民族横断的な心房細動ゲノム解析による新たな疾患メカニズムの解明と遺伝子リスクスコアによる心原性脳梗塞の予測

＜背景＞
心房細動は最も一般的な不整脈であり，脳梗塞や心不全といった致死的な疾患に繋がる可能性がある．最近発表されたゲノムワイド関連解析（GWAS）や遺伝子リスクスコア（PRS）は心房細動に多くの知見をもたらしてきたが，これらの研究の大半が欧米人で行われたものである．
＜方法＞
我々は，9,826 人の心房細動患者と 150,272 人の対照群を用いて，GWAS を行なった．そして，77,690 人の心房細動患者を含んだ，計 100 万人を超える大規模な民族横断的メタ解析を行なった．さらに，トランスクリプトームデータやエピゲノムデータとの統合解析を行うことにより，心房細動発症に関わる感受性座位の生物学的効果を検証した．また，民族横断的メタ解析から心房細動の遺伝子リスクスコアを導出し，心房細動に関連する疾患や臨床パラメーター，長期死亡率に対する影響を評価した．
＜結果＞
日本人 GWAS において，心房細動に関連する 5 つの新規遺伝子座を同定した．そのうちの 2 つは，日本人を含む東アジア人のみで認められるレアバリアントであった．民族横断的メタ解析において，33 個の新規心房細動関連遺伝子座を特定し，日本人 GWAS と合わせて合計 35 個の新規遺伝子座の発見となった．トランスクリプトームデータやエピゲノムデータとの統合解析により，*IL6R* や転写因子である ESRRG との関連が新たに示された．民族横断的メタ解析から得られた心房細動の遺伝子リスクスコアは，脳梗塞発症リスクだけでなく，心血管死のリスク上昇と有意に関連していた．
＜結語＞
日本人集団による大規模な GWAS と民族横断的メタ解析により，我々は心房細動の遺伝的基盤を解明した．心房細動の遺伝子リスクスコアは個人のリスク層別化の可能性を示し，精密医療の実現に向けた足掛かりとなるだろう．

※，※※　　※※　　※※　　※※※　　※
松永　紘　　伊藤　薫*　　宮澤　一雄　　鄒　兆南　　野村征太郎
※※※※　　※※※※※　　※※※　　※　　※
桃沢　幸秀　　寺尾知可史　　沖　真弥　　赤澤　宏　　小室　一成*

※東京大学大学院医学系研究科
循環器内科学
※※理化学研究所 生命医科学研究センター
循環器ゲノミクス・インフォマティクス
研究チーム
※※※京都大学大学院医学研究科 創薬医学講座
※※※※理化学研究所 生命医科学研究センター
基盤技術開発研究チーム
※※※※※理化学研究所 生命医科学研究センター
ゲノム解析応用研究チーム

民族横断的な心房細動ゲノム解析による新たな疾患メカニズムの解明と遺伝子リスクスコアによる心原性脳梗塞の予測

TRANS-ANCESTRY GENOME-WIDE ANALYSIS OF ATRIAL FIBRILLATION PROVIDES NEW INSIGHTS INTO DISEASE BIOLOGY AND ENABLES POLYGENIC PREDICTION OF CARDIOEMBOLIC RISK

※, ※※ ※※ ※※ ※※※ ※
Hiroshi MATSUNAGA, Kaoru ITO *, Kazuo MIYAZAWA, Zhaonan ZOU, Seitaro NOMURA1,
※※※※ ※※※※※ ※※※ ※ ※
Yukihide MOMOZAWA, Chikashi TERAO, Shinya OKI, Hiroshi AKAZAWA, Issei KOMURO *

※ Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
※※ Laboratory for Cardiovascular Genomics and Informatics, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan
※※※ Department of Drug Discovery Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan
※※※※ Laboratory for Genotyping Development, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan
※※※※※ Laboratory for Statistical and Translational Genetics, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan

Corresponding author: Kaoru Ito (1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama, Kanagawa 230-0045, Japan, email: kaoru.ito@riken.jp, Telephone +81-45-503-9347, FAX +81-45-503-9346) and Issei Komuro (7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan, email: komuro-tky@umin.ac.jp, Telephone +81-3-5800-6526, FAX +81-3-3815-2087)

Abstract

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia, which is potentially life-threatening such as stroke and heart failure. Recent genome-wide association studies (GWASs) and polygenic risk scores (PRSs) have provided many insights into AF, but the vast majority of these studies have been predominantly performed in European populations.

Methods

We performed a genome-wide association study (GWAS) for AF in the Japanese population, which included 9,826 cases and 150,272 controls. Then, we conducted a trans-ancestry meta-analysis of > 1 million individuals, which including 77,690 cases. Further, we investigated the biological role of the identified AF-associated loci by leveraging gene expression and epigenomic datasets. Additionally, we developed a PRS derived from the trans-ancestry meta-analysis and assessed the impact of the PRS on relevant phenotypes and long-term mortality.

Results

We identified five new susceptibility loci in the Japanese GWAS, including East Asian-specific rare variants. In the trans-ancestry meta-analysis, we found 33 novel loci, bringing the total number of new loci to 35. Leveraging gene expression and epigenomic datasets to prioritize putative causal genes and their transcription factors revealed the involvement of *IL6R* gene and transcription factor ESRRG besides the known ones. Further, a trans-ancestry PRS was associated with an increased risk of long-term cardiovascular and stroke mortality, and segregated individuals with cardioembolic stroke in undiagnosed AF patients.

Conclusions

In our large-scale Japanese and trans-ancestry genetic analyses, we showed the genetic underpinnings of AF. Our findings suggest the clinical utility of AF-PRS for individual risk stratification, leading to the realization of future precision medicine.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting approximately 46.3 million individuals worldwide[1]. The global prevalence of AF is increasing due to the rapid aging of the general population and intensified search for subclinical AF[2]. Despite progress in diagnostic and therapeutic technologies, a substantial number of patients with AF are admitted with life-threatening complications such as stroke and heart failure[3], causing a considerable burden on patients and public healthcare systems[4]. Besides conventional clinical risk factors such as ageing, obesity, hypertension, and heart failure, the genetic contribution to the development of AF is also widely recognized. Recent genome-wide association studies (GWASs) have identified more than 100 AF-associated loci, some of which are involved in cardiac developmental, electrophysiological, contractile, and structural pathways[5–8]. However, since the vast majority of AF-GWASs have been predominantly performed in European populations, the genetic pathophysiology of AF in non-European populations has not been comprehensively understood and it is difficult to apply polygenic risk scores (PRSs) derived from such GWASs to non-European populations.

Therefore, in the present study, we sought to explore the genetic architecture of AF in a non-European population and improve the statistical power of AF-GWASs by performing a large-scale Japanese GWAS, followed by conducting a trans-ancestry meta-analysis. Further, we investigated the biological role of the identified AF-associated loci by leveraging gene expression and epigenomic datasets. Additionally, we developed a PRS derived from the trans-ancestry meta-analysis and assessed the impact of the PRS on relevant phenotypes and long-term mortality, which may provide evidence for the clinical utility of AF-PRS and lay the foundation for the realization of precision medicine in AF.

Methods

Study populations

All subjects were Japanese who were registered in the BioBank Japan (BBJ) project (https://biobankjp.org/). The BBJ is a hospital-based national biobank project that collects DNA and serum samples and clinical information from 12 cooperative medical institutes throughout Japan (Osaka Medical Center for Cancer and Cardiovascular Diseases, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Juntendo University, Tokyo Metropolitan Geriatric Hospital, Nippon Medical School, Nihon University School of Medicine, Iwate Medical University, Tokushukai Hospitals, Shiga University of Medical Science, Fukujuji Hospital, National Hospital Organization Osaka National Hospital, and Iizuka Hospital). Approximately 200,000 patients with any of the 47 target diseases were enrolled between 2003 and 2007. All samples were at least 18 years old. Informed consent was obtained from all participants, and our study was approved by the relevant ethical committees at each facility.

For the quality control of GWAS, we excluded samples with a call rate < 0.98 and related individuals with PI_HAT > 0.2, which is an index of relatedness based on pairwise identity-by-descent implemented in PLINK 2.0 (20 Aug 2018 ver.). We then excluded samples with a heterozygosity rate > +4 s.d. To identify population stratification, we performed principal component analysis using PLINK 2.0. and excluded outliers from the Japanese cluster. For the case samples in GWAS, we selected individuals with atrial fibrillation or atrial flutter diagnosed by a physician based on general medical practices or documented on a 12-lead electrocardiogram. The demographic features of the case–control cohort are shown in Supplementary Table 1.

Supplementary Table 1 | Demographic features in the Japanese GWAS

Status	Total	Males	Age		Age of AF onset		HTN	BMI		DM	MI	HF
		n (%)	Mean	SD	Mean	SD	n (%)	Mean	SD	n (%)	n (%)	n (%)
Case	9,826	6,825 (69.459)	68.549	62.448	63.082	13.201	2,597 (26.430)	23.382	3.521	1,626 (16.548)	661 (6.727)	1,891 (19.245)
Control	140,446	7,4225 (52.849)	10.460	14.152	NA	NA	27,951 (19.902)	23.282	3.682	29,777 (21.202)	9,540 (6.793)	3,812 (2.714)

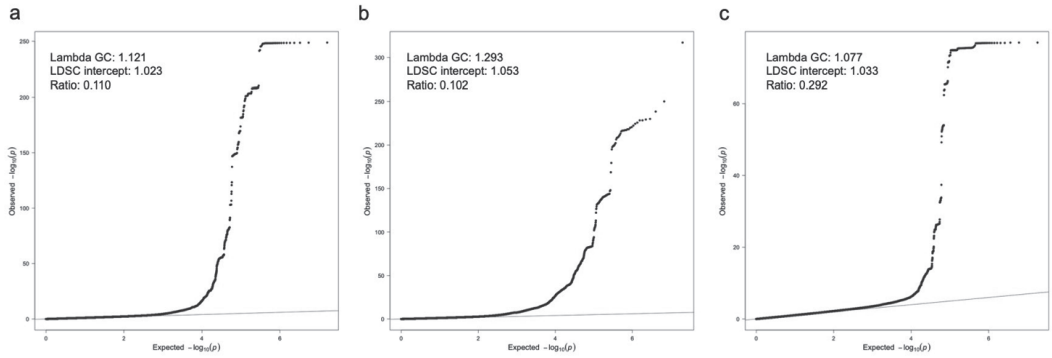
GWAS, genome-wide association study; AF, atrial fibrillation; HTN, hypertension; BMI, body mass index; DM diabetes mellitus; MI, myocardial infarction; HF heart failure; HF, heart failure; SD, standard deviation

Genotyping, imputation, and quality control

GWAS subjects were genotyped using the Illumina Human OmniExpress Genotyping BeadChip or a combination of Illumina HumanOmniExpress and HumanExome BeadChips (Illumina, San Diego, CA). For genotype quality control, we excluded variants with (i) SNP call rate < 0.99, (ii) MAF < 0.01, and (iii) Hardy–Weinberg equilibrium P value ≤ 1.0×10^{-6}. We pre-phased the genotypes using EAGLE and imputed dosages with the 1,000 Genome Project Phase 3 (1KG Phase 3; May 2012)[9] reference panel with 1,037 Japanese in-house reference panel from BBJ using minimac3. For the X chromosome, pre-phasing was performed in both males and females, and imputation was performed separately for males and females. Dosages of variants in X chromosomes for males were assigned between 0 and 2.

GWAS

In the Japanese GWAS, association was performed by logistic regression analysis assuming an additive model with adjustment for age, age^2, sex, and top 20 principal components using PLINK 2.0. We selected variants with minimac3 imputation quality score of > 0.3 and MAF ≥ 0.001. For the X chromosome, we conducted association analyses in males and females separately, and integrated the results using an inverse-variance weighted fixed-effects model implemented in METASOFT (v2.0.1). Heterogeneity between studies was calculated using the Cochran's Q test. We filtered variants with strong heterogeneity (P_{het}<1.0×10^{-4}). The genome-wide significance threshold was defined at P<5.0×10^{-8} for variants with MAF≥1% and P<5.71×10^{-9} for those with MAF<1% (0.05/8,753,038 variants). Although the genomic inflation factor (λ_{GC}) was 1.12, LD-score regression indicated that the inflation was primarily due to polygenic effects (LD-score regression intercept=1.02; Supplementary Fig. 1a). Adjacent genome-wide significant SNPs were grouped into one locus if they were within 1 Mb from each other. We defined a locus as the candidate region that was located within 500 Mb upstream and downstream



Supplementary Fig. 1 | Quantile-quantile plot for GWAS of three studies.
a, the Japanese GWAS. b, GWAS of a meta-analysis in European population (EUR).
c, GWAS in data from FinnGen project (FIN). GWAS, genome-wide association study.

of the genome-wide significant variants. When a locus was not in LD (r^2<0.10) with reported loci, we defined it as a novel locus. In sex-stratified association analysis of 81,050 males (6,825 cases and 74,225 controls) and 69,222 females (3,001 cases and 66,221 controls), we also performed logistic regression analysis in males and females separately using the same pipeline as described above. To investigate the difference in genetic susceptibility to AF between males and females, we compared effect sizes of the variants identified in the sex-stratified GWAS. Genotyped or imputed variants were annotated using ANNOVAR (7 July 2017 build) (http://annovar.openbioinformatics.org).

Stepwise conditional analysis

To identify independent association signals in the loci, we conducted a stepwise conditional analysis for genome-wide significant loci defined as described in the GWAS. First, we performed logistic regression conditioning on the lead variants of each locus. We set a locus-wide significance at $P<1.0\times10^{-5}$ and repeated this procedure until none of the variants reached locus-wide significance for each locus.

LD score regression and heritability

To estimate confounding biases such as cryptic relatedness and population stratification, we performed an LD score regression (Version 1.0.0). We selected SNPs with MAF≥0.01, and variants within the major histocompatibility complex region were excluded. For the regression, we used the East Asian LD scores provided by the authors (https://github.com/bulik/ldsc/).

Trans-ancestry meta-analysis

Summary results from two European AF GWASs (EUR and FIN) were obtained from a previously published website (http://csg.sph.umich.edu/willer/public/afib2018)[7] and from the FinnGen research project website (https://www.finngen.fi/en), respectively. EUR is a meta-analysis of six contributing AF data sources (The Nord-Trøndelag Health Study, deCODE, the Michigan Genomics Initiative, DiscovEHR, UK Biobank, and the AFGen Consortium). FIN is composed of 102,739 Finnish participants, and the phenotypes were derived from ICD codes in Finnish national hospital registries and cause-of-death registry as a part of the FinnGen project. To inspect the biases of these GWAS, we calculated the LD-score regression intercept for each study and confirmed that these two studies were well calibrated (LD score regression intercept for EUR=1.052 (s.e.m.=0.012) and FIN=1.033 (s.e.m.=0.010); Supplementary Fig. 1b, c). We also calculated the genetic correlation and found a significant genetic correlation between EUR and FIN (r_g=0.918, s.e.m.=0.035, $P=3.9\times10^{-155}$).

To account for the ancestral heterogeneity among the three studies, we applied the MANTRA algorithm in the trans-ancestry meta-analysis[10], which

allows for heterogeneity between diverse ancestry groups and improves performance compared to fixed-effects meta-analysis and random-effects meta-analysis. Variants with MAF≥1% in both the Japanese and European populations were selected for association. We considered SNPs with $\log_{10}$ BF>6 to be genome-wide significant.

Trans-ancestry genetic correlation

To estimate the trans-ancestry genetic correlation, we applied Popcorn software (v.1.0). We used East Asia or European samples of 1KG for the LD reference and excluded the variants within the major histocompatibility complex region according to the instructions of the software. To estimate the liability-scale genetic correlation, we assumed that the AF prevalence was 0.58% in the Japanese population, 1.38% in the United Kingdom population, and 0.97% in the Finnish population (https://vizhub.healthdata.org/gbd-compare/).

Credible set analysis

To construct sets of variants that likely include causal variants, we constructed a 99% credible set in each AF-associated locus using BF obtained from MANTRA results in the trans-ancestry meta-analysis. For each locus, we calculated the posterior probability (PP) for the j^{th} SNP using the following formula: $PPj = \frac{BF_j}{\sum_k BF_k}$, where BFj denotes the BF for the j^{th} SNP and BF_k denotes all of the variants included in the locus. We then constructed the 99% credible set by adding the variants in order of decreasing PP until the cumulative PP reached 0.99. To assess whether the 99% credible set derived from the trans-ancestry meta-analysis narrowed down the causal variants, we performed two additional meta-analyses (EUR + BBJ and EUR + FIN) using the MANTRA algorithm and constructed 99% credible sets for 150 AF-associated loci identified by the trans- ancestry meta-analysis. We then compared the number of variants in the 99% credible set for each locus. Among them, the loci where at least one variant surpassed genome-wide significance ($\log_{10}$ BF>6) in all meta-analyses were included in the test. The differences in the sizes of the credible sets were tested using the paired Wilcoxon rank-sum test.

Pleiotropy

We searched for AF-associated variants that overlapped with other diseases or traits using the NHGRI-EBI GWAS catalog on February 8, 2019. As reported previously[11], we selected the AF-associated variants in the trans-ancestry meta-analysis according to the following criteria: (i) variants with r^2>0.5 in both East Asian and European samples of 1KG if the publication in GWAS catalog included East Asians, (ii) variants with r^2>0.5 in European samples of 1KG if the original report did not study East Asian populations; and (iii) the physical distance from AF-associated lead variants in the trans-ancestry meta-analysis to variants reported in the GWAS catalog was within 25 kb. For the association analysis between AF-associated loci and QTL for clinical parameters, we used the summary statistics previously reported in the BBJ dataset[11~13]. We selected AF-associated variants (r^2>0.6 in East Asian samples of 1KG and clinical parameters of nine distinct categories: anthropometric (n=2), metabolic (n=6), serum protein (n=2), kidney-related (n=4), electrolyte (n=3), liver-related (n=5), other biochemical (n=5), hematological (n=5), and blood pressure (n=4). In QTL analysis, clinical measurements were corrected by taking into account the effect of medications as follows: for individuals taking cholesterol-lowering drugs, total cholesterol and low-density-lipoprotein cholesterol levels were corrected by dividing by 0.8 and 0.7, respectively[12]; for individuals taking antihypertensive drugs, 15 mmHg was added to the systolic blood pressure and 10 mmHg to the diastolic blood pressure readings[12]. Furthermore, linear regression models for these quantitative traits were adjusted for sex, age, age^2, the top 10 principal components, and disease status. Smoking status was also introduced into the model for white blood cell count and C-reactive protein levels. We chose QTL showing a genome-wide significant association (P<5.0×10^{-8}).

Tissue and gene set enrichment analysis

For tissue and gene set enrichment analysis, we used data-driven expression-prioritized integration for complex traits (DEPICT) software (https://data.broadinstitute.org/mpg/depict)[14]. To reduce the redundancy of the pathways, we applied affinity propagation clustering implemented in the apcluster package v.1.4.8 in R[15,16]. Using this algorithm, we obtained distinct clusters that contained 'exemplar' pathway and member pathways. We extracted 48 exemplar tissues and 1,157 gene sets for enrichment analysis and selected independent AF-associated variants with $\log_{10}$ BF>5 as applied in a previous study[17]. The significance level was set at $P=1\times10^{-3}$ (=0.05/48) for tissue enrichment analysis and $P=4.3\times10^{-5}$ (=0.05/1,157) for gene set enrichment analysis.

Transcriptome-wide association study

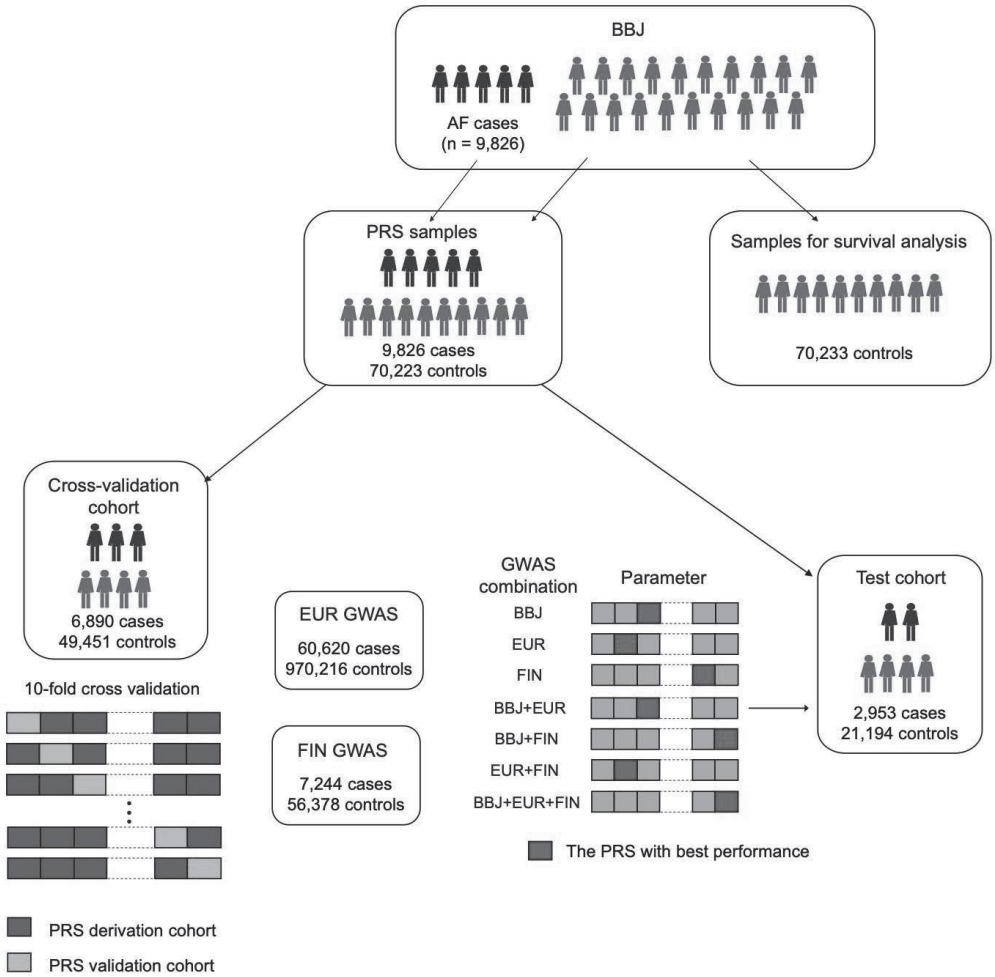
We performed a transcriptome-wide association study to assess gene-AF associations using MetaXcan v0.3.512[18], which estimates the association between predicted gene expression levels and a phenotype of interest using summary statistics and gene expression prediction models. We used precomputed prediction models with LD reference data in GTEx v7 for atrial appendage and left ventricular tissues and the summary statistic of the trans-ancestry AF-GWAS as input. Bonferroni significance level was set at $P=8.4\times10^{-6}$ (=0.05/5,988) for atrial appendage and $P=9.3\times10^{-6}$ (=0.05/5,378) for left ventricle to account for the number of genes tested in each tissue.

Enrichment analysis of transcription factor

To assess the enrichment of transcription factor in AF-associated loci, we defined AF-associated loci as regions within 500 Mb upstream and 500 Mb downstream of the AF-associated lead variants or proxies with $r^2>0.8$ in European samples of 1KG. We then searched for overlaps of peak-call data archived in the ChIP-Atlas dataset with AF-associated loci and control regions selected from all the genome regions by permutation test. *P*-values were calculated with the two-tailed Fisher's exact probability test (the null hypothesis is that the two regions overlap with the ChIP-Atlas peak-call data in the same proportion). The epigenetic landscapes around cardiac ion channel-related genes were visualized using ChIP-Atlas Peak Browser and Integrative Genomics Viewer[19].

PRS derivation and performance

We derived PRS using the pruning and thresholding methods. PRSs were created over a range of *P* value threshold (0.5, 5.0×10^{-2}, 5.0×10^{-4}, 5.0×10^{-6}, and 5.0×10^{-8}) and r^2 threshold (0.2, 0.5, and 0.8). For the survival analysis, we divided our dataset into three groups: (i) a discovery group to derive and validate PRS (6,890 cases and 49,451 controls), (ii) a test group to assess PRS performance (2,953 cases and 21,194 controls), and (iii) a group for the survival analysis (70,645 controls) (Supplementary Fig. 2). To secure independence between the PRS derivation and validation, we used a ten-fold cross-validation approach. First, we randomly split a discovery group into ten subgroups and used nine of these subgroups for PRS derivation and the remaining one for PRS validation. To determine the weight of PRS, we performed GWAS in combination with two European GWAS: (i) Japanese subgroup GWAS, (ii) two European GWAS (EUR or FIN), (iii) Japanese subgroup GWAS + EUR (fixed- or random-effect model), (iv) Japanese subgroup GWAS + FIN (fixed- or random-effect model), (v) EUR + FIN (fixed- or random-effect model, and (vi) Japanese subgroup GWAS + EUR + FIN (fixed- or random-effect model). Meta-analyses were performed using the METASOFT software. In the meta-analysis with the Japanese subgroup GWAS, LD was calculated separately based on East Asian or European samples of 1KG. We then calculated the PRSs for the withheld validation cohort using PLINK 2.0 and validated its performance. Changing the withheld validation cohort, we repeated these procedures ten times and obtained the performance measurements for each combination. Notably, the validation cohort was excluded from the derivation of GWAS. The performance of the PRS was



Supplementary Fig. 2 | Analytical scheme for PRS derivation, validation, and test cohorts and survival analysis. Schematic representation for cross-validation, performance testing of the AF-PRS in the independent test cohort, and survival analysis for AF-PRS. PRS, polygenic risk score; AF, atrial fibrillation.

measured as (1) Nagelkerke's pseudo R^2 obtained by modeling age, sex, and normalized PRS, and (2) the area under the curve of the receiver operator curve in the same model as Nagelkerke's pseudo R^2. The best model/parameter set for each combination model (BBJ, EUR, FIN, BBJ + EUR, BBJ + FIN, EUR + FIN, BBJ + EUR + FIN) was determined by averaging Nagelkerke's pseudo R^2 (Supplementary Table 2). Using the best models and parameters determined in the derivation and validation cohorts, we calculated the PRSs and assessed their performance for the independent test cohort. We applied bootstrapping to assess the distribution of performance of the PRS; randomly extracted the individuals in the test cohort with replacement and calculated the performance for the samples. By repeating this procedure 5.0×10^4 times, we estimated the distribution of the performance measures.

Association of AF-PRS with age of AF onset and stroke subtypes

To assess the association between AF-PRS and age at AF onset, we extracted AF case samples with the data (n=7,458, median age of AF onset was 63 years of age (IQR 56–71)), and estimated the difference

Supplementary Table 2 | The performance of AF-PRS in the cross-validation cohort

Summary statistics	Parameter				Median number	Performance	
	LD reference	P	r2	Effect model	of variants	Pseudo R2	AUCROC
BBJ	EAS	5.0.E-06	0.2	NA	130	0.12	0.72
BBJ	EAS	5.0.E-04	0.8	NA	1,985	0.12	0.72
BBJ	EAS	5.0.E-04	0.5	NA	1,374	0.12	0.72
BBJ	EAS	5.0.E-06	0.5	NA	206	0.12	0.72
BBJ	EAS	5.0.E-08	0.2	NA	65	0.12	0.72
BBJ	EAS	5.0.E-06	0.8	NA	350	0.12	0.72
BBJ	EAS	5.0.E-08	0.5	NA	111	0.12	0.72
BBJ	EAS	5.0.E-04	0.2	NA	1,070	0.12	0.72
BBJ	EAS	5.0.E-08	0.8	NA	205	0.11	0.71
BBJ	EAS	5.0.E-02	0.8	NA	86,953	0.10	0.70
BBJ	EAS	5.0.E-02	0.5	NA	63,015	0.09	0.69
BBJ	EAS	5.0.E-02	0.2	NA	46,787	0.09	0.69
BBJ	EAS	5.0.E-01	0.8	NA	739,368	0.09	0.69
BBJ	EAS	5.0.E-01	0.5	NA	494,448	0.08	0.68
BBJ	EAS	5.0.E-01	0.2	NA	305,173	0.08	0.68
EUR	EUR	5.0.E-06	0.5	NA	1,333	0.13	0.72
EUR	EUR	5.0.E-08	0.5	NA	668	0.12	0.72
EUR	EUR	5.0.E-06	0.8	NA	2,363	0.12	0.72
EUR	EUR	5.0.E-08	0.2	NA	364	0.12	0.72
EUR	EUR	5.0.E-06	0.2	NA	750	0.12	0.72
EUR	EUR	5.0.E-08	0.8	NA	1,196	0.12	0.71
EUR	EUR	5.0.E-04	0.2	NA	3,671	0.11	0.71
EUR	EUR	5.0.E-04	0.5	NA	5,479	0.10	0.70
EUR	EUR	5.0.E-04	0.8	NA	8,597	0.10	0.69
EUR	EUR	5.0.E-02	0.2	NA	81,351	0.08	0.68
EUR	EUR	5.0.E-02	0.5	NA	116,610	0.08	0.68
EUR	EUR	5.0.E-02	0.8	NA	166,235	0.08	0.68
EUR	EUR	5.0.E-01	0.2	NA	406,522	0.08	0.67
EUR	EUR	5.0.E-01	0.8	NA	1,104,286	0.07	0.66
EUR	EUR	5.0.E-01	0.5	NA	713,565	0.07	0.66
FIN	EUR	5.0.E-06	0.8	NA	248	0.11	0.70
FIN	EUR	5.0.E-08	0.8	NA	104	0.10	0.70
FIN	EUR	5.0.E-06	0.5	NA	161	0.10	0.70
FIN	EUR	5.0.E-08	0.5	NA	68	0.10	0.70
FIN	EUR	5.0.E-06	0.2	NA	111	0.10	0.70
FIN	EUR	5.0.E-08	0.2	NA	41	0.10	0.69
FIN	EUR	5.0.E-04	0.8	NA	2,313	0.09	0.69
FIN	EUR	5.0.E-04	0.5	NA	1,651	0.09	0.69
FIN	EUR	5.0.E-04	0.2	NA	1,288	0.08	0.68
FIN	EUR	5.0.E-02	0.8	NA	106,221	0.08	0.67
FIN	EUR	5.0.E-02	0.5	NA	76,300	0.08	0.67
FIN	EUR	5.0.E-02	0.2	NA	54,875	0.07	0.67
FIN	EUR	5.0.E-01	0.2	NA	334,891	0.07	0.67
FIN	EUR	5.0.E-01	0.5	NA	577,575	0.07	0.67
FIN	EUR	5.0.E-01	0.8	NA	881,894	0.07	0.67
BBJ/EUR	EUR	5.0.E-04	0.5	fixed	4,032	0.15	0.74
BBJ/EUR	EAS	5.0.E-04	0.5	fixed	4,380	0.14	0.73
BBJ/EUR	EUR	5.0.E-04	0.8	fixed	6,784	0.14	0.73
BBJ/EUR	EAS	5.0.E-04	0.2	fixed	2,984	0.14	0.73
BBJ/EUR	EUR	5.0.E-06	0.5	fixed	1,118	0.14	0.73
BBJ/EUR	EUR	5.0.E-04	0.2	fixed	2,617	0.14	0.73
BBJ/EUR	EAS	5.0.E-04	0.8	fixed	6,784	0.14	0.73
BBJ/EUR	EAS	5.0.E-06	0.2	fixed	745	0.14	0.73
BBJ/EUR	EAS	5.0.E-06	0.5	fixed	1,214	0.13	0.73
BBJ/EUR	EUR	5.0.E-02	0.8	fixed	95,388	0.13	0.73
BBJ/EUR	EAS	5.0.E-02	0.8	random	70,119	0.13	0.73
BBJ/EUR	EUR	5.0.E-06	0.2	fixed	647	0.13	0.73
BBJ/EUR	EAS	5.0.E-02	0.8	fixed	94,503	0.13	0.73
BBJ/EUR	EAS	5.0.E-04	0.8	random	4,514	0.13	0.73
BBJ/EUR	EUR	5.0.E-04	0.5	random	2,874	0.13	0.73
BBJ/EUR	EAS	5.0.E-04	0.5	random	3,091	0.13	0.73
BBJ/EUR	EUR	5.0.E-02	0.5	fixed	62,961	0.13	0.72
BBJ/EUR	EUR	5.0.E-08	0.5	fixed	1,053	0.13	0.73
BBJ/EUR	EAS	5.0.E-08	0.2	fixed	372	0.13	0.73
BBJ/EUR	EUR	5.0.E-06	0.8	fixed	2,013	0.13	0.72
BBJ/EUR	EUR	5.0.E-02	0.8	random	71,155	0.13	0.73
BBJ/EUR	EUR	5.0.E-08	0.2	fixed	316	0.13	0.72
BBJ/EUR	EUR	5.0.E-04	0.8	random	4,451	0.13	0.72
BBJ/EUR	EAS	5.0.E-02	0.5	random	49,287	0.13	0.72
BBJ/EUR	EAS	5.0.E-08	0.5	fixed	614	0.13	0.72
BBJ/EUR	EAS	5.0.E-02	0.5	fixed	64,151	0.13	0.72
BBJ/EUR	EAS	5.0.E-06	0.8	fixed	2,063	0.13	0.72
BBJ/EUR	EUR	5.0.E-08	0.8	fixed	1,053	0.13	0.72
BBJ/EUR	EUR	5.0.E-02	0.5	random	48,751	0.13	0.72
BBJ/EUR	EUR	5.0.E-06	0.5	random	711	0.12	0.72
BBJ/EUR	EAS	5.0.E-06	0.2	random	523	0.12	0.72
BBJ/EUR	EAS	5.0.E-04	0.2	random	2,231	0.12	0.72
BBJ/EUR	EAS	5.0.E-06	0.5	random	776	0.12	0.72
BBJ/EUR	EUR	5.0.E-04	0.2	random	1,992	0.12	0.72
BBJ/EUR	EAS	5.0.E-06	0.8	random	1,232	0.12	0.72
BBJ/EUR	EAS	5.0.E-08	0.8	fixed	1,089	0.12	0.72
BBJ/EUR	EAS	5.0.E-01	0.8	fixed	526,944	0.12	0.71
BBJ/EUR	EUR	5.0.E-02	0.2	fixed	41,575	0.12	0.72
BBJ/EUR	EAS	5.0.E-02	0.2	fixed	43,393	0.12	0.71
BBJ/EUR	EUR	5.0.E-06	0.8	random	1,207	0.12	0.72
BBJ/EUR	EUR	5.0.E-06	0.2	random	453	0.12	0.72
BBJ/EUR	EAS	5.0.E-08	0.2	random	244	0.12	0.71
BBJ/EUR	EAS	5.0.E-01	0.8	random	483,579	0.12	0.71
BBJ/EUR	EUR	5.0.E-01	0.8	fixed	565,455	0.12	0.71
BBJ/EUR	EUR	5.0.E-01	0.8	random	523,419	0.12	0.71
BBJ/EUR	EAS	5.0.E-02	0.2	random	34,904	0.11	0.71
BBJ/EUR	EUR	5.0.E-01	0.5	fixed	340,642	0.11	0.71
BBJ/EUR	EAS	5.0.E-08	0.8	random	605	0.11	0.71
BBJ/EUR	EAS	5.0.E-01	0.5	fixed	312,689	0.11	0.71
BBJ/EUR	EAS	5.0.E-08	0.2	random	207	0.11	0.71
BBJ/EUR	EUR	5.0.E-02	0.2	random	33,637	0.11	0.71
BBJ/EUR	EAS	5.0.E-01	0.5	random	291,939	0.11	0.71
BBJ/EUR	EUR	5.0.E-01	0.5	random	319,698	0.11	0.71
BBJ/EUR	EAS	5.0.E-08	0.5	random	368	0.11	0.71
BBJ/EUR	EUR	5.0.E-08	0.5	random	338	0.11	0.71
BBJ/EUR	EAS	5.0.E-01	0.2	fixed	167,187	0.11	0.70
BBJ/EUR	EUR	5.0.E-01	0.2	fixed	179,989	0.11	0.70
BBJ/EUR	EUR	5.0.E-08	0.8	random	580	0.11	0.71
BBJ/EUR	EUR	5.0.E-01	0.2	random	171,908	0.11	0.70
BBJ/EUR	EAS	5.0.E-01	0.2	random	159,328	0.10	0.70
BBJ/FIN	EAS	5.0.E-06	0.2	fixed	145	0.14	0.73
BBJ/FIN	EAS	5.0.E-04	0.8	fixed	2,064	0.13	0.73
BBJ/FIN	EAS	5.0.E-08	0.2	fixed	65	0.13	0.73
BBJ/FIN	EAS	5.0.E-04	0.5	fixed	1,411	0.13	0.73
BBJ/FIN	EUR	5.0.E-04	0.8	fixed	2,158	0.13	0.73
BBJ/FIN	EAS	5.0.E-06	0.5	fixed	231	0.13	0.73
BBJ/FIN	EUR	5.0.E-04	0.5	fixed	1,478	0.13	0.73
BBJ/FIN	EUR	5.0.E-06	0.5	fixed	248	0.13	0.72
BBJ/FIN	EUR	5.0.E-06	0.8	fixed	410	0.13	0.72
BBJ/FIN	EUR	5.0.E-06	0.2	fixed	157	0.13	0.72
BBJ/FIN	EAS	5.0.E-06	0.8	fixed	396	0.13	0.72
BBJ/FIN	EAS	5.0.E-04	0.2	fixed	1,053	0.13	0.72
BBJ/FIN	EUR	5.0.E-04	0.2	fixed	1,083	0.13	0.72
BBJ/FIN	EUR	5.0.E-08	0.2	fixed	68	0.13	0.72
BBJ/FIN	EAS	5.0.E-08	0.5	fixed	113	0.13	0.72
BBJ/FIN	EAS	5.0.E-04	0.8	random	1,376	0.12	0.72
BBJ/FIN	EAS	5.0.E-04	0.5	random	988	0.12	0.72
BBJ/FIN	EUR	5.0.E-08	0.8	fixed	189	0.12	0.72
BBJ/FIN	EUR	5.0.E-08	0.5	fixed	113	0.12	0.72
BBJ/FIN	EAS	5.0.E-08	0.8	fixed	197	0.12	0.72
BBJ/FIN	EAS	5.0.E-06	0.2	random	96	0.12	0.72
BBJ/FIN	EAS	5.0.E-06	0.5	random	138	0.12	0.72
BBJ/FIN	EUR	5.0.E-04	0.8	random	1,428	0.12	0.72
BBJ/FIN	EUR	5.0.E-06	0.2	random	93	0.12	0.72
BBJ/FIN	EUR	5.0.E-06	0.5	random	139	0.12	0.71
BBJ/FIN	EUR	5.0.E-04	0.5	random	1,014	0.12	0.72
BBJ/FIN	EUR	5.0.E-06	0.8	random	229	0.12	0.71
BBJ/FIN	EAS	5.0.E-06	0.8	random	225	0.12	0.71
BBJ/FIN	EUR	5.0.E-04	0.2	random	787	0.12	0.71
BBJ/FIN	EAS	5.0.E-04	0.2	random	772	0.12	0.71
BBJ/FIN	EAS	5.0.E-08	0.2	random	40	0.12	0.71
BBJ/FIN	EAS	5.0.E-08	0.5	random	58	0.12	0.71
BBJ/FIN	EUR	5.0.E-08	0.5	random	50	0.11	0.71
BBJ/FIN	EUR	5.0.E-08	0.2	random	34	0.11	0.71
BBJ/FIN	EUR	5.0.E-08	0.8	random	86	0.11	0.71
BBJ/FIN	EAS	5.0.E-02	0.8	fixed	65,458	0.11	0.71
BBJ/FIN	EAS	5.0.E-02	0.8	random	50,018	0.11	0.71
BBJ/FIN	EAS	5.0.E-08	0.8	random	94	0.11	0.71
BBJ/FIN	EUR	5.0.E-02	0.8	fixed	66,952	0.11	0.71
BBJ/FIN	EUR	5.0.E-02	0.8	random	51,088	0.11	0.71
BBJ/FIN	EUR	5.0.E-02	0.5	fixed	46,313	0.11	0.70
BBJ/FIN	EAS	5.0.E-02	0.5	fixed	45,730	0.10	0.70
BBJ/FIN	EAS	5.0.E-02	0.5	random	35,864	0.10	0.70
BBJ/FIN	EUR	5.0.E-02	0.5	random	34,157	0.10	0.70
BBJ/FIN	EUR	5.0.E-02	0.2	fixed	32,051	0.10	0.70
BBJ/FIN	EAS	5.0.E-02	0.2	fixed	32,364	0.10	0.70
BBJ/FIN	EAS	5.0.E-02	0.2	random	26,275	0.10	0.69
BBJ/FIN	EAS	5.0.E-01	0.8	fixed	438,117	0.10	0.69
BBJ/FIN	EUR	5.0.E-01	0.8	random	456,137	0.10	0.69
BBJ/FIN	EUR	5.0.E-01	0.8	fixed	505,946	0.10	0.69
BBJ/FIN	EAS	5.0.E-01	0.8	random	438,117	0.09	0.69
BBJ/FIN	EUR	5.0.E-01	0.5	fixed	311,410	0.09	0.69
BBJ/FIN	EUR	5.0.E-02	0.2	random	26,020	0.09	0.69
BBJ/FIN	EAS	5.0.E-01	0.5	fixed	299,065	0.09	0.69
BBJ/FIN	EUR	5.0.E-01	0.5	random	284,846	0.09	0.69
BBJ/FIN	EAS	5.0.E-01	0.5	random	273,827	0.09	0.69
BBJ/FIN	EAS	5.0.E-01	0.2	fixed	166,748	0.09	0.69
BBJ/FIN	EUR	5.0.E-01	0.2	fixed	168,475	0.09	0.69
BBJ/FIN	EUR	5.0.E-01	0.2	random	157,446	0.09	0.68
BBJ/FIN	EAS	5.0.E-01	0.2	random	155,799	0.09	0.69
EUR/FIN	EUR	5.0.E-04	0.5	random	4,284	0.13	0.73
EUR/FIN	EUR	5.0.E-04	0.5	fixed	5,839	0.13	0.73
EUR/FIN	EUR	5.0.E-06	0.5	random	1,077	0.13	0.72
EUR/FIN	EUR	5.0.E-06	0.5	fixed	1,534	0.13	0.72
EUR/FIN	EUR	5.0.E-04	0.8	random	6,637	0.13	0.72
EUR/FIN	EUR	5.0.E-08	0.5	fixed	780	0.13	0.72
EUR/FIN	EUR	5.0.E-08	0.5	random	547	0.13	0.72
EUR/FIN	EUR	5.0.E-08	0.2	random	324	0.12	0.72
EUR/FIN	EUR	5.0.E-04	0.8	fixed	9,335	0.12	0.72
EUR/FIN	EUR	5.0.E-06	0.8	random	1,866	0.12	0.72
EUR/FIN	EUR	5.0.E-06	0.2	random	642	0.12	0.72
EUR/FIN	EUR	5.0.E-08	0.8	random	943	0.12	0.72
EUR/FIN	EUR	5.0.E-02	0.8	fixed	146,145	0.12	0.72
EUR/FIN	EUR	5.0.E-08	0.2	fixed	417	0.12	0.72
EUR/FIN	EUR	5.0.E-02	0.8	random	109,131	0.12	0.72
EUR/FIN	EUR	5.0.E-06	0.2	fixed	845	0.12	0.72
EUR/FIN	EUR	5.0.E-06	0.8	fixed	2,742	0.12	0.72
EUR/FIN	EUR	5.0.E-08	0.8	fixed	1,415	0.12	0.72
EUR/FIN	EUR	5.0.E-02	0.5	random	77,031	0.12	0.71
EUR/FIN	EUR	5.0.E-02	0.5	fixed	100,447	0.12	0.71
EUR/FIN	EUR	5.0.E-04	0.2	fixed	3,851	0.12	0.71
EUR/FIN	EUR	5.0.E-04	0.2	random	2,964	0.11	0.71
EUR/FIN	EUR	5.0.E-01	0.8	fixed	914,270	0.11	0.70
EUR/FIN	EUR	5.0.E-02	0.2	random	54,487	0.11	0.70
EUR/FIN	EUR	5.0.E-01	0.5	fixed	589,023	0.10	0.70
EUR/FIN	EUR	5.0.E-02	0.2	fixed	68,464	0.10	0.70
EUR/FIN	EUR	5.0.E-01	0.8	random	841,099	0.10	0.70
EUR/FIN	EUR	5.0.E-01	0.5	random	547,595	0.10	0.69
EUR/FIN	EUR	5.0.E-01	0.2	fixed	335,381	0.10	0.69
EUR/FIN	EUR	5.0.E-01	0.2	random	316,738	0.09	0.69
BBJ/EUR/FIN	EAS	5.0.E-04	0.5	fixed	4,474	0.14	0.73
BBJ/EUR/FIN	EAS	5.0.E-04	0.5	fixed	4,862	0.14	0.73
BBJ/EUR/FIN	EAS	5.0.E-04	0.8	fixed	7,614	0.14	0.73
BBJ/EUR/FIN	EAS	5.0.E-04	0.8	random	4,896	0.14	0.73
BBJ/EUR/FIN	EUR	5.0.E-06	0.5	fixed	1,306	0.14	0.73
BBJ/EUR/FIN	EAS	5.0.E-02	0.8	random	68,426	0.14	0.73
BBJ/EUR/FIN	EAS	5.0.E-06	0.2	fixed	880	0.14	0.73
BBJ/EUR/FIN	EUR	5.0.E-04	0.8	fixed	7,443	0.14	0.73
BBJ/EUR/FIN	EAS	5.0.E-04	0.5	random	3,287	0.14	0.73
BBJ/EUR/FIN	EUR	5.0.E-04	0.2	fixed	2,835	0.14	0.73
BBJ/EUR/FIN	EAS	5.0.E-02	0.8	fixed	93,143	0.14	0.73
BBJ/EUR/FIN	EAS	5.0.E-04	0.2	fixed	3,275	0.14	0.73
BBJ/EUR/FIN	EUR	5.0.E-04	0.8	random	4,780	0.14	0.73
BBJ/EUR/FIN	EUR	5.0.E-06	0.2	fixed	740	0.13	0.73
BBJ/EUR/FIN	EUR	5.0.E-02	0.8	fixed	94,188	0.13	0.73
BBJ/EUR/FIN	EAS	5.0.E-06	0.5	fixed	1,447	0.13	0.72
BBJ/EUR/FIN	EUR	5.0.E-02	0.8	random	69,037	0.13	0.73
BBJ/EUR/FIN	EUR	5.0.E-04	0.5	random	3,013	0.13	0.73
BBJ/EUR/FIN	EAS	5.0.E-08	0.2	fixed	442	0.13	0.72
BBJ/EUR/FIN	EUR	5.0.E-02	0.5	fixed	61,445	0.13	0.73
BBJ/EUR/FIN	EUR	5.0.E-06	0.8	fixed	2,373	0.13	0.73
BBJ/EUR/FIN	EUR	5.0.E-08	0.5	fixed	675	0.13	0.73
BBJ/EUR/FIN	EAS	5.0.E-06	0.5	random	911	0.13	0.73
BBJ/EUR/FIN	EAS	5.0.E-02	0.5	random	47,546	0.13	0.73
BBJ/EUR/FIN	EAS	5.0.E-06	0.8	fixed	1,460	0.13	0.72
BBJ/EUR/FIN	EAS	5.0.E-08	0.5	fixed	733	0.13	0.72
BBJ/EUR/FIN	EUR	5.0.E-04	0.2	random	2,058	0.13	0.73
BBJ/EUR/FIN	EAS	5.0.E-06	0.8	random	1,460	0.13	0.72
BBJ/EUR/FIN	EAS	5.0.E-04	0.2	random	2,325	0.13	0.72
BBJ/EUR/FIN	EUR	5.0.E-08	0.2	fixed	369	0.13	0.72
BBJ/EUR/FIN	EUR	5.0.E-06	0.5	random	801	0.13	0.72
BBJ/EUR/FIN	EUR	5.0.E-02	0.5	random	46,529	0.13	0.72
BBJ/EUR/FIN	EUR	5.0.E-06	0.2	random	506	0.13	0.72
BBJ/EUR/FIN	EAS	5.0.E-06	0.2	random	590	0.13	0.72
BBJ/EUR/FIN	EUR	5.0.E-08	0.8	fixed	1,241	0.13	0.72
BBJ/EUR/FIN	EAS	5.0.E-02	0.5	fixed	62,810	0.13	0.72
BBJ/EUR/FIN	EUR	5.0.E-06	0.8	random	1,402	0.13	0.72
BBJ/EUR/FIN	EAS	5.0.E-08	0.8	fixed	1,291	0.13	0.72
BBJ/EUR/FIN	EAS	5.0.E-08	0.5	random	429	0.12	0.72
BBJ/EUR/FIN	EAS	5.0.E-08	0.2	random	278	0.12	0.72
BBJ/EUR/FIN	EUR	5.0.E-02	0.2	fixed	39,835	0.12	0.72
BBJ/EUR/FIN	EAS	5.0.E-01	0.8	fixed	498,303	0.12	0.72
BBJ/EUR/FIN	EAS	5.0.E-08	0.8	random	706	0.12	0.72
BBJ/EUR/FIN	EUR	5.0.E-08	0.8	random	666	0.12	0.72
BBJ/EUR/FIN	EUR	5.0.E-08	0.2	random	236	0.12	0.71
BBJ/EUR/FIN	EAS	5.0.E-01	0.8	random	461,151	0.12	0.71
BBJ/EUR/FIN	EUR	5.0.E-08	0.5	random	383	0.12	0.71
BBJ/EUR/FIN	EUR	5.0.E-02	0.2	random	31,591	0.12	0.71
BBJ/EUR/FIN	EUR	5.0.E-01	0.8	fixed	534,900	0.12	0.71
BBJ/EUR/FIN	EUR	5.0.E-01	0.8	random	496,020	0.12	0.71
BBJ/EUR/FIN	EUR	5.0.E-01	0.5	fixed	323,119	0.12	0.71
BBJ/EUR/FIN	EUR	5.0.E-02	0.2	fixed	42,038	0.12	0.71
BBJ/EUR/FIN	EAS	5.0.E-02	0.2	random	33,133	0.11	0.71
BBJ/EUR/FIN	EAS	5.0.E-01	0.5	fixed	296,688	0.11	0.71
BBJ/EUR/FIN	EAS	5.0.E-01	0.5	random	278,881	0.11	0.71
BBJ/EUR/FIN	EUR	5.0.E-01	0.5	random	303,625	0.11	0.71
BBJ/EUR/FIN	EAS	5.0.E-01	0.2	fixed	159,071	0.11	0.71
BBJ/EUR/FIN	EUR	5.0.E-01	0.2	fixed	170,897	0.11	0.71
BBJ/EUR/FIN	EAS	5.0.E-01	0.2	random	152,014	0.10	0.70
BBJ/EUR/FIN	EUR	5.0.E-01	0.2	random	163,231	0.10	0.70

AF, atrial fibrillation; PRS, polygenic risk score; LD, linkage disequilibrium; P, P-value; Pseudo R2, Nagelkerke's pseudo R2; AUCROC, area under the curve of the receiver operator curve

in the effect of AF onset age between individuals with top PRS to those with the remaining PRS using a linear regression model adjusted for sex and top 10 principal components. For the association analysis between AF-PRS and stroke subtype, we calculated ORs and associated *P* values using a logistic regression model adjusted for age, sex, and the top 10 principal components. Among the control samples (without AF diagnosis) in our dataset (n=140,447), we found 14,120 stroke phenotypes: 9,177 for cerebral infarction, 111 for cardioembolic stroke, 1,465 for atherothrombotic infarction, 1,266 for lacunar infarction, 1,143 for cerebral hemorrhage, and 967 for subarachnoid hemorrhage.

Survival analysis

For survival analysis, the Cox proportional hazards model was used to assess the association between AF-PRS and long-term mortality. We obtained survival follow-up data with the ICD-10 code for 132,737 individuals from the BBJ dataset[20,21]. The causes of death were classified according to ICD-10 codes: (i) cardiovascular death (I00–I99), (ii) heart failure death (I50), (iii) ischemic heart disease death (I20–I25), and (iv) stroke death (I60, I61, I63, and I64). The median follow-up period was 8.4 years (IQR 6.8 – 9.9). The Cox proportional hazards model was adjusted for sex, age, top 10 principal components, and disease status. Analyses were performed with the R package survival v.2.44, and survival curves were estimated using the R package survminer v.0.4.6, with modifications.

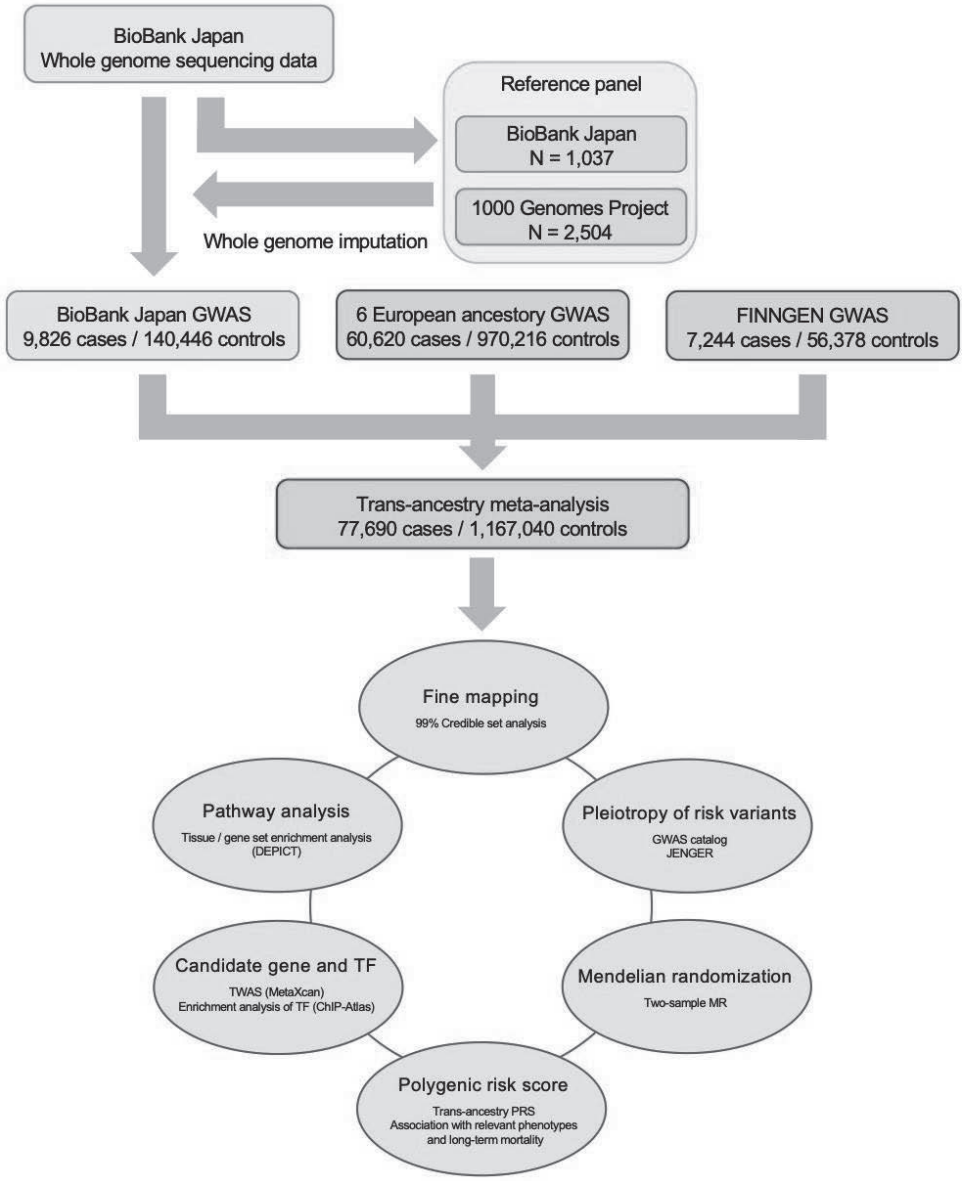
Mendelian randomization

We performed two-sample MR to test for a causal relationship between AF and relevant diseases or traits. Although the statistical power to detect the associations with AF decreased, we selected AF-associated variants from the trans-ancestry meta-analysis in combination with BBJ and FIN to avoid sample overlap, and extracted summary statistics from a large database of genetic associations in the UK biobank (http://www.nealelab.is/uk-biobank/). To identify independent variants for exposure, genome-wide significant variants ($P<5\times10^{-8}$) were pruned ($r^2<0.05$; LD window of 10,000 kb; using European samples of 1KG for LD reference) as applied previously[22]. First, we assessed whether AF is causally associated with cardiovascular diseases using AF-associated variants as instrument variables and variants associated with cardiovascular diseases as outcome variables. Next, we assessed the causal effects of quantitative traits related to anthropometry, metabolites, serum protein, kidney function, liver function, hematocyte count, and blood pressure on AF, where variants associated with quantitative traits were used as instrument variables and AF-associated variants as outcome variables. We used the inverse-variance-weighting (IVW) method. To exclude horizontal pleiotropic outliers, we performed MR-PRESSO for instrument variables[23]. We also calculated Cochran's Q statistics for heterogeneity between the causal effects of variants using IVW and the MR-Egger intercept for directional pleiotropy. All analyses were performed using R v4.0.3, with R packages TwoSampleMR and MRPRESSO.

Results

Five novel loci for AF identified in the Japanese GWAS

An overview of the study design is shown in Supplementary Fig. 3. We performed a GWAS on the case-control dataset from the BioBank Japan (BBJ) that comprised 9,826 AF cases and 140,446 controls, using 16,394,105 variants in the autosomes and 423,039 variants in the X chromosome with a minor allele frequency (MAF) > 0.1%. The GWAS identified 31 AF-associated loci with genome-wide significance, of which five were previously unreported (Table 1, Supplementary Table 3, Supplementary Fig. 4, and Supplementary Datasets 1 and 2). The proportion of the variation in AF (the single nucleotide polymorphism (SNP) heritability; h2) explained by the total genome-wide genetic variation detected in the current Japanese GWAS was estimated to be 6.1% (standard error of mean [s.e.m.] 1.4%), and the liability-scale h^2 was estimated at 11.7%



Supplementary Fig. 3 | Overview of the study design.

Top, overview of the Japanese cohort of 9,826 AF cases and 140,446 controls with reference panel. Middle, GWAS summary of each study and the trans-ancestry meta-analysis with the number of cases and controls. Bottom, overview of the downstream analyses for AF-associated variants in the trans-ancestry meta-analysis. GWAS, genome-wide association study; JENGER, Japanese ENcyclopedia GEnetic associations by Riken; MR, Mendelian randomization; PRS, polygenic risk score; TWAS, transcriptome-wide association study.

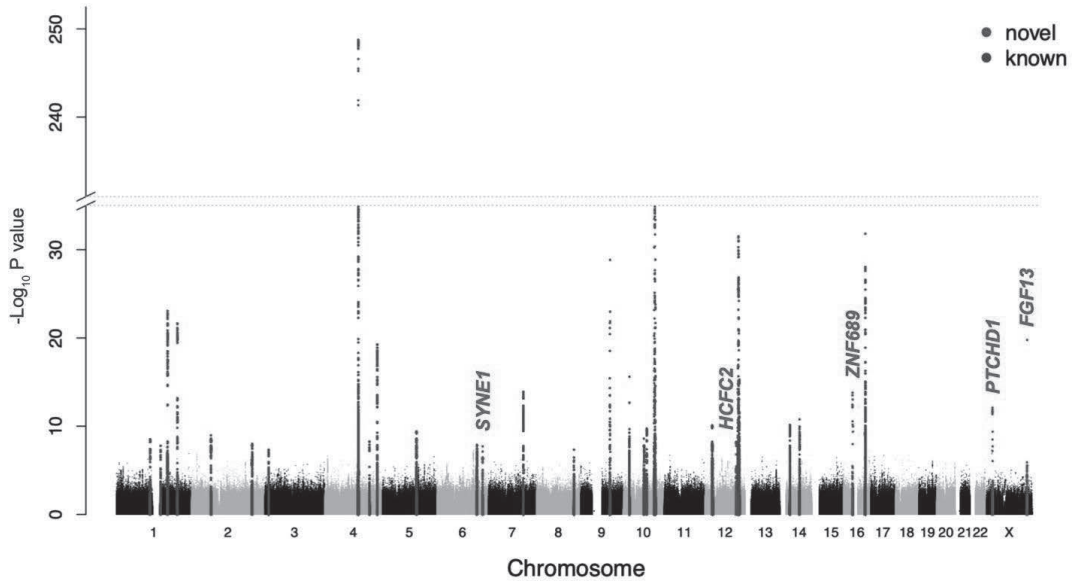
(s.e.m. 2.6%) using linkage disequilibrium (LD)-score regression.

We found two novel loci whose lead variants were observed only in East Asian according to the Genome Aggregation Database v2.1.1 (gnomAD)[24]: one low-frequency and one rare lead variant, rs202030113 (MAF=1.2%) and rs778479352 (MAF=0.25%), respectively. The lead variant on 6q25.1, rs202030113, was located in the intronic region three bases away from an exon-intron boundary of *SYNE1* and was predicted as

Supplementary Table 3 | Significant association loci in the Japanese GWAS

CHR	POS	Locus		REF	ALT	rsID	Gene	Annotation	AAF	Beta	SE	P	Status
		Start	End										
1	112392360	111879026	112915583	G	T	rs12044963	*KCND3*	intronic	0.499	0.088	0.015	2.89E-09	known
1	147228874	146722832	147728874	C	T	rs11240121	*GJA5*	3'UTR	0.489	0.084	0.015	1.58E-08	known
1	170631763	169751130	171143365	T	C	rs629234	*GORAB, PRRX1*	intergenic	0.461	-0.152	0.015	8.50E-24	known
1	203032038	202521116	203555101	G	T	rs11579558	*PPFIA4*	intronic	0.299	-0.163	0.017	2.08E-22	known
2	65355386	64768159	65885592	C	G	rs75251643	*RAB1A*	intronic	0.219	-0.115	0.019	1.07E-09	known
2	201163454	200659988	201785029	A	T	rs4673904	*MAIP1, SPATS2L*	intergenic	0.689	0.094	0.016	9.26E-09	known
3	12872995	12372995	13372995	C	T	rs75387493	*CAND2*	exonic	0.047	0.181	0.033	4.24E-08	known
4	111716513	110841397	113093765	C	T	rs12644625	*PITX2, C4orf32*	intergenic	0.455	0.510	0.015	1.70E-249	known
4	148936414	148433736	149469249	T	G	rs10213376	*ARHGAP10*	intronic	0.088	0.146	0.025	5.37E-09	known
4	174463916	173936866	175118863	C	T	rs187693118	*HAND2-AS1*	ncRNA intronic	0.110	0.204	0.022	5.30E-20	known
5	113749460	113202058	114269952	A	G	rs1013168	*KCNN2*	intronic	0.150	0.126	0.020	3.82E-10	known
6	133443662	132932323	134073257	C	T	rs6941949	*LINC00326, EYA4*	intergenic	0.307	0.091	0.016	1.25E-08	known
6	152466619	151966619	152966619	T	C	rs202030113	*SYNE1*	intronic	0.012	0.352	0.063	1.90E-08	novel
7	116198621	115508844	116726422	G	A	rs1997571	*CAV1*	intronic	0.667	0.124	0.016	1.24E-14	known
8	124635197	124135197	125135197	G	C	rs4871397	*FBXO32, KLHL38*	intergenic	0.931	-0.154	0.028	4.37E-08	known
9	97891869	96435520	98884974	C	T	rs149672087	*FANCC*	intronic	0.014	0.765	0.055	9.17E-44	known
10	21157621	20531514	21740532	G	T	rs2296610	*NEBL*	exonic	0.124	0.175	0.021	2.42E-16	known
10	69263759	68751616	69957002	C	CA	rs548764966	*CTNNA3*	intronic	0.317	0.097	0.016	2.41E-09	known
10	77936670	77420739	78451056	T	G	rs10458662	*LRMDA*	intronic	0.554	0.096	0.015	1.76E-10	known
10	105334707	102333335	107948060	A	G	rs185158502	*NEURL1*	intronic	0.007	1.428	0.056	3.20E-141	known
12	24801856	24258480	25321641	C	T	rs7973464	*LINC0047, ;BCAT1*	intergenic	0.874	0.157	0.024	7.46E-11	known
12	26596225	26096225	27105278	C	G	rs74763618	*ITPR2*	intronic	0.285	-0.096	0.017	1.39E-08	known
12	104471663	103967069	105021552	C	T	rs2930856	*HCFC2*	intronic	0.579	0.090	0.015	5.80E-09	novel
12	111609727	109346714	114213062	G	T	rs3809297	*CUX2*	intronic	0.235	-0.229	0.019	3.10E-32	known
12	114789226	114257807	115315524	G	A	rs2384407	*LINC02459, TBX5*	intergenic	0.420	0.122	0.015	5.25E-16	known
14	32912092	32396479	33498038	T	C	rs10138310	*AKAP6*	intronic	0.395	0.099	0.015	6.91E-11	known
14	64679960	64149737	65292764	A	G	rs2738413	*SYNE2*	intronic	0.635	-0.103	0.015	1.65E-11	known
16	30619745	29552041	32415761	C	T	rs1055894680	*ZNF689*	intronic	0.001	1.215	0.158	1.58E-14	novel
16	73053022	71808175	73585286	T	A	rs2359171	*ZFHX3*	intronic	0.306	0.300	0.016	3.29E-83	known
X	23399501	22894362	24046193	T	C	rs73205368	*PTCHD1*	intronic	0.285	0.089	0.012	7.50E-13	novel
X	137790580	137290580	138290580	T	C	rs778479352	*FGF13*	intronic	0.002	0.692	0.075	1.62E-20	novel

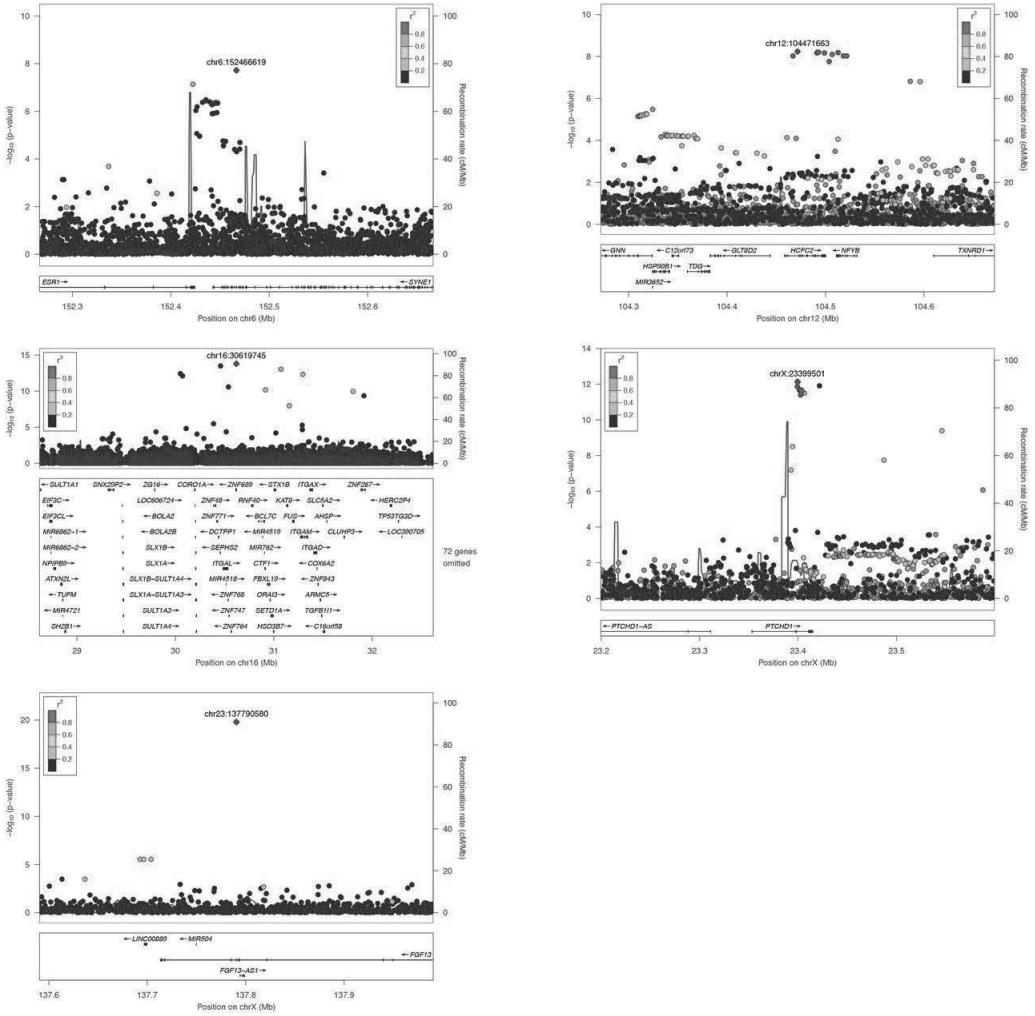
GWAS, genome-wide association study; CHR, Chromosome; POS, position(hg19); REF, reference allele; ALT, alternate allele; rsID, reference SNP cluster ID; AAF, alternate allele frequency; SE, Standard error; P, P-value; ncRNA, non-coding RNA; UTR, untranslated region



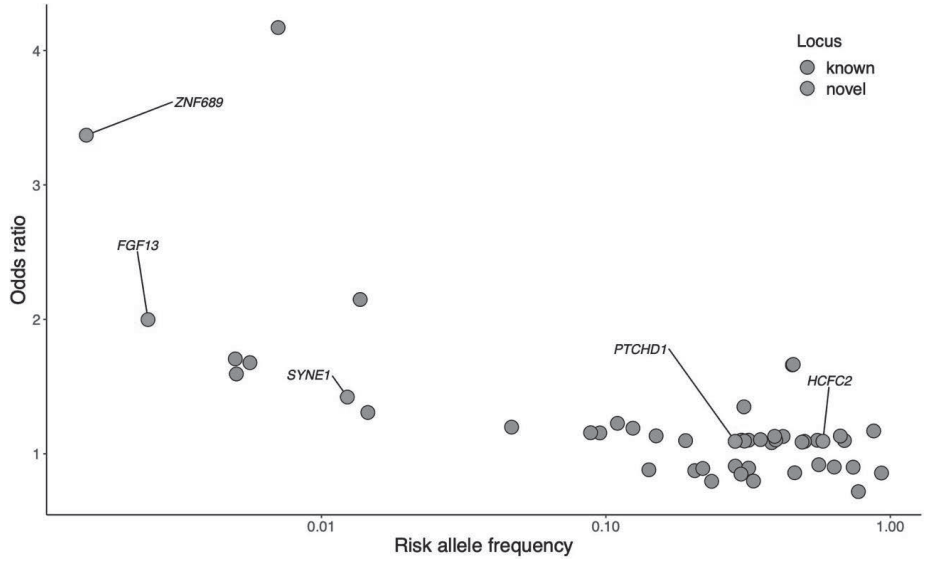
Supplementary Fig. 4 | Manhattan plot for the Japanese GWAS.

The results of the Japanese GWAS (9,826 AF cases and 140,446 controls) are shown. The negative $\log_{10}$ *P* values on the y-axis are shown against the genomic positions (hg19) on the x-axis. Association signals that reached a genome-wide significance level ($P<5.0\times10^{-8}$) are shown in blue if previously reported loci and in red if novel loci. GWAS, genome-wide association study; AF, atrial fibrillation.

1. Novel 5 loci in the Japanese GWAS



a splice donor loss with the spliceAI delta score of 0.33[25]. *SYNE1* en codes nesprin-1 (spectrin repeat) protein, and together with Sad1p/UNC84-domain-containing proteins (SUN1/2), compose the nuclear envelope protein complex via its nucleoplasmic domains to lamin A/C. Mutations in *LMNA* and *SYNE1* genes have been identified in patients with severe muscle dystrophy and dilated cardiomyopathy[26,27]. Mutations in the *SYNE1* gene cause defects in nuclear morphology, myoblast differentiation, and heart development[28], altering the nuclear envelope protein complex that contributes to the structural substrate in atrial arrhythmogenesis. A strong signal (odds ratio [OR] for AF development = 2.00, 95% confidence interval [CI] = 1.73-2.31, P=1.6×10^{-20}) was displayed by rs778479352, the lead variant located in an intron of *FGF13*. *FGF13* encodes a member of the fibroblast growth factor family, which possesses broad mitogenic and cell survival activities. *FGF13* directly binds to the C-terminus of the main cardiac sodium channel (NaV1.5) in the sarcolemma; knockdown of *FGF13* in rat cardiomyocytes showed a loss of function of NaV1.5-reduced Na^+ current density, decreased Na^+ channel availability, and slowed NaV1.5-reduced Na^+ current recovery from inactivation[29]. This evidence of conduction disturbance in cardiomyocytes indicates that *FGF13* is an important target gene associated with AF.



Supplementary Fig. 5 | Independent association signals in AF development.
The ORs for AF development of AF 49 independent signals in the Japanese GWAS (31 lead variants and 18 independent variants) were plotted against the risk allele frequencies. Novel variants are highlighted in orange with annotated genes. AF, atrial fibrillation; OR, odds ratio; GWAS, genome-wide association study.

Supplementary Table 4 | Additional independent signals in the Japanese GWAS

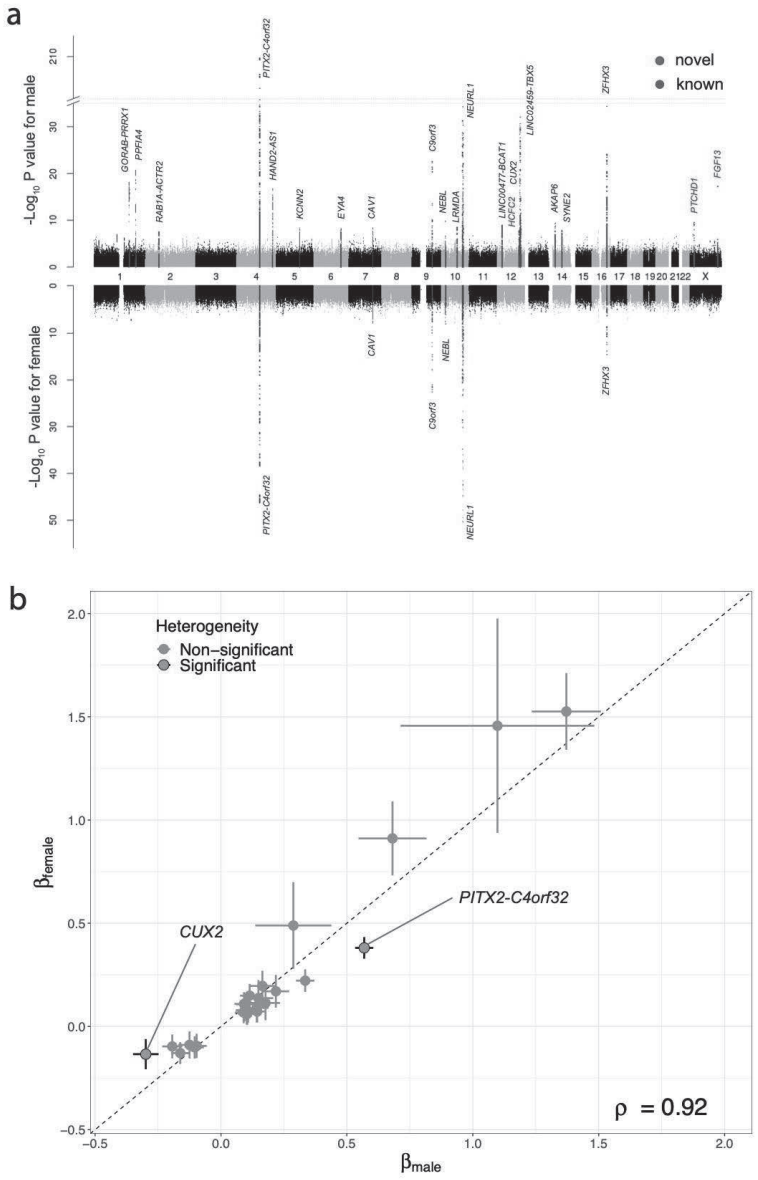
Locus					Independent signal									
CHR	Start	End	Lead variant	Gene	POS	REF	ALT	rsID	Gene	Annotation	AAF	Beta	SE	P
1	169751130	171143365	rs629234	*GORAB, PRRX1*	169878684	A	T	rs79553182	*SCYL3;KIFAP3*	intergenic	0.015	0.265	0.057	2.94E-06
1	202521116	203555101	rs11579558	*PPFIA4*	203055101	A	G	rs4950877	*MYOG*	5'UTR	0.560	-0.101	0.015	1.44E-11
4	110841397	113093765	rs12644625	*PITX2, C4orf32*	111701433	A	G	rs59788391	*PITX2;C4orf32*	intergenic	0.452	0.507	0.015	3.07E-246
4	110841397	113093765	rs12644625	*PITX2, C4orf32*	111724471	G	C	rs723364	*PITX2;C4orf32*	intergenic	0.772	0.103	0.018	1.53E-08
4	110841397	113093765	rs12644625	*PITX2, C4orf32*	111761487	T	C	rs3853445	*PITX2;C4orf32*	intergenic	0.330	-0.244	0.016	1.75E-49
4	110841397	113093765	rs12644625	*PITX2, C4orf32*	111849422	G	A	rs374582	*PITX2;C4orf32*	intergenic	0.740	-0.213	0.016	3.33E-39
4	110841397	113093765	rs12644625	*PITX2, C4orf32*	112577111	G	T	rs77502141	*PITX2;C4orf32*	intergenic	0.142	-0.125	0.022	1.87E-08
4	173936866	175118863	rs187693118	*HAND2-AS1*	174599459	T	C	rs4615152	*HAND2-AS1;LINC02269*	intergenic	0.392	0.124	0.015	2.70E-16
9	96435520	98884974	rs149672087	*FANCC*	97567106	G	C	rs577463446	*C9orf3*	intronic	0.005	0.455	0.096	2.41E-06
10	20531514	21740532	rs2296610	*NEBL*	20565750	G	T	rs965277670	*PLXDC2*	intronic	0.006	0.498	0.102	9.81E-07
10	102333335	107948060	rs185158502	*NEURL1*	105333613	C	T	rs12411463	*NEURL1*	intronic	0.095	0.315	0.023	1.66E-42
10	102333335	107948060	rs185158502	*NEURL1*	105340059	A	G	rs7068070	*NEURL1*	intronic	0.205	-0.156	0.019	3.59E-16
10	102333335	107948060	rs185158502	*NEURL1*	106367501	T	C	rs201901902	*LOC101927523;SORCS3*	intergenic	0.005	0.519	0.117	8.56E-06
12	114257807	115315524	rs2384407	*LINC02459, TBX5*	114857726	A	G	rs2551389	*TBX5-AS1;TBX3*	intergenic	0.191	0.077	0.019	3.15E-05
12	114257807	115315524	rs2384407	*LINC02459, TBX5*	115108361	T	C	rs1061651	*TBX3*	3'UTR	0.383	0.080	0.016	2.69E-07
14	32396479	33498038	rs10138310	*AKAP6*	32971599	G	C	rs8013209	*AKAP6*	intronic	0.349	0.098	0.016	5.62E-10
16	71808175	73585286	rs2359171	*ZFHX3*	72879660	T	C	rs740177	*ZFHX3*	intronic	0.317	-0.109	0.016	2.15E-11

GWAS, genome-wide association study; CHR, Chromosome; POS, position(hg19); REF, reference allele; ALT, alternate allele; rsID, reference SNP cluster ID; AAF, alternate allele frequency; SE, Standard error; P, P-value; UTR, untranslated region

To identify AF-associated variants independent of the lead variant at each locus, we performed a stepwise conditional analysis, in which 18 independent variants (locus-wide $P<5.0\times10^{-6}$) were additionally detected, increasing the total number of AF-associated signals to 49 (Supplementary Fig. 5 and Supplementary Table 4). We identified 10 loci that had multiple independent association signals, especially in the *PITX2-C4orf32* locus with 6 association signals (N_{signal}=2: *GORAB-PRRX1, CAND2, HAND2-AS1, FANCC, NEBL, AKAP6, ZFHX3* loci, N_{signal}=3: *LINC02459-TBX5* locus, N_{signal}=4: *NEURL1* locus, and N_{signal}=6: *PITX2-C4orf32* locus). Of these additional signals, three variants were observed only in East Asian populations in gnomAD (rs577463446 at the *FANCC* locus, MAF=0.5%, OR=1.58; rs965277670 at *NEBL* locus, MAF=0.6%, OR=1.65; rs201901902 at *NEURL1* locus MAF=0.5%, OR=1.68).

Sex-stratified GWAS for AF

Sex-related differences in the epidemiology, clinical presentation, and prognosis of AF have been consistently reported[30,31]. For example, the age-stratified prevalence of AF is lower in female than in male, despite a higher risk for AF-related outcomes such as stroke in female[32-34]. Thus, we first perfomed sex-stratified GWAS and calculated the genetic correlation



Supplementary Fig. 6 | Sex-stratified GWAS.

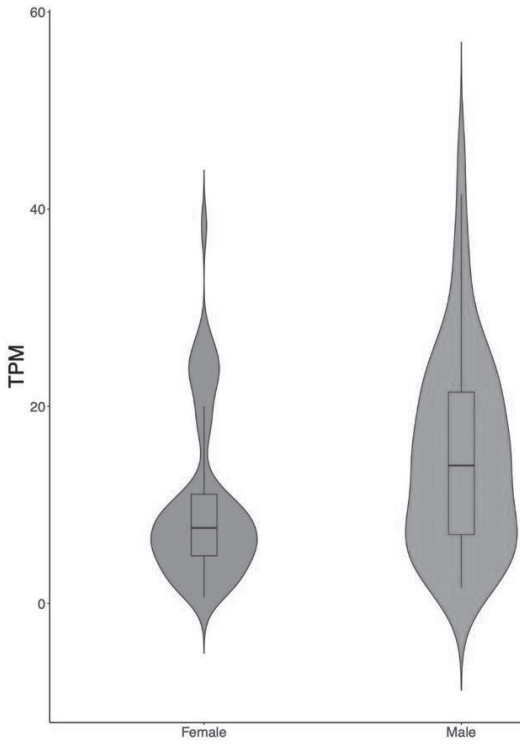
a, Miami plot for sex-stratified GWAS. Upper panel for male GWAS (N=81,050: 6,825 cases and 74,225 controls) and lower panel for female GWAS (N=69,222: 3,001 cases and 66,221 controls). Association signals that reached a genome-wide significance level (P<5.0×10^{-8}) are shown in blue if previously reported loci and in red if novel loci. **b**, Comparison of estimated effect sizes of the lead variants identified in both male and female GWAS. Data are presented as estimated β and 95% confidence. The lead variants with significant heterogeneity (P_{het} < 0.0001) are highlighted in orange, and ρ indicates Spearman's correlation coefficient. GWAS, genome-wide association study.

Supplementary Table 5 | Significant association loci in male and female Japanese GWAS

CHR	POS	rsID	REF	ALT	Gene	Annotation	AAF	Beta	SE	P	Status
Male GWAS											
1	170631763	rs629234	T	C	*GORAB, PRRX1*	intergenic	0.461	-0.162	0.018	7.07E-19	known
1	203032038	rs11579558	G	T	*PPFIA4*	intronic	0.300	-0.193	0.020	2.09E-21	known
2	65382261	rs9989843	G	T	*RAB1A, ACTR2*	intergenic	0.713	0.116	0.021	2.76E-08	known
4	111716513	rs12644625	C	T	*PITX2, C4orf32*	intergenic	0.459	0.569	0.018	1.87E-210	known
4	174451999	rs2276940	C	A	*HAND2-AS1*	ncRNA exonic	0.114	0.225	0.027	2.20E-17	known
5	113749460	rs1013168	A	G	*KCNN2*	intronic	0.150	0.142	0.024	4.09E-09	known
6	133565735	rs1582725060	A	AT	*EYA4*	intronic	0.167	0.135	0.023	7.24E-09	known
7	116198621	rs1997571	G	A	*CAV1*	intronic	0.667	0.114	0.019	4.79E-09	known
9	97768758	rs147288039	A	G	*C9orf3*	intronic	0.014	0.678	0.068	3.00E-23	known
10	21157621	rs2296610	G	T	*NEBL*	exonic	0.124	0.163	0.026	1.93E-10	known
10	77936670	rs10458662	T	G	*LRMDA*	intronic	0.554	0.108	0.018	3.23E-09	known
10	105334707	rs185158502	A	G	*NEURL1*	intronic	0.007	1.371	0.070	2.94E-85	known
12	24803849	rs60634518	G	A	*LINC00477, BCAT1*	intergenic	0.773	0.137	0.023	1.14E-09	known
12	104492003	rs2629755	A	G	*HCFC2*	intronic	0.418	-0.103	0.018	2.03E-08	novel
12	111609727	rs3809297	G	T	*CUX2*	intronic	0.239	-0.280	0.024	9.67E-33	known
12	114789226	rs2384407	G	A	*LINC02459, TBX5*	intergenic	0.421	0.144	0.018	2.06E-15	known
14	32974844	rs8010040	A	C	*AKAP6*	intronic	0.598	0.119	0.019	5.01E-10	known
14	64679960	rs2738413	A	G	*SYNE2*	intronic	0.635	-0.105	0.019	1.82E-08	known
16	73053022	rs2359171	T	A	*ZFHX3*	intronic	0.307	0.334	0.019	7.98E-72	known
X	23399501	rs73205368	T	C	*PTCHD1*	intronic	0.286	0.086	0.014	3.27E-10	novel
X	137790580	rs778479352	T	C	*FGF13*	intronic	0.003	0.691	0.080	6.12E-18	novel
Female GWAS											
4	111697653	rs78229461	C	T	*PITX2, C4orf32*	intergenic	0.450	0.385	0.027	5.66E-47	known
7	116191697	rs9886216	A	G	*CAV1*	intronic	0.288	-0.172	0.030	1.71E-08	known
9	97891869	rs149672087	C	T	*FANCC*	intronic	0.014	0.911	0.092	2.42E-23	known
10	21202360	rs3802729	C	T	*NEBL*	intronic	0.314	0.164	0.029	1.04E-08	known
10	105335361	rs373205748	C	T	*NEURL1*	intronic	0.008	1.483	0.092	2.47E-58	known
16	73053022	rs2359171	T	A	*ZFHX3*	intronic	0.304	0.222	0.028	2.39E-15	known

GWAS, genome-side association study; CHR, Chromosome; POS, position(hg19); REF, reference allele; ALT, alternate allele; rsID, reference SNP cluster ID; AAF, alternate allele frequency; SE, Standard error; P, P-value; ncRNA, non-coding RNA

between sexes using LD-score regression to explore the genetic heterogeneity. We then found a significant correlation (r_g=1.095, s.e.m. =0.112, P=1.2×10^{-22}). Next, we examined genetic loci with sex-dependent effects on AF development in the sex-stratified GWAS. We found 21 loci with genome-wide significance in the male GWAS, but only six loci in the female GWAS (Supplementary Fig. 6a and Supplementary Table 5). Furthermore, by comparing the effect sizes of the lead variants identified in the sex-stratified GWAS, we observed significant positive correlation and concordant allelic effects between sexes (Spearman's ρ=0.92, P=7.4×10^{-7}; Supplementary Fig. 6b). We found several variants with significant heterogeneity in the *PITX2-C4orf32* and *CUX2* loci (P_{het}<1.0×10^{-4}). Although the *PITX2-C4orf32* locus reached genome-wide significance in both sex-stratified GWAS (β_{male} (s.e.m.$_{male}$)=0.569 (0.018), P_{male}=1.9×10^{-210}; β_{female} (s.e.m.$_{female}$)=0.381 (0.027), P_{female}=3.0×10^{-46}, for rs12644625, the lead variant in the *PITX2-C4orf32* locus), the *CUX2* locus in the female GWAS did not achieve genome-wide significance level (β_{male} (s.e.m.$_{male}$)=-0.280 (0.024), P_{male}=9.7×10^{-33}; β_{female} (s.e.m.$_{female}$)=-0.105 (0.034), P_{female}=2.1×10^{-3}, for rs12644625, the lead variant in the *CUX2* locus). *CUX2* is a transcription factor regulating sex-biased gene expression in rat and mouse liver[35,36], and the variant in the *CUX2* locus is associated with a DNA methylation site near the *ALDH2* gene, encoding aldehyde dehydrogenase, which catalyzes the oxidation of aldehydes into carboxylic acids[37]. Moreover, according to Genotype-Tissue Expression (GTEx) data[38], *CUX2* gene expression in liver was significantly different between male and female (P=7.8×10^{-4}, Wilcoxon rank-sum test; Supplementary Fig. 7). These results suggest that sex-biased gene expression related to the metabolism of aldehydes in the liver may partially explain the sex-related differences in the genetic basis of AF.



Supplementary Fig. 7 | *CUX2* gene expression in liver. Violin plots showing the distribution of *CUX2* gene expression in the liver based on GTEx data.

Trans-ancestry meta-analysis identified 33 novel loci for AF

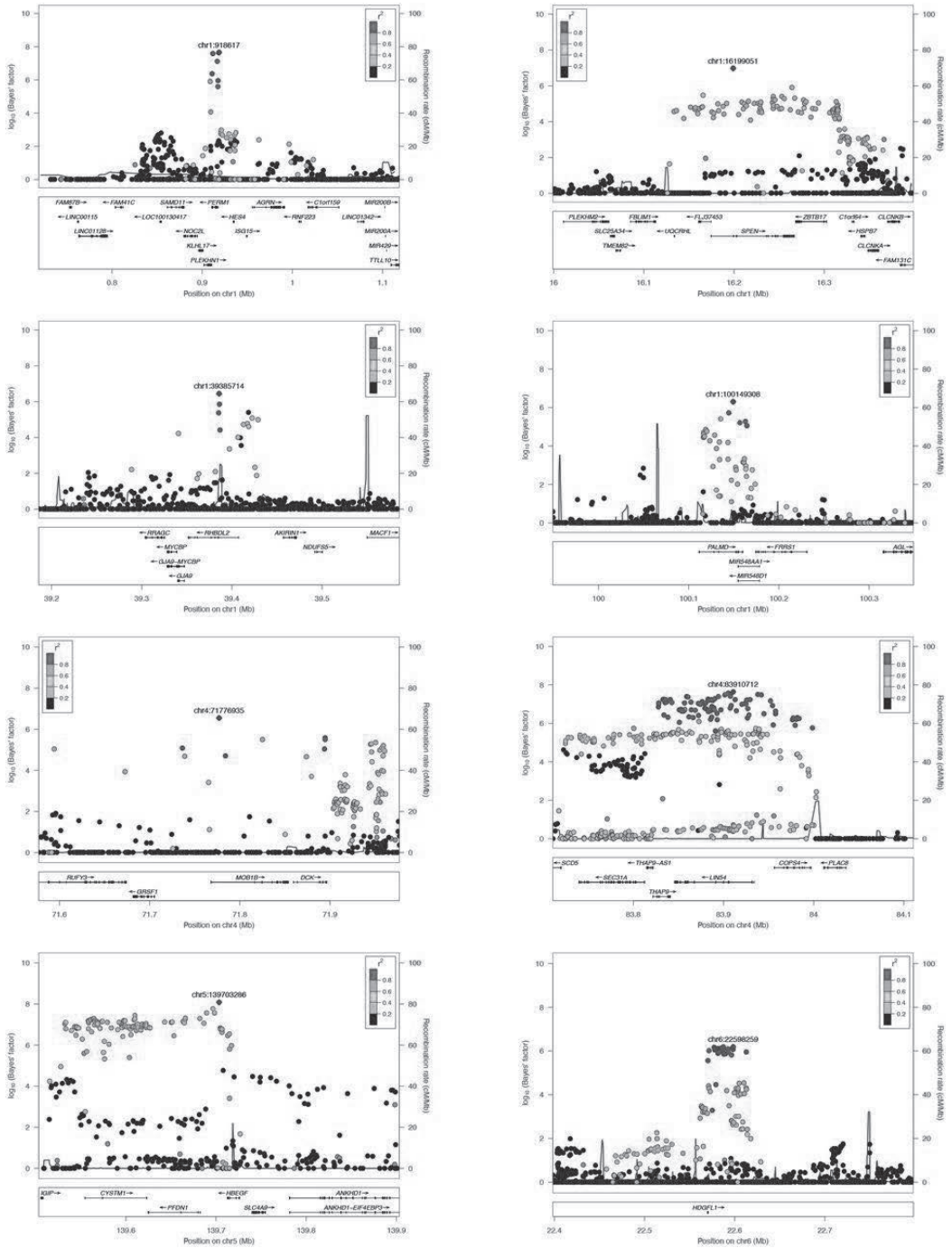
To improve the statistical power to detect further genetic associations with AF, we conducted a trans-ancestry meta-analysis by combining the current Japanese GWAS (BBJ) and two European GWASs: a large-scale meta-analysis of European populations (EUR)[7] and a biobank data of FinnGen data release 2 (FIN). All three datasets yielded 77,690 cases (BBJ: 9,826; EUR: 60,620; FIN: 7,244) and 1,167,040 controls (BBJ: 140,446; EUR: 970,216; FIN: 56,378). We tested a total of 5,158,449 variants with MAF ≥ 1% and identified 150 AF-associated loci with genome-wide significance ($\log_{10}$ Bayes factor (BF) > 6; Fig. 1, Supplementary Table 6, and Supplementary Datasets 3 and 4). Of these loci, 33 have not been reported previously, including three novel loci detected in the current Japanese GWAS. In total, we identified 35 novel loci through the current Japanese GWAS and trans-ancestry meta-analysis (Table 2). Of the 5,855 variants in LD ($r^2 > 0.6$) with 150 lead variants, 27 missense variants were observed (Supplementary Table 7). Among novel loci, we found a missense variant, rs848208 (p.Ala970Val), in the *SPEN* gene, encoding a hormone-inducible transcriptional co-regulator that activates and represses downstream targets. *SPEN*-deficient zebrafish embryos developed bradycardia, atrioventricular block, and heart chamber fibrillation with downregulation of connexin 43 expression[39], which is a well-known component of gap junctions and is associated with the cardiac conduction system[40]. Another missense variant in novel loci, rs3746471 (p.Arg1045Trp), was located on the *KIAA1755* gene, which is reported to be associated with heart rate[41] and heart rate variability[42]. Given the robust relationship between autonomic nervous dysfunction and AF[43], *KIAA1755* can be a potential target gene for neural modulation contributing to AF management; however, the biological association between the *KIAA1755* gene and AF has not been fully examined.

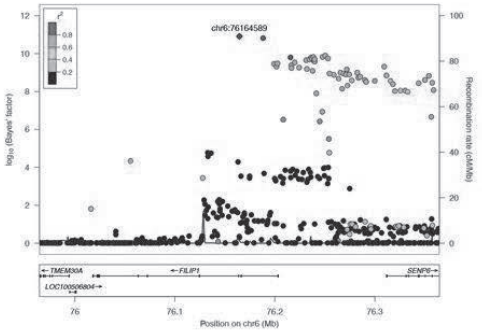
Shared allelic effects between Japanese and European populations and fine mapping/credible set analyses in the trans-ancestry meta-analysis

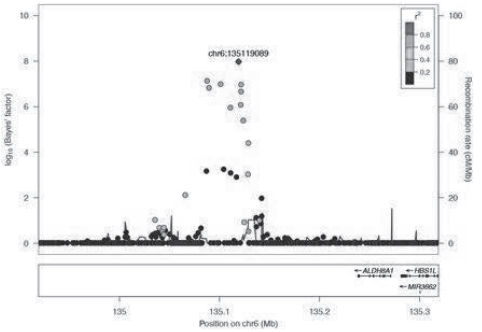
We compared alternate allele frequencies and allelic effects for 150 lead variants between BBJ, EUR, and FIN. Compared to substantial concordance in allele frequencies between EUR and FIN (Spearman's $\rho=0.974$, $P<2.2\times10^{-16}$), we observed a moderate correlation in allele frequencies between BBJ and EUR as well as BBJ and FIN ($\rho=0.592$, $P=1.5\times10^{-15}$ and $\rho=0.632$, $P<2.2\times10^{-16}$, respectively; Supplementary Fig. 8a-c). Additionally, we found a significant positive correlation between concordant allelic effects of these variants ($\rho=0.769$, $P< 2.2\times10^{-16}$ for BBJ vs. EUR; $\rho=0.769$, $P<2.2\times10^{-16}$ for BBJ vs. FIN; Supplementary Fig. 8d-f). To further explore the relationship of allelic effects between populations, we performed a trans-ancestry genetic correlation analysis, which showed strong correlation of BBJ with EUR and FIN (BBJ and

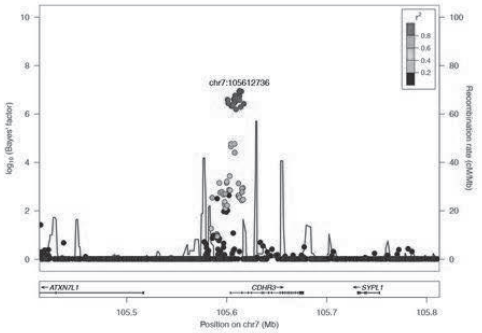
民族横断的な心房細動ゲノム解析による新たな疾患メカニズムの解明と遺伝子リスクスコアによる心原性脳梗塞の予測

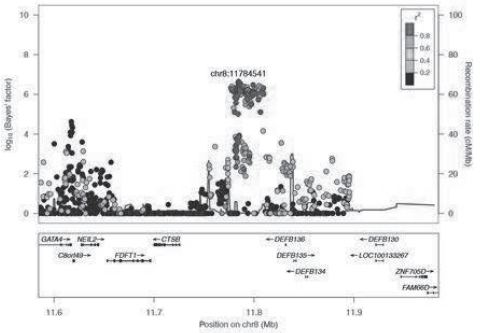
3. Novel 33 loci in the trans-ancestry meta-GWAS

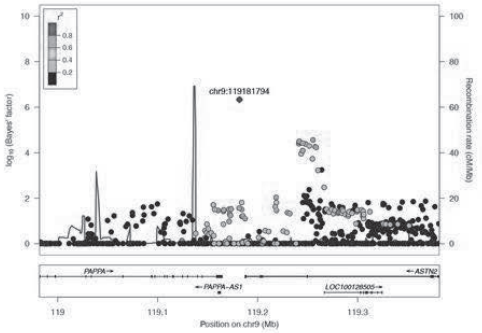


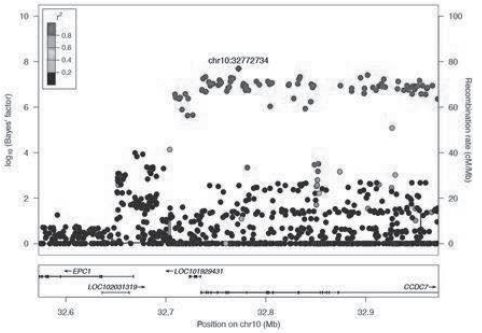

chr6:76164589
TMEM30A
FILIP1
SENP6
LOC100506804
Position on chr6 (Mb)

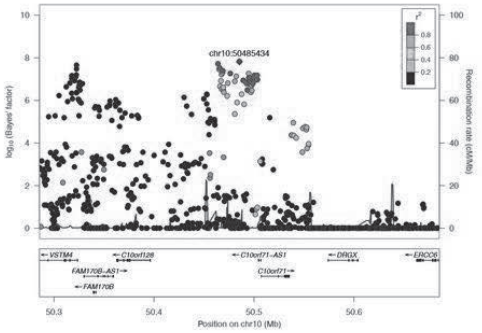

chr6:135119089
ALDH8A1
HBS1L
MRS2
Position on chr6 (Mb)

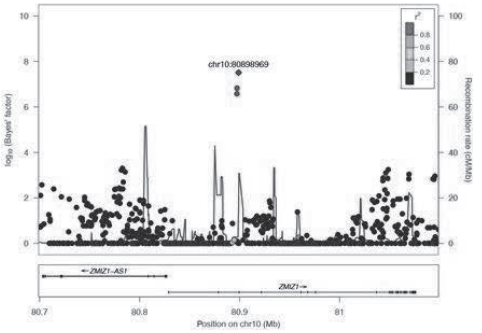

chr7:105612736
ATXN7L1
CDHR3
SYPL1
Position on chr7 (Mb)


chr8:11784541
GATA4
NEIL2
CTSB
DEFB136
DEFB130
C8orf49
FDFT1
DEFB135
LOC100133267
DEFB134
ZNF705D
FAM66D
Position on chr8 (Mb)

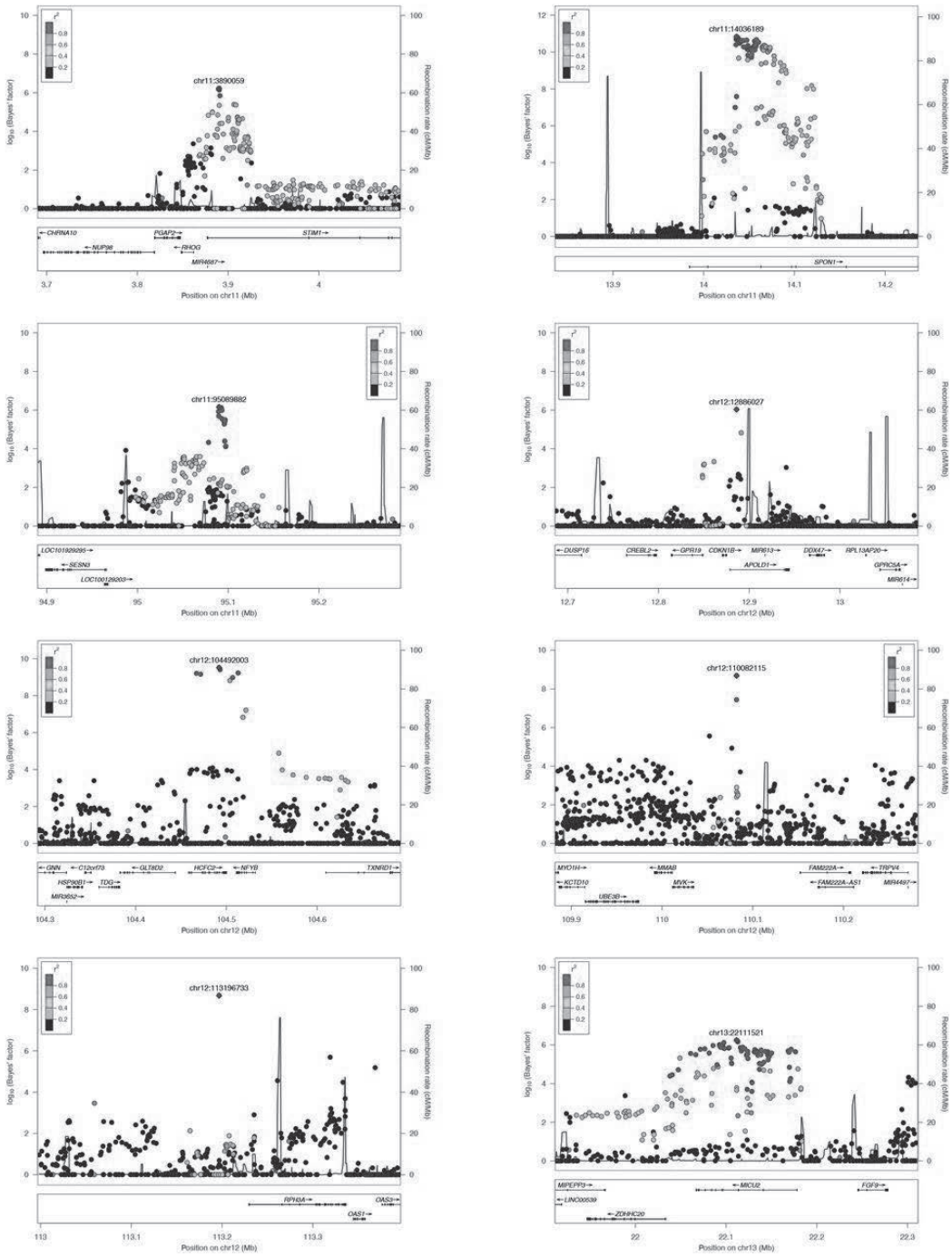

chr9:119181794
PAPPA
ASTN2
PAPPA-AS1
LOC100128505
Position on chr9 (Mb)

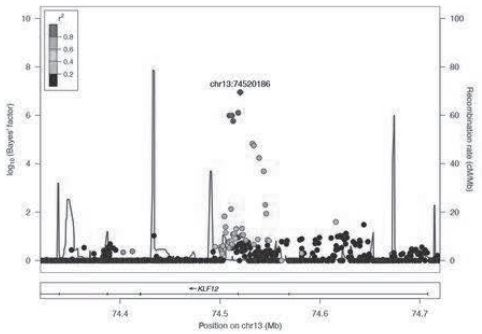

chr10:32772734
EPC1
LOC101929431
LOC102003319
CCDC7
Position on chr10 (Mb)

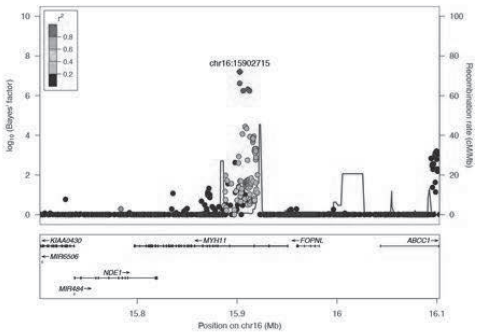

chr10:50485434
VSTM4
C10orf128
C10orf71-AS1
DRGX
ERCC6
FAM170B-AS1
C10orf71
FAM170B
Position on chr10 (Mb)

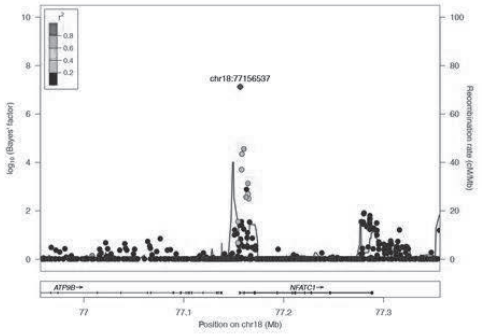

chr10:80898969
ZMIZ1-AS1
ZMIZ1
Position on chr10 (Mb)

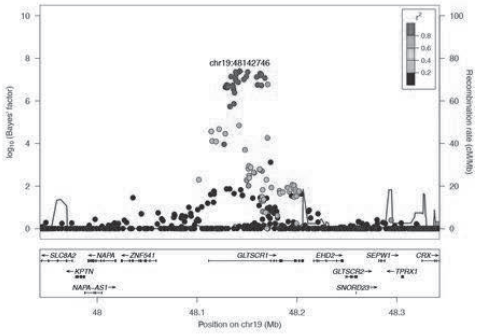
民族横断的な心房細動ゲノム解析による新たな疾患メカニズムの解明と遺伝子リスクスコアによる心原性脳梗塞の予測

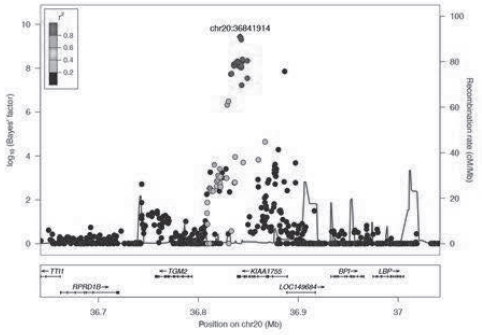


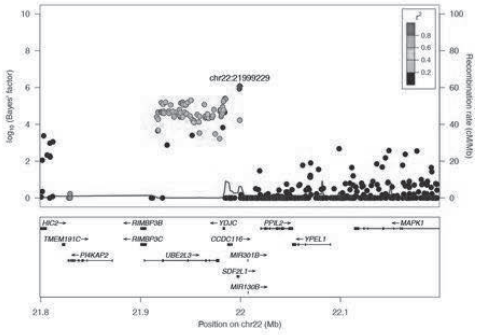

chr13:74520186
KLF12
Position on chr13 (Mb)

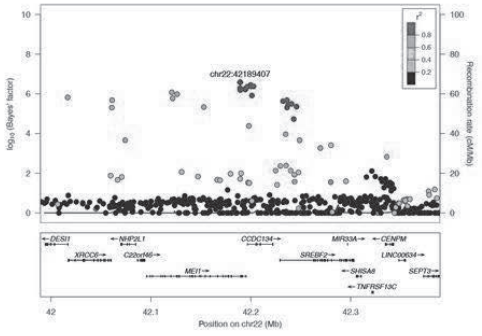

chr16:15902715
KIAA0430
MYH11
FOPNL
ABCC1
MIR8506
NDE1
MIR484
Position on chr16 (Mb)

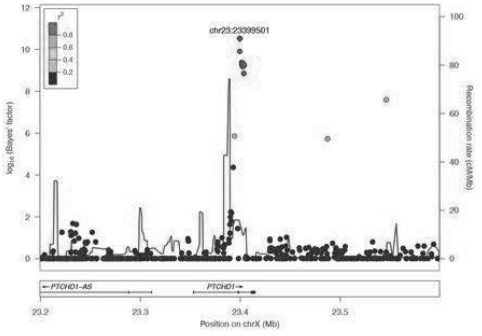

chr18:77156537
ATP9B
NFATC1
Position on chr18 (Mb)


chr19:48142746
SLC8A2
NAPA
ZNF541
GLTSCR1
EHD2
SEPW1
CRX
KPTN
NAPA-AS1
GLTSCR2
TPRX1
SNORD23
Position on chr19 (Mb)

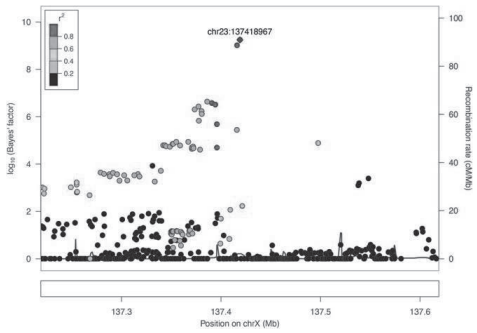

chr20:36841914
TTI1
TGM2
KIAA1755
BPI
LBP
TBPRD1B
LOC149684
Position on chr20 (Mb)


chr22:21999229
HIC2
RIMBP3B
YDJC
PPIL2
MAPK1
TMEM191C
RIMBP3C
CCDC116
YPEL1
P4HAP2
UBE2L3
MIR301B
SDF2L1
MIR130B
Position on chr22 (Mb)

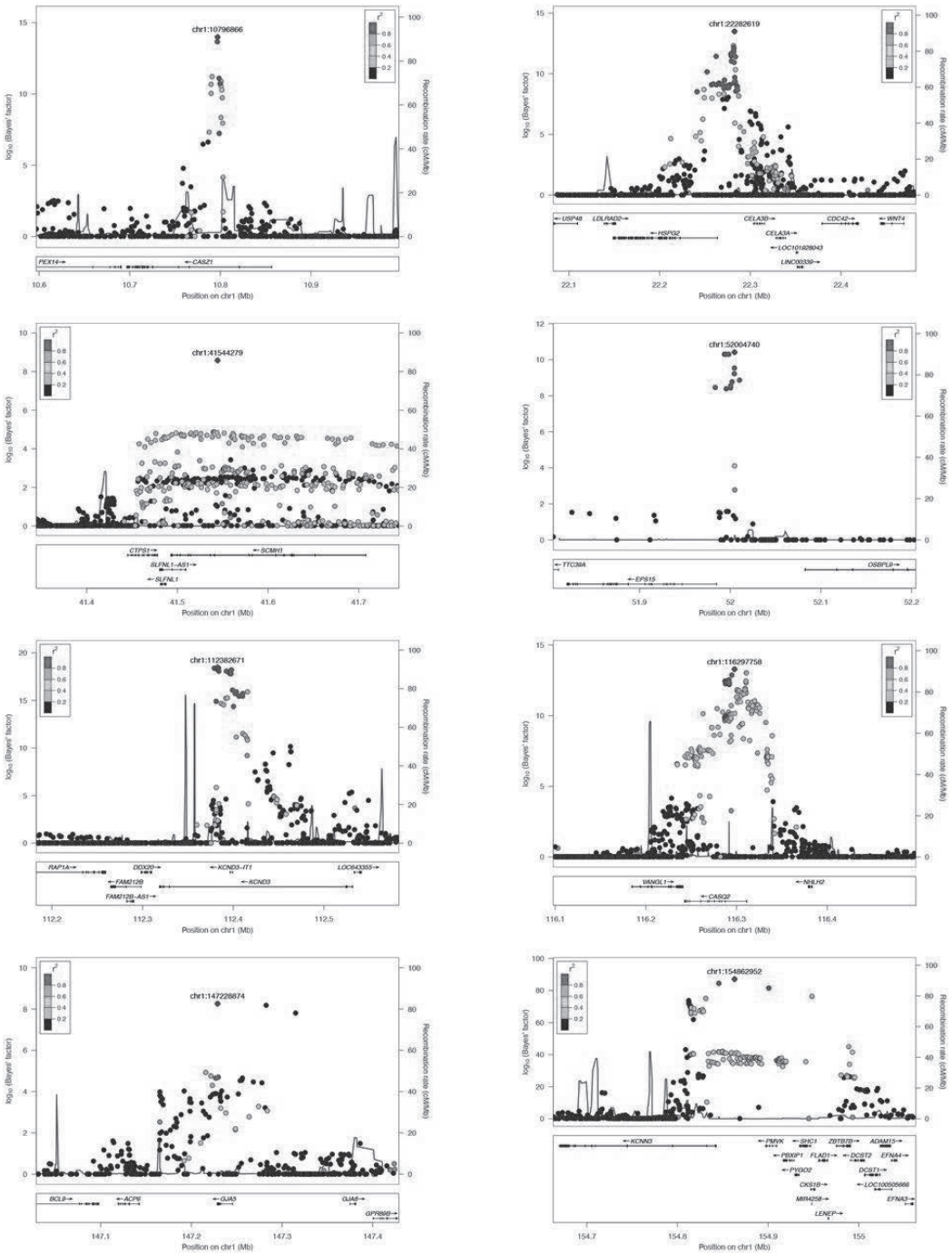

chr22:42189407
DESI1
NHP2L1
CCDC134
MIR33A
CENPM
XRCC6
C22orf46
SREBF2
LINC00634
ME1
SHISA6
SEPT3
TNFRSF13C
Position on chr22 (Mb)


chrX:23399501
PTCHD1-AS
PTCHD1
Position on chrX (Mb)

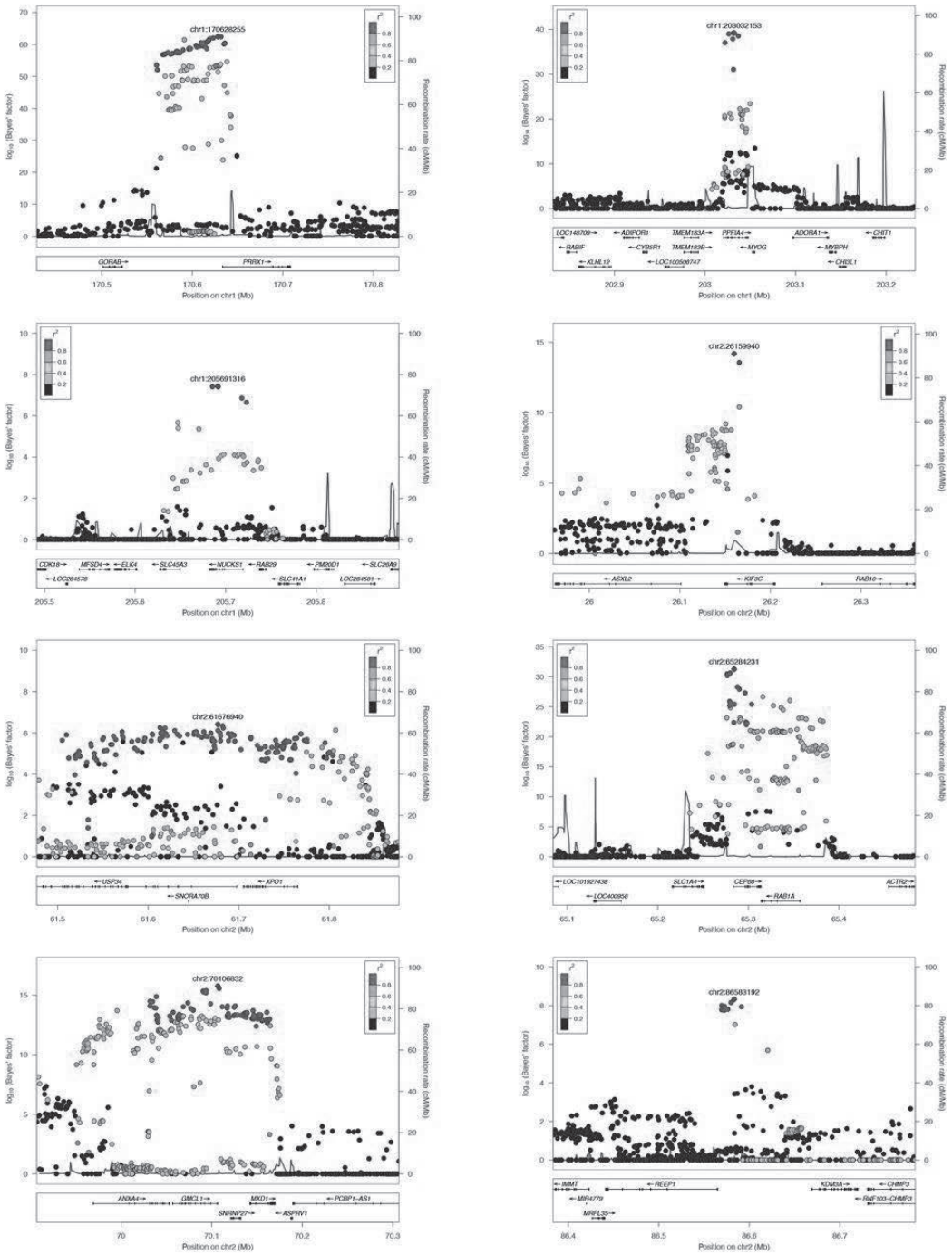
民族横断的な心房細動ゲノム解析による新たな疾患メカニズムの解明と遺伝子リスクスコアによる心原性脳梗塞の予測

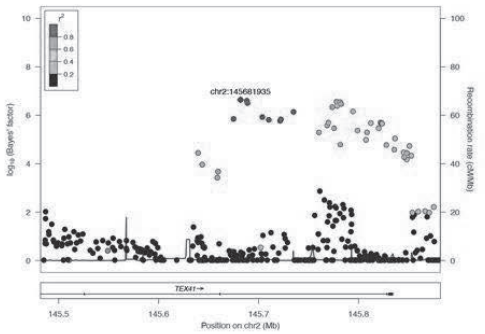


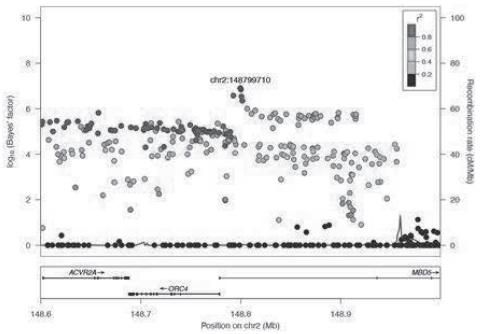
4. Previously reported 127 loci in the trans-ancestry meta-GWAS

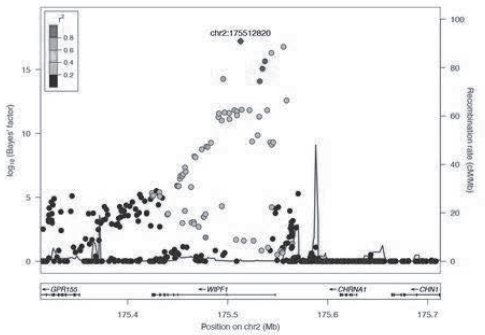


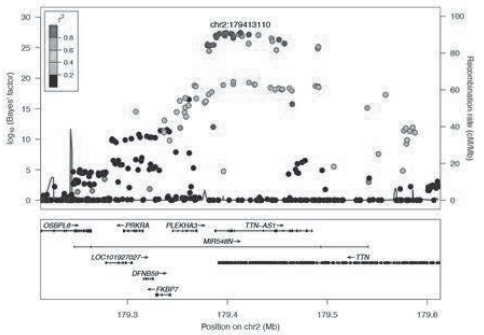
民族横断的な心房細動ゲノム解析による新たな疾患メカニズムの解明と遺伝子リスクスコアによる心原性脳梗塞の予測

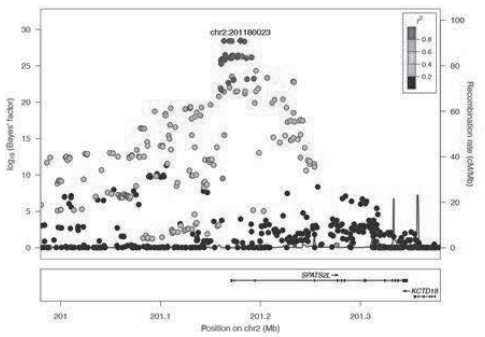


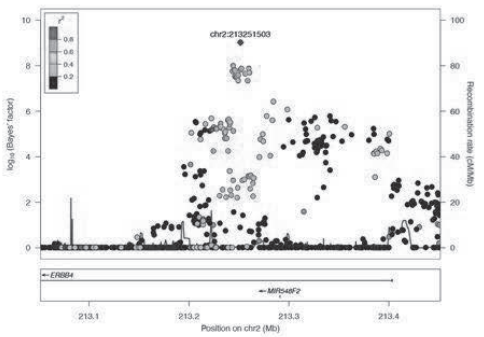

chr2:145681935
TEX41
Position on chr2 (Mb)

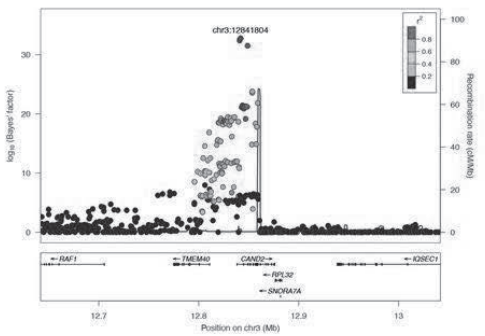

chr2:148799710
ACVR2A
ORC4
MBD5
Position on chr2 (Mb)

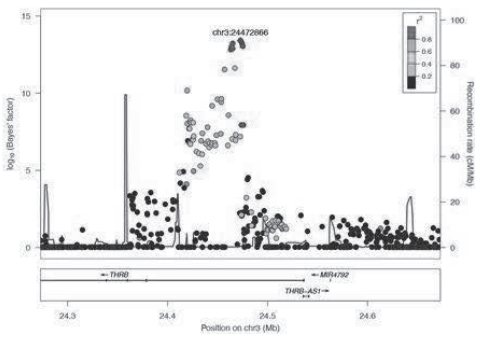

chr2:175512820
GPR155
WIPF1
CHRNA1
CHN1
Position on chr2 (Mb)


chr2:179413110
OSBPL6
PRKRA
PLEKHA3
TTN-AS1
MIR548N
LOC101927027
TTN
DFNB59
FKBP7
Position on chr2 (Mb)

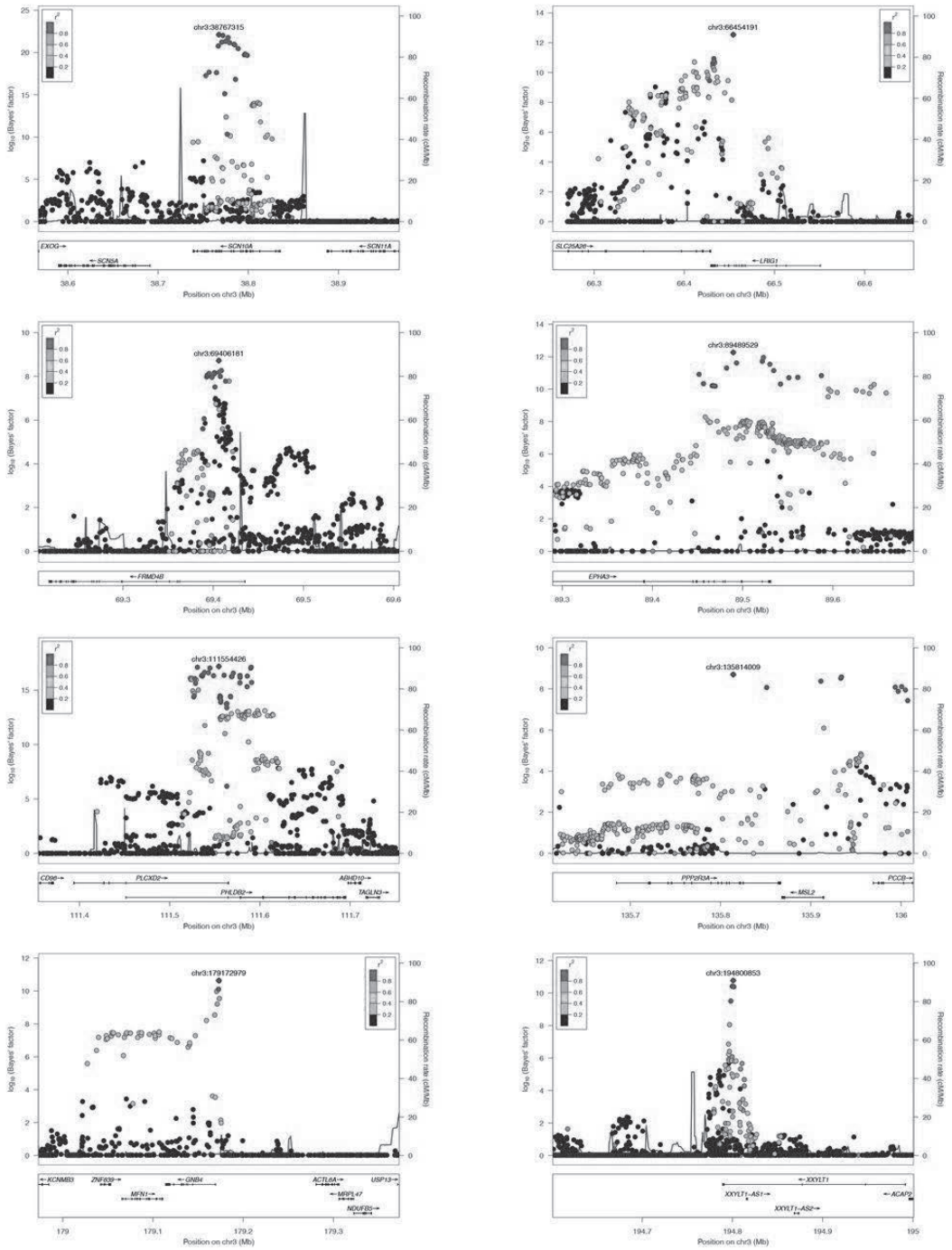

chr2:201180023
SPATS2L
KCTD18
Position on chr2 (Mb)

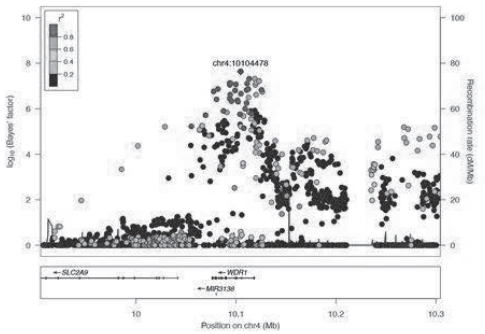

chr2:213251503
ERBB4
MIR548F2
Position on chr2 (Mb)

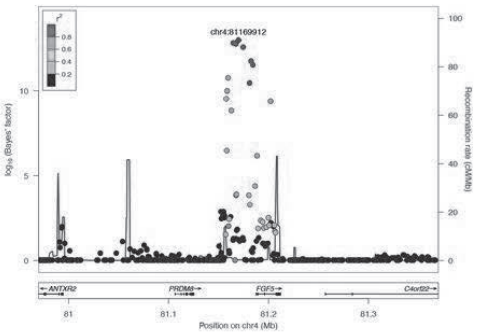

chr3:12841804
RAF1
TMEM40
CAND2
IQSEC1
RPL32
SNORA7A
Position on chr3 (Mb)

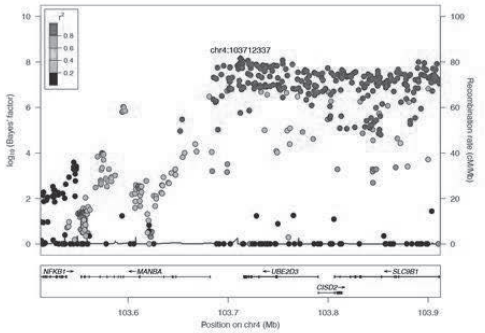

chr3:24472866
THRB
MIR4792
THRB-AS1
Position on chr3 (Mb)

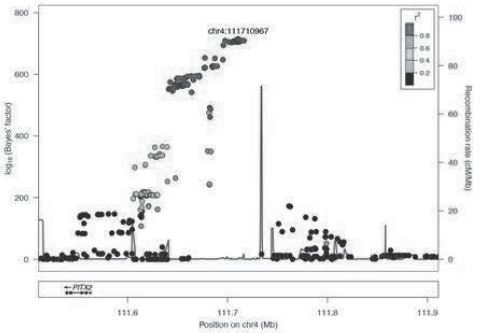
民族横断的な心房細動ゲノム解析による新たな疾患メカニズムの解明と遺伝子リスクスコアによる心原性脳梗塞の予測

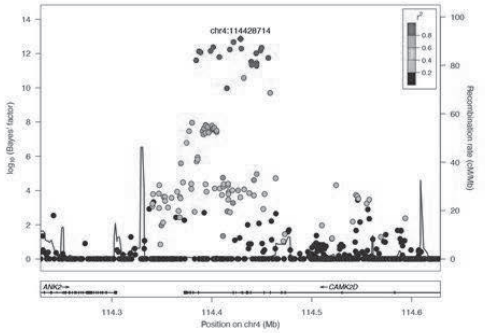


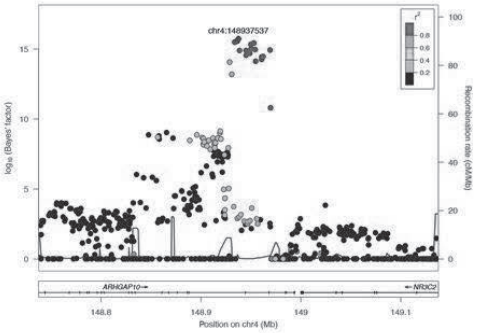

chr4:10104478
SLC2A9
WDR1
MRS1138
Position on chr4 (Mb)

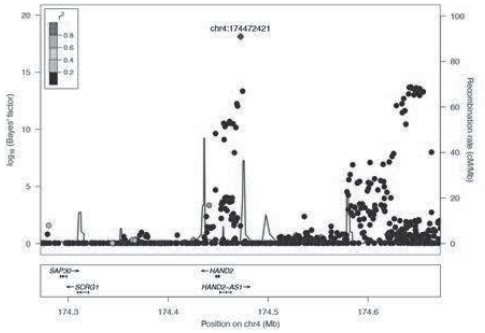

chr4:81169912
ANTXR2
PRDM8
FGF5
C4orf22
Position on chr4 (Mb)

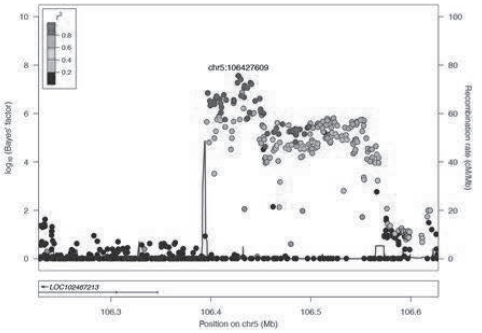

chr4:103712337
NFKB1
MANBA
UBE2D3
SLC9B1
CISD2
Position on chr4 (Mb)

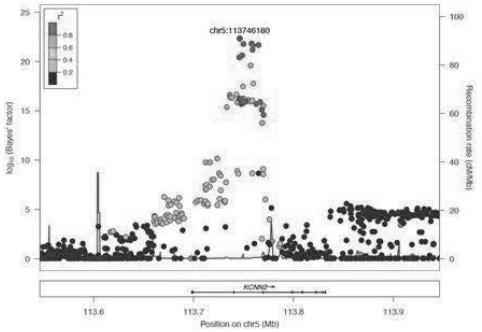

chr4:111710967
PITX2
Position on chr4 (Mb)

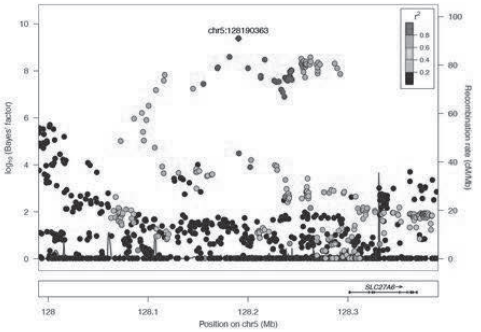

chr4:114428714
ANK2
CAMK2D
Position on chr4 (Mb)

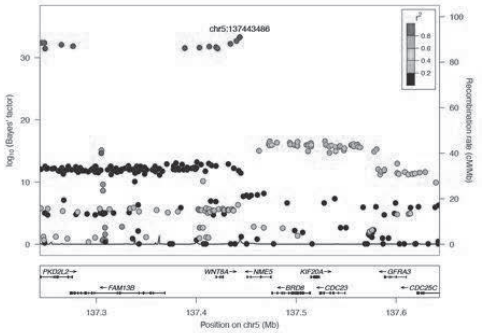

chr4:148937537
ARHGAP10
NR3C2
Position on chr4 (Mb)

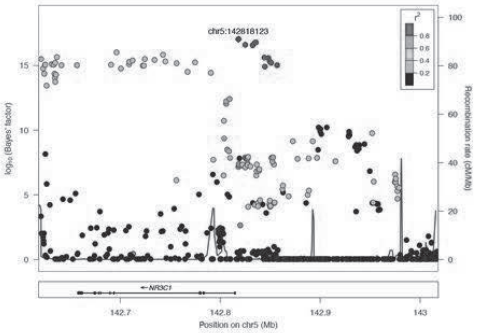

chr4:174472421
SAP30
SCRG1
HAND2
HAND2-AS1
Position on chr4 (Mb)

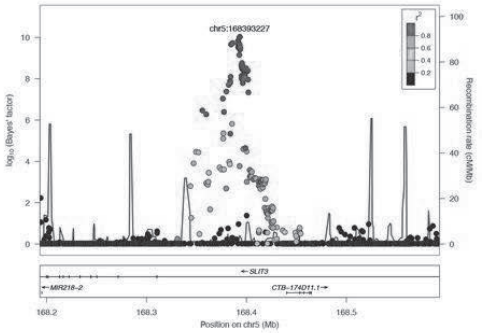

chr5:106427609
LOC102467213
Position on chr5 (Mb)

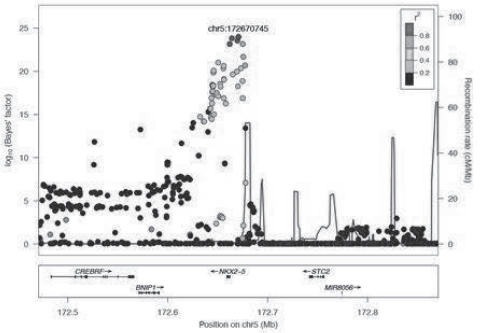

chr5:113746180
KCNN2
Position on chr5 (Mb)

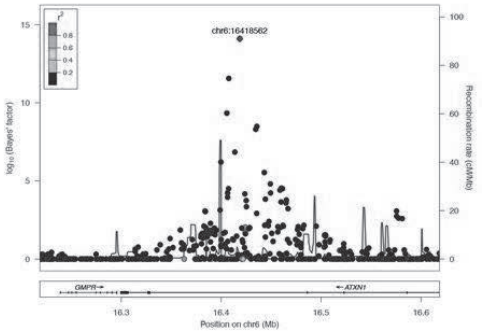

chr5:128190363
SLC27A6
Position on chr5 (Mb)

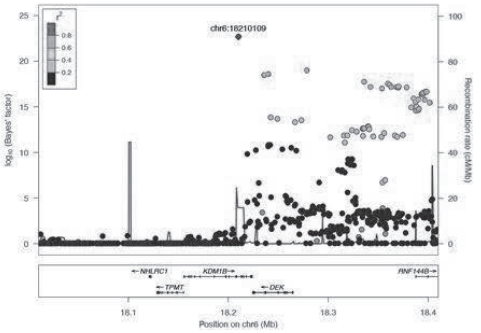

chr5:137443486
PKD2L2
FAM139
WNT8A
NME5
RPD8
KIF20A
CDC25
GFRA3
CDC25C
Position on chr5 (Mb)

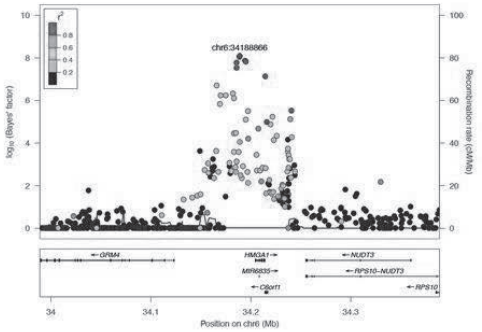

chr5:142818123
NR3C1
Position on chr5 (Mb)

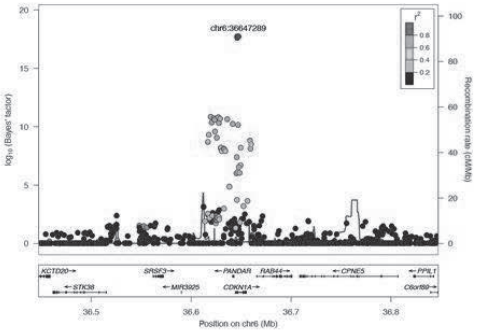

chr5:168393227
SLIT3
MIR218-2
CTB-174D11.1
Position on chr5 (Mb)

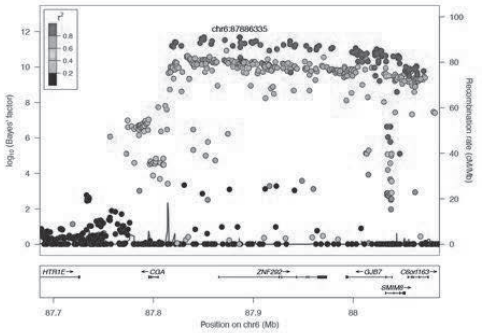

chr5:172670745
CREBRF
BNIP1
NKX2-5
MIR8056
STC2
Position on chr5 (Mb)

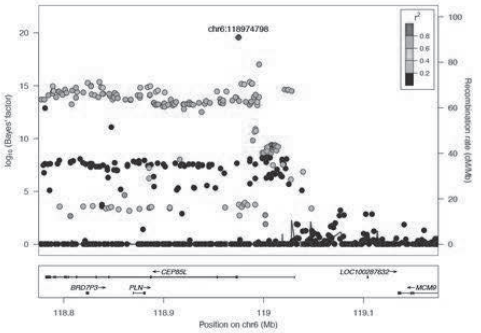

chr6:16418562
GMPS
ATXN1
Position on chr6 (Mb)

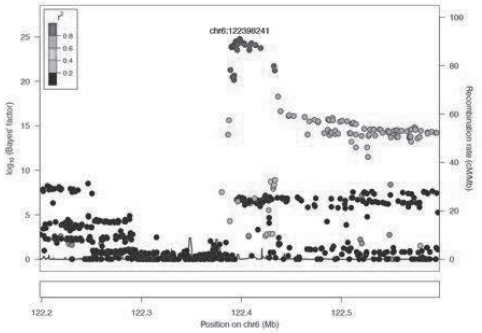

chr6:18210109
NHLRC1
KDM1B
TPMT
DEK
RNF144B
Position on chr6 (Mb)

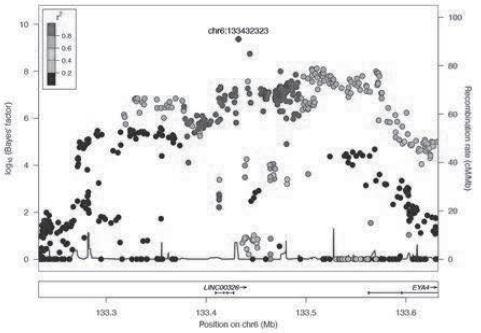

chr6:34188866
Position on chr6 (Mb)

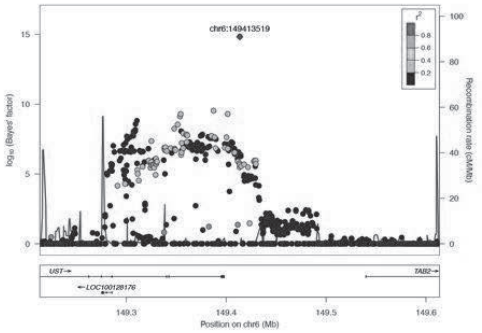

chr6:36647289
Position on chr6 (Mb)

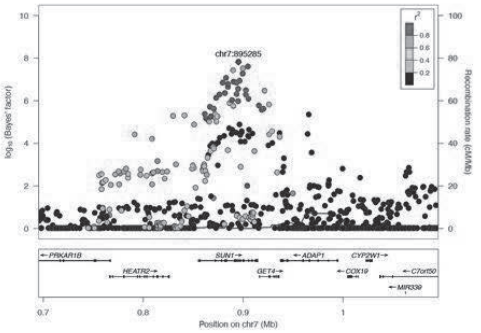

chr6:87886335
Position on chr6 (Mb)


chr6:118974798
Position on chr6 (Mb)

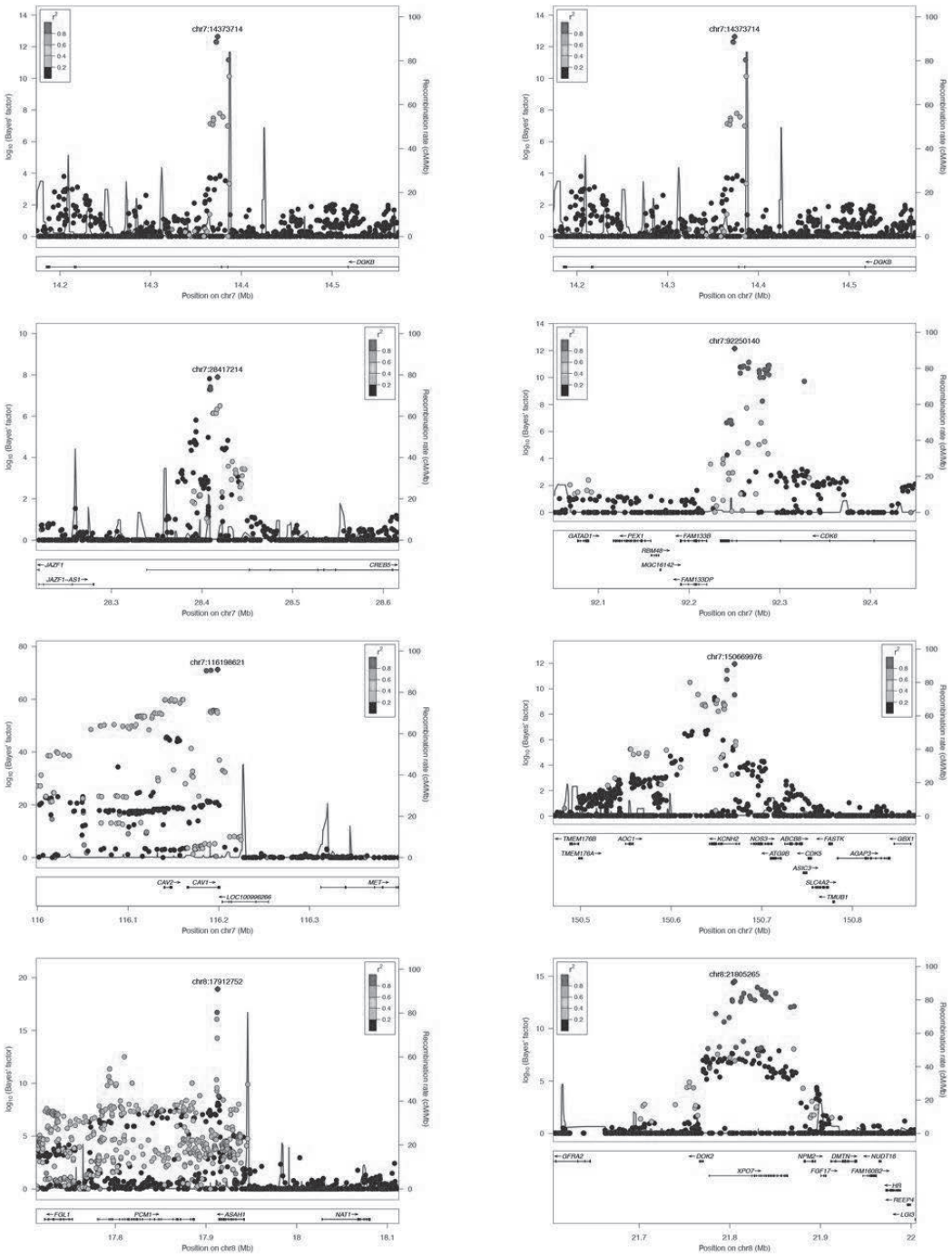

chr6:122398241
Position on chr6 (Mb)

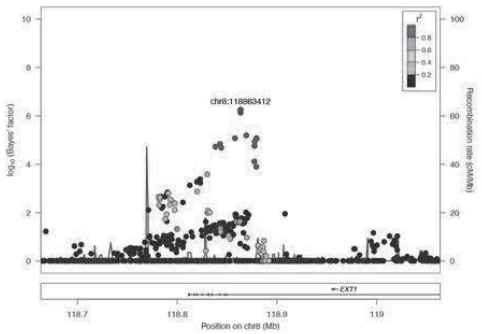

chr6:133432323
Position on chr6 (Mb)

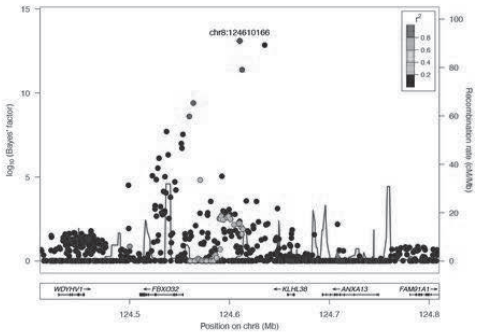

chr6:149413519
Position on chr6 (Mb)

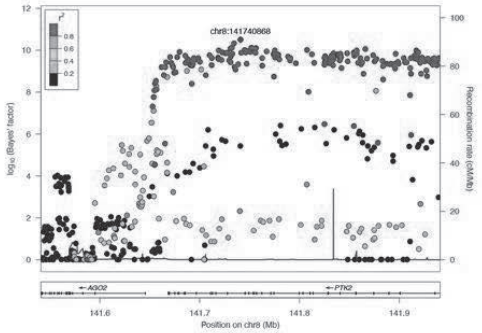

chr7:895285
Position on chr7 (Mb)

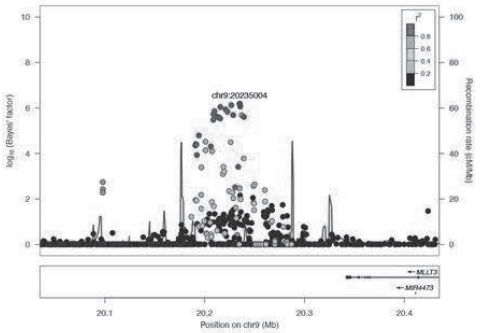
民族横断的な心房細動ゲノム解析による新たな疾患メカニズムの解明と遺伝子リスクスコアによる心原性脳梗塞の予測

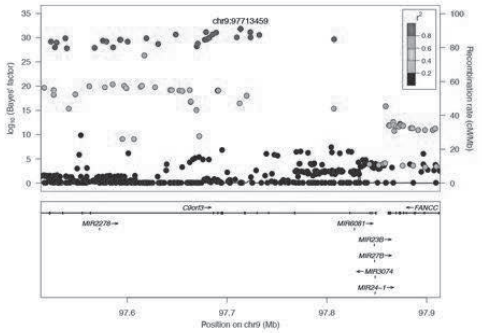


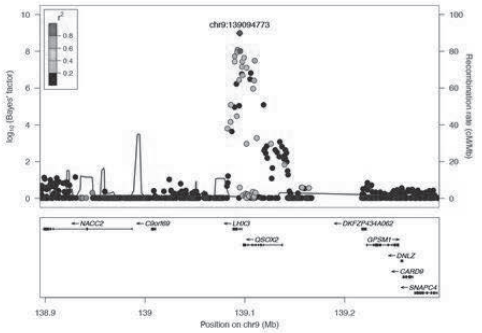

chr8:118863412
EXT1
Position on chr8 (Mb)

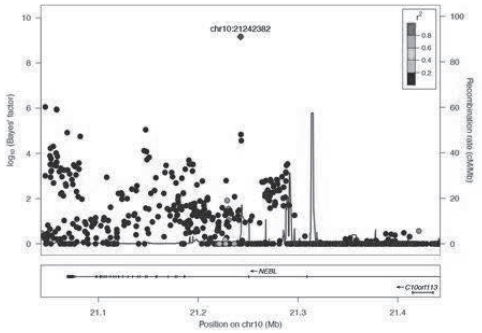

chr8:124610166
WDYHV1
FBXO32
KLHL38
ANXA13
FAM91A1
Position on chr8 (Mb)

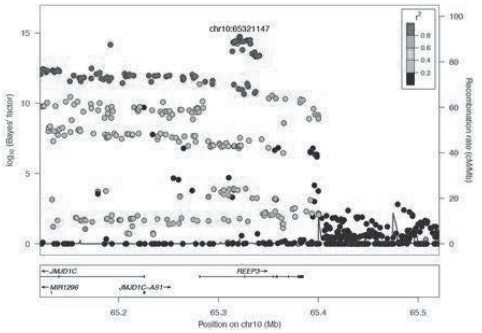

chr8:141740868
ASO2
PTK2
Position on chr8 (Mb)


chr9:20235004
MLLT3
MIR4473
Position on chr9 (Mb)

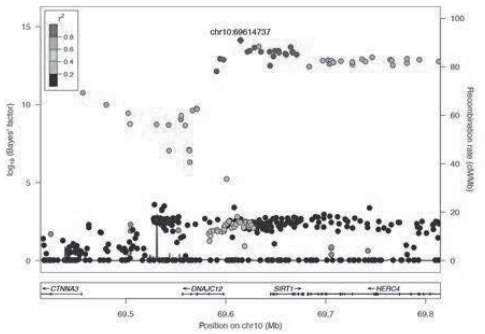

chr9:9713459
C9orf3
FANCC
MIR2278
MIR8061
MIR238
MIR378
MIR3074
MIR24-1
Position on chr9 (Mb)

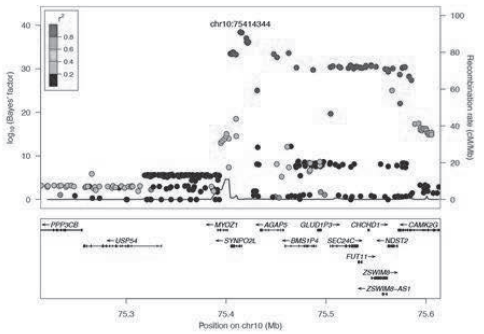

chr9:139094773
NACC2
C9orf69
LHX3
QSOX2
DKFZP434A062
GPSM1
DNLZ
CARD9
SNAPC4
Position on chr9 (Mb)

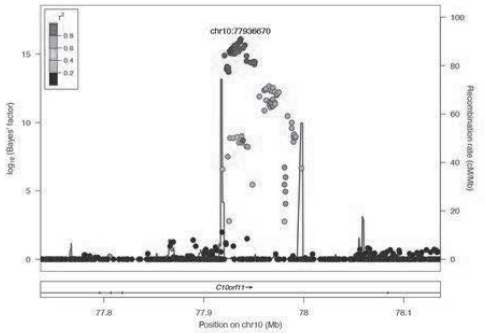

chr10:21242382
NEBL
C10orf113
Position on chr10 (Mb)

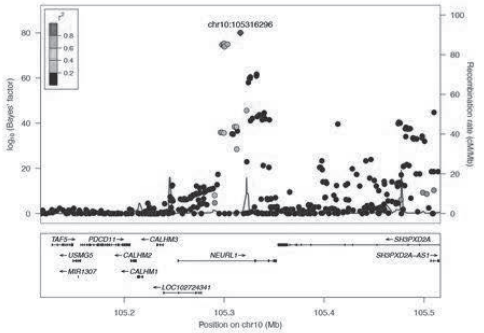

chr10:65321147
JMJD1C
MIR1296
JMJD1C-AS1
REEP3
Position on chr10 (Mb)

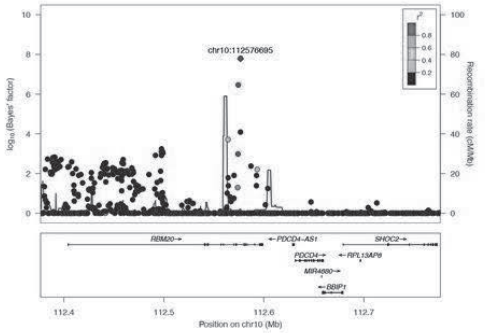
民族横断的な心房細動ゲノム解析による新たな疾患メカニズムの解明と遺伝子リスクスコアによる心原性脳梗塞の予測

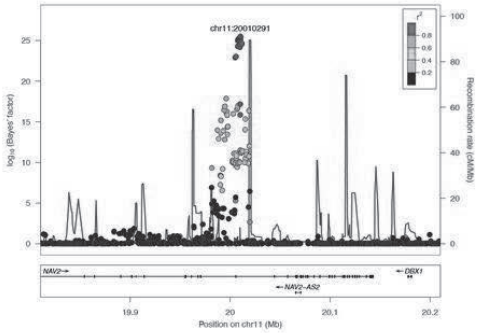


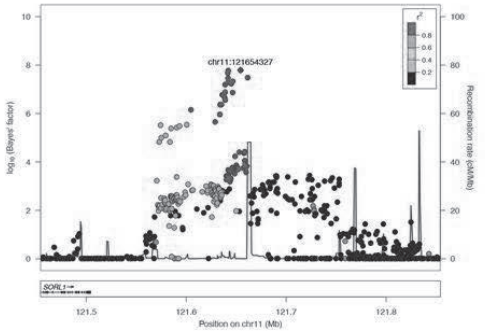


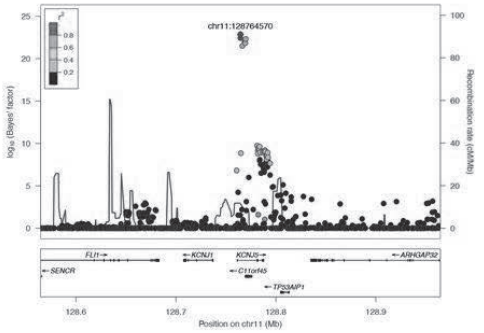


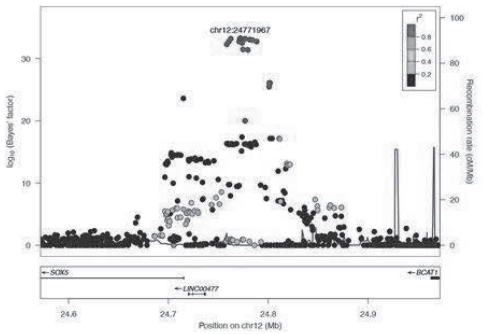


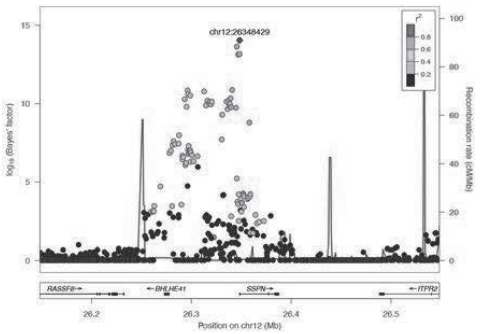


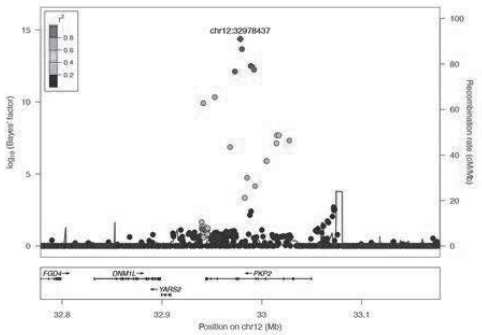


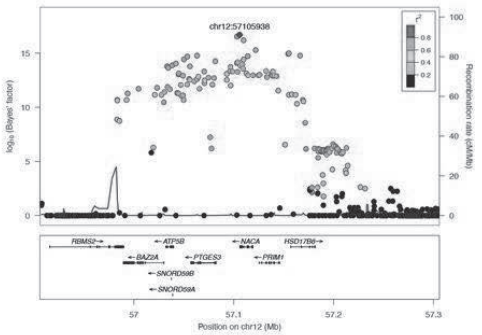


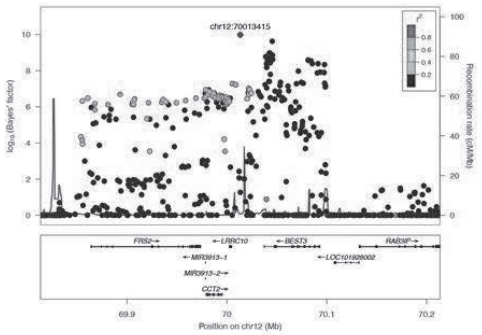


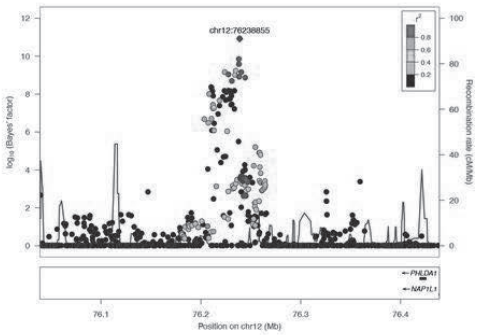

chr12:24771967
log10 (Bayes' factor)
Recombination rate (cM/Mb)
SOX5
LINC00477
BCAT1
Position on chr12 (Mb)

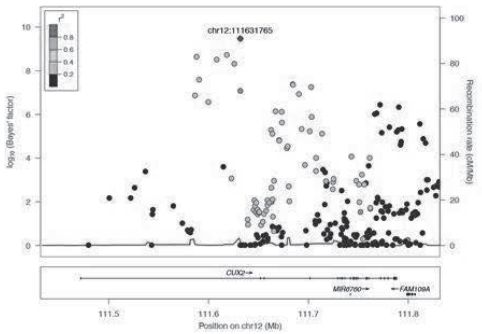

chr12:26348429
log10 (Bayes' factor)
Recombination rate (cM/Mb)
RASSF8
BHLHE41
SSPN
ITPR2
Position on chr12 (Mb)

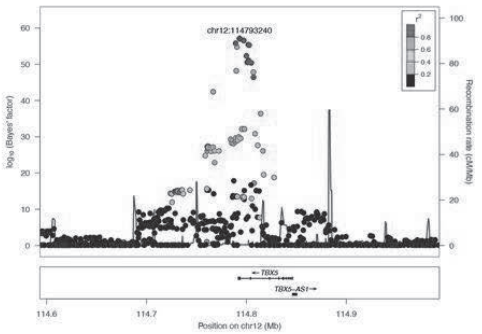

chr12:32978437
log10 (Bayes' factor)
Recombination rate (cM/Mb)
FGD4
DNM1L
YARS2
PKP2
Position on chr12 (Mb)


chr12:57105938
log10 (Bayes' factor)
Recombination rate (cM/Mb)
RBMS2
ATP5B
NACA
HSD17B8
BAZ2A
PTGES3
PRIM1
SNORD59B
SNORD59A
Position on chr12 (Mb)

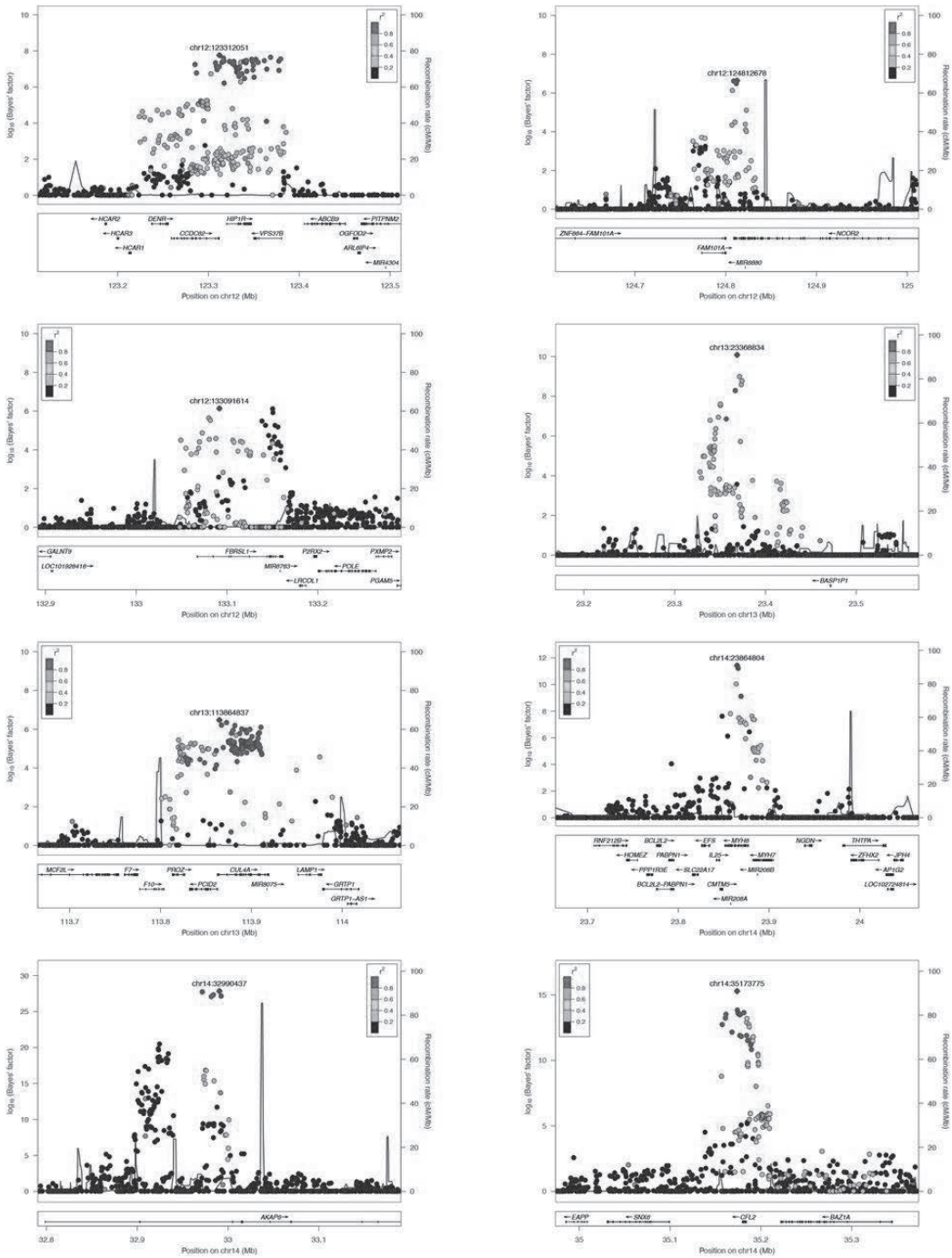

chr12:70013415
log10 (Bayes' factor)
Recombination rate (cM/Mb)
FRS2
LRRC10
BEST3
RAB3IP
MIR3913-1
LOC101928002
MIR3913-2
CCT2
Position on chr12 (Mb)

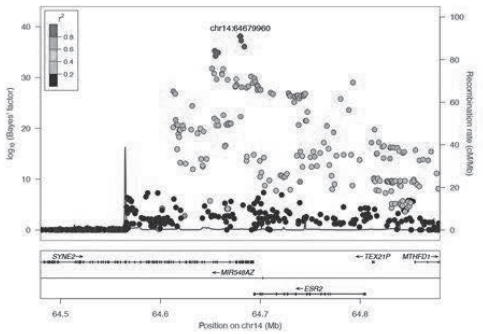

chr12:76238855
log10 (Bayes' factor)
Recombination rate (cM/Mb)
PHLDA1
NAP1L1
Position on chr12 (Mb)

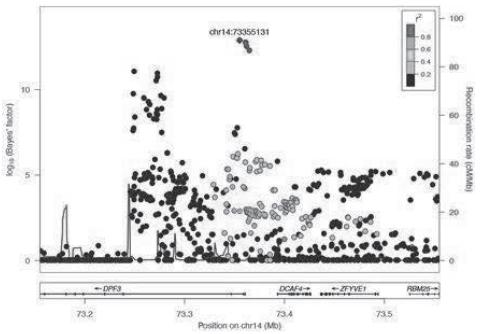

chr12:111631765
log10 (Bayes' factor)
Recombination rate (cM/Mb)
CUX2
MIR8750
FAM109A
Position on chr12 (Mb)

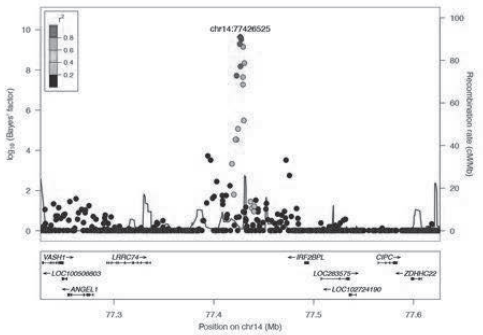

chr12:114793240
log10 (Bayes' factor)
Recombination rate (cM/Mb)
TBX5
TBX5-AS1
Position on chr12 (Mb)

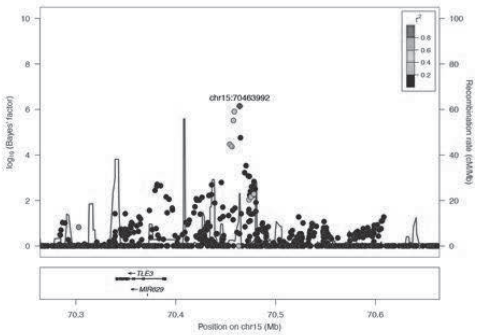
民族横断的な心房細動ゲノム解析による新たな疾患メカニズムの解明と遺伝子リスクスコアによる心原性脳梗塞の予測

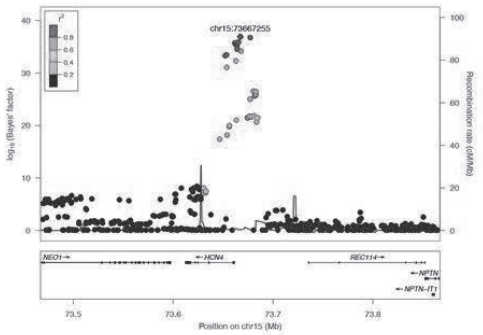


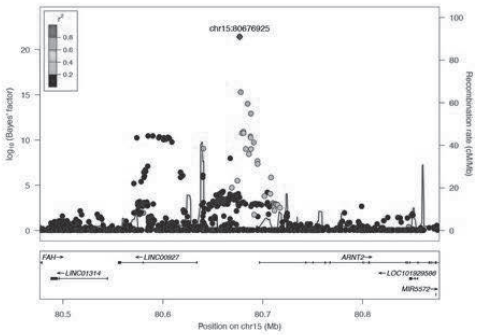

chr14:64679960
log10 (Bayes' factor)
Recombination rate (cM/Mb)
SYNE2
TEX21P
MTHFD1
MIR548AZ
ESR2
Position on chr14 (Mb)

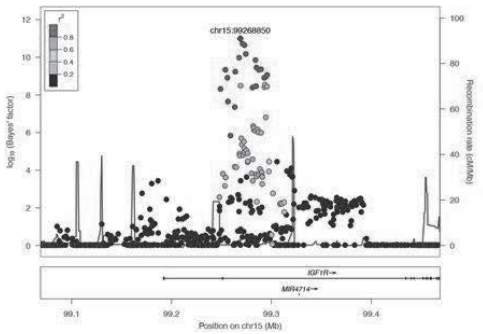

chr14:73355131
log10 (Bayes' factor)
Recombination rate (cM/Mb)
DPF3
DCAF4
ZFYVE1
RBM25
Position on chr14 (Mb)

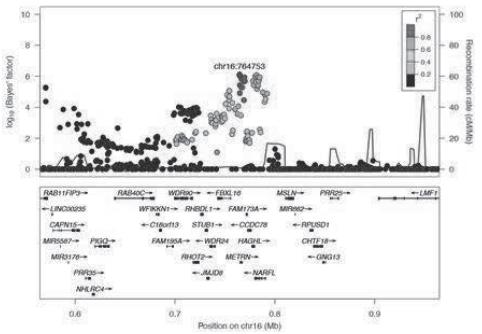

chr14:77426525
log10 (Bayes' factor)
Recombination rate (cM/Mb)
VASH1
LRRC74
IRF2BPL
CIPC
LOC100506883
LOC283575
ZFHX3
AK0EL1
LOC102724190
Position on chr14 (Mb)


chr15:70463992
log10 (Bayes' factor)
Recombination rate (cM/Mb)
TLE3
MIR629
Position on chr15 (Mb)

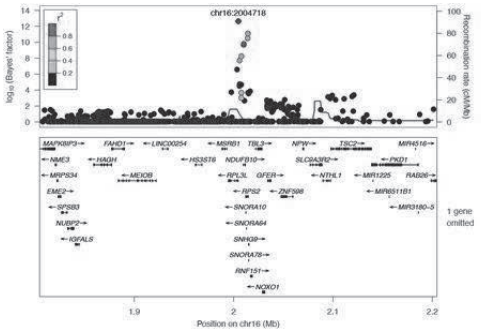

chr15:73667255
log10 (Bayes' factor)
Recombination rate (cM/Mb)
NEO1
HCN4
REC114
NPTN
NPTN-IT1
Position on chr15 (Mb)

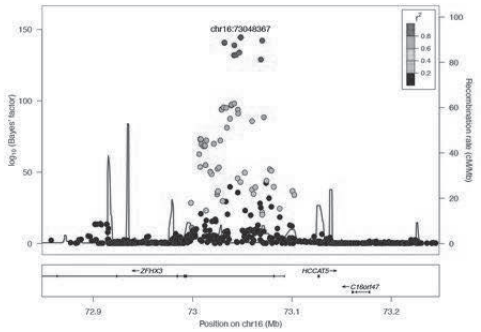

chr15:80676925
log10 (Bayes' factor)
Recombination rate (cM/Mb)
FAN1
LINC00927
ARNT2
LINC01314
LOC101928566
MIR3572
Position on chr15 (Mb)

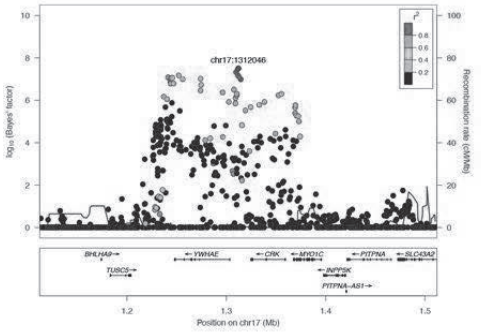

chr15:99268850
log10 (Bayes' factor)
Recombination rate (cM/Mb)
IGF1R
MIR4714
Position on chr15 (Mb)

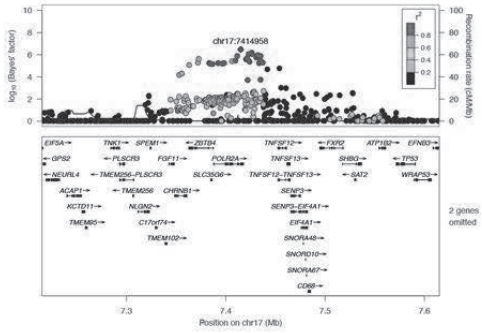

chr16:764753
log10 (Bayes' factor)
Recombination rate (cM/Mb)
RAB11FIP3
RAB40C
WDR90
FBXL16
MSLN
PRR25
LMF1
LINC00235
WFIKKN1
RHBDL1
FAM73A
MIR662
CAPN15
C16orf13
STUB1
CCDC78
RPUSD1
MIR5587
PIGQ
FAM195A
WDR24
HAGHL
CHTF18
MIR3178
RHOT2
METRN
GNG13
PRR35
JMJD8
NARFL
NHLRC4
Position on chr16 (Mb)

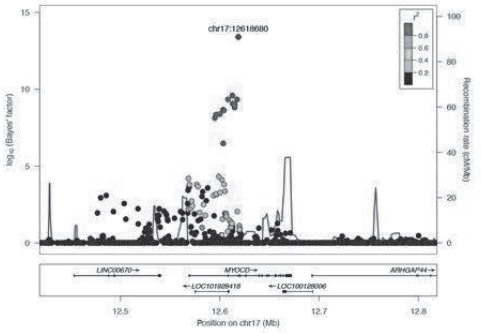
民族横断的な心房細動ゲノム解析による新たな疾患メカニズムの解明と遺伝子リスクスコアによる心原性脳梗塞の予測

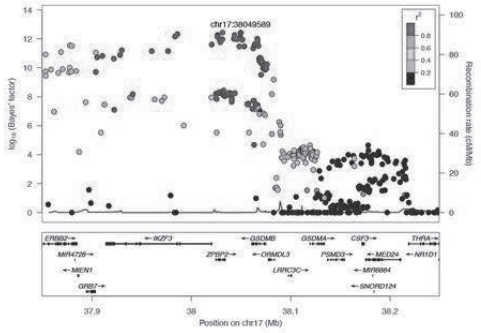


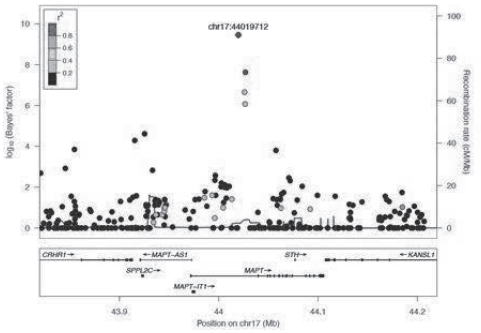


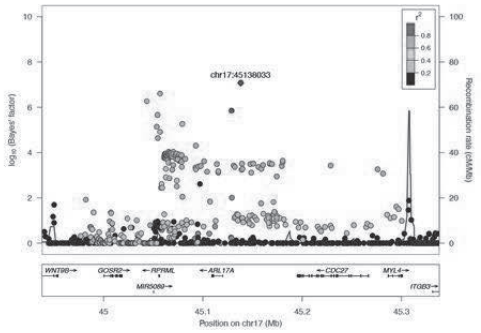


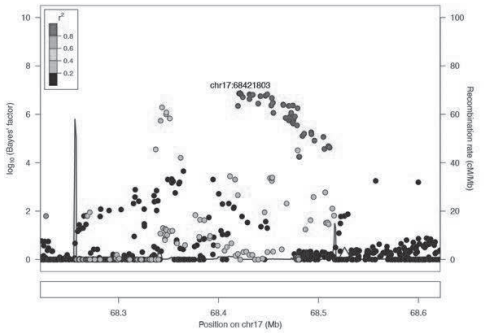


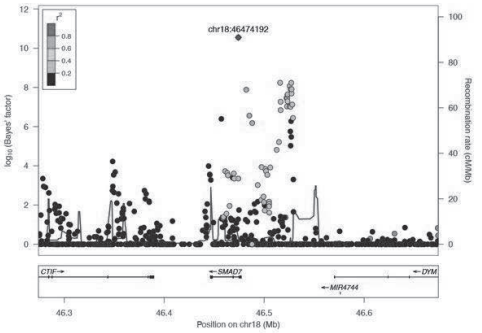


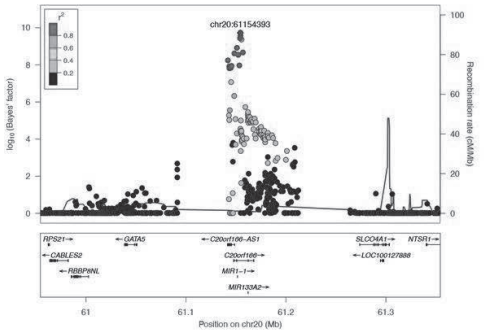


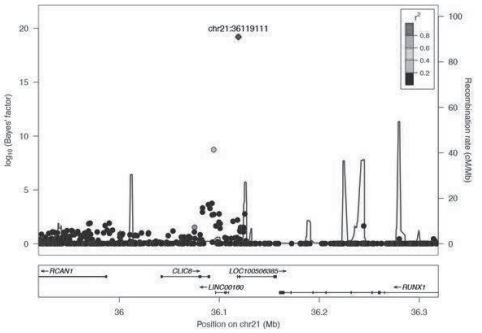


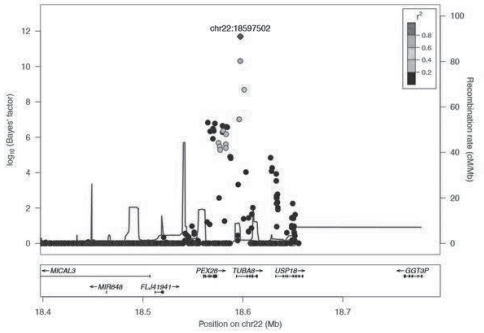


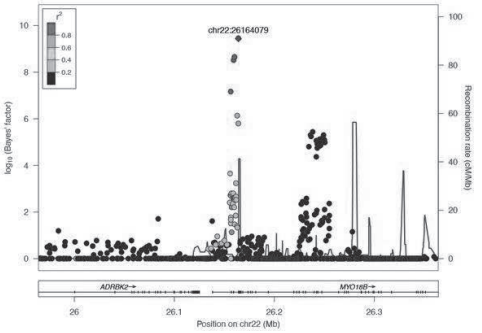

chr17:68421803
log10 (Bayes' factor)
Recombination rate (cM/Mb)
Position on chr17 (Mb)


chr18:46474192
log10 (Bayes' factor)
Recombination rate (cM/Mb)
CTIF
SMAD7
DYM
MIR4744
Position on chr18 (Mb)


chr20:61154393
log10 (Bayes' factor)
Recombination rate (cM/Mb)
RPS21
GATA5
C20orf166-AS1
SLCO4A1
NTSR1
CABLES2
C20orf166
LOC100127888
RBBP9NL
MIR1-1
MIR133A2
Position on chr20 (Mb)


chr21:36119111
log10 (Bayes' factor)
Recombination rate (cM/Mb)
RCAN1
CLIC6
LOC100506385
LINC00160
RUNX1
Position on chr21 (Mb)


chr22:18597502
log10 (Bayes' factor)
Recombination rate (cM/Mb)
MICAL3
PEX26
TUBA8
USP18
GGT3P
MIR648
FLJ41941
Position on chr22 (Mb)


chr22:26164079
log10 (Bayes' factor)
Recombination rate (cM/Mb)
ADRBK2
MYO16
Position on chr22 (Mb)

Supplementary Table 6 | Significant association loci in trans-ancestry meta-analysis

CHR	POS	Locus		REF	ALT	rsID	Gene	Annotation	log10BF	BBJ				EUR				FIN				Status
		Start	End							AAF	Beta	SE	P	AAF	Beta	SE	P	AAF	Beta	SE	P	
1	918617	410935	1418617	G	A	rs4970418	*PERM1, HES4*	intergenic	7.647	0.076	0.062	0.028	2.9.E-02	0.167	0.044	0.010	7.5.E-06	0.175	0.102	0.025	4.1.E-05	novel
1	10796866	10280727	11302468	T	C	rs880315	*CASZ1*	intronic	13.984	0.681	0.057	0.016	4.0.E-04	0.353	0.041	0.007	3.2.E-09	0.412	0.102	0.019	1.2.E-07	known
1	16199051	15699051	16699051	T	C	rs9782984	*MIR5096*	ncRNA intronic	6.970	0.723	-0.075	0.017	1.5.E-05	0.883	-0.055	0.014	8.4.E-05	0.835	-0.035	0.025	1.7.E-01	novel
1	22282619	21741185	22805915	T	C	rs7529220	*HSPG2, CELA3B*	intergenic	13.485	0.676	0.057	0.016	3.9.E-04	0.847	0.062	0.010	2.0.E-10	0.788	0.078	0.023	7.2.E-04	known
1	39385714	38885714	39885714	G	A	rs75414548	*RHBDL2*	intronic	6.439	0.060	0.068	0.032	3.5.E-02	0.077	0.068	0.015	4.4.E-06	0.059	0.106	0.040	8.2.E-03	novel
1	41544279	41044279	42044279	G	T	rs2885697	*SCMH1*	intronic	8.571	0.686	-0.005	0.016	7.5.E-01	0.648	-0.044	0.007	2.9.E-10	0.662	-0.056	0.020	5.1.E-03	known
1	52004740	51001896	52510097	T	A	rs12022114	*EPS15, OSBPL9*	intergenic	10.411	0.095	-0.008	0.025	7.5.E-01	0.033	0.145	0.020	1.7.E-13	0.040	0.019	0.047	6.9.E-01	known
1	100149308	99649308	100649308	G	A	rs1933723	*PALMD*	intronic	6.298	0.698	0.034	0.016	3.8.E-02	0.677	0.036	0.007	5.2.E-07	0.664	0.027	0.020	1.8.E-01	novel
1	112382671	111879026	112963617	G	A	rs11102343	*KCND3*	intronic	18.445	0.502	0.087	0.015	6.1.E-09	0.097	0.066	0.011	2.2.E-09	0.185	0.110	0.024	5.2.E-06	known
1	116297758	115734313	116839337	C	A	rs4073778	*CASQ2*	intronic	13.267	0.289	0.055	0.016	7.5.E-04	0.564	0.049	0.007	5.0.E-13	0.567	0.021	0.019	2.8.E-01	known
1	147228874	146728874	147814940	C	T	rs11240121	*GJA5*	3'UTR	8.256	0.489	0.084	0.015	1.6.E-08	0.195	0.034	0.008	4.5.E-05	0.186	0.017	0.024	4.8.E-01	known
1	154862952	153895125	156168700	C	T	rs11264280	*KCNN3, PMVK*	intergenic	87.114	0.085	0.071	0.026	6.2.E-03	0.333	0.135	0.007	3.1.E-79	0.361	0.125	0.020	1.6.E-10	known
1	170628255	169603834	171411565	G	A	rs680084	*GORAB, PRRX1*	intergenic	62.406	0.461	-0.150	0.015	2.0.E-23	0.535	-0.091	0.007	3.3.E-42	0.523	-0.072	0.019	1.2.E-04	known
1	203032153	202519737	203555101	A	G	rs4950913	*PPFIA4*	intronic	39.187	0.305	-0.157	0.017	3.8.E-21	0.552	-0.060	0.007	1.6.E-19	0.643	-0.078	0.020	8.0.E-05	known
1	205691316	205185352	206222958	G	A	rs4951258	*NUCKS1*	intronic	7.418	0.363	0.020	0.015	2.0.E-01	0.416	0.038	0.007	2.1.E-08	0.364	0.041	0.020	3.6.E-02	known
2	26159940	25609402	26665568	T	C	rs6546620	*KIF3C*	intronic	14.173	0.124	0.102	0.022	3.7.E-06	0.800	0.060	0.009	3.2.E-12	0.713	0.030	0.021	1.5.E-01	known
2	61676940	61071295	62306999	C	T	rs2694635	*USP34*	intronic	6.407	0.674	0.018	0.016	2.6.E-01	0.613	0.038	0.007	3.2.E-08	0.620	0.022	0.019	2.7.E-01	known
2	65284231	64735333	65886462	A	T	rs2540949	*CEP68*	intronic	31.262	0.325	-0.089	0.016	3.1.E-08	0.385	-0.066	0.007	2.9.E-22	0.340	-0.100	0.020	4.8.E-07	known
2	70106832	69405400	70675327	T	C	rs6747542	*GMCL1*	3'UTR	15.745	0.682	-0.038	0.016	1.8.E-02	0.464	-0.055	0.007	1.1.E-16	0.530	-0.031	0.019	1.0.E-01	known
2	86583192	86069404	87091272	T	C	rs13387570	*REEP1, KDM3A*	intergenic	8.311	0.194	-0.003	0.019	8.6.E-01	0.179	-0.053	0.009	9.5.E-10	0.149	-0.083	0.027	1.8.E-03	known
2	145681935	145181935	146294405	G	A	rs11679718	*TEX41*	ncRNA intronic	6.641	0.664	0.031	0.016	5.3.E-02	0.100	0.059	0.011	4.9.E-08	0.085	0.035	0.033	2.9.E-01	known
2	148799710	148292665	149306433	C	A	rs12992231	*MBD5*	intronic	6.893	0.504	0.039	0.015	9.3.E-03	0.357	0.031	0.007	5.0.E-06	0.363	0.052	0.020	8.4.E-03	known
2	175512820	174952275	176058804	G	A	rs7574892	*WIPF1*	intronic	17.213	0.390	0.046	0.016	3.3.E-03	0.485	0.055	0.007	2.0.E-16	0.484	0.045	0.019	1.7.E-02	known
2	179413110	178784643	180192967	G	A	rs3731748	*TTN*	exonic	27.396	0.435	0.052	0.015	5.1.E-04	0.140	0.094	0.009	8.3.E-24	0.153	0.119	0.026	4.4.E-06	known
2	201180023	199754002	201806139	T	C	rs3820888	*SPATS2L*	intronic	28.423	0.690	0.093	0.016	1.4.E-08	0.392	0.068	0.007	5.7.E-24	0.454	0.039	0.019	3.7.E-02	known
2	213251503	212743651	213798393	T	C	rs13019524	*ERBB4*	intronic	9.014	0.132	-0.043	0.022	5.6.E-02	0.344	-0.044	0.007	5.0.E-10	0.372	-0.030	0.019	1.2.E-01	known
3	12841804	12259080	12841804	A	G	rs7650482	*CAND2*	intronic	32.733	0.299	0.085	0.016	1.4.E-07	0.640	0.071	0.007	1.8.E-24	0.610	0.094	0.019	1.3.E-06	known
3	24472866	23918590	24975752	A	G	rs73032363	*THRB*	intronic	13.406	0.308	-0.064	0.016	9.7.E-05	0.295	-0.044	0.007	2.2.E-09	0.246	-0.090	0.022	4.6.E-05	known
3	38767315	37603776	39326179	T	C	rs6801957	*SCN10A*	intronic	22.109	0.784	0.066	0.018	3.2.E-04	0.602	0.062	0.007	6.9.E-20	0.546	0.052	0.019	6.3.E-03	known
3	66454191	65834633	66954191	G	A	rs34080181	*LRIG1*	intronic	12.534	0.215	-0.062	0.019	9.1.E-04	0.379	-0.045	0.007	1.3.E-10	0.323	-0.057	0.020	4.5.E-03	known
3	69406181	68889842	69917585	C	T	rs17005647	*FRMD4B*	intronic	8.711	0.718	0.025	0.017	1.4.E-01	0.364	0.041	0.007	2.7.E-09	0.336	0.044	0.020	2.6.E-02	known
3	89489529	88948196	90251353	T	C	rs6771054	*EPHA3*	intronic	12.261	0.149	-0.024	0.021	2.6.E-01	0.404	-0.046	0.007	2.4.E-11	0.487	-0.075	0.019	6.6.E-05	known
3	111554426	110923630	112190620	G	A	rs10804493	*PHLDB2, PLCXD2*	intronic	17.173	0.514	0.053	0.015	3.9.E-04	0.651	0.056	0.007	1.6.E-15	0.605	0.049	0.019	1.1.E-02	known
3	135814009	135314009	137000733	G	A	rs1278493	*PPP2R3A*	intronic	8.694	0.197	-0.040	0.020	4.7.E-02	0.565	-0.039	0.007	8.8.E-09	0.456	-0.045	0.019	1.8.E-02	known
3	179172979	178537434	179673620	G	T	rs7612445	*GNB4, ACTL6A*	intergenic	10.634	0.179	0.068	0.021	9.2.E-04	0.188	0.049	0.008	4.8.E-09	0.111	0.080	0.030	7.6.E-03	known
3	194800853	194295645	195301442	C	T	rs60902112	*XXYLT1*	intronic	10.767	0.604	0.049	0.015	1.3.E-03	0.226	0.045	0.008	1.7.E-08	0.188	0.082	0.024	6.1.E-04	known
4	10104478	9577638	10626235	T	C	rs12640611	*WDR1*	intronic	7.628	0.579	0.048	0.015	1.7.E-03	0.684	0.037	0.007	4.6.E-07	0.682	0.030	0.020	1.3.E-01	known
4	71776935	71276935	72276935	A	C	rs12512502	*MOB1B*	intronic	6.547	0.621	-0.039	0.016	1.4.E-02	0.623	-0.034	0.007	1.3.E-06	0.542	-0.030	0.019	1.2.E-01	novel
4	81169912	80657703	81702048	G	T	rs11099098	*PRDM8, FGF5*	intergenic	12.963	0.338	0.053	0.016	6.2.E-04	0.309	0.043	0.007	3.0.E-09	0.342	0.087	0.020	1.2.E-05	known
4	83910712	83327822	84483700	T	G	rs6841049	*LIN54*	intronic	7.628	0.342	-0.044	0.016	5.6.E-03	0.567	-0.037	0.007	6.0.E-08	0.608	-0.019	0.019	3.2.E-01	novel
4	103712337	103094918	104460768	A	T	rs223449	*LOC102723704*	ncRNA intronic	8.147	0.464	0.039	0.015	9.9.E-03	0.489	0.036	0.007	7.1.E-08	0.459	0.036	0.019	5.6.E-02	known
4	111710967	110777746	113087504	T	A	rs17042175	*PITX2, C4orf32*	intergenic	713.837	0.455	0.509	0.015	3.3.E-249	0.111	0.427	0.010	1.89e-395	0.152	0.478	0.026	5.1.E-76	known
4	114428714	113874813	114958402	C	T	rs55754224	*CAMK2D*	intronic	12.853	0.055	0.044	0.032	1.7.E-01	0.261	0.055	0.008	2.2.E-13	0.261	0.049	0.021	2.2.E-02	known
4	148937537	148335571	149469618	C	G	rs10213171	*ARHGAP10*	intronic	15.718	0.082	0.144	0.026	2.5.E-08	0.061	0.091	0.013	1.3.E-11	0.104	0.052	0.031	8.9.E-02	known
4	174472421	173947349	175181860	C	A	rs4282143	*HAND2-AS1*	ncRNA intronic	18.122	0.891	-0.202	0.023	3.6.E-19	0.993	-0.168	0.070	1.7.E-02	0.971	-0.097	0.057	8.6.E-02	known
5	106427609	105896918	106949990	C	A	rs6596717	*LINC01950, EFNA5*	intergenic	7.544	0.771	-0.014	0.018	4.3.E-01	0.605	-0.040	0.007	3.0.E-09	0.636	-0.034	0.020	8.3.E-02	known
5	113746180	113170474	114951109	A	G	rs337708	*KCNN2*	intronic	22.323	0.157	0.122	0.020	5.3.E-10	0.380	0.055	0.007	5.4.E-16	0.374	0.056	0.020	4.4.E-03	known
5	128190363	127287610	128792189	A	G	rs2012809	*FBN2, SLC27A6*	intergenic	9.374	0.920	0.039	0.028	1.6.E-01	0.790	0.058	0.009	4.9.E-10	0.799	0.058	0.024	1.4.E-02	known
5	137443486	136238113	138330420	T	C	rs529526	*WNT8A, NME5*	intergenic	33.262	0.376	0.018	0.015	2.5.E-01	0.306	0.083	0.007	1.8.E-30	0.286	0.119	0.021	1.1.E-08	known
5	139703286	139032339	140214751	T	C	rs17118812	*PFDN1, HBEGF*	intergenic	8.078	0.385	0.059	0.015	1.4.E-04	0.276	0.036	0.007	1.9.E-06	0.357	0.043	0.020	3.0.E-02	novel
5	142818123	142120736	143475754	A	G	rs6580277	*NR3C1, MIR5197*	intergenic	17.021	0.020	0.011	0.054	8.5.E-01	0.237	0.067	0.008	1.6.E-17	0.214	0.075	0.023	1.2.E-03	known
5	168393227	167855857	168901850	C	T	rs77328981	*SLIT3*	intronic	10.015	0.082	0.087	0.027	1.3.E-03	0.056	0.086	0.015	4.5.E-09	0.047	0.081	0.045	6.9.E-02	known
5	172670745	171975613	173893958	G	T	rs6891790	*NKX2-5, STC2*	intergenic	23.958	0.659	-0.058	0.018	9.1.E-04	0.283	-0.073	0.008	4.5.E-22	0.375	-0.063	0.020	1.3.E-03	known
6	16418562	15899680	16935743	C	T	rs9370893	*ATXN1*	intronic	14.087	0.378	0.011	0.016	4.6.E-01	0.273	-0.062	0.008	1.2.E-16	0.307	-0.056	0.020	5.9.E-03	known
6	18210109	17710109	18913026	G	A	rs34969716	*KDM1B*	intronic	22.659	0.345	0.071	0.017	2.6.E-05	0.305	0.070	0.008	1.6.E-19	0.331	0.058	0.020	4.4.E-03	known
6	22598259	22071323	23098259	C	T	rs7766436	*HDGFL1, LOC105374972*	intergenic	6.187	0.229	0.040	0.018	2.2.E-02	0.282	0.031	0.007	2.0.E-05	0.222	0.071	0.023	1.6.E-03	novel
6	34188866	33665721	34714322	C	T	rs12214804	*GRM4, HMGA1*	intergenic	8.090	0.856	-0.093	0.021	7.7.E-06	0.890	-0.055	0.012	5.1.E-06	0.947	-0.040	0.042	3.4.E-01	known
6	36647289	36116600	37159932	G	A	rs3176326	*CDKN1A*	intronic	17.705	0.107	-0.100	0.026	1.0.E-04	0.198	-0.063	0.009	1.4.E-13	0.173	-0.107	0.025	1.8.E-05	known
6	76164589	75664589	77067954	C	A	rs12209223	*LOC101928540*	ncRNA exonic	10.909	0.135	0.088	0.021	4.3.E-05	0.108	0.059	0.011	7.4.E-08	0.137	0.082	0.027	2.6.E-03	novel
6	87886335	87256580	88840568	A	G	rs7757330	*ZNF292*	intronic	11.670	0.444	-0.060	0.015	6.2.E-05	0.378	-0.043	0.007	3.6.E-10	0.363	-0.027	0.020	1.7.E-01	known
6	118974798	116971951	119539482	T	G	rs9481842	*CEP85L*	intronic	19.566	0.062	0.040	0.031	1.9.E-01	0.255	0.071	0.008	3.5.E-21	0.276	0.038	0.021	7.4.E-02	known
6	122398241	121202234	123272530	C	T	rs72966339	*GJA1, HSF2*	intergenic	24.740	0.277	-0.086	0.017	3.6.E-07	0.368	-0.062	0.007	7.4.E-19	0.293	-0.072	0.021	5.2.E-04	known
6	133432323	132817742	134100591	A	G	rs6902225	*LINC00326, EYA4*	intergenic	9.362	0.346	0.088	0.016	1.7.E-08	0.201	0.033	0.008	6.1.E-05	0.196	0.052	0.024	2.9.E-02	known
6	135119089	134587658	135621662	C	T	rs4896104	*LOC101928304, ALDH8A1*	intergenic	7.975	0.829	-0.052	0.020	8.2.E-03	0.556	-0.037	0.007	7.5.E-08	0.645	-0.036	0.020	7.1.E-02	novel
6	149413519	148786910	149914461	G	A	rs78811127	*UST, TAB2*	intergenic	14.815	0.074	-0.006	0.032	8.6.E-01	0.150	0.083	0.010	4.0.E-17	0.158	0.064	0.026	1.4.E-02	known
7	895285	372848	1421411	G	A	rs6461461	*SUN1*	intronic	7.810	0.305	0.035	0.016	2.9.E-02	0.399	0.035	0.007	2.5.E-07	0.434	0.054	0.019	4.5.E-03	known
7	14373714	13865616	14886532	C	T	rs12154315	*DGKB*	intronic	12.632	0.323	0.031	0.016	5.6.E-02	0.248	0.055	0.008	3.4.E-12	0.238	0.078	0.022	4.0.E-04	known
7	28417214	27908294	28919716	C	A	rs9639575	*CREB5*	intronic	7.886	0.988	-0.020	0.069	7.7.E-01	0.720	0.046	0.008	1.7.E-09	0.826	0.046	0.025	6.4.E-02	known
7	92250140	91741451	92827026	T	G	rs42044	*CDK6*	intronic	12.148	0.109	0.066	0.024	4.9.E-03	0.270	-0.052	0.008	6.8.E-12	0.256	-0.051	0.022	1.9.E-02	known
7	105612736	105100803	106117076	A	G	rs2727757	*CDHR3*	intronic	6.943	0.570	0.060	0.016	1.1.E-04	0.273	0.030	0.008	5.5.E-05	0.292	0.051	0.021	1.5.E-02	novel
7	116198621	115280581	116724638	G	A	rs1997571	*CAV1*	intronic	71.150	0.667	0.124	0.016	1.2.E-14	0.586	0.105	0.007	5.9.E-55	0.564	0.096	0.019	4.1.E-07	known
7	150669976	150114934	151169976	C	G	rs3778872	*KCNH2*	intronic	11.926	0.266	-0.050	0.017	3.7.E-03	0.173	-0.059	0.009	3.2.E-11	0.228	-0.049	0.023	2.9.E-02	known
8	11784541	11276904	12309421	C	T	rs6996342	*CTSB, DEFB136*	intergenic	6.622	0.014	0.024	0.088	7.9.E-01	0.410	0.037	0.007	2.6.E-07	0.349	0.049	0.020	1.4.E-02	known
8	17912752	17222615	18445990	A	T	rs399485	*PCM1, ASAH1*	intergenic	18.913	0.282	0.049	0.016	2.6.E-03	0.702	0.067	0.007	1.0.E-19	0.706	0.033	0.021	1.2.E-01	known
8	21805265	21270372	22370967	T	C	rs6998692	*XPO7*	intronic	14.474	0.109	-0.106	0.025	2.0.E-05	0.118	-0.064	0.010	5.4.E-10	0.104	-0.125	0.031	5.3.E-05	known
8	118863412	118363412	119363445	A	T	rs17430357	*EXT1*	intronic	6.245	0.230	0.027	0.018	1.2.E-01	0.180	0.040	0.009	4.9.E-06	0.160	0.082	0.026	1.4.E-03	novel
8	124610166	124029377	125135197	G	A	rs58847541	*FBXO32, KLHL38*	intergenic	13.091	0.133	0.088	0.022	5.5.E-05	0.147	0.063	0.009	1.5.E-11	0.140	0.043	0.027	1.1.E-01	known
8	141740868	141151733	142518135	A	C	rs6994744	*PTK2*	intronic	10.500	0.735	0.056	0.017	1.1.E-03	0.495	0.041	0.007	1.1.E-09	0.575	0.033	0.019	8.6.E-02	known
9	20235004	19715705	20735499	A	G	rs4977397	*SLC24A2, MLLT3*	intergenic	6.178	0.873	-0.072	0.022	1.2.E-03	0.391	-0.027	0.007	8.3.E-05	0.442	-0.058	0.019	2.2.E-03	known
9	97713459	96482190	98632921	C	A	rs10821415	*C9orf3*	intronic	31.754	0.264	0.027	0.017	1.1.E-01	0.413	0.082	0.007	2.9.E-34	0.355	0.042	0.020	3.1.E-02	known
9	119181794	118681794	119681794	G	A	rs17303101	*PAPPA, ASTN2*	intergenic	6.328	0.086	0.035	0.026	1.9.E-01	0.290	0.034	0.007	5.3.E-06	0.254	0.077	0.022	3.8.E-04	novel
9	139094773	138589679	139609861	A	G	rs2274115	*LHX3*	intronic	8.976	0.514	0.041	0.015	8.2.E-03	0.700	0.049	0.008	1.7.E-10	0.726	-0.002	0.021	9.1.E-01	known
10	21242382	20533698	21742382	G	A	rs7910227	*NEBL*	intronic	5.149	0.291	0.086	0.016	1.1.E-07	0.032	-0.027	0.020	1.6.E-01	0.094	0.139	0.032	1.6.E-05	known
10	32772734	32209192	33769397	C	T	rs11527634	*CCDC7*	intronic	7.692	0.303	-0.048	0.016	3.3.E-03	0.113	-0.051	0.011	1.9.E-06	0.103	-0.084	0.031	7.2.E-03	novel
10	50485434	49804998	51003524	G	A	rs76460895	*C10orf128, C10orf71-AS1*	intergenic	7.810	0.096	-0.083	0.026	1.4.E-03	0.053	-0.066	0.015	1.2.E-05	0.057	-0.138	0.041	7.2.E-04	novel
10	65321147	64374754	65900080	C	A	rs12245149	*REEP3*	intronic	14.712	0.321	-0.070	0.016	1.4.E-05	0.474	-0.047	0.007	1.7.E-12	0.484	-0.036	0.019	5.6.E-02	known
10	69614737	68751616	70396336	A	G	rs12360521	*DNAJC12, SIRT1*	intergenic	14.120	0.329	0.074	0.016	2.5.E-06	0.068	0.070	0.013	7.1.E-08	0.132	0.118	0.028	1.9.E-05	known
10	75414344	74894715	76163351	G	C	rs60212594	*SYNPO2L*	intronic	38.386	0.164	-0.065	0.020	1.4.E-03	0.144	-0.118	0.010	9.2.E-35	0.146	-0.133	0.027	6.2.E-07	known
10	77936670	76347993	78497672	T	G	rs10458662	*LRMDA*	intronic	16.095	0.554	0.096	0.015	1.8.E-10	0.172	0.054	0.009	6.9.E-10	0.151	0.044	0.026	9.5.E-02	known
10	80898969	80397384	81398969	G	T	rs1769758	*ZMIZ1*	intronic	7.505	0.715	0.052	0.017	2.7.E-03	0.490	0.034	0.008	5.4.E-06	0.501	0.062	0.019	1.1.E-03	novel
10	105316296	102838008	106194644	G	A	rs74154539	*NEURL1*	intronic	79.932	0.091	0.266	0.024	2.2.E-28	0.193	0.128	0.009	1.4.E-51	0.138	0.135	0.027	7.9.E-07	known
10	112576695	112074402	113076695	T	C	rs10749053	*RBM20*	intronic	7.782	0.970	-0.121	0.042	3.6.E-03	0.842	-0.056	0.010	1.0.E-08	0.873	-0.023	0.029	4.1.E-01	known
11	3890059	3389383	4390223	C	T	rs7126870	*STIM1*	intronic	6.216	0.661	-0.036	0.016	2.3.E-02	0.489	-0.030	0.007	5.1.E-06	0.484	-0.042	0.019	2.5.E-02	novel
11	14036189	13534698	14622134	G	A	rs10500790	*SPON1*	intronic	10.831	0.341	0.062	0.016	8.4.E-05	0.376	0.035	0.007	3.4.E-07	0.361	0.081	0.020	3.6.E-05	novel
11	20010291	19481419	20519716	A	G	rs4757877	*NAV2*	intronic	25.441	0.463	-0.069	0.015	4.0.E-06	0.755	-0.072	0.008	2.9.E-20	0.799	-0.084	0.023	3.0.E-04	known
11	95089882	94589882	95592398	C	T	rs517938	*LOC100129203, FAM76B*	intergenic	6.157	0.219	-0.022	0.018	2.3.E-01	0.670	-0.037	0.007	1.8.E-07	0.603	-0.028	0.019	1.5.E-01	novel
11	121654327	121104722	122161507	G	A	rs7946552	*SORL1, MIR100HG*	intergenic	7.790	0.699	-0.044	0.016	6.6.E-03	0.731	-0.044	0.008	6.4.E-09	0.722	-0.004	0.021	8.3.E-01	known
11	128764570	128260774	129294234	G	A	rs76097649	*KCNJ5*	intronic	22.835	0.061	0.073	0.034	2.9.E-02	0.093	0.115	0.012	1.3.E-20	0.098	0.136	0.032	2.0.E-05	known
12	12886027	12386027	13386027	G	A	rs10845620	*APOLD1*	intronic	6.031	0.104	0.064	0.026	1.3.E-02	0.132	0.049	0.010	2.3.E-06	0.134	0.037	0.028	1.8.E-01	novel
12	24771967	24196408	25373178	C	T	rs10842383	*LINC00477, BCAT1*	intergenic	33.251	0.121	-0.154	0.024	1.3.E-10	0.148	-0.099	0.010	2.9.E-25	0.106	-0.096	0.031	1.7.E-03	known
12	26348429	25778218	27110236	C	G	rs113819537	*SSPN*	5'UTR	14.032	0.302	-0.027	0.016	9.6.E-02	0.260	-0.052	0.008	9.5.E-12	0.309	-0.103	0.020	4.3.E-07	known
12	32978437	32441446	33527458	T	C	rs12809354	*PKP2*	intronic	14.362	0.098	0.034	0.025	1.6.E-01	0.144	0.072	0.009	2.9.E-14	0.140	0.087	0.027	1.6.E-03	known
12	57105938	56483252	57712827	A	C	rs2860482	*NACA*	downstream	16.674	0.636	-0.077	0.015	5.3.E-07	0.726	-0.054	0.008	1.2.E-12	0.813	-0.053	0.024	2.7.E-02	known
12	70013415	69355200	70598621	G	A	rs71454237	*LRRC10, BEST3*	intergenic	9.986	0.189	-0.013	0.019	5.1.E-01	0.209	-0.062	0.008	1.8.E-13	0.176	-0.016	0.025	5.1.E-01	known
12	76238855	75703505	76744249	C	T	rs1565765	*KRR1, PHLDA1*	intergenic	10.911	0.201	-0.060	0.019	1.5.E-03	0.528	-0.039	0.007	6.1.E-09	0.560	-0.064	0.019	8.0.E-04	known
12	104492003	103967069	105021552	A	G	rs2629755	*HCFC2*	intronic	9.505	0.420	-0.088	0.015	6.3.E-09	0.141	-0.038	0.009	6.7.E-05	0.152	-0.045	0.026	8.7.E-02	novel
12	110082115	109582115	110582154	T	C	rs1344543	*MVK, FAM222A*	intergenic	8.675	0.446	-0.097	0.015	1.5.E-10	0.537	-0.011	0.007	9.6.E-02	0.431	-0.012	0.019	5.2.E-01	novel
12	111631765	110859712	112290511	G	A	rs4766552	*CUX2*	intronic	9.471	0.464	-0.113	0.015	1.8.E-13	0.064	-0.021	0.014	1.3.E-01	0.080	0.031	0.035	3.7.E-01	known
12	113196733	112696733	114024987	G	A	rs11614295	*RPH3A*	intronic	8.669	0.417	-0.111	0.017	9.9.E-11	0.312	-0.009	0.008	2.1.E-01	0.252	-0.034	0.022	1.2.E-01	novel
12	114793240	114192036	115874959	C	T	rs883079	*TBX5*	3'UTR	57.064	0.419	0.121	0.015	6.3.E-16	0.707	0.098	0.007	2.8.E-40	0.689	0.105	0.020	2.3.E-07	known
12	123312051	122785131	123879477	C	T	rs897393	*CCDC62*	downstream	7.754	0.784	-0.039	0.018	2.8.E-02	0.863	-0.057	0.010	3.3.E-08	0.824	-0.040	0.025	1.1.E-01	known
12	124812678	123945569	125312678	T	G	rs3741508	*NCOR2*	intronic	6.634	0.338	0.011	0.016	5.0.E-01	0.130	0.048	0.010	8.5.E-07	0.262	0.086	0.022	6.1.E-05	known
12	133091614	132591614	133650210	G	A	rs4883571	*FBRSL1*	intronic	6.136	0.115	0.015	0.024	5.3.E-01	0.391	0.037	0.007	1.1.E-07	0.373	0.028	0.020	1.6.E-01	known
13	22111521	21592762	22612927	C	A	rs11841562	*MICU2*	intronic	6.240	0.324	0.026	0.016	1.1.E-01	0.404	0.030	0.007	8.8.E-06	0.388	0.064	0.019	8.6.E-04	novel
13	23368834	22839138	23874178	C	T	rs3904323	*LINC00540, LINC00621*	intergenic	10.082	0.946	-0.048	0.032	1.3.E-01	0.718	-0.045	0.008	2.9.E-09	0.784	-0.085	0.023	2.0.E-04	known
13	74520186	74018210	75020186	T	A	rs1886512	*KLF12*	intronic	6.943	0.195	0.047	0.018	1.1.E-02	0.357	0.036	0.007	2.8.E-07	0.360	0.024	0.020	2.3.E-01	novel
13	113864837	113364837	114410611	G	A	rs2316443	*CUL4A*	intronic	6.475	0.441	-0.021	0.015	1.6.E-01	0.226	-0.045	0.008	2.3.E-08	0.277	-0.021	0.021	3.1.E-01	known
14	23864804	23348311	24383739	T	C	rs422068	*MYH6*	intronic	11.418	0.139	0.076	0.021	3.0.E-04	0.349	0.044	0.007	3.9.E-10	0.273	0.047	0.021	2.8.E-02	known
14	32990437	32396479	33500955	T	C	rs11156751	*AKAP6*	intronic	27.827	0.350	0.099	0.016	7.6.E-10	0.285	0.072	0.008	6.9.E-21	0.408	0.057	0.019	3.2.E-03	known
14	35173775	34656561	35707496	C	T	rs73241997	*SNX6, CFL2*	intergenic	15.276	0.173	0.055	0.019	5.0.E-03	0.142	0.073	0.009	2.9.E-15	0.121	0.058	0.029	4.6.E-02	known
14	64679960	64066636	65378265	A	G	rs2738413	*SYNE2*	intronic	38.110	0.635	-0.103	0.015	1.6.E-11	0.505	-0.078	0.007	2.5.E-31	0.522	-0.039	0.019	3.7.E-02	known
14	73355131	72748367	73864698	T	C	rs2110552	*DPF3*	intronic	12.874	0.660	-0.074	0.015	1.5.E-06	0.346	-0.043	0.007	5.5.E-10	0.325	-0.041	0.020	4.3.E-02	known
14	77426525	76922803	77930681	C	T	rs10873298	*LINC01629*	ncRNA intronic	9.636	0.657	-0.050	0.016	1.4.E-03	0.634	-0.040	0.007	7.1.E-09	0.652	-0.034	0.020	8.7.E-02	known
15	70463992	69963992	70963992	A	C	rs2415081	*TLE3, LINC02205*	intergenic	6.141	0.326	-0.056	0.016	4.8.E-04	0.129	-0.041	0.010	6.6.E-05	0.116	-0.053	0.030	7.8.E-02	known
15	73667255	72965477	74184606	T	G	rs7172038	*HCN4, REC114*	intergenic	36.884	0.030	0.020	0.044	6.4.E-01	0.160	0.112	0.009	4.8.E-36	0.207	0.097	0.023	2.6.E-05	known
15	80676925	80073864	81566058	A	G	rs12908004	*LINC00927, ARNT2*	intergenic	21.405	0.063	0.142	0.029	1.5.E-06	0.164	0.073	0.009	4.1.E-16	0.201	0.096	0.023	4.2.E-05	known
15	99268850	98749029	99795650	C	G	rs4965430	*IGF1R*	intronic	10.989	0.462	-0.036	0.015	1.8.E-02	0.614	-0.044	0.007	1.3.E-10	0.643	-0.052	0.020	8.6.E-03	known
16	764753	264520	1281633	C	G	rs3809666	*METRN*	upstream	6.101	0.548	0.021	0.015	1.7.E-01	0.227	0.039	0.008	1.7.E-06	0.303	0.056	0.021	6.9.E-03	known
16	2004718	1503399	2514283	T	C	rs2815301	*RPL3L*	upstream	12.633	0.784	0.081	0.019	2.5.E-05	0.763	0.050	0.009	3.8.E-09	0.864	0.090	0.028	1.2.E-03	known
16	15902715	15402590	16412544	G	A	rs9284324	*MYH11*	intronic	7.200	0.194	-0.057	0.019	3.4.E-03	0.314	-0.035	0.007	1.2.E-06	0.335	-0.044	0.020	2.9.E-02	novel
16	73048367	71917516	73630109	C	T	rs67329386	*ZFHX3*	intronic	144.357	0.358	0.227	0.015	9.1.E-50	0.175	0.172	0.009	5.6.E-88	0.227	0.175	0.022	3.8.E-15	known
17	1312046	736956	2705923	G	T	rs61248729	*YWHAE, CRK*	intergenic	7.496	0.314	-0.036	0.017	2.9.E-02	0.120	-0.059	0.011	3.8.E-08	0.115	-0.053	0.029	7.4.E-02	known
17	7414958	6914958	7926695	G	C	rs2071502	*POLR2A*	intronic	6.473	0.487	-0.014	0.015	3.4.E-01	0.596	-0.038	0.007	2.0.E-08	0.526	-0.032	0.019	8.7.E-02	known
17	12618680	12095075	13118680	G	C	rs72811294	*MYOCD*	intronic	13.405	0.091	-0.121	0.027	8.7.E-06	0.113	-0.072	0.011	9.7.E-12	0.085	-0.044	0.034	2.0.E-01	known
17	38049589	36915544	38589717	C	T	rs7359623	*ZPBP2, GSDMB*	intergenic	12.407	0.265	-0.037	0.017	2.8.E-02	0.517	-0.044	0.007	4.4.E-11	0.562	-0.066	0.019	5.3.E-04	known
17	44019712	43519712	44526739	G	A	rs242557	*MAPT*	intronic	9.446	0.456	-0.078	0.015	2.0.E-07	0.379	-0.031	0.007	1.4.E-05	0.469	-0.053	0.019	5.3.E-03	known
17	45138033	44543508	45638033	A	G	rs145153053	*ARL17B, CDC27*	intergenic	7.065	0.019	-0.039	0.063	5.3.E-01	0.166	0.044	0.009	1.9.E-06	0.197	0.102	0.024	1.6.E-05	known
17	68421803	67843539	68979067	T	C	rs1396517	*KCNJ2, CASC17*	intergenic	6.863	0.715	0.065	0.017	1.0.E-04	0.502	0.029	0.007	1.7.E-05	0.381	0.042	0.019	3.1.E-02	known
18	46474192	45957096	47028787	T	C	rs9953366	*SMAD7*	intronic	10.549	0.445	0.025	0.015	9.5.E-02	0.663	0.049	0.007	1.8.E-11	0.632	0.043	0.020	2.9.E-02	known
18	77156537	76656537	77656537	C	G	rs8096658	*NFATC1*	intronic	7.120	0.305	0.054	0.017	1.2.E-03	0.488	0.038	0.007	1.3.E-07	0.446	0.010	0.019	6.2.E-01	novel
19	48142746	47628418	48670757	A	C	rs11881441	*BICRA*	intronic	7.384	0.818	0.045	0.020	2.2.E-02	0.660	0.036	0.007	5.9.E-07	0.708	0.051	0.021	1.4.E-02	novel
20	36841914	36328890	37386397	G	A	rs3746471	*KIAA1755*	exonic	9.429	0.430	0.050	0.015	8.0.E-04	0.469	0.035	0.007	2.3.E-07	0.437	0.057	0.019	2.9.E-03	novel
20	61154393	60641981	61656946	C	T	rs6089752	*MIR1-1HG*	intronic	9.720	0.492	0.071	0.015	4.0.E-06	0.521	0.033	0.007	2.2.E-06	0.562	0.061	0.019	1.3.E-03	known
21	36119111	35594354	37338008	T	G	rs2834618	*LINC01426*	ncRNA intronic	19.189	0.071	-0.143	0.031	2.7.E-06	0.106	-0.094	0.011	3.4.E-17	0.114	-0.050	0.030	9.9.E-02	known
22	18597502	18065048	19101415	T	C	rs464901	*TUBA8*	intronic	11.685	0.279	-0.030	0.017	6.9.E-02	0.335	-0.051	0.007	1.5.E-12	0.317	-0.040	0.020	4.8.E-02	known
22	21999229	21499229	22499229	C	G	rs5754508	*SDF2L1*	downstream	6.077	0.360	0.069	0.018	1.3.E-04	0.191	0.036	0.009	1.0.E-04	0.288	0.035	0.021	9.7.E-02	novel
22	26164079	25656431	26664079	C	T	rs133902	*MYO18B*	intronic	9.438	0.427	0.042	0.007	9.1.E-10	0.427	0.042	0.007	9.1.E-10	0.423	0.028	0.019	1.4.E-01	known
22	42189407	41620864	42702825	T	G	rs139557	*MEI1*	intronic	6.577	0.697	-0.025	0.016	1.3.E-01	0.676	0.038	0.007	1.7.E-07	0.682	0.070	0.020	5.7.E-04	novel
X	23399501	22899373	24046193	T	C	rs73205368	*PTCHD1*	intronic	10.514	0.285	0.089	0.012	7.5.E-13	0.051	0.009	0.024	7.1.E-01	0.021	0.148	0.054	5.7.E-03	novel
X	137418967	136873525	137918967	C	A	rs1891095	*ZIC3, LINC00889*	intergenic	9.242	0.079	0.091	0.020	5.9.E-06	0.180	0.038	0.011	7.5.E-04	0.192	0.086	0.019	9.3.E-06	novel

CHR, Chromosome; POS, position(hg19); REF, reference allele; ALT, alternate allele; rsID, reference SNP cluster ID; AAF, alternate allele frequency; SE, Standard error; P, P-value; ncRNA, non-coding RNA; UTR, untranslated region.

EUR: r_g=0.990, s.e.m.=0.097, BBJ and FIN r_g=0.955, s.e.m.=0.344).

To assess the contribution of trans-ancestry meta-analyses to the refinement of the putative causal variants, we constructed 99% credible sets for the 150 AF-associated loci detected by the current trans-ancestry meta-analysis, and compared the number of variants included in the 99% credible sets derived from three combinations of the meta-analysis (EUR+BBJ, EUR+FIN, BBJ+EUR+FIN; Supplementary Fig. 8g, h). The size of the 99% credible sets derived from EUR+BBJ significantly decreased compared with those from EUR+FIN (P=0.004, paired Wilcoxon rank-sum test). In addition, trans-ancestry meta-analysis of three datasets (BBJ+EUR+FIN) yielded the most significant decrease in the number of variants among all the combinations of meta-analyses (median number of variants=12; interquartile range [IQR] 5–36; Supplementary Table 8). In particular, a single variant, rs67329386, was identified on the *ZFHX3* locus with a high posterior probability of 0.995, only in the trans-ancestry meta-analysis of three datasets. In previous AF-GWAS, several variants were found in the *ZFHX3* locus[44,45], where a large transcription factor, *ZFHX3*, together with *PITX2*, facilitated DNA binding and transcription activity[46]. To corroborate the role of rs67329386 as a causal variant, we searched for transcription factors binding to this locus using the ChIP-seq dataset in ChIP-Atlas[47]. Compared to other AF-associated variants within this locus, rs67329386 was distinctly located on the binding site of CEBPB (Supplementary Fig. 9), aiding in the recognition and binding of target gene regulatory regions, leading to cell proliferation, differentiation, immune response, and tumor formation[48].

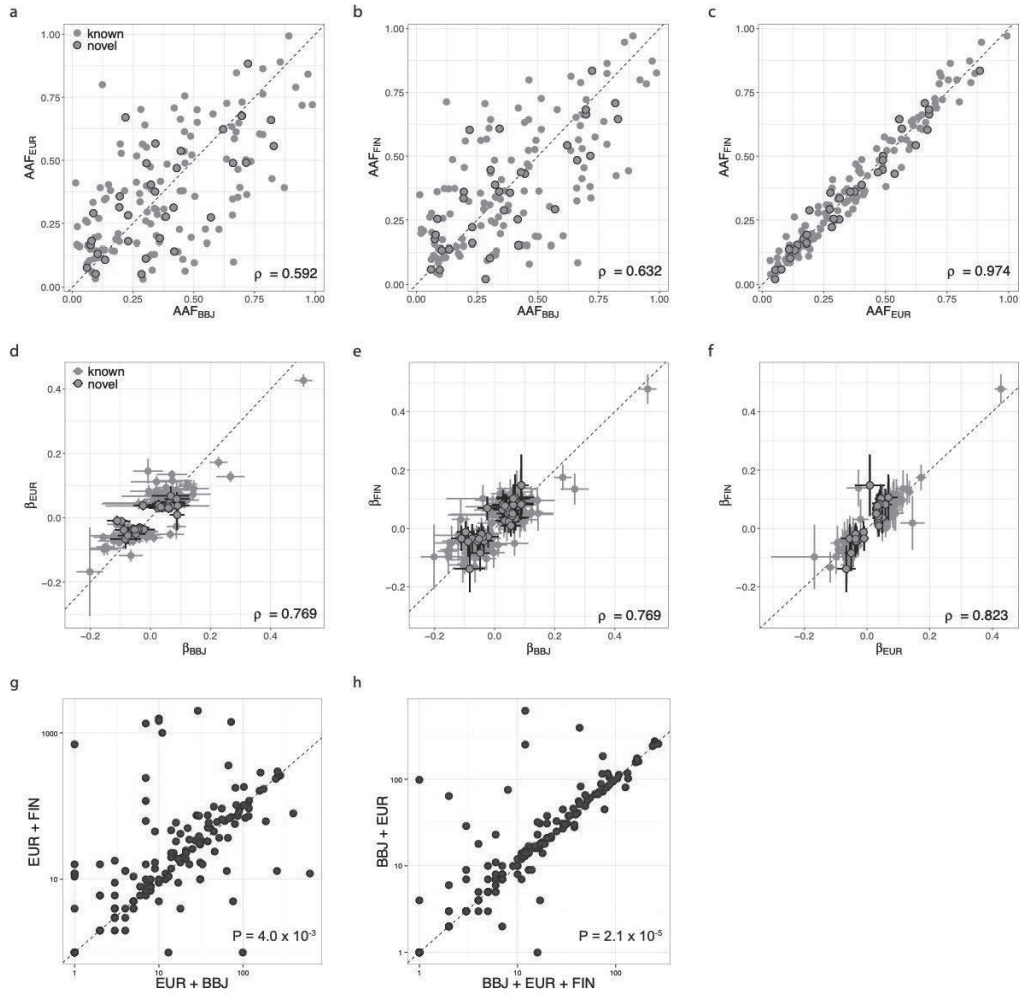
Pleiotropic effects and functional pathways of AF-associated loci

To characterize the AF-associated loci, we examined the pleiotropic effects of the identified lead variants and proxies using the NHGRI-EBI GWAS catalog database. Of the 150 AF-associated loci, 114

Supplementary Table 7 | Missense variants in linkage disequilibrium with the lead variants detected in trans-ancestry meta-analysis

CHR	POS	rsID	REF	ALT	Gene	Lead Variant			Functional impact						MAF in ExAC			ClinVar		Annotation	
						CHR	POS	rsID	SIFT score	SIFT pred	Polyphen2 HDIV score	Polyphen2 HDIV pred	CADD raw	CADD pred	EAS	NFE	FIN	Disease	Interpretation		
Novel loci																					
1	16255644	rs848208	C	T	*SPEN*	1	16199051	rs9782984	0.098	Tolerated	0.006	Benign	-0.317	0.608	0.240	0.102	0.168	NA	NA	nonsynonymous SNV	NM_015001:exon11:c.C2909T:p.A970V
4	83838262	rs897945	G	T	*THAP9*	4	83910712	rs6841049	0.499	Tolerated	0.906	Possibly damaging	-0.478	0.250	0.200	0.565	0.605	NA	NA	nonsynonymous SNV	NM_024672:exon5:c.G897T:p.L299F,NM_001317776:exon6:c.G465T:p.L155F
7	105615406	rs35008315	G	A	*CDHR3*	7	105612736	rs2727757	0.013	Deleterious	0.961	Probably damaging	5.531	26.300	0.269	0.196	0.179	NA	NA	nonsynonymous SNV	NM_152750:exon2:c.G163A:p.V55M
7	105615426	rs34426483	G	C	*CDHR3*	7	105612736	rs2727757	0.091	Tolerated	0.161	Benign	0.906	10.110	0.270	0.196	0.179	NA	NA	nonsynonymous SNV	NM_152750:exon2:c.G183C:p.Q61H
20	36841914	rs3746471	G	A	*KIAA1755*	20	36841914	rs3746471	0.059	Tolerated	0.003	Benign	2.905	21.900	0.457	0.501	0.499	NA	NA	nonsynonymous SNV	NM_001348708:exon12:c.C2086T:p.R696W,NM_001029864:exon14:c.C3133T:p.R1045W
Known loci																					
2	148716428	rs2307394	T	C	*ORC4*	2	148799710	rs12992231	0.184	Tolerated	0.082	Benign	1.476	13.190	0.553	0.367	0.357	Meier-Gorlin syndrome 2	Benign	nonsynonymous SNV	NM_001190882:exon4:c.A11G:p.N4S,NM_002552:exon5:c.A233G:p.N78S,NM_181741:exon5:c.A233G:p.N78S,NM_181742:exon5:c.A233G:p.N78S,NM_001190879:exon6:c.A233G:p.N78S
2	179397561	rs3829747	C	T	*TTN*	2	179413110	rs3731748	0	Deleterious	1.000	Probably damaging	4.497	24.300	0.434	0.146	0.148	Cardiomyopathy / Muscular dystrophy	Benign / Likely benign	nonsynonymous SNV	NM_003319:exon186:c.G76586A:p.R25529H,NM_133432:exon187:c.G76961A:p.R25654H,NM_133437:exon187:c.G77162A:p.R25721H,NM_133378:exon307:c.G96077A:p.R32026H,NM_001256850:exon308:c.G98858A:p.R32953H,NM_001267550:exon358:c.G103781A:p.R34594H
2	179444939	rs2303838	C	T	*TTN*	2	179413110	rs3731748	0.145	Tolerated	0.003	Benign	1.514	13.390	0.602	0.178	0.166	Cardiomyopathy / Muscular dystrophy	Benign / Likely benign	nonsynonymous SNV	NM_003319:exon146:c.G39880A:p.V13294I,NM_133432:exon147:c.G40255A:p.V13419I,NM_133437:exon147:c.G40456A:p.V13486I,NM_133378:exon267:c.G59371A:p.V19791I,NM_001256850:exon268:c.G62152A:p.V20718I,NM_001267550:exon318:c.G67075A:p.V22359I
2	179457147	rs16866406	G	A	*TTN*	2	179413110	rs3731748	0.167	Tolerated	0.008	Benign	2.159	17.240	0.435	0.146	0.148	Cardiomyopathy / Muscular dystrophy	Benign / Likely benign	nonsynonymous SNV	NM_003319:exon129:c.C32390T:p.P10797L,NM_133432:exon130:c.C32765T:p.P10922L,NM_133437:exon130:c.C32966T:p.P10989L,NM_133378:exon250:c.C51881T:p.P17294L,NM_001256850:exon251:c.C54662T:p.P18221L,NM_001267550:exon301:c.C59585T:p.P19862L
3	12848822	rs11718898	T	C	*CAND2*	3	12841804	rs7650482	0.502	Tolerated	0.000	Benign	1.109	11.260	0.310	0.652	0.610	NA	NA	nonsynonymous SNV	NM_001162499:exon3:c.T230C:p.V77A
3	12856856	rs2305398	A	G	*CAND2*	3	12841804	rs7650482	1	Tolerated	0.000	Benign	-0.382	0.427	0.279	0.617	0.564	NA	NA	nonsynonymous SNV	NM_012298:exon6:c.A944G:p.Q315R,NM_001162499:exon8:c.A1223G:p.Q408R
3	12857493	rs2305397	C	T	*CAND2*	3	12841804	rs7650482	0.144	Tolerated	0.137	Benign	3.986	23.600	0.161	0.535	0.513	NA	NA	nonsynonymous SNV	NM_012298:exon7:c.C1148T:p.P383L,NM_001162499:exon9:c.C1427T:p.P476L
3	38766675	rs6795970	A	G	*SCN10A*	3	38767315	rs6801957	1	Tolerated	0.000	Benign	-0.943	0.021	0.844	0.604	0.551	Not specified	Benign	nonsynonymous SNV	NM_001293307:exon16:c.T2924C:p.V975A,NM_001293306:exon17:c.T3215C:p.V1072A,NM_006514:exon17:c.T3218C:p.V1073A
3	89521693	rs35124509	T	C	*EPHA3*	3	89489529	rs6771054	0.229	Tolerated	0.000	Benign	2.291	18.100	0.205	0.392	0.503	NA	NA	nonsynonymous SNV	NM_005233:exon16:c.T2770C:p.W924R
6	87968565	rs9362415	A	G	*ZNF292*	6	87886335	rs7757330	1	Tolerated	0.000	Benign	-1.151	0.008	0.600	0.491	0.468	NA	NA	nonsynonymous SNV	NM_015021:exon8:c.A5218G:p.I1740V,NM_001351444:exon9:c.A4798G:p.I1600V
6	87994015	rs6934603	A	G	*GJB7*	6	87886335	rs7757330	0.548	Tolerated	0.000	Benign	-1.058	0.012	0.587	0.474	0.465	NA	NA	nonsynonymous SNV	NM_198568:exon3:c.T616C:p.F206L
7	881668	rs6461378	C	T	*SUN1*	7	895285	rs6461461	0.736	Tolerated	0.945	Possibly damaging	3.431	23.000	0.644	0.438	0.500	NA	NA	nonsynonymous SNV	NM_001130965:exon3:c.C352T:p.H118Y,NM_025154:exon3:c.C202T:p.H68Y,NM_001171944:exon4:c.C352T:p.H118Y,NM_001171946:exon4:c.C352T:p.H118Y,NM_001171945:exon5:c.C415T:p.H139Y
10	75406912	rs34163229	G	T	*SYNPO2L*	10	75414344	rs60212594	0.02	Deleterious	0.986	Probably damaging	2.766	21.200	0.221	0.150	0.134	NA	NA	nonsynonymous SNV	NM_024875:exon2:c.C1826A:p.S609Y,NM_001114133:exon4:c.C2498A:p.S833Y
10	75415677	rs60632610	C	T	*SYNPO2L*	10	75414344	rs60212594	0.02	Deleterious	0.997	Probably damaging	6.741	32.000	0.193	0.164	0.162	NA	NA	nonsynonymous SNV	NM_001114133:exon1:c.G4A:p.G2S
10	75576483	rs12217245	T	C	*CAMK2G*	10	75414344	rs60212594	NA	NA	NA	NA	NA	NA	0.1916	0.2369	0.2500	NA	NA	nonsynonymous SNV	NM_001320898:exon20:c.A1763G:p.N588S
12	57109792	rs2958149	A	G	*NACA*	12	57105938	rs2860482	1	Tolerated	0.000	Benign	1.812	15.060	0.748	0.737	0.820	NA	NA	nonsynonymous SNV	NM_001113203:exon5:c.T2063C:p.L688P
12	57114100	rs2926743	A	G	*NACA*	12	57105938	rs2860482	0.423	Tolerated	0.000	Benign	-1.298	0.005	0.747	0.735	0.798	NA	NA	nonsynonymous SNV	NM_001113203:exon3:c.T1214C:p.F405S
13	113909339	rs2302757	A	G	*CUL4A*	13	113864837	rs2316443	0.204	Tolerated	0.009	Benign	1.207	11.790	0.352	0.231	0.274	NA	NA	nonsynonymous SNV	NM_001008895:exon18:c.A1931G:p.K644R,NM_001278513:exon18:c.A1631G:p.K544R,NM_001278514:exon18:c.A1655G:p.K552R,NM_003589:exon18:c.A1631G:p.K544R
17	38028634	rs11557467	G	T	*ZPBP2*	17	38049589	rs7359623	0.045	Deleterious	0.295	Benign	1.537	13.510	0.259	0.501	0.564	NA	NA	nonsynonymous SNV	NM_198844:exon4:c.G452T:p.S151I,NM_199321:exon5:c.G518T:p.S173I
17	38062196	rs2305480	G	A	*GSDMB*	17	38049589	rs7359623	0.898	Tolerated	0.877	Possibly damaging	-1.352	0.004	0.258	0.453	0.515	NA	NA	nonsynonymous SNV	NM_018530:exon6:c.C865T:p.P289SNM_001042471:exon8:c.C892T:p.P298S,NM_001165959:exon8:c.C904T:p.P302S,NM_001165958:exon9:c.C931T:p.P311S
17	38062217	rs2305479	C	T	*GSDMB*	17	38049589	rs7359623	0.129	Tolerated	1.000	Probably damaging	3.505	23.100	0.259	0.493	0.553	NA	NA	nonsynonymous SNV	GSDMB:NM_018530:exon6:c.G844A:p.G282R,NM_001042471:exon8:c.G871A:p.G291R,NM_001165959:exon8:c.G883A:p.G295R,NM_001165958:exon9:c.G910A:p.G304R
22	26159289	rs133885	G	A	*MYO18B*	22	26164079	rs133902	1	Tolerated	0.000	Benign	1.100	11.220	0.822	0.439	0.441	NA	NA	nonsynonymous SNV	NM_001318245:exon3:c.G131A:p.G44E,NM_032608:exon3:c.G131A:p.G44E

CHR chromosome; POS, position (hg19); rsID, reference SNP cluster ID; REF, reference allele; ALT, alternate allele; ExAC, the exome aggregation consortium



Supplementary Fig. 8 | Comparison of allele frequencies and allelic effects among ancestries and fine mapping derived from credible set analyses

a-c,Comparisons of alternate allele frequencies of the 150 lead variants identified in the trans-ancestry meta-analysis (**a**, BBJ versus EUR; **b**, BBJ versus FIN; **c**, EUR versus FIN). **d-f**, Comparison of estimated effect sizes of 150 lead variants. Data are presented as estimated β and 95% CI in each study (**d**, BBJ versus EUR; **e**, BBJ versus FIN; **f**, EUR versus FIN). Grey points indicate previously reported loci, and orange points indicate newly identified loci in this study. ρ indicates Spearman's correlation coefficient. **g, h**, Comparisons of the number of variants included in the 99% credible sets derived from each combination of the meta-analysis (**g**, EUR + BBJ versus EUR + FIN; **h**, BBJ + EUR + FIN versus BBJ + EUR). Both the x and y axes represent the log-transformed number of variants in the 99% credible sets. BBJ, BioBank Japan; EUR, European population; FIN, FinnGen data release 2; CI, confidence interval.

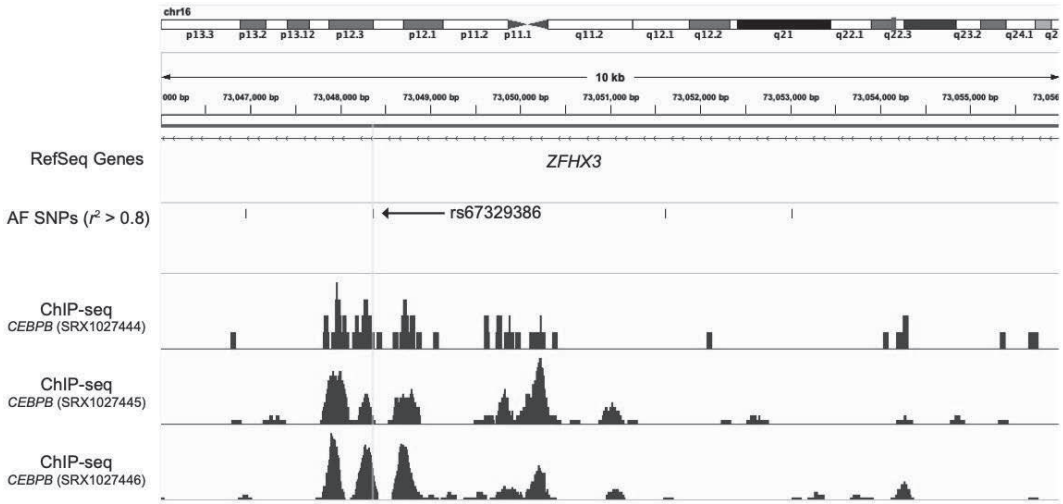
(76.0%) had at least one overlapping variant, and 739 variants overlapped with 200 diseases or traits (Supplementary Table 9). Among them, blood pressure-related traits were most frequently observed (13.0%), followed by traits related to electrocardiogram (10.1%) and heart rate (4.0%).

Given the heterogeneous study design and population in the GWAS catalog, we subsequently utilized the BBJ dataset[11~13] with a consistent study design and population, to investigate the pleotropic effects. In particular, to explore the biological pathways related to AF development, we searched for AF-

Supplementary Table 8 | Credibleset analysis for AF-associated loci in trans-ancestry meta-analysis

Locus					BBJ and EUR						EUR and FIN						BBJ and EUR and FIN					
No	CHR	Start	End	Gene	N	Top variant					N	Top variant					N	Top variant				
						CHR	POS	rsID	log10BF	PPA		CHR	POS	rsID	log10BF	PPA		CHR	POS	rsID	log10BF	PPA
1	1	410935	1418617	PERM1;HES4	8	1	910935	rs2340592	5.770	0.614	7	1	911595	rs7417106	6.929	0.400	7	1	918617	rs4970418	7.647	0.248
2	1	10280727	11302468	CASZ1	6	1	10796866	rs880315	9.667	0.538	6	1	10796866	rs880315	11.737	0.393	2	1	10796866	rs880315	13.984	0.689
3	1	15699051	16699051	MIR5096	72	1	16199051	rs9782984	6.854	0.710	1416	1	16199051	rs9782984	3.226	0.173	74	1	16199051	rs9782984	6.970	0.586
4	1	21741185	22805915	HSPG2;CELA3B	15	1	22282619	rs7529220	10.734	0.589	23	1	22282619	rs7529220	10.581	0.622	12	1	22282619	rs7529220	13.485	0.777
5	1	38885714	39885714	RHBDL2	14	1	39385714	rs75414548	4.845	0.325	14	1	39385714	rs75414548	5.457	0.446	11	1	39385714	rs75414548	6.439	0.632
6	1	41044279	42044279	SCMH1	99	1	41544279	rs2885697	7.110	0.950	1	1	41544279	rs2885697	9.699	0.999	1	1	41544279	rs2885697	8.571	0.992
7	1	51001896	52510097	EPS15;OSBPL9	12	1	51994894	rs12045600	10.777	0.615	12	1	52004740	rs12022114	10.212	0.227	11	1	52004740	rs12022114	10.411	0.279
8	1	99649308	100649308	PALMD	17	1	100149308	rs1933723	5.968	0.445	19	1	100144363	rs7540358	5.438	0.347	17	1	100149308	rs1933723	6.298	0.550
9	1	111879026	112963617	KCND3	14	1	112382671	rs11102343	14.404	0.215	23	1	112462984	rs6682872	11.303	0.148	13	1	112382671	rs11102343	18.445	0.148
10	1	115734313	116839337	CASQ2	28	1	116292176	rs9428218	12.728	0.105	75	1	116297758	rs4073778	10.744	0.242	38	1	116297758	rs4073778	13.267	0.227
11	1	146728874	147814940	GJA5	3	1	147228874	rs11240121	8.203	0.961	2	1	147282416	rs80079599	8.910	0.807	3	1	147228874	rs11240121	8.256	0.462
12	1	153895125	156168700	KCNN3;PMVK	1	1	154862952	rs11264280	78.054	0.997	1	1	154862952	rs11264280	86.519	0.996	1	1	154862952	rs11264280	87.114	0.998
13	1	169603834	171411565	GORAB;PRRX1	13	1	170631763	rs629234	59.541	0.507	1	1	170193825	rs72700114	52.183	1.000	11	1	170628255	rs680084	62.406	0.353
14	1	202519737	203555101	PPFIA4	3	1	203032153	rs4950913	35.958	0.483	9	1	203026214	rs10753933	20.565	0.278	5	1	203032153	rs4950913	39.187	0.360
15	1	205185352	206222958	NUCKS1	5	1	205685352	rs951366	6.486	0.262	5	1	205685352	rs951366	7.327	0.322	6	1	205691316	rs4951258	7.418	0.294
16	2	25609402	26665568	KIF3C	2	2	26159940	rs6546620	14.225	0.786	2	2	26159940	rs6546620	10.315	0.649	2	2	26159940	rs6546620	14.173	0.807
17	2	61071295	62306999	USP34	157	2	61806999	rs6733446	6.814	0.041	163	2	61437487	rs12998475	6.542	0.034	160	2	61676940	rs2694635	6.407	0.037
18	2	64735333	65886462	CEP68	5	2	65284231	rs2540949	26.272	0.590	5	2	65284231	rs2540949	24.771	0.518	5	2	65284231	rs2540949	31.262	0.620
19	2	69405400	70675327	GMCL1	45	2	70106832	rs6747542	15.383	0.329	99	2	70090579	rs13017134	14.338	0.155	77	2	70106832	rs6747542	15.745	0.269
20	2	86069404	87091272	REEP1;KDM3A	10	2	86583192	rs13387570	6.681	0.262	9	2	86583192	rs13387570	9.660	0.296	10	2	86583192	rs13387570	8.311	0.232
21	2	145181935	146294405	TEX41	27	2	145681935	rs11679718	6.451	0.150	34	2	145773702	rs34985138	6.790	0.103	29	2	145681935	rs11679718	6.641	0.119
22	2	148292665	149306433	MBD5	276	2	148799710	rs12992231	5.554	0.077	264	2	148454344	rs1919445	5.879	0.096	250	2	148799710	rs12992231	6.893	0.125
23	2	174952275	176058804	WIPF1	4	2	175555714	rs56181519	16.313	0.592	3	2	175555714	rs56181519	15.876	0.441	4	2	175512820	rs7574892	17.213	0.667
24	2	178784643	180192967	TTN	21	2	179398823	rs2857265	23.475	0.244	19	2	179411665	rs2288327	27.578	0.553	20	2	179413110	rs3731748	27.396	0.122
25	2	199754002	201806139	SPATS2L	9	2	201168758	rs56326533	28.247	0.317	17	2	201168758	rs56326533	22.052	0.303	13	2	201180023	rs3820888	28.423	0.215
26	2	212743651	213798393	ERBB4	23	2	213251503	rs13019524	8.692	0.449	16	2	213259857	rs6738011	8.344	0.138	16	2	213251503	rs13019524	9.014	0.570
27	3	12259080	12841804	CAND2	3	3	12840934	rs6810325	27.870	0.552	3	3	12841804	rs7650482	26.762	0.715	3	3	12841804	rs7650482	32.733	0.678
28	3	23918590	24975752	THRB	7	3	24463235	rs73041705	10.672	0.286	10	3	24463235	rs73041705	10.380	0.249	7	3	24472866	rs73032363	13.406	0.270
29	3	37603776	39326179	SCN10A	12	3	38771925	rs6790396	20.663	0.237	10	3	38767315	rs6801957	19.166	0.230	10	3	38767315	rs6801957	22.109	0.349
30	3	65834633	66954191	LRIG1	31	3	66454191	rs34080181	10.813	0.783	17	3	66454191	rs34080181	10.250	0.611	17	3	66454191	rs34080181	12.534	0.888
31	3	68889842	69917585	FRMD4B	46	3	69406181	rs17005647	7.679	0.228	24	3	69406181	rs17005647	8.243	0.256	37	3	69406181	rs17005647	8.711	0.218
32	3	88948196	90251353	EPHA3	21	3	89489529	rs6771054	9.412	0.379	25	3	89489529	rs6771054	12.409	0.317	21	3	89489529	rs6771054	12.261	0.382
33	3	110923630	112190620	PHLDB2;PLCXD2	30	3	111554426	rs10804493	16.011	0.335	74	3	111554426	rs10804493	14.551	0.125	30	3	111554426	rs10804493	17.173	0.128
34	3	135314009	137000733	PPP2R3A	72	3	135814009	rs1278493	7.501	0.210	71	3	135814009	rs1278493	7.862	0.135	68	3	135814009	rs1278493	8.694	0.171
35	3	178537434	179673620	GNB4;ACTL6A	23	3	179172979	rs7612445	9.289	0.432	35	3	179172979	rs7612445	8.249	0.245	6	3	179172979	rs7612445	10.634	0.387
36	3	194295645	195301442	XXYLT1	5	3	194800853	rs60902112	8.704	0.663	4	3	194800853	rs60902112	8.521	0.446	4	3	194800853	rs60902112	10.767	0.530
37	4	9577638	10626235	WDR1	106	4	10104478	rs11938486	7.190	0.118	69	4	10104478	rs55754224	5.618	0.119	86	4	10104478	rs55754224	7.628	0.153
38	4	71276935	72276935	MOB1B	61	4	72110394	rs1377284	6.094	0.169	63	4	72085452	rs2262946	5.218	0.133	55	4	71776935	rs12512502	6.547	0.389
39	4	80657703	81702048	PRDM8;FGF5	7	4	81164723	rs1458038	9.978	0.405	6	4	81164723	rs1458038	10.747	0.420	6	4	81169912	rs11099098	12.963	0.355
40	4	83327822	84483700	LIN54	102	4	83910712	rs6841049	7.694	0.051	183	4	83901562	rs4693066	5.982	0.032	134	4	83910712	rs6841049	7.628	0.048
41	4	103094918	104460768	LOC102723704	255	4	103712337	rs223449	7.370	0.021	250	4	103915618	rs3960788	6.767	0.017	251	4	103712337	rs223449	8.147	0.021
42	4	110777746	113087504	PITX2;C4orf32	2	4	111710967	rs17042175	640.783	0.842	6	4	111701798	rs1906615	506.418	0.593	2	4	111710967	rs17042175	713.837	0.942
43	4	113874813	114958402	CAMK2D	18	4	114428714	rs55754224	11.719	0.241	18	4	114449719	rs11938486	12.322	0.174	17	4	114428714	rs55754224	12.853	0.249
44	4	148335571	149469618	ARHGAP10	16	4	148936414	rs10213376	15.533	0.182	60	4	148912031	rs75759772	10.172	0.116	16	4	148937537	rs10213171	15.718	0.234
45	4	173947349	175181860	HAND2-AS1	1	4	174472421	rs4282143	18.081	1.000	16	4	174641184	rs12648245	13.282	0.189	1	4	174472421	rs4282143	18.122	1.000
46	5	105896918	106949990	LINC01950;EFNA5	118	5	106427609	rs6596717	6.782	0.071	119	5	106427609	rs6596717	7.899	0.154	132	5	106427609	rs6596717	7.544	0.131
47	5	113170474	114951109	KCNN2	8	5	113746180	rs337708	20.465	0.289	8	5	113746180	rs337708	15.570	0.287	7	5	113746180	rs337708	22.323	0.481
48	5	127287610	128792189	FBN2;SLC27A6	116	5	128190363	rs2012809	8.181	0.366	73	5	128190363	rs2012809	9.064	0.304	73	5	128190363	rs2012809	9.374	0.211
49	5	136238113	138330420	WNT8A;NME5	4	5	137081377	rs79329739	29.645	0.827	13	5	137443486	rs529526	34.899	0.587	17	5	137443486	rs529526	33.262	0.323
50	5	139032339	140214751	PFDN1;HBEGF	94	5	139703286	rs17118812	7.137	0.665	97	5	139703286	rs17118812	5.538	0.176	94	5	139703286	rs17118812	8.078	0.103
51	5	142120736	143475754	NR3C1;MIR5197	31	5	142818123	rs6580277	14.989	0.241	10	5	142818123	rs6580277	17.069	0.287	32	5	142818123	rs6580277	17.021	0.292
52	5	167855857	168901850	SLIT3	41	5	168393227	rs77328981	9.184	0.125	50	5	168391662	rs76381183	7.935	0.071	41	5	168393227	rs77328981	10.015	0.128
53	5	171975613	173893958	NKX2-5;STC2	5	5	172675034	rs62378332	21.886	0.408	4	5	172664163	rs6882776	21.808	0.452	5	5	172670745	rs6891790	23.958	0.428
54	6	15899680	16935743	ATXN1	1	6	16418562	rs9370893	13.364	1.000	1	6	16418562	rs9370893	15.963	1.000	1	6	16418562	rs9370893	14.087	0.997
55	6	17710109	18913026	KDM1B	1	6	18210109	rs34969716	20.999	0.998	12	6	18210109	rs34969716	18.803	0.958	1	6	18210109	rs34969716	22.659	1.000
56	6	22071323	23098259	HDGFL1;LOC105374972	45	6	22577718	rs13199041	4.686	0.065	45	6	22575096	rs12662891	5.237	0.054	29	6	22598259	rs7766436	6.187	0.055
57	6	33665721	34714322	GRM4;HMGA1	7	6	34188467	rs9469745	8.037	0.309	118	6	34188892	rs9689096	4.466	0.229	11	6	34188866	rs12214804	8.090	0.252
58	6	36116600	37159932	CDKN1A	3	6	36645968	rs730506	14.151	0.382	3	6	36645968	rs730506	14.699	0.391	3	6	36647289	rs3176326	17.705	0.362
59	6	75664589	77067954	LOC101928540	56	6	76188330	rs12211255	9.274	0.321	66	6	76164589	rs12209223	7.551	0.200	51	6	76164589	rs12209223	10.909	0.323
60	6	87256580	88840568	ZNF292	256	6	87871344	rs912815	11.417	0.041	300	6	87873042	rs9294371	8.734	0.022	272	6	87886335	rs7757330	11.670	0.038
61	6	116971951	119539482	CEP85L	17	6	118655020	rs72967533	19.884	0.229	9	6	118974798	rs9481842	19.339	0.292	13	6	118974798	rs9481842	19.566	0.343
62	6	121202234	123272530	GJA1;HSF2	21	6	122403559	rs13195459	22.040	0.131	23	6	122398241	rs72966339	19.452	0.138	22	6	122398241	rs72966339	24.740	0.165
63	6	132817742	134100591	LINC00326;EYA4	161	6	133443662	rs6941949	8.773	0.328	287	6	133414338	rs9493513	4.661	0.046	171	6	133432323	rs6902225	9.362	0.342
64	6	134587658	135621662	LOC101928304;ALDH8A1	8	6	135119089	rs4896104	7.190	0.759	8	6	135119089	rs4896104	6.589	0.453	7	6	135119089	rs4896104	7.975	0.675
65	6	148786910	149914461	UST;TAB2	1	6	149413519	rs78811127	13.606	1.000	1	6	149413519	rs78811127	16.185	1.000	1	6	149413519	rs78811127	14.815	1.000
66	7	372848	1421411	SUN1	38	7	889858	rs34398649	7.209	0.701	33	7	899710	rs12700166	7.371	0.204	33	7	895285	rs6461461	7.810	0.247
67	7	13865616	14886532	DGKB	4	7	14373714	rs12154315	10.511	0.615	4	7	14372009	rs55734480	12.617	0.402	4	7	14373714	rs12154315	12.632	0.521
68	7	27908294	28919716	CREB5	8	7	28417214	rs9639575	7.269	0.544	10	7	28408309	rs6948592	8.335	0.302	10	7	28417214	rs9639575	7.886	0.356
69	7	91741451	92827026	CDK6	19	7	92250140	rs42044	11.005	0.634	20	7	92278116	rs56201652	11.755	0.237	18	7	92250140	rs42044	12.148	0.629
70	7	105100803	106117076	CDHR3	22	7	105614700	rs2727747	5.751	0.085	50	7	105608411	rs2727753	4.505	0.087	22	7	105612736	rs2727757	6.943	0.090
71	7	115280581	116724638	CAV1	3	7	116191301	rs11773845	65.831	0.600	3	7	116191301	rs11773845	58.761	0.482	3	7	116198621	rs1997571	71.150	0.559
72	7	150114934	151169976	KCNH2	7	7	150669976	rs3778872	10.936	0.681	16	7	150661409	rs7789146	10.305	0.197	6	7	150669976	rs3778872	11.926	0.698
73	8	11276904	12309421	CTSB;DEFB136	113	8	11498149	rs12680985	6.345	0.139	103	8	11784541	rs6996342	6.570	0.027	108	8	11784541	rs6996342	6.622	0.027
74	8	17222615	18445990	PCM1;ASAH1	1	8	17912752	rs399485	18.947	0.995	1	8	17912752	rs399485	17.333	0.994	1	8	17912752	rs399485	18.913	0.993
75	8	21270372	22370967	XPO7	21	8	21830295	rs17060685	11.643	0.138	23	8	21805265	rs6998692	10.884	0.266	20	8	21805265	rs6998692	14.474	0.348
76	8	118363412	119363445	EXT1	252	8	118863412	rs17430357	4.177	0.172	13	8	118863412	rs17430357	5.691	0.391	12	8	118863412	rs17430357	6.245	0.445
77	8	124029377	125135197	FBXO32;KLHL38	3	8	124610166	rs58847541	12.770	0.948	4	8	124610166	rs58847541	9.915	0.849	3	8	124610166	rs58847541	13.091	0.632
78	8	141151733	142518135	PTK2	244	8	141740868	rs6994744	9.876	0.073	238	8	141740868	rs6994744	8.367	0.028	238	8	141740868	rs6994744	10.500	0.030
79	9	19715705	20735499	SLC24A2;MLLT3	38	9	20226646	rs7036564	4.539	0.123	51	9	20237050	rs7029765	4.716	0.179	20	9	20235004	rs4977397	6.178	0.139
80	9	96482190	98632921	C9orf3	14	9	97713459	rs10821415	31.150	0.417	20	9	97713459	rs10821415	32.334	0.460	18	9	97713459	rs10821415	31.754	0.511
81	9	118681794	119681794	PAPPA;ASTN2	620	9	119181794	rs17303101	4.421	0.555	12	9	119181794	rs17303101	5.981	0.916	12	9	119181794	rs17303101	6.328	0.890
82	9	138589679	139609861	LHX3	9	9	139094773	rs2274115	9.989	0.866	14	9	139095271	rs3758197	6.596	0.226	14	9	139094773	rs2274115	8.976	0.637
83	10	20533698	21742382	NEBL	29	10	21036186	rs10828120	6.909	0.355	2016	10	21240532	rs4543885	3.381	0.232	3	10	21242382	rs7910227	9.149	0.985
84	10	32209192	33769397	CCDC7	175	10	33047262	rs2484726	6.271	0.022	173	10	32772734	rs11527634	5.825	0.057	165	10	32772734	rs11527634	7.692	0.042
85	10	49804998	51003524	C10orf128;C10orf71-AS1	117	10	50322479	rs4838366	6.117	0.079	94	10	50322479	rs4838366	6.394	0.097	83	10	50485434	rs76460895	7.810	0.088
86	10	64374754	65900080	REEP3	83	10	65321147	rs12245149	13.949	0.142	104	10	65321147	rs12245149	10.930	0.052	44	10	65321147	rs12245149	14.712	0.106
87	10	68751616	70396336	DNAJC12;SIRT1	80	10	69614737	rs12360521	10.528	0.062	57	10	69632939	rs7092564	9.510	0.062	81	10	69614737	rs12360521	14.120	0.121
88	10	74894715	76163351	SYNPO2L	3	10	75415677	rs60632610	33.134	0.630	6	10	75420180	rs7915134	37.826	0.467	4	10	75414344	rs60212594	38.386	0.570
89	10	76347993	78497672	LRMDA	38	10	77936576	rs10458660	15.412	0.106	75	10	77936670	rs10458662	8.401	0.058	34	10	77936670	rs10458662	16.095	0.142
90	10	80397384	81398969	ZMIZ1	9	10	80898969	rs1769758	5.772	0.571	45	10	80898969	rs1769758	5.910	0.727	3	10	80898969	rs1769758	7.505	0.757
91	10	102838008	106194644	NEURL1	1	10	105316296	rs74154539	74.782	0.999	4	10	105342672	rs11598047	69.272	0.503	1	10	105316296	rs74154539	79.932	1.000
92	10	112074402	113076695	RBM20	2	10	112576695	rs10749053	7.837	0.731	2	10	112576695	rs10749053	6.593	0.919	2	10	112576695	rs10749053	7.782	0.955
93	11	3389383	4390223	STIM1	56	11	3890059	rs7126870	5.246	0.251	93	11	3890059	rs7126870	5.084	0.144	42	11	3890059	rs7126870	6.216	0.238
94	11	13534698	14622134	SPON1	68	11	14037543	rs1528669	8.003	0.033	68	11	14036189	rs10500790	7.861	0.061	62	11	14036189	rs10500790	10.831	0.045
95	11	19481419	20519716	NAV2	18	11	20010291	rs4757877	22.751	0.174	17	11	20008191	rs10766612	20.818	0.136	17	11	20010291	rs4757877	25.441	0.160
96	11	94589882	95592398	LOC100129203;FAM76B	32	11	95092398	rs565449	5.719	0.244	34	11	95089882	rs517938	5.921	0.209	16	11	95089882	rs517938	6.157	0.220
97	11	121104722	122161507	SORL1;MIR100HG	18	11	121661507	rs4935786	8.681	0.248	42	11	121661507	rs4935786	6.304	0.106	19	11	121654327	rs7946552	7.790	0.180
98	11	128260774	129294234	KCNJ5	7	11	128764570	rs76097649	18.851	0.313	7	11	128764570	rs76097649	22.069	0.451	7	11	128764570	rs76097649	22.835	0.481
99	12	12386027	13386027	APOLD1	7	12	12886027	rs10845620	5.649	0.904	244	12	12886027	rs10845620	4.709	0.426	3	12	12886027	rs10845620	6.031	0.932
100	12	24196408	25373178	LINC00477;BCAT1	13	12	24762501	rs11047527	31.068	0.131	11	12	24784139	rs4246224	25.144	0.148	11	12	24771967	rs10842383	33.251	0.180
101	12	25778218	27110236	SSPN	18	12	26346956	rs3809138	10.012	0.313	4	12	26348429	rs113819537	14.093	0.824	4	12	26348429	rs113819537	14.032	0.612
102	12	32441446	33527458	PKP2	5	12	32978437	rs12809354	12.296	0.810	5	12	32978437	rs12809354	14.363	0.820	5	12	32978437	rs12809354	14.362	0.812
103	12	56483252	57712827	NACA	16	12	57105938	rs2860482	15.556	0.257	33	12	57105938	rs2860482	11.622	0.342	15	12	57105938	rs2860482	16.674	0.459
104	12	69355200	70598621	LRRC10;BEST3	66	12	70013415	rs71454237	10.368	0.921	37	12	70013415	rs71454237	10.747	0.852	49	12	70013415	rs71454237	9.986	0.360
105	12	75703505	76744249	KRR1;PHLDA1	31	12	76238855	rs1565765	8.760	0.350	10	12	76237987	rs12426679	9.126	0.476	20	12	76238855	rs1565765	10.911	0.791
106	12	103967069	105021552	HCFC2	7	12	104492003	rs2629755	8.916	0.234	1350	12	104492003	rs2629755	3.722	0.166	7	12	104492003	rs2629755	9.505	0.269
107	12	109582115	110582154	MVK;FAM222A	11	12	110082154	rs1344542	8.600	0.643	1004	12	110234942	rs56365155	2.724	0.024	6	12	110082115	rs1344543	8.675	0.934
108	12	110859712	112290511	CUX2	1	12	111671076	rs11065836	14.880	0.998	702	12	111070549	rs11065683	2.573	0.080	16	12	111631765	rs4766552	9.471	0.347
109	12	112696733	114024987	RPH3A	10	12	113196733	rs11614295	8.448	0.656	1580	12	113027507	rs11832547	2.027	0.032	7	12	113196733	rs11614295	8.669	0.911
110	12	114192036	115874959	TBX5	7	12	114793240	rs883079	51.169	0.359	8	12	114797306	rs7955405	43.125	0.377	6	12	114793240	rs883079	57.064	0.584
111	12	122785131	123879477	CCDC62	49	12	123368419	rs10744434	7.260	0.057	61	12	123327900	rs10773657	6.778	0.071	49	12	123312051	rs897393	7.754	0.063
112	12	123945569	125312678	NCOR2	86	12	124427306	rs11057401	5.250	0.032	74	12	124811855	rs2272368	7.922	0.311	86	12	124812678	rs3741508	6.634	0.092
113	12	132591614	133650210	FBRSL1	30	12	133150210	rs6560886	6.179	0.465	39	12	133150210	rs6560886	6.429	0.415	38	12	133091614	rs4883571	6.136	0.240
114	13	21592762	22612927	MICU2	89	13	22300554	rs9552476	4.733	0.061	84	13	22111521	rs11841562	5.648	0.042	71	13	22111521	rs11841562	6.240	0.055
115	13	22839138	23874178	LINC00540;LINC00621	10	13	23368834	rs3904323	7.698	0.807	5	13	23368834	rs3904323	9.571	0.693	5	13	23368834	rs3904323	10.082	0.846
116	13	74018210	75020186	KLF12	6	13	74520186	rs1886512	6.588	0.649	8	13	74520186	rs1886512	5.364	0.246	6	13	74520186	rs1886512	6.943	0.696
117	13	113364837	114410611	CUL4A	102	13	113872712	rs35569628	6.230	0.086	104	13	113872712	rs35569628	6.637	0.047	104	13	113864837	rs2316443	6.475	0.099
118	14	23348311	24383739	MYH6	3	14	23864804	rs445754	10.293	0.689	4	14	23863802	rs445754	9.134	0.472	3	14	23864804	rs422068	11.418	0.607
119	14	32396479	33500955	AKAP6	5	14	32990437	rs11156751	26.258	0.555	5	14	32990437	rs11156751	20.143	0.311	5	14	32990437	rs11156751	27.827	0.415
120	14	34656561	35707496	SNX6;CFL2	13	14	35173775	rs73241997	14.429	0.882	11	14	35173775	rs73241997	13.689	0.816	12	14	35173775	rs73241997	15.276	0.845
121	14	64066636	65378265	SYNE2	2	14	64679960	rs2738413	38.086	0.840	6	14	64679960	rs2738413	28.975	0.479	2	14	64679960	rs2738413	38.110	0.882
122	14	72748367	73864698	DPF3	5	14	73355131	rs2110552	12.085	0.414	11	14	73249419	rs74884082	9.347	0.471	6	14	73355131	rs2110552	12.874	0.306
123	14	76922803	77930681	LINC01629	8	14	77427469	rs8181996	8.985	0.411	8	14	77426711	rs10873299	7.473	0.243	6	14	77426525	rs10873298	9.636	0.384
124	15	69963992	70963992	TLE3;LINC02205	76	15	70463992	rs2415081	5.492	0.811	5	15	70458576	rs4777245	6.379	0.512	8	15	70463992	rs2415081	6.141	0.528
125	15	72965477	74184606	HCN4;REC114	10	15	73677264	rs74022964	33.191	0.550	10	15	73667255	rs7172038	37.395	0.458	9	15	73667255	rs7172038	36.884	0.479
126	15	80073864	81566058	LINC00927;ARNT2	1	15	80676925	rs12908004	17.648	1.000	1	15	80676925	rs12908004	17.256	1.000	1	15	80676925	rs12908004	21.405	1.000
127	15	98749029	99795650	IGF1R	17	15	99268850	rs4965430	9.618	0.483	19	15	99268850	rs4965430	9.829	0.261	15	15	99268850	rs4965430	10.989	0.407
128	16	264520	1281633	METRN	186	16	764520	rs3809665	4.730	0.095	62	16	764520	rs3809665	6.272	0.127	74	16	764753	rs3809666	6.101	0.085
129	16	1503399	2514283	RPL3L	3	16	2004718	rs2815301	10.513	0.692	4	16	2004718	rs2815301	9.124	0.939	2	16	2004718	rs2815301	12.633	0.963
130	16	15402590	16412544	MYH11	7	16	15902715	rs9284324	6.398	0.660	63	16	15902715	rs9284324	5.556	0.458	5	16	15902715	rs9284324	7.200	0.618
131	16	71917516	73630109	ZFHX3	4	16	73048367	rs67329386	130.357	0.663	2	16	73053022	rs2359171	102.282	0.743	1	16	73048367	rs67329386	144.357	0.995
132	17	736956	2705923	YWHAE;CRK	81	17	1309850	rs7225165	6.961	0.147	178	17	1309850	rs7225165	7.469	0.120	126	17	1312046	rs61248729	7.496	0.125
133	17	6914958	7926695	POLR2A	31	17	7414958	rs2071502	6.059	0.334	30	17	7414958	rs2071502	6.925	0.288	29	17	7414958	rs2071502	6.473	0.198
134	17	12095075	13118680	MYOCD	1	17	12618680	rs72811294	13.315	1.000	11	17	12612632	rs55986665	9.771	0.199	1	17	12618680	rs72811294	13.405	1.000
135	17	36915544	38589717	ZPBP2;GSDMB	52	17	38049589	rs7359623	10.264	0.145	37	17	37983492	rs12944882	11.563	0.108	43	17	38049589	rs7359623	12.407	0.089
136	17	43519712	44526739	MAPT	3	17	44019712	rs242557	8.032	0.974	18	17	44025888	rs242559	6.286	0.479	2	17	44019712	rs242557	9.446	0.983
137	17	44543508	45638033	ARL17B;CDC27	394	17	45138033	rs145153053	4.297	0.299	80	17	45138033	rs145153053	7.334	0.515	43	17	45138033	rs145153053	7.065	0.595
138	17	67843539	68979067	KCNJ2;CASC17	39	17	68419387	rs9890689	6.116	0.079	60	17	68347453	rs312756	4.633	0.070	39	17	68421803	rs1396517	6.863	0.068
139	18	45957096	47028787	SMAD7	2	18	46474192	rs9953366	9.528	0.986	16	18	46474192	rs9953366	10.248	0.463	7	18	46474192	rs9953366	10.549	0.973
140	18	76656537	77656537	NFATC1	1	18	77156537	rs8096658	7.688	0.997	12	18	77156537	rs8096658	5.291	0.940	1	18	77156537	rs8096658	7.120	0.994
141	19	47628418	48670757	BICRA	30	19	48142746	rs11881441	6.057	0.064	31	19	48146728	rs2068832	6.375	0.079	31	19	48142746	rs11881441	7.384	0.077
142	20	36328890	37386397	KIAA1755	25	20	36886397	rs1205424	7.752	0.266	26	20	36842883	rs6127466	6.934	0.208	25	20	36841914	rs3746471	9.429	0.335
143	20	60641981	61656946	MIR1-1HG	14	20	61154393	rs6089752	7.958	0.529	47	20	61156946	rs6122011	6.698	0.311	12	20	61154393	rs6089752	9.720	0.320
144	21	35594354	37338008	LINC01426	1	21	36119111	rs2834618	19.296	1.000	1	21	36119111	rs2834618	15.210	1.000	1	21	36119111	rs2834618	19.189	1.000
145	22	18065048	19101415	TUBA8	2	22	18597502	rs464901	10.799	0.989	2	22	18597502	rs464901	10.802	0.851	2	22	18597502	rs464901	11.685	0.959
146	22	21499229	22499229	SDF2L1	67	22	21999229	rs5754508	5.486	0.298	361	22	21998833	rs12484001	3.603	0.125	66	22	21999229	rs5754508	6.077	0.191
147	22	25656431	26664079	MYO18B	4	22	26164079	rs133902	9.082	0.686	13	22	26164079	rs133902	8.116	0.620	4	22	26164079	rs133902	9.438	0.693
148	22	41620864	42702825	MEI1	33	22	42194561	rs1983554	5.022	0.221	16	22	42194561	rs1983554	7.715	0.142	25	22	42189407	rs139557	6.577	0.134
149	X	22899373	24046193	PTCHD1	10	23	23399501	rs73205368	8.841	0.132	1460	23	23021849	rs191831637	2.413	0.156	10	23	23399501	rs73205368	10.514	0.600
150	X	136873525	137918967	ZIC3;LINC00889	64	23	137416093	rs2129742	5.222	0.495	13	23	137497584	rs78426954	5.982	0.492	2	23	137418967	rs1891095	9.242	0.625

AF, atrial fibrillation; CHR chromosome; POS, position (hg19); rsID, reference SNP cluster ID; BF, bayes factor; PPA, posterior probability of association



Supplementary Fig. 9 | rs67329386 and transcription factor.
ZFHX3 locus showing rs67329386 (highlighted in yellow) and proxies with $r^2 > 0.8$ in European samples in 1KG along with ChIP-seq track of CEBPB experiments in mesenchymal stem cells.

associated variants overlapping with quantitative trait loci (QTL) for clinical measurements such as anthropometric, metabolic, kidney-related, and blood pressure data (Supplementary Table 10). We found 160 loci-phenotype association pairs, where distinct functional clusters were observed (Supplementary Fig. 10); positive impact on blood pressure: *CASZ1, PRDM8-FGF5, CUX2*, and *RPH3A*, and negative impact on renal function: *MIR5096, MBD5, DNAJC12-SIRT1, IGF1R*, and *NFATC1*. Moreover, we observed associations on chromosome 6p21.31 harboring *HMGA1*, in which AF-associated variants overlapped with QTLs for height (rs1759628) and body mass index (BMI) (rs6913361). Both rs1759628 and rs6913361 were located 7 kilobases (kb) and 25 kb upstream of *HMGA1*, respectively, and the risk alleles of these variants were significantly associated with increased height and BMI (β_{height} (s.e.m.$_{\text{height}}$)=0.090 (0.005), $P_{\text{height}}=8.7\times10^{-93}$; β_{BMI} (s.e.m.$_{\text{BMI}}$)=0.037 (0.005), $P_{\text{BMI}}=1.7\times10^{-12}$, respectively). *HMGA1* encoded a chromatin-associated protein that attach to AT-rich regions of DNA and recruit transcription factors, resulting in upregulation of the insulin receptor gene expression[49] and the variants in *HMGA1* were associated with increased risk of metabolic syndrome[50].

To enhance the biological understanding of the AF-associated loci, we performed in silico tissue and gene-set enrichment analysis using DEPICT software[14], which prioritizes candidate genes and tissues based on gene expression data from different tissues and cell types. Consistent with a previous study[7], we found significant enrichment of AF-associated loci predominantly in heart tissues ($P<1.2\times10^{-5}$ for heart and $P<2.3\times10^{-5}$ for heart atria; Supplementary Fig. 11 and Supplementary Table 11). Additionally, pathway analysis demonstrated that AF-associated loci were significantly enriched in 34 out of 1,157 gene sets, most of which were involved in heart development and morphogenesis (Supplementary Table 12). Among them, the regulation of cell adhesion was a previously unreported pathway ($P=1.6\times10^{-10}$), in which *ZMIZ1*, the nearest gene for rs1769758, was reported to regulate the activity of various transcription factors related to vascular development, androgen receptor coregulation, SMAD3 regulation, and coactivation of p53[51–53]. Knockdown of *ZMIZ1* in mice resulted in severe defects in the reorganization of the yolk sac vascular plexus and cell proliferation[54].

Supplementary Table 9 | Pleiotropy of AF-associated loci

Lead variant		Variant associated with other trait			Trait or disease
CHR	POS	CHR	POS	rsID	
Novel loci					
1	918617	1	894573	rs13303010	Pancreatic cancer
			895705	rs13303327	Heel bone mineral density
1	16199051	1	94368	rs3121567	Blood protein levels
			16133296	rs12738240	Hair color
			16188681	rs6701290	Heel bone mineral density
			16274769	rs868891	Heel bone mineral density
			16277082	rs848188	Hair color
			16271180	rs848216	Heel bone mineral density
			16316119	rs848302	Glomerular filtration rate
1	39389714	1	39380285	rs4246511	Menopause (age at onset)
			39364617	rs4970834	Age at menopause
5	139703280	5	139707439	rs11168036	Alzheimer's disease
			139714564	rs2074613	Body mass index
					General cognitive ability
					Intelligence
			139716988	rs2237078	Creatine kinase levels
			139719229	rs2282802	Intelligence
			139726641	rs4150196	Intelligence
			139689454	rs67432087	Intelligence
			139692515	rs6870103	Reaction time
			139703809	rs736954	Intelligence
6	22598259	6	22592707	rs13258437	Waist-hip ratio
			22593125	rs2876643	Coronary artery disease
			22612529	rs6909752	Coronary artery disease
			22598259	rs2766436	Coronary artery disease
6	76164589	6	76164589	rs11099079	Height
					Osteoarthritis (hip)
6	135119089	6	135119089	rs4896104	Pulse pressure
8	118863412	8	118856307	rs17430287	Highest math class taken
			118884173	rs72673647	Body mass index
9	119181768	9	119248059	rs13720032	Headache
			119263127	rs7873551	Total intracranial volume
10	80898969	10	80918517	rs279553	Waist-hip ratio
			80918517	rs780159	Waist circumference adjusted for BMI
11	3890099	11	3897176	rs11609179	Mean platelet volume
					Platelet distribution width
11	14036189	11	14066486	rs10822169	Blood protein levels
			14052119	rs11023056	Blood protein levels
			14021639	rs2618516	Brain connectivity
			14053332	rs2618521	Blood protein levels
11	95098982	11	95096371	rs7596851	Monocyte count
					White blood cell count
12	12886027	12	12890676	rs11053034	Birth weight
			12888438	rs2024365	Systolic blood pressure
			12871099	rs2066827	Prostate cancer
			12872748	rs4632?	Mean arterial pressure
			12870656	rs34330	Systemic lupus erythematosus
			12889289	rs4763297	Systolic blood pressure
			12878765	rs66561220	Lymphocyte counts
					White blood cell count
			12877983	rs77716619	Heel bone mineral density
					Lymphocyte counts
12	110082116	12	110054431	rs10850481	Neuroticism
			110069190	rs11067590	Aspartate aminotransferase levels
					HDL cholesterol
			110088272	rs79268462	Neutrophil count
12	111196779	12	111256685	rs2384034	Lipid traits
			112285503	rs2294822	Smoking status
13	22111521	13	22118292	rs11865168	PR interval
			22131897	rs2798269	PR segment
			22085659	rs718426	PR interval
			74520186	rs1886512	QRS duration
13	74520186	13	74531172	rs779976	QRS duration
					QT interval
			74538218	rs9573330	QRS duration
16	15902715	16	15910743	rs34916499	Pulse pressure
					Resting heart rate
					Systolic blood pressure
			15906130	rs8044595	Pulse pressure
			77161324	rs11777118	Lung function (FEV1/FVC)
					Blood urea nitrogen levels
17	77156537	17	77158225	rs549752	Creatinine levels
					Glomerular filtration rate
			77160236	rs58376587	Heel bone mineral density
			77156103	rs71359461	Glomerular filtration rate
			77156171	rs74183647	Serum creatinine levels
					Glomerular filtration rate
			77162423	rs8091189	Glomerular filtration rate
			77156537	rs8099658	Glomerular filtration rate
					Heel bone mineral density
					Glomerular filtration rate
19	48142746	19	48140857	rs2910996	Balding type 1
					Male-pattern baldness
20	36841914	20	36849007	rs4811601	Pulse pressure
			36849038	rs4811602	Psoriatic arthritis
			36843692	rs6059234	RR interval
					Heart rate variability traits
			36840156	rs61234771	Resting heart rate
					Heart rate
			36824720	rs75727053	Antibody status to Trypanosoma cruzi seropositivity
22	21999229	22	21979096	rs11089637	Rheumatoid arthritis
			21971859	rs139664736	Mean corpuscular volume
					Red cell distribution width
					Eczema
			21982054	rs1811069	Eosinophil counts
					HDL cholesterol
					Mean corpuscular hemoglobin
			21925017	rs2256609	Crohn's disease
					Crohn's disease
			21922908	rs2266959	Inflammatory bowel disease
					Juvenile idiopathic arthritis
			21979597	rs7265961	Chronic inflammatory diseases
					Inflammatory bowel disease
			21982892	rs2298428	Celiac disease or Rheumatoid arthritis
					Heel bone mineral density
			21982892	rs7479093	Mean corpuscular hemoglobin
					Systemic lupus erythematosus
			21973319	rs4871116	HDL cholesterol
					Hepatitis B
			21979289	rs4871174	Celiac disease
					Psoriasis
			21916166	rs67541???	Autoimmune traits
					Lymphocyte counts
			21916272	rs67541??	Intraocular pressure
					Total cholesterol
			21963786	rs6754344	HDL cholesterol
			21974703	rs6754387	Heel bone mineral density
			21983094	rs6754407	Systemic sclerosis-rheumatic diseases
			21917479	rs9998109	Lymphocyte percentage of white cells
					Neutrophil percentage of white cells
			21979934	rs7444	HDL cholesterol
					Systemic lupus erythematosus
			21977047	rs7448	HDL cholesterol
			21982749	rs878925	Red cell distribution width
					White blood cell count
22	42189407	22	42210597	rs11703813	Self-reported math ability
			42194551	rs1983354	Spherical equivalent or myopia (age of diagnosis)
			42184143	rs55950659	Pulse pressure
			42194917	rs1787519	Smoking initiation
			42201517	rs74705753	Intelligence
Known loci					
1	10796866	1	10799577	rs12026278	Diastolic blood pressure
					Pulse pressure
					Systolic blood pressure
			10796547	rs17031646	Systolic blood pressure
			10796499	rs34071855	Pulse pressure
					Blood pressure
					Cardiovascular disease
					Diastolic blood pressure
			10796866	rs880315	Hypertension
					Ischemic stroke
					Mean arterial pressure
					Pulse pressure
					Stroke
					Systolic blood pressure
1	22282619	1	22266330	rs11979633	Lung function (FVC)
			22268938	rs1200738	Height
1	41544279	1	41534357	rs12024115	Cognitive performance
					Educational attainment
					Highest math class taken
					Self-reported math ability
1	41544279	1	41509674	rs2749418	Lung function (FVC)
					Adrenarche/menses
1	41544279	1	41544279	rs2885697	Fat-free mass
					General risk tolerance
			41556253	rs660365	Height
			41530871	rs6868842	Height
1	112382671	1	112362360	rs12084663	Immune response to smallpox
			116320833	rs10923445	QRS duration
1	116297758	1	116297758	rs6072778	Pulse pressure
			116310967	rs6074535	QRS duration
1	154862963	1	154855003	rs1501500	Parkinson's disease
			154853977	rs7517623	Lung function (FEV1/FVC)
1	170639961	1	170623063	rs6659881	Lobe attachment
			170629953	rs4483857	Blood protein levels
1	205619316	1	205676263	rs12749851	White blood cell types
			205677149	rs3787973	Lung function (FVC)
			205669322	rs822009	Smoking initiation
			205685359	rs951366	Melanoma (age at onset)
2	26159940	2	26136904	rs189601688	Cough in response to angiotensin-converting enzyme inhibitor drugs
			26158663	rs3853365	Red blood cell count
2	61676940	2	61662655	rs1186589	Cardiovascular disease
			61437687	rs12984675	Lung function (FVC)
			61806899	rs6733445	Balding type 1
			61834235	rs7608487	Diastolic blood pressure
			61687214	rs378138	Morning person
			61781994	rs378756	Eosinophil counts
					Chronotype
			61680993	rs812925	Immature fraction of reticulocytes
					Morning person
					Cardiovascular disease
2	65284231	2	65276452	rs11099358	Type 2 diabetes
			65276049	rs1099360	Triglyceride
			65284157	rs111524956	Systolic blood pressure
					Triglyceride
			65297896	rs72491105	Lipid traits
					Systolic blood pressure
			65284623	rs2540948	Triglyceride
			65279223	rs2540950	Pulse pressure
			65267708	rs6728523	HDL cholesterol
			65283972	rs74181259	Pulse pressure
			65296798	rs7572857	Type 2 diabetes
2	70106832	2	70120078	rs55866046	Red cell distribution width
					Male-pattern baldness
2	145681935	2	145679114	rs10929235	Smoking status
			145681570	rs58117425	Diastolic blood pressure
			145701992	rs780232	General risk tolerance
2	148709710	2	148691661	rs10174306	Feeling hurt
					Neuroticism
			148800730	rs12105411	Red blood cell count
			148764288	rs12294718	Neuroticism
			148572160	rs12990959	Diastolic blood pressure
			148585833	rs13026220	Glomerular filtration rate
			148716428	rs2307394	Urate levels
			148614432	rs4972322	Neuroticism
			148834364	rs6430286	Loneliness
2	175512826	2	175529967	rs72914576	Systolic blood pressure
			201171191	rs10931898	Reaction time
2	201180023	2	201160771	rs1367858	Schizophrenia
			201081698	rs1729412	Educational attainment
					Reaction time
			201166099	rs295140	QT interval
			201232862	rs296790	Reaction time
			201161783	rs6573705	Reaction time
			201169893	rs4673912	Reaction time
			201167954	rs6435648	Cognitive performance
					Highest math class taken
			201187316	rs78681500	Schizophrenia
3	12841804	3	12830775	rs1467026	Waist-hip ratio
			12842223	rs4642105	P wave duration
			12840934	rs6810325	Lung function (FVC)
			12840426	rs11712061	Creatine kinase levels
3	34473866	3	34490476	rs11712061	Heel bone mineral density
			34491744	rs2043581	Heel bone mineral density
			38777554	rs10428132	Brugada syndrome
			38784029	rs6599250	PR interval
			38785976	rs6599251	Pulse pressure
			38796415	rs6599255	Resting heart rate
			38771925	rs6790396	P wave duration
					Electrocardiographic conduction measures
3	38767315	3	38766675	rs6795970	Electrocardiographic traits
					Heart rate response
					QRS duration
			38798816	rs6799815	PR interval
			38774832	rs6800541	PR interval
					P wave duration
					PR interval
			38767315	rs6801957	P wave duration
					PR segment
					Pulse pressure
					QRS duration
					QT interval
			38770639	rs7433306	PR interval
3	66454191	3	66503981	rs13706832	Non-glioblastoma glioma
			66437086	rs17831815	Pulse pressure
			66431822	rs2242285	QRS duration
			66434643	rs7996772	Heel bone mineral density
					Systolic blood pressure
			66462974	rs6147862	Mean corpuscular hemoglobin
					Mean corpuscular volume
			66442435	rs812481	Colorectal cancer
3	69406181	3	69410175	rs1483690	Resting heart rate
			69458802	rs900568	PR interval
3	89489529	3	89496562	rs6551412	Intelligence
			89534377	rs7632477	Orofacial clefts
			89587262	rs7652296	Intelligence
			135969645	rs17488771	Neuroticism
					Worry
			135814009	rs1278493	Neuroticism
					Neuroticism
					Worry
3	135814009	3	135828698	rs13088093	Sleep duration
			135822924	rs12486445	Intraocular pressure
			135798618	rs34896409	Triglycerides
			136029897	rs480330	Worry
			136994453	rs4959779	Neuroticism
					Worry
			135979698	rs589092	Worry
			135951491	rs632251	Systolic blood pressure
			135949727	rs483930	Systolic blood pressure
			179169230	rs7611674	Diastolic blood pressure
3	179172979	3	179179979	rs7612445	Heart rate
					Resting heart rate
3	194808853	3	194783033	rs10947051	Blood protein levels
4	99194479	4	99093851	rs3795822	Pulse pressure
			99094931	rs3822241	Smoking initiation
					Coronary artery disease
					Creatinine levels
					Diastolic blood pressure
			81181072	rs10857147	Mean arterial pressure
					Pulse pressure
					Red blood cell count
					Serum uric acid levels
					Systolic blood pressure
			81169912	rs11099098	Blood pressure
					Blood urea nitrogen levels
					Diastolic blood pressure
					Glomerular filtration rate
					Hematocrit
			81182554	rs12509595	Potassium levels
					Pulse pressure
					Red blood cell count
					Systolic blood pressure
					Glomerular filtration rate
					Cardiovascular disease
			81174982	rs13325101	Red blood cell count
					Systolic blood pressure
4	81169912	4	81158545	rs13149993	Mean arterial pressure
			81153106	rs141519038	Male-pattern baldness
			81164723	rs1458038	Blood pressure
					Diastolic blood pressure
					Systolic blood pressure
			81184341	rs16998073	Diastolic blood pressure
					Mean arterial pressure
					Pulse pressure
					Systolic blood pressure
			81157703	rs1902859	Diastolic blood pressure
					Hypertension
					Systolic blood pressure
			81192758	rs3796604	Balding type 1
			81194090	rs3796606	Monobrow
			81168372	rs6459247	Diastolic blood pressure
			83955397	rs12611915	Red cell distribution width
			83956318	rs13046652	Systolic blood pressure
			83895232	rs13103322	Red blood cell count
			83903995	rs2368708	White blood cell count
			83807210	rs67960857	Neutrophil percentage of white cells
			83885210	rs60005104	Lymphocyte percentage of white cells
			83890975	rs6535418	Pulse pressure
			83925895	rs6823199	Pulse pressure
			83916044	rs6845791	Red blood cell count
4	103712337	4	103827488	rs11722779	Schizophrenia
			103851962	rs222498	Sarcoidosis
			103893223	rs7681002	Cardiovascular disease
			111693026	rs13164447	Ischemic stroke
					Ischemic stroke
			111714419	rs13143308	Ischemic stroke (cardioembolic)
4	111710967	4			Stroke
			111720997	rs2123979	Appendicitis
			111719169	rs7690792	Ischemic stroke (cardioembolic)
					Stroke (ischemic)
			111718067	rs6843082	Stroke (ischemic)
			114410006	rs17446618	PR interval
4	114428714	4	114388529	rs2285703	P wave duration
			114439894	rs7700139	Chronotype
			106453988	rs10800196	Smoking initiation
5	106427609	5	106454641	rs2410948	Smoking initiation
			106420589	rs4957528	Smoking status
5	128190363	5	128190363	rs17884800	Red cell distribution width
5	137443686	5	137437485	rs6892844	Balding type 1
5	148359227	5	148358089	rs12188351	Inflammatory skin disease
5	177676749	5	177645766	rs6556059	Infantile hypertrophic pyloric stenosis
			177664163	rs6882776	Heart rate
6	16418562	6	16430021	rs2737199	Subcutaneous adipose tissue attenuation
			16399557	rs3819405	Breast cancer
			34178018	rs13897135	Hand-grip strength
			34189612	rs10947487	Body mass index
			34192036	rs147605666	Waist-hip ratio
			34714972	rs1150781	Anthropometric traits
					Height
			34188866	rs12214804	Height
			34187322	rs146229895	Red blood cell count
					Height
			34194866	rs1759645	Hip circumference adjusted for BMI
					Waist circumference adjusted for BMI
					Height
			34195011	rs1776897	Waist circumference adjusted for BMI
					Waist-hip ratio
			34177853	rs18139895	Red blood cell count
			34208223	rs149288155	Heel bone mineral density
6	34188866	6	34195177	rs2512?0930	Testosterone
					Anthropometric traits
			34199092	rs2780226	Height
					Waist circumference adjusted for BMI
			34219498	rs57026767	Height
			34179390	rs6913361	Body mass index
			34238514	rs6913561	Height
			34208190	rs13734859	Systolic blood pressure
			34173930	rs74374137	HDL cholesterol
					Systolic blood pressure
			34166771	rs7742369	Birth weight
					Height
			34222939	rs9368846	Smoking initiation
			34225075	rs9368805	Glomerular filtration rate
			34236430	rs9469762	Body fat distribution
			34188992	rs9480906	FEV1
					Lung function (FVC)

民族横断的な心房細動ゲノム解析による新たな疾患メカニズムの解明と遺伝子リスクスコアによる心原性脳梗塞の予測

6	36647289	6	36638636	rs1321309	Coronary artery disease
			36622900	rs1321311	Colorectal cancer
					Electrocardiographic traits
					QRS complex
					QRS duration
			36618821	rs1321313	Electrocardiographic conduction measures
			36645696	rs2395655	Triglyceride
			36647289	rs3176326	QRS duration
			36648816	rs3176336	Pulse pressure
					White blood cell count
					QRS duration
			36673379	rs9479361	QRS complex
					QRS duration
6	87886335	6	87837959	rs200638392	Granulocyte count
					Granulocyte percentage of myeloid white cells
					Myeloid white cell count
					Neutrophil count
					Sum basophil neutrophil counts
					Sum neutrophil eosinophil counts
					White blood cell count
			87816905	rs4574603	White blood cell count
			87848302	rs4645482	Mean corpuscular hemoglobin
6	118974798	6	119957557	rs117764195	Bipolar disorder or attention deficit hyperactivity disorder
					QT interval
			118962740	rs6908287	Electrocardiographic conduction measures
6	122398241	6	122388851	rs1402538	Optic cup area
			122392513	rs2684249	Optic cup area
			122389958	rs888153	Vertical cup-disc ratio
7	895285	7	874639	rs10950673	Red cell distribution width
7	14372714	7	14375977	rs13240040	Diastolic blood pressure
7	92250140	7	92273578	rs16229565	Mean corpuscular volume
			92253972	rs16269774	Waist circumference adjusted for BMI
			92256905	rs2040494	Mean corpuscular volume
			92264410	rs2282978	Diastolic blood pressure
					Height
					Pulse pressure
					Systolic blood pressure
			92237426	rs42032	Heel bone mineral density
			92237533	rs42033	Sum eosinophil basophil counts
			92259144	rs42034	Pulse rate
			92243719	rs42038	Systolic blood pressure
					Systolic blood pressure
			92244422	rs42039	Height
					Ischemic stroke
					Stroke
			92247112	rs42042	Mean corpuscular hemoglobin
					Red blood cell count
					Fat-free mass
			92250140	rs42044	Monocyte percentage of white cells
			92248076	rs42235	Heel bone mineral density
					Height
					Hip circumference adjusted for BMI
			92243672	rs42377	Heel bone mineral density
					Systolic blood pressure
			92236829	rs4272	Eosinophil counts
					Granulocyte percentage of myeloid white cells
					Rheumatoid arthritis
			92251072	rs527582137	Body fat distribution
			92230162	rs760847	Cardiovascular disease
			92236164	rs8179	Eosinophil counts
					Granulocyte count
					Myeloid white cell count
					Neutrophil count
					Sum basophil neutrophil counts
					Sum neutrophil eosinophil counts
					White blood cell count
7	116198821	7	116191301	rs11773845	PR interval
			116180375	rs13242816	P wave duration
			116198521	rs1997571	Heart rate response
			116169961	rs2109514	Heart rate increase
					Heart rate response
			116190597	rs3801995	P wave duration
			116186241	rs3807989	Electrocardiographic traits
					PR interval
					PR segment
					QRS duration
					High light scatter reticulocyte
			116200992	rs9920	Immature fraction of reticulocytes
					QT interval
					Reticulocyte
7	150669976	7	150652291	rs12668582	QT interval
			150645534	rs1805123	Body mass index
			150647998	rs2072413	QT interval
			150658678	rs35760656	Electrocardiographic traits
			150667319	rs3807375	QT interval
					Cardiovascular disease
			150690176	rs3918226	Coronary artery disease
					Diastolic blood pressure
					Eczema
					Systolic blood pressure
			150657095	rs56282717	Body fat distribution
			150684346	rs6946091	Fat-free mass
8	11784541	8	11776994	rs10430719	C-reactive protein levels or triglyceride levels
			11795586	rs13018930	LDL cholesterol
8	21805265	8	21791772	rs58141407	Mean corpuscular hemoglobin
					Mean corpuscular volume
					Red blood cell count
			21820813	rs7843479	Mean corpuscular volume
8	124610166	8	124610312	rs2385450	Heel bone mineral density
			124610168	rs3884541	Breast cancer
			124643201	rs6529013	Intraocular pressure
			124615571	rs6529014	Intraocular pressure
			124610526	rs6479159	Heel bone mineral density
			141886828	rs1008782	Diastolic blood pressure
8	141746868	8	141656159	rs11166980	Smoking status
			141760117	rs13266066	Smoking initiation
9	97713459	9	97679773	rs10993397	Polycystic ovary syndrome
			97723765	rs7864171	Polycystic ovary syndrome
9	139094773	9	139102831	rs10858246	Lung function (FVC)
			139108324	rs10858248	Blood protein levels
			139119218	rs10858250	Height
			139097358	rs11103379	Red cell distribution width
			139121746	rs12338076	Height
			139094171	rs12378344	Blood protein levels
			139110664	rs12868450	Lung function (FVC)
			139106567	rs398073595	Blood protein levels
			139100413	rs7024579	Lung function (FEV1)
					Lung function (FVC)
			139111870	rs7849585	Height
			139096979	rs7860634	Red blood cell count
					Thyroid hormone levels
10	65321147	10	65308750	rs10761784	Factor VII activity
			65318766	rs10761785	Red blood cell count
			65321753	rs10822184	Androgen levels
			65314731	rs2163188	Body mass index
			65224459	rs55739257	Basophil percentage of granulocytes
			65280595	rs5785580	Triglyceride
			65333648	rs647908	Diastolic blood pressure
			65336185	rs7077356	Intelligence
			65301725	rs7897379	Blood protein levels
					Triglyceride
			65191645	rs7924036	Body mass index
					Educational attainment
					Intelligence
			69855363	rs10823136	Pulse pressure
			69823273	rs17127055	Chronotype
10	75414344	10	75476599	rs11090792	Pulse pressure
					Systolic blood pressure
			75410652	rs12247028	Systolic blood pressure
			75421648	rs7394190	Systolic blood pressure
10	77336670	10	77337516	rs10824380	Red blood cell count
10	105316796	10	105309001	rs7284971	Intraocular pressure
			105319409	rs7284980	White matter hyperintensity burden
11	20010291	11	20013279	rs1372797	PR interval
			121635463	rs1944688	Smoking status
11	121654327	11	121634334	rs1944689	Smoking initiation
			121671498	rs6579951	Heel bone mineral density
11	128764570	11	128764571	rs7130942	Resting heart rate
12	24771967	12	24771967	rs10847383	Heart rate variability traits
			24788339	rs11047543	PR interval
			24776752	rs137913153	PR interval
			24775549	rs144974314	Heart rate response to exercise
					PR interval
			24770878	rs17287293	Heart rate
					PR interval
					Pulse pressure
					Resting heart rate
			24760456	rs34219605	Pulse pressure
			24784139	rs4246224	Heart rate response to exercise
					Heart rate increase
			24758480	rs4963772	Heart rate response
					Heart rate variability traits
					Resting heart rate
12	26348429	12	26339986	rs11048425	White blood cell count
12	57115136	12	57115136	rs10492457	Heel bone mineral density
			57114100	rs2926743	QRS duration
			57105293	rs2950390	Mean platelet volume
			57036023	rs2955393	Platelet distribution width
			57098046	rs7137749	Diastolic blood pressure
			57073284	rs941297	Platelet count
12	70013415	12	69997422	rs6929307	Systolic blood pressure
12	76238855	12	76243675	rs11220172	Non-glioblastoma glioma
			76263551	rs1279500	Non-glioblastoma glioma
			76220618	rs7307780	Sudden cardiac arrest
12	114793240	12	114855558	rs148020424	P wave duration
			114807039	rs1895582	P wave duration
			114802138	rs1895585	PR interval
			114795449	rs3825214	Electrocardiographic traits
					QRS duration
			114796974	rs7313679	P wave duration
					PR interval
			114793240	rs883079	QRS duration

12	123312051	12	123303586	rs11060180	Parkinson's disease
			123329101	rs11060344	Waist-hip ratio
			123296294	rs12817458	Parkinson's disease
			123329326	rs897392	Red cell distribution width
12	124812678	12	124826676	rs12314162	Fat-free mass
			124809706	rs1371309	Diastolic blood pressure
					Male-pattern baldness
			124801926	rs1809889	Height
					Hip circumference adjusted for BMI
			124826462	rs2229840	Balding type 1
			124812678	rs3741508	Lung function (FVC)
			124799642	rs4765540	Osteoarthritis (hip)
			123286888	rs11726541	Systolic blood pressure
12	130091614	12	133066894	rs12423664	Coronary artery disease and triglyceride levels
			133112395	rs34390795	Red blood cell count
			133104735	rs4883565	Red blood cell count
			133076439	rs61952071	Mean corpuscular hemoglobin
			133087959	rs7295014	Prostate cancer
13	113864837	13	113860301	rs35709060	Blood protein levels
			113839015	rs653316	Blood protein levels
			113845059	rs56990	Blood protein levels
			113895080	rs56129102	Mean corpuscular hemoglobin
					Red cell distribution width
			113853035	rs61966459	Mean corpuscular hemoglobin
					Mean corpuscular volume
			113860121	rs9549357	Blood protein levels
					Platelet distribution width
			113860900	rs9577481	Blood protein levels
14	23864804	14	23842661	rs11465506	PR interval
			23861811	rs365990	Diastolic blood pressure
					Electrocardiographic traits
					Heart rate
					Pulse pressure
					Resting heart rate
			23864804	rs422068	Resting heart rate
			23870752	rs432255	RR interval
			23863892	rs445754	P wave terminal force
					P wave duration
			23865885	rs452836	Pulse pressure
					Resting heart rate
14	35173775	14	35154381	rs12435790	Waist-hip ratio
14	64679960	14	64697037	rs1152579	Depression
			64674981	rs1152595	Educational attainment
			64703593	rs1256061	Hematocrit
					Hemoglobin concentration
					Red blood cell count
			64693912	rs5826369	Prostate cancer
			64688207	rs915057	Depression
15	73667255	15	73653485	rs2680344	Heart rate variability traits
			73665506	rs4489968	Heart rate
			73663902	rs7172389	Resting heart rate
15	80575225	15	80575244	rs7185355	Energy expenditure
			80672933	rs8042361	Red blood cell count
15	99268850	15	99240929	rs11854016	Glomerular filtration rate
			99258710	rs2018860	Fasting plasma glucose
			99260878	rs2860702	Blood urea nitrogen levels
			99248041	rs4965476	Platelet count
					Plateletcrit
			99264680	rs4966090	Global electrical heterogeneity phenotypes
					QRS duration
			99289607	rs50350108	Serum uric acid levels
			99271135	rs6598541	Urate levels
			99288741	rs7276592	Menarche (age at onset)
16	764753	16	746611	rs11861214	Smoking status
			740682	rs11865690	Educational attainment
			747454	rs12922098	Highest math class taken
			740404	rs4984682	Educational attainment
			749057	rs4984816	Smoking status
16	73048367	16	73059888	rs12922445	Ischemic stroke (cardioembolic)
			73024276	rs1858890	Hypospadias
			73070083	rs4788044	Body mass index
			73029160	rs7193343	Ischemic stroke (cardioembolic)
			73048678	rs879324	Stroke (ischemic)
17	1312046	17	1333598	rs12941318	Systolic blood pressure
			1290592	rs56007784	Schizophrenia
			1321116	rs8068017	Granulocyte count
					Neutrophil count
					Sum basophil neutrophil counts
			1331537	rs8070290	Lymphocyte percentage of white cells
			1406134	rs11658168	Heel bone mineral density
17	7414958	17	7429312	rs11658305	Myopia
			7372637	rs12942067	Diverticular disease
			7391624	rs4354991	Mean corpuscular hemoglobin
			7434819	rs8075280	Spherical equivalent or myopia (age of diagnosis)
			7417640	rs8703	Non-glioblastoma glioma
17	17618689	17	12637742	rs1984481	PR interval
			12635871	rs35713672	PR interval
17	38049589	17	38064605	rs11078927	Asthma
			38024169	rs11655198	Asthma
			38053207	rs12453507	Type 1 diabetes
			38043649	rs12930409	Rheumatoid arthritis
			38032188	rs12939457	Allergic rhinitis
					Crohn's disease
			37912377	rs12946510	Inflammatory bowel disease
					Multiple sclerosis
					Ulcerative colitis
			38008768	rs202126107	Eosinophil percentage of white cells
			38053889	rs2123685	Subcutaneous adipose tissue
					Acute lymphoblastic leukemia (childhood)
			38066240	rs2290400	Bronchial hyperresponsiveness in asthma
					Type 1 diabetes
			38062217	rs2305479	Asthma
			38062196	rs2305480	Asthma
					Rheumatoid arthritis
					Ulcerative colitis
					Crohn's disease
			38040763	rs2872507	Rheumatoid arthritis
					Ulcerative colitis
			37910368	rs2941522	Asthma
			38004930	rs34233420	Lymphocyte counts
			38032680	rs3732772	Chronic inflammatory diseases
			37962987	rs4795395	Primary biliary cholangitis
			38073745	rs4795397	Asthma
					Inflammatory bowel disease
			38067020	rs4795400	Allergy
			38031857	rs59716545	Rheumatoid arthritis
			38059949	rs7215389	Asthma
			38072402	rs8061777	Educational attainment
			38051348	rs8067378	Cervical cancer
					Primary biliary cirrhosis
			38057197	rs806976	Asthma
					Fractional exhaled nitric oxide (childhood)
			38068043	rs869402	Asthma
					Asthma or allergic disease
			37922259	rs907092	Asthma
			38069076	rs921450	Allergic disease (asthma-hay fever or eczema)
					Monocyte percentage of white cells
			37976469	rs9303077	Lymphocyte counts
					Primary biliary cholangitis
			38073968	rs9303279	Respiratory diseases
			38074031	rs9303280	Self-reported allergy
			38048244	rs9305951	Highest math class taken
17	44019712	17	44006601	rs17564829	Primary biliary cirrhosis
			44037491	rs17650842	Irritable mood
			44019717	rs2472557	Plasma t-tau levels
					Progressive supranuclear palsy
			44025888	rs242559	General cognitive ability
			44026739	rs7247562	QRS complex
					Reaction time
			44041107	rs56280951	Feeling miserable
			44018799	rs62061733	Eosinophil counts
					Feeling hurt
			44018488	rs62061734	Breast cancer
			44019785	rs7247564	Number of sexual partners
			44004994	rs7247565	Osteoarthritis (hip)
			44013475	rs79857651	Experiencing mood swings
			44002271	rs9904296	Depressed affect
17	45138033	17	44002271	rs17608766	Aortic root size
					Blood pressure
					Cardiovascular disease
					Coronary artery disease
					Pulse pressure
			44957530	rs79296666	QRS complex
					QRS duration
					Systolic blood pressure
					Pulse pressure
					Systolic blood pressure
			45055107	rs80335285	Pulse pressure
17	68421803	17	68446861	rs11654387	Waist-hip ratio
			68430993	rs11398115	QT interval
			68421803	rs1398517	Hip circumference adjusted for BMI
			68453345	rs8066985	Waist-hip ratio
			68453345	rs884577	Waist-hip ratio
18	46474192	18	46472621	rs12956326	Heel bone mineral density
			46451146	rs12956824	Eczema
			46474178	rs12967019	Heel bone mineral density
					Creatinine levels
					Glomerular filtration rate
			46440903	rs2337106	Heel bone mineral density
					Hematocrit
					Red blood cell count
					Glomerular filtration rate
			46463136	rs2878889	Hemoglobin concentration
			46451873	rs4939367	Colorectal cancer
			46451940	rs4939877	Colorectal cancer
					Mean corpuscular hemoglobin
			46446650	rs57633475	Eosinophil counts
			46454048	rs7226855	Colorectal cancer
			46459976	rs7229539	Colorectal cancer
			46465540	rs9952412	Heel bone mineral density
20	61154393	20	61178527	rs11371531	Macular thickness
			61179260	rs35572127	Systolic blood pressure
21	36119111	21	36107348	rs2834613	Adolescent idiopathic scoliosis
22	26164078	22	26192899	rs133885	Mathematical ability in children with dyslexia

AF, atrial fibrillation; CHR chromosome; POS, position (hg19); rsID, reference SNP cluster ID

Supplementary Table 10 | Pleiotropic effects of AF-associated loci with clinical measurements

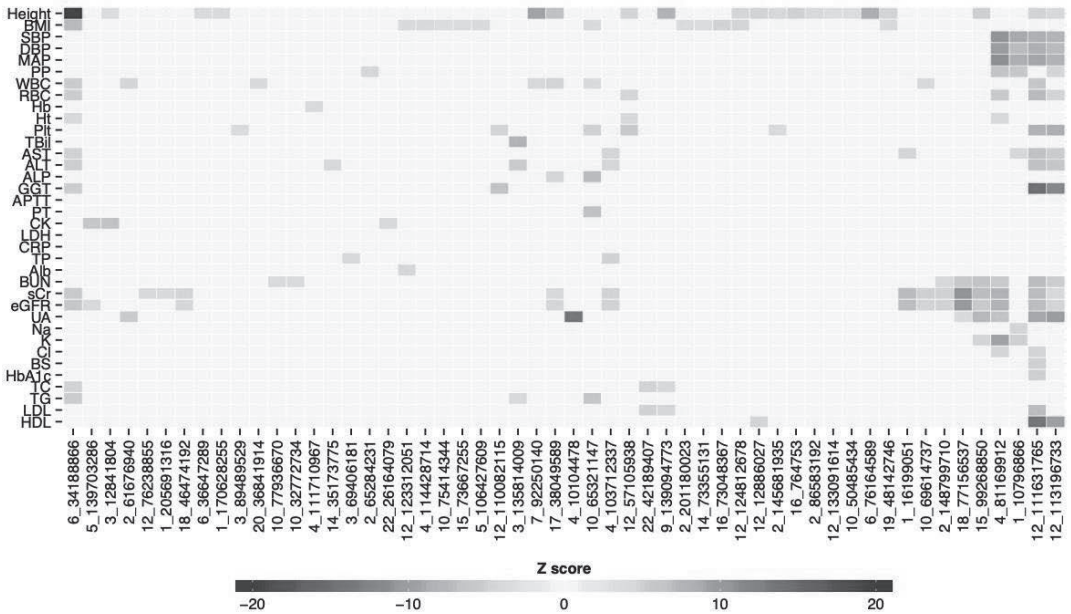
Lead variant		Variant associated with quantitative trait				AF				Phenotype	Quantitative trait			
CHR	POS	CHR	POS	rsID	RA	OA	RAF	Beta	SE	P		Beta	SE	P
1	10796868	1	10796547	rs71555646	A	G	0.401	0.048	0.006	8.3E-16	AST	-0.017	0.004	1.6E-05
1	10796868	1	10796547	rs71555646	A	G	0.401	0.046	0.006	8.3E-16	K	-0.021	0.004	5.0E-07
1	10796868	1	10796547	rs71555646	A	G	0.401	0.049	0.006	8.3E-16	Na	0.019	0.004	8.0E-06
1	10796868	1	10796868	rs880315	C	T	0.406	0.050	0.006	3.8E-16	DBP	0.028	0.004	3.5E-12
1	10796868	1	10796868	rs880315	C	T	0.406	0.050	0.006	3.8E-16	MAP	0.034	0.004	1.6E-16
1	10796868	1	10796868	rs880315	C	T	0.406	0.050	0.006	3.8E-16	PP	0.024	0.004	5.3E-09
1	10796868	1	10796868	rs880315	C	T	0.406	0.050	0.006	3.8E-16	SBP	0.031	0.004	7.1E-18
1	16199051	1	16335233	rs173881	G	A	0.176	0.039	0.008	3.4E-06	AST	-0.021	0.005	6.4E-06
1	16199051	1	16316119	rs848302	T	A	0.233	0.026	0.007	2.1E-04	eGFR	-0.029	0.004	1.3E-12
1	16199051	1	16316119	rs848302	T	A	0.233	0.026	0.007	2.1E-04	eCr	0.027	0.004	1.6E-11
1	17628258	1	17063142	rs827848	G	A	0.695	0.100	0.006	5.9.E-56	Height	-0.012	0.003	5.1.E-05
2	20981318	1	20564317	rs1772137	C	T	0.340	0.003	0.006	6.3.E-01	eCr	-0.014	0.004	1.8.E-04
2	61676940	2	61451744	rs7570707	C	T	0.511	0.022	0.006	1.7.E-04	UA	-0.014	0.004	2.7.E-08
2	61676940	2	61681428	rs778142	T	G	0.625	0.032	0.006	1.1.E-07	WBC	-0.021	0.005	5.1.E-06
2	65284231	2	65283972	rs74181209	T	C	0.612	0.017	0.006	1.2.E-24	PP	0.017	0.004	2.1.E-05
2	85581100	2	86640565	rs61591648	T	A	0.525	0.023	0.013	8.1.E-01	Height	0.018	0.005	3.6.E-05
2	145681916	2	145721524	rs13010313	T	C	0.265	0.049	0.009	7.3.E-08	Height	0.016	0.004	7.4.E-06
2	145681935	2	145782808	rs56014512	T	G	0.284	0.053	0.010	2.3.E-08	Plt	-0.018	0.005	9.6.E-05
2	148799735	2	148663568	rs12987286	T	G	0.326	0.030	0.006	1.3.E-06	eGFR	-0.018	0.004	1.8.E-06
2	148799759	2	148663568	rs12987286	T	G	0.326	0.030	0.006	1.9.E-06	eCr	0.019	0.004	6.2.E-07
2	148799759	2	148679813	rs4972328	C	A	0.438	0.031	0.006	1.2.E-07	BUN	0.015	0.004	2.6.E-05
2	201180023	2	200194279	rs7736119	A	C	0.582	0.060	0.006	1.7.E-23	BMI	-0.015	0.004	2.3.E-04
3	12841804	3	12840934	rs6810025	C	T	0.600	0.075	0.006	8.5.E-35	CK	-0.029	0.005	8.3.E-11
3	12841804	3	12855858	rs2355398	A	G	0.561	0.056	0.006	1.6.E-20	Height	-0.012	0.003	2.4.E-04
3	69406181	3	69399804	rs9310149	A	G	0.446	0.028	0.008	2.1.E-04	TP	-0.020	0.005	4.8.E-05
3	89489528	3	89530571	rs7550184	C	A	0.607	0.045	0.006	1.0.E-13	Plt	-0.024	0.007	2.1.E-04
3	135814069	3	135328622	rs445040	T	G	0.775	0.032	0.007	1.6.E-06	ALT	-0.027	0.005	3.7.E-08
3	135814069	3	135979998	rs486992	G	A	0.546	0.030	0.006	4.9.E-07	TG	0.020	0.005	7.9.E-05
3	135814069	3	136029975	rs17111170	C	A	0.617	0.028	0.006	1.0.E-05	TBil	-0.046	0.006	3.0.E-16
4	10024478	4	10197799	rs139834835	G	A	0.647	0.024	0.006	1.8.E-08	UA	-0.060	0.004	7.6.E-45
4	81169912	4	81167309	rs31089089	T	C	0.314	0.049	0.006	4.3.E-15	Hb	0.019	0.005	4.2.E-05
4	81169912	4	81174092	rs13125101	A	G	0.317	0.049	0.006	5.9.E-15	Cl	-0.019	0.004	5.3.E-06
4	81169912	4	81181072	rs10857147	T	A	0.305	0.046	0.006	7.8.E-13	DBP	0.043	0.004	2.1.E-22
4	81169912	4	81181072	rs10857147	T	A	0.305	0.046	0.006	7.8.E-13	MAP	0.049	0.004	1.8.E-27
4	81169912	4	81181072	rs10857147	T	A	0.305	0.046	0.006	7.8.E-13	PP	0.027	0.004	7.3.E-10
4	81169912	4	81181072	rs10857147	T	A	0.305	0.046	0.006	7.8.E-13	SBP	0.047	0.004	1.4.E-25
4	81169912	4	81181072	rs10857147	T	A	0.305	0.046	0.006	7.8.E-13	UA	-0.031	0.005	2.7.E-10
4	81169912	4	81181072	rs10857147	T	A	0.305	0.046	0.006	7.8.E-13	eCr	-0.035	0.004	1.5.E-16
4	81169912	4	81182504	rs12509595	C	T	0.306	0.047	0.006	6.0.E-14	BUN	-0.022	0.004	1.6.E-08
4	81169912	4	81182554	rs12509596	C	T	0.306	0.047	0.006	6.0.E-14	K	-0.041	0.004	1.2.E-21
4	81169912	4	81182554	rs12509596	C	T	0.306	0.047	0.006	6.0.E-14	RBC	0.027	0.005	1.8.E-08
4	81169912	4	81182554	rs12509596	C	T	0.306	0.047	0.006	6.0.E-14	eGFR	0.032	0.004	1.6.E-14
4	103712197	4	103679117	rs223490	T	G	0.374	0.037	0.006	5.9.E-10	TP	-0.021	0.004	1.5.E-06
4	103712197	4	103698786	rs223471	C	G	0.335	0.035	0.006	8.2.E-09	AST	-0.018	0.004	6.6.E-06
4	103712197	4	103698786	rs223471	C	G	0.335	0.035	0.006	8.2.E-09	eGFR	0.019	0.004	2.0.E-06
4	103712197	4	103698786	rs223471	C	G	0.335	0.035	0.006	8.2.E-09	eCr	-0.018	0.004	2.2.E-06
4	103712197	4	103712197	rs223451	A	G	0.481	0.038	0.007	1.0.E-07	ALT	-0.017	0.004	1.1.E-05
4	111710987	4	111682814	rs79687649	G	T	0.202	0.432	0.009	3.81e-463	Hb	0.019	0.005	6.4.E-05
4	114428114	4	114456506	rs35132791	G	C	0.255	0.052	0.007	7.1.E-14	BMI	0.035	0.006	2.8.E-09
5	139427409	5	139441453	rs28988604	C	T	0.038	0.032	0.006	4.1.E-08	BMI	0.033	0.004	9.5.E-15
5	139703288	5	139688365	rs72798894	A	G	0.240	0.041	0.007	2.2.E-09	eGFR	-0.016	0.004	3.1.E-05
5	139703288	5	139716988	rs2237078	C	G	0.274	0.036	0.007	5.2.E-08	CK	-0.027	0.005	2.8.E-09
6	34188866	6	34178058	rs10807136	G	A	0.141	0.030	0.009	5.3.E-04	ALT	-0.023	0.005	2.6.E-07
6	34188866	6	34179390	rs69113361	A	G	0.141	0.030	0.009	4.9.E-04	AST	-0.027	0.006	9.4.E-07
6	34188866	6	34179390	rs69113361	A	G	0.141	0.030	0.009	4.9.E-04	BMI	0.037	0.003	1.7.E-12
6	34188866	6	34183778	rs13017288	G	A	0.064	0.053	0.015	4.5.E-04	Hb	-0.036	0.007	5.1.E-08
6	34188866	6	34188467	rs9469745	G	A	0.115	0.063	0.010	2.7.E-10	GGT	-0.032	0.006	1.3.E-07
6	34188866	6	34190505	rs148811083	T	C	0.066	0.052	0.015	7.2.E-04	PBC	-0.035	0.007	3.4.E-07
6	34188866	6	34190505	rs148810613	T	C	0.066	0.052	0.015	7.2.E-04	WBC	-0.036	0.007	8.9.E-08
6	34188866	6	34197105	rs1759627	G	T	0.172	0.041	0.008	2.7.E-07	Ht	-0.024	0.006	7.3.E-05
6	34188866	6	34197188	rs1759623	C	T	0.091	0.038	0.013	3.8.E-03	Height	0.010	0.005	3.1.E-03
6	34188866	6	34223230	rs9348938	T	C	0.121	0.033	0.013	1.2.E-02	eGFR	-0.027	0.005	7.8.E-09
6	34188866	6	34236990	rs186766328	A	G	0.074	0.072	0.017	2.0.E-05	TC	-0.037	0.008	2.1.E-06
6	34188866	6	34236990	rs60952447	A	G	0.077	0.066	0.015	1.5.E-04	eCr	-0.033	0.008	3.6.E-08
6	36647289	6	36649968	rs730590	G	C	0.812	0.076	0.008	6.5.E-20	Height	-0.020	0.005	3.0.E-04
6	76164589	6	76154389	rs12209223	A	C	0.116	0.067	0.009	3.8.E-13	Height	0.018	0.005	7.4.E-17
6	92250140	6	92238014	rs9372439	G	A	0.750	0.029	0.007	2.2.E-01	WBC	-0.028	0.007	2.2.E-05
7	92250140	7	92247333	rs42043	A	G	0.769	0.032	0.007	3.0.E-06	Height	-0.047	0.005	9.8.E-21
9	139094773	9	139094773	rs2274115	G	A	0.670	0.043	0.007	5.7.E-11	Height	0.025	0.003	1.8.E-14
9	139094773	9	139099073	rs3780198	A	G	0.518	0.035	0.006	3.3.E-10	TC	-0.016	0.004	4.5.E-05
9	139094773	9	139108324	rs10858249	G	A	0.485	0.032	0.006	3.9.E-08	LDL-C	-0.023	0.005	1.3.E-05
10	32772738	10	32849404	rs10827078	G	A	0.413	0.029	0.008	2.6.E-04	BUN	-0.015	0.004	1.1.E-04
10	50485429	10	50503365	rs61610103	T	G	0.959	0.104	0.014	4.8.E-13	Height	0.021	0.006	1.8.E-04
10	65321147	10	65191645	rs7924628	T	G	0.539	0.048	0.006	2.5.E-16	TG	-0.028	0.005	1.3.E-09
10	65321147	10	65270672	rs7883823	C	G	0.781	0.049	0.007	1.6.E-11	ALP	0.033	0.005	9.1.E-12
10	65321147	10	65314971	rs7393984	C	T	0.546	0.049	0.006	1.6.E-16	Plt	0.023	0.005	5.1.E-07
10	65321147	10	65323997	rs4748203	G	T	0.549	0.051	0.006	6.6.E-16	PT	0.040	0.006	3.5.E-10
10	65321147	10	65331511	rs10947325	G	T	0.553	0.049	0.006	1.1.E-16	BMI	-0.010	0.004	7.5.E-05
10	65321147	10	65331511	rs3847321	G	C	0.553	0.049	0.006	1.1.E-16	WBC	-0.018	0.005	6.8.E-05
10	69614737	10	69644335	rs3740053	G	A	0.172	0.073	0.009	5.8.E-15	WBC	-0.018	0.005	1.1.E-04
10	69614737	10	69733175	rs4746722	G	T	0.220	0.073	0.008	1.4.E-19	eGFR	-0.018	0.004	4.1.E-06
10	69614737	10	69850466	rs9381450	T	G	0.222	0.072	0.009	2.5.E-15	eCr	0.018	0.004	4.1.E-07
10	75413444	10	75583034	rs59693993	C	T	0.857	0.055	0.008	1.9.E-10	BMI	0.017	0.005	4.7.E-04
10	77639676	10	77738995	rs7894093	A	G	0.313	0.030	0.007	1.7.E-09	BUN	-0.018	0.003	2.2.E-05
12	12886927	12	12886927	rs10845620	A	G	0.129	0.056	0.009	4.7.E-08	HDL-C	0.042	0.009	5.5.E-06
12	12886927	12	12886927	rs10845620	A	G	0.129	0.050	0.009	4.7.E-08	Height	0.026	0.005	2.6.E-07
12	57109538	12	56988342	rs4768	G	A	0.366	0.044	0.006	2.2.E-13	Height	0.015	0.003	3.5.E-06
12	57109538	12	57044670	rs10876913	A	G	0.325	0.046	0.006	5.9.E-14	Plt	0.025	0.004	1.5.E-08
12	57109538	12	57184005	rs7139025	T	C	0.255	0.036	0.009	3.7.E-05	Plt	-0.023	0.005	2.3.E-05
12	57109538	12	57184005	rs7139025	T	C	0.255	0.036	0.009	3.7.E-05	RBC	-0.025	0.005	6.1.E-06
12	76238855	12	76227612	rs2332299	G	C	0.555	0.039	0.006	4.6.E-11	eCr	-0.017	0.005	1.7.E-04
12	110082115	12	110082115	rs1344543	T	C	0.486	0.024	0.006	3.9.E-05	Plt	-0.019	0.004	5.5.E-06
12	110082115	12	110082115	rs1344543	T	C	0.486	0.024	0.006	3.6.E-05	GGT	0.025	0.004	6.5.E-10
12	111631765	12	111631765	rs4766552	G	A	0.774	0.054	0.010	3.3.E-08	BS	0.024	0.005	7.5.E-07
12	111631765	12	111631765	rs4766552	G	A	0.774	0.054	0.010	3.3.E-08	BUN	-0.027	0.004	1.1.E-12
12	111631765	12	111631765	rs4766552	G	A	0.774	0.054	0.010	3.3.E-08	DBP	0.033	0.004	2.8.E-16
12	111631765	12	111631765	rs4766552	G	A	0.774	0.054	0.010	3.3.E-08	LDL-C	0.039	0.006	2.5.E-12
12	111631765	12	111631765	rs4766552	G	A	0.774	0.054	0.010	3.3.E-08	MAP	0.036	0.004	7.5.E-19
12	111631765	12	111631765	rs4766552	G	A	0.774	0.054	0.010	3.3.E-08	SBP	0.033	0.004	4.1.E-16
12	111631765	12	111631765	rs4766552	G	A	0.774	0.054	0.010	3.3.E-08	WBC	-0.027	0.004	3.3.E-09
12	111631765	12	111631765	rs4766552	G	A	0.774	0.054	0.010	3.3.E-08	eGFR	-0.026	0.004	3.5.E-11
12	111631768	12	111631765	rs4766552	G	A	0.774	0.054	0.010	3.3.E-08	eCr	-0.028	0.004	8.1.E-13
12	111631768	12	111634281	rs4766553	T	G	0.753	0.027	0.008	1.1.E-04	Plt	-0.035	0.004	1.6.E-16
12	111631768	12	111671076	rs1060836	G	A	0.781	0.066	0.010	4.3.E-11	ALT	-0.025	0.004	2.2.E-10
12	111631768	12	111671076	rs11060838	G	A	0.781	0.066	0.010	4.3.E-11	AST	0.025	0.004	2.8.E-10
12	111631768	12	111671076	rs11060839	G	A	0.781	0.066	0.010	4.3.E-11	Cl	-0.019	0.004	4.1.E-06
12	111631768	12	111671076	rs11060840	G	A	0.781	0.066	0.010	4.3.E-11	GGT	0.060	0.004	1.3.E-45
12	111631768	12	111671076	rs11060839	G	A	0.781	0.066	0.010	4.3.E-11	HDL-C	0.073	0.005	1.4.E-41
12	111631768	12	111671076	rs11060836	G	A	0.781	0.066	0.010	4.3.E-11	HbA1c	-0.016	0.004	4.8.E-07
12	111631768	12	111671076	rs11060839	G	A	0.781	0.066	0.010	4.3.E-11	Height	0.015	0.003	1.7.E-06
12	111631768	12	111671076	rs11060839	G	A	0.781	0.066	0.010	4.3.E-11	RBC	-0.032	0.004	2.1.E-13
12	111631768	12	111671076	rs11060836	G	A	0.781	0.066	0.010	4.3.E-11	UA	0.038	0.004	1.9.E-18
12	111796733	12	111647107	rs10660883	C	A	0.674	0.027	0.007	5.5.E-05	Height	0.015	0.004	1.5.E-04
12	111796733	12	111796733	rs11614295	G	A	0.678	0.026	0.007	5.5.E-05	ALT	0.022	0.004	5.0.E-09
12	111796733	12	111796733	rs11614295	G	A	0.678	0.026	0.007	5.5.E-05	AST	0.020	0.004	7.5.E-08
12	111796733	12	111796733	rs11614295	G	A	0.678	0.026	0.007	5.5.E-05	BUN	-0.018	0.004	2.9.E-07
12	111796733	12	111796733	rs11614295	G	A	0.678	0.026	0.007	5.5.E-05	DBP	0.027	0.004	3.7.E-12
12	111796733	12	111796733	rs11614295	G	A	0.678	0.026	0.007	5.5.E-05	GGT	0.048	0.004	3.1.E-31
12	111796733	12	111796733	rs11614295	G	A	0.678	0.026	0.007	5.5.E-05	HDL-C	0.033	0.005	2.8.E-21
12	111796733	12	111796733	rs11614295	G	A	0.678	0.026	0.007	5.5.E-05	MAP	0.030	0.004	7.0.E-15
12	111796733	12	111796733	rs11614295	G	A	0.678	0.026	0.007	5.5.E-05	PP	0.017	0.004	6.1.E-06
12	111796733	12	111796733	rs11614295	G	A	0.678	0.026	0.007	5.5.E-05	Plt	-0.036	0.004	2.2.E-17
12	111796733	12	111796733	rs11614295	G	A	0.678	0.026	0.007	5.5.E-05	RBC	-0.020	0.004	4.0.E-06
12	111796733	12	111796733	rs11614295	G	A	0.678	0.026	0.007	5.5.E-05	SBP	0.029	0.004	3.1.E-14
12	111796733	12	111796733	rs11614299	G	A	0.678	0.026	0.007	5.5.E-05	UA	0.041	0.004	4.3.E-22
12	111796733	12	111796733	rs11614295	G	A	0.678	0.026	0.007	5.5.E-05	eGFR	0.017	0.004	6.9.E-06
12	111796733	12	111796733	rs11614295	G	A	0.678	0.026	0.007	5.5.E-05	eCr	-0.015	0.004	1.2.E-05
12	123312031	12	123307754	rs7854383	C	T	0.159	0.051	0.009	2.0.E-09	Alb	0.024	0.006	1.4.E-05
12	123312043	12	123389544	rs11060209	G	A	0.116	0.039	0.012	1.8.E-03	BMI	0.016	0.004	1.7.E-04
12	124812678	12	124812678	rs10846923	G	A	0.268	0.029	0.007	1.6.E-05	Height	0.015	0.003	2.5.E-06
12	124812678	12	124721858	rs2272348	G	A	0.197	0.044	0.008	1.1.E-08	BMI	-0.017	0.004	4.1.E-06
12	133016614	12	133116997	rs11146920	T	G	0.412	0.029	0.006	2.7.E-06	Height	0.015	0.005	4.4.E-04
14	35177175	14	35180541	rs8005490	T	C	0.390	0.048	0.006	1.7.E-15	ALT	-0.020	0.005	5.1.E-05
14	73263133	14	73361939	rs3824863	G	C	0.606	0.047	0.006	9.3.E-15	BMI	-0.013	0.004	4.8.E-04
15	73667255	15	73667255	rs7172038	G	T	0.161	0.107	0.008	2.7.E-39	BMI	0.042	0.011	1.9.E-04
15	89268850	15	89267568	rs4883439	G	T	0.418	0.041	0.006	3.6.E-12	K	0.018	0.004	6.8.E-06
15	89268850	15	89269147	rs4886431	G	A	0.432	0.038	0.006	1.4.E-10	eGFR	-0.023	0.004	1.7.E-08
15	89268850	15	89271135	rs6598541	A	G	0.389	0.043	0.006	3.9.E-13	BUN	0.022	0.004	1.0.E-09
15	89268850	15	89271135	rs6598541	A	G	0.389	0.043	0.006	3.9.E-13	Height	0.016	0.003	4.4.E-07
15	89268850	15	89294355	rs12898337	T	C	0.387	0.040	0.006	3.8.E-11	eCr	0.025	0.004	1.9.E-11
15	89268850	15	89295370	rs4886227	A	G	0.390	0.040	0.006	4.4.E-11	UA	-0.031	0.004	2.1.E-13
16	764753	16	764826	rs62032512	T	C	0.299	0.032	0.007	5.4.E-06	Height	0.016	0.003	2.0.E-07
16	73048367	16	73048367	rs67329386	T	C	0.221	0.185	0.007	1.2.E-146	BMI	-0.018	0.004	2.8.E-06
17	38049589	17	37903730	rs2941529	T	C	0.332	0.049	0.007	2.6.E-13	Height	-0.021	0.003	2.2.E-12
17	38049589	17	37903730	rs2941529	T	C	0.332	0.049	0.007	2.6.E-13	eGFR	0.018	0.004	1.1.E-05
17	38049589	17	37903730	rs2941526	T	C	0.332	0.049	0.007	2.6.E-13	eCr	-0.016	0.004	3.8.E-05
17	38049589	17	38043649	rs2293409	T	C	0.545	0.027	0.006	2.5.E-06	WBC	-0.023	0.005	2.4.E-06
17	38049589	17	38066509	rs7213668	A	G	0.289	0.042	0.007	2.3.E-09	ALP	0.021	0.005	7.3.E-06
18	46474192	18	46474192	rs9953366	C	T	0.623	0.043	0.006	1.1.E-12	eGFR	0.016	0.004	1.1.E-05
18	46474192	18	46474192	rs9953366	C	T	0.623	0.044	0.006	1.2.E-12	eCr	-0.017	0.004	1.4.E-06
18	77156537	18	77156537	rs8096658	G	C	0.458	0.037	0.006	2.8.E-09	UA	0.020	0.005	1.1.E-04
18	77156537	18	77158225	rs549752	A	G	0.843	0.031	0.007	2.7.E-06	BUN	0.023	0.004	5.6.E-09
18	77156537	18	77158225	rs549752	A	G	0.843	0.031	0.007	2.7.E-06	eGFR	-0.042	0.004	9.0.E-25
18	77156537	18	77158225	rs549752	A	G	0.843	0.031	0.007	2.7.E-06	eCr	0.042	0.004	1.4.E-25
19	48142746	19	48118943	rs66531872	G	C	0.867	0.043	0.009	1.2.E-06	Height	0.021	0.005	1.1.E-05
19	48142746	19	48138190	rs8108219	C	G	0.660	0.033	0.006	2.8.E-09	BMI	0.018	0.005	8.1.E-05
20	36841914	20	36830133	rs6068153	G	A	0.496	0.033	0.006	1.6.E-08	WBC	-0.017	0.004	9.3.E-05
22	26164019	22	26156431	rs133872	G	C	0.459	0.036	0.006	2.3.E-09	CK	0.026	0.006	1.5.E-05
22	42189407	22	42265510	rs3751187	A	G	0.810	0.026	0.009	8.5.E-01	LDL-C	-0.025	0.005	1.0.E-06
22	42189407	22	42268040	rs3751188	A	G	0.808	0.001	0.009	8.9.E-01	TG	-0.019	0.004	2.7.E-06

CHR, chromosome; POS, position (hg19); rsID, dbSNP ID; RA, risk allele; OA, other allele; SE, standard error; P, P value.

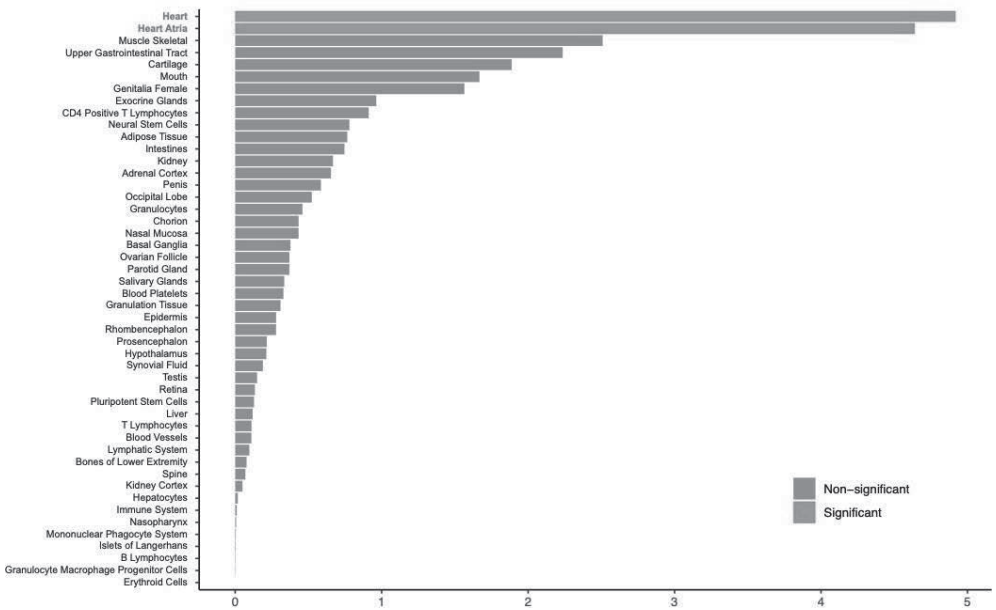
Prioritization of AF-associated genes and transcription factors using gene expression and epigenetic features

We performed a transcriptome-wide association study (TWAS) using the identified loci in the trans-ancestry meta-analysis and GTEx data[38] to identify candidate genes associated with AF. Given the enrichment of AF-associated loci in the heart tissue, we used the gene expression data of GTEx in the atrial appendage, respectively (Fig. 2a and Supplementary Table 13). We found only 14 and 15 overlapping genes between nearby genes located on the AF-associated loci and the candidate genes in the atrial appendage and left ventricle, respectively (Fig. 2b). Moreover, the median physical distances from the lead variants to the candidate genes were greater than 100 kb. Notably, 17.4% and 25.6% of the candidate genes were located 500 kb away from the lead variants (Fig. 2c). Further, to test whether the candidate genes were enriched in unique pathways, we used ingenuity pathway analysis and found several canonical pathways, including fatty acid metabolism-related pathways, in which the candidate genes prioritized in both atrial appendage and left ventricle were enriched (Fig. 2d). Intriguingly, *IL6R* was identified as a candidate gene associated with AF in the atrial appendage and was also involved in the canonical associated pathway. Despite increasing evidence for the role of inflammation in the AF pathophysiology[55], including a report on the suggestive association of the *IL6R* locus with AF (P=5.0×10^{-4})[56], the genetic contribution of inflammatory process to AF development has not been fully elucidated. Our transcriptome-wide analysis revealed a significant association between *IL6R* and AF development, providing supportive evidence for the contribution of inflammation through *IL6R* to the pathophysiological mechanism underlying AF.

Next, we sought to identify transcription factors that bind to AF-associated loci which orchestrate the expression of causative genes involved in AF development. We performed enrichment analysis using



Supplementary Fig. 10 | Overlap between AF-associated signals and variants associated with quantitative traits
Heat-map representation of the AF-associated loci, in which AF-associated variants in LD with $r^2 > 0.6$ in East Asian samples of 1KG overlapped with variants associated with at least one of the quantitative traits. The Z score of QTL alleles that were in accordance with the AF risk allele are shown. Positive values are shown in red, and negative values are shown in blue. The rows show quantitative traits, and the column shows the chromosome and base position of AF-associated signals. AF, atrial fibrillation; LD, linkage disequilibrium; QTL, quantitative trait loci.



Supplementary Fig. 11 Tissue enrichment and eQTL analysis
The results of tissue enrichment analysis ($\log_{10}$ BF > 5 and 16,181 variants). The *x-axis* indicates the -$\log_{10}$ *P* value. Forty-eight exemplar tissues (Methods) were tested, and the significance level was set at $P = 1 \times 10^{-3}$ (0.05/48). eQTL, expression quantitative trait locus; BF, Bayes factor.

Supplementary Table 11 | Tissue and cell type enrichment analysis

Exemplar				EUR+FIN		EUR+FIN+BBJ		Cluster member
MeSH	Organ	Tissue	System	P	Adjusted	P	Adjusted	
A10.165.114	Adipose Tissue	Tissues	Connective Tissue	3.6E-01	1.7E-03	1.7E-01	8.2E-04	Abdominal Fat, Adipocytes, Adipose Tissue, Adipose Tissue White, Aortic Valve, Heart Valves, Subcutaneous Fat, Subcutaneous Fat Abdominal
A07.231	Blood Vessels	Cardiovascular System	Blood Vessels	1.7E-01	8.0E-04	7.8E-01	3.7E-03	Arteries, Blood Vessels, Embryoid Bodies, Endothelial Cells, Muscle Cells, Muscle Smooth, Myocytes Smooth Muscle, Portal System, Serum, Umbilical Veins, Veins
A03.556.875	Upper Gastrointestinal Tract	Digestive System	Gastrointestinal Tract	9.6E-03	4.6E-05	5.8E-03	2.8E-05	Esophagus, Stomach, Upper Gastrointestinal Tract
A03.620	Liver	Digestive System	Liver	8.8E-01	4.2E-03	7.6E-01	3.6E-03	Liver
A06.407.071.140	Adrenal Cortex	Endocrine System	Endocrine Glands	6.9E-01	3.3E-03	2.2E-01	1.1E-03	Adrenal Cortex, Adrenal Glands
A07.541	Heart	Cardiovascular System	Heart	7.3E-05	3.5E-07	1.2E-05	5.8E-08	Heart, Heart Ventricles
A11.329.228	Fibroblasts	Cells	Connective Tissue Cells	6.9E-02	3.3E-04	3.6E-01	1.7E-03	Cervical Vertebrae, Chondrocytes, Chorion, Connective Tissue Cells, Extraembryonic Membranes, Fibroblasts, Joint Capsule, Joints, Mesenchymal Stem Cells, Osteoblasts, Spine, Stromal Cells, Synovial Membrane
A05.810.453.324	Kidney Cortex	Urogenital System	Urinary Tract	2.8E-01	1.4E-03	8.9E-01	4.3E-03	Kidney Cortex
A05.360.319	Genitalia Female	Urogenital System	Genitalia	3.0E-01	1.4E-03	2.7E-02	1.3E-04	Adnexa Uteri, Cervix Uteri, Endocrine Glands, Endometrium, Fallopian Tubes, Genitalia, Genitalia Female, Gonads, Lung, Myometrium, Ovary, Pancreas, Serous Membrane, Thyroid Gland, Uterus
A02.165	Cartilage	Musculoskeletal System	Cartilage	5.4E-03	2.6E-05	1.3E-02	6.2E-05	Cartilage
A03.556.500.760.464	Parotid Gland	Digestive System	Gastrointestinal Tract	7.1E-01	3.4E-03	4.3E-01	2.0E-03	Parotid Gland
A03.556.500.760	Salivary Glands	Digestive System	Gastrointestinal Tract	7.1E-01	3.4E-03	4.6E-01	2.2E-03	Salivary Glands
A07.541.358	Heart Atria	Cardiovascular System	Heart	3.2E-04	1.5E-06	2.3E-05	1.1E-07	Atrial Appendage, Heart Atria
A11.436.348	Hepatocytes	Cells	Epithelial Cells	8.5E-01	4.1E-03	9.6E-01	4.6E-03	Hepatocytes
A05.810.453	Kidney	Urogenital System	Urinary Tract	3.3E-01	1.6E-03	8.9E-01	4.3E-03	Kidney, Urinary Tract
A03.556.124	Intestines	Digestive System	Gastrointestinal Tract	1.3E-01	6.1E-04	1.8E-01	8.6E-04	Cecum, Colon, Colon Sigmoid, Gastrointestinal Tract, Ileum, Intestinal Mucosa, Intestine Large, Intestines, Intestine Small, Lower Gastrointestinal Tract, Membranes, Mucous Membrane, Rectum, Urinary Bladder
A05.360.444.492	Penis	Urogenital System	Genitalia	2.3E-01	1.1E-03	2.6E-01	1.2E-03	Foreskin, Keratinocytes, Penis
A10.336	Exocrine Glands	Tissues	Exocrine Glands	2.0E-01	9.4E-04	1.1E-01	5.2E-04	Exocrine Glands, Genitalia Male, Prostate
A11.118.637.415	Granulocytes	Cells	Blood Cells	8.8E-01	4.2E-03	3.5E-01	1.7E-03	Granulocytes, Neutrophils
A11.872.653	Neural Stem Cells	Cells	Stem Cells	6.0E-03	2.9E-05	1.7E-01	7.9E-04	Neural Stem Cells
A10.165.450.300	Cicatrix	Tissues	Connective Tissue	8.0E-02	3.8E-04	4.9E-01	2.3E-03	Cicatrix, Granulation Tissue, Keloid
A10.690.552.500	Muscle Skeletal	Tissues	Muscles	3.7E-02	1.8E-04	3.1E-03	1.5E-05	Muscles, Muscle Skeletal, Muscle Striated, Quadriceps Muscle
A02.835.583.443.800.800	Synovial Fluid	Musculoskeletal System	Skeleton	6.8E-01	3.2E-03	6.5E-01	3.1E-03	Synovial Fluid
A11.497.497.600	Oocytes	Cells	Germ Cells	9.4E-01	4.5E-03	9.5E-01	4.5E-03	Germ Cells, Oocytes, Ovum
A11.872.700.500	Induced Pluripotent Stem Cells	Cells	Stem Cells	7.5E-01	3.6E-03	7.4E-01	3.6E-03	Adult Stem Cells, Embryonic Stem Cells, Induced Pluripotent Stem Cells, Pluripotent Stem Cells
A15.382.812	Mononuclear Phagocyte System	Hemic and Immune Systems	Immune System	9.5E-01	4.6E-03	9.9E-01	4.7E-03	Antigen Presenting Cells, Bone Marrow Cells, Dendritic Cells, Hematopoietic System, Macrophages, Macrophages Alveolar, Monocytes, Mononuclear Phagocyte System, Myeloid Cells, Phagocytes
A03.734.414	Islets of Langerhans	Digestive System	Pancreas	6.9E-01	3.3E-03	9.9E-01	4.7E-03	Enteroendocrine Cells, Epithelial Cells, Glucagon Secreting Cells, Islets of Langerhans, Stem Cells
A06.407.312.497.535.300.500	Cumulus Cells	Endocrine System	Endocrine Glands	8.1E-01	3.9E-03	4.3E-01	2.0E-03	Cumulus Cells, Endocrine Cells, Granulosa Cells, Ovarian Follicle
A06.407.312.782	Testis	Endocrine System	Endocrine Glands	9.3E-01	4.4E-03	7.1E-01	3.4E-03	Testis
A09.531	Nose	Sense Organs	Nose	7.8E-01	3.7E-03	3.7E-01	1.8E-03	Epithelium, Nasal Mucosa, Nose, Respiratory Mucosa
A10.549	Lymphoid Tissue	Tissues	Lymphoid Tissue	7.6E-01	3.6E-03	8.0E-01	3.8E-03	Lymphatic System, Lymph Nodes, Lymphoid Tissue, Oropharynx, Palatine Tonsil, Spleen
A02.835.232.043	Bones of Lower Extremity	Musculoskeletal System	Skeleton	7.5E-01	3.6E-03	8.4E-01	4.0E-03	Anterior Eye Segment, Bones of Lower Extremity, Conjunctiva, Eye, Eyelids, Foot Bones, Tarsal Bones
A14.549	Mouth	Stomatognathic System	Mouth	4.2E-01	2.0E-03	2.1E-02	1.0E-04	Dentition, Mouth, Mouth Mucosa, Periodontium, Skin, Tongue, Vulva
A09.371.729	Retina	Sense Organs	Eye	4.2E-01	2.0E-03	7.3E-01	3.5E-03	Retina
A15.145.229.188	Blood Platelets	Hemic and Immune Systems	Blood	6.0E-01	2.9E-03	4.7E-01	2.2E-03	Blood Platelets
A08.186.211.730.885.287.249	Basal Ganglia	Nervous System	Central Nervous System	3.3E-01	1.6E-03	4.2E-01	2.0E-03	Basal Ganglia, Corpus Striatum
A08.186.211.730.317.357	Hypothalamus	Nervous System	Central Nervous System	4.2E-01	2.0E-03	6.1E-01	2.9E-03	Diencephalon, Hypothalamo Hypophyseal System, Hypothalamus, Hypothalamus Middle, Neurosecretory Systems
A08.186.211.730.885.287.500.571	Occipital Lobe	Nervous System	Central Nervous System	7.8E-01	3.7E-03	3.0E-01	1.4E-03	Occipital Lobe, Visual Cortex
A08.186.211.730	Prosencephalon	Nervous System	Central Nervous System	6.8E-01	3.3E-03	6.1E-01	2.9E-03	Brain, Central Nervous System, Cerebral Cortex, Cerebrum, Entorhinal Cortex, Frontal Lobe, Hippocampus, Limbic System, Mesencephalon, Parahippocampal Gyrus, Parietal Lobe, Prosencephalon, Telencephalon, Temporal
A08.186.211.865	Rhombencephalon	Nervous System	Central Nervous System	3.0E-01	1.4E-03	5.3E-01	2.5E-03	Brain Stem, Cerebellum, Metencephalon, Rhombencephalon
A10.272.497	Epidermis	Tissues	Epithelium	8.6E-01	4.1E-03	5.3E-01	2.5E-03	Epidermis
A11.063	Antibody Producing Cells	Cells	Antibody-Producing Cells	9.6E-01	4.6E-03	9.9E-01	4.8E-03	Antibody Producing Cells, B Lymphocytes, Lymphocytes, Plasma, Plasma Cells
A11.118.637.555.567.569	T Lymphocytes	Cells	Blood Cells	7.7E-01	3.7E-03	7.7E-01	3.7E-03	Killer Cells Natural, Lymphocytes Null, Lymphoid Progenitor Cells, Precursor Cells B Lymphoid, T Lymphocytes
A11.443	Erythroid Cells	Cells	Erythroid Cells	1.0E+00	4.8E-03	1.0E+00	4.8E-03	Erythrocytes, Erythroid Cells, Erythroid Precursor Cells, Megakaryocyte Erythroid Progenitor Cells
A11.872.378.590.635	Granulocyte Macrophage Progenitor Cells	Cells	Stem Cells	9.9E-01	4.7E-03	1.0E+00	4.8E-03	Granulocyte Macrophage Progenitor Cells, Granulocyte Precursor Cells, Hematopoietic Stem Cells, Monocyte Macrophage Precursor Cells, Myeloid Progenitor Cells
A14.724	Pharynx	Stomatognathic System	Pharynx	9.8E-01	4.7E-03	9.8E-01	4.7E-03	Nasopharynx, Pharynx
A15.145.229.637.555.567.569.200	CD4 Positive T Lymphocytes	Hemic and Immune Systems	Blood	3.0E-01	1.4E-03	1.2E-01	5.9E-04	CD4 Positive T Lymphocytes, T Lymphocytes Regulatory
A15.382	Immune System	Hemic and Immune Systems	Immune System	9.8E-01	4.7E-03	9.8E-01	4.7E-03	Blood, Blood Cells, Bone and Bones, Bone Marrow, Connective Tissue, Fetal Blood, Immune System, Leukocytes, Leukocytes Mononuclear, Skeleton

Supplementary Table 12 | Gene set enrichment analysis

Classification	Example gene set ID	Exemplar pathway	P	Adjusted P	Count/member of pathways
MP	MP:0003267	abnormal heart development	8.09E-09	1.38E-08	abnormal cuffow tract development, poor circulation, abnormal heart ventricle morphology, abnormal heart development, thin myocardium, abnormal fetal cardiomyocyte, abnormal interventricular septum morphology, abnormal heart development, failure of heart looping, abnormal heart tube morphology, dilated heart left ventricle, abnormal myocardial fiber physiology, enlarged heart, enlarged heart atrium, decreased cardiac muscle contractility, abnormal cardiovascular system physiology, cardiac fibrosis, thick ventricular wall, increased cardiomyocyte apoptosis, abnormal myocardium layer morphology, abnormal myocardial fiber morphology, thin ventricular wall, abnormal cardiac muscle relaxation, increased heart weight, decreased ventricle muscle contractility, thick interventricular septum, heart right ventricle hypertrophy, cardiac interstitial fibrosis, abnormal heart right ventricle morphology, dilated cardiomyopathy, heart left ventricle hypertrophy, dilated heart right ventricle, congestive heart failure, abnormal heart left ventricle morphology
MP	MP:0003787	abnormal dorsal aorta morphology	4.82E-07	3.32E-08	abnormal vascular regression, abnormal endocardium morphology, abnormal cardinal vein morphology, abnormal anterior cardinal vein morphology, necrosis, abnormal vascular endothelial cell development, absent vessel yolk sac blood islands, abnormal vitelline vascular remodeling, abnormal angiogenesis, abnormal vascular development, abnormal dorsal aorta morphology
MP	MP:0009404	centrally nucleated skeletal muscle fibers	7.14E-06	4.92E-09	decreased grip strength, abnormal skeletal muscle fiber morphology, dystrophic muscle, progressive muscle weakness, abnormal skeletal muscle morphology, myopathy, increased circulating creatine kinase level, decreased skeletal muscle mass, skeletal muscle fiber necrosis, decreased skeletal muscle fiber size, muscle weakness, abnormal muscle electrophysiology, centrally nucleated skeletal muscle fibers, increased variability of skeletal muscle fiber size, sarcolemma, MUSK subnetwork, DMD subnetwork
MP	MP:0011067	complete neonatal lethality	1.22E-05	4.25E-10	complete perinatal lethality, atelectasis, decreased fetal size, absent gastric milk in neonates, respiratory failure, decreased body length, eyelids open at birth, respiratory distress, complete postnatal lethality, abnormal breathing pattern, neonatal lethality, complete neonatal lethality, cyanosis, abnormal fetal morphology, abnormal suckling behavior, developmental growth
GO	GO:0000988	protein binding transcription factor activity	1.97E-08	5.11E-14	enlarged pericardium, complete embryonic lethality during organogenesis, prenatal lethality, pericardial effusion, hemorrhage, abnormal head mesenchyme morphology, abnormal cell morphology, failure of initiation of embryo turning, complete embryonic lethality before turning of embryo, abnormal transcription coactivator activity, TP73 subnetwork, SUMO2 subnetwork, CREBBP subnetwork, NFYA subnetwork, HOXA9 subnetwork, EP300 subnetwork
GO	GO:0001568	blood vessel development	3.91E-05	1.49E-08	abnormal intestine morphology, decreased vascular permeability, abnormal induced retinal neovascularization, abnormal artery morphology, persistence of hyaloid vascular system, abnormal vascular smooth muscle morphology, abnormal capillary morphology, lung hemorrhage, hemopericardium, intracranial hemorrhage, abnormal coronary vessel morphology, hydrops fetalis, increased vasodilation, abnormal vascular endothelial cell morphology, decreased angiogenesis, abnormal vascular branching morphogenesis, pattern ductus arteriosus, abnormal blood circulation, increased vascular permeability, abnormal blood vessel morphology, PTPRB subnetwork, blood vessel development, vasculogenesis, angiogenesis, blood vessel morphogenesis, vasculature development, regulation of anatomical structure morphogenesis, positive regulation of angiogenesis
GO	GO:0000209	morphogenesis of an epithelium	3.81E-06	7.00E-10	aneal atresia, abnormal ventral body wall morphology, morphogenesis of a branching structure, regulation of organ morphogenesis, branching morphogenesis of a tube, gland development, tissue morphogenesis, tube development, morphogenesis of a branching epithelium, regulation of embryonic development, morphogenesis of an epithelium, epithelium development, regulation of morphogenesis of a branching structure, epithelial tube morphogenesis
GO	GO:0002026	cardiac chamber morphogenesis	1.82E-07	1.61E-08	dilated heart atrium, cardiac ventricle development, cardiac atrium development, cardiac chamber development, cardiac ventricle morphogenesis, cardiac atrium morphogenesis, heart development, heart morphogenesis
GO	GO:0003779	actin binding	8.94E-06	2.37E-08	KEGG:04810:REGULATION OF ACTIN CYTOSKELETON, actin filament binding, actin filament, actin cytoskeleton, TUNA subnetwork, DNMBP subnetwork, SPTA1 subnetwork, ACTA1 subnetwork, ACTN4 subnetwork, ACTN1 subnetwork, SLIO3B subnetwork, TPM3 subnetwork, actin cytoskeleton organization, actin filament-based process
GO	GO:0005912	adherens junction	1.11E-06	1.70E-11	KEGG:04520:ADHERENS JUNCTION, abnormal cell adhesion, anchoring junction, basolateral plasma membrane, cell-cell adherens junction, adherens junction, cell-substrate adherens junction, focal adhesion, cell-substrate junction, CDH5 subnetwork, PKD1 subnetwork, FHL3 subnetwork, TRPT4 subnetwork, NPHP1 subnetwork, ZYX subnetwork, PTPN13 subnetwork, GIPC1 subnetwork, EPHB4 subnetwork
GO	GO:0019901	protein kinase binding	3.31E-06	3.37E-08	mitogen-activated protein kinase binding, protein kinase binding, kinase binding
GO	GO:0030155	regulation of cell adhesion	1.64E-05	1.38E-10	regulation of cell adhesion, cell adhesion mediated by integrin, negative regulation of cell-cell adhesion, positive regulation of cell adhesion
GO	GO:0030239	myofibril assembly	6.53E-06	7.72E-09	actomyosin structure organization, myofibril assembly, cardiac myofibril assembly, sarcomere organization
GO	GO:0044212	transcription regulatory region DNA binding	3.86E-07	9.61E-10	regulatory region nucleic acid binding, chromatin DNA binding, transcription regulatory region DNA binding, regulatory region DNA binding, RNA polymerase II distal enhancer sequence-specific DNA binding transcription factor activity, transcription factor complex, SRF subnetwork, MEF2C subnetwork, MEF2A subnetwork, SRF subnetwork
GO	GO:0048741	regulation of skeletal muscle fiber development	2.83E-05	7.21E-09	regulation of striated muscle cell differentiation, regulation of muscle cell differentiation, regulation of skeletal muscle tissue development, regulation of muscle organ development, muscle fiber development, regulation of skeletal muscle fiber development, skeletal muscle fiber development, myoblast differentiation, regulation of striated muscle tissue development
GO	GO:0051093	negative regulation of developmental process	2.97E-05	8.21E-09	negative regulation of developmental process, negative regulation of signal transduction, developmental maturation, positive regulation of cell differentiation, negative regulation of cell differentiation
GO	GO:0055007	cardiac muscle cell differentiation	5.39E-07	1.42E-08	cardiac cell differentiation, ventricular cardiac muscle cell differentiation, cardiac cell development, cardiac muscle cell development, cardiac muscle cell differentiation
GO	GO:0060090	binding, bridging	9.27E-06	5.64E-09	signaling adaptor activity, binding, bridging, cytoskeletal adaptor activity, protein binding, bridging, SH3/SH2 adaptor activity
GO	GO:0060828	regulation of canonical Wnt receptor signaling pathway	7.30E-06	3.19E-10	regulation of canonical Wnt receptor signaling pathway, positive regulation of canonical Wnt receptor signaling pathway, negative regulation of Wnt receptor signaling pathway, positive regulation of Wnt receptor signaling pathway, regulation of Wnt receptor signaling pathway, negative regulation of canonical Wnt receptor signaling pathway, Wnt receptor signaling pathway
GO	GO:0061061	muscle structure development	2.86E-09	2.46E-08	abnormal muscle regeneration, abnormal muscle morphology, abnormal diaphragm morphology, abnormal myogenesis, TEAD1 subnetwork, striated muscle cell differentiation, muscle organ development, skeletal muscle tissue development, striated muscle tissue development, muscle structure development, muscle cell differentiation, striated muscle cell development, muscle cell development, skeletal muscle organ development, muscle tissue development
PPI subnetwork	ENSG00000071564	TCF3 PPI subnetwork	1.81E-05	2.95E-08	E-box binding, MYOD1 subnetwork, TCF4 subnetwork, TCF3 subnetwork, MYOG subnetwork, ID2 subnetwork, ASCL1 subnetwork, TCF12 subnetwork, HEY1 subnetwork
PPI subnetwork	ENSG00000075618	MARK2 PPI subnetwork	3.48E-05	4.65E-10	CSNK2A1 subnetwork, PAK4 subnetwork, MLLT4 subnetwork, MAP2K2 subnetwork, BAD subnetwork, MARK2 subnetwork
PPI subnetwork	ENSG00000091831	ESR1 PPI subnetwork	3.77E-05	8.01E-09	NR3C1 subnetwork, ESR1 subnetwork, PTBN subnetwork, GSK3B subnetwork, THRB subnetwork, PGR subnetwork, ESR2 subnetwork, AR subnetwork, KLF5 subnetwork, YDR subnetwork
PPI subnetwork	ENSG00000107404	DVL1 PPI subnetwork	4.93E-06	6.30E-09	KEGG:04390:HIPPO SIGNALING PATHWAY, beta-catenin binding, DVL1 subnetwork, AXIN2 subnetwork, AXIN1 subnetwork, DVL3 subnetwork, DVL2 subnetwork
PPI subnetwork	ENSG00000114854	TNNC1 PPI subnetwork	4.92E-07	2.31E-12	KEGG:04260:CARDIAC MUSCLE CONTRACTION, decreased response of heart to stimulated stress, abnormal cardiac muscle contractility, cardiomyopathy, calcium-dependent protein binding, TNNC1 subnetwork, FHL2 subnetwork, ACTC1 subnetwork, MYH6 subnetwork, CBPZ subnetwork, PCDH12 subnetwork, HADHA subnetwork, MYOZ2 subnetwork, MYH7 subnetwork, TNNI1 subnetwork, HSPB1 subnetwork, CSRP3 subnetwork, HNRNPA0 subnetwork, CKM subnetwork, SDHB subnetwork, RBM24 subnetwork, CHCHD3 subnetwork, TNNI3 subnetwork
PPI subnetwork	ENSG00000143295	MEIS1 PPI subnetwork	2.47E-05	6.36E-12	abnormal seminal vesicle morphology, PKNOX1 subnetwork, ZMYND11 subnetwork, MEIS1 subnetwork, ENSG00000214628 subnetwork, PBX1 subnetwork
PPI subnetwork	ENSG00000183306	SPDYA PPI subnetwork	5.92E-11	1.60E-09	PPP1CA subnetwork, SPDYA subnetwork, PPP1CB subnetwork
PPI subnetwork	ENSG00000166913	YWHAB PPI subnetwork	1.72E-05	4.16E-10	YWHAQ subnetwork, YWHAB subnetwork, YWHAH subnetwork, YWHAG subnetwork, MTOR subnetwork, YWHAE subnetwork
PPI subnetwork	ENSG00000166949	SMAD3 PPI subnetwork	8.13E-07	6.11E-09	R-SMAD binding, BAG1 subnetwork, SMAD5 subnetwork, RUNX1 subnetwork, ZNF217 subnetwork, MAD1 subnetwork, SKIL subnetwork, RUNX2 subnetwork, SKAP2 subnetwork, SMAD7 subnetwork, SMAD2 subnetwork, CREB3 subnetwork, TRIM28 subnetwork, SMAD4 subnetwork, SMAD3 subnetwork, BTRC subnetwork
PPI subnetwork	ENSG00000170739	KIF3B PPI subnetwork	1.98E-05	1.10E-08	IRS2 subnetwork, BRAF subnetwork, BCAR1 subnetwork, HRAS1 subnetwork, WEE1 subnetwork, LSR1 subnetwork, CGN subnetwork, P4HB3 subnetwork, KLC2 subnetwork, KIF3B subnetwork, NARR3 subnetwork, LMO7 subnetwork, ARAF subnetwork
PPI subnetwork	ENSG00000188638	RYR3 PPI subnetwork	2.74E-05	8.38E-11	RYR3 subnetwork, RYR1 subnetwork

Adjusted P, P-values adjusted by Bonferroni correction; PPI, protein-protein interaction; MP, mouse phenotype; GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Supplementary Table 13 | AF-associated genes identified by transcriptome-wide association study using GTEx heart tissues

Gene				AF lead variant				Heart Atrial Appendage			Heart Left Ventricle		
Gene symbol	Gene	START	END	CHR	POS	rsID	Nearest gene	Effect size	Z score	P	Effect size	Z score	P
Novel loci													
RP11-728E22.3	ENSG00000269949.1	57827093	57827539	4	71776935	rs12512502	*MOB1B*	0.121	4.866	1.1.E-06	0.137	4.657	3.21E-06
TNAP9	ENSG00000168152.8	83821837	83841122	4	83910712	rs6841049	*LIN54*	-0.271	-5.415	6.1.E-08	-	-	-
PFDN1	ENSG00000113068.5	139624624	139682706	5	139703286	rs17118812	*HBEGF*	-0.061	-5.887	3.9.E-09	-0.054	-5.893	3.8.E-09
PCDHAC2	ENSG00000243232.3	140345820	140391936					0.366	6.009	1.9.E-09	-	-	-
PSMB7	ENSG00000136930.8	127115745	127177723	9	119181794	rs17303101	*ASTN2*	0.097	4.532	5.8.E-06	-	-	-
TMEM273	ENSG00000204161.9	50362773	50396630	10	50485434	rs76460895	*C10orf71-AS1*	-	-	-	0.071	4.446	8.7.E-06
Known loci													
LOLRAD2	ENSG00000187942.7	22138758	22151714	1	22282619	rs7529220	*HSPG2*	-	-	-	-0.351	-7.443	9.9.E-14
TCEA3	ENSG00000204219.5	23707554	23751233					-	-	-	0.065	5.138	2.8.E-07
CASQ2	ENSG00000118729.10	116242628	116311402	1	116297758	rs4073778	*CASQ2*	-0.131	-6.120	9.4.E-10	-0.235	-7.050	1.8.E-12
S100A1	ENSG00000160678.7	153600402	153604513					-0.079	-5.572	2.5.E-08	-0.059	-4.747	2.1.E-06
AQP10	ENSG00000143595.8	154293566	154297801					0.080	5.159	2.5.E-07	0.383	0.065	1.5.E-08
IL6R	ENSG00000160712.8	154377669	154441926	1	154862952	rs11264280	*KCNN3*	0.171	7.306	2.8.E-13	-	-	-
TDRD10	ENSG00000163239.8	154474695	154520623					-0.081	-5.677	1.4.E-08	-0.083	-5.754	8.7.E-09
DCST2	ENSG00000163154.10	154990995	155006257					-	-	-	0.168	5.831	5.5.E-09
ARHGEF2	ENSG00000116584.13	155916630	155976861					-	-	-	0.343	6.004	1.9.E-09
METTL18	ENSG00000171806.7	169761670	169764107					-	-	-	-0.049	-5.061	4.2.E-07
METTL11B	ENSG00000203740.3	170115142	170136931	1	170628255	rs680084	*PRRX1*	-	-	-	-0.187	-9.993	1.6.E-23
PRRX1	ENSG00000116132.7	170631869	170708560					-	-	-	-0.304	-17.068	2.6.E-65
RP1-79C4.4	ENSG00000271811.1	170636522	170638566					-0.205	-10.944	7.1.E-28	-0.220	-14.582	3.6.E-48
PM20D1	ENSG00000162877.8	205797150	205819260	1	205691316	rs4951258	*NUCKS1*	-	-	-	0.325	5.871	4.3.E-09
CENPO	ENSG00000138092.6	25016005	25045245	2	26159940	rs6546620	*KIF3C*	-0.202	-4.808	1.5.E-06	-	-	-
PTGES3P2	ENSG00000217643.1	26045338	26045819					-	-	-	0.319	6.538	6.2.E-11
CEP68	ENSG00000111523.9	65283500	65314138	2	65284231	rs2540949	*CEP68*	0.077	11.116	1.0.E-28	0.107	11.577	5.4.E-31
GMCL1	ENSG00000087338.4	70056774	70108528	2	70106832	rs6747542	*GMCL1*	0.324	8.899	5.6.E-19	0.191	6.598	4.2.E-11
SNRNP27	ENSG00000124380.6	70120692	70132707					0.138	5.721	1.1.E-08	-	-	-
ACVR2A	ENSG00000121989.10	148602086	148688393	2	148799710	rs12992231	*MBD5*	0.157	5.155	2.5.E-07	0.115	5.548	2.9.E-08
WIPF1	ENSG00000115935.12	175424300	175547644	2	175512820	rs7574892	*WIPF1*	-0.478	-7.888	3.1.E-15	-0.120	-7.366	1.8.E-13
FKBP7	ENSG00000079150.13	179328391	179343327	2	179413116	rs3731748	*TTN*	0.069	6.710	1.9.E-11	0.103	7.253	4.1.E-13
C2orf69	ENSG00000178074.5	200775979	200820658					0.248	6.623	3.5.E-11	-	-	-
SPATS2L	ENSG00000196141.8	201170604	201346986	2	201180023	rs3820888	*SPATS2L*	-0.141	-11.270	1.9.E-29	-0.205	-10.126	4.2.E-24
PPIL3	ENSG00000240344.4	201735630	201754026					-	-	-	1.445	7.813	5.6.E-15
THRB	ENSG00000151090.13	24158651	24536773	3	24472866	rs73032363	*THRB*	-0.147588	-6.628441	3.4.E-11	-	-	-
SCN5A	ENSG00000183873.11	38589548	38691164	3	38767315	rs6801957	*SCN10A*	0.113698	6.2483037	4.1.E-10	-	-	-
SCN10A	ENSG00000185313.6	38738293	38835501					-	-	-	0.253	6.770	1.3.E-11
SLC25A26	ENSG00000144741.13	66119285	66438540	3	66454191	rs34080181	*LRIG1*	-0.067	-4.974	6.6.E-07	-0.066	-6.637	3.2.E-11
PCCB	ENSG00000114054.9	135969148	136056738	3	135814009	rs1278493	*PPP2R3A*	0.052	4.584	4.6.E-06	0.196	5.555	2.8.E-08
GYG1	ENSG00000163754.13	148709128	148745419					0.109	5.188	2.1.E-07	-	-	-
RP11-145M9.4	ENSG00000269728.1	179113877	179115965	3	179172979	rs7612445	*GNB4*	0.058	6.794	1.1.E-11	0.056	7.070	1.6.E-12
GNB4	ENSG00000114450.5	179116990	179169378					0.057	6.416627643	1.4.E-10	0.058	6.980	3.0.E-12
CCDC158	ENSG00000163749.13	77234154	77343021	4	81169912	rs11099098	*FGF5*	0.072	4.542	5.6.E-06	-	-	-
LRRC37A15P	ENSG00000230069.3	103648431	103651878	4	103712337	rs223449	*LOC102723710*	-0.141	-5.626	1.8.E-08	-	-	-
UBE2D3	ENSG00000109332.15	103715540	103790053					-0.126	-5.850	4.9.E-09	-	-	-
FBN2	ENSG00000138829.6	127593601	127994878					-	-	-	-0.080	-6.866	6.6.E-12
SLC27A6	ENSG00000113396.8	127873706	128369335	5	128190363	rs2012809	*SLC27A6*	-0.055	-6.382	1.7.E-10	-0.051	-6.502	8.0.E-11
ISOC1	ENSG00000066583.7	128430444	128449721					-0.082	-6.169	6.9.E-10	-	-	-
FAM13B	ENSG00000310003.6	137273649	137387650					-	-	-	-0.679	-11.918	9.5.E-33
RP11-325L7.2	ENSG00000250260.1	137374888	137375668	5	137443486	rs529526	*NME5*	-0.346	-10.902	1.1.E-27	-	-	-
NME5	ENSG00000112981.3	137450866	137475132					1.269	7.098	1.3.E-12	-	-	-
REEP2	ENSG00000132563.11	137774706	137782658					-0.078	-7.818	5.4.E-15	-0.169	-11.297	1.4.E-29
C5orf47	ENSG00000185056.9	173400782	173433143	5	172670745	rs6891790	*NKX2-5*	-	-	-	-0.136	-6.781	1.2.E-11
NSG2	ENSG00000170091.6	173472607	173670504					-	-	-	-0.105	-7.137	9.5.E-13
TPMT	ENSG00000137364.4	18128542	18155305					0.172	8.788	1.5.E-18	-	-	-
KDM1B	ENSG00000165097.9	18155560	18224084	6	18210109	rs34969716	*KDM1B*	0.212	8.389	4.9.E-17	0.098	7.917	2.4.E-15
DEK	ENSG00000124795.10	18224099	18265054					0.069	7.935	2.1.E-15	0.161	9.690	3.3.E-22
RNF144B	ENSG00000137393.8	18368779	18469105					0.244	6.807	1.0.E-11	-	-	-
BTBD9	ENSG00000183826.12	38136227	38607924	6	36647289	rs3176326	*CDKN1A*	-	-	-	0.096	4.755	2.0.E-06
C6orf164	ENSG00000203871.4	88106840	88109467	6	87886335	rs7757330	*ZNF292*	-0.059	-4.772	1.8.E-06	-	-	-
C6orf165	ENSG00000213204.4	88117701	88174183					-0.194	-5.251	1.5.E-07	-	-	-
VGLL2	ENSG00000170162.9	117586721	117594728	6	118974798	rs9481842	*CEP85L*	0.087	5.918	3.2.E-09	-	-	-
SSXP10	ENSG00000217330.1	118910233	118910797					-0.060	-4.986	6.2.E-07	-	-	-
GPR146	ENSG00000164849.7	1084212	1098897	7	895285	rs6461461	*SUN1*	-	-	-	0.108	4.877	1.1.E-06
SEMA3C	ENSG00000075223.9	80371854	80551675	7	92250140	rs42044	*CDK6*	-	-	-	-0.106	-4.505	6.6.E-06
GPR85	ENSG00000164604.8	112718386	112727833	7	116198621	rs1997571	*CAV1*	-0.082	-4.958	7.1.E-07	-	-	-
TFEC	ENSG00000105967.11	115575202	115799950					-	-	-	0.204	8.918	4.8.E-19
ASAH1	ENSG00000104763.13	17913934	17942494	8	17912752	rs399485	*ASAH1*	-	-	-	0.141	8.028	9.9.E-16
MTSS1	ENSG00000170873.14	125563031	125740730	8	124610166	rs58847541	*KLHL38*	-	-	-	-0.040	-4.800	1.6.E-06
C9orf3	ENSG00000044459.10	97488983	97849441	9	97713459	rs10821415	*C9orf3*	-0.162	-9.888	4.7.E-23	-0.093	-4.496	6.9.E-06
NR0B2	ENSG00000148572.12	64893050	64914783	10	65321147	rs12245149	*REEP3*	0.154	5.595	2.2.E-08	-0.439	0.081	1.7.E-07
MRPL35P2	ENSG00000232075.1	65394077	65394587					-0.147	-6.339	2.3.E-10	-	-	-
DNAJC12	ENSG00000108176.10	69556427	69597924	10	69614737	rs12360521	*DNAJC12*	-	-	-	0.232	6.804	1.0.E-11
SIRT1	ENSG00000096717.7	69644427	69678147					-	-	-	0.138	4.656	3.2.E-06
RP11-344N10.5	ENSG00000272630.1	74857802	74861055					-	-	-	-0.359	-7.722	1.1.E-14
DNAJC9	ENSG00000213551.4	74943120	75008620					0.188	8.785	1.6.E-18	-	-	-
TTC18	ENSG00000156042.13	75013517	75118617					-	-	-	0.091	5.070	4.0.E-07
MYO21	ENSG00000177791.11	75391412	75401515					-0.078	-12.104	1.0.E-23	-	-	-
SYNPO2L	ENSG00000166317.7	75404639	75423561	10	75414344	rs60212594	*SYNPO2L*	0.256	10.570	4.1.E-26	-	-	-
AGAP5	ENSG00000172650.8	75434033	75457639					-0.237	-6.955	3.5.E-12	-	-	-
FUT11	ENSG00000196968.6	75532049	75540009					0.142	6.289	3.2.E-10	0.123	6.377	1.8.E-10
NOST2	ENSG00000166507.12	75561669	75571589					-0.456	-12.012	3.1.E-33	-	-	-
PLAU	ENSG00000122861.11	75668935	75677255					-0.145	-6.278	3.4.E-10	-	-	-
VDAC2	ENSG00000165019.9	76969912	76991206					-	-	-	0.286	5.175	2.3.E-07
DPCD	ENSG00000166171.8	103330317	103369425					0.145	5.530	3.2.E-08	-	-	-
PPRC1	ENSG00000148840.6	103892787	103910082					0.094	4.999	5.7.E-07	-	-	-
MARCKSL1P1	ENSG00000213277.3	104935311	104935851	10	105316296	rs74154539	*NEURL1*	0.137	4.515	6.3.E-06	-	-	-
SH3PXD2A	ENSG00000107957.12	105348285	105615301					-	-	-	-0.184	-6.945	3.8.E-12
STN1	ENSG00000107960.6	105642300	105677963					-0.254	-8.090	6.0.E-16	-	-	-
CACUL1	ENSG00000151893.10	120433679	120514761	10	112576695	rs10749053	*RBM20*	-0.039	-4.830	1.4.E-06	-	-	-
SEC23IP	ENSG00000107651.8	121652223	121702014					0.260	4.936	8.0.E-07	-	-	-
MPPED2	ENSG00000066382.12	30406040	30608419	11	20010291	rs4757877	*NAV2*	-	-	-	-0.091	-4.561	5.1.E-06
SSPN	ENSG00000123096.7	26274924	26452223	12	26348429	rs113819537	*SSPN*	0.225	7.924	2.3.E-15	0.377	7.501	6.3.E-14
NACA	ENSG00000196531.6	57106212	57125412	12	57105938	rs2860482	*NACA*	-	-	-	0.258	7.696	1.4.E-14
BEST3	ENSG00000127325.14	70037140	70093256	12	70013415	rs71454237	*LRRC10*	-	-	-	-0.124	-6.248	4.2.E-10
CCDC92	ENSG00000119242.4	124403207	124457378	12	124812678	rs3741508	*NCOR2*	-0.097	-5.374	7.7.E-08	-0.054	-4.757	2.0.E-06
DNAH10OS	ENSG00000250091.2	124410971	124419531					-0.137	-5.351	8.8.E-08	-0.065	-4.760	1.9.E-06
ZNF664	ENSG00000179195.1	124456392	124499886					-	-	-	-0.244	-5.278	1.3.E-07
PROZ	ENSG00000126231.9	113812968	113826694	13	113864837	rs2316443	*CUL4A*	0.106	5.116	3.1.E-07	0.170	5.149	2.6.E-07
SYNE2	ENSG00000054654.11	64319683	64693165	14	64679960	rs2738413	*SYNE2*	-0.076	-5.343	9.2.E-08	-0.167	-11.235	2.8.E-29
ESR2	ENSG00000140009.14	64550950	64804830					0.189	6.556	5.5.E-11	-	-	-
MTHFD1	ENSG00000100714.11	64854749	64926722					0.189	6.694	2.2.E-11	-	-	-
SPTB	ENSG00000070182.13	65213002	65346601					-	-	-	0.050	5.261	1.4.E-07
RP11-7F17.7	ENSG00000258602.1	77425981	77432145	14	77426525	rs10873298	*LINC01629*	0.044	6.796	1.1.E-11	0.050	8.708	2.0.E-11
RP11-7F17.1	ENSG00000243225.2	77435026	77435488					0.043	6.731	1.7.E-11	**0.051**	8.842	7.8.E-12
RP11-2E17.1	ENSG00000259417.2	80487826	80544555					0.080	8.510	1.7.E-17	0.031	4.577	4.7.E-06
RP11-210M15.2	ENSG00000259495.2	80637195	80695917	15	80676925	rs12908004	*ARNT2*	0.111	8.770	1.8.E-18	-	-	-
ARNT2	ENSG00000172379.14	80696692	80890278					0.069	8.583	9.3.E-18	-	-	-
ABHD17C	ENSG00000136379.7	80972025	81047962					0.249	5.570	2.5.E-08	-	-	-
IGF1R	ENSG00000140443.9	99192200	99507759	15	99268850	rs4965430	*IGF1R*	-	-	-	-0.099	-6.188	6.1.E-10
ZFP36L2	ENSG00000363829.5	432097	442960					-0.389	-4.558	5.2.E-06	-	-	-
ANTKMT	ENSG00000103254.5	770581	772601	16	764753	rs3809666	*METRN*	-	-	-	0.111	4.883	1.0.E-06
HAGHL	ENSG00000103253.13	776936	785525					0.052	5.423	5.9.E-08	0.041	5.139	2.8.E-07
NARFL	ENSG00000103245.9	779753	791329					0.104	5.268	1.4.E-07	0.149	5.364	8.1.E-08
RPL3L	ENSG00000140986.7	1993975	2007607	16	2004718	rs2815301	*RPL3L*	-0.193	-6.554	5.6.E-11	-	-	-
SRL	ENSG00000185739.9	4239375	4292081					-	-	-	-0.286	-4.559	5.1.E-06
MIR22HG	ENSG00000186594.8	1614805	1620468	17	1312046	rs61248729	*YWHAE*	-0.076	-4.470	7.8.E-06	-	-	-
CTB-58E17.5	ENSG00000227450.2	36905613	36906969					-	-	-	0.134	4.496	6.9.E-06
PPP1R1B	ENSG00000131771.9	37782993	37792879					0.162	6.286	3.3.E-10	-	-	-
PNMT	ENSG00000141744.3	37824234	37826728	17	38049589	rs7359623	*GSDMB*	0.067	5.825	5.7.E-09	0.224	5.566	2.6.E-08
PGAP3	ENSG00000161395.8	37827375	37853050					0.078	6.338	2.3.E-10	0.077	6.645	3.0.E-11
ERBB2	ENSG00000141736.9	37844167	37886679					0.198	6.622	3.5.E-11	-	-	-
RAPGEFL1	ENSG00000108352.7	38333263	38351908					0.189	4.581	4.6.E-06	-	-	-
DND1P1	ENSG00000264070.1	43663237	43664295	17	44019712	rs242557	*MAPT*	1.030	4.507	6.6.E-06	0.194	4.936	8.0.E-07
MAPT	ENSG00000186868.11	43971748	44105700					-0.10848	-6.205834	5.44E-10	-0.041	-6.101	1.1.E-09
RP11-259G18.3	ENSG00000262539.1	44336917	44337972					-	-	-	0.309	4.724	2.3.E-06
USP36	ENSG00000055483.15	76783463	76837523	17	68421803	rs1396517	*KCNJ2*	-	-	-	-0.082	-4.584	4.6.E-06

AF, atrial fibrillation; GTEx, the Genotype-Tissue Expression project; CHR chromosome; POS, position (hg19); rsID, reference SNP cluster ID; P, P-value

Supplementary Table 14 | Enrichment analysis of transcription factor using ChIP-seq dataset

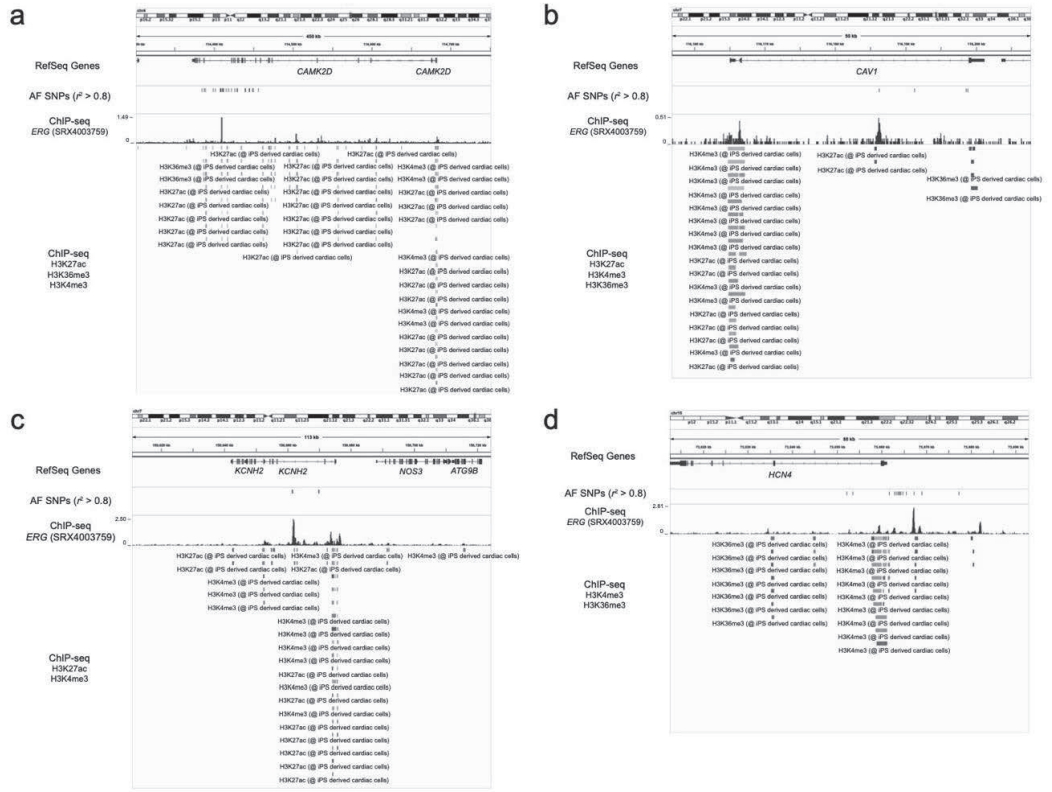
TF	Cell type class	Cell	NCBI ID	Fold enrichment	P
ERG	Pluripotent stem cell	iPS derived cardiac cells	SRX4003759	2.808	1.0E-08
ERG	Pluripotent stem cell	iPS derived cardiac cells	SRX4003760	3.200	3.9E-06
TAL1	Cardiovascular	Primary endothelial cells	SRX393516	1.914	1.5E-04
TBX5	Pluripotent stem cell	iPS derived cardiac cells	SRX2023713	3.556	1.6E-04
MED1	Muscle	Myoblasts	SRX668234	2.923	1.8E-04
ERG	Cardiovascular	HUVEC	SRX3601958	1.800	2.0E-04
MYOD1	Muscle	Myotube	SRX341011	2.034	2.1E-04
FLI1	Cardiovascular	HUVEC	SRX3601960	2.160	2.2E-04
TAL1	Cardiovascular	Primary endothelial cells	SRX393518	1.795	3.0E-04
RELA	Cardiovascular	HAEC	SRX7054666	1.909	3.1E-04
RELA	Cardiovascular	HAEC	SRX7054667	2.389	5.1E-04
ERG	Cardiovascular	HUVEC	SRX3601957	2.238	5.1E-04
RELA	Cardiovascular	HAEC	SRX7054670	1.933	5.8E-04
HDAC1	Muscle	RH-4	SRX4313223	1.903	6.3E-04
NFE2L2	Cardiovascular	HAEC	SRX2734392	2.040	8.4E-04
TBX5	Pluripotent stem cell	iPS derived cardiac cells	SRX2023758	3.375	9.6E-04
RELA	Cardiovascular	HAEC	SRX7054663	1.963	1.0E-03
RELA	Cardiovascular	HUVEC	SRX2207672	1.518	1.2E-03
TBX5	Pluripotent stem cell	iPS derived cardiac cells	SRX2023750	2.818	1.3E-03
TBX5	Pluripotent stem cell	iPS derived cardiac cells	SRX2023773	2.818	1.3E-03
RELA	Cardiovascular	HAEC	SRX7054616	1.962	1.4E-03
MLXIP	Muscle	Skeletal myotubes	SRX5391034	1.839	1.4E-03
RELA	Cardiovascular	HAEC	SRX7055007	1.692	1.6E-03
SS18	Muscle	SYO-1	SRX3927307	1.765	1.8E-03
MYOD1	Muscle	Rhabdomyosarcoma	SRX1998421	1.862	1.9E-03
RELA	Cardiovascular	HAEC	SRX2355085	1.862	1.9E-03
RELA	Cardiovascular	HAEC	SRX7054671	1.743	1.9E-03
EP300	Cardiovascular	HAEC	SRX5527609	2.095	1.9E-03
GATA4	Pluripotent stem cell	iPS derived cardiac cells	SRX2023698	3.429	2.0E-03
TBX5	Pluripotent stem cell	iPS derived cardiac cells	SRX1815017	3.000	2.2E-03
RELA	Cardiovascular	HAEC	SRX7054615	1.806	2.2E-03
JUN	Cardiovascular	HAEC	SRX2355072	1.781	2.3E-03
RELA	Cardiovascular	HUVEC	SRX2207673	1.500	2.5E-03
RELA	Cardiovascular	HAEC	SRX7055006	1.857	2.5E-03
ERG	Cardiovascular	HUVEC	SRX5527658	1.735	2.6E-03
RELA	Cardiovascular	HAEC	SRX7054614	1.735	2.6E-03
RELA	Cardiovascular	HAEC	SRX2355083	2.583	2.7E-03
RELA	Cardiovascular	HAEC	SRX7054661	1.694	3.0E-03
RELA	Cardiovascular	HAEC	SRX7054664	1.800	3.0E-03
EHMT2	Muscle	RH-41	SRX4561210	2.167	3.0E-03
JUN	Cardiovascular	HAEC	SRX2355073	1.676	3.1E-03
RBBP4	Muscle	RH-4	SRX7115500	1.885	3.2E-03
RELA	Cardiovascular	HAEC	SRX7054657	1.750	3.4E-03
RELA	Cardiovascular	HAEC	SRX7054621	1.852	3.5E-03
RELA	Cardiovascular	HAEC	SRX7055008	1.957	3.6E-03
RELA	Cardiovascular	HAEC	SRX7054619	1.793	4.1E-03
RELA	Cardiovascular	HAEC	SRX2355079	2.267	4.6E-03
ETS1	Pluripotent stem cell	hESC derived cardiac cells	SRX5705802	2.385	5.1E-03
EP300	Cardiovascular	HUVEC	SRX5527615	1.815	5.1E-03
EP300	Muscle	Rh-4	SRX1878906	2.188	5.3E-03
TBX5	Pluripotent stem cell	iPS derived cardiac cells	SRX2023721	3.143	5.4E-03
GATA4	Pluripotent stem cell	iPS derived cardiac cells	SRX2023734	3.143	5.4E-03
MYOD1	Muscle	RH-4	SRX5930141	1.676	5.6E-03
RELA	Cardiovascular	HAEC	SRX7054622	2.000	5.8E-03
RELA	Cardiovascular	HAEC	SRX2355081	2.118	6.1E-03
BRD9	Muscle	SYO-1	SRX3927308	2.118	6.1E-03
RELA	Cardiovascular	HAEC	SRX7054668	2.118	6.1E-03
MYOD1	Muscle	Rhabdomyosarcoma	SRX341012	1.840	6.3E-03
FOS	Cardiovascular	HUVEC	SRX150664	1.622	6.5E-03
RELA	Cardiovascular	HAEC	SRX7054672	2.417	6.6E-03
EP300	Cardiovascular	HUVEC	SRX5527617	1.808	6.9E-03
RELA	Cardiovascular	HAEC	SRX7054611	1.808	6.9E-03
RELA	Cardiovascular	HAEC	SRX7055004	1.808	6.9E-03
RELA	Cardiovascular	HAEC	SRX7054620	2.200	7.0E-03
NFE2L2	Cardiovascular	HAEC	SRX2734393	1.909	7.1E-03
ERG	Cardiovascular	HAEC	SRX7054938	2.333	1.0E-02
GATA4	Pluripotent stem cell	iPS derived cardiac cells	SRX2023766	4.667	1.0E-02
Epitope tags	Cardiovascular	HUVEC	SRX096362	1.636	1.1E-02
GATA4	Pluripotent stem cell	iPS derived cardiac cells	SRX2023714	6.000	1.1E-02
FOS	Cardiovascular	HUVEC	SRX070879	1.618	1.1E-02
RBPJ	Cardiovascular	HUVEC	SRX2207670	1.826	1.1E-02
RELA	Cardiovascular	HAEC	SRX2355078	2.063	1.2E-02
RELA	Cardiovascular	HAEC	SRX7054662	1.792	1.2E-02
HMGB1	Cardiovascular	HUVEC	SRX2207964	2.000	1.3E-02
ERG	Cardiovascular	HUVEC	SRX5236332	2.556	1.4E-02
ERG	Cardiovascular	HAEC	SRX7054997	2.857	1.4E-02
RELA	Cardiovascular	HUVEC	SRX2207671	1.818	1.5E-02
JUN	Cardiovascular	HUVEC	SRX150358	1.704	1.5E-02
RELA	Cardiovascular	HAEC	SRX7054618	1.679	1.6E-02
TCF21	Cardiovascular	HCASMC	SRX5904135	1.571	1.6E-02
TCF21	Cardiovascular	Coronary artery smooth muscle	SRX7299332	1.571	1.6E-02
ETS1	Pluripotent stem cell	hESC derived cardiac cells	SRX5705796	1.895	1.6E-02
MYOD1	Muscle	Rhabdomyosarcoma	SRX1998422	1.655	1.7E-02
EP300	Cardiovascular	Cardiac progenitor cells	SRX2671792	1.750	1.7E-02
JUNB	Cardiovascular	HAEC	SRX2355074	2.000	1.8E-02
EP300	Cardiovascular	HAEC	SRX5527607	1.850	1.8E-02
RELA	Cardiovascular	HAEC	SRX7054617	1.594	2.0E-02
RELA	Cardiovascular	HAEC	SRX7054609	1.692	2.0E-02
MYOD1	Muscle	RH-4	SRX5930145	1.667	2.1E-02
BRD4	Cardiovascular	HUVEC	SRX425254	2.714	2.2E-02
ERG	Cardiovascular	HAEC	SRX7054996	2.077	2.6E-02
ERG	Cardiovascular	HAEC	SRX7054994	2.500	2.8E-02
MYOD1	Muscle	Myoblasts	SRX341010	1.654	2.8E-02
CEBPD	Cardiovascular	HAEC	SRX2355057	2.000	3.0E-02
SS18	Muscle	SYO-1	SRX3927303	2.000	3.0E-02
YY1	Muscle	RH-4	SRX4313227	2.000	3.0E-02
SMAD2	Cardiovascular	HUVEC	SRX6476489	2.182	3.0E-02
MYC	Cardiovascular	HUVEC	SRX080151	2.333	3.3E-02
MYC	Cardiovascular	HUVEC	SRX102997	2.333	3.3E-02
HDAC3	Muscle	RH-4	SRX5930141	2.333	3.3E-02
BRD4	Muscle	Rh-4	SRX1878887	3.000	3.5E-02
NFATC1	Cardiovascular	HUVEC	SRX335070	2.200	3.8E-02
HDAC2	Muscle	RH-4	SRX4313220	2.200	3.8E-02
RELA	Cardiovascular	HAEC	SRX7054665	2.200	3.8E-02
ERG	Cardiovascular	HAEC	SRX7054933	2.375	4.2E-02
ERG	Cardiovascular	HAEC	SRX2355058	2.091	4.4E-02
ERG	Cardiovascular	HAEC	SRX7054942	2.091	4.4E-02
ERG	Cardiovascular	HAEC	SRX7054944	2.667	4.4E-02
JUN	Cardiovascular	HCASMC	SRX699737	1.436	4.7E-02
ERG	Cardiovascular	HAEC	SRX7055002	2.222	4.9E-02
GATA2	Cardiovascular	HUVEC	SRX150427	1.600	4.9E-02
NFATC1	Cardiovascular	HUVEC	SRX335071	2.000	4.9E-02

ChIP-seq, chromatin immunoprecipitation sequencing; TF, transcription factor; iPS, induced pluripotent stem; HUVEC, human umbilical vein endothelial cells; HAEC, human aortic endothelial cells; HCASMC, human coronary artery smooth muscle cells

the ChIP-Atlas[47] dataset, which comprised several high-throughput ChIP-seq experiments (15,109 experiments, 1,028 transcription factors). As a result, AF-associated loci were characterized by enriched binding of 33 distinct transcription factors ($P< 0.05$) in cardiovascular cells, pluripotent stem cells-derived cardiac cells, and muscle cells (Fig. 3a and Supplementary Table 14). Of these, ESRRG, TAL1, and TBX5 were among the top enriched transcription factors and are known to be involved in endothelial gene expression and differentiation[57,58]. In particular, ESRRG binding was significantly enriched with Bonferroni-corrected significance level of P=3.3×10^{-6} (0.05/15,109): ESRRG ChIP-seq peaks overlapped with AF-associated loci around genes encoding cardiac ion channels (*SCN10, KCNH2, HCN4*, and *CAMK2D*), where active histone markers such as H3K27ac and H3K4me3 in induced pluripotent stem cells (iPSC)-derived cardiac cells were also observed (Fig. 3b and Supplementary Fig. 12). These results suggest that ESRRG is a transcription factor that regulates the expression of AF-associated genes.

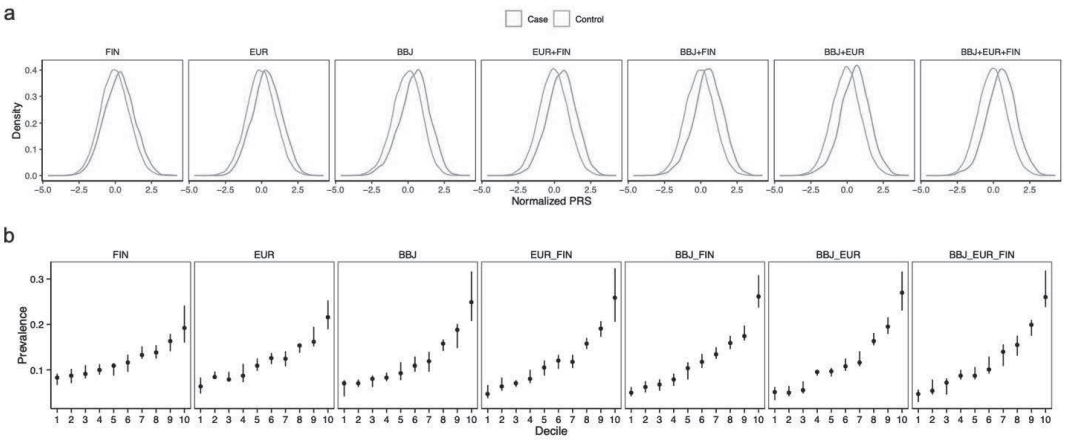
Predictive ability of PRS derived from single-population GWAS and trans-ancestry meta-GWAS

PRS has the potential for risk stratification of complex traits and diseases based on genetic data. However, the transferability of PRS from diverse populations to a population of another ancestry remains challenging. Therefore, we examined the performance of a PRS derived from various combinations of summary statistics in the Japanese population. We split our case-control samples into derivation, validation, and test datasets, and constructed 255 combinations of the summary statistics of three GWAS studies (BBJ, EUR, and FIN) and parameters for PRS derivation. Based on the PRS performance in the validation cohort, we determined the parameters that showed the best performance for each combination of summary statistics (BBJ, FIN, EUR, BBJ+FIN, BBJ+EUR, EUR+FIN, and BBJ+EUR+FIN) (Supplementary Table 2), and assessed the performance of the best model in the test cohort



Supplementary Fig. 12 | Ion channel-related gene and ERG.

a, *CAMK2D* locus **b**, *CAV1* locus, **c**, *KCNH2* locus **d**, *HCN4* locus showing AF-associated variants (r^2>0.8 in European samples in 1KG) and ChIP-seq track of ERG experiment (P=1.0×10^{-8}) and histone modification markers in iPSC-derived cardiac cells. iPSC, induced pluripotent stem cells.



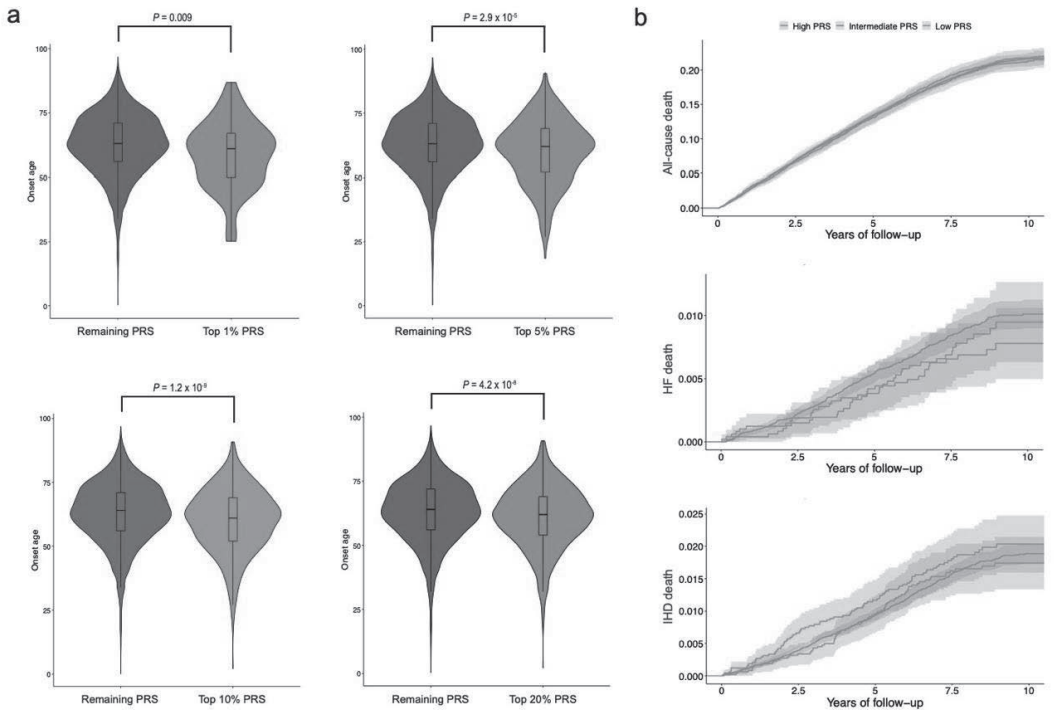
Supplementary Fig. 13 | PRS distribution and AF prevalence.

a, Distribution of PRS in the case and control samples for each combination of GWAS. **b** Prevalence of AF based on the AF-PRS deciles in each combination of GWAS. Data are presented as medians and 95% CI. PRS, polygenic risk score; AF, atrial fibrillation; GWAS, genome-wide association study; CI, confidence interval.

Supplementary Table 15 | The performance of AF-PRS in the test cohort

Summary statistics	Parameter				Number of variants	Pseudo *R*2			AUCROC		
	LD reference	P	r2	Effect model		Median	L95	U95	Median	L95	U95
BBJ	EAS	5.0.E-06	0.2	NA	141	0.123	0.111	0.133	0.719	0.708	0.727
EUR	EUR	5.0.E-04	0.5	NA	1,147	0.120	0.108	0.129	0.716	0.705	0.724
FIN	EUR	5.0.E-06	0.8	NA	201	0.100	0.089	0.108	0.698	0.687	0.706
BBJ/EUR	EUR	5.0.E-04	0.5	fixed	4,102	0.142	0.128	0.151	0.735	0.725	0.743
BBJ/FIN	EAS	5.0.E-06	0.2	fixed	155	0.129	0.116	0.139	0.724	0.713	0.732
EUR/FIN	EUR	5.0.E-04	0.5	random	3,799	0.125	0.112	0.134	0.721	0.711	0.729
BBJ/EUR/FIN	EUR	5.0.E-04	0.5	fixed	4,520	0.144	0.130	0.154	0.737	0.726	0.745

AF, atrial fibrillation; PRS, polygenic risk score; LD, linkage disequilibrium; P, P-value; Pseudo R2, Nagelkerke's pseudo R2; AUCROC, area under the curve of the receiver operator curve; L95, lower limit of 95% confidence interval; U95, upper limit of 95% confidence interval



Supplementary Fig. 14 | Impact of AF-PRS on the age of AF onset and long-term mortality

a, Comparison of the age of AF onset between samples with high PRS and those with remaining PRS. **b**, Kaplan-Meier estimates of cumulative events from all-cause death, heart failure death, and ischemic heart disease death with 95% CI. Individuals are classified into high PRS (top 10 percentile, red), low PRS (bottom 10 percentile, blue), and intermediate (others, green). AF, atrial fibrillation; PRS, polygenic risk score; CI, confidence interval.

(Fig. 4, Supplementary Fig. 13, and Supplementary Table 15). Concordant with the population specificity, the PRS derived from BBJ showed a significantly better performance than those from European studies (P<2.2×10^{-16} for both BBJ vs. EUR and BBJ vs. FIN). Furthermore, the performance of the PRS derived from meta-analysis that included different ancestry groups (EUR+BBJ and FIN+BBJ) significantly exceeded that from a single study (P<2.2×10^{-16} for all cases) as well as that from a meta-analysis of two European studies (P<2.2×10^{-16} for both EUR+BBJ vs. EUR+FIN and BBJvs FIN+EUR). Among all models, the PRS

derived from three studies with multi-ancestry and the largest sample size (BBJ+EUR+FIN) showed the highest performance (pseudo R^2=0.144, 95% CI=0.130–0.154, area under the curve of receiver operating characteristic=0.737, 95% CI=0.726–0.748).

Impact of AF-PRS on AF-relevant phenotypes and cardiovascular outcomes

To assess the potential for clinical applications of the PRS, we investigated the association between PRS and the onset age of AF in individuals from our BBJ case samples (n=7,459). We observed that the onset age decreased as the PRS increased, and individuals with the top 1% PRS were estimated to be approximately 4 years younger in AF onset compared to the remaining individuals (Fig. 5a, 5b, and Supplementary Fig. 14a). Next, we examined whether AF-PRS could explain the phenotypic variability of

Supplementary Table 16 | Mendelian randamization analysis

Outcome / Exposure	Number of variants	MR-IVW			MR-Egger			Pleiotropy		Cochran's Q
		Beta	SE	P	Beta	SE	P	Intercept	P	P
Causal effect of AF on cardiovascular and cerebrovascular disease										
Ischemic heart disease	193	0.086	0.012	9.0.E-13	0.036	0.023	1.2.E-01	0.004	1.3.E-02	3.1.E-08
Peripheral artery disease	197	0.069	0.024	3.5.E-03	0.115	0.047	1.5.E-02	-0.004	2.6.E-01	5.1.E-01
Heart failure	195	0.178	0.013	3.1.E-43	0.115	0.025	4.9.E-06	0.005	3.2.E-03	1.8.E-15
Cardiomyopathy	197	0.225	0.043	1.4.E-07	0.215	0.084	1.2.E-02	0.001	8.8.E-01	7.4.E-02
Valvular heart disease	172	0.181	0.023	1.1.E-14	0.081	0.044	7.0.E-02	0.009	8.9.E-03	1.4.E-02
Rheumatic valvular disease	196	0.206	0.028	1.0.E-13	0.156	0.054	4.4.E-03	0.004	2.9.E-01	1.9.E-03
Aortic aneurtsm and dissection	197	0.093	0.038	1.4.E-02	-0.033	0.073	6.5.E-01	0.011	4.8.E-02	3.0.E-01
Myocarditis	197	0.317	0.141	2.5.E-02	0.401	0.278	1.5.E-01	-0.007	7.2.E-01	2.1.E-01
Pericarditis	197	0.140	0.041	6.5.E-04	0.009	0.080	9.1.E-01	0.011	5.9.E-02	2.0.E-01
Endocarditis	197	-0.063	0.055	2.5.E-01	0.133	0.108	2.2.E-01	-0.017	3.6.E-02	3.1.E-01
Sinus node dysfunction	196	0.392	0.084	3.0.E-06	0.271	0.181	1.4.E-01	0.010	4.5.E-01	4.6.E-05
Atrioventricular block	196	0.226	0.036	6.1.E-10	-0.038	0.068	5.8.E-01	0.023	1.3.E-05	3.4.E-06
Other cardiac arrhythmia	192	0.084	0.012	7.1.E-13	0.040	0.023	8.1.E-02	0.004	2.5.E-02	3.2.E-07
Cardiac arrest	197	0.029	0.044	5.2.E-01	-0.020	0.086	8.2.E-01	0.004	5.2.E-01	4.5.E-01
Stroke	197	0.115	0.022	2.9.E-07	0.133	0.044	2.9.E-03	-0.002	6.4.E-01	1.9.E-01
Transient ischemic attack	197	0.116	0.029	5.9.E-05	0.146	0.057	1.1.E-02	-0.003	5.3.E-01	5.3.E-01
Intracerebral hemorrhage	134	0.069	0.045	1.3.E-01	-0.036	0.082	6.6.E-01	0.010	1.3.E-01	2.6.E-01
Subarachnoid hemorrhage	170	-0.011	0.056	8.4.E-01	-0.141	0.107	1.9.E-01	0.011	1.6.E-01	5.4.E-01
Vascular dementia	197	0.236	0.083	4.4.E-03	0.221	0.164	1.8.E-01	0.001	9.1.E-01	7.2.E-02
Ststemic embolism	197	0.070	0.053	1.9.E-01	0.194	0.104	6.3.E-02	-0.011	1.7.E-01	7.3.E-02
Causal effect of quantitative traits on AF										
Height	9	0.323	0.086	1.8.E-04	0.944	0.492	9.6.E-02	-0.034	2.4.E-01	5.9.E-01
Body mass index	782	0.149	0.028	7.6.E-08	0.191	0.081	1.8.E-02	-0.001	5.7.E-01	5.0.E-07
Systolic blood pressure	661	0.324	0.035	9.4.E-21	0.416	0.101	4.6.E-05	-0.002	3.3.E-01	4.1.E-20
Diastolic blood pressure	581	0.331	0.036	2.9.E-20	0.360	0.111	1.3.E-03	-0.001	7.8.E-01	6.6.E-22
Pulse pressure	582	0.199	0.039	3.0.E-07	0.221	0.107	3.9.E-02	0.000	8.2.E-01	1.7.E-27
White blood cell count	637	0.026	0.031	4.0.E-01	0.111	0.073	1.3.E-01	-0.002	2.0.E-01	2.5.E-07
Neutrophil count	489	0.033	0.029	2.7.E-01	0.061	0.071	3.9.E-01	-0.001	6.6.E-01	1.0.E-03
Eosinophil count	712	0.005	0.022	8.0.E-01	-0.049	0.046	2.8.E-01	0.002	1.7.E-01	1.4.E-06
Basophil count	139	-0.004	0.051	9.3.E-01	-0.208	0.110	6.1.E-02	0.005	4.0.E-02	3.7.E-01
Monocyte count	674	-0.026	0.021	2.1.E-01	-0.007	0.040	8.6.E-01	-0.001	5.7.E-01	5.1.E-07
Lymphocyte count	557	-0.079	0.029	6.5.E-03	-0.057	0.070	4.1.E-01	-0.001	7.3.E-01	4.4.E-06
Red blood cell count	864	-0.056	0.024	2.0.E-02	-0.229	0.051	6.7.E-06	0.005	1.1.E-04	6.2.E-13
Hemoglobin	568	-0.067	0.037	7.3.E-02	0.012	0.089	9.0.E-01	-0.002	3.3.E-01	1.5.E-11
Hematocrit	568	-0.111	0.036	2.1.E-03	-0.113	0.086	1.9.E-01	0.000	9.8.E-01	3.9.E-10
Mean corpuscular volume	846	0.012	0.019	5.1.E-01	0.067	0.035	5.4.E-02	-0.002	6.3.E-02	2.0.E-22
Mean corpuscular hemoglobin	804	0.031	0.019	1.0.E-01	0.068	0.036	5.6.E-02	-0.001	2.2.E-01	9.3.E-21
Mean corpuscular hemoglobin concentration	136	0.017	0.053	7.5.E-01	0.228	0.110	3.9.E-02	-0.007	3.0.E-02	1.3.E-03
Platelet count	1207	0.019	0.017	2.6.E-01	0.091	0.036	1.1.E-02	-0.002	2.2.E-02	2.5.E-28
High-density-lipoprotein cholesterol	666	-0.021	0.022	3.4.E-01	-0.043	0.038	2.7.E-01	0.001	4.9.E-01	1.6.E-12
Low-density-lipoprotein cholesterol	482	-0.079	0.027	2.9.E-03	0.001	0.052	9.9.E-01	-0.003	7.8.E-02	2.6.E-10
Triglyceride	484	-0.035	0.027	1.9.E-01	0.043	0.047	3.6.E-01	-0.003	4.3.E-02	4.7.E-10
Bolood sugar	139	-0.143	0.045	1.6.E-03	-0.101	0.083	2.3.E-01	-0.001	5.5.E-01	2.3.E-02
Total protein	414	0.018	0.035	6.2.E-01	0.035	0.077	6.5.E-01	-0.001	8.0.E-01	2.1.E-14
Albmin	361	-0.088	0.037	1.8.E-02	0.019	0.085	8.3.E-01	-0.003	1.6.E-01	1.7.E-07
Blood urea nitrogen	281	-0.027	0.045	5.5.E-01	-0.198	0.110	7.3.E-02	0.004	9.0.E-02	5.8.E-08
Serum creatinine	701	-0.055	0.032	8.0.E-02	-0.130	0.074	8.0.E-02	0.002	2.7.E-01	4.2.E-10
Estimated glomerular filtration rate	644	0.014	0.032	6.7.E-01	0.078	0.075	3.0.E-01	-0.002	3.4.E-01	8.2.E-15
Uric acid	485	0.011	0.032	7.3.E-01	-0.084	0.062	1.7.E-01	0.003	7.1.E-02	3.8.E-07
Aspartate aminotransferase	466	-0.078	0.034	2.0.E-02	-0.104	0.077	1.8.E-01	0.001	7.1.E-01	7.3.E-10
Alanine aminotransferase	356	-0.112	0.040	5.0.E-03	-0.139	0.089	1.2.E-01	0.001	7.3.E-01	7.3.E-06
Alkaline phosphatase	737	-0.003	0.019	8.8.E-01	0.014	0.034	6.7.E-01	-0.001	5.4.E-01	3.0.E-07
gamma-glutamyl transferase	603	-0.016	0.028	5.6.E-01	0.025	0.060	6.7.E-01	-0.001	4.3.E-01	1.9.E-14
C-reactive protein	409	-0.017	0.029	5.7.E-01	0.047	0.051	3.6.E-01	-0.002	1.3.E-01	1.7.E-13

MR, Mendelian randomization; IVW, inverse variance weighted; SE, standar error; P, P-value

stroke in individuals without a diagnosis of AF. We performed logistic regression analysis in 140,446 control samples in our dataset, and found significant associations of the PRS with increased risks of cerebral infarction (OR [95% CI]=1.055 [1.032–1.078], P=1.2×10^{-6}), cardioembolic stroke (OR [95% CI]=1.391 [1.155–1.676], P= 5.2×10^{-4}), atherothrombotic stroke (OR [95% CI]=1.054 [1.001–1.111], P=0.045), and cerebral hemorrhage (OR=1.068, 95% CI=1.008–1.133, P=0.027; Fig. 5c). Importantly, we observed the largest impact of the PRS on cardioembolic stroke among those with other stroke phenotypes, indicating that AF-PRS may reveal clinically undetectable AF (i.e., subclinical AF) or AF-related conditions, such as prothrombotic or hypercoagulable state, in individuals without AF.

To further explore the clinical utility of AF-PRS, we assessed the impact of PRS on mortality using long-term follow-up data in the BBJ. The Kaplan-Meier estimates of cumulative mortality rate were increased in individuals with a high PRS, especially in cardiovascular- and stroke-related mortality (Fig. 5d and Supplementary Fig. 14b). Cox regression analysis demonstrated that PRS was significantly associated with an increased risk of cardiovascular death (hazard ratio [HR] per 1 standard deviation [s.d.] of PRS=1.06, 95% CI=1.02–1.11, P=5.0×10^{-3}) and stroke death (HR [95% CI]=1.14 [1.04–1.24], P=4.0×10^{-3}; Fig. 5e). In contrast to evidence from clinical studies, the association between PRS and heart failure death did not reach statistical significance in the present study (HR [95% CI]=1.05 [0.95–1.16], P=0.39), because the statistical power might be hampered by a small fraction of heart failure deaths with relatively wide dispersion in our cohort.

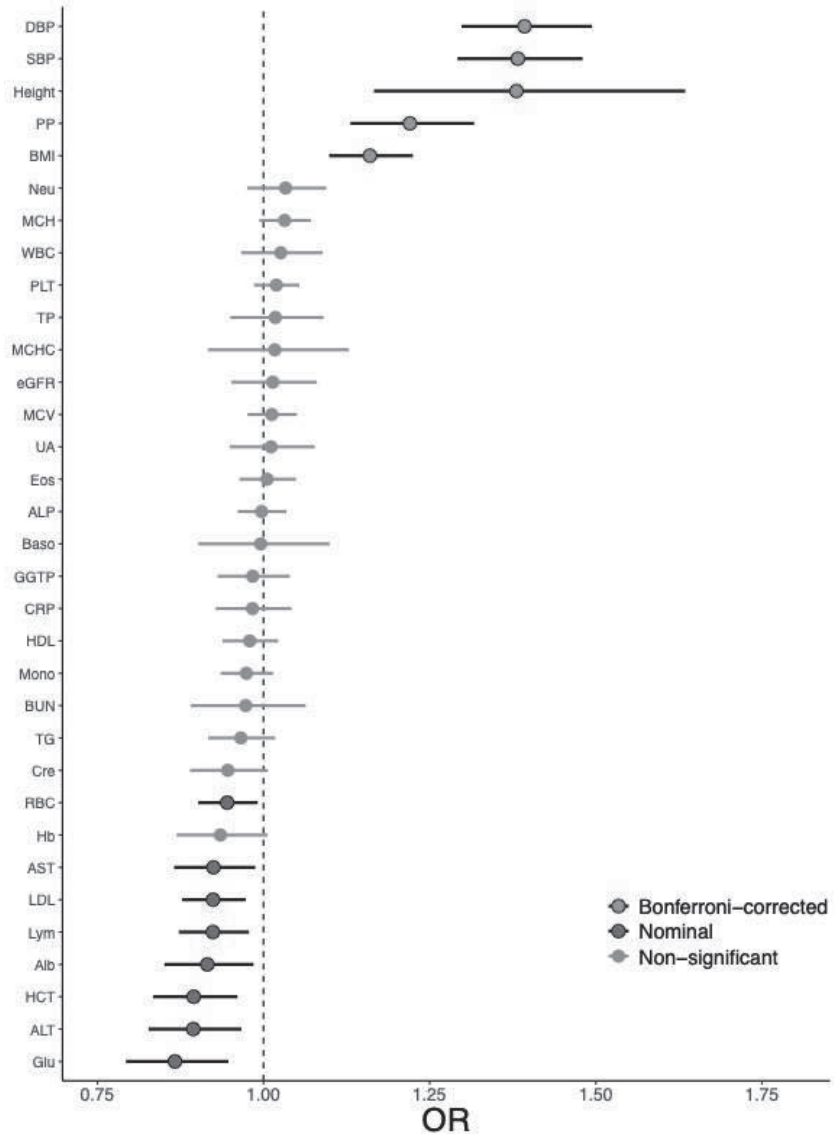
Genetic liability of AF to various cardiovascular diseases

AF is frequently associated with various cardiovascular diseases, such as valvular heart disease, heart failure, and stroke. The causal relationship between AF and cardiovascular diseases is clinically evident, but genetic causality is not comprehensively understood. Therefore, we estimated the directional effect of AF on a wide range of cardiovascular diseases using two-sample Mendelian randomization (MR), where the exposure was AF and all the distinct AF-associated variants from the trans-ancestry meta-analysis were used as instrumental variables. Consistent with clinical evidence, we observed significant causal effects on heart failure, cardiomyopathy, ischemic heart disease, valvular heart disease, and stroke (Fig. 6 and Supplementary Table 16). Notably, we found that AF was a significant predictor for sinus node dysfunction and atrioventricular block (OR [95% CI]=1.480 [1.255–1.745], P=3.0×10^{-6}; OR [95% CI]=1.253 [1.167–1.346], P=6.1×10^{-10}, respectively), indicating that genetic risk for AF contributes to the potential disturbance in the cardiac conduction system.

In contrast, AF is also known as the phenotype accumulated by multiple atherosclerotic- and metabolic-related traits. Therefore, we investigated whether genetic risks for such traits could affect the development of AF using two-sample MR, where the exposures represented quantitative traits, and selected the distinct variants associated with each trait as instrumental variables. As expected[59], height and BMI were significant predictors for AF (OR [95% CI]=1.381 [1.166–1.635], P=1.8×10^{-4}; OR [95% CI]=1.160 [1.099–1.225], P=7.6×10^{-8}, respectively). Furthermore, blood pressure showed a significant causal effect on AF (OR [95% CI]=1.383 [1.292–1.480], P=9.4×10^{-21} for systolic blood pressure; OR (95% CI)=1.393 (1.298–1.494), P=2.9×10^{-20} for diastolic blood pressure; OR (95% CI)= 1.220 (1.131–1.317), P=3.0×10^{-7} for pulse pressure; Supplementary Fig. 15 and Supplementary Table 16).

Discussion

We conducted a large-scale AF-GWAS with approximately 10,000 AF cases in the Japanese population and identified 31 genome-wide significant loci associated with AF. This includes five novel loci, where disease-relevant rare and highly East Asian-specific variants were found in the *SYNE1* and *FGF13* loci, suggesting the involvement of the functional



Supplementary Fig. 15 | Causal effect of quantitative traits on AF development

Each point and error bar represents the causal estimates on the OR scale and the 95% CI for these ORs, respectively. We analyzed the MR analysis to estimate the causal effects using variants after excluding horizontal pleiotropic outliers. The *P* values were determined using the IVW two-sample MR method. OR, odds ratio; MR, Mendelian randomization; IVW, inverse-variance-weighting; DBP, diastolic blood pressure; SBP, systolic blood pressure; PP, pulse pressure; BMI, body mass index; Neu, neutrophil count; MCH, mean corpuscular hemoglobin; WBC, white blood cell count; PLT, platelet count; TP, total protein; MCHC, mean corpuscular hemoglobin concentration; eGFR, estimated glomerular

filtration rate; MCV, mean corpuscular volume; UA uric acid; Eos, eosinophil count; ALP, alkaline phosphatase; Baso, basophil count; GGT, gamma-glutamyl transferase; CRP, C-reactive protein; HDL, high-density lipoprotein cholesterol; Mono, monocyte count; BUN, blood urea nitrogen; TG, triglyceride; Cre, serum creatinine; RBC, red blood cell; Hb, hemoglobin; AST, aspartate aminotransferase; LDL, low-density lipoprotein cholesterol; Lym, lymphocyte count; Alb, albumin; HCT, hematocrit; ALT, alanine aminotransferase; Glu, blood sugar

alteration in the nuclear envelope and the ion channel as a mechanism underlying AF.

Furthermore, we performed the largest trans-ancestry meta-analysis for AF to date, where 150 genome-wide significant loci were identified, resulting in the discovery of 35 novel loci. We further analyzed AF-associated genes and transcription factors using gene expression and epigenetic datasets. Transcriptome-wide analysis linked AF-associated loci to target genes, including *IL6R*, which indicated that inflammation plays a key role in the pathogenesis of AF. Additionally, our approach based on the ChIP-seq dataset clearly implicated ESRRG as a candidate transcription factor involved in the regulation of AF-associated gene expression. ESRRG is highly expressed in endothelial cells and regulates a wide range of targets and pathways involved in vascular homeostasis and angiogenesis[60]. Endothelial dysfunction is observed in patients with AF[61,62], but the association between AF and ESRRG had not been previously examined. This may be attributable to mutational constraints on the ESRRG gene according to the relatively low LOEUF score of 0.33 in gnomAD and embryonic lethality in ESRRG knockout mice with severe defects in vascular development[63,64]. Although the contribution of ESRRG signaling to AF development needs further confirmation by functional experiments, the results from this study suggest that ESRRG may play a critical role in the pathophysiology of AF through vascular development at early developmental stages.

We found shared allelic effects of lead variants in AF-associated loci and genetic correlations between Japanese and European populations. We then derived AF-PRS from the trans-ancestry meta-analysis, which outperformed that derived from a population-specific GWAS. In addition to the predictive ability for AF itself, AF-PRS segregated individuals with AF-related phenotypes, such as early onset of AF and cardioembolic stroke, as well as those with increased risks of long-term cardiovascular and stroke mortalities. These results indicated that the cumulative genetic risk for AF may be an indicator for early therapeutic intervention, including anticoagulation in at-risk individuals as a primary prevention of stroke. Taken together, our findings suggest the clinical utility of AF-PRS for individual risk stratification, leading to the realization of future precision medicine.

In conclusion, our large-scale Japanese and trans-ancestry genetic analyses identified 35 novel loci and provided insights into the distinct and shared genetic architecture of AF between Japanese and Europeans. Integrative analysis of transcriptome and epigenome data revealed the candidate genes and transcription factors involved in the mechanism of disease development. Furthermore, analyses of disease prediction and long-term survival demonstrated the clinical utility of the AF-PRS. These data highlight the importance of AF genetics in clinical settings and provide useful evidence for the implementation of genomic medicine.

References

1) Benjamin, E.J. *et al*. Heart Disease and Stroke Statistics-2019 Update: A Report From the American HeartAssociation. *Circulation* **139**, e56-e528 (2019).
2) Staerk, L., Sherer, J.A., Ko, D., Benjamin, E.J. & Helm, R.H. Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. *Circ. Res*. **120**, 1501-1517 (2017).
3) Healey, J.S. *et al*. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet* **388**, 1161-1169 (2016).
4) Kim, M.H., Johnston, S.S., Chu, B.C., Dalal, M.R. & Schulman, K.L. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ. Cardiovasc. Qual. Outcomes*. **4**, 313-320 (2011).
5) Christophersen, I.E. *et al*. Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation. *Nat. Genet*. **49**, 946-952 (2017).
6) Low, S.K. *et al*. Identification of six new genetic loci associated with atrial fibrillation in the Japanese population. *Nat. Genet*. **49**, 953-958 (2017).
7) Nielsen, J.B. *et al*. Biobank-driven genomic

discovery yields new insight into atrial fibrillation biology. *Nat. Genet*. **50**, 1234-1239 (2018).

8) Roselli, C. *et al*. Multi-ethnic genome-wide association study for atrial fibrillation. *Nat. Genet*. **50**, 1225-1233 (2018).
9) Abecasis, G.R. *et al*. A map of human genome variation from population-scale sequencing. *Nature* **467**, 1061-1073 (2010).
10) Morris, A.P. Transethnic meta-analysis of genomewide association studies. *Genet. Epidemio*l. **35**, 809-822 (2011).
11) Akiyama, M. *et al*. Genome-wide association study identifies 112 new loci for body mass index in the Japanese population. *Nat. Genet*. **49**, 1458-1467 (2017).
12) Kanai, M. *et al*. Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases. *Nat. Genet*. **50**, 390-400 (2018).
13) Akiyama, M. *et al*. Characterizing rare and low-frequency height-associated variants in the Japanese population. *Nat. Commun*. **10**, 4393 (2019).
14) Pers, T.H. *et al*. Biological interpretation of genome-wide association studies using predicted gene functions. *Nat. Commun*. **6**, 5890 (2015).
15) Frey, B.J. & Dueck, D. Clustering by passing messages between data points. *Science* **315**, 972-976 (2007).
16) Marouli, E. *et al*. Rare and low-frequency coding variants alter human adult height. *Nature* **542**, 186-190 (2017).
17) Malik, R. *et al*. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat. Genet*. **50**, 524-537 (2018).
18) Barbeira, A.N. *et al*. Exploring the phenotypic consequences of tissue specific gene expression variation inferred from GWAS summary statistics. *Nat. Commun*. **9**, 1825 (2018).
19) Robinson, J.T. *et al*. Integrative genomics viewer. *Nat. Biotechnol*. **29**, 24-26 (2011).
20) Nagai, A. *et al*. Overview of the BioBank Japan Project: Study design and profile. *J. Epidemiol*. **27**, S2-S8 (2017).
21) Hirata, M. *et al*. Cross-sectional analysis of BioBank Japan clinical data: A large cohort of 200,000 patients with 47 common diseases. *J. Epidemiol*. **27**, S9-S21 (2017).
22) Shah, S. *et al*. Genome-wide association and Mendelian randomisation analysis provide insights into the pathogenesis of heart failure. *Nat. Commun*. **11**, 163 (2020).
23) Verbanck, M., Chen, C.Y., Neale, B. & Do, R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat. Genet*. **50**, 693-698 (2018).
24) Karczewski, K.J. *et al*. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature* **581**, 434-443 (2020).
25) Jaganathan, K. *et al*. Predicting Splicing from Primary Sequence with Deep Learning. *Cell* **176**, 535-548.e24 (2019).
26) Bonne, G. *et al*. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. *Nat. Genet*. **21**, 285-288 (1999).
27) Capell, B.C. & Collins, F.S. Human laminopathies: nuclei gone genetically awry. *Nat. Rev. Genet*. **7**, 940-952 (2006).
28) Zhou, C. *et al*. Novel nesprin-1 mutations associated with dilated cardiomyopathy cause nuclear envelope disruption and defects in myogenesis. *Hum. Mol. Genet*. **26**, 2258-2276 (2017).
29) Wang, C. *et al*. Fibroblast growth factor homologous factor 13 regulates Na+ channels and conduction velocity in murine hearts. *Circ. Res*. **109**, 775-782 (2011).
30) Lip, G.Y. *et al*. Sex-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Observational Research Programme Pilot survey on Atrial Fibrillation. *Europace* **17**, 24-31 (2015).
31) Schnabel, R.B. *et al*. Gender differences in clinical presentation and 1-year outcomes in atrial fibrillation. *Heart* **103**, 1024-1030 (2017).
32) Ball, J., Carrington, M.J., Wood, K.A., Stewart, S.

& SAFETY Investigators. Women versus men with chronic atrial fibrillation: insights from the Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY). *PLoS One* **8**, e65795 (2013).

33) Benjamin, E.J. *et al*. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* **98**, 946-952 (1998).

34) Scheuermeyer, F.X. *et al*. There Are Sex Differences in the Demographics and Risk Profiles of Emergency Department (ED) Patients With Atrial Fibrillation and Flutter, but no Apparent Differences in ED Management or Outcomes. *Acad. Emerg. Med*. **22**, 1067-1075 (2015).

35) Conforto, T.L., Zhang, Y., Sherman, J. & Waxman, D.J. Impact of CUX2 on the female mouse liver transcriptome: activation of female-biased genes and repression of male-biased genes. *Mol. Cell. Biol*. **32**, 4611-4627 (2012).

36) Ling, G., Sugathan, A., Mazor, T., Fraenkel, E. & Waxman, D.J. Unbiased, genome-wide in vivo mapping of transcriptional regulatory elements reveals sex differences in chromatin structure associated with sex-specific liver gene expression. *Mol. Cell. Biol*. **30**, 5531-5544 (2010).

37) Lin, H. *et al*. Methylome-wide Association Study of Atrial Fibrillation in Framingham Heart Study. *Sci. Rep*. **7**, 40377 (2017).

38) Battle, A. *et al*. Genetic effects on gene expression across human tissues. *Nature* **550**, 204-213 (2017).

39) Rattka, M., Westphal, S., Gahr, B.M., Just, S. & Rottbauer, W. Spen deficiency interferes with Connexin 43 expression and leads to heart failure in zebrafish. *J. Mol. Cell. Cardiol*. **155**, 25-35 (2021).

40) Michela, P., Velia, V., Aldo, P. & Ada, P. Role of connexin 43 in cardiovascular diseases. *Eur. J. Pharmacol*. **768**, 71-76 (2015).

41) den Hoed, M. *et al*. Identification of heart rate-associated loci and their effects on cardiac conduction and rhythm disorders. *Nat. Genet*. **45**, 621-631 (2013).

42) Nolte, I.M. *et al*. Genetic loci associated with heart rate variability and their effects on cardiac disease risk. *Nat. Commun*. **8**, 15805 (2017).

43) Chen, P.S., Chen, L.S., Fishbein, M.C., Lin, S.F. & Nattel, S. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. *Circ. Res*. **114**, 1500-1515 (2014).

44) Gudbjartsson, D.F. *et al*. A sequence variant in ZFHX3 on 16q22 associates with atrial fibrillation and ischemic stroke. *Nat. Genet*. **41**, 876-878 (2009).

45) Zaw, K.T.T. *et al*. Association of ZFHX3 gene variation with atrial fibrillation, cerebral infarction, and lung thromboembolism: An autopsy study. *J. Cardiol*. **70**, 180-184 (2017).

46) Amendt, B.A., Sutherland, L.B., Semina, E.V. & Russo, A.F. The molecular basis of Rieger syndrome. Analysis of Pitx2 homeodomain protein activities. *J. Biol. Chem*. **273**, 20066-20072 (1998).

47) Oki, S. *et al*. ChIP-Atlas: a data-mining suite powered by full integration of public ChIP-seq data. *EMBO Rep*. **19**, e46255 (2018).

48) Ramji, D.P. & Foka, P. CCAAT/enhancer-binding proteins: structure, function and regulation. *Biochem. J* **365**, 561-575 (2002).

49) Bustin, M. & Reeves, R. High-mobility-group chromosomal proteins: architectural components that facilitate chromatin function. *Prog. Nucleic Acid Res. Mol. Biol*. **54**, 35-100 (1996).

50) Chiefari, E. *et al*. A polymorphism of HMGA1 is associated with increased risk of metabolic syndrome and related components. *Sci. Rep*. **3**, 1491 (2013).

51) Sharma, M. *et al*. hZimp10 is an androgen receptor co-activator and forms a complex with SUMO-1 at replication foci. *EMBO J*. **22**, 6101-6114 (2003).

52) Rodriguez-Magadán, H., Merino, E., Schnabel, D., Ramírez, L. & Lomelí, H. Spatial and temporal expression of Zimp7 and Zimp10 PIAS-like proteins in the developing mouse embryo. *Gene Expr. Patterns* **8**, 206-213 (2008).

53) Henderson, P., van Limbergen, J.E., Wilson, D.C., Satsangi, J. & Russell, R.K. Genetics of childhood-onset inflammatory bowel disease. *Inflamm. Bowel Dis*. **17**, 346-361 (2011).

54) Beliakoff, J. *et al*. The PIAS-like protein Zimp10 is essential for embryonic viability and proper vascular

development. *Mol. Cell. Biol*. **28**, 282-292 (2008).

55) Hu, Y.F., Chen, Y.J., Lin, Y.J. & Chen, S.A. Inflammation and the pathogenesis of atrial fibrillation. *Nat. Rev. Cardiol*. **12**, 230-243 (2015).

56) Schnabel, R.B. *et al*. Large-scale candidate gene analysis in whites and African Americans identifies IL6R polymorphism in relation to atrial fibrillation: the National Heart, Lung, and Blood Institute's Candidate Gene Association Resource (CARe) project. *Circ. Cardiovasc. Genet*. **4**, 557-564 (2011).

57) Nagai, N. *et al*. Downregulation of ERG and FLI1 expression in endothelial cells triggers endothelial-to-mesenchymal transition. *PLoS Genet*. **14**, e1007826 (2018).

58) Kalna, V. *et al*. The Transcription Factor ERG Regulates Super-Enhancers Associated With an Endothelial-Specific Gene Expression Program. *Circ. Res*. **124**, 1337-1349 (2019).

59) Levin, M.G. *et al*. Genetics of height and risk of atrial fibrillation: A Mendelian randomization study. *PLoS Med*. **17**, e1003288 (2020).

60) Shah, A.V., Birdsey, G.M. & Randi, A.M. Regulation of endothelial homeostasis, vascular development and angiogenesis by the transcription factor ERG. *Vascul. Pharmacol*. **86**, 3-13 (2016).

61) Guazzi, M. & Arena, R. Endothelial dysfunction and pathophysiological correlates in atrial fibrillation. *Heart* **95**, 102-106 (2009).

62) Khan, A.A., Thomas, G.N., Lip, G.Y.H. & Shantsila, A. Endothelial function in patients with atrial fibrillation. *Ann. Med*. **52**, 1-11 (2020).

63) Vijayaraj, P. *et al*. Erg is a crucial regulator of endocardial-mesenchymal transformation during cardiac valve morphogenesis. *Development* **139**, 3973-3985 (2012).

64) Birdsey, G.M. *et al*. The endothelial transcription factor ERG promotes vascular stability and growth through Wnt/β-catenin signaling. *Dev. Cell* **32**, 82-96 (2015).