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Genetic predictors of antipsychotic response to lurasidone identified in a genome wide association study and by schizophrenia risk genes

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ABSTRACT

Biomarkers which predict response to atypical antipsychotic drugs (AAPDs) increases their benefit/risk ratio. We sought to identify common variants in genes which predict response to lurasidone, an AAPD, by associating genome-wide association study (GWAS) data and changes (Δ) in Positive And Negative Syndrome Scale (PANSS) scores from two 6-week randomized, placebo-controlled trials of lurasidone in schizophrenia (SCZ) patients. We also included SCZ risk SNPs identified by the Psychiatric Genomics Consortium using a polygenic risk analysis. The top genomic loci, with uncorrected $p < 10^{-4}$, include: 1) synaptic adhesion (*PTPRD*, *LRRC4C*, *NRXN1*, *ILIRAPL1*, *SLITRK1*) and scaffolding (*MAGI1*, *MAGI2*, *NBEA*) genes, both essential for synaptic function; 2) other synaptic plasticity-related genes (*NRG1/3* and *KALRN)*; 3) the neuron-specific RNA splicing regulator, *RBFOX*1; and 4) ion channel genes, e.g. *KCNA10*, *KCNAB1*, *KCNK9* and *CACNA2D3*). Some genes predicted response for patients with both European and African Ancestries. We replicated some SNPs reported to predict response to other atypical APDs in other GWAS. Although none of the biomarkers reached genome-wide significance, many of the genes and associated pathways have previously been linked to SCZ. Two polygenic modeling approaches, GCTA-GREML and PLINK-Polygenic Risk Score, demonstrated that some risk genes related to neurodevelopment, synaptic biology, immune response, and histones, also contributed to prediction of response. The top hits predicting response to lurasidone did not predict improvement with placebo. This is the first evidence from clinical trials that SCZ risk SNPs are related to clinical response to an AAPD. These results need to be replicated in an independent sample.

1. Introduction

Antipsychotic drugs (APDs) are more effective to treat positive (psychotic) than negative symptoms or cognitive impairment in schizophrenia (SCZ). Psychotic symptoms respond to APDs in approximately 70% of patients with SCZ who may be classified as non-treatment resistant SCZ (non-TRS). The other ~30% have moderate-severe positive symptoms after two or more trials with APDs and are referred to as treatment resistant SCZ (TRS) (Meltzer, 2012). Individual genetic, epigenetic, adherence, and other factors which affect drug absorption, metabolism, and interaction with various concomitant treatments account for the large variation in extent and time course of clinical response to APDs. Identifying multiple genetic and other biomarkers which contribute to these differences would facilitate optimal drug choice and might also lead to novel targets for APDs.

Lurasidone is a novel atypical APD with a relatively benign side effect profile (Bruijnzeel et al., 2015). Three Phase III registration trials showed it to be significantly better than placebo in improving total psychopathology in acutely psychotic SCZ patients, as measured by the change in total Positive And Negative Syndrome Scale (PANSS) scores (Loebel et al., 2013b; Meltzer et al., 2011a; Nasrallah et al., 2013a). Pharmacologically, lurasidone can be characterized as a more potent serotonin $(5\text{-HT})_{2A}$ than dopamine (DA) D_2 receptor blocker, a potent 5-HT_7 antagonist, and a direct acting 5-HT_{1A} partial agonist (Ishibashi et al., 2010). These pharmacologic features are the principal determinants of its efficacy and differentiation from both typical APDs, e.g. haloperidol, and other atypical APDs, e.g. risperidone (Huang et al., 2014). Reliable genetic biomarkers would help to identify the optimal patient population to be treated with this drug.

Previous pharmacogenetic (candidate gene studies) and pharmacogenomic [non-hypothesis driven genome-wide association (GWAS)] studies have reported predictors of response to other APDs (Arranz and Munro, 2011; Hamilton, 2015). A GWAS based on a well-defined and operationalized intermediate or (endo)phenotype such as change in positive symptoms in acutely psychotic patients, and controlled for ethnicity, because the genes involved may have larger effect sizes, can produce meaningful results using sample sizes in this range. By contrast, many tens of thousands of subjects per group may be required to identify genetic risks with only moderate effect sizes (odds ratio = 1.1–1.2) in complex diseases, like SCZ, using unselected groups

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of SCZ patients (Consortium, 2014). The genetic risks for SCZ are subject to natural selection and those deleterious variants with bigger effect size are reduced in the population over time because of the low fitness in patients with SCZ. However, common variants associated with APD efficacy have been less affected by natural selection because APDs have been utilized only within the past 70 years. When a GWAS lacks the power to identify genetic variants as biomarkers for response because of individual small effect sizes, supplementary techniques which have been utilized here, are able to assist in identification of meaningful biomarkers. These include pathway analysis and polygenic risk scoring (Wang et al., 2010), and examining data from the most and least improved/worsened patient groups, omitting those with intermediate change scores (Lavedan et al., 2009).

Several small scale GWAS studies with identified pharmacogenomic biomarkers which predict response to APDs in SCZ have been reported. A GWAS of a phase III study of the atypical APD, iloperidone, in acutely psychotic patients identified six significant loci (Lavedan et al., 2009), one of which was a SNP near the genomic region of the 5-HT_7 receptor (HTR7). This is of special interest to this study because lurasidone is a 5-HT_7 receptor antagonist and this mechanism has been shown to be relevant to its ability to improve psychotic-like behavior and cognitive impairment in established rodent models (Galici et al., 2008). Next, the CATIE trial, an effectiveness trial in chronic SCZ patients (Lieberman et al., 2005), which randomized them to one of five APDs, was the basis for pharmacogenetic (Grossman et al., 2008; Need et al., 2009) and pharmacogenomic analyses (Adkins et al., 2011; McClay et al., 2011a; McClay et al., 2011b; Sullivan et al., 2009). Another pharmacogenomics study of Caucasian patients ($n = 89$) with schizophrenia reported the top marker associated with improvement in positive symptom from olanzapine or risperidone monotherapy was in the HLA region ($p = 1.76 \times 10^{-5}$) (Le Clerc et al., 2015). However, this SNP is not in linkage disequilibrium with SNPs identified by the PGC GWAS for genetic risk for SCZ. Recently, Stevenson et al. conducted an exploratory GWAS on antipsychotic response after 6-week treatment with risperidone in 86 first-episode patients with mixed ethnicities and diagnoses of SCZ, bipolar disorder, or major depression. SNPs inside a gene encoding glutamate receptor delta 2 (GRID2) were identified as the top markers (the lowest $p = 1.10 \times 10^{-8}$) associated with the change score in Brief Psychiatric Rating Scale (BPRS) (Stevenson et al., 2016).

A genetic overlap between risk for SCZ and APD mechanism of action has been recently reported and advocated as a means to identify both APD drug targets and potential biomarkers (Ruderfer et al., 2016). Previous studies conducted by the PGC have shown that the polygenic risk derived from SCZ GWAS could be, in part, related to genetic effects on disorganized and negative symptoms, leading the authors to conclude that the identified genes, which included HLA region genes, might be treatment targets (Fanous et al., 2012). Another study showed that the polygenic risk scores (PRS) derived from PGC GWAS were higher in clozapine responders than clozapine non-responders (Frank et al., 2015), suggesting that these risk genes might be targets for clozapine. Thus, there is a naturally utilizing for risk genes to identify biomarkers for drug response in well-controlled small clinical trials.

We reported here the results of a GWAS which analyzed data from two clinical trials of lurasidone in acutely psychotic SCZ patients with European or African Ancestry (AA) (Meltzer et al., 2011b; Nasrallah et al., 2013b). We identified SNPs and pathways associated with change in PANSS total (ΔPANSS-T) and PANSS subscales which predicted efficacy and identified possible novel drug targets. We determined whether the top biomarkers belong to functional networks and their relationship to expression of the HTR7 gene because of its important for the mechanism of action of lurasidone. Based on two polygenic modeling approaches, we tested whether the genetic variants from PGC GWAS significantly contributed to the variation of change in PANSS-total, positive, and negative subscales.

2. Methods and materials

2.1. The clinical trials, subjects, and genotyping

The two clinical trials used for this analysis are both six-week, randomized, double-blind, lurasidone, placebo-controlled, multicenter registration trials, of DSM-IV acutely psychotic SCZ patients (Meltzer et al., 2011b; Nasrallah et al., 2013b). Patients who met TRS criteria were excluded. There were four fixed-dose treatment arms: lurasidone 40 and 120 mg/day, another atypical APD, olanzapine, 15 mg/day, and placebo (Pearl 1) (Meltzer et al., 2011b) and lurasidone 40, 80, and 120 mg/day, and placebo (Pearl 2) (Nasrallah et al., 2013b). The percentages of patients who achieved the a priori determined response: ≥20% improvement in ΔPANSS-T, was 61% in both the Pearl 1 and 2 studies. A total of 171/63 Caucasian and 131/54 AA for lurasidone/placebo-treated patients consented to participate in the genetic study. Ethnicity was validated as described below.

The data from the two clinical trials were analyzed together and genotyped using the Affymetrix 6.0 SNP Array (Affymetrix, Santa Clara, CA, USA). Details of the method and Quality Control are provided in Supplemental material.

2.2. Evaluation of treatment response

The primary measure of efficacy, ΔPANSS-Total, was the difference between baseline and last observation carried forward (LOCF) for those with at least one PANSS rating after baseline. Results could be pooled across drug dosage arms because clinical change was not dose-related (data not presented). The intention-to-treat (ITT) population included 157, 73, and 156 patients who received 40, 80, and 120 mg/day doses of lurasidone, respectively. Subjects within the 30th percentiles for greatest or least improvement in PANSS-Total (referred to as best and worst responders, hereafter) were included in a secondary analysis as previously done for iloperidone (Lavedan et al., 2009). The five PANSS factors: Positive, Negative, Disorganization, Excitement, and Anxiety/Depression, were shown to be present at baseline in this sample (available upon request).

2.3. Data analysis

DATA QC was conducted to exclude samples with MAF < 0.05, genotyping rate < 0.95, and significant deviation from HWE ($p < 0.0001$). Principal component analysis (PCA) and association testing were conducted by PLINK 1.9 (Purcell et al., 2007). Linear regression with an additive model of minor alleles, adjusted for covariates, race, gender, and dosage, was utilized. False discovery rate (FDR) corrections for multiple testing were calculated using the Benjamini and Hochberg (BH) procedure. An unadjusted (without correction for multiple testing) p-value $< 1.0 \times 10^{-4}$ was arbitrarily set as the cut-off in the association test with ΔPANSS-T. SNP imputing was performed by IMPUTE2/SHAPEIT using 1000 genome phase 1 (EUR or AFR) as reference genome. Genes were annotated from genomic loci by scanDB. For identified loci in intergenic regions, the gene closest to the LD block within 250 MB was chosen as the annotated gene.

We performed pathway analysis using all SNPs (original and imputed) passing QC with p-value passing the cutoff. Multiple Association Network Integration Algorithm (GeneMANIA), text-mining to identify the interactome (GRAIL), functional prediction such as cis-eQTL (Braincloud), coexpression network (SEEK), protein-protein interaction (STRING), and tissue-specific gene expression (GTEx) were used for functional characterization and/or pathway(s) identification of the top GWAS hits.

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