

Large-scale multi-omics studies provide new insights into blood pressure regulation

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Supplementary Methods

In silico sequencing pipeline

Our locus definition was based on $r^2 > 0.5$ as linkage disequilibrium (LD) metric and a physical distance of 1 Mb on both sides of the lead SNP. For LD calculations we used PLINK v1.9 (1) based on the 1000 Genomes Project phase 3 (2) data, including only subjects of European ancestry. For variant annotations, we used ANNOVAR (3) (version 16 April 2018). We then used Ensembl variant effect predictor (VEP) (4) release 95 to identify gene names of BP linked non-synonymous SNPs (nsSNPs) and also to investigate the severity of their functional consequences indexed by SIFT and Polyphen scores.

Transcriptome-wide association studies (TWASs)

In order to identify genes where expression levels are associated with BP free of non-genetic confounders, we performed MX analysis for systolic-, diastolic-, and pulse pressure GWASs, separately, using gene expression prediction models from whole blood Depression Genes and Networks (DGN) data (5). We only included GWAS variants with minor allele frequency (MAF) ≥ 0.01 and excluded all SNPs and genes within the MHC region. According to 11,430 genes being tested in DGN analysis, a Bonferroni corrected significance level of $< 4.37 \times 10^{-6}$ was applied. We then excluded genes with prediction performance p-values larger than Bonferroni corrected thresholds i.e. $0.05/n_{\text{sign}}$ (where n_{sign} is the number of MX significant genes for BP) as suggested by Barbeira *et al.* (6).

To address the LD contamination concern in our MX significant genes, we also tested colocalization of association signals for BP and gene expression using the COLOC R package (7). The COLOC test is typically based on approximate Bayes factors on five hypotheses of 1) no causal variant (H_0), 2) causal variant for BP only (H_1), 3) causal variant for gene expression only (H_2), 4) two distinct causal variants (H_3) and 5) one common causal variant (H_4) for both traits.

We performed COLOC analysis on SBP, DBP, and PP GWASs separately using the eQTLGen whole blood eQTL dataset. This analysis was based on all SNPs in common between GWAS and eQTL datasets and no filtering was applied based on p-values. We took a probability of $H_3 < 0.5$ and $H_4 > 0.5$ as acceptable evidence of colocalized signals to filter out MX TWAS association results, which can be due to LD, as suggested by Barbeira *et al.* (6).

Further to investigate gene expression associations with BP using MR causal inference, we ran SMR analysis (8) on the three BP GWASs (SBP, DBP and PP). We also conducted the HEIDI test to exclude LD confounded results.

We used the blood cis-eQTL summary data from the eQTLGen consortium ($n \sim 32,000$) (9). The 1000 Genomes Project phase3 data of European population was used for LD calculations through SMR (8). We only included GWAS variants with $\text{MAF} \geq 0.01$ and excluded those variants with either inconsistent alleles or MAF differences > 0.20 amongst pairs of the three datasets,

i.e., GWAS, eQTL, and 1000 Genomes datasets. We also excluded all variants and expression probes within the MHC region.

Considering 15,368 genes being tested, we used a Bonferroni corrected significance level of $<3.25 \times 10^{-6}$ for SMR. We selected a p-value threshold of ≥ 0.01 for HEIDI as acceptable evidence of not being confounded by LD, which is more stringent than a Bonferroni corrected significance level.

Tissue prioritization

We repeated TWAS analyses using both MX and SMR methods over 48 GTEx datasets to find tissues in which gene expression associations with BP traits are stronger. For each tissue, we first calculated average squared Z-scores (the below formula) of genes against 3 BP traits and two TWAS methods (MX and SMR), i.e. six calculations per tissue.

$$Z_t^{(p)} = \frac{\sum_{i=1}^n Z_i^2}{n}$$

With t being the tissue, p the BP trait, i each individual gene, and n the total number of tested genes. Next, we normalized these $Z_t^{(p)}$ values for each TWAS method and against each BP outcome, using the mean and standard deviation of $Z_t^{(p)}$ values across tissues, to get harmonized comparable measures. Finally, we calculated for each tissue, the average of the six normalized $Z_t^{(p)}$ values as a measure of tissue priority for BP traits.

3xSMR analysis

We ran SMR analyses on the three BP GWASs (SBP, DBP and PP) using blood mQTL summary data. We used the mQTL results of a meta-analysis of the Brisbane Systems Genetics Study and Lothian Birth Cohorts (combined $n = 1,980$) reported by McRae *et al* (10).

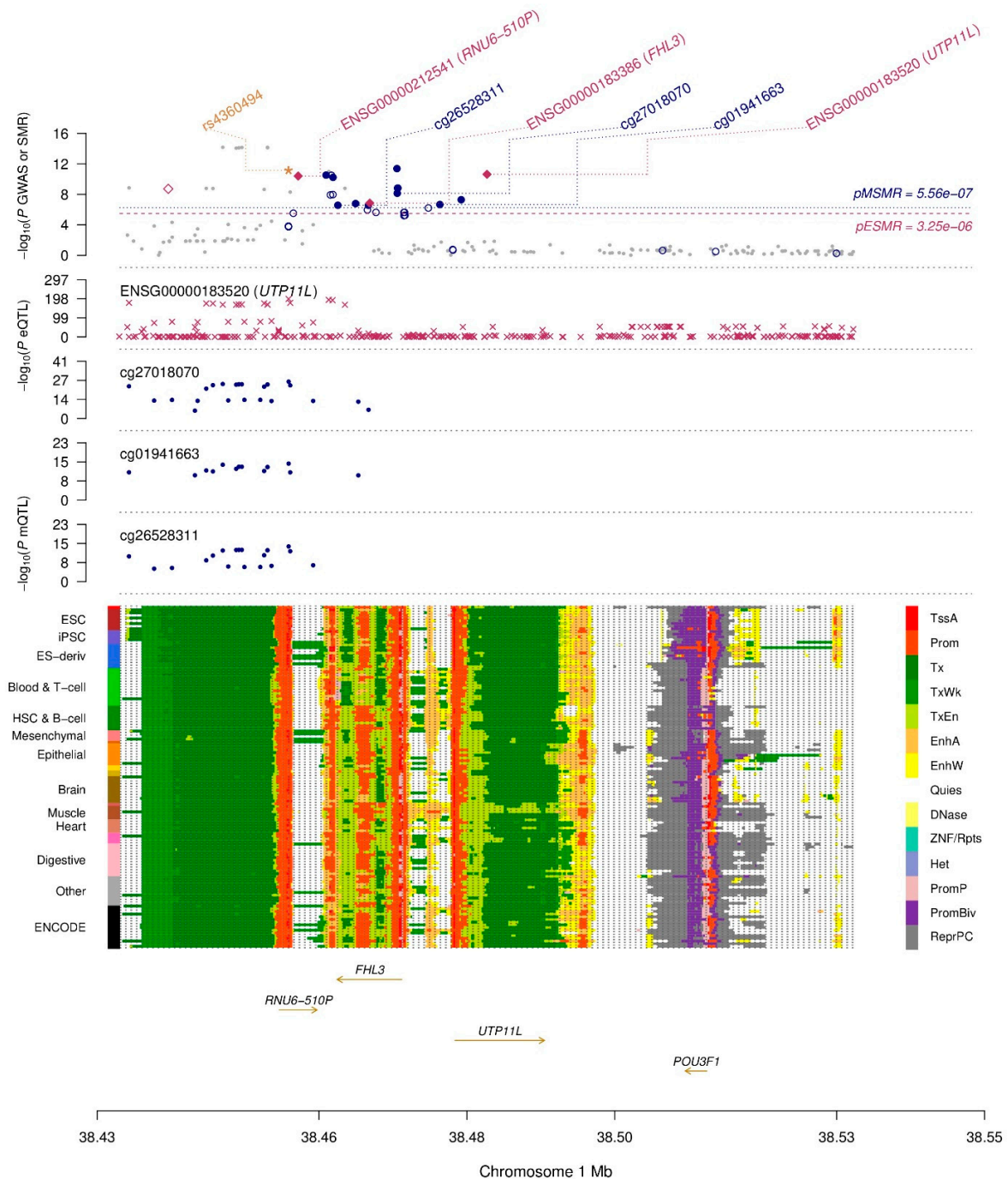
We assessed the novelty of DNA methylation (DNAm) probes according to the Epigenome-Wide Association Studies (EWAS) catalog and the recently published multi-omics study of BP in kidney (11,12). We also investigated whether the physical distance of DNAm probes to their nearest genes is deterministic in the functionality of those genes, by comparing the physical distance to DNAm sites between genes with and without biological evidence from our pipeline, as well as among genes with different lines of evidence.

Then for mapping methylation probes to their likely affected genes, we repeated SMR analysis on the mQTL data, described above, using eQTL data from the eQTLGen consortium (9). We only included GWAS variants with $MAF \geq 0.01$ and excluded all variant and methylation probes within the MHC region. We applied appropriate Bonferroni corrected significance thresholds for SMR tests and a stringent threshold of ≥ 0.01 for the HEIDI tests. LD reference data and settings for all HEIDI tests is the same as previously (see TWAS methods). Finally, merging the three sets

of SMR analyses (3xSMR) including GWAS vs. mQTL (MSMR), mQTL vs. eQTL (MESMR) and GWAS vs. eQTL (ESMR), enabled us to link DNA to BP through methylation mediated gene expression at specific sites (i.e., DNA→Methylation→Gene expression→BP).

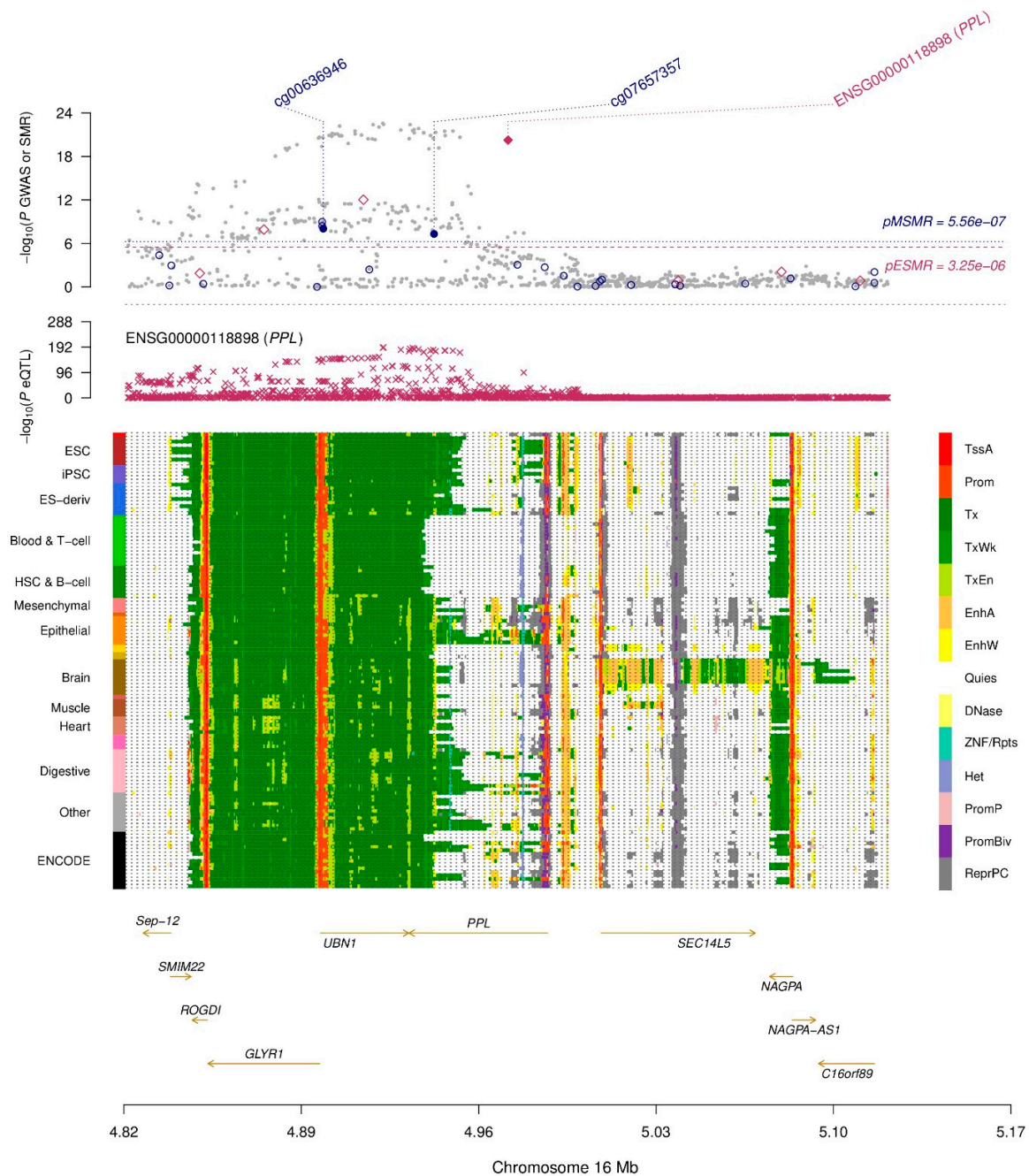
Afterwards we used the Roadmap Epigenomics Mapping Consortium (REMC) (13) and Encyclopedia of DNA Elements (ENCODE) project (14) data based on the Ensembl regulatory build (15) to annotate the known regulatory features of the 3xSMR significant loci and mediating methylation sites.

Supplementary Figures



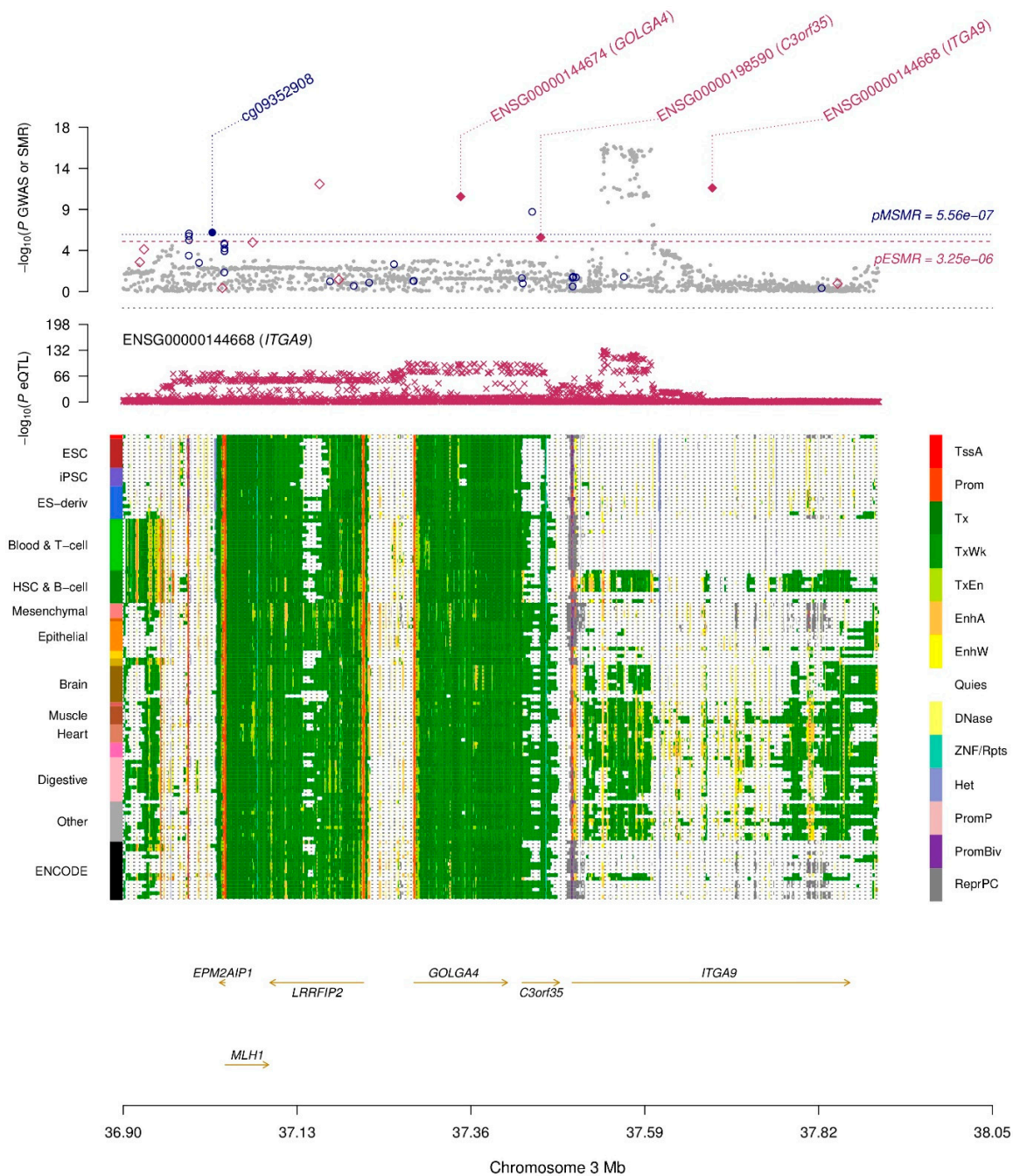
Supplementary Figure S1. Results of 3xSMR analyses for *UTP11L* gene. The top plot shows the meta-analysis $-\log_{10}(P\text{-values})$ of SNPs from the SBP GWAS. The red diamonds represent $-\log_{10}(P\text{-values})$ of SMR analysis of eQTL data (ESMR) and the blue circles represent $-\log_{10}(P\text{-values})$ of SMR analysis of mQTL data (MSMR). Probes which were not rejected by the HEIDI test are filled in with solid colors. The second plot shows $-\log_{10}(P\text{-values})$ of the association of eQTL SNPs for *UTP11L* and its expression level. The third plot shows $-\log_{10}(P\text{-values})$ of the associations of mQTL SNPs and

methylation probes for *UTP11L*. The bottom plot shows chromatin state annotations from REMC and ENCODE for different cells/tissue types.



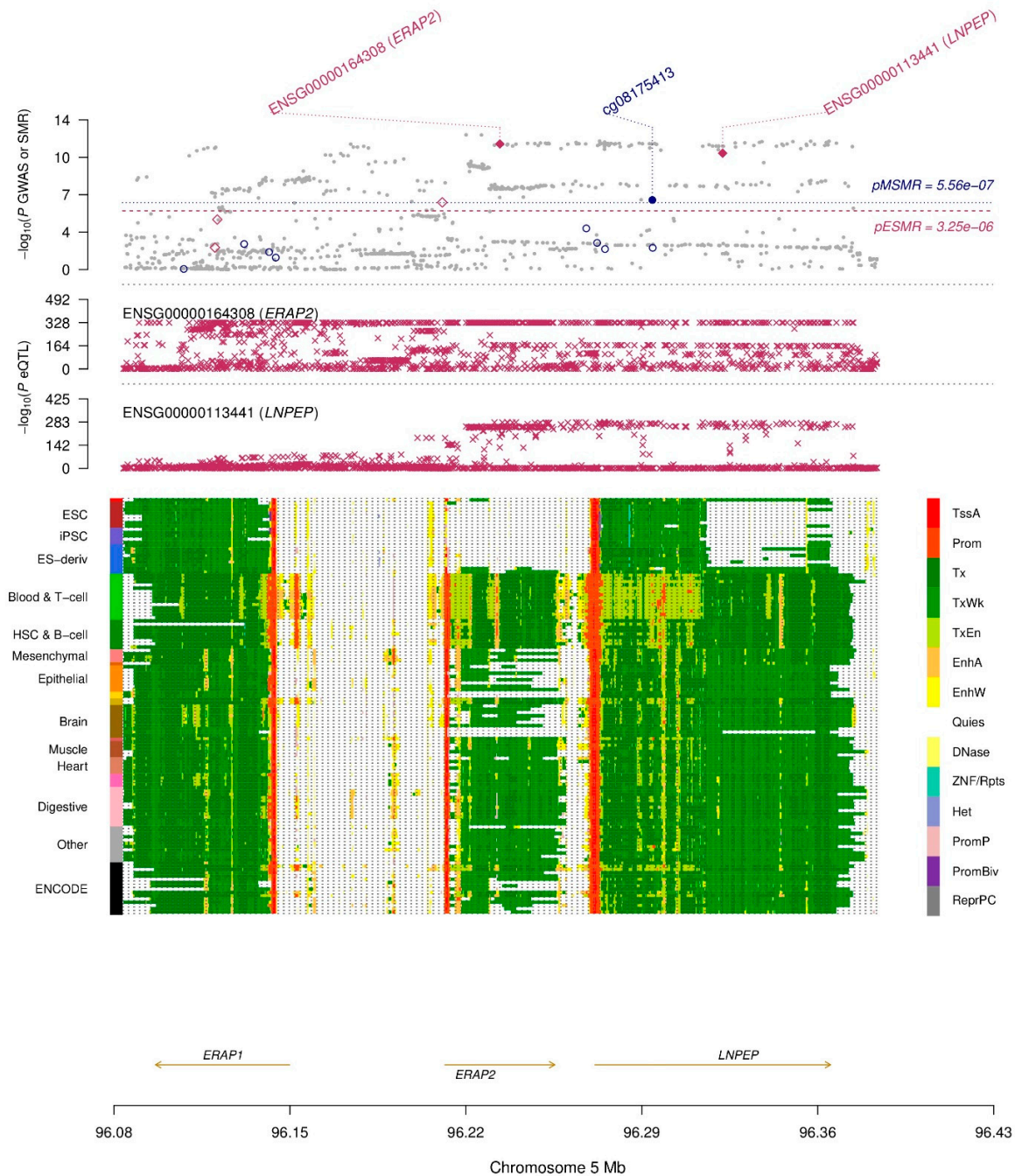
Supplementary Figure S2. Results of 3xSMR analyses for *PPL* gene. The plot shows results of SMR analyses using mQTL, eQTL and GWAS data. The top plot shows the meta-analysis $-\log_{10}(P\text{-values})$ of SNPs from the GWAS results. The red diamonds represent $-\log_{10}(P\text{-values})$ of SMR analysis of eQTL data (ESMR) and the blue circles represent $-\log_{10}(P\text{-values})$ of SMR analysis of mQTL data (MSMR). Probes which were not rejected by the HEIDI test are filled in with solid

colors. The second plot shows $-\log_{10}(\text{P-values})$ of the association of eQTL SNPs and their corresponding gene expression levels. The bottom plot shows chromatin state annotations from REMC and ENCODE for different cells/tissue types.



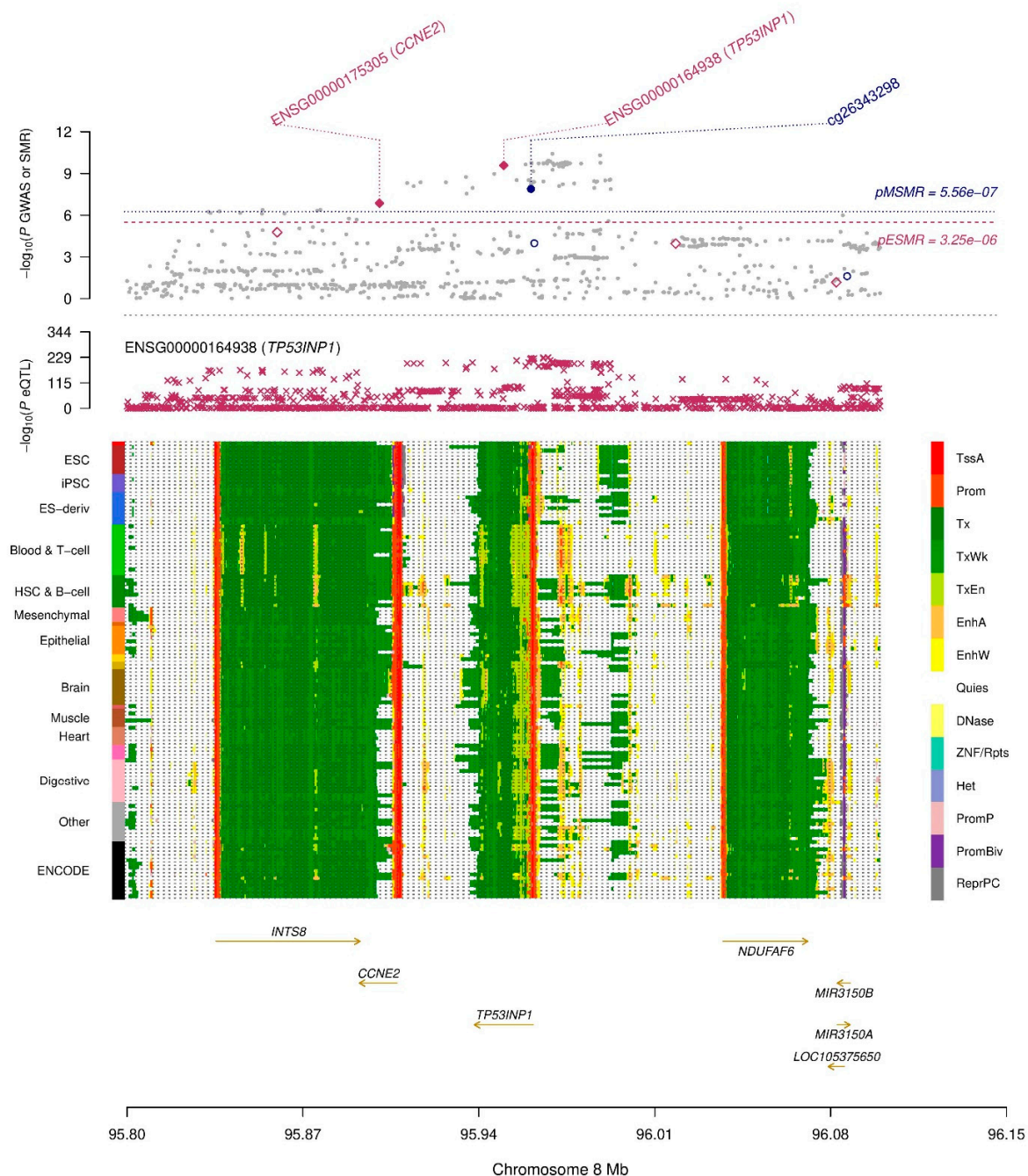
Supplementary Figure S3. Results of 3xSMR analyses for *ITGA9* gene. The plot shows results of SMR analyses using mQTL, eQTL and GWAS data. The top plot shows the meta-analysis $-\log_{10}(\text{P-values})$ of SNPs from the GWAS results. The red diamonds represent $-\log_{10}(\text{P-values})$ of SMR analysis of eQTL data (ESMR) and the blue circles represent $-\log_{10}(\text{P-values})$ of SMR analysis of mQTL data (MSMR). Probes which were not rejected by the HEIDI test are filled in with solid

colors. The second plot shows $-\log_{10}(\text{P-values})$ of the association of eQTL SNPs and their corresponding gene expression levels. The bottom plot shows chromatin state annotations from REMC and ENCODE for different cells/tissue types.



Supplementary Figure S4. Results of 3xSMR analyses for *ERAP2* gene. The plot shows results of SMR analyses using mQTL, eQTL and GWAS data. The top plot shows the meta-analysis $-\log_{10}(\text{P-values})$ of SNPs from the GWAS results. The red diamonds represent $-\log_{10}(\text{P-values})$ of SMR analysis of eQTL data (ESMR) and the blue circles represent $-\log_{10}(\text{P-values})$ of SMR analysis of mQTL data (MSMR). Probes which were not rejected by the HEIDI test are filled in with solid

colors. The second plot shows $-\log_{10}(\text{P-values})$ of the association of eQTL SNPs and their corresponding gene expression levels. The bottom plot shows chromatin state annotations from REMC and ENCODE for different cells/tissue types.



Supplementary Figure S5. Results of 3xSMR analyses for *TP53INP1* gene. The plot shows results of SMR analyses using mQTL, eQTL and GWAS data. The top plot shows the meta-analysis $-\log_{10}(\text{P-values})$ of SNPs from the SBP GWAS results. The red diamonds represent $-\log_{10}(\text{P-values})$ of SMR analysis of gene expression probes (ESMR) and the blue circles represent $-\log_{10}(\text{P-values})$ of SMR analysis of methylation probes (MSMR). Probes which were not rejected by the HEIDI test are filled in with solid colors. The second plot shows $-\log_{10}(\text{P-values})$ of the association of eQTL SNPs and their

corresponding gene expression levels. The bottom plot shows chromatin state annotations from REMC and ENCODE for different cells/tissue types

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2. 1000 Genomes Project Consortium; Auton, A.; Brooks, L.D.; Durbin, R.M.; Garrison, E.P.; Kang, H.M.; Korbel, J.O.; Marchini, J.L.; McCarthy, S.; McVean, G.A.; et al. A Global Reference for Human Genetic Variation. *Nature* 2015, 526, 68–74, doi:10.1038/nature15393.
3. Wang, K.; Li, M.; Hakonarson, H. ANNOVAR: Functional Annotation of Genetic Variants from High-Throughput Sequencing Data. *Nucleic Acids Res.* 2010, 38, e164–e164, doi:10.1093/nar/gkq603.
4. McLaren, W.; Gil, L.; Hunt, S.E.; Riat, H.S.; Ritchie, G.R.S.; Thormann, A.; Flicek, P.; Cunningham, F. The Ensembl Variant Effect Predictor. *Genome Biol.* 2016, 17, doi:10.1186/s13059-016-0974-4.
5. Battle, A.; Mostafavi, S.; Zhu, X.; Potash, J.B.; Weissman, M.M.; McCormick, C.; Haudenschild, C.D.; Beckman, K.B.; Shi, J.; Mei, R.; et al. Characterizing the Genetic Basis of Transcriptome Diversity through RNA-Sequencing of 922 Individuals. *Genome Res.* 2014, 24, 14–24, doi:10.1101/gr.155192.113.
6. Barbeira, A.N.; Dickinson, S.P.; Bonazzola, R.; Zheng, J.; Wheeler, H.E.; Torres, J.M.; Torstenson, E.S.; Shah, K.P.; Garcia, T.; Edwards, T.L.; et al. Exploring the Phenotypic Consequences of Tissue Specific Gene Expression Variation Inferred from GWAS Summary Statistics. *Nat. Commun.* 2018, 9, 1825, doi:10.1038/s41467-018-03621-1.
7. Giambartolomei, C.; Vukcevic, D.; Schadt, E.E.; Franke, L.; Hingorani, A.D.; Wallace, C.; Plagnol, V. Bayesian Test for Colocalisation between Pairs of Genetic Association Studies Using Summary Statistics. *PLoS Genet.* 2014, 10, e1004383, doi:10.1371/journal.pgen.1004383.
8. Vösa, U.; Claringbould, A.; Westra, H.-J.; Bonder, M.J.; Deelen, P.; Zeng, B.; Kirsten, H.; Saha, A.; Kreuzhuber, R.; Yazar, S.; et al. Large-Scale Cis- and Trans-EQTL Analyses Identify Thousands of Genetic Loci and Polygenic Scores That Regulate Blood Gene Expression. *Nat. Genet.* 2021, 53, 1300–1310, doi:10.1038/s41588-021-00913-z.
9. Zhu, Z.; Zhang, F.; Hu, H.; Bakshi, A.; Robinson, M.R.; Powell, J.E.; Montgomery, G.W.; Goddard, M.E.; Wray, N.R.; Visscher, P.M.; et al. Integration of Summary Data from GWAS and EQTL Studies Predicts Complex Trait Gene Targets. *Nat. Genet.* 2016, 48, 481–487, doi:10.1038/ng.3538.
10. McRae, A.F.; Marioni, R.E.; Shah, S.; Yang, J.; Powell, J.E.; Harris, S.E.; Gibson, J.; Henders, A.K.; Bowdler, L.; Painter, J.N.; et al. Identification of 55,000 Replicated DNA Methylation QTL. *Sci. Rep.* 2018, 8, doi:10.1038/s41598-018-35871-w.

11. Battram, T.; Yousefi, P.; Crawford, G.; Prince, C.; Babei, M.S.; Sharp, G.; Hatcher, C.; Vega- Salas, M.J.; Khodabakhsh, S.; Whitehurst, O.; et al. The EWAS Catalog: A Database of Epigenome-Wide Association Studies 2021.
12. Eales, J.M.; Jiang, X.; Xu, X.; Saluja, S.; Akbarov, A.; Cano-Gamez, E.; McNulty, M.T.; Finan, C.; Guo, H.; Wystrychowski, W.; et al. Uncovering Genetic Mechanisms of Hypertension 27 | Page through Multi-Omic Analysis of the Kidney. *Nat. Genet.* 2021, 53, 630–637, doi:10.1038/s41588-021-00835-w.
13. Roadmap Epigenomics Consortium; Kundaje, A.; Meuleman, W.; Ernst, J.; Bilenky, M.; Yen, A.; Heravi-Moussavi, A.; Kheradpour, P.; Zhang, Z.; Wang, J.; et al. Integrative Analysis of 111 Reference Human Epigenomes. *Nature* 2015, 518, 317–330, doi:10.1038/nature14248.
14. The ENCODE Project Consortium An Integrated Encyclopedia of DNA Elements in the Human Genome. *Nature* 2012, 489, 57–74, doi:10.1038/nature11247.
15. Zerbino, D.R.; Wilder, S.P.; Johnson, N.; Juettemann, T.; Flicek, P.R. The Ensembl Regulatory Build. *Genome Biol.* 2015, 16, doi:10.1186/s13059-015-0621-5.