Clinic *for* Special Children®

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FOR IMMEDIATE RELEASE

GENETIC VARIANT TIED TO RISK OF MAJOR DEPRESSIVE DISORDER

LANCASTER COUNTY, PA – A study uncovers a rare variant in the G protein-coupled receptor (GPCR) 156 gene associated with depression and finds that the variant is tied to hyperactivity in a brain region linked to mood regulation and stress sensitivity in mice. Major depressive disorder (MDD) is a leading cause of disability worldwide, and current treatments can be difficult to implement, access, or tolerate.

Kevin Strauss, Sander Markx, Bradley Miller, and colleagues analyzed genomic data and psychiatric assessments of 78 individuals in an extended Old Order Mennonite family and identified a rare variant in the *GPR156* gene that was associated with MDD. The authors generated mouse models expressing no GPR156, wild-type human GPR156, or human mutant GPR156 (harboring the variant found in the Mennonite family). GPR156 expression was highest in the mouse medial habenula, and mice expressing human mutant GPR156 exhibited hyperactivity in this brain region, which has been previously linked to mood regulation.

Mice expressing no GPR156 and mice expressing human mutant GPR156 exhibited depression-like symptoms, such as poor perseverance, increased stress avoidance, and increased startle responses, compared with wild-type mice and mice expressing wild-type human GPR156. Some of the symptoms of mice that expressed the human mutant GPR156 improved after nine weeks of treatment with the antidepressants fluoxetine or imipramine. According to the authors, the findings suggest that GRPR156 may be a therapeutic target for major depression.

"Major depressive disorder is a leading cause of disability worldwide and can affect people from all communities and backgrounds. Working closely with partners at

Columbia University and Regeneron Genetics Center, the Clinic for Special Children research team discovered a rare mutation in a gene called *GPR156* that increases susceptibility to major depression nearly three-fold and can be passed down through the generations. We found that GPR156 is expressed in a deep part of the brain called the medial habenula, which is known to play a crucial role in behavioral responses to stress. This work deepens our understanding of the causes of depression and introduces a new target for its treatment," shares Dr. Kevin A. Strauss, Head of Therapeutic Development at the Clinic for Special Children.

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The research was conducted by a team including the study's first author Bradley R. Miller from the Department of Psychiatry, Columbia University, New York, NY, and Division of Systems Neuroscience, New York State Psychiatric Institute, New York, NY, Claudia Gonzaga-Jauregui and Cristopher Van Hout from the Regeneron Genetics Center, Tarrytown, NY, and the International Laboratory for Human Genome Research, Universidad Nacional Autonoma de Mexico (UNAM), Juriquilla, Queretaro, Mexico, Karlla W. Brigatti, Erik G. Puffenberger, Millie Young from the Clinic for Special Children, Gordonville, PA, Job de Jong from the Department of Psychiatry, Columbia University, New York, NY, and Division of Molecular Therapeutics, New York State Psychiatric Institute, New York, NY, Robert S. Breese from Regeneron Pharmaceuticals, Inc., Tarrytown, NY, Seung Yeon Ko, Rene Hen, Steven A. Kushner, and Hilledna J. Gregoire from Department of Psychiatry, Columbia University, New York, NY, and Division of Systems Neuroscience, New York State Psychiatric Institute, New York, NY, Victor M Luna from the Alzheimer's Center at Temple, Lewis Katz School of Medicine, Temple University, Philadelphia, PA, Jeffrey Staples, Shane McCarthy, Bin Ye, Eli Stahl, Silvio Alessandro Di Gioia, Dadong Li, John D. Overton, Alan R. Shuldiner from the Regeneron Genetics Center, Tarrytown, NY, Michael B. First, Andrew J. Dwork, Lynn McDonald, and Gorazd Rosoklija from the Department of Psychiatry, Columbia University, New York, NY, Evangelos Pefanis, Susannah Brydges, Jose Rojas, Scott Mellis, Susan D. Croll, and Nicole Alessandri-Haber from Regeneron Pharmaceuticals, Inc, Tarrytown, NY, David Carey and Kevin Ellwood from Geisinger, Danville, PA, Aris N. Economides from the Regeneron Genetics Center and Regeneron Pharmaceuticals, Inc , Tarrytown, NY, Nao Chuhma and Stephen Rayport from the Division of Molecular Therapeutics, New York State Psychiatric Institute, New York, NY, Najaf Amin from the Department of Psychiatry and the Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands, Sander Marx from the Department of Psychiatry, Columbia University, New York, NY, and the Division of Molecular Therapeutics, New York State Psychiatric Institute, New York, NY, and Kevin A. Strauss from the Clinic for Special Children, Gordonville, PA, Department of Pediatrics, Penn Medicine-Lancaster General Hospital, Lancaster, PA, and the

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About the Clinic for Special Children

The Clinic for Special Children is a non-profit organization located in Lancaster County, PA, that provides primary care and advanced laboratory services to children and adults who live with genetic or other complex medical disorders. Founded in 1989, the organization provides services to 1,700 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