Above genes: epigenetics and psychiatry

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Epigenetics could provide some insights into the risk of developing psychiatric disease and uncover a potential therapeutic target if researchers can discover enough about the role of this intriguing biological mechanism. Mark Greener reports.

It is, arguably, somewhat surprising that psychiatric diseases are not even more common than they already are. About 8% of Americans develop post-traumatic stress disorder (PTSD), for example. Yet between 50% and 85% experience at least one traumatic event.1 So, why are some people especially vulnerable to mental illness? And why are some so remarkably resilient?

There’s no simple answer, of course. But, essentially, psychiatric diseases seem to arise from the interplay between genetic susceptibility, ‘constitution’ (such as resilience and vulnerability) and environmental factors, including stress, circumstances and culture. The interplay changes, for example, neuroendocrine and neuro-inflammatory processes, brain architecture and neurotransmission. These changes, in turn, underlie the emergence and persistence of psychiatric symptoms.

Genes, for example, may account for 70–80% of the risk of developing schizophrenia and bipolar depression, between 48% and 75% of the likelihood of suffering major depression and 30–70% of PTSD risk.1,2 Many genes linked to mental illnesses seem to modulate sensitivity and responses to environmental factors.2

But genes tell only part of the story. Biologists increasingly recognise the importance of epigenetics, which literally means ‘on top of the genes’, in determining the risk of developing psychiatric and other diseases as well as in the maintenance of our health and wellbeing. Epigenetics refers to alterations in gene expression that do not involve changes to the DNA sequence, but that are transmitted through cell division and, in some cases, may be passed to the next generation.1–3 Fundamentally, these epigenetic processes ‘instruct the cell/tissue to correctly interpret external signals and adjust its functions accordingly’.2 Studies of epigenetics help us understand the complex, complicated and enigmatic nature of psychiatric disease, which, in turn, raises the prospect of innovative new approaches to diagnosis, treatment and prevention.2,4

Epigenetic mechanisms

Human DNA is around two meters long, but the nucleus is only around six microns across. So, DNA is compacted around 10 000 times, in part by sections of 147 base pairs of DNA wrapping about 1.7 times around a core of eight histone proteins (an octamer) – an arrangement called chromatin.5 One epigenetic mechanism – DNA methylation – usually targets the promoter regions (sequences that switch genes on) containing runs where cytosine is adjacent to guanine. Methylation of these CG islands usually represses gene transcription.5

Another epigenetic mechanism targets the histone octamer complex. Modifying the histone protein opens (euchromatin) or closes chromatin (heterochromatin), which facilitates and represses transcription respectively.2,3 Both these types of epigenetic change are chemically stable and maintained during cell division.2 Indeed, epigenetic changes remain detectable in blood and postmortem brain samples decades after exposure to a trauma. This persistence raises the prospect that epigenetic changes might offer biomarkers for the diagnosis and monitoring of psychiatric diseases.2

Some researchers include the long and small non-coding RNAs that regulate gene expression within epigenetics, although these do not seem to produce stable, heritable changes.2 For instance, one small non-coding RNA, known as miR-124-3p, is specific for neurones and seems to regulate genes associated with stress responses and neural plasticity. The prefrontal cortex (in animal models of depression and postmortem samples from patients) and serum of people with major depression showed up-regulation of miR-124-3p, which is under epigenetic control. Four non-coding RNAs were downregulated in the blood of people who responded to eight weeks treatment with an antidepressant compared with those who did not. This suggests that non-coding RNA could offer a new therapeutic target and biomarker for depression.3

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Epigenetics and depression

Several other epigenetic processes seem to contribute to the risk of developing depression. For example, a growth factor called brain-derived neurotrophic factor (BDNF) mediates the development, plasticity and survival of numerous types of neurone. Animal models of depression and PTSD suggest that trauma in childhood or adult life produces long-lasting epigenetic changes that repress the gene that encodes BDNF.7

Peripheral blood from adults who received poor maternal care during childhood showed elevated DNA methylation levels of the gene encoding BDNF compared with those exposed to high care. People with depression also seem to show hypermethylation of the BDNF gene compared with controls. Indeed, the extent of hypermethylation was associated with a history of suicide attempts and ideation, as well as a poor response to antidepressants. Other studies showed differences in methylation of the genes encoding BDNF or its receptor in psychiatric disorders that exhibit depressive features as well as in postmortem brains from people with major depression, bipolar disorder, schizophrenia or borderline personality disorder who committed suicide.2

Furthermore, the enzyme catechol-O-methyltransferase (COMT) breaks down dopamine and other catecholamines. Low dopamine levels in the prefrontal cortex seem to be implicated in several of depression’s hallmark symptoms, including loss of interest, energy and motivation. Against this background, Na et al. enrolled 90 people with major depression and 90 controls. Methylation of the COMT gene was lower in people with depression than controls. Inhibition of the COMT gene may further reduce the amount of dopamine in the brain of people with depression and disrupt the connectivity of the prefrontal white matter. Indeed, methylation of the COMT gene seems to produce different effects on the prefrontal connectivity in patients and controls.7

The gene encoding the serotonin transporter also shows epigenetic changes that seem to be induced by environmental stressors in several disorders, such as major depression, bipolar disorder, PTSD, schizophrenia, attention deficit hyperactivity disorder (ADHD) and addiction.2 The serotonin transporter takes the neurotransmitter back into the presynaptic terminal and is, of course, the site of action for selective serotonin reuptake inhibitors.

The DNA sequence of the promoter sequence in the gene that encodes the serotonin transporter shows several genetic variations (polymorphisms). For example, people with ‘short’ alleles show low expression of the gene and reduced serotonin uptake. People with ‘long’ alleles show the converse. Some studies suggest that when facing a stressful life event, people with short alleles showed greater suicidality than those with two copies of the long allele (homozygotes). The risk does not seem to differ in the absence of stressful events.2

Meta-analyses, however, reached differing conclusions about whether the polymorphisms in the serotonin transporter gene influenced the interaction between depression and stress. Differences in epigenetics could help explain this discordance. Stressful life events (such as childhood abuse) and environments (eg neighbourhood crime or socioeconomic status), depressive symptoms and the response to antidepressants, and antisocial personality disorder all seem to be associated with alterations in DNA methylation of the gene that encodes the serotonin transporter.

In some cases, only people carrying the short allele were epigenetically susceptible to stressful life events. In other cases, only long homozygotes showed epigenetic changes. In other words, the effect of DNA methylation might depend on context.5 Nevertheless, blood methylation of the genes encoding the serotonin transporter or BDNF might predict responses to pharmacological or psychotherapeutic treatments.2

Transmitting mental illness

Although epigenetic research in psychiatry remains in its infancy,2 similar results emerged in studies of several other mental illnesses.2,3 But despite the clinical and mechanistic diversity, a common theme emerges: transient or chronic life events, alone or in combination with susceptibility genes, can alter neuropsychiatric systems. Epigenetic changes further alter a person’s ability to adapt by changing vulnerability or resilience to future stressors.7 And it is now clear that epigenetic changes can occur very early in life – DNA methylation in cord blood at birth predicted later ADHD symptoms3 – or even in utero.

For example, one study enrolled 50 Rwandan women who were pregnant during the genocide, half of whom lived abroad at the time. Not surprisingly, the mothers living in Rwanda during the genocide and their children were more likely to have PTSD and depression than controls living abroad. The mothers living in Rwanda and their children also showed higher methylation levels of the gene encoding a glucocorticoid receptor and lower cortisol levels than controls. While the study was relatively small and there was a risk of confounding, the investigation suggests that DNA methylation induced by trauma might be transmitted from parents to children.1
Further evidence of a transgenerational risk emerged in a study that looked at methylation changes of the gene encoding FK506 binding protein 5, which modulates glucocorticoid activity, in 32 Holocaust survivors and 22 offspring, as well as 8 control subjects and 9 offspring. Methylation levels were higher in Holocaust survivors, but lower in their offspring than among controls. Again the study is relatively small and the authors could not exclude other factors that might have influenced the results, such as the extreme starvation endured by Holocaust survivors. Nevertheless, in some cases, offspring might be able to accommodate the epigenetic changes transmitted from their parents. Further research into transgenerational transmission of epigenetic risk could profoundly change our conception of mental illness and perhaps raise the prospect of developing strategies to prevent psychiatric conditions.

**Prospects and problems**

In the future, a new generation of psychiatric drugs may modulate epigenetics by, for example, inhibiting DNA methylation or histone modifications. Valproic acid, used as an anticonvulsant and mood stabiliser, seems to inhibit an enzyme responsible for histone modifications. In animal models, drugs inhibiting histone modifications seem to enhance synaptic plasticity, ameliorate cognitive and neurological dysfunction, and mimic the effect of antidepressants or extinction of fear memories.

But epigenetic treatment will need to be targeted precisely. Widespread modulation of DNA methylation or histone modification could influence numerous genes and, in turn, potentially cause unacceptable side-effects, including teratogenicity. Moreover, epigenetic changes are important for normal responses to environmental changes and several basic biological functions. Changes in DNA methylation seem to be involved in learning, memory and neuronal plasticity, for example. However, techniques such as CRISPR-Cas9 can act as ‘molecular scissors’ and edit DNA at specific genetic sequences. Applied to epigenetics, CRISPR-Cas9 seems to induce long-lasting changes in DNA methylation or histones. Nanotechnology could deliver CRISPR-Cas9 to the CNS. Moreover, CRISPR-Cas9 can help test the functional consequences of epigenetic changes.

Despite the promise, investigating epigenetics can be challenging. For instance, age, sex, ethnic background and smoking status might influence the epigenetic landscape. Differences in symptoms and treatment responses might arise from epigenetic variations. Such factors require clinical studies that enrol a large, homogenous sample. To complicate matters further, early life stress does not invariably increase vulnerability to psychiatric disease. In some people, stress in early life promotes resilience in adulthood, again, partly mediated by epigenetic mechanisms. Interactions of epigenetic mechanisms and genes that encode plasticity probably contribute to such variation.

Moreover, epigenetic mechanisms seem to contribute to many other aspects of our health and wellbeing. Although further studies are needed, epigenetic changes can influence, for example, growth trajectories and cardio-metabolic risk. Epigenetic changes also seem to contribute to certain neurodevelopmental disorders and intellectual disabilities, including Rett and fragile X syndromes.

Despite the technical issues and epigenetics’ inherent complexity, it is clear that the relationship between genes and epigenetics ‘appears instrumental to understanding how genes and life adversity shape individuals into vulnerability or resistance states’. The studies raise the prospect of innovative new approaches to diagnosis, treatment and prevention of psychiatric and other diseases. After all, it is clear that epidemic changes can persist for decades, early experiences can influence the rest of the person’s life – and there is the intriguing prospect of transgenerational transmission. Indeed, epigenetics can create a psychiatric legacy that lasts for life and even beyond.

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**References**