Could a Methyl Group Predict Your Risk of Depression?

ARTICLE INFORMATION

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Reviewers and Section Editors
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ABSTRACT

Major Depressive Disorder (MDD) is a systemic condition that diminishes the daily quality of life of those affected. There are no current methods that can reliably diagnose depression on a biochemical level. The premise of this work is to report on a potential biochemical marker, DNA methylation of the serotonin transporter gene (5-HTT). This biochemical marker can serve as an indicator of gene expression patterns, ultimately leading to a biochemical imbalance in affected individuals. Studying this biomarker has the potential to improve diagnostic and therapeutic techniques in the future, and improve the prognosis of those with MDD.

Keywords: Major depressive disorder, serotonin, DNA methylation, biomarker

Major Depressive Disorder (MDD), or clinical depression, is one of the top ten global health burdens. The highest prevalence of the disorder is observed in the older-adult cohort, which are adults between the ages of 40 and 64. As characterized by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), depression is diagnosed upon experiencing a culmination of a minimum of five of the following criteria in the continuous duration of a two-week period: despondent mood, reduced satisfaction from and inclination to partake in daily activities, diminished appetite, fatigue, reduced physical activity, inapplicable or excessive feelings of guilt and worthlessness, decline in the ability to concentrate and reason, and the presence of suicidal thoughts or tendencies. One of the first two characteristics must be present for the diagnosis to be established. Depression is a multifactorial disorder, where the contributing factors stem from both genetic and environmental constituents. The current understanding of the etiology and pathophysiology of MDD is inadequate, hindering opportunities for a positive prognosis, especially in the older adult population who experience a more chronic outlook for most disorders, likely including MDD. Considering the scarcity of information pertaining to the root causes, chronicity, and its heterogeneous nature, genomic and epigenomic studies are conducted to investigate the biomarkers involved in acquiring MDD.

Epigenetics is the study of heritable modifications of gene expression that do not involve changes to the nucleotide sequence of the genome. Thereby, this field investigates the biochemical mechanisms of action and the phenotypic consequences of epigenetic markers such as methylation, acetylation, and phosphorylation, on the activity of genes in different cell types. Methylation is the addition of a methyl substrate onto a nucleotide and typically represses gene transcription. Methylation occurs at cytosine residues, which are usually immediately followed by guanine nucleotides. Together, these monomers are called CpG islands.

Previous studies on the neurobiology of depression have identified the deficit of the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT), the brain’s “happy” chemical, as the main biomarker of MDD. Although, the simultaneous disturbance of multiple biochemical mechanisms is now widely considered to iteratively postulate the likelihood of acquiring the disorder, research related to serotonin remains the current focal point in MDD etiology.

Serotonin is a chemical produced by the nerve cells and is involved in regulating the circadian rhythm, digestion, and cognitive functions. Consequently, it impacts many biological processes, including those related to the etiology of MDD. On a cellular level of neural communication, one neuron acts as a transducer, and the other acts as a recipient of a chemical signal. When serotonin is released by the transducing neuron,
it is localized in the synapse prior to its uptake by the receiving cell. In depression, the reduced amount of serotonin is due to the malfunction of the serotonin reuptake transporter (5-HTT), a protein that recycles the neurotransmitter before it arrives at the receiving neuron. Encoded by the serotonin transporter gene (5-HTT), its expression is regulated by an upstream repeat polymorphic promoter region (5-HTTLPR), which is generally shorter in individuals exhibiting depressive symptoms. Additionally, another regulatory region has been linked to the modulated expression of 5-HTT, a CpG island located upstream of exon one and the transcriptional start site of the transporter gene. DNA methylation of the CpG island has been associated with depression; however, mechanisms inducing this epigenetic modification are currently unknown.

A study by Lam et al. (2018) investigated the genotypic variation of the 5-HTT gene as a contributing factor to DNA methylation and depression in the older-adult cohort. In all subjects, depression was diagnosed using either DSM-IV or a score above 16 on the Center for Epidemiologic Studies Depression Scale (CES-D), a self-report depression scale. Both diagnostic measures signify high levels of depressive symptoms. A total of 302 individuals were recruited, and genomic DNA from white blood cells was sampled for analysis. Recruits were a cohort of 95 depressed and 207 non-depressed participants. Most individuals from the former group were underprivileged women with psychological and physical comorbidities.

Two investigations were performed from collected genomic samples: genotyping and methylation pattern assay. Genotyping is the process of identifying individual genetic differences in computational comparison to the reference sequence. Most individuals in the study exhibited a homozygous S or L genotype, where 5-HTT alleles were either short or long, respectively. Methylation patterns were assessed using sequencing post-bisulphite exposure, which is a treatment of the genomic sample that permits the identification of methylated regions. This allows for the simultaneous depiction of multiple CpG regions throughout the genome. Statistical analysis was executed to determine univariant relationships between genotype and DNA methylation, and DNA methylation and depression status. The analysis also accounted for confounding factors, such as a record of previous MDD, use of antidepressants, and documented comorbidities. Upon multivariate analysis and the implementation of the necessary statistical adjustments, the study ensured validity in its evaluation of the genotype, DNA methylation, and depression associations. Lam et al. (2018) identified a statistically significant relationship between genotype and DNA methylation prevalence. In individuals with homozygous S alleles, decreased methylation contributes to depression, whereas in those with homozygous L alleles, higher levels of this epigenetic mark are associated with depression.

Lam et al. (2018) have conducted a large-scale study with a diverse spectrum of participants, perpetuating a reliable extension of the findings to the general population. As a cross-sectional investigation, however, a major limitation is the lack of longitudinal data which would have been essential in understanding the patterns of DNA methylation that change with age. On the other hand, one must acknowledge the reversible nature of epigenetic modifications, and therefore, consider the colossal importance of the study of such mechanisms as a viable option for implementation in diagnostic and therapeutic regimens in the future. Additionally, in the study by Lam et al., (2018) DNA was collected from white blood cell (WBC) samples, discounting differential methylation patterns in other cell types, such as neural cell lines. However, depression is a systemic disorder that has the propensity to affect other organ systems. Given the infeasibility of sampling all the organ systems affected by these methylation patterns, WBCs are an appropriate source of genomic samples, as they are distributed ubiquitously throughout the body via the bloodstream.

To date, serotonin deficiency is one of the main working models as the cause of depression. Research by Lam et al. (2018) explored serotonin’s role by using DNA methylation and the 5-HTT genotype as associated factors. In light of the discussed findings, the main implication of this research is the implementation of 5-HTT DNA methylation as a biomarker for MDD.

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REFERENCES