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Case Report

A novel p.Va137A1a mutation in the GJB1 gene of a Chinese family with X-linked recessive Charcot-Marie-Tooth disease: a case report and literature review

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Abstract: We report a rare case of X-linked recessive Charcot-Marie-Tooth disease (CMTXR) in a Chinese male with a nucleotide variation of c.110T>C (p.Va137A1a) in gap junction protein β1 (GJB1) gene. To our knowledge, this is the first report linking the c.110T>C (p.Va137A1a) variant in the GJB1 gene to CMTXR. A 43-year-old Chinese man presented with poor movement of lower limbs for more than twenty years, recurrent lumbar pain for five years and difficulty walking for one month. The patient displayed tetraparesis. He suffered from amyotrophy of hypothenar eminences, bilateral leg muscles and thenar, pes cavus, and the disappearance of tendon reflexes in both lower limbs. The pathological signs were negative. The patient's grandfather and elder male cousin had similar symptoms. We performed genetic testing on the patient and his immediate family members. Results showed that the patient had a nucleotide variation (c.110T>C) in the GJB1 gene located on the X-chromosome that resulted in an amino acid change (p.Va137A1a). No large fragment variations in the PMP22 gene were found. Testing of the patient's immediate family members showed that his mother, younger sister, daughter, and third nephew were heterozygous carriers of the c.110T>C GJB1 gene variant.

Keywords: X-linked recessive Charcot-Marie-Tooth, GJB1 gene, c.110T>C, p.Va137A1a

Introduction

Charcot-Marie-Tooth disease (CMT) is a hereditary peripheral sensory and motor neuropathy [1]. It was first proposed by Charcot, Marie, and Tooth in 1886, and has an incidence rate of about 1/2500 [2]. From a genetic point of view, CMT is primarily an autosomal dominant (AD) disease, with rare occurrence as autosomal recessive (AR), X-linked dominant (XD), and X-linked recessive (XR) cases [3]. They are classified (CMT 1-7) based on the abnormalities and dysfunction of the myelin structure, development, and function [4]. According to neuroelectrophysiological and pathological features, CMT can be divided into demyelinating type (CMT1 type) which is characterized with a median nerve conduction velocity < 38 m/s; axonal type (CMT2 type) with median nerve conduction velocity >38 m/s, and intermediate type (ICMT type) in which demyelination and axonal variability coexist and median nerve conduction velocity is 25~45 m/s [5]. CMT can be further divided based on the underlying genetic cause, of which more than 80 genes have been implicated [6]. The main pathogenic mechanism involves mutation in genes that affect the cytoskeletal formation of myelin, cell membrane information transmission function, axonal transport and mitochondrial metabolism [7]. The main clinical manifestations of CMT include age of onset, distal extremity muscle weakness and muscle atrophy, sensory disturbances, reduced or absence of tendon reflexes, and skeletal deformities such as pes cavus and scoliosis [8]. Recently, we encountered a male patient who was initially misdiagnosed with osteoarthritis but was subsequently diagnosed

Table 1. Summary of nerve conduction velocity tests

Nerve	Stimulation	Latency (ms)	Amp (mV)	Velocity (m/s)
Motor				
Lt. ulnar	Wrist-ADM	2.67 (< 3.1)	10.0 (>7.0)	
	Elbow-Wrist	7.99	5.3	50.8 (>50.0)
Rt. ulnar	Wrist-ADM	3.4 (< 3.1)	5.5 (>7.0)	
	Elbow-Wrist	9.71	3.8	39.6 (>50.0)
Lt. median	Wrist-APB	4.66 (< 4.0)	0.98 (>7.0)	
	Elbow-Wrist	12.1	0.78	34.9 (>50.0)
Rt. median	Wrist-APB	4.66 (< 4.0)	0.88 (>7.0)	
	Elbow-Wrist	11.4	0.55	34.9 (>50.0)
Lt. common peroneal			No response	
Rt. common peroneal			No response	
Sensory			(μV)	
Lt. ulnar	Digit V-Wrist	2.45	9.4 (>7.0)	42.9 (>45.0)
Rt. ulnar	Digit V-Wrist	2.67	3.9 (>7.0)	43.1 (>45.0)
Lt. radial	Wrist-Digit I	3.16	11.2 (>5.0)	45.9 (>40.0)
Rt. radial	Wrist-Digit I	2.53	5.2 (>5.0)	45.5 (>40.0)
Lt. median	Digit III-Wrist	2.68	4 (>6.5)	46.6 (>46.5)
Rt. median	Digit III-Wrist	3.3	1.76 (>6.5)	43.9 (>46.5)
Lt. superficial peroneal	Middle fibula-Acrotarsium	4.09	1.65 (>5.0)	46.6 (>40.0)
Rt. superficial peroneal	Middle fibula-Acrotarsium	3.14	5 (>5.0)	48 (>40.0)
Lt. sural	Sural point-Lateral malleolus	1.79	3.2 (>5.0)	48.5 (>42.0)
Rt. sural	Sural point-Lateral malleolus	2.51	1.12 (>5.0)	47.8 (>42.0)

Abbreviations: SNCS Sensory Nerve Conduction Study, *MNCS* Motor Nerve Conduction Study, *Amp-amplitude, Lt left, Rt-right*, *APB* abductor pollicis brevis, *ADM* abductor digiti minimi.

with CMTXR based on genetic testing. The patient carries a c.110T>C mutation in the gap junction protein β1 (GJB1) gene that to our knowledge has not been previously reported.

Case report

A 43-year-old Chinese man was presented with poor movement of his lower limbs for more than twenty years, recurrent lumbar pain for five years and difficulty walking for one month. Physical examination showed lumbar scoliosis, limitation of activity, and interspinous tenderness in the L3/4, L4/5, L5/S1. Lasegue's sign and Bragard's sign were positive. He was initially diagnosed with Osteoarthritis (Lumbar). Routine blood tests showed WBC was 7.4× 10^9/L, neutrophil was 64.1%, erythrocyte sedimentation rate (ESR) was 10.00 mm/h, C reactive protein (CRP) was < 3.0200/L, antistreptolysin O (ASO) was 79.90 IU/ml, rheumatoid factor (RF) was < 11.50 IU/ml, and glucose was 5.85 mmol/L. Lumbar vertebrae magnetic resonance imaging (MRI) showed lumbar degenerative changes, bulging of the disk in L3/4, L4/5 and L5/S1, and an abnormal signal of the intervertebral foramen in T12/L1. The patient suffered from amyotrophy of thenar and hypothenar eminences and bilateral leg muscles, pes cavus, and an absence of tendon reflexes in both lower limbs. The proximal muscle strength of the upper limbs was grade 5, the right hand fingers in order to separate, close and opposition were grade 4^-, the left hand fingers were grade 4^+. Double lower extremity flexion muscle strength was grade 5, knee extension muscle strength was grade 4^-, bilateral ankle extensor strength was grade 4^-, flexor strength was grade 4^+, right toe extension muscle strength was grade 2^+, left toe back muscle strength was grade 1^+ and both toe flexor strength was grade 4^-. The pathological sign was negative. The nerve conduction velocity test indicated peripheral nerve injury (both sensory and motor involvement) (**Table 1**). Specifically, the bilateral conduction velocity and amplitude of the common peroneal nerve were not detected. The patient had no special medi-

Table 2. Summary of genetic tests

Nucleotide change	Amino acid change	Exon/ Intron	Variation type	Prediction of protein functional damage	ACMG grade
c.110T>C	p.Val37Ala	Exon 2	Hemizygote (male X chromosome)	Deleterious; Probably damaging; Disease_causing	Clinical significance unknown

Abbreviations: ACMG American College of Genetics and Genomics.

Table 3. Summary of genetic testing of family members

Father	Mother	First niece	Second niece	Third nephew	Eldest sister	Younger sister	Daugher
No variation	Heterozy-gosis	No variation	No variation	Hemizygote (male X chromosome)	No variation	Heterozy-gosis	Heterozy-gosis

cal history. The patient's grandfather and elder male cousin had similar symptoms. The grandfather died at the age of 73 due to acute cerebral infarction. With informed consent, we performed genetic tests on the patient and his family including the patient's mother, father, two sisters, two nieces, third nephew, and daughter. Our analysis identified a nucleotide variation (c.110T>C) in the GJB1 gene in the patient's DNA (**Table 2**) that resulted in an amino acid change (p.Va137A1a). The patient's mother, younger sister, daughter, and third nephew were heterozygous carriers of the c.110T>C variant (**Table 3**). We were unable to perform genetic testing on the elder male cousin because he refused to provide a blood sample. The third nephew carried the c.110T>C variant but has not showen symptoms associated with CMTXR, likely because he was only 13 years old at the time of testing. It will be important to follow this individual for potential signs of disease onset. None of the patient's family members who participated in the genetic testing had symptoms. Based on the physical findings, nerve conduction results and the families pedigree analysis (**Figure 1**), we deduced that the patient had CMTXR and that the phenotype was typically characterized by a mixture of demyelinating and axonal features, consistent with a ICMT sub-type.

Discussion

With informed consent to genetic testing, we identified a c.110T>C variation in the GJB1 gene located on chromosome X. No large fragment variations in the PMP22 gene were detected. The patient's mother, younger sister, daughter and third nephew carried the same heterozygous mutation. GJB1 is located on chromosome X, and the c.110T>C mutation is located in exon 2 and resulted in a Val to Ala amino acid change at position 37 (p.Val37Ala) (**Table 2**). Sorting Intolerant From Tolerant (SIFT), Polyphen 2, and Mutation Taster software predicted that the p.Val37Ala change affects the function of the GJB1 protein. Interestingly, a mutation at the same location, c110delT, has been described to be associated with X-linked hereditary skeletal muscle atrophy (CMT, X-linked) [9].

The c.110T>C mutation is not a polymorphic change and occurs very rarely in the population. Patients in this family were all male. Female family members were not symptomatic. There was a tendency of intergenerational disease, which presented cross genetics with male disease-causing genes being passed only to daughters. The causative genes of male patients can only come from mothers carrying the disease-causing genes. In our case, the mutation found in the GJB1 gene of the patient was inherited from his mother, who was heterozygous for the mutation. The patient's father did not have the variation. This is consistent with CMTXR, which is the least common of the four genetic subtypes (AR, AD, XD, and XR).

Table 4 summarizes the heterogeneity in underlying genetic causes of Charcot-Marie-Tooth Disease [10-19]. Only by understanding the clinical characteristics of the disease and its relationship to specific genetic mutations can we help to clarify the issues with genetic data analysis. Most of the literature link GJB1 mutations to CMTXD, while mutations in GJB1 leading to CMTXR are rare [20]. The GJB1 gene, also known as the Connexin32 (CX32) gene, is located at q13.1 on the X chromosome and encodes the gap junction protein β1 (GJB1) or Connexin32 (CX32) [21]. GJB1 consists of 283

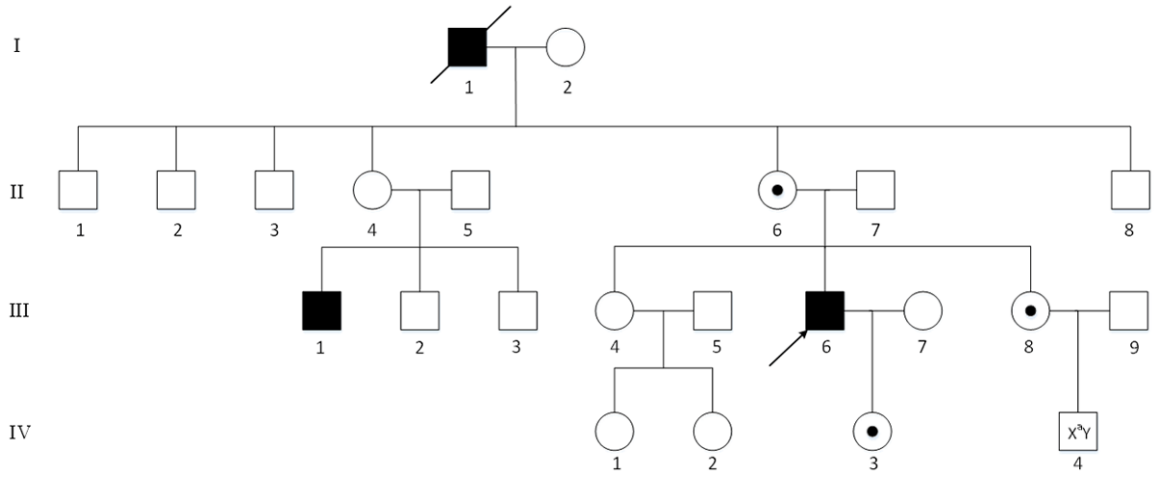

Figure 1. Family pedigree, Circles and squares represent women and men, respectively. Diagonal lines indicate deceased. Black indicates the affected member. The arrow indicates the proband. ⊙ indicates heterozygous.

amino acid residues, including four transmembrane domains, two extracellular loops, one intracellular loop, with both C-terminus and N-terminus located intracellularly [22]. GJB1 plays an important role in cellular communication. Gap junction proteins are components of intercellular pathways that accelerate the transport of nutrients and small molecules with intercellular communication signals [23]. The GJB1 gene is expressed in liver, pancreas, kidney and nervous tissues. In neural tissue, gap junction protein 1 is located in the membrane of Schwann cells [24]. Gap junction protein 1 forms a passage through the myelin, allowing efficient transport between the outer myelin layer and the inner Schwann cells. More than 400 mutations in this gene have been reported [25]. Some mutations produce proteins that are too long or too short, and most mutations result in amino acid changes in this protein. It is unclear how the GJB1 mutation causes demyelination or nerve impulse conduction to slow down. Though nonsense mutations, deletion mutations, insertion mutations, and frameshift mutations have also been reported, approximately 80% of *GJB1* mutations were missense [26], and it is a missense mutation in our report.

From this case and review of literature, we conclude that CMTXD patients can have typical CMT symptoms mostly in children or young people, characterized by slowly progressive weakness and atrophy of the distal muscles of the upper and lower extremities, especially the distal muscles of the lower extremities. It can be a typical foot deformity, accompanied by mild to moderate sensory disturbances at the distal end of the limb and weakened or diminished tendon reflexes. Most patients have difficulty walking and unusual gait. There are atypical symptoms such as pes cavus, hammer toes, scoliosis, flexion deformity of the toe and claw-shaped hand, and half of the patients have a positive family history [7]. The patients were all male, and females were only carriers of the mutated gene and do not have any clinical manifestations. In our case report, an abnormal gait due to the weakness of the distal lower extremities was the main symptom. However, this patient was unable to determine the exact onset time because it did not affect normal life at first. The disease progress slowly, and many people can have no clinical symptoms in the beginning. We believe that the actual disease onset time for this patient should be earlier than the time when clinical symptoms appeared.

With the advancement of molecular genetics, a genetic diagnosis has gradually become the main approach for the diagnosis of CMT. However, about 10% of patients' pathogenic genes are still unclear. It is speculated that the mutant protein may be prematurely degraded or banned from the cell and cannot reach the cell membrane to form a gap junction. Some mutant proteins reach the cell membrane but do

Table 4. Genetic Heterogeneity of Charcot-Marie-Tooth Disease

Type	Locus	Inheritance	Gene
CMT1A	17p11.2	AD	PMP22
CMT1B	11q22	AD	MPZ
CMT1C	16p13.3-p12	AD	LITAF/SIMPLE
CMT1D	10q21.1-q22.1	AD	EGR2
CMT1E	17p11.2	AD	PMP22
CMT1F	8p21	AD	NEFL
CMT2A1	1p36.2	AD	MFN2
CMT2A2	1p36	AD	KIF1B
CMT2B	3q21	AD	RAB7
CMT2C	12q23-q24	AD	Unknown
CMT2D	7p14	AD	GARS
CMT2E	8p21	AD	NEFL
CMT2F	7q11-q21	AD	HSP27
CMT2K	8q13-q21.1	AR	GDAP1
CMT2L	12q24	AD	HSP22
CMT4A	8q13-q21.1	AR	GDAP1
CMT4B1	11q22	AR	MTMR2
CMT4B2	11p15	AR	SBF2
CMT4B3	22q13.3	AR	SBF1
CMT4E	10q21-q22	AR	EGR2
CMTX1	Xq13.1	XD or XR	CX32/GJB1
CMTX2	Xp22.2	XR	Unknown
CMTX3	Xq26	XR	Unknown
CMTX4	Xq24-q26.1	XR	Unknown
CMTX5	Xq22.3	XR	Unknown
CMTX6	Xp22.11	XR	PDK3
DI-CMT A	10q24.1-q25.1	AD	Unknown
DI-CMT B	19p13.2-p12	AD	DNM2
DI-CMT C	1p34	AD	YARS

Abbreviations: PMP22 peripheral myelin protein 22, MPZ myelin protein zero, *EGR2* early growth response 2, *MFN2* mitofusin 2, *KIF1B* kinesin family member 1B, *RAB7* Ras-associated protein 7, *GARS* glycyl-tRNA synthetase, *NEEL* neurofilament light chain, *HSP27* heat shock protein 27, *GDAP1* ganglioside induced differentiation associated protein-1, *HSP22* heat shock protein 22, *MTMR2* myotubularin-related protein 2, *SBF2* SET-binding factor 2, *SBF1* SET-binding factor 1, *CX32/GJB1* connexin32/gap junction protein β1, *PDK3* pyruvate dehydrogenase kinase isoenzyme 3, *DNM2* dynamin 2, *YARS* tyrosyl-tRNA synthetase.

not form a functional pathway normally, whereas channels that lose normal function reduce the normal activity of Schwann cells [25]. These abnormal channels can also interfere with the communication between Schwann cells and intrinsic nerve cells, thereby affecting the conduction of nerve impulses.

Conclusion

The GJB1 gene mutation (c.110T>C) found in the genetic test of this patient has not been reported in the Human Gene Mutation Database (HGMD). There is no information on the frequency of this mutation in normal populations. The case in this report adds to the catalog of GJB1 gene mutations in CMTX patients in China. We should carry out the genetic testing as early as possible to improve diagnosis of patients and make hereditary inquiries in a patient's family. For disease-causing gene carriers who want to have a baby, prenatal genetic diagnosis and specific genetic counseling should be done to avoid the birth of CMTXR baby [27]. For carriers of the gene without clinical symptoms or in an early stage, close follow up and active treatment can be taken to delay the onset and prevent pes cavus or scoliosis. Finally, establishing an accurate genetic location and diagnosis will further expand our understanding of the key mechanisms, which is the best way to design more comphrensive treatments.

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Informed consent was obtained from the patient and this case report was approved by the ethics committee of the Second Hospital of Dalian Medical University.

Disclosure of conflict of interest

None.

Abbreviations

ACMG, American college of genetics and genomics; AD, autosomal dominant; AR, autosomal recessive; ASO, anti-streptolysin O; CX32,

connexin32; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; GJB1, gap junction protein β1; HGMD, human gene mutation database; ICMT type, intermediate type; MRI, magnetic resonance imaging; RF, rheumatoid factor; SIFT, sorting intolerant from tolerant; CMTXD, X-linked dominant Charcot-Marie-Tooth disease; CMTXR, X-linked recessive Charcot-Marie-Tooth disease; XD, X-linked dominant; XR, X-linked recessive.

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