Overexpression of tRNAHis rescues peripheral neuropathy caused by mutations in histidyltRNA synthetase

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Background: Dominantly inherited mutations in seven aminoacyl-tRNA synthetase (aaRSs) genes cause Charcot Marie-Tooth disease (CMT), a peripheral neuropathy characterized by progressive degeneration of motor and sensory axons. Prior work in glycyl-tRNA synthetase (GlyRS)–linked CMT demonstrated that overexpression of tRNAGly rescues neuropathy phenotypes in mouse and Drosophila models, supporting a mechanism in which mutant GlyRS sequesters tRNAGly, depleting charged tRNAGly pools, triggering ribosome stalling, and activating the integrated stress response. Unlike GlyRS, the functional impact of CMT-associated mutations in histidyl-tRNA synthetase (HisRS) is largely unclear. Method: Using Drosophila genetic models, we investigated whether CMT-HisRS arises from a toxic gain-of-function or dominant-negative loss-of-function mechanisms. Results: Knockdown of endogenous Drosophila HisRS (dHisRS) induced peripheral neuropathy phenotypes, supporting reduced aminoacylation activity as a potential disease mechanism. Overexpression of CMT-mutant human HisRS (hHisRS) did not induce neuropathy-like phenotypes. Overexpression of the corresponding Drosophila HisRS mutants induced neuromuscular synapse defects and reduced dendritic coverage in multidendritic sensory neurons. Importantly, these neuronal defects were rescued by co-overexpression of tRNAHis, suggesting that tRNAHis sequestration likely underlies CMT-HisRS and is likely a unifying mechanism in other forms of CMT-aaRS. Conclusion: Taken together, these findings support cognate tRNA supplementation as a viable RNA therapeutic strategy for CMT-aaRS