Supplementary material

GWAS meta-analysis of 30,000 samples identifies seven novel loci for quantitative ECG traits.

Jessica van Setten, Niek Verweij, Hamdi Mbarek, Maartje N. Niemeijer, Stella Trompet, Dan E. Arking, Jennifer A. Brody, Ilaria Gandin, Niels Grarup, Leanne M. Hall, Daiane Hemerich, Leo-Pekka Lyytikäinen, Hao Mei, Martina Müller-Nurasyid, Bram P. Prins, Antonietta Robino, Albert V. Smith, Helen R. Warren, Folkert W. Asselbergs, Dorret I. Boomsma, Mark J. Caulfield, Mark Eijgelsheim, Ian Ford, Torben Hansen, Tamara B. Harris, Susan R. Heckbert, Jouke-Jan Hottenga, Anita Iorio, Jan A. Kors, Allan Linneberg, Peter MacFarlane, Thomas Meitinger, Christopher P. Nelson, Olli T. Raitakari, Claudia T. Silva Aldana, Gianfranco Sinagra, Moritz Sinner, Elsayed Z. Soliman, Monika Stoll, Andre Uitterlinden, Cornelia M. van Duijn, Melanie Waldenberger, Alvaro Alonso, Paolo Gasparini, Vilmundur Gudnason, Yalda Jamshidi, Stefan Kääb, Jørgen K Kanters, Terho Lehtimäki, Patricia B. Munroe, Annette Peters, Nilesh J. Samani, Nona Sotoodehnia, Sheila Ulivi, James G. Wilson, Eco J.C. de Geus, J. Wouter Jukema, Bruno Stricker, Pim van der Harst, Paul I.W. de Bakker, Aaron Isaacs

Contents:

Cohort information

Discovery cohorts

ERF (Erasmus Rucphen Family Study)

The Erasmus Rucphen Family study[1] is comprised of a family-based cohort embedded in the Genetic Research in Isolated Populations (GRIP) program in the southwest of the Netherlands. The aim of this program is to identify genetic risk factors for the development of complex disorders. In ERF, twenty-two families that had a large number of children baptized in the community church between 1850 and 1900 were identified with the help of detailed genealogical records. All living descendants of these couples, and their spouses, were invited to take part in the study. Comprehensive interviews, questionnaires, and examinations were completed at a research center in the area; approximately 3,200 individuals participated. Examinations included 12 lead ECG measurements. Electrocardiograms were recorded on ACTA electrocardiographs (ESAOTE, Florence, Italy) and digital measurements of the PR, QRS, QT and RR intervals were made using the Modular ECG Analysis System (MEANS). Data collection started in June 2002 and was completed in February 2005. In the current analyses, 2442 participants for whom complete phenotypic, genotypic and genealogical information was available were studied.

Study design: family-based cohort

ECG recording information: A 10-second 12-lead ECG was recorded with an ACTA-ECG electrocardiograph (Esaote, Florence, Italy) with a sampling frequency of 500 Hz. Digital measurements of the ECG parameters were made using the Modular ECG Analysis System (MEANS).

Lifelines (LifeLines Cohort Study & Biobank)

LifeLines[2] is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 165,000 persons living in the North East region of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. Details of the protocol have been described elsewhere (https://www.lifelines.nl/lifelines-research/news). Standard 12-lead electrocardiograms were recorded with CardioPerfect equipment (Cardio Control; currently Welch Allyn, Delft, The Netherlands) and digital measurements of the QT intervals were extracted.

Study design: Population based

ECG recoding information: Standard 12 lead, Cardio Perfect equipment (Welch Allyn Cardio Control, Delft, The Netherlands)

NTR (The Netherlands Twin Register)

NTR[3, 4] participants are ascertained because of the presence of twins or triplets in the family and consist of multiples, their parents, siblings and spouses. Twins are born in all strata of society and NTR represents a general sample from the Dutch population.

Study design: Twin registry

ECG recording information: Resting ECG in sitting position for 4-8 minutes; 3-lead ECG – ECG100C module, Biopac Systems or 3-lead ECG (same type II configuration) VU-AMS5fs, Vrije Universiteit Amsterdam

Prevend (Prevention of Renal and Vascular End-Stage Disease)

Prevend[5] is a prospective study investigating the natural course of increased levels of urinary albumin excretion and its relation to renal and cardiovascular disease. Details of the protocol have been described elsewhere (www.prevend.org)

Study design: Population based

ECG recoding information: Standard 12 lead, Cardio Perfect equipment (Welch Allyn Cardio Control, Delft, The Netherlands)

PROSPER (PROspective Study of Pravastatin in the Elderly at Risk)

PROSPER[6-8] includes individuals >70 year, with an increased risk of cvd.

Study design: RCT/population based

ECG recording information: 12 Lead ECG

RS I, RS II, RS III (Rotterdam Study Cohort I, Rotterdam Study Cohort II, Rotterdam Study Cohort III)

The Rotterdam Elderly Study[9] is a prospective cohort study in the Ommoord district in the city of Rotterdam, the Netherlands [Hofman et al., 1991]. Following the pilot in 1989, recruitment started in January 1990. The main objectives of the Rotterdam Study were to investigate the risk factors of cardiovascular, neurological, ophthalmological and endocrine diseases in the elderly. Up to 2008, approximately 15,000 subjects aged 45 years or over have been recruited. Participants were interviewed at home and went through an extensive set of examinations, bone mineral densiometry, including sample collections for in-depth molecular and genetic analyses. Examinations were repeated every 3-4 years in potentially changing characteristics. Participants were followed for the most common diseases in the elderly, including coronary heart disease, heart failure and stroke, Parkinson's disease, Alzheimer's disease and other dementias, depression and anxiety disorders, macular degeneration and glaucoma, diabetes mellitus and osteoporosis.

Study design: Population based

ECG recoding information: ECG device: EACTA, ASOTE, florence, italy; software: MEANS

Replication cohorts (CHARGE consortium)

AGES (Age, Gene/Environment Susceptibility Reykjavik Study)

In anticipation of the sequencing of the human genome and description of the human proteome, the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik)[10] was initiated in 2002. AGES-Reykjavik was designed to examine risk factors, including genetic susceptibility and gene/environment interaction, in relation to disease and disability in old age. The study is multidisciplinary, providing detailed phenotypes related to the cardiovascular, neurocognitive (including sensory), and musculoskeletal systems, and to body composition and metabolic regulation. Relevant quantitative traits, subclinical indicators of disease, and medical diagnoses are identified by using biomarkers, imaging, and other physiologic indicators. The AGES-Reykjavik sample is drawn from an established population-based cohort, the Reykjavik Study. This cohort of men and women born between 1907 and 1935 has been followed in Iceland since 1967 by the Icelandic Heart Association. The AGES-Reykjavik cohort, with cardiovascular risk factor assessments earlier in life and detailed late-life phenotypes of quantitative traits, will create a comprehensive study of aging nested in a relatively genetically homogeneous older population. This approach should facilitate identification of genetic factors that contribute to healthy aging as well as the chronic conditions common in old age.

Study design: Population based

ECG recording information: Marquette 12SL

ARIC (Atherosclerosis Risk in Communities)

ARIC[11] is a prospective epidemiologic study conducted in four U.S. communities. ARIC is designed to investigate the etiology and natural history of atherosclerosis, the etiology of clinical atherosclerotic diseases, and variation in cardiovascular risk factors, medical care and disease by race, gender, location, and date.

Study design: Population-based

ECG recording information: The study ECGs were recorded with MAC PC ECG machines (Marquette Electronics, Milwaukee, WI) in all clinical centers. ECGs were initially processed in a central laboratory at the EPICORE Center (University of Alberta, Edmonton, Alberta, Canada) and during later phases of the study at the EPICARE Center (Wake Forest University, Winston-Salem, NC). All ECGs were visually inspected for technical errors and inadequate quality. Initial ECG processing was done by the Dalhousie ECG program, and processing was later repeated with the 2001 version of the GE Marquette 12-SL program (GE Marquette, Milwaukee, WI).

BRIGHT (British Genetics of Hypertension)
Hypertensive Cases: White Europeans from UK[12]
Study design: Hypertensive cases
ECG recording information: Twelve-lead ECG recordings (Siemens-Sicard 440)

CHS (Cardiovascular Health Study)
The CHS[13] is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥65 years conducted across four field centers. The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons was enrolled for a total sample of 5,888.
Study-design: Cohort study
ECG recording information: Twelve-lead resting electrocardiographs with standard lead placements were recorded during ten seconds at baseline using Marquette MAC PC-DT electrocardiographic recorder (Marquette Electronics Inc, Milwaulkee, Wisconsin).

GRAPHIC
The GRAPHIC[14] Study comprises 2024 individuals from 520 nuclear families recruited from the general population in Leicestershire, UK between 2003-2005 for the purpose of investigating the genetic determinants of blood pressure and related cardiovascular traits. Families were included if both parents aged 40-60 years and two offspring ≥18 years wished to participate. A detailed medical history was obtained from study subjects by standardized questionnaires and clinical examination was performed by research nurses following standard procedures. Measurements obtained included height, weight, waist-hip ratio, clinic and ambulatory blood pressure and a 12-lead ECG.
Study design: Population based
ECG recording information: Standard 12-lead ECGs were recorded on either Siemens 460 electrocardiographs or Burdick Eclipse or Atria models. Digital ECG data were transferred to the University of Glasgow ECG Core Lab based in Glasgow Royal Infirmary and ECGs were analysed by the University of Glasgow ECG analysis program.

INGI-Carlantino
The Carlantino cohort (INGI-CARL)[15] includes approximately 1000 samples from an isolated village of Southern Italy
Study design: Isolated population
ECG recording information: Digital caliper measurements were made on scanned paper ECGs recorded at 25 mm/sec. Mortara instrument ELI 250 was used to obtain ECG measurements.

INGI-FVG (INGI-FRIULI VENEZIA GIULIA)

INGI-FVG[15] is characterized by approximately 1700 samples from six isolated villages of Northern Italy

Study design: Isolated population

ECG recording information: Digital caliper measurements were made on scanned paper ECGs recorded at 25 mm/sec. Mortara instrument ELI 250 was used to obtain ECG measurements.

Inter99

The Inter99[16] was study carried out in 1999-2001 included invitation of 12934 persons aged 30-60 years drawn from an age- and sex-stratified random sample of the population. The baseline participation rate was 52.5%, and the study included 6784 persons. The Inter99 study was a population-based randomized controlled trial (CT00289237, ClinicalTrials.gov) and investigated the effects of lifestyle intervention on CVD. Here 5951 participants with information on ECG and exome chip were analysed.

Study design: Population-based

ECG recording information: MUSE Cardiology Information System (GE Healthcare, Wauwatosa, Wisconsin) analysed by Marquette 12SL algorithm version 21.

JHS (Jackson Heart Study)

The JHS[17] is a single-site cohort study of 5,301 extensively phenotyped African American women and men. Three clinical examinations have been completed, including the baseline examination, Examination 1 (2000–2004), Examination 2 (2005–2008), and Examination 3 (2009–2013), allowing comprehensive assessment of cardiovascular health and disease of the cohort at approximately four-year intervals. Ongoing monitoring of hospitalizations for cardiovascular events (coronary heart disease, heart failure and stroke) and deaths among cohort participants are accomplished by annual telephone follow-up interviews, surveillance of hospital discharge records (since 2000 for coronary heart disease and stroke, and since 2005 for heart failure), and vital records.

Study design: Single-site observational cohort study with a nested family cohort.

ECG recording information: A supine 12-lead digital electrocardiogram (ECG) was recorded with the Marquette MAC/PC digital ECG recorder (Marquette Electronics, Milwaukee, WI), and with electrode placement that duplicates that of the ARIC study. The ECGs are analyzed in accordance with the Minnesota Code Classification system. In-hospital surveillance ECGs are read visually according to the Minnesota Code Classification system.

KORA F3 and **KORA S4 (Kooperative Gesundheitsforschung in der Region Augsburg)**

The KORA Study[18, 19] is a series of population-based epidemiological surveys of persons living in Augsburg, Southern Germany, or its two adjacent counties. All survey participants are residents of German nationality identified through the registration office and between 25 and 75 years old at the time of enrollment. The KORA S4 study is a baseline survey that was conducted in the years 1999-2001.

Study design: Population based

ECG recording information: 12-lead resting electrocardiograms were recorded with digital recording systems (F3: Mortara Portrait, Mortara Inc., Milwaukee, USA, S4: Hörmann Bioset 9000, Hörmann Medizinelektronik,Germany).

TwinsUK

TwinsUK[20] is a nation-wide registry of volunteer twins in the United Kingdom, with about 12,000 registered twins (83% female, equal number of monozygotic and dizygotic twins, predominantly middle-aged and older). Over the last 20 years, questionnaire and blood/urine/tissue samples have been collected on over 7,000 subjects, as well as three comprehensive phenotyping assessments in the clinical facilities of the Department of Twin Research and Genetic Epidemiology, King's College London. The primary focus of study has been the genetic basis of healthy aging process and complex diseases, including cardiovascular, metabolic, musculoskeletal, and ophthalmologic disorders. Alongside the detailed clinical, biochemical, behavioral, and socio-economic characterization of the study population, the major strength of TwinsUK is availability of several 'omics' technologies for the participants. These include genome-wide scans of single nucleotide variants, next-generation sequencing, exome sequencing, epigenetic markers (MeDIP sequencing), gene expression arrays and RNA sequencing, telomere length measures, metabolomic profiles, and gut flora microbiomics.

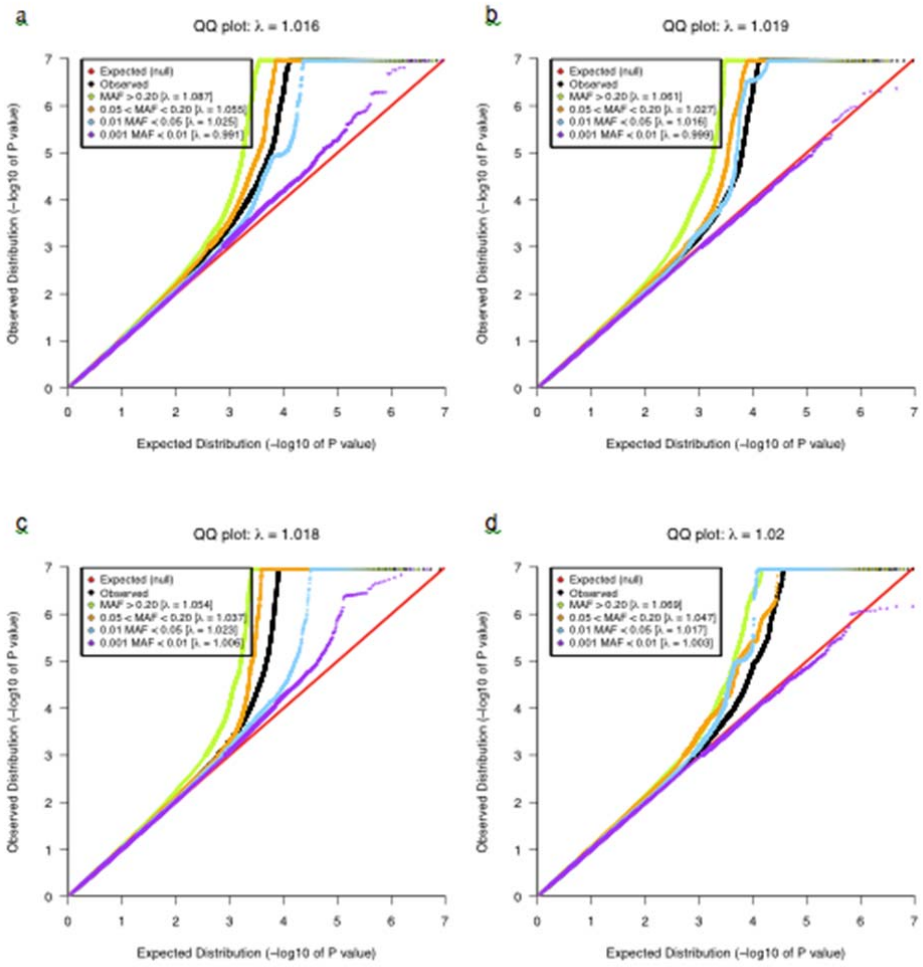
Study design: Twin registry

ECG recording information: 12-lead ECG- Cardiofax GEM machine 9020K (1997 onward), Phillips Page Writer Trim I Cardiograph ECG machine (2009 onward)

YFS (The Cardiovascular Risk in Young Finns Study)

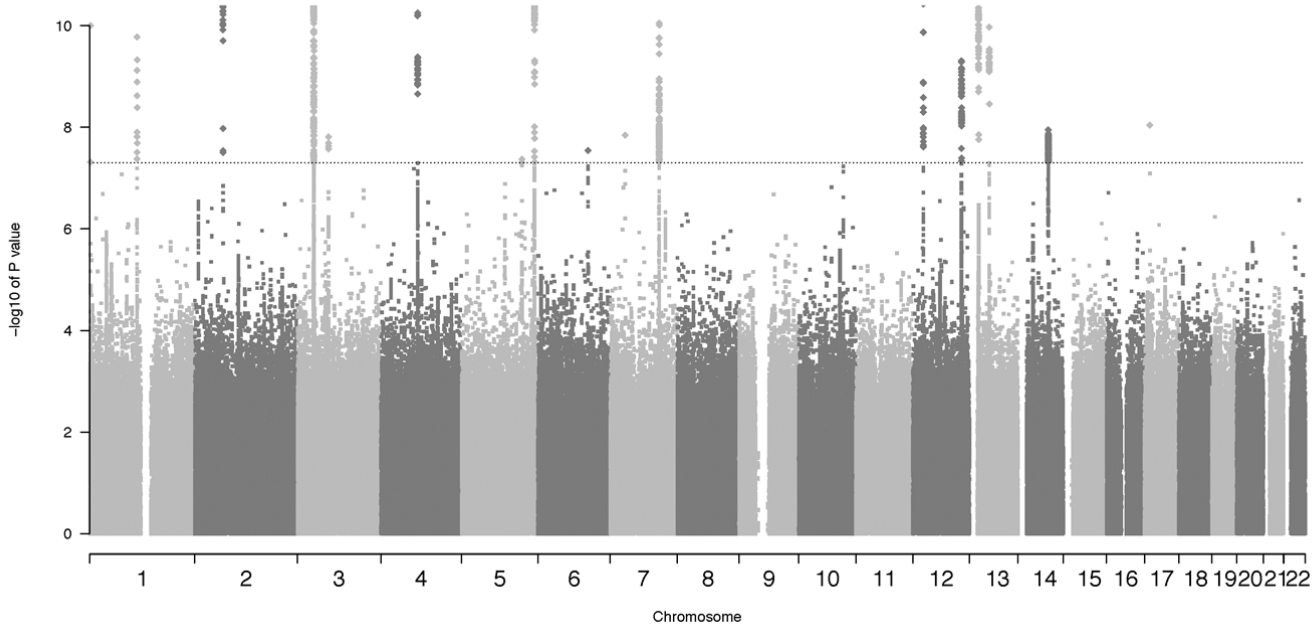
The YFS[21] is a population-based follow up-study started in 1980. The main aim of the YFS is to determine the contribution made by childhood lifestyle, biological and psychological measures to the risk of cardiovascular diseases in adulthood. In 1980, over 3,500 children and adolescents all around Finland participated in the baseline study. The follow-up studies have been conducted mainly with 3-year intervals. The latest 30-year follow-up study was conducted in 2010-11 (ages 33-49 years) with 2,063 participants. The study was approved by the local ethics committees (University Hospitals of Helsinki,

Turku, Tampere, Kuopio and Oulu) and was conducted following the guidelines of the Declaration of Helsinki. All participants gave their written informed consent.
Study design: Population based
ECG recording information: In 2001, a single channel ECG was recorded during a 3-minute period. The ECG signal was collected after the participants had remained comfortably in a supine position for at least 15 minutes. The three ECG leads were positioned diagonally as follows: 1) above sternum, 2) below sternum 3) above umbilicus. The resulting QRS complex corresponds to leads V1-V2. All ECG signals were examined visually by one operator.

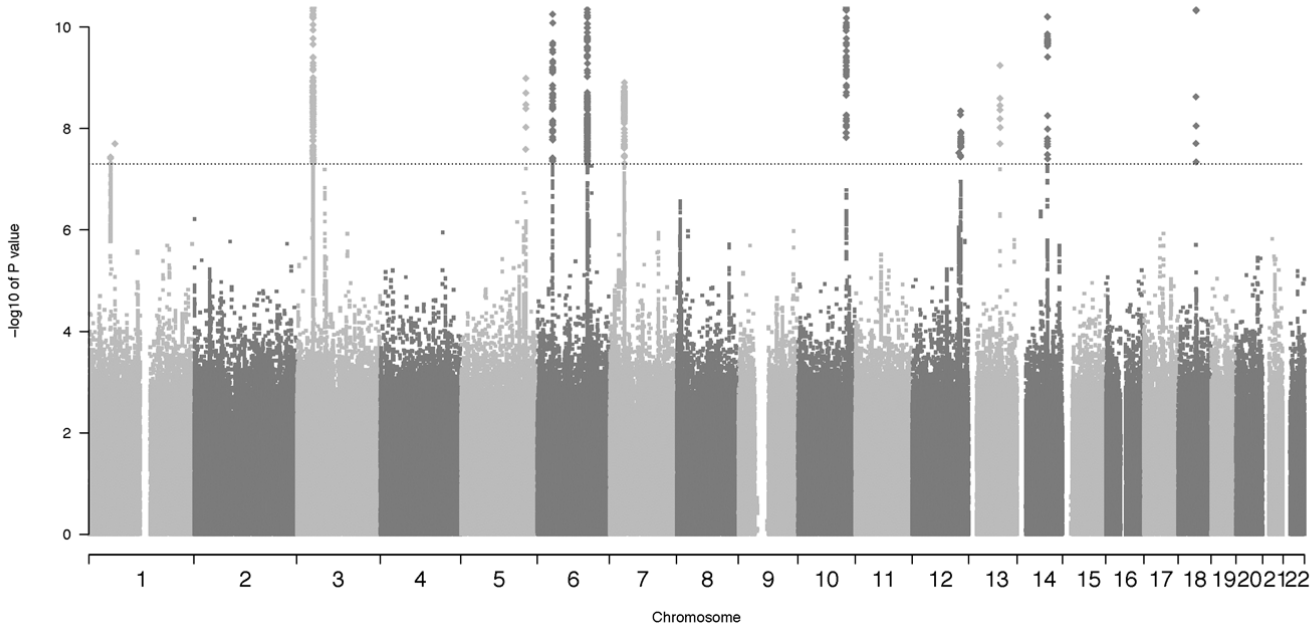


Supplementary Figure 1: Quantile-quantile plots of four GWAS meta-analyses. These plots show the observed versus expected distribution of *P*-values of meta-analysis results of PR interval (a), QRS duration (b), QT interval (c), and RR interval (d). The red line represents the null (expected) distribution, while the black dots show the observed distribution of all P-values. Green, orange, blue, and purple dots depict SNPs with minor allele frequency above 20%, between 5% and 20%, between 1% and 5%, and between 1% and 0.1%, respectively. SNPs with allele frequencies above 1% show clear deviation from the null for all four traits. All traits are predicted to be highly polygenic and this deviation indicates many additional loci that may be involved. The allele frequency bins below 1% have less power to detect associations and follow the null distribution, and lambda (λ) < 1.02 for all traits, suggesting that population stratification is minimal.

a

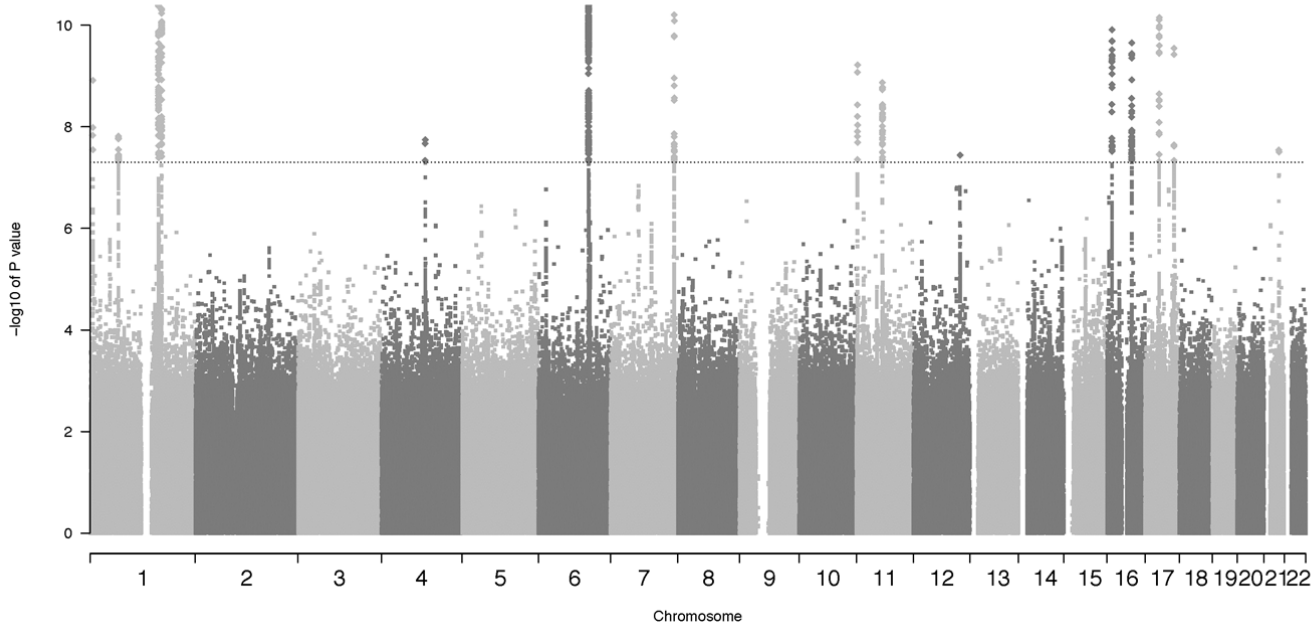


b

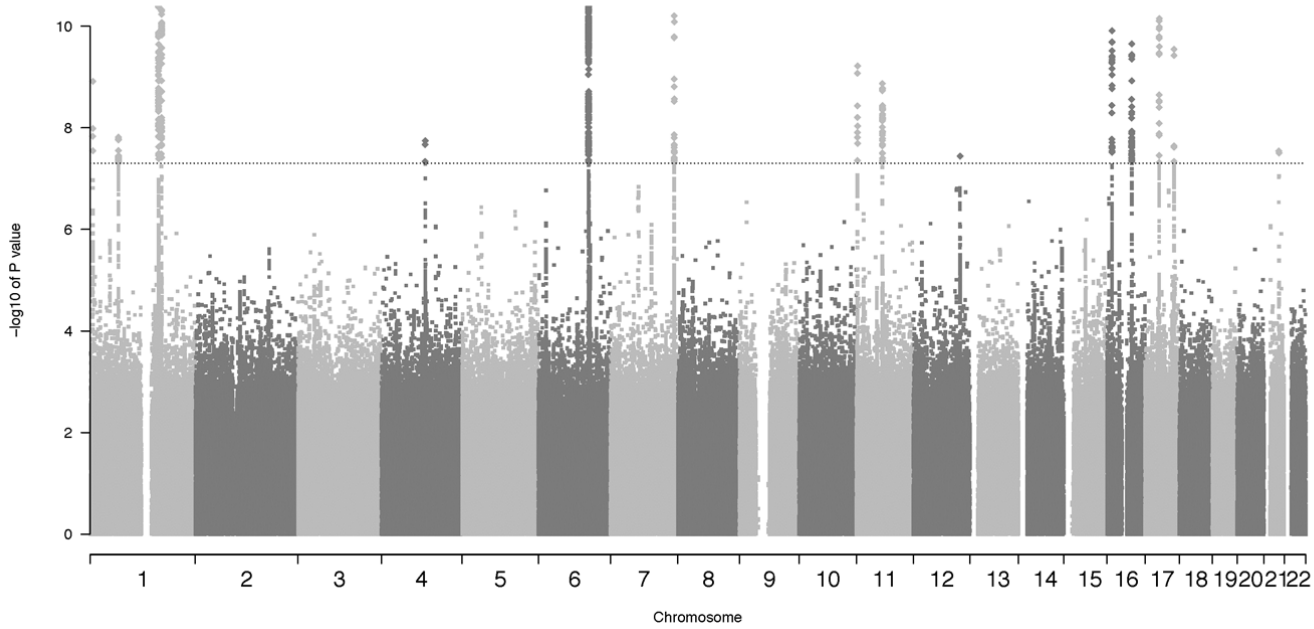


Supplementary Figure 2: Genome-wide results of four quantitative ECG traits in 30,000 individuals of European descent. Nineteen million SNPs were tested for association. The Manhattan plots show the meta-analysis association results for PR interval (a), QRS duration (b), QT interval (c), and RR interval (d). The dashed line marks the genome-wide significant level of 5×10^{-8}. The Y-axis is truncated at $P = 1 \times 10^{-10}$.

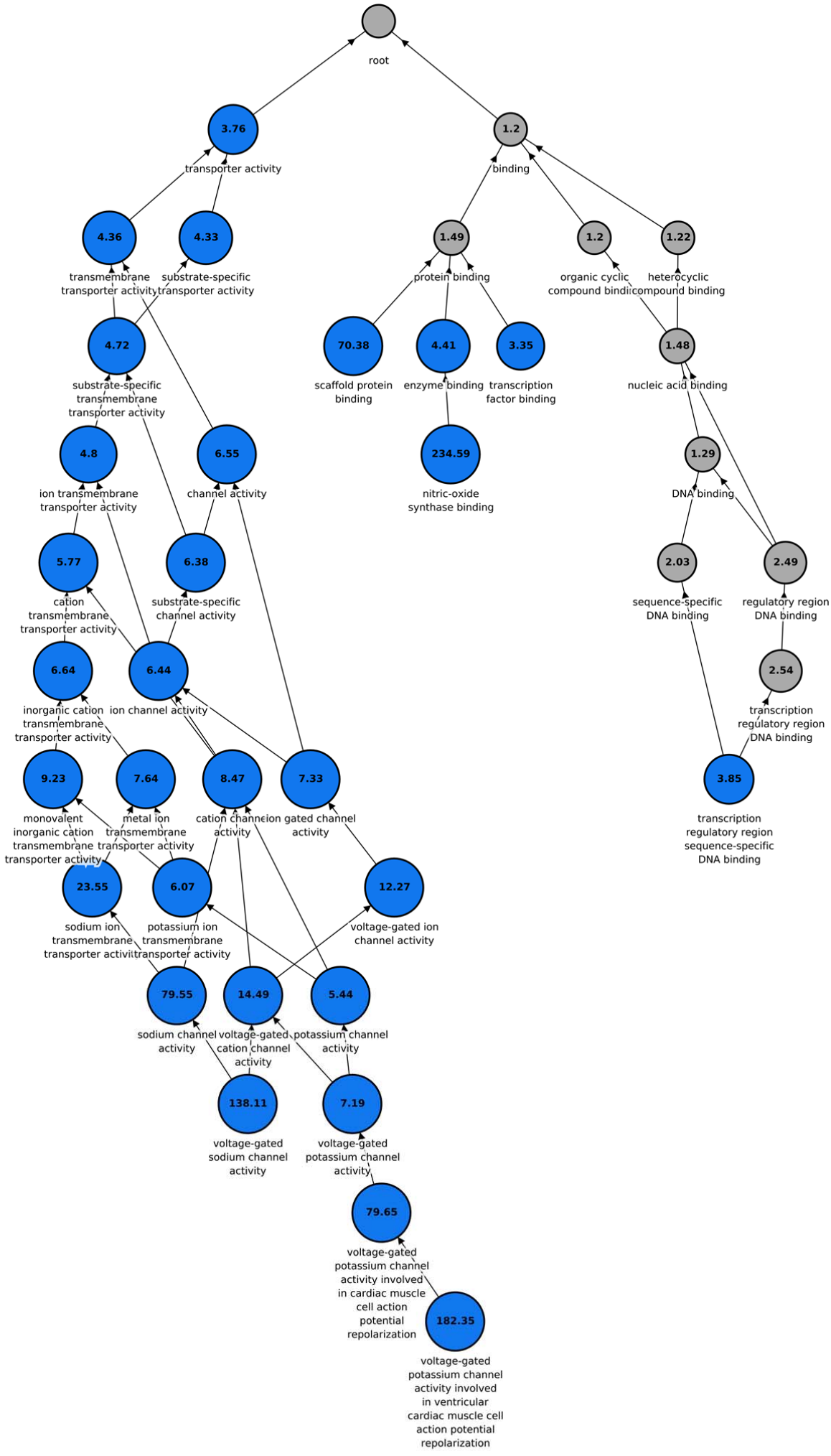
c


10
8
6
4
2
0
−log10 of P value
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Chromosome

d


10
8
6
4
2
0
−log10 of P value
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Chromosome

Next page: Supplementary Figure 3: Pathways involved in PR interval. QRS duration, QT interval, and RR interval. All 100 independent locus-trait associated SNPs were combined and mapped to genes based on *cis*-regulatory regions. Using GREAT,[22] enriched nodes were identified and combined into pathways. This figure shows all significant GO Molecular function nodes, most of which are in the same pathway. Significant nodes (FDR correction) are shown in blue, the numbers indicate fold-enrichment.


root
3.76
transporter activity
1.2
binding
4.36
transmembrane transporter activity
4.33
substrate-specific transporter activity
1.49
protein binding
1.2
organic cyclic compound binding
1.22
heterocyclic compound binding
4.72
substrate-specific transmembrane transporter activity
70.38
scaffold protein binding
4.41
enzyme binding
3.35
transcription factor binding
1.48
nucleic acid binding
4.8
ion transmembrane transporter activity
6.55
channel activity
234.59
nitric-oxide synthase binding
1.29
DNA binding
5.77
cation transmembrane transporter activity
6.38
substrate-specific channel activity
2.03
sequence-specific DNA binding
2.49
regulatory region DNA binding
6.64
inorganic cation transmembrane transporter activity
6.44
ion channel activity
2.54
transcription regulatory region DNA binding
9.23
monovalent inorganic cation transmembrane transporter activity
7.64
metal ion transmembrane transporter activity
8.47
cation channel activity
7.33
ion gated channel activity
3.85
transcription regulatory region sequence-specific DNA binding
23.55
sodium ion transmembrane transporter activity
6.07
potassium ion transmembrane transporter activity
12.27
voltage-gated ion channel activity
79.55
sodium channel activity
14.49
voltage-gated cation channel activity
5.44
potassium channel activity
138.11
voltage-gated sodium channel activity
7.19
voltage-gated potassium channel activity
79.65
voltage-gated potassium channel activity involved in cardiac muscle cell action potential repolarization
182.35
voltage-gated potassium channel activity involved in ventricular cardiac muscle cell action potential repolarization

Supplementary Table 1: Phenotype characteristics

COHORT	PR interval		QRS duration		QT interval		RR interval		Other				
	Sample size (n)	Mean PR interval (sd)	Sample size (n)	Mean QRS duration (sd)	Sample size (n)	Mean QT interval (sd)	Sample size (n)	Mean RR interval (sd)	Mean age (sd)	Mean height (sd)	Mean BMI (sd)	n Females (%)	Ancestry
AGES	2378	170.9 (26.8)	2280	90.3 (10.6)	2540	405.9 (34.8)	N/A	N/A	76.2 (5.4)	166.7 (9.2)	27.1 (4.5)	60.30%	European
ARIC	8038	160.2 (23.1)	8040	91.1 (9.5)	8040	398.7 (28.5)	N/A	N/A	54 (5.7)	168.6 (9.4)	26.8 (4.7)	4360 (54.2)	European
BRIGHT	1186	162.4 (19.5)	1229	93.0 (9.4)	1326	422.1 (26.5)	N/A	N/A	39.9 (11.0)	166 (9)	27.5 (3.8)	819 (61.8)	European
Carlantino	391	151.4 (21.8)	391	91.3 (13.5)	391	390.5 (28.5)	N/A	N/A	44.6 (20.2)	159.6 (9.5)	27.2 (5.2)	58.00%	European
CHS	2754	166.6 (27.9)	2833	88.3 (10.1)	2537	414.2 (31.3)	N/A	N/A	72.1 (5.2)	164.3 (9.2)	26.2 (4.5)	1781 (62.9)	European
ERF	2370	153.0 (22.6)	2177	97.1 (10.1)	2332	398.5 (28.3)	2006	951.0 (125.8)	48.0 (14.2)	167.7 (9.4)	26.8 (4.6)	1361 (55.7%)	European
FVG	981	156.6 (22.6)	981	94.8 (9.6)	981	399.0 (29.8)	N/A	N/A	48.5 (21.6)	168.1 (10.1)	24.8 (4.5)	57.29%	European
GRAPHIC	950	160 (20)	942	90 (10)	940	410 (20)	N/A	N/A	52.9 (4.4)	170.0 (9.0)	27.5 (4.3)	509 (50.1%)	European
Inter99	5907	158.3 (22.4)	5832	91.1 (9.9)	5869	403.5 (27.0)	N/A	N/A	46.1 (7.9)	172.2 (9.2)	26.3 (4.6)	51.10%	European
JHS	2070	170.9 (26.2)	2048	92.0 (9.9)	2048	410.3 (30.3)	N/A	N/A	49.9 (12.1)	169.8 (9.4)	32.3 (7.8)	60.56%	African American
KORA F3	2709	158.1 (20.7)	2599	91.9 (9.7)	2802	400.6 (29.4)	N/A	N/A	27.3 (12.9)	167.8 (9.4)	27.6 (4.6)	51%	European
KORA S4	3439	162.4 (22.2)	3273	91.5 (9.0)	3542	407.5 (27.4)	N/A	N/A	49.2 (13.9)	168.3 (9.3)	27.2 (4.7)	51%	European
Lifelines	12829	157.3 (21.8)	8817	92.6 (10.5)	8817	392.2 (24.8)	11519	906.2 (132.5)	48.7 (11.5)	174.4 (9.2)	26.4 (4.3)	7744 (58.2)	European
NTR	N/A	N/A	N/A	N/A	N/A	N/A	1482	898.1 (125.5)	27.9 (11.8)	N/A	23.1 (3.6)	882 (59.5)	European
Prevend	3301	159.1 (21.2)	3159	97.7 (10.6)	2446	395.1 (25.4)	3159	892.3 (132.0)	49.6 (12.5)	173.7 (9.1)	26.1 (4.3)	1768 (48.5)	European
PROSPER	4237	168.2(27.9)	3976	92.9 (10.9)	4571	414.5 (36.3)	3200	888.0 (126.8)	75.3 (3.4)	165.2 (9.4)	26.8 (4.2)	2720 (51.9)	European
RS I	4455	167.0 (24.5)	3442	96.0 (10.5)	4261	397.5 (28.4)	3456	862.5 (124.5)	68.1 (8.3)	167.0 (9.3)	26.3 (3.6)	61.7	European
RS II	1631	164.7 (22.3)	1353	96.6 (10.7)	1541	401.3 (27.2)	1354	867.6 (120.6)	64.5 (7.6)	168.5 (9.2)	27.3 (4.1)	55.9	European
RS III	2872	162.9 (21.3)	2585	97.3 (10.5)	2826	401.5 (26.6)	2522	873.0 (122.3)	56.9 (6.5)	170.9 (9.6)	27.6 (4.6)	57.7	European
TwinsUK	1807	158.0 (22.3)	1809	88.1 (8.4)	1788	403.1 (26.3)	N/A	N/A	51.2 (13.2)	163.2 (7.5)	25.9 (4.7)	91.5	European
YFS	1865	194.0 (22.7)	1923	84.4 (14.3)	1841	351.7 (26.5)	N/A	N/A	31.6 (5.0)	172.2 (9.1)	25.1 (4.4)	1320 (54.0)	European

Supplementary Table 2: Genotype characteristics

Cohort name	Genotyping array	Sample size	Call rate	Other exclusion criteria	Sample size in analysis	MAF	Call rate	HWE P-value	Other exclusion criteria	n SNPs before imputation	Reference panel	Quality control	Imputation	GWAS
AGES	Hu370CNV, Illumina	3660	97%	Mismatch previous genotypes, mismatch predicted sex, poor Illumina quality	3219	0.01	97%	1 x 10-6	SNPs not in Hapmap, remove G/C A/T SNPs	324603	1000G phase 1 v3	PLINK	Mach/Minimac	R
ARIC	Affymetrix 6.0	9747	95%	1st degree relatives, genetic outliers, not-matching existing genotype data	8040	0.005	95%	1 x 10-5	N/A	682749 autosomal	1000G phase 1 v3	PLINK	IMPUTE2	FAST
BRIGHT	Affymetrix GeneChip 500k array	2001	97%	Heterozygosity Outliers, Non European ancestry, duplicates, 1st or 2nd degree relatives, sex mismatch	1,948	>0	N/A	1 x 10-7	N/A	446472	1000G phase 1 v Dec 2013	PLINK	Minimac	R
CHS	Illumina 370CNV and ITMAT-Broad-CARe (IBC) Illumina iSELECT chip	3268	95%	Disconcordance with prior genotyping, sex mismatch	3,268	>0	97%	1 x 10-5	Errors in duplicate samples, Mendelian inconstancies in CEPH trios, hetero-zygote frequency of 0	359592	1000G phase 1 v3	R and BeadStudio	Minimac	R
ERF	Illumina 318/370 K, Affymetrix 250 K, and Illumina 6 K	2492	95%	No ECG or missing covariate or exclusion information.	2442	0.01	98%	1 x 10-6	Mendelian error	678524	GoNL v4	BeadStudio, R	miniMACH	GenABEL/ ProbABEL

GRAPHIC	Illumina HumanOmniExpress-12v1	1017	95%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1000 Genomes March 2012 Version 3	N/A	IMPUTE2	SNPTEST v2.5
INGI-Carlantino	Illumina 370K	1024	95%	NA	326	0.01	97%	1 x 10-5	N/A	310162	1000G phase 1 v3	GenABEL	IMPUTE2	GenABEL
INGI-FVG	Illumina 370K	1794	95%	NA	981	0.01	97%	1 x 10-5	N/A	337266	1000G phase 1 v3	GenABEL	IMPUTE2	GenABEL
Inter99	MetaboChip	5951	95%		5951		95%	1 x 10-5	N/A	N/A	N/A	PLINK, R	NA	PLINK
JHS	Illumina HumanExome BeadChip array	2986	95%	Ethnic outliers; individuals with high inbreeding coefficient defined as F >0.2 or < -0.2; Sex mismatch; duplicated individuals identified as IBD sharing π hat >0.9; individuals overlapped with ARIC cohort; poor concordance; individual with missing genotype > 5%	2125	N/A	95%	1 x 10-6	N/A	N/A	1000G phase 1 v3	R, PLINK and EIGENSOFT	MaCH	Linear mixed-effect model using the lmekin function of the R package kinship.
KORA F3	Illumina Omni 2.5 + Illumina Omni Express	4086	97%	excess heterozygosity, population outlier, sex check, phenotype availability	2709	0.01	98%	5 x 10-6	availability in good quality on both chips	600,641	1000genomes phase 1 all	R	SHAPEIT v2 + IMPUTE v2.3.0	R
KORA S4	Affymetrix Axiom	3788	97%		3788	0.01	98%	5 x 10-6		523,260	1000genomes phase 1 all	R	SHAPEIT v2 + IMPUTE v2.3.0	R

Lifelines	Illumina CytoSNP12 v2	13,302	95%	IBS (IBS>0.125)	13,302	0.01	95%	1 x 10-5	Sex mismatch, outliers based on PCA analysis.	257581	GoNL v4	MOLGENIS	Impute2	SNPtest v2
NTR	Affymetrix, 5.0,; Illumina 370; Illumina 660, Illumina Omni Express 1 M,Affymetrix 6.0	1482	90%	non-Dutch ancestry	1482	0.01	95%	1 x 10-5	imputation quality cutoff R2 < 0.30.	N/A	GoNL v4	PLINK, R	MaCH (version 1.0.18), Minimac (version 2012.10.9 beta)	Plink
Prevend	Illumina CytoSNP12 v2	3,648	95%	IBS (IBS>0.125)	3,648	0.01	95%	1 x 10-5	Sex mismatch, outliers based on PCA analysis.	232571	GoNL v4	MOLGENIS	Impute2	SNPtest v2
PROSPER	Illumina 660K Quad beadchip	5786	98%	family relatedness, gender mismatch, ancestry	5244	0.01	97.5 %	1 x 10-6	N/A	557192	GoNL v4	BeadStudio	IMPUTE	SNPTEST
RS I	Illumina HumanHap 550K V.3 ADHumanHap 550 V.3 DUO	7893	97.5 %	Duplicate samples, sex mismatch	6291	0.01	98%	1 x 10-6	Sample call rate < 98%, Missing DNA, Gender mismatch, Excess autosomal heterozigocity, Duplicates or family relations IBS>97%, Ethnic outliers (IBS distances > 4SD, Missing traits	512,849	GoNL v4	PLINK	Impute2 2.3.0	GRIMP
RS II	Illumina HumanHap 550K V.3 ADHumanHap 550 V.3 DUO	3011	97.5 %	Duplicate samples, sex mismatch	2160	0.01	98%	1 x 10-6		466,389	GoNL v4	PLINK	Impute2 2.3.0	GRIMP
RS III	Illumina HumanHap 610 quad	3932	97.5 %	Duplicate samples, sex mismatch	3045	0.01	98%	1 x 10-6		514,073	GoNL v4	PLINK	Impute2 2.3.0	GRIMP

TwinsUK	Illumina HumanHap300, Illumina Human610 arrays	2575	N/A	exclusions basex population stratification, heterozygosity, zygosity and sex checks	Up to 1809	0.01	N/A	N/A	N/A	N/A	1000 Genomes phase 1 v3 + UK10K Whole Genome Sequence (REL-2012-06-02, v2, N=3,781)	PLINK, R	SHAPEIT version 2 , IMPUTE version 2.2.0	GEMMA version 0.93 SNPTEST version 2.4.1
YFS	Illumina Human670-QuadCustom	2556	95%	gender mismatch, excess heterozygosity, cryptic relatedness	2443	0.01	95%	1 x 10-6	N/A	546674	1000 Genomes phase I integrated variant set release (v3)	Sanger genotyping pipe-line qc	IMPUTE v2.2.2	SNPTEST v2.4.1

Supplementary Table 3: Exclusion criteria

Exclusion criteria	PR	QT	QRS	RR
Pacemaker	X	X	X	X
Atrial fibrillation on baseline ECG	X	X	X	X
History of Myocardial Infarction or Heart failure	X		X	X
Pregnancy	X	X		
Wolff-Parkinson-White	X		X	
Class I and class III blocking medication	X		X	
Second or third degree heart block	X			X
Digoxin	X			X
QRS duration > 120ms or left or right bundle branch block and intraventricular conduction delay		X	X	
Extreme PR values (<=80ms or >=320 ms)	X			
Use of QT-shortening or QT-prolonging drugs		X		
Coded as incomplete LBTB, RBTB			X	
QRS axis smaller than -30 or larger than +90 (or left anterior hemiblock and left posterior hemiblock)			X	
Heart rate < 50 BPM or > 100 BPM				X
Use of beta blockers or non-dihydropyridin calcium-antagonists date of ECG				X

Supplementary Table 4: Association results for RR, PR, QRS, and QT. Independent genome-wide significant SNPs are listed.

Locus	SNP	Chr	Pos (hg19)	Coded allele	Non-coded allele	Coded allele frequency	Beta	SE	P-value	Conditional P-value	Closest gene
RR-1	rs2785638	1	208093719	G	A	0.474	-6.429	1.094	4.19E-09		CD34
RR-2	rs6911599	6	119009913	G	A	0.495	-6.727	1.069	3.14E-10		CEP85L
RR-3-1	rs9385199	6	121837314	G	A	0.584	6.672	1.130	3.49E-09	2.23E-07	GJA1
RR-3-2	rs9372667	6	122145892	G	T	0.106	-12.924	1.739	1.09E-13		GJA1
RR-4	rs3757868	7	100482720	A	G	0.191	-8.956	1.375	7.23E-11		SRRT
RR-5	rs9888363	12	33529288	C	T	0.614	6.601	1.134	5.85E-09		SYT10
RR-6	rs432256	14	23870752	A	G	0.250	-8.122	1.245	6.89E-11		MYH6
RR-7	rs6069234	20	36843992	G	A	0.481	6.553	1.138	8.58E-09		KIAA1755

Locus	SNP	Chr	Pos (hg19)	Coded allele	Non-coded allele	Coded allele frequency	Beta	SE	P-value	Conditional P-value	Closest gene
PR-1	rs2503715	1	2144107	G	A	0.878	2.221	0.343	9.93E-11		AL590822.1
PR-2-1	rs12145374	1	112480536	C	A	0.203	-1.419	0.238	2.40E-09	1.03E-06	KCND3
PR-2-2	rs75013985	1	112530430	G	A	0.033	-4.090	0.554	1.48E-13		KCND3
PR-3	rs6724747	2	66749828	A	G	0.346	1.379	0.193	7.90E-13		MEIS1
PR-4-1	rs7623452	3	37616229	A	G	0.521	1.061	0.185	9.91E-09	5.19E-07	ITGA9
PR-4-2	rs3828441	3	38356737	A	G	0.225	-1.384	0.251	3.59E-08	3.21E-06	SLC22A14
PR-4-3	rs73070938	3	38606159	A	C	0.108	2.109	0.328	1.34E-10	2.94E-11	SCN5A
PR-4-4	rs62241190	3	38607468	G	A	0.035	5.926	0.617	7.26E-22	5.02E-13	SCN5A
PR-4-5	rs3922843	3	38624343	G	A	0.748	2.622	0.219	3.53E-33	4.00E-14	SCN5A
PR-4-6	rs39351484	3	38638202	G	C	0.665	-1.733	0.198	2.05E-18	3.26E-19	SCN5A
PR-4-7	rs9832895	3	38661533	C	T	0.524	1.210	0.209	7.46E-09	4.79E-18	SCN5A

PR-4-8	rs7373065	3	38710315	C	T	0.978	8.200	0.726	1.45E-29	6.12E-17	SCN5A
PR-4-9	rs6801957	3	38767315	C	T	0.584	-4.062	0.185	4.91E-107		SCN10A
PR-4-10	rs9828912	3	38837009	A	T	0.083	2.714	0.471	8.06E-09	1.47E-06	SCN10A
PR-4-11	rs62244116	3	38845547	C	A	0.052	4.401	0.526	5.74E-17	4.07E-07	SCN10A
PR-5	rs4461368	3	73599305	T	C	0.626	1.102	0.195	1.54E-08		PDZRN3
PR-6	rs13111293	4	86682968	T	C	0.703	1.881	0.200	5.79E-21		ARHGAP24
PR-7	rs17287745	5	142655015	G	A	0.425	1.011	0.185	4.24E-08		NR3C1
PR-8	rs29797	5	172574176	C	G	0.573	1.283	0.186	4.85E-12		BNIP1
PR-9	rs74640693	6	118684824	T	A	0.049	2.376	0.428	2.88E-08		SLC35F1
PR-10	rs11763856	7	35545787	T	C	0.035	3.055	0.539	1.43E-08		HERPUD2
PR-11	rs11773845	7	116191301	A	C	0.573	-2.012	0.184	9.18E-28		CAV1
PR-12	rs10842383	12	24771967	T	C	0.144	-1.882	0.262	6.29E-13		BCAT1
PR-13-1	rs6489973	12	115156523	G	A	0.412	-1.157	0.186	4.92E-10		TBX3
PR-13-2	rs7301677	12	115381147	T	C	0.272	1.275	0.207	6.78E-10	9.27E-10	TBX3
PR-14	rs11840168	13	22118302	G	A	0.413	-1.280	0.187	6.88E-12		EFHA1
PR-15	rs9534461	13	47241834	A	T	0.642	-1.229	0.190	1.08E-10		LRCH1
PR-16	rs8019721	14	71834210	A	G	0.261	1.192	0.209	1.13E-08		AC004817.1
PR-17	rs35712872	17	12635871	G	A	0.233	1.408	0.245	9.08E-09		MYOCD

Locus	SNP	Chr	Pos (hg19)	Coded allele	Non-coded allele	Coded allele frequency	Beta	SE	P-value	Conditional P-value	Closest gene
QT-1	rs11121483	1	6263792	G	A	0.392	1.508	0.219	5.49E-12		RNF207
QT-2	rs6588213	1	67107894	T	C	0.126	1.596	0.282	1.53E-08		SGIP1
QT-3-1	rs142804708	1	162012135	T	C	0.045	-5.351	0.870	7.59E-10	1.52E-07	OLFML2B
QT-3-2	rs2010491	1	162021000	G	A	0.233	4.332	0.216	2.01E-89		NOS1AP
QT-3-3		1	162030285	A	G	0.142	4.671	0.329	1.17E-45	9.44E-10	NOS1AP

QT-3-4	rs10918592	1	162053449	T	C	0.021	7.231	0.851	1.89E-17	1.90E-10	NOS1AP
QT-3-5	rs59852339	1	162112966	C	T	0.109	3.206	0.300	1.16E-26	2.04E-10	NOS1AP
QT-3-6	rs12567315	1	162166646	A	G	0.196	3.331	0.228	2.91E-48	2.59E-13	NOS1AP
QT-3-7	rs115263373	1	162169913	G	T	0.056	-2.356	0.402	4.41E-09	5.28E-11	NOS1AP
QT-4-1	rs77915002	1	168686870	G	A	0.056	2.169	0.393	3.30E-08	5.68E-10	DPT
QT-4-2	rs1200118	1	169064630	G	A	0.478	-1.369	0.237	8.10E-09	1.77E-11	ATP1B1
QT-4-3	rs12035622	1	169102340	A	T	0.117	-2.287	0.282	5.54E-16		NME7
QT-5	rs11097788	4	103407428	G	A	0.561	1.048	0.186	1.81E-08		NFKB1
QT-6-1	rs11153730	6	118667522	C	T	0.499	2.249	0.181	1.80E-35		SLC35F1
QT-6-2	rs12206973	6	118711303	C	G	0.050	-3.450	0.423	3.38E-16	1.63E-10	CEP85L
QT-6-3	rs6911599	6	119009913	G	A	0.497	-2.128	0.182	1.60E-31	6.49E-08	CEP85L
QT-7-1	rs2072412	7	150647970	G	C	0.244	-1.885	0.225	4.61E-17	4.31E-08	KCNH2
QT-7-2	rs12668582	7	150657201	C	A	0.322	1.712	0.198	4.64E-18		KCNH2
QT-8-1	rs800340	11	2458393	A	T	0.980	7.264	1.284	1.54E-08	5.04E-06	LSP1
QT-8-2	rs800338	11	2473456	A	G	0.844	2.287	0.268	1.33E-17	1.24E-19	KCNQ1
QT-8-3	rs12271931	11	2478519	A	G	0.869	3.035	0.337	7.40E-20	1.02E-13	KCNQ1
QT-8-4	rs2074238	11	2484803	C	T	0.920	5.405	0.494	7.34E-28		KCNQ1
QT-8-5	rs12280952	11	2488873	A	G	0.164	2.498	0.250	1.56E-23	1.01E-22	KCNQ1
QT-9	rs174546	11	61569830	T	C	0.334	-1.238	0.204	1.35E-09		FADS1
QT-10	rs28637922	12	110819139	T	G	0.261	1.173	0.213	3.64E-08		ANAPC7
QT-11	rs11643990	16	11694062	A	G	0.333	-1.355	0.203	2.61E-11		LITAF
QT-12	rs950843	16	58620885	T	C	0.758	1.977	0.212	9.57E-21		CNOT1
QT-13	rs2074518	17	33324382	T	C	0.462	-1.330	0.183	3.43E-13		LIG3
QT-14	rs4793397	17	68520389	T	C	0.464	-1.178	0.187	2.87E-10		KCNJ2
QT-15	rs1805128	21	35821680	T	C	0.018	7.409	0.939	2.91E-15		KCNE1

Locus	SNP	Chr	Pos (hg19)	Coded allele	Non-coded allele	Coded allele frequency	Beta	SE	P-value	Conditional P-value	Closest gene
QRS-1	rs149288352	1	51349663	A	G	0.025	-1.515	0.275	3.67E-08		FAF1
QRS-2	rs6587924	1	61895257	A	C	0.508	-0.822	0.086	1.89E-21		NFIA
QRS-3-1	rs7429945	3	38591689	C	T	0.345	0.956	0.092	2.19E-25	1.78E-15	SCN5A
QRS-3-2	rs62241190	3	38607468	G	A	0.034	2.524	0.293	6.32E-18	1.99E-10	SCN5A
QRS-3-3	rs3922843	3	38624343	G	A	0.747	0.770	0.104	1.08E-13	1.68E-11	SCN5A
QRS-3-4	rs9851710	3	38719901	A	C	0.654	1.011	0.093	2.53E-27		SCN10A
QRS-3-5	rs4076737	3	38764782	T	G	0.549	-0.895	0.090	2.68E-23	3.47E-16	SCN10A
QRS-4	rs10076436	5	153871841	G	C	0.358	-0.809	0.092	9.68E-19		HAND1
QRS-5	rs3176326	6	36647289	A	G	0.202	1.177	0.114	4.49E-25		CDKN1A
QRS-6-1	rs3951016	6	118559658	A	T	0.459	-1.004	0.088	2.52E-30		SLC35F1
QRS-6-2	rs10457327	6	118692152	C	G	0.053	-1.281	0.196	5.80E-11	1.35E-06	SLC35F1
QRS-7-1	rs13232979	7	35310657	A	T	0.117	0.841	0.139	1.24E-09		TBX20
QRS-7-2	rs11764098	7	35505710	G	C	0.030	1.711	0.287	2.50E-09	9.39E-07	HERPUD2
QRS-8	rs6585178	10	114479277	G	A	0.239	0.714	0.103	4.67E-12		VTI1A
QRS-9	rs28637922	12	110819139	T	G	0.259	0.565	0.102	3.02E-08		ANAPC7
QRS-10-1	rs1248048	12	114856951	G	C	0.724	-0.570	0.098	5.38E-09	4.32E-08	TBX5
QRS-10-2	rs7487237	12	115353703	G	A	0.719	0.580	0.099	4.54E-09		TBX3
QRS-11	rs728926	13	74513122	T	C	0.375	-0.581	0.094	5.76E-10		KLF12
QRS-12	rs34991781	14	71921576	A	G	0.264	-0.810	0.099	2.25E-16		SIPA1L1
QRS-13	rs11661654	18	42441443	T	C	0.415	0.598	0.089	1.95E-11		SETBP1

Supplementary Table 5: Nodes that are significantly enriched for genes that are mapped to index SNPs. In total, 100 independent locus-trait associations were merged and mapped to genes using GREAT. SNPs were mapped to a gene is it was in a *cis*-regulatory region of that gene. Significant nodes are listed for GO terms, human phenotypes, and disease ontologies.

Supplementary Table 5a: GO molecular function

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
nitric-oxide synthase binding	1	5.34E-60	1.97E-56	234.5939	29	0.29
scaffold protein binding	4	1.08E-38	1.00E-35	70.38353	25	0.25
voltage-gated sodium channel activity	5	1.21E-38	8.91E-36	138.1109	21	0.21
sodium channel activity	6	2.07E-38	1.27E-35	79.55073	24	0.24
sodium ion transmembrane transporter activity	9	4.16E-28	1.71E-25	23.54955	26	0.26
voltage-gated cation channel activity	11	2.71E-27	9.09E-25	14.49064	31	0.31
voltage-gated ion channel activity	12	3.60E-25	1.11E-22	12.27158	31	0.31
monovalent inorganic cation transmembrane transporter activity	13	4.95E-23	1.41E-20	9.234968	33	0.33
metal ion transmembrane transporter activity	14	1.73E-22	4.55E-20	7.635562	36	0.36
enzyme binding	15	4.68E-22	1.15E-19	4.406918	51	0.51
cation channel activity	16	1.64E-20	3.79E-18	8.465701	31	0.31
inorganic cation transmembrane transporter activity	17	1.69E-20	3.66E-18	6.637147	36	0.36
cation transmembrane transporter activity	19	4.25E-19	8.25E-17	5.771739	37	0.37
ion gated channel activity	20	9.51E-19	1.75E-16	7.333553	31	0.31
channel activity	21	1.55E-18	2.73E-16	6.548074	33	0.33
substrate-specific transmembrane transporter activity	23	1.08E-17	1.73E-15	4.715709	40	0.4
ion transmembrane transporter activity	24	1.78E-17	2.74E-15	4.801418	39	0.39
ion channel activity	26	3.56E-17	5.05E-15	6.439358	31	0.31
substrate-specific channel activity	27	4.66E-17	6.37E-15	6.376701	31	0.31
transmembrane transporter activity	28	1.57E-16	2.07E-14	4.361665	40	0.4

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
substrate-specific transporter activity	29	2.08E-16	2.64E-14	4.326363	40	0.4
transporter activity	30	9.13E-15	1.12E-12	3.76182	41	0.41
voltage-gated potassium channel activity involved in ventricular cardiac muscle cell action potential repolarization	32	1.91E-14	2.20E-12	182.3488	7	0.07
voltage-gated potassium channel activity involved in cardiac muscle cell action potential repolarization	33	1.78E-13	1.98E-11	79.65021	8	0.08
potassium ion transmembrane transporter activity	47	7.52E-07	5.90E-05	6.066083	12	0.12
voltage-gated potassium channel activity	48	1.50E-06	1.15E-4	7.190786	10	0.1
transcription factor binding	50	6.12E-06	4.52E-4	3.347959	18	0.18
potassium channel activity	55	1.68E-05	0.0011	5.44302	10	0.1
transcription regulatory region sequence-specific DNA binding	73	2.90E-4	0.0146	3.845833	10	0.1

Supplementary Table 5b: GO biological process

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
regulation of cardiac muscle cell membrane potential	1	4.33E-61	4.52E-57	64.66527	40	0.4
cardiac conduction	2	4.09E-58	2.13E-54	65.51545	38	0.38
membrane repolarization	3	5.16E-55	1.80E-51	118.3191	31	0.31
regulation of ventricular cardiac muscle cell membrane repolarization	4	7.06E-55	1.84E-51	182.6363	28	0.28
regulation of cardiac muscle cell contraction	5	7.07E-54	1.48E-50	61.16414	36	0.36
membrane repolarization involved in regulation of cardiac muscle cell action potential	6	4.06E-52	7.06E-49	125.1537	29	0.29
regulation of atrial cardiac muscle cell membrane repolarization	7	3.64E-51	5.42E-48	336.9142	23	0.23

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
regulation of atrial cardiac muscle cell membrane depolarization	8	2.53E-50	3.31E-47	309.5837	23	0.23
regulation of heart rate	9	1.10E-49	1.27E-46	35.97524	39	0.39
regulation of heart rate by cardiac conduction	10	1.21E-49	1.26E-46	118.505	28	0.28
regulation of cardiac muscle contraction	11	4.50E-49	4.27E-46	34.6758	39	0.39
bundle of His cell to Purkinje myocyte communication	12	5.86E-49	5.09E-46	337.0679	22	0.22
regulation of striated muscle contraction	13	1.26E-48	1.01E-45	33.75919	39	0.39
regulation of membrane repolarization	14	2.76E-48	2.06E-45	92.13828	29	0.29
regulation of ventricular cardiac muscle cell action potential	15	8.54E-48	5.94E-45	117.8716	27	0.27
regulation of cardiac muscle cell action potential	16	3.92E-47	2.56E-44	58.58841	32	0.32
regulation of cardiac muscle cell action potential involved in contraction	17	6.50E-47	3.99E-44	72.70491	30	0.3
heart process	18	1.16E-46	6.72E-44	50.94095	33	0.33
AV node cell to bundle of His cell communication	19	2.61E-46	1.44E-43	321.0421	21	0.21
membrane depolarization involved in regulation of action potential	20	1.15E-45	6.00E-43	114.2408	26	0.26
cell-cell signaling involved in cardiac conduction	21	7.95E-45	3.95E-42	105.9987	26	0.26
regulation of heart contraction	22	4.67E-44	2.21E-41	19.65178	43	0.43
regulation of muscle contraction	23	8.90E-44	4.04E-41	21.96013	41	0.41
cell communication involved in cardiac conduction	24	3.11E-43	1.35E-40	69.666	28	0.28
membrane depolarization involved in regulation of cardiac muscle cell action potential	25	6.75E-42	2.82E-39	111.4422	24	0.24
regulation of ventricular cardiac muscle cell membrane depolarization	26	8.42E-42	3.38E-39	195.548	21	0.21
regulation of muscle system process	30	2.70E-40	9.38E-38	17.95286	41	0.41
muscle system process	34	5.93E-38	1.82E-35	14.79662	42	0.42

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
cardiac muscle contraction	36	8.13E-38	2.36E-35	56.64215	26	0.26
heart contraction	37	8.15E-38	2.30E-35	49.91578	27	0.27
regulation of membrane depolarization	38	8.19E-38	2.25E-35	87.9581	23	0.23
sodium ion transmembrane transport	39	5.91E-36	1.58E-33	62.69731	24	0.24
striated muscle contraction	41	1.96E-35	4.98E-33	40.61466	27	0.27
regulation of metal ion transport	42	3.77E-34	9.37E-32	14.85358	38	0.38
regulation of membrane potential	43	4.27E-34	1.04E-31	10.75013	44	0.44
positive regulation of sodium ion transport	44	4.53E-32	1.07E-29	66.7804	21	0.21
blood circulation	45	3.69E-31	8.56E-29	11.63122	39	0.39
cardiac ventricle development	46	4.28E-31	9.71E-29	18.0096	32	0.32
circulatory system process	47	4.87E-31	1.08E-28	11.54417	39	0.39
positive regulation of ion transport	48	6.83E-31	1.49E-28	20.76383	30	0.3
regulation of ion homeostasis	49	2.87E-30	6.12E-28	18.24977	31	0.31
regulation of ion transmembrane transport	50	7.77E-30	1.62E-27	10.18149	40	0.4
regulation of action potential	51	9.88E-30	2.02E-27	15.16162	33	0.33
membrane depolarization	52	1.26E-29	2.52E-27	24.46696	27	0.27
regulation of transmembrane transport	53	1.37E-29	2.70E-27	10.02939	40	0.4
regulation of actin filament-based process	54	4.49E-29	8.68E-27	11.99772	36	0.36
cardiac chamber development	55	1.11E-28	2.10E-26	15.02651	32	0.32
regulation of system process	56	3.40E-28	6.34E-26	6.889042	47	0.47
metal ion transport	57	6.53E-28	1.20E-25	7.313961	45	0.45
muscle contraction	58	1.14E-27	2.06E-25	13.91984	32	0.32
regulation of ion transport	59	2.70E-27	4.77E-25	7.647608	43	0.43
sodium ion transport	61	2.48E-26	4.25E-24	20.01457	26	0.26
cation transport	63	1.15E-25	1.90E-23	6.226637	46	0.46

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
odontogenesis of dentin-containing tooth	66	1.12E-24	1.77E-22	20.75163	24	0.24
heart development	67	6.48E-24	1.01E-21	6.77108	41	0.41
cardiovascular system development	68	7.86E-24	1.21E-21	4.825322	51	0.51
monovalent inorganic cation transport	69	1.05E-23	1.59E-21	9.714724	33	0.33
regulation of homeostatic process	72	8.13E-23	1.18E-20	9.086706	33	0.33
ion transmembrane transport	73	1.15E-22	1.65E-20	7.385485	37	0.37
odontogenesis	74	1.40E-21	1.97E-19	15.22058	24	0.24
regulation of cellular component movement	75	3.15E-21	4.39E-19	5.72716	41	0.41
ion transport	76	7.87E-21	1.08E-18	4.48278	48	0.48
regulation of multicellular organismal process	78	4.02E-19	5.38E-17	2.781644	66	0.66
regulation of transport	79	1.51E-18	1.99E-16	3.668435	51	0.51
transmembrane transport	81	1.50E-17	1.93E-15	4.670725	40	0.4
multicellular organismal signaling	82	2.09E-17	2.66E-15	4.350306	42	0.42
positive regulation of transport	86	5.04E-16	6.12E-14	5.371306	33	0.33
potassium ion export	87	1.31E-15	1.57E-13	92.97068	9	0.09
regulation of localization	88	3.28E-15	3.89E-13	2.885535	54	0.54
transport	92	4.47E-14	5.08E-12	2.309987	64	0.64
cell-cell signaling	93	4.52E-14	5.08E-12	3.497348	42	0.42
localization	96	5.50E-14	5.98E-12	2.029173	73	0.73
striated muscle tissue development	97	8.86E-14	9.54E-12	6.773797	24	0.24
establishment of localization	99	1.25E-13	1.32E-11	2.263259	64	0.64
muscle tissue development	102	3.66E-13	3.75E-11	6.336133	24	0.24
organ morphogenesis	103	4.42E-13	4.48E-11	3.526623	39	0.39
organ development	104	5.23E-13	5.25E-11	2.230675	63	0.63
cardiac muscle tissue development	108	5.70E-13	5.51E-11	8.787839	19	0.19

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
relaxation of cardiac muscle	111	1.55E-12	1.46E-10	41.91772	9	0.09
positive regulation of potassium ion transmembrane transport	113	3.82E-12	3.53E-10	85.08963	7	0.07
regulation of the force of heart contraction	114	4.61E-12	4.22E-10	27.83993	10	0.1
heart looping	115	5.15E-12	4.68E-10	17.85919	12	0.12
determination of heart left/right asymmetry	116	7.09E-12	6.38E-10	17.36805	12	0.12
determination of left/right symmetry	118	1.46E-11	1.29E-09	12.02453	14	0.14
His-Purkinje system cell differentiation	119	1.96E-11	1.72E-09	118.1391	6	0.06
cardiac pacemaker cell development	123	2.80E-11	2.38E-09	111.3156	6	0.06
embryonic heart tube morphogenesis	124	2.98E-11	2.51E-09	15.31357	12	0.12
cardiac pacemaker cell differentiation	128	3.72E-11	3.04E-09	106.1157	6	0.06
determination of bilateral symmetry	129	4.06E-11	3.28E-09	11.11383	14	0.14
relaxation of muscle	130	5.37E-11	4.31E-09	27.99133	9	0.09
specification of symmetry	132	6.28E-11	4.97E-09	10.74598	14	0.14
regulation of cell proliferation	133	7.05E-11	5.53E-09	2.804369	42	0.42
cardiac muscle cell fate commitment	141	3.99E-10	2.96E-08	71.18162	6	0.06
embryonic heart tube development	143	6.24E-10	4.55E-08	11.68972	12	0.12
regulation of response to stimulus	144	9.02E-10	6.54E-08	2.076933	56	0.56
bundle of His development	149	1.61E-09	1.13E-07	56.23119	6	0.06
positive regulation of ion transmembrane transport	152	1.69E-09	1.16E-07	35.14382	7	0.07
positive regulation of transmembrane transport	154	2.29E-09	1.55E-07	33.62332	7	0.07
positive regulation of potassium ion transport	165	1.54E-08	9.77E-07	25.40195	7	0.07
regulation of potassium ion transmembrane transport	169	2.68E-08	1.66E-06	23.41463	7	0.07
cardiac chamber formation	170	3.47E-08	2.13E-06	22.53021	7	0.07
cardiac septum morphogenesis	180	8.38E-08	4.86E-06	9.898889	10	0.1

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
regulation of striated muscle tissue development	187	1.70E-07	9.49E-06	6.279193	13	0.13
regulation of muscle organ development	188	1.88E-07	1.05E-05	6.222137	13	0.13
cardiac conduction system development	189	1.91E-07	1.05E-05	24.92734	6	0.06
regulation of muscle tissue development	190	2.34E-07	1.28E-05	6.104679	13	0.13
cardiac chamber morphogenesis	191	2.90E-07	1.59E-05	6.643675	12	0.12
striated muscle cell development	202	6.11E-07	3.16E-05	7.952528	10	0.1
cardiac muscle cell development	204	7.06E-07	3.61E-05	11.19376	8	0.08
atrial septum development	205	7.08E-07	3.61E-05	19.87219	6	0.06
cardiac atrium development	206	9.42E-07	4.77E-05	13.74158	7	0.07
cardiac cell development	208	1.16E-06	5.80E-05	10.47255	8	0.08
negative regulation of gene expression	210	1.22E-06	6.06E-05	2.507561	30	0.3
cardiac septum development	211	1.25E-06	6.19E-05	7.338107	10	0.1
potassium ion transport	212	1.38E-06	6.82E-05	5.717796	12	0.12
muscle cell development	215	1.84E-06	8.93E-05	7.026002	10	0.1
negative regulation of multicellular organismal process	222	3.26E-06	1.53E-04	3.897974	16	0.16
heart morphogenesis	223	3.33E-06	1.56E-04	4.436775	14	0.14
potassium ion transmembrane transport	224	3.33E-06	1.55E-04	6.566879	10	0.1
cardiac ventricle morphogenesis	225	3.44E-06	1.60E-04	7.560801	9	0.09
tissue development	229	3.55E-06	1.62E-04	2.127604	36	0.36
negative regulation of muscle cell differentiation	231	4.34E-06	1.96E-04	10.87666	7	0.07
muscle structure development	234	4.71E-06	2.10E-04	3.262061	19	0.19
blood vessel development	239	5.84E-06	2.55E-04	3.08493	20	0.2
cardiac left ventricle formation	242	6.19E-06	2.67E-04	88.29244	3	0.03
venous blood vessel development	245	7.54E-06	3.21E-04	19.09216	5	0.05
negative regulation of transcription from RNA	246	7.72E-06	3.28E-04	2.818835	22	0.22

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
polymerase II promoter						
regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	253	1.03E-05	4.25E-04	4.687032	12	0.12
vasculature development	255	1.30E-05	5.31E-04	2.921622	20	0.2
striated muscle cell differentiation	260	1.63E-05	6.53E-04	4.906724	11	0.11
regulation of cell death	275	3.14E-05	1.19E-03	2.21892	28	0.28
negative regulation of macromolecule metabolic process	277	3.36E-05	1.27E-03	2.018207	33	0.33
regulation of apoptotic process	279	3.58E-05	1.34E-03	2.249671	27	0.27
regulation of programmed cell death	286	4.36E-05	1.59E-03	2.22473	27	0.27
regulation of heart growth	288	4.76E-05	1.72E-03	7.466925	7	0.07
cardiac muscle tissue morphogenesis	290	5.19E-05	1.87E-03	7.362849	7	0.07
cardiac muscle cell differentiation	294	6.12E-05	2.17E-03	6.01858	8	0.08
tube morphogenesis	295	6.52E-05	2.31E-03	3.050725	16	0.16
cardiac right ventricle morphogenesis	296	6.68E-05	2.35E-03	12.04926	5	0.05
adult heart development	298	6.79E-05	2.38E-03	18.82567	4	0.04
regulation of organ growth	300	7.41E-05	2.58E-03	5.854405	8	0.08
muscle tissue morphogenesis	303	8.02E-05	2.76E-03	6.865293	7	0.07
cardiac atrium morphogenesis	304	8.02E-05	2.76E-03	11.58411	5	0.05
regulation of intracellular transport	306	8.13E-05	2.77E-03	3.529166	13	0.13
ventricular cardiac muscle tissue development	309	8.45E-05	2.86E-03	8.483715	6	0.06
morphogenesis of an epithelium	314	9.88E-05	3.28E-03	2.818979	17	0.17
regulation of cardiac muscle cell proliferation	315	1.03E-04	3.40E-03	8.184221	6	0.06
gap junction assembly	318	1.15E-04	3.78E-03	32.86493	3	0.03
muscle organ morphogenesis	319	1.18E-04	3.85E-03	6.449597	7	0.07
epithelial tube morphogenesis	320	1.22E-04	3.97E-03	3.030352	15	0.15

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
regulation of cardiac muscle tissue development	322	1.24E-04	4.02E-03	6.39381	7	0.07
positive regulation of cardioblast differentiation	324	1.29E-04	4.15E-03	31.64174	3	0.03
tissue morphogenesis	329	1.39E-04	4.40E-03	2.547119	19	0.19
muscle cell differentiation	337	1.59E-04	4.92E-03	3.521994	12	0.12
regulation of cardiac muscle tissue growth	338	1.63E-04	5.04E-03	7.509512	6	0.06
negative regulation of nitrogen compound metabolic process	343	1.84E-04	5.60E-03	2.084846	26	0.26
negative regulation of transcription, DNA-dependent	344	1.88E-04	5.69E-03	2.173046	24	0.24
muscle organ development	346	1.98E-04	5.97E-03	3.438438	12	0.12
cardiac ventricle formation	350	2.16E-04	6.45E-03	13.89182	4	0.04
positive regulation of stem cell differentiation	356	2.57E-04	7.53E-03	13.27277	4	0.04
negative regulation of RNA metabolic process	357	2.71E-04	7.92E-03	2.120624	24	0.24
regulation of tight junction assembly	358	2.84E-04	8.29E-03	24.12491	3	0.03
cardiocyte differentiation	366	3.53E-04	1.01E-02	4.645888	8	0.08
negative regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	368	3.69E-04	1.05E-02	5.336746	7	0.07
tube development	371	3.70E-04	1.04E-02	2.434048	18	0.18
caveola assembly	372	3.81E-04	1.07E-02	71.4661	2	0.02
blood vessel morphogenesis	373	3.88E-04	1.09E-02	2.719487	15	0.15
negative regulation of nucleobase-containing compound metabolic process	374	4.08E-04	1.14E-02	2.021039	25	0.25
pattern specification process	385	5.79E-04	1.57E-02	2.513343	16	0.16
negative regulation of cellular macromolecule biosynthetic process	387	6.09E-04	1.64E-02	2.00683	24	0.24
cellular response to extracellular stimulus	418	1.11E-03	2.76E-02	5.208432	6	0.06
cellular response to external stimulus	429	1.43E-03	3.47E-02	4.229112	7	0.07
lagging strand elongation	430	1.51E-03	3.66E-02	35.60409	2	0.02

Supplementary Table 5c: GO cellular component

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
voltage-gated sodium channel complex	1	2.74E-42	3.46E-39	206.3409	21	0.21
sodium channel complex	2	2.60E-41	1.64E-38	185.28	21	0.21
cation channel complex	4	7.06E-29	2.23E-26	15.25014	32	0.32
caveola	5	1.95E-26	4.92E-24	27.64923	23	0.23
ion channel complex	10	2.98E-21	3.77E-19	8.505308	32	0.32
integral to plasma membrane	13	7.01E-14	6.82E-12	3.145442	46	0.46
intrinsic to plasma membrane	14	2.50E-13	2.26E-11	3.038717	46	0.46
protein complex	19	3.65E-12	2.43E-10	2.114188	64	0.64
plasma membrane part	26	7.13E-10	3.47E-08	2.208306	52	0.52
voltage-gated potassium channel complex	33	3.88E-07	1.49E-05	8.36341	10	0.1
basolateral plasma membrane	42	2.18727E-05	6.59E-04	5.277137	10	0.1

Supplementary Table 5d: Human Phenotype

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
Torsade de pointes	1	9.11E-62	5.60E-58	477.6923	26	0.26
Ventricular arrhythmia	7	1.27E-55	1.11E-52	85.1162	34	0.34
Ventricular fibrillation	9	1.52E-51	1.04E-48	192.7478	26	0.26
Prolonged QT interval	15	2.90E-48	1.19E-45	143.9756	26	0.26
Atrial fibrillation	16	3.86E-48	1.48E-45	70.74319	31	0.31

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
Primary atrial arrhythmia	18	8.76E-48	2.99E-45	68.87866	31	0.31
Supraventricular tachycardia	19	9.02E-48	2.92E-45	68.81225	31	0.31
Supraventricular arrhythmia	20	3.04E-47	9.34E-45	66.14113	31	0.31
Abnormal EKG	21	3.61E-46	1.06E-43	88.87661	28	0.28
Syncope	22	4.92E-46	1.38E-43	87.89217	28	0.28
Arrhythmia	24	9.92E-43	2.54E-40	19.40566	42	0.42
Palpitations	26	3.21E-42	7.59E-40	137.1451	23	0.23
Tachycardia	27	8.96E-42	2.04E-39	43.83244	31	0.31
Lipoatrophy	33	1.22E-38	2.28E-36	53.5989	27	0.27
Sudden cardiac death	37	1.99E-36	3.30E-34	44.26903	27	0.27
Cardiac arrest	38	2.27E-36	3.68E-34	44.04376	27	0.27
Abnormality of adipose tissue	42	1.25E-34	1.84E-32	33.97156	28	0.28
Abnormality of cardiovascular system physiology	46	8.47E-32	1.13E-29	9.463796	44	0.44
Abnormality of cardiac ventricle	51	5.75E-29	6.93E-27	12.63251	35	0.35
Autosomal dominant inheritance	61	7.58E-26	7.64E-24	4.635263	56	0.56
Malformation of the heart and great vessels	63	7.76E-25	7.57E-23	6.157488	45	0.45
Abnormality of the heart	64	1.09E-24	1.05E-22	6.106177	45	0.45
Abnormality of the cardiovascular system	66	2.02E-23	1.88E-21	4.725592	51	0.51
Abnormality of muscle morphology	67	4.50E-23	4.13E-21	6.427283	41	0.41
Abnormality of the vasculature	75	1.38E-19	1.13E-17	7.459595	32	0.32
Shortened QT interval	93	2.93E-11	1.93E-09	63.40217	7	0.07
Aplasia of the pectoralis major muscle	103	6.97E-09	4.16E-07	79.66963	5	0.05
Hypoplastic left heart	123	6.13E-07	3.06E-05	32.0743	5	0.05
Hypoplastic heart	125	9.20E-07	4.53E-05	29.50443	5	0.05
Abnormality of the aorta	126	1.02E-06	4.96E-05	7.511795	10	0.1

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
Abnormality of the cardiac septa	132	2.11E-06	9.82E-05	4.617434	14	0.14
Atrioventricular canal defect	133	2.56E-06	1.18E-04	23.89849	5	0.05
Abnormality of the systemic arterial tree	136	3.35E-06	1.51E-04	5.814202	11	0.11
Defect in the atrial septum	173	4.10E-05	1.46E-03	4.896274	10	0.1
Abnormality of cardiac atrium	174	4.48E-05	1.58E-03	4.844632	10	0.1
Skin pits	269	8.28E-04	1.89E-03	9.696966	4	0.04
Secundum atrial septal defect	273	9.03E-04	2.03E-02	46.15891	2	0.02

Supplementary Table 5e: Disease ontology

# Term Name	Binom Rank	Binom Raw P-Value	Binom FDR Q-Val	Binom Fold Enrichment	Binom Observed Region Hits	Binom Region Set Coverage
sick sinus syndrome	1	3.47E-58	7.76E-55	1622.77	20	0.2
sudden infant death syndrome	3	5.18E-54	3.86E-51	61.69918	36	0.36
long QT syndrome	4	2.47E-52	1.38E-49	148.0153	28	0.28
congestive heart failure	8	5.69E-40	1.59E-37	47.27614	29	0.29
complex genetic disease	9	1.32E-36	3.27E-34	36.02883	29	0.29
heart failure	11	7.82E-36	1.59E-33	15.53121	39	0.39
medical disorder	13	5.40E-28	9.28E-26	4.972279	57	0.57
heart disease	15	2.09E-26	3.11E-24	6.484896	46	0.46
genetic disease	23	5.60E-18	5.44E-16	5.538534	36	0.36
congenital heart defect	25	7.46E-17	6.67E-15	18.53139	17	0.17
syndrome	29	5.99E-16	4.62E-14	2.833575	57	0.57
Romano-Ward syndrome	41	1.18E-13	6.43E-12	278.1592	6	0.06
cardiovascular system disease	44	3.05E-13	1.55E-11	2.394197	59	0.59
physical disorder	54	3.28E-10	1.36E-08	5.322649	21	0.21

heart septal defect	65	2.28E-08	7.84E-07	23.97941	7	0.07
atrial heart septal defect	74	5.11E-07	1.54E-05	33.29226	5	0.05
keratosis	83	3.57E-05	9.61E-04	9.930161	6	0.06
glaucoma	88	1.93E-04	4.92E-03	5.94135	7	0.07
ventricular septal defect	90	2.15E-04	05.22E-03	26.55344	3	0.03
nasopharynx carcinoma	116	1.89E-03	3.64E-02	3.573518	8	0.08
malignant neoplasm of oropharynx	119	2.24E-03	4.22E-02	29.01577	2	0.02

Supplementary Table 6: SNPs that are likely located at a binding site. Using RegulomeDB, we identified 308 SNPs that likely affect binding because they are located in regulatory regions of the genome. Positions are hg19. The scores reflect likeliness of the SNP to affect binding: 1: likely to affect binding and linked to the expression of a gene target, 2: likely to affect binding, and 3: less likely to affect binding.

Supplementary Table 6a: PR interval

Chr	Position	SNP	Score
1	112530430	rs75013985	2b
3	38172474	rs116544863	2b
3	38358796	rs73064832	2b
3	38359008	rs2268750	3a
3	38561307	rs17037814	2b
3	38647047	rs11711602	2b
3	38658057	rs73054554	3a
3	38685647	rs7372839	2b
3	38764782	rs4076737	3a
3	38767603	rs6799257	3a
3	38771994	rs9874633	2b
3	38778191	rs7428167	2b
3	38780971	rs9830687	2b
3	38796985	rs12630795	2a
3	38847152	rs7627881	3a
3	39025856	rs78768764	2b
4	86623373	rs1110777	2a
4	86629102	rs1871864	3a
4	86683729	rs11736641	3a
4	86699726	rs13105921	3a
5	172483023	rs29775	2b
5	172502618	rs2560324	2b
7	116003990	rs2157799	3a
7	116075363	rs67982517	3a
7	116078382	rs34645128	2b
7	116081121	rs4730738	1f
7	116083544	rs13221364	2b
7	116088721	rs1011441	3a
7	116090300	rs62471184	3a
7	116101588	rs62471189	3a
7	116104867	rs35505552	3a
7	116104911	rs35210394	3a
7	116109293	rs2188243	3a
7	116117587	rs35037267	3a
7	116125834	rs62468973	3a
7	116141778	rs3779511	2b
7	116142462	rs71529477	2b
7	116142808	rs11980719	2b
7	116145696	rs28587043	3a
7	116145957	rs4730743	3a
7	116150077	rs55701446	3a
7	116151784	rs3919515	2b
7	116169443	rs7778733	3a
7	116186241	rs3807989	3a
7	116187106	rs12672038	3a
7	116187690	rs12668226	3a
7	116194905	rs729949	2c
7	116203173	rs10280730	3a
7	116203323	rs10232369	3a
7	116217657	rs2109517	1d
12	24753152	rs1126279	2b
12	115128655	rs1910047	3a
12	115128768	rs35519587	2b
13	22115822	rs11616720	3a
13	47240876	rs7986036	2b
13	47241022	rs7987387	2b
13	47241289	rs7986508	3a
13	47242088	rs7993645	2b
13	47242761	rs4941564	2c
13	47243476	rs1886222	3a
14	71721797	rs61989250	2c
14	71729257	rs59697713	3a
14	71788946	rs12884929	2b
14	71789862	rs12891975	2b
14	71847117	rs61991243	2a
14	72022750	rs2108057	2c
14	72160321	rs7148679	2b

Supplementary Table 6b: QRS duration

Chr	Position	SNP	Score
1	61909126	rs12741766	3a
3	38172474	rs116544863	2b
3	38647047	rs11711602	2b
3	38658057	rs73054554	3a
3	38685647	rs7372839	2b
3	38764782	rs4076737	3a
3	38778191	rs7428167	2b
5	153871832	rs10054375	2c
5	153871841	rs10076436	2c
6	36617652	rs12207916	2b
6	36618821	rs1321313	2b
6	36621533	rs4713994	1f
6	36622900	rs1321311	1f
6	36623124	rs1321310	1d
6	36625272	rs6930671	1f
6	36625382	rs11969445	1d
6	36626322	rs6936993	1f
6	36628953	rs9462210	3a
6	36629444	rs10807170	1f
6	36629714	rs4713996	1f
6	36630525	rs9394368	1f
6	36632688	rs13196885	2b
6	36634156	rs6930083	1f
6	36636080	rs66761782	2b
6	36638175	rs4714001	1f
6	36638636	rs1321309	1f
6	36638691	rs1321308	1f
6	36645203	rs733590	1f
6	36645696	rs2395655	1f
6	36647680	rs4135240	2b
6	36648920	rs3176337	2b
6	36656256	rs12207548	3a
6	36668768	rs12528085	3a
6	36695519	rs236472	3a
6	36695661	rs236471	1f
6	36696330	rs236470	3b
6	36697201	rs236467	1b
6	36700437	rs86702	1f
6	118570990	rs281872	3a
6	118606000	rs283080	2b
6	118827252	rs62424199	3a
6	118846022	rs9481821	3a
6	118863789	rs12206329	3a
6	118876092	rs9481825	1f
6	118884092	rs12197337	3a
6	118884098	rs541442	3a
6	118895481	rs72952798	3a
6	118971913	rs62422235	2b
6	118986309	rs9320665	3a
6	118998481	rs2638550	3a
6	119027325	rs7746210	2b
7	35302017	rs1362209	2b
10	114455827	rs6585173	1f
10	114468438	rs7907540	1f
10	114481022	rs17585548	2b
10	114482409	rs6585179	3a
10	114506292	rs7096151	1f
10	114514051	rs6585184	3a
14	71698616	rs7156194	1b
14	71704261	rs57204407	2b
14	71704684	rs7160587	2b
14	71705928	rs61989239	3a
14	71712185	rs55896578	3a
14	71721797	rs61989250	2c
14	71729257	rs59697713	3a
14	71733790	rs17767362	1f
14	71757679	rs68073803	2b
14	71767848	rs71305837	3a
14	71788946	rs12884929	2b
14	71789862	rs12891975	2b
14	71847117	rs61991243	2a
14	71861278	rs34528131	3a
14	72022750	rs2108057	2c
14	72023489	rs7142343	3a
14	72030809	rs10135680	3a
14	72160321	rs7148679	2b

Supplementary Table 6c: QT interval

Chr	Position	SNP	Score
1	162005477	rs75192393	2b
1	162006862	rs12123710	3a
1	162010693	rs6666546	2b
1	162010787	rs10158975	3a
1	162024987	rs10429888	2b
1	162027992	rs7547308	3a
1	162033890	rs12143842	2b
1	162040305	rs12096347	2b
1	162040878	rs16849113	3a
1	162050670	rs144846894	3a
1	162101829	rs12093845	1f
1	162103510	rs10918723	3a
1	162103672	rs10918724	3a
1	162103772	rs61007280	3a
1	162104658	rs1337072	1d
1	162104763	rs1337071	1f
1	162105094	rs6663393	1f
1	162106150	rs10918732	1f
1	162106525	rs12090201	1f
1	162106636	rs12087337	1f
1	162106962	rs1415265	2b
1	162106967	rs1415264	2b
1	162112082	rs59127492	3a
1	162118984	rs10918762	3a
1	162122448	rs12064771	1a
1	162129466	rs144958472	2b
1	162129546	rs12068421	2b
1	162166919	rs6663969	2b
1	162182677	rs3934467	3a
1	162185546	rs4657173	2b
1	162191412	rs6683968	1f
1	162194498	rs3923374	1f
1	162196530	rs3923368	1f
1	162196574	rs3923367	1f
1	162210610	rs4657178	3a
1	162217432	rs7541606	2b
1	162217459	rs10918974	3a
1	162219101	rs4656362	2b
1	162249697	rs6659953	3a
1	162249715	rs6670958	2c
1	162255112	rs10800404	2b
1	162255286	rs6680461	3a
1	162255385	rs4657181	2b
1	162263270	rs10919096	2b
1	162263712	rs6692467	3a
1	162263714	rs386636157	3a
1	162317513	rs347273	2b
1	162319524	rs11577628	3a
1	169072992	rs79011457	2b
1	169073002	rs12079856	2b
1	169073384	rs1892093	3a
1	169073388	rs1320977	3a
1	169074268	rs75505858	2b
1	169074736	rs1534984	2b
1	169075348	rs12751593	2b
1	169079020	rs1200133	2b
1	169088679	rs2143290	1f
1	169088947	rs10919062	1f
1	169098734	rs72706963	3a
1	169099037	rs10919070	1f
1	169102340	rs12035622	1f
1	169163017	rs3766074	2b
1	169219185	rs114089179	3a
1	169453703	rs72706084	2b
1	169455435	rs2056926	2b
6	118570990	rs281872	3a
6	118606000	rs283080	2b
6	118630300	rs283043	3a
6	118827252	rs62424199	3a
6	118846022	rs9481821	3a
6	118847551	rs79477297	3a
6	118863789	rs12206329	3a
6	118876092	rs9481825	1f
6	118884092	rs12197337	3a
6	118884098	rs541442	3a
6	118895481	rs72952798	3a
6	118901793	rs9489448	2c
6	118971913	rs62422235	2b
6	118973953	rs9489486	3a
6	118986309	rs9320665	3a
6	118998481	rs2638550	3a
6	118998633	rs17349133	3a
6	119007427	rs62422258	3a

6	119027325	rs7746210	2b
7	150573236	rs4725974	3a
7	150573270	rs35399955	3a
7	150620701	rs6972137	2b
7	150640285	rs1547958	2b
7	150644394	rs3815459	2b
7	150655643	rs758890	2b
7	150657201	rs12668582	3a
7	150657209	rs6947240	1f
7	150658678	rs35760656	3a
7	150659051	rs3778874	2b
7	150661633	rs7789585	3a
11	2484803	rs2074238	2a
11	61549458	rs174534	1b
11	61565908	rs174541	3a
11	61569830	rs174546	1f
11	61570783	rs174547	1d
11	61571348	rs174548	1f
11	61571382	rs174549	1f
11	61579463	rs174554	3a
11	61579760	rs174555	1f
11	61580635	rs174556	1f
11	61582708	rs174561	2b
11	61593816	rs174568	1f
11	61596633	rs99780	2b
11	61597972	rs1535	1b
11	61603510	rs174576	1f
11	61604814	rs174577	1f
11	61609750	rs174583	1f
16	11692658	rs7191330	1f
16	11701021	rs72781039	3a
16	11707291	rs9932684	1a
16	11707567	rs9932278	2b
16	58529615	rs4356470	1f
16	58549932	rs4784046	2b
16	58550052	rs185639574	2b
16	58616984	rs17854029	3a
16	58648453	rs28580327	3a
16	58649139	rs1549605	3a
16	58671928	rs149166	3a
16	58686600	rs154439	2b
17	33307586	rs12945428	2b
17	33324382	rs2074518	1f
17	33331575	rs1052536	1f
17	33332629	rs12948362	1f
17	33341834	rs2074519	1f
17	33353332	rs3926358	1f
17	33382801	rs2339122	1f
17	33383030	rs1634800	1f
17	33414758	rs797989	1f
21	35969194	rs112728994	3a

Supplementary Table 6d: RR interval

Chr	Position	SNP	Score
1	208136236	rs650470	2b
6	121837314	rs9385199	3a
6	121941164	rs55993325	3a
6	121984911	rs11755453	3a
6	122138479	rs9388008	2b
6	122149831	rs9375064	3a
6	122171052	rs1919875	2b
6	122179724	rs79047865	3a
7	100465355	rs12705089	2b
7	100473550	rs12705092	2b
7	100494949	rs17883557	2b
7	100494959	rs17881088	2b
7	100494960	rs76181418	2b
7	100516003	rs10278546	1f
7	100518458	rs12705099	1f
12	33516963	rs1905408	3a
12	33529288	rs9888363	3b
12	33593127	rs6488162	3a
14	23868285	rs439735	1f
14	23873092	rs388914	1f
14	23874523	rs2277474	1f
14	23882144	rs2284651	1f
14	23882855	rs2331979	1f
14	23885887	rs3729829	1f
14	23888040	rs12894524	1f
14	23890982	rs743567	1f
20	36838422	rs6127448	2b
20	36839297	rs3746467	2b
20	36841914	rs3746471	3a
20	36842836	rs6024001	3a
20	36843334	rs6127467	3a

References

1. Pardo LM, MacKay I, Oostra B, van Duijn CM, Aulchenko YS. The effect of genetic drift in a young genetically isolated population. *Ann Hum Genet*. 2005;69:288-295.
2. Scholtens S, Smidt N, Swertz MA, Bakker SJ, Dotinga A, Vonk JM, et al. Cohort profile: Lifelines, a three-generation cohort study and biobank. *Int J Epidemiol*. 2015;44:1172-1180.
3. Boomsma DI, de Geus EJ, Vink JM, Stubbe JH, Distel MA, Hottenga JJ, et al. Netherlands twin register: From twins to twin families. *Twin Res Hum Genet*. 2006;9:849-857.
4. Willemsen G, de Geus EJ, Bartels M, van Beijsterveldt CE, Brooks AI, Estourgie-van Burk GF, et al. The netherlands twin register biobank: A resource for genetic epidemiological studies. *Twin Res Hum Genet*. 2010;13:231-245.
5. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation*. 2002;106:1777-1782.
6. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM, et al. The design of a prospective study of pravastatin in the elderly at risk (prosper). Prosper study group. Prospective study of pravastatin in the elderly at risk. *Am J Cardiol*. 1999;84:1192-1197.
7. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (prosper): A randomised controlled trial. *Lancet*. 2002;360:1623-1630.
8. Trompet S, de Craen AJ, Postmus I, Ford I, Sattar N, Caslake M, et al. Replication of ldl gwas hits in prosper/phase as validation for future (pharmaco)genetic analyses. *BMC Med Genet*. 2011;12:131.
9. Ikram MA, van der Lugt A, Niessen WJ, Krestin GP, Koudstaal PJ, Hofman A, et al. The rotterdam scan study: Design and update up to 2012. *Eur J Epidemiol*. 2011;26:811-824.
10. Harris TB, Launer LJ, Eiriksdottir G, Kjartansson O, Jonsson PV, Sigurdsson G, et al. Age, gene/environment susceptibility-reykjavik study: Multidisciplinary applied phenomics. *Am J Epidemiol*. 2007;165:1076-1087.
11. The atherosclerosis risk in communities (aric) study: Design and objectives. The aric investigators. *Am J Epidemiol*. 1989;129:687-702.
12. Caulfield M, Munroe P, Pembroke J, Samani N, Dominiczak A, Brown M, et al. Genome-wide mapping of human loci for essential hypertension. *Lancet*. 2003;361:2118-2123.
13. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The cardiovascular health study: Design and rationale. *Ann Epidemiol*. 1991;1:263-276.
14. Tobin MD, Tomaszewski M, Braund PS, Hajat C, Raleigh SM, Palmer TM, et al. Common variants in genes underlying monogenic hypertension and hypotension and blood pressure in the general population. *Hypertension*. 2008;51:1658-1664.

15. Girotto G, Pirastu N, Sorice R, Biino G, Campbell H, d'Adamo AP, et al. Hearing function and thresholds: A genome-wide association study in european isolated populations identifies new loci and pathways. *J Med Genet*. 2011;48:369-374.
16. Jorgensen T, Borch-Johnsen K, Thomsen TF, Ibsen H, Glumer C, Pisinger C. A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: Baseline results inter99. *Eur J Cardiovasc Prev Rehabil*. 2003;10:377-386.
17. Taylor HA, Jr., Wilson JG, Jones DW, Sarpong DF, Srinivasan A, Garrison RJ, et al. Toward resolution of cardiovascular health disparities in african americans: Design and methods of the jackson heart study. *Ethn Dis*. 2005;15:S6-4-17.
18. Holle R, Happich M, Lowel H, Wichmann HE, Group MKS. Kora--a research platform for population based health research. *Gesundheitswesen*. 2005;67 Suppl 1:S19-25.
19. Wichmann HE, Gieger C, Illig T, Group MKS. Kora-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen*. 2005;67 Suppl 1:S26-30.
20. Moayyeri A, Hammond CJ, Hart DJ, Spector TD. The uk adult twin registry (twinsuk resource). *Twin Res Hum Genet*. 2013;16:144-149.
21. Raitakari OT, Juonala M, Ronnemaa T, Keltikangas-Jarvinen L, Rasanen L, Pietikainen M, et al. Cohort profile: The cardiovascular risk in young finns study. *Int J Epidemiol*. 2008;37:1220-1226.
22. McLean CY, Bristor D, Hiller M, Clarke SL, Schaar BT, Lowe CB, et al. Great improves functional interpretation of cis-regulatory regions. *Nat Biotechnol*. 2010;28:495-501.

Funding

The Age, Gene/Environment Susceptibility Reykjavik Study is funded by National Institutes of Health [N01-AG-12100], the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament), in addition an Intramural Research Program Award [ZIAEY000401] from the National Eye Institute, an award from the National Institute on Deafness and Other Communication Disorders (NIDCD) Division of Scientific Programs [IAA Y2-DC_1004-02]. The study is approved by the Icelandic National Bioethics Committee, VSN: 00-063.

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]. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. Additional funding was provided by American Heart Association grant [16EIA26410001] (A.A.).

BRIGHT was funded by the Medical Research Council of Great Britain [grant number: G9521010D]. This work forms part of the research themes contributing to the translational research portfolio for the NIHR Barts Cardiovascular Biomedical Research Unit. The funders had no role in study design, data collection and analysis.

This CHS research was supported by National Heart, Lung, and Blood Institute [contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, HHSN268200960009C, HL080295, HL087652, HL105756, HL103612] with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org/.

The ERF study as a part of EUROSPAN (European Special Populations Research Network) was supported by European Commission FP6 STRP grant number 018947 [LSHG-CT-2006-01947] and also received funding from the European Community's Seventh Framework Programme (FP7/2007-2013)/grant agreement HEALTH-F4-2007-201413 by the European Commission under the programme “Quality of Life and Management of the Living Resources” of 5th Framework Programme [no. QLG2-CT-2002-01254]. The ERF study was further supported by ENGAGE consortium and CMSB. High-throughput analysis of the ERF data was supported by joint grant from Netherlands Organisation for Scientific Research and the Russian Foundation for Basic Research [NWO-RFBR 047.017.043].

The GRAPHIC study was funded by the British Heart Foundation.

Inter99 was financially supported by research grants from the Danish Research Council, the Danish Centre for Health Technology Assessment, Novo Nordisk Inc., Research Foundation of Copenhagen County, Ministry of Internal Affairs and Health, the Danish Heart Foundation, the Danish Pharmaceutical Association, the Augustinus Foundation, the Ib Henriksen Foundation, the Becket Foundation, and the Danish Diabetes Association. The Novo Nordisk Foundation Center for Basic Metabolic Research is an independent Research Center at the University of Copenhagen partially funded by an unrestricted donation from the Novo Nordisk Foundation (www.metabol.ku.dk).

The JHS is supported by the National Heart, Lung, and Blood Institute [contracts HHSN268201300046C, HHSN268201300047C, HHSN268201300048C, HHSN268201300049C, HHSN268201300050C] and the National Institute on Minority Health and Health Disparities. J.G.W. is supported by the National Institute of General Medical Sciences [U54GM115428].

The LifeLines Cohort Study, and generation and management of GWAS genotype data for the LifeLines Cohort Study is supported by the Netherlands Organization of Scientific Research NWO [grant 175.010.2007.006], the Economic Structure Enhancing Fund (FES) of the Dutch government, the Ministry of Economic Affairs, the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the Northern Netherlands Collaboration of Provinces (SNN), the Province of Groningen, University Medical Center Groningen, the University of Groningen, Dutch Kidney Foundation and Dutch Diabetes Research Foundation. N.V. is supported by Marie Sklodowska-Curie GF [call: H2020-MSCA-IF-2014, Project ID: 661395]

The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC-Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ.

Netherland Twin Register (NTR): Funding was obtained from the Netherlands Organization for Scientific Research (NWO) and The Netherlands Organisation for Health Research and Development (ZonMW) grants 904-61-090, 985-10-002, 912-10-020, 904-61-193,480-04-004, 463-06-001, 451-04-034, 400-05-717, Addiction-31160008, 016-115-035, 481-08-011, 056-32-010, Middelgroot-911-09-032, OCW_NWO Gravity program –024.001.003, NWO-Groot 480-15-001/674, Center for Medical Systems Biology (CSMB, NWO Genomics), NBIC/BioAssist/RK(2008.024), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI –NL, 184.021.007 an 184.033.111); Spinozapremie (NWO- 56-464-14192), KNAW Academy Professor Award (PAH/6635) and University Research Fellow grant (URF) to

DIB; Amsterdam Public Health research institute (former EMGO+) , Neuroscience Amsterdam research institute (former NCA) ; the European Science Foundation (ESF, EU/QLRT-2001-01254), the European Community's Seventh Framework Program (FP7- HEALTH-F4-2007-2013, grant 01413: ENGAGE and grant 602768: ACTION); the European Research Council (ERC Advanced, 230374, ERC Starting grant 284167), Rutgers University Cell and DNA Repository (NIMH U24 MH068457-06), the National Institutes of Health (NIH, R01D0042157-01A1, R01MH58799-03, MH081802, DA018673, R01 DK092127-04, Grand Opportunity grants 1RC2 MH089951, and 1RC2 MH089995); the Avera Institute for Human Genetics, Sioux Falls, South Dakota (USA). Part of the genotyping and analyses were funded by the Genetic Association Information Network (GAIN) of the Foundation for the National Institutes of Health. Computing was supported by NWO through grant 2018/EW/00408559, BiG Grid, the Dutch e-Science Grid and SURFSARA.

PREVEND genetics is supported by the Dutch Kidney Foundation [Grant E033], the National Institutes of Health [grant LM010098], The Netherlands Organization for Scientific Research [NWO-Groot 175.010.2007.006, NWO VENI grant 916.761.70 and NWO VIDI grant 917.13.350], ZonMW [90.700.441], and the Dutch Inter University Cardiology Institute Netherlands.

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].

The generation and management of GWAS genotype data for the Rotterdam Study (RS I, RS II, RS III) was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands. The GWAS datasets are supported by the Netherlands Organisation of Scientific Research NWO Investments [nr. 175.010.2005.011, 911-03-012], the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Research Institute for Diseases in the Elderly [014-93-015; RIDE2], the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) Netherlands Consortium for Healthy Aging (NCHA) [project nr. 050-060-810]. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam.

TwinsUK was funded by a grant from the British Heart Foundation [PG/12/38/29615].
The Young Finns Study has been financially supported by the Academy of Finland [grants 286284, 134309 (Eye), 126925, 121584, 124282, 129378

(Salve), 117787 (Gendi), and 41071 (Skidi)]; the Social Insurance Institution of Finland; Kuopio, Tampere and Turku University Hospital Medical Funds [grant X51001]; Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation of Cardiovascular Research; Finnish Cultural Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; and Yrjö Jahnsson Foundation.

Acknowledgments

AGES
The researchers are indebted to the participants for their willingness to participate in the study.

ARIC
The authors thank the staff and participants of the ARIC study for their important contributions.

BRIGHT
The BRIGHT study is extremely grateful to all the patients who participated in the study and the BRIGHT nursing team.

ERF
We are grateful to all study participants and their relatives, general practitioners and neurologists for their contributions to the ERF study and to P Veraart for her help in genealogy, J Vergeer for the supervision of the laboratory work and P Snijders for his help in data collection.

Inter99
The Inter99 was initiated by Torben Jørgensen (PI), Knut Borch-Johnsen (co-PI), Hans Ibsen and Troels F. Thomsen. The steering committee comprises the former two and Charlotta Pisinger.

JHS
We thank the Jackson Heart Study (JHS) participants and staff for their contributions to this work.

RS
We thank Pascal Arp, Mila Jhamai, Marijn Verkerk, Lizbeth Herrera and Marjolein Peters, MSc, and Carolina Medina-Gomez, MSc, for their help in creating the GWAS database, and Karol Estrada, PhD, Yurii Aulchenko, PhD, and Carolina Medina-Gomez, MSc, for the creation and analysis of imputed data. The authors are grateful to the study participants, the staff from the Rotterdam Study and the participating general practitioners and pharmacists. We would like to thank Karol Estrada PhD, Fernando Rivadeneira PhD, and Anis Abuseiris (Erasmus MC Rotterdam, The Netherlands), for their help in creating GRIMP, and we thank BigGRID for access to their grid computing resources.

YFS
The expert technical assistance in the statistical analyses by Irina Lisinen is gratefully acknowledged.