Researchers find novel mutation affecting YARS causes multisystem disease

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Researchers have identified a novel missense mutation in tyrosyl-tRNA synthetase (YARS c.499C>A, p.Pro167Thr) that causes a severe recessive disorder in affected individuals. The study, led by clinicians, researchers and collaborators of the Clinic for Special Children in Strasburg, PA, appears in *Human Molecular Genetics*. The report includes detailed clinical characterization of seven related Amish children who were homozygous for the variant. The children all

exhibited poor growth, developmental delay, abnormal brain white matter, hearing loss, involuntary eye movements, progressive cholestatic liver disease, pancreatic insufficiency, hypoglycemia, anemia, intermittent excess of protein in urine, recurrent bloodstream infections, and chronic pulmonary disease.

YARS directs the production of the aminoacyl-tRNA synthase protein, which catalyzes the attachment of the amino acid tyrosine to its corresponding tRNA as an essential step in the translation of the genetic code to protein. Functional assays in yeast demonstrated that the YARS p.Pro167Thr substitution causes reduced protein function and poor cell growth. Protein-protein interaction studies in human embryonic kidney cells also show that this change results in the reduced homodimerization process, which is essential for the protein's catalytic function. In contrast to previous reports of other variants in YARS, related adults heterozygous for the c.499C>A variant showed no evidence of damage to peripheral nerves on electromyography.

The children in the study share some of the same phenotypic features as children in previous reports, but also broaden the phenotypic spectrum to include auditory, hematologic and renal symptoms. This report is the first in the broader category of ARS-opathies that includes pancreatic dysfunction. A deeper understanding of YARS in human disease may inspire innovative therapies and improve the care of affected patients.

More information: Katie B Williams et al, Homozygosity for a mutation affecting the catalytic domain of tyrosyl-tRNA synthetase (YARS) causes multisystem disease, *Human Molecular Genetics* (2018). DOI: 10.1093/hmg/ddy344

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