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Genome-wide association study of PR interval

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Abstract

The electrocardiographic PR interval reflects atrial and atrioventricular nodal conduction, disturbances of which increase risk of atrial fibrillation (AF). To identify underlying common genetic variation, we meta-analyzed genome-wide association results for PR interval from seven community-based studies of European-ancestry individuals in the CHARGE consortium: AGES, ARIC, CHS, FHS, KORA, Rotterdam Study, and SardiNIA (N=28,517). Statistically significant loci ($P<5\times10^{-8}$) were tested for association with AF (N=5,741 cases). We identified nine loci associated with PR interval. At chromosome 3p22.2, we observed two independent associations in voltage gated sodium channel genes *SCN10A* and *SCN5A*, while six loci were near cardiac developmental genes *CAV1/CAV2*, *NKX2-5 (CSX1)*, *SOX5*, *WNT11*, *MEIS1*, and *TBX5/TBX3*. Another signal was at *ARHGAP24*, a locus without known relevance to the heart. Five of the nine loci, *SCN5A*, *SCN10A*, *NKX2-5*, *CAV1/CAV2*, *and SOX5*, were also associated with AF ($P<0.0056$). Common genetic variation, particularly in ion channel and developmental genes, contributes significantly to atrial and atrioventricular conduction and to AF risk.

Search Terms

genome-wide association study; quantitative trait; PR interval; PQ interval; developmental genes; voltage gated sodium channel; atrial fibrillation

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In myocardial excitation, the delay between the excitation of the atria and ventricles is determined by the sum of atrial and atrioventricular nodal conduction. This delay, measured in milliseconds, is reflected on the standard 12-lead electrocardiogram (ECG) by the PR interval or PQ interval. The PR interval has a substantial heritable component, with heritability estimates ranging between 30 and 50% (1,2,3,4).

Atrial fibrillation (AF) is the most common sustained arrhythmia and is independently associated with increased risk of stroke, heart failure, dementia, and death (5). AF prevalence increases markedly with age, to nearly 9% in those 80-89 years of age, and is estimated to triple by the year 2050. (6). Common genetic risk factors for AF (7) include variants on chromosome 4q25 near the *PITX2* gene (8), in 16q22.3 near the *ZFHX3* (*ATBF1*) gene (9), in 1q21 in the *KCNN3* gene (10) and the K897T variant in the *KCNH2* gene on 7q36.1 (11).

The PR interval is an intermediate phenotype for AF, as alterations in atrial action potential duration and in atrioventricular conduction influence both PR interval and AF risk (12). Longitudinal data from the Framingham Heart Study (FHS) and the Atherosclerosis Risk in Communities Study (ARIC) demonstrate that PR interval prolongation is a predictor of increased AF risk (13, 14). In addition, PR interval prolongation has been shown in FHS to be an independent predictor in a multifactorial risk score for AF predisposition (15).

We undertook a meta-analysis of GWAS to investigate the genetic determinants of the PR interval and their relationship to AF risk. Our goal was to identify genes that can provide insights into atrial disease and lead to novel opportunities for AF prevention and therapy.

We studied individuals of European descent from seven community based studies: the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES) (16), ARIC (17), the Cardiovascular Health Study (CHS) (18), FHS (19), the Kooperative Gesundheitsforschung in der Region Augsburg Study (KORA) (20), the Rotterdam Study (RS) (21), and the SardiNIA study (3) (Table 1 and Online Methods). Phenotypic data including resting 12-lead electrocardiography, height, weight, systolic blood pressure, and medication use were collected using standardized protocols in all studies. Exclusion criteria and covariates are described in Supplementary Table 1.

Study participants were genotyped using a variety of genome-wide SNP arrays. To facilitate comparison of results across studies, we imputed to the 2.5 million HapMap SNPs (22). A recent review supports the validity of combining results across statistical and genotyping platforms (23). Genotyping details, SNP quality control filters, and imputation methods for each study are summarized in Supplementary Table 2.

After exclusions, 28,517 individuals were available for study. The association of each SNP with the PR interval was adjusted for age, sex, RR interval, height, body mass index (BMI), systolic blood pressure, and study site in studies with multiple recruitment sites. Studies adjusted for or excluded individuals using drugs known to alter the PR interval including beta-blockers, diuretics and non-dihydropyridine calcium antagonists.

Due to restrictions imposed by Institutional Review Boards at several of the study sites on the sharing of individual genetic data, it was not possible to perform analyses based on combined individual-level data. Therefore, we conducted inverse variance-weighted fixed-effects meta-analysis of the beta estimates from linear regression of PR interval. The coefficients, generated for each SNP, estimate the difference in PR interval per additional copy of the minor allele, adjusted for the covariates in the model. The genome-wide significance threshold was 5×10^{-8}.

To determine if there was an association between the PR-associated loci and AF risk, we meta-analyzed results from 4 studies of AF in subjects of European descent. The first was a meta-analytic study of 896 prevalent AF cases and 15,768 referents from the CHARGE cohorts (9). The second was a meta-analytic study of 2,517 incident AF cases and 21,337 referents from the CHARGE cohorts. The third and fourth were independent case-control studies of prevalent AF: the German Competence Network on Atrial Fibrillation (AFNET, 2,145 cases and 4,073 controls) (10); and the Cleveland Clinic AF study (CCAF, 183 cases and 164 controls) (24) (Table 3 and Online Methods). We performed an inverse-variance weighted meta-analysis of the logistic-regression results from the prevalent AF studies and the proportional hazards results from the incident AF study. The Bonferroni adjusted significance threshold was $P = 0.05/9 = 0.0056$.

The study was performed in accordance with the Helsinki declarations and was approved by the local medical ethics and institutional review boards. All participants gave signed informed consent to use their DNA for genetic analyses.

The distribution of results from the meta-analysis of PR GWAS is summarized in Figure 1. The Q-Q plot in Figure 2 shows a clear excess of extreme p-values. Overall, nine loci showed independent association signals with $P<5\times10^{-8}$. We determined the genomic control factor (λ) for the linear regression analysis of PR interval to be 1.076 and report overall analysis results unadjusted for this λ value (25). We did not observe evidence of heterogeneity in effect sizes for any of the nine loci (I^2-statistic, all p>0.05, Table 2).

The strongest genome-wide association signal for PR interval was in chromosomal region 3p22.2. In this region we detected two association signals, one covering *SCN10A* (rs6800541, $P = 2.1\times10^{-74}$) and the other *SCN5A* (rs11708996, $P = 6.0\times10^{-26}$) (Figure 2 and Table 2). These variants are in low LD ($r^2 = 0.031$). In a meta-analysis of linear regression results from models including both SNPs, these SNPs remained independently associated with PR interval (rs6800541, $P= 9.7\times10^{-82}$; rs11708996, $P = 1.1\times10^{-33}$), suggesting they represent independent association signals.

SCN10A encodes the voltage gated sodium channel Nav1.8, essential for cold perception in afferent nociceptive fibers of sensory dorsal root ganglia (26). Nav1.8 is expressed in the peripheral sensory nervous system but has not been identified in the heart (27). In *SCN10A*, two common nonsynonymous SNPs are in high to moderate linkage disequilibrium with the sentinel SNP: rs6795970 (V1073A, r^2=0.933) and rs12632942 (L1092P, r^2=0.220) making both SNPs good candidates to mechanistically explain the strongest PR interval association identified in the human genome.

The neighboring *SCN5A* gene encodes Nav1.5, the major cardiac sodium channel, with mutations resulting in Brugada Syndrome, long-QT Syndrome, dilated cardiomyopathy, cardiac conduction disease, idiopathic ventricular fibrillation and AF (28). *SCN5A* sentinel SNP rs11708996 is in weak LD with rs1805124 (H558R, r^2=0.034) as well as with two non-coding variants, rs12053903 (r^2=0.030) and rs11129795 (r^2=0.058), recently reported to be associated with QT interval (29, 30). This suggests that the PR interval and QT interval modifying effects are distinct.

Six PR interval associations were identified in or near genes involved in human cardiac development (Figure 2 and Table 2). *NKX2-5* (rs251253 P= 9.5×10^{-13}) is the homolog of the Drosophila *tinman* gene and encodes the cardiac specific homeobox transcription factor Nkx2.5 (Csx). Mutations can cause atrium septum defect (ASD) with conduction defects (OMIM #108900), tetralogy of Fallot (OMIM #187500), and high degree AV block (31). In the *NKX2-5* gene region the association extends over 200Kb and includes three other genes *BNIP1*, *C5orf41*, and *ATP6V0E1*. The signal at the *TBX5/TBX3* locus is 230kb downstream of the paralog *TBX5* and *TBX3* genes (rs1896312, P= 3.1×10^{-17}). Both encode T-box containing transcription factors important for cardiac conduction system formation in the developing heart (32). *TBX5* is required for the patterning and maturation of the murine atrioventricular and bundle branch conduction system (33). Deletion of *TBX5* results in longer PR intervals in mice (34). Mutations are seen in Holt-Oram syndrome (OMIM #142900) with atrial and ventricular septal defects, conduction disease, and occasionally AF (35). *TBX3* controls formation of the sinus node and imposes pacemaker function on atrial cells (36). Mutations cause ulnar-mammary syndrome (OMIM #181450) with limb, mammary, tooth, genital and cardiac abnormalities (37).

The *CAV1* and *CAV2* genes (rs3807989, P = 3.7×10^{-28}) encode caveolins necessary for the development of caveolae involved in signal transduction (38). *CAV1* is expressed in atrial myocytes. Mice deficient in Cav1 develop dilated cardiomyopathy and pulmonary hypertension (39). *SOX5* (rs11047543, P = 3.3×10^{-13}) and the nearby *C12orf67* encode transcription factors. *SOX5* knockout mice die with heart failure marked by hepatic congestion and peripheral edema (40). *MEIS1* (rs11897119, P = 4.6×10^{-11}) encodes a homeobox transcription factor implicated in cardiac, hematopoietic and neural development. *MEIS1* deficient mice have malformed cardiac outflow tracts with overriding aorta and ventricular septal defect (41).

WNT11 (rs4944092, P = 3.2×10^{-8}) encodes a signaling protein inducing cardiogenesis in Xenopus and in mice by noncanonical WNT signaling (42). The nearest gene to a signal on chromosome 4 (rs7692808, P = 6.0×10^{-20}) is *ARHGAP24*, which encodes a Rho-GTPase-activating protein and key angiogenic regulator involved in cell polarity, cell morphology, and cytoskeletal organisation (43), but without known relevance to the heart.

Of the nine identified PR loci, five were associated with AF risk (p<0.0056). These were at *SCN10A* (rs6800541, P=1.5×10^{-4}) and *SCN5A* (rs11708996, P=7.0×10^{-4}), as well as at three regions harboring developmental genes, *NKX2-5* (P=2.3×10^{-3}), *CAV1/CAV2* (P=2.2×10^{-5}), and *SOX5* (P=2.1×10^{-4}). In all instances the minor alleles were associated with a

decrease in AF risk, irrespective of the direction of their association with PR interval (Table 4). Protective ratios against AF were between 0.93 and 0.88 for the minor alleles.

The observation that SNPs associated with both PR interval and AF risk did not exhibit consistent directions of effect may initially seem counterintuitive. However, PR interval is an amalgamated measure of atrial and atrioventricular nodal conduction, which independently affect AF risk. PR intervals at both high and low extremes may be associated with an increase in AF risk. Indeed, existing data from humans and animal models suggest that the effects of genetic variants on atrial repolarization and action potential duration, and their relationship with atrial arrhythmias, are complex (11). In analogy to the QT interval duration, where both long and short QT intervals are associated with increased ventricular tachycardia risk, assuming a linear association model for AF with PR interval and its underlying genetic variants may not capture the complexity of these relations.

Our study was subject to a number of potential limitations. False positive associations from multiple testing is a limitation of any GWAS, so we used a well-accepted genome-wide association significance threshold equivalent to a Bonferroni correction for 1 million independent tests to reduce false positive findings (44). Population stratification is also a concern, so we only included study subjects of European descent. The low genomic control inflation factor suggested there was no strong influence of population stratification on our results.

Our study also did not examine patterns of haplotype association. Thus complex haplotype associations may not have been captured. However, genome-wide meta-analysis of haplotypes is currently not feasible, and, in common with other GWAS, our use of imputation to the HapMap leverages available linkage disequilibrium information.

The identification of *SCN10A* was unexpected, as Nav1.8 was previously not thought to play a role in cardiac electrophysiology. In addition, *SCN10A* was the only locus where two common nonsynonymous variants were in high LD with a sentinel SNP and thus are likely causal candidates. The second key finding was that the majority of association signals we identified were in cardiac developmental genes including two, *NKX2-5* and *TBX5*, in which mutations are known to cause well-defined cardiac malformations involving the atrial septum and the atrioventricular junction. The biological mechanisms by which the identified variants influence PR interval and AF remain speculative, and detailed functional investigation will be required to determine the potential contribution of each genomic region.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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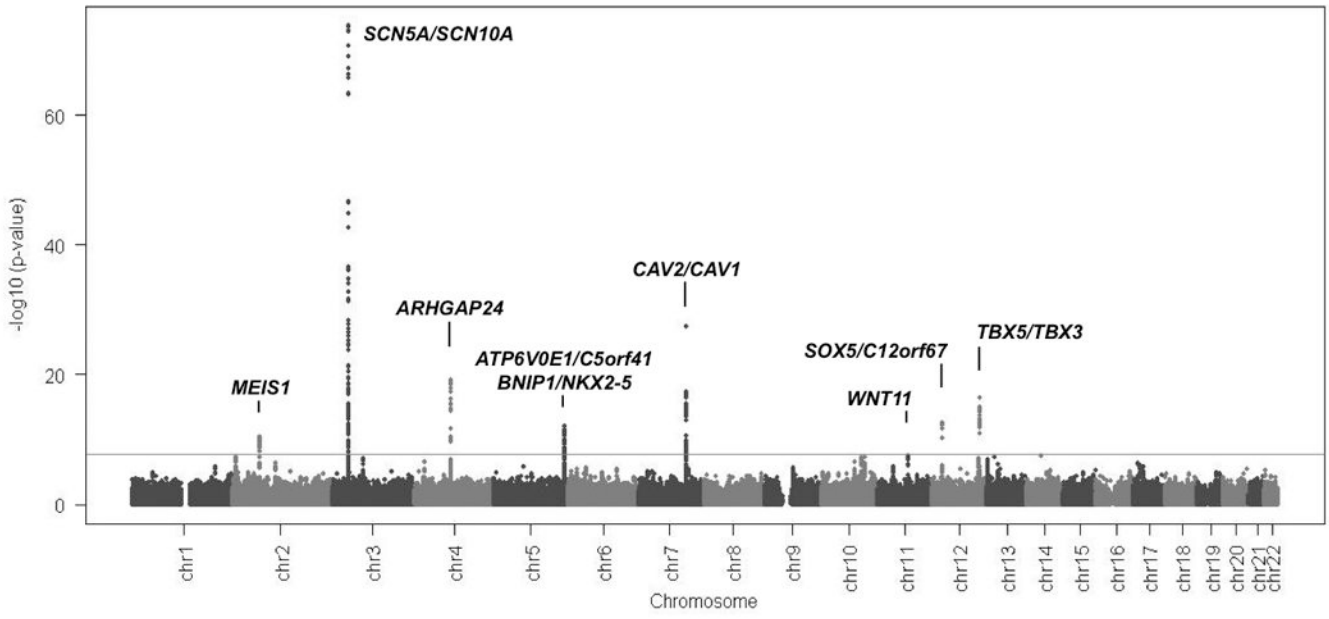

Figure 1.

Manhattan Plot of genome-wide association analyses. Genome-wide association results were combined across all studies by inverse variance weighting. The blue line marks the threshold for genome-wide significance ($P= 5\times10^{-8}$). Coordinates are given in NCBI build 36.

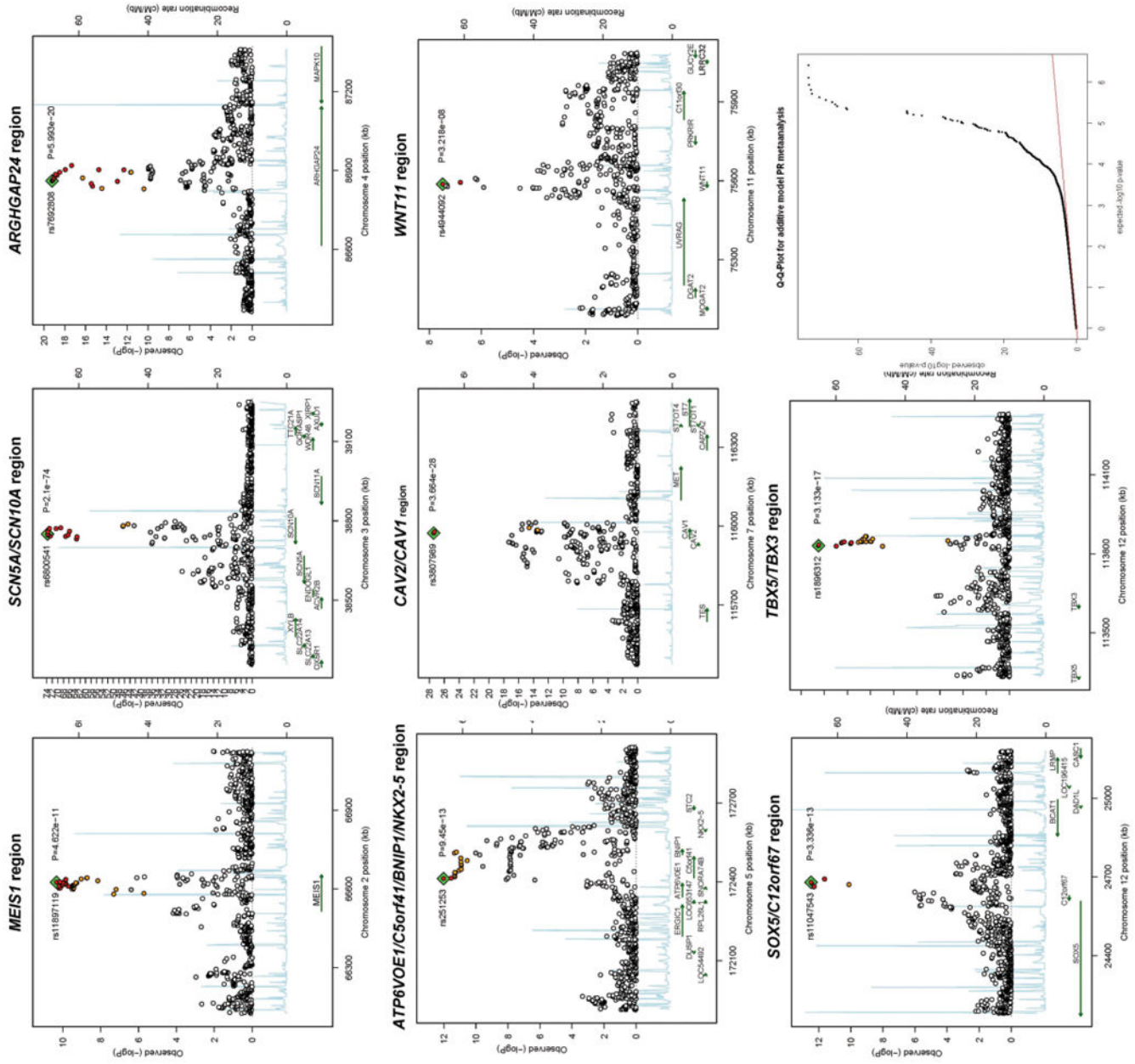

Figure 2.

Association results at each significant locus. Associated loci are displayed in genomic order from left to right: *MEIS1*, *SCN5A/SCN10A* region, *ARHGAP24*, *NKX2-5* region, *CAV1/CAV2* region, *WNT11*, *SOX5* region and *TBX5/TBX3* region. Each panel spans ±500 kb around each SNP and has known gene transcripts annotated at the bottom. The SNPs are colored according to their degree of linkage disequilibrium (r^2) with the leading variant highlighted with a blue square and displayed by name and achieved significance level in the meta-analysis. The lower right panel shows the QQ plot of the meta-analysis findings with a genomic control factor (λ) of 1.076.

Table 1

Characteristics of participants in the seven community cohorts included in the meta-analysis of genome-wide association studies of PR. Exclusion criteria is given in Supplementary Table 1. "Participants after exclusion with genome-wide genotypes available" gives the N used in the analysis. Standard deviation (SD) of PR interval is given after adjustment for all covariates. [f]Samples are from the three generations of the Framingham Heart Study (G1=685, G2=3178, G3=3773).

	AGES	ARIC	CHS	FHS	KORA F3	KORA S4	Rotterdam	SardiNIA
N - participants before exclusion	3,219	11,478	2,084	12,174[f]	1,644	1,100	5,271	4,305
N - participants after exclusion with genome-wide genotypes available	2,471	6,486	1,769	7,636[f]	1,427	927	3,710	4,091
Sex, Men, n (%)	922 (37.3)	2,977 (45.9)	773 (43.7)	3,511 (46.0)	728 (51.0)	447 (48.2)	1,541 (39.8)	1,782 (43.5)
Age, years, mean	76.1 ± 5.4	53.9 ± 5.7	72.9 ± 5.4	39.9 ± 10.3	61.6 ± 9.9	56.2 ± 7.1	67.8 ± 8.5	42.5 ± 17.1
PR interval, ms, mean	171.4 ± 27.7	162.7 ± 23.7	167.9 ± 28.5	152.1 ± 21.9	163.3 ± 23.3	164.6 ± 21.2	165.9 ± 24.1	154.2 ± 26.7
RR interval, ms, mean ± SD	925.9 ± 156.5	915.7 ± 132.4	949.1 ± 155.5	905.7 ± 174.8	963.5 ± 160.6	930.7 ± 139.2	861.9 ± 137.4	921.2 ± 152.2
BMI, kg/m2, mean ± SD	27.1 ± 4.4	26.7 ± 4.7	26.5 ± 4.5	26.1 ± 4.9	28.0 ± 4.4	27.8 ± 4.5	26.1 ± 3.5	25.2 ± 4.6
Height, cm, mean ± SD	166.4 ± 9.1	168.8 ± 9.4	164.9 ± 9.6	169.1 ± 9.5	167.1 ± 9.1	167.4 ± 8.8	167.3 ± 9.3	160.1 ±8.9
Systolic BP, mmHg, mean ± SD	143 ± 20	117.2 ± 16.3	137 ± 21	120 ± 15	134 ± 20	132 ± 19	139 ± 22	125 ± 18
Beta-Blockers (%)	780 (31.6)	Excluded	176 (10.0)	Excluded	283 (19.8)	99 (10.7)	Excluded	Excluded
Diuretics (%)	733 (29.7)	562 (8.7)	434 (24.5)	ND	273 (19.1)	76 (8.2)	292 (7.5)	45 (1.1)
Calcium Antagonists* (%)	131 (5.3)	Excluded	78 (4.4)	Excluded	ND	ND	Excluded	Excluded
SD of PR residual after adjustment for covariates, ms	25.9	23.0	26.9	20.5	21.3	20.1	23.0	25.5

Table 2

Genome-wide significant association findings for PR interval obtained at nine independent loci. In each locus at least one marker exceeds the genome-wide significant threshold of $P<5 \times 10^{-8}$. Betas estimate the difference in PR interval per one additional copy of the minor allele, adjusted for the covariates in the model. Column "Method" indicates whether a SNP was directly genotyped on one of the array platforms (G) or whether its genotype was imputed in all of the samples (I). The RSQR and the MAF are averages weighted by study size. RSQR (sometimes also termed OEvar) denotes the average of the observed by expected variance ratio of any SNP which indicates deviation from Hardy-Weinberg equilibrium and quality of imputation. All these SNPs met QC criteria in each study as outlined in Supplementary Tables 2 and 3. Effect size (beta) is reported in milliseconds (ms) per one copy of the minor allele. We observed no heterogeneity in effect size estimates between studies and report the I^2-statistic results as the ratio of between-study to overall variance in betas.

Locus	SNP	chr	Position (build 36)	Gene related position	minor/major allele	Meth od	RSQR (OEvar)	Freq coded (minor) allele	beta (ms)	SE (ms)	Association -P value	Heterogeneity – I^2 statistic	Heterogeneity – P value
MEIS1	rs1897119	2	66,625,504	Intron 8	C/T	G	1.008	0.389	1.3624	0.207	4.62×10^{-11}	0	0.803
SCN5A	rs1708996	3	38,608,927	Intron 14	C/G	I	0.927	0.149	3.0403	0.2886	6.00×10^{-26}	0.045	0.396
SCN10A	rs6800541	3	38,749,836	Intron 14	C/T	G	0.995	0.404	3.7687	0.2065	2.10×10^{-74}	0.490	0.056
ARHGAP24	rs2792808	4	86,860,173	Intron 2	A/G	I	0.984	0.306	-2.0146	0.2203	5.99×10^{-20}	0	0.711
NKX2-5	rs251253	5	172,412,942	3kb 5′ of C5orf41	C/T	G	0.971	0.399	-1.4924	0.2091	9.45×10^{-13}	0	0.926
CAV1/CAV2	rs807989	7	115,973,477	Intron 2 of CAV1	A/G	G	0.970	0.395	2.2959	0.2086	3.66×10^{-28}	0	0.626
WNT11	rs2944092	11	75,587,267	Intron 1	G/A	G	1.006	0.321	-1.1916	0.2155	3.22×10^{-08}	0	0.549
SOX5	rs7047543	12	24,679,606	51 kb 5′ of C12orf67	A/G	I	0.983	0.147	-2.0907	0.2872	3.34×10^{-13}	0	0.912
TBX5/TBX3	rs3396312	12	113,830,807	226 kb 5′ of TBX3	C/T	I	0.936	0.279	1.9505	0.2311	3.13×10^{-17}	0	0.768

Table 3

Characteristics of participants included in the meta-analysis of the association of the nine significant PR loci with atrial fibrillation. Overall the CHARGE prevalent AF sample included 896 cases, the CHARGE incident AF sample included 2,517 cases and the case-control sample included 2,328 cases [a]The n given is the number of participants in the CHARGE cohorts and the number of cases plus controls in case control studies, [b]Age was defined as age at DNA collection. BMI: body mass index; NA: age at onset of prevalent AF not available for CHS and RS.

Baseline Characteristics	**CHARGE studies: Prevalent AF Analysis**				**CHARGE studies: Incident AF Analysis**					**Case Control Studies: Prevalent AF Analysis**	
	AGES	**CHS**	**FHS**	**RS**	**AGES**	**ARIC**	**CHS**	**FHS**	**RS**	**AFNET**	**CCAF**
Participants											
n[a]	2,959	3,267	4,464	5,974	2,718	8,086	3,201	4,184	5,665	6,218	347
Sex, men, n (%)	1,154 (39.0)	1,278 (39.1)	2,004 (44.9)	2,427 (40.6)	1,011 (37.2)	3,814 (47.2)	1,241 (38.8)	1,830 (43.7)	2,282 (40.3)	3,569 (57.4)	202 (58.2)
Age[b], years, mean (SD)	76.5 (5.5)	72.3 (5.4)	65.5 (12.7)	69.4 (9.1)	76.3 (5.5)	57.0 (5.7)	72.2 (5.3)	64.7 (12.6)	69.1 (9.0)	52.7 (14.0)	56.4 (8.2)
Age[b], years, min-max	66-95	65-98	30-100	55-99	66-95	46-70	65-98	30-100	55-99	14-93	20-88
Hypertension, n (%)	2,260 (79.8)	1,711 (52.4)	2,263 (50.8)	1,997 (33.4)	2,145 (78.9)	2192 (27.1)	1,677 (52.4)	2,062 (49.4)	1,866 (32.9)	1,902 (30.6)	151 (43.5)
Cases											
Atriial fibrillarion cases	241	66	280	309	138	731	763	343	542	2,145	183
Age at AF onset, mean (SD)	76.9 (6.0)	NA	70.6 (10.6)	NA	80.6 (6.0)	67.0 (6.7)	81.2 (6.0)	77.4 (10.5)	77.7 (7.7)	59.7 (11.2)	46.0 (11.0)

Table 4

Meta-analytic results for the association of the nine significant PR loci with atrial fibrillation. Meta-analyzed were results from a meta-analysis of prevalent AF conducted in the CHARGE cohorts, results from a meta-analysis of incident AF conducted in the CHARGE cohorts, results from the AFNET case-control study and results from the CCAF case-control study. The Bonferroni adjusted table-wide significance threshold is *P*= 0.05/9= 5.6E-03, the p(adjusted) column reports the significance thresholds after adjustment for 9 tests. For all five SNPs we identified as associated with AF the minor allele decreased the risk of AF irrespective of the direction of its effect on PR interval.

Nearest gene	SNP	Chr	pos build36	PR prolonging allele	Frequency – PR prolonging allele	OR for AF – PR prolonging Allele	OR for AF – 95% CI lower bound	OR for AF – 95% CI upper bound	P (unadjusted)	P (adjusted)	Effect of PR prolonging allele towards AF risk	Effect of minor allele towards AF risk
MEIS1	rs11897119	2	66,625,504	C	0.39	1.01	0.97	1.06	0.65	-	ns	ns
SCN5A	rs11708996	3	38,608,927	C	0.15	**0.90**	**0.84**	**0.96**	**7.0E-04**	**6.30E-03**	**Decreased**	**Decreased**
SCN10A	rs6800541	3	38,749,836	C	0.40	**0.92**	**0.88**	**0.96**	**1.5E-04**	**1.35E-03**	**Decreased**	**Decreased**
ARHGAP24	rs7692808	4	86,860,173	G*	0.69	1.01	0.97	1.06	0.56	-	ns	ns
NKX2-5	rs251253	5	172,412,942	T*	0.61	**1.07**	**1.03**	**1.12**	**2.3E-03**	**2.07E-02**	**Increased**	**Decreased**
CAV1/CAV2	rs3807989	7	115,973,477	A	0.40	**0.91**	**0.87**	**0.95**	**2.2E-05**	**1.98E-04**	**Decreased**	**Decreased**
WNT11	rs4944092	11	75,587,267	A*	0.67	0.94	0.90	0.99	0.01	-	ns	ns
SOX5	rs11047543	12	24,679,606	G*	0.85	**1.13**	**1.06**	**1.20**	**2.1E-04**	**1.89E-03**	**Increased**	**Decreased**
TBX5/TBX3	rs1896312	12	113,830,807	C	0.30	0.99	0.95	1.04	0.72	-	ns.	ns.