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Dopamine D2 receptor genetic variation and clinical response to antipsychotic drug treatment: A meta-analysis

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Abstract

Objective—Several lines of evidence suggest that antipsychotic drug efficacy is mediated by dopamine D2 receptor blockade. Therefore, it seems plausible that variation in the *DRD2* gene is associated with clinical response to antipsychotic drug treatment. We conducted the first meta-analysis to examine the relationship between *DRD2* polymorphisms and antipsychotic drug response.

Method—Medline search (12/31/2008) yielded 18 prospective studies examining *DRD2* variation and antipsychotic response in schizophrenia patients, of which 10 independent studies met criteria for inclusion. Clinical response to antipsychotic treatment was defined as a 50% reduction of either BPRS or PANSS total score at approximately 8 weeks follow-up. Odds ratio (OR) was the primary effect size measure and was computed for each polymorphism in each study. Sufficient data were available for two *DRD2* polymorphisms, -141C Ins/Del and Taq1A.

Results—Six studies reported results on the -141C Ins/Del polymorphism (n=698). The Del allele carrier was significantly associated with poorer antipsychotic drug response, compared to the Ins/Ins genotype, OR=.65, p=.03. Eight studies assessed the Taq1A polymorphism and antipsychotic response (n=748). There was no significant difference in response rate in A1 carrier vs. A2/A2 genotype or A2 carrier vs. A1/A1 genotype.

Conclusion—*DRD2* genetic variation is associated with clinical response to antipsychotic drug treatment. This data may provide proof-of-principle for pharmacogenetic studies in schizophrenia.

Introduction

Schizophrenia is a chronic and debilitating disorder, for which antipsychotic drugs are the treatment of choice(1). However, many patients with schizophrenia discontinue or switch antipsychotic drug regimens due to lack of efficacy and/or treatment-emergent side effects, and a large proportion of patients remain symptomatic despite treatment(2-4). The factors that influence the variation in response to antipsychotic drug treatment have not been well-elucidated, rendering it difficult to develop effective treatment strategies tailored to individual patients.

Pharmacogenetics research focuses on the identification of genetic variants that predict who may optimally benefit from antipsychotic treatment(5). Variants in genes that code for neurotransmitter receptors have been the primary targets, including multiple loci in the dopamine and serotonin receptor systems. However, there remain surprisingly few studies on

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the relationship between the most obvious candidate gene, *DRD2*, and antipsychotic drug response. Several lines of evidence suggest that the D2 receptor plays a critical role in antipsychotic drug action. Earlier studies showed that antipsychotic clinical potency was highly correlated with the binding affinity to a particular type of dopamine receptor(6), which was later found to be the D2 receptor(7,8). Recent functional imaging studies suggest that binding to the D2 receptor by antipsychotic agents may be "necessary and sufficient" for antipsychotic efficacy(9). Finally, all known antipsychotic drugs bind to the D2 receptor, and drugs that have targeted non-D2 receptors without at least some element of D2 blockade have failed to treat schizophrenia effectively(8,10).

Some of the earliest studies of *DRD2* single nucleotide polymorphisms (SNPs, specifically, the -141C Ins/Del and Taq1A variants) revealed promising associations with antipsychotic efficacy(11-13). However, the subsequent literature has been marked by mixed results and small sample sizes, complicating the evaluation of such associations. A potentially useful methodology to overcome this limitation is by use of meta-analytic techniques that incorporate results from multiple studies in an unbiased fashion. In the present study, we conducted the first pharmacogenetics meta-analysis to examine the association between variation in the *DRD2* gene and antipsychotic drug response.

As described in detail below, relevant studies in the literature have utilized a variety of designs, trial durations, symptom measures, and response criteria. Consequently, we developed a systematic and consistent methodology to harmonize the reported phenotypes, contacting the original investigators when necessary to re-evaluate raw data. Additionally, while multiple *DRD2* SNPs have been studied, including Taq1B(14,15), Taq1D(15,16), T939C(14), S311C (17), and C957T(16,18), most of these SNPs were reported in only one or two studies, with the exception of the Taq1A and -141C Ins/Del variants. Finally, studies to date have included patients across all phases of the illness, ranging from first-episode schizophrenia patients with no or limited prior exposure to antipsychotic drugs to clozapine-treated patients with poor prior antipsychotic drug responses and lengthy prior medication histories. As antipsychotic drug exposure has been demonstrated to alter the expression of multiple CNS receptors(19), including the dopamine D2 receptor, this factor may introduce additional variance into studies of genetic sources of variability. Therefore, we conducted exploratory analyses to investigate whether studies examining first episode cohorts yielded stronger results than those comprised primarily of chronically ill subjects.

Methods

Literature Search

To identify studies eligible for this meta-analysis, we searched Medline for all publications available up to 12/31/2008 that examined the association between the *DRD2* gene and antipsychotic drug response. The following key words were used in the literature search: DRD2, polymorphism, antipsychotic, clinical response, gene, and schizophrenia. We also used the reference lists from identified papers and recent literature review articles to identify additional relevant studies. Furthermore, to find unpublished studies, we also searched meeting abstracts that were likely to contain relevant studies. Each paper included in the meta-analysis meets the following criteria: 1) reported the association between *DRD2* polymorphisms and clinical antipsychotic drug response; 2) the majority of patients met DSM-IV criteria for a diagnosis of schizophrenic or schizoaffective disorder, and diagnoses were confirmed with a standardized structured clinical interview; 3) drug response was assessed with a standardized rating scale, such as the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS), or the Clinical Global Impression scale (CGI), at baseline and follow-up; and 4) the follow-up period was no longer than three months. We selected this duration of follow-up because our major goal was to assess acute antipsychotic treatment

response, and response rates in treatment trials longer than three months may reflect other factors related to non-compliance(20), relapse prevention, illness course, and psychosocial variables(21), which may confound the genotype-drug response relationships.

Selection of candidate polymorphisms

DRD2 (see Figure 1) contains a number of SNPs with differing frequencies amongst populations. Several *DRD2* polymorphisms have been studied in association with antipsychotic drug response(22). In order to conduct a robust meta-analysis, we selected polymorphisms that were reported on in at least three studies. Two polymorphisms fit this criterion: the -141C Ins/Del and Taq1A polymorphisms. Minor allele frequency for the Taq1A ranges from 20% in Caucasians to 44% in other ethnic groups. Minot allele frequency for the -141C Ins/Del ranges from about 10% in Japanese and Caucasians to more than 50% in Africans.

***-141C Ins/Del* (rs1799732)—**This polymorphism represents a deletion (versus insertion) of cytosine at position -141, located in the 5′ promoter region of *DRD2*. In vitro data by Arinami and colleagues(23) showed that cell lines transfected with the Del allele were less active in a luciferase reporter assay than cell lines transfected with the Ins allele. In vivo data with PET imaging (22) have also suggested that this polymorphism may influence D2 receptor density in the striatum of healthy volunteers unexposed to antipsychotic drug treatment. For the purposes of this meta-analysis, we pooled the Del/Del and Ins/Del genotype groups into one group (Del carrier) because of the low frequency of the Del/Del genotype in the general population and then tested for association between this group versus the Ins/Ins genotype group.

***Taq1A* (rs1800497)—**This SNP involves a C >T substitution, located about 10kb downstream of *DRD2*. The A1 allele is associated with reduced *DRD2* gene expression(24, 25). Recently, the Taq1A SNP was found to be part of the kinase gene “ankyrin repeat and kinase domain containing 1” (ANKK1) (26,27). This SNP has been studied in association with substance abuse, alcohol dependence, eating disorder, and smoking cessation. Given the lack of unequivocal data for Taq1A genotype pooling, we tested both dominant and recessive hypotheses: A1/A1 versus A1/A2 + A2/A2, and A2/A2 versus A1/A2 + A1/A1.

Definition of clinical response

Clinical response to antipsychotic drug treatment was defined as a 50% reduction of either BPRS or PANSS total score from baseline to follow-up. Studies have shown that a 50% reduction of BPRS total score is approximately equivalent to a 50% reduction in PANSS total score, which equates to a rating of 1 or 2 on the CGI-Improvement scale(28). To be consistent across studies, we chose to define clinical response at the 8-week follow-up (or closest time point thereto), because this was the most common follow-up time point available. If a study did not use 50% reduction as the definition of clinical response, effort was made to contact the authors to obtain additional data. If data with 50% reduction was not obtainable, the original definition of clinical response reported in the paper was used in the meta-analysis.

Odds ratio (OR) was the primary effect size measure and was computed for each polymorphism in each study. If a study did not report the categorical outcomes of responders vs. non-responders, we requested data from the authors. If categorical data were not available, the study was not included in the meta-analysis.

Statistical analysis

Data were entered into and analyzed by the Cochrane Collaboration review manager software (RevMan version 5). Heterogeneity between the studies was assessed by the χ^2 test. Individual OR and associated 95% confidence intervals (CI) were calculated, and pooled to compute the mean effect size by the Mantel-Haenszel method(29). A fixed-effect model was used in all

analyses(30), a similar approach used in other pharmacogenetic meta-analyses(30,31). Separate meta-analysis was conducted for each SNP and for each genotype. Publication bias was assessed with the funnel plot, the "Trim and Fill" method(32), and Egger's test(33), which was conducted using the "metatrim" and "metabias" macro procedures in the Stata program version 7.

Results

To conduct the meta-analysis on the relationship between *DRD2* variation and antipsychotic drug response, we searched the literature with a cut-off date of 12/31/2008, which yielded 18 published papers. Six papers were not included in the meta-analysis: three studies only reported long-term outcomes greater than three months from baseline to follow-up(15,16,34); one study (35) was cross-sectional; one paper did not state duration of follow-up, and nor did it include the BPRS, PANSS, or CGI(36); and one study contained no data on the Taq1A or -141C Ins/Del polymorphisms(17). Two papers(37,38) published by the same research group contained overlapping data, and therefore were assessed as one study subsequent to the authors providing the additional data needed to compute categorical outcome of clinical response. Finally, we were unable to obtain sufficient information to calculate response rate from an additional study (39), therefore these data were not included in the meta-analysis.

In sum, ten independent studies (total sample size: 889) met criteria for inclusion in the meta-analysis. Figure 2 summarizes the literature search process. The clinical characteristics of each study are summarized in Table 1. Six studies reported outcomes conditioned on the -141C Ins/Del SNP (N = 687) and eight reported outcomes on the Taq1A SNP (N = 748). Six of the 10 studies reported continuous outcomes, but the authors generously provided the additional data needed to compute ORs.

-141C Ins/Del polymorphism and antipsychotic drug response

Six studies that met inclusion criteria reported results on the -141C Ins/Del polymorphism, with a total sample size of 687 patients. Figure 3 presents ORs for the individual studies and the pooled analyses in different genotype groups. There was a significant difference in response rate between the Del carrier vs. Ins/Ins genotypes (pooled OR = .65, 95% CI = .43 ~ .97, p = .03), indicating that Del carriers tend to have less favorable antipsychotic drug responses than patients with the Ins/Ins genotype. The heterogeneity χ^2 test was not significant, $\chi^2 = 9.23$, df = 5, p = .10, $I^2 = 46\%$. To deal with potentially undetected heterogeneity across samples, a sensitivity analysis was conducted excluding two studies with the largest and smallest effect size(12,14). Another reason to exclude these two studies was that they may be different from other studies because the 50% reduction of BPRS or PANSS was not used to define clinical response. For the sensitivity analysis, I^2 changed from 46% to 10%, and the χ^2 test for the heterogeneity analysis dropped from 9.23 to 3.33, which was non-significant and the p-value changed from .10 to .34. The pooled OR became .60, 95% CI = .38~.97, and p = .04.

As a post hoc analysis, we restricted our analysis to the studies comprised of patients with first-episode schizophrenia (N = 316). The pooled OR was .53 for Del carrier vs. Ins/Ins (95% CI = .28 ~ .99, p = .05), demonstrating poorer clinical response in Del carriers. In contrast, for the studies that did not include first-episode schizophrenic patients (N = 371), we obtained a pooled OR of .75 (95% CI = .44 ~ 1.27, p = .28). (Please see supplemental data Figure 1.)

Funnel plot is presented with Figure 3 and did not indicate evidence of publication bias. Duval and Tweedie's "trim and fill" analysis showed that it was not necessary to trim any existing study and fill any additional "unpublished" study. In addition, Egger's test did not show evidence of publication bias (B = .79, 95% CI = -3.05 ~ 4.63, p = .60).

Taq1A polymorphism and antipsychotic drug response

Eight studies assessed the Taq1A polymorphism and antipsychotic response, with a total sample size of 748 patients. Figure 4 presents ORs for the individual studies and the pooled analyses in different genotype groups. There was no significant difference in response rate in A1/A1 vs. A2 carrier or A1 carrier vs. A2/A2 genotype (pooled ORs = 1.39 and 1.30, p's = .13 and .14, respectively). There was no significant heterogeneity across studies in the two comparisons, χ^2 = 10.40 and 9.49, p's = .11 and .22, I^2 = 42% and 26%, respectively.

Funnel plots are presented in Figure 4. Duval and Tweedie's “trim and fill” analysis showed that it was necessary to “fill” an additional “unpublished” study for both the A1/A1 vs A2 carrier comparison and the A1 carrier vs A2/A2 comparison. The pooled OR's for the two comparisons with an additional “filled” study became 1.24 and 1.17, p's = .30 and .39, respectively. In contrast, Egger's test did not show evidence of publication bias for either comparison (B's = -.07 and -.60, p's = .93 and .26, respectively). In summary, the evidence regarding publication bias for the Taq1A polymorphism was inconsistent. Even if we were able to eliminate publication bias, it seemed that the association between the Taq1A polymorphism and antipsychotic drug response was still not significant.

Discussion

In order to assess the relationship between *DRD2* genetic variation and antipsychotic drug response, we conducted the first meta-analysis of two commonly studied *DRD2* SNPs: -141C Ins/Del and Taq1A, and clinical response to antipsychotic drug treatment. The primary result is that the -141C Ins/Del polymorphism significantly influences antipsychotic drug response (n = 687 patients), whereas we were not able to detect a relationship between clinical response and the Taq1A variant.

These data are consistent with prior research indicating an important role for the dopamine D2 receptor in antipsychotic drug response. Antipsychotic clinical potency is highly correlated with the binding affinity to the dopamine D2 receptor(6-8), D2 receptor occupancy by antipsychotic agents has been demonstrated to occur with all antipsychotic agents(9), and drugs targeting other receptor sites without dopamine D2 blockade have not yet been successfully developed as antipsychotics(8). To our knowledge, this is the first meta-analysis in pharmacogenetics to demonstrate the importance of *DRD2* genetic variation in antipsychotic drug response.

Of note, we observed a significant genotype-phenotype relationship in patients with first-episode schizophrenia. This may be due to the limited or lack of prior exposure to antipsychotic drugs in these patients. Differential amounts of prior drug exposure, as commonly observed in chronically ill samples, could result in considerable variation in levels of dopamine receptor up-regulation(40,41) and potentially mask subtle genetic effects on dopamine receptor availability(42) that could mediate antipsychotic response. However, other factors including greater drug response rates in first-episode patients should be considered, as well as the limitation that first-episode studies are less common than the studies that include chronic patients.

There was no significant association between the Taq1A genotype and antipsychotic drug response in the meta-analysis of eight studies and over 700 patients. Although the Taq1A polymorphism has been found to be associated with drug response in several studies(11,18, 38), it is not clear how it is related to *DRD2*, and it is actually located in a non-coding region of the *DRD2* locus. In contrast, we did find a significant association between the -141C Ins/Del polymorphism and antipsychotic drug response. This may be due to the fact that this SNP is located in the 5′ promoter region of *DRD2*, where it may influence modulation of

transcriptional activities(23) and D2 receptor density(42). Interestingly, another *DRD2* SNP, A-241G, which is also located in the promoter region of *DRD2*, has also been associated with antipsychotic drug response(43).

Although sample size limitations do not provide us with an opportunity to conduct drug-specific analysis, it is not unexpected that *DRD2* variation might influence clinical response to all antipsychotics. First, all antipsychotic drugs bind potently to the D2 receptors. Second, there are few data to suggest that any one antipsychotic has markedly improved efficacy over another, and similar response rates suggest phenotypic overlap and provide the rationale for grouping of individual drug responses for analysis. Third, and perhaps most importantly, each of these drugs was specifically developed because of the common mechanism of action of antagonism of dopamine D2 receptors, and therefore a common effect of *DRD2* variation across the antipsychotic drugs seems highly plausible. Nevertheless, the development of drugs with antipsychotic efficacy that do not act at the D2 receptor will be needed to empirically assess this question.

There are several limitations of the study. First, odds ratio was used as the effect size measure in the meta-analysis. Because this requires dichotomizing a continuous measure of either BPRS or PANSS, this may diminish statistical power, and may explain why some studies reported significant findings of an association between *DRD2* and antipsychotic drug response, whereas the OR's were not individually significant in the meta-analysis. Therefore, meta-analysis of OR may lack some sensitivity to detect small effect sizes. This is consistent with an exploratory sensitivity analysis using a random effect model (see supplemental data Figure 2), which produced a less robust p value than the fixed effect model. Nevertheless, categorical response, instead of incremental differences in scores on the BPRS or PANSS, may be more meaningful from a clinical perspective. To clarify the clinical relevance of *DRD2* genetic variations it may be necessary to use an even more clinically meaningful outcome measure, such as days to discharge following acute treatment or assessments of functional disability.

Second, variation in the antipsychotic drugs administered in these studies limited the possibility of examining the association of *DRD2* with any specific drug. In the studies included in the meta-analysis, multiple antipsychotic drugs were utilized, including typical agents such as chlorpromazine and haloperidol, and atypical drugs such as clozapine, risperidone, olanzapine, and aripiprazole. While all of these drugs act on the D2 receptor, they exhibit different affinity profiles for many of the candidate receptors(44), making direct comparisons more complex. For example, non-D2 receptors such as D3, D4, and 5-HT2A may also be important in antipsychotic drug action(44), as well as new mechanisms of action such as mGluR2 and mGluR3 stimulation(45). Additionally, it should be noted that studies have included patients from several different ethnic groups, with an over-representation of Asians (e.g., Chinese, Korean, and Japanese) and under-representation of individuals of African descent. As allele frequencies may vary considerably between ethnic groups, careful consideration of the potential impact of population genetics on genotypic and phenotypic distribution is warranted, but the limited samples currently available have hampered this effort. Finally, the relatively small number of studies included in the meta-analysis makes it difficult to conduct any meaningful moderator analyses.

Due to the heterogeneity of medication used, duration of illness in different samples, and racial groups, it is possible that we have under-estimated the effect size of the gene–drug response association. Furthermore, none of these studies formally accounted for medication non-compliance, which is prevalent among patients with schizophrenia. Put simply, when a patient does not take the prescribed antipsychotic drug, the measured effect size of gene-drug response association is assessed as zero, whereas the true effect of genotype on the phenotype is perhaps larger. Nevertheless, despite the potential under-estimation of effect size produced by these

uncontrolled factors, we were still able to detect a significant association between -141C Ins/Del and antipsychotic drug response in the meta-analysis. Data on -141C Ins/Del from larger studies such as the CATIE trial and industry efforts will be informative to further establishing the role of this SNP in antipsychotic drug response.

In summary, our meta-analysis indicates that *DRD2* genetic variation is significantly associated with antipsychotic drug response. SNPs in the *DRD2* promoter region, such as -141C Ins/Del, may be particularly important in predicting clinical response to antipsychotic drug treatment. Studies with larger cohorts examined with prospective designs may be needed to fully understand the nature of this relationship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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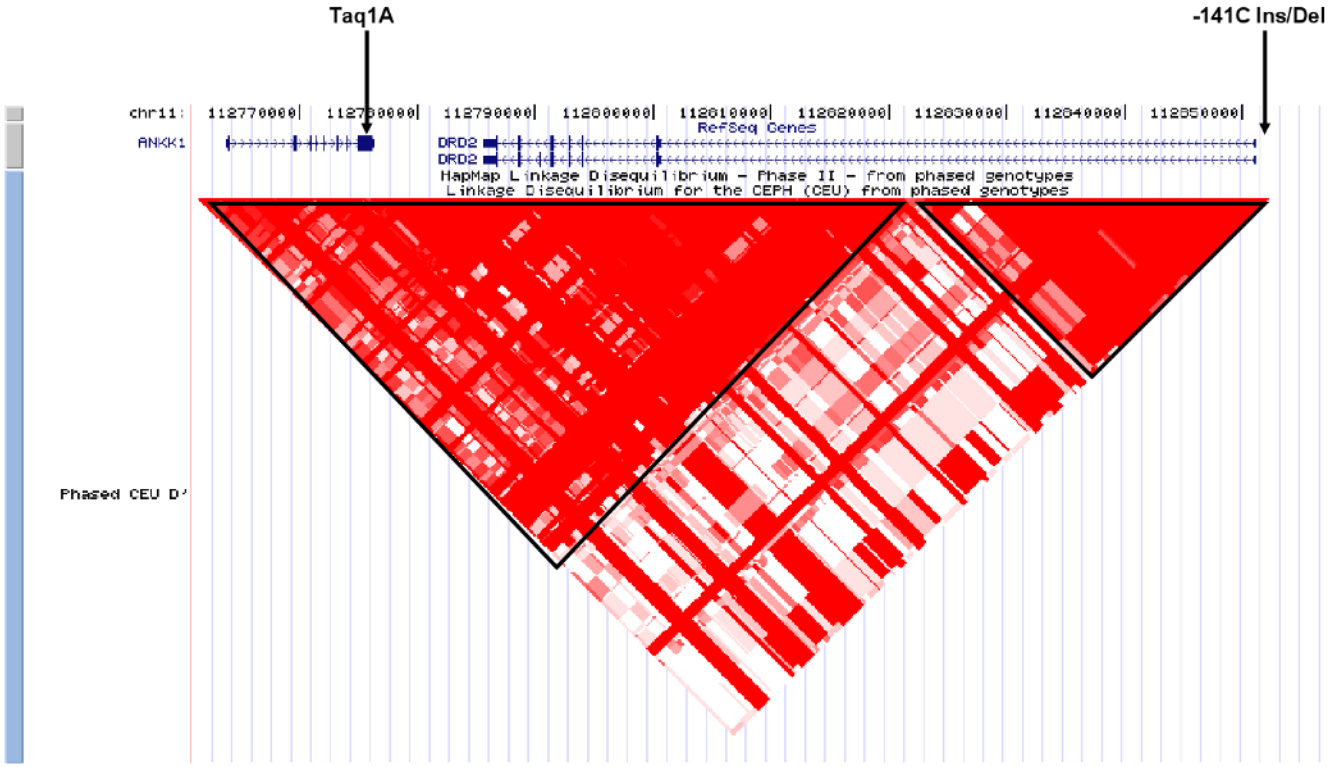


Figure 1.
Location of the Taq1A and -141C Ins/Del polymorphisms in the context of *ANKK1* and *DRD2* at chromosome 11q22. Red triangles represent areas of high linkage equilibrium (D′).

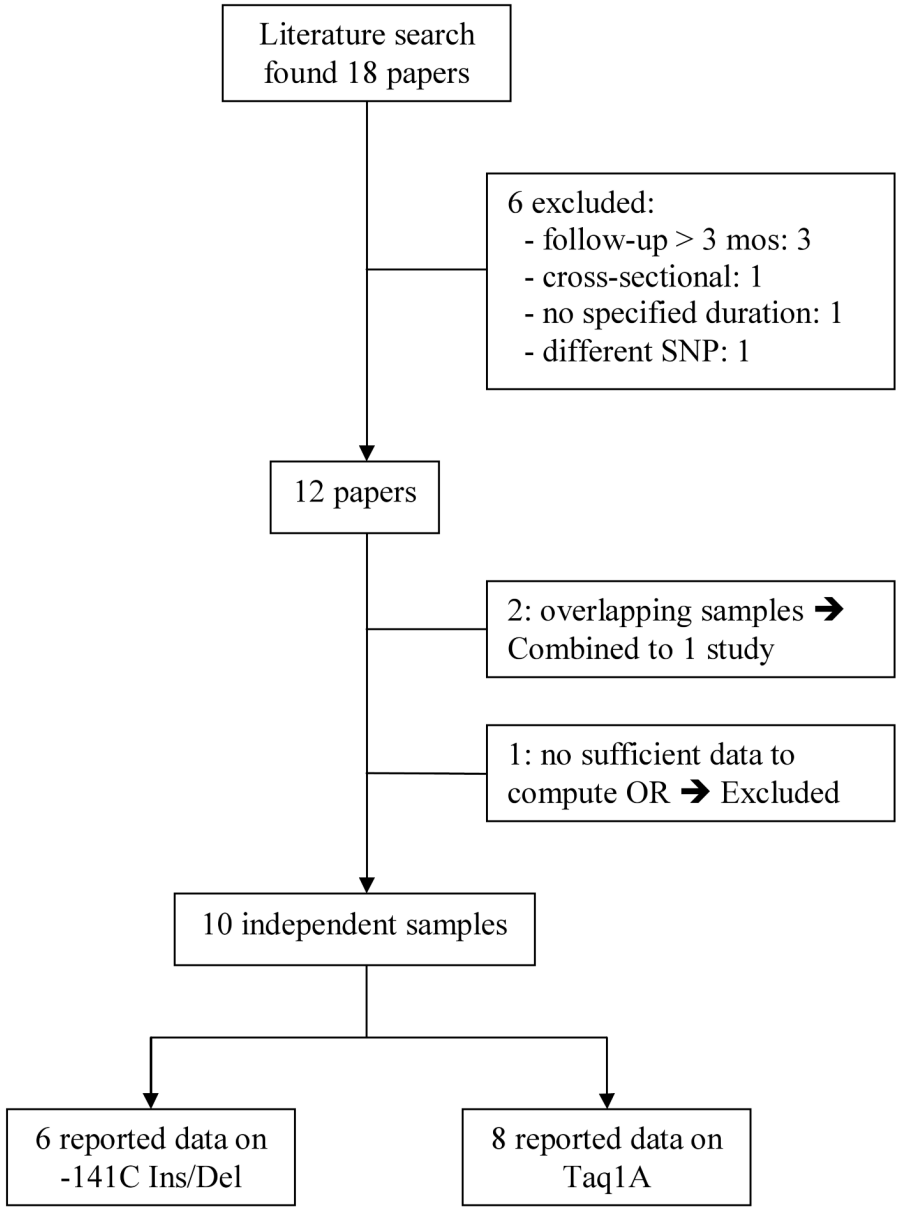


Figure 2.
Flow chart of literature search.

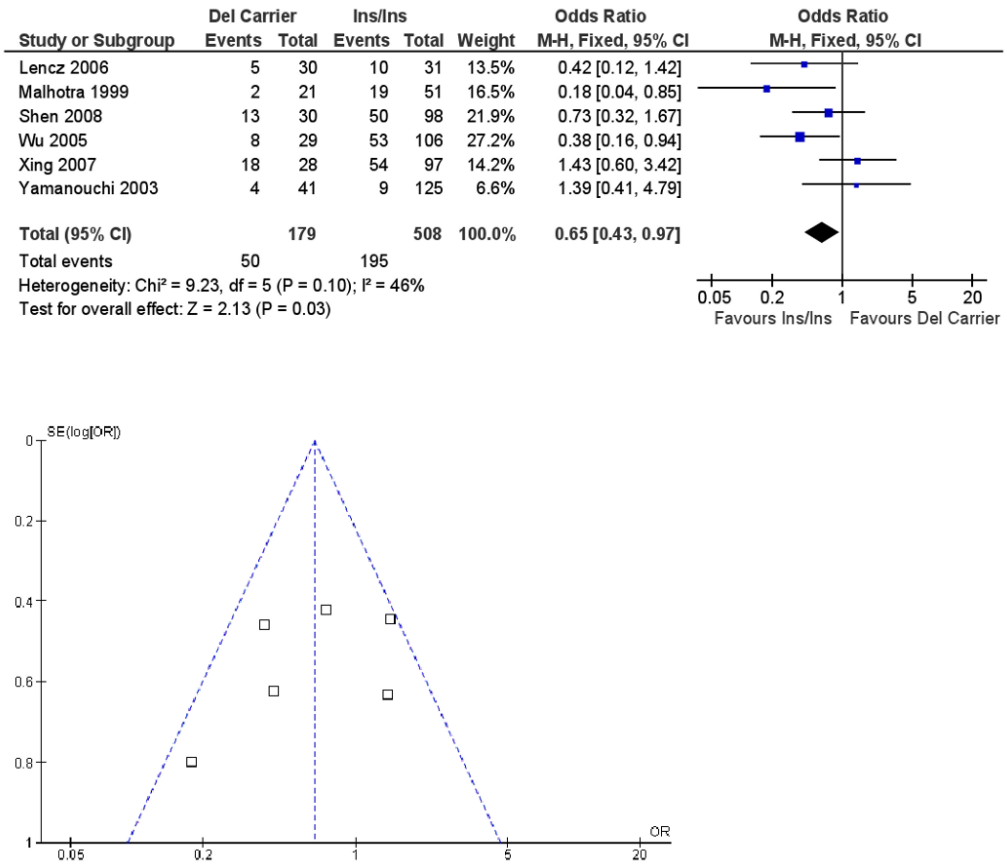


Figure 3.

Meta-analysis of the association between the -141C Ins/Del polymorphism (Del carrier vs. Ins/Ins) and antipsychotic drug response: Forrest plot and funnel plot.

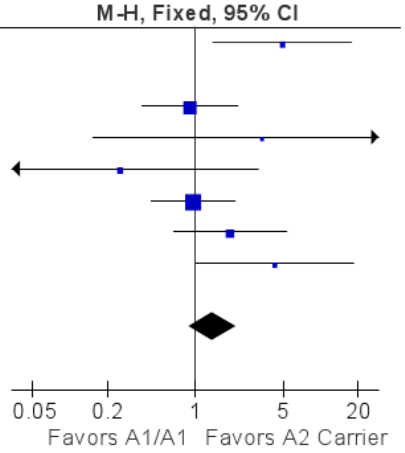
Note: M-H: Mantel-Haenszel method.

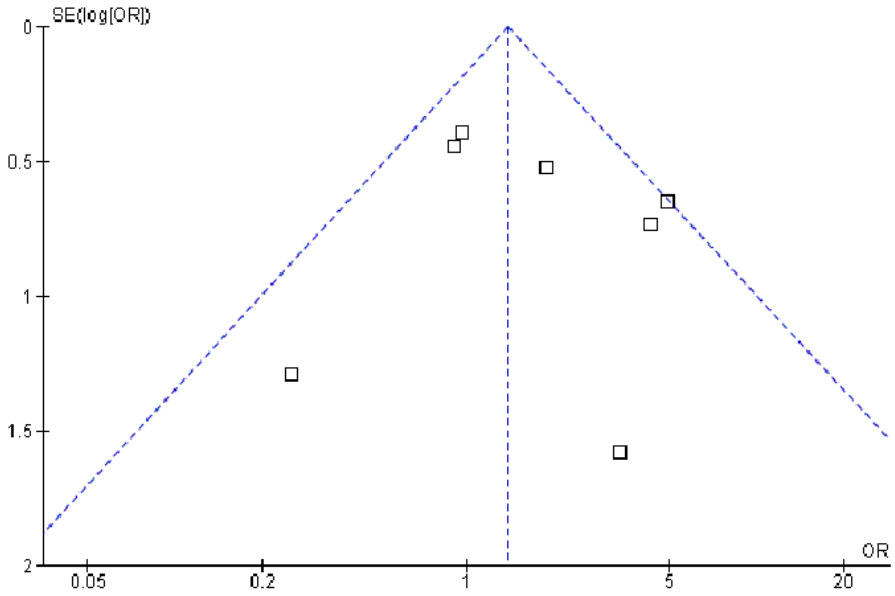
(a)

Study or Subgroup	A1/A1 Events	A1/A1 Total	A2 carrier Events	A2 carrier Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kwon 2008	6	14	9	68	5.0%	4.92 [1.38, 17.50]
Schafer 2001	0	0	0	0		Not estimable
Shen 2008	12	25	52	103	29.8%	0.91 [0.38, 2.17]
Suzuki 2000	3	3	15	22	1.6%	3.39 [0.15, 74.35]
Suzuki 2001	1	3	18	27	6.8%	0.25 [0.02, 3.14]
Wu 2005	16	36	45	99	37.7%	0.96 [0.45, 2.07]
Xing 2007	14	20	58	105	15.7%	1.89 [0.67, 5.30]
Yamanouchi 2003	3	13	10	153	3.4%	4.29 [1.02, 18.12]
Total (95% CI)		**114**		**577**	**100.0%**	**1.39 [0.91, 2.13]**
Total events	55		207			

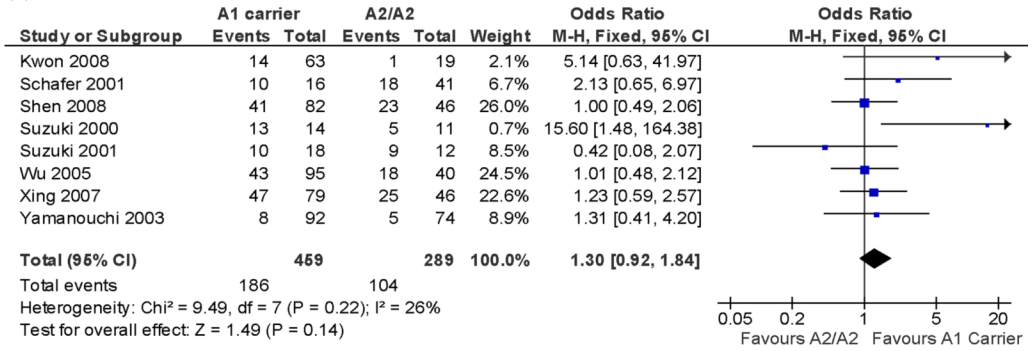
Heterogeneity: Chi² = 10.40, df = 6 (P = 0.11); I² = 42%

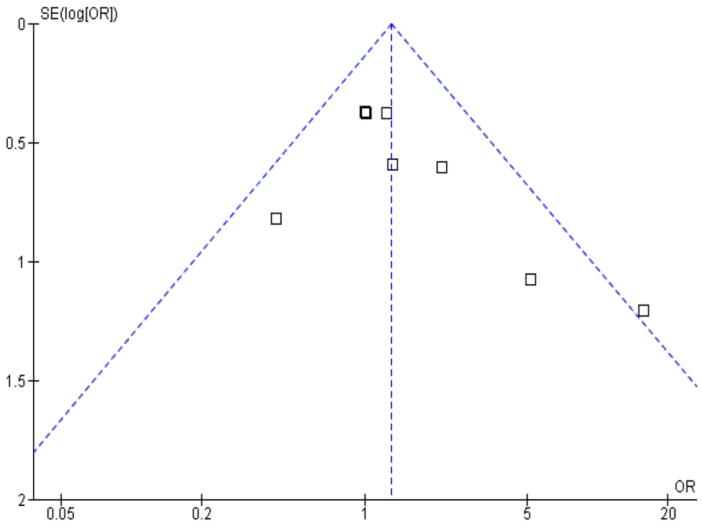
Test for overall effect: Z = 1.51 (P = 0.13)





(b)





Note: M-H: Mantel-Haenszel method.

Figure 4.

Meta-analysis of the association between the Taq1A polymorphism and antipsychotic drug response: Forrest plot and funnel plot. (a) A1/A1 vs. A2 carrier; (b) A1 carrier vs. A2/A2. Note: M-H: Mantel-Haenszel method.

Table 1

Characteristics of studies investigating the association between *DRD2* polymorphisms and antipsychotic drug response in schizophrenic patients.

Author/ year	N	Country	Ethnicity	Setting	Diagnosis	Study Design	Patient Type	Meds	*DRD2* SNP	Treatment Length	Outcome Measure	Follow-up Period	Definition of Response	Mean Change at Follow-up
Xing, 2007(14)	125	China	Chinese	not reported	SCZ	RCT	Chronic	Risperidone	-141C Ins/Del; Taq1A	8 weeks	BPRS	8 weeks	40% reduction	not reported
Schafer, 2001(11)	57	Germany	Caucasian	Inpatient	Mostly psychotic disorders	RCT	Acute	Haloperidol	Taq1A	4 weeks	PANAS	4 weeks	50% reduction	not reported
Wu, 2005(46)	135	China	Chinese	Inpatient	SCZ	RCT	Mostly 1st eptsode	Chlorpromazine	-141C Ins/Del; Taq1A	8 weeks	BPRS	8 weeks	50% reduction	not reported
Yamanouchi, 2003(37) **and Ikeda, 2008**(38)	166	Japan	Japanese	not reported	SCZ SAD	Open-label	120 were 1st episode	Risperidone	-141C Ins/Del; Taq1A	8 weeks	PANSS	8 weeks	50% reduction	23.1%
Lencz, 2006(43)	61	USA	Mixed Caucasian & AA	Inpatient	SCZ	RCT	1st episode	Risperidone Olanzapine	-141C Ins/Del	16 weeks	CGI-I	8 weeks	1 or 2	N/A
Malhotra, 1999(12)	72	USA	Mixed Causian & AA	Inpatient	SCZ	RCT	Treatment refractory	Clozapine	-141C Ins/Del	10 weeks	BPRS	10 weeks	20% reduction	not reported
Suzuki, 2000(13)	25	Japan	Japanese	Inpatient	SCZ	RCT	Acute	Nemonapride	Taq1 A	3 weeks	BPRS	3 weeks	50% reduction	65.9%
Suzuki, 2001(47)	30	Japan	Japanese	Inpatient	SCZ	RCT	Chronic	Bromperidol	Taq1 A	3 weeks	BPRS	3 weeks	50% reduction	56.8%
Kwon 2008(48)	90	South Korea	Korean	Inpatient	SCZ	RCT	Acute	Aripiprazole	Taq1A	26 weeks	PANSS	8 weeks	50% reduction	30.0%
Shen 2008(18)	128	Taiwan	Chinese	Inpatient	SCZ	Open-label	Chronic	Aripiprazole	-141C Ins/Del; Taq1A	4 weeks	PANSS	4 weeks	50% reduction	24.2%

Note: SCZ = Schizophrenia; BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale; CGI = Clinical Global Impression scale; AA = African American.