Genetic Characteristics and Transcriptional Regulation of Sodium Channel Related Genes in Chinese Patients With Brugada Syndrome

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Objective: To investigate the genetic characteristics and transcriptional regulation of the SCN5A gene of Brugada syndrome (BrS) patients in China.

Methods: Using PubMed, Medline, China National Knowledge Internet (CNKI), and Wanfang Database, Chinese patients with BrS who underwent SCN5A gene testing were studied.

Results: A total of 27 suitable studies involving Chinese BrS patients who underwent the SCN5A gene test were included. A total of 55 SCN5A gene mutations/variations were reported in Chinese BrS patients, including 10 from southern China and 45 from northern China. Mutations/variations of BrS patients from southern China mostly occurred in the regions of the α-subunit of Nav1.5, including DIII (Domain III), DIV, DIII-DIV, C-terminus regions, and the 3’UTR region. Furthermore, we analyzed the post-transcriptional modifications (PTMs) throughout the Nav1.5 protein encoded by SCN5A and found that the PTM changes happened in 72.7% of BrS patients from southern China and 26.7% from northern China.

Conclusions: SCN5A mutations/variations of BrS patients in southern China mostly occurred in the DIII-DIV to C-terminus region and the 3’-UTR region of the SCN5A gene, different from northern China. PTM changes were consistent with the mutation/variation distribution of SCN5A, which might be involved in the regulation of the pathogenesis of BrS patients.

Keywords: brugada, SCN5A, China, genetic characteristics, post-transcriptional modifications

INTRODUCTION

Brugada syndrome (BrS) is an inheritable arrhythmogenic disease. The typical electrocardiographic manifestations include ST segment elevation ≥2 mm and T wave inversion on the right thoracic lead (V1–V3) of ECG. BrS is prone to polymorphic ventricular tachycardia, ventricular fibrillation, and sudden cardiac death while the heart structure is normal (1, 2). It is more prevalent in Asian
population with an onset age of 30–40 years old, and the ratio of male to female is 8–10:1 (3, 4). The mortality accounted for 4–12% of sudden death each year and even for 20% sudden death without organic heart disease in Southeast Asia (5).

Up to date, 23 genes have been confirmed to be related to BrS (5–7), including gene mutations/variants that lead to ion channel dysfunction such as sodium, calcium, and potassium ions. About 30–35% of BrS patients were identified with pathogenic mutant genes, while SCN5A mutations/variants encoding the Nav1.5 α-subunit of the cardiac sodium channel accounted for 20 to 30% (5, 8–10). Currently, the recommended treatment for BrS is ICD implantation and medication (quinidine, isoproterenol, etc.); however, therapeutic effect is unsatisfactory.

The mutations/variants from BrS patients can significantly reduce the inward Na⁺ current by delaying activation, accelerating inactivation, delaying reactivation, or reducing the membrane expression of ion channels (11, 12). Furthermore, the decrease in the inward Na⁺ current has influence on the depolarization and repolarization of the cardiac action potential, thus causing the generation of typical ECG of BrS (2). Genetic distribution characteristics of BrS on the SCN5A mutations/variants from the world (9) and Japan (13) had been reported. However, there are no genetic distribution analyses on the SCN5A mutation/variation location sites in Chinese BrS patients until now. In the present study, we aim to analyze the reported SCN5A mutation/variation location sites of Chinese BrS patients and predict the PTMs affected by the mutations/variants.

MATERIALS AND METHODS

Information Retrieval and Inclusion Criteria

Two investigators searched Medline, PubMed, CNKI, and Wanfang Database. The query terms were “Brugada syndrome” “China” and “SCN5A.” Articles published in Chinese or English in peer-reviewed journals that met the following criteria were included in our study.

A. Inclusion of subjects with BrS were as previously defined (14).
B. Chinese patients.
C. Who underwent SCN5A gene DNA sequencing.

In addition, we also contacted the corresponding author of several studies in order to obtain more specific experimental data that were not included in the article. In order to resolve any difference or uncertainty between the two investigators, a third investigator was responsible for reexamining the source data and consultation.

Predictive Analysis the PTMs of SCN5A

First, we retrieved the amino acid sequence and analyzed the domain details of the α-subunit of SCN5A protein in the following website: https://www.uniprot.org/uniprot/Q14524, then predicted the PTM sites with the software on the amino acid sites and mapped on the mutation/variation sites reported from the literature in China. Furthermore, we analyzed the change of PTMs in the natural variant.

Statistical Analysis

Categorical variables were expressed as percentage and analyzed using the chi-square test. All analyses were conducted using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at \( p < 0.05 \).

RESULTS

Studies Retrieved and Information Extraction, and Distribution of the SCN5A Mutations/Variations on Nav1.5 Protein

A flow chart of the data research is shown in Figure 1. We excluded 306 unqualified studies that did not match the inclusion criteria or were duplicates. A total of 27 suitable studies were included, and details are shown in Table 1. Duplicated loci were removed, and a total of 55 mutations/variants including 45 sites from northern China and 10 sites from southern China (Guangdong, Guangxi, Hong Kong, Hainan, Jiangxi, Fujian,
| Location                | Nucleotide change | Amino acid change | Structural position | Investigator            |
|-------------------------|-------------------|-------------------|---------------------|-------------------------|
| China (Guangxi)         | G1712C            |                  | DIV S5-S6           | Chen et al. (15)         |
| China (Guangxi)         | A5471G            | N1774S            | C terminus          | Ren et al. (17)          |
| China                   | A29A              |                  | N terminus          | Liu et al. (18)          |
| China                   | E1061E            |                  | DII-DIII            | Liu et al. (18)          |
| China                   | D1818D            |                  | C terminus          | Liu et al. (18)          |
| China                   | 6365a>G 3'UTG     |                  |                     | Liu et al. (18)          |
| China                   | 7204t>A 3'UTG     |                  |                     | Liu et al. (18)          |
| China                   | 7205c>T 3'UTG     |                  |                     | Liu et al. (18)          |
| China                   | G3578A            | R1193Q            | DII-DIII            | Liu et al. (18)          |
| South China             | 4087insC          |                  | DIIIS4change, DIIIS5-S6 and DIV missing | Chen et al. (19)         |
| China                   | C1363F            |                  | DIV S5-S6           | Yan et al. (20)          |
| China                   | G283A             | V95I              | N terminus          | Liang et al. (21)        |
| China                   | C4946T            | A1649V            | DIV S4-S5           | Liang et al. (21)        |
| China                   | Exon 28 missing TCT | del1617        | DIV S3-S4           | Liang et al. (21)        |
| China (Hebei)           | C5457T            | A1818A            | C terminus          | Tian et al. (22)         |
| China                   | R1913C            |                  | C terminus          | Qiu et al. (23)          |
| China                   | G87A              |                  | N terminus          | Qiu et al. (23)          |
| China                   | 703+130G>A        |                  | Intron 6            | Qiu et al. (23)          |
| China                   | 1143-3C>A         |                  | Intron 9            | Qiu et al. (23)          |
| China                   | A1673G            | H588R             | DI-DII              | Qiu et al. (23); Tian et al. (24); Yi et al. (25) |
| China                   | G3578A            | R1193Q            | DII-DIII            | Qiu et al. (23)          |
| China                   | 3840+73G>A        |                  | Intron 21           | Qiu et al. (23)          |
| China                   | 4245+81G>T        |                  | Intron 23           | Qiu et al. (23)          |
| China                   | 4245+82A>G        | L1291L            | Intron 23           | Qiu et al. (23)          |
| China                   | 4299+83T>C        |                  | Intron 24           | Qiu et al. (23)          |
| China                   | T5457C            |                  | C terminus          | Qiu et al. (23)          |
| China (Gansu)           | G292A             | G98R              | N terminus          | Gong et al. (26)         |
| China (Hebei)           | C3549T            | T1183T            | DII-DIII            | Tian et al. (27)         |
| China                   | K317N             |                  | DIIS5-S6            | Yi et al. (28)           |
| China (Xinjiang or Shanxi) | R230Q          |                  | DI54                | Li et al. (28)           |
| China (Xinjiang or Shanxi) | V469V          |                  | DI-DII              | Li et al. (28)           |
| China (Xinjiang or Shanxi) | R511K          |                  | DI-DII              | Li et al. (28)           |
| China (Xinjiang or Shanxi) | V522A          |                  | DI-DII              | Li et al. (28)           |
| China (Xinjiang or Shanxi) | K698N          |                  | DI-DII              | Li et al. (28)           |
| China (Xinjiang or Shanxi) | G3687G          |                  | DI SS-S6            | Li et al. (28)           |
| China (Xinjiang or Shanxi) | T909           |                  | DISS5-S6            | Qin et al. (29)          |
| China (Fujian)          | c.4886G>A         | R1629Q            | DIV S4              | Zeng et al. (30)         |
| China (Fujian)          | C6996T            |                  | 3'UTR               | Zhao et al. (31)         |
| China (Fujian)          | c.5262G>A         | D1690N            | DIV S5-S6           | Zeng et al. (32)         |
| China                   | Q55X              |                  | N terminus          | Teng et al. (33)         |
| China                   | R535X             |                  | DI-DII              | Teng et al. (33)         |
| China                   | W822X             |                  | DIV S4              | Teng et al. (33)         |
| China                   | Q867X             |                  | DIV SS-S6           | Teng et al. (33)         |
| China                   | R1623X            |                  | DIV S4              | Teng et al. (33)         |
| China                   | S1812X            |                  | C terminus          | Teng et al. (33)         |
| China                   | Q1118X            |                  | DI-DII              | Teng et al. (33)         |
| South China             | c.1198G>A         | p.Gly404Arg        | DI S6               | Zhang et al. (34)        |
| South China             | c.4282G>T         | p.Ala1428Ser       | DIIS5-S6            | Zhang et al. (34)        |
TABLE 1 | Continued

| Location            | Nucleotide change | Amino acid change | Structural position | Investigator |
|---------------------|-------------------|-------------------|--------------------|--------------|
| South China         | c.5676delC        | p.Thr1893Profs*29 | C terminus         | Zhang et al. (34) |
| South China         | c.5692C>T         | p.Arg1898Cys      | C terminus         | Zhang et al. (34) |
| China               | c.1960G>T         | p.E654X           | DI-DII             | Liu et al. (35) |
| China               | 1651G>A           | A551T             | DI-DII             | Chiang et al. (36) |
| China (Hubei)       | c.4282G>T         | p.A1428S          | DIII S5-S6         | Zhu et al. (37) |
| China               | 3578G>A           | R1193Q            | DIII-DIV           | Li et al. (38) |
| China               | 3269C>T           | P1090I            | DII-DIII           | Juang et al. (39) |
| China               | 1776C>G           | N592K             | DI-DII             | Juang et al. (39) |
| China (Taiwan)      | rs11708996 G>C    |                   | Intron             | Juang et al. (40) |
| China               |                   | A226V             | DII-S4             | Mok et al. (41) |
| China               |                   | H681P             | DII-DII            | Mok et al. (41) |
| China               |                   | R1193Q            | DII-DIII           | Mok et al. (41) |
| China               |                   | V1951L            | C terminus         | Mok et al. (41) |

FIGURE 2 | Representation of SCN5A gene mutations/variants was labeled on the corresponding location of the Nav1.5 protein structure. The blue dots represented mutations/variants from southern China, and the red dots represented mutations/variants from northern China.

Taiwan) were included. Further analysis of these loci was performed as detailed below.

The Nav1.5 channel has four highly conserved homologous transmembrane-spanning domains (DI–DIV) that are connected by an interdomain linker (IDL), and each domain consists of six transmembrane α spins (S1–S6). In order to visualize the distribution of these loci, we marked the mutation/variation sites on Nav1.5 protein (excluding introns and 3′UTR, which were not translated into amino acids), as shown in Figure 2. The blue dots represented the SCN5A mutations/variants from northern China, and the red dots represented the SCN5A mutations/variants from southern China.

**Locational Distribution of SCN5A Gene Mutations/Variations in China**

The whole SCN5A gene was divided into 5′-UTR, N-Term (N-terminus), D I, IDL I-II, DII, IDL II-III, DIII, IDL III-IV, DIV, C-Term (C-terminus), 3′-UTR, and other regions. Mutation/variation loci distribution is shown in Figure 3. Distinguished by those 12 parts, the distribution in southern...
China and northern China were 5′-UTR (0 vs. 0), N-Term (0 vs. 11.1%), DI (0 vs. 8.9%), IDL I-II (0 vs. 22.2%), DII (0 vs. 6.7%), IDL II-III (0 vs. 11.1%), DIII (10 vs. 2.2%), IDL III-IV (0 vs. 0), DIV (30 vs. 6.7%), C-Term (30 vs. 8.9%), 3′-UTR (10 vs. 2.2%), and other (10 vs. 20%), respectively. It was found that SCN5A mutations/variations in northern China were mainly concentrated (60%) in 5′-UTR, N-Term, DI, IDL I-II, DII, and IDL II-III while mostly distributed (80%) in DIII, IDL III-IV, DIV, C-Term, and 3′-UTR in southern China.

Furthermore, the locations of SCN5A gene mutations/variations were divided into five parts as follows: N-Term, Transmembrane regions, IDL, C-Term, and others as shown in Figure 4A. The mutation/variation site distributions of SCN5A in southern China and northern China were 0, 50, 0, 30, and 20%, and 11.1, 24.5, 33.3, 8.9, and 22.2%, respectively (p = 0.000).

On the other hand, the locations of SCN5A gene mutations/variations were divided into three parts as follows: before-DIII, after-DIII, and others as shown in Figure 4B. The mutation/variation site distributions of SCN5A in southern China and northern China were 10, 80, and 10% and 60, 20, and 20%, respectively (p = 0.001).

Then, we compared the distributions of mutations/variations among China (southern China and northern China), Japan, and the world, as shown in Figure 5A. Japanese data refer to a Japanese multicenter register (42), and the global data are from the website http://triaf.fsm.it/cardmoc/. We distinguished the SCN5A mutation sites on the protein Nav1.5 structure by N-term, Transmembrane regions, IDL, and C-term and found 0, 62.5, 0, and 37.5% for each part in southern China; 14.3, 31.4, 42.9, and 11.4% in northern China; 4.4, 66.7, 20, and 8.9% in Japan; and 4.8, 71, 18.4, and 5.8% in the world, respectively (p = 0.000).

In addition, the structure of Nav1.5 protein was divided into two parts: DI, IDL I-II, DII, and IDL II-III were set as the first half part (before-DIII), and DIII, IDL III-IV, DIV, and C-Term were set as the second half part (post-DIII) as shown in Figure 5B. The results indicated that 88.9% of the mutation sites were located in the post-DIII region in southern China, while only 22.9% in northern China, 42.2% in Japan, and 47% in the world (p = 0.000).

PTMs Prediction for Nav1.5 Protein Change

As mutations that cause changes in amino acids may have influences on protein modification, we predictively analyzed the PTMs of SCN5A with software and mapped on the mutations/variations in China (Table 2), and found a tendency for amino acids to acquire more modification sites after mutation. PTM change was likely to occur in 72.7% of BrS patients from southern China and 26.7% from northern China (p = 0.000).

DISCUSSION

Our main findings in the study of the genetic characteristics of SCN5A in Chinese BrS patients were as follows: (1) More SCN5A gene mutations/variations were found in northern China than in southern China. (2) SCN5A mutations/variations of BrS patients in southern China mostly occurred in the DIII–DIV to C-terminus region and the 3′-UTR region of the SCN5A gene. (3) PTM changes were consistent with the mutation/variation distribution of SCN5A, which might be involved in the regulation of the pathogenesis of BrS patients.

BrS can be found all over the world, and the prevalence of BrS can reach 0.5‰ in high-prevalence areas. BrS is the leading cause of death for men less than 40 years old, only second to the death rate of traffic accidents in Southeast Asian countries (42, 43). In southern China, BrS patients were anticipated to have a relatively high incidence rate. However, our study revealed that SCN5A gene mutations published were found to be more...
in northern China than southern China. The possible reasons may be that BrS is a rare disease, and the total number of cases reported at present was not large and patients in many studies did not undergo DNA sequencing, which results in data bias. We will continue to pay attention to relevant reports and continue to collect cases to further confirm the data.

Further analysis showed that the locations of mutation sites had their own characteristics in southern China. Most mutation sites were clustered in the transmembrane regions in southern China statistically different from northern China. Mutation sites were mostly located in the second half part of the protein structure (post-DIII) in southern China, while in the first half part positions (before-DIII) in northern China, Japan, and the world.

The SCN5A gene, located on chromosome 3p21, contains 28 exons with a total length of about 80 kb and encodes the α-subunit protein Nav1.5. Some mutations lead to a decrease in current density, others do not lead to a decrease in INa, while some location-specific SCN5A mutations resulted in poorer outcomes during follow-up (44). As different mutation
FIGURE 5 | (A) The translation comparison of the SCN5A mutation/variation distribution on the Nav1.5 protein structure between southern China and northern China. Nav1.5 protein was distinguished by N-term, Transmembrane regions, IDL, C-term, and other parts. The light blue columns represent the N-terminus region. The orange columns represent the transmembrane region. The gray columns represent the IDL region. The yellow columns represent the C-terminus region.

|                | southern China | northern China | Japan | Global | P value |
|----------------|----------------|----------------|-------|--------|---------|
| N-Term         | 0              | 5              | 2     | 14     |         |
| Transmembrane  | 5              | 11             | 30    | 208    |         |
| IDL            | 0              | 15             | 9     | 54     |         |
| C-Term         | 3              | 4              | 4     | 17     | 0.000   |

(B) The translation comparison of the SCN5A mutation/variation distribution on the Nav1.5 protein structure between southern China and northern China. Nav1.5 protein was distinguished by before-DIII and after-DIII. The blue columns represent before-DIII parts. The orange columns represent after-DIII parts.

|                | southern China | northern China | Japan | Global | P value |
|----------------|----------------|----------------|-------|--------|---------|
| N-Term         | 0              | 5              | 2     | 14     |         |
| DII            | 1              | 4              | 7     | 57     |         |
| IDL I-II       | 0              | 10             | 5     | 31     |         |
| DIII           | 0              | 3              | 8     | 36     |         |
| IDL II-III     | 0              | 5              | 4     | 17     |         |
| DIV            | 1              | 1              | 9     | 71     |         |
| IDL III-IV     | 0              | 0              | 0     | 6      |         |
| C-Term         | 3              | 4              | 4     | 17     |         |
| 3’UTR          | 1              | 1              | 0     | 0      |         |
| Before-DIII    | 1              | 27             | 26    | 155    |         |
| After-DIII     | 8              | 8              | 19    | 138    | 0.000   |
## TABLE 2 | The PTMs of SCN5A variants in Chinese BrS patients.

| Nucleotide change | Mutations | The potential PTMs before mutation | The potential PTMs after mutation | Structural position | Location |
|-------------------|-----------|------------------------------------|----------------------------------|---------------------|----------|
| -                 | A29A      | -                                  | -                                | N terminus          | China    |
| G87A              | None      | None                               | None                            | N terminus          | China    |
| -                 | Q55X      | -                                  | -                                | N terminus          | China    |
| G283A             | V95I      | None                               | None                            | N terminus          | China    |
| G292A             | G98R      | Methylarginine                      | None                            | N terminus          | Gansu    |
| -                 | A226V     | None                               | None                            | DIS4                | China    |
| -                 | R230Q     | Pyrrolidone carboxylic acid         | DIS4                            | Xinjiang or Shanxi  |
| T909              | M303T     | O-linked_glycosylation, Phosphoserine| DIS5-S6                        | Xinjiang or Shanxi  |
| -                 | K317N     | N-linked_glycosylation              | DIS5-S6                         | China               |
| c.1198G>A         | p.G400R   | Methylarginine                      | DI S6                           | South China         |
| -                 | V469V     | -                                  | DI-DIII                         | China               |
| -                 | R511K     | Ubiquitination                      | DI-DIII                         | Xinjiang or Shanxi  |
| -                 | V522A     | -                                  | DI-DIII                         | Xinjiang or Shanxi  |
| -                 | R535X     | -                                  | DI-DIII                         | China               |
| 1651G>A           | A551T     | O-linked_glycosylation, Phosphoserine| DI-DII                         | China               |
| A1673G            | H588R     | Methylarginine                      | DI-DII                         | China               |
| 1776C>G           | N592K     | N-linked_glycosylation              | Ubiquitination                  | DI-DII             | China    |
| c.1960G>T         | p.E654X   | None                               | None                            | DI-DII             | China    |
| -                 | H681P     | Hydroxyproline                      | DI-DII                          | China               |
| -                 | K698N     | N-linked_glycosylation              | DI-DII                          | Xinjiang or Shanxi  |
| -                 | W822X     | None                               | DI S4                           | China               |
| -                 | G867X     | None                               | DI S5-S6                        | China               |
| 1651G>A           | G878G     | -                                  | DI S5-S6                        | Xinjiang or Shanxi  |
| 3269C>T           | P1090I    | None                               | None                            | DI-DII             | China    |
| -                 | Q1118X    | None                               | None                            | DI-DII             | China    |
| C3549T            | T1183T    | -                                  | DI-DII                          | Hebei              |
| G3578A            | R1193Q    | Pyrrolidone carboxylic acid         | DI-DII                          | China               |
| 4087insC          | None      | None                               | DII S4                          | South China         |
| -                 | C1363F    | None                               | DIII S-S6                       | China               |
| c.4282G>T         | p.A1428S  | Phosphoserine                       | DII S-S6                        | South China         |
| -                 | delF1617  | None                               | DII S3-S4                       | China               |
| -                 | R1623X    | None                               | DIII S4                         | China               |
| c.4886G>A         | R1629Q    | Pyrrolidone carboxylic acid         | DIII S4                         | Fujian             |
| C4948T            | A1649V    | None                               | DIII S4-S5                      | China               |
| c.5262G>A         | D1690N    | N-linked_glycosylation             | DIII S-S6                       | Fujian             |
| -                 | G1712C    | S-palmitoyl_cysteine               | DIII S-S6                       | Guangxi            |
| A5471G            | N1774S    | N-linked_glycosylation             | Phosphoserine                    | C terminus          | Guangxi            |
| -                 | S1812X    | None                               | C terminus                      | China               |
| -                 | D1818D    | None                               | C terminus                      | China               |
| c.5676delC        | p.T1893P  | Hydroxyproline                      | C terminus                      | South China         |
| c.5692C>T         | p.R1898C  | S-palmitoyl_cysteine               | C terminus                      | South China         |
| -                 | R1913C    | S-palmitoyl_cysteine               | C terminus                      | China               |
| -                 | V1951L    | None                               | C terminus                      | China               |
| 6366A>G           | None      | None                               | None                            | 3′UTR              | China    |
| C6995T            | None      | None                               | 3′UTR                           | Fujian             |
| 7204T>A           | None      | None                               | 3′UTR                           | China               |
| 7205C>T           | None      | None                               | 3′UTR                           | China               |
| 703+130G>A        | None      | None                               | None                            | Intron 6            | China    |
| 1143-3C>A         | None      | None                               | None                            | Intron 9            | China    |
TABLE 2 | Continued

| Nucleotide change | Mutations | The potential PTMs before mutation | The potential PTMs after mutation | Structural position | Location |
|-------------------|-----------|-----------------------------------|----------------------------------|---------------------|---------|
| 3840+73G>A       | None      | None                              | None                             | Intron 21           | China   |
| 4245+81G>T       | None      | None                              | None                             | Intron 23           | China   |
| 4245+82A>G       | None      | None                              | None                             | Intron 23           | China   |
| 4299+83T>C       | None      | None                              | None                             | Intron 24           | China   |
| rs11708996 G>C    | None      | None                              | None                             | Intron              | Taiwan, China |

Data from southern China are marked with a gray background.

locations lead to different pathological changes, we try to analyze whether protein functional modifications are involved in the mechanism.

PTM is a crucial modification method for protein transcription, such as phosphorylation, acetylation, ubiquitination, and glycosylation, which may bring a broad range of effects, such as protein stability, enzymatic activity, subcellular localization, and interactions. Multiple kinases including cyclic AMP-dependent protein kinase (PKA), protein kinase C (PKC), and calcium/calmodulin-dependent kinase II (CaMK II) phosphorylate regulate Nav1.5 channel physiology and pathology (45–48) including SUMOylation (49), ubiquitination (50), acetylation (51), etc. In our previous study, we revealed that miR-192-5p bound to the 3’-UTR of human SCN5A to negatively regulate the expression of Nav1.5 and reduce I_{Na} density. Our study demonstrated an important post-transcriptional role of miR-192-5p in post-transcriptional regulation of Nav1.5 (31).

Hence, we predicted the PTM sites with software and mapped on the mutations/variations in China. PTM change was likely to occur in 72.7% of BrS patients in southern China and 26.7% in northern China, suggesting that PTMs might be involved in the regulation of the pathogenesis of BrS, which provided new ideas and directions to further study the role of Nav1.5 in the pathogenesis of BrS.

CONCLUSION

The mutation sites of BrS patients from southern China mostly distributed in the DIII–DIV to C-terminus region and the 3’-UTR region of the SCN5A gene, which was different from northern China, Asia, and other countries around the world. PTM change might be involved in the regulation of the pathogenesis of BrS.

CONTRIBUTION TO THE FIELD STATEMENT

While BrS is a rare disease, it is especially young-male predominant and accounts for 20% sudden death without organic heart disease in Southeast Asia, which causes more and more concerns. We analyzed the genetic characteristics of SCN5A mutations/variations and found that SCN5A mutations/variations of BrS patients from southern China mostly occurred in the DIII–DIV to C-terminus region and the 3’-UTR region of the SCN5A gene, which was different from northern China, Japan, and the world. PTM changes predicted by the mutations/variations may be involved in the regulation of the pathogenesis of BrS. Our findings provide new ideas and directions to further study the role of Nav1.5 in the pathogenesis of BrS.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article-supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors participated in the design of the study, analysis and interpretation of the data, and review of the manuscript and approved the submitted version.

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