VIEWPOINT

Networking tips

BY **ALAN PACKER**

28 MAY 2013

Alan Packer

If you want to find out whether a group of genes implicated in autism share a common function, you have a number of experimental options.

One popular approach is to ask whether the genes interact with each other in complexes or networks in particular cell types or tissues. This approach is valuable, but also requires a great deal of labor-intensive bench work.

In a new paper, published 16 April in *Human Molecular Genetics*, **Lauren Weiss** and her colleagues describe a complementary approach. By reanalyzing existing datasets, they highlight a potential network of autism-relevant **genes that regulate the expression of SEMA5A**.

SEMA5A encodes a protein that guides axons — the long neuronal fibers along which signals travel — to their targets. In 2009, Weiss' team identified a variant flanking the gene as **one of the first common variants** to be associated with autism in a statistically convincing manner. She and her colleagues also found that SEMA5A expression is lower in postmortem brains from individuals with autism than in those from controls.

In the new study, the researchers asked whether the genes that regulate SEMA5A expression might also be autism risk factors. To do this, they applied a strategy called expression quantitative trait locus (eQTL) mapping.

Expressive variable:

Geneticists have long used ‘standard’ QTL mapping to learn whether particular genetic variants are associated with clinical features that exist as continuous variables — height and weight, for example — rather than those that either present or absent, such as a disease. In eQTL mapping, the continuous variable that is examined is simply the level of expression of a particular gene.

One of the most attractive features of the eQTL approach is that researchers can extract results by mining publicly available datasets of single-nucleotide polymorphisms and gene expression. You simply ask whether particular variants are associated with higher or lower levels of expression of the gene of interest in a group of samples.

What did Weiss and her colleagues find? It turns out that although there are a large number of common variants in the genome associated with SEMA5A levels, these variants are not over-represented in the available collections of samples from people with autism.

On the other hand, variants that overlap with regions harboring rare autism-related **copy number variants** are indeed significantly associated with SEMA5A expression. Among these are some well-established risk factors for autism and other neurodevelopmental disorders, including AUTS2, MBD5, KIRREL3, A2BP1/RBFOX1 and FOXP1.

In a clever twist, the authors included ‘eQTLs of the eQTLs’ (regulators of the regulators of SEMA5A expression), and found that these ‘master regulator’ variants are also over-represented in the autism samples.

I should point out a few caveats: As the researchers acknowledge, the dataset they used for the eQTL mapping was derived from lymphoblastoid cell lines, which is undoubtedly **an imperfect proxy for brain tissue**. Of greater concern, both SEMA5A and a number of the rare copy number variants identified as part of its network of regulators must be considered provisional autism risk factors until their associations are confirmed in larger studies.

The potential SEMA5A regulatory network associated with autism risk is nonetheless a provocative finding. The researchers suggest that SEMA5A is “the common downstream effector for all the genes in this network.”

That seems like a long shot to me, but it’s a testable hypothesis, and we may not have to wait long for an answer.

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