Researchers link spontaneous gene mutations to autism

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(Medical Xpress) -- Using high-throughput gene sequencing technology, researchers have identified several harmful spontaneous gene mutations in children with autism spectrum disorders (ASDs) that may cause the disorder.

The genetic basis for most cases of autism is unknown. ASDs are a diverse group of disorders for which the type and severity of symptoms vary considerably. People with ASDs can have defects in language and social ability, or restricted routines and repetitive movements. But the disorder's heterogeneity makes it difficult to identify its causes -- and there are likely to be many.

The results, described in an advance online publication in Nature Genetics on May 15, 2011, give new clues to the molecular pathways that underlie ASDs. Although the results are still preliminary, they also suggest that as many as 20 percent of sporadic autism cases can be explained by spontaneous gene mutations, says Howard Hughes Medical Institute investigator Evan E. Eichler at the University of Washington School of Medicine. "This a potentially major finding for a large number of families that are suffering from this disease."

Less than two percent of a person's DNA codes for protein, but mutations in these regions can drastically change a protein's function. In the past few years, scientists have developed new technology that makes it possible to completely sequence all of the protein-coding regions, or exons, in an individual's DNA, known collectively as his or her exome.

Exome sequencing allows one to identify rare, disease-causing mutations genome-wide. This is in sharp contrast to traditional genome-wide association studies, which are most efficient at identifying common alterations important in disease. When individually rare gene mutations can independently cause the same disease, as is the case for many complex conditions, the relevant sequence changes can be more difficult to find using genome-wide association studies.

To search for DNA changes that might contribute to autism, Brian J. O'Roak, a postdoctoral fellow in Evan Eichler's and Jay Shendure's labs, sequenced the exomes of 20 children with a sporadic ASD (meaning no other family members had any signs of autism), and compared those sequences to the exomes of their parents. An invaluable component to this study were the genetic samples from the Simons Simplex Collection, a permanent repository created by the Simons Foundation Autism Research Initiative that focuses on families with no history of autism. "What's nice about this collection is that it's been deeply phenotyped, so the whole families have been well characterized, allowing us to specifically examine sporadic autism," Eichler says.

The team identified 21 spontaneous mutations -- meaning they weren't inherited from either parent -- in the children's DNA. Eleven of these were mutations that would alter the protein encoded by the affected gene. In four of the 20 children, the researchers found mutations that were severe, some of which have been previously linked to autism, intellectual disability, and epilepsy.

For example, one child had a mutation in the GRIN2B gene, which is crucial for neuronal signaling. Mutations in the gene had already been seen in people with intellectual disability and epilepsy, suggesting that mutations in the same gene can manifest in a variety of ways.

Another individual had an extra nucleotide in FOXP1, a gene that, along

with its close relatives, has been heavily implicated in language defects. In the same child, an additional gene mutation that was inherited occurred within the same pathway, giving way to a genetic "double jeopardy," says Eichler. "It's probably not a coincidence that if we look at this family specifically, this child has the most severe speech delay of all the kids we've looked at," he adds.

These new findings support the 'multi-hit' model of autism, which suggests that having more than one mutation can cause or worsen symptoms of autism and other brain disorders. The different combinations of mutations may contribute to the heterogeneity in ASDs. "The idea that multiple genes are coming together in what's called the oligogenic model of autism is, I think, an exciting but also daunting prospect," Eichler says.

In previous work, Eichler and other groups have thoroughly investigated copy number variants (CNVs) -- large chunks of DNA that are duplicated or deleted -- in thousands of families, and found inherited and sporadic mutations that occur more often in people with ASDs than in healthy controls. The challenge of studying CNVs is that they usually include several genes, so it's hard to tease apart the roles of each one in autism. On the other hand, "exome sequencing is very specific, so I think the combination of the two is really quite powerful," Eichler says.

Interestingly, the types of genetic mutations seem more severe and disruptive when compared to individuals without autism. Last November, his group reported in Genome Research that spontaneous CNVs are more frequent in children with autism compared with unaffected siblings.

The new results are also consistent with other studies suggesting that ASDs are more likely in children born to older parents, and in particular, older fathers. "One thing that does seem to be clear [in the new study] is

that advanced parental age associates with a higher sporadic mutation rate," Eichler says.

The team is working on the next step, which is to analyze the exomes of hundreds more families affected by ASDs. "I think in the long term we'll need thousands," Eichler says, "but what I'm excited by is the prospects of being able to combine the morbidity maps we have from autism from CNV work with the kind of precision we get from exome sequencing."

Knowing autism's various causes is the first step in developing treatments. "You need to know what form of autism your child has, if you're going to have a smart therapy that's going to ameliorate some of the symptoms," Eichler says. "The genetic distinctions may be very important going forward."

Provided by Howard Hughes Medical Institute

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