Discovery of novel heart rate-associated loci using the Exome Chip
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Supplementary Material

1. Supplementary Figure Titles

Supplementary Figure 1: Quantile-Quantile (QQ) plot of the discovery phase meta-analysis of RR-interval among the European-ancestry individuals.

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Supplementary Figure 3: (a) Histogram showing the distribution of RR-interval phenotype in the 1958BC study; **(b)** Quantile-Quantile (QQ) plot of RR-interval phenotype in the 1958BC study.

Supplementary Figure 4: (a) Comparison of the betas between the RR-interval meta-analysis with and without beta-blocker users; **(b)** Comparison of the *P*-values between the RR-interval meta-analysis with and without beta-blocker users.

Supplementary Figure 5: Locus Zoom plots for the five unreported novel loci.

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2. Supplementary Tables

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Supplementary Table 8: Pathway Enrichment Analysis

Supplementary Table 9: Long-range interactors

Supplementary Table 10: Pathway enrichment including long-range interactors

Supplementary Table 11: Annotation of novel heart rate loci and information on candidate genes
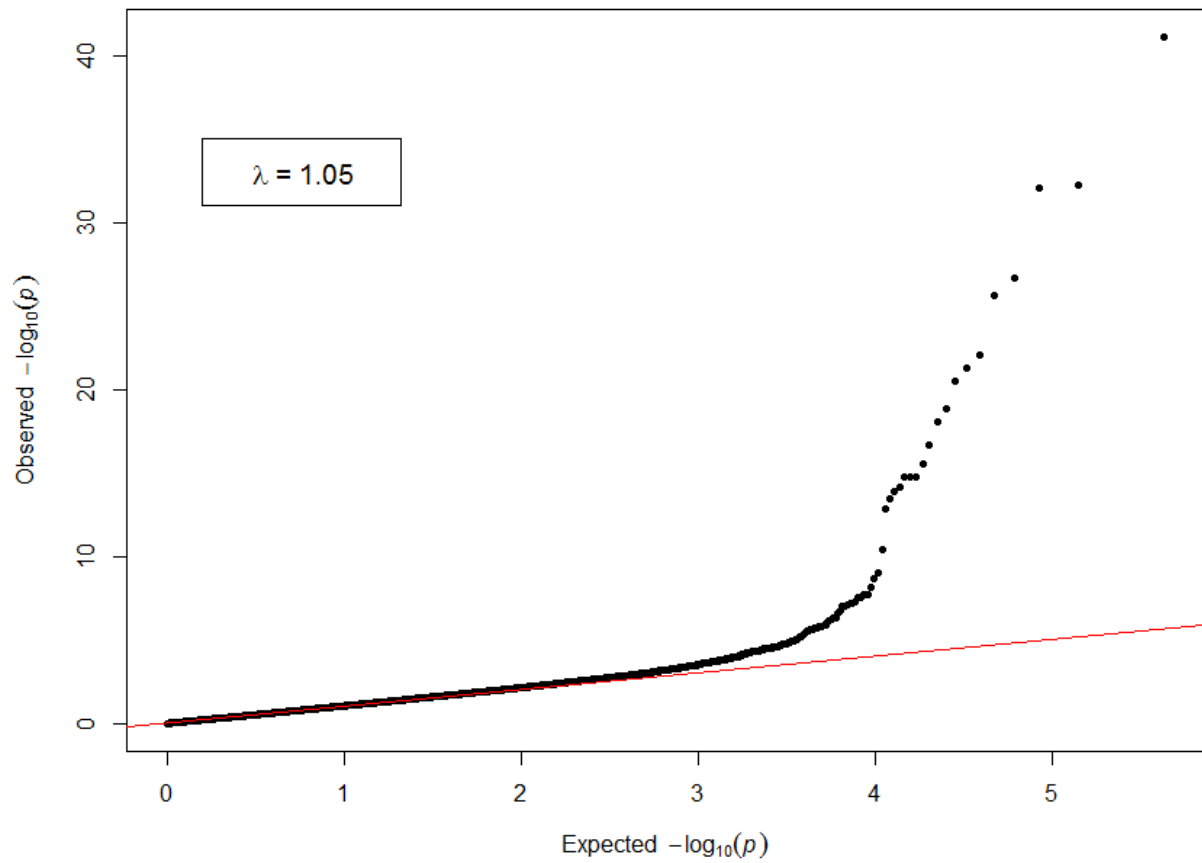
Supplementary Table 12: Cohort study information

Supplementary Table 13: Descriptive summary statistics within each cohort

Supplementary Table 14: Genetic information for each cohort
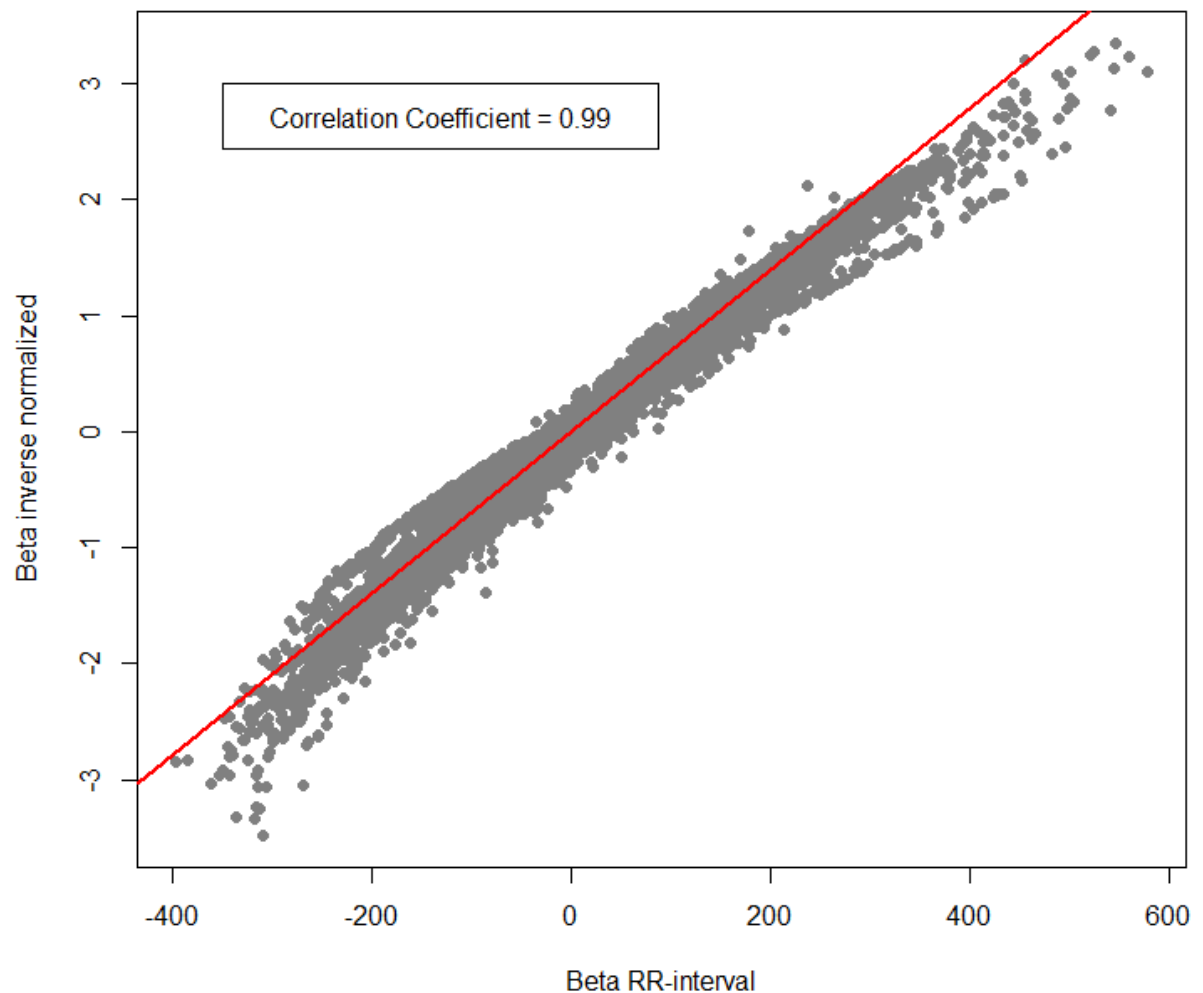
Supplementary Figures

Supplementary Figure 1: Quantile-Quantile (QQ) plot of the discovery phase meta-analysis of RR-interval among the European-ancestry individuals

The red line is the line Y = X. The lambda indicates the genomic inflation factor. P-values are plotted on a –log10 scale.

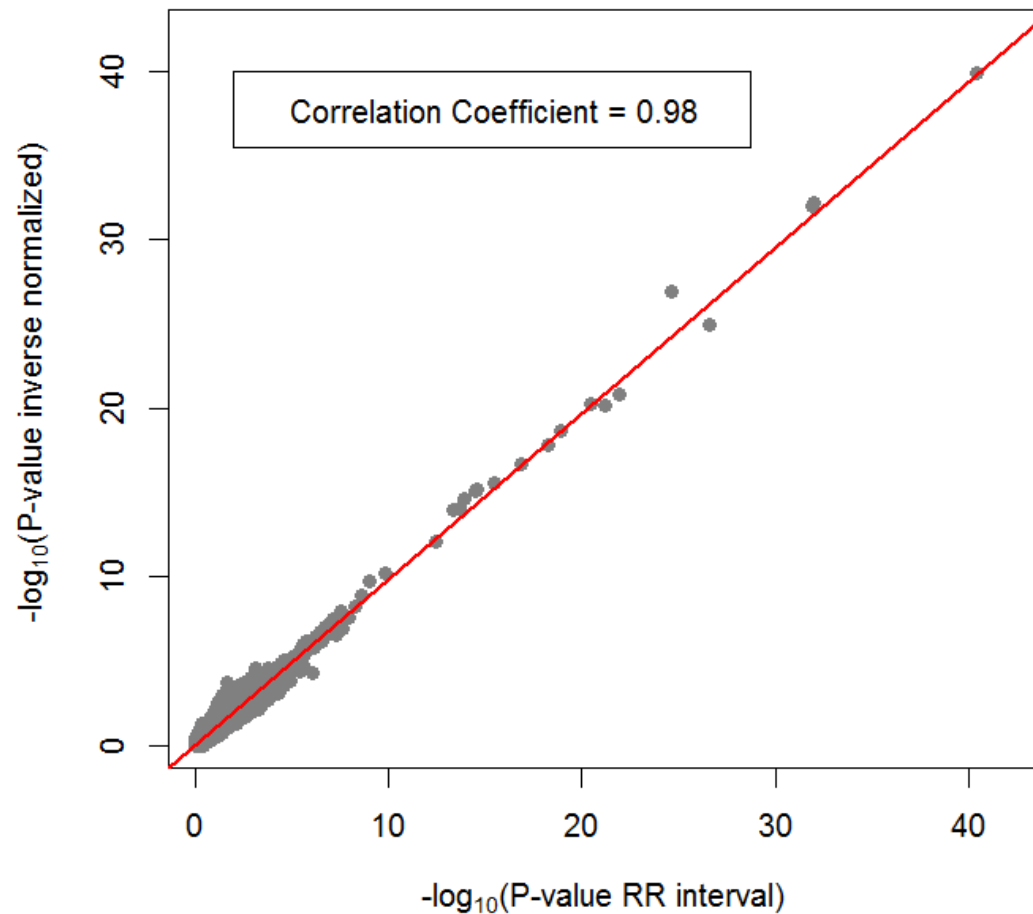**Supplementary Figure 2**

a: Comparison of the betas between the untransformed RR-interval meta-analysis

and the inverse normalized RR-interval residuals (RR-INVN) meta-analysis

Betas for RR interval (ms) are based on the meta-analysis of the 30 European-ancestry cohorts (N = 104,452). The red regression line is based on a linear regression with outcome Beta(RR-INVN) and determinant Beta (RR-interval). The Pearson's correlation coefficient is indicated.
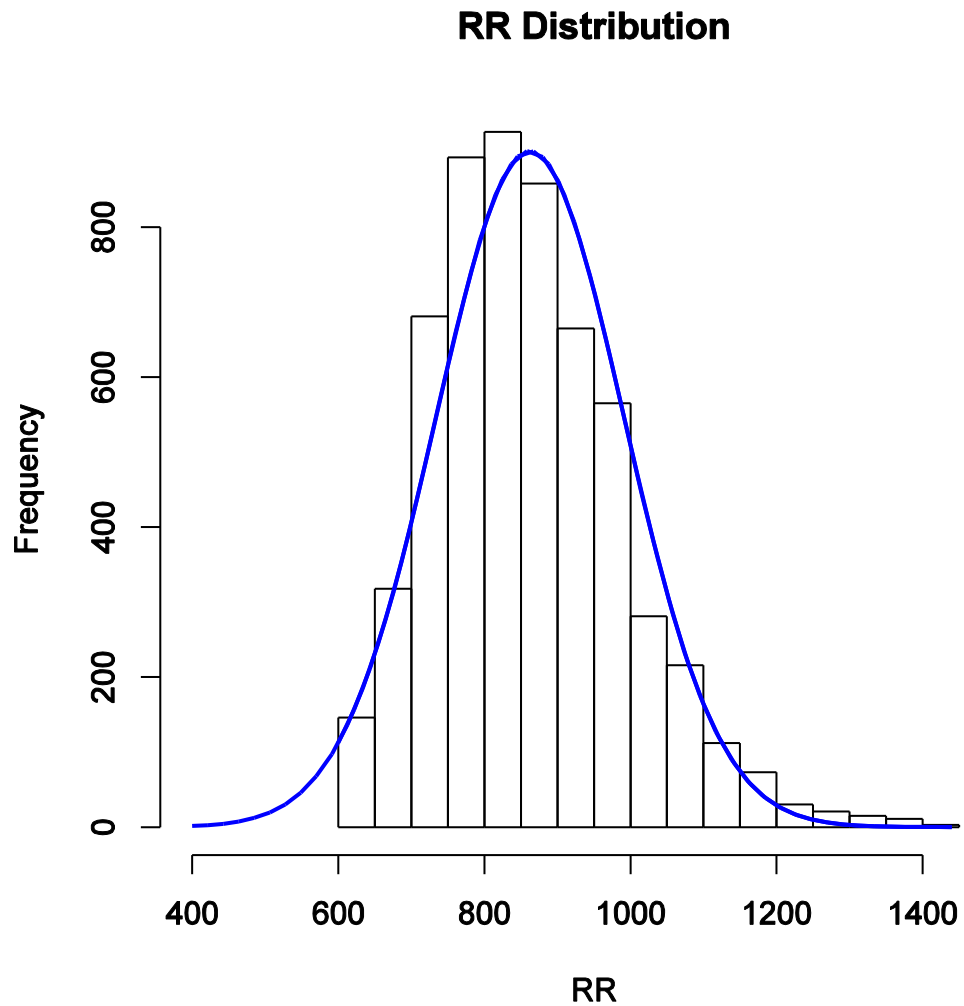
b: Comparison of the *P*-values between the untransformed RR-interval meta-analysis and the inverse normalized RR-interval residuals (RR-INVN) meta-analysis

P-value results are based on the meta-analysis of the 30 European-ancestry cohorts (N = 104,452). The red regression line is based on a linear regression with outcome *P*-value (RR-INVN) and determinant *P*-value (RR-interval). The Pearson's correlation coefficient is indicated.
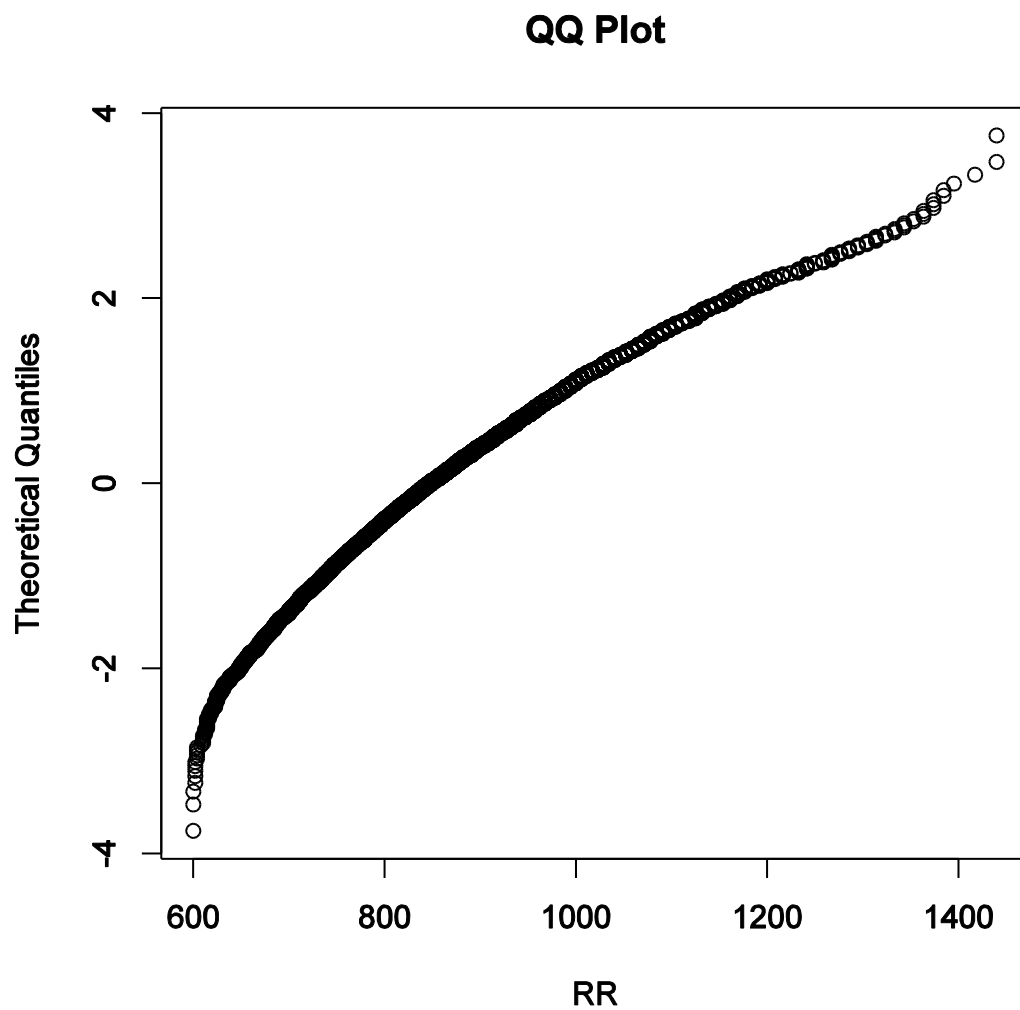
Supplementary Figure 3:

a. Histogram showing the distribution of RR-interval phenotype in the 1958BC study

RR Distribution

The normal distribution with the same mean and standard deviation as the data is

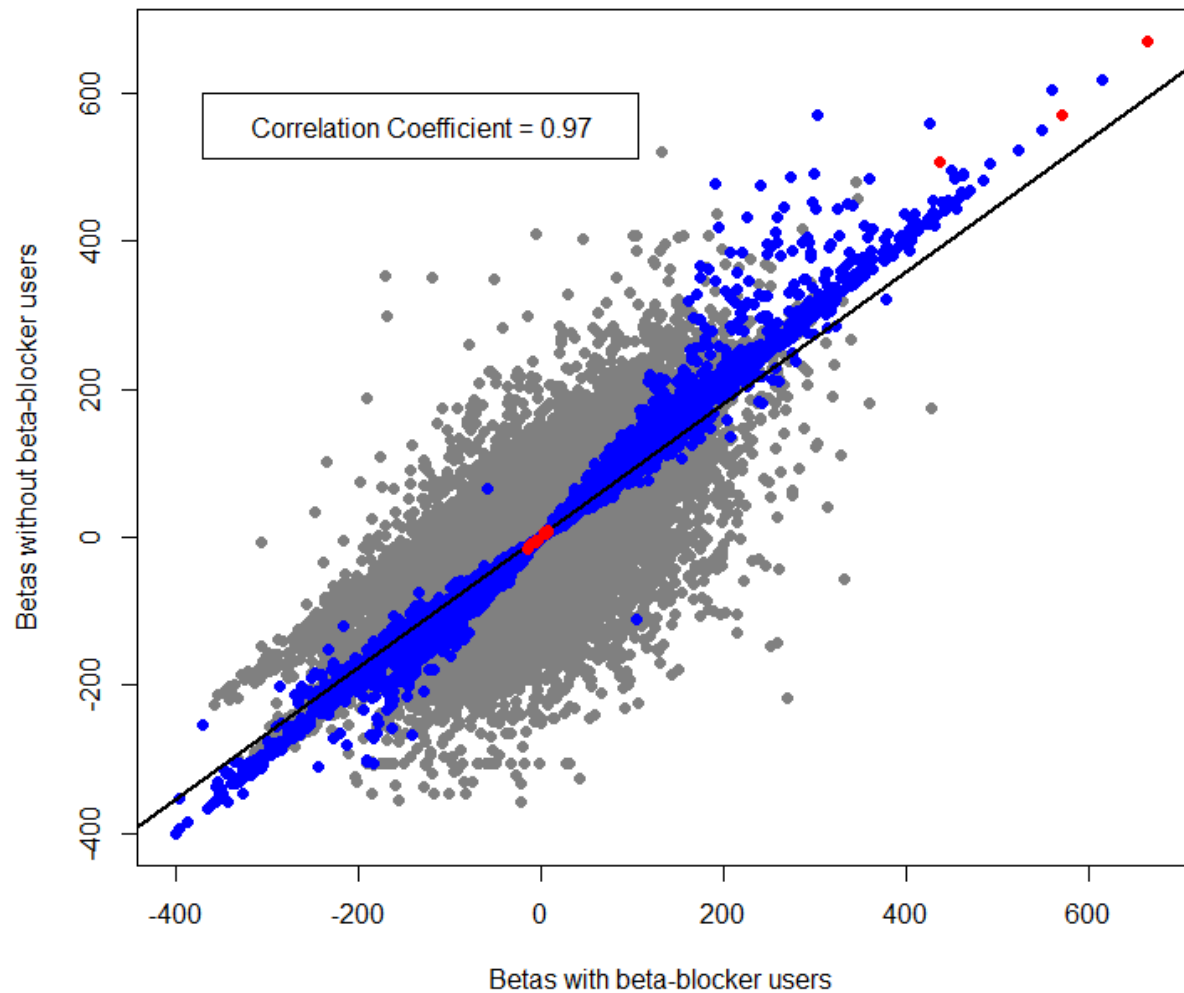shown in blue, for RR interval (ms).

b. Quantile-Quantile (QQ) plot of RR-interval phenotype in the 1958BC study

QQ Plot

The ranked RR-intervals (in milliseconds) of the 1985BC study are plotted against a ranked standard normal distribution.
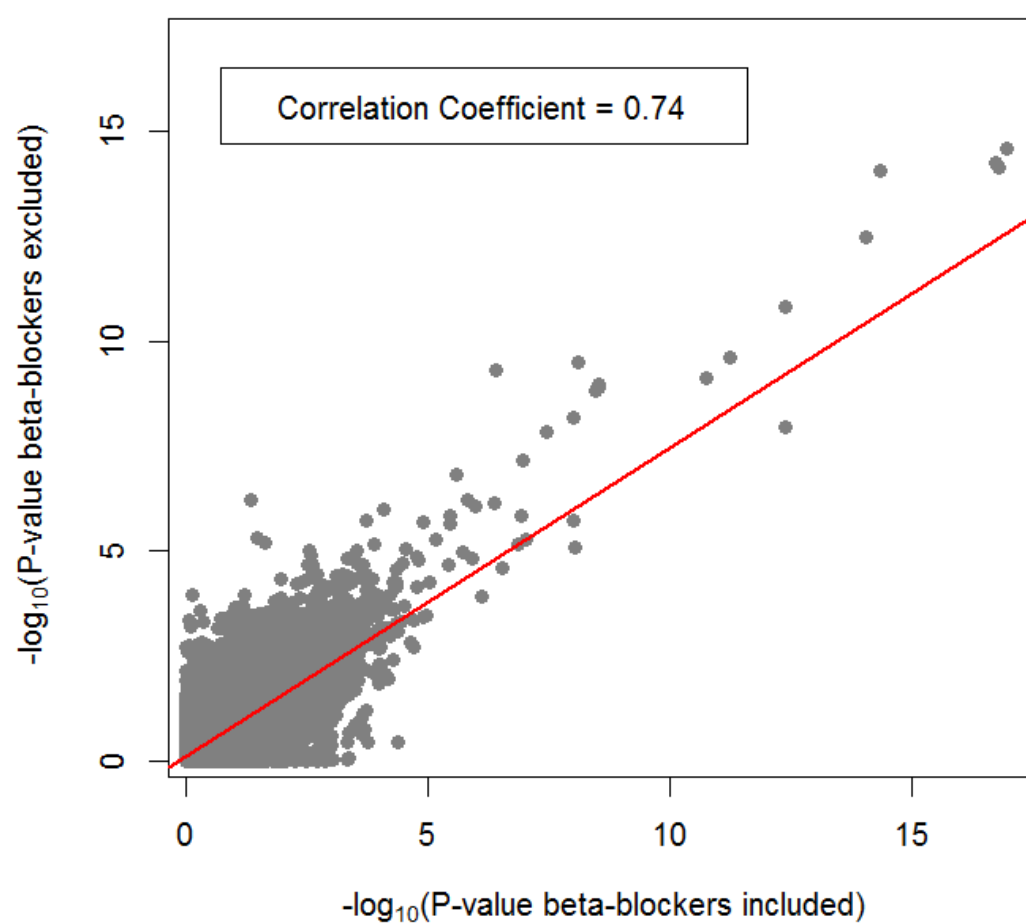
Supplementary Figure 4

a: Comparison of the betas between the RR-interval meta-analysis with and without beta-blocker users.

The beta results plotted are for RR interval in milliseconds. The blue points indicate SNVs with *P* values below 0.05; Red points indicate SNVs with *P* values below 1 x 10^{-5}, according to *P*-values from the final primary EUR discovery meta-analysis. The reported correlation coefficient is based on the SNVs with *P* value below 0.05 from the final primary European discovery meta-analysis. The three red points in the top right corner were excluded from the meta-analysis results after quality control due to their large betas and standard errors. The results for the meta-analysis with beta-

blocker users included were taken from data from the same 17 cohorts as those with beta-blocker users excluded: 1958BC, AGES, ASCOT-UK, ASCOT-SC, BRIGHT, CHS, ERF, GODARTS, Generation Scotland, KORCULA, UHP, MGH, NEO, RS, SardiNIA, SHIP, YFS (N=48,347).
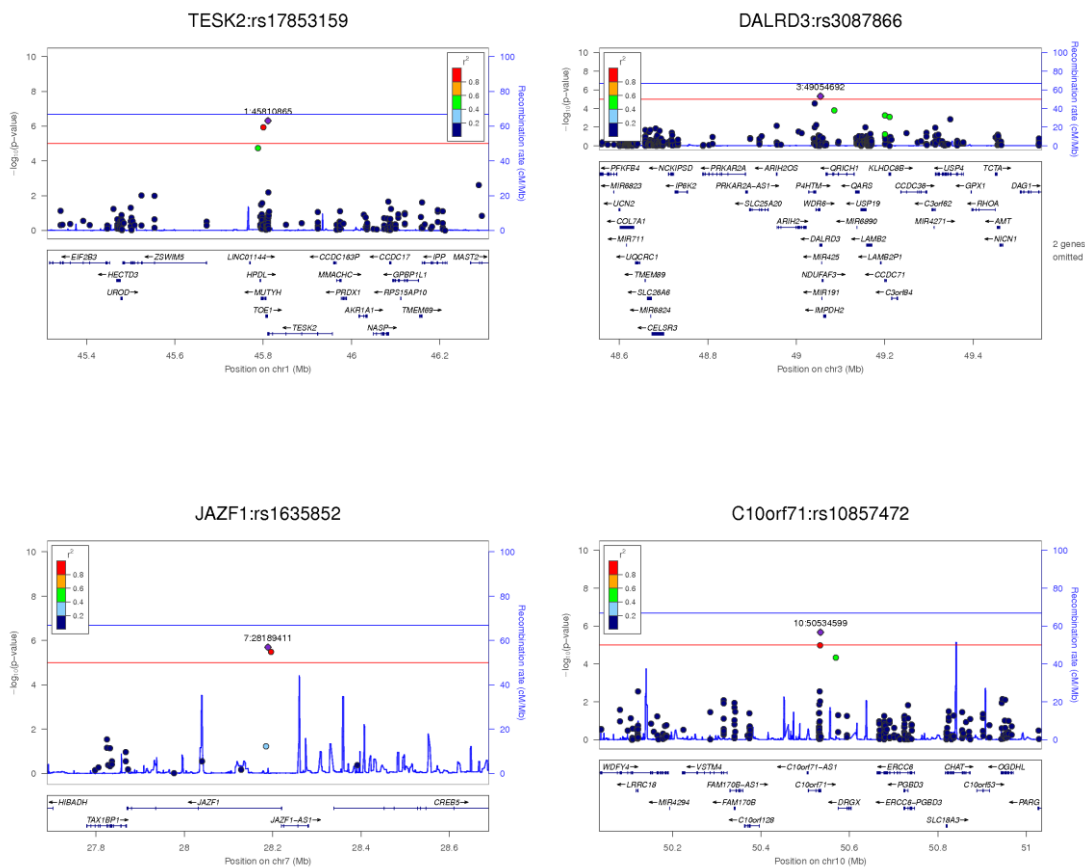
b: Comparison of the *P*-values between the RR-interval meta-analysis with and
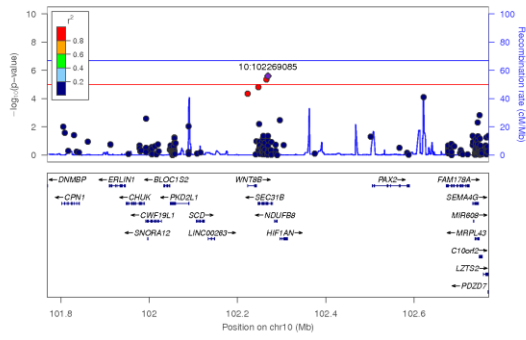
without beta-blocker users.

The results for the meta-analysis with beta-blocker users included were taken from

data from the same 17 cohorts as those with beta-blocker users excluded: 1958BC,

AGES, ASCOT UK, ASCOT SC, BRIGHT, CHS, ERF, GODARTS, Generation Scotland,

KORCULA, UHP, MGH, NEO, RS, SardiNIA, SHIP, YFS (N = 48,347)

Supplementary Figure 5: Locus Zoom plots for the five unreported novel loci
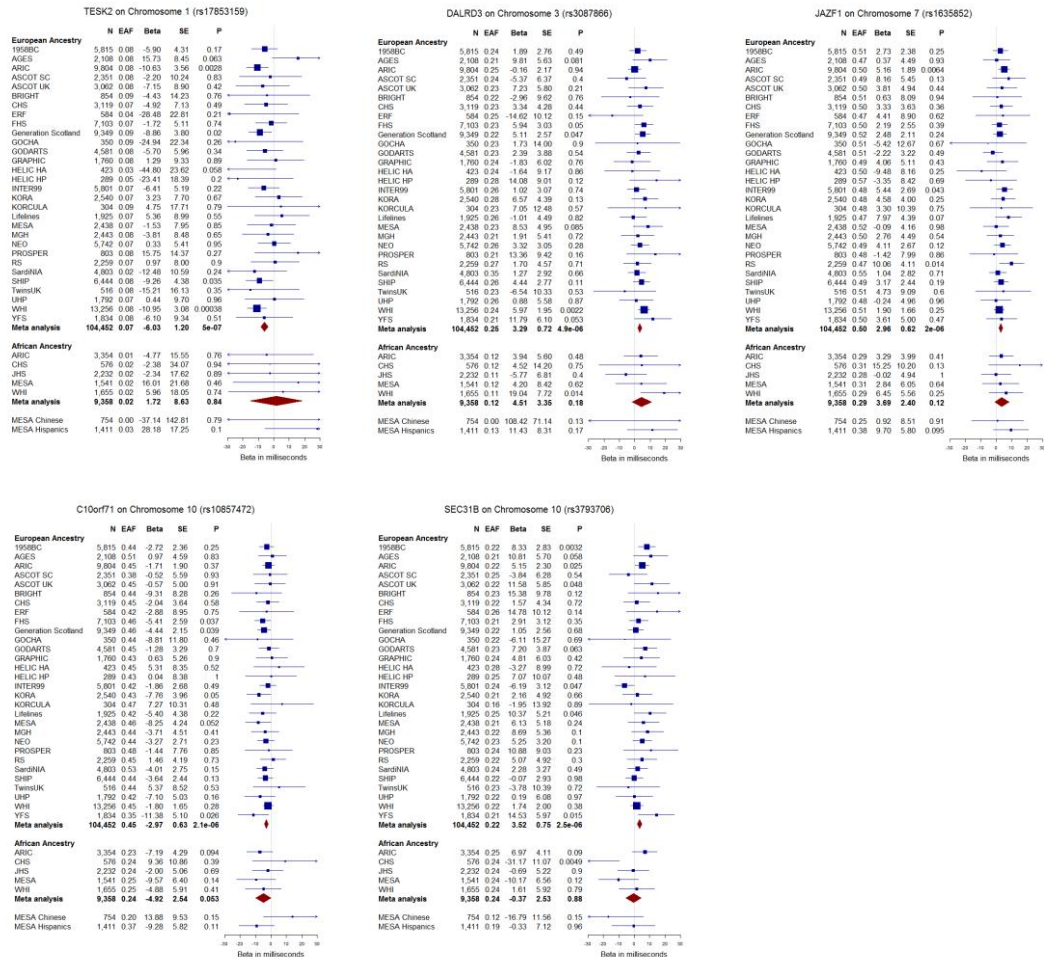
Locus Zoom plots are provided for each of the five unreported validated novel loci, showing association results from the RR-interval discovery meta-analysis in Europeans (N = 104,452). These were created using the stand-alone locus zoom plotting software (http://locuszoom.sph.umich.edu/). The linkage disequilibrium (LD) r^2 was user-supplied and calculated in PLINK software from Exome-chip data from a subset of available studies (ASCOT-UK, ASCOT-SC, BRIGHT and 1958BC). The red line indicates a *P*-value threshold of 1×10^{-5} corresponding to the lookup significance threshold and the blue line indicates a *P*-value threshold of 2×10^{-7} corresponding to exome-wide significance.
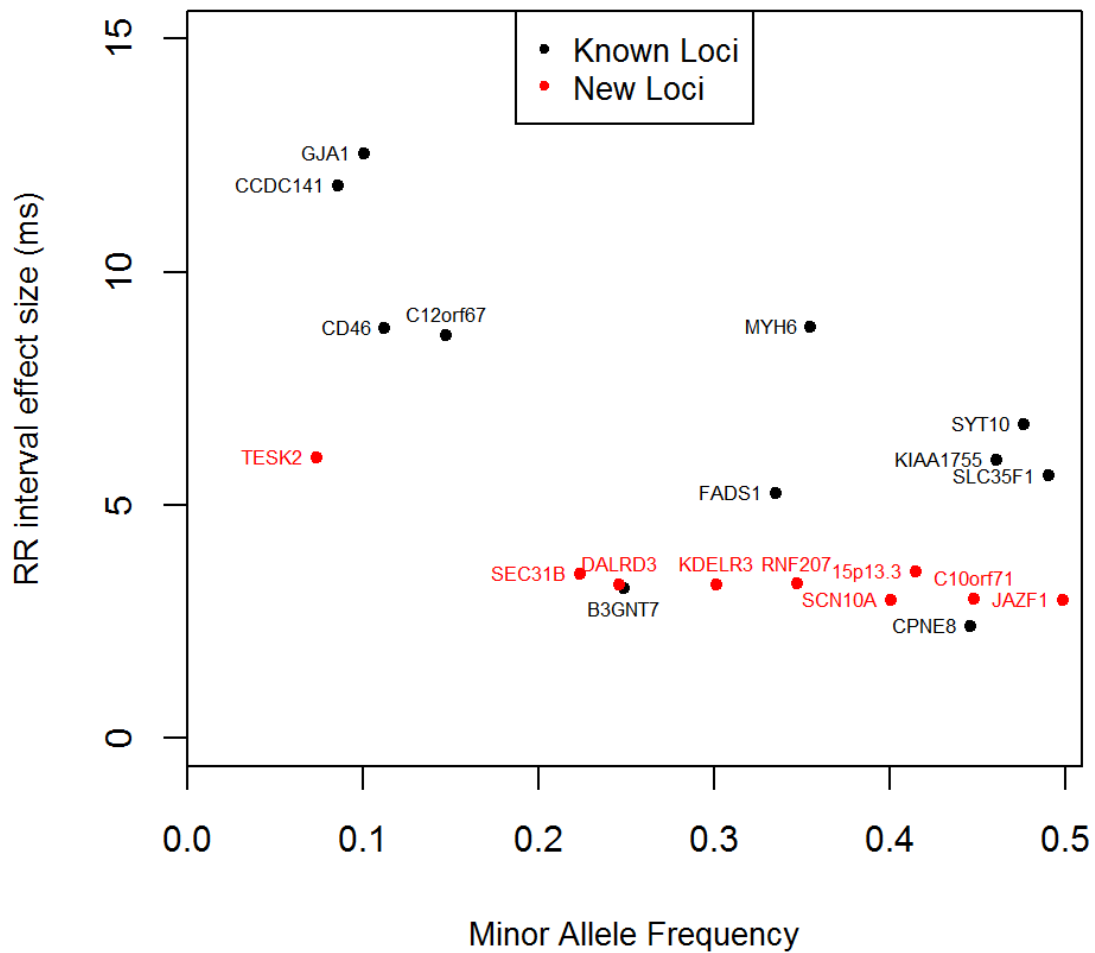
SEC31B:rs3793706

Supplementary Figure 6: Forest plots showing the associations of the five

unreported novel loci within all European discovery cohorts and non-European

studies

For each locus, the forest plot shows (in order): the study-level results for each of

the 30 European cohorts contributing to the discovery meta-analysis; the discovery

meta-analysis results; the study-level results for each of the five African ancestry

cohorts; the African-ancestry meta-analysis results; the ancestry-stratified results

within the MESA study for Chinese-Americans and Hispanics. In the forest plot,

study-level results are displayed in blue with effect estimate boxes proportional to

the sample size, and the meta-analysis results are displayed with red diamonds.

N: sample size; EAF: Effect Allele Frequency; Beta: effect size of RR-interval in milliseconds; SE: standard error; *P*: *P*-value

Supplementary Figure 7: Effect sizes of associated variants: Comparison between
novel loci and previously reported loci

The effect sizes in miliseconds for association of variants with RR Interval from the
primary Exome RR discovery meta-analysis in Europeans are plotted on the y-axis,
with minor allele frequency (MAF) plotted on the x-axis. The variants coloured in
black, denoted as "known loci", correspond to the 11 published HR variants with
strong evidence of support in our data, from the 12 previously reported GWAS
variants which are covered on the Exome chip. The variants coloured in red, denoted

as "new loci", correspond to the lead variants at all nine novel loci validated in our

study.