Autism linked to hundreds of genetic mutations

Three new studies conclude that autism disorders are genetically very complex, not caused by one or two gene defects. The potential changes in DNA may produce what are essentially different forms of autism.

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Autism is not caused by one or two gene defects but probably by hundreds of different mutations, many of which arise spontaneously, according to research that examined the genetic underpinnings of the disorder in more than 1,000 families.

The findings, reported in three studies published Wednesday in the journal Neuron, cast autism disorders as genetically very complex, involving many potential changes in DNA that may produce, essentially, different forms of autism.

The affected genes, however, appear to be part of a large network involved in controlling the development of synapses, the critical junctions between nerve cells that allow them to communicate, according to one of the three studies.

Although the work will have no immediate value to patients or their families, the insights provide a wealth of targets to pursue in developing treatments for the disorder, scientists said. Understanding the genetic causes of autism spectrum disorders may promote more accurate diagnoses, and research on synapse formation and function could yield treatments that address the flow of signals between nerve cells.

"For the first time we're getting a sense of how many areas of the genome are likely to contribute to autism," said Dr. Matthew W. State, associate professor of psychiatry and of genetics at Yale University and the lead investigator of one of the reports. "We know there are multiple, different ways to get autism."

Autism spectrum disorders are a group of conditions, ranging from severe to mild, that are characterized by problems with social interactions. Those with autism may exhibit repetitive behaviors and narrow, obsessive interests; some may have low IQs or problems with language development. About 1 in 110 U.S. children has an autism spectrum disorder, according to the Centers for Disease Control and Prevention.

An estimated 25% of autism spectrum disorder cases are linked to inherited gene mutations that are passed from parent to child. Some of these high-risk genes have already been identified. But researchers have been puzzled by the cause of the disorder in families with no history of autism.

To tackle the question, two independent groups of researchers used DNA data collected by the Simons Foundation Autism Research Initiative on more than 1,000 families with at least two children in which a single child had autism spectrum disorder but the parents and siblings did not.

The teams, led respectively by State at Yale and by Michael Wigler, a genetics researcher at Cold Spring Harbor Laboratory in Cold Spring Harbor, N.Y., then compared the DNA of those with autism to that of their unaffected siblings.

The scientists found that autism was associated with rare duplications and deletions of stretches of DNA that appear to have arisen spontaneously; in the study led by Wigler, these events occurred in 8% of children with autism spectrum disorder compared with 2% of unaffected siblings.

The scientists believe, though have not yet proved, that many of these changes — and more specifically, removal or duplication of certain genes that lie within the affected DNA regions — are responsible for the children's disorders.

"In many diseases, you see an inheritance pattern. You don't see that with autism," said Michael Ronemus, a coauthor of the Cold Spring Harbor team and a research investigator at that institution.

The two teams have identified a few dozen of these spontaneous mutations, but there could be as many as 300, Ronemus said. As studies continue, they may define a number of distinct sub-types of autism, he added.

The spontaneous mutations appear to occur in the parents' germ lines, which give rise to sperm and eggs, and either father or mother can be the source.

One compelling question is what is causing the mutations, said Irva Hertz-Picciotto, an autism researcher and professor of public health science at UC Davis who was not involved in the studies.

Reported rates of autism have risen in recent decades, and though some scientists believe that much of the change is due to greater awareness of the condition and thus increased diagnosis, some have questioned whether certain environmental exposures may be playing a role.

"The obvious conclusion one has to reach is that something environmental may well be the cause of these [spontaneous] changes in DNA," Hertz-Picciotto said.

The studies also yielded some intriguing clues about gender differences in autism spectrum disorders. Boys are four times more likely to develop autism

than girls. The analysis led by Wigler found that girls with autism had more of the rare duplications and deletions than boys with autism and that the events in girls also involved more genes — implying, perhaps, that girls require a higher number of genetic changes to develop the disorder.

"Mutations occur at the same rate in males and females, but in females the mutations will not have such a devastating impact," Ronemus said. "We don't understand the basis for that."

Both research teams pinpointed a region of chromosome No. 7 that appears key to the development of social personality. Researchers had known that deletion of that region, called 7q11.23, causes Williams-Beuren syndrome, a rare neurological disorder characterized by a highly social personality. The new studies showed that duplications in the same region are linked to autism spectrum disorder.

"What is it about that region? There has to be some biological factor that is playing a key role in defining social behavior," State said. "If we can understand the underlying biology of autism, we'll be able to do a far better job of treating it."