Identification of heart rate-associated loci and their effects on cardiac conduction and rhythm disorders

SUPPLEMENTARY INFORMATION

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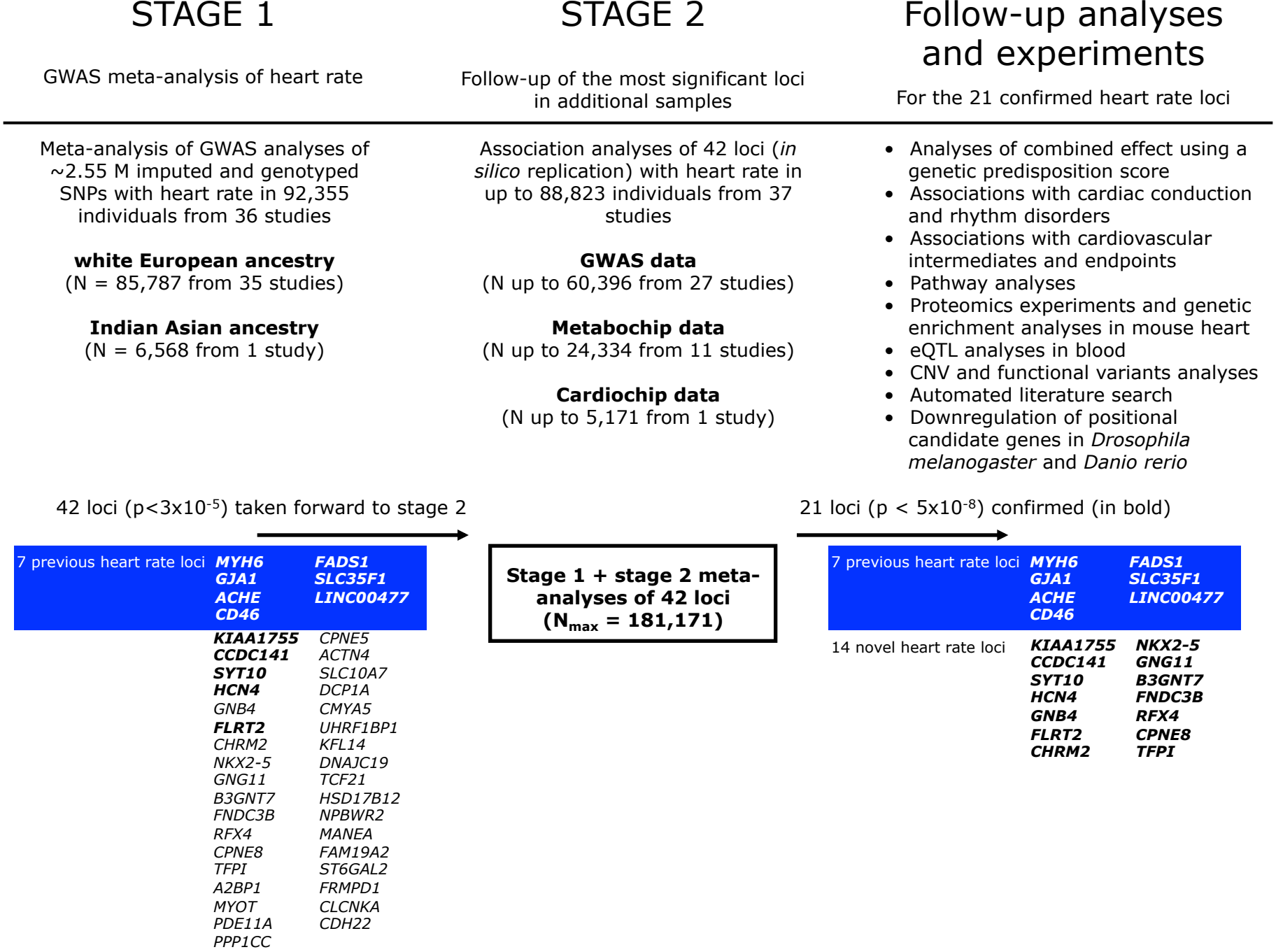
Nature Genetics: doi:10.1038/ng.2610

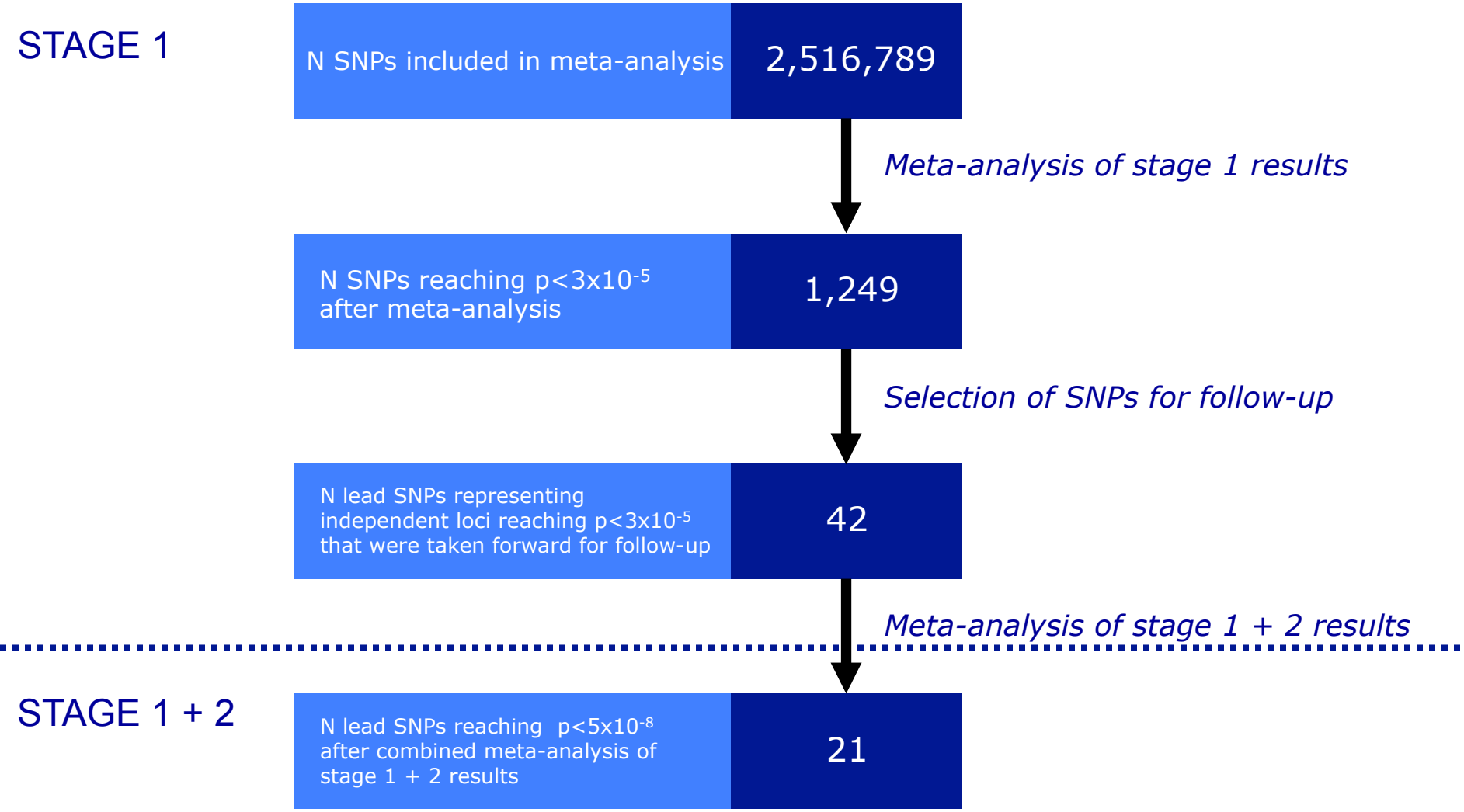
Hingorani, E Ingelsson, M Kivimaki, RA Kronmal, D Kuh, L Lind, NG Martin, BA Oostra, NL Pedersen, T Quertermous, JI Rotter, YT van der Schouw, WMM Verschuren, M Walker, D Albanes, DO Arnar, TL Assimes, S Bandinelli, M Boehnke, RA de Boer, C Bouchard, M Caulfield, JC Chambers, G Curhan, D Cusi, J Eriksson, L Ferrucci, WH van Gilst, N Glorioso, J de Graaf, L Groop, U Gyllensten, W-C Hsueh, FB Hu, HV Huikuri, DJ Hunter, C Iribarren, B Isomaa, M-R Jarvelin, A Jula, M Kähönen, LA Kiemeney, MM van der Klauw, JS Kooner, P Kraft, L Iacoviello, T Lehtimäki, M-LL Lokki, BD Mitchell, G Navis, MS Nieminen, C Ohlsson, NR Poulter, L Qi, OT Raitakari, EB Rimm, JD Rioux, F Rizzi, I Rudan, V Salomaa, PS Sever, DC Shields, AR Shuldiner, J Sinisalo, AV Stanton, RP Stolk, DP Strachan, J-C Tardif, U Thorsteinsdottir, J Tuomilehto, DJ van Veldhuisen, J Virtamo, J Viikari, P Vollenweider, G Waeber, E Widen, YS Cho, JV Olsen, PM Visscher, C Willer, L Franke, Global BPgen consortium, CARDIoGRAM consortium, J Erdmann, JR Thompson, PR GWAS consortium, A Pfeufer, QRS GWAS consortium, N Sotoodehnia, QT-IGC consortium, C Newton-Cheh, CHARGE-AF consortium, PT Ellinor, BHCh Stricker, A Metspalu, M Perola, JS Beckmann, G Davey Smith, K Stefansson, NJ Wareham, PB Munroe, OCM Sibon, DJ Milan, H Snieder, NJ Samani and RJF Loos.

1. SUPPLEMENTARY FIGURES AND TABLES

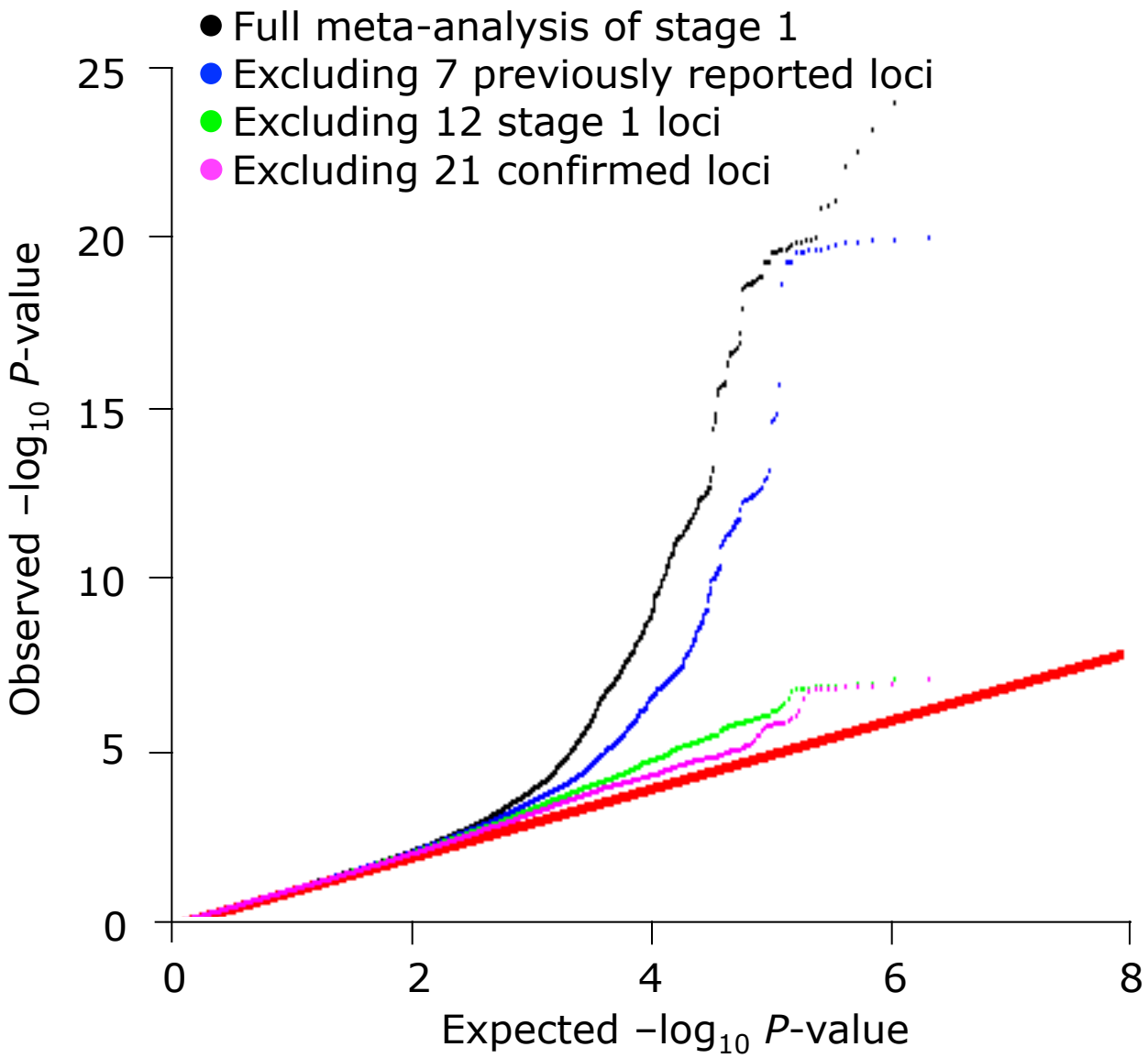
1.1 SUPPLEMENTARY FIGURES



Supplementary Figure 1 – Study Design
The blue box shows loci that were previously identified in GWAS for heart rate. Loci reaching $p<5x10^{-8}$ are highlighted in bold.



Supplementary Figure 2 – SNP Flow chart
The blue boxes show the number of SNPs that were of interest in each stage of the study.

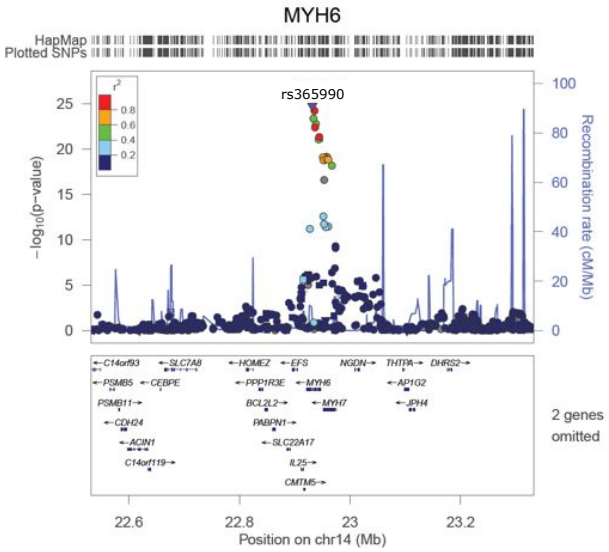


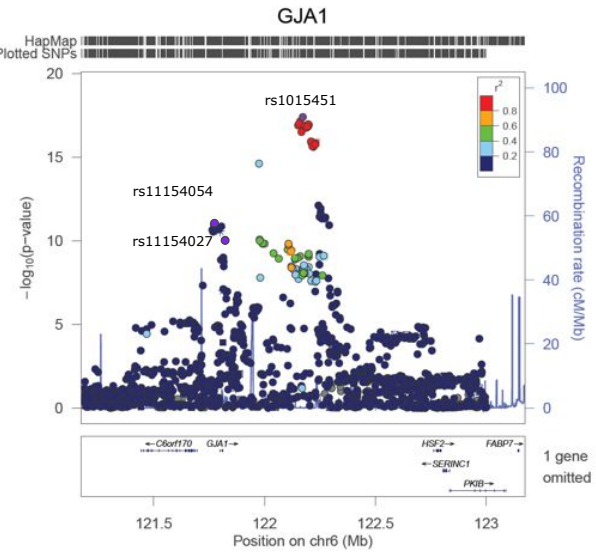
Supplementary Figure 3 – Quantile-quantile plot of SNPs after meta-analysis of stage 1 results
Data is shown for the full stage 1 meta-analysis (black), and after excluding SNPs within ± 1 MB of previously reported genome wide significant loci for heart rate (blue), after additionally excluding the 12 loci that reached $p<5x10^{-8}$ in stage 1 (green), and after excluding all SNPs located within 1 MB of the 21 heart rate-associated SNPs (pink).

Trait	N_{max}	p-value	Association confirmed	Direction
PR duration	28,482	1.3×10^{-4}	yes	increased
QRS duration	40,090	1.8×10^{-5}		decreased
QT duration	74,932	1.1×10^{-17}		decreased
Atrial Fibrillation	9,183 cases 91,625 controls	0.11	no	
Atrioventricular Block	319 cases 41,356 controls	0.15	no	
Sick Sinus Syndrome	903 cases 40,722 controls	2.3×10^{-4}	yes	decreased
Pacemaker Implantation	978 cases 40,976 controls	3.6×10^{-4}	yes	decreased
Sudden Cardiac Death	370 cases 41,305 controls	0.91	no	
Diastolic Blood Pressure	34,210	6.7×10^{-3}	no	
Systolic Blood Pressure	34,211	0.33		
Hypertension	9,777 cases 10,101 controls	0.87		
Coronary Artery Disease	21,928 cases 62,260 controls	0.45	no	
Myocardial Infarction	12,584 cases 41,163 controls	0.24		

Supplementary Figure 4 – Overview of results from follow-up analyses: associations between heart rate loci combined and related, clinically relevant traits

For each trait for which associations between the heart rate loci and clinically relevant traits were examined, the effective number of available participants (N for locus with maximal sample size) and p-value for association of the heart rate loci combined and the trait of interest are provided. Associations were considered confirmed when $p<2 \times 10^{-3}$.


MYH6
HapMap
Plotted SNPs
rs365990
−log10(p-value)
Recombination rate (cM/Mb)
2 genes omitted
Position on chr14 (Mb)


GJA1
HapMap
Plotted SNPs
rs1015451
rs11154054
rs11154027
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Recombination rate (cM/Mb)
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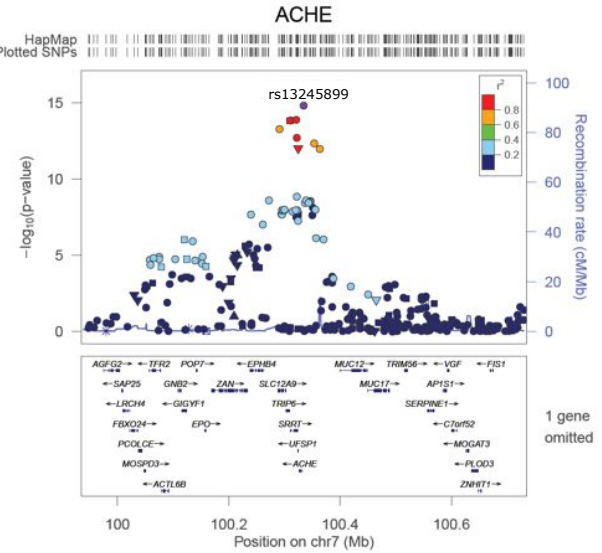
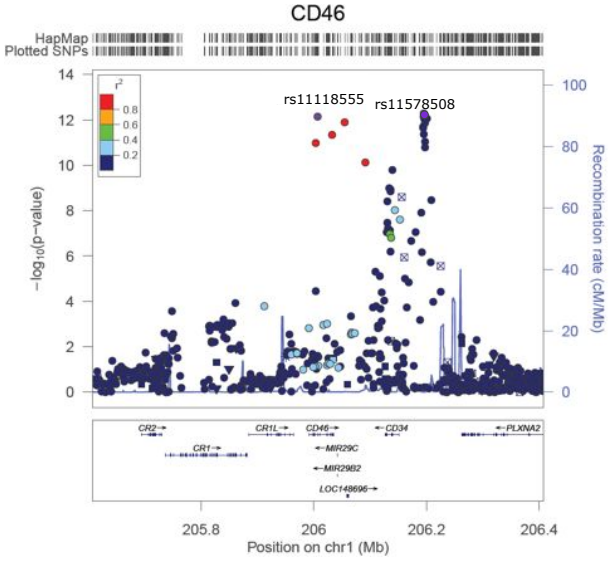
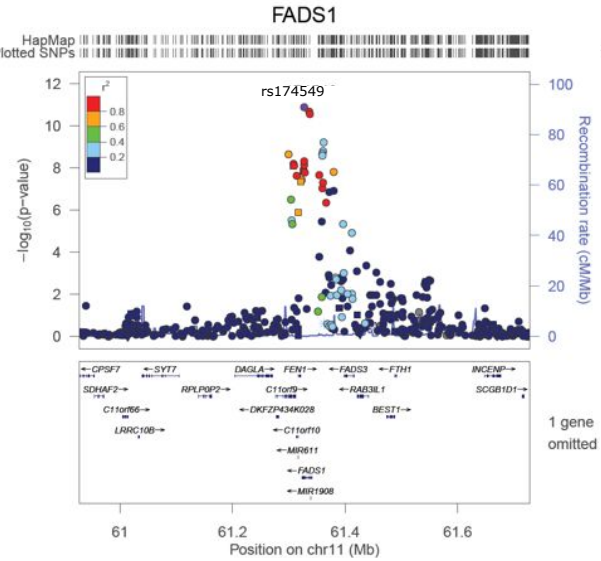
Position on chr6 (Mb)


ACHE
HapMap
Plotted SNPs
rs13245899
−log10(p-value)
Recombination rate (cM/Mb)
1 gene omitted
Position on chr7 (Mb)


CD46
HapMap
Plotted SNPs
rs11118555
rs11578508
−log10(p-value)
Recombination rate (cM/Mb)
Position on chr1 (Mb)


FADS1
HapMap
Plotted SNPs
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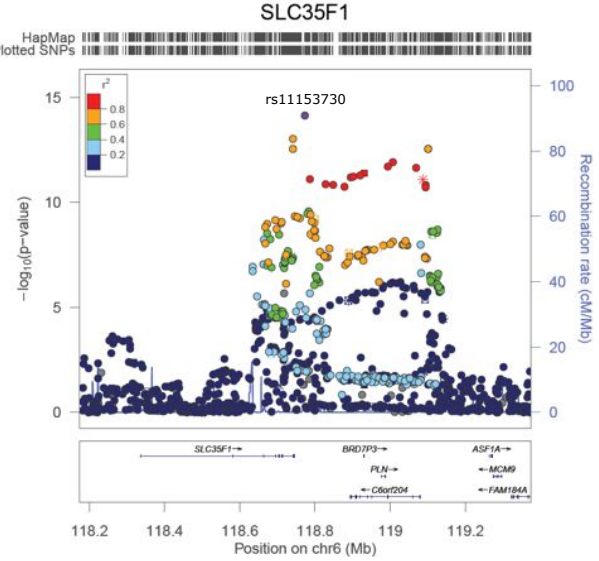
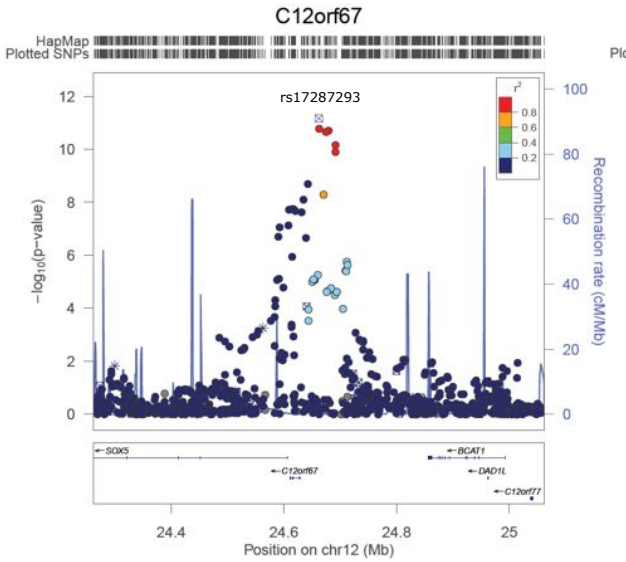
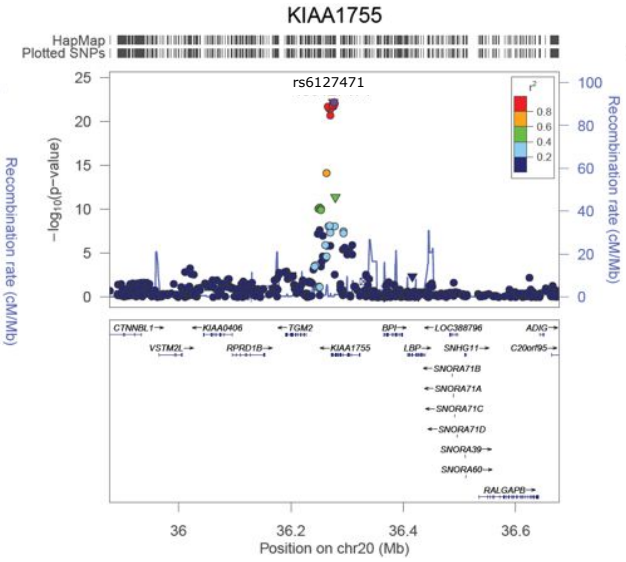
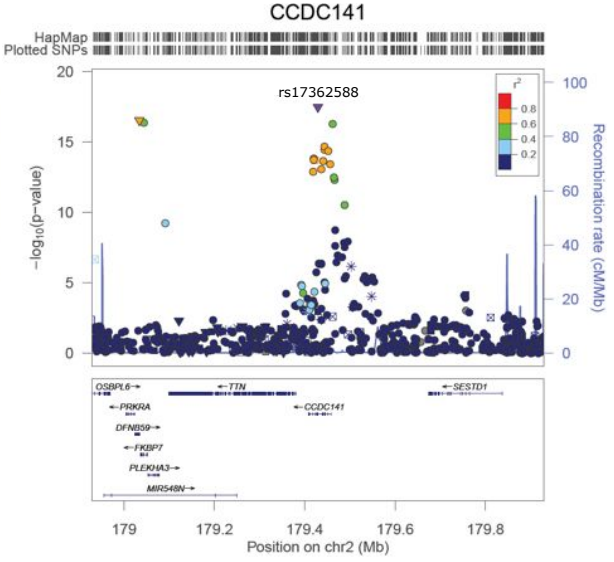
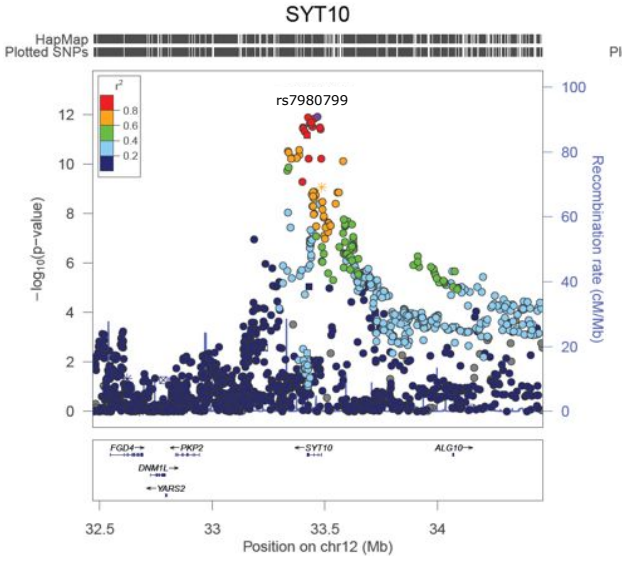
Recombination rate (cM/Mb)
1 gene omitted
Position on chr11 (Mb)

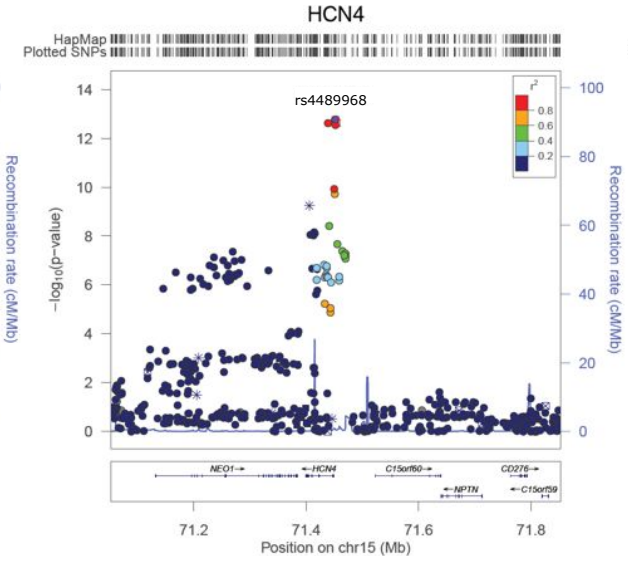

SLC35F1
HapMap
Plotted SNPs
rs11153730
−log10(p-value)
Recombination rate (cM/Mb)
Position on chr6 (Mb)

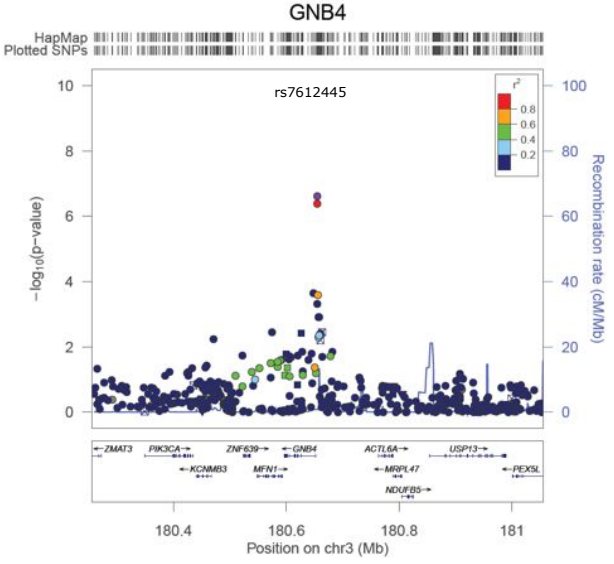

C12orf67
HapMap
Plotted SNPs
rs17287293
−log10(p−value)
Recombination rate (cM/Mb)
SOX5
C12orf67
BCAT1
DAD1L
C12orf77
Position on chr12 (Mb)

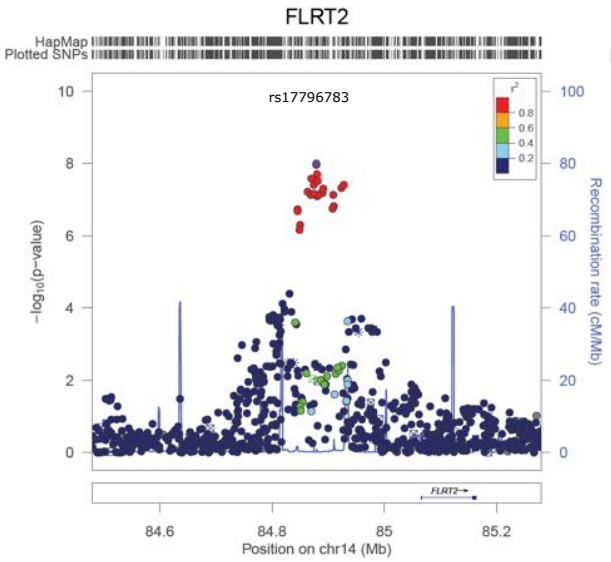

KIAA1755
HapMap
Plotted SNPs
rs6127471
−log10(p−value)
Recombination rate (cM/Mb)
CTNNBL1
KIAA0406
TGM2
BPI
LOC388796
ADIG
VSTM2L
RPRD1B
KIAA1755
LBP
SNHG11
C20orf95
SNORA71B
SNORA71A
SNORA71C
SNORA71D
SNORA39
SNORA60
RALGAPB
Position on chr20 (Mb)

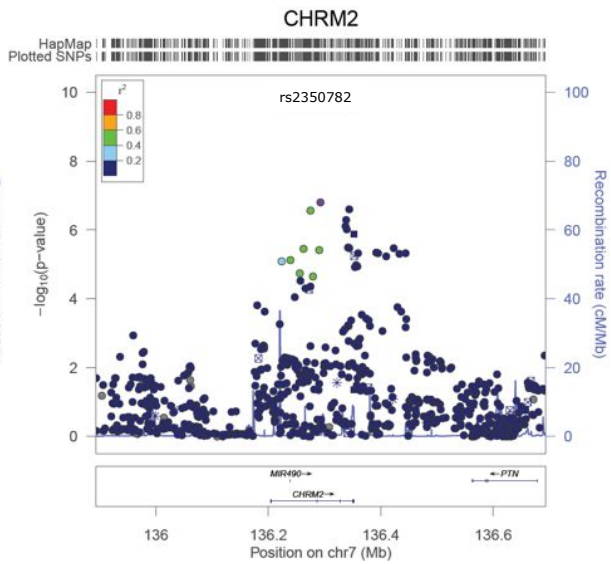

CCDC141
HapMap
Plotted SNPs
rs17362588
−log10(p−value)
Recombination rate (cM/Mb)
OSBPL6
TTN
SESTD1
PRKRA
CCDC141
DFNB59
FKBP7
PLEKHA3
MIR548N
Position on chr2 (Mb)

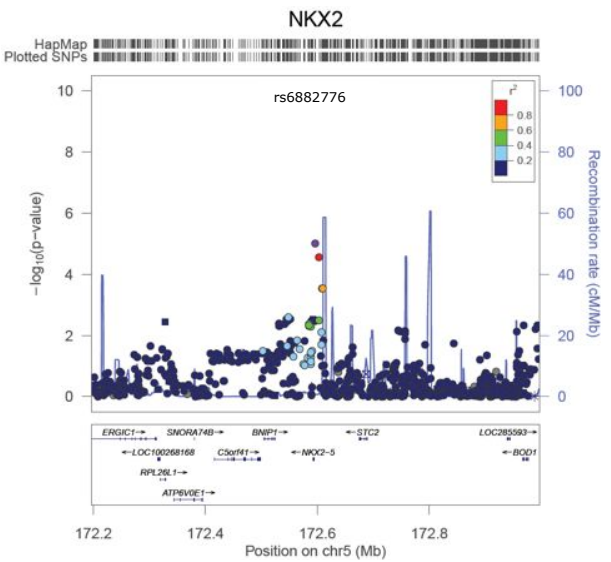

SYT10
HapMap
Plotted SNPs
rs7980799
−log10(p−value)
Recombination rate (cM/Mb)
FGD4
PKP2
SYT10
ALG10
DNM1L
VARS2
Position on chr12 (Mb)

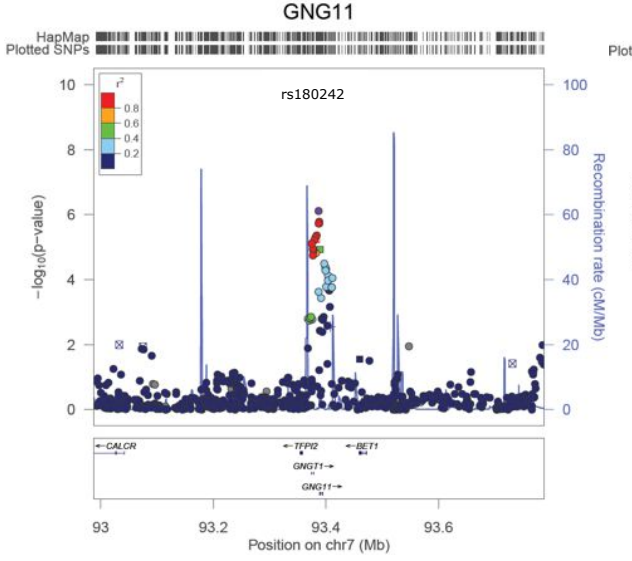

HCN4
HapMap
Plotted SNPs
rs4489968
−log10(p−value)
Recombination rate (cM/Mb)
NEO1
HCN4
C15orf60
CD276
NPTN
C15orf59
Position on chr15 (Mb)


GNB4
HapMap
Plotted SNPs
rs7612445
−log10(p−value)
Recombination rate (cM/Mb)
ZMAT3
PIK3CA
ZNF639
GNB4
ACTL6A
USP13
KCNMB3
MFN1
MRPL47
PEX5L
NDUFB5
Position on chr3 (Mb)


FLRT2
HapMap
Plotted SNPs
rs17796783
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
FLRT2→
84.6
84.8
85
85.2
Position on chr14 (Mb)


CHRM2
HapMap
Plotted SNPs
rs2350782
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
MIR490→
CHRM2→
←PTN
136
136.2
136.4
136.6
Position on chr7 (Mb)


NKX2
HapMap
Plotted SNPs
rs6882776
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
ERGIC1→
SNORA74B→
BNIP1→
←STC2
LOC285593→
←LOC100268168
C5orf41→
←NKX2-5
←BOD1
RPL26L1→
ATP6V0E1→
172.2
172.4
172.6
172.8
Position on chr5 (Mb)


GNG11
HapMap
Plotted SNPs
rs180242
r²
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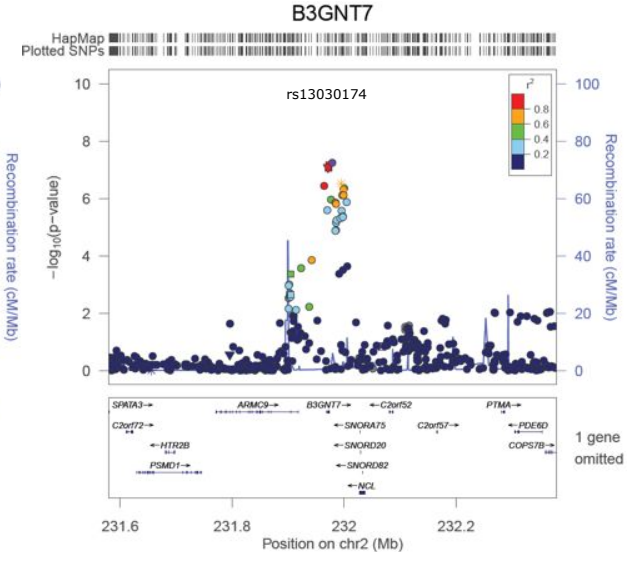
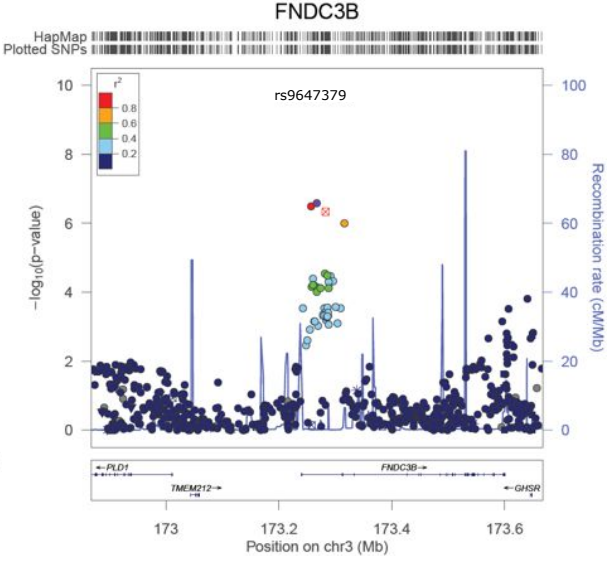
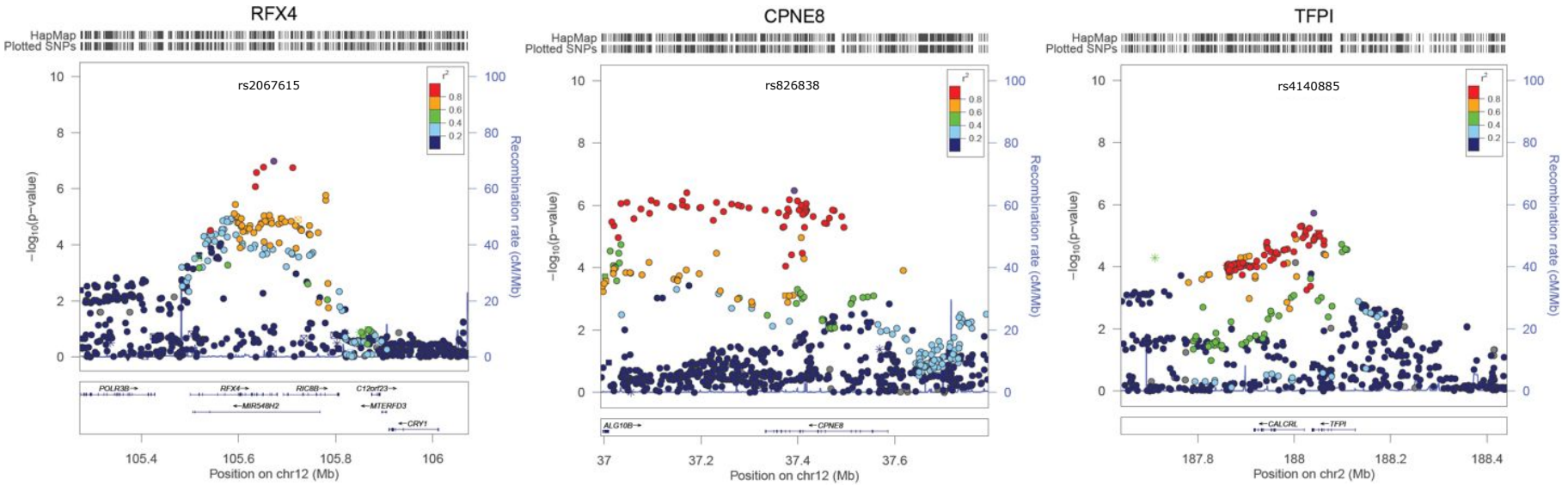
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
←CALCR
←TFPI2
←BET1
GNG11→
93
93.2
93.4
93.6
Position on chr7 (Mb)

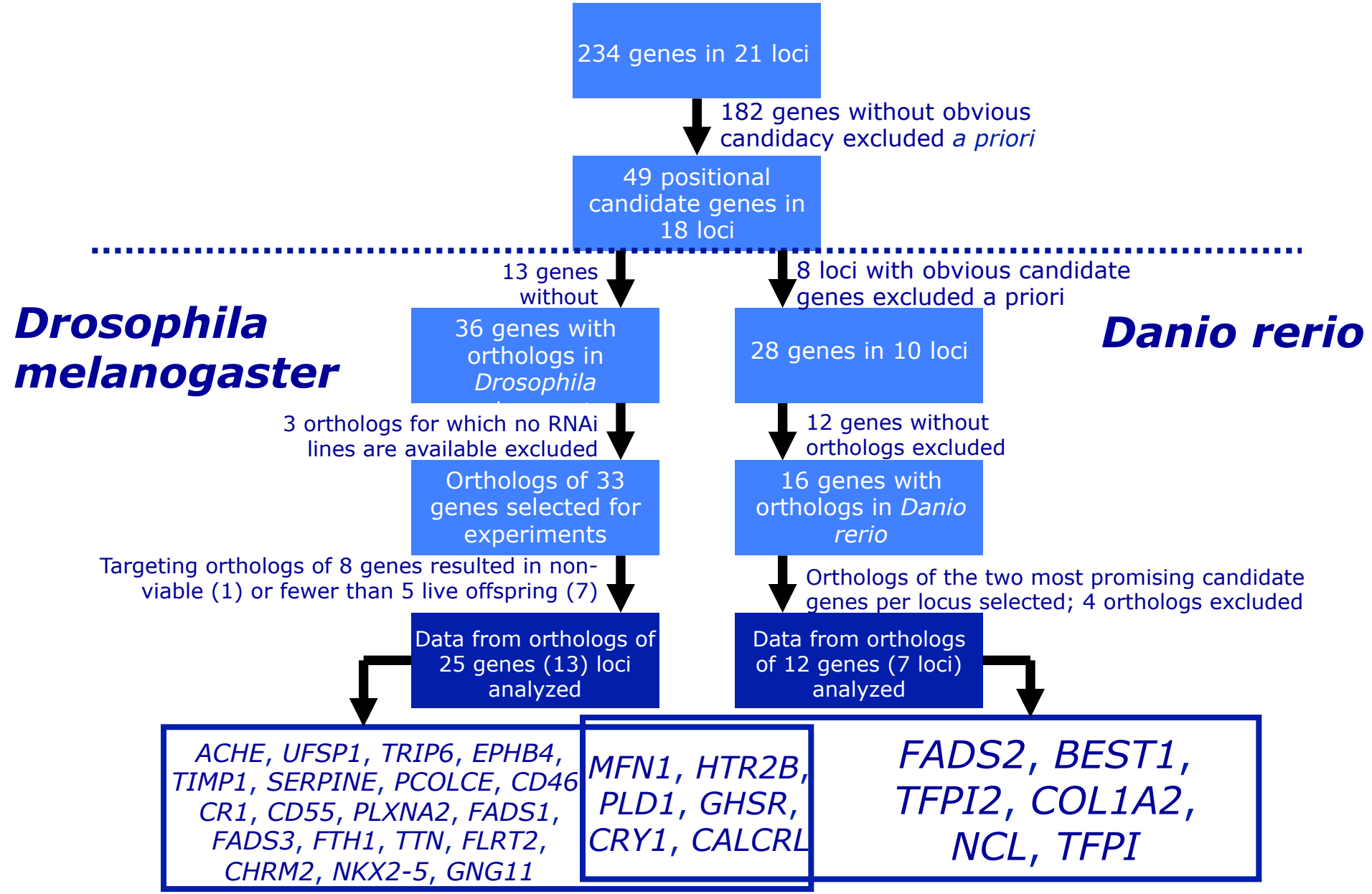

B3GNT7
HapMap
Plotted SNPs
rs13030174
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
SPATA3→
ARMC9→
B3GNT7→
←C2orf52
PTMA→
C2orf72→
←SNORA75
C2orf57→
←PDE6D
←HTR2B
←SNORD20
COPS7B→
PSMD1→
←SNORD82
←NCL
1 gene
omitted
231.6
231.8
232
232.2
Position on chr2 (Mb)


FNDC3B
HapMap
Plotted SNPs
rs9647379
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
←PLD1
FNDC3B→
TMEM212→
←GHSR
173
173.2
173.4
173.6
Position on chr3 (Mb)



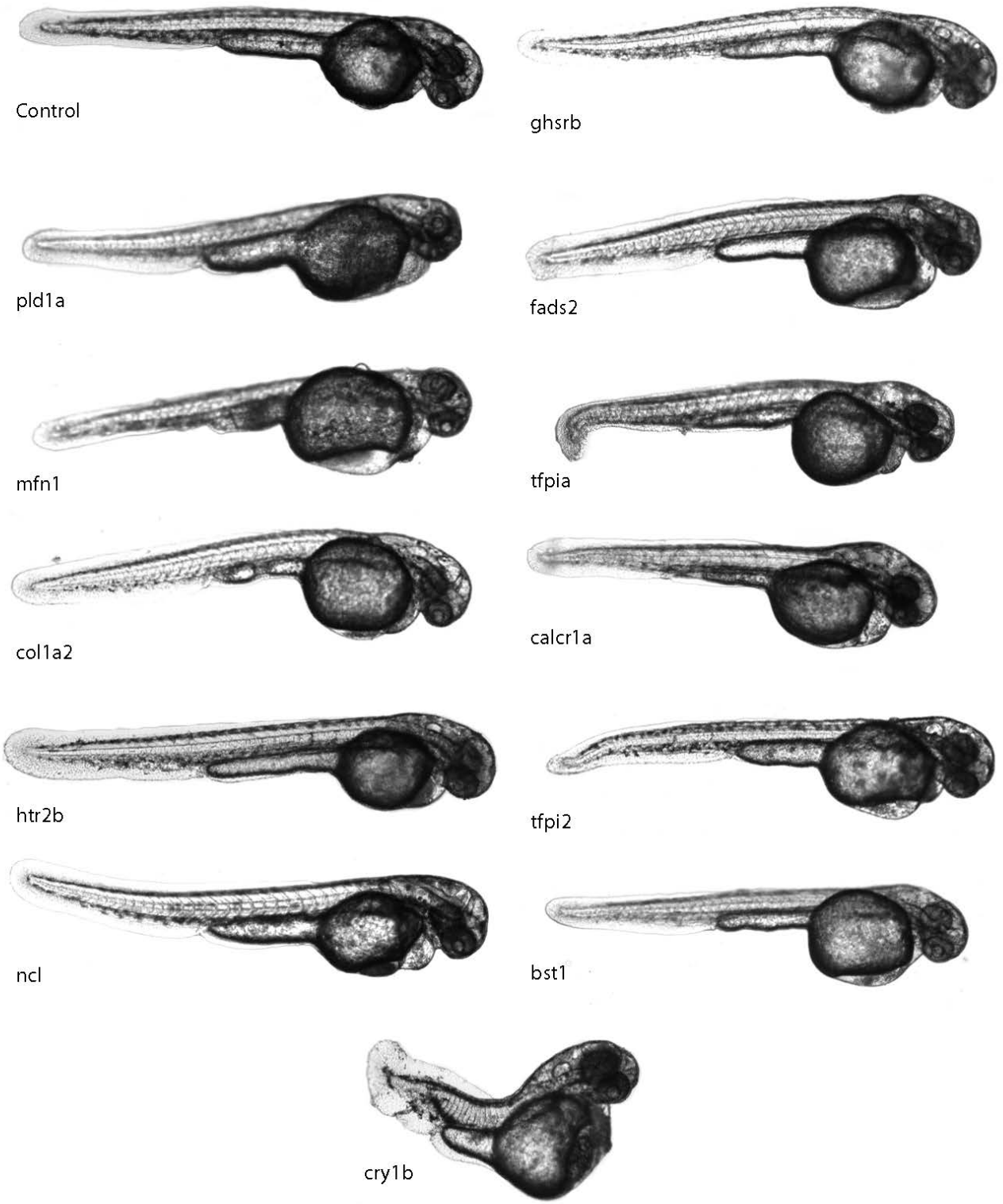
Supplementary Figure 5 – Regional plots of the 21 confirmed heart rate loci with non-synonymous variants and variants representing transcription factor binding sites

For each of the 21 confirmed heart rate loci, the $-\log_{10}$ of the p-value for association with heart rate is shown for all SNPs in the region, plotted by position on the chromosome. The seven previously identified loci are shown first (ordered by p-value after combined meta-analysis of stage 1 and 2 results), followed by the 14 novel loci (ordered by p-value). The lead SNP after meta-analysis of stage 1 is shown in purple and its rs-number is provided. For the *GJA1* and *CD46* loci the secondary SNPs identified by conditional analyses are shown in purple as well. Estimated recombination rates (from HapMap) are provided in cyan and reflect the local LD structure. The SNPs surrounding the most significant association are color-coded to reflect their LD with the lead SNP (taken from pairwise r^2 values from the HapMap CEU database). SNPs are functionally annotated as framestop or splice (triangle), nonsynonymous (inverted triangle), coding synonymous or UTR (square), TFBScons (star), MCS44placenta (square with diagonal cross) and none of the above (circle). Genes, positions of exons and direction of transcription are provided (taken from UCSC genome browser, genome.ucsc.edu). Hash marks represent SNP positions available in the meta-analysis. Plots were generated using LocusZoom (Pruim et al, 2010 [PMID 20634204]).



Supplementary Figure 6 – Flow chart for selection procedure for *Drosophila melanogaster* and *Danio rerio* orthologs of positional candidate genes for heart rate

The flow chart and Venn diagram illustrate the stepwise manner in which 49 positional candidate genes were reduced to orthologs of 25 genes in *Drosophila melanogaster* and 12 genes in *Danio rerio* (zebrafish).



Supplementary Figure 7 – Visible phenotypes in *Danio rerio* with down-regulated expression of orthologs of positional candidate genes

When compared with controls injected with PBS, embryos of *Danio rerio* injected with morpholino oligonucleotides targeting orthologs of positional candidate genes for heart rate show distinct visible phenotypes. We observed 1) edema in embryos with a reduced expression of mfn1 (*MFN1* in humans), tfpla (*TFPI*), tfpl2 (*TFPI2*) and bst1 (*BEST1*); 2) blood pooling in embryos with a reduced expression of fads2 (*FADS2*); 3) an unlooped heart in embryos with a reduced expression of pld1a (*PLD1*), htr2b (*HTR2B*) and ncl (*NCL*); 4) an unlooped heart and atrioventricular malformation in embryos with a reduced expression of calcr1a (*CALCRL*); and 5) dorsalization in embryos with a reduced expression of cry1b (*CRY1*). Embryos with a reduced expression of ghsrb (*GHRS*) and col1a2 (*COL1A2*) did not show distinct visible phenotypes.

1.2 SUPPLEMENTARY TABLES

Supplementary Table 1 Study design, number of individuals and sample quality control for genome-wide association studies of stage 1 (**p17-21)**

Supplementary Table 2 Information on genotyping methods, quality control of SNPs, imputation and statistical analysis for genome-wide association studies of stage 1 (**p22-24**)

Supplementary Table 3 Study-specific descriptive statistics for genome-wide association studies of stage 1 (**p25-29)**

Supplementary Table 4 Sensitivity analyses for meta-analysis of stage 1 results (**p30**)

Supplementary Table 5 The 42 loci associated with heart rate at $p < 3x10^{-5}$ at stage 1, which were taken forward to stage 2 (**p31-32**)

Supplementary Table 6 Conditional analyses using meta-analysis of stage 1 results (**p33**)

Supplementary Table 7 Study design, number of individuals and sample quality control of studies in stage 2 – *in silico* replication using data from studies with data from GWAS, Metabochip and Cardiochip (**p34-35**)

Supplementary Table 8 Information on genotyping methods, quality control of SNPs, imputation and statistical analysis in studies of stage 2 – *in silico* replication using data from studies with data from GWAS, Metabochip and Cardiochip (**p36**)

Supplementary Table 9 Study-specific descriptive statistics of studies contributing to *in silico* replication in stage 2 (**p37-39**)

Supplementary Table 10 Proxy SNPs included in meta-analysis of stage 2 (**p40**)

Supplementary Table 11 Association of previously confirmed GWAS loci for ECG-derived traits with heart rate in stage 1 results (**p41**)

Supplementary Table 12 Association of the heart rate loci with the risk of atrioventricular block, pacemaker implantation and sudden cardiac death in data from deCODE Genetics (**p42**)

Supplementary Table 13 Association of the heart rate loci with blood pressure and the prevalence of hypertension in data from the Global BPgen consortium (**p43**)

Supplementary Table 14 Association of the heart rate loci with the risk of cardiovascular disease in data from the CARDIoGRAM consortium (**44**)

Supplementary Table 15 Association of previously confirmed GWAS loci for blood pressure and prevalence of hypertension with heart rate in stage 1 results (**p45**)

Supplementary Table 16 Association of previously confirmed GWAS loci for prevalence of coronary artery disease and myocardial infarction with heart rate in stage 1 results (**p46**)

Supplementary Table 17 Genes within 500kb of heart rate loci (**p47**)

Supplementary Table 18 Gene set enrichment analysis (MAGENTA) of biological pathways using the heart rate GWAS meta-analysis of stage 1 results (**p48-52**)

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Supplementary Table 22 Potentially functional variants in LD with hart rate-associated SNPs (**p58**)

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Supplementary Table 25 Orthologs and RNAi lines for positional candidate genes in *Drosophila melanogaster* (**p65**)

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Supplementary Table 29 Effects on heart rate and related traits in *Danio rerio* embryos with orthologs of positional candidate genes for heart rate targeted by morpholino oligonucleotides (**p69**)

Supplementary Table 30 Characteristics of *Drosophila melanogaster* pupae and *Danio rerio* embryos transfected for orthologs of candidate genes for heart rate (**p70)**

Supplementary Table 1 - Study design, number of individuals and sample quality control for genome-wide association studies of stage 1

Study Short name	Full name	Study design	Total sample size (N)	Call rate [a]	Sample QC Sample specific QC criteria	Samples in analysis (N) [b]	HR assessment method	References
Advance	Atherosclerosic Disease, Vascular Function and Genetic Epidemiology	Population-based case-control study for CAD	1,028	99.8%	Call rate ≤ 98.5%; Sex and ethnicity verification using clustering	558 (276 CAD cases, 282 controls)	Peripheral pulse rate	[PMID 18443000] [PMID 21378990]
ALSPAC 12-yr old children	Avon Longitudinal Study of Parents And Children Replication	Population-based	1,760	97%	Samples not clustering with CEU in multidimensional scaling; One pair from each putatively related pair; Individuals with missingness > 5%; Individuals with unusual heterozygosities; Individuals with sex discrepancies	1,486	Peripheral pulse rate	[PMID 19181680]
ASCOT cases	Anglo-Scandinavian Cardiac Outcomes Trial	Case-control study of hypertension	3,802	99.7%	Call rate < 95%; Sample cryptic duplicates; first and second degree relatives; sample outliers in ancestry principal component analysis	3,802	Peripheral pulse rate	[PMID 11403364] [PMID 12686036] [PMID 16154016]
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Cohort nested case-control study	4,447	99%	none	4,364	Peripheral pulse rate	[PMID 8205268] [PMID 8127329]
B58C-T1DGC	British 1958 Birth Cohort (Type 1 Diabetes Genetic Consortium Controls)	Population-based birth cohort	2,592	≥ 98%	none	2,564	Peripheral pulse rate	[PMID 19430480] [PMID 17255346]
B58C-WTCCC	British 1958 Birth Cohort (Wellcome trust case control consortium)	Population-based birth cohort	1,480	≥97%	none	1,465	Peripheral pulse rate	[PMID 17554300]
BLSA	Baltimore Longitudinal Study of Aging	Population-based	1,230	>98.5%	Individual of non-European descent (n = 857); Individuals with sex discrepancies	844	Peripheral pulse rate	Shock, N.W., et al., Normal Human Aging: The Baltimore Study of Aging. 1984.
Bright	British Genetics of Hypertension Study	Hypertensive cases	2,000	95.0%	Call rate < 95%; minor allele frequency < 1%	1,879	Peripheral pulse rate	[PMID 12826435] [PMID 17554300]
CoLaus	Cohorte Lausannoise	Population-based	5,636	>98.5%	Individuals with call rate <90%; Related individuals	5,427	Peripheral pulse rate	[PMID 18366642]

Supplementary Table 1 - continued

Study Short name	Full name	Study design	Total sample size (N)	Call rate [a]	Sample QC Sample specific QC criteria	Samples in analysis (N) [b]	HR assessment method	References
Corogene	Corogene Study	Population-based ACS cases	2,169	99.8%	Individuals with heart rate > 100 bpm; Individuals with call rate < 95 %; Related individuals (pi hat > 0.2 with another sample); Individuals showing evidence of cryptic relatedness (pi hat 0.05-0.02 with many samples in dataset)	1,713	ECG	[PMID 21642350]
deCODE	deCODE Study	Population-based	~48,000	≥98%	Yield < 95% in cases or controls; minor allele frequency < 1% in the population; significant deviation from HWE in controls ($p < 0.001$); call rate < 98%	11,207	ECG	[PMID 21378987]
DGI	Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University and Novartis Institutes of Biomedical Research	Case-control of type 2 diabetes	3,142	>95%	Gender inconsistency; First degree cryptic relationship	2,678 (1,235 cases, 1,443 controls)	Peripheral pulse rate	[PMID 17463246]
EGCUT	Estonian Genome Centre, University of Tartu	Population-based	2,200	>98%	Individuals with call-rate ≤ 98%; Individuals with cryptic relatedness; Genetic outliers from PC analyses	2,045	Peripheral pulse rate	[PMID 19424496] Metspa;u, A. The Estonian Genome Project. Drug Development Research 62, 97-101 (2004).
EPIC-Norfolk	European Prospective Investigation into Cancer and Nutrition Norfolk	Population-based	2,566	94%	Heterozygosity < 23% or > 30%; > 5.0% discordance in SNP pairs with $r^2=1$ in HapMap; Ethnic outliers; Related individuals; Duplicates	2,413	Peripheral pulse rate	[PMID 10466767]
Fenland	Fenland study	Population-based	1,402	≥95%	Individuals with failed heterozygosity check (upperbound 0.2882 lowerbound 0.2735); Individuals with failed relatedness check (sample with lower call rate in related samples); Individuals with failed duplicate check (sample with lower call rate in duplicates)	1,402	Peripheral pulse rate	[PMID 21248185]
Fingesture	Fingesture study	Myocardial Infarction cases	1,039	99.6%	Sample genotyping rate ≤97%	494	ECG	[PMID 12932596] [PMID 17000909]

Supplementary Table 1 - continued

Study Short name	Full name	Study design	Total sample size (N)	Call rate [a]	Sample QC Sample specific QC criteria	Samples in analysis (N) [b]	HR assessment method	References
Finrisk	Finrisk study	Population-based	1,579	99.8%	Individuals with call rate < 95 %; Related individuals (pi hat > 0.2 with another sample); Individuals showing evidence of cryptic relatedness (pi hat 0.05-0.02 with many samples in dataset)	1,573	Peripheral pulse rate	The National FINRISK Study, National Institute for Health and Welfare. (Accessed 6.4.2011, at www.ktl.fi/portal/4168.)
Fusion	Finland – United States Investigation of NIDDM Genetics	Case-control of type 2 diabetes	2,333	>97.5%	Gender inconsistency; Related individuals	2,256 (1,086 cases, 1,170 controls)	Peripheral pulse rate	[PMID: 17463248]
GOOD	The Gothenburg Osteoporosis and Obesity Determinants Study	Population-based	1,056	97.5%	Heterozygosity > 33%; Ethnic outliers; Related individuals and duplicates	938	Peripheral pulse rate	[PMID: 16007330]
HAPI	Heredity and Phenotype Intervention Heart Study	Family-based	868	>93%	none	847	ECG	[PMID 18440328]
HBCS	Helsinki Birth Cohort Study	Population-based	1,676	99.8%	Individuals with call rate < 95 %; Related individuals (pi hat > 0.2 with another sample); Individuals showing evidence of cryptic relatedness (pi hat 0.05-0.02 with many samples in dataset)	1,293	Peripheral pulse rate	IDEFIX Study. National Institute for Health and Welfare, 2009. (Accessed 6.4.2011, 2010, at http://www.ktl.fi/portal/5481.)
Health2000	Health 2000 / GENMETS sub-study	Case-control of metabolic syndrome	2.118	99.9%	Individuals with call rate < 95 %; Related individuals (pi hat > 0.2 with another sample); Individuals showing evidence of cryptic relatedness (pi hat 0.05-0.02 with many samples in dataset)	1,737 (870 cases, 867 controls)	Peripheral pulse rate	[PMID 20673644]
Health ABC	Health Aging and Body Composition Study	Population-based	1,814	>97%	Sample failure; Genotypic sex mismatch; First-degree relatives based on genotype data	1663	ECG	[PMID 19435951] [PMID 12902529]
Heritage	Heritage Family Study	Family-based	499	99.9%	Individuals with call-rate ≤ 95%; Mendelian check; Inconsistent duplicates (12 samples genotyped in duplicate (100% concordance))	499	ECG	[PMID 11194095] [PMID 21183627]

Supplementary Table 1 - continued

Study Short name	Full name	Study design	Total sample size (N)	Call rate [a]	Sample QC Sample specific QC criteria	Samples in analysis (N) [b]	HR assessment method	References
HPFS CHD	Health Professional Follow-up Study	Nested case-control study (population-based) of coronary heart disease	1,313	99.8%	Individuals with call rate <98%; Sex discrepancy with genetic data from X-linked markers; Duplicates; First/second degree relatives; Ancestry outliers; Heterozygosity	1,065 (348 cases, 717 controls)	Self-reported peripheral pulse rate	[PMID 1678444]
HPFS Kidney stone disease	Health Professional Follow-up Study	Nested case-control study (population-based) of kidney stone disease	565	99.7%	Individuals with call rate <95%; Duplicates; First/second degree relatives; Ancestry outliers	530 (303 cases, 227 controls)	Self-reported peripheral pulse rate	[PMID 1678444]
HPFS type 2 diabetes	Health Professional Follow-up Study	Nested case-control study (population-based) of type 2 diabetes	2,487	99.7%	Individuals with call rate <98%; Sex discrepancy with genetic data from X-linked markers; Duplicates; First/second degree relatives; Ancestry outliers; Heterozygosity; Autosomal chromosome aberrations	2,271 (1,074 cases, 1,197 controls)	Self-reported peripheral pulse rate	[PMID 1678444]
Hypergenes	Hypergenes Study	Case-control of hypertension	4,058	>98.5%	Individuals with call rate <90%; Related individuals	3,146 (1,518 cases, 1,628 controls)	Peripheral pulse rate	
InCHIANTI	InCHIANTI Study	Population-based	1,210	>97%	Sex misspecification; Heterozygosity < 0.3	1,129	ECG	[PMID 11129752]
Korcula	CROATIA-Korcula	Population-based (isolated)	898	>97%	none	353	ECG	[PMID 1926014]
LifeLines	LifeLines Study	Population-based	3,367	95%	Non-Caucasian individuals; Related individuals (pi-hat > 0.4); Individuals with a gender mismatch	3,363	ECG	[PMID 18075776]
Lolipop Cohort	London Life Sciences Prospective Population Cohort	Population-based	2684	>90%	Duplicates; Individuals with call rate <90%; Related and contaminated samples	1,869	ECG	[PMID 18454146]
Lolipop	London Life Sciences Prospective Population Cohort	Case-control of coronary heart disease	6557	≥ 95%	Duplicates; Sex inconsistencies; Related individuals; Individuals with call rate <95%; Ethnic outliers	4,699 (1,448 cases, 3,251 controls)	ECG	[PMID 20062061]
NBS	Nijmegen Biomedical Study	Population-based	1,832	≥95%	none	551	Peripheral pulse rate	[PMID 19417041]
NFBC-1966	Northern Finland Birth Cohort 1966	Population-based	4,772	95%	First two principal components used to control for population structure	4,594	Peripheral pulse rate	[PMID 19060910]

Supplementary Table 1 - continued

Study Short name	Full name	Study design	Total sample size (N)	Call rate [a]	Sample QC Sample specific QC criteria	Samples in analysis (N) [b]	HR assessment method	References
NHS Cancer	Nurses' Health Study	Nested case-control study (population-based) of breast cancer	2,287	99.8%	Individuals with call rate <90%; Duplicates; First/second degree relatives; Ancestry outliers	1,889 (965 cases, 924 controls)	Self-reported peripheral pulse rate	[PMID 15864280]
NHS CHD	Nurses' Health Study	Nested case-control study (population-based) of coronary heart disease	1,146	99.8%	Individuals with call rate <98%; Individuals with sex discrepancy with genetic data from X-linked markers; Duplicates; First/second degree relatives; Ancestry outliers; Heterozygosity	1,020 (297 cases, 723 controls)	Self-reported peripheral pulse rate	[PMID 15864280]
NHS Kidney stone disease	Nurses' Health Study	Nested case-control study (population-based) of kidney stone disease	504	99.7%	Individuals with call rate <95%; Duplicates; First/second degree relatives; Ancestry outliers	457 (301 cases, 156 controls)	Self-reported peripheral pulse rate	[PMID 15864280]
NHS type 2 diabetes	Nurses' Health Study	Nested case-control study (population-based) of type 2 disease	3,286	99.7%	Individuals with call rate <98%; Sex discrepancy with genetic data from X-linked markers; Duplicates; First/second degree relatives; Ancestry outliers; Heterozygosity; Autosomal chromosome aberrations	2,878 (1,319 cases, 1,559 controls)	Self-reported peripheral pulse rate	[PMID 15864280]
NSPHS06	Northern Swedish Population Health Study 2006	Population-representative, pedigree-based	656	99.4%	Individuals with ID call rate <97%; Identical twins and genetic outliers	591	Peripheral pulse rate	[PMID 20568910] [PMID 18952825]
Prevend	Prevention of Renal and Vascular End-stage Disease	Population-based	8,592	>98%	Individuals of non-European descent; Individuals with gender inconsistencies; SNP genotyping rate > 98%	3,791	ECG	[PMID 21076409]
Split	CROATIA-Split	Population-based	499	>97%	none	396	ECG	[PMID 19260138]
YFS	Young Finns Study	Population-based	2,443	99.8%	Individuals with call rate < 95%; Related individuals (pi hat > 0.2 with another sample); Individuals showing evidence of cryptic relatedness (pi hat 0.05-0.02 with many samples in dataset)	2,083	Peripheral pulse rate	[PMID 18263651]

[a] Sample genotyping success rate, i.e. percentage of successfully genotyped SNPs per sample. [b] Ns reported are numbers for which association data was provided; Ns in paper may differ due to effective sample size in meta-analysis.

Supplementary Table 2 - Information on genotyping methods, quality control of SNPs, imputation and statistical analysis for genome-wide association studies of stage 1

Study	Genotyping						Imputation								
			Inclusion criteria					Inclusion criteria		SNPs in GWAS			λ_{GC}		
	Platform	Genotype calling algorithm	MAF	Call rate [a]	p HWE	SNPs that met QC criteria	Imputation software	MAF	Imputation quality [b]	Men	Women	Combined	Men	Women	Combined	Analysis software
Advance CAD cases	Illumina 550k	Beadstudio	none	≥98.5%	$>10^{-03}$	543,985	BimBam	none	proper-info ≥ 0.4	2,170,268	2,202,369	-	1.042	1.034	-	SNPtest
Advance CAD controls	Illumina 550k	Beadstudio	none	≥98.5%	$>10^{-03}$	543,985	BimBam	none	proper-info ≥ 0.4	2,188,816	2,222,325	-	1.013	0.980	-	SNPtest
ALSPAC 12-yr old children	Illumina 317k	Beadstudio	>1%	>95%	$>10^{-07}$	315,807	MACH	>1%	r^2 hat ≥ 0.3	2,469,776	2,470,902	-	0.982	1.000	-	MACH2QTL
ASCOT cases	Illumina Human 370CNV	Beadstudio	> 0%	>97%	$>10^{-07}$	283,291	MACH	none	r^2 hat ≥ 0.3	2,477,983	2,461,362	-	1.005	1.002	-	MACH2QTL
ATBC cases	Illumina 550k	Beadstudio	none	≥97%	none	589,345	IMPUTE	none	proper-info ≥ 0.4	2,532,074	-	-	1.014	-	-	SNPtest
ATBC controls	Illumina 550k	Beadstudio	none	≥97%	none	589,345	IMPUTE	none	proper-info ≥ 0.4	2,532,074	-	-	1.014	-	-	SNPtest
B58C-T1DGC	Illumina 550k	ILLUMINUS	>0%	none	none	539,458	MACH	none	r^2 hat ≥ 0.3	2,507,130	2,507,796	-	1.005	0.996	-	ProbABEL
B58C-WTCCC	Affymetrix GeneChip Human Mapping 500k	CHIAMO	>0%	none	none	490,032	IMPUTE	none	proper-info ≥ 0.4	2,442,062	2,440,831	-	1.025	1.008	-	SNPtest
BLSA	Illumina 550k	Beadstudio	≥1%	≥98.5	$>10^{-04}$	514,027	MACH	≥1%	r^2 hat ≥ 0.3	2,452,788	2,453,963	-	1.030	0.986	-	Merlin
Bright	Affymetrix GeneChip Human Mapping 500k	CHIAMO	≥5%	≥95%	$>10^{-06}$	387,666	IMPUTE	none	proper-info ≥ 0.4	1,566,044	1,569,765	-	1.014	1.000	-	SNPtest
CoLaus	Affymetrix GeneChip Human Mapping 500k	BRLMM	≥1%	≥70%	$>10^{-07}$	390,631	IMPUTE	none	proper-info ≥ 0.4	2,435,038	2,435,772	-	1.000	1.002	-	Matlab
Corogene	Illumina 610k	Illuminus	≥1%	≥95%	$>10^{-06}$	554,988	MACH	none	r^2 hat ≥ 0.3	2,476,908	2,455,987	-	1.006	1.004		ProbABEL
deCODE	Illumina HumanHap 300 / CNV370 / 610K / 1M	Beadstudio	≥1%	≥98%	$>10^{-03}$	306,060	IMPUTE	none	proper-info ≥ 0.4	-	-	2,499,244	-	-	1.185	SNPtest
DGI Cases	Affymetrix GeneChip Human Mapping 500k	BRLMM	>5%	≥95%	$>10^{-06}$	347,010	MACH	≥1%	r^2 hat ≥ 0.3	2,197,687	2,307,762	-	1.038	1.138	-	ProbABEL / PLINK
DGI controls	Affymetrix GeneChip Human Mapping 500k	BRLMM	>5%	≥95%	$>10^{-06}$	347,010	MACH	≥1%	r^2 hat ≥ 0.3	2,373,737	2.373,024	-	0.996	1.038	-	ProbABEL / PLINK
EGCUT	Illumina Human 370CNV	Beadstudio	≥1%	≥98%	$>10^{-06}$	299,484	IMPUTE	none	proper-info ≥ 0.4	2,449,580	2,452,359	-	1.005	1.013	-	SNPtest

Supplementary Table 2 - Continued

	Genotyping						Imputation								
			Inclusion criteria					Inclusion criteria	SNPs in GWAS			λ_{GC}			
Study	Platform	Genotype calling algorithm	MAF	Call rate [a]	*P* HWE	SNPs that met QC criteria	Imputation software	MAF	Imputation quality [b]	Men	Women	Combined	Men	Women	Combined	Analysis software
EPIC-Norfolk	Affymetrix GeneChip Human Mapping 500k	BRLMM	≥1%	≥90%	$>10^{-06}$	397,438	IMPUTE	none	proper-info ≥ 0.4	2,384,644	2,385,927	-	1.010	1.020	-	SNPtest
Fenland	Affymetrix GeneChip Human Mapping 500k	BRLMM	≥1%	≥90%	$>10^{-06}$	362,055	IMPUTE	none	proper-info ≥ 0.4	2,393,893	2,398,580	-	1.026	1.007	-	SNPtest
Fingesture	Affymetrix SNP 6.0	Birdsuite	>5%	≥95%	none	628,197	MACH	none	r^2 hat ≥ 0.3	2,413,618	2,302,288	-	0.992	1.013	-	MACH2QTL
Finrisk	Illumina 610k	Illuminus	≥1%	≥95%	$>10^{-06}$	554,998	MACH	none	r^2 hat ≥ 0.3	2,475,284	2,470,227	-	1.006	1.001	-	ProbABEL
Fusion cases	Illumina Infinium II HumanHap 300	Beadstudio	>1%	≥90%	$\geq 10^{-06}$	315,635	MACH	none	r^2 hat ≥ 0.3	2,452,444	2,441,621	-	0.989	1.036	-	MACH2QTL
Fusion controls	Illumina Infinium II HumanHap 300	Beadstudio	>1%	≥90%	$\geq 10^{-06}$	315,635	MACH	none	r^2 hat ≥ 0.3	2,449,757	2,451,127	-	0.984	1.017	-	MACH2QTL
GOOD	Illumina 610k	Beadstudio	≥1%	≥98%	$>10^{-06}$	521,160	MACH	none	r^2 hat ≥ 0.3	2,489,341	-	-	1.012	-	-	MACH2QTL via GRIMP
HAPI	Affymetrix GeneChip Human Mapping 500k	BRLMM	>1%	>95%	$\geq 10^{-06}$	338,593	MACH	none	r^2 hat ≥ 0.3	-	-	2,290,109	-	-	1.052	MMAP
HBCS	Illumina 670k	Illuminus	≥1%	≥95%	$>10^{-06}$	546,814	MACH	none	r^2 hat ≥ 0.3	2,468,180	2,474,682	-	0.994	1.001	-	ProbABEL
Health 2000 cases	Illumina 610k	Illuminus	≥1%	≥95%	$>10^{-06}$	555,388	MACH	none	r^2 hat ≥ 0.3	2,440,493	2,440,623	-	0.986	1.011	-	ProbABEL
Health 2000 controls	Illumina 610k	Illuminus	≥1%	≥95%	$>10^{-06}$	555,388	MACH	none	r^2 hat ≥ 0.3	2,440,282	2,443,226	-	0.997	1.004	-	ProbABEL
Health ABC	Illumina Human 1M	Beadstudio	≥1%	>97%	$\geq 10^{-06}$	914,263	MACH	≥1%	r^2 hat ≥ 0.3	2,502,586	2,500,872	-	1.015	1.003	-	R
Heritage	Illumina 370k	GenomeStudio	>1%	>95%	$>10^{-06}$	324,611	MACH	none	r^2 hat ≥ 0.3	-	-	2,227,923	-	-	1.042	Merlin
HPFS CHD cases	Affymetrix SNP 6.0	Birdseed	≥2%	≥98%	$\geq 10^{-04}$	724,881	MACH	none	r^2 hat ≥ 0.3	2,464,474	-	-	1.015	-	-	ProbABEL
HPFS CHD controls	Affymetrix SNP 6.0	Birdseed	≥2%	≥98%	$\geq 10^{-04}$	724,881	MACH	none	r^2 hat ≥ 0.3	2,489,985	-	-	1.013	-	-	ProbABEL
HPFS Kidneystone cases	Illumina 610k	Beadstudio	≥1%	≥95%	$\geq 10^{-05}$	546,344	MACH	none	r^2 hat ≥ 0.3	2,461,670	-	-	1.014	-	-	ProbABEL
HPFS Kidneystone controls	Illumina 610k	Beadstudio	≥1%	≥95%	$\geq 10^{-05}$	546,344	MACH	none	r^2 hat ≥ 0.3	2,437,287	-	-	0.991	-	-	ProbABEL
HPFS t2d cases	Affymetrix SNP 6.0	Birdseed	≥2%	≥98%	$\geq 10^{-04}$	706,040	MACH	none	r^2 hat ≥ 0.3	2,496,777	-	-	0.991	-	-	ProbABEL
HPFS t2d controls	Affymetrix SNP 6.0	Birdseed	≥2%	≥98%	$\geq 10^{-04}$	706,040	MACH	none	r^2 hat ≥ 0.3	2,497,949	-	-	0.987	-	-	ProbABEL

Supplementary Table 2 - Continued

	Genotyping						Imputation								
			Inclusion criteria					Inclusion criteria		SNPs in GWAS			λ_{GC}		
Study	Platform	Genotype calling algorithm	MAF	Call rate [a]	p HWE	SNPs that met QC criteria	Imputation software	MAF	Imputation quality [b]	Men	Women	Combined	Men	Women	Combined	Analysis software
Hypergenes cases	Illumina Human 1M	Beadstudio	>1%	>90%	$\geq 10^{-07}$	839,514	MACH	none	r^2 hat ≥ 0.3	2,497,650	2,483,920	-	1.000	1.000	-	Matlab
Hypergenes controls	Illumina Human 1M	Beadstudio	>1%	>90%	$\geq 10^{-07}$	839,514	MACH	none	r^2 hat ≥ 0.3	2,497,226	2,489,973	-	1.001	1.001	-	Matlab
Inchianti	Illumina 550k	Beadstudio	≥1%	≥97%	$>10^{-06}$	498,838	MACH	≥1%	r^2 hat ≥ 0.3	2,447,636	2,447,644	-	1.033	1.004	-	Merlin
Korcula	Illumina 370k	GenomeStudio	>1%	>98%	$>10^{-06}$	330,889	MACH	None	r^2 hat ≥ 0.3		-	2,381,518	-	-	1.058	GenABEL / ProbABEL
LifeLines	Illumina HumanCyto SNP 12 V2	GenomeStudio	>1%	>95%	$>10^{-05}$	247,151	IMPUTE	none	proper-info ≥ 0.4	2,435,581	2,437,849	-	1.008	1.007	-	SNPtest
Lolipop Cohort	Illumina HumanHap 300K	Beadstudio	≥1%	>90%	$>10^{-06}$	245,892	MACH	none	r^2 hat ≥ 0.3	1,896,229	-	-	0.992	-	-	MACH2QTL
Lolipop Cases	Illumina Human610	Beadstudio	≥1%	>90%	$>10^{-06}$	544,390	MACH	none	r^2 hat ≥ 0.3	2,225,030	2,222,309	-	1.004	0.989	-	MACH2QTL
Lolipop Controls	Illumina Human610	Beadstudio	≥1%	>90%	$>10^{-06}$	544,390	MACH	none	r^2 hat ≥ 0.3	2,225,021	2,224,640	-	1.007	0.996	-	MACH2QTL
NBS	Illumina Human 370CNV	beadstudio	none	≥98%	$\geq 10^{-10}$	302,140	IMPUTE	none	proper-info ≥ 0.4	-	-	1,813,776	-	-	0.980	SNPtest
NFBC-1966	Illumina 370k	Beadstudio	≥5%	≥95%	$>10^{-04}$	328,007	IMPUTE	none	proper-info ≥ 0.4	2,217,812	2,217,855	-	1.017	1.012	-	SNPtest
NHS Cancer cases	Illumina 550k	BeadStudio	≥1%	≥90%	none	546,646	MACH	none	r^2 hat ≥ 0.3	-	2,501,568	-	-	0.987	-	ProbABEL
NHS Cancer controls	Illumina 550k	BeadStudio	≥1%	≥90%	none	546,646	MACH	none	r^2 hat ≥ 0.3	-	2,500,201	-	-	1.014	-	ProbABEL
NHS CHD cases	Affymetrix SNP 6.0	Birdseed v2	≥2%	≥98%	$\geq 10^{-04}$	721,316	MACH	none	r^2 hat ≥ 0.3	-	2,449,640	-	-	1.026	-	ProbABEL
NHS CHD controls	Affymetrix SNP 6.0	Birdseed v2	≥2%	≥98%	$\geq 10^{-04}$	721,316	MACH	none	r^2 hat ≥ 0.3	-	2,488,711	-	-	1.011	-	ProbABEL
NHS Kidney stones cases	Illumina 610Q	BeadStudio	≥1%	≥95%	$\geq 10^{-05}$	546,344	MACH	none	r^2 hat ≥ 0.3	-	2,457,587	-	-	1.020	-	ProbABEL
NHS Kidney stones controls	Illumina 610Q	BeadStudio	≥1%	≥95%	$\geq 10^{-05}$	546,344	MACH	none	r^2 hat ≥ 0.3	-	2,389,337	-	-	1.008	-	ProbABEL
NHS t2d cases	Affymetrix SNP 6.0	Birdseed v2	≥2%	≥98%	$\geq 10^{-04}$	704,409	MACH	none	r^2 hat ≥ 0.3	-	2,498,519	-	-	1.002	-	ProbABEL
NHS t2d controls	Affymetrix SNP 6.0	Birdseed v2	≥2%	≥98%	$\geq 10^{-04}$	704,409	MACH	none	r^2 hat ≥ 0.3	-	2,500,345	-	-	1.021	-	ProbABEL
NSPHS06	Illumina Infinium II HumanHap 300v2	BeadStudio	≥1%	≥98%	$>10^{-06}$	318,236	MACH	none	r^2 hat ≥ 0.3	-	-	2,382,230	-	-	0.975	R / GenABEL / ProbABEL
Prevend	Illumina HumanCyto SNP	GenomeStudio	>1%	>95%	$>10^{-05}$	244868	BEAGLE	none	info > 0.8	1,330,278	1,330,539	-	1.017	1.006	-	PLINK
Split	Illumina 370k	GenomeStudio	>1%	>98%	$>10^{-06}$	316,643	MACH	none	r^2 hat ≥ 0.3	-	-	2,431,670	-	-	0.984	GenABEL / ProbABEL
YFS	Illumina 610k	Illuminus	≥1%	≥95%	$>10^{-06}$	546,677	MACH	none	r^2 hat ≥ 0.3	2,468,546	2,472,150	-	1.006	1.015	-	ProbABEL

[a] Sample genotyping success rate; that is, the percentage of successfully genotypes SNPs per sample.

[b] SNPtest calculates the 'proper info' statistics as a measure of the relative statistical information about the additive genetic effect being estimated. The proper info statistic has a direct relationship to the power of the test and ranges from 0 to 1, with 1 indicating perfect imputation. MACH calculates rsq_hat, which is the r^2 between each imputed genotype and its true underlying genotype. Rsq_hat ranges from 0 to 1, with 1 indicating perfect imputation.

Supplementary Table 3 - Study-specific descriptive statistics for genome-wide association studies of stage 1

Study	Trait	Men						Women					
		N	mean	SD	median	min	max	N	mean	SD	median	min	max
Advance CAD cases	Age (yrs)	113	40.5	3.9	41.3	20.4	45.1	160	49.5	4.7	50.5	34.0	55.0
	BMI (kg/m^2)	113	31.2	5.4	30.9	19.5	43.6	160	31.2	7.9	30.6	17.3	61.1
	HR (BPM)	113	62.2	9.6	62.0	43.0	95.0	160	63.8	10.4	62.0	42.0	103.0
Advance CAD controls	Age (yrs)	127	40.5	3.2	41.2	33.4	46.8	181	48.7	4.5	49.9	34.8	55.4
	BMI (kg/m^2)	127	27.0	4.5	26.3	17.9	49.4	181	26.1	6.4	24.7	15.8	54.1
	HR (BPM)	127	64.8	12.3	64.0	40.0	132.0	181	65.7	11.9	66.0	45.0	160.0
ALSPAC 12-yr old children	Age (yrs)	722	11.7	2.2	11.7	11.2	12.4	764	11.7	2.4	11.7	10.6	13.3
	BMI (kg/m^2)	722	18.6	3.1	17.9	12.8	30.9	764	19.0	3.2	18.4	12.4	34.1
	HR (BPM)	722	72.5	10.4	72.0	44.5	111.5	764	77.4	10.5	77.0	49.5	110.0
ASCOT cases	Age (yrs)	3,129	63.5	8.2	64.0	40.0	80.0	673	64.5	7.6	64.0	41.0	80.0
	BMI (kg/m^2)	3,129	28.9	4.6	28.4	15.1	88.8	673	29.4	5.7	28.7	16.5	52.1
	HR (BPM)	3,129	70.2	12.1	69.0	40.5	115.5	673	72.6	12.2	72.0	45.0	125.0
ATBC cases	Age (yrs)	2,782	58.2	4.9	58.0	49.0	70.0						
	BMI (kg/m^2)	2,782	26.0	3.7	25.7	16.9	49.4						
	HR (BPM)	2,782	72.1	10.9	72.0	42.0	132.0						
ATBC controls	Age (yrs)	1,582	57.8	5.1	57.0	49.0	70.0						
	BMI (kg/m^2)	1,582	26.4	3.8	26.2	16.1	45.7						
	HR (BPM)	1,582	70.8	10.9	70.0	46.0	118.0						
B58C T1DGC	Age (yrs)	1,249	45.3	0.3	45.3	44.5	46.0	1,315	45.3	0.3	45.3	44.5	46.0
	BMI (kg/m^2)	1,249	28.0	4.1	27.6	16.8	51.6	1,315	26.9	5.5	25.7	17.2	52.2
	HR (BPM)	1,249	70.3	11.0	42.0	70.0	109.0	1,315	72.3	10.1	72.0	39.0	111.0
B58C WTCCC	Age (yrs)	738	44.9	0.3	44.8	44.5	45.6	727	44.9	0.4	44.8	44.5	45.6
	BMI (kg/m^2)	738	27.8	4.3	27.2	15.9	48.4	727	26.8	5.2	25.5	17.3	54.0
	HR (BPM)	738	69.9	11.3	69.0	42.0	113.0	727	72.6	9.9	72.0	44.0	106.0
BLSA	Age (yrs)	460	70.8	15.8	74.0	22.0	96.0	384	65.5	17.5	66.0	21.0	97.0
	BMI (kg/m^2)	460	27.3	4.4	26.6	19.2	45.2	384	25.7	4.8	24.8	16.8	46.9
	HR (BPM)	460	65.1	12.0	64.0	40.0	108.0	384	68.1	10.8	67.0	42.0	128.0
Bright cases	Age (yrs)	746	56.0	12.0	57.0	17.0	82.0	1,133	54.0	12.0	55.0	17.0	82.0
	BMI (kg/m^2)	746	28.0	3.0	28.0	17.0	40.0	1,133	27.0	4.0	27.0	17.0	42.0
	HR (BPM)	746	69.0	12.0	69.0	42.0	112.0	1,133	70.0	12.0	69.0	40.0	111.0
CoLAUS	Age (yrs)	2,560	52.9	10.6	52.2	34.9	75.1	2,867	53.9	10.7	53.7	35.0	75.4
	BMI (kg/m^2)	2,560	26.6	4.0	26.2	11.7	81.1	2,867	25.2	4.8	24.2	8.1	59.2
	HR (BPM)	2,560	67.4	10.6	67.0	40.0	158.0	2,867	68.6	9.1	68.0	42.5	116.5
Corogene cases	Age (yrs)	1,166	64.5	11.5	64.6	26.5	91.8	547	70.6	11.1	71.9	33.3	98.8
	BMI (kg/m^2)	1,166	27.6	4.3	26.9	18.0	52.5	547	27.1	5.4	26.8	13.6	57.7
	HR (BPM)	1,166	66.5	13.2	65.0	32.0	100.0	547	68.1	13.1	67.0	37.0	100.0

Supplementary Table 3 - continued

Study	Trait	Men						Women					
		N	mean	SD	median	min	max	N	mean	SD	median	min	max
deCODE	Age (yrs)	4,743	70.8	12.5	72.8	16.9	101.7	6,464	68.7	14.7	71.1	18.9	103.8
	BMI (kg/m^2)	4,743	27.9	4.7	27.2	14.5	72.1	6,464	27.4	5.5	26.6	13.7	70.2
	HR (BPM)	4,743	72.5	14.9	70.5	38.0	173.0	6,464	75.4	15.1	73.1	32.0	160.0
DGI cases	Age (yrs)	620	62.4	10.1	63.5	36.9	90.5	615	64.5	10.4	65.2	31.1	86.4
	BMI (kg/m^2)	620	28.2	3.9	28.1	18.0	46.7	615	29.0	4.9	28.5	18.5	53.7
	HR (BPM)	620	65.1	15.3	66.0	30.0	100.0	615	67.6	14.1	70.0	30.0	100.0
DGI controls	Age (yrs)	695	58.0	10.2	58.4	31.7	83.6	748	58.8	10.0	59.3	33.7	85.8
	BMI (kg/m^2)	695	26.7	3.2	26.4	17.0	43.9	748	26.8	4.3	26.3	18.0	45.6
	HR (BPM)	695	63.5	10.3	64.0	30.0	93.0	748	65.3	11.9	66.0	30.0	100.0
EGCUT	Age (yrs)	938	40.0	16.4	37.0	18.0	90.0	1,107	41.3	15.9	40.0	18.0	92.0
	BMI (kg/m^2)	938	25.9	4.5	25.2	15.8	54.0	1,107	25.8	5.9	24.5	15.6	58.4
	HR (BPM)	938	69.0	10.1	68.0	44.0	120.0	1,107	68.7	8.2	68.0	44.0	120.0
EPIC-Norfolk	Age (yrs)	1,130	59.8	9.1	60.0	40.0	77.0	1,280	58.7	8.9	59.0	39.0	77.0
	BMI (kg/m^2)	1,130	26.6	3.2	26.2	16.9	42.1	1,280	26.2	4.3	25.5	16.1	47.6
	HR (BPM)	1,130	68.7	11.8	67.5	38.0	115.5	1,280	72.8	10.7	72.0	43.5	113.0
Fenland	Age (yrs)	615	44.5	7.3	45.0	30.0	57.0	787	45.3	7.2	46.0	30.0	57.0
	BMI (kg/m^2)	615	27.6	4.1	27.3	18.6	56.7	787	26.7	5.5	25.4	17.3	55.4
	HR (BPM)	615	60.6	8.8	59.0	38.0	102.0	785	63.8	8.4	63.0	43.0	105.0
Fingesture cases	Age (yrs)	377	60.0	9.9	61.0	34.0	76.0	117	64.3	9.6	66.0	28.0	76.0
	BMI (kg/m^2)	377	27.7	3.8	27.4	16.7	46.1	117	27.4	4.1	26.6	19.6	39.8
	HR (BPM)	360	64.2	11.4	62.5	42.1	115.4	117	68.5	13.6	66.7	46.5	112.2
Finrisk	Age (yrs)	1,000	54.3	12.2	55.0	25.0	74.0	878	57.0	12.0	59.0	25.0	74.0
	BMI (kg/m^2)	1,000	27.2	3.9	26.7	16.2	43.0	878	26.8	5.0	25.9	16.3	50.6
	HR (BPM)	1,000	70.1	12.6	68.0	44.0	122.0	878	71.1	11.1	70.0	44.0	116.0
Fusion cases	Age (yrs)	618	62.1	7.3	62.5	40.8	77.8	468	63.7	7.8	64.0	45.0	83.2
	BMI (kg/m^2)	618	29.4	4.0	29.1	18.2	43.1	468	31.2	5.3	30.7	16.0	47.6
	HR (BPM)	618	70.5	12.9	70.0	44.0	132.0	468	71.2	11.0	70.0	32.0	118.0
Fusion controls	Age (yrs)	571	63.4	7.6	64.0	46.0	90.9	599	63.7	7.3	64.8	42.6	89.2
	BMI (kg/m^2)	571	27.0	3.5	26.8	19.2	51.1	599	27.2	4.2	26.8	17.5	45.9
	HR (BPM)	571	64.8	12.1	64.0	40.0	168.0	599	69.5	15.2	68.0	44.0	164.0
GOOD	Age (yrs)	938	18.9	0.6	18.8	18.0	20.1						
	BMI (kg/m^2)	938	22.4	3.2	21.9	16.1	41.6						
	HR (BPM)	938	70.1	13.5	69.0	39.0	123.0						
HAPI	Age (yrs)	451	42.2	13.5	41.0	20.0	80.0	396	45.2	14.1	46.0	20.0	80.0
	BMI (kg/m^2)	451	25.6	3.2	25.3	18.4	38.0	396	27.7	5.4	27.3	17.3	46.8
	HR (BPM)	451	61.0	8.5	61.0	40.0	96.0	396	67.0	8.9	66.0	41.0	100.0

Supplementary Table 3 - continued

Study	Trait	Men						Women					
		N	mean	SD	median	min	max	N	mean	SD	median	min	max
HBCS	Age (yrs)	521	61.3	2.6	61.0	57.0	69.0	772	61.6	3.0	61.0	57.0	69.0
	BMI (kg/m^2)	521	27.1	3.8	26.6	18.8	41.8	772	27.4	4.9	26.6	14.8	50.1
	HR (BPM)	521	69.7	11.1	68.0	50.0	100.0	772	70.6	9.5	70.0	50.0	100.0
Health 2000 cases	Age (yrs)	424	49.2	10.4	49.0	30.0	75.0	446	52.4	11.7	51.0	30.0	75.0
	BMI (kg/m^2)	424	29.5	3.6	28.9	23.2	47.1	446	29.7	4.9	28.8	20.6	45.8
	HR (BPM)	424	68.2	11.3	68.0	44.0	120.0	446	70.3	10.4	70.0	44.0	110.0
Health 2000 controls	Age (yrs)	421	49.2	10.4	49.0	30.0	75.0	446	52.0	11.6	51.0	30.0	75.0
	BMI (kg/m^2)	421	25.4	3.2	24.9	17.1	39.0	446	25.1	4.1	24.3	17.5	44.3
	HR (BPM)	421	64.5	10.8	64.0	38.0	112.0	446	67.0	8.8	66.0	44.0	104.0
Health ABC	Age (yrs)	874	73.9	2.9	74.0	69.0	80.0	783	73.6	2.8	73.0	69.0	80.0
	BMI (kg/m^2)	874	27.0	3.7	26.6	17.6	44.2	783	26.0	4.5	25.6	15.6	44.7
	HR (BPM)	874	63.9	11.3	62.0	39.0	112.0	783	65.6	9.9	65.0	38.0	102.0
Heritage	Age (yrs)	245	36.6	15.0	32.0	17.0	64.3	256	35.1	14.1	31.2	17.2	65.2
	BMI (kg/m^2)	245	26.7	4.9	25.8	17.3	44.2	256	25.0	4.9	23.9	17.0	47.5
	HR (BPM)	245	62.1	8.3	62.4	40.3	84.2	255	66.9	8.7	67.0	44.0	105.3
HPFS CHD cases	Age (yrs)	348	62.6	8.9	63.3	45.2	79.1						
	BMI (kg/m^2)	348	25.8	3.0	25.4	18.5	38.4						
	HR (BPM)	348	68.1	9.2	68.0	34.0	100.0						
HPFS CHD controls	Age (yrs)	717	62.1	8.7	62.7	45.2	79.1						
	BMI (kg/m^2)	717	25.4	3.2	25.1	16.4	48.7						
	HR (BPM)	717	67.7	9.8	66.0	36.0	104.0						
HPFS Kidney stone disease cases	Age (yrs)	303	54.9	7.6	52.9	45.1	74.0						
	BMI (kg/m^2)	303	25.8	3.1	25.4	19.3	36.6						
	HR (BPM)	303	67.3	10.1	68.0	16.0	100.0						
HPFS Kidney stone disease controls	Age (yrs)	227	53.8	6.0	52.4	45.2	71.2						
	BMI (kg/m^2)	227	25.9	3.0	25.5	19.5	37.1						
	HR (BPM)	227	67.9	10.5	67.0	45.0	120.0						
HPFS t2d cases	Age (yrs)	1,074	61.0	8.6	61.6	45.2	79.1						
	BMI (kg/m^2)	1,074	27.9	4.3	27.3	16.3	56.5						
	HR (BPM)	1,074	70.3	10.8	70.0	35.0	165.0						
HPFS t2d controls	Age (yrs)	1,197	60.9	8.2	61.4	45.2	79.0						
	BMI (kg/m^2)	1,197	25.4	2.9	25.1	16.5	39.6						
	HR (BPM)	1,197	67.1	10.1	66.0	29.0	170.0						
Hypergenes cases	Age (yrs)	1,004	48.9	10.1	49.0	18.0	84.0	514	48.3	8.8	48.5	23.0	93.0
	BMI (kg/m^2)	1,004	27.5	3.5	27.1	16.0	47.4	514	26.9	5.0	26.4	16.8	46.3
	HR (BPM)	1,004	74.8	9.2	75.0	50.0	100.0	514	74.7	9.3	75.5	51.0	100.0

Supplementary Table 3 - continued

Study	Trait	Men						Women					
		N	mean	SD	median	min	max	N	mean	SD	median	min	max
Hypergenes controls	Age (yrs)	976	60.2	8.7	58.0	28.0	98.0	652	61.9	8.9	59.0	50.0	97.0
	BMI (kg/m^2)	976	26.0	3.4	25.6	14.7	43.2	652	25.1	4.1	24.6	16.5	46.7
	HR (BPM)	976	72.6	8.1	72.0	50.0	100.0	652	72.7	7.9	72.0	50.0	94.0
Inchianti	Age (yrs)	507	66.5	15.3	70.0	23.0	94.0	622	68.2	15.1	71.0	21.0	95.0
	BMI (kg/m^2)	507	27.0	3.4	27.0	18.1	37.4	622	27.3	4.7	27.0	18.0	46.6
	HR (BPM)	507	67.0	12.3	65.0	40.0	120.0	622	72.0	11.3	71.0	45.0	120.0
Korcula	Age (yrs)	127	55.7	13.8	57.0	20.0	88.0	226	53.5	23.4	54.0	18.0	84.0
	BMI (kg/m^2)	127	28.7	3.6	28.6	19.3	38.3	226	27.6	4.5	27.4	18.4	53.8
	HR (BPM)	127	65.0	10.7	63.0	51.0	99.0	226	67.0	8.9	67.0	51.0	99.0
LifeLines	Age (yrs)	1,371	56.2	9.6	54.0	21.9	87.6	1,992	54.8	10.0	52.0	23.3	89.0
	BMI (kg/m^2)	1,371	27.0	3.6	26.4	17.0	48.9	1,992	26.5	4.6	25.7	15.2	51.0
	HR (BPM)	1,371	66.9	11.4	66.0	38.0	146.0	1,992	69.6	11.3	68.0	40.0	128.0
Lolipop cohort	Age (yrs)	1,869	48.3	10.5	46.9	35.0	74.9						
	BMI (kg/m^2)	1,869	26.8	4.2	26.5	14.8	48.3						
	HR (BPM)	1,869	68.9	11.5	68.0	39.0	143.0						
Lolipop cases	Age (yrs)	1,062	61.8	9.8	63.0	26.7	82.4	386	61.8	9.0	62.9	32.3	78.4
	BMI (kg/m^2)	1,062	27.4	4.1	27.0	16.8	45.8	386	29.9	5.7	29.2	17.2	51.0
	HR (BPM)	1,062	65.8	11.7	65.0	38.0	123.0	386	68.1	11.5	67.0	37.0	108.0
Lolipop controls	Age (yrs)	2,663	55.0	9.9	54.0	32.1	81.0	588	53.6	9.3	54.3	35.2	78.3
	BMI (kg/m^2)	2,663	26.9	3.9	26.6	15.2	49.2	588	128.0	4.9	27.4	17.0	48.0
	HR (BPM)	2,663	68.4	11.2	67.0	32.0	152.0	588	70.4	10.5	69.0	47.0	112.0
NBS	Age (yrs)	269	65.3	4.3	65.5	51.8	72.0	282	60.4	5.3	60.3	50.5	71.1
	BMI (kg/m^2)	269	27.1	3.5	26.6	20.0	43.9	282	26.7	4.3	26.1	19.1	45.7
	HR (BPM)	269	63.9	10.2	63.0	40.0	103.0	282	66.1	10.4	65.0	39.0	121.0
NFBC-1966	Age (yrs)	2,242	31.2	0.4	31.0	31.0	31.0	2,337	31.2	0.4	31.0	31.0	31.0
	BMI (kg/m^2)	2,242	25.2	3.6	24.9	15.3	47.6	2,337	24.2	4.7	23.1	15.4	54.4
	HR (BPM)	2,242	67.4	10.4	66.0	40.0	124.0	2,337	71.4	10.3	70.0	38.0	118.0
NHS Cancer cases	Age (yrs)							965	58.7	6.4	59.2	43.6	69.9
	BMI (kg/m^2)							965	25.4	4.5	24.6	17.0	53.5
	HR (BPM)							965	71.8	8.3	72.0	57.0	94.5
NHS Cancer controls	Age (yrs)							924	59.0	6.4	59.5	43.8	69.4
	BMI (kg/m^2)							924	25.2	4.5	24.2	15.2	48.1
	HR (BPM)							924	71.6	8.7	72.0	57.0	94.5
NHS CHD cases	Age (yrs)							297	60.3	6.4	61.9	43.9	69.6
	BMI (kg/m^2)							297	25.7	2.0	24.9	15.5	52.7
	HR (BPM)							297	74.2	8.7	72.0	57.0	94.5

Supplementary Table 3 - continued

Study	Trait	Men						Women					
		N	mean	SD	median	min	max	N	mean	SD	median	min	max
NHS CHD controls	Age (yrs)							723	60.2	6.4	62.0	43.6	69.6
	BMI (kg/m^2)							723	24.9	4.2	24.0	17.2	44.4
	HR (BPM)							723	72.2	8.5	72.0	57.0	94.5
NHS Kidney stone disease cases	Age (yrs)							301	55.5	7.0	54.5	43.5	69.4
	BMI (kg/m^2)							301	25.8	4.8	25.1	16.1	46.8
	HR (BPM)							301	72.9	8.2	72.0	57.0	94.5
NHS Kidney stone disease controls	Age (yrs)							156	53.7	5.6	53.1	43.6	69.2
	BMI (kg/m^2)							156	23.9	3.9	23.0	18.3	41.2
	HR (BPM)							156	71.3	8.7	72.0	57.0	94.5
NHS t2d cases	Age (yrs)							1,319	58.0	6.7	58.6	43.5	69.7
	BMI (kg/m^2)							1,319	30.1	5.8	29.6	17.2	54.9
	HR (BPM)							1,319	74.2	9.0	72.0	57.0	94.5
NHS t2d controls	Age (yrs)							1,559	57.6	6.7	58.0	43.5	70.1
	BMI (kg/m^2)							1,559	25.5	4.9	25.5	15.0	53.2
	HR (BPM)							1,559	72.0	8.4	72.0	57.0	94.5
NSPHS	Age (yrs)	278	50.6	19.3	49.0	18.0	87.0	313	49.4	19.4	48.0	18.0	91.0
	BMI (kg/m^2)	278	27.2	4.4	26.5	18.4	46.5	313	26.4	5.0	25.5	17.1	46.7
	HR (BPM)	278	72.6	5.6	70.0	60.0	84.0	313	72.4	5.6	70.0	60.0	82.0
Prevend	Age (yrs)	1,943	50.9	12.7	50.0	28.0	75.0	1,848	48.1	12.0	47.0	28.0	75.0
	BMI (kg/m^2)	1,943	26.4	3.7	26.0	17.2	44.7	1,848	25.9	4.8	25.0	17.1	53.7
	HR (BPM)	1,943	67.2	12.3	65.0	33.0	146.0	1,848	70.7	12.4	70.0	43.0	176.0
Split	Age (yrs)	148	49.9	16.3	52.0	19.0	85.0	248	50.1	14.0	51.5	18.0	81.0
	BMI (kg/m^2)	148	28.1	3.8	27.4	20.8	43.4	248	26.3	4.4	25.7	18.2	43.4
	HR (BPM)	148	65.9	10.8	64.0	51.0	98.0	248	66.2	9.1	65.0	51.0	98.0
YFS	Age (yrs)	941	31.7	5.0	33.0	24.0	39.0	1,142	31.7	5.0	33.0	24.0	39.0
	BMI (kg/m^2)	941	25.8	4.1	25.2	15.7	47.8	1,142	24.5	4.6	23.5	15.7	47.2
	HR (BPM)	941	65.1	9.1	64.7	41.3	105.3	1,142	68.2	8.6	67.3	46.0	109.3

Supplementary Table 4 - Sensitivity analyses for meta-analysis of stage 1 results

SNP	Chr	Pos	Primary analyses [a]						Secondary analyses [a]					
			No exclusions	Individuals with hypertension excluded [c]	Individuals with type 2 diabetes excluded[d]	Individuals with cancer, kidney stones and obesity excluded[e]	Individuals of Indian Asian ancestry excluded [f]	12-yr old children excluded [g]	No exclusions	Individuals with hypertension excluded [c]	Individuals with type 2 diabetes excluded[d]	Individuals with cancer, kidney stones and obesity excluded[e]	Individuals of Indian Asian ancestry excluded [f]	12-yr old children excluded [g]
rs365990	14	22,931,651	$1.9x10^{-25}$	$2.8x10^{-25}$	$2.6x10^{-24}$	$1.1x10^{-23}$	$2.7x10^{-20}$	$1.2x10^{-19}$	$3.9x10^{-24}$	$1.9x10^{-24}$	$4.1x10^{-23}$	$4.3x10^{-22}$	$1.6x10^{-19}$	$7.1x10^{-19}$
rs6127471	20	36,277,452	$6.5x10^{-21}$	$2.3x10^{-20}$	$4.9x10^{-21}$	$6.7x10^{-20}$	$8.5x10^{-18}$	$8.4x10^{-18}$	$6.5x10^{-24}$	$8.7x10^{-23}$	$1.2x10^{-22}$	$8.9x10^{-22}$	$1.5x10^{-19}$	$1.4x10^{-19}$
rs1015451	6	122,173,184	$4.0x10^{-18}$	$2.4x10^{-16}$	$1.9x10^{-14}$	$1.6x10^{-13}$	$7.0x10^{-13}$	$6.8x10^{-13}$	$5.7x10^{-13}$	$3.8x10^{-12}$	$2.4x10^{-11}$	$1.4x10^{-10}$	$3.1x10^{-10}$	$3.2x10^{-10}$
rs17362588	2	179,429,291	$1.3x10^{-16}$	$5.0x10^{-16}$	$3.5x10^{-16}$	$1.6x10^{-15}$	$4.9x10^{-15}$	$2.7x10^{-14}$	$4.0x10^{-13}$	$5.9x10^{-13}$	$9.3x10^{-14}$	$2.4x10^{-13}$	$5.1x10^{-13}$	$2.5x10^{-12}$
rs13245899	7	100,335,067	$3.4x10^{-14}$	$1.1x10^{-13}$	$8.9x10^{-14}$	$4.3x10^{-14}$	$5.9x10^{-13}$	$1.1x10^{-12}$	$5.6x10^{-12}$	$1.7x10^{-11}$	$5.9x10^{-11}$	$2.6x10^{-11}$	$4.8x10^{-11}$	$8.5x10^{-11}$
rs11153730	6	118,774,215	$1.3x10^{-13}$	$2.4x10^{-13}$	$5.1x10^{-14}$	$3.5x10^{-14}$	$2.4x10^{-15}$	$6.3x10^{-15}$	$4.1x10^{-12}$	$1.1x10^{-12}$	$5.6x10^{-13}$	$1.9x10^{-13}$	$2.4x10^{-14}$	$6.1x10^{-14}$
rs4489968	15	71,452,559	$1.6x10^{-13}$	$3.3x10^{-12}$	$3.9x10^{-12}$	$4.6x10^{-12}$	$1.9x10^{-11}$	$1.9x10^{-10}$	$3.8x10^{-13}$	$4.6x10^{-12}$	$2.4x10^{-12}$	$4.7x10^{-12}$	$2.2x10^{-11}$	$2.1x10^{-10}$
rs11118555	1	206,007,476	$6.9x10^{-13}$	$4.3x10^{-11}$	$4.6x10^{-11}$	$2.1x10^{-11}$	$1.8x10^{-10}$	$4.8x10^{-10}$	$7.6x10^{-11}$	$4.9x10^{-10}$	$1.9x10^{-10}$	$1.2x10^{-10}$	$1.2x10^{-09}$	$3.1x10^{-09}$
rs7980799	12	33,468,257	$1.2x10^{-12}$	$2.1x10^{-11}$	$3.5x10^{-11}$	$7.6x10^{-11}$	$9.4x10^{-11}$	$7.9x10^{-11}$	$4.2x10^{-12}$	$5.9x10^{-11}$	$7.9x10^{-11}$	$8.9x10^{-11}$	$2.5x10^{-10}$	$2.2x10^{-10}$
rs174549	11	61,327,958	$1.3x10^{-11}$	$1.9x10^{-10}$	$6.1x10^{-10}$	$1.2x10^{-09}$	$5.1x10^{-09}$	$1.5x10^{-08}$	$2.8x10^{-09}$	$5.0x10^{-09}$	$2.3x10^{-08}$	$1.6x10^{-08}$	$4.0x10^{-08}$	$1.1x10^{-07}$
rs17287293	12	24,662,145	$6.8x10^{-11}$	$3.4x10^{-09}$	$3.2x10^{-09}$	$2.0x10^{-09}$	$1.0x10^{-08}$	$6.2x10^{-09}$	$3.5x10^{-09}$	$9.0x10^{-09}$	$1.0x10^{-08}$	$2.4x10^{-09}$	$1.5x10^{-08}$	$9.6x10^{-09}$
rs17796783	14	84,879,664	$9.8x10^{-09}$	$2.1x10^{-08}$	$4.3x10^{-08}$	$3.8x10^{-08}$	$5.7x10^{-07}$	$9.0x10^{-07}$	$1.3x10^{-05}$	$2.8x10^{-05}$	$8.8x10^{-05}$	$5.5x10^{-05}$	$3.4x10^{-04}$	$5.1x10^{-04}$
rs13030174	2	231,979,528	$5.6x10^{-08}$	$3.2x10^{-07}$	$2.7x10^{-06}$	$3.9x10^{-06}$	$5.2x10^{-05}$	$3.8x10^{-05}$	$8.2x10^{-07}$	$8.0x10^{-06}$	$1.7x10^{-05}$	$2.2x10^{-05}$	$3.7x10^{-04}$	$2.9x10^{-04}$
rs2029213	3	53,353,285	$7.8x10^{-08}$	$1.0x10^{-07}$	$1.2x10^{-07}$	$6.1x10^{-07}$	$1.3x10^{-06}$	$9.0x10^{-07}$	$4.3x10^{-07}$	$1.9x10^{-06}$	$1.5x10^{-06}$	$1.4x10^{-05}$	$1.5x10^{-05}$	$1.1x10^{-05}$
rs2067615	12	105,673,552	$4.2x10^{-07}$	$5.5x10^{-07}$	$1.1x10^{-06}$	$4.1x10^{-06}$	$2.2x10^{-05}$	$3.3x10^{-05}$	$3.8x10^{-04}$	$5.9x10^{-04}$	$8.5x10^{-04}$	$1.5x10^{-03}$	$4.1x10^{-03}$	$5.7x10^{-03}$
rs2350782	7	136,293,174	$6.1x10^{-07}$	$1.1x10^{-06}$	$7.3x10^{-07}$	$6.5x10^{-06}$	$1.6x10^{-05}$	$7.0x10^{-05}$	$8.1x10^{-08}$	$1.3x10^{-07}$	$9.0x10^{-08}$	$5.8x10^{-07}$	$2.3x10^{-06}$	$1.1x10^{-05}$
rs7612445	3	180,655,673	$9.0x10^{-07}$	$3.1x10^{-06}$	$5.7x10^{-07}$	$6.8x10^{-07}$	$1.6x10^{-06}$	$1.7x10^{-06}$	$6.4x10^{-06}$	$6.4x10^{-06}$	$3.1x10^{-06}$	$6.9x10^{-06}$	$8.4x10^{-06}$	$9.0x10^{-06}$
rs9647379	3	173,267,862	$9.6x10^{-07}$	$5.7x10^{-06}$	$3.4x10^{-06}$	$3.3x10^{-05}$	$2.5x10^{-04}$	$4.4x10^{-04}$	$1.3x10^{-06}$	$7.7x10^{-07}$	$6.6x10^{-07}$	$3.8x10^{-06}$	$1.8x10^{-05}$	$3.2x10^{-05}$
rs13413635	2	178,388,677	$1.1x10^{-06}$	$5.2x10^{-07}$	$6.6x10^{-07}$	$2.2x10^{-07}$	$2.1x10^{-07}$	$2.6x10^{-07}$	$4.2x10^{-04}$	$4.8x10^{-04}$	$6.4x10^{-04}$	$4.4x10^{-04}$	$4.5x10^{-04}$	$5.7x10^{-04}$
rs826838	12	37,392,998	$1.2x10^{-06}$	$1.8x10^{-06}$	$1.7x10^{-06}$	$2.0x10^{-06}$	$3.8x10^{-06}$	$1.8x10^{-06}$	$1.4x10^{-05}$	$1.8x10^{-05}$	$1.7x10^{-05}$	$1.1x10^{-05}$	$2.5x10^{-05}$	$1.3x10^{-05}$
rs12345385	9	37,739,508	$1.6x10^{-06}$	$4.0x10^{-06}$	$1.3x10^{-05}$	$1.5x10^{-05}$	$2.2x10^{-05}$	$1.3x10^{-05}$	$7.1x10^{-06}$	$2.2x10^{-05}$	$5.7x10^{-05}$	$7.6x10^{-05}$	$2.6x10^{-04}$	$1.7x10^{-04}$
rs910883	20	62,210,011	$2.3x10^{-06}$	$9.9x10^{-06}$	$6.5x10^{-05}$	$9.4x10^{-05}$	$2.2x10^{-04}$	$1.6x10^{-04}$	$1.2x10^{-06}$	$6.8x10^{-07}$	$2.2x10^{-06}$	$6.6x10^{-06}$	$4.5x10^{-05}$	$3.2x10^{-05}$
rs180242	7	93,387,532	$2.5x10^{-06}$	$2.5x10^{-07}$	$6.0x10^{-08}$	$1.5x10^{-08}$	$1.5x10^{-08}$	$9.8x10^{-09}$	$4.5x10^{-05}$	$2.2x10^{-06}$	$2.6x10^{-06}$	$1.8x10^{-06}$	$1.9x10^{-06}$	$1.5x10^{-06}$
rs7110523	11	43,706,952	$2.6x10^{-06}$	$7.9x10^{-06}$	$1.2x10^{-05}$	$5.7x10^{-06}$	$5.7x10^{-06}$	$6.6x10^{-06}$	$1.5x10^{-03}$	$2.1x10^{-03}$	$1.8x10^{-03}$	$1.2x10^{-03}$	$1.3x10^{-03}$	$1.5x10^{-03}$
rs4384785	2	106,488,398	$3.1x10^{-06}$	$1.0x10^{-06}$	$5.7x10^{-07}$	$1.2x10^{-06}$	$1.7x10^{-06}$	$6.1x10^{-06}$	$3.7x10^{-05}$	$8.1x10^{-06}$	$5.2x10^{-06}$	$2.0x10^{-05}$	$2.7x10^{-05}$	$8.7x10^{-05}$
rs10213084	4	147,718,788	$3.8x10^{-06}$	$3.1x10^{-05}$	$4.7x10^{-05}$	$3.3x10^{-05}$	$1.5x10^{-05}$	$2.0x10^{-05}$	$3.6x10^{-04}$	$9.8x10^{-04}$	$4.5x10^{-04}$	$3.5x10^{-04}$	$7.6x10^{-05}$	$1.0x10^{-04}$
rs1889785	1	16,221,316	$4.5x10^{-06}$	$6.9x10^{-05}$	$2.2x10^{-04}$	$7.0x10^{-05}$	$3.2x10^{-04}$	$2.3x10^{-04}$	$2.0x10^{-05}$	$3.2x10^{-05}$	$1.3x10^{-04}$	$4.9x10^{-05}$	$1.9x10^{-04}$	$1.4x10^{-04}$
rs4896011	6	134,263,946	$5.7x10^{-06}$	$3.0x10^{-05}$	$6.8x10^{-05}$	$9.6x10^{-05}$	$1.6x10^{-04}$	$3.0x10^{-04}$	$9.0x10^{-04}$	$1.4x10^{-03}$	$2.6x10^{-03}$	$3.3x10^{-03}$	$4.0x10^{-03}$	$6.6x10^{-03}$
rs4140885	2	188,041,309	$5.7x10^{-06}$	$1.7x10^{-04}$	$9.0x10^{-04}$	$8.5x10^{-04}$	$8.0x10^{-04}$	$6.2x10^{-04}$	$1.2x10^{-05}$	$1.8x10^{-04}$	$9.2x10^{-04}$	$9.4x10^{-04}$	$7.1x10^{-04}$	$5.5x10^{-04}$
rs1555773	6	34,866,111	$6.8x10^{-06}$	$8.0x10^{-06}$	$2.4x10^{-05}$	$1.2x10^{-04}$	$1.2x10^{-04}$	$3.6x10^{-05}$	$2.9x10^{-05}$	$1.8x10^{-05}$	$4.0x10^{-05}$	$1.2x10^{-04}$	$1.2x10^{-04}$	$3.8x10^{-05}$
rs11065706	12	109,388,458	$7.0x10^{-06}$	$3.3x10^{-05}$	$5.3x10^{-05}$	$3.4x10^{-05}$	$3.4x10^{-05}$	$2.2x10^{-05}$	$8.0x10^{-07}$	$1.7x10^{-06}$	$1.9x10^{-06}$	$3.2x10^{-06}$	$3.4x10^{-06}$	$2.0x10^{-06}$
rs17715440	12	60,866,046	$7.9x10^{-06}$	$1.2x10^{-05}$	$1.4x10^{-05}$	$9.1x10^{-06}$	$1.7x10^{-05}$	$1.4x10^{-05}$	$1.7x10^{-04}$	$5.5x10^{-04}$	$3.7x10^{-04}$	$1.6x10^{-04}$	$1.9x10^{-04}$	$1.6x10^{-04}$
rs2718767	3	182,392,734	$8.9x10^{-06}$	$1.6x10^{-05}$	$2.8x10^{-05}$	$1.1x10^{-04}$	$1.8x10^{-04}$	$8.5x10^{-05}$	$9.6x10^{-03}$	$7.2x10^{-03}$	$8.7x10^{-03}$	$2.0x10^{-02}$	$2.2x10^{-02}$	$1.4x10^{-02}$
rs2425787	20	44,280,798	$9.1x10^{-06}$	$1.7x10^{-04}$	$2.6x10^{-04}$	$3.9x10^{-04}$	$1.4x10^{-03}$	$1.9x10^{-03}$	$6.7x10^{-03}$	$2.0x10^{-02}$	$2.3x10^{-02}$	$2.5x10^{-02}$	$2.9x10^{-02}$	$3.7x10^{-02}$
rs7722600	5	137,222,661	$9.5x10^{-06}$	$1.5x10^{-05}$	$1.6x10^{-05}$	$2.4x10^{-06}$	$1.1x10^{-06}$	$2.7x10^{-06}$	$6.5x10^{-06}$	$1.7x10^{-05}$	$3.0x10^{-05}$	$5.7x10^{-06}$	$5.0x10^{-06}$	$1.2x10^{-05}$
rs11645781	16	6,836,129	$1.0x10^{-05}$	$9.0x10^{-05}$	$2.5x10^{-04}$	$2.9x10^{-04}$	$3.1x10^{-04}$	$3.4x10^{-04}$	$1.7x10^{-04}$	$5.3x10^{-04}$	$3.2x10^{-03}$	$2.0x10^{-03}$	$6.6x10^{-04}$	$7.4x10^{-04}$
rs10806489	6	95,409,563	$1.2x10^{-05}$	$8.7x10^{-05}$	$1.7x10^{-04}$	$8.5x10^{-05}$	$8.5x10^{-05}$	$1.1x10^{-04}$	$6.2x10^{-04}$	$8.7x10^{-04}$	$5.4x10^{-03}$	$2.7x10^{-03}$	$2.8x10^{-03}$	$3.5x10^{-03}$
rs11083475	19	43,879,952	$1.6x10^{-05}$	$2.7x10^{-04}$	$7.1x10^{-04}$	$1.2x10^{-03}$	$2.8x10^{-03}$	$3.0x10^{-03}$	$7.3x10^{-04}$	$4.5x10^{-04}$	$2.9x10^{-03}$	$3.1x10^{-03}$	$9.9x10^{-03}$	$1.1x10^{-02}$
rs10942901	5	79,060,913	$1.7x10^{-05}$	$3.7x10^{-06}$	$2.0x10^{-06}$	$1.4x10^{-05}$	$5.3x10^{-06}$	$1.7x10^{-05}$	$6.1x10^{-04}$	$5.7x10^{-04}$	$5.8x10^{-04}$	$4.3x10^{-03}$	$2.5x10^{-03}$	$5.7x10^{-03}$
rs236373	6	36,900,035	$1.8x10^{-05}$	$1.8x10^{-04}$	$7.3x10^{-05}$	$2.4x10^{-04}$	$4.2x10^{-03}$	$5.9x10^{-03}$	$1.2x10^{-04}$	$3.7x10^{-04}$	$3.3x10^{-04}$	$8.9x10^{-04}$	$9.2x10^{-03}$	$1.3x10^{-02}$
rs205712	7	130,263,348	$1.8x10^{-05}$	$1.0x10^{-04}$	$1.1x10^{-04}$	$1.7x10^{-04}$	$1.7x10^{-04}$	$5.1x10^{-04}$	$1.7x10^{-03}$	$2.3x10^{-03}$	$1.8x10^{-03}$	$1.2x10^{-03}$	$1.3x10^{-03}$	$3.3x10^{-03}$
rs6882776	5	172,596,769	$2.6x10^{-05}$	$1.6x10^{-04}$	$1.6x10^{-04}$	$9.0x10^{-05}$	$4.7x10^{-05}$	$9.7x10^{-05}$	$9.9x10^{-05}$	$1.4x10^{-04}$	$7.7x10^{-05}$	$4.9x10^{-05}$	$1.9x10^{-05}$	$3.9x10^{-05}$

[a] Primary analyses, no *a priori* exclusions applied in individual GWAS; [b] Secondary analyses, a priori exclusion of individuals 1) with prevalent myocardial infarction, heart failure, atrial fibrillation or 2nd / 3rd degree atrio-ventricular block; 2) who used heart rate altering medication at the time of the study, defined as the use of beta-blockers, non-dihydropiridine calcium antagonists or digoxin; 3) with a resting heart rate lower than 50 beats/min or higher than 100 beats/min applied in each individual GWAS (n ~19,500); [c] Exclusion of hypertensive cases, i.e. Advance cases, ASCOT cases, Bright cases, Corogene cases, Fingesture cases, HPFS CHD cases, Hypergenes cases, Lolipop cases, NHS cases (N = 11,772); [d] Additional exclusion of type 2 diabetes cases, i.e. DGI cases, Fusion cases, HPFS t2d cases, NHS t2d cases (N = 4,714); [e] Additional exclusion of cases with other diseases, i.e. Health2000 cases (obesity), HPFS kidney cases (kidney stones), NHS kidney cases, NHC cancer cases (N = 2,439); [f] Additional exclusion of individuals of Indian Asian descent, i.e. Lolipop cohort, Lolipop controls (N = 5,120); [g] Additional exclusion of 120yr old children, i.e. ALSPAC (N = 1,486)

Note: all exclusions are cumulative, resulting in samples of ~66,800 individuals for the primary analysis and ~58,000 for the secondary analysis after incorporating the maximal number of exclusions. SNPs were ordered by p-value in the primary analysis with no exclusions

Supplementary Table 5 – The 42 loci associated with heart rate at $p < 3x10^{-5}$ at stage 1, which were taken forward to stage 2

				Alleles			Stage 1			Stage 2			Heterogeneity		Stage 1 + 2		
Nearest gene	**lead SNP**	**Chr**	**Position (bp)**	**Effect**	**Other**	**EAF**	**N**	**dir**	**p-value**	**N**	**dir**	**p-value**	**I^2**	**p-value Q-statistic**	**N**	**dir**	**p-value**
MYH6	rs365990	14	22,931,651	g	a	0.343	90,433	+	$1.85x10^{-25}$	58,539	+	$2.19x10^{-21}$	0	0.88	148,972	+	$5.39x10^{-45}$
GJA1	rs1015451	6	122,173,184	c	t	0.110	92,355	+	$3.96x10^{-18}$	62,948	+	$2.14x10^{-17}$	21	0.10	155,303	+	$1.14x10^{-33}$
KIAA1755	rs6127471	20	36,277,452	c	t	0.543	88,545	+	$6.52x10^{-21}$	74,048	+	$2.98x10^{-10}$	29	0.03	162,593	+	$5.22x10^{-29}$
ACHE	rs13245899	7	100,335,067	g	a	0.198	90,451	+	$3.36x10^{-14}$	86,192	+	$3.27x10^{-14}$	0	0.61	176,643	+	$7.67x10^{-27}$
CCDC141	rs17362588	2	179,429,291	a	g	0.116	82,115	+	$1.27x10^{-16}$	53,946	+	$4.22x10^{-11}$	18	0.14	136,061	+	$3.57x10^{-26}$
CD46	rs11118555	1	206,007,476	a	t	0.129	83,533	+	$6.94x10^{-13}$	83,121	+	$7.49x10^{-15}$	21	0.08	166,654	+	$3.88x10^{-26}$
SYT10	rs7980799	12	33,468,257	a	c	0.402	85,489	+	$1.19x10^{-12}$	80,554	+	$7.87x10^{-13}$	2	0.34	166,043	+	$6.22x10^{-24}$
FADS1	rs174549	11	61,327,958	a	g	0.318	87,843	+	$1.32x10^{-11}$	85,004	+	$1.57x10^{-12}$	0	0.69	172,847	+	$1.38x10^{-22}$
SLC35F1	rs11153730	6	118,774,215	t	c	0.515	90,411	+	$1.33x10^{-13}$	66,372	+	$8.79x10^{-09}$	21	0.10	156,783	+	$7.55x10^{-21}$
LINC00477	rs17287293	12	24,662,145	a	g	0.849	92,354	+	$6.84x10^{-11}$	58,731	+	$3.98x10^{-11}$	1	0.33	151,085	+	$3.07x10^{-20}$
HCN4	rs4489968	15	71,452,559	t	g	0.833	92,292	+	$1.65x10^{-13}$	68,566	+	$3.34x10^{-08}$	0	0.38	160,858	+	$3.82x10^{-20}$
GNB4	rs7612445	3	180,655,673	g	t	0.815	86,602	+	$9.03x10^{-07}$	53,793	+	$7.78x10^{-10}$	16	0.16	140,395	+	$1.86x10^{-14}$
FLRT2	rs17796783	14	84,879,664	t	c	0.722	91,881	+	$9.84x10^{-09}$	53,954	+	$5.76x10^{-06}$	22	0.10	145,835	+	$2.69x10^{-13}$
CHRM2	rs2350782	7	136,293,174	c	t	0.128	81,895	+	$6.13x10^{-07}$	49,886	+	$2.63x10^{-07}$	8	0.24	131,781	+	$1.26x10^{-12}$
NKX2-5	rs6882776	5	172,596,769	g	a	0.660	85,491	+	$2.58x10^{-05}$	73,316	+	$7.43x10^{-09}$	0	0.45	158,807	+	$2.29x10^{-12}$
GNG11	rs180242	7	93,387,532	t	a	0.334	76,281	+	$2.54x10^{-06}$	71,830	+	$5.59x10^{-07}$	25	0.05	148,111	+	$6.78x10^{-12}$
B3GNT7	rs13030174	2	231,979,528	a	c	0.726	86,646	+	$5.60x10^{-08}$	58,164	+	$3.66x10^{-04}$	0	0.84	144,810	+	$1.04x10^{-10}$
FNDC3B	rs9647379	3	173,267,862	c	g	0.401	90,439	+	$9.63x10^{-07}$	46,875	+	$3.07x10^{-04}$	1	0.34	137,314	+	$1.17x10^{-09}$
RFX4	rs2067615	12	105,673,552	a	t	0.492	92,334	+	$4.24x10^{-07}$	58,863	+	$8.49x10^{-04}$	16	0.16	151,197	+	$1.58x10^{-09}$
CPNE8	rs826838	12	37,392,998	c	t	0.448	91,151	+	$1.21x10^{-06}$	75,481	+	$6.20x10^{-04}$	0	0.84	166,632	+	$3.73x10^{-09}$
TFPI	rs4140885	2	188,041,309	a	g	0.317	84,398	+	$5.75x10^{-06}$	85,997	+	$1.40x10^{-03}$	20	0.08	170,395	+	$4.72x10^{-08}$
A2BP1	rs11645781	16	6,836,129	g	a	0.696	90,389	+	$1.03x10^{-05}$	55,271	+	$4.33x10^{-03}$	4	0.29	145,660	+	$1.66x10^{-07}$
MYOT	rs7722600	5	137,222,661	a	g	0.815	92,348	+	$9.55x10^{-06}$	88,823	+	$4.65x10^{-03}$	0	0.56	181,171	+	$2.68x10^{-07}$
PDE11A	rs13413635	2	178,388,677	g	a	0.033	77,314	+	$1.06x10^{-06}$	38,468	+	0.05	0	0.57	115,782	+	$3.40x10^{-07}$
PPP1CC	rs11065706	12	109,639,914	t	c	0.756	81,930	+	$6.97x10^{-06}$	61,237	+	0.01	0	0.42	143,167	+	$5.90x10^{-07}$
CPNE5	rs236373	6	36,900,035	c	t	0.727	88,545	+	$1.80x10^{-05}$	59,151	+	0.01	0	0.65	147,696	+	$9.04x10^{-07}$
ACTN4	rs11083475	19	43,879,952	g	a	0.537	92,318	+	$1.60x10^{-05}$	64,113	+	0.03	0	0.61	156,431	+	$2.46x10^{-06}$
SLC10A7	rs10213084	4	147,718,788	g	t	0.869	90,454	+	$3.84x10^{-06}$	77,906	+	0.07	0	0.64	168,360	+	$3.77x10^{-06}$
DCP1A	rs2029213	3	53,353,285	c	t	0.639	92,309	+	$7.85x10^{-08}$	79,964	+	0.43	34	0.01	172,273	+	$7.45x10^{-06}$
CMYA5	rs10942901	5	79,060,913	g	a	0.138	86,667	+	$1.74x10^{-05}$	54,695	+	0.14	0	0.34	141,362	+	$1.78x10^{-05}$
UHRF1BP1	rs1555773	6	34,866,111	c	g	0.822	85,792	+	$6.84x10^{-06}$	56,730	+	0.25	22	0.01	142,522	+	$2.42x10^{-05}$
KLF14	rs205712	7	130,263,348	g	c	0.114	75,283	+	$1.82x10^{-05}$	54,332	+	0.20	0	0.43	129,615	+	$4.10x10^{-05}$
DNAJC19	rs2718767	3	182,392,734	t	g	0.146	92,320	+	$8.95x10^{-06}$	64,424	+	0.29	21	0.11	156,744	+	$4.24x10^{-05}$
TCF21	rs4896011	6	134,256,446	t	a	0.913	90,430	+	$5.65x10^{-06}$	60,502	+	0.39	11	0.21	150,932	+	$4.90x10^{-05}$
HSD17B12	rs7110523	11	43,706,952	a	g	0.082	76,460	+	$2.57x10^{-06}$	46,545	+	0.63	0	0.49	123,005	+	$6.12x10^{-05}$
NPBWR2	rs910883	20	62,210,011	g	a	0.918	90,487	+	$2.28x10^{-06}$	53,312	+	0.79	0	0.58	143,799	+	$9.02x10^{-05}$
MANEA	rs10806489	6	95,409,563	c	t	0.021	81,250	+	$1.24x10^{-05}$	46,552	+	0.55	16	0.16	127,802	+	$1.19x10^{-04}$
FAM19A2	rs17715440	12	60,866,046	t	c	0.106	86,381	+	$7.85x10^{-06}$	81,089	+	0.51	25	0.05	167,470	+	$2.39x10^{-04}$
ST6GAL2	rs4384785	2	106,488,398	a	g	0.099	79,925	+	$3.13x10^{-06}$	42,473	-	0.83	35	0.03	122,398	+	$2.67x10^{-04}$

Supplementary Table 5 – continued

Nearest gene	lead SNP	Chr	Position (bp)	Alleles		EAF	Stage 1			Stage 2			Heterogeneity		Stage 1 + 2		
				Effect	Other		N	dir	p-value	N	dir	p-value	I^2	p-value Q-statistic	N	dir	p-value
FRMPD1	rs12345385	9	37,739,508	g	a	0.278	90,045	+	$1.61x10^{-06}$	53,221	-	0.59	5	0.28	143,266	+	$5.00x10^{-04}$
CLCNKA	rs1889785	1	16,221,316	a	g	0.457	90,056	+	$4.45x10^{-06}$	57,019	-	0.20	22	0.09	147,075	+	$5.24x10^{-03}$
CDH22	rs2425787	20	44,280,798	g	a	0.075	91,958	+	$9.09x10^{-06}$	57,699	-	0.18	44	$5.78x10^{-03}$	149,657	+	$7.80x10^{-03}$

dir, direction of association with heart rate for effect allele, increasing (+) or decreasing (-); *P*-value for association between SNP and heart rate after adjusting for sex, age, age^2 and BMI, and adjusted for population stratification (GC) on a per study level and after meta-analysis (λ = 1.106); heterogeneity statistics are for results of meta-analysis stage 1 and samples of stage 2; I^2, proportion of variance that is due to true heterogeneity in effect size.

Supplementary Table 6 – Conditional analyses using meta-analysis of stage 1 results

Locus	nearest gene	SNP	Position (bp)	Alleles: Effect	Alleles: Other	Freq	p 1	p_{adj} 1	p 1 + 2	$beta_{adj}$ 1 + 2	SE_{adj} 1 + 2	p_{adj} 1 + 2	r^2 LD
2	*GJA1*	rs1015451	122,173,184	c	t	0.110	$3.96x10^{-18}$	$8.73x10^{-15}$	$1.82x10^{-21}$	0.61	0.07	$3.73x10^{-17}$	-
	GJA1	rs11154027	121,823,089	c	t	0.567	$2.75x10^{-13}$	$7.24x10^{-10}$	$9.00x10^{-16}$	0.32	0.05	$7.03x10^{-12}$	0.04
	GJA1	rs17083533	121,772,421	a	g	0.077	$2.10x10^{-12}$	$2.54x10^{-8}$	$2.57x10^{-13}$	0.74	0.13	$1.00x10^{-08}$	0.11
4	*CD46*	rs11118555	206,007,476	a	t	0.129	$6.94x10^{-13}$	$8.84x10^{-9}$	$9.39x10^{-21}$	0.51	0.06	$2.56x10^{-15}$	-
	CD34	rs11578508	206,195,688	a	g	0.665	$2.31x10^{-13}$	$1.66x10^{-9}$	$1.40x10^{-15}$	0.30	0.05	$4.04x10^{-10}$	0.21

Results from conditional analyses using summary statistics of meta-analyses. p 1, p-value for association with heart rate after meta-analysis of stage 1 results; p_{adj} 1, p-value for association with heart rate after conditioning on the other heart rate association(s) shown in the table; p 1+2, p-value for association with heart rate after combined meta-analysis of stage 1 + 2 results (including data from studies with heart rate as the dependent variable only, i.e. excluding data from the RRgen consortium and the ERF study); beta, SE and p_{adj} 1+2, beta, SE and p-values for association with heart rate after combined meta-analysis of stage 1 and 2 results and after conditioning on the other heart rate association(s) shown in the table; r^2 LD, r^2 for LD with the lead SNP.

Supplementary Table 7 - Study design, number of individuals and sample quality control of studies in stage 2 – *in silico* replication using data from studies with data from GWAS, Metabochip and Cardiochip

Study Short name	Full name	Study design	Total sample size (N)	Call rate [a]	Sample QC Sample specific QC criteria	Samples in analysis (N) [b]	HR assessment method	References
***In silico* follow-up studies: Genome-wide data**								
ALSPAC 12-yr old children	Avon Longitudinal Study of Parents And Children Replication	Population-based	9,545	>95%	Samples not clustering with CEU in multidimensional scaling; Putatively related individuals; Individuals with missingness > 3%; Individuals with unusual heterozygosities; Individuals with sex discrepancies;	4,000	Peripheral pulse rate	[PMID 19181680]
ACTS	Alcohol Challenge Twin Study	Population-based twin study	357	>97%	Ethnic outliers (non-European ancestry) (n=8)	349	Peripheral pulse rate	[PMID 4041178]
DESIR [c]	Data from an Epidemiological Study on the Insulin Resistance Syndrom	General population	4,993	>98%	Call rate > 95%	4,402	Peripheral pulse rate	[PMID 17293876]
EGCUT	Estonian Genome Center, University of Tartu	Population-based	893	98.0%	Individuals with call-rate > 98%; Individuals with cryptic relatedness; Genetic outliers from PC analyses	771	Peripheral pulse rate	[PMID 19424496] Metspalu, A. The Estonian Genome Project. Drug Development Research 62, 97-101 (2004)
ERF	Erasmus Rucphen Study	Population-based family study	2,834	98%	RRgen criteria (PMID 20639392)	233	ECG	[PMID 15845033]
FamHS	Family Heart Study	Population-based	4,135	≥98%	Technical errors; Discrepancies between reported sex and sex-diagnostic markers	3,729	Peripheral pulse rate	[PMID 8651220]
LifeLines2	Lifelines Study release 2	Population-based	5,580	95%	Non-caucasian individuals; Related individuals (pi-hat > 0.4); Gender mismatches	5,052	ECG	[PMID 18075776]
MESA	The Multi-Ethnic Study of Atherosclerosis	Population-based	6432	>95%	Unexplained duplication; Gender mismatches	2,618	ECG	[PMID 12397006]
NTR	Netherlands Twin Registry	Population-based twin study	5,408	99.9%	Individuals with call rate > 90%; Duplicates; Mendelian errors	537	ECG	[PMID 20477721]
RISC	Relationship between Insulin Sensitivity and Cardiovascular Disease Study	Population-based	1,500	>98.5%	Eigenvector analysis; Duplicates identified by PLINK	1,006	ECG	[PMID 17804762]
RRgen consortium	*Information for the 15 studies in the RRgen consortium can be found in Eijgelsheim et al (2010) [PMID 20639392]*					38,991	ECG	[PMID 20639392]
RS3	Rotterdam Study III	Population-based	2,420	>97.5%	Individuals with excess heterozygosity; IBS (>4 CEU-SD); IBD Gender mismatch	2,068	ECG	[PMID 20639392] [PMID 19728115]
Stanford IST cohort	Stanford Study	Population-based	448	>98.5%	Eigenvector analysis; Duplicates identified by PLINK	327	Peripheral pulse rate	The sample was drawn from multiple studies of insulin resistance at Stanford over the last ~10 years: PMIDs include 18572033, 19217456, 17023708, 18640389, 18572037, 19910937, 19962157

Supplementary Table 7 - continued

Study Short name	Full name	Study design	Total sample size (N)	Call rate [a]	Sample QC Sample specific QC criteria	Samples in analysis (N) [b]	HR assessment method	References
***In silico* follow-up studies: Metabochip**								
EGCUT	Estonian Genome Center, University of Tartu	Case-control study of type 2 diabetes	2,700	98.5%	Individual with call-rate > 98%; individuals with cryptic relatedness; Genetic outliers from PC analyses	2,585	Peripheral pulse rate	[PMID 19424496] Metspalu, A. The Estonian Genome Project. Drug Development Research 62, 97-101 (2004)
Ely	Ely Study	Population-based	1,602	≥95%	Individuals with gender inconsistencies	653	Peripheral pulse rate	[PMID 17257284]
EPIC-Norfolk	European Prospective Investigation into Cancer and Nutrition - Norfolk	Case-control study of type 2 diabetes	1,694	≥95%	Individuals with gender inconsistencies	1,686	Peripheral pulse rate	[PMID 20824172]
Fenland	Fenland Study	Population-based	3,186	≥95%	Individuals with gender inconsistencies	3,182	Peripheral pulse rate	[PMID 21248185]
Finrisk07	Finrisk 2007 Study	Population-based	3,952	99.9%	Individuals with call rate < 95%; Related individuals (pi hat > 0.2 with another sample); Individuals showing evidence of cryptic relatedness (pi hat 0.05-0.02 with many samples in dataset)	3,942	Peripheral pulse rate	The National FINRISK Study, National Institute for Health and Welfare. (Accessed 6.4.2011, at www.ktl.fi/portal/4168.)
NSHD	1946 British Birth Cohort	Population-based birth cohort	988	≥95%	Individuals with gender inconsistencies	959	Peripheral pulse rate	[PMID 16204333]
PIVUS	Prospective Investigation of the Vasculature in Uppsala Seniors	Population-based	998	99.6%	Individuals with call-rate < 90%; Individuals with excess heterozygosity (F-mean(F))/ sd(Z)=5); Ethnic outliers; Related individuals; Duplicates	968	ECG	[PMID 16141402]
STR	Swedish Twin Registry	Population-based twin study	2,755	99.9%	Individuals with call-rate < 90%; Individuals with excess heterozygosity (F-mean(F))/ sd(Z)=5); Ethnic outliers; Related individuals; Duplicates	2,203	Peripheral pulse rate	[PMID 17254424]
ULSAM	Uppsala Longitudinal Study of Adult Men	Population-based	1,146	99.7%	Individuals with call-rate < 90%; Individuals with excess heterozygosity (F-mean(F))/ sd(Z)=5); Ethnic outliers; Related individuals; Duplicates	1,103	Peripheral pulse rate	[PMID 16030278]
Whitehall II	Whitehall II Study	Population-based	3,377	≥95%	Individuals with gender inconsistencies	3,366	Peripheral pulse rate	[PMID 15576467]
***In silico* follow-up study: cardiochip**								
EPIC-NL	European Prospective Investigation into Cancer and Nutrition - Netherlands	Case-control study of coronary heart disease, stroke and type 2 diabetes	6,220	99.9%	Individuals with call rate < 95%; PI-HAT: ≥0.2; Heterozygosity: ≥ 3*SD; Individuals of non european descent (based on population substructure (Eigenstrat))	5,171 (2,704 cases, 2,467 controls)	Peripheral pulse rate	[PMID 19483199]

[a] Sample genotyping success rate, i.e. percentage of successfully genotyped SNPs per sample; [b] Ns reported are numbers for which association data was provided; Ns in paper may differ due to effective sample size in meta-analysis; [c] The DESIR sample was partly genotyped on a GWA platform (Illumina 370, N = 715), partly using Metabochip (N = 3,687).

Supplementary Table 8 - Information on genotyping methods, quality control of SNPs, imputation and statistical analysis in studies of stage 2 – *in silico* replication using data from studies with data from GWAS, Metabochip and Cardiochip

	Genotyping						Imputation			SNPs in meta-analysis			
							Inclusion criteria						
Study	**Platform**	**Genotype calling algorithm**	**MAF**	**Call rate [a]**	**p HWE**	**SNPs that met QC criteria**	**Imputation software**	**MAF**	**Imputation quality [b]**	**Combined**	**Men**	**Women**	**Analysis software**
***In silico* follow-up studies: Genome-wide data**													
ALSPAC 12-yr old children	Illumina 550k	GenCall	>1%	>97%	10^{-07}	488,325	MACH	>1%	r^2 hat ≥ 0.3	-	47	47	MACH2QTL
ACTS	Illumina Human CNV370-Quad v3 / 610-Quad v1 / Illumina 317K	GenomeStudio	≥1%	≥95%	$>10^{-06}$	269,840	MACH	≥1%	r^2 hat ≥ 0.3	44	-	-	Merlin
DESIR	Illumina 370	BeadStudio-Gencall v3.0	≥1%	≥95%	$\geq 10^{-04}$	308,846	IMPUTE	≥1%	proper info ≥ 0.4	-	47	47	SNPtest
EGCUT	Illumina 370CNV / OMNIExpress	BeadStudio-Gencall v3.0	1%	≥98%	$>10^{-06}$	194,589	IMPUTE	none	proper info ≥ 0.4	-	47	47	SNPtest
ERF	Illumina 318k / 370k / Affymetrix 250k	Beadstudio	none	98%	$>10^{-06}$	277,599	MACH	≥1%	r^2 hat ≥ 0.3	47	-	-	GenABEL / ProbABEL
FamHS	Illumina 550k / 610k / 1M	BeadStudio-Gencall v3.0	>1%	≥98%	$>10^{-06}$	503,187	MACH	none	r^2 hat ≥ 0.3	47	-	-	SAS / Metal
LifeLines2	Illumina CytoSNP12 v2	GenomeStudio	1%	98%	$>10^{-05}$	257,581	BEAGLE	none	info > 0.3	-	44	44	R
MESA	Affymetrix 6.0	Birdseed	none	>95%	none	389,107	IMPUTE	none	proper info ≥ 0.4	-	47	47	R
NTR	Affymetrix 500k Perlegen / 1M / Illumina 370k / 660k	BeadStudio / Perlegen Proprietary / Affymetrix Genotyping Studio	≥1%	>95%	$>10^{-05}$	465,474	IMPUTE	>1%	proper info ≥ 0.4	47	-	-	SNPtest
RISC	Affymetrix 6.0	BirdSeed	>2%	>90%	$>5x10^{-6}$	909,508	MACH	none	r^2 hat ≥ 0.3	-	47	47	MACH2QTL
RRgen consortium	*Information for the 15 studies in the RRgen consortium can be found in Eijgelsheim et al (2010) [PMID 20639392]*									47	-	-	
RS3	Illumina 610k Quad	BeadStudio	none	>95%	none	587,383	MACH	1%	r^2 hat ≥ 0.3	-	47	47	MACH2QTL
Stanford	Affymetrix 6.0	BirdSeed	>2%	>90%	$>5x10^{-06}$	909,508	MACH	none	r^2 hat ≥ 0.3	-	47	47	MACH2QTL
***In silico* follow-up studies: Metabochip**													
DESIR	Metabochip	BeadStudio-Gencall v3.0	≥1%	≥95%	$\geq 10^{-04}$	143,649	-	-	-	-	8	8	SNPtest
EGCUT cases	Metabochip	BeadStudio-Gencall v3.0	none	≥90%	$>10^{-06}$	184,420	-	-	-	-	16	16	SNPtest
EGCUT controls	Metabochip	BeadStudio-Gencall v3.0	none	≥90%	$>10^{-06}$	184,420	-	-	-	-	16	16	SNPtest
Ely	Metabochip	GenCall	>0%	≥90%	$>10^{-06}$	149,302	-	-	-	-	14	14	SNPtest
EPIC-Norfolk	Metabochip	GenCall	>0%	≥90%	$>10^{-06}$	143,294	-	-	-	-	13	13	SNPtest
Fenland	Metabochip	GenCall	>0%	≥90%	$>10^{-06}$	167,085	-	-	-	-	13	13	SNPtest
Finrisk07	Metabochip	GenCall	none	none	none	196,725	-	-	-	-	14	14	PLINK
NSHD	Metabochip	GenCall	>0%	≥90%	$>10^{-06}$	146,474	-	-	-	-	14	14	SNPtest
PIVUS	Metabochip	GenCall	none	≥90%	$>10^{-06}$	19	-	-	-	-	14	14	PLINK
STR	Metabochip	GenCall	none	≥90%	$>10^{-06}$	19	-	-	-	13	-	-	PLINK
ULSAM	Metabochip	GenCall	none	≥90%	$>10^{-06}$	19	-	-	-	-	13	-	PLINK
Whitehall II	Metabochip	GenCall	>0%	≥90%	$>10^{-06}$	171,257	-	-	-	-	13	13	SNPtest
***In silico* follow-up study: Cardiochip**													
EPIC-NL cases	Cardiochip	Manual	none	>97%	$>10^{-06}$	50,904	-	-	-	-	12	12	PLINK
EPIC-NL controls	Cardiochip	Manual	none	>97%	$>10^{-06}$	50,904	-	-	-	-	12	12	PLINK

[a] Sample genotyping success rate; that is, the percentage of successfully genotypes SNPs per sample; [b] SNPtest calculates the 'proper info' statistic as a measure of the relative statistical information about the additive genetic effect being estimated. The proper info statistic has a direct relationship to the power of the test and ranges from 0 to 1, with 1 indicating perfect imputation. MACH calculates rsq_hat, which is the r^2 between each imputed genotype and its true underlying genotype. Rsq_hat ranges from 0 to 1, with 1 indicating perfect imputation.

Supplementary Table 9 - Study-specific descriptive statistics of studies contributing to *in silico* replication in stage 2

Study	Trait	Men						Women					
		N	mean	SD	median	min	max	N	mean	SD	median	min	max
Follow-up studies: Genome-wide data													
ALSPAC 12-yr old children	Age (yrs)	1,967	11.8	0.2	11.8	10.8	13.5	2,033	11.8	0.2	11.8	10.7	13.6
	BMI (kg/m^2)	1,967	18.9	3.3	18.0	13.4	37.9	2,033	19.4	3.5	18.7	12.5	36.8
	HR (BPM)	1,967	73.8	10.7	74	45	114	2,033	78	10.7	77.5	47.5	124
ACTS	Age (yrs)	161	23.5	5.1	22	18	34	188	22.9	4.4	22	18	34
	BMI (kg/m^2)	161	22.3	2.8	21.7	15.4	31.0	188	21.6	2.5	21.2	17.0	32.3
	HR (BPM)	161	71.8	10.7	72	44	96	188	76	9.7	76	56	100
DESIR [a]	Age (yrs)	2,197	47.2	10.0	46.5	30.1	65.8	2,205	47.4	10.0	47.1	30.1	65.5
	BMI (kg/m^2)	2,197	25.4	3.3	25.1	16.7	45.4	2,205	24.0	4.1	23.3	15.4	53.6
	HR (BPM)	2,197	66.5	10.3	66	36	116	2,205	68.1	9.2	68	40	116
EGCUT	Age (yrs)	230	38.8	15.6	34	18	87	541	71.9	21.4	82	18	103
	BMI (kg/m^2)	230	26.1	4.1	25.7	17.4	48.3	541	26.7	5.2	26.0	11.9	50
	HR (BPM)	230	68	8.4	68	44	100	541	71.2	8.5	68	52	108
ERF	Age (yrs)	108	49.1	12.4	50.7	18.1	70.2	125	49.3	14.1	47.3	20.5	80.5
	BMI (kg/m^2)	108	26.7	3.5	26.3	17.4	38.5	125	26.1	4.7	25.3	17.7	45.5
	HR (BPM)	108	62.3	8.9	61	50	97	125	66.0	9.4	64	50	97
FamHS	Age (yrs)	1,776	52	13.9	54	25	91	1,953	52	13.4	54	25	94
	BMI (kg/m^2)	1,776	28.0	4.6	27.3	16	63.6	1,953	27.5	6.1	26.2	16.1	55.1
	HR (BPM)	1,776	33.3	5.5	33	19	64	1,953	35.1	5.1	35	15	62
LifeLines2	Age (yrs)	2,212	43.3	9.2	43.3	19.6	85.5	2,840	43.0	8.9	43.0	18.1	85.4
	BMI (kg/m^2)	2,212	26.4	3.7	26	14.4	45.4	2,840	25.6	4.7	25.6	13.9	51.8
	HR (BPM)	2,212	66.9	11.4	65	36	113	2,840	69.0	11.2	68	41	125
MESA	Age (yrs)	1,257	62.9	10.0	63	45	85	1,361	62.6	10.2	63	44	87
	BMI (kg/m^2)	1,257	28.0	4.2	27.5	17.4	44.3	1,361	27.6	5.8	26.6	16.9	49
	HR (BPM)	1,257	61.3	9.9	61	36	101	1,361	64.3	8.9	63	40	96
NTR	Age (yrs)	176	34.6	12.3	32.9	13.9	68.4	361	32.6	12.1	30.1	14.2	80.0
	BMI (kg/m^2)	176	24.4	3.6	24.1	17.3	36.0	361	23.6	3.7	23.2	15.7	44.5
	HR (BPM)	176	66.0	11.0	65.4	39	106.3	361	70.3	9.8	70	44.5	102.5
RISC	Age (yrs)	445	43.3	8.6	43	30	60	561	44.4	8.2	44	30	61
	BMI (kg/m^2)	445	26.3	3.6	26.1	17	43.9	561	24.7	4.2	23.9	16.9	41.7
	HR (BPM)	445	66.1	10.0	65	42	101	561	69.9	10.3	70	43	109
RRgen	Age (yrs)	*Descriptive information of the RRgen consortium in Eijgelsheim et al, 2010 [PMID 20639392]*											
	BMI (kg/m^2)												
	HR (BPM)												

Supplementary Table 9 - continued

Study	Trait	Men						Women					
		N	mean	SD	median	min	max	N	mean	SD	median	min	max
RS3	Age (yrs)	907	56.0	5.4	56.1	46.6	84.2	1,161	56.2	6.0	56.4	45.8	97.3
	BMI (kg/m^2)	907	28.0	4.1	27.3	18.4	46.7	1,161	27.5	5.1	26.5	16.7	56.9
	HR (BPM)	907	68.3	10.9	67.5	41.1	117.7	1,161	70.4	9.9	69.8	44.1	109.1
Stanford	Age (yrs)	146	51.6	8.7	53	28	71	181	51.1	9.0	52	22	70
	BMI (kg/m^2)	146	30.3	5.2	30.0	18.8	55.5	181	30.1	5.7	29.3	16.6	53.8
	HR (BPM)	146	68.6	10.4	67	45	102	181	69.1	10.7	67	46	101
Follow-up studies: Metabochip													
EGCUT cases	Age (yrs)	350	63.4	10.4	64	36	94	596	64.3	10.6	64	32	93
	BMI (kg/m^2)	350	32.3	5.0	31.7	18.7	51.4	596	33.7	5.8	33.0	18.4	56.9
	HR (BPM)	350	72.3	10.9	72	44	116	596	72.3	9.6	72	48	112
EGCUT controls	Age (yrs)	679	58.8	12.0	58	22	87	960	56.6	12.9	56	30	93
	BMI (kg/m^2)	679	25.7	4.6	24.7	16.7	43.9	960	25.0	5.3	23.5	14.6	51.0
	HR (BPM)	679	69.8	10.3	68	44	116	960	69.3	8.4	68	36	112
Ely	Age (yrs)	331	58.1	4.6	57.3	50.2	75.0	322	57.6	4.1	56.9	50.1	73.8
	BMI (kg/m^2)	331	27.3	3.8	26.9	17.9	40.8	322	26.5	4.6	25.6	18.1	46.3
	HR (BPM)	331	63.3	9.1	63	41	89	322	66.6	8.9	66	45	107
EPIC-Norfolk	Age (yrs)	848	61.0	8.7	61.6	40	79.1	844	60.2	9.4	60.4	33.9	77.4
	BMI (kg/m^2)	848	27.7	3.8	27.5	16.9	49.1	844	27.4	4.8	26.5	16.3	46.0
	HR (BPM)	848	69.8	12.5	68	37	126.5	844	73.3	12.1	72	38	125
Fenland	Age (yrs)	1,502	46.9	7.2	46.7	30.9	60	1,709	46.9	7.0	47.2	30.5	60
	BMI (kg/m^2)	1,502	27.0	4.1	26.5	16.4	50.6	1,709	26.5	5.5	25.3	16.9	59.9
	HR (BPM)	1,502	61.1	9.0	60	36	100	1,709	64.8	8.6	65	38	101
Finrisk07	Age (yrs)	1,794	55	13.5	53.3	25	74	2,148	51.8	13.6	53	25	74
	BMI (kg/m^2)	1,794	27.3	4.2	26.7	15.8	63.1	2,148	26.9	5.4	25.8	16.0	52.5
	HR (BPM)	1,794	67.1	11.9	66	38	120	2,148	68.6	11.3	68	36	132
NSHD	Age (yrs)	459	53	0	53	53	53	500	53	0	53	53	53
	BMI (kg/m^2)	459	27.6	4.1	26.9	18.2	43.1	500	27.5	5.2	26.5	18.6	52.9
	HR (BPM)	459	69.5	12.0	68	34	105	500	68.8	11.3	69	41	129
PIVUS	Age (yrs)	484	70.1	0.2	70.1	69.8	72.3	484	70.3	0.2	70.3	69.9	70.8
	BMI (kg/m^2)	484	27.1	3.7	27.0	17.7	43.4	484	27.1	4.9	26.5	16.6	49.8
	HR (BPM)	484	59.3	9.1	58	39	96	484	61.3	8.7	61	41	100
STR	Age (yrs)	829	74.4	10.2	76.7	45.8	93.4	1,374	76.4	9.9	78.4	39.8	103.8
	BMI (kg/m^2)	829	25.2	3.4	24.8	14.5	39.2	1,374	24.9	4.2	24.5	14.1	46.1
	HR (BPM)	829	68.4	11.8	67	37	122	1,374	71.9	11.7	71	39	125

Supplementary Table 9 - continued

Study	Trait	Men						Women					
		N	mean	SD	median	min	max	N	mean	SD	median	min	max
ULSAM	Age (yrs)	1,103	71.0	0.6	71.0	69.4	74.1						
	BMI (kg/m^2)	1,103	25.3	3.4	25.9	16.7	46.3						
	HR (BPM)	1,103	65.2	8.9	64	42	104						
Whitehall II	Age (yrs)	2,547	60.7	5.9	59.6	50.6	73.7	819	61.0	6.0	60.5	50.5	73.3
	BMI (kg/m^2)	2,547	26.6	3.7	26.3	17.9	48.7	819	27.3	5.5	26.2	15.8	49
	HR (BPM)	2,547	67.2	12.0	66	35	124	819	68.5	10.9	68	39	115
Follow-up study: Cardiochip													
EPIC-NL cases	Age (yrs)	647	51.5	7.9	52.9	22.3	65.7	2,057	58.0	7.8	58.5	21.4	70.1
	BMI (kg/m^2)	647	27.7	4.0	27.3	18.2	47.0	2,057	27.7	4.8	27	16	55.1
	HR (BPM)	647	73.1	11.3	72	48	112	2,057	74.7	12.0	73.5	40	139
EPIC-NL controls	Age (yrs)	489	44.0	11.1	45.5	21.0	65.0	1,978	53.3	10.5	54	20.3	70.1
	BMI (kg/m^2)	489	26.1	3.7	25.7	16.4	39.9	1,978	25.6	4.1	25	17.2	53.2
	HR (BPM)	489	71.6	10.7	72	42	110	1,978	73.5	11.0	72	36	113.5

[a] The DESIR sample was partly genotyped on a GWA platform (Illumina 370, n = 715), partly using Metabochip (n = 3,687).

Supplementary Table 10 - Proxy SNPs included in meta-analysis of stage 2

near candidate gene(s)	Most significant SNPs at stage 1	Metabochip [a]	Cardiochip [a]	Proxy [b]	Distance (bp)	Linkage disequilibrium r^2 [c]	Linkage disequilibrium D' [c]	Studies [d]
MYH6	rs365990		Cardio	-				
GJA1	rs1015451		Cardio	rs12110693 [C]	26,785	1	1	
TGM2	rs6127471	Metabo		rs6127466 [M]	1,155	1	1	
ACHE	rs13245899	Metabo	Cardio	-				
CCDC141	rs17362588			-				
CD46	rs11118555	Metabo		-				
ALG10	rs7980799	Metabo		-				
FADS1	rs174549	Metabo	Cardio	rs174548 [C]	34	0.964	1	
PLN	rs11153730	Metabo	Cardio	rs11970286 [C]	12,852	0.935	1	
LINC00477	rs17287293			-				
HCN4	rs4489968	Metabo	Cardio	rs8040533 [M]	765	1	1	
				rs7172808 [C]	1,874	1	1	
GNB4	rs7612445			-				
FLRT2	rs17796783			-				
CHRM2	rs2350782			-				
NKX2-5	rs6882776	Metabo		rs6891790 [M]	6,582	0.911	1	
GNG11	rs180242	Metabo		rs180267 [C]	9,054	0.859 [H]	0.927 [H]	
B3GNT7	rs13030174			-				
FNDC3B	rs9647379			rs4894803	15,088	0.933	0.966	LifeLines2
RFX4	rs2067615			-				
CPNE8	rs826838	Metabo		rs7953227 [M]	160,538	1	1	
TFPI	rs4140885	Metabo	Cardio	rs8176592 [C]	372	1	1	
A2BP1	rs11645781			rs7194057	168	0.959	1	LifeLines2
MYOT	rs7722600	Metabo	Cardio	-				
PDE11A	rs13413635			-				
PPP1CC	rs11065706	Metabo		rs10160981 [M]	251,456	0.846	0.945	
CPNE5	rs236373			rs9366917	1,391	0.955	1	LifeLines2
ACTN4	rs11083475		Cardio	rs3786837 [C]	16,070	1	1	
SLC10A7	rs10213084	Metabo		rs10014502 [M]	14,713	1	1	
DCP1A	rs2029213	Metabo		rs2306569 [M]	103,643	0.816	0.958	
CMYA5	rs10942901			-				
UHRF1BP1	rs1555773			-				
KLF14	rs205712			-				
DNAJC19	rs2718767		Cardio	rs2567648 [C]	48,644	0.841	1	
TCF21	rs4896011	Metabo		-				
HSD17B12	rs7110523			-				
NPBWR2	rs910883		Cardio	rs6089789 [C]	7,575	1.000 [H]	1.000 [H]	
MANEA	rs10806489			-				
FAM19A2	rs17715440	Metabo		-				
ST6GAL2	rs4384785			-				
RG9MTD3	rs12345385			-				
CLCNKA	rs1889785		Cardio	-				
				rs6604912	35,257	0.933	0.966	ACTS
CDH22	rs2425787			-				

[a] 'Metabo' or 'Cardio' indicates whether the locus is represented on Metabochip or Cardiochip, either by the exact SNP or by a proxy with r^2 for LD > 0.8; [b] 'M': Proxy SNP with r^2 > 0.8 available on Metabochip, 'C': Proxy SNP with r^2 > 0.8 available on Cardiochip; [c] LD structure based on 1000 genomes pilot study 1 (Johnson et al, 2008 [PMID 18974171]), except for SNPs marked by 'H' (Hapmap release 22); [d] Before embarking on stage 2, up to 3 proxy SNPs were selected for each of the 42 lead SNPs from stage 1. The selection of proxies was based on (in order of importance): 1) availability on Metabochip / Cardiochip; 2) r^2 for LD; 3) proximity to the lead SNP. If the lead SNPs were not available in GWAS of stage 2, they were replaced by the highest ranking available proxy. Studies in which such substitutions were applied in stage 2 are listed here. SNPs are ordered by their *P*-value in meta-analysis of stage 1 results.

Supplementary Table 11 - Association of previously confirmed GWAS loci for ECG-derived traits with heart rate in stage 1 results

			Alleles					
SNP	**Chr**	**Nearest gene**	**Effect**	**Other**	**EAF**	**dir**	**p-value**	**ref**
PR-interval								
rs365990	**14**	***MYH6***	**a**	**g**	**0.66**	**-**	**$1.85x10^{-25}$**	1
rs11047543	**12**	***LINC00477***	**g**	**a**	**0.85**	**+**	**$1.74x10^{-10}$**	2
rs6800541	3	*SCN10A*	c	t	0.42	-	$2.74x10^{-04}$	1-3
rs11897119	2	*MEIS1*	c	t	0.39	+	$7.14x10^{-03}$	1
rs11708996	3	*SCN5A*	c	g	0.16	-	0.05	2
rs251253	5	*C5orf41*	t	c	0.60	+	0.08	2
rs3807989	7	*CAV1*	a	g	0.42	-	0.27	1,2
rs7692808	4	*ARHGAP24*	g	a	0.65	-	0.58	1,2
rs4944092	11	*WNT11*	a	g	0.68	+	0.67	2
rs1896312	12	*TBX3*	c	t	0.29	-	0.67	2
rs3825214	12	*TBX5*	g	a	0.21	+	0.84	1
QRS-interval								
rs11153730	**6**	***SLC35F1***	**c**	**t**	**0.49**	**-**	**$1.33x10^{-13}$**	4
rs6801957	3	*SCN10A*	t	c	0.42	-	$6.47x10^{-04}$	1,3,4
rs9851724	3	*SCN10A*	t	c	0.66	-	$7.93x10^{-04}$	4
rs4074536	1	*CASQ2*	t	c	0.71	+	0.03	4
rs1362212	7	*TBX20*	a	g	0.16	-	0.03	4
rs11708996	3	*SCN5A*	c	g	0.16	-	0.05	4
r4687718	3	*TKT*	g	a	0.85	-	0.06	4
rs17608766	17	*GOSR2*	c	t	0.15	-	0.07	4
rs13165478	5	*HAND1*	g	a	0.64	+	0.11	4
rs7784776	7	*IGFBP3*	g	a	0.41	-	0.13	4
rs9436640	1	*NFIA*	t	g	0.49	-	0.15	4
rs17391905	1	*CDKN2C*	t	g	0.97	+	0.17	4
rs1733724	10	*DKK1*	a	g	0.29	+	0.18	4
rs1886512	13	*KLF12*	t	a	0.63	-	0.21	4
rs2242285	3	*LRIG1*	a	g	0.41	+	0.21	4
rs11710077	3	*SCN5A*	a	t	0.75	-	0.25	4
rs7342028	10	*VTI1A*	t	g	0.24	-	0.25	4
rs883079	12	*TBX5*	c	t	0.30	+	0.35	1,4
rs10850409	12	*TBX3*	g	a	0.73	+	0.51	4
rs17020136	2	*HEATR5B*	c	t	0.21	-	0.55	4
rs9912468	17	*PRKCA*	g	c	0.43	-	0.62	4
rs11848785	14	*SIPA1L1*	a	g	0.76	+	0.67	4
rs9470361	6	*CDKN1A*	a	g	0.24	+	0.74	1,4
rs7562790	2	*CRIM1*	g	t	0.42	-	0.84	4
rs2051211	3	*ENDOGL1*	a	g	0.74	-	0.85	4
rs10865879	3	*SCN5A*	a	c	0.75	-	0.90	4
rs991014	18	*SETBP1*	t	c	0.41	-	0.90	4
QT-interval								
rs11153730	**6**	***SLC35F1***	**c**	**t**	**0.49**	**-**	**$1.33x10^{-13}$**	5,6
rs12210810	**6**	***SLC35F1***	**g**	**c**	**0.95**	**-**	**$8.73x10^{-05}$**	7
rs2968863	7	*KCNH2*	c	t	0.78	-	0.04	5,7
rs12576239	11	*KCNQ1*	t	c	0.15	-	0.05	5
rs10919071	1	*ATP1B1*	a	g	0.87	+	0.06	7
rs12053903	3	*SCN5A*	t	c	0.65	+	0.12	5
rs17779747	17	*KCNJ2*	g	t	0.69	+	0.13	7
rs12296050	11	*KCNQ1*	t	c	0.23	-	0.16	7
rs4657178	1	*NOS1AP*	t	c	0.28	+	0.48	7
rs37062	16	*CNOT1*	a	g	0.74	+	0.48	5,7
rs1805128	21	*KCNE1*	a	g	0.04	-	0.52	5
rs12029454	1	*NOS1AP*	a	g	0.18	+	0.53	5
rs4725982	7	*KCNH2*	t	c	0.25	-	0.53	5
rs2074518	17	*LIG3*	c	t	0.51	-	0.55	5
rs12143842	1	*NOS1AP*	t	c	0.26	+	0.63	5-7
rs16857031	1	*NOS1AP*	g	c	0.12	+	0.79	5
rs11129795	3	*SCN5A*	g	a	0.75	+	0.83	7
rs8049607	16	*LITAF*	t	c	0.51	+	0.90	5,7
rs846111	1	*RNF207*	c	g	0.29	-	0.91	5,7
rs10494366	1	*NOS1AP*	g	t	0.38	-	0.94	6
rs2074238	11	*KCNQ1*	c	t	0.93	-	0.95	5
Atrial Fibrillation								
rs7164883	**15**	***HCN4***	**g**	**a**	**0.17**	**-**	**$2.29x10^{-13}$**	**8**
rs11047543	**12**	***LINC00477***	**g**	**a**	**0.85**	**+**	**$1.74x10^{-10}$**	**2**
rs6800541	3	*SCN10A*	t	c	0.58	+	$2.74x10^{-04}$	2
rs11708996	3	*SCN5A*	g	c	0.84	+	0.05	2
rs10824026	10	*SYNPO2L*	a	g	0.83	+	0.06	8
rs251253	5	*C5orf41*	t	c	0.60	+	0.08	2
rs7193343	16	*ATBF1*	t	c	0.20	+	0.10	9
rs6666258	1	*KCNN3*	c	g	0.28	+	0.16	8,10
rs1152591	14	*SYNE2*	a	g	0.48	-	0.16	8
rs2106261	16	*ATBF1*	t	c	0.19	+	0.26	11
rs3807989	7	*CAV1*	g	a	0.58	+	0.27	1,2,8
rs10821415	9	*C9orf*	a	c	0.42	+	0.35	8
rs10033464	4	*PITX2*	t	g	0.13	-	0.46	12
rs6817105	4	*PITX2*	c	t	0.13	+	0.59	8,11,12
rs3903239	1	*PRRX1*	g	a	0.43	+	0.79	8
rs3825214	12	*TBX5*	a	g	0.79	-	0.84	2
rs6843082	4	*PITX2*	g	a	0.25	+	0.97	10

SNP, reported in GWAS for ECG-derived traits; Effect allele, the allele that is associated with prolonged PR, QRS and QT-interval or increased prevalence of atrial fibrillation in GWAS for ECG-derived traits; EAF, the effect allele frequency after meta-analysis of stage 1 results; dir, the effect allele for the ECG-derived trait is associated with a higher (+) or lower (-) heart rate; ref, reference of GWAS; SNPs are ordered by p-value for association with heart rate in stage 1 results after GC-adjustment.

Heart rate loci that have previously been identified in GWAS for ECG-derived traits are shown in bold. For *MYH6*, *LINC00477 SCL35F1* and *HCN4* the most significant SNPs for ECG-derived traits and heart rate were in perfect LD. Rs251253 near-*C5orf41* (associated with PR and atrial fibrillation) is located near *NKX2-5*, but is in low LD with rs6882776 (heart rate) (r^2=0.026, D'=0.222).

Ref: 1, Holm et al., 2010 [PMID 20062063]; 2, Pfeufer et al., 2010 [PMID 20062060]; 3, Chambers et al., 2010 [PMID 20062061]; 4, Sotoodehnia et al., 2010 [PMID 2176409]; 5, Newton-Cheh et al., 2010 [PMID 19305408]; 6, Nolte et al., 2009 [PMID 19587794]; 7, Pfeufer et al., 2009 [PMID 1935409]; 8, Ellinor et al., 2012 [PMID 22544366]; 9, Gudbjartsson et al., 2009 [PMID 19597491]; 10, Ellinor et al., 2010 [PMID 20173747]; 11, Benjamin et al., 2009 [PMID 19597492]; 12, Gudbjartsson et al., 2007 [PMID 17603472].

Supplementary Table 12 – Association of the heart rate loci with the risk of atrioventricular block, pacemaker implantation and sudden cardiac death in data from deCODE Genetics

Locus	Nearest gene	Heart rate SNP	Alleles		Atrioventricular block			Pacemaker implantation			Sudden cardiac death		
			Effect	Other	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Previously identified heart rate loci													
1	*MYH6*	rs365990	g	a	0.944	0.79 - 1.12	0.51	0.914	0.83 - 1.01	0.08	0.991	0.85 - 1.16	0.92
2	*GJA1*	rs1015451	c	t	0.954	0.73 - 1.24	0.73	0.964	0.83 - 1.13	0.64	1.270	1.01 - 1.59	0.04
3	*ACHE*	rs13245899	g	a	1.016	0.82 - 1.27	0.88	0.955	0.84 - 1.09	0.48	0.895	0.73 - 1.10	0.29
4	*CD46*	rs11118555	a	t	0.805	0.62 - 1.04	0.10	0.905	0.78 - 1.05	0.18	0.746	0.58 - 0.95	0.02
5	*FADS1*	rs174549	a	g	1.001	0.85 - 1.18	0.99	1.011	0.92 - 1.12	0.82	1.131	0.97 - 1.32	0.12
6	*SLC35F1*	rs11153730	t	c	0.938	0.80 - 1.10	0.44	0.953	0.87 - 1.05	0.32	1.058	0.91 - 1.23	0.46
7	*LINC00477*	rs17287293	a	g	0.803	0.64 - 1.01	0.06	0.829	0.73 - 0.95	$5.75x10^{-03}$	1.012	0.81 - 1.26	0.92
Newly identified heart rate loci													
8	*KIAA1755*	rs6127471	c	t	1.153	0.97 - 1.37	0.10	0.956	0.78 - 1.06	0.37	0.966	0.82 - 1.13	0.67
9	*CCDC141*	rs17362588	a	g	0.948	0.73 - 1.22	0.68	0.937	0.81 - 1.09	0.39	1.079	0.86 - 1.35	0.51
10	*SYT10*	rs7980799	a	c	1.025	0.87 - 1.21	0.77	0.992	0.90 - 1.09	0.86	0.939	0.81 - 1.09	0.42
11	*HCN4*	rs4489968	t	g	0.808	0.65 - 1.01	0.06	0.910	0.80 - 1.04	0.17	0.992	0.80 - 1.23	0.94
12	*GNB4*	rs7612445	g	t	1.130	0.92 - 1.39	0.26	0.921	0.82 - 1.04	0.17	1.193	0.98 - 1.45	0.08
13	*FLRT2*	rs17796783	t	c	1.037	0.87 - 1.23	0.69	0.901	0.81 - 1.00	0.05	0.988	0.83 - 1.16	0.89
14	*CHRM2*	rs2350782	c	t	1.070	0.80 - 1.43	0.65	0.929	0.78 - 1.11	0.41	0.943	0.72 - 1.24	0.68
15	*NKX2-5*	rs6882776	g	a	1.066	0.89 - 1.28	0.49	1.088	0.98 - 1.20	0.12	1.190	1.00 - 1.41	0.04
16	*GNG11*	rs180242	t	a	0.995	0.84 - 1.18	0.95	1.010	0.92 - 1.11	0.84	1.079	0.93 - 1.27	0.34
17	*B3GNT7*	rs13030174	a	c	0.968	0.80 - 1.17	0.74	1.013	0.91 - 1.13	0.83	0.888	0.75 - 1.05	0.18
18	*FNDC3B*	rs9647379	c	g	0.970	0.82 - 1.15	0.73	0.993	0.90 - 1.10	0.89	0.978	0.83 - 1.15	0.78
19	*RFX4*	rs2067615	a	t	0.917	0.78 - 1.08	0.30	1.051	0.96 - 1.16	0.31	0.941	0.81 - 1.09	0.42
20	*CPNE8*	rs826838	c	t	1.093	0.93 - 1.28	0.28	0.935	0.85 - 1.03	0.16	0.949	0.82 - 1.10	0.49
21	*TFPI*	rs4140885	a	g	1.034	0.87 - 1.23	0.70	1.087	0.98 - 1.20	0.10	0.992	0.85 - 1.16	0.92
Multi-SNP predisposition score					0.714	0.45 - 1.12	0.15	0.606	0.46 - 0.80	$3.56x10^{-04}$	0.975	0.63 - 1.50	0.91

Effect allele, the allele that is associated with higher heart rate; p-value for association after GC-adjustment. Analyses were performed on data from 319 cases and 41,356 controls for atrioventricular block; 978 cases and 40,976 controls for pacemaker implantation; and 370 cases and 41,305 controls for sudden cardiac death. Multi-SNP predisposition score shows the combined effect of the 21 heart rate-associated SNPs per genetically predicted 5 bpm incease in heart rate, based on single SNP summary statistics and weighting by effect sizes for heart rate.

Supplementary Table 13 – Association of the heart rate loci with blood pressure and the prevalence of hypertension in data from the Global BPgen consortium

Locus	Nearest gene	Heart rate SNP	Alleles		Diastolic blood pressure				Systolic blood pressure				Hypertension			
			Effect	Other	N	beta (mm Hg)	SE (mm Hg)	p-value	N	beta (mm Hg)	SE (mm Hg)	p-value	N_{cases} /	OR	95% CI	p-value
Previously identified heart rate loci																
1	*MYH6*	rs365990	g	a	25,701	0.002	0.096	0.99	25,679	-0.155	0.144	0.28	8,215 / 8,428	1.001	0.947 - 1.058	0.97
2	*GJA1*	rs1015451	c	t	32,411	0.021	0.140	0.88	32,409	-0.462	0.208	0.03	9,729 / 10,063	0.931	0.859 - 1.009	0.08
3	*ACHE*	rs13245899	g	a	27,772	0.184	0.114	0.11	27,782	0.110	0.168	0.51	8,394 / 8,377	1.060	0.991 - 1.134	0.09
4	*CD46*	rs11118555	a	t	33,285	-0.049	0.128	0.70	33,308	-0.430	0.188	0.02	9,626 / 9,947	0.947	0.879 - 1.020	0.15
5	*FADS1*	rs174549	a	g	34,210	0.203	0.092	0.03	34,211	0.118	0.136	0.38	9,777 / 10,102	0.984	0.933 - 1.038	0.55
6	*SLC35F1*	rs11153730	t	c	33,580	0.093	0.085	0.27	33,578	0.205	0.127	0.11	9,624 / 9,927	1.075	1.024 - 1.129	$3.82x10^{-03}$
7	*LINC00477*	rs17287293	a	g	33,694	0.129	0.122	0.29	33,696	0.108	0.183	0.56	9,679 / 10,001	1.030	0.960 - 1.106	0.41
Newly identified heart rate loci																
8	*KIAA1755*	rs6127471	c	t	33,644	0.135	0.086	0.11	33,633	0.054	0.128	0.67	9,653 / 9,984	0.998	0.950 - 1.048	0.93
9	*CCDC141*	rs17362588	a	g	28,193	0.208	0.137	0.13	28,324	-0.043	0.205	0.83	8,251 / 8,436	1.007	0.930 - 1.090	0.87
10	*SYT10*	rs7980799	a	c	32,627	0.129	0.088	0.15	32,629	0.084	0.132	0.53	9,311 / 9,625	1.001	0.951 - 1.053	0.97
11	*HCN4*	rs4489968	t	g	30,711	0.169	0.117	0.15	30,707	0.141	0.174	0.42	9,044 / 9,131	1.041	0.972 - 1.114	0.26
12	*GNB4*	rs7612445	g	t	27,672	0.142	0.117	0.23	27,651	0.106	0.176	0.55	na	na	na	na
13	*FLRT2*	rs17796783	t	c	33,830	-0.089	0.094	0.35	33,839	-0.282	0.141	0.05	9,669 / 10,014	0.978	0.926 - 1.033	0.42
14	*CHRM2*	rs2350782	c	t	27,697	0.090	0.153	0.56	27,693	-0.005	0.229	0.98	7,889 / 8,083	1.018	0.931 - 1.113	0.69
15	*NKX2-5*	rs6882776	g	a	24,738	-0.136	0.101	0.18	24,733	-0.237	0.148	0.11	7,413 / 7,545	0.976	0.919 - 1.036	0.43
16	*GNG11*	rs180242	t	a	21,148	-0.116	0.106	0.27	21,212	-0.035	0.160	0.83	7,081 / 6,641	1.048	0.985 - 1.115	0.14
17	*B3GNT7*	rs13030174	a	c	29,428	0.150	0.099	0.13	29,421	0.105	0.147	0.48	8,537 / 8,540	1.006	0.949 - 1.067	0.84
18	*FNDC3B*	rs9647379	c	g	23,056	-0.120	0.098	0.22	23,102	-0.214	0.144	0.14	7,430 / 7,380	0.956	0.903 - 1.012	0.12
19	*RFX4*	rs2067615	a	t	34,022	0.091	0.084	0.28	34,029	0.168	0.126	0.18	9,720 / 10,043	0.988	0.941 - 1.037	0.63
20	*CPNE8*	rs826838	c	t	33,761	0.064	0.086	0.46	33,748	0.014	0.128	0.91	9,638 / 9,975	0.992	0.944 - 1.042	0.74
21	*TFPI*	rs4140885	a	g	31,800	-0.204	0.094	0.03	31,786	-0.278	0.140	0.05	9,136 / 9,440	0.967	0.916 - 1.021	0.23
Multi-SNP predisposition score						0.751	0.277	$6.71x10^{-03}$		-0.404	0.413	0.33		1.014	0.861 - 1.192	0.87

Effect allele, the allele that is associated with higher heart rate; p-value for association after GC-adjustment. Multi-SNP predisposition score shows the combined effect of the 21 heart rate-associated SNPs per 5 bpm incease in heart rate, based on single SNP summary statistics and weighting by effect sizes for heart rate.

Nature Genetics: doi:10.1038/ng.2610

Supplementary Table 14 – Association of the heart rate loci with prevalence of cardiovascular disease in data from the CARDIoGRAM consortium

Locus	Nearest gene	Heart rate SNP	Alleles		Coronary artery disease				Myocardial infarction			
			Effect	Other	N_{cases} / $N_{controls}$	OR	95% CI	p-value	N_{cases} / $N_{controls}$	OR	95% CI	p-value
Previously identified heart rate loci												
1	*MYH6*	rs365990	g	a	8,647 / 44,573	0.978	0.939 - 1.018	0.28	4,434 / 29,288	0.973	0.920 - 1.030	0.35
2	*GJA1*	rs1015451	c	t	20,816 / 61,734	0.994	0.950 - 1.039	0.77	11,763 / 40,651	0.995	0.940 - 1.053	0.87
3	*ACHE*	rs13245899	g	a	15,604 / 52,833	1.026	0.986 - 1.068	0.21	8,744 / 36,593	1.045	0.991 - 1.101	0.10
4	*CD46*	rs11118555	a	t	20,424 / 61,293	1.011	0.969 - 1.056	0.61	11,542 / 40,257	0.987	0.934 - 1.043	0.64
5	*FADS1*	rs174549	a	g	21,837 / 62,190	1.003	0.974 - 1.033	0.84	12,545 / 41,126	1.000	0.964 - 1.038	0.99
6	*SLC35F1*	rs11153730	t	c	20,129 / 60,894	0.996	0.969 - 1.023	0.76	11,323 / 39,894	1.003	0.968 - 1.039	0.87
7	*LINC00477*	rs17287293	a	g	20,363 / 61,227	0.997	0.959 - 1.037	0.90	11,424 / 40,141	1.019	0.969 - 1.071	0.47
Newly identified heart rate loci												
8	*KIAA1755*	rs6127471	c	t	20,326 / 61,434	1.019	0.991 - 1.047	0.18	11,404 / 40,503	1.031	0.996 - 1.068	0.09
9	*CCDC141*	rs17362588	a	g	18,799 / 59,536	1.005	0.963 - 1.048	0.83	10,370 / 38,769	1.007	0.954 - 1.063	0.80
10	*SYT10*	rs7980799	a	c	19,673 / 57,826	1.024	0.995 - 1.055	0.10	11,245 / 39,755	1.015	0.979 - 1.053	0.42
11	*HCN4*	rs4489968	t	g	19,280 / 59,785	1.015	0.976 - 1.055	0.46	10,178 / 38,745	1.005	0.956 - 1.058	0.83
12	*GNB4*	rs7612445	g	t	18,405 / 55,789	0.967	0.932 - 1.003	0.07	9,970 / 37,797	0.973	0.929 - 1.019	0.25
13	*FLRT2*	rs17796783	t	c	21,928 / 62,260	0.995	0.966 - 1.026	0.76	12,584 / 41,163	1.002	0.965 - 1.041	0.90
14	*CHRM2*	rs2350782	c	t	19,275 / 59,914	1.009	0.960 - 1.061	0.72	10,689 / 38,997	1.058	0.992 - 1.128	0.09
15	*NKX2-5*	rs6882776	g	a	13,482 / 53,461	1.017	0.981 - 1.055	0.35	6,656 / 33,910	1.020	0.973 - 1.070	0.41
16	*GNG11*	rs180242	t	a	14,595 / 53,135	0.997	0.963 - 1.031	0.85	7,215 / 33,350	1.012	0.966 - 1.061	0.60
17	*B3GNT7*	rs13030174	a	c	15,375 / 51,192	1.011	0.975 - 1.048	0.57	8,798 / 36,335	0.992	0.947 - 1.039	0.74
18	*FNDC3B*	rs9647379	c	g	10,756 / 31,233	1.007	0.969 - 1.047	0.71	6,209 / 31,733	1.004	0.957 - 1.053	0.86
19	*RFX4*	rs2067615	a	t	20,934 / 61,474	0.995	0.968 - 1.023	0.74	11,932 / 40,403	1.009	0.974 - 1.045	0.61
20	*CPNE8*	rs826838	c	t	21,797 / 62,105	0.997	0.970 - 1.025	0.83	12,498 / 41,011	0.995	0.961 - 1.030	0.76
21	*TFPI*	rs4140885	a	g	19,192 / 59,799	0.997	0.967 - 1.028	0.87	10,687 / 38,947	0.980	0.943 - 1.020	0.33
Multi-SNP predisposition score						1.035	0.946 - 1.133	0.45		1.075	0.954 - 1.210	0.24

Effect allele, the allele that is associated with higher heart rate; p-value for association after GC-adjustment. Multi-SNP predisposition score shows the combined effect of the 21 heart rate-associated SNPs per genetically predicted 5 bpm incease in heart rate, based on single SNP summary statistics and weighting by effect sizes for heart rate.

Supplementary Table 15 - Association of previously confirmed GWAS loci for blood pressure and prevalence of hypertension with heart rate in stage 1 results

				Alleles					
SNP	**Chr**	**Nearest gene**	**Trait**	**Effect**	**Other**	**EAF**	**dir**	**p-value**	**ref**
rs661348	11	*LSP1/TNNT3*	MAP	c	t	0.45	-	9.64×10^{-03}	1
rs13139571	4	*GUCY1A3/GUCY1B3*	DBP	c	a	0.76	-	0.01	2
rs2004776	1	*AGT*	Hypertension	t	c	0.24	-	0.02	1
rs17608766	17	*GOSR2*	SBP	c	t	0.15	-	0.07	2
rs12940887	17	*ZNF652*	SBP, DBP	t	c	0.38	-	0.09	2,3
rs11953630	5	*EBF1*	SBP, DBP	c	t	0.64	-	0.09	2
rs4590817	10	*C10orf107*	SBP, DBP, Hypertension	g	c	0.85	-	0.19	2,3
rs1173771	5	*NPR3*	SBP, DBP, Hypertension	g	a	0.60	-	0.23	2
rs11191548	10	*CYP17A1/NT5C2*	SBP, DBP	t	c	0.90	+	0.25	2,3,4
rs1378942	15	*CYP1A1/ULK3*	SBP, DBP, Hypertension	c	a	0.39	-	0.27	2,3,4
rs10850411	12	*TBX3/TBX5*	SBP, DBP	t	c	0.67	-	0.30	2,4
rs2782980	10	*ADRB1*	MAP	c	t	0.70	+	0.31	5
rs7129220	11	*ADM*	SBP	a	g	0.14	-	0.33	2
rs3184504	12	*SH2B3*	SBP, DBP	t	c	0.45	+	0.37	2,4
rs2932538	1	*MOV10*	SBP, DBP	g	a	0.75	+	0.40	2
rs17249754	12	*ATP2B1*	SBP, DBP, Hypertension	g	a	0.82	+	0.41	1,2,4
rs1327235	20	*JAG1*	SBP, DBP	g	a	0.45	+	0.41	2
rs653178	12	*ATXN2*		c	t	0.46	+	0.44	3
rs17477177	7	*PIK3CG*	PP	c	t	0.14	+	0.45	5
rs932764	10	*PLCE1*	SBP	g	a	0.47	-	0.46	2
rs12946454	17	*PLCD3*		t	a	0.27	+	0.47	3
rs4846049	1	*MTHFR/NPPB*	DBP	g	t	0.67	-	0.49	1
rs1446468	2	*FIGN*	MAP	c	t	0.55	-	0.49	5
rs17367504	1	*MTHFR/NPPB*	SBP, DBP, Hypertension	a	g	0.85	+	0.48	2,3
rs2014408	11	*SOX6*	MAP	t	c	0.20	+	0.52	1
rs319690	3	*MAP4*	MAP	t	c	0.62	+	0.55	5
rs11222084	11	*ADAMTS8*	PP	t	a	0.36	+	0.57	5
rs1813353	10	*CACNB2*	SBP, DBP, Hypertension	t	c	0.69	-	0.58	2,4
rs633185	11	*FJL32810/TMEM133*	SBP, DBP, Hypertension	c	g	0.71	-	0.59	2
rs6015450	20	*GNAS/EDN3*	SBP, DBP, Hypertension	g	a	0.14	+	0.67	2
rs13002573	2	*FIGN*	PP	a	g	0.77	-	0.67	5
rs4373814	10	*CACNB2*	SBP, DBP	c	g	0.46	-	0.71	2
rs805303	6	*BAT2/BAT5*	SBP, DBP, Hypertension	g	a	0.61	-	0.72	2
rs13082711	3	*SLC4A7*	DBP	c	t	0.22	-	0.72	2
rs13333226	16	*UMOD*	Hypertension	a	g	0.80	-	0.75	6
rs419076	3	*MECOM*	SBP, DBP	t	c	0.47	+	0.75	2
rs871606	4	*CHIC2*	PP	t	c	0.86	-	0.67	5
rs3774372	3	*ULK4/TRAK1*	DBP	c	t	0.19	+	0.82	2,4
rs1421811	5	*NPR3*	SBP	c	g	0.63	+	0.83	1
rs2521501	15	*FURIN/FES*	SBP, DBP	t	a	0.30	-	0.89	2
rs381815	11	*PLEKHA7*	SBP, DBP	t	c	0.26	-	0.89	2,4
rs1799945	6	*HFE*	SBP, DBP, Hypertension	g	c	0.14	+	0.89	2
rs13107325	4	*SLC39A8*	SBP, DBP	c	t	0.93	+	0.92	2
rs1458038	4	*FGF5*	SBP, DBP	t	c	0.31	+	0.99	2,3
rs2071518	8	*NOV*	PP	t	c	0.26	+	1.00	5
rs3918226	7	*NOS3*	DBP	t	c	na	na	na	1

SNP, reported in GWAS for diastolic blood pressure (DBP), systolic blood pressure (SBP) and prevalence of hypertension; Effect allele, the allele that is associated with increased blood pressure / prevalence of hypertension in GWAS; EAF, the effect allele frequency after meta-analysis of stage 1 results; dir, the effect allele for blood pressure and prevalence of hypertension is associated with a higher (+) or lower (-) heart rate; ref, reference of GWAS; SNPs are ordered by p-value for association with heart rate in stage 1 results after GC-adjustment.

Trait: Locus was identified as being associated with systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure (PP) and/or prevalence of hypertension.

Ref: 1, Johnson et al., 2011 [PMID 22100073]; 2, Ehret et al., 2011 [PMID 21909115]; 3, Newton-Cheh, 2009 [PMID 19430483]; 4, Levy et al, 2009 [PMID 19430479]; 5, Wain et al., 2011 [PMID 21909110]; 6, Padmanabhan et al., 2010 [PMID 21082022].

Supplementary Table 16 - Association of previously confirmed GWAS loci for prevalence of coronary artery disease and myocardial infarction with heart rate in stage 1 results

			Alleles					
SNP	**Chr**	**Nearest gene**	**Effect**	**Other**	**EAF**	**dir**	**p-value**	**ref**
Coronary Artery Disease								
rs12190287	6	*TCF21*	c	g	0.61	-	$1.52x10^{-03}$	1
rs12526453	6	*PHACTR1*	c	g	0.66	-	0.01	1
rs216172	17	*SMG6*	c	g	0.35	+	0.02	1
rs17321515	8	*TRIB1*	a	g	0.53	+	0.03	2
rs17609940	6	*ANKS1A*	g	c	0.80	-	0.03	1
rs12936587	17	*PEMT*	g	a	0.58	+	0.03	1
rs579459	9	*ABO*	c	t	0.22	-	0.06	1
rs2075650	19	*APOE/TMEM40*	g	a	0.15	-	0.07	3
rs501120	10	*CXCL12*	t	c	0.83	-	0.10	1,4,5
rs2706399	5	*IL5*	g	a	0.50	-	0.13	2
rs6725887	2	*WDR12*	c	t	0.13	+	0.18	1
rs9982601	21	*MRPS6*	t	c	0.15	-	0.19	1
rs2306374	3	*MRAS*	c	t	0.15	-	0.20	1
rs1333049	9	*CDKN2B*	c	g	0.47	-	0.21	1,4,5
rs17114036	1	*PPAP2B*	a	g	0.90	-	0.22	1
rs46522	17	*UBE2Z*	t	c	0.53	+	0.22	1
rs4977574	9	*CDKN2BAS*	g	a	0.47	-	0.26	1,4,5
rs11556924	7	*Z3HC1*	c	t	0.62	+	0.29	1
rs3184504	12	*SH2B3*	t	c	0.45	+	0.37	1
rs17465637	1	*MIA3*	c	a	0.73	-	0.40	1,4
rs599839	1	*PSRC1*	a	g	0.77	+	0.42	1,4,5
rs599839	1	*SORT1*	a	g	0.77	+	0.42	1
rs3825807	15	*ADAMTS7*	a	g	0.59	-	0.48	1
rs2246942	10	*LIPA*	g	a	0.38	-	0.48	2
rs12413409	10	*CYP17A1*	g	a	0.90	+	0.57	1
rs10455872	6	*LPA*	g	a	0.07	-	0.60	6
rs964184	11	*ZNF259*	g	c	0.20	+	0.75	1
rs4299376	2	*ABCG8*	g	t	0.29	+	0.62	2
rs964164	11	*APOA5/APOC3*	g	c	0.20	+	0.75	1
rs11206510	1	*PCSK9*	t	c	0.82	+	0.79	1
rs1122608	19	*LDLR*	g	t	0.75	+	0.79	1
rs4773144	13	*COL4A2*	g	a	0.44	-	0.84	1
rs2895811	14	*HHIPL1*	c	t	0.43	-	0.93	1
rs3798220	6	*LPA*	c	t	na	na	na	1
Myocardial Infarction								
rs12526453	6	*PHACTR1*	c	g	0.66	-	0.01	7
rs17321515	8	*TRIB1*	a	g	0.53	+	0.03	2
rs501120	10	*CXCL12*	t	c	0.83	-	0.10	4,7
rs2706399	5	*IL5*	g	a	0.50	-	0.13	2
rs6725887	2	*WDR12*	c	t	0.13	+	0.18	7
rs9982601	21	*MRPS6*	t	c	0.15	-	0.19	7
rs1333049	9	*CDKN2B*	c	g	0.47	-	0.21	4,7
rs17465637	1	*MIA3*	c	a	0.73	-	0.40	7
rs2246942	10	*LIPA*	g	a	0.38	-	0.48	2
rs646776	1	*CELSR2*	t	c	0.78	+	0.56	7
rs4299376	2	*ABCG8*	g	t	0.29	+	0.62	2
rs11206510	1	*PCSK9*	t	c	0.82	+	0.79	7
rs1122608	19	*SMARCA4*	g	t	0.75	+	0.79	7

SNP, reported in GWAS for prevalence of coronary artery disease (CAD) and myocardial infarction (MI); Effect allele, the allele that is associated with increased prevalence of CAD / MI in GWAS; EAF, the effect allele frequency after meta-analysis of stage 1 results; dir, the effect allele for prevalence of CAD and MI is associated with a higher (+) or lower (-) heart rate; ref, reference of GWAS. SNPs are ordered by p-value for association with heart rate in stage 1 results after GC-adjustment. rs3798220 was not available in our meta-analysis of stage 1 results.

Ref: 1, Schunkert et al., 2011 [PMID 21378990]; 2, Butterwortk et al., 2012 [PMID 21966275]; 3, Ronald et al., 2009 [PMID 19951432]; 4, Samani et al., 2009 [PMID 19164808]; 5, Samani et al., 2007 [PMID 17634449]; 6, Clarke et al., 2009 [PMID 20032323]; 7, Kathiresan et al., 2009 [PMID 19198609].

Supplementary Table 17 - Genes within 500 kb of the heart rate loci

Locus	Nearest gene	Other nearby genes
Previously identified heart rate loci		
1	*MYH6*	*MIR208A, CMTM5, C19orf10, MYH7, MIR208B, EFS, SLC22A17, BCL2L2-PABPN1, PABPN1, NGDN, BCL2L2, PPP1R3E, HOMEZ, ZFHX2, THTPA, AP1G2, JPH4, SLC7A8, DHRS2, CEBPE, C14orf119, ACIN1, CDH24, PSMB11, PSMB5, C14orf93, JUB, HAUS4, PRMT5, RBM23*
2	*GJA1*	*C6orf170*
3	*ACHE*	*UFSP1, SRRT, TRIP6, SLC12A9, EPHB4, ZAN, MUC12, MUC17, TIMP1, POP7, GIGYF1, GNB2, TRIM56, ACTL6B, TFR2, SERBP1, MOSPD3, PCOLCE, FBXO24, AP1S1, VGF, LRCH4, NAT16, SAP25, AGFG2, MOGAT3, PLOD3, ZNHIT1, CLDN15, FIS1, NYAP1, TSC22D4, C7orf61, RABL5, PPP1R35, MEPCE, ZCWPW1, PILRA*
4	*CD46*	*MIR29C, MIR29B2, CR1L, LOC148696, CD34, CR1, PLXNA2, CR2, CD55*
5	*FADS1*	*FEN1, MIR1908, TMEM258, mir611, C5H11orf9, FADS2, DKFZP434K028, DAGLA, FADS3, RAB3IL1, BEST1, FTH1, RPLP0P2, SYT7, LRRC10B, PPP1R32, INCENP, SDHAF2, CPSF7, SCGB1D1, SCGB2A1, TMEM216, TMEM138, SCGB1D2, CYBASC3, DAK, SCGB2A2, DDB1, SCGB1D4*
6	*SLC35F1*	*C6orf204, BRD7P3, PLN, LOC100287632, MCM9*
7	*LINC00477*	*SOX5, BCAT1, C12orf77, MIR920, LRMP, CASC1*
Newly identified heart rate loci		
8	*KIAA1755*	*TGM2, BPI, RPRD1B, RPSA, TTI1, LOC388796, SNOR71B, SNOR71A, SNOR71C, SNOR71D, SNHG11, SNORA39, SNORA60, RALGAPB, VSTM2L, CTNNBL1, ADIG, ARHGAP40*
9	*CCDC141*	*TTN, MIR548N, SESTD1, PLEKHA3, FKBP7, DFNB59, PRKRA, OSBPL6*
10	*SYT10*	
11	*HCN4*	*NEO1, C15orf60, NPTN, CD276, C15orf59*
12	*GNB4*	*MFN1, ACTL6A, ZNF639, MRPL47, NDUFB5, KCNMB3, USP13, PIK3CA, PEX5L, ZMAT3*
13	*FLRT2*	
14	*CHRM2*	*MIR490, PTN, DGKI*
15	*NKX2-5*	*BNIP1, STC2, CREBRF, ATP6V0E1, SNORA74B, RPL26L1, LOC100268168, ERGIC1, LOC285593, BOD1, DUSP12*
16	*GNG11*	*GNGT1, TFPI2, BET1, CALCR, MIR489, MIR653, COL1A2*
17	*B3GNT7*	*NCL, SNORA75, SNORD20, SNORD82, ARMC9, LINC00471, NMUR1, C2orf57, PSMD1, HTR2B, PTMAP4, MIR1244-2, MIR1244-1, MIR1244-3, PDE6D, C2orf72, COPS7B, SPATA3, LOC348761, GPR55, MIR1471*
18	*FNDC3B*	*TMEM212, PLD1, GHSR, TRAIL/TNFSF10*
19	*RFX4*	*RIC8B, C12orf23, MTERFD3, CRY1, POLR3B, TCP11L2*
20	*CPNE8*	*ALG10B*
21	*TFPI*	*CALCRL*

Supplementary Table 18 – Gene set enrichment analysis (MAGENTA) of biological pathways using the heart rate GWAS meta-analysis of stage 1 results

Database	Gene set / Pathway	Original # genes in gene set	# genes in gene set analyzed by MAGENTA [a]	Nominal GSEA p-value	FDR q-value	# genes expected above 95th percentile cut off	# genes observed above 95th percentile cut off	Genes in LD with 21 confirmed heart rate SNPs
KEGG	**Dilated cardiomyopathy**	**92**	**79**	**$3.00x10^{-05}$ ***	**0.01**	**4**	**14**	***MYH6, MYH7, PLN, TTN***
KEGG	**Hypertrophic cardiomyopathy**	**85**	**74**	**$1.00x10^{-04}$ ***	**0.03**	**4**	**12**	***MYH6, MYH7, TTN***
KEGG	**Cardiac muscle contraction**	**80**	**66**	**$6.00x10^{-04}$**	**0.02**	**3**	**11**	***MYH6, MYH7***
KEGG	**Arrhythmogenic right ventricular cardiomyopathy**	**76**	**67**	**$1.20x10^{-03}$**	**0.05**	**3**	**10**	***GJA1***
KEGG	**Alzheimers disease**	**169**	**152**	**$1.30x10^{-03}$**	**0.05**	**8**	**18**	**-**
KEGG	Hematopoietic cell lineage	88	73	$3.10x10^{-03}$	0.09	4	10	*CD34*
KEGG	Oocyte meiosis	114	105	$6.50x10^{-03}$	0.15	5	12	-
KEGG	Progesterone mediated oocyte maturation	86	78	0.02	0.26	4	9	-
KEGG	Vascular smooth muscle contraction	115	108	0.02	0.3	5	11	*CALCRL*
KEGG	RNA degradation	59	55	0.02	0.26	3	7	-
KEGG	Dorso ventral axis formation	25	23	0.02	0.24	1	4	-
KEGG	Huntingtons disease	185	167	0.04	0.4	8	14	*TGM2*
KEGG	Aldosterone regulated sodium reabsorption	42	39	0.04	0.36	2	5	-
BIOCARTA	MPR	34	34	$1.10x10^{-03}$	0.21	2	7	*GNGT1*
BIOCARTA	CSK	24	20	$2.50x10^{-03}$	0.14	1	5	*GNGT1*
BIOCARTA	MCALPAIN	25	24	$5.50x10^{-03}$	0.13	1	5	-
BIOCARTA	CXCR4	24	24	$5.70x10^{-03}$	0.12	1	5	*GNGT1*
BIOCARTA	AGR	36	34	$6.30x10^{-03}$	0.12	2	6	-
BIOCARTA	IL17	17	15	$6.60x10^{-03}$	0.11	1	4	*CD34*
BIOCARTA	TCRA	13	9	$7.40x10^{-03}$	0.1	0	3	-
BIOCARTA	TCAPOPTOSIS	11	9	$8.00x10^{-03}$	0.11	0	3	-
BIOCARTA	STATHMIN	19	19	0.01	0.15	1	4	-
BIOCARTA	BARR MAPK	12	12	0.02	0.14	1	3	*GNGT1*
BIOCARTA	CTL	15	12	0.02	0.13	1	3	-
BIOCARTA	THELPER	14	12	0.02	0.14	1	3	-
BIOCARTA	TCYTOTOXIC	14	12	0.02	0.12	1	3	-
BIOCARTA	CCR3	23	22	0.02	0.17	1	4	*GNGT1*
BIOCARTA	SPPA	22	22	0.02	0.18	1	4	*GNGT1*
BIOCARTA	ECM	24	24	0.03	0.19	1	4	-
BIOCARTA	MET	37	36	0.03	0.18	2	5	-
BIOCARTA	ERYTH	15	14	0.03	0.18	1	3	-
BIOCARTA	BAD	26	25	0.03	0.18	1	4	-
BIOCARTA	CDMAC	16	15	0.03	0.19	1	3	-
BIOCARTA	BARRESTIN SRC	15	15	0.04	0.18	1	3	*GNGT1*
BIOCARTA	EDG1	27	26	0.04	0.18	1	4	*GNGT1*
BIOCARTA	NO2IL12	17	16	0.04	0.19	1	3	-

Supplementary Table 18 – continued

Database	Gene set / Pathway	Original # genes in gene set	# genes in gene set analyzed by MAGENTA [a]	Nominal GSEA p-value	FDR q-value	# genes expected above 95th percentile cut off	# genes observed above 95th percentile cut off	Genes in LD with 21 confirmed heart rate SNPs
BIOCARTA	CTLA4	21	16	0.04	0.18	1	3	-
BIOCARTA	ARAP	18	16	0.04	0.18	1	3	-
BIOCARTA	MTA3	19	17	0.05	0.18	1	3	-
GO	**muscle contraction**	**99**	**90**	**3.20×10^{-05} ***	**0.09**	**5**	**15**	***GJA1, MYH6, MYH7, TTN, HCN4***
GO	**regulation of heart contraction**	**31**	**30**	**8.50×10^{-05}**	**0.07**	**2**	**8**	***CHRM2, MYH6, HCN4***
GO	**positive regulation of cell adhesion**	**16**	**16**	**1.00×10^{-04}**	**0.05**	**1**	**6**	***TGM2***
GO	actin binding	283	250	7.00×10^{-04}	0.27	13	25	*MYH6, MYH7*
GO	protein complex assembly	102	96	8.00×10^{-04}	0.29	5	13	-
GO	mammary gland development	29	28	1.70×10^{-03}	0.3	1	6	-
GO	structural constituent of muscle	42	38	2.20×10^{-03}	0.3	2	7	*MYH6, MYH7, TTN*
GO	transmembrane transporter activity	15	13	2.70×10^{-03}	0.34	1	4	*GJA1*
GO	exonuclease activity	33	30	3.20×10^{-03}	0.28	2	6	*FEN1*
GO	protein homodimerization activity	351	322	3.20×10^{-03}	0.38	16	28	*ACHE, NKX2-5, MYH6, MYH7,*
GO	embryonic forelimb morphogenesis	14	13	3.40×10^{-03}	0.26	1	4	-
GO	condensed nuclear chromosome	24	21	3.60×10^{-03}	0.28	1	5	*TTN*
GO	regulation of the force of heart contraction	13	13	3.60×10^{-03}	0.23	1	4	*MYH6, PLN*
GO	beta-amyloid binding	16	15	4.90×10^{-03}	0.29	1	4	*ACHE*
GO	laminin binding	10	8	4.90×10^{-03}	0.29	0	3	-
GO	embryonic digit morphogenesis	25	24	5.00×10^{-03}	0.3	1	5	-
GO	protein heterodimerization activity	190	177	5.90×10^{-03}	0.43	9	17	*NKX2-5, MYH6, MYH7, SOX5*
GO	mitochondrial proton-transporting ATP synthase complex	18	16	6.30×10^{-03}	0.28	1	4	-
GO	blood circulation	47	46	6.70×10^{-03}	0.38	2	7	*PLN, HCN4*
GO	nervous system development	376	336	7.60×10^{-03}	0.48	17	27	*ACHE, CHRM2*
GO	embryonic heart tube development	10	9	8.40×10^{-03}	0.28	0	3	*NKX2-5*
GO	G-protein signaling, coupled to cyclic nucleotide second messenger	39	38	0.01	0.4	2	6	*CHRM2, CALCRL*
GO	3'-5'-exoribonuclease activity	10	10	0.01	0.31	1	3	-
GO	acetylcholine binding	10	10	0.01	0.32	1	3	*ACHE*
GO	hydrogen ion transmembrane transporter activity	21	18	0.01	0.35	1	4	-
GO	striated muscle contraction	11	10	0.01	0.31	1	3	*MYH6, TTN*
GO	hormone-mediated signaling pathway	52	51	0.01	0.43	3	7	*GNG11, GNB4*
GO	sodium channel activity	11	11	0.01	0.33	1	3	*HCN4*
GO	cardiac muscle tissue development	12	11	0.01	0.33	1	3	*NKX2-5, PLN*
GO	SH3 domain binding	97	91	0.01	0.48	5	10	-
GO	dipeptidase activity	12	11	0.01	0.35	1	3	-

Supplementary Table 18 – continued

Database	Gene set / Pathway	Original # genes in gene set	# genes in gene set analyzed by MAGENTA [a]	Nominal GSEA p-value	FDR q-value	# genes expected above 95th percentile cut off	# genes observed above 95th percentile cut off	Genes in LD with 21 confirmed heart rate SNPs
GO	T cell receptor complex	12	11	0.01	0.34	1	3	-
GO	regulation of G-protein coupled receptor protein signaling pathway	31	30	0.01	0.43	2	5	*RIC8B*
GO	cellular calcium ion homeostasis	60	53	0.01	0.48	3	7	*PLN*
GO	sarcolemma	57	54	0.01	0.47	3	7	-
GO	negative regulation of tumor necrosis factor production	11	11	0.01	0.36	1	3	-
GO	sarcomere organization	11	11	0.01	0.35	1	3	*MYH6, TTN*
GO	protein serine/threonine phosphatase complex	12	12	0.01	0.38	1	3	-
GO	regulation of smooth muscle contraction	13	12	0.01	0.41	1	3	*CHRM2*
GO	calcium channel regulator activity	12	12	0.02	0.38	1	3	*PLN*
GO	mitochondrial ATP synthesis coupled proton transport	14	12	0.02	0.37	1	3	-
GO	cation channel activity	12	12	0.02	0.4	1	3	*HCN4*
GO	phosphoinositide-mediated signaling	35	33	0.02	0.48	2	5	*FEN1*
GO	estrogen receptor binding	13	13	0.02	0.4	1	3	-
GO	actin filament	25	22	0.02	0.45	1	4	-
GO	spindle organization	13	13	0.02	0.4	1	3	-
GO	branching morphogenesis of a tube	23	23	0.02	0.48	1	4	-
GO	positive regulation of gene-specific transcription	36	34	0.02	0.49	2	5	*NKX2-5*
GO	bone resorption	13	13	0.03	0.42	1	3	-
GO	receptor signaling complex scaffold activity	13	13	0.03	0.43	1	3	-
GO	insoluble fraction	35	34	0.03	0.51	2	5	-
GO	vasodilation	14	14	0.03	0.44	1	3	-
GO	male genitalia development	14	14	0.03	0.47	1	3	-
GO	protein transport	406	374	0.03	0.68	19	27	-
GO	actin cytoskeleton organization	119	103	0.03	0.59	5	10	-
GO	lipid transport	70	62	0.03	0.57	3	7	*OSBPL6*
GO	proton transport	57	48	0.03	0.59	2	6	-
GO	histone methyltransferase complex	16	15	0.03	0.48	1	3	-
GO	protein phosphatase type 2A regulator activity	17	15	0.04	0.48	1	3	-
GO	very-low-density lipoprotein particle	20	15	0.04	0.48	1	3	-
GO	calcium ion transport	115	106	0.04	0.64	5	10	-
GO	cell aging	27	26	0.04	0.53	1	4	-
GO	response to hormone stimulus	39	38	0.04	0.58	2	5	-

Supplementary Table 18 – continued

Database	Gene set / Pathway	Original # genes in gene set	# genes in gene set analyzed by MAGENTA [a]	Nominal GSEA p-value	FDR q-value	# genes expected above 95th percentile cut off	# genes observed above 95th percentile cut off	Genes in LD with 21 confirmed heart rate SNPs
GO	heterotrimeric G-protein complex	27	26	0.04	0.54	1	4	*GNG11, GNGT1*
GO	intracellular membrane-bounded organelle	140	121	0.04	0.67	6	11	*BNIP1*
GO	cytoskeletal protein binding	40	39	0.04	0.59	2	5	-
GO	calcium channel activity	41	39	0.04	0.58	2	5	-
GO	positive regulation of angiogenesis	28	27	0.04	0.58	1	4	-
GO	connexon complex	21	16	0.04	0.5	1	3	*GJA1*
GO	integral to membrane of membrane fraction	18	17	0.05	0.53	1	3	-
GO	integral to plasma membrane	1002	844	0.05	0.73	42	52	*CHRM2, GJA1, CD46, FADS2,*
GO	structural constituent of cytoskeleton	74	66	0.05	0.67	3	7	-
GO	transcription factor TFIID complex	20	17	0.05	0.56	1	3	-
PANTHER, BP	Ion transport	44	40	$3.00x10^{-03}$	0.34	2	7	*HCN4, ALG10, ALG10B*
PANTHER, BP	Neurotransmitter release	107	89	$4.10x10^{-03}$	0.44	4	11	*CHRM2, SYT10*
PANTHER, BP	Glycolysis	46	32	0.02	0.5	2	5	-
PANTHER, BP	mRNA transcription regulation	1459	1039	0.02	0.96	52	65	*NKX2-5, RFX4, SOX5*
PANTHER, BP	Steroid hormone-mediated signaling	52	34	0.02	0.49	2	5	-
PANTHER, BP	Gut mesoderm development	14	14	0.03	0.65	1	3	-
PANTHER, MF	Exoribonuclease	35	25	$1.50x10^{-03}$	0.11	1	6	-
PANTHER, MF	Protein phosphatase	145	125	$5.00x10^{-03}$	0.31	6	14	-
PANTHER, MF	Membrane traffic protein	60	53	$5.90x10^{-03}$	0.35	3	8	-
PANTHER, MF	Other ion channel	47	38	0.01	0.33	2	6	-
PANTHER, MF	Transfer/carrier protein	108	89	0.01	0.37	4	10	*PLEKHA3, OSBPL6*
PANTHER, MF	Other nucleic acid binding	41	30	0.02	0.34	2	5	*PLEKHA3*
PANTHER, MF	Gap junction	19	15	0.04	0.37	1	3	*GJA1*
PANTHER, MF	mRNA polyadenylation factor	16	16	0.04	0.41	1	3	-
PANTHER, MF	Other receptor	231	187	0.04	0.72	9	15	-
REACTOME	**Integration of energy metabolism**	**229**	**199**	**$3.90x10^{-05}$ ***	**0.08**	**10**	**24**	***GNG11, GNB4***
REACTOME	mRNA decay by 3 to 5 exoribonuclease	11	11	$1.30x10^{-03}$	0.14	1	4	-
REACTOME	ERFs are inactivated	12	12	$1.90x10^{-03}$	0.06	1	4	-
REACTOME	Inhibition of insulin secretion by adrenaline noradrenaline	30	28	$2.20x10^{-03}$	0.09	1	6	*GNG11, GNGT1, GNB4*
REACTOME	Formation of ATP by chemi-osmotic coupling	15	13	$2.90x10^{-03}$	0.08	1	4	-
REACTOME	Translocation of ZAP70 to immunological synapse	24	8	$5.30x10^{-03}$	0.08	0	3	-
REACTOME	Metabolism of RNA	96	92	$5.50x10^{-03}$	0.26	5	11	-
REACTOME	Muscle contraction	51	46	$7.10x10^{-03}$	0.23	2	7	*MYH6, TTN*
REACTOME	Metabolism of RNA	46	45	$7.30x10^{-03}$	0.25	2	7	-
REACTOME	Regulation of insulin secretion	212	184	$8.10x10^{-03}$	0.29	9	17	*GNG11, GNGT1, GNB4*

Supplementary Table 18 – continued

Database	Gene set / Pathway	Original # genes in gene set	# genes in gene set analyzed by MAGENTA [a]	Nominal GSEA p-value	FDR q-value	# genes expected above 95th percentile cut off	# genes observed above 95th percentile cut off	Genes in LD with 21 confirmed heart rate SNPs
REACTOME	Phosphorylation of CD3 and TCR zeta chains	26	10	0.01	0.17	1	3	-
REACTOME	ERK MAPK targets	21	19	0.01	0.26	1	4	-
REACTOME	Co-stimulation by the CD28 family	70	53	0.01	0.29	3	7	-
REACTOME	Glucose regulation of insulin secretion	161	137	0.02	0.35	7	13	-
REACTOME	CTLA4 inhibitory signalling	21	21	0.02	0.29	1	4	-
REACTOME	Glucagon signalling in metabolic regulation	34	33	0.02	0.28	2	5	*GNG11, GNB4*
REACTOME	Smooth muscle contraction	24	22	0.02	0.29	1	4	-
REACTOME	Nuclear events kinase and transcription factor activation	24	22	0.02	0.3	1	4	-
REACTOME	Betacatenin phosphorylation cascade	13	13	0.02	0.28	1	3	-
REACTOME	PD1 signalling	29	13	0.02	0.29	1	3	-
REACTOME	Regulation of insulin secretion by glucagon like peptide 1	61	58	0.03	0.34	3	7	*GNG11, GNGT1, GNB4*
REACTOME	G beta gamma signalling through PI3Kgamma	25	24	0.03	0.32	1	4	*GNG11, GNGT1, GNB4*
REACTOME	GAP junction assembly	19	15	0.03	0.29	1	3	*GJA1*
REACTOME	GS alpha mediated events in glucagon signalling	27	26	0.04	0.34	1	4	*GNG11, GNB4*
REACTOME	NCAM signalling for neurite out growth	69	64	0.04	0.42	3	7	-
REACTOME	G protein beta gamma signalling	28	27	0.04	0.35	1	4	*GNG11, GNGT1, GNB4*
REACTOME	Striated muscle contraction	31	28	0.04	0.36	1	4	*MYH6, TTN*
REACTOME	Class B2 secretion family receptors	85	80	0.05	0.45	4	8	*GNG11, GNGT1, CALCRL, GNB4*

Nominal gene set enrichment analysis (GSEA) p-values and false discovery rates were computed for biological gene-sets by applying MAGENTA (Segrè et al, 2010 [PMID 20714348]) to the stage 1 results of the heart rate meta-analysis. The biological gene-sets are from five different resources. Results are presented for the nominally significant pathways ($p < 0.05$). Bonferroni correction is done separately for each database due to considerable overlap of gene sets between databases. The Bonferroni corrected p-value cut-offs for the different databases are: KEGG (186 pathways): $p < 2.7 \times 10^{-4}$, BIOCARTA (214 pathways): $p < 2.3 \times 10^{-4}$, GO (1,778 pathways): $p < 2.8 \times 10^{-5}$, PANTHER, BP (Biological Processes; 217 pathways): $p < 2.3 \times 10^{-4}$, PANTHER MF (Molecular Function; 216 pathways): $p < 2.3 \times 10^{-4}$, REACTOME (430 pathways): $p < 1.2 \times 10^{-4}$. An asterisk marks gene sets that pass the Bonferroni cut-off and in bold are gene sets with FDR < 0.1. A description of the BioCarta pathways can be found at: http://www.broadinstitute.org/gsea/msigdb/genesets.jsp?collection=CP:BIOCARTA.

[a] The number of genes in each gene set analyzed by MAGENTA is after removing genes that were not assigned an association score due to lack of SNPs 110 kb upstream or 40 kb downstream to most extreme transcript boundaries, after correcting for physical proximity along the genome of two or more genes within a gene set (each subset of genes assigned the same best local SNP is represented by a single gene, the one with the most significant gene p-value), and after removing genes absent from our human gene list. Gene set size is restricted to 10 to 2,000 genes.

Supplementary Table 19 - Top ranked gene association scores for gene sets that are significantly enriched with common variant heart rate associations

			Gene information							Heart rate stage 1 meta-analysis						
										Alleles						
Gene Symbol	**Entrez ID**	**Adjusted p-value [a]**	**Chr**	**start position, bp [b]**	**end position, bp [b]**	**Size, kb**	**# SNPs**	**Best (local) SNP**	**Best SNP position**	**Effect**	**Other**	**Best SNP z-score**	**Best SNP Effect size**	**Best SNP Effect Lower 95% CI**	**Best SNP Effect Upper 95% CI**	**Best SNP p-value**	**1=Gene in LD (r^2>0.5) with 21 lead SNPs**
KEGG - Dilated cardiomyopathy																	
TTN	7273	$<1.0x10^{-16}$	2	179,098,963	179,380,395	281	366	rs17362588	179,429,291	a	g	8.292	0.779	0.603	0.954	$1.27x10^{-16}$	1
MYH6	4624	$<1.0x10^{-16}$	14	22,921,038	22,947,322	26	167	rs365990	22,931,651	g	a	8.300	0.606	0.498	0.715	$1.85x10^{-25}$	1
MYH7	4625	$<1.0x10^{-16}$	14	22,951,786	22,974,710	23	168	rs365990	22,931,651	g	a	8.300	0.606	0.606	0.606	$1.85x10^{-25}$	1
PLN	5350	$2.26x10^{-13}$	6	118,976,134	118,988,280	12	158	rs11968176	119,007,633	c	a	6.763	0.362	0.262	0.462	$1.35x10^{-11}$	1
CACNA1D	776	$2.60x10^{-05}$	3	53,504,070	53,821,532	317	431	rs13080668	53,418,394	t	c	5.212	0.305	0.196	0.414	$1.87x10^{-07}$	0
ATP2A2	488	$4.00x10^{-04}$	12	109,203,414	109,273,280	70	47	rs6606684	109,284,549	t	c	4.276	0.282	0.159	0.405	$1.90x10^{-05}$	0
DES	1674	0.01	2	219,991,342	219,999,705	8	78	rs4674397	220,010,793	t	c	3.779	0.237	0.120	0.353	$1.58x10^{-04}$	0
ITGA2	3673	0.01	5	52,320,912	52,426,366	105	452	rs870992	52,228,994	a	g	4.029	0.389	0.209	0.569	$5.61x10^{-05}$	0
IGF1	3479	0.02	12	101,313,774	101,398,508	85	220	rs10860859	101,277,457	a	g	3.768	0.263	0.133	0.392	$1.64x10^{-04}$	0
ITGA9	3680	0.02	3	37,468,816	37,836,285	367	496	rs2070482	37,668,149	g	a	4.010	0.218	0.117	0.319	$6.08x10^{-05}$	0
ADCY3	109	0.02	2	24,895,541	24,995,559	100	227	rs2891409	24,870,861	t	g	3.685	0.225	0.111	0.339	$2.29x10^{-04}$	0
DAG1	1605	0.02	3	49,482,568	49,548,052	65	71	rs3870341	49,559,749	g	a	3.501	0.216	0.107	0.324	$4.64x10^{-04}$	0
ITGA1	3672	0.02	5	52,119,892	52,285,242	165	512	rs870992	52,228,994	a	g	4.029	0.389	0.209	0.569	$5.61x10^{-05}$	0
CACNB2	783	0.03	10	18,469,611	18,870,694	401	758	rs17609633	18,625,364	t	c	4.015	0.476	0.255	0.697	$5.94x10^{-05}$	0
CACNA1C	775	0.03	12	2,032,676	2,677,376	645	829	rs2238017	2,048,806	a	g	4.147	0.246	0.135	0.356	$3.37x10^{-05}$	0
TPM1	7168	0.04	15	61,121,890	61,151,166	29	257	rs902025	61,019,454	a	g	3.609	0.249	0.120	0.377	$3.08x10^{-04}$	0
KEGG - Hypertrophic cardiomyopathy																	
TTN	7273	$<1.0x10^{-16}$	2	179,098,963	179,380,395	281	366	rs17362588	179,429,291	a	g	8.292	0.779	0.603	0.954	$1.27x10^{-16}$	1
MYH6	4624	$<1.0x10^{-16}$	14	22,921,038	22,947,322	26	167	rs365990	22,931,651	g	a	8.300	0.606	0.498	0.715	$1.85x10^{-25}$	1
MYH7	4625	$<1.0x10^{-16}$	14	22,951,786	22,974,710	23	168	rs365990	22,931,651	g	a	8.300	0.606	0.498	0.715	$1.85x10^{-25}$	1
CACNA1D	776	$2.60x10^{-05}$	3	53,504,070	53,821,532	317	431	rs13080668	53,418,394	t	c	5.212	0.305	0.196	0.414	$1.87x10^{-07}$	0
ATP2A2	488	$4.00x10^{-04}$	12	109,203,414	109,273,280	70	47	rs6606684	109,284,549	t	c	4.276	0.282	0.159	0.405	$1.90x10^{-05}$	0
DES	1674	0.01	2	219,991,342	219,999,705	8	78	rs4674397	220,010,793	t	c	3.779	0.237	0.120	0.353	$1.58x10^{-04}$	0
ITGA2	3673	0.01	5	52,320,912	52,426,366	105	452	rs870992	52,228,994	a	g	4.029	0.389	0.209	0.569	$5.61x10^{-05}$	0
IGF1	3479	0.02	12	101,313,774	101,398,508	85	220	rs10860859	101,277,457	a	g	3.768	0.263	0.133	0.392	$1.64x10^{-04}$	0
ITGA9	3680	0.02	3	37,468,816	37,836,285	367	496	rs2070482	37,668,149	g	a	4.010	0.218	0.117	0.319	$6.08x10^{-05}$	0
DAG1	1605	0.02	3	49,482,568	49,548,052	65	71	rs3870341	49,559,749	g	a	3.501	0.216	0.101	0.331	$4.64x10^{-04}$	0
ITGA1	3672	0.02	5	52,119,892	52,285,242	165	512	rs870992	52,228,994	a	g	4.029	0.389	0.209	0.569	$5.61x10^{-05}$	0
CACNB2	783	0.03	10	18,469,611	18,870,694	401	758	rs17609633	18,625,364	t	c	4.015	0.476	0.255	0.697	$5.94x10^{-05}$	0
CACNA1C	775	0.03	12	2,032,676	2,677,376	645	829	rs2238017	2,048,806	a	g	4.147	0.246	0.135	0.356	$3.37x10^{-05}$	0
TPM1	7168	0.04	15	61,121,890	61,151,166	29	257	rs902025	61,019,454	a	g	3.609	0.249	0.120	0.377	$3.08x10^{-04}$	0
KEGG - Arrhythmogenic right ventricular cardiomyopathy																	
GJA1	2697	$2.74x10^{-12}$	6	121,798,443	121,812,572	14	171	rs17083533	121,772,421	a	g	6.804	0.989	0.718	1.260	$1.02x10^{-11}$	1
CACNA1D	776	$2.60x10^{-05}$	3	53,504,070	53,821,532	317	431	rs13080668	53,418,394	t	c	5.212	0.305	0.196	0.414	$1.87x10^{-07}$	0
ATP2A2	488	$4.00x10^{-04}$	12	109,203,414	109,273,280	70	47	rs6606684	109,284,549	t	c	4.276	0.282	0.159	0.405	$1.90x10^{-05}$	0
ACTN4	81	$6.73x10^{-04}$	19	43,830,166	43,913,010	83	141	rs11083475	43,879,952	g	a	4.315	0.227	0.129	0.325	$1.60x10^{-05}$	0
DES	1674	0.01	2	219,991,342	219,999,705	8	78	rs4674397	220,010,793	t	c	3.779	0.237	0.120	0.353	$1.58x10^{-04}$	0
ITGA2	3673	0.01	5	52,320,912	52,426,366	105	452	rs870992	52,228,994	a	g	4.029	0.389	0.209	0.569	$5.61x10^{-05}$	0
ITGA9	3680	0.02	3	37,468,816	37,836,285	367	496	rs2070482	37,668,149	g	a	4.010	0.218	0.117	0.319	$6.08x10^{-05}$	0
DAG1	1605	0.02	3	49,482,568	49,548,052	65	71	rs3870341	49,559,749	g	a	3.501	0.216	0.101	0.331	$4.64x10^{-04}$	0
ITGA1	3672	0.02	5	52,119,892	52,285,242	165	512	rs870992	52,228,994	a	g	4.029	0.389	0.209	0.569	$5.61x10^{-05}$	0
CACNB2	783	0.03	10	18,469,611	18,870,694	401	758	rs17609633	18,625,364	t	c	4.015	0.476	0.255	0.697	$5.94x10^{-05}$	0
CACNA1C	775	0.03	12	2,032,676	2,677,376	645	829	rs2238017	2,048,806	a	g	4.147	0.246	0.135	0.356	$3.37x10^{-05}$	0
KEGG - Cardiac muscle contraction																	
MYH6	4624	$<1.0x10^{-16}$	14	22,921,038	22,947,322	26	167	rs365990	22,931,651	g	a	8.300	0.606	0.498	0.715	$1.85x10^{-25}$	1
MYH7	4625	$<1.0x10^{-16}$	14	22,951,786	22,974,710	23	168	rs365990	22,931,651	g	a	8.300	0.606	0.498	0.715	$1.85x10^{-25}$	1
CACNA1D	776	$2.60x10^{-05}$	3	53,504,070	53,821,532	317	431	rs13080668	53,418,394	t	c	5.212	0.305	0.196	0.414	$1.87x10^{-07}$	0
ATP2A2	488	$4.00x10^{-04}$	12	109,203,414	109,273,280	70	47	rs6606684	109,284,549	t	c	4.276	0.282	0.159	0.405	$1.90x10^{-05}$	0
UQCRC1	7384	$9.92x10^{-03}$	3	48,611,435	48,622,102	11	52	rs7633840	48,694,642	c	t	3.620	0.238	0.115	0.361	$2.95x10^{-04}$	0
hCG_25371	440567	0.01	1	16,006,243	16,006,781	1	69	rs6668183	16,046,401	c	g	3.711	0.198	0.098	0.297	$2.06x10^{-04}$	0
ATP1A4	480	0.02	1	158,387,975	158,423,391	35	156	rs16831388	158,362,249	g	a	3.848	0.309	0.159	0.459	$1.19x10^{-04}$	0
ATP1A2	477	0.02	1	158,352,171	158,379,998	28	197	rs16831388	158,362,249	g	a	3.848	0.309	0.159	0.459	$1.19x10^{-04}$	0

Supplementary Table 19 - continued

Gene Symbol	Entrez ID	Adjusted *P*-value [a]	Gene information: Chr	start position, bp [b]	end position, bp [b]	Size, kb	# SNPs	Best (local) SNP	Best SNP position	Heart rate stage 1 meta-analysis: Alleles Effect	Other	Best SNP z-score	Best SNP Effect size	Best SNP Effect Lower 95% CI	Best SNP Effect Upper 95% CI	Best SNP p-value	1=Gene in LD (r^2>0.5) with 21 lead SNPs
KEGG - Cardiac muscle contraction - continued																	
COX6A1	1337	0.03	12	119,360,286	119,362,912	3	72	rs12423303	119,270,068	a	g	3.444	0.398	0.183	0.613	$5.74x10^{-04}$	0
CACNB2	783	0.03	10	18,469,611	18,870,694	401	758	rs17609633	18,625,364	t	c	4.015	0.476	0.255	0.697	$5.94x10^{-05}$	0
CACNA1C	775	0.03	12	2,032,676	2,677,376	645	829	rs2238017	2,048,806	a	g	4.147	0.246	0.135	0.356	$3.37x10^{-05}$	0
ATP1B2	482	0.04	17	7,494,978	7,501,814	7	67	rs2955617	7,479,510	c	a	3.340	0.191	0.084	0.297	$8.37x10^{-04}$	0
TPM1	7168	0.04	15	61,121,890	61,151,166	29	257	rs902025	61,019,454	a	g	3.609	0.249	0.120	0.377	$3.08x10^{-04}$	0
KEGG - Alzheimers disease																	
CACNA1D	776	$2.60x10^{-05}$	3	53,504,070	53,821,532	317	431	rs13080668	53,418,394	t	c	5.212	0.305	0.196	0.414	$1.87x10^{-07}$	0
ATP2A2	488	$4.00x10^{-04}$	12	109,203,414	109,273,280	70	47	rs6606684	109,284,549	t	c	4.276	0.282	0.159	0.405	$1.90x10^{-05}$	0
NDUFB8	4714	$2.67x10^{-03}$	10	102,273,486	102,279,626	6	108	rs3750631	102,269,284	a	g	4.066	0.262	0.142	0.382	$4.78x10^{-05}$	0
ATP5G1	516	$5.84x10^{-03}$	17	44,325,146	44,328,231	3	92	rs606911	44,263,227	a	g	3.774	0.265	0.134	0.395	$1.61x10^{-04}$	0
IDE	3416	$6.88x10^{-03}$	10	94,203,579	94,323,832	120	129	rs7910605	94,229,773	a	g	3.848	0.305	0.157	0.453	$1.19x10^{-04}$	0
UQCRC1	7384	$9.92x10^{-03}$	3	48,611,435	48,622,102	11	52	rs7633840	48,694,642	c	t	3.620	0.238	0.115	0.361	$2.95x10^{-04}$	0
APH1A	51107	0.01	1	148,504,422	148,508,156	4	90	rs11806171	148,577,451	a	c	3.627	0.348	0.169	0.527	$2.87x10^{-04}$	0
SDHA	6389	0.01	5	271,355	309,814	38	170	rs2162869	304,792	g	a	3.795	0.342	0.174	0.510	$1.48x10^{-04}$	0
ATP5B	506	0.01	12	55,318,225	55,326,119	8	61	rs2926743	55,400,367	a	g	3.631	0.225	0.110	0.340	$2.83x10^{-04}$	0
APOE	348	0.01	19	50,100,878	50,104,490	4	76	rs4803759	50,019,299	t	c	3.772	0.230	0.116	0.343	$1.62x10^{-04}$	0
hCG_25371	440567	0.01	1	16,006,243	16,006,781	1	69	rs6668183	16,046,401	c	g	3.711	0.198	0.098	0.297	$2.06x10^{-04}$	0
CALML5	51806	0.02	10	5,530,659	5,531,510	1	127	rs12098712	5,601,911	t	c	3.745	0.311	0.156	0.465	$1.80x10^{-04}$	0
MAPK3	5595	0.02	16	30,032,926	30,042,131	9	26	rs2278557	30,001,280	c	g	3.394	0.190	0.086	0.295	$6.88x10^{-04}$	0
ATP5F1	515	0.02	1	111,793,265	111,806,048	13	171	rs7737	111,827,675	t	c	3.770	0.313	0.158	0.467	$1.63x10^{-04}$	0
COX6A1	1337	0.03	12	119,360,286	119,362,912	3	72	rs12423303	119,270,068	a	g	3.444	0.398	0.183	0.613	$5.74x10^{-04}$	0
MAPK1	5594	0.03	22	20,443,946	20,551,970	108	181	rs13515	20,445,886	c	t	3.466	0.236	0.109	0.362	$5.29x10^{-04}$	0
CACNA1C	775	0.03	12	2,032,676	2,677,376	645	829	rs2238017	2,048,806	a	g	4.147	0.246	0.135	0.356	$3.37x10^{-05}$	0
NAE1	8883	0.04	16	65,394,281	65,422,380	28	82	rs363170	65,400,864	a	g	3.360	0.326	0.145	0.506	$7.79x10^{-04}$	0
GO - Muscle contraction																	
TTN	7273	$<1.0x10^{-16}$	2	179,098,963	179,380,395	281	366	rs17362588	179,429,291	a	g	8.292	0.779	0.603	0.954	$1.27x10^{-16}$	1
MYH6	4624	$<1.0x10^{-16}$	14	22,921,038	22,947,322	26	167	rs365990	22,931,651	g	a	8.300	0.606	0.498	0.715	$1.85x10^{-25}$	1
MYH7	4625	$<1.0x10^{-16}$	14	22,951,786	22,974,710	23	168	rs365990	22,931,651	g	a	8.300	0.606	0.498	0.715	$1.85x10^{-25}$	1
HCN4	10021	$7.77x10^{-16}$	15	71,400,987	71,448,230	47	131	rs4489968	71,452,559	t	g	7.375	0.529	0.395	0.663	$1.65x10^{-13}$	1
GJA1	2697	$2.74x10^{-12}$	6	121,798,443	121,812,572	14	171	rs17083533	121,772,421	a	g	6.804	0.989	0.718	1.260	$1.02x10^{-11}$	1
MYOT	9499	$2.06x10^{-04}$	5	137,231,472	137,251,440	20	44	rs7722600	137,222,661	a	g	4.427	0.303	0.175	0.431	$9.55x10^{-06}$	0
MYH11	4629	$3.62x10^{-03}$	16	15,704,492	15,858,388	154	224	rs3915499	15,818,244	a	g	4.188	0.235	0.130	0.339	$2.81x10^{-05}$	0
CRYAB	1410	$7.19x10^{-03}$	11	111,284,559	111,287,683	3	48	rs14133	111,287,907	g	c	3.706	0.221	0.110	0.333	$2.10x10^{-04}$	0
DES	1674	0.01	2	219,991,342	219,999,705	8	78	rs4674397	220,010,793	t	c	3.779	0.237	0.120	0.353	$1.58x10^{-04}$	0
PXN	5829	0.02	12	119,132,632	119,187,946	55	98	rs16950047	119,213,881	a	c	3.546	0.438	0.208	0.668	$3.91x10^{-04}$	0
DAG1	1605	0.02	3	49,482,568	49,548,052	65	71	rs3870341	49,559,749	g	a	3.501	0.216	0.101	0.331	$4.64x10^{-04}$	0
ITGA1	3672	0.02	5	52,119,892	52,285,242	165	512	rs870992	52,228,994	a	g	4.029	0.389	0.209	0.569	$5.61x10^{-05}$	0
GJA5	2702	0.03	1	145,694,955	145,712,108	17	189	rs1495962	145,808,661	a	c	3.603	0.217	0.105	0.330	$3.15x10^{-04}$	0
SCN5A	6331	0.04	3	38,564,556	38,666,167	102	234	rs7433306	38,745,643	g	c	3.665	0.196	0.096	0.295	$2.47x10^{-04}$	0
TPM1	7168	0.04	15	61,121,890	61,151,166	29	257	rs902025	61,019,454	a	g	3.609	0.249	0.120	0.377	$3.08x10^{-04}$	0
GO - Regulation of heart contraction																	
MYH6	4624	$<1.0x10^{-16}$	14	22,921,038	22,947,322	26	167	rs365990	22,931,651	g	a	8.300	0.606	0.498	0.715	$1.85x10^{-25}$	1
HCN4	10021	$7.77x10^{-16}$	15	71,400,987	71,448,230	47	131	rs4489968	71,452,559	t	g	7.375	0.529	0.395	0.663	$1.65x10^{-13}$	1
CHRM2	1129	$4.76x10^{-05}$	7	136,203,938	136,352,311	148	315	rs2350782	136,293,174	c	t	4.987	0.463	0.290	0.636	$6.13x10^{-07}$	1
HSPB7	27129	$1.36x10^{-04}$	1	16,213,109	16,217,872	5	111	rs1889785	16,221,316	a	g	4.589	0.255	0.151	0.358	$4.45x10^{-06}$	0
DES	1674	0.01	2	219,991,342	219,999,705	8	78	rs4674397	220,010,793	t	c	3.779	0.237	0.120	0.353	$1.58x10^{-04}$	0
ADORA3	140	0.02	1	111,827,492	111,908,120	81	218	rs7737	111,827,675	t	c	3.770	0.313	0.158	0.467	$1.63x10^{-04}$	0
SCN5A	6331	0.04	3	38,564,556	38,666,167	102	234	rs7433306	38,745,643	g	c	3.665	0.196	0.096	0.295	$2.47x10^{-04}$	0
TPM1	7168	0.04	15	61,121,890	61,151,166	29	257	rs902025	61,019,454	a	g	3.609	0.249	0.120	0.377	$3.08x10^{-04}$	0
TGM2	7052	$<1.0x10^{-16}$	20	36,190,277	36,227,114	37	161	rs6127471	36,277,452	c	t	8.300	0.509	0.408	0.610	$6.52x10^{-21}$	1
FGF1	2246	$2.33x10^{-03}$	5	141,953,305	142,045,812	93	258	rs17099396	142,077,501	g	a	4.400	0.758	0.437	1.079	$1.08x10^{-05}$	0
ITGA2	3673	0.01	5	52,320,912	52,426,366	105	452	rs870992	52,228,994	a	g	4.029	0.389	0.209	0.569	$5.61x10^{-05}$	0

Supplementary Table 19 - continued

Gene Symbol	Entrez ID	Adjusted *P*-value [a]	Gene information					Best (local) SNP	Best SNP position	Heart rate stage 1 meta-analysis							
			Chr	start position, bp [b]	end position, bp [b]	Size, kb	# SNPs			Alleles Effect	Alleles Other	Best SNP z-score	Best SNP Effect size	Best SNP Effect Lower 95% CI	Best SNP Effect Upper 95% CI	Best SNP p-value	1=Gene in LD (r^2>0.5) with 21 lead SNPs
GO - Positive regulation of cell adhesion																	
PRSS2	5645	0.02	7	142,178,777	142,182,363	4	108	rs3114484	142,200,133	g	t	3.675	0.580	0.286	0.874	$2.38x10^{-04}$	0
VAV3	10451	0.03	1	107,915,304	108,309,068	394	684	rs4557997	107,993,913	t	c	3.912	0.290	0.152	0.428	$9.16x10^{-05}$	0
TPM1	7168	0.04	15	61,121,890	61,151,166	29	257	rs902025	61,019,454	a	g	3.609	0.249	0.120	0.377	$3.08x10^{-04}$	0
REACTOME - Integration of energy metabolism																	
TKT	7086	$3.36x10^{-07}$	3	53,234,703	53,264,998	30	113	rs2029213	53,353,285	c	t	5.371	0.296	0.193	0.398	$7.85x10^{-08}$	0
GNB4	59345	$2.39x10^{-05}$	3	180,596,569	180,652,065	55	113	rs7612445	180,655,673	g	t	4.912	0.360	0.223	0.497	$9.03x10^{-07}$	1
CACNA1D	776	$2.60x10^{-05}$	3	53,504,070	53,821,532	317	431	rs13080668	53,418,394	t	c	5.212	0.305	0.196	0.414	$1.87x10^{-07}$	0
GNB2	2783	$3.00x10^{-05}$	7	100,109,310	100,114,728	5	36	rs221794	100,119,704	t	c	4.656	0.350	0.210	0.490	$3.23x10^{-06}$	0
GNG11	2791	$1.61x10^{-04}$	7	93,388,951	93,393,762	5	173	rs180242	93,387,532	t	a	4.705	0.312	0.189	0.436	$2.54x10^{-06}$	1
PPP2R5D	5528	$7.35x10^{-04}$	6	43,060,307	43,088,058	28	110	rs3763236	43,010,486	c	t	4.248	0.230	0.129	0.331	$2.15x10^{-05}$	0
PPM2C	54704	$1.32x10^{-03}$	8	94,998,337	95,007,472	9	126	rs4735253	94,973,166	t	a	4.277	0.229	0.129	0.329	$1.90x10^{-05}$	0
PPP2R1B	5519	$1.88x10^{-03}$	11	111,102,841	111,142,379	40	71	rs11214003	111,167,774	c	a	3.989	0.247	0.132	0.362	$6.62x10^{-05}$	0
ATP5L	10632	$2.35x10^{-03}$	11	117,777,313	117,785,772	8	87	rs12274926	117,800,327	t	c	4.089	0.264	0.144	0.385	$4.34x10^{-05}$	0
NDUFB8	4714	$2.67x10^{-03}$	10	102,273,486	102,279,626	6	108	rs3750631	102,269,284	a	g	4.066	0.262	0.142	0.382	$4.78x10^{-05}$	0
ATP5G1	516	$5.84x10^{-03}$	17	44,325,146	44,328,231	3	92	rs606911	44,263,227	a	g	3.774	0.265	0.134	0.395	$1.61x10^{-04}$	0
UQCRC1	7384	$9.92x10^{-03}$	3	48,611,435	48,622,102	11	52	rs7633840	48,694,642	c	t	3.620	0.238	0.115	0.361	$2.95x10^{-04}$	0
SDHA	6389	0.01	5	271,355	309,814	38	170	rs2162869	304,792	g	a	3.795	0.342	0.174	0.510	$1.48x10^{-04}$	0
ATP5B	506	0.01	12	55,318,225	55,326,119	8	61	rs2926743	55,400,367	a	g	3.631	0.225	0.110	0.340	$2.83x10^{-04}$	0
ALDOA	226	0.02	16	29,971,991	29,989,236	17	56	rs11642740	29,968,156	a	g	3.460	0.192	0.088	0.295	$5.39x10^{-04}$	0
ADCY3	109	0.02	2	24,895,541	24,995,559	100	227	rs2891409	24,870,861	t	g	3.685	0.225	0.111	0.339	$2.29x10^{-04}$	0
ATP5F1	515	0.02	1	111,793,265	111,806,048	13	171	rs7737	111,827,675	t	c	3.770	0.313	0.158	0.467	$1.63x10^{-04}$	0
PRKAR2A	5576	0.02	3	48,763,096	48,860,274	97	58	rs9882443	48,724,068	a	g	3.517	0.224	0.105	0.343	$4.37x10^{-04}$	0
COX6A1	1337	0.03	12	119,360,286	119,362,912	3	72	rs12423303	119,270,068	a	g	3.444	0.398	0.183	0.613	$5.74x10^{-04}$	0
CACNB2	783	0.03	10	18,469,611	18,870,694	401	758	rs17609633	18,625,364	t	c	4.015	0.476	0.255	0.697	$5.94x10^{-05}$	0
PGAM1	5223	0.03	10	99,176,016	99,183,188	7	101	rs2236575	99,215,728	a	t	3.507	0.187	0.087	0.286	$4.53x10^{-04}$	0
CACNA1C	775	0.03	12	2,032,676	2,677,376	645	829	rs2238017	2,048,806	a	g	4.147	0.246	0.135	0.356	$3.37x10^{-05}$	0
SLC25A20	788	0.03	3	48,869,359	48,911,406	42	45	rs7621226	48,903,763	c	t	3.338	0.218	0.096	0.339	$8.43x10^{-04}$	0
PDP2	57546	0.04	16	65,471,936	65,479,356	7	74	rs363170	65,400,864	a	g	3.360	0.326	0.145	0.506	$7.79x10^{-04}$	0

[a] The adjusted gene association p-value is based on the heart rate meta-analysis association p-value of the most significant SNP of each gene's regional SNPs (within 110kb upstream and 40 kb downstream of each gene's most extreme transcript boundaries), followed by correcting for confounders (gene size, SNP density, estimated number of independent SNPs (in linkage equilibrium) per kb and number of hotspots per kb) using step-wise multivariate regression analysis (Segrè et al, 2010 [PMID 20714348]). Scores are listed only for genes that lie above the enrichment cutoff (95 percentile of all gene p-values in the genome was used here), a subset of which are predicted to be truly associated with heart rate. [b] Chromosome positions are based on build 36 / hg18. Genes are ordered by ascending adjusted p-values.

Supplementary Table 20 - Genes located within heart rate loci that are expressed in mouse heart at the protein level

Locus	Gene
1	***MYH6***
	MYH7
	ZFHX2
	ACIN1
	CDH24
	PSMB5
2	*GJA1*
3	*SRRT*
	GIGYF1
	GNB2
	TRIM56
	CLDN15
	FIS1
	TSC22D4
	MEPCE
4	*CD34*
	PLXNA2
5	*DAGLA*
	SYT7
	CPSF7
	DDB1
6	***PLN***
8	*RPRD1B*
	RPSA
	TGM2
9	***TTN***
	PRKRA
	CCDC141
11	*NEO1*
12	*MFN1*
	ACTL6A
	MRPL47
	NDUFB5
14	*CHRM2*
16	*BET1*
	COL1A2
17	***NCL***
	PSMD1
18	*FNDC3B*
19	*RIC8B*
	TCP11L2

Genes shown in bold are phosphorylated upon stimulation of the β1 adrenergic receptor, suggesting that these genes are relevant for heart rate regulation.

Supplementary Table 21 – Significant associations between heart rate loci and *cis* gene expression (*cis*-eQTLs) in blood

Locus	Heart rate SNP	Chr	EA	OA	Gene	Effect	p-value	p_{adj-1}	Peak SNP	r^2	p-value	p_{adj-2}
3	rs13245899	7	g	a	*TRIP6*	-	$6.63x10^{-11}$	0.87	rs314370	0.913	$8.96x10^{-13}$	0.20
5	rs174549	11	a	g	*C11orf10*	+	$9.68x10^{-13}$	0.10	rs174534	0.607	$2.19x10^{-13}$	0.02
					FADS1	+	$3.42x10^{-11}$	0.11	rs968567	0.504	$2.87x10^{-13}$	0.01
					BEST1 / FTH1	+	$2.11x10^{-06}$	0.06	rs3758977	0.074	$1.50x10^{-31}$	$1.50x10^{-25}$
					FADS2	+	$2.78x10^{-06}$	0.81	rs968567	0.504	$9.56x10^{-11}$	$1.82x10^{-03}$
					RAB3IL1	+	$1.02x10^{-05}$	$4.87x10^{-05}$	rs2524287	0.002	$1.72x10^{-13}$	$9.59x10^{-13}$
6	rs11153730	6	t	c	*CEP85L*	-	$1.53x10^{-11}$	0.65	rs11970286	0.894	$1.53x10^{-11}$	0.70
16	rs180242	7	t	a	*GNG11*	+	$1.60x10^{-03}$	$7.32x10^{-03}$	rs180284	0.012	$6.66x10^{-09}$	$6.66x10^{-09}$
17	rs13030174	2	c	a	*NCL / SNORD20*	+	$8.56x10^{-04}$	0.63	rs10445829	0.181	$3.57x10^{-08}$	$1.37x10^{-04}$

Effect, direction of effect for the allele associated with higher heart rate (EA); p-value, p-value for the heart rate-associated SNP; p_{adj-1}, p-value for the heart rate-associated SNP after conditioning on the most significant SNP for the gene transcript (Peak SNP); r^2, LD between the heart rate-associated SNP and the peak SNP; p_{adj-2}, *P*-value for the peak SNP after conditioning on the heart rate-associated SNP.

Supplementary Table 22 – Potentially functional variants in LD with heart rate-associated SNPs

locus	Heart rate SNP	Potentially functional variant	r^2	Gene	Type	Coding change	subPSEC	P_deleterious
1	rs365990	rs365990	1	*MYH6*	Non-synonymous	Ala1101Val	-1.79	0.229
3	rs13245899	rs12666989	0.87	*UFSP1*	Non-synonymous	Leu47Val	-0.99	0.118
6	rs11153730	rs4945623	0.84	*CEP85L*	Transcription Factor Binding Site			
8	rs6127471	rs3746471	1	*KIAA1755*	Non-synonymous	Arg1045Trp	-4.60	0.832
9	rs17362588	rs17362588	1	*CCDC141*	Non-synonymous	Trp360Arg		NA
16	rs180242	P2_M_061510_7_474	0.96	near *GNGT1 / GNG11*	Deletion (723 bp)			
17	rs13030174	rs2290130	1	*B3GNT7*	Non-synonymous	Val233Ile	-2.01	0.272
21	rs4140885	rs7586970	1	*TFPI*	Non-synonymous	Ser221Asn		NA

r^2, LD between the heart rate-associated SNP and the potential functional variant; coding change, amino-acid change resulting from non-synonymous SNPs. The first amino acid is encoded by the allele associated with higher heart rate; subPSEC score, the negative logarithm of the probability ratio of the wild-type and mutant amino acids at a particular position as calculated by PANTHER (Thomas et al, 2003 [PMID 12952881]). P_deleterious, the probability that a given variant will have a deleterious effect on protein function. For rs17362588 and rs7586970, the position does not align (NA) to the Hidden Markov Model (HMM), indicating that the substitution occurs at a position that is inserted relative to the consensus HMM for the given HMM. In most cases, these substitutions are unlikely to be deleterious (http://pantherdb.org/tips/tips_csnpScores.jsp).

Supplementary Table 23 - PubMed and OMIM hits for genes within 500kb of the 21 confirmed heart rate loci, using the search term 'heart'

Gene	Heart rate SNP	Chr	Position	Distance SNP-gene	Pubmed hit with search term 'heart'
Locus 1					
MYH6	rs365990	14	22,931,651	0	Abu-Daya A et al. "Absence of heartbeat in the Xenopus tropicalis mutation muzak is caused by a nonsense mutation in cardiac myosin myh6." Dev Biol. 2009 Dec 1;336(1):20-9. PMID 19769958
MYH6	rs365990	14	22,931,651	0	Ghosh TK et al. "Physical interaction between TBX5 and MEF2C is required for early heart development." Mol Cell Biol. 2009 Apr;29(8):2205-18. PMID 19204083
MYH6	rs365990	14	22,931,651	0	Granados-Riveron JT et al. "Alpha-cardiac myosin heavy chain (MYH6) mutations affecting myofibril formation are associated with congenital heart defects." Hum Mol Genet. 2010 Oct 15;19(20):4007-16. PMID 20656787
MYH6	rs365990	14	22,931,651	0	Gupta M et al. "Single-stranded DNA-binding proteins PURalpha and PURbeta bind to a purine-rich negative regulatory element of the alpha-myosin heavy chain gene and control transcriptional and translational regulation of the gene expression. Implications in the repression of alpha-myosin heavy chain during heart failure." J Biol Chem. 2003 Nov 7;278(45):44935-48. PMID 12933792
MYH6	rs365990	14	22,931,651	0	Hang CT et al. "Chromatin regulation by Brg1 underlies heart muscle development and disease." Nature. 2010 Jul 1;466(7302):62-7. PMID 20596014
MYH6	rs365990	14	22,931,651	0	Howarth FC et al. "Changing pattern of gene expression is associated with ventricular myocyte dysfunction and altered mechanisms of Ca2+ signalling in young type 2 Zucker diabetic fatty rat heart." Exp Physiol. 2011 Mar;96(3):325-37. PMID 21216827
MYH6	rs365990	14	22,931,651	0	Lv H et al. "Impaired thymic tolerance to α-myosin directs autoimmunity to the heart in mice and humans." J Clin Invest. 2011 Mar 23. PMID 21436590
MYH6	rs365990	14	22,931,651	0	Matkovich SJ et al. "MicroRNA-133a protects against myocardial fibrosis and modulates electrical repolarization without affecting hypertrophy in pressure-overloaded adult hearts." Circ Res. 2010 Jan 8;106(1):166-75. PMID 19893015
MYH6	rs365990	14	22,931,651	0	Nakao K et al. "Myosin heavy chain gene expression in human heart failure." J Clin Invest. 1997 Nov 1;100(9):2362-70. PMID 9410916
MYH7	rs365990	14	22,931,651	20,136	Gupta M et al. "Single-stranded DNA-binding proteins PURalpha and PURbeta bind to a purine-rich negative regulatory element of the alpha-myosin heavy chain gene and control transcriptional and translational regulation of the gene expression. Implications in the repression of alpha-myosin heavy chain during heart failure." J Biol Chem. 2003 Nov 7;278(45):44935-48. PMID 12933792
MYH7	rs365990	14	22,931,651	20,136	Hang CT et al. "Chromatin regulation by Brg1 underlies heart muscle development and disease." Nature. 2010 Jul 1;466(7302):62-7. PMID 20596014
MYH7	rs365990	14	22,931,651	20,136	Howarth FC et al. "Changing pattern of gene expression is associated with ventricular myocyte dysfunction and altered mechanisms of Ca2+ signalling in young type 2 Zucker diabetic fatty rat heart." Exp Physiol. 2011 Mar;96(3):325-37. PMID 212168
MYH7	rs365990	14	22,931,651	20,136	Kamisago M et al. "Sarcomere protein gene mutations and inherited heart disease: a beta-cardiac myosin heavy chain mutation causing endocardial fibroelastosis and heart failure." Novartis Found Symp. 2006;274:176-89; discussion 189-95, 272-6. PMID 17019812
MYH7	rs365990	14	22,931,651	20,136	Kong SW et al. "Heart failure-associated changes in RNA splicing of sarcomere genes." Circ Cardiovasc Genet. 2010 Apr;3(2):138-46. PMID 20124440
MYH7	rs365990	14	22,931,651	20,136	Morita H et al. "Single-gene mutations and increased left ventricular wall thickness in the community: the Framingham Heart Study." Circulation. 2006 Jun 13;113(23):2697-705. PMID 16754800
MYH7	rs365990	14	22,931,651	20,136	Will RD et al. "Myomasp/LRRC39, a heart- and muscle-specific protein, is a novel component of the sarcomeric M-band and is involved in stretch sensing." Circ Res. 2010 Nov 12;107(10):1253-64. PMID 20847312
Locus 2					
GJA1	rs1015451	6	122,173,184	360,612	Ai X et al. "Connexin 43 downregulation and dephosphorylation in nonischemic heart failure is associated with enhanced colocalized protein phosphatase type 2A." Circ Res. 2005 Jan 7;96(1):54-63. PMID 15576650
GJA1	rs1015451	6	122,173,184	360,612	Antzelevitch C et al. "M cells in the human heart." Circ Res. 2010 Mar 19;106(5):815-7. PMID 20299671
GJA1	rs1015451	6	122,173,184	360,612	Bowling N et al. "Protein kinase C-alpha and -epsilon modulate connexin-43 phosphorylation in human heart." J Mol Cell Cardiol. 2001 Apr;33(4):789-98. PMID 11273731
GJA1	rs1015451	6	122,173,184	360,612	Bruce AF et al. "Gap junction remodelling in human heart failure is associated with increased interaction of connexin43 with ZO-1." Cardiovasc Res. 2008 Mar 1;77(4):757-65. PMID 18056766
GJA1	rs1015451	6	122,173,184	360,612	Chen P et al. "Mutations of connexin43 in fetuses with congenital heart malformations." Chin Med J (Engl). 2005 Jun 20;118(12):971-6. PMID 15978203
GJA1	rs1015451	6	122,173,184	360,612	Hesketh GG et al. "Ultrastructure and regulation of lateralized connexin43 in the failing heart." Circ Res. 2010 Apr 2;106(6):1153-63. PMID 20167932
GJA1	rs1015451	6	122,173,184	360,612	Kim SK et al. "Cardiac cell therapy with mesenchymal stem cell induces cardiac nerve sprouting, angiogenesis, and reduced connexin43-positive gap junctions, but concomitant electrical pacing increases connexin43-positive gap junctions in canine heart." Cardiol Young. 2010 Jun;20(3):308-17. PMID 20346202
GJA1	rs1015451	6	122,173,184	360,612	Kostin S et al. "Zonula occludens-1 and connexin 43 expression in the failing human heart." J Cell Mol Med. 2007 Jul-Aug;11(4):892-5. PMID 17760848
GJA1	rs1015451	6	122,173,184	360,612	Martinez-Fernandez A et al. "iPS programmed without c-MYC yield proficient cardiogenesis for functional heart chimerism." Circ Res. 2009 Sep 25;105(7):648-56. PMID 19696409
GJA1	rs1015451	6	122,173,184	360,612	Pavlovic M et al. "Reduced atrial connexin43 expression after pediatric heart surgery." Biochem Biophys Res Commun. 2006 Mar 31;342(1):310-5. PMID 16480955
GJA1	rs1015451	6	122,173,184	360,612	Vetter C et al. "Connexin 43 expression in human hypertrophied heart due to pressure and volume overload." Physiol Res. 2010;59(1):35-42. PMID 19249908
GJA1	rs1015451	6	122,173,184	360,612	Wang B et al. "Mutation analysis of Connexon43 gene in Chinese patients with congenital heart defects." Int J Cardiol. 2010 Dec 3;145(3):487-9. PMID 19615768
GJA1	rs1015451	6	122,173,184	360,612	Yoshida K et al. "Pursuing enigmas on ischemic heart disease and sudden cardiac death." Leg Med (Tokyo). 2009 Mar;11(2):51-8. PMID 19042146
Locus 3					
ACHE	rs13245899	7	100,335,067	3,590	Collins P et al. "Gender Differences in the Clinical Presentation of Heart Disease." Curr Pharm Des. 2011 Mar 31;. PMID 21449890
ACHE	rs13245899	7	100,335,067	3,590	Danese C et al. "Takotsubo syndrome and brachydactyly: a new heart-hand syndrome?." Clin Ter. 2011 Jan-Feb;162(1):41-4. PMID 21448545
EPHB4	rs13245899	7	100,335,067	71,988	Xie J et al. "Endothelial-specific expression of WNK1 kinase is essential for angiogenesis and heart development in mice." Am J Pathol. 2009 Sep;175(3):1315-27. PMID 19644017
TIMP1	rs13245899	7	100,335,067	175,808	Aljabri MB et al. "Gene expression, function and ischemia tolerance in male and female rat hearts after sub-toxic levels of angiotensin II." Cardiovasc Toxicol. 2011 Mar;11(1):38-47. PMID 21170686

Supplementary Table 23 - continued

Gene	Heart rate SNP	Chr	Position	Distance SNP-gene	Pubmed hit with search term 'heart'
TIMP1	rs13245899	7	100,335,067	175,808	Barton PJ et al. "Increased expression of extracellular matrix regulators TIMP1 and MMP1 in deteriorating heart failure." J Heart Lung Transplant. 2003 Jul;22(7):738-44. PMID 12873541
TIMP1	rs13245899	7	100,335,067	175,808	Batlle M et al. "Down-regulation of matrix metalloproteinase-9 (MMP-9) expression in the myocardium of congestive heart failure patients." Transplant Proc. 2007 Sep;39(7):2344-6. PMID 17889183
TIMP1	rs13245899	7	100,335,067	175,808	Heymans S et al. "Increased cardiac expression of tissue inhibitor of metalloproteinase-1 and tissue inhibitor of metalloproteinase-2 is related to cardiac fibrosis and dysfunction in the chronic pressure-overloaded human heart." Circulation. 2005 Aug 23;112(8):1136-44. PMID 16103240
TIMP1	rs13245899	7	100,335,067	175,808	Kim YJ et al. "Effect of propofol on cardiac function and gene expression after ischemic-reperfusion in isolated rat heart." Korean J Anesthesiol. 2010 Feb;58(2):153-61. PMID 20498794
TIMP1	rs13245899	7	100,335,067	175,808	Milting H et al. "Plasma biomarkers of myocardial fibrosis and remodeling in terminal heart failure patients supported by mechanical circulatory support devices." J Heart Lung Transplant. 2008 Jun;27(6):589-96. PMID 18503956
TIMP1	rs13245899	7	100,335,067	175,808	Polyakova V et al. "Fibrosis in endstage human heart failure: Severe changes in collagen metabolism and MMP/TIMP profiles." Int J Cardiol. 2010 May 21;. PMID 20546954
TIMP1	rs13245899	7	100,335,067	175,808	Vo TK et al. "Transcriptomic biomarkers of the response of hospitalized geriatric patients admitted with heart failure. Comparison to hospitalized geriatric patients with infectious diseases or hip fracture." Mech Ageing Dev. 2011 Mar;132(3):131-9. PMID 21335025
TIMP1	rs13245899	7	100,335,067	175,808	Weiss TW et al. "The gp130 ligand oncostatin M regulates tissue inhibitor of metalloproteinases-1 through ERK1/2 and p38 in human adult cardiac myocytes and in human adult cardiac fibroblasts: a possible role for the gp130/gp130 ligand system in the modulation of extracellular matrix degradation in the human heart." J Mol Cell Cardiol. 2005 Sep;39(3):545-51. PMID 15890357
SERBP1	rs13245899	7	100,335,067	273,248	Brazionis L et al. "Plasminogen activator inhibitor-1 activity in type 2 diabetes: a different relationship with coronary heart disease and diabetic retinopathy." Arterioscler Thromb Vasc Biol. 2008 Apr;28(4):786-91. PMID 18239151
SERBP1	rs13245899	7	100,335,067	273,248	Mi X et al. "Structural equation modeling of gene-environment interactions in coronary heart disease." Ann Hum Genet. 2011 Mar;75(2):255-65. PMID 21241273
PCOLCE	rs13245899	7	100,335,067	291,333	Kessler-Icekson G et al. "Expression of procollagen C-proteinase enhancer-1 in the remodeling rat heart is stimulated by aldosterone." Int J Biochem Cell Biol. 2006 Mar;38(3):358 65. PMID 16300990
PCOLCE	rs13245899	7	100,335,067	291,333	Shalitin N et al. "Expression of procollagen C-proteinase enhancer in cultured rat heart fibroblasts: evidence for co-regulation with type I collagen." J Cell Biochem. 2003 Oct 1;90(2):397-407. PMID 14505355
FIS1	rs13245899	7	100,335,067	385,762	Jazbutyte V et al. "Mitochondrial dynamics: molecular mechanisms and the role in the heart." Minerva Cardioangiol. 2010 Apr;58(2):231-9. PMID 20440252
Locus 4					
CD46	rs11118555	1	206,007,476	0	Qv J et al. "Activation of complement in the discordant heart xenotransplantation of pig-to-monkey model and the impact of intrathymic inoculation of xenogeneic antigen combined with whole-body gamma-radiation." Transplant Proc. 2009 Nov;41(9):3905-8. PMID 19917409
CD46	rs11118555	1	206,007,476	0	Mañez R et al. "Transgenic expression in pig hearts of both human decay-accelerating factor and human membrane cofactor protein does not provide an additional benefit to that of human decay-accelerating factor alone in pig-to-baboon xenotransplantation." Transplantation. 2004 Sep 27;78(6):930-3. PMID 15385816
CD46	rs11118555	1	206,007,476	0	Toivonen R et al. "Dilated cardiomyopathy alters the expression patterns of CAR and other adenoviral receptors in human heart." Histochem Cell Biol. 2010 Mar;133(3):349-57. PMID 19957088
CD34	rs11118555	1	206,007,476	44,382	Carvalho VO et al. "Correlation between CD34+ and exercise capacity, functional class, quality of life and norepinephrine in heart failure patients." Cardiol J. 2009;16(5):426-31. PMID 19753521
CD34	rs11118555	1	206,007,476	44,382	Van Craenenbroeck EM et al. "The effect of acute exercise on endothelial progenitor cells is attenuated in chronic heart failure." Eur J Appl Physiol. 2011 Feb 3;. PMID 21290145
CD34	rs11118555	1	206,007,476	44,382	Rivas J et al. "[Usefulness of intracoronary therapy with progenitor cells in patients with dilated cardiomyopathy: Bridge or alternative to heart transplantation?]." An Pediatr (Barc). 2011 Mar 11;. PMID 21398194
CR1	rs11118555	1	206,007,476	125,743	Maegdefessel L et al. "Patients with insulin-dependent diabetes or coronary heart disease following rehabilitation express serum fractalkine levels similar to those in healthy control subjects." Vasc Health Risk Manag. 2009;5:849-57. PMID 19851523
CD55	rs11118555	1	206,007,476	406,542	Ashton-Chess J et al. "Cellular participation in delayed xenograft rejection of hCD55 transgenic pig hearts by baboons." Xenotransplantation. 2003 Sep;10(5):446-53. PMID 12950987
CD55	rs11118555	1	206,007,476	406,542	Brandl U et al. "Combining the hDAF transgene with the GP IIb/IIIa inhibitor tirofiban improves heart performance and reduces myocardial damage following hyperacute rejection in an ex vivo perfusion model." Transplant Proc. 2005 Jan-Feb;37(1):491-2. PMID 15808686
CD55	rs11118555	1	206,007,476	406,542	Brandl U et al. "Fluorescent microspheres reveal different regional blood flow in hyperacutely rejected nontransgenic and hDAF pig hearts." Transplant Proc. 2006 Apr;38(3):733-4. PMID 16647457
CD55	rs11118555	1	206,007,476	406,542	Brandl U et al. "Reduced fibrin deposition and intravascular thrombosis in hDAF transgenic pig hearts perfused with tirofiban." Transplantation. 2007 Dec 27;84(12):1667-76. PMID 18165780
CD55	rs11118555	1	206,007,476	406,542	Brenner P et al. "Combination of hDAF-transgenic pig hearts and immunoadsorption in heterotopic xenotransplantation of immunosuppressed baboons." Transplant Proc. 2005 Jan-Feb;37(1):483-6. PMID 15808683
CD55	rs11118555	1	206,007,476	406,542	Brenner P et al. "Mean xenograft survival of 14.6 days in a small group of hDAF-transgenic pig hearts transplanted orthotopically into baboons." Transplant Proc. 2005 Jan-Feb;37(1):472-6. PMID 15808680
CD55	rs11118555	1	206,007,476	406,542	Mañez R et al. "Transgenic expression in pig hearts of both human decay-accelerating factor and human membrane cofactor protein does not provide an additional benefit to that of human decay-accelerating factor alone in pig-to-baboon xenotransplantation." Transplantation. 2004 Sep 27;78(6):930-3. PMID 15385816
CD55	rs11118555	1	206,007,476	406,542	Verbakel CA et al. "Human decay-accelerating factor expressed on rat hearts inhibits leukocyte adhesion." Transpl Int. 2003 Mar;16(3):168-72. PMID 12664211

Supplementary Table 23 - continued

Gene	Heart rate SNP	Chr	Position	Distance SNP-gene	Pubmed hit with search term 'heart'
Locus 6					
PLN	rs11157370	6	118,774,215	201,920	Ferreira JC et al. "Angiotensin receptor blockade improves the net balance of cardiac Ca(2+) handling-related proteins in sympathetic hyperactivity-induced heart failure." Life Sci. 2011 Mar 28;88(13-14):578-85. PMID 21277865
PLN	rs11157370	6	118,774,215	201,920	Santos DG et al. "No evidence for an association between the -36A>C phospholamban gene polymorphism and a worse prognosis in heart failure." BMC Cardiovasc Disord. 2009 Jul 28;9:33. PMID 19638213
PLN	rs11157370	6	118,774,215	201,920	Sugano Y et al. "Activated expression of cardiac adenylyl cyclase 6 reduces dilation and dysfunction of the pressure-overloaded heart." Biochem Biophys Res Commun. 2011 Feb 18;405(3):349-55. PMID 21195051
PLN	rs11157370	6	118,774,215	201,920	Vittorini S et al. "SERCA2a, phospholamban, sarcolipin, and ryanodine receptors gene expression in children with congenital heart defects." Mol Med. 2007 Jan-Feb;13(1-2):105-11. PMID 17515962
PLN	rs11157370	6	118,774,215	201,920	Wang HS et al. "SERCA2a Superinhibition by Human Phospholamban Triggers Electrical and Structural Remodelling in Mouse Hearts." Physiol Genomics. 2011 Jan 25;. PMID 21266500
Locus 8					
BPI	rs6127471	20	36,277,452	88,514	Goebel JR et al. "Heart failure: the hidden problem of pain." J Pain Symptom Manage. 2009 Nov;38(5):698-707. PMID 19733032
Locus 9					
TTN	rs17362588	2	179,429,291	48,896	Bullard B et al. "Association of the chaperone alphaB-crystallin with titin in heart muscle." J Biol Chem. 2004 Feb 27;279(9):7917-24. PMID 14676215
TTN	rs17362588	2	179,429,291	48,896	van Hees HW et al. "Heart failure decreases passive tension generation of rat diaphragm fibers." Int J Cardiol. 2010 Jun 11;141(3):275-83. PMID 19150150
TTN	rs17362588	2	179,429,291	48,896	Makarenko I et al. "Passive stiffness changes caused by upregulation of compliant titin isoforms in human dilated cardiomyopathy hearts." Circ Res. 2004 Oct 1;95(7):708-16. PMID 15345656
TTN	rs17362588	2	179,429,291	48,896	Lange S et al. "Subcellular targeting of metabolic enzymes to titin in heart muscle may be mediated by DRAL/FHL-2." J Cell Sci. 2002 Dec 15;115(Pt 24):4925-36. PMID 12432079
TTN	rs17362588	2	179,429,291	48,896	Neagoe C et al. "Titin isoform switch in ischemic human heart disease." Circulation. 2002 Sep 10;106(11):1333-41. PMID 12221049
Locus 11					
HCN4	rs4489968	15	71,452,559	3,901	Aanhaanen WT et al. "Developmental origin, growth, and three-dimensional architecture of the atrioventricular conduction axis of the mouse heart." Circ Res. 2010 Sep 17;107(6):728-36. PMID 20671237
HCN4	rs4489968	15	71,452,559	3,901	Alig J et al. "Control of heart rate by cAMP sensitivity of HCN channels." Proc Natl Acad Sci U S A. 2009 Jul 21;106(29):12189-94. PMID 19570998
HCN4	rs4489968	15	71,452,559	3,901	Baruscotti M et al. "Deep bradycardia and heart block caused by inducible cardiac-specific knockout of the pacemaker channel gene Hcn4." Proc Natl Acad Sci U S A. 2011 Jan 25;108(4):1705-10. PMID 21220308
HCN4	rs4489968	15	71,452,559	3,901	Gao Z et al. "Catecholamine-Independent Heart Rate Increases Require CaMKII." Circ Arrhythm Electrophysiol. 2011 Mar 15;. PMID 21406683
HCN4	rs4489968	15	71,452,559	3,901	Liang H et al. "Electrophysiological basis of the first heart beats." Cell Physiol Biochem. 2010;25(6):561-70. PMID 20511701
HCN4	rs4489968	15	71,452,559	3,901	Luo X et al. "Down-regulation of miR-1/miR-133 contributes to re-expression of pacemaker channel genes HCN2 and HCN4 in hypertrophic heart." J Biol Chem. 2008 Jul 18;283(29):20045-52. PMID 18458081
HCN4	rs4489968	15	71,452,559	3,901	Schweizer PA et al. "cAMP sensitivity of HCN pacemaker channels determines basal heart rate but is not critical for autonomic rate control." Circ Arrhythm Electrophysiol. 2010 Oct 1;3(5):542-52. PMID 20693575
HCN4	rs4489968	15	71,452,559	3,901	Vicente-Steijn R et al. "The funny current channel HCN4 delineates the developing cardiac conduction system in the chicken heart." Heart Rhythm. 2011 Mar 18;. PMID 21421080
HCN4	rs4489968	15	71,452,559	3,901	Xia S et al. "Dynamic changes in HCN2, HCN4, KCNE1, and KCNE2 expression in ventricular cells from acute myocardial infarction rat hearts." Biochem Biophys Res Commun. 2010 May 7;395(3):330-5. PMID 20381460
HCN4	rs4489968	15	71,452,559	3,901	Zhang J et al. "Differentiation induction of cardiac c-kit positive cells from rat heart into sinus node-like cells by 5-azacytidine." Tissue Cell. 2011 Apr;43(2):67-74. PMID 21237473
Locus 12					
MFN1	rs7612445	3	180,655,673	61,971	Chen L et al. "Mitochondrial OPA1, apoptosis, and heart failure." Cardiovasc Res. 2009 Oct 1;84(1):91-9. PMID 19493956
MFN1	rs7612445	3	180,655,673	61,971	Jazbutyte V et al. "Mitochondrial dynamics: molecular mechanisms and the role in the heart." Minerva Cardioangiol. 2010 Apr;58(2):231-9. PMID 20440252
MFN1	rs7612445	3	180,655,673	61,971	Ong SB et al. "Inhibiting mitochondrial fission protects the heart against ischemia/reperfusion injury." Circulation. 2010 May 11;121(18):2012-22. PMID 20421521
Locus 13					
FLRT2	rs17796783	14	84,879,664	186,577	Müller PS et al. "The fibronectin leucine-rich repeat transmembrane protein Flrt2 is required in the epicardium to promote heart morphogenesis." Development. 2011 Apr;138(7):1297-308. PMID 21350012
Locus 14					
CHRM2	rs2350782	7	136,293,174	0	Colombo G et al. "Treatment with alpha-melanocyte stimulating hormone preserves calcium regulatory proteins in rat heart allografts." Brain Behav Immun. 2008 Aug;22(6):817-23. PMID 18178058
CHRM2	rs2350782	7	136,293,174	0	Hautala AJ et al. "Heart rate recovery after maximal exercise is associated with acetylcholine receptor M2 (CHRM2) gene polymorphism." Am J Physiol Heart Circ Physiol. 2006 Jul;291(1):H459-66. PMID 16501017
CHRM2	rs2350782	7	136,293,174	0	Hautala AJ et al. "Acetylcholine receptor M2 gene variants, heart rate recovery, and risk of cardiac death after an acute myocardial infarction." Ann Med. 2009;41(3):197-207. PMID 18979273
CHRM2	rs2350782	7	136,293,174	0	Laramie JM et al. "Multiple genes influence BMI on chromosome 7q31-34: the NHLBI Family Heart Study." Obesity (Silver Spring). 2009 Dec;17(12):2182-9. PMID 19461589
CHRM2	rs2350782	7	136,293,174	0	Wang H et al. "Expression of multiple subtypes of muscarinic receptors and cellular distribution in the human heart." Mol Pharmacol. 2001 May;59(5):1029-36. PMID 11306684

Supplementary Table 23 - continued

Gene	Heart rate SNP	Chr	Position	Distance SNP-gene	Pubmed hit with search term 'heart'
Locus 15					
NKX2-5	rs6882776	5	172,596,769	1,848	Dinesh SM et al. "Single-nucleotide polymorphisms of NKX2.5 found in congenital heart disease patients of Mysore, South India." Genet Test Mol Biomarkers. 2010 Dec;14(6):873-9. PMID 21091212
NKX2-5	rs6882776	5	172,596,769	1,848	Ding JD et al. "Preliminary exploration of transcription factor Nkx2.5 mutations and congenital heart diseases." Zhonghua Yi Xue Za Zhi. 2009 Apr 28;89(16):1114-6. PMID 19595143
NKX2-5	rs6882776	5	172,596,769	1,848	Draus JM Jr et al. "Investigation of somatic NKX2-5 mutations in congenital heart disease." J Med Genet. 2009 Feb;46(2):115-22. PMID 19181906
NKX2-5	rs6882776	5	172,596,769	1,848	Gioli-Pereira L et al. "NKX2.5 mutations in patients with non-syndromic congenital heart disease." Int J Cardiol. 2010 Feb 4;138(3):261-5. PMID 19073351
NKX2-5	rs6882776	5	172,596,769	1,848	Hahurij ND et al. "Accessory atrioventricular myocardial pathways in mouse heart development; substrate for supraventricular tachycardias." Pediatr Res. 2011 Mar 10;. PMID 21399557
NKX2-5	rs6882776	5	172,596,769	1,848	Martin LK et al. "Canonical WNT Signaling Enhances Stem Cell Expression in the Developing Heart without a Corresponding Inhibition of Cardiogenic Differentiation." Stem Cells Dev. 2011 Feb 25;. PMID 21351874
NKX2-5	rs6882776	5	172,596,769	1,848	van de Meerakker JB et al. "A novel autosomal dominant condition consisting of congenital heart defects and low atrial rhythm maps to chromosome 9q." Eur J Hum Genet. 2011 Mar 9;. PMID 21386876
NKX2-5	rs6882776	5	172,596,769	1,848	Mishra R et al. "Characterization and functionality of cardiac progenitor cells in congenital heart patients." Circulation. 2011 Feb 1;123(4):364-73. PMID 21242485
NKX2-5	rs6882776	5	172,596,769	1,848	Mizuta E et al. "Different distribution of Cav3.2 and Cav3.1 transcripts encoding T-type Ca(2+) channels in the embryonic heart of mice." Biomed Res. 2010;31(5):301-5. PMID 21079360
NKX2-5	rs6882776	5	172,596,769	1,848	Peng T et al. "Mutations of the GATA4 and NKX2.5 genes in Chinese pediatric patients with non-familial congenital heart disease." Genetica. 2010 Dec;138(11-12):1231-40. PMID 21110066
NKX2-5	rs6882776	5	172,596,769	1,848	Reamon-Buettner SM et al. "NKX2-5: an update on this hypermutable homeodomain protein and its role in human congenital heart disease (CHD)." Hum Mutat. 2010 Nov;31(11):1185-94. PMID 20725931
NKX2-5	rs6882776	5	172,596,769	1,848	Salazar M et al. "Search of somatic GATA4 and NKX2.5 gene mutations in sporadic septal heart defects." Eur J Med Genet. 2011 Jan 27;. PMID 21276881
NKX2-5	rs6882776	5	172,596,769	1,848	Stallmeyer B et al. "Mutational spectrum in the cardiac transcription factor gene NKX2.5 (CSX) associated with congenital heart disease." Clin Genet. 2010 Dec;78(6):533-40. PMID 20456451
NKX2-5	rs6882776	5	172,596,769	1,848	Takeuchi JK et al. "Chromatin remodelling complex dosage modulates transcription factor function in heart development." Nat Commun. 2011 Feb;2:187. PMID 21304516
NKX2-5	rs6882776	5	172,596,769	1,848	Vicente-Steijn R et al. "The funny current channel HCN4 delineates the developing cardiac conduction system in the chicken heart." Heart Rhythm. 2011 Mar 18;. PMID 21421080
NKX2-5	rs6882776	5	172,596,769	1,848	Wang J et al. "Identifying novel mutations of NKX2-5 congenital heart disease patients of Chinese Minority Groups." Int J Cardiol. 2011 Apr 1;148(1):102-4. PMID 21262546
NKX2-5	rs6882776	5	172,596,769	1,848	Zhang W et al. "Screening NKX2.5 mutation in a sample of 230 Han Chinese children with congenital heart diseases." Genet Test Mol Biomarkers. 2009 Apr;13(2):159-62. PMID 19371212
NKX2-5	rs6882776	5	172,596,769	1,848	Zhang WM et al. "GATA4 and NKX2.5 gene analysis in Chinese Uygur patients with congenital heart disease." Chin Med J (Engl). 2009 Feb 20;122(4):416-9. PMID 19302747
BNIP1	rs6882776	5	172,596,769	72,773	Dostanic S et al. "Chronic beta-adrenoreceptor stimulation in vivo decreased Bcl-2 and increased Bax expression but did not activate apoptotic pathways in mouse heart." Can J Physiol Pharmacol. 2004 Mar;82(3):167-74. PMID 15052282
Locus 16					
COL1A2	rs180242	7	93,387,532	474,277	Peacock JD et al. "Temporal and spatial expression of collagens during murine atrioventricular heart valve development and maintenance." Dev Dyn. 2008 Oct;237(10):3051-8. PMID 18816857
Locus 17					
B3GNT7	rs13030174	2	231,979,528	5,409	Jakovljevic DG et al. "Comparison of cardiac power output and exercise performance in patients with left ventricular assist devices, explanted (recovered) patients, and those with moderate to severe heart failure." Am J Cardiol. 2010 Jun 15;105(12):1780-5. PMID 20538130
Locus 18					
PLD1	rs9647379	3	173,267,862	256,895	Ahn M et al. "Increased expression of phospholipase D in the heart with experimental autoimmune myocarditis in Lewis rats." Immunol Invest. 2004 Feb;33(1):95-105. PMID 15015836
PLD1	rs9647379	3	173,267,862	256,895	Dent MR et al. "Expression of phospholipase D isozymes in scar and viable tissue in congestive heart failure due to myocardial infarction." J Cell Mol Med. 2004 Oct-Dec;8(4):526-36. PMID 15601581
PLD1	rs9647379	3	173,267,862	256,895	Moon C et al. "Transient expression of phospholipase D1 during heart development in rats." J Vet Med Sci. 2008 Apr;70(4):411-3. PMID 18460839
GHSR	rs9647379	3	173,267,862	375,379	Beiras-Fernandez A et al. "Altered myocardial expression of ghrelin and its receptor (GHSR-1a) in patients with severe heart failure." Peptides. 2010 Dec;31(12):2222-8. PMID 20804798
Locus 19					
CRY1	rs2067615	12	105,673,552	235,721	Huang J et al. "Postnatal ontogenesis of clock genes in mouse suprachiasmatic nucleus and heart." Lipids Health Dis. 2010 Mar 5;9:22. PMID 20202222
CRY1	rs2067615	12	105,673,552	235,721	Leibetseder V et al. "Clock genes display rhythmic expression in human hearts." Chronobiol Int. 2009 May;26(4):621-36. PMID 19444745
Locus 21					
TFPI	rs4140885	2	188,041,309	0	Opstad TB et al. "Gender differences of polymorphisms in the TF and TFPI genes, as related to phenotypes in patients with coronary heart disease and type-2 diabetes." Thromb J. 2010 May 5;8:7. PMID 20444258

Supplementary Table 23 - continued

Gene	Heart rate SNP	Chr	Position	Distance SNP-gene	Pubmed hit with search term 'heart'
CALCRL	rs4140885	2	188,041,309	20,043	Jia YX et al. "Intermedin1-53 protects the heart against isoproterenol-induced ischemic injury in rats." Eur J Pharmacol. 2006 Nov 7;549(1-3):117-23. PMID 16987513
CALCRL	rs4140885	2	188,041,309	20,043	Øie E et al. "Adrenomedullin is increased in alveolar macrophages and released from the lungs into the circulation in severe heart failure." Basic Res Cardiol. 2010 Jan;105(1):89-98. PMID 19823891
CALCRL	rs4140885	2	188,041,309	20,043	Wang YF et al. "[Increased atria expression of receptor activity-modifying proteins in heart failure patients]." Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2004 Aug;21(4):351-4. PMID 15300632

Supplementary Table 24 - Candidates genes for heart rate regulation within the 21 confirmed loci

Locus	chr	Gene	Relevance	*Drosophila*	*Danio rerio*
1	14	*MYH6*	F, P, S	-	-
1	14	*MYH7*	S	-	-
2	6	*GJA1*	S	-	-
3	7	*ACHE*	S	1	-
3	7	*EPHB4*	S	1	-
3	7	*FIS1*	S	-	-
3	7	*MOSPD3*	B	-	-
3	7	*PCOLCE*	S	1	-
3	7	*SERBP1*	S	1	-
3	7	*TFR2*	B	-	-
3	7	*TIMP1*	S	1	-
3	7	*TRIP6*	Q	1	-
3	7	*UFSP1*	F	1	-
4	1	*CD34*	S	-	-
4	1	*CD46*	S	1	-
4	1	*CD55*	S	1	-
4	1	*CR1*	S	1	-
4	1	*PLXNA2*	B	1	-
5	11	*BEST1*	S	-	1
5	11	*TMEM258*	S	-	-
5	11	*FADS1*	S	1	-
5	11	*FADS2*	Q	-	1
5	11	*FADS3*	B	1	-
5	11	*FTH1*	Q	1	-
5	11	*RAB3IL1*	Q	-	-
6	6	*CEP85L*	F, Q	-	-
6	6	*PLN*	P, S	-	-
8	20	*BPI*	S	-	-
8	20	*KIAA1755*	F	-	-
9	2	*CCDC141*	F	-	-
9	2	*TTN*	P, S	1	-
11	15	*HCN4*	S	-	-
12	3	*MFN1*	S	1	1
13	14	*FLRT2*	S	1	-
14	7	*CHRM2*	S	1	-
15	5	*BNIP1*	Q	-	-
15	5	*NKX2-5*	S	1	-
16	7	*COL1A2*	S	-	1
16	7	*GNG11*	F, Q	1	-
16	7	*TFPI2*	B	-	1
17	2	*B3GNT7*	F, S	-	-
17	2	*HTR2B*	B	1	1
17	2	*NCL*	Q, P	-	1
17	2	*SNORD20*	Q	-	-
18	3	*GHSR*	S	1	1
18	3	*PLD1*	S	1	1
19	12	*CRY1*	S	1	1
21	2	*CALCRL*	S	1	1
21	2	*TFPI*	F, S	-	1

Gene, the candidate gene that is located within ± 500 kb of the GWAS association; Relevance, indicates if candidacy is based on linkage disequilibrium with a potentially functional variant (r^2>0.8) (F), association with eQTL in blood (Q), results from proteomics experiments in mice showing that the gene is expressed in heart and is phosphorylated upon β1 adreneric stimulation (P); results from our automated literature search using SNIPPER (S), and/or biological candidacy (B); *Drosophila*, indicates for which genes heart rate measurements are available in at least five *Drosophila melanogaster* pupae with the ortholog knocked out by RNAi line(s); *Danio rerio* shows for which genes heart measurements are available in embryos of the zebrafish *Danio rerio* that were injected with morpholino oligonucleotides targeting the ortholog.

Supplementary Table 25 - Orthologs and RNAi lines for positional candidate genes in *Drosophila melanogaster*

			Drosophila ortholog		BLAST statistics			Identities		Positives		Gaps		RNAi line information		
Locus	Chr	Gene	Gene name	CG number	Bit score	Raw score	E-value	Abs	rel (%)	Abs	rel (%)	Abs	rel (%)	Line nr	viability	availability
1	14	*MYH6*	Mhc	CG17927	1828	4734	0	961 / 1,921	50.0	1,265 / 1,921	65.9	20 / 1,921	1.0	7164	LV	no
1	14	*MYH7*	Mhc	CG17927	1864	4828	0	979 / 1,923	50.9	1,306 / 1,923	67.9	13 / 1,923	0.7	7164	LV	no
2	6	*GJA1*	-	-	-	-	-	-	-	-	-	-	-	-	-	no
3	7	*ACHE*	Ace	CG17907	367	940	$2.68x10^{-101}$	203 / 582	34.9	298 / 582	51.2	50 / 582	8.6	3968, 105432	LV, V	yes
3	7	*EPHB4*	Eph	CG1511	668	1722	0	390 / 1,009	38.7	556 / 1,009	55.1	94 / 1,009	9.3	4771, 110448	V, LV	yes
3	7	*FIS1*	Fis1	CG17510	118	294	$3.02x10^{-27}$	61 / 122	50.0	84 / 122	68.9	3 / 122	2.5	not available	-	no
3	7	*MOSPD3*	-	-	-	-	-	-	-	-	-	-	-	-	-	no
3	7	*PCOLCE*	tok	CG6863	158	397	$1.92x10^{-38}$	94 / 276	34.1	137 / 276	49.6	40 / 276	14.5	2656, 110432	V, V	yes
3	7	*SERBP1*	Spn42Db	CG9454	149	374	$8.56x10^{-36}$	112 / 371	30.2	166 / 371	44.7	17 / 371	4.6	24033, 104263	V, LV	yes
3	7	*TFR2*	-	-	-	-	-	-	-	-	-	-	-	-	-	no
3	7	*TIMP1*	Timp	CG6281	56	134	$1.73x10^{-08}$	36 / 141	25.5	68 / 141	48.2	15 / 141	10.6	109427	V	yes
3	7	*TRIP6*	Zyx	CG32018	235	597	$1.32x10^{-61}$	101 / 180	56.1	135 / 180	75.0	0 / 180	0.0	21610	V	yes
3	7	*UFSP1*	CG16979	CG16979	63	152	$7.88x10^{-11}$	40 / 126	31.7	55 / 126	43.7	3 / 126	2.4	105386	V	yes
4	1	*CD34*	-	-	-	-	-	-	-	-	-	-	-	-	-	no
4	1	*CD46*	fw	CG1500	91	225	$1.41x10^{-18}$	67 / 243	27.6	96 / 243	39.5	18 / 243	7.4	106656	V	yes
4	1	*CD55*	fw	CG1500	89	218	$9.82x10^{-18}$	73 / 271	26.9	114 / 271	42.1	38 / 271	14.0	106656	V	yes
4	1	*CR1*	fw	CG1500	200	508	$1.57x10^{-50}$	174 / 664	27.0	263 / 644	40.8	75 / 644	11.6	106656	V	yes
4	1	*PLXNA2*	plexA	CG11081	1342	3471	0	784 / 1,923	40.8	1110 / 1923	57.8	125 / 1,923	6.5	4740, 107004	V, LV	yes
5	11	*BEST1*	Best1	CG6264	393	1009	$3.06x10^{-109}$	197 / 379	52.0	259 / 379	68.3	10 / 379	2.6	5963	NA	no
5	11	*TMEM258*	CG9669	CG9669	76	184	$8.88x10^{-15}$	38 / 61	62.3	46 / 61	75.4	3 / 61	4.9	not available	-	no
5	11	*FADS1*	CG6870	CG6870	66	159	$7.64x10^{-11}$	37 / 89	41.6	53 / 89	59.6	5 / 89	5.6	52570, 102803	V, V	yes
5	11	*FADS2*	-	-	-	-	-	-	-	-	-	-	-	-	-	no
5	11	*FADS3*	Cyt-b5-r	CG13279	38	87	$1.59x10^{-02}$	82 / 385	21.3	138 / 385	35.8	61 / 385	15.8	42472, 100507	V, V	yes
5	11	*FTH1*	Fer3HCH	CG4349	146	367	$1.62x10^{-35}$	76 / 167	45.5	112 / 167	67.1	6 / 167	3.6	40505	V	yes
5	11	*RAB3IL1*	-	-	-	-	-	-	-	-	-	-	-	-	-	no
6	6	*CEP85L*	-	-	-	-	-	-	-	-	-	-	-	-	-	no
6	6	*PLN*	-	-	-	-	-	-	-	-	-	-	-	-	-	no
8	20	*BPI*	-	-	-	-	-	-	-	-	-	-	-	-	-	no
8	20	*KIAA1755*	trio	CG18214	54	129	$7.33x10^{-07}$	53 / 228	23.2	95 / 228	41.7	15 / 228	6.6	not available	-	no
9	2	*CCDC141*	-	-	-	-	-	-	-	-	-	-	-	-	-	no
9	2	*TTN*	sls	CG1915	123	306	$2.18x10^{-27}$	77 / 266	28.9	129 / 266	48.5	25 / 266	9.4	47298, 47301	V, V	yes
11	15	*HCN4*	Ih	CG8585	653	1682	0	305 / 518	58.9	385 / 518	74.3	6 / 518	1.2	110274	LV	no
12	3	*MFN1*	Marf	CG3869	624	1609	$8.94x10^{-179}$	335 / 741	45.2	463 / 741	62.5	16 / 741	2.2	40478, 105261	V, V	yes
13	14	*FLRT2*	sli	CG8355	97	240	$4.20x10^{-20}$	97 / 413	23.5	163 / 413	39.5	92 / 413	22.3	108853	V	yes
14	7	*CHRM2*	mAcR-60C	CG4356	254	647	$1.93x10^{-67}$	120 / 202	59.4	147 / 202	72.8	1 / 202	0.5	33123, 101407	V, V	yes
15	5	*BNIP1*	CG2023	CG2023	110	274	$1.41x10^{-24}$	69 / 219	31.5	117 / 219	53.4	11 / 219	5.0	100264	LV	no
15	5	*NKX2-5*	scro	CG17594	134	337	$1.22x10^{-31}$	60 / 92	65.2	72 / 92	78.3	0 / 92	0.0	33902	V	yes
16	7	*COL1A2*	-	-	-	-	-	-	-	-	-	-	-	-	-	no
16	7	*GNG11*	Ggamma1	CG8261	50	119	$3.11x10^{-07}$	24 / 55	43.6	33 / 55	60.0	1 / 55	1.8	28844	V	yes
16	7	*TFPI2*	Ppn	CG33103	94	233	$8.79x10^{-20}$	57 / 171	33.3	79 / 171	46.2	3 / 171	1.8	16523, 108005	LV, NV	no
17	2	*B3GNT7*	-	-	-	-	-	-	-	-	-	-	-	-	-	no
17	2	*HTR2B*	D2R	CG33517	178	450	$1.38x10^{-44}$	126 / 388	32.5	192 / 388	49.5	58 / 388	14.9	11470, 11471, 107058	V, V, NV	yes
17	2	*NCL*	pAbp	CG5119	81	199	$3.26x10^{-15}$	90 / 345	26.1	166 / 345	48.1	44 / 345	12.8	22007	LV	no
17	2	*SNORD20*	-	-	-	-	-	-	-	-	-	-	-	-	-	no
18	3	*GHSR*	capaR	CG14575	160	402	$3.39x10^{-39}$	109 / 325	33.5	167 / 325	51.4	27 / 325	8.3	105556	V	yes
18	3	*PLD1*	Pld	CG12110	329	842	$1.46x10^{-89}$	157 / 354	44.4	224 / 354	63.3	17 / 354	4.8	38626, 106137	V, V	yes
19	12	*CRY1*	phr6-4	CG2488	527	1356	$1.70x10^{-149}$	256 / 494	51.8	330 / 494	66.8	13 / 494	2.6	108994	V	yes
21	2	*CALCRL*	Dh31-R1	CG32843	218	553	$1.53x10^{-56}$	139 / 380	36.6	192 / 380	50.5	29 / 380	7.6	8777, 101995	V, V	yes
21	2	*TFPI*	Ppn	CG33103	121	301	$1.73x10^{-27}$	73 / 214	34.1	101 / 214	47.2	36 / 214	16.8	16523, 108005	LV, NV	no

Gene, gene of the candidate gene for bearded vulture; Drosophila ortholog, gene name and CG number are provided for the *Drosophila melanogaster* ortholog of the positional candidate gene; Bit score, Raw score, E-value, BLAST statistics for the alignment between the protein product of the drosophila ortholog and the human gene; Identities, Positives, Gaps, the number of identities, positives and gaps in the alignment between the protein product of the drosophila ortholog and the human gene; Abs, absolute number; rel (%), relative number in percent; Identities, x / y means that x of the amino acids within the total stretch of y is congruent between the protein product of the drosophila ortholog and the human gene; Positives, amino acid substitutions that occur frequently and generally do not alter protein function receive a more positive score than amino acids that do not substitute frequently; Gaps, the number of gaps that need to be introduced to allign the sequence versus the theroretical maximal number of gaps; Line information, the identification number(s) of the RNAi line(s) targeting the drosophila ortholog as described in Dietzl et al., 2007 and as publicly available at the Vienna Drosophila RNAi Center (VDRC, http://stockcenter.vdrc.at/control/main); Viability, indicates whether crossings of drosophila to induce expression of specific RNAi constructs resulted in: 1) more than five live pupae, i.e. viable offspring (V); 2) 0-4 live pupae, i.e. less viable offspring (LV); 3) no live pupae, i.e. no viable offspring (NV). Where multiple RNAi lines were available for an ortholog, viability is indicated for each line separately in the order in which RNAi lines are presented under 'Line information'. For *BEST1,* none of the ordered pupae were alive at arrival (NA). Where multiple independent RNAi lines are available for the same ortholog, results from the available lines were combined using an inverse variance weighted fixed effects meta-analysis if the RNAi lines combined resulted in data from at least five live offspring. Availability shows whether results were ultimately available for the ortholog or not.

For sls, the drosophila ortholog of *TTN*, the quality control data are provided for the first 1200 amino acids; data for the last part of the ortholog is comparable.

Supplementary Table 26 - Meta-analyses of effects on heart rate of multiple independent RNAi lines targeting the same ortholog in *Drosophila melanogaster* pupae

Locus	Gene	Line	Heart rate at rest				Heart rate post-tachypacing				Heart rate post-tachypacing adjusted for heart rest at rest				N
			beta	SE	p	I^2	beta	SE	p	I^2	beta	SE	p	I^2	
3	*ACHE*	3968	-8.4	5.9	0.17		-3.1	15.4	0.84		-1.4	16.1	0.93		3
		105432	-20.1	4.0	$1.11x10^{-05}$		-25.0	8.3	$4.62x10^{-03}$		-19.4	10.7	0.07		11
		meta-analysis	-16.5	3.3	$6.70x10^{-07}$	62.9	-20.0	7.3	0.01	36.5	-13.8	8.9	0.12	0.0	14
3	*EPHB4*	4771	-18.0	3.9	$5.66x10^{-05}$		-9.1	9.7	0.35		-3.2	12.3	0.79		8
		110448	3.9	6.0	0.52		-46.4	14.9	$3.89x10^{-03}$		47.2	15.2	$2.70x10^{-03}$		3
		meta-analysis	-11.4	3.3	$5.41x10^{-04}$	89.2	-20.3	8.1	0.01	77.2	-20.7	9.5	0.03	80.3	11
3	*PCOLCE*	2656	-18.4	3.3	$1.80x10^{-06}$		12.6	8.3	0.14		16.0	11.4	0.17		10
		110432	-12.4	4.3	$7.19x10^{-03}$		18.4	10.8	0.10		22.7	12.1	0.07		6
		meta-analysis	-16.2	2.6	$4.89x10^{-10}$	18.4	14.8	6.6	0.03	0.0	19.1	8.3	0.02	0.0	16
3	*SERBP1*	24033	-2.4	4.3	0.58		16.2	10.7	0.14		17.0	10.8	0.12		6
		104263	-14.9	5.5	0.01		7.2	12.9	0.58		10.7	14.5	0.46		4
		meta-analysis	-7.2	3.4	0.03	68.9	12.6	8.2	0.13	0.0	14.7	8.7	0.09	0.0	10
4	*PLXNA2*	4740	-0.7	5.6	0.90		8.7	13.1	0.51		8.7	13.3	0.52		4
		107004	-22.0	4.0	$2.72x10^{-06}$		-19.4	9.1	0.04		-18.8	12.5	0.14		9
		meta-analysis	-14.8	3.2	$4.58x10^{-06}$	89.6	-10.3	7.5	0.17	67.7	-5.9	9.1	0.51	56.1	13
5	*FADS1*	52570	-12.3	4.0	$3.95x10^{-03}$		27.9	10.7	0.01		30.3	12.2	0.02		7
		102803	-14.3	4.7	$4.22x10^{-03}$		-21.7	12.1	0.08		-14.8	13.6	0.28		6
		meta-analysis	-13.2	3.0	$1.43x10^{-05}$	0.0	6.2	8.0	0.44	89.4	10.2	9.1	0.26	83.6	13
5	*FADS3*	42472	-6.5	4.9	0.19		-8.6	12.4	0.49		-5.9	12.7	0.65		5
		105007	-15.0	4.8	$3.66x10^{-03}$		-26.9	12.2	0.03		-26.0	14.1	0.07		5
		meta-analysis	-10.8	3.4	$1.51x10^{-03}$	34.7	-17.9	8.7	0.04	9.8	-14.9	9.4	0.11	11.2	10
9	*TTN*	47298	-13.4	4.2	$2.69x10^{-03}$		-13.4	9.3	0.16		-15.7	10.5	0.14		12
		47301	-34.2	4.7	$1.80x10^{-08}$		-35.9	10.4	$1.40x10^{-03}$		-22.6	16.2	0.17		8
		meta-analysis	-22.5	3.1	$7.72x10^{-13}$	90.7	-23.4	6.9	$7.29x10^{-04}$	61.8	-17.7	8.8	0.04	0.0	20
12	*MFN1*	40478	-22.6	4.5	$1.30x10^{-05}$		-71.4	9.7	$1.31x10^{-08}$		-68.1	12.9	$1.44x10^{-07}$		7
		105261	-27.7	5.3	$5.70x10^{-06}$		-16.1	9.2	0.09		-5.5	11.9	0.64		11
		meta-analysis	-24.7	3.4	$3.87x10^{-13}$	0.0	-42.3	6.7	$2.38x10^{-10}$	94.2	-34.2	8.8	$9.53x10^{-05}$	92.1	18
14	*CHRM2*	33123	-19.9	4.0	$1.42x10^{-05}$		1.9	10.5	0.86		13.0	13.6	0.35		8
		101407	-24.6	5.1	$2.87x10^{-05}$		-30.0	11.9	0.02		-26.5	15.8	0.10		5
		meta-analysis	-21.7	3.1	$3.86x10^{-12}$	0.0	-12.1	7.9	0.13	75.1	-3.8	10.3	0.71	72.1	13
17	*HTR2B*	11470	22.0	5.7	$5.20x10^{-04}$		25.8	14.4	0.08		12.8	17.2	0.46		4
		11471	-7.3	4.1	0.08		-0.7	8.6	0.94		0.4	9.0	0.97		10
		meta-analysis	2.6	3.3	0.43	94.3	6.2	7.4	0.40	59.8	3.1	8.0	0.70	0.0	14
18	*PLD1*	38626	-8.9	3.3	$9.75x10^{-03}$		2.3	7.5	0.76		7.8	8.0	0.33		15
		106137	-15.1	3.6	$1.91x10^{-04}$		-4.7	9.0	0.61		-1.0	11.0	0.93		9
		meta-analysis	-11.7	2.4	$1.69x10^{-06}$	35.8	-0.6	5.8	0.92	0.0	4.8	6.4	0.46	0.0	24
21	*CALCRL*	8777	-13.3	4.3	$4.23x10^{-03}$		11.6	10.0	0.26		16.3	11.3	0.15		7
		101995	9.0	4.9	0.08		-0.9	12.9	0.95		0.1	13.8	0.99		5
		meta-analysis	-3.6	3.3	0.27	91.3	6.9	7.9	0.38	0.0	9.8	8.8	0.27	0.0	12
	STWL	41009	-3.5	5.2	0.50		12.4	13.7	0.37		13.2	13.9	0.35		4
		102848	2.4	4.7	0.61		13.0	11.3	0.26		12.1	11.4	0.29		6
		meta-analysis	-0.3	3.5	0.94	0.0	12.7	8.7	0.14	0.0	12.6	8.8	0.16	0.0	10

Locus, the heart rate locus identified by GWAS; Gene, the candidate gene located within ± 500 kb of the GWAS association for which an obvious ortholog was targeted by two independent RNAi lines in Drosophila melanogaster. Line, the identification number of the RNAi line targeting the drosophila ortholog as ordered from the Vienna Drosophila RNAi Center (VDRC, http://stockcenter.vdrc.at/control/main); beta and SE, shows the heart rate of the pupae treated with the specified RNAi line as compared with the heart rate of 6000V control pupae (N=30) in beats/min (bpm). Where specified, beta and SE result from a fixed effects meta-analyis of results from individual RNAi lines using the inverse variance method. We measured heart rate at rest and after 20 min of tachypacing, which represents a physical stress to the heart. Heart rate was 113.4 ± 10.1 bpm at rest (mean ± SD) and 74.5 ± 25.3 bpm post-tachypacing in controls. I2, represents the proportion of the variance between individual RNAi lines that can be attributed to heterogeneity for each ortholog; N shows the number of pupae that were available for analysis in each line, as well as after meta-analysis of both lines. 'STONEWALL' is a randomly selected gene with no anticipated effect on heart rate that is considered an extra control group. Data are sorted by locus and subsequently by beta for heart rate at rest.

Supplementary Table 27 - Orthologs and morpholino oligonucleotides for positional candidate genes in *Danio rerio*

			BLAST statistics											
			Ortholog				Identities		Positives		Gaps		Morpholino and primer sequences		
Locus	Chr	Gene	Gene name	Bit score	Raw score	E-value	Abs	rel (%)	Abs	rel (%)	Abs	rel (%)	MO sequence	5' qPCR primer	3' qPCR primer
4	1	*CD34*	-												
4	1	*CD46*	-												
4	1	*CD55*	-												
4	1	*CR1*	-												
4	1	*PLXNA2*	-												
5	11	*BEST1*	best1	1553	602	0	295 / 480	61%	359 / 480	75%	12 / 480	3%	CTATGATGCCTTTACCTGTATGTGA	CTTCTGCGATGGAAAGGAAGC	cca gtc cga atg aca cag g
5	11	*TMEM258*	*												
5	11	*FADS1*	-												
5	11	*FADS2*	fads2	1395	541	0	254 / 375	68%	301 / 375	80%	0 / 375	0%	TGCAGGTTTTTTTACCGTGGCGTCT	GTGGGTGGTGGTGGAGAGG	gct ctc tta gca gcg gct tca gg
5	11	*FADS3*	-												
5	11	*FTH1*	*												
5	11	*RAB3IL1*	*												
8	20	*BPI*	-												
8	20	*KIAA1755*	-												
12	3	*MFN1*	mfn1	2716	1050	0	508 / 735	69%	609 / 735	83%	11 / 735	1%	GAAACCCCAACACTACGCACCTCTT	CCCTGGAGGAGCGAGAGT	gca ttt gag gcg acg ggt gg
13	14	*FLRT2*	-												
16	7	*COL1A2*	col1a2	3237	1251	0	966 / 1367	71%	1068 / 1367	78%	16 / 1367	1%	GCATATTTCAAACTTACATTGACA	GCTCAGCTTTGTGGATACCCG	ccg ggt ttt cca tca ggt ccc
16	7	*GNG11*	-												
16	7	*TFPI2*	tfpi2	435	172	$3.00x10^{-52}$	85 / 204	42%	122 / 204	60%	9 / 204	4%	GCTCAATGTTATCTTTACTTTAGGT	GGCGTGTGATTTACTCGGAGC	cca cag ccg ctg tag ctg
17	2	*B3GNT7*	**												
17	2	*HTR2B*	htr2b	1425	553	0	272 / 436	62%	347 / 436	80%	16 / 436	4%	CCTGTACGTTAACTTACTGTAAAGC	CCTGATGTCTCTGGCTG	cac aag tgc atg atg gac gc
17	2	*NCL*	ncl	776	303	$2.00x10^{-96}$	157 / 260	60%	206 / 260	79%	12 / 260	5%	TGACGGTAATATCTTACCTTAGCGA	ATGGTAAAGCTCGCTAAG	ggc agc agc ttt tcc gtt ttt c
17	2	*SNORD20*	-												
18	3	*GHSR*	ghsrb	1261	490	$9.00x10^{-173}$	241 / 343	70%	285 / 343	83%	3 / 343	1%	AGTAAAATCATCGCGCTCACCAAGC	CCCCGTCCTGTGTTTGACGG	caa gat acc gac cca c
18	3	*PLD1*	pld1a	3819	1475	0	724 / 1076	67%	838 / 1076	78%	76 / 1076	7%	TGTTCTGCATTTCTTTGACCTGTGC	CCACACAGAGAGAAGG	ctg gct cac atc aat aaa ctc c
19	12	*CRY1*	cry1b	2536	981	0	475 / 614	77%	525 / 614	86%	44 / 614	7%	CGCTCAAAAAGCAAACTCACCTCCA	CCCTTCATTGCGGGACTC	gga aag acg tct gta ggt tg
21	2	*CALCRL*	calcrla	1828	708	0	331 / 449	74%	388 / 449	86%	6 / 449	1%	GTGGCAAATAATCTTTCACCTCAGT	GACAGCGAGCTGCTGGACG	ctc ttg tgt ctt gac tgt tgt cc
21	2	*TFPI*	tfpia	396	157	$4.00x10^{-45}$	85 / 274	31%	143 / 274	52%	46 / 274	17%	ATCTGCTGAAGGTGGAAACAAGCCA	CCGCTGTATTAAAGTCAGAGG	gga ttg aac acg tat ctc ctc

Genes in loci 1, 2, 3, 6, 9, 11, 14 and 15 (not shown) were not considered for *Danio rerio* (zebrafish) experiments based on abundant evidence indicating a role in heart rate regulation for *MYH6* and *MYH7* (locus 1), *GJA1* (locus 2), *ACHE* (locus 3), *PLN* (locus 6), *TTN* (locus 9), *HCN4* (locus 11), *CHRM2* (locus 14), and *NKX2-5* (locus 15). Within each of the remaining loci, a maximum of two promising candidate genes with available orthologs were selected for zebrafish experiments in first instance. This resulted in exclusion of *C11orf10, FTH1,* and *RAB3IL1* in locus 5 (marked '*'), and *B3GNT7* in locus 17 (marked '**'). For the remaining candidate genes, gene name, BLAST statistics and primer information are provided for the zebrafish ortholog of the candidate gene that resulted in the highest Bit score in the BLAST search. A '-' indicates that no obvious ortholog was available for the candidate gene.

Gene, candidate gene for heart rate; Bit score, a measure of the similarity between the queried sequence and the observed sequence that takes into account the alignment of similar or identical residues, as well as any gaps introduced to align the sequences. Bit scores are normalized so that scores from different allignments can be compared and are calculated as: Bit score = (lambda * Raw score - ln(K)) / ln(2), where lambda and K are constants provided by te BLAST search. A higher Bit score implies a better fit; Raw score, the total of all matches, mismatches and gap penalties; E-value, describes the number of allignments one would expect to find by chance that have the same Bit score as the allignment under consideration when searching a database of the current size. The E-value decreases exponentially as the Bit score increases and is calculated as: E-value = (query length) * (length of the database) * ($2^{\text{Bit score}}$) An E-value <0.05 is typically considered biologically informative; Identities, x / y means that x of the amino acids within the total stretch of y is congruent between the protein product of the zebrafish ortholog and the human gene; Positives, amino acid substitutions that occur frequently and generally do not alter protein function receive a more positive score than amino acids that do not substitute frequently; Gaps, the number of gaps that need to be introduced to allign the sequence versus the theroretical maximal number of gaps; MO sequence, the sequence of the morpholino oligonucleotide targeting the ortholog of the candidate gene; 5' qPCR and 3'qPCR, sequences of the primers used.

Supplementary Table 28 - Effects on heart rate and arrhythmia in *Drosophila melanogaster* pupae with orthologs of positional candidate genes for heart rate targeted by RNAi

Locus	Gene	Heart rate at rest			Heart rate post-tachypacing			Heart rate post-tachypacing adjusted for heart rest at rest			Arrhythmic at rest			Arrhythmic post-tachypacing		
		beta	SE	p	beta	SE	p	beta	SE	p	N_{NA}	N_A	p	N_{NA}	N_A	p
3	*TRIP6*	-22.6	4.5	$1.60x10^{-05}$	-11.2	10.3	0.28	-0.8	13.4	0.95	6	1	0.19	2	5	$4.90x10^{-03}$
3	*ACHE*^{M}	-16.5	3.3	$6.70x10^{-07}$	-20.0	7.3	0.01	-13.8	8.9	0.12	13	1	0.32	4	10	$2.51x10^{-04}$
3	*PCOLCE*^{M}	-16.2	2.6	$4.89x10^{-10}$	14.8	6.6	0.03	19.1	8.3	0.02	15	1	0.35	3	13	$9.05x10^{-06}$
3	*UFSP1*	-14.2	3.7	$5.05x10^{-04}$	7.4	9.1	0.42	13.5	10.7	0.21	7	2	0.05	4	5	0.02
3	*EPHB4*^{M}	-11.4	3.3	$5.41x10^{-04}$	-20.3	8.1	0.01	-20.7	9.5	0.03	11	0	-	5	6	0.01
3	*SERBP1*^{M}	-7.2	3.4	0.03	12.6	8.2	0.13	14.7	8.7	0.09	10	0	-	10	0	0.56
3	*TIMP1*	-2.4	4.7	0.61	0.8	11.8	0.94	1.5	11.9	0.90	5	0	-	5	0	1.00
4	*PLXNA2*^{M}	-14.8	3.2	$4.58x10^{-06}$	-10.3	7.5	0.17	-5.9	9.1	0.51	12	1	0.30	5	8	$2.50x10^{-03}$
4	*CD55 / CD46 / CR1*	-10.2	4.2	0.02	-12.1	9.6	0.21	-7.8	10.3	0.45	9	0	-	9	0	0.56
5	*FADS1*^{M}	-13.2	3.0	$1.43x10^{-05}$	6.2	8.0	0.44	10.2	9.1	0.26	11	2	0.09	11	2	1.00
5	*FADS3*^{M}	-10.8	3.4	$1.51x10^{-03}$	-17.9	8.7	0.04	-14.9	9.4	0.11	9	1	0.25	1	9	$2.31x10^{-05}$
5	*FTH1*	-6.1	4.4	0.17	-11.4	12.4	0.37	-10.8	13.0	0.41	6	0	-	6	0	1.00
9	*TTN*^{M}	-22.5	3.1	$7.72x10^{-13}$	-23.4	6.9	$7.29x10^{-04}$	-17.7	8.8	0.04	20	0	-	16	4	0.70
12	*MFN1*^{M}	-24.7	3.4	$3.87x10^{-13}$	-42.3	6.7	$2.38x10^{-10}$	-34.2	8.8	$9.53x10^{-05}$	11	7	$4.32x10^{-04}$	3	15	$1.99x10^{-06}$
13	*FLRT2*	-9.9	5.2	0.07	3.7	11.2	0.74	10.5	11.3	0.36	7	0	-	7	0	0.57
14	*CHRM2*^{M}	-21.7	3.1	$3.86x10^{-12}$	-12.1	7.9	0.13	-3.8	10.3	0.71	11	2	0.09	5	8	$2.50x10^{-03}$
15	*NKX2-5*	5.7	4.4	0.21	4.0	10.7	0.71	2.0	11.0	0.85	6	0	-	6	0	1.00
16	*GNG11*	-18.0	4.9	$8.61x10^{-04}$	-5.9	13.1	0.66	4.1	15.5	0.79	5	0	-	1	4	0.01
17	*HTR2B*^{M}	2.6	3.3	0.43	6.2	7.4	0.40	3.1	8.0	0.70	14	0	-	14	0	0.29
18	*GHSR*	-22.3	3.7	$5.30x10^{-07}$	-17.6	8.7	0.05	-7.6	12.0	0.53	10	1	0.27	7	4	0.18
18	*PLD1*^{M}	-11.7	2.4	$1.69x10^{-06}$	-0.6	5.8	0.92	4.8	6.4	0.46	23	1	0.44	12	12	$6.10x10^{-03}$
19	*CRY1*	-17.6	4.7	$7.54x10^{-04}$	-6.9	11.8	0.56	-0.9	14.2	0.95	5	0	-	1	4	0.01
21	*CALCRL*^{M}	-3.6	3.3	0.27	6.9	7.9	0.38	9.8	8.8	0.27	12	0	-	12	0	0.31
	STONEWALL^M	-0.3	3.5	0.94	12.7	8.7	0.14	12.6	8.8	0.16	10	0	-	10	0	0.56

Heart rate was 113.4 ± 10.1 bpm at rest (mean ± SD) and 74.5 ± 25.3 bpm post-tachypacing in 6000V control pupae (N=30). None of the control pupae shod arrhythmia at rest; four control pupae show arrhythmia post-tachypacing. *'STONEWALL'* is a randomly selected gene with no anticipated effect on heart rate that is considered an extra control group. Data are sorted by locus and subsequently by beta for heart rate at rest.

Locus, the heart rate locus identified by GWAS; Gene, the candidate gene located within ± 500 kb of the GWAS association for which an ortholog is targeted by RNAi in *Drosophila melanogaster*. The suffix M indicates that data from two RNAi lines are available for the ortholog. For these orthologs summary statistics for heart rate are from a fixed

Supplementary Table 29 – Effects on heart rate and related traits in *Danio rerio* embryos with orthologs of positional candidate genes for heart rate targeted by morpholino oligonucleotides

Locus	Gene	Expression (%)		Heart rate at rest				Fractional shortening				Visible phenotype		
												Phenotype	Penetrance	
		mean	SD	$beta_{HR}$	SE_{HR}	p_{HR}	N_{HR}	$beta_{FS}$	SE_{FS}	p_{FS}	N_{FS}		%	N_P
5	*BEST1*	40.5	8.5	-26.0	3.2	$8.71x10^{-16}$	23 / 21	0.09	0.03	0.02	6 / 7	Edema	35	19 / 55
5	*FADS2*	77.1	1.0	-13.6	2.5	$3.49x10^{-08}$	26 / 26	-0.01	0.02	0.77	5 / 3	Blood pooling	78	42 / 54
12	*MFN1*	57.3	0.6	-9.3	2.0	$3.50x10^{-06}$	25 / 28	-0.09	0.04	0.04	7 / 6	Edema	73	11 / 15
16	*COL1A2*	1.6	0.0	-3.7	2.1	0.07	29 / 27	-0.16	0.04	$1.80x10^{-03}$	5 / 8	-	-	-
16	*TFPI2*	25.6	1.5	1.8	2.3	0.43	23 / 23	0.06	0.03	0.03	6 / 7	Edema	64	34 / 53
17	*HTR2B*	33.2	4.1	-9.6	2.5	$1.55x10^{-04}$	25 / 28	-0.05	0.03	0.16	7 / 6	Unlooped heart	33	7 / 21
17	*NCL*	57.4	0.9	-9.1	1.9	$1.19x10^{-06}$	35 / 37	-0.01	0.02	0.55	7 / 6	Unlooped heart	31	13 / 42
18	*PLD1*	62.3	0.8	-15.6	3.0	$1.91x10^{-07}$	28 / 29	0.03	0.03	0.39	3 / 3	Unlooped heart	51	27 / 53
18	*GHSR*	70.2	5.0	-6.4	3.9	0.11	28 / 27	-0.01	0.02	0.63	5 / 5	-	-	-
19	*CRY1*	3.3	0.2	-21.0	3.9	$6.99x10^{-08}$	20 / 20	-0.02	0.03	0.38	4 / 6	Dorsalization	88	49 / 56
21	*CALCRL*	16.6	1.0	-15.4	2.6	$1.59x10^{-09}$	27 / 30	0.07	0.06	0.24	6 / 6	Unlooped heart / AV malformation	57	30 / 53
21	*TFPI*	36.2	1.2	-3.8	3.5	0.28	19 / 23	-0.08	0.05	0.21	5 / 3	Edema	36	5 / 14

Locus, the heart rate locus identified by GWAS; Gene, the candidate gene located within ± 500 kb of the GWAS association for which an obvious ortholog is targeted by injecting morpholino oligonucleotides in *Dani rerio* (zebrafish) embryos; Expression (%), the expression of the ortholog in embryos injected with morpholino versus PBS, measured 48 h post-fertilization using qPCR; $beta_{HR}$ and SE_{HR}, the heart rate of embryos injected with morpholino versus PBS; N_{HR}, x / y indicates that data is available for x embryos injected with morpholino and y injected with PBS; $beta_{FS}$ and SE_{HR}, the fractional shortening of embryos injected with morpholino versus PBS. Fractional shortening is calculated as the end-diastolic diameter of the ventricular chamber divided by its end-systolic diameter; N_{FS}, analogue to N_{HR}; N_P, x / y indicates that x of y examined embryos injected with morphilino show the phenotype. Data are sorted by locus and subsequently by $beta_{HR}$.

Supplementary Table 30 - Characteristics of *Drosophila melanogaster* pupae and *Danio rerio* embryos transfected for orthologs of candidate genes for heart rate

Locus	Gene	*Drosophila melanogaster* pupae	*Danio rerio* embryos
3	*TRIP6*	Reduced heart rate at rest	-
	ACHE	Reduced heart rate at rest; increased risk of arrhythmia post-tachypacing	-
	PCOLCE	Reduced heart rate at rest; increased risk of arrhythmia post-tachypacing	-
	UFSP1	Reduced heart rate at rest	-
	EPHB4	Reduced heart rate at rest	-
	SERBP1	No associations	-
	TIMP1	No associations	-
4	*PLXNA2*	Reduced heart rate at rest	-
	CD55 / CD46 / CR1	No associations	-
5	*FADS1*	Reduced heart rate at rest	-
	FADS2	-	Reduced heart rate; blood pooling (78%)
	FADS3	Reduced heart rate at rest; increased risk of arrhythmia post-tachypacing	-
	BEST1	-	Reduced heart rate; edema (35%)
	FTH1	No associations	-
9	*TTN*	Reduced heart rate at rest	-
12	*MFN1*	Reduced heart rate at rest and post-tachypacing; increased risk of arrhythmia at rest and post-tachypacing	Reduced heart rate; edema (73%)
13	*FLRT2*	No associations	-
14	*CHRM2*	Reduced heart rate at rest	-
15	*NKX2-5*	No associations	-
16	*GNG11*	Reduced heart rate at rest	-
	TFPI2	-	Edema (64%)
	COL1A2	-	Reduced fractional shortening
17	*HTR2B*	No associations	Reduced heart rate; unlooped heart (33%)
	NCL	-	Reduced heart rate; unlooped heart (31%)
18	*PLD1*	Reduced heart rate at rest	Reduced heart rate; unlooped heart (51%)
	GHSR	Reduced heart rate at rest	No associations
19	*CRY1*	Reduced heart rate at rest	Reduced heart rate; dorsalization (88%)
21	*TFPI*	-	Edema (57%)
	CALCRL	No associations	Reduced heart rate; unlooped heart and AV canal malformation (57%)

Locus, the heart rate locus identified by GWAS; Gene, the candidate gene located within ± 500 kb of the GWAS association for which an ortholog is targeted by RNAi in *Drosophila melanogaster* pupae and by morpholino oligonucleotides in *Danio rerio.*

Proportions between brackets show the penetrance in *Danio rerio* embryos.

2 SUPPLEMENTARY NOTE

2.1 Candidate genes within the confirmed heart rate loci

Cardiac embryonic development proteins

- ***FLRT2* (locus 13):** The fibronectin leucine-rich repeat transmembrane protein (*FLRT2*) is required in the epicardium to promote heart morphogenesis[1].
- ***NKX2-5* (locus 15):** The transcription factor *NKX2-5*, which is abundantly expressed in the adult heart, is essential for early embryonic cardiac development[2-4]. Mutations in *NKX2-5* cause congenital heart diseases and atrio-ventricular conduction block[5-7].
- ***PLD1* (locus 18):** phospholipase D1 (*PLD1*) hydrolyzes phosphatidylcholine to phosphatidic acid and choline. Temporal changes in expression of *PLD1* suggest a role in proliferation and differentiation of cardiomyocytes during early postnatal development in rats[8], whereas changes in *PLD1* protein content and activity following myocardial infarction induced in rats suggest a role in the pathophysiology of congestive heart failure[9].

Cardiac conduction proteins

- ***GJA1* (locus 2):** *GJA* encodes connexin 43, the major cardiac gap junction channel that is responsible for intercellular conductance in the ventricles and synchronized contraction of the heart[10]. Cardiac expression of connexin 43 is reduced in patients with heart failure[11] and mutations in *GJA1* have been associated with atrial fibrillation[12].
- ***ACHE* (Locus 3):** Acetylcholinesterase, encoded by *ACHE*, hydrolyzes the neurotransmitter acetylcholine at neuromuscular junctions, thereby terminating signal transmission[13].
- ***HCN4* (locus 11):** The hyperpolarization-activated cyclic nucleotide-gated channel 4 (HCN4), expressed in the sinus node, is the major channel mediating sympathetic stimulation of (embryonic) pacemaker activity[14,15]. Mutations in *HCN4* have been

associated with sinus nodal dysfunction[16] and bradycardia[17]. Cardiac knockout of the gene in adult mice resulted in severe bradycardia and heart arrest within ~5 days[18]. Ivabradine, a selective heart rate-reducing agent, acts as an open channel blocker of *HCN4*[19].

- ***CHRM2* (locus 14):** The M2-muscarinic acetylcholine receptor (*CHRM2*) is primarily expressed in the heart[20] and plays an important role in mediating parasympathetic control of cardiac functions such as heart rate, conduction and contractility[21]. A mutation in *CHRM2* has been associated with dilated cardiomyopathy, sudden death, severe arrhythmia and heart failure[20].

Cardiac contractile proteins

- ***MYH6/MYH7* (locus 1):** *MYH6* and *MYH7* encode the fast α- and slow β-myosin heavy chain (MHC) isoforms, respectively. α-MHC is mainly expressed in atrial tissue[22], while β-MHC comprises 95% of functional myosin heavy chain protein present in adult ventricles.[23] Mutations in *MYH6* and *MYH7* have been associated with atrial septal defect[24] (*MYH6*), dilated[25] and familial hypertrophic[26] cardiomyopathy and sick sinus syndrome[27] (*MYH6*).
- ***TTN* (locus 9):** Titin plays a key role in myocardial elasticity and the Frank Starling mechanism[28,29]. Titin comes in two isoforms: a stiff (N2B) isoform and a more compliant (N2BA) isoform, which are differentially expressed in the left and right heart, as well as in atria and ventricles[30]. Mutations in *TTN* cause dilated cardiomyopathy[31].

Calcium regulation proteins

- ***FADS2/FADS1* (locus 5):** Δ^6-desaturase (*FADS2*) catalyzes the reaction forming γ-linoleic acid from linoleic acid (ω-6 fatty acid) as well as the reaction forming eicosapentaenoic acid from α-linoleic acid (ω-3 fatty acid); Δ^5-desaturase (*FADS1*) catalyses the reaction forming arachidonic acid from γ-linoleic acid. Arachidonic acid releases Ca^{2+} from the sarcoplasmic reticulum[32], which is integral to impulse

propagation, whereas ω-3 fatty acids have repeatedly been associated with reduced risk of ischaemia-induced arrhythmias and sudden cardiac death[33,34] and may reduce heart rate[34,35]. Variants in/near *FADS1* and *FADS2* have previously been associated with ω-3 and ω-6 acid levels[36-38], total and LDL cholesterol levels[38,39] and risk of coronary artery disease[36,40].

- ***PLN* (locus 6):** Phospholamban (*PLN*) is a key regulator of cardiac diastolic function and is involved in intracellular calcium regulation in cardiac muscle[41]. Mutations in *PLN* cause hypertrophic[42,43] and dilated[41,44] cardiomyopathy.

Angiogenesis and endothelial function proteins

- ***EPHB4* (locus 3):** Ephrin B4 (*EPHB4*) is a potent angiogenic factor.[45] Mice lacking *EPHB4* are characterized by early embryonic lethality with disturbed arteriovenous differentiation[46,47].
- ***TIMP1* (locus 3):** Tissue inhibitor of metalloproteinase-1 (*TIMP1*) has an inhibitory effect on angiogenesis[48]. Increased *TIMP1* protein levels have been observed in myocardial infarction[49], atrial fibrillation[50] and heart failure patients[51]. Variants in *TIMP1* have been associated with abdominal aortic aneurisms[52].
- ***PLXNA2* (locus 4):** The neurovascular guiding molecule and angiogenic factor semaphorin 3C (*SEMA3C*) and its receptor plexin A2 (*PLXNA2*) appear to be regulated directly by *GATA6*. Mutations in *GATA6* cause human cardiac outflow tract defects by disrupting semaphorin-plexin signaling[53].
- ***TFPI2* (locus 16):** Tissue factor pathway inhibitor-2 has direct anti-angiogenic effects on endothelial cells[54]. Methylation of *TFPI-2* was observed in atherosclerotic plaques, but not in control arteries[55].
- ***CALCRL* (locus 21):** Calcitonin receptor-like receptor (*CALCRL*) acts as a receptor for adrenomedullin[56], an autocrine regulator of local vasodilatation[57] and endothelial growth[58] that is expressed in cardiomyocytes[59]. Mice lacking the gene have cardiovascular defects and embryonic lethality[56].

Other pathways

- ***MFN1* (locus 12):** Mitofusion 1 (*MFN1*) controls mitochondrial fusion in mammalian cells and its elimination induces mitochondrial fragmentation[60]. *MFN1* is increased in dilated cardiomyopathy and failing human heart[61].
- ***HTR2B* (locus 17):** The 5-hydroxytryptamine (serotonin) receptor 2B (HTR2B) mediates regulation of cardiovascular functions and impulsive behavior[62]. Inhibiting *HTR2B* in incubating cells increases fat accumulation, similar to the phenotype observed after receptor knock-down[63].
- ***CRY1* (locus 19):** Chryptochrome 1 (*CRY1*) is expressed in human heart[64] and plays a role in circadian rhythm by potently inhibiting BMAL1-induced transcription[65]. A circadian rhythm of *CRY1* expression was shown in mouse[66] but not human[64] myocardium.
- ***TFPI* (locus 21):** Tissue factor pathway inhibitor (*TFPI*) is involved in the process of thrombin generation[67]. TFPI levels have been associated with carotid artery disease and coronary artery calcium[68].

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2.2 Acknowledgments

ACTS (Alcohol Challenge Twin Study) - We are grateful for the twins who participated in the Alcohol Challenge Twin Study and all those who helped in carrying it out. We would also like to thank staff at the Queensland Institute of Medical Research: Anjali Henders, Megan Campbell and staff of the Molecular Epidemiology Laboratory (sample processing and preparation); Sarah Medland, Dale Nyholt and Scott Gordon (imputation and genotyping QC). Phenotype collection was part of the Alcohol Challenge Twin Study which was funded by the Australian Brewers Foundation. Collection of DNA and genotyping was funded by grants from the Australian National Health and Medical Research Council (NHMRC) grant 159101; and U.S. National Institutes of Health (AA013320, AA013321, AA013326 and AA014041). Statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org), which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ADVANCE (Atherosclerosis Disease, Vascular Function and Genetic Epidemiology) - The ADVANCE study was supported by a grant from the Reynold's Foundation; and NHLBI grant HL087647.

AGES (Age, Gene/Environment Susceptibility Reykjavik Study) - The Age, Gene/Environment Susceptibility Reykjavik Study has been funded by National Institutes of Health (contract N01-AG-12100); the National Institute of Aging Intramural Research Program; Hjartavernd (the Icelandic Heart Association); and the Althingi (the Icelandic Parliament).

ALSPAC (Avon Longitudinal Study of Parents And Children) – David M Evans is supported by a Medical Research Council New Investigator Award (MRC G0800582 to David M Evans). John P Kemp is funded by a Wellcome Trust 4-year PhD studentship in molecular, genetic, and life course epidemiology (WT083431MA). We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council; the Wellcome Trust; and the University of Bristol; provide core support for ALSPAC. We thank the Sample Logistics and Genotyping Facilities at the Wellcome Trust Sanger Institute and also 23andME for generating the ALSPAC GWAS data. This publication is the work of the authors and they will serve as guarantors for the contents of this paper.

ARIC, CHARGE (Atherosclerosis Risk in Communities Study) - ARIC 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 contracts N01AG12109, and HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research.

ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) – Neil R Poulter received funding from the UK National Institute for Health Research Biomedical Research Centre funding scheme and senior investigator award. Peter S Sever received a BRC Award to Imperial College NHS Health Care Trust.

ATBC (Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study) - The ATBC Study was supported in part by U.S. Public Health Service (contract numbers N01-CN-45165, N01-RC-45035, N01-RC-37004, and HHSN261201000006C) from the National

Cancer Institute, Department of Health and Human Services; and Intramural Research Program of the U.S. National Cancer Institute.

B58C T1DGC (British 1958 Birth Cohort (Type 1 Diabetes Genetic Consortium Controls) - The B58C-T1DGC genotyping utilized resources provided by the Type 1 Diabetes Genetics Consortium, a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); National Institute of Allergy and Infectious Diseases (NIAID); National Human Genome Research Institute (NHGRI); National Institute of Child Health and Human Development (NICHD); and Juvenile Diabetes Research Foundation International (JDRF) and supported by U01 DK062418. B58C-T1DGC GWAS data were deposited by the Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research (CIMR), University of Cambridge, which is funded by Juvenile Diabetes Research Foundation International; the Wellcome Trust; and the National Institute for Health Research Cambridge Biomedical Research Centre; the CIMR is in receipt of a Wellcome Trust Strategic Award (079895).

B58C WTCCC (British 1958 Birth Cohort (Wellcome trust case control consortium) - We acknowledge use of phenotype and genotype data from the British 1958 Birth Cohort DNA collection, funded by the Medical Research Council grant G0000934; and the Wellcome Trust grant 068545/Z/02. (http://www.b58cgene.sgul.ac.uk/). Genotyping for the B58C-WTCCC subset was funded by the Wellcome Trust grant 076113/B/04/Z.

BLSA (Baltimore Longitudinal Study of Aging) - This study was supported in part by the Intramural Research Program of the NIH, National Institute on Aging. A portion of that support was through a R&D contract with MedStar Research Institute.

Bright (British Genetics of Hypertension Study) – The MRC Bright Study was funded by the Medical Research Council Programme G952010, The Wellcome Trust Case Control Consortium and is part of the portfolio of the Barts and The London NIHR Cardiovascular Biomedical Research Unit. Nilesh J Samani holds a Chair funded by the British Heart Foundation. The BRIGHT Study is part of the portfolio of research supported by the Leicester NIHR Biomedical Research Unit in Cardiovascular Disease. Sandosh Padmanabhan is funded by a British Heart Foundation travel fellowship to the Broad Institute of Harvard and MIT. Toby Johnson is a Wellcome Trust University Award Holder.

CHS, CHARGE (Cardiovascular Health Study) - The CHS research was supported by NHLBI contracts N01-HC-85239, N01-HC-85079 through N01-HC-85086; N01-HC-35129, N01-HC-15103, N01-HC-55222, N01-HC-75150, N01-HC-45133 and NHLBI grants HL080295, HL075366, HL087652, HL105756 with additional contribution from NINDS. Additional support was provided through AG-023629, AG-15928, AG-20098, and AG-027058 from the NIA. See also http://www.chs-nhlbi.org/pi.htm. DNA handling and genotyping was supported in part by National Center for Research Resources grant M01-RR00425 to the Cedars-Sinai General Clinical Research Center Genotyping core and National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

CoLAUS (Cohorte Lausannoise) - The CoLaus study was supported by research grants from GlaxoSmithKline; the Faculty of Biology and Medicine of Lausanne, Switzerland; and the Swiss National Science Foundation (grant no: 33CSCO-122661). Gérard Waeber and Peter Vollenweider received an unrestricted grant from GSK to build the CoLaus study. The authors express their gratitude to the participants in the Lausanne CoLaus study and to the investigators who have contributed to the recruitment, in particular Vincent Mooser, Dawn Waterworth, Vladimir Mayor, Mathieur Firmann, Yolande Barreau, Anne-Lise Bastian, Binasa Ramic, Martine Moranville, Martine Baumer, Marcy Sagette, Jeanne Ecoffey and Sylvie Mermoud for data collection.

COROGENE (COROGENE Study) – The COROGENE study was supported by the Aarno Koskelo Foundation; the Finnish Foundation for Cardiovascular Research; and the EVO funds of Helsinki University Central Hospital.

DESIR (Data from an Epidemiological Study on the Insulin Resistance Syndrom) - DESIR genetic studies were supported in part by the "Conseil Regional Nord-Pas-de-Calais: Fonds européen de développement économique et regional (CPER 2011-2013); Genome Quebec-Genome Canada; and the British Medical Research Council. We acknowledge the Inserm, NB-N' employer.

DGI (Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University and Novartis Institutes of Biomedical Research) – The DGI study was supported by a grant from Novartis. The Botnia PPP study was supported by grants from the Signe and Ane Gyllenberg Foundation; Swedish Cultural Foundation in Finland; Finnish Diabetes Research Society; the Sigrid Juselius Foundation; Folkhälsan Research Foundation; Foundation for Life and Health in Finland; Jakobstad Hospital; Medical Society of Finland; Närpes Research Foundation; the Vasa and Närpes Health centers; the European Community's Seventh Framework Programme (FP7/2007-2013); the European Network for Genetic and Genomic Epidemiology (ENGAGE); the Collaborative European Effort to Develop Diabetes Diagnostics (CEED/2008-2012); and the Swedish Research Council, including a Linné grant (No.31475113580).

EGCUT (Estonian Genome Centre, University of Tartu) - EGCUT authors received support from FP7 grants (201413 ENGAGE, 212111 BBMRI, 245536 OPENGENE). EGCUT authors also received targeted financing from Estonian Government (SF0180142s08); and by EU via the European Regional Development Fund, in the frame of Centre of Excellence in Genomics. EGCUT authors would like to acknowledge the personnel of EGCUT, especially Ms Merli Hass, as well as the staff of Estonian Biocenter, especially Mr Viljo Soo. EGCUT data analysis were carried out in part in the High Performance Computing Center of the University of Tartu.

Ely (Ely Study) - The MRC Ely Study was supported by the Medical Research Council and the Wellcome Trust. We thank all staff from the MRC Epidemiology Unit Functional Group Team.

EPIC-NL (European Prospective Investigation into Cancer and Nutrition – Netherlands) - The EPIC-NL study was funded by "Europe against Cancer" Programme of the European Commission (SANCO); Dutch Ministry of Health, Welfare and Sports (VWS); LK Research Funds; Dutch ZON (Zorg Onderzoek Nederland); and World Cancer Research Fund (WCRF) (The Netherlands). We thank Statistics Netherlands and Netherlands Cancer Registry (NKR) for follow-up data on cancer, cardiovascular disease, vital status and causes of death. Genotyping was funded by grant IGE05012 from the IOP Genomic Programme of NL Agency.

EPIC-Norfolk (European Prospective Investigation into Cancer and Nutrition Norfolk) – The EPIC-Norfolk Study is funded by program grants from the Medical Research Council UK; and Cancer Research UK. We thank all staff from the MRC Epidemiology Unit Functional Group Team.

ERF (Erasmus Rucphen Study) – The ERF study was supported by grants from the Netherlands Organization for Scientific Research (NOW, Pioneergrant); Erasmus Medical Center; the Centre for Medical Systems Biology (CMSB); and the Netherlands Kidney Foundation. We are grateful to all patients and their relatives, general practitioners and neurologists for their contributions and to P. Veraart for her help in genealogy, Jeannette Vergeer for the supervision of the laboratory work and P. Snijders for his help in data collection.

FamHS (Family Heart Study) - The Family Heart Study (FamHS) work was supported in part by NIH grants: 5R01HL08770003, 5R01HL08821502 (M.A.P.) from the NHLBI; and 5R01DK07568102, 5R01DK06833603 from the NIDDK (I.B.B.). The authors thank the staff and participants of the FHS for their important contributions.

Fenland (Fenland Study) – The Fenland Study is funded by the Welcome Trust; the Medical Research Council; the Support Funding programme; Camstrad; and the British Heart Foundation (BHF) (PG/07/108/23369). We are grateful to all volunteers for their time and help and to the General Practitioners and practice staff for help with recruitment. We thank the Fenland Study co-ordination team and the Field Epidemiology team of the MRC-Epidemiology Unit for recruitment and clinical testing.

FHS (Framingham Heart Study) - The FHS research was conducted in part using data and resources from the Framingham Heart Study of the National Heart, Lung, and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (contract number N01-HC-25195); and its contract with Affymetrix, Inc for genotyping services (contract number N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. Electrocardiographic measurements in the third generation of FHS were supported by grants from the National Institutes of Health and the Doris Duke Charitable Foundation to Christopher Newton-Cheh.

Fingesture (Fingesture Study) - The genetic work on this cohort was supported by the Montreal Heart Institute Foundation (www.fondationicm.org). Juhani Junttila and Heikki V Huikuri received funds from the Sigrid Juselius Foundation (www.sigridjuselius.fi/foundation); Juhani Junttila received funding from Fondation Leducq (www.fondationleducq.org).

Finrisk07 (Finrisk 2007 Study) – The FINRISK 2007 survey was primarily funded by the Finnish National Institute for Health and Welfare (THL). The GWAS genotyping was carried out at the Wellcome Trust Sanger Instute, Hinxon, UK. Additional support for genotyping and data analyses was obtained from the SALVE program of the Academy of Finland (grant number 129322 to Markus Perola and 129494 to Veikko Salomaa).

Fusion (Finland – United States Investigation of NIDDM Genetics) – Fusion was partly funded by the National Institutes of Health (DK062370). We would like to thank the many Finnish volunteers who generously participated in our study. The Center for Inherited Disease Research performed the GWA genotyping.

GOOD (The Gothenburg Osteoporosis and Obesity Determinants Study) - Financial support was received from the Swedish Research Council (K2010-54X-09894-19-3, 2006-3832 and K2010-52X-20229-05-3); the Swedish Foundation for Strategic Research; the ALF/LUA research grant in Gothenburg; the Lundberg Foundation; the Torsten and Ragnar Söderberg's Foundation; Petrus and Augusta Hedlunds Foundation; the Västra Götaland Foundation; the Göteborg Medical Society; the Novo Nordisk foundation; and the European Commission grant HEALTH-F2-2008-201865-GEFOS. We would like to acknowledge Maria Nethander at the Genomics core facility at the University of Gothenburg for statistical analyses. We would like to thank Dr. Tobias A. Knoch, Luc V. de Zeeuw, Anis Abuseiris, and Rob de Graaf as well as their institutions the Erasmus Computing Grid, Rotterdam, The Netherlands, and especially the national German MediGRID and Services@MediGRID part of the German D-Grid, both funded by the German Bundesministerium für Forschung und Technology under grants #01 AK 803 A-H and # 01 IG 07015 G for access to their grid resources. We would also like to thank Karol Estrada, Department of Internal Medicine, Erasmus MC, Rotterdam, Netherlands for advice regarding the grid resources.

HAPI (Heredity and Phenotype Intervention Heart Study) – HAPI was funded by grants AG000219, U01 HL72515 and P30 DK072488.

HBCS (Helsinki Birth Cohort Study) – We thank all study participants as well as everybody involved in the Helsinki Birth Cohort Study. Helsinki Birth Cohort Study has been supported by grants from the Academy of Finland, the Finnish Diabetes Research Society, Folkhälsan Research Foundation, Novo Nordisk Foundation, Finska Läkaresällskapet, Signe and Ane Gyllenberg Foundation, University of Helsinki, European Science Foundation (EUROSTRESS), Ahokas Foundation, Emil Aaltonen Foundation, Juho Vainio Foundation, and Wellcome Trust (grant number WT089062).

Health 2000 (Health 2000 / GENMETS sub-study) – The Health 2000 survey was funded by the Finnish National Institute for Health and Welfare (THL) in collaboration with the National Social Insurance Institution and the five university hospital districts. GENMETS genotyping was sponsored by the Wellcome Trust Sanger Institute, Hinxton, UK. Additional support for genotyping and data analyses was obtained from the SALVE program of the Academy of Finland (grant number 129322 to Markus Perola and 129494 to Veikko Salomaa).

Health ABC (Health aging and body composition study) - This research was supported by NIA contracts N01AG62101, N01AG62103 and N01AG62106. The genome-wide association study was funded by NIA grant 1R01AG032098-01A1 to Wake Forest University Health Sciences. Genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSN268200782096C. This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging. Dr Omer T. Njajou is supported by a "Training in Molecular & Genetic Epidemiology of Cancer, National Institutes of Health, National Cancer Institute" grant (R25 CA112355).

Heritage (Heritage Family Study) – Heritage received funding from the NIH/NHLBI HL045670 grant. Thanks are expressed to Drs. Arthur Leon, James Skinner and Jack Wilmore (supported by the NIH/NHLBI grants HL-47317, HL-47323, HL-47327 and HL-47321) for their contributions to the data collection.

HPFS (Health professional follow-up study) / NHS (Nurses Heath Study) - The NHS Breast Cancer GW scan was performed as part of the Cancer Genetic Markers of Susceptibility initiative of the NCI. The current research is supported by CA 40356 and U01-CA98233 from the National Cancer Institute. We particularly acknowledge the contributions of R. Hoover, A. Hutchinson, K. Jacobs and G. Thomas. The NHS/HPFS type 2 diabetes GWAS (U01HG004399) is a component of a collaborative project that includes 13 other GWAS funded as part of the Gene Environment-Association Studies (GENEVA) under the NIH Genes, Environment and Health Initiative (GEI) (U01HG004738, U01HG004422, U01HG004402, U01HG004729, U01HG004726, 01HG004735, U01HG004415, U01HG004436, U01HG004423, U01HG004728 and AHG006033); with additional support from individual NIH Institutes (NIDCR: U01DE018993 and U01DE018903; NIAAA: U10AA008401; NIDA: P01CA089392 and 01DA013423; and NCI: CA63464, CA54281, CA136792 and Z01CP010200). Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the GENEVA Coordinating Center (U01HG004446). Genotyping was performed at the Broad Institute of MIT and Harvard, with funding support from the NIH GEI (U01HG04424); and Johns Hopkins University Center for Inherited Disease Research, with support from the NIH GEI (U01HG004438); and the NIH contract "High throughput genotyping for studying the genetic contributions to human disease" (HHSN268200782096C). Additional funding for the current research was provided by the National Cancer Institute (NCI: P01CA087969 and P01CA055075); and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK: R01DK058845). The NHS/HPFS CHD GWAS was supported by HL35464, HL34594, CA87969 and CA55075 from the National Institutes of Health, with additional support for genotyping from Merck/Rosetta Research Laboratories, North Wales, PA. The NHS/HPFS Kidney GWAS was supported by NIDDK: 5P01DK070756. We acknowledge

the study participants in the HPFS and NHS for their contribution in making this study possible.

Hypergenes (Hypergenes Study) - HYPERGENES (funded by EU within FP7, HEALTH-F4-2007-201550). To HYPERGENES consortium took part: 1) University of Milano with Daniele Cusi, Project Coordinator, Fabio Macciardi, Cristina Barlassina, Erika Salvi, Sara Lupoli, Federica Torri, Maurizio Marconi, Gianna Petrini, Vincenzo Toschi, Giancarlo Mariotti, Maurizio Turiel; 2) University of Leuven, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, with Robert Fagard, Yu Jin, Tatiana Kuznetsova, Tom Richart, Jan A. Staessen, and Lutgarde Thijs; 3) Jagiellonian University Medical College, Krakow, with Kalina Kawecka-Jaszcz, Katarzyna Stolarz-Skrzypek, Agnieszka Olszanecka, Wiktoria Wojciechowska, Małgorzata Kloch-Badełek; 4) IBM Israel – Science and Technology LTD, with Amnon Shabo, Ariel Frakash, Simona Cohen, Boaz Carmeli, Dan Pelleg, Michal Rosen-Zvi, Hani Neuvrith-Telem; 5) I.M.S. – Istituto di Management Sanitario S.r.l., Milan, with Pietro Conti, Costanza Conti, Mariella D'Alessio, Maurizio Mercurio; 6) Institute of Internal Medicine, Siberian Branch of Russian Academy of Medical Science, Novosibirsk, with Yuri Nikitin, Galina Simonova, Sofia Malyutina, Elena Pello; 7) Imperial College of Science, Technology and Medicine, with Paolo Vineis and Clive J Hoggart; 8) INSERM – Institut National de la Santé et de la Recherche Médicale U772, with Xavier Jeunemaitre, Pierre-François Plouin, Michel Azizi; 9) University of Warwick, Cardiovascular Medicine & Epidemiology Group, Clinical Sciences Research Institute, with Francesco P Cappuccio, Michelle A Miller, Chen Ji; 10) Hypertension and Related Disease Centre-AOU, University of Sassari, Sassari, with Nicola Glorioso, Giuseppe Argiolas, Francesca Fau, Silvia Pitzoi, Emanuela Bulla, Roberta Zaninello, Patrizia Bulla, Simone Fadda, Gianclaudia Cappai, Siria Motroni, Chiara Maria Troffa; 11) STMICROELECTRONICS SRL, with Tony Barbuzzi; 12) Universite de Lausanne. Department of Medical Genetics, with Carlo Rivolta, Jacques S. Beckmann, Zoltan Kutalik, Paola Benaglio, Sven Bergmann, Murielle Bochud, Diana Marek; 13) Pharnext S.A.S., Paris, with Daniel Cohen and Ilya Chumakov; 14) Softeco Sismat Spa, Genova, with Stefano Bianchi; 15) Shanghai Institute of Hypertension, with Jiguang Wang and Li Yan; 16) Charles University in Prague. Department of Internal Medicine II, Pilsen, with Jan Filipovsky, Jitka Seidlerova, Otto Mayer Jr., Milena Dolejsova, Jana Hirmerova, Jana Strizova; 17) University of Padova, Department of Clinical and Experimental Medicine, with Valérie Tikhonoff; 18) Medical University of Gdansk, Hypertension Unit, Department of Hypertension and Diabetology, with Krzysztof Narkiewicz, Marzena Chrostowska, Wojciech Sakiewicz, Michal Wojtowicz, Michal Hoffmann; and 19) University Vita-Salute San Raffaele, with Paolo Manunta, Chiara Lanzani, Maria Teresa Sciarrone, Lorena Citterio, Laura Zagato, Giuseppe Bianchi; 20) and Catholic University, Campobasso, with Licia Iacoviello. Regarding the present work, cases and controls were recruited within specific cohorts/networks: FLEMENGHO/EPOGH cohort (Coordinator J Staessen, contributors Units 2,3,6,16,17,18); Wandsworth Heart & Stroke Study (WHSS, Coordinator F Cappuccio); Milano-Sassari cohort (coordinator D Cusi); SOPHIA cohort (coordinator N Glorioso); IMMIDIET cohort (coordinator L Iacoviello).

InCHIANTI (InCHIANTI Study) - The InCHIANTI baseline study (1998-2000) was supported as a "targeted project" (ICS110.1/RF97.71) by the Italian Ministry of Health (ICS110·1/RF97·71) and in part by the U.S. National Institute on Aging (Contracts: 263 MD 9164 and 263 MD 821336).

KORA (Kooperative Gesundheitsforschung in der Region Augsburg) - The KORA Augsburg studies were financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany; and supported by grants from the German Federal Ministry of Education and Research (BMBF); and by the State of Bavaria. Part of this work was financed by the German National Genome Research Network (NGFN-2 and NGFN-plus); the German National Competence network on atrial fibrillation (AFNET); and the Bioinformatics for the Functional Analysis of Mammalian Genomes program (BFAM) by grants to Stefan Kääb [NGFN 01GS0499, 01GS0838 and

AF-Net 01GI0204/N], Anette Peters [NGFN 01GR0803, 01GS0834 and 01EZ0874], H-Erich Wichmann [NGFN 01GI0204] and to Thomas Meitinger [NGFN 01GR0103]. Stefan Kääb is also supported by a grant from Fondation Leducq. Furthermore, this research was supported within the Munich Center of Health Sciences (MC Health) as part of LMUinnovativ.

Korcula (CROATIA-Korcula) - The KORCULA study was funded by grants from the Medical Research Council (UK); European Commission Framework 6 project EUROSPAN (Contract No. LSHG-CT-2006-018947); and Republic of Croatia Ministry of Science, Education and Sports research grants to Igor Rudan (108-1080315-0302). We would like to acknowledge the staff of several institutions in Croatia that supported the field work, including but not limited to The University of Split and Zagreb Medical Schools and Croatian Institute for Public Health. The SNP genotyping for the KORCULA cohort was performed in Helmholtz Zentrum München, Neuherberg, Germany.

LifeLines (LifeLines Study) – 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. We thank Behrooz Alizadeh, Annemieke Boesjes, Marcel Bruinenberg, Noortje Festen, Ilja Nolte, Lude Franke, Mitra Valimohammadi for their help in creating the GWAS database, and Rob Bieringa, Joost Keers, René Oostergo, Rosalie Visser, Judith Vonk for their work related to data-collection and validation. The authors are grateful to the study participants, the staff from the LifeLines Cohort Study and Medical Biobank Northern Netherlands, and the participating general practitioners and pharmacists. LifeLines Scientific Protocol Preparation: Rudolf de Boer, Hans Hillege, Melanie van der Klauw, Gerjan Navis, Hans Ormel, Dirkje Postma, Judith Rosmalen, Joris Slaets, Ronald Stolk, Bruce Wolffenbuttel; LifeLines GWAS Working Group: Behrooz Alizadeh, Marike Boezen, Marcel Bruinenberg, Noortje Festen, Lude Franke, Pim van der Harst, Gerjan Navis, Dirkje Postma, Harold Snieder, Cisca Wijmenga, Bruce Wolffenbuttel. Statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org), which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003); along with a supplement from the Dutch Brain Foundation and the VU University Amsterdam.

Lolipop (London Life Sciences Prospective Population Cohort) - The LOLIPOP study is supported by the National Institute for Health Research Comprehensive Biomedical Research Centre Imperial College Healthcare NHS Trust; the British Heart Foundation (SP/04/002); the Medical Research Council (G0700931); the Wellcome Trust (084723/Z/08/Z); and the National Institute for Health Research (RP-PG-0407-10371). Paul Elliot is an NIHR Senior Investigator. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. We thank the participants and research staff who made the study possible.

MESA (The Multi-Ethnic Study of Atherosclerosis) - MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support is provided by grants and contracts N01 HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, and RR-024156. MESA Air is conducted and supported by the United States Environmental Protection Agency (EPA); in collaboration with MESA Air investigators. Support is provided by grant RD83169701. Funding for SHARe genotyping was provided by NHLBI Contract N02-HL-6-4278.

MICROS (the Micros Study) - The MICROS study in South Tyrol was supported by the Austrian Ministry of Health and Department of Educational Assistance; University and Research of the Autonomous Province of Bolzano; and the South Tyrolean Sparkasse Foundation.

NBS (Nijmegen Biomedical Study) – The Nijmegen Biomedical Study (NBS) was initiated in 2000 as a large survey among the inhabitants of the municipality of Nijmegen by the departments of Epidemiology, Biostatistics and HTA, Clinical Chemistry, and Endocrinology of the Radboud University Nijmegen Medical Centre (RUNMC) in collaboration with the municipality of Nijmegen and the community health service of Nijmegen. Support was obtained from RUNMC. The measurements of heart rate (and other non-invasive measurements of atheroscloris (NIMA)) was supported by Grant 2003B057 of the Netherlands Heart Foundation. The genotyping was supported by deCODE Genetics, a biotechnology company in Iceland.

NESDA (Netherlands Study of Depression and Anxiety) - NESDA was supported by the Geestkracht program of ZonMW [grant 10-000-1002]; matching funds from universities and mental health care institutes involved in NESDA (GGZ Buitenamstel-Geestgronden, Rivierduinen, University Medical Center Groningen, GGZ Lentis, GGZ Friesland, GGZ Drenthe). Genotyping was funded by the Genetic Association Information Network (GAIN) of the Foundation for the US National Institutes of Health, and analysis was supported by grants from GAIN and the NIMH (MH081802). Genotype data were obtained from dbGaP (http://www.ncbi.nlm.nih.gov/dbgap, accession number phs000020.v1.p1).

NFBC1966 (Northern Finland Birth Cohort 1966) - Financial support was received from the Academy of Finland (project grants 104781, 120315 and Center of Excellence in Complex Disease Genetics); University Hospital Oulu; Biocenter, University of Oulu, Finland; the European Commission (EURO-BLCS, Framework 5 award QLG1-CT-2000-01643); NHLBI grant 5R01HL087679-02 through the STAMPEED program (1RL1MH083268-01); NIH/NIMH (5R01MH63706:02); ENGAGE project and grant agreement HEALTH-F4-2007-201413; and the Medical Research Council (studentship grant G0500539). The DNA extractions, sample quality controls, biobank up-keeping and aliquotting was performed in the National Public Health Institute, Biomedicum Helsinki, Finland and supported financially by the Academy of Finland and Biocentrum Helsinki. We thank Professor Paula Rantakallio (launch of NFBC1966 and 1986), Ms Outi Tornwall and Ms Minttu Jussila (DNA biobanking).

NHS (Nurses Health Study) – see HPFS.

NSHD (1946 British Birth Cohort) - NSHD is supported by the Medical Research Council Unit for Lifelong and Healthy Ageing (G0701044). The generation and preparation of Metabochip genotype data was supported by the Medical Research Council Epidemiology Unit through Medical Research Council Intramural funding and project funding (G0701863). We are grateful to NSHD study members who took part in this data collection for their continuing support.

NSPHS06 (Northern Swedish Population Health Study 2006) - The Northern Swedish Population Health Study (NSPHS) was funded by the Swedish Medical Research Council (project number K2007-66X-20270-01-3); and the Foundation for Strategic Research (SSF). The NSPHS as part of EUROSPAN (European Special Populations Research Network) was also supported by European Commission FP6 STRP grant number 01947 (LSHG-CT-2006-01947). This work was also supported by the Swedish Society for Medical Research (Åsa Johansson). The computations were performed on UPPMAX (http://www.uppmax.uu.se) resources under project p2008027. The authors are grateful for the contribution of district nurse Svea Hennix for data collection and Inger Jonasson for logistics and coordination of the health survey. Finally, the authors thank all the community participants for their interest and willingness to contribute to the study.

NTR (Netherlands Twin Registry) - Funding was obtained from the Netherlands Heart Foundation (90.313, 86.083 and 88.042); the Netherlands Organization for Scientific Research (NWO: MagW/ZonMW); Genetic basis of anxiety and depression (904-61-090); Genetics of individual differences in smoking initiation and persistence (NWO 985-10-002); Resolving cause and effect in the association between exercise and well-being (904-61-193); Twin family database for behavior genomics studies (480-04-004); Twin research focusing on behavior (400-05-717); Genetic determinants of risk behavior in relation to alcohol use and alcohol use disorder (Addiction-31160008); Genotype/phenotype database for behavior genetic and genetic epidemiological studies (911-09-032); Spinozapremie (SPI 56-464-14192); CMSB: Center for Medical Systems Biology (NWO Genomics); NBIC/BioAssist/RK/2008.024); BBMRI –NL: Biobanking and Biomolecular Resources Research Infrastructure; the VU University: Institute for Health and Care Research (EMGO+); Neuroscience Campus Amsterdam (NCA); the European Science Foundation (ESF): Genomewide analyses of European twin and population cohorts (EU/QLRT-2001-01254); European Community's Seventh Framework Program (FP7/2007-2013): ENGAGE (HEALTH-F4-2007-201413); the European Science Council (ERC) Genetics of Mental Illness (230374); Rutgers University Cell and DNA Repository cooperative agreement (NIMH U24 MH068457-06); Collaborative study of the genetics of DZ twinning (NIH R01D0042157-01A); and the Genetic Association Information Network, a public–private partnership between the NIH and Pfizer Inc., Affymetrix Inc. and Abbott Laboratories.

ORCADES, CHARGE (Orkney Complex Disease Study) - ORCADES was supported by the Chief Scientist Office of the Scottish Government; the Royal Society; the Medical Research Council (MRC) Human Genetics Unit and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). DNA extractions were performed at the Wellcome Trust Clinical Research Facility in Edinburgh. We would like to acknowledge the invaluable contributions of Lorraine Anderson and the research nurses in Orkney, the administrative team in Edinburgh and the people of Orkney.

PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) - Genotyping was performed by the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se). We thank Tomas Axelsson, Ann-Christine Wiman and Caisa Pöntinen for their excellent assistance with genotyping. The SNP Technology Platform is supported by Uppsala University, Uppsala University Hospital and the Swedish Research Council for Infrastructures. Erik Ingelsson and Ci Song are supported by grants from the Swedish Research Council; the Swedish Heart-Lung Foundation; the Swedish Foundation for Strategic Research; and the Royal Swedish Academy of Science.

PREVEND (Prevention of Renal and Vascular End-stage Disease) - PREVEND genetics is supported by the Dutch Kidney Foundation (Grant E033); the EU project grant GENECURE (FP-6 LSHM CT 2006 037697); the National Institutes of Health (grant LM010098); The Netherlands organization for health research and development (NWO VENI grant 916.761.70); and the Dutch Inter University Cardiology Institute Netherlands (ICIN).

RISC (Relationship between Insulin Sensitivity and Cardiovascular Disease Study) - The RISC Study was supported by European Union grant QLG1-CT-2001-01252; AstraZeneca; and Merck and Co, Inc. Weijia Xie was funded by a Diabetes UK Arthur and Sadie Pethybridge Studentship.

RRgen consortium – Acknowledgments of the studies included in the RRgen consortium (AGES, ARIC, CHS, FHS, KORA, MICROS, ORCADES, RS1-2, SardiNIA, SHIP and Twins UK) are provided for each study separately.

RS1-3 (Rotterdam Study I - III) – The generation and management of GWAS genotype data for the Rotterdam Study is supported by the Netherlands Organisation of Scientific Research NWO Investments [grant 175.010.2005.011, 911-03-012]. This study is funded by the Research Institute for Diseases in the Elderly [014-93-015, RIDE2]; and the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for

Scientific Research (NWO) [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. The Rotterdam Study used resources from the National German MediGRID and Services@MediGRID part of the German D-Grid, both funded by the German Bundesministerium fur Forschung und Technology [grant #01 AK 803 A-H, # 01 IG 07015]. This work was also supported by the Netherlands Heart Foundation (NHF) [2007B221 and 2009R014 to Mark Eijgelsheim].

SardiNIA - The SardiNIA team was supported by the National Institute on Aging [contract NO1-AG-1-2109] from and in part by the Intramural Research Program of the National Institutes of Health, National Institute on Aging. We would like to thank the Sardinian volunteers who generously supported the SardiNIA study and made it possible. We also acknowledge the support of the administration of Lanusei, Ilbono, Arzana and Elini (Sardinia, Italy).

SHIP (Study of Health in Pomerania) - SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research [grants 01ZZ9603, 01ZZ0103 and 01ZZ0403], the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg - West Pomerania. Generation of genome-wide data has been supported by the Federal Ministry of Education and Research [grant 03ZIK012] and a joint grant from Siemens Healthcare, Erlangen, Germany and the Federal State of Mecklenburg-West Pomerania. The University of Greifswald is a member of the 'Center of Knowledge Interchange' program of the Siemens AG.

Split (CROATIA-Split) - The SPLIT study is funded by grants from the Medical Research Council (UK); and Republic of Croatia Ministry of Science, Education and Sports research grants to Igor Rudan (108-1080315-0302). We would like to acknowledge the staff of several institutions in Croatia that supported the field work, including but not limited to The University of Split and Zagreb Medical Schools and Croatian Institute for Public Health. The SNP genotyping for the SPLIT cohort was performed by AROS Applied Biotechnology, Aarhus, Denmark.

Stanford IST cohort (Stanford Study) - The genotyping for the STANFORD IST study was supported by a grant from Merck & Co. Inc. Weijia Xie was funded by a Diabetes UK Arthur and Sadie Pethybridge Studentship.

STR (Swedish Twin Registry) - This work was supported by grants from the US National Institutes of Health (AG028555, AG08724, AG04563, AG10175 and AG08861); the Swedish Research Council; the Swedish Heart-Lung Foundation; the Swedish Foundation for Strategic Research; the Royal Swedish Academy of Science; and ENGAGE (within the European Union Seventh Framework Programme, HEALTH-F4-2007-201413). Genotyping was performed by the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se). We thank Tomas Axelsson, Ann-Christine Wiman and Caisa Pöntinen for their excellent assistance with genotyping. The SNP Technology Platform is supported by Uppsala University; Uppsala University Hospital; and the Swedish Research Council for Infrastructures.

Twins UK, CHARGE (Twins UK Study) - Twins UK was funded by the Wellcome Trust; European Community's Seventh Framework Programme (FP7/2007-2013) [grant HEALTH-F2-2008-201865-GEFOS] and (FP7/2007-2013) [ENGAGE grant HEALTH-F4-2007-201413] and the FP-5 GenomEUtwin Project (QLG2-CT-2002-01254). The study also receives support from the Dept. of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London. The project also received support from a Biotechnology and Biological Sciences Research Council (BBSRC) project [grant G20234]. Analyses were performed on the Genetic Cluster

Computer, which is financed by an NWO Medium Investment [grant 480-05-003] and by the Faculty of Psychology and Education of the VU University, Amsterdam, The Netherlands.

ULSAM (Uppsala Longitudinal Study of Adult Men) - Genotyping was performed by the SNP&SEQ Technology Platform in Uppsala (www.genotyping.se). We thank Tomas Axelsson, Ann-Christine Wiman and Caisa Pöntinen for their excellent assistance with genotyping. The SNP Technology Platform is supported by Uppsala University; Uppsala University Hospital; and the Swedish Research Council for Infrastructures. Erik Ingelsson and Ci Song are supported by grants from the Swedish Research Council; the Swedish Heart-Lung Foundation; the Swedish Foundation for Strategic Research; and the Royal Swedish Academy of Science.

Whitehall II (Whitehall II Study) - The work on Whitehall II was supported by the BHF (PG/07/133/24260, RG/08/008, SP/07/007/23671); and a Senior Fellowship to Professor Hingorani (FS/2005/125). Meena Kumari's and Mika Kivimaki's time on this manuscript was partially supported by the National Heart Lung and Blood Institute (NHLBI: HL36310). The Whitehall II study has been supported by grants from the Medical Research Council; British Heart Foundation; Health and Safety Executive; Department of Health; National Institute on Aging (AG13196); US, NIH; Agency for Health Care Policy Research (HS06516); and the John D and Catherine T MacArthur Foundation Research Networks on Successful Midlife Development and Socio-economic Status and Health.

YFS (Young Finns Study) – The Young Finns Study has been financially supported by the Academy of Finland: grants 126925, 121584, 124282, 129378, 117787 and 41071; The Social Insurance Institution of Finland; Kuopio, Tampere and Turku University Hospital Medical Funds; Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation of Cardiovascular Research and Finnish Cultural Foundation; Tampere Tuberculosis Foundation; and Emil Aaltonen Foundation. The expert technical assistance in data management and statistical analyses by Irina Lisinen and Ville Aalto are gratefully acknowledged.

***Drosophila melanogaster* experiments** – Bianca Brundel received funding from the European Community; European Fund for Regional Development (Operationeel Programma Noord-Nederland 2007-2012, OP-EFRO); the Province of Groningen; and the Innovative Action-program Groningen (IAG3). Ody Sibon received a VICI Grant from the NOW (865.10.012).

***Danio rerio* experiments** – The zebrafish experiments were financed using NIH grants awarded to David Milan (HL109004, DA026982) and Jodan T Shin (HL085280).

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