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ORIGINAL ARTICLE

Meta-analyses of genetic studies on major depressive disorder

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The genetic basis of major depressive disorder (MDD) has been investigated extensively, but the identification of MDD genes has been hampered by conflicting results from underpowered studies. We review all MDD case–control genetic association studies published before June 2007 and perform meta-analyses for polymorphisms that had been investigated in at least three studies. The study selection and data extraction were performed in duplicate by two independent investigators. The 183 papers that met our criteria studied 393 polymorphisms in 102 genes. Twenty-two polymorphisms (6%) were investigated in at least three studies. Seven polymorphisms had been evaluated in previous meta-analyses, 5 of these had new data available. Hence, we performed meta-analyses for 20 polymorphisms in 18 genes. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Statistically significant associations were found for the *APOE* ε2 (OR, 0.51), *GNB3* 825T (OR, 1.38), *MTHFR* 677T (OR, 1.20), *SLC6A4* 44 bp Ins/Del S (OR, 1.11) alleles and the *SLC6A3* 40 bpVNTR 9/10 genotype (OR, 2.06). To date, there is statistically significant evidence for six MDD susceptibility genes (*APOE*, *DRD4*, *GNB3*, *MTHFR*, *SLC6A3* and *SLC6A4*).
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Introduction

Major depressive disorder (MDD) is the leading cause of disability for individuals of 15–44 years of age and is expected to be the second cause of disability worldwide for individuals of all ages by the year 2020.[1] MDD is caused by a complex interaction of a large number of genetic and non-genetic factors, each with a relatively small contribution to the disorder.[2] The total contribution of genetic factors in the origin of disease, the heritability, is estimated at 37%.[3] First-degree relatives of MDD patients have a 2- to 3-fold increased risk of MDD compared to the general population.[4]

Since the first case–control study on the relationship between polymorphisms and depression in 1978,[5] many genetic association studies have been conducted. Nevertheless, this accumulation of research has not resulted in the identification of many MDD susceptibility genes, because the findings of the association studies have often been inconsistent.[4] A first explanation for these inconsistencies concern methodological differences between the studies, such as differences in study design, study population and MDD diagnostic criteria, which hamper the comparability of the studies. A second explanation is that many studies had small sample sizes and therefore insufficient statistical power to demonstrate statistically significant effects of these low-risk susceptibility genes.[6] The impact of the latter problem can be reduced by pooling single studies in meta-analyses.[7]

To date, meta-analyses for MDD have been conducted for seven polymorphisms in six genes (Table 1). These meta-analyses included the genes encoding for angiotensin I-converting enzyme (*ACE*), dopamine receptor D4 (*DRD4*), serotonin 5-HT-2A receptor (*HTR2A*), methylenetetrahydrofolate reductase (*MTHFR*), serotonin transporter (*SLC6A4*) and tyrosine hydroxylase (*TH*).[8–15] The *DRD4* gene was significantly associated to MDD (odds ratio (OR), 1.73; 95% confidence interval (CI), 1.29–2.32),[11] and the *MTHFR* was significantly associated to depression (OR, 1.36; CI, 1.11–1.67).[15] *SLC6A4* 44 bp Ins/Del is the most frequently studied polymorphism to date and has been evaluated in three previous meta-analyses.[8,12,13] The first meta-analysis, including only 275 patients, showed a statistically significant increased MDD risk for carriers of S allele (OR, 1.23),[13] but two subsequent larger meta-analyses were unable to confirm this finding.[8,12]

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Table 1 Meta-analyses on major depressive disorder published before June 2007

Gene	*Polymorphism*	*Comparison*	*Cases*	*Controls*	*OR*	*(95% CI)*	*Year*	*Reference*
ACE	Ins/Del intron 16	ID vs II	586	5169	0.85	(0.55–1.30)	2006	[14]
		DD vs II			1.01	(0.71–1.45)		
DRD4	48 bp VNTR Exon 3	2 vs others	319	808	1.73	(1.29–2.32)**	2005	[11]
HTR2A	T102C	C vs T	768	959	0.96	(0.84–1.11)	2003	[8]
MTHFR	C677T	T vs C	291	897	1.15	(0.97–1.36)	2006	[9]
		TT vs CC	1280	10429	1.36	(1.11–1.67)*	2006	[15a]
SLC6A4 (SERT)	VNTR intron 2	9 vs 12	299	772	1.16	(0.55–2.50)	1998	[13]
		10 vs 12			1.01	(0.83–1.23)		
		9 vs 10, 12	592	2094	1.24	(0.72–2.14)	2003	[8]
		10 vs 9, 12			0.96	(0.84–1.10)		
		12 vs 9, 10			1.03	(0.89–1.18)		
		Continuous[b]	653	1817	0.99	(0.92–1.06)	2005	[12]
	44 bp Ins/Del Promotor	S vs L	275	739	1.23	(1.01–1.42)*	1998	[13]
		S vs L	941	2110	1.08	(0.96–1.22)	2003	[8]
		S vs L	1961	3402	1.05	(0.96–1.14)	2005	[12]
TH	Tetranucleotide repeat	2 vs 1	204	359	0.86	(0.59–1.26)	1999	[10]
		3 vs 1			0.88	(0.57–1.34)		
		4 vs 1			0.99	(0.68–1.42)		
		5 vs 1			0.76	(0.55–1.05)		

[a]Also includes studies that identified cases by questionnaires for assessment of symptoms of depression.
[b]Odds ratio obtained from logistic regression analyses considering allele length as a continuous variable.
*$P \leqslant 0.05$.
**$P \leqslant 0.001$.

Many other genes have been studied in relation to MDD. Our aim is to review all case–control studies on the association between genetic polymorphisms and MDD and perform meta-analyses for polymorphisms that had been investigated in at least three studies.

Materials and methods

Data sources
We searched PubMed for genetic case–control association studies on MDD published before June 2007. The search strategy was based on the keywords unipolar depression, major depression, depressive disorder or affective disorder in combination with chromosome, gene, allele or polymorphism. A second search was carried out using the name of the genes identified in the first search in combination with a broader keyword search: unipolar, depression, depressive or affective. In addition, we searched the PubMed, HuGeNet, ISI Web of Science databases, the Genetic Association Database and the reference lists of the retrieved articles.

Study selection
Genetic association studies were selected if they had applied a case–control design and compared adults diagnosed with standard diagnostic criteria for MDD. Studies were excluded if (1) cases were selected by questionnaires assessing symptoms of depression, (2) the study population included bipolar patients, (3) the distribution of genotypes in the control population was not in Hardy–Weinberg equilibrium or (4) if the data were reused in a larger study on the same polymorphism. Study selection and data extraction were performed in duplicate by two independent investigators (SLL and AGZ) and discrepancies were discussed with a third investigator (ACJWJ).

Data synthesis
Meta-analyses were performed for polymorphisms that had been investigated in at least three studies. Published meta-analyses were updated when new studies were available. ORs were summarized using both random effects and fixed effects meta-analyses with 95% CIs as outlined by DerSimonian and Laird.[16] The degree of heterogeneity between the study results was assessed with the I^2 statistics.[17] Forest plots were obtained for meta-analyses with statistically significant results, presenting random effect meta-analyses if there was evidence of heterogeneity ($I^2 > 50$),[18] and fixed effects meta-analyses if there was no heterogeneity. Sources of heterogeneity were explored in sensitivity analyses by removing one study at a time and calculating pooled ORs on the remaining studies. Sensitivity analysis also examines the extent to which pooled ORs were determined by significant effects of the first published study.[6] Publication bias was evaluated by visual inspection of the funnel plots.[19] Cochrane Review Manager Version 4.2 was used for all statistical analyses. $P < 0.05$ (two-tailed) were considered statistically significant.

Results

Of the 215 articles that met our inclusion criteria, 32 were excluded. Five studies selected cases by questionnaires assessing symptoms of depression,[20–24] 9 studied MDD and bipolar depression without

reporting separate genotype frequencies for the subtypes,[25–33] 8 had genotype frequencies in controls that were not in Hardy–Weinberg equilibrium,[34–41] and 10 reported data that had later been reused in a larger study for the same polymorphism.[42–51] The remaining 183 articles studied 393 different polymorphisms in 102 genes (Figure 1). Of the 393 polymorphisms, 371 were investigated in one or two studies (Table 2). Only 22 (6%) polymorphisms in 20 (19%) genes were investigated in more than 3 studies.

Of the 22 polymorphisms, 7 had been reviewed in previous meta-analyses, of which for 5 polymorphisms (*ACE* I/D, *HTR2A* T102C, *MTHFR* C677T, *SLC6A4* VNTR and *SLC6A4* 44 bp Ins/Del) were new data available. Hence, we performed meta-analyses for 20 polymorphisms in 18 genes (Table 3). Five polymorphisms showed statistically significant association to MDD: apolipoprotein E (*APOE*), guanine nucleotide-binding protein (*GNB3*) 825T, *MTHFR* 677T, dopamine transporter (*SLC6A3*) 40 bp VNTR, and the *SLC6A4* 44 bp Ins/Del (Figure 2). Figure 3 shows the funnel plots for the statistically significant meta-analyses.

APOE

The *APOE* ε2 allele was examined in 7 studies including a total of 827 cases and 1616 controls.[108–114] One study found a very strong protective effect for the ε2 allele (OR, 0.06; CI, 0.02–0.21),[108] while the others showed moderate protective effects (OR varying from 0.45 to 1.03; Figure 2). The pooled OR of the ε2 allele compared to the ε3 allele was 0.51 (CI, 0.27–0.97). The per allele meta-analysis of studies in Caucasian populations also showed a statistically significant pooled OR (0.72; CI, 0.51–1.00) with no evidence for between-study heterogeneity.[109–113] There were not enough studies to perform a meta-analysis of only studies from Asian origin. The pooled OR of the ε2 allele was not statistically significant when the first published study was removed from the analysis (OR, 0.51; CI, 0.25–1.05).[112] The funnel plot shows that the three smaller studies had lower ORs than the larger studies (Figure 3), but that there was no convincing evidence for publication bias.

GNB3

The association between the *GNB3* C825T polymorphism and MDD was investigated in 3 studies with a total of 375 cases and 492 controls.[44,133,134] All ORs in the individual studies were greater than 1. The per allele meta-analysis, testing for a trend by the number of T alleles, showed a significant effect of the T allele (OR, 1.38; CI, 1.13–1.69; Figure 2).

MTHFR

Six studies investigated the *MTHFR* C677T polymorphism in a total of 875 cases and 3859 controls.[15,194–198] Five studies showed an increased MDD

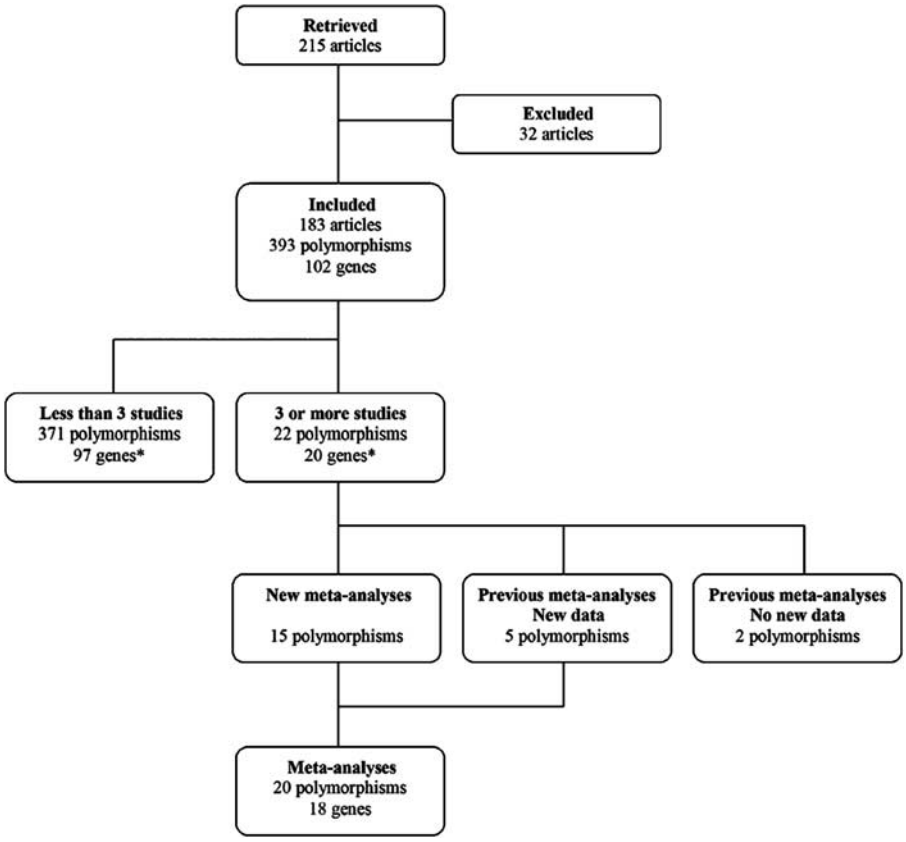

Figure 1 Selection of studies for the meta-analyses. *The number of genes does not add up to 102, because 8 genes were investigated for multiple polymorphisms of which some were addressed in more than three studies.

Table 2 Genes investigated in relation to major depressive disorder in less than three studies

AACT[67]	0/1	*CHRM2*[68]	1/1	*DRD1*[129]	1/7	*GABRA5*[69]	1/1	*HTR3A*[70,129]	0/18	*NOS3*[71]	0/3	*PDE11A*[72]	1/1
ACE[73,102]	2/38	*CHRNA7*[74]	1/1	*DRD2*[75,128,129]	1/12	*GABRA6*[76]	0/1	*HTR3B*[70]	1/12	*NPY*[77,78]	2/2	*PENK*[129]	0/2
ADCY9[79]	0/2	*CLOCK*[80]	0/1	*DRD3*[129]	0/2	*GADI*[81]	0/3	*HTR5A*[82,83]	2/2	*OASL*[84]	0/5	*POMC*[129]	0/6
ADORA2A[85]	0/1	*CNR1*[86]	0/1	*DRD4*[129]	0/6	*GCCR*[87,88]	4/6	*HTR6*[89]	0/1	*OPRD1*[129]	0/2	*PLA2G2A*[90,91]	2/2
ADRA2A[92]	0/1	*CNTF*[93,94]	0/2	*DRD5*[129]	0/1	*GMIP*[95]	4/4	*IL1B*[96]	0/1	*OPRK1*[129]	0/7	*SLC6A2*[97,199]	0/1
ADRB1[98]	0/1	*COMT*[122,123]	0/1	*DTNBP1*[99]	0/5	*GNAL*[100]	0/2	*IL6*[101]	0/1	*OPRM1*[129]	0/4	*SLC6A4*[129]	0/3
AR[140]	1/1	*CRHBP*[141]	2/7	*DUSP6*[142]	0/1	*GNAS*[100]	0/1	*IL10*[143]	0/1	*P2RX4*[84]	0/6	*TAC1*[73]	0/5
AVPR1B[144]	1/5	*CRHR1*[152]	1/3	*DXS7*[153]	1/1	*GPR50*[154]	2/3	*LBP*[115]	1/1	*P2RX7*[84]	1/16	*TACR1*[73]	0/5
BDNF[94,188]	0/2	*CRHR2*[155]	1/5	*ESR1*[140,156]	1/1	*GYPA*[158,159]	0/1	*LRP*[115]	0/1	*PAM*[73]	0/5	*TH*[10]	1/1
CAMKK2[84]	0/2	*CTLA4*[160]	0/1	*ESR2*[140]	1/1	*HP*[161,162]	0/1	*M6PR*[163]	1/1	*PDE2A*[72]	0/1	*TPH1*[129,219]	0/3
CCK[129,164]	0/4	*CYP2C9*[167]	1/1	*FACL4*[168]	1/1	*HTR1A*[129]	0/1	*MAOA*[169,170]	0/3	*PDE5A*[72]	1/1	*TPH2*[171–176]	7/34
CCKAR[129]	1/7	*D2S2944*[177–179,a]	1/1	*FZD3*[180]	0/4	*HTR1B*[129]	0/9	*MAOB*[169]	0/1	*PDE6C*[72]	0/2	*TNF*[181]	1/1
CCKBR[129]	0/4	*DDC*[182,183]	0/2	*G72*[184]	1/2	*HTR2A*[129]	0/2	*NGFR*[185]	1/1	*PDE9A*[72]	1/1	*WFS1*[186,192,193]	3/9
CCL2[203]	1/1	*DISC1*[204]	1/13	*GABRA1*[76,205]	0/5	*HTR2C*[129]	0/1	*NOS1*[206]	0/1	*PDE10A*[72]	0/3		

Numbers indicate the number of polymorphisms that were significantly associated to MDD out of the total number of different polymorphisms studied. Genes that were also included in the meta-analyses are here listed for other polymorphisms.
[a]Concerns a genetic marker.

risk for homozygous carriers of the T allele, but in only one study this association was statistically significant (Figure 2).[194] The combined OR was 1.20 (CI, 1.07–1.34) for the T allele, 1.38 (CI, 1.08–1.76) for homozygous carriers, and 1.22 (CI, 1.03–1.44) for heterozygous carriers. These associations were still statistically significant when the first published study was removed ($OR_{T\ vs\ C}$, 1.18; CI, 1.05–1.32, $OR_{TC\ vs\ CC}$, 1.22; CI, 1.03–1.44, $OR_{TT\ vs\ CC}$, 1.31; CI, 1.02–1.69).[194]

SLC6A3

The *SLC6A3* 40 bp VNTR polymorphism was investigated in 3 studies including a total of 151 cases and 272 controls.[121,128] Each study showed an increased MDD risk for carriers of the 9/10 genotype compared to the 10/10 genotype, but only one study was statistically significant.[121] The pooled OR for the 9/10 genotype compared to the 10/10 genotype was 2.06 (CI, 1.25–3.40).

SLC6A4

Twenty-four studies investigated *SLC6A4* 44 bp Ins/Del short/long (S/L) polymorphism including a total of 3752 cases and 5707 controls.[13,41,55,121,151,208,209,211,213–216,221–229] Twenty of the individual studies reported an OR higher than 1 for the S allele vs the L allele, but only in three studies this association was statistically significant (Figure 2).[214–216] The pooled OR for the S allele was 1.11 (CI, 1.04–1.19) and the pooled OR for homozygous carriers was 1.39 (CI, 1.20–1.61). When the first published study was removed, these ORs remained statistically significant ($OR_{S\ vs\ L}$, 1.11; CI, 1.01–1.22, $OR_{SS\ vs\ LL}$, 1.37; CI, 1.16–1.61).[55] The funnel plot shows asymmetry as 17 out of the 24 studies show a higher OR than the pooled estimate, but there was no evidence for publication bias toward studies with higher OR (Figure 3).

Other genes

The remaining meta-analyses were not significant, their ORs ranged from 0.74 to 0.99 for protective effects and from 1.09 to 1.63 for risk alleles/genotypes. Figure 4 shows the ORs in relation to the total number of cases and controls that were included in the meta-analyses. Fifteen out of 20 meta-analyses included less than 3000 subjects in total, of which 12 had less than 1000 cases. For example, the meta-analysis of *DRD3* Ser9Gly polymorphism included 541 cases and 606 controls. The OR of the homozygous carriers was 1.71 and was not significant. In contrast, the meta-analysis of the *SLC6A4* 44 bp Ins/Del polymorphism totalled more than 9000 persons and had a statistically significant OR of 1.11 for the S allele.

Discussion

In this review, we were able to perform meta-analyses for 18 out of 102 genes studied. We were not able to perform meta-analyses for 371 polymorphisms in 97 genes because there were less than three studies assessing the same polymorphism. We found significant evidence for five MDD susceptibility genes (*APOE*, *GNB3*, *MTHFR*, *SLC6A3* and *SLC6A4*).

The identified genes are involved in known biological pathways. The dopamine transporter (*SLC6A3*) mediates the active reuptake of dopamine from the synapse and is a principal regulator of dopaminergic neurotransmission. All antidepressants, in one way or the other, affect dopamine in the frontal area of the brain and in the nucleus accumbens.[56–58] The protein encoded by the *SLC6A4* gene is the drug target of serotonin reuptake inhibitors (SRIs) such as fluoxetine.[59] The 44 bp Ins/Del polymorphism is localized in the promotor region and may affect expression of the protein.[60] *GNB3* encodes for the β-subunit of G proteins, which is a target for antidepressant medication such as tricycles and mono-aminoxidase inhibitors.[61] *MTHFR* is a plausible candidate since the MTHFR enzyme metabolizes folate, and lower folate levels have been found associated with depression.[63] Furthermore, recovery

Table 3 Meta-analyses of genetic association studies on major depressive disorder

Gene	*Variant*	*Studies*	*Analysis*	*Heterozygotes*			*Homozygotes*			*Per allele*				
				Comparison	*OR (95% CI)*	I^2	*Comparison*	*OR (95% CI)*	I^2	*Studies*	*Comparison*	*OR (95% CI)*	I^2	*References*
ACE	Ins/Del -Intron 16	8	Fixed	ID vs II	0.94 (0.78–1.13)	27	DD vs II	1.15 (0.94–1.42)	26	8	D vs I	1.08 (0.97–1.20)	0	[14,102–107]
			Random		0.90 (0.71–1.13)			1.11 (0.85–1.45)				1.05 (0.91–1.21)		
APOE	ε2/ε3/ε4	5	Fixed	ε2/ε3 vs ε3/ε3	0.42 (0.28–0.62)***	72*	ε2/ε2 vs ε3/ε3	NA		7	ε2 vs ε3	0.51 (0.39–0.68)***	74***	[108–114]
			Random		0.41 (0.15–1.07)			NA				0.51 (0.27–0.97)*		
		5	Fixed	ε3/ε4 vs ε3/ε3	1.02 (0.78–1.35)	0	ε4/ε4 vs ε3/ε3	1.02 (0.44–2.37)	32	7	ε4 vs ε3	0.93 (0.76–1.14)	4	[108–115]
			Random		1.02 (0.78–1.35)			0.91 (0.25–3.33)				0.93 (0.75–1.15)		
BDNF	Val66Met	8	Fixed	Val/Met vs Val/Val	0.98 (0.89–1.09)	0	Met/Met vs Val/Val	1.05 (0.84–1.32)	53*	8	Met vs Val	1.01 (0.93–1.09)	55*	[116–120,188 b]
			Random		0.98 (0.89–1.09)			1.09 (0.72–1.65)				1.04 (0.90–1.21)		
COMT	Val158Met	6	Fixed	Val/Met vs Val/Val	1.14 (0.86–1.52)	29	Met/Met vs Val/Val	0.95 (0.67–1.33)	12	8	Met vs Val	0.98 (0.86–1.13)	43	[121–127]
			Random		1.13 (0.81–1.59)			0.95 (0.65–1.39)				1.00 (0.83–1.21)		
DRD3	Ser9Gly	4	Fixed	Ser/Gly vs Ser/Ser	0.92 (0.67–1.26)	33	Gly/Gly vs Ser/Ser	1.31 (0.80–2.14)	72*	4	Gly vs Ser	1.06 (0.85–1.34)	73**	[122,128–130]
			Random		0.96 (0.64–1.45)			1.71 (0.57–5.13)				1.19 (0.74–1.89)		
GABRA3	CA repeat -Intron 8	6	Fixed	*/1 vs 1/1	0.74 (0.49–1.12)	46	*/* vs 1/1	0.92 (0.40–2.11)	10	6	Others vs 1	0.91 (0.68–1.20)	49	[131,132]
			Random		0.63 (0.32–1.25)			0.97 (0.36–2.62)				0.88 (0.55–1.40)		
GNB3	C825T	3	Fixed	CT vs CC	1.25 (0.91–1.72)	50	TT vs CC	2.13 (1.39–3.28)**	67*	4	T vs C	1.38 (1.13–1.69)**	41	[44,133,134]
			Random		1.30 (0.81–2.09)			2.09 (0.97–4.51)				1.36 (1.04–1.77)*		
HTR1A	C-1019G	4	Fixed	CG vs CC	0.98 (0.72–1.33)	18	GG vs CC	1.33 (0.95–1.87)	79**	4	G vs C	1.16 (0.98–1.38)	77**	[129,135–137]
			Random		0.98 (0.69–1.38)			1.63 (0.72–3.70)				1.25 (0.85–1.84)		
HTR1B	G861C	3	Fixed	GC vs GG	0.99 (0.74–1.33)	42	CC vs GG	0.81 (0.46–1.41)	25	3	C vs G	0.96 (0.77–1.20)	48	[129,138,139]
			Random		0.98 (0.66–1.44)			0.79 (0.41–1.53)				0.94 (0.69–1.29)		
HTR2A	A-1438G	4	Fixed	AG vs AA	1.23 (0.88–1.73)	62*	GG vs AA	1.06 (0.73–1.55)	75**	4	G vs A	1.01 (0.85–1.21)	73**	[129,145–147]
			Random		1.15 (0.65–2.03)			0.98 (0.45–2.14)				0.96 (0.67–1.36)		
	T102C	8	Fixed	TC vs TT	1.00 (0.79–1.27)	0	CC vs TT	0.92 (0.71–1.21)	17	8	C vs T	0.96 (0.84–1.09)	26	[121,129,148–151,165]
			Random		1.00 (0.79–1.27)			0.92 (0.68–1.25)				0.96 (0.82–1.12)		
HTR2C	Cys23Ser	2	Fixed	Cys/Ser vs Cys/Cys	NA		Ser/Ser vs Cys/Cys	NA		13	Ser vs Cys	1.03 (0.85–1.25	50*	[121,129,166 b]
			Random		NA			NA				0.96 (0.73–1.28)		
MAOA	VNTR[a] -Promotor	4	Fixed	12 vs 22	1.34 (0.95–1.89)	17	11 vs 22	0.71 (0.49–1.02)	0	6	1 vs 2	0.86 (0.74–1.01)	65*	[62,157,187,189–191]
			Random		1.29 (0.87–1.91)			0.71 (0.49–1.03)				0.86 (0.65–1.13)		
MTHFR	C677T	6	Fixed	CT vs CC	1.22 (1.03–1.44)*	26	TT vs CC	1.38 (1.08–1.76)*	0	6	T vs C	1.20 (1.07–1.34)**	0	[15,194–198]
			Random		1.23 (0.95–1.58)			1.38 (1.08–1.77)*				1.20 (1.07–1.34)**		
SLC6A2	T-182C	3	Fixed	TC vs TT	1.21 (0.91–1.61)	52	CC vs TT	0.72 (0.45–1.14)	64	3	C vs T	0.97 (0.80–1.18)	68*	[199–201]
			Random		1.23 (0.81–1.85)			0.75 (0.33–1.67)				0.99 (0.70–1.40)		

Table 3 Continued

Gene	*Variant*	*Studies*	*Analysis*	*Heterozygotes*			*Homozygotes*			*Per allele*				
				Comparison	*OR (95% CI)*	I^2	*Comparison*	*OR (95% CI)*	I^2	*Studies*	*Comparison*	*OR (95% CI)*	I^2	*References*
SLC6A3 (DAT1)	40 bp VNTR -31-UTR region	3	Fixed	9/10 vs 10/10	2.06 (1.25–3.40)**	0	9/9 vs 10/10	1.46 (0.67–3.16)	0	3	9 vs 10	1.38 (0.98–1.94)	0	[121,128]
			Random		2.05 (1.24–3.40)**			1.47 (0.67–3.19)				1.38 (0.98–1.94)		
SLC6A4 (SERT)	44 bp Ins/Del –Promotor	22	Fixed	LS vs LL	1.05 (0.94–1.18)	0	SS vs LL	1.39 (1.20–1.61)**	0	24	S vs L	1.11 (1.04–1.19)**	30	[13,41,55,121,151,208,209,211,213–216,221–229]
			Random		1.05 (0.93–1.18)			1.39 (1.20–1.61)**				1.12 (1.03–1.22)**		
	VNTR Intron 2	8	Fixed	9/12 vs 12/12	1.25 (0.61–2.55)	0	9/9 vs 12/12	NA		11	9 vs 12	1.33 (0.78–2.27)*	0	[13,41,51,202,207–213,217]
			Random		1.22 (0.58–2.56)			NA	0			1.24 (0.69–2.23)		
		8	Fixed	10/12 vs 12/12	0.94 (0.74–1.20)	24	10/10 vs 12/12	1.17 (0.82–1.68)		11	10 vs 12	1.02 (0.89–1.17)	0	
			Random		0.98 (0.73–1.32)			1.18 (0.82–1.70)				1.04 (0.91–1.20)		
TPH1	A218C	9	Fixed	AC vs AA	1.10 (0.91–1.34)	49	CC vs AA	0.88 (0.71–1.09)	35	9	C vs A	0.94 (0.85–1.04)	6	[52–54,121,129,218–220 b]
			Random		1.14 (0.85–1.52)			0.86 (0.65–1.14)				0.94 (0.84–1.05)		

Abbreviations: CI, confidence interval; NA, not applicable, if data were available on less than three studies; OR, odds ratio.
I^2 = Heterogeneity, in percentage; *$P \leqslant 0.05$; **$P \leqslant 0.01$; ***$P \leqslant 0.001$.
[a]Allele 1, 30 bp repeat sequence present in three copies associated with lower transcription activity; allele 2, present in 3.5, 4 and 5 copies of 30 bp repeat sequence associated with higher transcription activity.
It was not possible to perform a meta-analyses for the *TPH2* G1463A polymorphism, because four out of five papers did not find the 1463A allele in cases nor in controls.
[b]References did not present complete information on genotype frequencies. Authors were contacted and all provided genotype data.

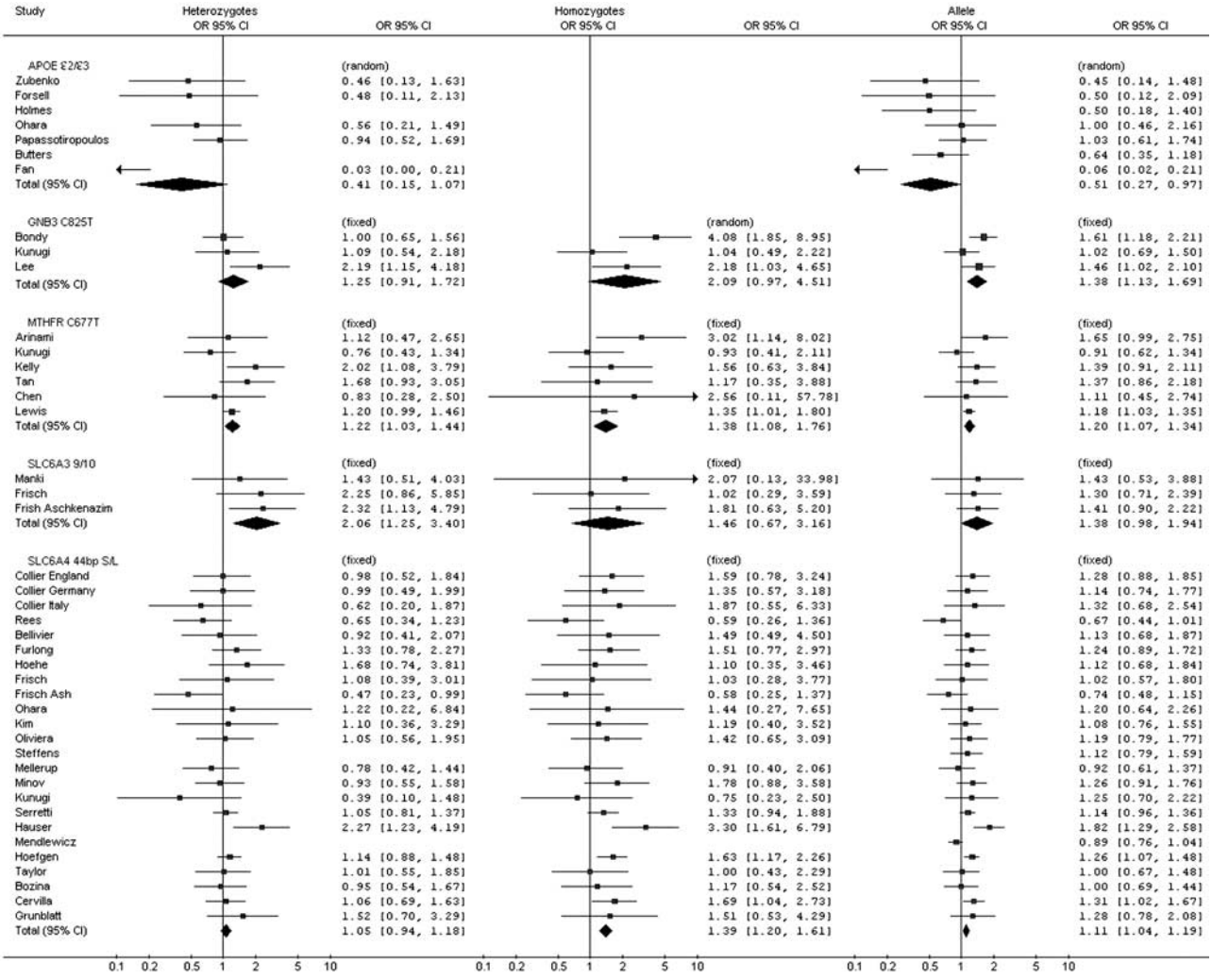

Figure 2 Forest plots for statistically significant meta-analyses. Pooled odds ratios.

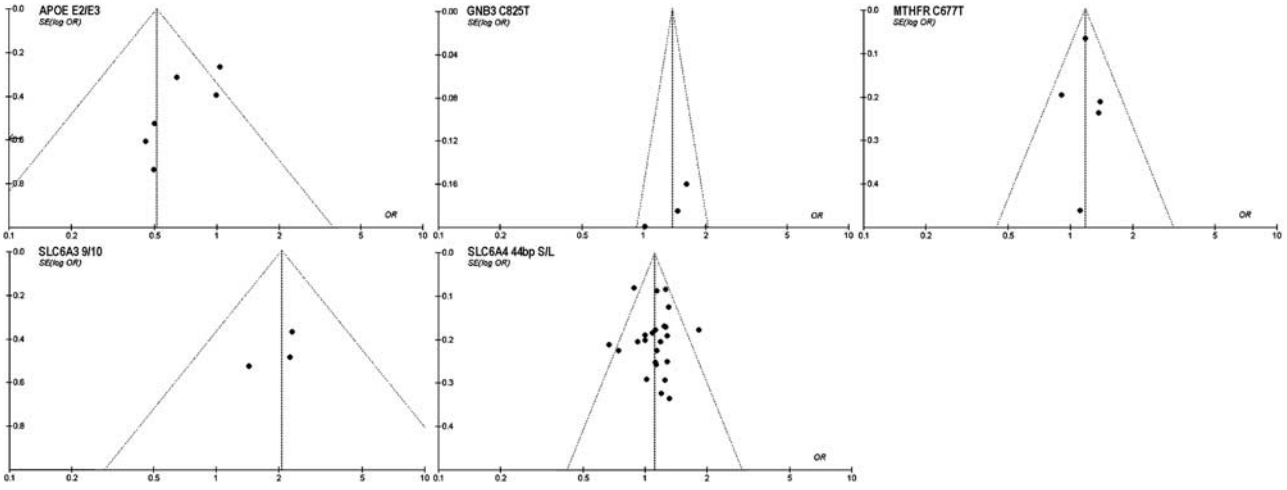

Figure 3 Funnel plots for statistically significant meta-analyses. Each dot represents one paper. S.e. (log OR) = s.e. of the log odds ratio.

from depression may be enhanced by folate supplements.[64] The most strongly associated gene in terms of the OR is *APOE*. APOE is recognized as a major determinant in lipoprotein metabolism, cardiovascular disease, Alzheimer's disease, cognitive function and immunoregulation;[65] and as each of these

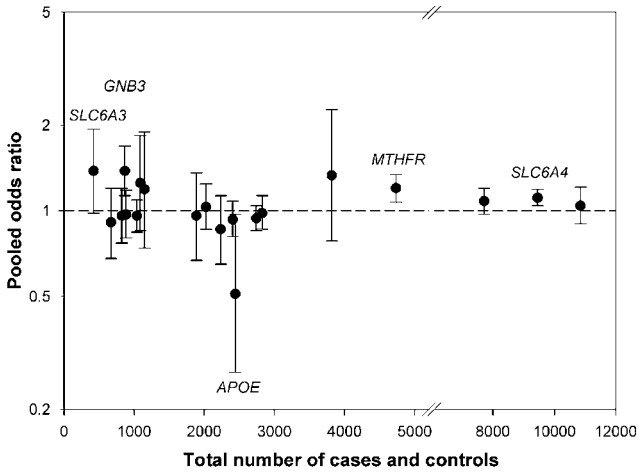

Figure 4 Pooled odds ratios in relation to the total number of cases and controls included in the meta-analyses. Odds ratios are reported for the per allele analyses.

disorders may be implicated in MDD, *APOE* remains at least a conceivable candidate gene to be studied further.

While these five genes were significantly associated to MDD in the meta-analyses, this does not mean the others may not be related. First, for many meta-analyses the total number of cases and controls studied was not large enough to detect moderate association to genes (OR $\sim$1.2–1.5). For example, the pooled ORs of *DRD3, HTR1A* and *SLC6A4* VNTR in intron 2 were 1.33–1.71, but not statistically significant. In terms of genetic effects for complex diseases, these are not small effects. In addition to small sample size, other reasons for the absence of statistical significance are the low frequencies of the risk variant and heterogeneity between studies.

Second, most studies have investigated only one single polymorphism per gene. Even if this single polymorphism appears not to be associated, there may still be other variants in the gene that are associated to MDD. The present meta-analyses only included two genes for which two polymorphisms were investigated (*HTR2A* and *SLC6A4*). The 44 bp Ins/Del polymorphism of the *SLC6A4* gene was found to be associated with MDD, while the VNTR intron 2 of *SLC6A4* was not. The latter shows that a negative meta-analysis on one polymorphism does not rule out significant associations of other polymorphisms in the same gene.

Most research on the genetic origin of MDD has focussed on a limited number of polymorphisms. Meta-analyses could only be performed for 22 of the 393 (6%) polymorphisms that had been investigated in relation to MDD. There were 371 polymorphisms that were only addressed in one or two studies, while 13 studies investigating the *HTR2C* Cys23Ser polymorphism and 24 studies investigated the *SLC6A4* 44 bp Ins/Del polymorphism. *SLC6A4* has been reviewed in three previous meta-analyses,[8,12,13] two showing no evidence for association with MDD. Differences between the meta-analyses may be explained by the inclusion of different studies, by heterogeneity between the results of individual studies, or by underestimation of effect sizes due to bi-allelic (S/L) instead of tri-allelic ($S/L_G/L$) grouping of the genotypes. The tri-allelic grouping distinguishes two long alleles (L_G/L), while the L_G expresses similar to the S allele.[60] The high numbers of studies of these polymorphisms are exceptions. For most polymorphisms reviewed in the meta-analyses the number of available studies was still small, and most meta-analyses did not include enough studies to investigate sources of heterogeneity in a meta-regression, or perform formal tests of publication bias. Meta-regression analysis would be useful to investigate whether the asymmetric funnel plots of the *SLC6A4* 44 bp Ins/Del and *APOE* ε2 are suggestive of publication bias or indicate true heterogeneity between populations. This review clearly demonstrates that more MDD genetic association studies are needed.

We excluded studies if they used questionnaires for the identification of cases, if they did not distinguish between MDD and bipolar depression, or if the genotype distributions in controls were not in Hardy–Weinberg equilibrium. Yet, we did not exclude studies or stratify the analyses based on other criteria, for example, whether controls were selected from the general population or whether they had been screened for the absence of depression, because the number of studies for each polymorphism was small. Such differences between studies may have contributed to the heterogeneity that was found in several of the meta-analyses. To investigate causes of between-study heterogeneity in future meta-analyses, it is essential that individual studies report key characteristics of their populations. To accumulate the evidence in genetic–epidemiological studies harmonizing designs, populations and measurements is deemed important and aimed for by the Network of Investigator Networks of the Human Genome Epidemiology Network.[66]

In conclusion, our meta-analyses found significant evidence for five MDD susceptibility genes (*APOE, GNB3*, *MTHFR*, *SLC6A3* and *SLC6A4*). Together with our previously published meta-analysis on *DRD4,*[11] there is evidence for six MDD susceptibility genes. The low coverage of genetic variants of candidate genes makes it impossible to exclude that the other genes studied are not involved in MDD. More research aiming to replicate findings in MDD is needed and efforts are required to standardize the methodology in research of MDD.

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