Published in final edited form as:

J Theor Biol. 2018 September 07; 452: 81–84. doi:10.1016/j.jtbi.2018.05.014.

Some Implications of an Epigenetic-Based Omnigenic Model of Psychiatric Disorders

Jacob Peedicayil^{a,*} and Dennis R. Grayson^b

^aDepartment of Pharmacology and Clinical Pharmacology, Christian Medical College, Vellore, India

^bCenter for Alcohol Research in Epigenetics, The Psychiatric Institute, Department of Psychiatry, College of Medicine, University of Illinois, Chicago, USA

Keywords

Epigenetic; genetic; omnigenic; psychiatric

1. Introduction

Jonathan Pritchard and his colleagues have proposed a new model for the inheritance of complex traits called the omnigenic model (Boyle et al., 2017). This model has generated considerable interest and discussion. The omnigenic model for the inheritance of complex traits was based on datasets of the inheritance pattern of height and three disorders which show complex patterns of inheritance: Crohn's disease, rheumatoid arthritis, and schizophrenia (SZ). According to the omnigenic model, most complex traits are directly affected by a modest number of genes or gene pathways with specific roles in the pathogenesis of disease, and their direct regulators. These are the so-called "core genes," which have biological roles in disease. Core genes generally contribute only a small amount to total heritability, and most "peripheral genes" also expressed in relevant disease cell types, likely also contribute to heritability. Peripheral genes greatly outnumber the core genes and together contribute the most to the heritability of traits. For this to be possible, the authors suggest that cell regulatory networks are highly interconnected such that any expressed gene regulates the expression and function of core genes. The regulatory networks probably include all layers of interactions among cellular molecules, including cis-acting regulatory networks, translational networks, post-translational modification networks, protein-protein interaction networks, and inter- and intra-cellular signalling pathways (Boyle, et al. 2017).

A huge amount of work across several decades has been done to determine the genetic basis of SZ, bipolar disorder (BD), and major depressive disorder (MDD). However, to date no

*Corresponding Author jpeedi@cmcvellore.ac.in (J. Peedicayil).

Conflicts of Interest: Nil

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single causative genetic mutation or polymorphism has been conclusively identified predisposing to these disorders, although some genetic associations have been identified (Alda, 2017; Fabbri & Seretti, 2017). Recently, we invoked abnormalities of epigenetic mechanisms of gene expression to propose an omnigenic model for common psychiatric disorders like SZ, BD, and MDD (Peedicayil & Grayson, 2018). Here we discuss some implications of an epigenetic-based omnigenic model for common psychiatric disorders.

2.1. Outline of Epigenetics

Epigenetics (above, or, in addition to, genetics) is commonly defined as the study of heritable changes of gene expression not involving changes in DNA sequence. It is presently an active area of biomedical research. It involves interacting molecular mechanisms like DNA methylation, histone modifications, and non-coding RNA (ncRNA) -mediated regulation of gene expression (Allis et al., 2015). Epigenetic mechanisms of gene expression are known to be influenced by environmental factors and to exhibit tissue- and cell-specificity (Allis et al. 2015). More details of epigenetic mechanisms of gene expression are given in our earlier article (Peedicayil & Grayson, 2018).

2.2. ncRNAs: Key Molecules in the Cell

Non-coding DNA encodes RNA that is not translated into protein, such RNA being termed ncRNA. There is a correlation between organismal complexity and non-coding DNA, and such DNA could hold the secret of what makes us human (Schonrock, et al. 2016). In humans, about 98% of all transcriptional output encodes ncRNAs which are not translated into protein (Schonrock et al, 2016). There are several thousand genes encoding ncRNAs in humans and they are located throughout the human genome (Esteller, 2011). There are several types of ncRNAs, comprising short ncRNAs which are less than 200 base pairs long and long ncRNAs (lncRNAs) which are more than 200 base pairs long (Allis et al., 2015). The best characterized ncRNAs are a type of short ncRNA called microRNAs (miRNAs). ncRNAs can be intronic, intergenic, and can also overlap with protein-coding regions of genes (Mattick, 2009). Since they are so abundant in the cell, ncRNAs have been termed “life’s indispensable molecules” (Allis et al., 2015). Some ncRNAs like miRNAs bind to target sequences in messenger RNAs (mRNAs), typically resulting in repressed gene expression (Allis et al., 2015).

3. The Role of ncRNAs in the Epigenetic-Based Omnigenic Model of Psychiatric Disorders

As discussed by Pritchard and colleagues in their paper on the omnigenic model for complex traits, genome-wide association studies (GWAS) of complex traits have resulted in two surprises (Boyle, et al. 2017). First, even the most important loci in the genome have small effect sizes, and the significant hits together explain only a small portion of the predicted variance, leading to the concept of “missing heritability.” The issue of the missing heritability has been largely resolved by studies showing that common single nucleotide polymorphisms (SNPs), with effect sizes much lower than genome-wide statistical significance, are largely responsible for this phenomenon. Secondly, unlike single gene (Mendelian) disorders, which mainly involve protein-coding changes, complex traits involve

non-coding variants, which probably affect gene regulation. Indeed, ncRNAs are known to be enriched in GWAS of complex human phenotypes (St. Laurent et al. 2014; Goulart et al., 2015), and about 93% of functional SNPs in the GWAS catalogue are in non-coding regions of the genome (Tak & Farnham, 2015).

GWAS of common psychiatric disorders have also implicated ncRNAs, particularly miRNAs, in the pathogenesis of these disorders. Hauberg et al. (2016) examined the role of miRNAs in SZ using summary statistics from the largest available GWAS meta-analysis along with publicly available data for predicted miRNA targets. The authors examined the role of miRNAs in the pathogenesis of SZ at 3 levels: by assessing whether SZ risk genes are overall more likely to be regulated by miRNAs; by gene set analyses to find conserved miRNAs that are regulators of SZ risk genes; and by targeted gene set analyses to systematically characterize the importance of miRNAs in previously identified loci from GWAS and copy number variations. The authors found that, similar to other complex traits, SZ risk genes are significantly more likely to be regulated by miRNAs. Forstner et al. (2015) performed gene-based analyses for all known autosomal miRNAs using the largest available GWAS dataset of BD. Brain-expressed miRNAs were investigated in target genes and pathway analyses. The authors found enrichment for miRNAs among BD-associated SNPs, suggesting that miRNAs and their targets may be implicated in the pathogenesis of BD.

ncRNAs are known to have crucial functions in the brain like taking part in the control of neurogenesis, neural development, cellular responses leading to changes in synaptic plasticity, and learning and memory (Peedicayil & Beveridge, 2014). There is increasing evidence that malfunction of ncRNAs is broadly implicated in neurodevelopmental disorders including common psychiatric disorders (Peedicayil & Beveridge, 2014). We suggest that DNA encoding ncRNAs comprises many peripheral genes of the omnigenic model for SZ, BD, and MDD. MIR-137, the gene that encodes the miRNA miR-137, could be a core gene of the omnigenic model, since miR-137 is thought to play a major role in brain development and its function is dysregulated in SZ (Peedicayil & Grayson, 2018). The gene encoding the miRNA miR-34a could be another core gene since dysregulation of miR-34a links abnormal neuronal development to the development of BD (Bavamian et al. 2015). However, it must be noted that the distinction between core and peripheral genes is somewhat arbitrary with respect to psychiatric disorders. This is because at present there are no well-established genetic or other biomarkers or measurements that define distinct psychiatric disease states (van de Leemput et al. 2016). Non-coding DNA encoding lncRNAs like Gomaflu, which is involved in brain development and SZ-associated alternative splicing, like non-coding DNA encoding short ncRNAs, may also comprise genes underlying common psychiatric disorders (Barry et al. 2013).

4. The Role of the Environment in the Epigenetic-Based Omnigenic Model of Psychiatric Disorders

As mentioned in section 2.1, environmental factors influence epigenetic mechanisms of gene expression. There is extensive evidence that environmental factors like early life trauma, nutrition, and stress act epigenetically to influence psychiatric disorders (Hoffmann &

Spengler, 2016). In the context of the omnigenic model for psychiatric disorders, there is evidence that such factors epigenetically impact both core and peripheral genes underlying common psychiatric disorders (Fig.1).

4.1. Epigenetic Effects of the Environment on Core Genes of the Omnigenic Model

Bator et al. (2018) investigated whether exposure to an enriched environment (EE) during adolescence affects the behavioral endophenotypes and biochemical changes induced by methylazoxymethanol (MAM) in the MAM-E17 rat model of SZ. An EE was introduced to animals in early adolescence (for post-natal days 23-29) and behavioral and biochemical studies were performed at postnatal day 70. The authors found that exposure to an EE prevents the development of adult behavioral endophenotypes induced by prenatal MAM administration. EE also prevented the decrease in glutamic acid decarboxylase 67 (Gad1) mRNA and GAD₆₇ protein levels induced by MAM in the medial prefrontal cortex of the rats. Dong et al. (2016) showed that adult mice subjected to prenatal restraint stress of pregnant dams exhibit behavioral endophenotypes reminiscent of behaviors associated with SZ, and DNA hypermethylation at the promoters of SZ candidate genes encoding GAD₆₇, reelin (Reln), and brain-derived neurotrophic factor (Bdnf). Tremolizzo et al. (2002) found that protracted treatment of mice with the essential amino acid methionine elicits a marked decrease of Reln and Gad1 mRNAs in the frontal cortex. There were also behavioral deficits suggestive of SZ in the methionine-treated mice. Satta and co-workers (2008) found that nicotine administered subcutaneously for 4 days to mice decreases DNA methyltransferase 1 expression and increases GAD₆₇ promoter DNA methylation in the frontal cortex and hippocampus of the mice. To simulate maternal infection during pregnancy, Labousse et al (2015) used a mouse model of prenatal immune challenge based on maternal treatment with the viral mimic poly I:C. The authors found that prenatal immune activation increases DNA methylation of the promoter of the *GAD1* gene in the prefrontal cortex of the mice. Tsankova and colleagues (2006) administered chronic social defeat stress to mice and observed changes in gene expression and epigenetic changes at promoters of *BDNF* in the hippocampus. The defeat stress induced a long lasting down-regulation of *BDNF* expression and robustly increased repressive histone methylation at the corresponding promoters. The genes encoding *Reln*, *Gad67* and *Bdnf* can be considered core genes in common psychiatric disorders since they have crucial functions in the brain (Peedicayil & Grayson, 2018).

4.2. Epigenetic Effects of the Environment on Peripheral Genes of the Omnigenic Model

Dwivedi et al. (2015) examined whether miRNAs are involved in chronic corticosterone-induced depression in rats. Rats given corticosterone 50 mg per Kg subcutaneously once a day for 21 days showed key behavioral features of depression. Gene expression analysis revealed differential regulation of 26 miRNAs (19 up-regulated and 7 down-regulated) in the prefrontal cortex of the rats. Su et al (2015) found that in a rat model of chronic stress-induced depression, there is increased expression of miR-132 in the hippocampus of these rats. The stress imposed on the rats consisted of a variable sequence of mild and unpredictable stressors.

5. Concluding Remarks

The omnigenic model for complex traits was proposed by Pritchard and colleagues (Boyle et al., 2017). We previously invoked abnormalities of epigenetic mechanisms of gene expression to propose an epigenetic-based omnigenic model of common psychiatric disorders like SZ, BD, and MDD (Peedicayil & Grayson, 2018). In the current article, we suggest that non-coding DNA comprises many peripheral genes of the omnigenic model of common psychiatric disorders. The core genes could also include non-coding DNA. Since epigenetic mechanisms of gene expression are known to be interrelated (Allis et al. 2015), non-coding DNA underlying common psychiatric disorders could also involve abnormalities of other epigenetic mechanisms of gene expression like abnormalities of DNA methylation. In this article we also give examples of environmental factors acting via the core genes and peripheral genes of the omnigenic model to influence the pathogenesis of common psychiatric disorders. Core genes include genes encoding *Reln*, *Gad67*, and *Bdnf* which are molecules crucial for the normal development and/or functioning of the brain (Peedicayil & Grayson, 2018).

Acknowledgements:

The authors acknowledge two anonymous Referees for their comments on the manuscript. This work was supported, in part, by the National Institute of Alcohol Abuse and Alcoholism (NIAAA) grant P50AA022538 (Center for Alcohol Research in Epigenetics) to DRG.

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HIGHLIGHTS:

- We recently proposed an epigenetic-based omnigenic model for common psychiatric disorders like schizophrenia, bipolar disorder, and major depressive disorder
- There is evidence that non-coding RNAs and environmental factors are involved in the pathogenesis of these disorders
- This article discusses the role of non-coding RNAs and environmental factors in the epigenetic-based omnigenic model for these disorders

Fig. 1.

Schematic diagram showing several of the major environmental factors that influence the pathogenesis of common psychiatric disorders. Such factors during prenatal life and childhood (like maternal stress, birth complications, early life trauma, poverty, urban upbringing, and diet) and adulthood (like psychosocial stress, poverty, urban life, drug abuse, diet, drugs and chemicals, and migration) can induce epigenetic changes in core genes (like genes encoding reelin, GAD₆₇, and BDNF) and peripheral genes (like genes encoding many miRNAs). This leads to an altered transcriptome, causing structural and/or functional brain defects, which can cause clinical features of schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MDD).