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Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism and response to antipsychotic drug therapy

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Brain-derived neurotrophic factor (BDNF) is a member of neurotrophin family crucial in the regulation of the neurogenesis, differentiation, survival, neuroplasticity, repair of neurons, cognition and adaptive processes underlying learning and memory. Therefore it might be responsible for the neural maldevelopment and disturbed neuroplasticity in schizoprenia. BDNF modulates synthesis, metabolism and neuronal activity of the main neurotransmitters including dopaminergic. This interaction of BDNF and dopaminergic system indicates its possible role in the therapeutic response to antipsychotic drugs in schizophrenia. A single nucleotide polymorphism (SNP) in the pre-domain of BDNF that results in valine to methionine substituition at codon 66 (Val66Met or rs6265) was associated with different psychiatric disorders. The Met allele has been shown to negatively affect intracellular trafficking and activity-dependent secretion of BDNF. The aim of this study was to investigate the association between BDNF Val66Met polymorphism and risperidone- and olanzapine-induced effectiveness in the treatment of schizophrenia. The study included 267 patients with schizophrenia (225 men and 42 women) with an average age of 35.5 years (ranging from 19 to 74 years). All patients were treated with atypical antipsychotics, risperidone (mean dose = 3.4 ± 0.8 mg/day, range 3-6 mg/day) and/or olanzapine (mean dose = 17.7 ± 2.8 mg/day, range 10-20 mg/day). Severity of schizophrenic symptoms was assessed according to the Clinical Global Impression Scale and the Positive and Negative Syndrome Scale for schizophrenia (PANSS), at study entry and days 7, 14, 28, 42, 56, 84 (12 weeks) and then every six weeks within the 36-week period. Clinical response to antipsychotic treatment was defined as a 30% reduction from baseline scores in total PANSS scores after 8 weeks of treatment. The association between BDNF Val66Met polymorphism and symptomatic remission in schizophrenia was also evaluated. Remission was defined as mild or less on both positive and negative symptoms over a period of 6 consecutive months as defined by the Remission in Schizophrenia Working Group in 2005. Genotyping was done using the TaqMan SNP Genotyping Assay. Results were evaluated with a χ^2 test. BDNF Val66Met polymorphism was significantly associated with a percentage of reduction in the PANSS positive symptom scores (χ^2=6.988, df=2, P=0.030), and this result was confirmed when patients were additionally grouped as the Met carriers (the combined Met/Met and Val/Met genotype) and Val/Val homozygotes (χ^2=5.947, df=1, P=0.015). The significant (χ^2=7.442, df=2, P=0.024) association between BDNF variants and remission in schizophrenia was also found. On the other hand, we failed to detect a significant effect of the BDNF genotype on the total (χ^2=4.422, df=2, P=0.110), negative symptom (χ^2=2.645, df=2, P=0.266), and general (χ^2=2.445, df=2, P=0.294) psychopathology scores of the PANSS after 8 weeks of antipsychotic treatment. Our results suggest that the variations in the BDNF gene may affect positive symptoms after treatment with risperidone and olanzapine in schizophrenia, suggesting that responders have more frequently Val/Val genotype, while Met allele is associated with poorer reduction in positive symptoms, and failure to achieve remission.