Novel SCN5A Frameshift Mutation in Brugada Syndrome Associated With Complex Arrhythmic Phenotype

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In this case report, we characterize a novel inherited frameshift mutation c.4700_4701del (p.Phe1567Cysfs*221) in a single copy of the SCN5A gene and its association with Brugada syndrome (BrS). The proband experienced a life-threatening ventricular arrhythmia successfully treated with DC-shock and he also suffered from supraventricular tachycardia. Ajmaline test confirmed the BrS diagnosis. No other mutation nor low frequency variants in the other 23 analyzed genes were detected. The same mutation was found in the father and sister, who were both diagnosed with BrS. We hypothesize that this mutation could be responsible for BrS and potentially linked to supraventricular tachycardias. Further studies are needed to confirm this observation and to assess the clinical relevance of this mutation, in terms of risk-stratification.

Keywords: Brugada syndrome, sudden cardiac death, genetic testing, mutation, SCN5A, sodium channel, arrhythmia, atrial fibrillation

INTRODUCTION

The Brugada syndrome (BrS) is characterized by a coved-type ST-segment elevation in the right precordial leads on the electrocardiogram (ECG) and an increased risk of sudden cardiac death (SCD). Diagnosis requires the presence of a type 1 BrS pattern on the ECG that occurs either spontaneously or after administration of a sodium channel blocking agent, such as ajmaline (Antzelevitch et al., 2016), which reveals the type 1 pattern. The arrhythmias that occur in BrS can be eliminated using transcatheter radiofrequency (RF) ablation of the arrhythmogenic substrate (AS) that is usually found in the epicardial surface of the right ventricle (RV). Ajmaline may be used to fully visualize the extent of the AS to improve the success of the procedure.

Brugada syndrome is inherited as an autosomal dominant condition with incomplete penetrance. The most commonly associated genetic mutations are found in the SCN5A gene, thought to be responsible for about 15–30% of BrS cases (Kapplinger et al., 2010). However, no genetic mutations of any kind are detected in the majority of BrS patients, perhaps due to both loci...
heterogeneity and large genomic rearrangements only detectable with other genetic analyses. The need exists to further understand the genetics of BrS, especially for the high rate of asymptomatic individuals who could undergo pre-symptomatic non-invasive genetic testing and, if mutated, be recommended for a specific arrhythmologic follow-up.

**CASE PRESENTATION**

Written informed consent of human subjects included in this case report was obtained for their participation in the study and for publication of this case report. The procedures employed were reviewed and approved by the local Ethics Committee. The proband is a 28-year-old male with a history of recurrent syncopal episodes. A 12-lead ECG performed at the age of 27 years demonstrated a type 3 BrS pattern. After a couple of weeks, the proband underwent a 12-lead ECG that demonstrated atrioventricular nodal reentrant tachycardia (AVNRT). One month later, he was admitted to the emergency room elsewhere because of a life-threatening tachycardia (AVNRT). After sinus rhythm restoration, a type 1 BrS pattern was noticed. The patient underwent an electrophysiological study (EPS) and was found to be inducible. Therefore, he received a subcutaneous ICD.

At this stage he came to our attention. All the performed clinical tests (metabolic assessment, EEG, anion-cation concentration, hormonal functions) were negative. Next, an ajmaline test confirmed BrS. Thereafter, he underwent catheter ablation of AVNRT, and the AS responsible for BrS (Figure 1). The EPS and ajmaline test were repeated after ablation and were both negative. A control echocardiogram showed no pericardial effusion.

**Genetic Studies**

After careful genetic counseling, we decided to perform a genetic analysis of genomic DNA extracted from saliva and study 24 genes known to be causative of BrS (ABCC9, AKAP9, CACNA1C, CACNA2D1, CACNB2, DSG2, GPD1L, HCN4, KCND2, KCND3, KCNE3, KCNE5, KCNH2, KCNJ8, MOG1, PKP2, RANGRF, SCN5A, SCN10A, SCN1B, SCN2B, SCN3B, SEMA3A, TRPM3). This analysis demonstrated that the proband carries the novel mutation c.4700_4701del (p.Phe1567Cysfs*221) in a single copy of the SCN5A gene. Genetic testing revealed the variant c.4700_4701del (p.Phe1567Cysfs*221) in a single copy of the SCN5A gene (Figure 2).

The proband’s 22-year-old sister experienced syncope after gastroenteritis at the age of 20 years. She also experienced recurrent unexplained syncopal episodes. Consequently, several 12-lead ECGs were performed, but none raised the suspicion of BrS. A positive ajmaline test confirmed a BrS diagnosis. For these reasons she received ICD. AS ablation was performed (Figure 4). Genetic testing revealed the variant c.4700_4701del (p.Phe1567Cysfs*221) in a single copy of the SCN5A gene.

The proband’s mother does not carry the familial variant in the SCN5A gene and any kind of consanguinity with her husband was excluded.

**DISCUSSION**

Many studies have described single copy SCN5A frameshift mutations in BrS (Probst et al., 2009; Dolz-Gaiton et al., 2013). It is known that SCN5A frameshift mutations can cause BrS alone or in compound heterozygosity with a missense mutation (Barajas-Martinez et al., 2013). Our hypothesis is that the novel frameshift mutation herein described is responsible for the proband’s clinical picture characterized by a complex arrhythmologic phenotype.

Brugada syndrome clinical expression varies from totally asymptomatic to life-threatening arrhythmias. BrS patients harboring a compound heterozygous mutation of the SCN5A gene seem to be affected by the worst clinical picture (Sacilotto et al., 2017). However, a possible rescue effect due to the different contributions of two mutations in the same gene has been reported (Nunez et al., 2013).

A relationship between syncopal episodes and pediatric arrhythmias was known even before the discovery of BrS (Romano et al., 1963). Further studies have highlighted the frequency of supraventricular arrhythmias in patients affected by BrS (Liu et al., 2015). A clinical study involving 46 BrS patients (39 male and 7 female) showed that 5 (3 male and 2 female) exhibited supraventricular tachycardias (Liu et al., 2015). Another clinical study (Hasdemir, 2016) emphasized the prevalence of atrial arrhythmias in BrS patients. In fact, mutations in the SCN5A gene have been found responsible for atrial fibrillation, Long QT syndrome type 3, sick sinus syndrome type 2, idiopathic ventricular fibrillation, and heart block type 1A (Olson et al., 2005). While atrial fibrillation is the most common arrhythmia to overlap with BrS, cases of supraventricular tachycardia have been described (Milanesi et al., 2015). An article by Hasdemir et al. (2015) studied 96 patients with AVNRT screened for BrS. The

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1 https://databases.lovd.nl/shared/variants/0000371905
**FIGURE 1** | Proband ECG and potential duration map at baseline, after ajmaline administration, and after ablation.
FIGURE 2 | (A) Identification of the heterozygous c.4700_4701del deletion by next generation sequencing. NGS paired-end reads loaded in the IGV genome browser. The gene sequence is in the reverse orientation on the chromosome. (B) Identification of the heterozygous c.4700_4701del deletion by sanger sequencing. Sanger sequencing confirmation of the deletion compared with the wild-type sequence. The wt (black) and mutated (red) sequences are reported. The position of the two bases deleted is indicated by the red arrow. Black arrows indicate the direction of the gene. (C) Family pedigree. Proband identified with an arrow. Square: male; Circle: female; Shaded: clinically affected by Brugada syndrome; Star: molecularly confirmed SCN5A mutation; Triangle: genetically tested and negative for SCN5A mutation.
result was that 26 out of 96 patients exhibited a BrS type 1 pattern after ajmaline challenge. Genetic testing was then performed on these patients exhibiting a dual phenotype, revealing mutations in genes known or suspected to be responsible for sodium channel loss-of-function (Hasdemir et al., 2015). In fact, several familial forms of AVNRT
have been reported (Hayes et al., 2004; Namgung et al., 2012). Thus, the overlap between AVNRT and BrS may well be underappreciated.

SCN5A mutations have been described as causative of a variety of pathologies. SCN5A missense mutations can be associated with BrS or atrial fibrillation, while frameshift mutations can result in pathologies including BrS and AVNRT (Chen et al., 1998). While it is certain that SCN5A mutations can cause BrS, it is less clear whether the SCN5A mutation described herein could be responsible for the other phenotypes. Variants in genes not tested for in our patients have been associated

![FIGURE 4 | Sister of the proband: ECG at baseline and after ajmaline administration. Epicardial arrhythmogenic substrate.](image)
with AVNRT (Andreasen et al., 2018). Thus, we cannot rule out the existence of AVNRT-causing variants that were not detected in this study. Additionally, we cannot exclude mitochondrial DNA variations between the proband and his sister that may account for variations in phenotype, as mitochondrial and nuclear genomes may cross-regulate each other (Kim et al., 2018). Regardless, the novel mutation herein described should be further investigated as a cause of BrS and possibly the other pathologies presented. Finally, BrS arrhythmogenic substrate ablation is a novel approach for this disease and long-term follow-up data are not yet available.

**CONCLUDING REMARKS**

In this report, we documented for the first time the novel inherited frameshift mutation c.4700_4701del (p.Phe1567CysfsX221) in a single copy of the SCN5A gene and its association with BrS. Further studies are needed to confirm this observation and to assess the clinical relevance of this mutation, in terms of risk-stratification.

**REFERENCES**

Andreasen, L., Ahlberg, G., Tang, C., Andreasen, C., Hartmann, J. P., Tfelt-Hansen, J., et al. (2018). Next-generation sequencing of AV nodal reentrant tachycardia patients identifies broad spectrum of variants in ion channel genes. *Eur. J. Hum. Genet.* 26, 660–668. doi: 10.1038/s41431-017-0092-0

Antzelevitch, C., Yan, G. X., Ackerman, M. J., Borggrefe, M., Corrado, D., Guo, J., et al. (2016). J-Wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. *Heart Rhythm* 13:e295–e324. doi: 10.1016/j.hrthm.2016.05.024

Barajas-Martinez, H., Hu, D., and Antzelevitch, C. (2013). [Genetic and molecular basis for sodium channel-mediated Brugada syndrome]. *Arch. Cardiol. Mex.* 83, 295–302. doi: 10.1016/j.acmx.2013.10.001

Chen, Q., Kirsch, G. E., Zhang, D., Brugada, R., Brugada, J., Brugada, P., et al. (1998). Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 392, 293–296. doi: 10.1038/32675

Dolz-Gaiton, P., Nunez, M., Nunez, L., Barana, A., Amoros, I., De La Fuente, M. G., Dolz-Gaiton, P., Gomez, R., et al. (2013). p.D1690N Nav1.5 rescues p.G1748D mutation gating defects in a compound heterozygous Brugada syndrome patient. *Heart Rhythm* 10, 264–272. doi: 10.1016/j.hrthm.2012.10.025

Olson, T. M., Michels, V. V., Ballew, J. D., Reyna, S. P., Karst, M. L., Herron, K. J., et al. (2005). Sodium channel mutations and susceptibility to heart failure and atrial fibrillation. *JAMA* 293, 447–454.

Probst, V., Wilde, A. A., Barc, J., Sacher, F., Babuty, D., Mabo, P., et al. (2009). SCN5A mutations and the role of genetic background in the pathophysiology of Brugada syndrome. *Circ. Cardiovasc. Genet.* 2, 552–557. doi: 10.1161/CIRCGENETICS.108.853374

Romano, C., Gemme, G., and Pongiglione, R. (1963). [Rare cardiac arrhythmias of the pediatric age. II. syncopal attacks due to paroxysmal ventricular fibrillation. (presentation of 1st case in italian pediatric literature)]. *Clin. Pediatr.* 45, 656–683.

Sacilotto, L., Epifanio, H. B., Darrieux, F. C., Wulkan, F., Oliveira, T. G., Hachul, D. T., et al. (2017). Compound heterozygous SCN5A mutations in a toddler - - are they associated with a more severe phenotype? *Arq. Bras. Cardiol.* 108, 70–73. doi: 10.5935/abc.20170006

**ETHICS STATEMENT**

Informed consent of human subjects included in this case series report was obtained. The procedures employed were reviewed and approved by the local Ethics Committee.

**AUTHOR CONTRIBUTIONS**

EM, GC, GV, MC, VM, LG, FG, AP, MS, PP, CD, SB, MF, VS, and CP collected the data. EM and MM wrote the manuscript. All authors interpreted the results, critically reviewed the manuscript, and approved the final version.

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