*Nature Reviews Genetics* | AOP, published online 15 May 2012; doi:10.1038/nrg3248

HUMAN GENETICS

# Fruits of exome sequencing for autism

Getty

> six genes were found to have a gene-disrupting *de novo* mutation in more than one individual with ASD

A clutch of recent papers have harnessed exome sequencing to study the contribution of single-nucleotide variants to the risk of autism spectrum disorder (ASD). Four studies have looked for *de novo* mutations, and a fifth looked at rare recessive mutations; together they highlight the extreme genetic heterogeneity of ASD and point towards biological pathways for further study.

A role for *de novo* mutations in ASD has been suggested by previous studies of copy number variation and smaller-scale exome sequencing studies. In the recent studies, Iossifov *et al.* sequenced 343 family 'quads' (the parents of a single child on the autism spectrum and its unaffected sibling), and Sanders *et al.* also included 200 quads in the 238 families they sequenced. O'Roak *et al.* selected 189 trios (a child with ASD and its parents), and Neale *et al.* also sequenced 175 trios. Although the details differ among the four studies, the findings reveal several shared patterns and interesting leads.

First, this wealth of sequencing data from parents and offspring enables estimation of mutation rates. The estimates for *de novo* point mutations are ~$2 \times 10^{-8}$ per base per generation, which is slightly higher than in previous studies. Although the studies do not find elevated mutation rates in the probands compared with their unaffected siblings, evidence is presented of a shift in the mutation spectrum towards mutations predicted to disrupt protein function in the probands. In addition, the studies show that more *de novo* mutations have a paternal origin than have a maternal origin and that there is an increase in the number of mutations with paternal age.

Each of the studies identified *de novo* mutations that are predicted to disrupt gene function in some of the affected children: the total haul is 127 gene-disrupting mutations. Although only a proportion of these would be expected to be causal — Iossifov *et al.* estimate 65 of them — it is particularly noteworthy that six genes were found to have a gene-disrupting *de novo* mutation in more than one individual with ASD, and many others genes are 'hit' by missense mutations more than once. These will be important leads for follow-up work.

In terms of the biology of ASD, among the genes with *de novo* mutations are many that have been previously implicated in other neurodevelopmental disorders. Some analyses of the pathways in which the genes with *de novo* events lie also point to areas for further study. For example, O'Roak *et al.* identified a network linked to β-catenin signalling and chromatin remodelling, and Iossifov *et al.* highlighted many genes that are associated with the fragile X protein.

*De novo* mutations are just one piece in the ASD puzzle, and the work of Chahrour *et al.* describes an approach to access another difficult piece: recessive mutations. These authors sequenced the exomes of 16 probands from an outbred population who had abundant homozygosity in their genomes, which may reflect shared ancestry. They found four candidate autism genes with homozygous missense mutations.

Overall, these studies confirm estimates of several hundred genes being associated with ASD, and future work will need to bring together knowledge of both *de novo* mutations and inherited genetic variation.

*Mary Muers*

**ORIGINAL RESEARCH PAPERS** Iossifov, I. *et al.* *De novo* gene disruptions in children on the autistic spectrum. *Neuron* **74**, 285–299 (2012) | Sanders, S. J. *et al.* *De novo* mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature* 4 Apr 2012 (doi:10.1038/nature10945) | O'Roak, B. J. *et al.* Sporadic autism exomes reveal a highly interconnected protein network of *de novo* mutations. *Nature* 4 Apr 2012 (doi:10.1038/nature10989) | Neale, B. M. *et al.* Patterns and rates of exonic *de novo* mutations in autism spectrum disorders. *Nature* 4 Apr 2012 (doi:10.1038/nature11011) | Chahrour, M. H. *et al.* Whole-exome sequencing and homozygosity analysis implicate depolarization-regulated neuronal genes in autism. *PLoS Genet.* **8**, e1002635 (2012)

**FURTHER READING** Gibson, G. Rare and common variants: twenty arguments. *Nature Rev. Genet.* **13**, 135–145 (2012)