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FOR IMMEDIATE RELEASE

RESEARCHERS FIND NOVEL MUTATION AFFECTING YARS CAUSES MULTISYSTEM DISEASE

STRASBURG, PA- 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



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pancreatic dysfunction. A deeper understanding of YARS in human disease may inspire innovative therapies and improve the care of affected patients.

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The research was conducted by a team including the study's lead author Katie B. Williams, from the Clinic for Special Children, Strasburg, PA; senior authors Kevin A. Strauss from the Clinic for Special Children, Strasburg, PA, Anthony Antonellis from Program in Cellular and Molecular Biology, Medical Scientist Training Program, and Department of Human Genetics, University of Michigan, Ann Arbor, MI, and Robert N. Jinks from Department of Biology, Biological Foundations of Behavior Program, Franklin & Marshall, Lancaster, PA; Karlla W. Brigatti, Erik G. Puffenberger, and Vincent J. Carson from the Clinic for Special Children, Strasburg, PA; Claudia Gonzaga-Jauregui, Jeffrey G. Reid, John D. Overton and Aris Baras from Regeneron Genetics Center, Tarrytown, NY, Laurie B. Griffin from Program in Cellular and Molecular Biology and Medical Scientist Training Program, University of Michigan, Ann Arbor, MI, Erick D. Martinez from Department of Biology, Biological Foundations of Behavior Program, Franklin & Marshall, Lancaster, PA, Olivia K. Wenger from New Leaf Center, Mount Eaton, OH and Department of Pediatrics, Akron Children's Hospital, Akron, OH, Mark Yoder from Northeast Ohio Medical University, Rootstown, OH, Vinay V.R. Furuya from Department of Medical Imaging, Nemours/Alfred I. duPont Hospital, Wilmington, DE, Michael D. Fox, Matthew M. Demczko and Laura Poskitt from Department of Pediatrics, Nemours/Alfred I. duPont Hospital, Wilmington, DE, and Department of Pediatrics, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, Katryn Furuya from Division of Pediatric Gastroenterology, Department of Pediatrics, Mayo Clinic, Rochester, MN and Nemours/Alfred I. duPont Hospital for Children, Orlando, FL, Lili Miles from Department of Pathology and Laboratory Medicine, Nemours/Alfred I. DuPont Hospital for Children, Orlando, FL, Kadakkal Radhakrishnan from Department of Gastroenterology, Children's Hospital at Cleveland Clinic, Cleveland, OH and Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH.

About the Clinic for Special Children

The Clinic for Special Children (CSC) is a non-profit organization located in Strasburg, PA, which provides primary pediatric care and advanced laboratory services to those who suffer from genetic or other complex medical disorders. Founded in 1989, the organization provides services to over 1,050 active patients and is recognized as a world-leader in translational and precision medicine. The organization is primarily supported through community fundraising events and donations. For more information, please visit www.ClinicforSpecialChildren.org