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# Poster P15

## Novel heterozygous NARS1 variant in a family with axonal peripheral neuropathy

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Introduction: Aminoacyl-tRNA synthetases (ARSs) are enzymes that charge tRNA molecules with cognate amino acids in the process of protein synthesis. Dysfunction of these ARSs have been implicated in different neurological disorders. Particularly dominant mutations in ARSs are associated with peripheral neuropathies including Charcot-Marie-Tooth (CMT) disease. NARS1 mutations have been observed in dominant and recessive inheritance. While recessive NARS1 variants are primarily associated with complex central nervous system disease and dominant NARS1 variants with peripheral neuropathies, some overlap between the associated phenotypes has been observed.

Methods: Whole-genome sequencing was performed in a family with 5 individuals affected by axonal CMT (CMT2). This analysis revealed a heterozygous candidate variant in NARS1. Sanger sequencing of an unaffected family member was performed for additional segregation. Additional yeast experiments to study the functional effect of the identified variant on NARS function are ongoing.

Results: We identified a heterozygous NARS1 variant NM_004539.4:c.896C>A, p.(Ser299Tyr) in all 5 affected individuals in this family. The variant could not be detected in another related unaffected individual. The variant is absent from gnomAD v4.1 and in-silico prediction of the variant supports pathogenicity (Revel 0.913; CADD 27.1). Yeast-complementation assays are ongoing to assess the potential and expected loss-of-function effect, a common feature of neuropathy-associated ARS variants.

Conclusion: We identified another putative pathogenic variant in NARS1, segregating with disease in a family with axonal CMT. Pathogenicity is to be further supported by yeast complementation assays, allowing the expansion of known dominant pathogenic NARS1 variants associated with peripheral nervous system phenotypes.