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Study Surprise Yields New Target for Assessing Genes Linked to Autism

DURHAM, N.C. – Researchers at Duke University Medical Center have uncovered a new genetic signature that correlates strongly with autism which doesn't involve changes to DNA sequence itself, but rather to the way the genes are turned off and on. The finding may suggest new approaches to diagnosis and treatment of autism.

The researchers found higher-than-usual numbers of gene-regulating molecules called methyl groups in a region of the genome that regulates oxytocin receptor expression in people with autism.

“In both blood samples and brain tissue, the methylation status of specific nucleotides in the oxytocin receptor gene is significantly higher in someone with autism, about 70 percent, compared to the control population, where it is about 40 percent,” said co-lead author Simon G. Gregory, Ph.D., assistant professor in the Duke Department of Medicine. The work appears in BMC Medicine journal online.

Oxytocin is a hormone secreted into the bloodstream from the brain, and also released within the brain, where it has a bearing on social interaction. Previous studies have shown that giving oxytocin can improve an autistic person's social engagement behavior and it is being explored as a potential treatment of the disorder. Higher methylation of the oxytocin receptor gene may make a person less sensitive to the hormone.

The findings by Dr. Gregory and his colleagues will potentially provide information about which individuals will respond better to treatment with oxytocin.

“We are excited about our findings because they represent one of the few occasions in which a mechanism other than genetic susceptibility or genome instability is implicated in the development of autism, Gregory said.

“These results provide a possible explanation of why social isolation forms part of the autism spectrum – because an autistic individual's ability to respond to oxytocin may be limited,” Gregory said. “Oxytocin has been tied to levels of trust and ability to read social cues.”

Although the methylation status of the OXTR gene is not a definitive diagnosis of autism by itself, a test for methylation might be used along with other clinical tests for diagnosing autism. Gregory said that methylation-modifying drugs also may be a new avenue for treatments.

Though not a change to the DNA sequence itself, methylation status can be inherited, by what is known as epigenetics - inherited changes in gene regulation.

“The epigenetic link to autism is extremely exciting as it provides another opportunity for us to explore the heritability of this disorder and argues the importance of exploring epigenetic markers in complex disease,” said co-lead author Jessica J. Connelly, Ph.D., assistant professor in the Department of Medicine at the University of Virginia.

The identification of differences in methylation status of OXTR in people with and without autism was discovered through a genome-wide study of genomic instability.

The researchers examined 119 individuals with autism to identify genomic rearrangements. One of these individuals had a DNA deletion of a region containing the OXTR gene. The group then examined the genomic make-up of the individual’s family members and established that the boy with the deletion had a brother with autism who didn’t have the deletion. (Their mother had symptoms of an obsessive-compulsive disorder, but not autism; autism and OCD share the symptom of intensely repetitive thoughts and behaviors).

The researchers examined the brother’s genome and found instances of elevated methylation. With this discovery, they looked again at independent collections of blood samples and brain tissue from a repository of specimens, and found consistent differences in OXTR methylation.

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Other authors include co-lead-author Jessica J. Connelly, now with the University of Virginia and formerly of the Duke Center for Human Genetics; Aaron Towers, J. Johnson, D Biscocho, and Christina Markunas of the Duke Center for Human Genetics; G.R. DeLong of the Duke Department of Medicine; S.K. Murphy of the Duke Departments of Obstetrics and Gynecology, and Pathology; Carla Lintas and Antonio. Persico of the Laboratory of Molecular Psychiatry and Neurogenetics, University Campus Bio-Medico, and the Department of Experimental Neurosciences, IRCCS “Fondazione Santa Lucia”, both in Rome; R.K. Abramson and H.H. Wright of the Department of Neuropsychiatry, SOM-USC in Columbia, S.C.; P. Ellis and C.F. Langford of Wellcome Trust Sanger Institute in Hinxton, U.K.; and Michael L. Cuccaro and Margaret A. Pericak-Vance of the John P. Hussman Institute for Human Genomics of the University of Miami Miller School of Medicine in Miami, Fla.

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