SUPPLEMENTARY MATERIAL: Common variants in 22 loci are associated with QRS duration and cardiac ventricular conduction

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DETAILS ON PARTICIPATING STUDIES:

Fourteen genome-wide association studies (GWAS) consisting of individuals of European descent from Europe and the United States contributed to the discovery phase of this study. To extend our analyses, we genotyped select variants representing nine loci in an additional cohort (PREVEND). All studies received approval from the appropriate institutional review committees, and the subjects in each cohort provided written informed consent.

AGES: The Age, Gene/Environment Susceptibility (AGES) Reykjavik Study was initiated to examine genetic susceptibility and gene/environment interaction as these contribute to phenotypes common in old age, and represents a continuation of the Reykjavik Study cohort begun in 1967 and is comprised of 5776 randomly recruited survivors from the original cohort. QRS interval duration was automatically measured from 12-lead electrocardiograms using the Marquette 12 SL analysis program (General Electric Marquette Medical Division, Milwaukee, Wisconsin, USA).

ARIC: The Atherosclerosis Risk in Communities study (http://www.cscc.unc.edu/aric/) includes 15,792 men and women from four communities in the United States (Jackson, Mississippi; Forsyth County, North Carolina; Washington County, Maryland; suburbs of Minneapolis, Minnesota) enrolled in 1987–1989 and prospectively followed. ECGs were recorded at baseline using MAC PC ECG machines (Marquette Electronics) and processed initially by the Dalhousie ECG program in a central laboratory at the EPICORE Center (University of Alberta). Processing was later repeated for the present study using the GE Marquette 12-SL program (2001 version) at the EPICARE Center (Wake Forest University). All ECGs were visually inspected for technical errors and inadequate quality. QRS interval was measured automatically from baseline ECGs.

BRIGHT: The MRC BRIGHT study (http://www.brightstudy.ac.uk/) comprises 2000 severely hypertensive probands ascertained from families with multiplex affected sibships or as parent-offspring trios. Case ascertainment and phenotyping has been described previously. Briefly, cases have BP readings ≥150/100 mmHg based on one reading or ≥145/95 mmHg based on the mean of three readings. Twelve-lead ECG recordings (Siemens-Sicard 440; http://www.brightstudy.ac.uk/info/sop04.html), which produces an

automated measurement of the QRS interval, were available for all subjects. All data were transferred from each recruitment centre by electronic modem to electrophysiologists from the West of Scotland Primary Prevention Study (Professor Peter MacFarlane) for central reporting. All individuals included in the analysis were of white British ancestry (up to level of grandparents).

CHS: The Cardiovascular Health Study (www.chs-nhlbi.org) is a prospective, longitudinal cohort study of risk factors for cardiovascular disease in the elderly, was begun in 1989 and included 4,925 self-described White participants. People 65 years of age or older were recruited from four field centers in the United States. The CHS study sample used in this analysis includes participants without clinically-recognized cardiovascular disease at baseline who described their race as White, consented to genetic testing, and had DNA available for genotyping. Study electrocardiograms were recorded using MAC PC ECG machines (Marquette Electronics, Milwaukee, Wisconsin) 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, North Carolina). All ECGs were visually inspected for technical errors and inadequate quality. QRS interval was measured using the baseline ECG for eligible subjects. 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, Wisconsin).

ERF: The Erasmus Rucphen Family study 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 minimum of five 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 QRS intervals were made using the Modular ECG Analysis

System (MEANS). The QRS detector of MEANS operates on multiple simultaneously recorded leads, which are transformed to a detection function that brings out the QRS complexes among the other parts of the signal. Data collection started in June 2002 and was completed in February 2005. In the current analyses, 1466 participants for whom complete phenotypic, genotypic and genealogical information was available were studied.

FHS: The Framingham Heart Study (http://www.framinghamheartstudy.org/) is a community-based, longitudinal cohort study comprising three generations of individuals in multigenerational pedigrees and additional unrelated individuals. The current study included individuals from Generation 1 (11th examination), Generation 2 (1st examination) and Generation 3 (1st examination). In FHS, paper electrocardiograms recorded on Marquette machines were scanned and digital caliper measurements were made using proprietary software (eResearchTechnology, generations 1 and 2) or using Rigel 1.7.2. (AMPS, LLC, New York, NY, USA, generation 3). The QRS duration was measured from the Q-onset to S-offset in two cardiac cycles from lead II and averaged.

KORA F3 and S4: The KORA study is a series of independent population-based epidemiological surveys of participants living in the city of Augsburg, Southern Germany, or the two adjacent counties. All survey participants are residents of German nationality identified through the registration office and aged between 25 and 74 years at recruitment. The baseline survey KORA S3 was conducted in the years 1994/95 and KORA S4 in 1999-2001. 3,006 participants from KORA S3 were reexamined in a 10-year follow-up (KORA F3) in the years 2004/05. Genomewide data for the analysis of the length of the QRS interval is available for random subsets of 1,644 persons from KORA F3 and 1,814 study participants from KORA S4. In both studies, 12-lead resting electrocardiograms were recorded with digital recording systems (F3: Mortara Portrait, Mortara Inc., Milwaukee, USA, S4: Hörmann Bioset 9000, Hörmann Medizinelektronik, Germany).

KORKULA: The KORCULA study sampled Croatians from the Adriatic island of Korcula, between the ages of 18 and 88. The fieldwork was performed in 2007 in the eastern part of the island, targeting healthy volunteers from the town of Korčula and the villages of Lumbarda, Žrnovo and Račišće. Mortara ELI 350 was used in ECG recording.

MICROS: The MICROS study (http://www.biomedcentral.com/1471-2350/8/29) is part of the genomic health care program 'GenNova' and was carried out in three villages of the Val Venosta on the populations of Stelvio, Vallelunga and Martello. This study was an extensive survey carried out in South Tyrol (Italy) in the period 2001-2003. Study participants were volunteers from three isolated villages located in the Italian Alps, in a German-speaking region bordering with Austria and Switzerland. Due to geographical, historical and political reasons, the entire region experienced a prolonged period of isolation from surrounding populations. Genotyping was performed on just under 1400 participants with 1334 available for analysis after data cleaning. Information on participants' health status was collected through a standardized questionnaire and clinical examinations, including digitized ECG measurements (Mortara Portrait, Mortara Inc., Milwaukee, USA). Individuals with identified U-waves were excluded from analysis. The Mortara portrait determines QRS complex by a proprietary algorithm (Michelucci 2002). Laboratory data were obtained from standard blood analyses.

ORCADES: The Orkney Complex Disease Study (ORCADES) is an ongoing family-based, cross-sectional study in the isolated Scottish archipelago of Orkney. Genetic diversity in this population is decreased compared to Mainland Scotland, consistent with high levels of endogamy historically. Participants included here were aged 18-92 years and came from a subgroup of ten islands. The Cardioview ECG device was used in the phenotyping.

ROTTERDAM STUDY (RS1 and RS2): The Rotterdam Study is a prospective population-based cohort study comprising 7,983 subjects aged 55 years or older (RS-I), which started in 1990. In 2000-2001, an additional 3,011 individuals aged 55 years or older were recruited (RS-II).[28] In the RS-I and RS-II, electrocardiograms were recorded on ACTA electrocardiographs (ESAOTE, Florence, Italy) and digital measurements of the QRS intervals were made using the Modular ECG Analysis System (MEANS). The QRS detector of MEANS operates on multiple simultaneously recorded leads, which are transformed to a detection function that brings out the QRS complexes among the other parts of the signal.

SHIP: The Study of Health in Pomerania (http://ship.community-medicine.de) is a longitudinal population-based cohort study in West Pomerania, a region in the northeast of Germany. From the total population comprising 212,157 inhabitants in 1995, a two-stage

stratified cluster sample of adults aged 20 to 79 years was drawn. From the net sample of 6265 eligible subjects, 4308 subjects (2192 women) of Caucasian origin participated in the baseline examination, SHIP-0 (response 68.8%). For the present analyses both electrocardiographic and genotyping data were available from 2985 participants of the SHIP baseline cohort without exclusion criteria. QRS intervals in SHIP were measured from digitally stored electrocardiograms (Personal 120LD, Esaote, Genova, Italy) using MEANS according to the method described above for the RS.

SPLIT: The SPLIT study samples Croatians from the town of Split, between the ages 18 and 85. The sampling started in 2008, and continues throughout 2010. Mortara ELI 350 was used in ECG recording.

TWINSUK: The Twins UK Registry (http://www.twinsuk.ac.uk) comprises unselected, mostly female volunteers ascertained from the general population through national media campaigns in the UK. Means and ranges of quantitative phenotypes in Twins UK were similar to an age-matched singleton sample from the general population. Zygosity was determined by standardized questionnaire and confirmed by DNA fingerprinting. QRS duration data were available on 2,726 of these individuals measured automatically by the Cardiofax ECG-9020K (Nihon Kohden UK Ltd., Middlesex, UK).

PREVEND: The Prevention of REnal and Vascular ENd stage Disease (PREVEND) study is an ongoing prospective study investigating the natural course of increased levels of urinary albumin excretion and its relation to renal and cardiovascular disease. Inhabitants 28 to 75 years of age (n=85,421) in the city of Groningen, The Netherlands, were asked to complete a short questionnaire, 47% responded, and individuals were then selected with a urinary albumin concentration of at least 10 mg/L (n = 7,768) and a randomly selected control group with a urinary albumin concentration less than 10 mg/L (n = 3,395). Details of the protocol have been described elsewhere (www.prevend.org). Standard 12-lead electrocardiograms were recorded with CardioPerfect equipment (Cardio Control; currently Welch Allyn, Delft, The Netherlands) and digital measurements of the QRS intervals were made using the Modular ECG Analysis System (MEANS). The QRS detector of MEANS operates on multiple simultaneously recorded leads, which are transformed to a detection function that brings out the QRS complexes among the other parts of the signal.

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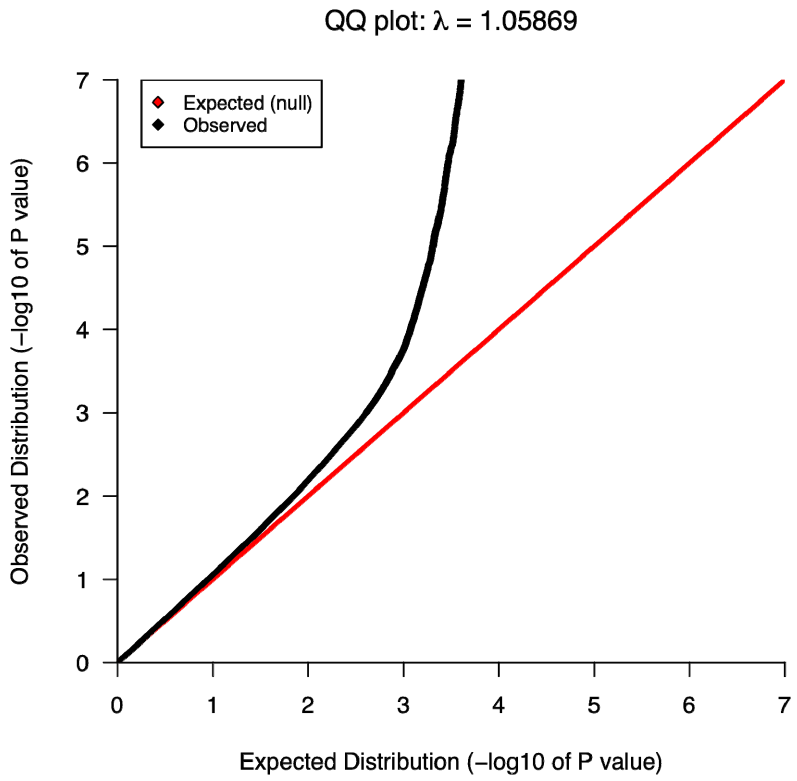
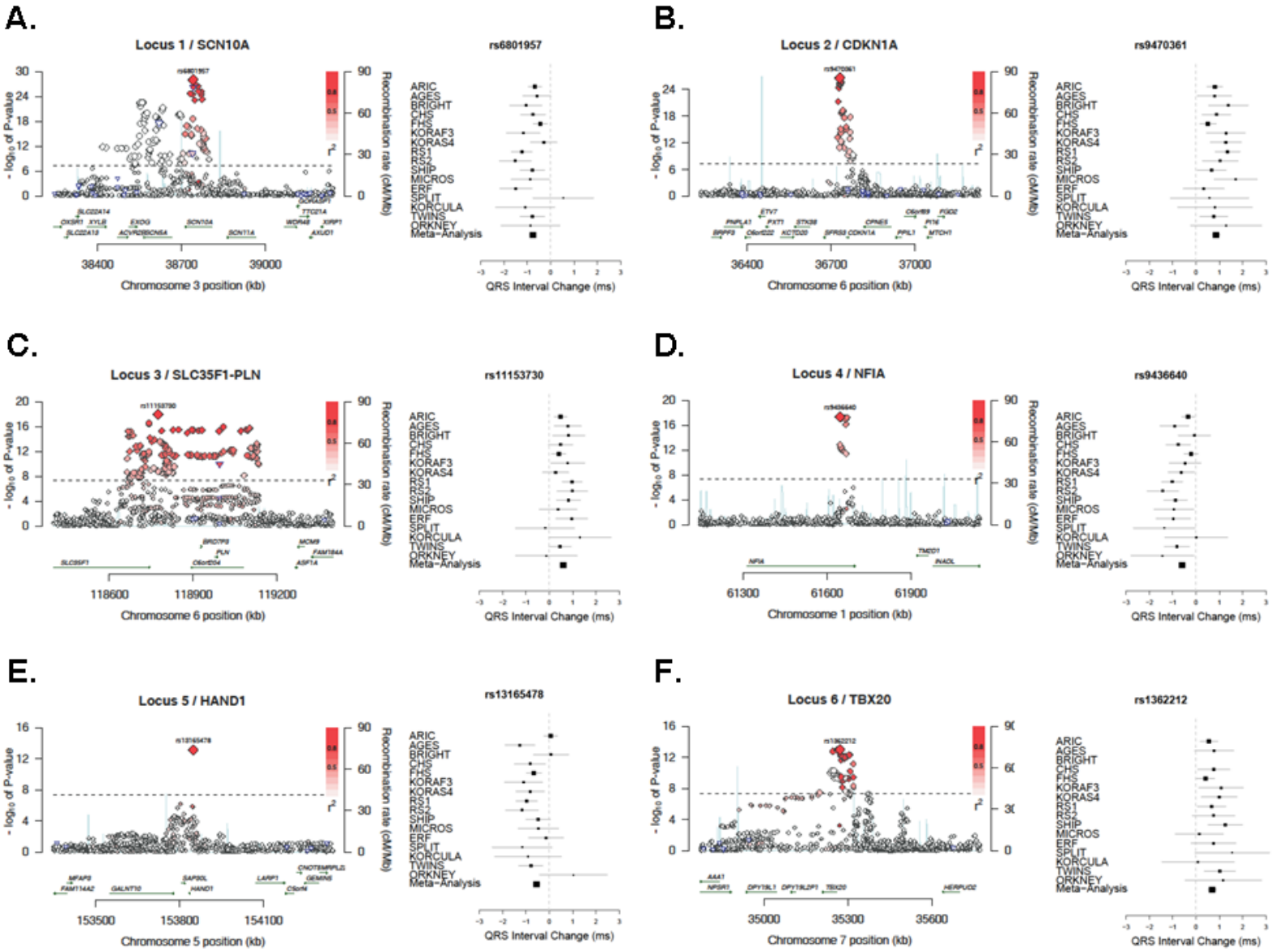
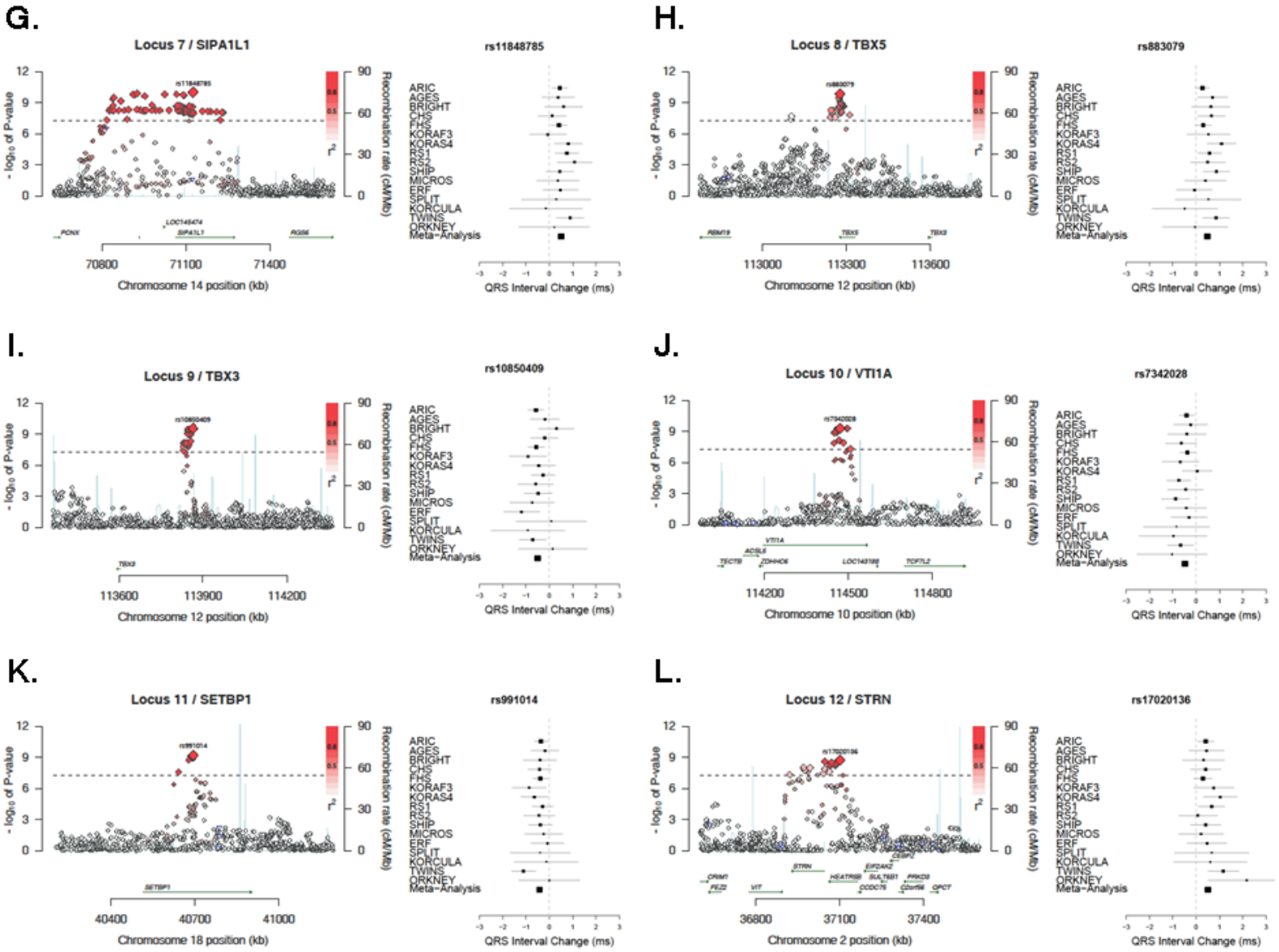
SUPPLEMENTARY FIGURES:

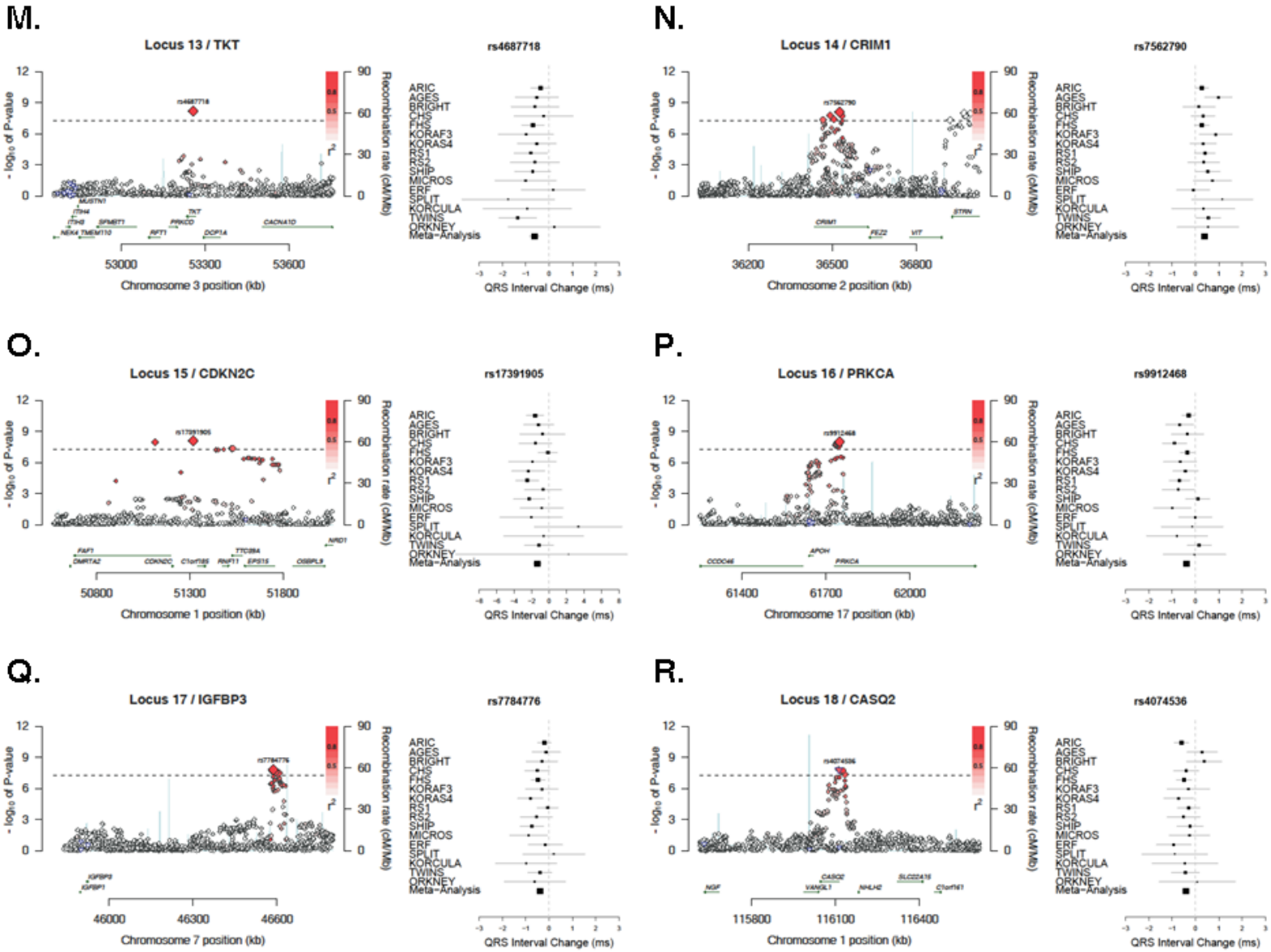
Supplementary Figure 1: Q-Q plot. The quantile-quantile (Q-Q) plots demonstrate robust behavior in the bulk of the distribution (lower-left corner) (consistent with a modest λ_{GC} of 1.05). In the tail of the distribution, we observe a departure away from the null hypothesis, presumably due to the presence of true associations.



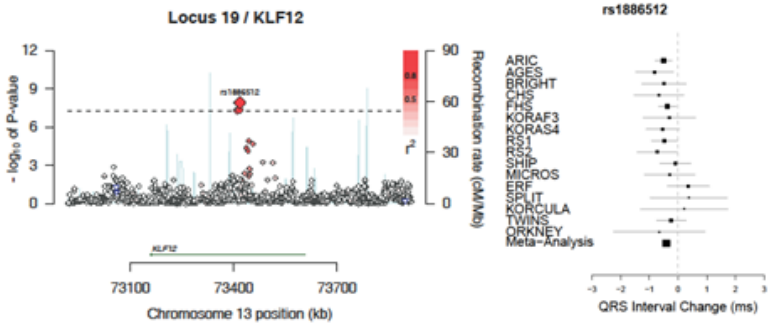
Supplementary Figure 2: Regional association plots. Association results at each significantly associated locus. Loci are displayed in the order listed in **Table 1**. Each SNP is plotted with respect to its chromosomal location (x-axis) and its *P*-value (y-axis on the left). Each panel spans approximately ±500 kb around each index SNP and has known gene transcripts annotated at the bottom. The SNPs are colored according to their degree of linkage disequilibrium (r^2) with the index variant which is highlighted with a red diamond and displayed by rs number and significance level achieved in the meta-analysis. The triangles indicate coding region SNPs. The tall blue spikes indicate the recombination rate (y-axis on the right) at that region of the chromosome. To the right of each association plot is the forest plot detailing the findings at the level of the individual study.


A.
Locus 1 / SCN10A
rs6801957
- log10 of P-value
Recombination rate (cM/Mb)
Chromosome 3 position (kb)
QRS Interval Change (ms)
B.
Locus 2 / CDKN1A
rs9470361
Chromosome 6 position (kb)
QRS Interval Change (ms)
C.
Locus 3 / SLC35F1-PLN
rs11153730
Chromosome 6 position (kb)
QRS Interval Change (ms)
D.
Locus 4 / NFIA
rs9436640
Chromosome 1 position (kb)
QRS Interval Change (ms)
E.
Locus 5 / HAND1
rs13165478
Chromosome 5 position (kb)
QRS Interval Change (ms)
F.
Locus 6 / TBX20
rs1362212
Chromosome 7 position (kb)
QRS Interval Change (ms)
ARIC
AGES
BRIGHT
CHS
FHS
KORAF3
KORAS4
RS1
RS2
SHIP
MICROS
ERF
SPLIT
KORCULA
TWINS
ORKNEY
Meta−Analysis

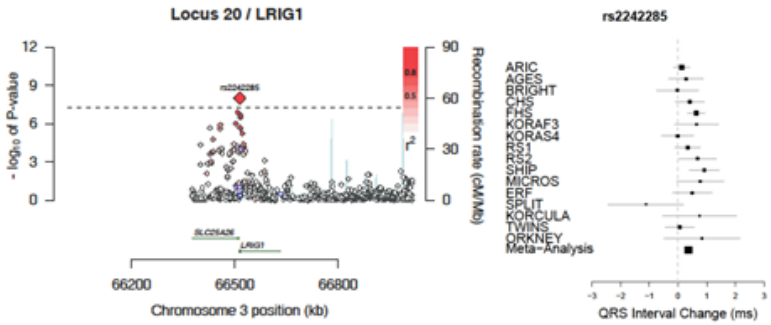

G.
Locus 7 / SIPA1L1
rs11848785
- log10 of P-value
Recombination rate (cM/Mb)
r2
ARIC
AGES
BRIGHT
CHS
FHS
KORAF3
KORAS4
RS1
RS2
SHIP
MICROS
ERF
SPLIT
KORCULA
TWINS
ORKNEY
Meta−Analysis
70800
71100
71400
Chromosome 14 position (kb)
QRS Interval Change (ms)
H.
Locus 8 / TBX5
rs883079
113000
113300
113600
Chromosome 12 position (kb)
QRS Interval Change (ms)
I.
Locus 9 / TBX3
rs10850409
113600
113900
114200
Chromosome 12 position (kb)
QRS Interval Change (ms)
J.
Locus 10 / VTI1A
rs7342028
114200
114500
114800
Chromosome 10 position (kb)
QRS Interval Change (ms)
K.
Locus 11 / SETBP1
rs991014
40400
40700
41000
Chromosome 18 position (kb)
QRS Interval Change (ms)
L.
Locus 12 / STRN
rs17020136
36800
37100
37400
Chromosome 2 position (kb)
QRS Interval Change (ms)


M.
Locus 13 / TKT
rs4687718
- log10 of P-value
Recombination rate (cM/Mb)
Chromosome 3 position (kb)
53000
53300
53600
ARIC
AGES
BRIGHT
CHS
FHS
KORAF3
KORAS4
RS1
RS2
SHIP
MICROS
ERF
SPLIT
KORCULA
TWINS
ORKNEY
Meta−Analysis
QRS Interval Change (ms)
N.
Locus 14 / CRIM1
rs7562790
Chromosome 2 position (kb)
36200
36500
36800
O.
Locus 15 / CDKN2C
rs17391905
Chromosome 1 position (kb)
50800
51300
51800
P.
Locus 16 / PRKCA
rs9912468
Chromosome 17 position (kb)
61400
61700
62000
Q.
Locus 17 / IGFBP3
rs7784776
Chromosome 7 position (kb)
46000
46300
46600
R.
Locus 18 / CASQ2
rs4074536
Chromosome 1 position (kb)
115800
116100
116400

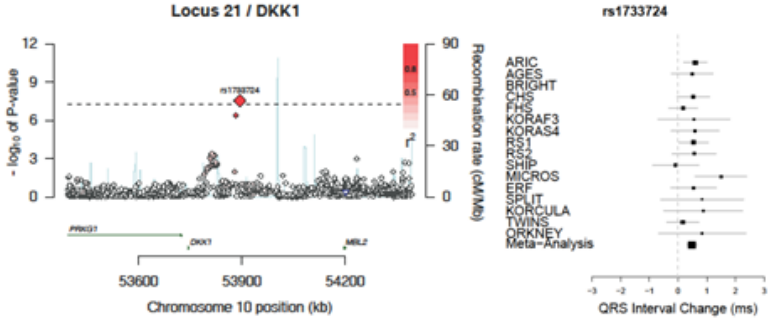
S.


Locus 19 / KLF12
rs1886512
- log10 of P-value
Recombination rate (cM/Mb)
r2
KLF12
73100
73400
73700
Chromosome 13 position (kb)
ARIC
AGES
BRIGHT
CHS
FHS
KORAF3
KORAS4
RS1
RS2
SHIP
MICROS
ERF
SPLIT
KORCULA
TWINS
ORKNEY
Meta-Analysis
QRS Interval Change (ms)

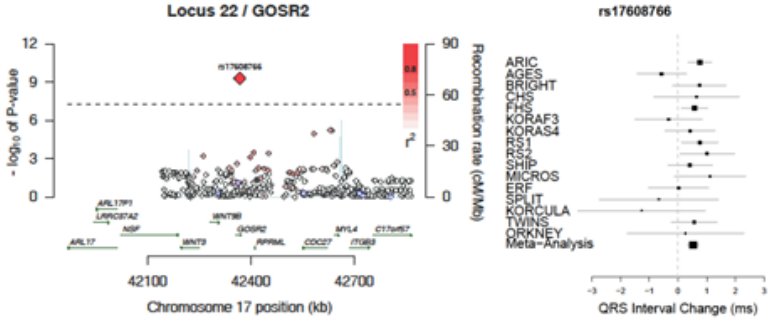
T.


Locus 20 / LRIG1
rs2242285
- log10 of P-value
Recombination rate (cM/Mb)
r2
SLC25A26
LRIG1
66200
66500
66800
Chromosome 3 position (kb)
ARIC
AGES
BRIGHT
CHS
FHS
KORAF3
KORAS4
RS1
RS2
SHIP
MICROS
ERF
SPLIT
KORCULA
TWINS
ORKNEY
Meta-Analysis
QRS Interval Change (ms)

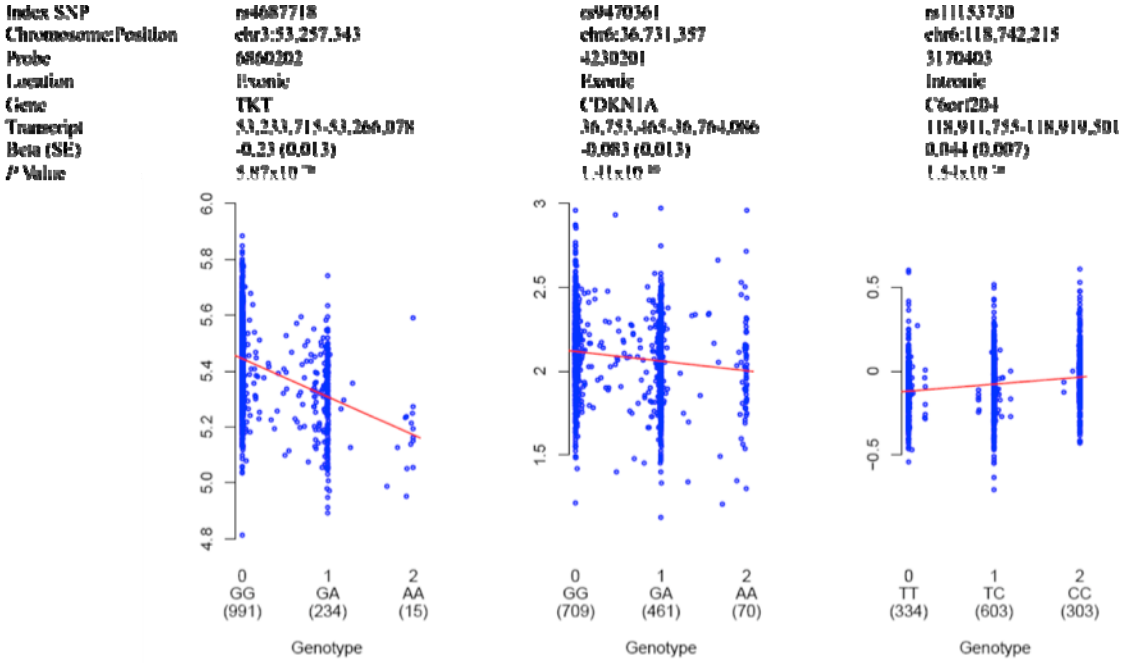
U.


Locus 21 / DKK1
rs1733724
- log10 of P-value
Recombination rate (cM/Mb)
r2
PRKG1
DKK1
MSL2
53600
53900
54200
Chromosome 10 position (kb)
ARIC
AGES
BRIGHT
CHS
FHS
KORAF3
KORAS4
RS1
RS2
SHIP
MICROS
ERF
SPLIT
KORCULA
TWINS
ORKNEY
Meta-Analysis
QRS Interval Change (ms)

V.


Locus 22 / GOSR2
rs17608766
- log10 of P-value
Recombination rate (cM/Mb)
r2
ARL17P1
LRRC37A2
NSF
WNT9B
GOSR2
MYL4
C17orf67
ARL17
WNT9
RPRML
CDC27
ITGB3
42100
42400
42700
Chromosome 17 position (kb)
ARIC
AGES
BRIGHT
CHS
FHS
KORAF3
KORAS4
RS1
RS2
SHIP
MICROS
ERF
SPLIT
KORCULA
TWINS
ORKNEY
Meta-Analysis
QRS Interval Change (ms)

Supplementary Figure 3a: Cis expression-genotype association analysis. The most striking cis eQTLs were observed for probes in exonic regions of *TKT* (rs4687718, P=5.87x10^{-70}) and *CDKN1A* (rs9470361, P=1.41x10^{-10}) and an intronic probe for *C6orf204* near *PLN* (rs11153730, P=1.54x10^{-10}). The y-axis indicates normalized expression data and the x-axis indicates the dosage genotype values. NCBI genomic build 36 was used in probe numbering.



Supplementary Figure 3b: Cis expression-genotype association results

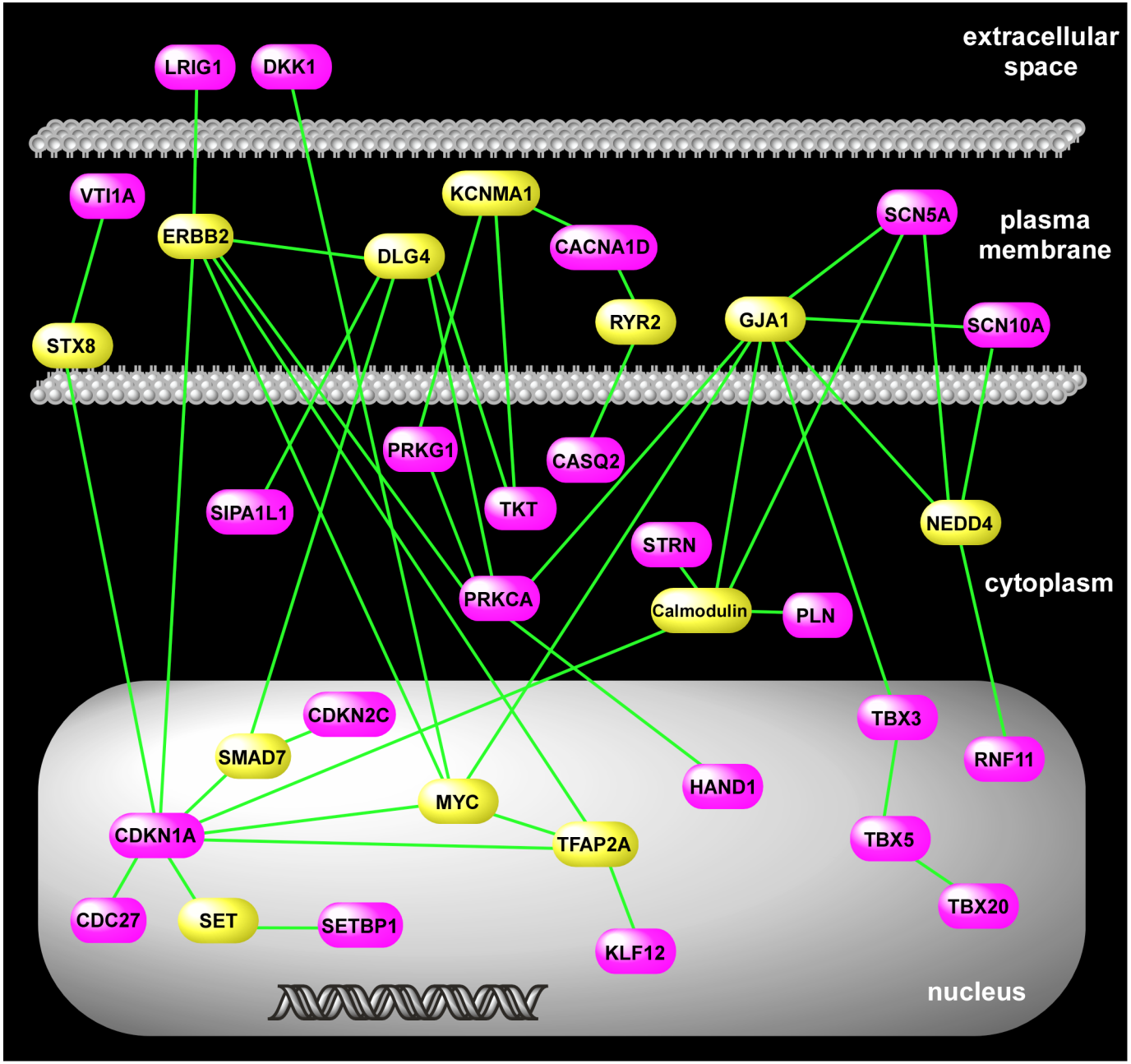
Locus	Index SNP	Chr	Coded/ Non-coded Allele	AF	Gene ID	Genomic location of probe	eQTL β	eQTL SE	eQTL *P*
13	rs4687718	3	**A**/G	0.11	TKT	Exon	-0.227	0.0128	**$5.87x10^{-70}$**
2	rs9470361	6	**A**/G	0.24	CDKN1A	Exon	-0.083	0.0129	**$1.41x10^{-10}$**
3	rs11153730	6	**C**/T	0.48	C6orf204	Intron	0.044	0.0069	**$1.54x10^{-10}$**
6	rs1362212	7	**A**/G	0.15	DPY19L1	Exon	0.036	0.0093	**$1.22x10^{-4}$**
			A/G		TBX20	Exon	-0.016	0.0057	$5.59x10^{-3}$
11	rs991014	18	**T**/C	0.43	SETBP1	Exon	0.027	0.0081	$9.03x10^{-4}$
14	rs7562790	2	**G**/T	0.4	AC007401.2/FEZ2	Exon	-0.025	0.0095	$7.96x10^{-3}$
22	rs17608766	17	**C**/T	0.16	NSF	Intron	0.027	0.0105	$9.49x10^{-3}$
5	rs13165478	5	**A**/G	0.34	HAND1	Exon	-0.01	0.004	$9.82x10^{-3}$

Supplementary Figure 3b : Cis expression-genotype association probe information

Locus	Index SNP	Chr	Position	Coded/ Non-coded Allele	HWE *P*	genotype_ Info	ProbeID	GeneID	Transcript Start	Transcript End
13	rs4687718	3	53,257,343	**A**/G	0.56	0.85	6860202	TKT	53,233,715	53,266,078
2	rs9470361	6	36,731,357	**A**/G	0.66	0.92	4230201	CDKN1A	36,753,465	36,764,086
3	rs11153730	6	118,774,215	**C**/T	0.33	0.99	3170403	C6orf204	118,911,755	118,919,501
6	rs1362212	7	35,271,831	**A**/G	0.85	0.95	3120379	DPY19L1	34,926,606	35,045,178
				A/G		0.93	6330100	TBX20	35,207,567	35,261,283
11	rs991014	18	40,693,884	**T**/C	0.46	1	5310079	SETBP1	40,513,861	40,899,771
14	rs7562790	2	36,527,059	**G**/T	0.11	1	6200053	AC007401.2/ FEZ2	36,619,732	36,656,875
22	rs17608766	17	42,368,270	**C**/T	0.28	0.88	2370411	NSF	42,107,119	42,125,492
5	rs13165478	5	153,849,233	**A**/G	0.11	0.86	3420035	HAND1	153,834,205	153,838,537

The *P*-values in **bold** are significant at $P<2.5x10^{-4}$, corresponding to Bonferroni corrected $P<0.05$. The **bolded** allele is the coded allele. Effect size (β) is reported in normalized units of gene expression per copy of the coded allele. Chr, chromosome; AF, coded allele frequency; SE, standard error; HWE, Hardy-Weinberg equilibrium.

Supplementary Figure 4. Network map. *In silico* relational network linking the loci associated with QRS interval duration. Most loci meeting genome-wide significance mapped to this network (shown in magenta). For loci where either multiple genes were independently associated with QRS interval duration (*SCN5A* and *SCN10A* in locus 1) or where it was difficult to discern to which of several genes the association signal might map (loci 3, 5, 12, 13, 15, 21, or 22), several genes (listed in **Table 1** for each of the loci) were included in the model. Of these seven latter loci, three (loci 13, 15, and 21) had 2 gene members map to the network. All interactions depicted in this relational network represent direct gene product interactions obtained from curated databases. To ensure that the interactome spanned across the maximum number of QRS-associated genes, several nodes (shown in yellow) were added to the network based on the strength of their connectivity with the original loci. Linker nodes were added only if they connected to a minimum of two network nodes, without bias in regards to function. The minimum number of linkers required to connect network nodes was selected. Our network analysis shows that many of the genetic loci associated with QRS duration interact with each other and are likely to be functionally linked, although the relevance of these relationships in the human heart needs to be experimentally assessed.


extracellular space
LRIG1
DKK1
VTI1A
ERBB2
DLG4
KCNMA1
CACNA1D
SCN5A
plasma membrane
RYR2
GJA1
SCN10A
STX8
PRKG1
CASQ2
SIPA1L1
TKT
NEDD4
STRN
cytoplasm
PRKCA
Calmodulin
PLN
CDKN2C
TBX3
SMAD7
RNF11
HAND1
MYC
CDKN1A
TFAP2A
TBX5
TBX20
CDC27
SET
SETBP1
KLF12
nucleus

SUPPLEMENTARY TABLES:

Supplementary Table 1a: Study participant characteristics								
Characteristic	**AGES**	**ARIC**	**BRIGHT**	**CHS**	**SPLIT**	**KORCULA**	**ERF**	**FHS**
N, Participants with ECG and genotype data	3188	9013	1566	3271	433	428	1591	7950
N, Participants after exclusion	2251	8085	1302	2845	395	378	1466	7499
Sex, women, %	64.0	54.4	63.0	62.8	63.5	62.5	59.5	54.1
Age, years, mean	76.0	54.0	58.8	72.1	49.3	54.5	47.8	39.2
Age, years, range	66 – 95	44 – 66	21 – 89	65 – 94	18 – 85	18 – 88	18 – 83	19 – 79
QRS interval, ms, mean	90.4	96.2	92.9	88.3	96.1	95.9	97.1	87.2
QRS interval, ms, range	60 – 120	61 – 120	66 – 118	56 – 120	70 – 120	76 – 119	68 – 120	59 - 120
Height, cm, mean	166.1	168.6	170.0	164.3	171.2	168.0	166.5	168.9
BMI, kg/m2, mean	27.0	26.8	27.4	26.2	26.7	28.0	26.7	26.2
Hypertension, %	77.8	24.1	100	51.9	25.2	28.8	15	8.3
Diabetes mellitus, %	10.4	7.6	0.1	11.2	3.6	6.1	2.8	1.6
Heart rate, bpm, mean	66.6	66.5	63.0	64.7	65.7	65.8	63.1	68.0

Supplementary Table 1a (continued): Study participant characteristics									
Characteristic	**KORA S4***	**KORA F3***	**MICROS**	**ORCADES**	**RS 1***	**RS 2***	**SHIP**	**TwinsUK**	**PREVEND****
N, Participants with ECG and genotype data	1814	1644	1244	719	5974	2157	3548	2687	7500
N, Participants after exclusion	1654	1393	1061	690	4081	1838	2985	2484	7170
Sex, women, %	52.5	51.7	57.8	54.9	62.9	57.9	52.6	95.0	53.0
Age, years, mean	53.5	61.4	44.2	53.3	68.3	64.8	48.1	51.3	48.7
Age, years, range	25 – 74	35 - 79	18 – 87	18 – 92	55 - 101	55 - 95	20 – 81	17 – 83	28 – 75
QRS interval, ms, mean	91.5	92.4	94.3	90.0	96.6	97.5	97.1	87.7	96.2
QRS interval, ms, range	64 – 120	62 – 120	69 – 120	60 – 120	64 – 120	70-120	60 – 120	60 – 120	50 – 120
Height, cm, mean	167.6	167.1	166.3	167.3	166.7	168.2	169.1	163.0	173.0
BMI, kg/m2, mean	27.6	27.9	25.3	27.6	26.3	27.3	27.0	25.7	26.0
Hypertension, %	16.6	41.6	15.5	24.9	51.8	58.5	49.5	16.4	31.1
Diabetes mellitus, %	3.0	8.8	3.1	2.7	8.6	9.3	6.3	1.5	3.2
Heart rate, bpm, mean	64.9	64.1	68.0	60.7	70.2	69.7	72.0	66.5	69.0

*The KORA and RS studies both have two separate cohorts. **PREVEND study participants were used for the candidate SNP extension genotyping only. All other studies were included in the GWAS meta-analysis.

Supplementary Table 1b: Study genome-wide genotyping characteristics

Characteristic	AGES	ARIC	BRIGHT	CHS	SPLIT	KORCULA	ERF	FHS
Array	Illumina CNV370	Affy 6.0	Affy 500K	Illumina CNV370	Illumina CNV370	Illumina CNV370	Illumin 318K, 370K, Affy 250K	Affy 500K, 50K MIP
Genotype calling software	Bead Studio	Birdseed	CHIAMO	Bead Studio	Bead Studio	Bead Studio	BeadStudio	BRLMM
SNP call rate exclusion	<97%	<95%	<95%	<95%	<98%	<98%	<98%	<=97%
SNP MAF exclusion	<0.01	<1%	<1%	<1%	<1%	<1%	NA	<0.01
P HWE exclusion	$<10x10^{-6}$	$<10x10^{-5}$	$<10x10^{-7}$	$<10x10^{-5}$	$<10x10^{-6}$	$<10x10^{-6}$	$<10x10^{-6}$	$<10x10^{-6}$
Imputation software	Mach1 v1.0.16	Mach1 v1.0.16	IMPUTE	BIMBAM	Mach v1.0.15	Mach v1.0.15	Mach v1.0.15	Mach v1.0.15
NCBI Build for imputation	Build 36	Build 35	Build 35	Build 36	Build 36	Build 36	Build 36	Build 36
GWAS statistical analysis	ProbABEL, R	Mach2QTL + plink	SNPTEST	R	GeneABEL, ProbABEL, R	GeneABEL, ProbABEL, R	GeneABEL, ProbABEL	R
Related individuals?	No	No	No	No	Yes	Yes	Yes	Yes
Familial adjustment method	N/A	N/A	N/A	N/A	Mmscore in ProbABEL	Mmscore in ProbABEL	Mmscore in ProbABEL	Kinship package in R
Genomic control factor (λ)	1.01	1.01	1.00	1.03	1.02	1.03	1.01	1.03

Supplementary Table 1b (continued): Study genome-wide genotyping characteristics

Characteristic	KORA S4	KORA F3	MICROS	ORCADES	RS 1	RS 2	SHIP	TwinsUK
Array	Affy 6.0	Affy 500K	Illumina HumHap300v 2	Illumina CNV370 & Illumina HumHap300v 2	Illumina550K	Illumina550K Duo, 610KQuad	Affy 6.0	Illumina Hap300 Duo, Hap300, Hap550, Hap610
Genotype calling software	Birdseed	BRLMM	BeadStudio	Bead Studio	BeadStudio	GenomeStudio	Birdseed	Illuminus
SNP call rate exclusion	<93%	<95%	<98%	<98%	<98%	<98%	None	<95%
SNP MAF exclusion	<1%	<1%	<1%	<1%	<1%	<1%	None	<1%
P HWE exclusion	$<10x10^{-5}$	$<10x10^{-5}$	$<10x10^{-6}$	$<10x10^{-6}$	$<10x10^{-6}$	$<10x10^{-6}$	None	$<10x10^{-4}$
Imputation software	Mach1 v1.0.16	Mach1 v1.010	Machv1.0.16	Mach 1.0 ML	Machv1.0.15	Machv1.0.16	Imputev0.5.0	Impute v0.3.2
NCBI Build for imputation	Build 36	Build 35	Build 36	Build 36	Build 36	Build 36	Build 36	Build 36
GWAS statistical analysis	ProbABEL v0.1-2	ProbABEL v0.1-2	ProbABEL	GeneABEL, ProbABEL, R	Mach2QTL as implemented in GRIMP	Mach2QTL as implemented in GRIMP	SNPTESTv.1.1.5	SNPTESTv.1.1.4
Related individuals?	No	No	Yes	Yes	No	No	No	Yes
Familial adjustment method	N/A	N/A	Mmscore in ProbABEL	Mmscore in ProbABEL	N/A	N/A	N/A	Huber-White robust variance estimation in R
Genomic control factor (λ)	1.01	1.01	1.00	1.00	1.01	1.02	1.04	1.02

Supplementary Table 2: Interaction with sex and age

Locus	Index SNP	Chr	Position	Overall β		Δ (males - females)	SE	*P*	Effect Stronger		Age β	SE	*P*	Effect Change
1	rs6801957	3	38,742,319	-0.774		0.013	0.214	0.95	female		-0.0078	0.0056	0.17	increase
	rs9851724	3	38,694,939	-0.656		0.044	0.145	0.77	female		**-0.0145**	**0.0056**	**0.014**	**increase**
	rs11710077	3	38,632,903	0.849		-0.342	0.189	0.10	female		**0.0114**	**0.0054**	**0.043**	**increase**
	rs11708996	3	38,608,927	0.796		0.236	0.121	0.08	male		0.0009	0.0056	0.87	increase
2	rs9470361	6	36,731,357	0.867		-0.018	0.160	0.92	female		0.0082	0.0056	0.15	increase
3	rs11153730	6	118,774,215	0.584		**0.383**	**0.101**	**0.004**	**male**		-0.0539 (0.00056)*	0.0288 (0.00028)	0.12	increase
4	rs9436640	1	61,646,265	-0.596		0.053	0.166	0.76	female		**-0.0094**	**0.0045**	**0.044**	**increase**
5	rs13165478	5	153,849,233	-0.558		-0.026	0.128	0.84	male		**0.0826 (-0.00088)***	**0.0370 (0.00035)**	**0.03**	**increase**
6	rs1362212	7	35,271,831	0.689		-0.101	0.151	0.52	female		0.0024	0.0047	0.61	increase
7	rs11848785	14	71,127,108	0.494		-0.239	0.195	0.25	female		-0.0025	0.0055	0.65	decrease
8	rs883079	12	113,277,623	0.492		-0.147	0.163	0.39	female		0.0073	0.0053	0.18	increase
9	rs10850409	12	113,866,123	-0.488		-0.237	0.212	0.29	male		**-0.0599 (0.00067)***	**0.0271 (0.00026)**	**0.009**	**decrease**
10	rs7342028	10	114,469,252	-0.476		0.002	0.121	0.97	female		-0.0037	0.0039	0.36	increase
11	rs991014	18	40,693,884	-0.415		-0.093	0.145	0.54	male		0.0033	0.0042	0.45	decrease
12	rs17020136	2	37,101,519	0.514		0.267	0.230	0.28	male		0.0058	0.0059	0.33	increase
13	rs4687718	3	53,257,343	-0.625		-0.382	0.226	0.13	male		0.0062	0.0059	0.30	decrease
14	rs7562790	2	36,527,059	0.400		0.121	0.118	0.33	male		0.0062	0.0046	0.18	increase
15	rs17391905	1	51,318,728	-1.310		-0.208	0.384	0.60	male		**-0.0337**	**0.0115**	**0.005**	**increase**
16	rs9912468	17	61,748,819	-0.398		-0.032	0.141	0.83	male		**-0.0102**	**0.0044**	**0.025**	**increase**
17	rs7784776	7	46,586,670	-0.386		-0.088	0.112	0.45	male		**0.0083**	**0.0039**	**0.039**	**decrease**
18	rs4074536	1	116,112,490	-0.427		0.083	0.092	0.39	female		0.0084	0.0045	0.07	decrease
19	rs1886512	13	73,418,187	-0.397		0.049	0.109	0.66	female		**-0.0104**	**0.0048**	**0.034**	**increase**
20	rs2242285	3	66,514,292	0.367		-0.043	0.124	0.74	female		-0.0079	0.0044	0.08	decrease

Interactions that are nominally significant are denoted in **bold**. None of the interactions with sex or age remained significant after Bonferroni correction for number of tests. Effect size for QRS (Overall β) is reported in milliseconds (ms) per copy of the coded allele, and combines both GWAS and PREVEND results. Effect size for age (β age) is reported in ms per year. Chr, chromosome; SE, standard error.
*Includes term for non-linear best-fit of regression model.

Supplementary Table 3a: Mean QRS duration and sample sizes for individuals stratified by QRS >120 ms and specific ventricular conduction defects

	QRS≤120 ms (mean±sd)	QRS >120 ms (mean±sd)	LBBB (mean±sd)	RBBB (mean±sd)	NIVCD (mean±sd)
ARIC	7996 (96.2±9.3)	213 (138.3±16.2)	26 (157.7±11.7)	62 (148.5±13.4)	125 (129.8±11.3)
Rotterdam	4769 (96.9±10.6)	306 (143.5±17.2)	81 (157.8±12.7)	107 (148.8±14.9)	118 (129.0±8.9)

Excludes individuals with prevalent heart failure or myocardial infarction. sd, standard deviation; LBBB, left bundle branch block; RBBB, right bundle branch block; NIVCD, non-specific intraventricular conduction defect.

Supplementary Table 3b: Effects of a weighted genotype risk score on QRS >120 ms and stratified on specific ventricular conduction defects

	QRS >120 ms		LBBB		RBBB		NIVCD	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
ARIC	**1.12 (1.04-1.22)**	**0.003**	1.11 (0.89-1.40)	0.34	1.00 (0.86-1.16)	0.98	**1.20 (1.08-1.33)**	**0.0006**
Rotterdam	1.04 (0.97-1.12)	0.21	1.00 (0.88-1.13)	0.97	1.02 (0.91-1.14)	0.73	1.11 (0.99-1.23)	0.07
Combined	**1.08 (1.02-1.13)**	**0.004**	1.02 (0.92-1.14)	0.67	1.01 (0.93-1.11)	0.79	**1.15 (1.07-1.25)**	**0.0002**

Excludes individuals with prevalent heart failure or myocardial infarction. **Bold** indicates significant results ($P < 0.05$). LBBB, left bundle branch block; RBBB, right bundle branch block; NIVCD, non-specific intraventricular conduction defect; OR, odds ratio; CI, confidence interval.

Supplementary Table 4a: Effect of QRS duration hits on PR interval and QT interval													
Locus	**Nearest Gene**	**Index SNP**	**Chr**	**Position**	**Coded/ Non-coded Allele**	**QRS β**	**QRS SE**	**PR β**	**PR SE**	**PR *P***	**QT β**	**QT SE**	**QT *P***
1	SCN10A	rs6801957	3	38,742,319	**T**/C	0.77	0.07	**3.79**	**0.21**	**$1.80x10^{-73}$**	**-0.67**	**0.20**	**$1.05x10^{-3}$**
	SCN10A	rs9851724	3	38,694,939	**C**/T	-0.66	0.07	**-1.70**	**0.22**	**$7.98x10^{-15}$**	**0.95**	**0.21**	**$6.66x10^{-6}$**
	SCN5A	rs11710077	3	38,632,903	**T**/A	-0.84	0.09	**-1.80**	**0.26**	**$3.18x10^{-12}$**	**0.92**	**0.24**	**$1.34x10^{-4}$**
	SCN5A	rs11708996	3	38,608,927	**C**/G	0.79	0.10	**3.04**	**0.29**	**$6.00x10^{-26}$**	**-0.93**	**0.28**	**$7.78x10^{-4}$**
2	CDKN1A	rs9470361	6	36,731,357	**A**/G	0.87	0.08	0.74	0.24	$2.01x10^{-3}$	-0.64	0.24	$6.64x10^{-3}$
3	C6orf204/SLC35F1/ PLN/ BRD7P3	rs11153730	6	118,774,215	**C**/T	0.59	0.07	-0.56	0.20	$6.20x10^{-3}$	**1.61**	**0.20**	**$5.19x10^{-16}$**
4	NFIA	rs9436640	1	61,585,698	**G**/T	-0.59	0.07	0.39	0.20	0.06	-0.44	0.20	0.024
5	HAND1/SAP30L	rs13165478	5	153,849,233	**A**/G	-0.55	0.07	0.39	0.22	0.07	-0.27	0.21	0.2
6	TBX20	rs1362212	7	35,078,546	**A**/G	0.69	0.09	0.50	0.27	0.07	-0.17	0.27	0.53
7	SIPA1L1	rs11848785	14	71,127,108	**G**/A	-0.50	0.08	0.66	0.23	$4.26x10^{-3}$	-0.09	0.22	0.67
8	TBX5	rs883079	12	113,255,960	**C**/T	0.49	0.08	**1.15**	**0.23**	**$9.08x10^{-7}$**	0.42	0.22	0.06
9	TBX3	rs10850409	12	113,844,460	**A**/G	-0.49	0.08	**1.70**	**0.23**	**$3.72x10^{-13}$**	-0.33	0.23	0.15
10	VTI1A	rs7342028	10	114,469,252	**T**/G	0.48	0.08	0.20	0.23	0.39	-0.22	0.22	0.33
11	SETBP1	rs991014	18	40,693,884	**T**/C	0.42	0.07	0.37	0.21	0.07	0.06	0.20	0.78
12	HEATR5B/STRN	rs17020136	2	37,159,666	**C**/T	0.51	0.08	-0.34	0.26	0.18	0.43	0.25	0.08
13	TKT/CACNA1D/PRKCD	rs4687718	3	53,257,343	**A**/G	-0.63	0.11	-0.27	0.32	0.40	0.11	0.30	0.71
14	CRIM1	rs7562790	2	36,585,206	**G**/T	0.39	0.07	-0.32	0.21	0.12	0.20	0.20	0.31
15	C1orf185/RNF11/ CDKN2C/FAF1	rs17391905	1	51,258,161	**G**/T	-1.35	0.23	**-3.01**	**0.71**	**$2.09x10^{-5}$**	-0.38	0.70	0.59
16	PRKCA	rs9912468	17	61,748,819	**G**/C	0.39	0.07	0.39	0.21	0.06	**-0.92**	**0.20**	**$3.66x10^{-6}$**
17	IGFBP3	rs7784776	7	46,393,385	**G**/A	0.39	0.07	0.17	0.21	0.41	0.15	0.20	0.46
18	CASQ2	rs4074536	1	116,023,009	**C**/T	-0.42	0.07	0.32	0.23	0.16	-0.63	0.22	4.47E-03
19	KLF12	rs1886512	13	73,418,187	**A**/T	-0.40	0.07	-0.40	0.22	0.06	0.28	0.22	0.19
20	LRIG1/SLC25A26	rs2242285	3	66,514,292	**A**/G	0.37	0.07	0.55	0.21	$8.27x10^{-3}$	0.07	0.20	0.73
21	DKK1	rs1733724	10	53,893,983	**A**/G	0.49	0.09	0.03	0.29	0.92	0.84	0.28	$2.46x10^{-3}$
22	GOSR2	rs17608766	17	42,368,270	**C**/T	0.53	0.10	0.48	0.30	0.12	0.88	0.29	$2.86x10^{-3}$

QT interval results are drawn from the QTSCD study.[12] **Bold** indicates significant SNPs after Bonferroni correction for the number of SNPs tested. The **bolded** allele is the coded allele. Effect size (β) is reported in milliseconds (ms) per copy of the coded allele. Chr, chromosome; AF, coded allele frequency; SE, standard error.

Supplementary Table 4b: Effect of PR and QT interval SNPs on QRS duration										
Trait	**Locus**	**Index SNP**	**Chr**	**Position**	**Coded/Non-coded Allele**	**Trait β**	**Trait SE**	**QRS β**	**QRS SE**	**QRS *P***
PR interval	SCN10A	rs6800541	3	38,749,836	**C**/T	**3.77**	**0.21**	**0.74**	**0.07**	**$5.85x10^{-29}$**
	SCN5A	rs11708996	3	38,608,927	**C**/G	**3.04**	**0.29**	**0.79**	**0.09**	**$1.66x10^{-17}$**
	TBX5-TBX3	rs1896312	12	113,830,807	**C**/T	**1.95**	**0.23**	**-0.44**	**0.07**	**$2.63x10^{-9}$**
	CAV1-CAV2	rs3807989	7	115,973,477	**A**/G	**2.30**	**0.21**	**0.30**	**0.07**	**$5.84x10^{-6}$**
	MEIS1	rs11897119	2	66,625,504	**C**/T	1.36	0.21	0.10	0.07	0.12
	NKX2-5	rs251253	5	172,412,942	**C**/T	-1.49	0.21	0.10	0.07	0.13
	SOX5	rs11047543	12	24,679,606	**A**/G	-2.09	0.29	0.10	0.09	0.29
	ARHGAP24	rs7692808	4	86,860,173	**A**/G	-2.01	0.22	-0.04	0.07	0.60
	WNT11	rs4944092	11	75,587,267	**G**/A	-1.19	0.22	0.04	0.07	0.60
QT interval	SCN5A	rs11129795	3	38,568,397	**A**/G	**-1.27**	**0.23**	**0.78**	**0.08**	**$1.95x10^{-24}$**
	PLN	rs11970286	6	118,787,067	**T**/C	**1.64**	**0.20**	**0.55**	**0.07**	**$7.07x10^{-17}$**
	PLN	rs12210810	6	118,759,897	**C**/G	**-3.13**	**0.43**	**-0.75**	**0.15**	**$4.08x10^{-7}$**
	NOS1AP	rs12143842	1	160,300,514	**T**/C	**2.88**	**0.23**	**-0.29**	**0.08**	**$1.25x10^{-4}$**
	ATP1B1	rs10919071	1	167,366,107	**G**/A	-2.05	0.29	-0.21	0.10	0.03
	LIG3	rs2074518	17	30,356,290	**T**/C	-1.23*	0.18*	-0.10	0.07	0.12
	KCNJ2	rs17779747	17	66,006,587	**T**/G	-1.16	0.21	-0.10	0.07	0.15
	KCNE1	rs1805128	21	34,743,550	**T**/C	4.03*	1.58*	-0.29	0.22	0.19
	KCNH2	rs4725982	7	150,268,796	**T**/C	1.58*	0.35*	-0.10	0.08	0.24
	NOS1AP	rs4657178	1	160,477,234	**T**/C	2.19	0.22	-0.08	0.07	0.27
	KCNQ1	rs12296050	11	2,445,918	**T**/C	1.44	0.25	-0.06	0.08	0.45
	NDRG4	rs7188697	16	57,179,679	**G**/A	-1.66	0.23	-0.06	0.08	0.46
	KCNH2	rs2968863	7	150,254,070	**T**/C	-1.35	0.23	0.05	0.08	0.55
	KCNQ1	rs2074238	11	2,441,379	**T**/C	-8.22*	1.05*	0.18	0.34	0.59
	RNF207	rs846111	1	6,201,957	**C**/G	1.49	0.25	-0.04	0.09	0.66
	LITAF	rs8049607	16	11,599,254	**T**/C	1.25	0.22	-0.01	0.07	0.88

QT results are drawn from the QTSCD study, unless otherwise noted. [12] PR results are from.[13] **Bold** indicates significant SNPs after Bonferroni correction for the number of SNPs tested. The **bolded** allele is the coded allele. Effect size (β) is reported in milliseconds (ms) per copy of the coded allele. Chr, chromosome; MAF, minor allele frequency; SE, standard error. *Genome-wide significant results ($P<5x10^{-8}$) are drawn from the QTGEN study, [11] and standardized beta estimates and SE were converted to ms using SD=17.5 ms.

Supplementary Table 5: Gene specific primers used in the animal studies

	Sense	Anti-sense
SCN10A	5'-AATCAGAGCGAGGAGAAGAC-3'	5'-CTAGTGAGCTAAGGATCGCA-3'
S26	5'-GCCATCCATAGCAAGGTTGT-3'	5'-GCCTCTTTACATGGGCTTTG-3'