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Roselli, C.; Chaffin, M.D.; Weng, L.C.; Aeschbacher, S.; Ahlberg, G.; Albert, C.M.; ... ; Ellinor, P.T.

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Multi-Ethnic Genome-wide Association Study for Atrial Fibrillation

A full list of authors and affiliations appears at the end of the article.

These authors contributed equally to this work.

Abstract

Atrial fibrillation (AF) affects over 33 million individuals worldwide¹ and has a complex heritability.² We conducted the largest meta-analysis of genome-wide association studies for AF to

Corresponding author: Patrick T. Ellinor, MD, PhD, Program in Medical and Population Genetics, The Broad Institute of MIT and Harvard Cardiovascular Research Center, Massachusetts General Hospital; Cambridge, MA 02142, T: 617-724-8729, ellinor@mgh.harvard.edu.

Author contributions

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Competing financial interests

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date, consisting of over half a million individuals including 65,446 with AF. In total, we identified 97 loci significantly associated with AF including 67 of which were novel in a combined-ancestry analysis, and 3 in a European specific analysis. We sought to identify AF-associated genes at the GWAS loci by performing RNA-sequencing and expression quantitative trait loci (eQTL) analyses in 101 left atrial samples, the most relevant tissue for AF. We also performed transcriptome-wide analyses that identified 57 AF-associated genes, 42 of which overlap with GWAS loci. The identified loci implicate genes enriched within cardiac developmental, electrophysiological, contractile and structural pathways. These results extend our understanding of the biological pathways underlying AF and may facilitate the development of therapeutics for AF.

Atrial fibrillation (AF) is the most common heart rhythm disorder, and is a leading cause of heart failure and stroke.³ Prior genome-wide association studies (GWAS) have identified at least 30 loci associated with AF.⁴⁻⁹ We conducted a large-scale analysis with over half a million participants, including 65,446 with AF, from more than 50 studies. Our AF sample was composed of 84.2% European, 12.5% Japanese, 2% African American, and 1.3% Brazilian and Hispanic populations (**Supplementary Table 1**). We used the Haplotype Reference Consortium (HRC) reference panel to impute variants from SNP array data for 75% of the samples (**Figure 1**). In the remainder, we included HRC overlapping variants from 1000 Genomes imputed data, or from a combined reference panel. We analyzed 8,328,530 common variants (minor allele frequency (MAF) >5%), 2,884,670 low frequency variants (1% > MAF < 5%), and 936,779 rare variants (MAF < 1%).

The combined-ancestry meta-analysis revealed 94 AF-associated loci, 67 of which were novel at genome-wide significance (P -value (P) < 1×10^{-8}). This conservative threshold accounts for testing independent variants with MAF < 0.1% using a Bonferroni correction, while use of a more commonly utilized threshold of 5×10^{-8} resulted in the identification of an additional 10 loci (**Supplementary Table 2**). The majority of sentinel variants ($n=92$) were common (MAF >5%), with relative risks ranging from 1.04 to 1.55. Two low frequency sentinel variants were identified within the genes *C1orf185* and *UBE4B* (**Figure 2, Table 1, Supplementary Table 3, Supplementary Figure 1**).

We then conducted a gene set enrichment analysis with the results from the combined-ancestry meta-analysis using MAGENTA. We identified 55 enriched gene sets or pathways that largely fall into cardiac developmental, electrophysiological, and cardiomyocyte contractile or structural functional groups (**Supplementary Table 4**). In total, 48 of the 67 novel loci contain one or more genes within 500kb of the sentinel variant that were part of an enriched gene set or pathway (**Supplementary Figure 2**).

Next, we performed ancestry-specific meta-analyses. Among individuals of European ancestry, we identified 3 additional loci associated with AF, each of which had a sub-threshold association ($P < 1 \times 10^{-6}$) in the combined-ancestry meta-analysis. These loci were located close to or within the genes *CDK6*, *EPHA3*, and *GOSR2* (**Supplementary Table 5, Supplementary Figure 3-4**). The region most significantly associated with AF in Europeans, Japanese, and African Americans (**Supplementary Figure 5-6**) was on chromosome 4q25, upstream of the gene *PITX2* (**Supplementary Figure 7**). We did not

observe significant heterogeneity of effect estimates across ancestries for most associations, suggesting that top genetic susceptibility signals for AF have a relatively constant effect across ancestries (**Table 1, Supplementary Table 3, Supplementary Figure 8**). The proportion of heritability explained by the loci from the European ancestry analysis was 42%, compared to previously reported 25%¹⁰ (**Supplementary Table 6**).

In conditional and joint analyses of the European ancestry results, we found 11 loci with multiple, independent AF-associated signals. At a locus centered on a cluster of sodium channel genes, we identified 3 regions that independently associate with AF within *SCN10A*, *SCN5A* and a third signal between both genes. At the previously described *TBX5* locus,⁸ we detected a novel independent signal close to *TBX3*. Pairwise linkage disequilibrium (LD) estimates between the independent variants at both loci were extremely low ($r^2 < 0.03$; **Supplementary Table 7**).

For 13 AF loci, the sentinel variant or a proxy ($r^2 > 0.6$) was a missense variant. A missense variant (rs11057401) in *CCDC92* was predicted to be damaging by 4 of 5 *in silico* prediction algorithms (**Supplementary Table 8**); and was previously associated with coronary artery disease.¹¹ Since most AF-associated variants reside in non-coding regions we sought to determine if the sentinel variants or their proxies ($r^2 > 0.6$) fell within regulatory regions in heart tissues based on chromatin states from the Roadmap Epigenomics Consortium. At 64 out of 67 novel loci, variants were located within regulatory elements (**Supplementary Table 9**); AF-associated loci were also significantly enriched within regulatory elements (**Supplementary Figure 9**).

We then sought to link risk variants to candidate genes by assessing their effect on gene expression levels. First, since AF often arises from the pulmonary veins and left atrium (LA), we performed RNA sequencing, genotyping, and eQTL analyses in 101 human left atrial samples without structural heart disease from the Myocardial Applied Genomics Network repository. Second, we identified eQTLs from right atrial (RA) and left ventricular (LV) cardiac tissue from the Genotype Tissue Expression (GTEx) project. Finally, we performed a transcriptome-wide analysis using the MetaXcan¹² method, which infers the association between genetically predicted gene expression and disease risk.

We observed eQTLs to one or more genes at 17 novel loci. Of the 10 eQTLs detected in LA tissue 8 were also detected in RA or LV, with consistent directionality. For example, we observed that rs4484922 was an eQTL for *CASQ2* in LA tissue only. Although we detected more AF loci with eQTLs in the RA or LV data, for many of these (n=8) the results pointed to multiple genes per locus (**Supplementary Table 10–12**). LA eQTL studies may facilitate the prioritization of candidate genes, but are currently limited by sample size.

For the transcriptome-wide analyses we used GTEx human atrial and ventricular expression data as a reference. We identified 57 genes significantly associated with AF. Of these, 42 genes were located at AF loci, whereas the remaining 15 were >500kb from an AF sentinel variant (**Supplementary Table 13, Figure 3**). The probable candidate genes at each locus are summarized in **Supplementary Table 12**. For example, at the locus with lead variant rs4484922 we observed results from all downstream analyses pointing towards the nearest

gene *CASQ2*, at rs12908437 towards the gene *IGFRI*, and at rs113819537 towards the gene *SSPN*. However, for many loci the evaluation of candidate genes remains challenging.

We then sought to assess the pleiotropic effects of the identified AF risk variants. First, we queried the NHGRI-EBI GWAS Catalog to detect associations to other phenotypes (**Supplementary Table 14**). Second, using the UK Biobank,¹³ we performed a phenome-wide association study (pheWAS) for 12 AF risk factors (**Supplementary Table 15**). As illustrated in **Figure 4**, distinct clusters of variants were associated with AF as well as height, BMI, and hypertension. For example, we observed a pleiotropic effect at rs880315 (*CASZI*) for blood pressure¹⁴ and hypertension¹⁴, that was also observed in the UK Biobank (association with hypertension, $P = 2.56 \times 10^{-34}$).

In sum, we identified a total of 97 distinct AF loci from 65,446 AF cases and more than 522,000 referents. In recent pre-publication results, Nielsen et al., reported 111 loci from 60,620 AF cases and more than 970,000 referents,¹⁵ including more than 18,000 AF cases from our prior report.⁸ We therefore performed a preliminary meta-analysis for the top loci in nonoverlapping participants from these two large efforts with a resulting total of over 93,000 AF cases and more than 1 million referents. In aggregate, we identified at least 134 distinct AF-associated loci (**Supplementary Table 16**).

Four major themes emerge from the identified AF loci. First, two AF loci contain genes that are primary targets for current antiarrhythmic medications used to treat AF. The *SCN5A* gene encodes a sodium channel in the heart, the target of sodium-channel-blockers such as flecainide and propafenone. Similarly, *KCNH2* encodes the alpha subunit of the potassium channel complex, the target of potassium-channel-inhibiting medications such as amiodarone, sotalol, and dofetilide. *SCN5A* and *KCNH2* have previously been implicated in AF through GWAS,⁸ candidate gene analysis¹⁶ and family-based studies.^{17,18}

Second, transcriptional regulation appears to be a key feature of AF etiology. *TBX3* and the adjacent gene *TBX5* encode transcription factors, that have been shown to regulate the development of the cardiac conduction system.¹⁹ Similarly, the *NKX2-5* encodes a transcription factor, that is an early cue for cardiac development and has been associated with congenital heart disease²⁰ and heart rate²¹ (**Supplementary Table 14**). Further, reduced function of the transcription factor encoded by *PITX2* has been associated with AF, shortening of the left atrial action potential, and with modulation of sodium channel blocker therapy in the adult left atrium.²²⁻²⁴ A transcriptional co-regulatory network governed by transcription factors encoded by *TBX5* and *PITX2* has been shown to be critical for atrial development.²⁵

Third, the transcriptome-wide analyses revealed a number of compelling findings. Decreased expression of *PRRX1* associated with AF, a result consistent with findings where reduction of *PRRX1* in zebrafish and stem cell-derived cardiomyocytes was associated with action potential shortening.²⁶ Further, increased expression of *TBX5* and *KCNJ5* was associated with AF, a finding consistent with gain-of-function mutations in *TBX5* reported in a family with Holt-Oram syndrome and a high penetrance of AF.²⁷ Similarly, *KCNJ5* encodes a potassium channel that underlies a component of the $I_{K_{ACh}}$ current, a channel that

is upregulated in AF. Thus, prior studies support both the role of *PRRX1*, *TBX5*, and *KCNJ5* in AF and the observed directionality.

Fourth, many of the novel loci implicate genes that underlie Mendelian forms of arrhythmia syndromes. Mutations in *CASQ2* lead to catecholaminergic polymorphic ventricular tachycardia.^{28,29} Pathogenic variants in *PKP2* impair cardiomyocyte communication and structural integrity, and are a common cause of arrhythmogenic right ventricular cardiomyopathy.^{30,31} Mutations in *GJA5*, *KCNH2*, *SCN5A*, *KCNJ2*, *MYH7*, *NKX2-5*, have been mapped in a variety of inherited arrhythmia, cardiomyopathy, or conduction system diseases.³² Our observations highlight the pleiotropy of variation in genes specifying cardiac conduction, morphology, and function, and underscore the complex, polygenic nature of AF.

In conclusion, we conducted the largest AF meta-analysis to date and report a more than three-fold increase in the number of loci associated with this common arrhythmia. Our results lay the groundwork for functional evaluations of genes implicated by AF risk loci. Our findings also broaden our understanding of biological pathways involved in AF and may facilitate the development of therapeutics for AF.

Online Methods

Samples

Participants from more than 50 studies were included in this analysis. Participants were collected from both case-control studies for atrial fibrillation (AF) and population based studies. The majority of studies were part of the Atrial Fibrillation Genetics (AFGen) consortium and the Broad AF Study (Broad AF). Additional summary level results from the UK Biobank (UKBB) and the Biobank Japan (BBJ) were included (**Figure 1**). Cases include participants with paroxysmal or permanent atrial fibrillation, or atrial flutter, and referents were free of these diagnoses. Adjudication of atrial fibrillation for each study is described in the **Supplementary Notes**. Ascertainment of AF in the UK Biobank includes samples with one or more of the following codes 1) Non-cancer illness code, self-reported (1471, 1483), 2) Operation code (1524), 3) Diagnoses – main/secondary ICD10 (I48, I48.0–4, I48.9), 4) Underlying (primary/secondary) cause of death: ICD10 (I48, I48.0–4, I48.9) 5) Diagnoses – main/secondary ICD9 (4273), 6) Operative procedures – main/secondary OPCS (K57.1, K62.1–4).^{8,10,33} Baseline characteristics for each study are reported in **Supplementary Table 17**. We analyzed: 55,114 cases and 482,295 referents of European ancestry, 1,307 cases and 7,660 referents of African American ancestry, 8,180 cases and 28,612 referents of Japanese ancestry, 568 cases and 1,096 referents from Brazil and 277 cases and 3,081 referents of Hispanic ethnicity. Samples from the UK Biobank, the Broad AF Study, and the following studies from the AFGen consortium: SiGN, EGCUT, PHB and the Vanderbilt Atrial Fibrillation Registry, were previously not included in primary AF GWAS discovery analyses. There is minimal sample overlap from the studies MGH AF, BBJ and AFLMU between this and previous analyses. Ethics approval for participation was obtained individually by each study. All relevant ethical regulations were followed for this work. Written informed consent was obtained from all study participants.

The Institutional Review Board (IRB) at Massachusetts General Hospital reviewed and approved the overall study.

Genotyping and Genotype Calling

Samples within the Broad AF Study were genotyped at the Broad Institute using the Infinium PsychArray-24 v1.2 Bead Chip. They were genotyped in 19 batches, grouped by origin of the samples and with a balanced case control mix on each array. Common variants ($\geq 1\%$ MAF) were called with GenomeStudio v1.6.2.2 and Birdseed v1.33,³⁴ while rare variants ($<1\%$ MAF) were called with zCall.³⁵ Batch specific quality control (QC) was performed on each call-set including $>95\%$ sample call rate, Hardy-Weinberg-Equilibrium (HWE) $P > 1 \times 10^{-6}$ and variant call-rate $>97\%$. For common variants, a consensus merge was performed between the call-sets from GenomeStudio and Birdseed. For each genotype only concordant calls between the two algorithms were kept. The common variants from the consensus call were then combined with the rare variants calls from the zCall algorithm. Samples from all batches were joined prior to performing pre-imputation QC steps. Detailed procedures for genotyping and genotype calling for the SiGN study,³⁶ the UK Biobank,^{37,38} and the Biobank Japan⁹ are described elsewhere. Details on genotyping and calling for all participating studies are listed in **Supplementary Table 18**.

Imputation

Pre-imputation QC filtering of samples and variants was conducted based on recommended guidelines as described in **Supplementary Table 19**. QC steps were performed by each study and are described in **Supplementary Table 18**. Most studies with European ancestry samples performed imputation with the HRC reference v1.1³⁹ panel on the Michigan Imputation Server v1.0.1.⁴⁰ Studies without available HRC imputation were included based on imputation to the 1000 Genomes Phase 1 integrated v3 panel (March 2012).⁴¹ Participants of the SiGN study were imputed to a combined reference panel consisting of 1000 Genomes phase 1 plus Genome of the Netherlands.⁴² Studies from Brazil were imputed with the HRC reference v1.1 panel. Studies of Japanese ancestry or Hispanic ethnicity were imputed to the 1000G Phase 1 integrated v3 panel (March 2012). Studies of African American ancestry were imputed to the HRC reference v1.1 panel or the 1000G Phase 1 integrated v3 panel (March 2012). Studies were advised to use the HRC preparation and checking tool (<http://www.well.ox.ac.uk/~wrayner/tools/>) prior to imputation. Prephasing and imputation methods for each study are described in **Supplementary Table 18**.

Primary statistical analyses

Genome-wide association testing on autosomal chromosomes was performed using an additive genetic effect model based on genotype probabilities. Each ancestry group was analyzed separately for each study. For the Broad AF Study, the primary statistical analysis was performed jointly on unrelated individuals, excluding one of each pair for related samples with PI_HAT >0.2 as calculated in PLINK v1.90.^{43,44} Samples with sex mismatches and sample call rate $<97\%$ were excluded. Ancestry groups were defined with ADMIXTURE⁴⁵ based on genotyped, independent, and high quality variants, using the

supervised method with 1000Genomes phase 1 v3 samples as reference. A cutoff of 80% European ancestry was used to define the European subset and a cutoff of 60% African ancestry was used to define the African American subset. A Brazilian cohort within the Broad AF Study was analyzed separately. Principal components were calculated within each ancestry group with the smartpca program from EIGENSOFT v6.1.1⁴⁶. For the UK Biobank, a European subset was selected within samples with self-reported white race (British, Irish, or other) and similar genetic ancestry. Genetic similarity was defined with the *aberrant*⁴⁷ package in R based on principal components, following the same method as described for the UK Biobank.³⁸ We excluded samples with sex mismatches, outliers in heterozygosity and missing rates, samples that carry sex chromosome configurations other than XX or XY, and samples that were excluded from the kinship inference procedure as flagged in the UK Biobank QC file. We further removed one sample for each pair of third degree or closer relatives (kinship coefficient >0.0442), preferentially keeping samples with AF case status. Primary analyses for all other studies were performed at the study sites and the summary level data of the results were provided. Prevalent cases were analyzed in a logistic regression model and most incident cases were analyzed in a Cox proportional hazards model. Studies with both prevalent and incident cases analyzed these either separately using a logistic regression model or Cox proportional hazards model respectively, or jointly in a logistic regression model. The following tools were used for primary GWAS: ProbABEL,⁴⁸ SNPTEST,⁴⁹ FAST,⁵⁰ mach2dat (<http://www.sph.umich.edu/csg/yli>), R,⁵¹ EPACTS (<http://genome.sph.umich.edu/wiki/EPACTS>), Hail (<https://github.com/hail-is/hail>) and PLINK⁴⁴ (**Supplementary Table 18**). Summary level results were filtered, keeping variants with imputation quality >0.3 and MAF * imputation quality * N events ≥ 10. Post-analysis QC steps of summary level results included a check of allele frequencies, inspection of Manhattan-plots, QQ-plots, PZ-plots, and the distribution of effect estimates and standard errors, calculation of genomic inflation (λ_{GC}), and consistent directionality for known AF risk variants.⁵

Meta-analyses

Summary level results were meta-analyzed jointly with METAL (released on 2011–03-25) using a fixed effects model with inverse-variance weighted approach, correcting for genomic control.⁵² Separate meta-analyses were conducted for each ancestry. The results for the Japanese⁹ and Hispanic⁸ specific analyses have previously been reported and therefore their ancestry-specific results are not shown. Variants were included if they were present in at least two studies and showed an average MAF ≥ 0.1%. To correct for multiple testing, a genome-wide significance threshold of $P < 1 \times 10^{-8}$ was applied for each analysis. This threshold is based on a naive Bonferroni correction for independent variants with MAF ≥ 0.1%, using an LD threshold of $r^2 < 0.8$ to estimate the number of independent variants based on European ancestry LD.⁵³ As these meta-analyses are based on effect estimates and standard errors from both logistic regression and Cox proportional hazards regression, we report variant effects as relative risk, calculated as the exponential of effect estimates. For sentinel variants reaching genome-wide significance in the combined ancestry meta-analysis, we assessed if effect estimates were homogeneous across ancestries by calculating an I^2 statistic⁵⁴ across ancestry specific meta-analyses. We account for multiple testing

across 94 variants using a Bonferroni correction, resulting in a significance threshold of $P < 5.32 \times 10^{-4}$ for the heterogeneity test.

Broad AF LD reference and proxies

A linkage disequilibrium (LD) reference file was created including 26,796 European ancestry individuals from the Broad AF study. The LD reference was based on HRC imputed genotypes. Monomorphic variants and variants with imputation quality < 0.1 were removed prior to conversion to hard calls. A genotype probability (GP) threshold filter of $GP > 0.8$ was applied during hard call conversion. For multi-allelic sites the more common alleles were kept. Variants were included in the final reference file if the variant call rate was $> 70\%$.

We identified proxies of sentinel variants as variants in LD of $r^2 > 0.6$ based on the Broad AF LD reference file, using PLINK v1.90.^{43,44}

Meta-analysis of provisional loci

We meta-analyzed 111 variants from externally reported¹⁵ provisional loci within predominantly non-overlapping samples from the Broad AF Study, BBJ, EGCUT, PHB, SiGN and the Vanderbilt AF Registry with METAL (released on 2011–03-25).⁵² The predominantly nonoverlapping samples included a total of 32,957 AF cases and 83,546 referents, with minimal overlap from the studies MGH AF, BBJ and AFLMU. We subsequently meta-analyzed these results with the reported provisional results with METAL using a fixed effects model with inverse-variance weighted approach. We analyzed a total of 93,577 AF cases and 1,053,762 referents. We compared our discovery results with the provisional loci using the same significance cutoff of $P < 5 \times 10^{-8}$ for both results. Overlapping loci were identified, if the reported sentinel variants were located within 500kb of each other. For overlapping loci with differing sentinel variants we calculated the LD between the sentinel variants, based on the Broad AF LD reference panel of European ancestry.

Variant consequence on protein coding sequence

The most severe consequence for variants was identified with the Ensembl Variant Effect Predictor version 89.7 using RefSeq as gene reference and the option “pick” to identify one consequence per variant with the default pick order.⁵⁵ We queried sentinel variants and their proxies to identify tagged variants with HIGH and MODERATE impact including the following consequences: “transcript_ablation”, “splice_acceptor_variant”, “splice_donor_variant”, “stop_gained”, “frameshift_variant”, “stop_lost”, “start_lost”, “transcript_amplification”, “inframe_insertion”, “inframe_deletion”, “missense_variant” and “protein_altering_variant”. We evaluated each identified consequence on the protein coding sequence with in silico prediction tools to assess potentially damaging effects. The evaluation included MutationTaster⁵⁶ (disease causing automatic or disease causing), SIFT⁵⁷ (damaging), LRT⁵⁸ (deleterious), Polyphen2⁵⁹ prediction based on HumDiv and HumVar (probably damaging or possibly damaging).

Chromatin states

Chromatin state annotation.—We identified chromatin states for sentinel variants and their proxies from the Roadmap Epigenomics Consortium 25-state model (2015)⁶⁰ using HaploReg v4.⁶¹ We looked for chromatin states occurring in any included tissues as well as chromatin states occurring in heart tissue. Heart tissues include E065: Aorta, E083: Fetal Heart, E095: Left Ventricle, E104: Right Atrium and E105: Right Ventricle.

Regulatory region enrichment.—1,000 sets of control loci were generated by matching SNPs to sentinel variants from the AF combined-ancestry analysis, with the SNPSnap⁶² tool. We used the European 1000 Genomes Phase 3 population to match via minor allele frequency, gene density, distance to nearest gene and LD buddies using $r^2 > 0.6$ as LD cutoff and otherwise default settings. We excluded input SNPs and HLA SNPs from the matched SNPs. Loci were defined as SNPs and their proxies with $r^2 > 0.6$ based on LD from the European 1000 Genomes Phase 3 population. We identified SNPs in regulatory regions across all tissues and in cardiac tissues (E065, E095, E104, E105) based on the Roadmap Epigenomics Consortium 25-state model (2015)⁶⁰ using HaploReg v4.⁶¹ Regulatory regions included the following states: 2_PromU, 3_PromD1, 4_PromD2, 9_TxReg, 10_TxEnh5, 11_TxEnh3, 12_TxEnhW, 13_EnhA1, 14_EnhA2, 15_EnhAF, 16_EnhW1, 17_EnhW2, 18_EnhAc, 19_DNase, 22_PromP and 23_PromBiv. We calculated the percent overlap of each annotation per locus, defined as number of SNPs per locus that fall in regulatory regions divided by total number of SNPs per locus. Statistical significance was calculated with a permutation test from the *perm* package in R.⁶³

Expression quantitative trait loci (eQTL)

Variants identified from GWAS were assessed for overlap with eQTLs from two sources: **1) Left atrial (LA) tissue from the Myocardial Applied Genomics Network (MAGNet) repository.** We performed RNA sequencing (RNA-seq) on 101 left atrial tissue samples from the MAGNet repository (<http://www.med.upenn.edu/magnet/>) on the Illumina HiSeq 4000 platform at the Broad Institute Genomic Services. Left atrial tissue was obtained at the time of cardiac transplantation from normal donors with no evidence of structural heart disease. All left atrial samples were from individuals of European ancestry. A summary of the clinical characteristics for these samples is shown in **Supplementary Table 20**. Reads were aligned to the reference genome by STAR v2.4.1a⁶⁴ and assigned to genes based on the GENCODE gene annotation.⁶⁵ Gene expression was measured in fragments per kilobase of transcript per million mapped reads (FPKM) and subsequently quantile-normalized and adjusted for age, sex, and the first 10 principal components. Genotyping was performed on the Illumina OmniExpressExome-8v1 array and imputed to the HRC reference panel. Principal components were calculated with the smartpca program from EIGENSOFT v6.1.1⁴⁶ and European ancestry was confirmed by assessing principal components in the samples combined with 1000 Genomes European samples.⁴¹ Associations between gene expression and genotypes were tested in a linear regression model with QTLtools v1.0,⁶⁶ in order to detect *cis*-eQTLs, defined as eQTLs within 1MB of the transcription start site of a gene. To account for multiple testing, an empirical false discovery rate (FDR) was used to identify significant eQTLs with a FDR <5%. **2) Genotype-Tissue Expression (GTEx) project.**⁶⁷ We queried the GTEx version 6p database for *cis*-eQTLs with significant

associations to gene expression levels in the two available heart tissues: left ventricle and right atrial appendage.⁶⁸

Association between predicted gene expression and risk of atrial fibrillation

To investigate transcriptome-wide associations between predicted gene expression and AF disease risk, we employed the method MetaXcan v0.3.5.¹² MetaXcan extends the previous method PrediXcan⁶⁹ to predict the association between gene expression and a phenotype of interest, using summary association statistics. Gene expression prediction models were generated from eQTL datasets using Elastic-Net to identify the most predictive set of SNPs. Only models that significantly predict gene expression in the reference eQTL dataset (FDR <0.05) were considered. Pre-computed MetaXcan models for the two available heart tissues (left ventricle and right atrial appendage) in the genotype-tissue expression project version 6p (GTEx)⁶⁸ were used to predict the association between gene expression and risk of AF. Summary level statistics from the combined ancestry meta-analysis were used as input. 4859 genes were tested for left ventricle and 4467 genes were tested for right atrial appendage. Bonferroni correction was applied to account for the number of genes tested across both tissues, resulting in a significance threshold of $P < 5.36 \times 10^{-6}$, calculated as $0.05 / (4859 + 4467)$.

Conditional and joint analyses

Conditional and joint analyses⁷⁰ of GWAS summary statistics were performed with Genomewide Complex Trait Analysis (GCTA v1.25.2)⁷¹ using a stepwise selection procedure to identify independently-associated variants on each chromosome. We used the Broad AF LD reference file for LD calculations.

Gene set enrichment analysis (GSEA)

A Meta-Analysis Gene-set Enrichment of variaNT Associations (MAGENTA) v2.4⁷² was performed with a combined gene set input database (GO_PANTHER_INGENUITY_KEGG_REACTOME_BIOCARTA) based on publicly available data. The analysis was conducted using the summary level results from the combined ancestry meta-analysis. 4045 gene sets were included and multiple testing was corrected via false discovery rate (FDR). Gene sets were manually assigned to one or more of the following functional groups: developmental, electrophysiological, contractile/structural, and other. Genes within 500 kilobases of a sentinel variant were identified based on the longest spanning transcribed region in the RefSeq gene reference. For each gene set, genes close to significant loci were listed. The selected genes were assigned to one or more functional groups based on their affiliation to gene sets. Functional groups from gene sets with a single label were preferentially assigned.

Association with other phenotypes

To determine if the sentinel AF risk variants had associations with other phenotypes, two sources of data were used:

1) GWAS catalog.

We queried the NHGRI-EBI Catalog of published genome-wide association studies^{73,74} (accessed 2017–08-31) to detect associations of AF risk variants with other phenotypes.

2) UK Biobank phenome-wide association study (PheWAS).

A PheWAS was conducted in the UK Biobank in European ancestry individuals. Ancestry definition and sample QC exclusions were performed in the same manner as for the primary statistical analysis, as described above. We further removed one sample for each pair of second degree or closer relatives (kinship coefficient >0.0884), preferentially keeping the sample with case status or non-missing phenotype. We included the following phenotypes: height, body mass index (BMI), smoking, hypertension, heart failure, stroke, mitral regurgitation, bradyarrhythmia, peripheral vascular disease (PVD), hypercholesterolemia, coronary artery disease (CAD), and type II diabetes. Phenotype definitions are shown in **Supplementary Table 21**. Number of samples analyzed, as well as case and referent counts for each phenotype are listed in **Supplementary Table 22**. Binary phenotypes were analyzed with a logistic regression model and quantitative phenotypes with a linear regression model using imputed genotype dosages in PLINK 2.00.⁴⁴ As covariates we included sex, age at first visit, genotyping array, and the first 10 principal components.

Proportion of heritability explained

We calculated SNP-heritability (h^2_g) of AF-associated loci with the REML algorithm in BOLT-LMM v2.2⁷⁵ in 120,286 unrelated samples of European ancestry from a subset of the UK Biobank dataset comprising a prior interim release as previously described in separate work from our group.¹⁰ We defined loci based on a 1MB (+/- 500kb) window around 84 sentinel variants from the European ancestry meta-analysis. We transformed the h^2_g estimates into liability scale (AF prevalence = 2.45% in UK Biobank). We then calculated the proportion of h^2_g explained at AF loci by dividing the h^2_g estimate of AF-associated loci by the total h^2_g for AF, that was based on 811,488 LD-pruned and hard-called common variants (MAF > 1%).¹⁰

Life Sciences Reporting Summary

Further information on experimental design is available in the Life Sciences Reporting Summary.

Data Availability and Accession Code Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request. The results of this study are available on the Cardiovascular Disease Knowledge Portal (<http://www.broadcvdi.org>). The left atrial RNAsequencing data can be accessed via dbGaP under the accession number phs001539.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Carolina Roselli^{#1}, Mark D. Chaffin^{#1}, Lu-Chen Weng^{#1,2}, Stefanie Aeschbacher^{3,4}, Gustav Ahlberg^{5,6,7}, Christine M. Albert⁸, Peter Almgren⁹, Alvaro Alonso¹⁰, Christopher D. Anderson^{1,11}, Krishna G. Aragam^{1,11}, Dan E. Arking¹², John Barnard¹³, Traci M. Bartz¹⁴, Emelia J. Benjamin^{15,16,17}, Nathan A. Bihlmeyer¹⁸, Joshua C. Bis¹⁹, Heather L. Bloom²⁰, Eric Boerwinkle²¹, Erwin B. Bottinger^{22,23}, Jennifer A. Brody¹⁹, Hugh Calkins²⁴, Archie Campbell²⁵, Thomas P. Cappola²⁶, John Carlquist^{27,28}, Daniel I. Chasman^{1,29}, Lin Y. Chen³⁰, Yii-Der Ida Chen³¹, Eue-Keun Choi³², Seung Hoan Choi¹, Ingrid E. Christophersen^{1,2,33}, Mina K. Chung¹³, John W. Cole^{34,35}, David Conen^{3,4,36}, James Cook³⁷, Harry J. Crijns³⁸, Michael J. Cutler²⁷, Scott M. Damrauer^{39,40}, Brian R. Daniels¹, Dawood Darbar⁴¹, Graciela Delgado⁴², Joshua C. Denny⁴³, Martin Dichgans^{44,45,46}, Marcus Dörr^{47,48}, Elton A. Dudink³⁸, Samuel C. Dudley⁴⁹, Nada Esa⁵⁰, Tonu Esko^{1,51}, Markku Eskola⁵², Diane Fatkin^{53,54,55}, Stephan B. Felix^{47,48}, Ian Ford⁵⁶, Oscar H. Franco⁵⁷, Bastiaan Geelhoed⁵⁸, Raji Grewal^{59,60}, Vilmondur Gudnason^{61,62}, Xiuqing Guo³¹, Namrata Gupta¹, Stefan Gustafsson⁶³, Rebecca Gutmann⁶⁴, Anders Hamsten⁶⁵, Tamara B. Harris⁶⁶, Caroline Hayward⁶⁷, Susan R. Heckbert^{68,69}, Jussi Hernesniemi^{52,70}, Lynne J. Hocking⁷¹, Albert Hofman⁵⁷, Andrea R. V. R. Horimoto⁷², Jie Huang⁷³, Paul L. Huang², Jennifer Huffman⁶⁷, Erik Ingelsson^{63,74}, Esra Gucuk Ipek²⁴, Kaoru Ito⁷⁵, Jordi Jimenez-Conde^{76,77}, Renee Johnson⁵³, J. Wouter Jukema^{78,79,80}, Stefan Kääh^{81,82}, Mika Kähönen⁸³, Yoichiro Kamatani⁸⁴, John P. Kane⁸⁵, Adnan Kastrati^{82,86}, Sekar Kathiresan^{1,11}, Petra Katschnig-Winter⁸⁷, Maryam Kavousi⁵⁷, Thorsten Kessler⁸⁶, Bas L. Kietselaer³⁸, Paulus Kirchhof^{88,89,90}, Marcus E. Kleber⁴², Stacey Knight^{27,91}, Jose E. Krieger⁷², Michiaki Kubo⁹², Lenore J. Launer⁶⁶, Jari Laurikka⁹³, Terho Lehtimäki⁷⁰, Kirsten Leineweber⁹⁴, Rozenn N. Lemaitre¹⁹, Man Li^{95,96}, Hong Euy Lim⁹⁷, Henry J. Lin³¹, Honghuang Lin^{15,16}, Lars Lind⁹⁸, Cecilia M. Lindgren⁹⁹, Marja-Liisa Lokki¹⁰⁰, Barry London⁶⁴, Ruth J. F. Loos^{22,101,102}, SiewKee Low⁸⁴, Yingchang Lu^{22,101}, Leo-Pekka Lyytikäinen⁷⁰, Peter W. Macfarlane¹⁰³, Patrik K. Magnusson¹⁰⁴, Anubha Mahajan⁹⁹, Rainer Malik⁴⁴, Alfredo J. Mansur¹⁰⁵, Gregory M. Marcus¹⁰⁶, Lauren Margolin¹, Kenneth B. Margulies²⁶, Winfried März^{107,108}, David D. McManus⁵⁰, Olle Melander¹⁰⁹, Sanghamitra Mohanty^{110,111}, Jay A. Montgomery⁴³, Michael P. Morley²⁶, Andrew P. Morris³⁷, Martina Müller-Nurasyid^{81,82,112}, Andrea Natale^{110,111}, Saman Nazarian¹¹³, Benjamin Neumann⁸¹, Christopher Newton-Cheh^{1,11}, Maartje N. Niemeijer⁵⁷, Kjell Nikus⁵², Peter Nilsson¹¹⁴, Raymond Noordam¹¹⁵, Heidi Oellers¹¹⁶, Morten S. Olesen^{5,6,7}, Marju Orho-Melander⁹, Sandosh Padmanabhan¹¹⁷, Hui-Nam Pak¹¹⁸, Guillaume Paré^{36,119}, Nancy L. Pedersen¹⁰⁴, Joanna Pera¹²⁰, Alexandre Pereira^{121,122}, David Porteous²⁵, Bruce M. Psaty^{69,123}, Sara L. Pulit^{1,124,125}, Clive R. Pullinger⁸⁵, Daniel J. Rader¹²⁶, Lena Refsgaard^{5,6,7}, Marta Ribasés^{127,128,129}, Paul M. Ridker⁸, Michiel Rienstra⁵⁸, Lorenz Risch^{130,131}, Dan M. Roden⁴³, Jonathan Rosand^{1,11}, Michael A. Rosenberg^{11,132}, Natalia Rost^{1,133}, Jerome I. Rotter¹³⁴, Samir Saba¹³⁵, Roopinder K. Sandhu¹³⁶, Renate B. Schnabel^{137,138}, Katharina Schramm^{81,112}, Heribert Schunkert^{82,86}, Claudia Schurman^{22,101}, Stuart A. Scott¹³⁹, Ilkka Seppälä⁷⁰, Christian Shaffer⁴³, Svati

Shah¹⁴⁰, Alaa A. Shalaby^{135,141}, Jaemin Shim¹⁴², M. Benjamin Shoemaker⁴³, Joylene E. Siland⁵⁸, Juha Sinisalo¹⁴³, Moritz F. Sinner^{81,82}, Agnieszka Slowik¹²⁰, Albert V. Smith^{61,62}, Blair H. Smith¹⁴⁴, J. Gustav Smith^{1,145}, Jonathan D. Smith¹³, Nicholas L. Smith^{68,69}, Elsayed Z. Soliman¹⁴⁶, Nona Sotoodehnia¹⁴⁷, Bruno H. Stricker^{148,149}, Albert Sun¹⁴⁰, Han Sun¹³, Jesper H. Svendsen^{5,7}, Toshihiro Tanaka¹⁵⁰, Kahraman Tanriverdi⁵⁰, Kent D. Taylor³¹, Maris Teder-Laving⁵¹, Alexander Teumer^{48,151}, Sébastien Thériault^{36,119}, Stella Trompet^{78,115}, Nathan R. Tucker^{1,2}, Arnljot Tveit^{33,152}, Andre G. Uitterlinden¹⁴⁸, Pim Van Der Harst⁵⁸, Isabelle C. Van Gelder⁵⁸, David R. Van Wagener¹³, Niek Verweij⁵⁸, Efthymia Vlachopoulou¹⁰⁰, Uwe Völker^{48,153}, Biqi Wang¹⁵⁴, Peter E. Weeke^{5,43}, Bob Weijis³⁸, Raul Weiss¹⁵⁵, Stefan Weiss^{48,153}, Quinn S. Wells⁴³, Kerri L. Wiggins¹⁹, Jorge A. Wong¹⁵⁶, Daniel Woo¹⁵⁷, Bradford B. Worrall¹⁵⁸, Pil-Sung Yang¹¹⁸, Jie Yao³¹, Zachary T. Yoneda⁴³, Tanja Zeller^{137,138}, Lingyao Zeng⁸⁶, Steven A. Lubitz^{#1,2,159}, Kathryn L. Lunetta^{#15,154}, and Patrick T. Ellinor^{#1,2,159}

Affiliations

¹Program in Medical and Population Genetics, The Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA ²Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts, USA ³University Hospital Basel, Basel, Switzerland ⁴Cardiovascular Research Institute Basel, Basel, Switzerland ⁵The Heart Centre, Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark ⁶Laboratory of Experimental Cardiology, Department of Biomedical Sciences, University of Copenhagen. The Danish National Research Foundation Centre for Cardiac Arrhythmia, Copenhagen, Denmark ⁷Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark ⁸Divisions of Preventive and Cardiovascular Medicine, Brigham and Women's Hospital & Harvard Medical School, Boston, Massachusetts, USA ⁹Department of Clinical Sciences, Lund University, Malmö, Sweden ¹⁰Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA ¹¹Center for Genomic Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA ¹²McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA ¹³Departments of Cardiovascular Medicine, Cellular and Molecular Medicine, Molecular Cardiology, and Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio, USA ¹⁴Cardiovascular Health Research Unit, Departments of Medicine and Biostatistics, University of Washington, Seattle, Washington, USA ¹⁵NHLBI and Boston University's Framingham Heart Study, Framingham, Massachusetts, USA ¹⁶Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, USA ¹⁷Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts, USA ¹⁸Predoctoral Training Program in Human Genetics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA ¹⁹Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, Washington, USA ²⁰Division of Cardiology, Emory University and Atlanta VA Medical Center, Atlanta,

Georgia, USA ²¹Human Genome Sequencing Center, Baylor College of Medicine, Houston, Texas, USA ²²The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA ²³Department of Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, New York, New York, USA ²⁴Johns Hopkins University, Baltimore, Maryland, USA ²⁵Generation Scotland, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK ²⁶Penn Cardiovascular Institute and Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA ²⁷Intermountain Heart Institute, Intermountain Medical Center, Murray, Utah, USA ²⁸Division of Cardiovascular Medicine, University of Utah, Salt Lake City, Utah, USA ²⁹Divisions of Preventive Medicine and Genetics, Brigham and Women's Hospital & Harvard Medical School, Boston, Massachusetts, USA ³⁰Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota, USA ³¹Institute for Translational Genomics and Population Sciences, Department of Pediatrics, LABioMed at Harbor-UCLA Medical Center, Torrance, California, USA ³²Seoul National University Hospital, Seoul, Korea ³³Department of Medical Research, Bæum Hospital, Vestre Viken Hospital Trust, Drammen, Norway ³⁴Baltimore Veterans Affairs Medical Center, Department of Neurology, Baltimore, Maryland, USA ³⁵University of Maryland School of Medicine, Department of Neurology, Baltimore, Maryland, USA ³⁶Population Health Research Institute, McMaster University, Hamilton, Canada ³⁷Department of Biostatistics, University of Liverpool, Liverpool, UK ³⁸Maastricht University Medical Center+ and Cardiovascular Research Institute Maastricht, Department of Cardiology, Maastricht, The Netherlands ³⁹Department of Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA ⁴⁰Department of Surgery, Corporal Michael Crescenz VA Medical Center, Philadelphia, Pennsylvania, USA ⁴¹University of Illinois Chicago, Chicago, Illinois, USA ⁴²Vth Department of Medicine, Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany ⁴³Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA ⁴⁴Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany ⁴⁵Munich Cluster for Systems Neurology (SyNergy), Munich, Germany ⁴⁶German Center for Neurodegenerative Diseases (DZNE), Munich, Germany ⁴⁷Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany ⁴⁸DZHK (German Centre for Cardiovascular Research), partner site: Greifswald, Greifswald, Germany ⁴⁹Cardiovascular Division and Lillehei Heart Institute, University of Minnesota, Minneapolis, Minnesota, USA ⁵⁰University of Massachusetts Medical School Worcester, Worcester, Massachusetts, USA ⁵¹Estonian Genome Center, University of Tartu, Tartu, Estonia ⁵²Heart Center, Department of cardiology Tampere University Hospital, Finland and Faculty of Medicine and Life Sciences, University of Tampere, Finland ⁵³Victor Chang Cardiac Research Institute, Darlinghurst, New South Wales, Australia ⁵⁴St Vincent's Hospital, Darlinghurst, New South Wales, Australia ⁵⁵Faculty of Medicine, University of New South Wales, Kensington, New

South Wales, Australia ⁵⁶Robertson Center for Biostatistics, University of Glasgow, Glasgow, UK ⁵⁷Department of Epidemiology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands ⁵⁸University of Groningen, University Medical Center Groningen, Department of Cardiology, Groningen, The Netherlands ⁵⁹Dept. of Neuroscience, Saint Francis Medical Center, Trenton, New Jersey, USA ⁶⁰School of Health and Medical Sciences, Seton Hall University, South Orange, New Jersey, USA ⁶¹Icelandic Heart Association, Kopavogur, Iceland ⁶²Faculty of Medicine, University of Iceland, Reykavik, Iceland ⁶³Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden ⁶⁴Division of Cardiovascular Medicine and Abboud Cardiovascular Research Center, University of Iowa, Iowa City, Iowa, USA ⁶⁵Cardiovascular Genetics and Genomics Group, Atherosclerosis Research Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden ⁶⁶Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Bethesda, Maryland, USA ⁶⁷MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK ⁶⁸Cardiovascular Health Research Unit and Department of Epidemiology, University of Washington, Seattle, Washington, USA ⁶⁹Kaiser Permanente Washington Health Research Institute, Seattle, Washington, USA ⁷⁰Department of Clinical Chemistry, Fimlab Laboratories and Finnish Cardiovascular Research Center-Tampere, Faculty of Medicine and Life Sciences, University of Tampere ⁷¹Musculoskeletal Research Programme, Division of Applied Medicine, University of Aberdeen, Aberdeen, UK ⁷²Laboratory of Genetics and Molecular Cardiology, Heart Institute, University of Sao Paulo, Sao Paulo, Brazil ⁷³Boston VA Research Institute, Inc., Boston, Massachusetts, USA ⁷⁴Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA ⁷⁵Laboratory for Cardiovascular Diseases, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan ⁷⁶Department of Neurology, Neurovascular Research Group IMIM-Hospital del Mar (Institut Hospital del Mar d'Investigacions Mèdiques), Barcelona, Spain ⁷⁷Universitat Autònoma de Barcelona, Medicine Department, Barcelona, Spain ⁷⁸Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands ⁷⁹Durrer Center for Cardiogenetic Research, Amsterdam, The Netherlands ⁸⁰Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands ⁸¹Department of Medicine I, University Hospital Munich, Ludwig-Maximilians-University, Munich, Germany ⁸²DZHK (German Centre for Cardiovascular Research), partner site: Munich Heart Alliance, Munich, Germany ⁸³Department of Clinical Physiology, Tampere University Hospital, and Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland ⁸⁴Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan ⁸⁵Cardiovascular Research Institute, University of California, San Francisco, California, USA ⁸⁶Deutsches Herzzentrum München, Klinik für Herz- und Kreislauferkrankungen, Technische Universität München, Munich, Germany ⁸⁷Department of Neurology, Medical University of Graz, Graz, Austria ⁸⁸Institute of Cardiovascular Sciences,

University of Birmingham, Birmingham, UK ⁸⁹Sandwell and West Birmingham Hospitals NHS Trust and University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK ⁹⁰AFNET, Münster, Germany ⁹¹Department of Medicine, University of Utah, Salt Lake City, Utah, USA ⁹²RIKEN Center for Integrative Medical Sciences, Yokohama, Japan ⁹³Department of Cardio-Thoracic Surgery, Heart Center, Tampere University Hospital, and Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland ⁹⁴Dept. Disease Genomics, Bayer, Wuppertal, Germany ⁹⁵Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland, USA ⁹⁶Division of Nephrology & Hypertension, Internal Medicine, School of Medicine, University of Utah, Salt Lake City, Utah, USA ⁹⁷Korea University Guro Hospital, Seoul, Korea ⁹⁸Department of Medical Sciences, Cardiovascular Epidemiology, Uppsala University, Uppsala, Sweden ⁹⁹Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK ¹⁰⁰Transplantation Laboratory, Medicum, University of Helsinki, Helsinki, Finland ¹⁰¹The Genetics of Obesity and Related Metabolic Traits Program, Icahn School of Medicine at Mount Sinai, New York, New York, USA ¹⁰²The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA ¹⁰³Institute of Health and Wellbeing, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK ¹⁰⁴Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden ¹⁰⁵Heart Institute, University of Sao Paulo, Sao Paulo, Brazil ¹⁰⁶Division of Cardiology, University of California, San Francisco, California, USA ¹⁰⁷Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria ¹⁰⁸Synlab Academy, Synlab Services GmbH, Mannheim, Germany ¹⁰⁹Department of Internal Medicine, Clinical Sciences, Lund University, Malmo, Sweden ¹¹⁰Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, Texas, USA ¹¹¹Dell Medical School, Austin, Texas, USA ¹¹²Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany ¹¹³University of Pennsylvania, Philadelphia, Pennsylvania, USA ¹¹⁴Department of Clinical Sciences, Lund University and Skåne University Hospital, Malmo, Sweden ¹¹⁵Section of Gerontology and Geriatrics, Department of internal medicine, Leiden University Medical Center, Leiden, The Netherlands ¹¹⁶Atrial Fibrillation NETwork, Muenster, Germany ¹¹⁷Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK ¹¹⁸Yonsei University Health System, Seoul, Korea ¹¹⁹Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Canada ¹²⁰Department of Neurology, Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland ¹²¹Laboratory of Genetics and Molecular Biology, Heart Institute, University of Sao Paulo, Sao Paulo, Brazil ¹²²Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA ¹²³Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, Washington, USA ¹²⁴Department of Genetics, Center for Molecular Medicine, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands ¹²⁵Li

Ka Shing Center for Health Information and Discovery, Big Data Institute, Oxford University, Oxford, UK ¹²⁶Division of Cardiovascular Medicine, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA ¹²⁷Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addiction, Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain ¹²⁸Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain ¹²⁹Biomedical Network Research Centre on Mental Health (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain ¹³⁰University Institute of Clinical Chemistry, University of Bern, Switzerland ¹³¹Labormedizinisches Zentrum Dr. Risch, Schaan, Liechtenstein ¹³²University of Colorado School of Medicine, Aurora, Colorado, USA ¹³³J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Boston, Massachusetts, USA ¹³⁴Institute for Translational Genomics and Population Sciences, Departments of Pediatrics and Medicine, LABioMed at Harbor-UCLA Medical Center, Torrance, California, USA ¹³⁵Division of Cardiology, University of Pittsburgh, Pennsylvania, USA ¹³⁶Division of Cardiology, University of Alberta, Edmonton, Canada ¹³⁷Department of General and Interventional Cardiology, University Heart Centre Hamburg, Hamburg, Germany ¹³⁸DZHK (German Centre for Cardiovascular Research), partner site: Hamburg/Kiel/Lübeck, Hamburg, Germany ¹³⁹Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, USA ¹⁴⁰Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, North Carolina, USA ¹⁴¹Cardiology Division, Pittsburgh VA Healthcare System, Pittsburgh, Pennsylvania, USA ¹⁴²Korea University Anam Hospital, Seoul, Korea ¹⁴³Heart and Lung Center HUS, Helsinki University Central Hospital, Helsinki, Finland ¹⁴⁴Division of Population Health Sciences, University of Dundee, Scotland, UK ¹⁴⁵Department of Cardiology, Clinical Sciences, Lund University and Skåne University Hospital, Lund, Sweden ¹⁴⁶Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston Salem, North Carolina, USA ¹⁴⁷Cardiovascular Health Research Unit, Departments of Medicine and Epidemiology, University of Washington, Seattle, Washington, USA ¹⁴⁸Department of Epidemiology and Internal Medicine, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands ¹⁴⁹Inspectorate of Health Care, Utrecht, The Netherlands ¹⁵⁰Department of Human Genetics and Disease Diversity, Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences, Tokyo, Japan ¹⁵¹Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany ¹⁵²Institute of Clinical Medicine, University of Oslo, Oslo, Norway ¹⁵³Interfaculty Institute for Genetics and Functional Genomics, University Medicine and Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany ¹⁵⁴Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA ¹⁵⁵Division of Cardiovascular Medicine, The Ohio State University, Columbus, Ohio, USA ¹⁵⁶Division of Cardiology, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada ¹⁵⁷University of Cincinnati College of Medicine, Cincinnati, Ohio, USA ¹⁵⁸University of Virginia Health System,

Departments of Neurology and Public Health Science, Charlottesville, Virginia, USA
 159Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston,
 Massachusetts, USA

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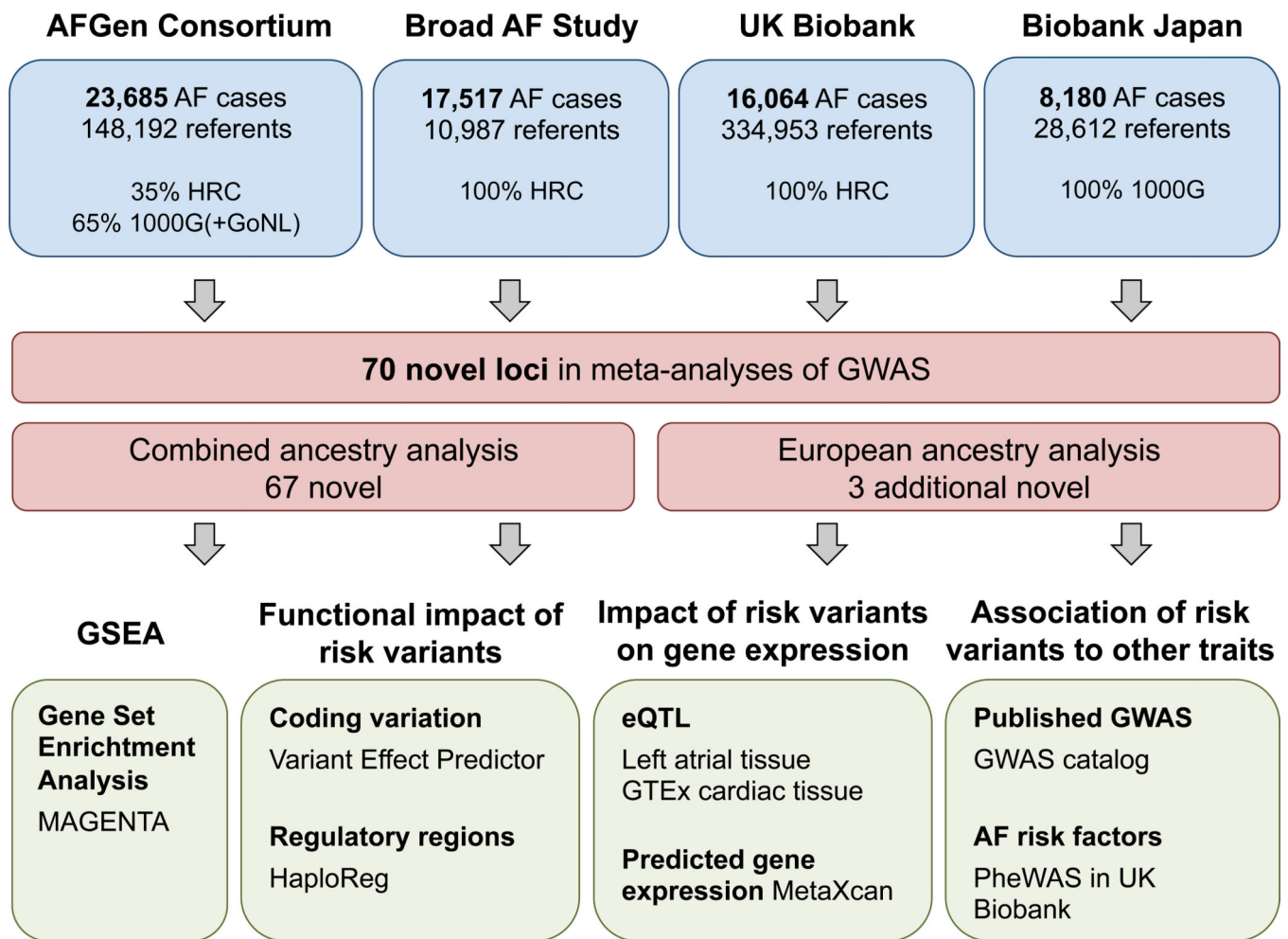


Figure 1. Study and analysis flowchart

Top, overview of the participating studies, number of AF cases and referents, and the percent of samples imputed with each reference panel. Middle, summary of the primary analyses and the newly discovered loci for AF. Bottom, overview of the secondary analyses to evaluate AF risk variants and loci.

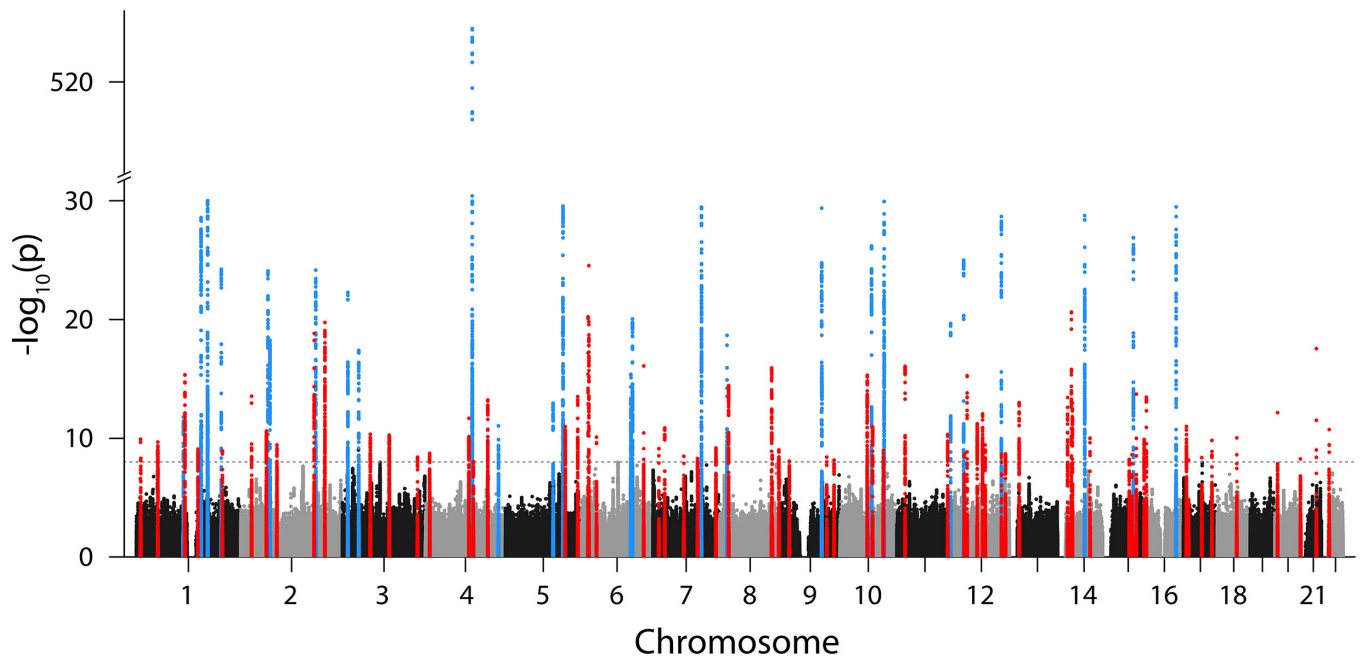


Figure 2. Manhattan plot of combined-ancestry meta-analysis

The plot shows 67 novel (red) and 27 known (blue) genetic loci associated with AF at a significance level of $P < 1 \times 10^{-8}$ (dashed line), for the combined-ancestry meta-analysis ($n=588,190$). The significance level accounts for multiple testing of independent variants with MAF 0.1% using a Bonferroni correction. P-values (two-sided) were derived from a meta-analysis using a fixed effects model with an inverse-variance weighted approach. The y-axis has a break between $-\log_{10}(P)$ of 30 and 510 to emphasize the novel loci

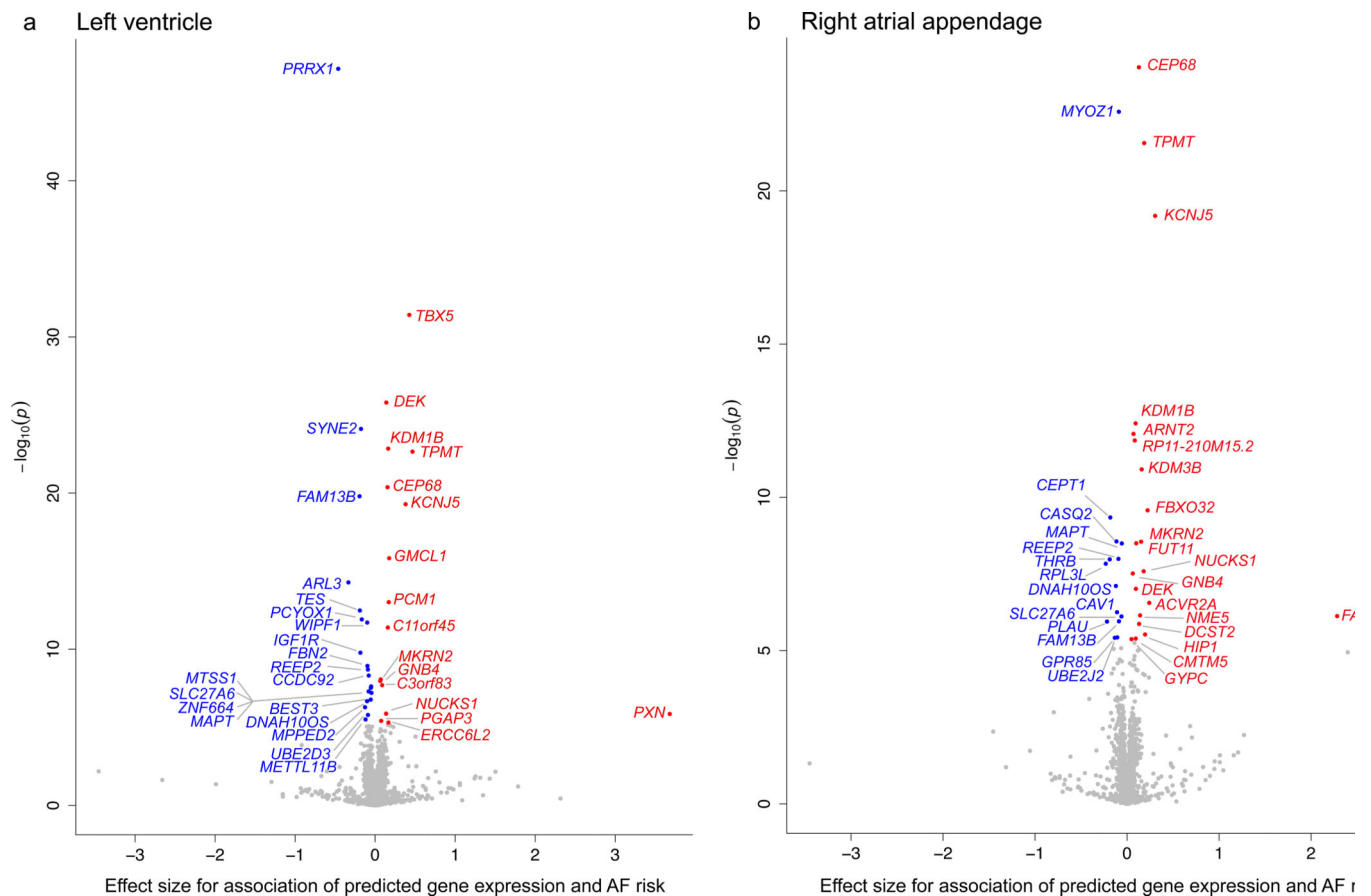


Figure 3. Volcano plot of transcriptome-wide analysis from human heart tissues

The plots show the results from the transcriptome-wide analysis based on left ventricle (a, n=190) and right atrial appendage (b, n=159) tissue from GTEx, calculated with the MetaXcan method based on the combined-ancestry summary level results (n=588,190). Each plotted point represents the association results for an individual gene. The x-axis shows the effect size for associations of predicted gene expression and AF risk for each tested gene. The y-axis shows the $-\log_{10}(P)$ for the associations per gene. Genes with positive effect (red) showed an association of increased predicted gene expression with AF risk. Genes with negative effect (blue) showed an association of decreased predicted gene expression with AF risk. The highlighted genes are significant after Bonferroni correction for all tested genes and tissues with a P-value $< 5.36 \times 10^{-6}$. The result for one gene for right atrial appendage (b) is not shown (*SNX4*, Effect = 6.94, P = 0.2).

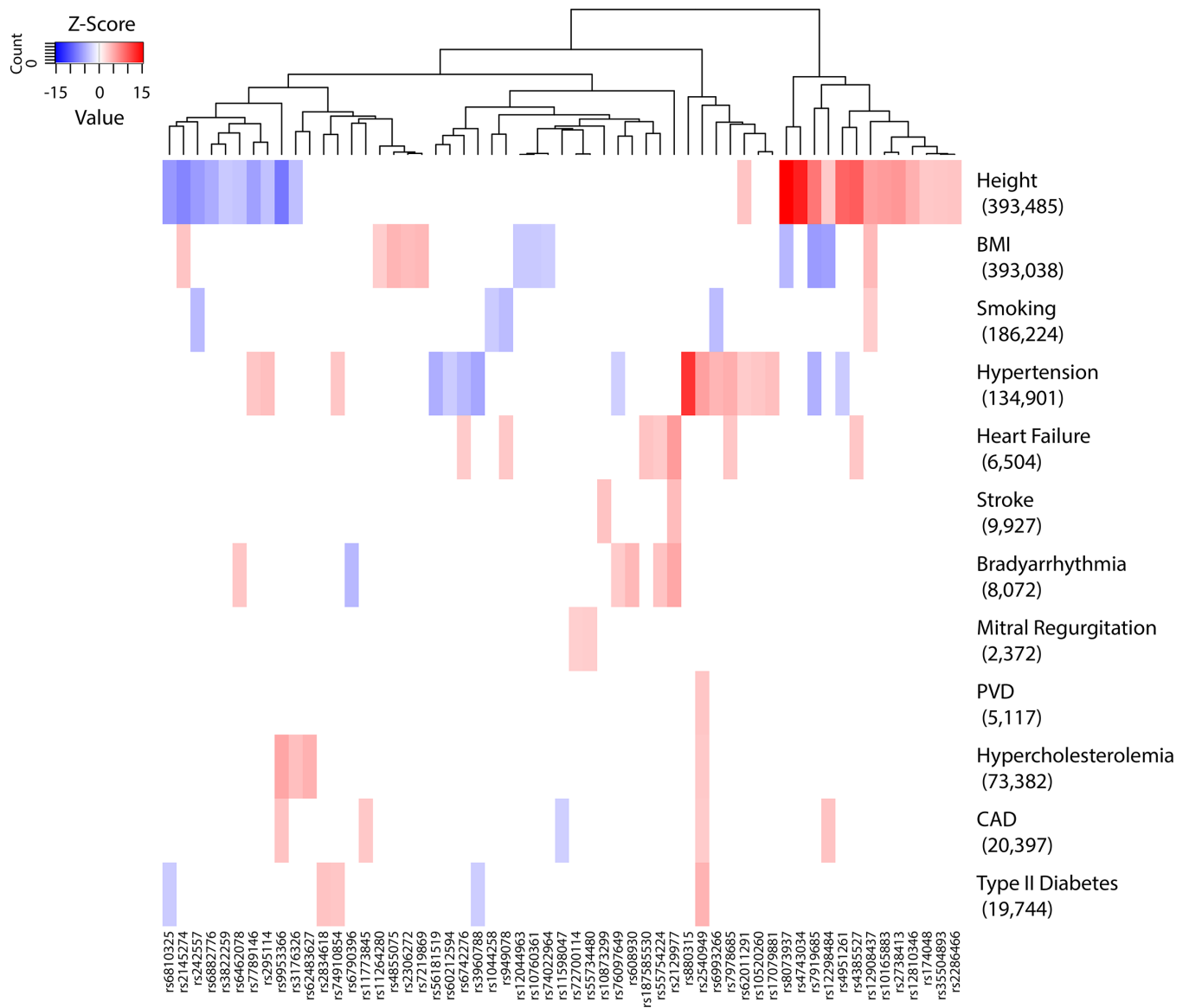


Figure 4. Cross-trait associations of AF risk variants with AF risk factors in the UK Biobank
The heatmap shows associations of novel and known sentinel variants at AF risk loci from the combined-ancestry meta-analysis. Shown are variants and phenotypes with significant associations after correcting for 12 phenotypes via Bonferroni with $P < 4.17 \times 10^{-3}$. P-values (two-sided) were derived from linear and logistic regression models. Listed next to each trait is the number of cases for binary traits or total sample size for quantitative traits. Hierarchical clustering was performed on a variant level using the complete linkage method based on Euclidian distance. Coloring represents Z-scores for each respective trait or disease, oriented toward the AF risk allele. Red indicates an increase in the trait or disease risk while blue indicates a decrease in the trait or disease risk. Abbreviations, BMI, body-mass index, CAD, coronary artery disease, PVD, pulmonary vascular disease.

Table 1.

Novel loci in combined-ancestry meta-analysis

RsId	Chr	hg19	Risk/Re f Allele	RA F [%]	RR	95% CI	P _{META}	Nearest Gene(s)*	Func	imp Qua I	F _{HET}	P _{HET}	
rs18758553	0	1	10167425	A/G	0.5	1.55	1.36–1.77	1.18×10 ⁻¹⁰	<i>UBE4B</i>	missense	0.81	0.0	1.000
rs880315	1	10796866	C/T	37.4	1.04	1.03–1.06	5.04×10 ⁻⁰⁹	<i>CASZ1</i>	intronic	0.97	40.7	0.150	0.150
rs14651872	6	51535039	A/G	2.6	1.18	1.12–1.24	2.05×10 ⁻¹⁰	<i>C1orf185</i>	intronic	0.96	0.0	1.000	1.000
rs4484922	1	116310818	G/C	68.3	1.07	1.05–1.08	4.57×10 ⁻¹⁶	<i>CASQ2</i>	intronic	0.98	0.0	0.689	0.689
rs79187193	1	147255831	G/A	94.8	1.12	1.08–1.16	8.07×10 ⁻¹⁰	<i>GJA5</i>	upstream	0.97	39.8	0.190	0.190
rs4951261	1	205717823	C/A	38.2	1.05	1.03–1.06	1.17×10 ⁻⁰⁹	<i>NUCKS1</i>	intronic	0.99	0.0	0.788	0.788
rs6546620	2	26159940	C/T	75.3	1.07	1.05–1.09	2.96×10 ⁻¹⁴	<i>KIF3C</i>	intronic	0.95	33.0	0.201	0.201
rs6742276	2	61768745	A/G	61.2	1.05	1.03–1.06	2.42×10 ⁻¹¹	<i>XPO1</i>	upstream	0.99	0.0	0.731	0.731
rs72926475	2	86594487	G/A	87.0	1.07	1.05–1.10	3.49×10 ⁻¹⁰	<i>REEP1,KDM3A</i>	intergenic	0.97	38.7	0.180	0.180
rs56181519	2	175555714	C/T	74.0	1.08	1.06–1.10	1.52×10 ⁻¹⁹	<i>WIPF1,CHRNA1</i>	intergenic	0.94	0.0	0.519	0.519
rs295114	2	201195602	C/T	59.7	1.07	1.05–1.09	1.76×10 ⁻²⁰	<i>SPATS2L</i>	intronic	1.00	21.9	0.275	0.275
rs2306272	3	66434643	C/T	31.8	1.05	1.04–1.07	4.54×10 ⁻¹¹	<i>LRIG1</i>	missense	0.99	30.6	0.218	0.218
rs17490701	3	111587879	G/A	85.7	1.07	1.05–1.10	5.43×10 ⁻¹¹	<i>PHLDB2</i>	intronic	0.97	46.8	0.111	0.111
rs4855075	3	179170494	T/C	14.3	1.06	1.04–1.08	4.00×10 ⁻⁰⁹	<i>GNB4</i>	upstream	0.95	10.1	0.348	0.348
rs3822259	4	10118745	T/G	67.9	1.05	1.03–1.06	1.93×10 ⁻⁰⁹	<i>WDR1</i>	upstream	0.96	0.0	0.922	0.922
rs3960788	4	103915618	C/T	42.4	1.05	1.04–1.07	2.09×10 ⁻¹²	<i>SLC9B1</i>	intronic	0.98	35.7	0.183	0.183
rs55754224	4	114428714	T/C	25.0	1.05	1.03–1.07	9.25×10 ⁻⁰⁹	<i>CAMK2D</i>	intronic	0.99	0.0	0.511	0.511
rs10213171	4	148937537	G/C	8.2	1.11	1.08–1.14	6.09×10 ⁻¹⁴	<i>ARHGAP10</i>	intronic	0.96	0.0	0.584	0.584
rs174048	5	142650404	C/T	15.7	1.07	1.05–1.09	1.05×10 ⁻¹¹	<i>ARHGAP26,NR3C1</i>	intergenic	0.99	0.0	0.852	0.852
rs6882776	5	172664163	G/A	67.2	1.06	1.05–1.08	3.18×10 ⁻¹⁴	<i>NKX2-5</i>	upstream	0.95	0.0	0.858	0.858
rs73366713	6	16415751	G/A	86.2	1.11	1.09–1.14	5.80×10 ⁻²¹	<i>ATXN1</i>	intronic	0.94	0.0	0.879	0.879
rs34969716	6	18210109	A/G	31.1	1.09	1.07–1.11	2.91×10 ⁻²⁵	<i>KDM1B</i>	intronic	0.80	19.5	0.290	0.290
rs3176326	6	36647289	G/A	80.4	1.06	1.04–1.08	7.95×10 ⁻¹¹	<i>CDKN1A</i>	intronic	0.95	0.0	0.450	0.450
rs11798485	3	149399100	T/G	8.9	1.12	1.09–1.15	8.38×10 ⁻¹⁷	<i>UST</i>	downstream	0.83	56.5	0.100	0.100
rs55734480	7	14372009	A/G	26.6	1.05	1.03–1.07	7.34×10 ⁻¹⁰	<i>DGKB</i>	intronic	0.94	0.0	0.441	0.441
rs6462078	7	28413187	A/C	74.7	1.06	1.04–1.08	1.35×10 ⁻¹¹	<i>CREB5</i>	intronic	0.98	22.2	0.278	0.278

RsId	Chr	hg19	Risk/Ref Allele	RA F [%]	RR	95% CI	P _{META}	Nearest Gene(s)*	Func	imp Qua I	I ² _{HET}	P _{HET}
rs74910854	7	74110705	G/A	6.9	1.10	1.07–1.13	3.36×10 ⁻⁰⁹	<i>GTF2I</i>	intronic	0.74	24.4	0.265
rs62483627	7	106856002	A/G	23.5	1.05	1.03–1.07	5.17×10 ⁻⁰⁹	<i>COG5</i>	intronic	0.98	15.1	0.318
rs7789146	7	150661409	G/A	80.3	1.06	1.04–1.08	6.51×10 ⁻¹⁰	<i>KCNH2</i>	intronic	0.96	66.0	0.019
rs7846485	8	21803735	C/A	86.8	1.09	1.07–1.12	3.71×10 ⁻¹⁵	<i>XP07</i>	intronic	0.99	0.0	0.676
rs62521286	8	124551975	G/A	6.7	1.13	1.10–1.16	1.24×10 ⁻¹⁶	<i>FBX032</i>	intronic	0.96	0.0	0.678
rs35006907	8	125859817	A/C	32.9	1.05	1.03–1.06	2.76×10 ⁻⁰⁹	<i>MTSS1, LINC00964</i>	regulatory reg.	0.97	0.0	0.542
rs6993266	8	141762659	A/G	53.8	1.05	1.03–1.06	9.73×10 ⁻¹⁰	<i>PTK2</i>	intronic	0.99	5.7	0.374
rs4977397	9	20235004	A/G	57.0	1.04	1.03–1.06	8.60×10 ⁻⁰⁹	<i>SLC24A2, MLLT3</i>	intergenic	0.95	38.3	0.166
rs4743034	9	109632353	A/G	23.4	1.05	1.03–1.07	3.98×10 ⁻⁰⁹	<i>ZNF462</i>	intronic	1.00	0.0	0.963
rs10760361	9	127178266	G/T	64.7	1.04	1.03–1.06	7.03×10 ⁻⁰⁹	<i>PSMB7</i>	upstream	0.97	0.0	0.680
rs7919685	10	65315800	G/T	53.3	1.06	1.04–1.07	5.00×10 ⁻¹⁶	<i>REEP3</i>	intronic	1.00	49.2	0.097
rs11001667	10	77935345	G/A	22.2	1.06	1.05–1.08	1.06×10 ⁻¹¹	<i>C10orf11</i>	intronic	0.98	26.8	0.243
rs1044258	10	103605714	T/C	66.2	1.05	1.03–1.06	1.07×10 ⁻⁰⁹	<i>C10orf76</i>	3' UTR	0.98	14.0	0.325
rs1822273	11	20010513	G/A	27.1	1.07	1.05–1.09	8.99×10 ⁻¹⁷	<i>NAV2</i>	intronic	0.98	0.0	0.764
rs949078	11	121629007	C/T	27.1	1.05	1.04–1.07	4.77×10 ⁻¹¹	<i>sotli, mir100hG</i>	intergenic	0.97	0.0	0.600
rs113819537	12	26348429	C/G	74.3	1.05	1.03–1.07	2.23×10 ⁻⁰⁹	<i>SSPN</i>	upstream	0.98	0.0	0.597
rs12809354	12	32978437	C/T	14.7	1.08	1.06–1.11	5.48×10 ⁻¹⁶	<i>PKP2</i>	intronic	0.97	31.5	0.211
rs7978685	12	57103154	T/C	27.9	1.06	1.04–1.07	5.99×10 ⁻¹²	<i>NACA</i>	downstream	0.98	2.4	0.393
rs35349325	12	70097464	T/C	54.1	1.05	1.04–1.07	9.04×10 ⁻¹³	<i>BEST3</i>	upstream	0.96	0.0	0.863
rs11180703	12	76223817	G/A	56.0	1.05	1.03–1.06	3.58×10 ⁻¹⁰	<i>KRR1, PHLDA1</i>	intergenic	0.97	0.0	0.482
rs12810346	12	115091017	T/C	14.9	1.07	1.05–1.09	2.34×10 ⁻⁰⁹	<i>TBX5-AS1, TBX3</i>	intergenic	0.84	0.0	0.428
rs12298484	12	124418674	C/T	67.4	1.05	1.03–1.06	2.05×10 ⁻⁰⁹	<i>DNAH10</i>	intronic	1.00	0.0	0.973
rs9580438	13	23373406	C/T	32.5	1.06	1.04–1.07	1.01×10 ⁻¹³	<i>LINC00540, BASP1P1</i>	intergenic	0.98	0.0	0.485
rs28631169	14	23888183	T/C	19.9	1.07	1.05–1.09	3.80×10 ⁻¹⁴	<i>MYH7</i>	intronic	0.97	14.5	0.319
rs2145587	14	32981484	A/G	28.1	1.08	1.06–1.10	2.32×10 ⁻²¹	<i>AKAP6</i>	intronic	0.94	0.0	0.888
rs73241997	14	35173775	T/C	16.4	1.07	1.05–1.10	1.10×10 ⁻¹³	<i>SNX6, CFL2</i>	intergenic	0.98	62.2	0.032
rs10873299	14	77426711	A/G	38.4	1.05	1.03–1.07	9.62×10 ⁻¹¹	<i>LRRC74, IRF2BP1</i>	intergenic	0.96	4.4	0.381
rs62011291	15	63800013	G/A	22.9	1.05	1.04–1.07	6.14×10 ⁻⁰⁹	<i>USP3</i>	intronic	0.96	0.0	0.727

Rsid	Chr	hg19	Risk/Ref Allele	RAF [%]	RR	95% CI	P _{META}	Nearest Gene(s)*	Func	impQual	I ² _{HET}	P _{HET}
rs12591736	15	70454139	G/A	82.0	1.06	1.04–1.08	2.47×10 ⁻⁰⁹	<i>TLE3,UACA</i>	intergenic	0.92	0.0	0.966
rs12908004	15	80676925	G/A	15.9	1.08	1.06–1.10	1.95×10 ⁻¹⁴	<i>LINC00927,ARNY2</i>	intronic	0.96	57.4	0.052
rs12908437	15	99287375	T/C	39.2	1.05	1.03–1.06	1.25×10 ⁻¹⁰	<i>IGFIR</i>	intronic	0.98	0.0	0.818
rs2286466	16	2014283	G/A	80.9	1.07	1.05–1.09	3.53×10 ⁻¹⁴	<i>RPS2</i>	synonymous	0.92	0.0	0.882
rs8073937	17	7435040	G/A	36.6	1.05	1.04–1.07	1.02×10 ⁻¹¹	<i>POLR2A, TNFSF12</i>	intergenic	0.96	12.3	0.335
rs72811294	17	12618680	G/C	88.7	1.07	1.05–1.09	6.87×10 ⁻⁰⁹	<i>MYOCD</i>	intronic	0.95	32.3	0.206
rs242557	17	44019712	G/A	61.3	1.04	1.03–1.06	4.35×10 ⁻⁰⁹	<i>MAPT</i>	intronic	0.94	62.1	0.032
rs7219869	17	68337185	G/C	43.9	1.05	1.03–1.06	1.49×10 ⁻¹⁰	<i>KCNJ2,CASC17</i>	intergenic	0.99	16.1	0.312
rs9953366	18	46474192	C/T	65.5	1.05	1.04–1.07	9.03×10 ⁻¹¹	<i>SMAD7</i>	intronic	0.93	0.0	0.565
rs2145274	20	6572014	A/C	91.3	1.11	1.08–1.14	6.97×10 ⁻¹³	<i>CASC20,BMP2</i>	regulatory reg.	0.96	19.0	0.295
rs7269123	20	61157939	C/T	58.5	1.05	1.03–1.06	5.59×10 ⁻⁰⁹	<i>C20orf166</i>	intronic	0.85	68.7	0.012
rs2834618	21	36119111	T/G	89.8	1.12	1.09–1.14	2.93×10 ⁻¹⁸	<i>LOC100506385</i>	intronic	0.93	21.6	0.277
rs465276	22	18600583	G/A	61.5	1.05	1.04–1.07	1.84×10 ⁻¹¹	<i>TUBA8</i>	intronic	0.90	0.0	0.654

Sentinel variants at novel genetic loci associated with AF at a significance level of $P < 1 \times 10^{-8}$, for the combined-ancestry meta-analysis ($n=588,190$). The significance level accounts for multiple testing of independent variants with MAF $>0.1\%$ using a Bonferroni correction. P_{META} (two-sided) was derived from a meta-analysis using a fixed effects model with an inverse-variance weighted approach. P_{HET} was derived from a Cochran's Q-test (two-sided) for heterogeneity. Abbreviations, Chr, chromosome, CI, confidence interval, Func, functional consequence (most severe consequence by variant effect predictor), HET, heterogeneity, I², I-square, impQual, average imputation quality, META, metaanalysis, P, P-value, RAF, risk allele frequency, reg, region, Ref, reference, RR, relative risk.

* Reported is either the gene that overlaps with the sentinel variant, or the nearest gene(s) up- and downstream of the sentinel variant (separated by comma).