Genesis of a complex disease

The largest genome-wide analysis of schizophrenia performed so far has identified more than 100 genetic regions that contribute to disease risk, establishing new leads for understanding this form of mental illness. [SEE ARTICLE P.421](#)

JONATHAN FLINT & MARCUS MUNAFÒ

A paper¹ published this week in *Nature* marks the culmination of a long debate about the genetic basis of a disorder sometimes considered psychiatry's heartland² — schizophrenia. No other psychiatric condition has evoked such diverse opinions. Its biological roots have often been denied and, in the anti-psychiatry movement of the 1970s, there was even outright rejection of its existence. The latest paper, from the Schizophrenia Working Group of the Psychiatric Genomics Consortium, reports an analysis of more than 150,000 people and finds more than 100 genetic regions associated with schizophrenia, laying to rest forever the idea that genetics is not an important cause of the illness.

Dispute over schizophrenia's genetic basis has been ferocious. This is hardly surprising given that Swiss psychiatrist Ernst Rüdin — an early proponent of the argument that the condition is a single-gene disorder — advocated the view that people with mental illnesses should not have children³, and justified the sterilization and murder of people with schizophrenia. Despite the disease's long and contentious history, by the end of the twentieth century there was consensus that genetic factors were involved⁴. But agreeing that genetics has a part to play is not the same as finding individual genetic regions (loci) that contribute to disease susceptibility. Progress in this arena has been marked by false starts^{5,6}, and by more than 800 genetic associations⁷ of dubious value.

Not unreasonably, many would ask why we should be any more confident that the consortium's geneticists have now got it right. The short answer is that the tests for associations between each gene in the human genome and disease are now mature. The correct criteria for determining significance in these tests are as familiar to human geneticists as their two-times table, and are exhaustively documented in the consortium's paper. Since the first genome-wide analyses for schizophrenia emerged in 2009 (refs 8, 9), the size of the studies has increased, as have the numbers of loci

Figure 1 | Progress in identifying schizophrenia-associated genes. Since 2009, genome-wide analyses of the genetic loci associated with schizophrenia (including the current study by the Schizophrenia Working Group of the Psychiatric Genomics Consortium¹, labelled 2014) have yielded increasing numbers of 'hits'^{1,9,15,16}. Over this time, there has been a correlation between the number of people tested and the number of susceptibility-associated loci found.

associated with the condition (Fig. 1).

The Psychiatric Genomics Consortium has now confirmed the existence of 108 loci that contribute to disease susceptibility. But even this number is insufficient to entirely explain the genetic causes of schizophrenia. So what does this discovery mean?

First and foremost, it confirms that genetics is a major cause of the illness. The risk variants now identified are common — they contribute in most, if not all, cases. This is a tremendous advance, of the sort that rewrites textbooks. Given the turbulent history of the field, this is a point that deserves emphasis and should be cause for well-earned celebration among those who carried out the work.

Second, we now know something about the probable genes involved. Readers not familiar with the vagaries of genome-wide association studies need to be aware that there is a difference between finding a genetic locus and finding a gene. Usually, it is assumed that the relevant gene is the one that lies nearest to the identified locus, but, as recently reported¹⁰ for a locus involved in obesity, this is not necessarily the case. As a rule of thumb, however,

the closest gene is probably a good place to start.

So what genes are involved? Expectant readers will have to turn to Table 3 of the Supplementary Information (go.nature.com/koxm8i) to find all the details. Those who take the trouble will be rewarded with some delightful insights. For many years, a leading hypothesis has been that schizophrenia arises from abnormal neuronal signalling involving dopamine. This theory was based on evidence¹¹ indicating that the efficacy of antipsychotic drugs correlates with their ability to block dopamine receptors. It turns out that those who championed the involvement of dopamine-related genes were right (a dopamine-receptor gene, *DRD2*, is associated). However, by no means all dopamine-related genes are involved (the gene encoding catechol-O-methyltransferase, an enzyme that metabolizes released dopamine, is not associated).

Having climbed a mountain of genetic analyses, it is perhaps a shame that the authors do not offer much of a view from the peak — no new biological hypotheses are presented. But it is clear that the idea that schizophrenia is merely a disorder of neuronal signalling (either dopamine- or glutamate-related) stands in need of revision. By far the most significant association is a locus on chromosome 6 that includes a region containing genes involved in acquired immunity: the major histocompatibility complex (MHC).

Given that the MHC also contains genes encoding various functional activities, the fact that the most significant association lies in the MHC is only suggestive of its role. However, Figure 2 in the paper contains another intriguing observation. The genetic effects in schizophrenia are enriched in regions outside the MHC that are also involved in acquired immunity. Is schizophrenia in part a disorder of acquired immunity? Surely this idea should start to be taken seriously. It is perhaps ironic that one of the earliest genetic associations reported¹² was with the MHC.

It is possible that environmental exposure explains some of the genetic associations

documented in this report. For instance, DNA-sequence variations in the *CHRNA5-A3-B4* gene cluster are strongly associated with heavy smoking¹³. Smoking is extremely common (more than 80% prevalence) in people with schizophrenia¹⁴, and the consortium's identification of an associated variant in the *CHRNA5-A3-B4* gene cluster might reflect a dose–response relationship between heaviness of smoking and schizophrenia risk, instead of — or as well as — a direct relationship. As ever-larger genome-wide association studies are conducted, we will presumably begin to pick up indirect effects. In other words, such studies may tell us about the environmental as well as the genetic causes of the disease. ■

Jonathan Flint is at the Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, UK.

Marcus Munafò is at the School of Experimental Psychology, University of Bristol, Bristol BS8 1TU, UK. e-mail: jf@well.ox.ac.uk

1. Schizophrenia Working Group of the Psychiatric Genomics Consortium. *Nature* **511**, 421–427 (2014).
2. Bebbington, P. & McGuffin, P. (eds) *Schizophrenia: The Major Issues* (Heinemann, 1988).
3. Torrey, E. F. & Yolken, R. H. *Schizophr. Bull.* **36**, 26–32 (2010).
4. Sullivan, P. F., Kendler, K. S. & Neale, M. C. *Arch. Gen. Psychiatry* **60**, 1187–1192 (2003).
5. Brzustowicz, L. M., Hodgkinson, K. A., Chow, E. W. C.,

- Honer, W. G. & Bassett, A. S. *Science* **288**, 678–682 (2000).
6. Levinson, D. F. *et al. Science* **296**, 739–741 (2002).
 7. www.schizophreniaforum.org/res/sczgene
 8. The International Schizophrenia Consortium. *Nature* **460**, 748–752 (2009).
 9. Stefansson, H. *et al. Nature* **460**, 744–747 (2009).
 10. Smemo, S. *et al. Nature* **507**, 371–375 (2014).
 11. Seeman, P., Lee, T., Chau-Wong, M. & Wong, K. *Nature* **261**, 717–719 (1976).
 12. McGuffin, P. *Psychol. Med.* **9**, 721–728 (1979).
 13. Ware, J. J., van den Bree, M. B. M. & Munafò, M. R. *Nicotine Tobacco Res.* **13**, 1167–1175 (2011).
 14. Hughes, J. R. *et al. Am. J. Psychiatry* **143**, 993–997 (1986).
 15. Ripke, S. *et al. Nature Genet.* **45**, 1150–1159 (2013).
 16. Ripke, S. *et al. Nature Genet.* **43**, 969–976 (2011).

EARTH SCIENCE

Rain on the parade

An analysis of landforms in the Bolivian Andes suggests that surface uplift has shaped the climate and landscape. This contrasts with previous work suggesting that climate controls topography and deformation along the mountain range.

ALISON M. ANDERS

Interactions between climate, erosion and deformation of the solid Earth have been hotly debated in recent decades. If climate dictates spatial patterns in erosion, as some researchers conclude, then it may also change mass distribution enough to influence deformation. A pair of papers^{1,2} from Whipple and Gasparini, published in *Lithosphere*, now examines relationships between climate, erosion, river-channel steepness and relief in the Bolivian Andes. The authors find unexpectedly little evidence for climatic control of erosion patterns or topography. Instead, they conclude that over the past 12 million years (Myr), the region has uplifted by approximately 3 kilometres.

The tantalizing potential for atmospheric processes to drive deformation of the solid Earth has inspired much research, with results being exuberantly paraded in support of this theory. The central Andean plateau is a compelling region in which to study this issue, because of the correlated spatial variability of its topography, climate and mountain-belt geometry (Fig. 1). Whipple and Gasparini's evidence¹ for recent, large-scale surface uplift comes from low-relief (largely flat) surfaces in the northern Bolivian Andes.

To understand their results, picture

the studied region as a series of small, gently sloping plateaus surrounded by steep river canyons on all sides. The authors interpolated the landscape between these plateaus and found

Figure 1 | Precipitation patterns across the Central Andean Plateau. The wet, steep and narrow northern Bolivian Andes strongly contrast with the broad, gently sloped and dry southern Bolivian Andes. Two papers propose^{1,2} that the topographic difference between them is driven mainly by changes in tectonic deformation of the mountain belt, and that precipitation varies as a function of topography. Solid lines are topographic contours; the contour interval is 500 metres. Precipitation data shown are from ref. 7.

that they form part of a ramp about 300 km long, gently dipping to the north and grading into sedimentary deposits of approximately 11–9 Myr old. This suggests that the topography of the region about 10 Myr ago was more gently sloping than it is now, and that the land surface has uplifted and tilted since that time.

Flat areas surrounded by incised river valleys are unusual. Typically, there is no difference in elevation at places where tributaries meet; smaller streams maintain steeper slopes to match the pace of erosion of the larger river. However, fluvial hanging valleys — which have floors that are higher than the main channel into which they flow — form in some tectonically active areas where small tributaries intersect with a river that is experiencing a sudden increase in erosion³. The stranded small tributaries, separated by waterfalls from the main stream, do not undergo the rapid erosion occurring around them, and are maintained as relicts of the former land surface.

Whipple and Gasparini used river channels on a relict surface to estimate the extent of downcutting of the main river, and assumed that this downcutting was caused by uplift of the surface since its formation. The authors extrapolated trends in channel slopes to reconstruct the channels' positions before the uplift. These reconstructed channels are roughly 2–3 km above current channel bottoms in the incised valleys — in other words, the surface has uplifted by this amount. The timing and magnitude of this surface uplift correspond approximately to estimates of these quantities for the southern Bolivian Andes⁴, suggesting that the northern and southern Bolivian Andes evolved in parallel, despite marked contrasts in climate and mountain-belt width for the two regions.

A strong point of these studies is the observation and interpretation