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Case Report

Clinical and Genetic Analysis of an Asian Indian Family with Charcot-Marie-Tooth Disease Type 4C

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Keywords

Charcot-Marie-Tooth disease type 4C · *SH3TC2* gene · Novel variants · Asian Indian

Abstract

Charcot-Marie-Tooth disease type 4C, an autosomal recessive genetic neuropathy, is caused by mutations in the *SH3TC2* (SH3 domain and tetratricopeptide repeats 2) gene. Interestingly, although mutations in this gene have been observed in European gypsies, a population that originated in India, there are few publications describing Indian patients. We report our analysis of a 50-year-old woman of Asian Indian descent with onset of progressive distal weakness and sensory loss in childhood. A clinical examination revealed the presence of a neuropathy with pes cavus without spinal abnormalities. Electrophysiological testing confirmed a sensorimotor length-dependent neuropathy with demyelinating features. A genetic analysis revealed she carries 2 novel mutations, c.2488G>T variant (rs879254317) and c.731+5G>A variant (rs879254316), in the *SH3TC2* gene. Further genetic testing demonstrated that her son is a carrier of the c.731+5G>A mutation. Our analysis confirms that this patient is a compound heterozygote inheriting these mutations, which are in trans, in an autosomal recessive pattern. Her son developed an episode of sciatic neuropathy with complete resolution. We hypothesize

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that in his case, haploinsufficiency caused by c.731+5G>A mutation may have predisposed him to the development of this focal neuropathy.

Introduction

Charcot-Marie-Tooth disease type 4C (CMT4C) is an autosomal recessive neuropathy with demyelinating features caused by mutations in the *SH3TC2* (SH3 domain and tetratricopeptide repeats 2) gene [1]. There is significant clinical heterogeneity in this condition, and although there are patients reported from all over the world, the majority of them are of European descent [2–5]. Interestingly, although mutations are described in gypsies, who originated from India, there have been few publications on patients of Asian Indian descent [6–9]. We report our analysis of a second patient of Asian Indian descent with novel mutations causing CMT4C.

Case Summary

Our patient, a woman of Asian Indian descent aged 50 years, presented for a neuromuscular evaluation with complaints of imbalance. She had difficulty walking in early childhood and at the age of 6 years was admitted to a hospital, where a diagnosis of polio was offered. In her teens, she was not able to run or walk and unable to participate in sports. Over the ensuing time period, she developed worsening of gait imbalance, sensory loss, and weakness in her legs. The remainder of the neurological review of her systems was unremarkable, with no complaints of difficulty speaking, chewing, or swallowing or diplopia. Her general medical history was also unremarkable.

A physical examination revealed no evidence of scoliosis. A neurological examination revealed no abnormalities of her mental status or cranial nerve examination. She was diffusely hyporeflexic with flexor plantar responses and had sensory loss testing for light touch, vibration, proprioception, and temperature in a stocking distribution worse distally in her feet. Power testing disclosed weakness and atrophy of the small hand muscles and grip. In addition, the patient had bilateral foot drop with Medical Research Council (MRC) grade 2/5 weakness of foot dorsiflexion, eversion, and inversion, and plantar flexion with better strength of MRC grade 4/5 in knee flexion and extension. No abnormalities of the cerebellar system were noted. She could not walk on her heels or toes and had a positive Romberg test result.

Routine serum chemistries showed that the following test results were normal: cell count and differential, serum protein electrophoresis and immunofixation, thyroid studies, anti-nuclear antibody, rheumatoid factor, anti-Sjögren-syndrome-related antigen A, anti-Sjögren-syndrome-related antigen B, anti-extractable nuclear antigen, anti-scleroderma 70 antibody, anti-Jo-1, anti-centromere antibody, complement C3 and C4, serological tests for human immunodeficiency virus and hepatitis C, vitamin B_1, vitamin B_6, vitamin B_{12}, folate, C-reactive protein, erythrocyte sedimentation rate, anti-neutrophil cytoplasmic antibody panel, and actin antibody.

Since the age of 41 years, the patient had undergone a series of 4 electromyography (EMG) studies, which confirmed and documented progressive worsening of a neuropathy. All of the studies showed evidence of a significant demyelinating polyneuropathy affecting both motor and sensory nerves. The nerve conduction velocities were diffusely slow with no evidence of conduction block or temporal dispersion (Table 1). Needle EMG documented the presence of secondary acute and chronic axonal features affecting the distal muscles of all extremities, but more severe in the legs corresponding to those muscles that were clinically most weak.

The patient's son presented for an evaluation of foot drop which had developed spontaneously at the age of 19 years. At the time this occurred, he denied any significant antecedent event such as backache, trauma, or a fall. He noted numbness of the right foot and an inability to run. The remainder of the neurological review of his systems was negative. The neurological examination showed a normal mental status and cranial nerve examination. His reflexes were normoactive, except that the right ankle reflex was not obtained. His plantar reflexes were flexor. He had sensory loss testing light touch and pin prick sensibility in a stocking distribution of the right leg. His strength was normal except for the right leg, where he had MRC grade 5/5 hip flexion, extension, adduction, and abduction on power testing. Knee flexion was minimally weak at MRC grade 5–/5, while extension was of normal strength. He had MRC grade 2/5 weakness of foot dorsiflexion and grade 3/5 foot eversion and inversion. Plantar flexion was MRC grade 4/5. He could not walk on his heels or toes. Overall, the clinical presentation and neurological examination localized the deficits to a sciatic nerve lesion proximal to the branch supplying the short head of the biceps. An EMG was done about 3 weeks after onset, when the patient started to clinically improve. The distal latencies and conduction velocities in both peroneal and tibial nerves were symmetrical and normal recording the extensor digitorum brevis and abductor hallucis brevis muscles, respectively. However, in both of these nerves, there were relatively reduced response amplitudes on the right compared to the left. The minimum F wave latency on the right was prolonged compared to the left by approximately 8 ms. The sensory potentials in sural, superficial peroneal, and saphenous nerves were normal and symmetrical. A concentric needle EMG showed 1+ to 2+ positive sharp waves in the tibialis anterior and peroneus longus and brevis muscles. These changes were observed to a lesser degree in the medial gastrocnemius and short head of the biceps muscles. In these same muscles, the interference pattern was reduced with maximal effort. No abnormalities were detected in sampling the iliopsoas, vastus lateralis, adductor magnus, or lower right lumbosacral paraspinal muscles. Reexamination of the patient 1 month later showed complete resolution of his neurological deficits. Follow-up 10 years later showed that he did not suffer any further neurological episodes and that his neurological examination remained normal.

Family History

The patient has 3 sisters, 2 older and 1 younger. None of the siblings are affected by a neurological condition. In addition, with the exception of her son, no other family member is affected by any neuromuscular disease. Although her parents are both of Gujarati descent, they come from small villages more than 30 miles apart, making consanguinity very unlikely.

Genetic Analysis

Whole exome sequence analysis was performed, and it identified 2 variants, a c.2488G>T variant (rs879254317) and a c.731+5G>A variant (rs879254316), in the *SH3TC2* gene (NM_024577.3). The c.2488G>T variant is located in exon 11 and results in p.E830X, causing loss of function by premature truncation of the protein or nonsense-mediated mRNA decay. This variant is found neither in the ExAC nor in the 1000 Genomes database and has not been observed in the NHLBI exome sequencing project (6,500 individuals). This exon is the most frequent site of all known mutations in this gene reported to cause CMT4C. The c.731+5G>A variant occurs in intron 6 of the *SH3TC2* gene and is predicted to disrupt the natural splice donor site, resulting in abnormal gene splicing. This variant also has not been reported in the ExAC or the 1000 Genomes database or in the 6,500 individuals included in the NHLBI exome sequencing project. The index patient's son is heterozygous for only the c.731+5G>A variant, indicating that these mutations are in trans. Overall, our analysis of the infrequency of these variants in combination with protein modelling of the putative consequences of these genetic changes provides strong evidence that these are disease-producing variants causing CMT4C.

Discussion

The *SH3TC2* gene encodes a protein that is required for proper myelination and integrity of the node of Ranvier [10]. Currently, 30 mutations have been described causing CMT4C on which clinical information has been provided. In addition, 20 other mutations, including those that are subject of this report, have been deposited in the ClinVar database without phenotypic information. It has been suggested that CMT4C is the most frequent cause of recessive CMT in patients of European Caucasian descent [4]. A study describing 17,000 patients with neuropathy who had been referred to a large company performing genetic analysis based in the USA was recently published [11]. It was found that of those with a positive genetic test result, 94.9% were positive for mutations in 4 genes which did not include the *SH3TC2* gene. The rate of positive results in the *SH3TC2* gene was only 0.8%, indicating that at least in this study population, mutations in this gene are an uncommon cause of CMT. However, there are certain populations where the incidence is higher. For example, in the European gypsy population, also known as Roma, the carrier rate of mutations in this gene can reach as high as 4% [6]. There are 4 founder mutations described in this group that left India more than 700 years ago and is characterized by high rates of intermarriage within the community.

Interestingly, there has only been 1 report on a patient from India. That Asian Indian patient, aged 10 years, was the product of a 3rd-degree consanguineous marriage, as reported by Kalane et al. [9]. She was homozygous for the R904X mutation that had previously been described in French Canadian patients. Clinically, this patient had mild pes cavus without evidence of a spinal deformity. A high frequency of spinal deformities has been noted, and it has been suggested that the combination of this abnormality and a demyelinating polyneuropathy should prompt an investigation specifically for CMT4C [12]. Our patient has novel mutations in the *SH3TC2* gene and also does not have evidence of spinal deformities. Although it is interesting to note that neither of these patients of Asian Indian descent has spinal abnormalities, a phenotypic analysis of many more patients with CMT4C will be needed to determine if this clinical feature is typical in this ethnic group. Our patient originates from a different Indian

state than the one previously reported on and carries novel mutations in the *SH3TC2* gene. Not unexpectedly, these results suggest that this disorder is genetically heterogeneous and not restricted to a particular ethnic or linguistic group in India.

In one of the first publications regarding CMT4C, it was reported that haploinsufficiency could result in a susceptibility to mild sensory neuropathy with a predisposition to carpal tunnel syndrome [13]. It is interesting to note that our patient's son developed right leg weakness which localized to a sciatic nerve lesion. Given his clinical course and electrophysiological testing results, it is likely that this was a demyelinating lesion which resolved spontaneously. It is possible that in his case, the haploinsufficiency caused by the c.731+5G>A mutation predisposed him to developing the sciatic nerve lesion.

Our study of this family expands the spectrum of mutations causing CMT4C with the discovery of 2 novel mutations in the *SH3TC2* gene. It also expands the phenotype that may be associated in individuals carrying only the c.731+5G>A mutation and confirms a worldwide distribution of patients with CMT4C.

Statement of Ethics

Informed consent was obtained from all individuals who participated in this study. The study was conducted following policies and procedures approved by the local Institutional Review Board.

Disclosure Statement

The authors have no conflict of interest to report.

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Table 1. Summary of nerve conduction parameters

Nerves	Distal latencies	Response amplitude	Conduction velocity	F wave latency	Comments
Motor	ms	mV	m/s	ms	
Bilateral tibial	NR	NR	NR	NR	recording the abductor hallucis brevis muscle
Bilateral peroneal	NR	NR	NR	NR	recording the tibialis anterior or extensor digitorum brevis muscle
Median					
Right	9.1 (<4.4)	3.2 (>4.0)	36 (>50)	60 (<31)	
Left	9.3 (<4.4)	2.0 (>4.0)	40 (>50)	41 (<31)	
Ulnar					
Right	6.5 (<3.3)	3.2 (>6.0)	35 (>50); 32 (elbow)	37 (<32)	
Left	4.9 (<3.3)	5.6 (>6.0)	31 (>50); 29 (elbow)	44 (<32)	
Sensory		μV	m/s		
Bilateral sural		NR	NR		
Bilateral superficial		NR	NR		
Bilateral median		NR	NR		
Ulnar					
Right		5 (>20)	34 (>50)		
Left		NR	NR		
Radial					
Right		19 (>15)	32 (>50)		
Left		16 (>15)	40 (>50)		

Values in parentheses denote normal values. NR, no response.