Selective methylation of brain derived neurotrophic factor gene promoter in Bipolar Disorder: differences between patients and controls

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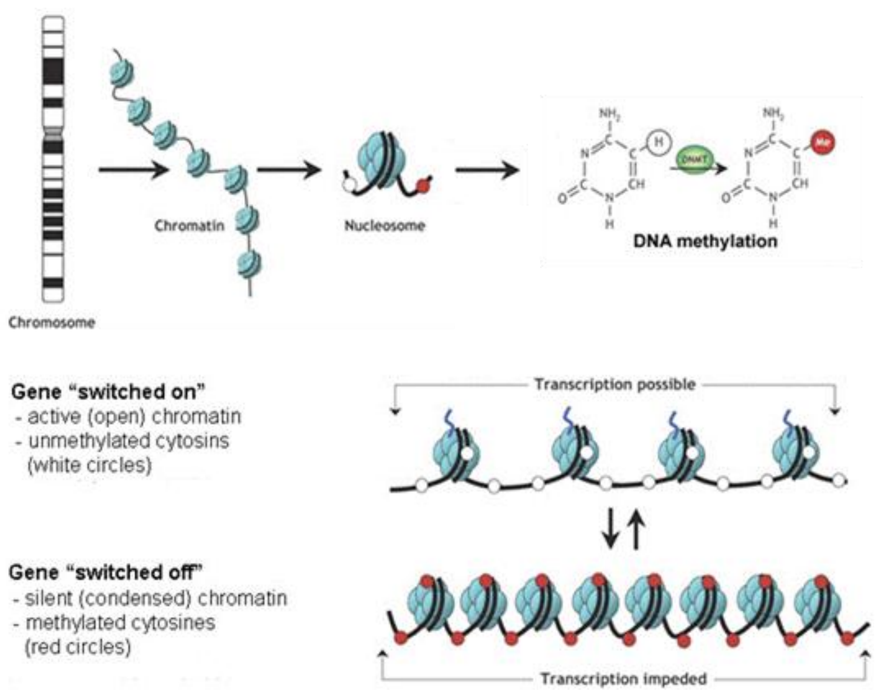
INTRODUCTION and AIMs

The etiology of bipolar disorder (BD) is still poorly understood. Many studies have focused on the interplay between genetic and environmental risk factors, but so far the epidemiological, clinical, and molecular evidence associated with major psychoses are difficult to explain with traditional gene- and environment-based approaches and a definitive molecular phenotype is lacking [1]. It has been proposed that altered expression of multiple mRNAs, affecting neurotransmission in psychotic subjects, may be due to epigenetic mechanisms (e.g., DNA methylation or histone modification) (Fig.1).
Among the candidate genes associated with major psychoses, the present collaborative study specifically investigated the brain-derived neurotrophic factor (BDNF) gene promoter [2]. The aim was to evaluate the degree of DNA methylation at this site, in peripheral blood mononuclear cells (PBMCs) isolated from patients with BD vs controls.

Figure 1



METHODS

DNA was isolated from 94 patients, both inpatients and outpatients, on stable pharmacological treatment, with a DSM-IV-TR diagnosis of BD, either type I (49 patients) and type II (45 patients) BD, and from healthy controls, sex and age matched with the patients sample. After bisulphite sodium conversion, a Real-Time Methylation Specific PCR has been performed on DNA samples. Statistical differences of BDNF gene expression and DNA methylation changes at BDNF promoter of BD patients versus control subjects was determined by analysis of variance (ANOVA) followed by Dunnett's test. P values lower than 0.05 were considered to be statistically significant (Fig.2).

Figure 2

workflow of the study

Clinical sample (PBMC)
⇩
DNA isolation
⇩
Bisulphite treatment
⇩
Real-time MSP
⇩
Data analysis

RESULTS

Figure 3

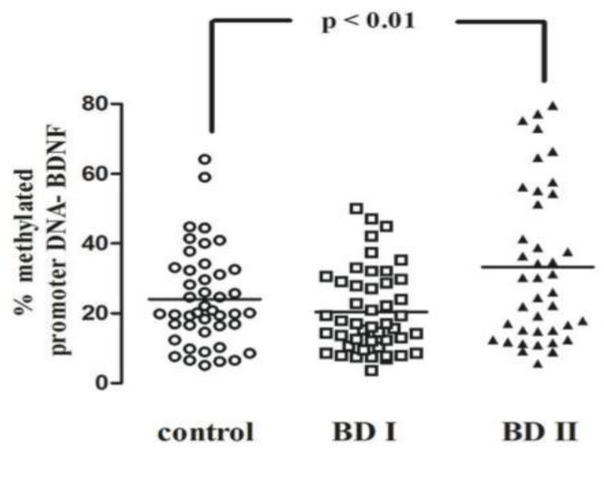
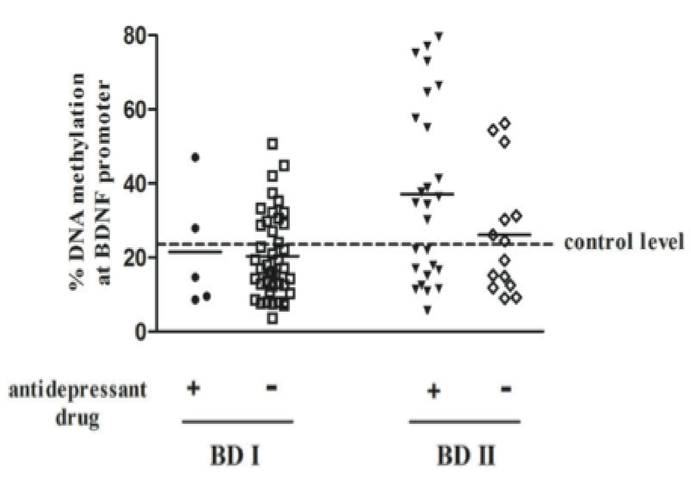


Figure 4



A significant BDNF gene expression down-regulation was observed in BD II (0.53±0.11%; p<0.05), but not in BD I (1.13±0.19%) patients, compared with controls (CONT: 1±0.2%) (fig.3) . Consistently, an hypermethylation of the BDNF promoter region was evident only in BD II patients (CONT: 24.0±2.1%; BDI: 20.4±1.7%; BDII: 33.3±3.5%, p< 0.05). Of note, higher levels of DNA methylation at BDNF promoter were observed in BD subjects on pharmacological treatment with mood stabilizers plus antidepressants (34.6 ±4.2%) compared with those exclusively on mood stabilizing agents (21.7±1.8%; p<0.01) (fig.4). Moreover, among the different pharmacological therapies, lithium (20.1 ±3.8%, p<0.05) and valproic acid (23.6±2.9 %,p < 0.05) were associated with a significant reduction in DNA methylation compared to other drugs (35.6±4.6%).

CONCLUSIONS

Present findings suggest selective changes in DNA methylation of BDNF promoter gene in subjects with BD, type II in particular, and highlight the importance of epigenetic factors in mediating the onset and/or susceptibility to BD, providing new insight into the mechanisms of gene expression. Moreover, they shed light on possible mechanisms of action of mood stabilizing compounds, compared to antidepressants, in the treatment of BD, indicating that epigenetic regulation of BDNF gene promoter seems to be a key target for their effect [3]. However, in order to further support BDNF role in the pathogenesis of major psychoses, these preliminary findings need to be replicated in a larger population.

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Authors declare that they do not have any affiliation or economic interest in any organization that may imply a conflict of interest with the present study.