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Case Report

The clinical characteristics of CACNA1S R528H mutation in a Chinese family with hypokalemic periodic paralysis

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Abstract: Familial hypokalemic periodic paralysis (FHPP) is an autosomal dominant skeletal muscle ion channelopathy. The most common mutations responsible for FHPP lie on CACNA1S and SCN4A. Few cases were reported in Chinese population. Here, we reported a Chinese family with CACNA1S R528H and summarized the clinical characteristics. One family diagnosed as FHPP was recruited. Their clinical characteristics were collected and summarized. Genomic DNA was obtained from each member of the family for mutation screening. Six of the twelve family members were diagnosed as FHPP. And each of them was found to carry CACNA1S R528H mutation while other family members were found not. The age of onset, frequency and duration of attack, and triggering factors were not the same as former studies reported. This study may enrich the epidemiology and demography of FHPP in Chinese population.

Keywords: Channelopathy, Chinese, familial hypokalemic periodic paralysis, CACNA1S, R528H

Introduction

Hypokalemic periodic paralysis (HPP) is characterized by recurrent attacks of muscle weakness associated with decreasing levels of serum potassium. In Eastern Asia, secondary HPP is more common, usually caused by hyperthyroidism. Primary HPP, especially familial HPP (FHPP) is relatively rare compared with western countries. FHPP is now considered as an autosomal dominant skeletal muscle channelopathy. Also, FHPP is usually caused by mutations in CACNA1S and SCN4A, which encode alpha submit of calcium channel Cav1.1 and alpha submit of sodium channel Nav1.4, respectively. However, the severity and frequency of symptoms vary within different mutations and different individuals.

Most cases about FHPP were reported in western countries. Only few cases were reported in Asia, especially in China [1]. The difference in genotype and clinical phenotype in FHPP between Western population and Chinese population remains unclear. In this study, we presented a Chinese FHPP case and compared the clinical phenotype with that reported in former studies.

Materials and methods

Patients: One family diagnosed as FHPP was recruited. All members of this family were asked to sign an informed consent form prior to the study. The study was also approved by the Ethic Committee of Suzhou Municipal Hospital. Blood biochemistry, routine urine examination, thyroid function, and ultrasound of the thyroid and adrenal glands were performed for the proband in order to exclude secondary HPP causes, especially hyperthyroidism.

Mutation Analysis: Blood samples were obtained from all the family members. Genomic DNA was isolated from peripheral blood leukocytes using a Genomic DNA Purification kit (Tiangen Biotech Co. Ltd) according to the manufacturer's instructions. Using polymerase chain reaction (PCR) sequencing, the proband was screened for the common mutation sites in

Table 1. PCR primers applied for detection of target exons in gene CACNA1S and SCN4A

Gene	Exon	Forward primer	Reverse 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	ACGCACTGATCCCCTCG	CCAGAGGCCCCTTCAGC
	19	GCCCTCCTAGGCGCCAT	GTAGAGGTTCACCTCGT

CACNA1S and SCN4A reported by previous studies. The target exons examined and the primers are listed in **Table 1**. The other family members were screened for the same mutation location found in proband. The primers were synthesized and the amplified products were sequenced by Biosune Biotechnology Co. Ltd (Shanghai, China). Sequencing results were BLAST searched (blast.ncbi.nlm.nih.gov/) against sequences in GenBank.

Results

The proband (III4) was a 21-year-old female, whose symptoms began at the age of 16, the concentration of serum potassium during paralysis attack was 1.7 mmol/L, and the frequency of HPP attacks was four to five times per year. Secondary HPP was excluded by laboratory examinations and ultra sound examination. Molecular analysis revealed R528H mutation in CACNA1S (**Figure 1**).

All of the 12 family members from 3 generations were recruited into the study. Six of them met the diagnosis of HPP, 4 female and 2 male. They were all found to carry CACNA1S R528H mutation. Moreover, the other members of the family without HPP clinical features were not found to have the same mutation (**Figure 1**, Supplementary Table 1). The clinical characteristics of mutation positive family members were summarized in **Table 2**.

Discussion

According to the previous studies [2, 3], the most common mutation associated with FHPP in western populations was CACNA1S R1239H. Furthermore, the CACNA1S R528H mutation was mostly secondary to CACNA1S R1239H. However, CACNA1S R528H is a prominent mutation reported in Asian population [4, 5]. A study [4] conducted in Korea involving 51 FHPP patients from 20 families revealed that 22 patients from 6 families were found to have this mutation. The clinical characteristics were also summarized. The first attack occurred during the second decade of life; the duration ranged from several hours to several days; the frequency of attacks ranged widely from once per week to once per year and became lower with growing age, usually disappeared in the thirties or forties. These characteristics are similar to those reported in western countries. However, there was some difference in clinical features in our present case, the age of the first attack of III 3 was five years old, while others with the same mutation from the same family were in their second decade. The first attack with CACNA1S R528H at five years old is much earlier than that reported by former studies. Usually, the first attack at such an early age is more commonly observed in patients with CACNA1S R1239H mutation or with SCN4A mutations [2, 6, 7], and quite uncommon in CACNA1S R528H mutation. Whether this is a rare case or a common phenomenon in Chinese patients with CACNA1S R528H mutation is unknown and needs to be confirmed by more cases.

The triggering factors of periodic attack are usually exercise, high carbs intake, cold, stress, alcohol, and etc. The studies [3, 7] conducted in western countries revealed that exercise was the most common triggering factor for CACNA1S R1239H mutation and high carbs intake was the most common triggering factor for CACNA1S R528H mutation. Meanwhile, the study conducted in Korea [4] concluded that exercise and high carbs intake were both as likely to trigger both CACNA1S R1239H and R528H mutations. In our study, patients with periodic attack reported that high carbs intake seemed to be the most common triggering factor. Considering the difference diet habit between Western and Asian countries, we believe that carbohydrate diet in Asian population makes great contribution to the attacks of hypokalemic periodic paralysis.

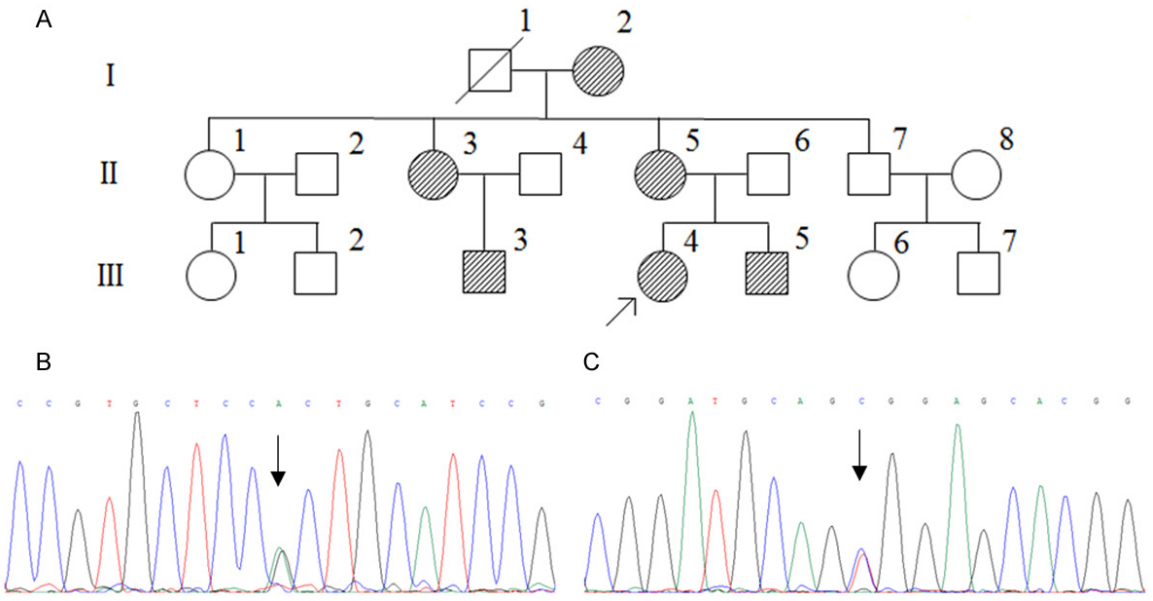

Figure 1. A. Pedigree of the FHPP family. Squares: men; circles: women; filled symbols: affected individuals. The proband is indicated by an arrow. B. Forward sequencing results for III 4. Arrow indicates the heterozygous 1583G>A mutation in CACNA1S exon 11, which caused a substitution of arginine to histidine at position 528 CGC (Arg, R)→CAC (His, H). C. Reverse sequencing results for III 4. Arrow indicates the heterozygous 1583G>A mutation in CACNA1S exon 11.

Table 2. Clinical characteristics of the family members

ID	Gender	Age	Age at onset	Frequency of attack	Duration of attack	Triggering factor
I 2	Female	72	16	3-4/month	1-2 days	High carbs intake
II 3	Female	49	15	3-4/year	1-2 days	High carbs intake, exercise
II 5	Female	45	15	3-4/year	1-2 days	High carbs intake, exercise
III 3	Male	26	5	0.5-1/month	1-3 days	High carbs intake, exercise, cold, stress
III 4	Female	21	16	2-3/year	1-2 days	High carbs intake, exercise
III 5	Male	12	10	1-2/year	0.5-1 day	High carbs intake

There is also gender difference in clinical characteristics [8]. The penetrance of HOKPP is different in male and female. Nearly half of women with CACNA1S R528H mutation and one third of women with CACNA1S R1239H are asymptomatic, while 90 percent of men with these two mutations have symptoms [9, 10]. Mutations of arginine-to-glycine substitution, such as R1239G and R528G mutations in CACNA1S, seem to have high penetrance [11, 12]. In our present study, all male and female with R528H mutation appeared to have periodic attack. Interestingly, the incomplete penetrance of R528H was also not observed in 22 CACNA1S R528H mutation carriers from 6 families in the Korean study [4]. As discussed above, high carbs intake may possibly trigger more attacks and elevate the penetrance, which may partly explain the reason why Asian populations with the same mutation have higher penetrance compared to Western populations. In mouse models, male mice with CACNA1S R528H mutation had more severe symptoms than female mice [13]. Clinical studies also found the frequency of periodic attack in male is relatively higher than that in female [14]. However, whether there is the difference of severity between male and female is still unclear. And, in our study, the male mutation carrier III 5 had a very mild phenotype and a low frequency of once to twice per year.

In conclusion, the clinical characteristics of the family with CACNA1S R528H mutation we are

reporting are not quite the same as previously reported in Western population and Koreans. There is difference in the penetrance, the onset of age, and the triggering factors. Whether the difference is due to different population requires studying more family cases before a definite conclusion is reached. We hope our study can enrich the epidemiology and demography of FHPP in Chinese population.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Sequencing results of CACNA1S exon11 of 12 members

Member	Sequence of CACNA1S exon11	
I 2	ACATTGCCAACCGGGTGCTGCTGTCCCTCTTCACCACTGAGATGCTGATGAAGATGTAC-GGGCTGGGCCTGCGCCAGTACTTCATGTCTATCTTCAACCGCTTCGACTGCTTCGTGGTGT-GTAGCGGTATCCTGGAGATCCTGCTGGTGGAGTCGGGTGCCATGACACCCCTGGGCATCTC-CGTGCTCCACTGCATCCGCCTCCTGAGGATCTTCAAGATCACCAA	Mutation
II 1	ACATTGCCAACCGGGTGCTGCTGTCCCTCTTCACCACTGAGATGCTGATGAAGATGTAC-GGGCTGGGCCTGCGCCAGTACTTCATGTCTATCTTCAACCGCTTCGACTGCTTCGTGGTGT-GTAGCGGTATCCTGGAGATCCTGCTGGTGGAGTCGGGTGCCATGACACCCCTGGGCATCTC-CGTGCTCCGCTGCATCCGCCTCCTGAGGATCTTCAAGATCACCAA	
II 3	ACATTGCCAACCGGGTGCTGCTGTCCCTCTTCACCACTGAGATGCTGATGAAGATGTAC-GGGCTGGGCCTGCGCCAGTACTTCATGTCTATCTTCAACCGCTTCGACTGCTTCGTGGTGT-GTAGCGGTATCCTGGAGATCCTGCTGGTGGAGTCGGGTGCCATGACACCCCTGGGCATCTC-CGTGCTCCACTGCATCCGCCTCCTGAGGATCTTCAAGATCACCAA	Mutation
II 5	ACATTGCCAACCGGGTGCTGCTGTCCCTCTTCACCACTGAGATGCTGATGAAGATGTAC-GGGCTGGGCCTGCGCCAGTACTTCATGTCTATCTTCAACCGCTTCGACTGCTTCGTGGTGT-GTAGCGGTATCCTGGAGATCCTGCTGGTGGAGTCGGGTGCCATGACACCCCTGGGCATCTC-CGTGCTCCACTGCATCCGCCTCCTGAGGATCTTCAAGATCACCAA	Mutation
II 7	ACATTGCCAACCGGGTGCTGCTGTCCCTCTTCACCACTGAGATGCTGATGAAGATGTAC-GGGCTGGGCCTGCGCCAGTACTTCATGTCTATCTTCAACCGCTTCGACTGCTTCGTGGTGT-GTAGCGGTATCCTGGAGATCCTGCTGGTGGAGTCGGGTGCCATGACACCCCTGGGCATCTC-CGTGCTCCGCTGCATCCGCCTCCTGAGGATCTTCAAGATCACCAA	
III 1	ACATTGCCAACCGGGTGCTGCTGTCCCTCTTCACCACTGAGATGCTGATGAAGATGTAC-GGGCTGGGCCTGCGCCAGTACTTCATGTCTATCTTCAACCGCTTCGACTGCTTCGTGGTGT-GTAGCGGTATCCTGGAGATCCTGCTGGTGGAGTCGGGTGCCATGACACCCCTGGGCATCTC-CGTGCTCCGCTGCATCCGCCTCCTGAGGATCTTCAAGATCACCAA	
III 2	ACATTGCCAACCGGGTGCTGCTGTCCCTCTTCACCACTGAGATGCTGATGAAGATGTAC-GGGCTGGGCCTGCGCCAGTACTTCATGTCTATCTTCAACCGCTTCGACTGCTTCGTGGTGT-GTAGCGGTATCCTGGAGATCCTGCTGGTGGAGTCGGGTGCCATGACACCCCTGGGCATCTC-CGTGCTCCGCTGCATCCGCCTCCTGAGGATCTTCAAGATCACCAA	
III 3	ACATTGCCAACCGGGTGCTGCTGTCCCTCTTCACCACTGAGATGCTGATGAAGATGTAC-GGGCTGGGCCTGCGCCAGTACTTCATGTCTATCTTCAACCGCTTCGACTGCTTCGTGGTGT-GTAGCGGTATCCTGGAGATCCTGCTGGTGGAGTCGGGTGCCATGACACCCCTGGGCATCTC-CGTGCTCCACTGCATCCGCCTCCTGAGGATCTTCAAGATCACCAA	Mutation
III 4 proband	ACATTGCCAACCGGGTGCTGCTGTCCCTCTTCACCACTGAGATGCTGATGAAGATGTAC-GGGCTGGGCCTGCGCCAGTACTTCATGTCTATCTTCAACCGCTTCGACTGCTTCGTGGTGT-GTAGCGGTATCCTGGAGATCCTGCTGGTGGAGTCGGGTGCCATGACACCCCTGGGCATCTC-CGTGCTCCACTGCATCCGCCTCCTGAGGATCTTCAAGATCACCAA	Mutation
III 5	ACATTGCCAACCGGGTGCTGCTGTCCCTCTTCACCACTGAGATGCTGATGAAGATGTAC-GGGCTGGGCCTGCGCCAGTACTTCATGTCTATCTTCAACCGCTTCGACTGCTTCGTGGTGT-GTAGCGGTATCCTGGAGATCCTGCTGGTGGAGTCGGGTGCCATGACACCCCTGGGCATCTC-CGTGCTCCACTGCATCCGCCTCCTGAGGATCTTCAAGATCACCAA	Mutation
III 6	ACATTGCCAACCGGGTGCTGCTGTCCCTCTTCACCACTGAGATGCTGATGAAGATGTAC-GGGCTGGGCCTGCGCCAGTACTTCATGTCTATCTTCAACCGCTTCGACTGCTTCGTGGTGT-GTAGCGGTATCCTGGAGATCCTGCTGGTGGAGTCGGGTGCCATGACACCCCTGGGCATCTC-CGTGCTCCGCTGCATCCGCCTCCTGAGGATCTTCAAGATCACCAA	
III 7	ACATTGCCAACCGGGTGCTGCTGTCCCTCTTCACCACTGAGATGCTGATGAAGATGTAC-GGGCTGGGCCTGCGCCAGTACTTCATGTCTATCTTCAACCGCTTCGACTGCTTCGTGGTGT-GTAGCGGTATCCTGGAGATCCTGCTGGTGGAGTCGGGTGCCATGACACCCCTGGGCATCTC-CGTGCTCCGCTGCATCCGCCTCCTGAGGATCTTCAAGATCACCAA	