in patients with these deletions are comparable to those of the general population of patients with schizophrenia.

With the removal of psychoses other than schizophrenia — as defined by strict diagnostic criteria — the association with the 1q21.1 and 15q11.2 loci drops just below significance. But Stefansson and colleagues rightly argue that there is no reason for disease features associated with a particular CNV to be confined to the current boundaries of psychiatric-disorder classification. The investigators also examined their cohort for deletion in the 22q11.2 locus, which causes velo-cardio-facial syndrome (VCFS), a condition often associated with schizophrenia. This deletion was identified in eight of 3,838 cases (0.2%), but was absent in 39,299 controls.

The authors found no significant association between schizophrenia and the 54–166 SNPs that map within each of the three chromosomal deletions. It has long been established[5] that CNVs can result in the misinterpretation of marker genotypes such as SNPs, because every locus is presumed to be biallelic — a person usually inherits one gene allele (copy) from each parent, but a locus becomes triallelic with a duplication and monoallelic with a deletion. As a result, linkage (co-inheritance) analysis is distorted. Perhaps CNVs also reduce the informativeness of association studies when a biallelic SNP assay is used. Moreover, as the authors contend, the markers used for SNP analysis might lack the ability to tag them, and thus rare SNPs at these loci that are associated with schizophrenia could be missed.

In a related paper, the International Schizophrenia Consortium[3] (page 237) performed a genome-wide survey of rare CNVs in 3,391 patients with schizophrenia and in 3,181 ancestrally matched controls. The authors found that, compared with controls, the total number of CNVs that are observed in less than 1% of the combined sample, and that are more than 100 kb in length, is increased in patients with schizophrenia. Moreover, other CNVs — deletions of 12p11.23 and 16p12.1–p12.2 — were observed in four patients each. These results reproduce recent data[6,7] obtained through studying much smaller patient sample sets (150 in one study[6] and 152 in another[7]), which found that an increased number of CNVs was associated with schizophrenia. The advantage of the much larger disease-sample size in the consortium study is that the authors could search for specific CNVs associated with schizophrenia.

Among the schizophrenia-associated CNVs described in this paper[3], rarer, single-occurrence CNVs and those that affect genes are more prominent. Also, as anticipated, deletions of the VCFS-associated 22q11.2 locus were detected in 0.4% of the disease cases. What's more, large deletions in the 1q21.1 and 15q13.3 loci — the same genomic regions identified by Stefansson *et al.*[2] — corresponded to previously unknown associations with schizophrenia, which remained significant after genome-wide corrections for multiple testing. Overall, the results provide strong support for a model of schizophrenia that includes the effects of rare CNVs occurring both across the whole genome and at specific loci, such as 1q21.1 and 15q13.3.

It is exciting that both papers[2,3] identify not only an association of the known 22q11.2 deletion with schizophrenia, but also two previously unidentified deletions. These two loci are flanked by low copy repeats — DNA sequences that are highly susceptible to mutation[8]. Although relatively rare, the two newly discovered CNVs indicate that schizophrenia can be caused by specific genomic rearrangements, and so perhaps can be classified as a genomic disorder[4].

A previous study[9] of some 1,000 patients with mental retardation of unknown cause reported a recurrent deletion CNV in the 15q13.3 locus that was associated with a mental retardation and seizure syndrome in nine individuals, including one with autism. Intriguingly, among the eight controls carrying the 15q13.3 deletion in Stefansson and colleagues' study[2], there was also one autistic individual. So it seems that the same deletion CNV can increase the risk of a broad range of clinical mental disorders.

As is often the case, many questions remain. How frequently do these deletion CNVs occur *de novo* and how often are they inherited? How frequently do they cause schizophrenia? What are the dosage-sensitive genes located in the deletion CNVs within the 1q21.1 and 15q13.3 loci? Are they involved in specific neural networks or pathways? Can this genome-wide screening approach for identifying rare CNVs also detect other genomic regions and genes associated with psychiatric illness, to provide yet further insights into the biology of these disorders? Will correcting abnormalities in gene dosage by RNA interference or epigenetic methods provide therapeutic avenues worth exploring? Nonetheless, although cautious optimism is warranted in these early days, such studies[2,3,6,7], together with work on autism[10–13], point to one fact: study of even complex traits should include an evaluation of CNVs and other genomic structural changes. ■

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1. Burmeister, M., McInnis, M. G. & Zöllner, S. *Nature Rev. Genet.* **9,** 527–540 (2008).
2. Stefansson, H. *et al. Nature* **455,** 232–236 (2008).
3. The International Schizophrenia Consortium *Nature* **455,** 237–241 (2008).
4. Lupski, J. R. *Trends Genet.* **14,** 417–422 (1998).
5. Lupski, J. R. *et al. Cell* **66,** 219–232 (1991).
6. Walsh, T. *et al. Science* **320,** 539–543 (2008).
7. Xu, B. *et al. Nature Genet.* **40,** 880–885 (2008).
8. Lupski, J. R. *Nature Genet.* **39,** S43–S47 (2007).
9. Sharp, A. J. *et al. Nature Genet.* **40,** 322–328 (2008).
10. Sebat, J. *et al. Science* **316,** 445–449 (2007).
11. Weiss, L. A. *et al. N. Engl. J. Med.* **358,** 667–675 (2008).
12. Kumar, R. A. *et al. Hum. Mol. Genet.* **17,** 628–638 (2008).
13. Morrow, E. M. *et al. Science* **321,** 218–223 (2008).

50 YEARS AGO

Theoretically, cancer therapeutic agents should be able to differentiate between malignant and normal human cells and should be more toxic to the malignant cells ... Early experiments with guinea pig sera gave the unexpected finding that leukaemic lymphocytes were frequently more sensitive to inactivated (56° C, 30 min.) than to fresh sera ... [H]uman leukaemic lymphocytes were sensitive to toxic factors in normal rabbit sera and in inactivated guinea pig sera. The rabbit sera usually killed the leukaemic lymphocytes in a few hours by 'fixation' and killed normal lymphocytes in a few days by intranuclear vacuolization.

ALSO:

This Slimming Business. By Prof. John Yudkin — [An] excellent account of nutrition that should enable the non-scientific reader to appreciate the reasons for the condemnation of much of the published nonsense on dieting.

From *Nature* 13 September 1958.

100 YEARS AGO

The Influence of Alcohol and other Drugs on Fatigue. By Dr. W. H. R. Rivers — [T]he author details the results obtained in an experimental research on the influence of certain drugs—caffeine, alcohol, cocaine, strychnine, and tobacco—on muscular and mental fatigue ... Caffeine in moderate doses (about 0.3 gram of the citrate) increases the capacity for both muscular and mental work, the stimulating action persisting for some time, and not being followed by any depressant action. Excessive doses, however ... are followed by a depressant action so marked that the drug in such circumstances becomes an accelerator of fatigue ... Alcohol in small doses (5–10 c.c.) seems to produce little effect, in larger doses (20–40 c.c.) the action was variable; in a subject not used to alcohol, sweating, giddiness, and other symptoms often ensued ... The capacity for mental work on the whole seemed to be lowered.

From *Nature* 17 September 1908.

50 & 100 YEARS AGO