

SCN1B and SCN2B gene variants analysis in dravet syndrome patients

Analysis of 22 cases

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Abstract

Previous research identified SCN1B variants in some cases of Dravet syndrome (DS). We investigated whether SCN1B and SCN2B variants are commonly happened in DS patients without SCN1A variants. A total of 22 DS patients without SCN1A variants and 100 healthy controls were enrolled in this genetic study. DNA from DS patients was sequenced by Sanger method in whole exons of SCN1B and SCN2B genes. We identified two exon variants (c.351C>T, p.G117G and c.467C>T, p.T156M), which were present both in 1000 egenomes database and in healthy controls with a frequency of 0.54% and 4%, 0.06% and 0%, respectively. Additionally, eight intron or 3 prime UTR variants showing benign clinical significance have also been identified. Our results suggest that variants of SCN1B and SCN2B may not be common causes of DS according to our data. Further large sample-size cohort studies are needed to confirm our conclusion.

Abbreviations: CBZ = carbamazepine, CT = computed tomography, DS = Dravet syndrome, EEG = electroencephalogram, LEV = levetiracetam, MRI = magnetic resonance imaging, OXC = oxcarbazepine, PB = phenobarbitone, PHT = phenytoin, TPM = topiramate, UTR = 3 prime untranslated regions, VPA = sodium valproate.

Keywords: dravet syndrome, SCN1B, SCN2B, variant

1. Introduction

Dravet syndrome (DS) is a kind of archetypal genetic infantile epileptic encephalopathy with genetic etiology in most patients.^[1–3] DS is characterized by an onset, in the first year

of an infant's life, of febrile or afebrile clonic or tonic-clonic seizures.^[1] DS patients are antiepileptic drug resistant and later ataxia, psychomotor development, mental decline are observed in DS patients.^[4,5]

DS has variants in SCN1A gene in 70%–80% of the patients^[1,2,6] and has rare variants in GABRG2, GABRB3, GABRA1, PCDH19, HCN1, and STXBPI genes.^[4,7] More recently, SCN1B variants were also identified in DS patients without SCN1A variants.^[8–10] However, these variants of SCN1B are found in individual patients, but not in cohort patients. A study found no variant of SCN1B in a cohort of 54 DS patients in whom SCN1A exons variant had been excluded.^[5]

Sodium channels are composed of one α subunit and two β subunits.^[11,12] SCN1B encodes the β 1 subunit of voltage-gated sodium channel 1, which contributes to regulate sodium channel gating and control the channel Na_v 1.1 expression and localization.^[12] SCN2B encodes the β 2 subunit and results showed that SCN2B-null neurons have reduced voltage-gated sodium channel expression in cell surface, which implies the modulation function of SNC2B in neurons.^[13]

In this study, we tested the hypothesis that SCN1B and SCN2B variants confer susceptibility to DS with SCN1A-variant free patients.

2. Methods

2.1. Subjects

Patients enrolled in this study were recruited from the Xiangya hospital and the Second Xiangya Hospital of Central South University according to the international epilepsy classification in previous studies.^[1,2] The whole blood was collected from the subjects, and DNA was extracted by the phenol-chloroform

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Table 1**Primer sequences of *SCN1B* and *SCN2B* genes.**

| Gene exon | Forward primer | Reverse primer |
|----------------|-------------------------------|------------------------------|
| SCN1B Exon 1 | 5'-TCTCCTCCCTCGTCCCTCCCT-3' | 5'-TCCGTCTTTCCCGTCCCAGTCT-3' |
| SCN1B Exon 2 | 5'-CAGTCTGTCTGCTGGTAATC-3' | 5'-AGTTCTGTCTTCCCTCCGTAA-3' |
| SCN1B Exon 3 | 5'-GACAGAATCAGGGTCAGGTAAGG-3' | 5'-GCCCCAGAGGTGTTGAGTGA-3' |
| SCN1B Exon 4-5 | 5'-AGGTTGAGCCACTCATCCAAG-3' | 5'-TGCCAGCCATCCGCCTTAC-3' |
| SCN2B Exon 1 | 5'-TTCCTCCCTTGTAGTTCTCG-3' | 5'-CATCCTCTTCACATTGCGGC-3' |
| SCN2B Exon 2 | 5'-GCCCTTTCAGCCAGACTC-3' | 5'-GCCCTTTCAGCCAGACTC-3' |
| SCN2B Exon 3 | 5'-CCCTTGCTCCAACCCAG-3' | 5'-CTGGCACCCAGCCTTCA-3' |
| SCN2B Exon 4 | 5'-GTGGCTCTGCTTCCCTTCC-3' | 5'-AGCAGGCAGGGTCACTGTA-3' |

method.^[14–16] The diagnostic criteria for DS were (1) the onset is before 1 year of age, (2) the seizure type is clonic and often unilateral instead of generalized tonic or tonic-clonic, (3) the seizure episodes are more prolonged and frequent, even when treated, and (4) the body temperature is not very high.^[17–19] First, patients were screened by *SCN1A* exons variant according to previous studies.^[20,21] Exclusion criteria were patients who did not have their blood drawn for sequencing and who were not diagnosed with DS. Then patients without *SCN1A* exons variant were enrolled in this study to investigate the variants of *SCN1B* and *SCN2B*. Healthy controls without any illness were randomly selected from Medical Examination Center of the Xiangya Hospital. A standardized questionnaire was administered to collect clinical details such as symptoms, seizure types and frequency, and AEDs used. Patient characteristics were collected from clinical records, including gender, age, age at onset, familial or sporadic, electroencephalogram, magnetic resonance imaging, computed tomography, duration of seizure, frequency of seizure, and current medication. The Ethics Committee of Institute of Clinical Pharmacology of Central South University approved the study. The Chinese Clinical Trial Register approved the clinical study admission (Registration Number: ChiCTR-TCH-0000813).

2.2. Variant analysis

DNA was extracted from the whole blood of the subjects according to previous standard procedures.^[15] The whole coding

exons of *SCN1B*, *SCN2B*, and *SCN1A* were screened for variants by PCR amplification and Sanger sequencing according to previous research (Table 1).^[22,23] ABI 3700 Genetic Analyzer analyzed PCR products. PubMed database (<https://www.ncbi.nlm.nih.gov/pubmed/>) was used to evaluate single nuclear acid variant information including the position, nucleotide changes, function changes, clinical significance, and 1000G frequency. SIFT database (<http://provean.jcvi.org/index.php>) and PolyPhen-2 database (<http://genetics.bwh.harvard.edu/pph2/index.shtml>) were used to predict the variant function.

3. Results

Of the total 48 DS patients, 26 patients had *SCN1A* variants (Table S1, <http://links.lww.com/MD/C896>). Twenty-two patients with DS without *SCN1A* exon variant were enrolled in further screening the exon variants of *SCN1B* and *SCN2B*. One hundred healthy controls also had their exon variants of *SCN1B* and *SCN2B* analyzed. The characteristics of DS patients were shown in Table 2. The 22 DS patients include 12 men and 10 women in the age range of 7.5 ± 5.1 months. The age of onset was 5.4 ± 2.99 months. The medications include valproic acid, topiramate, carbamazepine, oxcarbazepine, phenobarbital, and levetiracetam.

In general, no pathogenic *SCN1B* and *SCN2B* variants were detected in our study cohort. We found one exon variant (c.351 C>T, p.G117G), which is a synonymous codon with benign

Table 2**Characteristics of Dravet syndrome patients.**

| Case number | Gender | Age at onset (month) | Age (year) | Familial/Sporadic | EEG/MRI/CT | Duration of seizure | Frequency of seizure | Current medication |
|-------------|--------|----------------------|------------|-------------------|------------|---------------------|----------------------|--------------------|
| 276 | F | 6 | 5 | Familial | AB/N/N | 1–2 min | 1–2 m | VPA + CBZ |
| 572 | M | 8 | 7 | Familial | N/ND/N | 5–6 min | 1 w | VPA + CBZ |
| 576 | F | 4 | 6 | Familial | N/N/ND | 1 min | 1–2 w | VPA + LEV |
| 528 | F | 4 | 4 | Sporadic | AB/N/N | 1–2 min | 2–3 d | VPA + LTG |
| 457 | F | 3 | 5 | Familial | N/N/ND | 5–6 min | 1 w | VPA + CBZ |
| 394 | M | 12 | 8 | Familial | AB/N/N | 5–6 min | 1–2 d | CBZ + LTG |
| 434 | M | 8 | 22 | Familial | AB/ND/ND | 3 min | 3–5 d | CBZ + VPA |
| 476 | M | 2 | 3 | Sporadic | AB/ND/ND | 2–3 min | 2–3 d | VPA + PHT |
| 293 | M | 3 | 12 | Familial | AB/N/N | 1–2 min | 1–2 m | TPM + CBZ |
| 897 | M | 5 | 6 | Familial | AB/ND/ND | 2–3 min | 2–3 d | VPA + LTG |
| 231 | M | 6 | 8 | Sporadic | N/ND/N | 1 min | 2–3 d | OXC + VPA |
| 872 | F | 3 | 5 | Familial | N/ND/N | 2 min | 1–2 w | VPA + CBZ |
| 1013 | M | 8 | 14 | Sporadic | N/N/ND | 2–3 min | 1–2 w | VPA + LTG |
| a39 | F | 12 | 6 | Familial | N/N/ND | 2 min | 3 m | CBZ + LEV |
| a67 | F | 9 | 7 | Familial | AB/ND/ND | 2 min | 1–2 w | VPA + LEV |
| a71 | F | 5 | 20 | Familial | N/N/ND | 10 min | 3 m | OXC + PB |
| 15 | F | 5 | 4 | Familial | AB/N/N | 1–2 min | 3 m | CBZ + LEV |
| a164 | F | 5 | 5 | Sporadic | AB/ND/ND | 1–2 min | 1 w | VPA + LTG |
| 428 | M | 4 | 6 | Familial | N/N/ND | 1 min | 1–2 m | CBZ + LEV |
| 456 | M | 5 | 6 | Familial | AB/N/N | 2 min | 1–2 w | VPA + CBZ |
| 437 | M | 1 | 3 | Sporadic | AB/N/N | 1 min | 1 w | VPA + LTG |
| 82 | M | 2 | 3 | Familial | AB/ND/ND | 2 min | 1–2 w | VPA + LTG |

AB = abnormal, CBZ = carbamazepine, CT = computed tomography, d = days, EEG = electroencephalogram, F = female, LEV = levetiracetam, M = male, m = months, MRI = magnetic resonance imaging, N = normal, ND = not done, OXC = oxcarbazepine, PB = phenobarbitone, PHT = phenytoin, TPM = topiramate, VPA = sodium valproate, w = weeks, y = years.

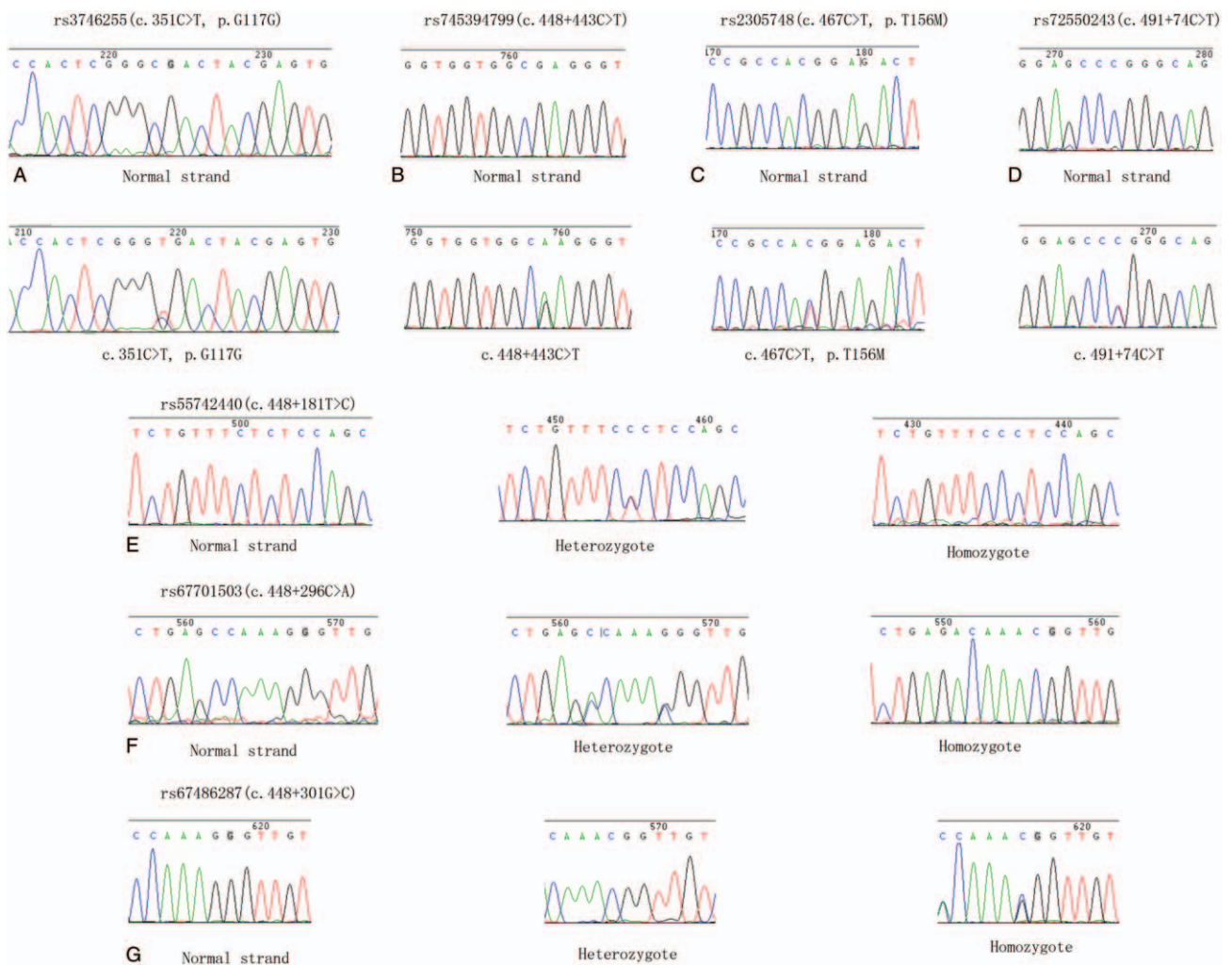


Figure 1. The identified *SCN1B* variants in Dravet syndrome. (a) rs3746255(c.351C>T, p.G117G); (b) rs745394799(c.448+443C>T); (c) rs2305748(c.467C>T, p.T156M); (d) rs72550243(c.491+74C>T); (e) rs55742440(c.448+181T>C); (f) rs67701503(c.448+296C>A); (g) rs67486287(c.448+301G>C).

clinical significance and is present in 1000 genomes database with a frequency of 0.54% (Fig. 1). And this mutant heterozygote was also found in four healthy controls (4%). We also found one missense variant changing the coding amino acid from threonine to methionine (c.467C>T, p.T156M) in one DS patient and the frequency of this variant is 0.06% in 1000 genomes database and 0% in healthy control. SIFT and PolyPhen-2 database to predict the function of missense variant and results showed damaging and neutral, respectively. We found no exon variant of *SCN2B*. Moreover, we also found six intron variants and two 3 prime untranslated regions (UTR) variants in patients and healthy controls (Fig. 2 and Table 3). Interestingly, we found one new variant in 3 prime UTR region of *SCN2B*, which was not in the dbSNP and 1000G database. This 3 prime UTR variant (c.*32C>T) was found in one DS patient and was not present in healthy controls.

4. Discussion

DS has variants in *SCN1A* gene in 70%–80% of the patients.^[1,2,6] We screened 48 DS patients and found 26 DS patients (54.2%) had *SCN1A* variants (Table S1, <http://links.lww.com/MD/C896>), which were also reported in previous

studies and database.^[30–32] Studies reported causative variants of *SCN1B* p.R125C in two infants with DS^[8,10] and *SCN1B* p.Ile106Phe in one of 67 DS patients.^[9] In order to find the pathogenesis of DS except *SCN1A* variants, we carried out this study to investigate the variants of *SCN1B* and *SCN2B* variants in DS patients.

In our study, we found one exon variant of *SCN1B* (c.351 C>T, p.G117G), which is a synonymous codon with benign clinical significance and is present in 1000 genomes database with a frequency of 0.54%. We also found one missense variant of *SCN1B* (c.467C>T, p.T156M) presented in 1000 genomes database with a frequency of 0.06%. We used SIFT and PolyPhen-2 database to predict the function of missense variant and results showed damaging and neutral, respectively. Other intron variants of *SCN1B* and *SCN2B* found in our cohort were not related to the pathogenesis of DS.

Voltage-gated sodium channels are composed of a large α -subunit and two smaller β -subunits ($\beta 1$ and $\beta 2$).^[22] Functional studies found the *SCN1B* gene which encodes that the $\beta 1$ -subunit regulates dorsal root ganglion nociceptor excitability in vivo.^[24] *SCN1B* variants (p.C121W, p.I70 E74del, p.R85C, p.R85H, and p.R125L) were also reported in genetic epilepsy with febrile seizure plus and absence epilepsy patients.^[10,25–27] Our

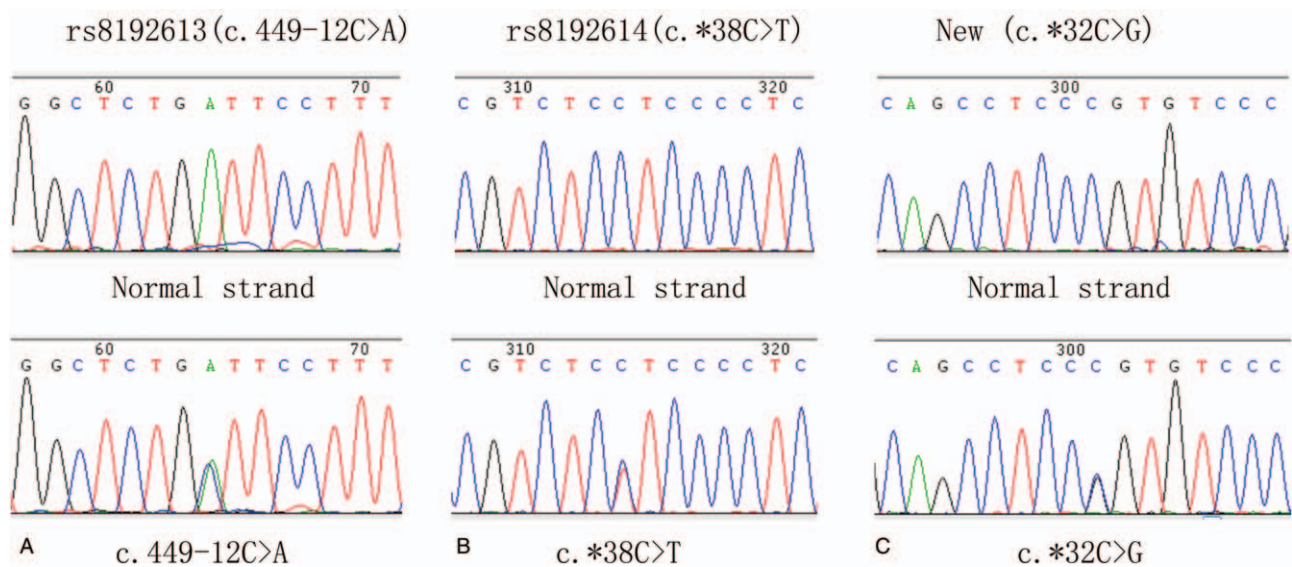


Figure 2. The identified *SCN2B* variants in dravet syndrome. (a) rs8192613(c.449-12C>A); (b) rs8192614(c.*38C>T); (c) New(c.*32C>G).

Table 3

Characteristics of *SCN1B* and *SCN2B* mutations identified in our cohort.

| Gene | Variants | Position | Nucleotide changes | Function changes | Clinical significance | 1000G frequency | Frequency in our cohort* | Frequency in healthy controls* |
|--------------|-------------|--------------|--------------------|------------------|-----------------------|-----------------|--------------------------|--------------------------------|
| <i>SCN1B</i> | rs3746255 | 19:35033642 | c.351C>T, p.G117G | Synonymous codon | Benign | 0.54% | (2+0)/22, 4.55% | (4+0)/50, 4% |
| | rs55742440 | 19:35033920 | c.448+181T>C | Intron | Benign | 37.76% | (9+2)/22, 29.5% | (21+5)/50, 3.1% |
| | rs67701503 | 19:35034035 | c.448+296C>A | Intron | Benign | 12.74% | (7+1)/22, 20.45% | (11+3)/50, 17% |
| | rs67486287 | 19:35034040 | c.448+301G>C | Intron | Benign | 11.92% | (6+2)/22, 22.73% | (8+3)/50, 14% |
| | rs745394799 | 19:35034182 | c.448+443C>T | Intron | NR | NR | (1+0)/22, 2.27% | (2+0)/50, 2% |
| | rs2305748 | 19:35039234 | c.467C>T, p.T156M | Missense | NR | 0.06% | (1+0)/22, 2.27% | (0+0)/50, 0% |
| | rs72550243 | 19:35039332 | c.491+74C>T | Intron | NR | 2.26% | (2+0)/22, 9.09% | (0+0)/50, 0% |
| <i>SCN2B</i> | rs8192613 | 11:118167098 | c.449-12C>A | Intron | Benign | 48.56% | (10+2)/22, 31.82% | (22+5)/50, 32% |
| | rs8192614 | 11:118166849 | c.*38C>T | 3 prime UTR | NR | 7.81% | (2+0)/22, 9.09% | (4+0)/50, 4% |
| | New | 11:118166855 | c.*32C>G | 3 prime UTR | NR | NR | (1+0)/22, 2.27% | (0+0)/50, 0% |

NR = not report, UTR = untranslated regions.

* Present as (mutant heterozygote + mutant homozygote)/total patients or healthy controls.

results found that *SCN1B* variants are not a common cause of DS, which is consistent with previous studies.^[5]

SCN2B gene encodes $\beta 2$ -subunit of voltage-gated sodium channel and the gene consists of 4 exons and is highly conserved in the coding region.^[22] *SCN2B* variant might be associated with the risk of Brugada syndrome but not with the idiopathic generalized epilepsy in previous research.^[15,22,28,29] We first screened the exon region of *SCN2B* in DS patients without *SCN1A* variant. There was no research about *SCN2B* variant in DS patients. Our research found no exon variant of *SCN2B* in DS patients.

SCN1A gene variants were found in 70%–80% of the DS patients, and *SCN1B* and *SCN2B* encoding $\beta 1/\beta 2$ subunits regulate sodium channel gating and control the channel $\text{Na}_v 1.1$ expression and localization. Therefore, *SCN1B* and *SCN2B* variants may influence the channel $\text{Na}_v 1.1$ function, inducing the seizure of DS patients. Lots of *SCN1A* variants were identified in DS patients at previous study and in our study. However, we found no combined variant of *SCN1A*, *SCN1B* and *SCN2B*, and *SCN1B* and *SCN2B* variant was rarely identified in DS patients. The roles of *SCN1B* and *SCN2B* variants contributed to the

etiology of DS patients were needed in large sample-size cohort studies and mechanism function studies.

Our study suggested that *SCN1B* and *SCN2B* variants are uncommon in DS patients according to our data. Further large sample-size cohort studies are needed to confirm our conclusion.

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