

[Abstract:0525] Genetic psychiatry**Hypomethylation of BDNF gene promoter in bipolar disorder patients**Umit Sertan Copoglu¹, Berna Ermis², Mehri Igci³, Esra Bozgeyik³, Yusuf Z. Igci³, M. Hanifi Kokacya¹, Mustafa Ari¹, Haluk A. Savas⁴¹Department of Psychiatry, Mustafa Kemal University, Faculty of Medicine, Hatay-Turkey²Bitlis State Hospital, Bitlis-Turkey³Department of Medical Biology, Gaziantep University, Faculty of Medicine, Gaziantep-Turkey⁴Department of Psychiatry, Gaziantep University, Faculty of Medicine, Gaziantep-Turkey

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INTRODUCTION: Bipolar disorder-1 (BD-1) is a mood disorder characterized with recurrent manic or mixed episodes, and the lifetime (and 12-month) prevalence estimate is 1%. The biological basis of the disease is still not very clear. It is known that genetic and environmental factors are involved in the pathogenesis of the disease. Family, twin and adoption studies provide strong evidence for the importance of genetic etiology of bipolar disorder. There could not be determined a major disease-associated locus because of the occurrence of bipolar disorder in interaction with multiple genes and environmental factors. All these data suggest that the genetics of bipolar disorder is very complex. Epigenetics has an important role in gene and environment interactions. This means environmental factors such as nutrition, maternal care and behavior, hormones and drugs, the early life experiences, and environmental agents in early development stages influence the gene expressions through epigenetic mechanisms¹. Brain Derived Neurotrophic Factor (BDNF) is a neurotrophin that regulates synaptic transmission and plasticity, and it has a role in proliferation, differentiation, survival and death of neuronal and non-neuronal cells². BDNF may also play a role in the pathophysiology of bipolar disorder. We hypothesized that there is a defect in DNA methylation mechanisms, and the BDNF gene is affected by these processes in bipolar disorder patients. Therefore, in order to test our hypothesis we aimed to investigate the DNA methylation status of two regions in the BDNF gene in patients with bipolar disorder.

MATERIALS AND METHODS: The study included 100 BD patients (Bipolar depression: 18, Mania: 33, Euthymic: 49; aged 30.8±9.3 years, 56 male and 44 female) with bipolar disorder and 59 healthy controls (aged 30.0±6.3 years, 29 male and 30 female). DNA was extracted from blood samples by using the salt-chloroform method. Determination of the methylation pattern of CpG islands was based on the principle that bisulfite treatment of DNA would result in conversion of unmethylated cytosine residues into uracil, whereas methylated cytosine residues would remain unmodified. Methylation-specific PCR was performed with primers specific for either methylated or unmethylated DNA.

RESULTS: In this study we found that there was a hypomethylation in BDNF gene promoter 1 in bipolar disorder patients compared to healthy controls ($p < 0.001$). The comparisons of the methylated or un-methylated status for each area according to the study groups are presented in Table 1. When patients were analyzed according to their attack type, there was a hypomethylation in BDNF gene promoter 1 in patients in depressive or manic episodes compared to healthy controls and euthymic episode ($p = 0.011$). However, BDNF gene promoter 2 was hypermethylated in patients in euthymic episode compared to healthy controls ($p = 0.010$).

CONCLUSION: DNA methylation plays a role in neuronal cell survival and maturation; balance of the methylation level is important for neuronal survival, and hypomethylation causes abnormalities in neuronal function. Although it is not clear, it has been mentioned that DNA hypomethylation may cause cell death by apoptosis. A normal level of DNA methylation is required for controlling genomic expressions. An animal study found that DNA hypomethylation is associated with genomic instability which may lead to cancer development. Cancer studies show that DNA hypomethylation caused chromosomal instability, abnormal gene expression, and loss of imprinting. Considering these data, it can be thought that DNA hypomethylation may cause diseases by affecting gene functions such as genomic instability and cell survival and maturation, and even through apoptosis. It is found that the methylation status is correlated with antidepressant treatment, and it is suggested that the methylation status is not associated with only the disease itself but can also be associated with pharmacological treatment³. Another study showed that antidepressants are associated with increased methylation, and mood stabilizers are associated with decreased methylation⁴. The methylation status was found lower in patients who received valproate or lithium. But the methylation status is higher in patients with antidepressant treatment compared to antidepressant and mood stabilizer combined (4). In addition to antidepressants and mood stabilizers, it is shown that antipsychotics have effects on DNA methylation. Except haloperidol and olanzapine, sulpirid and clozapin have demethylation effects on rats⁵. As seen from these data, antidepressants, mood stabilizers, and antipsychotics influence DNA methylation levels. However, it is not exactly known how these drugs affect the methylation status. The effects of gene methylation on treatment and clinical symptoms are unclear, too. It is thought that DNA methylation levels of related genes in bipolar disorder are involved in the etiopathogenesis of the disease. The level of methylation status of other candidate genes in relation with clinical disease should be investigated. Regulating DNA methylation may be a new therapeutic target for treatment of the disease.

Keywords: DNA methylation, hypomethylation, BDNF gene, bipolar disorder

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Bulletin of Clinical Psychopharmacology 2015;25(Suppl. 1):S50-S1

[Abstract:0535] Research methods in psychiatry

Eyes tell the psychopathology: preliminary findings

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OBJECTIVE: A number of studies on eye movement dysfunction in patients with psychiatric disease have been published. Glutamatergic neurotransmission mediated by the NMDA receptor is involved in the pathophysiology of schizophrenia and some neurological diseases¹. The frontal-thalamic-cerebellar circuit has been implicated in eye movements. The presence of eye-tracking abnormalities among schizophrenia patients and their biological correlates has been reported by numerous investigators examining smooth-pursuit and saccadic eye-movement measures, as well as measures of motion perception². An association between eye-tracking abnormalities and NMDA receptor antagonism is important because it indicates which neurophysiological mechanisms are related to eye-tracking abnormalities. There is strong evidence that eye-tracking abnormalities are related to genetic risk for schizophrenia³; thus, a relationship between eye tracking and NMDA antagonism may also help us understand the biological underpinnings of disease vulnerability. On the other hand, the behavioral and pharmacological effects of the noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine have been used to study important aspects of psychotomimetic action in humans. Several lines of evidence support the use of ketamine as a pharmacological model of schizophrenia. Schizophrenia patients administered subanesthetic doses of ketamine experience a brief exacerbation of positive, cognitive, and possibly negative symptoms. Ketamine also appears to provoke psychotic symptoms specific to a patient's disease history. Imaging studies have shown that ketamine changes the neuronal activity in areas thought to be involved in the pathophysiology of schizophrenia, including the medial frontal and anterior cingulate cortex, the hippocampus, and the cerebellum. Other studies have shown that ketamine causes schizophrenia-like positive, negative, and cognitive symptoms in normal healthy volunteers including deficits in sensory processing and eye-tracking performance. The non-competitive N-methyl-D-aspartate receptor antagonist ketamine leads to transient psychosis-like symptoms and impairments in oculomotor performance in healthy volunteers. In the literature, as far as we know, all studies have been conducted with specific tools (infrared oculography etc.) and special units for saccadic eye movements. In our study, we aimed to investigate the relationship between vertical eye position (VEP) and psychopathology via a scale designed by us.

METHOD: Patients with the diagnosis of a psychiatric disorder (n=228) and control subjects (n=340) were included into the study. All subjects gave written informed consent in accordance with guidelines from the institutional review board of the GATA Haydarpasa Training Hospital. Subjects underwent a medical history, a physical examination, and laboratory tests, including a drug screen. A scale designed for measurement of the distance between eye limbus and palpebrae called as VEP was applied.

RESULTS: There was a statistically significant difference in terms of VEP scores between patients with the diagnosis of psychotic disorders (other than paranoid psychosis), depressive disorders, antisocial personality disorder, and controls ($p < 0.001$). There was no difference in patients with diagnosis of anxiety disorders and paranoid psychosis.

CONCLUSIONS: These results suggest that VEP abnormalities may be related with psychopathology. Evidence from neuroimaging and microstimulation studies suggests that cerebellar circuitry is involved in integrating and coordinating smooth-pursuit and saccadic eye-movement information from the frontal cortex via a frontal-thalamic-cerebellar circuit. It has been argued that abnormalities in this circuit may underlie schizophrenia-related eye-tracking abnormalities. NMDA receptors are present on cells throughout the cortex, including the frontal/prefrontal cortex and the cerebellum, where they could play a functional role in eye-tracking abnormalities. In contrast, NMDA antagonism by ketamine is known to decrease neuronal activity in the cerebellum potentially, an action that can explain the observed deficits in pursuit initiation³ and pursuit maintenance as well as increases in disruptive leading saccades during smooth pursuit. Several investigators have noted