NEWS

Massive collaboration unearths inherited risk factor for autism

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17 JULY 2017

The largest-yet study to look for inherited risk factors for autism links a region on chromosome 10 to the condition.

The study includes thousands more individuals than the previous biggest attempt to find common genetic variants that boost autism risk. It shows that common variants — those present in more than 1 percent of the population — account for roughly one-third of autism cases.

The researchers analyzed data from the **Psychiatric Genomics Consortium**, an international effort to uncover the genetic underpinnings of autism, schizophrenia and other complex psychiatric conditions. More than 150 scientists worldwide collaborated on the project. They looked at data from 7,387 individuals with autism and 8,567 controls.

They also incorporated information from 7,783 people with autism in the Danish **iPSYCH** project and 1,369 from the Icelandic **deCODE** collection and the U.S. **Study to Explore Early Development** (SEED). They did not have access to the raw data for these individuals because of data-sharing agreements.

The study signals a new era in autism research, says **Elise Robinson**, assistant professor of epidemiology at Harvard University and one of the researchers. “It’s very exciting that we are now within the autism community finally beginning to associate these forms of data,” she says.

Schizophrenia researchers found themselves in a similar position in 2011, when a study of roughly 18,000 people with schizophrenia revealed seven common variants tied to the condition. Just three years later, a study of nearly 37,000 people with schizophrenia unearthed **108 common variants**, many of which had approached significance in the earlier study.

Elusive inheritance:

In the new study, published 22 May in *Molecular Autism*, the researchers looked for variants present more often in people with autism than in controls.[1] Only one variant passed the stringent statistical threshold they set to consider a variant an autism risk factor. This sobering result suggests researchers will need data from thousands more individuals with autism to identify more variants.

“[The study is] useful as a cautionary tale that common variants in autism are not that easy to find,” says **Ivan Iossifov**, associate professor at Cold Spring Harbor Laboratory in New York, who was not involved in the work. As the number of participants in studies continues to grow, he says, “I’m curious to see what will happen.”

The bulk of what researchers know about the genetic underpinnings of autism comes from studies that scour the genome for rare, harmful mutations that are not inherited. These *de novo* mutations have offered clues about the proteins and molecular pathways involved in autism. Current estimates suggest such mutations account for just 10 to 30 percent of autism cases, however, and they do not explain why autism runs in families.

“The rare-variant field has given a lot of great insight into biology,” says **Richard Anney**, senior lecturer in bioinformatics at Cardiff University in Wales, who led the new study. But there is a lot of biology that common variants can reveal, he says. “We’ve probably taken our eye off the ball in terms of common variants for autism.”

Looking forward:

The researchers used a statistical test to estimate how thousands of small genetic variants are inherited across the primary study population. Their analysis suggests that common variants together account for roughly 30 percent of the risk of autism. (Other studies have pegged this number **as high as 49 percent**.)

The newly identified variant lies in a region of chromosome 10 called 10q24.32. This region includes PITX3, a gene that plays a role in neuron development. The variant’s link to autism needs to be confirmed in another population, Anney says.

Data from the Psychiatric Genomics Consortium also turned up 180 variants that do not quite pass the threshold for statistical significance. The researchers then found that of these variants, 11 are enriched in the iPSYCH group and 8 in the deCODE/SEED group. One of the variants is in the gene **ASTN2**, which has been **linked to autism**.

The numbers of participants with autism are growing fast — and may unearth more such variants. The Danish iPSYCH project has data from roughly 5,000 people with autism not included in the new study. The project’s researchers also plan to combine this information with raw data from the Psychiatric Genomics Consortium. These new data have already yielded more information on common variants for autism risk, the researchers say.

REFERENCES:

1. Anney R.J.L. *et al. Mol. Autism* **8**, 21 (2017) **PubMed**