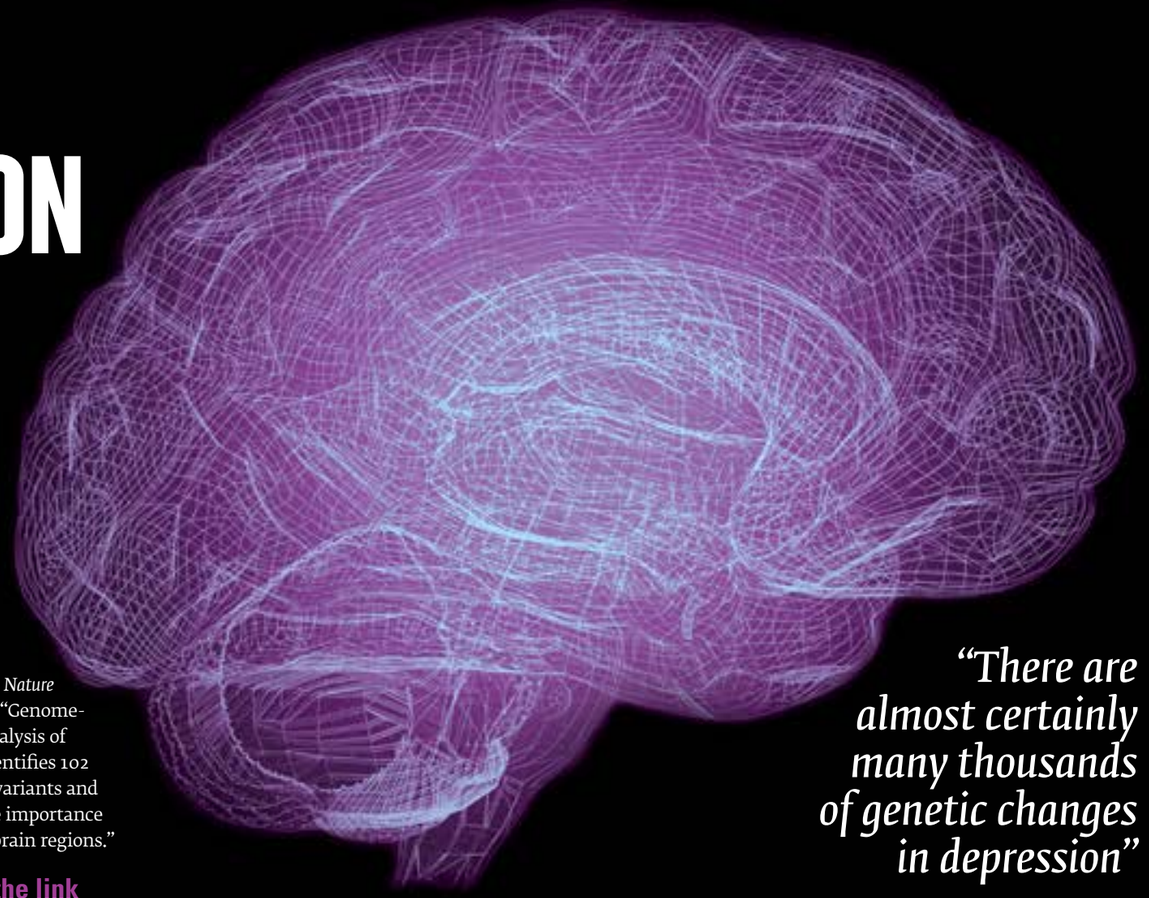
IS DEPRESSION GENETIC?

Andrew McIntosh discusses an international research study, which analysed genetic data from more than two million people.



According to the 2013 Global Burden of Disease study, the most widespread mental health problem around the world is depression. In the UK, the 2014 Adult Psychiatric Morbidity Survey found that one in six adults has a common mental health problem, such as depression or anxiety, and the same year an ONS study reported that almost 20% of people aged 16 and over in the UK had symptoms of depression or anxiety, with a gender split of 22.5% for women and 16.8% for men.

Mental health conditions such as depression may be as big a problem as any physical disease, and yet the mechanisms that underlie them remain imperfectly understood. They are deeply complex issues, originating as they do in that most intricate of human organs, the brain. These conditions are known to result from altered chemistry in the brain, but what triggers those changes and upsets the balance is at the heart of the mystery.

A link between mental health issues and genetic makeup has long been proposed, and that potential relationship was placed on a firm footing earlier this year with the publication in *Nature Neuroscience* of "Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of prefrontal brain regions."

Establish the link

As the title suggests, this international study, which analysed genetic data from more than two million people, has linked 102 genetic variants and 269 genes with depression, and found connections between the condition and a range of other issues. The findings could now throw the way open to new therapies for treating the disease.

While the idea that depression is related to a person's genes has been around for many years, it has taken some time for research to establish this link with conviction. The man who led the research, Andrew McIntosh, Professor of Biological Psychiatry and a senior clinical research fellow at the University of Edinburgh Centre for Clinical Brain Sciences, says it has been a matter of scale: "Genetic research in depression was initially limited to twin and family studies, which were able to show that there were genetic factors influencing risk, but without showing what the changes actually were. More recently, it has been possible to look at the molecular changes in individuals at greater scales using very reliable methods of genotyping and increasingly consistent and well-established methods of analysis. This has led incrementally to the identification of specific changes in the genomes of people with depression that influence risk."

The key was having genetic data from more than two million people – though that in itself presents big organisational and technical challenges for research. "The sheer size of genetic data can be very challenging, even before any analysis has been undertaken," says McIntosh. "But storage costs have reduced gradually over the years and computing speed has increased. In Edinburgh, like other universities, we have a parallel computing facility that can divide large, complex and slow processing tasks into thousands of smaller tasks. Individually, these smaller tasks take a few minutes to process and yield their findings, and because they can all take place together, and their results merged at the end, analyses can take place very quickly."

"There are almost certainly many thousands of genetic changes in depression"

Tip of the iceberg

While the results of this analysis may sound weighty – the 102 variants and 269 genes – the likelihood is that there are far more variants and genes waiting to be discovered. Indeed, McIntosh believes they have only isolated just the tip of the iceberg. "There are almost certainly many thousands of genetic changes involved in depression and, unlike many disorders, none seem to have large effect sizes," he says. "While individually the effects are small, when taken together genetic risk scores that estimate vulnerability from the genome are likely to become ever more accurate and informative for risk-stratification with potential wider application to personalised treatment."

These first gene variations detected by the research are clustered in the prefrontal regions of the brain, where the higher functions related to personality and complex thinking reside. The variations are thought to disturb the connections between the brain cells there, throwing some light on the mechanism that triggers depression. "The junctions between brain cells, the synapse, are understood to be very closely related to a number of behaviours and thinking skills, and studies of complex thinking skills and depression-prone dimensions of personality have repeatedly implicated the prefrontal cortex," says McIntosh.

"This knowledge has been gained through animal research, studies of human post-mortem tissue and neuropsychological investigations. Demonstrating similar findings using a genetic approach demonstrates the ability of genetics to provide insights into the underlying biology of depressive illness. As sample sizes and our knowledge of human genome grow, I expect it will be possible to shed even greater light on how the brain confers the symptoms of low mood."

Exploring all options

The research also established links between depression and other behaviour and disease traits, such as smoking. "The genetic correlations we found show that the changes associated with depression are associated with many other conditions and traits that are co-morbid with low mood," explains McIntosh. "This may simply tell us that the same genes have two or more effects, a process known as pleiotropy. It could also mean that the correlated traits are somehow causally associated with each other, something we explored in the paper using Mendelian randomisation. A third possibility, rarely explored in genetic studies to date, is that there are subgroups of depression with different aetiologies – one of which is strongly related to the trait with which depression is strongly correlated. We are exploring all of these options."

What's next for McIntosh and his colleagues? Their findings have raised the possibility of new research avenues, which could involve identifying targets for new drugs or even "obtaining cells from people at high and low risk of depression and then modelling depression in a dish".

Before that, the team is collaborating on a project called Genetic Links to Anxiety and Depression – or GLAD. It's looking for 40,000 UK volunteers to donate their saliva: to unlock further genetic secrets of depression. See gladstudy.org.uk for more

ANDREW MCINTOSH

- ✔ Trained in medicine at the University of Aberdeen
- ✔ Post-graduate training in Edinburgh in psychiatry and applied statistics
- ✔ Leads the Generation Scotland Expert Working Group for Psychiatric Disorders
- ✔ Co-chairs the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium
- ✔ Fellow of the Royal College of Psychiatrists.