World's largest DNA scan reveals rare variants that disrupt gene activity in autistic children

Science Daily

Published in the June 9 online edition of *Nature,* the findings emphasize the need for larger study samples to illuminate the diverse genetic causes of the brain disorder.

UCLA researchers from the David Geffen School of Medicine and Semel Institute for Neuroscience and Human Behavior were among the lead investigators of the three-year study by the Autism Genome Project, an international consortium of scientists from more than 60 institutions in 12 countries.

"We know that 10 million gene variants consistently exist in every individual's genome," explained Rita Cantor, UCLA professor of human genetics. "We used DNA chips to collect and analyze data on 1 million of these variations to shed light on how autism develops."

Using blood samples from 996 elementary school-age children diagnosed on the autism spectrum from the United States, Canada, and Europe, the scientific teams combed the children's DNA for rare deletions and duplications. In particular, they hunted for changes in the genetic information that a child inherits from each parent. The families consisted of parents with one autistic child.

"We discovered two striking things. First, the rare variants interfered nearly 20 percent more in the genes of autistic children than in the healthy children," said Dr. Daniel Geschwind, Gordon and Virginia MacDonald Distinguished Chair in Human Genetics and UCLA professor of neurology and psychiatry. "Second, we found a number of disruptions that are new, or de novo. The autistic child is the first in their family to carry that variant. The parents do not have it.

"This suggests that tiny genetic errors may occur during formation of the parents' eggs and sperm, and these variations are copied during creation of their child's DNA," added Geschwind, who is also director of the UCLA Center for Autism Research and Treatment. "The finding parallels what takes place in chromosomal disorders like Down's syndrome."

The study confirms earlier findings in smaller samples that some children carry private genetic mutations that are unique to them, contributing to their susceptibility to autism.

"We found many more disrupted genes in the autistic children than in the control group," said Dr. Stanley Nelson, UCLA professor of human genetics and psychiatry. "But here's where it gets tricky -- every child showed a different disturbance in a different gene. When we looked at the gene's function, however, certain categories of genes emerged that were more likely to be influenced by the mutation.

"Three of the disrupted genes, for example, participate in cellular communication," Nelson explained. "They all cluster at the synapse, the site where brain cells talk to each other. One of these genes has previously been tied to autism and intellectual disabilities."

The researchers' next step will be to uncover patterns by identifying groups of disrupted genes that work together in the body to establish key functions or biological processes. The results may reveal clues to where genes go awry and increase autism risk, offering hope for common treatments.

In the meantime, families affected by autism can help advance research efforts by participating in future genetic studies.

"This study's larger sample size enabled us to pinpoint rare variations that we could not have detected in a smaller group," emphasized Nelson. "Yet these findings explain only 3.3 percent of the genetic origins of autism. In order to identify all of autism's genetic causes, we need tens of thousands of families to volunteer their DNA samples for sequencing."

Many of the study's samples were provided by families who donated blood to the Los Angeles-based Autism Genetic Resource Exchange (AGRE), a gene bank created and funded by Cure Autism Now, (since renamed Autism Speaks), and a grant from the National Institute of Mental Health to the three UCLA authors.

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About Autism

Autism is a complex brain disorder that strikes in early childhood. The condition disrupts a child's ability to communicate and develop social relationships and is often accompanied by acute behavioral challenges. Autism spectrum disorders are diagnosed in one in 110 children in the United States, affecting four times as many boys as girls. Diagnoses have expanded tenfold in the last decade.

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