A FAMILY WITH NEUROPATHIES AND AN MFN2 VARIANT

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Background

Charcot-Marie-Tooth (CMT) is a phenotypically and genetically heterogeneous group of inherited peripheral neuropathies. With a prevalence of 1:2,500, it is the most common hereditary neurologic condition. CMT typically manifests as chronic, length-dependent motor and sensory loss resulting from demyelination (CMT1) or axonal loss (CMT2). Onset and severity are widely variable, even amongst individuals with identical mutations. Next-generation sequencing (NGS) has facilitated rapid CMT gene discovery in recent years. To date, >100 CMT-causative genes are reported, with substantial allelic and locus heterogeneity observed. Mutations in the mitofusin-2 (MFN2) gene cause axonal CMT (CMT2A), typically dominantly-inherited missense mutations. Additional MFN2-associated symptoms are common, including: optic atrophy, autonomic dysfunction, diaphragm/respiratory dysfunction, neuropathic pain.

Case Description & Results

We present a case of a 55-year-old man with chronic length-dependent sensorimotor symptoms, autonomic changes, and a positive family history.

Initial evaluation (age 52). Presented with painful parasthesias in bilateral feet and occasional orthostatic lightheadedness. Examination revealed decreased sensation below the ankles bilaterally with preserved strength and reflexes. NCS/EMG revealed similar symptoms in his mother (IB) and sister (IIB). Lab work was unremarkable. MFN2, a mitochondrial membrane GTPase, is essential for mitochondrial dynamics and trafficking. It is critically involved in axonal transport.

Re-evaluation (age 55). Presenting with worsening neuropathic and orthostatic symptoms. He reported severe orthostatic hypotension and exertional syncope. He endorsed subacute visual changes. Examination and NCS/EMG confirmed axonal polyneuropathy and reported additional symptoms (Table 2). MFN2-related disease was suspected in this family.

We describe the case of a 55-year-old man (proband, IIA) with axonal polyneuropathy, associated autonomic and visual symptoms, and a family history of the same symptoms. Genetic and clinical evaluation of the proband and 2 relatives (IB, IIB) suggests that the shared variant in MFN2 (c.1979C>A; p. Ala660Asp) is the most likely putative mutation in this family.

- All 3 patients had electrodiagnostic and clinical features of length-dependent axonal polyneuropathy (CMT2). All developed symptoms in adulthood, although onset ranged from 4th decade (IIA, IIB) to 6th decade (IB) of life. All had additional symptoms, which were consistent with those commonly reported in MFN2-related disease - neuropathic pain and visual symptoms (IIA, IIB), autonomic dysfunction (IIA, IIB), diaphragm weakness with respiratory difficulty (IB) - although severity was variable between family members. Pedigree suggests autosomal dominant inheritance.
- The identified MFN2 sequence variant yields a dominantly-inherited missense mutation, resulting in an amino acid substitution between C-terminal TM2 and HR2 domains. This alteration disrupts physiologic MFN2 protein function according to Invitae’s in silico functional protein modeling. This mutation is located far from the highly-conserved GTPase domain; such C-terminal (non-GTPase) mutations are associated with adult-onset, non-severe disease and phenotypic heterogeneity, consistent with this family’s phenotype.
- The other variant shared by all 3 patients, in PLEKHG5, is unlikely to be the culprit given its typical autosomal recessive inheritance pattern.

Despite an established link between MFN2 mutations and CMT2A, the molecular mechanisms by which MFN2 mutations lead to disease are largely unknown. This is likely due to the complex, multifunctional role of MFN2 in neurons. The genetic and clinical data in this report help to broaden the spectrum of MFN2-related disease and strengthen genotype-phenotype correlations in CMT. This understanding can improve genetic counseling of patients and support future disease-focused therapies.

Table 1. Nerve Conduction Studies (NCS) of proband (IIA) at age 55. Sensory NCS (top) and Motor NCS (bottom). Results suggest neuropathy progression with reduced (red font) or absent sensory amplitudes, and normal-range CMAP amplitudes that were decreased from prior study (at age 52). LE = Lower Extremity, Lat. = Latency, Amp. = Amplitude, CMAP = Compound Muscle Action Potential, SOV = Sensory Conduction Velocity, MCV = Motor Conduction Velocity, EDB = Extensor Digitorum Brevis muscle, AH = Abductor Hallucis muscle, A = Ankle, TH = Tibialis Posterior muscle, BF = Popliteal Fossa.

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Lat. (ms)</th>
<th>Amp. (mV)</th>
<th>CMAP (mV)</th>
<th>SOV (m/s)</th>
<th>MCV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial Personal N.</td>
<td>2.55</td>
<td>3.4</td>
<td>47</td>
<td>115</td>
<td>47</td>
</tr>
<tr>
<td>Median N.</td>
<td>2.97</td>
<td>3.7</td>
<td>47</td>
<td>116</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 2. Clinical features of proband (IIA) and symptomatic family members (IB, IIB). In all 3 individuals, sensorimotor symptoms were the presenting symptoms at onset. In patients IIA and IIB, autonomic symptoms began in 5th decade of life and were confirmed with quantitative autonomic function testing. LE = Lower Limb

<table>
<thead>
<tr>
<th>Patient (Proband)</th>
<th>EEG DIS</th>
<th>Ophthalmic</th>
<th>Sensory NCS</th>
<th>Motor NCS</th>
<th>Total</th>
<th>Additional Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA (proband)</td>
<td>55-64</td>
<td>5-7</td>
<td>0-4</td>
<td>0-4</td>
<td>0-4</td>
<td>Sensorimotor symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Severe orthostatic hypotension</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac arrhythmias</td>
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<td></td>
<td></td>
<td>Exertional syncope</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Respiratory dysfunction</td>
</tr>
</tbody>
</table>

[Table of clinical features and symptoms]

Figure 1. Family pedigree with summarized variant findings. Proband (IIA) is indicated by blue arrow. Shaded shapes represent symptomatic individuals. Pattern suggests likely autosomal dominant inheritance, m = mutated allele, wt = wild type (normal allele).

Figure 2. Schematic representation of MFN2 protein structure. MFN2 is a 757 AA protein with 4 major functional domains: 1 GTPase domain, 2 Heptad Repeat (HR) coiled-coil domains, and 2 transmembrane (TM) domains. The GTPase and HR2 domains interact to execute GTP hydrolysis during mitochondrial fusion; pathogenic MFN2 mutations are most commonly located in these domains (noted by star). GTPase mutations result in severe, childhood-onset CMT2A. Non-GTPase mutations are associated with less severe, adult-onset CMT2A with broad phenotypic heterogeneity.

Discussion & Conclusions

We describe the case of a 55-year-old man (proband, IIA) with axonal polyneuropathy, associated autonomic and visual symptoms, and a family history of the same symptoms. Clinical and genomic evaluation of the proband and 2 relatives (IB, IIB) suggests that the shared variant in MFN2 (c.1979C>A; p. Ala660Asp) is the most likely putative mutation in this family.

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