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Novel gap junction protein beta-1 gene mutation associated with a stroke-like syndrome and central nervous system involvement in patients with X-linked Charcot–Marie–Tooth Type 1: A case report and literature review

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ABSTRACT

Gap junction protein beta-1 (*GJB1*) gene mutations lead to X-linked Charcot–Marie–Tooth Type 1 (CMTX1). We studied a Chinese family with CMTX1 and identified a novel *GJB1* point mutation. Our patient had a transient stroke-like clinical manifestations and magnetic resonance imaging (MRI) changes. An analysis of the genomic DNA of the proband showed a T to C hemizygous mutation in the *GJB1* gene at nucleotide position 380, causing a predicted amino acid change from isoleucine to threonine at codon 127, which predicted structural alterations disrupting the function of the *GJB1* protein. This novel point mutation expanded the spectrum of *GJB1* mutations known to be associated with CMTX1. We performed a PubMed review of CMTX cases with central nervous system involvement in the English-language literature from the past 20 years, and summarized the demographic data, nucleotide and amino acid changes, clinical characteristics, clinical manifestations, and neuroimaging features.

1. Introduction

Charcot–Marie–Tooth (CMT) disease is one of the most common hereditary motor and sensory neuropathies. Its inheritance pattern can be autosomal dominant, autosomal recessive, X-linked dominant, or X-linked recessive. Based on the motor nerve conduction velocity (NCV) of the median nerve, CMT is divided into Type 1 (demyelination injury) and Type 2 (axon injury). The clinical phenotype is characterized by progressive muscle atrophy and weakness, areflexia, and variable sensory abnormalities. Central nervous system (CNS) manifestations sometimes occur. Here, we report a Chinese family with a novel X-linked CMT Type 1 (CMTX1) mutation in the *GJB1* gene, c.380 T > C (p.I127 T), which was associated with a recurrent stroke-like syndrome and CNS involvement. We reviewed all CMTX cases with CNS involvement reported in the past 20 years. All procedures in this research were approved by the Ethical Committee at Chinese PLA General Hospital (Beijing, PR China) and the Informed Consent was taken from the guardian.

2. Case presentation

A 20-year-old man presented with recurrent numbness of the lips and right upper limb, followed by dysarthria and dysphagia four times in 3 d. During each episode, these symptoms disappeared after 3–4.5 h and then returned 3.5–5 h later. Both distal lower limbs remained weak after the last episode. He had foot drop since he was 10 years old. His family members (mother, maternal cousin, and maternal grandfather) had pes cavus and foot drop; however, none of these family members experienced similar transient neurological episodes.

Physical examination revealed weakness of the distal lower limbs (Medical Research Council Grade 3–5–; ankle dorsiflexion worse than plantar flexion), hypo- or areflexia of all four limbs, and pes cavus. Brain magnetic resonance imaging (MRI) on Day 3 showed a hyperintense signal on T2 images and a hyperintense signal on fluid-attenuated inversion recovery (FLAIR) images in the white matter bilaterally. This was most prominent posteriorly and involved the splenium of the corpus callosum (Fig. 1A–C), with no enhancement. Laboratory tests, including a complete blood count, electrolytes, renal function,

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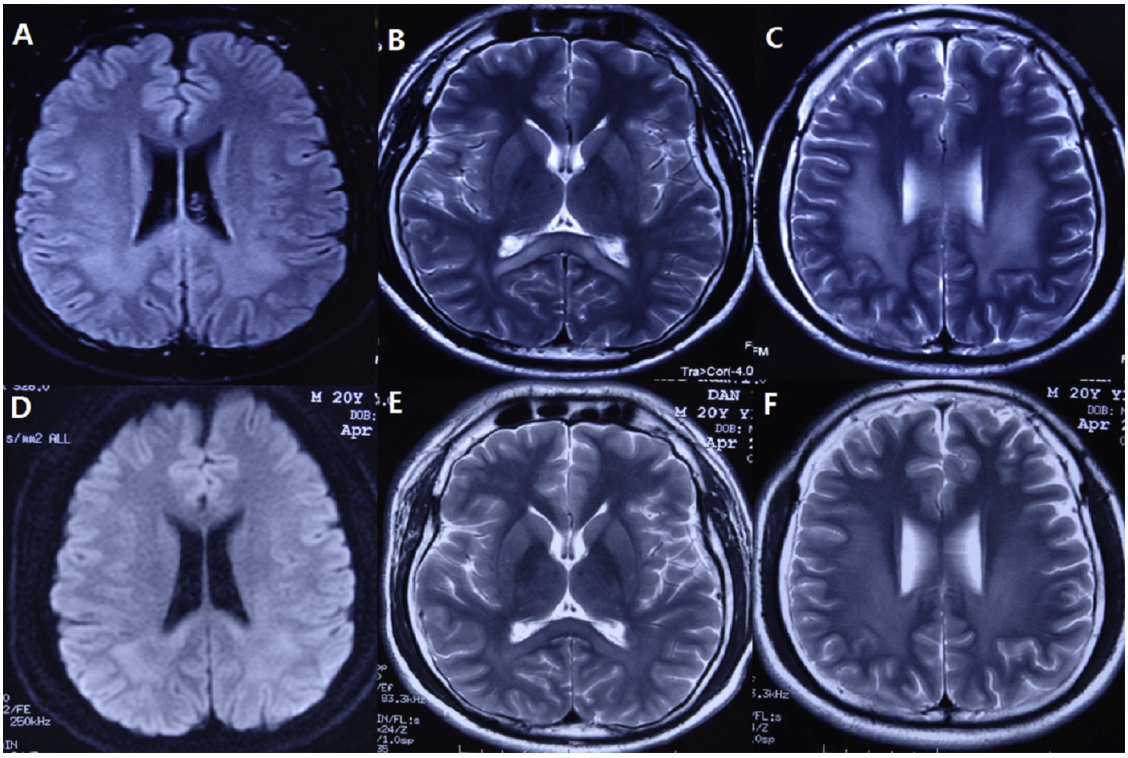

Fig. 1. Magnetic resonance imaging (MRI) on Day 3 (A: FLAIR image, B&C:T2-weighted image) and Day 9 (D: FLAIR image, E&F:T2-weighted image).

coagulation parameters, urinalysis, and urine toxicology screen, were normal. The cerebrospinal fluid (CSF) contained mildly elevated protein (651.1 mg/L) with a normal white blood cell count. MR angiography of the intracranial vessels and electroencephalography (EEG) were normal. His electromyography showed peripheral neuropathy. The motor NCV was markedly reduced (range 26.5–35.9 m/s) in the median, ulnar, common peroneal, and tibial nerves. The amplitude of the compound muscle action potential (CAMP) was also reduced (range 0.2–5.3 mV) in these nerves. No sensory nerve action potential (SNAP) was elicited in the right median, right ulnar, or bilateral sural nerves. The SNAP and sensory conduction velocity (SCV) were reduced in the right median (2.0 mV, 40.0 m/s) and ulnar (3.7 mV, 38.2 m/s) nerves.

Brain MRI of the patient's mother was normal, but her electromyography showed inactive denervation in the bilateral first dorsal interosseous, gastrocnemius, and tibialis anterior muscles. She had normal findings in the biceps and quadriceps bilaterally, the motor conduction velocity, and amplitude of CAMP, SCV, and SNAP in all four limbs. These results indicated subclinical peripheral nerve damage.

The patient recovered completely with no specific treatment, with only minimal weakness in ankle dorsiflexion remaining. Brain MRI performed on Day 9 (Fig. 1D–F) showed complete recovery of the hyperintense signal in the FLAIR images and partial recovery of the abnormal T2 signal, with some mild areas of persistent hyperintense T2 signal in the white matter.

Subsequent analysis of genomic DNA of the proband showed a T to C hemizygous mutation at nucleotide position 380 in GJB1, predicting an amino acid change from isoleucine to threonine at codon 127; this was not reported in GenBank. Gene analysis of his mother showed a heterozygous mutation at the same position, whereas his father's gene test was normal (Fig. 2). Because of the clinical manifestations, electromyography, and gene test results, CMTX1 was ultimately diagnosed.

3. Literature review

We searched the PubMed (http://www.ncbi.nlm.nih.gov/pubmed) database using the terms "X-linked Charcot–Marie–Tooth," "CMTX," or "X-linked CMT." The following limitations were used: English-language only, published from 1998 to 2017, and CNS involvement (including MRI or EEG changes or other evidence of CNS involvement). Exclusion criteria were: 1) no CNS changes in the imaging or electrophysical examination, or clinical manifestations; and 2) CMTX cases with other CNS disease (e.g., mitochondrial disease). Fig. 3 shows a flow diagram of the literature search.

Table 1 [1–21] summarizes the demographic data of 49 cases found in the literature review. There was male predominance (male:female = 44:5). The mean age of onset was 15 years and the mean age of follow-up was 25 years. Nucleotide and amino acid changes were also seen. The clinical characteristics and manifestations are shown in Table 2. Clinically, 38.8% (19/49) of the patients had reversible symptoms, and 24.5% (12/49) of the patients had hemiparesis. Dysarthria was seen in 32.7% (16/49) and dysphagia in 22.4% (11/49). In addition, pes cavus was observed in 61.2% (30/49) and numbness occurred in 38.8% (19/49).

In terms of abnormal imaging findings, white matter lesions were reported in 95.8% (47/49) of patients, some of which were demyelinating-like foci [1,8]. In addition to high signal intensities in the white matter of T2-weighted images (and/or diffusion-weighted images), we also found one case with reduced cerebellar blood flow on single-photon emission computed tomography [3]. In another case, there were no MRI alterations, but EEG changes indicated that the CNS was affected [1].

4. Discussion

CMTX1 is typically caused by mutations in *GJB1* mapped to chromosome Xq13 [22]: more than 400 *GJB1* mutations have been identified [23]. Connexins, which participate in the formation of intercellular gap junctions, are expressed in both glia and neurons of the CNS [2]. There are 21 members of the connexin family in humans [13]. *GJB1* encodes connexin 32, a 283-amino-acid gap junction protein expressed in peripheral nerve Schwann cells and myelinating oligodendrocytes in the CNS [24,25]. Connexin 32 is involved in the transport of ions,

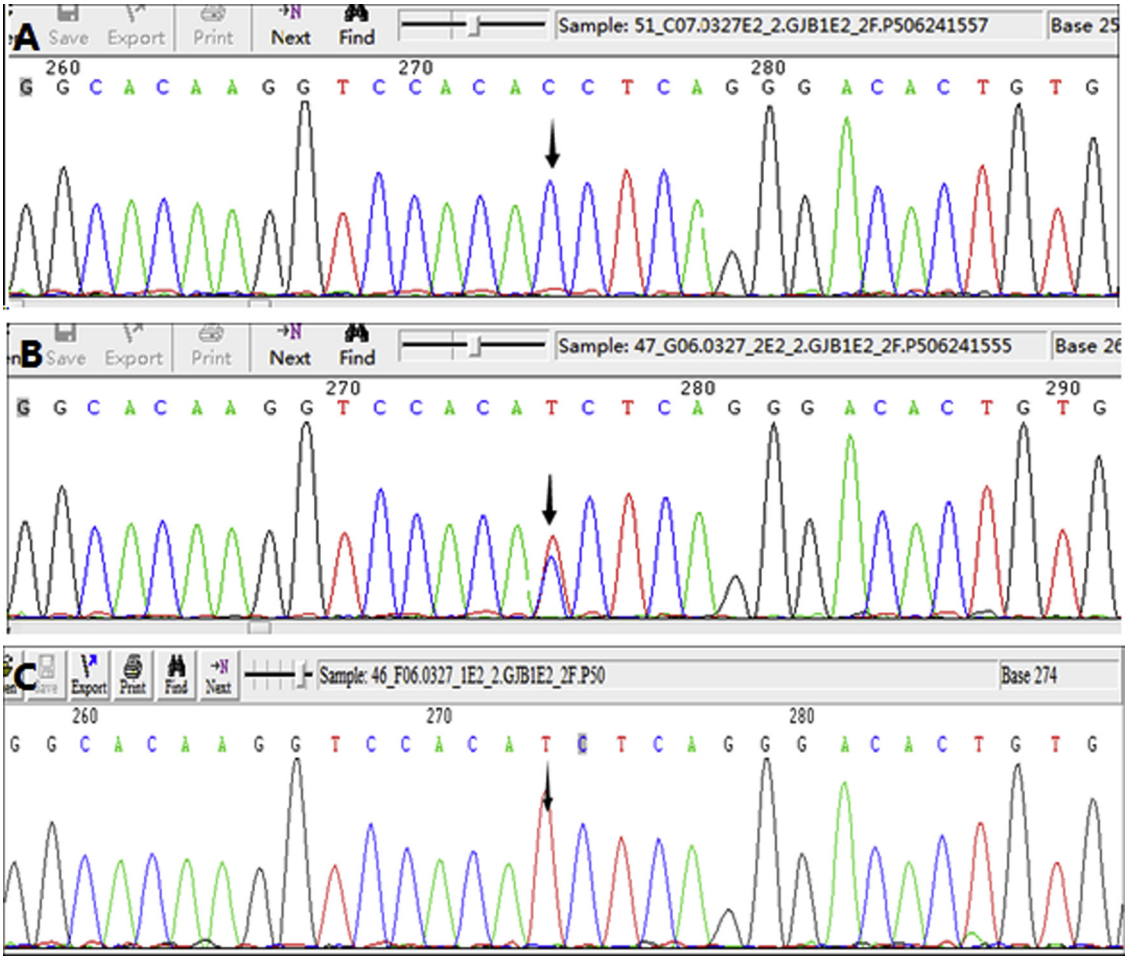

Fig. 2. Genetic testing results for the A) proband, and his B) mother and C) father.

signaling molecules, and small metabolites, and provides pathways for electrical and chemical coupling between cells [26,27]. Our novel mutation (c.380 T > C) was in a region of connexin 32 that is highly conserved across all mammalian species [21]. Two other alterations have already been reported [21,28] at nucleotide position 380 of *GJB1*: c.380 T > A and c. 380 T > G. MutationTaster software predicted that this mutation likely leads to loss of the topo-domain of the cytoplasmic protein.

CNS involvement is a special feature in CMTX1, and many patients with CMTX1 have abnormal evoked potentials [2]. In a recent study of

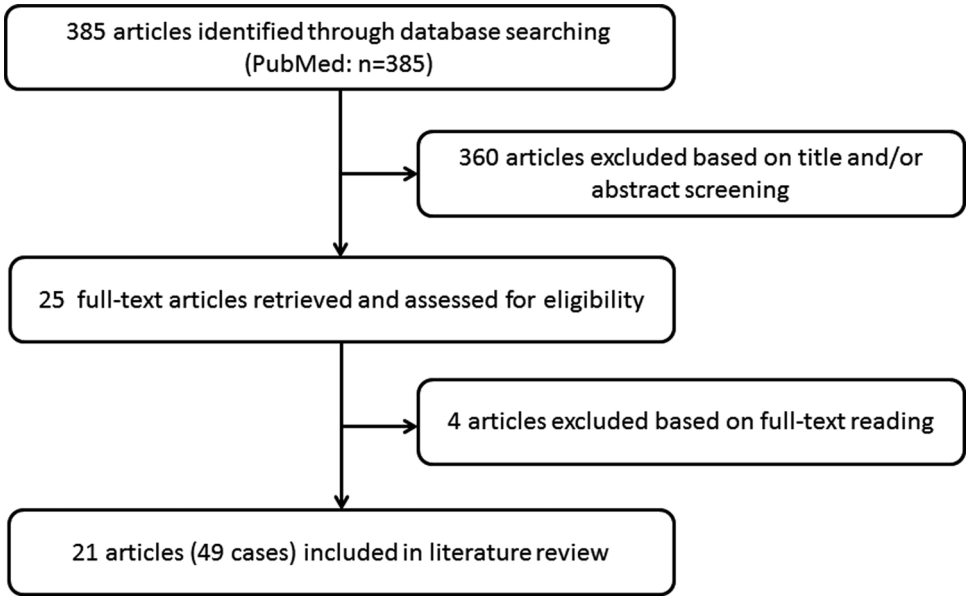

Fig. 3. Flow diagram of the literature search.

Table 1
Demographic data and nucleotide and amino acid changes. NM, not mentioned.

Patient Number	Source	Sex/Age			Gene/Amino Acid	
		Age	Onset Age	Sex	Nucleotide Changes	Amino Acid Changes
1	M Panas, 1998 [1]	19	19	M	c.164C > T	p.T55I
2	M Panas, 1998	63	54	M	c.164C > T	p.T55I
3	M Panas, 1998	21	10	M	c.164C > T	p.T55I
4	M Panas, 1998	58	48	M	c.491 G > A	p.R164Q
5	H Schelhaas, 2002 [2]	14	4	M	c.490C > T	p.R164W
6	H Kawakami, 2002 [3]	16	10	M	c.163_183dup	p.Y55_N61dup
7	M Lee, 2002 [4]	33	25	F	E109Stop	/
8	R Taylor, 2003 [5]	15	12	M	c.285C > T	p.R75W
9	C Hanemann, 2003 [6]	10	10	M	c.304_306delGAG	p.Q102del
10	C Hanemann, 2003	19	infancy	M	c.304_306delGAG	p.Q102del
11	J Kassubek, 2005 [7]	20	infancy	M	c.304_306delGAG	p.Q102del
12	R Basri, 2007 [8]	41	21	F	NM	p.R142W
13	C Fusco, 2010 [9]	14	14	M	c.491 G > A	p.R164Q
14	G Anand, 2010 [10]	7	7	M	c.530 T > C	p.V177A
15	T Rosser, 2010 [11]	10	10	M	c.65 G > A	p.R22Q
16	J.M. U-King-Im, 2011 [12]	11	11	M	c.196 G > A	p.D66N
17	C Stancanelli, 2012 [13]	61	35	F	c.41 A > G	p.N14S
18	J Mckinney, 2014 [14]	12	12	M	c.98 T > A	p.I33N
19	M Appu, 2014 [15]	14	14	M	c.179 G > A	p.C60Y
20	G Karadima, 2014 [16]	50	teens	M	c.191 G > A	p.C64Y
21	G Karadima, 2014	32	childhood	M	c.508 G > T	p.V170F
22	M Al-Mateen, 2014 [17]	14	14	M	c.260C > G	p.P87L
23	M Al-Mateen, 2014	17	10	M	c.477 G > A	p.V139M
24	Y Zhao, 2014 [18]	15	15	M	c.278 T > G	p.M93A
25	A Sagnelli, 2016 [19]	29	16	M	c.297_298insCAA	p.Q99_H100insQ
26	C Xie, 2016 [20]	24	18	M	c.445 T > C	p.F149L
27	C Xie, 2016	70	25	M	c.445 T > C	p.F149L
28	Y Lu, 2017 [21]	34	21	M	c.44 G > T	p.R15L
29	Y Lu, 2017	14	11	M	c.59 T > G	p.I20T
30	Y Lu, 2017	23	8	M	c.62 G > A	p.G21D
31	Y Lu, 2017	13	10	M	c.115 G > T	p.A39S
32	Y Lu, 2017	20	15	F	c.194 A > G	p.Y65C
33	Y Lu, 2017	24	14	M	c.263C > A	p.A88D
34	Y Lu, 2017	17	14	M	c.379 A > T	p.I127F
35	Y Lu, 2017	18	12	F	c.380 T > A	p.I127N
36	Y Lu, 2017	37	24	M	c.403_404insT	Y135fsX146
37	Y Lu, 2017	19	10	M	c.424C > T	p.R142W
38	Y Lu, 2017	50	32	M	c.424C > T	p.R142W
39	Y Lu, 2017	34	24	M	c.425 G > A	p.R142Q
40	Y Lu, 2017	15	10	M	c.425 G > A	p.R142Q
41	Y Lu, 2017	24	14	M	c.490C > T	p.R164W
42	Y Lu, 2017	13	11	M	c.533 A > G	p.D178G
43	Y Lu, 2017	44	42	M	c.548 G > A	p.R183H
44	Y Lu, 2017	26	18	M	c.548 G > A	p.R183H
45	Y Lu, 2017	27	15	M	c.547C > T	p.R183C
46	Y Lu, 2017	19	12	M	c.556 G > A	p.E186K
47	Y Lu, 2017	21	11	M	c.590C > T	p.A197V
48	Y Lu, 2017	19	14	M	c.614 A > G	p.N205S
49	Y Lu, 2017	12	1	M	c.818_819insGGGCT	p.L273fs

Chinese patients with CMTX1 [23], dysarthria and hemiparesis were the main symptoms; CNS symptoms developed after peripheral neuropathy symptoms in some patients. Our literature review indicated that numbness, dysarthria, and hemiparesis were the main common symptoms of CMTX1. More than 95% of the patients in our study had white matter lesions on brain MRI, most of which were bilateral. Lesions were also found in other areas, including the splenium of the corpus callosum, centrum semiovale, corticospinal tracts, and internal capsule, some of which were enhanced with gadolinium.

The exact mechanism of CMTX1 remains unclear. It has been postulated that mutated connexin 32 leads to abnormal connexin gating, voltage conductance, and permeability or pH dependence within oligodendrocytes [2]. Schwann cell and oligodendroglial connexins may be important in the spatial buffering of potassium during neuronal activity [2]. The diffusion of ions and small molecules may be restricted by connexin 32 mutations, which results in nerve function deficits [18].

CNS dysfunction is transient in CMTX1 [6,11,18,29–31]. Further, transient white matter lesions were observed in some cases [6,18,30]. The patients recovered completely without specific therapy. Disruptions in communication via the gap junctions between oligodendrocytes and astrocytes may be related to the CNS manifestations observed with *GJB1* mutations [5]. Abnormal gap junctions may lead to disordered communication between these two cell types [5,8,11,12], making both types more susceptible to abnormalities in the intercellular exchange of ions and small molecules under metabolic stress [29]. Sato *et al.* hypothesized that the transient CNS manifestations in CMTX were caused by reversible axonal damage in the white matter, resulting from the expression of mutant connexin 32 in oligodendrocytes [32].

Animal studies suggest that axon loss is secondary to demyelination in most forms of demyelinating CMT [2]. *GJB1* mutations lead to white matter abnormalities and CNS symptoms due to chronic demyelination because the communication between glial cells and neurons is disrupted, as some brain MRI showed demyelination-like lesions [8,29]. A recent animal study suggested that the already compromised oligodendrocyte homeostasis causing subclinical manifestations at baseline may decompensate under metabolic or inflammatory stress, leading to

Table 2
Clinical characteristics and manifestations.

Patient No.	Reversibility	Weakness	Dysarthria	Dysphagia	Pes excavatus	Numbness	White matter lesion(s)
1	NM	Y	Y	Y	Y	NM	Y
2	NM	N	N	N	Y	NM	Y
3	NM	Y	NM	NM	NM	NM	N
4	NM	N	N	N	NM	NM	Y
5	Y	Y	Y	Y	Y	N	Y
6	NM	N	Y	NM	Y	N	N
7	NM	NM	NM	NM	NM	NM	Y
8	Y	Y	Y	Y	NM	Y	Y
9	Y	Y	Y	N	Y	NM	Y
10	Y	N	Y	Y	NM	NM	Y
11	NM	N	NM	NM	NM	Y	Y
12	Y	N	Y	NM	Y	NM	Y
13	Y	Y	Y	NM	NM	NM	Y
14	Y	N	N	N	Y	Y	Y
15	Y	Y	Y	Y	NM	NM	Y
16	Y	N	N	N	N	NM	Y
17	Y	N	Y	Y	Y	Y	Y
18	NM	Y	Y	NM	Y	Y	Y
19	N	N	NM	NM	Y	Y	Y
20	N	N	NM	NM	Y	Y	Y
21	Y	N	NM	NM	N	Y	Y
22	Y	N	Y	Y	N	NM	Y
23	N	Y	Y	NM	Y	NM	Y
24	Y	Y	Y	Y	N	Y	Y
25	N	NM	NM	NM	Y	NM	Y
26	Y	Y	Y	NM	Y	Y	Y
27	Y	Y	Y	NM	Y	NM	Y
28–49	Y for 4/22	NM	NM	Y for 4/22	Y for 16/22	Y for 14/22	Y for 22/22

transient encephalopathy manifestations [33]. Ying *et al*. hypothesized that antigen exposure in Schwann cells or myelin triggers an autoimmune reaction that leads to abnormal brain MRI and CNS manifestations [34].

5. Conclusion

We report a new mutation in CMTX1, c.380 T > C (p.I127 T) in the *GJB1* gene. The reason for CNS involvement in patients with CMTX1 is unclear. On reviewing CMTX cases with CNS involvement reported over the last 20 years, we hypothesize that mutated connexin 32 leads to an abnormal microenvironment, as well as abnormal gap junctions. Further research should explore the mechanism of CNS involvement in CMTX.

Conflicts of interest

There is no conflict of interest.

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