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SYSTEMATIC REVIEW AND META-ANALYSIS

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The Association Between Genetic Variants in the Dopaminergic System and Posttraumatic Stress Disorder

A Meta-Analysis

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Abstract: Posttraumatic stress disorder (PTSD) is a complex mental disorder and can severely interfere with the normal life of the affected people. Previous studies have examined the association of PTSD with genetic variants in multiple dopaminergic genes with inconsistent results.

To perform a systematic literature search and conduct meta-analysis to examine whether genetic variants in the dopaminergic system is associated with PTSD.

Data Sources: PubMed, Cochrane Library, Embase, Google Scholar, and HuGE.

Study eligibility criteria and participants: The studies included subjects who had been screened for the presence of PTSD; the studies provided data for genetic variants of genes involved in the dopaminergic system; the outcomes of interest included diagnosis status of PTSD; and the studies were case–control studies.

Study appraisal and synthesis methods: Odds ratio was used as a measure of association. We used random-effects model in all the meta-analyses. Between-study heterogeneity was assessed using I^2, and publication bias was evaluated using Egger test. Findings from meta-analyses were confirmed using random-effects meta-analyses under the framework of generalized linear model (GLM).

A total of 19 studies met the eligibility criteria and were included in our analyses. We found that rs1800497 in *DRD2* was significantly associated with PTSD (OR = 1.96, 95% CI: 1.15–3.33; $P = 0.014$). The 3′-UTR variable number tandem repeat (VNTR) in *SLC6A3* also showed significant association with PTSD (OR = 1.62, 95% CI: 1.12–2.35; $P = 0.010$), but there was no association of rs4680 in *COMT* with PTSD ($P = 0.595$).

Sample size is limited for some studies; type and severity of traumatic events varied across studies; we could not control for potential confounding factors, such as age at traumatic events and gender; and we could not examine gene–environment interaction due to lack of data.

We found that rs1800497 in *DRD2* and the VNTR in *SLC6A3* showed significant association with PTSD. Future studies controlling for confounding factors, with large sample sizes and more homogeneous traumatic exposure, are needed to validate the findings from this study.

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Abbreviations: CI = confidence interval, COMT = catechol-o-methyltransferase, DBH = dopamine beta-hydroxylase, DRD2 = dopamine receptor D_2, GLM = generalized linear model, HWE = Hardy–Weinberg equilibrium, OR = odds ratio, PTSD = posttraumatic stress disorder, SLC6A3 = solute carrier family 6 (neurotransmitter transporter), member 3, VNTR = variable number tandem repeat.

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a complex mental disorder following a severe traumatic experience, and is usually accompanied by an intense sense of terror, fear, and helplessness.[1] PTSD can severely interfere with the normal life of the affected people. About 7% to 8% of the USA population (~8 million adults) will have PTSD at some time point during life, and a higher percentage of the Gulf War and Vietnam War veterans have PTSD.[2] PTSD can result from various types of traumatic incidents such as war, urban violence, and natural disasters (e.g., earthquake and flood). Although increasing knowledge for PTSD has been obtained using sophisticated genetic and brain-imaging techniques,[3] the exact underlying pathophysiology remains to be ambiguous and there is no effective treatment for PTSD available now.

The dopaminergic system consists of multiple genes involved in the biosynthesis, transport, degradation, transmission, and signaling transduction of the neurotransmitter

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dopamine, such as the solute carrier family 6 (neurotransmitter transporter), member 3 (*SLC6A3* or *DAT1*), dopamine degradation enzyme catechol-o-methyltransferase (*COMT*), and dopamine receptor D_2 (*DRD2*).[4] The dopaminergic signaling system plays important roles in many neurological processes such as rewarding and motivating, memory and learning, and fine motor control.[5] Abnormal dopaminergic signaling and function is associated with many neuropsychiatric disorders, such as schizophrenia and attention-deficit hyperactivity disorder (ADHD).[6,7]

Dysregulated dopamine is also associated with various PTSD symptoms related to attention, vigilance, arousal, and sleep.[8] Genetic variations in the dopaminergic system that are involved in dopamine synthesis, binding affinity, and signaling transduction may have influence on the ability to deal with stress stimuli in subjects who have been exposed to traumatic events.[9] Neuroimaging studies indicated that the dopamine system is usually dysregulated in PTSD patients to counteract or worsen the crisis response to the stressful stimuli.[10] In addition, dopamine can be converted to norepinephrine by dopamine beta-hydroxylase (DBH) enzyme.[11] Exposure to continued high stress leads to elevated norepinephrine concentration in cerebrospinal fluid and overactivation of norepinephrine receptors, which is associated with nightmares and flashbacks that are frequently experienced in the individuals with PTSD.[12,13]

Previous studies have examined the association of PTSD with genetic variants in several dopaminergic genes, with inconsistent results.[14] To the best of our knowledge, no meta-analysis has been performed to pool results from the existing literature. Therefore, in this study, we performed meta-analyses of the association of PTSD with multiple genetic variants in *DRD2*, *SLC6A3*, *COMT*, and *DBH*.

METHOD

Eligibility Criteria

The following inclusion criteria were used to determine study eligibility: The studies included subjects who had been screened for the presence of PTSD; the studies provided data for genetic variants of genes involved in the dopaminergic system; the outcomes of interest included diagnosis status of PTSD; and the studies were case–control studies.

Search Strategy

We performed a systematic literature search in Pubmed, Cochrane Library, Embase, Google Scholar, and HuGE (a navigator for human genome epidemiology) for papers published before May 31, 2015. The keywords used in the literature search can be found in the online supplementary file. We retrieved all potential publications to evaluate eligibility. We also manually searched the references of all relevant studies to screen studies that might have been missed. The literature search was performed independently by 2 authors (YB and JY) and was limited to studies published in English. Any discrepancies were resolved through a group discussion.

Data Extraction

Following a prespecified protocol for data extraction, 2 authors (LL and JY) independently extracted the following data: name of the 1st author, year of publication, characteristic of the participants including sample size, age, gender, race/country of participants, diagnostic instrument for PTSD, type of PTSD (lifetime vs current), type of traumatic events exposure, gene(s) studied, genotype data for patients with and without PTSD, or odds ratio (OR) and the corresponding 95% confidence interval (CI). Any discrepancies were resolved in a group meeting.

Data Analysis

OR was used as a measure to assess the association between genetic variants in the dopaminergic system and PTSD diagnosis. In all meta-analyses, we used random-effects models to calculate OR and the corresponding 95% CI. Between-study heterogeneity and publication bias was assessed using I^2 and a funnel plot and Egger test, respectively.

Traditional meta-analysis assumes approximate normal within-study likelihood and treats the standard errors as known. This approach has several disadvantages such as failing to account for the correlation between the estimate and the standard error.[15] It is especially problematic for sparse data when there are groups within individual studies that have few or even zero events. In such cases, standard errors are highly variable or undefined. Continuity corrections could influence the results and conclusions,[16,17] and noncontinuity correction methods often assume homogeneity among the studies. Therefore, to confirm our findings, we further employed a novel statistical method and conducted random-effects meta-analyses in the framework of a generalized linear model (GLM) using the metafor package in R.[15]

Sensitivity Analysis

In the meta-analysis for *DRD2*, there are several studies in which subjects in the control group did not experience traumatic events. We repeated the analysis by excluding these studies. Since the type of trauma experienced by the subjects varied across studies, we also performed separate meta-analyses by focusing on combat traumatic events which were adopted in many of the included studies. We also analyzed the association by ethnicity, where possible. Furthermore, we performed additional meta-analyses by including only studies that satisfied Hardy–Weinberg equilibrium (HWE) in the control. And finally, we did separate analysis by excluding studies which assessed lifetime PTSD instead of current PTSD.

As our study used a systematic review and meta-analysis, ethical approval of this study is not required. This work was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[18] All statistical analyses were performed using Stata 11.2 (StataCorp LP, College Station, TX), R (www.R-project.org), Matlab 8.1.0.604 (The MathWorks, Inc., Natick, MA), and SAS version 9.3 (SAS Institute Inc., Cary, NC). A P-value < 0.05 was considered statistically significant.

RESULTS

Study Selection and Characteristics

Figure 1 shows the literature search and selection of eligible studies. Our initial search identified a total of 188 potential publications. We excluded 160 publications either because they were irrelevant, review or meta-analysis, not in English, not about human subjects, or because they were published as abstracts. Of the remaining 28 studies which were retrieved for more detailed evaluations, we further excluded an additional 9 studies because they were insufficient data, or there were irrelevant. This led to 19 potentially relevant publications to be included in our analyses.[19–37]

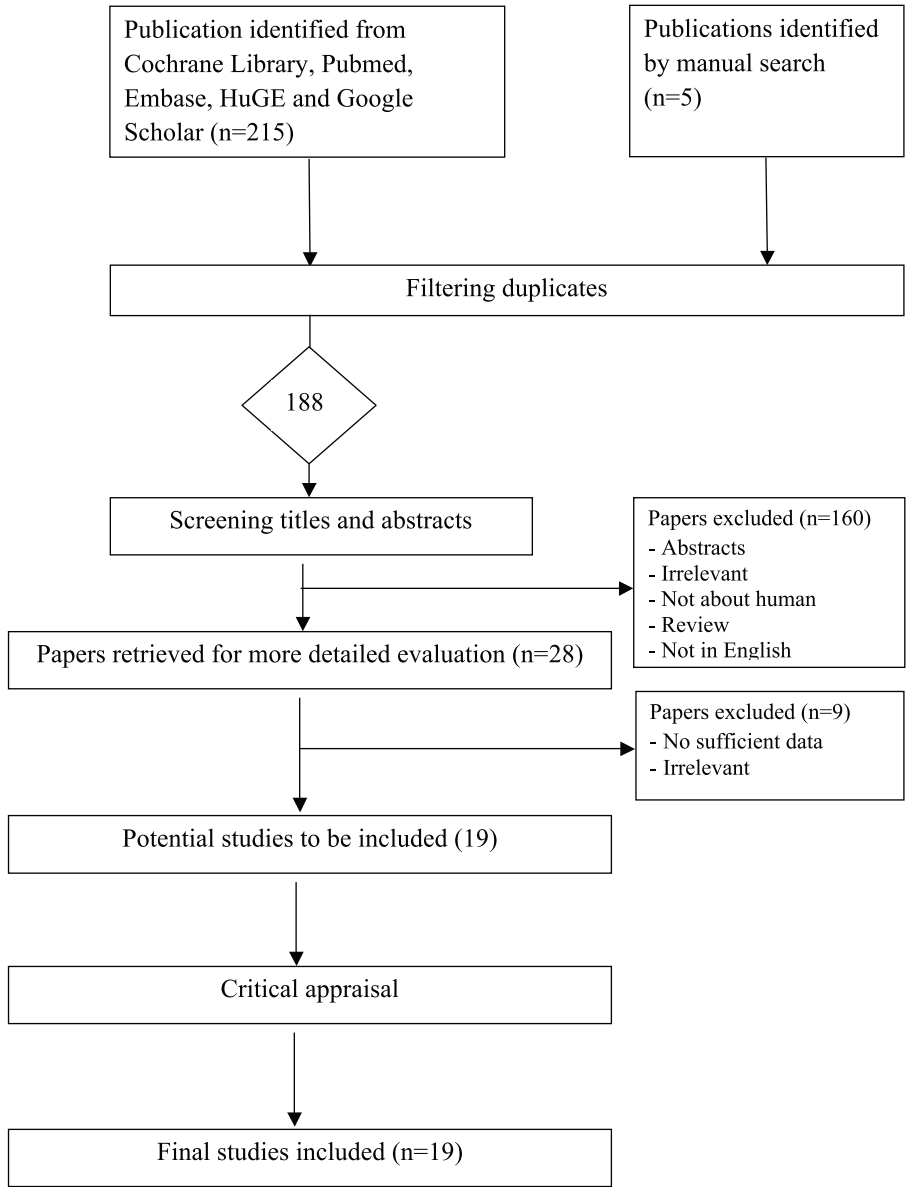

FIGURE 1. Flow diagram of the selection process of the studies included in the meta-analyses. Note: Please see the Methods section for additional details.

All qualified publications were published since 1991 and had sample sizes ranging from 56 to 1749 (Table 1). Of these 19 studies, 6 studies provided data for *DRD2*,[19–21,23,26,37] 3 for *SLC6A3*,[22,30,32] 5 for *COMT*,[27,29,31,34,35] and 2 for *DBH*.[24,28] These studies were included in the corresponding meta-analyses. The combined study included 1752 subjects in meta-analysis for rs1800497 in *DRD2*, 600 for the variable number tandem repeat (VNTR) in *SLC6A3*, 1044 for rs4680 in *COMT*, and 394 for rs161115 in *DBH*. For meta-analysis of rs1800497 in *DRD2*, the VNTR in *SLC6A3*, rs6480 in *COMT*, and rs161115 in *DBH*, the reference genotype is A2A2, 10R10R, VM+MM, and TC+CC, respectively.

One study provided association results for multiple SNPs in *DRD2*, *DRD3*, *SLC6A3*, and *DBH*,[33] 1 study provided data for 2 additional genetic variants in *DRD2*.[26] One study provided association results for multiple SNPs in *DRD3*.[36] And another studies provided data for a VNTR in *DRD4*.[25]

Assessment of Publication Bias

We found no evidence of publication bias for the meta-analysis of *DRD2* ($P = 0.143$, Figure 2), *SLC6A3* ($P = 0.730$, Figure 3), and *COMT* ($P = 0.238$, Figure 4). Assessment of publication bias for the meta-analysis of *DBH* is not meaningful due to limited number of studied included in the meta-analysis.

Association of rs1800497 in DRD2 with PTSD

Six studies including a total of 597 PTSD patients and 1155 controls examined the association of rs1800497 with PTSD. With the exception of 1 study, all studies seemed to indicate that

TABLE 1. Basic Characteristics of all Studies

Study (Author, year)	Race/Country	PTSD n	PTSD Age (Mean ± SD)	PTSD Male, %	Control n	Control Age (Mean ± SD)	Control Male, %	Gene Studied	Genetic Variants Reported*	Diagnostic Instrument	Type of Traumatic Events	Type of PTSD
Comings et al, 1991[19]	Caucasian	35	NA	NA	314	NA	NA	*DRD2*	rs1800497	DSM-III-R	Combat	Current
Comings et al, 1996[20]	Caucasian	37	NA	NA	19	NA	NA	*DRD2*	rs1800497	DSM-III-R	Combat	Current
Gelernter et al, 1999[21]	Mixed	52	NA	NA	87	NA	NA	*DRD2*	rs1800497	SCID, SADS-L, C-DIS or nonstructured interview	Combat	Current
Segman et al, 2002[22]	Jewish	102	39.7 ± 11.7	55.8%	104	33.9 ± 10.2	47.1%	*SLC6A3*	VNTR	DSM-IV	Mixed	Current
Young et al, 2002[23]	Caucasian	91	52.0 ± 0.7	100%	51	38.9 ± 1.9	35.3%	*DRD2*	rs1800497	DSM-IV	Combat	Current
Mustapic et al, 2007[24]	Caucasian	133	40.3 ± 7.2	NA	34	38.1 ± 4.2	NA	*DBH*	rs161115	SCID	Combat	Lifetime
Dragan et al, 2009[25]	Mixed	24	NA	NA	83	NA	NA	*DRD4*	VNTR	PTSD-F & PTSD-C	Flood	Current
Voisey et al, 2009[26]	Caucasian	127	NA	100%	228	NA	NA	*DRD2*	rs1800497, 957C>T, 141delC	DSM-IV	Combat	Current
Kolassa et al, 2010[27]	Mixed	340	NA	NA	84	NA	NA	*COMT*	rs4680	PDS	Mixed	Lifetime
Tang et al, 2010[28]	African American	69	43.9 ± 12.0	39.1%	158	43.9 ± 13.2	44.6%	*DBH*	rs161115	PSS	Mixed	Current
Schulz-Heik et al, 2011[29]	Mixed	51	49.3	94.1%	48	46.7	91.7%	*COMT*	rs4680	Clinician-Administered PTSD Scale	Combat	Current
Valente et al -a, 2011[30]	Mixed	65	37.9 ± 8.7	33.3%	34	44.0 ± 13.8	17.6%	*SLC6A3*	VNTR	Clinician-Administered PTSD Scale	Urban violence	Current
Valente et al -b, 2011[31]	Mixed	65	37.9 ± 8.7	33.3%	34	44.0 ± 13.8	17.6%	*COMT*	rs4680	Clinician-Administered PTSD Scale	Urban violence	Current
Chang et al, 2012[32]	Mixed	62	61	35%	258	52.2	43.4%	*SLC6A3*	VNTR	PCL-C	Mixed	Lifetime
Nelson et al, 2013[33]	Mixed	651	35.8 ± 8.6	46.9%	1098	36.6 ± 9.3	64.6%	*DRD2*, *DRD3*, *DBH*, *SLC6A3*	*DRD2*: rs12364283, rs12805897, rs4648317; *DRD3*: rs6787134; *DBH*: rs2519154; *SLC6A3*: rs6869645	Modified NCS	Mixed	Lifetime
Norrholm et al, 2013[34]	Primarily AA	98	40.3 ± 11.4	32.7%	172	37.6 ± 12.9	39.3%	*COMT*	rs4680	Modified PSS	Mixed	Current

Study (Author, year)	Race/Country	PTSD n	PTSD Age (Mean ± SD)	PTSD Male, %	Control n	Control Age (Mean ± SD)	Control Male, %	Gene Studied	Genetic Variants Reported*	Diagnostic Instrument	Type of Traumatic Events	Type of PTSD
Humphreys et al, 2014[35]	Mixed	72	NA	NA	80	NA	NA	*COMT*	rs4680	Modified Preschool Age Psychiatric Assessment	Mixed	Current
Wolf et al, 2014[36]	Mixed	438	NA	NA	654	NA	NA	*DRD3*	rs9868039, rs9817063, rs4646996, rs2134655, rs2251177, rs201252087, rs963468	CAPS & TLEQ	Mixed	Lifetime
Tian et al, 2015[37]	Asian	64	14.6 ± 1.7	57.8%	119	15.0 ± 1.6	52.1%	*DRD2*	rs1800497	PCL_C & SCID	Earthquake	Current

AA = African American, CAPS = the Clinician Administered PTSD Scale, C-DIS = Computerized Diagnostic Interview Schedule, COMT = catechol-o-methyltransferase, DBH = dopamine beta-hydroxylase, DRD2 = dopamine receptor D_2, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, MINI = Mini-International Neuropsychiatric Interview, NCS = National Comorbidity Survey, PCL-C = PTSD Checklist-Civilian Version, PDS = Posttraumatic Diagnostic Scale, PSS = PTSD Symptom Scale, SADS-L = Schedule for Affective Disorders and Schizophrenia, lifetime version, SCID = Structured Clinical Interview, SD = standard deviation, SLC6A3 = solute carrier family 6 (neurotransmitter transporter), member 3, TLEQ = Traumatic Life Event Questionnaire, VNTR = variable number tandem repeat.

* For each study, we only listed SNPs for which data were available.

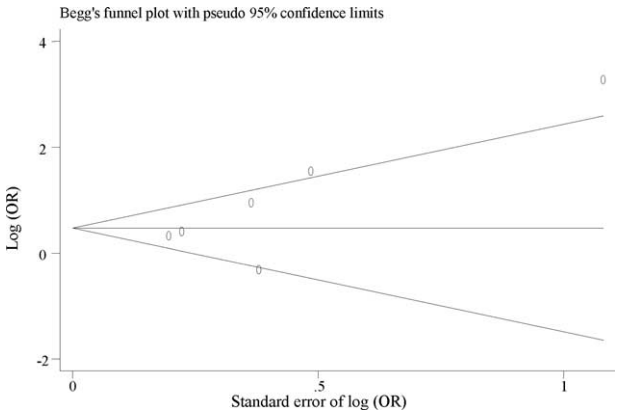

FIGURE 2. Funnel plot for meta-analysis of the association of rs1800497 in *DRD2* with PTSD. The x-axis is the standard error of the log-transformed OR (log [OR]), and the y-axis is the log-transformed OR. The horizontal line in the figure represents the overall estimated log-transformed OR. The 2 diagonal lines represent the pseudo 95% confidence limits of the effect estimate. OR = odds ratio, PTSD = posttraumatic stress disorder.

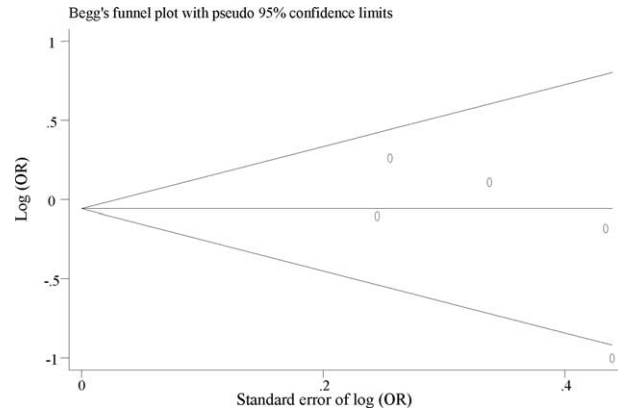

FIGURE 4. Funnel plot for meta-analysis of the association of rs4680 in *COMT* with PTSD. The x-axis is the standard error of the log-transformed OR (log [OR]), and the y-axis is the log-transformed OR. The horizontal line in the figure represents the overall estimated log-transformed OR. The 2 diagonal lines represent the pseudo 95% confidence limits of the effect estimate. *COMT* = catechol-o-methyltransferase, OR = odds ratio, PTSD = posttraumatic stress disorder.

the A1 allele increased PTSD risk (eTable 1, http://links.lww.com/MD/A774). Our meta-analysis found that rs1800497 is significantly associated with PTSD (OR = 1.96, 95% CI: 1.15–3.33; $P = 0.014$; Figure 5). There was heterogeneity among the included studies ($I^2 = 72.9\%$, $P = 0.002$). Random-effects meta-analysis under GLM confirmed our finding (OR = 1.35, 95% CI: 1.13–1.60, $P < 0.001$; Table 2).

Association of VNTR in SLC6A3 With PTSD

Three studies including a total of 213 PTSD patients and 387 controls examined the association of 3′-UTR VNTR with PTSD. All studies seemed to indicate that the 9R increased PTSD risk (eTable 2, http://links.lww.com/MD/A774). Our meta-analysis found that 9R is significantly associated with

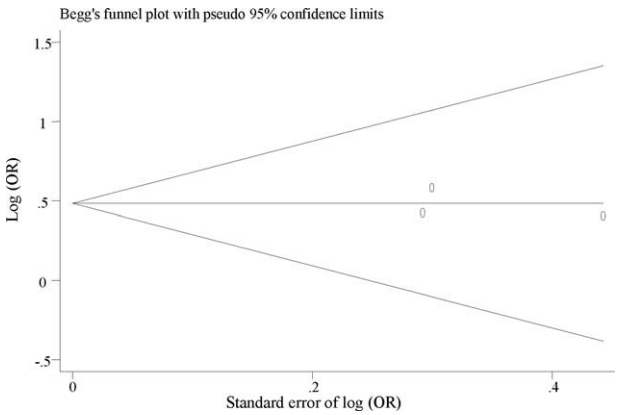

FIGURE 3. Funnel plot for meta-analysis of the association of VNTR in *SLC6A3* with PTSD. The x-axis is the standard error of the log-transformed OR (log [OR]), and the y-axis is the log-transformed OR. The horizontal line in the figure represents the overall estimated log-transformed OR. The 2 diagonal lines represent the pseudo 95% confidence limits of the effect estimate. OR = odds ratio, PTSD = posttraumatic stress disorder, *SLC6A3* = solute carrier family 6 (neurotransmitter transporter), member 3, VNTR = variable number tandem repeat.

PTSD (OR = 1.62, 95% CI: 1.12–2.35; $P = 0.010$; Figure 6). There was low heterogeneity among the included studies ($I^2 = 0\%$, $P = 0.915$). Association in the random-effects meta-analysis under GLM was attenuated but still indicated a trend for association (OR = 1.32, 95% CI: 0.99–1.74, $P = 0.056$; Table 2).

Association of rs4680 in COMT With PTSD

Five studies including a total of 626 PTSD patients and 418 controls examined the association of Val158Met (rs4680) with PTSD. Findings from these studies are inconsistent, with some[34,35] indicating that Val/Val increased PTSD risk while others[27,29,30] indicating decreased PTSD risk (eTable 3, http://links.lww.com/MD/A774). Our meta-analysis found that rs4680 is not significantly associated with PTSD (OR = 0.91, 95% CI: 0.63–1.30; $P = 0.595$; Figure 7). There was no heterogeneity among the included studies ($I^2 = 38.8\%$, $P = 0.162$). Random-effects meta-analysis under GLM confirmed our finding (OR = 0.98, 95% CI: 0.84–1.15, $P = 0.803$; Table 2).

Association of rs161115 in DBH With PTSD

Only 2 studies including a total of 202 PTSD patients and 192 controls examined the association of rs1611115 with PTSD. Our meta-analysis did not find a significant association of homozygous TT with PTSD risk (OR = 1.55, 95% CI: 0.39–6.20; $P = 0.536$; eTable 4, http://links.lww.com/MD/A774). However, these results should be interpreted with caution due to very limited sample size.

Sensitivity Analysis

We repeated the meta-analysis for rs1800497 in *DRD2* after excluding studies in which the subjects in the control might not have experienced traumatic events.[19,21,23,26] In such a case, we are testing the association with traumatic resilience. We did not find a significant association of rs1800497 with PTSD resilience (OR = 5.23, 95% CI: 0.30–90.03; $P = 0.255$; eTable 1, http://links.lww.com/MD/A774), probably due to larger variance owing to reduced sample size. Random-effects meta-analysis under GLM still indicated significant

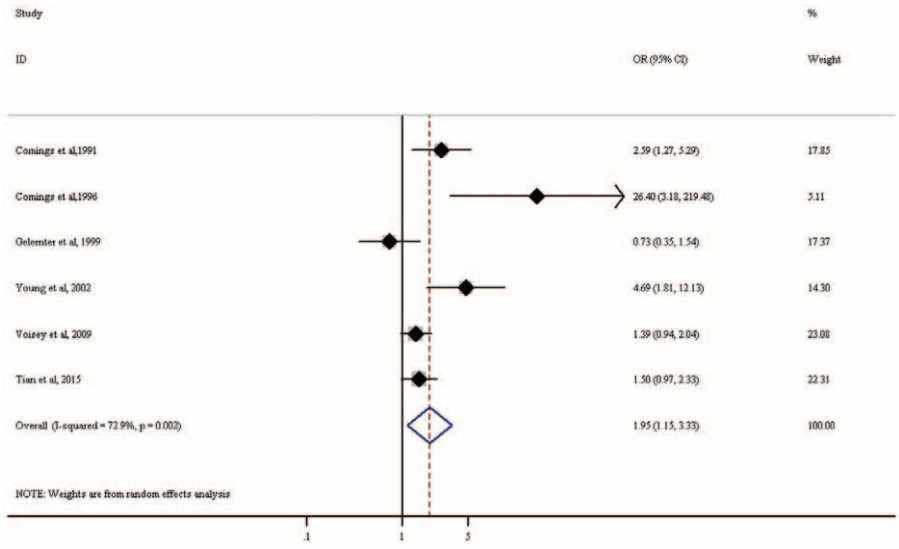

FIGURE 5. Forest plot for meta-analysis of the association of rs1800497 in *DRD2* with PTSD. Each study is represented by a square whose area is proportional to the weight of the study. The overall effect from meta-analysis is represented by a diamond whose width represents the 95% CI for the estimated OR. CI = confidence interval, *DRD2* = dopamine receptor D_2, OR = odds ratio, PTSD = posttraumatic stress disorder.

association of rs1800497 with PTSD (OR = 1.45, 95% CI: 1.07–1.96; $P = 0.018$; Table 2). Our observed association of rs1800497 with PTSD remained when we limit our analysis to studies including only Caucasian subjects (OR = 3.16, 95% CI: 1.34–7.43; $P = 0.008$), or only subjects who had experienced combat traumatic events (OR = 2.28, 95% CI: 1.08–4.81; $P = 0.032$).

The association of rs1800497 with PTSD was attenuated when we included only studies that satisfied HWE in the control group (OR = 1.77, 95% CI: 0.93–3.39; $P = 0.085$). Again, this is probably due to limited power owing to reduced sample size. All the included studies for meta-analysis of the VNTR in *SLC6A3* satisfied HWE in the control group. For meta-analysis of rs4680 in *COMT*, we observed similar nonsignificant association after excluding studies that violated HWE (OR = 1.03, 95% CI: 0.75–1.43; $P = 0.838$).

All the included studies for meta-analysis of rs1800497 assessed current PTSD. When we limit our analysis to include only studies assessing current PTSD, our results remained unchanged for the meta-analysis of the VNTR in *SLC6A3* (OR = 1.69, 95% CI: 1.04–2.75; $P = 0.034$) and rs4680 in *COMT* (OR = 0.88, 95% CI: 0.53–1.47; $P = 0.625$).

DISCUSSION

In this study, we performed a systematic literature search and conducted meta-analyses to examine the association of genetic variants in the dopaminergic system with PTSD. We found that rs1800497 in *DRD2* and the VNTR in *SLC6A3* showed significant association with PTSD risk, but not *rs4680* in *COMT*. To the best of our knowledge, this is the first meta-analysis on the association of genetic variants in the dopaminergic system with PSTD.

Previous studies have identified multiple SNPs in the dopaminergic system associated with PTSD;[9] however, their functions in the pathogenesis of PTSD is largely unknown. Dopamine receptors, including D1, D2, D3, D4, and D5, belong to the G-protein-coupled receptor family that inhibits adenylyl cyclase. The *DRD2* receptor is associated with pleasure and reward circuitry.[38] Missense and other mutations in *DRD2* are associated with movement disorder, myoclonus dystonia, and schizophrenia.[39] The *DRD2/ANKK1*-Taq1A polymorphism (rs1800497) was previously assigned to *DRD2*, but later it was found to reside in exon 8 of *ANKK1*. This polymorphism is related to the regulation of dopamine synthesis and *DRD2*

TABLE 2. Meta-Analysis of Association of Genetic Variants in *DRD2*, *SLC6A3*, and *COMT* With Posttraumatic Stress Disorder Using Metafor

Genetic Variant	Gene	Test of Heterogeneity	OR (95% CI)	*P*
rs1800497	*DRD2*	0.167	1.35 (1.13–1.60)	<0.001
rs1800497	*DRD2*[*]	0.203	1.45 (1.07–1.96)	0.018
VNTR	*SLC6A3*	0.875	1.32 (0.99–1.74)	0.056
rs4680	*COMT*	0.626	0.98 (0.84–1.15)	0.803

CI = confidence interval, COMT = catechol-o-methyltransferase, DRD2 = dopamine receptor D_2, OR = odds ratio, SLC6A3 = solute carrier family 6 (neurotransmitter transporter, dopamine), member 3, VNTR = variable number of tandem repeats.
[*]Used only studies in which the controls experienced traumatic events.

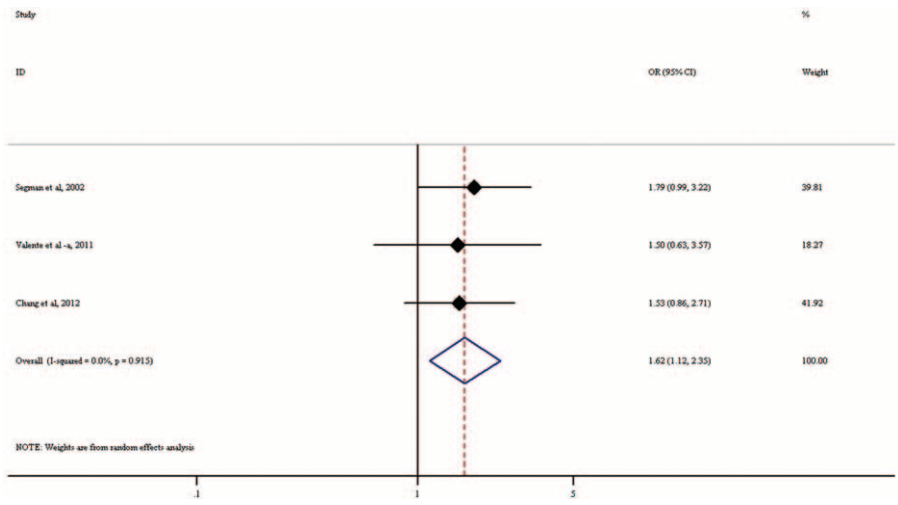

FIGURE 6. Forest plot for meta-analysis of the association of VNTR in *SLC6A3* with PTSD. Each study is represented by a square whose area is proportional to the weight of the study. The overall effect from meta-analysis is represented by a diamond whose width represents the 95% CI for the estimated odds ratio (OR). OR = odds ratio, PTSD = posttraumatic stress disorder, *SLC6A3* = solute carrier family 6 (neurotransmitter transporter), member 3, VNTR = variable number tandem repeat.

receptor density in the brain.[40] It has been linked with several neuropsychiatric disorders, such as ADHD and Tourette syndrome.[41] Most included studies on the association of PTSD with genetic variants in *DRD2* focus on rs1800497. One recent study found that several other polymorphisms in *DRD2*, such as rs12364283, exhibited strong associations with PTSD.[26] This functional *DRD2* promoter polymorphism rs12364283, located in a conserved repressor region of *DRD2* promoter, is in low linkage disequilibrium with rs1800497 ($r^2 = 0.001$). Another research found that rs12364283 was associated with enhanced *DRD2* expression.[42] Further analysis of the flanking conserved sequences of this SNP suggested that the minor C allele alters the binding sites of the putative transcription factor which upregulates *DRD2* expression.[42]

COMT, located on chromosome 22q11.1-q11.2, is an important enzyme involved in the catalyses and inactivation of catecholamines. *COMT* has a functional polymorphism at codon 158 (rs4680). Substitution of valine (Val) by methionine (Met) is associated with reduced enzyme activity.[43] This polymorphism has been found to be associated with multiple neuropsychiatric/psychological disorders, such as anxiety, depression, and diminished fear extinction which is a putative trait of PTSD.[44] Of the 5 studies examining the association of rs4680 with PTSD, only 1 study indicated significant association.[31] Subjects in this study all experienced urban violence, compared to other studies in which subjects experienced combat trauma or mixed types of trauma. Another study found no main effect of rs4680 on lifetime PTSD, but discovered a gene–

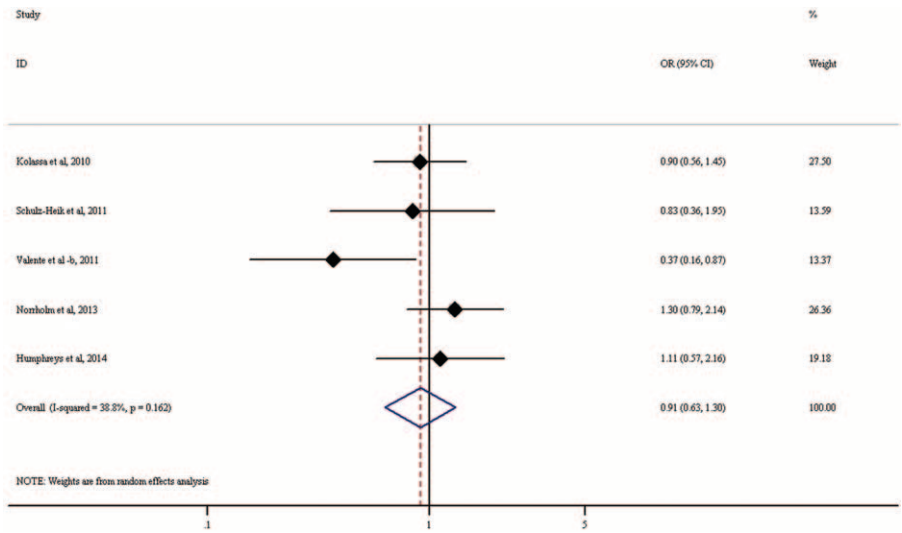

FIGURE 7. Forest plot for meta-analysis of the association of rs4680 in *COMT* with PTSD. Each study is represented by a square whose area is proportional to the weight of the study. The overall effect from meta-analysis is represented by a diamond whose width represents the 95% CI for the estimated odds ratio (OR). *COMT* = catechol-o-methyltransferase, OR = odds ratio, PTSD = posttraumatic stress disorder.

environment interaction such that Met/Met homozygote carriers exhibited higher risk of PTSD, independently of traumatic load, while carriers of other genotypes show increased PTSD risk only in subjects with more severe traumatic load.[27] However, the exact reasons accounting for the inconsistencies in the findings remain unclear.

Brain imaging technologies, including positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional MRI (fMRI), have experienced dramatic development to explore etiology of PTSD and to assess the effects of traumatic stress on the brain.[45] Imaging studies found that hippocampus and medial prefrontal cortex (including anterior cingulate) are implicated in PTSD and other psychiatric disorders.[46,47] Although PTSD shares a lot of similar and overlapping symptoms with other psychiatric disorders and traumatic brain injury (TBI), recent brain imaging studies identified the link between PTSD symptoms and specific brain activity, and showed that imaging techniques can distinguish PTSD from TBI.[48,49] Integrating genotyping of PTSD risk loci, once confirmed, with recently developed imaging techniques might help early detection and diagnosis of PTSD.

There are limitations with this study:

(1) The sample size is limited for some studies. More studies with larger sample sizes are needed to validate our findings.
(2) The type and severity of traumatic events varied across studies. The high level of heterogeneity of trauma exposure might partly explain the nonsignificant association between rs4680 in *COMT* with PSTD. However, lack of data regarding trauma exposure at an individual level prevented us from examining the genetic association by trauma type.
(3) Due to lack of data, we could not control for potential confounding factors, such as age at traumatic events and gender, and could not examine the gene–environment interaction.

In summary, in this study, we performed meta-analyses to analyze the association of PTSD with multiple genetic variants in the dopaminergic system. We found 1 genetic variant in *DRD2* and 1 in *SLC6A3* showing a significant association with PSTD susceptibility. More studies of larger sample sizes with more homogeneous traumatic exposure are needed to valid our findings and to explore additional PSTD risk loci.

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