VIEWPOINT

Schizophrenia milestone holds lessons for autism

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A long-awaited report on the largest-ever study to link common variants to the risk of developing schizophrenia appeared today in *Nature*[1].

This so-called genome-wide association study (GWAS) confirms what some investigators have been arguing for years: Given cases and controls numbering in the tens of thousands, researchers can identify a substantial number of common genetic risk factors for a complex neuropsychiatric disorder.

This is a milestone in the study of schizophrenia, and holds several lessons for autism researchers as well.

The results are reasonably straightforward. A consortium of dozens of investigators pooled DNA from nearly 37,000 people with schizophrenia and 113,000 controls and looked for associations of 9.5 million single-nucleotide variants across the genome. They found that 128 variants reach genome-wide significance, a level of statistical support that makes false-positive associations unlikely.

Of these, 108 map to distinct genomic regions, and 83 are completely new to schizophrenia risk. **Jonathan Flint** and **Marcus Munafò**, authors of an accompanying News & Views article[2], regard

this as an advance “of the sort that rewrites textbooks” — and I agree.

Notably, the researchers titled their paper, ‘Biological insights from 108 schizophrenia-associated genetic loci,’ underscoring the point that the genetic findings are only important insofar as they enable a better understanding of the underlying biology of the disorder.

So what are the genes and what do they tell us? The researchers highlight pathways that regulate neuronal function, such as glutamate-dependent neurotransmission and voltage-gated calcium channels. They also implicate genes involved in immune functions.

In this latter category, the most significant association by far is in the major histocompatibility complex, which encodes proteins that enable the immune system to recognize foreign molecules. Others have made this observation before, but it remains largely unexplained in terms of the biology of schizophrenia risk[3].

Genes involved in the immune response to pathogens are also on the list, implicating this process in the development of the disorder. Finally, it’s worth noting that many of the associated variants actually lower the risk of developing schizophrenia, which makes these of particular interest as potential drug targets.

Additive effects:

The subject of drug targets raises the issue that these common variants have small effects, each altering the risk of developing schizophrenia by 10 percent or less.

This raises the question of whether these really would be good targets for new drugs. The researchers have one good argument on their side, which is that the list of genome-wide significant hits includes the type 2 dopamine receptor (DRD2). DRD2 is the target of all effective antipsychotic drugs, suggesting that even modest genetic associations can identify drug targets of significant clinical impact.

As for autism, the contrast is clear. Although it is apparent that common variation is an **important component of autism risk**[4, 5], we can count the number of variants implicated with a high level of statistical support on one hand.

The number of genotyped autism samples is only in the range of 5,000 to 6,000, and if the genetic architecture of autism is anything like that of schizophrenia, this lack of statistical power by itself explains why autism research lags behind in this area.

Fortunately, efforts are ongoing to close this gap. The good news from the schizophrenia GWAS is that cases ascertained by physicians rather than research-based assessment using time-consuming methods allowed for a boost in power without introducing what the researchers call “a

crippling degree of heterogeneity." A similarly broad approach to ascertainment of autism samples should speed the accumulation of the sample sizes needed for gene discovery.

Finally, the schizophrenia study reveals significant overlap between genes implicated by both common and rare variant approaches. If this turns out to be true for autism as well, it may help us to solve a puzzle: that rare, spontaneous — or *de novo* — mutations in autism are largely restricted to individuals with **below-average intelligence quotients** (IQs).

As such, despite the success in identifying rare mutations in autism, we still know almost nothing about the genetic underpinnings of the disorder in individuals who have average or above-average IQs. Susceptibility to 'high-functioning' autism may be driven by particular **constellations of common variants of weak effect**. But we'll only know that for sure if the field examines groups of the scale that schizophrenia researchers have so painstakingly assembled.

Alan Packer is senior scientist at the Simons Foundation Autism Research Initiative.

References:

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5: Klei L. *et al. Mol. Autism* **3**, 9 (2012) **PubMed**