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Understanding the role of BDNF rs6265: leading to structural changes in brain of Bipolar Disorder patients

Sukhman Kaur[1], Ginjinder Kaur[2*], Rajnish Raj[3]
[1] Department of Human Genetics, Punjabi University, Patiala, Punjab, India
[2] Assistant Professor, Department of Human Genetics, Punjabi University, Patiala, Punjab, India
[3] Professor, Department of Psychiatry, Govt. Medical College & Rajindra Hospital, Patiala, Punjab, India
Corresponding Author: Ginjinder Kaur

Abstract
Background: Bipolar disorder is a chronic brain disorder marked by periods of both manic and depressive episodes, distinguished by a normal period too. It can last a lifetime and may cause significant impairment. The prefrontal cortex, anterior cingulate cortex, hippocampus, and amygdala are the most pivotal parts of brain responsible for emotions regulation, responses, and behavioural response to stimuli. The *BDNF* rs6265, known as the Val66Met polymorphism, is associated with cognitive impairment in bipolar disorder patients leading to various changes in the structure of brain which is responsible for cognitive impairment. The present study focused on the determination of presence of Val66Met polymorphism in bipolar patients.
Methodology: The data and blood collection were done from the recruited 200 bipolar disorder cases and 200 age-sex matched controls with an informed-written consent from Punjab (India). The DNA was extracted with standard phenol-chloroform method, followed by the genotyping of rs6265 (PCR-RFLP) and statistical analysis was done.
Results: The differences were found to be statistically significant for the frequencies of genotypes and alleles, with p value <0.0001. The increased risk of developing BD was found to be associated with BDNF (rs6265) CT genotype (OR=2.47, p <0.0001) and TT genotype (OR=2.55, p=0.031) with statistically significant difference. The data revealed that the minor allele (T) supplemented the BD risk by 2.04 times (OR=2.04, 95%CI=1.45-2.86, p<0.0001).
Conclusion: The findings concluded the association of rs6265 with bipolar disorder, thus suggesting the vital role of this polymorphism for cooccurrence of neurostructural changes and behavioral changes in bipolar disorder.

Keywords: Brain-derived neurotrophic factor, val66met polymorphism, bipolar disorder, cognitive impairment, mania, depression

Introduction

Bipolar disorder (BD), also known as manic-depressive illness is a chronic brain disorder marked by alternate periods of mania (or hypomania) and depressive episodes, distinguished with an episode of normal period too. It leads to an unusual shift in mood, energy, activity levels and affects the ability to carry out day-to-day tasks which can last a lifetime and may cause significant impairment throughout [1]. With a lifetime prevalence of 3.9 percent in the United States [2] and a range of 1.5 to 6.0 percent in the general population [3], bipolar disorders are a serious concern nowadays. Bipolar I disorder often occurs at age 18, while bipolar II disorder typically manifests at age 22 [4]. According to the National Comorbidity Study, rates were greater between 18 and 34 years than between 35 and 54, with onset usually occurring between 18 and 44 years [2]. Instead of major research achievements, the pathophysiology underlying the bipolar disorders, including molecular causes and mechanisms, is still obscure. A complex interplay between biological and environmental variables contributes to the pathophysiology of bipolar illness, which is a multifactorial disease. Increased concordance between first-degree relatives and dizygotic twins (5–10%) and monozygotic twins (40–70%) of BD diagnosis has previously been shown in classical investigations [5]. In particular, genes have been found to account for 60% of the phenotypic diversity in BD. The pathogenesis of BD has been repeatedly linked to the *BDNF* val66met polymorphism (rs6265). This genetic variant causes a substitution of valine (G) for methionine (A) at codon 66 and is found on chromosome 11p13. Neuronal and synaptic plasticity, as well as neuronal survival, development, and differentiation, are all influenced by the protein known as BDNF which is encoded by *BDNF* gene only [6]. The met-allele has been linked to decreased synaptic plasticity, poor learning and memory ability, and an increased risk of neurodegenerative and neuropsychiatric illnesses, including dementia. It also causes diminished BDNF release after neural stimulation (Fig. 1). The *BDNF* Val66Met polymorphism has been shown to affect brain shape in addition to the clinical course and vulnerability of mental diseases. In neurons and neurosecretory cells, a Met66 substitution results in three trafficking defects: 1) reduced distribution of variant BDNF into neuronal dendrites, 2) reduced targeting of variant BDNF to secretory granules, and 3) consequent disruption of controlled secretion [7]. The Met66 allele, when expressed together in the same cell, changes the intracellular trafficking of "wild type" *BDNF* (Val allele) by forming heterodimers that are less effectively sorted into the secretory pathway. This results in a reduction in BDNF secretion at the synapse overall when the Met66 allele is present. Because BDNF is crucial for neurogenesis, neuronal protection, cell survival, and synaptogenesis in the brain, bearers of the Met66 allele

should have lower brain sizes overall and in specific regions than Val/Val homozygotes [8, 9, 10]. The role of *BDNF* in several facets of BD has been thoroughly examined in earlier research, and have been linked to changes in the structure and function of the brain. The hippocampus is essential for controlling mood and behaviour, and the research on adult BD has well shown the link between aberrant hippocampus sizes and BD [11]. Additionally, neuroimaging studies have shown that aberrant hippocampus activity and varying anterior cingulate and hippocampus sizes are linked to *BDNF* allelic variants [12].

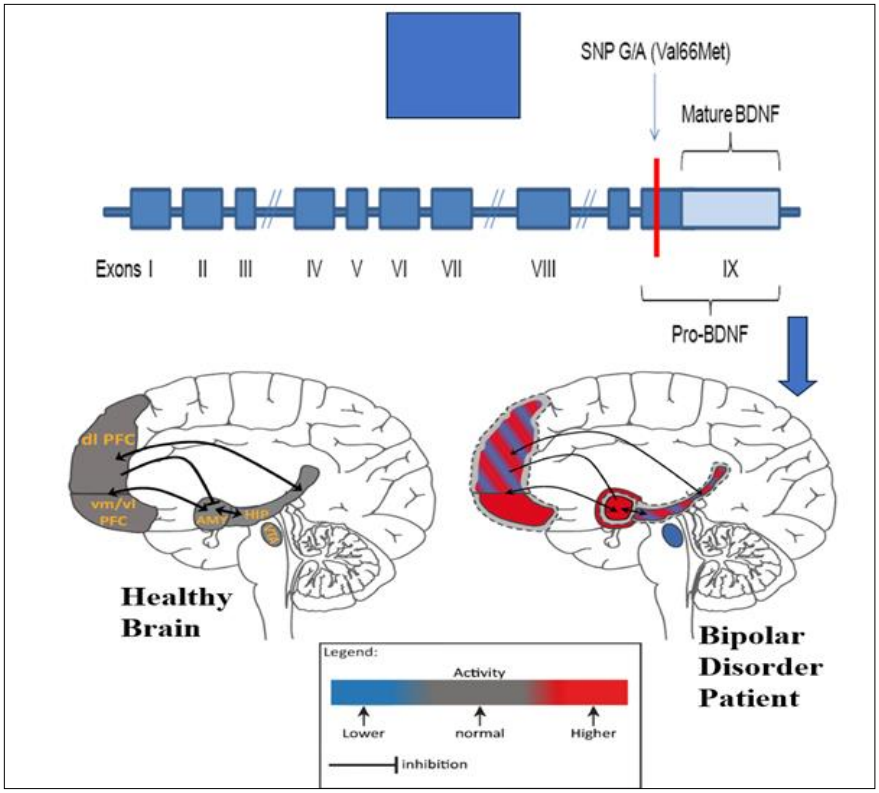

Fig 1: Various structural and functional changes in brain due to *BDNF* Val66Met polymorphism in BD patients

Nevertheless, numerous discoveries of potential gene connections have not been replicated. This is likely because individual genes have a limited impact size in a condition as diverse as BD. The data retrieved from the National DMDA (2000) indicated that it is typical for 10 or more years and evaluation by four or more clinicians have been passed between first complaint of symptoms and final diagnosis with bipolar disorder. An essential first step of the present study is in comprehending the pathophysiology of BD by evaluating the effect of potential gene (*BDNF* rs6265) polymorphism involving structural alterations in the brain linked to the beginning of BD episodes and the advancement of the condition.

Methods

For the present study, a total of 200 bipolar disorder diagnosed cases (according to DSM-V) and 200 age-sex matched controls were recruited in the present study as the participants. The ethical permission was taken from the Institutional Ethical Committee, Punjabi University, and Patiala with ref. no. 137/IEC-2019 and an informed-written consent was taken from all the participants to be volunteering being part of this study by conveying them the importance of the implications for this study. The inclusion criteria included the participants with age group 18 to 60 years and residing in Punjab (India) by birth. Moreover, the participants had the right to withdraw themselves at any point of time according to their own will.

A total of 2ml intravenous blood was withdrawn by a trained technician from all the participants and stored in EDTA coated vials at -20ºC until further experimentation. The collected blood was used to extract DNA by using standard phenol-chloroform method given by Sambrook *et al*. [13]. The quantity and quality check of the extracted DNA was done by spectrophotometer and agarose gel electrophoresis, respectively. Further, genotypic analysis for the presence of Val66Met (rs6265) was done by polymerase chain reaction (PCR) followed by the digestion of amplified DNA in specific restriction enzyme, known as restriction fragment length polymorphism (RFLP) (details given in Table 1). Amplification was performed in an automated thermal cycler with PCR conditions as: initial denaturation at 94°C (5 minutes), followed by 40 cycles of denaturation at 94°C (30 seconds), annealing at 62°C (2 minutes), and elongation at 72°C (1 minute), followed by 7 minutes of final extension at 72°C. The products were then analysed using gel electrophoresis on 1.5% agarose gel at 80 V run in 0.5× TAE buffer for 45 minutes staining with 0.5 µg/mL of ethidium bromide followed by the gel visualization using Gel-Doc (Vision works LS software ver-7.1).

The amplified products were then digested with 5 U of the specific enzyme at 37°C overnight followed by 2.5% agarose gel electrophoresis and visualized gel images using the same imager. The size of amplified product is 300 bp whereas the sizes of bands of post digestion products were 300 bp, 180 bp and 120 bp.

Table 1: Details for primers and restriction enzyme used for genotyping of *BDNF* (rs6265)

Gene (SNP)	Primers Sequence	Restriction Enzyme
BDNF (rs6265)	FP- 5'-ATCCGAGGACAAGGTGGC-3' RP- 5'-CCTCATGGACATGTTTGCAG-3'	*Eco72I*

The chi-square test was used to analyze the differences in frequency of different genotypes among cases and controls and further, the risk for the occurrence of disease was assessed by calculating odd's ratio with 95% confidence interval in additive models, allelic models, dominant model and recessive model separately.

Results

Genotypic frequencies were calculated for homozygous wild (AA), heterozygous (AG) and homozygous mutant (GG) for both cases and controls; as 98, 86 and 16, respectively for the former and 141, 50, and 9, respectively for the latter. The frequencies for a allele and G allele were found to be 282 and 118 respectively for cases whereas controls had 332 and 118 respectively. The differences were found to be statistically significant for the frequencies of genotypes with chi-square value 19.225 (<0.0001) and for alleles, the chi-square value was 17.512 (<0.0001) (Table no. 2).

Table 2: Frequency distribution of different genotypes and alleles among cases and controls

Model	Genotype/ Allele	Cases N (%)	Controls N (%)	Chi-square value	p value
Co-dominant	GG	98 (49)	141 (70.5)	19.225	<0.0001*
	GA	86 (43)	50 (25)		
	AA	16 (8)	9 (4.5)		
Allele	G	282 (70.5)	332 (83)	17.512	<0.0001*
	A	118 (29.5)	68 (17)		

The association of different genetic models of rs6265 for the risk of bipolar disorder was tested (Table no. 3). The increased risk of developing BD was found to be associated with BDNF (rs6265) GA genotype (OR=2.47, 95% CI=1.60-3.81, p <0.0001) and AA genotype (OR=2.55, 95% CI= 1.08-6.02, *p* =0.031) with statistically significant difference. The data revealed that the minor allele (A) supplemented the BD risk by 2.04 times (0R=2.04, 95%CI=1.45-2.86, P<0.0001). Dominant model (OR=2.48, 95%CI=1.64-3.75, p <0.0001) revealed an increased risk of developing BD but recessive model (OR=1.84, 95%CI=0.79-4.28, *p* =0.153) did not show the statistically significant increased risk. Moreover, results were found to be statistically significant for multiplicative models when compared among cases and controls and found to be associated with BD with OR (95% CI) = 2.04(1.46-2.87) and p value <0.0001.

Table 3: Disease association analysis of different models of BDNF rs6265 in BD patients

Models	Genotype/ Allele	Cases N (%)	Controls N (%)	OR (95%CI)	p value
Additive model	GG	98 (49)	141 (70.5)	Reference	-
	GA	86 (43)	50 (25)	2.47 (1.60-3.81)	<0.0001*
	AA	16 (8)	9 (4.5)	2.55 (1.08-6.02)	0.031*
Allelic model	G	282 (70.5)	332 (83)	2.04 (1.45-2.86)	<0.0001*
	A	118 (29.5)	68 (17)		
Dominant model	GG	98 (49)	141 (70.5)	2.48 (1.64-3.75)	<0.0001*
	GA+AA	102 (51)	59 (29.5)		
Recessive model	GG+GA	184 (92)	191 (95.5)	1.84 (0.79-4.28)	0.1535
	AA	16 (8)	9 (4.5)		
Multiplicative Model	2GG+GA	282	332	2.04 (1.46-2.87)	<0.0001*
	GA+2AA	118	68		

Discussion

This study investigated the association of Val66Met polymorphism in *BDNF* gene that plays a vital role in structural and functional changes of brain, leading to impairment among BD patients. The observations were found to be statistically significant (p <0.05), confirming the association of rs6265 SNP in making an individual more susceptible for co-occurrence of BD among adults. Regional increases in volume and SA may be caused by advancing age by BDNF interaction effect, given the intricate neurodevelopmental pathways and the function of BDNF in neuronal plasticity. With parts of the somatosensory cortex linking to several cortical and subcortical areas, it is proved that the brain is a highly complex structure. The somatosensory cortex's many connections enable it to perform a wide range of tasks, such as processing painful sensations, creating empathy and emotion, regulating emotions, generating tactile attention and physical representations, and sensory motor integration [14]. Emotional impairment is the major thing to be considered under the mood disorders which is being affected the most. Assessing a stimulus to see if it has an emotional meaning is the first stage in the emotional processing process. The next stage is to produce the right feeling, which calls for input from a number of bodily systems. Lastly, it is necessary to manage this emotional state and the behaviour that follows [15]. The somatosensory cortex may be involved in emotion regulation, according to research on cortical alterations in

mood disorders. More precisely, it has been demonstrated that the somatosensory cortex plays an integral part in every phase of emotion processing, suggesting that it plays a crucial function in emotion regulation [16, 17]. Adolphs *et al*. [18], showed that emotion perception involves the somatosensory cortex. Participants in this study who were having lesions in the right somatosensory cortex were less able to identify, label, and classify emotions as well as assess their severity, suggesting that the somatosensory cortex plays a role in the first phase of emotion processing. Given the amygdala's established function in emotion regulation and the somatosensory cortex's direct and indirect connections to the amygdala via the insula, this is one possible mechanism by which the somatosensory cortex may play a role in such identification1 [5]. According to Cunningham & Zelazo [19], the amygdala and surrounding areas re-evaluate inputs through neuronal processing to identify their emotional value. In this situation, the thalamus and limbic areas engage with the amygdala to perform early assessments, and the amygdala and somatosensory cortex subsequently interact to analyse later judgements. A common alteration seen in the somatosensory cortex in mood disorders is changes in grey matter volume. The postcentral gyri of those with early onset MDD show reduced cortical thickness [20], which is consistent in bipolar disorder too, where the left somatosensory cortex's grey matter volume has been shown to decrease [21].

Deficits in distinct types of hippocampus-dependent memory have been linked to a naturally occurring polymorphism in the human *BDNF* gene that results in a valine to methionine substitution at position 66 in the prodomain (Val66Met) [10, 22, 23]. The Val66Met polymorphism has been linked to a decline in creativity during a manic episode, according to studies by Soeiro-De-Souza *et al*. [24] and Nassan *et al*. [25]. Additionally, Nassan *et al*. [25] discovered that this genetic variant is more prevalent in early-onset BD. The *BDNF* gene polymorphism offers a crucial first indication of the function of neurotrophins in human behavioural processes [26] and serves as a crucial connection to earlier behavioural research in transgenic animals. Peripheral levels of brain-derived neurotrophic factor changed differently in bipolar disorder patients based on their Val66Met genotype over the course of treating mood episodes. Compared to Val homozygotes, Met carriers of the Val66Met genotype exhibited a distinct trajectory and a propensity for a less pronounced rise in peripheral levels [27]. It has also been observed to be linked with impaired cognitive impairment and suicidal behaviour [28].

Conclusion

Until now, no genetic associations have been identified linking neurotrophin genes (*BDNF* rs6265) to human cognitive functioning leading to bipolar disorder in Punjabi population. The implications of these findings for a larger population are still unknown. As was already established, not all ethnic groups or geographical areas of the world have an equal distribution of the M*et al*lele. Given that BDNF is known to mediate learning and memory processes, this greater vulnerability to cognitive impairment raises the possibility that variations in *BDNF* gene may influence nervous system functioning and contribute to the emergence of neuropsychiatric illnesses.

Declarations

Ethics approval: The ethical clearance was approved by the Institutional Ethical Committee, Punjabi University, Patiala (ref. no. 137/IEC-2019), and the written permission for blood and data collection was also taken from Govt. Medical College & Rajindra Hospital, Patiala.

Consent to participate: Participation was voluntary and anonymous, and the participants had the right to decline to participate in the study without penalty. The participants separately gave their written consent to the research at the beginning of the questionnaire.

Conflicts of interest: The authors declare that they do not have any known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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List of Abbreviations

BD: Bipolar Disorder
BDNF: Brain derived neurotrophic factor
DNA: Deoxyribonucleic Acid
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EDTA: Ethylenediaminetetraacetic acid
MDD: Major Depressive Disorder
Met: Methionine
OR: Odds Ratio
PCR: Polymerase Chain Reaction
RFLP: Restriction Fragment Length Polymorphism
SNP: Single Nucleotide Polymorphism
TAE: Tris-Acetate-EDTA
Val: Valine

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