Shared Genetic Predictors of Resting Heart Rate and All-Cause Mortality

ABSTRACT

Background

Resting heart rate is a heritable trait correlated with lifespan. Little is known about the genetic contribution of resting heart rate and its relationship with mortality.

Methods

We performed a genomewide association analysis of 19.9 million genetic variants in 134,251 individuals from UK Biobank to further our understanding of the genetic basis of resting heart rate. We then used the identified genetic variants as an instrument to study the association between resting heart rate, cardiovascular risk factors and all-cause mortality.

Results

Genomewide association analysis identified 78 loci associated with resting heart rate ($P<5\times10^{-8}$), 60 of these were novel. An increase in genetically predicted resting heart rate of 5 beats per minute was associated with a 19% increased mortality risk (hazard ratio 1.19, 95% CI of 1.11-1.28, $P=1.09\times10^{-6}$) translating to a 2.8 years reduction in life expectancy for males and 2.5 years for females. Genetically predicted resting heart rate was found to be associated with higher body-mass index and diastolic blood pressure, hypertension, diabetes, smoking, myocardial infarction, heart failure, supraventricular tachycardia, beta-blockers, calcium channel-blockers and device implantation (all $P<0.05$). However, we did not identify such factors as mediators on the causal pathway between resting heart rate and all-cause mortality. Candidate gene and pathway analyses provide strong support for a dominant role of cardiac development and structure.

Conclusion

We discovered 60 novel loci for resting heart rate. These provide evidence for shared genetic predictors of resting heart rate and all-cause mortality.

Among mammals, there exists an inverse semi-logarithmic relation between resting heart rate and life expectancy with only the human species deviating from this line[1,2]. In humans, resting heart rate is a well-established predictor of overall mortality in the general population[3-8], as well as in patients with hypertension[9], coronary artery disease (CAD)[10], and heart failure[11]. The association of heart rate with life expectancy or risk does not provide sufficient evidence for a shared or causal relationship. Heart rate is regulated by complex interactions of biological systems, including the autonomous nervous and hormonal systems[12]. In addition, resting heart rate is associated with many other cardiovascular risk factors, including blood pressure, smoking, glucose metabolism, lipids, C-reactive protein, metabolic syndrome, body mass index, and diabetes mellitus[13-16]. In some conditions, including heart failure, reduction of heart rate has been directly demonstrated to lead to event reduction providing evidence that heart rate is indeed a modifiable causal risk factor and not just a risk marker or a reflection of comorbidities[11]. However, in patients with CAD and hypertension, β-adrenergic receptor-blocking agent (beta-blockers) were not associated with lower risk of cardiovascular events beyond its effect on blood pressure[17,18], in patients with permanent atrial fibrillation, lenient rate control is as effective as strict rate control[19], and heart rate reduction with ivabradine did not improve outcomes in patients with CAD[20] but in patients with heart failure it did[21]. A mechanistic explanation linking higher resting heart rate with increased mortality remains enigmatic. To further our knowledge on genes influencing resting heart rate we performed a genomewide association study on 134,251 participants from UK Biobank[22]. Using the identified genetic variants (GVs) as instrumental variables we explored the relationship between resting heart rate with cardiovascular risk factors, comorbidities and fatal and non-fatal outcomes. Bioinformatic analyses of associated variants were also undertaken to identify potential biological pathways and mechanisms.

Methods

UK Biobank individuals

To identify GVs associated with resting heart rate we analyzed 134,251 participants from the UK Biobank cohort. The UK Biobank recruited persons aged 40 - 69 years who were registered with a general medical practitioner within the UK National

Health Service (NHS). In total, the study recruited 503,325 individuals between 2006 and 2010. The study has approval from the North West Multi-centre Research Ethics Committee, and all participants provided informed consent. Detailed methods used by UK Biobank have been described elsewhere[22]. For sensitivity analyses we defined a subgroup of healthy individuals which were free of any (prevalent or incident) disease(s) and diagnosis and confirmed they were not using heart rate modifying medication (beta-blockers, and calcium-channel blockers drugs (N=11,405)).

Ascertainment of resting heart rate

As detailed in the **Supplemental Methods**, resting heart rate was assessed by two methods: using an automated reading during blood pressure (in 501,340 participants) and during arterial stiffness measurement using the pulse waveform obtained of the finger with an infrared sensor (in 170,790 participants). Multiple available measurements for one individual were averaged.

Ascertainment of cardiovascular events and mortality

The prevalence and incidence of cardiovascular risk factors, conditions and events were captured through data collected at the Assessment Centre in-patient Health Episode Statistics (HES) as detailed in the **Supplementary Methods**. Information on the cause of death was obtained via the National Health Service (NHS) Information Centre for participants from England and Wales, and from the NHS Central Register, Scotland for participants from Scotland. All-cause mortality included all deaths occurring before February 17th 2014 (or December 31st 2012, for the participants enrolled in Scotland).

Genotyping and Imputation

Genotype imputation data was available for 152,249 (25%) individuals as of May 2015 [Interim Data Release]. In 49,923 individuals genotyping was performed as part of the UK Biobank Lung Exome Variant Evaluation (UK BiLEVE) project and in an additional 102,326 individuals genotyping was performed on the UK Biobank Axiom array (Affymetrix). Imputed genotype data was provided by UK Biobank based on merged UK10K and 1000 Genomes Phase 3 panel produced by the Wellcome Trust Centre for Human Genetics resulting in 72,355,667 single nucleotide polymorphisms, short indels and large structural variants. Quality control for genotyping has been

performed prior to analysis and described in detail elsewhere[23]. We excluded variants with minor allele frequency of <0.001, and information measure <0.3 leaving 19,941,912 variants for the current analyses. Samples were excluded from our analyses if they had at least one related sample (N=17,308) based on genetic relatedness factor data, and high missingness or excess heterozygosity (N=480).

Statistical Analysis

A genomewide association study (GWAS) was performed using SNPTEST with 19,941,912 genotyped or imputed genetic variants and resting heart rate in 134,251 individuals using linear regression assuming an additive genetic model. Covariates included in the model were: age, age^2, sex, the first 10 principal components, and genotyping array. To declare novel loci we applied the genomewide significance threshold of $P<5\times10^{-8}$. Independent genetic loci were defined as 1Mb at either side of the GV that showed the strongest association in a given locus. The strongest associated variant (lowest *P*-value) within a locus was designated the sentinel GV. We repeated the GWAS additionally including all sentinel GVs ($P<5\times10^{-8}$) as covariates in a conditional analysis to detect secondary associations not explained by the sentinel SNP at each locus. Potential modifier effects of gender, β-adrenergic receptor-blocking agent (beta-blockers), and calcium-channels blockers drugs on resting heart rate were assessed by an interaction test (Bonferroni adjusted for the number (*n*) of tests ($P<0.05/n$)).

We used GVs as instrumental variables to study the relationship of resting heart rate with outcomes (Mendelian Randomization). To this end we defined a larger set of independent loci at the previously specified hypothesis-generating threshold ($P<1\times10^{-5}$) in order to increase power[24,25]. For our main analysis we calculated β_3 values (the putative association between resting heart rate (per 5 beats per minute (bpm) and outcome mediated through that variant) from the direct measurements of β_1 (the effect size of the association between the variant and resting heart rate) and β_2 (the effect size of the association between the variant and outcome), as described previously[26]. The value of β_3 can be interpreted as the hazard ratio for outcome per 5 bpm increase in genetically determined resting heart rate. Inverse-variance-weighted random-effects meta-analysis was used to combine individual β_3 estimates providing additional power to assess the overall association between genetically determined resting heart rate and mortality. Cochran's Q

statistic was used to assess heterogeneity among β_3 estimates. We also created a weighted genetic risk score (GRS) by summing the number of resting heart rate-increasing alleles weighted for its β_1 of each associated GV. An unweighted GRS was created by summing the number of resting heart rate-increasing alleles 0-2 of each associated GV. We estimated the impact on life expectancy using the National Life Tables of the United Kingdom provided by the Office of National Statistics (ONS; www.ons.gov.uk) of 2011-2013 separately for males and females (**Supplemental Methods**).

To examine the robustness of our findings as well as the possibility of pleiotropic or other confounding and mediation effects we included covariates and the phenotype resting heart rate into the Cox regression models. We excluded all GVs that were also individually nominally associated (P<0.05) with covariates, and performed multivariable Mendelian randomization[27] to account for variables not available in UK Biobank, and used the MR-Egger regression method to test for evidence of pleiotropy[28] (details provided in **Supplementary Methods**). As an alternative strategy to exclude confounding due to prevalent disease or medication use, we estimated the associations of each GV with resting heart rate (β_1) in the subgroup of 11,405 healthy individuals (defined above) to calculate the hazard ratio for outcome.

Details of analyses performed to gain insights in the biological pathways and tissues underlying the genomewide significant loci are provided in the **Supplementary Methods**.

Results

UK Biobank participants

We studied 134,251 individuals participating in UK Biobank. The average age was 56.6 years (interquartile range [IQR] 50 to 63), and 47.2% of the participants were male. Baseline characteristics are presented in **Table 1**. The median duration of follow-up for mortality was 4.9 years (IQR 4.3 to 5.5 years).

Genetic variants associated with resting heart rate

We identified GVs at 78 loci associated with resting heart rate at $P<5\times10^{-8}$ (**Figure 1, Supplementary Table 1, Supplementary Figure 1**), including 18 (of 21) previously reported and 60 novel loci[29]. Two previously identified loci were nominally significant ($P<0.001$)[29]. The GVs at the 78 loci were well imputed with an info >0.9 except one (rs11183443) which had an information measure of 0.30. At 11 loci we found evidence for multiple independent associations with resting heart rate in conditional analyses (**Supplementary Table 2**). As expected, the magnitudes of the associations were small and ranged from 0.2 to 1.2 bpm per effect allele. Collectively, the total variance explained by the 78 loci for resting heart rate was 3.3%.

Effects of gender, beta-blockers and calcium-channel blockers

We studied the potential modifying effect of gender, beta-blockers and calcium-channel blockers on the association of GVs on resting heart rate but did not observe any significant interactions (**Supplementary Table 3**).

Resting heart rate associated variants and cardiovascular profile

We summed the number of resting heart rate increasing alleles weighted for the strength of the association of all loci to create a weighted GRS for each individual (**Supplementary Figure 2**), and evaluated associations with cardiovascular measures. Genetically determined higher resting heart rate was associated with higher body-mass index and diastolic blood pressure and higher odds of having hypertension, diabetes, active smoking behavior, experiencing supraventricular tachycardias, calcium channel-blockers usage and lower odds of myocardial infarction, beta-blocker usage and device implantation (all $P<0.05$; **Table 2, Supplementary Table 4**).

Genetic variants of resting heart rate are associated with mortality

In a random-effects meta-analysis of the GV-specific β_3 (the putative association between resting heart rate and outcome mediated through that variant) of all hypothesis generating loci ($P<1\times10^{-5}$) we observed a significant association between GVs associated with resting heart rate and all-cause mortality translating to a relative increase of 19%) in all-cause mortality risk per 5 bpm increase of resting heart rate (**Table 3**, **Supplementary Figure 3**). When restricting the number of GVs stepwise from $P<5\times10^{-5}$ to $P<5\times10^{-8}$ the hazard ratio reduced, as expected, but continued to remain significant (**Table 3**). Next we calculated weighted and unweighted GRS and found similar associations with all-cause mortality (**Table 3**). The Kaplan-Meier failure curves for all-cause mortality are shown in **Figure 2**. There was no specific cause of death driving the association (**Supplementary Table 5**). We extrapolated a relative risk of 1.19 to life expectancy using the National Life Tables of the United Kingdom and estimated a reduction of 2.8 years for males and 2.5 years for females per 5 bpm increase in resting heart rate.

Potential interpretations of the association with mortality

A conceptual figure of the potential explanations of the observed association between GVs of heart rate and outcome is provided as **Supplementary Figure 4**. We performed several analyses to test for pleiotropic effects, identify confounders and mediators. First, we ruled out the possibility that extreme associations drive the genetic association with all-cause mortality by repeating the meta-analysis without the 12 GV's that each showed an association with mortality at $P<0.05$ (**Table 3**). Second, we adjusted for resting heart rate in the Cox regression model predicting all-cause mortality. The association of the GVs with all-cause mortality was abolished suggesting the genetic association is mediated via resting heart rate (**Table 3**). Next, we adjusted for covariates observed to be associated with the identified GVs in UK Biobank (**Table 3**). Introducing baseline body-mass index, diastolic blood pressure, hypertension, diabetes, active smoking, a history of heart failure, supraventricular tachycardias, myocardial infarction, device implantation, beta-blockers and calcium channel-blockers did not affect the association between the GVs for heart rate and all-cause mortality (**Table 3**). Also when we excluded all GVs that individually showed nominal association ($P<0.05$) with any of significant variables in **Table 2** the association between the GVs for heart rate and all-cause mortality remained

significant. Next we considered potential confounders of variables not currently available in the UK Biobank cohort and performed multivariable Mendelian randomization to adjust for lipids (LDL, HDL, Total Cholesterol, Triglycerides) and red blood cell (RBC, PCV, MCV, and Hb) variables. The adjustments did not attenuate the association of the heart rate GVs with all-cause mortality (**Table 3**). The results of the MR-Egger method confirmed the absence of evidence for directional (unbalanced) pleiotropy (**Table 3**). Also when using GV coefficients derived from the associations with resting heart rate when restricted to healthy individuals (**Table 1**) the prediction of all-cause mortality remained similar (**Table 3**) further supporting the notion that underlying diseases or heart-rate lowering medication has not confounded our observation.

Biological insights

At 20 of our 78 loci the sentinel GV or a GV in high correlation (r^2 >0.8) have reported GWAS associations. These include: lipid, metabolic and blood pressure related traits (**Supplementary Table 6**). Our 78 loci were highly enriched for deoxyribonuclease I (DNase I) hypersensitive sites, marking transcriptionally active regions of the genome in human fetal heart tissue (**Figure 3A**). Enrichment testing of expression in 209 tissue and cell types identified cardiovascular tissues and the adrenal gland to be the most relevant for our association findings (**Figure 3B, Supplementary Table 7**). Across the 78 loci, 1,967 annotated genes are located within 1 Mb of all the sentinel GVs. Based on proximity, the presence of non-synonymous GVs in high linkage disequilibrium (LD), cis-expression quantitative trait loci (eQTL) and Data-driven Expression-Prioritized Integration for Complex Traits (DEPICT)[30] analyses we prioritized 123 potential candidate genes at our 78 loci (**Supplementary Note, Supplementary Tables 8-10**). A systematic search of our 123 candidate genes in Online Mendelian Inheritance in Man (OMIM) identified several Mendelian diseases with cardiac phenotypes. These were related to cardiomyopathies (*TTN, DES, SCN5A, DSP, PLN, MYH6, MYH7, SPEG*), Brugada syndrome (*SCN5A, CACNA1C, HCN4*), Long QT (*SCN5A, KCNJ5, ALG10*), arrhythmias (*SCN5A, HCN4, CACNA1D, MYH6*) and congenital heart disease (*NKX2-5, GATA6, PLN, TBX20, MYH6, MYH7*). The DEPICT tool identified 622 significantly (FDR<5%) enriched gene sets (**Supplementary Tables 11-12**). We clustered them on the basis of the correlation between scores for all genes

(**Supplementary Note**) resulting in 74 gene sets relevant to cardiac biology (**Figure 3C**).

Discussion

This work highlights the unprecedented opportunities provided by large scale projects such as UK Biobank, the 100,000 genomes[31], and the Precision Medicine Initiative[32] to discover novel genetic associations and to study links with outcomes and mortality. In this GWAS, performed in 134,251 participants from UK Biobank, we confirmed 20 and found 60 novel genetic loci associated with resting heart rate[29]. Several epidemiologic studies have reported an association between higher resting heart rate and increased mortality from both cardiovascular and non-cardiovascular causes[3-8]. In all of these studies, this association is potentially confounded by differences in demographics and physiological characteristics such as body-mass index, smoking, alcohol consumption and blood pressure. Also data from intervention trials are not providing a consistent link with heart rate reduction and improvement of clinical outcomes. Selective sinus-node inhibition with ivabradine has beneficial effects on outcomes in patients with chronic heart failure[21] but did not improve outcomes in patients with CAD[20].

In the present work we show that genetic variants associated with higher resting heart rate confer a risk for all-cause mortality. A unique feature of the current study is the sample size in a single cohort, allowing us to directly study the associations of GVs with resting heart rate with mortality in the same participants. We did not need to use estimates obtained elsewhere and possibly subjected to certain biases (e.g. publication bias). We studied the strength of these GVs with mortality and studied the role of heart rate in comparison of other, potential confounding variables closely associated with heart rate. The identified GVs associated with heart rate were also associated with potential measured (body mass index, diastolic blood pressure, hypertension, diabetes, smoking, myocardial infarction, heart failure, supraventricular tachycardia, device implantation, beta-blockers and calcium channel-blockers) and unmeasured confounders. However, also our analyses adjusting for covariates, allowing GVs to have pleiotropic effects, removing GVs associated with other traits, or using estimates derived from healthy participants consistently suggest that heart rate is linked to mortality, and by extension life-expectancy. Indeed, only heart rate itself attenuated the association of the GVs with the outcome to the null. This leaves two likely possibilities. Either the GVs exert their effect on mortality directly via heart rate as a mediator or,

alternatively, the GVs share underlying biology resulting in both increased heart rate as well as increased mortality risk. While direct specific intervention (sinus node inhibition) on heart rate does not consistently result in reduction in mortality[20,21,33] we hypothesize the association originates from a shared biology not targeted by sinus node inhibition. This could involve basic cellular biology behind heart rate and possibly involve vulnerability to cardiac arrhythmias causing (sudden) death which might contribute to all classifications of death and might eventually be relevant for a plethora of also non-cardiac diseases and conditions. This theory can be supported by the identification of predominant cardiac candidate genes at the identified loci and the co-localization of DNase hypersensitivity sites in cardiac tissue. However, also alternative speculations involving basic metabolic rate, energetics, free radicals, could result in cumulative general damage and affect life span[34].

In addition to an interpretation of causation, there are several other limitations of our study that are important to acknowledge. Among the loci identified, a number of candidate genes have a known function relevant for cardiac conditions however, for none of the genes have we proven it is the mechanism for the association with heart rate. The candidate gene list only provides a first interpretation using arbitrarily defined guidelines used in the GWAS community to suggest genes for further evaluation. Also heart rate is a complex trait and the principal reason for genes to be associated does not necessarily imply a role via the cardiac pacemaker or sinus node function.

In conclusion, in this GWAS, we have identified 60 novel loci associated with resting heart rate. The identified loci influencing resting heart rate are also implicated in overall mortality (and consequently life expectancy) and therefore warrent further research into the underlying mechanisms.

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Conflict of Interest

None declared.

Figure legends

Figure 1. Genomewide $-\log_{10}$ *P*-value plot and effects for significant loci.
Genomewide $-\log_{10}$ *P*-value plots are shown for heart rate. GVs within loci reaching genomewide significance are labeled in blue when previously identified and red when novel (±1Mb of lowest *P*-value). The dashed line indicates the genomewide significance threshold ($P=5\times10^{-8}$). Candidate genes have been identified by one or multiple strategies; n=nearest; c=coding, non-synonymous variant; e=eQTL; d=DEPICT tool.

Figure 2. Kaplan-Meier failure curve death weighted GRS.
Shown are cumulative all-cause mortality in (%) divided by individuals below and above the median of the weighted Genetic Risk Score (GRS).

Figure 3. Biological insights (A) The 78 genomewide associated variants were enriched within DHSs of fetal heart tissue (n=12) specifically, suggesting that functionality of regulatory DNA elements may underlie some of the associations. **(B)** DEPICT identified statistically significant enrichment for 9 tissue annotations of which cardiovascular tissues were the most relevant for the heart rate associated loci. **(C)** DEPICT pathway analysis identified 623 significantly enriched gene-sets relevant for heart rate. The 74 meta-gene set clusters are shown.

Table 1. Baseline characteristics of participants

	All (N=134,251)	Healthy Individuals (N=11,405)
Age	56.6 (8.0)	53.7 (7.6)
Sex (Male)	63,349 (47.2%)	5,993 (52.5%)
Body-mass index	27.5 (4.8)	26.3 (4.0)
Resting heart rate	69.5 (11.1)	68.3 (10.5)
Blood pressure		
Systolic	138.0 (18.6)	135.5 (17.7)
Diastolic	82.3 (10.1)	81.6 (9.8)
Smoking current	16,708 (12.4%)	1,390 (8.3%)
Medical History		
Hypertension	38,339 (28.6%)	0 (0%)
Diabetes	7,419 (5.5%)	0 (0%)
Myocardial Infarction	3,395 (2.5%)	0 (0%)
Heart failure	720 (0.5%)	0 (0%)
Atrial fibrillation / flutter	2,048 (1.5%)	0 (0%)
Supraventricular tachycardia	425 (0.3%)	0 (0%)
Device implantation	399 (0.3%)	0 (0%)
Medication		
Beta-blockers	9,526 (7.8%)	0 (0%)
Calcium channel-blockers	9,797 (8.0%)	0 (0%)

Table 2. Association between genetically determined heart rate and cardiovascular profile using a weighted GRS

	Participants (N= 134,251)	Estimated Association* (95% CI)	*P* value
Body-mass index	134,251 (100%)	0.23 (0.18 to 0.27)	1.90×10^{-24}
Blood pressure			
Systolic	134,217 (99%)	-0.04 (-0.20 to 0.11)	0.58
Diastolic	134,217 (99%)	0.99 (0.90 to 1.09)	1.57×10^{-103}
Hypertension	39,996 (29.8%)	1.07 (1.05 to 1.09)	1.04×10^{-10}
Diabetes	7,857 (5.9%)	1.12 (1.08 to 1.17)	7.67×10^{-9}
Smoking current	16,708 (12.4%)	1.07 (1.04 to 1.10)	5.36×10^{-7}
Myocardial Infarction	3,848 (2.9%)	0.94 (0.89 to 1.00)	0.03
Heart failure	1,131 (0.8%)	1.12 (1.01 to 1.24)	0.03
Atrial fibrillation / flutter	2,780 (2.1%)	0.98 (0.92 to 1.05)	0.61
Supraventricular tachycardia	546 (0.4%)	1.22 (1.06 to 1.41)	5.96×10^{-3}
Device implantation	482 (0.4%)	0.77 (0.66 to 0.90)	7.07×10^{-4}
Medication			
Beta-blockers	9,526 (7.8%)	0.95 (0.92 to 0.99)	0.01
Calcium channel-blockers	9,797 (8.0%)	1.08 (1.04 to 1.12)	2.83×10^{-5}

* The effect estimates with 95% Confidence Interval (CI) estimated using weighted GRS (per 5 bpm increase in resting heart rate) are shown as odds ratios for categorical variables (hypertension, diabetes, smoking current, myocardial infarction, heart failure, atrial fibrillation / flutter, supraventricular tachycardia, device implantation, beta-blockers and calcium-channel blockers) and β estimates for quantitative variables (body-mass index, systolic and diastolic blood pressure).

360 **Table 3. Association between genetically determined resting heart rate and all-cause mortality**

Association with mortality	Number of GV	Estimated Association HR* (95% CI)	*P* value
Standard MR with all			
GVs ($P<10^{-2}$)	1992	1.18 (1.14 to 1.23)	4.77×10^{-19}
GVs ($P<10^{-3}$)	1748	1.19 (1.14 to 1.23)	1.06×10^{-18}
GVs ($P<10^{-4}$)	851	1.18 (1.13 to 1.24)	1.47×10^{-11}
GVs ($P<10^{-5}$)	275	1.19 (1.11 to 1.28)	1.09×10^{-6}
GVs ($P<10^{-6}$)	123	1.14 (1.04 to 1.25)	3.95×10^{-3}
GVs ($P<10^{-7}$)	84	1.13 (1.02 to 1.24)	1.71×10^{-2}
GVs ($P<5\times10^{-8}$)	78	1.10 (1.00 to 1.22)	5.70×10^{-2}
GVs ($P<10^{-5}$) excluding those associated ($P<0.05$) mortality	263	1.15 (1.07 to 1.23)	1.88×10^{-4}
GVs ($P<10^{-5}$) with adj. for resting heart rate	275	1.01 (0.94 to 1.09)	0.71
GVs ($P<10^{-5}$) with adj. for covariates#	275	1.17 (1.09 to 1.26)	8.87×10^{-6}
GVs ($P<10^{-5}$) excluding those associated ($P<0.05$) with variable#	55	1.29 (1.09 to 1.53)	3.66×10^{-3}
GVs ($P<10^{-5}$) estimated on 11,405 healthy individuals	275	1.14 (1.07 to 1.22)	8.27×10^{-5}
GRS weighted GVs ($P<10^{-5}$)	275	1.17 (1.09 to 1.25)	5.55×10^{-6}
GRS unweighted GVs ($P<10^{-5}$)	275	1.05 (1.02 to 1.07)	7.04×10^{-5}
Multivariable MR with adj. for covariates#	275	1.18 (1.08 to 1.29)	5.42×10^{-4}
Multivariable MR with adj. for lipid covariates$	212	1.17 (1.09 to 1.26)	2.29×10^{-5}
Multivariable MR with adj. for red blood cell covariates@	176	1.18 (1.09 to 1.27)	6.04×10^{-5}
MR-Egger method ($P<10^{-5}$)	275	1.21 (1.05 to 1.39)	8.29×10^{-3}

*Hazard ratio (HR) with 95% Confidence Interval (CI) estimated with standard Mendelian Randomization (MR) and weighted Genetic Risk Score (GRS) per 5 bpm and for unweighted GRS per 5 summed risk alleles; Genetic Variants (GVs); Adjustment (adj.); [#]Baseline body-mass index, diastolic blood pressure, hypertension, diabetes, active smoking, and a history of heart failure, supraventricular tachycardias, myocardial infarction, device implantation, beta-blockers and calcium channel-blockers; [$]Lipid covariates including; Low Density Lipoprotein (LDL), High Density Lipoproteins (HDL) Total Cholesterol and Triglycerides; [@]Red blood cell covariates including; Red Blood Cell Count (RBC), Packed Cell Volume (PCV), Mean Corpuscular Volume (MCV) and Hemoglobin count (Hb)

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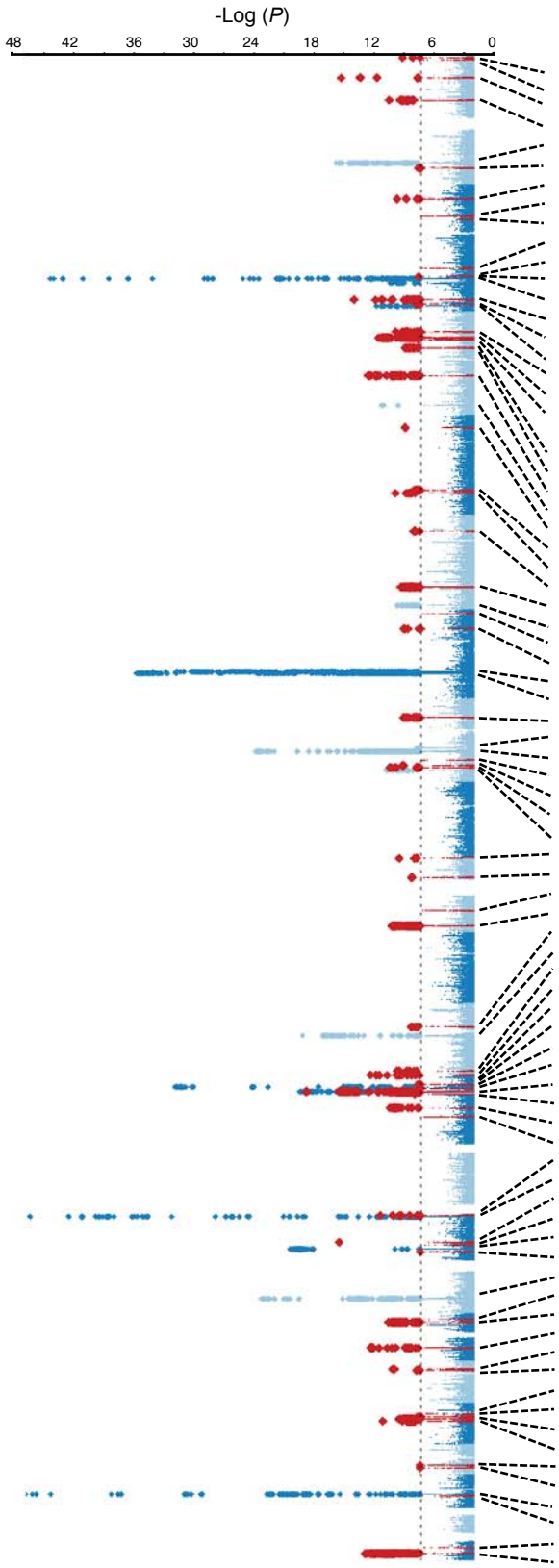
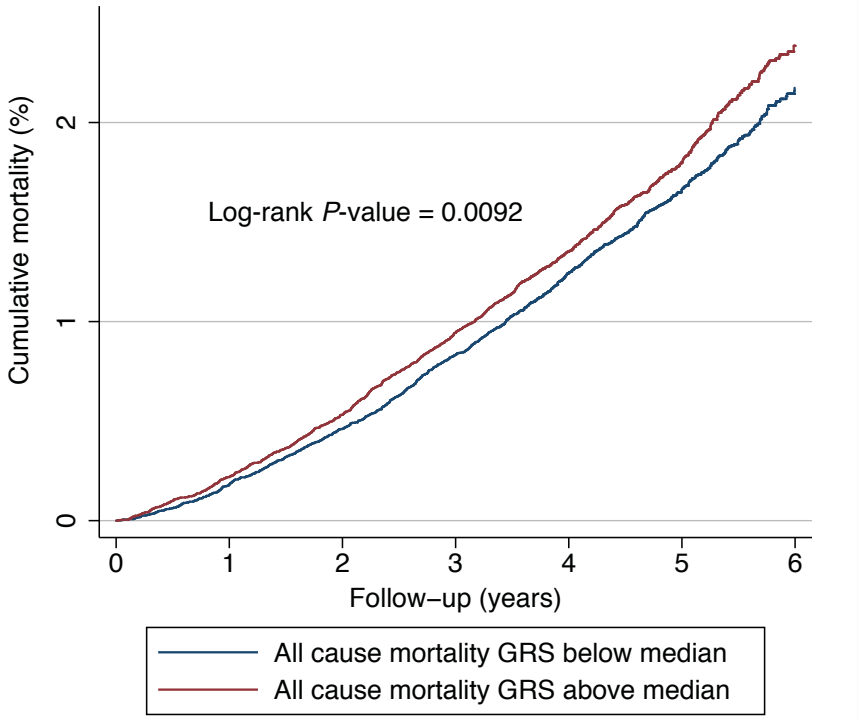
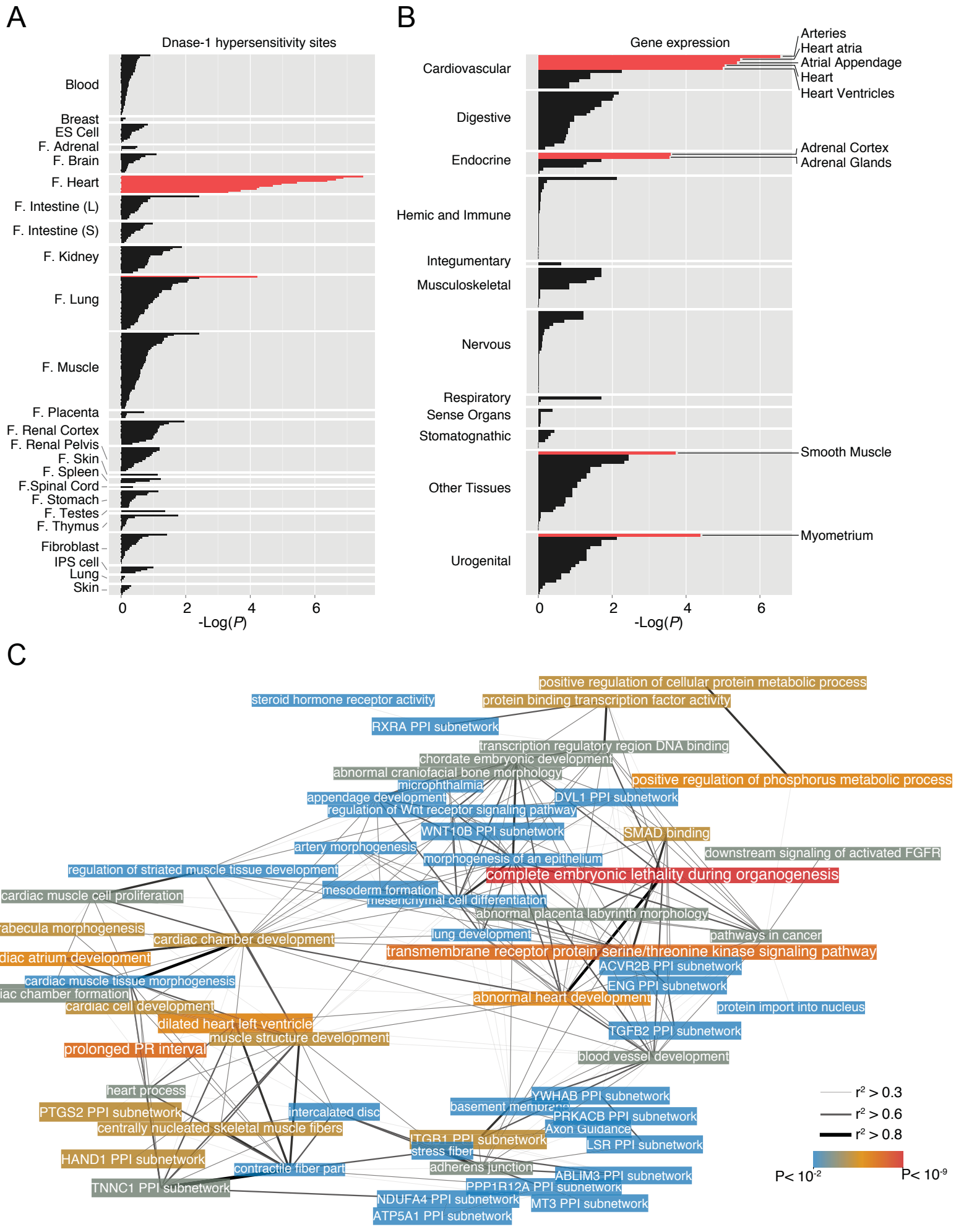


Region	rs ID	MAF	Candidate Genes
1p36.31	rs145358377	0.36	RNF207[nc]; ICMT[n]
1p36.22	rs182770070	0.01	NMNAT1[n]; LZIC[n]; UBE4B[d]
1p34.1	rs272564	0.28	RNF220[n]
1p22.3	rs2152735	0.33	LMO4[n]
1q32.2	rs41317993	0.10	CD46[n]; CD34[d]
1q41	rs11454451	0.26	GPATCH2[n]
2p23.3	rs1260326	0.39	GCKR[nc]
2p16.1	rs12713404	0.38	BCL11A[n]
2p14	rs62144050	0.28	MEIS1[nd]
2q24.2	rs17494056	0.27	TANC1[nd]
2q31.1	rs564190295	0.15	WIPF1[n]
2q31.2	rs151041685	0.09	CCDC141[ncd]; TTN[d]
2q32.1	rs62172372	0.19	CALCRL[ne]
2q35	rs907683	0.43	SPEG[nd]; DES[n]
2q36.3	rs4608502	0.33	COL4A3[n]
2q37.1	rs13002735	0.24	B3GNT7[nc]
3p22.2	rs41312411	0.15	SCN5A[nd]
3p21.31	rs7641050	0.22	IP6K2[n]; DALRD3[c]; KLHDC8B[ed]; P4HTM[e]; AMT[e]; QRICH1[ed]
3p21.31	rs3749237	0.32	IP6K1[n]; GMPPB[n]; FAM212A[d]; DAG1[d]; KLHDC8B[ed]; LAMB2[d]; PRKAR2A[d]; QRICH1[ed]
3p21.1	rs2358740	0.32	CACNA1D[n]
3p14.1	rs1483890	0.30	FRMD4B[n]
3q21.1	rs11920570	0.26	CCDC58[n]
3q26.33	rs7612445	0.19	GNB4[n]
4p15.2	rs12501032	0.31	PPARGC1A[n]
4q31.21	rs1425518	0.20	INPP4B[n]
4q31.23	rs6845865	0.16	ARHGAP10[nd]; EDNRA[d]
5p13.3	rs13165531	0.42	CDH6[n]
5q31.2	rs35284930	0.42	CDC23[n]
5q35.1	rs4868243	0.16	NKX2-5[n]
6p24.3	rs2744375	0.16	DSP[nd]
6p21.2	rs236349	0.34	PPIL1[ne]
6q22.2	rs3951016	0.47	SLC35F1[n]; PLN[d]
6q22.31	rs1320761	0.11	GJA1[n]
7p14.2	rs58437978	0.50	TBX20[n]
7q21.3	rs180239	0.35	GNGT1[n]; GNG11[n]
7q22.1	rs17881696	0.18	UFSP1[nc]; SRRT[n]; ACHE[ne]; EPHB4[d]; GIGYF1[d]; PCOLCE[d]
7q31.2	rs41748	0.45	MET[n]
7q31.33	rs11563648	0.27	ZNF800[n]
7q32.3	rs138186803	0.41	MKLN1[n]
7q33	rs73158705	0.16	CHRM2[n]
8q24.3	rs56233017	0.04	PLEC[n]
9p13.3	rs748802	0.34	HRCT1[n]
9q22.32	rs10820614	0.21	ZNF367[n]
9q33.3	rs10739663	0.45	MAPKAP1[ne]
11p11.2	rs12576326	0.34	TP53I11[n]
11q12.2	rs11320420	0.34	MYRF[n]; FEN1[e]; FADS2[e]; TMEM258[e]
11q24.3	rs75190942	0.09	KCNJ5[nd]; C11orf45[n]
12p13.33	rs2283274	0.18	CACNA1C[n]
12p12.2	rs10841486	0.22	PDE3A[nd]
12p12.1	rs4963772	0.15	SOX5[n]
12p11.22	rs1050288	0.34	KLHL42[n]
12pcen	rs1994135	0.47	SYT10[n]
12pcen	rs11526064	0.47	ALG10[n]
12qcen	rs11183443	0.13	ALG10B[n]
12q14.2	rs867400	0.43	RASSF3[nd]
12q21.31	rs12579753	0.23	PPFIA2[ne]
14q11.2	rs12889267	0.16	NDRG2[n]; ARHGEF40[ncd]; ZNF219[d]
14q11.2	rs422068	0.36	MYH6[nd]; MYH7[d]
14q24.2	rs17180489	0.14	RGS6[n]
14q24.3	rs1549118	0.28	ADCK1[n]
14q31.3	rs17201923	0.28	FLRT2[n]
14q32.11	rs4900069	0.37	C14orf159[n]
15q24.1	rs7173389	0.16	HCN4[n]; NEO1[d]
16p13.13	rs1592560	0.40	TEKT5[n]
16p13.11	rs3915499	0.32	MYH11[nd]
16q21	rs7194801	0.43	CDH11[n]
17p12	rs79121763	0.09	TEKT3[n]; PMP22[d]
17p11.2	rs12941356	0.42	SREBF1[n]; RAI1[nd]
18q11.2	rs117159291	0.05	CTAGE1[n]; GATA6[d]
18q12.1	rs11083258	0.17	CDH2[nd]
18q12.1	rs11081761	0.15	GAREM[n]
18q12.2	rs61735998	0.02	FHOD3[ncd]
19q13.2	rs16974196	0.32	C19orf47[nd]; MAP3K10[e]
19q13.32	rs12721051	0.18	APOE[n]; APOC1[n]; PVRL2[d]
20q11.23	rs6123471	0.46	KIAA1755[nc]
20q12	rs17265513	0.19	ZHX3[nc]; EMILIN3[d]
22q12.1	rs2283847	0.45	MN1[n]
22q13.1	rs2076028	0.29	SUN2[n]; CBY1[e]; FAM227A[e]; JOSD1[e]; TOMM22[e]; DDX17[d]; GTPBP1[d]


Cumulative mortality (%)
0
1
2
Log-rank P-value = 0.0092
0
1
2
3
4
5
6
Follow–up (years)
All cause mortality GRS below median
All cause mortality GRS above median


A
Dnase-1 hypersensitivity sites
Blood
Breast
ES Cell
F. Adrenal
F. Brain
F. Heart
F. Intestine (L)
F. Intestine (S)
F. Kidney
F. Lung
F. Muscle
F. Placenta
F. Renal Cortex
F. Renal Pelvis
F. Skin
F. Spleen
F.Spinal Cord
F. Stomach
F. Testes
F. Thymus
Fibroblast
IPS cell
Lung
Skin
0
2
4
6
-Log(P)
B
Gene expression
Cardiovascular
Digestive
Endocrine
Hemic and Immune
Integumentary
Musculoskeletal
Nervous
Respiratory
Sense Organs
Stomatognathic
Other Tissues
Urogenital
Arteries
Heart atria
Atrial Appendage
Heart
Heart Ventricles
Adrenal Cortex
Adrenal Glands
Smooth Muscle
Myometrium
0
2
4
6
-Log(P)
C
positive regulation of cellular protein metabolic process
steroid hormone receptor activity
protein binding transcription factor activity
RXRA PPI subnetwork
transcription regulatory region DNA binding
chordate embryonic development
abnormal craniofacial bone morphology
positive regulation of phosphorus metabolic process
microphthalmia
appendage development
DVL1 PPI subnetwork
regulation of Wnt receptor signaling pathway
WNT10B PPI subnetwork
SMAD binding
artery morphogenesis
morphogenesis of an epithelium
downstream signaling of activated FGFR
regulation of striated muscle tissue development
complete embryonic lethality during organogenesis
mesoderm formation
cardiac muscle cell proliferation
mesenchymal cell differentiation
abnormal placenta labyrinth morphology
trabecula morphogenesis
lung development
pathways in cancer
cardiac chamber development
transmembrane receptor protein serine/threonine kinase signaling pathway
cardiac atrium development
ACVR2B PPI subnetwork
cardiac muscle tissue morphogenesis
ENG PPI subnetwork
cardiac chamber formation
abnormal heart development
protein import into nucleus
cardiac cell development
dilated heart left ventricle
TGFB2 PPI subnetwork
muscle structure development
prolonged PR interval
blood vessel development
heart process
YWHAB PPI subnetwork
PTGS2 PPI subnetwork
intercalated disc
basement membrane
PRKACB PPI subnetwork
centrally nucleated skeletal muscle fibers
Axon Guidance
ITGB1 PPI subnetwork
LSR PPI subnetwork
stress fiber
HAND1 PPI subnetwork
contractile fiber part
adherens junction
ABLIM3 PPI subnetwork
TNNC1 PPI subnetwork
PPP1R12A PPI subnetwork
NDUFA4 PPI subnetwork
MT3 PPI subnetwork
ATP5A1 PPI subnetwork
r² > 0.3
r² > 0.6
r² > 0.8
P< 10-2
P< 10-9