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Review

Brugada Syndrome and *GPD1L*: Definite Genotype-Phenotype Association?

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Abstract: The *GPD1L* gene encodes a small cytoplasmic protein that is involved in the regulation of sodium currents. Alterations in this gene have been associated with Brugada syndrome. This rare arrhythmogenic syndrome is characterized by a typical electrocardiographic pattern, incomplete penetrance, variable expressivity, and risk of sudden cardiac death. To date, few families with a clinical diagnosis of Brugada syndrome caused by a rare alteration in the *GPD1L* gene have been reported worldwide. The increase in data focused on genetic variants allows us to improve the interpretation of their role in Brugada syndrome. In our study, we have compiled the *GPD1L* variants reported so far in patients with a definitive clinical diagnosis or suspected Brugada syndrome. We performed an exhaustive update and interpretation of each variant following the guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Our results showed that none of the variants described to date can be classified as truly harmful in Brugada syndrome. Despite this fact, more clinical and genetic data are needed to definitively rule out the *GPD1L* gene as a cause of Brugada syndrome. In summary, to date, there is insufficient evidence to conclude a definitive association between *GPD1L* and Brugada syndrome.

Keywords: arrhythmias; Brugada syndrome; *GPD1L*; genetics; reinterpretation

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1. Introduction

Brugada syndrome (BrS) is a rare inherited arrhythmogenic syndrome (IAS) characterized by malignant episodes, usually occurring at rest/night. A wide spectrum of phenotypic expressivity has been reported, from asymptomatic to syncope and sudden cardiac death (SCD), always in normal structural hearts [1]. The diagnosis is confirmed

by the typical elevation of the ST segment in the right precordial leads (V1-V3) followed by T wave negativity on the electrocardiogram (ECG), the so-called type 1 ECG. To date, hundreds of rare variants located in different genes have been suggested as the cause of BrS, but all of them together do not explain more than 35% of the diagnosed cases (*ABCC9*, *AKAP9*, *ANK2*, *CACNA1C*, *CACNA2D1*, *CACNB2*, *CASQ2*, *DSG2*, *DSP*, *FGF12*, *GPD1L*, *HCN4*, *HEY2*, *KCNAB2*, *KCNB2*, *KCND2*, *KCND3*, *KCNE3*, *KCNE5*, *KCNH2*, *KCNJ8*, *KCNJ16*, *KCNT1*, *LRRC10*, *PLN*, *PKP2*, *RANGRF*, *RyR2*, *SCN10A*, *SCN1B*, *SCN2B*, *SCN3B*, *SCN4A*, *SCN5A*, *SCNN1A*, *SEMA3A*, *SLMAP*, *TBX5*, *TKT*, *TRPM4*, *TTN*, *XIRP1*, and *XIRP2*). In fact, only the *SCN5A* gene has been definitively associated with BrS to date, which is responsible for almost 30% of BrS cases [2]. Most reported rare variants in BrS continue to have an ambiguous role, according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guidelines [3]. These variants are classified as of unknown significance (VUS), so it is yet to be clarified whether other genes play a suspected or conclusive damaging role in BrS [4]. The ongoing clinical and genetic data published in BrS may help clarify the role of these genes.

One of the current minority genes associated with BrS is *GPD1L* (HGNC: 28956/NCBI Gene: 23171). This gene encodes the glycerol-3-phosphate dehydrogenase-like protein 1 (G3PD1L), which is located on chromosome 3p22.3, near the *SCN5A* gene (main gene responsible for BrS). The *GPD1L* gene is composed of eight exons and covers 62.2 Kb, generating a protein of 351 amino acids. The protein encoded is cytoplasmic and is associated with the alpha subunit of the voltage-gated sodium channel type V (Nav1.5) protein, encoded by the *SCN5A* gene. The G3PD1L protein plays a role in the regulation of the Nav1.5 cardiac sodium channel along with other proteins associated with this sodium channel [5]. The first link between *GPD1L* and BrS was established by genetic linkage analysis [6], and in 2007, London et al. published the first candidate gene analysis [7] (phenotype MIM number: 611777/Gene-Locus MIM number: 611778). To our knowledge, 10 variants in the *GPD1L* gene have been published that have been associated with patients diagnosed with BrS or with a BrS-like phenotype to date.

In our study, we have focused on rare *GPD1L* variants associated with BrS to update the available data and clarify the role of these rare variants as a definitive or suspected cause of this malignant IAS.

2. Materials and Methods

Our study included all rare variants reported to date (November 2024) in the *GDP1L* gene associated with patients/families with a definitive diagnosis of BrS. All collected data were discussed and verified by the authors. No studies were eliminated due to inaccurate or incomplete clinical evaluations/diagnoses or genetic analyses. Clinical and genetic data were collected from PubMed, ClinGen, OMIM, Springer Link, and Science Direct. Only English language studies were included in this study. Genetic data were updated in MasterMind, Varsome, LOVD, ClinVar, and the Genome Aggregation Database. Finally, all rare variants identified in the *GPD1L* gene were reclassified following ACMG/AMP guidelines [3], including specific modifications/updates [8–12]. All authors also discussed and agreed on the updated genetic classification, and the definitive or potential deleterious role of each *GPD1L* variant in BrS.

3. Results

We identified 15 studies that reported a total of 10 rare variants in the *GPD1L* gene associated with BrS (Table 1). More than one rare variant was reported in six of these studies; concretely, four variants in Hedley et al. [13], three variants in Van Norstrand et al. [14], and two variants in four studies [15–19]. In addition, four rare variants were

identified in more than one study: p.(Ala280Val) in six studies [7,13,17,19,20], p.(Glu83Lys) in five studies [5,13,14,16,17], as also occurs with p.(Ile124Val) [13,14,16,21,22], and finally p.(Arg273Cys) identified in two studies [13,14]. All variants were reported in heterocigosis, which is located in the central exons of the gene (between exons 2 and 6), and were missense except for two: one intronic (c.48-30T>C) [15] and other nonsense, p.(Arg189Ter) [23] (Table 1; Figure 1).

Table 1. Genetic data of variants in the *GPD1L* gene potentially associated with Brugada Syndrome or phenotype-like (updated November 2024). ACMG/AMP: American College of Medical Genetics and Genomics and the Association for Molecular Pathology; LB: likely benign; NA: not available; VUS: variant of unknown significance.

Nucleotide	Protein	dbSNP/ClinVar	GnomAD (%)	ACMG/AMP	Reported
c.48-30T>C	NA	rs1700537085/NA	8/1367436 (0.0005%)	VUS	Makiyama, 2008
c.161A>T	p.(Asp54Val)	NA	NA	VUS	Yuan, 2021
c.247G>A	p.(Glu83Lys)	rs72552292/ VUS	245/1461762 (0.016%)	LB	Van Norstrand, 2007 Valdivia, 2009 Hedley, 2009 Paludan-Müller, 2019 Chen, 2019
c.257A>G	p.(Gln86Arg)	rs755240955/ VUS	6/1461764 (0.0004%)	VUS	Marshall, 2019
c.335C>T	p.(Pro112Leu)	rs1201810677/NA	5/1461802 (0.0003%)	VUS	Fan, 2020
c.370A>G	p.(Ile124Val)	rs72552293/ LB	2412/1461798 (0.16%)	LB	Van Norstrand, 2007 Hedley, 2009 Hasdemir, 2015 Paludan-Müller, 2019 Sahlin, 2019
c.465C>T	p.(Ala155Ala)	rs113645050/ LB	1276/1461858 (0.08%)	LB	Makiyama, 2008
c.565C>T	p.(Arg189Ter)	rs982730623/ VUS	NA	VUS	Huang, 2018
c.817C>T	p.(Arg273Cys)	rs72552294/ VUS	87/1461446 (0.005%)	LB	Van Norstrand, 2007 Hedley, 2009
c.839C>T	p.(Ala280Val)	rs72552291/ VUS	117/1461050 (0.008%)	LB	London, 2007 Hedley, 2009 Liu, 2009 Chen, 2019 Campuzano, 2019 Fan, 2020

All of these rare variants were reported as causing BrS at the time of first publication, but after updating the data available so far, none should be classified as pathogenic/likely pathogenic (P/LP) according to the ACMG/AMP guidelines. Actually, five variants should be classified as VUS: c.48-30T>C, p.(Asp54Val), p.(Gln86Arg), p.(Pro112Leu), and p.(Arg189Ter) (Table 1; Figure 1). These five variants show low population frequencies in recently updated databases, and in silico algorithms have conflicting predictions. Furthermore, the lack of family segregation data, as well as functional studies, does not allow us to obtain a conclusive role for each of these variants in BrS. Specifically, only two variants were functionally analyzed and a decrease in G3PD1L protein expression was identified in both: p.(Pro112Leu) and p.(Arg189Ter). The other five variants should be classified as likely benign (LB): p.(Glu83Lys), p.(Ile124Val), p.(Ala155Ala), p.(Arg273Cys), and p.(Ala280Val)

(Table 1; Figure 1). These last five variants currently have population frequencies that are too high to be harmful based on the prevalence of BrS. In addition, in silico algorithms show conflicting predictions or a tendency to be tolerated, thus ruling out a deleterious role in BrS.

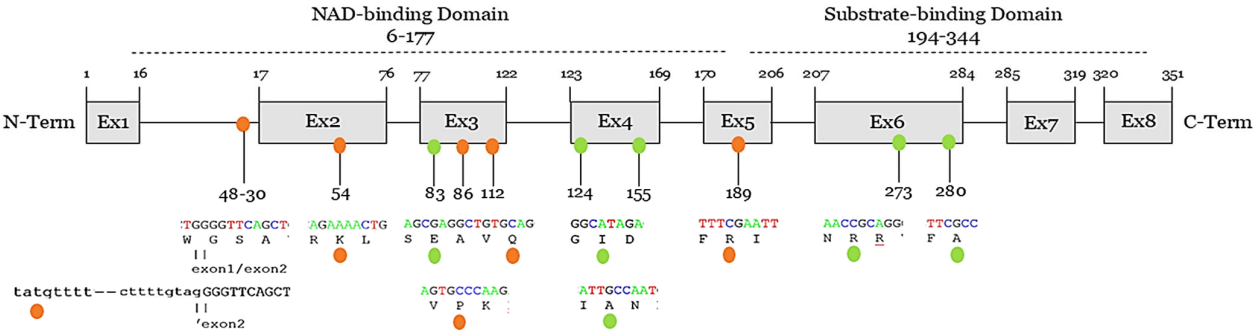

Figure 1. Diagram of rare variants reported in Brugada syndrome in the *GPD1L* gene. Numbers indicate amino acids of reported variants. Green cercles indicate variants classified as likely benign. Orange cercles indicate variants classified as ambiguous. C-Term: 3′ C-Terminal; Ex: exon; N-Term: 5′ N-Terminal; NAD: nicotinamide adenine dinucleotide.

4. Discussion

Our study is the first to comprehensively analyze the *GPD1L* variants associated with BrS. We identified 10 rare variants, all of which were potentially associated with the BrS phenotype. However, our comprehensive genetic reanalysis showed that none should be classified as P/LP according to the current ACMG/AMP guidelines. Therefore, the association between variants in *GPD1L* and BrS must be appropriately interpreted before clinical translation because of the limited evidence available to date. This result is consistent with the non-definitive association of this gene with BrS [2].

The first key point to consider is the establishment of a definite BrS diagnosis in the patients in which these variants were identified [7,15,24,25]. For instance, patients showing atrioventricular nodal re-entrant tachycardia (AVNRT) with concealed BrS [21], ventricular tachycardia with recurrent syncope [23], early repolarization syndrome (ERS) [19], and cases of sudden unexplained death (SUD)/sudden infant death syndrome (SIDS) [14,16,22] have also been reported. A conclusive clinical diagnosis of BrS is crucial before genetic testing because patients may show ST-segment elevation mimicking a type 1 BrS pattern due to causes unrelated to BrS, so-called Brugada ECG phenocopy [26]. Only five of the 10 variants reported in the *GPD1L* gene were identified in patients with a definitive diagnosis of BrS: c.48-30T>C, p.(Asp54Val), p.(Gln86Arg), p.(Ala155Ala), and p.(Ala280Val). However, none of these five variants showed a functional correlation with the pathophysiological mechanism implicated as the cause of BrS. Regarding population frequencies, one variant showed no MAF data to date: c.48-30T>C, and two variants showed very low MAF: p.(Asp54Val), p.(Gln86Arg). Finally, two variants showed a too high MAF to be considered deleterious: p.(Ala155Ala) and p.(Ala280Val). Taking all these items into account, the ACMG/AMP guidelines allowed for the classification of three variants as VUS: c.48-30T>C, p.(Asp54Val), and p.(Gln86Arg). Two variants were classified as LB: p.(Ala155Ala) and p.(Ala280Val).

Regarding functional analysis, only two variants reported so far have been evaluated in vitro: p.(Pro112Leu) [19] and p.(Arg189Ter) [23]. In both studies, a significant decrease in protein expression was reported, but the mechanisms of expression and abnormal intracellular transport of the G3PD1L protein have not yet been clarified. The missense variant p.(Pro112Leu) was reported in an ERS patient [19], and the nonsense variant p.(Arg189Ter) was reported in a family with ventricular tachycardia, recurrent syncope,

and cases of sudden death [23]. Taking these elements into account, the ACMG/AMP guidelines allow for the classification of these two variants as VUS. Therefore, further comprehensive functional studies with conclusive results may help clarify the role of these two rare variants, as well as the role of other reported *GPD1L* variants.

Currently, more than a hundred rare variants in different genes are proposed to be causative of BrS. In a previous study published by our group, we performed a comprehensive analysis of all genes potentially associated with BrS and concluded that only the *SCN5A* gene should be classified as having a definitive association with BrS based on the data published so far [27]. This conclusion is in concordance with the consensus published in 2022 by Wilde et al. [2]. Today, we stand by this statement and believe that only *SCN5A* should be included in the current list of genes associated with BrS to allow genetic diagnosis in the clinical setting. However, we cannot rule out the possibility that other alterations in minority genes not identified so far could be associated with BrS. Some minority genes, although not yet clearly associated with BrS, show a high probability of causality (*SCN2B, SCNN1A, SEMA3A,* and *SLMAP*) [27]. Based on the obtained data, we completed the aforementioned gene list, including *GPD1L*, because some of the analyzed variants remain classified as VUS and cannot be ruled out as deleterious in BrS.

In the field of genetic research, additional genetic approaches focusing mainly on whole genome sequencing (WGS) should be performed to discover new genetic alterations and/or genes. These alterations may help explain the genetic origin of more than 70% of families diagnosed with BrS but without a genetic diagnosis. In this way, genome-wide association studies (GWAS) in patients with BrS have identified rare non-coding variants at the *SCN5A* locus [28,29], but also common variants at this and other sodium channel-associated genes that may influence BrS susceptibility, suggesting a polygenic architecture [30–32]. Currently, these studies focus on the group of different proteins that are part of the protein complex and are involved in the correct functioning of the cardiac sodium channel. Therefore, further studies may uncover common and/or rare variants in the regulatory regions of the *GPD1L* gene that may cause BrS.

Previous studies suggested that the dysfunction of glycerol-3-phosphate dehydrogenase 1-like protein leads to a reduction in I_{Na} current through the GPD1-L-dependent phosphorylation of Nav1.5. It implies a decreased surface membrane expression of the Nav1.5 channel, leading to a reduction in the depolarizing current [5,7]. Due to the low number of patients carrying rare variants in the *GPD1L* gene, no exhaustive studies have been performed so far concerning drug-induced ECG type 1 in comparison to spontaneous diagnostic ECG. Despite this lack of data, clinical protocol and genetic testing for BrS patients carrying a rare variant in the *GPD1L* gene should be the same as *SCN5A* genetic carriers [33]. It is important to remark that the role of electrophysiological study (EPS) in risk stratification was not deeply analyzed in *GPD1L* genetic carriers; however, the last data concerning this critical point suggest that EPS does not seem to aid prognostic stratification in drug-induced type-1 BrS patients [34].

We acknowledge that our study has some limitations that we must mention. The current insufficient number of families with a definitive diagnosis of BrS reported worldwide carrying a rare variant in the *GDP1L* gene prevents an irrefutable association or rejection of this gene as a cause of BrS. Therefore, further studies in large cohorts should be conducted to resolve this genotype-phenotype gap. Furthermore, functional studies (in vivo and/or in vitro) are necessary to clarify the role of each variant and thus help to unravel an undisputable association between *GPD1L* and BrS. From our point of view, if all variants currently classified as VUS degrade their role, the real involvement of this gene as a cause of BrS should be ruled out.

5. Conclusions

In conclusion, BrS is a rare genetic disease associated with arrhythmogenic malignant events. Ten rare variants in the *GPD1L* gene have been reported as potential causes of BrS. Periodic updating of genetic variants should be performed due to the continuous viability of clinical and genetic data, especially if a variant remains classified as ambiguous. We identified that none of the rare variants reported so far in the *GPD1L* gene played a defined deleterious role in BrS. This finding implies a suspected but not definitive association of the *GPD1L* gene with BrS, so a personalized and careful translation of *GPD1L* variants in patients with BrS must be performed. We recommend including this gene in the genetic analysis of families diagnosed with BrS because, to date, no irrefutable data are available to definitively rule out this gene as a cause of BrS.

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