A GENETIC ROADMAP TO DEPRESSION

It has long been known that genetics plays a role in depression, but it is only recently that individual genes are being identified.

Depression is a condition that affects over 300 million people globally. According to the World Health Organisation, clinical depression is the leading cause of disability worldwide and costs the global economy as much as $1 trillion annually.

Depression ranges in seriousness from mild, temporary episodes of sadness to severe, persistent depression. Clinical depression, the more-severe form of this disease, is also known as major depressive disorder (MDD) and is characterised by at least two weeks of low mood. Persistent depressive disorder, bipolar disorder, postpartum depression, seasonal affective disorder (SAD) and atypical depression are among the more common and debilitating types of depression.

Depression is an extremely complex disease. No one knows exactly what causes it, but it can occur for various reasons. These range from environmental factors such as death or loss to substance abuse, medication, illness and a combination of genes and stress that can affect brain chemistry and reduce the ability to maintain mood stability. Changes in the balance of hormones might also contribute to the development of clinical depression.

That genetics plays a role in depression has long been known. Children, siblings and parents of people with severe depression are more likely to suffer from depression than members of the general population. For example, if one identical twin suffers from depression, there is a 70 per cent chance that the other twin will too. If one of your parents has schizophrenia, your chance of having the disease is 13 per cent. If one of your parents has bipolar disorder, your chance of having the disease is 15 per cent. The risks increase with each additional family member that has the disease.

It was surmised that multiple genes interacting with one another in special ways probably contribute to the various types of depression that occur in families. However, there was no concrete evidence until recently.

The successful completion of the Human Genome Project in 2003 marked the end of scientists' monumental effort to sequence the three billion DNA "letters" in the human genetic blueprint and marked the dawn of the genome era in medicine. Until then, scientists studying mental illness had concentrated on a few hundred genes, mainly those that encode neurotransmitters and their receptors. That is only the tip of the iceberg, as at least a third of the approximately 20,000 different genes that make up the human genome are active primarily in the brain.

Researchers in more than 20 countries participated in a genetic study of mental illness as part of the Psychiatric Genome-Wide Association Study Consortium. In 2013 they published their findings based on more than 50,00 people with mental illness. Among them were that common gene variants contribute to both schizophrenia and bipolar disorder, there are at least 11 regions of the genome that are strongly associated with both diseases, yet neither is caused

Above: Human Genome Project in 2003 marked the end of scientists' monumental effort to sequence the three billion DNA "letters" in the human genetic blueprint

by a single gene but by a combination of several genes and unidentified non-genetic factors.

Professor Vishwajit Nimgaonkar, a psychiatrist at the University of Pittsburgh Medical Center who specialises in genetics, said: "When we started to map the human genome 25 years ago, we thought we might find the answer to psychiatric illness in our genetic code. Unfortunately, a simple genetic cause has not been found."

In 2015, Dr Na Cai of the Wellcome Trust Centre for Human Genetics in Oxford and colleagues from around the world recruited 5,303 Han Chinese women with recurrent MDD and 5,337 healthy control subjects from 58 Chinese hospitals involved in the China, Oxford and Virginia Commonwealth University Experimental Research on Genetic Epidemiology (CONVERGE) consortium. They identified two genetic variants that contribute to the risk of major depressive disorder.

A 2016 study published in *Nature Genetics* that involved nearly 460,000 subjects revealed no fewer than 15 discrete regions on the human genome associated with the development of MDD.

A study published in *Nature Genetics* earlier this year tripled the number of gene regions linked to depression. The world's largest investigation into the impact of DNA on the mental disorder identified 44 gene variants that raise the risk of depression. This includes 30 that have never been connected to the condition before.

The study was an unprecedented global effort by more than 200 scientists who work with the Psychiatric Genomics Consortium and was led by the University of North Carolina School of Medicine and the University of Queensland in Australia. Professor Cathryn Lewis and Dr Gerome Breen, of King's College London, led the UK contribution, along with scientists and psychiatrists from the Universities of Edinburgh, Cardiff and UCL.

The researchers pooled seven separate datasets from the UK, the US, Iceland and Denmark to obtain genetic information on 135,000 people who reported having depression, and 345,000 mentally healthy individuals. The scientists then compared DNA across the groups to find gene variants that were more common in those with depression. The results revealed a substantial overlap in the genetics that underpins depression and other mental disorders such as anxiety, schizophrenia and bipolar disorder, but also body

"Depression genetics has advanced to the forefront of genetic discovery"

DR GEROME BREEN,
King's College London

mass index, where DNA that predisposes people to obesity also raises the risk of depression.

"With this study, depression genetics has advanced to the forefront of genetic discovery,' said Dr Breen. "The new genetic variants discovered have the potential to revitalize depression treatment by opening up avenues for the discovery of new and improved therapies."

By tripling the number of gene regions linked to depression, scientists now hope to understand more about why the disorder strikes some but not others, even when they have similar life experiences. The work could also help in the search for drugs to treat the condition, which affects as many as one in four people over a lifetime.

"If you have a lower genetic burden of depression, perhaps you are more resistant to the stresses we all experience in life," said Professor Lewis.

Some of the gene variants they found are linked to neurotransmitters such as serotonin, which existing antidepressants work on. Other gene variants point to new biological mechanisms that the next generation of drugs might target.

However, identifying the genes linked to depression is only part of the story. Genetics also determines how our bodies respond to medicines, especially genes used to break down drugs in the liver, kidneys and other organs.

Though genomics differ, doctors generally have taken a one-size-fits-all approach to prescribing medicines, taking into consideration age, sex and and weight, while overlooking growing evidence of differences based on genetic inheritance. If a medicine doesn't work, another prescription is tried.

For most people, this process of trial and error works. But for an estimated 10 to 30 per cent of patients being treated for depression, the outcome is less predictable – and the consequences can be dire. Side effects of common medications like Ativan, Xanax and Busparcan can include extreme exhaustion, hallucinations and confusion.

That is where pharmacogenetic tests that look for genes that break down active ingredients in common medications enter the picture. The potential upside of pharmacogenetic tests may be strongest for patients diagnosed with mental illnesses. In a study of 165 patients those using genetically guided medications saw an average 70 per cent improvement in depressive symptoms within eight weeks.

Another independently funded study published in *The Primary Care Companion for CNS Disorders* in 2015 analysed data from 685 patients with mood or anxiety disorders. The researchers found 87 per cent of the patients "showed clinically measurable improvement" three months after their physicians used commercially available genetic tests.

To treat depression better, we need to discover more effective therapies. Before we can achieve this, we need to first have a better understanding of depression. That is why continued genetic studies are so crucial.

Above left: Though genomics differ, doctors generally have taken a one-size-fits-all approach to prescribing medicines

Left: Side effects of common medications like Ativan, Xanax and Busparcan can include extreme exhaustion, hallucinations and confusion.