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Biallelic variants in the DARS2 gene as a novel cause of axonal Charcot-Marie-Tooth disease

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Aminoacyl-tRNA synthetases are associated with Charcot-Marie-Tooth (CMT) disease genetics and pathophysiology. DARS2, which encodes the mitochondrial aspartyl-tRNA synthetase, has been linked to leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate levels (LBSL). This study aims to explore the connection between biallelic DARS2 variants and axonal CMT.

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We examined five individuals from three unrelated families with axonal CMT and biallelic DARS2 variants. Functional studies in fibroblasts assessed effects on DARS2 expression, localization, and mitochondrial function. Enzymatic activity of recombinant proteins was tested in HEK293 cells.

The five individuals, including four adults, showed childhood-onset progressive axonal CMT. None had leukoencephalopathy, but one exhibited central nervous system involvement, with intellectual disability and epilepsy. Genetic analysis identified compound heterozygous DARS2 variants: Family A, p.Ser238Phe and p.Arg336Cys; Family B, p.Ser238Phe and p.Ile25Thrfs*38; Family C, c.492+2T>C and p.Pro503Leu. Functional studies in Family A revealed reduced DARS2 protein levels, abnormalities in the mitochondrial network, and impaired mitochondrial respiratory chain activity. The p.Pro503Leu variant showed 25% residual aminoacylation activity.

Our findings expand the spectrum of DARS2-related diseases by identifying a new link to axonal CMT. We propose that p.Ser238Phe is a hypomorphic variant that, when combined with more damaging variants, causes isolated axonal CMT. More severe combinations—even though less harmful than those in LBSL—result in axonal CMT with central nervous system involvement but without leukoencephalopathy. These results suggest that DARS2-associated diseases may exist on a continuum rather than representing strictly separate disorders of the central or peripheral nervous system.

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