Genomewide pharmacogenomic study of metabolic side effects to antipsychotic drugs

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Abstract

Understanding individual differences in the susceptibility to metabolic side effects as a response to antipsychotic therapy is essential to optimize the treatment of schizophrenia. Here we perform genomewide association studies (GWAS) to search for genetic variation affecting the susceptibility to metabolic side effects. The analysis sample consisted of 738 schizophrenia patients, successfully genotyped for 492K SNPs, from the genomic subsample of the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study. Outcomes included twelve indicators of metabolic side effects, quantifying antipsychotic-induced change in weight, blood lipids, glucose and hemoglobin A1c, blood pressure and heart rate. Our criterion for genomewide significance was a pre-specified threshold that ensures, on average, only 10% of the significant findings are false discoveries. Twenty-one SNPs satisfied this criterion. The top finding indicated a SNP in MEIS2 mediated the effects of risperidone on hip circumference ($q = .004$). The same SNP was also found to mediate risperidone's effect on waist circumference ($q = .055$).
Genomewide significant finding were also found for SNPs in PRKAR2B, GPR98, FHOD3, RNF144A, ASTN2, SOX5 and ATF7IP2, as well as several intergenic markers. PRKAR2B and MEIS2 both have previous research indicating metabolic involvement and PRKAR2B has previously been shown to mediate antipsychotic response. Although our findings require replication and functional validation, this study demonstrates the potential of GWAS to discover genes and pathways that potentially mediate adverse effects of antipsychotic medication.

Keywords
genomewide association; antipsychotics; pharmacogenomics; personalized medicine; metabolic side effects

Introduction

Antipsychotics are the cornerstone of acute and long-term treatment for schizophrenia. The first generation, sometimes referred to as the “typical” antipsychotics (e.g., haloperidol) was introduced in the 1950s. Despite treatment with these first generation antipsychotics, a substantial proportion of schizophrenia patients do not improve or relapse frequently. Furthermore, these drugs are often associated with significant side effects, including extrapyramidal symptoms (EPS)—involuntary movements that may occur in schizophrenia patients after long-term treatment with antipsychotic medication. Tardive dyskinesia (TD) is a particularly worrisome EPS because of its high annual incidence rates and potential irreversibility. Clozapine was reintroduced in 1989 marking the advent of a second generation of “atypical” antipsychotics. It has enhanced therapeutic effects in patients who respond poorly to treatment and a much lower risk of side effects such as TD. Clozapine has, however, been associated with severe agranulocytosis, necessitating hematologic monitoring and making it unsuitable as a first line drug. Clozapine's success stimulated efforts to develop new antipsychotics, resulting in other second generation drugs such as risperidone and olanzapine. These newer second generation drugs differ pharmacologically from first generation antipsychotics principally in their lower affinity for the dopamine 2 receptor, relatively greater affinities for other neuroreceptors such as serotonin, and in their ability to modulate glutamate receptor mediated functions and behaviors. These newer antipsychotics are also associated with a lower incidence of EPS/TD and do not share clozapine's risk of agranulocytosis.

Second generation antipsychotics are, however, associated with a variety of metabolic side effects such as dyslipidemia, elevated glucose levels, and weight gain, with medical consequences ranging from cosmetic concerns to increased rates of cardiovascular disease (e.g., hypertension, coronary artery disease) and diabetes. Careful monitoring and treatment of metabolic adverse effects is therefore recommended. Furthermore, these side effects are key factors underlying the substantial noncompliance characterizing antipsychotic therapy. Clearly, any ability to minimize metabolic side effects by matching individual patients to the optimal drug prior to treatment would have great clinical value.
Genetic factors likely explain a portion of individual differences in susceptibility to metabolic side effects. Studies have suggested associations with, for example, serotonin receptors\(^1\). The serotonergic system is involved in the regulation of feeding behavior and satiety control in the central nervous system, and serotonin receptors are expressed in central nervous system areas that are involved in energy balance\(^1\). Furthermore, antipsychotics such as olanzapine have high affinity for these receptors and are hypothesized to induce weight gain especially via 5-hydroxytryptamine (serotonin) receptor 2C antagonism\(^1\). Histamine receptor H1 antagonism has also been implicated\(^1\). However, robust, consistent evidence implicating any specific candidate gene or polymorphism has been rare\(^1\). Perhaps more importantly, the selection of candidate genes is restricted to current knowledge about underlying biological mechanisms, which is limited. Methods that systematically screen variants across the whole genome for association with metabolic side effect are therefore critical to discover relevant variants in novel genes. Such genomewide association studies (GWAS) have recently become feasible. Furthermore, the number of new replicated marker-disease associations has increased dramatically since the introduction of GWAS\(^1\) with some initial applications in the context of drug response\(^1\).

In this paper, we use GWAS to search for genetic variation affecting the susceptibility for antipsychotic-induced metabolic side effects. Our study sample consists of 738 schizophrenia patients from the CATIE study\(^2\). After filtering, 492K SNPs were available for analyses\(^2\). The analyses were performed on twelve quantitative variables related to weight gain, a blood lipid panel, glucose, hemoglobin A1c, blood pressure and heart rate.

**Methods**

**Study sample**

Subjects came from the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study and were diagnosed with schizophrenia using the Structured Clinical Interview for DSM-IV\(^2\). This study sample has been carefully described elsewhere\(^2\). In short, CATIE is a multiphase randomized controlled trial of six antipsychotic medications, including olanzapine, perphenazine, quetiapine, risperidone, ziprasidone and clozapine, which followed patients for up to 18 months. To maximize representativeness, the participants were recruited from 57 clinical settings around the United States. Males constituted 74% of the total sample. The mean age of the participants was 40.9 years (SD=11.0). On average, patients were treated for 16.7 year (SD=11.2) where they received antipsychotic medication for the first time 14.3 (SD=10.8) years ago. All participants or their legal guardians gave written informed consent, including consent for genetic studies. The institutional review board at each site approved the study.

**Metabolic and cardiovascular outcome measures**

The metabolic measures collected in CATIE have been described in detail previously\(^1\),\(^2\). To briefly restate, BMI (kg/m\(^2\)) was calculated in the standard fashion and waist and hip circumferences (inches) were measured at the narrowest and widest points, respectively.
Blood pressure (mm Hg) was measured as a single, seated determination, and heart rate (bpm) was measured as resting pulse count in 30 seconds×2.

For assessment of laboratory measures (i.e., glucose (mg/dL), hemoglobin A1c (%), triglycerides (mg/dL), total cholesterol (mg/dL) and HDL(mg/dL)), CATIE subjects were asked to present in a fasting state. However, as information on last meal was collected and suggested a significant range; we explicitly adjusted glucose and triglycerides for fasting time. Specifically, we estimated mixed models predicting glucose and triglycerides with fasting time, and output the residuals as our fasting time-adjusted measures. Additionally, an empirical screen of the influence of fasting time on other laboratory measure indicated that it explained significant amounts of variance in total cholesterol and hemoglobin A1c; thus, fasting time was regressed out of these measures as well. All metabolic laboratory measures were assessed at a single central laboratory.

Descriptive statistics presented in Table 1 confirm that, compared to a matched nationally representative sample from the National Health and Nutrition Examination Survey (NHANES) III, CATIE subjects generally exhibit less favorable metabolic profiles. For instance, CATIE subjects were characterized by significantly greater waist circumference (mean=40.42), BMI (mean=30.39), diastolic blood pressure (mean =78.85) and triglycerides (mean=209.81), and lower HDL (mean=42.82), than the NHANES III national averages. Heart rate (mean=79.98) was also relatively elevated, while glucose (mean=101.73) and hemoglobin A1c (mean=5.67) were consistent with age-adjusted national averages. Further, columns 3 and 4 of Table 1 indicate that, according to established criteria, the percentage of subjects with problematic levels of metabolic phenotypes increased from baseline for all phenotypes. It is important to note, however, that as different antipsychotics have different metabolic side effect profiles, these aggregate percentages may mask important differences between drugs (see Meyer and colleagues for further detail).

**Estimating treatment effects**

The right side of Table 1 shows that sample sizes were largest for olanzapine and risperidone and smallest for clozapine. The average number of assessments per subject was about 7.4 observations per patient for variables that did not require phlebotomy (e.g., weight gain-related measures, blood pressure). For variables requiring phlebotomy (e.g., lipids, glucose) there were about 4.9 observations with the exception of hemoglobin A1c, which had a somewhat lower average of 3.5 measurements per patient.

To maximize power for the GWAS, we developed a method to estimate treatment effects from all available information using mixed modeling. Our method first determines the optimal functional form of over-time drug response, then screens many possible covariates to select those that improve the precision of the treatment effect estimates, and finally generates the individual treatment effect estimates based on the best fitting model using best linear unbiased predictors (BLUPs). As this approach takes advantages of all available information in CATIE, it results in more precise estimates than traditional approaches (e.g., subtracting pre- from post-treatment observations) that estimate treatment effects using only two assessments.
Specifically, to determine the optimal model of over-time drug response for each metabolic outcome we fit a series of models specifying linear change for a given number of days on drug and flat thereafter. This series began with a model assuming that maximal drug response was achieved at day one. Each subsequent model specified an incrementally longer duration until maximal drug response was achieved with the final model assuming that the drug effect did not plateau (i.e., linear change throughout the trial). The model with the best fit of series was selected to determine the average number of days until maximal drug response. This duration varied across metabolic outcomes with triglycerides peaking earliest (20 days on drug), and diastolic blood pressure peaking latest (586 days on drug) (see Supplemental Material A for details).

After determining the optimal functional form of over-time drug response, 36 covariates were screened to identify those that improved the precision of the treatment effect estimates. These covariates consisted of design characteristics, socio-demographic measures, clinical information, confounding medications, and baseline antipsychotic treatment. The number of selected covariates ranged from zero (e.g. for BMI, waist and hip circumference) to four or greater (e.g. blood lipids). Design characteristics, hyperlipidemia treatment (e.g., statins) and baseline olanzapine treatment where the most commonly selected covariates (see Supplemental Material A for details). Finally, treatment effects were generated by employing a unique feature of the mixed model—random effects. To elaborate, the mixed model estimates two types of parameters, coefficients that describe the predictors' average effects for the full sample (i.e., fixed effects) and deviations from the average effects for each subject (i.e., random effects). Thus, for each of the six trial drugs investigated, we were able to output treatment effects as random drug effects. Intuitively, these treatment effects quantify how much each subject's metabolic phenotypes change in response to a given drug, relative to the average effect for all subjects who took the drug. Out of 72 possible treatment effect measures (6 drugs × 12 metabolic outcomes), in 10 instances there were no significant individual differences in drug response (perphenazine-glucose, quetiapine-glucose, ziprasidone-glucose, perphenazine-hemoglobin A1c, quetiapine-hemoglobin A1c, clozapine-hemoglobin A1c, risperidone-triglycerides, ziprasidone-triglycerides, clozapine-HDL cholesterol, risperidone-total cholesterol). These treatment effects were omitted from further analyses.

Genotyping

DNA sampling, genotyping and genotype quality control have been described by Sullivan et al.\textsuperscript{25} In total, 665,439 SNPs were genotyped using the Affymetrix 500K chipset (Santa Clara, CA, USA) and a custom 164K chip created by Perlegen (Mountain View, CA, USA). After quality control protocols were performed (see Supplemental Materials A), genotypes for 492,900 SNPs from 738 individuals remained for statistical analysis.

Population stratification

Approximately 57% of the CATIE subjects describe themselves as white/European American (EA), 29% as black/African American (AA) and the remaining 14% described themselves as more than one racial category or “other”. It is essential to control for these different ancestral backgrounds, which otherwise can cause false-positive association...
findings if differences in distribution of genotypes and phenotypes exists within the different strata defined by ancestry. To investigate population stratification we have used the multi-dimensional scaling (MDS) approach implemented in PLINK\textsuperscript{32}. Input data for the MDS approach were the genomewide average proportion of alleles shared identical by state (IBS) between any two individuals. The first MDS dimension from this genetic similarity matrix captures the maximal variance in the genetic similarity; the second dimension must be orthogonal to the first and captures the maximum amount of residual genetic similarity; and so on. The first five dimensions appeared to capture the vast majority of genetic substructure in the CATIE sample and were included in the GWAS analyses.

**Association testing, control of false discoveries and cross-outcome comparisons**

All GWAS association testing was conducted in PLINK\textsuperscript{32} using a linear regression model with the five population stratification MDS dimensions as covariates. The Wald test implemented in PLINK was used to test for an additive genetic effects by coding each as a 0, 1, or 2 count of the number of minor alleles.

As argued previously\textsuperscript{33}, we prefer a false discovery rate (FDR) based approach to declare significance because: a) it balances the competing goals of finding true effects versus controlling false discoveries, b) it provides comparable standards across studies because it is much less affected by the number of tests, and c) it is relatively robust to tests of correlated outcomes\textsuperscript{34,42}. We used an FDR threshold<0.1 for declaring genomewide significance\textsuperscript{33} and a threshold of 0.25 for identifying “potentially interesting” results. These thresholds mean that on average we expect that 10% and 25%, respectively, of the SNPs declared significant will be false discoveries. Operationally these FDR levels were controlled using \(q\)-values. \(Q\)-values are FD\(\text{R}\)s calculated using the \(p\)-value of the markers as thresholds for declaring significance\textsuperscript{35,43}. \(Q\)-values were estimated with the approach outlined by Bukszar et al.\textsuperscript{44}, which is slightly more conservative than conventional \(q\)-value approaches and has the desirable property of avoiding blocks of identical \(q\)-values despite different \(p\)-values.

The FDR was controlled for each GWAS separately rather than jointly across all GWAS. This avoids a loss of power for outcomes where the number and size of the effects are relatively larger. Note that performing many GWAS analyses will not only increase the number of false positives but also the number of true positives\textsuperscript{34}. This is because the FDR controls the expected ratio of false to all discoveries.

To avoid an all-or-nothing conclusion about whether a SNP is significant and improve the interpretation of our GWAS results, we also estimated for each SNP the local FDR (lFDR). The lFDR is the (posterior) probability that the SNP has no effect\textsuperscript{44}. The lFDR provides a marker-specific estimate that the GWAS finding is false. This is not the case for the \(q\)-value that essentially averages these probabilities across the whole group of markers declared significant. As a result, a marker with a very high probability of being a false discovery may simply have a small \(q\)-value because it was tested simultaneously with a marker that has a low probability of being a false positive\textsuperscript{45}.

After indentifying genomewide significant markers, we leverage the multiple metabolic phenotype, multiple drug study design to examine whether genomewide significant markers show association to other, related outcomes. For this examination we extract coefficients.
and $p$-values for the genomewide significant SNPs for all outcomes and conduct a $t$-test to determine if the total number of supporting findings (alternate outcomes with coefficients in the same direction as the genomewide finding and $p$-value $< 0.05$) is more than would be expected by chance. We then briefly note some patterns by drug and metabolic phenotypes. Finally, we discuss the top results of this cross-outcome robustness analysis.

**Results**

### Genomewide significant signals

Quantile-Quantile (QQ) plots and $p$-values for each outcome variable are available for download at [www.vipbg.vcu.edu/~edwin](http://www.vipbg.vcu.edu/~edwin). Figure 1 shows QQ plots for the 4 outcomes with the strongest SNP associations. The plots show that the distribution of the $p$-values from the GWAS are generally on a straight line, indicating the expected $p$-value distribution under the null hypothesis assuming no effects of the markers. However, in each of these 4 plots there is also evidence that markers in the right upper corner of the have $p$-values smaller than would be expected under the null hypothesis, suggesting true association between these markers and the outcome variable. The plots also list the lambda values (i.e., the ratio of the median observed $p$-value of the distribution to the expected $p$-value under the null hypothesis), which ideally should equal 1—indicating no systematic test statistic inflation.

Of the 62 outcomes analyzed, the mean lambda=0.991 and the maximum lambda=1.019, indicating that population stratification was adequately controlled by the 5 ancestral MDS covariates and not a confounding factor in the GWAS. Also notable, for 11 outcomes, primarily those involving clozapine, lambda values were slightly deflated (0.919<.98), suggesting that results may be conservative in these cases.

Table 2 shows the number of significant GWAS results at various FDR thresholds. For concision, the table presents significant results grouped by outcome and drug. Twenty-one SNPs were genomewide significant at our pre-specified threshold for declaring significance in genetic studies using a FDR threshold of $0.1^{33}$. When grouped by medication, the largest numbers of genomewide significant results were found for risperidone (N=7) and perphenazine (N=7); when grouped by phenotypic outcome, the largest number of findings were found for triglycerides and hip circumference. Using more liberal FDR thresholds of 0.25 and 0.5, we identified 48 and 118 potentially “interesting” results, respectively.

Table 3 shows the specific SNPs with $q$-values smaller than 0.25. The top finding involved rs1568679 ($p=1.28E-08$ and $q=0.004$), located in an intron of Meis homeobox 2 ($MEIS2$) on chromosome 15q14, which was indicated to mediate the effect of risperidone on hip circumference. This same SNP also reached genomewide significance ($p=6.82E-08$ and $q=0.055$) for the effect of risperidone on waist circumference. This SNP is polymorphic in both the African American (AA) and the European American (EA) subsamples with MAF of 0.44 and 0.10, respectively. Furthermore, haplotype tests suggested that in both subsamples the same high risk haplotype contributed to the total association signal for both outcome variables. An overall haplotype test did not improve the association signals.

The second most significant signal involved rs1967256 and rs11954387 ($p=2.80E-08$ and $q=0.012$), which were in complete LD and were associated with the effect of olanzapine on...
hemoglobin A1c. These SNPs were located in an intron of the G protein-coupled receptor 98 precursor (GPR98) on chromosome 5q14.3. The markers were polymorphic in both EA (MAF=0.08) and AA (MAF=0.24). Haplotype tests did not improve association signals.

For triglycerides, the outcome with the largest number of significant results (Table 2), the top finding involved rs13224682 mediating the effect of clozapine (p=6.30E-08 and q=0.015). This SNP is located in an intron of Homo sapiens protein kinase, cAMP-dependent, regulatory, type II, beta (PRKAR2B) on chromosome 7q22.3. This marker had a very low minor allele frequency (MAF=0.01) in AAs implying that the signal was mainly driven by the EA subsample.

For the combination perphenazine-triglycerides, six genomewide significant SNPs were detected (Table 3). Two of these were rs17651157 (p=1.07E-07 and q=0.016) and rs10502661 (p=1.61E-07 and q=0.021) located 2703 bp apart in an intron of the formin homology 2 domain containing 3 (FHOD3) gene on chromosome 18q12.2. These SNPs were in high LD (in AA r²=1.0 and in EA r²=0.78) and had fairly low minor allele frequencies (MAFs 0.03/0.07 in AA/EA). Haplotype testing improved the signal (p-values of 5.36E-8 and 3.09E-9 for a specific high risk haplotype and overall haplotype tests, respectively) in EAs but not the AA subsample.

As shown in Table 3, four additional genomewide significant SNPs were located within annotated genes and ten genomewide significant SNPs were located in intergenic regions. For the three SNPs on chromosome 11q23.1 mediating the effect of risperidone on hip circumference, the signal improved when conducting an overall versus individual haplotype tests.

**Cross-outcome analyses of genomewide significant markers**

One advantage of the current analysis is that its inclusion of multiple related phenotypes and various antipsychotic drugs allows an investigation of common mechanisms across outcomes. Specifically, this feature enables searching for patterns of significant SNPs across related phenotypes as a test of robustness; and also across drugs, allowing investigation of common biological pathways. To explore these patterns, we examined if the 48 genomewide significant markers showed association, in the expected direction, to other, related outcomes using a significance threshold of p<0.05. On average 4.1 (199/48) secondary associations were detected, which is significantly more than expected by chance (t=2.72; p =0.004). A majority of secondary associations were for initial genomewide significant findings involving risperidone (57) and clozapine (85). In 51% of cases (102/199), secondary associations were for outcomes involving the same drug as the genomewide significant finding. This was particularly true for risperidone (65%; 37/57) and clozapine (52%, 44/85).

Table 4 presents the number of significant secondary associations for all genomewide significant SNPs (q <0.1) and genic SNPs with q-values 0.1-0.25 (for complete list see Supplemental Material B). Results show that secondary associations were common within the weight gain, glucose, and blood pressure phenotype clusters. For instance, the correlation between the number of secondary associations for hip and waist circumferences was 0.73, between diastolic and systolic blood pressure was 0.51, and between glucose and
hemoglobin A1c was 0.32. This suggests that the genomewide significant associations observed in the GWAS generally represent robust signals that can be detected across related phenotypes and, in some cases, for different drugs' effects on the same phenotype.

The strongest secondary associations involved rs1568679, in MEIS2, and risperidone-BMI ($p=5.02E-06$). As discussed above, this SNP was indicated as genomewide significant ($q<0.1$) in two separate GWAS—risperidone-hip circumference and risperidone-waist circumference. It was also indicated to mediate risperidone's effect on diastolic and systolic blood pressure, as well as olanzapine's effect on glucose in the cross-outcome analysis. Rs13224682, in PRKAR2B, also showed a compelling secondary association pattern. It was implicated to mediate the effects of both clozapine and olanzapine on triglyceride levels, as well as clozapine’s effects on a wide range of other metabolic outcomes (BMI, waist circumference, hip circumference and glucose). The two SNPs in complete LD from GPR98 (rs1967256 and rs11954387) showed robust signals for mediating olanzapine's effects on both glucose and hemoglobin A1c, as well as clozapine’s effect on heart rate and perphenazine's influence on HDL.

**Discussion**

Understanding individual differences in the development of metabolic side effects as a response to antipsychotic therapy is essential to individualize the treatment of schizophrenia. In this study we performed GWAS on 12 quantitative metabolic side effect indicators including variables related to weight gain, a blood lipid panel, glucose, hemoglobin A1c, blood pressure and heart rate. We detected 21 SNPs, which, according to our pre-identified criteria (FDR controlled at 0.1 level), can be considered genomewide significant. For each of these markers the estimated posterior probability indicated a reasonable chance of a true finding.

Our top finding involved rs1568679 in MEIS2 reaching genomewide significance mediating the effect of risperidone on both hip and waist circumference and showing secondary associations with BMI, diastolic and systolic blood pressure. There was also some evidence that this SNP mediated olanzapine's effect on glucose. MEIS2 (Meis homeobox 2) is the second member of the human gene family with homology to the murine myeloid ecotropic viral integration site genes, involved in murine myeloid leukemia. The MEIS2 gene encodes a homeobox protein belonging to the TALE (Three Amino acid Loop Extension) family of homeodomain-containing proteins. TALE homeobox proteins are highly conserved transcription regulators and several members have been shown to be essential contributors to many developmental programs. In addition to critical roles in early development, usually acting as a Hox cofactor, MEIS2 has a transcriptional regulatory function in adults and is widely expressed in many tissues. Of particular note is its role in regulating the activity of PDX1, a transcription factor active in pancreatic $\beta$ and acinar cells. It has been shown that MEIS2 switches the activity of PDX1 by forming the trimeric complex PDX1-PBX1b-MEIS2. The full trimeric complex is necessary to activate a promoter for ELA1 in pancreatic acinar cells, while unbound PDX1 is necessary to activate insulin-producing $\beta$ cells. Thus, the transcriptional activity of variants of MEIS2 may be differentially influenced by second generation antipsychotics (particularly risperidone), causing downstream changes...
in insulin and/or digestive enzyme production. Further, it is also clear that not every function of MEIS2 has yet been determined, as it is a highly complex locus, known to exist as at least 27 distinct splice variants (AceView). Given the robustness of the current association finding across multiple metabolic outcomes and the plausible mechanism suggested by former research, MEIS2 should be considered a promising candidate for further study.

The second and third most significant findings were with GPR98, which were indicated to mediate the effects of olanzapine on hemoglobin A1c levels. GPR98 is a member of the G protein-coupled receptor superfamily of 7 transmembrane domain receptors. It binds calcium and is expressed in the central nervous system, although it is also expressed in a wide range of other tissues. GPR98 was originally known as VLGR1, or very large G protein-coupled receptor, because it is comprised of over 90 exons that span approximately 600kb, with the largest transcript variant encoding a peptide of 6307 amino acid residues, making it the largest known cell surface protein. GPR98 has been previously implicated in some forms of epilepsy and in Usher syndrome (a disorder involving congenital hearing loss and progressive retinitis pigmentosa). There is no current evidence linking it mechanistically with hemoglobin A1c or glucose levels.

SNP rs13224682 in PRKAR2B (Protein kinase, cyclic adensine monophosphate-dependent, regulatory, type II beta) was found to mediate clozapine’s and, to a lesser extent, olanzapine’s effects on triglyceride levels. The cAMP-dependent protein kinase system controls the cellular effects of cAMP, which acts as a second messenger in many signaling cascades. The kinase holoenzyme consists of two regulatory and two catalytic subunits that dissociate upon binding of cAMP molecules. The free, activated catalytic subunits then phosphorylate downstream proteins, thereby altering their activity or function. PRKAR2B, also known as RII beta, is one of several regulatory subunit proteins.

RII beta has previously been strongly implicated in metabolic phenotypes and, in separate studies, antipsychotic effects in laboratory animals. First, RII beta knockout mice appear healthy but have markedly diminished white adipose tissue despite normal food intake. They are protected against developing diet-induced obesity and fatty livers. Furthermore, disruption of RII beta reverses the obesity syndrome of Agouti lethal yellow mice. One possible mechanism by which RII beta regulates weight is via its known role in the thyroid, where its as an important mediator of thyroid-stimulating hormone (TSH) receptor and cAMP signals to downstream membrane and nuclear substrates. Another potentially relevant mechanism is suggested by a search with the SLEP bioinformatic tool, which indicated that the marker is <1 kb from an expression QTL (eQTL) for liver, within the same gene, PRKAR2B. Second, in relation to antipsychotic effects, mice harboring a targeted disruption of RII beta have a profound deficit in cAMP-stimulated kinase activity in the striatum. When treated with haloperidol, RII beta mutant mice fail to induce either c-fos or neurotensin mRNA and the acute cataleptic response of haloperidol is blocked. These effects appear to arise because of the importance of cAMP, both in the regulation of metabolism and the transducing of the antipsychotic effect. Our association findings implicating this gene as a mediator of multiple related antipsychotic-induced metabolic outcomes, in addition to ample functional evidence indicating both metabolic function and
antipsychotic mediation, make \textit{PRKAR2B} a compelling candidate for additional investigation.

Two SNPs at \textit{FHOD3} were shown to mediate perphenazine's effect on triglycerides at the \textit{q}<0.1 level. \textit{FHOD3} (Formin homology-2 domain-containing protein 3) appears to be expressed in the kidney, heart and brain with little to no expression in other tissues. Its function appears to be as an actin-organizing protein in the cellular cytoskeleton\textsuperscript{63}. Very little else is known of this gene and its function, with only two articles concerning it published to date. Clearly, given this lack of information no firm conclusions about its putative drug-metabolism interaction can be drawn.

A small number of candidate genes have been previously implicated in mediating the metabolic side effects of antipsychotic drugs. These studies have typically focused on weight gain as the outcome measure for second generation antipsychotics. A recent review by Arranz and de Leon\textsuperscript{64} catalogued previous findings, suggesting positive associations with \textit{ADRA2A, CYP2D6, GNB3, HTR2C, LEP} and \textit{SNAP25}. A recent large candidate gene study in CATIE\textsuperscript{65} also suggestively implicated \textit{HTR2A} and \textit{CHRNA7}. As the current study examined the same sample using different methods and a wider SNP panel, we examined the influence of these two candidate genes, as well as the six indicated by Arranz and de Leon. Additionally, we investigated five candidates indicated in a more recent pharmacogenetic study of antipsychotic-induced weight gain in a German sample\textsuperscript{66}, as well as several general metabolic candidates indicated in recent large meta-analyses of non-medicated samples\textsuperscript{67-73}. In total, 1338 SNPs within 45 candidate genes were selected on the basis of either being within the gene boundary or within 50kb flanking either end, leading to a total of 82,956 tests (1338 SNPs×62 outcomes). Numbers of SNPs per gene, a summary of analysis results and QQ plot are given in Supplemental Material A. The most significant findings were rs1962882 in \textit{ABCA1}, mediating the effects of ziprasidone on waist-hip ratio (\textit{p}=3.84E-05, \textit{q}=0.99), followed by rs6449050 at \textit{SLC2A9}, mediating the effects of olanzapine on glucose levels (\textit{p}=4.22E-05, \textit{q}=0.99). These poor \textit{q}-values, coupled with the fact that none of the genes showed more significant findings than expected by chance, suggests limited support for these as true effects.

While CATIE remains the largest, most comprehensive clinical trial of antipsychotic treatment for schizophrenia with whole genome data, it was not principally designed as a pharmacogenomics study and, consequently, has several limitations in this context. Chief among these is the fact that most subjects were non-naïve to antipsychotic treatment at baseline and were often taking other, potentially confounding, medications with metabolic effects, including antidepressants and mood stabilizers. Moreover, DNA collection took place after the clinical trial and only included a subsample of CATIE participants (51%). As previously described, the genomic subsample had lower symptom severity, less current drug/alcohol abuse/dependence and were less likely to identify as African-American than CATIE subjects not contributing DNA\textsuperscript{25}. Despite statistical adjustment for these factors, inference would be stronger if the trial had a more ideal pharmacogenomics design. Thus, we recommend that future data collection efforts consider the merits of enrolling antipsychotic-naïve subjects, employing stricter recruitment criteria for confounding medications and implementing a more representative sampling frame. Additionally, future
research can extend this line of research through incorporating dosage information into the calculation of treatment effects.

As with any genetic associations, our findings will require replication and functional validation. To facilitate this process we provide all \( p \)-values (www.vipbg.vcu.edu/~edwin) as a resource for investigators with the requisite samples to advance this line of research. However, the present study demonstrates the potential of GWAS to discover genes and pathways that mediate adverse effects of antipsychotic medication. A better understanding of these mechanisms and the role of specific polymorphisms may eventually help to personalize antipsychotic medication in order to minimize these adverse drug reactions for patients with schizophrenia.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
QQ plots for four outcomes showing strongest GWAS results
Table 1

Descriptive statistics (trial means and SD), percent of subjects experiencing ADRs and total number of assessments per drug

| Phenotype                  | Descriptive Statistics | ADRs (%) | Total Assessments (Subjects) per Drug |
|----------------------------|------------------------|----------|--------------------------------------|
|                            | Mean (SD)              | Base     | Intral | Olanzapine | Perphenazine | Quetiapine | Risperidone | Ziprasidone | Clozapine |
| BMI (kg/m2)                | 30.39 (7.02)           | 43.12    | 56.80  | 1225 (283) | 607 (145)    | 942 (277)  | 1102 (282) | 599 (200)   | 175 (52)  |
| Waist Circumference (in)   | 40.42 (6.54)           | 48.47    | 66.93  | 1199 (282) | 598 (144)    | 927 (273)  | 1089 (280) | 591 (199)   | 175 (52)  |
| Hip Circumference (in)     | 43.12 (5.73)           | 35.33    | 54.98  | 1193 (282) | 598 (144)    | 927 (273)  | 1089 (280) | 591 (199)   | 175 (52)  |
| Waist-Hip Ratio            | 0.94 (0.08)            | 29.92    | 54.98  | 1193 (282) | 598 (144)    | 927 (273)  | 1089 (280) | 591 (199)   | 175 (52)  |
| Systolic BP (mm Hg)        | 123.75 (15.56)         | 29.54    | 59.87  | 1227 (282) | 604 (145)    | 944 (278)  | 1099 (281) | 595 (197)   | 174 (52)  |
| Diastolic BP (mm Hg)       | 78.85 (10.79)          | 26.80    | 55.23  | 1227 (282) | 603 (145)    | 944 (278)  | 1099 (281) | 595 (197)   | 174 (52)  |
| Heart Rate (bpm)           | 79.98 (13.05)          | 5.36     | 22.02  | 1226 (282) | 602 (144)    | 944 (278)  | 1098 (280) | 595 (198)   | 174 (52)  |
| Glucose (mg/dL)            | 101.73 (44.33)         | 15.79    | 44.91  | 759 (282)  | 357 (142)    | 597 (266)  | 670 (272)  | 381 (195)   | 118 (53)  |
| Hemoglobin A1c (%)         | 5.67 (1.10)            | 12.91    | 19.60  | 529 (225)  | 241 (94)     | 386 (187)  | 465 (198)  | 224 (116)   | 82 (45)   |
| Triglycerides (mg/dL)      | 209.81 (181.51)        | 54.61    | 74.90  | 756 (281)  | 357 (142)    | 600 (266)  | 673 (272)  | 383 (194)   | 117 (53)  |
| HDL Cholesterol (mg/dL)    | 42.82 (13.70)          | 52.76    | 73.13  | 756 (281)  | 357 (142)    | 600 (266)  | 673 (272)  | 383 (194)   | 117 (53)  |
| Total Cholesterol (mg/dL)  | 199.46 (45.41)         | 47.31    | 62.82  | 755 (281)  | 358 (142)    | 600 (266)  | 673 (272)  | 384 (195)   | 117 (53)  |
Table 2

Number of significant GWAS results at various FDR thresholds

|                     | FDR threshold |          |          |          |
|---------------------|---------------|----------|----------|----------|
|                     | 0.1           | 0.25     | 0.5      |          |
| By Antipsychotic    | 0.1           | 0.25     | 0.5      |          |
| Olanzapine          | 2             | 4        | 9        |          |
| Perphenazine        | 7             | 13       | 26       |          |
| Quetiapine          | 1             | 2        | 8        |          |
| Risperidone         | 7             | 13       | 36       |          |
| Ziprasidone         | 1             | 1        | 3        |          |
| Clozapine           | 3             | 15       | 36       |          |
| **Sum**             | **21**        | **48**   | **118**  |          |

|                     |          |          |          |
| By Metabolic Phenotype |      |          |          |
| BMI                 | 1        | 1        | 4        |
| Waist Circumference | 1        | 1        | 2        |
| Hip Circumference   | 6        | 8        | 14       |
| Waist-Hip Ratio     | 0        | 0        | 3        |
| Systolic BP         | 0        | 0        | 3        |
| Diastolic BP        | 0        | 0        | 1        |
| Heart Rate          | 0        | 2        | 9        |
| Glucose             | 0        | 2        | 4        |
| Hemoglobin A1c      | 3        | 7        | 24       |
| Triglycerides       | 9        | 19       | 39       |
| HDL Cholesterol     | 1        | 3        | 7        |
| Total Cholesterol   | 0        | 5        | 8        |
| **Sum**             | **21**    | **48**   | **118**  |
GWAS results with $q$-values smaller than 0.25

| Outcome                        | SNP       | Gene symbol | Cytogenetic location | MAF  | N  | Eff | p-value     | $q$-value | FDR  |
|--------------------------------|-----------|-------------|----------------------|------|----|-----|------------|----------|------|
| Perphenazine - HDL             | rs1163585 | no          | 1p31.1               | 0.241| 139|   +  | 9.32E-07   | 0.249    | 0.614|
| Perphenazine - Triglycerides   | rs1740015 | no          | 1p21.2               | 0.063| 138|   +  | 1.52E-06   | 0.117    | 0.429|
| Perphenazine - Triglycerides   | rs6735179 | no          | 2p25.3               | 0.346| 138|   +  | 1.34E-07   | 0.018    | 0.08 |
| Perphenazine - Triglycerides   | rs6743189 | RNF144A     | 2p25.1               | 0.305| 138|   +  | 2.43E-07   | 0.029    | 0.127|
| Risperidone - Hip Circumference| rs1991126 | no          | 2p24.1               | 0.15 | 265|   +  | 8.98E-07   | 0.112    | 0.437|
| Risperidone - Hip Circumference| rs1117324 | no          | 2p24.1               | 0.156| 265|   +  | 3.47E-07   | 0.054    | 0.245|
| Perphenazine - Triglycerides   | rs1020223 | no          | 2p16.1               | 0.457| 138|   -  | 7.31E-07   | 0.068    | 0.279|
| Clozapine - Heart Rate         | rs399885  | no          | 2p12                 | 0.327| 52 |   +  | 5.11E-07   | 0.135    | 0.356|
| Clozapine - Heart Rate         | rs7570469 | no          | 2p12                 | 0.418| 52 |   +  | 5.50E-07   | 0.141    | 0.369|
| Clozapine - Triglycerides      | rs1534238 | RNF144A     | 2p25.1               | 0.138| 52 |   -  | 1.82E-06   | 0.218    | 0.583|
| Clozapine - Triglycerides      | rs1738567 | no          | 2q33.1               | 0.689| 53 |   +  | 3.44E-06   | 0.247    | 0.626|
| Perphenazine - Triglycerides   | rs1313495 | no          | 4q23                 | 0.337| 135|   +  | 2.19E-06   | 0.152    | 0.513|
| Perphenazine - Triglycerides   | rs1173207 | no          | 4q23                 | 0.338| 137|   +  | 1.30E-06   | 0.105    | 0.395|
| Ziprasidone - Hip Circumference| rs1405687 | no          | 4q23                 | 0.088| 183|   -  | 4.72E-08   | 0.038    | 0.181|
| Olanzapine - Hemoglobin A1c    | rs1967256 | GPR98       | 5q14.3               | 0.148| 207|   +  | 2.80E-08   | 0.012    | 0.068|
| Olanzapine - Hemoglobin A1c    | rs1195438 | GPR98       | 5q14.3               | 0.148| 207|   +  | 2.80E-08   | 0.012    | 0.068|
| Risperidone - Hemoglobin A1c   | rs1700049 | no          | 5q31.3               | 0.126| 186|   +  | 4.90E-07   | 0.078    | 0.236|
| Risperidone - Hemoglobin A1c   | rs1700050 | no          | 5q31.3               | 0.126| 184|   +  | 7.45E-07   | 0.103    | 0.301|
| Clozapine - Glucose            | rs9658108 | PPARD       | 6p21.31              | 0.052| 53 |   +  | 4.58E-07   | 0.191    | 0.478|
| Clozapine - Glucose            | rs1577917 | no          | 6q14.3               | 0.21 | 53 |   +  | 3.48E-06   | 0.248    | 0.628|
| Clozapine - Total Cholesterol  | rs1979096 | no          | 7p21.1               | 0.115| 53 |   -  | 6.02E-07   | 0.157    | 0.392|
| Clozapine - Total Cholesterol  | rs1049504 | no          | 7p21.1               | 0.11 | 52 |   -  | 4.34E-07   | 0.129    | 0.334|
| Clozapine - Triglycerides      | rs1322468 | PRKAR2B     | 7p22.3               | 0.072| 53 |   +  | 6.30E-08   | 0.015    | 0.055|
| Olanzapine - Total Cholesterol | rs977396  | no          | 8q22.3               | 0.089| 261|   +  | 3.27E-07   | 0.173    | 0.463|
| Clozapine - Glucose            | rs320209  | no          | 9q31.1               | 0.068| 53 |   +  | 3.94E-07   | 0.174    | 0.448|
| Perphenazine - Triglycerides   | rs4832255 | RNF144A     | 9q33.1               | 0.139| 135|   +  | 2.62E-07   | 0.031    | 0.135|
| Clozapine - Triglycerides      | rs1761258 | no          | 10p12.33             | 0.138| 51 |   +  | 1.30E-06   | 0.131    | 0.415|
| Clozapine - Triglycerides      | rs2994684 | no          | 10p11.22             | 0.155| 53 |   +  | 2.58E-07   | 0.041    | 0.153|
| Outcome                  | SNP         | Gene symbol | Cytogenetic location | MAF  | N   | Eff   | p-value     | q-value  | FDR  |
|-------------------------|-------------|-------------|----------------------|------|-----|-------|-------------|----------|------|
| Clozapine - Triglycerides | rs1771628   | no          | 10p11.22             | 0.191| 53  | +     | 6.66E-07    | 0.082    | 0.286 |
| Risperidone - Hip Circumference | rs7119817   | no          | 11q23.1              | 0.371| 264 | +     | 4.51E-07    | 0.067    | 0.292 |
| Risperidone - Hip Circumference | rs7105881   | no          | 11q23.1              | 0.367| 265 | +     | 3.27E-07    | 0.052    | 0.235 |
| Risperidone - Hip Circumference | rs7108821   | no          | 11q23.1              | 0.367| 263 | +     | 4.21E-07    | 0.063    | 0.279 |
| Clozapine - Triglycerides | rs620875    | KIRREL3     | 11q24.2              | 0.101| 53  | +     | 3.20E-06    | 0.236    | 0.61  |
| Perphenazine - HDL      | rs1464500   | SOX5        | 12p12.1              | 0.232| 138 | +     | 1.07E-07    | 0.058    | 0.204 |
| Quetiapine - HDL        | rs518590    | no          | 13q12.11             | 0.21 | 253 | +     | 1.60E-07    | 0.14     | 0.416 |
| Perphenazine - Total Cholesterol | rs1187614  | CLMN        | 14q32.13             | 0.313| 138 | -     | 2.37E-07    | 0.23     | 0.541 |
| Risperidone - Hip Circumference | rs1568679   | MEIS2       | 15q14                | 0.103| 265 | +     | 1.28E-08    | 0.004    | 0.018 |
| Risperidone - Waist Circumference | rs1568679  | MEIS2       | 15q14                | 0.103| 266 | +     | 6.82E-08    | 0.055    | 0.244 |
| Risperidone - Hemoglobin A1c | rs1335336   | ATF7IP2     | 16p13.13             | 0.078| 187 | +     | 7.09E-07    | 0.1      | 0.293 |
| Perphenazine - Triglycerides | rs153091    | LOC729993   | 16p13.12             | 0.227| 138 | +     | 1.85E-06    | 0.135    | 0.474 |
| Olanzapine - Total Cholesterol | rs4783227   | CLMN        | 16q23.3              | 0.424| 269 | -     | 3.95E-07    | 0.194    | 0.502 |
| Clozapine - Triglycerides | rs17216786  | CDH13       | 16q23.3              | 0.054| 53  | +     | 1.33E-06    | 0.133    | 0.42  |
| Perphenazine - Triglycerides | rs17651157  | FHOD3       | 18q12.2              | 0.068| 138 | +     | 1.07E-07    | 0.016    | 0.067 |
| Perphenazine - Triglycerides | rs10502661  | FHOD3       | 18q12.2              | 0.063| 138 | +     | 1.61E-07    | 0.021    | 0.093 |
| Risperidone - Hemoglobin A1c | rs8092443   | no          | 18q22.2              | 0.225| 186 | -     | 9.72E-07    | 0.123    | 0.348 |
| Risperidone - Hemoglobin A1c | rs11663206  | no          | 18q22.2              | 0.289| 187 | -     | 2.07E-06    | 0.197    | 0.498 |
| Risperidone - Hip Circumference | rs6092078   | no          | 20q13.2              | 0.115| 264 | -     | 2.61E-06    | 0.238    | 0.681 |

Locus information includes gene in region, cytogenetic location, location of SNP, and the minor allele frequency (MAF) calculated in the complete CATIE sample. For each test we report the sample size (N), direction of effect of minor allele frequency (Eff) where a “+” indicates positive association, q values and local FDRs as estimated using the method developed by Bukszar et al.44, and the number of other analyzed outcomes showing significant association to the SNP at p<.05 (#m). Genomewide significant results are indicated in bold. Consecutive shaded rows indicate SNPs in high LD (r^2 > 0.8).
Table 4

Number of alternate outcome associations ($p<.05$) to genomewide significant SNPs, by metabolic phenotype

| SNP     | Gene   | Genomewide $q$-value | Weight Gain | Lipids | Glucose | Blood Pressure |
|---------|--------|----------------------|-------------|--------|---------|----------------|
|         |        |                      | BMI Hips Waist W/H TChol Trig HDL Gluc A1c Dia Sys HR |        |        |                |
| rs1568679 | MEIS2  | 0.004                | 1 1* 1* 0 0 0 0 1 0 1 1 0 |        |        |                |
| rs11954387 | GPR98  | 0.012                | 0 0 0 0 0 0 0 1 1 1* 0 0 1 |        |        |                |
| rs1967256 | GPR98  | 0.012                | 0 0 0 0 0 0 0 1 1 1* 0 0 1 |        |        |                |
| rs13224682 | PRKAR2B | 0.015                | 1 1 1 0 0 2* 0 1 0 0 1 0 |        |        |                |
| rs17651157 | FHOD3  | 0.016                | 0 0 0 0 0 0 1* 0 0 0 0 0 |        |        |                |
| rs6735179 | no     | 0.018                | 1 0 1 1 0 1* 0 0 0 0 0 |        |        |                |
| rs10502661 | FHOD3  | 0.021                | 0 0 0 0 0 0 1* 0 0 0 0 0 |        |        |                |
| rs6741819 | RNF144A | 0.029                | 0 0 1 1 1 1 1* 1 0 2 0 1 0 |        |        |                |
| rs4838255 | ASTN2  | 0.031                | 0 0 0 1 1 0 1* 0 0 0 1 1 0 |        |        |                |
| rs1405687 | no     | 0.038                | 2 1* 1 0 0 0 0 0 0 2 0 0 |        |        |                |
| rs2994684 | no     | 0.041                | 1 2 2 0 0 0 2* 1 0 0 0 0 |        |        |                |
| rs7105881 | no     | 0.052                | 1 1* 1 0 0 0 1 0 0 1 1 0 |        |        |                |
| rs1117324 | no     | 0.054                | 1 1* 1 0 0 0 0 0 0 0 0 0 |        |        |                |
| rs1464500 | SOX5   | 0.058                | 0 0 0 0 0 0 1 1* 0 0 0 0 |        |        |                |
| rs1088221 | no     | 0.063                | 1 1* 1 0 0 0 0 0 0 1 1 0 |        |        |                |
| rs7119817 | no     | 0.067                | 1 1* 1 0 0 0 1 0 0 1 1 0 |        |        |                |
| rs10202231 | no    | 0.068                | 0 0 1 0 0 0 2* 0 0 0 0 0 |        |        |                |
| rs17100498 | no   | 0.078                | 1 0 0 1 0 0 0 0 1 1* 0 0 0 |        |        |                |
| rs1716268 | no     | 0.082                | 1 2 3 0 0 0 2* 1 1 1 0 0 0 |        |        |                |
| rs13335336 | ATF7IP2 | 0.1                  | 0 1 0 0 0 0 0 0 0 1* 0 0 0 |        |        |                |
| rs17216786 | CDH13  | 0.133                | 1 1 1 1 0 0 1* 0 0 0 0 0 |        |        |                |
| rs153091 | LOC729993 | 0.135              | 0 0 0 0 0 0 0 1* 0 0 0 0 0 |        |        |                |
| rs9658108 | PPARD  | 0.191                | 1 1 1 0 0 0 1 0 1* 0 0 0 |        |        |                |
| rs1187614 | CLMN   | 0.23                 | 1 0 1 0 0 1* 0 0 0 0 0 |        |        |                |
| rs620875 | KIRREL3 | 0.236                | 2 2 1 1 0 0 1* 0 1 1 0 0 0 |        |        |                |

Genomewide significant finding marked with asterisk.