Early-Onset Charcot-Marie-Tooth Disease with Diaphragmatic Weakness: A Case Report of an Autosomal Recessive *MFN2* Compound Heterozygote

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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 one of 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.

Tests Completed	Outcome
Urine organic acids	Normal
Plasma amino acids	Normal
Plasma acylcarnitine profile	Normal
Total and free carnitine	Normal
Serum biotinidase	Normal
Microarray	Normal
SMN testing (sequencing and del)	Normal
Ophthalmologic exam	Normal
Brainstem auditory evoked responses (BAER)	Normal
Brain MRI	Normal
Electromyography (EMG) and nerve conduction study	Evidence of motor/sensory axonal neuropathy
28-gene Charcot-Marie-Tooth panel	*MFN2* c.2054_2069+1170del pathogenic & *MFN2* c.392A>G (p.Asn131Ser) likely pathogenic, detected in trans

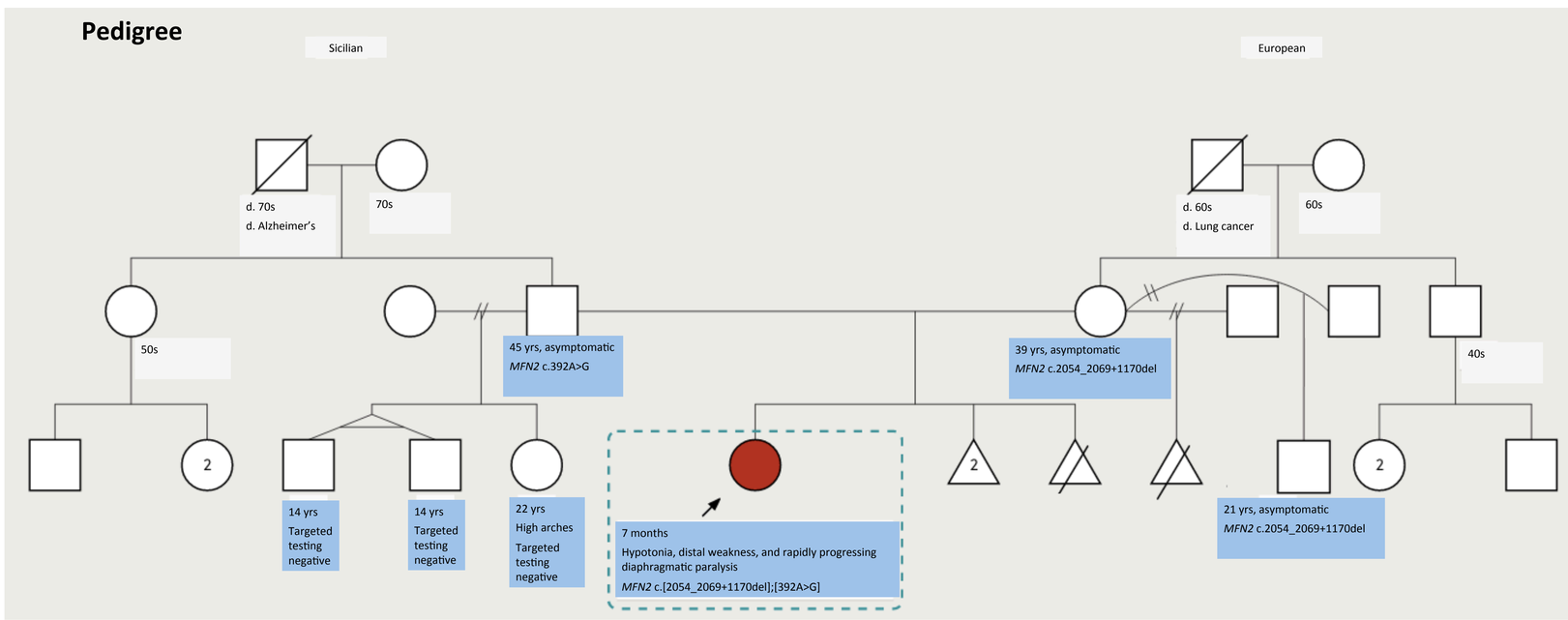
Molecular Testing

- 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.

Pedigree



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

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