Supplementary Information for

Genome-wide association study of PR interval

Arne Pfeufer[1,2*], Charlotte van Noord[3,4,5*], Kristin D. Marciante[6*], Dan E. Arking[7*], Martin G. Larson[8,9*], Albert Vernon Smith[10*], Kirill V. Tarasov[11,12*], Martina Müller[13,14], Nona Sotoodehnia[15], Moritz F. Sinner[14], Germaine C. Verwoert[3,16], Man Li[17], W.H. Linda Kao[17], Anna Köttgen[17], Josef Coresh[17], Joshua C. Bis[6], Bruce M. Psaty[6,18,19,20], Kenneth Rice[21], Jerome I. Rotter[22], Fernando Rivadeneira[3,16], Albert Hofman[3], Jan A. Kors[23], Bruno H.C. Stricker[3,16,24], André G. Uitterlinden[3,16], Cornelia M. van Duijn[3], Britt M. Beckmann[14], Wiebke Sauter[13], Christian Gieger[13], Steven A. Lubitz[25,26], Christopher Newton-Cheh[26,27,28], Thomas J. Wang[9,26,28], Jared W. Magnani[29], Renate B. Schnabel[9,30], Mina K. Chung[31], John Barnard[31], Jonathan D. Smith[31], David R. Van Wagoner[31], Ramachandran S. Vasan[9,29], Thor Aspelund[10,32], Gudny Eiriksdottir[10], Tamara B. Harris[33], Lenore J. Launer[33], Samer S. Najjar[11], Edward Lakatta[11], David Schlessinger[12], Manuela Uda[34], Gonçalo R. Abecasis[35], Bertram Müller-Myhsok[36], Georg B. Ehret[7], Eric Boerwinkle[37], Aravinda Chakravarti[7,38], Elsayed Z. Soliman[39], Kathryn L. Lunetta[40], Siegfried Perz[41], H.-Erich Wichmann[13,42,43], Thomas Meitinger[1,2], Daniel Levy[9,44], Vilmundur Gudnason[10,32*], Patrick T. Ellinor[26,27,28*], Serena Sanna[34*], Stefan Kääb[14*], Jacqueline C.M. Witteman[3,5*], Alvaro Alonso[45*], Emelia J. Benjamin[9,46,47*], Susan R. Heckbert[18,20*]

[*] These authors contributed equally to the study

[1] Institute of Human Genetics, Klinikum rechts der Isar der Technischen Universität München, Germany
[2] Institute of Human Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
[3] Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands
[4] Dutch Medicines Evaluation Board, the Hague, the Netherlands
[5] Netherlands Consortium on Healthy Aging (NCHA)
[6] Department of Medicine, University of Washington. Seattle WA, USA
[7] McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, MD, USA
[8] Department of Mathematics and Statistics, Boston University, Boston, MA, USA
[9] National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, MA, USA
[10] Icelandic Heart Association, Heart Preventive Clinic and Research Institute, Kopavogur, Iceland
[11] Laboratory of Cardiovascular Science, National Institute on Aging, Baltimore, MD, USA
[12] Laboratory of Genetics, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA
[13] Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
[14] Department of Medicine I, Klinikum Grosshadern, Munich, Germany
[15] Division of Cardiology, Department of Medicine, University of Washington, Seattle WA, USA
[16] Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands
[17] Department of Epidemiology, Johns Hopkins University, Baltimore, MD, USA
[18] Department of Epidemiology, University of Washington, Seattle WA
[19] Department of Health Services, University of Washington, Seattle WA
[20] Group Health Research Institute, Seattle, WA
[21] Department of Biostatistics, University of Washington, Seattle, WA, USA
[22] Medical Genetics Institute, Department of Common Diseases Genetics Program, Cedars-Sinai Med Center, West Hollywood, CA, USA
[23] Department of Medical Informatics, Erasmus Medical Center, Rotterdam, the Netherlands
[24] Inspectorate for Health Care, The Hague, the Netherlands
[25] Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA
[26] Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA
[27] Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA
[28] Cardiology Division, Massachusetts General Hospital, Boston, MA, USA
[29] Boston University School of Medicine, Boston, MA, USA
[30] Gutenberg Heart Study, Medical Clinic II (Cardiology), Johannes Gutenberg-University, Mainz, Germany
[31] Heart & Vascular and Lerner Research Institutes, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH, USA
[32] University of Iceland, Reykjavik, Iceland
[33] Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Baltimore, MD, USA
[34] Istituto di Neurogenetica e Neurofarmacologia, CNR, Monserrato, 09042 Cagliari, Italy
[35] Center for Statistical Genetics, Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA
[36] Statistical Genetics, Max Planck Institute of Psychiatry, Munich, Germany
[37] Human Genetics Center and Institute for Molecular Medicine, University of Texas Health Science Center, Houston, TX, USA
[38] Department of Medicine, Johns Hopkins University, Baltimore, MD, USA
[39] Epidemiological Cardiology Research Center (EPICARE), Department of Epidemiology and Prevention, Division of Public Health Sciences, Wake Forest University Medical Center, Winston-Salem, NC, USA
[40] Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA
[41] Institute of Biological and Medical Imaging, Helmholtz Center Munich, Germany
[42] Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany
[43] Klinikum Grosshadern, Munich, Germany.
[44] Center for Population Studies, National Heart, Lung, and Blood Institute, Bethesda, MD, USA
[45] Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA
[46] Department of Epidemiology, School of Public Health, Boston University, Boston, MA, USA
[47] Cardiology and Preventive Medicine Division, Evans Department of Medicine, Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, MA, USA

SUPPLEMENTARY NOTE

Cohort study investigators

AGES (Age, Gene/Environment Susceptibility-Reykjavik Study)
Albert Vernon Smith, Thor Aspelund, Gudny Eiriksdottir, Tamara B. Harris, Lenore J. Launer, Vilmundur Gudnarsson

ARIC (Atherosclerosis Risk in Communities)
Dan E. Arking, Man Li, Georg B. Ehret, Elsayed Z. Soliman, W.H. Linda Kao, Anna Köttgen, Josef Coresh, Eric Boerwinkle, Aravinda Chakravarti, Alvaro Alonso

CHS (Cardiovascular Health Study)
Kristin D. Marciante, Nona Sotoodehnia, Joshua C. Bis, Jerome I. Rotter, Kenneth Rice, Bruce M. Psaty, Susan R. Heckbert

CCAF (Cleveland Clinic AF Study)
Mina K. Chung, John Barnard, Jonathan D. Smith, David R. Van Wagoner

FHS (Framingham Heart Study)
Martin G. Larson, Kathryn L. Lunetta, Steven A. Lubitz, Patrick T. Ellinor, Daniel Levy, Jared W. Magnani, Christopher Newton-Cheh, Renate B. Schnabel, Ramachandran S. Vasan, Thomas J. Wang, Emelia J. Benjamin

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AFNET (German Competence Network on Atrial Fibrillation)
Arne Pfeufer, Martina Müller, Moritz F. Sinner, Britt M. Beckmann, Christian Gieger, Wiebke Sauter, Bertram Müller-Myhsok, Siegfried Perz, H.-Erich Wichmann, Thomas Meitinger, Stefan Kääb

RS (Rotterdam Study)
Charlotte van Noord, Germaine Verwoert, Fernando Rivadeneira, Albert Hofman, Jan Kors, Bruno Stricker, André Uitterlinden, Cornelia van Duin, Jacqueline Witteman

SardiNIA
Kirill V. Tarasov, Samer S. Najjar, Edward Lakatta, David Schlessinger, Manuela Uda, Gonçalo R. Abecasis, Serena Sanna

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SUPPLEMENTARY TABLES

	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
Applied exclusion criteria								
Atrial fibrillation	Y	Y	Y	Y	Y	Y	Y	Y
Pacemaker/AICD implant	Y	Y	Y	Y	Y	Y	Y	Y
WPW Syndrome	Y	Y	Y	Y	Y	Y	Y	Y
AV Block III°- total heart block	Y	Y	Y	Y	Y	Y	Y	Y
CHF	Y	Y	Y	Y	Y	Y	Y	Y
MI	Y	Y	Y	Y	Y	Y	Y	Y
Extreme PR trait values, excluded (ms)	<80,>320	<80,>320	<80,>320	N	<80, >320	<80, >320	<80, >320	<80; >320
Beta-Blockers	adjusted	Y	adjusted	Y	adjusted	adjusted	Y	Y
Diuretics	adjusted	adjusted	adjusted	N	adjusted	adjusted	adjusted	adjusted
Calcium antagonists*	adjusted	Y	adjusted	Y	N	N	Y	Y
Digoxin	Y	Y	Y	Y	Y	Y	Y	Y
Type 1 & III antiarrhythmic drugs	Y	Y	Y	Y	Y	Y	Y	Y

Supplementary Table 1: Exclusion criteria applied in the studies included in the genome-wide analysis of PR-interval. 'Y' indicates that participants with this characteristic at the time of DNA sampling were excluded; 'N' indicates that this exclusion criterion was not applied; 'adjusted' indicates that this characteristic was adjusted for rather than used as an exclusion criterion. [f]Samples are from three generations of FHS, N=11,275 had PR interval measurements available, additional exclusion criteria applied in FHS were bundle branch blocks (LBBB or RBBB) 0.7% prevalence, and valve disease (murmur) 3.5% prevalence.

Study:	AGES	ARIC	CHS	FHS	KORA F3	KORA S4	Rotterdam	SardiNIA
Array(s)	Illumina HH 370 CNV	Affymetrix 6.0	Illumina HH 370 CNV	Affymetrix 500k + 50K Human Gene Focused Panel	Affymetrix 500k	Affymetrix 6.0 and Illumina HH 550	Illumina HH 550	Affymetrix 500k
Calling	Bead Studio	Birdseed	Bead Studio	BRLMM	BRLMM	BRLMM, BeadStudio	BeadStudio	BRLMM
QC filters for exclusion of genotyped SNPs	call rate <95% MAF < 1% pHWE < 10^{-5}	call rate <95% MAF < 1% pHWE < 10^{-5}	call rate <95% At least one heterozygote pHWE < 10^{-5}	call rate <95% MAF < 1% pHWE < 10^{-6}	call rate <93% MAF < 5% pHWE < 10^{-5}	call rate <98% MAF < 5% pHWE < 10^{-5}	call rate <95% MAF < 1% pHWE < 10^{-5}	call rate <90% MAF < 5% pHWE < 10^{-6} excess Mendelian Inconsistencies
Imputation	Mach1 v1.0.15	Mach1 v1.0.16	Bimbam	Mach1 v1.0.15	Mach1 v1.0.10	Mach1 v1.0.10	Mach1 v1.0.15	Mach1 v1.0.10
Imputation Backbone / from NCBI Build	from build 35	from build 35	from build 36	from build 36	from build 35	from build 35	from build 35	from build 35
GWAS Statistical Analysis	plink	Mach2QTL + plink	R	LMEKIN	Mach2QTL + plink	Mach2QTL + plink	Mach2QTL + plink + R	Merlin --fastassoc
Lambda	1.054	1.027	1.023	1.028	1.027	1.010	1.017	1.103

Supplementary Table 2: Technical information on the genotyping and imputation methods used in the genome-wide analysis of PR interval. BRLMM denotes the Bayesian Robust Linear Modeling algorithm (www.affymetrix.com/support/ technical/whitepapers/brlmm_whitepaper.pdf);
BIMBAM (http://stephenslab.uchicago.edu/software.html);
PLINK (http://pngu.mgh.harvard.edu/purcell/PLINK/);
LMEKIN (http://bm2.genes.nig.ac.jp/RGM2/pkg.php?p=kinship);
MACH and Mach2QTL (http://www.sph.umich.edu/csg/abecasis/MaCH/index.html);
MERLIN (http://www.sph.umich.edu/csg/abecasis/merlin/)

					AGES					ARIC					CHS				
Locus	**SNP**	**chr**	**Pos (build 36)**	**minor/major allele**	**RSQR**	**MAF**	**beta**	**se**	**p-value**	**RSQR**	**MAF**	**beta**	**se**	**p-value**	**RSQR**	**MAF**	**beta**	**se**	**p-value**
MEIS1	rs11897119	2	66,625,504	C/T	0.9953	0.363	1.244	0.767	1.05E-01	1.000	0.398	1.221	0.413	3.08E-03	1.007	0.380	0.320	1.115	7.74E-01
SCN5A	rs11708996	3	38,608,927	C/G	0.9842	0.125	3.141	1.088	3.93E-03	0.983	0.155	3.051	0.571	9.12E-08	0.800	0.142	4.145	1.913	3.03E-02
SCN10A	rs6800541	3	38,749,836	C/T	G	0.355	4.796	0.743	1.33E-10	0.991	0.409	4.025	0.417	4.40E-22	1.000	0.403	4.680	1.111	2.52E-05
ARHGAP24	rs7692808	4	86,860,173	A/G	0.9986	0.268	-2.885	0.819	4.35E-04	0.997	0.301	-1.659	0.440	1.62E-04	0.979	0.318	-1.906	1.197	1.12E-01
NKX2-5	rs251253	5	172,412,942	C/T	0.9365	0.382	-0.815	0.749	2.76E-01	0.998	0.391	-1.424	0.415	5.99E-04	0.729	0.393	-0.592	1.398	6.72E-01
CAV1/CAV2	rs3807989	7	115,973,477	A/G	G	0.397	3.085	0.745	3.60E-05	0.990	0.407	2.680	0.414	9.84E-11	0.986	0.400	2.165	1.213	7.44E-02
WNT11	rs4944092	11	75,587,267	G/A	G	0.355	-1.367	0.775	7.78E-02	0.998	0.325	-0.320	0.428	4.55E-01	1.008	0.302	-1.385	1.261	2.72E-01
SOX5	rs11047543	12	24,679,606	A/G	0.9983	0.131	-3.038	1.094	5.54E-03	0.992	0.152	-2.316	0.569	4.65E-05	0.985	0.142	-0.778	1.748	6.56E-01
TBX5/TBX3	rs1896312	12	113,830,807	C/T	0.9953	0.361	2.627	0.760	5.51E-04	0.966	0.299	2.277	0.448	3.67E-07	0.948	0.282	1.589	1.234	1.98E-01

FHS					**KORA_F3**					**KORA_S4**					**Rotterdam**					**SardiNIA**				
RSQR	**MAF**	**beta**	**se**	**p-value**	**RSQR**	**MAF**	**beta**	**se**	**p-value**	**RSQR**	**MAF**	**beta**	**se**	**p-value**	**RSQR**	**MAF**	**beta**	**se**	**p-value**	**RSQR**	**MAF**	**beta**	**se**	**p-value**
1.034	0.379	1.170	0.362	1.24E-03	0.998	0.375	1.663	0.836	4.68E-02	1.000	0.406	2.055	0.951	3.07E-02	1.001	0.405	2.084	0.542	1.21E-04	G	0.395	1.137	0.838	1.96E-01
0.967	0.145	3.291	0.504	6.78E-11	0.721	0.178	3.479	1.199	3.72E-03	0.972	0.160	-0.298	1.315	8.21E-01	0.990	0.155	3.279	0.741	9.70E-06	0.748	0.145	2.771	1.123	1.88E-02
0.987	0.408	2.975	0.364	2.22E-16	0.974	0.388	3.461	0.845	4.22E-05	0.997	0.394	3.618	0.936	1.11E-04	1.009	0.410	4.928	0.542	9.00E-20	1.009	0.418	2.869	0.797	6.07E-04
0.984	0.329	-1.996	0.382	1.79E-07	0.985	0.324	-0.833	0.885	3.47E-01	0.992	0.323	-2.465	1.001	1.38E-02	0.991	0.284	-2.406	0.593	5.02E-05	0.937	0.303	-2.548	0.880	5.85E-03
1.010	0.410	-1.407	0.362	9.93E-05	0.998	0.397	-1.969	0.818	1.61E-02	0.996	0.402	-1.864	0.970	5.45E-02	0.921	0.395	-1.723	0.569	2.47E-03	G	0.416	-2.099	0.822	1.50E-02
0.983	0.379	1.900	0.369	2.54E-07	0.859	0.420	2.944	0.885	8.80E-04	0.991	0.404	1.612	0.944	8.79E-02	1.009	0.425	2.430	0.535	5.55E-06	0.874	0.356	1.450	0.844	1.02E-01
1.021	0.314	-1.434	0.382	1.73E-04	0.996	0.332	-1.675	0.852	4.93E-02	0.998	0.311	-1.130	0.989	2.53E-01	1.011	0.350	-1.690	0.555	2.34E-03	G	0.280	-1.555	0.887	9.55E-02
1.003	0.158	-2.265	0.489	3.62E-06	0.829	0.139	-1.124	1.253	3.70E-01	0.989	0.155	-1.921	1.310	1.43E-01	0.995	0.153	-1.603	0.740	3.02E-02	0.956	0.123	-1.810	1.245	1.66E-01
0.876	0.268	1.419	0.430	9.58E-04	0.934	0.277	1.993	0.906	2.79E-02	0.966	0.286	2.994	1.054	4.52E-03	0.985	0.297	1.704	0.591	3.94E-03	0.887	0.188	1.989	1.023	6.42E-02

Supplementary Table 3: Study specific results of the nine genome-wide significant loci for PR interval. The betas estimate the difference in PR interval per additional copy of the minor allele, adjusted for the covariates in the model. RSQR (sometimes also termed OEvar) denotes the average of the observed by expected variance ratio of any SNP weighted in the included samples for imputed SNPs which indicates deviation from Hardy-Weinberg equilibrium and quality of imputation weighted across all studies. Genotyped SNPs are denoted as (G).

Nearest gene	SNP	Chr	pos build36	Study	PR prolonging allele	Frequency of PR prolonging allele	OR for AF PR prolonging Allele	OR 95CI lower meta PR prolonging Allele	OR 95CI upper meta PR prolonging Allele	p (unadjusted)	p (adjusted)	Effect of PR prolonging allele towards AF risk
MEIS1	rs11897119	2	66,625,504	Metaanalysis	C	0.39	1.01	0.97	1.06	0.65	-	ns
				Prevalent AF		0.38	1.03	0.93	1.14	0.58	-	-+++
				Incident AF		0.39	1.03	0.98	1.10	0.25	-	+-+++
				CCAF		0.38	1.18	0.83	1.68	0.36	-	+
				AFNET		0.39	0.93	0.85	1.02	0.12	-	-
SCN5A	rs11708996	3	38,608,927	Metaanalysis	C	0.15	**0.90**	**0.84**	**0.96**	**7.0E-04**	**6.30E-03**	**Decreased**
				Prevalent AF		0.14	0.88	0.75	1.03	0.11	-	----
				Incident AF		0.15	0.94	0.86	1.02	0.12	-	----+
				CCAF		0.15	0.51	0.32	0.83	0.01	-	-
				AFNET		0.15	0.86	0.75	0.97	0.015	-	-
SCN10A	rs6800541	3	38,749,836	Metaanalysis	C	0.40	**0.92**	**0.88**	**0.96**	**1.5E-04**	**1.35E-03**	**Decreased**
				Prevalent AF		0.40	0.90	0.81	1.00	0.05	-	---+
				Incident AF		0.41	0.95	0.90	1.00	0.07	-	+--+-
				CCAF		0.40	0.94	0.67	1.31	0.70	-	-
				AFNET		0.39	0.86	0.79	0.94	1.4E-03	-	-
ARHGAP24	rs7692808	4	86,860,173	Metaanalysis	G*	0.69	1.01	0.97	1.06	0.56	-	ns
				Prevalent AF		0.70	0.94	0.85	1.05	0.26	-	-++-
				Incident AF		0.70	1.02	0.96	1.09	0.53	-	+--++
				CCAF		0.65	1.15	0.77	1.74	0.49	-	+
				AFNET		0.69	1.05	0.96	1.16	0.29	-	+
NKX2-5	rs251253	5	172,412,942	Metaanalysis	T*	0.61	**1.07**	**1.03**	**1.12**	**2.3E-03**	**2.07E-02**	**Increased**
				Prevalent AF		0.60	1.12	1.01	1.25	0.04	-	++++
				Incident AF		0.61	1.05	0.98	1.11	0.14	-	++++-
				CCAF		0.62	0.88	0.61	1.28	0.51	-	-
				AFNET		0.62	1.11	1.02	1.22	0.02	-	+
CAV1/CAV2	rs3807989	7	115,973,477	Metaanalysis	A	0.40	**0.91**	**0.87**	**0.95**	**2.2E-05**	**1.98E-04**	**Decreased**
				Prevalent AF		0.40	0.94	0.85	1.04	0.22	-	-+--
				Incident AF		0.41	0.91	0.86	0.97	2.3E-03	-	-+---
				CCAF		0.39	0.99	0.70	1.40	0.96	-	-
				AFNET		0.40	0.88	0.80	0.96	3.7E-03	-	-
WNT11	rs4944092	11	75,587,267	Metaanalysis	A*	0.67	0.94	0.90	0.99	0.01	-	ns
				Prevalent AF		0.66	0.97	0.88	1.08	0.63	-	+---
				Incident AF		0.67	1.00	0.94	1.06	0.99	-	-++-+
				CCAF		0.68	1.05	0.72	1.52	0.81	-	+
				AFNET		0.67	0.79	0.72	0.87	1.2E-06	-	-
SOX5	rs11047543	12	24,679,606	Metaanalysis	G*	0.85	**1.13**	**1.06**	**1.20**	**2.1E-04**	**1.89E-03**	**Increased**
				Prevalent AF		0.85	1.12	0.97	1.30	0.13	-	-+++
				Incident AF		0.85	1.14	1.05	1.24	2.8E-03	-	+-+++
				CCAF		0.86	0.98	0.59	1.61	0.93	-	-
				AFNET		0.80	1.12	0.98	1.27	0.09	-	+
TBX5/TBX3	rs1896312	12	113,830,807	Metaanalysis	C	0.30	0.99	0.95	1.04	0.72	-	ns
				Prevalent AF		0.30	0.94	0.84	1.05	0.27	-	+---
				Incident AF		0.29	1.02	0.96	1.08	0.60	-	+--+-
				CCAF		0.32	0.58	0.38	0.90	0.02	-	-
				AFNET		0.28	1.00	0.91	1.10	0.96	-	-

Supplementary Table 4: (please see legend on next page)

Supplementary Table 4: Meta-analytic and study specific results for the association of the nine genome wide significant PR SNPs with atrial fibrillation. Study specific results are from a meta-analysis of prevalent AF in the CHARGE cohorts (AGES, CHS, FHS, RS), a meta-analysis of incident AF in the CHARGE cohorts (AGES, ARIC, CHS, FHS, RS), and two case-control studies of AF, AFNET and CCAF. "*" indicates that the PR prolonging allele is the major and not the minor allele of the SNP. "+" (increased) and "-" (decreased) indicate effect size of PR prolonging allele towards AF risk in the individual studies. 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.