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Genetic analysis of individuals with autism finds gene deletions

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Using powerful genetic sequencing technology, a team of investigators, led by researchers at the Icahn School of Medicine at Mount Sinai, scanned the genome of hundreds of individuals, and discovered those diagnosed with autism spectrum disorder (ASD) were more likely to have gene deletions than were people without the disorder. That means those individuals—seven percent of the study group—had one copy of one or more genes when they should have had two.

The scientists further report, in the *American Journal of Human Genetics*, that their analysis suggests the deletions may result in the miswiring and altered activity of brain neurons.

"This is the first finding that small deletions impacting one or two genes appear to be common in autism, and that these deletions contribute to risk of development of the disorder," says the study's lead investigator, Joseph D. Buxbaum, PhD, Professor of Psychiatry, Genetics and Genomic Sciences and Neuroscience at the Icahn School of Medicine at Mount Sinai.

"This conclusion needs to be expanded in other independent samples of ASD so that we can truly understand how the risk manifests," he says.

That process is now ongoing, Dr. Buxbaum adds. The Autism Sequencing Consortium, a group of over 25 institutions, was awarded a $7 million grant from the National Institutes of Health to continue analyzing the genomes of thousands of ASD individuals at Mount Sinai.

First look for missing genes in autistic population

Autism, which affects about one percent of the population, is a developmental disorder thought to be caused by a complex interplay between genetic and environmental factors. Although the disorder is highly heritable, the majority of autism cases cannot be attributed to known inherited causes, Dr. Buxbaum says.

While research has indicated that there might be as many as 1,000 genes or genomic regions that contribute to ASD, most studies have looked for either single point mutations—a change in a single letter of DNA on a gene—or for large areas of the genome, encompassing many genes, that is altered.

In this study, the researchers looked for small copy number variation —deletion or duplication of genes— between ASD individuals and a "control" population without the disorder.

To conduct the study, they used exome sequencing to look at all 22,000 human genes in the sample set, and analyzed that data using the eXome Hidden Markov Model (XHMM) program. Together, the tools are the first that can find single gene-sized deletions or additions in the genome.

"This gives us the power, for the first time, to run one test from a blood sample and compare it to a reference genome to search for mutations and small copy number variation in patients," Dr. Buxbaum says.

They applied this method to analyze a databaseconsisting of 431 ASD cases and 379 matched controls, totaling 811 individuals. They found 803 gene deletions in the ASD group and 583 deletions in the control group, and the ASD population had a greater likelihood of having multiple small deletions.

Gene deletions not due to genetic inheritance.

"It is now known that imperfect gene copy number is one of the major sources of variability between people. One of the reasons we are different from each other is because of gene additions or deletions which are often inherited," he says. "But of the extra deletions we see in ASD not all are due to genetic inheritance. Some occur during the development of the egg or sperm, and deletions that develop in this way tend to be associated with the disorder."

The researchers then examined the deletions they found in the autistic group and found that a significant proportion of them related to autophagy, a key process that keeps cells healthy by replacing membranes and organelles.

"There is a good reason to believe that autophagy is really important for brain development because the brain produces many more synapses than it needs, and the excess needs to be pruned back," Dr. Buxbaum says. "Too many, or too few, synapses have the same effect of not making communication work very well. It could mean that some synaptic connections come in too late and may not solidify properly."

The researchers believe the findings will have clinical significance. "Key copy number variations—those that consistently appear in an autistic population—can impact genetic testing," Dr. Buxbaum says.

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