VIEWPOINT

Fuzzy network

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Researchers frequently ask: Do autism-associated genes cluster in particular biological pathways?

The answers typically come in the form of **'network' analyses**, which attempt to identify clusters of proteins that are more likely to physically interact or to have functions in common than a random set.

A new paper, published 11 June in *Translational Psychiatry*, is the latest such effort, and it highlights both the pitfalls and the promise of the approach[1].

The researchers took a seemingly comprehensive approach to network analysis — assemble as much data as you can on a large group of genes that have been implicated in autism, and ask what the puzzle looks like when you put the pieces together.

They started with data from five genome-wide association studies (GWAS), selecting as a statistical cutoff any variant for which an association was 'suggested' by the data. These criteria implicated about 200 genes, and the researchers found associations for many of them to be supported by independent lines of evidence.

The evidence includes rare mutations and **copy number variants** reported in the same genes, functional studies in animal models, and the fact that many of the genes are potential **targets of microRNAs** — small fragments of RNA that regulate gene expression — that have been implicated

in autism.

Based on all this, the researchers claim that nearly two-thirds of these genes fit neatly into networks representing three biological themes that have already been much discussed in the autism literature: steroid hormone production, excitatory signaling and outgrowth of neurites, the projections from cell bodies of neurons.

Suggestive evidence:

How can we evaluate the strength of these claims?

As the researchers acknowledge, the ‘suggestive evidence’ cutoff for including variants from **GWAS is an arbitrary one** (a much stricter cutoff is typically required to make a convincing claim of association). What’s more, only 13 of more than 200 genes on this list met the same statistical cutoff in an independent GWAS. Many of the independent lines of evidence supporting these genes are equally modest, and are likely to do little to bolster one’s confidence.

They do note that at least one-third of the genes associated with autism at any level of significance in the independent GWAS can be placed into one or more of the three biological themes. Given the broad nature of these themes, however, it’s hard to know how impressed one should be by this result.

An even stronger claim is made in the title and abstract of the paper, which is that the A-kinase anchoring proteins (AKAPs) “integrate signaling cascades within and between these networks.” There are more than 50 members of the AKAP family, whose role is to recruit protein kinase A to its many substrates and to regulate activity-dependent signaling at **synapses**, the junctions between neurons.

The authors marshal a fair amount of published data in support of the claim that AKAPs are significant players in autism risk, much of which nonetheless seems circumstantial or indirect. Unfortunately, the strongest genetic evidence implicating this protein family in autism goes unmentioned: the recent report that CHD8, the most commonly mutated gene found to date by exome sequencing, is itself an AKAP[2].

This recent finding on CHD8 makes me think that, despite the weaknesses in their input dataset, the new study might be on to something.

Like many of the network analyses that I’ve seen, however, this one could have been strengthened in two ways.

First, this is not the only such analysis ever published in the field of autism research, and yet there is no attempt to compare the results with previous findings[3, 4, 5] at anything other than a superficial

level.

Finally, why not make a prediction, or propose a small number of urgent experiments that are suggested by these results and that would constitute a rigorous test of the claims? Then we'd really be getting somewhere.

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References:

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