Novel variant of the Glycerol-3-Phosphate Dehydrogenase-1 Like (*GPD1-L*) Gene in Japanese Brugada Syndrome Patients

1. Department of Cardiovascular Medicine, Graduate School of Medical Science, Kanazawa University, 2. Omics Research Center, National Cerebral and Cardiovascular Center
3. Department of Cardiovascular Medicine, International University of Health and Welfare, 4. Department of Human Genetics, Nagasaki University Graduate School of Biomedical Sciences
Keisuke Usuda[1], Kenshi Hayashi[1], Taisuke Ishikawa[2], Yoshiyasu Aizawa[3], Takeshi Kato[1], Toyonobu Tsuda[1], Takashi Kusayama[1], Satoru Niwa[1], Soichiro Usui[1], Kenji Sakata[1], Masa-aki Kawashiri[1], Hiroyuki Mishima[4], Koh-ichiro Yoshiura[4], Naomasa Makita[2], Masayuki Takamura[1]

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).

	BrS probands	Healthy controls	All
All study patients	288	372	660
GPD1-L mutation (+)	2 (0.7%)	0	2 (0.3%)

Table 1.

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

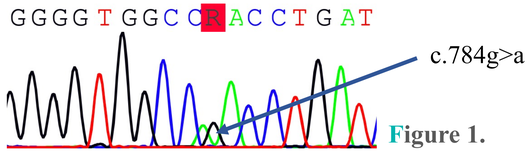


Figure 1.

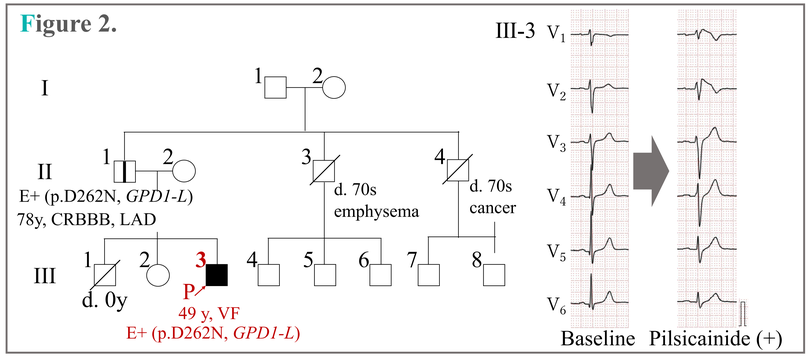
- The minor allele frequency of the variant is **0.0014% in gnomAD** (global database), **0% in East Asian from gnomAD** and **0.0066% in TogoVar** (Japanese database).

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.

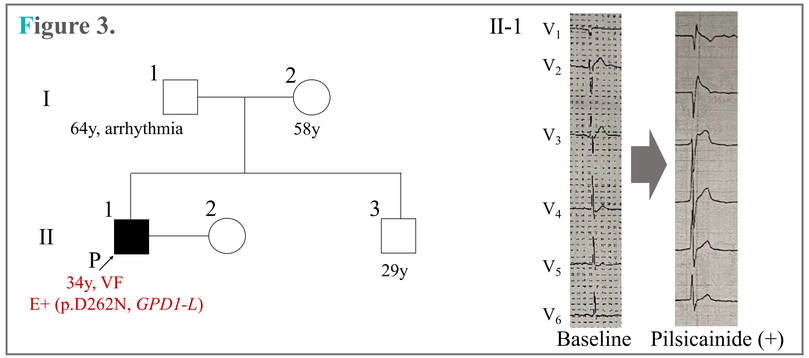
Figure 2.



Patient 2 (Figure 3)

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

Figure 3.



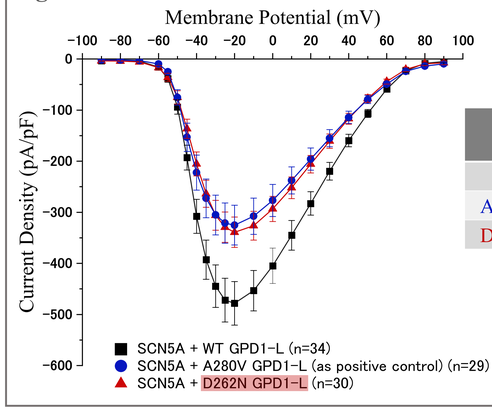
Computational evidence

Algorithms	Cutoff	Score	Prediction
SIFT	"deleterious" based on SIFT scores (<0.05)	0.031	damaging
PROVEAN	"deleterious" based on PROVEAN scores (<-2.5)	-4.36	deleterious
CADD	a score of 30 or greater indicates a raw score in the top 0.1%	33	likely deleterious

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})

Figure 4.



	Current density at -20 mV (pA/pF)
WT	-484 ± 43
A280V	-344 ± 29 *
D262N	-336 ± 39 *

P < 0.05 vs WT.
(ANOVA 1way)

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.