Phenotypic variation of a Thr704Met mutation in skeletal sodium channel gene in a family with paralysis periodica paramyotonica

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Abstract

***Objectives*—Patients with paralysis periodica paramyotonica exhibit a clinical syndrome with characteristics of both hyperkalaemic periodic paralysis and paramyotonia congenita. In several types of periodic paralysis associated with hyperkalaemia, mutations in the skeletal muscle sodium channel *(SCN4A)* gene have been previously reported. Phenotypic variations of mutations in *SCN4A*, however, have not been described yet. The present study aimed to evaluate genetic variations in a family with clinical and electrophysiological characteristics of paralysis periodica paramyotonia.**

***Methods*—Seven members of a family affected with symptoms of paralysis periodica paramyotonia were studied by electrophysiological and genetic analyses. There were increased serum potassium concentrations in four members during paralytic attacks induced by hyperkalaemic periodic paralysis provocation tests. Short exercise tests before and after cold immersion were carried out in four patients to distinguish electrophysiological characteristics of hyperkalaemic periodic paralysis and paramyotonia. Sequencing analyses of *SCN4A* were performed on one patient and a normal control to identify polymorphisms. Restriction fragment length polymorphism (RFLP) analysis was then performed at the identified polymorphic sites.**

***Results*—Electrophysiological studies showed both exercise sensitivity and temperature sensitivity. Compound motor action potential (CMAP) amplitudes were decreased (7.3%-28.6%) after short exercise tests. The CMAP amplitudes were even more severely decreased (21.7%-56.5%) in short exercise tests after cold exposure. Three polymorphic sites, Gln371Glu, Thr704Met, and Aspl376Asn were identified in *SCN4A*. RFLP analyses showed that all affected patients carried the Thr704Met mutation, whereas unaffected family members and a normal control did not.**

***Conclusion*— Phenotypic variation of the Thr704Met mutation, which was previously reported in patients with hyperkalaemic periodic paralysis, is described in a family affected with paralysis periodica paramyotonia.**

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Keywords: paralysis periodica paramyotonica; hyperkalaemic periodic paralysis; paramyotonia congenita; human skeletal muscle sodium channel (*SCN4A*) gene

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Patients with periodic paralysis exhibit recurrent episodes of skeletal muscle weakness followed by complete recovery.[1] To date, four syndromes of periodic paralysis have been described associated with hyperkalaemia: (1) hyperkalaemic periodic paralysis, (2) myotonic hyperkalaemic periodic paralysis, (3) paramyotonia congenita, and (4) paralysis periodica paramyotonica.[2 3] Patients with paralysis periodica paramyotonia exhibit both paralytic attacks of hyperkalaemic periodic paralysis and paramyotonia of paramyotonia congenita.[4 5]

Genetic analyses of patients with hyperkalaemic periodic paralysis, paramyotonia congenita, and paralysis periodica paramyotonia have shown that mutations of a gene at chromosome 17q, encoding the α-subunit of human skeletal muscle sodium channel *(SCN4A)*, were responsible for the symptoms.[6 7] Up to 20 different mutations in hyperkalaemic periodic paralysis, paramyotonia congenita, and paralysis periodica paramyotonia have been identified.[1 4] Clinically delineated phenotypes of potassium sensitive periodic paralyses are consistently associated with different mutations. For example, the Thr704Met, Met1592Val, or Thr698Met mutations in *SCN4A* was found in hyperkalaemic periodic paralysis.[4 8] Cold sensitive myotonia and paradoxical myotonia were often found in the Thr1313Met and Arg1448His mutations.[4 8] These genotype-phenotype relations suggest that each mutation correlates with a specific functional alteration in sodium channels leading to a unique phenotype.[8] However, the different phenotypes caused by an identical mutation have been described in an atypical family with periodic paralysis.[9] In addition, three clinically distinct myotonic syndromes were reported in three different mutations at the same position.[10–12]

A Thr704Met mutation has been well documented in hyperkalaemic periodic paralysis.[4 8 13] Phenotypic variation of the Thr704Met mutation in the *SCN4A* gene, however, has been rarely described to date. In this study, we report a phenotypic variation of the Thr704Met mutation in the *SCN4A* gene in a Korean family with paralysis periodica paramyotonia.

Methods

PATIENTS

Affected members in the investigated family had periodic paralyses and paramyotonic symptoms (table 1, fig 1 A). Among adult patients, periodic paralysis was first noted during their first decade. Among affected children,

Table 1 Clinical characteristics of a family with paralysis periodica paramyotonica

Patient	*Age (y)*	*Age at onset*	*Number of episodes /month*	*Duration of each episode*	*Paramyotonia/ Paradoxical myotonia*	*Precipitating factors of periodic paralysis*
I-1	68	9 y	3–4	7–10 d	+/+	RAE, cold, fasting, water melon
II-1	38	7 y	2	5–7 d	+/+	RAE, cold, fasting, water melon
II-3	35	7 y	2–3	2–3 d	+/+	Cold, fasting, pregnancy, stress
II-6	30	8 y	1	1–2 d	+/−	Cold, fasting
III-1	4	4 months	3–4	<2 h	+/−	Fasting
III-2	11	1 y	3–4	<2 h	+/−	RAE, fasting
III-3	7	2 months	4–5	<2 h	+/−	RAE, fasting, sleeping

RAE=Rest after exercise; cold=cold exposure; −=no abnormal findings in each item of clinical evaluation.

the first paralytic symptoms occurred during their neonatal period. During episodes, which occurred once or twice a month in adults and three to four times a month in children, affected patients could not move their limbs. The duration of symptoms insidiously increased as adult patients grew older. The duration of each paralytic episode ranged from 20 minutes to 2 hours in affected children and from 2 to 10 days in affected adults. Paramyotonic symptoms, such as muscle stiffness and eyelid lag on cold exposure, were experienced by all of the patients. Difficulty in eye opening and stiffness of hand muscles in cold temperatures were usually resolved within 1 to 2 hours with warming. Weakness of the hands, however, often persisted for several hours even after warming, long after the stiffness had resolved. In two adult patients, paradoxical myotonia, typified by eyelid lag after repeated forceful closing and opening of eyes, was seen (I-1 and II-1 in fig 1 A).

Fixed muscle weakness in the period between attacks was seen in all adult patients; this was more severe in proximal muscles than in distal ones. The patients had difficulty in standing from a chair or a squatting position. Additionally, calf hypertrophy was seen in all adult patients, although the muscle power was

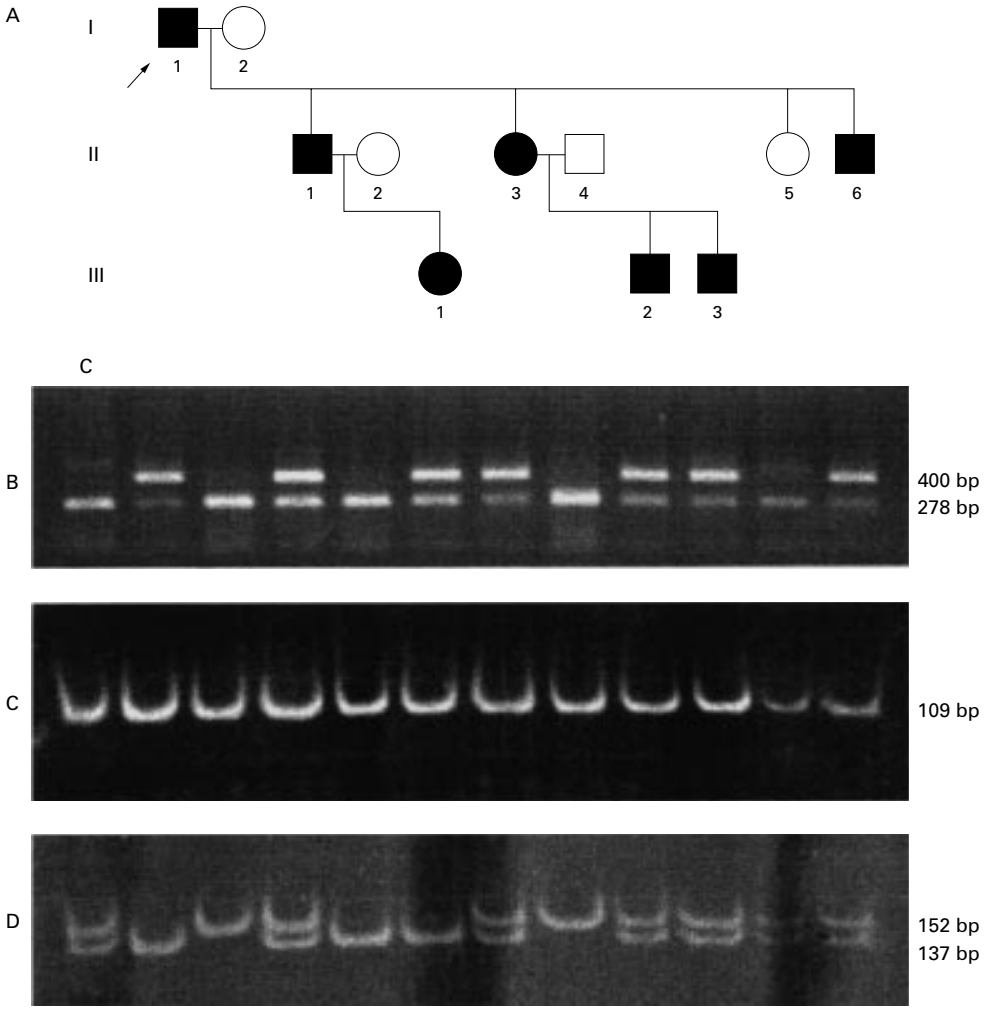

Figure 1 Family pedigree and results of RFLP analyses of exons 13, 8, 23. (A) Family pedigree. Square=male; circle=female; filled=affected member; empty=non-affected member; arrow=proband. (B) HgaI RFLP of exon 13. The patients were heterozygous for this RFLP (400 and 278 bp), although normal family members and a control C were homozygous (only 278 bp). (C) MnlI RFLP of exon 8. All tested subjects showed a single band of 109 bp. (D) PshAI RFLP of exon 23. Homozygous or heterozygous patterns of A/A, A/G, or G/G were shown in tested subjects without relation to symptom occurrence.

Table 2 Serum potassium concentration and motor power changes during provocation tests

	Patient							
	II-1		II-2		III-1		III-2	
	K^+	Motor power	K^+	Motor power	K^+	Motor power	K^+	Motor power
Preloading	4.5	GIV	3.9	GIV	3.5	GV	3.5	GV
Beginning	4.6	GIII	5.4	GII	NT	NT	5.0	GIII
Maximum	7.6	G0, RD	4.9	G0	5.3	GIII	4.8	GII
Recovery	4.3	GIV	3.8	GIV	3.8	GV	3.1	GV

K^+=Serum potassium concentration (mEq/l); motor power=motor power during provocation tests using the British Medical Council Scale; preloading=before the start of provocation; beginning=when the patient begins to feel the paralyses; maximum=when the paralysis fully aggravates; recovery=when the paralyses recovers to the previous motor power; RD=respiratory difficulty; NT=not tested.

weak. However, the affected children showed neither the fixed muscle weakness nor the hypertrophy.

Resting after exercise, fasting, or sleeping in cold temperatures were found to be important initiating factors of paralytic episodes in all affected members. Eating water melon also was an initiating factor in two of the family members, I-1 and II-1. They experienced paralytic weakness within 1 to 2 hours after eating this fruit. This family therefore voluntarily refrained from eating water melon to avoid the risk of paralytic episodes. A female family member, II-3, experienced paralytic episodes when she was pregnant and also in stressful situations.

Four affected members of the family, II-1, II-3, III-2 and III-3, were subjected to hyperkalaemic periodic paralysis provocation tests as described earlier.[14] Serum potassium concentrations during paralytic episodes were higher in these patients than before the onset of the paralyses (table 2). However, except for II-1, the serum concentrations remained within the normal range (3.5–5.3 mEq/l). When muscle strength recovered, serum potassium concentrations in all examined patients likewise returned to preparalytic values.

ELECTROPHYSIOLOGICAL EXAMINATIONS

Insertional and spontaneous activity was recorded by EMG, performed at room temperature (Excel, Cadwell, USA). Short exercise tests were performed with supramaximal stimulation of the ulnar nerve on an immobilised hand and forearm.[15] The compound muscle action potential (CMAP) was recorded with surface electrodes over the belly and the tendon of the hypothenar muscle. At least three basal CMAPs were recorded at 1 minute intervals. The patients then executed a voluntary maximal contraction for 5 minutes, with a brief rest (3 to 4 seconds) every 15 seconds. The CMAPs were repeatedly recorded at 1 minute intervals, during exercise and recovery, for at least 30 minutes, to ascertain that CMAP amplitudes had stabilised to their lowest level. In the cold immersion test, recording electrodes were placed over the hypothenar muscle and the stimulator was placed over the wrist.[14 15] A rubber glove was worn over the hand and forearm to maintain a constant position before and after cold immersion. After the basal CMAPs were recorded at room temperature, the hand and forearm were then placed in an ice water bath until the surface temperature fell to 16°C, and then left there for 3 minutes. The hand was removed from the cold water, and basal CMAPs were recorded again when the skin temperature was raised to 25°C. Short exercise tests were then performed as described above.

GENETIC ANALYSES

We designed 27 pairs of polymerase chain reaction (PCR) primers, for amplification of 24 exons of the *SCN4A* gene, to identify mutations cosegregating with the symptom. Amplification of the 27 primer pairs by PCR (GeneAmp 9600, Perkin Elmer, USA) and sequencing of their PCR products were carried out with an automated DNA sequencer (ABI PRISM 377 DNA Sequencer, Perkin-Elmer, USA) on patient I-1 and an unrelated normal control. The sequences were then compared with the previously reported sequences.[16 17] Finally, restriction fragment length polymorphism (RFLP) analyses were performed to identify polymorphisms in other affected and unaffected family members.

Results

ELECTROPHYSIOLOGICAL EXAMINATIONS

Cold immersion tests, EMG, and short exercise tests at room temperature, were performed in three adult patients, I-1, II-1, and II-3, and one child patient, III-2. Myotonic discharges were found in all patients on needle insertion with EMG at room temperature. Spontaneous positive sharp waves were also noted in the adult patients, but not the child (table 3). Amplitude changes in the CMAP of short exercise tests and cold immersion tests were compared with the basal CMAP amplitude at room temperature and after cold immersion. During short exercise, CMAP amplitudes were transiently increased (4.0%-24.3%) in all

Table 3 EMG findings and amplitude changes on a short exercise test and cold immersion tests

	EMG		Short exercise test (SET)			Cold immersion test			
	Myotonic discharge	Spontaneous activity	During SET	Lowest amplitude	Time to lowest amplitude (min)	Rewarming to 25°C	During SET	Lowest amplitude	Time to lowest amplitude (min)
I-1	+	+	16.4%↑	7.3%↓	45	72.4%↓	39.1%↑	21.7%↓	25
II-1	+	+	24.3%↑	24.3%↓	30	47.4%↓	28.3%↑	37.0%↓	15
II-3	+	+	21.9%↑	28.6%↓	20	70.1%↓	43.5%↑	56.5%↓	13
III-1	+	−	4.0%↑	23.8%↓	25	12.6%↓	6.3%↑	42.7%↓	15

During SET=CMAP amplitude changes compared with basal level during SET; Lowest amplitude=CMAP amplitude changes at the lowest amplitude compared with basal level; Rewarming to 25°C=CMAP amplitude changes at rewarming to 25°C after cold immersion compared with basal level; ↑=increase of amplitude change; ↓=decrease of amplitude change; −=absence of spontaneous activity.

patients. However, CMAP amplitudes progressively declined to their lowest level (7.3%-28.6%) over the 15 to 45 minutes after finishing the short exercise and persisted at this low level for hours. With exercise after cold immersion, and rewarming skin temperatures to 25°C, CMAP amplitudes became increased (6.3%-43.5%). However, CMAP amplitudes then markedly declined 21.7%-56.5% over the next 13 to 15 minutes.

GENETIC ANALYSES

Paralytic symptoms in this family followed an autosomal dominant inheritance pattern (fig 1 A). Our sequencing analysis of the *SCN4A* gene identified three nucleotide sequence variations, which affect the amino acid sequence of the skeletal sodium channel. One of the variations was identified as a C/T heterozygous pattern at the 2112th nucleotide position in exon 13 (fig 2 B), resulting in a change from Thr to Met at the 704th amino acid position of the sodium channel protein (SkM1). A homozygous C was noted at the same position in our normal control (fig 2A). The amplified PCR products of exon 13 are cut by *Hga*I into the fragments of 278 and 122 bp in sequences with C at the 2112th position. The uncut 400 bp fragment is what distinguished a T allele from a C allele. In all affected family members, I-1, II-1, II-3, II-6, III-1, III-2, and III-3, a heterozygous C/T pattern was found, but this was not present in normal spouses, I-2, II-2, and II-4, unaffected family member II-5, or in the unrelated normal control (fig 1 B). The data demonstrate a full penetrance pattern of Thr704Met mutation in this family.

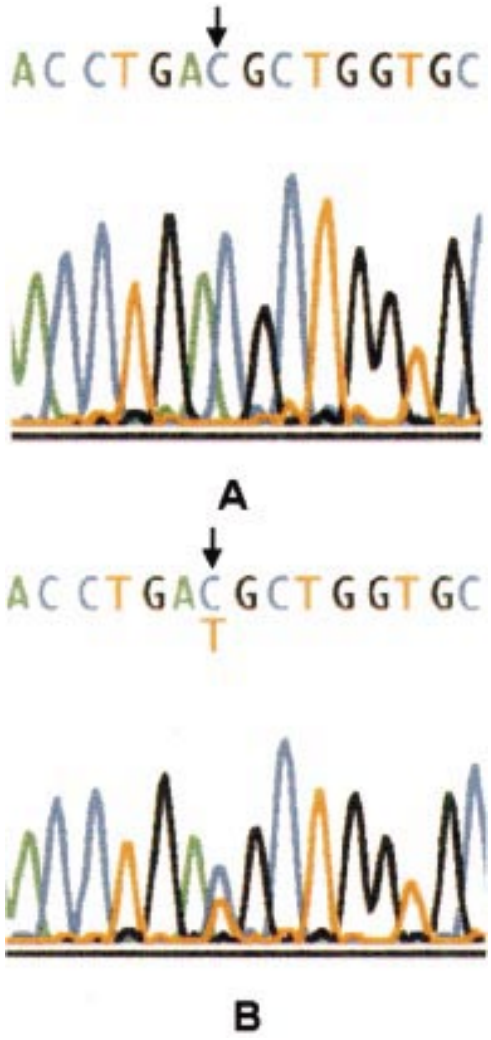

Figure 2 DNA sequence around the 2112th nucleotide position of exon 13. (A) C at the 2112th position (arrow) in a normal control. (B) C and T heterozygous sequence at the position (arrow) in a patient (I-1).

In addition, a C to G transversion at the 1111th nucleotide position in exon 8 resulted in a change from Gln to Glu at the 371st amino acid position of the SkM1. Previously, A, C, and G nucleotides have been reported at this position.[16 17] Amplified PCR products of exon 8 are cut by *Mnl*I into 137 and 27 bp fragments when the A nucleotide is at the 1111th position; into 95, 42, 26, and 21 bp fragments when C is present; and into 109, 27, 27, and 21 bp fragments when G is present. The G nucleotide was found exclusively at the 1111th position in all tested persons (fig 1 C).

Three allelic combinations, G/G, G/A, and A/A, were detected at the nucleotide position 4203 in exon 23. These variations resulted in Asp, Asp/Asn, and Asn, respectively, at the 1376th amino acid of the SkM1. Nucleotide sequence variation at this position in other family members was identified by PCR amplification with a mismatched primer yielding an artificial RFLP site near the polymorphic site. Amplified PCR products with the G nucleotide at the 4203rd position were cleaved into 137 and 16 bp fragments by *Psh*AI digestion, whereas PCR products with the A nucleotide at the same position would not be cleaved. A G/G homozygous pattern was found in I-1, II-2 and III-1; a G/A heterozygous pattern in II-1, II-3, II-5, II-6, III-2, III-3, and the normal control; and an A/A homozygous pattern in I-2 and II-4 (fig 1 D). This polymorphism at 4203 is unlikely to be correlated with paralytic symptoms.

Discussion

Paralysis periodica paramyotonica is characterised by clinical characteristics of paramyotonia congenita in addition to the periodic paralysis typical of hyperkalaemic periodic paralysis.[4 5] The hallmarks of hyperkalaemic periodic paralysis are (1) recurrent episodes of skeletal muscle weakness followed by complete recovery, (2) increase in serum potassium concentrations during provocation tests, (3) insertional myotonic discharges, and (4) subsequent decline of CMAP amplitudes after short exercise tests.[1 14] On the other hand, the hallmarks of paramyotonia congenita are (1) cold induced myotonic stiffness, followed by weakness in the face and distal limb muscles, along with paradoxical myotonia,[1] (2) greater falling of evoked CMAP amplitudes on short exercise tests after cooling the arm to 20°C than with normal skin temperature.[18] The patients described in this study exhibited clinical and electrophysiological features of both hyperkalaemic periodic paralysis and paramyotonia congenita, and were diagnosed as having

paralysis periodica paramyotonia. All affected members of the family had recurrent episodes of muscle weakness, increased serum potassium concentrations during the weakness, paramyotonic features after cold exposure, and paradoxical myotonia. Myopathic and myotonic discharges, along with decreased amplitudes after short exercise tests, represent electrophysiological features of hyperkalaemic periodic paralysis. An additional feature distinguishing the symptoms of the present family from those previously reported with hyperkalaemic periodic paralysis was a marked decrease of CMAP amplitudes after cooling, a phenomenon which has recently been described among patients with paramyotonia congenita.[18]

The duration of symptoms in previous studies of hyperkalaemic periodic paralysis was poorly described (as several minutes to an hour), overlooking clinical characteristics such as chronologically prolonged symptom duration and aggravation of fixed muscle weakness.[1 5 14] We described these characteristics based on clinical findings in the present family with paralysis periodica paramyotonia. Further studies are needed on age dependent variation of symptom manifestations in hyperkalaemic periodic paralysis and paralysis periodica paramyotonia to elucidate the pathophysiology of these diseases.

Two patient members in the family complained of paralytic episodes after eating water melon. This fruit contains large amounts of potassium (139 mg/100 g)[19] and may raise the serum potassium concentrations transiently after eating, and then act as an initiating factor for severe paralyses in these patients. Other fruits contain large amounts of potassium: pears 142 mg/100 g; concentrated orange juice 750 mg/100 g; and bananas 380 mg/100 g.[19] Patients diagnosed with periodic paralysis associated with hyperkalemia may be advised against eating large amounts of fruits.

Nosological distinction between hyperkalaemic periodic paralysis, paramyotonia congenita, and paralysis periodica paramyotonia is currently under debate. Ricker *et al* suggested that the aberration in paralysis periodica paramyotonica is more complex than in hyperkalaemic periodic paralysis and that the genetic mutations associated with each syndrome must differ from each other despite similarities in their membrane defect.[5] A certain mutation in the *SCN4A* can cause phenotypes of hyperkalaemic periodic paralysis, paramyotonia congenita, or paralysis periodica paramyotonica. Ser804Phe and Ala1156Thr mutations in the *SCN4A* gene were reported to be associated with paralysis periodica paramyotonica.[13] Different mutations have been found in hyperkalaemic periodic paralysis and paramyotonia congenita. Thr698Met, Thr704Met, Metl585Val, and Metl592Val mutations have been reported in hyperkalaemic periodic paralysis, whereas Gly13006Val, Thr1313Met, Arg1448His, Arg1448Cys, Leu1433Arg, and Val1589Met mutations have been reported in paramyotonia congenita.[3 4 8 13]

By contrast, a family was reported in which individual members had clinical features of either hyperkalaemic periodic paralysis or paramyotonia congenita despite common electrophysiological features.[9] An Ala1156Thr mutation was reported to be responsible for the development of hyperkalaemic periodic paralysis and paramyotonia congenita in one family.[9 12] Gly1306Ala/Glu/Val mutations have been also reported in three different phenotypes—myotonia fluctuans, myotonia permanens, and paramyotonia congenita.[10–12] An identical mutation in the *SCN4A*, Ser804Phe, had been reported in two different phenotypes of periodic paralysis—paralysis periodica paramyotonia and myotonia fluctuans.[10 12] It remains controversial whether a mutation in *SCN4A* is associated with a unique phenotype.

The Thr704Met mutation of *SCN4A* in the present family provides the first genetic evidence in paralysis periodica paramyotonia, although the mutation was seen in a family with hyperkalaemic periodic paralysis. These results support the idea that hyperkalaemic periodic paralysis and paramyotonia congenita of periodic paralysis represent a range of a single genetic disorder. It was thus suggested that mutant phenotypes result in variable clinical features.[20]

Our present data unambiguously demonstrate that members of this family with the Thr704Met mutation manifest clinical and electrophysiological characteristics of paralysis periodica paramyotonica. As the same mutation was found in a homogeneous family with hyperkalaemic periodic paralysis,[8 13] the phenotypic variation may be due to different genetic backgrounds. To understand the mechanisms of phenotypic differences between paralysis periodica paramyotonia and other periodic paralyses, detailed analysis of clinical as well as genetic data in additional families with paralysis periodica paramyotonia with Thr704Met are required.

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