

University of Groningen

Genetic basis of cardiovascular diseases

Roselli, Anna Carolina

DOI:

[10.33612/diss.827914096](https://doi.org/10.33612/diss.827914096)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Roselli, A. C. (2023). *Genetic basis of cardiovascular diseases*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen. <https://doi.org/10.33612/diss.827914096>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

SUPPLEMENTARY TEXT AND TABLES

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

INDEX

1. Supplementary tables

Supplementary Table 1. Baseline characteristics for the GWAS meta-analysis

Supplementary Table 2. Baseline characteristics for the ExWAS meta-analysis

Supplementary Table 3. Detailed description of the genes at novel atrial fibrillation loci

Supplementary Table 4. Results from Asian ancestry SKAT gene based test

Supplementary Table 5. Single variant association results for the variants that were analyzed in the two significant gene-based tests for *SH3PDX2A* in the Asian ancestry group

Supplementary Table 6. Results from ancestry-specific GWAS meta-analyses

Supplementary Table 7. Results from European and Asian ancestry ExWAS meta-analyses

Supplementary Table 8. Results from European incident atrial fibrillation GWAS meta-analysis

Supplementary Table 9. Results from European prevalent atrial fibrillation GWAS meta-analysis

Supplementary Table 10. Comparison of results for common variant loci between the AFGen Consortium combined ancestry analysis and the Biobank Japan study

Supplementary Table 11. Comparison of results for common variant loci between the AFGen Consortium combined ancestry analysis and the UK Biobank study.

Supplementary Table 12. Approximate and joint conditional analysis in European ancestry GWAS meta-analysis identify 20 independent genetic loci associated with atrial fibrillation

Supplementary Table 13. Overlap with atrial fibrillation risk factor GWAS loci

Supplementary Table 14. Association between novel atrial fibrillation loci and stroke subtypes in the Neuro-CHARGE Stroke Consortium

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Supplementary Table 15. Association between novel atrial fibrillation loci and stroke subtypes in the Metastroke Consortium

Supplementary Table 16. GO terms enriched in atrial fibrillation associated loci compared to GWAS catalog loci and to 1000 genomes matched loci

Supplementary Table 17. Summary of top eQTLs within atrial fibrillation associated loci

Supplementary Table 18. *In silico* eQTL analysis in GTEx database

Supplementary Table 19. eQTL analysis of in CCAF human atrial tissue samples

Supplementary Table 20. *In silico* functional evaluation of novel and replicated loci from GWAS and ExWAS combined ancestry analysis

Supplementary Table 21. Per study overlap of samples between GWAS and ExWAS analyses

Supplementary Table 22. GWAS information per study

Supplementary Table 23. General principles for quality control and filtering

Supplementary Table 24. ExWAS information per study

Supplementary Table 25. Baseline characteristics of African American ancestry replication studies

Supplementary Table 26. Results from replication in African American ancestry studies

Supplementary Table 27. Results from DEPICT pathway analysis of GWAS meta-analysis results

Supplementary Table 28. Top 5 enriched canonical pathways from Ingenuity Pathway Analysis of GWAS meta-analysis results

Supplementary Table 29. Enriched diseases or functions annotation from Ingenuity canonical pathway analysis of GWAS meta-analysis results

2. Supplementary Note

Detailed description of participating studies

Members of the AFGen Consortium, Neurology working group of the CHARGE Consortium, and METASTROKE Consortium

Ancestry-specific GWAS meta-analyses

GWAS meta-analyses of incident and prevalent atrial fibrillation in Europeans

Replication of genetic variants specific to African American ancestry GWAS meta-analysis

Pathway analysis

1. DEPICT

2. IPA

Acknowledgments

3. Supplementary References

1. SUPPLEMENTARY TABLES

Supplementary Table 1. Baseline characteristics for the GWAS meta-analysis

Race	Study name	Status/study	Total (n)	AF (n)	Males (%)	Age at DNA collection (mean±SD)	Age at DNA collection (range)	Age at AF onset (mean± SD)	HTN n (%)	BMI kg/m ² (mean±SD)	DM n (%)	MI n (%)	HF n (%)	
EUR														
								Prevalent						
AFLMU/	Cases	448	—	303 (68)	51±8	29-65	—	182 (41)	28±5	35 (8)	4 (1)	8 (2)		
KORA	Referents	438	—	221 (50)	56±7	45-69	—	198 (45)	28±4	18 (4)	0	3 (1)		
AGES	Cases	199	—	128 (64)	78±5	68-95	—	184 (92)	27±5	34 (17)	51 (26)	47 (24)		
	Referents	2989	—	1213 (41)	76±5	66-95	—	2387 (80)	—	332 (11)	346 (12)	50 (2)		
Beat-AF	Cases	1520	—	1090 (72)	68±12	19-94	61±13	1151 (76)	27±5	195 (13)	298 (20)	215 (14)		
	Referents	1520	—	705 (46)	36±5	23-44	—	212 (14)	25±4	7 (1)	0	0 (0)		
BioMe	Cases	291	—	200 (69)	75±9	56-89	—	263 (90)	28±5	47 (18)	21 (7)	122 (42)		
	Referents	860	—	474 (55)	70±9	37-89	—	614 (71)	27±6	164 (20)	29 (3)	98 (11)		
BioVU	Cases	428	—	245 (57)	72±12	24-98	—	356 (83)	29±6	117 (27)	17 (4)	—		
	Referents	9757	—	4911 (50)	62±17	18-100	—	6458 (66)	29±8	2018 (21)	313 (3)	—		
CCAF	Cases	606	—	460 (76)	59±11	20-85	52±12	331 (55)	30±6	59 (10)	0	0		
	Referents	2930	—	1109 (38)	29±22	0-87	—	—	—	—	—	—		
COROGENE	Cases	248	—	161 (65)	74±8	44-91	—	128 (52)	28±5	69 (28)	132 (53)	91 (37)		
	Referents	1978	—	1373 (69)	65±12	24-100	—	1042 (53)	28±5	388 (20)	578 (29)	482 (24)		
FHS	Cases	270	—	160 (60)	77±10	45-97	71±11	191 (71)	27±5	43 (16)	66 (24)	59 (22)		
	Referents	4134	—	1798 (44)	65±13	31-101	—	2025 (49)	28±5	327 (8)	229 (6)	53 (1)		
GS_SFHS	Cases	203	—	79 (39)	67±11	39-99	—	85 (42)	28±5	23 (11)	24 (12)	—		
	Referents	6651	—	3974 (60)	54±12	18-98	—	1134 (17)	27±5	290 (4)	391 (5)	—		
LURIC	Cases	368	—	262 (71)	66±9	32-88	—	278 (74)	28±4	167 (46)	117 (32)	112 (30)		
	Referents	2666	—	1861 (70)	62±11	17-92	—	1930 (72)	27±4	1050 (39)	1146 (43)	472 (18)		
MDCS	Cases	119	—	84 (71)	64±6	48-73	58±8	101 (85)	28±4	8 (7)	22 (18)	12 (10)		
	Referents	5758	—	2485 (43)	58±6	45-73	—	3775 (66)	26±4	276 (5)	167 (3)	16 (0.3)		
MGH AF study	Cases	366	—	295 (81)	53±101	21-77	46±12	85.8 (23)	28±5	12 (3)	4 (1)	10 (3)		
	Referents	911	—	485 (53)	48±9	18-83	—	—	—	—	—	—		
MGH CAMP	Cases	665	—	476 (72)	61±10	27-79	—	41 (6)	—	176 (26)	161 (24)	232 (35)		
	Referents	2128	—	1197 (56)	60±12	30-81	—	66 (3)	—	542 (25)	359 (17)	318 (15)		
SHIP	Cases	106	—	67 (63)	65±11	21-80	—	58 (55)	30±5	24 (23)	14 (13)	29 (27)		
	Referents	1815	—	859 (47)	50±15	20-80	—	437 (24)	27±5	192 (11)	54 (3)	158 (9)		
WTCCC2	Cases	330	—	168 (51)	70±12	45-92	70±12	197 (60)	—	—	—	—		
	Referents	797	—	410 (51)	63±11	51-83	—	—	—	—	—	—		
								Incident						
AGES	Cohort	2694	586	303 (52)	78±5	67-95	83±6	510 (87)	27±4	83 (14)	102 (17)	41 (7)		
ARIC	Cohort	8880	1420	4457 (47)	54±6	44-66	71±8	2547 (27)	27±5	818 (9)	390 (4)	360 (4)		
CHS	Cohort	3201	1011	1240 (39)	72±5	65-98	82±6	1679 (53)	26±4	377 (12)	0	0		
FHS	Cohort	4134	610	1798 (44)	65±13	31-101	78±11	2025 (49)	28±5	327 (8)	229 (6)	53 (1)		
MDCS	Cohort	5758	1113	2485 (43)	58±6	45-73	73±7	3775 (66)	26±4	276 (5)	167 (3)	16 (0.3)		
MESA	Cohort	2527	155	1206 (48)	63±10	44-84	76±8	975 (39)	28±5	151 (6)	62 (3)	52 (2)		
PIVUS	Cohort	949	154	474 (50)	70±0.2	70-71	—	650 (69)	27±4	123 (13)	65 (7)	32 (3)		
PREVEND	Cohort	3520	113	1811 (51)	50±12	28-75	68±8	974 (28)	26±4	133 (4)	86 (2)	6 (0.2)		
PROSPER	Cohort	5244	505	2524 (48)	75±3	69-83	78±3	3257 (62)	27±4	544 (10)	708 (14)	0		
TWINGENE	Cohort	6813	403	3239 (48)	65±8	47-94	69±10	3585 (53)	26±4	664 (10)	287 (4)	78 (1)		
ULSAM	Cohort	1120	294	1120 (100)	71±1	69-74	76±8	804 (72)	26±3	121 (11)	90 (8)	13 (1)		
WGHS	Cohort	20856	959	0 (0)	54±7	43-89	69±8	5024 (24)	26±5	503 (2)	—	—		
								Combined prevalent and incident						
ANGES	Prev + inc	779	226	496 (64)	64±10	36-88	69±10	479 (62)	28±4	232 (30)	272 (35)	100 (13)		
FINCAVAS	Prev + inc	2879	971	1737 (60)	59±11	19-85	64±12	2056 (71)	28±5	484 (17)	780 (27)	313 (11)		
RS1	Prev + inc	5947	1025	2410 (41)	69±9	55-99	78±8*	3433 (58)	26±4	674 (11)	419 (7)	210 (4)		
RS2	Prev + inc	1806	146	831 (46)	65±8	55-95	74±9*	1309 (73)	27±4	233 (13)	101 (6)	26 (1)		
RS3	Prev + inc	3030	121	1321 (44)	57±7	46-97	63±10*	1479 (49)	28±5	234 (8)	79 (3)	12 (0.4)		
AA														
								Prevalent						
BioMe	Cases	174	—	67 (39)	65±13	30-89	—	166 (95)	31±9	73 (50)	18 (10)	96 (55)		
	Referents	2132	—	723 (34)	56±14	22-89	—	1591 (75)	31±8	650 (33)	70 (3)	294 (14)		
								Incident						
ARIC	Cohort	2768	278	1068 (37)	53±6	44-66	70±7	1606 (56)	30±6	547 (19)	110 (4)	189 (7)		
CHS	Cohort	801	189	296 (37)	73±6	65-93	82±7	475 (59)	29±6	198 (25)	68 (9)	50 (6)		
AS														
								Prevalent						
Biobank Japan	Cases	837	—	572 (68)	68±10	25-94	—	—	24±4	394 (47)	70 (8)	219 (26)		
	Referents	3293	—	1810 (55)	52±16	3-96	—	—	22±4	220 (9)	37 (2)	18 (1)		
HISP	BioMe	277	—	136 (49)	70±12	31-89	—	268 (97)	29±6	129 (51)	37 (13)	160 (58)		
	Referents	3081	—	1114 (36)	58±15	20-89	—	2214 (72)	30±7	1035 (37)	140 (5)	372 (12)		
BRAZ	SPHFC	Cases	197	—	131 (63)	60±12	24-84	—	130 (66)	29±6	51 (26)	51 (26)	197 (100)	
	Referents	758	—	478 (67)	56±13	18-93	—	473 (62)	27±6	214 (28)	222 (29)	758 (100)		

Abbreviations: AF, atrial fibrillation; AA, African American; AS, Asian; BMI, body mass index; BRAZ, Brazilian; DM, diabetes mellitus; EUR, European ancestry; HF, heart failure; HISP, Hispanic; HTN, hypertension; MI, myocardial infarction; SPHFC, São Paulo Heart Failure Cohort. *Incident cases only.

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Supplementary Table 2. Baseline characteristics for the ExWAS meta-analysis

Race	Study name	Status /study	Total (n)	Males (%)	Age at DNA collection (mean±SD)	Age at DNA collection (range)	Age of AF onset (mean±SD)	HTN n (%)	BMI kg/m ² (mean±SD)	DM n (%)	MI n (%)	HF n (%)
EUR	AFLMU/KORA/MGH	Cases_all	2347	1760 (75)	57±11	17-93	55±12	1058 (45)	-	-	-	-
		Cases_AFNET	1645	1219 (74)	58±10	17-93	50±13	777 (47)	28±5	171 (7)	188 (13)	-
		Cases_MGH	702	541 (77)	56±12	18-86	56±10	281 (40)	29±6	35 (5)	25 (4)	43 (6)
		Referents	2844	1368 (48)	49±13	25-74	NA	993 (35)	27±5	81 (3)	52 (2)	87 (3)
	AGES	Cases incident	354	180 (51)	78±6	67-95	82±6	307 (87)	28±4	45 (13)	54 (15)	13 (4)
		Cases prevalent	280	165 (59)	78±5	67-95	-	256 (91)	27±5	44 (16)	61 (22)	28 (10)
		Referents	2341	1090 (41)	77±6	66-99	-	2142 (80)	27±5	44 (16)	304 (11)	41 (2)
	ARIC	Cases	1452	837 (58)	57±5	45-65	70±7	602 (41)	28±5	204 (14)	129 (9)	115 (8)
		Referents	9215	1786 (45)	54±6	44-66	-	983 (25)	27±5	323 (8)	131 (3)	114 (3)
	BEAT-AF	Cases	1532	1098 (68)	68±12	19-94	61±13	1161 (76)	27±5	198 (13)	216 (14)	299 (20)
		Referents	1532	711 (46)	35±5	23-44	-	213 (14)	25±4	7 (1)	0	0
	BioMe	Cases	371	265 (71)	74±9	49-89	-	339 (91)	28±6	72 (22)	39 (11)	172 (46)
		Referents	1178	710 (60)	68±10	32-89	-	862 (73)	28±6	244 (22)	57 (5)	144 (12)
	BioVU	Cases	991	454 (46)	76±12	23-99	-	809 (82)	28±7	183 (19)	66 (7)	-
		Referents	21,309	11,498 (54)	64±17	16-99	-	12,711 (60)	28±7	3198 (15)	816 (4)	-
	CHS	Cases incident	1377	649 (47)	73±5	65-95	82±6	831 (60)	26±4	295 (21)	167 (12)	68 (5)
		Cases prevalent	124	74 (60)	76±6	65-94	75±6	74 (60)	26±5	29 (23)	18 (15)	32 (26)
		Referents	2631	1094 (42)	72±5	65-100	-	1404 (53)	26±4	541 (21)	217 (8)	77 (3)
	FHS	Cases incident	376	184 (49)	73±11	43-100	79±10	162 (43)	28±6	58 (15)	31 (8)	5 (1)
		Cases prevalent	161	105 (65)	76±10	50-96	70±11	52 (33)	28±5	32 (20)	25 (16)	9 (6)
		Referents	1767	719 (41)	64±12	32-97	-	488 (28)	28±5	173 (10)	57 (3)	4 (0.2)
	GS_SFHS	Cases	203	79 (39)	67±11	39-99	-	85 (42)	28±5	23 (11)	24 (12)	-
		Referents	6651	3974 (60)	54±12	18-98	-	1134 (17)	27±5	290 (4)	391 (5)	-
	MESA	Cases	136	1206 (48)	63±10	44-84	76±8	975 (39)	28±5	151 (6)	62 (3)	52 (2)
		Referents	2,362	-	-	-	-	-	-	-	-	-
	MGH CAMP	Cases	668	479 (72)	61±10	27-79	-	41 (6)	-	178 (27)	162 (24)	233 (35)
		Referents	2138	1204 (56)	60±12	30-81	-	66 (3)	-	547 (26)	360 (17)	320 (15)
	RS I	Cases incident	346	170 (49)	72±8	55-93	-	226 (65)	27±4	50 (15)	26 (8)	14 (4)
		Cases prevalent	168	85 (51)	76±8	56-98	-	111(66)	26±3	28 (19)	34 (23)	-
		Referents	2370	1097 (46)	69±8	55-99	-	1259 (53)	26±4	222 (9)	143 (6)	56 (2)
	SHIP	Cases	96	63 (66)	64±12	21-80	-	72 (75)	30±5	21 (22)	14 (15)	-
		Referents	1749	841 (48)	50±15	20-80	-	901 (52)	27±5	175 (10)	53 (3)	-
		Cases - Trend	52	42 (81)	69±11	24-81	-	36 (72)	31±6	19 (37)	4 (8)	-
		Referents - Trend	3385	1636 (48)	52±15	20-82	-	1594 (47)	28±5	401 (12)	86 (3)	-
	WGHS	Cases incident	959	0	55±7	49-59	73±7	4812 (24)	25±7	485 (2)	0	0
		Referents	19307	0	-	-	-	-	-	-	-	-
	WHI_OS*	Cases prevalent	786	0	66±7	50-81	73±6	2081 (34)	27±6	301 (5)	237 (4)	115 (2)
		Cases incident	587	0	-	-	-	-	-	-	-	-
		Referents	4804	0	-	-	-	-	-	-	-	-
	WHI_CT**	Cases	119	0	-	-	-	-	-	-	-	-
		Referents	10,601	0	-	-	-	-	-	-	-	-
AA	ARIC	Cases	330	142 (43)	56±6	45-66	70±7	231 (70)	31±7	107 (32)	20 (6)	37 (11)
		Referents	3373	382 (38)	54±6	44-66	-	543 (54)	30±6	187 (19)	41 (4)	59 (6)
	BioMe	Cases	253	109 (43)	66±13	30-89	-	244 (96)	31±9	113 (53)	30 (12)	159 (63)
		Referents	2713	927 (34)	57±14	22-89	-	2134 (79)	31±8	949 (39)	107 (4)	435 (16)
	WHI_OS*	Cases prevalent	54	0	67±6	50-79	71±6	502 (43)	29±6	135 (12)	31 (3)	23 (2)
		Cases incident	44	0	-	-	-	-	-	-	-	-
		Referents	1204	0	-	-	-	-	-	-	-	-
AS	Biobank Japan	Cases	8180	5713 (70)	68±10	15-99	68±10	-	24±4	1798 (22)	699 (9)	2028 (25)
		Referents	28,612	11,223 (39)	56±10	20-81	-	-	-	1025 (5)	457 (2)	19 (0.1)

Abbreviations: AF, atrial fibrillation; AA, African American; AS, Asian; BMI, body mass index; DM, diabetes mellitus; EUR, European ancestry; HF, heart failure; HTN, hypertension; MI, myocardial infarction. *Observational study. **Clinical trial.

Supplementary Table 3. Detailed description of the genes at novel atrial fibrillation loci

Chromosomal location, Sentinel variant, Gene(s): Description of the genes at the locus.
GWAS loci
1q24, rs72700118, METTL11B/KIFAP3: The most significant variant at 1q24 lies downstream of the closest gene, <i>METTL11B</i> , which encodes an N-terminal mono-methyltransferase that regulates DNA-protein interactions. ³ It is an important cell cycle regulator and mediator of DNA repair mechanisms since <i>METTL11B</i> knockout mice either die shortly after birth or display various developmental defects. ⁴ Interestingly, it also has been shown that <i>METTL11B</i> might act as a tumor suppressor protein in breast cancer. ⁵ <i>METTL11B</i> is highly expressed in right atrial and left ventricular tissue in GTEx. Analyses revealed that <i>METTL11B</i> may potentially interact with the atrial specific myosin light chain gene (<i>MYL4</i>) that has been linked to atrial fibrillation. ^{6,7}
The locus also includes the gene <i>KIFAP3</i> , for which there also was a significant eQTL in the CCAF human atrial samples (Supplementary Table S17 and S19). <i>KIFAP3</i> encodes the kinesin associated protein 3, which regulates small G proteins by stimulating GDP/GTP exchange reactions or inhibiting their membrane interactions. ⁸ The gene is expressed in right atrial and left ventricular human tissue samples in the GTEx database. It is thought that this protein serves as a linker between human chromosome-associated polypeptide (HCAP) and KIF3A/B, a kinesin superfamily protein in the nucleus, and that this motor complex mediates binding to motor proteins enabling mainly anterograde transport of vesicles along microtubules. ^{9,10} <i>KIFAP3</i> variants have previously been associated with increased survival in sporadic amyotrophic lateral sclerosis and a combined phenotype of obesity and endometriosis in GWAS. ^{11,12} Reduced expression of <i>KIFAP3</i> has been demonstrated in clear cell renal carcinomas and was correlated with tumor aggressiveness and poorer patient outcomes, ¹³ whereas overexpression of the gene has been shown in breast cancer tumors. ¹⁴ In addition, <i>KIFAP3</i> has been shown to be involved in control of female puberty onset. ¹⁵ No relation to cardiac phenotypes have been noted for <i>KIFAP3</i> so far.
2p13, rs3771537, ANXA4/GMCL1: At 2p13, the most significant variant was intronic to <i>ANXA4</i> , whereas there were significant eQTLs for <i>ANXA4</i> , <i>GMCL1</i> , <i>PCYOX1</i> , and <i>SNRNP27</i> in GTEx left ventricle and skeletal muscle tissue (Supplementary Table S17-S18). <i>ANXA4</i> encodes Annexin 4, which is a Ca ²⁺ and phospholipid binding protein that modulates membrane permeability, growth, apoptosis. ¹⁶ It has been demonstrated to be overexpressed in various cancers like lung cancer, colorectal cancer or prostate cancer where it enhances tumor invasion and chemotherapy resistance. ¹⁷ It has further been shown that <i>ANXA4</i> is involved in β-adrenergic signaling since <i>Anxa4</i> ^{-/-} mice show increased cellular cAMP levels and enhanced left ventricle contraction force upon adrenergic stimulation, whereas calcium stimulation in the left atrium lead to increased contraction force relative to wildtype mice. ¹⁸ Moreover, annexin 4 has been shown to bind to adenylyl cyclase type 5; thus, it has been suggested that annexin 4 directly modulates the β-adrenoceptor cAMP-dependent signal transduction pathway by inhibiting adenylyl cyclase 5. ¹⁸ In line with this hypothesis, <i>ANXA4</i> has been shown to be upregulated in human failing hearts. ¹⁹
<i>GMCL1</i> , which encodes Germ Cell-Less protein 1, is predominantly expressed in the testis, where it is

involved in spermatogenesis.^{20,21} It has been demonstrated to regulate chromatin in germ cells by interacting with GAGE12I²² and might also have a role in oncogenesis since it is expressed in various cancers like B cell lymphoma.²³ A direct link to cardiac physiology or disease; however, is currently missing.

2p14, rs2540949, CEP68: The most significant variant at 2p14 was intronic to *CEP68*, which encodes the centrosomal protein 68 that is important for the cell cycle by regulating centrosome cohesion.²⁴ There were significant eQTLs for *CEP68* in both the CCAF human atrial samples (**Supplementary Table S17 and S19**) and GTEx atrial, left ventricle, and skeletal muscle tissue (**Supplementary Table S17-S18**). At the onset of mitosis *CEP68* dissociates from the centrosomes allowing the centrosomes to separate.²⁵ Variants in *CEP68* has been associated with aspirin-induced asthma²⁶ and acute urticaria/angioedema induced by non-steroidal anti-inflammatory drugs.²⁷

2p31, rs2288327, TTN/TTN-AS1: At 2q31 we identified six significant coding variants in the A-band and M-line of titin, which all were predicted to be benign by PolyPhen and SIFT. The *TTN* gene spans 363 exons and the encoded protein stretches through half the length of a sarcomere.²⁸ Titin ensures sarcomere integrity and elasticity, and binds actin and myosin, which are crucial players in the contractile machinery in striated muscle.^{29,30} Truncating mutations in titin have been shown to be the most important cause of dilated cardiomyopathy;³¹⁻³⁵ however, the gene displays considerable variation, making interpretation of mutational findings challenging.³⁶ Titin has been associated with the QT-interval in previous GWAS,^{37,38} but the lead variant in our study (rs2288327) was not in LD with the QT-associated *TTN* variant (rs7561149, $r^2=0.004$).

5q22, rs337711, KCNN2: The variant at 5q22 is located in an intron of the gene *KCNN2* that encodes the small-conductance calcium-activated potassium channel, subfamily N, member 2 or SK2 channel. There was a significant eQTL for *KCNN2* itself in the CCAF human atrial tissue samples (**Supplementary Table S19**). This ion channel is predominantly expressed in the atria³⁹ and is involved in electrical remodeling resulting in atrial fibrillation.^{39,40} In chronic atrial fibrillation, SK2 expression is reduced leading to significant changes in action potential duration (APD), a finding that has been confirmed in knockout mice. Furthermore, SK2 channels have been demonstrated to be involved in ventricular repolarization and also development of ventricular arrhythmias, especially in failing hearts where SK2 channels are upregulated both in patients and animal models.⁴¹⁻⁴⁵ Functional analysis revealed that the activation and modulation of SK2 channels is dependent on Ryr2-mediated calcium release⁴⁶ and that amiodarone can inhibit SK2 channels in a time- and voltage-independent but calcium-dependent mechanism, partly explaining its antiarrhythmic effects in failing hearts.⁴⁷ Additionally, genome-wide association studies have identified *KCNN2* as a susceptibility gene for coronary aneurysms in Kawasaki disease.^{48,49} SK2 channels have also been shown to be involved in ischemia-induced neuronal cell death,^{50,51} neuronal plasticity and learning,⁵²⁻⁵⁵ drug addiction,^{56,57} regulation of sleep duration,⁵⁸ and maintenance of the ionic milieu of the inner ear fluid.⁵⁹ They may be therapeutic targets for Parkinson's disease, since activation of SK2 channels provides protective effects in human dopaminergic neurons.⁶⁰

5q31, rs2967791, PKD2L2/KLHL3/WNT8A/FAM13B: *PKD2L2* encodes the polycystic kidney disease 2-like 2 protein that belongs to the transient receptor potential (TRP) superfamily and is highly expressed in human brain, kidney, and testis.^{61,62} In rodents, it is also expressed in the heart and has been demonstrated to be involved in calcium homeostasis, proliferation, and apoptosis.⁶¹⁻⁶³

KLHL3 encodes the gene Kelch Like Family Member 3 that is part of the E3 ubiquitin ligase complex regulating the sodium/chloride cotransporter (NCC), the epithelial sodium channel (ENaC), and the renal outer medullary potassium channel (ROMC) in the kidney.^{64,65} It is an important regulator of the electrolyte homeostasis and therefore the blood pressure.^{66,67} Genetic variants of *KLHL3* have been described to cause familial hyperkaliemic hypertension.^{65,68,69}

WNT8A is a member of the WNT/beta catenin-signaling network that plays an essential role in development and carcinogenesis.⁷⁰ *WNT8A* has been demonstrated to regulate body axis extension⁷¹ and neuroectodermal posteriorization.⁷² *WNT8A* polymorphisms have been shown to be associated with Hirschsprung's disease and its expression is upregulated in stenotic colon segments in patients.⁷³ Interestingly, *in vitro* overexpression of *WNT8* results in impaired calcium handling⁷⁴ and might therefore also be involved in atrial fibrillation pathophysiology.

For the 5q31 locus, we identified an eQTL for the gene *FAM13B* in eQTL enrichment analysis (**Supplemental table S17**). *FAM13B* (syn. *C5ORF5*) consists of 23 exons spanning over 27 kb; the transcript is 5.47 kb and encodes a protein of 915 amino acids.⁷⁵ It contains a putative rhoGAP domain at the N-terminus and two bipartite nuclear localization signals and is predominantly expressed in brain and male reproductive tissue⁷⁶ (Human Protein Atlas available from www.proteinatlas.org). So far, *FAM13B* has not been reported in a cardiovascular context.

8p22, rs7508, ASAHI/PCM1: At 8p22, the lead atrial fibrillation risk variant was associated with decreased expression of *ASAHI* (rs7508; $P = 5.1 \times 10^{-3}$) in CCAF human atrial samples and increased expression of *PCM1* (rs7508; $P = 9.6 \times 10^{-14}$) in both the CCAF samples (**Supplementary Table S17 and S19**) and GTEx left ventricle and skeletal muscle tissue (**Supplementary Table S17-S18**). *ASAHI* encodes the acid ceramidase 1 that is involved in lipid metabolism by degradation of ceramide into sphingosine and free fatty acids within lysosomes.^{77,78} Overexpression of ceramidase has been reported in several cancer cell types,⁷⁹⁻⁸¹ resulting in increased proliferation⁸² and invasiveness,^{83,84} predominantly in prostate cancer, which in turn has led to studies showing promising results of ceramidase inhibitors as new cancer therapeutics.^{85,86} Ceramidase has also been implicated in Farber's disease (lipogranulomatosis),^{87,88} spinal muscular atrophy with myoclonic epilepsy,⁸⁹ and Alzheimer's disease.⁹⁰ *ASAHI* is highly expressed in the heart.⁹¹ Accumulation of ceramide has been shown to result in oxidative stress, electron transport chain dysfunction, and cardiomyocyte apoptosis in rats.^{92,93}

PCM1 encoding pericentriolar material 1, has been demonstrated to be an integral component of centriolar satellites in ciliogenesis.⁹⁴ It has also been shown to be involved in neurogenesis,⁹⁵ the centrosomal actin network,⁹⁶ hematological neoplasms⁹⁷ and associated with schizophrenia.⁹⁸

10q24, rs35176054, SH3PXD2A: The variant at 10q24 is located intronic to the gene *SH3PXD2A* that encodes the SH3 and PX domain-containing protein 2A or Adapter protein TKS5 that plays an essential role in various malignancies. It interacts with Src tyrosine kinase to promote tumor growth and the formation of invadopodia resulting in degradation of extracellular matrix and invasion of cancer cells into surrounding tissue in breast, ovarian, colon, lung, prostate cancer, melanoma, and glioma.⁹⁹⁻¹⁰³ Its expression level has been demonstrated to be negatively correlated with tumor size and patient survival in ovarian cancer.^{104,105} However, it is also involved in normal embryonic development by regulating neural crest migration^{106,107} and in macrophage or microglia physiology.^{108,109}

11q24, rs75190942, KCNJ5: The genetic variant rs75190942 is located at 11q24 within the gene *KCNJ5*, that encodes the G protein-activated inward rectifier potassium channel 4 (Kir3.4/GIRK4). There was a significant eQTL for *KCNJ5* itself in CCAF human atrial tissue samples (**Supplementary Table S17 and S19**) and in GTEx left ventricle tissue (**Supplementary Table S17-S18**). GIRK4 is known to form heteromeres with Kir3.1/GIRK1/KCNJ3, constituting the $I_{K\text{ACh}}$ channel complex, which contributes to the regulation of the membrane potential in the sinoatrial node and atria – making it a therapeutic target for atrial fibrillation. This ion channel has been shown to regulate pacemaker activity and recovery of resting heart rate after sympathetic stimulation.¹¹⁰ GIRK4 inactivation can also rescue arrhythmias that are induced by genetic silencing of funny currents.¹¹¹ Furthermore, it determines inducibility, dynamics and termination of atrial fibrillation by regulating action potential duration.¹¹² Additionally, genetic polymorphisms in *KCNJ5* are associated with early-onset lone atrial fibrillation,¹¹³ whereas mutations in this gene have been shown to cause long QT syndrome.¹¹⁴ GIRK4 is also expressed in the ventricles and contributes to ventricular repolarization¹¹⁵ and has been shown to be significantly downregulated in patients with dilated cardiomyopathy.¹¹⁶ Furthermore, mutations in *KCNJ5* can cause Andersen-Tawil syndrome,¹¹⁷ primary aldosteronism¹¹⁸ and has been detected in adrenal tumors.¹¹⁹ Also, *KCNJ5* is associated with Tourette Syndrome and Attention-Deficit/Hyperactivity Disorder.¹²⁰

ExWAS loci

3p22, rs6800541, SCN10A: The variant rs6800541 is located intronic to *SCN10A*, the gene that encodes the sodium channel Nav1.8. It is highly expressed in primary sensory neurons and dorsal root ganglion neurons and has been linked to nociception, painful neuropathy, and multiple sclerosis.¹²¹ Recently, it has been shown that Nav1.8 is also expressed in the heart where it contributes to the late sodium current.^{122,123} Genome-wide association studies demonstrated genetic variants in *SCN10A* as risk loci for quantitative ECG traits like PR interval,^{124–128} and QRS duration,^{126,129,130} as well as for atrial fibrillation^{124,126,130,131} and Brugada Syndrome.¹³² Also, mutations in *SCN10A* has been shown to be responsible for a large fraction of cases of Brugada Syndrome.¹³³ Data suggest that *SCN10A* affects cardiac conduction either directly through cardiomyocytes, indirectly through intracardiac neurons, or by modulation of *SCN5A* expression.^{134,135}

12p12, rs11047543, SOX5: The most significant SNP at 12p12 is located downstream of the *SOX5* gene. *SOX5* is a transcription factor that has been shown to be involved in limb development,¹³⁶ chondrogenesis,¹³⁷ brain development,¹³⁸ and lung development.¹³⁹ Our current study confirmed previous genome-wide association studies that showed a significant association between *SOX5* and early-onset atrial fibrillation.^{124,140} Furthermore, *SOX5* has been demonstrated to be significantly associated with PR-interval,¹²⁴ left ventricular mass,¹⁴¹ resting heart rate,¹⁴² osteoporosis,¹⁴³ systemic sclerosis,¹⁴⁴ AIDS,¹⁴⁵ chronic obstructive pulmonary disease,¹³⁹ and non-obstructive azoospermia.¹⁴⁶ Additionally, it is involved in the development of lung cancer,¹⁴⁷ hepatocellular carcinoma,¹⁴⁸ follicular lymphoma,¹⁴⁹ and melanoma.¹⁶³

Locus identified in both GWAS and EWAS:

6q22, rs4946333 (GWAS), rs89107 (EWAS), SLC35F1/PLN: At 6q22 we identified a locus including the phospholamban gene (*PLN*), *SLC35F1*, and *CEP85L*. Phospholamban regulates cardiac contractility and relaxation through inhibiting the cardiac muscle sarcoplasmic reticulum calcium ATPase SERCA.¹⁶⁴ Mutations in this gene has been associated with hypertrophic^{165,166} and dilated cardiomyopathy.^{167,168}

SLC35F1 encodes a member of the solute carrier family 35. *SLC35F1* knockout mice display reduced levels of hemoglobin and lactate dehydrogenase but do not show any further phenotype. Previous GWAS have associated the locus surrounding *SLC35F1/PLN/CEP85L* with resting heart rate,^{6,15} QT-interval,^{12,14} and left ventricle internal diastolic diameter.¹¹ One of the variants associated with heart rate by den Hoed et al. also associated with atrial fibrillation in secondary analyses.⁶

Supplementary Table 4. Results from Asian ancestry SKAT gene based test

Gene	Chr	CMAF	N variants	P-value
<i>Filter: Variants predicted to be damaging</i>				
SH3PXD2A	10q24	0.4	6	4.77x10 ⁻¹¹
<i>Filter: Nonsynonymous and splice site variants</i>				
SH3PXD2A	10q24	0.4	11	4.21x10 ⁻¹¹

Chr, chromosome; CMAF, cumulative minor allele frequency per gene.

Supplementary Table 5. Single variant association results for the variants that were analyzed in the two significant gene-based tests for SH3PXD2A in the Asian ancestry group.

rsID	Risk/ref allele	Amino acid substitution**	RAF, %	OR	95% CI	P-value
rs149867987	A/G	p.His110Tyr	0.01	16.72	2.23-125.31	0.006
rs200938753*	G/A	p.Arg761Cys	99.89	1.45	0.74-2.84	0.27
rs202011870*	C/A	p.Leu396Arg	0.18	4.68	2.97-7.39	3.30E-11
rs201065560*	A/G	p.Arg1031Cys	0.02	2.03	0.55-7.47	0.29
rs74661743*	G/A	p.Arg1003Cys	99.93	1.02	0.42-2.47	0.97
rs79061932	G/A	p.Arg994Cys	99.99	1.13	0.07-18.44	0.93
rs201439736	C/T	p.Ala886Thr	99.97	1.44	0.46-4.52	0.54
rs201054626*	T/C	p.Arg302Gln	0.01	4.85	0.83-28.47	0.08
rs143819462	T/C	p.Arg269Gln	0.01	2.34	0.39-13.93	0.35
rs147297499	T/C	p.Asp231Asn	0.005	13.31	0.67-264.24	0.09
rs143409187*	T/C	p.Arg102Gln	0.007	2.85	0.15-55.03	0.49

The gene-based test was significant for the subset of nonsynonymous and splice site variants, which included all listed variants, and the subset of nonsynonymous possibly damaging variants, which included 6 of the listed variants (*). **NCBI Reference sequence accession and version number NP_055446.2. RAF, risk allele frequency; CI, confidence interval; OR, odds ratio.

Supplementary Table 6. Results from ancestry-specific GWAS meta-analyses

rsID	Chr	Gene	Location relative to gene	Risk/ref allele	RAF, %	OR	95% CI	P-value	
<i>15,993 cases, 113,719 referents</i>									
Novel associations									
rs10800507	1q24	<i>METTL11B/KIFAP3</i>	Intergenic	C/G	51	1.09	1.06-1.12	1.87x10 ⁻¹¹	
rs62133983	2p13	<i>ANXA4/GMCL1</i>	Intronic	G/T	52	1.09	1.06-1.12	1.36x10 ⁻¹⁰	
rs2723064	2p14	<i>CEP68</i>	Intergenic	T/C	61	1.09	1.06-1.12	1.88x10 ⁻¹⁰	
rs6864727	5q31	<i>PKD2L2/WNT8A/FAM13B</i>	Intronic	C/T	31	1.08	1.05-1.11	1.12x10 ⁻⁸	
rs281868	6q22	<i>SLC35F1/PLN</i>	Intronic	G/A	50	1.08	1.05-1.10	1.03x10 ⁻⁸	
rs7508	8p22	<i>ASAHI/PCM1</i>	3'UTR	A/G	73	1.10	1.06-1.13	6.34x10 ⁻¹⁰	
rs35176054	10q24	<i>SH3PXD2A</i>	Intronic	A/T	13	1.14	1.10-1.18	1.75x10 ⁻¹¹	
rs75190942	11q24	<i>KCNJ5</i>	Intronic	A/C	8	1.18	1.11-1.25	2.82x10 ⁻⁸	
rs2921421	15q21	<i>CGNL1</i>	Intergenic	G/C	3	1.72	1.42-2.09	3.29x10 ⁻⁸	
Previously known associations									
EUR	rs11264280	1q21	<i>KCNN3</i>	Intergenic	T/C	32	1.13	1.10-1.16	2.77x10 ⁻¹⁷
	rs651386	1q24	<i>PRRX1</i>	Intergenic	A/T	57	1.11	1.08-1.14	6.23x10 ⁻¹⁵
	rs2129977	4q25	<i>PITX2</i>	Intergenic	A/G	22	1.45	1.41-1.49	7.25x10 ⁻¹³⁶
	rs12664873	6q22	<i>GJA1</i>	Intergenic	T/G	69	1.08	1.05-1.12	1.80x10 ⁻⁸
	rs11773845	7q31	<i>CAV1/2</i>	Intronic	A/C	60	1.10	1.07-1.13	3.35x10 ⁻¹³
	rs7026071	9q22	<i>C9orf3</i>	Intronic	T/C	41	1.09	1.07-1.12	2.86x10 ⁻¹¹
	rs10824026	10q22	<i>SYNPO2L</i>	Intergenic	A/G	84	1.13	1.09-1.17	8.29x10 ⁻¹¹
	rs11598047	10q24	<i>NEURL1</i>	Intronic	G/A	17	1.18	1.14-1.22	3.16x10 ⁻²¹
	rs883079	12q24	<i>TBX5</i>	3'UTR	T/C	72	1.11	1.08-1.15	1.31x10 ⁻¹³
	rs7183206	15q24	<i>HCN4</i>	Intergenic	A/G	15	1.13	1.09-1.18	7.70x10 ⁻¹²
	rs2106261	16q22	<i>ZFHX3</i>	Intronic	T/C	18	1.19	1.15-1.23	4.01x10 ⁻²⁴
<i>641 cases, 4956 referents</i>									
AA	rs6843082	4q25	<i>PITX2</i>	Intergenic	G/A	30	1.40	1.24-1.58	4.31x10 ⁻⁸
	<i>837 cases, 2456 referents</i>								
Novel association									
AS	rs7138621	12q15	<i>CPSF6</i>	Intergenic	G/C	95	7.92	4.26-14.73	6.48x10 ⁻¹¹
	Previously known association								
rs2723334 4q25 <i>PITX2</i> Intergenic T/C 70 1.94 1.68-2.25 8.46x10 ⁻¹⁹									

The most significant variant at each genetic locus associated with atrial fibrillation is listed. Gene names in bold font indicate that the variant is located within the gene, whereas additional gene names indicate eQTL gene or gene strongly suspected to be causal due to the function of the encoded protein. For intergenic variants, the closest gene(s) are listed. Chr, chromosome; CI, confidence interval; OR, odds

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

ratio; EUR, European ancestry; AA, African American ancestry; AS, Asian ancestry; RAF, risk allele frequency.

Supplementary Table 7. Results from European and Asian ancestry ExWAS meta-analysis

rsID	Chr	Gene	Location relative to gene	Risk/ref allele	RAF, %	OR	95% CI	P-value	
<i>13,496 cases, 96,273 referents</i>									
Novel associations									
rs6800541	3p22	<i>SCN10A</i>	Intronic	T/C	60	1.08	1.05-1.12	8.75x10 ⁻⁷	
rs89107	6q22	<i>SLC35F1/PLN</i>	Intronic	G/A	50	1.09	1.06-1.13	2.71x10 ⁻⁷	
rs11047543	12p12	<i>SOX5</i>	Intergenic	G/A	85	1.13	1.08-1.18	4.65x10 ⁻⁷	
Previously known associations									
rs13376333	1q21	<i>KCNN3</i>	Intronic	T/C	31	1.14	1.10-1.17	1.58x10 ⁻¹³	
rs2200733	4q25	<i>PITX2</i>	Intergenic	T/C	12	1.60	1.52-1.67	9.95x10 ⁻⁹⁰	
rs3807989	7q31	<i>CAV1</i>	Intronic	G/A	59	1.09	1.06-1.13	2.93x10 ⁻⁸	
rs60632610	10q22	<i>SYNPO2L</i>	Exonic; nonsyn	C/T	85	1.13	1.08-1.18	2.53x10 ⁻⁸	
rs2106261	16q22	<i>ZFHX3</i>	Intronic	A/G	17	1.21	1.16-1.26	3.37x10 ⁻¹⁸	
<i>8180 cases, 28,612 referents</i>									
Novel associations									
AS	rs55952639	2p14	<i>CEP68</i>	Exonic; syn	T/C	76	1.13	1.07-1.18	1.29x10 ⁻⁶
	rs11047543	12p12	<i>SOX5</i>	Intergenic	G/A	88	1.18	1.10-1.26	1.16x10 ⁻⁶
Previously known associations									
rs17042171	4q25	<i>PITX2</i>	Intergenic	A/C	48	1.69	1.62-1.76	4.04x10 ⁻¹³⁷	

The most significant variant at each genetic locus associated with atrial fibrillation is listed. Gene names in bold font indicate that the variant is located within the gene, whereas additional gene names indicate eQTL gene or gene strongly suspected to be causal due to the function of the encoded protein. For intergenic variants the closest gene(s) are listed. Chr, chromosome; CI, confidence interval; OR, odds ratio; EUR, European ancestry; AA, African American ancestry; AS, Asian ancestry; nonsyn, nonsynonymous; syn, synonymous; RAF, risk allele frequency

Supplementary Table 8. Results from European incident atrial fibrillation GWAS meta-analysis

rsID	Chr	Gene	Location relative to gene	Risk/ref allele	RAF, %	OR	95% CI	P-value
rs11264280	1q21	<i>KCNN3</i>	Intergenic	T/C	32	1.12	1.08-1.16	3.57x10 ⁻⁹
rs6843082	4q25	<i>PITX2</i>	Intergenic	G/A	21	1.38	1.33-1.44	8.21x10 ⁻⁵⁷
rs7394190	10q22	<i>SYNPO2L</i>	Intergenic	G/A	84	1.15	1.09-1.21	3.09x10 ⁻⁸
rs60848348	10q24	<i>NEURL1</i>	Intronic	T/C	20	1.13	1.09-1.18	1.69x10 ⁻⁸
rs4499262	16q22	<i>ZFHX3</i>	Intronic	A/C	17	1.14	1.09-1.19	4.01x10 ⁻⁸

The most significant variant at each genetic locus associated with atrial fibrillation is listed. Gene names in bold font indicate that the variant is located within the gene. Chr, chromosome; CI, confidence interval; OR, odds ratio; RAF, risk allele frequency

Supplementary Table 9. Results from European prevalent atrial fibrillation GWAS meta-analysis

rsID	Chr	Gene	Location relative to gene	Risk/ref allele	RAF, %	OR	95% CI	P-value
Novel associations								
rs72700118	1q24	<i>METTL11B/KIFAP3</i>	Intergenic	A/C	11	1.24	1.17-1.31	9.93x10 ⁻¹³
rs6546550	2p13	<i>ANXA4/GMCL1</i>	Intronic	C/G	54	1.12	1.08-1.16	1.36x10 ⁻⁸
rs1454934	12p11	<i>PKP2</i>	Intronic	T/C	16	1.16	1.1-1.22	4.18x10 ⁻⁸
Previously known associations								
rs36004974	1q21	<i>KCNN3</i>	Intronic	G/A	32	1.14	1.1-1.19	4.36x10 ⁻¹⁰
rs577676	1q24	<i>PRRX1</i>	Intergenic	C/T	55	1.15	1.1-1.19	2.77x10 ⁻¹²
rs61303432	4q25	<i>PITX2</i>	Intergenic	T/C	14	1.71	1.62-1.8	6.66x10 ⁻⁹²
rs2109514	7q31	<i>CAV1/2</i>	Intergenic	A/G	51	1.15	1.11-1.19	6.73x10 ⁻¹³
rs11598047	10q24	<i>NEURL1</i>	Intronic	G/A	17	1.24	1.18-1.31	4.34x10 ⁻¹⁶
rs2106261	16q22	<i>ZFHX3</i>	Intronic	T/C	18	1.25	1.19-1.31	9.68x10 ⁻²⁰

The most significant variant at each genetic locus associated with atrial fibrillation is listed. Gene names in bold font indicate that the variant is located within the gene. Chr, chromosome; CI, confidence interval; OR, odds ratio; RAF, risk allele frequency

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Supplementary Table 10. Comparison of results for common variant loci between the AFGen Consortium combined ancestry analysis and the Biobank Japan study.

Ancestry	rsID	Chr	Gene(s)	Risk/ref allele	Discovery				Biobank Japan (8180 cases; 28,612 referents)															
					RAF, %	OR	95% CI	P-value	RAF, %	OR	95% CI	P-value												
GWAS*																								
Combined	Novel associations																							
	rs72700118	1q24	<i>METTL11B</i>	A/C	12	1.14	1.10-1.23	2.60×10^{-11}	No information (rare in East Asians)	32	1.06	1.01-1.11	1.39×10^{-2}											
	rs3771537	2p13	<i>ANXA4/GMCL1</i>	A/C	53	1.09	1.06-1.14	7.92×10^{-12}			68	1.16	1.11-1.21	2.93×10^{-10}										
	rs2540949	2p14	<i>CEP68</i>	A/T	61	1.08	1.06-1.13	2.93×10^{-10}			68	1.16	1.11-1.21	2.93×10^{-10}										
	rs2288327	2q31	<i>TTN/TTN-AS1</i>	G/A	20	1.09	1.06-1.14	2.05×10^{-8}			61	1.05	1.00-1.09	4.52×10^{-2}										
	rs337711	5q22	<i>KCNN2</i>	T/C	39	1.07	1.05-1.11	2.93×10^{-8}			14	1.16	1.10-1.23	4.97×10^{-7}										
	rs2967791	5q31	<i>3/WNT8A/FAM</i>	T/C	54	1.07	1.05-1.11	2.73×10^{-8}			89	1.05	0.98-1.13	1.68×10^{-1}										
	rs4946333	6q22	<i>SLC35F1/PLN</i>	G/A	50	1.08	1.05-1.12	1.89×10^{-9}			77	1.03	0.98-1.08	2.45×10^{-1}										
	rs7508	8p22	<i>ASAHI</i>	A/G	72	1.09	1.06-1.14	5.16×10^{-10}			55	1.05	1.01-1.10	1.67×10^{-2}										
	rs35176054	10q24	<i>SH3PXD2A</i>	A/T	13	1.14	1.10-1.22	8.63×10^{-12}			No information (monomorphic in Japanese)													
	rs75190942	11q24	<i>KCN5</i>	A/C	8	1.17	1.11-1.26	1.59×10^{-8}			5	1.06	0.94-1.20	3.12×10^{-1}										
	Previously known associations																							
Asian	rs11264280	1q21	<i>KCNN3</i>	T/C	31	1.12	1.09-1.21	6.41×10^{-17}	9	1.11	1.03-1.20	4.25×10^{-3}												
	rs520525	1q24	<i>PRRX1</i>	A/G	71	1.12	1.09-1.20	6.39×10^{-16}			64	1.1	1.06-1.16	1.28×10^{-5}										
	rs11718898	3p25	<i>CAND2</i>	C/T	65	1.08	1.05-1.11	4.68×10^{-8}			30	1.04	1.00-1.09	7.58×10^{-2}										
	rs6843082	4q25	<i>PITX2</i>	G/A	25	1.45	1.41-1.99	3.41×10^{-155}			68	1.84	1.75-1.94	9.85×10^{-127}										
	rs12664873	6q22	<i>GJA1</i>	T/G	70	1.08	1.05-1.12	1.19×10^{-8}			70	1.1	1.05-1.15	8.86×10^{-5}										
	rs1997572	7q31	<i>CAV1/2</i>	G/A	59	1.1	1.08-1.17	6.64×10^{-15}			67	1.18	1.13-1.24	6.83×10^{-13}										
	rs7026071	9q22	<i>C9orf3</i>	T/C	40	1.09	1.07-1.15	1.31×10^{-12}			28	1.05	1.00-1.10	4.21×10^{-2}										
	rs11598047	10q24	<i>NEURL1</i>	G/A	16	1.18	1.14-1.31	1.67×10^{-22}			9	1.41	1.32-1.51	6.17×10^{-24}										
	rs7915134	10q22	<i>SYNPO2L</i>	C/T	85	1.12	1.08-1.19	1.68×10^{-10}	83	1.07	1.01-1.13	1.84×10^{-2}												
	rs883079	12q24	<i>TBX5</i>	T/C	70	1.11	1.09-1.19	1.80×10^{-15}			42	1.18	1.13-1.24	5.45×10^{-15}										
	rs1152591	14q23	<i>SYNE2</i>	A/G	46	1.09	1.06-1.13	1.04×10^{-10}			36	1.08	1.04-1.13	4.09×10^{-4}										
	rs74022964	15q24	<i>HCN4</i>	T/C	17	1.12	1.08-1.19	2.37×10^{-11}			3	1.04	0.91-1.19	5.91×10^{-1}										
	rs2106261	16q22	<i>ZFHX3</i>	T/C	19	1.2	1.17-1.37	8.18×10^{-32}			31	1.33	1.27-1.39	9.63×10^{-36}										
Asian	Novel associations																							
	rs7138621	12q15	<i>CPSF6</i>	G/C	95	7.92	4.26-14.73	6.48×10^{-11}	94	1.02	0.93-1.11	7.13×10^{-1}												
	Previously known associations																							
	rs2723334	4q25	<i>PITX2</i>	T/C	70	1.94	1.68-2.25	8.46×10^{-19}			68	1.8	1.71-1.89	7.84×10^{-121}										
	ExWAS																							
	Novel associations																							
	rs6800541	3p22	<i>SCN10A</i>	T/C	61	1.08	1.05-1.12	8.79×10^{-7}	86	1.1	1.03-1.16	3.44×10^{-3}												
	rs89107	6q22	<i>SLC35F1</i>	G/A	58	1.07	1.04-1.10	9.51×10^{-7}			78	1.03	0.98-1.08	2.39×10^{-1}										
	rs11047543	12p12	<i>SOX5</i>	G/A	86	1.14	1.10-1.19	2.47×10^{-12}			88	1.18	1.10-1.26	1.57×10^{-6}										
	Previously known associations																							
Combined	rs13376333	1q21	<i>KCNN3</i>	T/C	12	1.13	1.09-1.16	1.46×10^{-12}	2	1.09	0.92-1.30	3.16×10^{-1}												
	rs17042171	4q25	<i>PITX2</i>	A/C	50	1.64	1.59-1.69	8.31×10^{-227}			45	1.71	1.64-1.78	9.69×10^{-135}										
	rs3807989	7q31	<i>CAV1</i>	G/A	58	1.09	1.06-1.12	6.52×10^{-8}			67	1.18	1.13-1.23	7.95×10^{-13}										
	rs60632610	10q22	<i>SYNPO2L</i>	C/T	85	1.12	1.08-1.15	1.54×10^{-10}	84	1.08	1.02-1.14	1.15×10^{-2}												
	rs10151658	14q23	<i>SYNE2</i>	C/A	6	1.07	1.04-1.09	5.16×10^{-7}			43	1.05	1.01-1.10	2.67×10^{-2}										
	rs2106261	16q22	<i>ZFHX3</i>	A/G	19	1.21	1.16-1.26	4.00×10^{-19}			31	1.33	1.27-1.39	9.63×10^{-36}										
	Results from AFGen exome chip gene-based test																							
Asian	rs202011870	10q24	<i>SH3PXD2A</i>	C/A	0.18	4.68	2.97-7.39	3.30E-11	0.2	4.03	2.63-6.19	1.80×10^{-10}												

For each genetic locus, we have reported the variant with the lowest P-value. Bold font indicates significant association with AF in Biobank Japan, when correcting for multiple testing of 33 variants ($P < 1.5 \times 10^{-3}$). *The GWAS analysis contained 837 cases and 3293 referents from BBJ. Chr, chromosome; RAF, risk allele frequency; OR, odds ratio; CI, confidence interval.

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Supplementary Table 11. Comparison of results for common variant loci between the AFGen Consortium combined ancestry analysis and the UK Biobank study.

rsID	Chr	Gene(s)	Risk / ref allele	Discovery				UK Biobank (3,366 cases; 139,852 referents)						
				RAF, %	OR	95% CI	P-value	RAF, %	OR	95% CI	P-value			
GWAS														
Novel associations														
rs72700118	1q24	<i>METTL11B/KIFAP3</i>	A/C	12	1.14	1.10-1.23	2.60x10 ⁻¹¹	12	1.21	1.12-1.29	2.59x10 ⁻⁷			
rs3771537	2p13	<i>ANXA4/GMCL1</i>	A/C	53	1.09	1.06-1.14	7.92x10 ⁻¹²	54	1.05	1.00-1.10	0.064			
rs2540949	2p14	<i>CEP68</i>	A/T	61	1.08	1.06-1.13	2.93x10⁻¹⁰	62	1.1	1.04-1.15	3.90x10⁻⁴			
rs2288327	2q31	<i>TTN/TTN-AS1</i>	G/A	20	1.09	1.06-1.14	2.05x10 ⁻⁸	16	1.08	1.01-1.16	0.016			
rs337711	5q22	<i>KCNN2</i>	T/C	39	1.07	1.05-1.11	2.93x10 ⁻⁸	40	1.04	0.99-1.09	0.144			
rs2967791	5q31	<i>KLHL3/WNT8A/FAM13B</i>	T/C	54	1.07	1.05-1.11	2.73x10⁻⁸	54	1.09	1.04-1.15	4.47x10⁻⁴			
rs4946333	6q22	<i>SLC35F1/PLN</i>	G/A	50	1.08	1.05-1.12	1.89x10 ⁻⁹	50	1.04	0.99-1.10	0.087			
rs7508	8p22	<i>ASAH1/PCM1</i>	A/G	72	1.09	1.06-1.14	5.16x10 ⁻¹⁰	73	1.06	1.00-1.12	0.038			
rs35176054	10q24	<i>SH3PXD2A</i>	A/T	13	1.14	1.10-1.22	8.63x10⁻¹²	11	1.24	1.15-1.33	5.7x10⁻⁹			
rs75190942	11q24	<i>KCNJ5</i>	A/C	8	1.17	1.11-1.26	1.59x10 ⁻⁸	9	1.12	1.03-1.22	0.005			
Previously known associations														
rs11264280	1q21	<i>KCNN3</i>	T/C	31	1.12	1.09-1.21	6.41x10 ⁻¹⁷	32	1.23	1.17-1.30	4.27x10 ⁻¹⁵			
rs520525	1q24	<i>PRRX1</i>	A/G	71	1.12	1.09-1.20	6.39x10⁻¹⁶	71	1.11	1.05-1.17	4.41x10⁻⁴			
rs11718898	3p25	<i>CAND2</i>	C/T	65	1.08	1.05-1.11	4.68x10 ⁻⁸	66	1.06	1.00-1.11	0.04			
rs6843082	4q25	<i>PITX2</i>	G/A	25	1.45	1.41-1.99	3.41x10⁻¹⁵⁵	20	1.6	1.51-1.69	1.75x10⁻⁶²			
rs12664873	6q22	<i>GJA1</i>	T/G	70	1.08	1.05-1.12	1.19x10 ⁻⁸	70	1.06	1.01-1.12	0.031			
rs1997572	7q31	<i>CAV1/2</i>	G/A	59	1.1	1.08-1.17	6.64x10 ⁻¹⁵	59	1.16	1.11-1.22	5.04x10 ⁻⁹			
rs7026071	9q22	<i>C9orf3</i>	T/C	40	1.09	1.07-1.15	1.31x10 ⁻¹²	40	1.13	1.07-1.19	1.80x10 ⁻⁶			
rs7915134	10q22	<i>SYNPO2L</i>	C/T	85	1.12	1.14-1.31	1.68x10 ⁻¹⁰	86	1.09	1.01-1.17	0.02			
rs11598047	10q24	<i>NEURL1</i>	G/A	16	1.18	1.08-1.19	1.67x10⁻²²	15	1.17	1.10-1.25	2.03x10⁻⁶			
rs883079	12q24	<i>TBX5</i>	T/C	70	1.11	1.09-1.19	1.80x10 ⁻¹⁵	73	1.11	1.05-1.17	4.06x10 ⁻⁴			
rs1152591	14q23	<i>SYNE2</i>	A/G	46	1.09	1.06-1.13	1.04x10 ⁻¹⁰	49	1.11	1.06-1.17	2.74x10 ⁻⁵			
rs74022964	15q24	<i>HCN4</i>	T/C	17	1.12	1.08-1.19	2.37x10 ⁻¹¹	15	1.08	1.01-1.15	0.029			
rs2106261	16q22	<i>ZFHX3</i>	T/C	19	1.2	1.17-1.37	8.18x10⁻³²	17	1.27	1.20-1.35	1.36x10⁻¹⁴			
ExWAS														
Novel associations														
rs6800541	3p22	<i>SCN10A</i>	T/C	61	1.08	1.05-1.12	8.79x10 ⁻⁷	60	1.08	1.02-1.13	0.004			
rs89107	6q22	<i>SLC35F1/PLN</i>	G/A	58	1.07	1.04-1.10	9.51x10 ⁻⁷	51	1.04	0.99-1.10	0.087			
rs11047543	12p12	<i>SOX5</i>	G/A	86	1.14	1.10-1.19	2.47x10 ⁻¹²	85	1.07	1.00-1.14	0.065			
Previously known associations														
rs13376333	1q21	<i>KCNN3</i>	T/C	23	1.13	1.09-1.16	1.46x10 ⁻¹²	31	1.17	1.11-1.23	1.10x10 ⁻⁹			
rs17042171	4q25	<i>PITX2</i>	A/C	21	1.64	1.59-1.69	8.31x10 ⁻²⁷	11	1.75	1.64-1.87	1.24x10 ⁻⁶⁰			
rs3807989	7q31	<i>CAV1</i>	G/A	58	1.09	1.06-1.12	6.52x10 ⁻⁸	59	1.16	1.10-1.22	1.22x10 ⁻⁸			
rs60632610	10q22	<i>SYNPO2L</i>	C/T	85	1.12	1.08-1.15	1.54x10 ⁻¹⁰	86	1.09	1.02-1.17	0.016			
rs10151658	14q23	<i>SYNE2</i>	C/A	49	1.07	1.04-1.09	5.16x10 ⁻⁷	57	1.05	1.00-1.10	0.076			
rs2106261	16q22	<i>ZFHX3</i>	A/G	17	1.21	1.16-1.26	4.00x10⁻¹⁹	17	1.27	1.20-1.35	1.36x10⁻¹⁴			

For each genetic locus, we have reported the variant with the lowest P-value. Bold font indicates significant association with AF in the UK Biobank, when correcting for multiple testing of 31 variants ($P < 1.6 \times 10^{-31}$). Chr, chromosome; RAF, risk allele frequency; OR, odds ratio; CI, confidence interval.

Supplementary Table 12. Approximate and joint conditional analysis in European ancestry GWAS meta-analysis identify 20 independent genetic loci associated with atrial fibrillation

rsID	Chr	Gene	Location relative to gene	P-value
rs11264280	1	KCNN3	Intergenic	2.77x10 ⁻¹⁷
rs10800507	1	METTL11B	Intergenic	1.87x10 ⁻¹¹
rs651386	1	PRRX1	Intergenic	6.23x10 ⁻¹⁵
rs2723065	2	CEP68	Intergenic	1.91x10 ⁻¹⁰
rs62133983	2	ANXA4	Intronic	1.36x10 ⁻¹⁰
rs2129977*	4	PITX2	Intergenic	7.25x10 ⁻¹³⁶
rs6864727	5	PKD2L2	Intronic	1.12x10 ⁻⁸
rs281868	6	SLC35F1	Intronic	1.03x10 ⁻⁸
rs7773091	6	GJA1	Intergenic	2.02x10 ⁻⁸
rs11773845	7	CAV1	Intronic	3.35x10 ⁻¹³
rs7508	8	ASAH1	3'UTR	6.34x10 ⁻¹⁰
rs7026071	9	C9orf3	Intronic	2.86x10 ⁻¹¹
rs11598047	10	NEURL1	Intronic	3.16x10 ⁻²¹
rs35176054	10	SH3PXD2A	Intronic	1.75x10 ⁻¹¹
rs10824026	10	SYNPO2L	Intergenic	8.29x10 ⁻¹¹
rs75190942	11	KCNJ5	Intronic	2.82x10 ⁻⁸
rs883079	12	TBX5	3'UTR	1.31x10 ⁻¹³
rs2921421	15	CGNL1	Intergenic	3.29x10 ⁻⁸
rs8040533	15	HCN4	Intergenic	3.09x10 ⁻¹¹
rs2106261	16	ZFHX3	Intronic	4.01x10 ⁻²⁴

Chr, chromosome; UTR, untranslated region. Bold font indicates that the variant lies within the gene.

*The 4q25/PITX2 region was not analyzed because the complexity of this association signal is not accurately evaluated with the GCTA method (**Online Methods**).

Supplementary Table 13. Overlap with atrial fibrillation risk factor GWAS loci

rsID	Chr	Closest gene*	rsID GWAS Catalog	LD	GWAS P-Value	HR	PR-S	PR-I	QRS	QT	Echo LVIDD	Stroke
ALL ANCESTRIES												
rs6843082	4	<i>PITX2</i> (dist=154788); <i>C4orf32</i> (dist=1348486)	rs6843082	1	3.41x10 ⁻¹⁵⁵							3
rs6843082	4	<i>PITX2</i> (dist=154788); <i>C4orf32</i> (dist=1348486)	rs12646447	0.51	1.12x10 ⁻¹⁴⁸							4
rs6843082	4	<i>PITX2</i> (dist=154788); <i>C4orf32</i> (dist=1348486)	rs2200733	0.51	2.32x10 ⁻¹⁵⁰							5
rs2967791	5	<i>KLHL3/WNT8A</i>	rs7722600	0.15	1.25x10 ⁻⁶	6						
rs4946333	6	<i>SLC35F1/PLN</i>	rs457162	<0.10	0.0686					7		
rs4946333	6	<i>SLC35F1/PLN</i>	rs11752626	0.43	0.0001					8		
rs4946333	6	<i>SLC35F1/PLN</i>	rs11970286	0.48	3.29x10 ⁻⁵					9,10		
rs4946333	6	<i>SLC35F1/PLN</i>	rs12210810	<0.10	0.001					10		
rs4946333	6	<i>SLC35F1/PLN</i>	rs12210733	<0.10	0.001					7		
rs4946333	6	<i>SLC35F1/PLN</i>	rs89107	0.99	4.03x10 ⁻⁹						11	
rs4946333	6	<i>SLC35F1/PLN</i>	rs3902035	<0.10	0.002					7		
rs4946333	6	<i>SLC35F1/PLN</i>	rs11756438	0.29	0.0008					12		
rs4946333	6	<i>SLC35F1/PLN</i>	rs6906287	0.38	5.84x10 ⁻⁵					13		
rs4946333	6	<i>SLC35F1/PLN</i>	rs11153730	0.45	2.01x10 ⁻⁵	6				7,14		
rs4946333	6	<i>SLC35F1/PLN</i>	rs281868	1	2.12x10 ⁻⁹	15						
rs1997572	7	<i>CAV1</i>	rs3807989	0.93	1.47x10 ⁻¹⁴		16	9,17,18	9			
rs1997572	7	<i>CAV1</i>	rs11773845	0.94	7.53x10 ⁻¹⁵			19,20				
rs1997572	7	<i>CAV1</i>	rs9920	0.15	0.0005					7		
rs883079	12	<i>TBX5</i>	rs883079	1	1.80x10 ⁻¹⁵					21		
rs883079	12	<i>TBX5</i>	rs7312625	0.90	1.03x10 ⁻¹⁴			22				
rs883079	12	<i>TBX5</i>	rs1895585	0.83	1.25x10 ⁻¹⁴			19				
rs883079	12	<i>TBX5</i>	rs7135659	0.88	9.59x10 ⁻¹⁵			20				
rs883079	12	<i>TBX5</i>	rs3825214	0.59	1.82x10 ⁻¹⁰			9	9	9		
rs74022964	15	<i>HCN4</i> (dist=15659); <i>C15orf60</i> (dist=58235)	rs4489968	0.77	4.59x10 ⁻¹¹	6						
rs2106261	16	<i>ZFHX3</i>	rs879324	0.91	1.13x10 ⁻²⁵							3

Table showing overlap of genetic associations between cardiac phenotypes, identified through interrogation of the NHGRI-EBI GWAS catalog.²

Numbers in superscript in the phenotype columns indicate references to the literature. Chr, chromosome; LD, linkage disequilibrium r^2 with lead SNP; HR, heart rate; PR-S, PR-segment; PR-I, PR-interval; LVIDD, Left Ventricle Internal Diastolic Diameter. *For intronic variants, the gene the variant is located within is listed; for intergenic variants, the closest genes upstream and downstream are listed.

Supplementary Table 14. Association between novel atrial fibrillation loci and stroke subtypes in the Neuro-CHARGE Stroke Consortium

rsID	Gene*	Risk/ref allele	All stroke		Ischemic stroke		Cardioembolic stroke	
			OR	P-value	OR	P-value	OR	P-value
rs72700118	<i>METTL11B</i>	A/C	1.01	0.70	1.02	0.61	1.09	0.38
rs3771537	<i>ANXA4/GMCL1</i>	A/C	1.00	0.85	0.99	0.75	0.99	0.88
rs2540949	<i>CEP68</i>	A/T	1.04	0.12	1.05	0.09	1.14	0.02
rs2288327	<i>TTN/TTN-AS1</i>	G/A	1.05	0.08	1.08	0.02	1.22	0.01
rs337711	<i>KCNN2</i>	T/C	0.97	0.16	0.96	0.18	0.97	0.63
rs2967791	<i>KLHL3/WNT8A/FAM13B</i>	T/C	1.03	0.14	1.04	0.10	1.11	0.05
rs4946333	<i>SLC35F1/PLN</i>	G/A	0.97	0.21	0.97	0.18	0.97	0.58
rs7508	<i>ASAHI</i>	A/G	1.04	0.12	1.04	0.17	1.11	0.14
rs35176054	<i>SH3PXD2A</i>	A/T	1.03	0.38	1.01	0.77	1.07	0.44
rs75190942	<i>KCNJ5</i>	A/C	1.01	0.85	1.04	0.45	-	-

OR, odds ratio. *Gene names in bold font indicate that the variant is located within the gene, whereas additional gene names indicate eQTL gene or gene strongly suspected to be causal due to the function of the encoded protein. For intergenic variants, the closest gene(s) are listed.

Supplementary Table 15. Association between novel atrial fibrillation loci and stroke subtypes in the Metastroke Consortium

			Ischemic stroke		Cardioembolic stroke		Large vessel disease		Small vessel disease	
rsID	Gene*	Risk/ref allele	OR	P-value	OR	P-value	OR	P-value	OR	P-value
rs72700118	<i>METTL11B/KIFAP3</i>	A/C	1.07	0.02	1.14	0.02	1.01	0.92	1.04	0.53
rs3771537	<i>ANXA4/GMCL1</i>	A/C	0.99	0.52	1.02	0.57	0.94	0.08	1.00	0.95
rs2540949	<i>CEP68</i>	A/T	0.99	0.63	1.03	0.40	1.05	0.18	0.97	0.54
rs2288327	<i>TTN/TTN-AS1</i>	G/A	1.02	0.54	1.03	0.61	1.02	0.66	1.07	0.21
rs337711	<i>KCNN2</i>	T/C	1.01	0.50	1.08	0.04	1.00	0.90	0.94	0.19
rs2967791	<i>KLHL3/WNT8A/FAM13B</i>	T/C	1.02	0.39	1.05	0.19	1.06	0.15	0.92	0.05
rs4946333	<i>SLC35F1/PLN</i>	G/A	0.98	0.26	0.91	0.01	0.89	0.003	1.01	0.79
rs7508	<i>ASAH1</i>	A/G	0.98	0.37	1.00	1.00	1.03	0.45	0.94	0.17
rs35176054	<i>SH3PXD2A</i>	A/T	1.01	0.67	1.07	0.25	0.96	0.46	1.10	0.13
rs75190942	<i>KCNJ5</i>	A/C	1.02	0.59	1.09	0.31	1.03	0.73	0.98	0.80

OR, odds ratio. *Gene names in bold font indicate that the variant is located within the gene, whereas additional gene names indicate eQTL gene or gene strongly suspected to be causal due to the function of the encoded protein. For intergenic variants, the closest gene(s) are listed.

Supplementary Table 16. GO terms enriched in atrial fibrillation associated loci compared to GWAS catalog loci and to 1000 genomes matched loci

Gene Ontology Description	P-value	FDR Q-value
Compared to 1000 Genomes Matched Loci		
Small conductance calcium-activated potassium channel activity	9.48x10 ⁻⁵	3.01x10 ⁻¹
Metal ion transport	1.62x10 ⁻⁴	1.00
Potassium channel activity	2.52x10 ⁻⁴	4.00x10 ⁻¹
Z disc	2.70x10 ⁻⁴	3.85x10 ⁻¹
Monovalent inorganic cation transport	3.52x10 ⁻⁴	1.00
Potassium ion transmembrane transport	5.08x10 ⁻⁴	1.00
Cellular potassium ion transport	5.08x10 ⁻⁴	1.00
Potassium ion transmembrane transporter activity	5.70x10 ⁻⁴	6.04x10 ⁻¹
Regulation of cardiac muscle contraction	6.92x10 ⁻⁴	1.00
Striated muscle tissue development	6.92x10 ⁻⁴	1.00
Potassium ion transport	7.08x10 ⁻⁴	1.00
Cation transport	7.34x10 ⁻⁴	1.00
Regulation of heart rate	9.10x10 ⁻⁴	1.00
Compared to GWAS catalog Loci		
Small conductance calcium-activated potassium channel activity	2.64x10 ⁻⁴	7.43x10 ⁻¹
Z disc	2.67x10 ⁻⁴	3.34x10 ⁻¹
Metal ion transport	3.17x10 ⁻⁴	1.00
Potassium channel activity	4.14x10 ⁻⁴	5.83x10 ⁻¹
Monovalent inorganic cation transport	7.01x10 ⁻⁴	1.00

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Supplementary Table 17. Summary of top eQTLs within atrial fibrillation associated loci

Index variant	Closest gene	Chr	eQTL variant	eQTL gene	Tissue	eQTL approach	P-value	FDR_gw*	r2**	Description of eQTL gene
rs11264280	<i>KCNN3</i>	1q21	1:154862564:C_C_A	<i>ADAM15</i>	Left atrial appendage	CCAF	8.38×10^{-4}	- ADAM Metallopeptidase Domain 15		
rs72700118	<i>METTL11B</i>	1q24	rs72700114	<i>KIFAP3</i>	Left atrial appendage	CCAF	1.65×10^{-2}	- Kinesin Associated Protein 3		
rs520525	<i>PRRX1</i>	1q24	rs525489	<i>PRRX1</i>	Left atrial appendage	CCAF	5.48×10^{-6}	0.29 Paired related homeobox 1		
rs520525	<i>PRRX1</i>	1q24	rs680084	<i>PRRX1</i>	Left ventricle	GTEX lookup	5.2×10^{-6}	0.35 Paired related homeobox 1		
rs520525	<i>PRRX1</i>	1q24	rs651822	<i>PRRX1</i>	Skeletal muscle	GTEX lookup	1.68×10^{-6}	0.89 Paired related homeobox 1		- LincRNA
rs520525	<i>PRRX1</i>	1q24	rs1234284	<i>RP1-79C4.4</i>	Left ventricle	GTEX lookup	2.52×10^{-8}			- LincRNA
rs520525	<i>PRRX1</i>	1q24	rs651822	<i>RP1-79C4.4</i>	Skeletal muscle	GTEX lookup	1.53×10^{-14}	0.89 LincRNA		
rs3771537	<i>ANXA4</i>	2p13	rs11126244	<i>ANXA4</i>	Left ventricle	GTEX lookup	1.55×10^{-6}	0.21 Annexin A4		
rs3771537	<i>ANXA4</i>	2p13	rs12619656	<i>GMCL1</i>	Left ventricle	GTEX lookup	1.06×10^{-6}	0.35 Germ cell-less, spermatogenesis associated 1		
rs3771537	<i>ANXA4</i>	2p13	rs56222989	<i>GMCL1</i>	Skeletal muscle	GTEX lookup	5.52×10^{-13}	0.36 Germ cell-less, spermatogenesis associated 1		
rs3771537	<i>ANXA4</i>	2p13	rs55866046	<i>PCYOX1</i>	Left ventricle	GTEX lookup	1.27×10^{-5}	0.27 Prenylcysteine oxidase 1		
rs3771537	<i>ANXA4</i>	2p13	rs2312555	<i>SNRNP27</i>	Skeletal muscle	GTEX lookup	1.55×10^{-13}	0.99 Small Nuclear Ribonucleoprotein U4/U6.US Subunit 27		
rs25404949	<i>CEP68</i>	2p14	rs2540950	<i>CEP68</i>	Left atrial appendage	CCAF		9.35×10^{-14}	0.93 Centrosomal protein 68kDa	
rs25404949	<i>CEP68</i>	2p14	rs2249105	<i>CEP68</i>	Atrial appendage	GTEX lookup	6.13×10^{-13}	0.93 Centrosomal protein 68kDa		
rs25404949	<i>CEP68</i>	2p14	rs74181299	<i>CEP68</i>	Left ventricle	GTEX lookup	9.45×10^{-8}	1.00 Centrosomal protein 68kDa		
rs25404949	<i>CEP68</i>	2p14	rs2540949	<i>CEP68</i>	Skeletal muscle	GTEX lookup	5.02×10^{-13}	1.00 Centrosomal protein 68kDa		
rs11718898	<i>CAND2</i>	3p25	rs11718898	<i>CAND2</i>	Skeletal muscle	GTEX lookup	2.24×10^{-20}	1.00 Cullin-associated NEDD8-dissociated protein 2		
rs11718898	<i>CAND2</i>	3p25	rs11718898	<i>KRT18P17</i>	Skeletal muscle	GTEX lookup	2.24×10^{-9}	1.00 Keratin 18 Pseudogene 17		
rs11718898	<i>CAND2</i>	3p25	rs11718898	<i>RP11-767C1.2</i>	Skeletal muscle	GTEX lookup	1.02×10^{-6}	1.00 Antisense RNA gene		
rs337711	<i>KCNN2</i>	5q22	rs337705	<i>KCNN2</i>	Left atrial appendage	CCAF		9.05×10^{-3}	0.99 Potassium Calcium-Activated Channel Subfamily N Member 2	
rs2967791	<i>KLHL3</i>	5q31	rs2967793	<i>FAM13B</i>	Atrial appendage	GTEX region based analysis	3.12×10^{-7}	0.15 Family with sequence similarity 13, member B		
rs2967791	<i>KLHL3</i>	5q31	rs11745324	<i>REEP2</i>	Left ventricle	GTEX region based analysis	1.02×10^{-5}	0.35 Receptor accessory protein 2		
rs1997572	<i>CAV1</i>	7q31	rs1049337	<i>CAV1</i>	Left atrial appendage	CCAF		4.96×10^{-4}	0.26 Caveolin 1	
rs1997572	<i>CAV2</i>	7q31	rs2270188	<i>CAV2</i>	Left atrial appendage	CCAF		1.83×10^{-8}	0.46 Caveolin 2	
rs7508	<i>ASAH1</i>	8p22	rs399485	<i>ASAH1</i>	Left atrial appendage	CCAF		2.08×10^{-3}	0.92 N-Acylsphingosine Amidohydrolase 1	
rs7508	<i>ASAH1</i>	8p22	rs7508	<i>PCM1</i>	Left atrial appendage	CCAF		9.56×10^{-14}	1.00 Pericentriolar material 1	
rs7508	<i>ASAH1</i>	8p22	rs7508	<i>PCM1</i>	Left ventricle	GTEX lookup	3.18×10^{-6}	1.00 Pericentriolar material 1		
rs7508	<i>ASAH1</i>	8p22	rs7508	<i>PCM1</i>	Skeletal muscle	GTEX lookup	1.12×10^{-6}	1.00 Pericentriolar material 1		
rs7508	<i>ASAH1</i>	8p22	rs483159	<i>RP11-806O11.1</i>	Left ventricle	GTEX region based analysis	1.93×10^{-7}	0.74 Processed transcript		
rs7915134	<i>SYNPO2L</i>	10q22	rs60212594	<i>MYOZ1</i>	Left atrial appendage	CCAF		8.27×10^{-34}	0.95 Myozenin 1	
rs7915134	<i>SYNPO2L</i>	10q22	rs4746139	<i>SYNPO2L</i>	Left atrial appendage	CCAF		6.32×10^{-6}	0.92 Synaptotagmin 2 Like	
rs7915134	<i>SYNPO2L</i>	10q22	rs3861036	<i>PLAU</i>	Atrial appendage	GTEX region based analysis	2.11×10^{-7}	0.16 Plasminogen activator, urokinase		
rs7915134	<i>SYNPO2L</i>	10q22	rs68170615	<i>USP54</i>	Left ventricle	GTEX region based analysis	2.38×10^{-5}	- Ubiquitin specific peptidase 54		
rs7915134	<i>SYNPO2L</i>	10q22	rs2177843	<i>MYOZ1</i>	Atrial appendage	GTEX lookup	5.93×10^{-24}	0.83 Myozenin 1		
rs7915134	<i>SYNPO2L</i>	10q22	rs147790633	<i>FUT11</i>	Skeletal muscle	GTEX lookup	3.84×10^{-6}	0.90 Fucosyltransferase 11 (alpha (1,3)fucosyltransferase)		
rs7915134	<i>SYNPO2L</i>	10q22	rs201617396	<i>RP11-137L10.6</i>	Left ventricle	GTEX region based analysis	2.38×10^{-5}	- PPP3CB antisense RNA 1 (head to head)		
rs11598047	<i>NEURL</i>	10q24	rs12268602	<i>USMG5;MIR1307</i>	Left atrial appendage	CCAF		3.25×10^{-2}	0.14 Up-regulated during skeletal muscle growth protein 5; MicroRNA1307	
rs75190942	<i>KCNJ5</i>	11q24	rs76097649	<i>KCNJ5</i>	Left atrial appendage	CCAF		2.77×10^{-2}	1.00 Potassium channel, inwardly rectifying subfamily J, member 5	
rs75190942	<i>KCNJ5</i>	11q24	rs76097649	<i>KCNJ5</i>	Left ventricle	GTEX lookup	3.15×10^{-6}	1.00 Potassium channel, inwardly rectifying subfamily J, member 5		
rs75190942	<i>KCNJ5</i>	11q24	rs78907918	<i>C11orf45</i>	Left ventricle	GTEX region based analysis	4.97×10^{-7}	0.83 Chromosome 11 open reading frame 45		
rs883079	<i>TBX5</i>	12q24	rs1946295	<i>TBX5</i>	Left atrial appendage	CCAF		1.69×10^{-3}	0.80 T-box 5	
rs883079	<i>TBX5</i>	12q24	rs2891503	<i>TBX5</i>	Left ventricle	GTEX lookup	3.84×10^{-6}	0.73 T-box 5		
rs1152591	<i>SYNE2</i>	14q23	rs2738413	<i>SYNE2</i>	Left atrial appendage	CCAF		7.47×10^{-12}	1.00 Spectrin repeat containing, nuclear envelope 2	
rs1152591	<i>SYNE2</i>	14q23	rs2738413	<i>SYNE2</i>	Left ventricle	GTEX lookup	2.54×10^{-11}	1.00 Spectrin repeat containing, nuclear envelope 2		

CCAF, Cleveland Clinic Atrial Tissue Bank and Arrhythmia Biorepository; Chr, chromosome; eQTL, expression quantitative trait locus; GTEX, Genotype-Tissue Expression database. *Genome-wide false discovery rate. **LD between index variant and eQTL variant. For some variants, there were no LD information available in the 1000 Genomes reference database (-).

Supplementary Table 18. continued

rs3771537	ANXA4	2	70041181	rs72839869	Skeletal muscle	GMCL1	T	-0.39	-15593	5.85E-12	
rs3771537	ANXA4	2	70041440	rs4853028	Skeletal muscle	GMCL1	A	-0.38	-15334	1.08E-11	
rs3771537	ANXA4	2	70042332	rs60168146	Skeletal muscle	GMCL1	G	-0.39	-14442	5.81E-12	
rs3771537	ANXA4	2	70042915	rs72839870	Skeletal muscle	GMCL1	A	-0.39	-13859	5.79E-12	
rs3771537	ANXA4	2	70043598	rs3771536	Skeletal muscle	GMCL1	A	-0.39	-13176	5.77E-12	
rs3771537	ANXA4	2	70043775	rs3771535	Skeletal muscle	GMCL1	T	-0.40	-12999	4.70E-12	
rs3771537	ANXA4	2	70045063	rs6744970	Skeletal muscle	GMCL1	A	-0.40	-11711	2.48E-12	
rs3771537	ANXA4	2	70046944	rs72839874	Skeletal muscle	GMCL1	A	-0.40	-9810	1.69E-12	
rs3771537	ANXA4	2	70047644	rs2290452	Skeletal muscle	GMCL1	A	-0.40	-9130	1.80E-12	
rs3771537	ANXA4	2	70049222	rs58819073	Skeletal muscle	GMCL1	A	-0.40	-7552	1.78E-12	
rs3771537	ANXA4	2	70050725	rs7563062	Skeletal muscle	GMCL1	A	-0.30	-6049	9.23E-12	
rs3771537	ANXA4	2	70053668	rs7600468	Skeletal muscle	GMCL1	G	-0.29	-3106	4.98E-10	
rs3771537	ANXA4	2	70053816	rs11900749	Skeletal muscle	GMCL1	C	-0.40	-2958	5.13E-12	
rs3771537	ANXA4(<i>dist</i> =1575);GMCL1(<i>dist</i> =1647)		2	70051751	rs33992437	Skeletal muscle	GMCL1	C	-0.40	-1603	4.20E-12
rs3771537	ANXA4(<i>dist</i> =1909);GMCL1(<i>dist</i> =1313)		2	70055055	rs1531025	Skeletal muscle	GMCL1	A	-0.30	-1269	1.20E-11
rs3771537	GMCL1	2	70056116	rs2278932	Skeletal muscle	GMCL1	G	-0.40	-658	1.86E-12	
rs3771537	GMCL1	2	70056365	rs2278933	Skeletal muscle	GMCL1	C	-0.39	-409	7.03E-12	
rs3771537	GMCL1	2	70057448	rs3732266	Skeletal muscle	GMCL1	G	-0.30	674	6.46E-12	
rs3771537	GMCL1	2	70059607	rs72839877	Skeletal muscle	GMCL1	C	-0.40	2833	4.56E-12	
rs3771537	GMCL1	2	70062276	rs72839879	Skeletal muscle	GMCL1	T	-0.40	5502	4.75E-12	
rs3771537	GMCL1	2	70062360	rs10167142	Skeletal muscle	GMCL1	C	-0.31	5586	5.31E-12	
rs3771537	GMCL1	2	70062454	rs10202159	Skeletal muscle	GMCL1	T	-0.31	5680	5.32E-12	
rs3771537	GMCL1	2	70063315	rs60483174	Skeletal muscle	GMCL1	T	-0.41	6541	2.31E-12	
rs3771537	GMCL1	2	70063527	rs4420721	Skeletal muscle	GMCL1	T	-0.37	6753	3.46E-11	
rs3771537	GMCL1	2	70063563	rs4401231	Skeletal muscle	GMCL1	C	-0.31	6789	4.38E-12	
rs3771537	GMCL1	2	70063660	rs4241261	Skeletal muscle	GMCL1	G	-0.31	6886	4.83E-12	
rs3771537	GMCL1	2	70064155	rs3377995	Skeletal muscle	GMCL1	G	-0.31	7381	4.45E-12	
rs3771537	GMCL1	2	70064435	rs3771534	Skeletal muscle	GMCL1	T	-0.41	7661	2.07E-12	
rs3771537	GMCL1	2	70064927	rs1377996	Skeletal muscle	GMCL1	A	-0.39	8153	1.41E-12	
rs3771537	GMCL1	2	70065997	rs12619656	Skeletal muscle	GMCL1	A	-0.42	9223	1.24E-12	
rs3771537	GMCL1	2	70066102	rs12613917	Skeletal muscle	GMCL1	G	-0.41	9328	1.77E-12	
rs3771537	GMCL1	2	70066891	rs11888098	Skeletal muscle	GMCL1	C	-0.41	10117	1.66E-12	
rs3771537	GMCL1	2	70066922	rs11888102	Skeletal muscle	GMCL1	G	-0.41	10148	1.65E-12	
rs3771537	GMCL1	2	70068057	rs3771533	Skeletal muscle	GMCL1	A	-0.41	11283	1.51E-12	
rs3771537	GMCL1	2	70068635	rs2872075	Skeletal muscle	GMCL1	T	-0.31	11861	2.29E-12	
rs3771537	GMCL1	2	70068755	rs2872076	Skeletal muscle	GMCL1	A	-0.41	11981	1.43E-12	
rs3771537	GMCL1	2	70071529	rs7575111	Skeletal muscle	GMCL1	G	-0.44	14755	3.33E-12	
rs3771537	GMCL1	2	70073703	rs6546551	Skeletal muscle	GMCL1	T	-0.31	16929	1.41E-12	
rs3771537	GMCL1	2	70076650	rs6546552	Skeletal muscle	GMCL1	C	-0.42	19876	1.07E-12	
rs3771537	GMCL1	2	70076954	rs4852349	Skeletal muscle	GMCL1	T	-0.30	20180	1.02E-11	
rs3771537	GMCL1	2	70077422	rs7577662	Skeletal muscle	GMCL1	G	-0.42	20648	1.07E-12	
rs3771537	GMCL1	2	70077433	rs7565230	Skeletal muscle	GMCL1	C	-0.42	20659	1.07E-12	
rs3771537	GMCL1	2	70079633	rs1551374	Skeletal muscle	GMCL1	T	-0.31	22859	2.58E-12	
rs3771537	GMCL1	2	70084977	rs921711	Skeletal muscle	GMCL1	G	-0.39	28203	8.05E-13	
rs3771537	GMCL1	2	70085961	rs7595635	Skeletal muscle	GMCL1	A	-0.39	29187	1.16E-12	
rs3771537	GMCL1	2	70086363	rs36081078	Skeletal muscle	GMCL1	G	-0.42	29589	5.54E-13	
rs3771537	GMCL1	2	70086728	rs72839885	Skeletal muscle	GMCL1	T	-0.42	29954	5.53E-13	
rs3771537	GMCL1	2	70087159	rs4852356	Skeletal muscle	GMCL1	G	-0.26	30385	4.91E-09	
rs3771537	GMCL1	2	70088016	rs13412830	Skeletal muscle	GMCL1	C	-0.38	31242	2.41E-12	
rs3771537	GMCL1	2	70089130	rs56222989	Skeletal muscle	GMCL1	G	-0.42	32356	5.52E-13	
rs3771537	GMCL1	2	70090579	rs13017134	Skeletal muscle	GMCL1	G	-0.29	33805	1.20E-11	
rs3771537	GMCL1	2	70090913	rs56168154	Skeletal muscle	GMCL1	T	-0.42	34139	1.25E-12	
rs3771537	GMCL1	2	70091246	rs10865380	Skeletal muscle	GMCL1	C	-0.28	34472	2.01E-11	
rs3771537	GMCL1	2	70091772	rs60390734	Skeletal muscle	GMCL1	C	-0.42	34998	1.25E-12	
rs3771537	GMCL1	2	70093647	rs57278310	Skeletal muscle	GMCL1	C	-0.28	36873	2.66E-11	
rs3771537	GMCL1	2	70093898	rs60248458	Skeletal muscle	GMCL1	G	-0.42	37124	1.25E-12	
rs3771537	GMCL1	2	70093910	rs60207187	Skeletal muscle	GMCL1	A	-0.29	37136	1.20E-11	
rs3771537	GMCL1	2	70097735	rs7568485	Skeletal muscle	GMCL1	C	-0.39	40961	1.16E-12	
rs3771537	GMCL1	2	70098808	rs3214007	Skeletal muscle	GMCL1	G	-0.31	42034	2.66E-12	
rs3771537	GMCL1	2	70099424	rs1013083	Skeletal muscle	GMCL1	G	-0.41	42650	1.48E-12	
rs3771537	GMCL1	2	70101889	rs61138247	Skeletal muscle	GMCL1	C	-0.38	45115	5.49E-12	
rs3771537	GMCL1	2	70102735	rs4853109	Skeletal muscle	GMCL1	G	-0.39	45961	3.62E-12	
rs3771537	GMCL1	2	70103504	rs17037193	Skeletal muscle	GMCL1	C	-0.42	46730	1.25E-12	
rs3771537	GMCL1	2	70103802	rs17037194	Skeletal muscle	GMCL1	C	-0.42	47028	1.25E-12	
rs3771537	GMCL1	2	70106832	rs6747542	Skeletal muscle	GMCL1	C	-0.29	50058	1.45E-11	
rs3771537	GMCL1	2	70107409	rs2124007	Skeletal muscle	GMCL1	G	-0.42	50635	1.32E-12	
rs3771537	GMCL1(<i>dist</i> =1529);SNRNP27(<i>dist</i> =12819)		2	70108256	rs1056482	Skeletal muscle	GMCL1	A	-0.28	51482	1.89E-11
rs3771537	GMCL1(<i>dist</i> =4984);SNRNP27(<i>dist</i> =9364)		2	70111711	rs5654653	Skeletal muscle	GMCL1	A	-0.28	54937	8.67E-11
rs3771537	GMCL1(<i>dist</i> =9724);SNRNP27(<i>dist</i> =4627)		2	70116448	rs60515724	Skeletal muscle	GMCL1	T	-0.38	59674	6.35E-11
rs3771537	GMCL1(<i>dist</i> =10288);SNRNP27(<i>dist</i> =4060)		2	70117015	rs10165883	Skeletal muscle	GMCL1	T	-0.30	60241	8.13E-12
rs3771537	GMCL1(<i>dist</i> =10347);SNRNP27(<i>dist</i> =4001)		2	70117074	rs2054046	Skeletal muscle	GMCL1	C	-0.39	60300	3.03E-11
rs3771537	GMCL1(<i>dist</i> =10449);SNRNP27(<i>dist</i> =3899)		2	70117176	rs12232914	Skeletal muscle	GMCL1	T	-0.29	60402	8.49E-11
rs3771537	GMCL1(<i>dist</i> =10645);SNRNP27(<i>dist</i> =3703)		2	70117372	rs12233079	Skeletal muscle	GMCL1	G	-0.28	60598	1.18E-10
rs3771537	GMCL1(<i>dist</i> =10694);SNRNP27(<i>dist</i> =3654)		2	70117421	rs2054047	Skeletal muscle	GMCL1	C	-0.29	60647	6.38E-11
rs3771537	GMCL1(<i>dist</i> =11661);SNRNP27(<i>dist</i> =2687)		2	70118388	rs13002091	Skeletal muscle	GMCL1	T	-0.28	61614	2.92E-10
rs3771537	GMCL1(<i>dist</i> =11700);SNRNP27(<i>dist</i> =2648)		2	70118427	rs13028508	Skeletal muscle	GMCL1	A	-0.27	61653	4.93E-10
rs3771537	GMCL1(<i>dist</i> =12742);SNRNP27(<i>dist</i> =1606)		2	70119469	rs3755389	Skeletal muscle	GMCL1	C	-0.28	62695	1.25E-10
rs3771537	SNRNP27	2	70120078	rs55866046	Skeletal muscle	GMCL1	C	-0.42	63304	3.31E-11	
rs3771537	SNRNP27	2	70124316	rs3752781	Skeletal muscle	GMCL1	A	-0.27	67542	7.47E-10	
rs3771537	SNRNP27	2	70124805	rs6720498	Skeletal muscle	GMCL1	C	-0.27	68031	1.76E-09	
rs3771537	SNRNP27	2	70125763	rs13015457	Skeletal muscle	GMCL1	T	-0.28	68989	2.05E-10	
rs3771537	SNRNP27	2	70125988	rs4852375	Skeletal muscle	GMCL1	G	-0.29	69214	1.28E-10	
rs3771537	SNRNP27	2	70126666	rs58206747	Skeletal muscle	GMCL1	G	-0.38	69892	1.07E-10	
rs3771537	SNRNP27	2	70127229	rs6716937	Skeletal muscle	GMCL1	A	-0.28	70455	2.07E-10	
rs3771537	SNRNP27	2	70128717	rs7598283	Skeletal muscle	GMCL1	G	-0.27	71943	7.20E-10	
rs3771537	SNRNP27	2	70131584	rs1048130	Skeletal muscle	GMCL1	A	-0.38	74810	1.82E-10	
rs3771537	SNRNP27	2	70132676	rs1048266	Skeletal muscle	GMCL1	G	-0.28	75902	2.06E-10	

Supplementary Table 18. continued

rs3771537	<i>SNRNP27</i> (<i>dist=3338</i>); <i>MXD1</i> (<i>dist=6467</i>)	2	70135706 rs6546554	Skeletal muscle	GMCL1	A	-0.28	78932	2.06E-10
rs3771537	<i>SNRNP27</i> (<i>dist=3392</i>); <i>MXD1</i> (<i>dist=6413</i>)	2	70135760 rs6546555	Skeletal muscle	GMCL1	G	-0.28	78986	2.81E-10
rs3771537	<i>SNRNP27</i> (<i>dist=4249</i>); <i>MXD1</i> (<i>dist=5556</i>)	2	70136617 rs11126249	Skeletal muscle	GMCL1	G	-0.37	79843	2.74E-10
rs3771537	<i>SNRNP27</i> (<i>dist=5130</i>); <i>MXD1</i> (<i>dist=4675</i>)	2	70137498 rs1979214	Skeletal muscle	GMCL1	C	-0.27	80724	6.84E-10
rs3771537	<i>SNRNP27</i> (<i>dist=5406</i>); <i>MXD1</i> (<i>dist=4399</i>)	2	70137740 rs736408	Skeletal muscle	GMCL1	T	-0.28	81000	2.06E-10
rs3771537	<i>SNRNP27</i> (<i>dist=5743</i>); <i>MXD1</i> (<i>dist=4062</i>)	2	70138111 rs6739780	Skeletal muscle	GMCL1	A	-0.28	81337	2.20E-10
rs3771537	<i>SNRNP27</i> (<i>dist=5802</i>); <i>MXD1</i> (<i>dist=4003</i>)	2	70138170 rs6754896	Skeletal muscle	GMCL1	C	-0.28	81396	2.06E-10
rs3771537	<i>SNRNP27</i> (<i>dist=6633</i>); <i>MXD1</i> (<i>dist=3172</i>)	2	70139001 rs6546556	Skeletal muscle	GMCL1	G	-0.28	82227	2.06E-10
rs3771537	<i>SNRNP27</i> (<i>dist=6766</i>); <i>MXD1</i> (<i>dist=3039</i>)	2	70139134 rs7592647	Skeletal muscle	GMCL1	T	-0.27	82360	6.50E-10
rs3771537	<i>SNRNP27</i> (<i>dist=7903</i>); <i>MXD1</i> (<i>dist=1902</i>)	2	70140271 rs897122	Skeletal muscle	GMCL1	T	-0.28	83497	2.07E-10
rs3771537	<i>MXD1</i>	2	70144596 rs11902198	Skeletal muscle	GMCL1	A	-0.28	87822	2.27E-10
rs3771537	<i>MXD1</i>	2	70145171 rs6546558	Skeletal muscle	GMCL1	T	-0.28	88943	1.87E-10
rs3771537	<i>MXD1</i>	2	70145833 rs6546559	Skeletal muscle	GMCL1	A	-0.27	89059	6.82E-10
rs3771537	<i>MXD1</i>	2	70146121 rs6721891	Skeletal muscle	GMCL1	G	-0.28	89347	2.06E-10
rs3771537	<i>MXD1</i>	2	70146125 rs6750488	Skeletal muscle	GMCL1	T	-0.28	89351	2.06E-10
rs3771537	<i>MXD1</i>	2	70146625 rs7419837	Skeletal muscle	GMCL1	C	-0.28	89851	2.63E-10
rs3771537	<i>MXD1</i>	2	70149225 rs1454498	Skeletal muscle	GMCL1	A	-0.28	92451	1.69E-10
rs3771537	<i>MXD1</i>	2	70149873 rs0352135	Skeletal muscle	GMCL1	A	-0.37	93099	3.41E-10
rs3771537	<i>MXD1</i>	2	70150215 rs6738174	Skeletal muscle	GMCL1	C	-0.28	93441	2.59E-10
rs3771537	<i>MXD1</i>	2	70150674 rs6725425	Skeletal muscle	GMCL1	C	-0.28	93900	1.69E-10
rs3771537	<i>MXD1</i>	2	70151471 rs10205487	Skeletal muscle	GMCL1	G	-0.27	94697	5.55E-10
rs3771537	<i>MXD1</i>	2	70152027 rs726920	Skeletal muscle	GMCL1	C	-0.28	95253	1.66E-10
rs3771537	<i>MXD1</i>	2	70153436 rs10496174	Skeletal muscle	GMCL1	G	-0.27	96662	5.11E-10
rs3771537	<i>MXD1</i>	2	70154037 rs7573442	Skeletal muscle	GMCL1	A	-0.27	97263	5.09E-10
rs3771537	<i>MXD1</i>	2	70154134 rs12713682	Skeletal muscle	GMCL1	A	-0.27	97360	5.84E-10
rs3771537	<i>MXD1</i>	2	70154187 rs11893500	Skeletal muscle	GMCL1	C	-0.27	97413	5.11E-10
rs3771537	<i>MXD1</i>	2	70155482 rs4144081	Skeletal muscle	GMCL1	A	-0.28	98708	1.67E-10
rs3771537	<i>MXD1</i>	2	70156540 rs6712827	Skeletal muscle	GMCL1	G	-0.27	99766	5.12E-10
rs3771537	<i>MXD1</i>	2	70156589 rs6741449	Skeletal muscle	GMCL1	G	-0.28	99815	1.71E-10
rs3771537	<i>MXD1</i>	2	70160658 rs897119	Skeletal muscle	GMCL1	C	-0.27	103884	8.16E-10
rs3771537	<i>MXD1</i>	2	70160982 rs897120	Skeletal muscle	GMCL1	G	-0.28	104208	1.79E-10
rs3771537	<i>MXD1</i>	2	70161032 rs6729760	Skeletal muscle	GMCL1	T	-0.28	104258	2.58E-10
rs3771537	<i>MXD1</i>	2	70161342 rs12613947	Skeletal muscle	GMCL1	G	-0.28	104568	1.63E-10
rs3771537	<i>MXD1</i>	2	70163316 rs34586537	Skeletal muscle	GMCL1	G	-0.28	106542	1.29E-10
rs3771537	<i>MXD1</i>	2	70163434 rs11126251	Skeletal muscle	GMCL1	G	-0.28	106660	1.07E-10
rs3771537	<i>MXD1</i>	2	70164034 rs771531	Skeletal muscle	GMCL1	C	-0.28	107260	1.26E-10
rs3771537	<i>MXD1</i>	2	70164805 rs771530	Skeletal muscle	GMCL1	C	-0.30	108031	6.75E-11
rs3771537	<i>MXD1</i>	2	70164840 rs771529	Skeletal muscle	GMCL1	A	-0.37	108066	3.32E-10
rs3771537	<i>MXD1</i>	2	70165966 rs7349311	Skeletal muscle	GMCL1	A	-0.41	109192	1.47E-10
rs3771537	<i>MXD1</i>	2	70167197 rs12475412	Skeletal muscle	GMCL1	T	-0.29	110423	7.37E-11
rs3771537	<i>MXD1</i> (<i>dist=1494</i>); <i>ASPRV1</i> (<i>dist=15654</i>)	2	70171570 rs897121	Skeletal muscle	GMCL1	T	-0.30	114796	8.46E-11
rs3771537	<i>MXD1</i> (<i>dist=2040</i>); <i>ASPRV1</i> (<i>dist=15108</i>)	2	70172116 rs1186934	Skeletal muscle	GMCL1	G	-0.22	115342	5.38E-07
rs3771537	<i>MXD1</i> (<i>dist=2390</i>); <i>ASPRV1</i> (<i>dist=14758</i>)	2	70172466 rs12713682	Skeletal muscle	GMCL1	G	-0.24	115692	4.54E-08
rs3771537	<i>MXD1</i> (<i>dist=2511</i>); <i>ASPRV1</i> (<i>dist=14637</i>)	2	70172587 rs756513	Skeletal muscle	GMCL1	A	-0.27	115813	7.70E-08
rs3771537	<i>MXD1</i> (<i>dist=3954</i>); <i>ASPRV1</i> (<i>dist=13194</i>)	2	70174030 rs7569566	Skeletal muscle	GMCL1	C	-0.27	117256	1.91E-09
rs3771537	<i>MXD1</i> (<i>dist=3978</i>); <i>ASPRV1</i> (<i>dist=13170</i>)	2	70174054 rs7581977	Skeletal muscle	GMCL1	G	-0.28	117280	9.81E-10
rs3771537	<i>AAK1</i> (<i>dist=90535</i>); <i>ANXA4</i> (<i>dist=7615</i>)	2	69961512 rs13402511	Skeletal muscle	SNRNP27	C	-0.19	159180	1.57E-05
rs3771537	<i>AAK1</i> (<i>dist=91163</i>); <i>ANXA4</i> (<i>dist=6987</i>)	2	69962140 rs6739197	Skeletal muscle	SNRNP27	G	-0.19	158552	1.57E-05
rs3771537	<i>AAK1</i> (<i>dist=92470</i>); <i>ANXA4</i> (<i>dist=5680</i>)	2	69963447 rs4852980	Skeletal muscle	SNRNP27	G	-0.19	157245	1.53E-05
rs3771537	<i>AAK1</i> (<i>dist=95312</i>); <i>ANXA4</i> (<i>dist=2838</i>)	2	69966289 rs2013427	Skeletal muscle	SNRNP27	T	-0.20	154403	5.64E-06
rs3771537	<i>AAK1</i> (<i>dist=95541</i>); <i>ANXA4</i> (<i>dist=2609</i>)	2	69966518 rs7424888	Skeletal muscle	SNRNP27	A	-0.19	154174	1.44E-05
rs3771537	<i>ANXA4</i>	2	69975819 rs10211658	Skeletal muscle	SNRNP27	A	-0.20	144873	3.58E-06
rs3771537	<i>ANXA4</i>	2	69976384 rs62133983	Skeletal muscle	SNRNP27	T	-0.20	144308	3.17E-06
rs3771537	<i>ANXA4</i>	2	69980174 rs7577493	Skeletal muscle	SNRNP27	G	-0.18	140518	1.71E-05
rs3771537	<i>ANXA4</i>	2	69980193 rs5753401	Skeletal muscle	SNRNP27	T	-0.18	140499	1.71E-05
rs3771537	<i>ANXA4</i>	2	69980910 rs10181122	Skeletal muscle	SNRNP27	T	-0.18	139782	1.71E-05
rs3771537	<i>ANXA4</i>	2	69981295 rs7567400	Skeletal muscle	SNRNP27	A	-0.18	139397	1.71E-05
rs3771537	<i>ANXA4</i>	2	70031797 rs73771541	Skeletal muscle	SNRNP27	G	-0.27	88895	4.90E-10
rs3771537	<i>ANXA4</i>	2	70031941 rs771540	Skeletal muscle	SNRNP27	G	-0.28	88751	2.71E-10
rs3771537	<i>ANXA4</i>	2	70034793 rs2168115	Skeletal muscle	SNRNP27	G	-0.27	85899	4.63E-10
rs3771537	<i>ANXA4</i>	2	70036711 rs13392884	Skeletal muscle	SNRNP27	G	-0.28	83981	1.07E-10
rs3771537	<i>ANXA4</i>	2	70038232 rs6546550	Skeletal muscle	SNRNP27	G	-0.28	82460	3.45E-10
rs3771537	<i>ANXA4</i>	2	70038792 rs771537	Skeletal muscle	SNRNP27	C	-0.28	81900	6.61E-12
rs3771537	<i>ANXA4</i>	2	70039224 rs4853027	Skeletal muscle	SNRNP27	T	-0.28	81468	2.53E-10
rs3771537	<i>ANXA4</i>	2	70039677 rs2305523	Skeletal muscle	SNRNP27	C	-0.28	81015	2.27E-10
rs3771537	<i>ANXA4</i>	2	70040542 rs2312555	Skeletal muscle	SNRNP27	A	-0.30	80150	1.55E-13
rs3771537	<i>ANXA4</i>	2	70040533 rs11673826	Skeletal muscle	SNRNP27	A	-0.30	79659	4.81E-13
rs3771537	<i>ANXA4</i>	2	70050725 rs7563062	Skeletal muscle	SNRNP27	A	-0.27	69967	7.39E-10
rs3771537	<i>ANXA4</i>	2	70053668 rs7600468	Skeletal muscle	SNRNP27	G	-0.27	67024	1.47E-09
rs3771537	<i>ANXA4</i> (<i>dist=1909</i>); <i>GMCL1</i> (<i>dist=1313</i>)	2	70055505 rs1531025	Skeletal muscle	SNRNP27	A	-0.27	65187	7.70E-10
rs3771537	<i>GMCL1</i>	2	70057448 rs7322266	Skeletal muscle	SNRNP27	G	-0.27	63244	1.15E-09
rs3771537	<i>GMCL1</i>	2	70062360 rs10167142	Skeletal muscle	SNRNP27	C	-0.26	58332	1.32E-09
rs3771537	<i>GMCL1</i>	2	70062454 rs10202159	Skeletal muscle	SNRNP27	T	-0.26	58238	1.30E-09
rs3771537	<i>GMCL1</i>	2	70063563 rs4401231	Skeletal muscle	SNRNP27	C	-0.27	57129	1.13E-09
rs3771537	<i>GMCL1</i>	2	70063660 rs4241261	Skeletal muscle	SNRNP27	G	-0.26	57032	1.28E-09
rs3771537	<i>GMCL1</i>	2	70064155 rs1377995	Skeletal muscle	SNRNP27	G	-0.27	56537	1.20E-09
rs3771537	<i>GMCL1</i>	2	70068635 rs2872075	Skeletal muscle	SNRNP27	T	-0.27	52057	9.44E-10
rs3771537	<i>GMCL1</i>	2	70073703 rs6546551	Skeletal muscle	SNRNP27	T	-0.27	46989	1.09E-09
rs3771537	<i>GMCL1</i>	2	70076954 rs4852349	Skeletal muscle	SNRNP27	T	-0.28	43738	2.27E-10
rs3771537	<i>GMCL1</i>	2	70079633 rs1551374	Skeletal muscle	SNRNP27	T	-0.26	41059	6.16E-09
rs3771537	<i>GMCL1</i>	2	70087159 rs4852356	Skeletal muscle	SNRNP27	G	-0.25	33533	2.09E-08
rs3771537	<i>GMCL1</i>	2	70090579 rs13017134	Skeletal muscle	SNRNP27	G	-0.28	30113	1.24E-11
rs3771537	<i>GMCL1</i>	2	70091246 rs10865380	Skeletal muscle	SNRNP27	C	-0.29	29446	4.19E-12
rs3771537	<i>GMCL1</i>	2	70093647 rs57278310	Skeletal muscle	SNRNP27	C	-0.28	27045	5.25E-12
rs3771537	<i>GMCL1</i>	2	70093910 rs60207187	Skeletal muscle	SNRNP27	A	-0.28	26782	1.24E-11
rs3771537	<i>GMCL1</i>	2	70098808 rs3214007	Skeletal muscle	SNRNP27	G	-0.27	21884	7.58E-10

Supplementary Table 18. continued

rs3771537	<i>GMCL1</i> (<i>dist</i> =1529); <i>SNRNP27</i> (<i>dist</i> =12819)	2	70108256	rs1056482	Skeletal muscle	SNRNP27	A	-0.28	-12436	9.89E-12
rs3771537	<i>GMCL1</i> (<i>dist</i> =4984); <i>SNRNP27</i> (<i>dist</i> =9364)	2	70111711	rs6546553	Skeletal muscle	SNRNP27	A	-0.28	-8981	1.97E-11
rs3771537	<i>GMCL1</i> (<i>dist</i> =10288); <i>SNRNP27</i> (<i>dist</i> =4060)	2	70117015	rs10165883	Skeletal muscle	SNRNP27	T	-0.28	-3677	1.61E-10
rs3771537	<i>GMCL1</i> (<i>dist</i> =10449); <i>SNRNP27</i> (<i>dist</i> =3899)	2	70117176	rs12232914	Skeletal muscle	SNRNP27	T	-0.28	-3516	8.61E-11
rs3771537	<i>GMCL1</i> (<i>dist</i> =10645); <i>SNRNP27</i> (<i>dist</i> =3703)	2	70117372	rs12233079	Skeletal muscle	SNRNP27	G	-0.28	-3320	1.02E-10
rs3771537	<i>GMCL1</i> (<i>dist</i> =10694); <i>SNRNP27</i> (<i>dist</i> =3654)	2	70117421	rs2054047	Skeletal muscle	SNRNP27	C	-0.27	-3271	3.38E-10
rs3771537	<i>GMCL1</i> (<i>dist</i> =11661); <i>SNRNP27</i> (<i>dist</i> =2687)	2	70118388	rs13002091	Skeletal muscle	SNRNP27	T	-0.28	-2304	9.10E-11
rs3771537	<i>GMCL1</i> (<i>dist</i> =11700); <i>SNRNP27</i> (<i>dist</i> =2648)	2	70118427	rs13028508	Skeletal muscle	SNRNP27	A	-0.28	-2265	9.03E-11
rs3771537	<i>GMCL1</i> (<i>dist</i> =12742); <i>SNRNP27</i> (<i>dist</i> =1606)	2	70119469	rs3755389	Skeletal muscle	SNRNP27	C	-0.28	-1223	9.75E-11
rs3771537	<i>SNRNP27</i>	2	70124316	rs3752781	Skeletal muscle	SNRNP27	A	-0.28	3624	6.28E-11
rs3771537	<i>SNRNP27</i>	2	70124805	rs6720498	Skeletal muscle	SNRNP27	C	-0.28	4113	9.58E-11
rs3771537	<i>SNRNP27</i>	2	70125763	rs13015457	Skeletal muscle	SNRNP27	T	-0.28	5071	4.93E-11
rs3771537	<i>SNRNP27</i>	2	70125988	rs4852375	Skeletal muscle	SNRNP27	G	-0.28	5296	5.43E-11
rs3771537	<i>SNRNP27</i>	2	70127229	rs6716937	Skeletal muscle	SNRNP27	A	-0.28	6537	4.95E-11
rs3771537	<i>SNRNP27</i>	2	70128717	rs7598283	Skeletal muscle	SNRNP27	G	-0.28	8025	6.99E-11
rs3771537	<i>SNRNP27</i>	2	70132676	rs1048266	Skeletal muscle	SNRNP27	G	-0.28	11984	4.94E-11
rs3771537	<i>SNRNP27</i> (<i>dist</i> =1739); <i>MDK1</i> (<i>dist</i> =8066)	2	70134107	rs10166011	Skeletal muscle	SNRNP27	G	-0.28	13415	5.98E-11
rs3771537	<i>SNRNP27</i> (<i>dist</i> =3338); <i>MDK1</i> (<i>dist</i> =6467)	2	70135706	rs6546554	Skeletal muscle	SNRNP27	A	-0.28	15014	4.94E-11
rs3771537	<i>SNRNP27</i> (<i>dist</i> =3392); <i>MDK1</i> (<i>dist</i> =6413)	2	70135760	rs6546555	Skeletal muscle	SNRNP27	G	-0.29	15068	3.97E-11
rs3771537	<i>SNRNP27</i> (<i>dist</i> =5130); <i>MDK1</i> (<i>dist</i> =4675)	2	70137498	rs1979214	Skeletal muscle	SNRNP27	C	-0.28	16806	5.78E-11
rs3771537	<i>SNRNP27</i> (<i>dist</i> =5406); <i>MDK1</i> (<i>dist</i> =4399)	2	70137774	rs6736408	Skeletal muscle	SNRNP27	T	-0.28	17082	4.94E-11
rs3771537	<i>SNRNP27</i> (<i>dist</i> =5743); <i>MDK1</i> (<i>dist</i> =4062)	2	70138111	rs6739780	Skeletal muscle	SNRNP27	A	-0.28	17419	6.68E-11
rs3771537	<i>SNRNP27</i> (<i>dist</i> =5802); <i>MDK1</i> (<i>dist</i> =4003)	2	70138170	rs6754896	Skeletal muscle	SNRNP27	C	-0.28	17478	4.94E-11
rs3771537	<i>SNRNP27</i> (<i>dist</i> =6633); <i>MDK1</i> (<i>dist</i> =3172)	2	70139001	rs6546556	Skeletal muscle	SNRNP27	G	-0.28	18309	4.94E-11
rs3771537	<i>SNRNP27</i> (<i>dist</i> =6766); <i>MDK1</i> (<i>dist</i> =3039)	2	70139134	rs7592647	Skeletal muscle	SNRNP27	T	-0.28	18442	7.87E-11
rs3771537	<i>SNRNP27</i> (<i>dist</i> =7903); <i>MDK1</i> (<i>dist</i> =1902)	2	70140271	rs897122	Skeletal muscle	SNRNP27	T	-0.28	19579	4.94E-11
rs3771537	<i>MDK1</i>	2	70144596	rs11902198	Skeletal muscle	SNRNP27	A	-0.29	23904	2.83E-11
rs3771537	<i>MDK1</i>	2	70145717	rs6546558	Skeletal muscle	SNRNP27	T	-0.28	25025	1.07E-10
rs3771537	<i>MDK1</i>	2	70145833	rs6546559	Skeletal muscle	SNRNP27	A	-0.28	25141	5.67E-11
rs3771537	<i>MDK1</i>	2	70146121	rs6721891	Skeletal muscle	SNRNP27	G	-0.28	25429	4.94E-11
rs3771537	<i>MDK1</i>	2	70146123	rs6750488	Skeletal muscle	SNRNP27	T	-0.28	25433	4.94E-11
rs3771537	<i>MDK1</i>	2	70146625	rs7419837	Skeletal muscle	SNRNP27	C	-0.28	25933	1.12E-10
rs3771537	<i>MDK1</i>	2	70149225	rs1454498	Skeletal muscle	SNRNP27	A	-0.29	28533	4.20E-11
rs3771537	<i>MDK1</i>	2	70150215	rs6738174	Skeletal muscle	SNRNP27	C	-0.29	29523	2.57E-11
rs3771537	<i>MDK1</i>	2	70150674	rs6725425	Skeletal muscle	SNRNP27	C	-0.29	29982	4.20E-11
rs3771537	<i>MDK1</i>	2	70151471	rs10205487	Skeletal muscle	SNRNP27	G	-0.28	30779	4.92E-11
rs3771537	<i>MDK1</i>	2	70152027	rs726920	Skeletal muscle	SNRNP27	C	-0.29	31335	4.20E-11
rs3771537	<i>MDK1</i>	2	70153436	rs10496174	Skeletal muscle	SNRNP27	G	-0.28	32744	4.99E-11
rs3771537	<i>MDK1</i>	2	70154037	rs7573444	Skeletal muscle	SNRNP27	A	-0.28	33345	4.91E-11
rs3771537	<i>MDK1</i>	2	70154134	rs12713682	Skeletal muscle	SNRNP27	A	-0.29	33442	3.82E-11
rs3771537	<i>MDK1</i>	2	70154187	rs11893500	Skeletal muscle	SNRNP27	C	-0.28	33495	4.99E-11
rs3771537	<i>MDK1</i>	2	70155482	rs4144081	Skeletal muscle	SNRNP27	A	-0.29	34790	4.08E-11
rs3771537	<i>MDK1</i>	2	70156540	rs6712827	Skeletal muscle	SNRNP27	G	-0.28	35848	4.80E-11
rs3771537	<i>MDK1</i>	2	70156589	rs7414449	Skeletal muscle	SNRNP27	G	-0.28	35897	4.08E-11
rs3771537	<i>MDK1</i>	2	70160658	rs897119	Skeletal muscle	SNRNP27	C	-0.28	39966	8.07E-11
rs3771537	<i>MDK1</i>	2	70160982	rs897120	Skeletal muscle	SNRNP27	G	-0.28	40290	3.99E-11
rs3771537	<i>MDK1</i>	2	70161032	rs6729760	Skeletal muscle	SNRNP27	T	-0.28	40340	2.18E-10
rs3771537	<i>MDK1</i>	2	70161342	rs12613947	Skeletal muscle	SNRNP27	G	-0.28	40650	4.34E-11
rs3771537	<i>MDK1</i>	2	70163316	rs34586537	Skeletal muscle	SNRNP27	G	-0.28	42624	5.99E-11
rs3771537	<i>MDK1</i>	2	70163434	rs11126251	Skeletal muscle	SNRNP27	G	-0.28	42742	1.15E-10
rs3771537	<i>MDK1</i>	2	70164034	rs771513	Skeletal muscle	SNRNP27	C	-0.28	43342	6.17E-11
rs3771537	<i>MDK1</i>	2	70164805	rs771513	Skeletal muscle	SNRNP27	C	-0.22	44113	5.57E-07
rs3771537	<i>MDK1</i>	2	70167197	rs12475412	Skeletal muscle	SNRNP27	T	-0.28	46505	5.54E-11
rs3771537	<i>MDK1</i> (<i>dist</i> =1494); <i>ASPRV1</i> (<i>dist</i> =15654)	2	70171570	rs897121	Skeletal muscle	SNRNP27	T	-0.25	50878	3.45E-08
rs3771537	<i>MDK1</i> (<i>dist</i> =2040); <i>ASPRV1</i> (<i>dist</i> =15108)	2	70172116	rs11686934	Skeletal muscle	SNRNP27	G	-0.27	51424	2.81E-10
rs3771537	<i>MDK1</i> (<i>dist</i> =2390); <i>ASPRV1</i> (<i>dist</i> =14758)	2	70172466	rs12713684	Skeletal muscle	SNRNP27	G	-0.24	51774	1.39E-08
rs3771537	<i>MDK1</i> (<i>dist</i> =3954); <i>ASPRV1</i> (<i>dist</i> =13194)	2	70174030	rs7569561	Skeletal muscle	SNRNP27	C	-0.21	53338	2.46E-06
rs3771537	<i>MDK1</i> (<i>dist</i> =3978); <i>ASPRV1</i> (<i>dist</i> =13170)	2	70174054	rs7581977	Skeletal muscle	SNRNP27	G	-0.21	53362	3.20E-06
rs11718898	<i>CAND2</i>	3	12848822	rs11718898	Skeletal muscle	CAND2	C	0.50	10851	2.24E-20
rs11718898	<i>CAND2</i>	3	12848822	rs11718898	Skeletal muscle	KRT18P17	C	0.42	-18652	2.24E-09
rs11718898	<i>CAND2</i>	3	12848822	rs11718898	Skeletal muscle	RP11-767C1.2	C	0.30	25405	1.02E-06
rs7508	<i>ASAH1</i>	8	17913970	rs7508	Left ventricle	PCM1	A	0.20	133621	3.18E-06
rs7508	<i>ASAH1</i>	8	17913970	rs7508	Skeletal muscle	PCM1	A	-0.20	133621	1.12E-06
rs7915134	<i>SYNPO2L</i>	10	75404300	rs11000728	Atrial appendage	MYOZ1	G	1.33	-2785	1.78E-21
rs7915134	<i>SYNPO2L</i>	10	75405633	rs41280404	Atrial appendage	MYOZ1	G	1.30	-4120	5.15E-21
rs7915134	<i>SYNPO2L</i>	10	75406141	rs3740293	Atrial appendage	MYOZ1	C	1.15	-4626	4.11E-18
rs7915134	<i>SYNPO2L</i>	10	75406912	rs34163229	Atrial appendage	MYOZ1	T	1.32	-5397	1.98E-21
rs7915134	<i>SYNPO2L</i>	10	75407290	rs3812629	Atrial appendage	MYOZ1	A	1.32	-5775	1.86E-21
rs7915134	<i>SYNPO2L</i>	10	75407649	rs4746139	Atrial appendage	MYOZ1	C	1.35	-6134	1.30E-20
rs7915134	<i>SYNPO2L</i> (<i>dist</i> =1417); <i>AGAP5</i> (<i>dist</i> =16784)	10	75417249	rs4746140	Atrial appendage	MYOZ1	C	1.12	-8362	5.93E-24
rs7915134	<i>SYNPO2L</i> (<i>dist</i> =3831); <i>AGAP5</i> (<i>dist</i> =14370)	10	75419663	rs11000734	Atrial appendage	MYOZ1	G	1.13	-18148	3.47E-16
rs7915134	<i>SYNPO2L</i> (<i>dist</i> =4282); <i>AGAP5</i> (<i>dist</i> =13919)	10	75420114	rs6480708	Atrial appendage	MYOZ1	A	1.12	-18599	3.98E-16
rs7915134	<i>SYNPO2L</i> (<i>dist</i> =4348); <i>AGAP5</i> (<i>dist</i> =13853)	10	75420180	rs7915134	Atrial appendage	MYOZ1	T	1.28	-18665	2.54E-20
rs7915134	<i>SYNPO2L</i> (<i>dist</i> =4738); <i>AGAP5</i> (<i>dist</i> =13463)	10	75420570	rs7900932	Atrial appendage	MYOZ1	C	1.28	-19055	5.55E-21
rs7915134	<i>SYNPO2L</i> (<i>dist</i> =5376); <i>AGAP5</i> (<i>dist</i> =12825)	10	75421208	rs10824026	Atrial appendage	MYOZ1	A	-1.12	-19693	3.98E-16
rs7915134	<i>SYNPO2L</i> (<i>dist</i> =5614); <i>AGAP5</i> (<i>dist</i> =12587)	10	75421446	rs7394152	Atrial appendage	MYOZ1	T	1.30	-19931	1.88E-21
rs7915134	<i>SYNPO2L</i> (<i>dist</i> =5748); <i>AGAP5</i> (<i>dist</i> =12453)	10	75421580	rs7394178	Atrial appendage	MYOZ1	A	1.27	-20065	5.46E-21
rs7915134	<i>SYNPO2L</i> (<i>dist</i> =5816); <i>AGAP5</i> (<i>dist</i> =12385)	10	75421648	rs7394190	Atrial appendage	MYOZ1	A	1.13	-20133	3.03E-16
rs7915134	<i>SYNPO2L</i> (<i>dist</i> =6482); <i>AGAP5</i> (<i>dist</i> =11719)	10	75422314	rs78249997	Atrial appendage	MYOZ1	T	1.32	-20799	7.49E-21
rs7915134	<i>SYNPO2L</i> (<i>dist</i> =12464); <i>AGAP5</i> (<i>dist</i> =5737)	10	75428296	rs148321568	Atrial appendage	MYOZ1	T	1.50	-26781	4.54E-21
rs7915134	<i>SYNPO2L</i> (<i>dist</i> =14169); <i>AGAP5</i> (<i>dist</i> =4032)	10	75430001	rs4745719	Atrial appendage	MYOZ1	G	-0.96	-28486	3.66E-11
rs7915134	<i>AGAP5</i>	10	75447582	rs147790633	Atrial appendage	MYOZ1	C	1.36	-46067	2.07E-20

Supplementary Table 18. continued

rs10824026	SYNPO2L	10	75407290	rs3812629	Atrial appendage	MYOZ1	A	1.32	-5775	1.86E-21
rs10824026	SYNPO2L	10	75407649	rs4746139	Atrial appendage	MYOZ1	C	1.35	-6134	1.30E-20
rs10824026	SYNPO2L	10	75409877	rs2177843	Atrial appendage	MYOZ1	T	1.34	-8362	5.93E-24
rs10824026	SYNPO2L	10	75414344	rs60212594	Atrial appendage	MYOZ1	C	1.36	-12829	1.52E-23
rs10824026	SYNPO2L	10	75415677	rs60632610	Atrial appendage	MYOZ1	T	1.35	-14162	4.70E-23
rs10824026	SYNPO2L	10	75416789	rs12570126	Atrial appendage	MYOZ1	G	1.13	-15274	3.20E-16
rs10824026	SYNPO2L(<i>dist</i> =1417);AGAP5(<i>dist</i> =16784)	10	75417249	rs4746140	Atrial appendage	MYOZ1	C	1.12	-15734	3.98E-16
rs10824026	SYNPO2L(<i>dist</i> =3831);AGAP5(<i>dist</i> =14370)	10	75419663	rs11000734	Atrial appendage	MYOZ1	G	1.13	-18148	3.47E-16
rs10824026	SYNPO2L(<i>dist</i> =4282);AGAP5(<i>dist</i> =13919)	10	75420114	rs6480708	Atrial appendage	MYOZ1	A	1.12	-18599	3.98E-16
rs10824026	SYNPO2L(<i>dist</i> =4348);AGAP5(<i>dist</i> =13853)	10	75420180	rs7915134	Atrial appendage	MYOZ1	T	1.28	-18665	2.54E-20
rs10824026	SYNPO2L(<i>dist</i> =4738);AGAP5(<i>dist</i> =13463)	10	75420570	rs7900932	Atrial appendage	MYOZ1	C	1.28	-19055	5.55E-21
rs10824026	SYNPO2L(<i>dist</i> =5376);AGAP5(<i>dist</i> =12825)	10	75421208	rs10824026	Atrial appendage	MYOZ1	A	-1.12	-19693	3.98E-16
rs10824026	SYNPO2L(<i>dist</i> =5614);AGAP5(<i>dist</i> =12587)	10	75421446	rs7394152	Atrial appendage	MYOZ1	T	1.30	-19931	1.88E-21
rs10824026	SYNPO2L(<i>dist</i> =5748);AGAP5(<i>dist</i> =12453)	10	75421580	rs7394178	Atrial appendage	MYOZ1	A	1.27	-20065	5.46E-21
rs10824026	SYNPO2L(<i>dist</i> =5816);AGAP5(<i>dist</i> =12385)	10	75421648	rs7394190	Atrial appendage	MYOZ1	A	1.13	-20133	3.03E-16
rs10824026	SYNPO2L(<i>dist</i> =6482);AGAP5(<i>dist</i> =1719)	10	75422314	rs78249997	Atrial appendage	MYOZ1	T	1.32	-20799	7.49E-21
rs10824026	SYNPO2L(<i>dist</i> =12464);AGAP5(<i>dist</i> =5737)	10	75428296	rs148321568	Atrial appendage	MYOZ1	T	1.50	-26781	4.54E-21
rs10824026	SYNPO2L(<i>dist</i> =14169);AGAP5(<i>dist</i> =4032)	10	75430001	rs4745719	Atrial appendage	MYOZ1	G	-0.96	-28486	3.66E-11
rs10824026	SYNPO2L(<i>dist</i> =15246);AGAP5(<i>dist</i> =2955)	10	75431078	rs3878005	Atrial appendage	MYOZ1	A	1.43	-29563	2.79E-20
rs10824026	AGAPS	10	75447582	rs147790633	Atrial appendage	MYOZ1	C	1.36	-46067	2.07E-20
rs10824026	AGAPS	10	75449789	rs76443711	Atrial appendage	MYOZ1	C	1.41	-48274	3.07E-21
rs10824026	AGAPS	10	75450901	rs138055607	Atrial appendage	MYOZ1	G	1.41	-49386	3.04E-21
rs10824026	BMS1P4	10	75462510	rs76192127	Atrial appendage	MYOZ1	C	1.40	-60995	5.05E-21
rs10824026	BMS1P4	10	75464587	rs4745721	Atrial appendage	MYOZ1	A	1.41	-63072	6.14E-21
rs10824026	ZSWIM8	10	75559077	rs11000780	Atrial appendage	MYOZ1	A	1.25	-157562	3.71E-15
rs10824026	NDST2	10	75562108	rs2075641	Atrial appendage	MYOZ1	A	1.17	-160593	1.67E-14
rs10824026	CAMK2G	10	75573778	rs2306327	Atrial appendage	MYOZ1	T	1.17	-172263	1.67E-14
rs10824026	CAMK2G	10	75575138	rs113799665	Atrial appendage	MYOZ1	T	1.17	-173623	1.66E-14
rs10824026	CAMK2G	10	75576405	rs12220394	Atrial appendage	MYOZ1	C	1.17	-174890	1.66E-14
rs10824026	CAMK2G	10	75576483	rs2217245	Atrial appendage	MYOZ1	C	1.17	-174968	1.67E-14
rs10824026	CAMK2G	10	75578720	rs4746151	Atrial appendage	MYOZ1	T	1.17	-177205	1.67E-14
rs10824026	CAMK2G	10	75578948	rs3843939	Atrial appendage	MYOZ1	C	1.17	-177433	1.67E-14
rs10824026	CAMK2G	10	75580226	rs188726810	Atrial appendage	MYOZ1	T	1.13	-178711	3.05E-13
rs10824026	CAMK2G	10	75583034	rs59693993	Atrial appendage	MYOZ1	T	1.22	-181519	1.78E-14
rs10824026	CAMK2G	10	75585307	rs2242254	Atrial appendage	MYOZ1	A	1.17	-183792	1.42E-13
rs10824026	SYNPO2L	10	75407649	rs4746139	Skeletal muscle	FUT11	C	-0.26	-125299	1.13E-05
rs10824026	SYNPO2L	10	75409877	rs2177843	Skeletal muscle	FUT11	T	-0.25	-123071	1.37E-05
rs10824026	SYNPO2L	10	75416789	rs12570126	Skeletal muscle	FUT11	G	-0.23	-116159	1.51E-05
rs10824026	SYNPO2L(<i>dist</i> =1417);AGAP5(<i>dist</i> =16784)	10	75417249	rs4746140	Skeletal muscle	FUT11	C	-0.24	-115699	7.13E-06
rs10824026	SYNPO2L(<i>dist</i> =3831);AGAP5(<i>dist</i> =14370)	10	75419663	rs11000734	Skeletal muscle	FUT11	G	-0.23	-113285	1.37E-05
rs10824026	SYNPO2L(<i>dist</i> =4282);AGAP5(<i>dist</i> =13919)	10	75420114	rs6480708	Skeletal muscle	FUT11	A	-0.23	-112834	1.43E-05
rs10824026	SYNPO2L(<i>dist</i> =4738);AGAP5(<i>dist</i> =13463)	10	75420570	rs7900932	Skeletal muscle	FUT11	C	-0.24	-112378	1.85E-05
rs10824026	SYNPO2L(<i>dist</i> =5376);AGAP5(<i>dist</i> =12825)	10	75421208	rs10824026	Skeletal muscle	FUT11	A	0.24	-111740	1.05E-05
rs10824026	SYNPO2L(<i>dist</i> =5616);AGAP5(<i>dist</i> =12385)	10	75421648	rs7394190	Skeletal muscle	FUT11	A	-0.25	-111300	5.90E-06
rs10824026	SYNPO2L(<i>dist</i> =5816);AGAP5(<i>dist</i> =12385)	10	75422314	rs78249997	Skeletal muscle	FUT11	T	-0.25	-110634	1.56E-05
rs10824026	SYNPO2L(<i>dist</i> =6482);AGAP5(<i>dist</i> =1719)	10	75428296	rs148321568	Skeletal muscle	FUT11	T	-0.26	-104652	1.38E-05
rs10824026	SYNPO2L(<i>dist</i> =12464);AGAP5(<i>dist</i> =5737)	10	75431078	rs3878005	Skeletal muscle	FUT11	A	-0.27	-101870	1.09E-05
rs10824026	SYNPO2L(<i>dist</i> =15246);AGAP5(<i>dist</i> =2955)	10	75447582	rs147790633	Skeletal muscle	FUT11	C	-0.27	-85366	3.84E-06
rs10824026	AGAPS	10	75449789	rs76443711	Skeletal muscle	FUT11	C	-0.27	-83159	1.10E-05
rs10824026	AGAPS	10	75450901	rs138055607	Skeletal muscle	FUT11	G	-0.27	-82047	1.12E-05
rs10824026	BMS1P4	10	75462510	rs76192127	Skeletal muscle	FUT11	C	-0.27	-70438	1.18E-05
rs10824026	BMS1P4	10	75464587	rs4745721	Skeletal muscle	FUT11	A	-0.27	-68361	1.20E-05
rs10824026	ZSWIM8	10	75559077	rs11000780	Skeletal muscle	FUT11	A	-0.31	-26129	4.62E-07
rs10824026	NDST2	10	75562108	rs2075641	Skeletal muscle	FUT11	A	-0.31	-29160	3.50E-07
rs10824026	CAMK2G	10	75573778	rs2306327	Skeletal muscle	FUT11	T	-0.31	-40830	3.50E-07
rs10824026	CAMK2G	10	75575138	rs113799665	Skeletal muscle	FUT11	T	-0.32	-42190	1.90E-07
rs10824026	CAMK2G	10	75576405	rs12220394	Skeletal muscle	FUT11	C	-0.30	-43457	6.60E-07
rs10824026	CAMK2G	10	75576483	rs12217245	Skeletal muscle	FUT11	C	-0.30	-43535	6.43E-07
rs10824026	CAMK2G	10	75578720	rs4746151	Skeletal muscle	FUT11	T	-0.30	-45772	6.43E-07
rs10824026	CAMK2G	10	75578948	rs3843939	Skeletal muscle	FUT11	C	-0.30	-46000	6.43E-07
rs10824026	CAMK2G	10	75583034	rs59693993	Skeletal muscle	FUT11	T	-0.31	-50086	5.81E-07
rs10824026	CAMK2G	10	75585307	rs2242254	Skeletal muscle	FUT11	A	-0.30	-52359	9.77E-07
r575190942	KCNJ5	11	128764570	rs76097649	Left ventricle	KCNJ5	A	0.58	3319	3.15E-06
r575190942	KCNJ5	11	128764571	rs75190942	Left ventricle	KCNJ5	A	0.58	3320	3.15E-06
rs883079	RBM19(<i>dist</i> =385634);TBX5(<i>dist</i> =1925)	12	114789810	rs2891503	Left ventricle	TBX5	G	0.26	56437	3.84E-06

ExWAS

Variants identified in combined ancestry analysis - eQTLs from GTEx Release V6										
rs60632610	SYNPO2L	10	75407290	rs3812629	Atrial appendage	MYOZ1	A	1.32	-5775	1.86E-21
rs60632610	SYNPO2L	10	75415677	rs60632610	Atrial appendage	MYOZ1	T	1.35	-14162	4.70E-23
Variants identified in European ancestry analysis - eQTLs from GTEx Release V6										
rs60632610	SYNPO2L	10	75406912	rs34163229	Atrial appendage	MYOZ1	T	1.32	-5397	1.98E-21
rs60632610	SYNPO2L	10	75407290	rs3812629	Atrial appendage	MYOZ1	A	1.32	-5775	1.86E-21
rs60632610	SYNPO2L	10	75415677	rs60632610	Atrial appendage	MYOZ1	T	1.35	-14162	4.70E-23

At each significantly associated AF locus, we defined a region based on LD span ($r^2 > 0.2$) with the Index SNP. All variants within this region were tested in the eQTL analyses. *The most significant variant in the region. **For intronic variants, the gene the variant is located within is listed; for intergenic variants, the closest genes upstream and downstream are listed.

+Variant tested. #eQTL gene. This table reports the variants (rsID) that were significantly associated with altered expression of the eQTL genes. SNP, single nucleotide polymorphism; Chr, chromosome; Tissue, eQTL tissue (only results shown for Skeletal muscle, Atrial appendage and Left ventricle); Effect Allele, eQTL effect allele; Beta, eQTL effect size; TSS, Transcription start site; P-value, eQTL p-value.

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Supplementary Table 20. *In silico* functional evaluation of novel and replicated loci from GWAS and ExWAS combined ancestry analysis

rsID	Chr	Position	Gene*	Functional Annotation	eQTL CCAF	eQTL GTEx	Chromatin States	Chromatin States, Heart	DHS	DHS Heart	Protein Binding	Motifs Changed	N MC	R_DB Score
GWAS combined ancestry analysis														
rs11264280	1	154862952	KCNN3 (<i>dist</i> =20198); PMVK (<i>dist</i> =34256)	intergenic	ADAM15 MUC1	ZBTB7B			No	No	Mtf1_1_Zbtb3	2	7	
rs520525	1	170638333	PRRX1	intronic	PRRX1	RP1-79C4.4 PRRX1	10_TssBiv, 6_EnhG, 11_BivFlnk, 2_TssAFlnk	7_Enh	Yes	Yes	SUZ12	1_known5_Gcm1, THAP1_disc2, Zfp281_YY1_disc2	7	3a
rs72700118	1	170194823	METTL11B (<i>dist</i> =57900); LOC246888 (<i>dist</i> =45723)	intergenic	KIFAP3		7_Enh	7_Enh	No	No		PLAG1_Mtf1_1, Myf_1	3	5
rs2288327	2	179411665	TTN; TTN-AS1	ncRNA_intronic			6_EnhG		No	No		HNF1_1_HNF1_7, Mef2_known1	3	6
rs2540949	2	65284231	CEP68	intronic	CEP68	CEP68	10_TssBiv, 1_TssA, 2_TssAFlnk	1_TssA	Yes	Yes	TAL1_HDAC2_Mrg_2 HMGN3_GATA1		1	4
rs3771537	2	70038792	ANXA4	intronic	ANXA4 SNRNP27 GMCL1 PCYOX1		6_EnhG		No	No		RXRA_known4	1	5
rs11718898	3	12848822	CAND2	exonic	KRT18P17 RP11- 767C1.2 CAND2		6_EnhG, 12_EnhBiv, 7_Enh	6_EnhG, 7_Enh	Yes	Yes	ERRA, CTCF, RAD21, CMYC	SMC3_disc1, CTCF_known1, SMC3_disc4, Rad21_disc1, TRA_disc2, CTCF_disc1, RXRA_disc2	7	2a
rs6843082	4	111718067	PITX2 (<i>dist</i> =154788); C4orf32 (<i>dist</i> =1348486)	intergenic			7_Enh		Yes	Yes		ZEB1_known2_RhoX11	2	6
rs2967791	5	137013106	KLHL3	intronic					No	No			0	7
rs337711	5	113748571	KCNN2	intronic	KCNN2		7_Enh		Yes	No	STAT3, RFX5		0	4
rs12664873	6	122463191	GJA1 (<i>dist</i> =692318); HSF2 (<i>dist</i> =257505)	intergenic					No	No		PLZF_Foxp1_Hoxa9	3	7
rs4946333	6	118565665	SLC35F1	intronic					No	No		STAT_known11_Hsf_known1_UF1H3BETA	3	7
rs1997572	7	116198828	CAV1	intronic	CAV1 CAV2		6_EnhG	6_EnhG	Yes	No		Gf1_1_Foxp1_Pouf2_known2_ZBRK1	4	6
rs7508	8	17913970	ASAHI	UTR3	PCM1 ASAHI	PCM1	6_EnhG		Yes	No		Foxj2_1	1	6
rs7026071	9	97492520	C9orf3	intronic					No	No		E2F_known2_E2F_known3_Zbtb3_CEPBPB_known5	4	6
rs11598047	10	105342672	NEURL	intronic	USMG5 MIR1307		12_EnhBiv,7_E nh,2_TssAFlnk		Yes	No		Ets_disc5	1	4
rs35176054	10	105480387	SH3PXD2A	intronic								Nkx2_4_Pouf2_known8_COMP1_GATA_known2	4	2b
rs7915134	10	75420180	SYNPO2L (<i>dist</i> =4348); AGAP5 (<i>dist</i> =13853)	intergenic	MYOZ1 SYNPO2L	MYOZ1 FUT11	7_Enh		No	No		SETDB1_disc1_NRSE_disc9_ELF1_disc3_Myc_disc10	4	7
rs75190942	11	128764571	KCNJ5	intronic	KCNJ5	KCNJ5	12_EnhBiv,7_E nh	7_Enh	Yes	Yes	GATA2	STAT_known8_NF-kappaB_disc2_Nkx2_4_NF-kappaB_known4_N_F-kappaB_known5_N_kx5_Nkx2_11	7	2b
rs883079	12	114793240	TBX5	UTR3	TBX5	TBX5	6_EnhG,7_Enh	7_Enh	Yes	Yes		Evi-1_3	1	5
rs1152591	14	64680848	SYNE2	intronic	SYNE2	SYNE2	6_EnhG,3_TxFI nk,7_Enh,1_Ts sA,2_TssAFlnk	3_TxFlnk,1_Ts sA,2_TssAFlnk	Yes	Yes		GR_known6	1	5
rs74022964	15	73677264	HCN4 (<i>dist</i> =15659); C15orf60 (<i>dist</i> =58235)	intergenic					No	No		ERalpha-a_known4_Esr2_Po_u1f1_2	3	7
rs2106261	16	73051620	ZFHX3	intronic			6_EnhG,7_Enh	6_EnhG,7_Enh	No	No		Pax-6_1_CEPBPB_known5	2	7

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Supplementary Table 20. continued

EWAS combined ancestry analysis													
rs13376333	1	154814353	KCNN3	intronic		12_EnhBiv, 7_Enh, 6_EnhG, 1_TssA	No	No			13	1f	
rs6800541	3	38774832	SCN10A	intronic		7_Enh	No	No			0	7	
rs17042171	4	111708287	PITX2 (<i>dist=145008</i>); C4orf32 (<i>dist=1358266</i>)	intergenic		7_Enh	No	No			7	5	
rs89107	6	118578043	SLC35F1	intronic			No	No	AP-3	1	5		
rs3807989	7	116186241	CAV1	intronic	CAV1 CAV2	7_Enh, 6_EnhG 7_Enh, 6_EnhG	Yes	Yes	CMYC, USF1, TAL1, GATA2	Myf_2, E2A_2, Myc_knowm1	3	3a	
rs60632610	10	75415677	SYNPO2L	exonic; nonsynonymous	MYOZ1 SYNPO2L	MYOZ1 1_TssA 2_TssAFlnk, 1_TssA	Yes	Yes			0	4	
rs11047543	12	24788339	LINC00477 (<i>dist=51237</i>); BCAT1 (<i>dist=174619</i>)	intergenic		7_Enh	Yes	No	HNF4_known5, RORalpha1_1, Pax-4_2, HMG-IY_2, PLZF, RXRA_known3		6	7	
rs10151658	14	64612858	SYNE2	exonic; nonsynonymous	SYNE2		No	No	NF-I_1	1	6		
rs2106261	16	73051620	ZFHX3	intronic		7_Enh, 6_EnhG 7_Enh, 6_EnhG	No	No	CEBPP_known5, Pax-6_1		2	7	

Bold font indicates novel AF associated loci. Chr, chromosome; DHS, DNAse Hypersensitivity Site; N MC, number of motifs changed; R_DB, Regulome Database; TssA, Active TSS; TssAFlnk, Flanking Active TSS; TxFlnk, Transcr. at gene 5' and 3'; Tx, Strong transcription; TxWk, Weak transcription; EnhG, Genic enhancers; Enh, Enhancers; ZNF/Rpts, ZNF genes & repeats; Het, Heterochromatin; TssBiv, Bivalent/Poised TSS; BivFlnk, Flanking Bivalent TSS/Enh; EnhBiv, Bivalent Enhancer; ReprPC, Repressed PolyComb; ReprPCWk, Weak Repressed PolyComb; Quies, Quiescent/Low. *For intronic variants, the gene the variant is located within is listed; for intergenic variants, the closest genes upstream and downstream are listed.

Supplementary Table 21. Per study overlap of samples between GWAS and ExWAS analyses

Study	Overlap	
	Cases	Controls
BioVU	206	3811
WGHS	934	20,266
FHS - incident	411	1612
FHS - prevalent	181	2123
CHS - incident	922	1979
CHS -prevalent	60	2900
AGES	354	2989
RS	346	2370
CAMP	665	2128
SHIP	99	2710
AFLMU/KORA	349	415
MGH	333	0
ARIC EA	1253	3415
ARIC AA	233	742
MESA	155	2372
GS:SFHS	203	6651
BioMe EA	290	857
BioMe AA	166	2041
BioMe HA	255	2800
BEAT-AF	1520	1516
BBJ	782	0
Total	9717	63,697

Supplementary Table 22. GWAS information per study

Study	R	Array	Calling Algorithm	Per variant call rate	HWE p-value	Mendelian errors	Excess heterozygosity	MAF	Selection criteria for PCs	PCs	N variants for imputation	Imputation software	GWAS Statistical Analysis	N variants analyzed	Inflation factor, lambda
AFLMU /KORA	¹⁶⁹	Illumina HumanCNV3 70 + Illumina Human550K	BeadStudio	≥98%	<10 ⁻⁵	-	-	>1%	P<0.05	1	306,838	SHAPEIT v2.r790 + IMPUTE v.2.1.2	SNPTEST v2.5	7,540,650	1.023
AGES	¹⁷⁰	Illumina HumanCNV3 70-Duo BeadChip	BeadStudio	≥97%	<10 ⁻⁶	-	-	≥1%	P<0.05	0	329,804	MaCH v.1.0.16 + minimac	ProbABEL, R	I: 7,602,716 P: 6,085,662	I: 1.068 P: 1.006
ANGES	¹⁷¹	Illumina Metabochip	GenomeStudio	≥95%	≥10 ⁻⁶	-	>3.18 SD from the mean removed	-	first 4 PCs	4	121,545	SHAPEIT v.2.r790 + IMPUTE2 v.2.3.0	SNPTEST v2.4.1	5,861,502	P&I: 1.011
ARIC	^{172,173}	Affymetrix 6.0	Birdseed	≥95%	<10 ⁻⁵	-	-	EA: >0.5% AA: >1%	Analysis committee recommendations	EA: 4 AA: 10	EA: 711,589 AA: 806,416	(1) Pre-phasing with Shapelt (v1.r532) (2) Imputation with IMPUTE2.1.0	FAST	EA: 9,428,893 AA: 8,978,558	EA: 1.011 AA: 0.991
Beat-AF	¹⁷⁴	Illumina HumanCoreExome	BeadStudio	≥95%	>10 ⁻⁶	-	>3 SD from the mean removed	≥1%	First 10 PCs	10	254,488	SHAPEIT v2.r790 + IMPUTE v.2.3.2	SNPTEST v2.5	9,309,201	1.022

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Study	R	Array	Calling Algorithm	Per variant call rate	HWE p-value	Mendelian errors	Excess heterozygosity	MAF	Selection criteria for PCs	PCs	N variants for imputation	Imputation software	GWAS Statistical Analysis	N variants analyzed	Inflation factor, lambda
BBJ	175	Illumina Human610 Quad and Illumina Human Hap550v3 BeadChip	Beadstudio	≥99%	>10 ⁻⁶	-	-	≥1%	First 2 PCs	2	432,042	MaCH + minimac	PLINK v1.07	6,429,092	1.024
BioMe	176	Illumina HumanOmni ExpressExome-8 v1.0	zCall (GenomeStudio)	≥90%	p>10 ⁻⁶	-	-	≥1%	first 4 PCs	4	768,517	IMPUTE2	SNPTEST v.2.5	EA: 7,022,478 AA: 8,200,353 HA: 8,139,248	EA: 1.008 AA: 1.019 HA: 1.026
BioVU	177	Illumina Omni5 + Omni1 + 1M + 660K	GenomeStudio	≥98%	<10 ⁻⁵	-	-	≥1%	First 2 PCs	2	4,167,400	IMPUTE2 v2.3.0	PLINK v1.90	660: 3,187,278 omni: 4,373,169	660: 1.003 Omni: 1.01
CCAF	169	Hap550 v1&v3 chip + Hap610 v1 chip	BeadStudio	≥95%	FDR>10 ⁻⁴	-	FDR>0.01	≥1%	P<0.05	4	516,461	Shapeit v2.r727 + IMPUTE v.2.3.0	SNPtest v.2.5	8,122,372	1.026
CHS - AA	178	HumanOmni 1-Quad_v1	GenomeStudio	≥97%	≥10 ⁻⁵	≤1 in CEPH trios	-	>0.01 %	PCs with P<0.05 and all PCs before the associated PC	3	963,248	IMPUTE version 2.2.2	R	8,152,032	1.001
CHS - EA	178	Illumina 370 CNV + ITMAT-Broad-CARe (IBC) Illumina iSELECT chip	BeadStudio	≥97%	≥10 ⁻⁵	≤2 in CEPH trios	-	>0.01 %	PCs with P<0.05 and all PCs before the associated PC	0	359,592	MaCH + minimac	R	8,278,530	1.045

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Study	R	Array	Calling Algorithm	Per variant call rate	HWE p-value	Mendelian errors	Excess heterozygosity	MAF	Selection criteria for PCs	PCs	N variants for imputation	Imputation software	GWAS Statistical Analysis	N variants analyzed	Inflation factor, lambda
COROGENE	¹⁷⁹	Illumina Metabochip + CoreExome	GenomeStudio	≥95%	≥10 ⁻⁵	-	-	≥1%	-	0	553,581	IMPUTE v2.2.2	SNPTEST v2.4.1	6,956,681	1.019
FHS	^{180,181}	Affymetrix, Gene Chip®, 500K Array Set & 50K Human Gene Focused Panel	BRLMM	≥97%	<10 ⁻⁶		Subject heterozygosity >5 SD away from the mean	≥1%	All PCs unassociated, p>0.05	0	385,958	Mach1 v1.0.15	R packages kinship, GEE, COXPH	I: 7525764 P: 6556225	I: 1.019 P: 1.04
FINCAVAS	¹⁸²	Illumina Metabochip + CoreExome	GenomeStudio	≥95%	≥10 ⁻⁶	-	>3.23 SD from the mean removed	-	First 4 PCs	4	Metabochip : 120,689 CoreExome: 277,211	SHAPEIT v.2.r790 + IMPUTE2 v.2.3.0	SNPTEST v2.4.1	8,384,365	P&I: 1.04
GS:SFFS	¹⁸³	Illumina Omni Express Plus Exome	BeadStudio	Omni ≥98% Exome ≥99%	<10 ⁻⁶	-	-	Omni <1% Exome <0.01 %	PCs associated after adjustment for sex and age with p<0.05)	1	706,198 (690,759 Autosomes)	ShapeIt2 (pre-phasing), IMPUTE2 (imputation)	ProbABEL	6,563,971	0.997
HNR	¹⁸⁴	Illumina: Omni Express, Omni1, CoreExomeA and CoreExomeB			<10 ⁻⁵		Subject heterozygosity >5 SD away from the mean	MAF ≥0.01 and ≤99.9	First 10 PCs	10	Omni1: 682,618 OmniEx: 646,304 CoreExB: 255,584 CoreExA: 256,445	Impute v.2.3.0	SNPTEST	Excluded due to sample size	
LURIC	¹⁸⁵	Affymetrix 6.0	Birdseed v.2	≥98%	0.0001	-	-	≥1%	First 3 PCs	3	686,195	IMPUTE v.2	SNPtest v.2.5	7,270,779	1.003

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Study	R	Array	Calling Algorithm	Per variant call rate	HWE p-value	Mendelian errors	Excess heterozygosity	MAF	Selection criteria for PCs	PCs	N variants for imputation	Imputation software	GWAS Statistical Analysis	N variants analyzed	Inflation factor, lambda
MDCS	¹⁸⁶	Illumina Human Omni Express Exome 1.0	GenomeStudio	≥95%	0.0001	-	-	≥1%	All PCs unassociated, p>0.05	0	816,728	IMPUTE v.2	SNPtest v.2.5	I: 8,981,701 P: 5,392,317	I: 0.99 P: 1.00
MESA	^{187, 88}	Affymetrix 6.0	Birdseed v1.33	≥95%	<10 ⁻⁶	-	-	≥1%	First 2 PCs	2	881,666	IMPUTE2	ProbABEL	5,340,434	1.027
MGH AF study	¹⁶⁹	Affymetrix 6.0	Birdseed	≥97%	<10 ⁻⁶	-	-	≥1%	-	0	663,637	IMPUTE v2	PLINK v1.07	6,764,173	1.028
MGH CAMP		Infinium HumanCoreExome-24 BeadChips	zCall (GenomeStudio)	≥95%	≥10 ⁻⁶	-	-	≥1%	PC1-PC10	10	224,343	IMPUTE2	PLINK v1.08	8,262,143	1.01
MGH Stroke	^{3,189}	Affymetrix 6.0 + Illumina 610	Birdseed / GenCall	>95% MAF >5%	<10 ⁻⁶	-	>±3 SD from the mean	>5%	-	2	GASROS Affymetrix: 579,083 GASROS Illumi-: 398,434 GOCHA: 521,363	IMPUTE2 v.2.3.0	SNPtest v.2.4.1	Excluded due to sample size	
WTCCC 2 Munich	^{3,190}	Illumina 660	GenCall	>98%	>10 ⁻⁵	-	-	>1%	-	0	495,851	MACH+minimac	SNPTTEST	5,891,675	1.019

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Study	R	Array	Calling Algorithm	Per variant call rate	HWE p-value	Mendelian errors	Excess heterozygosity	MAF	Selection criteria for PCs	PCs	N variants for imputation	Imputation software	GWAS Statistical Analysis	N variants analyzed	Inflation factor, lambda
PIVUS	191	Illumina OmniExpress +Metabochip	GenCall	≥99% (MAF<5%) or ≥95% (MAF≥5%)	>10 ⁻⁶	-	>3 SD from the mean	≥1%	First 2 PCs	2	738,879	IMPUTE v.2.2.2	SNPTEST v.2.5	6,045,282	1.006
PREVENT	192	Illumina CytoSNP12 v2	GenomeStudio	>95%	>10 ⁻⁶	-	-	≥1%	First 5 PCs	5	232,571	IMPUTE1	SNPTEST v.2	5,091,540	1.031
PROSPEK	193	Illumina Beadchip 660Quad	BeadStudio	≥98%	<10 ⁻⁶	-	-	>1%		4	557,192	IMPUTE v.2.2.2	SNPTEST	7,819,558	1.009
RS	194	Illumina Infinium HumanHap550 chip v3.0	BeadStudio	≥98%	<10 ⁻⁶	-	>0.336	>1%	First 4 PCs	4	512,849	Mach 1 vs 1.0.151	ProbABEL	RSI: 7,695,631 RS1: 1.022 RS2: 5,543,119 RS2: 1.003 RS3: 5,224,770 RS3: 1.033	P&I
SPHFC	195	Affymetrix Axion Brazilian Biobank Array	Birdseed v.2	≥97%	<10 ⁻⁶	-	-	≥1%	First 3 PCs			IMPUTE v3	PLINK v1.08	7,104,209	1.02
SHIP	196	Affymetrix Genome-Wide Human SNP Array 6.0	Birdseed2	≥80%	>0.0001	-	-	≥1%	First 10 PCs	-	905,910	IMPUTE v.2.2.2	QUICKTEST v0.95	5,289,189	0.997
TWINGENE	197	Illumina HumanOmni Express	GenCall	≥97%	>10 ⁻⁷	-	>5 SD from the mean	≥1%	First 3 PCs	3	644,556	minimac (release 2012-10-03)	SNPTEST v.2.5	7,201,417	0.983

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Study	R	Array	Calling Algorithm	Per variant call rate	HWE p-value	Mendelian errors	Excess heterozygosity	MAF	Selection criteria for PCs	PCs	N variants for imputation	Imputation software	GWAS Statistical Analysis	N variants analyzed	Inflation factor, lambda
ULSAM	¹⁹⁸	Illumina Omni2.5+Metabochip	GenCall	≥99% (MAF<5%) or ≥95% (MAF≥5%)	>10 ⁻⁶	-	>3 SD from the mean	≥1%	First 2 PCs	2	1,587,454	IMPUTE v.2.2.2	SNPTEST v.2.5	7,297,774	0.996
WGHS	¹⁹⁹	Illumina HumanHap 300 DuoPlus	BeadStudio v. 3.3	≥90%	>10 ⁻⁶	-	-	≥1%	PCs 1,2, & 10	3	332,927	MaCH v.1.0.16 + minimac (release 5/29/2012)	ProbABEL	8,144,887	1.02

Supplementary Table 23. General principles for quality control and filtering

<p><u>Pre-imputation:</u></p> <p>Per marker quality control:</p> <ul style="list-style-type: none">Call rate (exclude markers if <95%)Hardy-Weinberg Equilibrium (exclude markers if marked deviation)Duplicate concordance (exclude markers with high discordance rates)Mendelian inconsistencies (exclude markers with an excess of Mendelian inconsistencies)Genotype completeness (exclude markers with relatively high missingness)Polymorphism check (exclude monomorphic markers which can represent assay failures) <p>Per individual quality checks typically include:</p> <ul style="list-style-type: none">Principal Component AnalysisExclude samples with high degree of missingnessExclude samples with unusual heterozygosityExclude monomorphic markers which can represent assay failures <p>Exclude related individuals for non-family studies</p>
<p><u>Imputation:</u></p> <p>Cases and controls imputed together</p> <p>Criteria for imputation:</p> <ul style="list-style-type: none">1000G release used for imputation: 20110521 Phase 1 Integrated release ALLGene reference assembly: GRCh37SNPs oriented to forward/+ strand
<p><u>Individuals study analysis:</u></p> <p>Account for genotype uncertainty of imputed SNPs</p> <p>Control for population stratification</p>
<p><u>Meta-analysis:</u></p> <p>Criteria for including variants (GWAS/EWAS)</p> <ul style="list-style-type: none">Imputation quality >0.3MAF ≥ 0.01 (GWAS), MAF ≥ 0.005 (EWAS)Variant present in ≥ 2 studiesEffect allele frequency x imputation quality (INFO) x number of cases ≥ 10 <p>Criteria for including genes (gene based tests)</p> <ul style="list-style-type: none">Cumulative MAF per gene ≤ 0.005 <p>Quality control:</p> <ul style="list-style-type: none">Estimate genomic inflation factor lambda for each study, and adjust if lambda > 1Check distribution of meta-analysis $-\log_{10}(p\text{-values})$ using QQ plots

Supplementary Table 24. ExWAS information per study

Study	R	Array	Calling Algorithm	Per variant call rate	HWE p-value	Mendelian errors	Excess heterozygosity	MAF	Selection criteria for PCs	PCs	Total N variants analyzed
AFLMU/ MGH AF	¹⁶⁹	Illumina Infinium HumanExome BeadChip v1.0	CHARGE	-	-	-	Exclude het >5 SD	-	p<0.01 in association adjusted for age and sex; derived under exclusion of candidate regions	11	241,465
AGES	¹⁷⁰	Illumina Exome Chip v1.0	Illumina GenomeStudio 2011.1	≥95%	<10 ⁻⁶	-	-	-	p<0.05	0	247,501
ARIC	¹⁷²	Illumina HumanExome Beadchip v.1.0	Centrally at CHARGE	0.95	-	-	-	-	First 10 PCs	10	223,577
BBIJ	¹⁷⁵	Infinium OmniExpressExome-8 BeadChip Kit	Illumina GenCall	>0.99	>10 ⁻⁶ in control	no trios in samples; QC done using IBS	Yes	Exclude monomorphic in either control or case	Eigenstrates	2	61,024
BEAT-AF	¹⁷⁴	Illumina HumanCoreExome	BeadStudio	≥95%	>10 ⁻⁶	-	> 3 SD from the mean removed	ALL	First 10 PCs	10	495,970
BioMe	¹⁷⁶	Illumina HumanOmniExpress Exome-8 v1.0	zCall (GenomeStudio)	≥90%	>10 ⁻⁶	-	-	≥1%	first 4 PCs	4	241,465
BioVU	¹⁷⁷	Illumina Infinium HumanExome BeadChip	GenomeStudio	>0.95	>10 ⁻⁶	>1 removed	Yes (rate >0.44)	-	first 3 PCs	3	247,039
CHS	¹⁷⁸	Illumina HumanExome BeadChip v1.0	GenomeStudios	≥97%	None	Any among CEPH trio controls	None	None	5 unless others are associated with the outcome	5	247,870

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Study	R	Array	Calling Algorithm	Per variant call rate	HWE p-value	Mendelian errors	Excess heterozygosity	MAF	Selection criteria for PCs	PCs	Total N variants analyzed
FHS	^{180,181}	Illumina HumanExome BeadChip v1.0	GenomeStudio v. 2011.1 and zCall following CHARGE protocol ²⁰⁰	-	-	-	-	-	p<0.01 in association adjusted for age and sex	0	247,501
GS:SFHS	¹⁸³	Illumina HumanExome Beadchip v.1-A	GenomeStudio v. 2011.1 CHARGE protocol	0.98	-	-	-	Remove Monomorphic	First 3 PCs	1	247,870
KORA	^{201,202}	Illumina Infinium HumanExome BeadChip v1.0	CHARGE	-	-	-	Exclude het >5 SD	-	p<0.01 in association adjusted for age and sex; derived under exclusion of candidate regions	11	241,465
LURIC	¹⁸⁵										Excluded
MESA	^{187,200}	Illumina Exome Chip v1.0	GenomeStudio v. 2011.1 and zCall following CHARGE protocol	0.95	>10 ⁻⁶	-	-	ALL	Eigenstrates	2	247,039
MGH CAMP		Infinium HumanCoreExome-24 BeadChips	zCall (GenomeStudio)	≥95%	≥10 ⁻⁷	-	-	≥1%	First 10 PCs	10	247,501
RS	¹⁹⁴	Illumina Human Exome BeadChip v1.0	zCall following CHARGE	<0.97	-	-	Het excess >0.1 AND Het excess ≤0.9	28,471 monomorphic SNPs were excluded (MAF<1E-9)	First 5	5	247,870
SHIP/SHIP-Trend	¹⁹⁶	Illumina HumanExome Beadchip v.1.0	SOP v5, zCall v3.3	-	-	-	-	-	First 10 PCs	First 10 PCs	247,039
WGHS	^{199,203}	Illumina HumanExome Beadchip v.1.1A	GenomeStudio v. 2011.1 and zCall following CHARGE protocol	0.95	-	-	-	-		0	247,727
WHI - CT		Illumina Human	GenomeStudio	0.95	-	-	-	-	Plink	2	246,670

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Study	R	Array	Calling Algorithm	Per variant call rate	HWE p-value	Mendelian errors	Excess heterozygosity	MAF	Selection criteria for PCs	PCs	Total N variants analyzed
		Exome BeadChip v1.0	v2010.3								
WHI - OS		Illumina Human Exome BeadChip v1.0	GenomeStudio v2010.3	0.95	-	-	-	-	Plink	2	246,670

Supplementary Table 25. Baseline characteristics of African American ancestry replication studies

	Cases	Controls	Total
N	447	442	889
Women, %	44	48	46
Age at enrollment, mean (SD)	55 (11)	61 (14)	60 (14)
Age at diagnosis, mean (SD)	58 (14)	-	-
Age range (Q1-Q3)	50-61	52-72	51-69
HTN, %	88	87	88
DM, %	37	41	39
HF, %	24	8	16
MI, %	8	3	6

SD, standard deviation; HTN, hypertension; DM, diabetes mellitus; HF, heart failure; MI, myocardial infarction.

Supplementary Table 26. Results from replication in African American ancestry studies

rsID	Risk allele	RAF, %	OR	95% CI	P-value
rs115339321	T	97	1.53	0.82-2.18	0.18
rs79433233	A	3	1.36	0.75-2.47	0.31

RAF, risk allele frequency; OR, odds ratio; CI, confidence interval.

Supplementary Table 27. Results from DEPICT pathway analysis of GWAS meta-analysis results

Original gene set ID	Original gene set description	Nominal P-value
KEGG ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY ARVC	KEGG ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY ARVC	1.27x10 ⁻⁶
KEGG_TIGHT_JUNCTION	KEGG TIGHT JUNCTION	1.75x10 ⁻⁶
MP:0003157	impaired muscle relaxation	2.28x10 ⁻⁶
GO:0016459	myosin complex	8.31x10 ⁻⁶
GO:0060429	epithelium development	1.17x10 ⁻⁵
MP:0000751	myopathy	1.25x10 ⁻⁵
GO:0030855	epithelial cell differentiation	1.67x10 ⁻⁵
KEGG HYPERTROPHIC CARDIOMYOPATHY HCM	KEGG HYPERTROPHIC CARDIOMYOPATHY HCM	3.07x10 ⁻⁵
REACTOME MUSCLE CONTRACTION	REACTOME MUSCLE CONTRACTION	4.18x10 ⁻⁵
GO:0031589	cell-substrate adhesion	8.50x10 ⁻⁵

Supplementary Table 28. Top 5 enriched canonical pathways from Ingenuity Pathway Analysis of GWAS meta-analysis results

Ingenuity Canonical Pathways	P-value	Ratio	Molecules
Coagulation System	0.0088	3/35 (8.6%)	F11, KLKB1, PLAU
Clathrin-mediated Endocytosis Signaling	0.011	7/197 (3.6%)	MET, UBD, FGF17, ACTR2, AAK1, HIP1, PCYOX1
Protein Ubiquitination Pathway	0.013	8/255 (3.1%)	UBD, UBE2G2, USP18, UBE2Q1, BAG1, PSMD5, USP54, PSMD3
Superpathway of Geranylgeranyldiphosphate Biosynthesis I (via Mevalonate)	0.018	2/17 (11.8%)	FDPS, PMVK
Ephrin Receptor Signaling	0.02	6/174 (3.4%)	ACTR2, SHC1, EFNA3, CREB5, EFNA4, EFNA1

Supplementary Table 29. Enriched diseases or functions annotation from Ingenuity canonical pathway analysis of GWAS meta-analysis results

Diseases or Functions Annotation	P-value	N molecules	Molecules
Arrhythmia of heart ventricle	3.0x10 ⁻⁹	12	CASQ2, CSF3, DSG2, HCN4, KCNG2, KCNJ5, PKP2, SCN10A, SCN5A, TBX5, THRA, TTN
Ventricular tachycardia	1.7x10 ⁻⁸	10	CASQ2, CSF3, DSG2, HCN4, KCNG2, KCNJ5, PKP2, SCN5A, TBX5, THRA
Tachycardia	2.5x10 ⁻⁸	11	CASQ2, CSF3, DSG2, HCN4, KCNG2, KCNJ5, PITX2, PKP2, SCN5A, TBX5, THRA
Arrhythmia	5.0x10 ⁻⁸	16	CASQ2, CSF3, DSG2, HCN4, KCNG2, KCNJ5, NR3C1, PITX2, PKP2, PLN, SCN10A, SCN5A, TBX5, THRA, TTN, TUBA8
Ventricular fibrillation	9.5x10 ⁻⁷	7	DSG2, KCNG2, KCNJ5, PKP2, SCN5A, THRA, TTN
Cardiomyopathy of heart ventricle	1.2x10 ⁻⁶	6	CAV1, DSG2, HCN4, PKP2, SCN5A, TTN
Cardiac fibrillation	1.6x10 ⁻⁶	11	DSG2, KCNG2, KCNJ5, NR3C1, PITX2, PKP2, PLN, SCN5A, THRA, TTN, TUBA8
Hypertrophy of cardiac muscle	5.5x10 ⁻⁶	10	CAV1, CSF3, FBXO32, IL6R, mir-23, PLAU, RAB1A, SHC1, TBX5, TTN
Arrhythmogenic right ventricular dysplasia	5.7x10 ⁻⁶	5	DSG2, HCN4, PKP2, SCN5A, TTN

2. Supplementary Note

Detailed Description of participating studies

The meta-analyses described in this manuscript included the following studies described elsewhere: The **Age, Gene/Environment Susceptibility Study (AGES) Reykjavik study**¹⁶⁹, the **Atrial Fibrillation Biobank LMU (AFLMU)** in the context of the **Arrhythmia-Biobank-LMU** (formerly known as **AFNET**) and the **Cooperative Health Research in the Region of Augsburg (KORA)**¹⁶⁹, the **Atherosclerosis Risk in Communities (ARIC) study**¹⁶⁹, **Cleveland Clinic Lone Atrial Fibrillation GeneBank Study (CCAF)**¹⁶⁹, the **Cardiovascular Health Study (CHS)**¹⁶⁹, **Framingham Heart Study (FHS)**¹⁶⁹, **Massachusetts General Hospital (MGH) AF study**¹⁶⁹, the **Rotterdam Study (RS)**¹⁶⁹, the **Study of Health in Pomerania (SHIP)**¹⁶⁹, **BioVU²¹²**, the **Women's Genome Health Study (WGHS)**¹⁶⁹, The **PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)**¹⁷⁵, **Biobank Japan (BBJ)**¹⁷⁵, in addition to the studies described here:

ANGES: The Angiography and Genes Study (ANGES) population consists of 1,000 Finnish individuals participating in the ongoing ANGES study. Angiographic, genetic, and covariate data was available for 808 individuals (516 men and 292 women; mean age 62±10). The data was collected between September 2002 and July 2005. All patients underwent coronary angiography at Tampere University Hospital due to clinically suspected coronary artery disease. The study is a cross-sectional study, and after the angiography, patients were treated according to the Finnish Current Care Guidelines. Patients were also interviewed by a study nurse, and a questionnaire was used to collect general information - age, sex, body mass index, alcohol consumption, smoking, medication, as well as traditional risk factors of atherosclerosis and myocardial infarction. The study has been approved by the Ethics Committee of Pirkanmaa Hospital District and written informed consent was obtained from each patient.

BEAT-AF: The Basel Atrial Fibrillation Cohort Study (BEAT-AF) is a prospective observational, multicenter cohort study. Between 2010 and 2014, 1550 patients with documented atrial fibrillation were enrolled across 7 centers in Switzerland. Exclusion criteria were the inability to sign informed consent and the presence of short transient forms of atrial fibrillation. At baseline, patients completed detailed questionnaires about personal, medical, nutritional and lifestyle factors, current atrial fibrillation symptoms and co-morbidities. Current medications were recorded. A resting 12-lead electrocardiogram (ECG) was recorded and all patients underwent venous blood sampling at the local study center, including DNA from leukocytes. Yearly follow-ups by mailed questionnaires and phone interviews were performed in all patients in order to collect similar information as at baseline and to obtain details about adverse events.

Referents were enrolled from the ‘genetic and phenotypic determinants of blood pressure and other cardiovascular risk factors’ (GAPP) study, which is an ongoing prospective population-based cohort study among healthy adults in the Principality of Liechtenstein. Between 2010 and 2013, all inhabitants of the Principality of Liechtenstein aged between 25 and 41 years were invited and 2170 agreed to participate in the study. Main exclusion criteria were established cardiovascular disease, chronic kidney disease, diagnosed sleep apnea, a body mass index (BMI) > 35 kg/m², intake of antidiabetic drugs or any other severe illness. Examinations included detailed assessment of personal, medical, lifestyle and nutritional factors, standardized assessment of weight, height and waist circumference, blood pressure measurement, electrocardiography, bioimpedance analysis, blood, urinary and genetic sampling, spirometry and sleep pulse oximetry with nasal flow measurement. Follow-up examinations are scheduled every 3-5 years. The detailed study design has previously been published.¹⁷⁴

BioMe: The Mount Sinai BioMe Biobank is an ongoing, prospective, hospital- and outpatient- based population research program operated by The Charles Bronfman Institute for Personalized Medicine (IPM) at Mount Sinai and has enrolled over 33,000 participants since September 2007. BioMe is an Electronic Medical Record (EMR)-linked biobank that integrates research data and clinical care information for consented patients at The Mount Sinai Medical Center, which serves diverse local communities of upper Manhattan with broad health disparities. BioMe populations include 25% of African ancestry (AA), 36% of Hispanic Latino ancestry (HL), 30% of white European ancestry (EA), and 9% of other ancestry. The BioMe disease burden is reflective of health disparities in the local communities. BioMe operations are fully integrated in clinical care processes, including direct recruitment from clinical sites waiting areas and phlebotomy stations by dedicated recruiters independent of clinical care providers, prior to or following a clinician standard of care visit. Recruitment currently occurs at a broad spectrum of over 30 clinical care sites.

Information on atrial fibrillation, age, sex, body mass index (BMI), type 2 diabetes (T2D), hypertension (HYP), heart failure (HF FAIL), and myocardial infarct (MI) was derived from participants' EMRs: Age, sex and BMI were derived from the day of enrolment to the BioMe biobank. Prevalent atrial fibrillation cases were defined as BioMe participants with the ICD-9 code 427.31 (atrial fibrillation) and/or 427.32 (atrial flutter) and controls as individuals who have had ECG's but did not have atrial fibrillation or flutter ICD-9 codes. HYP, HF FAIL, and MI were defined using the ICD-9 codes 401.*, 428.*, and 410.*, respectively. In addition to the ICD-9 codes, also individuals taking antihypertensive drugs were considered as having HYP. T2D was defined using the eMerge T2D case and control definition algorithms.²¹³ The algorithms used were developed by a multidisciplinary team of scientists, clinicians and software specialists and have been validated with excellent performance statistics; 100% sensitivity and >98% positive predictive value for cases, and ≥98% sensitivity and ≥98% positive predictive value for controls.

BioMe participants were genotyped with the Illumina HumanOmniExpressExome-8 v1.0 beadchip array and imputed to the 1000 Genomes Project Phase 1 (March12) reference panel using IMPUTE2. Genome-wide association studies (GWAS) were carried out using SNPTEST 2.4.1 after stratifying by self-reported ancestry (AA: 174 atrial fibrillation cases and 2130 controls; EA: 291 atrial fibrillation cases and 860 controls; HL: 277 atrial fibrillation cases and 3081 controls) and adjustment for a) age, sex and the first 4 GWAS PCs (Model1) and b) age, sex, BMI, T2D, HYP, HF FAIL, MI, and the first 4 GWAS PCs (Model2). To ensure high quality of the association results, variants with imputation quality < 0.3, Hardy-Weinberg p-value < 1x10⁻⁵ or minor allele frequency < 0.01 were excluded.

BioVU: BioVU is the Vanderbilt University Medical Center's biorepository linked to de-identified electronic health records. BioVU operations²¹² and ethical oversight²¹⁴ have been described elsewhere. Briefly, DNA is collected from discarded blood samples remaining after routine clinical testing at Vanderbilt outpatient clinics in Nashville, Tennessee and surrounding areas, and is linked to a de-identified version of the patient's electronic health record termed the "Synthetic Derivative." atrial fibrillation cases were defined as individuals who were aged >18 years, had an ICD-9 diagnosis for atrial fibrillation or flutter (ICD-9: 427.3, 427.31, and 427.32), or a cardiologist diagnosis of atrial fibrillation as identified by a natural language processing tool from the unstructured free text of the ECG impression. In all instances, patients with a history of a heart transplant were excluded (Current Procedural Terminology: 33935, 3394, and 580; ICD-9: V42.1, 996.83).¹⁷⁷

Corogene: The Corogene study was designed as a large cohort to study mainly CAD, but also other related heart diseases such as heart failure and aortic valve disease. We selected the patients from the CAD point of view, and decided to include over 5000 consecutive patients assigned for coronary angiogram. In Finland, coronary angiogram is performed to practically all patients assigned for invasive

heart examination. Despite technical developments in diagnostics, coronary angiogram is still the gold standard for evaluating coronaries. The purpose of this study is to follow contemporary trends in coronary heart disease, and related heart disease risk factors, genetics and epigenetics by collecting cohorts referred to heart examination. New cohorts will be collected at 5-year intervals in order to see trends in CAD, its risk factors and epigenetics.

FINCAVAS: The purpose of the Finnish Cardiovascular Study (FINCAVAS) is to construct a risk profile - using genetic, haemodynamic and electrocardiographic (ECG) markers - of individuals at high risk of cardiovascular diseases, events and deaths. All patients scheduled for an exercise stress test at Tampere University Hospital, who gave informed consent to participate, were recruited between October 2001 and December 2007. The total number of participants was 4,567. In addition to repeated measurements of heart rate and blood pressure, digital high-resolution ECG at 500 Hz was recorded continuously during the entire exercise test, including the resting and recovery phases. About 20% of the patients were examined with coronary angiography. Genetic variations known or suspected to alter cardiovascular function or pathophysiology were analyzed to elucidate the effects and interactions of these candidate genes, exercise, and commonly used cardiovascular medications.

GS:SFHS: Generation Scotland: Scottish Family Health Study (GS:SFHS) is a family-based genetic epidemiology study of ~24,000 volunteers from ~7000 families across Scotland with the capacity for follow-up through record linkage and re-contact. Participants completed a demographic, health and lifestyle questionnaire and provided biological samples including DNA, and ~21,500 participants underwent detailed clinical assessment, including anthropometric, cardiovascular, respiratory, cognition and mental health. Genetic analysis (GWAS) is complete on 20,000 participants with full baseline data and CHI linkage, with linkage to SMR, prescriptions and dental records. A full cohort description can be found elsewhere.¹⁸³ Atrial fibrillation was ascertained as a diagnosis of atrial fibrillation by linkage to one or more inpatient visits with ICD-10 code I48 or ICD-9 427.31 in the Scottish Morbidity Record (SMR1) database before or after recruitment to GS:SFHS.

HNR: The study population of the Heinz Nixdorf Recall (HNR) study has been described in detail elsewhere.¹⁸⁴ Approved by the relevant institutional ethics committees, the study follows strict internal and external quality assurance protocols. Briefly, the study cohort comprises 4,814 men and women aged 45 – 75 years from the three adjacent Ruhr cities Essen, Bochum and Mülheim/Ruhr. The vast majority of the study population is of central European ancestry. The study area covers a region of approximately 600 km² with almost 1.2 million inhabitants. Subjects were randomly selected from statutory lists of residence and gave informed consent. The baseline examinations were from 2000–2003, the 5-Year follow-Up from 2006–2008 and the 10-Year follow-up from 2011–2015. A standardized digital 12-lead resting surface ECG was sampled at 250 Hz and recorded on a MAC 5000® ECG recorder (GE Healthcare, Freiburg, Germany). ECGs were interpreted automatically using the integrated 12SL-Code® [12SL ECG analysis with age & gender specific criteria. Physician's guide. PN 416791-004 Revision A. GE Medical Systems IT, 2000]. ECG findings were coded and transferred to our database. The ECG-codes #161 and #162 are for atrial fibrillation and atrial flutter, respectively and were combined for the purpose of this analysis.

LURIC: The Ludwigshafen Risk and Cardiovascular Health (LURIC) study is an ongoing prospective study of more than 3,300 individuals of German ancestry in whom cardiovascular and metabolic phenotypes (CAD, MI, dyslipidemia, hypertension, metabolic syndrome and diabetes mellitus) have been defined or ruled out using standardized methodologies in all study participants.¹⁸⁵ Inclusion criteria for LURIC were: German ancestry (limitation of genetic heterogeneity), clinical stability (except for acute coronary

syndromes) and availability of a coronary angiogram. Exclusion criteria were: any acute illness other than acute coronary syndromes, any chronic disease where non-cardiac disease predominated and a history of malignancy within the last five years. Genome-wide analyses using the Affymetrix 6.0 have been completed in all participants. A 10-year clinical follow-up for total and cause specific mortality has been completed.

MDCS: The Malmö Diet and Cancer study (MDCS) is a community-based prospective epidemiologic cohort of middle-aged individuals from Southern Sweden.¹⁸⁶ In total, 30,447 subjects attended a baseline exam in 1991-1996, when they filled out a questionnaire and underwent anthropometric and blood pressure measurements. Prevalent or incident cases of atrial fibrillation were ascertained from nation-wide hospital registers with high validity as described previously.¹⁸⁶ Genome-wide genotyping of single nucleotide variants was performed using the Illumina Human Omni Express Exome BeadChip kit. Genotyping was performed in a nested case-cohort design, including a random subset of 5878 subjects.

MESA: The Multi-Ethnic Study of Atherosclerosis (MESA) is a study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. The cohort is a diverse, population-based sample of 6,814 asymptomatic men and women aged 45-84. Approximately 38 percent of the recruited participants are white, 28 percent African American, 22 percent Hispanic, and 12 percent Asian (predominantly of Chinese descent). Participants were recruited during 2000-2002 from 6 field centers across the U.S. (at Wake Forest University; Columbia University; Johns Hopkins University; the University of Minnesota; Northwestern University, and the University of California – Los Angeles). All underwent anthropomorphic measurement and extensive evaluation by questionnaires at baseline, followed by 4 subsequent examinations at intervals of approximately 2-4 years. Age and sex were self-reported. Current atrial fibrillation at baseline was an exclusion criterion. Follow-up phone calls to study participants (every 9-12 months) were used to identify all hospitalizations. Medical records, including discharge diagnoses, were obtained for each hospitalization. Incident atrial fibrillation was defined by International Classification of Disease codes 427.31 or 427.32 (9th revision). In addition, new diagnoses of atrial fibrillation were identified at follow-up by the presence of atrial fibrillation or atrial flutter on a study ECG at Exam 5 (approximately 10 years after baseline). Further information can be found at http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000209.v13.p3.

MGH CAMP: The MGH Cardiology and Metabolic Patient (MGH CAMP) cohort comprises 3857 subjects recruited between 2008 and 2012. Two thirds of the subjects were drawn from patients who had appointments with a physician in the MGH Heart Center, whereas one third were recruited independent of any hospital visit. All subjects had plasma and serum samples collected, as well as blood for genomic DNA. Subjects with known diabetes had vascular reactivity measurements (FMD of brachial artery), while subjects without known diabetes had an oral glucose tolerance test. Exome Core Chip genotyping was performed on all subjects. Atrial fibrillation was defined as a self-reported history of fibrillation or flutter at study enrollment, or based on a validated medical record ascertainment algorithm (PPV 88%) that utilizes electrocardiographic and relevant diagnostic, procedure, and medication data.²¹⁵

MGH Stroke study: The Genetics of Cerebral Hemorrhage on Anticoagulation (GOCHA) study is a multicenter study of the genetics of intracerebral hemorrhage in the USA, based at the Massachusetts General Hospital. The cases are individuals presented with acute primary hemorrhagic stroke, aged more than 55 years. The controls were recruited from ambulatory clinics in the same centers in which cases were enrolled.

The Genes Affecting Stroke Risk and Outcome Study (GASROS) is a single-center prospective cohort that enrolled cases with acute ischemic stroke, aged more than 18 years who presented to MGH from 2003 to 2011. Ischemic stroke was defined as a clinical syndrome associated with a radiographically proven acute infarction consistent with a vascular pattern and without radiographic evidence of a demyelinating or neoplastic disease or other structural disease. In all subjects, the diagnosis was confirmed by diffusion weighted imaging (DWI) completed within 48 hours after symptom onset. Only patients of self-reported European ancestry were enrolled. Controls were matched to cases on the basis of age, sex and race/ethnicity.

In both GOCHA and GASROS, atrial fibrillation status was determined by reviewing medical records, and/or interview subjects or their families. The diagnosis of atrial fibrillation was established if the subject either had a pre-existing diagnosis or was diagnosed with atrial fibrillation in the hospital. The diagnosis was not confirmed by ECG in all cases.

PIVUS: The participants were randomly sampled from all men and women at age 70 living in Uppsala County in 2001 (www.medsci.uu.se/PIVUS). Of the 2025 individuals invited, 1016 participated. The participants underwent a medical examination including a detailed questionnaire on lifestyle and socioeconomic factors, fasting blood sampling, blood pressure measurement and anthropometric measurements, as previously described.¹⁹¹ Blood and plasma samples have been frozen until analysis, and blood tests performed include a wide variety of traditional and more recent CVD risk factors, along with DNA extraction. In addition, the individuals have undergone extensive phenotyping including whole body MRI, echocardiography, endothelial function measurements, carotid ultrasound, DXA, and spirometry. The participants have been re-examined at age 75 and 80. Atrial fibrillation was defined by 12-lead ECG at the examinations, as well as diagnosis of atrial fibrillation or flutter in the Swedish National Patient Register before or after the baseline examination (inpatient and specialist outpatient care; ICD-9 code, 427.3 and ICD-10 code, I48).

PREVEND: The PREVEND cohort study was founded in 1997, and is an ongoing community-based cohort study including 8592 inhabitants of the city of Groningen, The Netherlands. PREVEND is investigating the natural course of microalbuminuria and its relation to renal and cardiovascular disease. Details of the protocol, atrial fibrillation ascertainment and covariate definitions have been described elsewhere (www.prevend.org). The baseline screening program consisted of 2 outpatient visits to assess demographic factors, anthropometric measurements, cardiovascular and metabolic risk factors, and health behavior and to collect blood samples and 2 24-h urine samples on 2 consecutive days. Participants were seen at 3-year intervals in the PREVEND outpatient clinic. Atrial fibrillation was ascertained if either atrial flutter or atrial fibrillation was present on a 12-lead ECG obtained at one of the three PREVEND follow-up visits, or at an outpatient visit or hospital admission in the two hospitals in the city of Groningen (University Medical Center Groningen and Martini Hospital). Participants without an electrocardiogram (ECG) (n=248), as well as participants with prevalent atrial fibrillation at the baseline screening (n=79) and without GWAS information (n=4632) were excluded, leaving 3633 for analysis.²¹⁶

SPHFC: Participants for the Sao Paolo Heart Failure Cohort (SPHFC) were prospectively enrolled from the outpatient clinic at the Heart Institute, the University of Sao Paulo Medical School, Sao Paulo, Brazil. Only patients older than 18 years and with symptomatic heart failure (stage C) were enrolled. Different heart failure etiologies were included. Patients with prior myocardial infarction (<3 months), unstable angina, hypertrophic cardiomyopathy, valve heart disease candidates to surgical treatment, obstructive pulmonary disease, severe renal or hepatic dysfunction, current history of cancer, severe peripheral

arterial disease, cerebrovascular disease and active infection were excluded. Atrial fibrillation status was determined if either atrial flutter or atrial fibrillation was present on a 12-lead ECG at baseline evaluation or prior and could be confirmed by electronic medical record review.

TWINGENE: The Swedish Twin Registry contains data regarding health, health-related behaviors, physical activity, eating habits, and environmental stressors, along with other information from Swedish national registries. TWINGENE includes twins born before 1958 that were contacted to participate at the baseline examination between April 2004 and December 2008.²¹⁷ Health and medication data were collected from self-reported questionnaires, while blood sampling and in-person testing, including blood pressure measurement and anthropometrics were completed at a local health care center. Several biomarkers, including lipid profiles, fasting glucose, HbA1C and CRP, have been measured, and aliquoted serum is stored at the Karolinska Institutet Biobank. Atrial fibrillation was defined as a diagnosis of atrial fibrillation or flutter in the Swedish National Patient Register before or after the baseline examination (inpatient and specialist outpatient care; ICD-9 code, 427.3 and ICD-10 code, I48).

ULSAM: All men born between 1920 and 1924 in Uppsala, Sweden were invited to participate at age 50 in this longitudinal cohort study that was started in 1970. Participants were reinvestigated at the ages of 60, 70, 77, 82 and 88 years.¹⁹⁸ Blood samples for DNA extraction and main cardiovascular risk factors were available from the investigation at age 70. The participants have undergone extensive phenotyping at repeated time points, including euglycemic clamps, oral glucose tolerance tests, DXA, echocardiography, 24-h ambulatory blood pressure measurement, and a range of biomarkers. Atrial fibrillation was defined by 12-lead ECG at the examinations, as well as diagnosis of atrial fibrillation or flutter in the Swedish National Patient Register (inpatient and specialist outpatient care; ICD-9 code, 427.3 and ICD-10 code, I48).

WHI: The Women's Health Initiative (WHI) is one of the largest (n=161,808) studies of women's health ever undertaken in the United States. The WHI studies consisted of randomized CT, which assigned 68,132 women to active or placebo hormone therapy (HT), dietary modification or control, and/or calcium/vitamin D, supplementation or placebo with specific outcomes of common diseases of aging in women, and also an observational study (OS), which collected data on biological and lifestyle factors and health outcomes. A diverse population including 26,045 (17%) women from minority groups were recruited from 1993-1998 at 40 clinical centers across the U.S. Details of the study design have been previously described.^{218,219} For the CT and OS participants enrolled in WHI and who had consented to genetic research, DNA was extracted by the Specimen Processing Laboratory at the Fred Hutchinson Cancer Research Center (FHCRC) using specimens that were collected at the time of enrollment in to the study (between 1993 and 1998).

Baseline atrial fibrillation was determined by an initial questionnaire, which probed for self-reported atrial fibrillation or by presence of atrial fibrillation on the baseline 12-lead electrocardiogram. Women were followed up with a medical history update questionnaire at years 3 to 8, which specifically probed for self-reported atrial fibrillation and hospitalizations.

WTCCC2-Munich: The Wellcome Trust Case Control Consortium 2 Munich (WTCCC2-Munich) study is a hospital-based study on ischemic stroke genetics. Only consecutive European Caucasians recruited from a single dedicated Stroke Unit from South-German origin were selected for this study from the Department of Neurology, Klinikum Großhadern, Ludwig-Maximilians-University, Munich. Age, sex and clinical risk factors were collected. Atrial fibrillation was identified by ECG measurement on day of admission. For the German samples controls were Caucasians of German origin participating into the

population KORAgen study (www.gsf.de/kora/en/english.html). This survey represents a gender- and age stratified random sample of all German residents of the Augsburg area and consists of individuals 25 to 74 years of age, with about 300 subjects for each 10-year increment. All controls were free of a history of stroke, atrial fibrillation or other cardiovascular diseases.

African American replication studies included:

Penn Medicine Biobank: The Penn Medicine BioBank was started in 2009 and aims to recruit patients within the University of Pennsylvania Health System to donate venous blood. All samples are linked to de-identified electronic medical records. Participation is completely voluntary and written and informed consent are obtained prior to sample collection. For this project, all samples were collected within the inpatient and outpatient sections of the cardiovascular division at the University of Pennsylvania. Atrial fibrillation cases were limited to adults >18 years of age. Atrial fibrillation was ascertained through an ICD-9 diagnosis of atrial fibrillation, atrial flutter or documentation within the medical record.

Duke Biobank: The CATHeterization GENetics (CATHGEN) biorepository collected biospecimens and clinical data on individuals age ≥ 18 undergoing cardiac catheterization for concern of ischemic heart disease at a single center (Duke University Medical Center) from 2000-2010; a total of N=9334 individuals were collected. Samples were matched at the individual level to clinical data collected at the time of catheterization and stored in the Duke Databank for Cardiovascular Diseases (DDCD). Clinical data included subject demographics, cardiometabolic risk factors, cardiac history including symptoms, age-of-onset of cardiovascular diseases, coronary anatomy and cardiac function at catheterization, laboratory data, and yearly follow-up for hospitalizations, vital status, medication use and lifestyle factors. Atrial fibrillation cases were defined as individuals who had ever had atrial fibrillation based on any ECG available at Duke University or ICD-9 code for atrial fibrillation used for inpatient or outpatient billing.

Members of the AFGen Consortium, Neurology working group of the CHARGE Consortium and METASTROKE Consortium

AFGen Consortium Members

Ingrid E. Christophersen, MD, PhD,^{1–3} Michiel Rienstra, MD, PhD,⁴ Carolina Roselli, MSc,^{1,5,6} Xiaoyan Yin, PhD,^{7,8} Bastiaan Geelhoed, PhD,⁴ John Barnard, PhD,⁹ Honghuang Lin, PhD,^{7,8} Dan E. Arking, PhD,¹⁰, Albert V. Smith, PhD,^{11,12} Christine M. Albert, MD, MPH,¹³ Mark Chaffin, MSc¹, Nathan R. Tucker, PhD,^{1,2} Molong Li, MD,² Derek Klarin, MD,¹ Nathan A. Bihlmeyer, BS,¹⁴ Siew-Kee Low, PhD,¹⁵ Peter E. Weeke, MD, PhD,^{16,17} Martina Müller-Nurasyid, PhD,^{5,18,19} J. Gustav Smith, MD, PhD,^{1,20} Jennifer A. Brody, BA,²¹ Maartje N. Niemeijer MD,²² Marcus Dörr, MD,^{23,24} Stella Trompet, PhD,²⁵ Jennifer Huffman, PhD,²⁶ Stefan Gustafsson, PhD,²⁷ Claudia Schurmann, PhD,^{28,29} Marcus E. Kleber, PhD,³⁰ Leo-Pekka Lytykäinen, MD,³¹ Ilkka Seppälä, MD,³¹ Rainer Malik, PhD,³² Andrea R. V. R. Horimoto, PhD,³³ Marco Perez, MD,³⁴ Juha Sinisalo, MD, PhD,³⁵ Stefanie Aeschbacher, MSc,^{36,37} Sébastien Thériault, MD, MSc,^{38,39} Jie Yao, MS,⁴⁰ Farid Radmanesh, MD, MPH,^{1,41} Stefan Weiss, PhD,^{24,42} Alexander Teumer, PhD,^{24,43} Seung Hoan Choi, PhD,¹ Lu-Chen Weng, PhD^{1,2} Sebastian Clauss, MD,^{2,18} Rajat Deo, MD, MTR,⁴⁴ Daniel J. Rader, MD,⁴⁴ Svat Shah, MD, MHS,⁴⁵ Albert Sun, MD,⁴⁵ Jemma C. Hopewell, PhD,⁴⁶ Stephanie Debette, MD, PhD,^{47–50} Ganesh Chauhan, PhD,^{47,48} Qiong Yang, PhD,⁵¹ Bradford B. Worrall, MD, MSc,⁵², Guillaume Paré, MD, MSc,^{38,39} Yoichiro Kamatani, MD, PhD,¹⁵ Yanick P. Hagemeijer, MSc,⁴ Niek Verweij, PhD,⁴ Joylene E. Siland, BSc,⁴ Michiaki Kubo, MD, PhD,⁵³ Jonathan D. Smith, PhD,⁹ David R. Van Wagoner, PhD,⁹ Joshua C. Bis, PhD,²¹ Siegfried Perz, MSc,⁵⁴ Bruce M. Psaty, MD, PhD,^{21,55–57} Paul M. Ridker, MD, MPH,¹³ Jared W. Magnani, MD, MSc,^{7,58} Tamara B. Harris, MD, MS,⁵⁹ Lenore J. Launer, PhD,⁵⁹ M. Benjamin Shoemaker, MD, MSci,¹⁶ Sandosh Padmanabhan, MD,⁶⁰ Jeffrey Haessler, MS,⁶¹ Traci M. Bartz, MS,⁶² Melanie Waldenberger, PhD,^{19,54,63} Peter Lichtner, PhD,⁶⁴ Marina Arendt, MSc,⁶⁵ Jose E. Krieger, MD, PhD,³³ Mika Kähönen, MD, PhD,⁶⁶ Lorenz Risch, MD, MPH,⁶⁷ Alfredo J. Mansur, MD, PhD,⁶⁸ Annette Peters, PhD,^{19,54,69} Blair H. Smith, MD,⁷⁰ Lars Lind, MD, PhD,⁷¹ Stuart A. Scott, PhD,⁷² Yingchang Lu, MD, PhD,^{28,29} Erwin B. Bottinger, MD,^{28,73} Jussi Hernesniemi, MD, PhD,^{31,74} Cecilia M. Lindgren, PhD,⁷⁵ Jorge A Wong, MD,⁷⁶ Jie Huang, MD, MPH,⁷⁷ Markku Eskola, MD, PhD,⁷⁴ Andrew P. Morris, PhD,^{75,78} Ian Ford, PhD,⁷⁹ Alex P. Reiner, MD, MSc,^{61,80} Graciela Delgado, Msc,³⁰ Lin Y. Chen, MD, MS,⁸¹ Yii-Der Ida Chen, PhD,⁴⁰ Roopinder K. Sandhu, MD, MPH,⁸² Man Li, PhD,^{83,84} Eric Boerwinkle, PhD,⁸⁵ Lewin Eisele, MD,⁶⁵ Lars Lannfelt, MD, PhD,⁸⁶ Natalia Rost, MD, MPH, FAAN,^{1,87} Christopher D. Anderson, MD, MMSc,^{1,41} Kent D. Taylor, PhD,⁴⁰ Archie Campbell, MA,⁸⁸ Patrik K. Magnusson, PhD,⁸⁹ David Porteous, PhD,⁸⁸ Lynne J. Hocking, PhD,⁹⁰ Efthymia Vlachopoulou, PhD,⁹¹ Nancy L. Pedersen, MA, PhD,⁸⁹ Kjell Nikus, MD, PhD,⁷⁴ Marju Orho-Melander, PhD,⁹² Anders Hamsten, MD, PhD,⁹³ Jan Heeringa, MD, PhD,²² Joshua C. Denny, MD,¹⁶ Jennifer Kriebel, PhD,^{54,63,69} Dawood Darbar, MD,⁹⁴ Christopher Newton-Cheh, MD, MPH,^{1,2} Christian Shaffer, BS,¹⁶ Peter W. Macfarlane, PhD, DSc,⁹⁵ Stefanie Heilmann, PhD,^{96,97} Peter Almgren, MSc,⁹² Paul L. Huang, MD, PhD,² Nona Sotoodehnia, MD, MPH,⁹⁸ Elsayed Z. Soliman, MD, MSc, MS,⁹⁹ Andre G. Uitterlinden, PhD,¹⁰⁰ PhD, Albert Hofman, MD, PhD,²² Oscar H. Franco, MD, PhD,²² Uwe Völker, PhD,^{24,42} Karl-Heinz Jöckel, PhD,⁶⁵ Moritz F. Sinner, MD, MPH,^{18,19} Henry J. Lin, MD,⁴⁰ Xiuqing Guo, PhD,⁴⁰ METASTROKE Consortium of the ISGC, Neurology Working Group of the CHARGE Consortium, Martin Dichgans, MD,^{32,101,102} Erik Ingelsson, MD, PhD,^{27,103} Charles Kooperberg, PhD,⁶¹ Olle Melander, MD, PhD,¹⁰⁴ Ruth J. F. Loos, PhD,^{28,29,105} Jari Laurikka, MD, PhD,¹⁰⁶ David Conen, MD, MPH,^{36–38} Jonathan Rosand, MD, MSc,^{1,41} Pim van der Harst, MD, PhD,⁴ Marja-Liisa Lokki, PhD,⁹¹ Sekar Kathiresan, MD,¹ Alexandre Pereira, MD, PhD,¹⁰⁷ J. Wouter Jukema, MD, PhD,^{25,108,109} Caroline Hayward, PhD,²⁶ Jerome I. Rotter, MD,¹¹⁰

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

Winfried März, MD,¹¹¹ Terho Lehtimäki, MD, PhD,³¹ Bruno H. Stricker, MD, PhD,¹¹² Mina K. Chung, MD,⁹ Stephan B. Felix, MD,^{23,24} Vilmundur Gudnason, MD, PhD,^{11,12} Alvaro Alonso, MD, PhD,¹¹³ Dan M. Roden, MD,¹⁶ Stefan Kääb, MD, PhD,^{18,19} Daniel I. Chasman, PhD,^{1,114} Susan R. Heckbert, MD, PhD,^{55,56} Emelia J. Benjamin, MD, ScM,^{7,58,115} Toshihiro Tanaka, MD, PhD,^{116,117} Kathryn L. Lunetta, PhD,^{7,8} Steven A. Lubitz, MD, MPH,^{1,2,118} Patrick T. Ellinor, MD, PhD,^{1,2,118}

AFGen Consortium Member Affiliations

1. Program in Medical and Population Genetics, The Broad Institute of MIT and Harvard, Cambridge, MA, USA.
2. Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA.
3. Department of Medical Research, Bærum Hospital, Vestre Viken Hospital Trust, Norway.
4. Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
5. Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany.
6. Institute of Medical Informatics, Biometry and Epidemiology, Chair of Genetic Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany.
7. NHLBI and Boston University's Framingham Heart Study, Framingham, MA, USA.
8. Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA.
9. Departments of Cardiovascular Medicine, Cellular and Molecular Medicine, Molecular Cardiology, and Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA.
10. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.
11. Icelandic Heart Association, Kopavogur, Iceland.
12. Faculty of Medicine, University of Iceland, Reykavik, Iceland.
13. Divisions of Preventive and Cardiovascular Medicine, Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA.
14. Predoctoral Training Program in Human Genetics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.
15. Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan.
16. Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.
17. The Heart Centre, Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.
18. Department of Medicine I, University Hospital Munich, Ludwig-Maximilians-University, Munich, Germany.
19. DZHK (German Centre for Cardiovascular Research), partner site: Munich Heart Alliance, Munich, Germany.
20. Molecular Epidemiology and Cardiology, Clinical Sciences, Lund University, Lund, Sweden.
21. Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA.
22. Department of Epidemiology, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands.
23. Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany.

24. DZHK (German Centre for Cardiovascular Research), partner site: Greifswald, Germany.
25. Department of Cardiology, Leiden University Medical Center, The Netherlands.
26. MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, UK.
27. Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden.
28. The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
29. The Genetics of Obesity and Related Metabolic Traits Program, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
30. Vth Department of Medicine, Medical Faculty Mannheim, Heidelberg University, Germany.
31. Department of Clinical Chemistry, Fimlab Laboratories and University of Tampere School of Medicine, Tampere, Finland.
32. Institute for Stroke and Dementia Research, Klinikum der Universität München, Ludwig-Maximilians University, München, Germany.
33. Laboratory of Genetics and Molecular Cardiology, Heart Institute, University of São Paulo, São Paulo, Brazil.
34. Stanford University, Stanford, CA, USA.
35. Heart and Lung Center HUS, Helsinki University Central Hospital, Helsinki, Finland.
36. University Hospital Basel, Switzerland.
37. Cardiovascular Research Institute Basel, Switzerland.
38. Population Health Research Institute, Hamilton, Canada.
39. Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Canada.
40. Institute for Translational Genomics and Population Sciences, Department of Pediatrics, LABioMed at Harbor-UCLA Medical Center, Torrance, CA, USA.
41. Center for Human Genetics Research, Massachusetts General Hospital, Boston, MA, USA.
42. Interfaculty Institute for Genetics and Functional Genomics, University Medicine and Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany.
43. Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany.
44. Division of Cardiovascular Medicine, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA.
45. Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, NC, USA.
46. CTSU - Nuffield Department of Population Health, University of Oxford, Oxford, UK.
47. Inserm Center U1219 (Bordeaux Population Health Centre), Bordeaux, France.
48. University of Bordeaux, Bordeaux, France.
49. Department of Neurology, Bordeaux University Hospital, Bordeaux, France.
50. Department of Neurology, Boston University School of Medicine, Boston, MA, USA.
51. Biostatistics Department, School of Public Health, Boston University, Boston, MA, USA.
52. University of Virginia Health System, Departments of Neurology and Public Health Science, Charlottesville, VA, USA.
53. RIKEN Center for Integrative Medical Sciences, Yokohama, Japan.
54. Institute of Epidemiology II, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany.

55. Department of Epidemiology and Cardiovascular Health Research Unit, University of Washington, Seattle, WA, USA.
56. Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA.
57. Department of Health Services, University of Washington, Seattle, WA, USA.
58. Department of Medicine, Boston University School of Medicine, Boston, MA, USA.
59. Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Bethesda, MD, USA.
60. Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK.
61. Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA.
62. Cardiovascular Health Research Unit, Departments of Medicine and Biostatistics, University of Washington, Seattle, WA, USA.
63. Research unit of Molecular Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany.
64. Institute of Human Genetics, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany.
65. Institute for Medical Informatics, Biometry, and Epidemiology, University Hospital, University Duisburg-Essen, Germany.
66. Department of Clinical Physiology, Tampere University Hospital and University of Tampere School of Medicine, Tampere, Finland.
67. University Institute of Clinical Chemistry, University of Bern, Switzerland and labormedizinisches zentrum Dr. Risch, Schaan, Liechtenstein.
68. Heart Institute, University of Sao Paulo, Sao Paulo, Brazil.
69. German Center for Diabetes Research, Neuherberg, Germany.
70. Division of Population Health Sciences, University of Dundee, Scotland, UK.
71. Department of Medical Sciences, Cardiovascular Epidemiology, Uppsala University, Uppsala, Sweden.
72. Department of Genetics and Genomic Sciences , Icahn School of Medicine at Mount Sinai, New York, NY, USA.
73. Department of Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
74. Department of Cardiology, Heart Hospital, Tampere University Hospital and University of Tampere School of Medicine, Tampere, Finland.
75. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.
76. Division of Cardiology, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada.
77. Boston VA Research Institute, Inc., Boston, MA, USA.
78. Department of Biostatistics, University of Liverpool, Liverpool, UK.
79. Robertson Center for Biostatistics, University of Glasgow, Glasgow, UK.
80. Department of Epidemiology, University of Washington, Seattle, WA, USA.
81. Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, Minneapolis, MN, USA.
82. Division of Cardiology, University of Alberta, Edmonton, Canada.
83. Department of Epidemiology, Johns Hopkins University, Baltimore, MD, USA.

84. Division of Nephrology & Hypertension, Internal Medicine, School of Medicine, University of Utah, UT, USA.
85. Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA.
86. Department of Public Health and Caring Sciences, Geriatrics, Uppsala University, Uppsala, Sweden.
87. Acute Stroke Services, Massachusetts General Hospital, Boston, MA, USA.
88. Generation Scotland, Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, UK.
89. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.
90. Musculoskeletal Research Programme, Division of Applied Medicine, University of Aberdeen, Aberdeen, UK.
91. Transplantation Laboratory, Medicum, University of Helsinki, Helsinki, Finland.
92. Department of Clinical Sciences, Lund University, Malmö, Sweden.
93. Cardiovascular Genetics and Genomics Group, Atherosclerosis Research Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden.
94. University of Illinois, Chicago, IL, USA.
95. Institute of Health and Wellbeing, College of Medical, Veterinary and Life Sciences, University of Glasgow, UK.
96. Institute of Human Genetics, University of Bonn, Germany.
97. Department of Genomics, Life & Brain Research Center, University of Bonn, Germany.
98. Cardiovascular Health Research Unit, University of Washington Medical Center, Seattle, WA, USA.
99. Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston Salem, NC, USA.
100. Department of Epidemiology and Internal Medicine, Erasmus University Medical Center Rotterdam, the Netherlands.
101. Munich Cluster for Systems Neurology (SyNergy), München, Germany.
102. German Center for Neurodegenerative Diseases (DZNE), Munich, Germany.
103. Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA, USA.
104. Department of Internal Medicine, Clinical Sciences, Lund University, Malmö, Sweden.
105. The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
106. Department of Cardio-Thoracic Surgery, Heart Hospital, Tampere University Hospital and University of Tampere School of Medicine, Tampere, Finland.
107. Laboratory of Genetics and Molecular Biology, Heart Institute, University of São Paulo, São Paulo, Brazil and Department of Genetics, Harvard Medical School, Boston, MA, USA.
108. Durrer Center for Cardiogenetic Research, Amsterdam, The Netherlands.
109. Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands.
110. Institute for Translational Genomics and Population Sciences, Departments of Pediatrics and Medicine, LABioMed at Harbor-UCLA Medical Center, Torrance, CA, USA.
111. Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria and Synlab Academy, Synlab Services GmbH, Mannheim, Germany.

112. Department of Epidemiology and Internal Medicine, Erasmus University Medical Center Rotterdam, the Netherlands and Inspectorate of Health Care, Utrecht, the Netherlands.
113. Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA.
114. Divisions of Preventive Medicine and Genetics, Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA.
115. Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA.
116. Laboratory for Cardiovascular Diseases, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan.
117. Department of Human Genetics and Disease Diversity, Tokyo Medical and Dental University Graduate School of Medical and Dental Sciences, Tokyo, Japan.
118. Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston, MA, USA.

Neurology Working Group of the CHARGE Consortium Members

Ganesh Chauhan, PhD; Corey R Arnold, BSc; Audrey Y Chu, PhD; Myriam Fornage, PhD; Azadeh Reyahi, MSc; Joshua C Bis, PhD; Aki S Havulinna, DSc; Muralidharan Sargurupremraj, PhD; Albert V Smith, PhD; Hieab H H Adams, MSc; Seung Hoan Choi, MA; Stella Trompet, PhD; Melissa E Garcia, MPH; Alexander Teumer, PhD; Céline Bellenguez, PhD; Xueqiu Jian, PhD; Claudia L Satizabal, PhD; Yongmei Liu, PhD; Susan R Heckbert, MD; Kenneth Rice, PhD; Nicholas L Smith, PhD; Reinhold Schmidt, MD; Hugo J Aparicio, MD; Didier Leys, MD; Claudine Berr, MD; Jean-François Dartigues, MD; Cecilia M Lindgren, PhD; Albert Hofman, MD; Peter J Koudstaal, MD; André G Uitterlinden, PhD; Anton J M de Craen, PhD; Andrew D Johnson, PhD; Hans Jörgen Grabe, MD; Yoichiro Kamatani, MD; Oscar L Lopez, MD; Jerome I Rotter, MD; Rebecca F Gottesman, MD; David S Knopman, MD; B Gwen Windham, MD; Alexa Beiser, PhD; Curtis R French, PhD; Mark Lathrop, PhD; Vilmundur Gudnason, MD; Tobias Kurth, MD; Bruce M Psaty, MD; Tamara B Harris, MD; Stephen S Rich, PhD; Anita L deStefano, PhD; Carsten O Schmidt, PhD; Veikko Salomaa, MD; Thomas H Mosley, PhD; Erik Ingelsson, MD; Cornelia M van Duijn, PhD; Ordan J Lehmann, MD; Christophe Tzourio, MD; Lenore J Launer, PhD; M Arfan Ikram, MD; Peter Carlsson, PhD; Daniel I Chasman, PhD; Sarah J Childs, PhD; William T Longstreth, Jr, MD; Sudha Seshadri, MD; Stéphanie Debette, MD

Neurology Working Group of the CHARGE Consortium member affiliations

University Medicine Greifswald, Institute for Community Medicine, SHIP-KEF, Greifswald, Germany (AT, COS); University Medicine Greifswald, Department of Psychiatry and Psychotherapy, Greifswald, Germany (HJG); Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA (DIC, AYC, TK); Harvard Medical School, Boston, MA, USA (DIC); Inserm Research Center for Epidemiology and Biostatistics (U897) - Team Neuroepidemiology, Bordeaux, France (TK, MS, CT, JFD, GC, SD); University of Bordeaux, College of Health Sciences, Bordeaux, France (TK); University of Virginia, Charlottesville, VA USA (SSR); National institute for Health and Welfare, Helsinki, Finland (ASH, VS); Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands (HHHA, AH, CMvD, MAI); Department of Neurology, Erasmus MC, Rotterdam, The Netherlands (PJK); Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands (AGU); Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA (JCB, BMP); Department of Epidemiology, University of Washington, Seattle, WA, USA (BMP, WTL, NLS, SRH); Department of Health Services, University of Washington, Seattle, WA, USA (BMP); Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA (BMP); Institute

for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, USA (JIR); Division of Genomic Outcomes, Department of Pediatrics, Harbor-UCLA Medical Center, California, USA (JIR); UCLA, California, USA (JIR); Department of Biostatistics, University of Washington, Seattle, WA, USA (KR); Department of Neurology; University of Washington, Seattle, WA, USA (WTL); Seattle Epidemiologic Research and Information Center of the Department of Veterans Affairs Office of Research and Development, Seattle, WA, USA (NLS); Department of Cardiology, Leiden University Medical Center, Leiden The Netherlands (ST); Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands (ST, AJMdC); Center for Human Genetics, Division of Public Health Sciences, Wake Forest School of Medicine, Winston Salem, NC, USA (YL); Laboratory of Epidemiology and Population Sciences, National Institute on Aging, Bethesda, MD, USA (TBH, MEG); Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden (EI); Genetic and Genomic Epidemiology Unit, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK (CML); University of Bordeaux, Bordeaux, France (MS, CT, JFD, GC, SD, TK); Université de Montpellier, France (CeB); Institut Pasteur de Lille, Lille, France (CeB); Université Lille Nord de France, Lille, France (DL); Department of Neurology, Lille University Hospital, Lille, France (DL); INSERM U1171, Lille, France (DL); INSERM U1061, Montpellier, France (CIB); University Montpellier 1, Montpellier, France (CIB); Department of Neurology, Bordeaux University Hospital, Bordeaux, France (SD, JFD); Boston University School of Medicine, Boston, MA, USA (SD); IRP/NIA/NIH, Bethesda, MD, USA (LJL); Department of Neurology, University of Pittsburgh, PA, USA (OLL); Icelandic Heart Association, Kópavogur, Iceland (VG, AVS); University of Iceland, Faculty of Medicine, Reykjavik, Iceland (VG); Institute of Molecular Medicine and Human Genetics Center; University of Texas Health Science Center at Houston, Houston, TX, USA (MF, XJ); Department of Neurology; Johns Hopkins University, Baltimore, MD, USA (RFG); Department of Neurology; Mayo Clinic, Rochester, MN, USA (DSK); Department of Medicine, Division of Geriatrics; University of Mississippi Medical Center, Jackson, MS, USA (THM, BGW); McGill University and Genome Quebec Innovation Center (ML); Department of Neurology, Clinical Division of Neurogeriatrics, Medical University Graz, Austria (RS); National Heart, Lung, and Blood Institute's Framingham Heart Study Cardiovascular Epidemiology and Human Genomics Branch, Framingham, Massachusetts, USA (ADJ); Fondation Jean Dausset, Centre d'Etude du Polymorphisme Humain (CEPH), Paris, France (YK); Center for Integrative Medical Sciences, RIKEN, Yokohama, Japan (YK); Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, USA (AB, ALD, HJA, SS, CLS, SHC); Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA (AB, ALD, SS, SHC); The National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA (AB, ADJ, ALD, AYC, HJA, SS, CLS, SHC); Department of Ophthalmology, University of Alberta, Edmonton, Alberta, Canada (CRF, OJL); Alberta Children's Hospital Research Institute and Department of Biochemistry and Molecular Biology, University of Calgary, Calgary, Alberta, Canada (CRA, SJC); Department of Medical Genetics, University of Alberta, Edmonton, Alberta, Canada (OJL); Department of Chemistry and Molecular Biology, University of Gothenburg, Gothenburg, Sweden (AR, PC).

METASTROKE Consortium Contributors

Study	Investigator
ASGC	Elizabeth Holliday Chris Levi
BRAINS	Pankaj Sharma Iona Cotlarciuc

Chapter 2 – Online supplement

Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation

GASROS	Jonathan Rosand
GEOS	Steven Kittner
	John Cole
HPS	Jemma Hopewell
	Robert Clarke
ISGS/SWISS	James Meschia
	Mike Nalls
MILANO	Giorgio Boncoraglio
VISP	Bradford B. Worrall
	Michéle Sale
	Wei-Min Chen
WHI	Alex Reiner
WTCCC2-D	Martin Dichgans
	Rainer Malik
WTCCC2-UK	Hugh Markus
	Steve Bevan
CADISP	Stephanie Debette
	Ganesh Chauhan
Krakow	Agnieszka Slowik
	Joanna Pera
Leuven	Vincent Thijs
	Robin Lemmens
Lund	Arne Lindgren
Münster	E Bernd Ringelstein
	Klaus Berger
SIGN	Brackie Mitchell
Portugal	Sofia A Oliveira
	Jose M Ferro
	Astrid M Vicente
RACE	Danish Salaheen
USA	Dan Woo

Other METASTROKE participants

ARIC	Myriam Fornage
CHS	Bruce Psaty
	Josh Bis
deCODE	Solveig Gretarsdottir
FHS	Sudha Seshadri
	Qiong Yang
	Claudia L. Satizabal Barrera
HVH	Bruce Psaty
Rotterdam	Arfan Ikram
Barcelona	Israel Fernandez
BSS	Massimo Pandolfo

	Sherine Abboud
Copenhagen	Marianne Benn
	Børge G Nordestgaard
ESS	Cathie Sudlow
	Kristina Rannikmae
Glasgow	Matthew Walters
	Peter Higgins
GoDarts	Colin N A Palmer
	Alexander S F Doney
Graz	Reinhold Schmidt
INTERSTROKE	Guillame Pare
Karolinska	Konstantinos Kostulas
SMART	Paul de Bakker
	Ale Algra
Athero-Express	Sander van der Laan
	Gerald Pasterkamp
Sifap	Anne-Katrin Giese

Ancestry-specific GWAS meta-analyses

Separate GWAS in 15,993 cases and 113,719 referents of European ancestry revealed one additional association on chromosome 15q21 (rs2921421, OR 1.72, 95% CI 1.42-2.09, $P=3.29\times 10^{-8}$, **Supplementary Table 6**); however, there was only one significant variant at this locus and the variant was imputed with low quality across all studies reducing our confidence in this finding. Additional replication in another European ancestry study is needed to clarify the relevance of rs2921421. In meta-analysis of 837 cases and 2456 referents of Asian ancestry we identified an association on chromosome 12q15 (rs7138621, OR 7.92, 95% CI 4.26-14.73, $P=6.48\times 10^{-11}$), which was not significant in *in silico* replication in 8180 cases and 28,612 referents in the Biobank Japan (**Supplementary Table 10**). Separate meta-analyses in individuals of Brazilian and Hispanic descent did not identify additional loci; however, our power was limited in each of these sub-groups.

GWAS meta-analyses of incident and prevalent atrial fibrillation in Europeans

Separate GWAS meta-analyses of incident (7232 cases) and prevalent (8656 cases) atrial fibrillation in Europeans showed similar results to the European ancestry analysis (**Supplementary Tables 8-9**, **Supplementary Figs. 7-8**); however, we did reveal a novel atrial fibrillation locus associated with prevalent atrial fibrillation at chromosome 12p11 (rs1454934, OR 1.16, 95% CI 1.1-1.22, $P=4.18\times 10^{-8}$). The most significant variant at this locus was intronic to the gene plakophilin-2 (*PKP2*), which encodes an important component of the desmosome and is known to be associated with arrhythmogenic right ventricular cardiomyopathy²²⁰ and Brugada syndrome.^{221,222}

Replication of genetic variants specific to African American ancestry GWAS meta-analysis

The variants rs115339321 (OR 1.53, 95% CI 0.82-2.18, $P=0.18$) and rs79433233 (OR 1.36, 95% CI 0.75-2.47, $P=0.31$) were not significantly associated with atrial fibrillation in 447 atrial fibrillation cases and 442 referents of African American ancestry (**Supplementary Table 25-26**). The lack of replication may be caused by the small sample size of the replication study. Further replication in a larger sample of African American ancestry is needed to clarify the role of the variants rs115339321 and rs79433233.

Pathway analyses

1. DEPICT

The most significant pathway identified using the DEPICT software was the arrhythmogenic right ventricular cardiomyopathy (ARVC) pathway ($P=1.3\times 10^{-6}$, **Supplementary Table 27**). None of the pathways analyzed reached an FDR <5%.

2. IPA

The most significantly enriched biological pathway was the coagulation system ($P=0.0088$). In addition, many genes were involved in the clathrin-mediated endocytosis signaling pathway ($P=0.011$) and the protein ubiquitination pathway ($P=0.013$). The most significant pathways are listed in **Supplementary Table 28**. None of the pathways reached the significance threshold (FDR<5%). In addition, many of the genes investigated were involved in arrhythmia mechanisms (**Supplementary Table 29**).

ACKNOWLEDGMENTS

AFLMU/KORA: This work is funded by the European Commission’s 7th Framework Programme FP7-HEALTH-2013 No. 602299: EU-CERT-ICD to Dr. Kääb and the European Commission’s Horizon 2020 Framework Programme EU-H2020-PHC-RIA No.633196: CATCH-ME to Dr. Sinner. It is further supported by the DZHK (German Centre for Cardiovascular Research), partner site: Munich Heart Alliance, Munich, Germany, the BMBF Spitencluster personalized medicine m4 (01 EX1021E), the LMU Excellence Initiative (42595-6), and the Munich Center of Health Sciences (MC Health) as part of LMUinnovativ, all to Dr. Kääb. The KORA platform is funded by the BMBF and by the State of Bavaria.

AGES: The Age, Gene/Environment Susceptibility Reykjavik Study has been funded by NIH contract N01-AG-12100, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament).

ANGES: The Angiography and Genes Study (ANGES) has been financially supported by the Competitive Research Funding of the Tampere University Hospital (Grant 9M048 and 9N035), the Finnish Cultural Foundation, the Finnish Foundation for Cardiovascular Research, the Emil Aaltonen Foundation, Finland, and the Tampere Tuberculosis Foundation.

ARIC: The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. Funding support for “Building on GWAS for NHLBI-diseases: the U.S. CHARGE consortium” was provided by the NIH through the American Recovery and Reinvestment Act of 2009 (ARRA) (5RC2HL102419).

BEAT-AF: Swiss National Science Foundation (PP00P3_133681 and PP00P3_159322); Swiss Heart Foundation; University of Basel; University Hospital Basel

Biobank Japan: The BioBank Japan Project was supported by the Ministry of Education, Culture, Sports, Sciences and Technology of the Japanese government.

BioMe: The Mount Sinai BioMe Biobank Program is supported by The Andrea and Charles Bronfman Philanthropies. Analyses of BioMe data was supported in part through the computational resources and staff expertise provided by the Department of Scientific Computing at the Icahn School of Medicine at Mount Sinai.

BioVU: The dataset used in the analyses described were obtained from Vanderbilt University Medical Centers BioVU which is supported by institutional funding and by the Vanderbilt CTSA grant UL1TR000445 from NCATS/NIH. Genome-wide genotyping was funded by NIH grants RC2GM092618 from NIGMS/OD and U01HG004603 from NHGRI/NIGMS.

CCAF is funded by National Institutes of Health grants R01 HL090620 and R01 HL111314 to MKC, JB, JS, and DVW, the NIH National Center for Research Resources for Case Western Reserve University and The Cleveland Clinic Clinical and Translational Science Award UL1-RR024989, and the Department of Cardiovascular Medicine philanthropic research fund, Heart and Vascular Institute, Cleveland Clinic

CHS: This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, HHSN268200960009C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL120393, R01HL130114, R01HL068986, and R01HL085251 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Corogene: The Corogene study has been financially supported by the Aarno Koskelo Foundation (partial); the Finnish Foundation for Cardiovascular Research (partial); the Paulo Foundation (partial); Jenny and Antti Wihuri Foundation (partial); EVO funds of Helsinki University Central Hospital; Wellcome Trust, UK (the genetic part).

FINCAVAS: The Finnish Cardiovascular Study (FINCAVAS) has been financially supported by the Competitive Research Funding of the Tampere University Hospital (Grant 9M048 and 9N035), the Finnish Cultural Foundation, the Finnish Foundation for Cardiovascular Research, the Emil Aaltonen Foundation, Finland, and the Tampere Tuberculosis Foundation.

FHS: This research was conducted using data and resources from Framingham Heart Study (FHS) of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine based on analyses by Framingham Heart Study investigators participating in the SNP Health Association Resource (SHArE) project. This work was supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195) and its contract with Affymetrix, Inc for genotyping services (Contract No.N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. Other support came from 1R01 HL092577, 1RO1 HL076784, 1R01 AG028321, Evans Center for Interdisciplinary Biomedical Research ARC on Atrial Fibrillation at Boston University (<http://www.bumc.bu.edu/evanscenteribr/the-arcs/the-arcs/> (Benjamin), 6R01-NS 17950 and American Heart Association 09FTF2190028.

GS:SFHS: Generation Scotland received core support from the Chief Scientist Office of the Scottish Government Health Directorate [CZD/16/6] and the Scottish Funding Council [HR03006]. Genotyping of the GS:SFHS samples was carried out by the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, Edinburgh, Scotland and was funded by the Medical Research Council UK and the Wellcome Trust (Wellcome Trust Strategic Award "STratiFying Resilience and Depression Longitudinally" (STRADL) (Reference 104036/Z/14/Z).

HNR: The Heinz Nixdorf Recall Study thanks the Heinz Nixdorf Foundation (Germany) and projects SI 236/8-1 and SI 236/9-1 from the German Research Council for the generous support of this study. We acknowledge the support of the Sarstedt AG & Co. (Nümbrecht, Germany) for laboratory equipment. We are indebted to all study participants and to the dedicated personnel of the study center of the Heinz Nixdorf Recall study. Advisory Board: Meinertz T, Hamburg, Germany (Chair); Bode C, Freiburg, Germany; de Feyter PJ, Rotterdam, Netherlands; Güntert B, Hall i.T., Austria; Gutzwiller F, Bern, Switzerland; Heinen H, Bonn, Germany; Hess O, Bern, Switzerland; Klein B, Essen, Germany; Löwel H, Neuherberg, Germany; Reiser M, Munich, Germany; Schwaiger M, Munich, Germany; Steinmüller C, Bonn, Germany; Theorell T, Stockholm, Sweden; Willich SN, Berlin, Germany.

LURIC: LURIC was supported by the 7th Framework Program (integrated project AtheroRemo, grant agreement number 201668 and RiskyCAD, grant agreement number 305739) of the European Union, by the INTERREG IV Oberrhein Program (Project A28, Genetic mechanisms of cardiovascular diseases) with support from the European Regional Development Fund (ERDF) and the Wissenschaftsoffensive TMO

MDCS: The MDCS was made possible by grants from the Malmö city council. J. Gustav Smith was supported by The Märta Winkler foundation, Swedish Heart Association, Swedish Heart-Lung Foundation, the European Research Council, the Swedish Research Council, the Crafoord Foundation, governmental funding of clinical research within the Swedish National Health Service, Skåne University Hospital in Lund.

MESA: The Multi-Ethnic Study of Atherosclerosis (MESA) is supported by NIH contracts HHSN2682015000031, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169 and by grants UL1-TR-000040, UL1-TR-001079, and UL1-RR-025005 from NCRR. Funding for MESA Family was provided by grants R01-HL-071205, R01-HL-071051, R01-HL-071250, R01-HL-071251, R01-HL-071252, R01-HL-071258, and R01-HL-071259, and by UL1-RR-025005 and UL1RR033176 from NCRR. Funding for MESA SHArE genotyping was provided by NHLBI Contract N02-HL-6-4278. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

MGH AF: This work was supported by grants from the National Institutes of Health to Dr. Ellinor (1RO1HL092577, R01HL128914, K24HL105780). Dr. Christophersen is supported by a mobility grant from the Research Council of Norway [240149/F20]. Dr. Ellinor is also supported by an Established Investigator Award from the American Heart Association (13EIA14220013) and by the Fondation Leducq (14CVD01). Dr. Lubitz is supported by grants from the NIH (K23HL114724) and by a Doris Duke Charitable Foundation Clinical Scientist Development Award (2014105).

MGH CAMP: The recruitment, collection of samples, and genotyping was supported by Pfizer. Analysis of data was a three way collaboration between MGH, the Broad Institute, and Pfizer. Dr. Huang is supported by grants from the NIH (NS33335, NS055104).

MGH Stroke study: The GOCHA study was supported by the grant R01NS059727 from the NINDS. The GASROS study was supported by the grant U01 NS069208-01 from the NINDS.

PIVUS: These projects were supported by Knut and Alice Wallenberg Foundation (Wallenberg Academy Fellow), Swedish Diabetes Foundation (2013-024), Swedish Research Council (2012-1397 and 2015-02907), and Swedish Heart-Lung Foundation (20140422). Computations were performed on resources provided by SNIC through Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) under Project b2011036. Genotyping was funded by the Wellcome Trust under awards WT064890 and WT086596. Analysis of genetic data was funded by the Wellcome Trust under awards WT098017 and WT090532. Andrew P Morris is a Wellcome Trust Senior Fellow in Basic Biomedical Science, under award WT098017.

PREVEND: The PREVEND study is supported by the Dutch Kidney Foundation (grant E0.13) and the Netherlands Heart Foundation (grant NHS2010B280). Dr. M. Rienstra is supported by grants from the Netherlands Organization for Scientific Research (Veni grant 016.136.055), the EHRA Academic Fellowship program, and from the Netherlands Cardiovascular Research Initiative: an initiative supported by the Netherlands Heart Foundation, CVON 2014–9: “Reappraisal of Atrial Fibrillation: interaction between hyperCoagulability, Electrical remodelling, and Vascular destabilization in the progression of atrial fibrillation (RACE V)”.

PROSPER: The PROSPER study was supported by an investigator initiated grant obtained from Bristol-Myers Squibb. Prof. Dr. J. W. Jukema is an Established Clinical Investigator of the Netherlands Heart Foundation (grant 2001 D 032). Support for genotyping was provided by the seventh framework program of the European commission (grant 223004) and by the Netherlands Genomics Initiative (Netherlands Consortium for Healthy Aging grant 050-060-810).

RS: The Rotterdam Study is supported by the Erasmus Medical Center and Erasmus University Rotterdam; The Netherlands Organization for Scientific Research; The Netherlands Organization for Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly; The Netherlands Heart Foundation; the Ministry of Education, Culture and Science; the Ministry of Health Welfare and Sports; the European Commission; and the Municipality of Rotterdam. Support for genotyping was provided by The Netherlands Organization for Scientific Research (NWO) (175.010.2005.011, 911.03.012) and Research Institute for Diseases in the Elderly (RIDE). This study was supported by The Netherlands Genomics Initiative (NGI)/Netherlands Organization for Scientific Research (NWO) project nr. 050-060-810.

SPHFC: The Heart Failure Cohort was supported by the Samaritan Hospital of São Paulo and Brazilian Ministry of Health - Programa de Apoio ao Desenvolvimento Institucional do Sistema Único de Saúde (PROADI-SUS), the Sao Paulo Research Agency Fapesp (grant 2013/17368-0).

SHIP: SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania, and the network ‘Greifswald Approach to Individualized Medicine (GANI_MED)’ funded by the Federal Ministry of Education and Research (grant 03IS2061A). Genome-wide data have been supported by the Federal Ministry of Education and Research (grant no. 03ZIK012) and a joint grant from Siemens Healthcare, Erlangen, Germany and the Federal State of Mecklenburg-West Pomerania. The University of Greifswald is a member of the ‘Center of Knowledge Interchange’ program of the Siemens AG.

TWINGENE: These projects were supported by Ministry for Higher Education, GenomEUtwin (EU/QLRT-2001-01254; QLG2-CT-2002-01254), NIH grant DK U01-066134, Knut and Alice Wallenberg Foundation (Wallenberg Academy Fellow), Swedish Diabetes Foundation (2013-024), Swedish Research Council (M-2005-1112, 2009-2298, 2012-1397 and 2015-02907), and Swedish Heart-Lung Foundation (20140422). Computations were performed on resources provided by SNIC through Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) under Project b2011036. We thank the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se) for excellent genotyping.

ULSAM: These projects were supported by Knut and Alice Wallenberg Foundation (Wallenberg Academy Fellow), Swedish Diabetes Foundation (2013-024), Swedish Research Council (2012-1397 and 2015-02907), and Swedish Heart-Lung Foundation (20140422). Computations were performed on resources provided by SNIC through Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) under Project b2011036. Genotyping was funded by the Wellcome Trust under awards WT064890 and WT086596. Analysis of genetic data was funded by the Wellcome Trust under awards WT098017 and WT090532. We thank the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se) for excellent genotyping.

WGHS: The Women's Genome Health Study (WGHS) is supported by the National Heart, Lung, and Blood Institute (HL043851 and HL080467 [both Buring]) and the National Cancer Institute (CA047988 [Buring] and UM1CA182913 [Buring and Lee]) with collaborative scientific support and funding for genotyping provided by Amgen (Chasman and Ridker). Atrial fibrillation endpoint confirmation was supported by HL-093613 (Albert) and HL116690 (Albert) and a grant from the Harris Family and Watkin's Foundation (Tedrow).

WHI: The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. A full listing of the WHI investigators can be found at <https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf>. We thank the Women's health Initiative investigators, staff, and study participants for their contributions.

WTCCC2-Munich: This work was supported by grants received from the German Federal Ministry of Education and Research (BMBF) in the context of the e:Med program (e:AtheroSysMed), the FP7 European Union project CVgenes@target (261123), the DFG as part of the CRC 1123 (B3), the Corona Foundation, and the Fondation Leducq (Transatlantic Network of Excellence on the Pathogenesis of Small Vessel Disease of the Brain).

Penn Biobank: This work was supported by grants from the National Institutes of Health to Dr. Deo (K23-DK089118).

Duke Biobank: This work was supported by grants from the National Heart, Lung and Blood Institute (HL 095987 [Shah] and HL101621 [Kraus]).

Role of the Sponsor:

None of the funding agencies had any role in the study design, data collection or analysis, interpretation of the data, writing of the manuscript, or in the decision to submit the manuscript for publication.

3. SUPPLEMENTARY REFERENCES

1. Pruijm, R. J. *et al.* LocusZoom: Regional visualization of genome-wide association scan results. *Bioinformatics* **26**, 2336–2337 (2010).
2. Welter, D. *et al.* The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. *Nucleic Acids Res.* **42**, D1001-6 (2014).
3. Traylor, M. *et al.* Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE collaboration): a meta-analysis of genome-wide association studies. *Lancet Neurol.* **11**, 951–62 (2012).
4. Dichgans, M. *et al.* Shared genetic susceptibility to ischemic stroke and coronary artery disease: a genome-wide analysis of common variants. *Stroke*. **45**, 24–36 (2014).
5. Gretarsdottir, S. *et al.* Risk variants for atrial fibrillation on chromosome 4q25 associate with ischemic stroke. *Ann. Neurol.* **64**, 402–9 (2008).
6. den Hoed, M. *et al.* Identification of heart rate-associated loci and their effects on cardiac conduction and rhythm disorders. *Nat. Genet.* **45**, 621–31 (2013).
7. Arking, D. E. *et al.* Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. *Nat. Genet.* **46**, 826–36 (2014).
8. Smith, J. G. *et al.* Impact of ancestry and common genetic variants on QT interval in African Americans. *Circ. Cardiovasc. Genet.* **5**, 647–55 (2012).
9. Holm, H. *et al.* Several common variants modulate heart rate, PR interval and QRS duration. *Nat. Genet.* **42**, 117–22 (2010).
10. Pfeufer, A. *et al.* Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nat. Genet.* **41**, 407–414 (2009).
11. Vasan, R. S. *et al.* Genetic Variants Associated With Cardiac Structure and Function. *JAMA* **302**, 168 (2009).
12. Newton-Cheh, C. *et al.* Common variants at ten loci influence QT interval duration in the QTGEN Study. *Nat. Genet.* **41**, 399–406 (2009).
13. Ritchie, M. D. *et al.* Genome- and phenome-wide analyses of cardiac conduction identifies markers of arrhythmia risk. *Circulation* **127**, 1377–85 (2013).
14. Nolte, I. M. *et al.* Common genetic variation near the phospholamban gene is associated with cardiac repolarisation: meta-analysis of three genome-wide association studies. *PLoS One* **4**, e6138 (2009).
15. Eijgelsheim, M. *et al.* Genome-wide association analysis identifies multiple loci related to resting heart rate. *Hum. Mol. Genet.* **19**, 3885–94 (2010).
16. Verweij, N. *et al.* Genetic Determinants of P Wave Duration and PR Segment. *Circ. Cardiovasc. Genet.* **7**, 475–81 (2014).
17. Pfeufer, A. *et al.* Genome-wide association study of PR interval. *Nat. Genet.* **42**, 153–159 (2010).
18. Sano, M. *et al.* Genome-wide association study of electrocardiographic parameters identifies a new association for PR interval and confirms previously reported associations. *Hum. Mol. Genet.* **23**, 6668–76 (2014).
19. Butler, A. A. M. *et al.* Novel loci associated with PR interval in a genome-wide association study of 10 African American cohorts. *Circ. Cardiovasc. Genet.* **5**, 639–646 (2012).
20. Hong, K.-W. *et al.* Identification of three novel genetic variations associated with electrocardiographic traits (QRS duration and PR interval) in East Asians. *Hum. Mol. Genet.* **23**, 6659–67 (2014).
21. Sotoodehnia, N. *et al.* Common variants in 22 loci are associated with QRS duration and cardiac ventricular conduction. *Nat. Genet.* **42**, 1068–76 (2010).

22. Smith, J. G. *et al.* Genome-wide association studies of the PR interval in African Americans. *PLoS Genet.* **7**, e1001304 (2011).
23. Petkowski, J. J. *et al.* NRMT2 is an N-terminal monomethylase that primes for its homologue NRMT1. *Biochem. J.* **456**, 453–62 (2013).
24. Bonsignore, L. A. *et al.* NRMT1 knockout mice exhibit phenotypes associated with impaired DNA repair and premature aging. *Mech. Ageing Dev.* **146–148**, 42–52 (2015).
25. Bonsignore, L. A., Butler, J. S., Klinge, C. M. & Schaner Tooley, C. E. Loss of the N-terminal methyltransferase NRMT1 increases sensitivity to DNA damage and promotes mammary oncogenesis. *Oncotarget* **6**, 12248–12263 (2015).
26. Orr, N. *et al.* A mutation in the atrial-specific myosin light chain gene (MYL4) causes familial atrial fibrillation. *Nat. Commun.* **7**, 11303 (2016).
27. Gudbjartsson, D. F. *et al.* Large-scale whole-genome sequencing of the Icelandic population. *Nat. Genet.* **47**, 435–444 (2015).
28. Shimizu, K. *et al.* SMAP, an Smg GDS-associating protein having arm repeats and phosphorylated by Src tyrosine kinase. *J. Biol. Chem.* **271**, 27013–7 (1996).
29. Shimizu, K., Shirataki, H., Honda, T., Minami, S. & Takai, Y. Complex formation of SMAP/KAP3, a KIF3A/B ATPase motor-associated protein, with a human chromosome-associated polypeptide. *J. Biol. Chem.* **273**, 6591–4 (1998).
30. Hirokawa, N. Stirring up development with the heterotrimeric kinesin KIF3. *Traffic* **1**, 29–34 (2000).
31. Rahmioglu, N. *et al.* Genome-wide enrichment analysis between endometriosis and obesity-related traits reveals novel susceptibility loci. *Hum. Mol. Genet.* **24**, 1185–99 (2015).
32. Landers, J. E. *et al.* Reduced expression of the Kinesin-Associated Protein 3 (KIFAP3) gene increases survival in sporadic amyotrophic lateral sclerosis. *Proc. Natl. Acad. Sci. U. S. A.* **106**, 9004–9 (2009).
33. Gotoh, M. *et al.* Comprehensive exploration of novel chimeric transcripts in clear cell renal cell carcinomas using whole transcriptome analysis. *Genes. Chromosomes Cancer* **53**, 1018–32 (2014).
34. Telikicherla, D. *et al.* Overexpression of Kinesin Associated Protein 3 (KIFAP3) in Breast Cancer. *J. Proteomics Bioinform.* **5**, 122–126 (2012).
35. Choi, J. *et al.* Kinesin superfamily-associated protein 3 is preferentially expressed in glutamatergic neurons and contributes to the excitatory control of female puberty. *Endocrinology* **149**, 6146–56 (2008).
36. Satoh, A. *et al.* Characterization of human p33/41 (annexin IV), a Ca²⁺ dependent carbohydrate-binding protein with monoclonal anti-annexin IV antibodies, AS11 and AS17. *Biol. Pharm. Bull.* **20**, 224–9 (1997).
37. Yao, H., Sun, C., Hu, Z. & Wang, W. The role of annexin A4 in cancer. *Front. Biosci. (Landmark Ed.)* **21**, 949–57 (2016).
38. Heinick, A. *et al.* Annexin A4 is a novel direct regulator of adenylyl cyclase type 5. *FASEB J.* **29**, fj.14-269837- (2015).
39. Matteo, R. G. & Moravec, C. S. Immunolocalization of annexins IV, V and VI in the failing and non-failing human heart. *Cardiovasc. Res.* **45**, 961–70 (2000).
40. Kimura, T. *et al.* Mouse germ cell-less as an essential component for nuclear integrity. *Mol. Cell. Biol.* **23**, 1304–1315 (2003).
41. Kleiman, S. E. *et al.* Reduced human germ cell-less (HGCL) expression in azoospermic men with severe germinal cell impairment. *J. Androl.* **24**, 670–5
42. Gjerstorff, M. F. *et al.* GAGE cancer-germline antigens are recruited to the nuclear envelope by germ cell-less (GCL). *PLoS One* **7**, e45819 (2012).

43. Fournier, A. *et al.* 1q12 chromosome translocations form aberrant heterochromatic foci associated with changes in nuclear architecture and gene expression in B cell lymphoma. *EMBO Mol. Med.* **2**, 159–71 (2010).
44. Graser, S., Stierhof, Y.-D. & Nigg, E. A. Cep68 and Cep215 (Cdk5rap2) are required for centrosome cohesion. *J. Cell Sci.* **120**, 4321–31 (2007).
45. Man, X., Megraw, T. L. & Lim, Y. P. Cep68 can be regulated by Nek2 and SCF complex. *Eur. J. Cell Biol.* **94**, 162–72 (2015).
46. Kim, J.-H. *et al.* Genome-wide and follow-up studies identify CEP68 gene variants associated with risk of aspirin-intolerant asthma. *PLoS One* **5**, e13818 (2010).
47. Cornejo-García, J. A. *et al.* Variants of CEP68 gene are associated with acute urticaria/angioedema induced by multiple non-steroidal anti-inflammatory drugs. *PLoS One* **9**, e90966 (2014).
48. Bang, M. L. *et al.* The complete gene sequence of titin, expression of an unusual approximately 700-kDa titin isoform, and its interaction with obscurin identify a novel Z-line to I-band linking system. *Circ. Res.* **89**, 1065–72 (2001).
49. Gregorio, C. C. *et al.* The NH₂ terminus of titin spans the Z-disc: its interaction with a novel 19-kD ligand (T-cap) is required for sarcomeric integrity. *J. Cell Biol.* **143**, 1013–27 (1998).
50. Linke, W. A. & Granzier, H. A spring tale: new facts on titin elasticity. *Biophys. J.* **75**, 2613–4 (1998).
51. Siu, B. L. *et al.* Familial dilated cardiomyopathy locus maps to chromosome 2q31. *Circulation* **99**, 1022–6 (1999).
52. Roberts, A. M. *et al.* Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease. *Sci. Transl. Med.* **7**, 270ra6 (2015).
53. Gerull, B. *et al.* Mutations of TTN, encoding the giant muscle filament titin, cause familial dilated cardiomyopathy. *Nat. Genet.* **30**, 201–4 (2002).
54. Herman, D. S. *et al.* Truncations of titin causing dilated cardiomyopathy. *N. Engl. J. Med.* **366**, 619–28 (2012).
55. Akinrinade, O., Alastalo, T.-P. & Koskenvuo, J. W. Relevance of Truncating Titin Mutations in Dilated Cardiomyopathy. *Clin. Genet.* (2016). doi:10.1111/cge.12741
56. Akinrinade, O., Koskenvuo, J. W. & Alastalo, T.-P. Prevalence of Titin Truncating Variants in General Population. *PLoS One* **10**, e0145284 (2015).
57. Marroni, F. *et al.* A genome-wide association scan of RR and QT interval duration in 3 European genetically isolated populations: the EUROSPAN project. *Circ. Cardiovasc. Genet.* **2**, 322–8 (2009).
58. Li, N. *et al.* Ablation of a Ca²⁺-activated K⁺ channel (SK2 channel) results in action potential prolongation in atrial myocytes and atrial fibrillation. *J. Physiol.* **587**, 1087–100 (2009).
59. Yu, T. *et al.* Decreased expression of small-conductance Ca²⁺-activated K⁺ channels SK1 and SK2 in human chronic atrial fibrillation. *Life Sci.* **90**, 219–227 (2012).
60. Parajuli, N. *et al.* Determinants of ventricular arrhythmias in human explanted hearts with dilated cardiomyopathy. *Eur. J. Clin. Invest.* **45**, 1286–96 (2015).
61. Yu, C.-C. *et al.* Small Conductance Calcium-Activated Potassium Current Is Important in Transmural Repolarization of Failing Human Ventricles. *Circ. Arrhythmia Electrophysiol.* **8**, 667–676 (2015).
62. Terentyev, D. *et al.* Sarcoplasmic reticulum Ca²⁺ release is both necessary and sufficient for SK channel activation in ventricular myocytes. *AJP Hear. Circ. Physiol.* **306**, H738–H746 (2014).
63. Gui, L. *et al.* Ventricular tachyarrhythmias in rats with acute myocardial infarction involves activation of small-conductance Ca²⁺-activated K⁺ channels. *Am. J. Physiol. Heart Circ. Physiol.* **304**, H118-30 (2013).
64. Chang, P.-C. *et al.* Heterogeneous upregulation of apamin-sensitive potassium currents in failing

- human ventricles. *J. Am. Heart Assoc.* **2**, e004713 (2013).
65. Mu, Y.-H. *et al.* RyR2 modulates a Ca²⁺-activated K⁺ current in mouse cardiac myocytes. *PLoS One* **9**, e94905 (2014).
66. Turker, I. *et al.* Amiodarone inhibits apamin-sensitive potassium currents. *PLoS One* **8**, e70450 (2013).
67. Kim, J.-J. *et al.* Identification of KCNN2 as a susceptibility locus for coronary artery aneurysms in Kawasaki disease using genome-wide association analysis. *J. Hum. Genet.* **58**, 521–5 (2013).
68. Lee, J.-K. *et al.* Consortium-Based Genetic Studies of Kawasaki Disease in Korea: Korean Kawasaki Disease Genetics Consortium. *Korean Circ. J.* **45**, 443–8 (2015).
69. Allen, D. *et al.* SK2 channels are neuroprotective for ischemia-induced neuronal cell death. *J. Cereb. Blood Flow Metab.* **31**, 2302–12 (2011).
70. Orfila, J. E. *et al.* Increasing small conductance Ca²⁺ -activated potassium channel activity reverses ischemia-induced impairment of long-term potentiation. *Eur. J. Neurosci.* **40**, 3179–3188 (2014).
71. McKay, B. M. *et al.* Increasing SK2 channel activity impairs associative learning. *J. Neurophysiol.* **108**, 863–70 (2012).
72. Ohtsuki, G., Piochon, C., Adelman, J. P. P. & Hansel, C. SK2 channel modulation contributes to compartment-specific dendritic plasticity in cerebellar Purkinje cells. *Neuron* **75**, 108–120 (2012).
73. Sun, J. *et al.* UBE3A Regulates Synaptic Plasticity and Learning and Memory by Controlling SK2 Channel Endocytosis. *Cell Rep.* **12**, 449–461 (2015).
74. Willis, M. *et al.* Small-conductance calcium-activated potassium type 2 channels (SK2, KCa2.2) in human brain. *Brain Struct. Funct.* (2016). doi:10.1007/s00429-016-1258-1
75. Cadet, J. L. *et al.* Genome-wide DNA hydroxymethylation identifies potassium channels in the nucleus accumbens as discriminators of methamphetamine addiction and abstinence. *Mol. Psychiatry* (2016). doi:10.1038/mp.2016.48
76. Fakira, A. K., Portugal, G. S., Carusillo, B., Melyan, Z. & Morón, J. A. Increased Small Conductance Calcium-Activated Potassium Type 2 Channel-Mediated Negative Feedback on N-methyl-D-aspartate Receptors Impairs Synaptic Plasticity Following Context-Dependent Sensitization to Morphine. *Biol. Psychiatry* **75**, 105–114 (2014).
77. Tatsuki, F. *et al.* Involvement of Ca²⁺-Dependent Hyperpolarization in Sleep Duration in Mammals. *Neuron* **90**, 70–85 (2016).
78. Kim, S. H. *et al.* Electrogenic transport and K(+) ion channel expression by the human endolymphatic sac epithelium. *Sci. Rep.* **5**, 18110 (2015).
79. Dolga, A. M. *et al.* Subcellular expression and neuroprotective effects of SK channels in human dopaminergic neurons. *Cell Death Dis.* **5**, e999 (2014).
80. Xiao, Y. *et al.* Overexpression of Trpp5 contributes to cell proliferation and apoptosis probably through involving calcium homeostasis. *Mol. Cell. Biochem.* **339**, 155–61 (2010).
81. Guo, L. *et al.* Identification and characterization of a novel polycystin family member, polycystin-L2, in mouse and human: sequence, expression, alternative splicing, and chromosomal localization. *Genomics* **64**, 241–51 (2000).
82. Volk, T., Schwoerer, A. P., Thiessen, S., Schultz, J.-H. & Ehmke, H. A polycystin-2-like large conductance cation channel in rat left ventricular myocytes. *Cardiovasc. Res.* **58**, 76–88 (2003).
83. Ferdaus, M. Z. & McCormick, J. A. The CUL3/KLHL3-WNK-SPAK/OSR1 pathway as a target for antihypertensive therapy. *Am. J. Physiol. Renal Physiol.* **310**, F1389-96 (2016).
84. Schumacher, F.-R. *et al.* Characterisation of the Cullin-3 mutation that causes a severe form of familial hypertension and hyperkalaemia. *EMBO Mol. Med.* **7**, 1285–306 (2015).
85. Shibata, S., Zhang, J., Puthumana, J., Stone, K. L. & Lifton, R. P. Kelch-like 3 and Cullin 3 regulate electrolyte homeostasis via ubiquitination and degradation of WNK4. *Proc. Natl. Acad. Sci. U. S. A.*

- A. **110**, 7838–43 (2013).
86. Boyden, L. M. *et al.* Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. *Nature* **482**, 98–102 (2012).
87. Glover, M. *et al.* Detection of mutations in KLHL3 and CUL3 in families with FHht (familial hyperkalaemic hypertension or Gordon's syndrome). *Clin. Sci. (Lond.)* **126**, 721–6 (2014).
88. Louis-Dit-Picard, H. *et al.* KLHL3 mutations cause familial hyperkalemic hypertension by impairing ion transport in the distal nephron. *Nat. Genet.* **44**, 456–60, S1–3 (2012).
89. Saitoh, T. & Katoh, M. Molecular cloning and characterization of human WNT8A. *Int. J. Oncol.* **19**, 123–7 (2001).
90. Cunningham, T. J., Kumar, S., Yamaguchi, T. P. & Duester, G. Wnt8a and Wnt3a cooperate in the axial stem cell niche to promote mammalian body axis extension. *Dev. Dyn.* **244**, 797–807 (2015).
91. Ma, Y. *et al.* The Chromatin Remodeling Protein Bptf Promotes Posterior Neuroectodermal Fate by Enhancing Smad2-Activated wnt8a Expression. *J. Neurosci.* **35**, 8493–506 (2015).
92. Gao, H. *et al.* Polymorphisms and expression of the WNT8A gene in Hirschsprung's disease. *Int. J. Mol. Med.* **32**, 647–52 (2013).
93. Lozano-Velasco, E. *et al.* Pitx2 impairs calcium handling in a dose-dependent manner by modulating Wnt signalling. *Cardiovasc. Res.* **109**, 55–66 (2016).
94. Lai, F. *et al.* cDNA cloning and genomic structure of three genes localized to human chromosome band 5q31 encoding potential nuclear proteins. *Genomics* **70**, 123–30 (2000).
95. Uhlén, M. *et al.* Proteomics. Tissue-based map of the human proteome. *Science* **347**, 1260419 (2015).
96. GATT, S. ENZYMIC HYDROLYSIS AND SYNTHESIS OF CERAMIDES. *J. Biol. Chem.* **238**, 3131–3 (1963).
97. Gatt, S. Enzymatic hydrolysis of sphingolipids. I. Hydrolysis and synthesis of ceramides by an enzyme from rat brain. *J. Biol. Chem.* **241**, 3724–30 (1966).
98. Seelan, R. S. *et al.* Human acid ceramidase is overexpressed but not mutated in prostate cancer. *Genes. Chromosomes Cancer* **29**, 137–46 (2000).
99. Norris, J. S. *et al.* Combined therapeutic use of AdGFPFasL and small molecule inhibitors of ceramide metabolism in prostate and head and neck cancers: a status report. *Cancer Gene Ther.* **13**, 1045–51 (2006).
100. Musumarra, G., Barresi, V., Condorelli, D. F. & Scirè, S. A bioinformatic approach to the identification of candidate genes for the development of new cancer diagnostics. *Biol. Chem.* **384**, 321–7 (2003).
101. Saad, A. F. *et al.* The functional effects of acid ceramidase overexpression in prostate cancer progression and resistance to chemotherapy. *Cancer Biol. Ther.* **6**, 1455–60 (2007).
102. Selzner, M. *et al.* Induction of apoptotic cell death and prevention of tumor growth by ceramide analogues in metastatic human colon cancer. *Cancer Res.* **61**, 1233–40 (2001).
103. Beckham, T. H. *et al.* Acid ceramidase-mediated production of sphingosine 1-phosphate promotes prostate cancer invasion through upregulation of cathepsin B. *Int. J. Cancer* **131**, 2034–43 (2012).
104. Kus, G., Kabadere, S., Uyar, R. & Kutlu, H. M. Induction of apoptosis in prostate cancer cells by the novel ceramidase inhibitor ceranib-2. *In Vitro Cell. Dev. Biol. Anim.* **51**, 1056–63 (2015).
105. Zeidan, Y. H. *et al.* Molecular targeting of acid ceramidase: implications to cancer therapy. *Curr. Drug Targets* **9**, 653–61 (2008).
106. Frohbergh, M., He, X. & Schuchman, E. H. The molecular medicine of acid ceramidase. *Biol. Chem.* **396**, 759–65 (2015).
107. Koch, J. *et al.* Molecular cloning and characterization of a full-length complementary DNA encoding human acid ceramidase. Identification Of the first molecular lesion causing Farber

- disease. *J. Biol. Chem.* **271**, 33110–5 (1996).
108. Rubboli, G. *et al.* Spinal muscular atrophy associated with progressive myoclonic epilepsy: A rare condition caused by mutations in ASAHI. *Epilepsia* **56**, 692–8 (2015).
109. Huang, Y. *et al.* Elevation of the level and activity of acid ceramidase in Alzheimer's disease brain. *Eur. J. Neurosci.* **20**, 3489–97 (2004).
110. Li, C.-M. M. *et al.* The human acid ceramidase gene (ASAHI): structure, chromosomal location, mutation analysis, and expression. *Genomics* **62**, 223–31 (1999).
111. Baranowski, M., Blachnio, A., Zabielski, P. & Gorski, J. Pioglitazone induces de novo ceramide synthesis in the rat heart. *Prostaglandins Other Lipid Mediat.* **83**, 99–111 (2007).
112. Monette, J. S. *et al.* (R)- α -Lipoic acid treatment restores ceramide balance in aging rat cardiac mitochondria. *Pharmacol. Res.* **63**, 23–29 (2011).
113. Wang, L., Lee, K., Malonis, R., Sanchez, I. & Dynlacht, B. D. Tethering of an E3 ligase by PCM1 regulates the abundance of centrosomal KIAA0586/Talpid3 and promotes ciliogenesis. *Elife* **5**, (2016).
114. Zhang, W. *et al.* MiRNA-128 regulates the proliferation and neurogenesis of neural precursors by targeting PCM1 in the developing cortex. *Elife* **5**, (2016).
115. Farina, F. *et al.* The centrosome is an actin-organizing centre. *Nat. Cell Biol.* **18**, 65–75 (2015).
116. Schwaab, J. *et al.* Limited duration of complete remission on ruxolitinib in myeloid neoplasms with PCM1-JAK2 and BCR-JAK2 fusion genes. *Ann. Hematol.* **94**, 233–8 (2015).
117. Sakamoto, S. *et al.* Four polymorphisms of the pericentriolar material 1 (PCM1) gene are not associated with schizophrenia in a Japanese population. *Psychiatry Research* **216**, 288–289 (2014).
118. Stylli, S. S. *et al.* Expression of the adaptor protein Tks5 in human cancer: prognostic potential. *Oncol. Rep.* **32**, 989–1002 (2014).
119. Burger, K. L. *et al.* Src-dependent Tks5 phosphorylation regulates invadopodia-associated invasion in prostate cancer cells. *Prostate* **74**, 134–48 (2014).
120. Blouw, B. *et al.* The invadopodia scaffold protein Tks5 is required for the growth of human breast cancer cells in vitro and in vivo. *PLoS One* **10**, e0121003 (2015).
121. Oikawa, T. *et al.* Tks5-dependent formation of circumferential podosomes/invadopodia mediates cell-cell fusion. *J. Cell Biol.* **197**, 553–68 (2012).
122. Stylli, S. S., I, S. T. T., Kaye, A. H. & Lock, P. *Prognostic significance of Tks5 expression in gliomas*. *Journal of Clinical Neuroscience* **19**, (2012).
123. Wang, F., Chang, J. T.-H., Kao, C. J. & Huang, R. S. High Expression of miR-532-5p, a Tumor Suppressor, Leads to Better Prognosis in Ovarian Cancer Both In Vivo and In Vitro. *Mol. Cancer Ther.* **15**, 1123–31 (2016).
124. Blouw, B., Seals, D. F., Pass, I., Diaz, B. & Courtneidge, S. A. A role for the podosome/invadopodia scaffold protein Tks5 in tumor growth in vivo. *Eur. J. Cell Biol.* **87**, 555–567 (2008).
125. Murphy, D. A. *et al.* A Src-Tks5 pathway is required for neural crest cell migration during embryonic development. *PLoS One* **6**, e22499 (2011).
126. Cejudo-Martin, P. *et al.* Genetic disruption of the sh3pxd2a gene reveals an essential role in mouse development and the existence of a novel isoform of tks5. *PLoS One* **9**, e107674 (2014).
127. Burger, K. L., Davis, A. L., Isom, S., Mishra, N. & Seals, D. F. The podosome marker protein Tks5 regulates macrophage invasive behavior. *Cytoskeleton (Hoboken)* **68**, 694–711 (2011).
128. Vincent, C., Siddiqui, T. A. & Schlichter, L. C. Podosomes in migrating microglia: components and matrix degradation. *J. Neuroinflammation* **9**, 190 (2012).
129. Mesirca, P. *et al.* The G-protein-gated K⁺ channel, IKACH, is required for regulation of pacemaker activity and recovery of resting heart rate after sympathetic stimulation. *J. Gen. Physiol.* **142**, 113–26 (2013).

130. Mesirca, P. *et al.* Cardiac arrhythmia induced by genetic silencing of ‘funny’ (f) channels is rescued by GIRK4 inactivation. *Nat. Commun.* **5**, 4664 (2014).
131. Bingen, B. O. *et al.* Atrium-Specific Kir3.x determines inducibility, dynamics, and termination of fibrillation by regulating restitution-driven alternans. *Circulation* **128**, 2732–2744 (2013).
132. Jabbari, J. *et al.* Common polymorphisms in KCNJ5 are associated with early-onset lone atrial fibrillation in Caucasians. *Cardiology* **118**, 116–120 (2011).
133. Wang, F. *et al.* The phenotype characteristics of type 13 long QT syndrome with mutation in KCNJ5 (Kir3.4-G387R). *Hear. Rhythm* **10**, 1500–1506 (2013).
134. Liang, B. *et al.* G-protein-coupled inward rectifier potassium current contributes to ventricular repolarization. *Cardiovasc. Res.* **101**, 175–84 (2014).
135. Molina-Navarro, M. M. *et al.* Differential gene expression of cardiac ion channels in human dilated cardiomyopathy. *PLoS One* **8**, e79792 (2013).
136. Kokunai, Y. *et al.* A Kir3.4 mutation causes Andersen-Tawil syndrome by an inhibitory effect on Kir2.1. *Neurology* **82**, 1058–64 (2014).
137. Azizan, E. A. B. & Brown, M. J. Novel genetic determinants of adrenal aldosterone regulation. *Curr. Opin. Endocrinol. Diabetes. Obes.* **23**, 209–17 (2016).
138. Chen, A. X., Nishimoto, K., Nanba, K. & Rainey, W. E. Potassium channels related to primary aldosteronism: Expression similarities and differences between human and rat adrenals. *Mol. Cell. Endocrinol.* **417**, 141–148 (2015).
139. Gomez, L. *et al.* Association of the KCNJ5 gene with Tourette Syndrome and Attention-Deficit/Hyperactivity Disorder. *Genes. Brain. Behav.* **13**, 535–42 (2014).
140. Han, C., Huang, J. & Waxman, S. G. Sodium channel Nav1.8: Emerging links to human disease. *Neurology* **86**, 473–83 (2016).
141. Yang, T. *et al.* Blocking Scn10a channels in heart reduces late sodium current and is antiarrhythmic. *Circ. Res.* **111**, 322–332 (2012).
142. Verkerk, A. O. *et al.* Functional NaV1.8 channels in intracardiac neurons: The link between SCN10A and cardiac electrophysiology. *Circ. Res.* **111**, 333–343 (2012).
143. Chambers, J. C. *et al.* Genetic variation in SCN10A influences cardiac conduction. *Nat. Genet.* **42**, 149–152 (2010).
144. Denny, J. C. *et al.* Identification of genomic predictors of atrioventricular conduction: using electronic medical records as a tool for genome science. *Circulation* **122**, 2016–21 (2010).
145. Savio-Galimberti, E. *et al.* SCN10A/Nav1.8 modulation of peak and late sodium currents in patients with early onset atrial fibrillation. *Cardiovasc. Res.* **104**, 355–63 (2014).
146. Bezzina, C. R. *et al.* Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. *Nat. Genet.* **45**, 1044–1049 (2013).
147. Hu, D. *et al.* Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. *J. Am. Coll. Cardiol.* **64**, 66–79 (2014).
148. Park, D. S. & Fishman, G. I. Navigating through a complex landscape: SCN10A and cardiac conduction. *J. Clin. Invest.* **124**, 1460–2 (2014).
149. van den Boogaard, M. *et al.* A common genetic variant within SCN10A modulates cardiac SCN5A expression. *J. Clin. Invest.* **124**, 1844–1852 (2014).
150. Aza-Carmona, M. *et al.* NPPB and ACAN, two novel SHOX2 transcription targets implicated in skeletal development. *PLoS One* **9**, e83104 (2014).
151. Liu, C.-F. & Lefebvre, V. The transcription factors SOX9 and SOX5/SOX6 cooperate genome-wide through super-enhancers to drive chondrogenesis. *Nucleic Acids Res.* **43**, 8183–203 (2015).
152. Baroti, T. *et al.* Transcription factors Sox5 and Sox6 exert direct and indirect influences on oligodendroglial migration in spinal cord and forebrain. *Glia* **64**, 122–38 (2016).

153. Hersh, C. P. *et al.* SOX5 is a candidate gene for chronic obstructive pulmonary disease susceptibility and is necessary for lung development. *Am. J. Respir. Crit. Care Med.* **183**, 1482–9 (2011).
154. Olesen, M. S. *et al.* Genetic loci on chromosomes 4q25, 7p31, and 12p12 are associated with onset of lone atrial fibrillation before the age of 40 years. *Can. J. Cardiol.* **28**, 191–5 (2012).
155. Della-Morte, D. *et al.* A follow-up study for left ventricular mass on chromosome 12p11 identifies potential candidate genes. *BMC Med. Genet.* **12**, 100 (2011).
156. Wen, Y. *et al.* Integrative analysis of genome-wide association studies and gene expression profiles identified candidate genes for osteoporosis in Kashin-Beck disease patients. *Osteoporos. Int.* **27**, 1041–6 (2016).
157. Jin, J., Chou, C., Lima, M., Zhou, D. & Zhou, X. Systemic Sclerosis is a Complex Disease Associated Mainly with Immune Regulatory and Inflammatory Genes. *Open Rheumatol. J.* **8**, 29–42 (2014).
158. Le Clerc, S. *et al.* Genomewide association study of a rapid progression cohort identifies new susceptibility alleles for AIDS (ANRS Genomewide Association Study 03). *J. Infect. Dis.* **200**, 1194–201 (2009).
159. Tu, W. *et al.* Genome-Wide Loci Linked to Non-Obstructive Azoospermia Susceptibility May Be Independent of Reduced Sperm Production in Males with Normozoospermia. *Biol. Reprod.* **92**, 41–41 (2015).
160. Al Zeyadi, M. *et al.* Whole genome microarray analysis in non-small cell lung cancer. *Biotechnol. Biotechnol. Equip.* **29**, 111–118 (2015).
161. Wang, D., Han, S., Wang, X., Peng, R. & Li, X. SOX5 promotes epithelial-mesenchymal transition and cell invasion via regulation of Twist1 in hepatocellular carcinoma. *Med. Oncol.* **32**, 461 (2015).
162. Shiseki, M. *et al.* Identification of the SOX5 gene as a novel IGH-involved translocation partner in BCL2-negative follicular lymphoma with t(12;14)(p12.2;q32). *Int. J. Hematol.* **102**, 633–8 (2015).
163. Kordaß, T. *et al.* SOX5 is involved in balanced MITF regulation in human melanoma cells. *BMC Med. Genomics* **9**, 10 (2016).
164. Kranias, E. G. & Hajjar, R. J. Modulation of cardiac contractility by the phospholamban/SERCA2a regulatome. *Circ. Res.* **110**, 1646–60 (2012).
165. Minamisawa, S. *et al.* Mutation of the phospholamban promoter associated with hypertrophic cardiomyopathy. *Biochem. Biophys. Res. Commun.* **304**, 1–4 (2003).
166. Landstrom, A. P., Adekola, B. A., Bos, J. M., Ommen, S. R. & Ackerman, M. J. PLN-encoded phospholamban mutation in a large cohort of hypertrophic cardiomyopathy cases: summary of the literature and implications for genetic testing. *Am. Heart J.* **161**, 165–71 (2011).
167. Schmitt, J. P. *et al.* Dilated cardiomyopathy and heart failure caused by a mutation in phospholamban. *Science* **299**, 1410–3 (2003).
168. van Spaendonck-Zwarts, K. Y. *et al.* Genetic analysis in 418 index patients with idiopathic dilated cardiomyopathy: overview of 10 years' experience. *Eur. J. Heart Fail.* **15**, 628–36 (2013).
169. Ellinor, P. T. *et al.* Meta-analysis identifies six new susceptibility loci for atrial fibrillation. *Nat. Genet.* **44**, 670–5 (2012).
170. Harris, T. B. *et al.* Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. *Am. J. Epidemiol.* **165**, 1076–87 (2007).
171. Raitoharju, E. *et al.* Common variation in the ADAM8 gene affects serum sADAM8 concentrations and the risk of myocardial infarction in two independent cohorts. *Atherosclerosis* **218**, 127–133 (2011).
172. The ARIC investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am. J. Epidemiol.* **129**, 687–702 (1989).
173. Alonso, A. *et al.* Incidence of atrial fibrillation in whites and African-Americans: the

- Atherosclerosis Risk in Communities (ARIC) study. *Am Hear. J* **158**, 111–117 (2009).
174. Conen, D. *et al.* Genetic and phenotypic determinants of blood pressure and other cardiovascular risk factors (GAPP). *Swiss Med. Wkly.* **143**, w13728 (2013).
175. Sinner, M. F. *et al.* Integrating genetic, transcriptional, and functional analyses to identify 5 novel genes for atrial fibrillation. *Circulation* **130**, 1225–35 (2014).
176. Locke, A. E. *et al.* Genetic studies of body mass index yield new insights for obesity biology. *Nature* **518**, 197–206 (2015).
177. Weeke, P. *et al.* Examining rare and low-frequency genetic variants previously associated with lone or familial forms of atrial fibrillation in an electronic medical record system: a cautionary note. *Circ. Cardiovasc. Genet.* **8**, 58–63 (2015).
178. Fried, L. P. *et al.* The cardiovascular health study: Design and rationale. *Ann. Epidemiol.* **1**, 263–276 (1991).
179. Vaara, S. *et al.* Cohort Profile: the Corogene study. *Int. J. Epidemiol.* **41**, 1265–71 (2012).
180. Dawber, T. R., Meadors, G. F. & Moore, F. E. Epidemiological approaches to heart disease: the Framingham Study. *Am. J. Public Health Nations. Health* **41**, 279–81 (1951).
181. Kannel, W. B., Feinleib, M., McNamara, P. M., Garrison, R. J. & Castelli, W. P. An investigation of coronary heart disease in families. The Framingham offspring study. *Am. J. Epidemiol.* **110**, 281–90 (1979).
182. Nieminen, T. *et al.* The Finnish Cardiovascular Study (FINCAVAS): characterising patients with high risk of cardiovascular morbidity and mortality. *BMC Cardiovasc. Disord.* **6**, 9 (2006).
183. Smith, B. H. *et al.* Cohort Profile: Generation Scotland: Scottish Family Health Study (GS:SFHS). The study, its participants and their potential for genetic research on health and illness. *Int. J. Epidemiol.* **42**, 689–700 (2013).
184. Schermund, A. *et al.* Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: Rationale and design of the Heinz Nixdorf RECALL Study. *Am. Heart J.* **144**, 212–218 (2002).
185. Winkelmann, B. R. *et al.* Rationale and design of the LURIC study--a resource for functional genomics, pharmacogenomics and long-term prognosis of cardiovascular disease. *Pharmacogenomics* **2**, S1-73 (2001).
186. Smith, J. G., Platonov, P. G., Hedblad, B., Engström, G. & Melander, O. Atrial fibrillation in the Malmö Diet and Cancer study: a study of occurrence, risk factors and diagnostic validity. *Eur. J. Epidemiol.* **25**, 95–102 (2010).
187. Bild, D. E. *et al.* Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am. J. Epidemiol.* **156**, 871–81 (2002).
188. Rasmussen-Torvik, L. J. *et al.* Fasting glucose GWAS candidate region analysis across ethnic groups in the Multiethnic Study of Atherosclerosis (MESA). *Genet. Epidemiol.* **36**, 384–91 (2012).
189. Genes for Cerebral Hemorrhage on Anticoagulation (GOCHA) Collaborative Group. Exploiting common genetic variation to make anticoagulation safer. *Stroke* **40**, S64-6 (2009).
190. International Stroke Genetics Consortium (ISGC) *et al.* Genome-wide association study identifies a variant in HDAC9 associated with large vessel ischemic stroke. *Nat. Genet.* **44**, 328–33 (2012).
191. Lind, L., Fors, N., Hall, J., Marttala, K. & Stenborg, A. A comparison of three different methods to evaluate endothelium-dependent vasodilation in the elderly: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. *Arterioscler. Thromb. Vasc. Biol.* **25**, 2368–75 (2005).
192. Hillege, H. L. *et al.* Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* **106**, 1777–82 (2002).
193. Shepherd, J. *et al.* Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a

- randomised controlled trial. *Lancet* **360**, 1623–30 (2002).
194. Hofman, A. *et al.* The Rotterdam Study: 2016 objectives and design update. *Eur. J. Epidemiol.* **30**, 661–708 (2015).
195. Gioli-Pereira, L. *et al.* Genetic and ElectroNic medical records to predict oUtcomeS in Heart Failure patients (GENIUS-HF) - design and rationale. *BMC Cardiovasc. Disord.* **14**, 32 (2014).
196. Völzke, H. *et al.* Cohort profile: the study of health in Pomerania. *Int. J. Epidemiol.* **40**, 294–307 (2011).
197. Hong, Y., Pedersen, N. L., Brismar, K. & de Faire, U. Genetic and environmental architecture of the features of the insulin-resistance syndrome. *Am. J. Hum. Genet.* **60**, 143–52 (1997).
198. Ingelsson, E., Sundström, J., Arnlöv, J., Zethelius, B. & Lind, L. Insulin resistance and risk of congestive heart failure. *JAMA* **294**, 334–41 (2005).
199. Ridker, P. M. *et al.* Rationale, design, and methodology of the Women’s Genome Health Study: a genome-wide association study of more than 25,000 initially healthy american women. *Clin. Chem.* **54**, 249–55 (2008).
200. Grove, M. L. *et al.* Best practices and joint calling of the HumanExome BeadChip: the CHARGE Consortium. *PLoS One* **8**, e68095 (2013).
201. Holle, R., Happich, M., Löwel, H., Wichmann, H. E. & MONICA/KORA Study Group. KORA--a research platform for population based health research. *Gesundheitswes. (Bundesverband der Ärzte des Öffentlichen Gesundheitsdienstes)* **67 Suppl 1**, S19–25 (2005).
202. Wichmann, H.-E., Gieger, C., Illig, T. & MONICA/KORA Study Group. KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen* **67 Suppl 1**, S26-30 (2005).
203. Paynter, N. P. *et al.* Cardiovascular disease risk prediction with and without knowledge of genetic variation at chromosome 9p21.3. *Ann. Intern. Med.* **150**, 65–72 (2009).
204. Kuriyama, S. *et al.* The Tohoku Medical Megabank Project: Design and Mission. *J. Epidemiol.* **26**, 493–511 (2016).
205. The GTEx Consortium. The Genotype-Tissue Expression (GTEx) project. *Nat. Genet.* **45**, 580–5 (2013).
206. Boyle, A. P. *et al.* Annotation of functional variation in personal genomes using RegulomeDB. *Genome Res.* **22**, 1790–1797 (2012).
207. Ward, L. D. & Kellis, M. HaploReg: a resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. *Nucleic Acids Res.* **40**, D930–4 (2012).
208. Sherry, S. T. *et al.* dbSNP: the NCBI database of genetic variation. *Nucleic Acids Res.* **29**, 308–11 (2001).
209. Arnold, M., Raffler, J., Pfeuffer, A., Suhre, K. & Kastenmüller, G. SNiPA: An interactive, genetic variant-centered annotation browser. *Bioinformatics* **31**, 1334–1336 (2015).
210. Pers, T. H. *et al.* Biological interpretation of genome-wide association studies using predicted gene functions. *Nat. Commun.* **6**, 5890 (2015).
211. Purcell, S. *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* **81**, 559–75 (2007).
212. Roden, D. M. *et al.* Development of a large-scale de-identified DNA biobank to enable personalized medicine. *Clin. Pharmacol. Ther.* **84**, 362–9 (2008).
213. Wei, W.-Q. *et al.* Impact of data fragmentation across healthcare centers on the accuracy of a high-throughput clinical phenotyping algorithm for specifying subjects with type 2 diabetes mellitus. *J. Am. Med. Inform. Assoc.* **19**, 219–24
214. Pulley, J., Clayton, E., Bernard, G. R., Roden, D. M. & Masys, D. R. Principles of human subjects protections applied in an opt-out, de-identified biobank. *Clin. Transl. Sci.* **3**, 42–8 (2010).

215. Khurshid, S., Keaney, J., Ellinor, P. T. & Lubitz, S. A. A Simple and Portable Algorithm for Identifying Atrial Fibrillation in the Electronic Medical Record. *Am. J. Cardiol.* **117**, 221–225 (2016).
216. Vermond, R. A. *et al.* Incidence of Atrial Fibrillation and Relationship With Cardiovascular Events, Heart Failure, and Mortality. *J. Am. Coll. Cardiol.* **66**, 1000–1007 (2015).
217. Magnusson, P. K. E. *et al.* The Swedish Twin Registry: establishment of a biobank and other recent developments. *Twin Res. Hum. Genet.* **16**, 317–29 (2013).
218. Hays, J. *et al.* The women's health initiative recruitment methods and results. *Ann. Epidemiol.* **13**, S18–S77 (2003).
219. Anderson, G. L. *et al.* Implementation of the Women's Health Initiative study design. *Ann. Epidemiol.* **13**, S5–S17 (2003).
220. Gerull, B. *et al.* Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. *Nat. Genet.* **36**, 1162–1164 (2004).
221. Cerrone, M. *et al.* Missense mutations in plakophilin-2 cause sodium current deficit and associate with a brugada syndrome phenotype. *Circulation* **129**, 1092–1103 (2014).
222. Peters, S. Arrhythmogenic cardiomyopathy and provable Brugada ECG in a patient caused by missense mutation in plakophilin-2. *Int. J. Cardiol.* **173**, 317–8 (2014).