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The efficacies of clozapine and haloperidol in refractory schizophrenia are related to *DTNBP1* variation

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Abstract

Objective—The prototypical atypical antipsychotic agent, clozapine, is more efficacious for refractory schizophrenia than the "typical" antipsychotics, but the mechanism underlying this enhanced efficacy is still under investigation. Since 2002, at least 22 association studies have demonstrated that the *DTNBP1* can be associated with the risk for schizophrenia. We hypothesized that *DTNBP1* might also influence the response to antipsychotic treatments. The present study aimed to investigate the relationship between the *DTNBP1* and the effects of clozapine and haloperidol on refractory schizophrenia.

Methods—Patients with refractory schizophrenia were assigned to clozapine (n=85) or haloperidol (n=96) and followed for 3 months. Symptom improvement was evaluated by PANSS score. Six markers at *DTNBP1* and 38 ancestry informative markers (AIMs) were genotyped in all subjects. The relationships between the effects of antipsychotics and the diplotypes, haplotypes, genotypes, and alleles of *DTNBP1* were tested by ANCOVA, ANOVA, and t-test.

Results—Patients with diplotype ACCCTC/GTTGCC, genotypes T/T+T/C, or allele T of marker rs742105 (P1333) have better response to clozapine ($0.005 \leq p \leq 0.049$), and patients with diplotype ACCCTC/GCCGCC, genotype A/G, or allele A of marker rs909706 (P1583) have better response to haloperidol ($0.007 \leq p \leq 0.080$) in European-Americans (EAs), African-Americans (AAs), and/or the combined sample; EA patients with diplotype ACCCTC/GCCGCC have worse response to clozapine on positive symptoms ($p=0.011$).

Conclusions—The present study demonstrates that the *DTNBP1* gene modulates the effects of both the atypical antipsychotic clozapine, and the typical antipsychotic haloperidol. Subjects with different *DTNBP1* diplotypes, haplotypes, genotypes, or alleles might have different responses to these antipsychotics.

Keywords

Clozapine; Haloperidol; Refractory Schizophrenia; *DTNBP1*

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INSTRUCTION

Clozapine was the first antipsychotic agent to be clearly and consistently shown to be more effective than typical antipsychotic medications among patients with residual symptoms despite prolonged prior treatment with a typical antipsychotic medication [1–5]. Although more expensive than typical antipsychotic treatment, clozapine was shown to be cost neutral to healthcare systems because its increased expense was balanced by other reductions in healthcare costs, such as reduced days that patients spent in the hospital [4]. The introduction of clozapine stimulated a “second generation” of antipsychotic medications. The new “atypical” antipsychotic medications attempted to capture the efficacy and extrapyramidal side (EPS) profile of clozapine without producing unwanted side effects of clozapine, particularly hematoxicity. The atypical antipsychotic agents proved to be extremely popular with clinicians. By 1999, 58.8% of all patients with schizophrenia who received an antipsychotic in the US Department of Veterans Affairs (VA) were prescribed an atypical medication [6,7], and the proportion had increased to 64.4% by 2000 [8]. One consequence of this prescription pattern is that atypical antipsychotic medications constitute an enormous economic burden on healthcare systems. The recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study [9], however, suggests that the enhanced efficacy and tolerability of atypical antipsychotics over the typical neuroleptic, perphenazine, may be modest or even non-existant. Thus, the question of which patients differentially benefit from the prescription of typical or atypical antipsychotic medications has emerged as an important clinical and economic public health issue [9–11].

A familial pattern of treatment response has been observed [12,13]. Clinical response to antipsychotic drugs may be influenced by genetic variation. Alterations in genes coding for receptor proteins may affect their binding affinities for antipsychotics, and may affect the efficiency of signal transduction or their levels of expression that may therefore alter the drug’s therapeutic action. Multiple genetic loci have been reported to contribute to the pharmacogenetics of clozapine response, but no single factor can fully account for heterogeneity in response to clozapine [14–17].

Pharmacogenetic studies have the potential to inform prognostic and therapeutic considerations among patients with schizophrenia. A growing number of genes have been associated with antipsychotic treatment response and with the side effects of these medications among patients with schizophrenia [18]. In pharmacogenetic studies of schizophrenia conducted to date, investigators commonly explore the impact of variation in genes associated with the risk for schizophrenia upon treatment responses, particularly the comparison of typical and atypical antipsychotic medications.

A protein coded by a gene that plays a role in the etiology of schizophrenia might also be a target of interest for treatment. Many studies have demonstrated that genes that encode some specific receptors or enzymes related to risk for schizophrenia, are implicated in the effects of clozapine that might target those receptors or enzymes. The dysbindin gene *DTNBP1* is a promising target for pharmacogenetic studies of clozapine effect on schizophrenia. Using a family-based association method, Straub et al. [19] initially identified the *DTNBP1* at 6p22.3 as a susceptibility gene for schizophrenia in 270 Irish high-density pedigrees and found several polymorphisms within this gene associated with schizophrenia. Twenty-two positive replications have emerged from among at least 30 family-based or population-based association studies (reviewed in [20]). Also, one linkage study from an isolated Israeli population directly located a risk region for major psychiatric disorders at *DTNBP1* locus [21]. Our initial study also demonstrated the *DTNBP1*-schizophrenia association [20]. These *DTNBP1*-schizophrenia associations suggest that *DTNBP1* might be a candidate gene of interest for clozapine effect, although this hypothesis remains controversial [22]. Dysbindin

is localized to presynaptic glutamatergic neural elements, where it may influence glutamate release [23,24] and postsynaptic density, an anchoring structure for NMDA glutamate receptors [25,26]. In light of preclinical [27–29] and clinical [30,31] evidence that clozapine shows greater efficacy than typical antipsychotics in attenuating the impact of deficits in NMDA glutamate receptor function, one might expect that variation in *DTNBP1* would be differentially associated with treatment outcomes for clozapine and haloperidol.

The effects of clozapine might be different among populations. For example, clozapine is reportedly more efficacious for Korean-American patients than for EAs [32]. Compared to Australia Caucasian patients, Singapore Asian patients with chronic schizophrenia appeared to have a lower clozapine dosage requirement for clinical efficacy [33]. These suggest that the effects of clozapine may be population-specific. Many *DTNBP1* allele frequencies are also known to vary by population (summarized in [20]). Thus, the relationship between genes and the effects of clozapine might be affected by population stratification and admixture effects. Many previous studies on the relationship between genes and the effects of clozapine ignored or at least insufficiently guarded against these effects. For example, African-Americans (AAs) are a highly genetically admixed population, and a small degree of admixture has also been detected in European-Americans (EAs) [34], but the studies by Masellis et al. [35,36] and Hwang et al. [37] using AA, EA, or combined AA and EA samples ignored the potential admixture effects. The present study takes these effects into account.

MATERIALS AND METHODS

1. Subjects

The study population consisted of 181 unrelated schizophrenic inpatients who were among the 423 patients who participated in the VA Cooperative Study that compared the efficacy of haloperidol (n=96) and clozapine (n=85), who contributed DNA for analysis and who remained on the assigned study medication for three months [4]. Sample sizes, baseline total PANSS scores (T), baseline positive symptom scores (P), baseline negative symptom scores (N) and general psychopathology symptom scores (G) before trial, the sex distribution, the ethnicity distribution, the mean admixture rates, and the dosages of clozapine and haloperidol for these subjects are shown in Table 1. Study power was calculated using the PAWE program (http://linkage.rockefeller.edu/pawe/pawe.cgi). Two treatment groups showed a roughly matched age distribution. The ethnicity for individuals was classified by ancestry proportions rather than self-report.

Eligibility criteria for the parent study, described in detail elsewhere [38], included (1) a DSM-III-R diagnosis of schizophrenia using the Semi-structured Clinical Interview for Diagnosis; (2) refractoriness, defined as persisting psychotic symptoms despite adequate treatment trials of two or more antipsychotic drugs at 1000-mg chlorpromazine equivalents unless limited by adverse effects; (3) severe symptoms, indicated by scores on the Brief Psychiatric Rating Scale and the Clinical Global Impressions Scale; (4) serious social dysfunction for the previous two years; and (5) a high level of use of inpatient services, defined as 30–364 days of psychiatric hospitalization in the year prior to study entry. Subjects were recruited at the VA Connecticut Healthcare System, West Haven Campus, or 14 other Veterans Affairs medical centers [4]. The study was approved by the Institutional Review Boards (IRB) at all sample collection sites. All subjects signed informed consent.

2. Design of the clinical trial

This double-blind randomized comparison of haloperidol and clozapine efficacy was conducted in 15 VA Medical Centers. After base-line assessments had been completed,

patients were randomly assigned to haloperidol (5–30mg/d, mean 11±10 mg/d) or clozapine (40–900mg/d, mean 203±241 mg/d) and followed for 12 months, at maximum tolerable doses. Dose adjustment was made as clinically indicated. Haloperidol-treated patients also received benztropine mesylate (2–10mg/d) for EPS effects and participated in weekly red blood cell counts as required for clozapine treatment. Clozapine-treated patients received placebo benztropine capsules. This report is limited to the first three months of treatment to maximize the sample sizes for each treatment group.

3. Comparison of the effects of clozapine and haloperidol

Symptoms were assessed with the structured clinical interview version of the Positive and Negative Syndrome Scale (PANSS) [39], in which higher scores indicate worse symptoms. Reduction rate of PANSS scores from the baseline assessment to that at the latter of the 3-month interviews can be calculated by the equation R=(P1-P2)/(P1-B)×100%, where R denotes reduction rate of PANSS scores, P1 denotes the PANSS scores before treatment, P2 denotes the PANSS scores after 3-month treatment, and “B” is the lowest possible score on the PANSS, i.e., the score obtained in the absence of any symptoms [PANSS total score (T): B=30; PANSS positive symptom score (P): B=7; PANSS negative symptom score (N): B=7; and PANSS general psychopathology symptom score (G): B=16]. Response to treatment was defined as 20 percent improvement on standard scales of symptoms, i.e., R≥20%. The normality of distributions of reduction rates in each treatment group was tested by the One-Sample Kolmogorov-Smirnov Test implemented in SPSS, which showed that they all were normally distributed (data not shown). Reduction rates were compared between clozapine and haloperidol using t-test.

4. Marker inclusion

Six markers within *DTNBP1* were genotyped in the present study, including two markers (P1583: rs909706 and P1578: rs1018381) at intron 1, one marker (P1320: rs760761) at intron 3, one marker (P1655: rs2619539) at intron 5, one marker (P1333: rs742105) at intron 7, and one marker (P1328: rs742106) at intron 9. These markers were selected from the original 12 markers in the study by Straub et al. (2002b), because they could be genotyped by multiplex PCR in the MassARRAY system, and we could validate their allele frequencies in a small sample prior to the high-throughput genotyping. All six markers have also been examined in many other studies and most of them were found to be associated with schizophrenia (reviewed in ref. 20). The six markers span a total of 136Kb, with an average intermarker distance of 22kb. Most of them are tagSNPs in the HapMap database (www.hapmap.org), and cover most (but not all) of the information content of *DTNBP1*.

5. Genotyping

Genomic DNA was extracted from peripheral blood by standard methods. Six SNPs were genotyped by Matrix-Assisted Laser Desorption Ionization - Time of Flight (MALDI-TOF) Mass Spectrometry via the Sequenom MassARRAY system (SEQUENOM, Inc., San Diego, CA, USA) in three 2-plex PCRs, using six pairs of primers [20].

The Duffy antigen gene (FY) marker (rs2814778) was genotyped by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) technique as described previously [40]. The 37 short tandem repeats (STRs) were genotyped by a Fluorescence Capillary Electrophoresis (FCE) technique using the ABI PRISM 3100 semiautomated capillary fluorescence sequencer as described in detail elsewhere [41].

6. Estimation of ancestry proportions

The EA and AA subjects are genetically admixed. We estimated the different ancestry proportions for each individual, using a molecular genetic method. This model-based clustering method examined ancestry proportions of each subject by utilizing the ancestry information content from a set of ancestry-informative markers (AIMs). The algorithm is a Bayesian approach that is implemented in the program STRUCTURE [42]. This set of AIMs includes 37 STRs and one highly ancestry-informative *FY* marker (rs2814778), and the detailed characteristics of these AIMs and the procedure for running STRUCTURE were introduced elsewhere [41,43]. The analysis conditioning on ancestry proportions can control for the effects of population stratification and admixture.

7. Estimation of haplotype and diplotype probabilities

The program PHASE [44,45] was used to reconstruct haplotypes and to estimate the probabilities of all likely pairs of haplotypes (i.e., diplotypes) for every individual in this study. This program was based on a Bayesian approach and the Partition Ligation algorithm. These algorithms have been claimed to be more accurate in reconstructing haplotypes than the Expectation-Maximum (EM) algorithm [44–46]. The haplotypes were reconstructed within two separate subgroups, that is, the genetically-inferred EAs (European ancestry proportion>0.5) and the genetically-inferred AAs (African ancestry proportion>0.5).

8. Multifactorial analysis of the relationship between medication efficacy and *DTNBP1* (Table 2) and multiple testing issues

A backward stepwise linear regression analysis or analysis of covariance (ANCOVA) was used to test associations between gene and efficacies. These powerful analytic approaches have been successfully applied in many previous studies (e.g., [34,47–49]). We modeled the analysis with the following equation: $Y = \beta_0 + \sum\beta_i X_i + \Sigma\beta_{ij} X_i X_j$, where Y was the reduction rate and β was regression coefficient. Four kinds of regression models were employed in the present study. X_i included age, sex, dosage, African ancestry proportions predicted by the program STRUCTURE, and diplotype probabilities (model 1), haplotype probabilities (model 2), genotypes (model 3), or alleles (model 4). Those analyses involving diplotypes, haplotypes, genotypes or alleles were called diplotypewise, haplotypewise, genotypewise and allelewise analyses respectively in the context. The ancestry proportions served as one covariate to control for population stratification and admixture effects. In models 1 and 2, only diplotypes or haplotypes with frequencies >0.03 were included; the interaction effects between haplotypes were also considered (diplotypes and haplotypes *per se* had incorporated the interaction information between SNPs). In models 3 and 4, genotypes and alleles were included; and the two-way interaction effects between any two alleles or between two genotypes from different SNPs were included as well. Among the four regression models, the diplotype trend regression model (model 1) was most powerful.

These analyses were separated by ethnicity; then they were also performed in the combined sample (i.e., EAs + AAs) to increase power. These analyses were performed separately for clozapine and haloperidol treatments, then some of them which showed suggestive results (p close to 0.050), were also performed in the combined sample (i.e., clozapine + haloperidol treatment) to increase power (data not shown). In this case we were considering predictors of treatment response *per se*, as opposed to response to a particular therapeutic agent.

Because, to multigenic phenotypes like the efficacies of antipsychotics, every contributory gene usually only contributes minor effects, and because our sample sizes, especially for the AA subjects, might be not large enough to provide sufficient power to detect such minor effects, any suggestive findings ($0.05<p<0.08$) were also presented in our study (see Table 2).

9. Unifactorial analysis on the relationship between medication efficacy and *DTNBP1* (Table 3)

Each marker has two alleles and two or three genotypes. Individuals were divided into two allelic groups or two or three genotypic groups. Reduction rates between these groups were compared by t-test (for allele analysis and two-genotype analysis) or ANOVA (for three-genotype analysis) to test the relationship between the effect of clozapine or haloperidol and each marker. These analyses were performed separately within genetic EAs and genetic AAs, then jointly in the combined subjects (i.e., EAs + AAs). These analyses decomposed and repeated the findings from the above multifactorial analyses, although they ignored the admixture effects. The mean reduction rates and their standard errors in different genotype and allele groups can be derived by these analyses (i.e., t-test and ANOVA).

RESULTS

1. Clozapine was more effective than haloperidol for refractory schizophrenia (Table 4) in this part of the sample, as it was for the entire sample [4]

The rates of response (reduction rate ≥ 0.2) to clozapine on T, P, N and G scores were higher than those to haloperidol in EAs, in AAs, and in the whole sample. The rates of response to both clozapine and haloperidol were in the following descending order: P>G>N. Both clozapine and haloperidol had better effects on AA subjects than EA subjects.

The reduction rates of T, P, N and G scores in clozapine treatment group were higher than those in haloperidol treatment group in EAs, in AAs, and in the whole sample. This difference between two treatment groups was most statistically significant in the combined sample, secondly significantly in the EAs, and thirdly in the AAs (which is probably related to the sample sizes). In the whole sample, this difference between treatment groups was most significant on T scores ($p=0.004$), secondly significant on P ($p=0.014$) and N scores ($p=0.013$), and suggestively significant on G scores ($p=0.084$). In the whole sample and in the EAs, haloperidol exacerbated the negative symptoms (reduction rates are −0.076 and −0.054, respectively); in all other subgroups, both clozapine and haloperidol alleviated the T, P, N and G symptoms.

Some of the above differences between clozapine and haloperidol were suggestive, but not statistically significant ($0.05<p<0.08$); most of the others were nominally significant ($p<0.05$); and many of them were significant after correction for multiple testing ($p<0.05$ for T score; $p<0.017$ (=0.05/3) for P, N and G scores; see Table 4).

2. The effects of clozapine and haloperidol were related to *DTNBP1*: results from multifactorial regression analysis (Table 2)

Diplotypewise analysis showed that the effect of clozapine on EA patients was nominally related to a rare diplotype ACCCTC/GTTGCC ($f=0.030$; T: $\beta=0.587$, $p=0.029$; G: $\beta=0.736$, $p=0.027$). When expanding the sample size by incorporating AA subjects and controlling for the population stratification and admixture effects, this relationship became highly significant for T scores ($\beta=0.476$, $p=0.009$) and more significant for P scores ($\beta=0.549$, $p=0.044$) and G scores ($\beta=0.513$, $p=0.024$). The effect of clozapine on P scores in EA patients was also nominally related to another diplotype ACCCTC/GCCGCC ($f=0.109$; $\beta=-0.556$, $p=0.011$). The effect of haloperidol was suggestively related to a rare diplotype ACCCTC/GCCGCC both in EA patients ($f=0.080$; T: $\beta=0.297$, $p=0.063$; G: $\beta=0.479$, $p=0.007$) and in combined sample (T: $\beta=0.267$, $p=0.073$; P: $\beta=0.454$, $p=0.072$; G: $\beta=0.399$, $p=0.015$).

Haplotypewise analysis showed consistent results with diplotypewise analysis. The effect of clozapine on EA patients was nominally related to the interaction of haplotypes ACCCTC × GTTGCC (T: β=2.364, *p*=0.029; G: β=2.990, *p*=0.025). When expanding the sample size by incorporating AA subjects and controlling for the population stratification and admixture effects, this relationship became highly significant for T scores (β=1.978, *p*=0.007) and more significant for P scores (β=2.303, *p*=0.037) and G scores (β=2.213, *p*=0.016). The effect of clozapine on P scores in EA patients was also nominally related to the interaction of haplotypes ACCCTC × GCCGCC (β=−2.227, *p*=0.012). The effect of haloperidol was nominally related to the interaction of haplotypes ACCCTC × GCCGCC both in EA patients (T: β=1.129, *p*=0.080; G: β=1.814, *p*=0.011) and in combined sample (T: β=1.094, *p*=0.067; G: β=1.569, *p*=0.017).

Allelewise analysis showed that the effect of clozapine on AA patients was nominally related to the allele T of rs742105 (*f*=0.417; T: β=0.183, *p*=0.028; N: β=0.228, *p*=0.049; G: β=0.304, *p*=0.030). Genotypewise analysis showed consistent but more significant results with allelewise analysis; that is, the effect of clozapine on AA patients was nominally related to the genotypes T/T+T/C of rs742105 (*f*=0.667; T: β=0.286, *p*=0.005; G: β=0.483, *p*=0.004).

Allelewise analysis showed that the effect of haloperidol on AA patients was suggestively related to the allele A of rs909706 (*f*=0.133; T: β=0.183, *p*=0.077; P: β=0.259, *p*=0.068); if expanding the sample size by combining clozapine- and haloperidol-treated subjects, this effect became more significant (T: β=0.157, p=0.013; P: β=0.202, *p*=0.023; data not shown in Table 2). Genotypewise analysis showed consistent results with allelewise analysis; that is, the effect of haloperidol on AA patients was nominally related to the genotype A/G of rs909706 (*f*=0.273; T: β=0.203, *p*=0.077; P: β=0.305, *p*=0.048); if expanding the sample size by combining clozapine- and haloperidol-treated subjects, this effect became more significant (T: β=0.195, p=0.010; P: β=0.293, *p*=0.005; data not shown in Table 2).

Some of the above associations were suggestive, but not statistically significant (0.05<p<0.08); most of the others were nominally significant (p<0.05). Some associations remained significant after Bonferroni correction for multiple testing, e.g., if corrected for four regression models (i.e., diplotype, haplotype, genotype, and allele), the association between diplotype ACCCTC/GTTGCC or haplotype ACCCTC × GTTGCC and T scores in combined EAs+AAs (p=0.009, 0.007, respectively) and the association between genotype rs742105^T/T+T/C and T or G scores in AAs (p=0.005, 0.004, respectively; see Table 2) remained significant. But if further conservatively corrected by the number of predictor variables in regression models and the number of populations, these associations became suggestive (i.e., p values close to α).

3. The effects of clozapine and haloperidol were related to *DTNBP1*: results from unifactorial analysis (Table 3)

Allelewise analysis showed that the AA subjects with the allele T of rs742105 had better response to clozapine than those with the allele C of rs742105 (T: p=0.019; N: p=0.049; G: p=0.020); this allelic difference in response becomed more significant (T: p=0.013; P: p=0.008; G: p=0.007) if incorporating the haloperidol treatment group. Genotypewise analysis showed that the AA subjects with the genotypes C/T+T/T of rs742105 had better response to clozapine than those with genotype C/C of rs742105 (T: p=0.005; G: p=0.003). AA subjects with the genotype A/G of rs909706 had suggestively better response to haloperidol than those with the genotype G/G (T: p=0.077; P: p=0.048); this genotypic difference in response becomed more significant (T: p=0.007; P: p=0.006; G: p=0.011) if incorporating the clozapine treatment group. Allelewise analysis showed that the AA subjects with allele A of rs909706 had suggestively better response to haloperidol than those

with the allele G (T: p=0.071; P: p=0.001; G: p=0.003); this allelic difference in response becomed much more significant (T: p=0.013; P: p=0.001; G: p=0.003) if incorporating the clozapine treatment group. In the EA subjects and the combined subjects (i.e., EAs + AAs), no significant allelic or genotypic difference in response was found.

Some of the above associations were suggestive, but not statistically significant ($0.05<p<0.08$); most of others were nominally significant ($p<0.05$). Many significant associations ($p<0.05$) became suggestive or non-significant after Bonferroni correction for multiple testing, i.e., corrected for the number of populations (i.e., EA and AA), the number of markers, the number of analysis models (i.e., genotype and allele), and the number of PANSS subscores (i.e., P, N, G) (see Table 3).

The minimal allele frequency differences between responders and non-responders that our sample sizes have 80% of power to statistically significantly detect, assuming that $\alpha=0.05$, $\beta=0.2$, were (1) 0.230–0.260 in EAs, (2) 0.350–0.425 in AAs, and (3) 0.200–0.220 in combined samples, respectively.

DISCUSSION

The present study suggested a possibility that *DTNBP1* gene variation was related to the efficacies of both the atypical antipsychotic clozapine, and the conventional antipsychotic haloperidol. Subjects with different *DTNBP1* diplotypes, haplotypes, genotypes, or alleles might have different responses to these antipsychotics.

The rates of response (symptom scale reduction rate ≥ 0.2) to clozapine and haloperidol showed that both of these agents (especially clozapine) were more efficacious on T, P, N, and G scores in AA subjects than EA subjects, which reflected the population-specificity of antipsychotic effects, consistent with many previous studies (reviewed above). These rates were within the range of those reported in numerous previous studies, but a little higher than that reported by Kane et al. [50], which might be (1) attributable to our more conservative calculation equation for these rates, that is, we deducted the baseline scores in the equation, and (2) because we assessed treatment efficacy for 3 months, longer than 6 weeks in the study by Kane et al. [50]. Clozapine was more effective than haloperidol on T, P, N and G scores of refractory schizophrenia in both EAs and AAs, consistent with numerous previous reports. This efficacy difference between clozapine and haloperidol was more significant in EAs than in AAs and was most significant in the combined sample. This efficacy difference between clozapine and haloperidol reflected that the subjects with refractory schizophrenia might respond to clozapine and haloperidol via neurobiological pathways that were not completely common. Thus, two treatment groups were separately analyzed in the present study. However, both clozapine and haloperidol were efficacious for schizophrenia, and the rates of response to both antipsychotics were in a same descending order: P>G>N, which suggested that clozapine and haloperidol might also exert some of their effects on schizophrenia via somewhat common pathways, and it was therefore reasonable that some gene effects could be additive if jointly analyzing the two treatment groups. Thus, the two treatment groups were also analyzed jointly, to increase the power for those common gene effects in the present study.

Diplotype ACCCTC/GTTGCC and the interaction of haplotypes ACCCTC × GTTGCC were nominally significantly associated with the effect of clozapine on T, P and G scores in EA patients and highly significantly associated with this effect in the combined sample (EAs + AAs). Diplotype ACCCTC/GCCGCC and the interaction of haplotypes ACCCTC × GCCGCC were nominally significantly associated with the effect of clozapine on P scores in EA patients, and suggestively associated with the effect of haloperidol on T, P and G

scores both in EA patients and in combined sample. These associations suggested that *DTNBP1* might harbor contributory sites affecting the efficacies of clozapine and haloperidol; the putative contributory sites might be in LD with these diplotypes and haplotypes. In AAs, allelewise and genotypewise regression analyses (Table 2), which controlled for population stratification and admixture effect and took the interaction between markers into account, fine-mapped the contributory locus for the effect of clozapine at rs742105 and for the effect of haloperidol at rs909706. The contributory allele T and genotypes T/T+T/C of rs742105 were components of the contributory diplotype ACCCTC/GTTGCC, and the contributory allele A and genotypes A/G of rs909706 were components of the contributory diplotype ACCCTC/GCCGCC. However, if conservatively corrected for multiple testing by Bonferroni correction, the above associations became suggestive. Unifactorial analysis (Table 3), which did not control for admixture effects, showed similar results as those from regression analysis. In EAs, we did not find any specific marker was associated with the efficacies, which probably is because we did not analyze on the multiple-way inter-marker interaction effects.

Allele A of rs909706 has been reported to be a component of a risk haplotype for schizophrenia in Chinese [51]. Allele T of rs742105 has been reported to be a risk factor for schizophrenia in Irish [19]. These two alleles were also contributory factors to the effects of clozapine and haloperidol on schizophrenia, respectively. Some contributory diplotypes or haplotypes to the effects of antipsychotics overlap with those reported to be related to risk for schizophrenia too. For example, the haplotype GTTGCC in the contributory diplotype ACCCTC/GTTGCC for clozapine effects in the present study overlaps with the risk haplotype GTT*** for schizophrenia in EAs in the study by Funke et al [52]; the haplotype GCCGCC in the contributory diplotype ACCCTC/GCCGCC for haloperidol effects in the present study overlaps with the risk haplotype GC*G** for schizophrenia in Irish in the study by Funke et al [52]. These findings support our hypothesis that the disease-risk gene influences a neural mechanism targeted by these antipsychotic medications.

Many of the gene effects on the efficacies were nominally highly statistically significant. For example, the effects of the diplotype ACCCTC/GTTGCC and the interaction effects of haplotypes ACCCTC × GTTGCC on the efficacy of clozapine in EAs + AAs (T: p=0.009, 0.007, respectively), the effect of the diplotype ACCCTC/GCCGCC on the efficacy of haloperidol on G scores in EAs (p=0.007), the effects of the genotype T/T+T/C of rs742105 on the efficacy of clozapine in AAs (T: p=0.005; G: p=0.003), the effect of the allele T of rs742105 on the efficacy of both antipsychotics in AAs (P: p=0.008; G: p=0.007), the effects of the genotype A/G of rs909706 on the efficacy of both antipsychotics in AAs (T: p=0.007; P: p=0.006), and the effect of the allele A of rs909706 on the efficacy of both antipsychotics in AAs (P: p=0.001; G: p=0.003). However, after Bonferroni correction for multiple testing, these effects became suggestive or non-significant. Some of other gene effects were nominally weak (p values close to 0.05), which we presume is because our sample sizes, especially for the AA subjects, have not provided sufficient power. For multigenic phenotypes like the efficacies of antipsychotics, every contributory gene usually only contributes minor effects to the phenotypes and therefore quite large sample size is required to detect such effects.

These findings suggested that *DTNBP1* might be an important moderator of antipsychotic pharmacological action. But because the markers in the present study are all intronic, they might not affect these actions directly. We speculate that the contributory markers may be in LD with a functional site which can influence the binding of dysbindin protein to antipsychotics; the contributory markers may be involved in the post-transcription alternative RNA splicing process from same pre-mRNA to distinct mature mRNAs, which can be translated to distinct dysbindin proteins with differing activities, and thus influence

the binding to antipsychotics; or these contributory intronic variants and their diplotypes and haplotypes *per se* might directly affect the expression of dysbindin protein in the brain and thus directly affect the binding ability to antipsychotics. At least five pathways by which dysbindin protein might be involved in schizophrenia have been proposed (reviewed in [20]). These pathways might also be those through which antipsychotics exert their effects on schizophrenia; further investigations are warranted.

Our subjects mostly came from the US VA Healthcare system and mainly were males, which is one limitation of the design. Also, there is disagreement regarding correction for multiple testing. Conservative Bonferroni correction might result in information loss, thus, we do not exclude the possibility of false negative interpretation under the current correction strategy. Additionally, only one candidate gene was investigated in the present study. We do not exclude the possibility that the positive association may only reflect a gene-phenotype association, but not a cause-result relationship; and further, certain other variants would clearly be of interest in this context, for example, variants in drug-metabolizing enzyme genes, such as the *CYP2D6* gene.

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Table 1

Demographic data (clozapine group vs. haloperidol group)

	Clozapine treatment	Haloperidol treatment
Sample size (n)	85	96
Baseline PANSS score	91.0±15.2	92.4±13.0
Baseline positive score	23.7±5.0	24.3±4.8
Baseline negative score	22.8±5.8	22.4±5.5
Baseline general score	44.4±8.3	45.7±6.9
Male %	98.7	97.8
"Genetic" EAs/AAs (n)	58/27	69/27
Mean admixture rates:		
In "genetic" EAs (%)	5.2	2.3
In "genetic" AAs (%)	5.9	2.3
Dosage range (mg/d)	40–900	5–30
Mean dosage (mg/d)	203±241	11±10

EA, European-American; AA, African-American. There is no significant difference in baseline scores, male%, and race proportions between two treatment groups.

Table 2

Multifactorial analysis on the relationship between *DTNBP1* and the effects of clozapine and haloperidol.

				European-Americans			African-Americans			Combined Americans		
Treatment	**Models**	**PANSS**	**Variates**	***f***	**β**	***p***	***f***	**β**	***p***	***f***	**β**	***p***
Clozapine	Diplotypewise	Total	ACCCTC/GTTGCC	0.030	0.587	**0.029**				0.044	0.476	**0.009**
		Positive	ACCCTC/GTTGCC							0.044	0.549	0.044
		Positive	ACCCTC/GCCGCC	0.109	−0.556	**0.011**						
		General	ACCCTC/GTTGCC	0.030	0.736	0.027				0.044	0.513	0.024
	Haplotypewise	Total	ACCCTC × GTTGCC		2.364	**0.029**					1.978	**0.007**
		Positive	ACCCTC × GTTGCC								2.303	0.037
		Positive	ACCCTC × GCCGCC		−2.227	**0.012**						
		General	ACCCTC × GTTGCC		2.990	0.025					2.213	**0.016**
	Genotypewise	Total	rs742105^T/T+T/C				0.667	0.286	**0.005**			
		General	rs742105^T/T+T/C				0.667	0.483	**0.004**			
	Allelewise	Total	rs742105^T				0.417	0.183	**0.028**			
		Negative	rs742105^T				0.417	0.228	0.049			
		General	rs742105^T				0.417	0.304	0.030			
Haldol	Diplotypewise	Total	ACCCTC/GCCGCC	0.080	0.297	0.063				0.065	0.267	0.073
		Positive	ACCCTC/GCCGCC							0.065	0.454	0.072
		General	ACCCTC/GCCGCC	0.080	0.479	**0.007**				0.065	0.399	**0.015**
	Haplotypewise	Total	ACCCTC × GCCGCC		1.129	0.080					1.094	0.067
		Positive	ACCCTC × GCCGCC								1.798	0.076
		General	ACCCTC × GCCGCC		1.814	**0.011**					1.569	**0.017**
	Genotypewise	Total	rs909706^A/G				0.273	0.203	0.077			
		Positive	rs909706^A/G				0.273	0.305	0.048			
	Allelewise	Total	rs909706^A				0.133	0.183	0.077			
		Positive	rs909706^A				0.133	0.259	0.068			

f, frequency; β, regression coefficients; p, p-values; "×", interaction between. Corrected α was set at 0.05 for PANSS Total score testing and 0.017 for PANSS subscore (i.e., Positive, Negative, and General scores) testing. Bold denotes p<α.

Table 3

Unifactorial analysis on the relationship between *DTNBP1* and the effects of clozapine and haloperidol.

			African-Americans		
Treatment		**Alleles or genotypes**	**Reduction**	***f***	**p**
Clozapine	Total	P1333rs742105^T	0.322±0.052	0.417	
		^C	0.139±0.152	0.583	**0.019**
	Negative	P1333rs742105^T	0.205±0.209	0.417	
		^C	−0.023±0.146	0.583	0.049
	General	P1333rs742105^T	0.411±0.100	0.417	
		^C	0.107±0.253	0.583	0.020
	Total	P1333rs742105^C/T+T/T	0.311±0.053	0.667	
		^C/C	0.025±0.076	0.333	**0.005**
	General	P1333rs742105^C/T+T/T	0.395±0.108	0.667	
		^C/C	−0.088±0.012	0.333	**0.003**
Haldol	Total	P1583rs909706^G	0.110±0.241	0.870	
		^A	0.283±0.181	0.130	0.071
	Positive	P1583rs909706^G	0.113±0.330	0.870	
		^A	0.372±0.170	0.130	0.068
	Total	P1583rs909706^G/G	0.080±0.244	0.739	
		^A/G	0.283±0.181	0.261	0.077
	Positive	P1583rs909706^G/G	0.067±0.336	0.739	
		^A/G	0.372±0.170	0.261	0.048
Cloz+Hal	Total	P1333rs742105^T	0.299±0.110	0.278	
		^C	0.144±0.241	0.722	**0.013**
	Positive	P1333rs742105^T	0.290±0.140	0.278	
		^C	0.071±0.331	0.722	**0.008**
	General	P1333rs742105^T	0.345±0.114	0.278	
		^C	0.156±0.284	0.722	**0.007**
	Total	P1583rs909706^G	0.153±0.239	0.793	
		^A	0.311±0.164	0.207	**0.013**
	Positive	P1583rs909706^G	0.177±0.346	0.793	
		^A	0.379±0.166	0.207	**0.001**

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			African-Americans		
Treatment		**Alleles or genotypes**	**Reduction**	***f***	**p**
	General	P1583rs909706^G	0.154±0.259	0.793	
		^A	0.322±0.169	0.207	**0.003**
	Total	P1583rs909706^G/G	0.108±0.241	0.610	
		^A/G	0.307±0.169	0.390	**0.007**
	Positive	P1583rs909706^G/G	0.110±0.362	0.610	
		^A/G	0.390±0.165	0.390	**0.006**
	General	P1583rs909706^G/G	0.109±0.269	0.610	
		^A/G	0.312±0.169	0.390	**0.011**

f, frequency; p, p-value; Cloz+Hal, Clozapine and Haloperidol. Corrected α was set at 0.05 for PANSS Total score testing and 0.017 for PANSS subscore (i.e., Positive, Negative, and General scores) testing. Bold denotes p<α.

Table 4

Significant difference in the effects on schizophrenia between clozapine and haloperidol

		European-Americans (n=127).				African-Americans (n=54).				Combined sample (n=181).			
PANSS	**Treatment**	**Size**	**Responser**	**Reduction**	**p**	**Size**	**Responser**	**Reduction**	**p**	**Size**	**Responser**	**Reduction**	**p**
Total	Clozapine	58	0.397	0.171 ± 0.221		27	0.593	0.225 ± 0.206		85	0.459	0.188 ± 0.217	
	Haldal	69	0.333	0.080 ± 0.228	**0.025**	27	0.333	0.115 ± 0.235	0.073	96	0.333	0.090 ± 0.230	**0.004**
Positive	Clozapine	58	0.586	0.245 ± 0.297		27	0.741	0.307 ± 0.297		85	0.635	0.265 ± 0.296	
	Haldal	69	0.420	0.142 ± 0.365	0.089	27	0.444	0.148 ± 0.315	0.062	96	0.427	0.144 ± 0.350	**0.014**
Negative	Clozapine	58	0.345	0.092 ± 0.303		27	0.481	0.129 ± 0.293		85	0.388	0.104 ± 0.298	
	Haldal	69	0.232	−0.076 ± 0.544	0.039	27	0.333	0.003 ± 0.472	0.244	96	0.260	−0.054 ± 0.523	**0.013**
General	Clozapine	58	0.397	0.137 ± 0.328		27	0.593	0.213 ± 0.253		85	0.459	0.161 ± 0.307	
	Haldal	69	0.362	0.071 ± 0.291	0.234	27	0.370	0.120 ± 0.259	0.189	96	0.365	0.085 ± 0.282	0.084

Combined samples = European-Americans + African-Americans; Responser, reduction rate ≥ 0.2; R, reduction rate of PANSS score; p, p-value for reduction rate comparison between clozapine and haloperidol Corrected α was set at 0.05 for PANSS Total score testing and 0.017 for PANSS subscore (i.e., Positive, Negative, and General scores) testing. Bold denotes $p<\alpha$.