# Genetics, epigenetics and BDNF in depression

**Jurij Bon[1,*], Peter Pregelj[1], Alja Videtič Paska[2]**

**[1] University Psychiatric Clinic, Ljubljana, Slovenia**

**[2] Institute of Biochemistry, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia**

***Corresponding author email: jure.bon@gmail.com**

## Abstract

Major depressive disorder is a multifactorial psychiatric disorder, in which different genetic, epigenetic and environmental factors play a causal role. We discuss novel findings in the genetics and epigenetics of depression, with special emphasis on the role of the brain derived neurotrophic factor (BDNF). Many studies show changes in BDNF levels as a result of treatment for depression, including as a result of treatment with non-invasive brain stimulation. We highlight the role of BDNF as a possible biomarker of depression and an indicator of treatment response to antidepressant medication or non-invasive brain stimulation.

## Introduction

Most psychiatric disorders are moderately to highly heritable. The degree to which genetic variation is unique to individual disorders or shared across disorders remains unclear (1). Recent research aimed at explaining genetic influences in individuals with a psychiatric disorder can be divided into three approaches (2). The traditional approach assumes a direct relationship between genes and behaviour, a so-called "main effects" analysis, which tries to determine a direct association between genotype and diagnosis by linkage or association analysis. From this perspective, major depressive disorder (MDD) is characterized as a common and moderately heritable disorder (3). Most studies of this kind have considered functional polymorphisms relevant to monoaminergic neurotransmission but have failed to find direct links, even when employing genome-wide association studies with very large samples (4). Although the evidence for association has been replicated for a few genes, replication failures are routine and overall progress remains slow (2). Meta-analyses suggest small positive associations between polymorphism in the serotonin transporter promoter region (5-HTTLPR) and specific diagnostic categories related to MDD, like bipolar depression or suicidal behaviour, but not to MDD itself (3). This failure to determine associations with main MDD diagnostic categories is sometimes explained as a consequence of the high prevalence of the disorder, which implies that much larger research samples would be needed to detect a main effect (4).

A more promising approach is to refine the main-effects analyses by using intermediate phenotypes instead of diagnostic categories. These endophenotypes are heritable neurophysiological, biochemical, endocrine, neuroanatomical or neuropsychological constituents of disorders. They are thought to have much simpler genetic underpinnings and could also serve as biomarkers for MDD (2). Studies of this kind employ the findings about development and functioning of brain networks implicated in mood regulation (5, 6), using either behavioural traits, like subjective well-being, depressive symptoms and neuroticism (7), or so-called "imaging genetics", to link genes to structural and functional variation in brain systems related to cognition and emotion (5).

The latest and probably most promising approach is the study of gene-environment (GxE) interactions implicated in the development of psychiatric disorders (2). GxE interaction research does not assume that genes cause specific disorders, but suggests that environmental pathogens play the major role, while genes influence susceptibility to these pathogens. The role of genes in psychiatric disorders is probably enacted through their influence on nervous system reactivity (2). Life stress, such as childhood adversity or recent stressful events, is a known risk factor for depression, while genetic variation moderates the impact of stress on the risk of depression (8). Imaging of GxE (iGxE) can contribute to our understanding of neural mechanisms, which convey the influence of genetic variation and stress on structure and function of stress-related cortico-limbic networks, the neuroendocrine stress hormone system and the hypothalamic-pituitary-adrenal (HPA) axis (9). Genes related to neurotoxic and neuroprotective (neurotrophic) processes can lead to over-activation of the hypothalamic-pituitary axis. There is mixed evidence regard-

ing the association of MDD with polymorphisms in one such gene: BDNF, brain-derived neurotrophic factor (3). The interaction between BDNF and life stress in depression seems to be stronger for stressful life events than for childhood adversity (8) and is probably mediated by epigenetic mechanisms which include DNA methylation, histone modifications, nucleosome repositioning, higher-order chromatin remodeling, non-coding RNAs, and RNA and DNA editing (10).

## Genetic and epigenetic influences on depression

Based on family, twin and adoption studies, the molecular genetic component plays an important role in depression. The targets of currently used antidepressants are the serotonin and norepinephrine neurotransmitter systems (11). The commonly prescribed selective serotonin reuptake inhibitors (SSRIs) bind to the serotonin transporter (5-HTT) and upregulate the serotonin levels (12). 5-HTTLPR, a functional polymorphism that modulates gene expression, has been determined in the SLC6A4 gene, which codes for the 5-HTT protein (13). The presence of the short instead of long allele is associated with lower gene expression level (14). It has been shown that subjects homozygous for the short allele display lower remission and response rates when treated with SSRIs in comparison to the subjects who carry the long allele (15). Subjects with the short allele were also more prone to develop major depression if they suffered physical and emotional abuse during childhood (16). Although there has been an important breakthrough in the techniques for the determination of target genes and polymorphisms in genome-wide association studies (GWAS), and some results of the molecular genetic studies seem to determine a number of candidate genes for MDD, a recent meta-analysis confirmed only six - APOE, DRD4, GNB3, MTHFR, SLC6A3 and SLC6A4 (17).

The effect of environmental factors can be expressed through epigenetic changes. The most commonly studied epigenetic mechanism is DNA methylation, which involves a covalent modification of the cytosine residues in the CpG dinucleotides. Methylation has a regulatory function; namely, methylated promoter regions are less efficiently transcribed and consequently the gene is silenced. SLC6A4 has been widely studied and site-specific methylation changes have been associated with decreased levels of the 5-HTT mRNA and in subjects exposed to maternal prenatal stress or childhood maltreatment. Significant associations with higher promoter methylation status of SLC6A4 were found for childhood adversities, family history of depression, higher perceived stress, and more severe psychopathology (18).

For the BDNF gene, which codes for BDNF, changes in methylation status in patterns of exon I between patients with MDD and controls were determined (19). Higher promoter methylation status was also associated with suicidal attempt history in patients with MDD (20), as well as in suicide victims (21).

## BDNF as a biomarker in depression

Biological markers are defined as biochemical, physiological or anatomical traits that are specific to particular conditions and can be used as diagnostic tools. Ideally, they should have predictive power, be available for routine assays in clinical practice, allow the identification of individuals at risk, and help with the monitoring of disease progress and its response to treatment (22).

Preclinical results indicate that hippocampal BDNF levels correlate with antidepressant-like effects in behavioural models of depression (23). Impairment of BDNF signalling is, on the contrary, associated with depression-related behaviours and impairment of the antidepressant action, indicating that BDNF could serve as a promising biological marker for stress-related synaptic plasticity associated with depression (24). These kinds of studies, combined with clinical data, have led to the proposal of the neurotrophin hypothesis of depression, which implicates BDNF in its pathogenesis (25). Earlier studies showed that the expression of BDNF is increased in the brains of patients with depression treated with antidepressants, compared to untreated patients (26). Decreased expression of BDNF in different brain regions of suicide victims with MDD was also reported (27, 28) and it is possible that these observations are associated with BDNF gene polymorphism (BDNF Val66Met), which was also observed in suicide victims (29). It is unclear at present whether the peripheral levels of BDNF in serum or platelets are different in depressed subjects with or without antidepressant treatment (30). Some studies have reported lower serum and plasma BDNF levels in patients with depression compared with controls and this decrease was negatively correlated with the severity of depression (31), but a recent systematic review and meta-analyses on 179 asso-

ciations did not confirm consistent associations between serum BDNF concentrations and the symptom severity of depression (32). Peripheral BDNF levels lack spatial resolution (different levels that can easily be differentiated), which further hinders their usability as a biological marker for depression (22).

In contrast to unipolar depression, a recent meta-analysis of 52 studies indicated that peripheral BDNF levels could serve as a potential biomarker of disease activity in bipolar disorder, but not as a marker of the stage. The authors also suggested that peripheral BDNF might in future be used as a part of a blood-protein composite measure to assess disease activity in patients with bipolar disorder (33).

### BDNF as an indicator of treatment response in depression

Numerous studies showed that levels of BDNF increase with various anti-depressive treatments. However, a recent qualitative systematic review of clinical trials concluded that the variety of methods for BDNF collection and analysis used in different studies make the comparison of results difficult. Nevertheless, despite the variation in methodology, the levels of BDNF seem to increase after treatment of major depression (34).

A recent systematic and quantitative meta-analysis reported that serum and plasma levels of BDNF were decreased in acute MDD, whereas they did not differ between the euthymic state and control subjects. The same meta-analysis also reported that anti-depressive treatment increased serum BDNF levels in MDD in responders and remitters, compared to non-responders, indicating that serum BDNF might be regarded as a biomarker for the successful treatment of MDD (35).

Possible biological markers for MDD were also reviewed in the context of non-invasive brain stimulation trials using transcranial magnetic stimulation (TMS). Biological markers determined included immune and endocrine serum markers, neuroimaging and electrophysiological findings. In utilizing SPECT, PET, fMRI, MRS, cortical excitability (measured with TMS) and BDNF, BDNF consistently showed a correlation with treatment results and was found to be the best predictor of the likelihood of patients to respond. However, the number of studies investigating biological markers in TMS is still small and further studies are recommended (22).

In contrast, another recent systematic review and meta-analysis of BDNF blood levels after non-invasive brain stimulation interventions in MDD did not report that peripheral BDNF levels increased. The authors suggested that such a biomarker might therefore not be suitable to index non-invasive brain stimulation antidepressant efficacy (36).

### Conclusion

Depression is a multifactorial disorder, with moderate heritability. Regarding the genetic factors, only a few target genes and polymorphisms have been identified in genome-wide association studies: APOE, DRD4, GNB3, MTHFR, SLC6A3 and SLC6A4. Epigenetic modifications are probably very important in depression and are potentially reversible after treatment with antidepressants. DNA methylation related to stress plays a major role. One of the genes affected by methylation codes for BDNF. Impairment of BDNF signalling is associated with depression-related behaviours and decreased antidepressant treatment efficacy, indicating that BDNF could serve as a promising biological marker for stress-related synaptic plasticity associated with depression. Successful anti-depressive treatment in MDD increases serum BDNF levels in responders and remitters compared to non-responders, indicating that serum BDNF might be regarded as an indicator of a treatment response in MDD.

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