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SNP-based analysis of neuroactive ligand-receptor interaction pathways implicates PGE2 as a novel mediator of antipsychotic treatment response: Data from the CATIE Study

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Dear Editors

Limitations in current knowledge of antipsychotic drug mechanisms of action (MoA) hamper the development of improved agents and the tailoring of extant antipsychotics to optimize efficacy. Genomewide association studies (GWAS) offer a promising avenue toward elucidating antipsychotic MoA. However, recent research has suggested that conventional “one SNP at a time” GWAS methods offer suboptimal power to detect genetic effects, compared to approaches aggregating signals across relevant genomic units and/or incorporating high-quality prior information (Wang et al., 2010). Here, we applied these insights, leveraging the broadly supported axiom that antipsychotics act through modulating neurotransmitter function (Miyamoto et al., 2005), to investigate the impact of genomic variation underlying a comprehensive list of neuroactive biological pathways on antipsychotic response. Specifically, we employed bioinformatics tools to aggregate SNP-based GWAS data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) into 58 neuroactive ligand-receptor interaction pathways, then systematically screened associations between these pathways and antipsychotic treatment efficacy.

Briefly, CATIE is a multiphase, randomized controlled trial of antipsychotics in which DSM-IV-diagnosed schizophrenia patients were followed for up to 18 months (Lieberman et al., 2005). Subjects were initially randomized to one of five treatment arms (olanzapine, quetiapine, risperidone, ziprasidone or perphenazine) and, if initial treatment was unsuccessful, were sequentially switched to alternative treatment arms until attaining satisfactory treatment or exiting the study. Treatment efficacy was repeatedly assessed (7.5 assessments/subject) using the Positive and Negative Syndrome Scale (PANSS). A

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subsample of 738 subjects was genotyped using Affymetrix 500K and customized Perlegen 164K chips (Sullivan et al., 2008). Subject-level treatment effects were estimated using mixed models, which analyze all available assessments—improving treatment effect precision and power to detect genetic effects, relative to traditional approaches using only two (e.g., pre- minus post-treatment) assessments (van den Oord et al., 2009). The primary CATIE GWAS of these antipsychotic treatment effects has been described elsewhere (McClay et al., 2011; *p*-values available at: www.people.vcu.edu/~jlmccclay). In brief, population stratification was controlled using MDS covariates and association tests were conducted as linear regressions in PLINK (<http://pngu.mgh.harvard.edu/~purcell/plink>).

To begin, the list of human neuroactive ligand-receptor interactions was retrieved from KEGG (<http://www.genome.jp/kegg/pathway/hsa/hsa04080.html>). From this ligand-receptor interaction list, we identified all known genes encoding receptors for each ligand. Obtaining metabolic synthesis and degradation pathway genes for particular neuroactive ligand is, however, not straightforward, as metabolic reactions are extensively interconnected. Thus, reactions common to biosynthesis of multiple compounds cannot be considered specific to any particular pathway. To address this, we used a previously compiled genome-scale human metabolic reactions set (Ma et al., 2007), representing reaction pathways as networks, with metabolites as nodes and reactions as edges. Starting from a particular neuroactive compound node, reactions participating in its biosynthesis/degradation were traced until reaching branching points where the precursor/product participates in a reaction within another pathway, at which point the neuroactive pathway of interest concluded (Ma et al., 2007). Genes corresponding to identified metabolic reactions were concatenated with the list of neuroactive receptors to generate the final list of genes nested within pathways. In total, our list included 58 neuroactive pathways, with a mean of ~3 genes/pathway, and ~40 CATIE SNPs/pathway (SNP list, organized by pathway and gene, available at: www.people.vcu.edu/~ejvandenoord/).

Permutation testing was used to assess the statistical significance of neuroactive pathway-antipsychotic efficacy associations. Specifically, we first identified the minimum SNP *p*-value observed for each pathway in the actual, nonpermuted dataset. This minimum pathway *p*-value was then compared to the null distribution of the test statistic obtained through 10,000 permutations. More precisely, in each permutation, the SNP genotypes in the actual pathway were replaced with randomly selected genotypes from the full GWAS data. Association testing was conducted on the permuted pathway SNPs and the minimum permuted pathway *p*-value was extracted. For each pathway, this was repeated 10,000 times to derive the null distribution of pathway *p*-values against which the actual pathway *p*-value was compared. Thus, our approach may be characterized as using raw genotype input data and competitive hypothesis testing of pathway-based test statistics (Wang et al., 2010).

Thirteen different pathways were found nominally significant ($p < 0.05$) across the five antipsychotic response phenotypes (Table 1). Known response mediating pathways, including those related to dopamine, serotonin and histamine were implicated for quetiapine. Among the most promising results, the PGE₂ pathway, known to be involved in inflammation response, was implicated in three of five examined antipsychotics, and melanin concentrating hormone and PGF₂ pathways were each implicated in two of five antipsychotics (Table 1). To consider whether the same pathway influenced response across drugs, we combined *p*-values across antipsychotics (for all five antipsychotics and for the four pharmacologically similar “atypical” drugs) using Fisher’s method, and adjusted the joint *p*-values for multiple testing using an FDR approach (Storey, 2003). FDR results provided further support for PGE₂ as a mediator of antipsychotic response, particularly for atypicals (all antipsychotics: $q = 0.11$; atypicals-only: $q = 0.04$), but not for other pathways. PGE₂ is a pro-inflammatory prostaglandin and elevated PGE₂ levels have been associated

with schizophrenia (Martinez-Gras et al., 2011). Considering the proposed role of immunological factors in schizophrenia etiology, it is plausible that PGE₂-mediated antipsychotic response may occur via moderating immunological imbalances. This is supported by a recent study demonstrating decreased PGE₂ in rat brain following exposure to olanzapine (Cheon et al., 2011), one of the antipsychotics showing association with PGE₂-mediated response in our study .

In conclusion, identifying specific neuroactive pathways involved in antipsychotic pharmacology is vital to developing improved therapeutic strategies for schizophrenia. Our results implicate the PGE₂ pathway as a novel biomarker mediating response to three atypical antipsychotic drugs.

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Table 1
P-values of top neuroactive pathways for each drug treatment outcome measured on PANSS.

Pathways	Olanzapine	Perphenazine	Quetiapine	Risperidone	Ziprasidone
Angiotensin	0.814	0.680	0.032	0.934	0.423
Dopamine	0.677	0.951	0.004	0.749	0.842
Galanin	0.143	0.780	0.011	0.297	0.899
Histamine	0.661	0.643	0.004	0.303	0.983
Leptin	0.567	0.610	0.038	0.818	0.052
Luteinizing Hormone	0.780	0.912	0.696	0.023	0.505
Melanin Concentrating Hormone	0.038	0.858	0.234	0.130	0.048
Melanocortin	0.830	0.207	0.041	0.609	0.605
PGE ₂	0.040	0.754	0.044	0.003	0.281
PGF ₂	0.712	0.025	0.869	0.453	0.021
Serotonin	0.190	0.674	0.007	0.834	0.571
Thromboxane	0.575	0.360	0.660	0.462	0.009
Vasoactive Intestinal Peptide	0.814	0.680	0.032	0.934	0.423

Significant *p*-values (i.e., <0.05) are highlighted in bold.