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Letter to Editor

An epigenetic basis for an omnigenic model of psychiatric disorders

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1. Introduction

On the basis of family, twin, and adoption studies, it is well established that common psychiatric disorders like schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MDD) have a genetic basis (Bargmann and Gilliam, 2013). For the past few decades it has been thought that such disorders are not simple single gene (Mendelian) disorders, and are instead polygenic disorders, and influenced by environmental factors (Bargmann and Gilliam, 2013). Polygenic disorders are thought to follow various modes of transmission. According to one model, many genetic mutations in the population can contribute to the disorder, but each genetic mutation is individually rare and has a strong effect. This is called the "heterogeneity model" (Yang et al., 2005). Another model posits that a small number of relatively common genetic mutations, each of which individually has a small effect on risk for the disorder, interact to cause the disorder. This model is sometimes called the "common disease-common variant model" (Yang et al., 2005). Recently, Boyle et al. (2017) proposed a new model for complex traits which they termed the "omnigenic model". This model has generated widespread interest and discussion. Here we discuss the possible role of the omnigenic model in relation to psychiatric disorders like SZ, BD, and MDD, invoking epigenetic mechanisms of gene expression to support this model for these disorders.

2. The omnigenic model of complex traits

The omnigenic model of complex traits proposed by Boyle et al. (2017) was based on datasets of the inheritance pattern of height and three disorders which show complex patterns of inheritance: two autoimmune disorders, Crohn's disease and rheumatoid arthritis, and one disorder of the central nervous system, SZ. Based on their analyses, the authors came to the following conclusions: (1) There is an extremely large number of causal variants with tiny effect sizes on height as well as Crohn's disease, rheumatoid arthritis and SZ, and these causal variants are spread very widely across the genome. (2) The genetic contribution to disease is markedly concentrated in regions that are transcribed or marked by active chromatin in relevant cell types and tissues. (3) For several traits the largest effect variants are modestly enriched in specific genes or pathways that play direct roles in disease. However, the single nucleotide polymorphisms (SNPs) that contribute the most to heritability of disease tend to be spread across the genome and are not close to genes with disease-specific functions.

These conclusions led the authors to formulate the omnigenic model of complex traits according to which most complex traits are directly affected by a modest number of genes or gene pathways with specific roles in the etiology of disease, as well as their direct regulators. These are "core genes" and have biological roles in disease. The core genes generally contribute only a little to total heritability, and most "peripheral genes" expressed in relevant cell types could also contribute to heritability. The peripheral genes greatly outnumber the core genes and together contribute to most of the heritability of the traits. For this to be possible, the au-

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thors suggest that cell regulatory networks are highly interconnected so that any expressed gene regulates the function of core genes. The regulatory networks likely include all layers of interactions among cellular molecules, including transcriptional networks, post-translational modifications, protein-protein interactions, and intercellular signaling.

The authors mention that there are great challenges for fully understanding the implications of the omnigenic model for complex traits. They suggest several questions and tests for future work on the omnigenic model. The authors also suggest that some complex disorders may not even have core genes, and instead, in such disorders the global activity (including gene expression) of all genes may set cellular system states that determine cellular function and disease risk.

3. Epigenetic mechanisms of gene expression

Epigenetics, above, or, in addition to genetics, is presently an active area of biomedical research. It involves interacting molecular mechanisms including DNA methylation, histone modifications, and noncoding RNA (ncRNA)-mediated regulation of gene expression (Allis et al., 2015). Epigenetic regulation of gene expression is influenced by environmental factors and can result in either activation or repression of gene expression (Allis et al., 2015). Epigenetic changes are known to display tissue-and cell type-specificity in response to environmental stimuli (Bettscheider et al., 2012). DNA methylation occurs due to the conversion of cytosine to 5-methylcytosine (5mC) by the addition of a methyl group and is associated with gene silencing. This reaction is catalyzed by DNA methyltransferases using S-adenosylmethionine as the source of the methyl group. The 5mC can be further modified to 5-hydroxymethylcytosine (5hmc) by the action of the ten eleven translocation (TET) family of enzymes (Allis et al., 2015). Histone modifications like acetylation, methylation, and phosphorylation occur mainly on the tails protruding from the globular domains of the histones. Such modifications cause changes in the accessibility of DNA to the transcription machinery leading to changes in gene expression. Regarding ncRNA- mediated regulation of gene expression, there are several types of ncRNAs, including short ncRNAs which are less than 200 base pairs long and long ncRNAs which are more than 200 base pairs long (Allis et al., 2015). There are several thousand genes encoding ncRNAs in humans and they are located throughout the human genome (Esteller, 2011). The most widely studied among the ncRNAs are the microRNAs (miRNAs), and there are about 2500 miRNAs that have been catalogued in humans (RNAcentral Consortium, 2015). Each miRNA can bind to hundreds of different messenger RNAs (mRNAs) which collectively results in the regulation of more than 60% of protein-coding genes in humans (Esteller, 2011).

4. Relevance of epigenetics to the omnigenic model of psychiatric disorders

Despite a huge effort by genetic mapping studies, to date, no genetic mutations or polymorphisms predisposing to SZ, BD, and MDD have been definitively identified, although some associations have been found (Gebicke-Haerter, 2016). However, there is increasing evidence that there are abnormalities of epigenetic mechanisms of gene expression underlying these disorders (Lee and Avramopoulos, 2014; Gebicke-Haerter, 2016). Such epigenetic abnormalities include changes in DNA methylation, histone modifications, and ncRNA-mediated regulation of gene expression.

An epigenetic basis for psychiatric disorders like SZ, BD, and MDD supports the omnigenic model of Boyle and colleagues for complex traits in many ways (Fig. 1): (1) According to the omnigenic model predisposing genes are spread across the genome. In

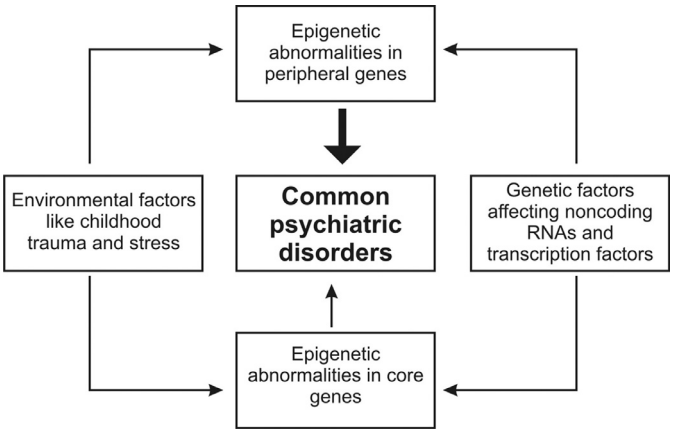

Fig. 1. Schematic diagram demonstrating that epigenetic abnormalities in core and peripheral genes predispose to common psychiatric disorders. Peripheral genes are much greater in number than core genes and have a greater effect on the disorders (represented by a thick arrow). Environmental and genetic factors influence the expression of core and peripheral genes.

this regard, there is accumulating evidence that there are genome-wide epigenetic abnormalities in the brain underlying these disorders. Viana et al. (2017) conducted a genome-wide study of DNA methylation changes in the post-mortem brain of patients with SZ in comparison to controls (41 SZ patients and 47 controls without any psychiatric disorder). Multiple brain regions (prefrontal cortex, striatum, hippocampus, and cerebellum) were assessed for DNA methylation changes across the genome. The authors found that more than 50 loci in each brain region in patients with SZ showed significant DNA methylation changes when compared with controls. These findings suggest that DNA methylation abnormalities are spread across the genome in the brain of patients with SZ. Hannon et al. (2016) used an integrated epigenetic-genetic approach to provide evidence for co-localization of genetic associations and differential DNA methylation across the epigenome in patients with SZ. (2) According to the omnigenic model for complex traits, there are an extremely large number of genes that are implicated in these traits. In this context, as mentioned above, Viana et al. (2017) detected DNA methylation abnormalities at more than 50 loci in multiple brain regions in SZ patients in comparison to controls. Ruzicka et al. (2015) studied DNA methylation levels at 1308 glutamic acid decarboxylase1 (GAD1) regulatory network-associated CpG loci in post-mortem hippocampus in patients with SZ and BD, and normal controls (8 subjects in each of the 3 groups). A total of 146 differentially methylated positions with a false detection rate lower than 0.05 were found. Thus, it appears that large numbers of genes are epigenetically associated with SZ and BD. (3) According to the omnigenic model of complex traits, there are highly interconnected networks involved in the development of complex traits. In this context, several ncRNAs have been implicated in the pathogenesis of SZ, BD, and MDD. Kim et al. (2010) studied the expression of 667 miRNAs in the post-mortem prefrontal cortex of 35 SZ patients and 35 BD patients in comparison to control subjects. They found that 22 miRNAs were differentially expressed in the patients in comparison with controls. As mentioned in Section 3, epigenetics involves interacting molecular mechanisms, and miRNAs regulate the expression of hundreds of genes and together they regulate more than 60% of protein-coding genes in humans. (4) Some genes are consistently modified epigenetically in patients with psychiatric disorders in comparison to controls. In SZ and BD, there are DNA methylation abnormalities in the *GAD1* gene encoding GAD_{67} and the *reelin (RELN)* gene that encodes a protein involved in brain development and synaptogenesis (Guidotti and Grayson, 2014). In