Genetic Risk Prediction of Atrial Fibrillation

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ABSTRACT

Background: Atrial fibrillation (AF) is common and has a substantial genetic basis. Identification of individuals at greatest AF risk could minimize the incidence of cardioembolic stroke.

Methods: To determine whether genetic data can stratify risk for development of AF, we examined associations between AF genetic risk scores and incident AF in five prospective studies comprising 18,919 individuals of European ancestry. We examined associations between AF genetic risk scores and ischemic stroke in a separate study of 509 ischemic stroke cases (202 cardioembolic [40%]) and 3,028 controls. Scores were based on 11 to 719 common variants (≥5%) associated with AF at *P*-values ranging from $<1x10^{-3}$ to $<1x10^{-8}$ in a prior independent genetic association study.

Results: Incident AF occurred in 1,032 (5.5%) individuals. AF genetic risk scores were associated with new-onset AF after adjusting for clinical risk factors. The pooled hazard ratio for incident AF for the highest versus lowest quartile of genetic risk scores ranged from 1.28 (719 variants; 95%CI, 1.13-1.46; $P=1.5x10^{-4}$) to 1.67 (25 variants; 95%CI, 1.47-1.90; $P=9.3x10^{-15}$). Discrimination of combined clinical and genetic risk scores varied across studies and scores (maximum C statistic, 0.629-0.811; maximum ΔC statistic from clinical score alone, 0.009-0.017). AF genetic risk was associated with stroke in age- and sex-adjusted models. For example, individuals in the highest quartile of a 127-variant score had a 2.49-fold increased odds of cardioembolic stroke, versus those in the lowest quartile (95%CI, 1.39-4.58; $P=2.7x10^{-3}$). The effect persisted after excluding individuals (n=70) with known AF (odds ratio, 2.25; 95%CI, 1.20-4.40; *P*=0.01).

Conclusions: Comprehensive AF genetic risk scores were associated with incident AF beyond clinical AF risk factors, with magnitudes of risk comparable to other clinical risk factors, though offered small improvements in discrimination. AF genetic risk was also associated with

cardioembolic stroke in age- and sex-adjusted analyses. Efforts to determine whether AF genetic risk may improve identification of subclinical AF or distinguish stroke mechanisms are warranted.

Key words: atrial fibrillation, stroke, genetic, risk, prediction

CLINICAL PERSPECTIVE

What is new?

- Studies have identified several genetic loci associated with AF, yet it is unclear whether genetic profiling can identify individuals at greatest risk for AF or cardioembolic stroke.
- Using genome-wide data from an independent large-scale analysis, we tested comprehensive AF genetic risk scores for association with new-onset AF in five prospective studies, and with stroke in a separate stroke case-control sample.
- Genetic risk scores were associated with AF beyond established clinical risk factors, but improved prediction minimally.
- AF genetic risk was strongly associated with cardioembolic stroke, suggesting that elevated AF genetic risk might serve as a surrogate for thromboembolism from AF.

What are the clinical implications?

- Our findings underscore the complementary information provided by both clinical and genetic factors.
- However, since genetic information currently affords small improvements in discrimination of AF risk, widespread use of genetic risk profiling does not need to be incorporated into routine clinical decision-making at this time.
- Our findings raise the possibility that AF genetic risk may serve as a signature for strokes caused by thromboembolism from AF.
- Future studies are warranted to determine whether AF genetic risk can distinguish stroke etiologic mechanisms, or identify individuals with strokes that have subclinical AF.

Atrial fibrillation (AF) is a heritable[1] and common arrhythmia associated with substantial morbidity and economic costs.[2] Approximately one in five ischemic strokes are attributable to cardioembolic events from AF.[3] Strokes due to AF are associated with more disability and mortality than strokes from other etiologies.[4] Since many strokes caused by AF are preventable with effective anticoagulation,[5] and because AF may be undetected in some individuals, there is a critical need to identify those at greatest risk for the arrhythmia.

In recent years, risk models for AF prediction have been developed based on clinical and demographic variables.[6-9] We and others have identified common genetic variants associated with AF,[10-17] and some of these have been associated with incident AF[18] and ischemic stroke[19] after adjustment for clinical risk factors. Yet it remains unclear whether a comprehensive AF genetic risk score can facilitate identification of individuals at greatest risk for AF or cardioembolic stroke, since such individuals might benefit from stroke prevention efforts.

We therefore sought to determine whether comprehensive AF genetic risk scores are associated with incident AF beyond clinical risk factors, and might facilitate identification of individuals at greatest risk for the arrhythmia. In addition, we sought to examine whether AF genetic risk is associated with ischemic stroke, and in particular, cardioembolic stroke.

METHODS

Participants

We examined the association between AF genetic risk and incident AF in five prospective studies. Briefly, these studies were the Malmö Diet and Cancer Study (MDCS),[20] the Multi-Ethnic Study of Atherosclerosis (MESA),[21] the Prevention of Renal and Vascular Endstage Disease (PREVEND) study,[22] the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER),[23] and the Vanderbilt University de-identified DNA biobank (BioVU).[24] We also examined the association between AF genetic risk and stroke in the Massachusetts General Hospital Genes Associated with Stroke Risk and Outcomes Study (MGH-GASROS), a hospital-

based case-control study of acute ischemic stroke patients (enrolled between July 2000 and 2011) and referent individuals from the Myocardial Infarction Genetics Consortium (without a history of myocardial infarction).[25,26] All stroke cases in MGH-GASROS underwent etiologic stroke subtyping in a uniform fashion, according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[27] Descriptions of each study are provided in the **online supplement**, including details on clinical risk factor and outcome ascertainment, genotyping, and imputation. For all analyses, samples were restricted to individuals of self-reported European ancestry. Each study was approved by its Institutional Review Board, and participants provided written informed consent.

AF genetic risk

To estimate genetic risk using a minimal set of single nucleotide polymorphisms (SNPs), we selected uncorrelated SNPs by pruning[28] 2.2 million HapMap variants included in a prior independent meta-analysis of genome-wide association studies for AF from the AFGen consortium (6,707 individuals with and 53,436 without AF).[15] We considered all SNPs that had allele frequencies ≥ 5% and were nominally associated with AF ($P<1x10^{-3}$). We then selected the most significantly associated SNP within a given 250 kilobase locus that was not in linkage disequilibrium with another more significantly associated SNP at that locus ($r^2<0.1$). In total, 719 uncorrelated SNPs were selected for construction of genetic risk scores (**Supplemental Table 1)**.

For each individual, we calculated AF genetic risk scores by summing the dosage of each AF risk allele (ranging from 0 to 2) weighted by the natural logarithm of the relative risk for each SNP. Weights were determined in our earlier, independent meta-analysis.[15] Thus, a genetic risk score for an individual is a single linear predictor variable. Since the optimum number of risk alleles that should be used for genetic risk scores has not been fixed, we constructed seven different scores for each individual based on the strength of association

between each SNP and AF in the earlier analysis.[15] We selected the seven different significance thresholds *a priori*: $P<1x10^{-3}$, $<1x10^{-4}$, $<1x10^{-5}$, $<1x10^{-6}$, $<1x10^{-7}$, $<5x10^{-8}$, and $<1x10^{-8}$. Liberal inclusion of SNPs was motivated by observations that uncorrelated SNPs demonstrating less significant associations with a trait may still explain a substantial proportion of the heritability of the trait.[29-32]

Statistical analysis

Within each prospective study, we used proportional hazards regression to examine associations between the different AF genetic risk scores and incident AF over a 5-year time horizon. For all incident AF analyses, person-time in each cohort began at DNA collection or baseline enrollment. Individuals were treated as censored at the time of death or loss to follow-up. Models were adjusted for variables included in a previously validated composite risk score for 5-year AF risk prediction (CHARGE-AF risk score).[9] The composite CHARGE-AF risk score included age, height, weight, systolic and diastolic blood pressures, smoking status, antihypertensive medication use, diabetes status, heart failure status, myocardial infarction status, electrocardiographic evidence of left ventricular hypertrophy, and PR interval. Electrocardiographic variables that were not available were omitted from the scores on a study-by-study basis (left ventricular hypertrophy was unavailable in MDCS, MESA, PREVEND, and PROSPER; PR interval was unavailable in MDCS, PREVEND, PROSPER, and BioVU). Race was not included in the models since we restricted our sample to individuals of European ancestry. Proportional hazards assumptions were verified with multiplicative interaction terms between covariates and the natural logarithm of follow-up time.

For each model, we calculated goodness-of-fit statistics using Akaike's Information Criterion, a penalized likelihood metric in which lower values indicate better fit.[33] We also assessed discrimination using the C statistic for time-to-event data.[34] Calibration of the

prediction models was assessed using the Hosmer-Lemeshow statistic modified for survival analysis.[35]

In exploratory analyses we combined model parameters from each study by use of an inverse variance random-effects meta-analysis approach, and calculated heterogeneity using the I^2 statistic.[36] We utilized a random-effects approach owing to inherent differences in study design (see **supplemental methods** for details). We then multiplied the summary score beta coefficient by the difference between the 12.5th and 87.5th percentiles of AF genetic risk scores from a common reference population (**Supplemental Table 2**). The resulting values estimate the relative risk comparing individuals in the highest and lowest quartiles across each study and score, in a standard fashion. The common reference population used was a pooled sample of 12,801 individuals from the Framingham Heart Study (n=2,551),[37] the Atherosclerosis Risk in Communities Study (n=7,278),[38] and the Cardiovascular Health Study (n=2,972)[39] with genome-wide genotyping data.[15]

We then examined whether AF genetic risk was associated with AF, ischemic stroke, and cardioembolic stroke in MGH-GASROS using multivariable logistic regression. Since several of the identified pruned AF SNPs were not available in the MGH-GASROS sample, we utilized proxy SNPs on the basis of linkage disequilibrium when available (**Supplemental Table 1**). The number of SNPs in some genetic risk scores differed slightly based on inability to identify proxies. Models were adjusted for age and sex only, because extended clinical information was not available in the referent participants. Since AF was ascertained only in stroke cases, we assumed that AF was not present among referents for analyses of AF (an assumption that would be expected to bias the results toward a null association between genetic risk and AF due to the potential for misclassified individuals who have AF among the referent sample). We then examined associations between AF genetic risk and ischemic stroke, as well as the association with the TOAST cardioembolic stroke classification (a subset of ischemic stroke). We utilized the same referent sample set for analyses of ischemic and

cardioembolic stroke. Because AF may occur as a subclinical condition, we examined in exploratory analyses whether AF genetic risk scores were associated with stroke in individuals without known AF, again assuming that referent subjects did not have AF.

None of the studies in our analysis of incident AF were used in any aspect of the derivation of genetic risk or the CHARGE-AF scores. The *a priori* significance threshold for all analyses was $P<0.05$ using two-sided tests. Meta-analyses were conducted using the rmeta[40] package in R.[41] Other software utilized for analyses is described in the **supplement**.

RESULTS

AF genetic risk scores and incident AF

Among 18,919 individuals across all studies in our analyses of incident AF, the mean age ranged from 58-75 years, and the proportion of women ranged from 47-52%. During the 5-year follow-up window, 1,032 (5.5%) individuals developed incident AF (**Table 1**). AF genetic risk scores were associated with incident AF after accounting for clinical risk factors (**Supplemental Figure 1** and **Supplemental Table 3**). Heterogeneity of effect estimates was modest between studies. Generally, the models with the best fit included scores with between 25 and 129 SNPs, as indicated by the AIC (**Supplemental Table 3**).

For each of the seven groups of genetic risk scores, we estimated hazard ratios comparing individuals in the highest quartile of each genetic risk score with those in the lowest quartile. Across the genetic risk scores, those in the highest quartile had a 1.28-fold (719 SNPs; 95% CI, 1.13-1.46; $P=1.5\times10^{-4}$) to 1.67-fold (25 SNPs; 95%CI, 1.47-1.90; $P=9.3\times10^{-15}$) increased hazard for AF (**Figure 1**). C statistics for the clinical risk factor model without AF genetic risk scores ranged from 0.615 to 0.802 across cohorts (**Supplemental Table 3**). Adding AF genetic risk scores to the clinical risk factor model resulted in a maximum change in the C-statistic of between 0.009 and 0.017 across all cohorts and scores. The maximum change of up to 0.065 in PROSPER may have been driven by the small sample size and was considered an

outlier. To illustrate the impact of clinical and genetic risk on incident AF detection, we plotted the cumulative incidence of AF stratified by dichotomized clinical risk, as well by both clinical and genetic risk together, for one representative study (MDCS) in **Supplemental Figure 2**.

AF genetic risk scores and ischemic stroke

We examined the association between AF genetic risk scores and stroke among 509 independent individuals with stroke from MGH-GASROS and 3,028 controls (**Table 2**). Among the stroke cases, 202 (40%) were classified as having had a cardioembolic stroke by TOAST criteria. In total, 87 (17%) individuals with ischemic stroke had documented AF.

In MGH-GASROS, modest associations between AF genetic risk scores and AF, ischemic stroke (all subtypes), and the subset of cases with cardioembolic stroke were observed using continuous genetic risk scores (**Supplemental Table 4**). The most significantly associated score with AF, as judged by the score with the smallest *P*-value, occurred with a score constructed from 127 SNPs, corresponding to SNPs with *P* values $<1x10^{-4}$ for associations with AF in the prior independent AFGen analysis.[15] Individuals in the highest quartile of the 127-SNP genetic risk score had a 3.13-fold (95%CI, 1.47-7.21; *P*=0.005) increased odds of AF relative to those in the lowest quartile.

In the analysis of ischemic stroke cases and referent individuals, AF genetic risk scores were also modestly associated with both ischemic stroke (all subtypes) and cardioembolic stroke (**Supplemental Table 3**). Those in the highest quartile of the 127-SNP genetic risk score had a 1.73-fold (95%CI, 1.15-2.61; $P=9.0x10^{-3}$) increased odds of ischemic stroke, and a 2.49-fold (95%CI, 1.39-4.58; $P=2.7x10^{-3}$) increased odds of cardioembolic stroke (after excluding other stroke subtypes, **Figure 2**). After omitting the 87 stroke cases with known AF (70 of whom had cardioembolic strokes), the associations between AF genetic risk and both ischemic and cardioembolic stroke remained but were slightly attenuated (**Supplemental Table 5**). Specifically, the relative odds of ischemic stroke comparing those in the highest with those in

the lowest quartile of a 127-SNP AF genetic risk score were 1.55 (95%CI, 1.03-2.36; *P*=0.04) for ischemic stroke, and 2.25 (95%CI, 1.20-4.40; *P*=0.01) for cardioembolic stroke (**Figure 2**).

DISCUSSION

In our analysis of nearly 19,000 individuals of European ancestry, scores reflecting the burden of AF risk alleles were associated with 5-year risks of new-onset AF, after adjusting for clinical risk factors. Individuals in the highest quartile of the genetic scores had up to a 67% higher risk of new-onset AF than those in the lowest quartile, although incremental discrimination beyond clinical risk factors was small regardless of the number of SNPs included in the genetic risk score. In an independent sample, individuals in the highest quartile of a score comprised of 127 AF-associated genetic markers had roughly two-fold higher odds of cardioembolic stroke, compared with those in the lowest quartile after adjustment for age and sex. Associations between AF genetic risk scores and cardioembolic stroke persisted after excluding individuals with known AF.

Our findings support and extend prior observations that AF genetic risk is associated with both AF and stroke. We previously observed an association between familial AF and incident AF in the Framingham Heart Study, beyond associations for clinical risk factors.[1] Subsequently, we observed an approximately 4 to 5-fold gradient in risk between those in the highest versus lowest tails of a 12-SNP AF genetic risk score (based on nine loci) in case-referent and cohort studies.[16] The Women's Genome Health Study reported an association between an AF genetic risk score based on 12 SNPs and occurrence of incident AF,[18] although the AF-associated SNPs used in the analysis were identified in a previous discovery study using the same study sample. Earlier work also described associations between the top AF-associated variants on chromosomes 4q25 and 16q22 with ischemic (and in particular, cardioembolic) stroke.[13,26,42-44] Recently, we and others reported a 2-fold increased hazard of AF and a 1.23-fold increased hazard of ischemic stroke for individuals in the highest versus lowest

quintiles of scores based on a 12-SNP genetic risk model during an average follow-up of 14 years in the MDCS, subjects of which were included in the present analysis of incident AF.[19] Thus, by using well-characterized independent study samples, our current findings extend prior reports that AF genetic risk is associated with incident AF, as well as ischemic stroke.

Our observations have three major implications. First, our finding that AF genetic risk is associated with incident AF beyond the effects observed for accepted clinical risk factors highlights the ability of common genetic variation to capture complementary information. Indeed, the 28%-67% increased risk of AF among individuals in the highest versus the lowest quartile of genetic risk is comparable to the magnitude of risk conferred by traditional clinical risk factors for AF.[9] Nevertheless, even by including a large number of genetic variants and assessing associations with incident AF in large cohorts, the magnitudes of risk associated with genetic risk improved discrimination minimally beyond clinical factors. Such findings underscore the challenges of improving clinical prediction models even when including highly associated predictors.[45]

Second, our observations, coupled with prior findings that AF genetic risk may be preferentially associated with cardioembolic stroke,[13,42,43] raise the possibility that AF genetic risk may serve as a signature for strokes caused by thromboembolism due to AF. Our observation that AF genetic risk was associated with an increased risk of cardioembolic stroke even after excluding individuals with known AF is consistent with the hypothesis that AF genetic risk may be a clinically relevant marker for subclinical, or previously undiagnosed, AF. Although AF genetic risk has a limited impact beyond knowledge of clinical risk factors on AF prediction over a 5-year time horizon, it is possible that such genetic profiling may provide insights into stroke mechanisms and therefore screening and treatment options for secondary prevention. Future analyses are warranted to determine if AF genetic risk discriminates effectively between different stroke subtypes, to assess whether AF genetic risk can identify cryptogenic stroke

patients at elevated risk for recurrent stroke due to AF, and whether estimating AF risk can enhance secondary stroke prevention efforts.

Third, our observation that genetic risk scores constructed from liberally selected SNPs were nevertheless associated with AF and AF-related stroke emphasizes the polygenic nature of AF. Therefore, true AF susceptibility variants are likely to exist even though they may not meet the stringent genome-wide significance criteria currently utilized. Future genetic discovery efforts in larger samples with better power are warranted to identify additional AF susceptibility signals. Indeed, since publication of the most recent AFGen meta-analysis,[15] additional *bona fide* subthreshold AF signals have been identified, and some appear to be associated with stroke.[17] It remains to be determined whether future assessment of AF genetic risk based on associations derived from larger samples will enhance specificity of prediction models.

Our study should be interpreted in the context of the study design. First, all participants were of European descent, and therefore our findings may not be generalizable to individuals of other ancestral groups. Second, the genetic risk models were linear in nature with a single predictor variable, and did not account for potential non-additive genetic effects, interactions between genetic variants, or interactions between genetic variants and environmental factors. Additional modeling methods, including penalized regression or other techniques, may yield more precise genetic risk models. Third, other important determinants of AF risk were not available in our study, including plasma biomarkers such as brain natriuretic peptide.[46] Similarly, in analyses of ischemic stroke, clinical covariates beyond age and sex were unavailable, so we could not evaluate whether the genetic risk score adds appreciably to prediction afforded by the CHA_2DS_2-VASc score[47] or individual stroke risk factors. Future studies are warranted to determine whether genetic risk adds additional information to other clinical and biomarker factors related to AF and stroke. Fourth, our genetic risk models were comprised of common SNPs genotyped in the HapMap reference populations,[48] many of which are likely tag-SNPs and serve as proxies for true causal variation. Through the use of larger sample sizes and

newer techniques to comprehensively assess genomic variation, such as whole genome sequencing, we anticipate better power to identify causal variants underlying AF in the future. Inclusion of causal variants in genetic risk scores may improve the specificity of the models. Fifth, the genetic predictors of prevalent stroke may not be identical to those of incident stroke due to potential survival biases. Therefore, the clinical utility of AF genetic risk factors for identifying individuals at risk for incident stroke merits future study.

Conclusions

We observed that comprehensive AF genetic risk scores were associated with incident AF, exceeding effects of clinical risk factors, in individuals of European ancestry. We further observed that AF genetic risk is associated with both ischemic and cardioembolic stroke after adjustment for age and sex, even among individuals with cardioembolic stroke without established AF. Our findings underscore the polygenic nature of AF and the independent value of genetic information beyond clinical risk factors for the identification of individuals at risk for AF. However, although genetic risk scores are highly associated with AF, genetic information currently affords small improvements in discrimination of AF risk, and therefore does not yet need to be incorporated into routine clinical decision-making. Future clinical trials are necessary to rigorously assess whether AF genetic risk is an effective clinical marker of cardioembolic stroke etiology, and can identify individuals with subclinical AF.

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FIGURE LEGENDS

Figure 1. Pooled 5-year relative hazard of incident atrial fibrillation among individuals in the highest quartile of AF genetic risk relative to those in the lowest quartile.

SNPs included in scores were derived using different thresholds of association between each SNP and atrial fibrillation in an earlier, independent study.[15]

Figure 2. Risk of cardioembolic stroke in MGH-GASROS according to atrial fibrillation genetic risk.

Odds ratios for cardioembolic stroke in relation to atrial fibrillation genetic risk scores among cardioembolic stroke cases and 3,028 controls. Blue histograms show distributions of genetic risk scores among cases and controls. Black dots indicate odds ratios for stroke for each quartile of genetic risk scores (bars indicate 95% confidence intervals). For panels A-C, genetic risk scores were based on 45 (A), 127 (B), and 701 (C) SNPs among 202 cardioembolic stroke cases (including 70 with known AF) and controls. For panels D-F, genetic risk scores were based 45 (D), 127 (E), and 701 (F) SNPs among 152 cardioembolic stroke cases (none with known AF) and controls. SNP totals may not equal those used in the incident atrial fibrillation analysis since some SNPs were unavailable in MGH-GASROS, in which case proxies were used when available (Supplemental Table 1).

Table 1. Characteristics of participants included in analyses of incident atrial fibrillation.

	MDCS	MESA	PREVEND	PROSPER*	BioVU
No. total	8,226	2,451	1,624	5,212	1,388
No. incident AF	190	76	34	503	229
Age, years	59±7	63±10	58±8	75±3	60±11
Women	4,275 (52)	1,321 (52)	770 (47)	2,716 (52)	678 (49)
Height, cm	169±9	169±10	172±9	165±9	171±11
Weight, kg	75±14	79±16	80±14	73±13	86±22
Systolic blood pressure, mmHg	145±20	124±20	135±21	155±22	131±20
Diastolic blood pressure, mmHg	87±10	75±10	77±10	84±11	75±30
History of smoking	2,513 (31)	1,401 (55)	671 (41)	1,388 (27)	619 (45)
Antihypertensive medication	1,799 (22)	840 (33)	362 (22)	3,854 (74)	1,339 (96)
History of diabetes	542 (7)	151 (6)	98 (6)	540 (10)	359 (26)
History of heart failure	39 (0.5)	52 (2)	4 (0.2)	NA	161 (12)
History of myocardial infarction	487 (9)	63 (3)	71 (4)	697 (13)	284 (20)

Data presented as mean ± standard deviation, or No. (%)
*Maximum follow-up in PROSPER was 4 years.

Table 2. Characteristics of participants of European ancestry included in analyses of ischemic stroke from MGH-GASROS and referents.

	Cases	**Referents**
N	509	3,028
Age, years	66.9 ± 14.4	42.3 ± 7.8
Women	214 (24.2)	732 (42.0)
Atrial fibrillation	87 (17)	–

Data presented as mean ± standard deviation, or No. (%)
Stroke etiologic subtype: cardioembolic (n=202, 39%), large artery (n=114, 22%), small vessel / lacunar (n=62, 12%), other (n=124, 24%), undetermined (n=7, 1%).
P for comparison of age and sex between cases and controls <0.001.

Figure 1.

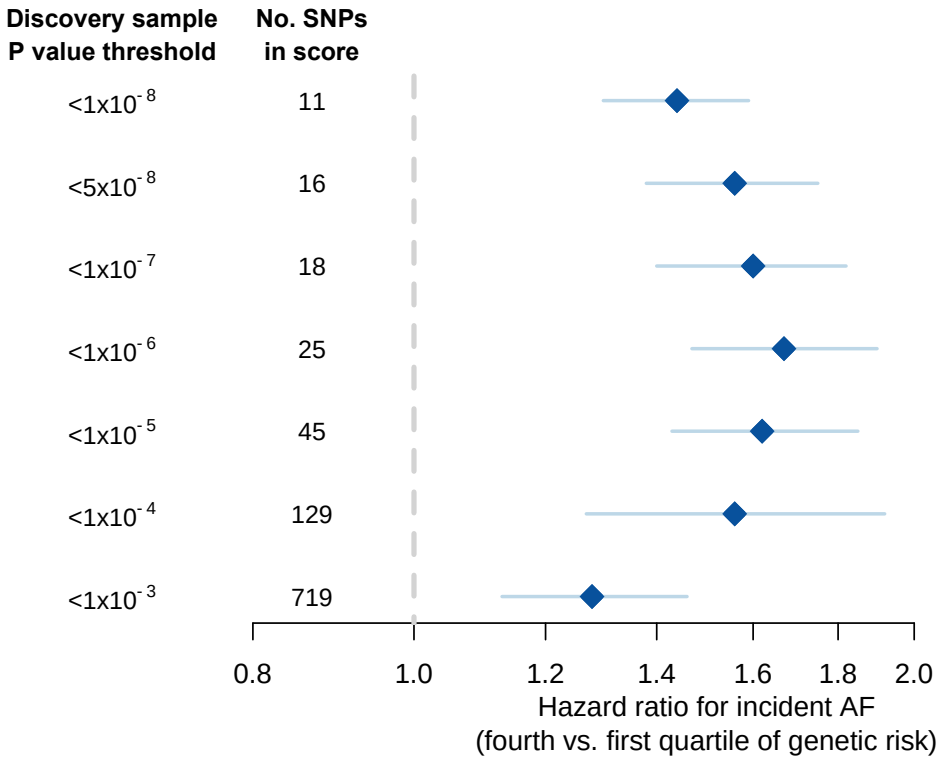
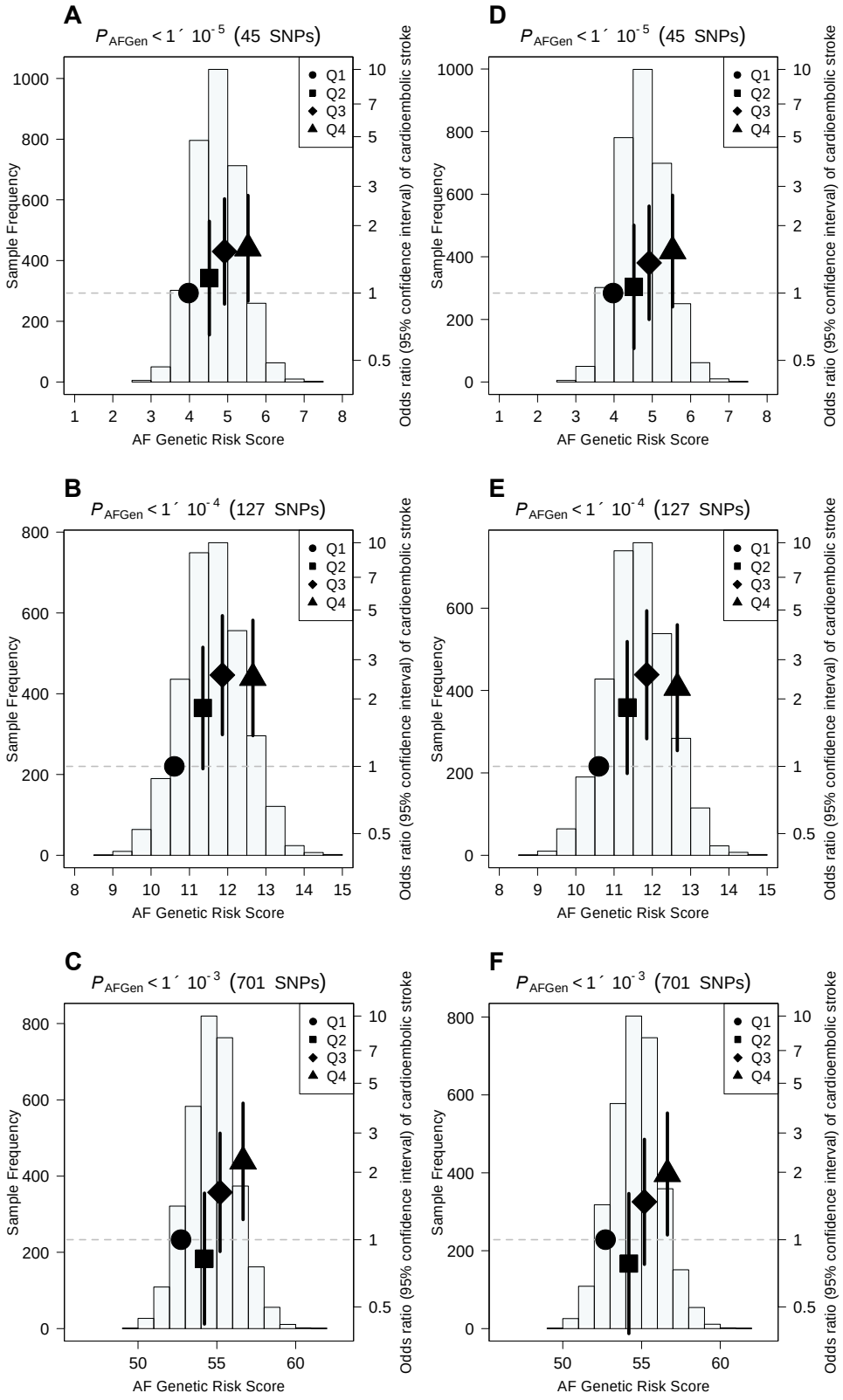

Discovery sample
P value threshold
No. SNPs
in score
<1x10-8
11
<5x10-8
16
<1x10-7
18
<1x10-6
25
<1x10-5
45
<1x10-4
129
<1x10-3
719
0.8
1.0
1.2
1.4
1.6
1.8
2.0
Hazard ratio for incident AF
(fourth vs. first quartile of genetic risk)

Figure 2.


A
$P_{AFGen} < 1 \times 10^{-5}$ (45 SNPs)
B
$P_{AFGen} < 1 \times 10^{-4}$ (127 SNPs)
C
$P_{AFGen} < 1 \times 10^{-3}$ (701 SNPs)
D
$P_{AFGen} < 1 \times 10^{-5}$ (45 SNPs)
E
$P_{AFGen} < 1 \times 10^{-4}$ (127 SNPs)
F
$P_{AFGen} < 1 \times 10^{-3}$ (701 SNPs)
Q1
Q2
Q3
Q4
Sample Frequency
Odds ratio (95% confidence interval) of cardioembolic stroke
AF Genetic Risk Score

Online Supplement

Atrial Fibrillation Genetic Risk, Incident Atrial Fibrillation, and Ischemic Stroke

Index

DESCRIPTIONS OF PARTICIPATING STUDIES

Malmö Diet and Cancer Study (MDCS)

MDCS is a community-based prospective epidemiologic cohort of middle-aged individuals from Southern Sweden.[1] In total, 30,447 subjects attended a baseline exam in 1991-1996, when they filled out a questionnaire and underwent anthropometric and blood pressure measurements. Hypertension was defined as self-reported use of antihypertensive medications or measured blood pressure ≥140/90 mmHg. Prevalent or incident cases of atrial fibrillation (AF), heart failure and ischemic heart disease were ascertained from nation-wide hospital registers with high validity as described previously.[2] Prevalent or incident diabetes was ascertained from a variety of regional and nationwide registers as described previously.[3] Genome-wide genotyping of single nucleotide variants was performed using the Illumina Human Omni Express Exome BeadChip kit. Genotyping was performed in a nested case-cohort design, including a random subset of 5248 subjects and 3098 cases with incident coronary disease or stroke. Imputation was performed to genotypes in the 1000 Genomes Project phase 1 using IMPUTE.[4] Analyses were performed using SAS version 9.3 for Windows (SAS institute, Cary, NC).

Multi-Ethnic Study of Atherosclerosis (MESA)

MESA is a community-based sample of 6,814 men and women without symptomatic cardiovascular disease aged 45-84 years (38% white; 28% African American; 22% Hispanic; and 12% Asian -- mainly of Chinese descent).[5] Participants were recruited during 2000-2002 from 6 field centers across the U.S. (at Wake Forest University; Columbia University; Johns Hopkins University; the University of Minnesota; Northwestern University, and the University of California – Los Angeles). All underwent anthropometric measurement and extensive evaluation by questionnaires at baseline, followed by 4 subsequent examinations at intervals of approximately 2-4 years. Current AF at baseline was an exclusion criterion. Follow-up phone calls to study participants (every 9-12 months) were used to identify all hospitalizations. Medical records, including discharge diagnoses, were obtained for each hospitalization. Incident AF was defined by International Classification of Disease codes 427.31 or 427.32 (9th revision). In addition, new diagnoses of AF were identified at follow-up by the presence of AF or atrial flutter on a study ECG at Exam 5 (approximately 10 years after baseline). Age and sex were self-reported. Further information can be found at:
http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000209.v13.p3

European ancestry participants were genotyped on the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA) at the Affymetrix Research Services Lab. Plate-based genotype calling was with Birdseed v2. Additional genotypes were imputed to the 1000 Genomes Phase I integrated variant set (NCBI build 37/hg19) separately in each ethnic group, by use of the IMPUTE2 program.[4] Data freezes from 23 November 2010 (low-coverage whole-genome) and 21 May 2011 (high-coverage exome), phased haplotypes released March 2012 (v3), and phased haplotypes for 1,092 individuals and 39+ million variants were used. Analyses were performed using ProbABEL software.[6]

PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)

PROSPER was a prospective multicenter randomized placebo-controlled trial to assess whether treatment with pravastatin diminishes the risk of major vascular events in the elderly.[7] Between December 1997 and May 1999, subjects were screened and enrolled in Scotland (Glasgow), Ireland (Cork), and the Netherlands (Leiden). Men and women aged 70-82 years were recruited if they had pre-existing vascular disease or increased risk of such disease because of smoking, hypertension, or diabetes. A total of 5,804 subjects were randomly assigned to pravastatin or placebo. A large number of prospective tests were performed including BioBank tests and

cognitive function measurements. New diagnoses were identified by self-report or a physician diagnosis of AF, or by the presence of AF or atrial flutter on a study ECG done annually and at study run-out or at the time of an adverse event. Genome-wide genotyping was performed in the sequential PHASE project with the use of the Illumina 660K BeadChip in 5,763 subjects in whom DNA was available for genotyping. After QC exclusions (call rate <95%) 5,244 subjects and 557,192 SNPs were left for analysis, including 507 individuals with incident AF. These SNPs were imputed to 2.5 million SNPs based on the HapMap build 36 with MACH imputation software.[8] Analyses were performed using Plink 1.07[9] and IBM SPSS statistics version 20.

Prevention of Renal and Vascular Endstage Disease (PREVEND)

The PREVEND cohort study was founded in 1997, and is an ongoing community-based cohort study including 8592 inhabitants of the city of Groningen, The Netherlands.[10] PREVEND is investigating the natural course of microalbuminaria and its relation to renal and cardiovascular disease. Details of the protocol, AF ascertainment and covariate definitions have been described elsewhere (www.prevend.org). AF was ascertained if either atrial flutter or AF was present on a 12-lead ECG obtained at one of the three PREVEND follow-up visits, or at an outpatient visit or hospital admission in the two hospitals in the city of Groningen (University Medical Center Groningen and Martini Hospital). Systolic and diastolic blood pressures were calculated as the mean of the last two measurements of the two visits, using an automatic GE Dinamap XL Model 9300 series device. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or use of antihypertensive drugs. Use of antihypertensive drugs was based on available information from the pharmacy prescription database. Type 2 diabetes was defined as a fasting plasma glucose >7.0 mmol/L (126 mg/dL), a nonfasting plasma glucose >11.1 mmol/L, or use of anti-diabetic drugs. Smoking was defined as any smoking within the last five years. History of myocardial infarction or stroke was defined as participant-reported hospitalization for at least 3 days as a result of this condition. A committee of heart failure experts adjudicated all participants with heart failure at baseline according to previously published criteria. Genotyping was performed using the Illumina CytoSNP12v2 array. Genotype calling was performed using GenomeStudio, and imputation was performed using Beagle[11] with the HapMap release 22 CEU referent panel. Analyses were performed with Plink v1.07[9] and R.[12]

Vanderbilt DNA Bio-bank *(BioVU)*

Subjects were included from the Vanderbilt DNA Bio-bank (BioVU), for which a description of methods has been published.[13-16] Inclusion criteria for patients selected from BioVU include age ≥40 years, self-identified European or African American race, and no known previous history of AF as of December 2005. Patients with an ICD-9 code or CPT code for heart transplant were also excluded. Additionally, patients must have had at least three visits to the Vanderbilt Internal Medicine clinic within a 24-month period to ensure adequate follow-up for ascertainment of incident AF. Ascertainment of incident AF was achieved with a previously validated algorithm which uses natural language processing of cardiologist-interpreted ECG impressions and billing codes, with a positive predictive value of >95%.[13] Patients with preexisting ICD-9 codes for AF or mention of AF in ECG interpretations or in the structured problem lists were excluded. Sex, race, age, weight, height, body mass index, and systolic and diastolic blood pressure were directly extracted from structured fields in the BioVU. History of myocardial infarction, heart failure, and diabetes mellitus were determined by using ICD-9 codes incorporating laboratory values and medication records. Treatment for hypertension was assessed using a previously validated algorithm incorporating medication records. This algorithm was previously shown to have a sensitivity and positive predictive value of 88% and 93%, respectively.[14,15] PR interval and left ventricular hypertrophy were obtained from outpatient ECG reports. Current smoking status was determined by using an existing algorithm with a positive predictive value of 93% in

Vanderbilt medical records. AF susceptibility SNPs were available within BioVU based on one of two GWAS chips (Illumina OMNI-Quad or Illumina HumanOmni5-Quad). Analyses were performed using PLINK v1.07.[9]

Massachusetts General Hospital Genes Associated with Stroke Risk and Outcomes Study (MGH-GASROS)

MGH-GASROS enrolled ischemic stroke subjects as part of a single-center prospective cohort study of consecutive patients with ischemic stroke aged ≥18 years admitted to the Massachusetts General Hospital Stroke Unit (Boston, MA, U.S.A.) between 2000 and 2011 after presenting to the emergency department within 24 hours of symptom onset.[17-19] Ischemic stroke was defined as a clinical syndrome of any duration associated with a radiographically proven acute infarct consistent with a vascular pattern of involvement and without radiographic evidence of a demyelinating or neoplastic disease or other structural disease, including vasculitis, subacute bacterial endocarditis, vasospasm due to subarachnoid hemorrhage or cocaine abuse, or primary intracerebral hemorrhage. Diagnosis of acute cerebral ischemia was confirmed for all subjects in the present study by admission diffusion weighted imaging completed within 48 hours after symptom onset. Vascular and critical care neurologists subtyped ischemic strokes by systematic medical record review using the TOAST criteria.[20] Referents were matched to cases on the basis of age, sex and race/ethnicity and drawn from stroke-free individuals who received care at primary care practices within Massachusetts General Hospital or from the Myocardial Infarction Genetics Consortium study who did not have a history of myocardial infarction.[21] All cases included in this analysis were genotyped on the Affymetrix 6.0 array. Genotypes were imputed with the 1000 genomes reference panel-imputed dataset using MACH 1.0.[8] Analyses were performed using PLINK[9] and R v3.2.3.[12]

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PREVEND: The PREVEND study is supported by the Dutch Kidney Foundation (grant E0.13) and the Netherlands Heart Foundation (grant NHS2010B280).

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Supplemental Table 1. SNPs used to construct atrial fibrillation genetic risk scores.

SNP	Risk Allele	Risk Allele Weight	P-value, prior AFGen analysis	Proxy SNP for stroke analysis	Proxy Risk Allele for stroke analysis	Proxy Risk Allele Weight for stroke analysis	Proxy P-value, prior AFGen analysis
rs999790	G	0.0709	0.00042	Same	–	–	
rs9997270	C	0.2009	0.0009509	Same	–	–	
rs9995522	A	0.1631	0.0003767	Same	–	–	
rs996831	A	0.077	0.0005751	Same	–	–	
rs9967820	G	0.1263	4.51E-06	Same	–	–	
rs9959337	T	0.0765	0.000182	Same	–	–	
rs9952696	A	0.1151	0.0003895	Same	–	–	
rs9950749	C	0.0778	0.0001595	Same	–	–	
rs9945543	G	0.0892	6.93E-05	Same	–	–	
rs9916520	C	0.0937	0.0005965	Same	–	–	
rs988965	A	0.0884	0.0004757	Same	–	–	
rs9857326	A	0.0864	3.86E-05	Same	–	–	
rs9855666	G	0.078	0.0005965	Same	–	–	
rs9842908	A	0.1248	0.000498	Same	–	–	
rs9808055	G	0.2947	0.0008073	Same	–	–	
rs972691	G	0.0733	0.0005745	Same	–	–	
rs971215	A	0.0706	0.0003552	Same	–	–	
rs967582	C	0.0742	0.0002823	Same	–	–	
rs967417	A	0.0683	0.0005426	Same	–	–	
rs966985	T	0.0939	0.0004213	Same	–	–	
rs96501	T	0.0943	0.0004979	Same	–	–	
rs964329	G	0.1455	0.0003223	Same	–	–	
rs9641292	C	0.1145	0.0007157	Same	–	–	
rs9612028	C	0.1013	0.00077	Same	–	–	
rs9604978	G	0.115	0.0003395	Same	–	–	
rs9597111	T	0.1419	0.000275	Same	–	–	
rs9576962	T	0.1294	0.0006991	Same	–	–	
rs9576555	A	0.0916	0.000114	Same	–	–	
rs9537252	T	0.0728	0.0004041	Same	–	–	
rs9537090	G	0.1604	6.27E-05	Same	–	–	
rs9527662	T	0.0749	0.0004779	Same	–	–	
rs9521715	T	0.0774	0.0008422	Same	–	–	
rs9509908	T	0.0677	0.0007851	Same	–	–	
rs9506441	A	0.2623	0.0001901	Same	–	–	
rs9471552	G	0.0818	0.0007915	Same	–	–	
rs947142	T	0.0699	0.000959	Same	–	–	
rs943165	A	0.091	0.000233	Same	–	–	
rs9408879	T	0.0721	0.0004965	Same	–	–	
rs939046	A	0.0787	0.0006821	Same	–	–	
rs9370893	C	0.0766	0.000605	Same	–	–	
rs9367983	C	0.0876	0.0001479	Same	–	–	
rs9357699	C	0.1352	0.0007776	Same	–	–	
rs9326957	A	0.1534	0.0003096	Same	–	–	
rs9324924	T	0.0876	0.0003213	Same	–	–	
rs9305560	A	0.1737	5.77E-06	Same	–	–	
rs9302230	T	0.075	0.000543	Same	–	–	
rs9290226	C	0.1375	0.0004203	Same	–	–	
rs9284844	G	0.1152	2.66E-05	Same	–	–	
rs928462	T	0.0928	0.0009445	Same	–	–	
rs9283513	A	0.0798	0.0003553	Same	–	–	
rs9267992	G	0.1108	3.97E-05	Same	–	–	
rs926198	T	0.0775	0.0002435	Same	–	–	
rs907687	T	0.0765	0.0001474	Same	–	–	
rs905938	C	0.0786	0.0006768	Same	–	–	
rs903369	C	0.0686	0.0005633	Same	–	–	
rs894915	T	0.0679	0.0008269	Same	–	–	
rs894486	T	0.0656	0.0009246	Same	–	–	
rs892779	T	0.1117	0.000555	Same	–	–	
rs882272	G	0.0658	0.0009908	Same	–	–	
rs879596	A	0.186	0.0003045	Same	–	–	
rs867039	T	0.0938	0.0008669	Same	–	–	
rs8601	T	0.0904	0.0002579	Same	–	–	
rs851340	T	0.0805	0.0006082	Same	–	–	
rs833632	A	0.0951	9.49E-05	Same	–	–	

rs831430	T	0.0929	0.0004522	Same	–	–
rs831157	T	0.1531	0.0005754	Same	–	–
rs8190612	T	0.1109	0.0003253	Same	–	–
rs818539	T	0.1179	0.0002205	Same	–	–
rs8110127	G	0.0987	0.0005929	Same	–	–
rs8108108	C	0.0744	0.0003449	Same	–	–
rs8100255	T	0.0864	0.0004184	Same	–	–
rs8097177	C	0.078	0.0001023	Same	–	–
rs8055406	G	0.1078	0.0002013	Same	–	–
rs804877	G	0.128	0.0002775	Same	–	–
rs8040533	G	0.1512	1.18E-08	Same	–	–
rs8031860	T	0.0823	0.0007623	Same	–	–
rs8018219	C	0.0984	0.0008182	Same	–	–
rs800683	T	0.1615	0.0003792	Same	–	–
rs7994886	C	0.0744	0.0004458	Same	–	–
rs7989027	A	0.0845	0.0002692	Same	–	–
rs7987944	C	0.0862	4.88E-05	Same	–	–
rs7943633	C	0.1442	0.0001747	Same	–	–
rs7937519	T	0.1224	0.0006523	None	–	–
rs7922194	A	0.2135	0.0007589	Same	–	–
rs7915465	T	0.1263	0.0004347	Same	–	–
rs7900898	A	0.1333	0.0006515	Same	–	–
rs7872739	C	0.0984	0.0005469	Same	–	–
rs785437	G	0.0793	0.0008837	Same	–	–
rs7835679	C	0.1794	2.24E-05	Same	–	–
rs7816647	T	0.0847	0.0006835	Same	–	–
rs7816571	C	0.0694	0.0008364	Same	–	–
rs778308	C	0.0881	0.0008865	Same	–	–
rs7781814	C	0.1015	0.0004185	Same	–	–
rs7773151	C	0.0799	0.0007361	Same	–	–
rs7763785	G	0.09	0.0008738	Same	–	–
rs7753843	T	0.088	3.00E-05	Same	–	–
rs7740137	A	0.1279	0.0001804	Same	–	–
rs7736938	G	0.1074	0.0001888	Same	–	–
rs768347	T	0.1077	1.35E-05	Same	–	–
rs7682872	G	0.0877	2.77E-05	Same	–	–
rs7653939	A	0.0678	0.0009816	Same	–	–
rs765039	G	0.0715	0.0004416	Same	–	–
rs7650184	C	0.0789	0.0002269	Same	–	–
rs7638909	T	0.0992	9.33E-05	Same	–	–
rs7635053	A	0.0721	0.0006369	Same	–	–
rs7635004	A	0.1087	0.000617	Same	–	–
rs762919	G	0.088	0.0004319	Same	–	–
rs7608839	T	0.0942	0.0001427	Same	–	–
rs7600577	A	0.0984	0.0008042	Same	–	–
rs7591917	A	0.1438	0.0004477	Same	–	–
rs7568221	G	0.0754	0.0007074	Same	–	–
rs7556675	C	0.0747	0.0007203	Same	–	–
rs7553796	A	0.0866	1.40E-05	Same	–	–
rs7537634	A	0.1566	0.000959	Same	–	–
rs7506639	T	0.0748	0.0004676	Same	–	–
rs7434264	G	0.0844	0.0004807	Same	–	–
rs7427154	G	0.1322	0.0003427	Same	–	–
rs740854	A	0.1463	0.0002195	Same	–	–
rs739455	G	0.2157	8.41E-05	Same	–	–
rs737558	T	0.0722	0.0009392	Same	–	–
rs7359646	T	0.0734	0.0004197	Same	–	–
rs7330782	A	0.0718	0.0008629	Same	–	–
rs731341	G	0.0863	0.0002601	Same	–	–
rs7295704	T	0.0974	4.85E-05	Same	–	–
rs7285376	G	0.1149	0.0002265	Same	–	–
rs727716	G	0.1004	0.0009923	Same	–	–
rs727037	A	0.0677	0.0007911	Same	–	–
rs7270354	A	0.1069	0.0002324	Same	–	–
rs7269069	A	0.1222	0.0006223	Same	–	–
rs7246182	C	0.0861	0.0001722	Same	–	–
rs7235339	G	0.0758	0.000745	Same	–	–
rs723370	G	0.1166	8.75E-05	Same	–	–
rs7227127	A	0.1062	0.000611	Same	–	–
rs7182401	T	0.074	0.0009984	Same	–	–

rs7179371	T	0.0771	0.0001613	Same	–	–
rs7171648	C	0.1597	6.03E-07	Same	–	–
rs716226	A	0.0962	0.0002127	Same	–	–
rs7160770	T	0.0818	4.98E-05	Same	–	–
rs715888	G	0.0779	0.0004704	Same	–	–
rs7154452	T	0.0894	8.67E-05	Same	–	–
rs7149330	G	0.0918	0.0008075	Same	–	–
rs7143846	A	0.1826	0.00014	Same	–	–
rs7068070	A	0.0956	7.00E-05	Same	–	–
rs7046258	C	0.1113	7.46E-05	Same	–	–
rs7035855	A	0.1106	0.0001165	Same	–	–
rs698809	T	0.0983	8.88E-05	Same	–	–
rs6978506	T	0.0813	0.0008759	Same	–	–
rs6968408	C	0.1518	1.82E-05	Same	–	–
rs696815	A	0.075	0.0003945	Same	–	–
rs6960162	G	0.0785	0.0003706	Same	–	–
rs6937605	C	0.0993	0.0002454	Same	–	–
rs6889305	C	0.0936	0.0003172	Same	–	–
rs6884185	C	0.092	4.47E-05	Same	–	–
rs6882776	G	0.0981	3.72E-05	Same	–	–
rs6843738	A	0.0808	9.28E-05	Same	–	–
rs6838973	C	0.19	8.83E-20	Same	–	–
rs6817105	C	0.493	1.79E-74	Same	–	–
rs6802120	C	0.0959	0.0005904	Same	–	–
rs6799133	A	0.0693	0.0009501	Same	–	–
rs6783573	G	0.0753	0.0003241	Same	–	–
rs6773303	A	0.1001	0.0007051	Same	–	–
rs6771278	T	0.0724	0.0004924	Same	–	–
rs6760338	C	0.261	9.28E-05	Same	–	–
rs6756513	G	0.0871	0.0001274	Same	–	–
rs6749773	A	0.0807	4.88E-05	Same	–	–
rs6740528	A	0.1255	0.0001158	Same	–	–
rs6731358	A	0.085	6.46E-05	Same	–	–
rs6706362	G	0.069	0.0005745	Same	–	–
rs6706171	C	0.0705	0.0004507	None	–	–
rs670217	G	0.1002	0.0003183	Same	–	–
rs6701767	C	0.0885	0.0009411	Same	–	–
rs6688119	T	0.0738	0.0009302	Same	–	–
rs6684191	A	0.08	0.0001631	Same	–	–
rs6669826	T	0.0854	0.0008446	Same	–	–
rs6669689	A	0.0835	0.0001496	Same	–	–
rs6666258	C	0.1665	1.99E-14	Same	–	–
rs6601786	T	0.0753	0.0004841	Same	–	–
rs6599254	G	0.0981	1.32E-06	Same	–	–
rs6585467	G	0.0692	0.0008571	Same	–	–
rs6580289	C	0.0692	0.0004702	Same	–	–
rs6575317	A	0.0779	0.0001291	Same	–	–
rs6544745	C	0.166	0.0003509	Same	–	–
rs6540690	C	0.1124	3.60E-05	Same	–	–
rs6505893	C	0.155	9.84E-05	Same	–	–
rs6492689	G	0.0722	0.0006586	Same	–	–
rs6480771	T	0.081	5.94E-05	Same	–	–
rs6479643	C	0.0765	0.0007205	Same	–	–
rs6479562	A	0.0898	6.36E-06	Same	–	–
rs6464716	A	0.0756	0.0006204	Same	–	–
rs6463968	C	0.0992	0.0006955	Same	–	–
rs6455760	A	0.1092	0.0001525	Same	–	–
rs6428323	C	0.0801	0.0004511	Same	–	–
rs6426872	A	0.108	3.53E-05	Same	–	–
rs6151704	T	0.0664	0.0008943	Same	–	–
rs6086773	T	0.1121	0.0005113	Same	–	–
rs6062468	C	0.0926	4.69E-05	None	–	–
rs6027956	T	0.0667	0.0009729	Same	–	–
rs6025056	G	0.1221	0.0002237	Same	–	–
rs6021268	T	0.1338	0.00071	Same	–	–
rs582679	C	0.0934	0.0001896	Same	–	–
rs574344	A	0.1272	0.0008018	Same	–	–
rs570557	T	0.1064	0.0007349	Same	–	–
rs549793	T	0.0859	0.0007425	Same	–	–
rs542214	A	0.0873	0.0002498	Same	–	–

rs526428	T	0.1318	0.0002971	Same	–	–
rs525476	T	0.073	0.0006471	Same	–	–
rs519862	A	0.0956	0.0008055	Same	–	–
rs5021390	A	0.0876	0.0004046	Same	–	–
rs4999127	A	0.1244	4.78E-05	Same	–	–
rs4976490	C	0.0687	0.0007676	Same	–	–
rs4972960	C	0.0952	0.0009473	Same	–	–
rs4963646	G	0.0804	0.0004239	Same	–	–
rs495558	T	0.0732	0.0003349	Same	–	–
rs4954876	C	0.0693	0.00054	Same	–	–
rs4953359	T	0.069	0.0004393	Same	–	–
rs4953340	C	0.0942	5.13E-05	Same	–	–
rs4948721	G	0.0752	0.0005691	Same	–	–
rs4948002	A	0.099	0.0009979	Same	–	–
rs4935117	T	0.1253	0.000646	Same	–	–
rs4935020	C	0.0678	0.0007237	Same	–	–
rs4934284	G	0.116	0.0009329	Same	–	–
rs4920085	A	0.1449	0.0002021	Same	–	–
rs4919621	A	0.0707	0.0004468	Same	–	–
rs4918068	T	0.1067	0.0007752	Same	–	–
rs4906630	G	0.1009	0.0004169	Same	–	–
rs4905933	C	0.0661	0.0009254	Same	–	–
rs4905434	G	0.0966	0.0003021	Same	–	–
rs4885350	A	0.1571	0.0002617	Same	–	–
rs4884651	G	0.0693	0.0009082	Same	–	–
rs4883463	T	0.0931	0.0007186	Same	–	–
rs4876578	A	0.1619	0.0004301	Same	–	–
rs4871397	G	0.1787	4.79E-05	Same	–	–
rs4871385	C	0.0821	0.0009759	Same	–	–
rs4833233	G	0.0695	0.0003512	Same	–	–
rs4824051	C	0.101	4.63E-05	None	–	–
rs4820556	G	0.0998	0.0005384	Same	–	–
rs4817760	C	0.0871	0.0002949	Same	–	–
rs478438	A	0.129	0.0001138	Same	–	–
rs4771852	T	0.1153	0.0008374	Same	–	–
rs4751029	A	0.1431	0.0005413	Same	–	–
rs4735076	C	0.1298	0.0005567	Same	–	–
rs4733547	T	0.0944	0.0003332	Same	–	–
rs4692402	G	0.0906	0.0003912	Same	–	–
rs4686419	T	0.0741	0.0009283	Same	–	–
rs4663039	A	0.1226	0.0005702	None	–	–
rs4636640	A	0.0807	0.0007712	Same	–	–
rs4625692	A	0.111	8.00E-06	Same	–	–
rs4624886	A	0.0971	0.000315	Same	–	–
rs4595097	T	0.0841	0.0005249	Same	–	–
rs4543168	G	0.1012	0.0007033	Same	–	–
rs4540309	C	0.0985	0.000629	Same	–	–
rs4530555	T	0.101	0.0001293	Same	–	–
rs4501708	T	0.0845	0.0007866	Same	–	–
rs445	C	0.1157	0.0008584	Same	–	–
rs4429865	T	0.078	0.0004962	Same	–	–
rs4403607	T	0.1034	0.0002978	Same	–	–
rs4401604	A	0.0971	0.0003168	Same	–	–
rs4384031	T	0.0743	0.0003445	Same	–	–
rs4358298	G	0.0761	0.0006723	Same	–	–
rs4321363	T	0.1296	0.0005855	Same	–	–
rs4301399	T	0.1654	0.0001795	Same	–	–
rs4246224	G	0.1485	2.23E-07	Same	–	–
rs4243595	T	0.0664	0.0009938	Same	–	–
rs4238314	A	0.0841	2.72E-05	Same	–	–
rs4235054	A	0.0723	0.0003747	Same	–	–
rs4234206	T	0.0766	0.0008328	Same	–	–
rs416532	T	0.0932	5.38E-06	Same	–	–
rs414871	C	0.101	0.0003497	Same	–	–
rs4131707	C	0.0971	0.0003903	Same	–	–
rs413113	G	0.0869	0.0008832	Same	–	–
rs413089	C	0.0971	0.0005648	Same	–	–
rs4124163	A	0.2757	9.12E-07	Same	–	–
rs4112823	C	0.1083	0.0004601	Same	–	–
rs4032974	C	0.1809	2.57E-08	Same	–	–

rs3922843	A	0.099	9.65E-06	Same	–	–		
rs3917686	T	0.116	0.0008529	Same	–	–		
rs3908748	A	0.3312	0.0005776	None	–	–		
rs3866823	A	0.114	3.42E-08	Same	–	–		
rs3855819	C	0.0955	0.0005116	Same	–	–		
rs3853444	T	0.1541	8.47E-10	Same	–	–		
rs3848421	A	0.0681	0.0009705	Same	–	–		
rs3846687	T	0.0697	0.0007337	Same	–	–		
rs3826046	G	0.1454	0.0004443	Same	–	–		
rs3824359	C	0.1121	9.25E-05	Same	–	–		
rs3821120	C	0.0728	0.0008406	Same	–	–		
rs3807989	G	0.1308	9.60E-11	Same	–	–		
rs3803833	G	0.0893	0.0006764	Same	–	–		
rs3790999	A	0.0745	0.000441	Same	–	–		
rs378892	C	0.084	0.0001332	Same	–	–		
rs3782464	C	0.0886	3.31E-05	Same	–	–		
rs3780190	G	0.1	6.27E-06	Same	–	–		
rs3772584	C	0.2015	0.0009454	Same	–	–		
rs3765618	G	0.1622	0.0007342	Same	–	–		
rs3748608	A	0.0791	0.0004114	Same	–	–		
rs3739287	C	0.141	8.29E-05	Same	–	–		
rs3731399	T	0.1203	0.0004015	Same	–	–		
rs364926	T	0.0741	0.0008743	Same	–	–		
rs363895	A	0.0678	0.0008601	Same	–	–		
rs361540	A	0.0745	0.0003824	Same	–	–		
rs352193	G	0.1143	0.0007381	Same	–	–		
rs352101	T	0.069	0.0007602	Same	–	–		
rs345523	T	0.0981	0.0001086	Same	–	–		
rs3427	T	0.0786	0.0006064	Same	–	–		
rs34022	C	0.0753	0.0003105	Same	–	–		
rs337711	T	0.0673	0.0008797	Same	–	–		
rs325609	G	0.1603	5.39E-05	Same	–	–		
rs325410	C	0.0802	0.0007824	rs170522	T		0.0789	0.0008017
rs31864	G	0.0721	0.0002855	Same	–	–		
rs3135005	A	0.0982	0.0003759	Same	–	–		
rs3117572	A	0.0886	0.0006333	Same	–	–		
rs3099794	C	0.0697	0.0006863	Same	–	–		
rs306290	C	0.0737	0.0005804	Same	–	–		
rs304586	C	0.07	0.0005192	Same	–	–		
rs2989724	T	0.0789	0.0003493	Same	–	–		
rs2980785	G	0.1288	0.0001589	Same	–	–		
rs2975424	C	0.0905	0.0003967	Same	–	–		
rs2973501	G	0.0727	0.0008289	Same	–	–		
rs297005	C	0.0759	0.0003989	Same	–	–		
rs295136	G	0.0781	0.0001581	Same	–	–		
rs2941405	C	0.0998	4.79E-05	Same	–	–		
rs2922431	T	0.0728	0.0009478	Same	–	–		
rs287927	A	0.0802	0.0005006	Same	–	–		
rs2876520	C	0.0797	9.99E-05	Same	–	–		
rs2872583	G	0.1159	0.0009051	Same	–	–		
rs2838561	A	0.098	0.0001766	Same	–	–		
rs2836546	A	0.0704	0.0007485	Same	–	–		
rs2834618	T	0.1269	0.0002241	Same	–	–		
rs2833575	G	0.0751	0.0004759	Same	–	–		
rs2833272	T	0.0679	0.0006061	Same	–	–		
rs283077	T	0.0728	0.0002076	Same	–	–		
rs2827784	T	0.067	0.0009029	Same	–	–		
rs2824430	T	0.1196	0.0004646	Same	–	–		
rs2816146	C	0.1048	0.0003766	Same	–	–		
rs2813865	G	0.0964	0.0001445	Same	–	–		
rs276857	G	0.1452	1.00E-05	Same	–	–		
rs2738627	A	0.094	0.0002961	Same	–	–		
rs2729553	A	0.0815	0.0001028	Same	–	–		
rs2724028	A	0.0789	0.0009407	Same	–	–		
rs2723065	A	0.0996	9.71E-07	Same	–	–		
rs2705081	C	0.1269	0.0008007	Same	–	–		
rs2685217	T	0.1066	2.58E-05	Same	–	–		
rs2681581	A	0.1649	0.0005694	Same	–	–		
rs2680702	G	0.0718	0.0005217	Same	–	–		
rs2670005	T	0.085	0.0001239	Same	–	–		

rs2668132	C	0.0724	0.0003518	Same	–	–		
rs2656924	C	0.1142	0.0009033	Same	–	–		
rs2648034	A	0.0726	0.0002611	Same	–	–		
rs2642444	G	0.0893	0.000932	Same	–	–		
rs2620805	A	0.0768	0.0009405	Same	–	–		
rs260105	G	0.0971	0.0002333	Same	–	–		
rs2595102	G	0.1529	3.08E-13	Same	–	–		
rs2595098	T	0.2634	0.0005396	Same	–	–		
rs2586047	A	0.0735	0.0003488	Same	–	–		
rs2585844	C	0.0907	0.0001395	Same	–	–		
rs2570514	T	0.0791	0.0004178	Same	–	–		
rs256241	A	0.1059	0.000163	Same	–	–		
rs2543593	C	0.0753	0.0006126	Same	–	–		
rs2537730	C	0.0954	0.0002322	Same	–	–		
rs2536929	A	0.0958	0.0001397	Same	–	–		
rs2532144	T	0.0917	2.97E-05	rs2532170	A		0.0812	0.0001016
rs2487030	C	0.0831	0.0009809	Same	–	–		
rs2449442	G	0.0949	0.0001377	Same	–	–		
rs2431626	C	0.0705	0.0009197	Same	–	–		
rs2427653	A	0.078	0.0006965	Same	–	–		
rs2415062	A	0.0734	0.0005245	Same	–	–		
rs239731	C	0.1077	0.0001126	Same	–	–		
rs2377868	T	0.0856	0.0008476	Same	–	–		
rs2372523	A	0.0794	0.0003789	Same	–	–		
rs2358891	G	0.102	1.46E-05	Same	–	–		
rs2356121	G	0.0695	0.0009046	Same	–	–		
rs233297	C	0.1466	0.000485	Same	–	–		
rs2332010	A	0.1222	0.0007228	Same	–	–		
rs2329198	A	0.0647	0.0009603	Same	–	–		
rs2323453	A	0.0681	0.000886	Same	–	–		
rs2312586	C	0.0865	0.0003701	Same	–	–		
rs2305826	T	0.0682	0.0007273	Same	–	–		
rs2305398	G	0.097	4.21E-06	Same	–	–		
rs2304921	C	0.1542	0.0003267	Same	–	–		
rs2301556	A	0.1205	0.0005997	Same	–	–		
rs2300255	G	0.1334	0.0008987	Same	–	–		
rs2293793	T	0.0731	0.0006585	Same	–	–		
rs2287933	C	0.1405	0.0001837	Same	–	–		
rs2285655	T	0.1572	0.0007498	Same	–	–		
rs2283229	A	0.1029	0.0003326	Same	–	–		
rs2278008	C	0.0807	0.0006333	Same	–	–		
rs2270307	G	0.0737	0.0008804	Same	–	–		
rs2269252	T	0.0919	0.0002533	Same	–	–		
rs2256154	C	0.0781	0.0001369	Same	–	–		
rs2256109	C	0.0689	0.0009157	Same	–	–		
rs2255648	G	0.0742	0.000235	Same	–	–		
rs2249965	A	0.1067	5.67E-07	Same	–	–		
rs2239650	A	0.1473	0.0004591	Same	–	–		
rs223484	A	0.0658	0.0009278	Same	–	–		
rs2204224	T	0.1721	3.58E-05	Same	–	–		
rs2204037	A	0.0686	0.0006245	Same	–	–		
rs2203298	G	0.1174	0.0008067	Same	–	–		
rs2191502	C	0.099	0.0009714	Same	–	–		
rs2179434	G	0.0766	0.0001084	Same	–	–		
rs2166451	G	0.0784	0.0002175	Same	–	–		
rs216495	G	0.0908	0.000135	Same	–	–		
rs2145587	A	0.1037	2.01E-05	Same	–	–		
rs2145274	A	0.1261	0.0005466	Same	–	–		
rs2129531	G	0.0802	0.0008973	Same	–	–		
rs2118254	C	0.0821	3.54E-05	Same	–	–		
rs2106261	T	0.2119	3.21E-16	Same	–	–		
rs2080859	C	0.1756	0.0002154	Same	–	–		
rs2074897	A	0.0761	0.000427	Same	–	–		
rs2070450	A	0.1534	0.0003574	Same	–	–		
rs2070394	A	0.0708	0.000759	Same	–	–		
rs2060915	C	0.0891	0.0001147	Same	–	–		
rs20583	T	0.0773	0.0001107	Same	–	–		
rs2049170	T	0.1249	0.000119	Same	–	–		
rs2040862	T	0.1403	3.23E-08	Same	–	–		
rs2038750	C	0.0743	0.0008719	Same	–	–		

rs2033570	C	0.0846	4.29E-05	Same	–	–		
rs2026943	A	0.0753	0.0005803	Same	–	–		
rs2012056	A	0.0845	0.0009872	Same	–	–		
rs2012	C	0.1066	5.90E-05	Same	–	–		
rs2011708	T	0.0705	0.0008875	Same	–	–		
rs1998713	C	0.0976	0.0009139	Same	–	–		
rs1979325	G	0.0861	9.54E-05	Same	–	–		
rs1956889	C	0.0856	0.0005242	Same	–	–		
rs1930006	A	0.0712	0.0006367	Same	–	–		
rs1927551	G	0.0968	0.0003716	Same	–	–		
rs1924755	T	0.1071	0.0006807	Same	–	–		
rs1912432	T	0.0755	0.0007791	Same	–	–		
rs186385	A	0.1344	0.0006239	Same	–	–		
rs1863244	C	0.0785	0.0001569	Same	–	–		
rs1858810	A	0.0963	1.75E-06	Same	–	–		
rs1845823	A	0.1637	0.0003139	Same	–	–		
rs1829794	G	0.076	0.0009071	Same	–	–		
rs1822010	T	0.1602	0.0004568	Same	–	–		
rs1814331	T	0.1463	1.75E-05	Same	–	–		
rs179141	G	0.0882	0.0007204	Same	–	–		
rs17825517	G	0.2147	7.15E-05	Same	–	–		
rs17782302	T	0.1042	0.0004657	Same	–	–		
rs17763750	T	0.1151	0.0003792	Same	–	–		
rs17714333	A	0.0689	0.0007347	Same	–	–		
rs17688347	C	0.0727	0.0004262	Same	–	–		
rs17656084	G	0.1936	0.0006964	Same	–	–		
rs17644458	G	0.0862	6.51E-05	Same	–	–		
rs17602834	C	0.0834	0.000105	Same	–	–		
rs17588172	T	0.0961	3.59E-06	Same	–	–		
rs17547641	A	0.0764	0.0009608	Same	–	–		
rs17513835	T	0.1722	0.0004954	Same	–	–		
rs17497040	T	0.1064	0.0003674	Same	–	–		
rs17488597	T	0.1584	0.0001377	Same	–	–		
rs17461036	T	0.1419	0.0006682	Same	–	–		
rs1742424	A	0.1399	0.0002221	Same	–	–		
rs17382780	T	0.1422	0.0008297	Same	–	–		
rs17375901	T	0.2051	7.65E-07	Same	–	–		
rs17367630	G	0.0771	0.0007701	Same	–	–		
rs17360555	C	0.1009	0.0007306	Same	–	–		
rs17353336	T	0.0685	0.0005781	Same	–	–		
rs17318925	T	0.089	0.000694	Same	–	–		
rs17314711	C	0.1674	0.000232	Same	–	–		
rs17312183	C	0.1257	0.0008118	Same	–	–		
rs17311216	C	0.1087	0.0009252	Same	–	–		
rs17272614	C	0.0868	0.0006487	Same	–	–		
rs17251567	C	0.0893	0.0005805	Same	–	–		
rs17231256	A	0.1094	0.0002389	Same	–	–		
rs17220640	C	0.1696	0.0004408	Same	–	–		
rs17175458	G	0.0974	8.22E-05	Same	–	–		
rs17153945	C	0.1328	0.0004457	Same	–	–		
rs17150049	A	0.0916	6.74E-05	Same	–	–		
rs1714520	C	0.0828	0.0006938	Same	–	–		
rs17144562	T	0.1165	0.0002255	Same	–	–		
rs17141635	A	0.1632	0.0009238	Same	–	–		
rs17131865	T	0.1403	0.0009596	Same	–	–		
rs17130025	A	0.1109	0.0004965	Same	–	–		
rs17126643	G	0.1671	0.0003271	Same	–	–		
rs17092243	C	0.087	0.0006306	Same	–	–		
rs17083278	C	0.0988	0.0004775	Same	–	–		
rs17077544	G	0.1475	6.80E-05	Same	–	–		
rs17076	G	0.0885	0.0004944	Same	–	–		
rs17073625	T	0.1234	0.0006776	Same	–	–		
rs17066602	A	0.0696	0.0004673	Same	–	–		
rs17066205	A	0.1317	0.0009994	Same	–	–		
rs17059827	G	0.1432	0.000871	Same	–	–		
rs17058126	C	0.189	0.0009206	Same	–	–		
rs17014446	T	0.1476	0.0003945	Same	–	–		
rs16994191	A	0.1268	0.0003505	Same	–	–		
rs16991711	A	0.1246	0.000802	Same	–	–		
rs16987853	C	0.1124	5.89E-05	rs11897611	T		0.1103	6.52E-05

rs16969763	A	0.2226	0.0005382	Same	–	–		
rs16935005	A	0.1589	3.71E-05	Same	–	–		
rs16931023	G	0.098	0.0001825	Same	–	–		
rs169260	C	0.1635	0.0003675	Same	–	–		
rs16890706	G	0.1106	0.0004265	Same	–	–		
rs16866575	G	0.1207	0.0007645	Same	–	–		
rs16839275	A	0.0705	0.000742	Same	–	–		
rs16829334	A	0.153	0.0001607	Same	–	–		
rs1649987	G	0.0923	0.0004631	Same	–	–		
rs1642294	C	0.0989	0.0003718	Same	–	–		
rs1628543	G	0.0742	0.0002296	Same	–	–		
rs1615708	T	0.1038	0.0005336	Same	–	–		
rs1609560	A	0.0887	0.0003465	Same	–	–		
rs1602932	A	0.087	0.0001905	Same	–	–		
rs1592418	G	0.0723	0.0006115	Same	–	–		
rs1575738	C	0.1636	0.0009177	Same	–	–		
rs1575017	A	0.1328	0.00083	Same	–	–		
rs1573379	A	0.073	0.000623	Same	–	–		
rs1567451	A	0.1044	0.0008447	Same	–	–		
rs1560002	C	0.0781	0.0008729	Same	–	–		
rs1547189	T	0.0928	0.0002198	Same	–	–		
rs1543511	T	0.0686	0.0009882	Same	–	–		
rs1539289	T	0.0672	0.0007177	Same	–	–		
rs153675	T	0.0966	0.0001437	Same	–	–		
rs1535507	T	0.0935	0.0009928	Same	–	–		
rs1509798	G	0.1015	0.0004494	Same	–	–		
rs1476221	A	0.1023	0.000242	Same	–	–		
rs1469968	C	0.1418	1.52E-06	rs751664	A		0.0705	0.0005874
rs1458041	A	0.0784	0.0007931	Same	–	–		
rs1454934	T	0.0954	0.000418	Same	–	–		
rs1421168	T	0.1592	0.0002344	Same	–	–		
rs1416731	G	0.0885	0.0001145	Same	–	–		
rs1396114	C	0.0897	0.0007521	Same	–	–		
rs1381453	T	0.086	0.0002942	Same	–	–		
rs1376803	T	0.0978	0.0002489	Same	–	–		
rs137576	T	0.2537	0.0004097	Same	–	–		
rs1375617	T	0.1387	0.0009448	Same	–	–		
rs1369890	T	0.0777	0.000253	Same	–	–		
rs136866	A	0.077	0.000605	Same	–	–		
rs1366798	T	0.0692	0.0005711	Same	–	–		
rs1366398	G	0.1169	0.000164	Same	–	–		
rs1355846	G	0.0741	0.0003103	Same	–	–		
rs1348388	T	0.0965	0.0007986	Same	–	–		
rs1347832	A	0.0723	0.000998	Same	–	–		
rs13439337	T	0.2294	3.34E-05	Same	–	–		
rs13424875	A	0.0851	0.0005089	Same	–	–		
rs134101	T	0.0853	0.000953	Same	–	–		
rs13379000	T	0.3715	0.0006509	Same	–	–		
rs13378344	C	0.0833	0.0007269	Same	–	–		
rs13313289	C	0.1514	0.0009002	Same	–	–		
rs13287050	T	0.0845	0.0003014	Same	–	–		
rs13259395	G	0.207	3.53E-05	Same	–	–		
rs13259235	C	0.0849	0.0007139	Same	–	–		
rs13257090	C	0.0764	0.0001481	Same	–	–		
rs13247344	A	0.0718	0.0009817	Same	–	–		
rs13244286	A	0.173	0.000181	Same	–	–		
rs13216675	T	0.0929	4.99E-05	Same	–	–		
rs13213991	T	0.1305	0.0002955	Same	–	–		
rs1320362	T	0.0754	0.0001197	Same	–	–		
rs13173061	A	0.0684	0.0006922	Same	–	–		
rs13169864	G	0.1183	4.49E-05	Same	–	–		
rs13144278	G	0.1252	0.0003107	Same	–	–		
rs13133886	A	0.0874	0.0004338	Same	–	–		
rs13129710	C	0.079	0.0004948	Same	–	–		
rs13128039	G	0.0763	0.0003942	Same	–	–		
rs13121382	G	0.1948	2.56E-06	Same	–	–		
rs13119825	A	0.1497	0.0001882	Same	–	–		
rs13117963	G	0.0913	0.0003584	Same	–	–		
rs13116667	A	0.1177	0.000933	Same	–	–		
rs13114658	G	0.0707	0.0006705	Same	–	–		

rs13107566	A	0.0771	0.0002135	Same	–	–		
rs13019524	T	0.0823	0.0003081	Same	–	–		
rs13008704	C	0.0744	0.0003145	Same	–	–		
rs12993399	G	0.0773	0.0008498	Same	–	–		
rs12991989	C	0.098	1.49E-06	Same	–	–		
rs12970058	C	0.0782	0.0004819	Same	–	–		
rs12966713	C	0.0789	0.0005937	Same	–	–		
rs12936839	G	0.0681	0.0007991	Same	–	–		
rs12933988	G	0.1477	0.0002238	Same	–	–		
rs12917875	T	0.0714	0.0004632	Same	–	–		
rs12900128	C	0.0763	0.0004364	Same	–	–		
rs12805818	G	0.1956	0.0008002	Same	–	–		
rs12803794	G	0.1618	0.0004517	Same	–	–		
rs12760630	A	0.1304	8.87E-11	Same	–	–		
rs12739480	G	0.1016	0.0008327	Same	–	–		
rs12733930	C	0.1019	3.18E-05	Same	–	–		
rs12699203	G	0.0817	0.0005795	Same	–	–		
rs12699137	A	0.1266	0.0002113	Same	–	–		
rs12692738	C	0.0809	0.0006643	Same	–	–		
rs12680985	C	0.0817	0.0002605	Same	–	–		
rs12675482	C	0.0688	0.0008246	Same	–	–		
rs12651348	G	0.1619	0.0004729	Same	–	–		
rs12648289	A	0.1027	3.40E-05	Same	–	–		
rs12634159	A	0.1833	0.0004992	Same	–	–		
rs12621260	T	0.0993	0.0002596	Same	–	–		
rs12610400	T	0.0796	0.00028	Same	–	–		
rs12610304	C	0.0764	0.0003714	Same	–	–		
rs12579648	G	0.1095	0.0003799	Same	–	–		
rs12569209	A	0.0654	0.000878	Same	–	–		
rs12550637	A	0.1322	0.0007816	Same	–	–		
rs12549065	C	0.0784	0.0005413	Same	–	–		
rs12533255	T	0.0872	0.0008112	Same	–	–		
rs12526522	C	0.1809	0.0009076	Same	–	–		
rs12517640	G	0.0835	0.0007697	Same	–	–		
rs12500546	A	0.0698	0.000777	Same	–	–		
rs12496661	G	0.0762	0.0006425	Same	–	–		
rs12458508	C	0.0739	0.0005776	Same	–	–		
rs12452256	C	0.0951	0.0005434	Same	–	–		
rs12422762	C	0.122	0.0002054	Same	–	–		
rs12415501	T	0.1441	9.04E-08	rs12253987	A		0.132	1.70E-07
rs12406668	T	0.1442	4.92E-05	Same	–	–		
rs12373097	T	0.1356	4.56E-06	Same	–	–		
rs12370365	G	0.0967	4.35E-05	Same	–	–		
rs12353280	T	0.1002	0.000237	Same	–	–		
rs12325019	C	0.1572	0.0004565	Same	–	–		
rs12284979	A	0.0989	0.0008668	Same	–	–		
rs12282538	T	0.2263	6.29E-05	Same	–	–		
rs12277614	A	0.1276	0.0009173	Same	–	–		
rs12273915	T	0.1106	0.0001782	Same	–	–		
rs1218582	A	0.1212	6.85E-09	Same	–	–		
rs12160956	G	0.0697	0.0007948	Same	–	–		
rs12149832	A	0.0698	0.0006778	Same	–	–		
rs12135308	T	0.1139	0.0003854	Same	–	–		
rs12129729	C	0.0737	0.0006107	Same	–	–		
rs12122623	C	0.1674	0.0001725	Same	–	–		
rs1205023	C	0.0826	0.0008063	Same	–	–		
rs12047527	T	0.0735	0.0008813	Same	–	–		
rs1203678	G	0.0715	0.0006396	Same	–	–		
rs12031401	A	0.1031	0.0008578	Same	–	–		
rs11977362	G	0.0743	0.0002148	Same	–	–		
rs11959439	G	0.1055	0.0006381	Same	–	–		
rs11957853	G	0.0735	0.0006144	Same	–	–		
rs11897732	G	0.0713	0.0004167	Same	–	–		
rs11869535	G	0.1686	0.0006289	Same	–	–		
rs11857308	T	0.164	0.0002207	Same	–	–		
rs11851570	T	0.0881	0.0006583	Same	–	–		
rs11851174	T	0.1116	0.0001181	Same	–	–		
rs11845845	A	0.1322	0.0005709	Same	–	–		
rs11842292	T	0.0805	0.0001725	Same	–	–		
rs11780023	T	0.0805	0.0001307	Same	–	–		

rs11764828	A	0.1149	0.0007117	Same	–	–		
rs11750489	G	0.0938	0.0008977	Same	–	–		
rs11742784	A	0.1536	0.0005564	Same	–	–		
rs11737595	C	0.1488	0.0008658	Same	–	–		
rs11737346	C	0.1091	0.0004448	Same	–	–		
rs11714471	G	0.0857	7.90E-05	Same	–	–		
rs11697158	G	0.0743	0.0002943	Same	–	–		
rs11690108	A	0.1881	0.0009061	Same	–	–		
rs11687201	T	0.0859	0.0004058	Same	–	–		
rs11652243	C	0.1479	0.0005433	Same	–	–		
rs11627864	A	0.0863	7.86E-05	Same	–	–		
rs11613339	A	0.0931	0.0003997	Same	–	–		
rs11598558	G	0.122	0.000847	Same	–	–		
rs1152591	A	0.1265	6.21E-10	Same	–	–		
rs1150975	A	0.0768	0.0002637	Same	–	–		
rs11265957	T	0.105	0.0008724	Same	–	–		
rs11257794	G	0.1069	0.0003809	Same	–	–		
rs11256613	G	0.0957	0.0002686	Same	–	–		
rs1125322	G	0.1136	0.0001704	Same	–	–		
rs11249478	T	0.1193	0.000564	Same	–	–		
rs1122157	T	0.0871	8.51E-05	Same	–	–		
rs11215000	T	0.0766	0.0008479	Same	–	–		
rs11203855	G	0.1269	6.21E-05	Same	–	–		
rs11200014	G	0.072	0.0007214	Same	–	–		
rs11197047	T	0.0784	0.000929	Same	–	–		
rs11131367	C	0.0681	0.0008139	Same	–	–		
rs11103439	A	0.1365	0.0005334	Same	–	–		
rs1109241	A	0.1638	0.0002143	Same	–	–		
rs11085953	A	0.1197	0.0001203	Same	–	–		
rs1108182	A	0.1202	0.0007987	Same	–	–		
rs11081680	A	0.1278	0.0004198	Same	–	–		
rs11067489	C	0.0839	6.36E-05	Same	–	–		
rs11067228	G	0.0704	0.0004696	Same	–	–		
rs11044373	T	0.0825	0.000666	Same	–	–		
rs11043723	C	0.0809	0.000287	Same	–	–		
rs11038581	T	0.1351	0.0007064	Same	–	–		
rs11003402	G	0.0975	0.000991	rs4268426	T		0.1028	0.001925
rs11002740	C	0.2983	0.000192	Same	–	–		
rs10987905	C	0.0764	0.0005911	Same	–	–		
rs10986333	T	0.0965	2.17E-06	Same	–	–		
rs10947261	G	0.1627	2.68E-05	Same	–	–		
rs10947260	T	0.1631	2.87E-05	Same	–	–		
rs10927872	C	0.0675	0.0007785	Same	–	–		
rs10919369	T	0.1136	2.55E-06	Same	–	–		
rs10893224	G	0.1219	9.56E-05	Same	–	–		
rs10876041	C	0.0723	0.0004396	Same	–	–		
rs10873891	C	0.0863	0.0001626	Same	–	–		
rs10863942	C	0.0756	0.0007836	Same	–	–		
rs10860423	C	0.0755	0.0005078	Same	–	–		
rs10853869	A	0.0821	0.0004268	Same	–	–		
rs10849152	T	0.0837	4.92E-05	Same	–	–		
rs10845399	G	0.0711	0.0007615	Same	–	–		
rs10839849	A	0.1703	0.0002095	Same	–	–		
rs10838436	T	0.0761	0.0001474	Same	–	–		
rs10824026	A	0.1593	1.74E-08	Same	–	–		
rs10821415	A	0.1235	7.88E-09	Same	–	–		
rs10820859	A	0.1544	0.0004841	Same	–	–		
rs10811889	T	0.1355	0.0002793	Same	–	–		
rs10802521	G	0.089	0.0003087	Same	–	–		
rs10800507	C	0.1024	8.76E-07	Same	–	–		
rs10790497	A	0.0773	0.0004651	Same	–	–		
rs10777685	G	0.0787	0.0004016	Same	–	–		
rs10762941	A	0.0835	3.91E-05	Same	–	–		
rs10739630	T	0.124	0.000414	Same	–	–		
rs10519099	C	0.0802	0.0003183	Same	–	–		
rs10518972	T	0.1102	0.0002787	Same	–	–		
rs10515496	C	0.119	1.41E-06	Same	–	–		
rs10514479	A	0.1527	0.0004469	Same	–	–		
rs10513893	T	0.1335	0.0008148	Same	–	–		
rs10507248	T	0.122	8.53E-08	Same	–	–		

rs10506937	G	0.0682	0.000747	Same	–	–
rs10506569	C	0.0773	0.0001017	Same	–	–
rs10493679	A	0.2307	8.18E-05	Same	–	–
rs10483245	T	0.1304	0.0004691	Same	–	–
rs10466111	T	0.0989	0.0008499	Same	–	–
rs10465833	C	0.09	0.0007858	Same	–	–
rs10410258	T	0.0727	0.0009221	Same	–	–
rs10267684	T	0.097	4.12E-06	Same	–	–
rs10242171	G	0.1036	0.0004904	Same	–	–
rs10215877	T	0.0816	0.0009548	Same	–	–
rs10212121	A	0.0924	1.79E-05	Same	–	–
rs10189500	C	0.0693	0.0007051	Same	–	–
rs10187054	T	0.1138	0.0008774	Same	–	–
rs10178963	C	0.0706	0.0005022	Same	–	–
rs10177711	T	0.0723	0.0003784	Same	–	–
rs10171651	A	0.1118	0.0006836	Same	–	–
rs10137710	T	0.126	1.79E-06	Same	–	–
rs10136508	G	0.0778	0.0001522	Same	–	–
rs10095754	G	0.0802	0.0004232	Same	–	–
rs10081671	C	0.0786	0.0006838	Same	–	–
rs10067153	C	0.1031	0.0008213	Same	–	–
rs10063810	A	0.074	0.0002635	Same	–	–
rs10028494	A	0.1186	0.0003522	Same	–	–
rs10017096	A	0.0871	6.52E-05	Same	–	–
rs10011149	C	0.1206	0.0002152	Same	–	–

Supplemental Table 2. Distribution of atrial fibrillation genetic risk scores in a referent sample of 12,801 individuals from the Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, and Framingham Heart Study**.**

Genetic risk score	P_{AFGen} threshold	Mean ± standard deviation
11 SNPs	$<10^{-8}$	1.43 ± 0.40
16 SNPs	$<5x10^{-8}$	1.95 ± 0.44
18 SNPs	$<10^{-7}$	2.18 ± 0.45
25 SNPs	$<10^{-6}$	3.29 ± 0.49
45 SNPs	$<10^{-5}$	5.18 ± 0.62
129 SNPs	$<10^{-4}$	14.19 ± 0.84
719 SNPs	$<10^{-3}$	65.84 ± 1.67

SNP=single nucleotide polymorphism

Supplemental Table 3. Model fit and discrimination with or without atrial fibrillation genetic risk in relation to incident atrial fibrillation.

Model / No. SNPs in GRS	P_{AFGen} threshold	AIC	*C* *(95% CI)*	HL *P-value*
		MDCS		
CHARGE-AF score	–	3223.1	0.753 (0.720-0.786)	0.99
+ GRS (11 SNPs)	$<10^{-8}$	3216.8	0.760 (0.727-0.793)	0.93
+ GRS (16 SNPs)	$<5x10^{-8}$	3212.8	0.763 (0.730-0.796)	0.98
+ GRS (18 SNPs)	$<10^{-7}$	3212.6	0.764 (0.731-0.796)	0.87
+ GRS (25 SNPs)	$<10^{-6}$	3208.3	0.767 (0.734-0.799)	0.87
+ GRS (45 SNPs)	$<10^{-5}$	3207.5	0.768 (0.735-0.801)	0.96
+ GRS (129 SNPs)	$<10^{-4}$	3204.7	0.770 (0.738-0.802)	0.62
+ GRS (719 SNPs)	$<10^{-3}$	3218.9	0.758 (0.725-0.792)	0.56
		MESA		
Model / No. SNPs in GRS	P_{AFGen} **threshold**	**AIC**	***C*** ***(95% CI)***	**HL** ***P-value***
CHARGE-AF score	–	1859.3	0.802 (0.755-0.850)	0.97
+ GRS (11 SNPs)	$<10^{-8}$	1855.3	0.806 (0.758-0.853)	0.99
+ GRS (16 SNPs)	$<5x10^{-8}$	1848.3	0.809 (0.762-0.857)	0.97
+ GRS (18 SNPs)	$<10^{-7}$	1846.9	0.809 (0.761-0.856)	0.97
+ GRS (25 SNPs)	$<10^{-6}$	1845.0	0.808 (0.761-0.855)	0.93
+ GRS (45 SNPs)	$<10^{-5}$	1848.0	0.810 (0.762-0.857)	0.99
+ GRS (129 SNPs)	$<10^{-4}$	1849.2	0.811 (0.764-0.858)	0.98
+ GRS (719 SNPs)	$<10^{-3}$	1857.2	0.804 (0.756-0.852)	0.73
		PREVEND		

Model / No. SNPs in GRS	P_{AFGen} threshold	AIC	*C* *(95% CI)*	HL *P-value*
CHARGE-AF score	–	485.2	0.756 (0.657-0.854)	0.43
+ GRS (11 SNPs)	$<10^{-8}$	470.1	0.804 (0.711-0.898)	0.88
+ GRS (16 SNPs)	$<5x10^{-8}$	467.0	0.818 (0.732-0.904)	0.24
+ GRS (18 SNPs)	$<10^{-7}$	466.8	0.817 (0.728-0.907)	0.25
+ GRS (25 SNPs)	$<10^{-6}$	460.9	0.820 (0.739-0.900)	0.50
+ GRS (45 SNPs)	$<10^{-5}$	456.6	0.821 (0.737-0.905)	0.14
+ GRS (129 SNPs)	$<10^{-4}$	469.2	0.790 (0.708-0.872)	0.12
+ GRS (719 SNPs)	$<10^{-3}$	474.7	0.795 (0.715-0.875)	0.83

PROSPER

Model / No. SNPs in GRS	P_{AFGen} threshold	AIC	*C* *(95% CI)*	HL *P-value*
CHARGE-AF score	–	8267.7	0.615 (0.590-0.640)	$<1.0x10^{-4}$
+ GRS (11 SNPs)	$<10^{-8}$	8260.9	0.621 (0.596-0.645)	$<1.0x10^{-4}$
+ GRS (16 SNPs)	$<5x10^{-8}$	8253.7	0.624 (0.600-0.649)	$<1.0x10^{-4}$
+ GRS (18 SNPs)	$<10^{-7}$	8251	0.625 (0.601-0.650)	$<1.0x10^{-4}$
+ GRS (25 SNPs)	$<10^{-6}$	8248.3	0.628 (0.603-0.653)	$<1.0x10^{-4}$
+ GRS (45 SNPs)	$<10^{-5}$	8246.9	0.629 (0.604-0.654)	$<1.0x10^{-4}$
+ GRS (129 SNPs)	$<10^{-4}$	8246.3	0.629 (0.604-0.654)	$<1.0x10^{-4}$
+ GRS (719 SNPs)	$<10^{-3}$	8255.5	0.627 (0.602-0.651)	$<1.0x10^{-4}$

BioVU

Model / No. SNPs in GRS	P_{AFGen} threshold	AIC	*C* *(95% CI)*	HL *P-value*
CHARGE-AF score	–	3207.0	0.671	0.73

			(0.637-0.704)	
+ GRS (11 SNPs)	$<10^{-8}$	3197.9	0.684 (0.652-0.716)	0.70
+ GRS (16 SNPs)	$<5x10^{-8}$	3196.5	0.684 (0.653-0.716)	0.70
+ GRS (18 SNPs)	$<10^{-7}$	3196.6	0.684 (0.653-0.716)	0.72
+ GRS (25 SNPs)	$<10^{-6}$	3196.1	0.685 (0.653,0.717)	0.43
+ GRS (45 SNPs)	$<10^{-5}$	3200.7	0.681 (0.649-0.714)	0.71
+ GRS (129 SNPs)	$<10^{-4}$	3205.7	0.674 (0.641-0.707)	0.63
+ GRS (719 SNPs)	$<10^{-3}$	3206.1	0.674 (0.641-0.707)	0.37

All scores with SNPs are adjusted for the CHARGE-AF clinical score.[22-25]
SNP=single nucleotide polymorphism; GRS=genetic risk score; AIC = Akaike's Information Criterion; HL = Hosmer-Lemeshow

Supplemental Table 4. Association of atrial fibrillation genetic risk with atrial fibrillation, ischemic stroke, and cardioembolic stroke in MGH-GASROS.

		Atrial fibrillation		All ischemic stroke		Cardioembolic stroke	
	No. cases	87		509		202	
	No. controls	3,450		3,028		3,028	
No. SNPs in GRS (P_{AFGen} threshold*)	**Mean ± SD of GRS**	**OR (95% CI) per 1-unit change in GRS**	***P***	**OR (95% CI) per 1-unit change in GRS**	***P***	**OR (95% CI) per 1-unit change in GRS**	***P***
11 ($<10^{-8}$)	1.35±0.42	1.81 (1.02-3.23)	0.04	1.46 (1.06-2.02)	0.02	1.35 (0.86-2.13)	0.19
16 ($<5\times10^{-8}$)	1.87±0.45	1.54 (0.90-2.64)	0.12	1.35 (1.00-1.82)	0.05	1.31 (0.86-2.00)	0.20
18 ($<10^{-7}$)	2.04±0.46	1.62 (0.96-2.74)	0.07	1.36 (1.01-1.83)	0.04	1.37 (0.90-2.07)	0.14
25 ($<10^{-6}$)	3.05±0.50	1.71 (1.06-2.77)	0.03	1.31 (1.00-1.72)	0.05	1.41 (0.97-2.06)	0.08
45 ($<10^{-5}$)	4.74±0.62	1.66 (1.13-2.44)	9.4×10^{-3}	1.30 (1.05-1.62)	0.02	1.43 (1.06-1.93)	0.19
127 ($<10^{-4}$)	11.63±0.82	**1.75 (1.29-2.37)**	**3.1×10^{-4}**	1.34 (1.14-1.58)	4.9×10^{-4}	1.45 (1.16-1.83)	1.4×10^{-3}
701 ($<10^{-3}$)	54.74±1.59	1.24 (1.05-1.47)	0.01	**1.24 (1.13-1.36)**	**5.4×10^{-6}**	**1.31 (1.15-1.50)**	**3.7×10^{-5}**

All models adjusted for age, sex, principal components of ancestry, and genotyping platform. For each analysis, the GRS with the smallest *P* value is bolded.
*Refers to the *P*-value for association between each SNP included in the genetic risk score and atrial fibrillation in an independent genome-wide association study of atrial fibrillation.[26] SNP totals may not equal those used in the incident atrial fibrillation analysis since some SNPs were unavailable, in which case proxies were used when available (Supplemental Table 1).
GRS=genetic risk score, SNP=single nucleotide polymorphism, HR=hazard ratio, CI=confidence interval.

Supplemental Table 5. Association of atrial fibrillation genetic risk with ischemic stroke and cardioembolic stroke in MGH-GASROS in subjects without known AF.

		All ischemic stroke		Cardioembolic stroke	
	No. cases	422		132	
	No. controls	3,028		3,028	
No. SNPs in GRS (P_{AFGen} threshold†)	**Mean ± SD of GRS**	**OR (95% CI) per 1-unit change in GRS**	***P***	**OR (95% CI) per 1-unit change in GRS**	***P***
11 ($<10^{-8}$)	1.34±0.41	1.48 (1.07-2.05)	0.02	1.32 (0.82-2.14)	0.25
16 ($<5\times10^{-8}$)	1.86±0.45	1.36 (1.01-1.84)	0.05	1.31 (0.84-2.05)	0.23
18 ($<10^{-7}$)	2.04±0.45	1.36 (1.01-1.84)	0.04	1.35 (0.87-2.10)	0.19
25 ($<10^{-6}$)	3.05±0.49	1.30 (0.99-1.71)	0.06	1.40 (0.94-2.09)	0.10
45 ($<10^{-5}$)	4.73±0.62	1.28 (1.03-1.59)	0.03	1.41 (1.03-1.93)	0.04
127 ($<10^{-4}$)	11.61±0.81	1.30 (1.10-1.53)	2.4×10^{-3}	1.37 (1.07-1.75)	0.01
701 ($<10^{-3}$)	54.68±1.55	**1.22 (1.11-1.34)**	**3.10×10^{-5}**	**1.27 (1.11-1.46)**	**7.2×10^{-4}**

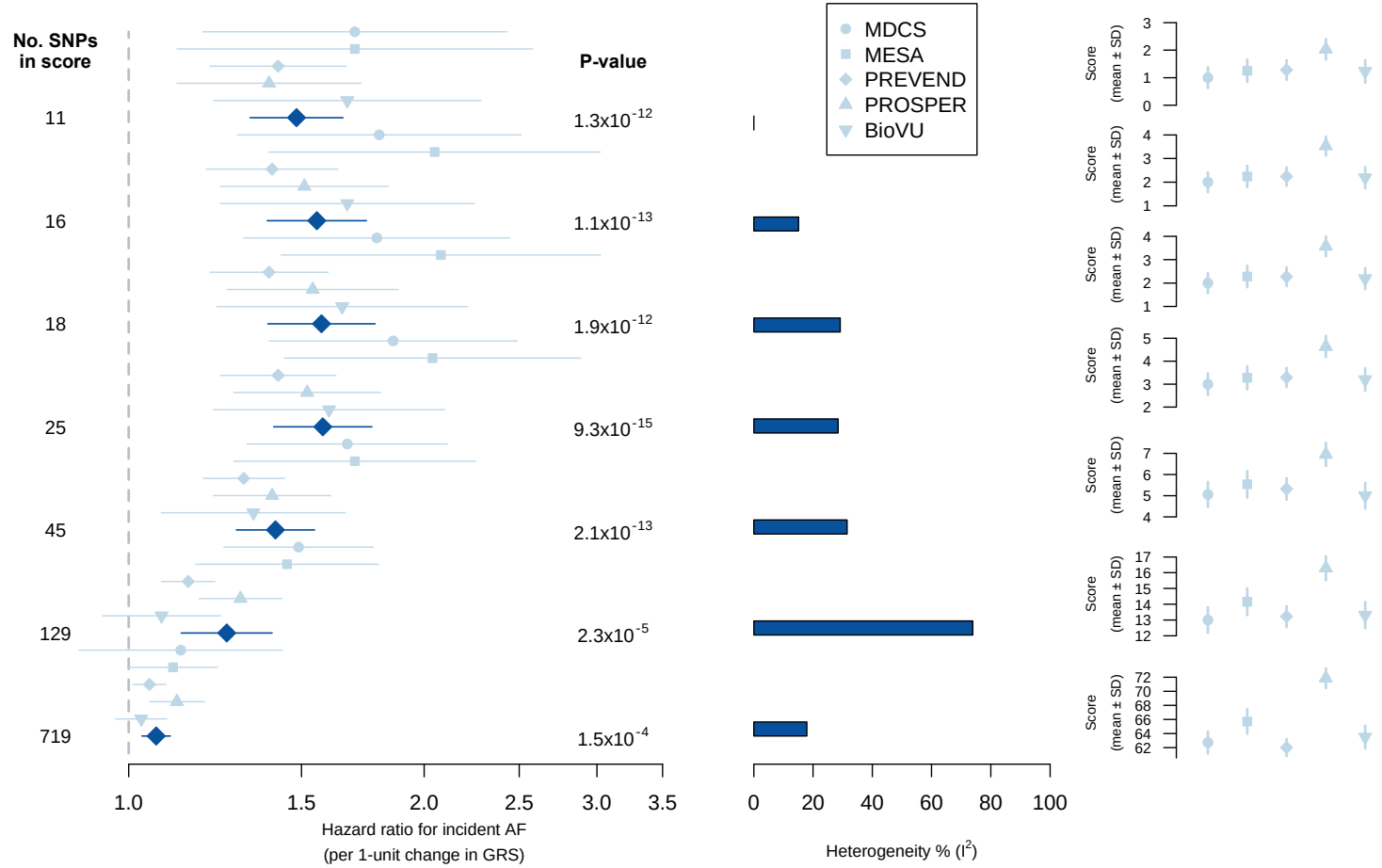
All models adjusted for age, sex, principal components of ancestry, and genotyping platform. For each analysis, the GRS with the smallest *P* value is bolded.

*Refers to the *P*-value for association between each SNP included in the genetic risk score and atrial fibrillation in an independent genome-wide association study of atrial fibrillation.[26] SNP totals may not equal those used in the incident atrial fibrillation analysis since some SNPs were unavailable, in which case proxies were used when available (Supplemental Table 1).

GRS=genetic risk score, SNP=single nucleotide polymorphism, HR=hazard ratio, CI=confidence interval.

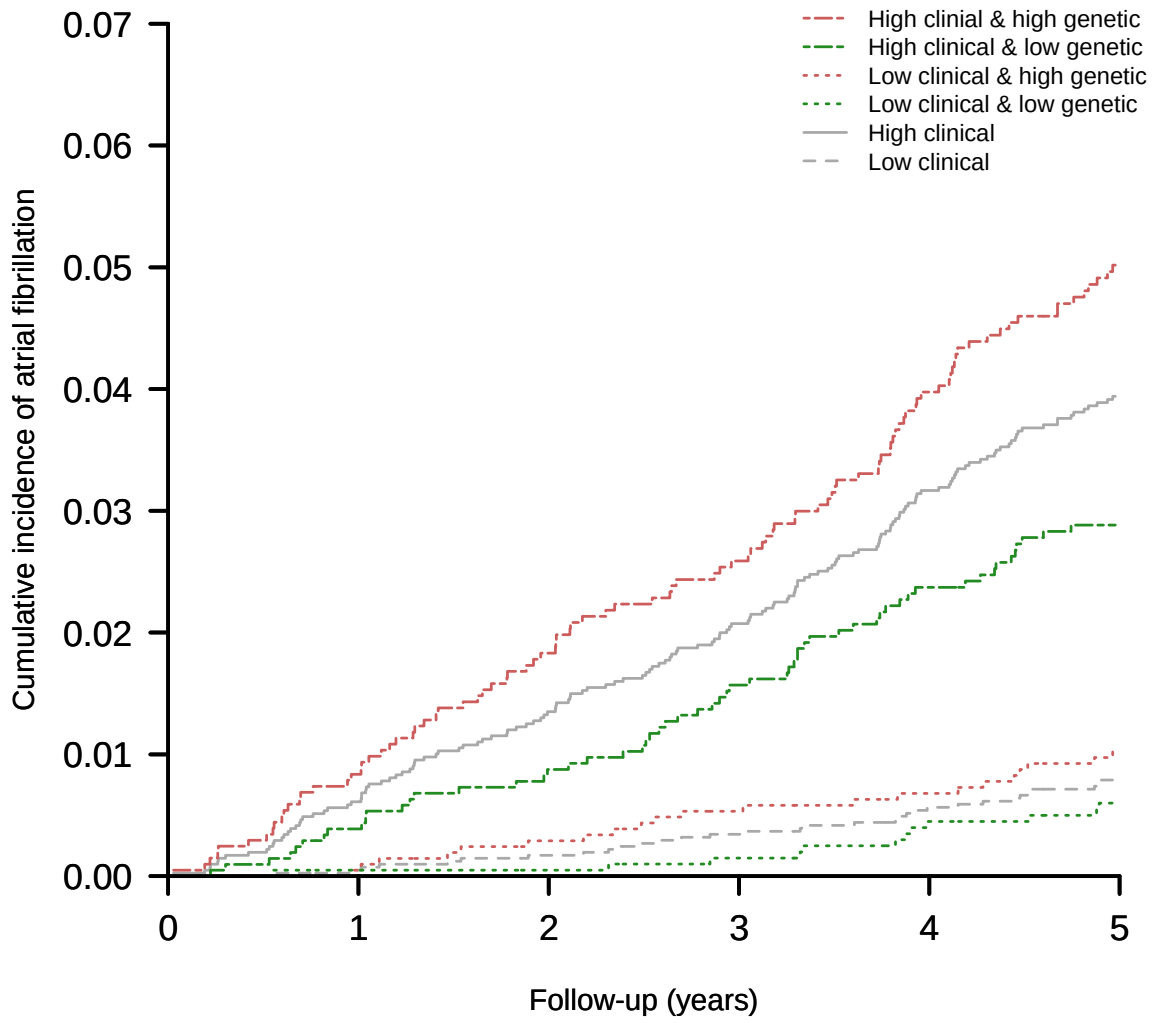
Supplemental Figure 1. Associations between atrial fibrillation genetic risk and incident atrial fibrillation in five prospective studies including 18,919 individuals.

SNPs included in scores were derived using different thresholds of association between each SNP and atrial fibrillation in an earlier, independent study[26] (11 SNPs [$P<1x10^{-8}$], 16 SNPs [$P<5x10^{-8}$], 16 SNPs [$P<1x10^{-7}$], 18 SNPs [$P<1x10^{-6}$], 25 SNPs [$P<1x10^{-5}$], 45 SNPs [$P<1x10^{-4}$], 129 SNPs [$P<1x10^{-3}$], and 719 SNPs [$P<1x10^{-3}$]. Hazard ratios with 95% confidence intervals are displayed. All scores are adjusted for age, height, weight, systolic and diastolic blood pressure, history of smoking, antihypertensive medication use, diabetes status, heart failure status, myocardial infarction status, and electrocardiographic left ventricular hypertrophy and PR interval as noted in the text. SD=standard deviation; SNP=single nucleotide polymorphism.



Supplemental Figure 2. Five-year cumulative incidence of atrial fibrillation according to clinical and genetic risk in MDCS.

The five-year cumulative incidence of atrial fibrillation was plotted using the Kaplan-Meier method based on dichotomized clinical risk in blue. The incremental contribution to atrial fibrillation risk estimation of dichotomized genetic risk beyond clinical risk is overlaid on the plot in red. Risk scores were calculated for each patient as described in the manuscript and were dichotomized at the median value.



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