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【 CASE REPORT 】

MFN2-related Charcot-Marie-Tooth Disease with Atypical Ocular Manifestations

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Abstract:

We herein describe a Charcot-Marie-Tooth disease (CMT) family with a *MFN2* mutation with atypical ocular manifestations. The proband, his mother, his third daughter, and his deceased maternal grandfather all had symptoms of CMT and a visual impairment (either cataracts or severe astigmatism). On whole-exome sequencing for the proband having CMT and congenital cataracts, we identified a c.314C>T (p.Thr105Met) mutation in *MFN2,* but no mutation in the causative genes associated with cataracts. This missense mutation in *MFN2* co-segregated with CMT and the atypical ocular manifestations in this family. The findings of this study might help to expand the clinical phenotype of heterogeneous *MFN2*-related CMT.

Key words: Charcot-Marie-Tooth disease, *MFN2*, visual impairment, cataracts, astigmatism

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Introduction

Charcot-Marie-Tooth disease (CMT) comprises the most common group of degenerative disorders of the peripheral nervous system and it is both clinically and genetically heterogeneous. Mutations in the mitofusin 2 (*MFN2*) gene, which encodes a mitochondrial GTPase mitofusin protein, have been reported to cause Charcot-Marie-Tooth 2A (CMT 2A), and hereditary motor and sensory neuropathy type VIA with optic atrophy (HMSN6A) (1). Mutations in *MFN2* are the most prevalent cause of CMT2, accounting for up to 20% of all such patients and families (2). However, CMT1, as well as intermediate CMT phenotypes, have also been reported (3).

CMT caused by *MFN2* mutations presents complex phenotypes including not only neuropathy-related features but also systemic impairment of the central nervous system (3). Although optic atrophy has been frequently reported, mutations in *MFN2* have only rarely been associated with cataracts. We herein report a Japanese CMT family with atypical ocular manifestations of cataracts or severe astigmatism with a p.T105M mutation in *MFN2*.

Case Report

The pedigree is shown in Figure A. The proband (Figure A, III-1) was the first child of unrelated parents. He had congenital cataracts in both eyes and could not see clearly after birth. He could not even identify people's faces or recognize his school bag in kindergarten, so he chose to go to a school for the blind. He had drop feet and a steppage gait from age 4. At age 6, he underwent his first cataract surgery. His muscle weakness and atrophy of the lower limbs both gradually worsened. He experienced difficulty in climbing stairs from his late teens, and experienced unsteadiness, clumsiness, and recurrent falls from 30 years of age. At 20 years of age, he underwent his second cataract surgery and intraocular lens implantation was performed. He had experienced frequent cramping since childhood and had developed severe pain in the waist and hips from age 39. On examination at age 40, he showed a steppage gait, drop feet, stork legs, a pes cavus deformity, hammertoes, absent Achilles tendon reflexes, distal muscle weakness, and atrophy in the lower extremities, and moderately decreased sensitivity to vibration and pain. Other than Achilles tendon reflexes, he

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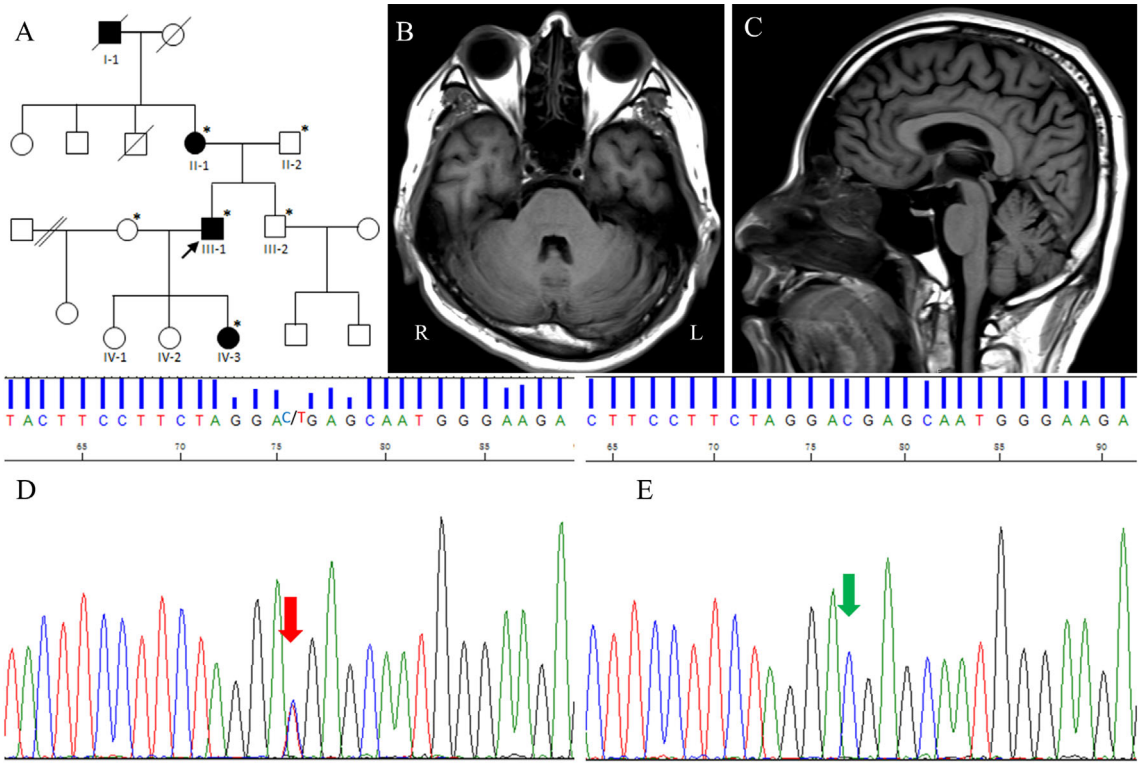

Figure. **A: The pedigree of the present family. The proband is indicated (arrow). Squares indicate men, circles women, and slashes deceased individuals, while shaded (black) symbols indicate individuals with symptoms of CMT and visual impairment, while unshaded ones show individuals without symptoms of CMT or visual impairment. Individuals evaluated both clinically and genetically are denoted by asterisks. B, C: Brain MRI of the proband showed mild cerebellar atrophy and mild enlargement of the fourth ventricle. R and L indicate right and left. D: Sanger sequencing revealed the c.314C>T mutation in *MFN2* to be in a heterozygous state in the proband, his mother, and his youngest daughter. E: The c.314C>T mutation in *MFN2* was not detected in the proband's father, his wife, or his younger brother.**

showed slightly exaggerated deep tendon reflexes and positive bilateral Babinski signs. Tongue atrophy and fasciculation, and mild dysphonia were also detected. Electrophysiological studies showed motor conduction velocity (MCV) for the median nerve of 37.7 m/s and sensory conduction velocity (SCV) for the sural nerve of 19.1 m/s, respectively, and Amps of 11.1 mV and 9.4 uV, respectively. Nerve conduction studies showed a tendency toward more severe neuropathies in the lower extremities, as well as significantly reduced compound motor action potentials (CMAPs) and reduced sensory responses, indicative of the presence of sensory-motor neuropathy (Table 1). Brain magnetic resonance imaging (MRI) revealed mild cerebellar atrophy (Figure B, C), but no white matter alterations were observed.

The proband's mother (Figure A, II-1), a 73-year-old woman, had drop feet and a steppage gait since early childhood. Her symptoms gradually worsened and she lost flexibility in her hands. She was wheelchair-bound due to a lumbar fracture that had occurred 10 years previously. She also had senile cataracts. The proband's deceased maternal grandfather (Figure A, I-1) also had confirmed age-related cataracts and gait disturbance. It is notable, however, that he was first diagnosed with age-related cataracts at 60 years of age. The proband's 6-year-old third daughter (Figure A, IV-3) exhibited drop feet and a steppage gait, unsteadiness, clumsiness and recurrent falls after birth. Mild mental retardation was also noted. She also presented with severe visual impairment after birth, and at 4 years of age she was diagnosed to have severe astigmatism at a local clinic.

No other family members are known to have been affected by this pedigree. The proband's younger brother (34 years of age; Figure A, III-2), and first and second daughters (15 and 6 years of age; Figure A, IV-1 and IV-2) have not shown any neurological or visual abnormalities thus far.

Genetic Study

We carried out whole-exome sequencing of genomic DNA from the proband. The genomic DNA was isolated from peripheral blood leukocytes using standard methods. Exome capture was performed with a SureSelect Human All Exon V6+UTR (89Mb) Kit (Agilent Technologies, Santa Clara, USA). Paired-end sequencing was carried out on a HiSeq2500 (Illumina, San Diego, USA) using a HiSeq SBS Kit V4 (Illumina), which generated 100-bp reads. The reference databases utilized included hg19 (GRCh37) (http://genome.ucsc.edu), HGMD (https://portal.biobase-international.co

Table 1. Electrophysiologic Studies of the Proband Reported in This Study.

	Proband	Normal range
Median nerves		
DML (ms)	3.7	<4.4
MCV (m/s)	37.7	>49
Distal CMAP (mV)	11.1	>4
Proximal CMAP (mV)	5.4	>4
SCV (m/s)	34	>45
SNAP (μv)	6.1	>7
Ulnar nerves		
DML (ms)	2.9	<3.3
MCV (m/s)	50.5	>49
Distal CMAP (mV)	5.3	>6
Proximal CMAP (mV)	0.99	>6
SCV (m/s)	47.1	>47
SNAP (μv)	5.6	>3
Peroneal nerves		
DML (ms)	10.4	<5.8
MCV (m/s)	25.5	>41
Distal CMAP (mV)	0.23	>4
Proximal CMAP (mV)	0.26	>4
Tibial nerves		
DML (ms)	5.0	<5.8
MCV (m/s)	9.3	>41
Distal CMAP (mV)	0.64	>4
Proximal CMAP (mV)	0.25	>4
Sural nerves		
SCV (m/s)	19.1	>40
SNAP (μv)	9.4	>6

DML: distal motor latency, MCV: motor conduction velocity, CMAP: compound muscle action potential, SCV: sensory conduction velocity, SNAP: sensory nerve action potential

m), GnomAD (http://gnomad.broadinstitute.org), and dbSNP (https://www.ncbi.nlm.nih.gov/snp/). We examined the variants of a total of 172 genes known to be responsible for CMT or hereditary spastic paraplegia (HSP) (Table 2). Through this analysis, we identified a c.314C>T (p.Thr105Met) mutation in exon 3 of the *MFN2* gene and ruled out mutations in other causative genes for CMT and HSP. We then examined exon 3 in the *MFN2* gene in the proband, the proband's mother (Figure A, II-1) and father (Figure A, II-2), the younger brother (Figure A, III-2), the wife, and the youngest daughter (Figure A, IV-3) using polymerase chain reaction (PCR). On Sanger sequencing, we reconfirmed the c.314C>T (p.Thr105Met) mutation in exon 3 of the *MFN2* gene, which was in a heterozygous state in the proband, his mother and his youngest daughter (Figure D). On the other hand, this mutation was not detected in the proband's father, wife, or younger brother without symptoms (Figure E). We also examined variants of a total of 146 genes known to be responsible for or associated with cataracts (Table 2). Nevertheless, on whole-exome sequencing for the proband, we could not find any mutations in the causative genes associated with cataracts. Therefore, we considered that this missense mutation in *MFN2* might have been co-segregated with CMT and the atypical ocular manifestations in this family.

Discussion

To date, the p.Thr105Met mutation in *MFN2* has been reported in eight families throughout the world (1, 4-10). It appears to be a mutational spot exhibiting a high frequency in *MFN2*. The clinical features of patients or families with this mutation are shown in Table 3. There were some common clinical characteristics with this mutation, including a first-decade onset, bilateral foot drop, Achilles areflexia, distal loss of pinprick sensation greater than vibratory sensory loss, and distal muscle weakness severer in the lower than upper limbs. The initial symptoms were mostly walking difficulties caused by weakness of the distal lower limbs. None of the patients with this mutation have developed optic atrophy or have been reported to have any visual impairment so far. Interestingly, the inheritance mode of this mutation was *de novo* in a significant proportion of the carriers.

Among the families with this p.T105M mutation, our family has some unique characteristics: including pyramidal signs, dysphonia, and both tongue atrophy and fasciculation. These features had also been reported in CMT2A families with other mutations in *MFN2* (3, 9, 11), suggesting a *MFN 2*-induced systemic impairment. CMT with a pyramidal feature is an axonal form of CMT with variable pyramidal features but without frank spasticity (12). In the present study, extensor plantar responses and increased reflexes were found in the proband, while brain MRI findings revealed no white matter alterations. However, our patient had no frank spasticity, which is differentiated from spastic paraplegia. These findings are similar to those described in the previous reports (1, 13), indicating that *MFN2*-related CMT can present with pyramidal features. Above all, although electrophysiologic examinations revealed axonal neuropathy in most families with p.Thr105Met mutation reported previously, our case showed a decreased MCV in the median, peroneal, and tibial nerves. Although amplitude reductions of CMAP were found in the peroneal and tibial nerves, a severe reduction of SCV for the sural nerves was identified with the CMAP amplitudes being preserved. Therefore, the proband might be classified within either the CMT1 or intermediate CMT phenotypes. The electrophysiological data of other affected family members should be further investigated with a co-segregation analysis. Unfortunately, we were not able to further perform electrophysiological studies on other affected family members.

HMSN6A caused by a heterozygous mutation in *MFN2* is typically characterized by severe peripheral neuropathy with optic atrophy (1). As far as we know, only one previous report has described two patients with both optic atrophy and cataracts in a large family associated with a missense mutation (c.629A>T, p.D210V) in *MFN2* (14). However, the author did not mention whether the cataracts were congenital, and the other 10 patients with the same mutation in this

Table 2. Genes Known to Be Associated with CMT, HSP, or Cataracts.

(1) Genes known to be responsible for CMT or HSP.
ATL1 SPAST NIPA1 KIAA0196 ALDH18A1 KIF5A RTN2 HSPD1 BSCL2 REEP1 ZFYVE27 SLC33A1 REEP2 CPT1C CYP7B1 SPG7 SPG11 ZFYVE26 ERLIN2 SPG20 SPG21 B4GALNT1 DDHD1 FA2H PNPLA6 C19orf12 GJC2 NT5C2 GBA2 AP4B1 AP5Z1 TECPR2 AP4M1 AP4E1 AP4S1 VPS37A DDHD2 C12orf65 CYP2U1 TFG KIF1C USP8 WDR48 ARL6IP1 ERLIN1 AMPD2 ENTPD1 ARSI PGAP1 FLRT1 RAB3GAP2 MARS ZFR IBA57 MAG MT-CO3 MT-TI MT-ND4 MT-ATP6 L1CAM PLP SLC16A2 BICD2 CHS IFIH1 CCT5 FAM134B ALS2 EXOSC3 GAD1 HACE1 LYST SACS AARS ABHD12 AIFM1 ARHGEF10 ARSA ASAH1 COX6A1 CTDP1 DCAF8 DGAT2 DHH DHT DNAJB2 DNAJC3 DNM2 DRP2 DYNC1H1 EGR2 EMILIN1 FBLN5 FGD4 FIG4 GALC GAN GARS GDAP GDAP1 GJB1 GJB3 GNB4 HARS HINT1 HK1 HOXD10 HSPB1 HSPB8 IFRD1 IGHMBP2 INF2 KARS SLC12A6 KIF1B LITAF LMNA LRSAM1 MED25 MFN2 MME MORC2 MPZ MTMR2 NAGLU NDRG1 NEFH NEFL PDK3 PEX7 PHYH PLA2G6 PLEKHG5 PMM2 PMP22 PRPS1 PRX RAB7 SBF1 SBF2 SCYL1 SH3TC2 SLC25A46 SOX10 SPTLC1 SPTLC2 SPTLC3 SURF1 TDP1 TRIM2 TRPV4 TUBB3 VCP YARS KIF1A UBAP1 HPDL SELENOI PCYT2 KCNA2 KIDINS220 UCHL1 ATP13A2 FARS2 CAPN1 KLC2 SOD1 ACO2 RNF170 TPP1 WASHC5 MTTV

(2) Genes known to be responsible for or associated with cataracts.
ABCA3 TRAPPC11 SLURP1 RIMS1 PANK4 MED13 IARS2 GDF3 EPHA2 CRYBB3 ABHD12 TRNT1 STX3 RNLS PARK7 MFSD6L IDO1 GEMIN4 ERCC2 CRYGA ACKR1 TRPM3 TAF1A RRAGA PAX6 MIP INPP5K GFER EYA1 CRYGB ADAM9 TAPT1 RRM2B PEX11B MIR184 INTS1 GJA3 EZR CRYGC ADAMTS18 TUBA1A TDRD7 RYR1 PIGY MVK IPO13 GJA8 FAM126A CRYGD ADD3 TUBB TFR2 SC5D PITX2 MYH9 JAM3 GLS FAR1 CRYGS AGK UCHL1 TMCO3 SIL1 PITX3 MYOC KCNA4 GNPAT FBN1 CTDP1 AKR1E2 UNC45B TMEM114 SIPA1L3 POLG NACC1 LEMD2 GSR FOXE3 CYP1B1 ALDH18A1 VIM TMEM70 SIX5 PRX NECAP2 LIM2 GSTM1 FTL CYP27A1 APP VSX2 CLPB SLC16A12 PXDN NECTIN3 LONP1 GSTT1 FYCO1 CYP51A1 BCOR WDR36 COL4A1 SLC33A1 RGS6 NHS LSS HSF4 GALE DNA2 BEST1 WDR87 COL4A2 SLC40A1 RIC1 OCRL MAF HSF4 GALK1 DNM2 BFSP1 WFS1 CRYAA CRYBA4 CDK5RAP2 OGG1 DYNC1H1 BMP4 GALT DNMBP BFSP2 WRN CRYAB CRYBB1 CHD7 OPA1 EFNA5 BRD4 GCNT2 ZNF350 XYLT2 CRYBA1 CRYBB2 CHMP4B OPA3 EIF2B2 CRYBA2

family did not present with cataracts.

In our family, the proband presented with congenital cataracts, the proband's mother and deceased maternal grandfather also had confirmed age-related cataracts, and the proband's youngest daughter presented with congenital visual impairment, which was initially diagnosed as astigmatism. It is noteworthy that the last time the proband's youngest daughter went to an ophthalmological clinic had been 2 years previously when she still had visual impairment even with corrective lenses. It is possible that cataracts might have since developed or may develop in the near future. Unfortunately, the proband refused permission for further ophthalmologic examinations of his daughter and thus we could not get more information regarding this factor. The other family members without this mutation in *MFN2* showed no ocular symptoms. Interestingly, Zhao et al. (15) demonstrated in mice that a *MFN2* gene conditional knockout could lead to congenital cataracts due to mitochondrial dysfunction in lens cells. It is interesting to note that the human and mouse MFN2 proteins exhibit over 95% sequence identity and the residue found mutated in our family is conserved in mouse *MFN2*. The mutant $MFN2^{T105M}$ protein was non-functional in regard to mitochondrial fusion when expressed alone or in the presence of wild-type MFN2 in mouse embryonic fibroblast cells, thus suggesting that this mutation is a loss-of-function type (16). The p.T105M mutation is located within the GTPase domain of MFN2, which was knocked out in Zhao's study. Therefore, their morphologic study may provide genetic evidence of the role of the p.T105M mutation in *MFN2* in cataracts, thereby delineating the distinct function of MFN2 in regulating lens growth and development.

The present study is associated with some limitations. The ocular phenotype found in this pedigree is heterogeneous. Cataracts and astigmatism display different pathogenic mechanisms. The pathogenesis of congenital cataracts might be different from that of senile cataracts in this family. Moreover, the eight families in the rest of the world with this p.T105M mutation did not exhibit either cataracts or any other ocular phenotypes. Therefore, there might be some unknown genetic etiology underlying the ocular manifestations in our family that could not be identified on whole-exome sequencing. Nevertheless, the clinical features we describe herein might corroborate with the findings of Zhao et al. in their animal study (15). More clinical cases need to be identified to confirm the atypical ocular findings in *MFN2*-related CMT.

In summary, we herein described a Japanese CMT family with cataracts or severe astigmatism with a p.T105M mutation in *MFN2*. The findings of this family might expand the clinical phenotype of heterogeneous CMT and provide an opportunity to further study the genotype-phenotype correla-

Table 3. Clinical Features of Patients or Families with the P.Thr105Met Mutation in *MFN2* Reported in the Literature.

Ethnic origin	North America	America, Utah State	Korea	America, Detroit	France	China	China	Dominican Republic	Japan (this report)
Mode of inheritance	AD	*De novo*	*De novo*	*De novo*	AD	AD	*De novo*	NR	AD
Onset age (years)/Age at exam (years)	3-15/ NR	First decade/13	11/12	1/32	1/63	12/32	4/5	1/10	1/40
Symptoms at onset	NR	Difficulty running or walking, clumsiness and unsteadiness	NR	Distal weakness	Walking difficulties, falls, ankle and knee sprains and cramps	Weakness of the distal lower limbs	Abnormal gait	Inability to walk or sit straight	Drop feet and steppage gait
Distal muscle weakness and atrophy, UL/LL	+/+++	+/+	+/++	+/+	+++/+++	++/+++	+/++	-/+	-/+
Proximal muscle weakness	-	-	-	-	+++	+	-	+	-
Distal proprioception sensory loss	+	+	+	-	+	++	+	NR	+
Distal cutaneous sensory loss	+	++	+	-	+	+++	+	NR	+
CMTNS (Severity)	NR	(Mild)	6 (Mild)	(Mild)	27 (Severe)	(Severe)	15 (Intermediate)	(Severe)	13 (Intermediate)
Pes cavus	NR	Yes	Yes	NR	Yes	Yes	No	No	Yes
Achilles tendon reflex	Absent	Absent	Absent	NR	Absent	NR	Diminished	Absent	Absent
MCV (CV/Amp)	Median 47-52	Ulnar 55.6 (5.6)	Median 54.8 (12.9)	NR	Median 40-59	Median 38.8 (4.5)	Median 53.7 (8.4)	NR	Median 37.7 (11.1)
SCV (CV/Amp)	NR	Sural 46.7 (8.7)	Median 37.5 (9.9)	NR	NR	NR	Median 39.8 (3.3)	NR	Sural 19.1 (9.4)
Other symptoms	Ataxia, scoliosis	NR	Tremor	NR	Hip dysplasia	POEMS	NR	Cerebellar ataxia, intellectual disability	Cataracts, astigmatism, tongue atrophy and fasciculation, dysphonia
Reference	6	5	1	4	9	7	8	10	This study

AD: autosomal dominant, Muscle weakness and sensory loss: -: normal, +: mild, ++: moderate, +++: severe, UL: upper limbs, LL: lower limbs, proprioception based on joint position sensation and cutaneous sensation based on pinprick examination. CMTNS: Charcot-Marie-Tooth disease neuropathy score. Patients with mild, intermediate, and severe disabilities typically have a CMTNS between 1 and 10, 11 and 20, and 21 or greater, respectively. CV: conduction velocity (in m/s), MCV: motor conduction velocity, SCV: sensory conduction velocity, Amp: amplitude (for motor: in mV; for sensory: in μV), POEMS: Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes, NR: Unknown or observation not recorded

tion of *MFN2* and cataracts.

The present clinical and genetic study was approved by the institutional review board of Yamanashi University, and written informed consent was obtained from all participating individuals.

The authors state that they have no Conflict of Interest (COI).

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