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COMMENTARY

Genetic and epigenetic regulation of the serotonin transporter gene in late-life depression

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Recently we published research that investigated epigenetic regulation of the serotonin transporter gene (*SLC6A4*) in peripheral blood and genetic variation in late-life depression [1]. We found that functional *SLC6A4* genetic variation interacts with DNA methylation at this locus to influence late-life depression risk. Although further research is required for robust independent replication of these findings, the outcomes of our research have potentially important implications.

Late-life depression is a clinically heterogenous condition that is often chronic with a high illness burden. It is underdiagnosed and undertreated, and when treatment is given, it can be ineffective. This is partly a result of the significant gaps in our understanding of the aetiology and pathophysiology of late-life depression, which likely results from a combination of numerous genetic and environmental factors. Studies of gene and environment interactions have become increasingly common in this field, given their potential to provide important clues to this debilitating condition. Much research has focused on genetic variation in the serotonin transporter gene (*SLC6A4*) and exposure to early-life trauma or lifetime stress, known risk factors for depression. *SLC6A4* encodes a protein which transports the neurotransmitter serotonin from synapses to the presynaptic neurons. Disruptions in the serotonergic system play a role in depression pathophysiology. Common antidepressant treatments target this system, blocking the reuptake of serotonin from the synaptic cleft. A degenerate repeat polymorphic region in the gene (*5-HTTLPR)* has been linked to a dysregulated stress signalling and may increase risk of stress-related psychopathology, including depression.

The role of *5-HTTLPR* as a modulator of stress-sensitivity and vulnerability to depression has been one of the most widely investigated in the field of gene-by-environment interactions, but also quite controversial. There is evidence that individuals with the short ('S') allele have lower SLC6A4 gene expression that long ('L') allele carriers and this could increase their susceptibility to the effects of trauma or stress in terms of depression[2]. Numerous subsequent studies have replicated these findings, yet a recent meta-analysis showed no significant interaction between the *5-HTTLPR* and stress in influencing depression risk[3]. This highlights the likely complexities and involvement of other underlying factors. Associations may be dependent on the type of stress and/or age at exposure. Epigenetic factors may also be involved[4].

Considerable advances in our understanding of the genome and how it is regulated over the last decade have had a substantial impact on the landscape of psychiatric research. Epigenetic mechanisms are environmentally sensitive potentially reversible modifications 'above' the DNA which regulate gene activity. They provide a plausible mechanisms to account for gene-environment interactions in depression. Epigenetics could also help explain the recognised association between early-life exposures (e.g childhood stress) and major depressive episodes occurring decades after the event (e.g onset in adulthood/old age). Epigenetic mechanisms can result in changes in gene expression which remain relatively stable over time, modulating

biological processes such as stress-responses systems, and with long-term effects on behaviour and mental health[4].

In addition to its likely role in the aetiology of depression, the field of epigenetics also holds promise for its potential utility as a biomarker of disease status and treatment response. The search for a reliable biomarker of psychiatric disorders remains of strong interest given the absence of objective diagnostic criteria which can contribute to misdiagnosis, and the inability to clearly monitor the effectiveness of treatments. Epigenetic biomarkers measured in peripheral tissue, may prove useful markers of depression status and treatment outcomes.

In our study of 302 individuals aged 65+, individuals with late-life depression, compared to non-depressed, were more likely to be both L and S homozygous for *5-HTTLPR* [5]. While some previous studies have indicated that the S allele carriers are more susceptible to depression following stressful events, our own and others work indicates that this could be age dependent, with a switch from the S allele to the L allele in older age[6, 7]. We found no association between other SNPs spanning the *SLC6A4* gene and late-life depression, which is concordant with large scale genome-wide association studies (GWAS) of depression, which have failed to identify SNPs in this gene.

The most novel findings of our work however, concerned DNA methylation. Overall DNA methylation was a weak biomarker of late-life depression, even when taking into account factors such as exposure to early-life trauma, antidepressant use and depression history [1]. However, accounting for both genetic and epigenetic variation in *SLC6A4*, clear differences were observed between individuals with and without depression. Genetic variation in the *SLC6A4* gene was a significant modifier of the association between depression and DNA methylation. For individuals S homozygous, late-life depression was associated with decreased DNA methylation, but the reverse association was observed for L homozygous individuals, with depression being associated with higher methylation.

Importantly, in addition to 5-HTTLPR, *SLC6A4* promoter methylation has also been associated with functional changes in gene expression [8]. Peripheral *SLC6A4* methylation in the promoter region can suppress transcriptional activity of the gene, and is associated with lower brain serotonin synthesis (a marker of central 5-HT function) [9]. Both *5-HTTLPR* and peripheral *SLC6A4* methylation have also been independently associated with alterations in the hippocampus and corpus callosum, brain regions implicated in depression. It is thus not surprising that together they could both contribute to influence serotonergic signalling and

depression risk. An important point however, is that peripheral DNA methylation is not a direct indicator of methylation in the brain or changes which might contribute to the underlying disease mechanisms, as epigenetic marks are cell and tissue specific. However, given the inherent difficulties with sampling brain tissue from living humans, a peripheral biomarker of depression would have strong utility even if it wasn't directly correlated with brain levels (as long as it consistently distinguishs depressed from non-depressed individuals). Depression is also increasingly recognised as a systemic disease with physiological changes being observed across a range of peripheral tissues.

Another limitation to be considered when interpreting these findings is that our study used a candidate gene approach. As mentioned above, depression is a polygenic disorder involving the interaction between multiple variants of small effects. Focusing on a single gene raises the possibility of false positive findings and indeed prior GWAS studies of depression have not identified significant SNPs near *SC6A4*. We had a strong *a priori* rationale to investigate this gene however, given it is the most frequently investigated in the field of gene-environment interactions in depression.

Despite their lmitations, our work contributes to a growing body of research highlighting the interaction between genetic and epigenetic factors in influencing the risk of psychiatric disorders. Epigenetic changes may help compensate for genotype-dependent differences in stress sensitivity [10] and allele specific DNA methylation has now been reported in a number of contexts. Recent work focused on another gene involved in stress signalling, the glucocorticoid inhibitor FKBP5, has provided direct evidence for genetic variation and DNA methylation can combine to influence risk. Klengel and colleagues demonstrated that structural, at the level of the DNA, carriers of the risk allele for a specific SNP (*rs1360780*) exhibited a distinct 3D conformation that permitted demethylation of an intronic region of the gene following exposure to stress [11]. This resulted in long-term dysregulation of the stress response and consequently increased vulnerability to psychopathology in adulthood. This emphasises the need to consider both genetic an epigenetic factors together, particularly in the context of potential biomarker discovery.

The other finding from this work which requires further consideration is *5-HTTLPR's* potential role in moderating vulnerability to stress-related psychopathology. Epigenetics regulation of the *SLC6A4* could also help account for the divergent findings reported in the literature [3], although it is difficult to tease apart the influence of various related factors on depression risk. Exposure to stress (both early-life and recent), stress signalling, depression history and

antidepressant treatment are all factors which could contribute to and interact together to impact risk. Likewise, these factors can influence *SLC6A4* DNA methylation [9, 11], which in turn increases susceptibility to depression. DNA methylation may be one of the underlying mechanisms whereby stress and trauma regulate *SLC6A4* gene expression and thus risk for stress-related psychopathology, including depression. A study of 200 adults exposed to a laboratory stressor demonstrated a significant gene by DNA methylation interaction on stress reactivity [10]. Individuals with the S allele and low levels of *SLC6A4* methylation (but not those with high levels) had increased cortisol stress reactivity. This aligns with the results of our study showing increased risk of depression in SS individuals with low *SLC6A4* methylation.

In conclusion, there is growing evidence that there is a complex interplay between not only genetic and environmental factors in influencing late-life depression, but with potential epigenetic regulation or biomarkers which are reflective of more complex processes. Taking into account epigenetics, in combination with other established factors, may provide important new clues about the diagnosis, treatment and management of late-life depression.

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