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Glucagon-like Peptide 1 Receptor (GLP1R) Genetic Variants Impact Response to Olanzapine and Risperidone in Multiple Cohorts Across Two Independent Studies

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Abstract

Background: Pharmacogenetic markers of antipsychotic response have the potential to reduce trial and error prescribing, leading to better outcomes. GLP1R genetic variation has previously shown PGx potential. This study was intended to identify testable GLP1R PGx markers and replicate their impact across multiple cohorts and studies.

Methods and Findings: This study assigned haplotypes and biomarker status to subjects treated with olanzapine (n=172) or risperidone (n=181) in two independent cohorts of the Clinical Trials of Antipsychotic Intervention Effectiveness (CATIE) and an additional independent clinical study of schizophrenia and bipolar disorder at Vanderbilt University (ID NCT00179062). In each cohort subjects were assigned biomarker positive or negative status GLP1R Antipsychotic Response Predictor (GARP 1 and 3 respectively) and evaluated for change in Positive and Negative Syndrome Scale from baseline. GARP 1 status predicted greater symptom reduction in olanzapine-treated subjects in both CATIE cohorts (p=0.007 and 0.02, combined p=0.0004) and Vanderbilt (p=0.03). GARP 3 status predicted poorer symptom reduction in risperidone-treated subjects in the combined CATIE cohort (p=0.01) and Vanderbilt (p=0.01).

Conclusions: In this study, we refined previous results that identified two PGx markers (GARP 1 and GARP 3) that predicted response to olanzapine and risperidone in the CATIE trial. We then replicated these findings in an independent clinical trial PGx. These PGx markers offer physicians a potential tool for more effective antipsychotic selection.

Part of this unmet need could be ameliorated by predictive markers of efficacy. Pharmacogenetics (PGx) offers the potential to develop better treatment algorithms and to enhance outcomes. However, to date only one PGx marker of antipsychotic efficacy has been replicated across multiple studies/cohorts [1,2]. Additional replicated markers would enhance treatment further.

Previously, we published data showing that genetic variation in the glucagon-like peptide 1 receptor gene (*GLP1R*) impacted response to several antipsychotics, including olanzapine and risperidone in the blinded phases of the Clinical Trials of Antipsychotic Intervention Effectiveness (CATIE) study [3]. These differences correlated with variation in a haplotype block that contained two coding SNPs: rs6923761 (Gly168) and rs1042044 (Leu260). Each of these coding variants tagged a specific haplotype and has been shown *in vitro* to have alterations in expression and/or function compared to wild-type [4].

GLP1R represents an intriguing PGx target for antipsychotics. Not only does GLP1R signaling have a tremendous impact on weight gain (one of the key limiting side-effects of atypical antipsychotics) but it also influences the hypothalamic-pituitary-adrenal axis (HPA) activation, stress and anxiety-related behaviours [5,6]. GLP1R also has significant effect on dopaminergic neurotransmission, a key target of antipsychotic drug action [7]. Drugs that target GLP1R can lead to decreased appetite and weight loss [8,9]. Furthermore, data from animal studies suggest that GLP1R agonists may have antipsychotic or antipsychotic-like effects, with one study showing antipsychotic effect comparable to haloperidol [10].

Additionally, the two drugs studied herein, olanzapine and risperidone, have been approved to treat multiple diagnoses and are used broadly off-label for many additional psychiatric conditions. Olanzapine is approved in the United States for the treatment of schizophrenia, bipolar disorder, and treatment-resistant depression. It is also used off-label to treat anxiety disorders, post-traumatic distress disorder, dementia, and many other behavioural disorders. Risperidone is approved in the United States for the treatment of schizophrenia, bipolar disorder, and autism. It is also used off-label to treat anxiety

Keywords: LP1R; Pharmacogenetics; Antipsychotic; Olanzapine; Risperidone; Sure gene

Introduction

Despite numerous antipsychotics on the market, achieving symptom control in serious mental illness remains challenging.

disorders, post-traumatic distress disorder, Tourette's syndrome, and many other behavioural disorders.

For the present study, we had three goals. First, we converted the haplotype assessment of GLP1R antipsychotic effect into a diagnostic marker structure more suitable for PGx testing. Next, we report the impact of the new definition of diagnostic markers on olanzapine and risperidone response in the blinded phases of the CATIE study. Finally, we determined if the GLP1R effect observed in CATIE can be replicated in a prospective analysis of an independent clinical trial.

Methods

Clinical samples

CATIE sample: The design of the CATIE study has been described in detail elsewhere [10,11], and we have previously described our use of those subjects in this analysis in detail [1-3]. Briefly, we evaluated subjects treated with olanzapine (n=139) and risperidone (n=143) in Phase 1, Phase 1B and 2, and all blinded phases combined (1,1B, and 2).

Vanderbilt sample: We have described the Vanderbilt sample previously [1]. For this study, we evaluated 33 olanzapine-treated and 38 risperidone-treated subjects who provided consented DNA, from a double-blind, 6 month safety and efficacy study conducted at Vanderbilt University. This study included subjects with diagnosis of either bipolar disorder or schizophrenia.

Genetic model analysis

We previously described the identification and classification of the four GLP1R haplotypes, which were assigned names haplotype 1 through 4 based on descending frequency [3]. We used EM algorithm to assign diplotypes to each subject. Based on previous results, we assigned an overall phenotype response marker status label called Glucagon-like peptide 1 receptor Antipsychotic Response Predictor (GARP) 1 through 4 as described in the results section. Each drug evaluated had one phenotype of interest that created a binary analysis of the impact of the presence or absence of that marker on antipsychotic response.

Table 1: Conversion of GLP1R diplotypes to GARP status; ¹Haplotype assignment based on EM algorithm, ²Biomarker assignment based on rationale described in text.

rs6923761	rs2300615	rs1042044	HAPLOTYPES A ¹	HAPLOTYPES B ¹	Response Marker ²
G-G	T-T	A-A	GLP1R-1	GLP1R-1	GARP 1
A-G	T-T	A-C	GLP1R-1	GLP1R-2	GARP 2
G-G	G-T	A-C	GLP1R-1	GLP1R-3	GARP 3
G-G	T-T	A-C	GLP1R-1	GLP1R-4	GARP 4
A-A	T-T	C-C	GLP1R-2	GLP1R-2	GARP 2
A-G	G-T	C-C	GLP1R-2	GLP1R-3	GARP 2
A-G	T-T	C-C	GLP1R-2	GLP1R-4	GARP 2

Definition and evaluation of response

For both CATIE and Vanderbilt samples, we used the primary efficacy endpoint defined by the studies, change in Positive and Negative Syndrome Scale (PANSS) from baseline to last observation, labelled as Last Observation Carry Forward (LOCF). For olanzapine, we analysed the difference in LOCF PANSS between subjects that had the *GARP 1* genetic marker and those that lacked the marker using the standard T-test to evaluate the null-hypothesis that the two groups had equivalent response. Similarly, we evaluated the impact of *GARP 3* status on risperidone response using the T-test for the null hypothesis that LOCF PANSS scores were the same in positive and negative subjects. For each arm evaluated, we report p-values and effect size (Hedge's G).

Results

Categorizing GLP1R haplotypes into functional categories

Table 1 lists the ten possible permutations of the four primary GLP1R haplotypes. The numerical order of the GLP1R haplotypes is based on descending order of frequency as described previously [3]. The haplotype regression and genetic model analysis from our prior work suggested genetic models wherein response was linked to coding variants with observed impact on expression and activity. Specifically, a model that described subjects using a recessive model for rs1042044 (Leu260) and a dominant model for rs6923761 (Gly168) provides the most consistent and broad conversion of haplotypes to a unified genetic model suited for a genetic testing environment. Both of these models are consistent with literature reports of *in vivo* impact on human phenotypes of morning cortisol (Leu260) and glycemic response to gliptins (Gly168) [11,12]. In Table 1, these genetic models are consolidated to produce a 4-state marker for GLP1R Antipsychotic Response Predictor (GARP) 1 through 4. Of particular relevance for this study are GARP 1 and GARP 3. GARP 1 is defined as subjects homozygous for rs1042044 (Leu260). GARP 3 is defined as subjects who possess at least one copy of the GLP1R-3 haplotype, no copies rs6923761 (Gly168), and no more than one copy of rs1042044 (Leu260).

G-G	G-G	C-C	GLP1R-3	GLP1R-3	GARP 3
G-G	G-T	C-C	GLP1R-3	GLP1R-4	GARP 3
G-G	T-T	C-C	GLP1R-4	GLP1R-4	GARP 4

Impact of GARP status on olanzapine and risperidone response in CATIE with replication in an independent study

Olanzapine: As shown in Table 2, olanzapine-treated CATIE subjects with GARP 1 positive status, i.e. subjects homozygous for rs1042044 (Leu260), displayed significantly superior response than those subjects that were GARP 1 negative in both Phase 1 ($p=0.007$, effect size=0.65) and the Phase 1B plus 2 groups ($p=0.02$, effect size=0.85). As no overlaps existed between these groups, they can be considered independent cohorts, albeit from the same overall study. When combined into a single CATIE analysis, the impact of GARP 1 status on olanzapine response was highly significant ($p=0.0004$, effect size=-0.71). Based on the CATIE findings, we designed a prospective analysis of an additional clinical trial conducted at

Vanderbilt. In that analysis, we replicated the GARP 1 impact on olanzapine response ($p=0.03$, effect size=0.89). In the Vanderbilt sample, diagnosis did not alter the impact of GARP 1.

Risperidone: As shown in Table 2, risperidone-treated CATIE subjects with GARP 3 positive status displayed a trend for worse response than those subjects that were GARP 3 negative in both Phase 1 ($p=0.11$, effect size=0.43) and the Phase 1B plus 2 groups ($p=0.08$, effect size=0.71). When combined into a single CATIE analysis, the impact of GARP 3 status on risperidone response was significant ($p=0.03$, effect size=0.52).

Based on the CATIE findings, we designed a prospective analysis of an additional clinical trial conducted at Vanderbilt. In that analysis, we replicated the GARP 3 impact on risperidone response ($p=0.01$, effect size 1.06). In the Vanderbilt sample, diagnosis did not alter the impact of GARP 1.

Table 2: GARP status predicts response to olanzapine (GARP 1) and risperidone (GARP 3) as defined as change in PANSS at LOCF; ¹Positive status indicates that the subject was classified as GARP 1 (olanzapine cohorts) or GARP 3 (risperidone cohorts) and negative otherwise, ²Mean difference in baseline and LOCF PANSS scores; negative value indicates decrease in symptoms at LOCF and improvement, ³Standard deviation of the mean, ⁴Significance of the differences of the means of biomarker positive and biomarker negative groups using the T-test, ⁵Hedges G negative value represents greater symptom reduction in biomarker positive subjects and positive values represent greater symptom reduction in biomarker negative subjects, ⁶Phase 1 and Phase 2 of CATIE are independent cohorts within CATIE that do not have overlapping membership, ⁷CATIE combined includes all CATIE subjects treated with a given drug in the blinded phases of CATIE.

		Biomarker Positive ¹			Biomarker Negative ¹				
Olanzapine GARP 1		n	Mean ²	SD ³	n	Mean ²	SD ³	P-value ⁴	Effect Size ⁵
CATIE	Phase 1 ⁶	22	-17.9	16	66	-6.9	16.3	0.007	-0.65
CATIE	Phase 2 ⁶	9	-21.6	25.3	42	-7.8	12.9	0.02	-0.85
CATIE	Combined ⁷	31	-19	18.8	108	-7.2	15	0.0004	-0.71
Vanderbilt		7	-25.1	10.1	26	-12.5	14.1	0.03	-0.89
Risperidone GARP 3		n	Mean	SD	n	Mean	SD	P-value	Effect Size
CATIE	Phase 1 ⁶	18	1.3	19.7	79	-6.8	18.3	0.11	0.43
CATIE	Phase 2 ⁶	7	8.4	36.5	39	-7.3	17.9	0.08	0.71
CATIE	Combined ⁷	25	3.3	24.9	118	-7	18.1	0.01	0.52
Vanderbilt		7	-1.1	15.5	31	-16.5	13	0.01	1.06

Discussion

Given the current limitations of antipsychotic treatment and relatively poor likelihood of treatment success, valid biomarkers of antipsychotic response would provide meaningful benefit to patients, providers, caregivers, and payers. We previously identified GLP1R as such a potential biomarker. In addition to the those prior genetic findings, GLP1R is not only a central player in the primary atypical antipsychotic side effects of weight gain and metabolic syndrome but also has evidence of

being an antipsychotic drug target in animal models of psychosis. Therefore, replication of previous findings in an independent clinical trial would provide compelling evidence for a new pharmacogenetic marker of antipsychotic efficacy.

GARP 1 positive status, which may include enhanced calcium signalling capability, predicted superior response to olanzapine across three independent cohorts in two studies. The effect size observed in these three cohorts had a consistently larger magnitude (-0.65 to -0.89) than that observed when comparing

olanzapine treatment to placebo (-0.59) [13-16]. In other words, the difference in reduction in psychopathology between olanzapine-treated subjects with the GARP 1 marker and those without the marker was greater than the difference between olanzapine versus placebo.

Risperidone-treated subjects with the GARP 3 marker displayed less improvement in PANSS scores than those subjects without GARP 3 across three independent cohorts in two studies. In the individual CATIE cohorts, the impact of GARP 3 status on risperidone response trended towards significant with effect sizes (0.43 and 0.71) that bracket the magnitude of the effect size for risperidone versus placebo (-0.59). The combined CATIE analysis was significant ($p=0.03$, effect size=0.52). The GARP 3 effect on risperidone response was replicated in an independent study ($p=0.01$) with an effect size (1.06) nearly twice that of risperidone versus placebo.

In this study, we present replication of the impact of genetic variation of the *GLP1R* gene on antipsychotic response. We identified two markers, GARP 1 and GARP 3 that predicted response to olanzapine and risperidone, respectively. The average magnitude of the observed differential response for both markers exceeded the magnitude of the response difference between the individual drugs and placebo as reported in previous studies. Given the large effect size and replication in multiple cohorts, these markers may be well-suited for pharmacogenetic testing in antipsychotic-treated patients. Furthermore, the inclusion of subjects with differing diagnoses without impacting the effect of biomarker status suggests that GARP status may have relevance for antipsychotic response without regard for diagnosis.

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