대 한 소 아 신 경 학 회 지
Vol. 20, No. 1, March, 2012

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An Arg528His Mutation of the *CACNL1A3* Gene in a Korean Family with Hypokalemic Periodic Paralysis

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= Abstract =

Familial hypokalemic periodic paralysis (HOPP) is an autosomal dominant disorder characterized by episodic attacks of muscle weakness with concomitant hypokalemia (<3.5 mEq/L). The onset of HOPP usually occurs within the first and second decade of life. Mutations in the skeletal muscle calcium (*CACNL1A3*) and sodium channel (*SCN4A*) genes have been reported to be responsible for familial HOPP. Voltage-sensitive ion channels mediate action potentials in electrically excitable cells and play important roles in signal transduction in other cell types. Therefore, abnormalities in a channel's function lead to disarray of signal transduction and thus various neurological symptoms. Those are called channel diseases, which include familial HOPP. We report a 14-year-old boy with HOPP from a family in which two members of two generations are affected. Genetic examination identified a mutation causing a codon change from arginine to histidine at the amino acid portion #528 (R528H) in the calcium channel gene *CACNL1A3*.

Key Words : Hypokalemic periodic paralysis, *CACNL1A3*, Arg528His mutation, Korean

Introduction

Familial HOPP is a rare autosomal dominant disease characterized by reversible attacks of muscle weakness occurring with episodic hypokalemia. The onset of this disease is usually in the first or second decade of life. Acute crises most frequently occur at night and in the early morning. Paralytic attacks are frequently triggered by emotional stress, meals rich in carbohydrates and salt, strenuous exercise, or cold exposure. The episodes do not usually affect respiratory and cardiac muscles, however[1, 2].

Mutations in the *CACNA1S* gene, which encodes the alpha 1-subunit of the skeletal muscle L-type voltage-dependent calcium channel, are responsible for the majority (70%) of cases of familial HOPP[3, 4]. Missense mutations in the *SCN4A* gene, which encodes the skeletal muscle voltage-gated sodium channel alpha subunit, account for approximately 10% of cases. Each mutation has different penetrance of phenotype, depending on gender[5, 6].

Several Korean cases of familial HypoPP have been reported, but cases with identified gene mutations are rare, especially in children. We herein report a case of a 14-year-old boy and his unaf-

접수 : 2011년 11월 25일, 수정 : 2012년 3월 27일
승인 : 2011년 3월 30일
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fected mother with a nucleotide 1583 G to A substitution at codon 528 of the *CACNL1A3* gene that resulted in a change from alginine to histidine (*CACNA1A3* Arg528His).

Case Report

A 14 year-old boy presented to our hospital due to episodic paralysis, which began about six years prior to his arrival. The symptoms usually appeared in the early morning when he was awakened or after vigorous exercise like Taekwondo. He should have been previously admitted because of severe attacks that occurred approximately 2-5 times a year. During the severe attacks, the patient experienced breathing difficulties, and the weakness lasted several minutes to several hours. The patient usually recovered from the weakness in the afternoon.

A review of family history revealed that neither his parents nor his two sisters had similar symptoms. During paralytic episodes, the patient showed low serum potassium levels (2.0 mmol/L) and hypokalemic ECG findings, such as ST segment depression and U-waves. At that time, the patient developed numbness in his hands and feet, followed by a flaccid paralysis involving the entire body, with a rating of 1 in the lower limbs and 2 in the upper limbs using the Medical Research Council scale. In addition, the patient showed non-specific findings on radiological and laboratory examinations of muscle enzymes and thyroid hormone testing, sensory/motor nerve conduction study, and electromyography.

Mutation analysis of the candidate locus responsible for familial HOPP (e.g. exon 11, 21, 26, 30) was performed in the patient and his parents using PCR, direct sequencing. DNA examination identified a nucleotide 1583 G to A mutation of the *CACNA1S* gene. That mutation predicts codon change from arginine to histidine. Also, 1491C was replaced by T and 1551C by T, but a Single nucleotide peptide (SNP) that had no changes in amino acids was found (Fig. 1). That mutation was found in the patient and in the clinically unaffected mother. The boy was treated with acetazolamide, oral potassium chloride, and spironolactone and was instructed to avoid precipitating triggers such as vigorous exercise. After the medication and lifestyle modification, the frequency and severity of the attacks gradually decreased in the patient.

Discussion

Periodic paralyses constitute a group of human hereditary muscle disorders. Based on the variations of blood potassium levels, triggers, myotonia, and cardiac arrhythmia during attacks, periodic paralyses have been classified into four types[7]. HOPP is the most common type and has the most severe clinical manifestations.

A mutation of the *CACNL1A3* gene that causes familial HOPP was found in the patient. A calcium channel is composed of five subunits, α1, α2, γ, and δ. The α1-subunit constitutes the ion-conducting pore[8, 9], and it is composed of four transmembrane domains (DI to DIV), each of them containing six transmembrane α helices (S1 to S6). The S4 segment, the fourth helix, is the voltage sensor that moves out of the cell and opens channels when depolarized. The amino acids in the S4 segment (the voltage sensor) are replaced in a missense mutation found in the CACNL1A gene, and three kinds of mutations are known. The amino acid substitutions in the three mutations are as follows: the replacement of a positively-charged arginine in position 528 in segment S4 of domain II by a weakly-positive histidine (R528H) and an arginine in position 1239 in the S4 segment of the fourth

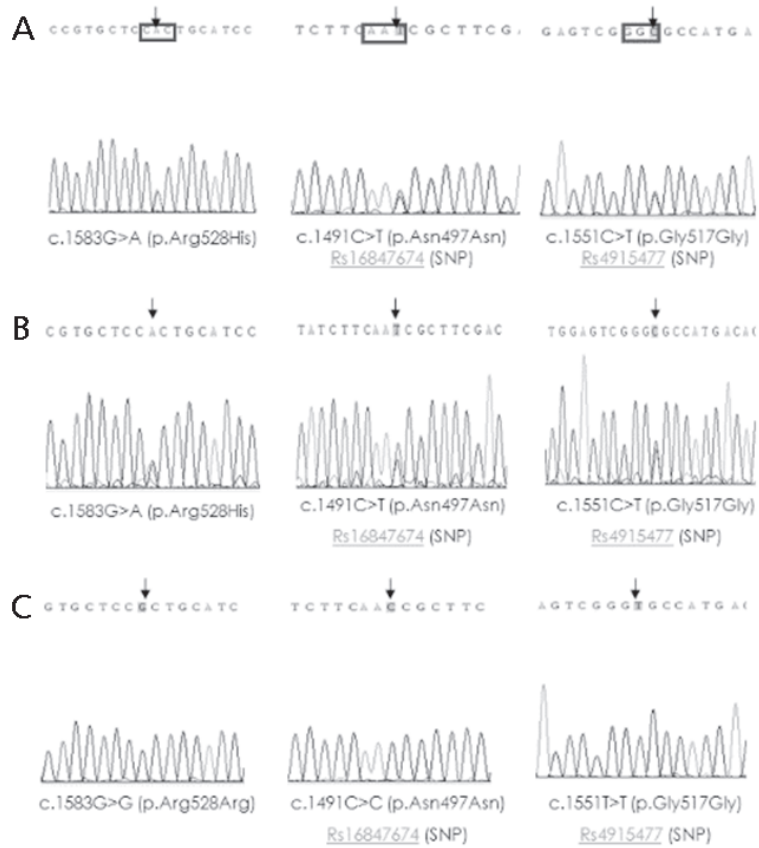

Fig. 1. Electropherogram from the patient (A), his affected mother (B), and unaffected father (C). Direct sequence analysis of *CACNL1A3* shows an identical heterozygous G to A substitution at codon 528, resulting in an Arg528His mutation in the patient and his affected mother. (an arrow indicating the nucleotide substitution); however, no mutation was observed in his unaffected father.

domain by either a histidine or a glycine (R1239H and R1239G)[10, 11].

Recently, mutations in the sodium channel gene (*SCN4A*) in HOPP have been discovered. The structure of the sodium channel is similar to that of the calcium channel and is composed of four domains, each with six segments. Those mutations were found in domain II of the S4 segments[3, 12]. Three *SCN4A* mutations are currently known: Arg669His, Arg672Gly, and Arg672Cys[13].

Seventy percent of familial HOPP patients show missense mutation in the *CACNLA3* gene on chromosome 1q32[4]. According to reports by Kim et al.[13], among 20 families with a member with familial HOPP, 12 (60%) showed known mutations, and among those 12, 9 (75%) were associated with the *CACNLA3* gene, and 3 (25%) were associated with the *SCN4A* gene. The Arg528His mutation of *CACNLA3* was detected most often.

Elbaz et al.[14] reported that the R528H and the R1239H mutations had a similar mean age of onset, number of acute attacks, and precipitating factors. The mean age at onset of the disease was younger in those with mutations (average, 11 yr; range, 1-

19 yr) than in those without (average, 17 yr; range, 1–34 yr) (P<0.05)[13].

Patients with the Arg528His *CACNLA3* mutation show paralytic symptoms once a month on average. Compared to the frequency of paralysis in reports by Miller et al.[23], episodes of paralysis were less frequent in Korean patients.

In contrast, patients with Arg1239Gly *CACNLA3* and Arg672Gly *SCNA4* mutations show paralytic symptoms everyday, even after the age of 30. Compared to patients with other mutations, patients with R528H were less sensitive to exposure to cold. Although drinking alcohol has been reported to be a trigger in many reports, all patients with Arg 1239His and most patients with Arg528His did not show paralytic symptoms after ingesting alcohol[13].

The R528 mutation in women shows incomplete penetrance. In cases of children, boys showed relatively significant symptoms, early onset, and more frequent paralytic manifestation. However, the mother of the affected child did not have clinical symptoms although she had the same gene mutation, which indicates incomplete penetrance of phenotype. That phenomenon was prominently found in women, so we inferred that this is due to female hormones[14].

A case has been reported in which a Chinese family with the Arg672His mutation showed incomplete penetrance of phenotype despite the *SCN4A* mutation[15]. In a recent case report, a patient's grandmother, three sons, an aunt, and her son did have the Arg222Trp mutation but did not show any paralytic symptoms. This was the first case report that revealed incomplete penetrance of phenotype associated with the Arg222Trp mutation.

Acetazolamide is a carbonic anhydrase inhibitor known to be very effective in most familial HOPP patients[16]. However, some patients with mutations in specific calcium channels or sodium channels did not improve or had symptoms that were aggravated even after taking acetazolamide[3, 17]. Patients got worse if they had R672G and R672S mutations in the *SCNA4* gene. Spironolactone and its derivative can be an alternative option if empirical treatment is not effective[18–20]. In this case report, the patient took spironolactone but still showed intermittent paralytic symptoms and thereafter was given acetazolamide. At present, he does not show paralytic symptoms, and his potassium level is stable, as he is taking spironolactone, acetazolamide, and potassium chloride.

As a result, genetic diagnosis of familial HOPP confirms the disease, provides the appropriate treatment, and proves very useful in providing the family genetic counseling.

한 글 요 약

저칼륨혈증 주기성 마비를 보이는 한국인 가족에서 발견된 *CACNL1A3* 유전자의 Arg528His 돌연변이

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가족성 저칼륨성 주기성 마비는 상염색체 우성으로 유전되는 질환으로 십대 전후의 청소년기에 저칼륨혈증을 동반하는 간헐적인 골격근 마비가 시작된다. 주로 당분이 풍부한 음식을 섭취한 후, 심리적 스트레스, 추위에 노출되었을 때 또는 힘든 운동 후 휴식 시에 자주 발생하며 밤이나 아침 일찍 주로 발생하고 수시간에서 수일 간 지속된다. 하지만 생명을 위협하는 호흡근이나 심근의 마비는 일으키지 않는다.

골격근의 가족성 주기적 마비는 칼슘과 소디움 채널의 유전자 돌연변이에 의하여 유발된다. 70% 환자에서 발견되는 *CACNA1S* 유전자는 골격근의 L형 칼슘채널 알파 1-아단위(subunit)을 암호화하며 염색체 1q31-32 부위에 존재한다. *SCN4A* 유전자는 소디움 채널의

4형 알파 아단위를 암호화한다. 각 돌연변이는 성별에 따라 표현형의 투과성이 다르다.

국내에서 소아의 가족성 저칼륨성 주기성 마비가 수예 보고된 바 있지만, 유전자 분석을 통해 변이가 확인된 예는 드물다. 이에 저자들은 칼슘채널의 arginine 528이 histidine (R528H)으로 치환된 변이에 의한 저칼륨성 주기성 마비로 진단된 14세 남자환아 1례를 경험하였기에 보고하는 바이다.

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