DISEASE GENETICS

Converging models for autism

Two approaches to dissect the molecular genetic basis of autism have improved our understanding of the developmental processes and functional interactions involved in this heterogeneous condition. One paper reports dysregulation of transcription and splicing in autistic brains, and another describes an interactome of autism-associated proteins that points to there being common mechanisms underlying different autistic phenotypes.

Voineagu and colleagues analysed the transcriptome of post-mortem brains of individuals with autism and control individuals. Of the three regions that were studied, only the cortex showed significant gene-expression differences between the groups. More surprisingly, in autistic brains, the difference in expression between the frontal and temporal cortex was much less pronounced than in controls (in whom 174 differentially expressed genes were seen, compared to none in autistic individuals), suggesting that the pathology of autism involves altered cortical patterning.

To pin down the functions affected by differentially transcribed loci, the authors searched for gene co-expression modules that were differentially expressed between the normal brain and the autistic brain. One such module was under-expressed in autistic cases and was enriched for genes involved in synaptic and neuronal signalling, as well as in known autism-susceptibility genes. A second module, however, was over-expressed in autistic cases and was enriched for genes involved in immunity. The first module contained the autism-implicated gene *A2BP1* (also known as *RBFOX1*), which encodes a splicing regulator; the lower expression of *A2BP1* in autistic brains was shown by RNA-seq to be associated with dysregulated splicing of *A2BP1* target exons. The fact that this neuronal module is also enriched for autism candidate loci identified by genome-wide association studies justifies investigating this gene network further. Conversely, the upregulation of the immune response seen in autistic patients cannot be attributed to genes contained in the second module.

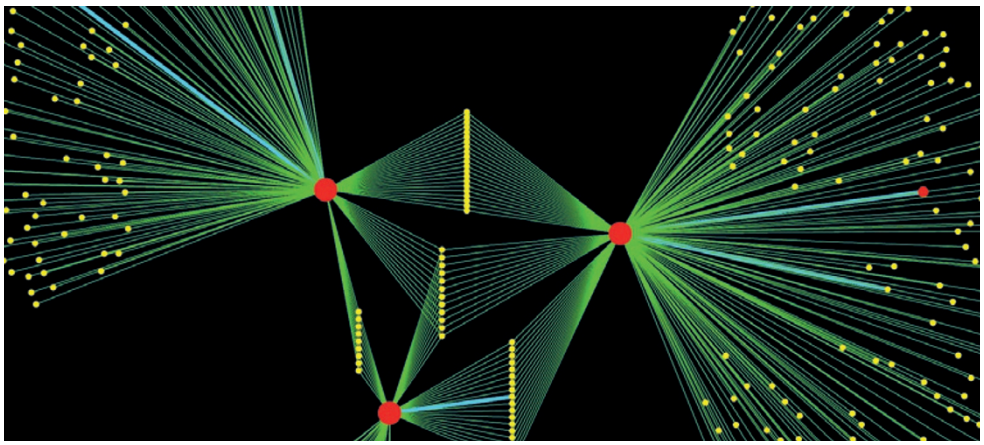
The starting point of the second study was a set of 26 genes that are causal for, or associated with, syndromic autism. Although these genes encode a range of varied biological functions, the authors reasoned that they might converge on only a few functional pathways. To investigate this hypothesis, they built an autism protein–protein interaction map based on a yeast two-hybrid assay using fragments of the autism-associated proteins as baits.

The interactome map assembled from the 539 proteins identified in this screen highlighted new pathological interactions and pathways relevant to autism pathogenesis, including unsuspected ones: for example, it revealed tight links between SHANK3 and hamartin (also known as TSC1), mutations in which cause Phelan–McDermid syndrome and tuberous sclerosis complex, respectively. This is an important finding, as it suggests a common molecular cause for the autistic features seen in classic autism and in the many broad neurodevelopmental disorders that show autistic phenotypes.

Further proof of the utility of the protein–protein interaction analysis came from finding that classic autism cases were more likely than controls to contain copy number variants in genes in this interactome. The authors also identified *de novo* copy number variants spanning genetic loci of three network genes in classic autism cases, showing that the interaction map can also be used in disease-gene discovery.

The two papers therefore suggest convergent mechanisms for autism but do so by different routes — the first by screening for mechanisms in an unbiased manner and the second by building on previous knowledge. Identifying the network of functional molecules involved in a genetically heterogeneous condition such as autism is an important step in identifying diagnostic and therapeutic targets, and these two studies have provided many such leads.

Tanita Casci



A portion of the autism interaction network showing how proteins encoded by autism-associated genes (red circles) share many partners (yellow). Turquoise lines show previously known interactions; green lines show new interactions identified by Sakai *et al.* Image courtesy of Y. Sakai, H. Zoghbi and C. Shaw, Baylor College of Medicine, Houston, Texas, USA.

ORIGINAL RESEARCH PAPERS Voineagu, I. *et al.* Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature* 25 May 2011 (doi:10.1038/nature10110) | Sakai, Y. *et al.* Protein interactome reveals converging molecular pathways among autism disorders. *Sci. Trans. Med.* **3**, 86ra49 (2011)