The human brain is the most complicated object in the known universe. Considering that complexity, and the number of jobs it has to do—from regulating appetite to thinking great thoughts—the brain goes wrong surprisingly rarely. But go wrong it sometimes does, with ruinous consequences for the lives of both the sufferer and his family and friends.

Some brain ailments, such as Alzheimer’s disease, leave visible scars in the organ’s fabric. These are the province of neurology. Others, such as schizophrenia, which leave no visible scar, belong to psychiatry. Erasing that distinction, by finding the biological underpinnings of psychiatric diseases, might let new treatments be devised. And that is the goal of the Psychiatric Genomics Consortium (PGC), a multinational alliance of researchers who, by pooling their findings, are able to gather the large numbers of patients needed for statisticians to spot, among the billions of DNA straws in each person’s genomic haystack, the needles of causation.

The consortium’s latest publication, on schizophrenia, was co-ordinated by Michael O’Donovan of Cardiff University, in Britain, and is published in Nature this week. The list of authors, though, runs to more than 300 scientists from 35 countries. These researchers have looked at the DNA of more than 34,000 people with schizophrenia and, for comparison, more than 45,000 without it. The result is the most comprehensive investigation so far of the genetics of a psychiatric disorder.

Altogether, the paper’s authors have discovered 108 places in the human genome, known as loci, where a change in a single DNA “letter” (a single nucleotide polymorphism, or SNP) correlates with the manifestation of schizophrenia. All previous work in the field had come up with only 30 of these. Encouragingly, 25 of those 30 were among the 108—thus independently confirming their reality.
A locus is not the same thing as a gene. It is a heritable DNA region rather than a functional unit. But the genes within or near it will be known, thanks to the Human Genome Project. The paper’s authors are thus able to say that three-quarters of the loci they fingered contain a gene or genes, and a further 8% are close to one. Intriguingly, only ten of the SNPs are actually inside a gene, and thus able to affect its composition. The others are thought to be in bits of DNA that regulate the activity of nearby genes.

The nature of those genes is telling. First, and no surprise, is \textit{DRD2}. This encodes a receptor for dopamine—one of the chemicals nerve cells use to transmit signals between each other, across junctions called synapses. \textit{DRD2} is the target for all existing antipsychotic drugs.

Potential new targets emerged as well, though. Some are involved in the activity of a second transmitter molecule, glutamate; others regulate the flow of calcium ions into cells. That, in turn, controls the flow of neurotransmitters across synapses. And it is this activity which ultimately results in the physical remodelling of synapses that is the fundamental mechanism by which brains develop and learn things.

These discoveries will not be easy targets for drugmakers. Glutamate is the commonest transmitter in the brain, involved in a host of processes there. And calcium ions flow not just in the brain, but in the entire body. Picking off and treating the processes involved in schizophrenia without creating side effects will be tricky. But this knowledge does give pharmaceutical scientists something new to work with.

Another link the consortium’s researchers have helped clarify is between schizophrenia and the body’s immune response. Such a connection has long been suspected. Several past studies suggest exposure to viral infection in the womb or in early childhood increases someone’s chance of developing the condition, and in 2009 a connection was made with a single immune-system gene. That lone hit has now been joined by several others.

Compare and contrast

All this, then, adds up to an important step forward in understanding schizophrenia. Nor does the consortium restrict its work to that condition alone. Last year, in a paper in \textit{Nature Genetics}, its researchers compared what was then known of the DNA underpinnings of a range of conditions (schizophrenia, bipolar disorder, major depression, autism and attention-deficit/hyperactivity disorder) to look for overlaps. They found some, particularly between schizophrenia, bipolar disorder and depression. Other work has discovered overlaps between schizophrenia and autism. And just this week a paper in Psychiatric Genetics, on a single glutamate-related gene, \textit{GRM3}, has shown it is connected both to schizophrenia and depression, and also to alcoholism.
It will therefore be interesting to repeat the approach this study used to try to create comprehensive lists of loci for these other conditions. That will help resolve an old question: just how truly distinct are the various diagnoses psychiatrists come up with? The field’s bible, the American Psychiatric Association’s “Diagnostic and Statistical Manual of Mental Disorders”, currently into its fifth edition, tends to split things up, multiplying the number of allegedly different ailments. Many practitioners disagree with this approach. Genomics may help illuminate who is right.

This paper, then, is an important scientific step forward. And its publication coincided with a pragmatic advance, too. The Stanley Centre, in Cambridge, Massachusetts, which contributed a third of the samples used in the paper, and which is one of the leading centres of research into the genetic links between different forms of psychiatric illness, announced receipt of a donation of $650m from Ted Stanley, a retired businessman who is its eponymous patron. That is a useful sum of money in a field that is not yet well financed. The Stanley Centre is part of the Broad Institute. This grew, in turn, out of the Whitehead Institute, a big contributor to the Human Genome Project. Some people have questioned the value of that project, which they say has not delivered practical medical advances as quickly as was promised at the time. This criticism has some truth, for the link between genetics and disease has proved harder to discern than many had hoped. But discerned, at last, it is being—as this latest paper shows.

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