# 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

(Intern Med 60: 3969-3974, 2021)  
(DOI: 10.2169/internalmedicine.7463-21)

| Introduction | Case Report |
|--------------|-------------|
| 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. | 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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Received: March 2, 2021; Accepted: April 29, 2021; Advance Publication by J-STAGE: June 12, 2021

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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.

HMS6N6A 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
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 did not present with cataracts or severe astigmatism with a p.T105M mutation did not exhibit either cataracts or severe astigmatism with a p.T105M mutation, 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 did not present with cataracts.

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

| Genes known to be responsible for CMT or HSP |
|---------------------------------------------|
| ATLA1, SPAST, NIPA1, KIAA0196, ALDH1A1, KIF5A, RTN2, HSPD1, BCL2L2, RPEEP2, CPT1C, CYP7B1, SPG7, SPG11, ZFYVE27, SLC33A1, EEF2, CYP7B1, SPG7, SPG11, ZFYVE26, ERLIN2, SPG20, SPG21, B4GALNT1, DDHD1, FA2H, PNP, PLA2G6, C1orf12, GIC2, NTSC2, GBA2, AP4B1, AP5Z1, TECPB2, AP4M1, AP4E1, VPS37A, DDHD2, C12orf65, CYP2U1, TGF, KIF1C, USP8, WDR48, ARL6IP1, ERLN1, ANPD2, ENTPD1, ARSI, PGAP1, FLRT1, RAB3GAP2, MARS, ZFR, IBA57, MAG, MT-C03, MT-TI, MT-ND4, MT-ATP6, L1CAM, PLP, SLC16A2, BICD2, CHS1, IFH1, CCT5, FAM134B, ALS2, EXOSC3, GAD1, HACE1, IYST, SACS, AARS, ADH2, AIFM1, ARHGEF10, ARSA, AASSH1, COX6A1, TD, DCP1, DCAP8, DGAT2, DH11, DHT, DNAJB2, DNAJC5, DNAJ2, DRP2, DYN1C1H1, EGR2, EMLN1, FBXL5, FGST4, FIG4, GALC, GAN, GARS, GDAP1, GB1, GJB1, GNB4, HARS, HINT1, HK1, HOXD10, HSPB1, HSPB8, IFRD1, IGHMBP2, INF2, KARS, SLC12A6, KIF1B, LITA, LMNA, LRSAM1, MED25, MFF, MORC2, MPZ, MTA2, MUB2, NAGLU, NDRG1, NEF, NEFL, PDK3, PEX6, PH2Y, PLA2G6, PLEKHG5, PMM2, PMP22, PRPS1, PRX, RAB7, SFB1, SB2, SCY1, SH3TC2, SLC25A46, SOX10, SPTLC1, SPTLC2, SPTLC3, SURF1, TDP1, TRIM2, TRPV4, TUBB3, VCP, YARS, KIF1A, UBA1, HDP1, SELENOL, PCTY2, KNCNA2, KIDINS220, UCHL1, ATP13A2, FARS2, CAPN1, KLC2, SOD1, ACC20, RNFI, TFP1, WASHC5, MTTV. |

| Genes known to be responsible for cataracts or associated with CMT or HSP |
|--------------------------------------------------------------------------|
| ABCA3, TRAPP1C11, SLURP1, RIMS1, PANK4, MED13, IARS2, GDF3, EPHA2, CRYBB3, ABHD12, TRNT1, STX3, RNLS, PARK7, MFSD6L, IDO1, GEMIN4, ERCC2, CRYGA, ACRK1, TRPM3, TFAT1A, RRAGA, PAX6, MIP, INP5K, GFER, EYA1, CRYGB, ADAM9, TAP1, RRM2B, PEX11B, MR184, INT5, GI3, E3K, CRYGC, ADAMTS18, TUBA1A, TDRD7, RYR1, PIGV, M15, IPO13, GI5A, FAM126A, CRYG4, ADD3, TUBB, TFR2, SCSD, PITX2, SNY89, IAM3, GLS, FAR1, CRYGS, AGK, UCHL1, TMCO3, SIL1, PITX3, MYOC, KNCNA4, GNPAT, FBN1, CTD1P1, AKR1E2, UNC45B, TMEM114, SAPII1, POLG, NACC1, LEMD2, GSR, FOXE3, CYP1B1, ALDH1A1, VIM, TMEM70, SI5, PRX, NECAP2, LIM2, GSTM1, FTL, CYP27A1, APP, VXX2, CLPB, SLC16A12, PXDN, NECST3, LONP1, GSTT1, FFCO1, CYP51A1, BOCR, WDR36, COAL4, SLC35A1, RG56, NLS, SLS, HSFD, GALC, DNA2, BEST1, WDR87, COAL2, SLC40A1, RCI1, OCRL, MAF, HSFD, GALK1, DNM2, BDFS1, WSFI, CRYAA, CRYBA4, CDK5RAP2, OOG1, DYN1C1H1, BMP4, ALG1, DNM, BDFS2, WRN, CRYAB, CRYB1B, CHD7, OPA1, EFN4, BRD4, GCNT2, ZNF350, XILTL, CRYBA1, CRYBB2, CHMP4B, OPA3, EF1B2, CRYBA2, CRYAB2. |

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 correlation.
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).**

**Financial Support**

This work was supported by Grants-in-Aid from the Research Committee for Ataxic Disease (Y.T.), the Ministry of Health, Labor and Welfare, Japan, and JSPS KAKENHI Grant Number JP 18K07495 (Y. T.) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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**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)              | 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 | 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 | NR |
| 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) | (Severe) | Intermediate | (Severe) | (Intermedimate) |
| Pes cavus                      | No            | 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 38.4 (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 pinpoint 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.
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