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15	The genetics of blood pressure regulation and its target organs from
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1 ABSTRACT

2 To dissect the genetic architecture of blood pressure and assess effects on target-organ damage, 3 we analyzed 128,272 SNPs from targeted and genome-wide arrays in 201,529 individuals of European ancestry and genotypes from an additional 140,886 individuals were used for validation. We identified 4 5 66 blood pressure loci, of which 17 were novel and 15 harbored multiple distinct association signals. 6 The 66 index SNPs were enriched for *cis*-regulatory elements, particularly in vascular endothelial cells, 7 consistent with a primary role in blood pressure control through modulation of vascular tone across 8 multiple tissues. The 66 index SNPs combined in a risk score showed comparable effects in 64,421 9 individuals of non-European descent. The 66-SNP blood pressure risk score was significantly associated 10 with target-organ damage in multiple tissues, with minor effects in the kidney. Our findings expand 11 current knowledge of blood pressure pathways and highlight tissues beyond the classic renal system in 12 blood pressure regulation.

1 INTRODUCTION

2 There are considerable physiological, clinical and genetic data that point to the kidney as the 3 major regulator of blood pressure (BP) and to renal damage as a consequence of long-term BP elevation. However, alternative hypotheses, such as increasing systemic vascular resistance, are also serious 4 5 contenders to explain the rise of BP with increasing age, but with limited genetic support. The genetic 6 basis of elevated blood pressure or hypertension (HTN) involves many loci that have been identified using large-scale analyses of candidate genes^{1,2}, linkage studies, and genome-wide association studies 7 8 $(GWAS)^{3-12}$. The genes underlying BP regulation can help resolve many of the open questions regarding BP (patho-) physiology. While ~40-50% of BP variability is heritable 13,14 , the genetic variation identified 9 to date explains only $\sim 2\%^{1-12}$. 10

11 The Cardio-MetaboChip is a custom genotyping microarray designed to facilitate cost-effective 12 follow-up of nominal associations for metabolic and cardiovascular traits, including BP. This array 13 comprises 196,725 variants, including ~5,000 SNPs with nominal (*P* <0.016) evidence of BP association in 14 our previous GWAS meta-analysis⁵. Furthermore, the array includes several dense scaffolds for fine 15 mapping of selected loci spanning, on average, genomic regions of 350 kilobases^{5,16}, of which 24 include 16 genome-wide significant BP association in the current study^{5,16}.

17 RESULTS

18 Novel genetic loci associated with systolic and diastolic BP

We performed meta-analyses of association summary statistics from a total of 201,529
 individuals of European (EUR) ancestry from 74 studies: (i) 109,096 individuals from 46 studies
 genotyped on Cardio-MetaboChip; and (ii) 92,433 individuals from 28 studies with imputed genotype
 data from genome-wide genotyping at variants included on the Cardio-MetaboChip. Twenty-four of the
 28 studies with genome-wide genotyping data had contributed to previous analyses (Supplementary
 Tables 1-3)^{5,7}.

BP was measured using standardized protocols in all studies^{5,17} (**Supplementary Table 1, Online methods**). Association statistics for systolic and diastolic BP (SBP and DBP) in models adjusting for age, age², sex, and body mass index (BMI), were obtained for each study separately, with study-specific genomic control applied to correct for possible population structure. Fixed-effects meta-analysis proceeded in 4 stages, separately for the following SNP associations: Stage 1, using results based on 46 studies using Cardio-MetaboChip genotypes of 109,096 participants; Stage 2, using additional results based on imputed genotypes from genome-wide genotyping arrays in 4 previously unpublished studies;

Stage 3 using imputed genotypes from genome-wide genotyping arrays in 24 previously published
studies⁵; and Stage 4, the joint meta-analysis of Stages 1-3 including a total of 201,529 independent
individuals (Supplementary Figure 1, Supplementary Tables 2-3, Supplementary Note). To account for
population structure between studies in Stages 1-3 of our meta-analysis, genomic control correction was
applied to meta-analysis results from each of these stages in an approach aggregating summary
statistics from GWAS and Cardio-MetaboChip studies^{18,19}.

7 After stage 4, 67 loci attained genome-wide significance ($P < 5 \times 10^{-8}$), 18 of which were not previously reported in the literature (Supplementary Table 4). Quantile-quantile plots of the stage 4 8 9 meta-analysis showed an excess of small P values, with an elevated genomic control lambda estimate 10 that was persistent, albeit attenuated, after excluding all 66 loci (Supplementary Figure 2). This 11 observation is compatible with either residual uncorrected population stratification or the presence of a 12 large number of variants that are truly associated with BP but fail to achieve genome-wide significance 13 in the current meta-analysis. The Cardio-MetaboChip array's inclusion of SNPs from a prior BP GWAS⁵ 14 does not appear to be the sole explanation, as we did not observe a significant decrease of the excess of 15 small P values after exclusion of all SNPs that were included on the Cardio-MetaboChip based on 16 nominal BP association (Supplementary Figures 3 and 4). Since the quantile-quantile plots continued to 17 show deviation from the null expectation, we sought additional validation for 18 variants attaining genome-wide significance, but without prior support in the literature, in up to 140,886 individuals of 18 European ancestry from UK Biobank²⁰. For these SNPs, we performed a stage 5 meta-analysis combining 19 20 the association summary statistics from stage 4 and UK Biobank, in a total of up to 342,415 individuals

21 (Supplementary Table 5).

22 Upon stage 5 meta-analysis, 17 of 18 variants retained genome-wide significance for the primary 23 trait (SBP or DBP result with the lower P value). The one variant that was not genome-wide significant had a borderline P value of 4.49×10^{-8} at stage 4. These findings are consistent with appropriate 24 25 calibration of the association test statistics at stage 4 such that observing one failure among 18 validation tests is consistent with the use of a threshold ($P < 5 \times 10^{-8}$) designed to have a 1 in 20 chance 26 of a result as or more extreme solely due to chance. In total, 66 loci attained genome-wide significance: 27 13 loci for SBP only, 12 loci for DBP only, and 41 loci for both traits. Of these, 17 BP loci were novel, 28 while 49 were previously reported at genome-wide significance (Table 1 and Figure 1). 29 Compared with previously reported BP variants^{5,7,21}, the average absolute effect size of the 30

newly discovered variants is smaller, with comparable minor allele frequency (MAF), presumably owing
to the increased power of a larger sample size (**Table 2**). As expected from the high correlation between

SBP and DBP effects, the observed directions of effects for the two traits were generally concordant
 (Supplementary Figure 5), and the absolute effect sizes were inversely correlated with MAF (Table 1
 and Supplementary Figure 6). The 66 BP SNPs explained 3.46% and 3.36% of SBP and DBP variance,
 respectively, a modest increase from 2.95% and 2.78% for SBP and DBP, respectively, for the 49
 previously reported SNPs (Supplementary Note). The low percent variance explained is consistent with
 estimates that large numbers of common variants with weak effects at a large number of loci influence
 BP⁵.

8 Signal refinement at the 66 BP loci

9 To identify distinct signals of association at the 66 BP loci and the variants most likely to be 10 causal for each, we started with an approximate conditional analysis using a model selection procedure implemented in the GCTA-COJO package^{22,23} as well as a detailed literature review of all published BP 11 12 association studies. GCTA-COJO analysis was performed using the association summary statistics for SBP 13 and DBP from the Stage 4 EUR ancestry meta-analyses, with the linkage disequilibrium (LD) between 14 variants estimated on the basis of Cardio-MetaboChip genotype data from 7,006 individuals of EUR ancestry from the GoDARTS cohort²⁴. More than one distinct BP association signal was identified at 13 15 loci at $P < 5 \times 10^{-8}$ (Supplementary Table 6, Supplementary Figures 7, and Supplementary Note). At six 16 loci, the distinct signals were identified for both SBP and DBP analyzed separately; these trait-specific 17 associations were represented by the same or highly correlated ($r^2 > 0.8$) SNPs at 5 of the 6 loci 18 19 (Supplementary Tables 7 and 8). We repeated GCTA-COJO analyses using the same summary 20 association results, but with a different reference sample for LD estimates (WTCCC1-T2D/58BC, N = 21 2,947, Supplementary Note) and observed minimal differences arising from minor fluctuations in the 22 association P value in the joint regression models (Supplementary Tables 7 and 8). LD-based 23 comparisons of published association signals at established BP loci, and the current study's findings 24 suggested that at 10 loci, the signals identified by the single-SNP and the GCTA-COJO analyses were 25 distinct from those reported in the literature (Supplementary Table 9). 26 We then performed multivariable regression modeling in a single large cohort (Women's 27 Genome Health Study, WGHS, N = 23,047) with simultaneous adjustment for both 1) all combinations of

putative index SNPs for each distinct signal from the GCTA-COJO conditional analyses, and 2) all index
SNPs for all potential distinct signals identified by our literature review (Supplementary Table 9,

30 **Supplementary Note**). Although WGHS is very large as a single study, power is reduced in a single

31 sample compared to that in the overall meta-analysis (23k vs. 342k individuals) and consequently the

failure to reach significance does not represent non-replication for individual SNPs. The WGHS analysis
supported two distinct association signals at eight of 13 loci identified in the GCTA-COJO analysis, but
could not provide support for the remaining five (Supplementary Table 10). The joint SNP modeling in
WGHS additionally supported two distinct signals of association at three other loci (*GUCY1A3-GUCY1B3*, *SYNPO2L* and *TBX5-TBX3*), at which the SNP identified in the current study is distinct from that
previously reported in the literature^{5,11}.

7 We sought to refine the localization of likely functional variants at loci with high-density 8 coverage on the Cardio-MetaboChip. We followed a Bayesian approach to define, for each signal, 9 credible sets of variants that have 99% probability of containing or tagging the causal variant 10 (Supplementary Note). To improve the resolution of the method, the analyses were restricted to 24 11 regions selected to fine map (FM) genetic associations, and that included at least one SNP reaching 12 genome-wide significance in the current meta-analyses (Supplementary Table 11). Twenty-one of the 13 Cardio-MetaboChip FM regions were BP loci in the original design, with three of the newly discovered 14 BP loci in FM regions that were originally selected for other non-BP traits. We observed that the 99% 15 credible SNP sets at five BP loci spanned <20kb. The greatest refinement was observed at the SLC39A8 16 locus for SBP and DBP, and at the ZC3HC1 and PLCE1 loci for DBP, where the 99% credible sets included 17 only the index variants (Supplementary Table 12). Although SNPs in credible sets were primarily noncoding, they included one synonymous and seven non-synonymous variants that attained high posterior 18 19 probability of driving seven distinct association signals at six BP loci (Supplementary Table 12). Of 20 these, three variants alone account for more than 95% of the posterior probability of driving the 21 association signal observed at each of three loci (Supplementary Table 12 and 13). Despite reduced 22 statistical power, the analyses restricted to the samples with Cardio-MetaboChip genotypes only 23 (N = 109,096) identified the majority of SNPs identified in the GWAS+Cardio-MetaboChip data 24 (Supplementary Table 12). The full list of SNPs in the 99% credible sets are listed in Supplementary 25 Table 13.

26 What do the BP variants do?

Index SNPs or their proxies (r² > 0.8) altered amino acid sequence at 11 of 66 BP loci (**Table 1**).
Thus, the majority of BP-association signals are likely driven by non-coding variants hypothesized to
regulate expression of some nearby gene in *cis*. To characterize their effects, we first sought SNPs
associated with gene expression (eSNPs) from a range of available expression data which included
hypertension target end organs and cells of the circulatory system (heart tissue, kidney tissue, brain

tissue, aortic endothelial cells, blood vessels) and other tissue/cell types (CD4⁺ macrophages, monocytes 1 2 lymphoblastoid cell lines, skin tissue, fat tissue, and liver tissue). Fourteen BP-associated SNPs at the 3 MTHFR-NPPB, MDM4, ULK4, CYP1A1-ULK3, ADM, FURIN-FES, FIGN, and PSMD5 loci were eSNPs across different tissues (Supplementary Table 14). Of these 14 eSNPs, three were also predicted to alter the 4 5 amino acid sequence at the MTHFR-NPPB, MAP4 and ULK4 loci, providing two potential mechanisms to 6 explore in functional studies. Second, we used gene expression levels measured in whole blood in two 7 different samples each including >5,000 individuals of EUR descent. We tested whether the lead BP SNP 8 was associated with expression of any transcript in *cis* (<1Mb from the lead SNP at each locus) at a false 9 discovery rate (FDR) of < 0.05, accounting for all possible *cis*-transcript association tests genome-wide. 10 It is likely that we did not genotype the causal genetic variant underlying each BP association signal; a 11 nearby SNP-transcript association, due to LD, may therefore reflect an independent genetic effect on 12 expression that is unrelated to the BP effect. Consequently, we assumed that the lead BP SNP and the most significant eSNP for a given transcript should be highly correlated ($r^2 > 0.7$). Furthermore, we 13 14 assumed that the significance of the transcript association with the lead BP SNP should be substantially 15 reduced in a conditional model adjusting for the best eSNP for a given transcript. Eighteen SNPs at 15 16 loci were associated with 22 different transcripts, with a total of 23 independent SNP-transcript 17 associations (three SNPs were associated with two transcripts each, Supplementary Table 15, Supplementary Note). The genes expressed in a BP SNP allele-specific manner are clearly high-priority 18 19 candidates to mediate the BP association. In whole blood, these genes included obvious biological candidates such as GUCY1A3, encoding the alpha subunit of the soluble guanylate cyclase protein, and 20 ADM, encoding adrenomedullin, both of which are known to induce vasodilation^{25,26}. There was some 21 22 overlap of eSNPs between the whole blood and other tissue datasets at the MTHFR-NPPB, MDM4, 23 PSMD5, ULK4 and CYP1A1-ULK3 loci, illustrating additional potentially causal genes for further study. 24 An alternative method for understanding the effect on BP of non-coding variants is to determine 25 whether they fall within DNasel hypersensitivity sites (DHSs). We performed two analyses to investigate whether BP SNPs or their LD proxies ($r^2 > 0.8$) were enriched in DHSs in a cell-type-specific manner 26 (Supplementary Note). First, we used Epigenomics Roadmap and ENCODE DHS data from 123 adult cell 27 lines or tissues²⁷⁻²⁹ to estimate the fold increase in the proportion of BP SNPs mapping to DHSs 28 29 compared to SNPs associated at genome-wide significance with non-BP phenotypes from the NHGRI GWAS catalog³⁰. We observed that 7 out of the 10 cell types with the greatest relative enrichment of BP 30 31 SNPs mapping to DHSs were from blood vessels (vascular or micro-vascular endothelial cell-lines or cells) 32 and 11 of the 12 endothelial cells were among the top quarter most enriched among the 123 cell types

(Figure 2 and Supplementary Table 16). In a second analysis of an expanded set of tissues and cell lines,
 in which cell types were grouped into tissues (Supplementary Table 17), BP-associated SNP enrichment
 in DHSs in blood vessels was again observed (P = 1.2 x 10⁻⁹), as well as in heart samples (P = 5.3 x 10⁻⁸;
 Supplementary Table 18).

5 We next tested whether there was enrichment of BP SNPs in H3K4me3³¹ sites, a methylation 6 mark associated with both promoter and enhancer DNA. We observed significant enrichment in a range 7 of cell types including CD34 primary cells, adult kidney cells, and muscle satellite cultured cells 8 (**Supplementary Table 19**). Enrichment of BP SNPs in predicted strong and weak enhancer states and in 9 active promoters³² in a range of cell types was also observed (**Supplementary Table 20, Supplementary** 10 **Figure 8**).

We used Meta-Analysis Gene-set Enrichment of variaNT Associations (MAGENTA)³³ to attempt 11 12 to identify pathways over-represented in the BP association results. No gene sets meeting experiment-13 wide significance for enrichment for BP association were identified by MAGENTA after correction for 14 multiple testing, although some attained nominal significance (Supplementary Table 21, Supplementary **Note**). We also adapted the DEPICT³⁴ pathway analysis tool (Data-driven Expression Prioritized 15 Integration for Complex Traits) to identify assembled gene-sets that are enriched for genes near 16 17 associated variants, and to assess whether genes from associated loci were highly expressed in particular tissues or cell types. Using the extended BP locus list based on genome-wide significant loci 18 19 from this analysis and previously published SNPs that may not have reached genome-wide significance 20 in the current analysis (**Supplementary Table 9**), we identified five significant (FDR \leq 5%) gene sets: 21 abnormal cardiovascular system physiology, G Alpha 1213 signaling events, embryonic growth 22 retardation, prolonged QT interval, and abnormal vitelline vasculature morphology. We also found that 23 suggestive SBP and DBP associations ($P < 1 \times 10^{-5}$) were enriched for reconstituted gene-sets at DBP loci 24 (mainly related to developmental pathways), but not at SBP loci (Supplementary Table 22, 25 Supplementary Note). In a final analysis, we assessed Cardio-MetaboChip SNPs at the fine-mapping loci using formaldehyde-assisted isolation of regulatory elements (FAIRE-gen) in lymphoblastoid cell lines³⁵. 26 Our results provided support for two SNPs, one of which SNP (rs7961796 at the TBX5-TBX3 locus) was 27 located in a regulatory site. Although the other SNP (rs3184504 at the SH2B3 locus) is a non-28 synonymous variant, there was also a regulatory site indicated by DNaseI and H3K4me1 signatures at 29 the locus, making the SNP a potential regulatory variant (Supplementary Table 23)³⁶. Both SNPs were 30 31 included in the list of 99% credible SNPs at each locus.

1 Asian- and African ancestry BP SNP association

2 We tested the 66 lead SNPs at the established and novel loci for association with BP in up to 3 20,875 individuals of South Asian (SAS) ancestry (PROMIS and RACE studies), 9,637 individuals of East Asian (EAS) ancestry (HEXA, HALST, CLHNS, DRAGON, and TUDR studies), and 33,909 individuals of 4 5 African (AFR) ancestry (COGENT-BP consortium, Jupiter, SPT, Seychelles, GXE, and TANDEM studies). As 6 expected, the effect allele frequencies are very similar across studies of the same ethnicity, but 7 markedly different across different ancestry groups (Supplementary Figure 9). Many associations of 8 individual SNPs failed to reach P < 0.05 for the BP trait with the lower P value (Supplementary Table 24), 9 which could potentially be due to the much lower statistical power at the sample sizes available, 10 different patterns of LD at each locus across ancestries, variability in allele frequency, or true lack of association in individuals of a given non-European ancestry. The low statistical power for the great 11 12 majority of SNPs tested is visible considering SNP-by-SNP power calculations using European ancestry 13 effect sizes (Supplementary Table 24). However, concordant directions of allelic effects for both SBP 14 and DBP were observed for 45/66 SNPs in SAS, 36/60 SNPs in EAS, and 42/66 SNPs in AFR samples: the 15 strongest concordance with SAS may not be surprising because South Asians are more closely related to 16 Europeans than are East Asians or Africans. Moreover, strong correlation of effect sizes was observed 17 between EUR samples with SAS, EAS, or AFR samples (r = 0.55, 0.60, and 0.48, respectively). A 66-SNP SBP or DBP risk score were significant predictors of SBP and DBP in all samples. A 1 mm Hg higher SBP or 18 19 DBP risk score in EUR samples was associated with a 0.58/0.50 mm Hg higher SBP/DBP in SAS samples $(SBP P = 1.5 \times 10^{-19}, DBP P = 3.2 \times 10^{-15}), 0.49/0.50 \text{ mm Hg higher SBP/DBP in EAS samples (SBP)}$ 20 $P = 1.9 \times 10^{-10}$, DBP $P = 1.3 \times 10^{-7}$), and 0.51/0.47 mm Hg higher SBP/DBP in AFR samples (SBP 21 $P = 2.2 \times 10^{-21}$, DBP $P = 6.5 \times 10^{-19}$). The attenuation of the genetic risk score estimates in non-European 22 23 ancestries is presumably due to inclusion of a subset of variants that lack association in the non-24 European or admixed samples.

25 We subsequently performed a trans-ethnic meta-analysis of the 66 SNPs in all 64,421 samples across the three non-European ancestries. After correcting for 66 tests, 12/66 SNPs were significantly 26 associated with either SBP or DBP ($P < 7.6 \times 10^{-4}$), with a correlation of EUR and non-EUR effect 27 estimates of 0.77 for SBP and 0.67 for DBP; the European-ancestry SBP or DBP risk score was associated 28 with 0.53/0.48 mm Hg higher BP per predicted mm Hg SBP/DBP respectively (SBP $P < 6.6 \times 10^{-48}$, DBP 29 $P < 1.3 \times 10^{-38}$). For 7 of the 12 significant SNPs, no association has previously been reported in genome-30 31 wide studies of non-European ancestry. Some heterogeneity of effects was observed between 32 European and non-European effect estimates (Supplementary Table 24). Taken together, these findings

suggest that, in aggregate, BP loci identified using data from individuals of EUR ancestry are also
 predictive of BP in non-EUR samples, but larger non-European sample sizes will be needed to establish

3 precisely which individual SNPs are associated in a given ethnic group.

4 Impact on hypertensive target organ damage

5 Long-term elevated BP causes target organ damage, especially in the heart, kidney, brain, large blood vessels, and the retinal vessels³⁷. Consequently, the genetic effect of the 66 SBP and DBP SNPs on 6 end-organ outcomes can be directly tested using the risk score, although some outcomes lacked results 7 8 for a small number of SNPs. Interestingly, BP risk scores significantly predicted (Supplementary Note) 9 coronary artery disease risk, left ventricular mass and wall thickness, stroke, urinary albumin/creatinine 10 ratio, carotid intima-medial thickness and central retinal artery caliber, but not heart failure or other 11 kidney phenotypes, after accounting for the number of outcomes examined (Table 3). Because outlier 12 effects can affect risk scores, we repeated the risk score analysis removing iteratively SNPs that 13 contributed to statistical heterogeneity (SNP-trait effects relative to SNP-BP effects). Heterogeneity was 14 defined based on a multiple testing adjusted significance threshold for Cochran's Q test of homogeneity 15 of effects (Supplementary Note). The risk score analyses restricted to the subset of SNPs showing no 16 heterogeneity of effect revealed essentially identical results, with the exception that urinary 17 albumin/creatinine ratio was no longer significant. The per-SNP results are provided in **Supplementary** Table 25 and Supplementary Figures 10. Because large-scale GWAS of non-BP cardiovascular risk 18 19 factors are available, we examined the BP risk scores as predictors of other cardiovascular risk factors: 20 LDL-cholesterol, HDL-cholesterol, triglycerides, type 2 diabetes, BMI, and height. We observed nominal 21 (P < 0.05) associations of the BP risk scores with risk factors, although mostly in the opposite direction to 22 the risk factor-CVD association (Supplementary Table 26). The failure to demonstrate an effect of BP 23 risk scores on heart failure may reflect limited power from a modest sample size, but the lack of 24 significant effects on renal measures suggests that the epidemiologic relationship of higher BP and 25 worse renal function may not reflect direct consequences of BP elevation.

26 **DISCUSSION**

The study reported here is the largest to date to investigate the genomics of BP in multiple continental ancestries. Our results highlight four major features of inter-individual variation in BP: (1) we identified 66 (17 novel) genome-wide significant loci for SBP and DBP by targeted genotyping in up to 342,415 individuals of European ancestry that cumulatively explain ~3.5% of the trait; (2) the variants were enriched for *cis*-regulatory elements, particularly in vascular endothelial cells; (3) the variants had

broadly comparable BP effects in South Asians, East Asian and Africans, albeit in smaller sample sizes;
and, (4) a 66 SNP risk-score predicted target organ damage in the heart, cerebral vessels, carotid artery
and the eye with little evidence for an effect in kidneys. Overall, there was no enrichment of a single
genetic pathway in our data; rather, our results are consistent with the effects of BP arising from
multiple tissues and organs.

6 Genetic and molecular analyses of Mendelian syndromes of hypertension and hypotension point 7 largely to a renal origin, involving multiple rare deleterious mutations in proteins that regulate saltwater balance³⁸. This is strong support for Guyton's hypothesis that the regulation of sodium excretion 8 9 by the kidney and its effects on extracellular volume are a prime pathway determining intra-arterial pressure³⁹. However, our genetic data from unselected individuals in the general community argues 10 against a single dominant renal effect. The 66 SNPs we identified are not chance effects, but have a 11 12 global distribution and impact on BP that are consistent as measured by their effects across the many 13 studies meta-analyzed. That they are polymorphic across all continental ancestries argues for their 14 origin and functional effects prior to human continental differentiation.

15 However several of the 17 novel loci contain strong positional biological candidates, these are 16 described in greater detail in Supplementary Table 27 and the Supplementary Note. The single most 17 common feature we identified was the enrichment of regulatory elements for gene expression in vascular endothelial cells. The broad distribution of these cells across both large and small vessels and 18 19 across all tissues and organs suggest that functional variation in these cells affects endothelial 20 permeability or vascular smooth muscle cell contractility via multiple pathways. These hypotheses will 21 need to be rigorously tested in appropriate models, to assess the contribution of these pathways to BP 22 control, and these pathways could also be targets for systemic anti-hypertensive therapy as they are for the pulmonary circulation⁴². 23

In summary, these genetic observations may contribute to an improved understanding of BP
biology and a re-evaluation of the pathways considered relevant for therapeutic BP control.

1 SUPPLEMENTARY NOTE

2 Supplementary Note is available in the online version of the paper.

3 SUMMARY STATISTICS

4 Full summary statistics (P values) are in the online version of the paper (file "ICBPCMfinalMeta.csv.zip").

5 URLs

- 6 http://hgdownload.cse.ucsc.edu/goldenPath/hg19/encodeDCC/wgEncodeUwDnase for enrichment
- 7 analyses. Accessed 3/13/2013.
- 8 http://www.genome.gov/gwastudies for enrichment analyses. Accessed 3/13/2013.
- 9 http://genome.ucsc.edu/ENCODE/cellTypes.html for enrichment analyses. Accessed 3/13/2013.

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- 12 funding sources is provided in the **Supplementary Note.**

13 AUTHOR CONTRIBUTIONS

14 Analysis group

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18 Cardio-MetaboChip or new GWAS

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- 7 FENLAND (MetaboChip): Study phenotyping: R.J.F.L., J.a.L., N.J.W., K.K.O. Genotyping or analysis:
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- 16 GenNet: Study phenotyping: R.S.C., A.B.W. Genotyping or analysis: A.C., V.P., M.X.S., D.E.A., G.B.E.
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- 37 Study PI: J.Sundstrom
- 38 PIVUS: Study phenotyping: L.Lind, J.Sundstrom Genotyping or analysis: L.Lind, N.E., J.Sundstrom, T.A.
- 39 Study PI: L.Lind, J.Sundstrom
- 40 MRC NSHD: Study phenotyping: D.K. Genotyping or analysis: A.Wong, J.a.L., D.K., K.K.O. Study PI: D.K.
- 41 ASCOT: Study phenotyping: A.Stanton, N.P. Genotyping or analysis: T.J., M.J.C., P.B.M. Study PI: P.S.,
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- 43 THISEAS: Genotyping or analysis: L.S.R., S.Kanoni, E.M., G.Kolovou Study PI: G.Dedoussis, P.D.
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- 48 Secondary analyses

- 1 Allele-specific FAIRE: Design of secondary analysis: A.J.P.S. Computation of secondary analysis: A.J.P.S.,
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- 3 ASAP eQTL: Design of secondary analysis: A.F.C. Computation of secondary analysis: L.Folkersen,
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- 5 CARDIOGENICS eQTL: Computation of secondary analysis: L.Lataniotis
- 6 CM design: P.B.M., C.N.-C., T.J., B.F.V.
- 7 Comprehensive literature review: Design of secondary analysis: P.B.M. Computation of secondary
- 8 analysis: K.W., P.B.M.
- 9 DEPICT: Design of secondary analysis: L.Franke, T.H.P., J.N.H. Computation of secondary analysis: T.H.P.
- 10 DHS and methylation analysis by tissue:Design of secondary analysis: C.J.W. Computation of secondary
- 11 analysis: E.M.S.
- 12 DHS and methylation by cell-line: Design of secondary analysis: D.I.C. Computation of secondary
- 13 analysis: D.I.C., F.Giulianini
- 14 FHS eSNP: Design of secondary analysis: R.Joehanes Computation of secondary analysis: R.Joehanes
- 15 ICBP SC: C.N.-C., M.J.C., P.B.M., A.C., K.M.R., P.-O'R., W.P., D.L., M.D.T., B.M.P., A.D.J., P.Elliott, C.M.v.D.,
- 16 D.I.C., A.V.S., M.Bochud, L.V.W., H.Snieder, G.B.E.
- 17 Kidney eQTL: Computation of secondary analysis: H.J.G., S.K.K.
- 18 MAGENTA: Design of secondary analysis: D.I.C. Computation of secondary analysis: D.I.C.
- 19 Miscellaneous: Computation of secondary analysis: H.Warren
- 20 MuTHER eQTL: Design of secondary analysis: P.D. Computation of secondary analysis: L.Lataniotis, T.-21 P.Y.
- 22 NESDA eQTL: Design of secondary analysis: R.Jansen Computation of secondary analysis: R.Jansen, A.V.
- NTR eQTL: Design of secondary analysis: R.Jansen Computation of secondary analysis: R.Jansen, J.-J.H.
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- 26 A.Metspalu
- 27 eQTL, Groningen:Design of secondary analysis: L.Franke Computation of secondary analysis: H.J.W.,
- 28 L.Franke
- 29 Public eSNP and methylation: Design of secondary analysis: A.D.J., J.D.E. Computation of secondary
- 30 analysis: A.D.J., J.D.E.
- 31 PubMed search: Design of secondary analysis: G.B.E. Computation of secondary analysis: G.B.E., L.Lin
- 32 WGHS conditional: Design of secondary analysis: D.I.C. Computation of secondary analysis: D.I.C.,
- 33 F.Giulianini, L.M.R.

34 Lookup of Cardio-MetaboChip variants

- 35 HEXA: Genotyping or analysis: Y.J.K., Y.K.K., Y.-A.S. Study PI: J.-Y.L.
- 36 RACe: Study phenotyping: D.Saleheen, W.Zhao, A.R., A.R. Genotyping or analysis: W.Zhao, A.R., A.R.
- 37 Study PI: D.Saleheen
- HALST: Study phenotyping: C.A.H. Genotyping or analysis: J.I.R., Y.-D.C., C.A.H., R.-H.C., I.-S.C. Study PI:
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- 40 CLHNS: Study phenotyping: N.R.L., L.S.A. Genotyping or analysis: Y.W., N.R.L., L.S.A. Study PI: K.L.M.,
- 41 L.S.A.
- 42 GxE/Spanish Town: Study phenotyping: B.O.T., C.A.M., R.W. Genotyping or analysis: C.D.P. Study PI:
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- 45 E.K., D.A., K.D.T., X.G. Study PI: W.H.-H.S.
- 46 SEY: Study phenotyping: P.B. Genotyping or analysis: M.Bochud, G.B.E., F.M. Study PI: P.B., M.Bochud,
- 47 M.Burnier, F.P.

- 1 TUDR: Study phenotyping: W.H.-H.S., I-Te Lee, W.-J.L. Genotyping or analysis: J.I.R., Y.-D.C., E.K., K.D.T.,
- 2 X.G. Study PI: W.H.-H.S.
- 3 TANDEM: Study phenotyping: P.B., M.Bochud Genotyping or analysis: G.B.E., F.M. Study PI: P.B.,
- 4 M.Bochud, M.Burnier, F.P.

5 Imputed genotypes

- 6 FHS: Study phenotyping: D.L. Genotyping or analysis: D.L. Study PI: D.L.
- ARIC: Study phenotyping: E.B. Genotyping or analysis: G.B.E., E.B., A.C.M., A.C., S.K.G. Study PI: E.B.,
- 8 A.C.
- 9 RS: Genotyping or analysis: G.C.V., A.G.U. Study PI: A.Hofman, A.G.U., O.H.F.D.
- 10 CoLaus: Study phenotyping: P.V. Genotyping or analysis: Z.K. Study PI: P.V.
- 11 NFBC1966: Study phenotyping: M.R.J. Genotyping or analysis: P.O.R. Study PI: M.R.J.
- 12 SHIP: Study phenotyping: R.Rettig Genotyping or analysis: A.T.
- 13 CHS: Study phenotyping: B.M.P. Genotyping or analysis: K.M.R. Study PI: B.M.P.
- 14 EPIC (GWAS): Study phenotyping: N.J.W., R.J.F.L., J.a.L. Genotyping or analysis: N.J.W., J.H.Z., J.a.L.
- 15 Study PI: N.J.W., K.-T.K.
- 16 SU.VI.MAX: Study phenotyping: S.H. Genotyping or analysis: S.H., P.M. Study PI: P.M.
- 17 Amish: Genotyping or analysis: M.E.M. Study PI: A.Parsa
- 18 FENLAND (GWAS): Study phenotyping: N.J.W., J.a.L., R.J.F.L., K.K.O. Genotyping or analysis: N.J.W.,
- 19 J.a.L., R.J.F.L., K.K.O. Study PI: N.J.W.
- 20 DGI: Study phenotyping: C.N.C. Genotyping or analysis: C.N.C., G.Kosova Study PI: C.N.C.
- 21 ERF (EUROSPAN): Genotyping or analysis: N.A. Study PI: C.M.v.D.
- 22 MIGEN: Study phenotyping: S.Kathiresan, R.E. Genotyping or analysis: S.Kathiresan, R.E. Design of
- 23 secondary analysis: S.Kathiresan, R.E.
- 24 MICROS: Study phenotyping: P.P.P. Genotyping or analysis: A.A.H. Study PI: A.A.H., P.P.P.
- 25 FUSION: Genotyping or analysis: A.U.J. Study PI: M.Boehnke, F.S.C., K.L.M., J.Saramies
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- 27 PROCARDIS: Genotyping or analysis: M.Farrall, A.G. Study PI: M.Farrall
- 28 BLSA: Study phenotyping: L.Ferrucci Genotyping or analysis: T.T. Study PI: L.Ferrucci
- 29 ORCADES: Study phenotyping: J.F.W. Study PI: J.F.W.
- 30 Croatia-Vis: Genotyping or analysis: V.V., C.H. Study PI: V.V., C.H.
- 31 NSPHS: Genotyping or analysis: S.Enroth Study PI: U.G.
- 32 InCHIANTI: Genotyping or analysis: T.T. Study PI: S.Bandinelli
- 33 AGES Reykjavik: Study phenotyping: V.G. Genotyping or analysis: A.V.S. Study PI: V.G.
- 34 Lookup
- 35 CARDIoGRAMplusC4D: Genotyping or analysis: P.D. Study PI: J.Danesh, H.Schunkert, T.L.A., J.E.,
- 36 S.Kathiresan, R.Roberts, N.J.S., P.D.
- 37 CHARGE cIMT: Genotyping or analysis: C.O'D., J.C.B.
- 38 CHARGE EYE: Genotyping or analysis: T.Y.W., X.S., R.A.J. Study PI: T.Y.W.
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- 41 CKDGen: Genotyping or analysis: M.G., V.M.
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- 48 NeuroCHARGE: Genotyping or analysis: M.Fornage, M.A.I. Study PI: M.A.I.

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- 3 SEED: Study phenotyping: T.Y.W., C.-Y.C. Genotyping or analysis: E.-S.T, C.-Y.C., C.-Y.C. Study PI: C.-Y.C.,
- 4 T.Y.W.
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7 COMPETING FINANCIAL INTERESTS

- 8 The authors declare competing financial interests (see corresponding section in the Supplementary
- 9 Note).
- 10

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43		

1 FIGURE LEGENDS

2 Figure 1. Manhattan plots for SBP and DBP from the stage 4 Cardio-MetaboChip-wide meta-analysis.

3 *P* values (expressed as $-\log_{10}P$) are plotted by physical genomic position labeled by chromosome. SNPs in 4 new loci (3.5MB window around the index SNP), identified in this study, are labeled in dark red (SBP) or 5 dark blue (DBP); SNPs in previously known loci are labeled in orange (SBP) or light blue (DBP). The locus 6 names are indicated. The grey crosses indicate genomic positions at which the y-axis was truncated 7 (SNPs with $P < 10^{-15}$).

8 Figure 2. Enrichment of DNAse hypersensitive sites among BP loci in different cell-types. Enrichment

9 analyses of SBP or DBP associated loci according to discovery *P* value using narrow peaks (panel A) or

10 broad peaks (panel B). SNPs were selected according to different P value cutoffs (x-axis) and a fold

11 enrichment of overlap with DNAse hypersensitive sites compared to unrelated GWAS SNPs was

12 calculated (y-axis) (see Supplementary Note). The 12 endothelial cell-lines are indicated in color and for

each endothelial cell-type the rank using the 10^{-14} P value cutoff is indicated. EC denotes endothelial

14 cells.

15 TABLE LEGENDS

16 **Table 1. SBP and DBP association at 66 loci.**

17 Meta-analysis results of up to 342,415 individuals of European ancestry for SBP and DBP: Established 18 and new loci are grouped separately. Nearest genes are shown as locus labels but this should not be 19 interpreted as support that the causal gene is the nearest gene. The lead SNP with the lowest P value 20 for either BP trait is shown as the lead SNP and both SBP and DBP results are presented even if both are not genome-wide significant. The SNP effects are shown according to the effect in mm Hg per copy of 21 the coded allele (that is the allele coded 0, 1, 2) under an additive genetic model. "*" in the lead SNP 22 column indicates a non-synonymous coding SNP (either the SNP itself or another SNP in r^2 >0.8). # 23 24 Established loci have smaller total sample sizes relative to novel loci (see Supplementary Note).

25 Table 2. Overview of novel and known BP variant properties.

Key characteristics of the novel and established BP loci are shown. MAF and effect size estimates are derived from the Cardio-MetaboChip data. Variance explained estimates are estimated from one large study (**Supplementary Note**). Novel loci are classified as previously unknown to be linked to BP by a systematic PubMed review of all genes in a 200kb window (**Supplementary Note**).

1 Table 3. Prediction of hypertensive target organ damage by a multi-BP SNP score.

2 Shown are the estimated effects of a BP risk score comprised of up to 66 SNPs (see column "Total 3 #SNPs") on risk of dichotomous outcome (as odds ratios) or increment in continuous measures per predicted mmHg of the SBP or DBP score. The effect sizes are expressed as incremental change in the 4 5 phenotype for quantitative traits and natural logarithm of the odds ratio for binary traits, per 1 mmHg 6 predicted increase in SBP or DBP. P values are bolded if they meet an analysis-wide significance 7 threshold (< 0.05/18 = 0.0028). Results for all SNPs ("all") and for pruned results ("p") are shown. The 8 pruned results were obtained by iterative removal of SNPs from the risk score starting with the SNP with 9 lowest heterogeneity P value. Iterations to remove SNPs were continued until the heterogeneity P value 10 was < 0.0028 (see **Supplementary Note**). The number of SNPs removed when calculating the pruned results is indicated by "# SNPs rem.". The results per individual SNP can be found in Supplementary 11 12 Table 15. CAD: coronary artery disease, LV: left ventricle, CKD: chronic kidney disease, eGFR: estimated 13 glomerular filtration rate, cr: creatinine, cIMT: carotid intima: media thickness. Var. type denotes the 14 variable type and cont. for continuous, or dic. for dichotomous. Eth. = Ethnicity, Consort. = Consortium, 15 EUR = European ancestry, EAS = East Asian ancestry.

1 Table 1. New and known BP loci.

Locus no.	Locus name	Lead SNP	Chr	Position (hg19)	CA /NC	Coded allele freq	Traits	SBP			DBP				
								Effect	SE	P value	Total N	Effect	SE	P value	Total N#
NEW 1	HIVEP3	rs7515635	1	42,408,070	T/C	0.468	SBP	0.307	0.0444	4.81E-12	340,969	0.1365	0.0263	2.05E-07	340,934
NEW 2	PNPT1	rs1975487	2	55,809,054	A/G	0.464	DBP	-0.2107	0.045	2.81E-06	337,522	-0.1602	0.0266	1.75E-09	337,517
NEW 3	FGD5	rs11128722	3	14,958,126	A/G	0.563	SBP & DBP	-0.3103	0.0469	3.61E-11	310,430	-0.1732	0.0279	5.16E-10	310,429
NEW 4	ADAMTS9	rs918466	3	64,710,253	A/G	0.406	DBP	-0.0865	0.0459	5.94E-02	336,671	-0.1819	0.027	1.73E-11	336,653
NEW 5	TBC1D1-FLJ13197 TRIM36	rs2291435	4	38,387,395	T/C	0.524	SBP & DBP	-0.3441	0.0449	1.90E-14	331,382	-0.156	0.0266	4.26E-09	331,389
NEW 6 NEW 7	CSNK1G3	rs10077885 rs6891344	5 5	114,390,121	A/C A/G	0.501 0.819	SBP & DBP DBP	- 0.284 0.2811	0.0444 0.058	1.64E-10 1.24E-06	338,328	-0.1735 0.2311	0.0263 0.0343	3.99E-11 1.58E-11	338,323
NEW 8	CHST12-LFNG	rs2969070	5	123,136,656 2,512,545	A/G A/G	0.639	SBP & DBP	-0.2811	0.058 0.0464	1.24E-06 1.44E-10	338,688 335,991	-0.1821	0.0343	2.92E-11	338,678 335,972
NEW 9	ZC3HC1	rs11556924	7	129,663,496	T/C	0.384	SBP & DBP	-0.2705	0.0468	7.64E-09	325,929	-0.2141	0.0276	8.15E-15	325,963
NEW 10	PSMD5	rs10760117	9	123,586,737	T/G	0.415	SBP	0.283	0.0457	6.10E-10	333,377	0.0999	0.0269	2.08E-04	333,377
NEW 11	DBH	rs6271*	9	136,522,274	T/C	0.072	SBP & DBP	-0.5911	0.0899	4.89E-11	306,394	-0.4646	0.0532	2.42E-18	306,463
NEW 12	RAPSN, PSMC3, SLC39A13	rs7103648	11	47,461,783	A/G	0.614	SBP & DBP	-0.3349	0.0462	4.43E-13	335,614	-0.2409	0.0272	9.03E-19	335,592
NEW 13	LRRC10B	rs751984	11	61,278,246	T/C	0.879	SBP & DBP	0.4074	0.0691	3.80E-09	334,583	0.3755	0.0409	4.20E-20	334,586
NEW 13	SETBP1	rs12958173	18	42,141,977	A/C	0.306	SBP & DBP	0.3614	0.0489	1.43E-13	331,007	0.1789	0.0289	5.87E-10	331,010
NEW 15	INSR	rs4247374	19	7,252,756	T/C	0.143	SBP & DBP	-0.5933	0.0673	1.23E-18	302,458	-0.3852	0.0396	2.08E-22	302,459
NEW 16	ELAVL3	rs17638167	19	11,584,818	T/C	0.047	DBP	-0.4784	0.1066	7.13E-06	333,137	-0.3479	0.0632	3.71E-08	333,107
NEW 17	CRYAA-SIK1	rs12627651	21	44,760,603	A/G	0.288	SBP & DBP	0.3905	0.0513	2.69E-14	310,738	0.2037	0.0301	1.36E-11	310,722
EST 1	CASZ1	rs880315	1	10,796,866	T/C	0.641	SBP & DBP	-0.475	0.062	2.09E-14	184,226	-0.257	0.038	1.34E-11	184,212
EST 2	MTHFR-NPPB	rs17037390	1	11,860,843	A/G	0.155	SBP & DBP	-0.908	0.081	5.95E-29	195,493	-0.499	0.05	1.20E-23	195,481
EST 3	ST7L-CAPZA1-MOV10	rs1620668	1	113,023,980	A/G	0.822	SBP & DBP	-0.535	0.076	1.45E-12	197,966	-0.285	0.047	9.00E-10	197,948
EST 4	MDM4	rs4245739	1	204,518,842	A/C	0.737	DBP	0.326	0.068	1.37E-06	191,594	0.243	0.041	4.63E-09	191,578
EST 5	AGT	rs2493134*	1	230,849,359	T/C	0.579	SBP & DBP	-0.413	0.058	9.65E-13	199,505	-0.275	0.036	9.53E-15	199,502
EST 6	KCNK3 NCAPH	rs2586886	2 2	26,932,031	T/C	0.599	SBP & DBP	- 0.404 -0.072	0.059	5.94E-12	197,269	-0.254	0.036	1.92E-12	197,272
EST 7 EST 8	FIGN-GRB14	rs772178 rs1371182	2	96,963,684 165,099,215	A/G T/C	0.64 0.443	DBP SBP & DBP	-0.072 - 0.444	0.061 0.058	2.39E-01 1.89E-14	192,513 196,262	-0.208 -0.252	0.038 0.036	3.58E-08 1.50E-12	192,501 196,240
EST 9	HRH1-ATG7	rs2594992	3	11,360,997	A/C	0.607	SBP	-0.334	0.06	2.31E-08	189,895	-0.136	0.037	2.20E-04	189,854
EST 10	SLC4A7	rs711737	3	27,543,655	A/C	0.604	SBP	0.334	0.058	9.93E-09	200,282	0.17	0.036	2.24E-06	200,260
EST 11	ULK4	rs2272007*	3	41,996,136	T/C	0.18	DBP	-0.11	0.077	1.52E-01	193,915	0.328	0.047	3.94E-12	193,900
EST 12	MAP4	rs6442101*	3	48,130,893	T/C	0.692	SBP & DBP	0.396	0.062	1.62E-10	200,543	0.303	0.038	1.60E-15	200,534
EST 13	MECOM	rs6779380	3	169,111,915	T/C	0.539	SBP & DBP	-0.439	0.06	1.85E-13	186,535	-0.239	0.037	6.87E-11	186,521
EST 14	FGF5	rs1458038	4	81,164,723	T/C	0.3	SBP & DBP	0.659	0.065	5.36E-24	188,136	0.392	0.04	7.36E-23	188,088
EST 15	ARHGAP24	rs17010957	4	86,719,165	T/C	0.857	SBP	-0.498	0.082	1.51E-09	196,325	-0.173	0.051	6.63E-04	196,292
EST 16	SLC39A8	rs13107325	4	103,188,709	T/C	0.07	SBP & DBP	-0.837	0.127	4.69E-11	175,292	-0.602	0.078	1.63E-14	175,372
EST 17	GUCY1A3-GUCY1B3	rs4691707	4	156,441,314	A/G	0.652	SBP	-0.349	0.06	7.10E-09	198,246	-0.163	0.037	1.08E-05	198,226
EST 18 EST 19	NPR3-C5orf23 EBF1	rs12656497 rs11953630	5 5	32,831,939	T/C T/C	0.403 0.366	SBP & DBP SBP & DBP	-0.487 -0.38	0.06 0.065	3.85E-16 3.91E-09	194,831	-0.228	0.037 0.04	4.73E-10 8.07E-09	194,829
EST 20	HFE	rs1799945*	6	157,845,402 26,091,179	C/G	0.857	SBP & DBP	-0.58	0.085	3.28E-12	167,698 185,306	-0.23 -0.43	0.04	3.10E-16	167,708 185,273
EST 21	BAT2-BAT5	rs2187668	6	32,605,884	т/с	0.126	DBP	-0.291	0.092	1.60E-03	189,806	-0.372	0.057	4.31E-11	189,810
EST 22	ZNF318-ABCC10	rs6919440	6	43,352,898	A/G	0.57	SBP	-0.337	0.058	4.92E-09	200,733	-0.125	0.035	4.25E-04	200,730
EST 23	RSPO3	rs1361831	6	127,181,089	T/C	0.541	SBP & DBP	-0.482	0.058	7.38E-17	197,027	-0.271	0.036	2.34E-14	197,012
EST 24	PLEKHG1	rs17080093	6	150,997,440	T/C	0.075	DBP	-0.564	0.111	3.83E-07	194,728	-0.411	0.068	1.71E-09	194,734
EST 25	HOTTIP-EVX	rs3735533	7	27,245,893	T/C	0.081	SBP & DBP	-0.798	0.106	6.48E-14	197,881	-0.445	0.065	1.09E-11	197,880
EST 26	PIK3CG	rs12705390	7	106,410,777	A/G	0.227	SBP	0.619	0.069	2.69E-19	198,297	0.059	0.042	1.63E-01	198,290
EST 27	BLK-GATA4	rs2898290	8	11,433,909	T/C	0.491	SBP	0.377	0.058	8.85E-11	197,759	0.167	0.036	3.17E-06	197,726
EST 28	CACNB2	rs12243859	10	18,740,632	T/C	0.326	SBP & DBP	-0.402	0.061	6.13E-11	199,136	-0.335	0.038	8.11E-19	199,124
EST 29 EST 30	C10orf107 SYNPO2L	rs7076398 rs12247028	10 10	63,533,663 75,410,052	A/T A/G	0.188 0.611	SBP & DBP SBP	-0.563 -0.364	0.076 0.063	1.72E-13 8.16E-09	187,013 180,194	- 0.409 -0.159	0.047 0.039	2.55E-18 3.89E-05	187,024 180,094
EST 30	PLCE1	rs932764*	10	95,895,940	A/G	0.554	SBP & DBP	-0.364	0.059	6.88E-17	195,577	-0.139 -0.224	0.039 0.036	6.28E-10	180,094 195,547
EST 32	CYP17A1-NT5C2	rs943037	10	104,835,919	T/C	0.087	SBP & DBP	-1.133	0.105	2.35E-27	193,818	-0.482	0.064	4.48E-14	193,799
EST 33	ADRB1	rs740746	10	115,792,787	A/G	0.73	SBP & DBP	0.486	0.067	4.59E-13	184,835	0.32	0.041	8.63E-15	184,868
EST 34	LSP1-TNNT3	rs592373	11	1,890,990	A/G	0.64	SBP & DBP	0.484	0.063	2.02E-14	177,149	0.282	0.039	3.61E-13	177,134
EST 35	ADM	rs1450271	11	10,356,115	T/C	0.468	SBP & DBP	0.413	0.059	3.40E-12	191,246	0.199	0.036	4.11E-08	191,221
EST 36	PLEKHA7	rs1156725	11	16,307,700	T/C	0.804	SBP & DBP	-0.447	0.072	5.65E-10	200,889	-0.292	0.044	3.67E-11	200,899
EST 37	SIPA1	rs3741378*	11	65,408,937	T/C	0.137	SBP	-0.486	0.084	8.04E-09	194,563	-0.183	0.052	4.17E-04	194,551
EST 38	FLJ32810-TMEM133	rs633185	11	100,593,538	C/G	0.715	SBP & DBP	0.522	0.067	6.97E-15	183,845	0.288	0.041	2.38E-12	183,825
EST 39 EST 40	PDE3A	rs3752728	12 12	20,192,972	A/G	0.737		0.331	0.066 0.081	4.32E-07 3.88E-29	200,440	0.319	0.04 0.05	2.35E-15	200,408
EST 40 EST 41	ATP2B1 SH2B3	rs11105354 rs3184504*	12	90,026,523 111,884,608	A/G T/C	0.84 0.475	SBP & DBP SBP & DBP	0.909 0.498	0.081	3.88E-29 9.97E-16	195,206 177,067	0.459 0.362	0.05	2.61E-20 1.28E-21	195,195 177,122
EST 41	TBX5-TBX3	rs2891546	12	111,884,008	A/G	0.475	DBP	-0.529	0.002	1.36E-07	172,012	-0.38	0.058	4.71E-10	171,980
EST 43	CYP1A1-ULK3	rs936226	15	75,069,282	T/C	0.722	SBP & DBP	-0.549	0.067	3.06E-16	187,238	-0.363	0.041	1.03E-18	187,221
EST 44	FURIN-FES	rs2521501	15	91,437,388	A/T	0.684	SBP & DBP	-0.639	0.069	3.35E-20	164,272	-0.358	0.042	1.85E-17	164,255
EST 45	PLCD3	rs7213273	17	43,155,914	A/G	0.658	SBP	-0.413	0.066	4.71E-10	164,795	-0.185	0.041	7.23E-06	164,788
EST 46	GOSR2	rs17608766	17	45,013,271	T/C	0.854	SBP	-0.658	0.083	2.27E-15	188,895	-0.218	0.051	1.95E-05	188,928
EST 47	ZNF652	rs12940887	17	47,402,807	T/C	0.38	DBP	0.321	0.06	7.06E-08	192,546	0.261	0.037	1.07E-12	192,524
EST 48	JAG1	rs1327235	20	10,969,030	A/G	0.542	SBP & DBP	-0.395	0.059	2.23E-11	192,680	-0.308	0.036	1.78E-17	192,659
EST 49	GNAS-EDN3	rs6026748	20	57,745,815	A/G	0.125	SBP & DBP	0.867	0.089	3.15E-22	192,338	0.552	0.055	4.86E-24	192,327

Table 2. Overview of novel and known BP variant properties.

	17 new loci	49 established loci	66 loci
Minor allele frequency (mean, range)	32.1% [5%-50%]	28.9% [7%-49%]	29.8% [5%-50%]
Effect size SBP [mmHg] (range, mean)	0.09-0.59, 0.34	0.07-1.13, 0.5	0.07-1.13, 0.46
Effect size DBP [mmHg] (range, mean)	0.1-0.46, 0.23	0.06-0.60, 0.3	0.06-0.6, 0.28
Variance explained SBP	0.52%	2.95%	3.46%
Variance explained DBP	0.58%	2.78%	3.36%

Table 3.	BP risk score	effects on	disease	outcomes.
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Phenotype	Var. type (cont./	Eth.	Consort.	Total N or no. ca/co	Total #SNPs	SBP_score					DBP_score				
	dic.)					effect (all)	P value (all)	het. <i>P</i> value (all)	<i>P</i> value (p)	# SNPs rem.	effect (all)	P value (all)	het. <i>P</i> value (all)	<i>P</i> value (p)	# SNPs rem.
HEART															
CAD	dich.	EUR SAS	CARDIoG RAMplus C4D	63,746 /130,681	61	1.042	1.72E-44	1.75E-25	4.08E-32	10	1.069	1.19E-42	6.63E-27	2.2E-38	10
heart failure	dich.	EUR	CHARGE	2,526 /18,400	66	1.021	2.77E-02	1.63E-01	2.77E-02	0	1.035	2.31E-02	1.70E-01	2.31E-02	0
LV mass	cont.	EUR	CHARGE	11,273	66	0.480	6.43E-04	3.58E-01	6.43E-04	0	0.754	1.23E-03	3.21E-01	1.23E-03	0
LV wall thickness	cont.	EUR	CHARGE	11,311	66	0.004	4.45E-06	5.83E-02	4.45E-06	0	0.007	3.19E-06	6.40E-02	3.19E-06	0
KIDNEY															
CKD	dich.	EUR	CHARGE	6,271 /68,083	65	1.010	1.37E-01	1.77E-03	2.65E-01	1	1.008	4.49E-01	1.25E-03	7.69E-01	1
eGFR (based on cr)	cont.	EUR	CHARGE	74,354	65	0.000	7.07E-01	3.12E-05	3.22E-01	2	0.000	9.41E-01	3.02E-05	9.65E-01	2
eGFR (based on cystatin)	cont.	EUR	CHARGE	74,354	65	0.001	9.05E-02	9.28E-06	4.11E-01	1	0.001	3.30E-01	5.64E-06	6.9E-01	1
creatinine	cont.	EUR	KidneyGE N	23,812	66	0.000	9.42E-01	6.31E-03	9.42E-01	0	0.000	4.11E-01	7.16E-03	4.11E-01	0
microalbuminuria	dich.	EUR	CHARGE	2,499 /29,081	65	0.011	2.10E-01	4.79E-02	2.1E-01	0	0.023	1.02E-01	5.66E-02	1.02E-02	0
urinary albumin/cr ratio	cont.	EUR	CHARGE	31,580	65	0.009	2.52E-03	3.02E-04	0.53E-03	1	0.015	2.40E-03	3.08E-04	8.31E-03	1
STROKE															
stroke, all subtypes	dich.	EUR	CHARGE	1,544 /18,058	66	0.056	6.11E-06	8.26E-02	6.11E-06	0	0.085	3.79E-05	4.98E-02	3.79E-05	0
stroke, ischemic subtype	dich.	EUR	CHARGE	1,164 /18,438	66	0.067	3.33E-06	1.75E-01	3.33E-06	0	0.096	5.63E-05	8.82E-02	5.63E-05	0
stroke, ischemic subtype	dich.	EUR	MetaStro ke	11,012 /40,824	66	0.036	1.69E-10	4.72E-02	1.69E-10	0	0.056	1.29E-09	2.51E-02	1.29E-09	0
VASCULATURE															
cIMT	cont.	EUR	CHARGE	27,610	66	0.004	4.80E-15	5.06E-08	7.32E-10	4	0.005	4.15E-11	3.84E-10	6.2E-07	5
EYE															
mild retinop.	dich.	EUR	CHARGE	1,122 /18,289	66	1.021	1.37E-01	6.01E-03	1.37E-01	0	1.046	5.78E-02	7.81E-03	5.78E-02	0
central retinal artery caliber	cont.	EUR	CHARGE	18,576	66	0.343	3.29E-14	2.56E-06	2.06E-13	2	0.570	3.61E-14	2.44E-06	7.05E-13	3
mild retinop.	dich.	EAS	SEED	289 /5,419	66	1.033	2.55E-01	2.42E-01	2.55E-01	0	1.087	8.55E-02	2.87E-01	8.55E-02	0
central retinal artery caliber	cont.	EAS	SEED	6,976	63	0.320	1.39E-04	9.07E-01	1.39E-04	0	0.533	2.19E-04	8.91E-01	2.19E-04	0

ONLINE METHODS

Cohorts contributing to systolic (SBP) and diastolic blood pressure (DBP) analyses

Studies contributing to BP association discovery including community- and population-based collections as well as studies of non-BP traits, analyzed as case and control samples separately. Details on each of the studies including study design and BP measurement are provided in **Supplementary Table 1**, genotyping information in **Supplementary Table 2**, and participant characteristics in **Supplementary Table 3**. All participants provided written informed consent and the studies were approved by local Research Ethics Committees and/or Institutional Review Boards.

European ancestry meta-analysis

BP was measured using standardized protocols in all studies regardless of whether the primary focus was BP or another trait. We initially analyzed affected and unaffected individuals from samples selected as cases (e.g. type 2 diabetes) or controls, separately. However, because sensitivity analyses did not reveal any significant difference in BP effect size estimates between case and control samples (data not shown), we analyzed all samples combined. When available, the average of two BP measurements was used for association analyses (**Supplementary Table 1**). If an individual was taking a BP-lowering treatment, the underlying systolic BP (SBP) and diastolic BP (DBP) were estimated by adding 15 mmHg and 10 mmHg, respectively, to the measured values, as done in prior analyses.

A meta-analysis of 340,934 individuals of European descent was undertaken in four stages with subsequent validation in an independent cohort. Because stage 1 Cardio-MetaboChip samples included many SNPs selected on the basis of association with BP in earlier GWAS, we performed genomic control using a set of putative null SNPs based on P > 0.10 in earlier GWAS of SBP and DBP or both. Stage 2 samples with genome-wide genotyping used the entire genome-wide set of SNPs for genomic control given the lack of ascertainment. The study design is summarized in **Supplementary Figure 1**, and further details are provided in **Supplementary Tables 2-5** and the **Supplementary Note**.

Systematic PubMed search +/- 100kb of each newly discovered index SNP

All genes with any overlap with a 200kb region centered around each of the 17 newly discovered lead SNPs were identified using the UCSC Genome Browser. A search term was constructed for each gene including the short and long gene name and the terms "blood pressure" and "hypertension" (e.g. for *NPPA* on chr 1: "NPPA OR natriuretic peptide A AND (blood pressure OR hypertension)") and the search results of each search term from PubMed were individually reviewed.

Trait variance explained

The trait variance explained by 66 lead SNPs at novel and known loci was evaluated in one study that contributed to the discovery effort: the Atherosclerosis Risk in Communities (ARIC) study. We constructed a linear regression model with all 66 or the subset of 49 known SNPs as a set of predictors of the BP residual after adjustment for covariates of the adjusted treatment-corrected BP phenotype (SBP or DBP). The r² from the regression model was used as the estimate of trait variance explained.

European ancestry GCTA-COJO analysis

To identify multiple distinct association signals at any given BP locus, we undertook approximate conditional analyses using a model selection procedure implemented in the GCTA-COJO software package^{44,45}. To evaluate the robustness of the GCTA-COJO results to the choice of reference data set, model selection was performed using the LD between variants in separate analyses from two datasets of European descent, both with individuals from the UK with Cardio-MetaboChip genotype data: GoDARTS with 7,006 individuals and WTCCC1-T2D/58BC with 2,947 individuals. Assuming that the LD between

SNPs more than 10 Mb away or on different chromosomes is zero, we undertook the GCTA-COJO stepwise model selection to select SNPs that were conditionally-independently associated with SBP and DBP, in turn, at a genome-wide significance, given by $P < 5 \times 10^{-8}$ (**Supplementary Tables 6-8**) using the stage 4 combined European GWAS+ Cardio-MetaboChip meta-analysis.

Conditional analyses in the Women's Genome Health Study (WGHS)

Multivariable regression modeling was performed for each possible combination of putative independent SNPs from a) model selection implemented in GCTA-COJO and b) a comprehensive manual review of the literature (**Supplementary Table 9**). Any SNP with $P < 5 \times 10^{-8}$ in a previous reported BP GWAS was considered. A total of 46 SNPs were examined (**Supplementary Table 10**). Genome-wide genotyping data imputed to 1000 Genomes in the WGHS (N = 23,047) were used. Regression modeling was performed in the R statistical language (**Supplementary Table 10**).

Fine mapping and determination of credible sets of causal SNPs

The GCTA-COJO and WGHS conditional analyses identified multiple distinct signals of association at multiple loci (**Supplementary Tables 6 and 10**). Of the 24 loci considered in fine-mapping analyses, 16 had no evidence for the existence of multiple distinct association signals, so it is reasonable to assume that there is a single causal SNP and therefore the credible sets of variants could be constructed using the association summary statistics from the unconditional meta-analyses. However, in the remaining eight loci, where evidence of secondary signals was observed from GCTA-COJO, we performed approximate conditional analyses across the region by conditioning on each index SNP (**Supplementary Table 11**). By adjusting for the other index SNPs at the locus, we can therefore assume a single variant is driving each "conditionally-independent" association signal, and we can construct the 99% credible set of variants on the basis of the approximate conditional analysis from GCTA-COJO (**Supplementary Tables 12-13**). At five of the eight loci with multiple distinct signals of association, one index SNP mapped outside of the fine-mapping region, so a credible set could not be constructed.

eQTL analysis: Whole Blood

NESDA/NTR: Whole blood eQTL analyses were performed in samples from the Netherlands Study of Depression and Anxiety (NESDA)⁴⁶ and the Netherlands Twin Registry (NTR)⁴⁷ studies. RNA expression analysis was performed in the statistical software R. The residuals resulting from the linear regression analysis of the probe set intensity values onto the covariates sex, age, body mass index (kg/m²), smoking status coded as a categorical covariate, several technical covariates, and three principal components were used. The eQTL effects were detected using a linear mixed model approach, including for each probe set the expression level (normalized, residualized and without the first 50 expression PCs) as dependent variable; the SNP genotype values as fixed effects; and family identifier and zygosity (in the case of twins) as random effects to account for family and twin relations⁴⁸.

The eQTL effects were defined as *cis* when probe set–SNP pairs were at distance < 1M base pairs. At a FDR of 0.01 applied genome-wide, not just for candidate SNPs, the *P* value threshold was 1×10^{-4} for the *cis*-eQTL analysis. For each probe set that displayed a statistically significant association with at least one SNP located within its *cis* region, we identified the most significantly associated SNP and denoted this as the top *cis*-eQTL SNP. See **Supplementary Note** for details.

eQTL analysis: Selected published eQTL datasets

Lead BP SNP and proxies ($r^2 > 0.8$) were searched against a collected database of expression SNP (eSNP) results. The reported eSNP results met criteria for statistical thresholds for association with gene transcript levels as described in the original papers. The non-blood cell tissue eQTLs searched included

aortic endothelial cells⁴⁹, left ventricle of the heart ⁵⁰, cd14+ monocytes ⁵¹ and the brain ⁵². The results are presented in **Supplementary Tables 14-15**.

Enrichment analyses: Analysis of cell-specific DNase hypersensitivity sites (DHSs) using an OR method

The overlap of Cardio-MetaboChip SNPs with DHSs was examined using publicly available data from the Epigenomics Roadmap Project and ENCODE, choosing different cutoffs of Cardio-MetaboChip *P* values. The DHS mappings were available for 123 mostly adult cells and tissues ⁵³ (downloaded from The DHS mappings were specified as both "narrow" and "broad" peaks, referring to reduction of the experimental data to peak calls at 0.1% and 1.0% FDR thresholds, respectively. Thus, the "narrow" peaks are largely nested within the "broad" peaks. Experimental replicates of the DHS mappings (typically duplicates) were also available for the majority of cells and tissues.

SNPs from the Cardio-MetaboChip genome-wide scan were first clumped in PLINK in windows of 100kb and maximum $r^2 = 0.1$ among LD relationships from the 1000 Genomes European data. Then, the resulting index SNPs at each *P* value threshold were tagged with $r^2 = 0.8$ in windows of 100kb, again using LD relationships in the 1000 Genomes, restricted to SNPs with MAF > 1% and also present in the HapMap2 CEU population. A reference set of SNPs was constructed using the same clumping and tagging procedures applied to GWAS catalog SNPs (available at http://www.genome.gov/gwastudies/, accessed 3/13/2013)⁵⁴ with discovery *P* < $5x10^{-8}$ in European populations. A small number of reference SNPs or their proxies overlapping the BP SNPs or their proxies were excluded. After LD pruning and exclusions, there were a total of 1,196 reference SNPs. For each cell type and *P* value threshold, the enrichment of SBP or DBP SNPs (or their LD proxies) mapping to DHSs was expressed as an odds ratio (OR) relative to the GWAS catalog reference SNPs (or their LD proxies), using logistic mixed effect models treating the replicate peak determinations as random effects (glmer package in R). The significance of the enrichment ORs was derived from the significance of beta coefficients for the main effects in the mixed models (**Figure 2, Supplementary Table 16**).

Enrichment analyses: Analysis of tissue-specific enrichment of BP variants and H3K4me3 sites

An analysis to test for significant cell-specific enrichment in the overlap of BP SNPs (or their proxies) with H3K4me3 sites was performed as described in Trynka et al, 2013⁵⁵. The measure of overlap is a "score" that is constructed by dividing the height of an H3K4me3 ChIP signal in a particular cell by the distance between the nearest test SNP. The significance of the scores (i.e. *P* value) for all SNPs was determined by a permutation approach that compares the observed scores to scores of SNPs with similar properties to the test SNPs, essentially in terms of LD and proximity to genes (**Supplementary Note**). The number of permutations determined the number of significant digits in the *P* values and we conducted 10,000 iterations. Results are shown in **Supplementary Table 19**.

Enrichment analyses: Analysis of tissue-specific DHSs and chromatin states using GREGOR

The DNase-seq ENCODE data for all available cell types were downloaded in the processed "narrowPeak" format. The local maxima of the tag density in broad, variable-sized "hotspot" regions of chromatin accessibility were thresholded at FDR 1% with peaks set to a fixed width of 150bp. Individual cell types were further grouped into 41 broad tissue categories by taking the union of DHSs for all related cell types and replicates. For each GWAS locus, a set of matched control SNPs was selected based on three criteria: 1) number of variants in LD ($r^2 > 0.7$; ± 8 variants), 2) MAF (± 1%), and 3) distance to nearest gene (± 11,655 bp). To calculate the distance to the nearest gene, the distance to the 5' flanking gene (start and end position) and to the 3' flanking gene was calculated and the minimum of these 4 values was used. If the SNP fell within the transcribed region of a gene, the distance was 0. The probability that a set of GWAS loci overlap with a regulatory feature more often than we expect by chance was estimated.

Enrichment analyses: FAIRE analysis of BP variants in fine-mapping regions in lymphoblastoid cell lines

FAIRE analysis was performed on a sample of 20 lymphoblastoid cell lines of European origin. All samples were genotyped using the Cardio-MetaboChip genotyping array, and BP SNPs and LD proxies ($r^2 > 0.8$) at the fine mapping loci (N = 24, see **Supplementary Table 23**) were assessed to identify heterozygous imbalance between non-treated and FAIRE-treated chromatin. A paired t-test was used to compare the B allele frequency (BAF) arising from formaldehyde-fixed chromatin sheared by sonication and DNA purified to the BAF when the same chromatin sample underwent FAIRE to enrich for open chromatin. Three hundred and fifty-seven Cardio-MetaboChip BP SNPs were directly genotyped across the fine mapping regions. The Bonferroni-corrected threshold of significance is P < 0.0001 (0.05/357). The results for SNPs with P < 0.05 are reported in (**Supplementary Table 23**). FAIRE results were not available for some SNPs with missing data due to genotype failure or not having >3 heterozygous individuals for statistical analysis. Therefore there are no results for three lower frequency BP loci (*SLC39A8, CYP17A1-NT5C2* and *GNAS-EDN3*) and for the second signal at the following loci: *MTHFR-NPPB* (rs2272803), *MECOM* (rs2242338) and *HFE* rs1800562).

Pathway analyses: MAGENTA

MAGENTA tests for enrichment of gene sets from a precompiled library derived from GO, KEGG, PATHTER, REACTOME, INGENUITY, and BIOCARTA was performed as described by Segré et al, 2010^{56} . Enrichment of significant gene-wide *P* values in gene sets is assessed by 1) using LD and distance criteria to define the span of each gene, 2) selecting the smallest *P* value among SNPs mapping to the gene span, and 3) adjusting this *P* value using a regression method that accounts for the number of SNPs, the LD, etc. In the second step, MAGENTA examines the distribution of these adjusted *P* values and defines thresholds for the 75%ile and the 95%ile. In the third step, MAGENTA calculates an enrichment for each gene set by comparing the number of genes in the gene set with *P* value less than either the 75th or 95th %ile to the number of genes in the gene set with *P* value greater than either the 75th or 95th %ile, and then comparing this quotient to the same quotient among genes not in the gene set. This gene-set quotient is assigned a *P* value based on reference to a hypergeometric distribution. The results based on our analyses are indicated in **Supplementary Table 21**.

Pathway analyses: DEPICT

We applied the DEPICT ⁵⁷ analysis separately on genome-wide significant loci from the overall blood pressure (BP) Cardio-MetaboChip analysis including published blood pressure loci (see **Supplementary Table 22**). SNPs at the *HFE* and *BAT2-BAT5* loci (rs1799945, rs1800562, rs2187668, rs805303, rs9268977) could not be mapped. As a secondary analysis, we additionally included associated loci ($P < 1x10^{-5}$) from the Cardio-MetaboChip stage 4 combined meta-analyses of SBP and the DBP. DEPICT assigned genes to associated regions if they overlapped or resided within associated LD blocks with r² > 0.5 to a given associated SNP.

Literature review for genes at the newly discovered loci

Recognizing that the most significantly associated SNP at a locus may not be located in the causal gene and that the functional consequences of a SNP often extends beyond 100kb, we conducted a literature review of genes in extended regions around newly discovered BP index SNPs. The genes for this extensive review were identified by DEPICT (**Supplementary Table 22**).

Non-European meta-analysis

To assess the association of the 66 significant loci from the European ancestry meta-analysis in non-European ethnicities, we obtained lookup results for the 66 index SNPs for participants of South-Asian ancestry (8 datasets, total N = 20,875), East-Asian ancestry (5 datasets, total N = 9,637), and African- and African-American ancestry (6 datasets, total N = 33,909). The association analyses were all conducted with the same covariates (age, age², sex, BMI) and treatment correction (+15/10 mm Hg in the presence of any hypertensive medication) as the association analyses for the discovery effort in Europeans. Tests for heterogeneity across effect estimates in European, South Asian, East Asian and African derived samples were performed using GWAMA⁵⁸.

Genetic risk score and cardiovascular outcomes

The gtx package for the R statistical programming language was used to estimate the effect of the SNP-risk score on the response variable in a regression model⁵⁹.

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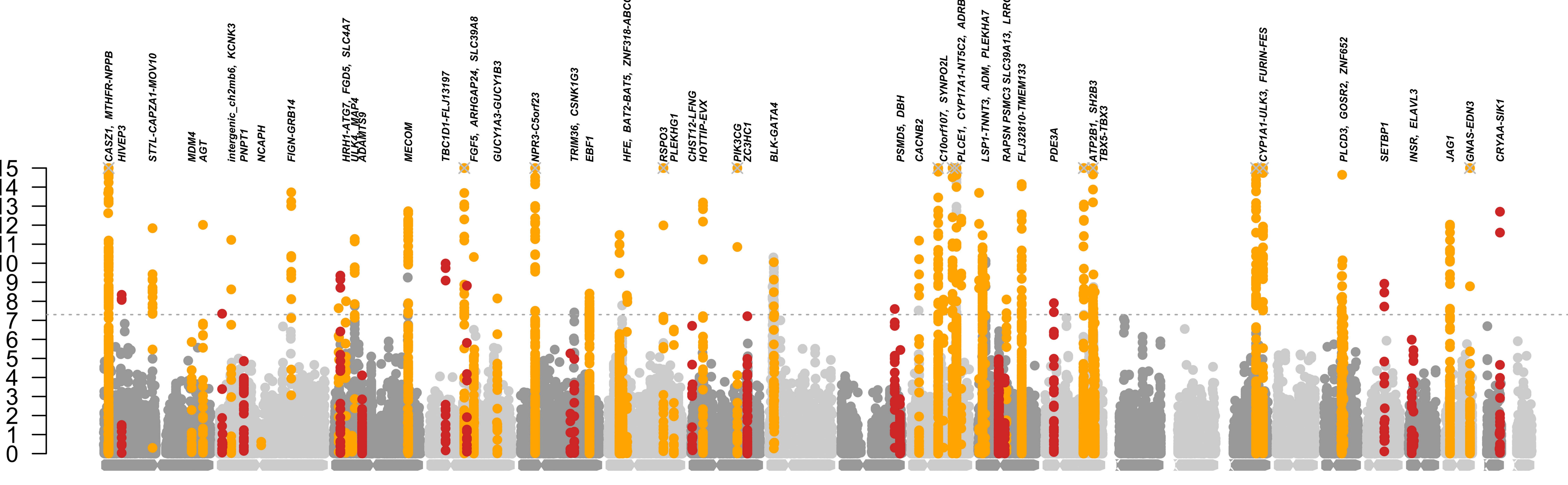
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ČCYP1A1-ULK3, FURIN-FES PLCD3, GOSR2, ZNF652 PLCD3, GOSR2, ZNF652 SETBP1 SETBP1 INSR, ELAVL3 INSR, ELAVL3 INSR, ELAVL3 INSR, ELAVL3 INSR, ELAVL3 CRYAA-SIK1 CRYAA-SIK1

new established p-value lower than 10^-15

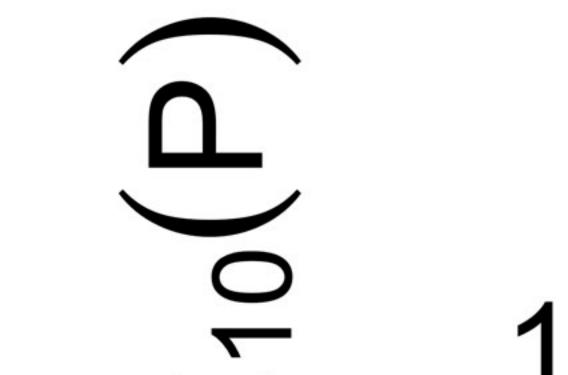
SBP





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Genomic position by chromosome



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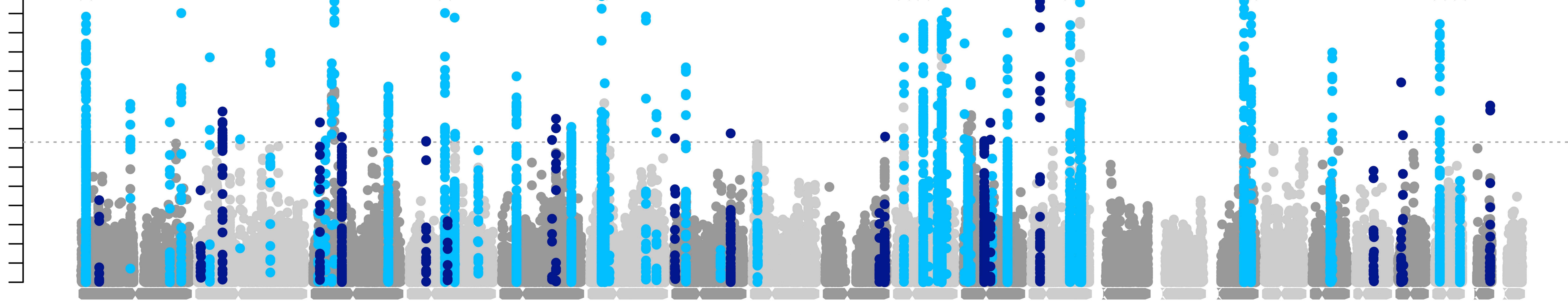
Caszt, MTHFR-NPPB HIVEP3 ST7L-CAPZA1-MOV10 ST7L-CAPZA1-MOV10 ST7L-CAPZA1-MOV10 MDM4 intergenic_ch2mb6, KCNK3 MDM4 FIGN-GRB14 FIGN-GR

SYP1A1-ULK3, FUF SYP1A1-ULK3, FUF CCD3, GOSR2, ZN CCD3, GOSR2, ZN SETBP1 STBP1 STBP1 STBP1 STBP1 STBP1 STBP1 STBP1 STAA-SIK1

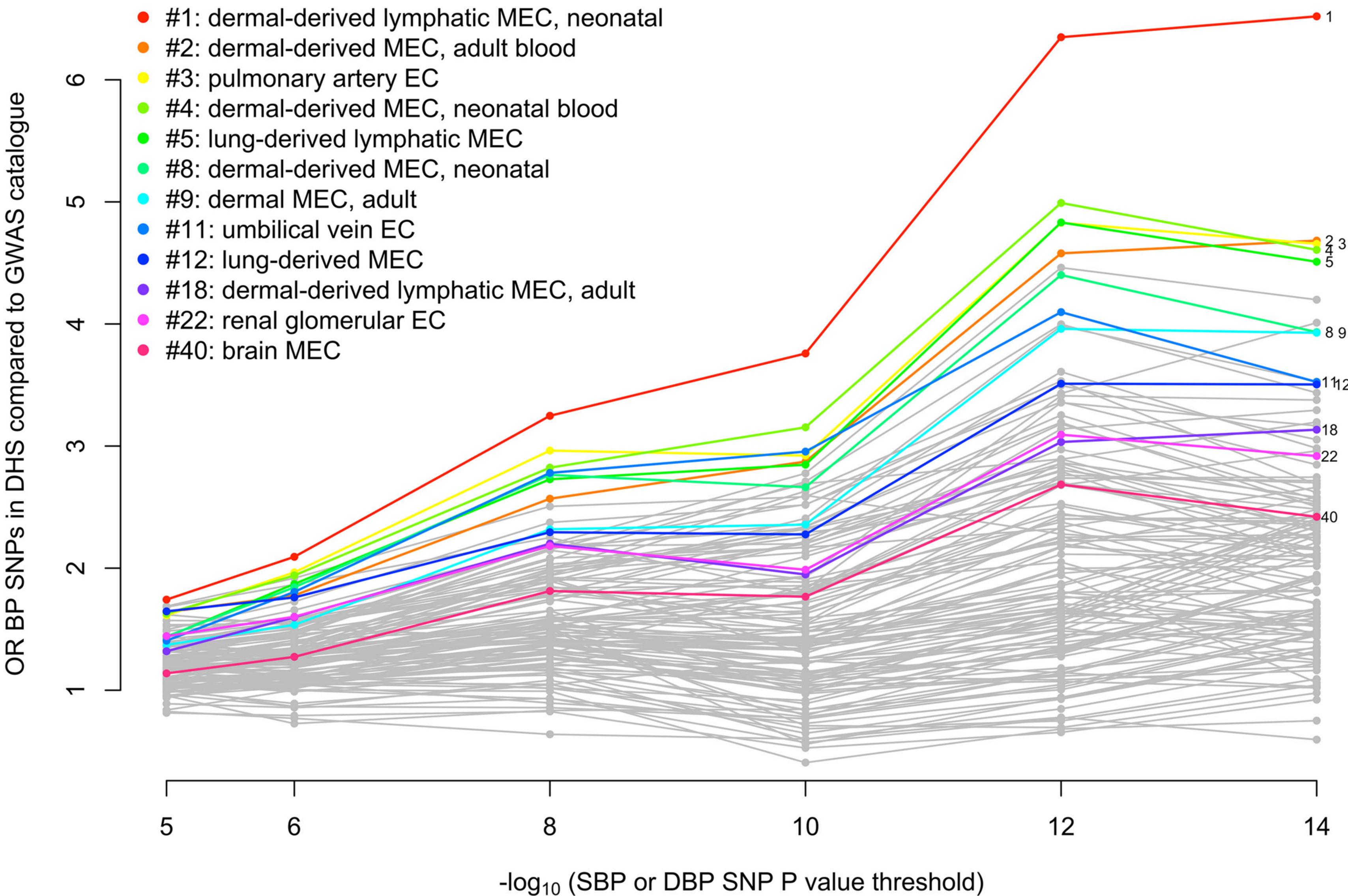
new established × p-value lower than 10^-15

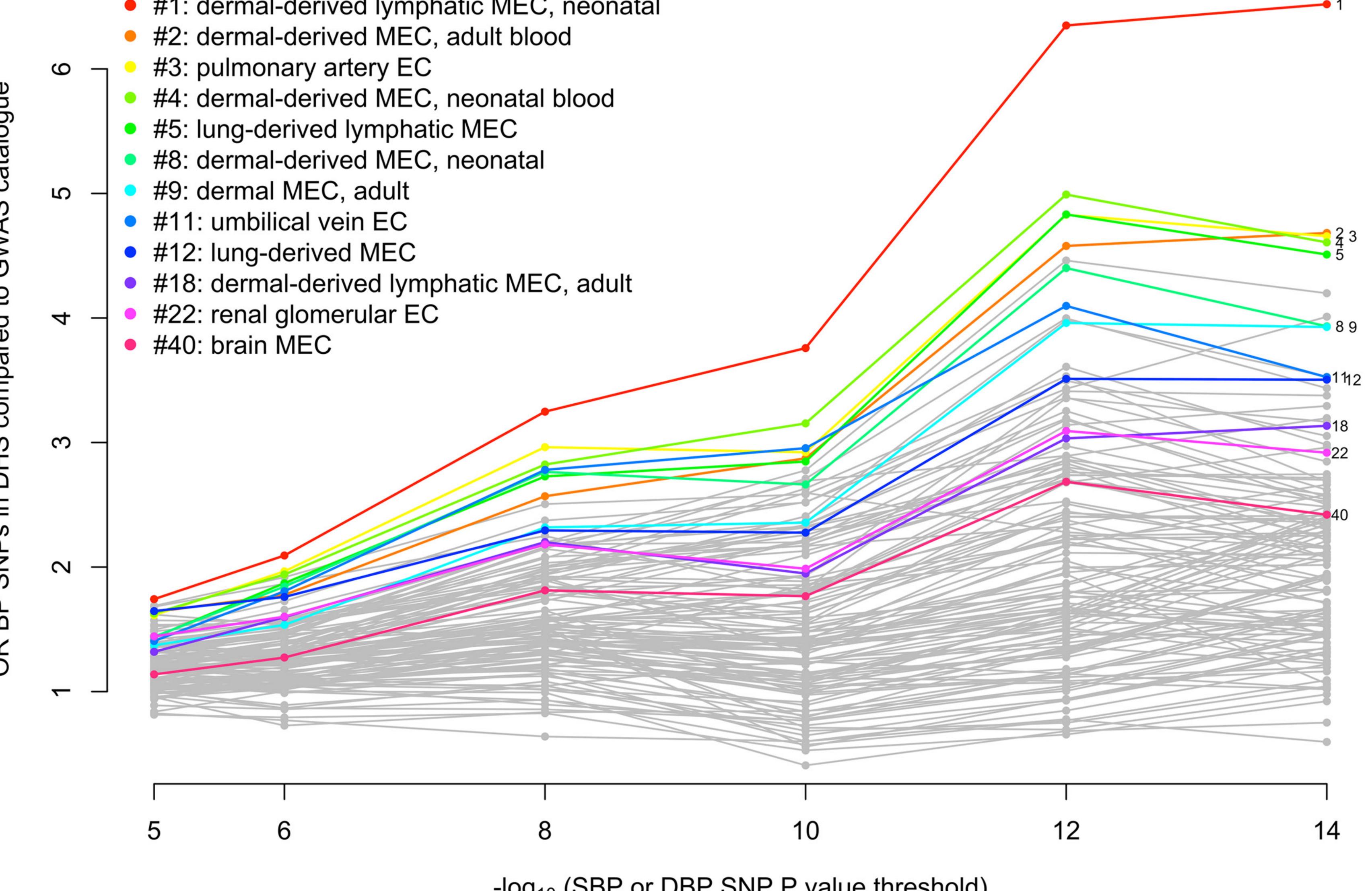






A) Narrow DHS region definition





B) Broad DHS region definition

- #17: brain MEC

