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A genome-wide interaction analysis of tri/tetracyclic antidepressants and RR and QT intervals: a pharmacogenomics study from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium

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Abstract

Background—Increased heart rate and a prolonged QT interval are important risk factors for cardiovascular morbidity and mortality, and can be influenced by the use of various medications, including tri/tetracyclic antidepressants (TCAs). We aim to identify genetic loci that modify the association between TCA use and RR and QT intervals.

Methods and Results—We conducted race/ethnic-specific genome-wide interaction analyses (with HapMap Phase II imputed reference panel imputation) of TCAs and resting RR and QT intervals in cohorts of European (n=45,706; n=1,417 TCA users), African (n=10,235; n=296 TCA users) and Hispanic/Latino (n=13,808; n=147 TCA users) ancestry, adjusted for clinical covariates. Among the populations of European ancestry, two genome-wide significant loci were identified for RR interval: rs6737205 in *BRE* ($\beta = 56.3$, $P_{interaction} = 3.9e^{-9}$) and rs9830388 in *UBE2E2* ($\beta = 25.2$, $P_{interaction} = 1.7e^{-8}$). In Hispanic/Latino cohorts, rs2291477 in *TGFBR3* significantly modified the association between TCAs and QT intervals ($\beta = 9.3$, $P_{interaction} = 2.55e^{-8}$). In the meta-analyses of the other ethnicities, these loci either were excluded from the meta-analyses (as part of quality control), or their effects did not reach the level of nominal statistical significance ($P_{interaction} > 0.05$). No new variants were identified in these ethnicities. No additional loci were identified after inverse-variance-weighted meta-analysis of the three ancestries.

Conclusion—Among Europeans, TCA interactions with variants in *BRE* and *UBE2E2*, were identified in relation to RR intervals. Among Hispanic/Latinos, variants in *TGFBR3* modified the relation between TCAs and QT intervals. Future studies are required to confirm our results.

Keywords

drug-gene interaction; Genome Wide Association Study; tri/tetracyclic antidepressants; RR interval; QT interval electrocardiography

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Disclosures

None.

Introduction

An increased resting heart rate and a prolonged QT interval are independent risk factors for cardiovascular morbidity and mortality[1–4]. To date, multiple medications have shown clinically significant effects on heart rate, the heart-rate corrected QT interval (QTc), or both[5–7]. For example, the tri/tetracyclic antidepressants (TCAs) have tachycardic and QT-prolonging effects originating from their anticholinergic properties (through antagonizing acetylcholine neurotransmitter signaling[5 7–11]). Despite drug safety warnings, particularly in at risk populations (e.g., the elderly), TCAs are still commonly prescribed in Western societies[12–14] for the treatment of depression, anxiety, insomnia, and neuropathic pain[12].

Both resting heart rate and QT interval duration are heritable, with hereditability estimates ranging from 55–77% for resting heart rate and 35–51% for QT intervals[15–16]. To date, multiple single nucleotide polymorphisms (SNPs) have been identified in genome-wide association studies of resting heart rate[17–19] and QT interval[20–21] among different ethnicities. However, the identified loci (21 for resting heart rate and 35 for QT interval duration[17–20]) explain only 0.8–0.9% and 8–10% of the total variance in these traits[17–20]. Inability to fully explain variance in heart rate and QT intervals may be related to the presence of gene-gene and gene-environment interactions[22]. To examine this possibility, a genome-wide, TCA-SNP interaction meta-analysis of QT was previously conducted in individuals of European ancestry within the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium[23]. However, no significant TCA-SNP interactions were identified, possibly due to the small number of TCA users in the study or its cross-sectional design[23]. Since then, new statistical methods have been developed to incorporate data from multiple visits[24], and additional cohorts of different ancestral origins have been included to increase statistical power.

The present effort collaboratively leverages these methods in a study designed to identify TCA-SNP interactions capable of explaining variation in heart rate (or RR interval) and QT, while also providing insights into the biology of tachycardic and QT-prolonging medications.

Methods

Study populations

The present study used data from 21 different cohorts of three ancestral populations (European [14 cohorts], African [5 cohorts], and Hispanic/Latino [2 cohorts, noting that “Hispanic/Latino” captures a diverse population][25]) that were assembled and analyzed by the Pharmacogenomics Working Group in the CHARGE consortium[26]. All cohorts conducted the analyses within their own study on the basis of a predefined protocol. Cohorts with genetic data were eligible to participate when data on medication use and on the study outcomes were both collected during the same visit. Genotype data had to be imputed with either the HapMap Phase 2[27] or 1000 Genomes reference panel[28]. One of the studies (Anglo-Scandinavian Cardiac Outcomes Trial [ASCOT]) did not record electrocardiograms (ECGs), and therefore participated in analyses on only RR, and not on QT. All studies were

approved by local ethics committees, and all participants gave written informed consent. Cohort-specific descriptions of the study design can be found in the Supplementary Materials.

Inclusion and exclusion criteria

All participants with data on medication use and a high quality ECG (when available), and who were successfully genotyped, were eligible for inclusion in the analyses. Participants with atrial fibrillation, a pacemaker, and/or second or third degree atrioventricular block were excluded from the analyses, as were participants with heart failure or a QRS duration ≥120 milliseconds (ms).

Drug exposure assessment

Most cohorts collected information on medication use by inventory (Supplementary Table 1). However, the Rotterdam Study (RS) defined medication use on the basis of pharmacy dispensing data (from 1991 onwards). For these individuals, exposure was defined as a prescription filled for a medication of interest within 30 days preceding the ECG recording. Cohorts were asked to define exposures to the following medications (or medication classes): TCAs (ATC code “N06AA”), beta-blocking agents (ATC code “C07”), verapamil (ATC code “C08DA01”), diltiazem (ATC code “C08DB01”), and medications known to definitely prolong QT intervals or that are generally accepted to increase the risk of torsade de pointes. Categorization of medications as “definite” for QT prolongation was based on classification from the Arizona Center for Education and Research on Therapeutics (UAZ CERT) as of March 2008[29].

Assessment of QT and RR interval

In each cohort, research technicians recorded a standard 12-lead ECG or pulse rate (in the case of ASCOT) in the resting state for each participant (Supplementary Table 2). Almost all cohorts measured RR and QT intervals automatically, to decrease measurement error and inter-individual variation. Studies conducted all analyses longitudinally, allowing multiple visits per participant in the analyses when multiple ECGs were available (and when data on medication use were also collected).

Genotyping and imputation

Genome-wide SNP genotyping was performed within each cohort separately, using commercially available genotyping arrays from Affymetrix (Santa Clara, CA, USA) or Illumina (San Diego, CA, USA; Supplementary Table 3). Duplicates and samples with gender mismatches were excluded from all studies. First-degree relatives were excluded from all studies, except for the family-based Framingham Heart Study (FHS), Jackson Heart Study (JHS), and Hispanic Community Health Study/Study of Latinos (HCHS/SOL); HCHS/SOL investigators also used methods that accounted for admixture, population structure, and Hardy-Weinberg-departures, when estimating kinship coefficients[25]. Cohort-specific thresholds for genotyping call rates ranged from 95% to 99%. To increase homogeneity between cohorts with respect to the SNPs genotyped by the different platforms, as well as to increase coverage, summary results were based on SNPs from the

HapMap Phase 2 (build 36) reference population[27], given the uniform availability of HapMap2-imputed SNPs and the computational burdens associated with performing analyses for reference panels with much larger numbers of SNPs.

Genome-wide TCA-SNP interaction analyses and meta-analysis

The statistical approaches used to estimate TCA-SNP interactions on RR or QT intervals depended on the study design (e.g., family-based) and the availability of ECG and medication data (e.g., cross-sectional or longitudinal). Cohorts with longitudinal ECG and medication data (e.g., Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, RS, and Women's Health Initiative [WHI]) used generalized estimating equations (GEE)[30] with independent working correlation structure. The family-based FHS and HCHS/SOL studies used linear mixed models that accounted for relatedness, sampling design (HCHS/SOL), and heterogeneity of outcome variance by drug use (HCHS/SOL). Cohorts with unrelated participants and with cross-sectional assessment of ECG and drug data used linear regression models with robust standard errors, as implemented in the ProbABEL software package[31] or in the "bosswithDF" package as implemented in the R statistical environment. Assuming that exposure to TCAs varies randomly across within-person visits for the analyses on RR, we had a power of 0.91 to observe interaction effects of at least 35 milliseconds for variants with a minor allele frequency (MAF) of at least 0.25 (Supplementary Table 4). For QT, we had a power 0.91 to observe interaction effects of at least 7 milliseconds for a MAF of at least 0.25.

TCA-SNP interaction analyses on both RR and QT were adjusted for age and sex. The analyses of RR were additionally adjusted for the use of beta-blocking agents, verapamil, and diltiazem. Similarly, analyses of QT were additionally adjusted for the use of medications that definitely prolong the QT interval and for the resting RR interval. Studies also adjusted for study-specific covariates, as necessary (e.g., study site and principal components).

The robust standard error estimates led to inflated type I errors when the number of participants exposed to the drug and the MAF were both small[24]. We addressed this potential for false-positive results by incorporating variability in the standard error estimates, through use of a *t*-reference distribution with degrees of freedom approximated via Satterthwaite's methods[32–33]. However, at the lowest combinations of minor allele frequency and use of TCAs, the variability of the standard errors was poorly estimated, requiring exclusion of SNPs where 2*(number of exposed participants)*MAF*imputation quality < 10, as described previously [24]. An inverse-variance-weighted meta-analysis was then performed with genomic control using METAL, to combine the results from the different studies [34]. To avoid high type I errors from robust standard error estimates, standard errors were "corrected" using the *t*-distribution-based P-values. These "corrected" standard error estimates were used as inputs for the inverse-variance-weighted meta-analysis. Meta-analyses were performed for each ethnic group separately and for all ethnic groups together. To be considered in our study, SNPs had to be present, after quality control, in at least three cohorts (two cohorts in case of the Hispanic/Latino meta-analysis).

A two-sided P-value <5e^{-8} for TCA-SNP interactions was considered statistically significant in the genome-wide association analyses. Detailed summary results of the ethnic-specific analyses (including rs numbers, MAF values, effect sizes, and P-value) are available through dbGaP (https://www.ncbi.nlm.nih.gov/gap).

Evaluation of previously identified SNPs associated with resting heart rate and QT intervals

Within our European ancestry meta-analysis, we evaluated SNPs that were previously found to have main effects on heart rate or QT in the GWAS of European ancestry as done with HapMap Phase II imputed reference panel imputation [17–20]. From the European GWAS meta-analysis, we extracted all SNPs that had statistically significant effects on heart rate or QT interval (P-value <5e^{-8}) and were present in at least three cohorts (after all quality control steps). We adjusted the P-value threshold for statistical significance using the Bonferroni correction: 2.38e^{-3} for RR intervals (21 independent loci) and 1.43e^{-3} for QT intervals (35 independent loci).

The 21 SNPs associated with RR intervals and the 35 SNPs associated with QT intervals from the meta-analysis in Europeans were further used to calculate a combined multi-locus effect estimate on the TCA-SNP interaction. The resulting multi-locus effect can be interpreted as a Mendelian randomization analysis to assess whether a high resting heart rate and prolonged QT interval are causal effect modifiers of TCA-induced increases in heart rate or QT intervals[35]. This data-driven inverse-variance weighted approach[36] has been implemented in the “gtx” statistical package in the R statistical software environment[37].

Results

Study characteristics

The number of TCA users for each ethnic group were: Europeans, 1,417 (out of 45,706); African Americans, 295 (out of 10,235); and Hispanics/Latinos, 174 (out of 13,808) (Table 1). Cohorts had a mean age ranging from 40.2 (FHS) to 75.3 (Prospective Study of Pravastatin in the Elderly at Risk), and the percentage of included women ranged from 17.8% (ASCOT) to 100% (WHI). Mean RR intervals ranged from 875 (RS1) to 981 (FHS) ms, and QT intervals ranged from 397 (RS1) to 416 (HCHS/SOL) ms.

Genome-wide interaction analysis between tricyclic antidepressants and RR intervals

Within the cohorts of European ancestry, two independent loci reached statistical significance (Table 2; Figure 1A). A q-q plot of the meta-analysis in European cohorts is presented in Figure 1B. The top independent loci comprised the rs6737205 polymorphism on chromosome 2 (Figure 1C), and the rs9830388 polymorphism on chromosome 3 (Figure 1D). Variant rs6737205 (passed quality control in four European cohorts) mapped within the *BRE* gene and was associated with a 56.3 ms prolongation of the RR interval in TCA users, beyond the difference attributed to the allele among nonusers (Effect allele frequency [EAF]: 0.94; P-value = 7.66e^{-9}). Variant rs9830388 (passed quality control in all European cohorts), mapped within the *UBE2E2* gene, and was associated with a 25.2 ms longer RR interval in TCA users, beyond the difference attributed to the allele among nonusers (EAF: 0.51; P-

value = $1.72e^{-8}$). Furthermore, rs11877129 (passed quality control in 11 studies) mapped within the *ABCA3* gene and was suggestively (P-value < $1e^{-7}$) associated with a 36.7 ms longer RR interval in TCA users, beyond the difference attributed to the allele among nonusers (EAF: 0.09; P-value = $2.57e^{-7}$). There was no significant heterogeneity between studies in the observed estimates (P-values > 0.05). These three SNPs, however, did not reach nominal statistical significance in the meta-analyses of the African American cohorts and the Hispanic/Latino cohorts (Table 2, Supplementary Figure 1). Regional plots are presented in Supplementary Figure 2. A meta-analysis of the three ethnicities together did not yield any additional loci with statistically significant effects (Supplementary Figure 3).

Genome-wide interaction analysis between tricyclic antidepressants and QT intervals

Results of the QT meta-analysis in the cohorts of European ancestry are presented in Figure 2. Within this analysis, no significant TCA-SNP interactions were observed. There was one locus in the Hispanic/Latino meta-analysis that reached genome-wide significance, represented by variant rs2291477 (which mapped to *TGFBR3*; β = 9.3; EAF: 0.88; P-value = $2.55e^{-8}$; Supplementary Figure 4/Supplementary Table 5). However, effects of this locus either did not reach nominal statistical significance or did not pass quality control in the European and African American meta-analyses (P-values > 0.05). Furthermore, no genome-wide significant TCA-SNP interactions were observed in the meta-analysis of the three ethnicities together (Supplementary Figure 5).

Previously identified loci for heart rate and QT intervals

The TCA-SNP interactions on RR and QT for SNPs that were previously associated with heart rate and QT are presented in Supplementary Tables 6 and 7. None of the loci previously associated with heart rate or QT showed TCA-SNP interactions on RR or QT respectively (after Bonferroni correction for the number of SNPs included). Furthermore, multi-locus effects of all loci for RR and QT were not statistically significant (Supplementary Figures 6 and 7; P-values = 0.35 and 0.74 for RR and QT, respectively).

Discussion

In a study population of 45,706 European individuals, among whom 1,417 individuals used a TCA at the moment of an ECG recording, we identified two independent loci (and one suggestive locus) that modified the association between TCAs and RR intervals. The significant loci were represented by variants rs6737205 (*BRE*) and rs9830388 (*UBE2E2*), and the suggestive locus by variant rs11867129 (*ABCA3*). As it is well-known that the anticholinergic activity of TCAs may increase heart rates and thus decrease the RR interval, these findings may have a biological basis. Although the variance explained by our findings was not calculated, it is likely modest in view of the low number of exposed individuals. The three loci (*BRE*, *UBE2E2*, and *ABCA3*) either were excluded from the meta-analyses of African and Hispanics/Latino ancestry participants (as part of quality control, e.g., DF <10) or their effects were not nominally significant in the meta-analyses ($P_{interaction}$ >0.05). There were no genome-wide significant loci that modified the association between TCA use and QT intervals in cohorts of European and African American ancestry, although one locus had an effect in Hispanic/Latino cohorts (*TGFBR3*, represented by rs2291477). None of the loci

previously observed to be associated with RR and QT intervals modified TCA effects on their intervals. Furthermore, there was no multi-locus effect of variants previously associated with heart rate or QT intervals on TCA-SNP interactions with RR or QT intervals.

Genetic variation in *BRE* has not been related to any study outcome in prior GWAS reports. The association detected in our meta-analysis appeared to be driven by the estimate observed in ASCOT, although the P-value for heterogeneity among studies was not statistically significant. However, the directions of possible *BRE* effects were similar in the other three studies in which the *BRE* variant passed quality control. ASCOT was the only cohort that examined RR without ECGs, but this difference should have increased inter-individual variation and would decrease statistical power. Therefore, future replication studies of this variant are warranted.

Genetic variation in *UBE2E2* was previously identified in GWAS reports on type 2 diabetes mellitus[38] and motion sickness[39]. To the best of our knowledge, no studies have been published on genetic variation in *UBE2E2* in relation to cardiac conduction (e.g., heart rate or QT intervals) or pharmacological responses to medications. However, variant rs9830388 was associated with mRNA expression levels of *UBE2E2* in blood, based on eQTL data[40–41]. Although significant in Europeans, the results on *UBE2E2* were not generalized in African and Hispanic/Latino ancestry cohorts, perhaps due to limited sample sizes or the smaller effect size. Also, the linkage structure in this part of the genome may differ among ethnicities, as seen in the regional plots.

Genetic variation in *ABCA3*, which produced a suggestive TCA-SNP interaction for RR intervals, has been previously described in relation to the pharmacological response to imatinib in chronic myeloid leukemia [42]. However, we did not find evidence in the literature that *ABCA3* is related to the electrophysiology of the heart.

Despite increasing our sample size and adding repeated ECG assessments to our previous effort on this research topic[23], no significant TCA-SNP interactions were identified for the QT interval in the meta-analysis of European cohorts (for which we had the largest number of TCA users). The single locus with a significant effect in the Hispanic/Latino meta-analysis (represented by rs2291477 in *TGFBR3*) did not have a nominally significant effect among Europeans and African Americans. The observation may suggest that *TGFBR3* influences the QT interval specifically in Hispanic/Latino populations. Alternatively, effects of the TCA-SNP interactions for QT intervals were too small (if any) to be detected with the available sample size. Previously, this variant was identified in GWAS in relation to optic disc morphology[43], but not cardiac conduction. Therefore, potential explanations for the results of our study include lack of TCA-SNP interactions for QT intervals or presence of only small effects that could not be detected, even with the large sample size amassed in this study.

Earlier it was shown that TCA effects on QTc are related to the anticholinergic effects of TCAs on heart rate [12]. When the QT interval was corrected for heart rate by methods other than Bazett's formula, the association between TCA use and QT intervals diminished. Moreover, when using the statistical model adopted herein, the effect of TCAs on QT

intervals was shown to be negligible [12]. Furthermore, prescribed TCA doses and duration of TCA use can be variable among individuals and cohorts. Such variability can increase heterogeneity, making it more difficult to observe significant TCA-SNP interactions on QT intervals. However, it remains possible that TCAs increase the QT interval duration in rare cases (e.g., in association with low frequency genetic variants).

In addition, we showed that neither any genetic variants previously associated with a higher resting heart rate or QT intervals, nor a multi-locus score of these variants significantly modified the association between TCAs and resting RR or QT intervals[17–20]. The results of the multi-locus score analysis can be largely interpreted as a Mendelian randomization analysis, estimating whether a high resting heart rate or prolonged QT interval modified the TCA-SNP interactions. The results may indicate that participants with higher resting heart rates or prolonged QT intervals are not at higher risk for further TCA-induced increases in resting heart rate or QT duration. However, the variance explained by SNPs associated with mainly resting heart rate is low (0.8–0.9%)[17], which could affect the validity of this assumption.

A limitation of the study was the relatively low number of TCA users (especially in non-European ancestry cohorts), although our study is the largest effort assessing TCA-SNP interactions on RR and QT intervals to date. With limited power TCA interactions with relatively low frequency SNPs or in small samples could have been missed. Attempts at replication in non-European ancestry cohorts could have been underpowered. Second, our study was unable to account for prescribed TCA dosages, duration of use, and treatment adherence, which likely vary among cohorts from different countries. Such differences may have resulted in heterogeneity among studies. Third, results on RR from the European ancestry meta-analysis were not replicated in independent cohorts of a different ancestry. Fourth, one cohort determined RR intervals from heart rates (ASCOT). This method would increase RR measurement error, but independent of TCA exposures and genotypes. Any misclassification would have led to findings in the direction of the zero hypothesis. Furthermore, previously no heterogeneity in results was observed when comparing RR intervals from ECGs and pulse recordings [17]. Fifth, we were not able to adjust for potential confounders of SNP-TCA interactions. However, confounders with strong effects on the drug-outcome association were shown to only modestly bias the results [44]. And last, TCA doses may have been titrated to provide optimal blood concentrations, according to participant *CYP2D6* and *CYP2C19* genotypes. Because we defined TCA exposures as present or absent, SNP-TCA interactions caused by pharmacokinetic genes might have been missed.

For the present study, a well-powered, independent replication was not feasible, due to the limited availability of populations with high quality ECGs (twelve-lead), reliable assessment of drug use, and genome-wide SNP data. Our discovery effort should therefore be viewed as hypothesis generating. Future studies should attempt to replicate and validate our findings, to understand the pharmacological mechanisms involved.

In summary, we identified 2 independent genetic loci (*BRE* and *UBE2E2*) that modify the association between TCAs and heart rate in populations of European ancestry, and 1 locus

that modifies the association between TCAs and QT intervals in Hispanic/Latino ancestry populations. If replicated and validated, these results may provide new insights into biological mechanisms underlying the effect of TCAs on heart rate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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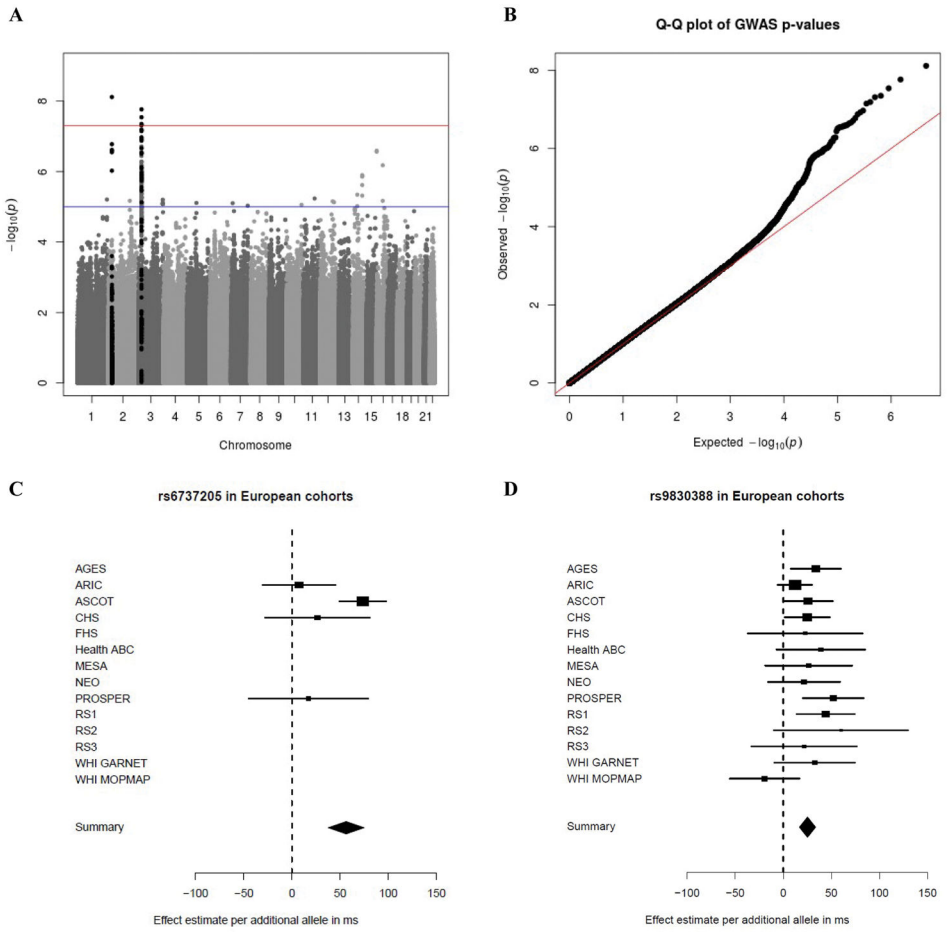

Figure 1. Genome-wide interaction analysis between tricyclic antidepressants and RR interval sin European cohorts

Abbreviations: AGES, Age, Gene/Environment Susceptibility – Reykjavik Study; ARIC, Atherosclerosis Risk in Communities Study; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; GARNET, Genome-wide Association Research Network into Effects of Treatment; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; Health ABC, Health, Aging, and Body Composition Study; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; MOPMAP, Modification of PM-Mediated Arrhythmogenesis in Populations; NEO, Netherlands Epidemiology of Obesity; $N_{exposed}$, number of independent participants using tricyclic antidepressants; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; RS, Rotterdam Study; SD, standard deviation; SHARe, WHI CT, Women's Health Initiative Clinical Trials. **A)** –Log(p) plot of all SNPs present in at least 3 European cohorts and passing all quality control steps. In black are all SNPs within a 40 kb distance from the top result on chromosomes 2 and 3. **B)** Q-Q plot of the meta-analysis in European cohorts. $\lambda = 1.031$. **C)** Cohort-specific and meta-analysis estimate for rs6737205 on chromosome 2. Results are presented as the effect estimate of the interaction between rs6737205 and TCA-use status on RR intervals (with the 95% confidence interval). **D)** Cohort-specific and meta-analysis estimate for rs9830388 on chromosome 3. Results are

presented as the effect estimate of the interaction between rs9830388 and TCA-use status on RR intervals (with the 95% confidence interval).

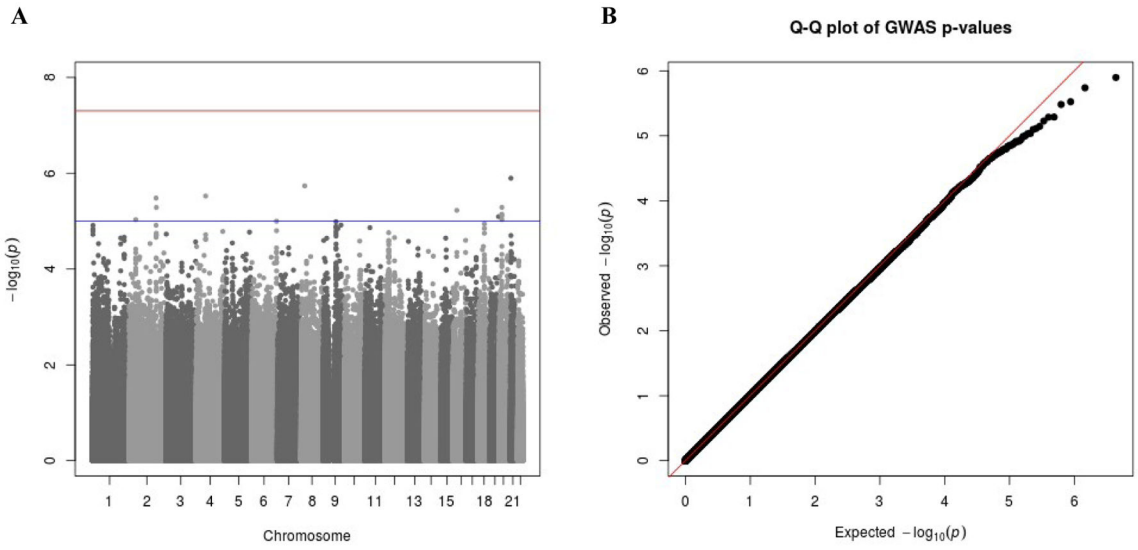

Figure 2. Genome-wide interaction analysis between tricyclic antidepressants and QT intervals in European cohorts

A) –Log(p) plot of all SNPs present in at least 3 European cohorts and passing all quality control steps. **B)** Q-Q plot of the meta-analysis in European cohorts. $\lambda = 1.022$.

Table 1

Study characteristics

Cohorts	$N_{exposed}$	N_{total}	RR in ms, mean (SD)	QT in ms, mean (SD)	Age in years, mean (SD)	Females, %	QTdef, %	Beta blockers, %	Verapamil, %	Diltiazem, %
AGES	67	1,976	938 (153)	406 (33.6)	74.6 (4.7)	64.2	3.0	13.7	1.7	3.5
ARIC	343	8,132	929 (138)	399 (28.8)	54.0 (5.7)	53.0	3.4	10.2	1.8	2.0
ASCOT	167	3,755	877 (153)	--	63.6 (8.1)	17.8	--	45.1	0.3	1.5
CHS	165	2,893	953 (151)	414 (32.2)	72.1 (5.2)	62.8	3.3	10.8	3.4	3.3
FHS	56	3,168	981 (159)	414 (29.9)	40.2 (8.8)	39.5	0.3	3.5	NA	NA
Health ABC	43	1,442	952 (153)	414 (32.3)	73.7 (2.8)	49.4	3.5	13.8	3.5	5.7
MESA	55	2,384	977 (149)	412 (29.3)	62.3 (10.1)	52.1	0.9	7.1	0.3	0.1
NEO	84	5,366	940 (150)	406 (29.3)	55.9 (5.9)	47.0	1.4	12.6	0.3	0.2
PROSPER	151	4,555	932 (163)	414 (36.0)	75.3 (3.3)	46.6	2.6	20.2	2.1	5.4
RS1	85	4,805	875 (148)	397 (28.8)	68.8 (8.6)	60.2	2.6	15.3	0.7	1.6
RS2	31	1,889	886 (140)	406 (28.6)	65.0 (7.6)	56.6	2.3	15.5	0.3	1.2
RS3	23	1,950	881 (131)	401 (26.0)	56.0 (5.7)	54.1	1.1	10.5	0.1	0.4
WHI GARNET	60	1,391	928 (139)	401 (30.3)	65.0 (6.8)	100.0	1.4	11.4	2.4	2.1
WHI MOPMAP	87	2,000	929 (135)	402 (30.1)	63.0 (6.6)	100.0	0.9	13.3	1.9	1.9
Summary	*1417*	*45,706*	*875–981*	*397–414*	*40.2–75.3*	*17.8–100*	*0.3–3.5*	*3.5–45.1*	*0.3–3.5*	*0.1–5.7*
African Americans										
ARIC	114	2,191	927 (151)	400 (32.8)	53.0 (5.8)	62.4	2.8	9.8	3.5	1.7
CHS	24	707	921 (166)	409 (35.3)	72.6 (5.6)	64.6	2.9	11.2	5.8	6.2
Health ABC	24	1,014	932 (143)	411 (34.8)	73.4 (2.9)	57.6	3.1	10.1	5.9	6.3
JHS	35	2,096	948 (150)	411 (30.1)	49.5 (11.8)	60.5	1.3	8.6	2.7	3.1
WHI CT SHARe	98	4,227	921 (149)	401 (33.8)	61.0 (6.8)	100.0	1.3	11.7	4.8	4.0
Summary	*295*	*10,235*	*921–948*	*400–411*	*49.5–73.4*	*57.6–100*	*1.3–3.1*	*8.6–11.7*	*2.7–5.9*	1.7–6.3
Hispanic/Latinos										
WHI CT SHARe	41	1,784	928 (133)	402 (29.7)	60.0 (6.4)	100.0	1.0	8.2	2.5	1.8
HCHS/SOL	133	12,024	975 (143)	416 (28.4)	45.7 (13.8)	59.5	0.7	6.4	0.4	0.3
Summary	*174*	*13,808*	*928–975*	*402–416*	*45.7–60.0*	*59.5–100*	*0.7–1.0*	*6.4–8.2*	*0.4–2.5*	*0.3–1.8*
Total summary	*1886*	*69,749*	*875–981*	*397–416*	*40.2–75.3*	*17.8–100*	*0.3–3.5*	*3.5–45.1*	*0.3–5.9*	*0.1–6.3*

Abbreviations: AGES, Age, Gene/Environment Susceptibility – Reykjavik Study; ARIC, Atherosclerosis Risk in Communities Study; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; GARNET, Genome-wide Association Research Network into Effects of Treatment; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; Health ABC, Health, Aging, and Body Composition Study; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; MOPMAP, Modification of PM-Mediated Arrhythmogenesis in Populations; NA, not available. NEO, Netherlands Epidemiology of Obesity; $N_{exposed}$, number of participants using tricyclic antidepressants; N_{total}, total number of participants contributing in the analysis; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; RS, Rotterdam Study; SD, standard deviation; SHARe, Single nucleotide polymorphism (SNP) Health Association Resource project; WHI CT, Women's Health Initiative Clinical Trials.

Table 2

Most significant independent loci in the genome-wide interaction analysis between tricyclic antidepressants and RR interval

SNP	CHR	Mapped gene	Ethnicity	EAF	N studies	Effect allele	$Beta_{int}$	SE_{int}	P_{int}	P_{het}
rs6737205	2	*BRE*	EA	0.94	4	A	56.3	9.7	**$7.66e^{-9}$**	0.16
			AA	Did not pass quality control						
			HSP	Did not pass quality control						
rs9830388	3	*UBE2E2*	EA	0.51	14	A	25.2	4.5	**$1.72e^{-8}$**	0.44
			AA	0.30	5	A	18.1	11.5	0.11	0.72
			HSP	0.55	2	A	−8.2	12.4	0.51	0.44
rs11867129	16	*ABCA3*	EA	0.09	11	T	35.7	6.9	$2.57e^{-7}$	0.05
			AA	Did not pass quality control						
			HSP	0.41	2	T	4.5	13.5	0.74	0.12

Abbreviations: AA, African Americans; *ABCA3*, ATP binding cassette subfamily A member 3; *BRE*, brain and reproductive organ-expressed; CHR, chromosome; EA, Europeans ; EAF, effective allele frequency; HSP, Hispanic/Latinos; N, number of studies included in the meta-analysis after quality control. P_{het}, P-value for heterogeneity between studies; P_{int}, P-value of the interaction; SE_{int}, standard error of the interaction; *UBE2E2*, ubiquitin conjugating enzyme E2E 2. Only independent genetic variants with a P-value for interaction below $5e^{-7}$ are displayed.