Supplementary information for

Shared Genetic Contributions to Atrial Fibrillation and Ischemic Stroke Risk

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Code and data release

For access to code, sample identifiers, SNP identifiers, and SNP weights used in the construction of the genetic risk score, please see this GitHub repository: https://github.com/UMCUGenetics/Afib-Stroke-Overlap.

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Supplementary Tables

Supplementary Table 1 | Atrial fibrillation cases and controls available from the Stroke Genetics Network (SiGN) Consortium.

*As classified by the CCS Causative system (note that this table is a repeat of **Table 1** from the main manuscript):*

Phenotype	Total	Cardioembolic	Large artery atherosclerosis	Small artery occlusion	Undetermined	
					Incomplete/ unclassified	Cryptogenic/ CE minor
Atrial fibrillation	1,751	1,495	63	32	151	0
Paroxysmal atrial fibrillation	1,315	1,088	52	23	138	0
Left atrial thrombus	48	37	3	3	4	0
Sick sinus syndrome	79	65	5	3	4	0
Atrial Flutter	106	90	4	2	10	0
Total	3,190	2,684	123	61	298	0

As classified by the CCS Phenotypic system (note that this system allows a case to be classified into more than one subtype):

Phenotype	Total	Cardioembolic	Large artery atherosclerosis	Small artery occlusion	Undetermined
Atrial fibrillation	1,751	1,751	161	58	0
Paroxysmal atrial fibrillation	1,315	1,315	126	61	0
Left atrial thrombus	48	48	7	4	0
Sick sinus syndrome	79	79	8	4	0
Atrial Flutter	106	106	11	3	0
Total	3,190	3,190	302	126	0

As classified by the TOAST system:

Phenotype	Total	Cardioembolic	Large artery atherosclerosis	Small artery occlusion	Undetermined
Atrial fibrillation	1,751	1,254	26	23	170
Paroxysmal atrial fibrillation	1,315	880	25	19	178
Left atrial thrombus	48	35	1	1	9
Sick sinus syndrome	79	48	0	1	13
Atrial Flutter	106	75	2	3	12
Total	3,190	2,207	54	47	371

Overlap of atrial fibrillation and cardioembolic stroke in the three subtyping systems in SiGN (CCSc, CCS Causative; CCSp, CCS Phenotypic; TOAST):

Phenotype	CCSc Cardioembolic	CCSp Cardioembolic	TOAST Cardioembolic
Atrial fibrillation	1,495	1,751	1,254
Paroxysmal atrial fibrillation	1,088	1,315	880
Left atrial thrombus	37	48	35
Sick sinus syndrome	65	79	48
Atrial Flutter	90	106	75
No atrial fibrillation phenotypes	316	418	903
Total	3,000	3,608	3,333

Supplementary Table 2 | Look-up of previously-associated atrial fibrillation SNPs in SiGN. After performing a GWAS of atrial fibrillation in the SiGN data, we looked up the 26 known genetic risk loci for atrial fibrillation, as identified in the latest GWAS.[1] Twenty-four of the 25 signals present in the SiGN data were directionally consistent with the previous GWAS. The only signal not directionally consistent was discovered through eQTL analysis. One signal, a rare variant burden signal, was absent from our data (all SNPs here have allele frequency > 1%).

Supplementary Table 2 is provided as a separate, downloadable Excel spreadsheet as well as a tab-delimited text available at the project GitHub repository (download: https://github.com/saralpulit/Afib-Stroke-Overlap/blob/master/SupplementaryTable2.afib.hits.SiGN-lookup.txt). The first 14 columns are taken from *Christophersen, et al. Large-scale analysis of common and rare variants identify 12 new loci associated with atrial fibrillation. Nature Genetics, 2017.*[1] Those columns are:

SNP	single-nucleotide polymorphism; rs identifier
CHR	chromosome
BP	basepair (hg19)
Genes	Closest gene(s)
Location	Where the SNP resides relative to the listed gene
Risk	Risk allele
Ref	Reference allele
RAF	Risk allele frequency
OR	Odds ratio
CI95_1	95% confidence interval for the odds ratio (lower bound)
CI95_2	95% confidence interval for the odds ratio (upper bound)
Pval	Association p-vlaue
Mean_imp	Imputation quality
Analysis	The analysis the variant or gene was discovered in (ExWAS, expression QTL analysis; Meta, meta-analysis; RVAS, rare variant association study)

The remaining columns provided are data points extracted from the atrial fibrillation GWAS in SiGN. They are:

SiGN_RAF	Risk allele frequency in SiGN
SiGN_INFO	Imputation quality (info score) in SiGN
SiGN_BOLT_BETA	Beta of the SNP taken from BOLT-LMM; note that this is a beta that results from a linear mixed model
SiGN_LIAB_BETA	The beta, converted to the liability scale
SiGN_OR	Odds ratio in SiGN
SiGN_SE	Standard error of SIGN_BOLT_BETA
SiGN_P_BOLT	P-value from BOLT-LMM (for the infinitesimal model only)

Supplementary Table 3 | Heritability calculations in atrial fibrillation and ischemic stroke subtypes. (a) We calculated the SNP-based heritability (h_g^2) of atrial fibrillation, all ischemic stroke, and the stroke subtypes using GCTA[2]. All SNPs used had minor allele frequency > 1% and imputation quality > 0.8 (for imputed SNPs). Imputed SNPs were converted to best-guess genotypes. We assumed a trait prevalence of 1% for all phenotypes and tested the robustness of h_g^2 estimates to SNPs included in the GRM by using four different GRMs: (i) genotyped only; (ii) genotyped, pruned, and filtered (see **Supplemental Methods**); (iii) imputed; and (iv) imputed, pruned, and filtered. (b) We performed the exact same analysis but using BOLT-LMM to estimate h_g^2. BOLT-LMM estimates were converted to the liability scale (see **Supplemental Methods**).

Geno, genotyped; SE, standard error; CCSc, CCS Causative; CCSp, CCS Phenotypic

a. h_g^2 estimates in GCTA

Subtype	Subtyping system	Cases	Geno h_g^2 (SE)	Geno, filtered h_g^2 (SE)	Imputed h_g^2 (SE)	Imputed, filtered h_g^2 (SE)
Large artery athero-sclerosis	CCSc	2,385	0.115 (0.020)	0.124 (0.020)	0.127 (0.020)	0.160 (0.024)
	CCSp	2,449	0.117 (0.020)	0.113 (0.019)	0.140 (0.020)	0.149 (0.023)
	TOAST	2,318	0.139 (0.021)	0.135 (0.021)	0.169 (0.022)	0.282 (0.025)
Cardio-embolic	CCSc	3,000	0.166 (0.017)	0.139 (0.016)	0.172 (0.017)	0.219 (0.019)
	CCSp	3,608	0.145 (0.014)	0.125 (0.014)	0.136 (0.014)	0.181 (0.016)
	TOAST	3,333	0.139 (0.015)	0.115 (0.015)	0.156 (0.016)	0.224 (0.018)
Small artery occlusion	CCSc	2,262	0.118 (0.021)	0.114 (0.020)	0.121 (0.021)	0.144 (0.024)
	CCSp	2,419	0.106 (0.020)	0.097 (0.019)	0.114 (0.019)	0.122 (0.022)
	TOAST	2,631	0.122 (0.019)	0.120 (0.018)	0.135 (0.019)	0.162 (0.021)
Undeter-mined	CCSc	4,574	0.087 (0.012)	0.077 (0.011)	0.120 (0.012)	0.168 (0.014)
	CCSc (INCUNC)	2,280	0.123 (0.021)	0.118 (0.021)	0.205 (0.022)	0.284 (0.024)
	CCSc (CRYPTCE)	2,294	0.092 (0.021)	0.086 (0.020)	0.109 (0.021)	0.179 (0.025)
	CCSp	1,096	0.132 (0.042)	0.091 (0.040)	0.159 (0.041)	0.249 (0.050)
	TOAST	3,479	0.096 (0.015)	0.089 (0.014)	0.141 (0.015)	0.214 (0.017)
--	All stroke	13,390	0.069 (0.005)	0.059 (0.005)	0.082 (0.005)	0.107 (0.006)
--	Atrial fibrillation	3,190	0.182 (0.016)	0.156 (0.019)	0.178 (0.016)	0.228 (0.019)

b. h_g^2 estimates in BOLT-LMM

Subtype	Subtyping system	Geno h_g^2 (SE)	Geno, filtered h_g^2 (SE)	Imputed h_g^2 (SE)	Imputed, filtered h_g^2 (SE)	Imputed, filtered h_g^2 (SE)
Large artery athero-sclerosis	CCSc	2,385	0.116 (0.020)	0.120 (0.020)	0.120 (0.020)	0.155 (0.024)
	CCSp	2,449	0.121 (0.020)	0.119 (0.019)	0.142 (0.020)	0.152 (0.023)
	TOAST	2,318	0.130 (0.021)	0.121 (0.020)	0.145 (0.021)	0.241 (0.025)
Cardio-embolic	CCSc	3,000	0.157 (0.017)	0.129 (0.016)	0.159 (0.017)	0.195 (0.019)
	CCSp	3,608	0.138 (0.014)	0.117 (0.014)	0.127 (0.014)	0.164 (0.016)
	TOAST	3,333	0.131 (0.015)	0.108 (0.015)	0.144 (0.015)	0.210 (0.018)
Small artery occlusion	CCSc	2,262	0.147 (0.021)	0.151 (0.020)	0.179 (0.022)	0.230 (0.026)
	CCSp	2,419	0.133 (0.020)	0.127 (0.019)	0.161 (0.020)	0.196 (0.024)
	TOAST	2,631	0.142 (0.019)	0.142 (0.018)	0.168 (0.019)	0.211 (0.022)
Undeter-mined	CCSc	4,574	0.090 (0.012)	0.086 (0.011)	0.130 (0.012)	0.182 (0.014)
	CCSc (INCUNC)	2,280	0.133 (0.021)	0.118 (0.021)	0.128 (0.021)	0.282 (0.024)
	CCSc (CRYPTCE)	2,294	0.112 (0.021)	0.112 (0.021)	0.143 (0.021)	0.237 (0.026)
	CCSp	1,096	0.159 (0.042)	0.136 (0.041)	0.213 (0.042)	0.341 (0.052)
	TOAST	3,479	0.101 (0.015)	0.099 (0.014)	0.153 (0.015)	0.228 (0.017)
--	All stroke	13,390	0.169 (0.012)	0.059 (0.005)	0.084 (0.005)	0.114 (0.006)
--	Atrial fibrillation	3,190	0.169 (0.016)	0.140 (0.015)	0.156 (0.016)	0.200 (0.018)

Supplementary Table 4 | Genetic correlations between atrial fibrillation and ischemic stroke subtypes. To estimate genetic correlation between atrial fibrillation and ischemic stroke subtypes, we calculated Pearson's r between SNP z-scores in the Atrial Fibrillation Genetics (AFGen) GWAS of atrial fibrillation and in GWAS of ischemic stroke subtypes and atrial fibrillation performed here in the SiGN data. The correlation calculations are provided in this table, which is split into two parts and is available to download in text format here:

Part A: correlations calculated across all genome-wide SNPs
https://github.com/saralpulit/Afib-Stroke-Overlap/blob/master/SuppTable4.partA.SiGN.AFGen.trait.correlations.txt

Part B: correlations calculated across all genome-wide SNPs except those ±2Mb from the PITX2 and ZFHX3 index SNPs provided in Supplementary Table 2
https://github.com/saralpulit/Afib-Stroke-Overlap/blob/master/SuppTable4.partB.SiGN.AFGen.trait.correlations.drop-pitx2-zfhx3.txt

The headers of the two files are exactly the same:

Column	Definition
Z.threshold	Z-score threshold used to subset AFGen SNPs
EduYrs.Z	Correlation with z-scores from educational attainment GWAS
afib.broad.Z	Correlation with z-scores from atrial fibrillation (broadly defined phenotype) GWAS
allstroke.Z	Correlation with z-scores from all stroke GWAS
CCScCEmajor.Z	Correlation with z-scores from CCSc CE GWAS
CCScCRYPTCE.Z	Correlation with z-scores from CCSc CRYPTCE GWAS
CCScINCUNC.Z	Correlation with z-scores from CCSc INCUNC GWAS
CCScLAA.Z	Correlation with z-scores from CCSc LAA GWAS
CCScSAO.Z	Correlation with z-scores from CCSc SAO GWAS
CCScUNDETER.Z	Correlation with z-scores from CCSc UNDETER GWAS
CCSpCEmajincl.Z	Correlation with z-scores from CCSp CE GWAS
CCSpCryptoincl.Z	Correlation with z-scores from CCSp Cryptogenic GWAS
CCSpLAAmajincl.Z	Correlation with z-scores from CCSp LAA GWAS
CCSpSAOmajincl.Z	Correlation with z-scores from CCSp SAO GWAS
toastCE.Z	Correlation with z-scores from TOAST CE GWAS
toastLAA.Z	Correlation with z-scores from TOAST LAA GWAS
toastSAO.Z	Correlation with z-scores from TOAST SAO GWAS
toastUNDETER.Z	Correlation with z-scores from TOAST UNDETER GWAS

CCSc, CCS Causative subtyping system; CCSp, CCS Phenotypic subtyping system; TOAST, TOAST subtyping system; CE, cardioembolic stroke; LAA, large artery atherosclerosis; SAO, small artery occlusion; UNDETER, undetermined; INCUNC, incomplete/unclassified; CRYPTCE, cryptogenic and CE minor.

Supplementary Table 5 | Association between the atrial fibrillation genetic risk score and ischemic stroke subtypes. We tested the association between a genetic risk score (GRS) constructed from atrial fibrillation-associated SNPs and all stroke subtypes. The results of those association tests are shown here. We used two groups of controls: all available controls (N = 28,026) and all controls that were free of atrial fibrillation (AF, N = 3,860). All analyses were adjusted for sex and principal components (PCs). Regression analyses were optionally adjusted for clinical covariates (age, cardiovascular disease, type 2 diabetes status, smoking status, and hypertension).

Significant results (p = 0.0062, Bonferroni-corrected for four subtype groups and two independent subtyping classifications -- CCS and TOAST -- are bolded).

SE, standard error; CCSc, CCS Causative; CCSp, CCS Phenotypic.

Large artery atherosclerosis (LAA):

Case definition	Control definition	Cases	Controls	Logistic regression, adjusted for PCs and sex			Logistic regression, adjusted for PCs, sex, and clinical covariates		
				Beta	SE	P-value	Beta	SE	P-value
CCSc LAA	Non-AF controls	2,385	3,860	0.008	0.015	0.600	0.002	0.018	0.929
CCSc LAA	All controls	2,385	28,026	-0.002	0.012	0.885	-0.004	0.013	0.786
CCSp LAA	Non-AF controls	2,449	3,860	0.016	0.016	0.315	0.010	0.018	0.570
CCSp LAA	All controls	2,449	28,026	0.004	0.011	0.694	0.002	0.013	0.850
TOAST LAA	Non-AF controls	2,318	3,860	0.010	0.016	0.528	0.000	0.018	0.980
TOAST LAA	All controls	2,318	28,026	-0.006	0.012	0.594	-0.008	0.014	0.550

Cardioembolic stroke (CE):

Case definition	Control definition	Cases	Controls	Logistic regression, adjusted for PCs and sex			Logistic regression, adjusted for PCs, sex, and clinical covariates		
				Beta	SE	P-value	Beta	SE	P-value
CCSc CE	Non-AF controls	3,000	3,860	0.187	0.014	**1.59E-42**	0.218	0.018	**1.40E-34**
CCSc CE	All controls	3,000	28,026	0.169	0.010	**1.01E-65**	0.173	0.012	**1.45E-48**
CCSp CE	Non-AF controls	3,608	3,860	0.178	0.013	**6.98E-43**	0.203	0.017	**8.34E-34**
CCSp CE	All controls	3,608	28,026	0.161	0.009	**2.43E-70**	0.163	0.011	**1.05E-49**
TOAST CE	Non-AF controls	3,333	3,860	0.171	0.013	**3.17E-37**	0.172	0.015	**3.22E-29**
TOAST CE	All controls	3,333	28,026	0.149	0.009	**3.00E-56**	0.146	0.011	**4.43E-41**

Small artery occlusion (SAO):

Case definition	Control definition	Cases	Controls	Logistic regression, adjusted for PCs and sex			Logistic regression, adjusted for PCs, sex, and clinical covariates		
				Beta	SE	P-value	Beta	SE	P-value
CCSc SAO	Non-AF controls	2,262	3,860	0.023	0.017	0.170	0.026	0.019	0.163
CCSc SAO	All controls	2,262	28,026	0.002	0.012	0.842	0.006	0.013	0.660
CCSp SAO	Non-AF controls	2,419	3,860	0.025	0.016	0.124	0.029	0.018	0.109
CCSp SAO	All controls	2,419	28,026	0.003	0.012	0.787	0.007	0.013	0.602
TOAST SAO	Non-AF controls	2,631	3,860	0.021	0.016	0.209	0.019	0.018	0.289
TOAST SAO	All controls	2,631	28,026	0.001	0.011	0.902	0.003	0.013	0.826

Undetermined strokes:

Case definition	Control definition	Cases	Controls	Logistic regression, adjusted for PCs and sex			Logistic regression, adjusted for PCs, sex, and clinical covariates		
				Beta	SE	P-value	Beta	SE	P-value
CCSc UNDETER	Non-AF controls	4,574	3,860	0.036	0.013	**0.004**	0.031	0.014	0.022
CCSc UNDETER	All controls	4,574	28,026	0.021	0.009	0.013	0.021	0.010	0.030
CCSc INCUNC	Non-AF controls	2,280	3,860	0.046	0.016	**0.003**	0.045	0.017	0.010
CCSc INCUNC	All controls	2,280	28,026	0.028	0.012	0.015	0.029	0.013	0.025
CCSc CRYPTCE	Non-AF controls	2,294	3,860	0.030	0.016	0.051	0.026	0.017	0.124
CCSc CRYPTCE	All controls	2,294	28,026	0.015	0.012	0.212	0.017	0.013	0.192
CCSp Crypto	Non-AF controls	1,096	3,860	0.035	0.020	0.090	0.029	0.022	0.195
CCSp Crypto	All controls	1,096	28,026	0.019	0.016	0.258	0.021	0.018	0.245
TOAST UNDETER	Non-AF controls	3,479	3,860	0.033	0.013	0.015	0.028	0.014	0.055
TOAST UNDETER	All controls	3,479	28,026	0.021	0.010	0.027	0.022	0.011	0.042

UNDETER, undetermined; INCUNC, incomplete and unclassified; CRYPTCE, cryptogenic and CE minor; Crypto, cryptogenic

Supplementary Table 6 | Sensitivity analysis for the atrial fibrillation genetic risk score. As a sensitivity analysis for the genetic risk score (GRS), we constructed 3 additional GRSs, including SNPs +/- 25kb, +/- 50kb, and +/- 100kb from the SNPs included in the original score. All scores remain highly significant when tested for association with cardioembolic stroke (using a logistic regression model). P-values after additionally adjusting for clinical covariates are also shown. Clinical covariates: age, cardiovascular disease, type 2 diabetes status, smoking status, and hypertension.

PCs, principal components; MAF, minor allele frequency; INFO, imputation (info) score.

GRS SNPs	Filters	Total SNPs	GRS p-value	
			Adjusted for PCs, sex	*Adjusted for PCs, sex, clinical covariates*
Original SNPs	MAF > 1% Info > 0.8	975	1.01×10^{-65}	1.44×10^{-48}
Original SNPs +/- 25kb	MAF > 1% Info > 0.8	146,631	9.13×10^{-50}	1.32×10^{-37}
Original SNPs +/- 50kb	MAF > 1% Info > 0.8	258,870	5.76×10^{-48}	1.40×10^{-36}
Original SNPs +/- 100kb	MAF > 1% Info > 0.8	462,146	4.47×10^{-44}	1.77×10^{-32}

Supplementary Table 7 | Clinical covariates available in the SiGN data. We adjusted our analyses of a genetic risk score for a series of clinical covariates that are associated with atrial fibrillation. Summary-statistics on these covariates are shown below for those samples classified as (a) cardioembolic stroke or (b) undetermined stroke. The number of samples with missing data are provided in parentheses where relevant.

Cardioembolic

Phenotype	CCS Causative	CCS Phenotypic	TOAST
Female	1,588	1,859	1,618
Male	1,247	1,541	1,520
Age: mean (sd)	74.7 (12.4)	74.5 (12.3)	71.0 (15.1)
Hypertensive (missing)	2,195 (18)	2,665 (21)	2,272 (16)
Diabetes mellitus (missing)	763 (26)	950 (29)	799 (8)
CAD (missing)	989 (64)	1206 (83)	911 (119)

Smoking
  Current
  Former
  Never
	379
	694
	1,737
		468
		865
		2,055
			513
			776
			1,905

Total	3,000	3,608	3,333

Undetermined

Phenotype	CCS Causative	CCS Causative	CCS Causative	CCS Phenotypic	TOAST
Female	1,880	1,024	856	420	1,445
Male	2,151	1,014	1,137	543	1,635
Age: mean (sd)	63.9 (15.4)	67.7 (13.9)	69.0 (15.9)	58.9 (15.7)	63.7 (16.1)
Hypertensive (missing)	2,833 (23)	1,512 (14)	1,321 (9)	612 (3)	2,110 (29)
Diabetes mellitus (missing)	958 (26)	513 (14)	445 (12)	202 (4)	708 (25)
CAD (missing)	739 (169)	421 (86)	318 (83)	115 (46)	573 (100)

Smoking
  Current
  Former
  Never
	1,090
	1,050
	2,202
		582
		516
		1,081
			508
			534
			1,121
				239
				235
				548
					813
					772
					1,711

Total	4,574	2,280	2,294	1,096	3,479

Supplementary Table 8: Variance explained by the atrial fibrillation genetic risk score in cardioembolic stroke. To determine the variance explained by the atrial fibrillation genetic risk score (GRS) in cardioembolic stroke, we constructed a model in BOLT-LMM that consisted of two variance components: (1) a variance component made up of SNPs for the genetic relationship matrix, and (2) a variance component made up of SNPs from the GRS. After computing the estimated variance explained for each component in BOLT-LMM, we converted the estimate to the liability score. Below is variance explained for each of the cardioembolic stroke phenotypes as determined by the three subtyping systems available in SiGN: CCS Causative, CCS Phenotypic, and TOAST. Standard errors of each estimate appear in parentheses. Explained variance is shown for a GRS including the *PITX2* (chromosome 4) and *ZFHX3* (chromosome 16) loci, as well as excluding ±2Mb around these loci (see https://github.com/UMCUGenetics/Afib-Stroke-Overlap for lists of SNPs that fall in these regions). Because a large number of SNPs is needed to construct a variance component to calculate variance explained, we performed the calculation using the atrial fibrillation GRS including SNPs ±100kb from the original GRS SNPs, and then pruning SNPs a linkage disequilibrium of 0.2.

CE, cardioembolic; GRS, genetic risk score; AF, atrial fibrillation

Subtyping System	h_g^2 CE stroke	h_g^2 atrial fibrillation GRS ±100kb	Proportion of CE h_g^2 explained by AF GRS
GRS including the PITX2 and ZFHX3 loci			
CCSc	0.195 (0.019)	0.045 (0.010)	23.1%
CCSp	0.164 (0.016)	0.040 (0.008)	24.4%
TOAST	0.210 (0.018)	0.051 (0.01)	24.3%
GRS excluding the PITX2 and ZFHX3 loci			
CCSc	0.195 (0.019)	0.037 (0.010)	19.0%
CCSp	0.164 (0.016)	0.032 (0.008)	19.5%
TOAST	0.210 (0.018)	0.044 (0.009)	21.0%

Supplementary Figures

Supplementary Figure 1 | Genome-wide association study (GWAS) of atrial fibrillation in SiGN. (A) We performed a GWAS of 3,190 cases with atrial fibrillation, or paroxysmal atrial fibrillation, as well as other diagnoses suggestive of underlying atrial fibrillation, including left atrial thrombus, sick sinus syndrome, and atrial flutter. We additionally included 28,026 referents. We used a linear mixed model and adjusted the model for principal components and sex. The majority of atrial fibrillation risk loci identified through previous GWAS efforts were identified here at nominal significance or better (see **Supplementary Table 2**). The Manhattan plot only shows QC-passing SNPs with minor allele frequency > 1% and imputation quality score > 0.8. (B) Quantile-quantile (QQ) plot indicating SNPs stratified by minor allele frequency and the corresponding genomic inflation factor (lambda, λ) for each stratum. (C) QQ plot showing SNPs stratified by imputation quality and the corresponding lambda for each stratum. Figures D-F are identical to those of A-C, but for the analysis performed in atrial fibrillation cases only (N = 1,751). We performed this is an internal sensitivity analysis only, to ensure that more broadly defining the atrial fibrillation phenotype was not introducing additional phenotypic noise.

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D

E

QQ plot: λ = 0.954

F

QQ plot: λ = 0.954
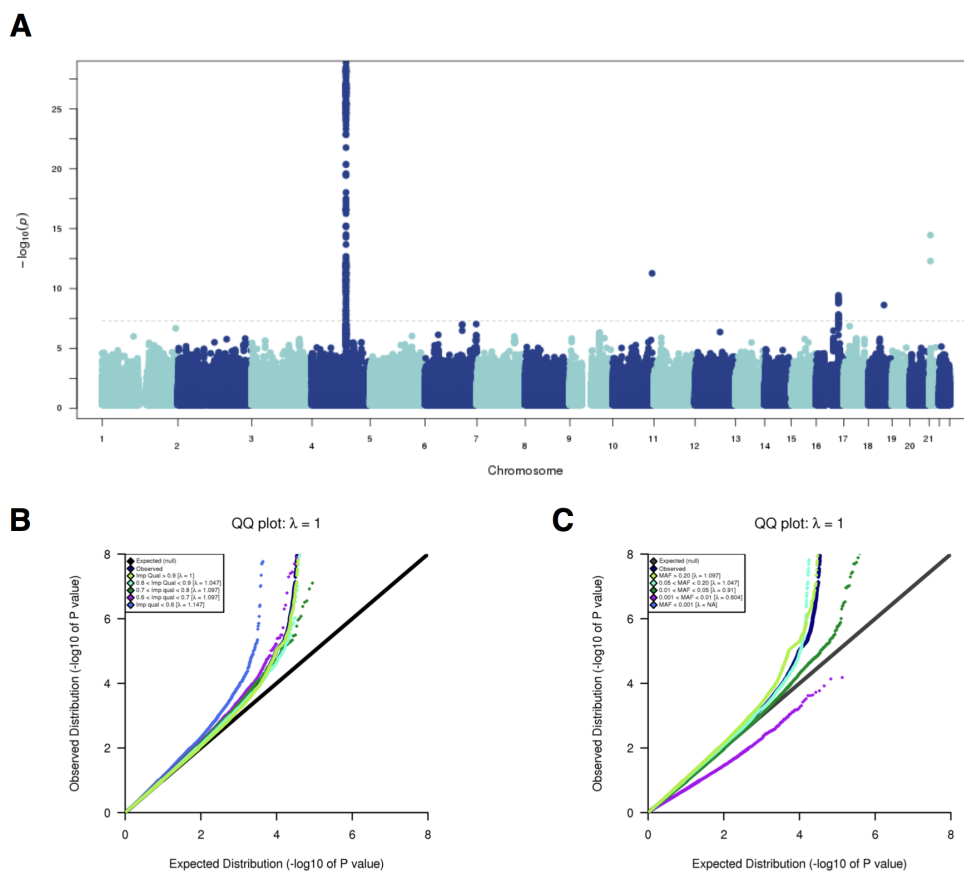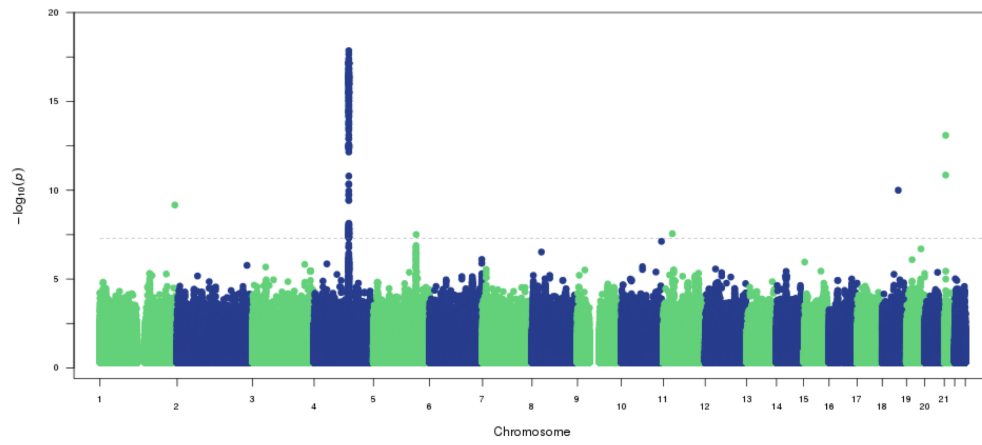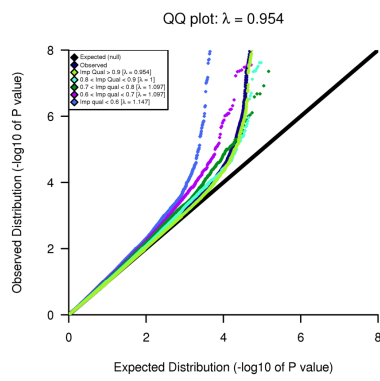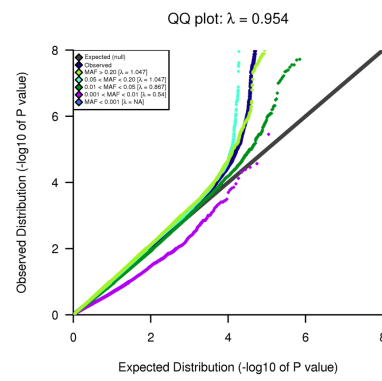
Supplementary Figure 2 | Heritability of ischemic stroke, its subtypes, and atrial fibrillation. We computed the SNP-based heritability of all stroke, all stroke subtypes, and atrial fibrillation using BOLT-LMM (top row) and GCTA (bottom row). All SNPs used for analysis had a minor allele frequency > 1% and imputation quality > 0.8 (for imputed SNPs). Imputed SNPs were converted to best-guess genotypes. We assumed a trait prevalence of 1% for all phenotypes and tested the robustness of h^2 estimates to SNPs included in the GRM by using four different GRMs: (a) genotyped SNPs only; (b) genotyped, pruned, and filtered (see **Supplemental Methods**); (c) imputed; and (d) imputed, pruned, and filtered. We converted the imputed SNPs to hard-call genotypes before performing heritability analyses. Estimates are shown below, including error bars. The underlying data for these figures are provided in **Supplementary Table 3**.

LAA, large artery atherosclerosis; CE, cardioembolic stroke; SAO, small artery occlusion; UNDETER, undetermined; INCUNC, incomplete/unclassified; CRYPTCE, cryptogenic and CE minor; Cryptoincl, cryptogenic; CCSc, CCS Causative subtyping system; CCSp, CCS Phenotypic subtyping system; TOAST, TOAST subtyping system.
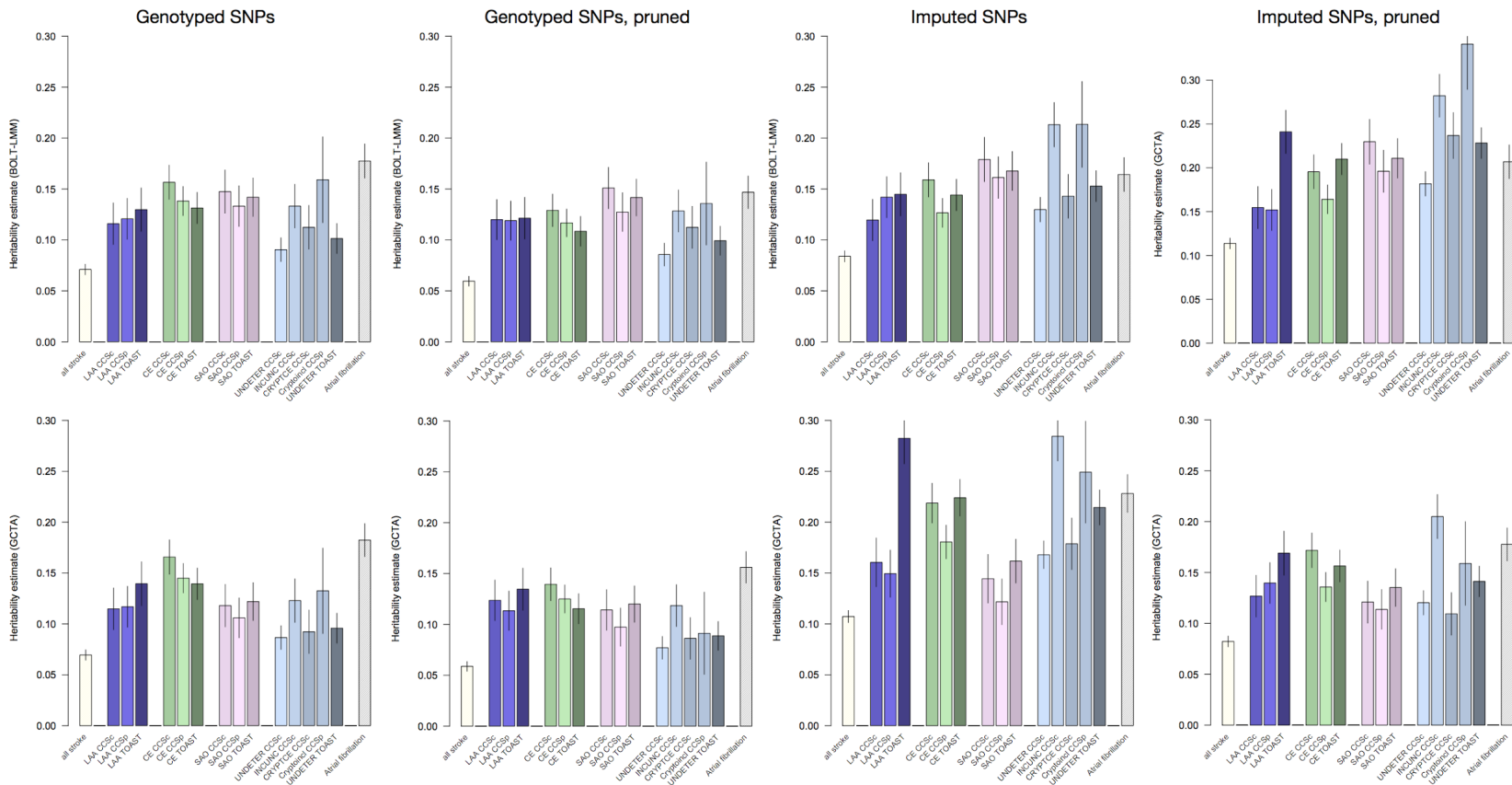
Supplementary Figure 3 | Comparison of heritability estimates from BOLT-LMM and GCTA. We computed the heritability of all stroke, all stroke subtypes, and atrial fibrillation using BOLT-LMM and GCTA, as shown in **Supplementary Figure 2**. Below, you will find a comparison of the two methods, with BOLT-REML on the x-axis and GCTA estimates on the y-axis. Error bars are shown for the respective estimates.

AF, atrial fibrillation; CE, cardioembolic stroke; LAA, large artery atherosclerosis; SAO, small artery occlusion; UNDETER, undetermined; INCUNC, incomplete/unclassified; CRYPTCE, cryptogenic/CE minor; c, CCS Causative; p, CCS Phenotypic; t, TOAST.
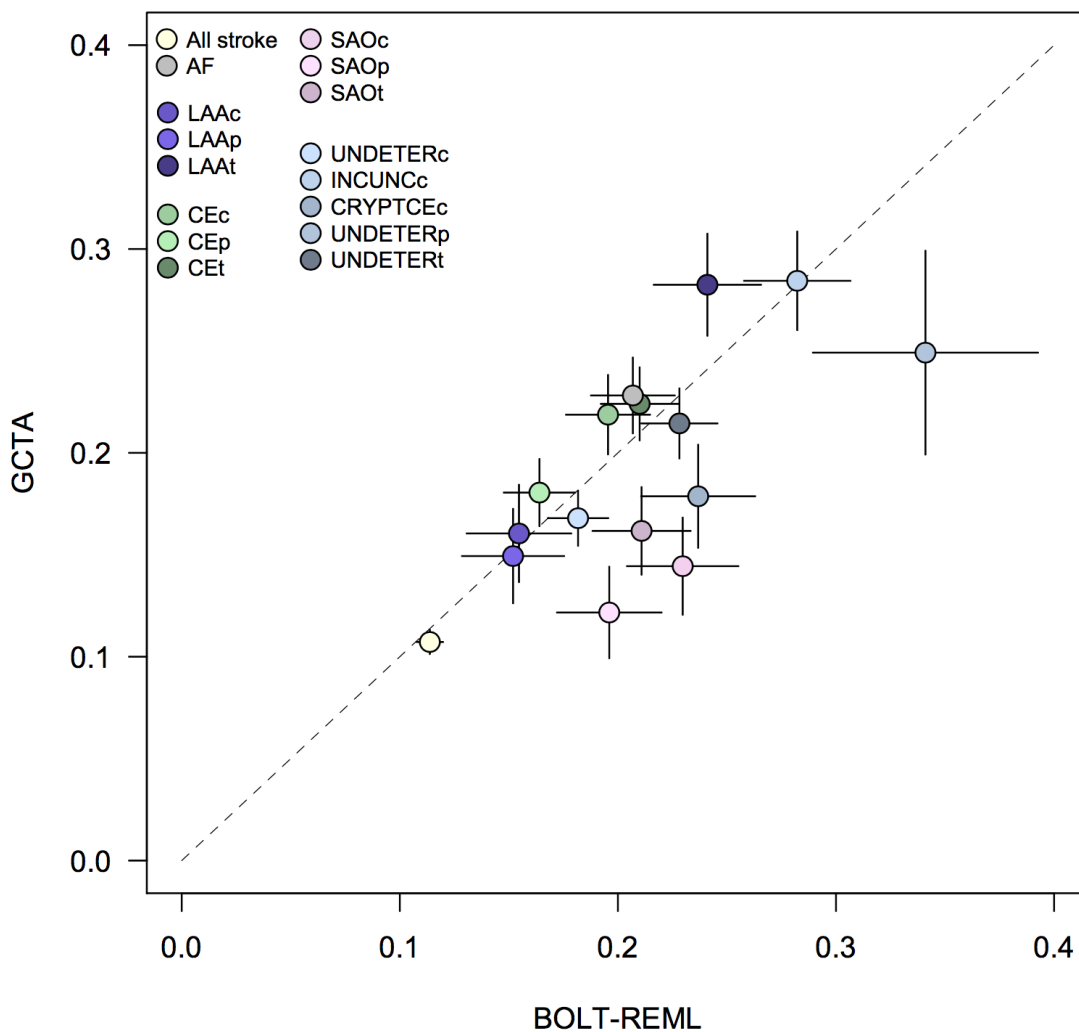
Supplementary Figure 4 | Genetic correlations between atrial fibrillation and ischemic stroke subtypes. To estimate genetic correlation between atrial fibrillation and ischemic stroke subtypes, we calculated Pearson's r between SNP z-scores in the AFGen GWAS of atrial fibrillation and in GWAS of ischemic stroke subtypes and atrial fibrillation performed here in the SiGN data. Here, we present data identical to that shown in Figure 2 of the main manuscript, but removing ±2Mb around the two most significant loci discovered in atrial fibrillation and cardioembolic stroke: the region around *PITX2* (chromosome 4) and the region around *ZFHX3* (chromosome 16). (a) Genome wide, atrial fibrillation in AFGen and in SiGN correlate with increasing strength as the z-score in AFGen increases. Educational attainment is included here as a null comparator. (b) Genetic signal in cardioembolic stroke also correlates strongly with atrial fibrillation genetic signal in AFGen, but we do not observe correlation between atrial fibrillation and the other primary stroke subtypes. (c) Removing the *PITX2* and *ZFHX3* regions leaves only somewhat modest correlation between the incomplete/unclassified undetermined subtype and atrial fibrillation. Panels (d-f) show underlying data.

Correlations restricted to those SNPs used in the genetic risk score for atrial fibrillation were: AFGen vs atrial fibrillation in SiGN, r = 0.78; AFGen vs. cardioembolic stroke in SiGN, r = 0.75.
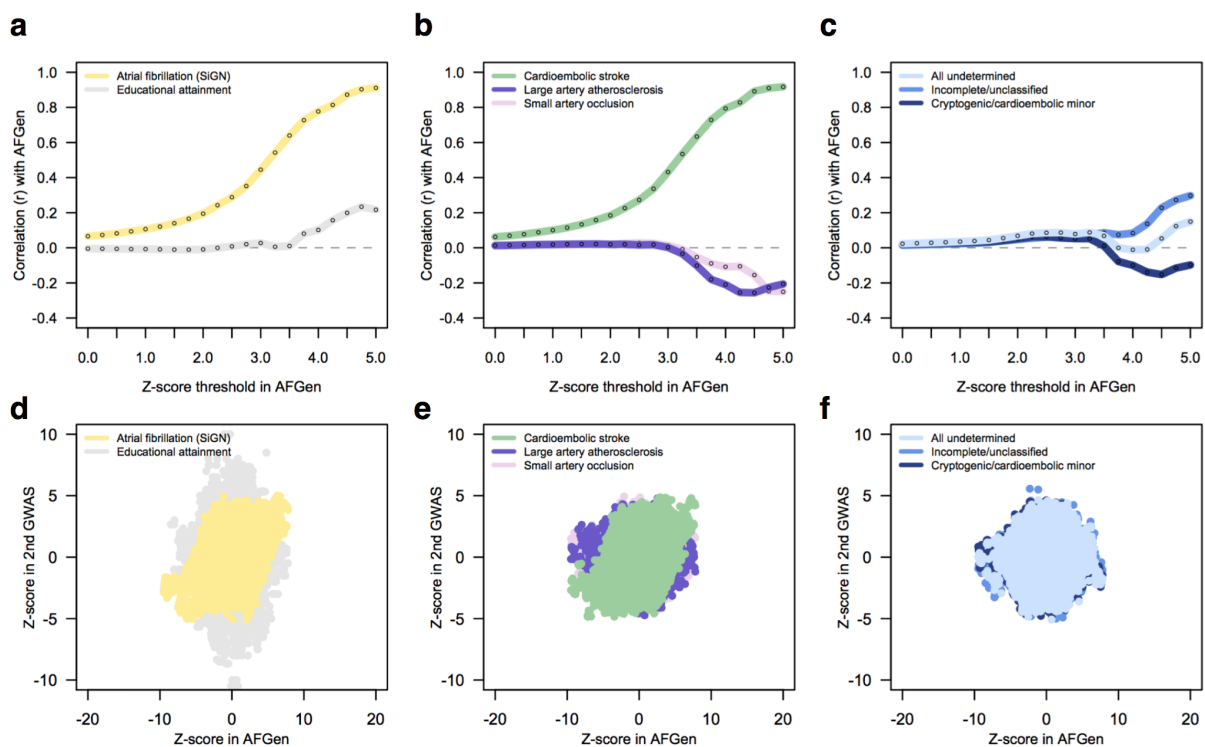
Supplementary Figure 5 | Genetic correlation and phenotypic correlation of atrial fibrillation and stroke subtypes in SiGN. (a) Using genome-wide SNP effects extracted from GWAS of atrial fibrillation, all stroke, and stroke subtypes, we calculated the Pearson's correlation (r) between each pair of available phenotypes (blue indicates strong negative correlation; orange indicates strong positive correlation). Here, we show all correlations. Correlations are indicated by circle size in the upper half of the square, and the exact correlation values are shown in the lower half of the square.

CE, cardioembolic stroke; LAA, large artery atherosclerosis; SAO, small artery occlusion; UNDETER, undetermined; INCUNC, incomplete/unclassified; CRYPTCE, cryptogenic and CE minor; Cryptoincl, cryptogenic; CCSc, CCS Causative subtyping system; CCSp, CCS Phenotypic subtyping system; TOAST, TOAST subtyping system.

a.
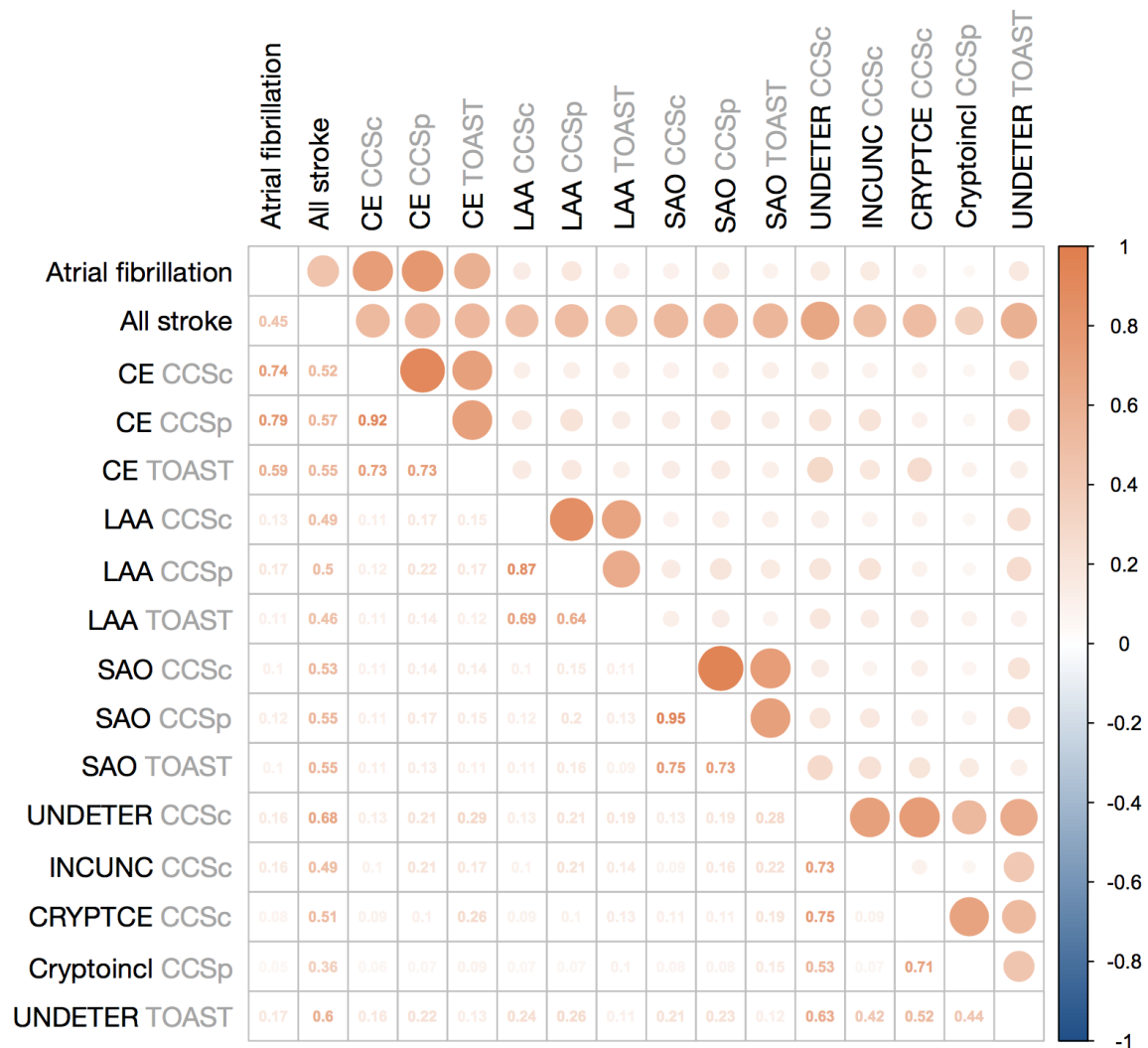
b. Same correlation calculations as in (a), but this time using the phenotypic data only (and looking in cases only, as all controls have the same phenotype). Note that the atrial fibrillation phenotypes and cardioembolic stroke phenotypes are highly correlated in the SiGN data (r = 0.83 between atrial fibrillation and cardioembolic stroke as determined by the CCS Causative subtype system).

CE, cardioembolic stroke; LAA, large artery atherosclerosis; SAO, small artery occlusion; UNDETER, undetermined; INCUNC, incomplete/unclassified; CRYPTCE, cryptogenic and CE minor; Cryptoincl, cryptogenic; CCSc, CCS Causative subtyping system; CCSp, CCS Phenotypic subtyping system; TOAST, TOAST subtyping system.
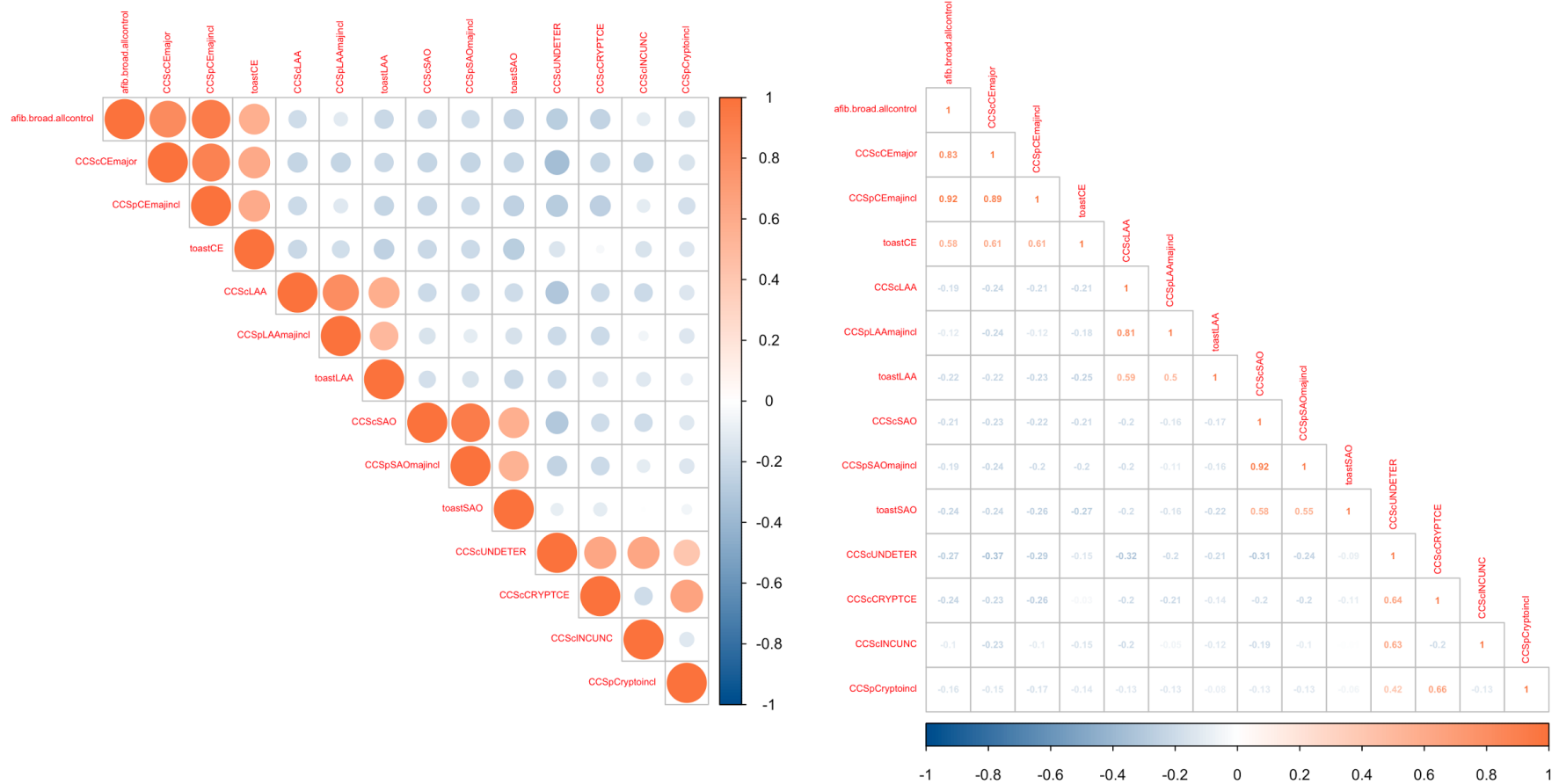
Supplementary Figure 6 | Association of atrial fibrillation genetic risk score in ischemic stroke subtypes. We constructed a genetic risk score (GRS) from atrial fibrillation-associated SNPs, and tested for association between the score and ischemic stroke subtypes using (a) all available controls (N = 28,026) and (b) controls without atrial fibrillation (N = 3,861). All subtypes from all available subtyping systems are shown here. The GRS strongly associated to cardioembolic stroke (subtypes highlighted in green font) in both sets of controls. In the atrial fibrillation-free set of controls (b) we observed nominal association of the GRS to incomplete/unclassified stroke. Undetermined subtypes are indicated in blue font.

CE, cardioembolic stroke; LAA, large artery atherosclerosis; SAO, small artery occlusion; UNDETER, undetermined; INCUNC, incomplete/unclassified; CRYPTCE, cryptogenic and CE minor; Cryptoincl, cryptogenic; CCSc, CCS Causative subtyping system; CCSp, CCS Phenotypic subtyping system; TOAST, TOAST subtyping system.
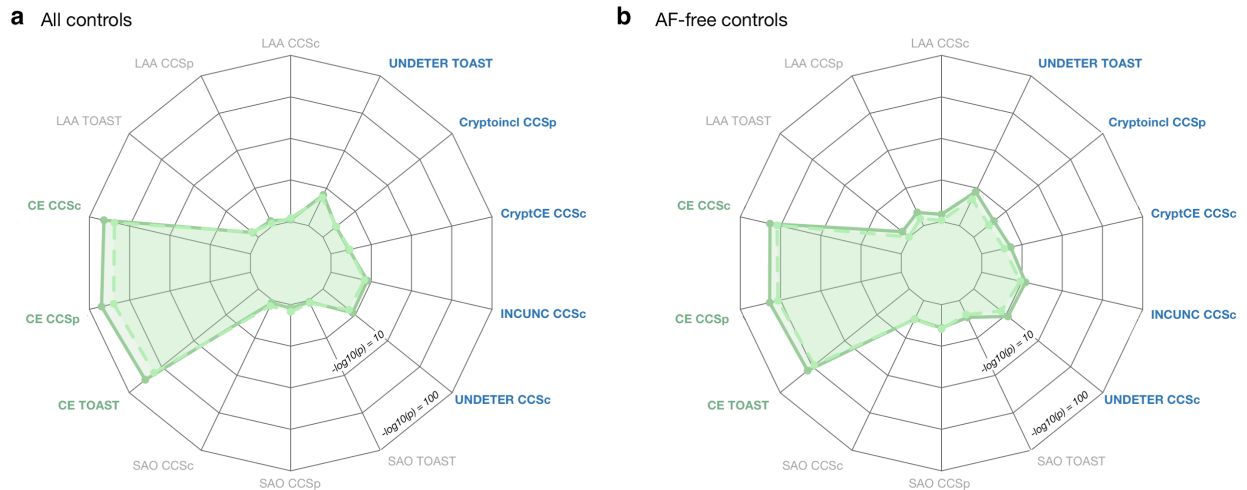
# Supplementary Methods

Relevant code for the analyses performed in this paper can be found here: https://github.com/saralpulit/Afib-Stroke-Overlap.

This repository primarily consists of:

Call to BOLT-LMM to run GWAS

Call to GCTA and BOLT-LMM to calculate heritability

Call to PLINK[3,4] to calculate the genetic risk score (GRS)

An R script for converting observed heritability in BOLT-LMM to the liability scale (see below)

A script in R to check association between the GRS and various phenotypes.

A call to PLINK[3,4] to calculate a GRM to run GCTA

Sample identifiers for those individuals analyzed in this paper

SNP identifiers and weights for those markers included in the construction of the genetic risk score

A complete README accompanies the GitHub repository.

Case and referent data

The full list of cohorts that are included in the SiGN genome-wide association study can be found in the Supplementary Material of "Loci associated with ischaemic stroke and its subtypes (SiGN): a genome-wide association study,"[5] which can be downloaded here: https://paperpile.com/shared/nvNXQf.

Referent datasets

Referent datasets downloaded from the Database of Genotypes and Phenotypes (dbGaP) are:

	dbGAP accession #
Genetics Resource with the Health and Retirement Study	phs000428.v2.p2
Whole Genome Association Study of Visceral Adiposity in the HABC study	phs000169.v1.p1

Case datasets

A large number of cases and a small number of controls (from Belgium and Poland) were genotyped at the initiation of the SiGN GWAS. These data have been uploaded to dbGaP and are available here:

> The National Institute of Neurological Disorders and Stroke (NINDS) Stroke Genetics Network (SiGN) (phs000615.v1.p1)

Sample and SNP identifiers used in these analyses

A file containing:

> the dbGaP sample identifiers
>
> the cohort the sample is drawn from
>
> the continental group the sample is in (as determined in the first SiGN GWAS effort[5])
>
> a list of quality control-passing SNPs used in the initial GWAS

Is available on this paper's GitHub repository.

Summary-level genome-wide association study data

The summary-level data from the original SiGN GWAS has been made publicly available through the Cerebrovascular Disease Knowledge Portal, which can be accessed here: http://www.cerebrovascularportal.org/

These summary-level results are available for cardioembolic stroke (CE), large artery atherosclerosis (LAA), small artery occlusion (SAO), and undetermined (UNDETER) stroke, for three different subtyping systems (TOAST, CCS Causative, CCS Phenotypic).

The summary-level results for the atrial fibrillation genome-wide association studies (performed in broadly-defined or strictly-defined cases versus all controls) are available here:

Broadly-defined atrial fibrillation cases vs. all referents:
https://doi.org/10.5281/zenodo.1035871

Strictly-defined atrial fibrillation cases vs. all referents:
https://doi.org/10.5281/zenodo.1035873

SNP-based heritability calculations in GCTA and BOLT-LMM

A description of heritability calculations is available in the Materials and Methods section of the primary calculation. Here, we provide additional analytic details. Heritability estimates were performed using GCTA[2] and BOLT-LMM[6] using BOLT-REML assuming a trait prevalence of 1%. The genetic relationship matrix (GRM, referred to by the --bfile and 'modelSNPs' option in BOLT-LMM) were selected four ways:

(1) Genotyped SNPs only (minor allele frequency > 1%)
115,553 SNPs total

(2) Genotyped SNPs, pruned at a linkage disequilibrium threshold (r2 threshold) of 0.2, and removing the MHC, *LCT* locus, and two chromosomal inversions.
60,432 SNPs total

(3) Imputed SNPs (minor allele frequency > 1% and imputation info > 0.8) converted to best-guess genotypes.
1,128,985 SNPs total

(4) Imputed SNPs (minor allele frequency > 1% and imputation info > 0.8); pruned at a linkage disequilibrium threshold (r2 threshold) of 0.2; removing the MHC, *LCT* locus, and two chromosomal inversions; and converted to best-guess genotypes.
250,209 SNPs total

As calculating GRMs in GCTA can be extremely computationally intensive, we calculated the GRMs using PLINK 1.9 and then used those GRMs to estimate heritability. A script that shows how to do this is included in the GitHub repository noted above.

The genomic locations (hg19) for excluded markers are as follows:

The lactase (*LCT*) locus
Chromosome 2, positions 129,883,530 - 140,283,530

The major histocompatibility complex (MHC)
Chromosome 6, positions 24,092,021 - 38,892,022

Inversion 1
Chromosome 8, positions 6,612,592 - 13,455,629

Inversion 2
Chromosome 17, positions 40,546,474 - 44,644,684

All non-autosomal SNPs

BOLT-LMM produces heritability estimates on the observed scale. To convert to the liability scale (i.e., the scale on which GCTA produces heritability estimates) we performed a conversion in R. Running the conversion requires knowing the trait prevalence, total cases analyzed, total controls analyzed, and the heritability on the observed scale. This code snippet is available in the accompanying GitHub repository for this paper.

Appendix I

Members of the Atrial Fibrillation Genetics (AFGen) Consortium

Please note that the AFGen Consortium participants evolve over time. Further information on the AFGen Consortium can be found at www.afgen.org.

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