Introduction

- Pathogenic variants in the MFN2 gene are the most common cause of autosomal dominant axonal Charcot-Marie-Tooth (CMT2) disease, accounting for approximately 20–30% of all cases of CMT2.
- Patients with MFN2 variants have a heterogeneous clinical presentation and an age of onset that can range from 1 to 45 years of age.
- Despite the clinical variability, CMT2 patients have been reported to typically fall into two distinct groups: (1) those with early onset (i.e., under the age of 10, mean age 3.5) and a relatively severe phenotype and (2) those with late onset (i.e., over the age of 10, mean age 20.5) and a milder phenotype (Verhoeven et al. 2006).
- Rarely, autosomal recessive inheritance has been observed (Polke et al. 2011, Bombelli et al. 2014, Nicholson et al. 2008).

Case Report

Clinical Features

- The patient is a Caucasian female who presented with hypotonia and distal weakness at 7 months of age.
- Patient had rapidly progressing diaphragmatic paralysis over a 2-month period (documented by ultrasound), which necessitated tracheostomy and mechanical ventilation.
- Patients with CMT2 typically present with classic features of CMT (weakness, atrophy, sensory loss, foot deformities). In addition, MFN2 pathogenic variants have also been associated with optic atrophy, scoliosis, hearing loss, tremor, and white-matter lesions (Verhoeven et al. 2006, Nicholson et al. 2008, Polke et al. 2011, Brockmann et al. 2008).

Molecular Testing

- Next-generation sequencing of 28 genes (CMT full panel with deletion/duplication analysis, Invitae, San Francisco, CA) identified two significant sequence changes in the MFN2 gene, a novel deletion (c.2054–2069+1170del) and a missense variant (c.392A>G; p.Asn131Ser).
- Pathogenic MFN2 c.2054–2069+1170del
  - The c.2054–2069+1170del eliminates the last 6 amino acids and the donor-splice site of exon 17 and is predicted to disrupt mRNA splicing and lead to an absent or truncated protein.
  - This deletion has not been previously reported, but truncating variants in MFN2 are expected to be pathogenic (Verhoeven et al. 2005)
- Likely pathogenic MFN2 c.392A>G; p.Asn131Ser
  - The c.392A>G missense is not present in population databases and was found to be homozygous in two affected cousins from a large consanguineous family with autosomal recessive CMT1 (Fisher et al. 2012).

Family Testing

- Parental testing revealed that the truncating and missense variants are in trans in the patient (on opposite chromosomes); the mother (age 40) carried the truncating variant, and the father (age 46) carried the missense variant.
- Both parents had a normal neurologic exam, although electrodiagnostic studies were not done.
- Three paternal half siblings (two clinically asymptomatic and one with high arches) were found to be negative for the paternal variant.
- Maternal half brother with no symptoms at age 21 carried the truncating variant.

Discussion

- Although there are reports of recessively inherited MFN2 variants in the literature, these cases are relatively rare (Polke et al. 2011, Bombelli et al. 2014, Nicholson et al. 2008).
- Patients with CMT2 typically present with classic features of CMT (weakness, atrophy, sensory loss, foot deformities). In addition, MFN2 pathogenic variants have also been associated with optic atrophy, scoliosis, hearing loss, tremor, and white-matter lesions (Verhoeven et al. 2006, Nicholson et al. 2008, Polke et al. 2011, Brockmann et al. 2008).
- In this case, the patient was noted to have a rapidly progressing diaphragmatic paralysis (documented by ultrasound) over a 2-month period, which necessitated tracheostomy and mechanical ventilation. Her ophthalmologic exam did not reveal any optic nerve findings, brainstem auditory evoked response was normal, and a brain MRI did not show any white-matter changes.
- This case highlights several clinical findings not typically associated with MFN2 mutations, including an unusually young age of onset, early and severe diaphragmatic weakness, and autosomal recessive inheritance.

Conclusion

- These findings suggest that the truncating and missense variants in this family are causative for CMT with a recessive inheritance pattern.
- The combination of both atypical clinical features in this patient and an atypical mode of inheritance for the MFN2 gene demonstrate the utility of broad panel testing for patients with a suspicion of Charcot-Marie-Tooth disease.
- Continued broad panel testing for patients with CMT will likely provide a more complete picture of the clinical variability of this disease and further confirm the importance of testing CMT genes that have not been associated with a patient’s phenotype.

References