AUTISM

The importance of getting the dose right

Autism spectrum disorders (ASDs) have a strong genetic component, but the genetic events that contribute to the aetiology of ASDs have mostly remained elusive. Three studies published in *Neuron* used data from the same, large cohort of families to show that 5–8% of simplex cases of ASD are due to rare or unique *de novo* copy number variations involving genes that are mainly associated with synaptogenesis, axon guidance and neuron motility.

Genome-wide association studies (GWASs) have found a number of common polymorphisms that may be associated with ASDs. However, common polymorphisms seem to have a very small effect — if any — on the risk for ASDs, and researchers have therefore started to focus their attention on the role of rare genetic variants in ASDs, including structural changes known as copy number variations (CNVs). CNVs can include deletions and duplications of chromosomal regions, and often involve multiple genes.

The three studies made use of a large collection of genetic material from so-called simplex families, in which two unaffected parents had only one child with ASD and, in this cohort, at least one unaffected child. This enabled the authors to look for *de novo* (that is, non-inherited) CNVs associated with ASD. Levy *et al.* and Sanders *et al.* used different microarray platforms to analyse data from over 1,000 families in the collection. Both studies detected ~80 rare *de novo* CNVs in total and found that CNVs were approximately four times more common in children with ASD than in their unaffected siblings. In addition, CNVs in affected children were larger — overlapping with more genes — than CNVs found in unaffected siblings. Levy *et al.* also found that *de novo* CNVs occurred more frequently and were larger in females with ASD than in males with ASD. Considering that ASDs are about four times more common in males than in females, this finding could suggest that females are less vulnerable to ASDs and require more or larger genomic changes for ASDs to emerge.

Although most of the observed *de novo* CNVs were unique, a few CNVs from autistic children overlapped in the same region of the genome. Several such 'recurrent' regions were found, some of which had also been found in earlier studies. Two regions — 16p11.2 and 7q11.23 — were identified as recurrent regions in both studies, with both deletions and duplications occurring at 16p11.2, and 7q11.23 hosting only duplications. Interestingly, deletions at 7q11.23 are known to cause Williams syndrome, which is characterized by highly sociable behaviour (among other traits). This suggests that the 'dosage' of one or more genes in this region strongly contributes to an individual's social phenotype.

These two studies show that *de novo* structural genomic changes may cause a relatively high proportion of simplex cases of ASD. In the third paper, Gilman *et al.* used a network-based analysis to assess whether the genes that were included in the *de novo* CNVs identified by Levy *et al.* are functionally connected. They first constructed a likelihood network based on the functional and imputed relationships between any two (known) genes, and showed that many of the genes affected by the *de novo* CNVs were not randomly distributed in this network but clustered together. Further analysis showed that the clustered genes were predominantly linked to specific processes: synapse development, axon guidance and neuron motility.

These studies emphasize the importance of rare *de novo* genetic changes in sporadic cases of ASD and begin to identify the biological networks in which the affected genes operate. Simplex cases of ASD may have unique genetic aetiologies, but a picture emerges that the unique genomic changes converge, leading in many cases to altered synaptic connectivity and function.

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ORIGINAL RESEARCH PAPERS Sanders, S. J. *et al.* Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. *Neuron* **70**, 863–885 (2011) | Levy, D. *et al.* Rare de novo and transmitted copy-number variation in autistic spectrum disorders. *Neuron* **70**, 886–897 (2011) | Gilman, S. R. *et al.* Rare de novo variants associated with autism implicate a large functional network of genes involved in formation and function of synapses. *Neuron* **70**, 898–907 (2011)