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No Association of Genetic Variants in *BDNF* With Major Depression: A Meta- and Gene-Based Analysis

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Abstract

Major depressive disorder (MDD) is a complex psychiatric condition with strong genetic predisposition. The association of MDD with genetic polymorphisms, such as Val66Met (rs6265), in the brain derived neurotrophic factor *(BDNF)*, have been reported in many studies and the results were conflicting. In this study, we performed a systematic literature search and conducted random-effects meta-analysis to evaluate genetic variants in *BDNF* with MDD. A gene-based analysis was also conducted to investigate the cumulative effects of genetic polymorphisms in *BDNF*. A total of 28 studies from 26 published articles were included in our analysis. Meta-analysis yielded an estimated odds ratio (OR) of 0.96 (95% CI: 0.89–1.05; *P*= 0.402) for Val66Met (rs6265), 0.83 (95% CI: 0.67–1.04; *P*= 0.103) for 11757C/G, 1.16 (95% CI: 0.74–1.82; *P*= 0.527) for 270T/C, 1.03 (95% CI: 0.18–5.75; *P*= 0.974) for 712A/G and 0.98 (95% CI: 0.85–1.14; *P*= 0.831) for rs988748. The gene-based analysis indicated that *BDNF* is not associated with MDD (P>0.21). Our updated meta- and novel gene-based analyses provide no evidence of the association of *BDNF* with major depression.

Keywords

major depressive disorder; *BDNF*; polymorphism; meta-analysis; gene-based analysis

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INTRODUCTION

Major depressive disorder (MDD) is a complex psychiatric condition [Sullivan et al., 2000] defined by nearly constant depressed mood and/or anhedonia lasting for weeks [American Psychiatric Association, 2000]. MDD is a huge and growing public health problem around the world [Kessler et al., 2003; Ustun et al., 2004]. Although lifestyle and environmental factors are significant contributors to the etiology of MDD, genetic predisposition has been found to play a strong role [Sullivan et al., 2000]. Elucidating genetic factors involved in the etiology of depression will facilitate the design and implementation of novel treatments for this under-treated and often poorly managed condition.

The brain derived neurotrophic factor (*BDNF*) gene was discovered for the role of its protein product in promoting neuron survival [Hofer and Barde, 1988; Jones and Reichardt, 1990; Maisonpierre et al., 1991]. Investigation into the common genetic variants of the gene in the human population revealed a single nucleotide polymorphism (SNP) that changes the 66th amino acid in the protein from the ancestral valine to methionine (rs6265 or Val66Met). Initial tests for association between MDD and Val66-Met in case control studies were conflicting, with many published reports in favor of the hypothesis [Jiang et al., 2005; Schumacher et al., 2005; Hwang et al., 2006; Iga et al., 2007] and opposed [Hong et al., 2003; Tsai et al., 2003; Oswald et al., 2005; Choi et al., 2006; Surtees et al., 2007; Kim et al., 2008]. The first meta-analyses of this single allele found no net effect of the Val66Met allele [Chen et al., 2008; Lopez-Leon et al., 2008]. Recent genome-wide association studies (GWAS) on MDD also indicate there are no large or consistent effects of any common *BDNF* single-nucleotide polymorphisms [Sullivan et al., 2009; Lewis et al., 2010; Muglia et al., 2010; Shi et al., 2011]. However, new reports continuously emerge suggesting that the Val66Met polymorphism plays a role in processes that might influence prevalence of MDD, such as response rate for common treatments [Kato and Serretti, 2010; Zou et al., 2010].

Meanwhile, a growing number of studies have tested for association of other genetic variants in *BDNF* with MDD. Data has accumulated to make it possible to conduct meta-analyses on some minor variants with modest prevalence in the population. This also makes it possible to pool the effects of multiple SNPs for a gene-based analysis [Neale and Sham, 2004]. Thus, we conducted an updated meta-analysis of the Val66Met polymorphisms and other genetic variants in *BDNF* gene, and also performed a gene-based analysis to examine the cumulative association of *BDNF* with MDD.

METHODS

Search Strategy

We did an extensive literature search in July 2012 in MEDLINE, Cochrane Library and Web of Science for studies on the association of genetic variants in *BDNF* with major depressive disorder. Search terms included “major depression,” “depressive disorder,” “genetic variant,” “polymorphism,” “brain-derived neurotrophic factor,” and “*BDNF*.” References of all relevant publications were also hand searched for additional studies missed by the database search.

Inclusion Criteria

Studies were included in our analysis if they met the following criteria: (1) studies on human subjects; (2) outcome measures include major depression; and (3) case–control studies reporting genotype or allele frequencies of individual SNPs in *BNDF* of subjects with MDD and non-depressed controls. Case status was defined as having diagnosis of MDD assessed by psychiatric interviews. We include studies of any ethnic group or any age category. We did not include subsyndromal depression in our analysis. Case only studies were excluded,

as well as studies only reporting the effect of *BDNF* genetic variants on depression-related phenotypes, such as anxiety or anti-depressant treatments. We did not specify Hardy–Weinberg equilibrium as an inclusion criterion. All potentially relevant publications were retrieved and evaluated for inclusion. Only studies published in the English language were included. Two authors (W.Y. and J.Y.) performed the search independently. Disagreement over eligibility of a study was resolved by discussion until a consensus was reached.

Data Extraction

Reviewers (W.Y. and J.Y.) independently extracted the following data according to a pre-specified protocol: first author's name, year of publication, characteristics (sample size, age, and prevalence of MDD) of the study populations, criteria for diagnosing MDD, genotype data for subjects with MDD and controls. No efforts were made to contact the authors for additional information. Extracted data were entered into a computerized spreadsheet for analysis and compared between reviewers. Discrepancies were resolved by discussion.

Statistical Analysis

Odds ratio (OR) was used as a measure of the association of the genetic variants in *BDNF* with MDD. In the presence of heterogeneity among the studies, we used random-effects models to calculate the OR and the corresponding 95% confidence interval (CI); otherwise, a fixed-effect model was used. The Z-test was used to calculate the *P*-value of the overall effect for the meta-analysis. We used a forest plot to graphically present the calculated pooled ORs and the 95% CIs. Each study was represented by a square in the plot, and the area of the square is proportional to the weight of the study. In the random-effects meta-analysis, we used the inverse of the variance of each study as the weight for the study. The overall effect from meta-analysis is represented by a diamond, with its width representing the 95% CI for the estimate. We used a Chisquared heterogeneity test for assessment of between-study heterogeneity. Publication bias was assessed visually using a funnel plot and tested with Egger's regression test [Egger et al., 1997].

In order to assess the overall association of *BDNF* with MDD, we conducted a gene-based analysis using the *P*-values of the association of genetic variants in *BDNF* with MDD calculated from published literature and from our meta-analysis. We used four popular *P*-value combination methods to assess this association: the Fisher's method, [Fisher, 1932] the Simes method, [Simes, 1986] the modified inverse normal method [Hartung, 1999] and the truncated product method (TPM) [Zaykin et al., 2002; Sheng and Yang, 2012]. To deal with differences in sample size in studies assessing the association of each individual SNP, we calculated unweighted and weighted TPM. Un-weighted TPM disregards the difference in sample size and weighted TPM employs the sample size as its weight, allowing studies with larger sample size to play a larger role in the calculation [Zaykin et al., 2002] A detailed description of the four methods was reported elsewhere [Sheng and Yang, 2012; Wang et al., 2012a]. Because these *P*-values are most likely to be dependent, we used 100,000 simulations to estimate the *P*-value for TPM.

Meta-analysis was performed using Stata 11.2 (StataCorp LP, College Station, TX). All the other analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC) and Matlab 7.10.0.499 (The MathWorks, Inc., Natick, MA).

RESULTS

Literature Search and Eligible Studies

Figure 1 is the flow diagram showing the process of selection of studies included in our analysis. Using our pre-defined search strategy, we identified a total of 193 potential studies

through our initial search. After screening of the abstracts of these studies, 113 were excluded either because they were irrelevant,the study was not about human subjects, or the record was a duplicate search result. The remaining 80 studies were retrieved for more detailed evaluations, which excluded an additional 55 studies because no sufficient genotype data were reported, the outcome of interest is not MDD or a review or meta-analysis study, leaving 25 potentially relevant papers (total studies = 26) to be included in our analysis. A further review of the references of these studies and review article identified one more article with two studies. As a result, a total of 28 studies from 26 articles met the eligibility criteria and were included in our analyses [Hong et al., 2003; Tsai et al., 2003; Oswald et al., 2005; Schumacher et al., 2005; Choi et al., 2006; Hwang et al., 2006; Anttila et al., 2007; Frodl et al., 2007; Iga et al., 2007; Ribeiro et al., 2007; Surtees et al., 2007; Enoch et al., 2008; Gratacos et al., 2008; Taylor et al., 2008; Chi et al., 2010, 2011; Kim et al., 2010; Ozan et al., 2010; Zhang et al., 2010; Chen et al., 2011; Cole et al., 2011; Kanellopoulos et al., 2011; Sun et al., 2011; Pae et al., 2012; Quinn et al., 2012; Wang et al., 2012b].

All qualified articles included in this study were published since 2003 and had sample sizes ranging from 38 to 7,173 participants (Table I). Prevalence of MDD ranges from 6% to 72%. Of these 28 studies, 23 reported a summary of genotype data for Val66Met, three studies for 11757C/G [Oswald et al., 2005; Chen et al., 2011], and two studies for 270T/C [Chen et al., 2011; Sun et al., 2011], 712A/G [Chen et al., 2011; Sun et al., 2011] and rs988748 [Oswald et al., 2005], respectively, and they were included in the corresponding meta-analysis for each of the five SNPs (Tables II and III). In addition to these five SNPs, three other studies also reported summaries of genotype data of a total of 12 other SNPs in *BDNF* [Gratacos et al., 2008; Zhang et al., 2010; Pae et al., 2012]. We computed the association of these SNPs with MDD and the results were included in our gene-based analysis. Different genetic models were used in the calculation of the association of genetic variants in *BDNF* with MDD. For simplicity, we only report the results of minor allele versus major allele. Results for other genetic comparisons show a similar pattern (Fig. 2).

Assessment of Publication Bias

Both funnel plot and Egger's test were used to assess publication bias (Fig. 3). The funnel plot for the meta-analysis of Val66Met seems symmetrical, suggesting no evidence of publication bias. Egger's test also shows no publication bias (α=−0.38, 95% CI: −1.99, 1.23; P=0.63). There was significant publication bias for the metaanalysis of 11757C/G (α = −4.79, 95% CI: −6.95, −2.63; P = 0.023). The Egger's test was not available for meta-analysis of 270T/C, 712A/G and rs988748 due to too few studies.

Association of Individual SNPs With MDD

Twenty-three studies provided summaries of genotype data of Val66Met (minor allele vs. major allele). Random-effects metaanalysis indicates no association of the SNP with MDD (OR = 0.96 for Met vs. Val; 95% CI: 0.89–1.05; P = 0.402), (Fig. 2b, Table II). There was significant between-study heterogeneity (χ^2 =35.26, P=0.036).

Three studies provided summaries of genotype data of 11757C/G with MDD [Oswald et al., 2005; Chen et al., 2011]. Fixed-effect meta-analysis gives an estimated odds ratio of 0.83 (95% CI: 0.67–1.04; P= 0.103), indicating no significant association with MDD (Table III). There was no significant between-study heterogeneity (χ^2 = 1.76, P=0.415).

Two studies provided summaries of genotype data of 270T/C [Chen et al., 2011; Sun et al, 2011]. Fixed-effect meta-analysis gives an estimated odds ratio of 1.16 (95% CI: 0.74–1.82; P= 0.527), indicating no significant association with MDD (Table III). There was no significant between-study heterogeneity (χ^2 = 0.43, P=0.515).

Two studies provided summaries of genotype data of 712A/G [Chen et al., 2011;Sun et al., 2011]. Random-effects meta-analysis gives an estimated odds ratio of 1.03 (95% CI: 0.18–5.75; $P = 0.974$), indicating no significant association with MDD (Table III). There was significant between-study heterogeneity ($\chi^2 = 7.22$, $P = 0.007$).

Two studies provided summaries of genotype data of rs988748 with MDD [Oswald et al., 2005]. Fixed-effect meta-analysis gives an estimated odds ratio of 0.98 (95% CI: 0.85–1.14; $P = 0.831$), indicating no association with MDD (Table III). There was no significant between-study heterogeneity ($\chi^2 = 0.51$, $P = 0.474$).

In addition to the above five SNPs, three other studies [Gratacos et al., 2008; Zhang et al., 2010; Pae et al., 2012] reported genotype information of 12 additional SNPs in *BDNF*. We calculated the association (minor allele vs. major allele) of these SNPs with MDD and summarized them in Table IV with results from the meta-analyses.

Gene-Based Analysis

Using the P-values obtained above; we performed a gene-based association study to examine the cumulative association of these genetic variants with MDD. All the methods indicate no significant association of *BDNF* with MDD (all $P > 0.21$; Table V). We examined whether the association between *BDNF* and MDD was influenced by Val66Met, the most widely reported genetic variant in *BDNF*. After removing this SNP, the gene-based association did not change dramatically (all $P > 0.19$; Table V).

DISCUSSION

In this article, we did a systematic literature search of studies on the association between genetic variants in *BDNF* and MDD. Out of the five individual SNPs evaluated, our meta-analyses found no significant association of genetic polymorphisms in *BDNF* with major depression. Gene-based analysis also indicates that *BDNF* shows no significant cumulative association with MDD. To the best of our knowledge, this is the first study on the association of polymorphisms in *BDNF* with MDD through a gene-based approach.

Most studies on the effect of genetic polymorphisms in *BDNF* on MDD focus on Val66Met, with conflicting results being reported. Among the 23 studies on Val66Met, only three studies show significant association of this SNP with MDD, with one study [Sun et al., 2011] showing marginal association (OR = .77,95% CI: 0.60–0.99; $P = 0.039$) and two other studies [Hwang et al, 2006; Ribeiro et al, 2007] reporting stronger association (both $P < 0.006$) but in different directions. All other studies fail to detect a significant association. Similarly, the study by Sun et al. [2011] found a significant association of 712A/G with MDD in 548 participants in China (OR = 2.28, 95% CI: 1.40–3.71; $P = 9.57 \times 10^{-4}$). However, a study by Chen et al. [2011] failed to detect a strong association in 483 participants in China (OR = 0.39; 95% CI: 0.12–1.28; $P = 0.121$). It is unclear what factors contribute to the conflicting results reported in these studies. Differences in genetic structure, sample size, gender distribution and definition and measurement of MDD might contribute to the disparity in results. Of course, other factors, such as environment and diet, might play roles in these differences as well.

It appears that *BDNF*'s status as a candidate gene for MDD risk is waning. The hypothesis that genetic variants in the *BDNF* gene are associated with risk of MDD emerged from studies in animal models suggesting functional relationships between *BDNF* and stressful experiences [Smith et al., 1995] and antidepressant treatment response [Nibuya et al., 1995]. In vitro studies suggested that theVal66Met polymorphism could influence the function of *BDNF* in neurons [Egan et al., 2003; Chen et al., 2004], and in early candidate gene studies

was associated with reduced hippocampal size, [Pezawas et al., 2004] which is a neurological feature believed to be shared with MDD [Videbech and Ravnkilde, 2004]. However, new experimental evidence has emerged indicating *BDNF*'s effect in brain regions outside the hippocampus plays opposing roles in anxiety and depression that could directly counteract and thus nullify *BDNF*'s overall role in MDD [Groves, 2007].

The meta-analyses to date, including our own, indicate that the initial reports of a main effect of Val66Met on MDD were probably false positives. The issue of heterogeneity between studies could be mediated by a variety of factors, but the possibility remains that the Val66Met does influence depression risk by certain mechanisms that remain unclear. The Val66Met knock-in mouse model appears to confirm a role of this genetic variant in certain aspects of anxietylike behavior [Chen et al., 2006; Spencer et al., 2010]. However, when findings in mutant mice do not necessarily translate between strains of the same species [Phillips et al., 1999], it remains difficult to interpret how these particular findings—even for a knock-in of the human mutation—are directly relevant to the human condition.

In our meta-analysis, we performed tests for publication bias where a sufficient number of observations were available. However, in three out of the five SNPs used in meta-analyses and in the 12 additional SNPs also included in the gene-based analysis, we could not test for or rule out publication bias. This might lead to bias in the resulting meta-analytic data influencing the validity of the overall gene-based analysis. In two out of the five meta-analyses, we found significant between-study heterogeneities (meta-analysis of Val66-Met and 712A/G). The heterogeneity can be due to various clinical and methodological factors. For example, diagnostic criteria for MDD vary across studies (Table I). Variation in the accuracy and sensitivity of these approaches can lead to differences in the estimation of the effects [Glasziou and Sanders, 2002]. Differences in the study designs can also contribute to the heterogeneity between studies. For example, some studies used age and sex-matched controls [Ribeiro et al., 2007], while most other studies did not match by age and sex in recruiting non-depressed controls. Some studies recruited elderly or geriatric MDD participants [Taylor et al., 2008], while many other studies did not consider age as an inclusion criterion in recruiting. To handle the heterogeneity between the studies, we used random-effects meta-analyses when statistical analysis indicates the presence of heterogeneity.

Future gene-based analyses on increasingly large and well-characterized groups of people needs to consider pooling individuals based on alleles that confer dramatic reductions or complete absence of *BDNF* protein to test for effects of the most extreme variants in functional signaling of this conserved protein. But considering that MDD is a highly complex disorder and *BDNF* is part of redundant signaling network regulated by multiple negative feedback pathways, there is much less reason to expect a substantial main effect in population-level analyses [McClearn 2006; Plomin et al., 2010]. To be considered trustworthy, follow-up work probably needs to await the availability of sequence data from a very large number of MDD phenotyped subjects.

This study has some limitations. First, although the meta-analysis of Val66Met involves a large number of studies, the number of studies involved in the meta-analysis of other genetic variants in *BDNF* is relatively small, due to limited availability of published results. Moreover, we could only perform meta-analysis for five SNPs in *BDNF*. The association of the remaining 12 SNPs was based on the results from single studies. We expect that a more accurate estimation of the cumulative association of *BDNF* with MDD could be obtained when more studies become available. Second, the definition of MDD is not consistent across the studies for the meta- and gene-based analyses (Table I). Third, due to limited data, we did not stratify analysis by ethnicity and gender. A recent meta-analysis found no significant

association of Val66Met in the total sample, nor in a stratified analysis by ethnicity (Asian vs. Caucasian), but did detect a significant effect of this genetic polymorphism in men, [Verhagen et al., 2010] perhaps due to the gender-related differences in the etiology of MDD. Future studies on the effects of genetic polymorphisms in *BDNF* should take into account gender and/or ethnicity differences, including planned analyses of sex by gene interactions and similar tests for empirically observed genetic stratification in the populations. Fourth, due to lack of consistently available information on comorbidities of MDD, we were unable to control for them in our analyses, which might influence the conclusions of this study.

In summary, we conducted a systematic literature search and performed meta- and gene-based analyses to assess the association of genetic variants in *BDNF* with major depressive disorder. Our updated meta-analysis and novel gene-based analysis did not detect any SNP in *BDNF* showing significant association with MDD. The gene-based analysis indicated that, based on current evidence from published studies, the cumulative effect of polymorphisms in *BDNF* is not significantly associated with MDD. Further investigation is warranted on the association between genetic polymorphisms in *BDNF* with MDD, particularly studies with larger sample size that resequence the gene to fully evaluate rare variants while taking into account potential interactions between gender and ethnicity.

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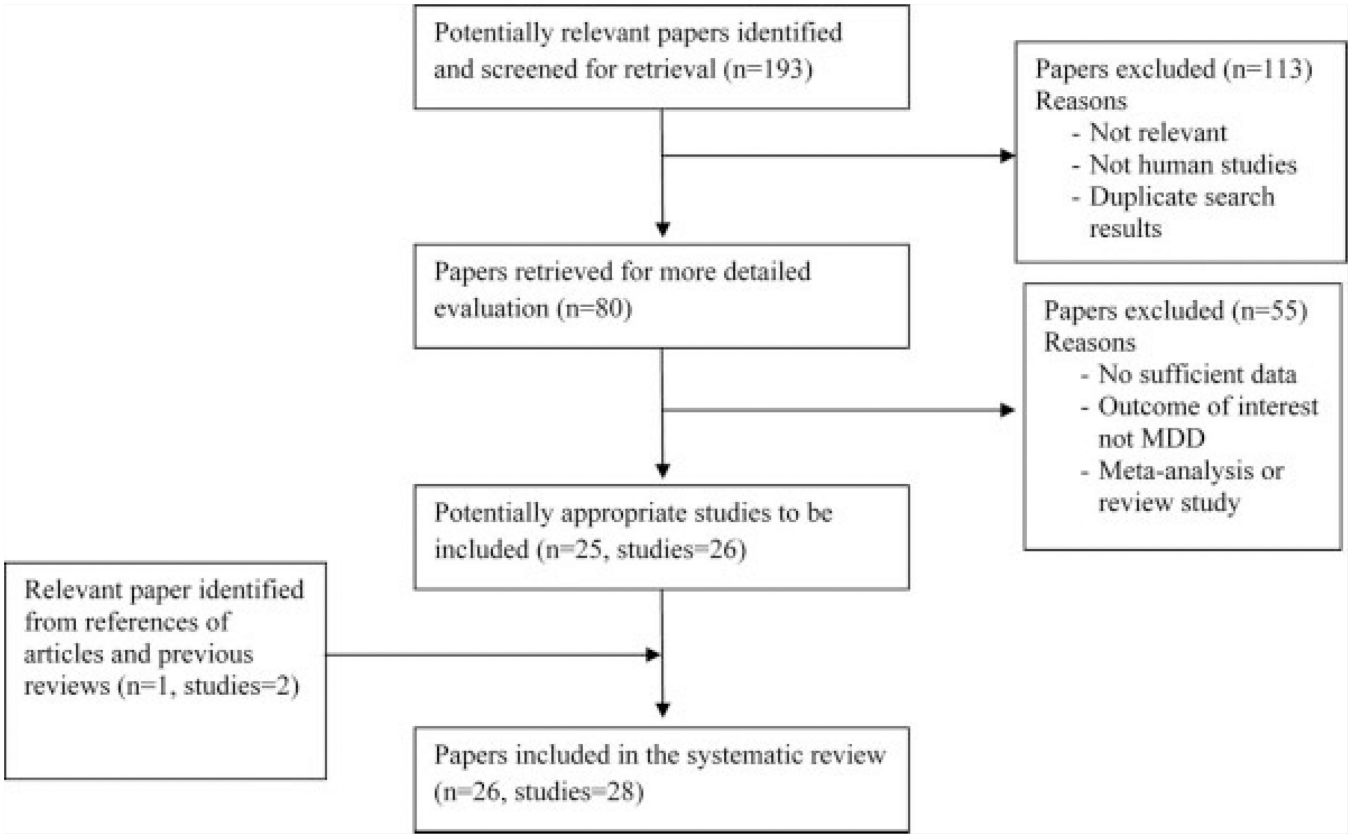

FIG. 1.
Flow diagram of studies included in the systematic review

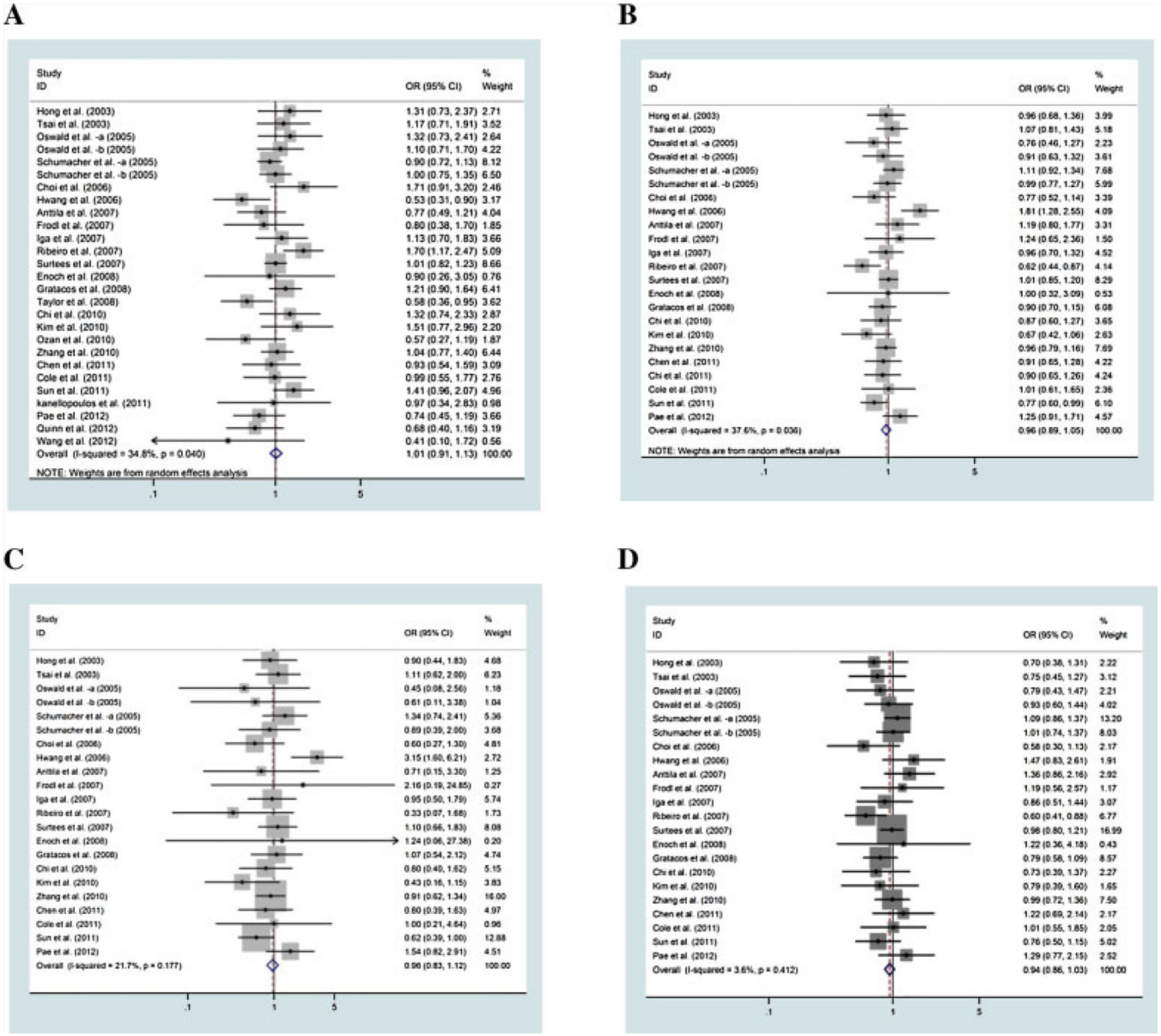

FIG. 2.

Odds ratios of Val66Met (rs6265) with major depressive disorder (A: Val/val vs. met;B:Met vs. val; C: Met/met vs. val/val; D:Met/val vs. val/val).

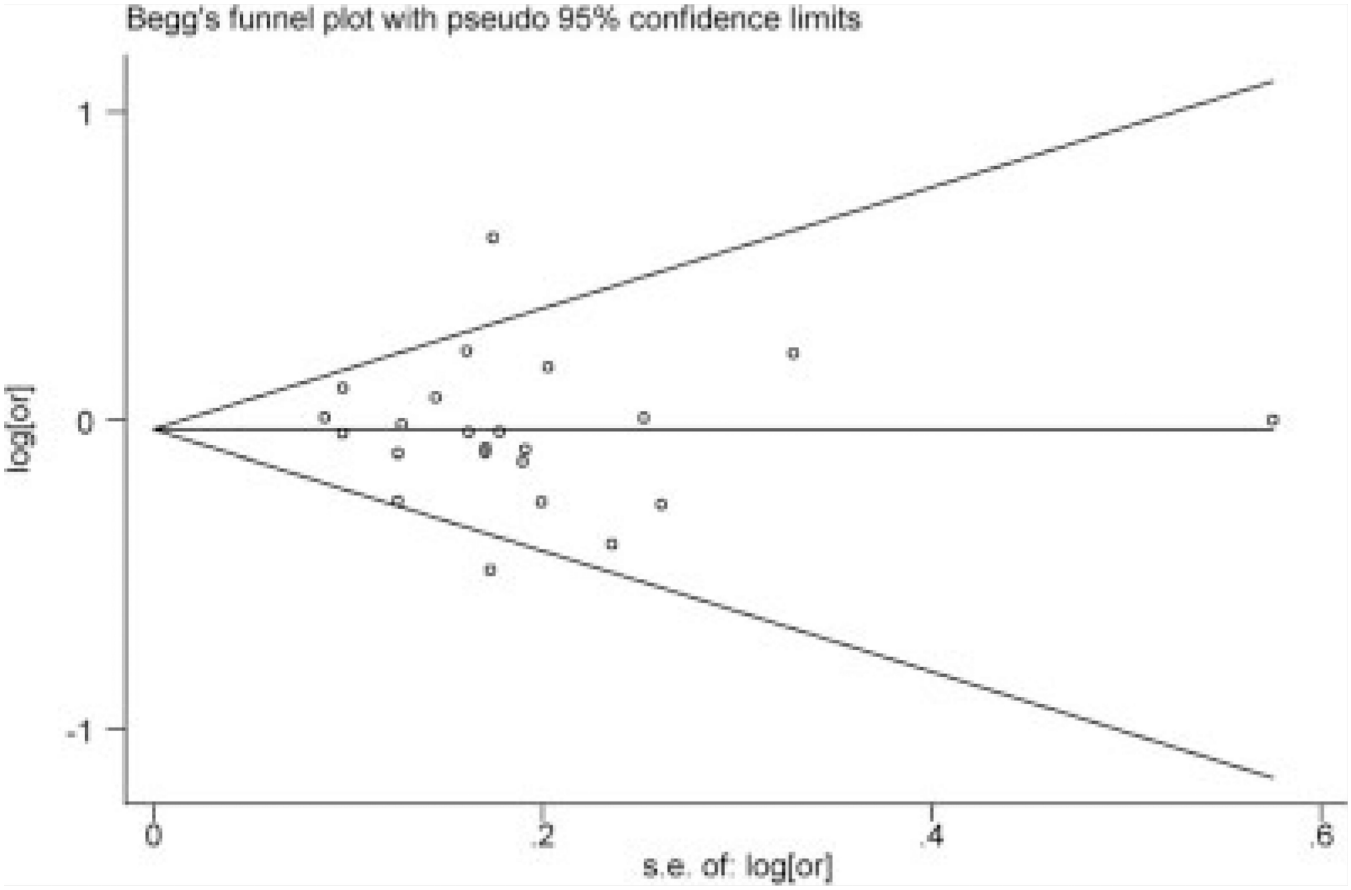

FIG. 3.
Funnel plot for meta-analysis of Val66Met.

TABLE 1

Basic Characteristics of All Studies

	MDD		Control			
Study (author, year)	**n**	**Mean age**	**n**	**Mean age**	**Definition of MDD**	**Diagnosis method**
Wang et al. [2012a, b]	18	NA	20	NA	DSM-IV	—
Quinn et al. [2012]	128	40.1	128	40.1	DSM-IV	Structured interview using MINI by research officers trained and supervised by psychiatrists
Pae et al. [2012]	145	41.4 ±14.1	170	38.8 ±12.8	DSM-IV	Using MINI
Chi et al. [2011]	198	40.7 ±14.2	106	34.0 ±12.7	DSM-IV	Structured interview by experienced psychiatrists using MINI
Cole et al. [2011]	84	33.0±9.2	111	48.8 ±8.9	DSM-IV	Structured interview using SCAN
Chen et al. [2011]	83	57.9 ± 11.1	400	64.5 ±5.8	DSM-IV	—
Kanellopoulos et al. [2011]	33	72.3	23	70.9	DSM-IV	Structured interview
Sun et al. [2011]	202	NA	346	NA	DSM-IV	Structured interview by two psychiatrists
Chi et al. [2010]	117	36.2 ±12.6	106	34.0 ±12.7	DSM-IV	Structured interview using a Chinese version of MINI
Zhang et al. [2010]	447	27.8±8.0	432	28.3 ±8.7	DSM-IV	Structured interview by at least two consultant psychiatrists using the Chinese version of SCID-I/P
Kim et al. [2010]	42	NA	349	NA	DSM-IV	Structured interview by board-certified psychiatrists
Ozan et al. [2010]	66	34.0	56	33.0	DSM-IV	Structured interview using SCID-I/P
Taylor et al. [2008]	245	69.7±7.5	94	69.8 ±5.8	NIMH DIS plus DSM-IV	A self-report questionnaire plus an interview with a geriatric psychiatrist
Enoch et al. [2008]	15	NA	101	NA	DSM-III-R	—
Ribeiro et al. [2007]	278	39.0 ±9.9	320	NA	DSM-IV	Structured interview by experienced clinical investigators using SCID-I/P
Iga et al. [2007]	154	45.1 ±14.2	154	45.0 ±14.0	DSM-IV	Consensus by at least two trained psychiatrists
Gratacos et al. [2008]	374	57.2 ± 15.3	342	39.8 ±11.9	DSM-IV	Structured interview by experienced psychiatrists using SCID-I/P
Frodl et al. [2007]	60	44.2 ±11.8	60	41.6 ±12.3	DSM-IV	Consensus of at least two psychiatrists based on structured interview
Anttila et al. [2007]	119	57.5 ±14.0	392	44.4 ±11.1	DSM-IV	—
Choi et al. [2006]	83	53.9 ±11.7	128	40.7 ±15.5	DSM-IV plus K-DIGS	Structured interview by trained psychiatrists
Hwang et al. [2007]	110	75.0 ±5.3	171	76.0 ±5.5	DSM-IV	—
Surtees et al. [2007]	429	57.0 ±8.6	6,744	60.4 ±9.2	HLEQ	Structured self-assessment
Schumacher et al. [2005]—a	312	52.2 ±13.4	444	50.5 ±12.8	DSM-IV	Combination of multiple sources of information including a personal structured interview using SCID-I/P, medical records, and the family history; assessed by least two experienced psychiatrists or psychologists
Schumacher et al. [2005]—b	446	47.4 ±13.7	1,084	44.6 ±15.9	DSM-IV	Structured interview using SCAN
Tsai et al. [2003]	152	45.3 ±17.0	164	45.7 ±13.1	DSM-IV	—

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	MDD		Control			
Study (author, year)	**n**	**Mean age**	**n**	**Mean age**	**Definition of MDD**	**Diagnosis method**
Hong et al. [2003]	84	47.9 ±17.4	392	44.8 ±21.4	DSM-IV	Combination of interview, clinical observation, medical records, past history and re-assessed by a psychiatrist
Oswad et al. [2005]—a	66	25.7 ±3.5	66	32.2±9.7	DSM-IV	Semi-structured interview by a trained psychiatrist using MINI
Oswad et al. [2005]—b	92	50.2 ±12.1	92	40.1 ±7.8	DSM-IV	Semi-structured interview by a trained psychiatrist using MINI

DSM-IV, diagnosis and statistical manual of mental health disorders, fourth edition.

MINI, the mini international neuropsychological interview, a structured psychiatric interview based on DSM-IV.

SCID-I/P, the modified structured clinical interview for DSM-IV TR Axis I disorders, patient edition.

K-GIGS, the Korean version of diagnostic interview for genetic studies.

HLEQ, a structured self-assessment version of DSM-IV.

SCAN, schedule for clinical assessment in neuropsychiatry.

TABLE II

Meta-Analysis of the Association Val66Met With Major Depression

	Case	Controls	OR (95% CI)	*P*	*P*for heterogeneity
Val/val versus met carrier	4,447	12,979	1.01 (0.91–1.13)	0.823	0.040
Met versus val	4,173	12,747	0.96 (0.89–1.05)	0.402	0.036
Met/met versus val/val	3,975	12,641	0.96 (0.83–1.12)	0.618	0.177
Met/val versus val/val	3,975	12,641	0.94 (0.86–1.03)	0.189	0.412

TABLE III

Meta-Analysis of Other SNPs in BDNF With Major Depression

SNP	Study	Cases	Controls	OR (95% CI)	*P*
11757C/G	Chen et al.	83	400	0.93 (0.66–1.29)	0.654
	Oswald et al.—a	92	92	0.62 (0.38–1.02)	0.060
	Oswald et al.—b	156	196	0.86 (0.59–1.24)	0.410
	Total	331	688	0.83 (0.67–1.04)	0.103
270T/C	Chen et al.	83	400	0.94 (0.43–2.04)	0.870
	Sun et al.	202	346	1.29 (0.74–2.24)	0.372
	Total	285	746	1.16 (0.74–1.82)	0.527
712A/G	Chen et al.	83	400	0.39 (0.12–1.28)	0.121
	Sun et al.	202	346	2.28 (1.40–3.71)	0.001
	Total	285	746	1.03 (0.18–5.75)	0.974
rs988748	Oswald et al.—a	465	1,097	1.02 (0.85–1.23)	0.797
	Oswald et al.—b	312	444	0.92 (0.72–1.17)	0.483
	Total	777	1,541	0.98 (0.85–1.14)	0.831

TABLE IV

Summary of Association of Individual SNPs in BDNF With Major Depression *

SNP	Alleles[a]	OR (95% CI)	*P*
Val66Met (rs6265)	A/G	0.96(0.89–1.05)	0.402
11757C/G	C/G	0.83 (0.67–1.04)	0.103
270T/C	T/C	1.16 (0.74–1.82)	0.527
712A/G	A/G	1.03 (0.18–5.75)	0.974
rs988748	C/G	0.98 (0.85–1.14)	0.831
rs10501087	C/T	1.01 (0.79–1.29)	0.929
rs11030096	C/T	1.12 (0.91–1.38)	0.295
rs12273363	C/T	1.03 (0.78–1.36)	0.845
rs1491850	C/T	1.00 (0.81–1.23)	0.990
rs1491851	T/C	1.18 (0.96–1.46)	0.122
rs908867	A/G	0.78 (0.53–1.16)	0.224
rs925946	T/G	0.93 (0.73–1.20)	0.598
rs10835210	A/C	0.78 (0.56–1.10)	0.156
rs11030101	T/A	0.78 (0.56–1.10)	0.156
rs2030324	T/C	0.77 (0.56–1.05)	0.102
rs7103873	G/C	0.76 (0.56–1.04)	0.088
rs7124442	T/C	1.34 (0.91–1.96)	0.138

[a] Major/minor

* Calculated based on meta-analysis and published literature

TABLE V

Gene-Based Analysis of Genetic Variants in BDNF With Major Depression

	Fisher	Simes	Inverse	TPM	
BDNF	0.212	0.379	0.291	Un-weighted	0.627
				Weighted	0.625
BDNF[a]	0.199	0.357	0.309	Un-weighted	0.603
				Weighted	0.603

[a]Excluding Val66Met