Recurrent episodes of reversible posterior leukoencephalopathy in three Chinese families with GJB1 mutations in X-linked Charcot-Marie-tooth type 1 disease: case reports

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Case report

Keywords: X-linked form of Charcot-Marie-Tooth disease type 1, gap-junction beta-1 gene, reversible posterior leukoencephalopathy

Posted Date: August 21st, 2019

DOI: https://doi.org/10.21203/rs.2.13259/v1

Version of Record: A version of this preprint was published on December 16th, 2019. See the published version at https://doi.org/10.1186/s12883-019-1563-4.

Abstract

Background The X-linked form of Charcot-Marie-Tooth disease type 1(CMTX1) is an inherited peripheral neuropathy that arises in patients with mutations in the gap-junction beta-1 gene (GJB1). Case presentation Three young male patients from Southern China with pes cavus experienced multiple episodes of transient central nervous system (CNS) dysfunction. Three patients all had reversible posterior leukoencephalopathy as detected by brain diffusion-weighted magnetic resonance imaging (MRI-DWI). Nerve conduction velocity (NCV) showed sensorimotor polyneuropathy with mixed demyelinating and axonal features. Genetic testing indicated a c.425G>A (p. Arg 142 Glu) or c.563 C>T (p. Thr 188 Ile) or c.103G>C (p. Val 35 Leu) mutation in GJB1. The unique feature of this report is two novel mutations: c.563 C>T and sc.103G>C of GJB1 gene detected in two families respectively. Another unique feature is that peripheral neuropathy symptoms in three patients were insidious and found at the onset of CNS symptoms Conclusions Central nervous system involvement in patients with CMTX1 indicates that myelin damage in the CNS and peripheral nerve system may have similar pathogenetic mechanisms.

Background

The X-linked form of Charcot-Marie-Tooth disease type 1 (CMTX1) is an inherited peripheral neuropathy that arises in patients with mutations in the gap-junction beta-1 gene (GJB1). GJB1 encodes the transmembrane channel protein, connexin 32 (Cx32). Cx32 has been found in myelinating Schwann cells, oligodendrocytes, and astrocytes; it is believed to develop intracellular channels between adjacent myelin loops to form a pathway for small molecules or ions across the myelin sheath[1].

Here, we describe three patients from three families from South China with CMTX1 who experienced multiple episodes of transient central nervous system (CNS) dysfunction associated with reversible posterior leukoencephalopathy, which was confirmed by family history, brain magnetic resonance images (MRI), nerve conduction velocity (NCV), and GJB1 mutations. Two novel mutations of GJB1 gene were detected in our patients.

Case Presentation

Family 1. The proband, a 17-year-old male, was admitted to our hospital on July 25, 2018 after experiencing acute onset of profound dysarthria, chorea-choreiform movements, and confusion. His abnormal movements and confusion resolved over the course of several hours, but the slurred speech remained. In the following two days, he experienced two episodes of similar symptoms and recovered after few hours, but no triggering factors were identified.

A review of the patient's past records revealed that he had experienced an episode of weakness in all four limbs at the age of 12. The episode was of sudden onset and resolved completely over the course of three hours without special treatment. He was evaluated at once with head CT scanning and no abnormalities were found in the first episode.

His physical examination was notable for his pes cavus when he arrived in our department. A detailed pedigree of other family members revealed that the patient's mother, maternal grandfather, three maternal aunts, and so on also had pes cavus deformities, although none reported sudden onset of weakness or dysarthria episodes.

His neurological examination revealed the atrophy of his distal lower extremities, mild weakness of ankle dorsi- and plantar-flexion, absent deep tendon reflexes in the lower extremities, and negative bilateral Babinski signs.

Polymerase chain reaction (PCR) for Coxsackievirus IgG was positive in serum but negative for Coxsackievirus IgM. The rest of the routine serum analyses were within the normal range. A serum lactic acid exercise test was applied to exclude mitochondrial encephalomyopathy. Serum lactic acid before exercise was 3.49 mmol/L(0.63~2.44 mmol/L), 3.73 mmol/L after exercise, and 6.75 mmol/L 30 minutes after exercise. Cell count, protein, glucose, and chloride were normal in the cerebrospinal fluid (CSF). CSF and serum were negative for antibodies against AMPAR1 and AMPAR2, NMDAR, GABABR, LGI1, and Caspr2. A wide range of abnormalities in slow waves was found on the electroencephalograms (EEG). A brain diffusion-weighted magnetic resonance imaging (DWI) obtained on July 24, 2018 showed hyperintensities in the splenium of the corpus callosum and posterior subcortical white matter (Fig. 1-A). MR angiography (MRA) and MR spectroscopy (MRS) were normal. Two weeks later, a second MRI performed on August 6, 2018 showed only minor white matter lesions in the splenium of the corpus callosum and posterior periventricular areas. MRS was normal (Fig. 1-B). NCV and electromyography demonstrated a mild-to-moderate sensorimotor polyneuropathy with mixed demyelinating and axonal features. Genetic testing showed a c.425G>A (p. Arg 142 Glu) hemizygous point mutation in GJB1. His mother, older maternal aunt and her daughter, as well as a younger maternal aunt, who all had pes cavus also had the same point mutations in GJB1 (Fig. 2). CMTX1 coexistence with reversible posterior leukoencephalopathy was thus diagnosed by his family history, brain MRI, NCV data, and GJB1 mutation.

Intravenous methylprednisolone (500 mg/day for 3 days) followed by oral prednisolone (1 mg/kg/day) was administered because acute demyelinative encephalitis was diagnosed at arrival. Prednisolone was tapered when reversible posterior leukoencephalopathy was confirmed. The patient's slurred speech improved without episode onset of chorea-choreiform movements and confusion when he was discharged on August 7, 2018. He had recovered to his baseline and symptoms of peripheral neuropathy remained at a 3-month outpatient follow-up.

Family 2. The proband, a 15-year-old male, presented with acute onset of dysarthria, weakness, and numbness in all four limbs on February 16, 2018. In 2 hours, his symptoms had improved but he experienced another two episodes with similar symptoms and recovered after a few hours on the next day. The initial brain MRI DWI on February 17, 2018 showed hyperintensities in both posterior periventricular areas and subcortical white matter of occipital and parietal lobe (Fig. 3-A); MRA and MRS were normal. A possible diagnosis of adrenoleukodystrophy was made when he was admitted to our

hospital on March 3, 2018. His physical examination was normal except for pes cavus and diminished deep tendon reflexes in all extremities. The patient's mother, maternal grandfather, aunt and her daughter also had pes cavus (Fig. 4). His routine serum and CSF analyses were within normal range. The serum very-long-chain fatty acids, adrenal cortical hormones, and adrenal gland CT with enhancement were checked to exclude adrenoleukodystrophy and all were normal. The findings in EEGs were unremarkable. NCV indicated sensorimotor polyneuropathy on both upper and lower extremities. Eighteen days later, a second MRI performed on March 6, 2018 showed normal (Fig. 3-B). Whole-exome sequencing of this patient showed a c.563 C>T (p. Thr 188 Ile) hemizygous point mutation in GJB1.

He had recovered to his baseline without episodes of dysarthria, weakness, and numbness with no special treatment when he was discharged on March 13, 2018. He presented normal at a 3-month outpatient follow-up.

Family 3. The proband, an 18-year-old male, presented with acute onset of left arm weakness on January 24, 2019. Within 20 hours, his symptoms had gradually improved, but he experienced new symptoms as dizziness, weakness and numbness in all four limbs, difficulties in raising head and opening mouth, dysarthria, and dysphagia with normal CT scanning on 11AM, January 25, 2019 and recovered after treatment in local hospital in a few hours. He had another two episodes with similar symptoms and recovered in a few hours on January 25 and 26. The brain MRI DWI on January 26, 2019 indicated hyperintensities in both posterior periventricular areas (Fig. 5-A). He was admitted to our hospital with diagnosis of adrenoleukodystrophy on January 29, 2019. He fell from a 2-meter height in the middle of December, 2018 and was treated in the hospital with diagnosis of abdominal injury, spleen and left kidney contusion, and both lumbar transverse process fracture. His physical examination was normal except for diminished deep tendon reflexes in all extremities.

His neurological examination revealed pes cavus, horizontal nystagmus on both eyes, atrophy in his hands and distal lower extremities, normal muscle strength, and absent deep tendon reflexes in all extremities. The finger-nose test and heel–knee test showed mild dysmetria on right limbs when closing eyes. The Romberg sign was positive, no matter when opening or closing eyes. NCV findings were suggestive of a mild-to-moderate sensorimotor polyneuropathy with mixed demyelinating and axonal features. Genetic testing showed a c.103G>C (p. Val 35 Leu) hemizygous point mutation in GJB1. His great-grandmother, grandmother's brother and grandfather who had pes cavus also had the same point mutations in GJB1 (Fig. 6).

He had recovered to his baseline without special treatment when he was discharged on January 31, 2019. He presented a normal brain MRI DWI within 2 weeks (on February 11, 2019, Fig. 5-B) and within one month (February 26, 2019, Fig. 5-C) during outpatient follow-up.

Discussion

To date, over 30 cases of white matter lesion involvement in patients with Charcot-Marie-Tooth disease and 22 GJB1 gene mutations have been described[2-15]. Most these cases, as well as our cases, have similar clinical features: (1) Young males with onset age at 10-20 years; however, a female patient has been reported in previous literature[3]. (2) Patients and their maternal female relatives having pes cavus deformities with X-linked dominant inheritance. (3) Experiences of recurrent and transient episodes of CNS symptoms which recover after a few hours or days. There are also diffuse hyperintense lesions in the periventricular areas and corpus callosum as well as deep cerebral white matter with a posterior predominance found in T2WI or DWI. These signal abnormalities largely disappeared in a few weeks or months. (4) NCV data that shows mixed demyelinating and axonal sensorimotor neuropathy. Electrophysiological characteristics in these three male probands were shown in Table 1 and 2. NCV demonstrated no response of motor conduction velocities (MCV) and sensory conduction velocities (SCV) in the 0~50 m/s range in lower limbs. MCV in the 0~27 m/s range and SCV in the 0~52 m/s range were detected in upper limbs. Long latency was detected in most sensory and motor nerves in four limbs. Markedly low amplitude of sensory and motor responses was found in both peroneal nerves. (5) Genetic testing that identifies a hemizygous point mutation in GJB1. The molecular characteristics of the GJB1 mutations in these three unrelated Chinese families were summarized in Table 3. Two novel mutations: c.563 C>T and c.103G>C of GJB1 gene were detected in two patients respectively. (6) Triggering factors such as returning from high altitudes, intense exercise, febrile illness, hyperventilation, and concussion or trauma were found in some cases[16-18]. Positive Coxsackievirus IgG and negative IgM in serum indicates past Coxsackievirus infection in our case 1. This fact indicates virus infection may be one of the triggering factors; trauma and following surgeries may trigger CNS lesions in our case 3. (7) The outcome of CNS lesions in most cases is good with or without treatment of steroids. In our experience, if patients experience severe CNS symptoms, such as our patient 1 who was admitted to the neurological intensive care unit upon arrival, they may benefit from treatment with steroids.

Connexin32 is expressed by not only Schwann cells in peripheral nerves, but also by myelinating oligodendrocytes and astrocytes in the central nervous system[1]. Interruption of the gap junction-mediated coupling between oligodendrocytes and astrocytes likely causes to an inability of these cells to properly regulate ion communication and fluid exchange, which may explain the restricted diffusion seen on the MRI of the patient with GJB1 gene mutations[19].

The interesting and unique feature of this present report is the identification of two novel mutations in GJB1, which were detected in Family 2: c.563 C>T (p. Thr 188 Ile) and Family 3: c.103G>C (p. Val 35 Leu). However, the symptoms present in our three patients are similar even if the GJB1 gene mutations are different.

Another unique and interesting feature of this present report is that the peripheral neuropathy in our patients was insidious and only found at onset of CNS symptoms. This is a common reason for initial misdiagnosis. The initial diagnosis of patient 1 was mitochondrial encephalomyopathy according to his

CNS symptoms, brain MRI, and elevated serum lactic acid level after exercise. In the case of patient 2, extensive investigations were performed to exclude adrenoleukodystrophy.

The time point relation between CNS symptoms and lesions in the MRI is also interesting. In patient 1, the second MRI in twelve days showed that only minor white matter lesions remained when his CNS symptoms diminished after 10 days. The second MRI for patient 2 was normal when his CNS symptoms relived in eighteen days. For patient 3, the second and third MRI after two weeks and one month were all normal. A closer MRI scanning may be helpful to further explore this relationship.

The limitation of this study is that the three cases lack nerve biopsy data because the patients refused invasive examinations.

In conclusion, we presented 3 cases in which recurrent episodes of a reversible posterior leukoencephalopathy in patients with CMTX1 disease with a c.425G>A (p. Arg 142 Glu) or c.563 C>T (p. Thr 188 Ile) or c.103G>C (p. Val 35 Leu) mutation in the GJB1 gene. Central nervous system involvement in patients with peripheral neuropathy indicates that myelin damage either in the CNS or peripheral nerve system may have similar pathogenetic mechanisms to some extent.

Abbreviations

CMTX1: X-linked form of Charcot-Marie-Tooth disease type 1

GJB1: gap-junction beta-1

CNS: central nervous system

MRI: magnetic resonance image

DWI: diffusion-weighted magnetic resonance imaging

NCV: Nerve conduction velocity (

CSF: cerebrospinal fluid

EEG: electroencephalograms

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of First Affiliated Hospital, Guangxi Medical University. Written informed consent was obtained from the patients or patient's parent to participate.

Consent to publication

Written informed consent was obtained from the patients or patient's parent for publication of this paper and any accompanying images.

Availability of data and materials

Data generated during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

Data collection, analysis, and interpretation of the study were supported by grants from the Natural Science Foundation of Guangxi Province (CN) (2017GXNSFAA198042).

Authors' contributions

YLL, JLL, YW, DBC, LHM and WH were all directly involved in the clinical management of this case. YW was a major contributor in writing the manuscript under the guidance of WH. All authors read and approved the final manuscript.

Acknowledgments

We gratefully thank the participants and their families.

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Tables

Table 1 Motor/sensory nerve conduction in lower limbs of three propands with CMTX

		Case1	Case2	Case3
Peroneal .L				
Conduction velocity	M	nr	nr	nr
	S	nr	nr	50m/s□□40□
Amplitude	M	0.1mV□□5□	0.3mV□□5□	2.2mV□□5□
	S	nr	nr	4.2mV□□5□
Latency	M	5.4ms□□3.2□	4.9ms□□3.2□	4.6ms□□3.2□
	S	nr	nr	3.5ms□□3.2□
Peroneal .R				
Conduction velocity	M	nr	nr	nr
	S	nr	nr	49m/s□□40□
Amplitude	M	nr	nr	1.6mV□□5□
	S	nr	nr	3.5mV□□5□
Latency	M	nr	nr	4.2ms□□3.2□
	S	nr	nr	4.8ms□□3.2□
Tibial.L				
Conduction velocity	M	nr	nr	nr
	S	nr	nr	39m/s□□40□
Amplitude	M	0.5mV□□5□	0.5mV□□5□	6.0mV□□5□
	S	nr	nr	4.4mV□□5□
Latency	M	3.9ms□□3.2□	10.1ms□□3.2□	4.4ms□□3.2□
	S	nr	nr	4.2ms□□3.2□
Tibial.R				
Conduction velocity	M	nr	nr	nr
	S	33m/s□□40□	nr	41m/s□□40□
Amplitude	M	0.3mV□□5□	0.3mV□□5□	6.6mV□□5□
	S	4.4mV□□5□	nr	4.0mV□□5□
Latency	M	6.3ms□□3.2□	10.1ms□□3.2□	5.8ms□□3.2□
	S	3.4ms□□3.2□	nr	4.3ms□□3.2□

M: Motor nerve; S: Sensory nerve; nr: no response; (): normal values

Table 2 Motor/sensory nerve conduction in upper limbs of three propands with CMTX

		Case1	Case2	Case3
Median.L				
Conduction velocity	M	nr	nr	nr
	S	38m/s□□45□	nr	50m/s□□45□
Amplitude	M	9.6mV□□5□	2.9mV□□5□	5.1mV□□5□
	S	4.7mV□□15□	nr	2.8mV□□15□
Latency	M	4.4ms□□3□	5.8ms□□3□	3.6ms□□3□
	S	3.7ms□□2.4□	nr	2.2ms□□2.4□
Median.R				
Conduction velocity	M	27m/s□□45□	nr	nr
	S	41m/s□□45□	nr	44m/s□□45□
Amplitude	M	4.2mV□□5□	2.1mV□□5□	9.4mV□□5□
	S	4.6mV□□15□	mV□□15□	3.6mV□□15□
Latency	M	4.5ms□□3□	6.8ms□□3□	3.8ms□□3□
	S	3.4ms□□2.4□	nr	1.3ms□□2.4□
Ulnar.L				
Conduction velocity	M	nr	nr	nr
	S	nr	nr	52m/s□□45□
Amplitude	M	4.6mV□□5□	3.9mV□□5□	5.4mV□□5□
	S	nr	nr	2.7mV□□5□
Latency	M	3.6ms□□3□	5.6ms□□3□	2.4ms□□3□
	S	nr	nr	2.1ms□□3□
Ulnar.R				
Conduction velocity	M	nr	nr	nr
	S	36m/s□□45□	nr	48m/s□□45□
Amplitude	M	2.7mV□□5□	4.0mV□□5□	5.7mV□□5□
	S	4.5mV□□5□	nr	2.8mV□□5□
Latency	M	3.5ms□□3□	5.2ms□□3□	2.8ms□□3□
	S	3.6ms□□3□	nr	2.3ms□□3□

M: Motor nerve; S: Sensory nerve; nr: no response; (): normal values

Table 3 GJB1 mutations identified in three unrelated Chinese families with CMTX

Family	locus	mutation	protein	genotype	Variant status
1	chrX-70443982	c.425G>A	p. Arg 142 Glu	hemizygous	Probably pathogenic
2	chrX-70444120	c.563 C>T	p. Thr 188 Ile	hemizygous	Uncertain
3	chrX-70443660	c.103G>C	p. Val 35 Leu	hemizygous	Uncertain

Figures

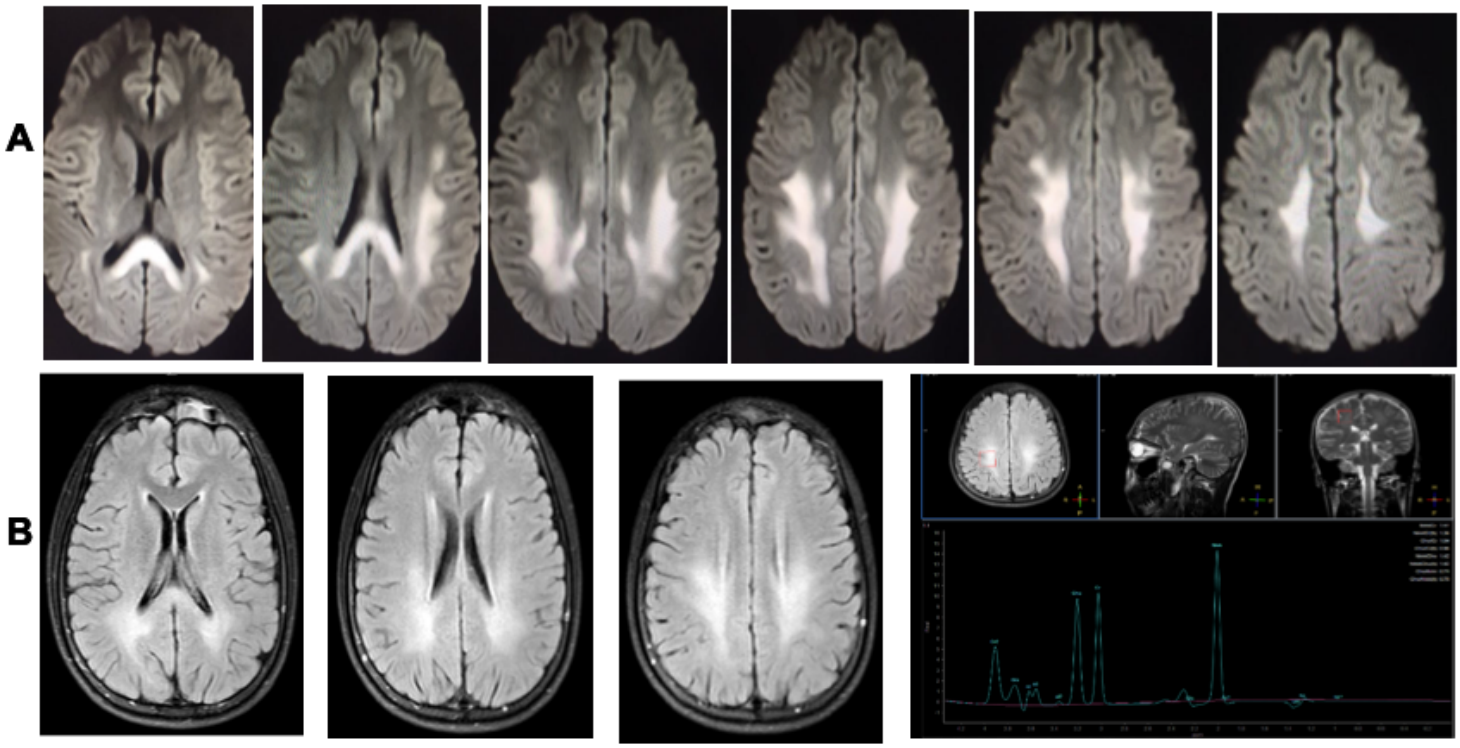

Figure 1

Brain magnetic resonance images of patient 1. A: MRI on 24 July 2018: Diffuse white matter lesions in posterior subcortical areas and the splenium of the corpus callosum. MRA was normal. B: MRI on 6 August 2018: the demyelinating changes of white matter had largely disappeared. MRS was normal.

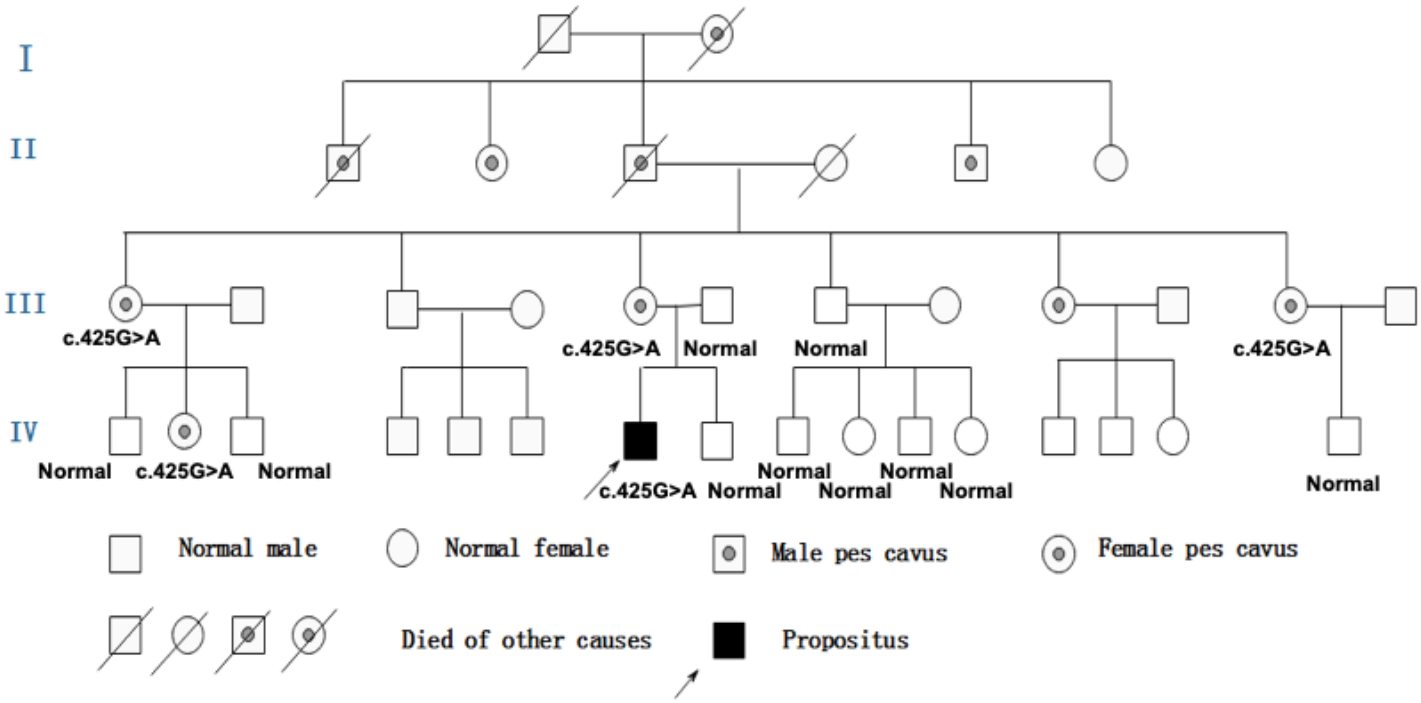

Figure 2

Pedigree of Family 1. The proband, his mother, older maternal aunt and her daughter as well as younger maternal aunt who have pes cavus deformities have a c.425G>A (p. Arg 142 Glu) hemizygous point mutation in the GJB1 gene.

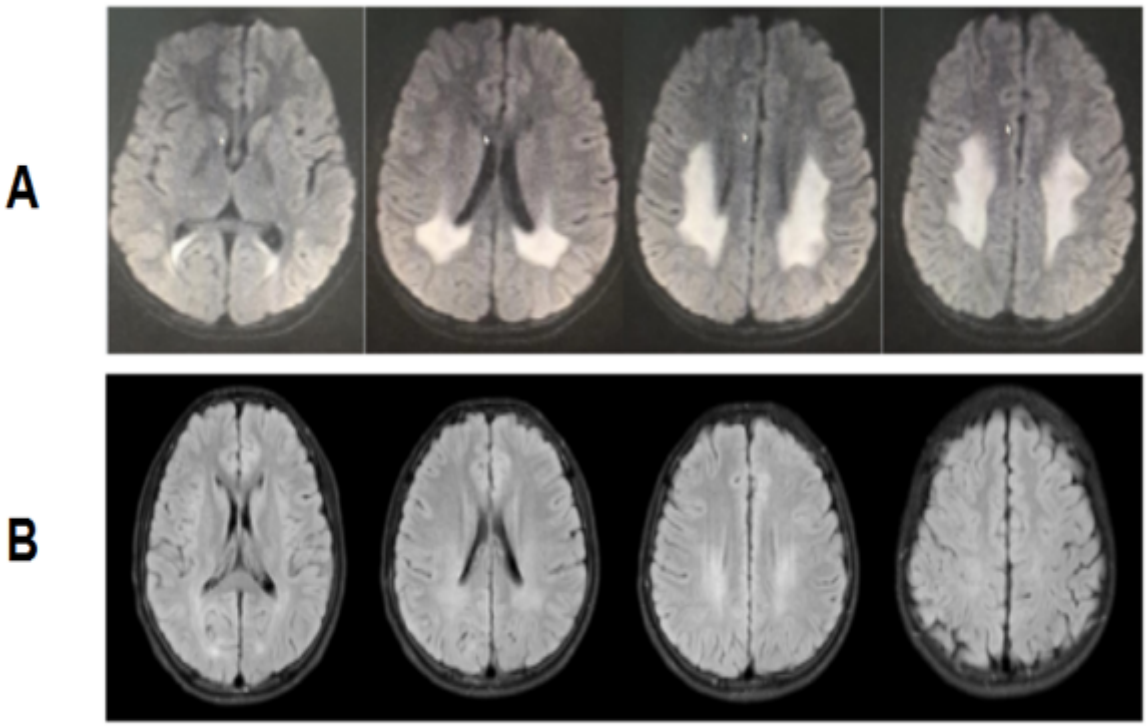

Figure 3

Brain MRI of patient 2. A: MRI on 17 February 2018 indicated white matter lesions in bilateral posterior ventricular areas B: White matter lesions nearly complete resolution on 6 March 2018. MRS was normal.

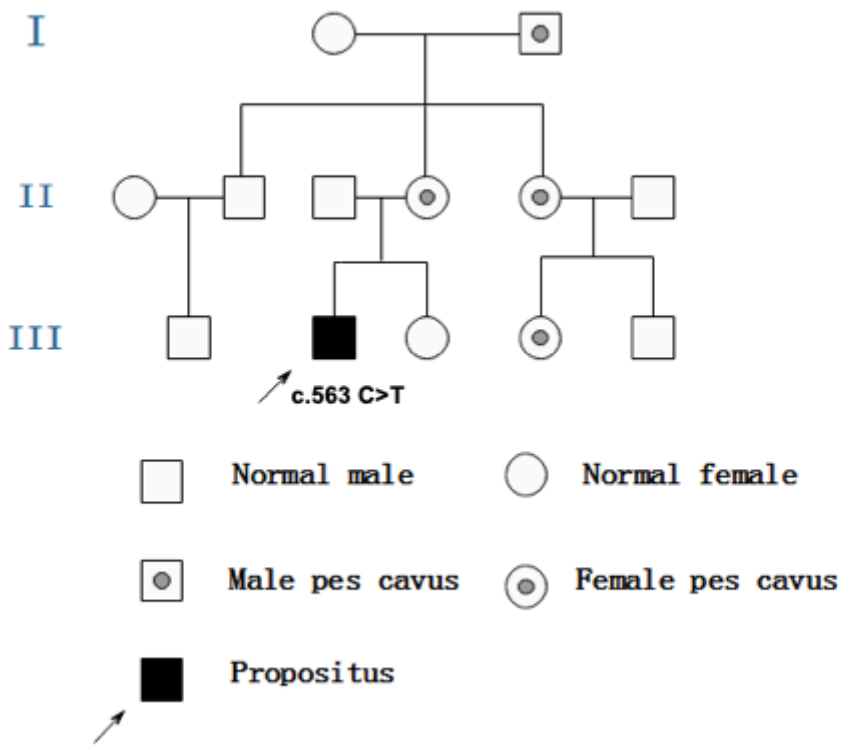

Figure 4

Pedigree of Family 2. The proband has a c.563 C>T (p. Thr 188 Ile) hemizygous point mutation in the GJB1 gene.

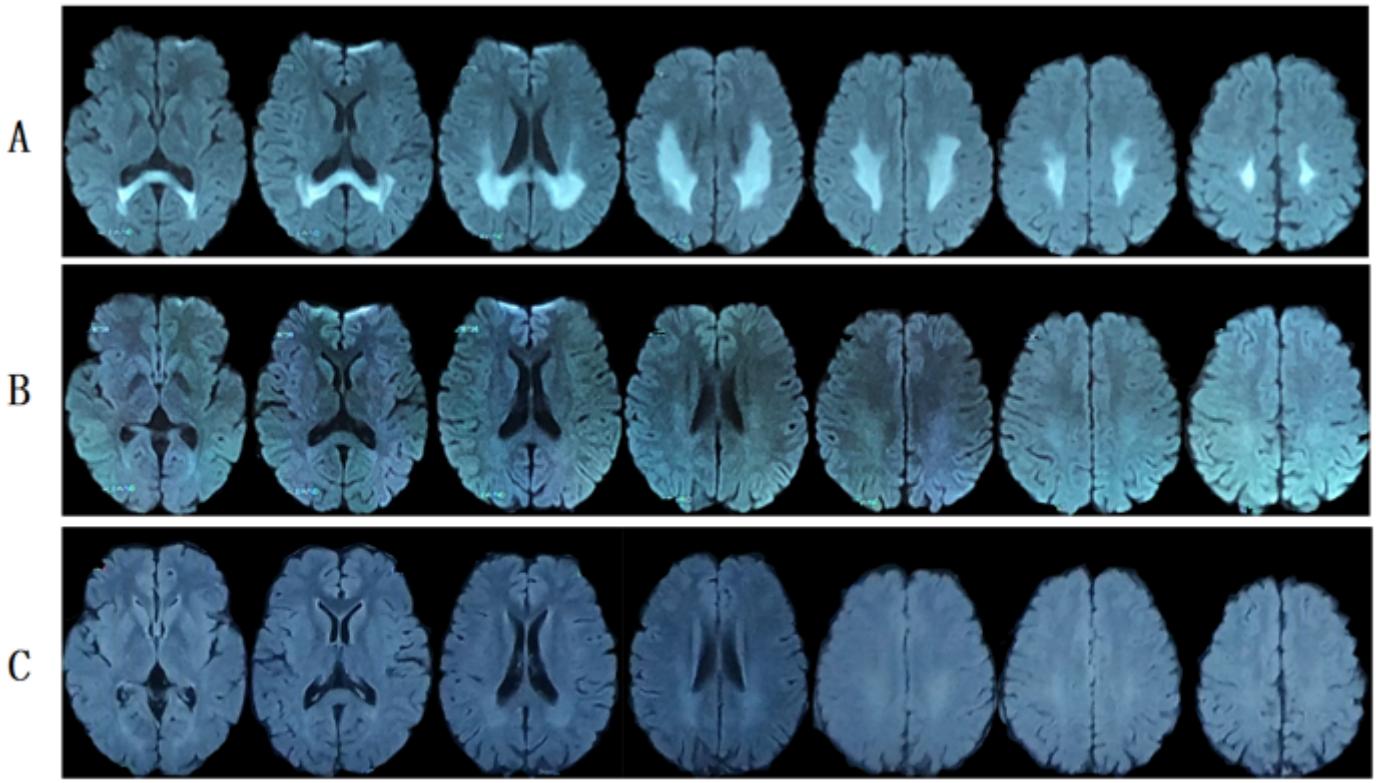

Figure 5

Brain MRI of patient 3. A: MRI on January 26, 2019 showed white matter lesions in bilateral posterior ventricular areas and the splenium of the corpus callosum；B: MRI on February 11, 2019 showed the abnormal signal almost complete resolution；C: MRI on February 26, 2019 showed no obvious abnormality.

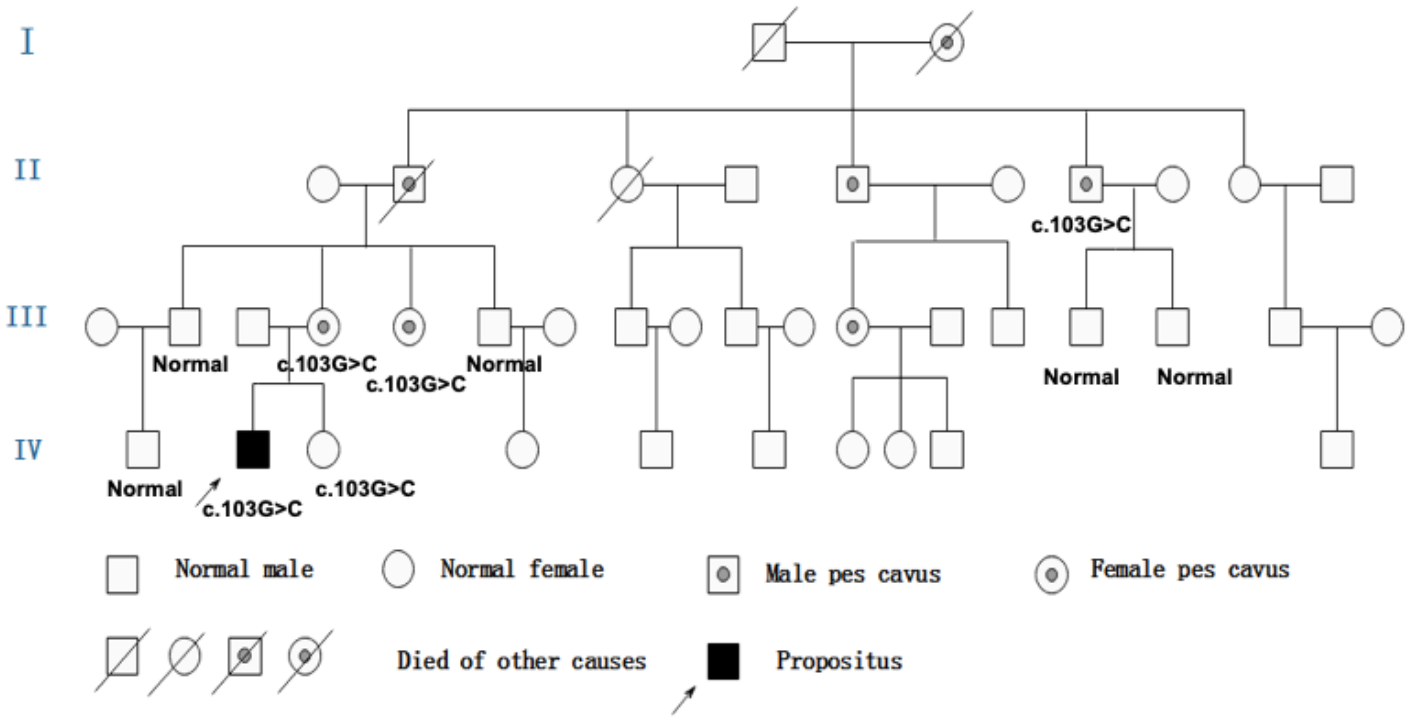

Figure 6

Pedigree of Family 3 . The proband, his mother, yonger maternal aunt and maternal grandfather who have pes cavus deformities have a c.103G>C (p. Val 35 Leu) hemizygous point mutation in the GJB1 gene.