CMT2C with vocal cord paresis associated with short stature and mutations in the *TRPV4* gene

D.-H. Chen, MD, PhD
Y. Sul, BSc
M. Weiss, MD
A. Hillel, MD
H. Lipe, ARNP
J. Wolff, BSc
M. Matsushita, BSc
W. Raskind, MD, PhD
T. Bird, MD

Address correspondence and reprint requests to Dr. Thomas D. Bird, 1660 S Columbian Way, S-182-GRECC, Seattle, WA 98108
tomnroz@uw.edu

ABSTRACT

Background: Recently, mutations in the transient receptor potential cation channel, subfamily V, member 4 gene (*TRPV4*) have been reported in Charcot-Marie-Tooth Type 2C (CMT2C) with vocal cord paresis. Other mutations in this same gene have been described in separate families with various skeletal dysplasias. Further clarification is needed of the different phenotypes associated with this gene.

Methods: We performed clinical evaluation, electrophysiology, and genetic analysis of the *TRPV4* gene in 2 families with CMT2C.

Results: Two multigenerational families had a motor greater than sensory axonal neuropathy associated with variable vocal cord paresis. The vocal cord paresis varied from absent to severe, requiring permanent tracheotomy in 2 subjects. One family with mild neuropathy also manifested pronounced short stature, more than 2 SD below the average height for white Americans. There was one instance of dolichocephaly. A novel S542Y mutation in the *TRPV4* gene was identified in this family. The other family had a more severe, progressive, motor neuropathy with sensory loss, but less remarkable short stature and an R315W mutation in *TRPV4*. Third cranial nerve involvement and sleep apnea occurred in one subject in each family.

Conclusion: CMT2C with axonal neuropathy, vocal cord paresis, and short stature is a unique syndrome associated with mutations in the *TRPV4* gene. Mutations in *TRPV4* can cause abnormalities in bone, peripheral nerve, or both and may result in highly variable orthopedic and neurologic phenotypes. *Neurology*® 2010;75:1968-1975

GLOSSARY

CMAP = compound muscle action potential; **CMT** = Charcot-Marie-Tooth; **CMT2C** = Charcot-Marie-Tooth Type 2C; **HMSN** = hereditary motor and sensory neuropathy; **NCV** = nerve conduction velocity; **RFLP** = restriction fragment length polymorphism; **SMA** = spinal muscular atrophy; **SNAP** = sensory nerve action potential; **SPSMA** = scapuloperoneal spinal muscular atrophy.

More than 30 genes and genetic loci have been associated with the Charcot-Marie-Tooth hereditary neuropathy syndrome (CMT), also known as hereditary motor and sensory neuropathy (HMSN).¹ CMT is categorized by a combination of genetic, electrophysiologic, and clinical features. CMT1 is autosomal dominant with slow nerve conduction velocities (demyelinating). CMT2 is autosomal dominant with normal or near normal nerve conduction velocities and reduced compound muscle action potentials (axonal). The most common form of CMT2 is associated with mutations in the Mitofusin gene (*MFN2*).^{2,3} However, in 1994, Dyck and colleagues⁴ described a syndrome of hereditary motor and sensory neuropathy with diaphragm and vocal paresis designated as CMT2C. This category was subsequently confirmed and linked to chromosome 12q23-24.⁵⁻⁸ Recently a few groups have described several families with autosomal dominant CMT2C, scapuloperoneal spinal muscular atrophy (SPSMA), and congenital distal spinal muscular

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From the Departments of Neurology (D.-H.C., M.W., T.B.), Medicine (Y.S., M.M., W.R., T.B.), and Otolaryngology (A.H.), Psychiatry and Behavioral Sciences (W.R., T.B.), University of Washington Medical School, Seattle; and Geriatric (H.L., J.W., T.B.) and Mental Illness (W.R.), Research Education and Clinical Centers, VA Puget Sound Health Care System, Seattle, WA.

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atrophy (SMA) having mutations in the calcium permeable ion channel gene (transient receptor potential cation channel, subfamily V, member 4; *TRPV4*).⁹⁻¹² Independently, 2 groups previously reported other mutations in the *TRPV4* gene associated with the bone disorders spondylometaphyseal dysplasia, metatropic dysplasia, and brachyolmia^{13,14} (recently further expanded¹⁵). We now describe 2 families having both CMT2C and short stature caused by mutations in *TRPV4* (one novel), thereby enlarging and unifying the phenotypic spectrum associated with mutations in this gene.

METHODS Subjects. Subjects were evaluated in the Neurogenetics Clinic of the University of Washington Medical School. Vocal cord analysis was conducted in the Otolaryngology Clinic

by A.H. EMG and nerve conduction studies (NCV) were performed using a Viking IV (Nicolet, Madison, WI). Leukocyte DNA was extracted from peripheral blood samples by standard methods to analyze for mutations in the *TRPV4* gene.

Standard protocol approvals, registrations, and patient consents. The protocol and consent forms used in this study were approved by the Human Subject Review Committee of the University of Washington.

Mutation detection. Initial mutation screening for *TRPV4* was conducted in affected members III-2 in family 1 and II-2 in family 2, and a normal control. The 15 coding exons (exons 2–16) of *TRPV4* and their corresponding splice junctions were amplified (for sequences of primers, see the supplemental data on the *Neurology*[®] Web site at www.neurology.org).

Amplifications were performed with FastStart Taq polymerase (Roche, IN) as described,¹⁶ with optimized annealing temperatures of 58 °C, and direct DNA sequencing was performed as previously described.¹⁶ Briefly, sequencing reaction were carried out using the BigDye V3.1 Cycle Sequencing Kit (Applied Biosystems, CA) with the same forward primers as in the PCR amplification, and sequencing products were electrophoresed on an ABI PRISM 3130xl Genetic Analyzer. To confirm the mutations, exon 6 and exon 10 were also sequenced in reverse.

The identified nucleotide substitution 943 C>T creates a new restriction endonuclease recognition site for *Afl*III and the substitution 1625 C>A eliminates a restriction endonuclease recognition site for *Eco*RI. Restriction fragment length polymorphism (RFLP) analysis with *Afl*III digestion of the 516 bp of exon 6 PCR amplicon generates fragments of 186 bp and 330 bp for the mutant allele. RFLP with *Eco*RI digestion of the 708 bp of exon 9–10 amplicon generates 152 bp and 556 bp fragments for the wild-type allele. RFLP analyses with these enzymes (New England Biolabs, MA) were performed on samples from the available family members, and 200 unrelated normal controls, under conditions suggested by the manufacturer. Restriction fragments were separated on 2% agarose gels.

Twenty subjects from separate families with a CMT syndrome (16 CMT2 and 4 CMT1) but without vocal cord paresis and unrelated to any known gene were also screened for *TRPV4* mutations by sequencing the coding exons as described above.

RESULTS Clinical findings. Family 1. The pedigree is shown in figure 1A. Individual III-1 is a 53-year-old woman who is 54.5 inches tall (4 feet 6.5 inches; 138.4 cm). She has always noted difficulty breathing especially when exposed to certain perfumes or cheeses. Her neurologic examination shows normal cranial nerve function (except for slightly hoarse voice and stridor), absent deep tendon reflexes, downgoing plantar reflexes, mild high arches and hammertoes, decreased appreciation of vibration in the toes that was felt at the ankles, and normal appreciation of position, light touch, temperature, and pinprick. She is fully ambulatory without assistance. There is mild weakness of dorsiflexion of her feet and she cannot walk on her heels. She has no weakness or atrophy of other proximal or distal muscles. Although she has short stature, her hands, feet, and limbs appeared proportional to the rest of her body size. Electrophysiologic testing revealed normal mo-

Figure 1 Pedigrees of family 1 (A) and family 2 (B)

Square = male; circle = female; diamond = either sex; black = affected; age under each symbol; mutation genotype under each symbol; + = normal wild-type gene.

Table Clinical characteristics of CMT2C subjects

Family	Subject no.	Sex	Onset age, y	Current age, y	Height, ft/in (cm)	Vocal paresis	DTR	Distal weakness	Sensory loss	Motor NCV, m/s	CMAP amplitudes, mV	TRPV4 mutation	Comments
1	II-1	F	NA	73	4'6" (139.5)	+	↓	+	–	UI 62	↓ Per 1.2 (normal >1.5)	S542Y	
1	III-1	F	1 ^a	53	4'6.5" (138.4)	+	↓	+	+ Mild	UI 60	↓ Per 1.0 (normal >1.5)	S542Y	
1	III-2	F	10 ^a	d.44	4'10" (147)	+ (trach)	↓	+	–	Med 53 UI 60	↓ UI 2.0 (normal >5.0)	S542Y	
1	IV-2	M	Asym	28	5'3" (159.2)	Raspy voice	↓	–	–	Per 54 Tib 46	NL	S542Y	Dolichocephaly
1	IV-4	M	10 ^a	29	5'4" (162)	+	↓	+	+ Mild	UI 59	NL	S542Y	
1	IV-5	F	25	26	4'9" (146)	–	↓	–	–	Med 47 (DL 7.0 ms ^c)	↓ Tib 2.4 (normal >3.0)	S542Y	Abnormal pupils, sleep apnea, CTS
2	I-1	M	~45 ^b	63 (age at death)	5'9"	–	↓	+	+	Med 36 ^d UI 39 ^d	↓ Med 3.2 (normal >4.5)	NA	
2	II-2	F	1 ^a /7 ^b	47	4'11.5" (152)	+ (trach)	↓	+	+	Med 47 (DL 4.7 ms ^c)	↓ Med 1.8 (normal >4.5) Tib 0.1 (normal >3.0)	R315W	
2	III-2	F	1 ^a	26	5'1.5" (156)	+	↓	+	+	Med 48 UI 59 Tib 44	↓ Tib 1.8 (normal >3.0) Med 2.6 (normal >4.5) UI 4.2 (normal >5.0)	R315W	Sleep apnea, congenital III CN palsy

Abbreviations: ↓ = decreased; + = present; – = absent; Asym = asymptomatic; CMAP = compound muscle action potential; CMT2C = Charcot-Marie-Tooth Type 2C; CN = cranial nerve; CTS = carpal tunnel syndrome; DL = distal latency; DTR = deep tendon reflexes; Med = median; NA = not available; NCV = nerve conduction velocities; Per = peroneal; Tib = anterior tibial; trach = tracheotomy; UI = ulnar.

^a Hoarse voice/whistling.

^b Neuropathy.

^c Abnormal; normal <4.5 ms.

^d Abnormal; normal >44 m/s.

Figure 2

Images of vocal cords from video stroboscopic examination during breathing of (A) normal subject, (B) individual III-1 in family 1, and (C) individual III-2 in family 2

The 2 affected family members have limited and asymmetric opening of the vocal cords during breathing compared with the wide open cords in the normal subject (A).

tor and sensory NCVs with reduced amplitude of the peroneal compound muscle action potential (CMAP) (table). Laryngoscopic observation of her vocal cords showed incomplete closure with a glottic gap during phonation and asymmetrically and incomplete opening during breathing (figure 2). X-rays of her cervical, thoracic, and lumbar spine showed reduced height of all vertebral bodies.

The major clinical features of other family members are shown in the table. Muscle weakness was typically mild and distal in the lower limbs but varied from absent in IV-2 to moderate in III-2, who also

had mild to moderate proximal weakness of the upper and lower limbs. III-2 had a quadriceps muscle biopsy that showed chronic neurogenic atrophy. She had reduced phrenic nerve CMAP amplitude (150 mV; normal >200 mV), chest fluoroscopy showing decreased movement of both diaphragms, and she died of respiratory problems and heart failure at home at age 44. There was mild sensory loss to vibration in the feet of 2 persons.

Electrophysiologic studies showed that sensory and motor nerve conductions were normal except for occasional prolonged distal latencies (IV-5 with carpal tunnel syndrome; table). CMAP amplitudes were decreased. Electromyograms of 3 persons all showed positive sharp waves, increased amplitudes of motor unit action potentials, and decreased recruitment in muscles of both upper and lower limbs.

Vocal cord paresis occurred in 4 persons (1 requiring tracheotomy) and a raspy voice was noted in IV-2. EMG of the vocal cords in II-1 was normal on the right and showed decreased recruitment on the left. Hoarseness and stridor in IV-4 improved after lysis of a posterior arytenoid scar band.

IV-5 had large pupils that were slow to react to light and were more reactive to near accommodation, suggesting Adie's pupils. No pharmacologic testing was done.

The 4 affected and examined women in this family have an average height of 4 feet 8 inches (142.2 cm), which is more than 2 SD below the mean (5 feet 4.9 inches; 164.8 cm) for non-Hispanic white American women.¹⁷ The 2 affected men had heights of 5 feet 3 inches (159.2 cm) and 5 feet 4 inches (162 cm), both more than 2 SD below the mean heights of non-Hispanic white men.¹⁷ Unaffected family member IV-3 is of normal height at 5 feet 11 inches (180.3 cm). Little is known about family member I-2 except that she was approximately 4 feet 6 inches and died at age 70. In addition, dolichocephaly observed in IV-2 was corroborated by skull X-rays (biparietal diameter/fronto-occipital diameter ratio of 0.72; normal >0.74) and an enlarged occipital-frontal circumference of 61 cm.

Family 2. This family is Kinship 2 reported in the original description of CMT2C in 1994.⁴ The index case (II-2, figure 1B) is now 47 years old. Between ages 6 months and 3 years, she had numerous episodes of acute respiratory stridor that required the placement of a permanent tracheotomy for partial vocal cord paresis at age 3 years. Laryngoscopy at age 6 years revealed no movement of the right cord and slight movement of the left cord with a raspy but understandable voice. At age 7, she was discovered to have a peripheral neuropathy, which has been slowly progressive. As an adult, she has weakness and atro-

phy of all intrinsic muscles of her hands, marked weakness of the extensors and flexors of her ankles, absent tendon reflexes, and loss of position, vibration, and pinprick sensation in her hands and feet. She uses a wheelchair but can walk short distances with assistance. At age 27, her motor and sensory NCV were normal but her median CMAP amplitudes and sural sensory nerve action potential (SNAP) amplitudes were reduced. Several other SNAPs were normal at that age. Twenty years later, there was further reduction of CMAP amplitudes and complete loss of previously preserved SNAPs (with slightly delayed median motor distal latency). She is 4 feet 11.5 inches (152 cm) tall.

At age 8 months, her daughter (III-2) had recurrent episodes of severe stridor. At age 6, she was noted to have bilateral vocal cord paresis. Her tendon reflexes were absent with mild atrophy of her intrinsic hand muscles, mild weakness of ankle dorsiflexion, and normal sensory examination. She had normal motor and sensory NCV with reduced CMAP amplitudes of several nerves. As an adult she is 5 feet 2 inches (156 cm) tall, has marked bilateral foot drop, and uses a wheelchair, although she can ambulate short distances with a walker. She has loss of position and vibration sensation in her feet. She has a congenital strabismus with partial right third nerve deficit and a history of sleep apnea. Video stroboscopic evaluation of her vocal cords showed an immobile right cord and partially mobile left cord. During simple phonation, there was almost complete glottis closure, but there was a 0.5-cm glottic gap during speech and humming and some paradoxical movement of the left cord during deep inspiration.

The father (I-1) of the index case had no stridor, wheezing, or breathing or voice problems. He had onset of a peripheral neuropathy at about age 45. His tendon reflexes were absent with bilateral foot drop and bilateral atrophy of intrinsic hand muscles. He had mild loss of the appreciation of vibration and pinprick in both feet. He was 5 feet 8 inches (172.7 cm) tall. Electrophysiologic testing revealed a mixed axonal/demyelinating neuropathy with reduced CMAP amplitudes and mildly reduced NCVs.

Genetic studies. The 15 protein coding exons in *TRPV4* and their splice junctions were PCR-amplified and sequenced in an affected individual (III-2 in figure 1) and her affected son (IV-4 in figure 1) in family 1 and a normal control. A heterozygous C to A transversion was identified at nucleotide 1625 (figure 3) in exon 10 in both affected individuals. This sequence change predicts substitution of tyrosine for serine in residue 542 (S542Y). In II-2 in family 2, a heterozygous C to T transversion was found in nucleotide 943 in exon 6 (figure 3). This

Figure 3 Sequence chromatograms of portions of exons 6 and 10 of *TRPV4* from affected individuals with CMT2C in 2 families

(A) A heterozygous C to A transversion at nucleotide 1625 (in exon 10) in an affected subject in family 1. This change predicts amino acid alteration of S542Y. (B) A heterozygous C to T transversion at nucleotide 943 in an affected subject in family 2. This change predicts amino acid alteration of R315W.

change predicts substitution of tryptophan for arginine at residue 315 (R315W). No other sequence alterations were found. Ser542 and Arg315 are evolutionarily conserved in all mammals and invertebrates. By RFLP analyses with *EcoRI* or *AflIII*, we confirmed that affected members were heterozygous for 1625 C>A and 943 C>T mutations in family 1 and family 2, respectively, and available unaffected relatives had the wild-type sequence. A 95-year-old woman in family 1 (the maternal aunt of II-1) is short (4 feet 8.5 inches, 144.8 cm) but tested negative for the S542Y mutation. These 2 nucleotide changes were not detected in 200 controls (400 chromosomes).

We then screened the *TRPV4* coding region in 20 other unrelated subjects with a familial CMT syndrome but no known genetic cause and no vocal cord paresis. No pathologic nucleotide changes were identified in those cases. In one family, a nucleotide change leading to an amino acid alteration (1684 G>A, V521I) was identified but this is a known polymorphism (NCI database; NM_021625.3).

DISCUSSION Two mutations in the *TRPV4* gene causing autosomal dominant brachyolmia, a syndrome of moderate short trunk, short stature, mildly

short limbs and digits, and no extra skeletal findings were reported in 2008.¹³ Subsequently, 8 additional mutations in *TRPV4* causing a variety of skeletal dysplasia phenotypes including spondylometaphyseal dysplasia and metatropic dysplasia were described.^{14,15} These are autosomal dominant syndromes of short stature and kyphoscoliosis, frequently progressive and severe, and associated with abnormalities in vertebra and tubular bones. None of these families have associated neurologic problems. However, more recently 4 separate groups reported additional families with 5 mutations in *TRPV4* associated with CMT2C including a previously described syndrome of SPSMA and congenital distal SMA.⁹⁻¹² The SPSMA family had variable skeletal abnormalities that included congenital hip dysplasia, scoliosis, smaller hands with clinodactyly, and one arm or leg shorter than the other.^{9,18} The family members were not described as being short, but a subsequent sporadic case was noted to have short stature (height not given) compatible with the more detailed findings of the present study.¹²

In the present study, we enlarge and unify the phenotypic spectrum associated with mutations in

the *TRPV4* gene. The 2 families reported here share the common characteristics of axonal neuropathy, vocal cord paresis, and short stature. In family 1, the neuropathy was generally mild and associated with normal NCVs and reduced CMAP amplitudes but preserved SNAPs. Although the syndrome was generally quite mild in family 1, III-2 was more severely affected with proximal weakness and the phrenic nerve involvement may have contributed to her respiratory failure and death. In family 2, the neuropathy produced much more prominent weakness, was associated with decreased CMAP amplitudes, but also reduced SNAP amplitudes, with progression of these changes over time.

Both families exhibited short stature that was more prominent in family 1 and also seemed to be more evident in females. The males also tended to be short, although fewer males were available for examination. One unaffected man without the *TRPV4* mutation in family 1 has normal height, providing additional evidence that short stature is associated with CMT2C and the *TRPV4* mutation. However, the short stature of the unaffected 95-year-old woman in family 1 suggests there could be more than one type of short stature in this family. The short stature related to mutant *TRPV4* is presumed to be on the basis of a slight reduction in the height of all vertebral bodies and may be the result of a mild metaphyseal dysplasia. The digits and limbs of the affected family members were proportional to their height. Therefore, the metaphyseal defect must be affecting all bones proportionally. No abnormalities were noted on plain X-rays of digits or long bones. It is of interest that one member in family 1 had dolichoceph-

aly, which may also be the result of a bone growth defect.

The vocal cord paresis was also highly variable in both families. Some family members had no laryngeal difficulty whereas several had hoarse voices and 2 had significant paresis requiring permanent tracheotomy. It has been assumed that the vocal cord paresis is part of the underlying axonal neuropathy. However, it is possible that a soft tissue or cartilage defect is playing a role in this problem.¹⁹ Our observations in the 20 CMT subjects without vocal cord paresis who tested negative for *TRPV4* mutations document that pathologic *TRPV4* mutations are unlikely to be found in CMT patients in the absence of a personal or family history of vocal cord paresis. Although it is a defining characteristic of CMT2C, vocal cord paresis is not unique to CMT2C. For example, it has been described relatively often in association with CMT4A caused by mutations in the ganglioside-induced differentiation-associated protein gene (*GDAP1*).²⁰ Other cranial nerves may also be involved in CMT2C as evidenced by the 2 persons in our families with third cranial nerve deficits. Pupillary abnormalities have been described in a variety of patients with CMT2²¹ and oculomotor nerve abnormalities have been reported with patients with axonal neuropathy and mutations in *TUBB3*.²²

TRPV4 has a key regulatory role in the bone growth plate, perhaps modulated through interactions with *SOX9*, *TRPP1*, and *TRPP2*.²³ It may also be involved in keratinocyte regulation and ciliary function in cartilage and growth plates. *TRPV4* is a known member of the TRP superfamily of cation

Figure 4 Schematic structure of *TRPV4* protein and mutations identified in the gene

Functional domains are predicted by the SMART database. The protein contains a proline-rich domain (PRD), an ankyrin repeat domain (ARD), which includes ankyrin repeats (A 1–6), 6 transmembrane segments (S1–S6), and a putative pore region. The mutations associated with CMT2C and related neurologic syndrome and their corresponding positions in the gene are indicated at the top of the protein. The mutations identified in this report are indicated by asterisks. The mutations associated with skeletal dysplasias and their positions in the gene are indicated underneath the protein. Note that 2 mutations (S542Y and V620I) have been associated with both neurologic syndrome and short stature.

channels mediating the influx of extracellular calcium that then activates pathways leading to the secretion of K^+ and Cl^- and loss of intracellular water.^{24,25} It is not clear how perturbations of this system would affect neuronal or axonal function. It is of interest that the mutation in our family 2, also found in family 1 of Auer-Grumbach et al.,¹¹ occurs in a codon (315) adjacent to the codon (316) mutated in the SPSMA family reported by Deng et al.⁹ Perhaps this region is a hot spot for mutations in *TRPV4* associated with CMT. Five of 6 previously published mutations associated with neurogenic weakness syndromes (including CMT2C) cluster in the ankyrin repeat domain (figure 4). Although the mutations responsible for skeletal dysplasias are scattered along the gene, 8 of 11 mutations are located in the transmembrane domain. It is interesting that the novel mutation S542Y found in our family 1 with CMT2C and short stature and the V620I mutation associated with distal weakness and short stature¹² are both in the transmembrane domain (figure 4). Correlation of the different phenotypes with the various mutations will require further evaluation. Our family 1 has a less severe syndrome than family 2, but both kindreds share muscle weakness and atrophy, vocal cord paresis, and skeletal abnormalities. Our family 2 has prominent sensory loss and reduced SNAP amplitudes, which is uncommon in the other reported families and occurred in only 7/42 subjects (17%) in the 5 families described by Auer-Grumbach et al.¹¹ Many TRPV channels play a role in several sensory functions and TRPV4 is found in dorsal root ganglion cells, so it is not surprising to find sensory deficits associated with a mutation in *TRPV4*.^{24,26}

Mutations in the *TRPV4* gene may cause a wide spectrum of clinical phenotypes that vary from familial skeletal dysplasias to axonal neuropathies. Mutations in this gene are not a common cause of CMT, as shown by their absence in the 20 additional cases screened in this study. However, clinical neurologists should think of the *TRPV4* gene when they identify a patient with axonal neuropathy and vocal cord paresis, especially if associated with short stature. In addition, families with metaphyseal dysplasia and mutations in *TRPV4* should be investigated further for subtle signs of axonal neuropathy.

DISCLOSURE

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