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Evidence for a *SULT4A1* haplotype correlating with baseline psychopathology and atypical antipsychotic response

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Abstract

Aim—This study evaluated the impact of *SULT4A1* gene variation on psychopathology and antipsychotic drug response in Caucasian subjects from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study and a replication sample.

Patients & methods—*SULT4A1* haplotypes were determined using SNP data. The relationship to baseline psychopathology was evaluated using linear regression of Positive and Negative Syndrome Scale (PANSS) total score. Drug response was evaluated using Mixed Model Repeat Measures (MMRM) for change in PANSS.

Results—For the CATIE sample, patients carrying a haplotype designated *SULT4A1-1*(+) displayed higher baseline PANSS ($p = 0.03$) and, when treated with olanzapine, demonstrated a significant interaction with time ($p = 0.009$) in the MMRM. *SULT4A1-1*(+) patients treated with olanzapine displayed improved response compared with *SULT4A1-1*(−) patients treated with olanzapine ($p = 0.008$) or to *SULT4A1-1*(+) patients treated with risperidone ($p = 0.006$). In the replication sample, *SULT4A1-1*(+) patients treated with olanzapine demonstrated greater improvement than *SULT4A1-1*(−) patients treated with olanzapine ($p = 0.05$) or than *SULT4A1-1*(+) patients treated with risperidone ($p = 0.05$).

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Financial & competing interests disclosure

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Conclusion—If validated, determination of *SULT4A1-1* haplotype status might be useful for identifying patients who show an enhanced response to long-term olanzapine treatment.

Keywords

CATIE; olanzapine; pharmacogenomics; risperidone

Previous studies have implicated allelic variation of the sulfotransferase-4A1 gene (*SULT4A1*) in the genetic etiology of schizophrenia spectrum disorders. This gene encodes the major cytoplasmic sulfotransferase in the CNS and is particularly abundant in the cortex [1]. Its function is little understood, but likely includes effects on brain monoamines [1–3], including dopamine and nor-epinephrine, both of which have been implicated in schizophrenia and the mechanism of action of antipsychotic drugs. Specific alleles of the gene are overtransmitted in offspring with schizophrenia in families with multiple affected individuals [4]. In addition, in Caucasians, genotypes for SNPs in this gene have been associated with measures of psychopathology and cognitive dysfunction in patients diagnosed with schizophrenia and schizoaffective disorder [5].

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study was a large federally funded outpatient pragmatic clinical trial designed to assess the effectiveness of antipsychotic drugs in a 'real-world setting' [6,7]. As part of the CATIE trial, detailed clinical evaluations were conducted, including Positive and Negative Syndrome Scale (PANSS) measurements at baseline and multiple time points thereafter. Previous studies have reported the use of the CATIE trial to study the role of genes in predicting baseline psychopathology and drug response [8–13].

The present study examined the role of common haplotypes of the *SULT4A1* gene in the psychopathology of schizophrenia and in the response of patients to antipsychotic medications. One of the six common *SULT4A1* haplotypes in Caucasian patients correlated with both the severity of clinical presentation and drug response in the CATIE trial. In a second randomized clinical trial of patients with schizophrenia treated with olanzapine or risperidone from Vanderbilt University (TN, USA), haplotype status also correlated with altered drug response.

Patients & methods

Subjects

CATIE sample—The design of the CATIE study has been described in detail [6,7]. Briefly, in the initial phase of the study (Phase I; considered herein), schizophrenia patients were randomly assigned to one of four atypical antipsychotic drugs; olanzapine, quetiapine, risperidone or ziprasidone, or to perphenazine, a typical antipsychotic drug, with patients with tardive dyskinesia not permitted to receive perphenazine. The duration of the trial was 18 months, with all cause time to discontinuation as the primary end point. A total of 417 Caucasian subjects consented to provide DNA for genetic study. Details regarding SNP genotyping and quality control have been reported [8]. Only retrospective genetic analyses, judged to be exempt from human study requirements by an institutional review board, were conducted in the current study. Supplementary Table 1 (www.futuremedicine.com/doi/suppl/10.2217/pgs.10.205) provides an overview of demographic data for the CATIE sample and for the replication sample (described later).

Replication sample—Between September 2000 and June 2006, 204 outpatients were screened and 193 patients meeting Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV; American Psychological Association, Washington, DC USA, 2000)

criteria for schizophrenia or schizoaffective disorder from three community-based clinical sites in the USA were deemed eligible according to entry criteria. A preliminary report of this study has been published [14]. The study protocol was approved by the institutional review boards of Vanderbilt University School of Medicine and each individual site. All subjects provided written informed consent after being explained the nature of the study risks, potential benefits and alternatives. A separate consent was obtained for pharmacogenetic testing. The protocol was registered as ID NCT00179062 [101].

Entry criteria—All patients were between the ages of 18–64 years. Patients who were not currently receiving antipsychotic drugs had previously received them and had either discontinued them of their own accord or on the advice of their physicians. Patients who had been treated with olanzapine, risperidone or clozapine within 1 month of screening were excluded from the study. Patients receiving a mood stabilizer, antidepressant or anxiolytic medications, or some combination thereof, at the time of study entry, were permitted to participate. The mood stabilizers were continued during the course of the study. Patients with pre-existing and stable Type 2 diabetes mellitus were also eligible. Substance abuse on an occasional basis was permitted, but not substance dependence.

Pharmacotherapy—After completing baseline metabolic and clinical (e.g., PANSS) assessments, patients were randomly assigned to either oral risperidone at 2–6 mg/day or olanzapine at 5–20 mg/day, on an open basis. Initial doses of drug for risperidone and olanzapine were 2 and 10 mg/day, respectively. Both drugs were flexibly dosed to achieve optimal efficacy and tolerability. As noted above, patients could receive other psychotropic drugs during the course of the study, except that no other antipsychotic drug was permitted.

Data—Genotype and phenotype data for the CATIE trial were obtained through The National Institute of Mental Health, Center for Collaborative Genetic Studies on Mental Disorders (MD, USA). The present study evaluated all 417 CATIE patients who self-reported as having exclusively European ancestry and who consented to genetic testing. This same patient population was described in the study by Sullivan and coworkers that confirmed that there was no hidden population stratification in the sample [8].

Similarly, we evaluated only those patients from the Vanderbilt sample who were self-described as having Caucasian ancestry. This included at total of 32 patients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder.

The CATIE clinical dataset included baseline PANSS scores based on clinical assessments prior to initiation of the assigned therapy, but following a brief washout period for patients previously on antipsychotic medication. Follow-up PANSS data for the CATIE trial were collected at each visit as described in detail by others [7]. For the Vanderbilt sample, baseline PANSS assessments were carried out at the time of enrollment, and follow-up PANSS measurements were carried out at 1, 3 and 6 months after initiation of anti-psychotic treatment. To model drug response, data were fitted using Mixed Model Repeat Measures (MMRM) as described in the ‘Genetic and statistical methods’ section below.

The present study evaluated the *SULT4A1* gene only. The CATIE genotype data included a total of 11 SNPs located between the previously evaluated rs138110, in the promoter region, and the terminal exon of the gene [4,5,15]. From lowest to highest base pair position on the chromosome, the CATIE SNPs were: rs138067, rs138079, rs470089, rs2285161, rs2285162, rs2285164, rs2285167, rs470091, rs138099, rs138102 and rs138110. The Vanderbilt sample was genotyped using an Illumina (CA, USA) Human-610 Quad Beadchip at Duke University’s Institute for Genome Sciences and Policy Genotyping Core (NC, USA). Detailed descriptions of the genotyping and quality control procedures were described

previously [16]. The Illumina array contained five SNPs in the *SULT4A1* gene that are identical to SNPs genotyped in the CATIE study: rs470089, rs2285161, rs2285164, rs2285167 and rs138099. As described below, these allowed unambiguous assignment of *SULT4A1* haplotype status.

Genetic & statistical methods

The initial genetic analysis to determine the influence of *SULT4A1* haplotypes on quantitative PANSS values was performed using the PLINK 1.03 whole-genome analysis toolset developed by Purcell and coworkers [17,102]. This software assigns expectation–maximization (EM) algorithm-based haplotypes to each individual. Using these haplotype assignments, PANSS Total scores were analyzed as quantitative traits in PLINK by linear regression.

For all subsequent analyses, we focused exclusively on the single haplotype, designated *SULT4A1-1*. EM algorithm haplotypes were assigned to each patient using HelixTree software, Version 6.4.1 (Golden Helix, MT, USA), and each individual was scored as being positive or negative for the presence of the haplotype. We only assigned *SULT4A1-1* haplotype status to those individuals for whom EM algorithm assignment could be made with error probabilities of <1%. This included a total of 407 patients from the CATIE study and 32 patients in the Vanderbilt sample. With the exception of four of the 407 patients in the CATIE study, *SULT4A1-1* haplotype status could be assigned with error probabilities of $<1 \times 10^{-5}$.

To determine the effect of *SULT4A1-1* haplotype status on drug response, differences in percentage change of PANSS scores from baseline in Phase I of the CATIE trial were analyzed using MMRM analysis [18], with haplotype and drug therapy status as predictors. Missing values were treated as missing at random. Patients on ziprasidone were omitted from the analysis since ziprasidone was added midway through Phase I of CATIE, leaving four drug therapies (olanzapine, risperidone, quetiapine and perphenazine) for analysis. Potentially important covariates (sex, age of onset and baseline PANSS) were also evaluated and included if significant. All drug therapy by *SULT4A1-1* haplotype terms were included in the model and checked for interaction with time (day of visit). A lack of interaction with time indicates that the effect of drug therapy remains constant after the initial visit at approximately 1 month, similar to the repeated measures models reported to fit the CATIE response data well [10]. Random effects for both intercept and slope (interaction with time) were also evaluated and included if significant. The likelihood ratio test was used to compare fitted models and to test for the significance of both fixed-effects parameters and random effects. Model fitting for testing models with different fixed effects, but the same random effects, was performed using maximum likelihood estimation; whereas for comparing models with different random effects, but the same fixed effects, residual maximum likelihood was used for parameter estimation. A predetermined set of contrasts for differences in percentage change PANSS by haplotype within each drug therapy (four comparisons) and by drug therapy within each haplotype (12 comparisons) were evaluated. Statistical significance was determined using Wald tests.

For the Vanderbilt study, we evaluated whether differences in percentage change in PANSS scores from baseline occurred according to *SULT4A1-1* and drug therapy status using a MMRM analysis [18]. Haplotype and drug therapy status were entered as fixed effects, with subjects as random effects having follow-up at 1, 3 and 6 months. Missing values were treated as missing at random, as with the CATIE analysis.

All statistical analyses were conducted using R version 2.8.1 [103]. Mixed models were fitted using the nlme package [19].

Results

Correlation of a *SULT4A1* haplotype with elevated baseline psychopathology

The 11 *SULT4A1* SNPs genotyped in the CATIE study make up a single haplotype block as determined by Haploview (Figure 1) [20]. EM maximum likelihood phasing of the 11 SNPs from the CATIE study indicated that these markers define only six common haplotypes in Caucasians (Table 1). The least frequent haplotype, designated *SULT4A1-1*, occurs at a frequency of 11.6%. This haplotype demonstrated nominally significant association with baseline PANSS score ($p = 0.034$), explaining approximately 1% of the variance with a β weight of 4.0, corresponding to an increase in total PANSS score of 4.0 associated with the haplotype (Table 1).

Accordingly, to determine if the *SULT4A1-1* haplotype affected baseline psychopathology in an independent sample, we scored individuals from the Vanderbilt sample for the presence of the haplotype and compared with baseline PANSS scores for the group with the haplotype (*SULT4A1-1*[+]) to the group without the haplotype (*SULT4A1-1*[−]). For comparison purposes, Table 2 shows the baseline PANSS Total scores for the two haplotype groups (with mean and standard deviation) in both the CATIE and replication samples. In the replication sample, the *SULT4A1-1*(+) patients had higher baseline PANSS scores on average than the *SULT4A1-1*(−) patients (3.25 points difference vs 4.0 points in CATIE), but the difference was not statistically significant.

SULT4A1-1 haplotype association with differential response to antipsychotic drugs

Next, we tested whether the *SULT4A1-1* haplotype might relate to clinical response to the four antipsychotic drugs (olanzapine, quetiapine, risperidone and perphenazine) that were available for use throughout Phase I of the CATIE trial. Of the 355 patients treated with these four drugs in Phase I, 77 (21.7%) were *SULT4A1-1*(+). To model the variation in response profiles, a MMRM was fitted to the percentage reduction in PANSS score from baseline. Table 3 presents the parameter estimates from the final fitted model, while the full model details are given in the Supplementary Material. Complete summary data for all time points are found in Supplementary Table 2. As expected, based on previous work [10], most treatment-by-haplotype combinations demonstrated a decrease in PANSS score from baseline at 1 month. The exceptions were *SULT4A1-1*(+) patients on olanzapine or risperidone, whose decreases were not statistically significant at 1 month. Percentage reduction in PANSS score at 1 month for these drugs was approximately 5–6%, with the exception of *SULT4A1-1*(+) patients treated with perphenazine, who demonstrated a 11.18% reduction. Also in agreement with the previous findings for the CATIE trial as a whole, time on drug in months beyond the first month, represented by the variable month in Table 3, did not have a significant impact on response ($p = 0.176$). The effect of baseline PANSS Total was highly significant, with higher baseline scores associated with larger percentage reductions. By contrast, patient's sex and age of onset were nonsignificant predictors of change.

To determine if *SULT4A1-1* haplotype status impacted response beyond 30 days, a *SULT4A1-1*-by-drug-by-time interaction term was added to the model. For all drugs except olanzapine, the interaction terms were not significant and were subsequently dropped from the final model. However, *SULT4A1-1*(+) patients treated with olanzapine demonstrated a significant time-on-drug effect ($p = 0.009$). The *SULT4A1-1*(+) patients treated with olanzapine had a greater decrease in PANSS Total of approximately 1% for every month on therapy past the first month. As shown in Figure 2, in agreement with our model, most individual *SULT4A1-1*(+) patients treated with olanzapine displayed continued improvement after 30 days, unlike the flat response beyond 30 days predicted by the model of van den

Oord and coworkers [10]. By contrast, with few exceptions, the response profiles of individual patients for other drug-by-*SULT4A1-1* combinations did not demonstrate improvement beyond 30 days (data not shown).

The various drug-by-*SULT4A1-1* groups were examined for differences in response levels. Pairwise comparisons of percentage reduction in PANSS Total between *SULT4A1-1*(+) versus *SULT4A1-1*(−) patients for all four drugs (four comparisons) and between each drug for *SULT4A1-1*(+) versus *SULT4A1-1*(−) patients (12 comparisons) were all nonsignificant at 1 month. Since the *SULT4A1-1*(+) patients treated with olanzapine displayed a significant interaction with time, pairwise comparisons of *SULT4A1-1*(+) patients versus *SULT4A1-1*(−) patients treated with olanzapine, and of *SULT4A1-1*(+) patients treated with olanzapine versus *SULT4A1-1*(+) patients treated with the three other drugs, were also conducted for the 3, 6, 9, 12, 15 and 18 month time points. The estimated difference in percentage reduction in PANSS scores for *SULT4A1-1*(+) versus *SULT4A1-1*(−) patients treated with olanzapine became significant beginning at month 9. At month 9, this difference was −9.6% (95% CI: −18.5– −0.75; p = 0.034), and by month 18 the difference increased to −18.45% (95% CI: −31.97– −4.93; p = 0.008). The difference between *SULT4A1-1*(+) patients treated with olanzapine versus risperidone was also significant by 9 months; −11.6% (95% CI: −22.26– −1.07; p = 0.031); this difference expanded to −20.49% (95% CI: −35.1– −5.78; p = 0.006) at 18 months. Differences between *SULT4A1-1*(+) patients treated with olanzapine versus quetiapine reached significance by month 15 at −14.0% (95% CI: −27.05– −1.06; p = 0.034). Differences between *SULT4A1-1*(+) patients treated with olanzapine versus perphenazine were not statistically significant for any of the time points evaluated.

To evaluate the clinical importance of the *SULT4A1-1* haplotype, we calculated the percentage of the treatment response variance to olanzapine that was accounted for by the haplotype. For the entire cohort of patients in the CATIE Phase I trial, 6.1% of the variation in olanzapine treatment response was explained by SULT4A1-1 status. We further assessed clinical relevance of the difference in treatment response by calculating effect sizes for each of the estimated differences, with an estimate of the total variance in response rates calculated based on the variance components in the MMRM model. At 12 months, the effect sizes for all estimated contrasts ranged from −0.36 (*SULT4A1-1*[+], olanzapine vs perphenazine) to −0.78 (*SULT4A1-1*[+], olanzapine vs risperidone), while at 18 months the same effect sizes ranged from −0.68 to −1.1.

We used the Vanderbilt sample to test whether the findings in the CATIE trial regarding the differential impact on response of the *SULT4A1-1* haplotype for olanzapine and risperidone replicated in an independent study. In the Vanderbilt trial, percentage reduction in baseline PANSS scores was assessed at 1, 3 and 6 months for patients on either olanzapine or risperidone. A total of 13 Caucasian patients randomized to olanzapine and 12 patients randomized to risperidone returned for at least one evaluation. Of these, eight (32%) carried the *SULT4A1-1* haplotype. The results in Table 4 indicate that the differential pattern of response is similar to that seen in the CATIE trial, in that *SULT4A1-1*(+) patients treated with olanzapine demonstrated greater reduction in PANSS scores as compared with either *SULT4A1-1*(−) patients treated with olanzapine or *SULT4A1-1*(+) patients treated with risperidone.

An MMRM model was fitted to the percentage reduction in PANSS score from baseline for the Vanderbilt trial. The final model specification is provided in the Supplementary Material, and the parameter estimates are presented in Table 5. Unlike the CATIE trial, there was an overall significant effect of time on treatment for the Vanderbilt study, and there were no significant interactions between SULT4A1-1 status and drug therapy with time. The

likelihood ratio test for the overall effect of the *SULT4A1-1* haplotype was only marginally significant in the Vanderbilt sample (p = 0.095). However, the haplotype did account for 17.3% of the variance in treatment response. Comparisons between drug therapies within each SULT4A1-1 group and between SULT4A1-1 groups within each drug therapy are provided in Table 6. *SULT4A1-1*(+) patients showed greater improvement than did *SULT4A1-1*(−) patients when treated with olanzapine (p = 0.054) and also improved more than *SULT4A1-1*(+) patients treated with risperidone (p = 0.05). The estimated effect sizes for these differences were −1.1 and −1.3, respectively.

Discussion

The major findings of the present study are that a specific haplotype of the *SULT4A1* gene correlates with severity of clinical symptoms and that this haplotype predicts improved long-term response to olanzapine in two independent trials. While the haplotype analysis reported here is in general agreement with previous work demonstrating that commonly occurring genetic variation for this highly conserved gene is predictive of the severity of psychopathology in patients with schizophrenia [5], the precise comparison of the current results with these earlier observations is not possible. Preliminary results indicate that the *SULT4A1-1* haplotype affects primarily negative symptoms [Brennan M, Ramsey T, Unpublished Data], but larger datasets will be required to thoroughly elucidate the impact of various *SULT4A1* gene haplotypes on specific aspects of psychopathology.

Our analysis of the CATIE Phase I data found a significant effect of time on the percentage change in total PANSS for the *SULT4A1-1*(+) patients randomized to olanzapine only. The relatively low dropout rate for *SULT4A1-1*(+) patients on olanzapine cannot account for the observed effect of time on improvement in PANSS Total for these patients because, unlike last observation carried forward models, MMRM approaches take into account the full history of observations for each patient rather than focusing solely on the last observation. Clinical application of these findings could be limited given that the better response relative to the other groups was not seen until 9 months for the CATIE study. Nonetheless, since long-term adherence to and tolerance of drug therapy clearly has clinical relevance, further study seems warranted.

Although clearly more replication is needed given the low prior probability inherent to our candidate gene approach, there are noteworthy observations common to both the CATIE and replication samples. Specifically, in both studies *SULT4A1-1*(+) status correlated with higher baseline PANSS values and better response to olanzapine. In terms of antipsychotic response, the effect sizes for both the comparisons between *SULT4A1-1*(+) versus *SULT4A1-1*(−) subjects treated with olanzapine, and between *SULT4A1-1*(+) subjects treated with olanzapine versus risperidone are similar in magnitude to the effect sizes seen for olanzapine versus placebo [21].

The patient populations in both studies are comparable to patients seen in outpatient clinics on a regular basis who wish to try medications other than those they are currently taking or have received in the past. Neither sample included patients hospitalized for acute exacerbation of psychosis, and patients in both groups were moderately ill. Nonetheless, there are obvious differences between the two samples. The CATIE trial was a double-blind practical clinical trial, and the Vanderbilt study was an open label trial designed to evaluate metabolic side effects. In addition, the CATIE trial was longer than the Vanderbilt study. Thus, it is not surprising that response models generated by the MMRM differed between the two studies with regards to the impact of the time on drug response.

One limitation of the Vanderbilt study was the small sample size. To obtain an unbiased assessment of the significance of the observed replication between the CATIE and Vanderbilt samples, we determined the number of SNPs demonstrating replication at the level we observe for the *SULT4A1-1* haplotype. As an initial screen, we used the model created by van den Oord and coworkers [10] to select SNPs that predicted difference in response for olanzapine (at 30 days and beyond), with a p-value of <0.008. Of the 106,294 SNPs held in common between the genotyping platforms for the CATIE and Vanderbilt samples, 875 survived this screen. Of these, a total of only 41 predicted differential response for olanzapine in the Vanderbilt sample (using our mixed model) with a p-value of ≤0.05, resulting in an overall empirical false-discovery rate of 3.85×10^{-4}.

Conclusion

The ability to identify subsets of patients who respond relatively well to particular anti-psychotic drugs would provide guidance for the use of antipsychotics in individuals with schizophrenia [22,23]. In particular, olanzapine appears to be at least as effective as other atypical anti-psychotics for nontreatment-resistant patients with schizophrenia, but it is also more likely than the other drugs to increase weight and to elevate blood sugar and plasma lipids [21,24]. Owing to the side effect burden of olanzapine, it would be advantageous to identify patients who might respond well prior to initiation of treatment with this agent. The *SULT4A1-1* haplotype could potentially provide such a biomarker, if the results presented here are confirmed in additional studies and the use of the haplotype as a biomarker is supported by formal risk–benefit analysis and Bayesian statistics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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103. R Development Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing; Vienna, Austria: 2009. www.R-project.org

Executive summary

- Previous studies have implicated *SULT4A1* in schizophrenia risk and clinical presentation.
- This study examined haplotypic variation in *SULT4A1* and whether or not this variation impacted psychopathology and/or atypical antipsychotic response.

Patients & methods

- Subjects were moderately ill schizophrenia participants of Caucasian origin in two randomized clinical trials of antipsychotic treatment.
- Drug response was determined using a Mixed Model Repeat Measures for change in Positive and Negative Syndrome Scale (PANSS) score.

Results

- A *SULT4A1* haplotype, *SULT4A1-1*, correlated with higher baseline psychopathology as measured by total PANSS score.
- *SULT4A1-1*(+) status demonstrated a significant interaction with olanzapine treatment over time in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) sample.
- In the CATIE sample, olanzapine-treated *SULT4A1-1*(+) subjects demonstrated superior response compared with olanzapine-treated *SULT4A1-1*(−) subjects and *SULT4A1-1*(+) subjects treated with quetiapine and risperidone. In an independent study, olanzapine-treated *SULT4A1-1*(+) subjects displayed a superior response to olanzapine-treated *SULT4A1-1*(−) subjects and to *SULT4A1-1*(+) subjects treated with risperidone.

Conclusion

- Determining *SULT4A1-1* status may identify a patient segment that displays preferential response to olanzapine.

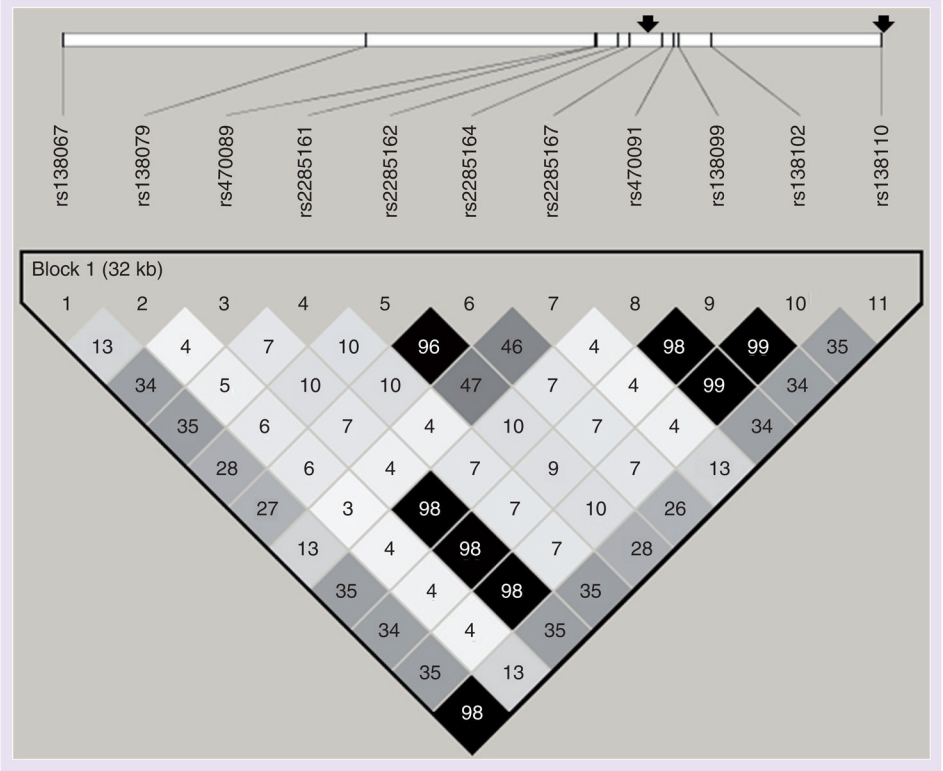

Figure 1. Summary of linkage disequilibrium data for the *SULT4A1* SNPs from the Clinical Antipsychotic Trials of Intervention Effectiveness study

Based on the total sample of cases and controls, Haploview identifies a single haplotype block for the 11 SNPs [20]. Pairwise r^2 values are given in the diamonds. The locations of previously studied SNPs, rs138097 and rs138110, are indicated by arrows. Only the latter was included in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. Previously studied marker rs138060 is located approximately 5 kb to the left of rs138067, outside the region covered by the *SULT4A1* SNPs in CATIE.

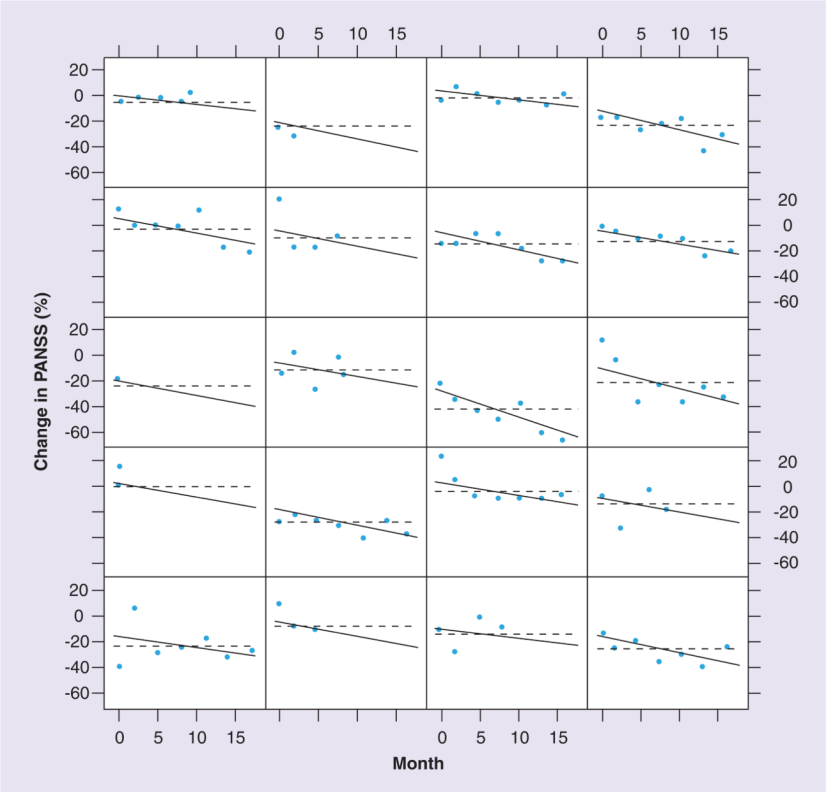

Figure 2. Predicted and observed response profiles for *SULT4A1-1*(+) patients treated with olanzapine in the Clinical Antipsychotic Trials of Intervention Effectiveness study

Each panel represents an individual subject. The points indicate observed percentage change in PANSS values at each time point. The solid lines represent the response predicted over time by our Mixed Model Repeat Measures model. The dashed, horizontal lines provide the predicted response based on the model of van den Oord and coworkers [10].

PANSS: Positive and Negative Syndrome Scale.

Table 1

Correlation of *SULT4A1* haplotypes with Positive and Negative Syndrome Scale Total score.

Haplotype (designation)†	Frequency	β‡	p-value§
ACGCAAGCTCA (1)	0.116	4.00	0.034
ACGCCGGCTCA (2)	0.125	0.46	0.723
ACGCAAACTCA (3)	0.145	−0.05	0.753
ATGCCGGCTCA (4)	0.158	−2.04	0.287
GCACCGGTCTG (5)	0.222	−1.67	0.344
GCGTCGGCTCG (6)	0.237	0.17	0.784

†Haplotypes for the 11 CATIE SNPs were calculated by expectation–maximization algorithm maximization in PLINK. The marker order is rs138067, rs138079, rs470089, rs2285161, rs2285162, rs2285164, rs2285167, rs470091, rs138099, rs138102 and rs138110. SNP rs138110 was used in previous studies and is designated by underlining.

‡β weights (regression coefficients) for quantitative trait, general linear model in PLINK.

§Asymptotic p-value for the t-statistic.

CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness.

Table 2

Relationship of *SULT4A1-1* status with baseline Positive and Negative Syndrome Scale score[†].

Sample	*SULT4A1-1*(+)	*SULT4A1-1*(−)
CATIE	75.9 (17.9), n = 88	71.8 (17.3), n = 319
Vanderbilt	84.25 (16.3), n = 8	81.0 (19.7), n = 24

[†]Total PANSS scores, mean (standard deviation) for patients whose *SULT4A1-1* haplotype status could be assigned with error probabilities of <1%.

CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness; PANSS: Positive and Negative Syndrome Scale.

Table 3

Parameter estimates from Mixed Model Repeat Measures fitted to Clinical Antipsychotic Trials of Intervention Effectiveness Phase I data.

Parameter	Estimate	Standard error	95% CI	p-value
Olanzapine/*SULT4A1-1*(−)†	−5.36	1.88	−9.06— −1.66	0.005
Perphenazine/*SULT4A1-1*(−)†	−5.17	2.01	−9.12— −1.22	0.011
Quetiapine/*SULT4A1-1*(−)†	−4.85	1.89	−8.56— −1.14	0.011
Risperidone/*SULT4A1-1*(−)†	−5.60	1.83	−9.21— −1.99	0.002
Olanzapine/*SULT4A1-1*(+)†	−6.17	3.59	−13.23—0.89	0.086
Perphenazine/*SULT4A1-1*(+)†	−11.18	4.26	−19.56— −2.80	0.009
Quetiapine/*SULT4A1-1*(+)†	−6.82	3.38	−13.46— −0.17	0.044
Risperidone/*SULT4A1-1*(+)†	−3.32	3.52	−10.25—3.60	0.346
Month‡	−0.14	0.10	−0.34—0.06	0.176
Month × olanzapine/*SULT4A1-1*(+)‡	−0.98	0.37	−1.72— −0.24	0.009
Baseline PANSS§	−0.31	0.05	−0.40— −0.21	<0.001

† Parameter estimates are percentage change from baseline values at 1 month.

‡ Parameter estimates are percentage change per month after 1 month.

§ Parameter estimates are percentage change per unit increase in baseline PANSS.

PANSS: Positive and Negative Syndrome Scale.

Table 4

Antipsychotic response in the Vanderbilt sample[†].

	SULT4A1-1(+)			SULT4A1-1(−)		
	Month 1	**Month 3**	**Month 6**	**Month 1**	**Month 3**	**Month 6**
Olanzapine	−23.8 (27.7), n = 4	−37.7 (18.5), n = 3	−39.4 (2.8), n = 3	−4.7 (10.4), n = 9	−20.8 (14.0), n = 8	−21.7 (10.4), n = 6
Risperidone	−5.0 (19.8), n = 4	−9.1 (18.9), n = 3	−11.8 (20.7), n = 3	−11.4 (10.4), n = 7	−18.3 (24.7), n = 5	−29.7 (17.1), n = 4

[†]Percentage change from baseline PANSS scores, mean (standard deviation).

PANSS: Positive and Negative Syndrome Scale.

Table 5

Parameter estimates from Mixed Model Repeat Measures fitted to the Vanderbilt study for schizophrenia patients.

Parameter	Estimate	Standard error	95% CI	p-value
Olanzapine/*SULT4A1-1*(−)†	−8.42	4.83	−18.18—1.34	0.096
Olanzapine/*SULT4A1-1*(+)†	−25.6	7.16	−40.07— −11.14	0.002
Risperidone/*SULT4A1-1*(−)†	−12.5	5.17	−22.94— −2.06	0.025
Risperidone/*SULT4A1-1*(+)†	−4.92	7.16	−19.39—9.54	0.50
Month‡	−2.67	0.75	−4.19— −1.15	0.001

† Parameter estimates are percentage change from baseline values at 1 month.

‡ Parameter estimates are percentage change per month after 1 month.

Table 6

Estimated differences in mean percentage change in Positive and Negative Syndrome Scale for the Vanderbilt sample[†].

Schizophrenia patients comparison[‡]	Difference	95% CI	p-value
Olanzapine, *SULT4A1-1*(+)vs *SULT4A1-1*(−)	−17.18	−34.65—0.29	0.054
Risperidone, *SULT4A1-1*(−) vs *SULT4A1-1*(+)	−7.57	−25.53—10.38	0.39
SULT4A1-1(+), olanzapine vs risperidone	−20.68	−41.31— −0.04	0.050
SULT4A1-1(−), olanzapine vs risperidone	4.08	−10.14—18.29	0.56

[†]Estimated differences in mean percentage change in PANSS from baseline, according to the Mixed Model Repeat Measures. Terms in the Mixed Model Repeat Measures included main effects for month, therapy drug, *SULT4A1-1* haplotype and drug-by-*SULT4A1-1* haplotype interaction.

[‡]Difference in percentage change in PANSS score for the first group minus that for the second group. The negative values (larger decrease in PANSS score) correspond to a greater response for the first group.

PANSS: Positive and Negative Syndrome Scale.