Editorial

Epigenetics: the missing link between genes and psychiatric disorders?

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Most studies describing epigenetic modifications have focused on DNA methylation, but fewer studies have focused on histone modifications and noncoding RNAs. Chromatin architecture and CCCTC-binding factor represent important noncoding regulatory elements that warrant further investigation in order to improve our understanding of the genomic basis of complex diseases such as psychiatric disorders.

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Psychiatric disorders are polygenic and multifactorial disorders resulting from a complex interplay between genetic and nongenetic environmental factors. The highest heritability estimates have been observed in schizophrenia, bipolar disorders, or attention-deficit-hyperactivity disorders (60% to 80%) as compared with depression (~40%) or addictive disorders (~50%),[1] (Penner-Goeke and Binder, in this issue, p 397). The lack of underpinning identified biological markers make the genetic studies more difficult as compared with other polygenic and multifactorial diseases such as diabetes. In fact, there is a large heterogeneity between clinical phenotypes. Genome-wide association studies conducted in large case–control populations have led to the identification of numerous single-nucleotide polymorphisms. Most of these common at-risk variants do not alter protein structure but rather have diverse regulatory functions. Moreover, some of these variants are common to different psychiatric diseases. In schizophrenia, common variants explain only 30% to 50% of the variance. Rare de novo copy number variants may also significantly increase the risk of schizophrenia as well as of bipolar disorder or autism when they are present. Finally, "nongenetic" processes such as gene-environment interactions contribute significantly. Epigenetics, through DNA methylation, histone post-translational modifications, or noncoding RNAs, may induce changes in gene expression without any variation in the DNA sequence. Epigenetic processes are mainly influenced by environment. They are stable and can be transmitted through cell division but might also be reversible. Most of these epigenetic changes are tissue-specific, and postmortem studies are important in order to identify them. In addition to neuronal cells, glial cells can also be involved in epigenetic changes.

The epigenetics of stressful early life adversity has been extensively studied in anxiety and depressive disorders. In this regard, the brain-derived neurotrophic factor (BDNF), hypothalamic–pituitary–adrenal (HPA) axis, and FKBP5 (a critical regulator of the HPA cortisol response) genes, as well as the gene encoding the serotonin transporter, have been extensively studied as candidate genes. Interestingly, variants in genes encoding for epigenetic modifiers have also been reported on. Epigenome-wide associated studies (EWAS) were also recently conducted in large populations. Several papers in this issue will review these topics. Most studies describing epigenetic modifications have focused on DNA methylation, but fewer studies have focused on histone modifications and noncoding RNAs. Most studies

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have been conducted using peripheral tissues which do not necessarily reflect brain epigenetic changes. In addition, controlling environmental factors that may contribute to epigenetic changes is not easy in large cohorts.

In addition to these latter epigenetic changes, there is a higher-order chromatin organization within the nucleus; the human genome folds in three dimensions to form thousands of chromatin loops. Superimposed upon nucleomoses are topologically associating domains (TADs). Sequences within TADs are more likely to come into contact with each other than with loci from outside domains. Moreover, TAD boundaries and chromatin loop formations are often delimited by CTCF (DNA binding proteins). CCCTC-binding factor (CTCF) is an important epigenetic regulator, widely expressed in the tissues of vertebrates, which modifies the transcription of genes by altering their location within the nucleus. In fact, chromatin loops allow distal regulatory elements to come into contact with gene promoters in order to regulate gene expression. CTCF is also required for inter-chromosomal interactions such as pairing of the X chromosomes. Furthermore, point mutation and loss of heterozygosity of CTCF is associated with human cancer.[2] In addition, robust and intact CTCF looping is required for the induction of a rapid and accurate myocardial stress response in animal models, which may play a role in heart failure. This may open new pathways to pharmacological treatments in cardiac diseases.[3] In summary, chromatin architecture and CTCF binding are important noncoding regulatory elements that are already investigated in oncology and cardiology and that warrant further investigation to help understanding of the genomic basis of complex diseases such as psychiatric disorders.

Some pharmacologic treatments such as DNA methyl-transferase inhibitors or histone acetylase inhibitors (valproic acid) are already used in psychiatry and oncology. The clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein-9 nuclease (Cas9)—CRISPR-dCas9—an epimodifier complex, has been shown to demethylate the BDNF gene specifically, activating its expression[4,5] (see also Day, in this issue p 359).

Epigenetics opens up new pathways in the understanding of complex diseases and in the search for biological markers and, possibly, new treatments. ■

References

1. Kular L, Kular S. Epigenetics applied to psychiatry: Clinical opportunities and future challenges. *Psychiatry Clin Neurosci*. 2018;72:195-211.
2. Kemp CJ, Moore JM, Moser R, et al. CTCF haploinsufficiency destabilizes DNA methylation and predisposes to cancer. *Cell Rep*. 2014;7(4):1020-1029.
3. Lee DP, Tan WLW, Anene-Nzelu CG, et al. Robust CTCF-based chromatin architecture underpins epigenetic changes in the heart failure stress-gene response. *Circulation*. 2019;139:1937-1956.
4. Pandey SC, Kyzar EJ, Zhang H. Epigenetic basis of the dark side of alcohol addiction. *Neuropharmacology*. 2017;122:74-84.
5. Halldorsdottir T, Binder EB. Gene x environment interactions: From molecular mechanisms to behavior. *Annu Rev Psychol*. 2017;68:215-241.