Analysis of Gene Variants Previously Associated With Iloperidone Response in Patients With Schizophrenia Who Are Treated With Risperidone

Bonnie A. Fijal, PhD; Virginia L. Stauffer, PharmD; Bruce J. Kinon, MD; Robert R. Conley, MD; Vicki Poole Hoffmann, PhD; Michael M. Witte, PhD; Fangyi Zhao, PhD; and John P. Houston, MD, PhD

ABSTRACT

Objective: We examined 6 single nucleotide polymorphisms (SNPs) previously reported to be associated with response to iloperidone therapy for association with response to risperidone therapy.

Method: Patients with schizophrenia (*DSM-IV*) were assessed during 2006 and 2007 for response/nonresponse (defined as ≥ 20%/<20% improvement in Positive and Negative Syndrome Scale [PANSS] total score) after 2 weeks of risperidone treatment (2 to 6 mg/d). Responders continued risperidone treatment; nonresponders were randomly assigned to either risperidone or olanzapine treatment (10 to 20 mg/d) for an additional 10 weeks. Associations between change in PANSS total (primary outcome measure), positive, and negative scores and the 6 SNPs were examined in risperidone-treated patients (N = 145). Genotype frequencies and improvement in PANSS total scores were analyzed for those SNPs significantly associated with change in PANSS total score.

Results: The SNPs *XKR4* rs9643483 and *GRIA4* rs2513265 were significantly associated with change in PANSS total response (adjusted $P < .05$ for both), with the same direction of effect as reported for iloperidone. For patients with nonresponsive genotypes for these SNPs, mean improvement in PANSS total score for African Americans was two-thirds that seen for whites (*XKR4*: −13.9 versus −21.4; *GRIA4*: −12.5 versus −20.9).

Conclusions: In this retrospective pharmacogenomic analysis, we found that 2 SNPs previously linked to iloperidone response were also associated with response to risperidone.

Trial Registration: clinicaltrials.gov Identifier: NCT00337662

J Clin Psychiatry 2012;73(3):367–371

Submitted: *August 18, 2010; accepted December 21, 2010.*
Online ahead of print: *July 12, 2011 (doi:10.4088/JCP.10m06507).*
Corresponding author: *John P. Houston, MD, PhD, Lilly USA, LLC, Lilly Corporate Center, Drop Code 4133, Indianapolis, IN 46285 (Houston_John_P@Lilly.com).*

Variation in response to antipsychotic medication in patients with schizophrenia remains a significant treatment challenge. One in 3 patients will fail to show even mild improvement in response to a given antipsychotic, and 2 in 3 patients will fail to show moderate improvement.[1,2] The ability to predict response to a given medication might allow clinicians to reduce or eliminate the possibility of exposing their patients to ineffective medications and associated adverse events, which could, in turn, prevent patients and their families from becoming discouraged with treatment. In addition, the ability to predict treatment response may make it possible to reduce long-term functional outcome declination and substantial health care expenses associated with delays in remission.[3]

Pharmacogenomics markers have been successfully used to identify those patients with breast cancer who are more likely to respond to specific chemotherapeutic agents.[4,5] However, results from pharmacogenomics analyses of antipsychotic agents have been conflicting, and reliable genetic profiles have yet to be established. The earliest analyses focused on clozapine, involved small numbers of patients, or included multiple medications.[6] The recommended sample size for evaluating genetic associations is upwards of 200 patients, and in a recent review[6] of such studies, only 8% of them had an adequate sample size. Moreover, ~ 24% of these studies did not analyze differences in response due to the use of different antipsychotics.[6] These limitations may explain why results from earlier studies have not been replicated in more recent analyses of response to treatment with single antipsychotics other than clozapine.[7] Furthermore, it remains unclear whether markers examined in the prior reports are "generic" indicators of sensitivity to 1 or more classes of antipsychotic agents or whether they are uniquely associated with a single drug or class of drugs.

Lavedan et al[8] performed a genome screen of single nucleotide polymorphisms (SNPs) in patients with schizophrenia and found 6 SNPs that were associated with response to iloperidone following 4 weeks of treatment. In a follow-up analysis, Volpi et al[9] reported that response to ziprasidone was not associated with these 6 SNPs, either individually or as part of a multi-SNP model. They suggested that the 6-SNP model might represent a unique signature for response to iloperidone treatment. However, as they noted, their small sample size may have limited the likelihood of observing statistically significant associations between genotype and response to treatment.

Like iloperidone, risperidone is a benzisoxazole that lacks a tricyclic structure but has a multiple receptor binding profile like other second-generation antipsychotics. Given the similarity in structure between the 2 compounds, we hypothesized that treatment response to risperidone might be impacted by some of the same SNPs associated with response to iloperidone.

METHOD

Parent Study

The parent study (clinicaltrials.gov identifier NCT00337662)[2] used a 12-week, randomized, double-blind, flexible-dose design to assess how well early response to atypical antipsychotic treatment predicted clinical and functional outcomes at week 12 of treatment. The study enrolled 628 patients with a *DSM-IV* diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder during

© Copyright 2011 Physicians Postgraduate Press, Inc.

Clinical Points

- Six gene variants have previously been reported to be associated with iloperidone response in patients with schizophrenia.
- Two of these variants were also found to be associated with risperidone response.
- Additional analyses with other antipsychotics are needed to determine whether these variants are generalized predictors of response.

2006 and 2007. After 2 weeks of treatment with risperidone 2 to 6 mg/d, patients were identified as "early responders" or "early nonresponders" based on a 20% threshold for improvement in baseline Positive and Negative Syndrome Scale (PANSS)[10] total score. Early responders continued risperidone treatment, while early nonresponders were randomly assigned to treatment with risperidone 2 to 6 mg/d or olanzapine 10 to 20 mg/d for an additional 10 weeks. The protocol was approved by the ethical review boards at individual study sites and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All participating patients or their legal guardians provided written informed consent consistent with all regulatory requirements prior to receiving any study therapy or undergoing any study procedure. Details of the study[2] and a pharmacogenomic analysis of data not pertaining to the SNPs associated with iloperidone response have been published.[11]

Selection of SNPs and Genotyping

The 6 SNPs identified as being associated with response to iloperidone and included in this analysis were *NPAS3* rs11851892, in the neuronal period/aryl hydrocarbon receptor/single-minded (PAS) domain protein 3 gene; *XKR4* rs9643483, upstream of the XK, Kell blood group complex subunit-related family, member 4 gene; *TNR* rs875326, near the tenascin-R gene; *GFRA2* rs7837682, near the glial cell line-derived neurotropic factor α-2 receptor gene; *GRIA4* rs2513265, upstream of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 4 (AMPA 4), an ionotropic glutamate receptor; and *NUDT9P1* rs4528226, between the *NUDT9P1* pseudogene and the serotonin receptor 7 gene.[9] For each of these SNPs, Lavedan et al[8] summarized the chromosomal location, the principal gene near the SNP, the protein that the gene codes for, the function of that protein, where in the central nervous system the protein is expressed, animal models involving the gene, and relationships to the clinical entity of schizophrenia. Genotyping was performed by Cogenics (Newton, Massachusetts) using Sequenom DNA MassARRAY iPlex.[12]

Statistical Analysis

All patients included in this analysis consented to deoxyribonucleic acid (DNA) testing, had PANSS data at baseline and 1 postbaseline visit, received at least 1 dose of risperidone, and were African American or white. Because early nonresponders who were assigned to olanzapine treatment were previously treated for 2 weeks with risperidone, association analyses on these patients could potentially be difficult to interpret. Therefore, our analyses included patients who were receiving risperidone treatment only; that is, early responders and early nonresponders randomized to risperidone treatment. To account for "informative missingness" due to random allocation of half of the nonresponders to olanzapine at week 2, data from the nonresponders who were randomly allocated to risperidone were given twice the weight in this analysis. All testing was 1-sided and performed under the genetic models presented in Lavedan et al[8] (Table 1). Adjusted P values $\leq .05$ were considered significant if the direction of effect was the same as that reported by Lavedan et al.[8]

A mixed-model repeated-measures analysis with terms for baseline score, visit, genotype, and genotype by visit was used to evaluate the association between the 6 SNPs and change from baseline (week 0) to endpoint (week 12) in PANSS total, positive, and negative scores. For the primary outcome measure, change in PANSS total score, Nyholt's method[13] was used to adjust for multiple comparisons. Using this method, the effective number of SNPs for the 6 SNPs being tested was 5.6.

For SNPs that were significantly associated (adjusted $P < .05$) with change in PANSS total score, genotype frequencies and least squares mean and standard error (SE) of change in PANSS total score were examined. The analysis was performed with and without stratification by race so that results could be compared to those in Lavedan et al.[8] For each SNP that was significantly associated with response, sensitivity, specificity, positive predictive value, and negative predictive value were calculated using a last-observation-carried-forward analysis.

RESULTS

Demographic and Baseline Characteristics

Genetic testing was completed on 139 of the 628 patients (22%) enrolled in the parent study,[2] and of those 139 patients, 31 (22%) were identified as early responders to risperidone at week 2 of treatment. The remaining 108 patients were randomly allocated to further treatment with risperidone (n = 57) or olanzapine (n = 51). As mentioned above, olanzapine patients were not included in this analysis. Early nonresponders who were randomized to risperidone were given twice the weight in the analysis to account for the informative missingness due to random allocation of half of the nonresponders to olanzapine at week 2; hence, the sample size for this genetic analysis was 145. The mean (standard deviation [SD]) age of patients included in the pharmacogenomic analysis was 43.3 (10.6) years. The ratio of African American to white patients was 3:2 (60% and 40%, respectively). The mean (SD) PANSS total, positive, and negative scores at baseline were 89.0 (11.4), 23.3(3.5), and 21.5 (4.8), respectively, indicating moderate to marked symptom severity at baseline.[14]

Table 1. Genetic Models Taken From Lavedan et al[8] Under Which SNPs Were Tested

Gene and SNP	Good Responders, Genotype	Poor Responders, Genotype
PAS3 rs11851892	A/A + A/G	G/G
XKR4 rs9643483	G/T + T/T	G/G
TNR rs875326	A/A + G/G	A/G
GRIA4 rs2513265	A/A + A/T	T/T
GFRA2 rs7837682	T/C + C/C	T/T
NUDT9P1 rs4528226	G/T + T/T	G/G

Abbreviation: SNP = single nucleotide polymorphism.

Table 2. *P* Values for the Associations Between the 6 SNPs in the Iloperidone Response Model and Change in PANSS Total Score in Response to Treatment With Risperidone

Gene and SNP	PANSS Total, *P* Value		PANSS Positive, *P* Value	PANSS Negative, *P* Value
	Adjusted[a]	Unadjusted		
NPAS3 rs11851892	> .99	.20	.42	.38
XKR4 rs9643483	.022	.004	.006	.005
TNR rs875326	> .99	.32	.21	.02
GRIA4 rs2513265	.006	.001	.01	.05
GFRA2 rs7837682	> .99	.50	.002	.33
NUDT9P1 rs4528226	> .99	.33	.37	.31

[a]Adjusted for multiple comparisons using Nyholt's method.[13]
Abbreviations: PANSS = Positive and Negative Syndrome Scale, SNP = single nucleotide polymorphism.

Study completion rates, mean PANSS total scores at week 2, and mean PANSS total scores at week 12 are provided in eTables 1, 2, and 3, respectively, with results stratified by race, response status at week 2, and genotype.

Genetic Associations

Unadjusted *P* values for the associations between SNPs and change in PANSS total, positive, and negative scores in response to risperidone are shown in Table 2. The SNPs *XKR4* rs9643483 and *GRIA4* rs2513265 were significantly associated with improvement in PANSS total ($P = .004$ and $P = .001$, respectively), positive ($P = .006$ and $P = .01$, respectively), and negative scores ($P = .005$ and $P = .05$, respectively). Even after adjustment for multiple comparisons, both *XKR4* rs9643483 and *GRIA4* rs2513265 remained significantly associated with change in PANSS total score.

Genotype frequency and least squares mean change in PANSS total score following up to 12 weeks of risperidone treatment are shown in Table 3 (SNPs significantly associated with response) and eTable 4 (SNPs not significantly associated with response). Results are presented both before and after stratification by race. The direction of effect was the same as that previously reported for iloperidone[8] for *XKR4* rs9643483 and *GRIA4* rs2513265. For *XKR4* rs9643483, patients without the G/G genotype improved more than those with the G/G genotype (−21.2 vs −15.1, $P = .004$), and for *GRIA4* rs2513265, patients without the T/T genotype improved more than those with the T/T genotype (−20.9 vs −17.2, $P = .001$). In contrast, for *GRIA4* rs2513265, the frequency of responsive and nonresponsive genotypes did not differ significantly by race ($P = .73$).

Predictive Characteristics

Table 4 shows the sensitivity, specificity, positive predictive values, and negative predictive values for the 2 SNPs from the iloperidone signature that were associated with response in patients treated with risperidone. Positive and negative predictive values were 52% and 56%, respectively, for *XKR4* rs9643483, and were 57% and 62%, respectively, for *GRIA4* rs2513265.

DISCUSSION

In this pharmacogenomic analysis of 6 SNPs previously identified as being associated with response to iloperidone, we report significant associations with the same direction of effect for 2 SNPs, *XKR4* rs9643483 and *GRIA4* rs2513265, with response to risperidone as measured by change in PANSS total score. Although the direction of effect seen with *XKR4* rs9643483 and *GRIA4* rs2513265 was the same as reported by Lavedan et al,[8] we observed a smaller difference in response between patients with responder and nonresponder genotypes. For example, for SNP *XKR4* rs9643483, mean changes in PANSS total score for patients with responder (G/T and T/T) and nonresponder (G/G) genotypes, respectively, were −21.2 and −15.1 in the current study, and −15.0 and −3.3 in the Lavedan et al[8] study. For *GRIA4* rs2513265, mean changes in PANSS total score for patients with responder (A/A and A/T) and nonresponder (T/T) genotypes, respectively, were −20.9 and −17.2 in the present study, and −15.2 and −3.3 in the Lavedan et al[8] study. These differences in magnitude may reflect the difference in study design, patient characteristics, baseline illness level, or genotype frequencies. For example, the Lavedan et al[8] study examined response at week 4, and this analysis examined response at week 12. Leveraging data from additional time points may have increased the power to detect SNPs that had a smaller impact. It may also indicate different receptor binding profiles or the chemical and metabolic characteristics of the drugs. Alternatively, this may be an example of "winner's curse," which is a form of bias in genome-wide association analyses, and an effect in which the initial discovery provides more impressive results than are seen in subsequent studies.[15–18]

For *GRIA4* rs2513265, there appeared to be a difference in the magnitude of genetic effect between African American and white patients. This disparity could have been due to differences in allele frequency between racial cohorts or in the impact of the SNP between cohorts, reflecting genetic background and/or nongenetic factors. In our sample, the distribution of responsive and nonresponsive alleles was similar between the races, thus favoring the latter explanation.

The predictive characteristics reported for SNPs *XKR4* rs9643483 and *GRIA4* rs2513265 in iloperidone-treated patients were only slightly better than those observed for risperidone-treated patients in this study. Lavedan et al[8] reported positive and negative predictive values of 54% and 74%, respectively, for *XKR4* rs9643483 and 52% and 69%, respectively, for *GRIA4* rs2513265. In the current analysis, the positive predictive values for response to risperidone

Table 3. Change in PANSS Total Score From Baseline to End Point, Genotype Frequencies, and *P* Values for the Difference in Improvement Between Responder and Nonresponder Genotypes for SNPs That Were Significantly Associated With Improvement in Patients Treated With Risperidone

Gene and SNP	n	PANSS Total Score, LS Mean Change (SE)	Patients With Genotype, %	PANSS Total Score, LS Mean Change (SE)	Patients With Genotype, %	PANSS Total Score, LS Mean Change (SE)	Patients With Genotype, %	PANSS Total Score, LS Mean Change (SE)	Patients With Genotype, %	*P* Value
		T/T Genotype		G/T Genotype		G/G Genotype		T/T + G/T Genotype		
XKR4 rs9643483										
All	145	−20.7 (2.1)	36.6	−21.7 (2.1)	36.6	−15.1 (2.5)	26.9	−21.2 (1.5)	73.1	.004
African American	87	−16.2 (3.4)	19.5	−21.3 (2.2)	43.7	−13.9 (2.3)	36.8	−19.7 (1.8)	63.2	.07
White	58	−23.6 (3.0)	62.1	−18.3 (4.9)	25.9	−21.4 (10.0)	12.1	−22.5 (2.4)	87.9	.01
		A/A Genotype		A/T Genotype		T/T Genotype		A/A + A/T Genotype		
GRIA4 rs2513265										
All	145	−20.4 (2.9)	18.6	−21.1 (1.9)	44.8	−17.2 (2.3)	36.6	−20.9 (1.6)	63.5	.001
African American	87	−19.6 (2.9)	20.7	−21.2 (2.3)	41.4	−12.5 (2.4)	37.9	−20.7 (1.8)	62.1	< .001
White	58	−21.4 (6.4)	15.5	−22.2 (3.3)	50.0	−20.9 (4.5)	34.5	−22.2 (2.9)	65.5	.24

Abbreviations: LS = least squares, n = total number in cohort, PANSS = Positive and Negative Syndrome Scale, SE = standard error, SNP = single nucleotide polymorphism.

Table 4. Predictive Characteristics of SNPs Previously Identified as Associated With Response to Iloperidone That Were Also Associated With Response to Risperidone, as Measured by Change in PANSS Total Score

Gene and SNP	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
XKR4 rs9643483	76	30	52	56
GRIA4 rs2513265	72	45	57	62

Abbreviations: PANSS = Positive and Negative Syndrome Scale, SNP = single nucleotide polymorphism.

treatment were very similar (differing by ~5%), while the negative predictive values were inferior by 7%–18%. These results suggest that both of these SNPs are associated with response to iloperidone and risperidone treatment, but their clinical value to the individual patient may be limited.

The limited number of matching SNPs may have been due to the large number (over 300,000) of SNPs analyzed by Lavedan et al,[8] which increased the likelihood of identifying false-positives. Alternatively, the limited number of matches could reflect differences in receptor binding profiles or chemical and metabolic characteristics of the drugs, or differences between study populations. Also, the current analysis was most likely underpowered for capturing associations with all 6 SNPs. Even if all 6 SNPs truly impacted response to risperidone and the power of identifying each individual SNP was as high as 90%, the probability of identifying all of them simultaneously would have been only 53%. For SNPs where no association with response to risperidone was identified, however, a true difference in genetic susceptibility may exist between treatments, and that difference might prove clinically useful. Further genetic analyses involving larger samples of patients treated with other atypical antipsychotics are needed to clarify whether SNPs in the iloperidone signature are associated with a more generalized response to atypical antipsychotics.

This analysis had several potential methodological limitations. First, because half of the early nonresponders were randomly allocated to receive further treatment with olanzapine, data for the nonresponders allocated to risperidone were doubly weighted to account for informative missingness. To assess the sensitivity of this approach, we repeated the analysis without weighing for missing risperidone data, and the results were similar. Another potential limitation was that summary statistics for predicting response were based on change in symptom scores at differing time points: 12 weeks for our study and 4 weeks for the Lavedan et al[8] study. Still, we considered such comparisons meaningful because early response and nonresponse have been shown to be strongly predictive of later response, with the majority of improvement occurring by week 4 of treatment.[1,19,20] However, the threshold chosen to define early response and the timing of that assessment did not take into account those patients with a < 20% symptom improvement who may have demonstrated greater responsiveness at a later time point. In our sample, only 22% of patients were identified as early responders. Finally, our study sample included a mix of patients with schizophrenia and schizoaffective disorder, and this approach does not take into consideration phenotypic or underlying genotypic differences that might influence response patterns. Unfortunately, our sample size was too small to permit meaningful analyses following stratification by illness, and even within the same diagnosis, important phenotypic differences may contribute to heterogeneity of response.

Additionally, the lack of association seen between 4 of the SNPs and risperidone response seen here may be false-negatives. This was primarily an exploratory analysis with respect to risperidone response, with limited power due to its small sample size. Consequently, statistical significance of the primary end points was calculated with and without adjustment for multiple comparisons. Finally, it was not clear whether the magnitude of genotypic impact for risperidone would be as great as that seen for iloperidone treatment.[8] For example, if the magnitude of the difference between *NPAS3* rs11851892 good and poor responder genotypes was similar to that seen in Lavedan et al[8]— that is, a difference of 10.9 PANSS total score points—then the power to detect that difference would have been 89%. However, if the PANSS total score difference between good and poor responder genotypes

was 6 points, the power to detect a difference would have been less than 50%. Nevertheless, the *P* values for genetic association between response to risperidone and both *GRIA4* rs2513265 and *XKR4* rs9643483 were sufficiently low to survive multiple testing correction for the 6 SNPs tested in this analysis.

In their pharmacogenomic analysis of response to iloperidone and ziprasidone treatment, Volpi et al[9] proposed a multi-SNP model utilizing the 6 SNPs examined here. They defined 4 patient groups based on the number of genotypes that were associated with enhanced response and found that the likelihood of response to iloperidone increased stepwise from 10.2% to 81.5% as the number of responsive genotypes increased. We explored several multi-SNP models for response to risperidone treatment, with unimpressive results, likely due to having only 2 associated SNPs on which to build the model. Genetic models that reliably predict response to atypical antipsychotics will most likely include numerous SNPs that individually provide little predictive power but, when considered together, account for a substantial portion of variation in response. Identifying all of the relevant SNPs and creating and validating multi-SNP models will require much larger datasets than are usually available in individual trials of patients with schizophrenia.

In this retrospective pharmacogenomic analysis, we found that 2 of the 6 SNPs previously associated with iloperidone response[8] were also associated with response to risperidone, as measured by change in PANSS total score. These data combined with those from other, similar analyses may help to identify patients for whom iloperidone and risperidone may be appropriate treatments. Similar studies using other atypical antipsychotics to determine the degree to which 1 or more of these SNPs serve as generalized indicators of antipsychotic responsiveness are needed.

Drug names: clozapine (Clozaril, FazaClo, and others), iloperidone (Fanapt), olanzapine (Zyprexa), risperidone (Risperdal and others), ziprasidone (Geodon).

Author affiliations: Lilly USA, Indianapolis (Drs Fijal, Conley, Hoffmann, Witte, Zhao, and Houston); Eli Lilly and Company, Indianapolis (Drs Stauffer and Kinon); and Department of Psychiatry, Indiana University School of Medicine, Indianapolis (Dr Houston).

Potential conflicts of interest: **Drs Fijal, Conley, Hoffmann, Witte**, and **Zhao** receive compensation as employees of Lilly USA and are stockholders of Eli Lilly. **Drs Kinon** and **Stauffer** receive compensation as employees and are stockholders of Eli Lilly. **Dr Houston** is an employee of and has received grant/research support from Lilly USA and is a stock shareholder in Eli Lilly.

Funding/support: Funding for this study was provided by Eli Lilly and/or one of its subsidiaries.

Role of sponsor: Employees of Eli Lilly were responsible for study design; for the collection, analysis, and interpretation of data; for contracting the writing and editorial support; and for decisions regarding submission of the paper for publication.

Acknowledgments: Appreciation is expressed to Jennie Jacobson, PhD, and Tamara Ball, MD, for writing and editorial support. Dr Jacobson is an employee of Lilly USA. Dr Ball is a scientific writer employed by i3 Statprobe, a division of Ingenix, which is a subsidiary of United Health Group. Eli Lilly contracted the technical writing of this article with i3 Statprobe. Dr Jacobson is a stockholder in Eli Lilly, and Dr Ball has no additional conflicts of interest to report.

Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. Kinon BJ, Chen L, Ascher-Svanum H, et al. Predicting response to atypical antipsychotics based on early response in the treatment of schizophrenia. *Schizophr Res*. 2008;102(1–3):230–240.
2. Kinon BJ, Chen L, Ascher-Svanum H, et al. Early response to antipsychotic drug therapy as a clinical marker of subsequent response in the treatment of schizophrenia. *Neuropsychopharmacology*. 2010;35(2):581–590.
3. Ascher-Svanum H, Nyhuis AW, Faries DE, et al. Clinical, functional, and economic ramifications of early nonresponse to antipsychotics in the naturalistic treatment of schizophrenia. *Schizophr Bull*. 2008;34(6):1163–1171.
4. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783–792.
5. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2002;20(3):719–726.
6. Arranz MJ, de Leon J. Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. *Mol Psychiatry*. 2007;12(8):707–747.
7. Steimer W. Pharmacogenetics and psychoactive drug therapy: ready for the patient? *Ther Drug Monit*. 2010;32(4):381–386.
8. 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*. 2009;14(8):804–819.
9. Volpi S, Potkin SG, Malhotra AK, et al. Applicability of a genetic signature for enhanced iloperidone efficacy in the treatment of schizophrenia. *J Clin Psychiatry*. 2009;70(6):801–809.
10. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
11. Fijal BA, Kinon BJ, Kapur S, et al. Candidate-gene association analysis of response to risperidone in African-American and white patients with schizophrenia. *Pharmacogenomics J*. 2009;9(5):311–318.
12. Jurinke C, van den Boom D, Cantor CR, et al. Automated genotyping using the DNA MassArray technology. *Methods Mol Biol*. 2002;187:179–192.
13. Nyholt DR. A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. *Am J Hum Genet*. 2004;74(4):765–769.
14. Leucht S, Kane JM, Kissling W, et al. What does the PANSS mean? *Schizophr Res*. 2005;79(2–3):231–238.
15. Ioannidis J, Lau J. Evolution of treatment effects over time: empirical insight from recursive cumulative metaanalyses. *Proc Natl Acad Sci U S A*. 2001;98(3):831–836.
16. Ioannidis JP, Trikalinos TA, Ntzani EE, et al. Genetic associations in large versus small studies: an empirical assessment. *Lancet*. 2003;361(9357):567–571.
17. Ioannidis JP. Why most published research findings are false. *PLoS Med*. 2005;2(8):e124.
18. Ioannidis JP, Ntzani EE, Trikalinos TA, et al. Replication validity of genetic association studies. *Nat Genet*. 2001;29(3):306–309.
19. May PR, Van Putten T, Yale C. Predicting outcome of antipsychotic drug treatment from early response. *Am J Psychiatry*. 1980;137(9):1088–1089.
20. Leucht S, Busch R, Kissling W, et al. Early prediction of antipsychotic nonresponse among patients with schizophrenia. *J Clin Psychiatry*. 2007;68(3):352–360.

See supplementary material for this article at PSYCHIATRIST.COM.

THE JOURNAL OF CLINICAL PSYCHIATRY

Supplementary Material

Article Title: Analysis of Gene Variants Previously Associated With Iloperidone Response in Patients With Schizophrenia Who Are Treated With Risperidone

Author(s): Bonnie A. Fijal, PhD; Virginia L. Stauffer, PharmD; Bruce J. Kinon, MD; Robert R. Conley, MD; Vicki Poole Hoffmann, PhD; Michael M. Witte, PhD; Fangyi Zhao, PhD; and John P. Houston, MD, PhD

DOI Number: 10.4088/JCP.10m06507

List of Supplementary Material for the article

1. eTable 1 — Study Completion Rates for Risperidone-treated Patients Stratified by Race, Response Status at Week 2, and Genotype
2. eTable 2 — LS Mean PANSS Total Scores at Week 2 for Risperidone-treated Patients Stratified by Race, Response Status at Week 2, and Genotype
3. eTable 3 — LS Mean PANSS Total Scores at Week 12 for Risperidone-treated Patients Stratified by Race, Response Status at Week 2, and Genotype
4. eTable 4 — Change in PANSS Total Score From Baseline to Endpoint, Genotype Frequencies, and p Values for the Difference in Improvement Between Responder and Non-responder Genotypes For SNPs That Were Not Significantly Associated with Improvement in Patients Treated With Risperidone

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eTable 1. Study Completion Rates for Risperidone-treated Patients Stratified by Race, Response Status at Week 2, and Genotype

Characteristic	Completion Rate (%)
	N=145
Race	
African American	65.5 (57/87)
White	69.0 (40/58)
Response status at week 2	
Early responder	48.4 (15/31)
Early non-responder	71.9 (82/114)
Genotype	
NPAS3 rs11851892	
C/C	64.8 (68/105)
C/T	77.1 (27/35)
T/T	40.0 (2/5)
XKR4 rs9643483	
G/G	63.9 (23/36)
G/T	75.4 (43/57)

T/T	59.6 (31/52)
TNR rs875326	
C/C	73.6 (53/72)
C/T	53.6 (30/56)
T/T	82.4 (14/17)
GRIA4 rs2513265	
A/A	62.5 (20/32)
A/T	69.6 (48/69)
T/T	65.9 (29/44)
GFRA2 rs7837682	
C/C	72.7 (8/11)
C/T	64.4 (29/45)
T/T	67.4 (60/89)
NUDT9P1 rs4528226	
G/G	61.8 (21/34)
G/T	73.3 (55/75)
T/T	58.3 (21/36)

eTable 2. LS Mean PANSS Total Scores at Week 2 for Risperidone-treated Patients Stratified by Race, Response Status at Week 2, and Genotype

	PANSS Total Score LS Mean (SD)
Characteristic	**N=145**
Race	
African American	76.2 (11.9)
White	79.0 (14.6)
Response status at Week 2	
Early responder	65.7 (13.8)
Early non-responder	80.5 (10.9)
Genotype	
NPAS3 rs11851892	
C/C	74.8 (13.1)
C/T	76.3 (16.0)
T/T	76.3 (20.3)
XKR4 RS9643483	
G/G	71.8 (12.9)
G/T	76.8 (14.7)

T/T	76.1 (13.7)
TNR RS875326	
C/C	74.7 (16.6)
C/T	76.3 (11.0)
T/T	74.0 (12.7)
GRIA4 rs2513265	
A/A	76.1 (11.0)
A/T	75.4 (15.6)
T/T	74.3 (13.5)
GFRA2 rs7837682	
C/C	86.2 (12.4)
C/T	72.8 (13.1)
T/T	75.3 (14.2)
NUDT9P1 rs4528226	
G/G	78.64 (14.1)
G/T	73.11 (14.4)
T/T	76.63 (12.0)

Abbreviations: LS=least squares; SD=standard deviation

eTable 3. LS Mean PANSS Total Scores at Week 12 for Risperidone-treated Patients Stratified by Race, Response Status at Week 2, and Genotype

Characteristic	PANSS Total Score LS Mean (SD) N=98
Race	
African American	67.7 (11.2)
White	69.3 (16.2)
Response Status at week 2	
Early responder	58.7 (14.4)
Early non-responder	70.2 (12.5)
Genotype	
NPAS3 rs11851892	
C/C	68.5 (14.5)
C/T	64.9 (11.9)
T/T	54.5 (20.5)
XKR4 rs9643483	
G/G	60.4 (13.1)
G/T	70.2 (12.9)

T/T	67.9 (15.1)
TNR rs875326	
C/C	69.5 (16.1)
C/T	64.7 (9.6)
T/T	65.9 (18.7)
GRIA4 rs2513265	
A/A	68.6 (17.4)
A/T	64.8 (12.1)
T/T	68.7 (14.6)
GFRA2 rs7837682	
C/C	69.0 (5.7)
C/T	67.6 (16.2)
T/T	65.1 (6.8)
NUDT9P1 rs4528226	
G/G	70.8 (18.4)
G/T	65.8 (10.6)
T/T	64.6 (14.2)

Abbreviations: LS=least squares; SD=standard deviation

eTable 4. Change in PANSS Total Score From Baseline to Endpoint, Genotype Frequencies, and *p* Values for the Difference in Improvement Between Responder and Non-responder Genotypes For SNPs That Were Not Significantly Associated with Improvement in Patients Treated With Risperidone.

Gene and SNP		**LS Mean Change (SE) in PANSS Total and**				
Race/Ethnicity	**n**	**Percent of Patients with Each Genotype**				***p* value**
NPAS3 rs11851892		A/A	A/G	G/G	Non-G/G	
All	145	–15.1 (6.1) 3.5%	–23.2 (2.4) 29.7%	–18.2 (1.6) 66.9%	–22.1 (2.2) 33.1%	.20
African American	87	–11.0 (6.1) 4.6%	–18.9 (2.8) 29.9%	–17.3 (1.8) 65.5%	–17.8 (2.6) 34.5%	.37
White	58	–24.7 (16.9) 1.7%	–27.4 (4.3) 29.3%	–17.7 (3.2) 69.0%	–27.2 (4.1) 31.0%	.23
TNR rs875326		A/A	A/G	G/G	Non-A/G	

All	139	–20.2 (2.9) 18.7%	–21.3 (2.2) 33.8%	–19.1 (2.1) 47.5%	–19.2 (1.7) 66.2%	.32
African American	83	–17.2 (2.7) 26.5%	–18.5 (2.0) 44.6%	–18.9 (3.3) 28.9%	–17.1 (2.1) 55.4%	.45
White	56	–24.1 (7.8) 7.1%	–33.4 (6.0) 17.9%	–21.9 (2.8) 75.0%	–21.8 (2.6) 82.1%	.07
GFRA2 rs7837682		G/G	A/G	A/A	Non-A/A	
All	143	–22.1 (5.5) 5.6%	–17.3 (2.1) 37.1%	–20.8 (1.7) 57.3%	–17.9 (2.0) 42.7%	.50
African American	85	–13.5 (5.9) 7.1%	–16.4 (2.1) 45.9%	–19.9 (2.2) 47.1%	–15.7 (2.0) 52.9%	.41
White	58	–44.5 (11.3) 3.5%	–16.9 (5.1) 24.1%	–22.0 (2.8) 72.4%	–21.1 (4.7) 27.6%	.24
NUDT9P1 rs4528226		G/G	G/T	T/T	Non-G/T	

All	145	–23.0 (2.7) 21.4%	–15.7 (1.9) 46.2%	–22.0 (2.2) 32.4%	–22.4 (1.7) 53.8%	.33
African American	87	–19.7 (5.3) 6.9%	–14.2 (2.2) 46.0%	–20.0 (2.1) 47.1%	–20.0 (1.9) 54.0%	.36
White	58	–25.2 (3.5) 43.1%	–17.5 (3.2) 46.6%	–35.0 (7.1) 10.3%	–27.0 (3.2) 53.4%	.27

Abbreviations: LS=least squares; PANSS=Positive and Negative Syndrome Scale; SE=standard error; SNP=single nucleotide polymorphism.