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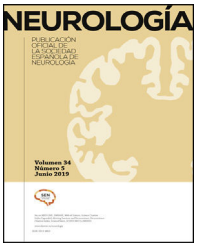

REVIEW ARTICLE

Genetic predisposition of *BDNF* (rs6265) gene is susceptible to Schizophrenia: A prospective study and updated meta-analysis

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KEYWORDS
Schizophrenia;
Genetic polymorphism;
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Abstract
Introduction: Genetic polymorphism in the *BDNF* gene has been found to cause neuronal alterations and has been identified as a causal factor for many neuropsychiatric disorders. Therefore, various neurological case—control studies and meta-analyses have been conducted to find the possible link between *BDNF* and susceptibility to schizophrenia.
Method: This meta-analysis gathered data from 25 case—control studies including a total of 8384 patients with schizophrenia and 8821 controls in order to identify the relationship between the rs6265 single nucleotide polymorphism and the disease, evaluating the combined odds ratio and 95% confidence intervals under 5 different genetic models. Validation followed the ''Leave one out'' method, and we used the Egger test and Begg's funnel plot to identify publication bias.
Results: Research into the rs6265 (G/A) polymorphism revealed a non-significant association with schizophrenia in all 5 genetic models; in the subgroup analysis, no association was found between white and Asian populations, with a p value > .05.
Conclusions: Overall, the updated meta-analysis revealed that rs6265 exonic polymorphisms do not increase susceptibility to this disease. However, to better understand the pathogenesis of the disease, there is a need for further case—control studies into the *BDNF* polymorphism including larger sample sizes and different ethnic groups.

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PALABRAS CLAVE
Esquizofrenia;
Polimorfismo genético;
Metaanálisis;
BDNF;
Trastorno neuropsiquiátrico

Asociación entre el gen *BDNF* (rs6265) y predisposición a la esquizofrenia: estudio prospectivo y metaanálisis actualizado

Resumen
Introducción: Se sabe que los polimorfismos del gen *BDNF* provocan alteraciones neuronales y parecen ser un factor causal en muchos trastornos neuropsiquiátricos. Es por ello que se han llevado a cabo varios metaanálisis y estudios de casos y controles con el objetivo de evaluar la posible relación entre *BDNF* y la esquizofrenia.
Método: Realizamos un metaanálisis de 25 estudios de casos y controles, que incluyó un total de 8.384 pacientes con esquizofrenia y 8.821 controles. Se analizó la relación entre el polimorfismo de nucleótido simple rs6265 y la esquizofrenia mediante odds ratios combinados y sus intervalos de confianza del 95% con 5 modelos genéticos diferentes. Utilizamos el método de validación cruzada dejando uno fuera («leave one out»), la prueba de Egger y el gráfico en embudo de Begg para identificar posibles sesgos de publicación.
Resultados: Los estudios sobre el polimorfismo rs6265 (G/A) muestran una asociación no significativa con la esquizofrenia en los 5 modelos genéticos. En el análisis por subgrupos, no se encontró relación con las poblaciones caucásica y asiática ($p > 0{,}05$).
Conclusiones: La presencia de polimorfismos rs6265 no aumenta la predisposición a desarrollar esquizofrenia. Sin embargo, se deben realizar más estudios de casos y controles sobre polimorfismos de *BDNF*, con muestras más numerosas y con individuos de diferentes grupos étnicos, para comprender mejor los mecanismos patogénicos de la enfermedad.

Introduction

Schizophrenia (SCZ) affects 1% of the world's total population, and it is one of the essential neurologic disorders.[1] The etiopathogenesis of this disease is quite complex and involves the interaction between several genetic and environmental factors.[2,3] Genetic associations and neuropathological studies indicate that the modifications in synapse density cause these variations in the organization of the macroscale connectome in this psychiatric disease.[4–7] Younger adults with this psychiatric condition are prone to age-related diseases, such as diabetes and cardiovascular disease. The age of onset of this disease from early childhood (6 years) to the youngest adults (20 years old), and earlier studies have shown that the mean age of 19 years has an ultra-high risk of this disease.[8] Young SCZ adults are susceptible to aging-related conditions like diabetes mellitus (DM) and cardiovascular diseases (CVD).[9–12] The average life expectancy of the individual with this disease condition is between 15 and 20 years lesser than that of the healthy individual,[13,14] and the patients have 2—12 times the overall age-related mortality rate than the general population.[15–17] GWAS on the genetic association of SCZ has recently been published, and it has been reported that the genes *DRD2, GRM3, GRIN2A, SRR, GRIA1, BDNF, NRG1, COMT*, and *AKT1* are associated with the pathogenesis of this disease.[18] Among these genes, *BDNF* is the most acceptable studied gene to find the relationship and pathogenesis of this disease,[19] and this gene expansion is a brain-derived neurotrophic factor that belongs to the group of neurotrophins on chromosome 11 (11p14.1).[20] It is responsible for various brain development processes such as neuronal development, neurite growth, and neuron survival.[21] Many single nucleotide polymorphisms (SNPs) have been studied to identify the link to schizophrenia.[22–24] A main functional genetic variation was discovered at the molecular level of this gene at codon 66, which leads to the substitution of valine (Val) and methionine (Met). The alteration in neurons and *BDNF* secretion affects the hippocampal brain function due to this polymorphism.[25] rs6265 is also known as Val66Met or G196A. It has been extensively studied in relationship with schizophrenia among Asian, Caucasian, and Mixed populations.[26–28] Many research projects can show results of type I (false positive) and therefore cannot recognize type II (false negative), which makes it challenging to make medical decisions when the data published contain conflicts or tiny sample sizes, which are shown by meta-analysis.[29] We have investigated the relationship between the rs6265 polymorphism and susceptibility to SCZ based on the PRISMA guidelines.[30]

Subjects, materials, and methods

Data sources

Online databases (Google Scholar, Medline, PubMed, PsycINFO, and Embase) were reviewed checked from January 2005 to May 2021 for all case—control studies assessing any genetic variants and schizophrenia in humans. Abstract, letters, and other than English language articles were omitted in this study. The Medical terms and keywords used for the search were schizophrenia or SCZ or *BDNF* or rs6265

Table 1 The characteristics of included studies in the meta-analysis.

Author name	Year	Study region	Ethnicity	Source of DNA	Diagnostic criteria	No. of cases/controls		NOS	Genotyping method
Anttila et al.	2005	Finland	Caucasian	Blood	DSM-IV	94	98	7	RT-PCR
Chen et al.	2006	China	Asian	Blood	DSM-IV	560	576	7	PCR
Chen et al.	2014	Taiwan	Asian	Blood	DSM-IV	151	126	8	PCR
Ho et al.	2006	USA	Caucasian	Blood	DSM-III-R or DSM-IV	293	144	6	PCR
Kawashima et al.	2009	Japan	Asian	NA	DSM-IV	1111	1100	6	NA
Kim	2018	Korea	Asian	Blood	DSM-IV	157	241	6	PCR
Kumar et al.	2020	India	Asian	Blood	DSM IV and ICD10	50	50	6	ARMS-PCR
Li et al.	2013	China	Asian	Blood	DSM-IV	373	318	6	RFLP
Lu et al.	2012	China	Asian	Blood	DSM-IV	112	394	6	NA
Morozova et al.	2021	Russia	Caucasian	Blood	ICD-10	767	655	7	RT-PCR
Naoe et al.	2007	Japan	Asian	Blood	DSM-IV	211	205	7	PCR
Pae et al.	2012	Korea	Asian	Blood	DSM-IV	221	170	6	PCR
Pereira et al.	2005	UK	Caucasian	Blood	DSM-IV	321	350	7	PCR
Qian et al.	2007	China	Asian	Blood	DSM-IV	604	650	6	NA
Ryabokowski et al.	2008	Poland	Caucasian	NA	NA	129	92	7	NA
Sotiropoulou et al.	2013	Greece	Caucasian	Blood	GHQ-28	275	297	6	PCR
Takahashi et al.	2008	Japan	Asian	Blood	ICD-10	33	29	6	PCR
Tochigi et al.	2006	Japan	Asian	Blood	DSM-IV	401	569	6	NA
Watanabe et al.	2006	Japan	Asian	Blood	DSM-IV	349	423	6	NA
Wysiecka et al.	2013	Poland	Caucasian	NA	ICD-10	194	96	6	NA
Yi et al.	2011	China	Asian	Blood	DSM-IV	353	394	6	NA
Zakharyan et al.	2014	Armenia	Asian	Blood	ICD-10, DSM-IV	103	105	6	NA
Zhang et al.	2012	USA	Caucasian	Blood	DSM-IV	441	649	7	NA
Zhang et al.	2018	China	Asian	Blood	DSM-IV-TR Axis I	694	725	6	TaqMan assays
Zhou et al.	2010	China	Asian	Blood	DSM-IV	387	365	7	PCR

NA; not available, PCR; polymerase chain reaction, RT; real-time; NOS; Newcastle Ottawa Scale; RFLP; Restriction Fragment Length Polymorphism, DSM-IV; Diagnostic and Statistical Manual of Mental Disorders-IV, ICD-10; International Classification of Diseases 10th Revision, GHQ-28; General Health Questionnaire-28.

gene polymorphism or Psychosis susceptibility syndrome or mutation or genes or genotype.

Study selection

The research articles were examined on the source of our selection criteria for further procedures. The study includes a case—control design for assessing risk links between *BDNF* polymorphism and SCZ, articles including sample size, allelic and genotypic frequencies were freely accessible, schizophrenic patients diagnosed on the DSM-IV criteria. Therefore, the research performed by cell lines, animal models, state of the art, case report, insufficient genotypic information were excluded.

Data extraction

Two authors (VM and RV) individually obtained the data and variations fixed by a group conversation. The obtained information: author name, year of publication, country of study, population background, source of DNA, sample size (cases/controls), Hardy Weinberg Equilibrium (HWE), NOS score, and genotyping approaches were mined from certain studies (Table 1). Based on the HWE with p-value (<0.05) and NOS, the value of those studies was evaluated. The selection of the study, comparability between the parameters of the study, and study exposure are the three critical features of NOS with a rating of six or more were examined for this study.

Statistical analysis

BDNF genes were selected to identify the significant association with SCZ. The author has selected the SNP rs6265 based on the number of studies available in the electronic database. The risk association was considered by odds ratios (ORs) with a 95% confidence interval (CIs) with p-value (<0.05) under allelic (G vs. A) (G-major, A-minor allele), homozygote (GG vs. AA), heterozygote (GA vs. AA), dominant (GG + GA vs. AA) and recessive (GG vs. GA + AA) genetic models. Q-statistic tests and I^2 values were considered to identify the heterogeneity of the selected SNP.[31] Based on

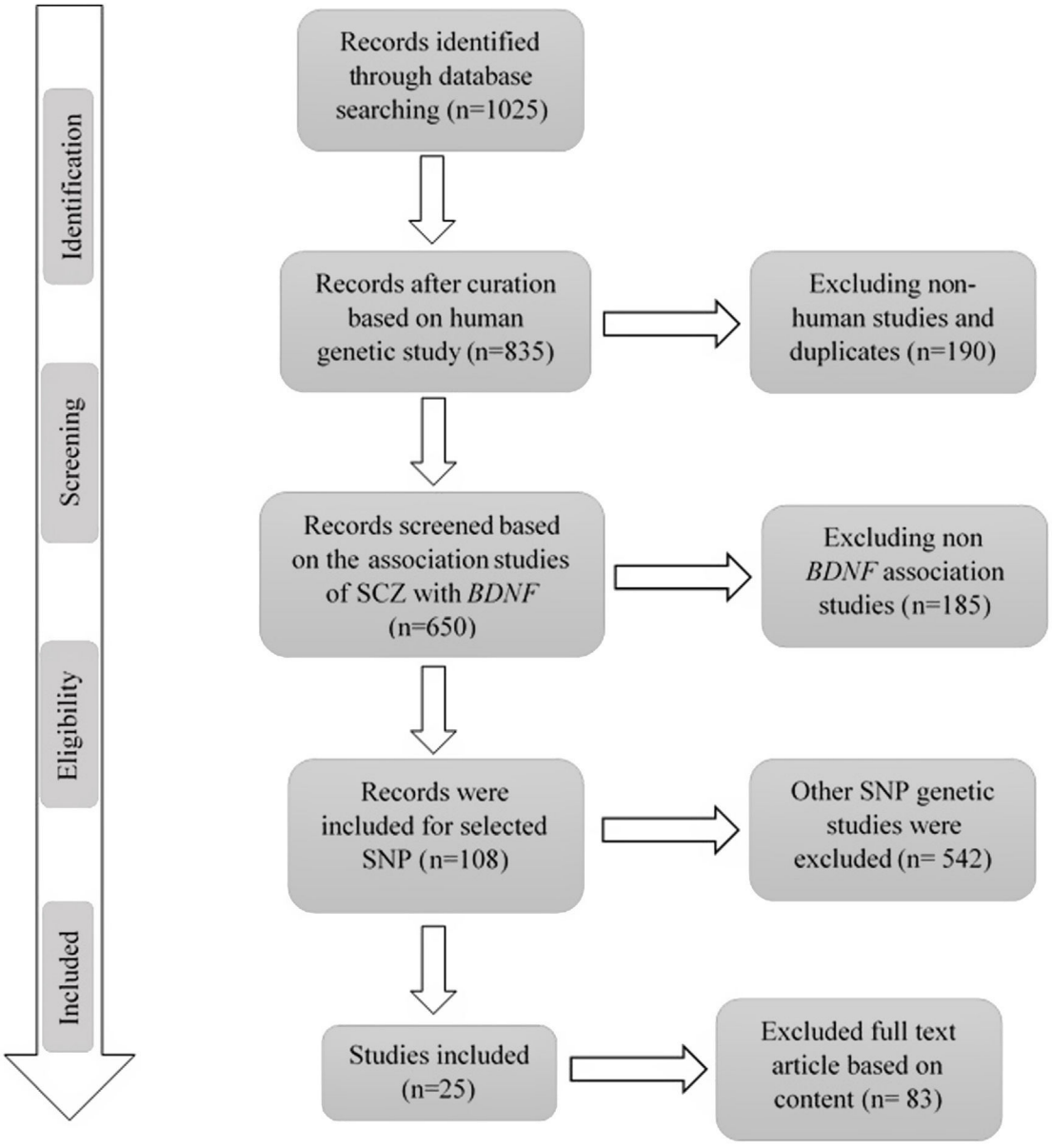

Figure 1 Study flow diagram.

the I^2 value, random-effects (DerSimonian and Laird's) and fixed-effects (Mantel-Haenszel) were implemented.[32] The Begg's funnel plot and Egger's linear test were done to avoid publication bias.[33] The leave one out method was used to confirm the adaptability of this meta-analysis for the sensitivity test: the Rev-Man 5.4 software generated all the statistical meta-analyses, forest plots, and funnel plots.

Results

Literature extraction

835 potentially relevant studies were identified through different databases related to genetic polymorphism in schizophrenia. 650 studies based on abstracts or full study articles were skipped due to irrelevant genetic information. There are 108 possibly eligible articles selected that are related to the objective of this research. The study flow diagram shows that only 25[26–28,34–55] articles were considered based on the eligibility criteria (Fig. 1). All selected studies were evaluated using HWE and NOS. The information obtained from the selected studies is mentioned in Table 2.

BDNF gene polymorphism with SCZ

Meta-analysis of rs6265

The heterogeneity was carried out in this SNP and found the no significance in homozygous, heterozygous and recessive ($I^2 = 0\%$) and moderate I^2 in allelic model ($I^2 = 33\%$) and dominant model ($I^2 = 39\%$) was adopted fixed effect model. The *p*-value (>0.05) exposed irrelevant relationship with

Table 2 Genotypic and allelic frequency of rs6265 polymorphism.

Author name & year	Case			Allelic frequency		Control			Allelic frequency		HWE/Chi
	GG	GA	AA	G	A	GG	GA	AA	G	A	
Anttila et al., 2005	65	26	3	156	32	73	20	5	166	30	0.03/4.43
Chen et al., 2006	157	259	144	573	547	158	291	127	607	545	0.75/0.10
Chen et al., 2014	35	79	37	149	153	38	57	31	133	119	0.29/1.08
Ho et al., 2006	182	100	11	464	122	95	43	6	233	55	0.68/0.16
Kawashima 2009	394	516	201	1304	918	365	529	206	1259	941	0.56/0.34
Kim 2018	45	88	24	178	136	75	123	43	273	209	0.54/0.37
Kumar et al., 2020	29	18	3	76	24	35	12	3	82	18	0.19/1.75
Li et al., 2013	104	187	82	395	351	75	170	73	320	316	0.22/1.52
Lu et al., 2012	27	56	29	110	114	111	193	90	415	373	0.73/0.12
Morozova et al., 2021	566	188	13	1320	214	459	177	19	1095	215	0.69/0.15
Naoe et al., 2007	71	107	33	249	173	77	104	24	258	152	0.21/1.56
Pae et 2012	77	106	38	260	182	58	81	31	197	143	0.77/0.10
Pereira 2005	229	83	9	541	101	208	131	11	547	153	0.07/3.21
Qian et al., 2007	152	312	140	616	592	174	309	167	657	643	0.21/1.57
Ryabokowski 2008	84	34	11	202	56	56	33	3	145	39	0.48/0.50
Sotiropoulou et al., 2013	79	134	62	292	258	84	129	84	297	297	0.02/5.12
Takahashi et al., 2008	12	15	6	39	27	13	11	5	37	21	0.34/0.99
Tochigi et al., 2006	151	185	65	487	315	201	273	95	675	463	0.88/0.02
Watanabe et al., 2006	122	163	64	407	291	142	207	74	491	355	0.92/0.01
Wysiecka et al., 2013	136	51	7	323	65	72	22	2	166	26	0.83/0.04
Yi et al., 2011	93	186	74	372	334	111	193	90	415	373	0.73/0.12
Zakharyan et al., 2014	46	51	6	143	63	68	35	2	171	39	0.30/1.10
Zhang et al., 2012	104	236	101	444	438	175	347	127	697	601	0.05/3.67
Zhang et al., 2018	173	352	169	698	690	217	345	163	779	671	0.24/1.34
Zhou et al., 2010	94	208	85	396	378	91	197	77	379	351	0.12/2.40

HWE; Hardy Weinberg Equilibrium.

SCZ risk in allelic, homozygote, heterozygote, dominant and recessive model shows (OR = 1.01, 95% CI = 0.96—1.05, $z = 0.34$, $p = 0.73$: OR = 1.03, 95% CI = 0.94—1.14, $Z = 0.70$, $p = 0.48$; OR = 1.00, 95% CI = 0.92—1.09, $z = 0$, $p = 1.00$; OR = 1.01, 95% CI = 0.95—1.08, $z = 0.29$, $p = 0.77$; OR = 1.01, 95% CI = 0.93—1.10, $z = 0.26$, $p = 0.80$). The Meta-analysis data was generated as a forest plot shown in Figs. 2—6. In the investigated models, the Egger's test and Begg's funnel plot (Supplementary file 1) were performed to identify the publication bias.

Subgroup investigation of rs6265 polymorphism with SCZ

To analyze the association between the ethnicity and rs6265 polymorphism in SCZ, the authors have done the subgroup analysis by separating the selected studies as Caucasian, Asian and mixed. From a total of 25 studies, it was found that 17 are Asian and 8 have Caucasian ethnic origins. The subgroup analysis of the Asian population revealed no heterogeneity in all the investigated genotypic models {allelic ($I^2 = 10\%$); homozygous, heterozygous, recessive ($I^2 = 0\%$); dominant ($I^2 = 25\%$)}. Hence, the fixed effect was implemented for all the genetic models which showed no relationship in the SCZ with allelic, homozygote, heterozygote, dominant and recessive model shows (OR = 1.02, 95% CI = 0.97—1.08, $z = 0.89$, $p = 0.37$; OR = 1.04, 95% CI = 0.94—1.15, $z = 0.73$, $p = 0.47$; OR = 1.00, 95% CI = 0.91—1.09, $z = 0.10$, $p = 0.92$; OR = 1.01, 95% CI = 0.99—1.04, $z = 1.05$, $p = 0.30$; OR = 1.02, 95% CI = 0.93—1.11, $z = 0.36$, $p = 0.72$).

Likewise, the subgroup analysis of SNP in rs6265 in Caucasian population revealed no heterogeneity in homozygous ($I^2 = 25\%$) and recessive ($I^2 = 29\%$), moderate heterogeneity in heterozygous ($I^2 = 30\%$), substantial heterogeneity in allelic ($I^2 = 55\%$), and dominant ($I^2 = 55\%$). Depend on the I^2 value, the random and fixed effect was applied which revealed insignificant association in the SCZ with allelic, homozygote, heterozygote, dominant and recessive model shows (OR = 0.96, 95% CI = 0.82—1.13, $z = 0.55$, $p = 0.58$, OR = 1.01, 95% CI = 0.80—1.27, $z = 0.09$, $p = 0.93$; OR = 1.02, 95% CI = 0.83—1.27, $z = 0.22$, $p = 0.83$; OR = 0.96, 95% CI = 0.78—1.17, $z = 0.41$, $p = 0.68$; OR = 0.98, 95% CI = 0.80—1.20, $z = 0.18$, $p = 0.86$). The meta-data subgroup analyses were represented as forest plots and Begg's funnel plots (Supplementary file 2).

Sensitivity analysis

The sensitivity test was implemented using the leave-one-out procedure to analyze the influence on pooled ORs of each research. There were no changes in pooled ORs that consistently confirmed our results. In addition, Begg's funnel plot and Egger's test were used to identifying the study's publication bias and conclude that there is no publication

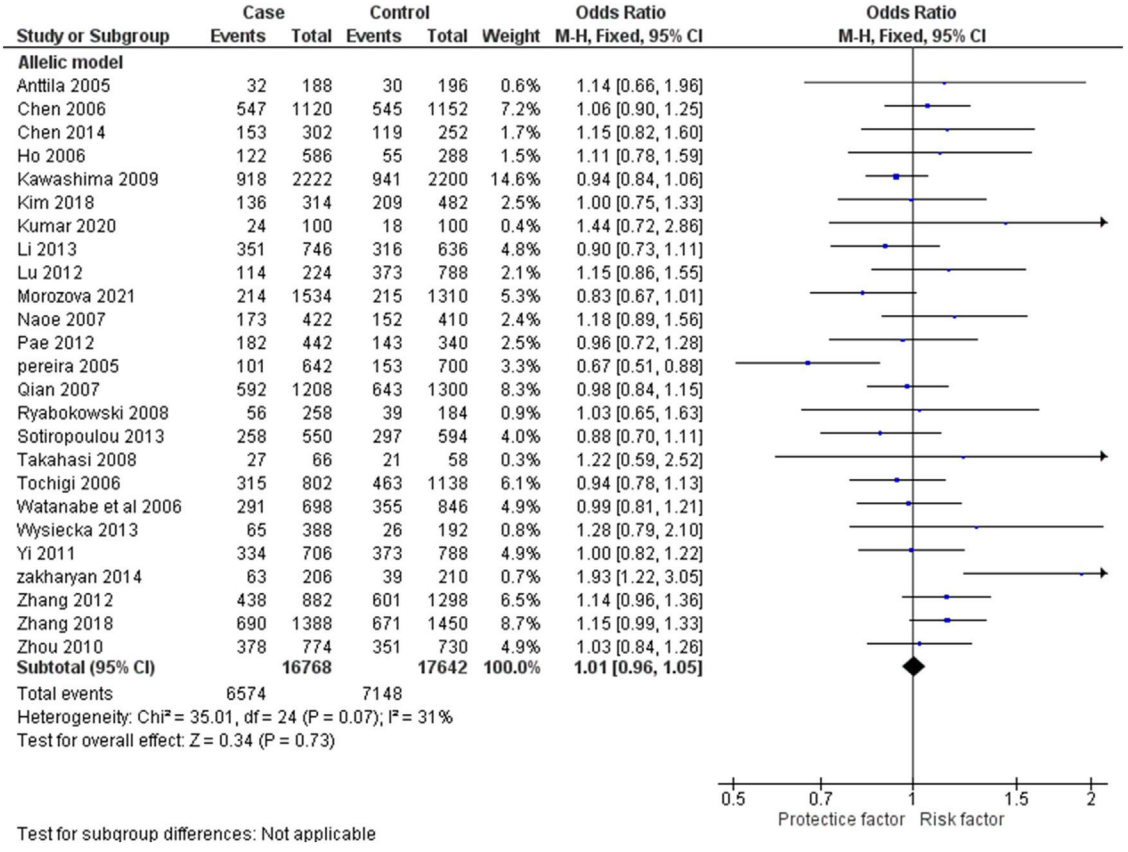

Figure 2 Forest plots representing the overall risk for SNP (rs6265) polymorphism in the allelic model.

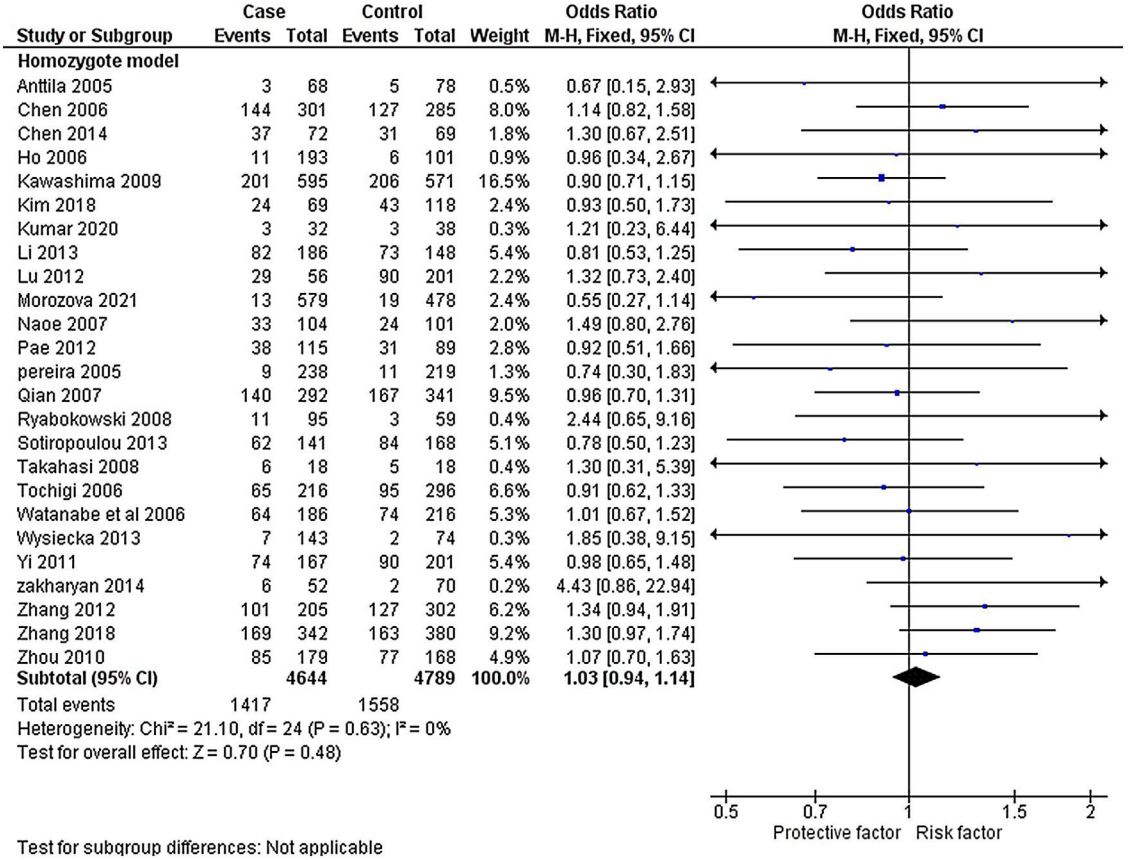

Figure 3 Forest plots representing the overall risk for SNP (rs6265) polymorphism in homozygote model.

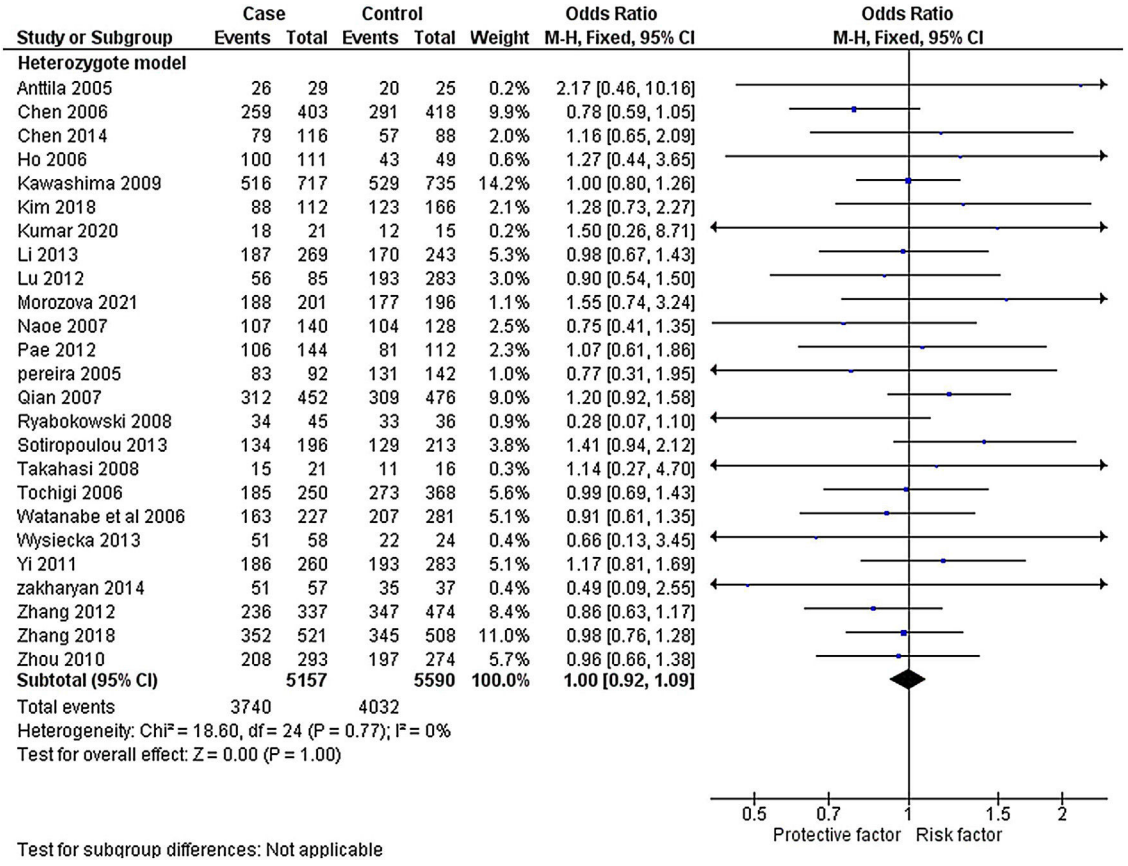

Figure 4 Forest plots representing the overall risk for SNP (rs6265) polymorphism in heterozygote model.

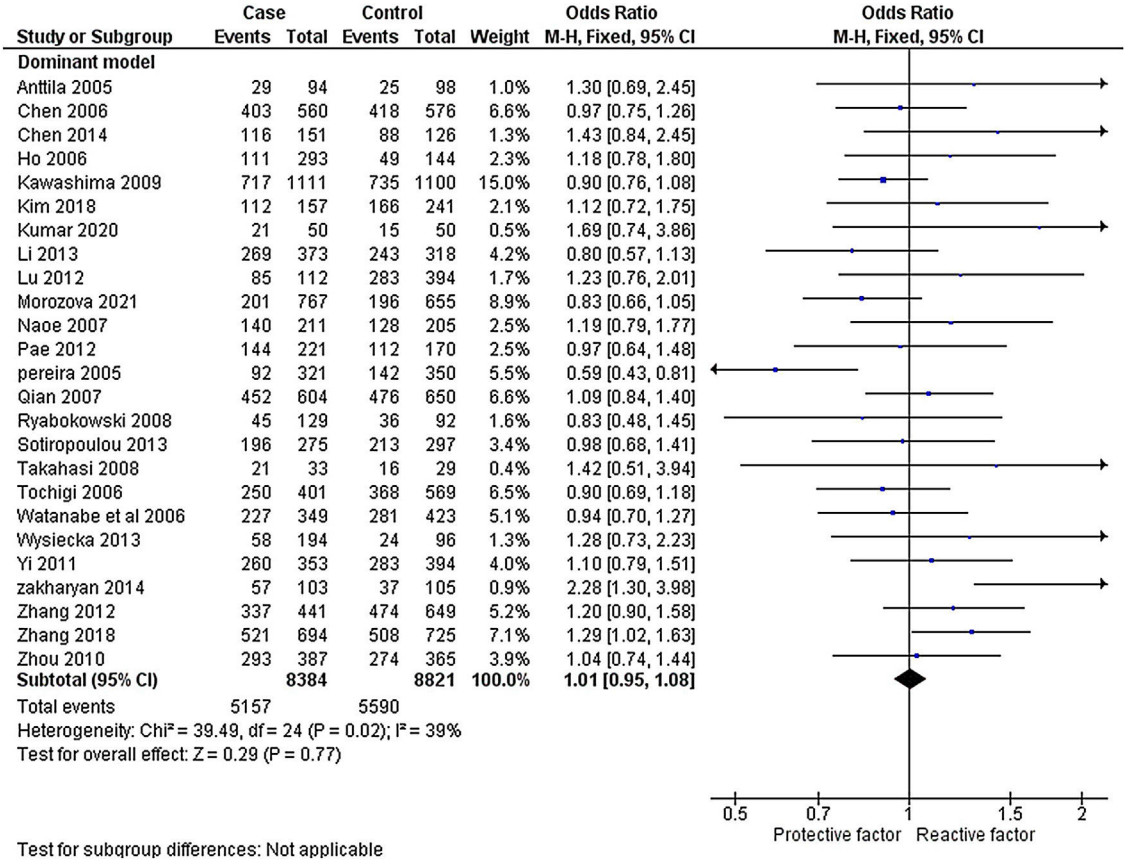

Figure 5 Forest plots representing the overall risk for SNP (rs6265) polymorphism in the dominant model.

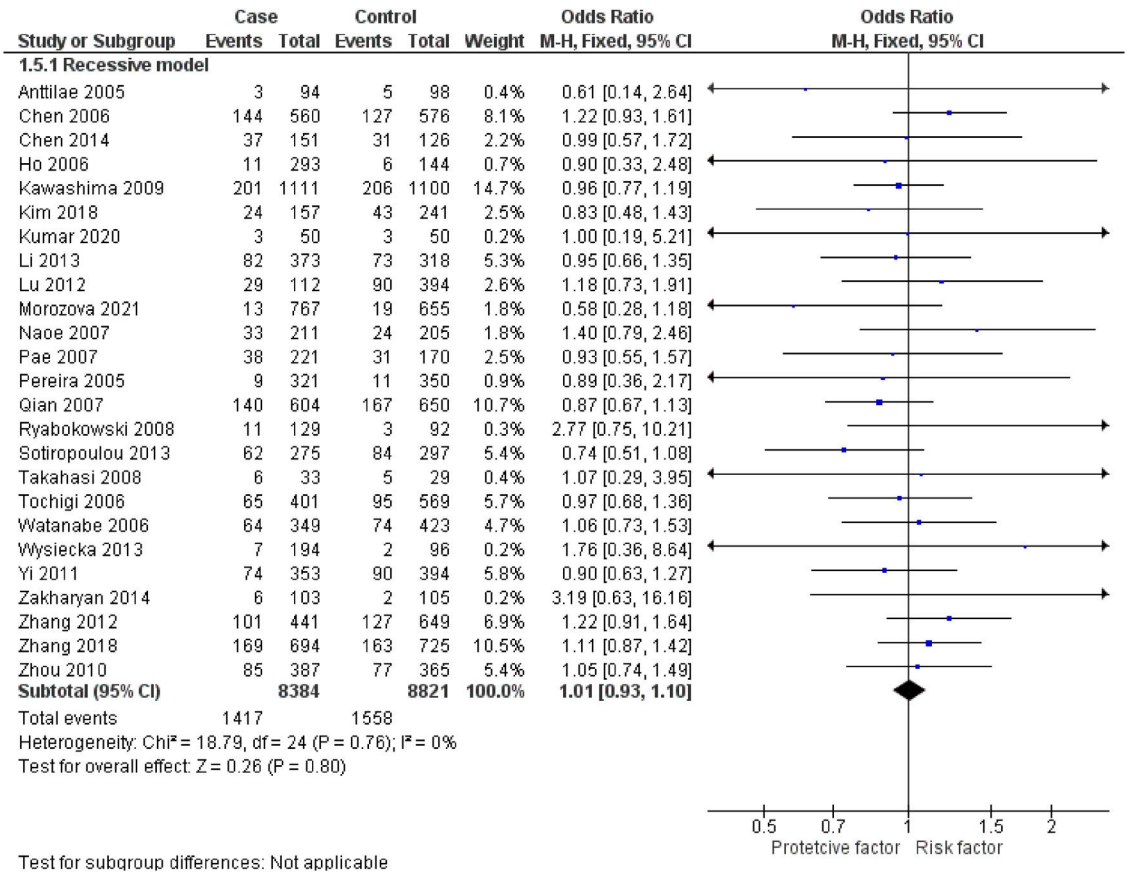

Figure 6 Forest plots representing the overall risk for SNP (rs6265) polymorphism in recessive model.

bias for the investigated polymorphism in any of the genetic models.

Discussion

Schizophrenia is a complex inheritance disease that weakens neurons in the brain, and the symptoms of this neuropsychiatric disorder are delusions, hallucinations, disorganized thoughts, and lack of motivation.[56] The successful investigation of many genes in the last few decades has provided valuable insights into the molecular epidemiology of this disease.[57] Numerous studies on genetic polymorphism found the > 100 schizophrenia-linked loci and revealed that it is a multiple genetic disorder (polygenic) defined by distinct genetic variations but with a small effect size.[58,59] Studies of the association of candidate genes have revealed specific genes that could be assumed to contribute to this psychiatric condition in both functional and positional, such as neuregulin 1 (*NRG1*),[60] brain-derived neurotrophic factor (*BDNF*),[61] catechol-O-methyltransferase (*COMT*)[62] and protein kinase 1 (*AKT1*).[63] The most extensively studied SNP is rs6265 in the *BDNF* gene, which shows the possible association with this disease.[19] Therefore, a *BDNF* meta-analysis of the rs6265 polymorphism was achieved, which can help assess the polymorphism's effect in a larger sample. In addition, through the genotyping testing, it might be helpful to diagnose this disease in the earlier stage. This meta-analysis did the subgroup investigation of Asian and Caucasian ethnic backgrounds that contradict the findings of existing case—control researches.

The meta-analysis of *BDNF* rs6265 genetic alteration showed an inconsistent relationship with all the genetic models with a p-value > 0.05. The subgroup analysis also revealed no association between the selected SNP (rs6265) with schizophrenia in Caucasian and Asian populations. Three studies[34,47,52] investigated the rs6265 polymorphism had insignificant sample sizes, representing probable population classification. The cross-validation was done by the leave one out method, Egger's test, and generating Begg's funnel plot to identify the publication bias. In agreement with our results, earlier meta-analyses have also recommended that *BDNF* rs6265 polymorphism is not associated with SCZ.[19,38,63]

In contrast,[64] study showed a significant association with the heterozygous model (Met/Met carriers) with schizophrenia, and[23] revealed a significant association between Met/Met carriers with Asian, Caucasian, and mixed SCZ populations. However, this study consists of 8384 patients with schizophrenia and 8821 controls (no sign of any psychiatric disorder) for the current meta-analysis. Compared to earlier meta-studies, the sample size is small, but the authors have included the most recently published case—control studies and compared for the same (Kumar et al., 2020, Morozova et al., 2021). The main limitation of this meta-study is that we did not identify the possible relationship between the

rs6265 polymorphism and the heterogeneity of subclinical schizophrenic conditions.

Conclusion

In this meta-analysis, the SNP rs6265 in *BDNF* exposed the irrelevant association with this disease, and the gene is not susceptible to schizophrenia. The collected literature studies might indicate that the role of *BDNF* in several neuropsychiatric disorders, but it is not a functional gene in this disease. More research has been done in the same parameters in the past few decades, but only a few studies have shown the associated results. Therefore, *BDNF* could be a perfect target for this psychiatric condition to diagnose the disease pathogenesis. However, as expected, the results were not obtained in the previous case—control studies due to the lack of research design, inadequate sample size, and ethnic selection. So, in the future, to understand the pathogenesis of this disease through this gene, the researcher should choose a proper ethnic background with larger sample size.

Author's contributions

VM extracted the literature from the database, assessed the allelic and genotypic frequency, done the statistical analysis, and generated the plots.

RV design, revise and corrected the manuscript.

Availability of data and material

Not applicable.

Code availability

Not applicable.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

All authors approved the manuscript for publication.

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Conflict of interest

The authors declare no conflict of interest to report.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.nrl.2021.10.006.

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