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Genes' role in autism a complicated connection

Though scientists know genetic factors play a part in the array of autism disorders, the vast number of genes involved, plus possible environmental considerations, make narrowing the cause a vastly difficult goal.

By Amanda Leigh Mascarelli, Special to the Los Angeles Times

June 21, 2010

Though the causes of autism are unclear, and many researchers believe that environmental factors play some kind of role, they are sure of one thing: Genes are strongly involved.

Scientists once harbored hopes that autism might be linked to a handful of genetic mutations that would clearly explain why someone develops it. But the genetic roots of autism (known these days as autism spectrum disorders because behaviors and severity differ widely) are proving much trickier to untangle than anticipated**.**

One problem is that the number of people in most studies has been limited; another is that the small tweaks in genes that scientists have linked to autism so far are very rare in the human population. Nonetheless, as new techniques make it easier to inspect the human genome in fine detail, researchers are uncovering a dizzying array of genes that play a role in autism in different people. Clues to the biological processes affected by these genes are beginning to emerge — and some offer hope for one day reversing the symptoms of this range of related disorders.

So far, scientists know this much: Autism is linked to different genes in different people, and multiple genes could be involved in each person. These genetic factors, in turn, interplay with environmental ones — possibly ones a fetus is exposed to in the womb — but researchers don't yet know just what the environmental factors are.

"Even as we're narrowing the playing field, we're learning that the playing field is more complex, because it's not just one gene that's causing the syndrome; it's many," says Dr. John Constantino, a pediatric psychiatrist at Washington University in St. Louis.

Complicated genetics

Researchers have known for decades from twin and family studies that autism is heritable. They also know that disorders of brain development related to autism, such as fragile X and Rett syndromes, can be traced back to a single gene in all people affected.

However, it's now known that new genetic mutations also appear in children whose parents do not carry the mutation. Further complicating the matter, in cases where underlying genetic mutations have been identified, the gene aberrations don't necessarily predict the disorder. "Do we really know that every time you make that mutation or you delete one copy of that gene, you cause autism?" Constantino says. "We have no idea."

In the most comprehensive DNA-autism study to date, an international consortium of researchers scanned the genomes of 996 individuals with autism spectrum disorders and 1,287 healthy controls and looked for large deletions or duplications, known as copy number variants, in the genetic sequence. The effort, published earlier this month in the journal Nature, revealed that people with autism have 20% more interruptions in stretches of DNA that contain the code for proteins than unaffected individuals. What's more, these variants were prevalent in areas where genes implicated in autism spectrum disorders and learning disabilities occur.

The group also flagged more than 100 potential new autism risk genes and revealed new physiological pathways that are likely to be involved in the disorder.

Yet the new study only explains about 3% of autism cases — and, taken together with previous studies, researchers say they can only find a convincing genetic cause in less than 15% of all cases of autism.

In the study, nearly every mutation the researchers found was unique to one individual of the nearly 1,000.

"That gives us some hints as to how complex the genetic causes of autism are likely to be," says Dr. Stanley Nelson, professor of human genetics and psychiatry at UCLA and an author on the study. "It's essentially saying that there are likely to be hundreds to maybe many hundreds of different genes which, when mutated, substantially change your risk for developing autism."

However, the genes involved are clustering around a set of common biochemical pathways in the brain that could eventually paint a complete picture of how brain development goes awry in individuals with autism.

Some of these rare mutations occur in genes that facilitate communication between brain cells and cell movement. In order to form normal connections with neighboring cells during development and throughout life, brain cells have to shift and move to specific locations and form finger-like projections. "What we think happens at least in some children with autism is that there is some interruption of these connections between the nerve cells," says Dr. Joachim Hallmayer, a psychiatric geneticist at Stanford University and also an author on the new study.

It is possible that the broken or malfunctioning wiring in some of these pathways might be reparable, scientists say. For instance, several studies have found that the effect of the key brain chemical glutamate is impaired by gene mutations linked to autism. A handful of animal and human trials are focusing on altering the levels of glutamate in the brain with hopes that this might restore impaired connections between brain cells and improve cognitive functioning.

"The new science that is coming from the work in genetics is for the first time giving us hope that we can develop drugs that target core autism symptoms," says Geraldine Dawson, chief science officer of Autism Speaks, an autism science and advocacy organization that spearheaded the new research.

However, researchers know that genetics only tells part of the story, and other influences, such as

environmental exposures and so-called epigenetic changes — tiny chemical tags that attach to DNA and modify activity of genes — can play a role. "I think you probably need some constellation of genes and some constellation of environmental factors that would contribute to the development of autism," says Rita Cantor, professor of human genetics at UCLA and an author on the study.

A number of studies are exploring whether environmental influences tip a person who's at genetically heightened risk for autism toward developing the disorder. Studies have implicated factors such as pre-term births, nutrition during pregnancy, birth complications, exposure to toxic chemicals such as pesticides or heavy metals, and increased age of the parents. The vast majority of researchers do agree, however, that the role of childhood vaccines in autism has been thoroughly explored and refuted.

Autism studies

Because the sample sizes of studies have been such a problem, researchers emphasize that there is a critical need for autistic children and their families to participate in autism research. Larger population studies will increase the likelihood of spotting rare mutations in individuals with autism. "I really think it's all about numbers," Nelson says. Once researchers pinpoint specific gene mutations that repeatedly lead to a higher risk of autism, they can zero in on what role those genes play in brain development.

Though the complexity of autism is daunting, researchers feel optimistic that they are making significant strides toward understanding it and one day improving the lives of people with the disorder. "We've always been relegated to just treating symptoms in autism," says Dr. Matthew State, associate professor of psychiatry and genetics at Yale University. "The idea that you could shift from thinking about moderating symptoms to attacking the underlying pathology is really a significant shift."

Want to get involved? The Interactive Autism Network makes it easy for families to participate in genetic studies of autism. Parents can fill out Web-based questionnaires, sign an online consent and take their children to one of 1,600 blood-draw sites nationwide.

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