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Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder

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This systematic review summarizes pharmacogenetic studies on antidepressant response and side effects. Out of the 17 genes we reviewed, 8 genes were entered into the meta-analysis (SLC6A4, HTR1A, HTR2A, TPH1, gene encoding the β-3 subunit, brain-derived neurotrophic factor (BDNF), HTR3A and HTR3B). TPH1 218C/C genotype (7 studies, 754 subjects) was significantly associated with a better response (odds ratio, OR = 1.62; *P* = 0.005) with no heterogeneity between ethnicities. A better response was also observed in subjects with the Met variant within the BDNF 66Val/Met polymorphism (4 studies, 490 subjects; OR = 1.63, *P* = 0.02). Variable number of tandem repeats polymorphism within intron 2 (STin2) 12/12 genotype showed a trend toward a better response in Asians (STin2: 5 studies, 686 subjects; OR = 3.89, *P* = 0.03). As for side effects, pooled ORs of serotonin transporter gene promoter polymorphism (5-HTTLPR) I (9 studies, 2642 subjects) and HTR2A −1438G/G (7 studies, 801 subjects) were associated with a significant risk modulation (OR = 0.64, *P* = 0.0005) and (OR = 1.91, *P* = 0.0006), respectively. Interestingly, this significance became more robust when analyzed with side effect induced by selective serotonin reuptake inhibitors only (5-HTTLPR: *P* = 0.0001, HTR2A: *P* < 0.0001). No significant result could be observed for the other variants. These results were not corrected for multiple testing in each variant, phenotype and subcategory. This would have required a Bonferroni significance level of *P* < 0.0023. Although some heterogeneity was present across studies, our finding suggests that 5-HTTLPR, STin2, HTR1A, HTR2A, TPH1 and BDNF may modulate antidepressant response.
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Introduction

Major depressive disorder is a severe and increasingly important disease for its high prevalence and association with serious consequences such as suicide and substantial negative impact on social health, with both direct and indirect considerable costs worldwide.[1] The introduction of antidepressant drugs (ADs) has revolutionized the treatment of mood disorders. However, even though different classes of ADs have been used to treat depressive symptoms, the treatment efficacy is considerably incomplete and 60–70% of patients do not experience remission and 30–40% do not show a significant response.[2] Moreover, it usually takes 2–4 weeks to respond to antidepressants and, accordingly, clinical guidelines recommend to wait for at least 4–6 weeks before switching to another AD when an antidepressant response is not achieved. This delays patients to reach remission with high risks of clinical worsening and premature discontinuation.[3] Eventually, as for side effects, it is not possible to predict their occurrence as there is a wide interindividual variability, side effects are so common (40–90%[4]) that the clinical choice of a specific drug is partially determined by the probability of unwanted effects occurrence, based on the general knowledge of the drugs' properties and patient clinical status. Therefore, to minimize the disorder duration and the medical costs and to reduce the occurrence of side effects, it would be useful to know in advance the best therapeutic tool that is likely to be effective and tolerable for each patient. The genetically determined investigation of pharmacological responses would be much helpful in this direction.[5,6] However, the growing body of research in this field makes it difficult to summarize each candidate gene contribution to ADs response and intolerance. A useful previous contribution is mainly focused on pharmacokinetic aspects.[7]

This paper summarizes available literature of pharmacogenetic studies on depression from the pharmacodynamic point of view and aggregates such information into concise recommendations with meta-analysis techniques.[8–10]

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Materials and methods

Methods of pharmacogenetics data selection

To identify studies eligible for this meta-analysis, we searched Medline for all publications available up to March 2008 focusing on therapeutic response and adverse drug reactions of antidepressants in relation to genetic parameters. References were retrieved from Medline using search combinations of the terms: 'affective', 'depression', 'mood', 'antidepressant', 'polymorphism', 'genetic', 'gene', 'treatment response', 'side effect' and 'adverse drug reactions'. We also used reference lists from identified articles and reviews to find additional articles not indexed by Medline. Additionally we used data from our one in-press article.[11] Studies were included in the current meta-analysis if they evaluated the association between clinical response or intolerance to antidepressants treatments and genetic polymorphism in adult patients diagnosed with major depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders-IV criteria. Studies were excluded from the analysis if outcome for treatment response was not evaluated as response or remission rate on a depression scale, and studies with overlapping patient samples were excluded to only include the study with the larger number of patients. Remission was defined as a final Hamilton Rating Scale for Depression (HAM-D) total score of 7 or less and response was defined as at least 50% decrease in HAM-D or Montgomery and Asberg Depression Rating Scale (MADRS) total score. For the analysis, we followed the following protocol to minimize the heterogeneity of treatments and assessments across studies. The response rate was used if assessed within 4 weeks after treatment because it is a sensitive measure to evaluate speed of response[12,13] and the remission rate was instead used if evaluated at 6 or more weeks when possible, and, in defect of data, we used different observation lengths. Given the lack of unequivocal data about dominance for each single nucleotide polymorphism (SNP) genotype pooling, we tested the most reported assortment of variants. Bipolar disorder was excluded only to include the major depressive disorder, if separated data were available. If possible, subjects with concomitant medication such as lithium, pindolol or other psychotropic drugs were excluded from analysis. When needed, further analyses stratified by the ethnicity or class of ADs was performed. Hardy–Weinberg equilibrium was examined in studies where genotype frequencies were included. Data were entered into the Cochrane Collaboration review manager software (RevMan version 4.2) and analyzed by RevMan analysis 1.01. Heterogeneity between the studies was assessed with χ^2-test. Individual and pooled odds ratio (OR) and associated 95% confidence intervals (CIs) were calculated. We presented the result by random effect model when significant heterogeneity, defined with a threshold of $P<0.10$, was observed otherwise the result by fixed-effect model was presented. To control for potential publication bias, the funnel plots, OR against s.e. log OR, were presented and formally analyzed by the method of Egger *et al*.,[14] which is based on a weighted linear regression of standard normal deviation of the OR (standardized effect) on the inverse of the s.e. of the OR (precision). The larger the deviation of each study from the funnel curve, the more pronounced the asymmetry. Additionally in case of a first positive paper, we calculated the common ORs with stratified data from the first paper viewpoint with the Mantel–Haenszel method, then we also meta-regressed the individual study effect size against year of publication. Candidate genes for the review were selected if evaluated by two or more studies and entered to meta-analysis if data for the same polymorphism from three or more studies were available except for serotonin transporter gene promoter polymorphism (5-HTTLPR) on treatment response that we previously reported.[15] No statistical correction for the meta-analysis was applied for 11 main analyses and 11 subcategorical analyses in accordance with standard of the field;[16–21] however, we repeated analyses correcting for those factors.

Review and meta-analysis results

Serotonergic system

Serotonin transporter. Serotonin transporter gene promoter polymorphism: 5-HTTLPR. The molecular mechanism of ADs action, in particular, selective serotonin reuptake inhibitors (SSRIs), involves the inhibition of the serotonin transporter and thus modulates the serotonergic activity. The human gene-encoding serotonin transporter (SLC6A4), located on chromosome 17q11.1–q12,[22] is potentially involved in mood regulation and this makes it an ideal candidate for pharmacogenetic studies. Heils and co-workers identified a functional polymorphism in the transcriptional control region upstream of the SLC6A4-coding sequence (5-HTTLPR), it is a 44-bp insertion/deletion involving 2 U in a sequence of 16-repeat elements that could affect SLC6A4 expression.[23] Indeed the l 5-HTTLPR allele has twice the SLC6A4 expression in the basal state than the *s* form. Since 1998, the 5-HTTLPR has been investigated as a marker of ADs response in more than 20 studies (Table 1). Allele frequencies of this variant between Caucasians and Asians are different, the s allele being present in 42% of Caucasians but in 79% of Asians.[59] Nakamura *et al*.[60] examined the polymorphic region in detail and identified 10 sequence variants, concluding that the alleles previously reported as *s* and *l* should be further divided into four and six allelic variants, respectively. Alleles consist of a number of repetitive elements; the most frequent 14-repeat s allele was named 14A. The 14A and 14D variants differ from each other for the sixth repeat, the 14C variant differs from the 14A variant for the 11th repeat and the 14B

Table 1 Serotonin transporter gene polymorphisms and antidepressant response

Authors	*Number of subjects (male/female), mean age*	*Diagnosis and prescribed drug*	*Scale and study period (week)*	*Variant*	*Result*	*Ethnicity*
Smeraldi *et al.*[24a]	$N=53$ (16/37), 49.0 years	BP + MDD Fluvoxamine	HAM-D21 remission score change (6)	5-HTTLPR	l Allele showed better treatment outcome, $P=0.017$	Caucasian
Zanardi *et al.*[25]	$N=58$ (15/43), 47.7 years	BP + MDD Paroxetine	HAM-D21 remission score change (6)	5-HTTLPR	l Allele showed faster treatment outcome, $P<0.001$	Caucasian
Pollock *et al.*[26]	$N=57$ (NR), 72.0 years	MDD geriatric paroxetine or nortriptyline	HAM-D17 response score change (12)	5-HTTLPR	l/l showed faster treatment outcome to paroxetine, $P=0.028$	Caucasian
Kim *et al.*[27a]	$N=120$ (42/78), 54.2 years	BP + MDD + dythimia Fluoxetine or paroxetine	HAM-D17 response score change (6)	5-HTTLPR and STin2	s/s showed better treatment outcome, $P=0.007$; 12/12 showed better treatment outcome, $P=0.0001$	Asian
Zanardi *et al.*[28]	$N=155$ (47/108), 52.0 years	BP + MDD Fluvoxamine ± pindolor or lithium	HAM-D21 remission score change (6)	5-HTTLPR	l Allele showed better treatment outcome, $P=0.029$	Caucasian
Minov *et al.*[29]	$N=104$ (NR), 49.9 years (total sample)	MDD various ADs and ECT	HAM-D17 score change CGI (4)	5-HTTLPR	No association with treatment outcome	Not defined
Yoshida *et al.*[30]	$N=54$ (22/32), 51.2 years	MDD Fluvoxamine	MADRS response score change (6)	5-HTTLPR	s Allele showed better treatment outcome $P=0.01$	Asian
Ito *et al.*[31a]	$N=54$ (22/32), 51.2 years	MDD Fluvoxamine	MADRS response score change (6)	STin2	No association with treatment outcome	Asian
Takahashi *et al.*[32b]	$N=54$ (22/32), 51.2 years	MDD Fluvoxamine	side effect (6)	5-HTTLPR STin2	No association of both variants with drug-induced nausea	Asian
Yu *et al.*[33]	$N=121$ (70/51), 44.7 years	MDD Fluoxetine	HAM-D21 response score change (4)	5-HTTLPR	l/l showed better treatment outcome, $P=0.013$	Asian
Joyce *et al.*[34]	$N=139$ (NR), 31.8 years (total sample)	BP + MDD Fluoxetine or nortriptyline	MADRS response score change (6)	5-HTTLPR	l Allele showed better treatment outcome in patients >25 years, $P=0.026$	Caucasian
Perlis *et al.*[35b]	$N=36$ (MDD)	MDD Fluoxetine	HAM-D17 score change side effect (12)	5-HTTLPR	l Allele showed better outcome, $P=0.03$; l allele showed less side effects, $P=0.001$	Caucasian
Arias *et al.*[36]	$N=131$ (31/100), 40.0 years	MDD Citalopram	HAMD21 response remission score change (12)	5-HTTLPR	l Allele showed better treatment outcome, $P=0.006$	Caucasian
Durham *et al.*[37]	$N=106$ (47/59), 69.7 years	MDD geriatric sertraline	HAMD17 response score change CGI (8)	5-HTTLPR	l/l showed better treatment outcome at weeks 1 and 2, $P=0.01$	Mostly Caucasian
Serretti *et al.*[38]	$N=221$ (75/146), 50.6 years	BP + MDD Fluvoxamine or paroxetine ± lithium	HAM-D21 remission score change (6)	5-HTTLPR	l Allele showed better treatment outcome, $P=0.034$	Caucasian
Lee *et al.*[39]	$N=128$ (31/97), 48.3 years	MDD various ADs	CGI score change (3 years)	5-HTTLPR	l Allele showed better treatment outcome at 1–3 years, $P=0.005$	Asian

Table 1 Continued

Authors	*Number of subjects (male/female), mean age*	*Diagnosis and prescribed drug*	*Scale and study period (week)*	*Variant*	*Result*	*Ethnicity*
Murphy *et al.*[40b]	$N=244$ (119/125), 72.0 years	MDD geriatric Paroxetine or mirtazapine	HAMD17 GDS score change side effect (8)	5-HTTLPR	l/l showed better treatment outcome ($P=0.01$) and less discontinuation in paroxetine group ($P<0.05$); l/l showed more discontinuation in mirtazapine group, $P<0.05$	Mostly Caucasian
Yoshida *et al.*[41a]	$N=80$ (28/52), 51.4 years	MDD Milnacipran	MADRS response score change (6)	5-HTTLPR STin2	No associations of both variants with treatment outcome	Asian
Peters *et al.*[42]	$N=96$ (47/49), 37.1 years	MDD Fluoxetine	CGI response (12)	SLC6A4 20 variants including 5-HTTLPR and Stin2	rs25533 associated with treatment outcome, $P=0.037$	Mostly Caucasian
Kraft *et al.*[43]	$N=96$ (47/49), 37.1 years	MDD Fluoxetine	CGI response (12)	SLC6A4 27 variants including 5-HTTLPR	Better treatment outcome with l allele if rs25531 = A s allele if rs25531 = G	Mostly Caucasian
Kato *et al.*[44]	$N=81$ (45/36), 44.8 years	MDD Paroxetine or fluvoxamine	HAM-D21 response remission score change side effects (6)	5-HTTLPR	l Allele showed better treatment outcome to fluvoxamine, $P=0.012$ but no association with side effects	Asian
Smeraldi *et al.*[45]	$N=228$ (66/162), 52.6 years	BP + MDD Fluvoxamine ± lithium	HAM-D21 remission score change (6)	5 variants within 5-HTTLPR	16D l allele showed better treatment outcome than 16A l allele, $P=0.047$	Caucasian
Hong *et al.*[46a]	$N=224$ (93/131), 44.0 years	MDD Fluoxetine	HAM-D21 response (4)	5-HTTLPR STin2	l/l showed better treatment outcome, $P<0.001$ but no association of STin2 with treatment outcome	Asian
Kato *et al.*[47b]	$N=100$ (56/44), 43.7 years	MDD Paroxetine or fluvoxamine	HAM-D21 response remission score change side effects (6)	5-HTTLPR	l Allele showed better treatment outcome, $P=0.015$ but no association with side effects	Asian
Kirchheiner *et al.*[48]	$N=190$ (67/123), 46.0 years	BP + MDD various ADs	HAM-D21 response score change (3)	5-HTTLPR	No association with treatment outcome	Caucasian
Kim *et al.*[49a]	$N=208$ (52/156), 55.3 years	MDD SSRIs or nortriptyline	HAM-D17 response score change (6)	5-HTTLPR STin2	s/s showed better treatment outcome to SSRIs, $P=0.006$ and nortriptyline, $P=0.003$. 12/12 showed better treatment outcome to SSRIs, $P<0.001$	Asian

Table 1 Continued

Authors	*Number of subjects (male/female), mean age*	*Diagnosis and prescribed drug*	*Scale and study period (week)*	*Variant*	*Result*	*Ethnicity*
Popp *et al.*[50b]	$N=109$(43/66), 49.0 years	BP + MDD various ADs ± mood stabilizer	Retrospective study side effects (4)	5-HTTLPR STin2	l Allele showed less side effects, $P=0.002$ 12; allele showed less side effects, $P=0.004$	Mixed
Ng *et al.*[51]	$N=35$(17/18), 41.56 years	MDD Sertraline	HAM-D17 response side effect (6)	5-HTTLPR	No association with treatment outcome and side effects	Asian and Caucasian
Hu *et al.*[52b]	$N=1655$ (NR), 42.4 years (total sample)	MDD from STAR*D sample Citalopram	QIDS-C16 response remission side effect (12)	768 Variants including 5-HTTLPR	No association with treatment outcome l allele showed less side effects, $P=0.006$	Mixed
Bozina *et al.*[53a]	$N=130$ (69/61), 45.0	MDD Paroxetin 20 mg(fix) ± diazepam up to 30 mg	HAM-D17 response score change (6)	5-HTTLPR STin2	l Allele showed better treatment outcome, $P=0.0004$; 10/10 showed better treatment outcome, $P=0.035$	Caucasian
Kang *et al.*[54]	$N=101$ (29/72), 50.3 years	MDD Mirtazapine	HAM-D21 response (4)	5-HTTLPR	s/s showed better treatment outcome, $P=0.006$	Asian
Smits *et al.*[55b]	$N=212$(NR), 48.5 years (total sample)	MDD SSRIs	Side effect (6)	5-HTTLPR STin2	l/l showed less side effects but no association of STin2 with side effect	Caucasian
Kronenberg *et al.*[56]	$N=74$ (41/33), 7-18 years	MDD + Anxiety disorder adolescent Citalopram	CDRS-R score change side effect (6)	5-HTTLPR	l Allele showed better treatment outcome, $P=0.04$; l allele associated with agitation induced by citalopram, $P=0.05$	Jewish
Wilkie *et al.*[57a,b]	$N=163$(NR), 43.4 years (total sample)	MDD Various ADs	HAM-D response remission side effect (6 or more)	5-HTTLPR STin2	l Allele showed better treatment outcome, $P=0.02$; 10 allele showed better treatment outcome, $P=0.01$	Caucasian
Tanaka *et al.*[58b]	$N=72$(35/37), 47.0 years	MDD + Anxiety disorder Paroxetine	Side effect (12)	5-HTTLPR	No association with nausea induced by paroxetine	Asian

Abbreviations: AD, antidepressant drug; BP, bipolar disorder; CDRS-R, Children's Depression; Rating Scale–Revised; CGI, Clinical Global Impressions; ECT, electroconvulsive therapy; GDS, Geriatric Depression Scale; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; NR, not reported; QIDS-C, Quick Inventory of Depressive Symptomatology–Clinician Rated; 5-HTTLPR, serotonin transporter gene promoter polymorphism; STin2; VNTR polymorphism within serotonin transporter gene intron 2.

[a]Entered into meta-analysis of treatment outcome.

[b]Entered into meta-analysis of side effects.

variant is different from the 14D variant for the seventh repeat. According to the 16-repeat l alleles (16A, 16B, 16C, 16D, 16E and 16F), they differ from each other for the sixth, seventh and eighth repeats, 16A being the most frequent.

Pharmacogenetic studies of 5-HTTLPR: As regarding 5-HTTLPR efficacy on treatment response, we only present the summary of related studies in Table 1 because, as described in 'Materials and methods' section, we already reviewed and performed a meta-analysis that resulted in a significant association between 5-HTTLPR l variant and better response compared to s variant in both remission rate and response rate in Asian and Caucasian populations. Since then, three studies reported efficacy of some other polymorphisms linked to 5-HTTLPR on ADs response. We have investigated the antidepressant response to fluvoxamine in 228 depressed individuals carrying different l and s variants according to the Nakamura findings and we have observed a better and faster response in among l carriers according to the type of l allele. Specifically, 16F l carriers showed only a partial response, although 16D l carriers showed a marginally significantly better response than 16A l allele carriers.[45] Similarly, Hamilton and co-workers[42,43] reported a significant association of a functional SNP (rs25531) located just upstream of the 5-HTTLPR, indicating the same variant, with antidepressant response to fluoxetine treatment. In the presence of the G allele of this SNP, the l allele of 5-HTTLPR seems to be associated with nonresponse, although this is the case for the s allele in presence of the A allele of the SNP. However, we do not have sufficient data to meta-analyze this finding.

As for side effects of the traditional 5-HTTLPR, in a double-blind study of geriatric outpatients s-allele carriers treated with paroxetine showed a worse tolerability and higher discontinuation rates compared to l/l homozygotes, although in a subgroup on mirtazapine the s allele was associated with a better tolerability and fewer discontinuations[40] (Table 1). Other studies confirmed s variant as associated with side effects induced by SSRIs[55] including the large STAR*D sample[52] and by various ADs.[57] Furthermore s allele was shown to identify patients at risk for developing insomnia and agitation with fluoxetine treatment,[61] although one study focusing on children showed higher risk of l-allele carriers for agitation induced by citalopram.[56] Other studies reported no association between 5-HTTLPR variants and adverse reactions induced by SSRIs.[32,47,51,58]

Meta-analysis of 5-HTTLPR on side effects: For meta-analysis, the study by Ng *et al.*[51] was excluded because of defect of available data. Pooled OR of nine studies of side-effects rate induced by ADs including 2642 subjects was significant with a reduced risk of side effects for the l allele (0.64, CI: 0.49–0.82, $P=0.0005$; Figure 1).[32,40,47,50,52,55,57,58,61] Stronger significance was observed in pooled OR of eight studies when considering only SSRIs-induced side effects with 2323 subjects (0.58, CI: 0.45–0.77, $P=0.0001$).[32,40,47,52,55,57,58,61] This association was reduced when comparing l homozygotes to s-allele carriers (OR = 0.72, CI: 0.55–0.95, $P=0.02$). This significance reduction could be because of the exclusion for lack of data of the high-weight study by Perlis *et al.* or it might indicate a dominant effect of l variant. Four studies specified gastrointestinal side effects induced by SSRIs but the pooled OR of gastrointestinal side effects with 435 subjects was not significant (0.71, CI: 0.44–1.13, $P=0.15$);[32,47,55,58] however, a trend similar to the previous one was observed. These results indicate 5-HTTLPR as a possible predictor for intolerance to ADs, especially to SSRIs, as well as for treatment response. Given the heterogeneity among studies, further studies that evaluate specific side-effects symptoms are needed.

VNTR polymorphism within intron 2: Ogilvie *et al.*[63] identified a variable number of tandem repeats polymorphism within intron 2 (STin2) variant that contains 9, 10 or 12 copies of 16- or 17-bp repeats.[62] STin2, such as 5-HTTLPR, can influence SLC6A4 transcription and this polymorphism may have a synergistic effect with 5-HTTLPR.[64] STin2

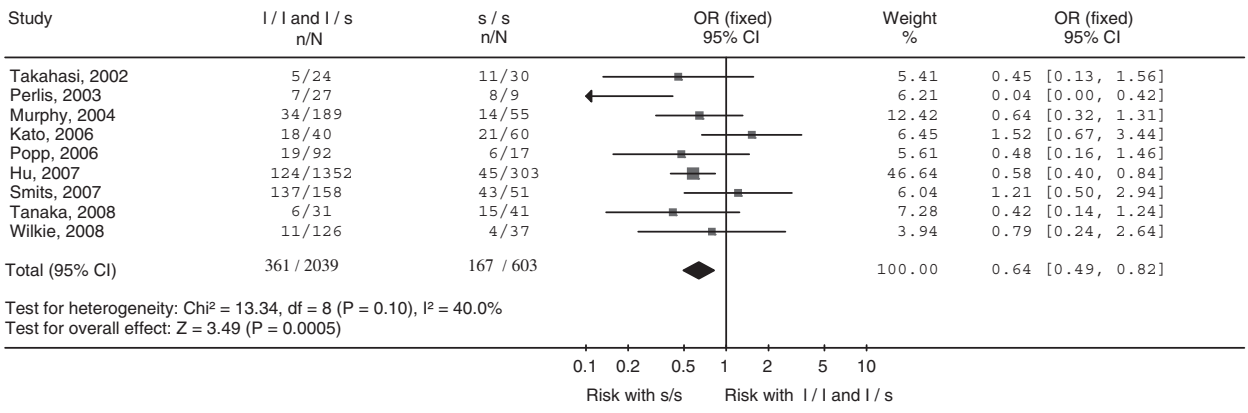

Figure 1 5-HTTLPR and side effects. Outcome data for l/l and l/s versus s/s.

allele frequencies between Caucasians and Asians are different, the l allele being present in 59% of Caucasians but in 89% of Asians.[59]

Pharmacogenetic studies of STin2: STin2 12 variant was associated with ADs better response in a Korean sample[27,49] but subsequent studies could not replicate it with negative[31,41,42,46] or opposite results[53,57] (Table 1). Furthermore, Kim *et al*.[49] reported that subjects carrying both STin2^{-}12/12 and 5-HTTLPR-s/s had the highest response rate compared to those of the other three genotype groups; Moreover, Bozina *et al*.[53] reported more sophisticated haplotype analyses indicating that a combination of the s variant of STin2–12 and 5-HTTLPR-s variant was overrepresented in the group of nonresponders, although haplotypes with STin2–10 and 5-HTTLPR-l were overrepresented in the group of responders. One study reported association of STin2–12 with less side effects induced by various kind of ADs but with a retrospective approach;[50] however, other studies found no associations.[32,55,57]

Meta-analysis of STin2 on treatment efficacy: We performed a meta-analysis of STin2 for treatment response retrieving seven studies with 979 subjects.[27,31,41,46,49,53,57] The study by Peters *et al*.[42] with 96 subjects was excluded from this analysis and also from subsequent analyses for HTR1A, HTR2A and TPH1 for lack of sufficient data. The pooled OR was significant (1.78, CI: 1.31–2.41, $P=0.0002$) but with evidence for large heterogeneity across studies ($P<0.00001$). The pooled OR in Asian populations was highly significant as well (3.71, CI: 2.43–5.66, $P<0.00001$) though heterogeneity across studies still remained. Because of the observed significant heterogeneity among studies we additionally performed a random effect model meta-analysis. The pooled OR was higher than those of fixed effect model but the *P*-value turned to no significance (2.17, CI: 0.76–6.23, $P=0.15$; Figure 2a); however, the pooled OR in Asians remained marginally significant (3.89, CI: 1.18–12.85, $P=0.03$). In detail, the OR was because of the sum of two studies by the same author showing a better response effect of the 12 of 12 genotype.[27,49] Moreover, those two studies had the lowest weight. However, the OR of all studies performed in Asian populations was higher than 1 whereas lower than 1 in Caucasians.

Meta-analysis of STin2 on side effects: As for side effects, the pooled OR of four studies with 535 subjects was not significant in both fixed (0.78, CI: 0.43–1.42, $P=0.42$) and random effect models (0.91, CI: 0.27–3.07, $P=0.88$; Figure 2b).[32,50,55,57] The OR was higher than 1 with less side effects of 10 of 10 carriers in all studies except in one retrospective study; however, the pooled OR excluding the retrospective study was not significant either. These results could indicate a possible association between STin2 and clinical response to ADs in opposite directions in different ethnicities, a phenomenon already observed and previously discussed regarding 5-HTTLPR.[15,65] This ethnic difference might be because of the

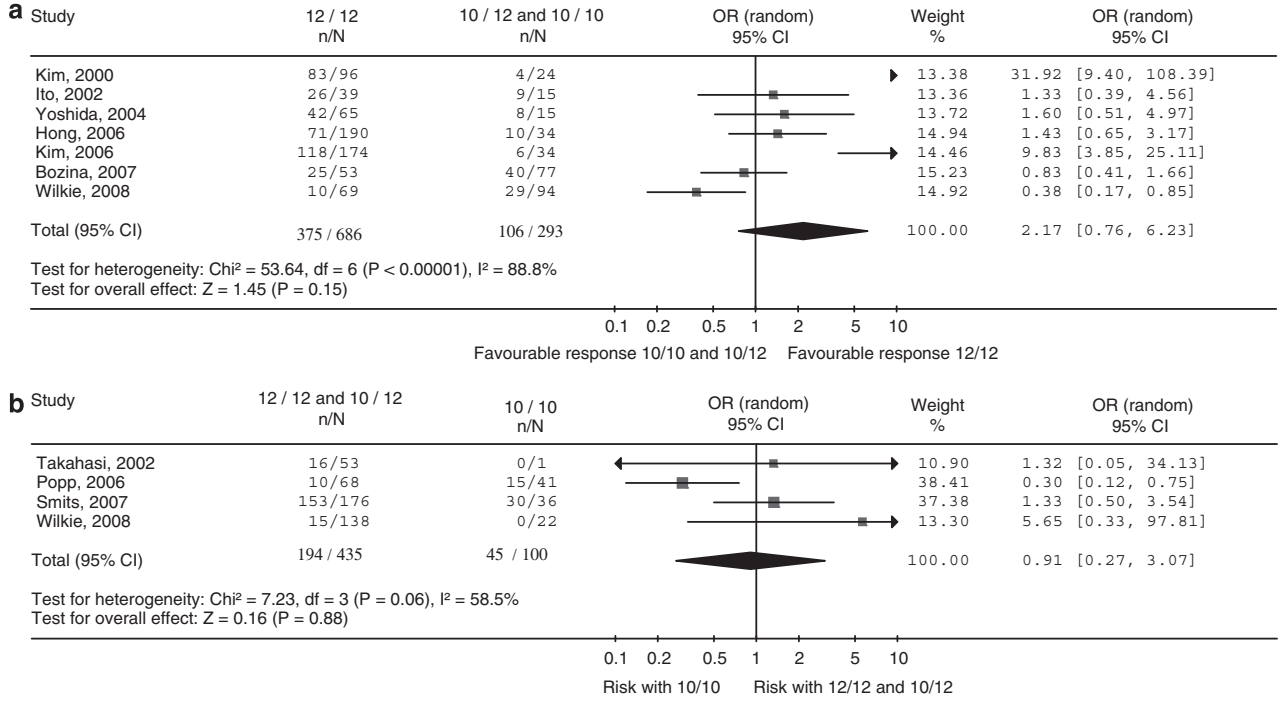

Figure 2 (**a**) STin2 and treatment response. Outcome data for 12/12 versus 10/12 and 10/10. (**b**) STin2 and side effects. Outcome data for 12/12 and 10/12 versus 10/10.

different allele frequency and its functional linkage to other polymorphism such as 5-HTTLPR whose effect also varies among ethnicities.

Serotonin receptors. Serotonin receptors are among the most important candidates for modulation of ADs response as most ADs increase the concentration of serotonin present in the synaptic cleft. The increased amounts of serotonin will then act on postsynaptic and presynaptic receptors.

Serotonin-1A receptor. The Serotonin-1A receptor (5-HT1A) gene (HTR1A), mapped on chromosome 5q11.2–13, is intronless and it spans about 1200 bp. A total of 50 SNPs are known so far and most of them are in strong linkage disequilibrium (LD) because of its short and intronless extension.[66] Among them −1019C/G (rs6295), in the promoter region of the gene, has been found to be associated with an altered expression and the function of HTR1A.[67–69] This variant was involved in the regulation of the transcription rate of the HTR1A gene. When the G allele is present, it prevents the binding of the putative repressor to DNA, leading, in this way, to an increase of 5-HT1A auto receptors and to a reduction of serotonergic neurotransmission.[70] For this variant, discrepancy of allele frequency could be observed between ethnicities; the G allele being present in about 50% of Caucasians, but only in 21% of Asians.[71,72] When performing a meta-analysis about −1019C/G, we have to consider the genotyping definition of this SNP in advance. We realized that the genotyping definition of C/G was not correct in two previous pharmacogenetic studies and one association study by the same research group in Asian depressed patients.[46,72,73] In fact, the restriction enzyme cutting produced results opposite to the published ones. That is, many authors consider the C allele as uncut while the G allele is uncut. Therefore their result that patients with the C/C genotype had a significantly better response than patients with the G allele actually means that G/G genotype carriers had a better response compared to C-allele carriers. Further, two earlier studies by Arias *et al.*[74,75] presented the same miss-definition. These miss-definitions with opposite result were confirmed by private correspondence with authors of these studies.[46,72,74,75]

Pharmacogenetic studies of HTR1A: In Caucasian samples, we previously observed a moderate liability effect of G variants in antidepressant response in bipolar disorder but not in major depression[76] (Table 2). The study by Lemonde *et al.*,[77] reporting the response of G variants as worse compared to C/C in patients prescribed with flibanserin but not with fluoxetine should be considered as a negative result from the perspective of the type of prescribed drug. One study reported similar findings with less responders in G/G carriers in a small sample.[69] Although the study by Baune *et al.*[80] revealed opposite findings as also in the one by Arias *et al.*,[75] but this significance could be seen only after considering the genetic variation together with the 5-HTTLPR. Thus, results seem discrepant in Caucasian samples; however, most studies reported negative findings.[42,75–77,79] In the Asian population, three studies reported significant results with better response for G/G compared to C-allele carriers.[11,46,72] A different 272Gly/Asp (rs1800042) polymorphism was explored in Japanese depressive outpatients treated with fluvoxamine[78] (Table 2). Asp-allele carriers showed a more marked reduction in depressive symptomatology compared to Gly/Gly homozygotes. This finding was not confirmed by subsequent studies,[72,79] although this polymorphism was found to be in strong LD with −1019C/G.[72] We previously reported a significant association of treatment response with two other SNPs, rs10042486 in the promoter region and rs1364043 is in downstream region, and also found that the minor allele homozygous combination −1019G-rs10042486C-rs1364043T (all in strong LD) was robustly associated with a better response and fast remission (Table 2).[11] Further variants with large samples should be investigated to cover all the gene.[81]

Meta-analysis of HTR1A −1019C/G on treatment efficacy: In Figure 3, we reported the meta-analysis results based on six studies and including data from 893 subjects. The study by Yu and co-workers was excluded from the analysis because the analyzed sample was the same as the study by Hong and co-workers.[46,72] The study by Levin *et al.*[79] was excluded for the lack of description about assessment procedure with no use of common assessment tools such as HAM-D or MADRS and because it was a retrospectively assessed study. The study by Baune *et al.*[80] was excluded because of the defect of available data. The assessment definitions were widely different across studies. Our study showed both response and remission rate at weeks 2, 4 and 6.[11] Studies of Lemonde *et al.*[77] and Hong *et al.*,[46] assessed response rate at week 4. Other studies assessed remission rate but one study evaluated it at 1 year after treatment[82] whereas other studies at week 6–12.[75,76] The pooled OR of six studies including 893 subjects was not significant (1.00, CI: 0.69–1.46, $P = 0.98$).[11,46,75–77,82] No heterogeneity could be seen among studies; however, there were also evident ethnic differences between Asian and Caucasian populations; in fact an OR of all studies performed in Caucasians was lower than 1 whereas higher than 1 in two Asian studies. Pooled OR of the studies in Caucasian only was not significant; however, in Asian studies only the effect was significant (4.56 CI: 1.42–14.69, $P = 0.01$), although only two studies with 361 subjects were included. At this time −1019C/G of HTR1A could be therefore considered as a possible predictor for ADs response in the Asian population. Ethnic differences based on different allele frequencies among ethnicities and other SNPs possibly linked to this SNP could be reasons of this

Table 2 Serotonin receptor 1A gene polymorphisms and antidepressant response

Authors	*Number of subjects (male/female), mean age*	*Diagnosis and prescribed drug*	*Scale and study period (week)*	*Variant*	*Result*	*Ethnicity*
Lemonde *et al.*[77a]	$N=118$ (NR), 47.0 years (total sample)	MDD Fluoxetine + pindolor nefazodone + pindolor flibanserin	HAM-D17 response score change (4)	HTR1A −1019C/G	C/C showed better treatment outcome to flibanserin, $P=0.039$ but no association with ADs	Caucasian
Serretti *et al.*[76a]	$N=262$ (89/173), 51.2 years	BP + MDD Fluvoxamine ± lithium	HAM-D21 remission score change (6)	HTR1A −1019C/G	C/C showed better treatment outcome in BP, $P=0.036$ but no association in MDD	Caucasian
Suzuki *et al.*[78]	$N=52$ (29/23), 40.9 years	MDD Fluvoxamine	HAM-D17 response remission score change (12)	HTR1A 272Gly/Asp	Asp showed better treatment outcome, $P=0.036$	Asian
Peters *et al.*[42]	$N=96$ (47/49), 37.1 years	MDD Fluoxetine	CGI response (12)	HTR1A 10 SNPs including −1019C/G	No association with treatment outcome	Mostly Caucasian
Arias *et al.*[75a]	$N=130$ (31/99), 40.0 years	MDD Citalopram	HAM-D21 remission score change (12)	HTR1A −1019C/G	G with 5-HTTLPR l showed better treatment outcome, $P=0.009$	Caucasian
Parsey*et al.*[69a]	$N=22$ (4/18), 40.9 years	MDD Various ADs and ECT	HAM-D24 remission (1 year)	HTR1A −1019C/G	C Allele showed better treatment outcome 1 year after treatment, $P=0.005$	Caucasian
Hong *et al.*[46a]	$N=224$ (93/131), 44.0 years	MDD Fluoxetine	HAM-D21 response (4)	HTR1A −1019C/G	G/G showed better treatment outcome, $P=0.005$	Asian
Yu *et al.*[72]	$N=222$ (94/128) 43.6 years	MDD Fluoxetine	HAM-D21 response (4)	HTR1A -1019C/G 272Gly/Asp	G-Asp showed better treatment outcome $P=0.0021$	Asian
Levin *et al.*[79]	$N=130$ (22/32), 51.2 years	Not define SSRIs	Retrospective study without adequate assessment	HTR1A 7 SNPs including −1019C/G 272Gly/Asp	No association with treatment outcome	Asian
Baune *et al.*[80]	$N=335$ (143/192), 49.7 years (MDD sample)	BP + MDD Various ADs ± mood stabilizers and/or neuroleptics	HAM-D21 score change (6)	HTR1A −1019C/G	G showed better treatment outcome in melancholic depression, $P=0.01$	Caucasian
Kato *et al.*[11a]	$N=137$ (75/62), 45.8 years	MDD Fluvoxamine, paroxetine or milnaciplan	HAM-D21 response remission score change side effects (6)	HTR1A −1019C/G rs10042486 rs1364043	−1019G/G ($P<0.0001$), rs10042486C/C ($P<0.0001$), rs1364043T/T ($P=0.018$) and minor allele homozygotes of these 3 SNPs ($P<0.0001$) showed better treatment outcome	Asian

Abbreviations: AD, antidepressant drug; BP, bipolar disorder; CGI, Clinical Global Impressions; ECT, electroconvulsive therapy; HAM-D, Hamilton Rating Scale for Depression; HTR1A, serotonin receptor 1A gene; MDD, major depressive disorder; NR, not reported.
[a]Entered into meta-analysis of treatment outcome.

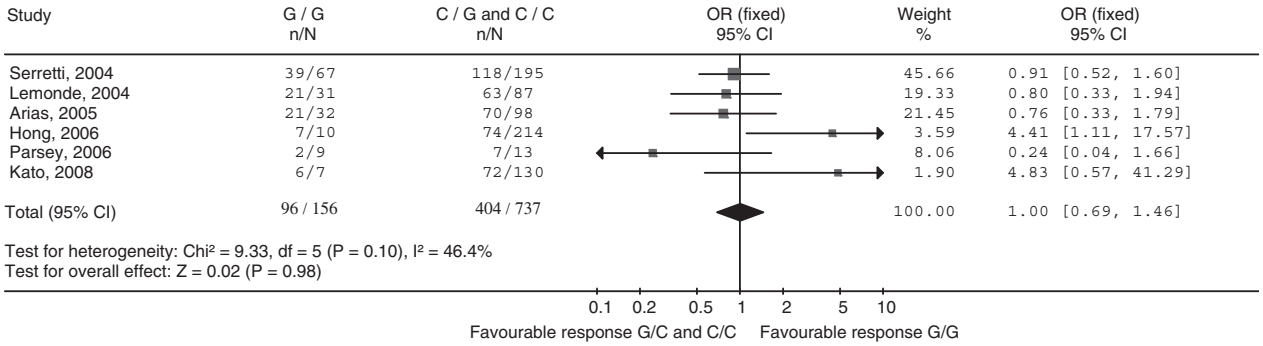

Figure 3 HTR1A −1019C/G and treatment response. Outcome data for G/G versus C/G and C/C.

discrepancy. Further studies should investigate the association of HTR1A with ADs response, especially in Asian samples.

Serotonin-2A receptor (5-HT2A): 5-HT2A gene (HTR2A) is located in position 13q14-q21, it consists of three exons separated by two introns and it spans over 20 kb.[83,84] Two important common SNPs 102T/C (rs6313) and −1438A/G (rs6311) are in almost complete LD, that is, T allele of 102T/C is in complete LD with the A allele at −1438A/G as well as C allele of 102T/C SNP with G allele at −1438A/G.[85,86] Allele frequencies of these variants were not different between Caucasians and Asians, the −1438G (102C) allele being present in about 50% of subjects. A postmortem brain study found that the C variant of 102T/C was associated with lower messenger ribonucleic acid (mRNA) and lower protein expression compared to the T variant.[87] Another study reported that the presence of the A variant of −1438A/G significantly increased promoter activity compared to the G variant.[88] However, one study failed to replicate the differences in mRNA expression.[89]

Pharmacogenetic studies of HTR2A: Some studies reported an association of HTR2A −1438G variants or 102C variants with good response to ADs,[47,29,90] whereas other studies gave no association (Table 3).[41,42,46,57,91,92,98] As concerns other SNPs within this gene, three studies investigated the nonsynonymous SNP rs6314, although results were inconsistent.[29,42,57] One study showed a marginal association of −1420C/T (rs6306) with SSRI response. Two studies analyzing a large number of SNPs reported one SNP in the 3′ UTR, rs1923882, and two SNPs in the second intron, rs3125 and rs7997012, as associated with ADs response.[42,96]

As for association with intolerance to ADs, five studies found significant associations of −1438G/G or 102C/C with appearance of side effects[47,57,94,95,97] although two studies found no association.[58,93]

Meta-analysis of HTR2A −1438A/G (102 T/C) on treatment efficacy: Figure 4a presents results of the meta-analysis for HTR2A −1438A/G and 102 T/C. In this analysis, 102C variant was considered as −1438G whereas 102T as −1438A, as previously described. The study by Minov *et al.*, Mcmahon *et al.* and Kang *et al.* were excluded from the analysis because data of response or remission rate were not available.[29,96,98] Pooled OR of seven studies of response or remission including 1012 subjects demonstrated a nonsignificant result (1.06 CI: 0.78–1.44, $P=0.69$; Figure 4a).[41,46,47,57,90–92] However, we found a marginal significance in pooled OR of four studies with 429 subjects evaluating response rate to SSRIs treatment only with favorable response in the G/G genotype carriers compared to A/G or A/A carriers (1.69 CI: 1.03–2.75, $P=0.04$).[46,47,90,92] This analysis turned out to include only studies in Asian population.

Meta-analysis of HTR2A −1438A/G (102 T/C) on side effects: As for side effects, interestingly, pooled OR of seven studies with 801 subjects was significant (1.91, CI: 1.32–2.78, $P=0.0006$; Figure 4b)[47,57,58,93–95,97] with an higher risk of side effects for the G/G genotype, furthermore pooled OR of side-effects rate induced by SSRIs only, including 590 subjects was highly significant (2.33, CI: 1.53–3.56, $P<0.0001$). Four studies specified gastrointestinal symptom induced by SSRIs and interestingly the pooled OR of gastrointestinal side effect with 311 subjects was significant (2.30, CI: 1.26–4.21, $P=0.007$) in the same direction of the total side effects even with smaller number of subjects.[47,58,93,95] These results suggest that −1438A/G and 102 T/C SNP of HTR2A could be useful predictors for intolerance to ADs in particular to SSRIs, and have a possibility to be a predictor for treatment response to SSRIs in Asian population. Also for this SNP, we found inconsistent results between Asian and Caucasian samples although the allele frequencies are the same in both ethnicities. This may lead to the hypothesis that other SNPs linked to this SNP or cultural or social differences could also influence ADs response. A more complete coverage of the gene would in any case be preferable.[99]

Serotonin-3A and -3B receptors (5-HT3A and 5-HT3B): To date, five subtypes of 5-HT3 genes (HTR3) have been cloned, HTR3A and HTR3B have been best characterized and identified to have some genetic

Table 3 Serotonin receptor 2A gene polymorphisms and antidepressant response

Authors	*Number of subjects (male/female), mean age*	*Diagnosis and prescribed drug*	*Scale and study period (week)*	*Variant*	*Result*	*Ethnicity*
Minov *et al.*[29]	*N*=104 (NR), 49.9 years (total sample)	MDD Various ADs and ECT	HAM-D17 score change CGI (4)	HTR2A 102T/C rs6314C/T	102C allele showed better treatment outcome, *P*=0.023	Not defined
Cusin *et al.*[91a]	*N*=408 (130/278), 51.9 years	BP+MDD Fluvoxamine or paroxetine±lithium and/or pindolor	HAM-D21 remission score change (6)	HTR2A 102T/C -1420C/T	No association of 102T/C with treatment outcome −1420C allele showed better treatment outcome, *P*=0.001	Caucasian
Sato *et al.*[92a]	*N*=54 (22/32), 51.2 years	MDD Fluvoxamine	MADRS response score change (6)	HTR2A −1438A/G	No association with treatment outcome	Asian
Yoshida *et al.*[93b]	*N*=54 (22/32), 51.2 years	MDD Fluvoxamine	Side effect (6)	HTR2A −1438A/G	No association with nausea induced by fluvoxamine	Asian
Murphy *et al.*[94b]	*N*=246 (120/126), 72.2 years	MDD Paroxetine or Mirtazapine	Side effect (8)	HTR2A 102T/C	C/C associated with discontinuation due to paroxetine side effects (*P*=0.001) but not with those of mirtazapine	Caucasian
Peters *et al.*[42]	*N*=96 (47/49), 37.1 years	MDD Fluoxetine	CGI response (12)	HTR2A 17 SNPs including −1438A/G 102T/C	rs1923882 (*P*=0.00076), rs6314 (*P*=0.020) and rs3125 (*P*=0.026) associated with treatment outcome	Mostly Caucasian
Yoshida *et al.*[41a]	*N*=80 (28/52), 51.4 years	MDD Milnacipran	MADRS response score change (6)	HTR2A −1438A/G	No association with treatment outcome	Asian
Choi *et al.*[90a]	*N*=71 (20/51), 52.7 years	MDD Citalopram	HAM-D21 response remission score change (4)	HTR2A −1438A/G	G/G showed better treatment outcome, *P*=0.034	Asian
Suzuki *et al.*[95b]	*N*=96 (47/49), 40.3 years	MDD Fluvoxamine	Side effect (12)	HTR2A −1438A/G	G Allele with low metabolizer of CYP2D6 associated with the gastrointestinal side effects, *P*=0.004	Asian
Hong *et al.*[46a]	*N*=224 (93/131), 44.0 years	MDD Fluoxetine	HAM-D21 response (4)	HTR2A 102T/C	No association with treatment outcome	Asian
McMahon *et al.*[96]	*N*=859+438 (NR), 42.7 years (total sample)	MDD from STAR*D sample Citalopram	QIDS-C16 response remission (6)	768SNPs including HTR2A SNPs	rs799701 associated with treatment outcome, *P*=0.000002	Mixed
Bishop *et al.*[97b]	*N*=81 (61/20), 26.6 years	MDD Various SSRIs	Side effect (6)	HTR2A −1438A/G	G/G associated with more sexual dysfunction induced by SSRIs, *P*=0.022	Mostly Caucasian
Kato *et al.*[47a,b]	*N*=100 (56/44), 43.7 years	MDD Paroxetine or fluvoxamine	HAM-D21 response remission score change side effects (6)	HTR2A −1438A/G	G/G showed better treatment outcome, *P*=0.034 G/G associated with nausea induced by paroxetine, *P*=0.014	Asian
Kang *et al.*[98]	*N*=101 (29/72), 50.3 years	MDD Mirtazapine	HAM-D21 score change (8)	HTR2A −1438A/G	No association with treatment outcome	Asian
Wilkie *et al.*[57a,b]	*N*=163(NR), 43.4 years (total sample)	MDD Various ADs	HAM-D response remission side effect (6 or more)	HTR2A 102T/C rs6314C/T	102C/C associated with side effects induced by paroxetine, *P*=0.007 rs6314C/T showed better treatment outcome than C/C and T/T, *P*=0.002	Caucasian
Tanaka *et al.*[58b]	*N*=72 (35/37), 47.0 years	MDD+Anxiety disorder Paroxetine	Side effect (12)	HTR2A 102T/C	No association with nausea induced by paroxetine	Asian

Abbreviations: AD, antidepressant drug; BP, bipolar disorder; CGI, Clinical Global Impressions; ECT, electroconvulsive therapy; HAM-D, Hamilton Rating Scale for Depression; HTR2A, Serotonin receptor 2A gene; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; NR, not reported; QIDS-C, Quick Inventory of Depressive Symptomatology–Clinician Rated.
[a]Entered into meta-analysis of treatment outcome.
[b]Entered into meta-analysis of side effects.

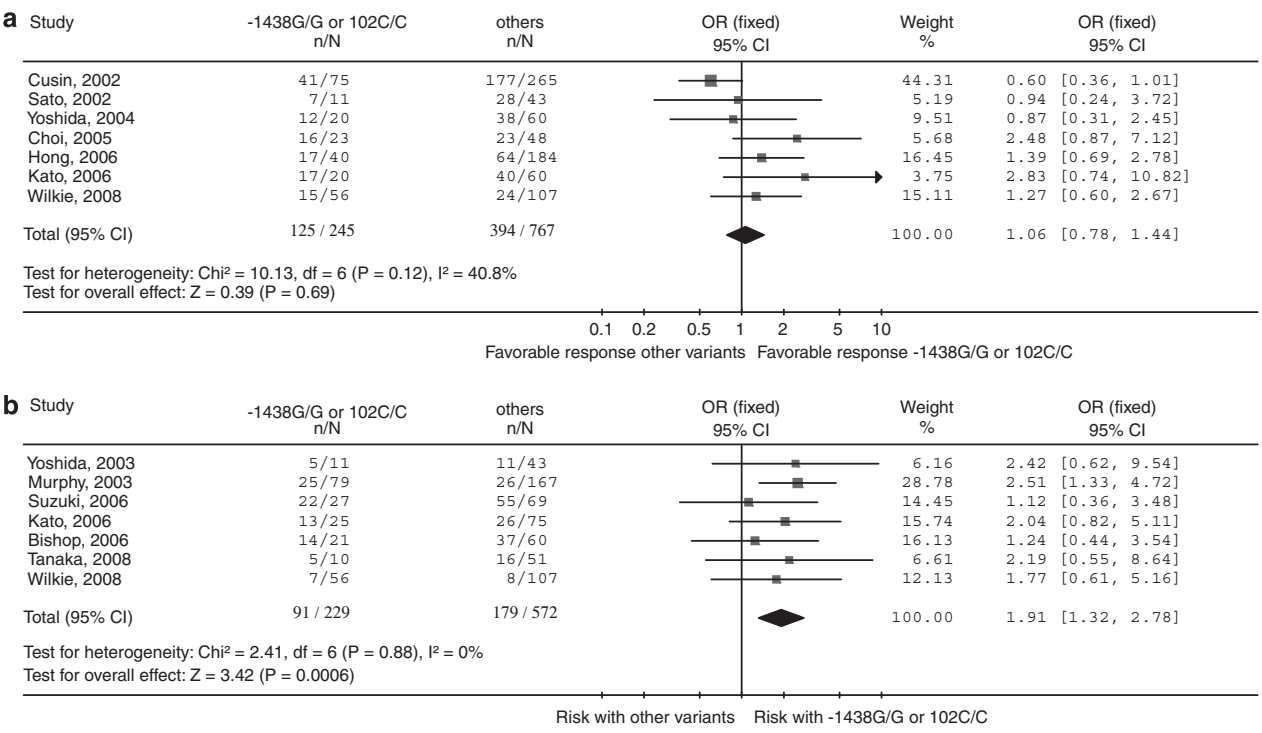

Figure 4 (**a**) HTR2A −1438A/G(102T/C) and treatment response. Outcome data for −1438G/G or 102C/C versus other variants. (**b**) HTR2A −1438A/G(102T/C) and side effects. Outcome data for −1438G/G or 102C/C versus other variants.

polymorphisms.[100–103] HTR3A is located directly downstream of HTR3B on chromosome 11, it consists of nine exons and spans over 15 kb whereas HTR3B also consists of nine exons but with a length of over 41 kb.[102–104] Tremblay *et al.*[105] found a significant association between homozygosity for the −100 to −102 AAG deletion variant of the HTR3B and the intensity of vomiting and nausea after cancer chemotherapy with antiemetics. Tzvetkov *et al.*[106] recently showed a different transcriptional regulation of the HTR3B gene in the peripheral and the central nervous system that leads to the expression of transcripts with variations in the 5′-coding sequence.

Pharmacogenetic studies of HTR3A and 3B: Table 4 shows pharmacogenetic studies of HTR3A and 3B. We previously observed a significant association of HTR3A 178C/T T/T carriers with better response to SSRIs, although no association of this SNP with side effects including nausea could be observed.[47] Two other studies also found no association of HTR3A 195C/T as well as 178C/T SNPs with gastrointestinal symptom induced by SSRIs.[95,107] One of these studies found a significant association of HTR3B 129Tyr/Ser (rs1176744) polymorphism with nausea induced by paroxetine[107] whereas others could not found any association with fluvoxamine-[95] or paroxetine[58] -induced nausea. We previously reported no significant correlation between SSRIs induced side effects including nausea and HTR3B −100 to −102 AAG insertion/deletion polymorphism,[47] although another study found a significant association.[58]

Meta-analysis of HTR3A 178C/T on side effects: The pooled ORs of three studies with 254 subjects about the influence of HTR3A 178C/T on total side effects (1.64, CI: 0.81–3.31, $P=0.17$) as well as on gastrointestinal side effects (1.70, CI: 0.80–3.62, $P=0.17$; Figure 5) were not significant possibly because of small sample size because ORs of all studies were higher than 1.3 with more frequent side effects for C/C carriers.[47,95,107]

Meta-analysis of HTR3B 129Tyr/Ser on side effects: The pooled ORs of three studies including 246 subjects about the influence of HTR3B 129 Tyr/Ser variant on total side effects was not significant with some heterogeneity across studies (2.04, CI: 0.66–6.34, $P=0.22$; Figure 6).[58,95,107] All studies investigating pharmacogenetic effect of HTR3A and 3B used SSRIs in Japanese samples. Given the small number of studies performed only in Japanese subjects, further studies will be needed.

Serotonin-6 receptor (5-HT6). 5HT-6 gene (HTR6) is coded in position 1p36-p35 and it spans over 15 kbp with three exons and two introns.[110] A mutant receptor in which serine 267 was changed to lysine shows a 10-fold higher affinity for serotonin than the native receptor and it demonstrates agonist-independent activity.[111]

Pharmacogenetic studies of HTR6: Three studies investigated the involvement of a silent cytosine to thymidine polymorphism at position 267 (267C/T;

Table 4 Serotonin receptor 3A, 3B and 6 gene polymorphisms and antidepressant response

Authors	*Number of subjects (male/female), mean age*	*Diagnosis and prescribed drug*	*Scale and study period (week)*	*Variant*	*Result*	*Ethnicity*
Suzuki *et al.*[95a]	$N=96$ (47/49), 40.3 years	MDD Fluvoxamine	Side effect (12)	HTR3A 178C/T 195C/T HTR3B 129Tyr/Ser	No association with side effect	Asian
Sugai *et al.*[107a]	$N=78$ (28/50), 38.4 years	Retrospective study with various psychiatric disorder Paroxetine	Side effect (not defined)	HTR3A 178C/T 195C/T HTR3B 129Tyr/Ser	3B129Tyr/Tyr associated with nausea induced by paroxetine, $P=0.038$	Asian
Kato *et al.*[47a]	$N=100$ (56/44), 43.7 years	MDD Paroxetine or fluvoxamine	HAM-D21 response remission score change side effects (6)	HTR3A 178C/T HTR3B −100 to 102ins/del	3A178T/T showed better treatment outcome, $P=0.025$; HTR3B −100 to 102ins/ins showed better treatment outcome, $P=0.047$ but no association with side effects	Asian
Tanaka *et al.*[58a]	$N=72$ (35/37) 47.0 years	MDD + Anxiety disorder Paroxetine	Side effect (12)	HTR3A 3SNPs HTR3B 11 variants	HTR3B −100_to 102AAG del associated with nausea induced by paroxetine, $P=0.0029$	Asian
Wu *et al.*[108]	$N=34$ (13/21), 47.3 years	MDD Venlafaxine or fluoxetine	CGI (4)	HTR6 267C/T	No association with treatment outcome	Asian
Lee *et al.*[109]	$N=91$ (25/66), 46.7 years	MDD Various ADs	HAM-D21 score change (8)	HTR6 267C/T	C/T showed better treatment outcome than C/C and T/T, $P=0.029$	Asian
Wilkie *et al.*[57]	$N=163$(NR), 43.4 years (total sample)	MDD Various ADs	HAM-D response remission side effect (6 or more)	HTR6 267C/T	No association with treatment outcome and side effect	Caucasian

Abbreviations: AD, antidepressant drug; CGI, Clinical Global Impressions; HAM-D, Hamilton Rating Scale for Depression; HTR, Serotonin receptor gene; MDD, major depressive disorder; NR, not reported.
[a]Entered into meta-analysis of side effects.

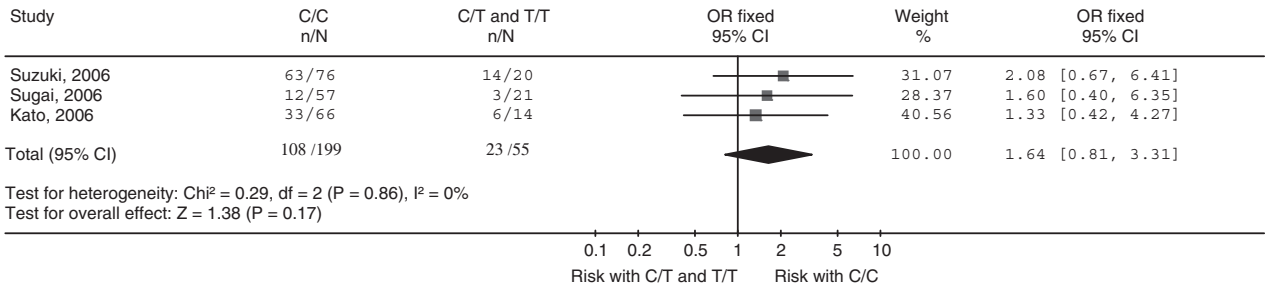

Figure 5 HTR3A 178C/T and side effects. Outcome data for C/C versus C/T and T/T.

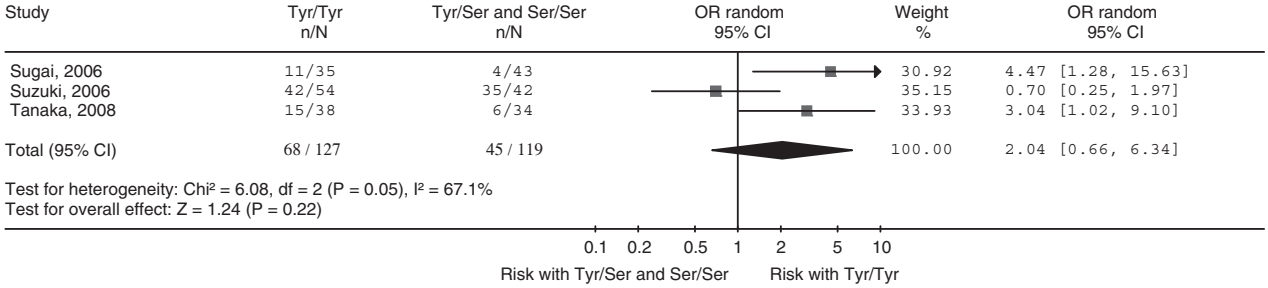

Figure 6 HTR3B 129Tyr/Ser and side effects. Outcome data for Tyr/Tyr versus Tyr/Ser and Ser/Ser.

rs1805054), within the first exon of HTR6, in ADs response[57,108,109] but the results were inconsistent (Table 4). Meta-analysis could not be performed for lack of sufficient data from these studies. Further, the functional efficacy of this SNP has not been identified. Further functional and pharmacogenetic studies about SNPs within HTR6 with larger samples in homogenous ADs treatment are needed.

Serotonin biosynthesis

Tryptophan hydroxylase. Tryptophan hydroxylase 1: Tryptophan hydroxylase (TPH) has two isoforms coded by TPH1 and TPH2 genes. TPH1 is located to chromosome 11 (11p15.3–p14),[112] predominantly expressed in peripheral organs such as the gut, pineal gland, spleen and thymus and less frequently in the brain compared to TPH2.[113,114] A recent study found that TPH1 was expressed preferentially during the late developmental stage in the mouse brain and it had higher affinity for tryptophan as well as a stronger enzyme activity than TPH2 in a condition reflecting that of the developing brainstem.[115] A biallelic SNP on position 218 (TPH1 218A/C) is located in intron 7 and is in strong LD with TPH1 779A/C.[116] To date, no definite information is available about the possible functional consequences of the TPH1 218A/C polymorphism. But the location as a potential GATA transcription factor-binding site, lower cerebrospinal fluid concentrations of 5-hydroxyindoleacetic acid in male healthy volunteers with the TPH1 A allele and complete LD with functional polymorphism in the promoter region of the TPH1 suggest the possibility that it can affect TPH gene expression.[116–118] Allele frequencies of TPH1 218A/C are not different between Asian and Caucasian samples, the A allele being present in about 45% of subjects.[46,119–121]

Pharmacogenetic studies of TPH1: TPH1 218A allele was found to be associated with worse response to ADs treatment in some studies,[119,120,122] although no significant association could be seen with intolerance as well as treatment response in other studies[32,42,46,121,123,124] (Table 5). Another study also reported no effect of the TPH1 218A/C SNP on fluoxetine treatment but with a significant effect of three different TPH1 polymorphisms in the promoter region: −7180T/G, −7065T/C and −5806T/G.[42]

Meta-analysis of TPH1 218A/C on treatment efficacy: In Figure 7, the meta-analysis for TPH1 218A/C retrieving seven studies with data from 754 subjects was performed.[46,119–124] The pooled OR was significant (1.62, CI: 1.15–2.27, $P=0.005$) with no evidence for heterogeneity across studies. Interestingly, the significant OR is because of the sum of three studies that evaluated remission rate with favorable improvement in the C/C genotype.[119,120,122] This significance could be also demonstrated in pooled OR of six studies with 661 subjects evaluating SSRIs treatment only (1.71 CI: 1.20–2.44, $P=0.003$).[46,119–122,124] These results could indicate a significant association of TPH1 218A/C with clinical response to ADs, in particular with achievement of remission.

Tryptophan hydroxylase 2. Tryptophan hydroxylase 2 is in position 12q21.1, and its variations have

Table 5 Tryptophan hydroxylase 1 and 2 gene polymorphisms and antidepressant response

Authors	*Number of subjects (male/female), mean age*	*Diagnosis and prescribed drug*	*Scale and study period (week)*	*Variant*	*Result*	*Ethnicity*
Serretti *et al.*[119a]	$N=217$ (73/144), 51.2 years	BP + MDD Fluvoxamine ± lithium and/or pindolor	HAM-D21 remission score change (6)	TPH1 218A/C	C/C showed better treatment outcome, $P=0.003$	Caucasian
Serretti *et al.*[120a]	$N=119$ (35/86), 48.0 years	BP + MDD Paroxetine ± lithium and/or pindolor	HAM-D21 remission score change (4)	TPH1 218A/C	C/C showed better treatment outcome, $P=0.005$	Caucasian
Yoshida *et al.*[124a]	$N=54$ (22/32), 51.2 years	MDD Fluvoxamine	MADRS response score change (6)	TPH1 218A/C	No association with treatment outcome	Asian
Takahashi *et al.*[32]	$N=54$ (22/32), 51.2 years	MDD Fluvoxamine	Side effect (6)	TPH1 218A/C	No association with nausea induced by fluvoxamine	Asian
Peters *et al.*[42]	$N=96$ (47/49), 37.1 years	MDD Fluoxetine	CGI response (12)	TPH1 19 SNPs including 218A/C TPH2 14 SNPs	TPH1 −7180T/G ($P=0.022$), −7065T/C ($P=0.035$), −5806T/G ($P=0.022$), TPH2 rs1843809 ($P=0.020$), rs1386492 ($P=0.042$), rs1487276 ($P=0.035$) associated with treatment outcome	Mostly Caucasian
Ham *et al.*[123a]	$N=93$ (25/68), 46.8 years	MDD Various ADs	HAM-D21 response score change (8)	TPH1 218A/C	No association with treatment outcome	Asian
Garriock *et al.*[125]	$N=182$ (NR), NR	BP + MDD No treatment definition	No definition	TPH2 1463G/A, 1487C/G, 1578T/G	No association with treatment resistant	Mixed
Hong *et al.*[46a]	$N=224$ (93/131), 44.0 years	MDD Fluoxetine	HAM-D21 response (4)	TPH1 218A/C	No association with treatment outcome	Asian
Ham *et al.*[122a]	$N=105$ (29/76), 46.8 years	MDD Citalopram	HAM-D21 response remission (8)	TPH1 218A/C	C/C showed better treatment outcome, $P=0.047$	Asian
Kato *et al.*[121a]	$N=100$ (56/44) 43.7 years	MDD Paroxetine or fluvoxamine	HAM-D21 response remission score change side effects (6)	TPH1 218A/C	No association with treatment outcome and side effects	Asian

Abbreviations: AD, antidepressant drug; BP, bipolar disorder; CGI, Clinical Global Impressions; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; NR, not reported; TPH, tryptophan hydroxylase gene.
[a]Entered into meta-analysis of treatment outcome.

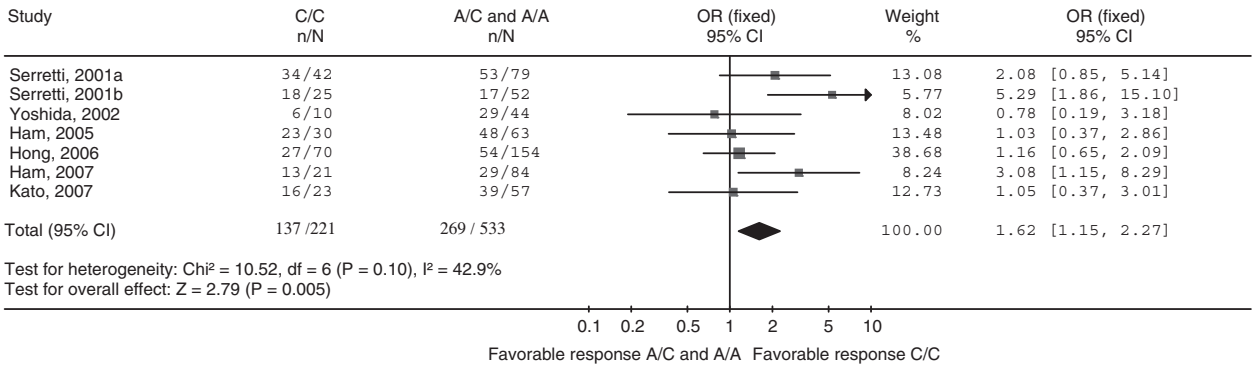

Figure 7 TPH1 218A/C and treatment response. Outcome data for C/C versus A/C and A/A.

been associated with major depression[126] and suicidal behavior.[127] Zhang *et al.*[128] found that 5HT levels from cells expressing Arg447 were reduced by approximately 55% compared to cells expressing Pro447. Moreover, in individuals with major depression, Zhang *et al.*[129] identified another functional SNP, 1463G/A, which replaces the highly conserved Arg441 with His and resulted in approximately 80% loss of function in serotonin production when TPH2 was expressed in PC12 cells. They also found the association of the mutant allele of this SNP with susceptibility to major depression while no association was found with bipolar disorder patients, although an inconsistent result was also reported.[125]

Pharmacogenetic studies of TPH2: Pharmacogenetic studies by Peters *et al.*[42] found a marginal association of three SNPs, rs1843809, rs1386492 and rs1487276, within TPH2 with antidepressant response to fluoxetine. Another study reported no association of three nonsynonymous SNPs with treatment resistance to ADs[125] (Table 5).

In addition to these SNPs, other recently investigated polymorphisms have been associated with different expression or function of TPH2 or impact on depressive or suicidal history,[130–133] with possible interesting suggestions for pharmacogenetic investigations. SNPs used in these investigations were widely different from each other with varying results. Further studies with genotyping selection based on appropriate procedures such as functional SNP, tagging SNP or haplotypes that covers overall TPH2 gene are needed.

Norepinephrinergic system. Norepinephrine transporter: The SLC6A2 gene encodes a norepinephrine transporter and it is localized in position 16q12.2. A total of 267 genetic variations of this gene are known so far.[134] This transport system is the target for dual serotonin/norepinephrine reuptake inhibitors, SNRIs as well as tricyclic antidepressants.

Pharmacogenetic studies of NET: Recently the T allele of the −182T/C (rs2242446) polymorphism in the promoter region was found to be associated with a better response to SNRI, milnacipran, compared to C allele, whereas the 1287G/A (rs5569) polymorphism was not associated with SNRI response in Japanese patients with major depression[41] (Table 6). On the contrary, a study in a Korean sample found a significant association between 1287G/A G/G carriers and better response to nortriptyline.[49] Such findings need further replication, particularly in Caucasian samples, despite the fact that functional consequences of these SNPs remain unclear.

Monoamine catabolism. Monoamine oxidase A: The gene encoding monoamine oxidase A (MAO-A) is located in position Xp11.23,[141] it is composed by 15 exons and 155 variations are known so far. A VNTR located 1.2 kb upstream, the MAO-A coding sequences was reported to affect the transcription of the MAO-A promoter: alleles with 3.5 or 4 copies of the repeat sequence are transcribed 2–10 times more efficiently than those with 3 or 5 copies of the repeat, suggesting an optimal length for the regulatory region.[141]

Pharmacogenetic studies of MAO-A: Four studies reported no influence of this polymorphism on SSRIs treatment efficacy in patients with major depressive disorder[42,91,124] or on MAO-I,[135] whereas one study reported a significant better response of the three-repeat variant compared to four-repeat variant in female patients[136] (Table 6). However, meta-analysis could not be performed for lack of sufficient data from these studies. As for side effects, no efficacy of this polymorphism was also reported, investigating fluvoxamine-induced nausea.[93] Significant associations have been also reported in other SNPs of MAO-A[42,137] (Table 6). MAO-A gene polymorphism efficacy on ADs response is therefore still not unequivocal and results seems discrepant depending on gender and the class of prescribed ADs.

*Catechol-*O*-methyltransferase:* The Catechol-*O*-methyltransferase (COMT) gene has been mapped to chromosome 22 (22q11.1–q11.2).[142] Lachman *et al.*[143] reported a functional G to A SNP at codon 158 leading

Table 6 Norepinephrine transporter and Monoamine catabolism gene polymorphisms and antidepressant response

Authors	*Number of subjects (male/female), mean age*	*Diagnosis and prescribed drug*	*Scale and study period (week)*	*Variant*	*Result*	*Ethnicity*
Yoshida *et al.*[41]	$N=80$ (28/52), 51.4 years	MDD Milnacipran	MADRS response score change (6)	NET T-182C G1287A	−182T allele showed better treatment outcome, $P=0.03$ but association of G1287A with treatment outcome	Asian
Kim *et al.*[49]	$N=208$ (52/156), 55.3 years	MDD SSRIs or nortriptyline	HAM-D17 response score change (6)	NET G1287A	G/G genotype showed better treatment outcome to nortriptyline, $P<0.001$	Asian
Cusin *et al.*[91]	$N=443$ (146/297), 51.4 years	BP + MDD Fluvoxamine or paroxetine ± lithium and/or pindolor	HAM-D21 remission score change (6)	MAO-A VNTR	No association with treatment outcome	Caucasian
Muller *et al.*[135]	$N=62$ (14/48); 52.0 years	MDD Moclobemide	HAM-D response (6)	MAO-A VNTR	No association with treatment outcome	No definition
Yoshida *et al.*[124]	$N=54$ (22/32), 51.2 years	MDD Fluvoxamine	MADRS response score change (6)	MAO-A VNTR	No association with treatment outcome	Asian
Yoshida *et al.*[93]	$N=54$ (22/32), 51.2 years	MDD Fluvoxamine	Side effect (6)	MAO-A VNTR	No association with nausea induced by fluvoxamine	Asian
Peters *et al.*[42]	$N=96$ (47/49), 37.1 years	MDD Fluoxetine	CGI response (12)	8 SNPs in MAO-A including VNTR	rs1465108G/A ($P=0.027$) and rs6323A/C ($P=0.049$) associated with treatment outcome	Mostly Caucasian
Yu *et al.*[136]	$N=228$ (95/133), 44.3 years	MDD Fluoxetine	HAM-D21 score change (4)	MAO-A VNTR	Three-repeat variant showed better treatment outcome in female, $P=0.024$	Asian
Tadic *et al.*[137]	$N=102$ (27/75), 48.5 years	MDD Mirtazapine or paroxetine	HAM-D17 response score change (6)	MAO-A 941T/G	T/T showed better treatment outcome to mirtazapine in female, $P=0.039$	No definition
Szegedi *et al.*[138]	$N=102$ (27/75), 48.5 years	MDD Mirtazapine or paroxetine	HAM-D17 response score change (6)	COMT 158Val/Met	Val allele showed better treatment outcome to mirtazapine $P=0.011$	No definition
Arias *et al.*[139]	$N=346$ (97/249), NR	BP + MDD Fluvoxamine paroxetine or citalopram	HAM-D21 response remission score change (6)	COMT 158Val/Met	Val allele showed better treatment outcome, $P=0.006$	Caucasian
Yoshida *et al.*[140]	$N=81$ (29/52) 51.1 years	MDD Milnacipran	MADRS response remission score change (6)	COMT 158Val/Me	Val allele showed better treatment outcome, $P=0.046$	Asian

Abbreviations: BP, bipolar disorder; CGI, Clinical Global Impressions; COMT, catechol-*o*-methyltransferase; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; MAO-A, monoamine oxidase A gene; MDD, major depressive disorder; NET, norepinephrine transporter gene; NR, not reported.

to a Val to Met substitution in membrane-bound-COMT (and in position 108 in soluble COMT). It has been shown that the Met allele results in a 3- to 4-fold lower enzymatic activity than the Val allele.[144] Consistently with the previously shown assumption, this polymorphism has been associated with higher risk of suicidal behavior and personality traits.[145]

Pharmacogenetic studies of COMT: Two pharmacogenetic studies found similar effects of this SNP on ADs treatment indicating that Val variant was associated with better response to mirtazapine,[138] citalopram[139] and milnacipram.[140] Out of these, two studies could not found this efficacy on response to paroxetine[138,139] (Table 6).

Intracellular signal transduction pathways. G-protein β-3 subunit: G-proteins are key components of intracellular signal transduction in all cells of the body, including neurons. The gene encoding the β-3 subunit (GNB3), located on chromosome 12p13,[146] includes 11 exons and 10 introns. A polymorphism in GNB3 exon 10, GNB3 825C/T (rs5443), has been found to modulate signal transduction and ion transport activity.[147] Allele frequencies of this variant between Caucasians and Asians are different, the T allele being present in 30% of Caucasians but in 50% of Asians.[34,46,148,149]

Pharmacogenetic studies of GNB3: Thus far, some studies reported significant associations of the T variant with better response to various classes of antidepressant,[149,150] to SSRIs[148] and to nortriptyline in less than 25-year-old subjects[34] whereas other studies found no association of this SNP with SSRIs[34,46,151] and mirtazapine response.[152] One study also found opposite results[153] (Table 7). As for side effects no significant association was reported.[97,151,153]

Meta-analysis of GNB3 825C/T on treatment efficacy: The meta-analysis for GNB3 825C/T retrieved eight studies with data from 1387 subjects.[34,46,148,149–152] Because of lack of reported response/remission rates in the study by Zill *et al.*,[150] we derived those data from figures in the paper. From the study of Joyce *et al.*, the most common genotype pooling, that is C/C versus C/T and T/T, was not available; therefore, we considered C/T and T/T as T/T but we also repeated the analysis excluding this paper without any significant change. The pooled OR demonstrated no significance (1.13, CI: 0.89–1.43, $P=0.31$; Figure 8) with no heterogeneity across the studies. This could indicate no contribution of this SNP to ADs response, although further studies are needed.

Other candidate genes. Brain-derived neurotrophic factor: Recent data suggest that ADs increase the synthesis and signaling of brain-derived neurotrophic factor (BDNF), and BDNF signaling appears to be involved in behavioral effects induced by ADs.[154] BDNF secretion and intercellular trafficking are regulated by a functional polymorphism in the BDNF gene (chromosome 11p13), resulting in a valine to methionine substitution in the 5′ pro-region (66Val/Met; rs6265).[155]

Pharmacogenetic studies of BDNF: Five studies investigated the efficacy of this polymorphism[153,156–159] or other SNPs[158,159] on ADs response with inconsistent results (Table 8). Study by Gratacos *et al.*[159] was excluded from the consequent meta-analysis because of lack of available data.

Meta-analysis of BDNF 66Val/Met on treatment efficacy: Pooled OR of four studies about 66Val/Met including 490 subjects was significant (1.63, CI: 1.08–2.46, $P=0.02$; Figure 9) with a favorable response in Met allele carriers.[153,156–158] Given the importance of BDNF in antidepressant response and the small number of studies, further studies are greatly needed. A homozygosis effect was also observed with a favorable response of Val/Met subjects;[158] this effect could bias our results in the direction of a reduced significance.

Other candidate genes potentially playing a role in the antidepressant response are presented in Table 8. An intronic insertion (I)/deletion (D) polymorphism in the angiotensin-converting enzyme (ACE) has a dramatic impact on substance P levels and may affect ADs activity. Indeed, the D allele, which determines higher ACE plasma levels,[171] was associated with higher substance P levels[172] and a faster response to ADs treatments,[160] especially among women,[162] although negative results were also reported.[161] Some genes coding for components of the hypothalamic–pituitary–adrenal axis have been explored as modulators of ADs response. Corticotrophin-releasing hormone receptor 1 gene (CRHR1) is a promising candidate as CRHR1 antagonists have consistently demonstrated ADs properties in experimental animals and humans.[173,174] Research on CRHR1 pharmacogenetics is at a very early stage; however, two studies identified contribution of three SNP haplotype to ADs response.[167,168] The influence of SNPs within the gene encoding the hsp90 co-chaperone FKBP5 (a part of the mature glucocorticoid receptor (GR) heterocomplex that regulates GR sensitivity) was also investigated by four studies with inconsistent results.[163–166] Two studies investigated the efficacy of dystrobrevin-binding-protein 1 gene (DTNBP1) that is involved in the glutamatergic pathway in brain,[175,176] on ADs response, without consistent results.[169,170]

Publication bias analysis: We applied a series of strategies to investigate possible publication biases. Figure 10 presented the funnel plots for the statistically significant meta-analyses, OR against s.e. log OR. No publication bias was presented in the present study by Egger *et al.*'s analysis.[14] As for HTR1A in Asian, small numbers of studies make it difficult to analyze the symmetry by the model of Egger; however, this plots appeared symmetrical,

Table 7 G-protein β-3 subunit gene polymorphism and antidepressant response

Authors	*Number of subjects (male/female), mean age*	*Diagnosis and prescribed drug*	*Scale and study period (week)*	*Variant*	*Result*	*Ethnicity*
Zill *et al.*[150a]	$N=88$ (29/59), 51.6 years	BP + MDD Various ADs and ECT	HAM-D17 score change (4)	GNB3 C825T	T allele showed better treatment outcome, $P=0.012$	Not defined
Serretti *et al.*[148a]	$N=490$ (156/334), 51.3 years	BP + MDD Fluvoxamine or paroxetine ± lithium and/or pindolor	HAM-D21 remission score change (6)	GNB3 C825T	T/T showed better treatment outcome, $P=0.009$	Caucasian
Joyce *et al.*[34a]	$N=159$ (NR), 31.8 years (total sample)	BP + MDD Fluoxetine or nortriptyline	MADRS response score change (6)	GNB3 C825T	T allele showed better treatment outcome to nortriptyline in patients >25 years, $P=0.01$	Caucasian
Lee *et al.*[149a]	$N=106$ (28/78), 47.1 years	MDD Various ADs	HAM-D response remission score change (8)	GNB3 C825T	T allele showed better treatment outcome, $P=0.023$	Asian
Hong *et al.*[46a]	$N=224$ (93/131), 44.0 years	MDD Fluoxetine	HAM-D21 response (4)	GNB3 C825T	No association with treatment outcome	Asian
Bishop *et al.*[97]	$N=81$ (61/20), 26.6 years	MDD Various SSRIs	Side effect (6)	GNB3 C825T	No association with sexual side effects	Caucasian
Kang *et al.*[152a]	$N=101$ (29/72), 50.3 years	MDD Mirtazapine	HAM-D21 response score change (8)	GNB3 C825T	No association with treatment outcome	Asian
Wilkie *et al.*[153a]	$N=163$ (NR), 43 years (total sample)	MDD Various ADs	HAM-D17 response remission side effect (6 or more)	GNB3 C825T	C Allele showed better treatment outcome, $P=0.02$ but no association with side effect	Caucasian
Kato *et al.*[151a]	$N=146$ (77/69), 45.1 years	MDD Paroxetine or fluvoxamine	HAM-D21 response remission side effect score change (6)	GNB3 C825T	No association with treatment outcome and side effects	Asian

Abbreviations: AD, antidepressant drug; BP, bipolar disorder; ECT, electroconvulsive therapy; GNB3, G-protein β-3 gene; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression; MDD, major depressive disorder; NR, not reported.
[a]Entered into meta-analysis of treatment outcome.

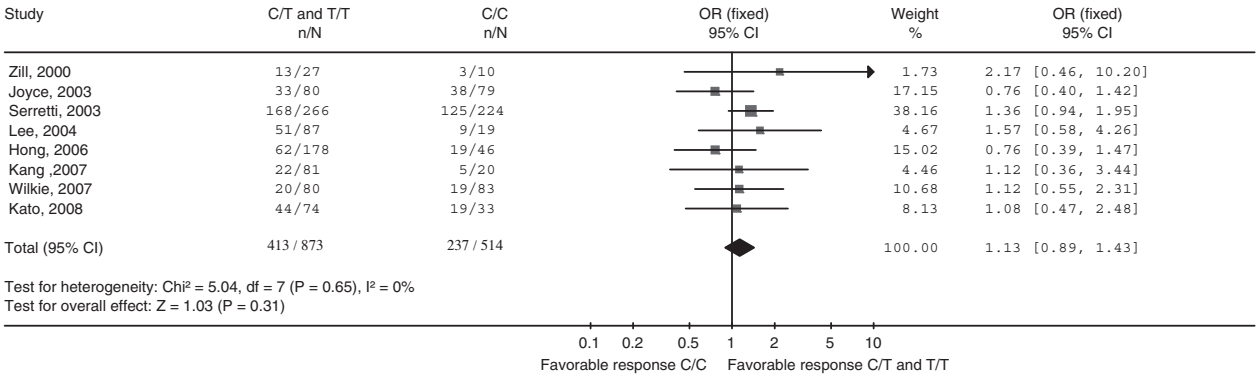

Figure 8 GNB3 825C/T and treatment response. Outcome data for C/T and T/T versus C/C.

indicating an absence of publication bias. As presented in Tables and Figures, in 3 (STin2, TPH1 218A/C and GNB3 825C/T) out of 10 variants included in the meta-analysis, the first paper reported a significant result. The common ORs of these variants estimated by Mantel–Haenszel method were similar to the pooled ORs (STin2: OR = 1.97, CI: 1.49–2.60, $P < 0.00001$; TPH1 218A/C: OR = 1.56, CI: 1.13–2.16, $P = 0.007$ and GNB3 825C/T: OR = 0.95, CI: 0.76–1.18, $P = 0.654$) and no significant heterogeneity was observed between ORs of the first published study and the following ones except for STin2, although both ORs of this variant were higher than 1.6. No significance could be observed against publication year in meta-regression analysis either. These results indicate that first publication bias should not be a confounding effect on our results. However, publication of positive results only could make negative findings unavailable and this may bias the result in a way not possible to control for.

Discussion

We reviewed a panel of candidate genes in the field of pharmacogenetic studies on ADs response and side effects and performed meta-analyses for treatment response with STin2, HTR1A −1019C/G, HTR2A −1438A/G (102T/C), TPH1 218A/C, GNB3 825C/T and BDNF 66Val/Met variants and for side effects with 5-HTTLPR, STin2, HTR2A −1438A/G (102T/C), HTR3A 178C/T and HTR3B 129Tyr/Ser. The results of our meta-analyses indicate a better treatment response to ADs with TPH1 218C/C, and BDNF 66Met as well as with the previously reported 5-HTTLPR-l and also a contribution of STin2–12/12, HTR1A −1019G/G and HTR2A −1438G/G (102C/C) toward a better response to Ads, particularly, in the Asian population. Moreover, 5-HTTLPR-l and HTR2A −1438A (102T) were also associated with less ADs (and particularly SSRI)-induced side effects. We also observed that this specifically applies to HTR2A −1438A/G (102T/C) for gastrointestinal symptoms, but for 5-HTTLPR the small number of studies does not allow to identify a specific pattern. This is in line with the gastrointestinal expression of the three genes and particularly with the fact that HTR2A is located on smooth muscle cells in the gut and vessels as well as on postsynaptic neurons.[177]

All the polymorphisms considered presenting significant results are known to be functional and can modulate gene transcription and gene/protein expression,[23,63,69,87,88] except for TPH1 218A/C. Although clear functional influence remains unknown about TPH1 218A/C, previous studies suggested the possibility that this SNP may affect gene expression.[116–118] However, prediction at clinical levels needs more variance explained[6] but our result can provide evidence to investigate association of ADs response and intolerance with the combination of the identified liability polymorphisms, in addition to previously reported important pharmacokinetic genes that contribute to function of cytochrome P450 enzyme or P-glycoprotein.[7,178,179] In fact, genes interact in a complex way, with some gene variants acting additively with others, in a multiplicative way or with a compensatory effect,[180,181] that is, a number of susceptibility genes interacting with each other and with the environment. Heterogeneity across the studies including ethnic difference could also make it difficult for these candidates to be translated into treatment recommendations. Clearly, different results between ethnicities were observed for treatment response with STin2, HTR1A −1019C/G and HTR2A −1438A/G (102T/C), possibly because of efficacy of other polymorphisms, different allele frequency, differential effect depending on specific symptoms and cultural or social differences between Asians and Caucasians.[182–184] Our protocol of meta-analysis could minimize the heterogeneity among studies as much as possible but the considerable range of methodologies including heterogeneity of prescribed ADs, concomitant medications, length of treatment and assessment procedures for side effects may still bias the result of the present meta-analysis as well as limit the representativeness of our findings. Additionally, the wide range of sampling source (inpatients versus outpatients and primary versus tertiary settings), diagnostic procedure and environmental confounding variables (life events, social support and temperament) are considered as potentially modulators to the

Table 8 Other genes polymorphisms and antidepressant response

Authors	*Number of subjects (male/female), mean age*	*Diagnosis and prescribed drug*	*Scale and study period (week)*	*Variant*	*Result*	*Ethnicity*
Tsai *et al.*[156a]	$N=110$ (NR), 45.3 years (total sample)	MDD Fluoxetine	HAM-D21 response remission score change (4)	BDNF 66Val/Met	No association with treatment outcome	Asian
Choi *et al.*[157a]	$N=83$ (24/59), 53.9 years	MDD Citalopram	HAM-D21 response score change (8)	BDNF 66Val/Met	Met allele showed better treatment outcome, $P=0.003$	Asian
Yoshida *et al.*[158a]	$N=134$ (50/84), 51.3 years	MDD Fluvoxamine or milnacipran	MADRS response score change (6)	BDNF 66Val/Met 132C/T	66 Val/Met showed better treatment outcome than Val/Val and Met/Met, $P=0.0004$	Asian
Gratacos *et al.*[159]	$N=374$ (133/244), 57.2 years	BP + MDD Various ADs and ECT	HAM-D21 remission (2 months)	BDNF, 8 SNPs including 66Val/Met	rs90887 A ($P=0.0025$) and TAT haplotype of rs12273363, rs908867, rs1491850T ($P=0.007$) associated with better treatment outcome	Caucasian
Wilkie *et al.*[153a]	$N=163$ (NR), 43 years (total sample)	MDD Various ADs	HAM-D17 response remission side effect score change (6 or more)	BDNF 66Val/Met	No association with treatment outcome and side effects	Caucasian
Baghai *et al.*[160]	$N=99$ (35/64), 52.3 years	MDD Various ADs, ECT and TMS	HAM-D17 remission score change (4)	ACE I/D	D Allele showed better treatment outcome, $P<0.0001$	Caucasian
Hong *et al.*[161]	$N=35$ (14/21), 47.2 years	MDD Venlafaxine or fluoxetine	HAM-D21 score change (4)	ACE I/D	No association with treatment outcome	Asian
Baghai *et al.*[162]	$N=313$ (119/194), 49.4 years	BP + MDD Various ADs, ECT and TMS	HAM-D17 score change (4)	ACE I/D	D Allele showed better treatment outcome in female, $P=0.003$	Caucasian
Binder *et al.*[163]	$N=294+85$, (NR) NR	BP + MDD Various ADs ± mood stabilizers and/or neuroleptics	HAM-D21 response remission score change (5)	FKBP5 52SNPs	T/T of rs1360780C/T showed better treatment outcome, $P=0.006$	Caucasian
Tsai *et al.*[164]	$N=125$ (56/69), 42.1 years	MDD + dysthymia Fluoxetine	HAM-D21 response score change (4)	FKBP5 rs1360780	No association with treatment outcome	Asian
Papiol *et al.*[165]	$N=159$ (35/124), 39.5 years	MDD Citalopram	HAM-D21 response remission score change (4)	FKBP5 rs1360780 and CRHR1 2SNPs	No association with treatment outcome	Caucasian
Lekman *et al.*[166]	$N=1809$ (NR) NR	MDD from STAR*D sample Citalopram	QIDS-C16 response remission score change (14)	FKBP5, rs1360780, rs4713916, rs3800373	A Allele of rs4713916G/A showed better treatment outcome, $P=0.049$	Mixed
Licinio *et al.*[167]	$N=80$ (22/58), 40.4 years	MDD Fluoxetine or desipramine	HAM-D21 response score change (8)	CRHR1 9SNPs	GAG Haplotype of rs1876828, rs242939, rs242941 showed better treatment outcome, $P=0.03$	Mexican-American
Liu *et al.*[168]	$N=127$ (55/72), 30.5 years	MDD Fluoxetine	HAM-D21 response score change (8)	CRHR1, 3 SNPs	GAG haplotype of rs1876828, rs242939, rs242941 showed better treatment outcome, $P=0.01$	Asian
Zill *et al.*[169]	$N=293$ (110/183), 49.6 years	MDD Various ADs, ECT and TMS	HAM-D17 response score change (4)	DTNBP1 5SNPs	No association with treatment outcome	Caucasian
Pae *et al.*[170]	$N=104$ (29/75), 42.7 years	MDD Various ADs	MADRS10 score change (no definition)	DTNBP1 5SNPs	rs2005976G ($P=0.00055$), rs760761C ($P=0.0058$), rs2619522A ($P=0.0025$) and these haplotype ($P=0.0096$) showed better treatment outcome	Asian

Abbreviations: ACE, angiotensin-converting enzyme; AD, antidepressant drug; BDNF, Brain-derived neurotrophic factor; BP, bipolar disorder; CRHR1, corticotropin-releasing hormone receptor 1; DTNB1, dystrobrevin-binding-protein 1; ECT, electroconvulsive therapy; FKBP5, FK506-binding protein 5; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression; MDD, major depressive disorder; NR, not reported; TMS, transcranial magnetic stimulation.
[a]Entered into meta-analysis of treatment outcome.

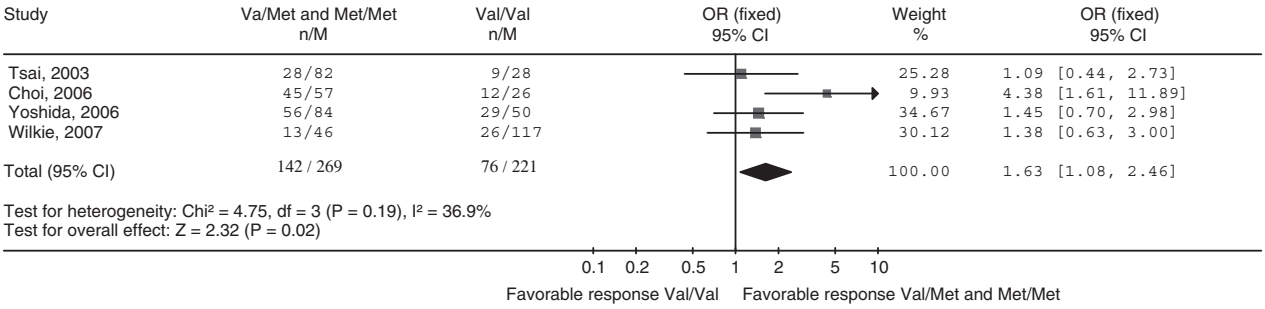

Figure 9 BDNF 66Val/Met and treatment response. Outcome data for Val/Met and Met/Met versus Val/Val.

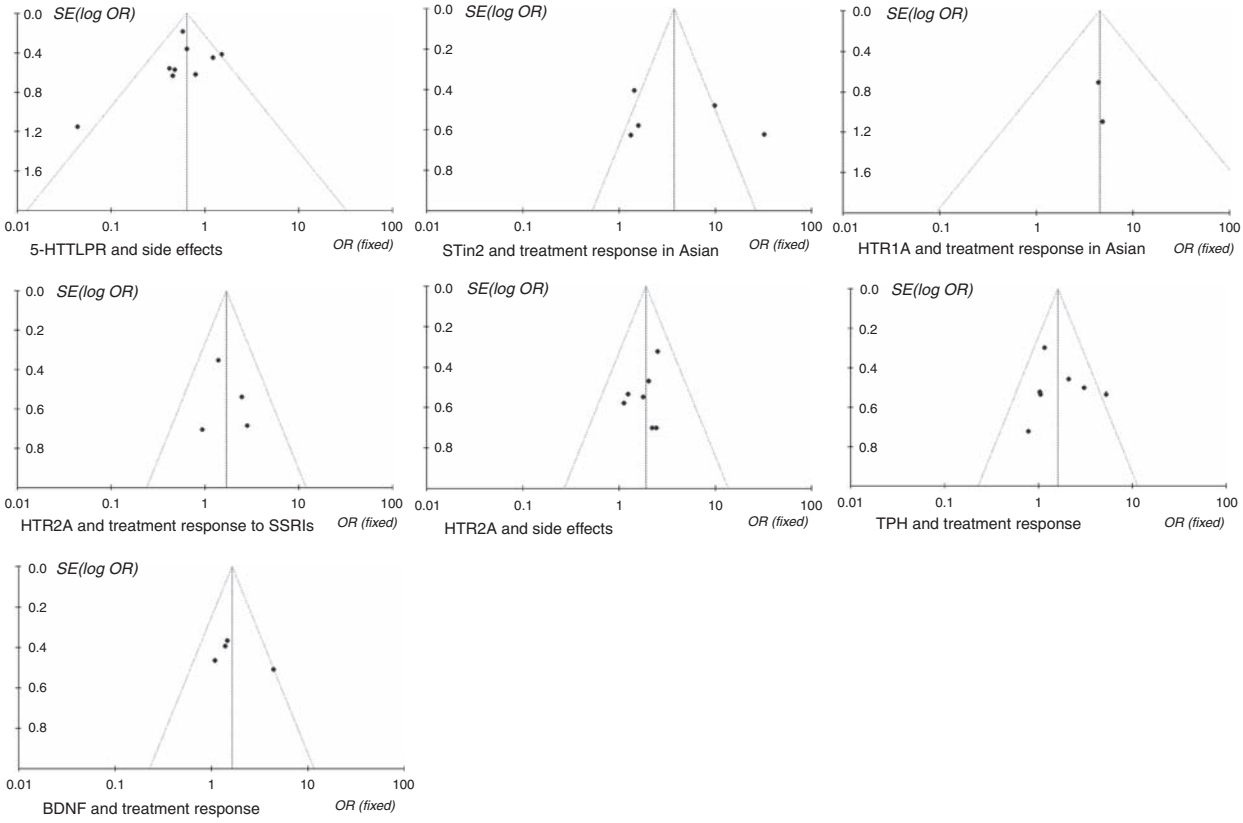

Figure 10 Funnel plots of s.e. (log OR) by the OR on statistically significant meta-analyses. Each dot represents one paper. s.e. (log OR) = standard error of the log OR.

results of pharmacogenetic studies.[13] Furthermore, for the assessment of side effects, there was not a standard tool that was used in pharmacogenetic studies and this might prevent replication of findings. Imbalance of published papers about key candidates was seen between Asians and Caucasians; therefore, some candidates should be investigated more in Caucasians (STin2, HTR2A, 3A and 3B) and others in Asians (HTR1A). To improve homogeneity for future studies, our published methodological guidelines should also be considered.[13] Alternative approaches using as an example genome-wide association studies could also help for candidate gene detection but only if complemented with detailed clinical descriptions.

Finally, further controls of gene expression by copy number of variation (CNV) or methylation should be investigated in this field. Our results were not corrected for multiple testing; however, even after applying Bonferroni correction with 22 analysis (6 treatment responses, 5 side effects, 3 subethnicities, 3 submedications, 3 subsymptom and 1 alternative grouping of variant) with the significance level set to *P*<0.0023, associations still remain significant for the variants with sufficient number of studies (5-HTTLPR, HTR2A −1438A/G), although it turn to nonsignificance for the other variants and subcategorical analyses with small number of studies. However, such correction is likely to be excessively conservative and not suitable for the meta-analysis.

To the best of our knowledge, our study is the first article investigating the association of a series of pharmacodynamic variants with treatment response and intolerance to ADs treatment with a meta-analytic technique. Another partial meta-analysis has been reported but from the pharmacokinetic perspective or only about antipsychotic response.[7]

In conclusion, we summarized 90 studies and meta-analyzed them to aggregate such information into concise recommendations. Five variants within four genes (SLC6A4, HTR1A, HTR2A, TPH1 and BDNF) may contribute to the ADs treatment response and/or intolerance. Although the significant results of pooled ORs in this meta-analysis seem a moderate effect, it is in line with the hypothesis of minor effect genes and it adds an important piece of information for future pharmacogenetic studies in ADs response and could be a further step to the clinical use of gene profiles as predictors of therapeutic efficacy.

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