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Genomewide Pharmacogenomic Analysis of Response to Treatment with Antipsychotics

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Abstract

Schizophrenia is an often devastating neuropsychiatric illness. Understanding the genetic variation affecting response to antipsychotics is important to develop novel diagnostic tests to match individual schizophrenic patients to the most effective and safe medication. Here we use a genomewide approach to detect genetic variation underlying individual differences in response to treatment with the antipsychotics olanzapine, quetiapine, risperidone, ziprasidone and perphenazine. Our sample consisted of 738 subjects with DSM-IV schizophrenia who took part in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). Subjects were genotyped using the Affymetrix 500K genotyping platform plus a custom 164K chip to improve genomewide coverage. Treatment outcome was measured using the Positive and Negative Syndrome Scale (PANSS). Our criterion for genomewide significance was a pre-specified threshold that ensures, on average, only 10% of the significant findings are false discoveries. The top statistical result reached significance at our pre-specified threshold and involved a SNP in an intergenic region on

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chromosome 4p15. In addition, SNPs in *ANKS1B* and *CNTNAP5* that mediated the effects of olanzapine and risperidone on Negative symptoms were very close to our threshold for declaring significance. The most significant SNP in *CNTNAP5* is nonsynonymous, giving rise to an amino acid substitution. In addition to highlighting our top results, we provide all *p*-values for download as a resource for investigators with the requisite samples to carry out replication. This study demonstrates the potential of GWAS to discover novel genes that mediate effects of antipsychotics, which eventually could help to tailor drug treatment to schizophrenic patients.

Keywords

genomewide association; antipsychotic; pharmacogenetics; schizophrenia; personalized medicine; single nucleotide polymorphism

Introduction

Schizophrenia is a serious and often devastating neuropsychiatric illness, with a median lifetime morbid risk of 0.7–0.8%1. It is ranked ninth in global burden of illness2 and the projected lifespan for individuals with schizophrenia is some 15 years less than the general population3. Clearly, efforts to better understand and treat this disorder are of paramount public health importance4.

Etiologically, schizophrenia is best viewed as a complex trait influenced by multiple small genetic and environmental risks. A substantial heritable component is now accepted and several specific genes are considered to be likely risk factors. However, from a biological perspective, the etiology of schizophrenia remains poorly defined5. One eventual goal of improved biological understanding is to facilitate the development of better therapeutic compounds6. However, the development of new drugs is extremely expensive and takes several years7. Arguably, a more immediate role for genetics in the treatment of schizophrenia is tailoring the prescription of existing drugs to individual patients based upon genotype8.

The impetus driving the search for such “individualized” antipsychotic therapy emerges from several observations. First, only a proportion of patients typically respond to any given antipsychotic drug9. Second, it may take several weeks before a clinician can declare a treatment ineffective and this delay leaves the patient vulnerable to continuing social dysfunction and suicide10. Third, the administration of ineffective drugs leaves the patient at risk for adverse events or side effects. Finally, research into other non-genetic predictors of antipsychotic response, such as clinical or demographic variables, has met with limited success8.

The clinical benefits of a genetic test to identify the most effective antipsychotic treatment for each patient at time of first presentation would be considerable11. This observation has led to a proliferation of schizophrenia pharmacogenetics research in the last decade12. To date, studies have tended to focus on candidate genes, selected for encoding of drug targets (pharmacodynamic candidates) or for involvement in the metabolism of the drug itself (pharmacokinetic candidates). Pharmacodynamic candidates in schizophrenia include

dopamine or serotonin receptors and several studies have shown positive associations between, for example, dopamine receptors D2 (*DRD2*) and D3 (*DRD3*) and antipsychotic response (see Arranz and de Leon12 for a review). Pharmacokinetic candidates, particularly the cytochrome P450 genes, are well known to harbor genetic variation affecting the metabolism of antipsychotics13. The importance of these variants, with respect to dosing and other clinical considerations, has led to the introduction of diagnostic microarrays that are already on the market14.

Despite these advances, the pharmacogenetics of schizophrenia is still in its infancy. A major limitation of previous studies is that the selection of candidate genes is restricted to current knowledge about the mechanisms of drug action. For example, a recent study by Need et al.15 genotyped almost 3,000 SNP markers in several candidate genes related to antipsychotic response. However, no significant results were found in that study for improvement in schizophrenia symptoms, after correcting for multiple testing. More exploratory methods that systematically screen the whole genome for association with drug response likely represent a superior strategy for discovering relevant genetic variation. In the past two years, such genomewide association studies (GWAS) have become technically and economically feasible. It is now clear that GWAS can be a successful strategy, as there have been multiple successes with the identification of highly compelling candidate genes for age-related macular degeneration16, body mass index17, inflammatory bowel disease18 and type 2 diabetes mellitus19–21.

In this study, we use the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)22,23 to detect genetic variation underlying symptom severity and individual differences in response to treatment with olanzapine, quetiapine, risperidone, ziprasidone and perphenazine. The sample consisted of 738 CATIE subjects with DSM-IV schizophrenia diagnoses who were genotyped using the Affymetrix 500K genotyping platform plus a custom 164K chip to improve genome-wide coverage24. Treatment outcome was measured using the Positive and Negative Syndrome Scale (PANSS)25.

Methods

Subjects

A detailed description of the CATIE study design can be found elsewhere22,23. Briefly, CATIE is a multiphase randomized controlled trial of antipsychotic medications where patients with DSM-IV schizophrenia were followed for up to 18 months. Preliminary diagnoses of schizophrenia were established by the referring psychiatrists and independently re-evaluated by CATIE personnel using the SCID (Structured Clinical Interview for DSM-IV)26. The main exclusion criteria were a first episode of illness (because of diagnostic uncertainty) or being treatment-refractory (as alternative therapeutic approaches are indicated). To maximize representativeness, subjects were ascertained from clinical settings across the US (e.g., public mental health, academic, Veterans' Affairs, and managed care centers).

CATIE assessments began with a baseline assessment followed by Phase 1, a double-blinded randomized clinical trial comparing treatment with the second generation

antipsychotics olanzapine, quetiapine, risperidone, or ziprasidone versus perphenazine (a midpotency first generation antipsychotic). If the initially assigned medication was discontinued, typically because of a lack of efficacy or adverse effects, the subject and clinician could choose between one of the following Phase 2 trials: (1) randomization to open-label clozapine or a double-blinded second generation drug that was available but not assigned in Phase 1; or (2) double-blinded randomization to ziprasidone or another second generation drug that was available but not assigned in phase 1. Phase 3 was for patients who discontinued the treatment assigned in phase 2 and involved an open-label treatment chosen collaboratively by the clinician and patient. The followup phase was for patients who were no longer willing to continue taking study medication or who had discontinued their phase 3 medication before 18 months from the time of initial randomization had elapsed. Followup phase participants were not provided with study medication but were followed naturalistically on their treatment of choice.

Genotyping

Following provision of informed consent, a peripheral venous blood sample was obtained and sent to the Rutgers University Cell and DNA Repository (RUCDR). DNA is currently available for 765 CATIE subjects. All these subjects were genotyped by Perlegen Sciences (Mountain View, CA, USA) using the Affymetrix 500K genotyping platform plus a custom 164K chip to improve genome-wide coverage24. The genotype and clinical data are available to the scientific community from the controlled-access repository of the National Institutes of Mental Health (NIMH: www.nimhgenetics.org).

Details of the quality control (QC) analyses can be found in Sullivan et al.24 who performed a GWAS with case-control status as the outcome variable. In short, genotype calls were generated with a proprietary Perlegen algorithm27 applied to the .cel files. There were 500,568 SNPs on the Affymetrix 500K chip and 164,871 on the Perlegen custom chip (665,439 SNPs in total). A variety of QC checks such as genotyping a subset of the samples twice and comparing genotype calls using alternative software confirmed the general quality of the samples and genotypes. However, an extensive set of analyses were performed to individual samples and genotypes that did not meet high QC standards. First, a more stringent quality score cutoff (≥7) than that applied by Perlegen was used. Second, an identity-by-state matrix for all autosomal genotypes was generated using PLINK28 for all pairwise combinations of subjects. In four instances, CATIE subjects were found to be cryptic duplicates and one member of each pair was removed. Subjects with more than 10% missing SNPs were also deleted. In addition, we deleted SNPs that had more than 10% missing genotypes and SNPs with minor allele frequencies smaller than 0.01. SNPs were not excluded based solely on deviations from Hardy-Weinberg Equilibrium29, given the ancestries of the subjects and as there are informative reasons for departures from HWE30. After application of these filters 738 subjects remained with 492,900 SNPs available for analysis.

Estimating treatment effect

In this article we focus on the Positive and Negative Syndrome Scale (PANSS)25, which is one of the main outcome measures in CATIE. The 30 items of the PANSS measure a broad

range of the symptoms typical for schizophrenia. To unravel the structure of the PANSS items, a considerable number of factor analyses have been performed. Although variation exists, partly because of methodological differences31, a five factor structure is generally preferred32. Because of their very large sample size (N = 5,769), we used the five scales derived by Van der Gaag et al.33 (using the bold items in their Table 3) that are labeled Positive, Negative, Disorganization, Excitement, and Emotional distress, along with the Total symptom score which is the sum of the 30 PANSS items.

The mean number of assessments for each subject was 7.5. Clearly, a more traditional approach that would define treatment using only 2 observations would not take advantage of all available information. In a previous article34, we described a systematic method using mixed effects modeling to estimate treatment effects for a given outcome. This condenses all information collected during the CATIE trial in an optimal, empirical fashion. The method consisted of first studying the best way to model drug effects, then screening many possible covariates to select those that improve the precision of the treatment effect estimates, and finally generating individual drug effect estimates based on the best fitting model. A model assuming it takes on average about 30 days for a treatment to exert an effect that will then remain about the same for the rest of the trial showed the best fit to the data34. Treatment effects were estimated for the five main drugs in the trial: olanzapine, quetiapine, risperidone, ziprasidone and perphenazine. For each drug, we estimated treatment effects for each of the five PANSS subscales outlined above, in addition to PANSS Total. This is because the antipsychotics in the study show considerable variation in efficacy, both in terms of total symptom improvement and symptom improvement for specific psychopathology35,36.

The distributions of the 30 outcome measures, i.e. 5 drugs × 6 PANSS scales, were checked for non-normality. Relative to the normal distribution, ten of the outcome measures (five of them involved Excitement) showed skewness and/or kurtosis indices in excess of −1 or +1. Visual inspection of the distribution revealed that in all instances this non-normality was caused by outliers. Removing on average 2.2 outliers resulted in approximately normal distributions (skewness and kurtosis indices between −1 and +1 and mean skewness 0.22 and mean kurtosis 0.44).

Controlling for sample stratification

Given the ancestral diversity of the CATIE sample, false positive findings due to genetic subgroups are a realistic threat. Sullivan et al.24 performed an extensive evaluation of multiple statistical methods to avoid such false positive findings including: self-reported race, genomic control37, structured association38, principal components39, multi-dimensional scaling28 and partial least squares relating phenotype to ancestry-informative markers40. They concluded that the principal components controlled this risk best, capturing both subtle and extensive variation due to both genomic and experimental features. This approach uses the genotyping matrix to infer continuous axes of genetic variation (principal components) which then serve as covariates. All autosomal GWAS SNPs were used as input to EigenSoft39,41 and default parameters were used except that the outlier removal option was turned off in order to generate estimates for all subjects.

Analyses

The SNPs passing QC were tested in PLINK28 for association with each of the 30 outcome measures. The Wald test was used to test for additive SNP effects after the seven extracted EigenSoft dimensions were regressed out to control for genetic substructure. To control the risk of false discoveries, we calculated for each *p*-value a so-called *q*-value42,43 (see supplementary material). A *q*-value is an estimate of the proportion of false discoveries among all significant markers (i.e. *q*-values are false discovery rates or FDRs) when the corresponding *p*-value is used as the threshold for declaring significance. As argued previously44, we prefer this FDR-based approach because it a) represents a good balance between the competing goals of finding true effects versus controlling false discoveries, b) provides comparable standards across studies because it is much less affected by the number of (sets of) tests, which is an arbitrary factor, c) is relatively robust to having correlated tests42,45–52 and d) rather than an all-or-nothing conclusion, gives a more subtle picture of the possible role of the tested markers.

For the most promising SNPs we performed a variety of additional analyses to examine the robustness of the signal. First, we tested the SNP in the subjects who self-identified as European Americans (EA) only. We considered the proportion of explained variance rather than the *p*-value, which assuming the effect is real would be lower because EA comprise only 67% of the total sample. A large drop in explained variance could point to ethnic differences or stratification effects not accounted for by our principal components. Next, for each SNP we looked at the test results of all six PANSS scales and counted the number of *p*-values that were smaller than 0.05. Although it is possible that SNP effects are PANSS scale specific, observing associations with multiple scales excludes the possibility of significant effects due to scale specific outliers and is informative from a clinical perspective. We also performed haplotype analyses for significant SNPs that were in close proximity, to examine if they represented the same signal. In addition, for each SNP we performed "proxy" analyses that considered other SNPs in that region. Such analyses may provide a technical validation of the single SNP result (e.g. all SNPs in substantial LD, defined here as $r^2 > 0.8$, should also show evidence for association) or point to a haplotype that is even more associated. Finally, we explored whether the SNP was in a copy number variant (CNV) region using calls generated specifically for this sample.

Examination of common SNP effects across drugs

Antipsychotic drugs may act on common pathways and therefore a gene or SNP may mediate the effect of multiple drugs, particularly if they are pharmacologically similar. However, it is important to point out that in CATIE patients were switched from a drug if clinical response was inadequate. As a result treatment effects are negatively correlated across drugs34. This suggests that the likelihood of observing common SNPs effects for multiple drugs in CATIE is somewhat diminished, if we aggregate all drug treatments over the course of the trial into a single outcome. To work around this limitation, we performed GWAS on response to the *first* drug prescribed to each patient only (i.e. CATIE Phase I), thereby avoiding potential difficulties arising from drug switching. Except for this difference, the six outcome measures (improvement in the five PANSS subscales and

PANSS Total for all of the 5 main CATIE drugs combined) were generated and the GWAS carried out using identical methods to those described above.

Results

Descriptive statistics for the genotyped sample can be found in Table 1 in Sullivan et al.24. In summary, the cases had been ill for a mean of 14 years and the mean PANSS scores are consistent with a moderately ill sample. CATIE subjects who provided DNA samples had lower symptom severity (PANSS total 74 vs. 77), lesser current drug/alcohol abuse/dependence (29% vs. 36%) and less likely to describe themselves as African-American (29% vs. 40%) than the total sample.

Quantile-Quantile (QQ) plots and *p*-values for each outcome variable are available to download at www.vipbg.vcu.edu/~edwin. Table 1 shows a summary of the number of *q*-values below various thresholds. One SNP was significant at our pre-specified threshold for declaring significance in genetic studies of $q < 0.144$ and several other SNPs were close to that threshold. Our analysis of common SNP effects across drugs did not yield any *q*-values less than 0.6 (see Table S1 in the Supplementary Material).

Table 2 shows the specific SNPs with *q*-values smaller than 0.5. The top finding was with rs17390445 on chromosome 4p15, which mediated the effect of ziprasidone on Positive symptoms. The effect was robust when tested in EA only and the SNP was significantly associated with 3 additional PANSS scales when tested at the 0.05 level. A neighboring SNP, rs11722719, that was 1.6kb from our top finding, had a q value < 0.15. Both of these SNPs tag a region that is gene poor. The closest validated gene is >1Mb distant, while the closest predicted gene (LOC727819) is approximately 200kb telomeric to the region defined by the SNPs.

SNP rs7968606 in the *ANKS1B* gene showed a *q*-value very close to 0.1 for mediating the effect of olanzapine on Negative symptoms. In addition, the signal was robust when tested in the EA subsample and this SNP was significantly associated with olanzapine response on all six PANSS scales. Unfortunately no other SNPs were genotyped in the region around rs7968606 that could serve as a technical replicate (closest SNPs were over 70–80kb away with $r^2 < 0.07$). The finding for SNP rs17727261 in *CNTNAP5*, mediating the effects of risperidone on Negative symptoms, was also robust in the EA subsample and affected almost all PANSS scales. Although LD was very modest ($r^2 = 0.12$), rs6706476, which is located 17.1kb away from rs17727261, also provided evidence for association ($p = 0.0042$). The SNP rs17815774 in *TRPM1* mediated the effects of risperidone on Negative symptoms and PANSS Total. Although several SNPs were genotyped in the area around rs17815774, consistent with the HapMap data none of these SNPs were in LD with it (e.g. maximum r^2 of the 20 closest SNPs, together spanning 40kb, was 0.02). Thus, there were no technical replicates.

According to the calls specifically generated for the CATIE data, the only SNP in Table 2 that was in a copy number variant (CNV) was rs10888501, located on chromosome 1, that mediated the effect of olanzapine on Negative symptoms. Less than half of a percent

(0.48%) of the sample showed a deletion here. This very low frequency makes it unlikely that the CNV caused the reported association signal in Table 2.

Table 3 shows the results from candidate gene analyses. Using the PLINK retrieval interface, SNPs were selected using the TAMAL database53, based chiefly on UCSC genome browser files54, HapMap55, and dbSNP56. A liberal definition of the gene boundary is used (+/− approximately 200kb), to avoid excluding SNPs in the region that may be in LD with others within the gene itself. Caution is required when interpreting the *q*-values in these analyses, because far fewer tests are performed and FDR-based *q* values are known to be too liberal in these scenarios57.

To select candidate genes for drug effects, we selected all genes that had previously shown positive associations with response to any antipsychotic drug, as reviewed by Arranz and de Leon12, plus any further genes with reported positive associations since publication of that article58–63. We also included all assayed SNPs that corresponded to genes involved in the major and secondary metabolic pathways of antipsychotic drugs12. 39 genes were selected, of which 33 had SNPs genotyped, to give 2032 SNPs total (see supplementary material). The top result was for rs12860002 that is 120kb outside *HTR2A* and had a *q*-value smaller than 0.1 when testing the effects of quetiapine on Negative symptoms. In addition, results held in the EA subsample and seemed to affect Total symptoms ($p = 0.00098$) and to a lesser extent Positive symptoms ($p = 0.01435$). Unfortunately, no other SNPs were in high LD with rs12860002 so that we did not have a technical replicate.

Several SNPs in *FMO5* were associated with quetiapine response on the Emotional distress scale. The top SNP, rs12122534, was in high LD ($r^2 = 0.85$) with rs12122453 that showed the next best results, and in relatively low LD with other SNPs (average $r^2 = 0.15$) that were less significant. A common (54%) haplotype (CCCCCTC) probably explains the signal observed for *FMO5*. This haplotype spans over 413 kb and, although the top SNP is not in the gene, includes the gene. The haplotype analyses did not really improve the signal suggesting that only rs12122534 may be needed to capture the association.

Discussion

Understanding the biological factors affecting response to antipsychotics may be crucial to develop diagnostic tests to match individual schizophrenic patients to the most safe and effective medication. In this study we performed a GWAS in 738 subjects from the CATIE study to detect genetic variation underlying individual differences in response to treatment with antipsychotics.

The top statistical GWAS result overall was rs17390445 on chromosome 4, reaching significance according to our pre-specified threshold allowing for 10% false discoveries. The finding involved Positive symptoms and ziprasidone. An adjacent SNP (rs11722719) also reached significance with the same phenotype, making it unlikely that the finding was caused by a genotyping error. However, the closest annotated gene is over 1Mb from the region encompassed by these SNPs. It is therefore difficult to speculate on how this locus may be mediating the effects of ziprasidone, even in light of the robust statistical association

with Positive symptoms and significant findings with 3 other PANSS scales. Nevertheless, the lack of genes does not preclude the possibility of a true finding. There is a precedent for such intergenic associations to replicate in independent samples, such as found with a region on chromosome 9 in Type II diabetes mellitus64. It is conceivable that such findings are indicative of long range regulatory effects mediated by these genomic regions, or other mechanisms that are not yet fully understood.

The analysis identified SNPs located in 3 specific genes: *ANKS1B*, *CNTNAP5* and *TRPM1*. The Ankyrin Repeat and Sterile Alpha Motif Domain-Containing Protein 1B (*ANKS1B*, NCBI gene id: 56899) is a tyrosine kinase signal transduction gene, primarily expressed in the brain. It contains 2 SAM domains and one PTB domain65. SAM domains are found in most Eph-family tyrosine kinase receptors, which orchestrate axonal guidance and bundling66. PTB domains have proven roles in regulating cell proliferation and differentiation, and those in *ANKS1B* are related to the Numb family of *Drosophila* neuronal cell fate-determining factors65. The Contactin-Associated Protein-Like 5 gene (*CNTNAP5*, NCBI gene id: 129684) belongs to a subgroup of the neurexin family of multidomain transmembrane proteins that are involved in cell adhesion and intercellular communication in the central nervous system (CNS)67. The SNP at *CNTNAP5* showing strongest association, rs17727261, gives rise to an amino acid substitution (Ser-452-Leu). Transient Receptor Potential Cation Channel, subfamily M, member 1 (*TRPM1*, NCBI gene id: 4308) is expressed in brain (UniGene). It is a member of the Transient Receptor Potential superfamily of Ca^{2+}-permeable cation channels68. As with *CNTNAP5*, the strongest association with *TRPM1* is with a nonsynonymous SNP, rs17815774 (Met-605-Val). None of these genes have been investigated in relation to antipsychotics before. Nevertheless, all 3 are expressed in the brain and are implicitly associated with the CNS. The top SNPs in *CNTNAP5* and *TRPM1* are both nonsynonymous, strongly suggesting functional relevance.

Our results employing pharmacogenetics candidate genes yieled several interesting findings. The most significant association was with rs12860002 at *HTR2A*, which mediated the effects of quetiapine on Negative symptoms. However, due to our liberal definition of SNP selection, this marker was some 120kb from the actual gene. HapMap data indicated the marker to be in a block of 18kb, which therefore does not include the *HTR2A* gene itself. Nevertheless, several previous association studies have shown positive findings with *HTR2A* and antipsychotics12. Furthermore, *in vitro* functional work by Davies et al.69 has demonstrated how nonsynonymous nucleotide substitutions in the coding sequence of the *HTR2A* gene can alter the receptor's binding affinity and the cellular functional effects of quetiapine, the specific drug with which we found our association. *HTR2A* would therefore appear to be an increasingly firm candidate antipsychotic pharmacogene.

Several markers close to the *FMO5* locus showed association for mediating the effects of quetiapine on Emotional distress symptoms. However, the FMO5 enzyme is not generally considered to be a major metabolizer of quetiapine70. Although quetiapine appears to undergo a complex metabolic fate, *in vitro* studies suggest that this is largely via CYP3A4 (see Mauri et al.71). Nevertheless, to our knowledge, the metabolism of quetiapine by FMO5 has never been specifically tested. In the absence of definitive functional data on the

relationship between quetiapine and FMO5, our result immediately suggests a direction for future study.

Our genotyping methods were chosen to optimize genomewide coverage, and there are some notable gaps whereby specific candidate genes were not assayed (e.g. some of the Cytochrome P450 genes, see Supplementary Material). Therefore, it is possible that some relevant genetic variation in candidate genes was missed. In a recent study, Need et al.15 genotyped 2,769 SNP in 118 candidate genes in CATIE versus our subset of 2032 SNPs in 32 genes. A direct comparison of the results is hampered by the many differences that exist between our candidate genes analyses and those by Need et al. For instance, they genotyped different SNPs even for the small subset of overlapping candidate genes, b) they used a very different approach to define treatment effects that essentially calculated post- minus pre-treatment scores using Phase 1 data only, and c) they used a different method to control for stratification that is based on many fewer markers compared to the present study. Nevertheless, it was interesting that both efforts implicated markers close to or within *HTR2A*, although it should be noted their results with the PANSS did not withstand correction for multiple testing.

Our GWAS analyses focused on discovering SNPs predicting to what specific antipsychotic a patient responds. That is, because all patients who respond to a specific antipsychotic will have a high treatment score and all patients who do not respond will get a low high treatment score for that specific drug, the SNP discriminates between the two response groups. Our analyses are therefore aimed directly at finding the markers needed for the goal, outlined in the Introduction, of individualizing antipsychotic therapy.

Antipsychotics may partly improve disease symptoms through common pathways. For several reasons, finding genetic variants that are associated with treatment response through common pathways is of scientific interest, but it was not the primary goal of this paper. First, the fact that a considerable proportion of schizophrenic patients do not respond to a specific antipsychotic and are switched to another drug due to lack of efficacy suggests that common antipsychotic pathways may not be that critical for treatment response. That is, if they would be critical and universal, there would be no need to tailor antipsychotic therapy to individual patients. The more important clinical challenge therefore seems to predict who will respond to what drug, and markers predicting general antipsychotic response are not helpful in this respect. Second, the CATIE design seems more suitable for finding variants predicting the response to a specific drug than finding variants predicting general antipsychotic response. For example, opposite to what is expected assuming common mechanisms of antipsychotics, drug effects are negatively correlated in CATIE34. This negative correlation probably occurs because in CATIE patients are switched to another drug when the first drug is not efficacious. Hence it may very well be that patients who respond to one drug also respond to another drug, but the resulting positive correlation may not be observed in CATIE because these patients will remain on the efficacious drug. The practical implication is that simply combining treatment effects in CATIE across drugs may not result in an accurate measure of general drug effect.

Although we are currently working on more sophisticated approaches, we have performed GWAS analyses using treatment effects estimated from Phase I data only. This will probably increase the power to find SNPs affecting common drug pathways, because data from patients that are switched to other drugs (i.e. do not benefit from the drug effect on a possible common pathway) are less likely to dilute any signals. A limitation of this Phase I general drug effect measure is that we assume that all CATIE drugs share the same common pathways. A less stringent assumption would be that a subset of CATIE drugs share similar pathways. To explore this possibility, we examined whether top findings for one drug were also significant for the other drugs.

Results Table S1, shown in the Supplementary Material, provided little evidence for genetic variants affecting the response to multiple drugs. This could mean that common drug pathways are not that critical for drug response or point to limitations of the methods we used. Drugs could, for example, not be effective for certain subgroups of patients where the disorder involves biological systems different from the ones targeted by the drug72. This is particularly plausible for schizophrenia, which is considered to be a highly heterogeneous disorder. Further studies and more sophisticated statistical tools may shed further light on these issues73.

In terms of their translational potential to personalize drug treatment, genetic markers have a number of advantages such as being cost-efficient, prognostic (i.e. can be used prior to starting drug treatment), and can be measured in biomaterial (blood, saliva) that is easy to collect. On the other hand, these markers may explain only a modest proportion of the variance meaning that the majority of the relevant genetic variation will need to be identified to obtain an accurate prediction. In this respect it was encouraging that our top SNPs in the GWAS explained as much as 10–15% of the variance in drug response. However, assuming our top findings are true, these effect sizes are likely to be overestimates. That is, due to sampling error, effect sizes in the initial study are often larger than in subsequent replications74,75.

Our findings require replication and functional validation. To facilitate that process we provide all *p*-values for download (at www.vipbg.vcu.edu/~edwin) as a resource for investigators with the requisite samples to carry out replication. However, the present study demonstrates the potential of GWAS to discover novel genes that potentially mediate effects of antipsychotics, which could eventually help to tailor treatment for individual schizophrenic patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Number of GWAS *q*-values below various thresholds

		***q*-value threshold**				
By PANSS scale		0.1	0.25	0.5	0.75	0.95
Total symptoms		0	0	0	1	1
Positive		1	2	2	9	30
Negative		0	3	6	9	47
Disorganization		0	0	0	10	13
Excitement		0	0	3	3	48
Emotional distress		0	0	0	0	6
	Sum	1	5	11	32	145
By effect						
Olanzapine		0	1	5	8	8
Perphenazine		0	0	0	0	14
Quetiapine		0	0	0	3	37
Risperidone		0	2	4	10	65
Ziprasidone		1	2	2	11	21
	Sum	1	5	11	32	145

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Table 2

GWAS results with *q*-values smaller than 0.5

Outcome	Locus		Test								Robustness		
		Gene	Chr	bp	MAF	N	Eff	r^2	*p* value	*q* value	r^2_a	#s	#d
Ziprasidone –Positive	rs17390445	no	4	34716421	0.441	160	−	0.165	9.82E-08	0.049	0.182	4	1
Ziprasidone – Positive	rs11722719	no	4	34718016	0.355	161	−	0.147	5.38E-07	0.133	0.195	3	1
Risperidone – Negative	rs888219	no	9	126008577	0.220	240	+	0.107	2.25E-07	0.111	0.074	5	1
Olanzapine – Negative	rs7968606	*ANKS1B*	12	98319310	0.130	245	+	0.102	3.20E-07	0.158	0.107	6	1
Risperidone – Negative	rs17727261	*CNTNAP5*	2	124998140	0.039	243	+	0.099	5.41E-07	0.134	0.079	5	2
Olanzapine – Negative	rs10888501	no	1	149351027	0.469	245	−	0.091	1.41E-06	0.349	0.101	4	1
Olanzapine – Excitement	rs1040994	no	6	12305199	0.155	242	−	0.091	1.84E-06	0.491	0.101	5	1
Olanzapine – Excitement	rs10484256	no	6	12303136	0.161	244	−	0.087	2.67E-06	0.491	0.104	5	1
Olanzapine – Excitement	rs7635839	no	3	193150479	0.054	240	−	0.088	2.98E-06	0.491	0.050	2	1
Risperidone – Negative	rs12526186	no	6	30844130	0.158	236	+	0.089	3.07E-06	0.408	0.147	2	1
Risperidone – Negative	rs17815774	*TRPM1*	15	29121654	0.025	243	+	0.086	3.30E-06	0.408	0.120	2	2

Locus information includes chromosome number (Chr), location of SNP (bp, Genome Build 35), and minor allele frequency (MAF). For each test we report the sample size (N), direction of effect of minor allele frequency (Eff) where a "+" means a better drug effect (i.e. larger decrease in PANSS scores), the estimated proportion of variance explained by the SNP in the outcome (r^2), and the *p* and *q* values of the test. In the section titled robustness we report the estimated proportion of variance explained by the SNP in the subsample of EA only (r^2_a) and (#s) is the number out of six PANSS scales that were significantly associated at $p < 0.05$ with that SNP. The final column (#d) is the number of drugs out of the five tested showing a significant association ($p < 0.05$) with that SNP. Note that because of the CATIE design this may be underestimated (see text). Shaded rows within blocks indicate SNPs in high LD ($r^2 > 0.8$) with each other.

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Table 3

Candidate genes results with *q*-values smaller than 0.5

Outcome	Locus				Test						Robustness		
		Gene	Chr	bp	MAF	N	Eff	r^2	*p* value	*q* value	r^2_a	#s	#d
Quetiapine – Negative	rs12860002	HTR2A	13	46501961	0.038	217	−	0.077	0.0000	0.068	0.093	3	1
Quetiapine – Emotion	rs12122534	FMO5	1	143729215	0.365	224	−	0.070	0.0001	0.125	0.075	1	1
Quetiapine – Emotion	rs12122453	FMO5	1	143728930	0.387	226	−	0.060	0.0002	0.216	0.058	1	1
Quetiapine – Emotion	rs6688154	FMO5	1	144142348	0.289	225	−	0.041	0.0023	0.478	0.047	3	2
Quetiapine – Emotion	rs12728058	FMO5	1	144127895	0.246	224	−	0.043	0.0017	0.478	0.049	3	1
Quetiapine – Emotion	rs2353967	FMO5	1	144127002	0.285	226	−	0.042	0.0019	0.478	0.047	3	2
Quetiapine – Emotion	rs2353969	FMO5	1	144118370	0.289	226	−	0.041	0.0023	0.478	0.047	3	2
Quetiapine – Emotion	rs11584787	FMO5	1	143853295	0.187	226	−	0.049	0.0008	0.403	0.073	1	1
Perphenazine – Disorganiz.	rs2382121	HRH2	5	175176888	0.232	127	-	0.116	0.0001	0.181	0.203	2	1
Perphenazine – Negative	rs3899033	HRH2	5	175146681	0.142	127	−	0.087	0.0007	0.418	0.090	3	1
Perphenazine– Emotion	rs13174727	HRH2	5	175208091	0.115	125	+	0.105	0.0002	0.473	0.169	3	1
Quetiapine– Emotion	rs2036702	RGS4	1	159913592	0.146	226	+	0.052	0.0005	0.376	0.091	2	2
Perphenazine– Emotion	rs2684878	RGS4	1	159554429	0.118	126	−	0.094	0.0005	0.491	0.056	4	2
Perphenazine– Negative	rs7829383	NRG1	8	32660202	0.323	125	−	0.088	0.0008	0.418	0.188	2	1
Perphenazine– Negative	rs6988339	NRG1	8	32665458	0.321	127	−	0.082	0.0011	0.456	0.189	2	1
Perphenazine– Negative	rs7823899	NRG1	8	32662583	0.494	127	−	0.096	0.0004	0.418	0.130	2	1
Perphenazine– Negative	rs887829	UGT1A4	2	234450570	0.355	123	−	0.089	0.0008	0.418	0.164	4	1
Quetiapine– Emotion	rs2454513	HRH1	3	11524596	0.138	223	+	0.041	0.0023	0.478	0.059	3	1
Quetiapine– Emotion	rs2445223	TPH1	11	18182154	0.252	221	−	0.043	0.0019	0.478	0.042	1	2

Locus information includes chromosome number (Chr), location of SNP (bp, Genome Build 35), and minor allele frequency (MAF). SNPs were selected using a liberal definition of the gene boundary (approximately +/− 200kb) in order to provide as comprehensive coverage as possible. For each test we report the sample size (N), direction of effect of minor allele frequency (Eff) where a "+" means a better drug effect (i.e. larger decrease in PANSS scores), the estimated proportion of variance explained by the SNP in the outcome (r^2), and the *p* and *q* values of the test. In the section titled robustness we report the estimated proportion of variance explained by the SNP in the subsample of EA