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## Supplementary appendix

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# Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study

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## Supplemental Methods

### Quality Control Procedures

Quality control procedures were implemented for the IWPC and UAB cohorts prior to analysis. Plate effect were assessed used our previously published method.[1] Samples from two patients from the IWPC GWAS cohort failed to validate by gender misspecification check using X chromosome heterogeneity in PLINK, and were excluded from further analyses.[2, 3] Genome-wide genotype data were used to estimate identity-by-descent (IBD) between all pairwise combinations of samples in order to identify sample duplicates, contaminated samples, and cryptic relationships. Three subjects with an IBD coefficient greater than 0.125 were excluded from the analysis. For each pair, the sample with the highest call rate was retained, and the other was excluded. No sample had a call rate of less than 95%.

For the GWAS meta-analysis, the full marker set for the IWPC cohort included 592,343 SNPs, and the UAB cohort included 1,199,187 SNPs, with a genotyping rate of 0.998 and 0.958, respectively, before quality control checks. No markers were excluded for deviation from Hardy Weinberg equilibrium (HWE) given the genotyped cohorts were admixed; however, those that showed significant departures (Fisher's exact test, $p \leq 0.0001$) were flagged in subsequent analyses. None of the SNPs reported as associated with stable warfarin dose showed significant departures from HWE. SNPs with a minor allele frequency (MAF) less than 2% were excluded from further analysis except for SNPs within VKORC1and CYP2C9, which were retained because of evidence for involvement in predicting warfarin dose.[4-6] Additionally, all monomorphic SNPs and SNPs that mapped to several genomic locations were removed from the analyses. We also employed a graded call rate cut-off, in which SNPs with a MAF of 3% or greater were excluded if the call rate was < 98%, and SNPs with a MAF of 2-3% were excluded if the call rate was < 99%. Samples were excluded for a call rate < 95%.

### Imputation

Imputation of additional SNPs not present on either of the two genotyping platforms was performed using hidden Markov models via MACH v1.0 (http://www.sph.umich.edu/csg/abecasis/MACH/)to obtain allelic dosages.[7, 8] To account for the admixture in African Americans, the phased reference haplotypes from the combined HapMap phase II White (CEU) and African (YRI) descent were used as reference populations at equal proportions (NCBI build 36, release 22 from http://hapmap.ncbi.nlm.nih.gov/downloads/genotypes/2009-

02_phaseII+III/forward/non-redundant/).[9] SNPs that were either polymorphic in both populations or monomorphic in only one population were included. The quality metric ($R^2$) was calculated for all imputed SNPs. SNPs with $R^2$ values of less than 0.8 were flagged; however, no SNPs reported herein were below this cut-off. We successfully imputed an additional 2,486,891 and 2,141,338 SNPs for the IWPC and UAB cohorts, respectively, yielding 3,044,177 and 3,091,345 experimentally determined and imputed autosomal SNPs in each cohort. The distribution of the imputation quality scores for each cohort is shown in Supplementary Figure 1.

The top reported SNP was an imputed SNP (rs12777823); HWE p values for the top SNPs were 1.0 and 0.1728 for the IWPC and UAB cohorts, respectively.

**Global ancestry and covariate selection**

To account for population structure, principal components analysis (PCA) was conducted using an LD-pruned ($r^2 > 0.2$) set of 9,131 and 66,445 markers for the UAB and IWPC cohorts, respectively.[10] We used the HapMap release 22 for CEU, Asian (CHB and JPT) and YRI populations as reference populations. The first and second principal components separated these three populations, with the first principal component used as a global estimate of African ancestry. All of the subjects in both the IWPC and UAB cohorts clustered between the HapMap CEU and YRI samples as expected (Supplementary Figure 2). No subject was removed from analysis based on ancestry misspecification.

All covariates collected in each cohort and the first 10 principal components obtained through EIGENSTRAT were tested as single covariates in a PLINK additive model analysis.[10] Mean height and weight by sex were used for subjects missing covariates for the IWPC cohort. The p-values associated with each covariate at each SNP were then averaged. All covariates with a mean p-value (across all SNPs) of less than 0.05 and whose distribution of p-values did not contain values greater than 0.05, were included in the GWAS analysis in both cohorts and meta-analysis.

**Genome-wide association analysis and meta-analysis**

For all analyses, the primary phenotype (weekly stable warfarin dose) was log transformed to produce a normal distribution. We excluded all individuals missing data on non-genetic covariates associated with warfarin dose. For both the IWPC and UAB cohorts, GWAS analysis was performed in PLINK with a linear regression additive genetic model, using the covariates shown to be significantly associated with stable warfarin dose. Cohort-specific GWAS results were combined using fixed effects meta-analysis. We pre-specified a genome-wide significance threshold of $5 \times 10^{-8}$. Heterogeneity was assessed between cohorts by the Cochran's Q test of heterogeneity, as well as the $I^2$ heterogeneity index. Following meta-analysis with significantly associated covariates, we also conducted a stepwise conditional meta-analysis in which we conditioned first for *VKORC1*-1639G>A, followed by the composite genotype (expressed as presence or absence of a variant allele) of *CYP2C9*2* and *CYP2C9*3*. We chose a composite allele variable because of the low minor allele frequencies of *CYP2C9*2* and **3* in African Americans. QQ plots and the genomic inflation factors for both these meta-analysis association tests can be found in the supplementary material (Supplementary Figure 3)

Thirteen SNPs were successfully assessed in the replication cohort. Quality control measures, such as HWE genotype call rate and sample call rate, were assessed using the criteria outlined for the meta-analysis. No SNP or sample failed the QC criteria in the replication cohort. Genetic association was tested using PLINK with a linear regression additive genetic model, using the same covariates used in the meta-analysis. We then ran conditional analysis using *VKORC1-1639*G>A and the composite *CYP2C9*2/*3* SNP variable.

**Supplemental Table 1. Detailed description of data provided by IWPC sites**

| | |
|---|---|
| **Gender** | Male, Female or not known = -99 |
| **Race (Reported)** | Self-reported information, confirmed by Eiganstrat analysis |
| **Race (OMB)** | Racial categories used are as defined by the Office of Management and Budget (OMB). *American Indian or Alaska Native*: A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment. *Asian*: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.) *Black or African American*: A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." *Native Hawaiian or Other Pacific Islander*: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. *White:* A person having origins in any of the original peoples of Europe, the Middle East, or North Africa. |
| **Ethnicity (Reported)** | Self-reported information |
| **Ethnicity (OMB)** | Ethnicity categories used are as defined by the Office of Management and Budget. *Hispanic or Latino:* A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino." or *Not Hispanic or Latino* |
| **Country of Origin** | Birthplace of Subject |
| **Age at Time of Consent** | Reported in years |
| **Height (cm)** | Reported in centimeters |
| **Weight (kg)** | Reported in kilograms |
| **Primary Indication for Warfarin Treatment** | DVT, PE, Afib/flutter, Heart Valve, Cardiomyopathy/LV Dilation, Stroke, Post-Orthopedic, Other , Combined DVT/PE or NA |
| **Comorbidities (Disease States)** | List of diseases co-occuring in the patient |
| **Diabetes** | yes, not present or not known (NA) |
| **Congestive Heart Failure and/or Cardiomyopathy** | yes, not present or not known (NA) |
| **Mechanical Valve Replacement** | yes, not present or not known (NA) |
| **Tissue Valve Replacement** | yes, not present or not known (NA) |
| **Which medications were taken when warfarin stable, if any** | List of medicines taken |
| **Aspirin** | yes, not present or not known (NA) |
| **Was Dose of Aspirin Less Than 100 mg/day?** | yes, not present or not known (NA) |
| **Was Dose of Aspirin Greater Than 100 mg/day?** | yes, not present or not known (NA) |
| **Acetaminophen or Paracetamol (Tylenol)** | yes, not present or not known (NA) |
| **Was Dose of Acetaminophen or Paracetamol (Tylenol) >1300mg/day** | yes, not present or not known (NA) |
| **Simvastatin (Zocor)** | yes, not present or not known (NA) |
| **Atorvastatin (Lipitor)** | yes, not present or not known (NA) |

**Supplemental Table 1 (continued). Detailed description of data provided by IWPC sites**

| | |
|---|---|
| **Fluvastatin (Lescol)** | yes, not present or not known (NA) |
| **Lovastatin (Mevacor)** | yes, not present or not known (NA) |
| **Pravastatin (Pravachol)** | yes, not present or not known (NA) |
| **Rosuvastatin (Crestor)** | yes, not present or not known (NA) |
| **Cerivastatin (Baycol)** | yes, not present or not known (NA) |
| **Amiodarone (Cordarone)** | yes, not present or not known (NA) |
| **Carbamazepine (Tegretol)** | yes, not present or not known (NA) |
| **Phenytoin (Dilantin)** | yes, not present or not known (NA) |
| **Rifampin or Rifampicin** | yes, not present or not known (NA) |
| **Sulfonamide Antibiotics** | Includes Septra, Bactrim, Cotrim and Sulfatrim; yes, not present or not known (NA) |
| **Macrolide Antibiotics** | Includes erythromycin, azithromycin, and clarithromycin; yes, not present or not known (NA) |
| **Anti-fungal Azoles** | yes, not present or not known (NA) |
| **Herbal Medications, Vitamins, Supplements** | Includes garlic, ginseng, danshen, donquai, vitamins, zinc, iron, magnesium, etc. yes, not present or not known (NA) |
| **Herbal Medications** | List of herbal medicines taken separated by semi-colons. |
| **Target INR** | Target International Normalized Ratio single value or range. NA if not known. |
| **Subject Reached Stable Dose of Warfarin** | yes, not present or not known (NA) |
| **Therapeutic Dose of Warfarin** | Dose given in milligrams/week as defined by stable dose |
| **INR on Reported Therapeutic Dose of Warfarin** | International Normalized Ratio on the Therapeutic Dose of Warfarin Reported Above |
| **Warfarin Dose on Day 1** | Total dose given in milligrams/week on the first day |
| **Warfarin Dose on Day 2** | Total dose given in milligrams/week on the second day |
| **Warfarin Dose on Day 3** | Total dose given in milligrams/week on the third day |
| **INR after the first week** | Target International Normalized Ratio after the first week |
| **INR after the first month (4 weeks)** | Target International Normalized Ratio after the first month |
| **Time to stability** | Number of Days from initiation of warfarin therapy to when the patient has reached the stable, Therapeutic Dose of warfarin as defined above |
| **Major Bleeds (WHO classification)** | yes, not present or not known (NA)<br>A bleeding event was assessed as serious if it fulfilled the World Health Organization (WHO) criteria for a serious adverse drug reaction, that is, if it was lethal, life-threatening, permanently disabling, or lead to hospital admission or prolongation of hospital stay. |
| **Minor Bleeds** | yes, not present or not known (NA); Any bleed that is not a major bleed. |
| **Number of bleeding events** | Number of bleeding events (both major and minor). |
| **Time to first major bleed from initiation of therapy** | Number of days to first major bleed from the initiation of warfarin therapy |
| **Dosing Method** | manual, computerized, or combination |
| **Ever Smoked** | yes, not present or not known (NA) |
| **Current Smoker** | yes, not present or not known (NA) |
| **Alcohol intake** | yes, not present or not known (NA) |
| **Alcohol Use** | If details are available, describe alcohol use. |
| **Cyp2C9 genotypes** | Please specify for both alleles: *1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, or *13 |
| **VKORC1 genotype: 3730 G>A (9041); chr16:31009822(hg18); rs7294** | A/A, A/G, G/G or NA |

**Supplemental Table 1 (continued). Detailed description of data provided by IWPC sites**

| | |
|---|---|
| **VKORC1 genotype: 2255C>T (7566); chr16:31011297 (hg18); rs2359612** | C/C, C/T, T/T or NA |
| **VKORC1 genotype: 1542G>C (6853); chr16:31012010(hg18); rs8050894** | C/C, C/G, G/G or NA |
| **VKORC1 genotype: 1173 C>T (6484); chr16:31012379(hg18); rs9934438** | C/C, C/T, T/T or NA |
| **VKORC1 genotype: 497T>G (5808); chr16:31013055(hg18); rs2884737** | G/G, G/T, T/T or NA |
| **VKORC1 genotype: -1639 G>A (3673); chr16:31015190(hg18); rs9923231** | A/A, A/G, G/G or NA |
| **VKORC1 genotype: -4451 C>A (861); Chr16:31018002(hg18); rs17880887** | A/A, A/C, C/C or NA |

**Supplemental Table 1 (continued). Detailed description of data provided by IWPC sites**

| | |
|---|---|
| **Dosing Method** | manual, computerized, or combination |
| **Ever Smoked** | yes, not present or not known (NA) |
| **Current Smoker** | yes, not present or not known (NA) |
| **Alcohol intake** | yes, not present or not known (NA) |
| **Alcohol Use** | If details are available, describe alcohol use. |
| **Cyp2C9 genotypes** | Please specify for both alleles: *1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, or *13 |
| **VKORC1 genotype: 3730 G>A (9041); chr16:31009822(hg18); rs7294** | A/A, A/G, G/G or NA |
| **VKORC1 genotype: 2255C>T (7566); chr16:31011297 (hg18); rs2359612** | C/C, C/T, T/T or NA |
| **VKORC1 genotype: 1542G>C (6853); chr16:31012010(hg18); rs8050894** | C/C, C/G, G/G or NA |
| **VKORC1 genotype: 1173 C>T (6484); chr16:31012379(hg18); rs9934438** | C/C, C/T, T/T or NA |
| **VKORC1 genotype: 497T>G (5808); chr16:31013055(hg18); rs2884737** | G/G, G/T, T/T or NA |
| **VKORC1 genotype: -1639 G>A (3673); chr16:31015190(hg18); rs9923231** | A/A, A/G, G/G or NA |
| **VKORC1 genotype: -4451 C>A (861); Chr16:31018002(hg18); rs17880887** | A/A, A/C, C/C or NA |

**Supplemental Table 2: Consortia site information for the GWAS discovery cohort (UAB and IWPC cohorts)**

| Group | Number of subjects* | Definition of stable warfarin dose |
|---|---|---|
| **University of Alabama, Birmingham** | 206 | Stable warfarin dose was defined as the dose (with up to a 10% change) that resulted in a therapeutic INR between 1.8 and 3.2 for at least 3 consecutive clinic visits at least two weeks apart |
| **Vanderbilt University, Nashville, TN** | 34 | Average weekly dose (irrespective of achieved INR) that the patient received during the observation period, excluding the first 28 days after warfarin initiation. |
| **University of Florida, Gainesville, FL** | 21 | A a dose that did not vary by more than 10% between clinic visits. In addition, the INR at each of the 3 visits had to be in the patient's specific goal INR range. |
| **University of Illinois at Chicago, Chicago, IL** | 122 | The same warfarin dose for at least 3 consecutive clinic visits. No INR criteria to define stable dose was used because it was assumed that either the INR was in range at each visit or was not sufficiently out-of-range to elicit a change in dose. |
| **University of Chicago, Chicago, IL** | 115 | The same warfarin dose for at least 3 consecutive clinic visits (minimum of 30 days between first and last visit) that produced an INR within therapeutic range (1.9 to 3.1). |
| **University of California, San Francisco, CA** | 6 | Warfarin dose that lead to the target INR, usually 2-3 on 1 or more occasions over a minimum of 30 days. |
| **Aurora Healthcare** | 34 | Clinician selected patients on stable warfarin dose and two most recent INR measurements (taken over a 5-7 day period) within the patient's specific INR range |
| **Stanford University, Stanford, CA** | 3 | Stability is defined as having 3 or more consecutive warfarin doses at the same value. |
| **University of North Carolina, Chapel Hill, NC** | 10 | Subjects were required to be on warfarin and managed in the warfarin clinic for a minimum of 3 months before entry into the study, and thus dosing had stabilized by the time data collection for the study began. Values reported for warfarin dose are the average over the entire time of participation in the study (average = 20.6 months). |

* Represents the numbers of participants from each site included in the analysis

**Supplemental Table 3: Consortia site information for the replication cohort**

| Group | Number of subjects* | Definition of stable warfarin dose |
|---|---|---|
| **Vanderbilt University, Nashville, TN** | 145 | Individuals were identified with INR values between 2.0 and 3.0 for at least 3 weeks with no out-of-range INRs and two clinical encounters at least 3 weeks apart. |
| **Mount Sinai School of Medicine, New York, NY** | 24 | Dose at which the INR was between 2.0 and 3.0 and at least two consecutive INR measurements, separated by at least 1 week, were within the therapeutic range |
| **University of Illinois at Chicago, Chicago, IL** | 134 | The same warfarin dose for at least 3 consecutive clinic visits. No INR criteria to define stable dose was used because it was assumed that either the INR was in range at each visit or was not sufficiently out-of-range to elicit a change in dose. |
| **University of Chicago, Chicago, IL** | 57 | The same warfarin dose for at least 3 consecutive clinic visits (minimum of 30 days between first and last visit) that produced an INR within therapeutic range (1.9 to 3.1). |
| **University of Alabama, Birmingham AL** | 80 | A dose that did not vary by more than 10% between at least 3 consecutive clinic visits (at least 2 weeks apart) where the INR was maintained within the 1.8-3.2 range. |
| **University of North Carolina, Chapel Hill, NC** | 6 | Subjects were required to be on warfarin and managed in the warfarin clinic for a minimum of 3 months before entry into the study, and thus dosing had stabilized by the time data collection for the study began. Values reported for warfarin dose are the average over the entire time of participation in the study (average = 20.6 months). |

* Represents the numbers of participants from each site included in the analysis

**Supplemental Table 4. SNPs associated with warfarin dose variability in the GWAS meta-analysis from 533 African Americans**

| SNP | Chrom. | Gene/nearby gene | Mean MAF | p-value |
|---|---|---|---|---|
| rs9934438 | 16 | *VKORC1* | 0.10 | 2.08E-09 |
| rs9923231 | 16 | *VKORC1* | 0.10 | 2.08E-09 |
| rs749671 | 16 | *ZNF646* | 0.10 | 1.66E-08 |
| rs10871454 | 16 | *STX4* | 0.10 | 1.67E-08 |
| rs881929 | 16 | *ZNF668* | 0.10 | 2.00E-08 |
| rs11150604 | 16 | NA | 0.10 | 2.75E-08 |
| rs9939417 | 16 | NA | 0.10 | 4.65E-08 |
| rs889548 | 16 | *MYST1* | 0.13 | 1.14E-07 |
| rs14235 | 16 | *BCKDK* | 0.13 | 1.20E-07 |
| rs1549293 | 16 | *PRSS8/MYST1* | 0.13 | 1.49E-07 |
| rs9925964 | 16 | *MYST1* | 0.13 | 1.60E-07 |
| rs12597511 | 16 | *PRSS8* | 0.13 | 1.74E-07 |
| rs2032915 | 16 | NA | 0.07 | 2.91E-07 |
| rs9341106 | 2 | *IGFBP2* | 0.05 | 3.75E-07 |
| rs1036696 | 16 | *FBRS* | 0.02 | 5.83E-07 |
| rs1064524 | 16 | *ITGAL* | 0.02 | 6.06E-07 |
| rs749670 | 16 | *ZNF646* | 0.07 | 6.85E-07 |
| rs2104162 | 10 | *CYP2C9* | 0.36 | 8.02E-07 |
| rs12777823 | 10 | *CPY2C18* | 0.26 | 9.67E-07 |

Abbreviations: NA, not available; MAF, Minor Allele Frequency; Chrom. Chromosome

**Supplemental Table 5: Most significant SNPs in the GWAS meta-analysis after conditioning on *VKORC1* -1639G>A, *CYP2C*2*, and *CYP2C9*3*.** A total of 13 SNPs that represented each genomic region (shown in italics) were tested in the replication cohort.

| Chromosomal region | SNP[a,b] | Gene/nearby gene | Mean MAF | Meta-analysis p-value | Replication cohort p-value |
|---|---|---|---|---|---|
| ***10*** | ***rs12777823*** | ***CYP2C18*** | ***0.26*** | ***1.51E-08*** | ***5.04E-05*** |
| | rs2104162 | *CYP2C9* | | 9.50E-08 | |
| | rs7085563 | *CYP2C18* | | 2.86E-07 | |
| | rs12772169 | *CYP2C18* | | 1.58E-06 | |
| | rs1998591 | *CYP2C18* | | 2.11E-06 | |
| | rs12772675 | *CYP2C9* | | 2.11E-06 | |
| | rs4918766 | *CYP2C9* | | 2.11E-06 | |
| | rs1326837 | *CYP2C18* | | 9.28E-06 | |
| | rs1010570 | *CYP2C18* | | 7.98E-06 | |
| ***1*** | ***rs7547797*** | ***RGS7*** | ***0.11*** | ***7.41E-07*** | ***0.99*** |
| | rs6694752 | *TTLL7* | | 4.67E-06 | |
| **13** | **rs2987340** | ***KIAA0774*** | **0.06** | **2.07E-06** | **UT** |
| | rs2987341 | *KIAA0774* | | 2.48E-06 | |
| | rs2987338 | *KIAA0774* | | 6.13E-06 | |
| | rs2987339 | *KIAA0774* | | 7.54E-06 | |
| | rs4480688 | NA | | 7.68E-06 | |
| ***4*** | ***rs7691841*** | ***NA*** | ***0.27*** | ***2.13E-06*** | ***0.37*** |
| | rs13132502 | NA | | 2.52E-06 | |
| ***2*** | ***rs10207440*** | ***DIRC3*** | ***0.19*** | ***2.97E-06*** | ***0.95*** |
| | rs10192115 | *DIRC3* | | 3.13E-06 | |
| | rs12466055 | *DIRC3* | | 4.47E-06 | |
| | rs10186413 | *DIRC3* | | 7.68E-06 | |
| ***11*** | ***rs11216674*** | ***IL10RA*** | ***0.18*** | ***3.19E-06*** | ***0.54*** |
| **18** | **rs12456105** | ***ZNF532*** | **0.06** | **3.38E-06** | **UT** |
| | rs12607707 | NA | | 5.89E-06 | |
| | rs10431083 | *IL10RA* | | 7.31E-06 | |
| | rs12223288 | *IL10RA* | | 7.78E-06 | |
| ***11*** | ***rs7951320*** | ***GALNTL4*** | ***0.21*** | ***3.24E-06*** | ***0.42*** |
| | rs7117593 | *GALNTL4* | | 6.77E-06 | |
| ***3*** | ***rs6789971*** | ***SEC22A*** | ***0.07*** | ***4.24E-06*** | ***0.72*** |
| ***6*** | ***rs4945637*** | ***MAN1A1*** | ***0.29*** | ***4.94E-06*** | ***0.14*** |
| | rs1079606 | *GLO1* | | 7.44E-06 | |
| ***19*** | ***rs891036*** | ***PEPD*** | ***0.04*** | ***6.07E-06*** | ***0.61*** |
| ***7*** | ***rs17647163*** | ***AHR*** | ***0.02*** | ***7.47E-06*** | ***0.71*** |
| ***20*** | ***rs742446*** | ***NA*** | ***0.04*** | ***8.67E-06*** | ***0.93*** |
| ***4*** | ***rs6811772*** | ***NA*** | ***0.12*** | ***9,16E-06*** | ***0.37*** |
| ***3*** | ***rs9848736*** | ***NA*** | ***0.14*** | ***9.86E-06*** | ***0.71*** |

Abbreviations: UT, Untyped; NA, not available;

a. **Bold - Targeted SNPs**
b. *Italicized - SNP Typed in the replication cohort.*

## Supplementary Figure Legends

**Supplemental Figure 1: Imputation quality in each GWAS cohort**
Distribution of the R-squares metric of imputation quality for each cohort. Both cohorts were imputed to the phased reference haplotypes from the combined HapMap phase II White (CEU) and African (YRI) descent

**Supplemental Figure 2: Graph of principal components (PC) 1 and 2**
Principal component analysis was used to assess/confirm ancestry for both cohorts as they relate to the three HapMap populations (White – CEU, Yuruba – YRI, and Asian – ASN). A) IWPC GWAS and B) UAB GWAS

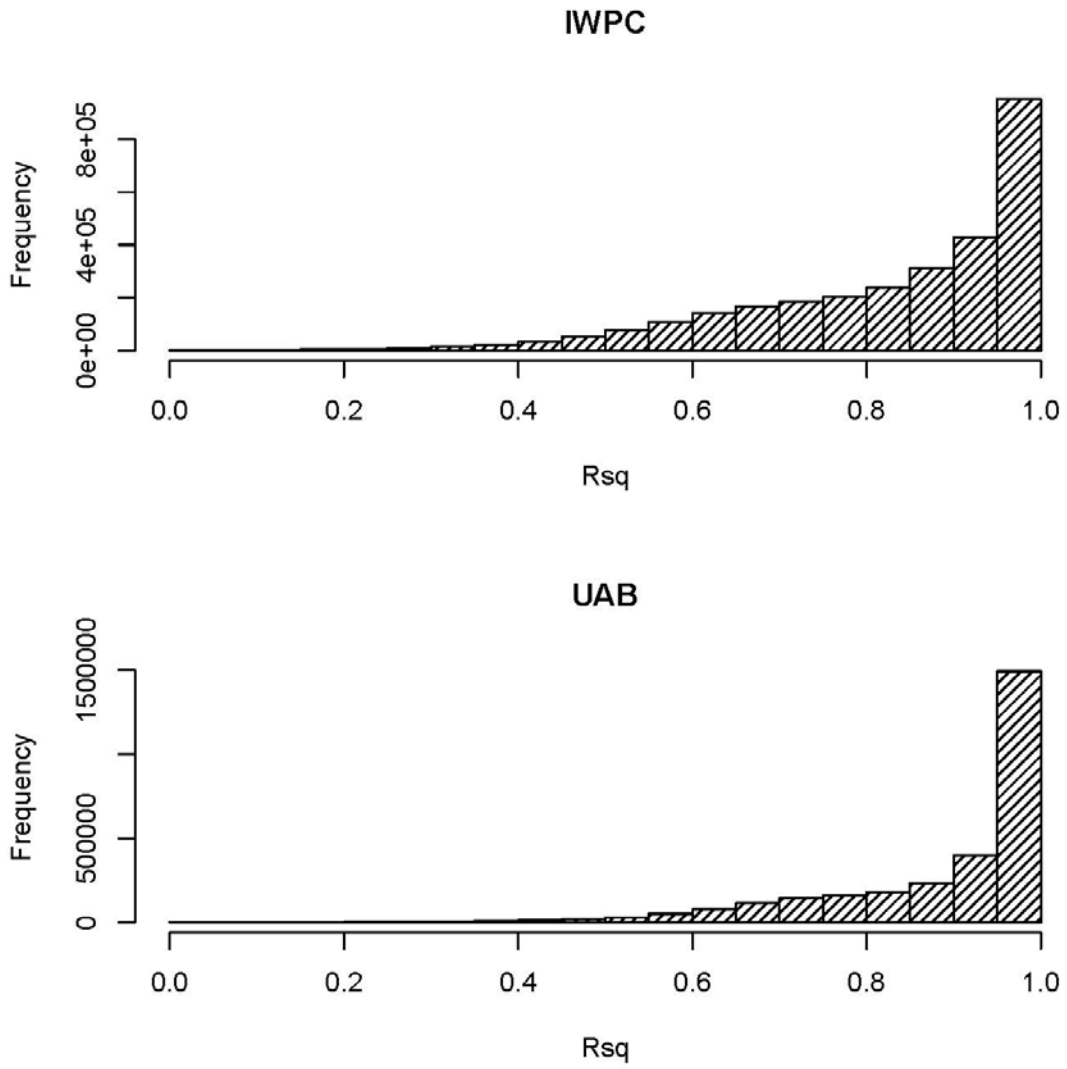
**Supplemental Figure 3: Q-Q plots for the meta-analysis**

A) Q-Q plot of the meta-analysis with IWPC and UAB cohorts after adjusted for significant non-genetic covariates
B) Meta-analysis with the IWPC and UAB cohorts adjusted for significant non-genetics covariates and conditioning on *VKORC1*-1639G>A and *CYP2C9*2* and **3*

**Supplemental Figure 4: Region plot of the meta-analysis SNP associations flanking rs12777823.**

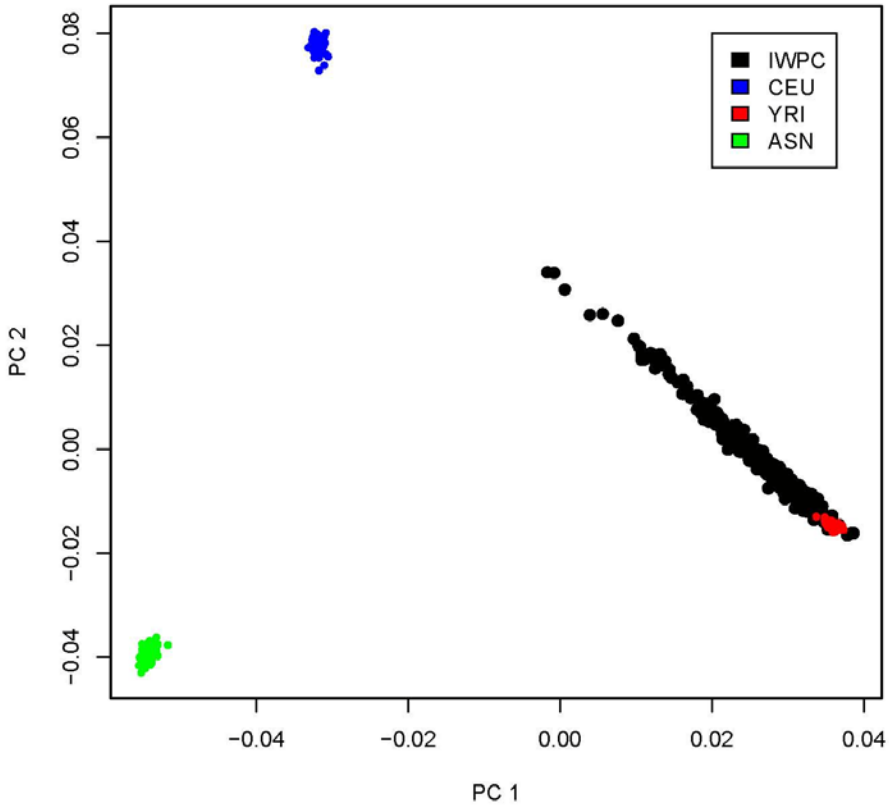
The regional plot of chromosome 10 flanking the SNP rs1277823 is shown. The colored dots represent SNPs (both imputed and typed) and their corresponding LD to rs12777823 (shown in purple). The gene annotation for the region can be found below the plot.

**Supplemental Figure 1: Imputation quality in each GWAS cohort**

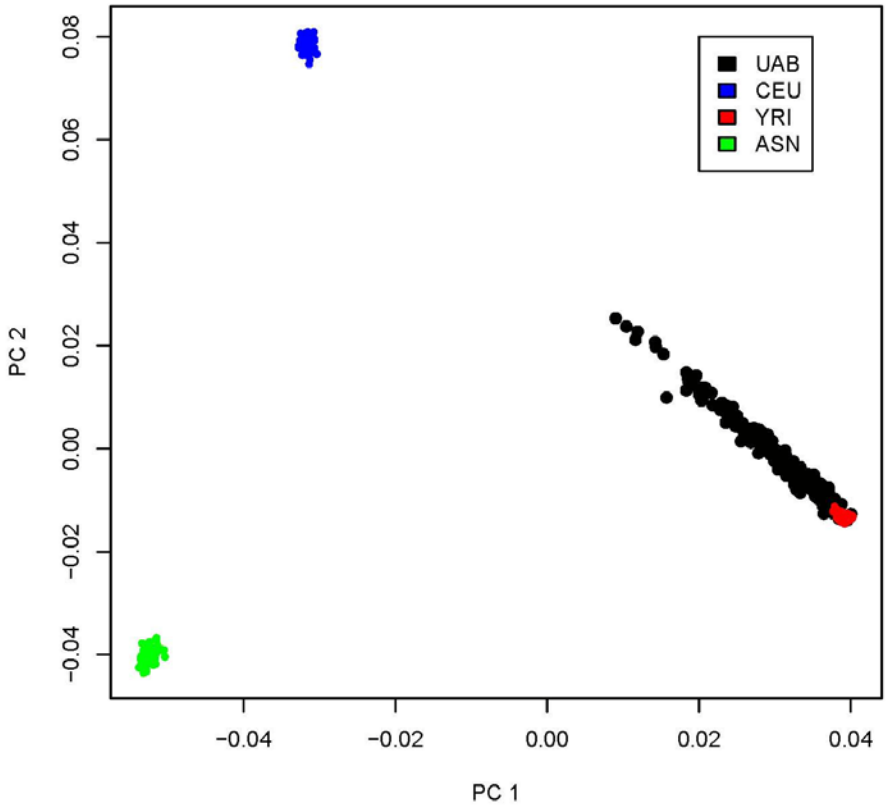


**Supplemental Figure 2: Graph of principal components (PC) 1 and 2 in each cohort**

A)

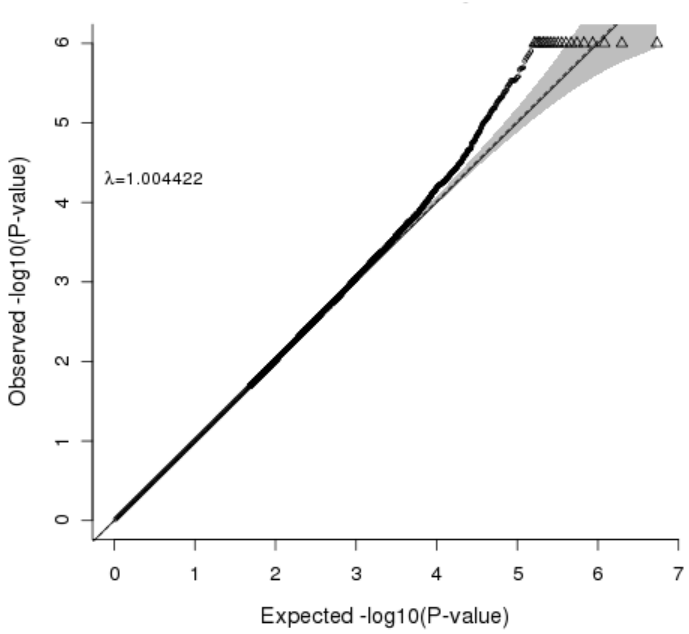



B)

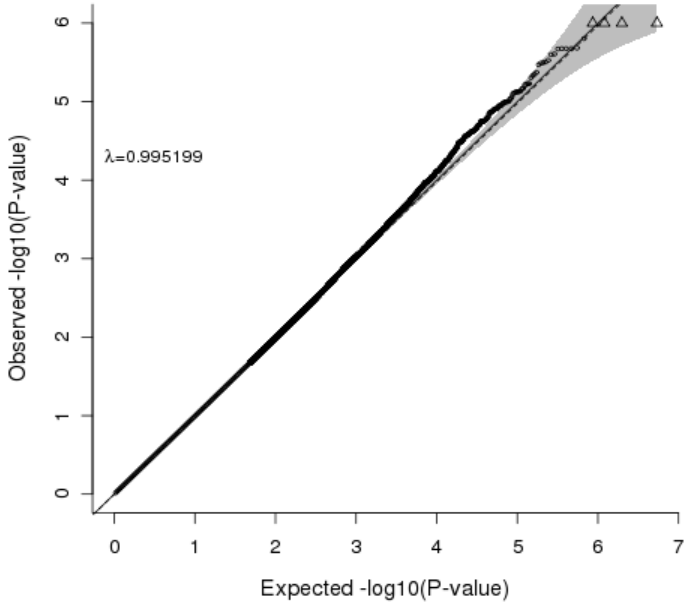


**Supplemental Figure 3: Q-Q plots for the meta-analysis**

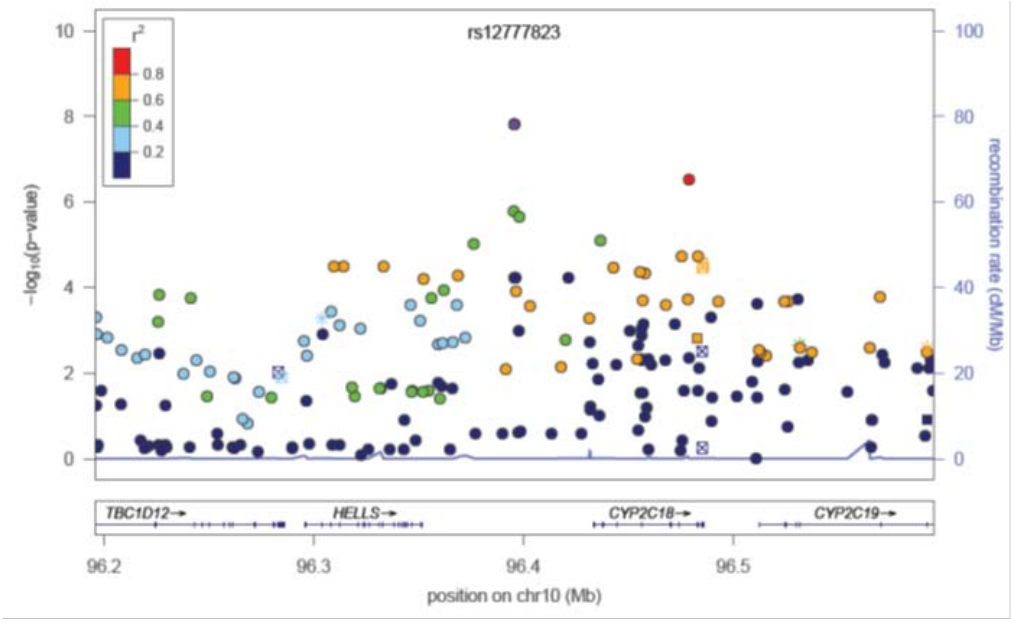
A)




B)



**Supplemental Figure 4: Region plot of the meta-analysis SNP associations flanking rs12777823.**



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