Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk

The UK Biobank Cardio-metabolic Traits Consortium Blood Pressure Working Group.

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Abstract:

Elevated blood pressure is the leading heritable risk factor for cardiovascular disease worldwide. We report genetic association of blood pressure (systolic, diastolic, pulse pressure) among UK Biobank participants of European ancestry with independent replication in other cohorts, and robust validation of 107 independent loci. We also identify new independent variants at 11 previously reported blood pressure loci. Combined with results from a range of *in silico* functional analyses and wet bench experiments, our findings highlight new biological pathways for blood pressure regulation enriched for genes expressed in vascular tissues and identify potential therapeutic targets for hypertension. Results from genetic risk score models raise the possibility of a precision medicine approach through early lifestyle intervention to offset the impact of blood pressure raising genetic variants on future cardiovascular disease risk.

Elevated blood pressure (BP) is a strong, heritable[1-4] and modifiable driver of risk for stroke and coronary artery disease and a leading cause of global mortality and morbidity[5,6]. At the time of analysis, genome-wide association study (GWAS) meta-analyses, and analyses of bespoke or exome content, have identified and replicated genetic variants of mostly modest or weak effect on blood pressure at over 120 loci[7-11]. Here, we report association analyses between BP traits and genetic variants among ~150,000 participants in UK Biobank, a prospective cohort study of 500,000 men and women aged 40-69 years with extensive baseline phenotypic measurements, stored biological samples[12], and follow-up by electronic health record linkage[13]. We undertake independent replication in large international consortia and other cohorts, providing robust validation of our findings and new biological insights into BP regulation.

Our study design is summarized in **Fig. 1**. Briefly, data are available for 152,249 UK Biobank participants genotyped using a customised array (including GWAS and exome content) and with genome-wide imputation based on 1000 Genomes and UK10K sequencing data[14]. (Further details on the UK Biobank imputation are available at the UK Biobank website.) After quality measures and exclusions (see Online Methods), we study 140,886 unrelated individuals of European ancestry with two seated clinic BP measurements using the Omron HEM-7015IT device (**Supplementary Table 1**). We carry out GWAS analyses of systolic (SBP), diastolic (DBP) and pulse pressure (PP) using single-variant linear regression under an additive model, based on ~9.8 million single nucleotide variants (SNVs) with minor allele frequency (MAF) $\geq$1% and imputation quality score (INFO) >0.1. For SNVs with $P < 1 \times 10^{-6}$, we take forward for replication the sentinel SNV (i.e. with lowest *P*-value) at each locus, defined by linkage disequilibrium (LD) $r^2 < 0.2$, within a 1Mb interval. We similarly analyze exome content for variants with MAF $\geq$0.01%, including rare variants, taking into replication the sentinel SNV ($P < 1 \times 10^{-5}$) from loci that are non-overlapping ($r^2 < 0.2$) with the GWAS findings. Overall we took sentinel SNVs from 240 loci into replication: 218 from GWAS and 22 from exome analysis ($r^2 < 0.2$ and >500kb from previously reported BP SNVs at the time of analysis and not annotated to previously reported BP genes; **Supplementary Table 2**).

The replication resources comprise individuals of European ancestry from a large BP meta-analysis consortium (ICBP cohorts listed in **Supplementary Note**) and further cohorts with 1000 Genomes data for GWAS (**Supplementary Table 3**), and two large BP exome consortia. We use $P < 5 \times 10^{-8}$ to denote genome-wide significance in the combined (discovery and replication) meta-analyses, with $P < 0.01$ for support in the replication data alone and concordant direction of effect. Additionally, we take forward for replication potential secondary signals at 51 previously reported BP loci at the time of analysis (excluding the HLA region).

To better understand the functional consequences of our findings, we carry out a series of *in silico* investigations and experimental analysis of gene expression in relevant vascular tissue for selected putative functional SNVs (**Supplementary Fig. 1**).

RESULTS

Genetic variants at novel and previously unvalidated loci

Of the 240 loci taken forward to replication, we validate 107 loci at $P < 5x10^{-8}$, of which 102 derive from the GWAS analysis replicated and meta-analyzed in a total of 330,956 individuals (**Tables 1-3**; **Supplementary Fig. 2a-c; Supplementary Fig. 3a**), and a further five from the exome analysis in a total of 422,604 individuals (**Tables 1-3** and **Supplementary Fig. 3b; Supplementary Tables 4, 5** and **6**). Thirty-two of these validated loci are novel findings. Since the time of analysis, the remaining 75 loci have also been reported in another study[15], although at least 53 of these were previously unvalidated (**Tables 1-3**), hence we now validate these loci for the first time. We therefore present results here for all 107 validated loci in our study. Most SNVs also show association with hypertension in the UK Biobank data, for example 93 of the 107 validated sentinel SNVs are nominally significant ($P < 0.01$) (**Supplementary Table 7**).

Of the 107 validated loci, 24 are reported for association with SBP as the primary trait (most significant from combined meta-analysis), 41 for DBP and 42 for PP, although many loci are associated with more than one BP trait (**Supplementary Fig. 4**). For example, in the combined meta-analysis, 24 validated loci are associated with both SBP and DBP, 11 with SBP and PP, one locus with DBP and PP and four loci (*NADK-CPSF3L*, *GTF2B*, *METTL21A*-AC079767.3 and *PAX2*) with all three traits at genome-wide significance (**Fig. 2**).

After conditional analysis on the sentinel SNV we identify an independent validated secondary SNV at five of the 107 loci (**Supplementary Table 8a; Supplementary Table 9**). Compared with previously reported SNVs at the time of analysis, the contribution of our validated loci increases the percentage trait variance explained by ~1%, e.g. to 3.56% for SBP.

We report signals at known hypertension drug targets, including the angiotensin converting enzyme (*ACE*) locus (rs4308, $P = 6.8 \times 10^{-14}$, ACE-inhibitors), *CACNA2D2* (rs743757, $P = 2.4 \times 10^{-10}$, calcium channel blockers), *MME* (rs143112823 in the RP11-439C8.2 locus, $P = 1.4 \times 10^{-14}$, omapatrilat), *ADRA2B* (rs2579519 in the *GPAT2-FAHD2CP* locus, $P = 4.8 \times 10^{-12}$, beta blockers), *SLC14A2* (rs7236548, $P = 2.0 \times 10^{-18}$, nifedipine), and phosphodiesterase 5A (*PDE5A*; rs66887589, $P = 3.4 \times 10^{-15}$, sildenafil).

Additionally, we evaluate our validated SNVs, where available, in cohorts of non-European ancestry[9-11], while recognizing that these analyses are likely underpowered (**Supplementary Table 10**). We find concordance in direction of effect ($P < 0.05$) for GWAS SNVs for all three BP traits among individuals of East Asian ancestry and for DBP for South Asian ancestry, also for exome SNVs among individuals of Hispanic ancestry, pointing to cosmopolitan effects for many of the BP associated variants.

A PhenoScanner[16] search showed that 27 of our 107 validated sentinel SNVs (or proxies; $r^2 \geq 0.8$) exhibit genome-wide significant associations with other traits (**Supplementary Fig. 5**), including coronary artery disease and myocardial infarction (where BP is likely on the causal pathway[17]), cardiovascular risk factors (e.g. lipids, height, body mass index) and non-cardiovascular traits (e.g. lung function, cancer, Alzheimer's).

Variants at previously reported loci at time of analysis

In conditional analyses, we identify 22 secondary SNVs (17 common, one rare, four low-frequency variants) that are conditionally independent of the BP associated SNVs at 16

previously reported loci at the time of analysis (**Supplementary Table 8b; Supplementary Tables 11** and **12**). One rare variant (rs138582164, MAF=0.1%) in the *CDH17* locus anticipated to act as an exonic stop/gain mutation at the *GEM* gene is associated with a relatively large effect on PP (3.5 mm Hg per allele copy, **Supplementary Table 8b**). At three previously reported loci (*EBF1*, *PDE3A*, *JAG1*) we identify multiple independent secondary SNVs in addition to the previously reported SNVs (**Supplementary Table 11**).

The UK Biobank data show support ($P < 0.01$) for 119 of 122 previously reported BP loci at the time of analysis (159 of 163 SNVs) for one or more BP traits (**Supplementary Fig. 2 a-c; Supplementary Table 13**). We do not show support for one SNV (rs11066280, *RPL6-ALDH1*) identified from a GWAS of East Asian ancestry[18], which may indicate ancestry-specific effects. We compare the MAF and effect sizes in UK Biobank with published results of previously reported variants (**Supplementary Fig. 6**), indicating consistency of results between the two sources of data.

We also examine findings for low-frequency and rare gene mutations previously reported to be associated with monogenic hypertension disorders[19] and included on the UK Biobank gene array. Despite lack of power overall, the variant with the lowest *P*-value (rs387907156; *KLH3*; MAF=0.02%) has a seemingly large effect on BP: 8.2 mm Hg (SE=4.1, $P = 0.046$) per allele for SBP; 5.6 mm Hg (SE=2.6, $P = 0.048$) for PP (**Supplementary Table 14**).

Functional analyses

We annotate the 107 validated loci to 212 genes (based on LD $r^2 \geq 0.8$) and seek putative function from *in silico* analyses and gene expression experiments. Candidate genes with the strongest supporting evidence are indicated in the last column of **Supplementary Table 4** with an indication of the supporting data source. All genome-wide significant variants in LD ($r^2>0.8$) with the variants reported here, ranked by supporting evidence, are annotated in **Supplementary Table 15**. Of the 107 validated sentinel SNVs three are Indels; all other variants are single nucleotide polymorphisms (SNPs). We identify non-synonymous SNVs at 13 of the 107 validated loci (**Supplementary Table 16**), three of which are predicted to be damaging (ANNOVAR) in *TFAP2D* (rs78648104), *NOX4* (rs56061986) and *CCDC141* (rs17362588, reported to be associated with heart rate[20]) (**Supplementary Fig. 5a**). Beyond the coding regions we identify 29 SNVs in 3'UTRs which are predicted to significantly weaken or cause loss of miRNA regulation by altering the recognition motif in seven genes, and strengthen or create target sites for miRNA binding in 13 genes (based on miRNASNP db, **Supplementary Table 16**).

From our expression Quantitative Trait locus (eQTL) analysis (GTEx), 59 of the 107 validated loci contain variants with eQTLs in at least one tissue (**Supplementary Table 17**); arterial tissue has the largest number of loci with eQTLs (**Supplementary Fig. 7**), with targeted *in silico* analysis showing six loci with eQTLs in arterial tissue (**Supplementary Table 16**). For example, the GTEx tibial artery eQTL in *SF3A3* (rs4360494) shows strong *in silico* supporting evidence, including an arterial DNase I site within which the major C allele removes a predicted AP-2

binding site **(Supplementary Fig. 8**). Hence we prioritized this gene for *in vitro* functional analysis (see below).

By considering all loci reported here (our 107 validated loci, and previously reported loci at the time of analysis), our DEPICT analysis identifies enrichment of expression across 31 tissues and cells (**Supplementary Fig. 9; Supplementary Table 18**), with greatest enrichment in the arteries (P = 1.9 x 10^{-6}, false discovery rate (FDR) < 1%). We use FORGE to investigate and identify significant (FDR, P <0.05) cell type specific enrichment within DNase I hypersensitive sites in a range of tissues including dermal and lung microvascular endothelial cell types, and cardiac fibroblasts (**Supplementary Fig. 10**). For a set of curated candidate regulatory SNVs from our 107 validated loci (see Supplementary Note), widespread enrichment is found in microvascular endothelium, aortic smooth muscle, aortic fibroblasts, vascular epithelium, heart and skin (**Supplementary Fig. 10**). In addition, we identify significant enrichment of histone marks in a wide range of cell types, including strong enrichment seen for H3K4Me3 (an activating modification found near promoters) marks in umbilical vein endothelial cells (HUVEC) (**Supplementary Fig. 11**). To explore expression at the level of cardiovascular cell types specifically, we use Fantom5 reference transcript expression data (see Online Methods) to cluster the 212 genes annotated to our 107 validated loci according to tissue specificity (**Supplementary Fig. 12**), with the significantly clustered genes forming four tissue-specific clusters, including a vascular smooth muscle cell (VSMC) and fibroblast cluster, an endothelial cell cluster (including probable endothelial cells in highly vascularized tissues), and a combined vascular cell cluster.

Additionally, Ingenuity pathway analysis and upstream transcriptional analysis show enrichment of canonical pathways implicated in cardiovascular disease, including those targeted by antihypertensive drugs, such as the alpha-adrenergic, CXCR4, endothelin signalling and angiotensin receptor pathways (**Supplementary Table 19**). In keeping with vascular mediation of genetic influence we identify diphenyleneiodonium, an inhibitor of flavin-containing oxidases, including NAD(P)H oxidase (NOX), which is reported to reverse endothelial dysfunction (and hypertension) in a rat model[21].

To identify long range target genes of non-coding variants, we use chromatin interaction (Hi-C) data from HUVEC, as enhancers and silencers often form chromatin loops with their target promoter. In most loci the strongest promoter interaction involves a gene in high LD with the SNV, but for 21 loci we find a distal potential target gene (**Supplementary Table 16**). Pathway analysis of the distal genes shows greatest enrichment in regulators of cardiac hypertrophy.

We evaluate pleiotropy using the Genomic Regions Enrichment of Annotations Tool (GREAT) to study enrichment of mouse phenotype and human disease ontology terms across all loci reported here. These highlight cardiovascular system abnormalities and vascular disease as the most highly enriched terms (**Supplementary Fig. 5b & 5c**).

Collectively evidence from eQTLs, DEPICT, DNase I sites, histone marks, Hi-C data and ontological analyses indicates predominant vascular and cardiovascular tissue involvement for genes within the BP associated loci.

We also look for association of our validated sentinel SNVs with metabolomic signatures. Three SNVs within the *NOX4*, *KCNH4* and *LHFPL2* loci show significant associations (family-wise error rate < 5%) with lipoprotein sub-fractions from ^{1}H Nuclear Magnetic Resonance (NMR) spectroscopy analysis of 2,000 Airwave study samples (**Supplementary Tables 20** and **21**). The results for these variants suggest a link between BP regulation and lipid metabolism. Eleven SNVs (including at *LHFPL2* locus) show association (family wise error rate < 5%) with metabolites in blood or urine from the publicly available "Metabolomics GWAS Server" resource based on mass spectrometry[22,23] (**Supplementary Table 21**), including sugar acids, sphingolipids, fatty acids, glycerophospholipids, organic acids and benzene derivatives.

Several genes and variants with putative function are highlighted in our *in silico* analysis as having biological support (e.g. eQTLs or nsSNVs) and those with novelty and tractability to laboratory investigation (e.g. expression in available tissue models) are prioritized. Sentinel variants in three genes which were highly significant in the combined meta-analysis (**Tables 2** and **3**) are selected for experimental testing and were successfully genotyped, each for at least 100 samples. We select *ADAMTS7* due to strong biological support (e.g. mouse knockout phenotype), *SF3A3* due to eQTLs, and *NOX4* as it contains a rare nsSNV (**Supplementary Table 9**) in addition to common variant associations. We use quantitative polymerase chain reaction (qPCR) to study the impact of these sentinel variants on gene expression in human VSMCs and endothelial cells (ECs) (see Online Methods). For *SF3A3*, the major C allele of variant rs4360494 associated with increased PP (0.278 mmHg ±0.03, P=3.7x10^{-16}, N=307,682) is associated with *SF3A3* expression in human VSMCs, although not in endothelial cells (**Supplementary Fig. 13a**); and the T allele of SNV rs62012628 in *ADAMTS7* associated with lower DBP (0.238 mmHg ±0.03, P=5.1x10^{-12}, N=244,143), is associated with reduced *ADAMTS7* expression in human VSMCs (**Supplementary Fig. 13b**), while the minor A allele of SNV rs2289125 at the *NOX4* locus associated with lower PP (-0.377 mmHg ±0.04, P=9.1x10^{-22}, N=282,851) correlates with increased *NOX4* expression in ECs though not VSMCs (**Supplementary Fig. 13c**). Our study thus finds evidence for novel *cis*-eQTLs in *ADAMTS7* and *NOX4* in addition to validating the previously reported GTEx eQTL in *SF3A3*, and supports the vascular expression of these genes.

Genetic risk score analyses

We create an unbiased genetic risk score (GRS) (**Supplementary Table 22**) to evaluate, in an independent cohort (Airwave, see Online Methods), the impact of the combination of all loci reported here on BP levels and risk of hypertension. When compared with the lowest quintile of the distribution of the GRS, individuals >50 years in the highest quintile have sex-adjusted mean SBP higher by 9.3 mm Hg (95% CI 6.9 to 11.7 mm Hg, P =1.0 x 10^{-13}) and an over two-fold higher risk of hypertension (OR 2.32 95% CI 1.76 to 3.06; P=2.8 x 10^{-9}) compared with individuals in the lowest quintile (**Fig. 3; Supplementary Table 23**). Similar results were obtained from GRS associations with BP and hypertension within UK Biobank (**Supplementary Table 24**). In UK Biobank − based on self-reported health data, record linkage to Hospital Episode Statistics and mortality follow-up data (**Supplementary Table 25**) − we show that the GRS is associated with increased risk of stroke, coronary heart disease and all cardiovascular outcomes; comparing the upper and lower fifths of the GRS distribution, sex-adjusted odds ratios are 1.34 (95% CI 1.20 to 1.49, P =1.5×10^{-7}), 1.38 (95% CI 1.30 to 1.47, P= 4.3×10^{-23}) and

1.35 (95% CI 1.27 to 1.42, P=1.3×10^{-25}) respectively (**Fig. 3; Supplementary Table 26**). Results are also provided for incident-only cases (**Supplementary Table 27**).

DISCUSSION

A key attribute of this study is the combination of a large, single discovery sample with standardized BP measurement and dense 1000 Genomes/UK10K imputation, yielding a high quality dataset with ~9.8 million variants[14], taking advantage of major international consortia for parallel replication of common and low-frequency variants. In total we include GWAS data from 330,956 individuals and exonic SNVs from a total of 422,604 individuals. This strategy resulted in 107 robustly validated loci for BP traits, including 32 loci that have not previously been reported, and at least 53 further loci validated for the first time. Despite its size, our study is still under-powered to find low-frequency variants. Our findings are mostly common variants, with similarly modest effect sizes as variants previously reported at the time of analysis (**Supplementary Fig. 14**). The lack of rare variant discovery could also be due to the challenge of detecting rare variants from imputed data. There may be greater potential for identifying rare variants from the future release of genetic data for all 500,000 UK Biobank participants.

Our findings point to new biology as well as highlighting gene regions in systems that have previously been implicated in the genetics of BP. Several of our validated loci affect atherosclerosis or vascular remodelling *(ADAMTS7, THBS2, CFDP1)* and exhibit locus pleiotropy in prior genome-wide association studies for coronary artery disease or carotid intimal-media thickness[24-26] (**Supplementary Fig. 5a** and **Fig. 4**). In previous work we have shown that expression of *ADAMTS7* is upregulated and increases vascular smooth muscle cell migration in response to vascular injury in relation to a distinct coronary artery variant (rs3825807, not in LD with our sentinel SNV; r^2 = 0.17)[27]. In endothelial cells *ADAMTS7* encodes a metalloproteinase to cleave thrombospondin-1 encoded by *THBS2* which leads to reduced endothelial cell migration and plays a role in neo-intimal repair in the vessel wall[27]. Our functional work indicates that the allele associated with lower DBP is also associated with lower *ADAMTS7* expression in human VSMCs; this fits with the murine knockout that exhibits reduced atherosclerosis. *SF3A3* encodes a splicing factor with no prior links to BP other than our reported association and eQTL. At the *CFDP1* locus our sentinel SNV is in high LD (r^2 = 0.95) with a variant previously associated with carotid intimal-medial thickness. Collectively our findings highlight a potential common mechanism among these genes in vascular remodelling that has previously been observed in small resistance arteries in essential hypertension[28].

NADPH oxidase 4 (*NOX4*) has an established role in the endothelium where it enhances vasodilatation and reduces blood pressure *in vivo*[29]. This oxidase generates reactive oxygen species in the endothelium and may contribute to salt sensitive hypertension in the kidney and the vasculature[30-32]. We found that the allele of the common variant at the *NOX4* locus correlates with increased tissue specific *NOX4* expression in endothelial cells rather than VSMCs (**Supplementary Fig. 13c**). *NOX4* mediates endothelial cell apoptosis and facilitates

vascular collagen synthesis contributing to endothelial dysfunction and arterial stiffness, and may explain the association with PP[33,34].

We identify several loci containing genes involved in vascular signalling and second messenger systems such as *PDE5A* and *PDE10A*[35-37]. The phosphodiesterase PDE5A hydrolyzes cyclic GMP and is inhibited by sildenafil which leads to vasodilatation[38]. This finding fits with our previous discoveries of a role for gene loci encoding elements of natriuretic peptide-nitric oxide pathway and guanylate cyclase signalling systems in BP regulation[18,39,40]. Our findings strengthen the case for evaluating the opportunity to repurpose PDE5A inhibitors for use in hypertension.

The importance of microvascular function is emphasised by the solute carrier transporters such as *SLC14A2* encoding a urea transporter, which has previously been linked to autosomal dominant Streeten type orthostatic hypotensive disorder[41] and BP response to nifedipine, a calcium channel blocker antihypertensive drug[42]. *SLC8A1* encodes a sodium calcium exchanger expressed in cardiomyocytes which alters cardiac contractility and hypertrophy and shows abnormal BP in SLC8A1 transgenic mice[43]. Variants at *SLC35F1* have previously been associated with resting heart rate and ventricular size which could contribute to BP elevation[44].

We also identify loci that are involved in cardiovascular development (*GATA2, KIAA1462, FBN2*, *FN1* and *HAND2)* such as fibrillin 2 (*FBN2*) which overlaps in action with fibrillin 1 in development of the aortic matrix[45-49]. In addition, fibronectin expression is increased in hypertension and in atherosclerosis but it may also play a role in the development of the heart[49-51].

Our analysis validates loci containing genes with prior physiological connection to BP such as *BDNF, FAM208A,* and *CACNA2D2*[52-54]. The neurotrophin Brain Derived Neurotrophic Factor (BDNF) modulates angiotensin 11 in the brain to elevate BP in experimental models; higher serum levels correlate with reduced risk of cardiovascular disease and mortality[52]. In experimental models FAM208A, which is thought to be a transcription factor, is a strong candidate for a QTL for BP[54]. The gene *CACNA2D2* encodes a subunit of the L-type calcium channel that is most abundantly expressed in the atrium and in neurones and may be a target for negatively chronotropic and inotropic calcium channel antagonists which reduce BP[55].

We examine long range genomic interactions using Hi-C, whereby the promoter region has a strong chromatin interaction with a novel SNV. One example is *EPAS1*, which is ~200kb away from the SNV (rs11690961). It encodes hypoxia-inducible factor 2alpha, which affects catecholamine homeostasis, protects against heart failure and mutations in the gene are associated with pulmonary hypertension[56]. Another such gene is *INHBA*, 1.3Mb away from the SNV (rs12531683**)**, which is elevated in pulmonary hypertension and contributes to vascular remodelling by inducing expression of endothelin-1 and plasminogen activator inhibitor-1 in pulmonary smooth muscle cells[57].

Our observation of 9-10 mm Hg higher BP at age 50+ years when comparing the top vs bottom fifths of the BP GRS distribution has potential clinical and public health implications. We stratified by age due to a significant interaction of the GRS with age (*P* ranging between

9.96×10^{-11} and 1.16×10^{-3} for interaction with continuous BP traits, $P = 0.012$ for hypertension). Measuring the GRS in early life raises the possibility of adopting an early precision medicine approach to offset the genetic risk through lifestyle intervention (i.e. reduced sodium intake, increased potassium intake, maintenance of optimal weight, low adult alcohol consumption and regular exercise)[58-60]. Studies of non-pharmacologic approaches to BP control indicate that 10 mm Hg or more reduction in SBP is an achievable goal through lifestyle measures alone[61], while recent evidence suggests that favorable lifestyle may offset the cardiovascular sequelae associated with high genetic risk[62]. As the above data are observational, the extent to which adherence to lifestyle recommendations amongst high genetic risk individuals might result in favorable outcomes remains uncertain; given the substantial effect of GRS on BP by middle-age, the potential for adopting early lifestyle intervention amongst individuals at high genetic risk, along with population-wide measures to lower BP, warrants further study.

Since the completion of our study, another BP GWAS using UK Biobank data has been published[15], as part of a larger single-stage combined meta-analysis without replication; it reported a total of 316 loci, including 241 loci identified from the meta-analysis involving UK Biobank that were not tested for validation. Of the 107 validated loci reported in our study, 32 are discovered and validated for the first time in our analysis of UK Biobank. In addition, 75 sentinel SNVs are in LD ($r^2 \geq 0.2$) with the recently reported loci[15] and we validate at least 53 of these for the first time in our study (indicated by "GIU" in **Tables 1-3**). Furthermore we note that 49 of the reported loci from the recent study[15] did not validate in our large independent replication resource.

In summary we describe 107 validated loci for BP offering new biology, identifying potential new therapeutic targets and raising the possibility of a precision medicine approach to modify risk of hypertension and cardiovascular outcomes. Altogether, this represents a major advance in our understanding of the genetic architecture of BP.

Data Availability Statement:

The data generated during the current study are available from the UK Biobank data repository (http://biota.osc.ox.ac.uk), which can be accessed by researchers upon application. This includes the derived GWAS analysis results summary data from our UK Biobank discovery data for all three BP traits. The genetic and phenotypic UK Biobank data are also available upon application to the UK Biobank (https://www.ukbiobank.ac.uk). All replication data generated during this study are included in the published article. For example, association results of look-up variants from our replication analyses and the subsequent combined meta-analyses are contained within all Supplementary Tables provided.

URLs

UK Biobank: https://www.ukbiobank.ac.uk/

Genotype imputation and genetic association studies using UK Biobank data: http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=157020

UK Biobank Axion Array Content Summary: http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=146640

Exome chip design: http://genome.sph.umich.edu/wiki/Exome_Chip_Design

Genotype-Tissue Expression (GTEx) database: www.gtexportal.org

GREAT Enrichment: http://bejerano.stanford.edu/great

Ingenuity Pathway Analysis (IPA) software: www.qiagen.com/ingenuity

Chembl: www.ebi.ac.uk/chembl/

Drug Gene Interaction database: dgidb.genome.wustl.edu

FORGE (accessed 16 Aug 2016): http://browser.1000genomes.org/Homo_sapiens/UserData/Forge?db=core

Fantom5 data (accessed 16 Aug 2016): http://fantom.gsc.riken.jp/5/

ENCODE DNase I data (wgEncodeAwgDnaseMasterSites; accessed 20 Aug 2016 using Table browser)

ENCODE cell type data (accessed 20 Aug 2016), http://genome.ucsc.edu/ENCODE/cellTypes.html.

Servier Medical Art: www.servier.fr/servier-medical-art

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Conflicts/Disclosures

MJC is Chief Scientist for Genomics England, a wholly owned UK government company. He leads the 100,000 Genomes Project which includes syndromic forms of blood pressure.

Author Contributions

Central analysis: HRW, CPC, HG, MRB, MPSL, MR, IT, BM, IK, EE.

Writing of the paper: HRW*, MRB, EE, CPC, HG, IT, BM, MR, MJC*, PE* (*Writing group leads).
Working group membership: MJC*, HRW, EE, IT, PBM, LVW, NJS, MT, JMMH, MDT, IN, BK, HG, MRB, CPC, JSK, PE* (*Co-Chairs).
Replication consortium contributor: [ICBP-1000G] GBE, LVW, DL, AC, MJC, MDT, POR, JK, HS; [CHD Exome+ Consortium] PSu, RC, DSa, JMMH [ExomeBP Consortium] JPC, FD, PBM [T2D-GENES Consortium and GoT2DGenes Consortium] CML; [CHARGE] GBE, CL, AK, DL, CNC, DIC; [iGEN-BP] ML, JCC, NK, JH, EST, PE, JSK, PVDH.
Replication study contributor: [Lifelines] NV, PVDH, HS, AMS; [GS:SFHS] JM, CH, DP, SP; [EGCUT] TE, MA, RM, AM; [PREVEND] PVDH, NV, RTG, SJLB; [ASCOT] HRW, MJC, PBM, PS, NP, AS, DS, ST; [BRIGHT] HRW, MJC, PBM, MB, MF, JC; [Airwave] HG, EE, MPSL, IK, IT, PE.
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Figure 1: Study design schematic for discovery and validation of loci. N: sample size; QC: Quality Control; PCA: Principal Component Analysis; BP: blood pressure; SBP: systolic BP; DBP: diastolic BP; PP: pulse pressure; SNVs: single nucleotide variants; BMI: body mass index; UKB: UK Biobank; UKBL: UK BiLEVE; GWAS: Genome-wide association study; MAF: Minor Allele Frequency; *P*: P-value; LD: Linkage Disequilibrium; 1000G: 1000 Genomes. UKBBvsUKBL: a binary indicator variable for UK Biobank vs UK BiLEVE to adjust for the different genotyping chips

Figure 2: Venn diagram of 107 validated loci from our study. This shows concordance of significant associations across the three blood pressure phenotypes for the 107 validated sentinel variants (Tables 1-3) from both the GWAS and exome analyses, according to genome-wide significance in the combined meta-analysis. The locus names labelled within the Venn Diagram correspond to Tables 1-3, and relate to the nearest annotated gene. The loci names in bold font highlight the 32 novel loci which are reported for the first time in our study.

Figure 3: Distribution of Genetic Risk Score (GRS) and its relationship with blood pressure, hypertension and CVD outcomes. The GRS is based on all reported loci: both previously reported loci at the time of analysis; and all validated blood pressure variants from this study. (a) Distribution of GRS in Airwave and sex-adjusted odds ratio of hypertension in age 50+ comparing each of the upper four GRS quintiles with the lowest quintile; dotted lines represent the upper 95% confidence intervals. (b) Mean blood pressures and standard deviation in bracket in Airwave age 50+ across GRS quintiles. (c) Distribution of GRS in UKB and sex-adjusted odds ratio of CVD, CAD and stroke comparing each of the upper four GRS quintiles with the lowest quintile; dotted lines represent the upper 95% confidence intervals. (d) Count of CVD, CAD and stroke (events and deaths) across GRS quintiles in UKB participants

Figure 4: Summary of gene cardiovascular expression from validated loci. Genes are shown on the basis of their tissue expression and supporting evidence summarised in Supplementary Table 16, based on Knockout (KO) phenotype, previously reported blood pressure biology or a strong functional rationale: eQTL (expression Quantitative Trait Loci), nsSNV (non-synonymous SNV), Hi-C. Multiple lines of evidence indicate the central importance of the vasculature in blood pressure regulation and we thus highlight existing drugged (*) and druggable (#) targets among these genes. Illustrations used elements with permission from Servier Medical Art. We note that some druggable genes may carry a safety liability, such as *GJA1*, which has known association with QT interval[20]

Table 1: Loci validated with SBP as primary trait: combined meta-analysis results from (a) GWAS and (b) Exome for the sentinel variant

Locus	Chr	Pos	rsID	EA	EAF	N	Beta	SE	*P*	Note
(a) GWAS										
NADK-CPSF3L	1	1,685,921	rs139385870	D	0.5	281,890	-0.352	0.05	$1.3x10^{-12}$	GIU
CELA2A	1	15,798,197	rs3820068	A	0.81	310,776	0.425	0.06	$1.1x10^{-12}$	GIU
GTF2B	1	89,360,158	rs10922502	A	0.62	323,666	-0.382	0.05	$2.2x10^{-15}$	GIU
FOSL2	2	28,635,740	rs7562	T	0.52	319,942	0.263	0.05	$1.9x10^{-8}$	
PRKD3	2	37,517,566	rs13420463	A	0.77	330,307	0.356	0.05	$7.0x10^{-11}$	GIU
METTL21A-AC079767.3	2	208,526,140	rs55780018	T	0.54	304,567	-0.391	0.05	$5.9x10^{-16}$	GIU
RYK	3	134,000,025	rs9859176	T	0.4	322,428	0.322	0.05	$1.3x10^{-11}$	G
NPNT	4	106,911,742	rs13112725	C	0.76	306,370	0.435	0.06	$1.5x10^{-14}$	GIU
TMEM161B	5	87,514,515	rs10059921	T	0.08	298,543	-0.526	0.09	$4.0x10^{-9}$	GIU
FBN2	5	127,868,199	rs6595838	A	0.3	328,401	0.344	0.05	$7.6x10^{-12}$	GIU
CASC15	6	22,130,601	rs6911827	T	0.45	326,471	0.296	0.05	$2.0x10^{-10}$	GIU
TFAP2D	6	50,683,009	rs78648104	T	0.92	305,426	-0.481	0.08	$1.3x10^{-8}$	
MKLN1	7	131,059,056	rs13238550	A	0.4	325,647	0.331	0.05	$1.9x10^{-12}$	
HIPK2	7	139,463,264	rs1011018	A	0.2	325,110	-0.329	0.06	$1.5x10^{-8}$	
ZFAT	8	135,612,745	rs894344	A	0.6	329,834	-0.258	0.05	$3.2x10^{-8}$	
PAX2	10	102,604,514	rs112184198	A	0.1	323,791	-0.659	0.08	$3.6x10^{-18}$	GIU
MCF2L	13	113,636,156	rs9549328	T	0.23	313,787	0.318	0.06	$1.5x10^{-8}$	GI
FERMT2	14	53,377,540	rs9888615	T	0.29	326,235	-0.318	0.05	$3.5x10^{-10}$	GIU
PPP2R5E	14	63,928,546	rs8016306	A	0.8	329,869	0.335	0.06	$3.7x10^{-9}$	
ABHD17C	15	81,013,037	rs35199222	A	0.45	323,407	0.322	0.05	$5.2x10^{-12}$	GI
CFDP1	16	75,331,044	rs11643209	T	0.42	309,242	-0.339	0.05	$1.8x10^{-12}$	GI
CRK	17	1,333,598	rs12941318	T	0.49	299,739	-0.269	0.05	$2.5x10^{-8}$	GIU
ACOX1	17	73,949,045	rs2467099	T	0.22	326,401	-0.307	0.06	$3.3x10^{-8}$	GIU
(b) Exome										
SSPN	12	26,438,189	rs6487543	A	0.77	244,842	0.3	0.05	$6.3x10^{-10}$	

Locus: named according to nearest annotated gene(s); Chr: chromosome; Pos: build 37; EA: effect allele; EAF: EA frequency in UK Biobank; Beta: effect estimate; SE: Standard Error of effect; P: P-value; N: total sample size analyzed; Note: indicates loci published since our analysis[15] from GERA (G), GERA+ICBP(HapMap) (GI) or GERA+ICBP(HapMap)+UKB (GIU) analyses.

Table 2: Loci validated with DBP as primary trait: combined meta-analysis results from (a) GWAS and (b) Exome for the sentinel variant

Locus	Chr	Pos	rsID	EA	EAF	N	Beta	SE	*P*	Note
(a) GWAS										
chr1mb25	1	25,030,470	rs6686889	T	0.25	322,575	0.185	0.03	$3.6x10^{-9}$	
DNM3	1	172,357,441	rs12405515	T	0.56	328,543	-0.165	0.03	$1.4x10^{-9}$	GIU
GPATCH2	1	217,718,789	rs12408022	T	0.26	320,983	0.198	0.03	$2.4x10^{-10}$	GIU
CDC42BPA	1	227,252,626	rs10916082	A	0.73	327,636	-0.177	0.03	$8.4x10^{-9}$	
WNT3A	1	228,191,075	rs2760061	A	0.47	312,761	0.23	0.03	$2.1x10^{-16}$	GIU
SDCCAG8	1	243,471,192	rs953492	A	0.46	325,253	0.22	0.03	$7.4x10^{-16}$	G
ADCY3	2	25,139,596	rs55701159	T	0.89	321,052	0.285	0.04	$7.2x10^{-11}$	
SLC8A1	2	40,567,743	rs4952611	T	0.58	309,395	-0.157	0.03	$4.0x10^{-8}$	
AC016735.1	2	43,167,878	rs76326501	A	0.91	318,127	0.419	0.05	$3.6x10^{-18}$	
GPAT2-FAHD2CP	2	96,675,166	rs2579519	T	0.63	311,557	-0.197	0.03	$4.8x10^{-12}$	
TEX41	2	145,646,072	rs1438896	T	0.3	329,278	0.234	0.03	$2.0x10^{-15}$	GIU
CCDC141	2	179,786,068	rs79146658	T	0.91	321,318	-0.311	0.05	$2.4x10^{-10}$	G
TMEM194B	2	191,439,591	rs7592578	T	0.19	304,672	-0.24	0.04	$9.5x10^{-12}$	
TNS1	2	218,668,732	rs1063281	T	0.6	315,354	-0.2	0.03	$1.3x10^{-12}$	GIU
CAMKV-ACTBP13	3	49,913,705	rs36022378	T	0.8	319,983	-0.202	0.03	$4.7x10^{-9}$	GIU
CACNA2D2	3	50,476,378	rs743757	C	0.14	328,836	0.245	0.04	$2.4x10^{-10}$	GIU
FAM208A	3	56,726,646	rs9827472	T	0.37	323,058	-0.177	0.03	$4.3x10^{-10}$	GIU
RP11-439C8.2	3	154,707,967	rs143112823	A	0.09	297,343	-0.403	0.05	$1.4x10^{-14}$	GIU
SENP2	3	185,317,674	rs12374077	C	0.35	327,513	0.163	0.03	$9.2x10^{-9}$	GIU
PDE5A	4	120,509,279	rs66887589	T	0.52	324,397	-0.215	0.03	$3.4x10^{-15}$	GIU
POC5	5	75,038,431	rs10078021	T	0.63	314,172	-0.164	0.03	$1.3x10^{-8}$	G
CPEB4	5	173,377,636	rs72812846	A	0.28	312,601	-0.209	0.03	$2.2x10^{-11}$	GIU
PKHD1	6	51,832,494	rs13205180	T	0.49	325,419	0.168	0.03	$7.0x10^{-10}$	GIU
PDE10A	6	166,178,451	rs147212971	T	0.06	296,010	-0.36	0.06	$1.6x10^{-9}$	GIU
SLC35F1	6	118,572,486	rs9372498	A	0.08	330,625	0.334	0.05	$1.8x10^{-11}$	GIU
SNX31	8	101,676,675	rs2978098	A	0.54	324,424	0.165	0.03	$1.5x10^{-9}$	
RP11-273G15.2	8	144,060,955	rs62524579	A	0.53	268,645	-0.175	0.03	$3.8x10^{-9}$	GIU
MTAP	9	21,801,530	rs4364717	A	0.55	327,173	-0.175	0.03	$1.3x10^{-10}$	
BDNF	11	27,728,102	rs11030119	A	0.31	330,002	-0.163	0.03	$2.9x10^{-8}$	GIU
MYEOV	11	69,079,707	rs67330701	T	0.09	276,760	-0.367	0.05	$2.1x10^{-12}$	GIU
RP11-321F6.1	15	66,869,072	rs7178615	A	0.37	318,076	-0.179	0.03	$2.6x10^{-10}$	
ADAMTS7	15	79,070,000	rs62012628	T	0.29	244,143	-0.238	0.03	$5.1x10^{-12}$	
chr15mb95	15	95,312,071	rs12906962	T	0.68	319,952	-0.221	0.03	$5.6x10^{-14}$	GIU
PPL	16	4,943,019	rs12921187	T	0.43	326,469	-0.174	0.03	$2.5x10^{-10}$	G
FBXL19	16	30,936,743	rs72799341	A	0.24	324,502	0.185	0.03	$5.8x10^{-9}$	GIU
CMIP	16	81,574,197	rs8059962	T	0.42	319,839	-0.17	0.03	$1.3x10^{-9}$	
ACE	17	61,559,625	rs4308	A	0.37	319,394	0.213	0.03	$6.8x10^{-14}$	GIU
MAPK4	18	48,142,854	rs745821	T	0.76	330,954	0.189	0.03	$1.4x10^{-9}$	
CCNE1	19	30,294,991	rs62104477	T	0.33	320,347	0.177	0.03	$1.2x10^{-9}$	GIU
PLCB1	20	8,626,271	rs6108168	A	0.25	327,368	-0.211	0.03	$1.1x10^{-11}$	
(b) Exome										
MRAS	3	138,119,952	rs2306374	T	0.84	281,715	-0.184	0.03	$7.4x10^{-9}$	GIU

Locus: named according to nearest annotated gene(s); Chr: chromosome; Pos: build 37; EA: effect allele; EAF: EA frequency in UK Biobank; Beta: effect estimate; SE: Standard Error of effect; P: P-value; N: total sample size analyzed; Note: indicates loci published since our analysis[15] from GERA (G), GERA+ICBP(HapMap) (GI) or GERA+ICBP(HapMap)+UKB (GIU) analyses.

Table 3: Loci validated with PP as primary trait: combined meta-analysis results from (a) GWAS and (b) Exome for the sentinel variant

Locus	Chr	Pos	rsID	EA	EAF	N	Beta	SE	*P*	Note
(a) GWAS										
chr1mb9	1	9,441,949	rs9662255	A	0.43	310,618	-0.207	0.03	1.9×10^{-10}	GIU
SF3A3	1	38,455,891	rs4360494	C	0.55	282,851	0.278	0.03	3.7×10^{-16}	G
RP4-710M16.1-PPAP2B	1	56,576,924	rs112557609	A	0.35	325,952	0.227	0.03	6.8×10^{-12}	
FGGY	1	59,653,742	rs3889199	A	0.71	329,486	0.351	0.03	1.8×10^{-24}	G
C2orf43	2	20,881,840	rs2289081	C	0.36	329,140	-0.223	0.03	5.5×10^{-12}	GI
PRKCE	2	46,363,336	rs11690961	A	0.88	327,847	0.34	0.05	3.9×10^{-12}	GIU
CEP68	2	65,283,972	rs74181299	T	0.62	324,224	0.23	0.03	9.6×10^{-13}	GIU
TCF7L1	2	85,491,365	rs11689667	T	0.54	330,634	0.176	0.03	1.7×10^{-8}	GIU
FN1	2	216,300,482	rs1250259	A	0.74	325,485	-0.314	0.04	8.7×10^{-19}	G
GATA2	3	128,201,889	rs62270945	T	0.03	279,925	0.607	0.1	1.8×10^{-9}	GIU
PALLD	4	169,717,148	rs1566497	A	0.42	320,948	0.236	0.03	1.9×10^{-13}	GI
chr4mb174	4	174,584,663	rs17059668	C	0.92	313,277	-0.332	0.06	2.8×10^{-8}	
LHFPL2	5	77,837,789	rs10057188	A	0.46	325,985	-0.205	0.03	6.7×10^{-11}	GIU
GJA1	6	121,781,390	rs11154027	T	0.47	316,708	0.207	0.03	1.1×10^{-10}	
ESR1	6	152,397,912	rs36083386	I	0.11	323,303	0.439	0.05	1.5×10^{-18}	G
FNDC1	6	159,699,125	rs449789	C	0.14	325,584	0.359	0.05	2.4×10^{-15}	GIU
THBS2	6	169,587,103	rs1322639	A	0.78	319,866	0.316	0.04	4.8×10^{-17}	G
SUGCT	7	40,447,971	rs76206723	A	0.1	328,162	-0.346	0.05	7.4×10^{-12}	GIU
SLC20A2	8	42,324,765	rs2978456	T	0.55	304,964	-0.188	0.03	1.2×10^{-8}	GIU
TRAPPC9	8	141,060,027	rs4454254	A	0.63	330,022	-0.261	0.03	5.1×10^{-16}	
SCAI	9	127,900,996	rs72765298	T	0.87	316,271	-0.374	0.05	2.7×10^{-14}	GI
KIAA1462	10	30,317,073	rs9337951	A	0.34	299,646	0.28	0.04	2.5×10^{-15}	G
ARHGAP12	10	32,082,658	rs10826995	T	0.71	327,373	-0.212	0.03	1.1×10^{-9}	GIU
PRDM11	11	45,208,141	rs11442819	I	0.11	326,483	-0.279	0.05	7.1×10^{-9}	GIU
NOX4	11	89,224,453	rs2289125	A	0.21	307,682	-0.377	0.04	9.1×10^{-22}	G
CEP164	11	117,283,676	rs8258	T	0.38	327,038	0.236	0.03	2.9×10^{-13}	G
CCDC41	12	94,880,742	rs139236208	A	0.1	291,244	-0.363	0.06	1.6×10^{-10}	G
RP11-61O1.1	14	98,587,630	rs9323988	T	0.63	327,551	-0.212	0.03	4.1×10^{-11}	GIU
VAC14	16	70,755,610	rs117006983	A	0.01	250,766	0.986	0.14	4.1×10^{-12}	
CDH13	16	83,045,790	rs7500448	A	0.75	321,958	0.329	0.04	1.1×10^{-19}	G
KIAA0753	17	6,473,828	rs7226020	T	0.56	303,389	-0.256	0.03	2.3×10^{-14}	GIU
TP53-SLC2A4	17	7,571,752	rs78378222	T	0.99	294,053	0.904	0.14	1.8×10^{-10}	GIU
KCNH4-HSD17B1	17	40,317,241	rs79089478	T	0.97	318,326	0.584	0.1	3.1×10^{-9}	
PYY	17	42,060,631	rs62080325	A	0.66	315,689	-0.186	0.03	4.0×10^{-8}	
MRC2	17	60,767,151	rs740698	T	0.56	311,450	-0.228	0.03	3.1×10^{-12}	
SLC14A2	18	43,097,750	rs7236548	A	0.18	330,075	0.352	0.04	2.0×10^{-18}	G
SLC24A3	20	19,465,907	rs6081613	A	0.28	315,546	0.263	0.04	1.6×10^{-13}	GIU
ARVCF	22	19,967,980	rs12628032	T	0.3	310,292	0.24	0.03	5.5×10^{-12}	GIU
XRCC6	22	42,038,786	rs73161324	T	0.05	267,722	0.496	0.07	2.8×10^{-11}	
(b) Exome										
CD34	1	208,024,820	rs12731740	T	0.1	279,078	-0.249	0.04	1.1×10^{-8}	
ZNF638	2	71,627,539	rs3771371	T	0.57	280,285	-0.16	0.03	5.8×10^{-9}	GIU
CRACR2B	11	828,916	rs7126805	A	0.73	145,162	0.222	0.04	3.3×10^{-9}	

Locus: named according to nearest annotated gene(s); Chr: chromosome; Pos: build 37; EA: effect allele; EAF: EA frequency in UK Biobank; Beta: effect estimate; SE: Standard Error of effect; P: P-value; N: total sample size analyzed; Note: indicates loci published since our analysis[15] from GERA (G), GERA+ICBP(HapMap) (GI) or GERA+ICBP(HapMap)+UKB (GIU) analyses.

Online Methods

UK Biobank data

Our GWAS analysis is performed using data from the interim release of the first ~150k UK Biobank (UKB) participants (**Supplementary Note**): ~100k individuals from UK Biobank genotyped at ~800,000 single nucleotide variants (SNVs) with a custom Affymetrix UK Biobank Axiom Array chip and ~50k individuals genotyped with a custom Affymetrix UK BiLEVE Axiom Array chip from the UK BiLEVE study[63], a subset of UKB. SNVs were imputed centrally by UKB using a merged UK10K sequencing + 1000G imputation reference panel. UK Biobank array design and protocols are available on the UK Biobank website.

Quality control

Following QC procedures already carried out centrally by UKB, we exclude discordant SNVs and samples with QC failures, gender discordance and high heterozygosity/missingness. We further restrict our data to a subset of individuals of European ancestry. By applying *kmeans* clustering to the Principal Component Analysis (PCA) data a total of N=145,315 Europeans remain (**Supplementary Fig. 15**). We use the kinship data to exclude 1st and 2nd degree relatives, with N=141,647 unrelated individuals remaining. Finally we restrict our data to non-pregnant individuals with two automated BP measurements available, resulting in a maximum of N=140,886 individuals for analysis (**Supplementary Note**).

Phenotypic data

After calculating the mean SBP and DBP values from the two BP measurements, we adjust for medication use by adding 15 and 10 mmHg to SBP and DBP, respectively, for individuals reported to be taking BP-lowering medication (21.4% of individuals)[64]. PP is calculated as SBP minus DBP, according to the medication-adjusted traits. Hypertension, used in secondary analyses, is defined as: (i) SBP ≥ 140 mmHg, or (ii) DBP ≥ 90 mmHg, (iii) or taking BP-lowering medication; otherwise individuals are classified as non-hypertensive. Descriptive summary statistics are provided for all individuals (**Supplementary Table 1**).

Statistical methods

Statistical approaches used for the discovery and replication of loci are reported in detail below. We also describe methods used for: identification of secondary signals; lookups in non-European populations and for monogenic BP genes; functional and experimental methods; construction of a genetic risk score for analysis with BP traits and cardiovascular outcomes. All *P*-values are from two-sided tests.

Analysis models

For the GWAS, we perform linear regression analyses of the three (untransformed) continuous, medication-adjusted BP traits (SBP, DBP, PP) for all measured and imputed genetic variants in dosage format using SNPTEST software[65] under an additive genetic model. We carry out a similar analysis for the exome content. Quantile-quantile plots are shown in **Supplementary Fig. 16**. Each analysis includes the following covariates: sex, age, age^2, body mass index, top ten PCs and a binary indicator variable for UK Biobank vs UK BiLEVE to adjust

for the different genotyping chips. We also run an association analysis within UKB for validated BP SNVs and hypertension using logistic regression under an additive model with adjustments as above. There are 76,554 hypertensive cases and the 64,384 remaining participants are treated as non-hypertensive controls. This sample size is slightly larger than the N=140,866 used in the main analyses, since participants with only one BP measurement, but with reported BP-lowering medication, could be included as hypertensive.

Previously reported variants

We compile a list of all SNVs previously reported to be associated with BP at the time of analysis (**Supplementary Table 13**). This list includes all published SNVs which have been identified and validated from previous GWAS, CardioMetabochip and exome chip projects[7-11]. We augment this list to include all 34,459 SNVs in Linkage Disequilibrium (LD) with these previously reported SNVs, according to a threshold of $r^2 \geq 0.2$. Results for all these variants are extracted for each of the three BP traits, to check previously reported BP associations in the UKB data, according to whether the sentinel SNV or a variant at the locus in LD ($r^2 \geq 0.2$) with it showed evidence of support ($P < 0.01$) for association with at least one of the three BP traits.

Replication strategy

We use three independent external data sets for replication (**Supplementary Note**). First, for the GWAS analysis based on advanced 1000G imputation enhanced by UK10K data we consider SNVs with MAF ≥ 1% and perform a reciprocal replication exchange with the International Consortium of Blood Pressure (ICBP) 1000G meta-analysis (max N = 150,134). The imputation strategy for ICBP 1000G meta-analysis is based on an earlier imputation grid for the 1000G project. In addition, we recruit further cohorts with 1000G data which had not contributed to the ICBP-1000G discovery meta-analysis: ASCOT-UK (N = 3,803), ASCOT-SC (N = 2,462), BRIGHT (N = 1,791), Generation Scotland (GS) (N = 9,749), EGCUT (N = 5,468), Lifelines (N = 13,292) and PREVEND (N = 3,619). This gives a total of N = 190,318 independent replication samples for the GWAS analysis.

Second, because the UK Biobank and UK BiLEVE genotyping chips contain exome content, we sought replication from two BP exome consortia (European exome consortium and the Cohorts for Heart and Ageing research in Genome Epidemiology – CHARGE BP exome consortium), to allow validation of coding variants and variants with lower frequency. The European exome consortium (N = 161,926) and CHARGE consortium (N = 119,792) give a total of N = 281,718 independent replication samples for the exome analysis.

Note that the lookups for GWAS and exome discovery are distinct sets of SNVs. Loci are assigned sequentially, prioritising the primary GWAS discovery first, then considering any remaining loci with non-overlapping exome content for replication in the independent exome replication resources.

Statistical criteria for replication

For the GWAS discovery, there are ~9.8 million SNVs with MAF ≥ 1% and INFO > 0.1. We consider for follow-up any SNVs with $P < 1 \times 10^{-6}$ for any of the three BP traits. For the exome

discovery, there are 149,026 exome SNVs (**Supplementary Note**) which were polymorphic with INFO > 0.1; for follow-up we consider all SNVs with MAF ≥ 0.01% and $P < 1x10^{-5}$. All such SNVs are annotated to loci according to both an LD threshold of $r^2 \geq 0.2$ and a 1Mb interval region (see **Supplementary Note**), and signals are classified either as belonging to unvalidated loci, or being potential secondary signals at previously reported loci at the time of analysis.

Selection of variants for follow-up

The sentinel (most significant) SNV from each association signal is selected for follow-up, all of which are pairwise-independent by LD ($r^2 < 0.2$). For the GWAS discovery, we check that potential lookup SNVs are covered within the ICBP-1000G replication data (**Supplementary Note**; **Supplementary Tables 28** and **29**). Of the 235 novel loci containing previously unreported SNVs with MAF ≥ 1%, INFO > 0.1 and $P<1x10^{-6}$, 218 are covered, and similarly 100 of the 123 potential secondary SNVs at 51 of the 54 previously reported BP loci are available for follow-up. For the exome discovery, by following up SNVs with MAF ≥ 0.01%, INFO > 0.1 and $P < 1x10^{-5}$ across the three BP traits, we carry forward for replication sentinel SNVs at 22 unvalidated loci, and potential secondary SNVs at three previously reported loci at the time of analysis. We produce locus zoom plots for each of the lookup variants.

Replication meta-analyses

The replication and combined meta-analyses are performed within METAL software[66] using fixed effects inverse variance weighted meta-analysis (**Supplementary Note**). The combined meta-analysis of both the UKB discovery (N = 140,886) and GWAS replication meta-analysis (max N = 190,070) include a total maximum sample size of N = 330,956. For the exome combined meta-analysis, we synthesize data from the UKB discovery exome content (max N=140,866), with the replication dataset from both exome consortia (total max N=281,718), giving a maximum sample size of N=422,604.

Validation Criteria

In our study a signal is declared validated if it satisfies ALL of the following three criteria:

(i) the sentinel SNV is genome-wide significant ($P < 5\times10^{-8}$) in the combined meta-analysis for any of the three BP traits;

(ii) the sentinel SNV shows evidence of support ($P < 0.01$) in the replication meta-analysis alone for association with the most significantly associated BP trait from the combined meta-analysis (NB: $P < 0.01$ is more stringent than a range of thresholds calculated according to False Discovery Rate (FDR), see Supplementary Methods);

(iii) the sentinel SNV has concordant direction of effect between the UKB discovery and the replication meta-analysis for the most significantly associated BP trait from the combined meta-analysis.

Secondary signals

By conditional analysis within UKB data we assess all validated secondary signals from our validated and previously reported loci at the time of analysis for independence from the

sentinel or previously reported SNV, respectively (**Supplementary Note**). We declare a secondary signal to be independent of the previously reported SNV if there is less than a 1.5 fold difference between the main association and conditional association *P*-values on a –log10 scale, i.e. if –log10(*P*) / -log10(*P*_cond) < 1.5. Note that the lookup criteria already ensure that the secondary variant is not in LD ($r^2 < 0.2$) with the previously reported SNV. If more than one SNV in a region is found to be independent we undertake further rounds of iterative conditional analysis.

Lookups in non-European ancestries

As a secondary analysis, we look up 102 and 5 validated SNVs from the GWAS and exome analyses, respectively, in non-European ancestry samples. These comprise analysis of East Asian (N = 31,513) and South Asian (N = 33,115) ancestry data from the iGEN-BP consortium[11] for the GWAS lookups, and South Asian (N = 25,937), African American (N = 21,488) and Hispanic (N = 4,581) ancestry data from the CHARGE BP exome consortium[10] and CHD+ Exome consortium[9], for the exome content lookups (**Supplementary Note**). We carry out a binomial (sign) test based on the number of SNVs with consistent directions of effect between UKB and each of the non-European ancestry samples.

Monogenic blood pressure gene lookups

The UKB arrays include some rare coding variants for monogenic disorders. We collate a list of all specific mutation variants within genes known to be associated with monogenic BP disorders[19]. Results from the UKB association analyses for all three BP traits are extracted for any of these SNVs directly covered within the UKB dataset (**Supplementary Table 14**). Note that a search of proxies did not augment the list of available variants, so results are reported for the specific variants only.

Functional analyses

In order to prioritize associated SNVs, we use an integrative bioinformatics approach to collate functional annotation (**Supplementary Table 30**) at both the variant and gene level for each SNV within the BP loci (all SNVs in LD $r^2 \geq 0.8$ with the BP-associated SNVs). At the variant level we use ANNOVAR[67] to obtain comprehensive functional characterization of variants, including gene location, conservation and amino acid substitution impact based on a range of prediction tools including SIFT and polyphen2. All nonsynonymous variants were predicted damaging by two or more methods.

We use the University of California Santa Cruz (UCSC) genome browser to review sequence specific context of SNVs in relation to function, particularly in the Encyclopedia of DNA Elements (ENCODE) dataset[68]. We use the UCSC table browser to annotate SNVs in ENCODE regulatory regions. We evaluate SNVs for impact on putative micro RNA target sites in the 3' un-translated regions (3'UTR) of transcripts by a query of the miRNASNP database[69]. We evaluate all SNVs in LD ($r^2 \geq 0.8$) with our validated sentinel SNVs for evidence of mediation of expression quantitative trait loci (eQTL) in all 44 tissues using the Genotype-Tissue Expression (GTEx) database, in order to identify validated loci which are highly expressed, and to highlight specific tissue types which show eQTLs for a large proportion of validated loci.

We further seek to identify validated loci with the strongest evidence of eQTL associations in arterial tissue, in particular.

At the gene level, we use Ingenuity Pathway Analysis (IPA) software (IPA®,QIAGEN Redwood City) to review genes with prior links to BP, based on annotation with the "Blood Pressure" Medline Subject Heading (MESH) term which is annotated to 684 genes. We also use IPA to identify genes which interact with BP MESH annotated genes, and evaluate genes for evidence of small molecule druggability based on queries of Chembl and Drug Gene Interaction database.

We then perform overall enrichment testing across all loci. Firstly, we use DEPICT[70] (Data-driven Expression Prioritized Integration for Complex Traits) to identify highly expressed tissues and cells within the BP loci. DEPICT uses a large number of microarrays (~37k) to identify cells and tissues where the genes are highly expressed and uses precomputed GWAS phenotypes to adjust for co-founding sources. DEPICT provides a *P*-value of enrichment and false discovery rates adjusted *P*-values for each tissue/cells tested.

Furthermore, to investigate regulatory regions, we employ a two tiered approach to investigate cell type specific enrichment within DNase I sites using FORGE, which tests for enrichment of SNVs within DNase I sites in 123 cell types from the Epigenomics Roadmap Project and ENCODE[71] (**Supplementary Note**). Validated sentinel SNVs from our study are analysed along with previously reported SNVs at the time of analysis and secondary signals (with *P*-value < 1×10^{-4}) to evaluate the overall tissue specific enrichment of BP associated variants. In a second analysis we use FORGE (with no LD filter) to investigate directly our curated candidate regulatory SNVs for overlap with cell-specific DNase I signals.

GenomeRunner[72] is used to search for enrichment of validated and previously reported sentinel SNVs with histone modification mark genomic features (Supplementary Note). Relevant cardiovascular tissue expression is investigated using Fantom5 reference transcript expression data (fantom.gsc.riken.jp/5) (**Supplementary Note**).

We use IPA (IPA®,QIAGEN Redwood City) to identify biological pathways and transcriptional upstream regulators enriched for genes within the BP loci. The transcriptional upstream regulator analysis aims to identify transcription factors, compounds, drugs, kinases and other molecules, for which the target is one of the BP genes under investigation.

We query SNVs against PhenoScanner[16] to investigate trait pleiotropy, extracting all association results with nominal significance at $P < 0.05$ for full reporting (**Supplementary Table 16**), and then extract genome-wide significant results to highlight the validated loci with strongest evidence of association with other traits (**Supplementary Fig. 5a**). We also use the Genomic Regions Enrichment of Annotations Tool (GREAT) to study gene set enrichment of mouse phenotype and disease ontology terms within our validated and previously reported loci at the time of analysis, using default SNV to gene mapping settings[73].

We carry out metabolomics analysis using two sets of data. First we use ^{1}H NMR lipidomics data on plasma from a subset of 2,000 participants of the Airwave Health Monitoring Study[74,75] (**Supplementary Note**). For each validated BP-associated SNV we ran association

tests with the lipidomics data using linear regression analyses, adjusted for age and sex. We computed significance thresholds using a permutation derived family wise error rate (5%) to account for the high correlation structure of these data (ENT=35)[76]. We also test each validated SNV against published genome-wide vs metabolome-wide associations in plasma and urine using publicly available data from the "Metabolomics GWAS Server" to identify metabolites that have been associated with variants of interest at $P < 3.0 \times 10^{-4}$ (Bonferroni corrected *P* for validated signals)[22,23].

Experimental methods

We prioritize genes for laboratory testing on the basis of evidence for SNV function (including coding variants, eQTLs and Hi-C interactions), biological support for relevance to BP (from literature review) and transgenic phenotype. We perform genotyping and Quantitative Reverse-Transcription Polymerase Chain Reaction (q RT-PCR) for the selected sentinel variants of interest using human vascular smooth muscle cells and endothelial cells and test for expression levels (**Supplementary Note**; **Supplementary Table 31**). All three SNVs were tested using an additive model.

Genetic risk scores

Genetic risk scores (GRS) are constructed using the independent Airwave study[74] data to assess the combined effect of the BP-associated variants on BP and risk of hypertension (**Supplementary Note**), whilst avoiding bias by "winners curse". We create weighted GRSs for all pairwise-independent, LD-filtered ($r^2 < 0.2$) previously reported variants at the time of analysis and our validated variants (sentinel and secondary SNVs) combined, using available SNVs (**Supplementary Table 22**). For the previously reported variants, we weight BP increasing alleles by the beta coefficients from the UKB analysis. For our validated variants, beta coefficients of the replication meta-analysis are used as independent, unbiased weights.

For the variance explained analyses within the independent Airwave cohort, we use three trait-specific GRSs (SBP, DBP, PP). Each GRS includes all variants, but weights are trait-specific, using the beta coefficients from the analysis of each of the three different BP traits, e.g. the SBP-GRS is weighted by the beta coefficients from the SBP-GWAS. To calculate the percent of variance for each BP trait explained by its corresponding trait-specific GRS, not accounted for by known factors, we generate the residuals from the regression model of each trait against covariates of age, age^2, sex and body mass index. We then fit a second linear model for the trait residuals with all the variants in the GRS plus the top 10 PCs.

For risk score analyses we calculate a single BP GRS, as the average of the SBP and DBP GRSs. We standardize the average GRS to have mean of zero and standard deviation of one. We assess the association of the continuous average GRS variable with each BP trait by simple linear regression. We also run a logistic regression to examine the association of the average GRS with risk of hypertension. We perform each analysis both with and without adjustment for sex. We test for interaction between age (< 50, and ≥50 years) and the effect of the GRS on BP. We then compare BP levels and risk of hypertension for individuals in the top and bottom 20% of the GRS distribution at ≥50 years using linear and logistic regression, respectively.

We also assess the association of the average BP GRS with cardiovascular outcomes in the UKB data. We include all pairwise-independent previously reported BP variants at the time of analysis, and our validated variants. We use logistic regression with binary outcome variables for coronary heart disease, stroke and cardiovascular disease (see **Supplementary Note**) and GRS as explanatory variable (with and without sex adjustment).

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Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk

SUPPLEMENTARY NOTE

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Supplementary Methods

1. UK Biobank data

The UK Biobank cohort includes ~500,000 volunteers aged 40-69 years of age ascertained through NHS registers[1]. Following informed consent participants completed a standardised questionnaire on life course exposures, medical history and treatments and underwent a standardised portfolio of phenotypic tests including two blood pressure measurements taken seated after two minutes rest using an appropriate cuff and an Omron HEM-7015IT digital blood pressure monitor. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2) with weight measured using an electronic weighing scales (Tanita BC-418). The participants undergo longitudinal life course linkage to electronic health data including Hospital Episode Statistics and Office for National Statistics cause of death data.

The UK Biobank and UK BiLEVE genotyping arrays overlap with over 95% of SNVs content in common. These customised chips were designed to give genome-wide coverage of SNVs, including some insertion deletion polymorphisms (indels) and include validated exome content from the first 55K participants in the UK exome chip study. With approved access to the full genetic data, a total of ~73 million autosomal genetic variants were available for analysis, of which ~9.8 million SNVs with minor allele frequency (MAF) >1% and imputation quality INFO > 0.1 are analysed here for GWAS.

2. Quality Control

All SNVs had passed central Quality Control (QC) checks, such as tests of Hardy-Weinberg Equilibrium, batch and plate effects, multi-allelic SNVs and poorly called SNVs. The SNVs which failed QC were set to missing for all individuals in the corresponding batch within the final genetic data files provided. Likewise, the QC performed centrally for each sample tested for heterozygosity and missing rates. Samples were further investigated for relatedness and Principal Components Analysis (PCA) was performed. Full details of the QC of the genetic data performed centrally by UK Biobank are available[2].

We performed additional QC of the genetic data, using QC files provided by UK Biobank. Variants were excluded according to two lists provided by UK Biobank: (i) 417 SNVs with discordant results between the two 1000 Genomes control samples added to each plate; (ii) 65 SNVs which were later found by UK Biobank to be discordant. Samples were excluded after application of basic QC filters following the central QC tests: (i) N=480 individuals indicated in the data, which were recommended for exclusion due to high missingness or heterozygosity rates; (ii) N=459 individuals flagged as QC failures from UK BiLEVE; (iii) N=191 individuals whose phenotypic sex differs from the genetically inferred sex.

We restricted our data to a subset of unrelated European ancestry individuals for analysis. First, we selected European ancestry individuals using the Principal Component (PC) results from the centrally generated PCA, which included the first 15 PCs for all ~150k samples. We performed a 4-means clustering according to each of PC1 and PC2 separately using the *kmeans* algorithm in R statistical software, corresponding to four ethnic groups (White, Black, Asian, Chinese) and created an intersection of these two clusterings, to create five final clusters (White, Black, Asian, Chinese, Mixed/Other) (**Supplementary Fig. 15**). We selected individuals corresponding to the White cluster, and further removed any remaining individuals with self-reported mixed ethnicity. A total of N=145,315 Europeans remained in the data for further QC. We note that this is larger than the subset of 120,286 individuals which UK Biobank classified as being “probable Caucasians amongst

people who self-identified as British" and used as a homogeneous European ancestry sample for variant QC[2], as stricter homogeneity is required for QC than for analysis.

Furthermore, we used the results of the central UK Biobank kinship analyses, which provided kinship coefficients and IBS0 estimates. We identified pairs of related samples and restricted the data to a set of unrelated individuals, by removing the individual with highest missingness rate within any pair of twins, 1st or 2nd degree relatives. Overall a total of N=141,647 unrelated European ancestry individuals remained post-QC.

3. Phenotypic data

In parallel, the phenotypic data were also considered for QC. In order to calculate the mean of the two blood pressure (BP) measurements, we restricted the data to individuals with both measurements available. From the full original dataset, this led to the exclusion of N=142 individuals with missing data for both 1st and 2nd BP readings, and N=139 / N=135 with only 1 of the 2 measurements available for systolic BP (SBP) / diastolic BP (DBP) respectively, as well as the exclusion of N=95 individuals who only had BP measurements from a manual sphygmomanometer. Individuals with missing covariates were removed from the data, hence excluding N=324 individuals with missing BMI. Furthermore we excluded N=35 pregnant women. These phenotypic sample exclusions were applied to all individuals who had passed the above genetic QC. Following both genetic and phenotypic data QC, the sample size for analysis therefore included N=140,882 and N=140,886 unrelated European ancestry individuals for SBP and DBP, respectively.

Analysis of the summary descriptive statistics of the UK Biobank sample (**Supplementary Table 1**) shows there were small but significant differences when comparing the UK Biobank vs UK BiLEVE participants, for age and BMI, due to large sample sizes. UK BiLEVE participants were slightly older and heavier compared to the UK Biobank participants. Moreover males and females were equally represented in the UK BiLEVE sample whereas more females (54.3%) were included in UK Biobank data.

4. Linkage Disequilibrium calculations

Linkage Disequilibrium (LD) was calculated between sets of variants within the full genetic dataset using PLINK software[3]. In order to do this, all genetic data were converted from BGEN format to PLINK binary format. For any given SNV for which LD calculations were performed, the LD was estimated for all variants within a 500kb window downstream and upstream of this reference SNV. All variants in LD with the reference SNV reaching an $r^2 \geq 0.2$ threshold were identified.

5. Exome variants

Considering all 247,870 SNVs from the exome chip (Illumina HumanExome BeadChip arrays) annotation file, we searched for all 241,561 autosomal SNVs from the polymorphic SNVs within our data. There were 149,325 SNVs covered directly, and a further 486 exome chip SNVs were covered by proxies ($r^2 > 0.7$) according to LD from the 1000G reference data set (phase3 v5a.20130502 and phase1 v3.20101123), giving a total of 149,811 SNVs to consider. All SNVs are directly genotyped on the exome chip within the two exome replication datasets.

6. **Post-results Quality Control (QC)**

We undertook further QC checks for any potential outliers. The additional QC included plots comparing trends between Minor Allele Frequency (MAF), Standard Error (SE), betas and *P*-values, Quantile-Quantile plots (**Supplementary Fig. 16**) with and without exclusion of known-LD variants (all variants in LD with previously reported variants at the time of analysis), and the corresponding lambda values for genomic inflation were also calculated. After inspection of our QQ-plots, we applied the LD score regression approach[4] to determine whether any inflation was due to polygenicity or underlying population stratification. In particular, inspection and comparison of such plots enabled the selection of the optimal threshold for MAF and INFO filters, where INFO is the imputation quality score output from SNPTEST. We applied a post-analysis filter using an INFO threshold of 0.1, to exclude SNVs with low imputation quality from our results. Inspection of the plots from UKB documentation[5] shows that imputation quality is high for SNVs with MAF ≥ 1%, and any SNVs with INFO ≤ 0.1 are mostly rare SNVs. Note that an INFO threshold of 0.1 is lower than previously used in smaller GWAS, but appears suitable due to the much larger sample size and high statistical power in UK Biobank[5]. Furthermore, our validated findings all have good imputation quality.

For the UK Biobank exome discovery, there were 149,026 Exome SNVs which were polymorphic with INFO > 0.1. Inspection of QC diagnostic plots specifically for these SNVs alone suggested an optimal MAF filter of 0.01%, thus excluding rare variant outliers with large beta and SE values. This gave 114,641 remaining SNVs. In keeping with other exome-based studies of rare variants, we chose a less stringent *P*-value threshold for these analyses to account for the lower statistical power to detect effects of rare variants. We considered for follow-up all SNVs with MAF ≥ 0.01%, INFO > 0.1 and $P < 1x10^{-5}$ for any of the three BP traits.

7. Loci assignment and classification

SNVs achieving the lookup threshold from both the UK Biobank GWAS and exome discovery efforts were combined with the previously reported BP associated SNVs at the time of analysis to identify all variants in LD, referred to as the LD-lookup SNVs. We define a locus according to both an LD threshold of $r^2 \geq 0.2$ and a 1Mb interval region. Hence variants reaching an $r^2 \geq 0.2$ threshold within 500kb downstream and upstream of the LD-lookup SNVs were identified and assigned to loci sets. A locus set is composed of all SNVs linked by LD regardless of their association *P*-value and whether previously reported or not. For example, if SNV *A* is in LD with SNV *B*, and SNV *B* is in LD with SNV *C*, but SNV *A* and *C* are not in direct LD; SNV *A*, *B* and *C* would be part of the same locus set as SNV *B* is in LD with both *A* and *C*. The loci were then classified into three different types: (i) non-significant previously reported locus, if it contained at least one SNV from the set of previously reported-LD variants for previously reported variants at the time of analysis, but did not reach any of the lookup thresholds so was not contained in the list of SNVs for replication, (ii) UK Biobank-GWAS locus, if it contained at least one SNV reaching the lookup criteria threshold from the GWAS discovery, (iii) UK Biobank-exome locus, otherwise, containing SNVs which exclusively came from the UK Biobank-exome discovery lookups and are not in LD with any of the GWAS discovery lookups and are therefore not contained in a UK Biobank-GWAS locus. All UK Biobank GWAS and exome top-loci were screened to check for the presence of previously reported LD variants, to distinguish our discovery loci from previously reported BP loci at the time of analysis. From here onwards, we use the word “novel” to distinguish from anything which had been previously reported at the time of analysis, and “previously reported” refers to all known variants that had been reported and validated at the time of analysis.

A second stage of loci assignment was performed on the novel and previously reported loci to identify potential secondary signals within these loci. Each novel locus was reduced only to the set of SNVs which met the lookup criteria thresholds, and these remaining SNVs were reassigned to new locus subsets by $r^2 \geq 0.2$, and denoted as signals. This allows the partitioning of loci into separate, independent signals, not in direct LD with each other, i.e. some loci may have multiple pairwise-independent ($r^2 < 0.2$) signals within a 1Mb region. Similarly, in order to identify potential secondary signals in the previously reported loci, each locus was reduced to the variants in LD meeting the lookup thresholds, and these variants were reassigned to new locus subsets. All subsets which contained at least one variant in direct LD with the previously reported SNVs were removed, leaving the remaining subsets as potential secondary signals. If validated, these potential secondary signals at novel and previously reported loci could then be subsequently tested for statistical independence by conditional analysis.

These final sets, novel and previously reported, are referred to as the discovery association signals. For each discovery association signal we identified the most significantly associated SNV within the set, with minimum *P*-value across all three BP traits, and refer to this as the sentinel SNV. Similarly, for any novel loci containing multiple signals within the 1Mb locus region, the sentinel signal was identified as the most significant SNV.

All SNVs within the loci were mapped to genes (GRCh37.75) when the variant localized within 5kb of the start or end of the gene's transcription (bedtools v2.17). Any genes which were annotated from previously reported-LD variants were listed, and referred to as previously reported BP genes (**Supplementary Table 2**).

A signal was classified as secondary within a previously reported region if it satisfied at least one of the following conditions: i) it is a secondary signal from a locus that contains at least one previously reported-LD variant (as above), ii) at least one of the SNVs within the signal's corresponding locus maps to a previously reported BP gene or feature (**Supplementary Table 30**), such as long non-coding RNA, pseudogenes, or long non-coding transcripts, iii) the sentinel SNV is within 500kb of a previously reported BP-associated SNV, or iv) the signal is within the HLA region (chr 6: 25–34 Mb) as for simplicity, due to the complicated LD structure, we treat the entire HLA region as a previously reported BP region.

All other signals are classified as not previously reported at the time of analysis, in order to be followed-up as potential novel loci.

8. Selection of variants for follow-up

For the primary discovery analysis, the sentinel signal SNV at each novel locus was considered for validation and then any other validated SNV signals within the 1Mb locus region were considered as potential secondary signals for conditional analysis investigation.

Due to the slightly different coverage from the imputation strategies and reference panels used by ICBP-1000G and UK Biobank, the list of UK Biobank-GWAS lookup signals was cross-referenced with the list of SNVs available within the ICBP-1000G data, in order to check that any SNVs selected for follow-up were covered within ICBP-1000G for possible replication. Of the total 235 SNVs selected for replication, 218 were covered within ICBP-1000G data, either directly or by proxies, or with an alternative SNV available within the locus. The proxies were in high LD with the sentinel SNV ($r^2 > 0.8$; using LD calculated within UK Biobank), for which the proxy with the highest r^2, then closest position to the sentinel SNV was selected. For loci where the sentinel SNV was not covered either

directly or by a proxy, the most significantly associated SNV across all BP traits with $P < 1x10^{-6}$ within the LD set, which was covered within ICBP-1000G data, was selected as the alternative SNV. Only 17 loci could not be followed-up, due to a lack of coverage in the replication resources (**Supplementary Table 29**). However, most of these signals were sets containing only a few associated SNVs, including many 'singletons' with only one SNV within the LD set at the $P < 1x10^{-6}$ lookup threshold, and therefore less likely to be covered in ICBP-1000G, and perhaps more likely to be potential spurious findings. We further checked that each SNV selected for follow-up had concordant single nucleotide polymorphism (SNP) vs Indel status in both UK Biobank and ICBP-1000G. Similarly, of the 54 previously reported BP loci containing potential secondary SNVs, 51 loci could be followed-up with the potential secondary SNVs covered within ICBP-1000G data. In summary, a total of 218 SNVs from the GWAS discovery association signals were requested for lookups.

9. **Replication datasets**

The following studies contributed to the replication of the UK Biobank-GWAS lookups. More information on the individual cohorts can be found within **Supplementary Table 3** (study characteristics, summary descriptives, genetic data information and quality control applied):

ICBP-1000G: The International Consortium for Blood Pressure GWAS 1000G analyses.

The individual studies who contributed to the ICBP-1000G discovery analyses are listed below:

AGES: Age, gene/Enviroment Susceptibility-Reykjavik Study

ARIC: Atherosclerosis Risk in Communities

ASPS: Austrian Stroke Prevention Study

B58C: British 1958 birth cohort

BHS: Busselton Health Study

CHS: Cardiovascular Health Study

COLAUS: Cohorte Lausannoise

COROGENE: Genetic Predisposition of Coronary Heart Disease in Patients Verified with Coronary Angiogram (controls for this study are a part of the National FINRISK Studies)

CROATIA-Korcula: CROATIA-Korcula

CROATIA-Split: CROATIA-Split

CROATIA-Vis: CROATIA-Vis

EGCUT: Estonian Genome Center

EGCUT2: Estonian Genome Center

EPIC: European Prospective Investigation in Cancer and Nutrition

ERF: Erasmus Rucphen Family

Fenland Fenland Study

FHS: Framingham Heart Study

FINNRISK CASE: Predicting CVD in FINRISK cohorts, cases

FINRISK_ctrl: Predicting CVD in FINRISK cohorts, controls

FUSION: Finland-United States Investigation of NIDDM Genetics Study

GRAPHIC: Genetic Regulation of Ambulatory Blood Pressure in the Community

H2000: Health 2000 controls

Health ABC The Health Aging and Body Composition Study

HTO

INGI_VB: Italian Network of Genetic Isolates - Val Borbera

INGI-Cilento: Italian Network on Genetic Isolates - Carlantino Project

INGI-FVG: Genetic Park of Cilento and Vallo di Diano Project

INIG-CARL: Italian Network on Genetic Isolates - Friuli Venezia Giulia Genetic Park

IPM: Charles R. Bronfman Institute for Personalized Medicine (IPM) BioBank Genome Wide Association Study of Cardiovascular, Renal and Metabolic Phenotypes

KORAS3: Kooperative Gesundheitsforschung in der Region Augsburg

KORAS4: Cooperative Health Research in the Region of Augsburg (Survey 4)

LBC1921: Lothian Birth Cohort 1921

LBC1921: Lothian Birth Cohort 1936

LOLIPOP_EW610: London Life Sciences Prospective Population Study

MESA: Multi-Ethnic Study of Atherosclerosis

MICROS: MICROS

MIGen: Myocardial Infarction Genetics Consortium

NESDA: Netherlands Study of Depression and Anxiety

NSPHS: The Northern Sweden Population Health Study

NTR: Netherlands Twin Register

ORCADES: Orkney Complex Disease Study

PHASE: Prospective Investigation of the Vasculature in Uppsala Seniors

PIVUS: Precocious Coronary Artery Disease

PROCARDIS: PHArmacogenetic Study of Statins in the Elderly at risk

RSI: Rotterdam Study 1

RSII: Rotterdam Study 2

RSIII: Rotterdam Study 3

SHIP: Study of Health in Pomerania

STR: Swedish Twin Register

TRAILS: Tracking Adolescents' Individual Live Surveys

TRAILS-CC: Tracking Adolescents' Individual Live Surveys - Clinical Cohort

ULSAM: Uppsala Longitudinal Study of Adult Men

WGHS: Women's Genome Health Study YFS The Young Finns Study

YFS: The Young Finns Study

ASCOT[6]: The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) includes (19,342 hypertensives) enrolled in a randomised controlled trial of calcium channel blocker based regimen or a beta-blocker based regimen with blood pressure greater than 140/90 mm Hg on treatment of 160/100 mm Hg off treatment and followed for 5.5 years. Only a subset of the participants consented to DNA extraction for genetic studies. Data was genotyped separately for patients from UK/Ireland (ASCOT-UK: N = 3,803) and Scandinavia (ASCOT-SC: N = 2,462).

BRIGHT[7]: The MRC British Genetics of Hypertension study (2,001 hypertensives) included white European individuals with hypertension drawn from the upper 5% of the blood pressure distribution and usually on treatment subjected to GWAS.

EGCUT[8]: The Estonian Biobank is the population-based biobank of the Estonian Genome Center of the University of Tartu (EGCUT). The project is conducted according to the Estonian Gene Research Act and all participants have signed broad informed consent. The cohort size is currently 51,535 people from 18 years of age and up. All subjects are volunteers and were recruited randomly by general practitioners (GP) and physicians in hospitals. A Computer Assisted Personal Interview is conducted at the doctor's office to record personal data (place of birth, place(s) of living, nationality etc.), genealogical data (family history spanning four generations), educational and occupational history, lifestyle data (physical activity, dietary habits – food frequency questionnaire, smoking, alcohol consumption, women's health, quality of life). The EGCUT database has been linked with the national registries and hospital databases for obtaining up-to-date phenotypic information, including but not limiting to Death Registry, Health Insurance Registry and epicrisis from major hospitals. Medical history and current health status are recorded according to the ICD10, medication according to the ATC. Anthropometric measurements, blood pressure (sitting position at the end of the interview), and resting heart rate are measured; 30-50 mL of venous blood are collected into EDTA Vacutainers. These are transported to the central laboratory of the EGCUT at +4…+6 ^{0}C (in 6 to 36h) where DNA, plasma and WBC are immediately isolated and kept in aliquots in MAPI straws in liquid N_2. All procedures are run according to ISO 9000-2008 (www.biobank.ee)

GenScot[9]: Generation Scotland: Scottish Family Health Study (GS:SFHS) is a family-based genetic epidemiology study of ~24,000 volunteers from ~7000 families across Scotland with the capacity for follow-up through record linkage and re-contact. Participants completed a demographic, health and lifestyle questionnaire and provided biological samples including DNA, and ~21,500 participants underwent detailed clinical assessment, including anthropometric, cardiovascular, respiratory, cognition and mental health (http://www.ed.ac.uk/generation-scotland).

Lifelines[10]: This is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 165,000 persons living in the North East region of The Netherlands. It employs a broad range of investigative procedures in

assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. Details of the protocol have been described elsewhere (https://www.lifelines.nl/lifelines-research/news).

PREVEND[11]: The Prevention of REnal and Vascular ENd-stage Disease (PREVEND) study is an ongoing prospective population-based study of individuals from the Netherlands, investigating the natural course of increased levels of urinary albumin excretion and its relation to renal and cardiovascular disease. Further details are available on the study website: www.prevend.org.

The following consortia contributed to the replication of the UK Biobank exome lookups:

European exome consortium[12]: Consortium comprises 51 studies from various European countries within 3 contributing consortia (CHD exome+ consortium, ExomeBP consortium, T2D-GENES/GoT2DGenes consortium). Samples from all studies were genotyped using a version of the Illumina exome array. Central QC was performed to identify studies with QC issues and remove variants failing quality thresholds. 3 quantitative traits were analysed (DBP, SBP, PP) with and without applying inverse rank normalisation, and HTN was analysed as a binary trait. The 51 contributing studies are: Airwave, ASCOT_SC, ASCOT_UK, 1958BC, BRIGHT_CASES, BRIGHT_CONTROLS, CROATIA-Korcula, DIABNORD, EGCUT, FENLAND, FINRISK97/02, GS:SFHS, GLACIER_Controls, GODARTS_diab, GODARTS_nondiab, GRAPHIC, HELICMANOLIS, HUNT, INCIPE, LBC1921, LBC1936, LIFELINES, MDC, Northern Finland Birth Cohorts 1966 and 1986, OBB, PIVUS/ULSAM, TwinsUK, UHP, UKHLS, ADDITION, DPS, DR'S EXTRA Study, FIN-D2D 2007, FINRISK 2007, FUSION, Health 2006/2008, Inter99, PPP, SDC, SDR/ANDIS, VejleCases, VejleCtrl, CCHS, CGPS, CIHDS, EPIC-CVD, EPIC-InterAct, MORGAM, PROSPER, WOSCOPS.

CHARGE BP exome consortium[13]: The CHARGE BP exome Consortium includes 16 studies from the CHARGE+ consortium including a total of 146,562 samples, of which N=120,473 are European ancestry. Samples from all studies were genotyped using Illumina Infinium Human Exome Array (v 1.0 or 1.1). QC was performed either centrally (10 studies) or by individual cohorts (6 studies) to identify studies with QC issues and remove variants failing quality thresholds. Four quantitative traits (DBP, SBP, mean arterial pressure, pulse pressure) were analysed with and without applying inverse rank normalisation. Hypertension was analysed as a binary trait. The 16 contributing studies are: AGES, ARIC, BioVU, CARDIA, CHS, FamHS, FHS, Health ABC, HRS, JHS, MESA, Mt. Sinai, Rotterdam Study, SHIP, WGHS, Women's Health Initiative.

10. Meta-analyses

The UK Biobank-GWAS replication meta-analysis combined the ICBP-1000G meta-analysis data with the lookup results from the seven other replication studies. As the ICBP-1000G data had been generated from a large meta-analysis of many studies, N-effective was provided, calculated as the product of the sample size and imputation quality per SNV within each study and summed over the whole ICBP-1000G meta-analysis. We therefore used N-effective as the input N for ICBP-1000G within METAL. For the seven individual studies, to take account of imputation quality and apply further QC prior to analysis, SNVs with imputation quality < 0.3 were excluded from the meta-analysis input, and sample size N was used for all remaining SNVs. Allele frequencies and strand alignments were tracked for consistency within the meta-analysis. For consistency with the SNVs present in the replication data sets, the results for the proxy SNVs were used within the UK Biobank

discovery input for the variants that required proxies or alternative SNVs to the sentinel SNVs for the UK Biobank-GWAS lookups. Overall, sentinel and proxy SNVs had similar levels of association in the UK Biobank-BP discovery analysis (**Supplementary Table 28**). Genomic control (GC) had already been applied to the ICBP-1000G meta-analysis and their post-GC results were used as the input into our meta-analysis. No further GC corrections were applied in METAL for our UK Biobank-GWAS replication or combined meta-analyses.

The UK Biobank-exome meta-analysis synthesized meta-analysis data of individuals of European ancestry from two BP exome consortia (European exome consortium and CHARGE BP exome consortium) for the lookup variants. As in the GWAS analysis the allele frequencies and strand alignments were tracked for consistency within the meta-analysis.

11. Significance thresholds

We note that the standard genome-wide significance threshold ($P < 5 \times 10^{-8}$) is suitable for validation from our combined meta-analysis. The UK Biobank-GWAS analysis follows up 9.8 million SNVs with MAF ≥ 1% and coverage in 1000G data, while recent simulations in the literature[14] suggest a similar significance threshold of $P < 3\times10^{-8}$ based on denser Whole-Genome Sequencing (WGS) studies filtered at MAF ≥ 1% with an LD-independence r^2 threshold of 0.8. In addition, we require replication support of $P < 0.01$ which is more stringent than a range of thresholds calculated according to False Discovery Rate (FDR) which gives FDR thresholds of $0.03 < P < 0.04$ using the approaches proposed by Benjamini and Hochberg [15]and Benjamini and Yekutieli[16] respectively. As a further protection against false positive findings, we require concordance in direction of effect between the discovery and replication resources.

12. Conditional analyses

Within the novel loci containing potential secondary validated SNVs within the 1Mb locus region, i.e. in addition to the sentinel SNV, conditional analysis was performed, conditioning on the sentinel SNV, to test for independence of the secondary SNV according to a 1.5 fold threshold for reduction in *P*-value, with adjustment for covariates as in the discovery GWAS. For validated novel loci with more than one secondary SNV, conditional analysis results were considered for all pairwise combinations of SNVs within the locus, sequentially in order of main discovery association significance, to conclude with a set of pairwise conditionally independent SNV association signals.

For previously reported loci at the time of analysis, each validated secondary known signal is matched to its corresponding locus according to the criteria which defined it as a secondary signal at that locus, i.e. either (i) the locus that it was partitioned from during the annotation pipeline, (ii) matching according to the annotated gene in common, or (iii) the locus containing the previously reported SNV which is within 500kb. As noted above, signals within the HLA region were excluded from further conditional analysis. For each of these loci the previously reported SNV(s) within the region are listed (**Supplementary Table 13**). Within SNPTEST, a conditional analysis is run for each previously reported region containing a validated secondary signal, allowing the region of analysis to cover both the previously reported locus and the secondary signal.

Further rounds of conditional analysis are performed for regions containing more than one independent validated secondary signal. The secondary signals are ordered by significance according to the UK Biobank discovery association *P*-values for their validated BP trait, and a second round of analysis then conditions further on the most associated secondary signal as well as the sentinel SNV

to assess whether any further SNVs pass the 1.5 fold threshold test of independence. This iterative conditioning process continues until no remaining secondary SNVs pass the conditional test.

13. Lookups in non-European ancestries

The following consortia and studies contributed to the non-European ancestry lookups:

iGEN-BP[17]: The International Genomics of Blood Pressure Consortium (iGEN-BP) genome-wide association was analyzed in a total of 31,516 individuals of East Asian ancestry and 33,126 of South Asian ancestry. Imputation was carried out using haplotypes from HapMap Phase 2. Quality control checks included on the distribution of effect sizes across phenotypes and comparison of allele frequencies against those expected from HapMap populations. There were between 2,127,883 (SBP) and 2,166,286 (hypertension) SNPs for analysis after quality control. Associations of SNPs with phenotype were tested in each cohort separately in single-marker tests, using regression analysis and an additive genetic model. Principal components and other study-specific factors were included as covariates to account for population substructure. Test statistics from each cohort were then corrected for their respective genomic control inflation factor to adjust for residual population substructure. SNPs with information score <0.5 and minor allele frequency (MAF) <1% (weighted average across the cohorts) as well as sample size <50% of the maximum n for the phenotype were removed. SNPs showing heterogeneity of effect ($P\_het < 1 \times 10^{-8}$) were also removed. The 23 studies contributing to the East Asian ancestry meta-analysis are: AASC, CAGE-Amagasaki, CAGE_GWAS1, CAGE-KING_Ommi, CAGE-KING_Quad, CLHNS, GenSalt, KARE, NHAPC, SCES, SiMES, SP2-1m, SP2-550, SP2-610, SRS_Cases, SRS_Controls, TWSC, Vanderbilt_birdsuite, Vanderbilt_panscan, Vanderbilt_CRC_GWAS (SHANGHAI1), Vanderbilt_CRC_GWAS (SHANGHAI2), Vanderbilt_upperGI (SMHS), Vanderbilt_upperGI (SWHS). The 13 studies contributing to the South Asian ancestry meta-analysis are: AIDHS/SDS_Cases, AIDHS/SDS_Controls, LOLIPOP_IA300, LOLIPOP_IA610_Cases, LOLIPOP_IA610_Controls, LOLIPOP_IAP, PROMIS_GWAS1_Cases, PROMIS_GWAS1_Controls, PROMIS_GWAS2_Cases, PROMIS_GWAS2_Controls, RHS, RHS_610K, SINDI.

The CHD exome+ consortium[18] contributed South Asian samples from two studies: N=5,756 individuals from BRAVE (Bangladesh Risk of Acute Vascular Events study) and N=22,094 individuals from PROMIS (Pakistan Risk of Myocardial Infarction Study; http://www.phpc.cam.ac.uk/ceu/research/promis/).

CHARGE BP exome consortium[13]: The CHARGE BP Exome Consortium also contributed samples of African (N=21,503) and Hispanic (N=4,586) ancestry.

Note: Only SNVs available in at least 60% of the samples within each study were considered within the non-European lookup analyses.

14. Airwave Study data

The Airwave Health Monitoring Study (Airwave)[19] was used as an independent cohort for risk score analyses (see Methods Online) and for analysis of metabolomics data. The Airwave analyses included 14,002 participants with imputed genetic data. Systolic and diastolic blood pressures were measured as three consecutive readings using a digital blood pressure monitor (Omron HEM 705-CP digital BP monitor). Mean SBP and DBP adjusted for medication (as previously defined) were calculated from available readings and were used as dependent variables in the analyses.

Genetic risk scores (GRS) were constructed from a combination of both previously reported variants at the time of analysis, and validated SNVs from our study. Genetic dosages were extracted from the

Airwave 1000G imputed data, extending to proxies ($r^2 > 0.8$) if required. The previously reported BP variants were filtered by LD (r^2 of 0.2) and of the remaining 152 independent SNVs, 144 SNVs were covered exactly, and proxies were available for another 2 SNVs, providing a total of 146 pairwise-independent SNVs. All the 115 validated novel variants were available in the Airwave data. Weights were applied to all previously reported and novel SNVs in the GRS, as described in the Online Methods and in **Supplementary Table 22**.

From the Airwave plasma ^{1}H NMR metabolomics dataset measured using MRC-NIHR National Phenome Centre protocols, we undertook a lipoprotein subclass analysis using a regression-based prediction of lipid concentrations to characterise lipids (cholesterol, free cholesterol, phospholipids and triglycerides) and apolipoproteins (Apo-A1, ApoA2 and Apo-B) for VLDL, IDL, LDL and HDL classes, as well as six subclasses of VLDL and LDL and four subclasses HDL (data provided by Brucker Biospin GmbH, Rheinstetten Germany [20]). Overall, 105 different lipoprotein subclasses were generated from the deconvolution the CH3-group signal of the lipoproteins at 0.8ppm. (**Supplementary Table 20**).

15. Cardiovascular outcomes data in UK Biobank

To classify cardiovascular disease (CVD) outcomes we used self-reported baseline information on CVD prevalence available in UKB, and linkage to Hospital Episodes Statistics (HES) and mortality data. HES provide detailed information for participants admitted to hospital and includes coded data on diagnoses and operations. Coronary artery disease, stroke and peripheral artery disease were classified using International Classification of Disease (ICD) 9 and 10 codes and operation codes (**Supplementary Table 25**). The large UK Biobank cohort with sufficient numbers of cardiovascular events enables the assessment of cardiovascular risk within the same data set, noting that results are still independent, as the variants within the GRS are selected for their association with BP, not for cardiovascular outcomes.

16. Functional analyses

A structured approach was used to identify candidate regulatory variants, using two sources of regulatory information for annotation: ENCODE annotated DNase I sites in 123 cell types (wgEncodeAwgDnaseMasterSites) and a reference data set of over 3 million DNase "footprint variants". Footprint variants were defined by Moyerbrailean et al, (2016)[21] from a set of functional regulatory regions that integrate sequence position weight matrices with ENCODE and NIH Roadmap DNase I footprinting data to predict the impact of a sequence change on transcription factor binding in a panel of 650 cell-types. All variants in LD ($r^2 \geq 0.8$) with the sentinel SNV were reviewed and the variant with the lowest imputed *P*-value (for the same trait association as the sentinel) overlapping a DNase site was selected as the best regulatory candidate in each locus.

Hi-C analyses: Since SNVs in intergenic regulatory regions may act through long-range promoter-enhancer/silencer chromatin interactions, we aim to identify distant target genes of SNVs using chromatin folding data. Chromatin interaction can be assayed with the Hi-C technique, which identifies interacting genomic regions from the number of paired-end sequence reads that connect two genomic regions after crosslinking the cells, digesting the genome with a restriction enzyme and ligating fragment ends that are held together by 3D chromatin interactions. The 3D folding of the genome is tissue specific, therefore In order to identify potential target genes of SNVs, we used a cell type relevant to the BP phenotype, human umbilical vein endothelial cells (HUVEC)[22].

To find regulatory loops, from our validated GWAS loci, we took the location of either the sentinel SNV, if it was in a DNaseI hypersensitivity site (DHS), or the next most significant SNV for the same trait within a DHS and therefore potentially a regulatory SNV. Then using 5kb resolution HUVEC Hi-C data, taking only reads MAPQ>30, we identified the strongest SNV interacting regions after Knight&Ruiz (KR) normalisation of interaction strength and distance normalization. Taking the strongest interaction where the interacting region overlapped with a promoter region, as annotated by the ChIPseeker R package, we defined the potential target genes of these regulatory SNVs.

Enrichment testing: In order to distinguish enrichment of the validated variants from our study against the previously reported variants at the time of analysis, we performed two sets of enrichment analyses. The first only included our validated SNVs and their proxies in high LD ($r^2 \geq 0.8$) (**Tables 1-3**), and the second investigated all SNVs together (SNVs validated in our study, previously reported variants at the time of analysis, and secondary SNVs) and their proxies in high LD ($r^2 \geq 0.8$). The two analyses allow us to identify properties of our findings as well as highlighting mechanisms (e.g. pathways, tissues, cells, etc.) for all BP-associated variants.

FORGE[23] analysis: FORGE compares the frequency of query SNVs in different cell types with a reference set of 1204 control SNVs from the NHGRI GWAS catalog with discovery *P*-values $< 5 \times 10^{-8}$ in European ancestry populations. For each cell-type and *P*-value threshold, the enrichment of query SNVs mapping to footprints is expressed as a *P*-value derived from a logistic mixed effect model.

GenomeRunner[24] analysis of histone marks: GenomeRunner tests whether co-localization of a set of BP-associated SNVs with genome annotation features is significantly different from what would be expected by chance for a similar sized random set of SNVs. Tracks of histone modifications obtained by ChIP-seq from ENCODE were used for the assessment of histone marks, and significant enrichment of histone marks was investigated in a wide range of cell types. We also tested for cell type specificity of enrichments of SNV sets, which compares whether a cell type-specific enrichment is significantly different from the overall enrichment of a SNV set.

Fantom5[25] analysis of tissue clustering: Cardiovascular relevant tissue expression was investigated, using Fantom5 reference transcript expression data (fantom.gsc.riken.jp/5). Kmeans clustering was performed on BP-associated genes at our validated loci with Gene Cluster 3.0[26] using a Euclidean distance similarity matrix and K=5. Clusters were visualized using Java Treeview[27].

17. Experimental studies

Gene expression associated with sentinel SNVs in *SF3A3*, *ADAMTS7*, *NOX4* was tested using vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) isolated from human umbilical cord artery and vein (Royal London hospital, UK) respectively according to established protocol[28], and approved by the appropriate local ethics committee (08/H0704/140). VSMCs and ECs were harvested from flasks and suspended in 500µL lysis buffer (10 mM Tris PH 8.0, 10 mmol/L EDTA, 100 mmol/L NaCl, 0.5 % w/v SDS), and were then administered 250µL 5mmol/L NaCl. The mixture was centrifuged at 12,000g for 5min and the supernatant transferred to a fresh eppendorf then 500µL isopropanol added. The DNA pellet was collected and washed with 500µL 70% ethanol, then resolved in 40µL nuclear free water. The concentration of DNA was quantified by NanoDrop and adjusted to 5ng/µL for further genotyping. The Kbiosciences Competitive Allelic-specific PCR SNP genotyping system (KASPar; LGC Genomics Kbiosciences) was used for genotyping according to product introductions. Primers targeting the allelic specific DNA amplification were designed by Primer-Picker (Kbiosciences) (**Supplementary Table 31**). 10ng DNA from each sample plus the master mix was plated in a 384-well plate and subjected to PCR (ABI 7900HT machine).

Total RNA was extracted from human VSMCs and ECs, using the SV total RNA isolation system (Promega), then reverse transcribed into complementary DNA (cDNA) with the ImProm-IITM Reverse Transcription System (Promega) according to manufacturer's instructions. qRT-PCR for *SF3A3*, *ADAMTS7*, *NOX4* and 18S (internal control) was performed on cDNA in duplicate by using Power Up SYBR® Green PCR Master Mix kit (Life Technologies) according to the product guide using real-time quantitative PCR instrument (ABI 7900HT machine). Three pairs of primers were designed (**Supplementary Table 31**) and tested specificity and only primer pairs that had good specificity were chosen for the qPCR. The expression levels of *SF3A3, ADAMTS7 and NOX4* relative to 18S from independently repeated experiments were then determined by the $2^{-\Delta\Delta Ct}$ method[29].

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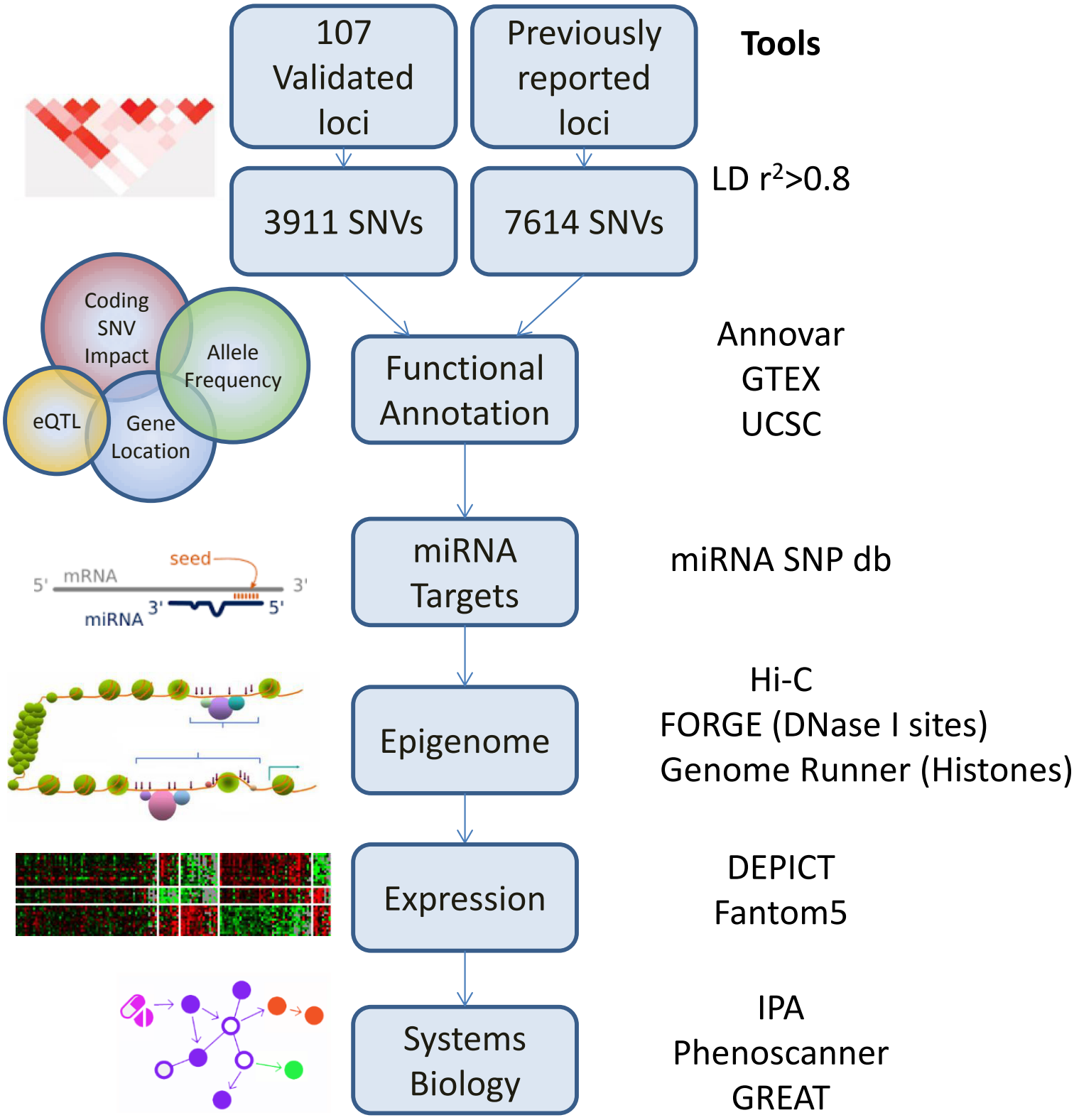
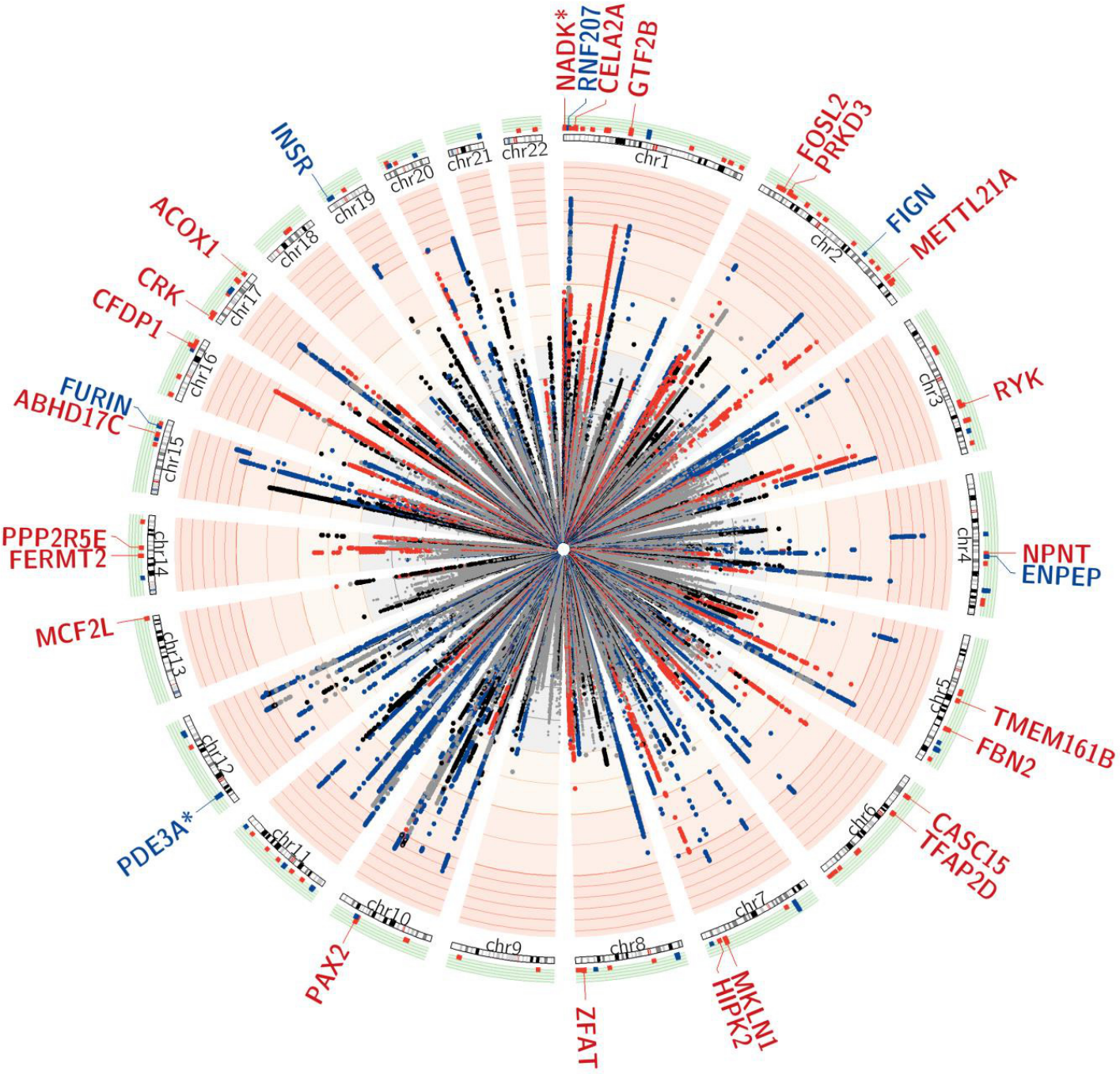
Supplementary Figure 1: Functional analyses schematic for the functional annotation and prioritisation of GWAS associated variants and genes. SNVs: single nucleotide variants; LD: Linkage Disequilibrium; eQTL: expression Quantitative Trait Loci; UCSC: University of California Santa Cruz (UCSC) genome browser; IPA: Ingenuity Pathway Analysis (IPA) software (IPA®,QIAGEN Redwood City,www.qiagen.com/ingenuity); DEPICT: Data-driven Expression Prioritized Integration for Complex Traits; GREAT: Genomic Regions Enrichment of Annotations Tool.

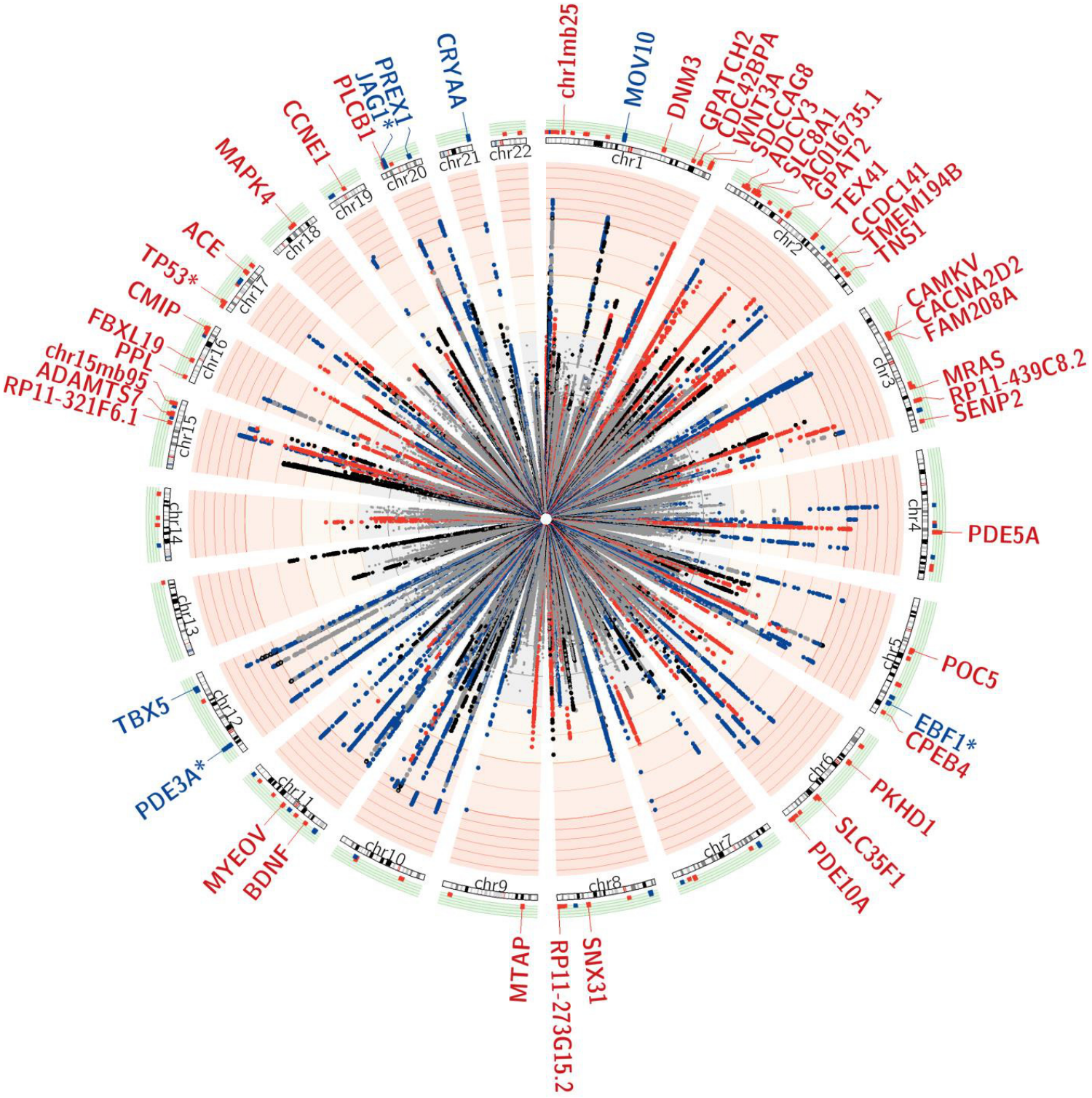


Supplementary Figure 2: UK Biobank GWAS discovery circos Manhattan plots (a), (b) and (c) for systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP) respectively. *P*-value results are plotted on a –log10 scale (see legend) for all ~9.8 million variants with Minor Allele Frequency (MAF) ≥ 1% and imputation quality INFO > 0.1 analysed within the GWAS discovery. Associations are plotted in red for all variants within the 107 validated loci from our study, in black for variants within unreported loci at the time of our analysis which were looked-up ($P<1\times10^{-6}$) in replication data but did not replicate, in blue for all variants within blood pressure loci that were previously reported at the time of our analysis, and grey otherwise. Loci names labelled around the edge are specific to each blood pressure trait, with red labels corresponding to loci validated in our analysis for the given trait (102 validated loci from Tables 1- 3 in total across all three plots from GWAS), and blue labels corresponding to previously reported loci at the time of analysis within which new independent secondary variants were identified (20 GWAS variants in total from Supplementary Table 8b)

(a) SBP



(b) DBP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ADCY3
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TEX41
CCDC141
TMEM194B
TNS1
CAMKV
CACNA2D2
FAM208A
MRAS
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SENP2
PDE5A
POC5
EBF1*
CPEB4
PKHD1
SLC35F1
PDE10A
SNX31
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MTAP
BDNF
MYEOV
PDE3A*
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CMIP
TP53*
ACE
MAPK4
CCNE1
PLCB1
JAG1*
PREX1
CRYAA
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chr2
chr3
chr4
chr5
chr6
chr7
chr8
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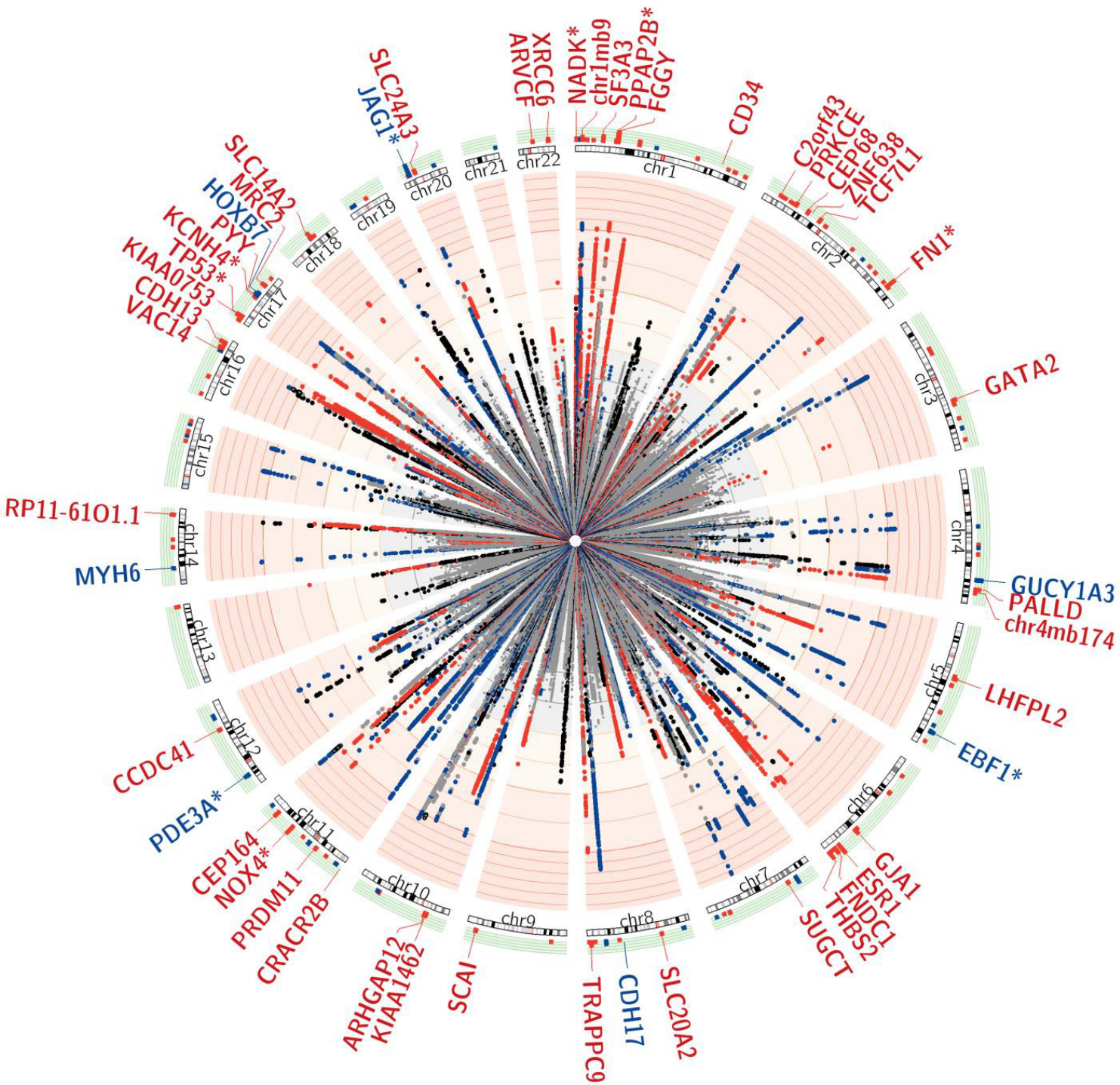
chr22

(c) PP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PRKCE
CEP68
ZNF638
TCF7L1
FN1*
GATA2
GUCY1A3
PALLD
chr4mb174
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GJA1
ESR1
ENDC1
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SUGCT
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CCDC41
MYH6
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CDH13
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PYY
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MRC2
SLC14A2
JAG1*
SLC24A3
ARVCF
XRCC6
NADK*
chr1mb9
SF3A3
PPAP2B*
FGGY

Supplementary Figure 3: Locus zoom plots of (a) 102 validated sentinel variants from UK Biobank GWAS discovery and (b) 5 validated sentinel variants from UK Biobank exome discovery. Linkage Disequilibrium is calculated within UK Biobank, with grey corresponding to $r^2 < 0.1$. SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAF: Minor Allele Frequency; INFO: Imputation quality score from SNPTEST.

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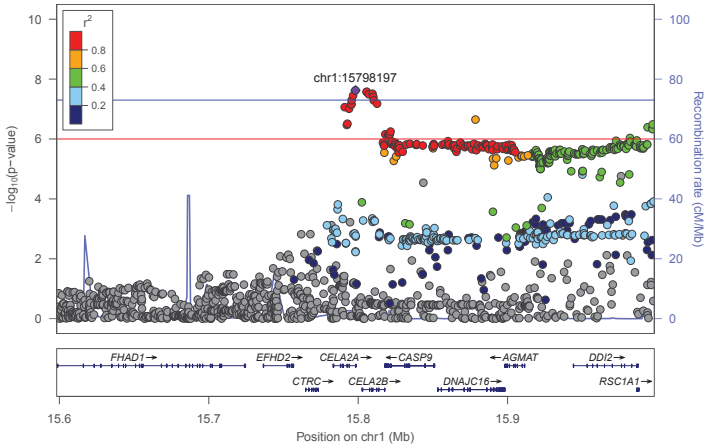

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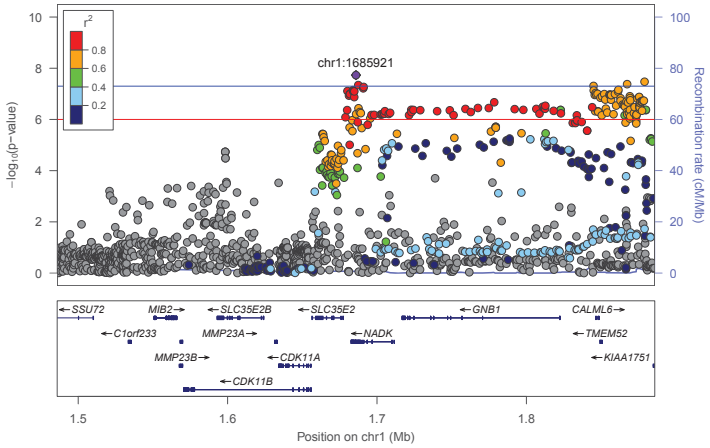

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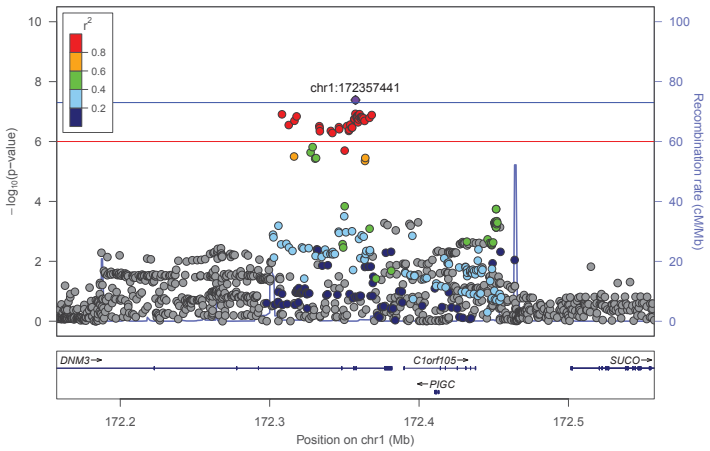

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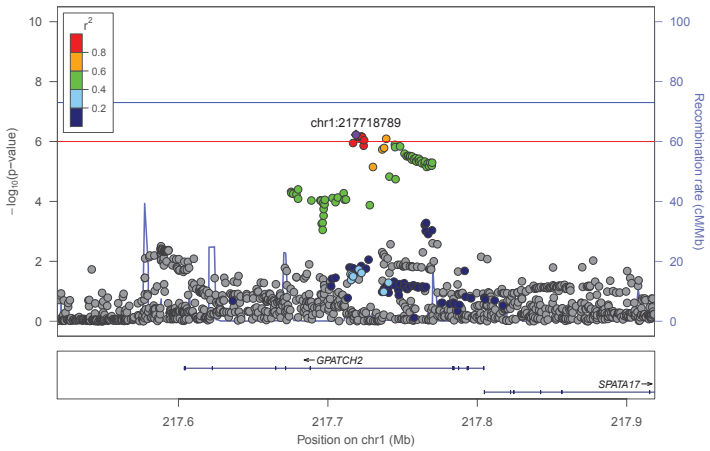

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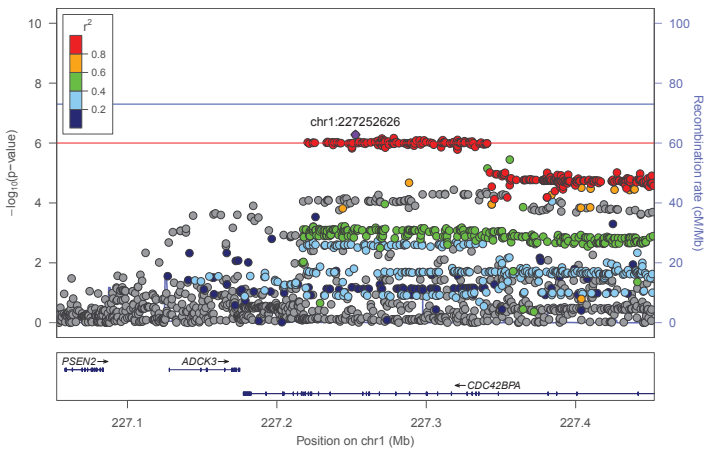

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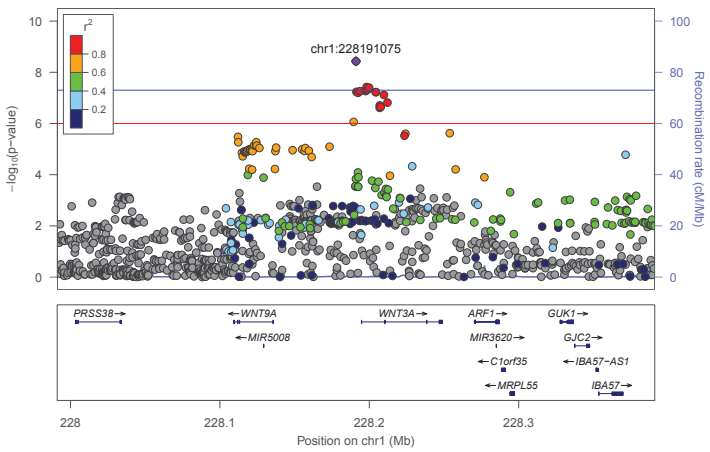

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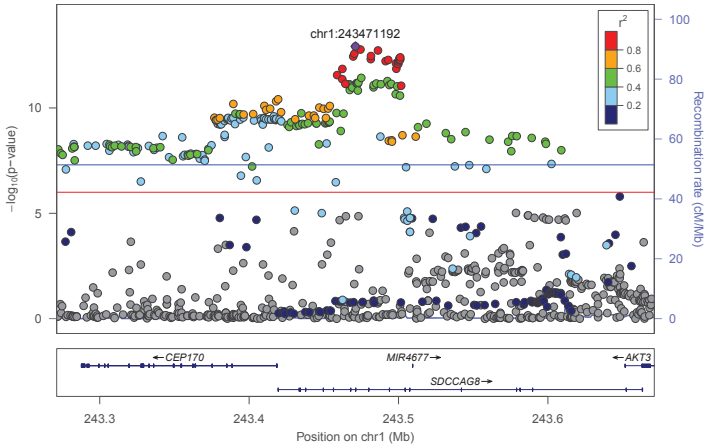

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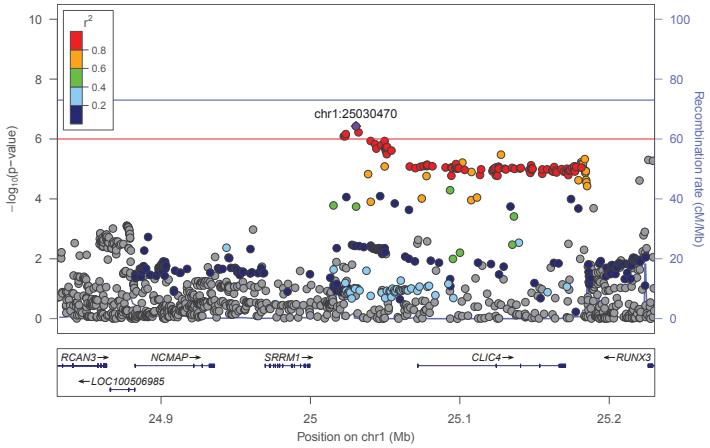

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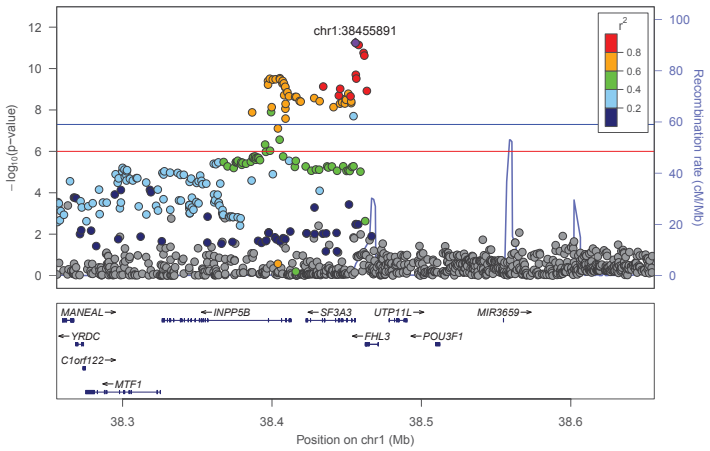

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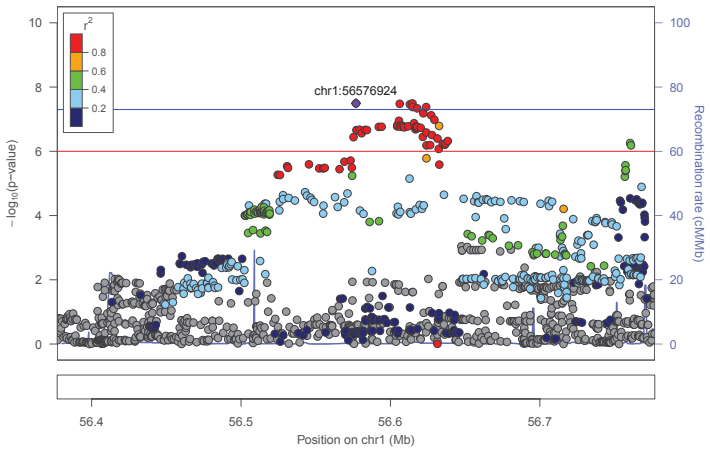

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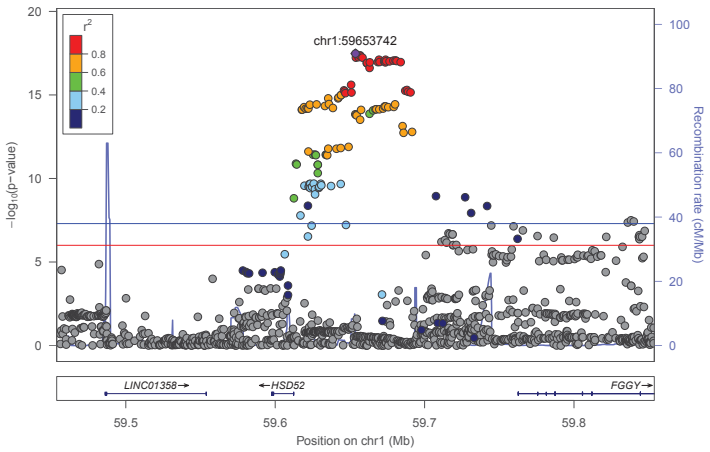

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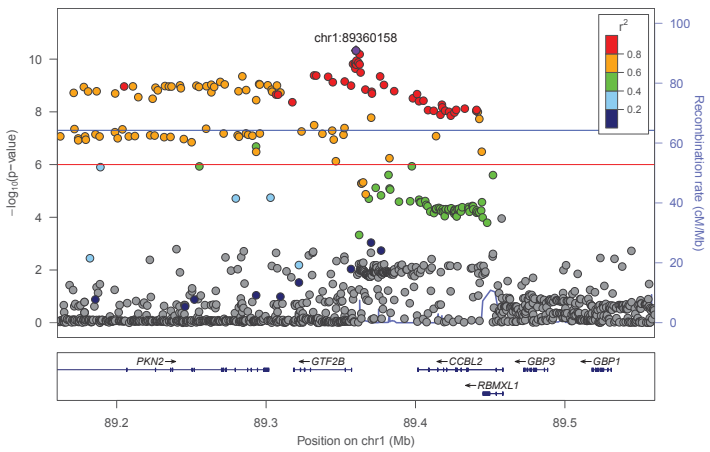

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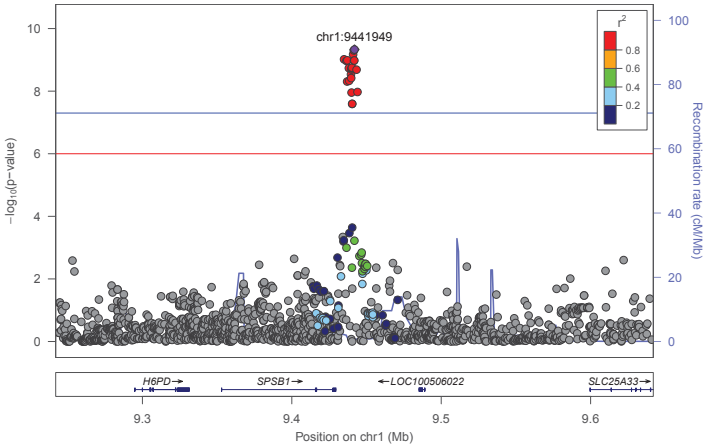

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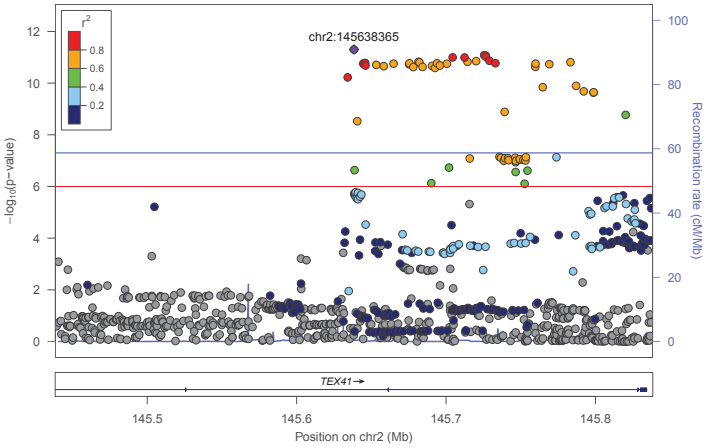

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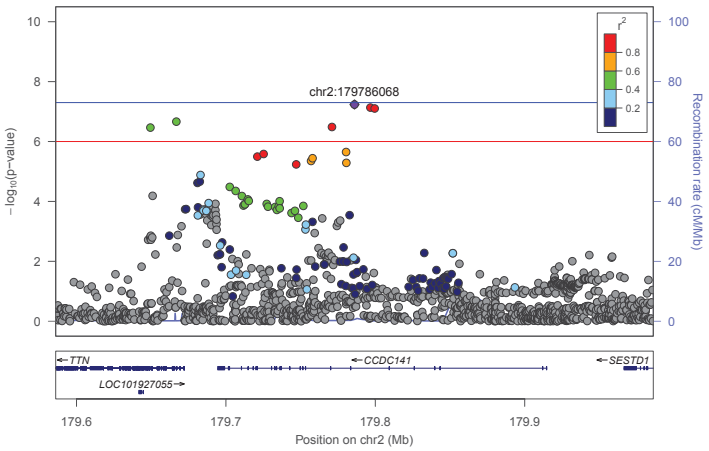

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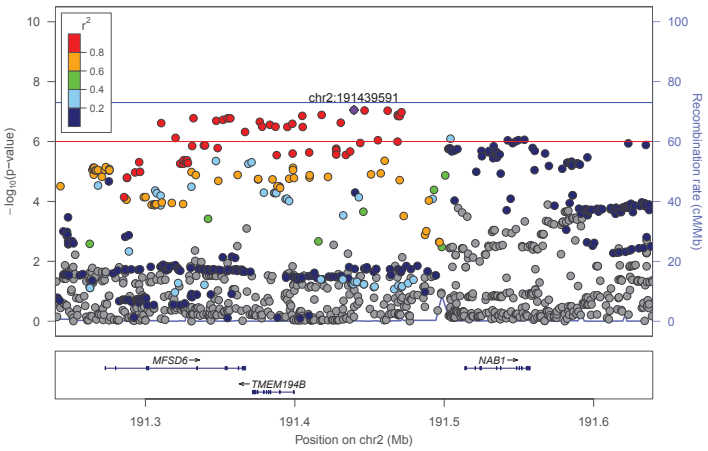

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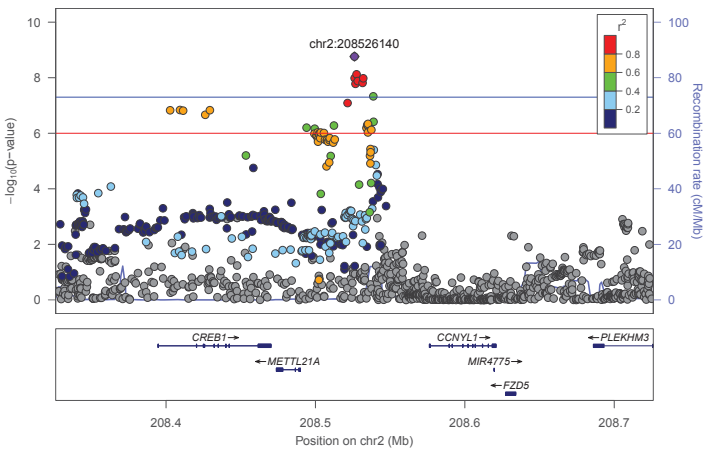

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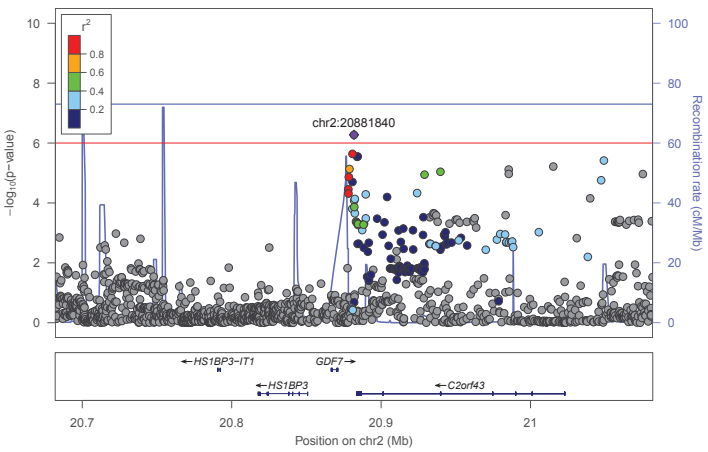

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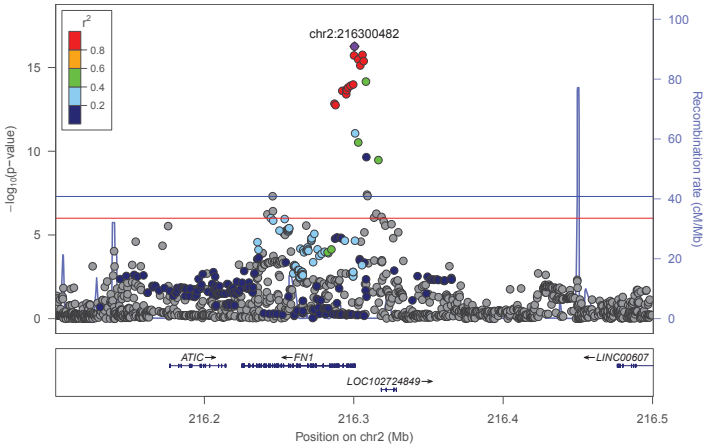

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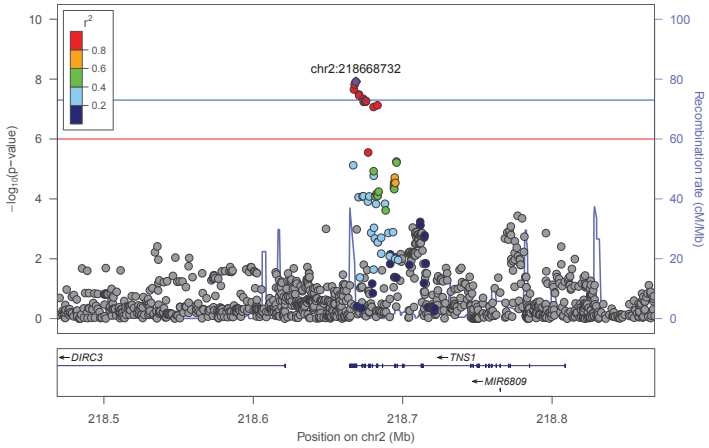

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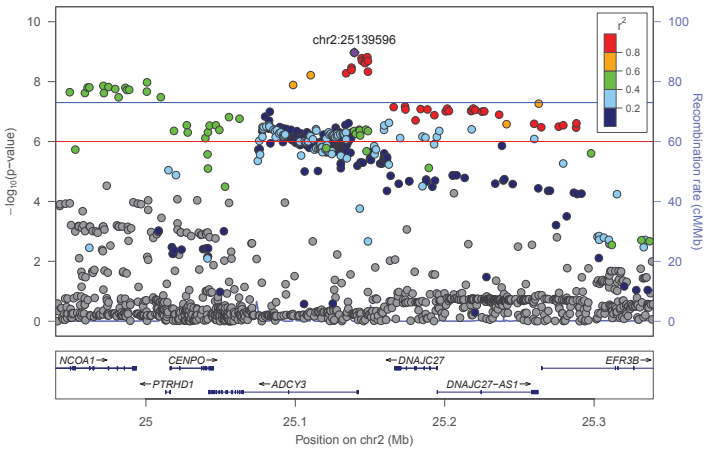

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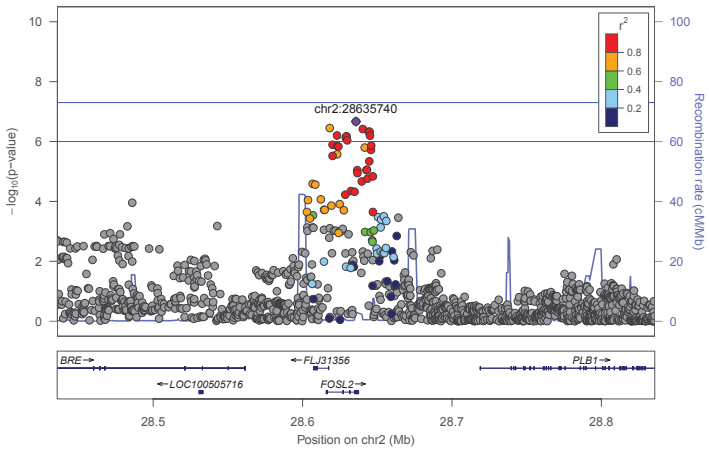

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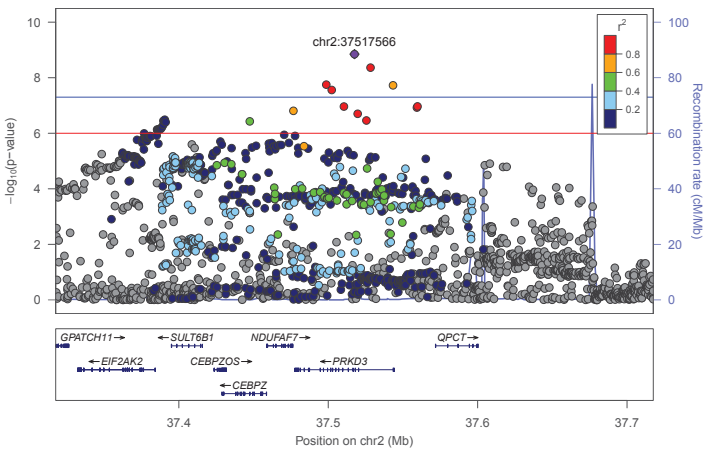

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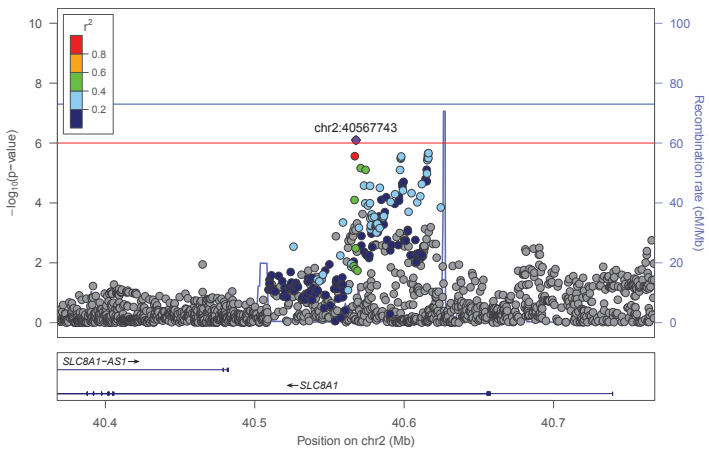

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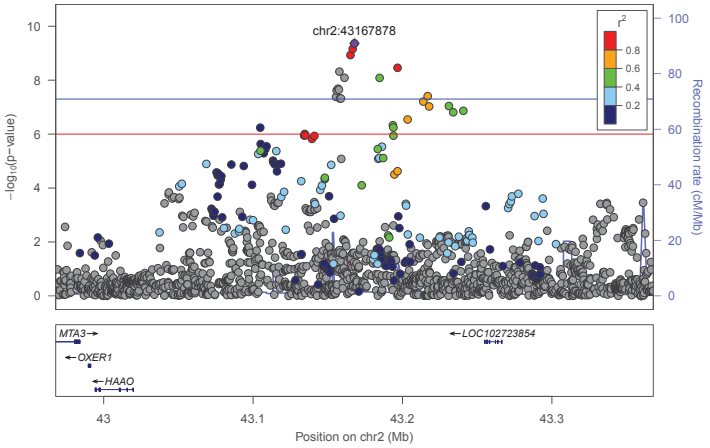

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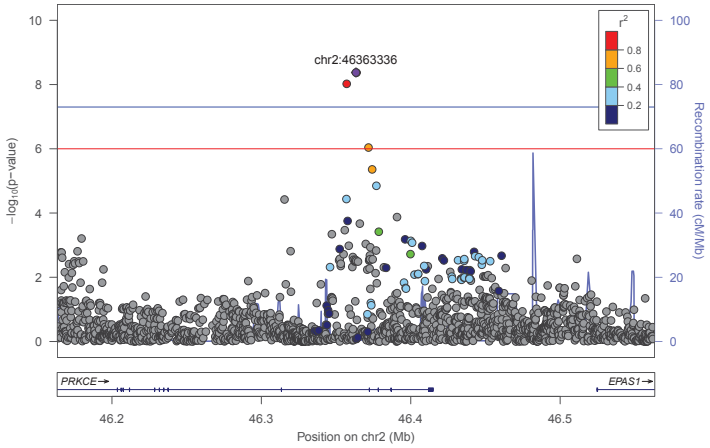

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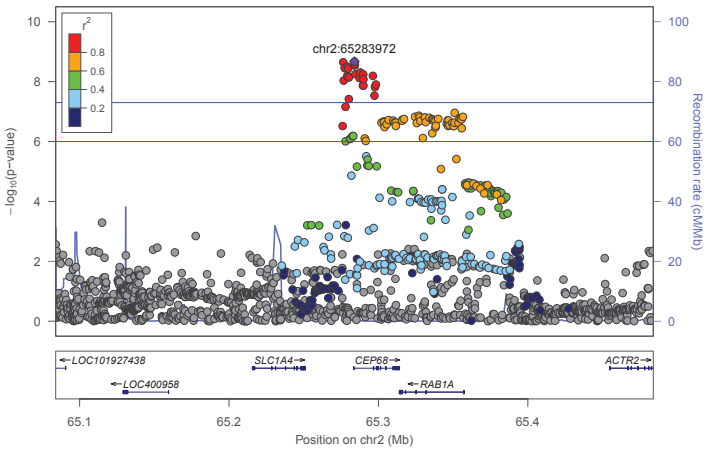

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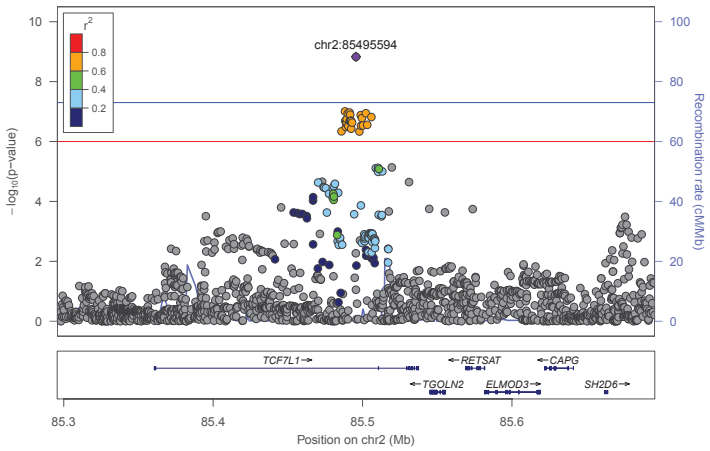

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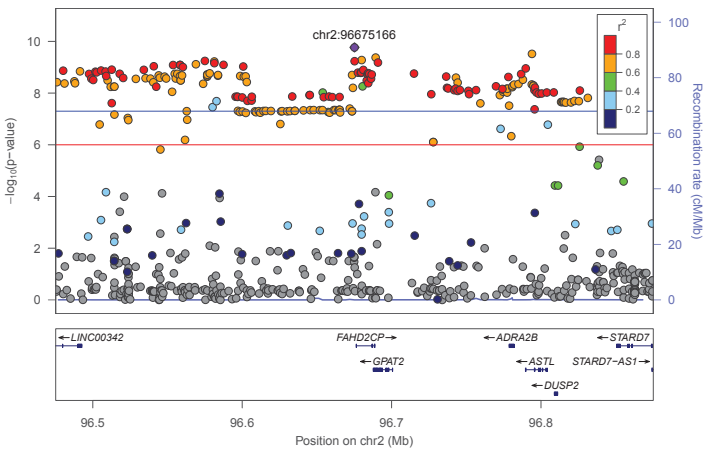

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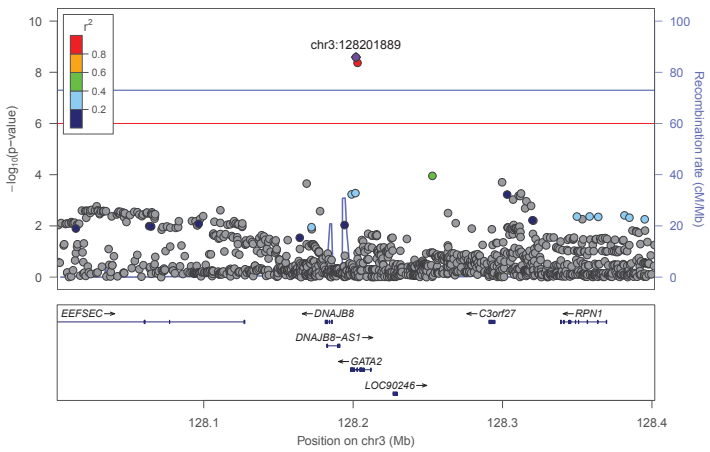

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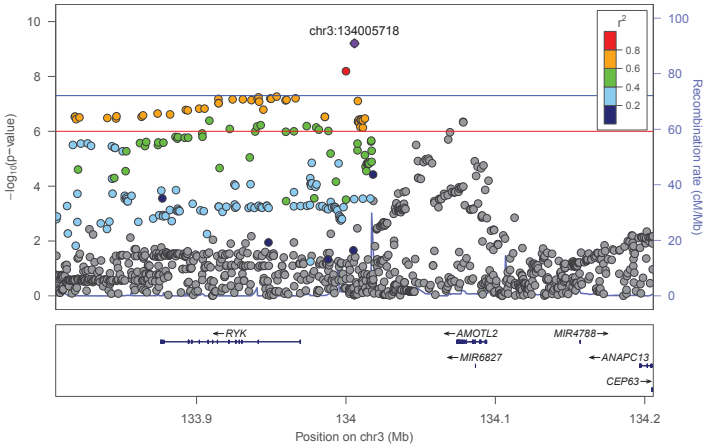

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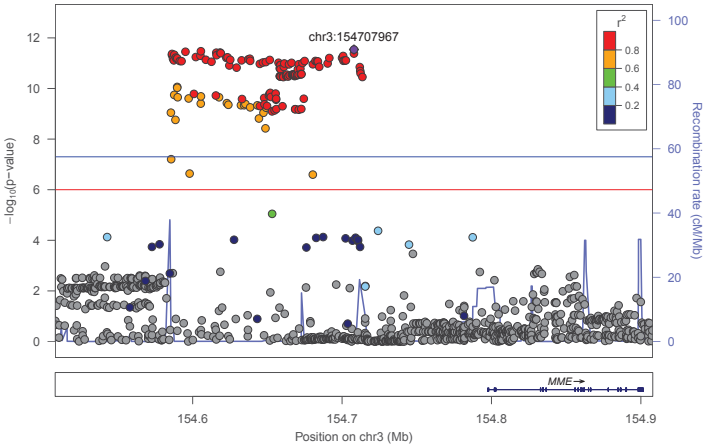

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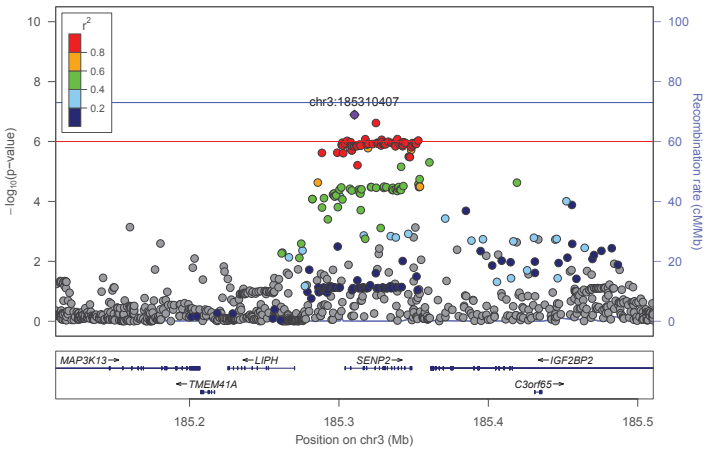

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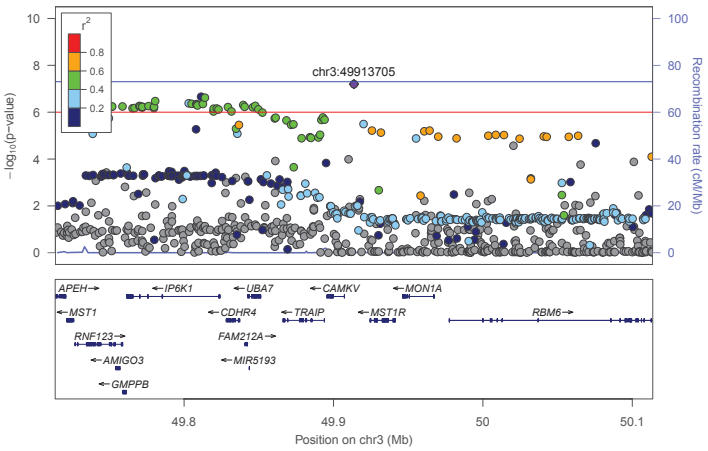

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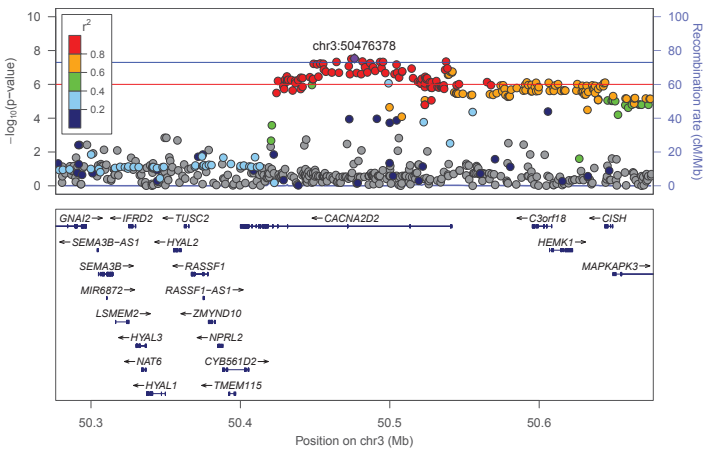

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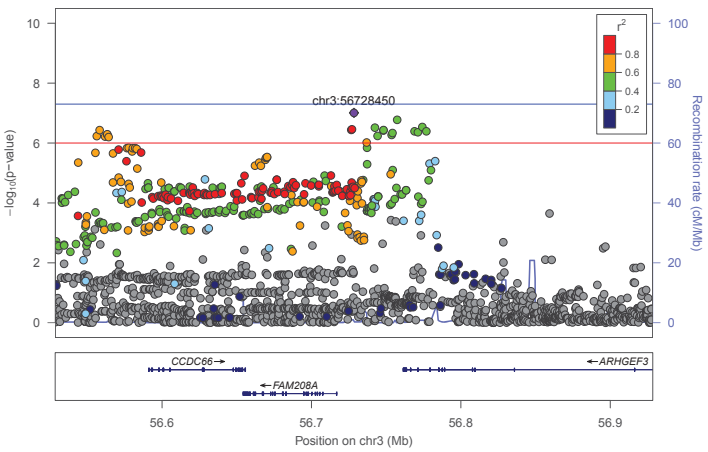

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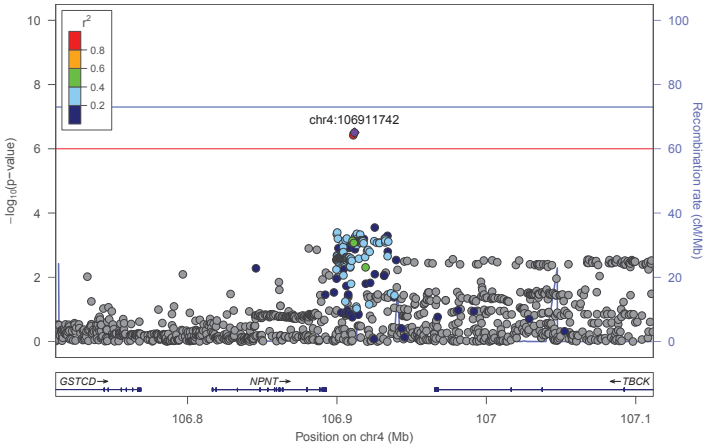

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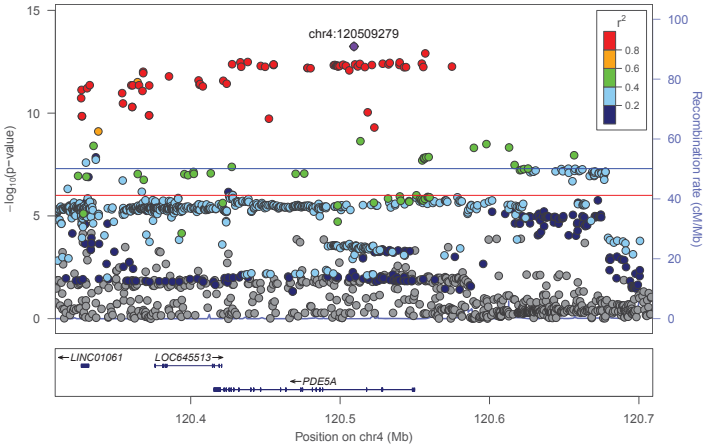

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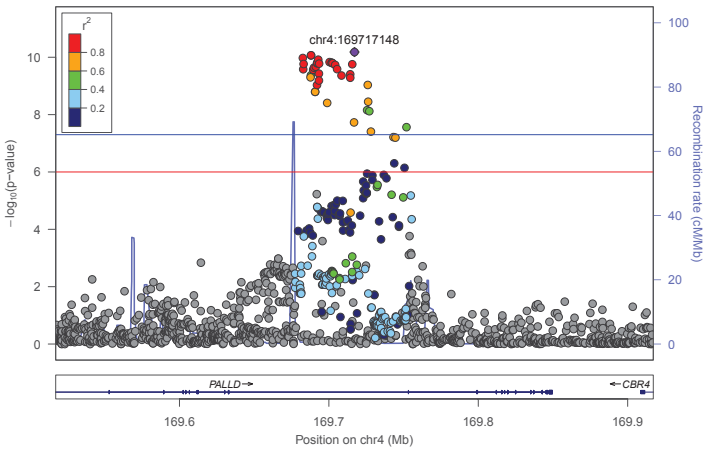

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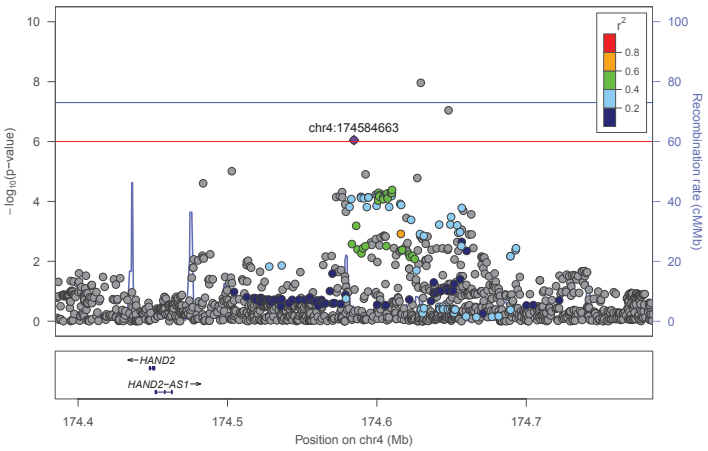

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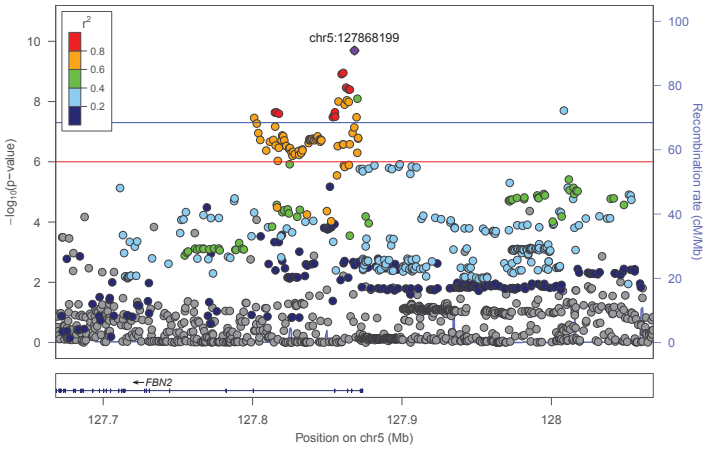

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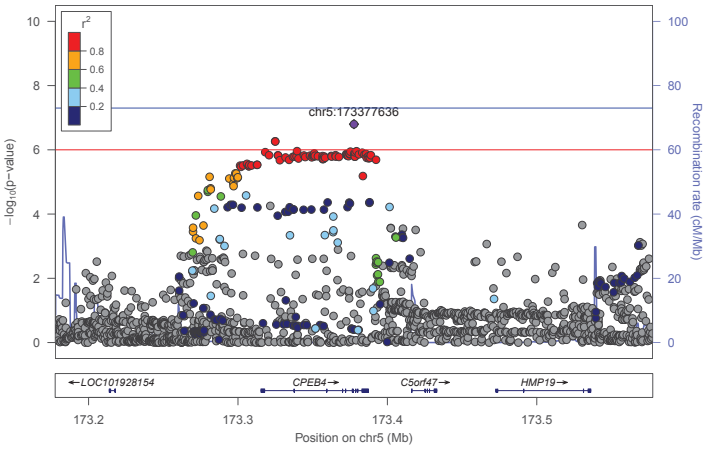

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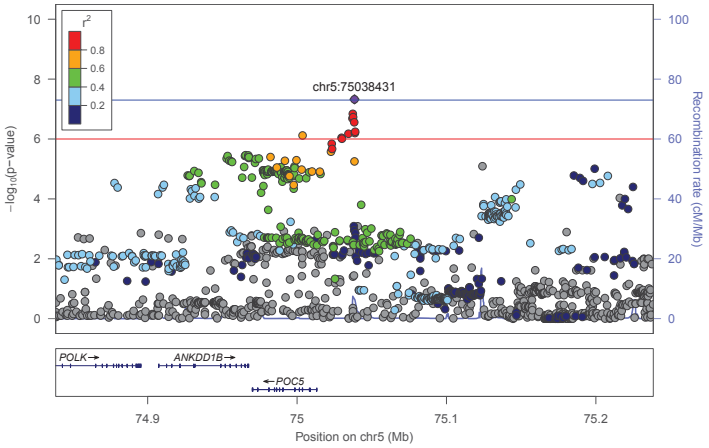

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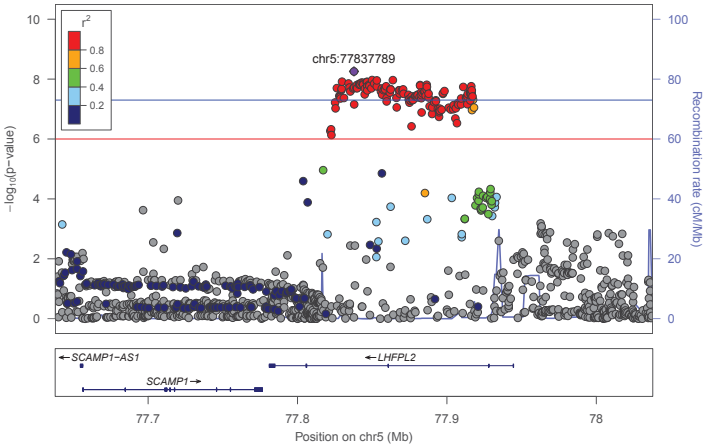

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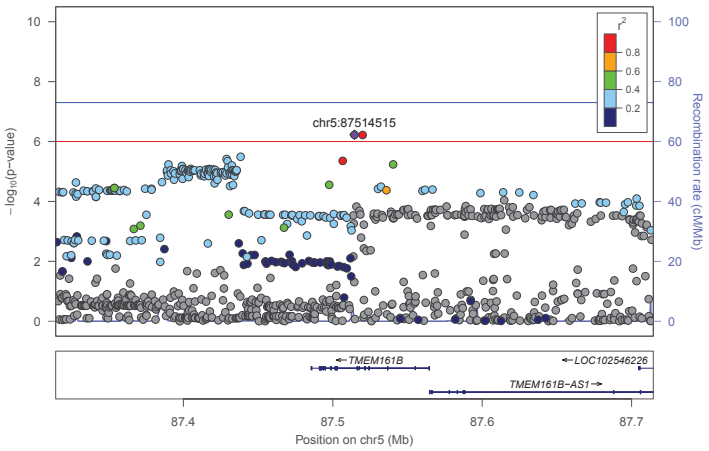

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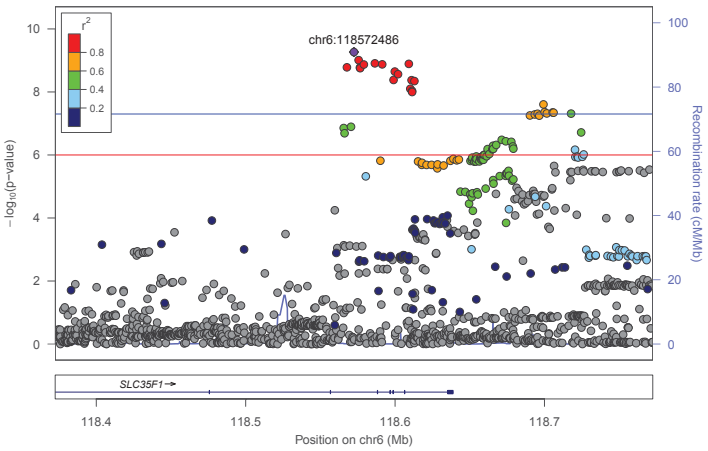

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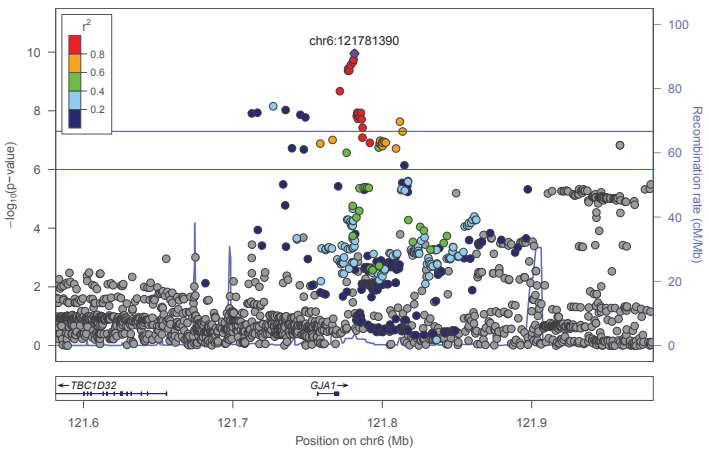

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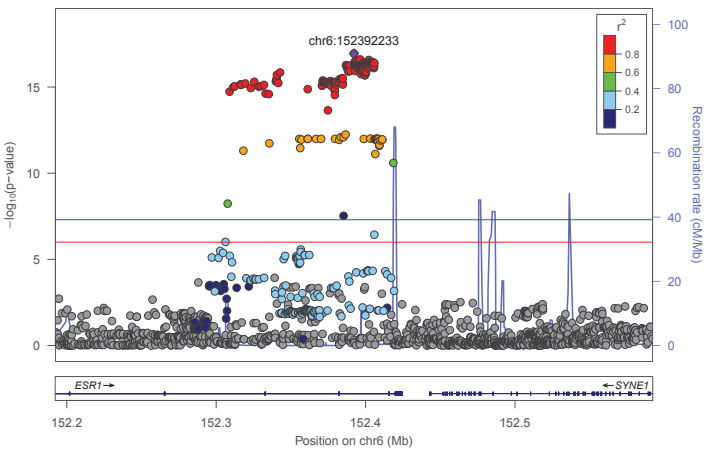

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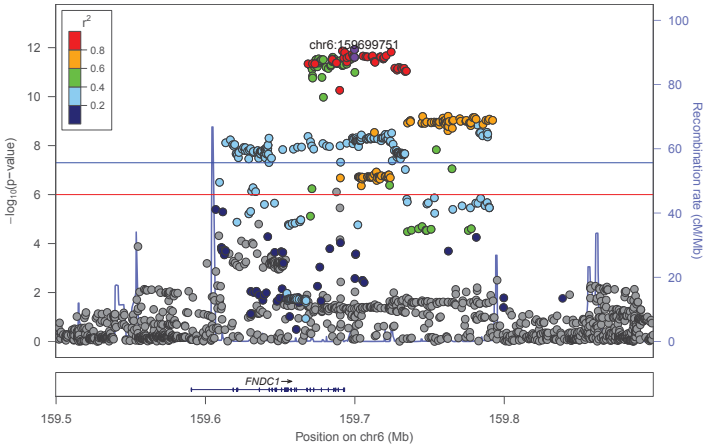

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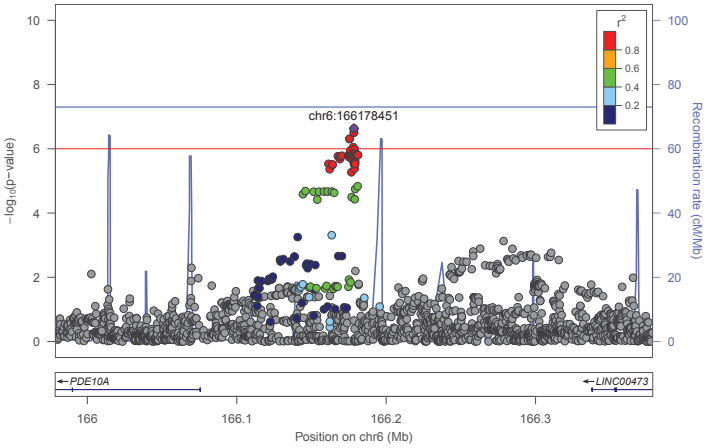

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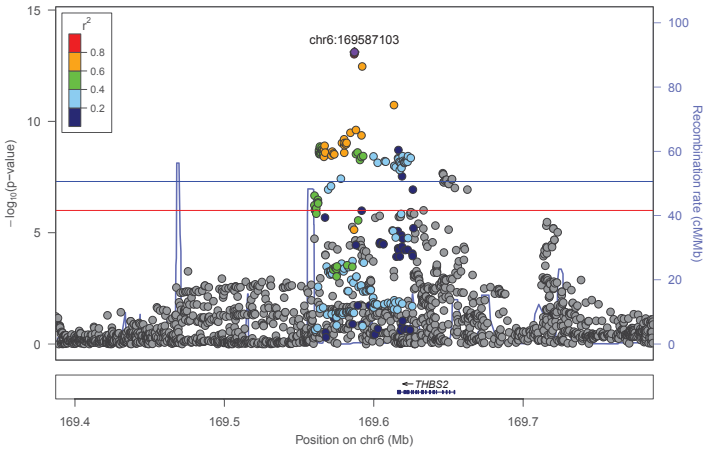

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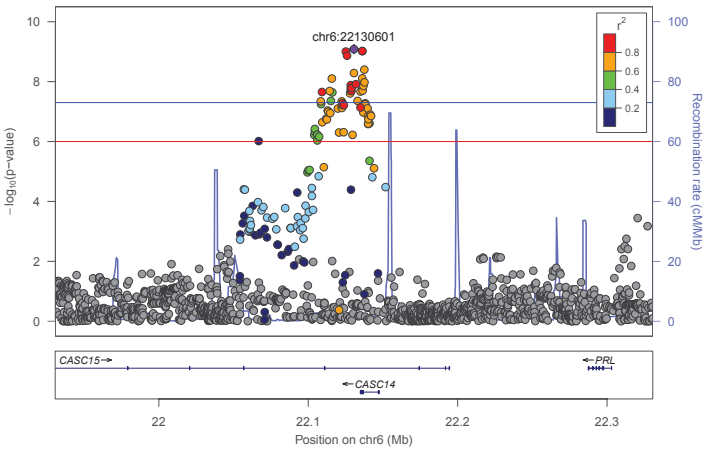

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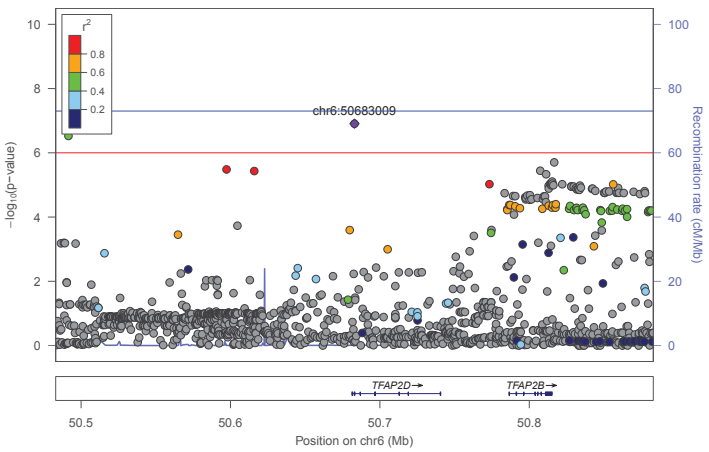

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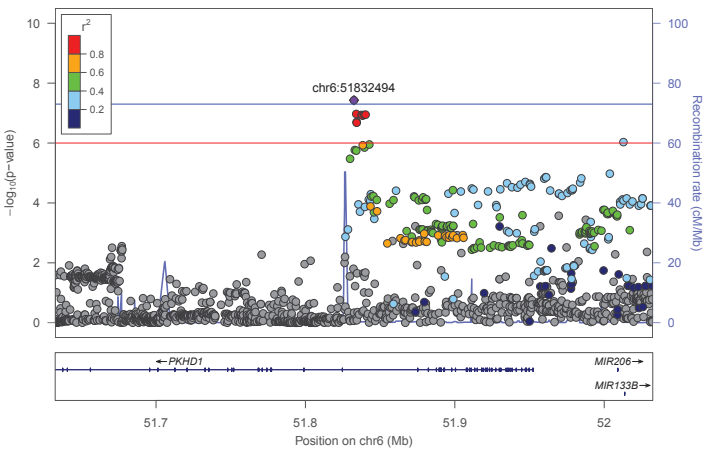

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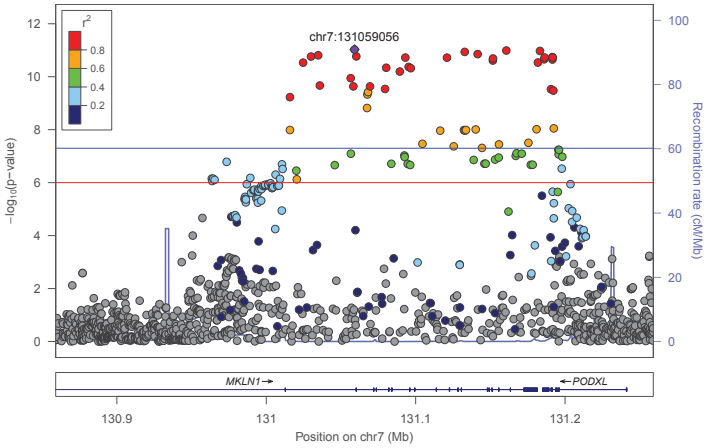

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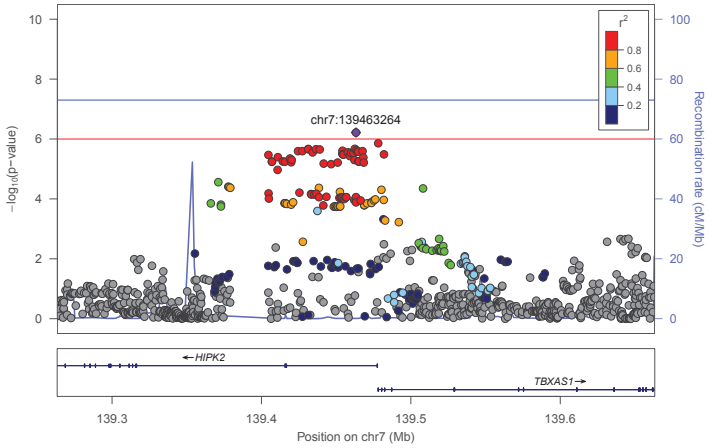

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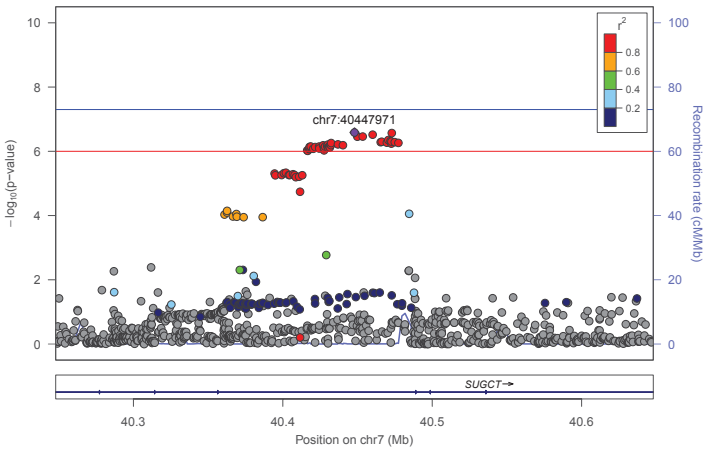

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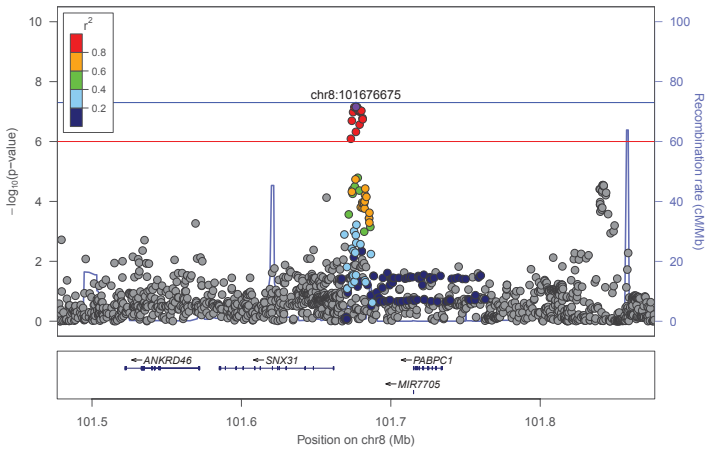

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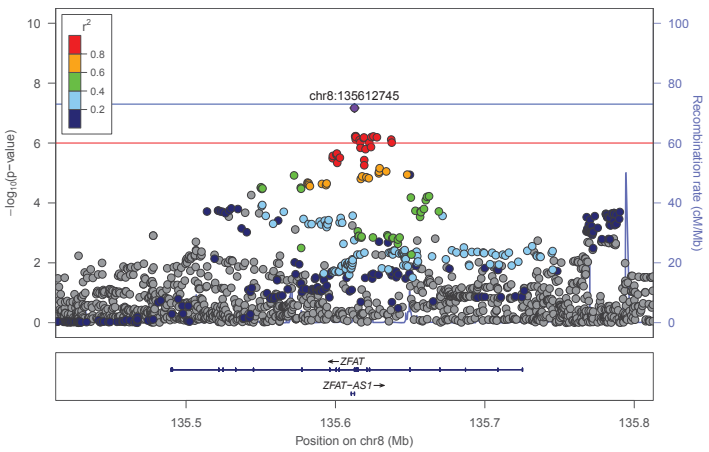

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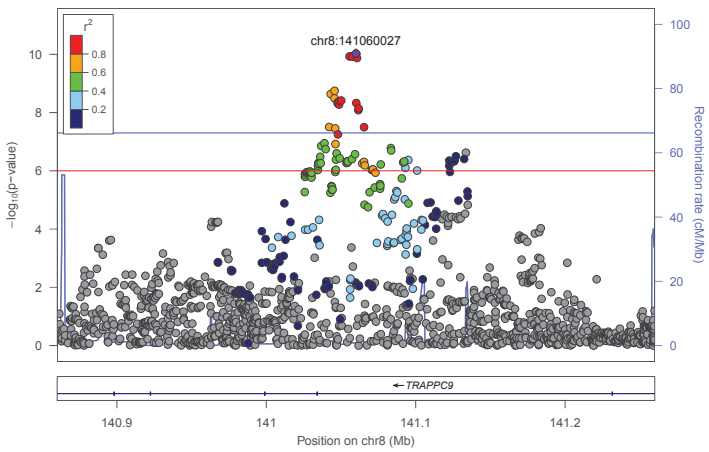

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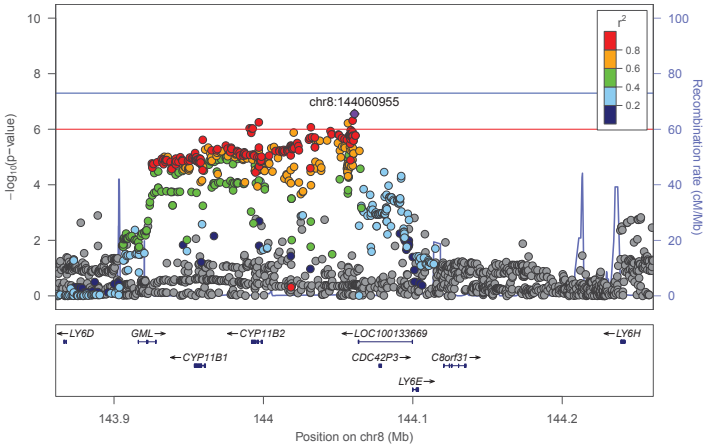

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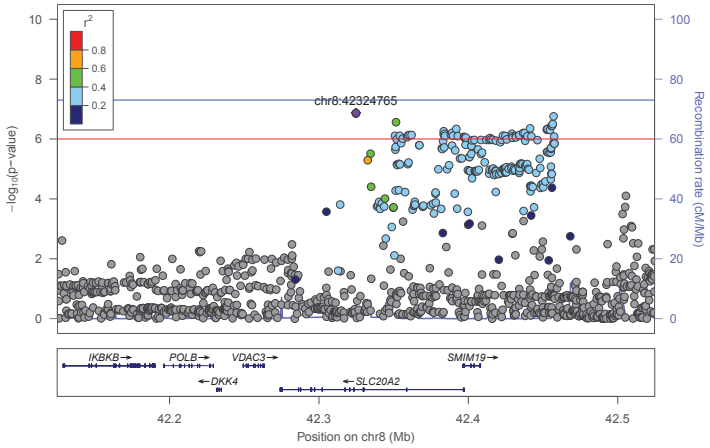

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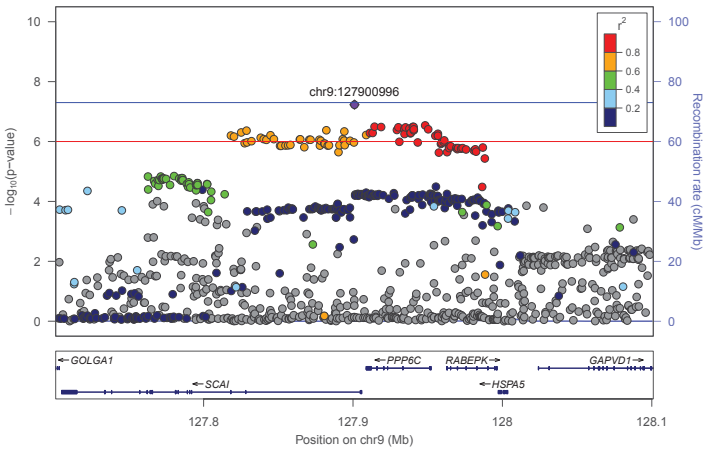

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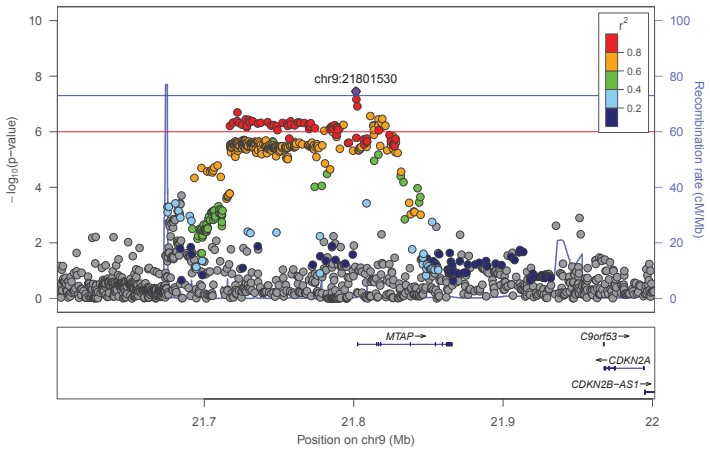

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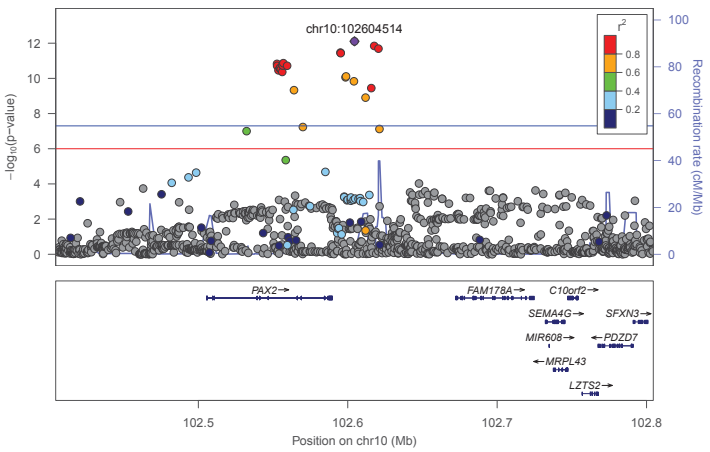

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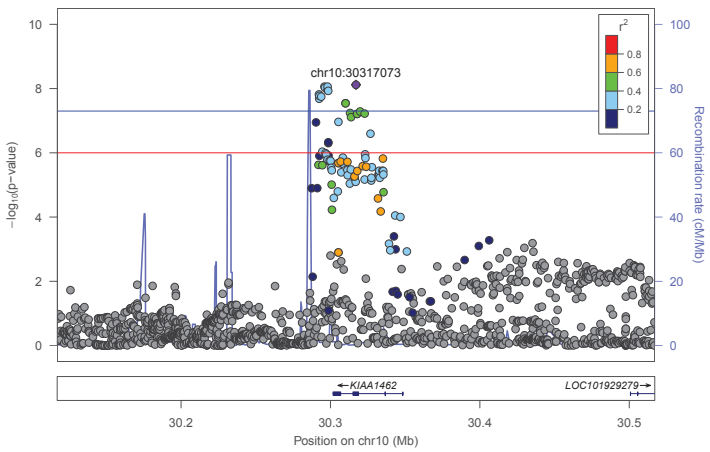

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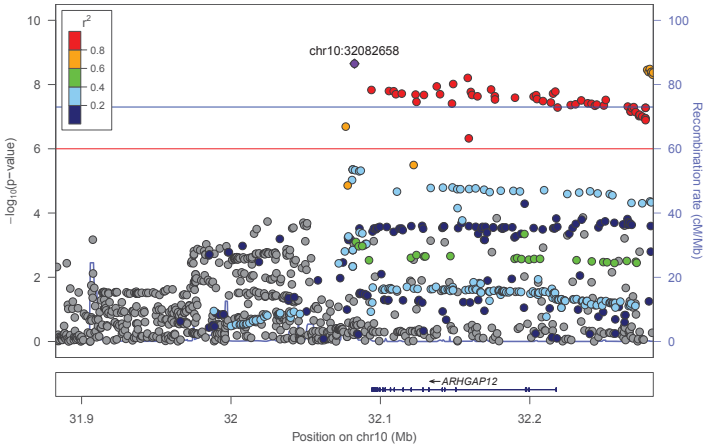

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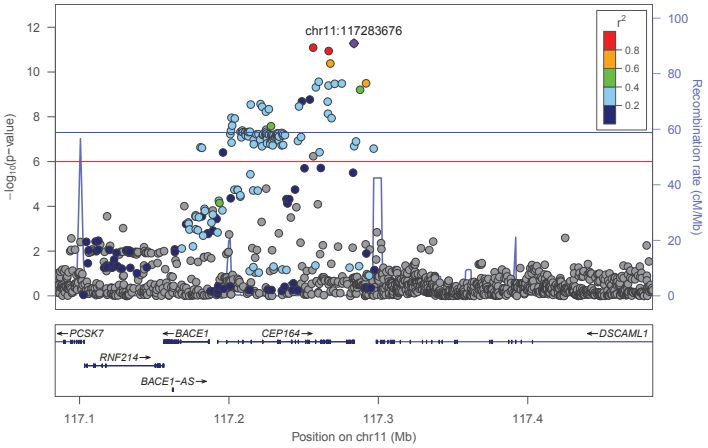

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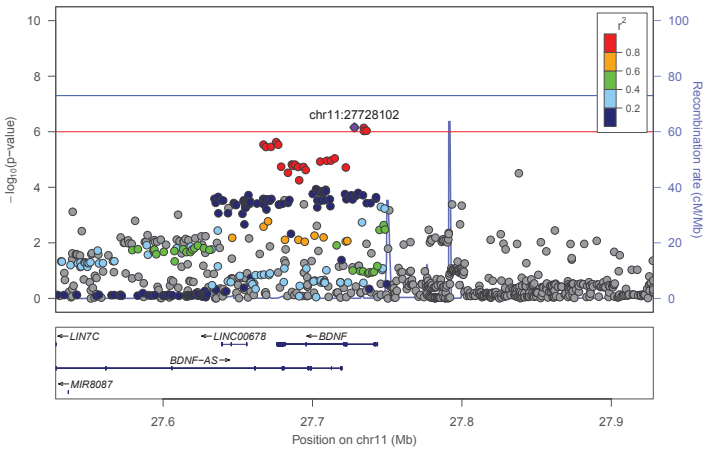

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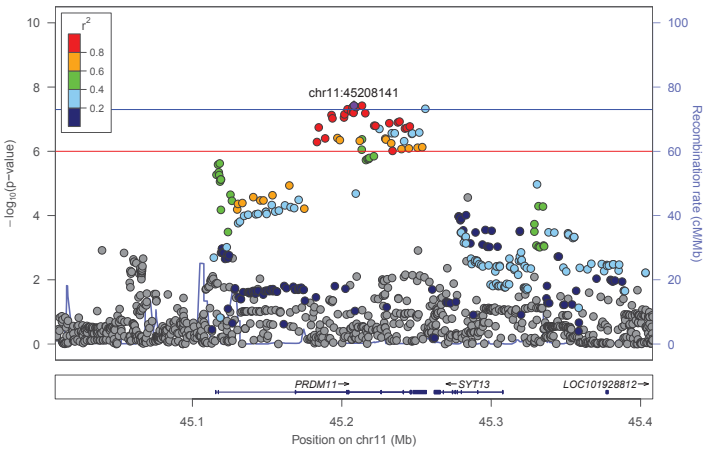

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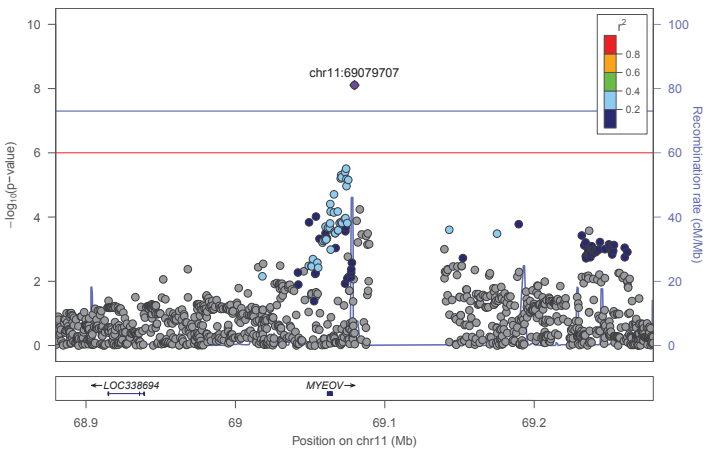

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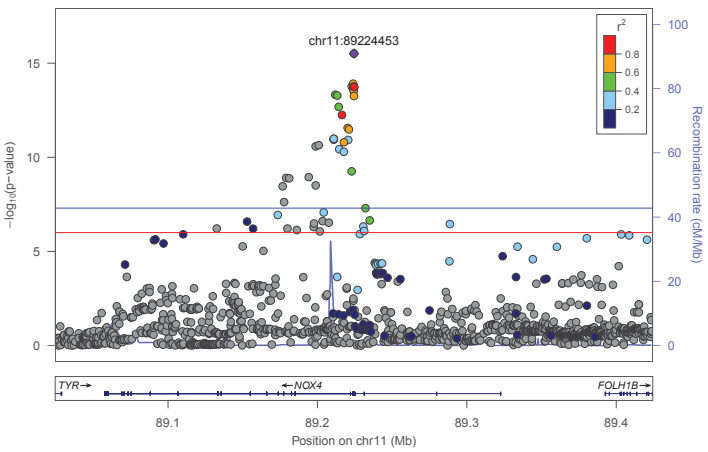

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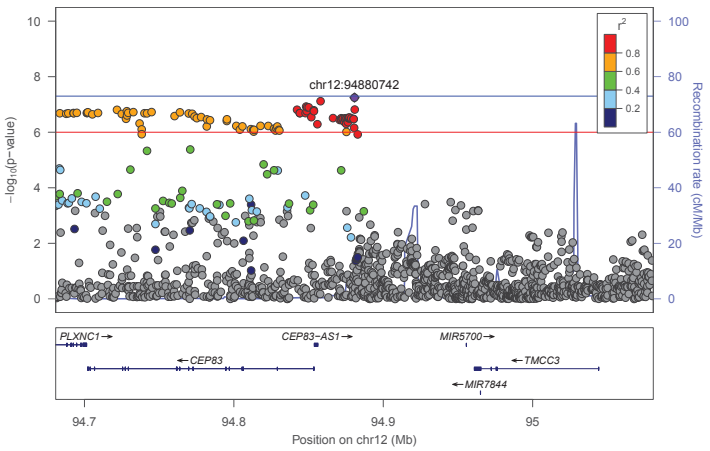

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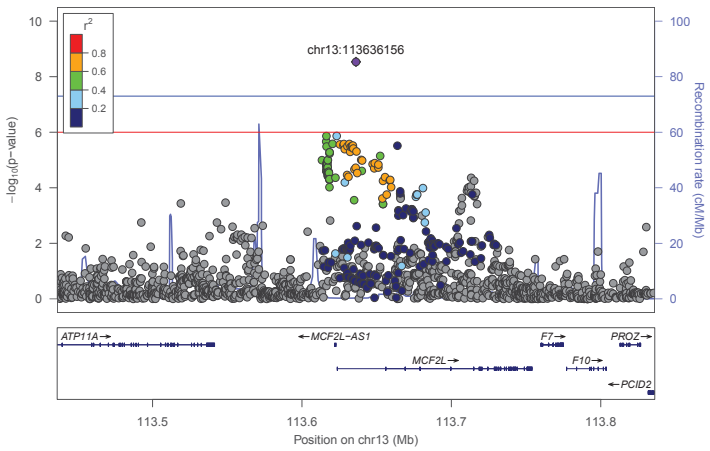

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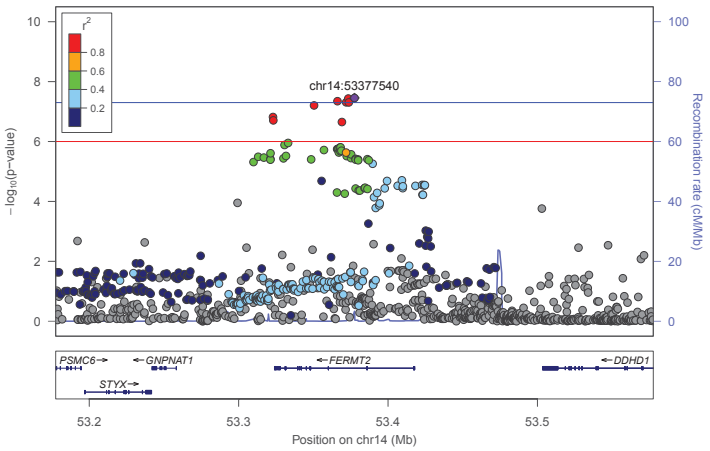

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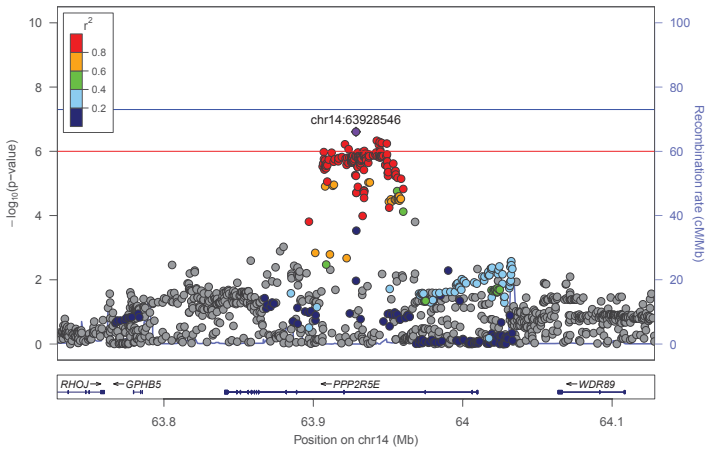

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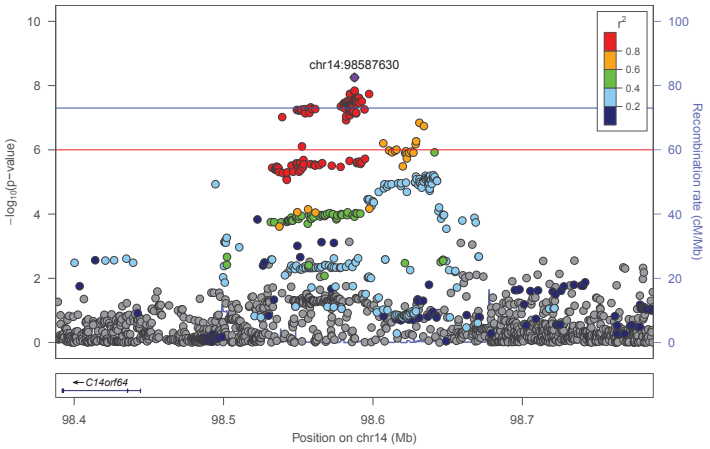

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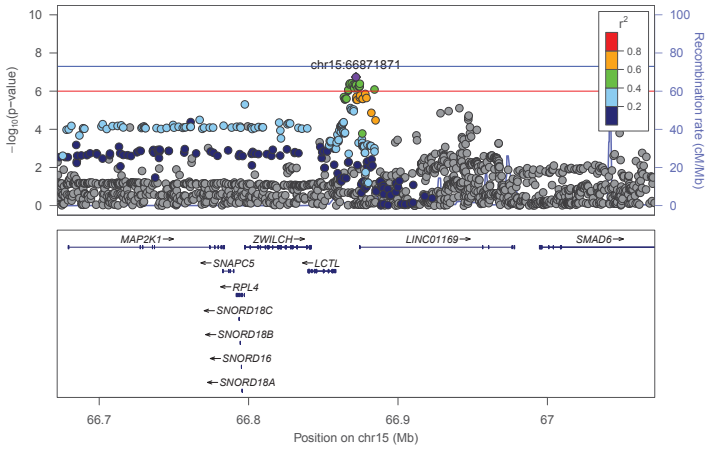

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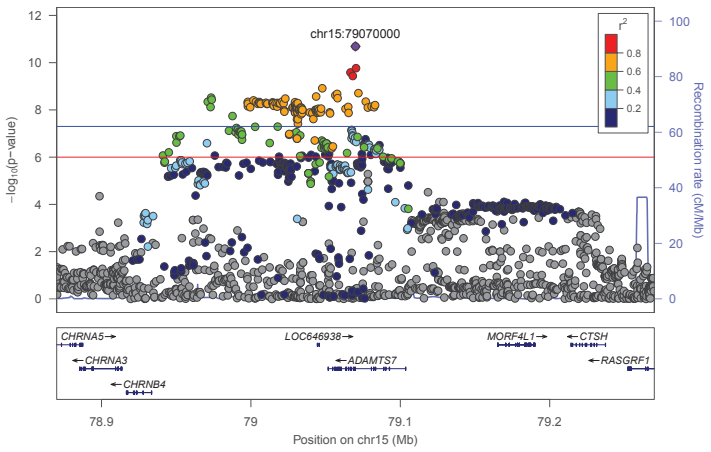

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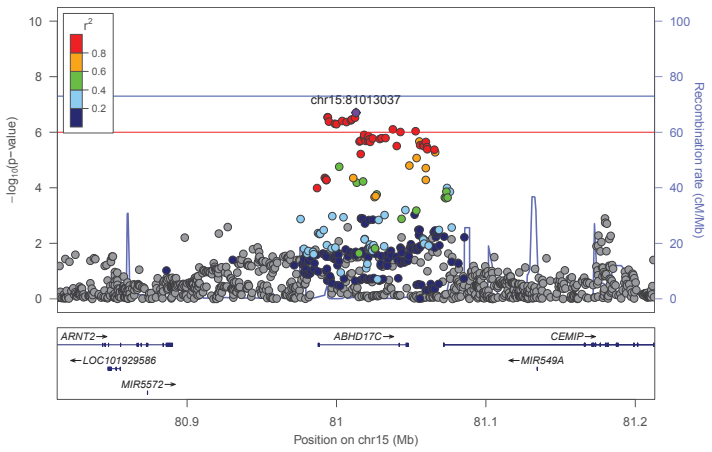

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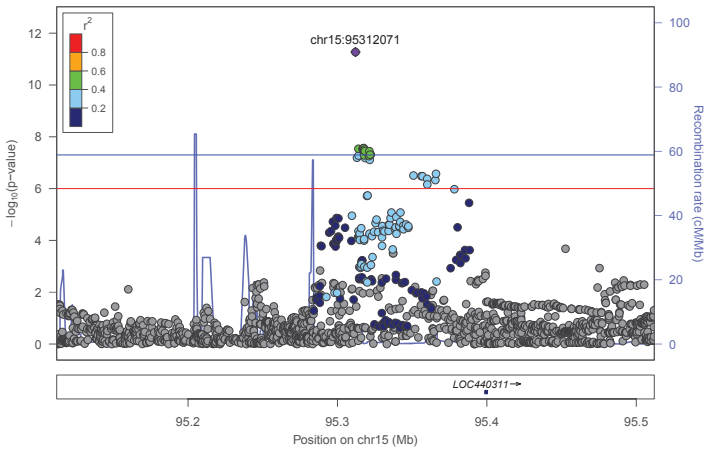

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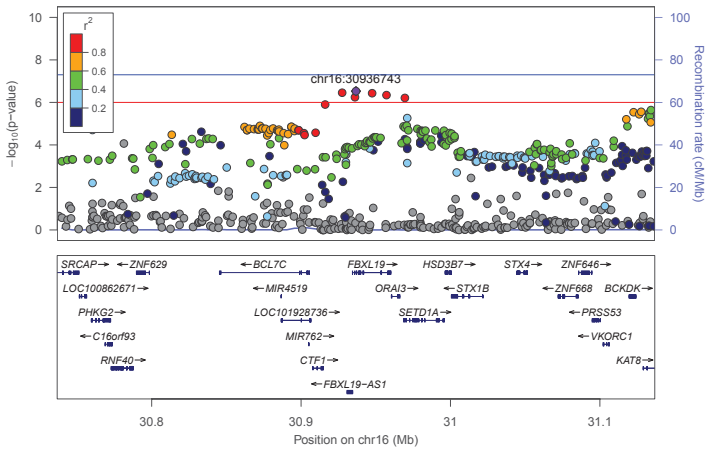

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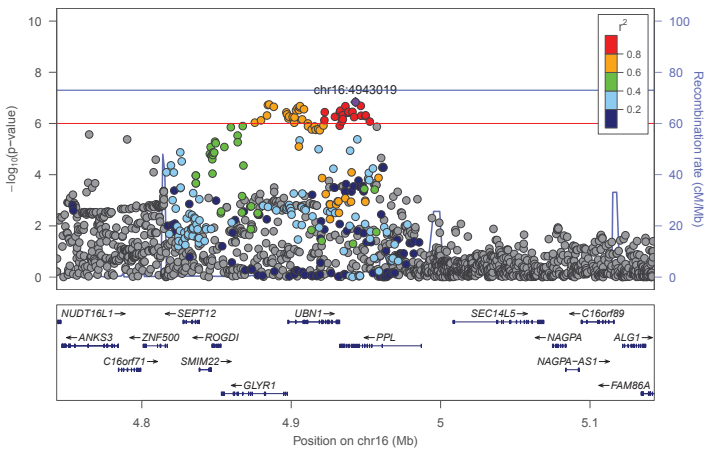

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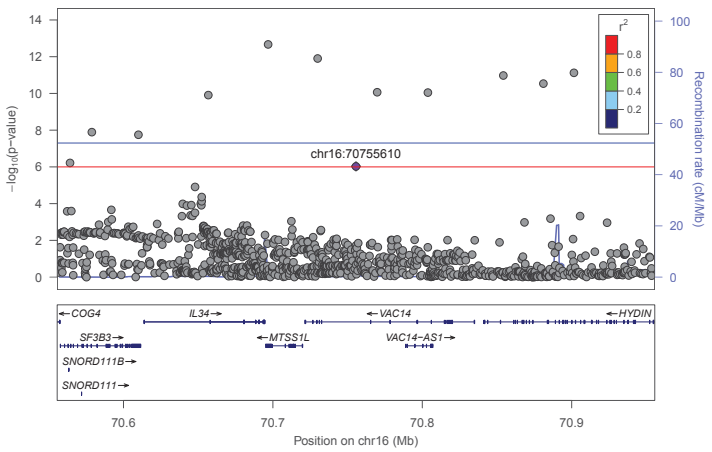

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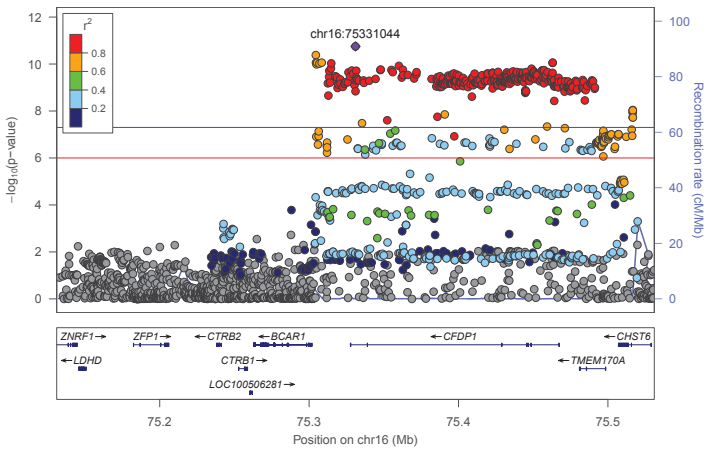

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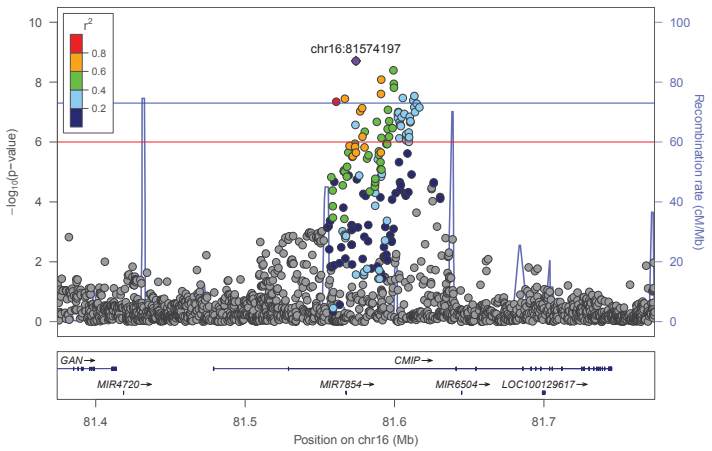

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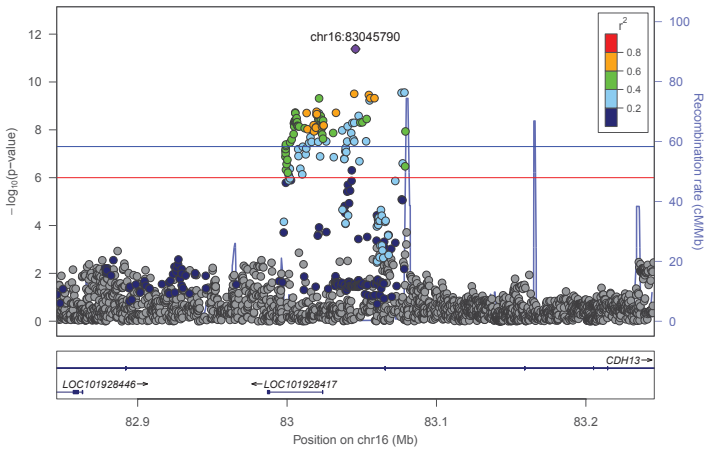

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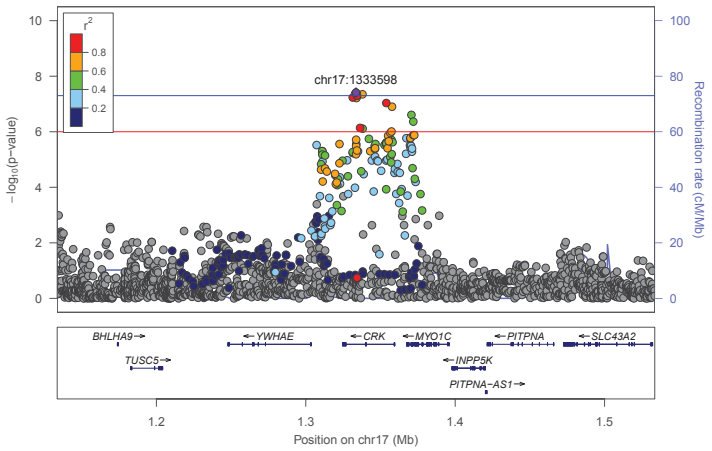

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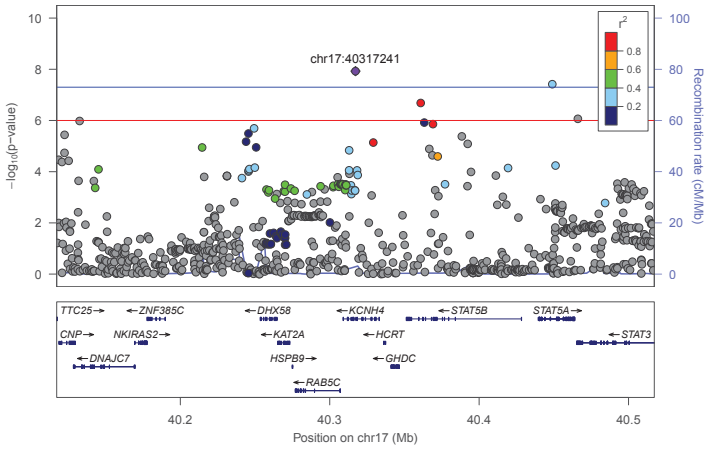

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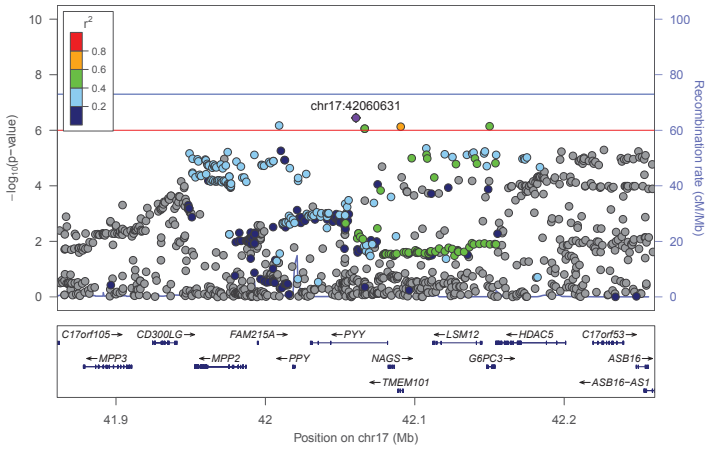

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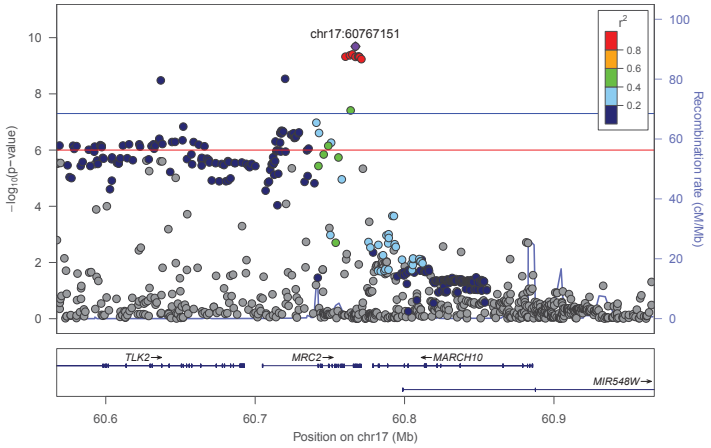

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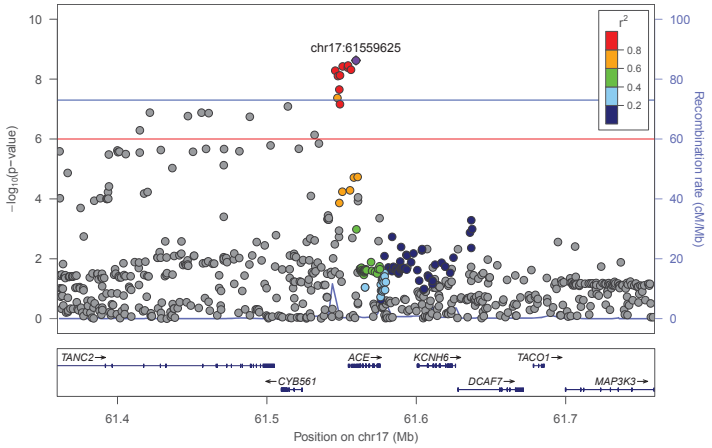

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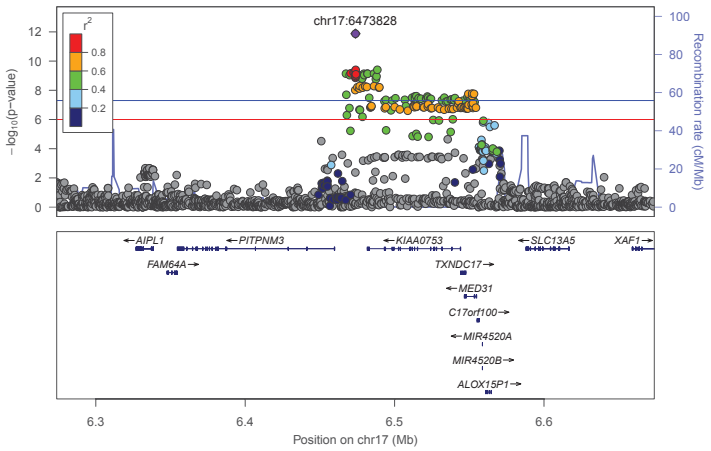

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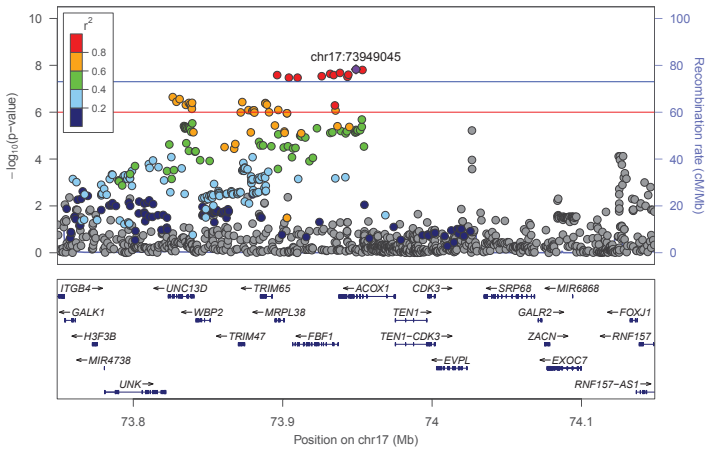

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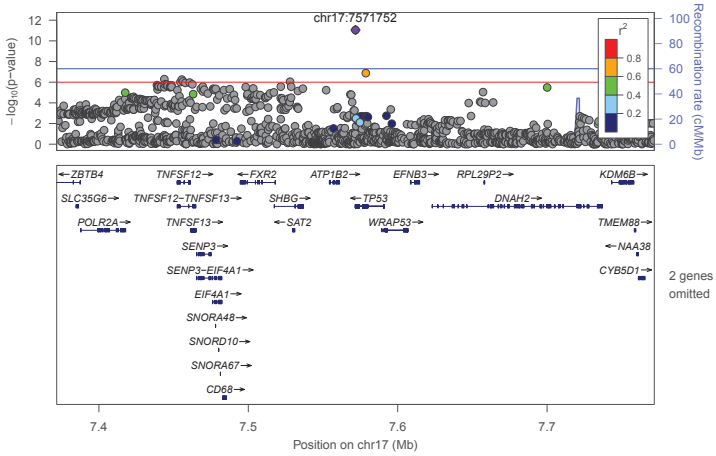

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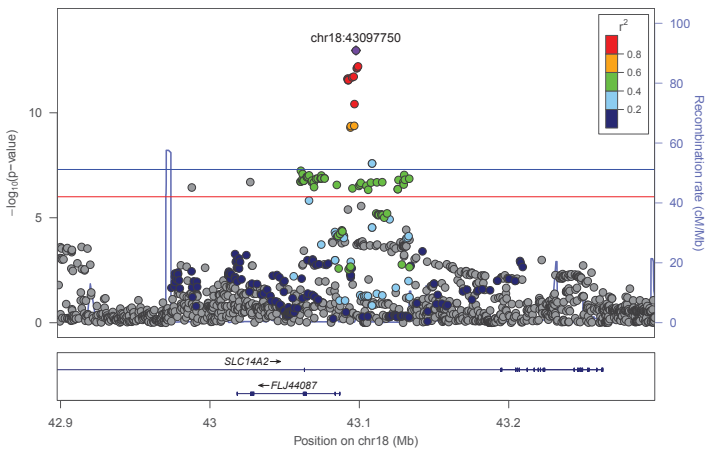

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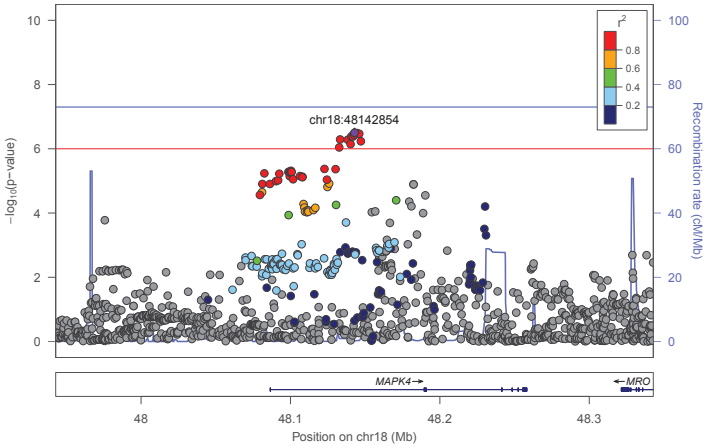

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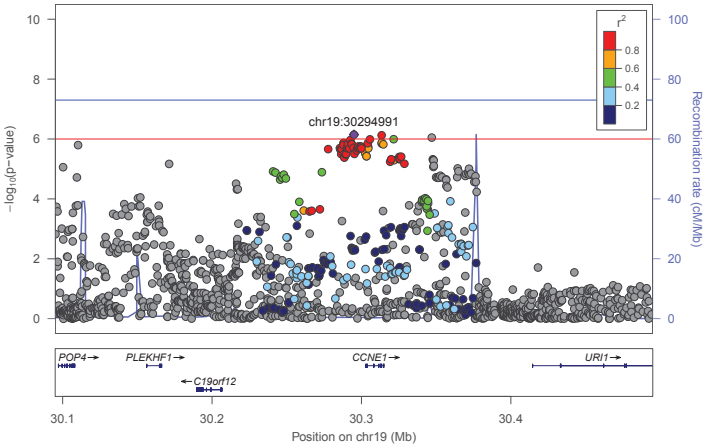

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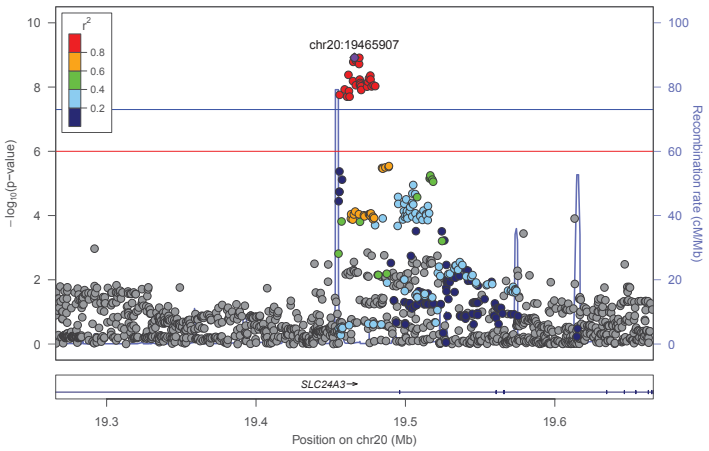

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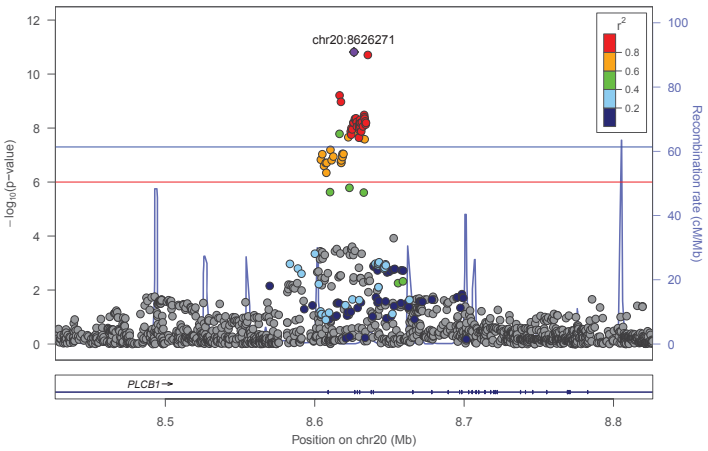

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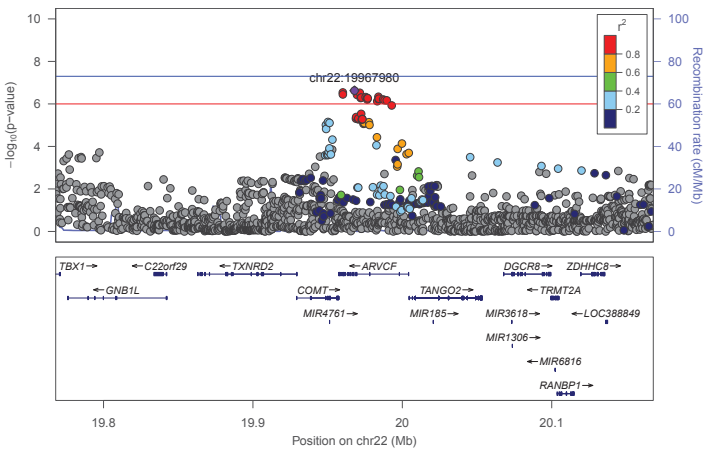

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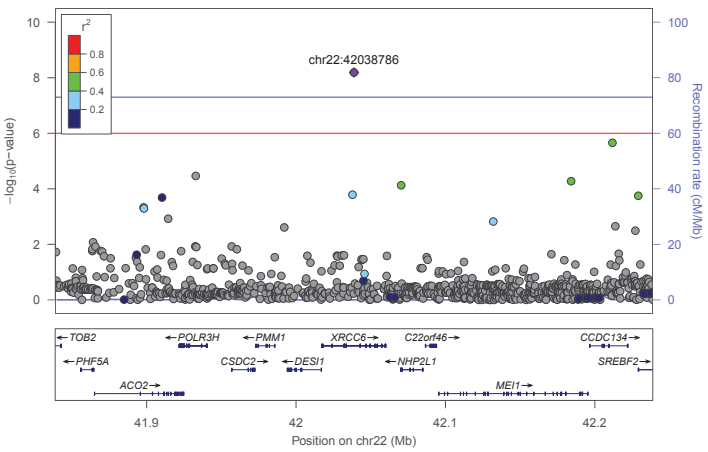

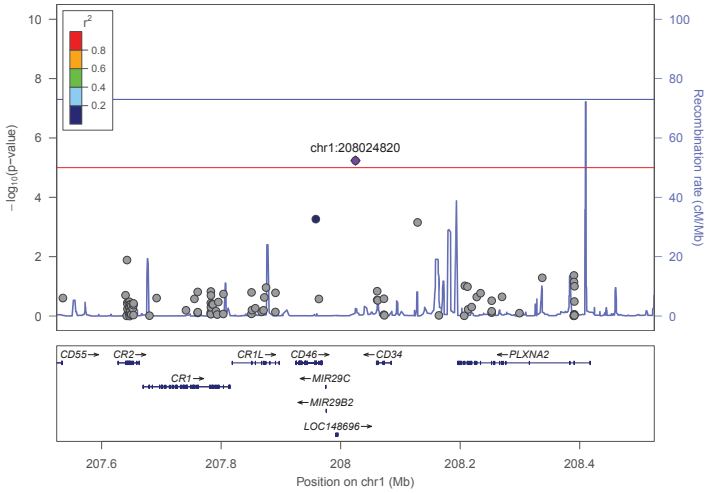
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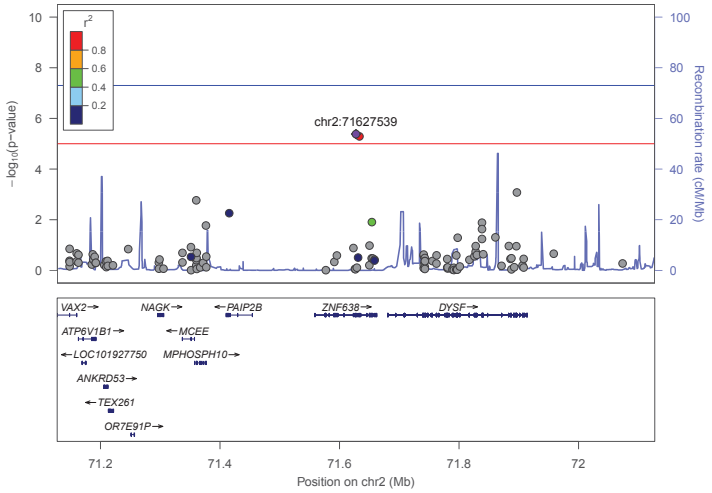
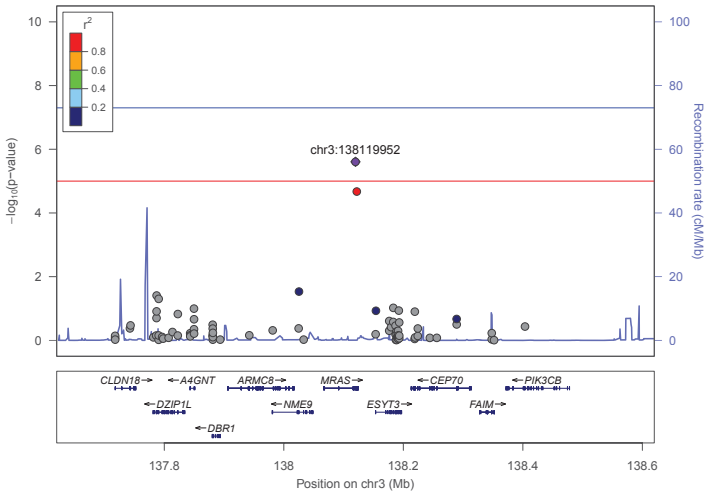
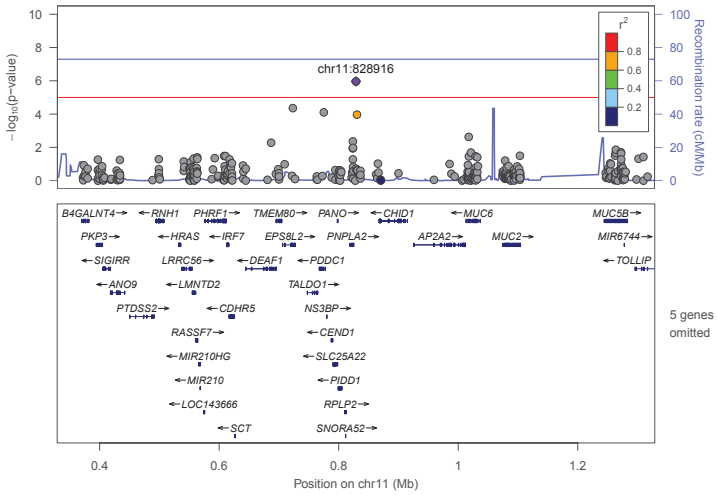
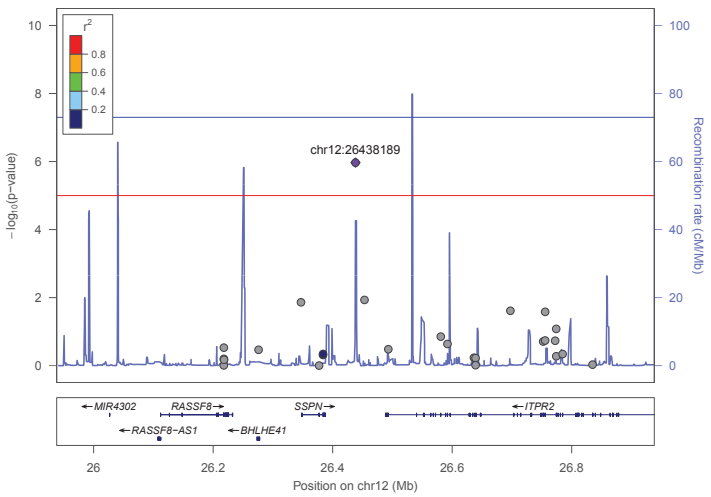
CD55→ CR2→ CR1L→ CD46→ ←CD34 ←PLXNA2
←CR1 ←MIR29C ←MIR29B2 ←LOC148696
207.6 207.8 208 208.2 208.4
Position on chr1 (Mb)
Recombination rate (cM/Mb)

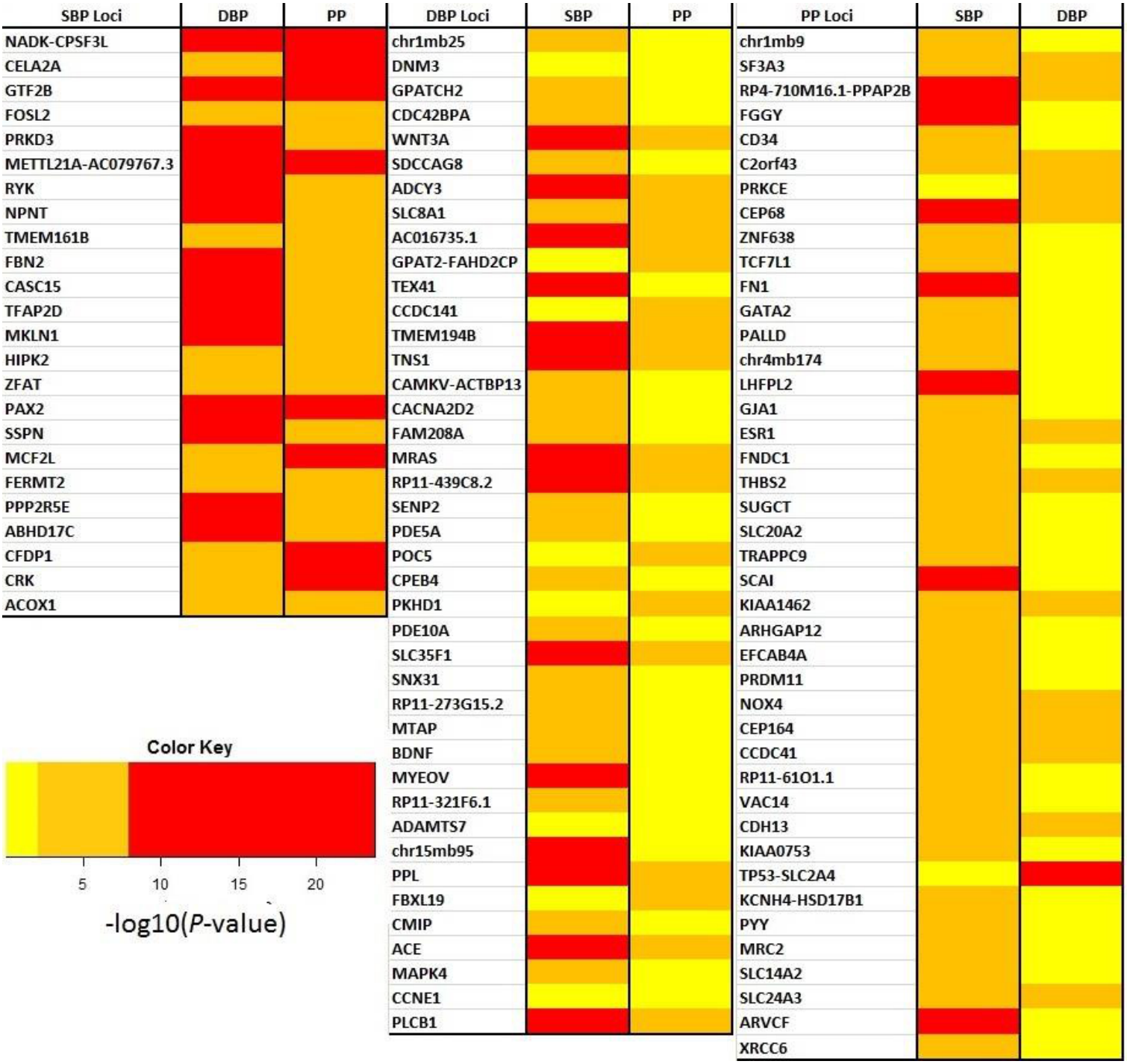

chr2:71627539
VAX2→ NAGK→ ←PAIP2B ZNF638→ DYSF→
ATP6V1B1→ ←MCEE
←LOC101927750 MPHOSPH10→
ANKRD53→ ←TEX261 OR7E91P→
71.2 71.4 71.6 71.8 72
Position on chr2 (Mb)
Recombination rate (cM/Mb)


chr3:138119952
CLDN18→ ←A4GNT ARMC8→ MRAS→ ←CEP70 ←PIK3CB
←DZIP1L ←NME9 ESYT3→ FAIM→ ←DBR1
137.8 138 138.2 138.4 138.6
Position on chr3 (Mb)
Recombination rate (cM/Mb)

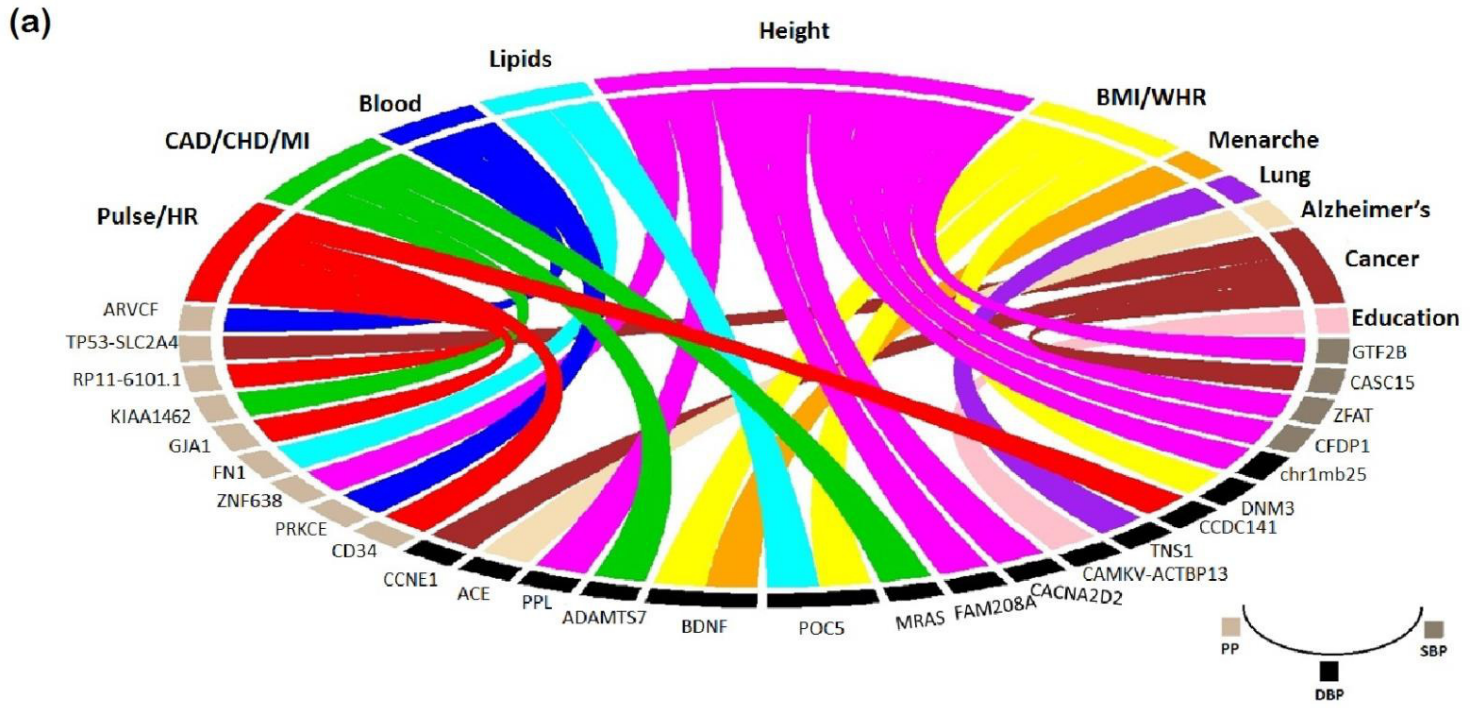

chr11:828916
B4GALNT4→ ←RNH1 PHRF1→ TMEM80→ PANO→ ←CHID1 ←MUC6 MUC5B→
PKP3→ ←HRAS ←IRF7 EPS8L2→ PNPLA2→ AP2A2→ MUC2→ MIR6744→
←SIGIRR LRRC56→ ←DEAF1 ←PDDC1 ←TOLLIP
←ANO9 ←LMNTD2 TALDO1→
PTDSS2→ ←CDHR5 NS3BP→
RASSF7→ ←CEND1
←MIR210HG ←SLC25A22
←MIR210 ←PIDD1
←LOC143666 RPLP2→
←SCT SNORA52→
5 genes omitted
0.4 0.6 0.8 1 1.2
Position on chr11 (Mb)
Recombination rate (cM/Mb)

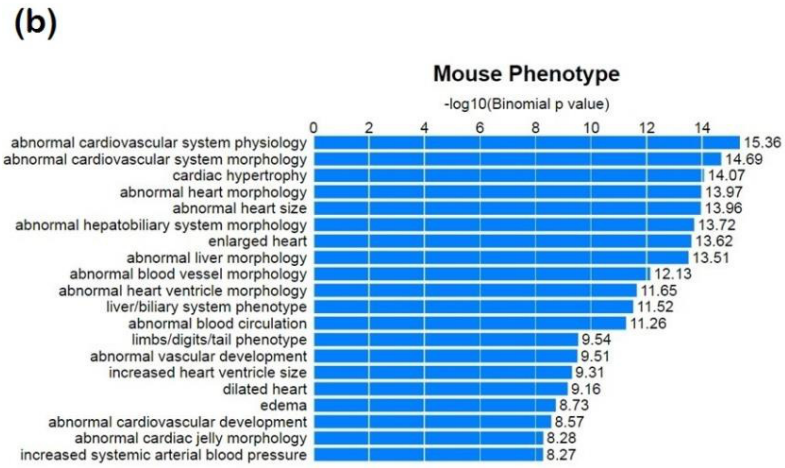

chr12:26438189
←MIR4302 RASSF8→ SSPN→ ←ITPR2
←RASSF8-AS1 ←BHLHE41
26 26.2 26.4 26.6 26.8
Position on chr12 (Mb)
Recombination rate (cM/Mb)

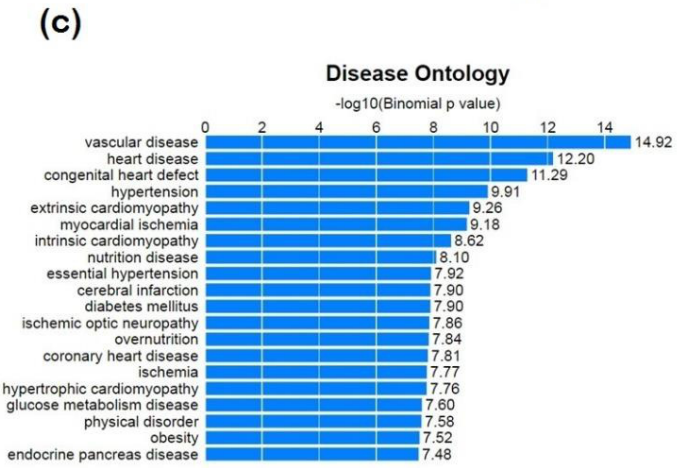
Supplementary Figure 4: Heat map of blood pressure associations using –log10(*P*-values) from the combined meta-analysis. The rows of the heat map are the 107 sentinel validated SNVs from Tables 1-3 from both GWAS and exome discovery, ordered by trait, then by chromosome and genomic position base pairs. Red shows genomewide significance ($P < 5x10^{-8}$), orange shows moderate significance ($5x10^{-8} \leq P < 0.01$) and yellow shows no significant association ($P \geq 0.01$). SBP: systolic BP; DBP: diastolic BP; PP: pulse pressure.



Supplementary Figure 5: Association of blood pressure loci with other traits. Plot (a) shows results for associations with other traits which were extracted from the PhenoScanner database for the sentinel variants from Tables 1-3, including proxies in Linkage Disequilibrium ($r^2 \geq 0.8$), with genome-wide significant associations ($P < 5 \times 10^{-8}$). The loci are grouped by blood pressure traits ordered right to left according to the loci in Tables 1-3. There are four systolic blood pressure associated loci, 14 diastolic blood pressure associated loci and nine pulse pressure associated loci with associations with other traits reported in the literature. Traits are grouped into different disease categories: "Pulse/HR" includes pulse, heart rate, pulse wave velocity and aortic stiffness traits; "CAD/CHD/MI": Coronary Artery Disease / Coronary Heart Disease / Myocardial Infarction; "Blood" traits: Haemoglobin levels and platelet counts; "Lipids": LDL and Total Cholesterol; "BMI/WHR" includes Body Mass Index, weight, obesity, waist or hip circumference, Waist-Hip-Ratio; "Menarche": age at menarche; "Lung": lung function (FEV1); "Alzheimer's" traits refers to Cerebrospinal fluid levels of Alzheimer's disease related proteins; "Cancer" includes carcinomas, neuroblastomas, bladder cancer; "Education": years of educational attainment.
Plots (b) and (c) show mouse phenotype enrichment and disease ontology enrichment, respectively, of validated novel and previously reported variants. Enrichment was performed using the GREAT tool with the sentinel SNVs as query.

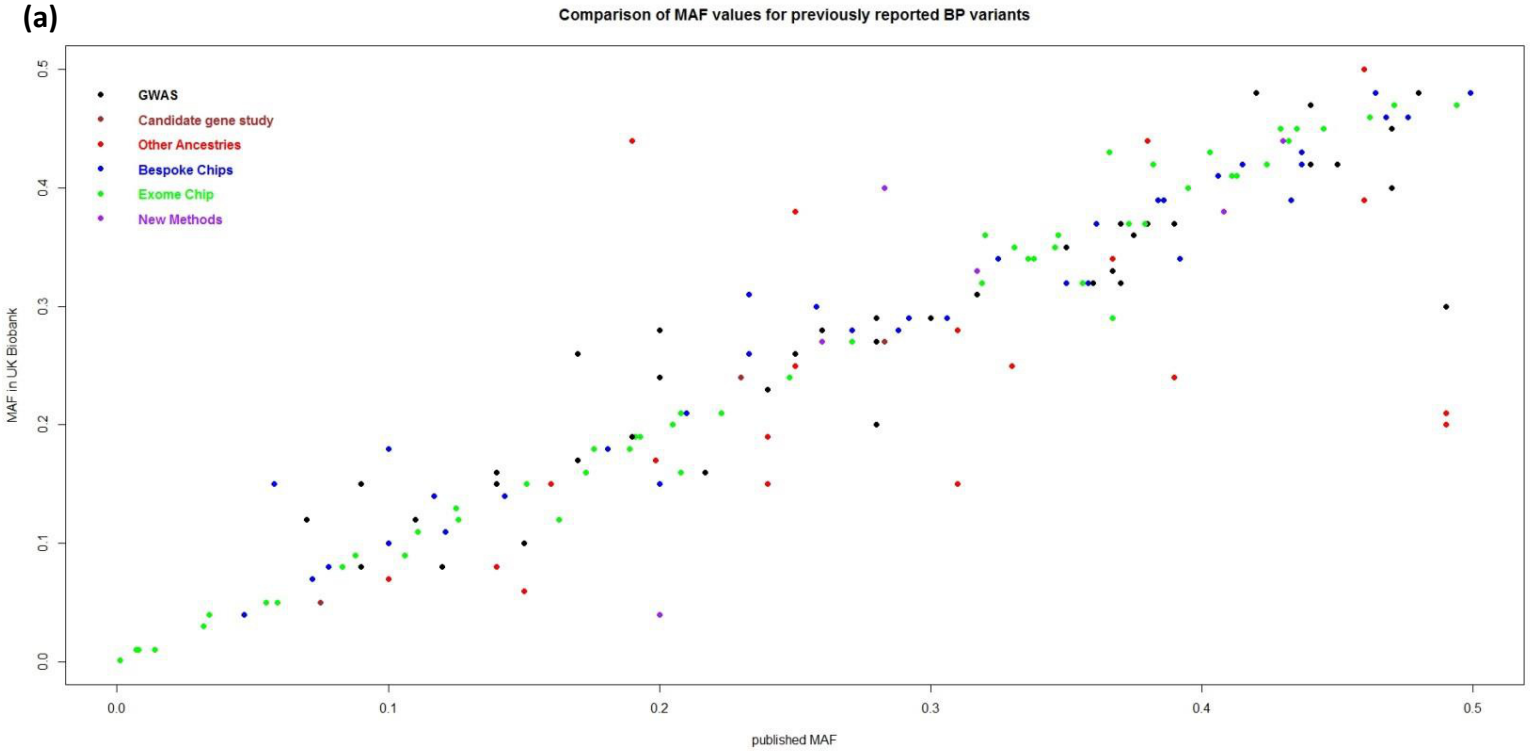




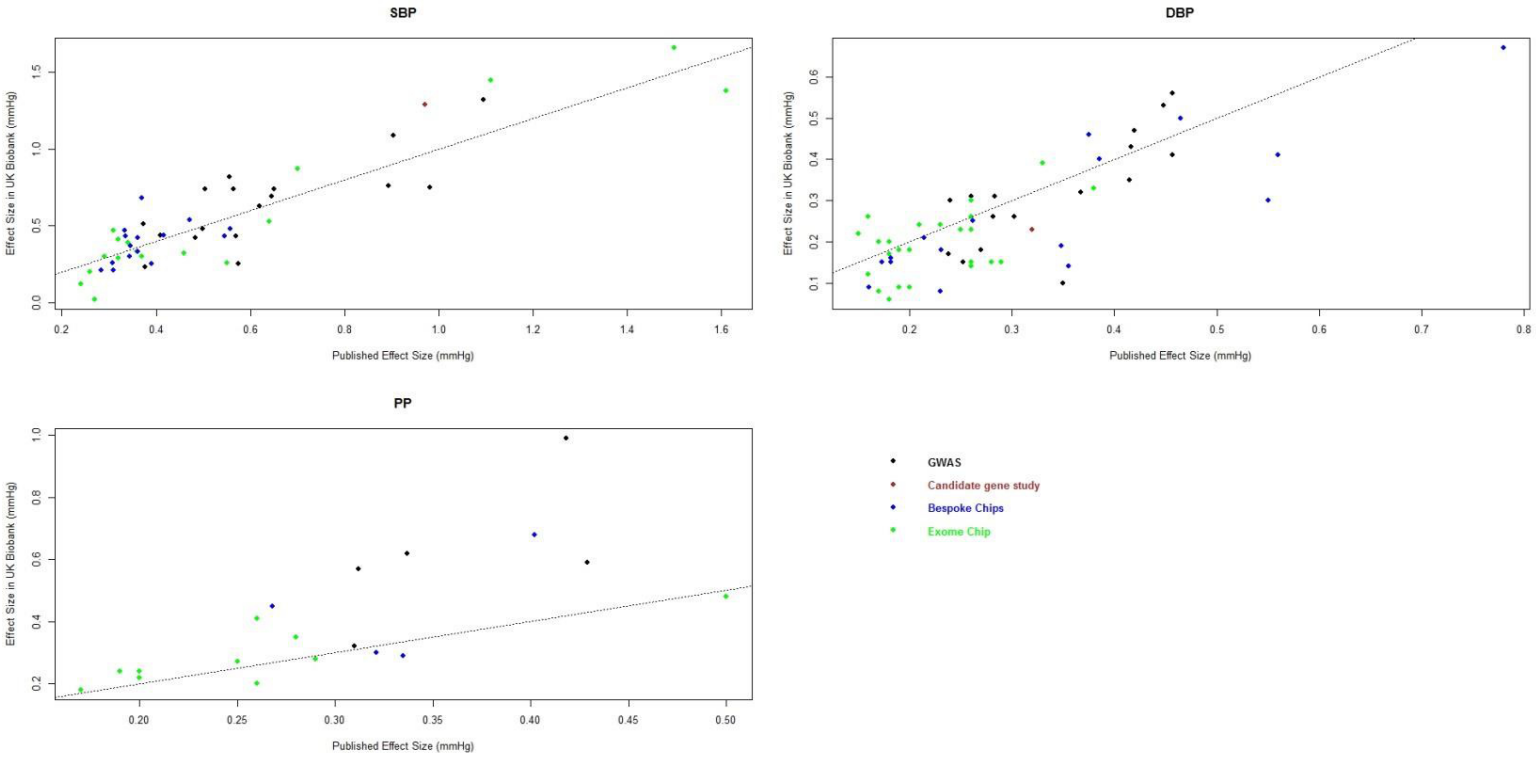


Supplementary Figure 6: Results of previously reported variants at the time of analysis: comparison of UK Biobank (UKB) and originally published results. Plot (a) compares the Minor Allele Frequency (MAF) values in UK Biobank with those from the originally published studies, for all 163 previously reported blood pressure (BP) variants at the time of analysis. The plotted points are colour-coded according to the type of genetic association study that each variant was identified from. For example, "GWAS" refers to standard Genome-Wide Association Studies in Europeans, whereas "Other Ancestries" refers to analyses in non-Europeans; "Bespoke chips" refers to e.g. studies using the CardioChip or MetaboChip; "New Methods" refers to analyses using other methodological strategies which were not main-effect associations, e.g. interaction analyses or multivariate analyses. Plot (b) compares the effect sizes for a subset of these previously reported variants, restricted to non-rare variants (1 variant excluded from "Exome-chip" with MAF < 1% in UKB) from main effect analyses (excluding "New Methods" category) of people of European ancestry ("Other Ancestries" category excluded). Three separate plots are provided for systolic (SBP), diastolic (DBP) and pulse pressure (PP) traits (hence any variants identified for hypertension or Mean Arterial Pressure are excluded), with effect sizes given in mmHg units. Each variant is plotted only once, for the primary BP trait that was originally reported. In each plot, the dotted line represents the Y=X line, and the r^2 values report the statistical correlation between the UK Biobank and the published effect sizes.

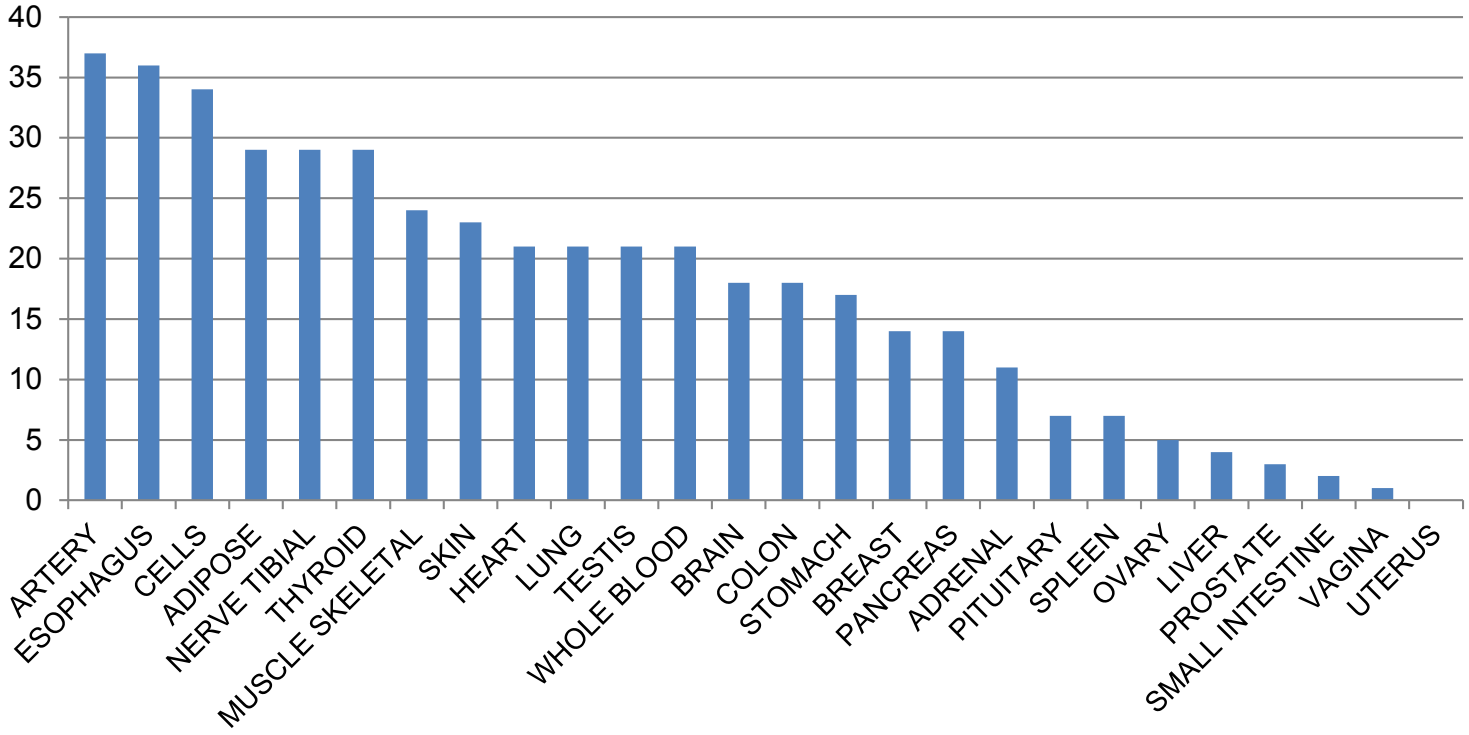
(a)



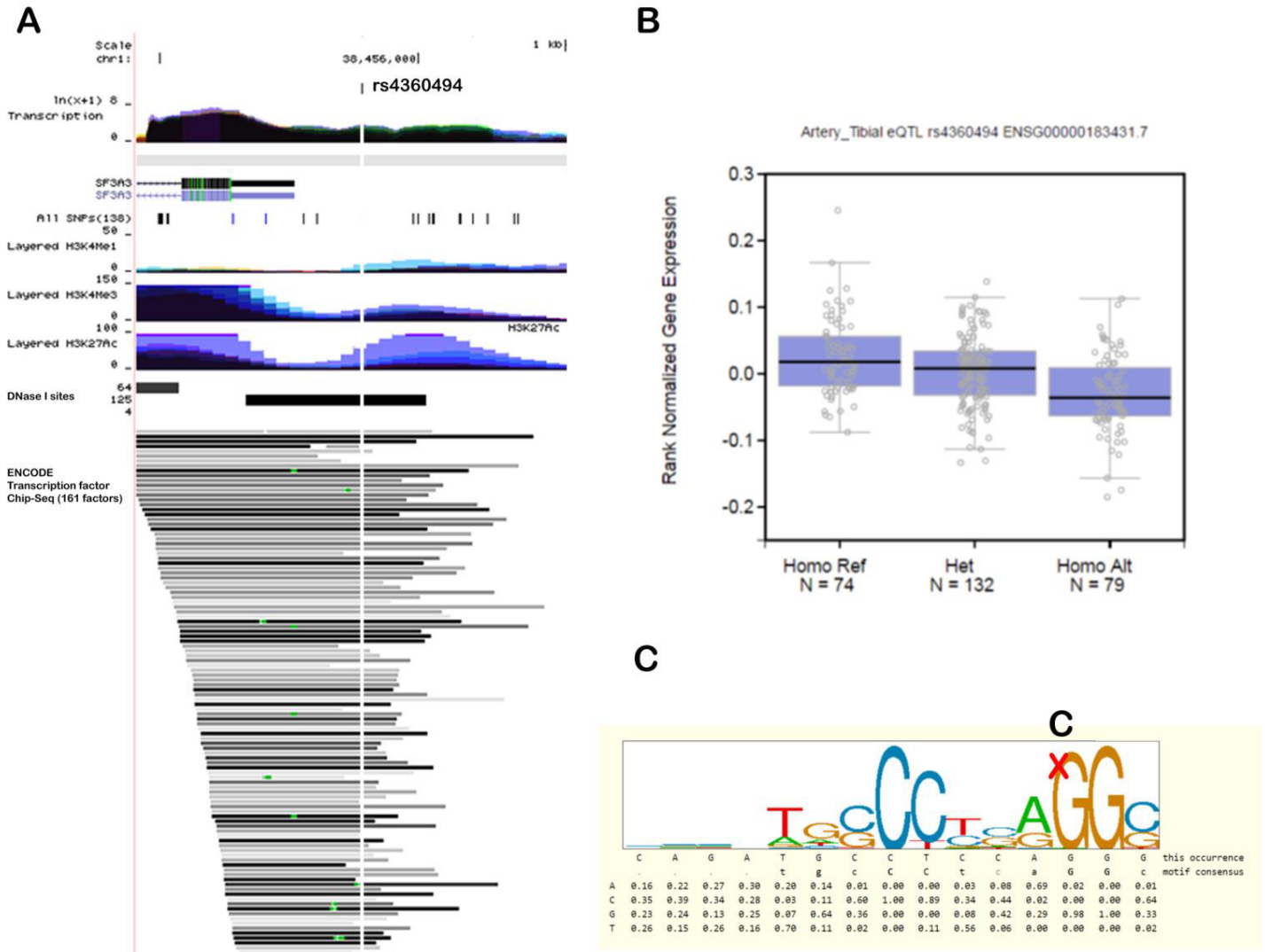
(b)



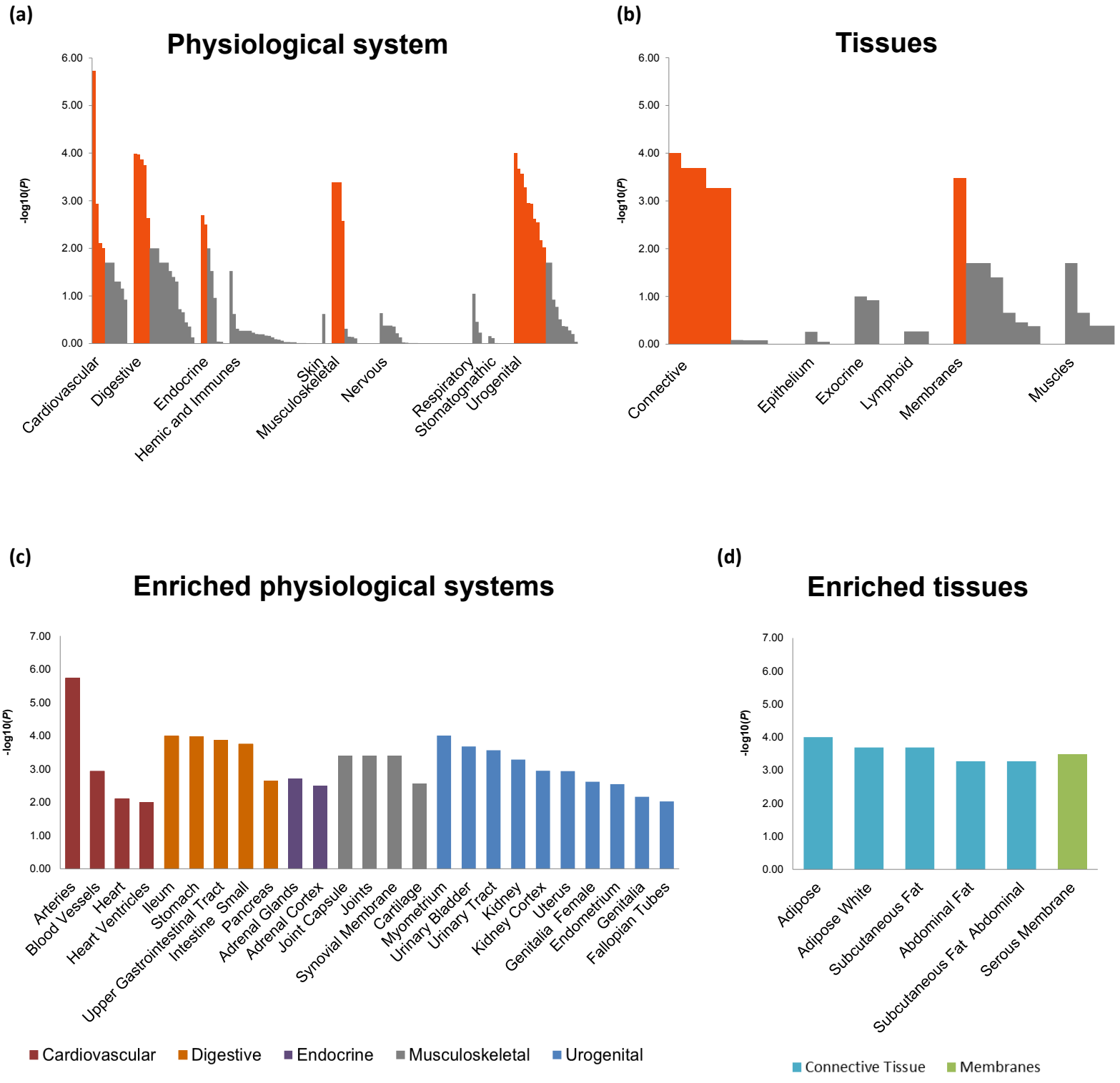
Supplementary Figure 7: Validated loci eQTLs across all tissues. The figure represents the number of validated loci from our study (total n=107) which contain at least one variant (in LD of $r^2 \geq 0.8$ with the sentinel SNV) with an eQTL association observed for each tissue type, according to the GTEx database. eQTL: expression quantitative trait loci ; LD linkage disequilibrium; SNV: single nucleotide variant; GTEx The Genotype-Tissue Expression project.



Supplementary Figure 8: In silico evidence supporting an eQTL in the *SF3A3* gene. (A) UCSC (University of California Santa Cruz) Genome Browser view of the 3' region of *SF3A3*. ENCODE (Encyclopedia of DNA Elements) Transcription factor Chip-Seq data shows widespread binding in the region of rs4360494, including the transcription Factor AP-2 Alpha/Gamma B) GTEX Tibial Artery eQTL demonstrating decreased expression of *SF3A3* in homozygous minor allele carriers. (C) G>C transversion removes predicted AP-2 binding. (eQTL: expression Quantitative Trait Locus)

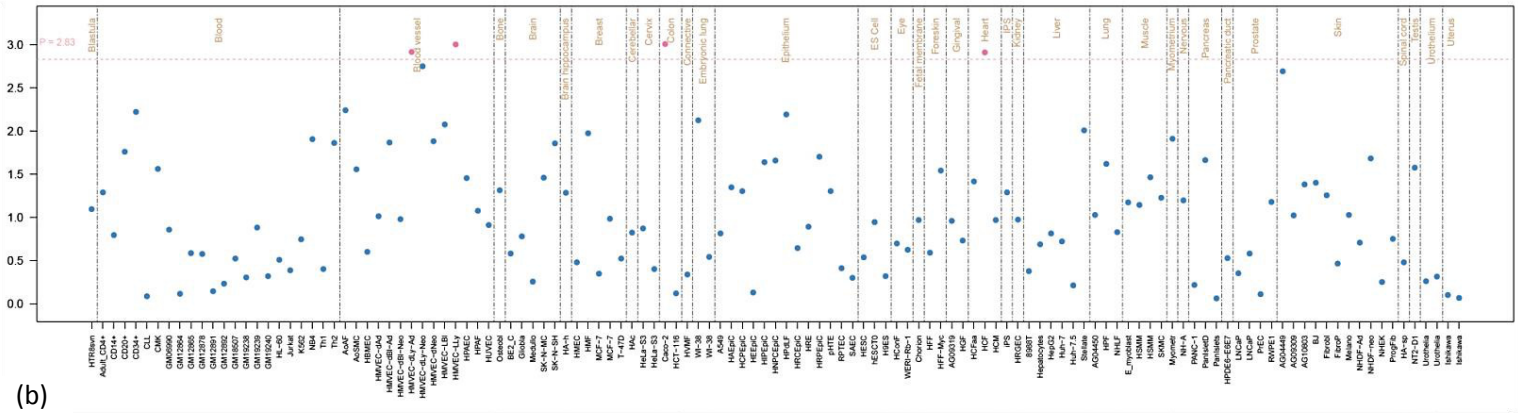


Supplementary Figure 9: DEPICT tissue enrichment across all reported blood pressure associations (both validated loci from our study, and variants previously reported at the time of analysis). We find enrichment of expression across 31 tissues and cells, with highest enrichment found in arteries (P = 1.9×10^{-6}; FDR < 0.01). Enrichment association passing false discovery testing is indicated in red. Figures: (a) Physiological systems tissue enrichment; (b) Tissue enrichment; (c) Cardiovascular system enrichment; (d) Endocrine system enrichment. Figures (c) and (d) are detailed subsections for tissues of interest taken from figure (a). DEPICT: Data-driven Expression Prioritized Integration for Complex Traits; FDR: False discovery rate.

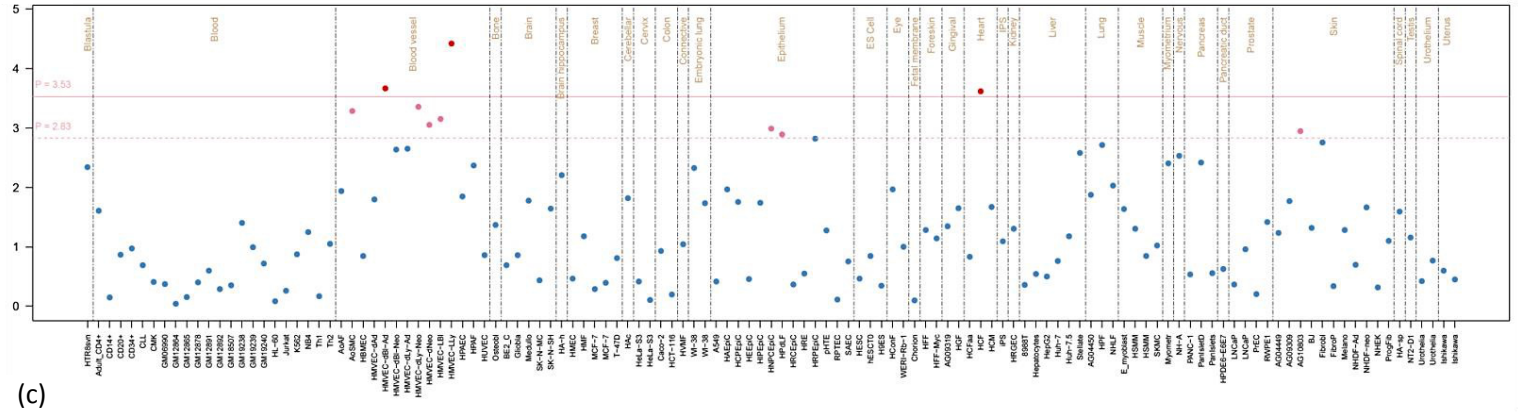


Supplementary Figure 10: FORGE results. Sentinel variants for association with blood pressure are investigated for enrichment in ENCODE (Encyclopedia of DNA Elements) DNase I regulatory regions using FORGE. (a) FORGE DNase I sensitive region enrichment for all reported sentinel variants (both validated variants from our study, and variants previously reported at the time of analysis). Strongest enrichment is seen in vasculature (MVEC, Microvascular Endothelium) and highly vascularised tissues. Tissues in red are significant after correction for false discovery. (b) To further investigate the regulatory basis of the associated loci, candidate regulatory variants are selected for (b) 107 validated loci from our study and (c) all reported loci (both 107 validated loci from our study, and previously reported loci at the time of analysis). Again enrichment is seen for vascular tissue especially vascular smooth muscle and endothelial cell types.

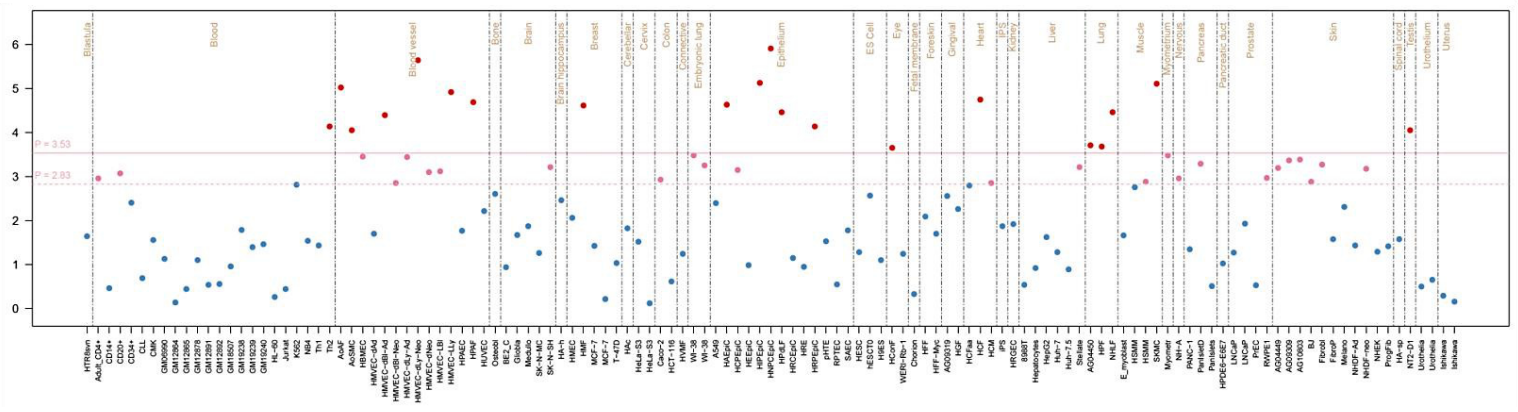
(a)



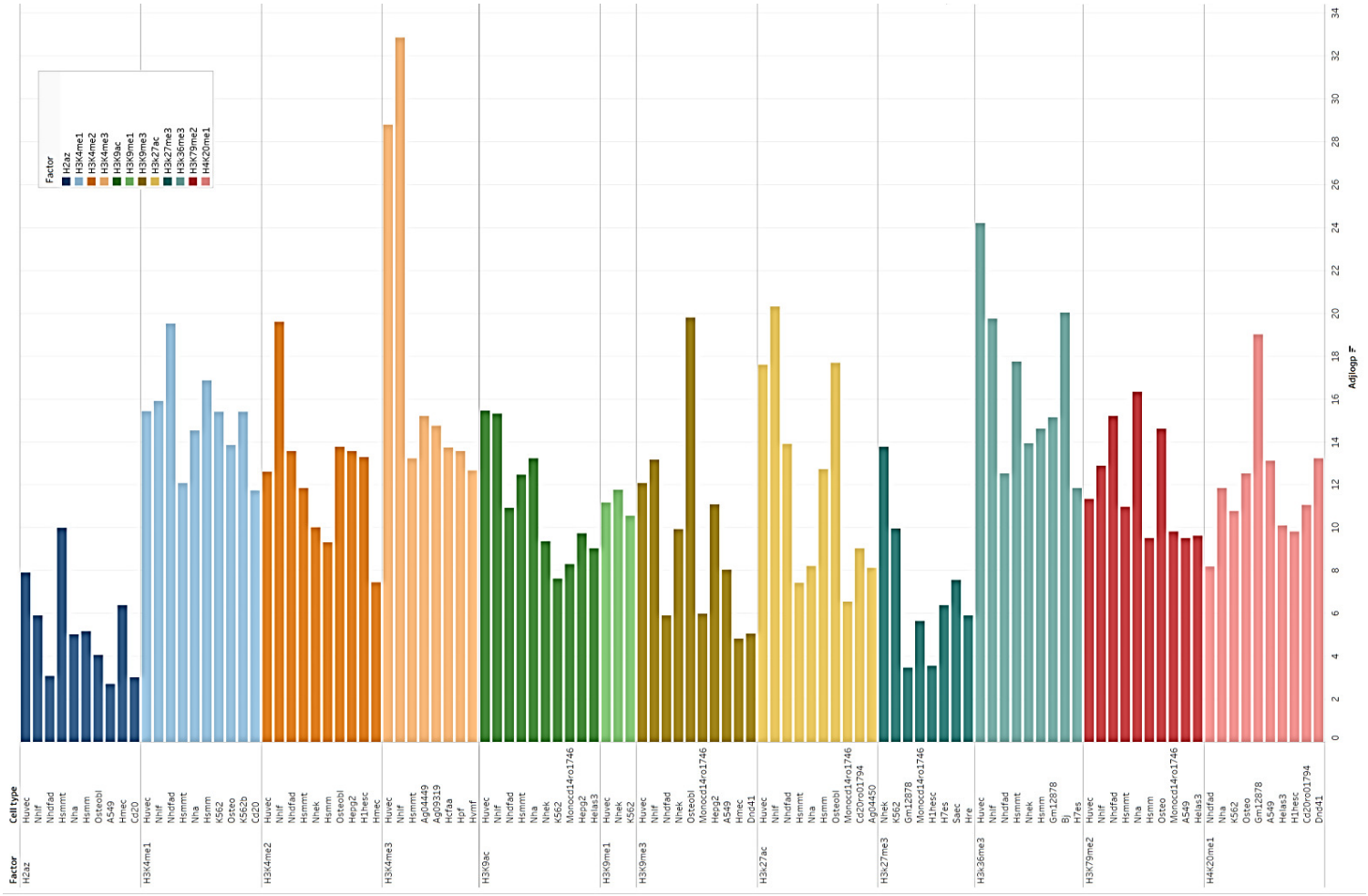
(b)



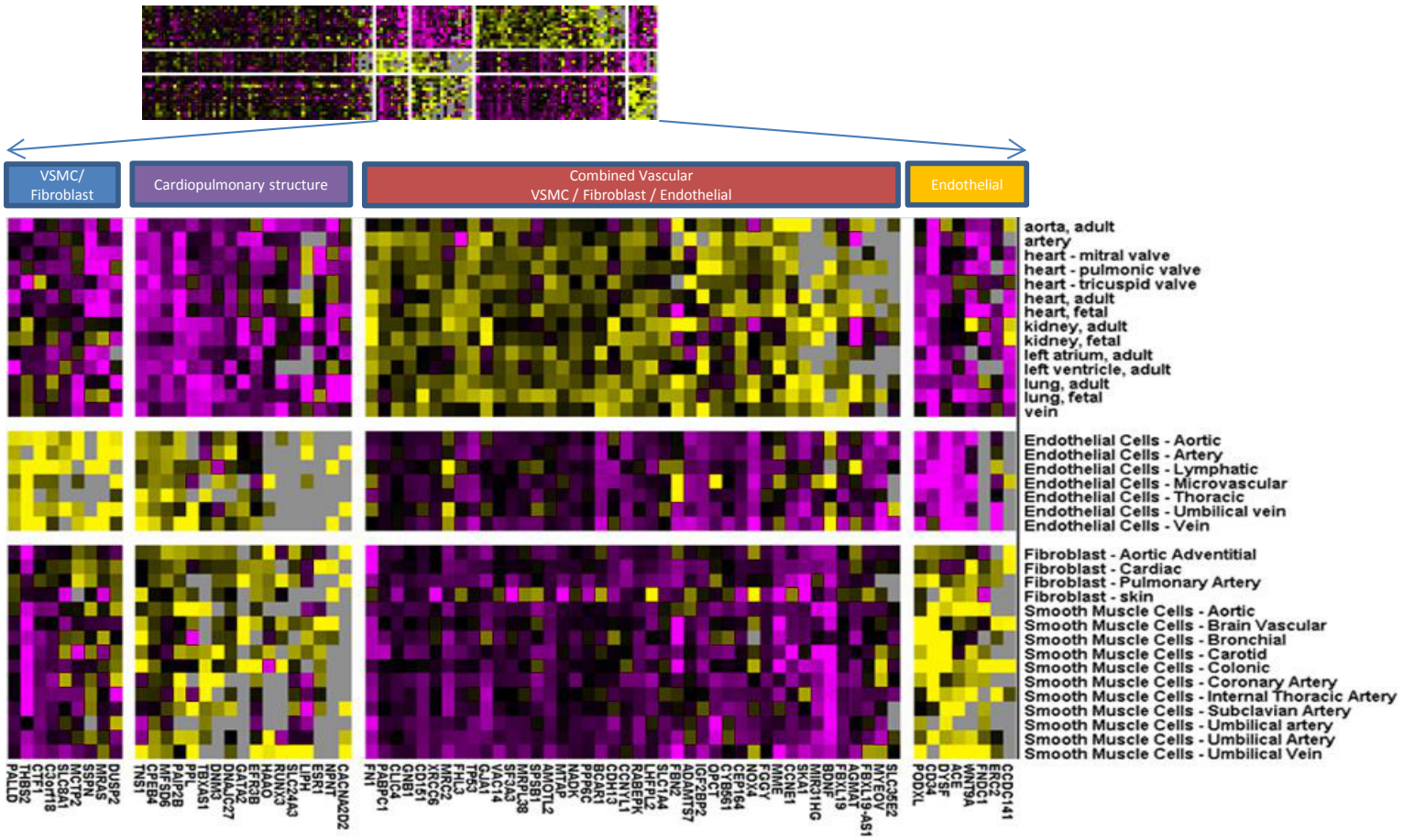
(c)



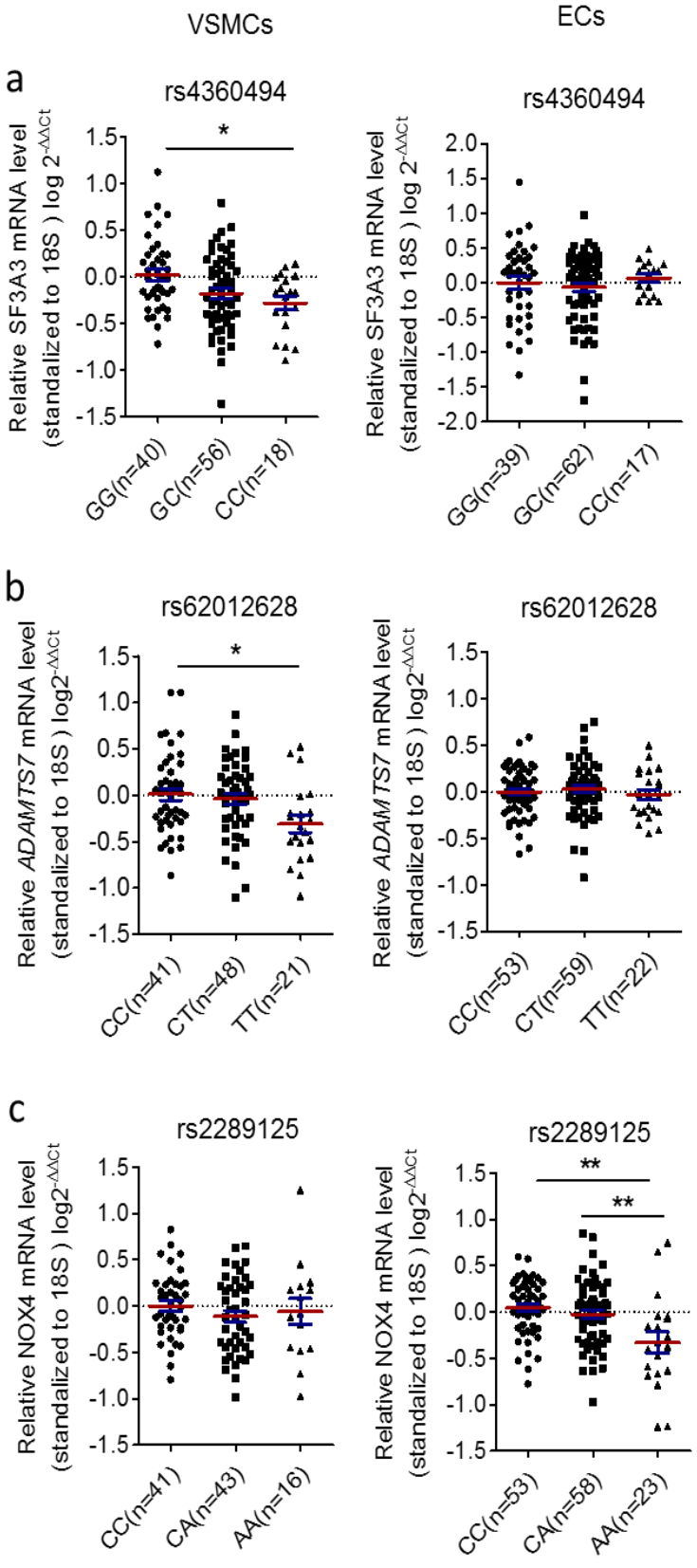
Supplementary Figure 11: Genome-wide enrichment of histone methylation marks among all reported sentinel variants (from both the 107 validated loci from our study, and previously reported variants at the time of analysis) for association with blood pressure. Histone mark enrichment is investigated using GenomeRunner.



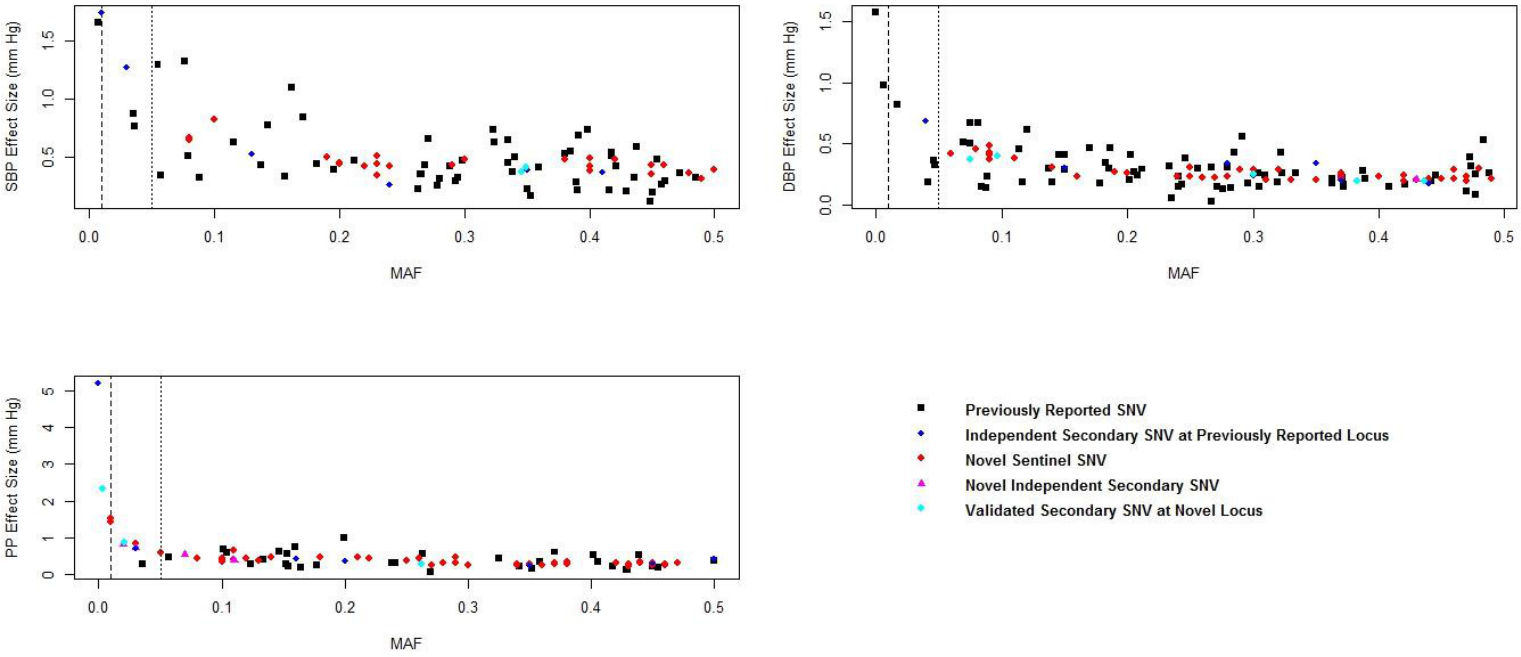
Supplementary Figure 12: The expression of genes contained within the 107 validated loci is investigated using K-means clustering in the fantom5 gene expression reference data set, focusing on cardiovascular relevant tissues that show evidence of enrichment in DEPICT (Data-driven Expression Prioritized Integration for Complex Traits) and FORGE analysis. With K-means set to 5 clusters, tissue specific clusters are apparent, including vascular smooth muscle cells (VSMC) and fibroblasts, endothelial cells (including probable endothelial cells in highly vascularised tissues), and a combined vascular cell cluster. Clusters are also apparent for cardiopulmonary genes. A further 65 genes do not cluster within tissue groups (not shown) and 71 genes are not detected in the fantom5 data. Yellow indicates down-regulation, purple indicates up-regulation.



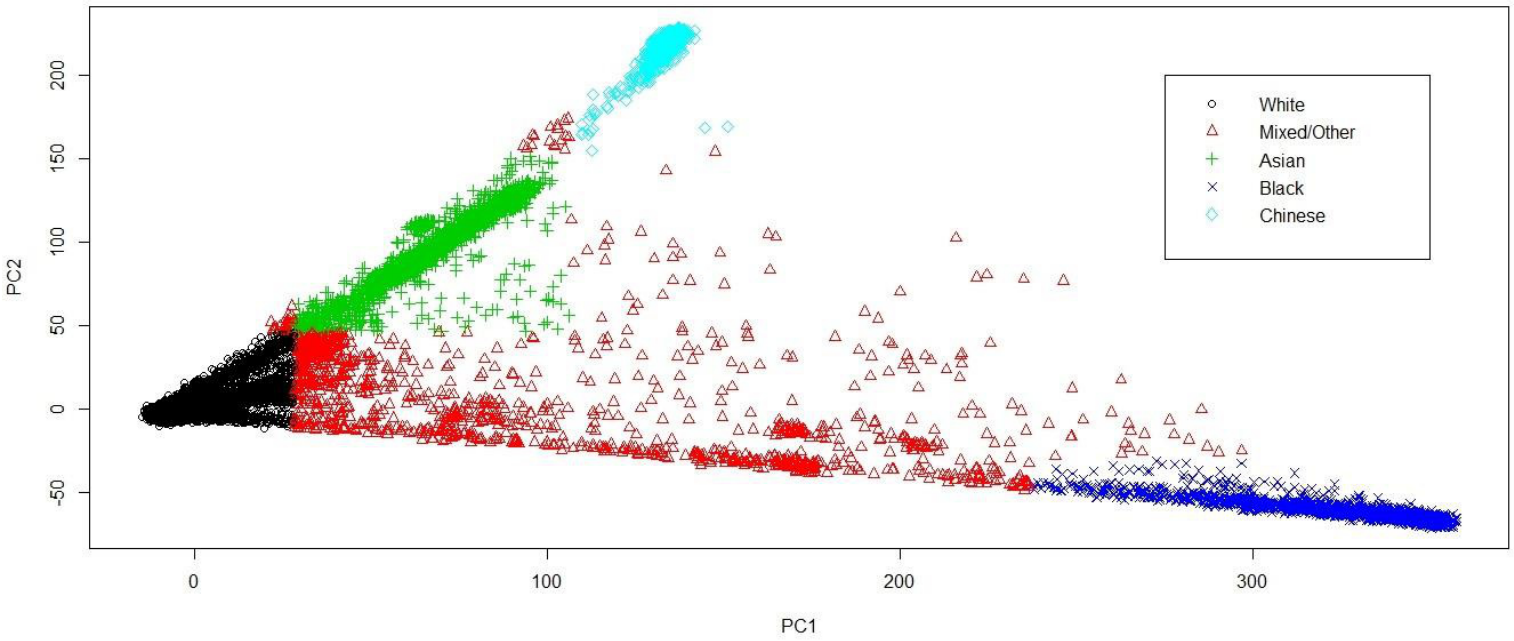
Supplementary Figure 13: Gene expression in human vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) detected by quantitative Polymerase Chain Reaction (qPCR) with standardization to internal control of 18S. Dots represent individual samples from each genotype with numbers indicated. Data are analysed using the $2^{-\Delta\Delta Ct}$ method, log transformed and shown as mean with error bars, Standard Error of the Mean (SEM) on left (VSMCs) and right (ECs) of each panel. Differences are determined by one-way Analysis of Variance (ANOVA) with Bonferroni correction for multiple comparisons. In (a): the sentinel variant rs4360494 at the *SF*3*A*3 locus is significantly associated with expression of *SF*3*A*3 in cell type-specific manner, with the major C allele associated with increased expression of *SF*3*A*3 in human VSMCs, but no genetic difference in ECs. In (b): A similar cell-type specificity is shown for genetic effect of sentinel variant rs62012628 on *ADAMTS7* expression, with a significantly lower expression level for the minor T allele in human VSMCs. In (c) the minor A allele of sentinel variant rs2289125 at *NOX4* gene locus is significantly related with a lower *NOX4* expression level in human ECs.



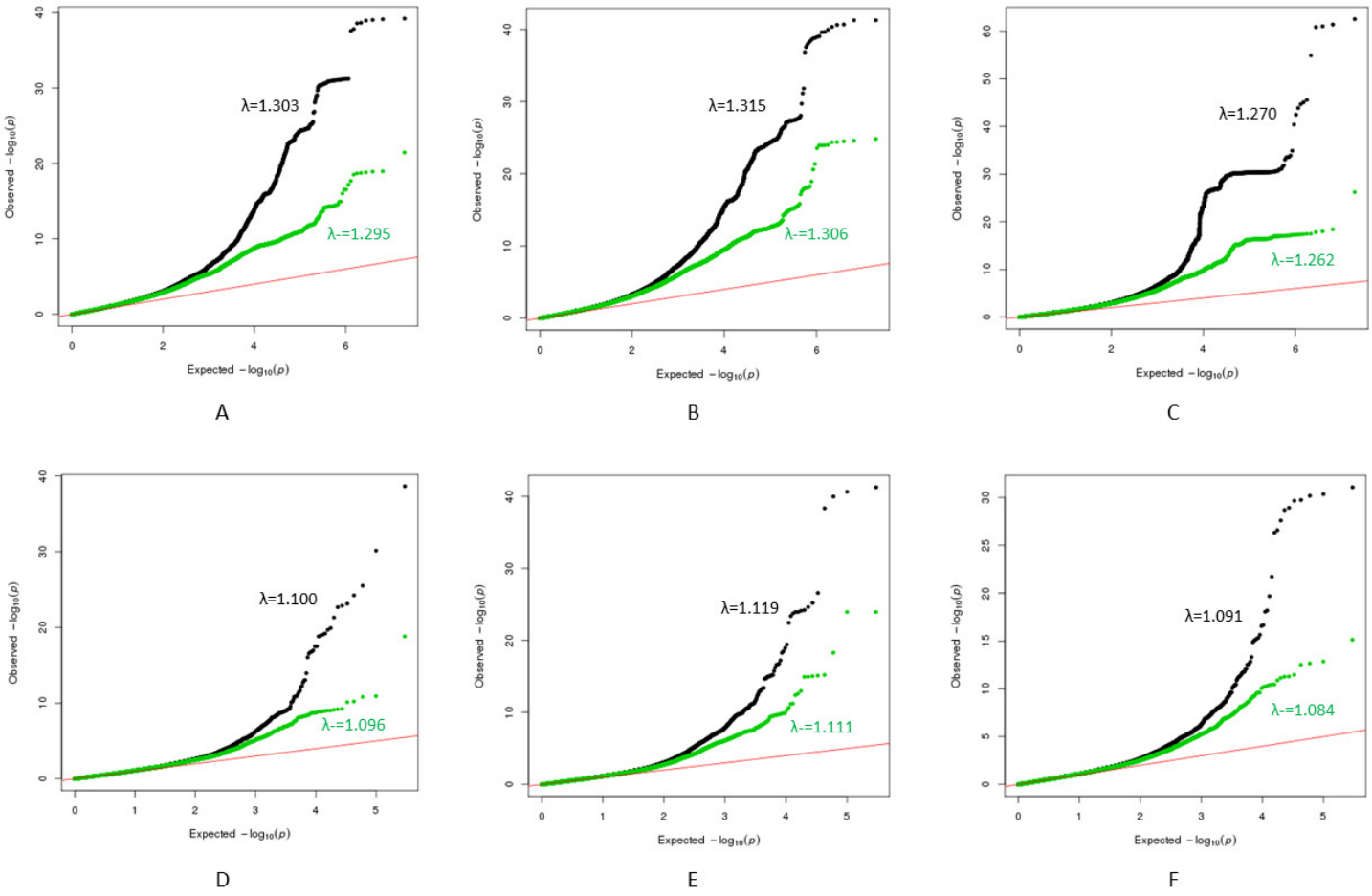
Supplementary Figure 14: Relationship between allele frequency and effect size of blood pressure associated variants, comparing the 107 validated variants in our study and the previously reported variants at the time of analysis. The MAF values and effect sizes, all taken from UK Biobank discovery results, are plotted according to the most significant trait in the UK Biobank discovery data for previously reported variants, and for the validated trait for all other variants. Variants are colour coded according to the type of variant (see legend: "Previously reported" is at the time of analysis; "novel" refers to all 107 validated loci in our study, many of which were validated for the first time). Note that the "validated secondary SNVs" are validated SNVs at "novel" loci which were not independent of the sentinel SNV after conditional analysis. SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAF: Minor Allele Frequency; SNV: single nucleotide variant.



Supplementary Figure 15: Ethnicity clustering performed using PCA. PC1 is plotted against PC2 for all N~150,000 UK Biobank participants, colour-coded according to the five ethnic clusters created from our K-means PCA clustering, from which only "White" Caucasians are selected for analysis of individuals of European ancestry. PCA: Principal Component Analysis; QC: Quality Control; PCs: Principal Components.



Supplementary Figure 16: Quantile-Quantile plots of results for (A) systolic blood pressure (SBP) from UK Biobank GWAS, (B) diastolic blood pressure (DBP) from GWAS, (C) pulse pressure (PP) from GWAS, (D) SBP from UK Biobank exome, (E) DBP from exome and (F) PP from exome. The black curves are based on all the variants in the corresponding analysis, with ~9.8 million variants with Minor Allele Frequency ≥ 1% and imputation quality INFO > 0.1 for GWAS for plots (A-C) and ~150,000 exome variants for plots (D-F). The green curves are results after excluding previously reported blood pressure variants at the time of analysis and all variants in Linkage Disequilibrium with them ($r^2 \geq 0.2$). The genomic inflation factor, λ, is reported (NB: LD Score regression analysis yields λ~1.05 for each BP-GWAS, confirming that any inflation in the GWAS findings reflects polygenic influence on blood pressure).



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CHARGE+ Exome Chip Blood Pressure Consortium

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