Compound Heterozygote Mutation of *C12orf65* Causes Distal Motor Neuropathy and Optic Atrophy

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Key words: C12orf65 Protein; Inherited Peripheral Neuropathy; Optic Atrophy

The *C12orf65* gene is a nuclear gene that encodes a mitochondrial matrix protein contributing to mitochondrial translation.[1] *C12orf65* gene-related diseases are rare and present with large heterophenotypes.[1-4] Most of the reported patients have had optic atrophy with intellectual disability, encephalomyopathy, spastic paraplegia, and ophthalmoplegia.[1-3] Peripheral neuropathy has been reported in one family.[3] Here, we report a case of a Chinese patient with optic atrophy and distal motor neuropathy due to a novel compound heterozygous mutation in the *C12orf65* gene.

The girl in this case is an 8-year-old, single offspring of a nonconsanguineous couple. Her delivery was normal, with normal motor and mental development in infancy. At the age of 3 years, she showed insidious progressive loss of visual acuity. Ophthalmic examination revealed 20/100 vision in both eyes. Her visual acuity decreased to 15/100 vision at the age of 5 years. Fundoscopic examination demonstrated bilateral optic atrophy [Figure 1a]. The median value of the latency of flash visual-evoked potentials was delayed, indicating axonal damage of the optic nerves. Optical coherent tomography revealed a general reduction of the retinal nerve fiber layer thickness [Figure 1b]. Ophthalmic examination exposed a temporal visual field defect [Figure 1c]. At the age of 7 years, she had running difficulty due to foot drop and pes cavus. At the age of 8 years, she had a high steppage gait due to a deteriorated foot drop and required the daily use of ankle splints during walking. Neurological examination revealed loss of visual acuity with bilateral optic atrophy. Sensitivity to pinprick, touch, temperature, positioning, and vibration was normal in all the limbs. The muscle strength was normal in the upper limbs, 4/5 in foot flexion (Medical Research Council Scale, Grade 0–5), and 2/5 in foot dorsiflexion. There was wasting of the calves with normal muscle tone in all limbs. Deep tendon reflexes were normal in the upper limbs. In addition to the brisk reflexes of the knee and the ankle, there were no other pyramidal signs. The feet appeared to have a pes cavus deformity with a flexion contracture of the toes.

Brain magnetic resonance imaging studies showed bilateral optic atrophy. The other cerebral structures were unremarkable. Nerve conduction velocity studies were consistent with bilateral motor axonal neuropathy in all limbs, sparing the sensory nerves [Table 1]. Motor nerve conduction velocities (MNCVs) were not evoked in the distal lower limbs, while very low amplitudes of compound motor action potential and mildly decreased MNCVs in the other motor nerves were recorded. Sensory nerve conduction velocities were within normal limits in all the limbs. Needle electromyography revealed a neurogenic pattern in the right upper limb and both lower limbs.

A compound heterozygous mutation in the *C12orf65* gene was found in the blood sample [Figure 1d]. The c.394C>T (p.R132X) mutation was located on exon 3 in the *C12orf65* gene and has been reported previously.[3] The same mutation was identified in the patient's mother. The mutation c.6_7delCA (p.T3Rfs*54) was identified on exon 2, creating a pathological premature stop codon. This mutation has not been reported previously in Human Gene Mutation Database

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Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.198019

Received: 14-10-2016 **Edited by:** Yuan-Yuan Ji
How to cite this article: Fang XJ, Zhang W, Lyu H, Wang ZX, Wang WW, Yuan Y. Compound Heterozygote Mutation of *C12orf65* Causes Distal Motor Neuropathy and Optic Atrophy. Chin Med J 2017;130:242-4.

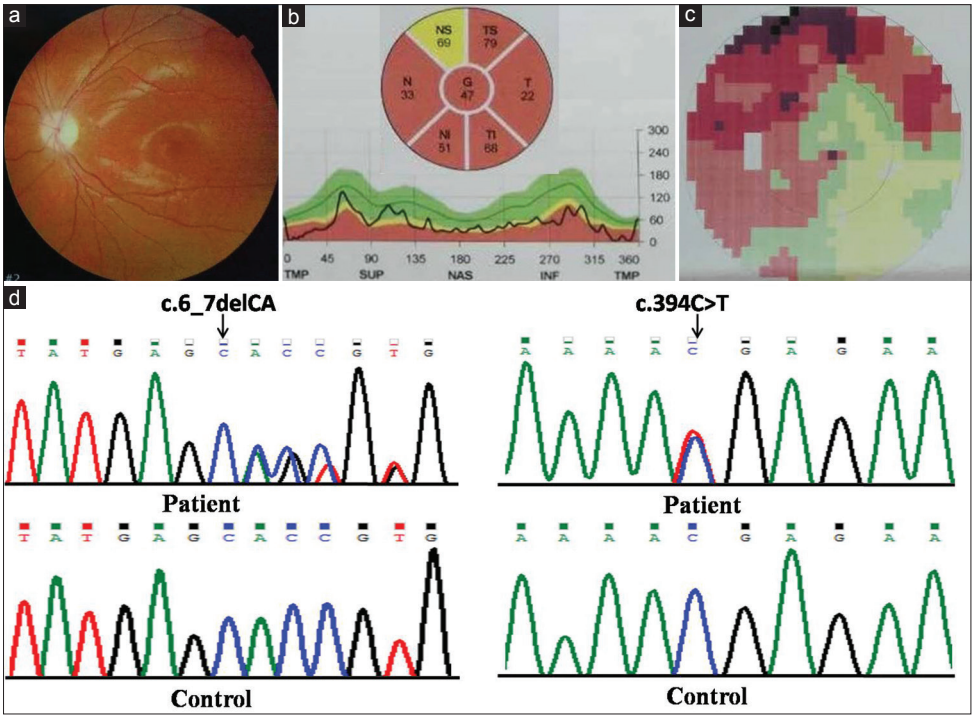

Figure 1: (a) Left eye color fundus examination of the patient showing pallor of the optic disc. (b) Peripapillary retinal nerve fiber layer of the left eye. Optical coherent tomography study showing generalized thinning of the retinal nerve fiber (yellow color: Borderline thickness; red color: Clear thinning). (c) Visual field study of the left eye illustrating temporal visual field loss. (d) The c.6_7delCA (p.T3Rfs*54) mutation on exon 2 and the c.394C>T (p.R132X) mutation on exon 3 in the *C12orf65* gene.

Table 1: Nerve conduction studies of the 8-year-old girl with optic atrophy and distal motor neuropathy

Items	CMAP (μV)	MNCV (m/s)	SAP (μV)	SNCV (m/s)
Ulnar	11.40	57.8	9.2	55.4
Median	7.50	55.8	8.5	43.6
Tibial	0.03	27.5	7.3	46.9
Common peroneal	–	–	8.8	40.8

MNCV: Motor nerve conduction velocity; SNCV: Sensory nerve conduction velocity; SAP: Sensory action potential; CMAP: Compound motor action potential. –: Nerve conduction was not evoked.

Professional. This novel mutation was also identified in the patient's father.

Discussion

The presented patient's initial symptom was insidious visual loss at the age of 3 years, earlier than the reported patients with visual loss at the age of 5 years.[4] Ophthalmic examination revealed optic atrophy with a temporal visual field defect, but no ophthalmoplegia was observed. Optic atrophy appears in all cases of *C12orf65* mutations reported previously.[1-5] Spiegel *et al*. have reported patients with bitemporal predominant visual field impairment and ophthalmoplegia.[4]

We confirmed that peripheral neuropathy developed later after optic symptoms. This girl developed weakness and muscle atrophy in her distal lower limbs, with pes cavus deformity starting at the age of 7 years. This finding is consistent with the patients reported by Shimazaki *et al*.[3] In contrast to the patients with both sensory and motor function disturbance reported previously,[3,4] the presented case showed pure distal motor neuropathy without sensory loss in the limbs.

Our patient had no evidence for spastic paraparesis. She only presented with a brisk deep tendon reflex in the lower limbs, representing a slight pyramidal sign. Similar clinical symptoms also have been reported in a 7-year-old boy; however, other patients in the same family presented with spastic paraparesis by their second decade.[4] We propose that the upper motor neurons might be damaged later than peripheral nerves and that the progression is slow. Our patient is in the early stage of the disease.

The mutation of c.394C>T (p.R132X) has been reported by Shimazaki *et al*.,[3] which is predicted to cause a loss of normal protein function through protein truncation. C.6_7delCA (p.T3Rfs*54) is a novel mutation. It is predicted to cause a truncating mutation and might interrupt a highly conserved glycine-glycine-glutamine motif in the Class I peptide chain release factors.[5] Both mutations resulted in *C12orf65*-related diseases in this girl.

Acknowledgments

We thank the patient and her family for their participation in this study. We also thank the MyGenome Institute for their kind administrative assistance.

Financial support and sponsorship

This study was supported by a grant of the National Natural Science Foundation of China (No. 81471185).

Conflicts of interest

There are no conflicts of interest.

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