

Research Highlights

Highlights from the latest articles in epigenetics



Epigenetic changes to serotonin receptor gene expression in schizophrenia and bipolar disorder

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Evaluation of: Abdolmaleky HM, Yaqubi S, Papageorgis P *et al.* Epigenetic dysregulation of HTR2A in the brain of patients with schizophrenia and bipolar disorder. *Schizophr. Res.* 129(2–3), 183–190 (2011); Carrard A, Salzmann A, Malafosse A, Karege F. Increased DNA methylation status of the serotonin receptor *5HTR1A* gene promoter in schizophrenia and bipolar disorder. *J. Affect Disord.* 132(3), 450–453 (2011).

Carrard *et al.* used a high resolution melting technique to investigate DNA methylation in the promoter of the serotonin receptor type-1A (*5HTR1A*) gene in peripheral blood leukocytes of patients diagnosed with schizophrenia and bipolar disorder, compared with healthy controls, reporting a small but significant increase in methylation in both patient groups [8]. Given that increased promoter DNA methylation is often inversely correlated with gene expression [10], the reported disease-associated increase in DNA methylation is consistent with previous studies reporting decreased *5HTR1A* mRNA levels in these disorders [3].

Dysfunction to the brain's serotonergic system is believed to be a primary factor in the pathogenesis of schizophrenia and bipolar disorder [1], two psychiatric diseases that make a significant contribution to the global burden of disease. Serotonin has many functions in the CNS, regulating synapse formation, neuronal growth, cognitive processes and mood. Several of the most effective antipsychotic drugs are known to bind to serotonin receptors in the brain [2], and alterations in serotonin receptor levels have been reported in many psychiatric disorders, including schizophrenia and bipolar disorder [3]. Polymorphisms in the genes encoding these receptors are considered good candidates for mediating susceptibility to psychosis, and they have been widely studied in genetic association studies [4]. Recently, increasing emphasis has been placed on the potential role of epigenetic dysfunction in the etiology of psychosis [5,6], and converging evidence suggests that epigenetic factors are important in the regulation of serotonin receptor gene expression [7–9].

Although an analysis of the *5HTR1A* gene expression in the same samples would have further consolidated this association, it is of note that the reported hypermethylation is observed in both schizophrenia and bipolar disorder, a finding consistent with previous data, suggesting that they share common etiological factors [11]. Unfortunately, the high resolution melting method used in this study is unable to resolve allele-specific DNA methylation patterns at base-pair resolution and although blood is a useful tissue for observing epigenetic changes occurring during early embryogenesis, the authors note that it would be optimal to replicate these data in a disease-relevant tissue (i.e., the brain), given the tissue-specific nature of the epigenome. It is also plausible that the blood cells studied here are liable to DNA methylation changes resulting from factors associated with the disease itself (e.g., medication exposure), making conclusions about the causal nature of the observed differences difficult.



Abdolmaleky and colleagues address some of these issues in their investigation of another serotonin receptor gene, *5HTR2A*, using frontal lobe brain samples from psychosis patients and healthy controls [7]. Bisulfite sequencing and quantitative methylation-specific PCR were used to quantify DNA methylation around two SNPs (-1438A/G and T102C) that have been previously associated with expression of *5HTR2A*. They report that DNA methylation and genotype appear to interact to ‘fine tune’ *5HTR2A* expression in psychosis and that the epigenetic down-regulation of the gene is associated with the early age of disease onset. Based on observations from their previous work, they also investigated the relationship between the expression of *HTR2A* and other candidate genes in the dopaminergic and serotonergic systems. They report significant correlations between the expression of *5HTR2A* and the genes encoding reelin (*RELN*), membrane-bound catechol-*O*-methyltransferase (*MB-COMT*), the dopamine D1 receptor (*DRD1*) and the dopamine D2 receptor (*DRD2*). One interpretation of these results is that *HTR2A* promoter DNA methylation influences the expression of other pathways involved in the

pathogenesis of psychosis. Alternatively, the authors suggest that a common risk factor could independently influence the expression of multiple genes involved in psychiatric phenotypes.

Both these studies add to the growing body of evidence linking epigenetic disruption in the etiology of psychiatric illness, and provide further insight into the role of the serotonin system in psychosis. Whilst additional research is required, using larger samples and more sensitive methylation profiling methods to replicate these findings and assign causality to the observed changes, they offer some hope for the development of new therapeutic approaches based on the downstream effects of serotonin.

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