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Single nucleotide polymorphism of *BDNF* Val66Met (rs6265) and its association to neuropsychiatric disorders

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ABSTRACT: Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophin in the central nervous system and was shown to be involved in neuronal growth, differentiation and synaptic plasticity. A single nucleotide polymorphism at the pro-region of the *BDNF* gene (rs6265) has been reported to alter the amino acid from valine to methionine at codon 66 and was associated with neuropsychiatric disorders in several studies. To date, the results on the association of *BDNF* rs6265 to the aetiology of the neuropsychiatric illnesses have been inconsistent with some studies reporting a positive association and others reporting no association. Concerning the past inconsistent reports, this mini-review aims at determining the association of *BDNF* rs6265 and neuropsychiatric disorders among the different studies. Firstly, we discuss the findings on studies reporting the association of *BDNF* rs6265 with depression whereby a positive association between the BDNF variant and depression was obtained in several studies on the Caucasian, German, Chinese, and Malaysian population but not in studies on the Korean and other populations. Likewise, some studies found the occurrence of the SNP to be associated with a reduction in the BDNF level in depressed cases, but others found no effect at all. We then reported findings on the association of *BDNF* rs6265 with anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, bipolar disorder, and schizophrenia. Val allele has been found associated with these disorders, whereas some studies reported the involvement of the Met allele, and some reported no association at all. Similarly, the association of the *BDNF* variant with the BDNF level remains controversial. It is, therefore, essential to conduct more studies with larger sample sizes and look at the haplotype level to determine the association.

Keywords: major depressive disorder; panic disorder; anxiety; post-traumatic stress disorder; obsessive-compulsive disorder; bipolar disorder; schizophrenia

1.0 INTRODUCTION

Neurotrophins are a family of growth factors that play a crucial role during neuronal growth, differentiation, and synaptic plasticity (Huang & Reichardt, 2001). In mammals, four neurotrophins have been identified, namely: nerve growth factor (NGF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), and the brain-derived neurotrophic factor (BDNF). Among the four neurotrophins, BDNF is the most abundant neurotrophin in the brain and is produced primarily by the glial cells of the brain and spinal cord (Leibrock et al., 1989). In the peripheral nervous system, BDNF is produced by the Schwann cells (Acheson et al., 1991). In the brain, BDNF is mostly distributed in regions regulating mood and behaviour such as the hippocampus, cerebellum, hypothalamus, neocortex, and amygdala (Marosi & Mattson, 2014). Studies on rodents have shown that *BDNF* mRNA was also found in the heart (Hiltunen et al., 1996), aorta (Scarisbrick et al., 1993), kidney, ovary, lung (Maisonpierre et al., 1990, 1991), muscle, endothelial cells, immune cells (B and T cells) (Kerschensteiner et al., 1999), and platelets (Yamamoto & Gurney, 1990).

BDNF gene is located on human chromosome 11, band p13, spanning about 70kb. It consists of 9 functional promoters and 11 exons (Pruunsild et al., 2007) and is synthesized as a 27kDa pre-pro-BDNF (precursor protein) in the endoplasmic reticulum (Leßmann & Brigadski, 2009). Upon cleavage, a 32kDa pro-BDNF is produced and is transported into the Golgi apparatus. The proteolytic cleavage of pro-BDNF by endoproteases or pro-protein convertases results in the production of the mature 14kDa BDNF protein (Greenberg et al., 2009) that can be activated upon binding to the BDNF receptors. BDNF brings about its biological function by binding to two receptors, namely, tropomyosin receptor kinase B (TrkB) (high-affinity receptor) and p75 neurotrophin receptor (p75NTR) (low-affinity receptor) (Barbacid, 1994). BDNF was found to be mostly distributed in the brain in regions regulating mood and behaviour such as the hippocampus, cerebellum, hypothalamus, neocortex, and amygdala. Initially, BDNF was thought only to enhance the development of the spinal sensory neurons (Barde et al., 1982). Subsequent studies revealed broader roles of BDNF in neuronal growth and differentiation and in supporting the outgrowth and survival of ganglionic, sensory, cholinergic, GABAergic, dopaminergic, and motor neurons (Henderson, 1996; Lewin & Barde, 1996).

Naturally occurring single nucleotide polymorphisms (SNPs) have been reported in *BDNF*. *BDNF* rs6265 is one of the most common and investigated functional nonsynonymous SNPs located at Chr.11:27658369 resulting in alteration at the 5' promoter region in the pro-BDNF from G (reference allele) to A (variant allele). The change occurs in the coding region at the 196th nucleotide leading to the amino-acid residue substitution from valine (Val) to methionine (Met) at codon 66 (Val66Met polymorphism) within the pro-region of BDNF, affecting the aberrant sorting of BDNF into the secretory vesicles that lead to a reduction in the activity-dependent secretion of BDNF. a. *BDNF* rs6265 is widely reported to be associated with the pathophysiology of neuropsychiatric diseases such as schizophrenia, bipolar disorder, and depression. Among the Asian population, approximately 70% of the Chinese, Japanese and Korean populations were homozygous for the Met variant form of the *BDNF* gene as compared to the Met variant that was found in about 30% to 50% of the Caucasian populations (cohorts from the U.S., Croatia and Italy) (refer to the extensive review by Shen et al., 2018). Besides occurring in human beings, the Val66Met polymorphism was reported to occur naturally in other vertebrate species, such as rhesus macaques (Cirulli et al., 2011). In *BDNF* Met variant carriers, *BDNF* Val/Met heterozygous and Met/Met homozygous, the pro-domain structure of the gene was altered (Anastasia et al., 2013). The replacement of Val by Met was also shown to impair the hippocampal sorting of the BDNF vesicles to the neuronal activity-dependent secretory pathway leading to reductions in the level of the mature BDNF protein (Egan et al., 2003).

There is a plethora of evidence showing the association of the *BDNF* Val66Met polymorphism with the reduction in the brain volume of patients with bipolar disorder, schizophrenia, and depression. The majority of these studies focused on the hippocampal region owing to its vital role in emotions, memory, and learning (Cunha et al., 2010). Also, a reduction in hippocampal volume has been associated with deficits in learning and memory in neuropsychiatric disorders (Baig et al., 2010; Egan et al., 2003). Compared to the homozygous Val-allele carriers, the homozygous Met-allele carriers were

prone to or at higher risk of developing neuropsychiatric disorders (Gratacòs et al., 2007) and had a reduced volume in the prefrontal cortex and hippocampus (Pezawas et al., 2004; Szeszko et al., 2005). Subjects with Met-allele also demonstrated weaker performance in tests on episodic memory (Egan et al., 2003; Hariri et al., 2003). A study by Frodl et al., (2007) reported a significantly reduced hippocampal volume in depressed and control subjects homozygous for the Met-allele as compared to subjects homozygous for the Val-allele. Contrary to the findings, meta-analysis studies reported no differences in the hippocampal volume, although Met-allele carriers were having a smaller mean value (Kambeitz et al., 2012; Molendijk et al., 2011). A study by Carballedo and colleagues reported that the Met-allele carriers that were exposed to childhood trauma (early life adversity) showed lower hippocampal volumes as compared to carriers without early life adversity (Carballedo et al., 2013). In the same study, the Met-allele carriers without a history of early life adversity displayed larger hippocampal volume as compared to subjects with Val-allele that had no history of early life adversity. This suggests that on its own, Met-allele is not sufficient for causing reductions in the hippocampal volume.

For the past decades, many genetic studies investigated the *BDNF* rs6265 polymorphism and associated the effects of polymorphism on neuropsychiatric disorders. Dysregulation of BDNF was implicated in enhanced vulnerability to various neuropsychiatric disorders such as depression, anxiety disorder, bipolar disorder, post-traumatic stress disorder (PTSD), suicidal behaviour, and schizophrenia. However, various inconsistencies in findings related to *BDNF* Val66Met as a genetic risk to neuropsychiatric disorders suggest that its penetrance may be influenced by many factors such as gender, age, environmental factors, ethnicity, and genetic model used for analysis. Here, we reviewed the literature on *BDNF* Val66Met polymorphism (*BDNF* rs6265) in neuropathological conditions intending to understand its potential involvement and association with the acquisition of neuropsychiatric disorders.

2.0 THE EFFECTS OF *BDNF* RS6265 ON NEUROPSYCHIATRIC DISORDERS

2.1 Depression

Major depressive disorder (MDD) is a debilitating mental illness characterized by having two or more weeks of a depressed mood, loss of interest in almost all everyday activities and several other symptoms such as weight change (weight loss or weight gain), sleep changes (hypersomnia, insomnia), fatigue, feeling of guilt or worthlessness, retardation or psychomotor agitation, inability to concentrate, and thoughts of death and suicide (American Psychiatric Association [APA], 2013). These symptoms negatively influence an individual's social and occupational performance and are clinically significant and are not due to the effect of a substance or any other medical condition (APA, 2013). The severity of the illness depends on the number of symptoms and the extent of functional deterioration. The depression course may re-emit, and relapse and the symptoms may continue between episodes.

It is not clear whether the presence of the rs6265 variant in the *BDNF* gene confers susceptibility to the development of MDD. Studies based on animal models, however, concur with the findings that *BDNF* rs6265 is a possible predictor for the development of MDD in the future (Z.-Y. Chen et al., 2006, 2008). Furthermore, studies on humans indicated that Met-allele carriers were more susceptible to the development of geriatric depression as compared to individuals with Val-allele (Hwang et al., 2006; Lin, 2009; Taylor et al., 2007). Several findings reported the genotype of *BDNF* rs6265 as a relevant risk factor to MDD (Aldoghachi et al., 2019; Licinio et al., 2009), a risk for suicidal behaviour (Sarchiapone et al., 2008; Schenkel et al., 2010) and negative thinking or rumination (Beevers et al., 2009). On the contrary, a meta-analysis on 14 studies concluded that no association exists between the allele and genotype of *BDNF* rs6265 and depression (Verhagen et al., 2010). The summary of the findings is tabulated in Table 1.

Several genetic studies have been performed to study whether *BDNF* rs6265 is associated with ethnicity. A positive association between MDD and *BDNF* rs6265 has been observed in the Caucasian population (Ribeiro et al., 2007), the German population (Schumacher et al., 2005) and the Chinese population (Hwang et al., 2006), suggesting its role in the risk of developing depression. In contrary, some studies found no association of *BDNF* rs6265 to major depression in the Korean (Choi et al., 2006), Chinese (Hong, Huo, et al., 2003), Japanese (Iga et al., 2007) Caucasian and other populations (Surtees et al., 2007). Patients with MDD displayed a significant reduction in the serum BDNF level among MDD cases and healthy controls (patients: 20.8 ng/ml vs controls: 26.8 ng/ml; p=0.015) (Gonul et al., 2005), (patients: 17.6 ng/ml vs controls: 27.7 ng/ml; p=0.002) (Shimizu et al., 2003), (patients: 22.6 ng/ml vs controls:26.5 ng/ml ; p<0.01) (Karege et al., 2002). Losenkov and colleagues found an association between *BDNF* rs6265 and the 17-item Hamilton depression rating scale (p=0.014) but not

between *BDNF* rs6265 and the BDNF level. In the same study, the BDNF level was not reported to be associated with depression, indicating that *BDNF* rs6265 may only be involved in the severity of the disorder (Losenkov et al., 2020). Similarly, no significant difference was observed in the BDNF levels of 61 medicated depression patients and 50 controls (p=0.81), even following a course of electroconvulsive therapy. However, carriers of the Met allele had a higher plasma BDNF level when compared to carriers of the Val allele (Ryan et al., 2018). On the other hand, Youssef and colleagues conducted a study on 37 post-mortem suicide subjects with major depression and 53 non-suicide controls. They observed a significantly reduced BDNF level in the caudal brain stem (p=0.02) and anterior cingulate cortex (p=0.04) among the MDD patients as compared to the controls. However, no significant difference was observed on the effect of the genotypes on the BDNF level (Youssef et al., 2018). The inability to obtain a significant association of the genotypes to the BDNF level may be due to the small sample size used in the study. Hence, the requirement of a similar study with a larger sample size may be necessary to confirm the findings.

2.2 Anxiety disorders

Anxiety disorders include a group of mental disorders such as generalized anxiety disorder (GAD), panic disorder, specific phobia, social phobia, obsessive-compulsive disorder (OCD), and PTSD (APA, 2013). Several studies have associated the Met allele of the *BDNF* rs6265 polymorphism to anxiety in animal models and traits linked to anxiety in humans. In conflict settings, the mice with the *BDNF* variant ($BDNF^{Met/Met}$) showed elevated anxiety-related behaviours as compared to the wild type controls suggesting a possible genetic link between the variant and anxiety (Z.-Y. Chen et al., 2006). Findings from the knock-in animal models are further supported by a genetic association study on 610 Caucasian subjects in which the Met/Met genotype was associated with high trait anxiety (Montag et al., 2010). Another study that involved 98 university students showed a higher risk of anxiety in the cold pressure test among carriers of the Met/Met genotype in comparison to carriers of the Val/Val genotype (Colzato et al., 2011). Concurring with the finding, a study on 480 individuals from various ethnicities (American Caucasians, African Americans, and American Indians) showed that the Met allele was found in most of the individuals with anxiety disorder, suggesting that it may serve as a risk allele for the development of the disorder (Jiang et al., 2005). There are also studies reporting a significant association between carriers of the Met allele and an elevated risk of anxiety disorders in the Brazilian (Tocchetto et al., 2011) and Mexican populations (González-Castro et al., 2019). Contrary to the findings, no significant difference was obtained when the alleles and genotypes of *BDNF* rs6265 were compared between patients with generalized social anxiety disorders and healthy controls (Park et al., 2011). Likewise, no significant association was obtained between the *BDNF* rs6265 variant and anxiety disorders in a meta-analysis study on 1092 cases and 8394 controls from different ethnicities (American, Korean, British, and Japanese) (Frustaci et al., 2008).

In a study on 27 patients with anxiety disorders and 31 healthy controls, functional magnetic resonance imaging (MRI) was used to study the link between the genotypes of *BDNF* in response to emotional faces. The study found that carriers of the Met allele displayed significant activation of amygdala-hippocampal responses to emotional stimuli (Lau et al., 2010). In addition, a study on 183 healthy subjects who were subjected to magnetic resonance imaging and were asked to fill a Temperament and Character Inventory (TCI) questionnaire, the different scores of harm avoidance were correlated to the neuroanatomy of the whole brain using voxel-based morphometry. The study found that higher anxiety-related traits were associated with lower volume in the right hippocampus in both males and females (Yamasue et al., 2008). Studies on the BDNF level in different anxiety disorders have demonstrated inconsistent results. In a study on 121 GAD Brazilian patients and 695 controls, the Met allele was significantly associated with increased BDNF in GAD patients (Moreira et al., 2015). Additionally, patients with GAD displayed a reduction in the plasma BDNF level as compared to the healthy controls (GAD patients: 2.10±1.88 ng/ml vs controls: 4.09±2.00 ng/ml) (F. Wang et al., 2015). On the contrary, a study on the Italian population reported the absence of any impact of the *BDNF* rs6265 polymorphism on circulating concentrations of serum BDNF (subjects with anxiety disorders: 25.62 ng/ml vs controls: 27.58 ng/ml, p=0.06) (Carlino et al., 2015).

2.2.1 Post-traumatic stress disorder (PTSD)

PTSD is a chronic mental health condition that occurs following a single or an extended exposure to a threatening life event. The Met/Met genotype was linked to an elevated predisposition to PTSD in several studies. A review on *BDNF* rs6265 and PTSD indicated an increased risk of the disorder in carriers of Met/Met genotype and diminished gene expression (Frielingsdorf et al., 2010). Similarly, significantly diminished

Table 1. Allele and genotype distributions for the Val66Met polymorphisms of *Brain-derived neurotrophic factor (BDNF)* in subjects with neuropsychiatric disorders in different ethnicities.

Ethnicity	Cohort	Patient/ Controls (n)	Allele frequency			Genotype				References
			A (Met)%	G (Val) %	χ^2/OR (95% CI) (p value)	A/A (Met/Met) %	G/A (Val/Met) %	G/G (Val /Val) %	χ^2/OR (95% CI) (p value)	
Depression										
Asian	China	110	53.2	46.8	(*P*=0.001)	30.9	44.5	24.5	2.49 (*P*=0.003)	(Hwang et al., 2006)
		171	38.6	61.4		15.2	46.8	38.0		
	Korea	83	54.2	45.8	χ^2= 1.734 (*P*=0.188)	22.9	45.8	31.3	χ^2= 2.809 (*P*=0.245)	(Choi et al., 2006)
		128	47.7	52.3		21.1	53.1	25.8		
	Malaysia	300	55.0	46.0	-	33.0	42.0	24.0	2.05 (*P*=0.008)	(Aldoghachi et al., 2019)
		300	45.0	55.0		23.0	45.0	32.0		
	Taiwan	84	51.8	48.2	(*P*=0.497)	26.2	50.0	23.8	(*P*=0.598)	(Hong, Huo, et al., 2003)
		392	48.8	51.2		23.5	57.3	19.2		
Caucasian	Germany*	465	21.0	80.0	-	4.0	34.0	63.0	1.10 (*P*=0.314)	(Schumacher et al., 2005)
		1097	19.0	81.0		3.0	32.0	65.0		
	Germany#	312	21.0	79.0	-	3.0	36.0	61.0	1.02 (*P*=0.881)	
		444	21.0	79.0		4.0	36.0	61.0		
	USA	284	-	-	-	0.7	20.1	79.1	1.7 (*P*=0.005)	(Ribeiro et al., 2007)
		331	-	-		1.9	29.1	69.1		
	USA	245	21.0	79.0	-	4.0	35.0	61.0	1.92 (*P*=0.024)	(Taylor et al., 2007)
		94	13.0	87.0		1.0	22.0	71.0		
Anxiety Disorder										
Asian	Korea	73	48.6	51.4	χ^2=0.415 (*P*=0.519)	24.7	47.9	27.4	χ^2= 0.961 (*P*=0.619)	(Park et al., 2011)
		152	45.4	54.6		19.1	52.6	28.3		
Mexican	Mexico	75	-	-	-	1.3	17.3	81.3	χ^2 = 4.57 (*P*=0.10)	(González-Castro et al., 2019)
		137	-	-		3.6	28.5	67.9		
	Mexico	150	10.0	90.0	1.96 (*P*=0.03)	-	-	-	-	
		274	17.9	82.1		-	-	-		
Post-traumatic Stress Disorder (PTSD)										
Asian	Korea	107	47	53	1.21 (*P*=0.57)	20.5	53.3	26.2	χ^2= 0.43 (*P*=0.81)	(Lee et al., 2006)
		161	45	55		19.3	50.9	29.8		
European-American	USA	96	14.6	85.4	(*P*=0.233)	1.0	27.1	71.9	(P=0.306)	(Zhang et al., 2006)
		250	18.8	81.2		4.0	29.6	66.4		

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Obsessive-Compulsive Disorder (OCD)										
Asian	India	377	14.6	85.5	$\chi^2 = 5.04$	23.8	24.1	73.4	$\chi^2 = 4.93$	(Taj M J et al., 2017)
		449	18.6	81.5	(*P*=0.02)	37.8	29.6	66.6	(*P*=0.08)	
Caucasian	Netherlands	220	23.0	77.0	(*P*=0.065)	5.9	34.1	60.0	(*P*=0.123)	(Katerberg et al., 2009)
		535	18.7	81.3		3.2	31.0	65.8		
	South Africa	199	20.1	79.9	(*P*=0.602)	4.5	31.2	64.3	(*P*=0.784)	
		115	18.3	81.7		2.6	31.3	66.1		
Mexican	Mexico	232	13.0	87.0	$\chi^2 = 24.7$	3.0	20.0	77.0	$\chi^2 = 23.7$	(Márquez et al., 2013)
		283	25.0	75.0	(*P*=0.0001)	8.0	35.0	57.0	(*P*=0.0001)	
South Africans	South Africa	112	20.1	79.9	-	5.3	29.5	65.2	-	(Hemmings et al., 2008)
		140	16.8	83.2		1.4	30.7	67.9		
Panic Disorder										
Asian	Japan	638	42.0	58.0	(*P*=0.97)	18.0	48.0	34.0	(*P*=0.74)	(Otowa et al., 2009)
		589	42.0	58.0		19.0	46.0	35.0		
	Japan	109	1.8	98.2	χ^2= 0.29	0.0	3.7	96.3	χ^2= 0.63	(Shimizu et al., 2005)
		178	2.5	97.5	(*P*=0.59)	0.60	3.9	95.5	(*P*=1.00)	
	Korea	106	51.3	48.7	χ^2=0.79	30.2	43.4	26.4	χ^2=4.16	(Lim et al., 2007)
		160	46.7	53.3	(*P*=0.37)	19.4	51.3	29.4	(*P*=0.125)	
	Taiwan	103	45.1	54.9	(*P*=0.163	19.4	51.5	29.1	(*P*=0.140)	(Lam et al., 2004)
		180	51.4	48.6		21.7	59.4	18.9		
Bipolar Disorder										
Asian	China	197	39.6	60.4	$\chi^2 = 1.277$	16.2	46.7	37.1	$\chi^2 = 1.538$	(Tang et al., 2008)
		208	43.5	56.5	(*P*=0.285)	18.3	50.5	31.2	(*P*=0.463)	
	Japan	519	40.8	59.2	(*P*=0.830)	17.7	46.1	36.2	(*P*=0.980)	(Kunugi et al., 2004)
		588	40.3	59.7		17.3	45.9	36.7		
	Japan	130	41.5	58.5	χ^2 =0.02	15.4	52.3	32.3	χ^2 = 0.32	(Nakata et al., 2003)
		190	42.1	57.9	(*P*=0.94)	17.4	49.5	33.1	(*P*=0.85)	
	Han Chinese	498	47.3	52.7	(*P*=0.425)	25.5	43.6	30.5	1.44	(Xu et al., 2010)
		501	45.5	54.5		19.2	52.7	28.1	(*P*=0.009)	
	Taiwan	108	45.4	54.6	(*P*=0.489)	20.4	50.0	29.6	(*P*=0.762)	(Hong, Huo, et al., 2003)
		392	48.2	51.8		23.5	57.3	19.2		

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Caucasian	Belgium	108	23.1	76.9	(*P*=0.94)	1.9	42.6	55.6	χ^2=2.0 (*P*=0.37)	(Oswald et al., 2005)
		158	21.2	78.8		3.2	36.1	60.8		
	USA	258	22.9	77.1	-	7.0	30.2	62.8	1.30 (*P*=0.04)	(Nassan et al., 2015)
		764	17.9	82.1		3.0	29.8	67.2		
	USA	621	17.9	82.1	1.22 (*P*=0.028)	3.5	28.7	67.8	(*P*=0.062)	(Lohoff et al., 2005)
		998	21.0	79.0		4.1	33.9	62.0		
Schizophrenia										
Asian	China	373	47.1	52.9	χ^2 = 954 (*P*=0.33)	22.0	50.1	27.9	χ^2 = 1.663 (*P*=0.44)	(Li et al., 2013)
		318	49.7	50.3		23.0	53.4	23.6		
	China	387	48.8	51.2	(*P*=0.77)	22.0	53.7	24.3	1.03 (*P*=0.95)	(Zhou et al., 2010)
		365	48.1	51.9		21.1	54.0	24.9		
	China- Han	560	48.8	51.2	(*P*=0.53)	25.7	46.3	28.0	0.941 (*P*=0.2575)	(Q. Chen et al., 2006)
		576	47.3	52.7		22.0	50.5	27.4		
	Japan	401	39.3	60.7	χ^2 = 0.39 (*P*=0.53)	16.2	46.1	37.7	χ^2 = 0.56 (*P*=0.76)	(Tochigi et al., 2006)
		569	40.7	59.3		16.7	48.0	35.3		
	Japan	349	41.7	58.3	(*P*=0.918)	18.3	46.7	35.0	(*P*=0.828)	(Watanabe et al., 2006)
		423	42.0	58.0		17.5	48.9	33.6		
	Taiwan	93	54.3	45.7	(*P*=0.657)	32.3	44.1	23.7	(*P*=0.055)	(Hong, Yu, et al., 2003)
		198	52.3	47.7		22.7	59.1	18.2		
Caucasian	Germany	533	22.0	79.0	1.17 (*P*=0.093)	6.0	32.0	63.0	1.17 (*P*=0.093)	(Schumacher et al., 2005)
		1097	19.0	81.0		3.0	32.0	65.0		
	UK	321	15.8	84.2	1.48 (*P*=0.0049)	2.8	26.0	71.2	1.68 (*P*=0.0015)	(Neves-Pereira et al., 2005)
		350	21.8	78.2		3.1	37.4	59.5		

* Samples from the University of Bonn; # Samples from the Munich area (Schumacher et al., 2005).

neuroticism levels (one of the risk factors for PTSD) had been observed among carriers of the Met allele as compared to carriers of other alleles (Frustaci et al., 2008). In a systematic review conducted using 11 studies to determine the association of *BDNF* and PTSD, a marginally significant effect was obtained between the Met allele and the risk of PTSD (OR 1.20; CI 0.99-1.26; p=0.057) (Bountress et al., 2018). Pitts and colleagues conducted a study on European American U.S. military veterans and reported that Met allele carriers had a significantly more severe lifetime and current PTSD symptoms. The same study also reported that the veterans with high lifetime trauma burden exhibited significantly greater severity of lifetime and past-month PTSD symptoms (Pitts et al., 2019). Likewise, in a study on 576 veterans, the Met allele was observed more in the psychotic PTSD patients as compared to the non-psychotic PTSD veterans or healthy veterans (Pivac et al., 2012). Similar findings were found in a study on 461 soldiers of the United States Army Special Operations, where the Met allele frequency was doubled in the probable-PTSD personal as compared to controls supporting the involvement of the *BDNF* Met allele in the development of the disorder (Zhang et al., 2014).

In contrary, no association was obtained between the variant allele and the genotype of *BDNF* rs6265 and PTSD in 96 PTSD patients and 250 healthy controls (genotype: p=0.306, allele: p=0.233), and the authors claimed that the low statistical power has contributed to this insignificant difference (Zhang et al., 2006). Likewise, Wang conducted a meta-analysis on the association of the *BDNF* rs6265 and PTSD and reported no genetic association of this SNP with vulnerability to PTSD (T. Wang, 2015). In agreement with the findings, no association was obtained between the alleles (p=0.57) and genotypes (p= 0.81) of *BDNF* rs6265 and PTSD in the Korean population (Lee et al., 2006). Also, in a case-control study on 151 Caucasian PTSD veterans and 106 controls, no significant difference was obtained between the *BDNF* rs6265 and PTSD (p=0.54). To further increase the statistical power, data from the study were added in a metanalysis, including 3625 participants. However, no significant difference was obtained, and upon the removal of two studies that deviated from HWE, a decreased risk of PTSD was observed in the carriers of the VAL/VAL genotype as compared to the heterozygous carriers (Bruenig et al., 2016).

2.2.2 Obsessive-compulsive disorder (OCD)

OCD is a severe psychiatric condition with evident genetic roots. Genetic variants of *BDNF* have been repeatedly shown to be associated with clinical criteria of OCD, such as family history and age of onset of the disorder, symptoms severity and deterioration in decision making (Hall et al., 2003; Hemmings et al., 2008; Katerberg et al., 2009). In a study on 112 South African patients and 140 controls, the male group displayed a significant association between the Met allele and early onset of OCD development (Hemmings et al., 2008). Contrary to the findings on males, in the same study, the female subjects showed an association of the Val/Val genotype with increased severity of OCD (Hemmings et al., 2008). A study on Caucasian populations from South Africa and Dutch population showed that *BDNF* rs6265 was not significantly different in the allelic and genotypic distribution among the cases and controls, except for the OCD females carrying the Met/Met genotype that displayed a positive association with the late age onset of this disorder (Katerberg et al., 2009). It is known that the Met-allele impacts the intracellular processing of the pro-BDNF polypeptide preventing its release from the active neuronal cells. Hall and colleagues conducted a family-based study using haplotype analysis and found that a haplotype marked by the *BDNF* Met66 allele to be under transmitted and, therefore, suggested that this variant acts as a protective allele in this disorder (Hall et al., 2003). Besides, a study on the Mexican population showed that there was a significantly higher frequency of Val/Val genotype and Val allele in OCD subjects as compared with the control group (Márquez et al., 2013). A similar result pattern was reported in South Indian population whereby a higher frequency of the Met allele was observed among controls as compared to cases, indicating a possible protective effect of the Met variant against the development of the disorder (Taj M J et al., 2017). Despite the availability of studies with a positive association of the BDNF variant to OCD, some studies found negative results. There was no significant association between the Val66Met polymorphism and OCD reported in the Japanese population (Umehara et al., 2016) and a meta-analysis of eight studies involving a total of 1632 OCD patients and 2417 healthy controls (J. Wang et al., 2015).

Some studies investigated the serum or plasma BDNF levels in OCD patients. In a study on the Chinese population, compared to the healthy group, there was a significant reduction in the plasma BDNF levels of the treatment naïve and treated OCD patients (treated OCD patients: 1.98±1.54 ng/ml; treatment naïve OCD patients: 1.97± 1.80 ng/ml; healthy controls: 4.09± 2.00 ng/ml; p<0.001) (Wang et al., 2011). Similarly, another study on Brazilians reported that there was a

significantly lower level of serum BDNF in OCD patients (0.47±0.038 pg/ug) when compared to healthy controls (0.75±0.060 pg/ug) (dos Santos et al., 2011). In a study on the Italian population, serum BDNF levels were significantly (p=0.043) reduced in OCD patients (36.90±6.42 ng/ml) in comparison to the healthy controls (41.59±7.82 ng/ml) (Maina et al., 2010). However, to date, the knowledge regarding the association of the genotypes to the BDNF level is lacking and requires further investigations.

2.2.3 Panic disorder

Panic disorder is an anxiety disorder characterized by a sudden continuous fear that results in several physical responses when there is no actual cause. Most of the studies on panic disorder did not find a significant association between the *BDNF* variants and panic disorder. There was no significant association between *BDNF* rs6265 and panic disorder among the cases and healthy controls reported in Japanese (Otowa et al., 2009; Shimizu et al., 2005), Taiwanese (Lam et al., 2004) and Korean populations (Han et al., 2015). This implies that the *BDNF* rs6265 plays a minimal role in the aetiology of panic disorder in the East Asian population. As for BDNF levels, a study on 110 Korean patients with panic disorder and 110 healthy controls reported a significantly reduced plasma BDNF levels among the cases as compared to the controls (controls: 693.75 pg/ml; cases: 92.50 pg/ml, p<0.001) (S.-A. Lee et al., 2015). Similarly, lower serum BDNF levels were reported in the Japanese (Kobayashi et al., 2005) and German populations (Ströhle et al., 2010). The potential link between an increased risk of panic disorder and *BDNF* variants remains to be investigated in the future.

2.3 Bipolar disorder

Bipolar disorder or manic-depressive disorder is a mental illness that results in changes in mood, levels of activity, energy, and efficiency in conducting day to day tasks. A study on Caucasians reported a positive association between the *BDNF* rs6265 SNP and the disorder (Nassan et al., 2015) (Table 1). A positive association was also obtained in the Han Chinese population (p=0.008) whereby carriers of the Met allele were at higher risk of developing MDD as compared to the healthy controls (OR=1.44; 95% CI= 1.070-1.950; p=0.016) (Xu et al., 2010). The Met allele was also shown to be significantly associated with the disorder in a family-based association study in New Zealand on bipolar probands and their relatives (first and second-degree relatives) (Sears et al., 2011). Also, in a different study on euthymic South Africans with bipolar disorder, carriers of the Met variant displayed significant elevated hyperthymic temperament scores, seen in most bipolar disorder patients (Savitz et al., 2008). Also, most of the patients who responded well to the lithium prophylaxis were found to be the carriers of the Met/Val genotype, suggesting a possible role of the SNP in predicting the treatment response (Rybakowski et al., 2005).

Contrary to the above findings associating the Met allele to the disorder, some family-based association studies reported that the Val allele was shown to confer susceptibility to the development of the disorder (Neves-Pereira et al., 2002; Sklar et al., 2002). The findings are further supported by studies that reported a significant association between the Val allele and bipolar disorder in a study on Caucasian (Lohoff et al., 2005) and Asian populations (Tang et al., 2008). However, some studies on Belgian (Oswald et al., 2005), Chinese (Hong, Huo, et al., 2003), and Japanese populations (Kunugi et al., 2004; Nakata et al., 2003) revealed no significant association between the *BDNF* variant and the development of the disorder. To date, the biological relevance of the overrepresentation of the Val allele in BPD remains unknown.

As for the neurophysiological studies, bipolar disorder patients carrying the Met allele exhibited deterioration in the Wisconsin Card sorting test as compared to those with the Val/Val genotype indicating that the Met allele elevates the risk of impairment in the cognitive function of the prefrontal lobe (Rybakowski et al., 2003, 2006). Additionally, bipolar disorder patients with Met/Val genotype displayed a reduction in the volume of the anterior hippocampus, anterior cingulate, and dorsolateral prefrontal cortex as compared to those with Val/Val genotype (Chepenik et al., 2009; Matsuo et al., 2009). Similarly, a reduction in the volume of the grey matter in bipolar patients with Met allele carriers has been observed as compared to non-carriers (McIntosh et al., 2007). A recent study reported larger hippocampal volumes in homozygotes for the Val allele when compared to heterozygote subjects (Szeszko et al., 2005). Thus, the increased Val allele protein expression among bipolar probands might alter the hippocampal formation and predispose individuals to the disorder.

Several studies showed a significant reduction in the serum BDNF levels in both treated and untreated bipolar disorder patients with both manic and depressive episodes as compared to healthy controls. The studies have also shown that these levels were negatively associated with the severity of the symptoms (manic and depressive) (Cunha et al., 2006; de Oliveira

et al., 2009; Fernandes et al., 2009; Machado-Vieira et al., 2007). Similarly, there were significant reductions in the BDNF levels among patients with mania (0.26±0.10 pg of BDNF/ug protein) as compared to the healthy controls (0.31±0.05 pg of BDNF/ug protein). Upon treatment, the BDNF levels were significantly increased in patients (0.38±0.14 pg of BDNF/ug protein), suggesting a possible association with the treatment outcome in acute mania (Tramontina et al., 2009).

2.4 Schizophrenia

Schizophrenia is a chronic disabling mental disorder that is manifested with a minimum of two symptoms that last for one or more months (APA, 2013). These symptoms include delusions, hallucinations, disorganized speech and behaviour, and reductions in the ability to maintain social, occupational relationships, and personal hygiene.

Studies associating the *BDNF* rs6265 and schizophrenia yielded inconsistent results; some studies showed a positive association between the Met allele and schizophrenia (Hong, Yu, et al., 2003; Schumacher et al., 2005), whereas others found an association between the Val allele and the disorder (Neves-Pereira et al., 2005; Rosa et al., 2006) (Table 1). In a study on 159 Japanese schizophrenia patients, patients homozygous for Met/Met genotype were significantly associated with an early age of onset of the disorder as compared to patients with Val/Val (p=0.023) (Numata et al., 2006). On the contrary, a study on the Scottish population revealed that schizophrenic patients showed a significantly higher frequency of Val-allele as compared to controls (Neves-Pereira et al., 2005). Findings on the Asian population reported no significant association between *BDNF* rs6265 and schizophrenia (Q. Chen et al., 2006; Hong, Yu, et al., 2003; Tochigi et al., 2006; Watanabe et al., 2006; Zhou et al., 2010) indicating that in the Asian population, *BDNF* rs6265 role may not be significant in the development of the disorder.

It is interesting to note that two meta-analysis studies revealed no significant association between the *BDNF* rs6265 polymorphism and schizophrenia (Xu et al., 2007; Zintzaras, 2007). This observation is further supported by studies conducted on the Chinese population, reporting no significant difference in both the allele and genotype distributions of *BDNF* rs6265 between the cases and controls (Li et al., 2013; Wang et al., 2010; Zhai et al., 2013). In a study on the Asian population, no significant association was found between *BDNF* rs6265 and schizophrenia. However, in the same study, using the single locus, a significant association with schizophrenia has been obtained at the haplotype level whereby the haplotype A-274-C-T was higher in controls as compared to the cases indicating a protective effect against schizophrenia (Qian et al., 2007). On the contrary, a study on the haplotype C-281A (rs28383487) and Val66Met (rs6265) found no association with schizophrenia (Suchanek et al., 2012). Despite the difficulty in obtaining a positive association between *BDNF* rs6265 and schizophrenia, several studies found an association between the Met allele and the age of onset of the disorder and the severity of the clinical symptoms (Numata et al., 2006; Sun et al., 2013; Zakharyan et al., 2011). In a study on 375 schizophrenia patients and 334 healthy controls of the Han Chinese population, no significant difference was observed in the distribution of alleles and genotypes of the three polymorphisms studied. However, when looking at the haplotype level, a significant difference was observed in the patients with the haplotype ATC of rs6265-rs12273539-rs10835210 as compared to controls (p=0.027) (Li et al., 2013). These findings indicate that more studies are required to determine the association of the *BDNF* rs6265 and schizophrenia at the haplotype level.

The effect of the *BDNF* rs625 genotypes and the BDNF level have been studied in schizophrenia. In 103 Armenian schizophrenic patients and 103 healthy controls matched for age and sex, a reduction in the plasma BDNF level was observed among schizophrenic patients treated with antipsychotics and drug naïve schizophrenic patients as compared to controls (antipsychotic treated patients vs healthy controls: 169.7 ± 39.3 pg/ml vs 245.3 ± 30.4 pg/ml; drug naïve patients vs healthy controls: 175.9 ± 13.5 pg/ml vs 245.3 ± 30.4 pg/ml). In the same study, the influence of the *BDNF* rs6265 on the BDNF plasma level was also studied. The subjects with homozygous mutant (Met/Met) and the heterozygous (Val/Met) genotypes displayed a significant reduction in the BDNF level in both the cases and controls as compared to subjects with the wildtype genotype (Val/Val) (cases: 155.8 ± 46.1 pg/ml vs 181.1 ± 28.3 pg/ml; controls: 231.3 ± 22.7 pg/ml vs 268.3 ± 27.5 pg/ml) (Zakharyan & Boyajyan, 2014).

3.0 CONCLUSION

Being one of the most functional and commonly reported single nucleotide polymorphisms in the *BDNF* gene, BDNF has been widely associated with neuropsychiatric disorders. Despite the subtle association between *BDNF* rs6265 and different neuropsychiatric disorders, to date, the results have been inconsistent. The inconsistency may be due to the

different methods, sample sizes, and ethnicities involved in different studies that may contribute to the variation. The need to replicate the association studies on a large sample size to obtain more reliable statistical power is required. For those studies with a positive association, the need to carry more studies at the cellular and animal level is required to obtain a better understanding of the role of this SNP. Also, a limited number of studies associated the SNP to the function and volumes of different brain regions and BDNF levels. Several studies, especially in schizophrenia, did not obtain an association between *BDNF* rs6265 and the disorder at a single locus, but they obtained an association at the haplotype level. Thus, it indicates a need for studies on the association of SNP and neuropsychiatric disorders at the haplotype as well as the genome-wide level. This includes further studies to investigate the effect of the environment and the role of epigenetic regulation of *BDNF* gene expression on the onset and progression of neuropsychiatric disorders.

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