# Co-occurrence of Pathogenic Variants in *MPZ* and *LRSAM1* in Charcot-Marie-Tooth Disease: Implications for Genetic Counseling for Multi-Gene Panel Testing

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## Background

Charcot-Marie-Tooth disease (CMT) is a group of hereditary neuropathies characterized by progressive muscle weakness and sensory loss in the arms and legs. It is the most common inherited disorder of the peripheral nervous system. CMT is both clinically and genetically heterogeneous, and its genetic causes include mutations in at least 50 genes with alterations in *PMP22*, *GJB1*, *MPZ*, and *MFN2* accounting for the majority of cases. Next-generation sequencing (NGS) is being used more frequently in genetic testing to interrogate multiple genes simultaneously. Although panel testing reduces costs and allows clinicians to cast a wide diagnostic net, it can also provide unanticipated results. We describe the clinical and molecular findings in a family in which multiple individuals had pathogenic variants in both *MPZ* and *LRSAM1*, which are each associated with autosomal dominant CMT.

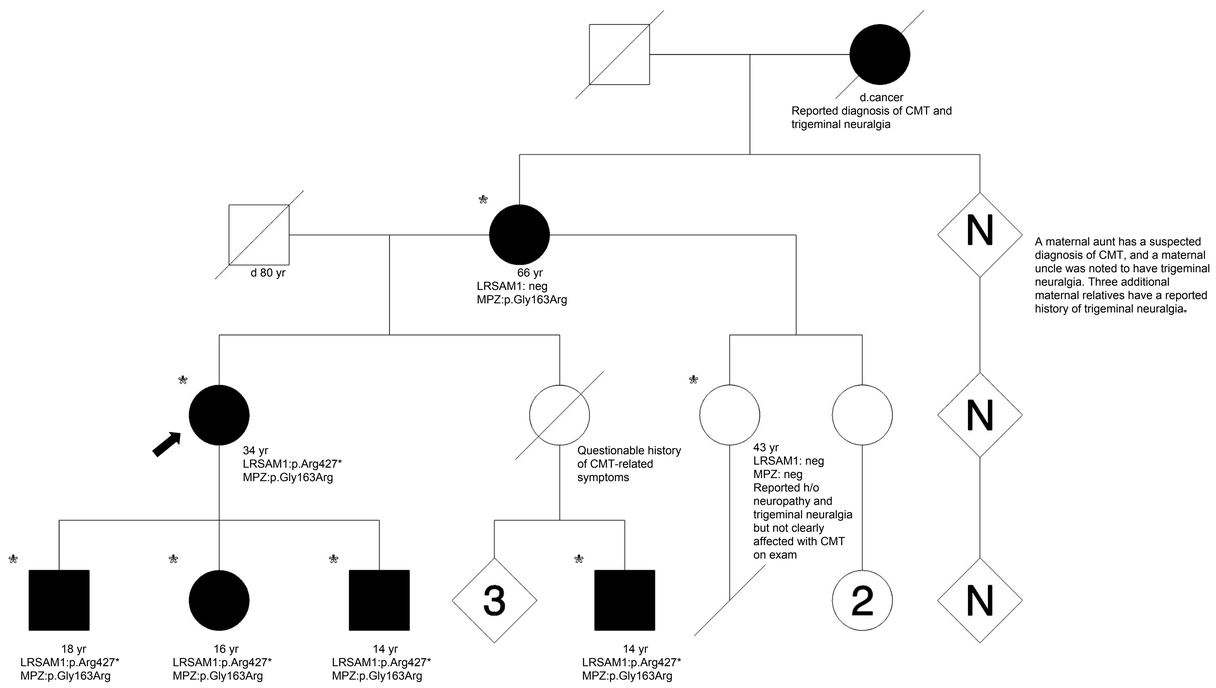
## Case Report

The proband is a 34-year-old woman who presented with loss of sensation in her lower extremities that prompted an electromyogram and nerve conduction testing. The results suggested a neuropathy consistent with CMT type 1 (CMT1). Her medical history was also notable for pes planus as a child that developed into pes cavus as an adult, kyphoscoliosis diagnosed at age 12 that required rod placement, and trigeminal neuralgia causing facial spasms. Foot and sensory abnormalities were also noted in the proband's daughter (age 16 years) and two sons (aged 18 and 14 years). Additional family members were described as having a clinical diagnosis or suspicion of CMT, including the proband's mother, maternal half sibling, maternal grandmother, and maternal aunt. A history of trigeminal neuralgia was also reported in six maternal relatives.

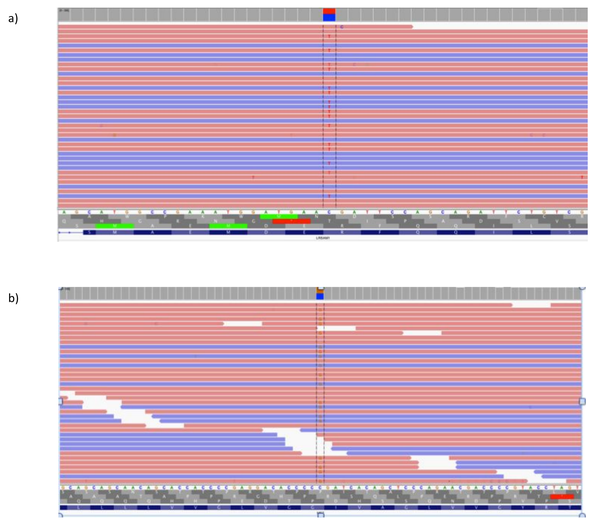
**Molecular Testing:** NGS of the following 32 genes was performed: *AARS, AIFM1, DNM2, DYNC1H1, EGR2, FGD4, FIG4, GARS, GDAP1, GJB1, GNB4, HSPB1, LITAF, LMNA, LRSAM1, MED25, MFN2, MPZ, MTMR2, NDRG1, NEFL, PDK3, PMP22, PRPS1, PRX, RAB7A, SBF2, SH3TC2, TRPV4*, and *YARS* (Charcot-Marie-Tooth Disease Comprehensive Panel, Invitae, San Francisco, CA). The following heterozygous variants were identified:

| Gene | Variant | Classification |
|---|---|---|
| *LRSAM1* | c.1279C>T (p.Arg427*) | Pathogenic |
| *MPZ* | c.487G>C (p.Gly163Arg) | Pathogenic |

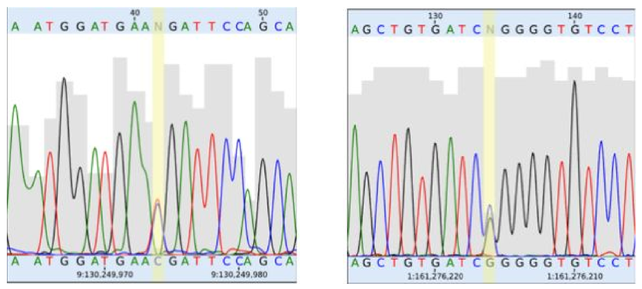
The *LRSAM1* nonsense variant is expected to result in an absent or disrupted protein product. Although this variant has not been previously reported in the literature, loss-of-function variants in *LRSAM1* are known to be pathogenic (PMID:22012984, 22781092). This *MPZ* missense variant is absent in population databases and reportedly segregates with disease in two families affected with CMT1 (PMID:12207932, 15170620). In addition, another nucleotide substitution (c.487G>A) that causes the same amino acid change has been reported in an affected individual (PMID:88000924)




**Family Testing:** Due to the findings in the proband, additional family members underwent clinical evaluation, genetic counseling, and testing (indicated by asterisks). The *MPZ* variant was identified in the proband's mother (the proband's father was unavailable for testing for the *LRSAM1* variant). Subsequent testing also identified both *MPZ* and *LRSAM1* pathogenic variants in all three of the proband's children and a maternal nephew.




Integrative Genomics Viewer images of NGS data of the (a) *LRSAM1* c.1279C>T (p.Arg427*) pathogenic variant; (b) *MPZ* c.487G>C (p.Gly163Arg) pathogenic variant.




Sanger sequencing confirmation of the proband's *LRSAM1* c.1279C>T (p.Arg427*) and *MPZ* c.487G>C (p.Gly163Arg) variants.

## Discussion

Digenic inheritance in CMT has not been widely reported in the literature, and such results have implications when providing genetic counseling to patients undergoing multi-gene panel testing. Whether the co-occurrence of the *MPZ* and *LRSAM1* variants leads to a more severe phenotype is unclear. *LRSAM1* mutations are associated with CMT type 2P, and *MPZ* mutations have been identified in a number of CMT types (CMT1B, CMT2I, CMT2J, DI-CMTD) with variable expressivity of symptoms.

The identification of multiple pathogenic variants allows for the screening for CMT associated with both mutations and has implications for at-risk family members. Had a more targeted testing approach been used initially, the pathogenic variant in *LRSAM1* may not have been identified. Our findings thus highlight an additional benefit of multi-gene panel testing to elucidate the etiology of genetically heterogeneous conditions and illustrate the implications for genetic counseling when pathogenic variants causing more than one genetic subtype of CMT are identified through this testing.