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Hyperkalemic periodic paralysis and paramyotonia congenita caused by a *de novo* mutation in the *SCN4A* gene

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Abstract

Familial hyperkalemic periodic paralysis is an autosomal-dominant channelopathy characterized by reversible paralysis associated with episodic hyperkalemia. Mutations in the skeletal muscle voltage-gated sodium channel gene (*SCN4A*) have been reported to be responsible for this disorder. Paramyotonia congenita is also caused by mutations in the *SCN4A* gene. Here, we report the case of a 17-year-old boy who presented with both hyperkalemic periodic paralysis and paramyotonia congenita. A molecular analysis of the *SCN4A* gene revealed a heterozygous T>C transition at nucleotide 2078, leading to an Ile693Thr mutation. This mutation was absent in the patient's parents supporting a *de novo* Ile693Thr mutation in our patient.

INTRODUCTION

Familial hyperkalemic periodic paralysis and paramyotonia congenita are autosomal-dominant disorders caused by mutations in the skeletal muscle voltage-gated sodium channel gene (*SCN4A*).[1] Hyperkalemic periodic paralysis is characterized by episodic attacks of muscle weakness with hyperkalemia lasting for minutes to hours, triggered by fasting, ingestion of potassium-containing foods, or vigorous exercise. The hallmarks of paramyotonia congenita are cold-induced muscle stiffness chiefly affecting the face and hand muscles, as well as paradoxical myotonia.[2]

Recent molecular studies have revealed that the majority of cases of familial hyperkalemic periodic paralysis are caused by one of nine mutations in the *SCN4A* gene.[3-7] Paramyotonia congenita is also caused by mutations in the *SCN4A* gene, and phenotypic variations in some patients with specific mutations have been reported.[8]

In this report, we describe a patient with features of both hyperkalemic periodic paralysis and paramyotonia congenita. There was no known family history and genetic analysis of the patient and his immediate family members revealed a *de novo* mutation in the *SCN4A* gene. This mutation predicts a codon change from isoleucine to threonine at residue 693 (Ile693Thr).

CASE REPORT

A 17-year-old Korean boy was referred to our clinic because of episodic attacks of muscle stiffness and weakness affecting the face, limbs, and trunk. These symptoms first developed when he was approximately one year of age. The attacks increased in frequency during puberty, occurring three or four times a week and lasting at least 1 hour and sometimes for as long as 1 week. Attacks mainly occurred in the morning. The symptoms started with myotonic stiffness and were often followed by flaccid weakness. The symptoms were more frequent and intense during winter and were triggered by long periods of fasting, vigorous exercise, and emotional stress. The patient was the eldest of three siblings; no other members of the family described similar symptoms.

The patient was admitted on a cold winter day with muscle stiffness affecting his facial muscles and intrinsic hand muscles. The cold-induced eyelid myotonia and myotonia of the hand muscles resolved within 30 minutes of warmth in the hospital. The eyelid lag sign was provoked by repeated forceful closing and opening of the eyes; there was no grip or percussion myotonia noted on physical examination. Muscle testing showed normal muscle strength. Electrocardiography, radiology, and laboratory testing revealed no abnormalities, with the exception of an increased level of serum creatine kinase (542 IU/L; normal range 32–294 IU/L).

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Cooling of the hand and forearm according to the standard protocol[9] resulted in muscle stiffness. Electromyography showed spontaneous positive waves at room temperature and increased myotonic discharges after cold immersion. Myotonia induced by cold water was further increased with repeated contraction (Figure 1). Acute attacks of muscle stiffness followed by transient weakness lasted for approximately one hour after the cold immersion test and exercise-induced test. Serum electrolyte values were within normal range (e.g., potassium: 3.9 mEq/L; normal range 3.5–5.0 mEq/L) and serum creatine kinase levels were elevated (694 IU/L) during the attacks. Myotonic stiffness in the face and all four limbs occurred 30 minutes after the ingestion of oral potassium chloride (2.4 g) given as a provocation test for paralysis, and flaccid muscle weakness occurred after one hour of ingestion. During paralysis, the muscle tone of all extremities was decreased (Medical Research Council scale:1), and the deep tendon reflexes were absent. However, there were no pathological reflexes, sensory abnormalities, or cognitive dysfunctions. The patient showed increased levels of serum potassium (6.5 mEq/L) and creatine kinase (620 IU/L). All other laboratory values remained within their normal ranges. Electrocardiography showed characteristic tall and peaked T waves during the acute attack of muscle weakness. The patient recovered completely 30 minutes after intravenous injections of glucose and insulin. After recovery of the muscle strength, the serum potassium concentration returned to its normal range.

Mutation screening was performed by sequencing the entire coding region of the *SCN4A* gene as previously described.[10] All participants provided written informed consent in compliance with the Institutional Review Board of Konyang University Hospital.

Direct sequencing of *SCN4A* exon 13 revealed a heterozygous T>C transition at nucleotide 2078 (Figure 2), resulting in the substitution of an isoleucine by a threonine residue at codon 693 (Ile693Thr). This mutation was not found in the patient's parents and siblings. Parental identity was verified by genotyping 15 short tandem repeat markers by using a PowerPlex 16 system (Promega, Madison, WI, USA).

The patient was treated with acetazolamide (250 mg BID) and advised to avoid potassium-rich foods, fasting, strenuous work, and exposure to cold. The patient has been followed-up on an outpatient basis, with no further symptoms of paralysis.

DISCUSSION

Several types of periodic paralyses and myotonia are caused by mutations in the *SCN4A* gene, which encodes the human skeletal muscle voltage-gated sodium channel responsible for the initiation and propagation of action potentials. These include hyperkalemic periodic paralysis, paramyotonia congenita, and potassium-aggravated myotonia.[11] Despite some overlapping characteristics between hyperkalemic periodic paralysis and paramyotonia congenita, clinicians have attempted to differentiate between these diseases mainly because the therapeutic response to medications is somewhat different.[12] Molecular genetic testing of the *SCN4A* gene provides a more definitive diagnosis allowing genotype-phenotype correlations to be made in the two diseases.

In the present study, DNA sequence analysis of the *SCN4A* gene revealed a *de novo* Ile693Thr mutation in the patient. This mutation was first reported in a family with an unusual type of paramyotonia congenita where muscle stiffness, cold-induced myotonia, or paradoxical myotonia has not been observed.[11] In this family, 8 members were affected and showed an autosomal-dominant pattern of inheritance.[11] Our patient exhibited the characteristic clinical, laboratorial, and electrophysiological features of both hyperkalemic periodic paralysis and paramyotonia congenita. The patient presented with episodic attacks of muscle weakness aggravated by fasting, emotional stress and rest after exercise suggestive of hyperkalemic periodic paralysis, as well as muscle stiffness induced in cold environments and increased by repetitive movements indicative of paramyotonia congenita.

Two missense mutations (Arg1448His and Arg1448Cys) in the *SCN4A* gene, which were originally described in paramyotonia congenita, have also been reported to be associated with hyperkalemic periodic paralysis.[8] The reason for this clinical variability is not known. The variability within families in previous reports[4,11] excludes the possible effect of different ethnic backgrounds. This phenotypic variation may be the result of other genetic and/or environmental factors.

In summary, we identified a patient with hyperkalemic periodic paralysis and paramyotonia congenita caused by a *de novo* Ile693Thr mutation in the *SCN4A* gene. Our findings further expand the phenotypic variation of the Ile693Thr mutation and may help diagnosis and genetic counseling of an isolated family member who has phenotypic features of the two diseases.

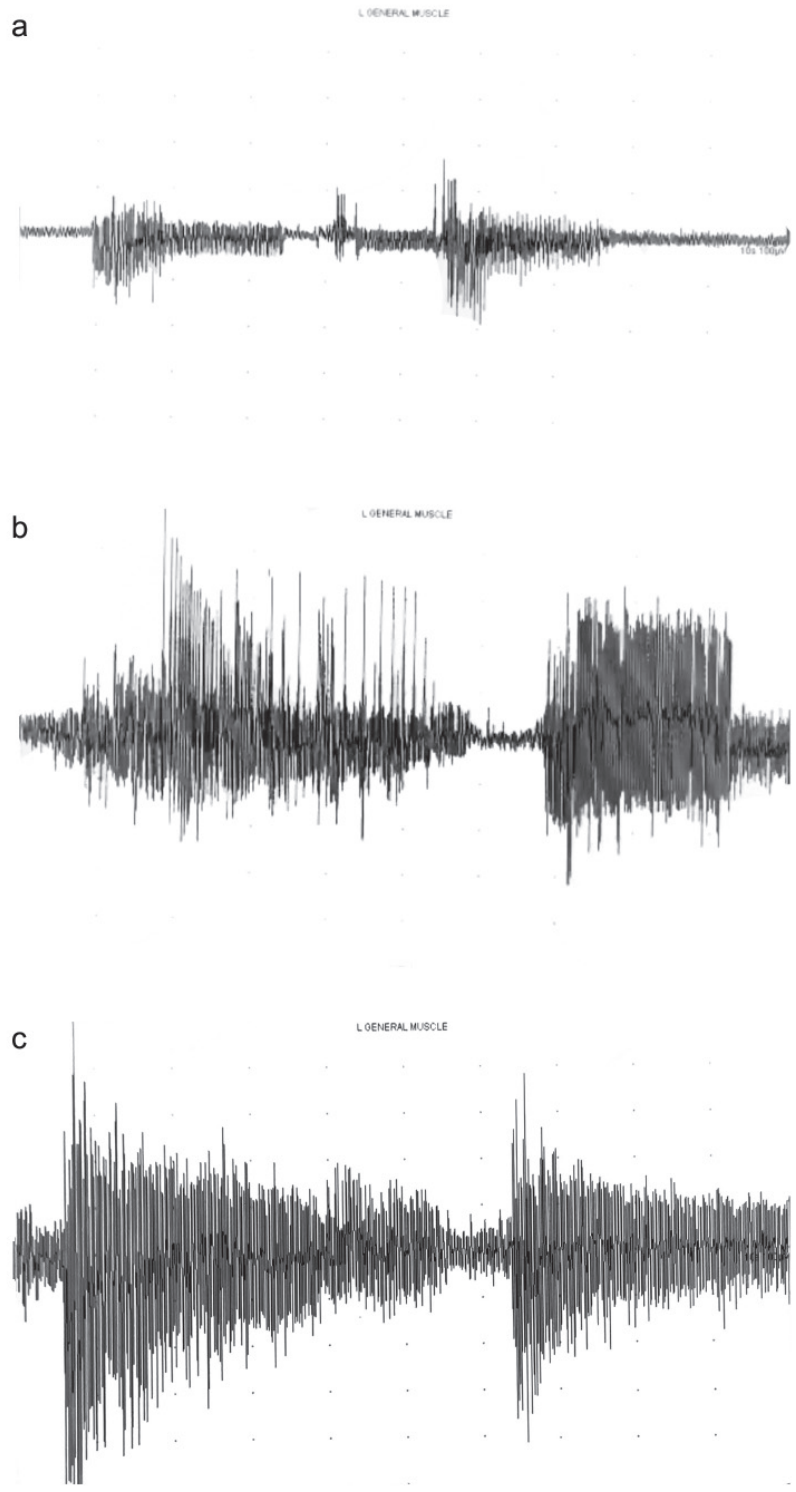

Figure 1. Electromyographic findings showing myotonic discharges in the patient between attacks at room temperature (a), during attacks after cold immersion (b), and at an aggravation of symptoms with exercise after cold immersion (c).

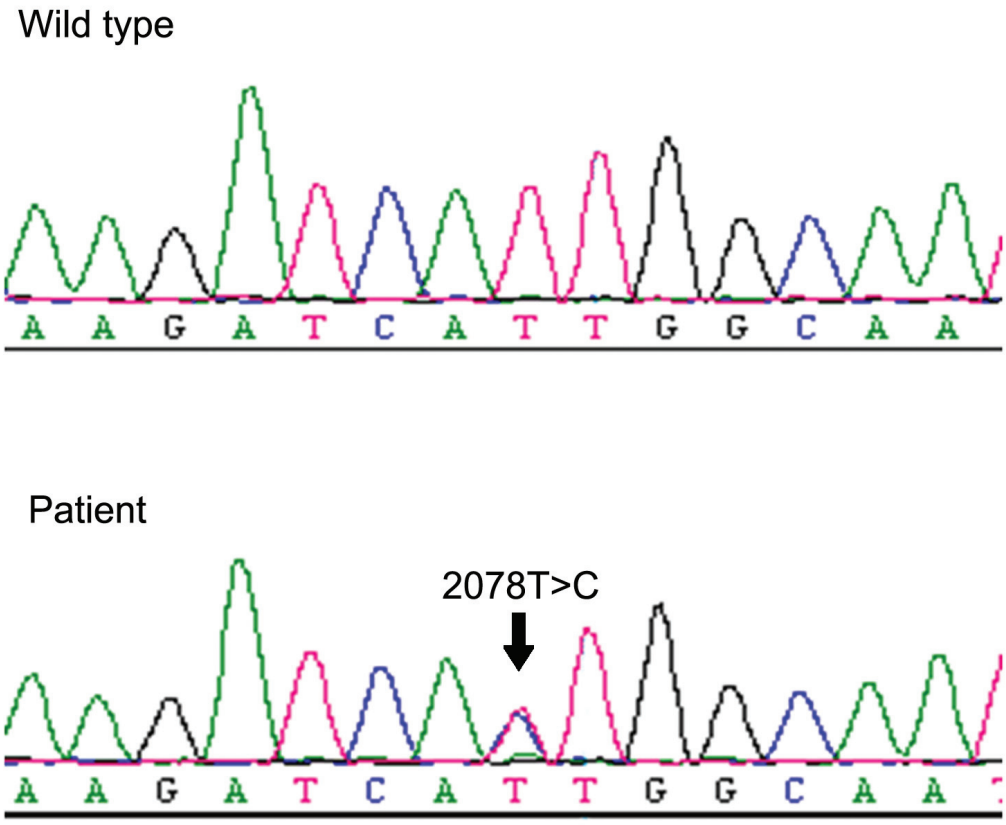

Figure 2. Comparison of sequence electropherograms from a normal control (upper panel) and the patient (lower panel). Sequence analysis showed a heterozygous T>C transition (indicated by an arrow) at nucleotide 2078 of the patient's *SCN4A* gene.

DISCLOSURE

There is no conflict of interest to declare.

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