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Transcriptomic analysis of autistic brain reveals convergent molecular pathology

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Autism spectrum disorder (ASD) is a common, highly heritable neurodevelopmental condition characterized by marked genetic heterogeneity[1, 2, 3]. Thus, a fundamental question is whether autism represents an aetiologically heterogeneous disorder in which the myriad genetic or environmental risk factors perturb common underlying molecular pathways in the brain[4]. Here, we demonstrate consistent differences in transcriptome organization between autistic and normal brain by gene co-expression network analysis. Remarkably, regional patterns of gene expression that typically distinguish frontal and temporal cortex are significantly attenuated in the ASD brain, suggesting abnormalities in cortical patterning. We further identify discrete modules of co-expressed genes associated with autism: a neuronal module enriched for known autism susceptibility genes, including the neuronal specific splicing factor *A2BP1* (also known as *FOX1*), and a module enriched for immune genes and glial markers. Using high-throughput RNA sequencing we demonstrate dysregulated splicing of *A2BP1*-dependent alternative exons in the ASD brain. Moreover, using a published autism genome-wide association study (GWAS) data set, we show that the neuronal module is enriched for genetically associated variants, providing independent support for the causal involvement of these genes in autism. In contrast, the immune-glial module showed no enrichment for autism GWAS signals, indicating a non-genetic aetiology for this process. Collectively, our results provide strong evidence for convergent molecular abnormalities in ASD, and implicate transcriptional and splicing dysregulation as underlying mechanisms of neuronal dysfunction in this disorder.

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Contributions

I.V. and D.H.G. designed the study and wrote the manuscript. I.V. performed experiments, analysed the data and conducted the GWAS set enrichment analysis. X.W. and B.J.B. analysed the RNA sequencing data. J.K.L. contributed to the GWAS set enrichment analysis. Y.T. performed some of the microarray qRT-PCR validation experiments. R.M.C. supervised the GWAS set enrichment analysis. S.H. supervised the WGCNA analysis. P.J. and J.M. provided dissected tissue for the replication experiment. All authors discussed the results and commented on the manuscript.

Competing financial interests

The authors declare no competing financial interests.

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Supplementary information

Excel files

1. Supplementary Data (12.9M)
   This file contains Supplementary Data.

PDF files

1. Supplementary Figures (6.6M)

This file contains Supplementary Figures 1-9 with legends.

2. Supplementary Tables (1.1M)
   This file contains Supplementary Tables 1-14.

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