Epigenetics in mental illness: Hope or hype?

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Recently there has been increasing interest in genome-wide epigenetics (or epigenomics) of healthy controls (reference) compared to samples with a specific mental illness, based in part on evidence from rodent models that alterations in epigenetic modifications are implicated in behavioural phenotypes related to mental illness.[1–3] Unlike genetic sequences, epigenetic modifications are variable and depend on cellular phenotype and environmental conditions.[4] Genetics is considered insensitive to these conditions, since the same genetic sequence is present in the organism throughout life, with the exception of sporadic mutations. Epigenetics includes a large number of reversible covalent modifications that do not alter the genome (DNA sequence), which include covalent modification of DNA (DNA methylation) and acetylation, methylation and phosphorylation of histones and DNA-associated proteins. Typically, DNA methylation is associated with regions of condensed chromatin structure and silencing of gene expression, and is often associated with histone deacetylation and histone methylation (especially at Lys-9).[5–7] Specific epigenetic changes at discrete sites in candidate genes have been correlated with alterations in specific gene expression, leading to altered lifelong behavioural phenotypes.[1–3] The implication is that by understanding the full spectrum of epigenetic modifications across the genome, valuable markers of behavioural or disease phenotypes will emerge, using bioinformatics analysis to reveal specific changes that correlate with behaviour.

Epigenetics: the hype

Based in part on evidence that epigenetic modifications are sensitive to environmental change, several groups forming the International Human Epigenome Consortium are characterizing the epigenome of healthy cell types, tissues or individuals to obtain "reference" epigenomes using high-density genome-wide next-generation sequence analysis.[4,8,9] It is argued that the vast amount of information provided by epigenomic sequencing will inevitably lead to new clues as to the etiology and treatment of pathological processes. With the results of several genome-wide associations in depression, schizophrenia and bipolar depression yielding interesting but not always reproducible associations, it is unclear whether epigenetic association studies in mental illness would be more productive. Large sample sets encounter problems such as appropriateness of the "hyper-normal" control group (screened for lack of mental illness and/or addiction), diagnostic variability, heterogeneity of illness and variations owing to mixed race, all of which will detract from the reliability and power of association.[10-12] Epigenetics substantially adds to the complexity of measurement, since epigenenetic modifications are not "all or none." For example, typically individual DNA methylation sites are partially methylated; hence, multiple sequences from the same cell type or tissue preparation must be run to estimate the percentage of methylated nucleotides.

Another important limitation of epigenomics is the cell and tissue specificity of epigenetic modifications such as DNA methylation.[13] Epigenetic modifications are variable and depend on cell type, differentiation state and hormonal and environmental conditions.[4] In other words, every individual neuron could have distinct patterns of DNA methylation or histone modification in their genome. Hence, the value of determining a reference cell epigenome may be of limited applicability for neuronal cells in particular owing to their inherent diversity. On the surface, epigenomic mapping appears to provide little advantage over gene array, proteomic or other "omic" approaches for providing markers of brain function. However, there is evidence that a specific epigenetic modification can be propagated across the genome and may serve as a marker for specific states or conditions. For example, histone-H3K4-trimethylation is considered a specific marker of transcription start sites.[13] Global histone-H3 dimethylation is increased in nucleus accumbens of mice via induction of the histone methylase G9a, specifically following chronic cocaine treatment, and may serve as an addiction marker.[14] Another advantage of epigenetics over gene arrays and proteomics is that it is independent of RNA or protein abundance, as there are 2 copies of every gene. Thus, it is possible to test

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J Psychiatry Neurosci 2010;35(6):366-8.

DOI: 10.1503/jpn.100148

alterations in genes with low abundance transcripts as readily as higher transcribed genes. However, since it is tissue-specific, epigenetic analysis would require human post-mortem brain tissue for valid analysis. Thus, unless parallel changes occur in blood and biopsy tissue, epigenomic markers would not be appropriate as diagnostic or prognostic markers. Furthermore, although DNA methylation patterns may persist into adulthood, histone modifications are more plastic and are strongly affected by environmental changes throughout life. Thus an epigenomic reference map must ensure that the basal reference condition has not been acutely perturbed by even subtle uncontrolled events.

Epigenetics: the hope

Despite the above challenges, the excitement regarding epigenomics is the hope that specific epigenetic markers, such as DNA methylation, may provide quantifiable measures of lifetime environmental stress or heritable predisposition to mental illness. The association of DNA methylation (e.g., of the reelin gene) with behavioural phenotypes, such as reduced prepulse inhibition in animal models, suggested a role in schizophrenia.[15,16] Studies from Weaver and colleagues[1] have shown that offspring of rat mothers that provide poor maternal care acquire an adult phenotype of increased stress reactivity. This behavioural phenotype is associated with increased DNA methylation at a specific site of the glucocorticoid receptor promoter to reduce hippocampal glucocorticoid receptor expression, resulting in attenuated negative feedback regulation of the stress axis.[1] The DNA methylation changes observed in rats were reversible in early life, but became fixed in the adult, suggesting that early-life behavioural environment has a particularly strong effect on adult brain DNA methylation pattern and adult behavioural phenotype. Similarly, persistent demethylation of the vasopressin promoter is associated with early-life stress in mice, leading to hypersecretion of vasopressin and hypersensitivity to stress.[17] In this light, early childhood abuse has been associated with increased DNA methylation of the analogous site of the human glucocorticoid receptor gene in the postmortem hippocampus of suicide completers.[18] Thus, DNA methylation is an epigenetic change that could translate environmental stressors or enrichment to altered expression of genes that persists throughout life and influences lifelong behavioural phenotype.[19] However, we do not know the extent to which such epigenetic changes may be reversible in humans.

Already, understanding the patterns and roles of epigenetic modifications is revealing their potential importance as therapeutic targets. The hope is that by modifying DNA methylation by inhibition of histone deacetylation, the consequences of epigenetic changes on behaviour can be reversed.[20] Histone deacetylase inhibitors can reverse the effects of chronic social defeat stress in mice to reduce histone-H3 acetylation, similar to the actions of the antidepressant fluoxetine.[21] Valproate, a widely used mood stabilizer, has many actions, including inhibition of histone deacetylation, and the similar actions of antidepressant and histone deacetylase inhibition suggest that more selective histone deacetylase inhibitors could be useful as treatments to reverse the effects of early-life stress or disease. However, attempts to alter brain function in humans early in life must be done with great caution given the possibility of causing undesirable effects that may be irreversible.[22] Animal studies suggest that intervening in early life appears to be crucial to reverse the methylation changes produced by early-life stress, suggesting that over time DNA methylation patterns become fixed and irreversible. However, in humans the window of therapeutic opportunity remains to be addressed. Hence there is a need for more specific agents to modify DNA methylation at specific sites by targeting specific DNA or methyl-binding proteins or the signaling pathways that modify these proteins.[23]

Conclusion

The question remains whether epigenomics will result in markers for risk of mental illness. For example, will a genome-wide scan of DNA methylation establish a correlation between genomic regions of high methylation and risk for depression? Studies focusing on individual gene promoters have revealed biologically meaningful correlations between behaviours relevant for mental illnesses in animals and epigenetic modification in specific genes and tissues. Since gene silencing by repressor and DNA methylation mechanisms is often propagated across several adjacent genes, epigenomics, that is probing a large number of epigenetic loci using high-throughput techniques, may help to identify these regional modifications and shed light on the potential players implicated in the behaviour under study. Ultimately, epigenomic studies may reveal patterns of association between behavioural disorders and epigenetic markers scattered over the entire genome. However, the use of this information to predict or prevent mental illness may be limited because of the likely importance of examining these changes in discrete brain regions and even neuronal cell types, which are inaccessible in living humans. But the identification of dysregulated gene clusters may provide important information to understand mental illness and the design of new treatment strategies. A greater understanding of the players that regulate DNA methylation, as well as the knowledge of the effects of these players on genome-wide methylation patterns, will be crucial to evaluate their efficacy and specificity for treating specific loci of altered methylation that lead to mental illness. For example, blocking DNA methylation for cancer treatment using 5-azacytidine incorporates into DNA and blocks all DNA methylases, activating the p16 tumour suppressor, but also activating metastatic genes: by targeting a specific DNA methylase, DNMT1, this side effect can be minimized.[20] Similarly, inhibition of specific histone-modifying enzymes, such as G9a, may be selective enough to better target addiction or mental illness[14] than a nonselective inhibitor like valproate, which inhibits all histone deacetylation. Thus, the promise of understanding epigenetic modifications in mental illness may lie in developing new and more selective pharmacological agents to modify these changes.

Competing interests: None declared.

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