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Research Article

Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism and Obsessive Compulsive Disorder Risk

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Abstract

Brain-Derived Neurotrophic Factor (BDNF) is required for neuron growth and maintenance. Single nucleotide polymorphisms (SNP) are reported in BDNF gene, which reduces proteins activity, Val66Met polymorphism is very well studied and reported as a risk factor for psychiatric diseases. Numerous case-control studies have evaluated the role BDNF Val 66Met (dbSNP: rs6265;196G>A) polymorphism in OCD susceptibility and provided ambiguous findings, hence present meta-analysis was designed to get an exact association between BDNF Val66Met polymorphism and OCD risk. A total of 14 case - control articles were identified through PubMed, Google Scholar, Science Direct and Springer link databases search, up to July 11, 2024. Odds ratios (ORs) with 95% con¬fidence intervals (CIs) were used as association measure. All statistical analyses were done by MetaDiSc (version 1.4).

Fourteen case-control studies involving 2,765 OCD cases and 5,585 controls were included in present meta-analysis. The results showed that the BDNF Val66Met polymorphism was not associated with OCD risk (allele contrast odds ratio OR_{AvsG} = 0.96, 95% CI= 0.82-1.12, p= 0.000; homozygote OR_{AAvsGG} = = 0.79, 95%CI= 0.59-1.06, p= 0.0058; dominant model $OR_{AA+GAvsGG}$ = 0.96, 95%CI= 0.86-1. 06, p= 0.17). In conclusion, the BDNF Val66Met polymorphism was not related to increased OCD susceptibility.

Keywords: Obsessive Compulsive Disorder; BDNF; Val66Met polymorphism; Susceptibility; Neurotrophin

INTRODUCTION

Obsessive compulsive disorder (OCD) is a mental health condition characterized by repetitive intrusive thoughts, images and impulses (obsessions) and repetitive behaviours (compulsions). It is a leading cause of mental disability worldwide [1], with a lifetime prevalence of 1.3 - 2.3% [2,3]. In addition to being associated with significant functional impairment in daily living and quality of life [4,5], OCD has been associated with neurocognitive deficits, as measured using neuropsychological assessment. The average age of onset is around 19 years old. It affects men and women equally, but the onset in males is earlier than in females.

Genome-wide and twin studies reported higher involvement of hereditary factors in OCD [1, 6]. Published studies have reported numerous OCD candidates genes including COMT, SERT, SLC1A1, DLGAP1, PTPRD, NRXN1, HTR2A, CTTNBP2, REEP3 and BDNF [1,6]. BDNF (Brain-Derived Neurotrophic Factor) is a crucial protein belonging to the neurotrophin family, which supports the survival, development, neural plasticity and function of neurons [7 -10]. BDNF helps in the generation of new neurons from neural stem cells in hippocampus. BDNF has been reported to affect the synthesis of neurotransmitters and expression of their receptors. It regulates moods and reduced /altered BDNF expression involved in the pathophysiology of various psychiatric and neurodegenerative disorders, including depression, anxiety, schizophrenia, and bipolar disorder. It is reported very well that antidepressants and other medications up regulate BDNF expression.

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BDNF gene is located at chromosome 11p14.1, spans about 70 kb and has a complex structure, it consists of 11 exons (I–IX, plus Vh and VIIIh), the coding sequence resides only in exon 9, and all upstream exons encode promoters, regulating regional and cell-type-specific expression (Figure 1). The gene contains multiple promoters that allow for tissue-specific and activity-dependent expression of BDNF. BDNF expression is tuned in response to various intrinsic and extrinsic stimuli. Exon IX, encodes precursor-BDNF protein (pre-pro-BDNF; ~ 27 kDa) in endoplasmic reticulum [11].

Several single nucleotide polymorphism are reported in BDNF genes include rs6265, rs11030101, rs12291186, rs7934165, rs11030104, rs1519480, rs8192466, rs539177035, and rs551669106 [12-14]. Val66Met polymorphism is located in exon 9 in which G is substituted by A at 196 position (G196A), resulting in substitution of amino acid valine with methionine at 66th codon (Val66Met). Val66Met alteration affects the activity-dependent secretion of BDNF, which is important for neuronal development, synaptic plasticity, neurogenesis and cognitive function. Val/Val genotype is generally associated with normal BDNF function. Met carriers (Val/Met or Met/Met) is often exhibit reduced activity-dependent BDNF secretion. Imaging and autopsy studies have reported functional and structural alterations in met allele carriers especially in hippocampus and prefrontal cortex regions. BDNF levels are associated with cognitive functions, mood regulation, and overall brain health. Decreased BDNF levels have been linked to cognitive decline and mood disorders such as depression. After knowing clinical implications of Val66Met polymorphism, authors designed and performed meta-analysis of case control studies to shed light on exact association between Val66Met polymorphism and OCD susceptibility.

MATERIALS AND METHODS

Eligible studies were identified by searching Pubmed, Springer link, Science Direct and Google Scholar databases up to July 11, 2024. The following search terms were used: “Brain Derived Neurotrophic Factor” or “BDNF”, and “Val158Met” in combination with “Obsessive compulsive disorder”, or “OCD”. Inclusion criteria for selection of studies were: (i) study should be published, (ii) case control approach was used by authors, and (iii) allele number/ genotypes numbers were reported in the study to calculate OR with 95%CI. Studies were excluded from the meta-analysis if: (i) studies based on pedigree data (ii) study was review, letter to editor or editorial and (iii) other genes variants are analysed in OCD patients.

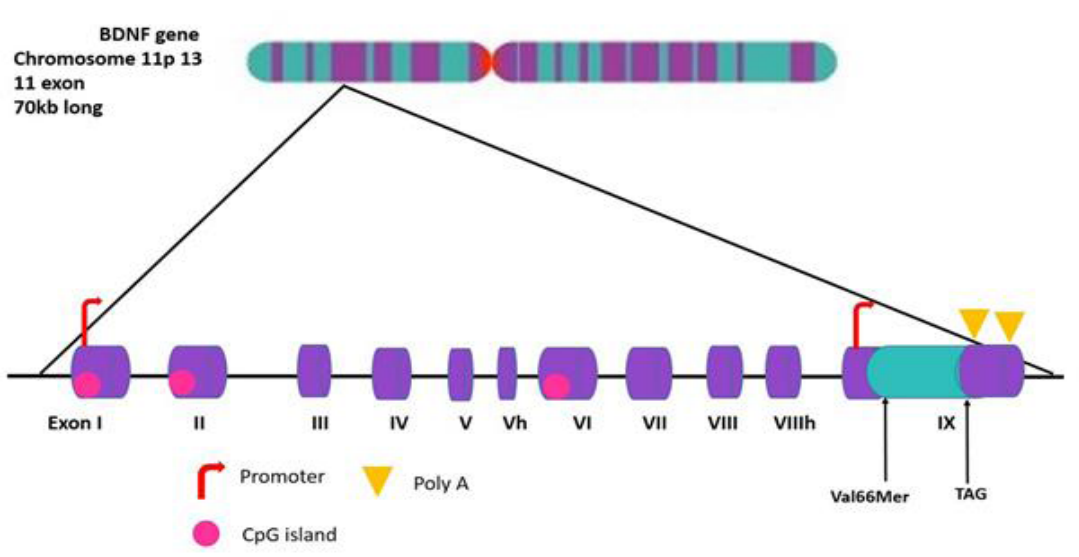

Figure 1 : BDNF gene structure showing Val66Met polymorphism .

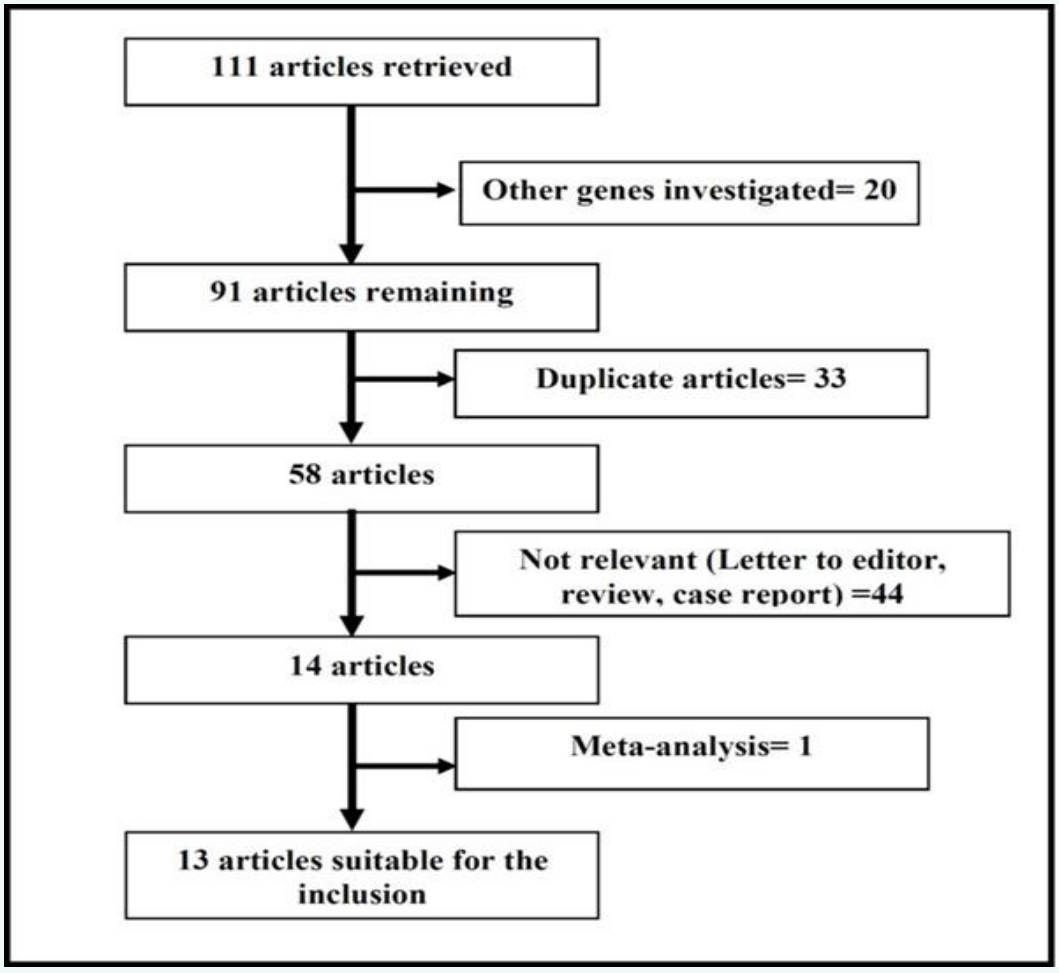

Figure 2 : Flow diagram of article selection

Table 1: Details of included fourteen studies in present meta-analysis

Study	Ethnicity	Country	Case No.	Cont. No.	Case Genotypes			Control Genotypes			Case Alleles		Control Alleles	
					GG	GA	AA	GG	GA	AA	G	A	G	A
Wendland et al., 2007	Caucasian	America	295	657	192	92	11	428	206	23	476	114	1062	252
Hemmings et al., 2008	Caucasian	South Africa	112	170	73	33	6	95	73	2	179	45	263	77
Katerberg et al., 2009 I	Caucasian	South Africa	199	115	128	62	9	76	36	3	318	80	188	42
Katerberg et al., 2009 II	Caucasian	Netherlands	220	535	132	75	13	352	166	17	339	101	870	200
Wang et al., 2009	Asian	China	148	94	31	76	41	24	51	19	138	158	99	89
Da Rocha et al., 2010	Caucasian	Brazil	127	124	83	33	11	95	21	8	199	55	211	37
Tukel et al., 2012	Caucasian	Turkey	100	110	23	54	23	29	51	30	100	100	109	111
Hemmings et al., 2013	Caucasian	South Africa	121	187	85	33	3	131	50	6	203	39	312	62
Liu et al., 2013	Asian	China	190	309	40	107	43	60	167	82	187	193	287	331
Marquez et al., 2013	NS	Mexico	232	283	179	47	6	162	99	22	405	59	423	143
Liu et al., 2015	Asian	China	321	426	101	166	54	110	211	105	368	274	431	421
Wang et al., 2015	Asian	China	148	99	31	76	41	24	54	21	138	158	102	96
Umehara et al., 2016	Asian	Japan	175	2027	59	83	33	686	1002	339	201	149	2374	1680
Taj et al., 2017	Asian	India	377	449	277	91	9	299	133	17	645	109	731	167

The following data was extracted from each included study: (i) first author's family name, (ii) country name and ethnicity, (iii) number of cases and controls and (iv) number of alleles and/or number of genotypes in both cases and controls for recalculation of ORs with 95% CI (Confidence Interval).

Pooled OR with corresponding 95% confidence Interval (CI) was used as association measure to assess the risk between Met allele and OCD susceptibility. A pooled OR was estimated on the basis of the individual ORs. OR was estimated either by using fixed effects [15], or random effects [16], model depending upon heterogeneity (I^2). If I^2 > 50% then random effect model was used. Pooled ORs were calculated using different genetic models, viz.: (i) allelic contrast model (A vs.G), (ii) homozygote model (AA vs. GG), (iii) dominant model (AA+ GA vs. GG), and (iv) recessive model (AA vs. GA+ GG) [17]. Method of Guo et al. [18], was adopted for quality score assessment. The quality scores ranged from 0 to 10 and studies with score <5 was defined as low quality, and studies with score ≥7 was defined as high quality. Meta-analysis was undertaken by free program MetaDiSc (version 1.4), developed by Zamora et al. [19]. All P values are two-tailed with a significance level at 0.05.

RESULTS AND DISCUSSION

After applying inclusion and exclusion criteria, total 13 studies were found to be eligible for present meta-analysis [1,20-31] (Table 1). In one study [22], authors analysed cases from two countries viz.- South Africa and The Netherland, so both samples were included separately in the meta-analysis. Hence, total studies included in current meta-analysis was fourteen. In included meta-analysis, samples with several countries/population were analysed like-America [20], Brazil [24], China [23, 27, 29], India [1], Japan [31], Mexico [28], South Africa [21,26], The Netherlands [22], and Turkey [25] (Table 1).

In total 14 included studies, the number of cases were 2765 and number of controls was 5585. GG, GA and AA genotypes number in cases are 1434, 1028, and 303, respectively. In controls, GG, GA, AA genotypes number were 2571, 2320 and 694, respectively (Table 1) (Figure 3). In cases and controls T allele frequencies were 29.55 % and 33.2%.

Meta-analysis of samples of 14 studies, adopting allele contrast model (A vs. G) showed no significant association with both fixed and random effects models. Higher heterogeneity was observed (I^2= 71.5%), so random effect model was adopted. The random effect pooled $OR_{Avs\ G}$ was 0.96 (95% CI= 0.82-1.12; p= 0.000) and Cochran Q was 45.55 (df = 13; p=0.000). The tau squared is 0.0596 (Figure 4).

Association between OCD and Val66Met polymorphism using homozygote (AA vs GG; homozygote model), was also not found ($OR_{AAvs\ GG}$= 0.79; 95%CI= 0.59-1.06; p= 0.0058; Cochran Q=29.35), higher heterogeneity (I^2=55.7%) was present, so random effect was adopted (Figure 5). Results of meta-analysis using dominant models ($OR_{AA+GAvs\ GG}$= 0.96; 95%CI= 0.86-1. 06; p= 0.17; Cochran Q=15.56; I^2 =25.9) did not show significant association.

Egger's test were performed to estimate the risk of publication bias. Except allele contrast and homozygote model, publication bias was absent (G vs. A: $P_{Egger's\ test}$= 0.03; AG vs. AA: $P_{Egger's\ test}$= 0.29; GG vs. AA: $P_{Egger's\ test}$ P= 0.03; Dominant model GG+AG vs. AA: $P_{Egger's\ test}$= 0.06; Recessive model GG vs. AG+GG: $P_{Egger's\ test}$= 0.05)

It is very well established fact that BDNF is required for overall brain/neuron health and mutation in this gene affects brain activities and modulates moods, hence is reported a risk factor for psychiatric as well as neurodegenerative disorders including anxiety disorders [32], obsessive-compulsive disorder [33], depression [34, 35], bipolar disorder

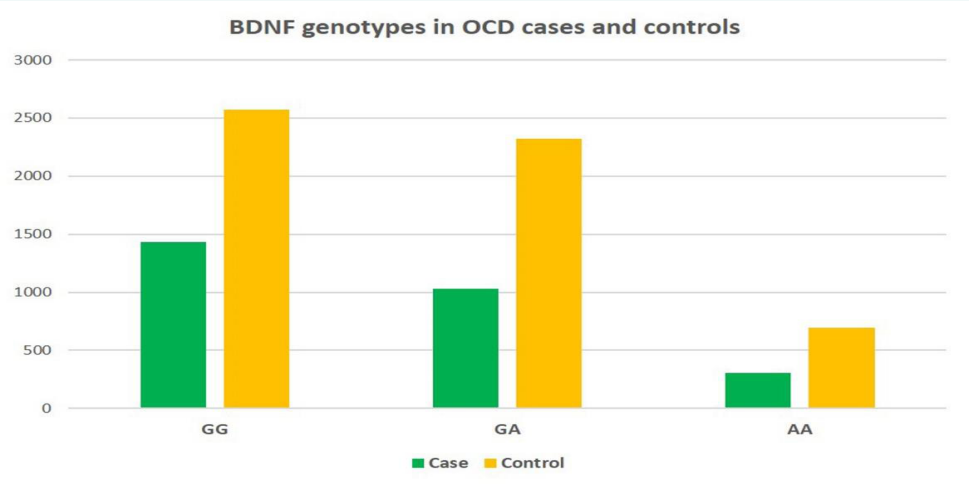

Figure 3 : Bar diagram showing number of GG, GA and AA genotypes in case and control samples of included studies.

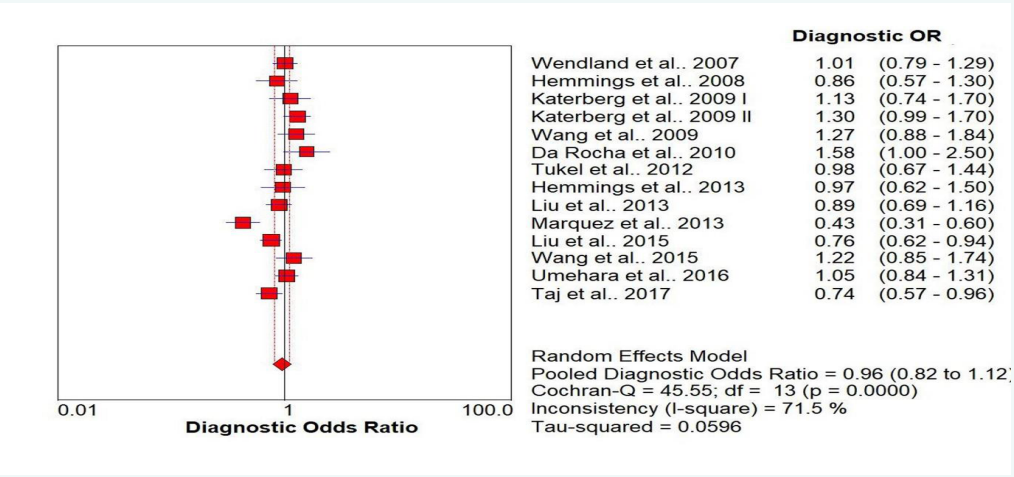

Figure 4 : Allele contrast forest plot adopting random effect model

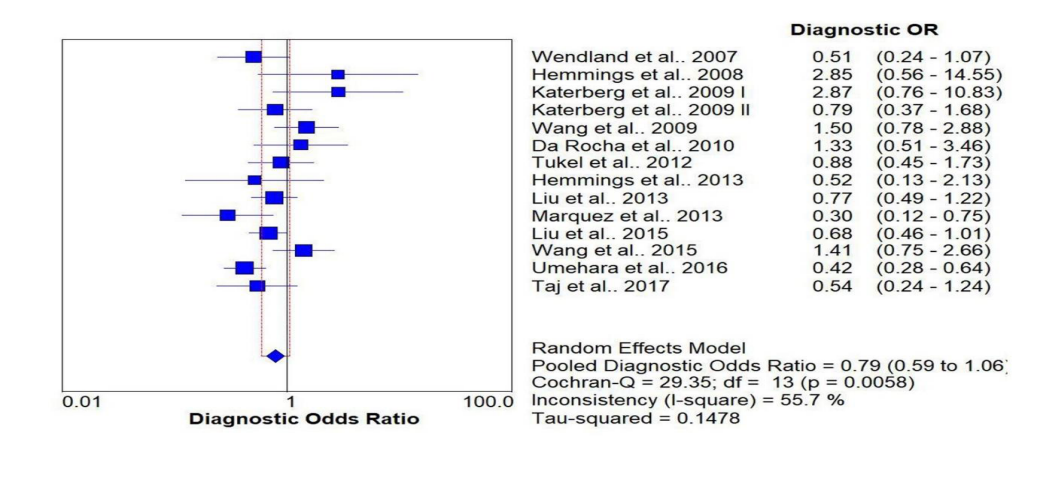

Figure 5 : Homozygote contrast forest plot adopting random effect model.

[34], schizophrenia [34,36], eating disorders [37], as well as alcohol and substance-use disorders [38], Alzheimer's disease [39], Parkinson's disease [40], and multiple sclerosis [41]. The results of present meta-analysis suggested that Met (A) allele is not risk for OCD, instead A/met allele protects against OCD

During past thirty years, meta-analysis is used for summarization and revalidation of results of individual case –control studies. Meta-analysis are continuously published to evaluate disease risk of small effect genes like- tuberculosis [42], Cleft lip and Palate [43], NTD [44], Down syndrome [45-47], Obsessive compulsive disorder [48], depression [49,50], schizophrenia [51], bipolar disorder [52,53], autism [54], alcohol dependence [55-57], migraine [58], epilepsy [59], Alzheimer's disease [60], male infertility [61], osteoporosis [62], recurrent pregnancy loss [63], uterine leiomyoma [64], lung cancer [65], digestive tract cancer [66], breast cancer risk [67,68], esophageal cancer [69], prostate cancer [70-72], endometrial cancer [73], ovary cancer [74], and MTRR [75].

Present meta-analysis had few limitations also, that should also be acknowledged- (i) case sample size is small, (ii) used crude ORs without adjustment, (iii) single BDNF polymorphism is considered and (iv) gene environment interaction is not considered.

In conclusion, the present meta-analysis reported no association between the BDNF Val66Met polymorphism and OCD risk. Met allele is not a risk for OCD, instead plays a protective role. However, due to presence of higher heterogeneity, results should be cautiously interpreted. In future, well-designed meta-analysis considering cofounding factors and gene-environment interactions should be performed to confirm exact associations in different ethnic populations.

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