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FOR IMMEDIATE RELEASE

THE EFFECTS OF *NPRL3* LOSS DESCRIBED IN NEW STUDY IN OLD ORDER MENNONITE POPULATION

STRASBURG, PA – A new study published in this month's issue of *Brain* details the effects of the loss of gene products from *NPRL3* on seizure threshold, cortical lamination, mTOR localization, and neuron structure. This study reports the largest and genealogically oldest known *NPRL3* patient pedigree. The 12-generation, Old Order Mennonite pedigree dates back to a founder *NPRL3* variant originating in a couple from 1727. The study was a collaborative effort led by clinicians and researchers from the Clinic for Special Children and the University of Maryland School of Medicine.

Despite a common founder variant in the Old Order Mennonite pedigree, affected individuals showed a range of phenotypes. This spectrum ranged from normal brain imaging to malformations of cortical development, and seizure freedom to drug resistant epilepsy. Researchers did not identify a gene modifier that would explain the varying seizure phenotypes.

Murine *NPRL3* knockout *in vitro* studies caused mTOR pathway hyperactivation, cell soma enlargement, and the formation of cellular clustering which were prevented with rapamycin. To model human malformations in cortical development associated with *NPRL3* variants, the researchers created a *NPRL3* knockout cells as well as a focal *NPRL3* knockout in fetal mouse cerebral cortex using in utero electroporation. The researchers found changes in cortical lamination and abnormal neurons within the white matter. These effects were prevented with rapamycin treatment.

EEG recordings showed hyperexcitability and reduced seizure threshold. The researchers concluded that *NPRL3* variants, with their highly variable clinical phenotypes, result from mTOR-dependent effects on cell structure, cortical

development, and network organization. The study provides a pre-clinical platform for future studies that examine the efficacy of mTOR inhibitors in patients with genetic variants in *NPRL3* and other GATOR1 complex genes.

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The research was conducted by a team including the study's first author Philip H. Iffland, from University of Maryland School of Medicine Departments of Neurology and Pharmacology, Baltimore, MD; Mariah Everett, Lauren E. Bowser, Erik G. Puffenberger, and Vincent J. Carson, from Clinic for Special Children, Strasburg, PA; Katherine M. Cobb-Pitstick, from UPMC Children's Hospital of Pittsburgh Department of Neurology, Pittsburgh, PA; Claudia Gonzaga-Jauregui, Regeneron Genetics Center, Regeneron Pharmaceuticals Inc., Tarrytown, NY; Allan E. Barnes, Janice K. Babus, Andrea J. Romanowski, Marianna Baybis, Soad Elziny, Alexandros Poulopoulos, and Peter B. Crino from University of Maryland School of Medicine Departments of Neurology and Pharmacology, Baltimore, MD.

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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 live with genetic or other complex medical disorders. Founded in 1989, the organization provides services to over 1,050 individuals 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