Research Article
For reprint orders, please contact: reprints@futuremedicine.com

Pharmacogenomics

Replication of SULT4A1-1 as a pharmacogenetic marker of olanzapine response and evidence of lower weight gain in the high response group

Timothy L Ramsey[1], Qian Liu[1] & Mark D Brennan*[,1]
[1]SureGene, LLC, 600 Envoy Circle, Louisville, KY 40299, USA
*Author for correspondence:
Tel.: +1 502 569 1070
mark.brennan@suregene.net

Aim: Antipsychotic efficacy biomarkers have the potential to improve outcomes in psychotic patients. This study examined the effect of SULT4A1-1 haplotype status (rs2285162 [A]-rs2285167 [G]) on olanzapine response. **Patients & methods:** We evaluated 87 olanzapine treated subjects from Phases 1, 1B and 2 of the CATIE trial for the impact of SULT4A1-1 status on change in Positive and Negative Syndrome Scale (PANSS) total score using two models of response. We also examined weight change. **Results:** SULT4A1-1-positive status correlated with superior olanzapine response in Phase 1 ($p = 0.004$ for model 1 and $p = 0.001$ for model 2) and Phases 1B/2 ($p = 0.05$ for model 1 and $p = 0.007$ for model 2). SULT4A1-1-positive subjects gained significantly less weight per month on olanzapine, 0.15 lbs, than did SULT4A1-1-negative subjects, 2.27 lbs ($p = 0.04$). **Conclusion:** This study provides a second replication of superior olanzapine response in SULT4A1-1-positive subjects compared with SULT4A1-1-negative subjects. SULT4A1-1-positive subjects treated with olanzapine also gained less weight than SULT4A1-1-negative subjects.

Original submitted 19 December 2013; Revision submitted 17 March 2014

Keywords: antipsychotic response • biomarker • CATIE trial • weight gain

Background

The economic, medical and social burden of treating serious mental illness has remained extremely high even after the introduction of numerous new antipsychotic treatments in the last few years [1]. Hundreds of thousands of individuals suffering from mental illness are hospitalized each year with a cost in the tens of billions of US dollars [1,2]. Thus, the ability to identify which antipsychotics are most likely to benefit a given patient would represent a significant improvement in the treatment of mental illness.

Numerous genome-wide association studies and candidate gene studies have attempted to identify markers of antipsychotic response, but few, if any, markers have produced consistent, replicated results [3–10]. Several studies of markers in candidate genes such as *DRD3* [11], *KCNH2* [12], *HTR2A* [13,14] and *SV2C* [15] have produced positive findings for olanzapine response. However, these markers lack either sufficient replication or have various inconsistencies that limit their current usefulness in clinical practice. In particular, interstudy differences in the genetic models that predict superior response and differences in phenotypes (e.g., positive vs negative symptoms) have limited the clinical utility of these markers for making informed medication selection decisions despite a reasonable likelihood that they do impact olanzapine response in some manner.

A specific haplotype of the *SULT4A1* gene called SULT4A1-1 has been reported to correlate with superior response to olanzapine [16]. In the original report, the haplotype displayed both a consistent phenotype, that is, superior response to olanzapine for reduction of total psychopathology symptom burden, and a consistent genetic model in Phase 1 of CATIE and in an independent

Future Medicine part of fsg

clinical sample from Vanderbilt University. Individuals with at least one copy of SULT4A1-1 were classified as SULT4A1-1 positive. In both the discovery and replication sample, SULT4A1-1-positive subjects treated with olanzapine displayed significantly superior response, as measured by change in Positive and Negative Syndrome Scale (PANSS) total score (PANSS-T), compared with SULT4A1-1-negative subjects treated with olanzapine. A follow-up study demonstrated that SULT4A1-1-positive olanzapine-treated subjects suffered significantly fewer hospitalization events in CATIE [17]. This reduction in hospitalization was particularly pronounced in subjects with recent hospitalizations where SULT4A1-1-positive status predicted an eightfold reduction in the hospitalization risk in olanzapine-treated patients.

An additional replication of superior response to olanzapine in SULT4A1-1-positive subjects would help to confirm the status of the SULT4A1-1 haplotype as a consistent, well-replicated biomarker of response for olanzapine. Accordingly, the present study evaluated whether SULT4A1-1-positive subjects displayed superior response to olanzapine compared with SULT4A1-1-negative subjects in the later blinded phases of CATIE, Phases 1B and 2. Furthermore, since olanzapine treatment for the entire CATIE sample was associated with both increased weight gain and superior efficacy, we examined impact of SULT4A1-1 status on olanzapine-induced weight gain.

Patients & methods

Intent to treat population

The patient population and the CATIE data used are described in detail elsewhere [6,18–20]. Briefly, the current study was limited to self-described Caucasian subjects. All subjects in this study provided informed consent for genetic testing and participated in at least one of the randomized phases of the study, Phases 1A, 1B and 2 [19]. The NIMH Center for Collaborative Genetic Studies on Mental Disorders (CCGSM) provided genotype and phenotype data for the CATIE trial [21].

In this study, we examined olanzapine-treated subjects for response and all atypical antipsychotics for weight gain. We included only subjects with no known exposure to the drug being evaluated. While the CATIE protocol allowed subjects to be randomized to drug(s) that the subjects were taking at the time of screening, this does not reflect normal clinical practice. For this reason, most clinical trials, including the Vanderbilt sample previously used as a replication sample for the SULT4A1-1 haplotype, use prior exposure to the study drug as an exclusion criterion [16,20]. The CATIE study group provided a variable, olz_0, for olanzapine use at time of enrollment. Using this variable, we excluded subjects with exposure to olanzapine prior to Phase 1 from the intent to treat population (ITTP). Thus, this ITTP was a subset of that previously analyzed for Phase 1 of the CATIE study. A total of 55 Phase 1 subjects met the criteria for the current study. As this ITTP differed slightly from the population previously analyzed for Phase 1, we reanalyzed Phase 1 for this ITTP using the two models described below. We also combined Phases 1B and 2 into a new, single analysis group (Phases 1B/2) in order to maximize sample size for analysis using the same two models. None of the subjects in the Phase 1B/2 analysis group were treated with olanzapine in Phase 1 or immediately prior to entry into CATIE. Thus, this second analysis group was completely independent of the Phase 1 analysis group with regard to olanzapine treatment. When looking at weight gain, we similarly excluded patients with a history of prior treatment for the other drugs. Olanzapine dose was calculated as 7.5 mg/capsule × CAPSULES (a CATIE defined variable for number of capsules per day provided by CCGSM).

Assigning SULT4A1-1 status

SULT4A1-1 status was assigned to all CATIE subjects as described in Ramsey *et al.* [16] using rs2285162 (A) and rs2285167 (G) as the haplotype tagging SNPs. The frequency of the *SULT4A1-1* haplotype in the HapMap Utah residents of northern and western European ancestry (CEU) population is 0.128, which yields an expected SULT4A1-1-positive status frequency of 0.24 [22]. In the ITTP, SULT4A1-1-positive status occurred with frequencies of 0.27 for Phase 1 and 0.25 in Phase 1B/2 olanzapine-treated subjects.

Response models

We have included two separate response models in the analysis. In both cases, the dependent variable is change in PANSS-T. The first model used an implementation of the response model developed by Van den Oord *et al.* (the 'Van den Oord' Model) as an independently developed model free from any *post hoc* selection bias, previously reported as a good fit for describing antipsychotic response in the CATIE trial [23]. In brief, this model incorporates a 30 day lag for response, which remains flat thereafter. As a separate measure of treatment response, so as to replicate exactly the previously published results, we also applied the mixed model repeat measures (MMRM) model previously used for the analysis of the Vanderbilt University sample ('Vanderbilt' model) [16]. This model included both time and baseline PANSS scores as variables. Both of the models provide a predicted ΔPANSS-T for each subject. Strictly speaking, baseline PANSS values were not available for the Phase 1B/2 sample, as there was no washout period prior to entry into these phases. Instead, the PANSS-T score at the end of the previous phase was used as a proxy for baseline values for Phase 1B/2 subjects.

Weight gain

Data for subjects from all studied phases were combined for the weight change analysis. Each subject had a unique duration on a drug in a given phase, ranging from 0.42 to 20.5 months in the ITTP. Therefore, monthly weight change was calculated as weight change/time in phase. Weight change (C_WT) and time in phase (TMDISC1, TMDISC1B and TMDISC2 for Phases 1, 1B and 2, respectively) were predefined variables in the data provided by CCGSM.

Comparison of means

T-test was used to calculate the significance of the difference between the means of two comparison groups for both predicted change in PANSS-T and monthly weight gain.

Effect size calculation

Effect sizes were calculated using Cohen's D, where D = (Mean of population 1 – mean of population 2)/(standard deviation [SD] of the combined group mean) [24]. For clarity, we use |D| since superior response is indicated by a negative number, thus comparison of SULT4A1-1 positive versus negative will have a positive Cohen's D.

Results

Demographics

In this study, we examined 87 Caucasian olanzapine-treated subjects without known prior exposure to olanzapine. Table 1 shows the sex and age for each of the SULT4A1-1 categories. Table 1 also includes average olanzapine dose. No significant differences were found between the groups for any of these variables.

As expected based on earlier work, for Phase 1, SULT4A1-1-positive subjects had higher baseline PANSS-T, (84.4 ± 16.7; mean ± SD) than SULT4A1-1-negative subjects (74.3 ± 20.6). However, due to the smaller sample size for the ITTP, this difference was not significant ($p = 0.1$). By contrast, the starting PANSS-T values at entry into Phase 1B/2, for which there was no washout period, were similar for SULT4A1-1-positive and -negative patients (78 ± 19.6 and 77 ± 20.6, respectively).

Response

Table 2 provides the mean response for each SULT4A1-1 category for both of the response models tested. Consistent with previous results, SULT4A1-1-positive subjects had significantly better response than SULT4A1-1-negative subjects in Phase 1, regardless of the response model. The analysis of Phases 1B/2 provides a replication of the finding that SULT4A1-1-positive subjects display superior response to olanzapine compared with SULT4A1-1-negative subjects. Depending on the model used and the study phase analyzed, the effect sizes for the difference between the SULT4A1-1-positive and -negative subjects range from 0.78 to 1.15.

Similar conclusions can be drawn looking at both response frequencies and completion status for the two CATIE samples (Table 3). If we look at the number of patients showing positive response to olanzapine (defined as a reduction of ≥20% PANSS-T using the Vanderbilt model), 63% of the SULT4A1-1-positive subjects responded in Phase 1 compared with only 23% of SULT4A1-1-negative subjects. The numbers were similar for the Phase 1B/2 sample, with 75% of the SULT4A1-1-positive subjects responding versus only 21% of the SULT4A1-1-negative subjects. Similarly, completion rates were significantly higher for the SULT4A1-1-positive subjects compared with negative subjects in Phase 1 (67 vs 38%, respectively). However, for the Phase 1B/2 sample, SULT4A1-1-positive and -negative subjects had similar completion rates (38%).

Weight gain

Olanzapine caused more weight gain than the other commonly used atypical antipsychotics evaluated in the CATIE trial – quetiapine, risperidone and ziprasidone [19]. To determine if SULT4A1-1 status might impact weight gain, we examined monthly weight gain in the olanzapine-treated subjects in all phases (Phases 1, 1B and 2) combined, segmented by SULT4A1-1 status, and compared both of these groups to the weight gain induced by other atypical antipsychotics as a group (quetiapine, risperidone and ziprasidone) without regard to SULT4A1-1 status. As shown in Figure 1, SULT4A1-1-positive subjects treated with olanzapine gained significantly less weight per month than SULT4A1-1-negative subjects treated with olanzapine. When compared with the study-wide monthly weight gain average of the other atypical antipsychotics, SULT4A1-1-negative subjects gained significantly more weight than subjects treated with other atypical antipsychotics, but SULT4A1-1-positive patients did not.

Discussion

SULT4A1-1 status has now been shown to impact olanzapine response in three clinical data sets, CATIE Phase 1, CATIE Phases 1B/2 and Vanderbilt [16]. SULT4A1-1-positive subjects have consistently shown superior response to olanzapine compared with SULT4A1-1-negative subjects. This superior response held true for both the Vanderbilt MMRM response model and for the response model published by Van den Oord and coworkers [23].

The effect sizes attributed to SULT4A1-1 status in this study (average of 0.93) may be classified as

Table 1. Demographic and dosing information for study subjects.

Clinical trial	SULT4A1-1 positive				SULT4A1-1 negative			
	n	Male, n (%)†	Age, mean (SD)‡	Dose, mean (SD)§	n	Male, n (%)†	Age, mean (SD)‡	Dose, mean (SD)§
Phase 1	15	12 (80)	37.5 (10.8)	21 (9)	40	28 (70)	41.2 (10.7)	21 (7.5)
Phase 1B/2	8	7 (88)	36.8 (12.1)	21.8 (10.5)	24	19 (79)	40.4 (11.1)	21 (8.3)

†Number (percentage) males in the given group.
‡Mean and standard deviation of age at study entry in the given group.
§Mean and standard deviation of dose, in mg/day, at end of the phase.
SD: Standard deviation.

'large' [24]. In comparison, a recent meta-analysis has shown that the effect size for the difference between olanzapine and placebo in randomized trials is only 0.59 [25]. Thus, the magnitude of the difference in olanzapine response in SULT4A1-1-positive subjects is approximately 1.5-times as large as that seen when comparing the efficacy of olanzapine to placebo. For patients not segmented by SULT4A1-1 status, olanzapine displays modest superiority compared with quetiapine or risperidone (effect sizes estimated at ~0.2 and ~0.1, respectively [26]). Therefore, when evaluating relative response to atypical antipsychotics, SULT4A1-1-positive subjects, on average, should experience even more benefit from olanzapine compared with quetiapine and risperidone than currently expected.

Since weight gain was associated with increased treatment response in the CATIE trial, the results of the weight gain analysis were of considerable interest [19]. In this study, the higher response group (SULT4A1-1-positive subjects) actually gained less weight than the lower response group (SULT4A1-1-negative subjects), despite having no dosing differences. Moreover, while the olanzapine-treated SULT4A1-1-negative subjects gained significantly more weight that those subjects treated with other atypical antipsychotics, the olanzapine-treated SULT4A1-1-positive subjects did not gain more weight than those treated with other antipsychotics. While some SULT4A1-1-positive individuals did experience clinically significant weight gain, this weight gain did not correlate with improved response, and so it is likely that this weight gain is driven by other genetic or environmental variables [8,27].

As for potential biological explanations for the impact on weight gain, no known coding variants exist for *SULT4A1* [28]. Therefore SULT4A1-1 haplotype likely modulates either the quantity of protein production or creates some as yet undiscovered splice variant. Biochemically, there are three potential mechanisms based on *in vitro* binding assay work by Allali-Hassani *et al.* [29]. SULT4A1 binds neural steroids (particularly estrogen), thyroid hormone and epinephrine/norepinephrine. Any, all, or none of these pathways could be responsible for the reduction in weight gain. Furthermore, it should be noted that there is significant linkage disequilibrium for the *SULT4A1* region. The SULT4A1-1 haplotype is one of six common haplotypes in Caucasians [16]. In total, the region of strong linkage disequilibrium covers approximately 70 kb and includes the entire *SULT4A1* coding region, its promoter, and the last two exons and 3′-UTR of the adjacent *PNPLA5* gene [22]. Clearly, more work is needed to identify

Table 2. Change in PANSS-T for olanzapine treated patients segmented by SULT4A1-1 status.

Clinical trial	SULT4A1-1 positive			SULT4A1-1 negative			p-value‡	ES§
	n	Mean†	SD†	n	Mean†	SD		
Van den Oord model¶								
Phase 1	15	-21.9	12.8	40	-9.8	13.6	0.004	0.85
Phase 1B\2	8	-19.2	9.5	24	-11.1	9.9	0.05	0.78
Vanderbilt model#								
Phase 1	15	-22.7	13.6	40	-9.0	13.3	0.001	0.94
Phase 1B\2	8	-21.2	7.7	24	-11.5	8.5	0.007	1.15

†Mean and standard deviation of model-predicted change in PANSS-T from baseline to end of study.
‡p-value for t-test of difference between the means of SULT4A1-1 positive and negative subjects.
§Effect size (Cohen's D).
¶Model described by Van den Oord *et al.* for antipsychotic response in the CATIE trial [23].
#Vanderbilt model is the mixed model repeat measures utilized to describe the response of the Vanderbilt University sample in Ramsey *et al.* [16].
ES: Effect size (IDI see methods); PANSS-T: Positive and Negative Syndrome Scale total score.

Table 3. Response rates and completer status for olanzapine treated patients based on SULT4A1-1 status.

Clinical trial	SULT4A1-1 positive		SULT4A1-1 negative	
	Response†	Completers‡	Response†	Completers‡
Phase 1	60%§	67%¶	23%§	38%¶
Phase 1B/2	75%#	38%	21%#	38%

†Fraction of responders with response defined as ≥20% reduction in predicted PANSS-T using the Vanderbilt model.
‡Fraction of completers defined as completion of the trial in phase as represented by the CATIE provided variable 'comp'.
§Fishers exact p-value for comparison of Phase 1 response rates = 0.02.
¶Fishers exact p-value for comparison of Phase 1 completion rate = 0.07.
#Fishers exact p-value for comparison of Phase 1B/2 response rates = 0.01.
PANSS-T: Positive and Negative Syndrome Scale total score.

the exact mechanism responsible for this decreased weight gain.

In summary, SULT4A1-1 status should be clinically useful for determining which patients to treat with olanzapine. SULT4A1-1-positive individuals demonstrate unprecedented superior response to olanzapine compared with SULT4A1-1-negative individuals. Moreover, it appears that a major limitation on olanzapine use, weight gain, may not be a major factor for the majority of SULT4A1-1-positive subjects.

Conclusion

SULT4A1-1-positive status has been shown to predict superior response to olanzapine in three clinical groups. This is the first biomarker to demonstrate this level of replication for antipsychotic response. Consequently, use of the haplotype as a biomarker to guide antipsychotic treatment selection, by increasing olanzapine use in SULT4A1-1-positive patients and decreasing it for SULT4A1-1-negative patients, has the potential to significantly improve patient outcomes.

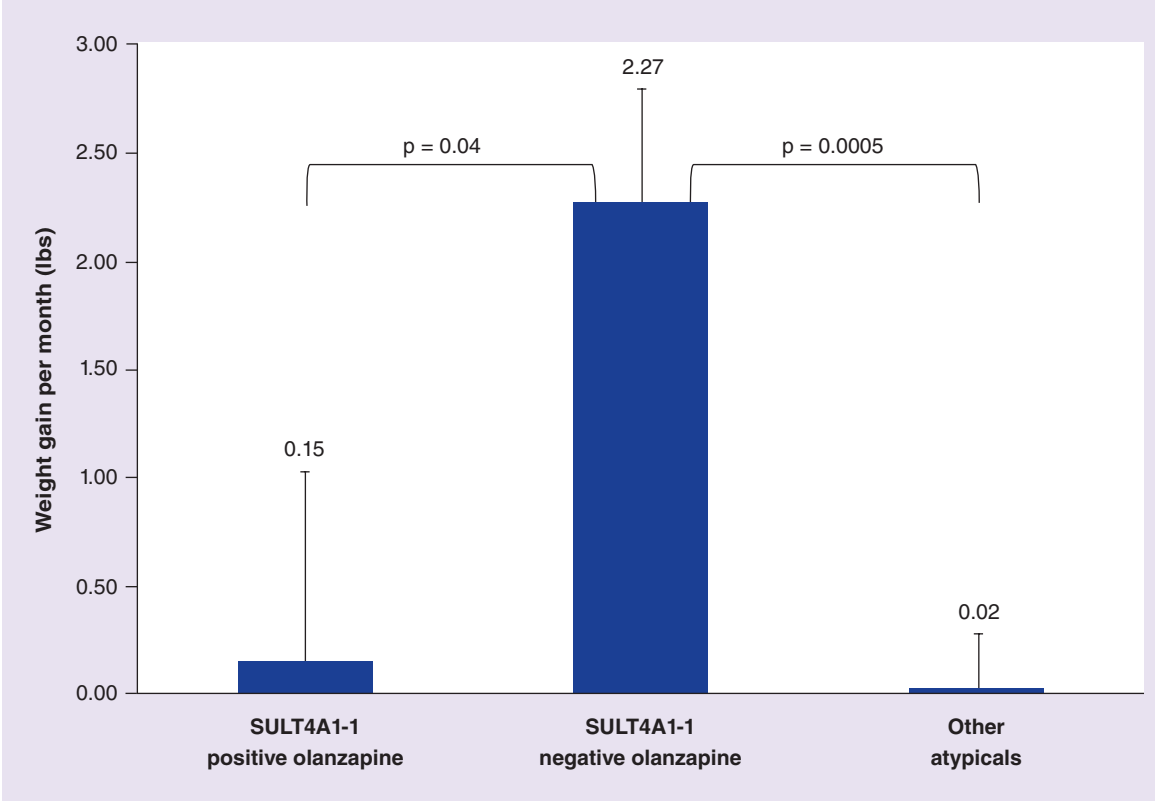

Figure 1. Impact of *SULT4A1-1* haplotype status on weight gain in CATIE. Mean monthly weight change was calculated for SULT4A1-1 positive (n = 23) and negative (n = 64) olanzapine-treated subjects as well as subjects treated with other atypical antipsychotics (quetiapine, risperidone and ziprasidone; n = 330). The solid bars and the numbers above the error bars represent the mean monthly change. The error bars represent the standard error of each group. p-values represent the results of a t-test between the means of the two groups linked by the bar.

Future perspective

The inability to select the most promising antipsychotic mediation to treat a given patient represents a substantial unmet medical need in the treatment of mental illness. At this time, biomarkers for treatment response and adverse events appear to hold the most promise. Currently, the key limitation to developing more biomarkers for antipsychotic efficacy is access to clinical samples. As most of the atypical antipsychotics are now generic, major pharmaceutical firms should be encouraged open up their clinical trial data sets for biomarker development. Hopefully, SULT4A1-1 is the first of many biomarkers for antipsychotic efficacy.

Financial & competing interests disclosure

MD Brennan and TL Ramsey are equity holders of SureGene, LLC. This work was supported by National Institutes of Mental Health grant MH078437 to MD Brennan. The principal investigators of the CATIE trial were JA Lieberman, TS Stroup and JP McEvoy. The CATIE trial was funded by a grant from the National Institute of Mental Health (N01 MH900001) along with MH074027 (principal investigator: PF Sullivan). Prior genotyping expenses for the CATIE study was funded by Eli Lilly and Company. The funding sources had no input into the design of the study or the writing of the manuscript. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined inthe 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.

Executive summary

Background

- This study was designed to provide a second replication showing that SULT4A1-1 positive subjects display superior response to olanzapine.

Patients & methods

- Eighty-seven olanzapine-treated patients from the CATIE study were evaluated for impact of SULT4A1-1 status on changes in PANSS-T using two different response models.

Results

- Demographics
  - No significant differences in age, sex or dose were observed between the SULT4A1-1 groups.
- Response
  - SULT4A1-1 positive subjects displayed superior response to olanzapine compared with SULT4A1-1 negative subjects in multiple phases of CATIE using two difference response models.
  - The average effect size for comparing SULT4A1-1 positive subjects to SULT4A1-1 negative subjects treated with olanzapine is 0.93.
- Weight gain
  - SULT4A1-1-positive subjects treated with olanzapine gain significantly less weight than SULT4A1-1 negative subjects treated with olanzapine.
  - SULT4A1-1-positive subjects treated with olanzapine did not gain more weight than subjects treated with other atypical antipsychotics, but SULT4A1-1-negative subjects did experience significantly more weight gain when treated with olanzapine compared with subjects treated with other atypical antipsychotics.

Conclusion & future perspective

- This is the second replication showing that SULT4A1-1-positive subjects have a superior response to olanzapine.
- The effect size for SULT4A1-1-positive versus -negative subjects treated with olanzapine is 1.5-times as large for olanzapine versus placebo.
- Determining SULT4A1-1 status provides an avenue to improve patient care through modification of medication selection in both SULT4A1-1-positive and -negative subjects.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1 Feldman R, Bailey RA, Muller J, Le J, Dirani R. Cost of schizophrenia in the Medicare program. *Popul. Health Manag.* doi:10.1089/pop.2013.0062 (2013) (Epub ahead of print).

2 Ascher-Svanum H, Zhu B, Faries DE *et al.* The cost of relapse and the predictors of relapse in the treatment of schizophrenia. *BMC Psychiatry* 10, 2 (2010).

3 Need AC, Keefe RS, Ge D *et al.* Pharmacogenetics of antipsychotic response in the CATIE trial: a candidate gene analysis. *Eur. J. Hum. Genet.* 17, 946–957 (2009).

4 Adkins DE, Aberg K, McClay JL *et al.* Genomewide pharmacogenomic study of metabolic side effects to antipsychotic drugs. *Mol. Psychiatry* 16, 321–332 (2011).

5 Lee ST, Ryu S, Kim SR *et al.* Association study of 27 annotated genes for clozapine pharmacogenetics: validation of preexisting studies and identification of a new candidate gene, *ABCB1*, for treatment response. *J. Clin. Psychopharmacol.* 32, 441–448 (2012).

6 Liu Q, Jamba M, Patrick C, III, Padmanabhan S, Brennan MD. Targeted pharmacogenetic analysis of antipsychotic response in the CATIE study. *Pharmacogenomics* 13, 1227–1237 (2012).

7 McClay JL, Adkins DE, Aberg K *et al.* Genome-wide pharmacogenomic analysis of response to treatment with antipsychotics. *Mol. Psychiatry* 16, 76–85 (2011).

• **Describes genome-wide association study analysis of the CATIE study using the Van den Oord response model** [23].

8 Muller DJ, Chowdhury NI, Zai CC. The pharmacogenetics of antipsychotic-induced adverse events. *Curr. Opin. Psychiatry* 26, 144–150 (2013).

9 Lavedan C, Licamele L, Volpi S *et al.* Association of the *NPAS3* gene and five other loci with response to the antipsychotic iloperidone identified in a whole genome association study. *Mol. Psychiatry* 14, 804–819 (2009).

10 Laika B, Leucht S, Heres S, Schneider H, Steimer W. Pharmacogenetics and olanzapine treatment: *CYP1A2*1F* and serotonergic polymorphisms influence therapeutic outcome. *Pharmacogenomics J.* 10, 20–29 (2010).

11 Adams DH, Close S, Farmen M, Downing AM, Houston JP. Dopamine receptor D3 genotype association with greater acute positive symptom remission with olanzapine therapy in predominately Caucasian patients with chronic schizophrenia or schizoaffective disorder. *Human Psychopharmacol.* 23, 267–274 (2008).

12 Apud JA, Zhang F, Decot H, Bigos KL, Weinberger DR. Genetic variation in *KCNH2* associated with expression in the brain of a unique hERG isoform modulates treatment response in patients with schizophrenia. *Am. J. Psychiatry* 169, 725–734 (2012).

13 Ellingrod VL, Lund BC, Fleming F Perry P, Holman TL, Bever-Stille K. 5-HT2A receptor promoter polymorphism, -1438G/A and negative symptom response to olanzapine in schizophrenia. *Psychopharmacol. Bull.* 37, 109–112 (2003).

14 Olajossy-Hilkesberger L, Godlewska B, Schosser-Haupt A, Olajossy M, Wojcierowski J, Kasper S. Polymorphisms of the 5-HT2A receptor gene and clinical response to olanzapine in paranoid schizophrenia. *Neuropsychobiology* 64, 202–210 (2011).

15 Ramsey TL, Liu Q, Massey BW, Brennan MD. Genotypic variation in the *SV2C* gene impacts response to atypical antipsychotics the CATIE study. *Schizophr. Res.* 149, 21–25 (2013).

16 Ramsey TL, Meltzer HY, Brock GN *et al.* Evidence for a *SULT4A1* haplotype correlating with baseline psychopathology and atypical antipsychotic response. *Pharmacogenomics* 12, 471–480 (2011).

•• **First report of *SULT4A1-1* haplotype influencing olanzapine response in CATIE Phase I with replication in the Vanderbilt sample. Also described is the Vanderbilt mixed model repeat measures model for response.**

17 Liu Q R, Ramsey TL, Meltzer HY, Massey BW, Padmanabhan S, Brennan MD. Sulfotransferase 4A1 haplotype 1 (SULT4A1-1) is associated with decreased hospitalization events in antipsychotic-treated patients with schizophrenia. *Prim. Care Companion CNS Disord.* 14, 3 (2012).

• **Reports that *SULT4A1-1* haplotype positive patients are less likely to be hospitalized due to lack of efficacy when treated with olanzapine.**

18 Sullivan PF, Lin D, Tzeng JY *et al.* Genomewide association for schizophrenia in the CATIE study: results of stage 1. *Mol. Psychiatry* 13, 570–584 (2008).

• **Describes the CATIE sample, genotyping and informed consent.**

19 Lieberman JA, Stroup TS, McEvoy JP *et al.* Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N. Engl. J. Med.* 353, 1209–1223 (2005).

20 Stroup TS, McEvoy JP, Swartz MS *et al.* The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. *Schizophr. Bull.* 29, 15–31 (2003).

21 NIMH Center for Collaborative Genetic Studies on Mental Disorders. www.nimhgenetics.org

22 The International HapMap Project. http://hapmap.ncbi.nlm.nih.gov

23 Van den Oord EJ, Adkins DE, McClay J, Lieberman J, Sullivan PF. A systematic method for estimating individual responses to treatment with antipsychotics in CATIE. *Schizophr. Res.* 107, 13–21 (2009).

•• **Describes the Van den Oord response model used here.**

24 Cohen J. *Statistical Power Analysis for the Behavioral Sciences (2nd Edition).* Lawrence Erlbaum, NJ, USA (1988).

25 Leucht S, Arbter D, Engel RR, Kissling W, Davis JM: How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Mol. Psychiatry* 14(4), 429–447 (2009).

26 Leucht S, Komossa K, Rummel-Kluge C *et al.* A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am. J. Psychiatry* 166, 152–163 (2009).

27 Kao AC, Müller DJ. Genetics of antipsychotic-induced weight gain: update and current perspectives. *Pharmacogenomics* 14, 2067–2083 (2013).

28 Lewis AG, Minchin RF. Lack of exonic sulfotransferase 4A1 mutations in controls and schizophrenia cases. *Psychiatr. Genet.* 19(1), 53–55 (2009).

29 Allali-Hassani A, Pan PW, Dombrovski L *et al.* Structural and chemical profiling of the human cytosolic sulfotransferases. *PLoS Biol.* 5(5), e97 (2007).