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Genome-wide association study of antipsychotic induced QTc interval prolongation

Karolina Åberg, PhD[a,*], **Daniel E. Adkins, PhD**[a], **Youfang Liu, PhD**[b], **Joseph L. McClay, PhD**[a], **József Bukszár, PhD**[a], **Peilin Jia, PhD**[c], **Zhongming Zhao, PhD**[c], **Diana Perkins, MD**[d], **T. Scott Stroup, MD**[e], **Jeffrey A. Lieberman, MD**[e], **Patrick F. Sullivan, MD**[b,f], and **Edwin J.C.G. van den Oord, PhD**[a]

[a]Center for Biomarker Research and Personalized Medicine, School of Pharmacy, Virginia Commonwealth University, Richmond VA 23289, USA

[b]Departments of Genetics, Psychiatry and Epidemiology, University of North Carolina at Chapel Hill, NC 27599, USA

[c]Departments of Biomedical Informatics, Psychiatry and Cancer Biology, Vanderbilt University Medical Center, Nashville, TN 37203, USA

[d]Department of Psychiatry, University of North Carolina at Chapel Hill, NC 27514, USA

[e]Department of Psychiatry, Columbia University, New York, NY 10032, USA

[f]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 17177 Stockholm, Sweden

Abstract

QT prolongation is associated with increased risk of cardiac arrhythmias. Identifying the genetic variants that mediate antipsychotic induced prolongation may help to minimize this risk, which might prevent the removal of efficacious drugs from the market. We performed candidate gene analysis and five drug specific genome-wide association studies (GWAS) with 492K SNPs to search for genetic variation mediating antipsychotic induced QT prolongation in 738

[*]Correspondence to: Karolina Åberg, Center for Biomarker Research and Personalized Medicine, School of Pharmacy, Medical College of Virginia of Virginia Commonwealth University, 1112 East Clay Street, P.O. Box 980533, Richmond, VA 23298., Tel: +1 804-628 3023, Fax: +1 804-628 3991, kaaberg@vcu.edu.

Supplementary Information

Supplementary Information accompanies the paper on the The Pharmacogenomics Journal website (http://www.nature.com/tpj)

Conflict of Interest Statement

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schizophrenia patients from the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study.

Our candidate gene study suggests the involvement of *NOS1AP* and *NUBPL* (p-values $=1.45\times10^{-05}$ and 2.66×10^{-13}, respectively). Furthermore, our top GWAS hit achieving genome-wide significance, defined as a q-value <0.10, (*p*-value $=1.54\times10^{-7}$, *q*-value =0.07), located in *SLC22A23*, mediated the effects of quetiapine on prolongation. *SLC22A23* belongs to a family of organic ion transporters that shuttle a variety of compounds including drugs, environmental toxins, and endogenous metabolites across the cell membrane. This gene is expressed in the heart and is integral in mouse heart development. The genes mediating antipsychotic induced QT prolongation partially overlap with the genes affecting normal QT interval variation. However, some genes may also be unique for drug induced prolongation. This study demonstrates the potential of GWAS to discover genes and pathways that mediate antipsychotic induced QT prolongation.

Keywords

candidate gene analysis; genome-wide association study; schizophrenia; adverse effects; CATIE

Introduction

The QT interval is an electrocardiogram feature (ECG) that begins with the onset of the ventricular depolarization (Q wave) and ends with completion of repolarization (T wave). The interval shortens with increasing heart rate and is therefore commonly corrected for heart rate (QTc). QT prolongation, in particular in combination with other risk factors including female gender, heart disease, hypokalemia, or old age, is associated with an increased risk of potentially lethal cardiac arrhythmias and is therefore of major concern[1, 2]. QT interval prolongation can be congenital or mediated by numerous medications and drugs of abuse as well as by e.g., infections and electrolyte disturbance.

Antipsychotic drugs are the cornerstones of acute and long-term treatment for schizophrenia. The risk of suddendeath for patients receiving antipsychotic drugs has been estimated to 2.39 times the risk of untreated controls [3]. Part of this increased risk may be due to the disease itself. Untreated schizophrenia patients have a higherresting heart rate than healthy individuals indicating higher levels of arousal. Furthermore, schizophrenia is strongly associated with smoking, putting schizophrenia patients at increased risk of cardiovascular mortality. Another part of the increased risk is attributable to antipsychotic drugs [4–6].

Current guidelines, intended to predict whether an antipsychotic agent carries an increased risk of serious cardiac arrhythmias, place much emphasis on QT interval prolongation as a (pre-clinical) indicator [7]. Although sudden death is rare and antipsychotic induced QT prolongation is not always linked to arrhythmia [8], QT prolongation is among the most common reasons antipsychotic agents are restricted or removed from the market. Sertindole was voluntarily suspended, droperidol was withdrawn, and restricted labeling was introduced for thioridazine and pimozide. Ziprasidone seems toprolong the QT interval more than haloperidol, olanzapine, quetiapine, and risperidone but less than sertindole and thioridazine. The identification of the mechanisms underlying antipsychotic induced QTc

prolongation is a critical step to develop diagnostic tools that could help minimize risk in general and avoid that efficacious drugs are removed from the market because of a few highly susceptible patients.

Understanding the genetic components involved in the development of antipsychotic induced QT prolongation might facilitate a priori identification of patients with increased susceptibility. Genetic research of the QT interval has largely relied on family-based designs studying rare congenital Mendelian QT syndromes. These studies have identified a number of genes in which rare mutations affect the QT interval and increase the risk of sudden cardiac death. Some of these genetic mutations have been found in patients with medication-induced QT prolongation [9]. Although these rare variants may only explain a minority of drug induced QT prolongation, it suggests that genetic variants could be risk factors for drug induced QT prolongation.

Recently a common genetic variant in the nitric oxide synthase 1 adaptor protein gene (*NOS1AP)* that affects cardiac repolarization was identified [10]. This finding was replicated in several independent samples [11–13]. Further common variants were suggested by two recent meta-analyses of genome-wide association studies (GWAS) of the QT interval. One meta-analysis used genome-wide data from five population-based cohorts with a total of 15,842 individuals of European ancestry [14]. In addition to confirming the *NOS1AP* association, they identify nine loci at p-value $<5\times10^{-8}$. Four loci map near the above mentioned Mendelian long-QT syndrome genes, two loci include genes with established electrophysiological function, whereas three genes have not previously been implicated in cardiac electrophysiology. The second meta-analysis included three GWAS from 13,685 individuals of European ancestry [15]. These authors replicated the *NOS1AP* findings, genes involved in Mendelian long-QT syndromes and identified five new loci.

Although genetic variants affecting congenital long QT could mediate drug-induced QT prolongation, drug specific genetic factors may be involved as well. A recent GWAS of QT prolongation after 14 days of treatment with iloperidone [16] suggested the possible role of six genes. Whereas the two meta-analyses of the QTc interval showed considerable overlap, none of the genes identified for drug-induced QT prolongation were among the genome-wide significant results in the two meta-analyses.

Our study aims to detect genetic variants that mediate the effects of five commonly prescribed antipsychotic drugs on QT prolongation. The sample consists of 738 schizophrenia patients from the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study [17, 18]. We perform drug specific GWAS to detect novel genetic variants as well as conduct specific analysis of potential candidate genes.

Materials and Methods

Study sample

The CATIE study sample has been carefully described elsewhere [17, 18]. In short, CATIE is a multiphase randomized controlled trial. The patients were diagnosed with schizophrenia using the Structured Clinical Interview for DSM-IV [19] and followed for up to 18 months.

The main study drugs were olanzapine, perphenazine, quetiapine, risperidone and ziprasidone. The participants were recruited from 57 clinical settings around the United States. 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.

Phenotype measures

Electrocardiograms (ECG) were conducted at the screening phase prior to entering the study, at the end of each treatment phase, one month after a new treatment phase started, and at month 18. Patients who at screening had QTc prolongation (for men QTc >450 and for women QTc >470) were excluded from CATIE. Furthermore, subjects with a history of QTc prolongation, a recent myocardial infarction, a history of sustained cardiac arrhythmia, uncompensated congestive heart failure, completed left bundle branch block, first-degree heart block or currently were prescribed any concurrent treatment were excluded from the CATIE study. Patients were discontinued from participation if QTc prolongation was observed on a follow-up ECG. However, this occurred only three times. All ECGs were transmitted electronically to Cardiac Alert (Quintiles ECG) and automated QTc measures confirmed by cardiologists. Prior to analyses, the QT interval was corrected for the heart rate (QTc) according to Bazett's method [20].

Genotyping and genotype quality control

DNA sampling, genotyping and genotype quality control have been described by Sullivan et al. [21]. In total, 665,439 SNPs were genotyped using the Affymetrix 500K 'A' chipset (Santa Clara, CA, USA) and a custom 164K SNP-chip created by Perlegen (Mountain View, CA, USA). After quality control, 492,000 SNP genotypes from 738 individuals remained for statistical analysis.

Statistical analyses

We have previously described [22] and applied [23, 24] a systematic method to estimate treatment effects in CATIE. This approach uses mixed modeling [25, 26] to condense all measurements collected during the CATIE trial in an optimal, empirical fashion. Our method first tests the best way to model antipsychotic effects, 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 using best linear unbiased predictors (BLUPs) [27]. As this approach takes advantages of all available information detected at multiple time points in CATIE, it is more powerful than traditional approaches (e.g., subtracting pre- from post-treatment observations) that use only two time points (see Supplementary Information for modeling details).

Approximately 57% of the CATIE subjects self-identify themselves as white/European American (EA) and 29% as black/African American (AA). The remaining 14% of the patients consider themselves to have other ancestral origins or to belong to multiple ancestral categories. If ancestry associated differences in both genotype and phenotype distributions exist, there will be a risk of false-positive association findings. To avoid such false positives, it is essential to take the different ancestral backgrounds into account. For this purpose, we used the multi-dimensional scaling (MDS) approach implemented in

PLINK [28] that is essentially equivalent to the principal component method implemented in EigenSoft [29]. Input data for the MDS approach are the genome-wide average proportion of alleles shared identical by state (IBS) between any two individuals. From this (genetic) similarity matrix ancestral MDS dimension are extracted. The first dimension 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 orthogonal dimensions appeared to capture the vast majority of genetic substructure in the CATIE sample and were used in further analysis. All association testing was conducted in PLINK [28] using a linear regression model with the five population stratification MDS dimensions as covariates to avoid false positives due to the possible effects of ancestral background. Other precision-enhancing covariates were accounted for in the modeling of the BLUPs and thus were not included as separate covariates in PLINK.

To address the issue of multiple testing and controlling the risk of false discovery rate (FDR) we calculated Storey's *q*-values [30, 31]. We used a threshold of *q*-value <0.1 for declaring genome-wide significance [32]. This threshold ensures, on average, that only 10% of the SNPs declared significant will be false 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 (*l*FDR). This estimated *l*FDR equals the posterior probability that the SNP has no effect [33]. It is important to note that this estimate is sensitive to the larger effects only so that SNPs with *l*FDR=1 could still have a true but (very) small effect. The main advantage of the *l*FDR is that it provides a marker-specific estimate of 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 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 [34].

Candidate gene analyses

To study gene specific enrichment and overall signal enrichment of the entire set of candidate genes, we used a chi-square test to examine whether the total number of observed markers with *p*-values <0.05 deviated significantly from the number expected under the null hypothesis assuming no enrichment. In order to minimize the risk that a detected enrichment is an effect of non-independence between the tests (*i.e.* linkage disequilibrium) we conducted permutations for the genes with enriched signals. That is, while keeping the genotype and MDS information consistent we conducted association testing as described for the GWAS, with the exception that we randomly assigned the phenotypes (BLUPs) 10,000 times to an individual, and recorded the number of times enrichment was detected with the permutated phenotypes. Furthermore, a threshold of *q*-value <0.1 was again used to declare significance for individual candidate gene markers.

Results

Descriptive statistics and antipsychotic induced QTc effects

The average QTc interval in our sample was 405.0 msec (SD=24.9). Table 1 presents descriptive statistics for an array of demographic and clinical variables, as well as the effect of these variables on QTc estimated by mixed model regression analyses. Males constituted 74% of the sample, the mean age of the participants was 40.4 years. On average patients received antipsychotic medication for the first time 13.8 years prior to entering into CATIE. As expected, average QTc was substantially shorter (12.48 msec) in males than in females. The QTc tended to be longer in older subjects but self-identified race did not significantly affect QTc. QTc was significantly prolonged in patients who were treated with antipsychotic agents for a longer time. Table 1 shows that blood pressure and body mass index are positively associated with QTc. No significant associations were found with blood lipids.

The left side of Table 2 shows that the number of subjects/assessments included in the study ranged between 121–249/200–397. The average number of assessments per subject was 3.4. The right side of Table 2 shows the effects of the five major CATIE trial antipsychotic drugs on standardized QTc as estimated by linear mixed regression models and controlling for the antipsychotic drugs that the subjects used directly prior to the current study phase. The average antipsychotic effect on QTc prolongation (Table 2, column b) was somewhat larger than those reported in Table 1 for the demographic and clinical variables where the sign of effects for olanzapine and risperidone was negative. However, this pattern can easily be explained by the smaller sample sizes. Indeed, only the effect of quetiapine was significant (b=0.193, p_b=0.026).

The aim of this study is to identify genetic variants explaining individual differences in antipsychotic effects on the QTc interval. For this purpose, the significance of the average effect (Table 2, column b) is irrelevant. Instead, significant individual variations of the drug effects are essential. The proportion of the total variance accounted for by individual differences in drug effects calculated at the point where antipsychotic-induced QTc change plateaus (i.e. reaches its maximum effect) are shown (Table 2, column u). Our results show, for all antipsychotic drugs individual differences were large and statistically significant. At the point where drug effects plateau, on average 10% of the total variance was accounted for by individual difference in drug responses. Ziprasidone showed the largest (u=0.220) and olanzapine the smallest (u=0.030) degree of variation accounting for 22% and 3% of the total variance respectively.

Candidate gene analyses

Disease-associated genes have been found to impact drug efficacy, even when the proteins of interest are not known to be directly involved in the pharmacologic actions of the drug [35]. Therefore, we investigate if ten candidate genes and two multi-gene loci previously identified in recent meta-analyses [14, 15] for the QTc interval also mediate antipsychotic induced QTc prolongation. Furthermore, we investigated six suggestive genes from a recently reported GWAS of iloperidone induced QT prolongation [16]. Investigations in CATIE of the mean QTc interval across all observations after the drug specific in-trial

(temporal/dynamic) changes are regressed out (Liu et al., in preparation) replicated the effects of *NOS1AP* and other candidate genes for non-drug related variation in QT interval such as *RNF207* and multiple-gene locus 2 (MLOC2) including *CNOT1, GINS3, NDRG4* and *SETD6.* These replications add confidence to the validity of our methods and analyses in CATIE. *NOS1AP*, the most frequently replicated candidate gene for QTc interval variation, showed enrichment (p-value $<1.45\times10^{-5}$) of potentially interesting signals for drug induced QT prolongation in our study (Table 3, top). In addition, *NUBPL* (nucleotide binding protein-like), one of six candidate genes for drug induced QT prolongation (Table 3, bottom) showed enrichment (p-value = 2.66×10^{-13}) for SNPs with p-values <0.05. The total set of candidate genes for drug induced QT prolongation was slightly enriched (p-values = 0.002). No overall enrichment was seen for the total set of candidates for QTc interval (Table 3). No specific SNP reached significance at our threshold of q-value <0.1.

Genome-wide association analyses (GWAS)

Figure 1 shows the distribution of the p-values from all GWAS using Quantile-Quantile (QQ) plots. Under the null hypothesis, assuming no effects of the markers, the p-values are expected to fall on a straight line in these plots. As we do not expect a large number of SNPs with true effects, systematic deviations from a straight line indicate test statistic inflation that could, for instance, be caused by residual effects of ancestral background. Figure 1 shows no evidence of test statistic inflation, which is confirmed by the reported lambdas [36] that are all close to one. Particularly for quetiapine and risperidone there are markers with p-values, in the upper right corner of the QQ plots that deviate from the straight line and are smaller than expected under the null hypotheses. This pattern suggests a possible association between these specific markers and the outcome variable.

Table 4 shows our most promising findings. According to our pre-specified criteria (q-value <0.1) one finding reached genome-wide significance (p-value = 1.54×10^{-7}, q-value = 0.07), the association between rs4959235 and quetiapine/QTc. This SNP is located within an intron of the gene *SLC22A23* (solute carrier family 22, member 23) that is located on chromosome 6p25.2. Although p-values of markers in the immediate neighborhood of rs4959235 tended to be somewhat better than those of SNPs further away, the main association signal involved rs4959235 (for a regional plot see Supplementary Figure 1). The explanation is the very modest LD between this marker and other investigated markers in the flanking 100 Kb regions (LD <0.2). The posterior probability (*l*FDR = 0.47) for this marker indicated that this particular finding has 53% chance of being a true signal with an (large) effect. Furthermore, subsample-specific tests suggested that this finding was strongly supported by the European American (EA) subsample (p-value = 1.69×10^{-6}) and to some degree supported by the African American (AA) subsample (p-value = 1.77×10^{-2}). Multi-degree of freedom haplotype testing in the subsamples did not significantly improve the signals.

The second most significant drug specific marker, rs10458561, (p-value = 3.89×10^{-7}, q-value = 0.19, *l*FDR = 0.60) was located in an intergeneic region on chromosome 1p31.1. For this marker the posterior probability indicated a 40% chance of truly mediating risperidone's effect on QTc. Subsample-specific tests indicated support from both the AA (p-value = 8.98×10^{-4}) and the EA (p-value = 3.98×10^{-4}) subsamples.

Two additional markers, rs16895513 and rs6468544, (p-value = 1.26×10^{-6}, q-value = 0.20, lFDR = 0.79; and p-value = 8.42×10^{-7}, q-value = 0.20, lFDR = 0.73 for the two markers, respectively) located 2792 base pair apart in an intergenic region on chromosome 8q22.1 were associated with risperidone/QTc. LD between these two markers was close to complete (r^2 = 0.99) suggesting that they represented a single signal. The posterior probabilities for these markers indicated a 21–27% likelihood of a true signal. The subsample-specific tests showed that both AA (p-value = 3.25×10^{-4}) and EA (p-value = 9.04×10^{-4}) contributed to this association signal.

Discussion

Antipsychotic drugs are among the drugs causing QT prolongation. A thorough understanding of the underlying mechanisms is critical to minimize the risk of these serious side effects and to avoid that potentially efficacious drugs causing QT prolongation are not available to schizophrenia patients. Our study indicated that as much as 17–55% of the total variance in the QTc interval was accounted for by individual difference in antipsychotic responses and as much as 10–12% of this variation can be explained by each of the four top GWAS findings (table 4). Some, if not all, of the explained variation might overlap between the SNPs. In particular, this is the case for markers in high LD. We performed candidate gene analysis and GWAS to search for genetic variation mediating the antipsychotic induced individual variation in QTc prolongation in 738 schizophrenia patients from the CATIE study.

Our top hit, achieving genome-wide significance, defined as a q-value ≤0.10, was with SNP rs4959235 at *SLC22A23* that mediated the effects of quetiapine on QTc. The gene is a member of solute carrier family 22, a large family of organic ion transporters that shuttle a variety of compounds including drugs, environmental toxins and endogenous metabolites across the cell membrane [37]. *SLC22A23* is a relatively uncharacterized member of this family, being first described in 2007[38]. While the substrate for this transporter is as yet undetermined, it is known to be expressed in the heart and mouse studies suggest it is integral in heart development [39]. As an organic ion transporter, the mechanism of *SLC22A23*'s involvement in antipsychotic-induced QTc prolongation could be via clearance of the drug from the heart, or via shuttling of molecules involved in cardiac function. The determination of *SLC22A23*'s organic ion substrate would appear to be the first step in elucidating any possible mechanistic relationship.

Our candidate gene analysis suggests that *NOS1AP*, a frequently replicated candidate gene for variations in QTc interval that through nitric oxide synthase signaling accelerates cardiac repolarization [40], might also be involved in drug induced QT prolongation. Furthermore, our study provides support for the *NUBPL* gene as a potential candidate gene for QTc prolongation. This gene belongs to the Mrp/NBP35 ATP-binding proteins family and is involved in nucleotide and ATP binding but the exact function and the potential involvement of this gene in QT prolongation remains to be identified.

In conclusion, our study suggests that there are genes in common for regulation of the QTc interval and drug induced QT prolongation. Furthermore, our GWAS and candidate gene

analyses suggest that genes not known to affect the regulation of the QTc interval potentially mediate drug induced QT prolongation. These genes may be of specific interest in order to personalize treatment for individual patients. Our findings require replication and functional validation. To facilitate the process we provide all *p*-values (http://www.people.vcu.edu/~kaaberg) as a resource for investigators with the requisite samples to carry out replication. Finally, the present study demonstrates the potential of GWAS in order to discover genes and pathways that potentially mediate antipsychotic induced QT prolongation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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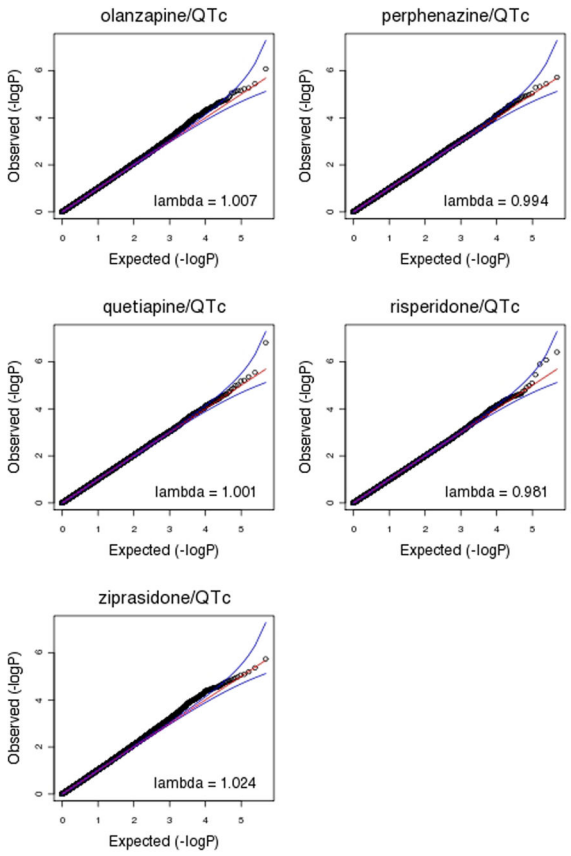

Figure 1.

QQ plots of five genome-wide association analyses. In each plot the ordered observed *p*-values (on a $-\log_{10}(P)$ scale) obtained from the single-marker tests are plotted against the expected *p*-values under the complete null hypothesis (i.e. none of the markers has an effect). The two curved lines indicate the 95% probability interval for the ordered *p*-values. In each plot we also report the estimated lambda that has an expected value of one in the absence of test statistic inflation.

Table 1

Descriptive statistics and mixed model estimates of effects on standardized QTc for demographic and clinical predictors.

	Descriptive Statistics		Effects on QTc	
	Mean	**SD**	***b***	***p***
Male	0.74	0.44	−0.5010	<0.001
Age (years)	40.42	10.97	0.0162	<0.001
White	0.67	0.47	0.0903	0.145
Black	0.30	0.46	−0.1199	0.058
Time since 1st Antipsychotic (years)	13.79	10.71	0.0084	0.002
Systolic blood pressure (mmHg)	124.03	15.56	0.0056	<0.001
Diastolic blood pressure (mmHg)	78.89	10.84	0.0093	<0.001
Body mass index (kg/m^2)	30.32	6.98	0.0176	<0.001
Triglycerides (mg/dL)	203.61	157.44	0.0002	0.127
Total Cholesterol (mg/dL)	199.35	47.04	0.0008	0.123

The descriptive statistics show the mean and standard deviation (SD) for the CATIE study sample (N=738). Note that participants could report belonging to more than one ancestry group. Mixed model parameter *b* is the (fixed) antipsychotic effect, *p* the *p*-value of *b*. The QTc is standardized, for each change of 1 unit in the predictor, QTc changes by *b* standard deviations.

Table 2

Number of subjects/assessments and mixed model estimates of antipsychotic effects on QTc

	Number of Observations		Mixed model estimates			
	Subjects	**Assess.**	***b***	p_b	***u***	p_u
Olanzapine	249	397	−0.104	0.136	0.030	<0.001
Perphenazine	121	200	0.044	0.686	0.091	<0.001
Quetiapine	224	339	0.193	0.026	0.032	<0.001
Risperidone	239	371	−0.144	0.057	0.110	<0.001
Ziprasidone	189	307	0.014	0.887	0.220	<0.001

Mixed model parameter *b* is the (fixed) antipsychotic effect, p_b the *p*-value of *b*, *u* is the random effect standard deviation, and p_u is *p*-value of the random effect. The fixed effects are presented after controlling for antipsychotic drug used directly prior to the current study phase.

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Table 3

Enrichment tests in CATIE for candidate genes/loci previously associated with the QT interval and drug induced QT prolongation.

Gene/Locus	Number of SNPs in gene	Observed	Expected	(O-E)/E	Chi^2 test *p*-value
ATP1B1	44	9	11	−0.18	0.536
KCNE1	40	5	10	−0.50	0.105
KCNH2	14	5	3.5	0.43	0.411
KCNJ2	25	3	6.25	−0.52	0.182
KCNQ1	76	26	19	0.37	0.099
LIG3	18	6	4.5	0.33	0.468
LITAF	24	6	8	0.00	1.000
NOS1AP	**140**	**60**	**35**	**0.71**	**1.45×10^{-05}***
RNF207	8	1	2	−0.50	0.468
SCN5A	43	8	10.75	−0.26	0.389
MLOC1	111	24	27.75	−0.14	0.465
MLOC2	34	7	8.5	−0.18	0.598
Total:	577	160	144.25	0.11	0.178
BRUNOL4	80	21	20	0.05	0.819
CERKL	37	8	9.25	−0.14	0.673
NRG3	276	82	69	0.19	0.108
NUBPL	**39**	**32**	**9.75**	**2.28**	**2.66×10^{-13}***
PALLD	137	44	34.25	0.28	0.087
SLCO3A1	117	25	29.25	−0.15	0.420
Total:	**647**	**212**	**171.5**	**0.24**	**0.002**

Top section shows candidate genes for QTc interval [14, 15]. Multiple-gene locus 1 (MLOC1) includes PLN and SLC35F1. MLOC2 includes CNOT1, GINS3, NDRG4 and SETD6. Bottom section shows candidate genes for drug induced QT prolongation [16]. Observed (O) denotes the number of observed *p*-values < 0.05 while Expected (E) denotes the number of expected *p*-values < 0.05 assuming no effect. The number of tests is 5 x the number of SNPs in the genes. Significant results (p-value <0.01) are indicated in bold.

* Permutations showed that p-values what were detected for NOS1AP and NUBPL are likely to occur by chance eleven and zero times, respectively, out of 10,000.

Table 4

Top results from the genome-wide association studies.

Phenotype	dbSNP	Cytogenetic Location	Location (bp)	Gene Symbol	Number of Individuals	*p*-value	*q*-value	Local FDR
risperidone/QTc	rs10458561	1p31.1	70633194	-	225	3.89×10^{-07}	0.19	0.60
quetiapine/QTc	**rs4959235**	**6p25.2**	**3304336**	**SLC22A23**	**214**	$\mathbf{1.54\times10^{-07}}$	**0.07**	**0.47**
risperidone/QTc	rs16895513*	8q22.1	98396149	-	226	1.26×10^{-06}	0.20	0.79
risperidone/QTc	rs6468544*	8q22.1	98398941	-	224	8.42×10^{-07}	0.20	0.73

Location is given in base pairs (bp) from the p-telomer (Genome Build 35). Bold text indicates genome-wide significance (*q*-value < 0.1).

*Indicate that the markers are in high linkage disequilibrium (LD) ($r^2 = 0.99$)