D_2 Receptor Genetic Variation and Clinical Response to Antipsychotic Drug Treatment: A Meta-Analysis

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Objective: Several lines of evidence suggest that antipsychotic drug efficacy is mediated by dopamine type 2 (D_2) receptor blockade. Therefore, it seems plausible that variation in the *DRD2* gene is associated with clinical response to antipsychotic drug treatment. The authors conducted the first meta-analysis to examine the relationship between *DRD2* polymorphisms and antipsychotic drug response.

Method: A MEDLINE search of articles available up to December 31, 2008, yielded 18 prospective studies examining *DRD2* gene 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 the Brief Psychiatric Rating Scale total score or Positive and Negative Syndrome Scale total score at approximately 8 weeks of follow-up evaluation. Odds ratio was the primary effect-size measure and 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 for the –141C Ins/Del polymorphism (total sample size: N=687). The Del allele carrier was significantly associated with poorer antipsychotic drug response relative to the Ins/Ins genotype. Eight studies assessed the Taq1A polymorphism and antipsychotic response (total sample size: N=748). There was no significant difference in the response rate among A1 allele carriers relative to individuals with the A2/A2 genotype or A2 allele carriers relative to individuals with the A1/A1 genotype.

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

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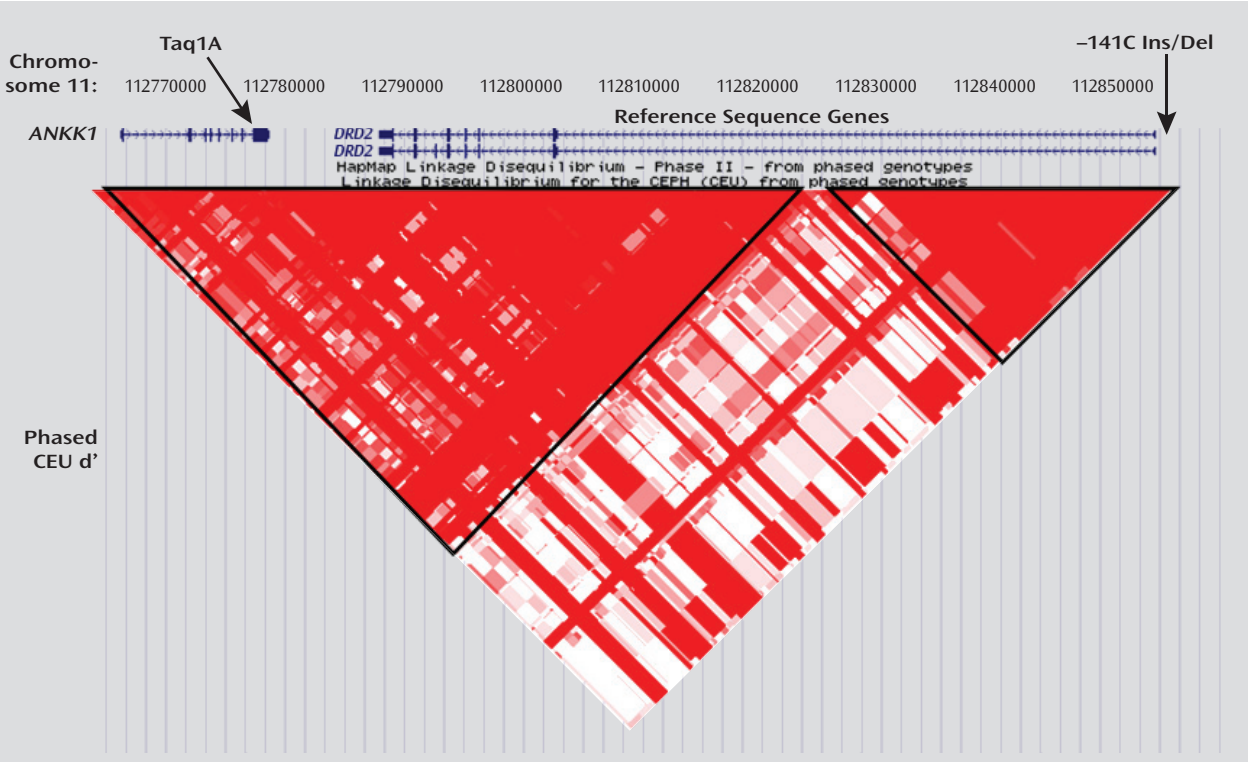
Schizophrenia is a chronic and debilitating disorder for which antipsychotic drugs are the treatment of choice (1). However, many patients with schizophrenia discontinue or switch antipsychotic drug regimens as a result of lack of efficacy and/or treatment-emergent side effects, and a large proportion 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 which individuals 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 the relationship between the most obvious candidate gene, *DRD2*, and antipsychotic drug response. Several lines of evidence suggest that the dopamine type 2 (D_2) receptor plays a critical role in antipsychotic drug action. Earlier studies showed that antipsychotic clinical potency is highly correlated with the binding affinity to a particular type of dopamine receptor (6), which was later found to be the D_2 receptor (7, 8). Recent functional imaging studies suggest that binding to the D_2 receptor by antipsychotic agents may be "necessary and sufficient" for antipsychotic efficacy (9). Finally, all known antipsychotic drugs bind to the D_2 receptor, and drugs that have targeted non-D_2 receptors without at least some element of D_2 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, 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 the 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 we describe in detail, relevant studies in the literature have utilized a variety of designs, trial durations, symptom

FIGURE 1. Location of the Taq1A and –141C Ins/Del Polymorphisms in the Context of Genes *ANKK1* and *DRD2* at Chromosome 11q22[a]



[a] Red triangles depict areas of high linkage equilibrium (d′). CEPH=Centre d'Etude du Polymorphisme Humain; CEU=CEPH Utah.

measures, and response criteria. Consequently, we developed a systematic and consistent methodology to harmonize the phenotypes reported, contacting the original investigators when re-evaluating raw data was necessary. 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 medication histories. Since antipsychotic drug exposure has been demonstrated to alter the expression of multiple CNS receptors (19), including the D_2 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 consisting primarily of chronically ill subjects.

Method

Literature Search

To identify studies eligible for this meta-analysis, we searched MEDLINE for all publications available up to December 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 articles and recent literature reviews to identify additional relevant studies. Furthermore, to find unpublished studies, we searched meeting abstracts that were likely to contain relevant research. Each article included in our meta-analysis meets the following criteria: 1) the association between *DRD2* polymorphisms and clinical antipsychotic drug response was reported; 2) the majority of patients had a diagnosis of schizophrenia or schizoaffective disorder based on DSM-IV criteria, and diagnoses were confirmed using a standardized structured clinical interview; 3) drug response was assessed using a standardized rating scale, such as the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS), or the Clinical Global Impression (CGI), at baseline and follow-up evaluations; and 4) the follow-up period was no longer than 3 months. We selected a ≤3-month follow-up evaluation period because our major goal was to assess acute antipsychotic treatment response, and response rates in treatment trials longer than 3 months may reflect other factors related to noncompliance (20), relapse prevention, illness course, and psychosocial variables (21), which may confound the genotype-drug response relationships.

Selection of Candidate Polymorphisms

The *DRD2* gene contains a number of SNPs with differing frequencies among populations (Figure 1). 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 in at least three studies. The following two polymorphisms fit this criterion: –141C Ins/Del and Taq1A. Minor allele frequency for the Taq1A polymorphism ranges from 20% in the Caucasian population to

44% in other ethnic populations. Minor allele frequency for the –141C Ins/Del polymorphism ranges from approximately 10% in Japanese and Caucasian populations to more than 50% in individuals of African descent.

–141C Ins/Del (rs1799732) polymorphism. The –141C Ins/Del (rs1799732) polymorphism represents a deletion (versus insertion) of cytosine at position –141, located in the 5′ promoter region of the *DRD2* gene. In vitro data reported 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 from positron emission tomography imaging (22) have also suggested that this polymorphism may influence D_2 receptor density in the striatum of healthy volunteers unexposed to antipsychotic drug treatment. For the purposes of the present 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 Del carrier group and antipsychotic drug response relative to the association between the Ins/Ins genotype group and antipsychotic drug response.

Taq1A (rs1800497) polymorphism. The Taq1A (rs1800497) SNP involves a C >T substitution, located approximately 10 kb downstream from the *DRD2* gene. 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 *ANKK1* (ankyrin repeat and kinase domain containing 1) (26, 27). This SNP has been studied in association with substance abuse, alcohol dependence, eating disorders, and smoking cessation. Given the lack of unequivocal data for Taq1A genotype pooling, we tested both dominant and recessive hypotheses as follows: A1/A1 versus A1/A2 + A2/A2 and A2/A2 versus A1/A2 + A1/A1.

Definition of Clinical Response

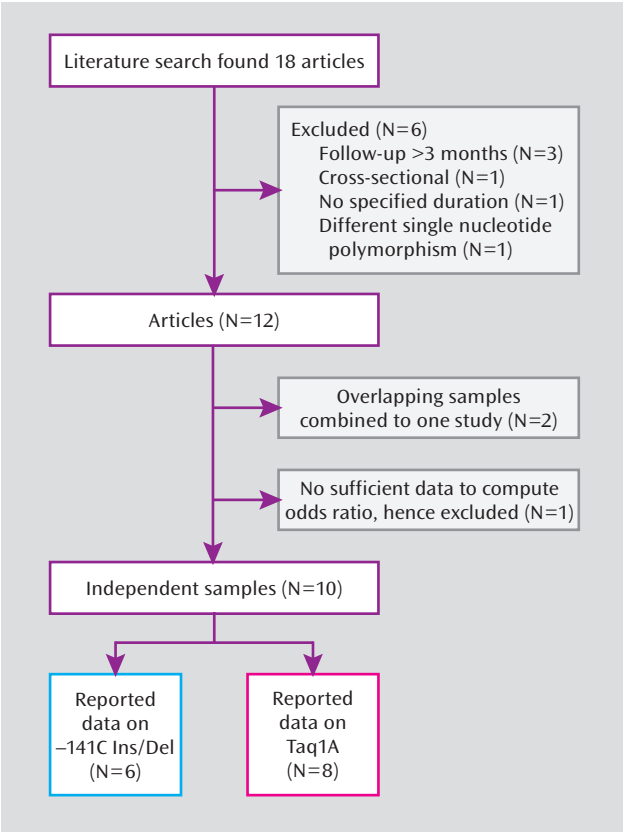
Clinical response to antipsychotic drug treatment was defined as a 50% reduction of either the BPRS total score or the PANSS total score from baseline to follow-up assessment. Studies have shown that a 50% reduction of the BPRS total score is approximately equivalent to a 50% reduction in the PANSS total 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 evaluation (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 for a study, we used the study's original definition of clinical response.

Odds ratio was the primary effect-size measure and computed for each polymorphism in each study. If a study did not report the categorical outcomes of subjects who responded to treatment relative to those who did not respond to treatment, we requested these data from the authors. If categorical data were not available, we did not include the study in our meta-analysis.

Statistical Analysis

Data were entered into and analyzed by Cochrane Collaboration Review Manager (RevMan), Version 5.0 (Nordic Cochrane Centre, Cochrane Collaboration, Blegdamsvej, Denmark). Heterogeneity among the studies was assessed using a chi-square test. Individual odds ratios and associated 95% confidence intervals (CIs) were calculated and pooled to compute the mean effect size using the Mantel-Haenszel method (29). A fixed-effect model was used in all analyses (30), which is an approach similar to the approaches used in other pharmacogenetic meta-analyses (30, 31). A separate meta-analysis was conducted for each SNP and each genotype. Publication bias was assessed using the funnel plot method, the Duval and Tweedie "trim and fill" method (32), and Egger's test (33), conducted with "metatrim" and "metabias" macro procedures in Stata, Version 7.0 (StataCorp, LP, College Station, Tex.).

FIGURE 2. Flow Chart of Literature Search for Studies Examining *DRD2* Gene Variation and Antipsychotic Drug Response in Schizophrenia Patients



Results

To conduct our meta-analysis on the relationship between *DRD2* gene variation and antipsychotic drug response, we searched for literature available up to December 31, 2008, which yielded 18 published articles. Of these, six articles were not included because three (15, 16, 34) only reported long-term outcomes >3 months from baseline to follow-up evaluation, one (35) was cross-sectional, one (36) did not state the duration of follow-up evaluation or include a standardized rating scale such as the BPRS, PANSS, or CGI, and one (17) contained no data on Taq1A or –141C Ins/Del polymorphisms. Two articles published by the same research group (37, 38) contained overlapping data and therefore were assessed as one study, subsequent to the authors providing the additional data needed to compute the categorical outcome of clinical response. Finally, in one other study (39), we were unable to obtain sufficient information to calculate response rates, and therefore we did not include data from that study.

TABLE 1. Studies Investigating the Association Between the *DRD2* Polymorphism and Antipsychotic Drug Response in Schizophrenia Patients

Study	Sample Size	Country	Ethnicity	Setting	Diagnosis	Study Design
Xing et al. (14)	125	China	Chinese	Not reported	Schizophrenia	Randomized controlled trial
Schäfer et al. (11)	57	Germany	Caucasian	Inpatient	Mostly psychotic disorders	Randomized controlled trial
Wu et al. (46)	135	China	Chinese	Inpatient	Schizophrenia	Randomized controlled trial
Yamanouchi (37) and Ikeda et al. (38)	166	Japan	Japanese	Not reported	Schizophrenia, schizo-affective disorder	Open-label trial
Lencz et al. (43)	61	United States	Caucasian and African American	Inpatient	Schizophrenia	Randomized controlled trial
Malhotra et al. (12)	72	United States	Caucasian, African American, Japanese	Inpatient	Schizophrenia	Randomized controlled trial
Suzuki et al. (13)	25	Japan	Japanese	Inpatient	Schizophrenia	Randomized controlled trial
Suzuki et al. (47)	30	Japan	Japanese	Inpatient	Schizophrenia	Randomized controlled trial
Kwon et al. (48)	90	South Korea	Korean	Inpatient	Schizophrenia	Randomized controlled trial
Shen et al. (18)	128	Taiwan	Chinese	Inpatient	Schizophrenia	Open-label trial

[a] Clinical response to antipsychotic drug treatment was defined as the percent of reduction in the total score on the BPRS or PANSS or equivalent rating on the CGI from baseline to follow-up assessment.

[b] Data represent 120 patients.

A total of 10 independent studies (total sample size: N=889) met criteria for inclusion in the present meta-analysis. Figure 2 illustrates 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 (total sample size: N=687), and eight studies reported outcomes conditioned on the Taq1A SNP (total sample size: N=748). In addition, six studies reported continuous outcomes, but the authors generously provided the additional data needed to compute odds ratios.

–141C Ins/Del Polymorphism and Antipsychotic Drug Response

As mentioned earlier, 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 odds ratios for the individual studies and the pooled analyses in different genotype groups. There was a significant difference in the response rate between the Del carrier and Ins/Ins genotype groups (pooled odds ratio=0.65, 95% CI=0.43 to 0.97, p=0.03), indicating that Del carriers tend to have less favorable antipsychotic drug responses than individuals with the Ins/Ins genotype. The chi-square test assessing heterogeneity did not reveal significance (χ^2=9.23, df=5, p=0.10; I^2=46%). To deal with potentially undetected heterogeneity across samples, we conducted a sensitivity analysis that excluded the study with the largest effect size (12) and the study with the smallest effect size (14). Another reason to exclude these two studies was that they may be different from other studies because the 50% reduction of the BPRS or PANSS total score was not used to define clinical response. For the sensitivity analysis, I^2 was changed from 46% to 10% and the chi-square test for heterogeneity revealed a decrease from 9.23 to 3.33, which was nonsignificant, with a change in the p value from 0.10 to 0.34. The pooled odds ratio became 0.60, with a 95% CI range of 0.38–0.97 and p value of 0.04.

In a post hoc analysis, we restricted our investigation to studies consisting of patients with first-episode schizophrenia (total sample size: N=316). The pooled odds ratio for Del carrier patients relative to patients with the Ins/Ins genotype was 0.53 (95% CI=0.28 to 0.99, p=0.05), demonstrating poorer clinical response in Del carriers. In contrast, for studies that did not include first-episode schizophrenia patients (total sample size: N=371), we obtained a pooled odds ratio of 0.75 (95% CI=0.44 to 1.27, p=0.23) (see Figure 1 in the data supplement accompanying the online version of this article).

As seen in Figure 3, funnel plot analysis did not demonstrate evidence of publication bias. The Duval and Tweedie (32) trim and fill method indicated that it was not necessary to trim any existing study and fill any additional unpublished study. In addition, Egger's test (33) also revealed no evidence of publication bias (beta=0.79, 95% CI=–3.05 to 4.63, p=0.60).

Patient Type	Medication	DRD2 Single Nucleotide Polymorphism	Duration of Treatment (Weeks)	Outcome Measure	Duration of Follow-Up Evaluation (Weeks)	Definition of Treatment Response[a]	Mean Change at Follow-Up Evaluation (%)
Chronic	Risperidone	–141C Ins/Del; Taq1A	8	Brief Psychiatric Rating Scale (BPRS)	8	40% reduction in total score	Not reported
Acute	Haloperidol	Taq1A	4	Positive and Negative Syndrome Scale (PANSS)	4	50% reduction in total score	Not reported
Mostly first episode	Chlorpromazine	–141C Ins/Del; Taq1A	8	BPRS	8	50% reduction in total score	Not reported
First episode[b]	Risperidone	–141C Ins/Del; Taq1A	8	PANSS	8	50% reduction in total score	23.1
First episode	Risperidone, olanzapine	–141C Ins/Del	16	Clinical Global Impression–Improvement (CGI–I)	8	1 or 2	N/A
Treatment refractory	Clozapine	–141C Ins/Del	10	BPRS	10	20% reduction in total score	Not reported
Acute	Nemonapride	Taq1A	3	BPRS	3	50% reduction in total score	65.9
Chronic	Bromperidol	Taq1A	3	BPRS	3	50% reduction in total score	56.8
Acute	Aripiprazole	Taq1A	26	PANSS	8	50% reduction in total score	30.0
Chronic	Aripiprazole	–141C Ins/Del; Taq1A	4	PANSS	4	50% reduction in total score	24.2

Taq1A Polymorphism and Antipsychotic Drug Response

As previously discussed, eight studies assessed the Taq1A polymorphism and antipsychotic response, with a total sample size of 748 patients. Odds ratios for the individual studies and the pooled analyses in different genotype groups are shown in Figure 4 and Figure 5. There was no significant difference in the treatment response rate among individuals with the A1/A1 genotype relative to A2 allele carriers (pooled odds ratio=1.39, p=0.13 [Figure 4]) or A1 allele carriers relative to individuals with the A2/A2 genotype (pooled odds ratio=1.30, p=0.14 [Figure 5]). Further, there was no significant heterogeneity across studies in these two comparisons (A1/A1 genotype relative to A2 allele carriers: χ^2=10.40, p=0.11; I^2=42%; A1 allele carriers relative to individuals with the A2/A2 genotype: χ^2=9.49, p=0.22; I^2=26%).

The Duval and Tweedie trim and fill analysis showed that it was necessary to fill an additional unpublished study for both the A1/A1 genotype versus A2 allele carrier comparison (pooled odds ratio=1.24, p=0.30) and A1 allele carrier versus A2/A2 genotype comparison (pooled odds ratio=1.17, p=0.39). In contrast, Egger's test revealed no evidence of publication bias for either comparison (A1/A1 genotype versus A2 allele carrier: beta=–0.07, p=0.93; A1 allele carrier versus A2/A2 genotype: beta=–0.60, p=0.26). In summary, the evidence regarding publication bias for the Taq1A polymorphism was inconsistent. Even if we were able to eliminate publication bias, it appears that the association between the Taq1A polymorphism and antipsychotic drug response would still not be significant.

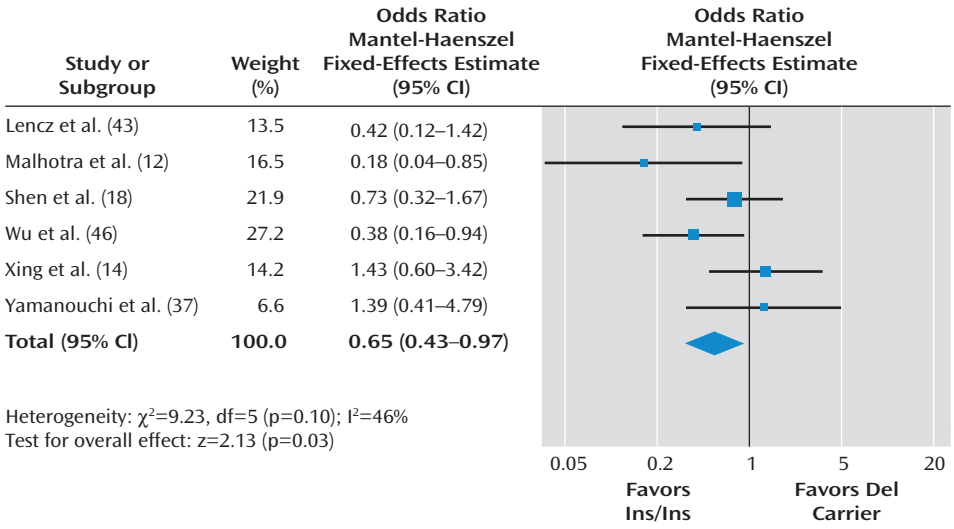
Discussion

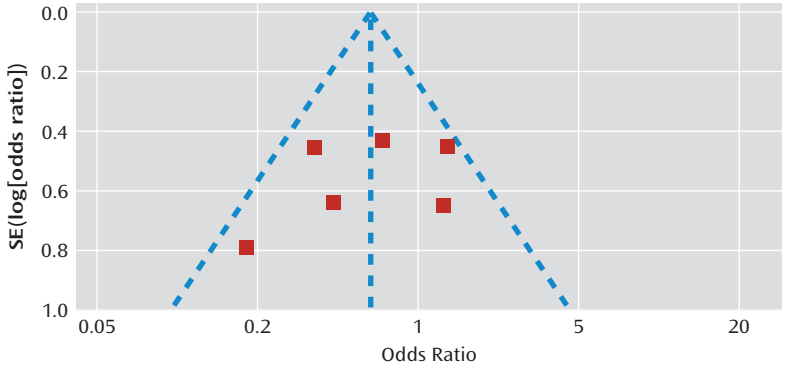
In order to assess the relationship between *DRD2* genetic variation and antipsychotic drug response, we conducted the first meta-analysis of the –141C Ins/Del and Taq1A polymorphisms, two commonly studied *DRD2* SNPs, and clinical response to antipsychotic drug treatment. The primary result was that the –141C Ins/Del polymorphism significantly influenced antipsychotic drug response (total sample size: N=687), 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 D_2 receptor in antipsychotic drug response. Antipsychotic clinical potency is highly correlated with the binding affinity to the D_2 receptor (6–8); D_2 receptor occupancy by antipsychotic agents has been demonstrated to occur with all antipsychotic agents (9); and drugs targeting other receptor sites without D_2 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.

FIGURE 3. Association Between the –141C Ins/Del Polymorphism (Del Carrier vs. Ins/Ins Genotype) and Antipsychotic Drug Response



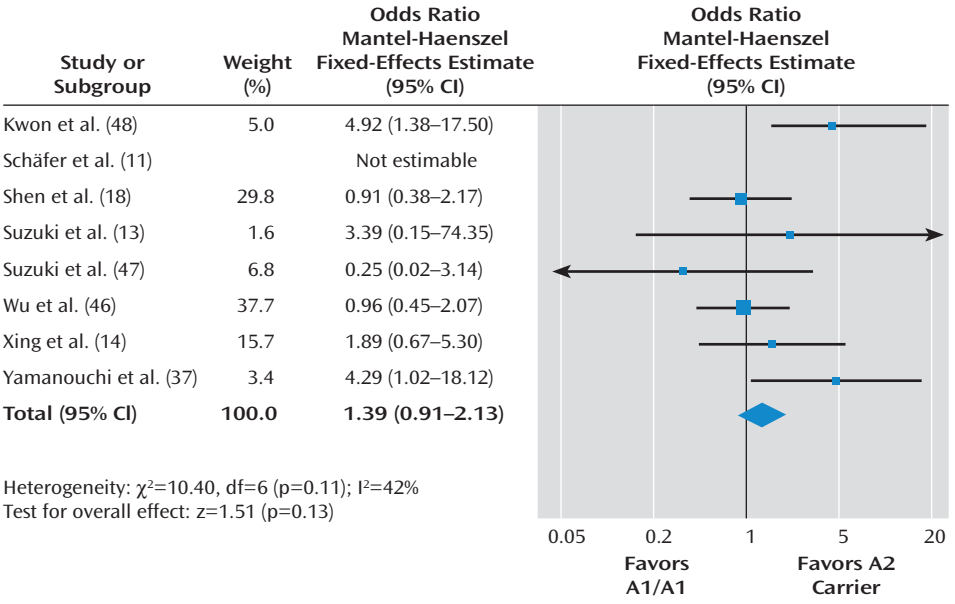


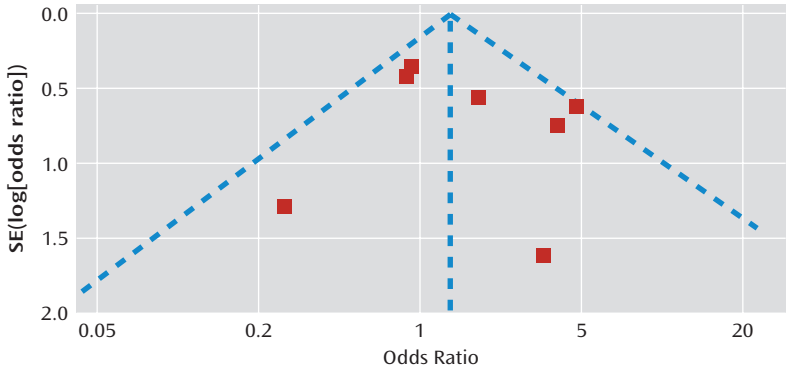
This may be the result of limited or lack of prior exposure to antipsychotic drug treatment in these patients. Differential amounts of prior drug exposure, as commonly observed in chronically ill samples, could result in considerable variation in levels of dopamine receptor up-regulation (40, 41) and 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 studies on first-episode patients are less common than studies on chronically ill patients.

There was no significant association between the Taq1A polymorphism and antipsychotic drug response in the eight studies reporting outcomes conditioned on the Taq1A SNP, with a total sample size of 748 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 the *DRD2* gene, and it is actually located in a noncoding 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 because this SNP is located in the 5′ promoter region of *DRD2*, where it may influence modulation of transcriptional activities (23) and D_2 receptor density (42). Interestingly, another *DRD2* SNP, A-241G, which is also located in the promoter region, has 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 D_2 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 the grouping of individual drug responses for analysis. Third, and perhaps most importantly, each of the antipsychotic drugs was specifically developed because of the common mechanism of action of antagonism of D_2 receptors, and therefore a common effect of *DRD2* variation across these drugs seems highly plausible. Nevertheless, the development of drugs with antipsychotic efficacy that does not act at the D_2 receptor will be needed to empirically assess this issue.

FIGURE 4. Association Between the Taq1A Polymorphism and Antipsychotic Drug Response in Individuals With the A1/A1 Genotype Relative to A2 Allele Carriers

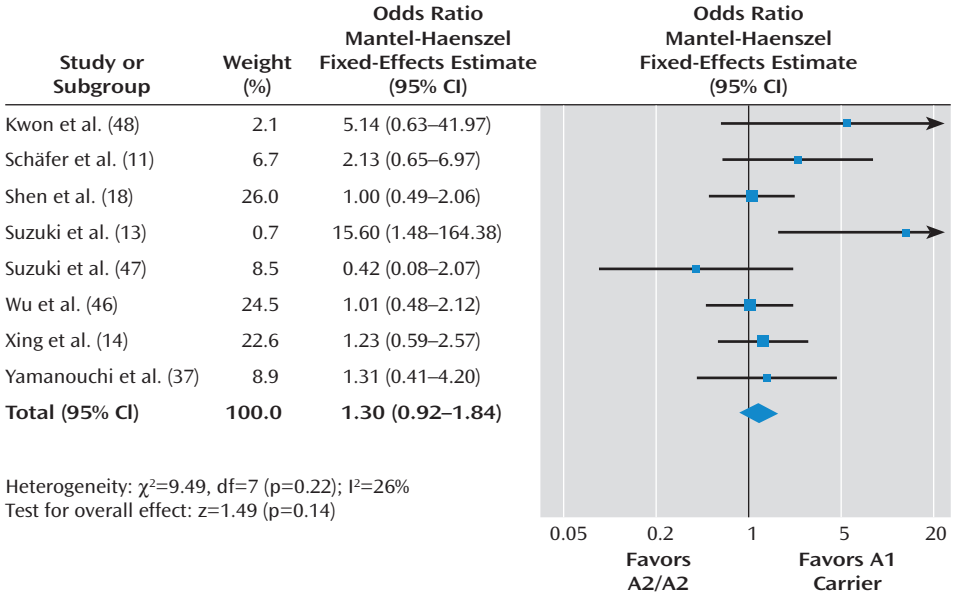


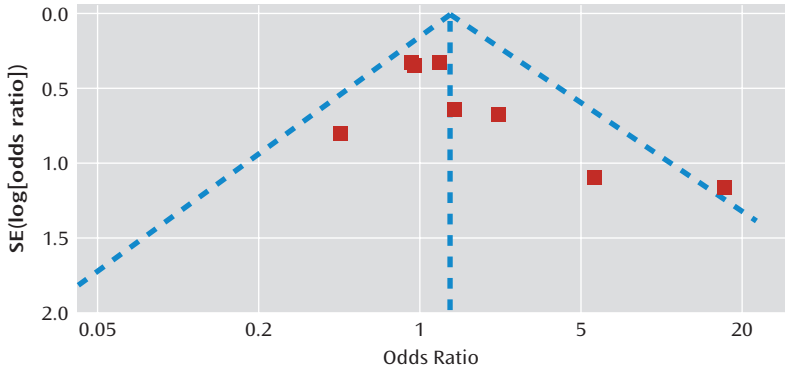


There are several limitations of this study. First, odds ratio was used as the effect-size measure. Because this requires dichotomizing a continuous measure of either BPRS or PANSS scores, statistical power may have been diminished and it may explain why some studies reported significant findings of an association between *DRD2* and antipsychotic drug response while the odds ratios were not individually significant. Therefore, meta-analysis of odds ratios may lack some sensitivity to detect small effect sizes. This is consistent with an exploratory sensitivity analysis using a random-effect model (see Figure 2 in the online data supplement), 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 the number of days to hospital discharge following acute treatment or assessments of functional disability.

Second, variation in the antipsychotic drugs administered in the studies we analyzed limited the possibility of examining the association of *DRD2* with any specific drug. In these studies, multiple antipsychotic drugs were utilized, including typical agents such as chlorpromazine and haloperidol and atypical drugs such as clozapine, risperidone, olanzapine, and aripiprazole. Although all of these drugs act on the D_2 receptor, they exhibit different affinity profiles for many of the candidate receptors (44), making direct comparisons more complex. For example, non-D_2 receptors, such as D_3, D_4, and serotonin 5-HT_{2A}, may also be important in antipsychotic drug action (44) as well as new mechanisms of action, such as metabotropic glutamate receptor 2 and receptor 3 stimulation (45). Additionally, it should be noted that the studies included patients from several different ethnic groups, with an overrepresentation of Asian patients (e.g., Chinese, Korean, and Japanese populations) and an underrepresentation of individuals of African descent. Since allele frequencies may vary considerably between ethnic groups, careful consideration of the potential effect of population

FIGURE 5. Association Between the Taq1A Polymorphism and Antipsychotic Drug Response in A1 Allele Carriers Relative to Individuals With the A2/A2 Genotype





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 this meta-analysis makes it difficult to conduct any meaningful moderator analyses.

As a result of the heterogeneity of medication used, the duration of illness in different samples, and the different racial groups, it is possible that we have underestimated the effect size of the gene-drug response association. Furthermore, none of the studies formally accounted for medication noncompliance, which is prevalent in 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 underestimation of effect size produced by these uncontrolled factors, we were still able to detect a significant association between the –141C Ins/Del polymorphism and antipsychotic drug response. Data on the –141C Ins/Del polymorphism from larger studies, such as the Clinical Antipsychotic Trials of Intervention Effectiveness and industry efforts, will be informative and important in 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.

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