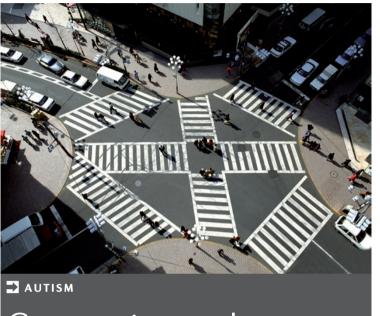
## RESEARCH HIGHLIGHTS



Converging pathways

Autism spectrum disorder (ASD) encompasses a range of cognitive and behavioural phenotypes, and the genetic and environmental factors that are thought to contribute to the disorder are equally diverse. Whether these factors converge onto common downstream pathogenic pathways is unclear. Using advanced genetic analysis techniques, Geschwind and colleagues now show that particular abnormalities in RNA expression and gene splicing are common in individuals with ASD.

The authors compared RNA transcript expression in post-mortem cortical tissue from control subjects and individuals with ASD, and found 444 genes with altered expression in the ASD samples. To probe these

differences, they employed weightedgene co-expression network analysis, which examines the expression of 'modules' of co-expressed genes and constructs a module network based on the correlations of expression of individual genes. They found that differences in transcript expression between the frontal and temporal cortex that were present in control samples were lost in ASD, suggesting that a defect in developmental patterning might contribute to the disorder.

Further analysis revealed that two co-expression modules - M12 and M16 - were altered in ASD. Genes in M12, which were mainly associated with synaptic function, vesicular transport and neuronal

projection, were downregulated, whereas genes in M16, which were predominantly markers of microglia, astrocytes and inflammation, were upregulated. Interestingly, analysis of the dataset of a previous genome-wide association study showed that M12 is enriched in statistically significant common genetic polymorphisms, suggesting a genetic basis for the changes in M12 expression. By contrast, M16 genes did not show such enrichment, suggesting that changes in inflammation are secondary to the primary effects of gene mutations.

One hub of the M12 network was the splicing regulator RNA binding protein, FOX1 homologue (A2BP1). Using high-throughput RNA sequencing, the authors showed altered splicing in several targets of A2BP1 in ASD. Many of these targets were also linked to synaptic function, suggesting that A2BP1 downregulation and consequent synaptic dysfunction, as well as splicing dysregulation in general, might be key contributors to ASD.

This study is the first to demonstrate a common molecular pathway that is disrupted in many cases of ASD (about three-quarters of the individuals tested), suggesting a convergence point for multiple risk factors. The findings might form the basis of targets for therapeutic intervention that could benefit a wide range of individuals with ASD.

Katherine Whalley

ORIGINAL RESEARCH PAPER Voineagu, I. et al. Transcriptomic analysis of autistic brain reveals convergent molecular pathway. Nature 25 May 2011 (doi:10.1038/nature10110)