NEWS

Family sequencing study boosts two-hit model of autism

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Point break: New mutations that arise in egg or sperm cells or in the fertilized egg itself can disrupt fetal development.

A new analysis of children with autism and their unaffected parents provides the best evidence to date that mutations in multiple genes may work together to cause autism and related disorders.

In the study, published today in *Nature Genetics*, researchers sequenced the entire exome — the protein-coding parts of the genome — of 20 children with autism[1]. Comparing the exomes to those of the unaffected parents, the researchers found four *de novo* mutations — which are not inherited, but spontaneously occur in egg or sperm cells or in the fertilized egg itself — in autism-associated genes.

Individuals with autism or schizophrenia have previously been shown to have a higher rate of *de novo* mutations compared with typical controls[2].

People with autism also **harbor more *de novo* copy number variations** — deletions or duplications of DNA — in protein-coding regions of the genome than controls do[3].

In the new study, researchers were looking for *de novo* point mutations, in which a single

nucleotide is inserted, deleted or replaced with another.

They found that 3 of the 20 children have harmful *de novo* mutations in genes previously linked to autism, intellectual disability and epilepsy. One child has a mutation not previously associated with autism. Those four children have lower intelligence quotients and more severe autism than others in the study.

Two of the four carry not one but two harmful mutations: one *de novo* and one inherited. These two children are the most severely affected, and have autism combined with intellectual disability, epilepsy and severe language delay.

"The development of the brain is probably very sensitive to dosage imbalances," says lead investigator **Evan Eichler**, professor of genome sciences at the University of Washington in Seattle. "One insult might be enough in a certain context to have you go a certain way in terms of a disease, but two insults cripple you and force you into a more severe disease outcome."

Double jeopardy:

The 20 families in the study are part of the **Simons Simplex Collection**, a database of genetic and clinical information from more than 2,500 families with a single child affected by autism.

The project, funded by SFARI.org's parent organization, the Simons Foundation, aims to test the hypothesis that *de novo* mutations underlie the seemingly random appearance of autism in families with no prior history of the disorder.

In the new study, researchers sequenced exomes to identify genetic differences between the parents and the affected child. This process typically produces thousands of possible hits.

Excluding the genetic variants common in the general population and focusing on those that are likely to alter protein function is easy enough. Zeroing in on potentially harmful mutations is more difficult — and finding mutations that are meaningfully linked to a given disorder is more of an art than a science, says **Brett Abrahams**, assistant professor of genetics at the Albert Einstein College of Medicine in New York City.

"If you sequence an exome, you'll pull out 10,000 different variants in any one individual," he says. "Whittling that down to two and providing concrete evidence for their functional interaction, as they've done here, is really beautiful."

Three of the *de novo* mutations are in genes already associated with autism, intellectual disability and epilepsy: FOXP1, **GRIN2B**, and **SCN1A**. LAMC3, a new candidate identified in this study,

belongs to a family of proteins with structural similarities to synaptic proteins implicated in autism.

One of the two children who sustained a double-hit carries a missense mutation — a change in a single base pair that can disrupt protein function — in SCN1A, which has been linked to epilepsy. He also carries a deletion on chromosome 15q11.2, known to be associated with schizophrenia and epilepsy, inherited from his mother. The child has mild intellectual disability, early-onset autism, delayed language development and epilepsy.

The other child has a small mutation in FOXP1, a member of a family of genes **associated with speech and language disorders**. He also carries a missense mutation in **CNTNAP2**, a gene strongly **linked to autism and language disorders**.

FOXP1 and CNTNAP2 seem to be part of a common pathway that is critical in **language development**.

"What's striking is that of all the families we looked at, this child had the greatest severity in terms of language development," says Eichler.

Another group of researchers reported last year that *de novo* **mutations in FOXP1** are associated with severe language impairment, autism and intellectual disability[4].

"It essentially confirms our study," says **Guy Rouleau**, director of the Réseau de Médecine Génétique Appliquée du Québec in Montreal and a co-investigator on that study.

"The implications for autism are not well-developed, but the story will unfold with new data," Rouleau says. "They only looked at 20 cases, and this represents a lot of work, but ultimately technology will allow thousands to be studied."

The findings also illustrate how *de novo* mutations can combine to create different outcomes by disrupting key pathways, Eichler says.

Epigenetic effects — which alter gene expression without changing the DNA sequence — can also change protein function and contribute to disorders.

"Sometimes they manifest as autism, sometimes as epilepsy or schizophrenia or intellectual disability," Eichler says. "It's the gestalt of all the variation that exists, genetically and epigenetically as the fetus develops *in utero* and perhaps in early development, that changes that trajectory."

***Correction**: This article has been modified from the original. It has been changed to correct an error in the number of identified mutations previously linked to autism.*

References:

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