

There are no known biological causes for any of the psychiatric disorders apart from dementia and some rare chromosomal disorders. Consequently, there are no biological tests such as blood tests or brain scans that can be used to provide independent objective data in support of any psychiatric diagnosis.

A simplistic biological reductionism has increasingly ruled the psychiatric roost... [we have] learned to attribute mental illness to faulty brain chemistry, defects of dopamine, or a shortage of serotonin. It is biobabble as deeply misleading and unscientific as the psychobabble it replaced.

Andrew Skull, Professor of History of Psychiatry, Princeton University, in The Lancet

There are two dominant myths with respect to the origins of mental health conditions. The first is that changes in mood can be traced to chemical imbalances. The second is that genes play a central role in the onset of mental disorders. We have reviewed the lack of evidence for the chemical imbalance theory under 'Myth of the chemical imbalance' on the CEP website, and so here we will focus on the genetic hypothesis.

Genetics¹

Twenty years ago when the Human Genome Project was up and running there was great anticipation of finding singular gene mutations (or causes) for most emotionally or cognitively related problems. This was inspired by a few interesting discoveries related to what are now known as the organic brain diseases. Perhaps the best-known example is Huntington's disease. This is caused by a gene carried on chromosome 4 that destroys brain cells on the frontal lobes, leading to impairments in cognitive functioning. But these clear cut cases in the realm of mental health, are very much the exception. Most genetic influences on disease are greatly more complicated than those early pioneers of the genome project could have dreamed. For instance, in the realm of psychiatry there is no known gene or clear genetic variants for around 97% of all the mental disorders now contained in the current DSM and ICD. And even where genes may be implicated in disorders like bi-polar disorder and schizophrenia, research now reveals such mind-boggling complexity that nothing definitive can be said about 'this causing that'.

A central complicating factor is our growing understanding of epigenetics. Modern genetics now broadly accepts that it is virtually impossible to understand how our biology works outside the context of our environment. To put the new genetics in the simplest terms, virtually no neurological and psychological disorders have been demonstrated to result from the mutation of a single gene. Rather they are now known to involve molecular disturbances that implicate multiple genes and the signals that control their expression.² In other words, the popular idea that so-and-so gene causes so-and-so mental trait has been surpassed by the notion that it is interactions between our genes and their environment that actually shape us. This is because we now know there to be thousands of molecules attached to our DNA that can literally turn our genes on and off. These molecules, or 'epigenetic markers' as they are more technically known, actually alter and develop as an individual adapts to their environment.

The equation therefore runs something like this: because our environment affects these molecules, and because these molecules can turn our genes on or off, the environment can no longer be seen as irrelevant to how our genes determine our functioning and development.

Studies of rats have illustrated this point well. Baby rats born to mothers who rarely licked their pups where given to foster mothers who were very affectionate (who licked them a lot). Dissection revealed that the affectionately raised rats had brain characteristics different to those receiving little affection: the former possessed more of the neuron receptors considered crucial steppingstones in slowing down the production of stress hormones. In short, a stretch of DNA, serving as a switch for a gene related to these neural receptors, had been suppressed in the less-affectionately raised rats. The conclusion is that adult

personality differences related to stress weren't determined by genes inherited from their biological mothers, but were an outcome of how they were raised as pups.³

The same groups of researchers performed a related study on human beings, which analysed the brains of 36 people post mortem. Twelve of these people had died of natural causes, while the rest (24) had committed suicide. And of the 24 suicide victims, 12 of these had been abused as children, whereas the other 12 had not. When the brains of these three groups were compared, the brains of those in the group that had suffered childhood abuse shared the same pattern of fewer receptors linked to stress hormones. Their brains, via epigenetic changes, had reacted to the environmental abuse – leading them to grow in a direction different to brains receiving environmental care.⁴

Studies like these show that genes can be 'switched on or off' by molecules that are themselves altered by environmental factors.⁵ We know, for example, that there are two genes strongly associated with hereditary breast cancer (BRCA1 and BRCA2). But we also know these genes are responsible for only about 10 per cent of all breast cancers (and that only about a further 10%-20% of breast cancers are related to any kind of gene or variant). This means that most women who develop breast cancer may not be hereditarily disposed to do so.⁶ But even if they are hereditarily disposed, it also means they won't necessarily develop the condition. As the American Society for Clinical Oncology (ASCO) asserts, woman with a 75% chance of developing breast cancer may remain perfectly healthy, while a woman with a 25% chance of developing breast cancer may eventually develop the disease.⁷ Again, the presence of the relevant gene alone is not enough to account for the disease's onset. The environment influencing epigenetic factors play a crucial role.

In the face of such complexity, research into the genetics of 'mental disorders' such as depression, schizophrenia and bi-polar has continued. In 2003, for example, a study was published in the journal *Science* that asked why stressful experiences lead to depression in some people but not in others. After analysing 847 patients over time, it found that those who had one or two copies of a gene variant that interfered with serotonin transport were three times as likely to develop depression if subjected to certain stressful life events, like losing a job or getting divorced. This study was thought to provide evidence of a gene-by-environment interaction, in which an individual's response to environmental stresses is moderated by his or her genetic makeup.⁸ This finding generated a great deal of excitement, until another study, published a few years later, tried to replicate these findings. This next study assessed over 14,000 people via a meta-analysis of over 14 studies. But the conclusion it reached, dampen the previous excitement: 'This meta-analysis yielded no evidence that the serotonin transporter genotype alone or in interaction with stressful life events is associated with an elevated risk of depression in men alone, women alone, or in both sexes combined.'⁹

Another major study that scanned the genetic sequences of 20,000 normal people and then compared them with the sequence of 10,000 patients with schizophrenia revealed that over 10,000 different gene variants could have a role in the onset of schizophrenia. And this study did not take the findings of epigenetics into account (the environmentally susceptible molecules that interfere with these genetic variants).¹⁰

While it is important to support work in genetics, it is also important to be clear about what this work so far allows us to say. Given the ever-complex developments in fields like epigenetics, all we can do today is embrace a position littered with caveats: where genetics play a role in our mental lives, they do so via a given, yet-defined, constellation of genes that may predispose a person to an unknown degree of vulnerability to developing a given form of mental distress if other social or psychological conditions trigger it, and if environmentally influenced epigenetic factors permit it. Such tentativeness is now slowly trickling through to the mental health establishment, as can be seen from the World Health Organisation's recent official statement on the causes of depression:

Depression is a complex disorder which can manifest itself under a variety of circumstances and due to a multiplicity of factors... biological (genetic and biochemical), sociological (stressors) and psychological (development and life experiences) factors interact to produce a picture of depression. Research during the last fifty years indicates that there is no single factor which can explain the cause for depression.¹¹

The WHO does not say genes or biochemical imbalances cause depression. All it says is all anyone can say: of course our biology is implicated in mental distress, just as it is implicated in any emotional, physical or mental state that is experienced as either positive or negative. But precisely how it's implicated, and precisely to what degree, we do not really know.

CEP supports ongoing research into the biology of all human behaviours, emotions and traits. It also believes in respecting our current level of knowledge and not going beyond what the research permits us to say.

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¹ The following sections are paraphrased from Davies, J, 2013, *Cracked: why psychiatry is doing more harm than good* (London: Icon Books)

² Tsankova N., Renthal W., Kumar A., Nestler E.J., 2007, Epigenetic Regulation in Psychiatric Disorders, *May*;8(5):355-67.

³ Kaffman A., Meaney M.J., 2007, Neurodevelopmental Sequelae of Postnatal Maternal Care in Rodents: clinical and research implications of molecular insights, 48(3-4):224-44. A really good journalistic account of this study can be found here: Zimmer. C, 2010, The Brain: The Switches That Can Turn Mental Illness On and Off, *Discover Magazine* - published online June 16, 2010

⁴ McGowan P.O. et al, 2009, Epigenetic Regulation of the Glucocorticoid Receptor in Human Brain Associates with Childhood Abuse, *Nat Neurosci*,12(3):342-348

⁵ Jacob Peedicayil, J., 2007, The Role of Epigenetics on Mental Disorders, *Indian J Med Res* 126:105-111; Tsankova, T., Renthal, W., Kumar A., Nestler, E.J., 2007, Epigenetic Regulation in Psychiatric Disorders, *Nature Reviews Neuroscience* 8, 355-367

⁶ Olopade, O.I. et al, 2008, Advances in Breast Cancer: Pathways to Personalized Medicine, *Clinical Cancer Research* 14; 7988-7999

⁷ ASCO website: <http://www.cancer.net/patient/All+About+Cancer/Genetics/Genetic+Testing>, retrieved May 2012

⁸ Caspi, A. et al, 2003, Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT, *Gene Science*, 301 (5631): 386-389

⁹ Quoted in: Carlat, D, 2010, *Unhinged: The Trouble with Psychiatry – a doctor’s revelations about a profession in crisis* (New York: First Free Press p. 80)

¹⁰ See: Joseph, J., Ratner, C. Website:
<http://www.councilforresponsiblegenetics.org/pageDocuments/1NX6VC0254.pdf>

¹¹ World Health Organisation, Mental Health and Substance Abuse, Facts and Figures Conquering Depression, accessed online Aug 2010, see:
http://www.searo.who.int/en/Section1174/Section1199/Section1567/Section1826_8101.htm