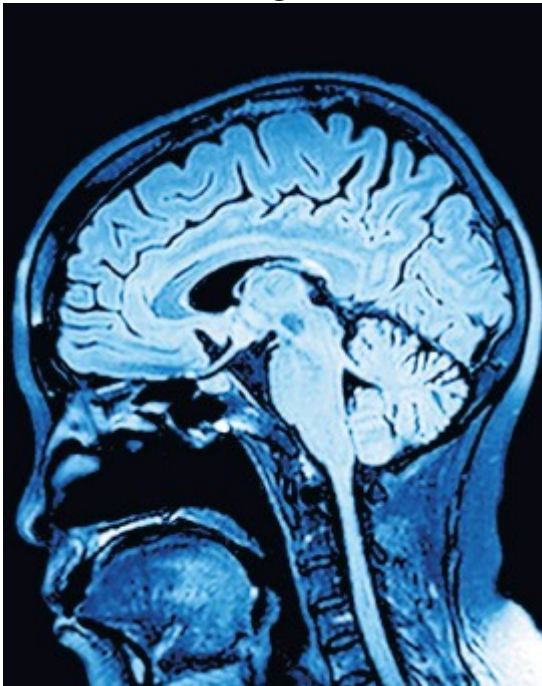


This revolution in our understanding of depression will be life-transforming

The discovery of genes that are linked to the crippling condition throws up exciting new possibilities for its successful treatment

The Observer Domestic edition · 29 apr. 2018 · Edward Bullmore

Depression runs in families, we know. But it is only very recently, and after considerable controversy and frustration, that we are beginning to know how and why. The major scientific discoveries reported last week by the Psychiatric Genomics Consortium in *Nature Genetics* are a hardwon breakthrough in our understanding of this very common and potentially disabling disorder.



If your parents have been depressed, the chances that you have been or will be depressed are significantly increased. The background risk of depression in the general population is about one in four – each of us has a 25% chance of becoming depressed at some point in our lives. And if your parents have been depressed, your risk jumps by a factor of three. However, controversy has long swirled around the question of nature or nurture. Is the depressed son of a depressed mother the victim of her inadequate parenting and the emotionally chilly, unloving environment she provided during the early years of his life? Or is he depressed because he inherited her depressive genes that biologically determined his emotional fate, regardless of her parenting skills? Is it nature or nurture, genetics or environment, which explain why depression runs in families?

In the 20th century, psychiatrists ingeniously teased out some answers to these questions. For example, it was found that pairs of identical twins, with 100% identical DNA, were

more likely to have similar experiences of depression than were pairs of nonidentical twins, with 50% identical DNA. This indicated clearly that depression is genetically heritable. But well into the 21st century, the precise identity of the “genes for depression” remained obscure. Since 2000, there has been a sustained international research effort to discover these genes, but the field has been bedevilled by false dawns and inconsistent results.

That is why the study published last week is such a significant milestone. For the first time, scientists around the world, with leading contributions from the UK’s world-class centres of psychiatric genetics research largely funded by the Medical Research Council at the University of Cardiff University, University of Edinburgh University and King’s College London, have been able to combine DNA data on a large enough sample to pinpoint which locations on the genome are associated with an increased risk of depression. So we now know, with a high degree of confidence, something important about depression that we didn’t know this time last year. We know that there are at least 44 genes, out of the 20,000 genes comprising the human genome, which contribute to the transmission of risk for depression.

However, this raises at least as many issues as it resolves. Let’s first dwell on the fact that there are many risk genes, each of which contributes a small quantum of risk. In other words, there is not a single smoking gun, a solitary rogue gene that works like a binary switch, inevitably causing depression in those unfortunate enough to inherit it. More realistically, all of us will have inherited some of the genes for depression and our chances of becoming depressed will depend in part on how many and their cumulative impact. As research continues and even larger samples of DNA become available for analysis, it is likely that the number of genes associated with depression will increase further still.

This is telling us that we shouldn’t be thinking about a black-and-white distinction between us and them, between depressed patients and healthy people: it is much more likely that our complex genetic inheritance puts all of us on a continuous spectrum of risk.

What are these genes and what do they tell us about the root causes of depression? It turns out that many of them are known to play important roles in the biology of the nervous system. This fits with the basic idea that disturbances of the mind must reflect some underlying disturbance of the brain.

More surprisingly, many of the risk genes for depression also play a part in the workings of the immune system. There is growing evidence that inflammation, the defensive response of the immune system to threats such as infection, can cause depression. We are also becoming more aware that social stress can cause increased inflammation of the body. For decades we’ve known that social stress is a major risk factor for depression. Now it seems that inflammation could be one of the missing links: stress provokes an inflammatory response by the body, which causes changes in how the brain works, which in turn cause the mental symptoms of depression.

Knowing the risk genes for depression also has important implications for practical treatment. There have been no major advances in treatment for depression since about 1990, despite it being the major single cause of medical disability in the world. We need to find new ways forward therapeutically and new genetics is a great place to start the search for

treatments that can cut through more precisely to the cause or mechanism of depression. It is easy to imagine how new antidepressant drugs could in future be designed to target inflammatory proteins coded by depression risk genes. It is exciting to think that the new genetics of depression could unlock therapeutic progress in psychiatry as well.

Finally, although I think these genetic discoveries are fundamental, I don't see them as ideologically divisive. They don't prove that depression is "all in the brain" or that psychological treatment is pointless. The genetics will be biologically pre-eminent but, as we understand more about what all these "genes for depression" do, we may discover that many of them control the response of the brain or the body to environmental stress. In which case, the treatment that works best for an individual patient could be a drug targeting a gene or intervention targeting an environmental factor such as stress.

In short, I believe that a deeper understanding of the genetics of depression will lead us beyond the question we started from: is it nature or nurture, gene or environment? The answer will turn out to be both.

Edward Bullmore is head of the department of psychiatry, Cambridge University and author of *The Inflamed Mind*