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NEURODEVELOPMENTAL DISORDERS

Unlocking the secrets of autism through whole-exome sequencing

Autism spectrum disorders (ASDs) are a group of conditions that are associated with neurodevelopmental abnormalities. Although a genetic basis for these disorders has been proposed, few autism risk genes have been identified. In three studies, published in *Nature*, researchers used whole-exome sequencing to show that *de novo* single nucleotide variants (SNVs) in brain-related genes are associated with risk of autism. An autism-associated protein network was also identified, which could point towards targets for future research and therapy.

"Identifying the genes that contribute to autism is the most direct route to understanding the biology of the condition," says Stephan Sanders, lead author of one of the papers. Risk of autism has been linked to *de novo* copy number variants—deletions or duplications of large DNA regions. But, owing to the multigenic nature of these regions, determination of the causative gene is difficult. It has been proposed that *de novo* SNVs, which affect only one nucleotide on one gene, could also be linked to autism.

"Our first research goal was to establish whether SNVs contribute to autism and, if so, how much risk they carry," says Sanders. After performing whole-exome sequencing of 238 families from the Simons Simplex Collection—a group of families in which one child has a non-inherited ASD—Sanders and colleagues compared the exomes of patients with autism to that of their unaffected siblings, and found the rate of *de novo* SNVs to be higher in individuals with the disorder.

The researchers used computer simulation to model the likelihood that a given SNV occurred in the same gene in different individuals by chance, or whether the gene could be associated with the autism phenotype. "This was a key step as *de novo* SNVs are found in many siblings, so simply stating that an SNV was seen in a proband is not sufficient to claim that it is an autism gene," explains Sanders. Indeed, *de novo* SNVs in brain-expressed genes were associated with autism; these mutations conferred risk of the disorder in at least 14% of the individuals studied.

O'Roak *et al.* performed whole-exome sequencing of 189 trios (parents and their child with autism), also from the Simons Simplex Collection. 248 *de novo* autism-associated mutations were detected, 120 of which were designated as severe (that is, the mutation affected protein function). "Surprisingly, 39% of the most disruptive genes were part of one highly interconnected protein network, related to β-catenin and chromatin remodelling," says Evan Eichler, a senior author of the paper. Another key finding was that new mutations were fourfold more likely to come from the father's germline than from the mother's, with a correlation between paternal age and number of *de novo* SNVs in their offspring.

In the third paper, Neale *et al.* sequenced whole exomes of 175 children with autism and their parents, and found the rate of SNVs in patients with autism to be only slightly higher than in unaffected controls. In agreement with the findings of O'Roak *et al.*, proteins that were affected by structural mutations seemed to be more connected with one another in terms of function than would be expected by chance. "Specifically, these mutations showed unexpectedly high connectivity in terms of protein–protein interactions and their distance from known autism genes," explains Kathryn Roeder, a senior contributor to the research.

Most of the autism-related *de novo* SNVs identified in the three studies were found in independent genes, indicating the genetic heterogeneity of ASDs. By use of statistical modelling, Sanders *et al.* showed that the presence of two or more *de novo* loss-of-function SNVs in a given gene is sufficient to demonstrate a genetic association with autism. "We identified one such gene in our own data, *SCN2A*, which encodes a voltage-gated sodium channel," summarizes Sanders, "and two further genes when considering our data alongside that of the two accompanying papers: *CHD8*, a gene involved in chromatin regulation, and *KATNAL2*, a gene involved in cystoskeletal regulation."

The research groups plan to perform whole-exome sequencing in further patient samples to identify new autism genes and networks. "Once we prove a certain gene is pathogenic, it, along with its pathway, will become a target for diagnostics and future therapy," says Eichler. How SNVs in certain genes disrupt brain development and lead to the autism phenotype remains to be determined. "*De novo* variants act as sign posts, guiding researchers towards a biological understanding of autism," says Sanders. "For the first time we can say that there is a clear route towards unlocking the secrets of autism."

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Original articles Sanders, S. J. *et al. De novo* mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature* doi:10.1038/nature10945 | O'Roak, B. J. *et al.* Sporadic autism exomes reveal a highly interconnected protein network of *de novo* mutations. *Nature* doi:10.1038/nature10989 | Neale, B. M. *et al.* Patterns and rates of exonic *de novo* mutations in autism spectrum disorders. *Nature* doi:1038/nature11011