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Case Report

A SCN5A gene mutation (c.1768 A>C, p.K590Q) in a patient with Brugada syndrome: a case report

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Abstract: Background: Brugada syndrome (BrS) is an arrhythmia disorder most commonly associated with loss-of-function variants in the SCN5A gene. We report a 33-year-old man presenting with spontaneous type-1 BrS electrocardiographic (ECG) pattern and recurrent syncope. Case summary: Sequencing revealed a heterozygous SCN5A variant, c.1768 A>C (p.K590Q), which was absent from the Human Gene Mutation Database (HGMD), gnomAD (allele frequency 0.000004), ClinVar, and the 1000 Genomes database. The substituted lysine is highly conserved across species (HomoloGene) and resides in the domain II-III linker at the extracellular pore entrance. In silico analyses (PolyPhen-2 and MutationTaster) predicted a deleterious effect. Following implantation of an implantable cardioverter-defibrillator, the patient has remained asymptomatic for 14 months. The same variant was detected in his 6-year-old son, who currently shows no ECG abnormalities. Conclusion: The SCN5A c.1768 A>C substitution represents a novel, ultra-rare missense change variant. Its evolutionary conservation, predicted pathogenicity, and familial segregation support a probable association with BrS, warranting further functional characterization.

Keywords: Brugada syndrome, SCN5A, gene mutation

Introduction

Brugada syndrome (BrS) is a rare autosomal dominant cardiac ion channel disorder characterized by the absence of structural cardiac abnormalities and the presence of distinctive electrocardiographic (ECG) features. These include a coved or saddleback-type ST-segment elevation in leads V1-V3, with or without right bundle branch block, and are often accompanied by polymorphic ventricular tachycardia, ventricular fibrillation, recurrent syncope, and a high risk of sudden cardiac death, especially among young and middle-aged men [1-3]. BrS accounts for approximately 4% of all sudden death and about 20% of sudden deaths in individuals without structural heart disease, with sudden death being the initial manifestation in many patients, making prevention and treatment particularly challenging [4].

With advances in molecular genetics, several genes have been implicated in the pathogenesis of BrS, among which SCN5A, as a gene encoding the α-subunit of the cardiac sodium channel, is the most commonly affected. Mutations in SCN5A accounts for about 20%-25% of BrS cases [5, 6]. Such mutations can lead to sodium channel dysfunction, affect the depolarization and repolarization of cardiomyocytes, and lead to ECG abnormalities and predispose individuals to ventricular arrhythmias [7].

In this case report, we describe a patient with BrS carrying a rare SCN5A mutation (c.1768 A>C), which is rarely reported, with no prior case analysis. Through genetic testing, in silico functional prediction, and comprehensive analysis of the patient's clinical data, ECG findings, and family history, we aim to elucidate the relationship between this rare SCN5A gene mutation and BrS, providing new insights for its prevention, diagnosis, and treatment.

Clinical data

A 33-year-old male was admitted to Jincheng People's Hospital on June 6, 2022. The family consisted of five members across three generations, with no consanguinity among relatives. The patient's father had a history of recurrent

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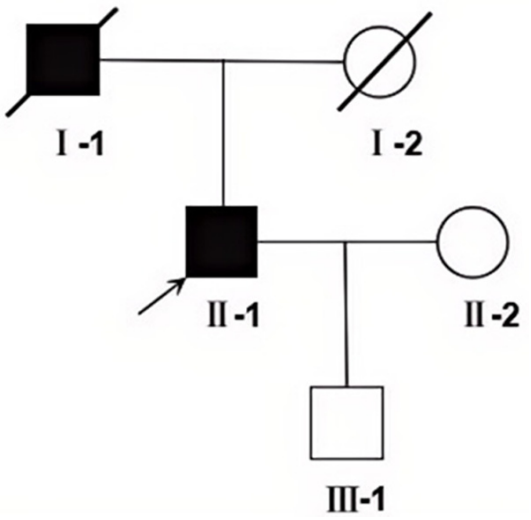

Figure 1. Family pedigree. Note: ■ affected male (suspected); ⬭ unaffected female; □ unaffected male; / deceased, and the arrow indicates the proband.

syncope and died suddenly in his sleep at the age of 44 years. Written informed consent was obtained from the patient and his family members. The family diagram is shown in **Figure 1**, where II-1 denotes the proband and III-1 denotes his son. After obtaining consent, both II-1 and III-1 were enrolled in this study for genetic and clinical evaluation.

The proband (II-1), a 33-year-old male, was admitted to the hospital for evaluation of a single episode of syncope. At approximately 9:00 p.m. on June 4, 2022, he experienced dizziness and sweating triggered by emotional stress while using his mobile phone. Within seconds, he lost consciousness and collapsed, without chest tightness, chest pain, dyspnea, limb twitching, or tongue biting. The episode lasted about 10 seconds, after which he regained full consciousness and was able to communicate normally. He presented to a local emergency department but did not receive specific treatment, and no recurrent episodes occurred. On June 6, 2022, he was referred to our hospital for further evaluation.

His past medical history was unremarkable, with no similar episodes and no history of hypertension, hyperthyroidism, coronary heart disease, or diabetes. On physical examination, he was alert and oriented. No lymphadenopathy was detected. Pulmonary auscultation revealed clear breathing sounds bilaterally. Cardiac examination showed normal cardiac borders, a regular rhythm at 76 beats per minute, and no murmurs. The abdomen was flat and soft without tenderness or rebound tenderness, rebound pain, or shifting dullness. No edema of the lower extremities was noted, and the neurological examination was unremarkable. Laboratory tests, including complete routine blood testing, urinalysis, routine stool exam, liver and renal function, electrolytes, and cardiac enzymes, were all within normal limits. ECG showed sinus rhythm with ST-segment elevation in leads V1-V3 and type 1 Brugada pattern in the right precardiac leads (coved-type ST-segment elevation ≥2 mm followed by an inverted T wave) (**Figure 2A**). Brain CT and EEG examination showed no abnormalities.

Although the presentation appeared to be “simple syncope”, several features supported BrS: ① The syncopal episode occurred abruptly without prodromal symptoms, lasted less than <10 s, and was followed by rapid recovery-features consistent with an arrhythmic rather than reflex or orthostatic mechanism. ② The patient was a 33-year-old man, belonging to the demographic group in which BrS shows the highest penetrance and in which sudden cardiac death frequently represents the first manifestation. ③ A 12-lead ECG obtained in the emergency department revealed spontaneous coved-type ST-segment elevation ≥2 mm in V1-V2 followed by inverted T waves, fulfilling the 2013 HRS/EHRA/APHRS diagnostic criteria for a spontaneous type-1 Brugada ECG pattern. According to these guidelines, a single syncopal episode in the presence of a spontaneous type-1 ECG is sufficient for a clinical diagnosis of BrS and warrants risk stratification for sudden cardiac death (Class I recommendation).

The family history further reinforced suspicion: the patient’s father had experienced recurrent unexplained syncope and died suddenly during sleep at the age of 44, findings highly suggestive of familial sudden cardiac death. This prompted us to consider an inherited arrhythmia syndrome rather than a benign cause.

A systematic evaluation excluded common mimics. Fever, hyperkalaemia, early repolarization, right ventricular ischemia, and structural heart disease were ruled out based on normal biochemical tests, negative cardiac enzyme

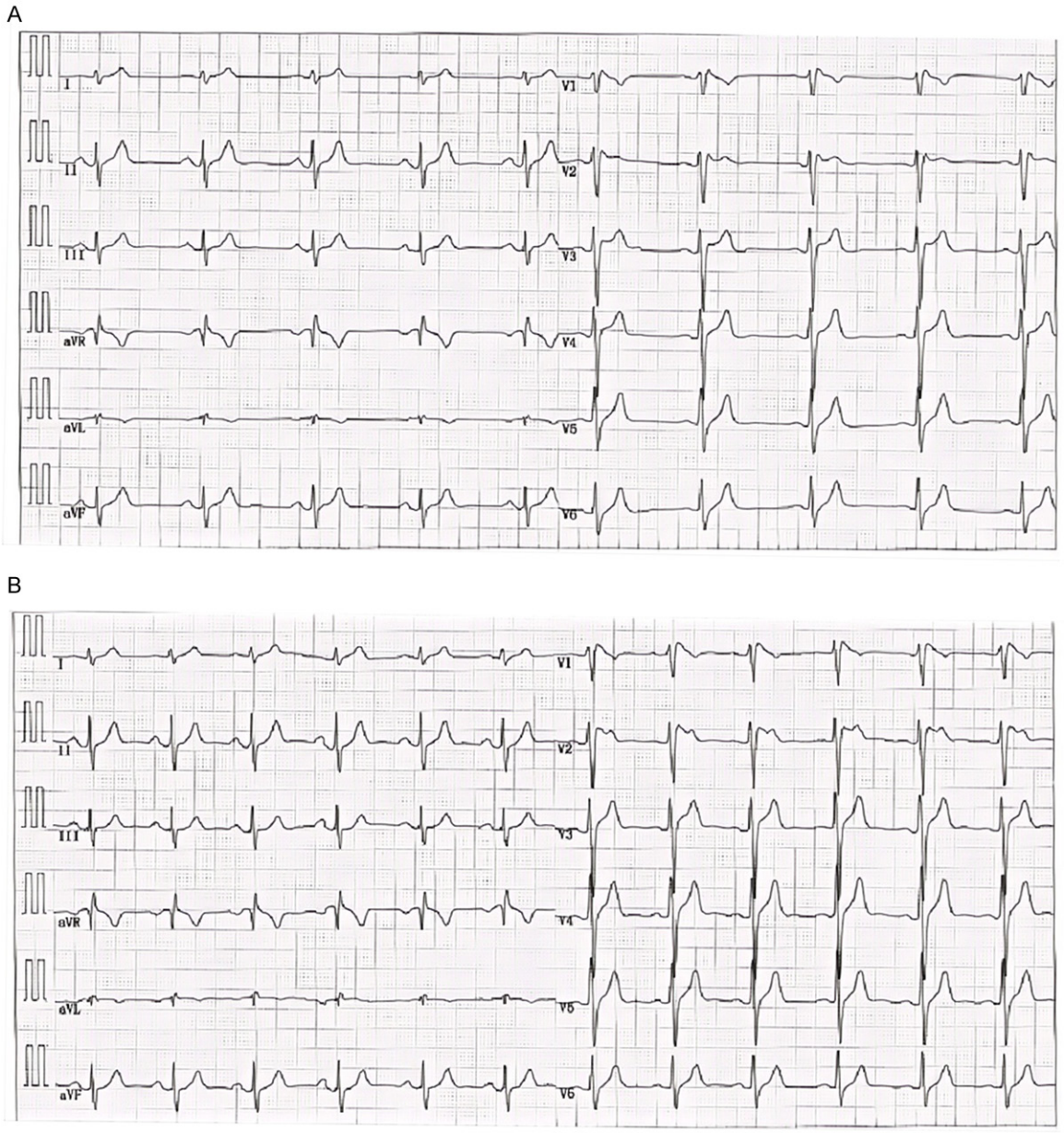

Figure 2. Electrocardiogram of proband (II-1). A. ECG at admission: ST segment elevation in leads V1-V3, showing type 1 Brugada wave; B. ECG reexamination at 3 months after surgery: normal range.

results, unremarkable EGC, and a normal cardiac MRI. An ajmaline challenge was therefore deemed unnecessary, as the patient already displayed a spontaneous type-1 ECG pattern.

Based on the patient's medical history, family history, clinical manifestations, and ECG findings, a diagnosis of BrS was established. Given the syncopal episode and the high risk of recurrence and sudden cardiac death (SCD), the patient met the indications for cardioverter-defibrillator (ICD) implantation. After confirming the absence of contraindications and obtaining informed consent from the patient and his family, and ICD was successfully implanted. The postoperative ECG is shown in **Figure 2B**.

BrS is inherited in an autosomal-dominant pattern with variable penetrance, meaning that first-degree relatives carry an approximately 50% a priori risk of carrying the pathogenic variant. Early identification of carriers enables

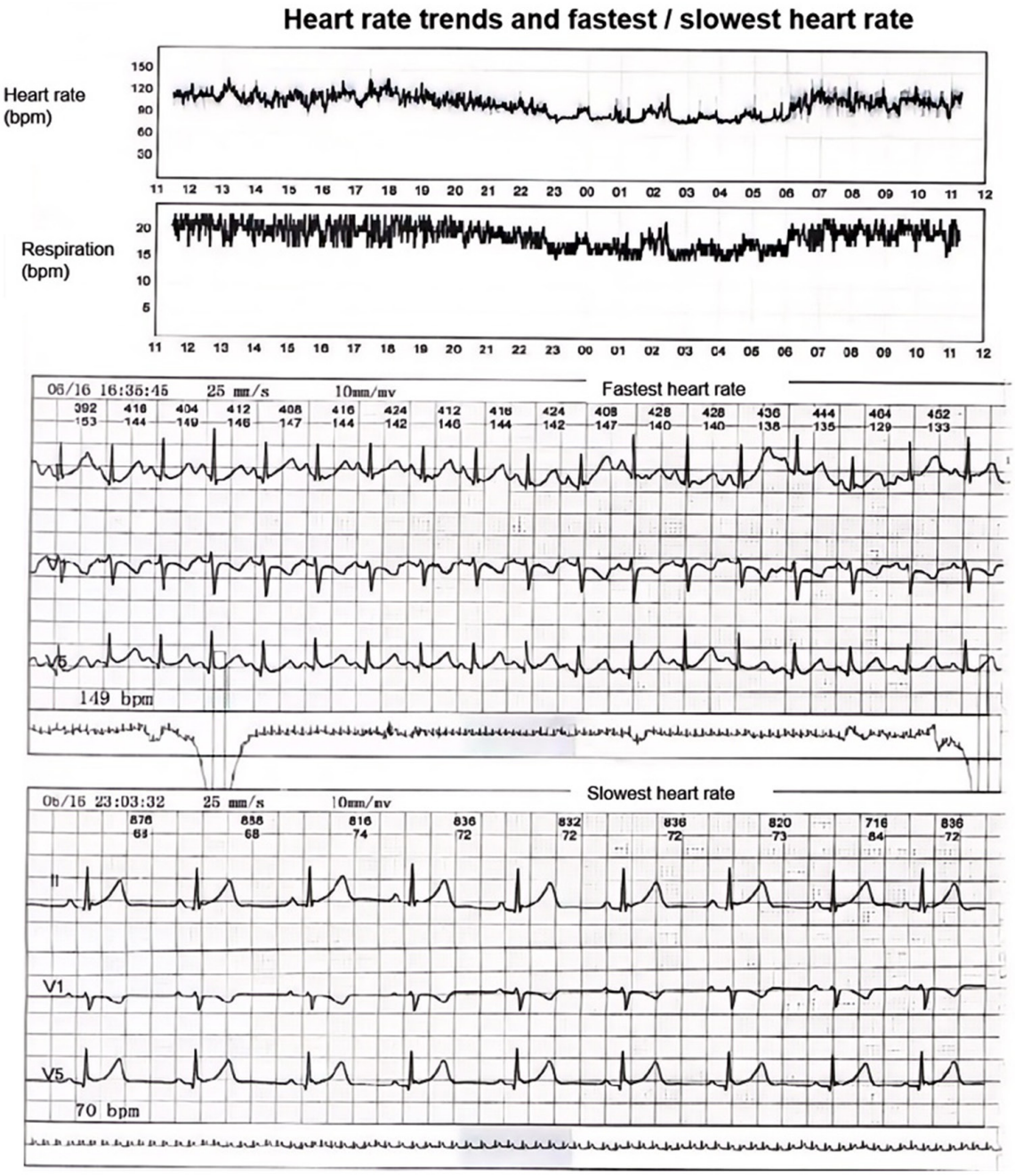

Figure 3. Dynamic electrocardiogram of III-1.

appropriate lifestyle counselling, fever management, and long-term rhythm surveillance. After obtaining informed consent, a 12-lead ECG and 24-h Holter monitoring were performed on the patient's 6-year-old son (III-1). Although he was asymptomatic, his Holter recording showed decreased heart rate variability (**Figure 3**), supporting the decision to proceed with genetic testing. The Holter analysis recorded 23 hours and 47 minutes of monitoring, with a total of 147,421 heart beats, an average heart rate 102 bpm (70-151 bpm), and no pauses exceeding 3.0 seconds. The report concluded: (1) Sinus rhythm without abnormal ST-T change; and (2) decreased heart rate variability.

Experimental methods

Gene sequencing

Gene sequencing was performed on the patient (II-1) and his son (III-1) to confirm the molecular

diagnosis. According to the 2022 HRS/EHRA/APHRS expert consensus, in patients with a definite diagnosis of BrS and a documented arrhythmic event (syncope, ventricular tachycardia/fibrillation), tier-1 genetic testing should begin with the major disease gene SCN5A, which accounts for 20-25% of BrS probands. Extended panel testing (SCN1B-SCN4B, GPD1L, CACNA1C, CACNB2B, etc.) is recommended only when SCN5A testing is negative. Because our patient fulfilled the diagnostic criteria for BrS (type-1 ECG pattern plus syncope) and comprehensive multigene sequencing were not covered by the local insurance system, we followed the stepwise testing algorithm and restricted initial analysis to the SCN5A gene. Peripheral venous blood samples (5 ml) from II-1 and III-1 were collected in EDTA anticoagulant tubes. Genomic DNA was extracted from leucocytes using standard protocols. Although leukocytes are electrically non-excitable, they contain the identical germline DNA as cardiomyocytes; therefore, Sanger sequencing of PCR-amplified exons reliably detects variant present in cardiac tissue. This approach represents the standard of care for hereditary cardiac channelopathies and has been validated in over 1,000 BrS families.

PCR amplification of the SCN5A coding region was performed using specific primers, and the resulting products were subjected to Sanger sequencing. The sequencing data were compared with the SCN5A reference sequence in the NCBI GenBank database to identify pathogenic variants.

Conservation and pathogenicity analysis

To evaluate the evolutionary conservation of SCN5A gene mutations across species, homologous SCN5A sequences were retrieved from the NCBI HomoloGene database. The conservation status of mutation sites was compared among humans and other species. Pathogenicity prediction was performed using the PolyPhen-2 and Mutation Taster.

Protein structure modeling

To assess the potential structural impact of the variant, the linear topological information of the sodium channel α-subunit was obtained from the UniProt database. Based on the SCN5A sequence and an appropriate structural template, homology modeling was conducted using the Swiss-Model server. The resulting three-dimensional protein structure of the mutant channel was visualized and analyzed with PyMOL version 1.0.

Results

Genetic testing results revealed that both the proband and his son carried a heterozygous variants in the *SCN5A* gene (NM-001099404.2): c.1768 A>C (p.K590Q) (**Figure 4A**). Sanger sequencing confirmed a heterozygous nucleotide substitution in exon 12, where adenine (A) was replaced by cytosine (C) at position 1768, converting the lysine codon (AAG) at position 590 into a glutamine codon (CAG), resulting in the missense mutation p.K590Q. This variant has not been reported in the HGMD, 1000 Genome Project (1000G), ExAC, or other public variant repositories. Its allele frequency in the gnomAD database is low (0.000004031). The clinical significance of this variant is listed as "uncertain" in Clinvar and dbSNP. Further conservation analysis showed that the affected amino acid residue is highly conserved across various species (**Figure 4B**). In silico pathogenicity prediction supported a likely deleterious effect: PolyPhen-2 classified the variant as "probably damaging" (score = 0.997, sensitivity = 0.41; Specificity = 0.98), while Mutation Taster software predicted it to be "disease-causing" (score = 0.9998). According to the American College of Medical Genetics and Genomics (ACMG) guidelines [8], the pathogenicity of this variant was assessed as "uncertain significance (VUS)", based on supporting evidence from computational and phenotypic data (criteria PP3 + PP4).

SCN5A encodes a large transmembrane protein consisting of 2016 amino acid residues. The protein comprises four homologous domains (I, II, III, IV), each with five hydrophobic fragments (S1, S2, S3, S5, S6) and a positively charged fragment (S4). The N-terminus, three interdomain linkers (I-II, II-III, and III-IV), and the C-terminus connect these domains. In each domain, segments S1-S4 form the voltage-sensing domain, while helices S5 and S6 constitute the pore-forming domain [7]. Protein topology and three-dimensional modeling demonstrated that the variant residue (p.K590Q) is located on the extracellular side of the trans-

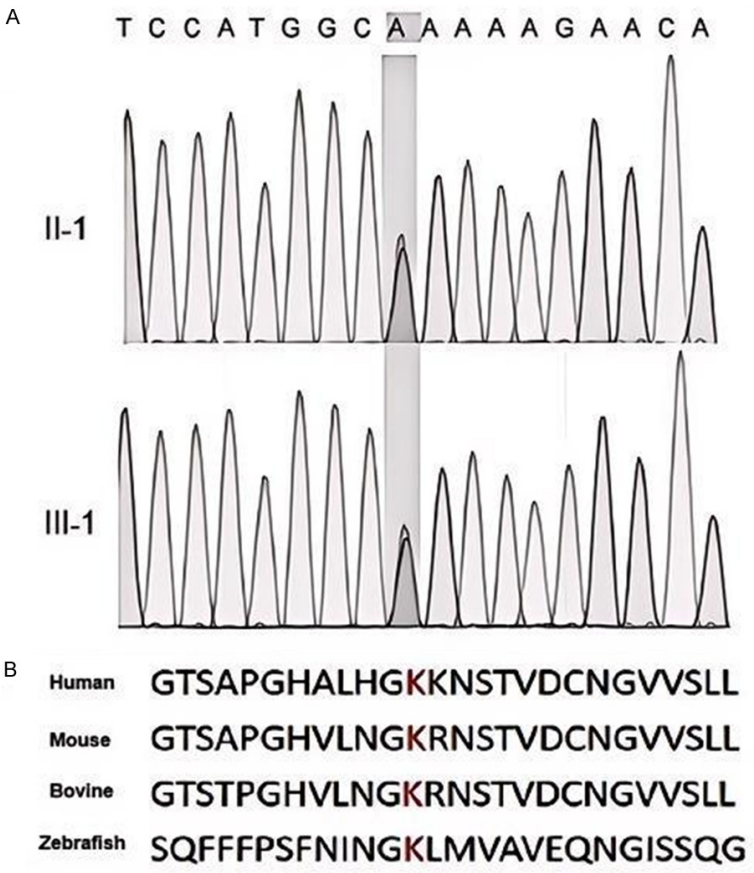

Figure 4. Sanger Sequencing (A) and Species Conservation (B).

membrane channel within the domain II-III linker (**Figure 5A**). The 3D structure model suggests that this variant site is involved in the formation of the sodium ion conduction pore (**Figure 5B**), potentially affecting transmembrane Na^+ transport.

Discussion

This study reports a 33-year-old male patient diagnosed with BrS. Genetic sequencing identified a heterozygous SCN5A variant, c.1768 A>C (p.K590Q), in both the patient and his son, resulting in the substitution of lysine with glutamine at position 590 of the encoded protein. Although this variant was classified as having uncertain significance according to the ACMG guidelines, it remains clinically noteworthy [9]. Conservation analysis showed that the c.1768 A>C variant site is highly conserved across species, indicating that this site is critical to the function of the Nav1.5 channel [10]. Highly conserved amino acids are often closely related to the core function or structural stability of proteins; mutations at such sites may disrupt normal protein folding or ion conduction, potentially leading to disease [11]. Therefore, the high conservation of this locus suggests evolutionary importance and possible functional relevance.

In addition, several bioinformatics tools (PolyPhen-2 and Mutation Taster) predicted that the mutation site is likely pathogenic, further supporting its potential association with BrS [12]. Mutations in *SCN5A* represent the most common genetic cause of BrS. The Nav1.5 channel encoded by SCN5A is responsible for the initiation and propagation of the action potential in cardiomyocytes. A c.1768 A>C mutation may impair sodium channel function, alter Na^+ transmembrane transport, and modify the electrophysiological characteristics of cardiomyocytes. These changes could shorten the action potential duration and promote early repolarization, thereby increasing the risk of ventricular arrhythmia, which is consistent with the known pathophysiology of BrS [13]. Although the association between SCN5A gene mutation and BrS is well established, the specific effects of individual variant sites on Nav1.5 channel function differ substantially.

To determine the novelty of the p.K590Q variant, we queried the HGMD Professional database (release 2024.03), ClinVar (2024.02) and the Japanese multicentre BrS registry, which includes 1,187 unique *SCN5A* missense variants. None of these records contained a substitution at codon 590. The three adjacent variants - p.R589H, p.E591K, and p.F592S - also reside in the same cytoplasmic II-III linker and have been reported to impair fast inactivation or enhance the late sodium current. In contrast, c.1768 A>C replaces a positively charged lysine with an uncharged, polar glutamine, a chemical change not previously modelled. Thus, the p.

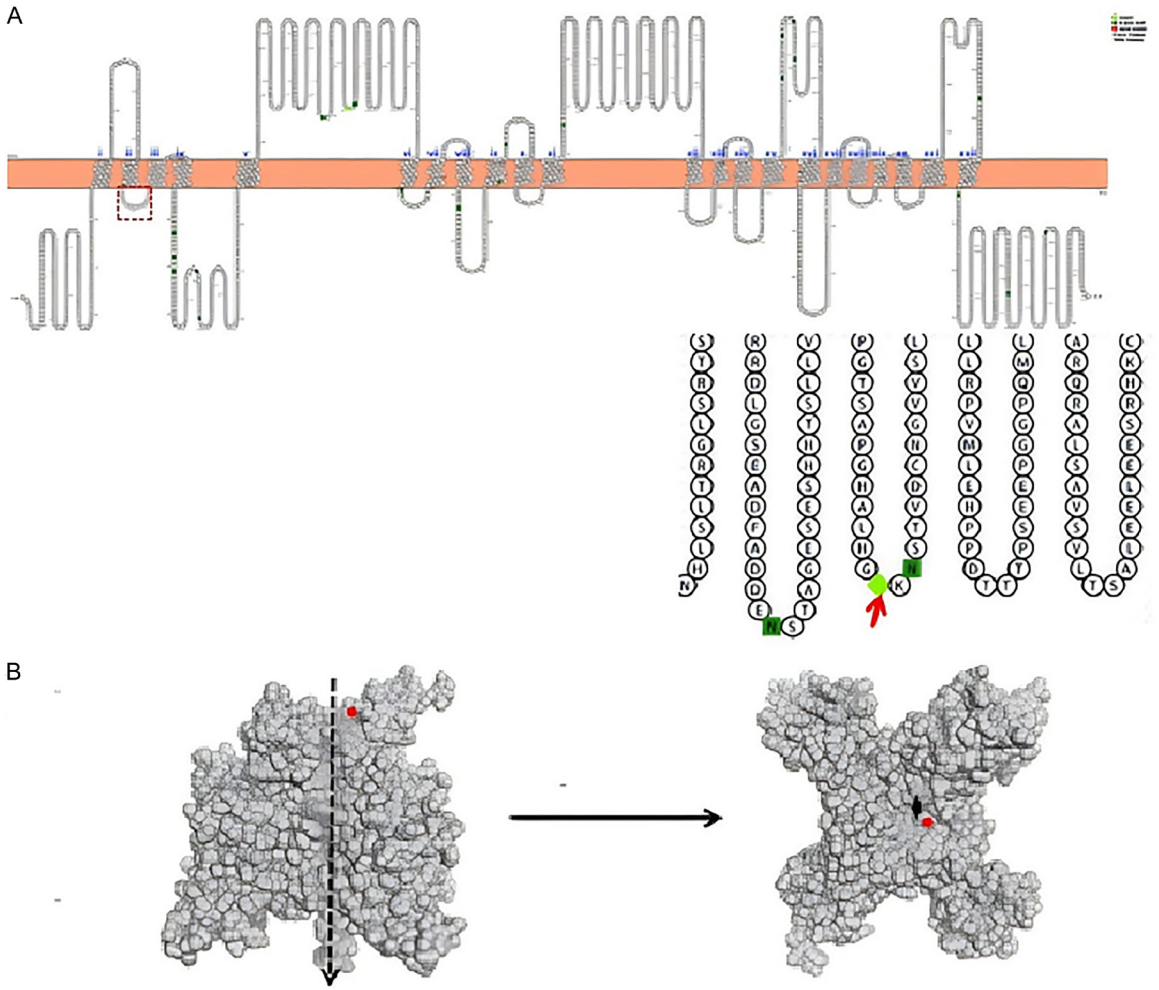

Figure 5. Protein topology and 3D structure modeling. A. Protein topology: The mutant residue is located on the extracellular side of the transmembrane protein within the linker between domains II and III, as indicated by the red arrow. B. 3D structural modeling: mutation site participates in the formation of Na^+ channel pores.

K590Q substitution expands the known mutational spectrum of the II-III linker from three to four functionally distinct residues and represents a previously unreported pathogenic candidate. Consistent with previous research results, the c.1768 A>C mutation has not been reported in any existing literature or genetic databases, suggesting that it may be a rare mutation [14].

In this study, the mutant amino acid was located on the extracellular side of the transmembrane protein, specifically within the linker between domains II and III. This region connects adjacent voltage-sensing domains and plays a crucial role in maintaining the overall conformation and gating mechanism of the sodium channel. Three-dimensional structural modeling revealed that the mutation site lies near the pore-forming region of the Na^+ channel, suggesting a potential effect on sodium ion transmembrane transport [15]. The amino acid substitution (lysine to glutamine) caused by c.1768 A>C mutation likely alters the chemical properties and spatial conformation of the *SCN5A*-encoded Nav1.5 channel. This change may affect Na^+ transmembrane transport and cardiac electrophysiological processes through the following reasons: ① Lysine is a positively charged amino acid, whereas glutamine is uncharged; this alteration in local charge distribution may affect the surrounding electric field, thereby affecting the stability and permeability of the Na^+ channel pore [16]. ② The mutation may destroy the existing intermolecular interactions, such as hydrogen bonds and salt bridges,

resulting in subtle conformational instability of the channel and reduced sodium transport efficiency [17]. ③ Because this mutation site lies at the interface between the voltage-sensing and pore domains, it may interfere with voltage-dependent gating, altering the activation and inactivation kinetics of the channel. Such disturbances could lead to abnormal prolongation or shortening of cardiomyocyte action potential, thereby increasing the risk of arrhythmia [18]. Yamagata et al. [19] reported that *SCN5A* variation in the pore region are associated with a higher incidence of cardiac events, which is consistent with our findings.

This study has several shortcomings. This study only analyzed the *SCN5A* mutation in a single BrS family, and the limited sample size restricts the generalization of the results. At the same time, genetic testing was conducted only in the proband and his son. Because the patient was an only child and both parents were deceased, testing of the father was not possible, thereby limiting confirmation of the inheritance pattern. In future research, identification of the same variant in more confirmed BrS patients would help substantiate the pathogenicity of the c.1768 A>C mutation in the SCN5A gene, while further in vitro and/or in vivo functional studies are also warranted to further elucidate its electrophysiological consequences [20].

In conclusion, we identified a heterozygous *SCN5A* c.1768 A>C (p.K590Q) variant classified as of uncertain significance. The mutation resides in a critical functional region of the *SCN5A* gene and is highly conserved across species. Both software prediction results and conservative analysis supported the possibility that the mutation is pathogenic. Therefore, future in-depth study of this mutation will help us understanding the relationship between SCN5A gene mutation and BrS, thereby providing new insights for clinical diagnosis and treatment.

Disclosure of conflict of interest

None.

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