

# Mutation analysis of CACNA1S and SCN4A in patients with hypokalemic periodic paralysis

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**Abstract.** Mutations in CACNA1S (calcium channel, voltage-dependent, L type, alpha 1S subunit) and SCN4A (sodium channel, voltage-gated, type IV, alpha subunit) are associated with hypokalemic periodic paralysis (HPP). The aim of the current study was to investigate CACNA1S and SCN4A mutations in patients with HPP. Mutations in CACNA1S and SCN4A were detected in three familial hypokalemic periodic paralysis (FHPP) pedigrees and in two thyrotoxic hypokalemic periodic paralysis (THPP) pedigrees using polymerase chain reaction, DNA sequencing and sequence alignment with GenBank data. A single base mutation from cytosine to guanine at site 1582 was identified in exon 11 of CACNA1S in one FHPP pedigree, resulting in an arginine to glycine (R528G) substitution. A single base mutation from thymine to cytosine at site 2012 was identified in exon 12 of SCN4A in one THPP pedigree, resulting in a phenylalanine to serine (F671S) substitution. No mutations in CACNA1S or SCN4A were identified in the remaining three pedigrees. The present study indicated that CACNA1S and SCN4A mutations are relatively rare in patients with HPP, and further studies are required to determine whether these mutation-associated substitutions are representative of patients with HPP.

## Introduction

Hypokalemic periodic paralysis (HPP) is characterized by recurrent attacks of hypokalemia and muscle weakness and is widely recognized as a typical skeletal muscle channelopathy. Primary HPP is categorized into either familial HPP (FHPP) or sporadic HPP (SHPP). Thyrotoxic HPP (THPP) is representative

of all secondary HPP conditions and although familial cases have been reported, the majority cases of THPP are sporadic.

According to pedigree analysis, FHPP is an autosomal dominant disease with lower penetrance in females (1). The pathogenesis of FHPP is attributed to mutations in genes encoding ion channels in skeletal muscle, although the underlying mechanism remains unclear. Associated mutations have been most commonly reported in the genes encoding the voltage-dependent L type calcium channel subunit alpha 1S (CACNA1S) and the voltage-gated sodium channel type IV alpha subunit (SCN4A) (2,3). Several point mutations (4,5) in CACNA1S and SCN4A have been identified to have associations with FHPP, including Arg1239His/Gly and Arg528His in CACNA1S, and Arg669His, Arg672His/Gly and Arg672Ser in SCN4A. Additional rare substitutions have also been reported (6). Some overlap in the mutations in FHPP, SHPP (7), and THPP (8) has been reported.

To date, the majority of genetic studies of HPP have been conducted in Western populations (2,6). Fewer HPP cases have been reported in China compared with Western countries, and information on HPP in Chinese populations remains limited (2,6). The aim of the current study was to screen for mutations in CACNA1S and SCN4A in Chinese patients with HPP. The present study aimed to determine whether mutations associated with HPP in Chinese cases are the same as those in Western populations, and to provide further epidemiological evidence for HPP.

## Materials and methods

**Study subjects.** Informed consent was obtained from all participating patients and the study was approved by the medical ethics committee of the Chinese People's Liberation Army Navy General Hospital (Beijing, China). In total, three FHPP and two THPP pedigrees were investigated and all patients involved were free from any other inherited systemic diseases or congenital disorders and presented with typical periodic attacks of limb paralysis with severe hypokalemia. The pedigree analysis is presented in Fig. 1.

**Reagents and materials.** High fidelity Pyrobest DNA polymerase and dNTPs were purchased from Takara Bio, Inc.

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Table I. Polymerase chain reaction primers designed for analysis of common mutation sites.

Gene	Primers (5'-3')	Amplified sites	Fragment length
CACNA1S	L:CACTGAGATGCTGATGAAGATGTA	528	192 bp
	R:GCACTCACTTGGTGATCTTGAA		
	L:ATGAGAGTGCCCGCATCTCC	1239	181 bp
	R:CTGTTGCACCTGGAAGGACTTG		
SCN4A	L:CTCTGTGACAGGGCCTCATG	669, 672	250 bp
	R:TCCTCACCCACCCCATCC		

L, left primer; R, right primer; bp, base pairs.

Table II. Polymerase chain reaction primers for amplification of CACNA1S and SCN4A exons.

Exon number	Left primer	Right primer
CACNA1S		
11	GGGAGTCAGGAGAATGG	GGGAAGTCTGGGCAAGG
20	CCAGGCTGCTGCCTCTT	CCTTGCCGCTGCTCACT
21	ACAGGCCTGTTCTCCAC	TCCTTGTGCTTGAGAGT
22	ACAGGCCTGTTCTCCAG	TCCTTGTGCTTGAGAGT
26	CTGTGATAACTCAATGG	AATAAACCATAAGTGCC
30	GCCCCTTACCCCTCTGT	CCAGGTACGTGCAGTTT
SCN4A		
5	GACCCTGTGGTACCCCT	GCTGCCTCTCAAACGCC
12	CTACGCTCCTTCAGTCT	GAAGACCCGCAGCAGAC
18	ACGCACTGATCCCTCG	CCAGAGGCCCTTCAGC
19	GCCCTCCTAGGCGCCAT	GTAGAGGTTACCTCGT

(Otsu, Japan), and Wizard™ Genomic DNA Purification kits, T4 DNA ligase, plasmid pGEM-T and bacteria JM109 were all purchased from Promega Corporation (Madison, WI, USA).

**Mutation analysis.** Blood samples from confirmed HPP patients were obtained, and genomic DNA was isolated from white blood cells using a Genomic DNA Purification kit according to the manufacturers instructions. Sequence analysis was conducted to identify previously reported common and infrequent mutation sites in CACNA1S and SCN4A. CACNA1S fragments containing the sequences encoding Arg528 and Arg1239 and a SCN4A fragment containing the sequence encoding Arg669 and Arg672 were amplified by polymerase chain reaction (PCR) with the primers presented in Table I. For the pedigrees free from mutations in the above common sites, alternative PCR primers, presented in Table II, were designed to specifically amplify other fragments in CACNA1S and SCN4A. All primers were synthesized by AuGCT Biotechnology Co., Ltd. (Beijing, China). The PCR products were separated by 2% agarose gel electrophoresis (Beijing Huahai Henghui Technology Co., Ltd.) and collected using a gel extraction kit (Promega Corporation). The PCR products were used as templates for subsequent PCR expansion, following which

the products were collected again. PCR was performed using a reaction solution containing 50  $\mu$ l PCR buffer containing 100  $\mu$ mol/l dNTPs, 0.2  $\mu$ mol/l primers, 2 units Taq DNA polymerases and 50 ng DNA template. The cycling conditions consisted of one cycle of denaturation at a temperature of 94°C for 5 min, followed by denaturation at a temperature of 94°C for 30 sec, and annealing at a temperature of 55°C for 30 sec and extension at a temperature of 72°C for 30 sec, for a total of 30 cycles. A final extension step was performed at a temperature of 72°C for 5 min. All amplified products were sequenced using an ABI PRISM® 377 DNA Sequencer (Thermo Fisher Scientific, Inc., Waltham, MA, USA). Sequencing results were BLAST searched (blast.ncbi.nlm.nih.gov/) against sequences in GenBank.

## Results

**Clinical features.** The patients selected for the current study all displayed clinical symptoms in accordance with the diagnostic criteria of HPP. All patients were suffering from irregular muscle weakness with hypokalemia and muscle weakness predominantly in the limbs. Potassium supplements had been effective for all the probands of these pedigrees. Patients in pedigree D and pedigree E also exhibited symptoms of hyperthyroidism, with the hyperthyroidism confirmed by thyroid

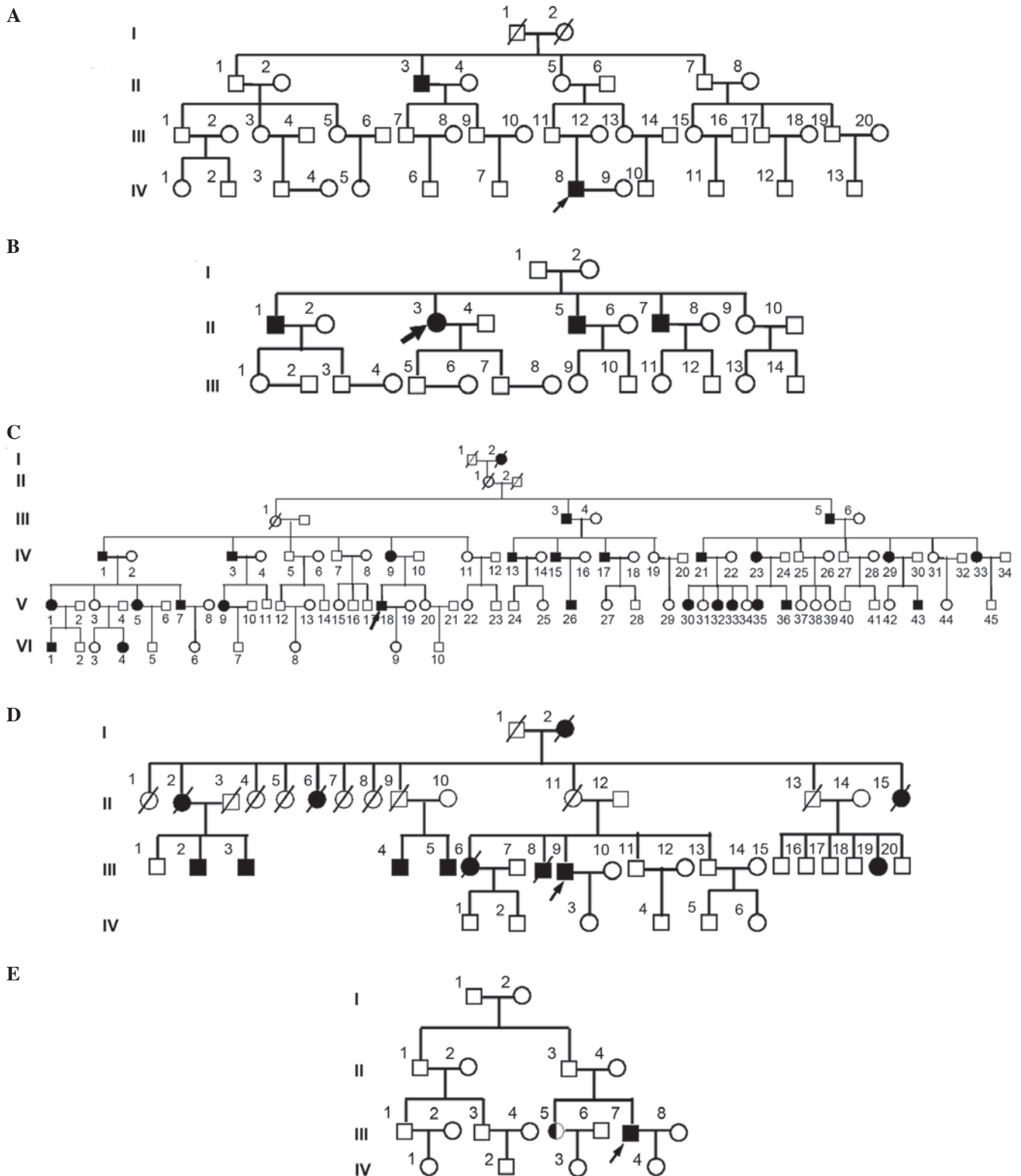


Figure 1. HPP pedigrees. (A) Chinese HPP pedigree A. (B) Chinese HPP pedigree B. (C) Chinese HPP pedigree C. (D) Chinese THPP pedigree D. (E) Chinese THPP pedigree E. Open square, healthy male; open circle, healthy female; filled square, male patient; filled circle, female patient; arrow, proband; crossed out symbol, deceased individual. HPP, hypokalemic periodic paralysis; THPP, thyrotoxic hypokalemic periodic paralysis.

function analysis. The probands were IV8 of pedigree A, II3 of pedigree B, VI8 of pedigree C, III9 of pedigree D and III7 of pedigree E, and their ages of onset were 22, 40, 15, 45 and 43 years old, respectively. As presented in Fig. 1, the ratio of male to female patients in these pedigrees was 2:0, 3:1,

14:13, 6:6 and 1:1, respectively, and atavism was observed in all five pedigrees.

**Results of DNA sequencing.** Mutation analysis was first conducted in probands and healthy controls from each

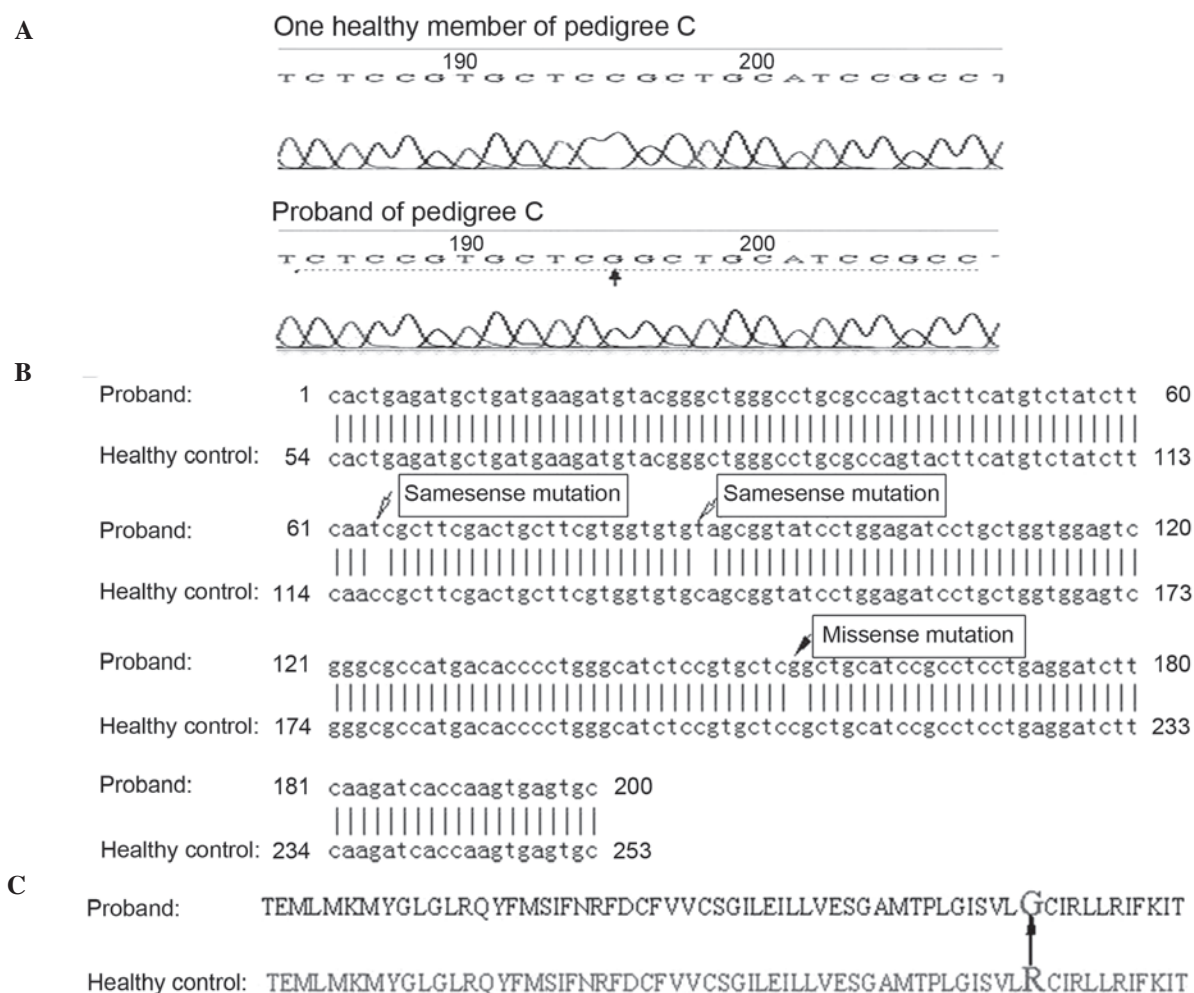


Figure 2. Sequence analysis of the CACNA1S region encoding amino acid site 528 in pedigree C. (A) Sequencing maps of the amplified fragment in the proband and one healthy member of pedigree C. (B) Sequence alignment. The sequence of the healthy control from GenBank. (C) The change in amino acid sequence resulting from the missense mutation of cytosine to guanine at nucleotide 1582 in CACNA1S. CACNA1S, voltage-dependent L type calcium channel subunit alpha 1S.

pedigree. Gene fragments of CACNA1S, containing the 528 and 1239 mutation sites, and of SCN4A, containing the 669 and 672 mutation sites were sequenced. In pedigree C (Fig. 2A), a cytosine to guanine mutation was identified at site 195 in the 192 base pair amplified fragment containing amino acid site 528 of CACNA1S. Following sequence alignment, the mutation was identified as a missense mutation at nucleotide 1582 in exon 11 of CACNA1S, resulting in a substitution of glycine for arginine at site 528 in CACNA1S (Fig. 2B and C). Two additional mutations observed in the same fragment were confirmed as same-sense mutations (Fig. 2B). In pedigree D (Fig. 3A), a substitution mutation of thymine to cytosine was identified in the 250 base pair SCN4A fragment containing amino acid sites 669 and 672. Following sequence alignment, the mutation was confirmed as a missense mutation at nucleotide 2012 in exon 12 of SCN4A, resulting in a substitution of serine for phenylalanine at site 671 (Fig. 3B and C). Two additional mutations observed in the CACNA1S fragment containing nucleotide 1239 were confirmed as same-sense mutations. No mutations in these fragments containing the common mutation sites were identified in the probands of the other three pedigrees.

Gene fragments encompassing the sites of alternative reported mutations in CACNA1S and SCN4A were then sequenced in the remaining three pedigrees. In pedigree A, among 43 family members in four generations, mutations in 33 subjects, including two patients (IV8 and II3), were detected. In pedigree B, among 26 family members in three generations, mutations in 20 subjects, including four patients (III1, II3, II5 and II7), were detected. In pedigree E, among 18 family members in four generations, mutations in 12 subjects, including one confirmed patient (III7) and one suspected patient (III5), were detected. No mutations previously identified in exons 11, 20, 21, 22, 26 and 30 of CACNA1S, and in exons 5, 12, 18 and 19 of SCN4A were identified in these three pedigrees. Sequencing maps, ranging from nucleotide 1567-1596 in exon 11 of CACNA1S, and from nucleotide 1999-2028 in exon 12 of SCN4A, are presented in Figs. 4 and 5, respectively.

## Discussion

HPP is a disease detrimental to the quality of life of the patients and can lead to death resulting from unexpected respiratory paralysis or arrhythmia (9,10). Due to variation in the age of



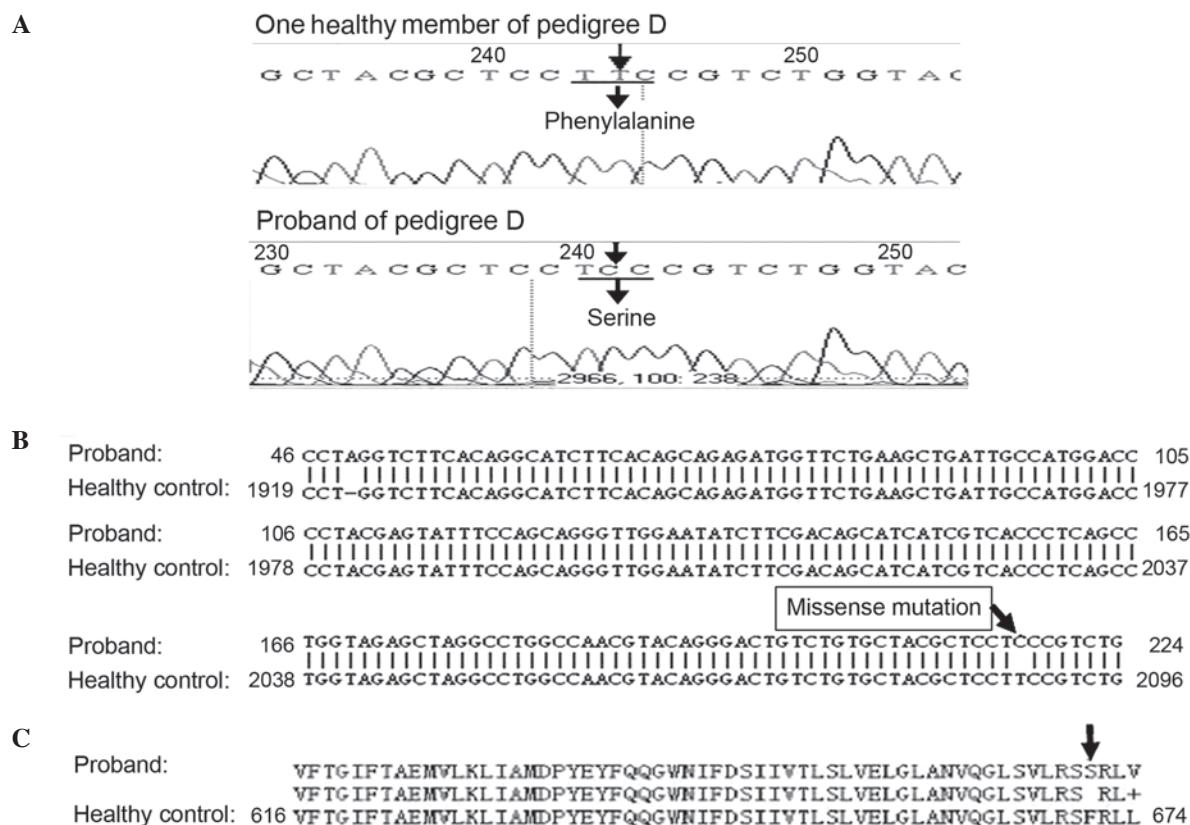


Figure 3. Sequence analysis of SCN4A region encoding amino acid sites 669 and 672 in pedigree D. (A) Sequencing maps of the amplified fragment in the proband and one healthy member of pedigree D. (B) Sequence alignment. The sequence of the healthy control from GenBank. (C) The change in the amino acid sequence resulting from the missense mutation of thymine to cytosine at nucleotide 2012 in SCN4A. SCN4A, voltage-gated sodium channel type IV alpha subunit.

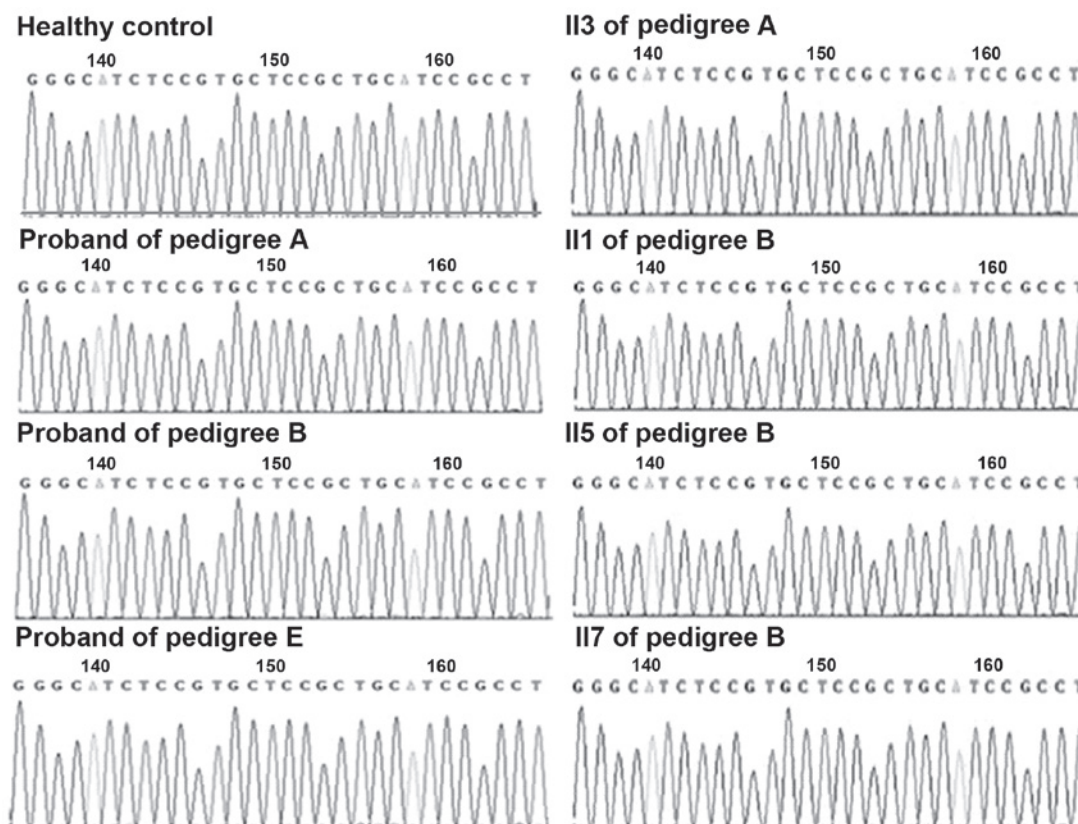


Figure 4. Sequence maps of bases from sites 1567-1596 in exon 11 of CACNA1S in a healthy control, probands and other patients of pedigrees A, B and E. CACNA1S, voltage-dependent L type calcium channel subunit alpha 1S.

Table III. Verified mutation sites in CACNA1S and SCN4A in patients with hypokalemic periodic paralysis.

Gene	Exon number	Mutation sites
CACNA1S	11	R528H (6), R528G (6)
	20	V876E (11), R897S (12)
	21	R900G (13), R900S (6)
	22	H916Q (14)
	26	R1086C (6)
	30	R1239H (6), R1239G (6)
SCN4A	5	R222W (6), R669H (6)
	12	F671S (6), R672H (6), R672G (6), R672C (6), R672S (6)
	18	R1132Q (6), R1135H (6)
	19	P1158S (15)

CACNA1S, voltage-dependent L type calcium channel subunit alpha 1S; SCN4A, voltage-gated sodium channel type IV alpha subunit; R, arginine; G, glycine; H, histidine; S, serine; C, cysteine; Q, glutamine; P, proline; V, valine; E, glutamic acid; W, tryptophan; F, phenylalanine.

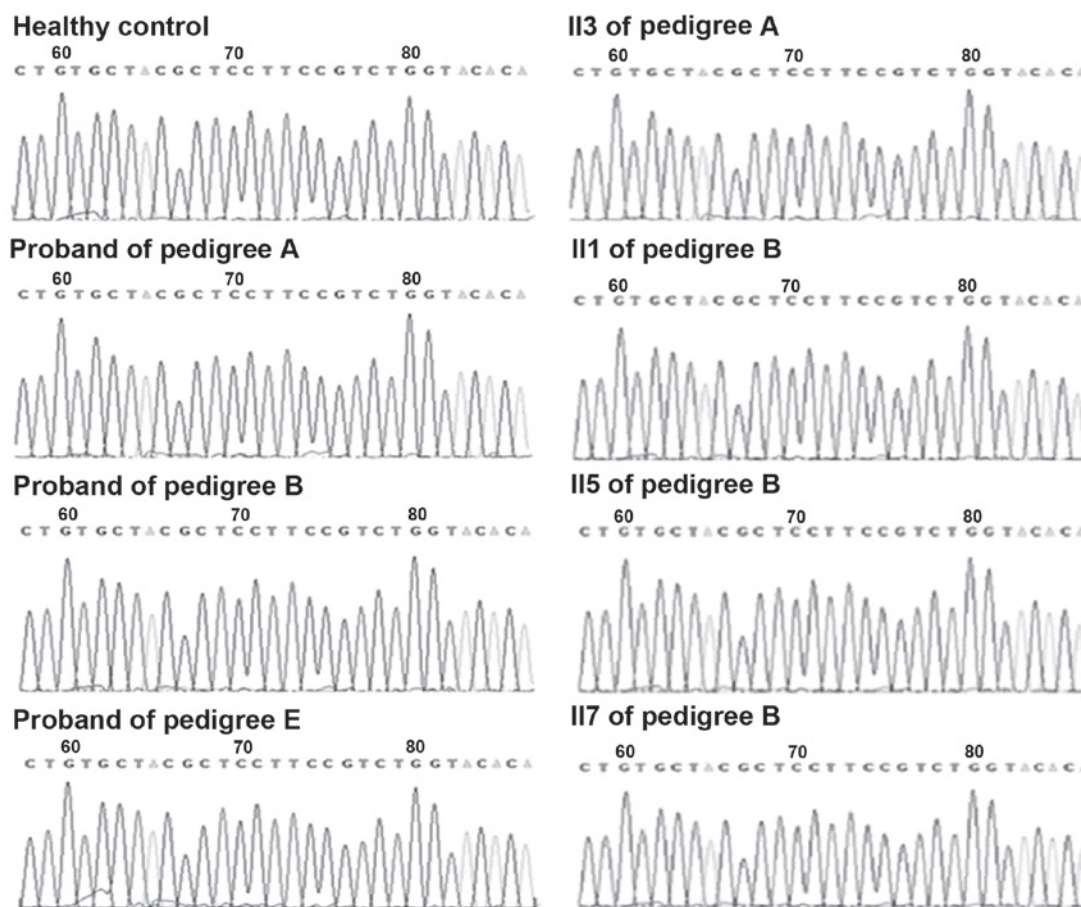


Figure 5. Sequence maps of bases from sites 1999-2028 in exon 12 of SCN4A in a healthy control, probands and other patients of pedigrees A, B and E. SCN4A, voltage-gated sodium channel type IV alpha subunit.

onset, duration, frequency and severity of attacks, the diagnosis of HPP is predominantly made according to clinical history, attack characteristics and serum potassium levels during attacks (16). Although the specific mechanism of HPP remains unclear, mutations in genes encoding ion channels in skeletal muscle have been suggested to be involved (17), and genetic analysis may aid

in elucidating the pathogenesis of the disease. The inheritance pattern of HPP is known to be autosomal dominant, however it has incomplete penetrance, particularly in females (16). With several family members in the same pedigree suffering HPP, the incomplete penetrance of pathogenic genes is considered to be involved in the atavism of the pedigrees in the current study.

Previous studies have indicated the familial transmission of HPP-associated mutations (2,18). Although SCN4A mutations are also involved (19,20), mutations in CACNA1S occur primarily in patients with HPP. In a study involving 58 HPP pedigrees (2), the rate of mutation detection was 77.6%, including 40 pedigrees with CACNA1S mutations (69.0%) and five pedigrees with SCN4A mutations (8.6%) (no mutations were observed in the remaining 13 pedigrees). The two most common mutations in CACNA1S were R528H and R1239H, which account for 45.0 and 24.0% of mutations detected, respectively. In an additional study involving 83 cases of HPP (6), the rate of mutation was 87.9%, including 65 cases with CACNA1S mutations, accounting for 78.3%, and eight cases with SCN4A mutations, accounting for 9.6%.

Compared with Western populations, mutations observed in Eastern populations are very similar, however the rate of mutation detection is markedly lower. In a study of Chinese patients (21), one case with the R1239H mutation and two cases with the R672H mutation were identified in the probands of 14 pedigrees, the mutation rate of which was 21.4%, and only one case with the R672C mutation was observed in 71 sporadic patients. Mutation screening in Taiwanese patients with HPP detected one case with R528H in 12 sporadic patients, accounting for 8.3%, with no cases detected in 36 patients with THPP (7). An additional study in Taiwanese patients reported four cases with mutations among 60 sporadic patients with HPP, including one case with R1239H, two cases with R669H and one case with R1135H, with the mutation rate in the current study at 6.6% (22). Mutations have been rarely reported in populations from China (23,24). Accordingly, the present study additionally demonstrated a lower rate of HPP-associated gene mutations.

The known mutations in CACNA1S and SCN4A are presented in Table III. The majority of mutation sites in the table have been identified in Western populations, excluding R528G, R900G, R916Q and R1239G. In studies of Asian populations, mutations in CACNA1S were predominantly reported in case studies (9,13,25-31) and pedigree studies (7,14,32-34). In the current study, a rare R528G mutation in CACNA1S in a Chinese HPP pedigree was observed, and this mutation has been previously reported in another Chinese pedigree with HPP (27). THPP shares certain common characteristics with HPP, however, the identification of pathogenic genes between them are not similar (35-37). In contrast with HPP, mutations in CACNA1S are not associated with THPP (35). To date, gene mutations have been confirmed in three THPP pedigrees, including a pedigree with an R83H mutation in KCNE3 (38), a pedigree with an M58V mutation in KCNE4 (36), and a Chinese pedigree with an F671S mutation in SCN4A (the current study). R83H and M58V have not been identified in Chinese patients with THPP, however it remains controversial whether R83H is a causative mutation in THPP, due to the fact that it is additionally present in ~2% of healthy individuals (39).

In conclusion, mutations in CACNA1S and SCN4A are relatively rare in Chinese HPP cases compared with cases in Western individuals. This indicates a racial difference and the possibility of other pathogenic genes or factors in Chinese patients. Due to the fact that the sample sizes in Asian pedigree studies have been relatively small, and the newly

identified mutations in Chinese cases are often identified in case studies (13,14), further research is required to investigate whether R528G in HPP and F671S in THPP are common in Chinese populations. Future studies should aim to identify novel mutations in Chinese patients in CACNA1S and SCN4A in addition in other genes, and to establish animal models with known mutations to further clarify the pathophysiological mechanisms of HPP.

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