Meta-analysis of the association between the monoamine oxidase-A gene and mood disorders

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Objective **To evaluate the controversial, putative associations between the three common polymorphisms [promoter variable number tandem repeat (uVNTR), T941G, (CA) repeat] of monoamine oxidase A (MAOA) and mood disorders (major depressive or bipolar disorders, BPD) by systematically meta-analyzing published case-control association studies.**

Methods **We queried PubMed using the keywords 'MAOA', 'association' and 'depression' or 'bipolar'. Nine studies on uVNTR, seven studies on T941G, and eight studies on CA met the inclusion criteria. The meta-analysis was performed by sex and ethnicity.**

Main results **Our meta-analysis showed a significant association between uVNTR and MDD for the Asian group [odds ratio (OR) = 1.23 (1.02–1.47), *P* = 0.03] and male Asian group [OR = 1.47 (1.06–2.05), *P* = 0.02]. For the CA polymorphism, we found a significant association with BPD in the Caucasian group [OR = 1.28 (1.01–1.62), *P* = 0.04] and female Caucasian group [OR = 1.36 (1.031–1.81), *P* = 0.03]. For the CA polymorphism, we identified significant associations with BPD in all Caucasians for the overall alleles and for the specific alleles in a6 [OR = 1.35 (1.11–1.64), *P* = 0.002] and in female Caucasians for the overall alleles and for the specific alleles in a2 [OR = 0.65 (0.48–0.90), *P* = 0.009], a5 [OR = 1.44 (1.04–1.99), *P* = 0.03], and a6 [OR = 1.41 (1.12–1.78), *P* = 0.004].**

Conclusion **Our meta-analysis suggests a significant association of the MAOA gene with major depressive disorder and BPD within specific groups, indicating that these three polymorphisms of the MAOA gene may be associated with mood disorders by sex and ethnicity. Moreover, our systematic meta-analysis has revealed that although MAOA may be a common candidate gene for mood disorders, different polymorphisms and alleles appear to play different roles in major depressive disorder and BPD. *Psychiatr Genet* 20:1–7 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BPD) are among the most common psychiatric disorders. Twin, family, and adoption studies have suggested that susceptibility to both disorders is strongly influenced by genetic factors. In recent years, significant progress has been made in identifying the specific risk alleles for MDD and BPD. Another widely accepted concept is that mood disorders (MDD and BPD) share some degree of common genetic predisposition. For example, the dopaminergic and noradrenergic pathways seem to play important roles in the pathology of mood disorders (Brown and Gershon, 1993; Craddock *et al.*, 2001; Levinson, 2006).

Monoamine oxidase (MAO) is a mitochondrial enzyme involved in the metabolism of some biological amines such as dopamine, serotonin, and norepinephrine (Brunner *et al.*, 1993), which are important factors in the pathogenesis of psychiatric diseases. Brain serotonin and norepinephrine concentrations are increased in mice with a deletion of the MAOA gene (Cases *et al.*, 1995). Thus, the MAOA, located at Xp11.3, is a good candidate gene for severe mood disorders such as MDD and BPD.

Genetic association studies on the MAOA gene have primarily focused on the following three common polymorphisms: (i) a promoter variable number tandem repeat polymorphism (uVNTR) (Sabol *et al.*, 1998; Deckert *et al.*, 1999); (ii) a G/T polymorphism at position 941 of the cDNA sequence, a silent mutation in extron 8 (Lim *et al.*, 1995); and (iii) a dinucleotide repeat in intron 2 (MAOA-CA) (Black *et al.*, 1991). The uVNTR polymorphism consists of alleles which have 2, 2.5, 3, 3.5, 4, 5 repeats of a 30-base pair repetitive sequence. Deckert *et al.* (1999) showed that these different alleles are associated with MAOA transcriptional activity and that long alleles (3.5, 4, 5 repeats) have more transcription activity than short alleles (3 repeats). Another study suggests that the presence of the long allele ('L) of the MAOA gene promoter may be a risk factor for MDD in females (Schulze *et al.*, 2000). Earlier studies referred to

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the T941G polymorphism as Fnu4HI RFLP (e.g. Lim *et al.*, 1995; Muramatsu *et al.*, 1997; Furlong *et al.*, 1999), but later studies referred to it as T941G (e.g. Sasaki *et al.*, 1998; Tadic *et al.*, 2003). In addition, Hotamisligil and Breakefield (1991) related it to MAOA activity, which may also play an important role in MDD or BPD. Moreover, two studies found MAOA-CA to be associated with MDD or BPD for the a2 and the a5 alleles (alleles a0–a6 of Kawada *et al.*, 1995, correspond to alleles 126–114 of Muramatsu *et al.*, 1997). However, the reported associations between uVNTR, T941G or CA and MDD or BPD are controversial. For example, one study (Schulze *et al.*, 2000) suggested an association between uVNTR and MDD in females; whereas another (Gutierrez *et al.*, 2004) suggested no significant association with uVNTR in either MDD or BPD. Therefore, we reviewed and systematically meta-analyzed the association of the MAOA gene from published case-control association studies with two key mood disorders, MDD and BPD.

Materials and methods

Literature search

In order to obtain the literature included in this study, we queried PubMed using the keywords 'MAOA', 'association' and 'depression' for the MDD meta-analysis, carefully examined the reference lists of the identified articles and also checked all articles which cited the identified articles to find additional papers not indexed by PubMed. We followed the same procedure for the BPD study, but substituted the word 'bipolar' for 'depression'. The data covers all articles fit the above criteria from English language publications up through October 2008.

Inclusion criteria

Eligible studies had to meet the following criteria: (i) they had to have been published in a peer-reviewed journal; (ii) they had to contain independent data; (iii) they had to provide sufficient data to enable the calculation of the odds ratio (OR) with a confidence interval and *P* value; (iv) they had to be case-control studies of associations between the uVNTR, T941G or CA and MDD or BPD; and (v) they had to have studied MDD or BPD patients who had been diagnosed according to the International Classification of Disease, Diagnostic and Statistical Manual of Mental Disorders or had satisfied the Research Diagnostic Criteria. We contacted authors when there were questions regarding their studies.

Statistics

Using Revman 4.2, a powerful tool for effective meta-analysis supplied by Cochrane Collaboration, we analyzed each sex separately, subdividing the studies by ethnicity and sex. We tested the differences in overall alleles between cases and controls for the MAOA-CA polymorphism using CLUMP, Version 2.3, which implements a Monte Carlo simulation strategy (Sham and Curtis, 1995). We constructed a two-by-two table using data from each case-control study and classified individuals by diagnostic category and type of allele.

To assess the level of heterogeneity between studies, we performed Cochran's χ^2-based test (confidence interval of 95%). If the level of heterogeneity was high, we adopted a random effect model in order to get a wider confidence interval, or we adopted a fixed effect model if the level was low. To assess the significance of the overall OR, we used a *Z*-test. To evaluate the stability of the pooled estimates, we performed a sensitivity test by removing each study one by one and recalculating the pooled OR and the 95% confidence interval for the remaining studies. This allowed us to evaluate the influence of each study on the pooled result. We also performed a funnel plot asymmetry test to assess publication bias using the method in Egger *et al.* (1997) and evaluated the significance of the intercept deviation from zero using a *T*-test.

Results

The studies associating MDD and BPD with various alleles revealed that the allele frequencies from Asian studies were markedly different from those of Caucasians. Consequently, we analyzed the groups of Caucasians and Asians separately, and we also subdivided the ethnic groups by sex. Therefore, in addition to obtaining results on Caucasians and Asians as separate groups, we obtained results on subgroups of male Asians, male Caucasians, female Asians, and female Caucasians. Because all the studies only found associations between MAOA polymorphisms and BPD in females, we also expected to only find significant associations in women but not in men in the meta-analysis of BPD.

Meta-analysis of monoamine oxidase promoter uVNTR

The literature search produced 15 articles that associated uVNTR with MDD or BPD, but we only retained nine (Table 1) of those studies, rejecting the following studies for the following reasons: One study (Serretti *et al.*, 2002) lacked control participants; one study (Kirov *et al.*, 1999) used the transmission disequilibrium test method, rather than a case-control method; and two other studies (Craddock *et al.*, 1995; Muramatsu *et al.*, 1997) investigated a VNTR that was located within the first intron (Hinds *et al.*, 1992). Two studies (Du *et al.*, 2004; Huang *et al.*, 2004) combined Asian and Caucasian patients, so we could not use these studies. The remaining nine studies included 2045 cases and 2178 controls for the association with MDD, and 1467 cases and 1815 controls for the association with BPD. In the case of Schulze *et al.* (2000) study, we combined the data from patients who had a single episode with those who had recurrent major depression. We omitted one study (Furlong *et al.*, 1999) when doing the genotypic analysis of uVNTR with MDD, and three studies (Furlong *et al.*, 1999; Huang *et al.*, 2008; Lin *et al.*, 2008) with BPD because the genotypic data

Table 1 Characteristics of included studies of uVNTR in MDD and BPD

Author, year	Diagnose	Ethnic	Criteria	Ca and Co	Male	OR (95% CI)	Female	OR (95% CI)
Kunugi *et al.* (1999)	MDD + BPD	Japanese	DSM-IV	Control	125		129	
				MDD	37	1.26 (0.60–2.66)	61	0.96 (0.62–0.49)
				BPD	59	1.14 (0.60–2.14)	101	1.08 (0.75–1.58)
Gutierrez *et al.* (2004)	MDD + BPD	Spanish	DSM-IV,	Control	79		77	
			DSM-III-R	MDD	89	0.97 (0.51–1.84)	212	1.01 (0.67–1.52)
				BPD	36	1.35 (0.57–3.21)	52	1.02 (0.59–1.76)
Syagailo *et al.* (2001)	MDD + BPD	German	DSM-IV	Control	134		95	
				MDD	34	0.68 (0.32–1.47)	40	1.40 (0.79–2.49)
				BPD	40	0.90 (0.43–1.87)	60	1.03 (0.63–1.66)
Schulze *et al.* (2000)	MDD	German	DSM-IV	Control	33		68	
				MDD	44	1.28 (0.45–3.61)	102	1.37 (0.87–2.14)
Yu *et al.* (2005)	MDD	Han Chinese	DSM-IV	Control	103		110	
				MDD	95	2.07 (1.17–3.67)	133	1.64 (1.13–2.37)
Huang *et al.* (2007)	MDD	Han Chinese	DSM-IV	Control	197		111	
				MDD	107	1.23 (0.76–1.99)	170	0.91 (0.64–1.28)
Furlong *et al.* (1999)	MDD + BPD	Caucasian	RDC	Control	103		112	
				MDD	47	0.72 (0.34–1.52)	78	1.31 (0.85–2.02)
				BPD	50	0.72 (0.35–1.50)	55	1.05 (0.65–1.69)
Lin *et al.* (2008)	BPD	Han Chinese	DSM-IV	Control	52		42	
				BPD	53	0.61 (0.28–1.32)	47	1.29 (0.71–2.33)
Huang *et al.* (2008)	BPD	Han Chinese	DSM-IV	Control	190		111	
				BPD	217	1.05 (0.70–1.57)	191	0.93 (0.67–1.31)

BPD, bipolar disorder; Ca, cases; CI, confidence interval; Co, controls; DSM, Diagnostic and Statistical Manual of Mental Disorders; MDD, major depressive disorder; OR, odds ratio; RDC, Research Diagnostic Criteria.

from those studies was not available. No evidence for publication bias was found in either the MDD or BPD studies, as indicated by the fact that the funnel plot test of asymmetry had no P values of less than 0.05.

We adopted a random effect model for the male Caucasian group because heterogeneity was found at a P value of 0.04. For other groups, we adopted a fixed effect model because no heterogeneity was found at any P value of less than 0.05. Our study showed a significant association between uVNTR and MDD for Asian group [OR = 1.23(1.02–1.47), $P = 0.03$] and male Asian group [OR = 1.47(1.06–2.05), $P = 0.02$]. However, we found no significant association of uVNTR with MDD in any of the other groups (Table 4). In addition, we found no significant association for genotypes with an S allele (S/S and S/L vs. L/L) or genotypes with an L allele (S/S vs. S/L and L/L). The percentage of long alleles ('L') varied across the control populations, being higher in Caucasians (65.6%) than in Asians (38.0%).

Additionally, the meta-analysis showed no significant association of uVNTR with BPD in allelic analyses. Genotypic analysis also revealed no significant association of BPD with either the L-containing or the S-containing genotypes (Table 4).

Meta-analysis of monoamine oxidase A T941G

We found eight studies that associated MAOA T941G with MDD or BPD but excluded one study (Rubinsztein *et al.*, 1996) because it used the data that overlapped with those of Furlong *et al.* (1999). Thus, we analyzed the data from the remaining seven studies, as listed in Table 2. The MDD studies included 548 cases and 1202 controls, and the BPD studies included 1093 cases and 1164 controls. We found no evidence of publication bias in the BPD studies, as indicated by the fact that the funnel plot test of asymmetry yielded no P values of less than 0.05. However, we did find evidence for publication bias in the MDD studies, as indicated by a funnel plot test of asymmetry in which $P = 0.03$.

A fixed effect model was adopted because no heterogeneity was found in any of the groups. The meta-analysis results for MDD showed no significant associations in any groups. We found a significant association of MAOA T941G with BPD in the Caucasians [OR = 1.28 (1.01–1.62), $P = 0.04$] and in the female Caucasians [OR = 1.36 (1.03–1.81), $P = 0.03$], but not in any other groups (Table 4). We did not perform the genotypic analysis for this polymorphism because genotypic data was not reported in most of the studies we analyzed [for BPD studies, only one (Sasaki *et al.*, 1998) out of six studies reported genotypic data, and for MDD studies, only two (Sasaki *et al.*, 1998; Tadic *et al.*, 2003) out of four studies]. The frequencies of the risk allele 'T' in Caucasians varied and from 64.4 to 73.3% in controls; whereas in Asians it varied from 45.5 to 58.3% in controls.

Meta-analysis of monoamine oxidase A T941G

We found ten studies that associated MAOA-CA with MDD or BPD but excluded two studies, one study (Rubinsztein *et al.*, 1996) because of overlapping data with Furlong *et al.* (1999) and the other study (Kawada *et al.*, 1995) because it combined data from males and females. Thus, we analyzed the data from eight studies, as listed in Table 3. The MDD studies included 386 cases and 661 controls, and the BPD studies included 1259 cases and 1309 controls. We found no evidence of

Table 2 Characteristics of included studies of T941G in MDD and BPD

Author, year	Diagnose	Ethnic	Criteria	Ca and Co	Male	OR (95% CI)	Female	OR (95% CI)
Muramatsu *et al.* (1997)	MDD + BPD	Japanese	DSM-III-R	Control	48		52	
				MDD	20	0.58 (0.20–1.67)	32	0.90 (0.48–1.68)
				BPD	32	0.63 (0.26–1.55)	28	1.54 (0.79–3.03)
Sasaki *et al.* (1998)	MDD + BPD	Japanese	DSM-IV	Control	77		92	
				MDD	13	0.53 (0.15–1.88)	30	0.81 (0.45–1.47)
				BPD	54	1.11 (0.55–2.24)	78	0.98 (0.64–1.50)
Furlong *et al.* (1999)	MDD + BPD	Caucasian	RDC	Control	119		131	
				MDD	47	0.90 (0.41–1.96)	78	1.35 (0.87–2.09)
				BPD	50	0.72 (0.34–1.50)	55	1.17 (0.72–1.90)
Craddock *et al.* (1995)	BPD	British	DSM-III-R	Control	30		37	
				BPD	31	1.89 (0.54–6.62)	49	1.11 (0.57–2.17)
Lim *et al.* (1995)	BPD	Western European	RDC	Control	17		38	
				BPD	15	1.50 (0.33–6.83)	40	3.12 (1.44–6.76)
Preisig *et al.* (2000)	BPD	Western European	DSM-IV	Control	69		52	
				BPD	113	1.24 (0.64–2.38)	149	1.24 (0.76–2.03)
Tadic *et al.* (2003)	MDD	German	DSM-IV	Control	144		132	
				MDD	28	1.06 (0.44–2.51)	80	1.12 (0.74–1.69)

BPD, bipolar disorder; Ca, cases; CI, confidence interval; Co, controls; DSM, Diagnostic and Statistical Manual of Mental Disorders; MDD, major depressive disorder; OR, odds ratio; RDC, Research Diagnostic Criteria.

Table 3 Characteristics of included studies of CA in MDD and BPD

Author, year	Diagnose	Ethnic	Criteria	Ca and Co	Male	OR (95% CI)	Female	OR (95% CI)
Craddock *et al.* (1995)	BPD	British	DSM-III-R	Control	42		42	
				BPD	34	0.99 (0.24–4.00)[a]	50	1.17 (0.55–2.51)[a]
						0.67 (0.18–2.50)[b]		1.95 (0.65–5.86)[b]
						1.21 (0.48–3.05)[c]		1.26 (0.70–2.25)[c]
Lim *et al.* (1995)	BPD	Western European	RDC	Control	17		41	
				BPD	14	3.00 (0.46–19.59)[a]	42	0.26 (0.10–0.68)[a]
						0.58 (0.05–7.12)[b]		2.72 (1.06–6.96)[b]
						0.53 (0.13–2.20)[c]		1.62 (0.88–3.00)[c]
Muramatsu *et al.* (1997)	MDD + BPD	Japanese	DSM-III-R	Control	48		52	
				MDD	20	0.67 (0.21–2.16)[a]	32	0.97 (0.44–2.15)[a]
						1.24 (0.28–5.51)[b]		0.59 (0.20–1.75)[b]
						1.63 (0.50–5.32)[c]		1.11 (0.58–2.12)[c]
				BPD	32	0.78 (0.29–2.08)[a]	28	1.83 (0.86–3.88)[a]
						0.72 (0.17–3.13)[b]		0.54 (0.17–1.74)[b]
						1.73 (0.62–4.80)[c]		0.93 (0.47–1.87)[c]
Lin *et al.* (2000)	MDD + BPD	Han Chinese	DSM-III-R	Control	47		41	
				MDD	21	1.01 (0.36–2.86)[a]	39	0.98 (0.52–1.84)[a]
						0.95 (0.22–4.11)[b]		0.76 (0.30–1.92)[b]
						1.16 (0.34–3.93)[c]		1.40 (0.68–2.87)[c]
				BPD	32	0.71 (0.28–1.79)[a]	31	1.09 (0.56–2.12)[a]
						1.06 (0.30–3.68)[b]		2.03 (0.88–4.68)[b]
						0.69 (0.21–2.24)[c]		0.68 (0.29–1.61)[c]
Parsian and Todd (1997)	BPD	Caucasian	RDC, DSM-III-R	Control	42		40	
				BPD	32	0.28 (0.06–1.44)[a]	51	0.81 (0.37–1.75)[a]
						0.44 (0.11–1.81)[b]		1.81 (0.77–4.24)[b]
						2.38 (0.93–6.09)[c]		1.21 (0.67–2.17)[c]
Preisig *et al.* (2000)	BPD	Western European	DSM-IV	Control	70		52	
				BPD	115	0.56 (0.24–1.29)[a]	155	0.68 (0.35–1.32)[a]
						0.84 (0.37–1.88)[b]		1.16 (0.66–2.02)[b]
						1.71 (0.93–3.15)[c]		1.82 (1.16–2.86)[c]
Furlong *et al.* (1999)	MDD + BPD	Caucasian	RDC	Control	118		131	
				MDD	47	1.00 (0.36–2.77)[a]	78	0.63 (0.37–1.06)[a]
						0.93 (0.34–2.55)[b]		1.34 (0.80–2.24)[b]
						0.70 (0.36–1.39)[c]		1.06 (0.72–1.58)[c]
				BPD	50	2.17 (0.93–5.05)[a]	55	0.59 (0.32–1.07)[a]
						0.87 (0.32–2.37)[b]		1.13 (0.62–2.04)[b]
						0.74 (0.38–1.43)[c]		1.19 (0.76–1.85)[c]
Lin *et al.* (2008)	BPD	Han Chinese	DSM-IV	Control	39		44	
				BPD	46	NA	40	NA
						1.01 (0.43–2.41)[b]		0.69 (0.37–1.27)[b]
						6.82 (0.80–58.11)[c]		1.59 (0.61–4.19)[c]

BPD, bipolar disorder; Ca, cases; CI, confidence interval; Co, controls; DSM, Diagnostic and Statistical Manual of Mental Disorders; MDD, major depressive disorder; OR, odds ratio; RDC, Research Diagnostic Criteria.
[a]OR of study with a2 allele.
[b]OR of study with a5 allele.
[c]OR of study with a6 allele.

publication bias in either the MDD or BPD studies, as indicated by a funnel plot test of asymmetry that yielded no *P* value of less than 0.05.

We adopted a fixed effect model because no heterogeneity was found in any groups. The meta-analysis showed no significant associations with MDD for the overall alleles or for a2, a5 or a6 in any of the groups. In the BPD studies, we found significant differences in the distribution of overall alleles between cases and controls in the groups of Caucasians and of female Caucasians (Table 4). For risk alleles (a2, a5, a6), we found significant differences between patients and controls in the Caucasian group for allele a6 [OR = 1.35 (1.11–1.64), $P = 0.002$], and in the female Caucasian group for alleles a2 [OR = 0.65 (0.48–0.90), $P = 0.009$], a5 [OR = 1.44 (1.04–1.99), $P = 0.03$], and a6 [OR = 1.41 (1.12–1.78), $P = 0.004$] (Table 4). We did not do genotypic analysis for this polymorphism, because none of the included studies provided genotypic data. In BPD studies with MAOA-CA, the respective frequencies of the alleles a2, a5, and a6 were 18.3, 14.1, and 47.9% in Caucasians but were 32.0, 23.3, and 20.1% in Asians.

Discussion

To our knowledge, the present meta-analysis is the first to assess the association between the MAOA-uVNTR polymorphism and both MDD and BPD. However, this meta-analysis provided only partial support for an association between MAOA markers and mood disorders. The pooled OR and *P* value indicate a significant

Table 4 Results of allelic and genotypic association analysis for the uVNTR, T941G and CA in MDD and BPD

	MDD			BPD		
Makers/groups	OR (95% CI)	P(Z)	P(Q)	OR (95% CI)	P(Z)	P(Q)
uVNTR						
Asian	1.23 (1.02–1.47)	0.03	0.08	1.02 (0.84–1.22)	0.87	0.73
Caucasian	1.12 (0.92–1.36)	0.24	0.62	0.96 (0.75–1.22)	0.72	0.94
Male Caucasian	0.86 (0.59–1.25)	0.43	0.74	0.93 (0.60–1.44)	0.74	0.56
Male Asian	1.47 (1.06–2.05)	0.02	0.36	0.98 (0.72–1.33)	0.89	0.41
Female Caucasian	1.24 (0.99–1.55)	0.07	0.70	0.97 (0.73–1.29)	0.83	1.00
Female Asian	1.13 (0.77–1.65)	0.53	0.05	1.04 (0.82–1.31)	0.75	0.63
Genotypic (SL + LL)/SS						
Caucasian	1.21 (0.76–1.91)	0.42	0.65	1.19 (0.60–2.37)	0.60	0.84
Asian	1.19 (0.73–1.95)	0.49	0.04	0.99 (0.62–1.59)	0.97	0.57
Genotypic (SL + SS)/LL						
Caucasian	0.97 (0.57–1.66)	0.91	0.04	0.95 (0.59–1.53)	0.84	0.76
Asian	1.14 (0.80–1.62)	0.48	0.74	1.13 (0.66–1.94)	0.65	0.85
T941G						
Asian	0.78 (0.53–1.13)	0.19	0.84	1.05 (0.77–1.41)	0.77	0.45
Caucasian	1.16 (0.89–1.52)	0.27	0.82	1.28 (1.01–1.62)	0.04	0.31
Male Caucasian	0.97 (0.54–1.72)	0.91	0.78	1.10 (0.71–1.70)	0.67	0.52
Male Asian	0.56 (0.25–1.26)	0.16	0.91	0.90 (0.52–1.56)	0.71	0.33
Female Caucasian	1.22 (0.90–1.65)	0.20	0.54	1.36 (1.03–1.81)	0.03	0.15
Female Asian	0.85 (0.56–1.31)	0.47	0.82	1.12 (0.78–1.60)	0.55	0.26
MAOA-CA*						
Caucasian	0.69 (0.43–1.10)[a]	0.12	0.42	0.76 (0.51–1.33)[a]	0.18	0.05
	1.24 (0.78–1.95)[b]	0.36	0.53	1.19 (0.90–1.55)[b]	0.22	0.46
	0.96 (0.68–1.35)[c]	0.80	0.31	1.35 (1.11–1.64)[c]	0.002	0.40
Asian	0.93 (0.62–1.42)[a]	0.75	0.95	1.10 (0.74–1.63)[a]	0.65	0.38
	0.78 (0.44–1.40)[b]	0.41	0.88	0.93 (0.64–1.33)[b]	0.68	0.38
	1.26 (0.83–1.92)[c]	0.28	0.93	1.12 (0.76–1.64)[c]	0.56	0.29
Male Caucasian	1.00 (0.36–2.77)[a]	0.99	1.00	0.98 (0.61–1.60)[a]	0.95	0.07
	0.93 (0.34–2.55)[b]	0.89	1.00	0.73 (0.44–1.22)[b]	0.24	0.94
	0.70 (0.36–1.39)[c]	0.31	1.00	1.23 (0.87–1.76)[c]	0.24	0.16
Male Asian	0.84 (0.39–1.82)[a]	0.66	0.60	0.74 (0.38–1.46)[a]	0.39	0.88
	1.08 (0.38–3.07)[b]	0.89	0.81	0.96 (0.51–1.81)[b]	0.90	0.91
	1.38 (0.59–3.22)[c]	0.46	0.69	1.54 (0.78–3.05)[c]	0.21	0.76
Female Caucasian	0.63 (0.37–1.06)[a]	0.08	1.00	0.65 (0.48–0.90)[a]	0.009	0.18
	1.34 (0.80–2.24)[b]	0.27	1.00	1.44 (1.04–1.99)[b]	0.03	0.47
	1.06 (0.72–1.58)[c]	0.76	1.00	1.41 (1.12–1.78)[c]	0.004	0.66
Female Asian	0.98 (0.60–1.60)[a]	0.93	0.98	1.36 (0.83–2.24)[a]	0.22	0.31
	0.68 (0.34–1.38)[b]	0.29	0.73	0.91 (0.58–1.42)[b]	0.68	0.08
	1.23 (0.76–1.99)[c]	0.40	0.64	1.96 (0.61–1.54)[c]	0.88	0.43

The L allele of uVNTR, the T allele of T941G and the a2, a5, a6 alleles of the MAOA-CA were assigned as the risk allele, respectively.
BPD, bipolar disorder; CI, confidence interval; MAOA, monoamine oxidase A; MDD, major depressive disorder; OR, odds ratio; P(Q), Cochran's χ^2-based *Q* statistic test used to assess the heterogeneity; P(Z), *Z* test used to determine the significance of the overall OR.
[a]OR of study with a2 allele.
[b]OR of study with a5 allele.
[c]OR of study with a6 allele.
*Comparisons using CLUMP program showed that significant difference for overall alleles between cases and controls in Caucasians ($\chi^2 = 39.285$, d.f. = 11, $P = 0.005$) and female Caucasians ($\chi^2 = 48.225$, d.f. = 11, $P = 0.002$), but not in Asians ($\chi^2 = 9.063$, d.f. = 11, $P = 0.510$), male Asians ($\chi^2 = 1.882$, d.f. = 11, $P = 0.970$) and female Asians ($\chi^2 = 11.494$, d.f. = 11, $P = 0.300$).

association between uVNTR and MDD in the Asian and male Asian group. But when we analyzed for an association with BPD, we did not find any significant associations in either the allelic or genotypic analysis, indicating that uVNTR is not a good candidate for being a gene marker for BPD. We found significant associations with BPD in the Caucasian and female Caucasian groups from the T941G allelic analysis but none with MDD. We found significant associations of the MAOA-CA polymorphism with BPD in female Caucasians. The a2, a5, and a6 alleles differ from each other in that the a5 and a6 alleles were more frequently found in the patients than in the controls; whereas the a2 allele was less frequent in the patients than in the controls. Therefore, these results may indicate that although MAOA is a common candidate gene for mood disorders, different polymorphisms and alleles may play different key roles in MDD and BPD.

T941G and promoter uVNTR are two polymorphisms of the MAOA gene, including its promoter region. These are different from each other in that Hotamisligil and Breakefield (1991) correlated the former with MAOA activity *in vitro*, whereas Sabol *et al.* (1998) established the latter as affecting the transcriptional activity of the MAOA promoter. The three polymorphisms of this gene act in different ways. Specifically, the MAOA-uVNTR marker seems to be associated with MDD in Asians and male Asians; whereas both the MAOA-T941G and the MAOA-CA markers appear to be associated with BPD in Caucasians and female Caucasians. Thus, our results may suggest that the T941G, the uVNTR and the MAOA-CA polymorphisms cause different responses depending on sex and ethnicity.

Areas for further consideration

Several specific details merit further consideration. First, ethnic stratification may exist. Our meta-analysis suggests a significant association of uVNTR with MDD in Asian populations and of T941G with BPD in Caucasian populations and of MAOA-CA with BPD, also in the Caucasian group. As noted above, the frequencies of the L and T alleles of uVNTR and T941G, respectively, varied in frequency between Asian and Caucasian populations. Therefore ethnic genetic stratification may help to explain ethnic differences in the development of MDD and BPD.

A second consideration is that when performing the sensitivity analysis, we found that certain studies seemed to affect the final result disproportionately. For example, regarding the association of uVNTR with MDD in the Asian group, if we removed the males, and separately the females, from the study by Yu *et al.* (2005), the association was no longer significant. Since the OR calculated using it was relatively larger [OR = 2.17 (1.17–3.67) for males, OR = 1.64 (1.13–2.37) for females] than that of the other studies, the Yu *et al.* (2005) study had a great impact on the pooled OR. The association of T941G with BPD in the Caucasian group was no longer significant after removing the female data from Lim *et al.* (1995), the male data from Craddock *et al.* (1995), or the female data from Preisig *et al.* (2000). Moreover, when we performed the sensitivity analysis of MAOA-CA with BPD in the Caucasian group, the association was significant if we removed one of these studies at a time – the males from Furlong *et al.* (1999) and the males from Lim *et al.* (1995) for allele a2. This indicates that more studies should be performed to confirm the conclusions of this meta-analysis.

In summary, this meta-analysis suggests a significant association between MAOA and mood disorders in specific groups. However, the relatively small number of individuals included in the meta-analysis is an impediment for more definitive conclusions, so further studies are necessary to confirm or refine the conclusions of the current meta-analysis.

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