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Genetic alterations in shared biological pathways as major risk factor for ASD

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A substantial proportion of risk for developing autism spectrum disorders (ASD), resides in genes that are part of specific, interconnected biological pathways, according to researchers from the Icahn School of Medicine at Mount Sinai, who conducted a broad study of almost 2,500 families in the United States and throughout the world. The study, titled "Convergence of Genes and Cellular Pathways Dysregulated in Autism Spectrum Disorders," was first published online in the *American Journal of Human Genetics* on April 24.

ASD affects about one percent of the population in the United States and is characterized by impairments in social interaction and communication, as well as by repetitive and restricted behaviors. ASD ranges from mild to severe levels of impairment, with cognitive function among individuals from above average to intellectual disability.

Previously, ASD has been shown to be highly inheritable, and genomic studies have revealed that that there are various sources of risk for ASD, including large abnormalities in whole chromosomes, deletions or duplications in sections of DNA – called copy number variants (CNVs), and even changes of single nucleotides (SNVs) within a gene; genes contain instructions to produce proteins that have various functions in the cell.

The researchers reported numerous CNVs affecting genes, and found that these genes are part of similar cellular pathways involved in brain development, synapse function and chromatin regulation. Individuals

with ASD carried more of these CNVs than individuals in the control group, and some of them were inherited while others were only present in offspring with ASD.

An earlier study, results of which were first published in 2010, highlighted a subset of these findings within a cohort of approximately 1,000 families in the U.S. and Europe; this larger study has expanded that cohort to nearly 2,500 families, each comprising "trios" of two parents and one child. By further aggregating CNVs and SNVs (the latter identified in other studies), Mount Sinai researchers discovered many additional genes and pathways involved in ASD.

"We hope that these new findings will help group individuals with ASD based upon their genetic causes and lead to earlier diagnosis, and smarter, more focused therapies and interventions for autism spectrum disorders," said first author Dalila Pinto, PhD, Assistant Professor of Psychiatry, and Genetics and Genomic Sciences at the Icahn School of Medicine at Mount Sinai. Dr. Pinto is a Seaver Foundation Faculty Fellow, and a member of the Mindich Child Health & Development Institute, the Icahn Institute for Genomics and Multiscale Biology, and the Friedman Brain Institute at the Icahn School of Medicine at Mount Sinai; other Mount Sinai researchers on this study include Mafalda Barbosa, Graduate Student in Psychiatry; Xiao Xu, PhD, Postdoctoral Fellow in Psychiatry; Alexander Kolevzon, MD, Clinical Director of the Seaver Autism Center and Associate Professor of Psychiatry and Pediatrics; and Joseph D. Buxbaum, PhD, Director of the Seaver Autism Center, Vice Chair for Research in Psychiatry, and Professor of Psychiatry, Neuroscience, and Genetics and Genomic Sciences.

Provided by The Mount Sinai Hospital

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