Disease Causing Mutations in Patients with Charcot-Marie-Tooth Disease

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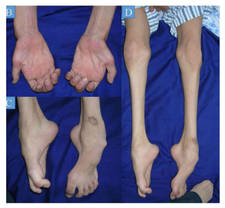
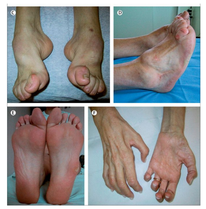
Introduction

Charcot-Marie-Tooth (CMT) Disease is a rare peripheral neuropathy that results in loss of motor or sensory functions in the hands, arms, legs, and feet of patients. CMT is hereditary with varying modes of inheritance, thus identifying the mutations causing disease can help inform future decisions. Additionally, depending on the genetic cause for the disease, there are available treatments, helping improve health outcomes for patients. In this study, three patients with CMT were analyzed and the associated mutations were investigated.

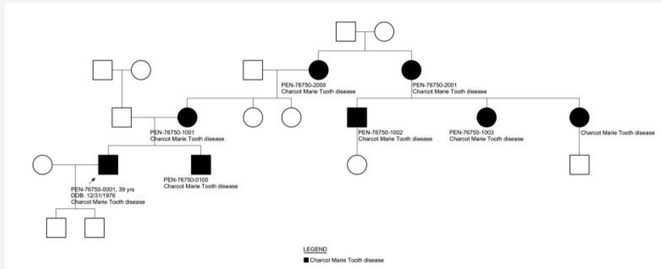




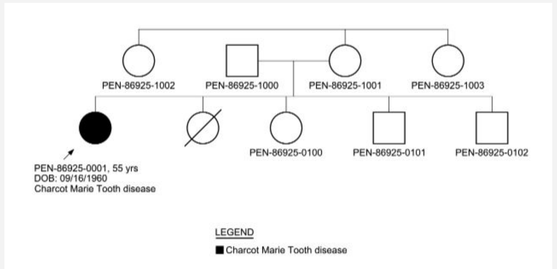
Methods

- Initial Vetting of Patients by Dr. Steven Scherer based on specific characteristics
- Blood Kits sent out to good candidates who are willing to participate
- Once returned, blood samples sent out to partners of lab (GeneDX, Invitae, UMiami Genomics Lab) where a WES analysis of the samples is done
- Samples analyzed using analysis software Genesis, with results examined based on segregation of disease, clinvar significance, mutation location, and rarity

Mitochondrial Inheritance in Patient 1



Recessive Inheritance in Patient 3



Patient 1 Variant Details in MT-ATP6 Gene

Gene	Variant type	Chromosome position	cDNA change	Protein change
MT-ATP6	Missense	ChrM:9185	c.659T>C	Leu220Pro

MT-ATP6 gene is involved in oxidative phosphorylation in the mitochondria. Mutations in the MT-ATP6 gene can lead to reduced signal strength, causing the symptoms of peripheral neuropathy.

Patient 2 Variant Details in POLG Gene

Gene	Variant type	Chromosome position	cDNA change	Protein change
POLG	Missense	Chr15:89872271	c.926G>A	Arg309His

POLG gene is involved in creating Pol γ which acts in the mitochondria. Similarly, mutations in the POLG gene can cause reduced signal strength which causes the symptoms of peripheral neuropathy.

Patient 3 Variant Details in POLG Gene

Gene	Variant type	Chromosome position	cDNA change	Protein change
POLG	Missense	Chr15:89866657	c.2243G>C	Trp748Ser

Conclusions

For Patient 1:
- Solved Mutation: MT-ATP6 (Leu220Pro)
- Mitochondrial Inheritance; Patient is Male so there is no risk to offspring

For Patient 2:
- Solved Mutation: POLG (Arg309His)
- Compound Heterozygous; Recessive; risk to offspring if mate is a carrier

For Patient 3:
- Solved Mutation: POLG (Trp748Ser)
- Autosomal Recessive; risk to offspring if mate is a carrier

Future Directions

- Analyze more patients and identify other causative mutations to expand the current database of patients
- Look into trends of these mutations across various patients
- Investigate potential biotechnological solutions that directly mitigate the symptoms caused by the mutation on a cellular level

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