by denaturing high-performance liquid chromatography (Table 1).

We identified SCN5A mutations in 8 of the 80 patients (10%). Regarding GPD1L mutation analysis, we identified 1 synonymous mutation, c.465C>T (p.A155A), as well as 1 intronic variant, 48-30T>C, which were not present in 220 control alleles (Fig 1A). Neither of the probands experienced syncopal episodes nor did they have a family history of sudden death. However, both of them underwent implantable cardioverter defibrillator implantation because of inducible ventricular fibrillation during electrophysiological studies. Additionally, we detected a single-nucleotide polymorphism (*21G>T) in the 3’UTR in 4 patients (Fig 1A). The allele frequency of *21G>T in BrS patients (4/160) was not significantly different from that of normal controls (11/220). None of the GPD1L-variant carriers had SCN5A mutations. Fig 1B is a schematic of GPD1L and the location of the identified variants. Synonymous mutations and intronic variants might influence the splicing of exons and thereby cause various human diseases, so we examined whether these variants might be predicted to cause splicing abnormality, using the splice-site prediction web interface (http://www.fruitfly.org/index.html). The variants did not change the scores of the splice donor or acceptor sites, suggesting they are unlikely to affect the splicing of GPD1L.

Recently, Antzelvitch et al reported that L-type cardiac calcium-channel gene mutations cause a specific type of BrS associated with short QT syndrome. Koopmann et al investigated a number of candidate genes (GPD1L, Caveolin-3, Irx-3, Irx-4, Irx-5, Irx-6, Plakoglobin, Plakophilin-2, SCN1B, SCN2B, SCN3B, and SCN4B) in 38 Dutch BrS patients, but no mutations were found. Despite enormous efforts, the genetic cause of the majority of BrS patients remains unknown. Nongenetic factors or unrecognized environmental factors may be responsible, but further studies are needed.

In conclusion, the present data suggest that the GPD1L does not appear to be a major cause of BrS in the Japanese population.
population.

References

Table 1  
GPD1L Primer Sequences and DHPLC Analysis Conditions

<table>
<thead>
<tr>
<th>Exon</th>
<th>Forward primer sequence</th>
<th>Reverse primer sequence</th>
<th>PCR annealing temp (°C)</th>
<th>DHPLC temp (°C)</th>
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<tbody>
<tr>
<td>1</td>
<td>ACGGTCCAGGCGGCTACATT</td>
<td>GCAAGCAGTGTCCTCTGTTG</td>
<td>61.8</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>CTCTCCCGCCCAAAGTTGTT</td>
<td>CCAAGTGCTGTCAGCAGCAAG</td>
<td>62</td>
<td>67, 65.3</td>
</tr>
<tr>
<td>3</td>
<td>CCGTGGGACGGCAGAGGTT</td>
<td>TGCTCTAGCCCTGGCACAGCT</td>
<td>62</td>
<td>61.2, 62.5</td>
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<tr>
<td>4</td>
<td>GCGCTTGTGCTTCTCTCTAA</td>
<td>TAAAGGAGCAGGAGAAGAGT</td>
<td>62</td>
<td>61.4</td>
</tr>
<tr>
<td>5</td>
<td>TCCCTGTGCTAACTCTTTCT</td>
<td>TGATGAACCTCTCCCTGTAG</td>
<td>56</td>
<td>60, 61</td>
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<tr>
<td>6</td>
<td>GGTGGCGTGAAGCCTCTGCT</td>
<td>CCAAGCGAGGACGTTGACAGT</td>
<td>62</td>
<td>62.8, 64.5</td>
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<tr>
<td>7</td>
<td>TTCTTAGCTTTACCTCATGT</td>
<td>ATGGAAAAGTGGACAGCTTTA</td>
<td>50</td>
<td>57.5, 60, 61.5</td>
</tr>
<tr>
<td>8</td>
<td>CAACGGCCTAATTTGTCT</td>
<td>AGTCGGCAGTACCTTTGCT</td>
<td>56</td>
<td>58, 59</td>
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</table>

GPD1L, glycerol-3 phosphate dehydrogenase-1 like; DHPLC, denaturing high-performance liquid chromatography; PCR, polymerase chain reaction.

Fig 1. Genetic analysis and schematic representation of glycerol-3 phosphate dehydrogenase-1 like gene. (A) Denaturing high-performance liquid chromatography (DHPLC) elution profiles (Upper) and DNA sequencing electropherograms (Lower). (B) Exons and introns are shown as boxes and lines, and coding and non-coding regions are indicated by closed and open boxes, respectively.