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Drug-gene interactions and the search for missing heritability: a cross-sectional pharmacogenomics study of the QT interval

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Abstract

Variability in response to drug use is common and heritable, suggesting that genome-wide pharmacogenomics studies may help explain the "missing heritability" of complex traits. Here, we describe four independent analyses in 33,781 participants of European ancestry from ten cohorts that were designed to identify genetic variants modifying the effects of drugs on QT interval duration (QT). Each analysis cross-sectionally examined four therapeutic classes: thiazide diuretics (prevalence of use=13.0%), tri/tetracyclic antidepressants (2.6%), sulfonylurea hypoglycemic agents (2.9%), and QT prolonging drugs as classified by the University of Arizona Center for Education and Research on Therapeutics (4.4%). Drug-gene interactions were estimated using covariable adjusted linear regression and results were combined with fixed-effects meta-analysis. Although drug-SNP interactions were biologically plausible and variables were well-measured, findings from the four cross-sectional meta-analyses were null ($P_{\text{interaction}}>5.0\times10^{-8}$). Simulations suggested that additional efforts, including longitudinal modeling to increase statistical power, are likely needed to identify potentially important pharmacogenomic effects.

Keywords

QT interval; pharmacogenomics; gene-environment interaction

INTRODUCTION

The role of inheritance in response to drug exposure has long been appreciated, dating to as early as 1932 when the inability to taste phenylthiocarbamide was demonstrated to follow an autosomal recessive inheritance pattern.[1] Today, the promise of pharmacogenomics lies in its potential to tailor drug prescription and dosing to individual patients,[2–4] a practice exemplified by the use of a patient's genotype to inform warfarin dosing,[5, 6] to avoid anemia during hepatitis C treatment,[7] or to predict benefit from and therefore guide chemotherapy in breast cancer.[8] Documented heterogeneity of drug response has also prompted the

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CONFLICT OF INTEREST

Conflicts of Interest and Source of Funding

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suggestion that examining drug-gene interactions may help explain a notable proportion of the heritability for complex traits that remains unexplained by genome wide association (GWA) studies.[9, 10] Yet to date, large scale pharmacogenomics studies are few in number.[11]

The duration of the QT interval (QT), a non-invasive measure of the ventricular action potential estimated from the resting, standard twelve-lead electrocardiogram (ECG), offers a good model for examining the value of pharmacogenomics. In addition to being well-measured,[12] heritable,[13, 14] and heterogeneous among those exposed to what are now called "QT-prolonging drugs",[15] QT prolongation is the most common cause of withdrawal or restricted marketing of pharmaceuticals[16] largely because of its established association with ventricular tachyarrhythmia,[17] sudden cardiac death, and all-cause mortality.[18, 19, 20] However, prospectively identifying subpopulations at risk for drug-induced QT prolongation and its sequelae remains a challenge.[16]

Although heritability estimates suggest a substantial genetic component underlying QT, genetic variation at the 26 single nucleotide polymorphisms (SNPs) identified to date by GWA studies together explain approximately 5–8% of the variance in QT.[21–27] Popular explanations for this missing heritability include rare variants that are poorly represented on commercial genotyping arrays as well as gene-gene and gene-environment interactions.[10] In search of this missing heritability, we assessed pharmacogenomic influences on QT by conducting four cross-sectional GWA analyses in ten populations of European ancestry. The goal of the studies was to identify genetic variants modifying the association between drugs in four therapeutic classes previously associated with QT prolongation or sudden death[28–32] and the duration of QT.

METHODS

Study populations

A meta-analysis of ten cohorts with GWA data that included 33,781 participants of European descent was performed to investigate cross-sectional drug-SNP interactions in QT. Five cohorts were from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium:[33] the Age, Gene/Environment Susceptibility – Reykjavik Study (AGES), the Atherosclerosis Risk in Communities study (ARIC), the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), and the Rotterdam Study (RS). Since the inception of CHARGE, five additional cohorts have joined the effort: the Erasmus Rucphen Family study (ERF), Health 2000, the Health Aging, Body and Composition (Health ABC) study, the Multi-Ethnic Study of Atherosclerosis (MESA), and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). At baseline for all cohorts, drug exposure was queried and participants underwent standardized ECGs, which were read for QT duration. Each cohort followed a pre-specified analysis protocol and findings from the within-cohort analyses were then combined by meta-analysis. All studies were approved by local ethics committees and all participants provided written informed consent. Additional information on the participating studies is provided in the Supplementary Material.

Study design; inclusion and exclusion criteria

Within each cohort, we performed four separate cross-sectional analyses using drug, covariate, and ECG data collected at the baseline examination. Participants with the following characteristics were excluded from the analysis: poor quality ECG, extreme QRS duration prolongation including that due to bundle branch block (QRS > 120 ms), atrial fibrillation/flutter on ECG, paced rhythm, or second or third degree atrioventricular block. Heart failure at study baseline was an additional exclusion for the thiazide diuretic, sulfonylurea hypoglycemic agent, and tri/tetracyclic antidepressant analyses. Users of loop diuretics, regardless of thiazide use, also were excluded from analyses examining thiazide diuretics.

Definition of drug exposure

Drug use was assessed by method of medication inventory or pharmacy database (Supplemental Table 1). Six of the nine cohorts using the medication inventory method captured medications used within one to two weeks preceding ECG assessment. The remaining three cohorts currently using medication inventory methods assessed medications used on the day of ECG recording. The Rotterdam Study was the only cohort that assessed drug exposure via pharmacy databases; investigators classified a participant as exposed if he/she filled a prescription for a drug class of interest within 30 days preceding the ECG recording.

Four classes of therapeutic drugs previously associated with QT prolongation were examined: thiazide diuretics,[30, 32] tri/tetracyclic antidepressants,[31] sulfonylurea hypoglycemic agents,[29] and University of Arizona Center for Education and Research on Therapeutics (UAZ CERT)-classified QT prolonging drugs.[28] Participants were classified: as thiazide users if they took a thiazide or thiazide-like diuretic in a single or combination preparation, with or without potassium sparing diuretic or potassium supplements; as sulfonylurea users if they took a first or second generation sulfonylurea anti-diabetic; and as tri/tetracyclic users if they took a tricyclic or tetracyclic antidepressant, ignoring concomitant use of other therapeutic drug classes.

The UAZ CERT classification was used to group medications into four classes based on the likelihood of QT-prolongation: definite, possible, conditional, or no/unknown. Participants using two or more drugs classified as conditional were reclassified as possible. When participants took drugs from more than one UAZ CERT class, the highest class was assigned. For the UAZ CERT analyses, participants classified as users of definite or possible QT prolonging drugs were classified as exposed; participants classified as no/unknown were classified as unexposed; and those reporting use of one conditional QT prolonging agent were excluded.

QT measurement

For each study, technicians digitally recorded resting, supine (or semi-recumbent), standard twelve-lead ECGs for each participant (Supplementary Table 2) on the same day drug exposure was recorded. Studies used comparable procedures for preparing participants, placing electrodes, recording, transmitting, processing and controlling quality of the ECGs,

although QT in the various studies was measured by different automated systems and therefore will be subject to a small variation equivalent to inter observer error. The ECG from the baseline visit was selected when multiple ECGs were available.

Genotype arrays and imputation

Genome-wide SNP genotyping was performed within each cohort using either the Affymetrix or Illumina genotyping arrays (Supplemental Table 3). Gender mismatches and duplicate samples were excluded. First-degree relatives were excluded in all cohorts except the family-based FHS and ERF, which accounted for relatedness in the association analysis. DNA samples with genotyping success rates between <95% and <99%, depending on the cohort, were excluded. SNPs also were excluded when genotyping call rate thresholds were between 95% and 99%, and minor allele frequencies (MAF) ≤ 1%, the determination of which was cohort-specific.

To increase coverage and facilitate evaluation of the same SNPs across cohorts, genotypes were imputed using BIMBAM,[34] MACH[35] or BEAGLE,[36] which applied algorithms that inferred unobserved genotypes in a probabilistic manner. Imputation was performed for ~2.5 million autosomal SNPs based on the HapMap Phase 2 (build 36) CEU reference population (Supplemental Table 3).

Statistical analysis

Each cohort performed four GWA analyses of QT across approximately 2.5 million SNPs comparing drug users to non-users. Study designs that restricted to those on treatment were not chosen because of the large potential for type I error due to the inseparability of the SNP main effect and interaction effect estimates.[37] Each drug-genotype interaction was estimated using linear regression, under an additive genetic model, and using robust standard errors except in the family-based FHS and ERF cohorts, which used linear mixed-effects models as implemented in the GWAF package for R (FHS)[38] and GenABEL/ProbABEL (ERF).[39, 40] All regressions adjusted for the following covariates: age (year), sex, RR interval (ms), recruitment site when appropriate, and principal components summarizing participants' global genetic ancestry to account for confounding by race/ethnicity. Additionally, the four-category UAZ CERT drug categorization was included as a nominal covariate in the thiazides, sulfonylureas, and tri/tetracyclic analyses.

For some SNPs, the numbers of genetic variants among participants on drug therapy were too small to permit use of standard asymptotic results. Therefore, cohort-specific inference used a (Student's) t as the reference distribution. The degrees of freedom for the t reference distribution were calculated as the cohort- and SNP-specific product of: the number of drug-exposed participants, the SNP imputation quality (range: 0, 1), and the MAF (range: 0, 0.50). For each SNP, cohort-specific *P*-values were calculated by comparing β/standard error estimates to this reference, with the resulting P-values then meta-analyzed using the standard weighted Z-statistic method,[41] with weights based on the number exposed to the drug multiplied by the SNP imputation quality.

Cohort-specific results were corrected by their respective genomic inflation factors (λs).[42] The genome-wide threshold for significant drug-SNP interaction was $P < 5.0 \times 10^{-8}$. The software packages R, ProbABEL, GenABEL, PLINK, and GRIMP were used to estimate cohort-specific results (Supplemental Table 3) and METAL[41] was used to generate summary meta-analytic estimates of the drug-SNP interaction parameters. Quantile-quantile (Q-Q) plots were used to identify systematic miscalibration of the test statistic for the drug-genotype interactions.

Statistical power simulations

Power to detect drug-SNP interactions using cross-sectional and longitudinal modeling approaches was estimated via simulation studies. Assumptions, which were informed by study data, included: (1) 20,000–30,000 participants, (2) a two-sided, per-SNP $\alpha = 5.0 \times 10^{-8}$, (3) a mean heart-rate corrected QT (standard deviation) = 426 (20) ms, (4) a prevalence of drug exposure = 0.10 for the longitudinal simulations and 0.03 – 0.14 for the cross-sectional simulations, (5) a mean drug effect for those with zero copies of the minor allele = 1 ms, (6) a mean SNP effect for those not exposed to drug = 1, (7) a MAF = 0.20 for the longitudinal simulations and MAF 0.05–0.30 for the cross-sectional simulations, and (8) an additive model of inheritance. The drug-SNP interaction effect was varied in size. To evaluate the power that could be gained by incorporating repeated measures over time, the simulation incorporated up to 2–6 measurements of QT duration and drug exposure for each participant, and the within-person correlation in QT was set at 0.5 based on unpublished observations. Drug use was either temporally constant or variable. When variable, drug exposure was assumed to be completely random at each time. An attrition rate of 5% per visit, plus random missingness of 5% of remaining measurements, was assumed. Linear models with robust standard errors were used for cross-sectional analyses, and generalized estimating equations (GEE) with exchangeable working correlation were used for longitudinal analyses.

RESULTS

GWA analyses were performed to examine whether common genetic variants modified the effects of exposure to drugs in four therapeutic classes on QT. The ten participating cohorts of European descent varied in size (range: 1,435 – 8,132, Table 1). On average, participants were predominantly female (percent female range: 49.4%–62.5%) and middle-aged to elderly (mean age range = 40–75 years). The estimated prevalence of drug exposure at study baseline was highest for thiazides (13.6%), lowest for the tri/tetracyclics (2.6%), and intermediate for the sulfonylurea hypoglycemic agents (2.9%) and UAZ CERT-classified QT-prolonging drugs (4.4%). After applying genotyping and imputation quality control measures, a total of approximately 2.5 million autosomal SNPs were available for analysis.

Quantile-quantile plots based on meta-analyses of the cohort-specific, drug-SNP interaction test statistics revealed moderately conservative distributions, as demonstrated by $\lambda < 1.0$ (range: 0.89–0.99) and slightly earlier departure of *P*-values in the direction of conservatism, compared to what would have been expected by chance alone (Figure 1). In line with statistical theory, overstated significance due to miscalibration, which was common using

standard asymptotic methods, was not observed using the t-reference approach. These patterns did not differ by the prevalence of medication use at study baseline.

No genome-wide significant cross-sectional interactions ($P < 5.0 \times 10^{-8}$) were detected for any of the four drug classes (Figure 2). The top five loci (Supplemental Table 4) also were inconsistent across drug classes. Cross-sectional meta-analyses restricted to the 26 SNPs reported by previously published GWA studies of QT main effects were similarly null (interaction $P \geq 0.01$, Table 2), as were results for SNPs reported by recent pharmacogenomic studies of QT and drug-induced QT prolongation (Supplemental Table 5).[43–47]

Statistical power

Given the robustly null results and because four cohorts (52.2% of total sample size) had repeated ECG recordings and drug exposure assessments (range: 2, 10; Supplemental Table 2), we examined statistical power for the cross-sectional analysis and the degree to which analyses incorporating repeated measures would increase statistical power. Simulations demonstrated that all cross-sectional analyses were underpowered, especially for drug categories with 3% prevalence (Supplemental Figure 1). However, when the prevalence of drug use increased to 14% (e.g. thiazides) and the SNP was common, we achieved 80% power to detect an effect of 3.25 ms. Incorporating repeat ECG measures with constant drug exposure yielded a moderate increase in statistical power, although the greatest increase was associated with a time-varying drug exposure, i.e. observed QT measurement on and off drug within an individual (Figure 3). For example, we had > 80% power to detect interactive drug-SNP effects less than 2 ms when a time-varying drug exposure was examined at least four different times.

DISCUSSION

In this study composed of approximately 35,000 participants of European descent from ten cohorts, we examined cross-sectional evidence for drug-SNP interactions influencing QT. We did not identify any variants that significantly modified the association between QT and drugs in four therapeutic classes previously associated with QT prolongation. An analysis limited to SNPs with previously identified genome-wide significant main effects yielded similarly null results, as did one restricted to recent pharmacogenomic studies of QT and drug-induced QT prolongation.[43–47]

It remains unclear how much “missing heritability” future gene-environment interaction studies will explain, as GWA studies of interaction effects are only beginning to emerge. Drug exposure likely represents a good candidate for gene-environment interrogation, as medication use is highly prevalent[48, 49] and pharmacogenomics is one of the few fields in which gene-environment interactions have been consistently replicated across studies.[50–54] It is also biologically plausible that the human genome contains variants that modify the association between drug exposure and phenotype, as such common variant alleles would have emerged long before the appearance of modern pharmacotherapies.[55]

We chose a well-measured phenotype[12] with biologically plausible pharmacogenomic effects[15] and our drug assessment methods were sensitive and reliable,[56, 57] yet were unable to detect any genome-wide significant interactions. One possible explanation is statistical power. Using stringent genome-wide significance thresholds, we remained underpowered to detect cross-sectional interactions below six ms for low prevalence drugs (e.g. the sulfonylurea hypoglycemic agents, UAZ CERT, and tri/tetracyclic antidepressants analyses). Although 80% power is achieved when a more common drug exposure is examined (e.g. thiazides), three ms is outside the range of typical genetic effects observed for QT.

Statistical power remains a challenge in gene-environment interaction studies, although the potential utility of longitudinal models to increase power has been shown here and described previously.[58] Increases in power from longitudinal models are due in part to increased precision in outcome measurement; but when exposure varies over time, power increases are also due to within-person comparisons of the outcome under each drug status. Therefore, longitudinal analyses increase power more than expanding sample sizes when there is variability in exposure over time and minimal concern about time-dependent confounding that would complicate the interpretation of longitudinal estimates. Analyses of drug-gene interaction effects on QT satisfy both conditions. However, longitudinal models remain rare in GWA studies examining both main and interactive effects and likely reflect the considerable computational complexities associated with implementing a longitudinal model that accommodates the scale of a typical GWA study. We are currently developing methods to implement longitudinal analyses on a genome-wide scale and future work will include re-evaluation of gene-drug interactions on QT interval using available longitudinal data.

In addition to performing a GWA study of QT-prolonging drug use and QT, as a sensitivity analysis we separately evaluated 26 SNPs previously associated with QT main effects. Restricting interaction analyses to SNPs with replicated main effects is not uncommon in GWA interaction studies,[59] and likely reflects statistical power concerns given the stringent GWA study significance thresholds. Here, we demonstrated that none of the previously identified QT SNPs modified the association between QT prolonging drug use and QT. This is not surprising, as SNPs selected on the basis of an extreme *P*-value for a single main effect may be less likely to harbor heterogeneity across population subgroups.

Several limitations of the present study warrant consideration to inform future efforts examining pharmacogenomic influences on QT. First, we did not address the potential for bias related to duration of use. It is difficult to gauge the overall influence of duration of use effects, in which participants taking the drugs for years or decades are those least likely to have experienced side effects, as they likely differ by drug class. For example, intraclass correlation coefficients (ICC) estimated in the ARIC study suggest intermittent patterns of use for the UAZ CERT class (ICC =0.39), but long-term usage patterns for thiazide diuretics (ICC = 0.69). Although we can suppose that drugs with intermittent patterns of use are less influenced by selection bias related to duration of use than those characterized by long-term usage patterns, further studies examining the robustness of pharmacogenomic findings to such biases are clearly warranted. Second, confounding by contraindication also could result from the comorbidities that influence drug use and QT. However, previous simulations indicated that confounding by contraindication has very modest effects on estimates of

interaction in pharmacogenomic studies.[37] Third, our results are statistically conservative, given the evidence of under-statement of significance for the drug-SNP interaction estimates suggested by QQ plots. However, it is unlikely that the bias would be so large as to cause truly genome-significant loci to be reclassified as non-significant. Fourth, we relied on medication inventory and pharmacy data to ascertain medication usage. Although neither source of information guarantees exposure, validation studies suggest good agreement between serum drug concentrations and several (e.g. thiazide diuretic) exposures ascertained by medication inventory.[56] Pharmacy data appear to be even more accurate in this regard.[60]

Finally, the drug classes considered herein, particularly the UAZ CERT class, combine QT-prolonging drugs that may have heterogeneous mechanisms of action, thereby reducing the sensitivity for detecting SNPs possessing important, population-level interactive effects. However, disagreement among classifications is much lower in the highest ventricular arrhythmia risk category[16] and for older drugs, including the majority of those taken by participants at the time of their past examinations. Relatively systematic attempts to exhaustively identify, classify, and update current lists of QT-prolonging medications in pharmacologically more meaningful ways are also unavailable. Moreover, nearly all drugs that prolong QT and cause ventricular arrhythmias inhibit the rapidly activating delayed rectifier potassium current.[16, 61]

In conclusion, our findings suggest that additional efforts are required to realize the potential of pharmacogenomics. In addition to careful selection of the phenotype of interest, researchers interested in pharmacogenomics should increase the number of measures per participant and invest in longitudinal modeling infrastructure scalable to GWA studies to help increase statistical power. Although these cross-sectional analyses do not support strong drug-gene interactions for QT, future efforts incorporating longitudinal modeling are needed to determine whether the reported associations are underpowered or genuinely null.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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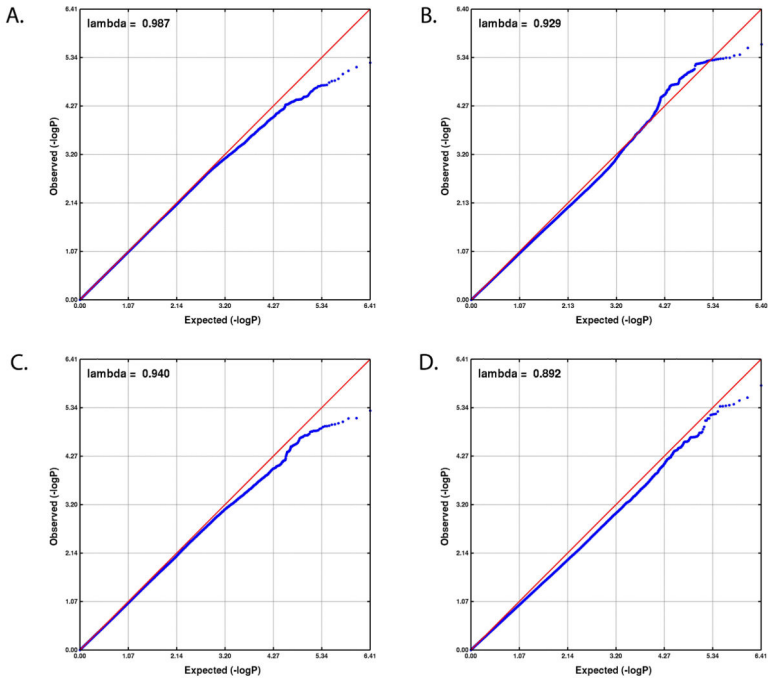

FIGURE 1.

Quantile-quantile (Q-Q) plots of drug-SNP interaction estimates after meta-analysis of summary results from ten cohorts of European descent. Drug classes are as follows: panel A, thiazide diuretics; panel B, sulfonylurea hypoglycemic agents; panel C, University of Arizona Center for Education and Research on Therapeutics (UAZ CERT)-classified QT prolonging drugs; panel D, tri/tetracyclic antidepressants.

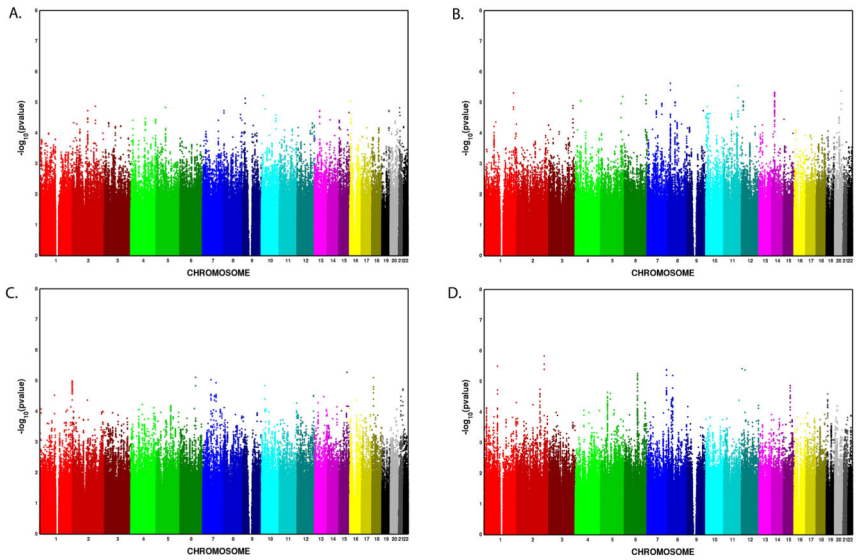

FIGURE 2.

Manhattan plots of drug-SNP interaction estimates after meta-analysis of summary results from ten cohorts of European descent. Drug classes are as follows: panel A, thiazide diuretics; panel B, sulfonylurea hypoglycemic agents; panel C, University of Arizona Center for Education and Research on Therapeutics (UAZ CERT)-classified QT prolonging drugs; panel D, tri/tetracyclic antidepressants.

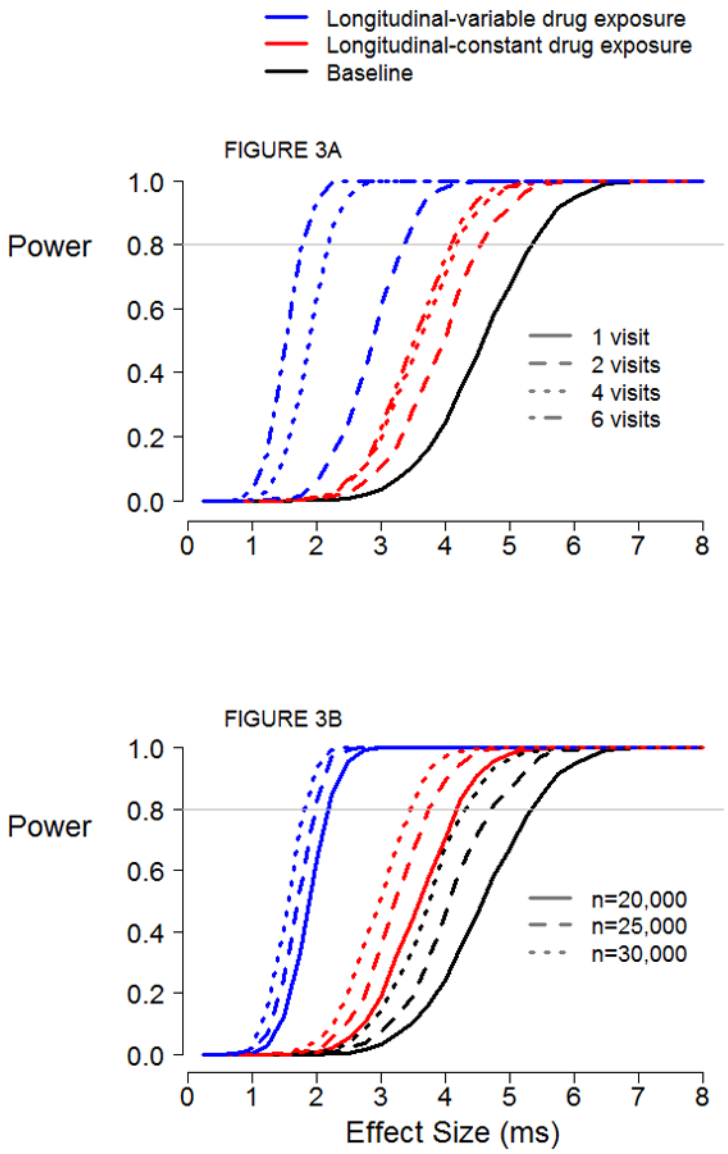

FIGURE 3.

Statistical power of a simulated pharmacogenomics study of QT. The following assumptions were used for the calculations; 2–6 serial visits measuring ECGs and drug exposure, n=20,000–30,000 participants, a SNP minor allele frequency of 0.20, and the prevalence of drug exposure at any one visit of 10%. The solid black lines represent a cross-sectional analysis, the red lines a longitudinal model evaluating drug exposure measured at baseline and repeated ECG measures, and the blue lines a longitudinal model with drug exposure and ECG assessed at all visits. Figure 3A assumes 20,000 participants, with variable number of visits. Figure 3B assumes four visits, with a variable number of participants.

TABLE 1

Baseline characteristics of ten cohorts examining pharmacogenomic effects on the QT interval.

					Prevalence of Drug Exposure			
Cohort	**N**[†]	**QT (ms)**	**Age (years)**	**Female**	**Thiazides**	**Sulfonylureas**	**TCAs**	**UAZ CERT**[‡]
AGES	2,587	406 (35)	76 (5)	1,606 (62.1)	624 (24.1)	62 (3.1)	95 (4.8)	147 (7.3)
ARIC	8,132	398 (28)	54 (6)	4,279 (52.6)	951 (11.7)	152 (1.9)	227 (2.8)	360 (4.5)
CHS	2,813	414 (32)	72 (5)	1, 760 (62.5)	582 (20.7)	110 (3.9)	94 (3.2)	143 (5.1)
ERF	1,503	398 (28)	48 (14)	887 (59.0)	29 (2.0)			49 (3.3)
FHS	3,168	414 (30)	40 (9)	1,920 (60.0)	89 (2.8)	23 (0.83)	56 (1.8)	132 (4.8)
Health ABC	1,435	413 (36)	74 (3)	709 (49.4)	218 (11.1)	81 (6.2)	43 (3.0)	108 (8.2)
Health 2000	2,124	389 (30)	50 (11)	1,104 (52.0)	104 (7.2)			27 (1.3)
MESA	2,217	412 (29)	62 (10)	1,156 (52.1)	281 (12.7)	55 (2.4)	44 (1.9)	104 (4.6)
PROSPER	4,556	414 (36)	75 (3)	2,445 (54.0)	1,175 (25.8)	243 (4.9)	151 (3.3)	281 (5.7)
RS1	3,647	397 (28)	68 (8)	2,184(59.9)	251 (6.9)	95 (2.5)	38 (1.0)	105 (2.8)
RS2	1,599	402 (28)	64 (8)	890 (55.7)	92 (5.8)	48 (3.1)	24 (1.5)	47 (3.0)
Summary:	33,781	Range: 389, 414	Range: 40, 75	Range: 49.4, 62.5%	4,396 (13.0)	869 (2.9)	772 (2.6)	1,503 (4.4)

[*] Data presented as mean (standard deviation) or N (proportion).

[†] Number of participants varied by analysis. Number of participants meeting common exclusion criteria presented.

[‡] Included drugs classified as definite and possible QT prolonging agents. AGES, Age, Gene/Environment Susceptibility – Reykjavik Study. ARIC, Atherosclerosis Risk in Communities study. CHS, Cardiovascular Health Study. ERF, Erasmus Rucphen Family study. FHS, Framingham Heart Study. Health ABC, Health Aging, Body and Composition. MESA, Multi-Ethnic Study of Atherosclerosis. MS, milliseconds. N, number. PROSPER, Prospective Study of Pravastatin in the Elderly at Risk. RS, Rotterdam Study. SNP, single nucleotide polymorphism. TCA, tri-/tetra-cyclic antidepressants. UAZ CERT, University of Arizona Center for Education and Research on Therapeutics QT prolonging agents classification.

TABLE 2

t-distribution meta-analytic *P*-values from ten cohorts examining drug-SNP interactions limited to 26 SNPs with genome-wide significant effects reported in prior studies of the QT-SNP association among populations of European descent.

				Interaction *P*-value‡			
Previously identified locus*	**European index SNP**	**Alleles†**	**CAF**	**Thiazides**	**Sulfonylureas**	**UAZ CERT**	**TCAs**
RNF207	rs846111[24, 26]	C/G	0.28	0.90	0.43	0.67	0.02
NOS1AP	rs12143842[24–26]	T/C	0.25	0.60	0.85	0.11	0.40
	rs12029454[24]	A/G	0.15	0.10	0.26	0.87	0.66
	rs16857031[24]	C/G	0.87	0.01	0.96	0.98	0.85
	rs4657178[26]	T/C	0.25	0.52	0.76	0.15	0.78
	rs2880058[23, 27]	A/G	0.67	0.84	0.36	0.56	0.62
	rs10494366[22]	T/G	0.64	0.35	0.93	0.25	0.74
ATP1B1	rs10919071[26]	A/G	0.87	0.92	0.68	0.66	0.73
SCN5A	rs12053903[24]	T/C	0.68	0.32	0.18	0.93	0.74
	rs11129795[26]	A/G	0.24	0.09	0.26	0.95	0.57
PLN, SLC35F1	rs11756438[24]	A/C	0.48	0.90	0.36	0.24	0.74
	rs11153730[25]	T/C	0.50	0.64	0.20	0.80	0.72
	rs11970286[26]	T/C	0.47	0.39	0.63	0.70	0.73
	rs12210810[26]	C/G	0.06	0.70	0.65	0.28	0.70
KCNH2	rs4725982[24]	T/C	0.22	0.76	0.65	0.28	0.75
	rs2968864[24]	T/C	0.76	0.62	0.59	0.44	0.11
	rs2968863[26]	T/C	0.24	0.58	0.84	0.17	0.11
KCNQ1	rs2074238[24]	T/C	0.06	0.02	0.90	0.18	0.67
	rs12576239[24]	T/C	0.13	0.05	0.16	0.98	0.34
	rs12296050[26]	T/C	0.18	0.03	0.12	0.64	0.77
Intergenic	rs2478333[23]	A/C	0.36	0.35	0.15	0.10	0.22
LITAF	rs8049607[24, 26]	T/C	0.50	0.01	0.55	0.03	0.20
NDRG4	rs7188697[26]	A/G	0.74	0.36	0.39	0.79	0.62
	rs37062[24]	A/G	0.75	0.49	0.39	0.23	0.63
LIG3,RFFL	rs2074518[24]	T/C	0.46	0.29	0.35	0.33	0.86

				Interaction *P*-value‡			
Previously identified locus*	**European index SNP**	**Alleles†**	**CAF**	**Thiazides**	**Sulfonylureas**	**UAZ CERT**	**TCAs**
KCNJ2	rs17779747[26]	T/G	0.33	0.50	0.90	0.85	0.18

*All SNPs reported in genome-wide literature are examined. No linkage disequilibrium filter was applied.

†Coded allele listed first.

‡Meta-analysis was performed on interaction *P*-values. CAF, coded allele frequency. SNP, single nucleotide polymorphism. TCA, tri-/tetra-cyclic antidepressants. UAZ CERT, University of Arizona Center for Education and Research on Therapeutics QT prolonging agents classification.