NEUROGENETICS

Genome-wide search for autism loci

Autism has been described as 'living in a bubble'. Children who suffer from this neurodevelopmental disorder — it is usually diagnosed between 18 and 48 months of age — have impaired communication and social interaction skills, imagination and behaviour. Although various environmental factors have been suggested to promote it, the high concordance among twins and the familial pattern of autism-like phenotypes argue in favour of an oligogenic basis. The largest genome-wide linkage scan to date for loci associated with autism risk has just been reported by The Autism Genome Project Consortium. A combination of linkage and copy number variation analyses identifies new candidate loci and provides further evidence that a gene involved in glutamate synaptic function might contribute to autism.

The Consortium assembled 1,496 families in which at least two individuals were affected and used an Affymetrix SNP array for genotyping. As well as being used for linkage analysis, the SNP arrays were also assessed for copy number variants (CNVs). To achieve the latter, the authors developed an approach that used comparative analysis of hybridization intensities; as well as being able to identify CNVs as putative risk loci, this approach helps to stratify the samples, thereby reducing genetic heterogeneity.

Genome-wide linkage scans have previously identified 2q, 7q and 17q as regions that might harbour susceptibility loci. Although the current scan found some linkage to regions on 2q and 7q, but not to 17q, the linkage signals were not statistically significant. Instead, the data point to a new region on chromosome 11p12–13, which has previously shown only modest levels of linkage.

Analysis of CNVs, which identified many such abnormalities, highlighted the potential importance of small-scale chromosome rearrangements in the aetiology of autism. Interestingly, the authors found a hemizygous deletion in the coding portion of neurexin 1 (*NRXN1*) in a pair of siblings. Not only have point mutations in *NRXN1* been previously associated with autism, but its product interacts with neuroligins. Mutations that affect these proteins have been found in association with autism and mental retardation. Both neurexins and neuroligins have a crucial role in glutamate-activated synaptic transmission, abnormalities in which are considered an important risk factor in autism. In addition to previously reported evidence for an association with a mitochondrial aspartate/glutamate carrier, the 11q13–12 linkage region harbours several loci with products that might be involved in glutamatergic synaptic function. Positional candidate-gene analysis should cast more light on this biological mechanism that might have an important role in the aetiology of autism.

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ORIGINAL RESEARCH PAPER The Autism Genome Project Consortium. Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nature Genet.* **39**, 319–328 (2007)

FURTHER READING Wang, W. Y. S. *et al.* Genome-wide association studies: theoretical and practical concerns. *Nature Rev. Genet.* **6**, 109–118 (2005) | Hirschhorn, J. N. & Daly, M. J. Genome-wide association studies for common diseases and complex traits. *Nature Rev. Genet.* **6**, 95–108 (2005)