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HUMAN DISEASE

Chipping away at psychiatric disorders

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Schizophrenia, and related mental disorders, have proven as frustrating for geneticists to study as they can be for psychiatrists to define. Multiple claims of genetic linkage or association have been made with much fanfare and then are never replicated, or are actually disproven by further studies. Three groups have now reported further genetic associations for schizophrenia; by expanding the range of variants surveyed and using larger sample sizes, these studies provide both solid associations and new avenues to explore in schizophrenia genetics.

Two papers just published in *Nature* took a different approach to previous studies by looking for association between rare copy number variants (CNVs) and schizophrenia. Both groups used microarrays to genotype population samples, with the Stefansson group examining parent–child trios in their first phase, and the International Schizophrenia Consortium (ISC) examining patients and ancestry-matched controls (also done by Stefansson *et al.* in phase II). Both groups identified deletions on chromosomes 1q21.1 and 15q13.3, which showed significant associations with schizophrenia, in addition to CNVs specific to each study. These deletions are in areas that have been reported to be deleted in rare cases of mental dysfunction, and are areas of genes flanked by regions of homologous segmental duplication, presumably raising the chances of deletion between the homologous areas during erroneous recombination events.

Because of their study design, the ISC was also able to compare the overall load of CNVs between control genomes and those of patients with schizophrenia. They found increased variation in the patients, supporting recent publications, but backed up by a much larger sample size. However, it's still unclear exactly what this slight but significant increase in genomic variation means for disease, and how the increase arises. The data certainly suggest testing a hypothesis of schizophrenia (and maybe other mental disorders) as a 'genomic disorder' in a number of cases.

A third paper, published in *Nature Genetics*, reports on a genome-wide association study, based on SNP markers, for schizophrenia and bipolar disorder. Markers reaching significance clustered in different areas from the CNV studies: in the gene *ZNF804A* at chromosome 2q32.1 for both schizophrenia and bipolar disorder, and in intergenic regions at 11p14.1 and 16p13.2 for schizophrenia alone. The authors highlight the difficulty in obtaining sufficient patient samples to get strong statistical support in genome-wide association studies — a problem that has left doubt hanging over conclusions from previous studies, but is surmounted here by replication testing in over 16,000 samples.

Future work is needed to explore how each deletion and gene association could lead to schizophrenia, as well as the overall question of the relevance of the increased variation in the genomes of these patients. Like all good research, these studies raise other important questions. For example, were the deletions inherited, and if so, why was disease not present in the relevant parent? And do the deletions lead to different phenotypes depending on the extent and location of the DNA removed? We are clearly chipping away at the genetics of mental disorders, but we still have a long way to go.

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ORIGINAL RESEARCH PAPERS
Stefansson, H. *et al.* Large recurrent microdeletions associated with schizophrenia. *Nature* 30 Jul 2008 (doi:10.1038/nature07229) | The International Schizophrenia Consortium. Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature* 30 Jul 2008 (doi:10.1038/nature07239) | O'Donovan, M. C. *et al.* Identification of loci associated with schizophrenia by genome-wide association and follow-up. *Nature Genet.* 30 Jul 2008 (doi:10.1038/ng.201)
FURTHER READING Burmeister, M., McInnis, M. G. & Zöllner, S. Psychiatric genetics: progress amid controversy. *Nature Rev. Genet.* **9**, 527–540 (2008)