CROSS TALK

Should autism research focus on common or rare risk factors?

BY **GREG BOUSTEAD**

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In July, we reported on a large population-based study, published in *Nature Genetics*, which estimates that common genetic variants compose about **half the risk for autism**.

The study analyzed new epidemiological data from a large Swedish sample, as well as from the Autism Genome Project, the **Simons Simplex Collection**(funded by the Simons Foundation, SFARI.org's parent organization) and other groups.

Some geneticists found the estimated contribution of rare variants — at about 3 percent — unexpectedly low. The work also raised questions about whatresearchers should do with these '**pies of risk**.'

Should researchers focus more on common variants, rare variants or spontaneous non-inherited ones? How should researchers weigh data from studies that model proportional risk across populations, versus risk in individuals, for whom rare mutations with large effects are more significant?

We sought answers from leading statistical and analytic geneticists who study risk factors for neuropsychiatric disorders, as part of our discussion series**Cross Talk**.

What do you think? Share your reactions and follow-up questions in the comments section below.

Elliott Sherr

Professor of Neurology, Pediatrics,University of California, San Francisco

An underestimate of non-inherited burden

Professor of Neurology; Director, Comprehensive Center for Brain Development, University of California, San Francisco

Surprising slices: "The *Nature Genetics* paper is a bold attempt to model the causes of autism. The results suggest that the heritability for autism is high — in the range of 50 to 60 percent — but that most of this heritability, according to their model, comes from common and not rare variants. Moreover, the risk of acquiring autism from *de novo* **copy number variation**s — spontaneous duplications or deletions of large regions of DNA — or from *de novo* single nucleotide variationseems unexpectedly low in the general autism population."

Beyond the exome: "The study provides a novel and exciting framework for considering autism risk. However, there are a few limitations worth considering. One concern I have is the way they incorporate *de novo* mutations into their model. The authors only examined *de novo* single nucleotide variants that are either missense or truncating, and they captured only a subset of noncoding regions. This approach certainly leads to an underestimate of the overall burden of *de novo* variants in autism, especially of noncoding mutations. There were no apparent adjustments in the model for variants that lie outside of the **exome**, the protein-coding region of the genome."

Autism higher in dads: "Studies over the past five or so years show a higher rate of *de novo* mutations per generation when looking at the **sperm of aging fathers**. Those results suggest that a significant percentage of the overall autism risk for populations arises from this higher *de novo* rate. The authors of the *Nature Genetics* paper, however, do not account for this in their model."

Diagnostic domains: "Another issue for any large population-based study relates to the issue of diagnosis. While the researchers here do deal with the difference between autism, autism spectrum disorder and other broader definitions, they do not address the deeper biological question of what 'unit' of autism is truly heritable within families. For example, if we were to **refine how we measure** the different domains of social impairment, we might find much higher heritability if we separately measured the degree of social motivation or social anxiety within families, instead of just measuring the overall autism with a thumbs-up or thumbs-down approach to diagnosis."

Michael Owen

Director,Neuroscience and Mental Health Research Institute

Common and rare paths forward

Director, MRC Centre for Neuropsychiatric Genetics and Genomics; Director, Neuroscience and Mental Health ResearchInstitute, Cardiff University, U.K.

Common interests: “These findings are of interest for a number of reasons. First, they show that heritability estimates — whether based on twin studies or newer sequencing techniques — are converging around 50 percent. Such estimates carry a degree of uncertainty, but they do suggest that environmental and/or random variation as well as genes are implicated in the disorder. Second, the findings indicate that common genetic variants play a substantial role in autism.”

Go big: “This is not surprising. The findings show that both common and rare variants play a role in autism and that, in this regard, it is similar to other common disorders, **notably schizophrenia**. Comparison of findings from autism and schizophrenia suggest that the failure of geneticists to identify specific common risk variants is likely due to the fact that autism researchers simply haven’t studied large enough samples.”

Rare or common? “The question now is whether to focus on common or rare variant discovery, or both, and this comes down to what will give us the best handle on the neurobiology and identifying new treatment targets. Identifiable rare risk alleles tend to have relatively large individual effect sizes. In contrast, common alleles are associated with low individual risk and are less readily actionable in neurobiological studies.

“However, given that common variants can now be seen to contribute quite substantially to autism risk, it would be sensible to push on and identify specific common associated variants in the hope that, as with other disorders, this will implicate specific areas of biology that impact a substantial proportion of cases.

“The way forward should include both common and rare variant studies. In fact, both will depend upon **access to very large samples**, and the autismcommunity needs to now focus on putting together many **tens of thousands of genomes** to study.”

Benjamin Neale

Assistant Professor, Instructor, Associated Researcher,Massachusetts General Hospital, Harvard Medical School, Broad Institute

A robust genetic starting point

Assistant Professor of Analytic and Translational Genetics, Massachusetts General Hospital
Promising trajectory: “Over the past few years, there has been a serious debate in the community about the role ofcommon variation in neuropsychiatric disorders such as schizophrenia and autism. Some of the earliest genome-wide association studies (GWAS) for schizophrenia demonstrated that there was polygenic inheritance — many small-effect variants scattered across the genome. But these early studies failed to identify significant loci. With newer GWAS of schizophrenia, however, we have found more than 100 significantly associated loci, effectively removing all doubt as to whether a genome-wide approach can identify regions relevant to disease. “GWAS of autism are in a similar position as the early attempts in schizophrenia, failing to identify unequivocal genome-wide significant loci. However, the work presented here strengthens the case that they may in fact yield significant loci for autism.
Complicated numbers: “In terms of the precise estimates and how valuable they are, the story is a little more complex. Any attempt to quantify what fraction of the variance in a trait is attributable to common genetic variants requires a number of assumptions as well as considerations in interpretation. For example, the estimate in this paper is much higher than what was seen for the **Psychiatric Genomics Consortium analysis** using a similar methodology, but both datasets support an important role for common variation.”
Incomplete story: *“*I think the landscape is quite complicated and that chasing both common and rare variants has value. It is most certainly the case that analysis of non-inherited mutations in autism has successfully identified novel risk genes and variants. That is without question at this point. However, strong mutations with large effects may not tell the whole story. If we consider other complex traits, such as lipid levels or height, it is certainly the case that there are strong-acting variants that can cause individuals to have extremely high or extremely low lipids or be extremely tall or extremely short. The GWAS of these traits, however, reveal a much more complex biological landscape than can be pieced together simply from powerful mutations.”