NEWS

International effort expands list of genes tied to autism

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A massive sequencing study spanning seven countries links 38 new genes to autism or developmental delay and intellectual disability[1].

The study, published Monday in *Nature Genetics*, underscores the power of collaboration: Researchers from 15 institutions teamed up to recruit more than 13,000 people with one of the conditions.

The work highlights genetic differences between the conditions. Autism, intellectual disability and developmental delay share several risk genes, which has led some researchers to speculate that autism is, in some cases, a **form of developmental delay**.

The new study suggests that autism is distinct from developmental delay and intellectual disability and that some genes are significant in only one condition.

“I'm convinced that autism and developmental delay are not the same thing — that there are, in fact, genes that are going to predispose to one and not the other,” says lead researcher **Evan Eichler**, professor of genome sciences at the University of Washington in Seattle.

Eichler and his colleagues compiled a list of more than 200 genes involved in autism, developmental delay or both conditions. They sequenced this shortlist of genes in enough people to statistically link many new genes to the conditions.

The researchers were able to reconnect with the participants after analyzing the sequencing data. This allowed them to examine the effects of certain mutations on clinical features.

“The ability to go back and phenotype these individuals once you have found mutations in these genes is so important,” says **Santhosh Girirajan**, assistant professor of biochemistry and

molecular biology at Pennsylvania State University, who was not involved in the study.

Global reach:

Sequencing studies over the past few years have delivered **a list of roughly 60 genes** with strong ties to autism. In these studies, researchers **scoured the protein-coding regions of the genome** for harmful spontaneous mutations in individuals with autism. However, researchers often found each mutation in a single individual with autism — not enough to statistically connect the mutation to the condition.

Eichler and his team looked at 208 genes flagged as contributors to either autism or developmental delay in these and other studies. They hoped that sequencing these genes in thousands of people would confirm their link to the conditions, says **Holly Stessman**, assistant professor of pharmacology at Creighton University, in Omaha, Nebraska.

The team partnered with researchers across four continents to recruit people with autism or developmental delay who had never before participated in a sequencing study. They sequenced the genes in 6,342 people with autism, 7,065 people with intellectual disability or developmental delay, and nearly 3,000 unaffected family members.

Combining their findings with evidence from earlier studies revealed 91 genes with statistically significant ties to the conditions. Of these, 38 are genes that had not previously been strongly linked to the conditions. The new analysis reveals some of the “higher-hanging fruit,” Eichler says.

The majority of these genes harbor spontaneous, or *de novo,* mutations. The researchers tied 13 of them to the conditions by comparing them against **a control database** of more than 45,000 sequences.

New approaches:

The new study pegged five genes with the strongest ties to autism or developmental delay: **SCN2A** , **ADNP**, **CHD8**, **DYRK1A** and **POGZ**. Previous studies had highlighted all five as strong candidates for autism.

Some of the other candidates are surprising, says **Brian O’Roak**, assistant professor of molecular and medical genetics at Oregon Health and Science University, who was not involved in the study.

“I don’t think you could have picked before you had done the study which genes were the ones that were going to validate,” he says. “We still don’t really have an understanding of what they do and how they would be involved in autism risk, so that’s going to be a really exciting thing to figure out,” he says.

Among the new candidates is a gene called **NAA15**. This gene is needed for adding a certain chemical group to proteins. Eichler and his team collected clinical data from 13 people with NAA15 mutations and found a high incidence of autism, intellectual disability and speech delay in the group.

“It still gets me excited, finding brand-new genes that aren’t even part of the pathways that we know of,” Eichler says. “Hopefully, someday [this knowledge] will be used to treat people.”

Condition connection:

The researchers identified eight genes that were mutated more often in individuals with a primary diagnosis of autism than in those with developmental delay. Among these are the top autism candidate CHD8 and its molecular cousin, **CHD2**. Another 17 genes were mutated more often in people with developmental delay than in those with autism.

However, without clinical assessments of each individual, it is impossible to rule out the possibility that someone with a primary diagnosis of developmental delay also has autism, and vice versa, Eichler says.

The researchers recruited 88 participants with mutations in 25 of the new candidate genes to undergo detailed assessments. They also reviewed findings from case reports of people with mutations in the same genes. They found that 11 of the 25 genes are strongly associated with autism.

Individuals with mutations in these genes tend to have enlarged heads and fewer seizures than those with mutations in the other genes. Mutations in the autism genes are also found more often in **males than in females**, supporting the idea of a **sex bias in autism**.

REFERENCES:

1. Stessman H. *et al. Nat. Genet.* Epub ahead of print (2017) **PubMed**