Background & Purpose
The incidence of Brugada syndrome (BrS) varies among racial groups. Several studies reported Glycerol-3-Phosphate Dehydrogenase-1 Like (GPD1-L) gene is associated with BrS. However, most of these studies were reported from Western countries, so the evidence about GPD1-L mutation is limited among Asian BrS patients. This study aimed to search for rare variants in GPD1-L among Japanese BrS patients and to investigate the pathogenicity.

Methods
• We performed whole-exome sequencing for patients with Brugada type 1 ECG pattern from Japanese multicenter BrS cohort consisting of SCN5A mutation negative BrS probands (n=288) and controls (n=372).
• We conducted patch-clamp study in human embryonic kidney (HEK) 293 cells cotransfected with the wild-type sodium channel (SCN5A) and wild-type or mutant GPD1-L expression plasmid.
• The HEK cells were cotransfected with 0.6 μg wild-type SCN5A (i.e. cardiac sodium channel) and 0.6 μg wild-type or mutant GPD1-L IRES-GFP construct.

Results
• We identified a rare variant in GPD1-L, p.D262N (c.784g>a) in 2 of 288 unrelated BrS probands by whole-genome sequencing (Table 1).

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<tr>
<th></th>
<th>BrS probands</th>
<th>Healthy controls</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>All study patients</td>
<td>288</td>
<td>372</td>
<td>660</td>
</tr>
<tr>
<td>GPD1-L mutation (+)</td>
<td>2 (0.7%)</td>
<td>0</td>
<td>2 (0.3%)</td>
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</table>

Table 1.

The variant was confirmed with Sanger sequencing (Figure 1).

Characteristics of the patients with GPD1L p.D262N
Patient 1 (Figure 2)
• The patient 1 (III-3) was a 49-year-old man who was a survivor of unexplained ventricular fibrillation (VF).
• Pilsicainide unmasked a coved type ST elevation.
• His father (II-1) with the same GPD1-L variant was asymptomatic and did not show brugada-type ECG.

Patient 2 (Figure 3)
• The patient 2 (II-1) was a 34-year-old with unexplained VF.
• Pilsicainide unmasked a coved type ST elevation.

Computational evidence

Electrophysiological Studies
• We conducted patch clamp technique for SCN5A+ wild-type GPD1L, SCN5A+ A280V GPD1L, which has been previously reported as a pathogenic variant, and SCN5A+ D262N, which was identified in this study.
• SCN5A+ A280V GPD1L and SCN5A+ D262N significantly reduced inward Na+ currents compared to SCN5A+ wild-type GPD1L. (Figure 4 shows current-voltage relationship for peak I(Na).

Discussion
• There are no reports showing non-synonymous GPD1-L variant in Japanese BrS patients but this study identified a rare non-synonymous variant in GPD1-L, D262N in 2 of 288 unrelated BrS probands.
• Computational predictive programs supported the deleterious effect of GPD1-L, D262N. Also, we confirmed that this variant, as well as GPD1-L p.A280V, significantly reduced sodium currents compared to wild-type GPD1-L.
• These findings indicated a possibility of pathogenicity although all genes reported to be associated with BrS have not yet established clinical validity, excepting SCN5A.

Conclusions
We identified a rare variant in GPD1-L at the rate of 0.7% in Japanese BrS patients without SCN5A mutations. GPD1-L p.D262N reduces inward sodium currents and may be a novel susceptible variant for BrS in the Japanese population.