Figure S1. Results of the multiple-tissue analysis for traits with at least one tissue/cell type passing FDR<5% that are not displayed in **Figure 2.** Each point represents a tissue/cell type from either the GTEx data set or the Franke lab data set. Large points pass the FDR<5% cutoff, $-\log_{10}(P)=2.75$. GWAS data is described in **Table S4**, gene expression data is described in the Online Methods and **Tables S2-3**, and the statistical method is described in the Overview of Methods and the Online Methods. Numerical results are reported in **Table S6**.

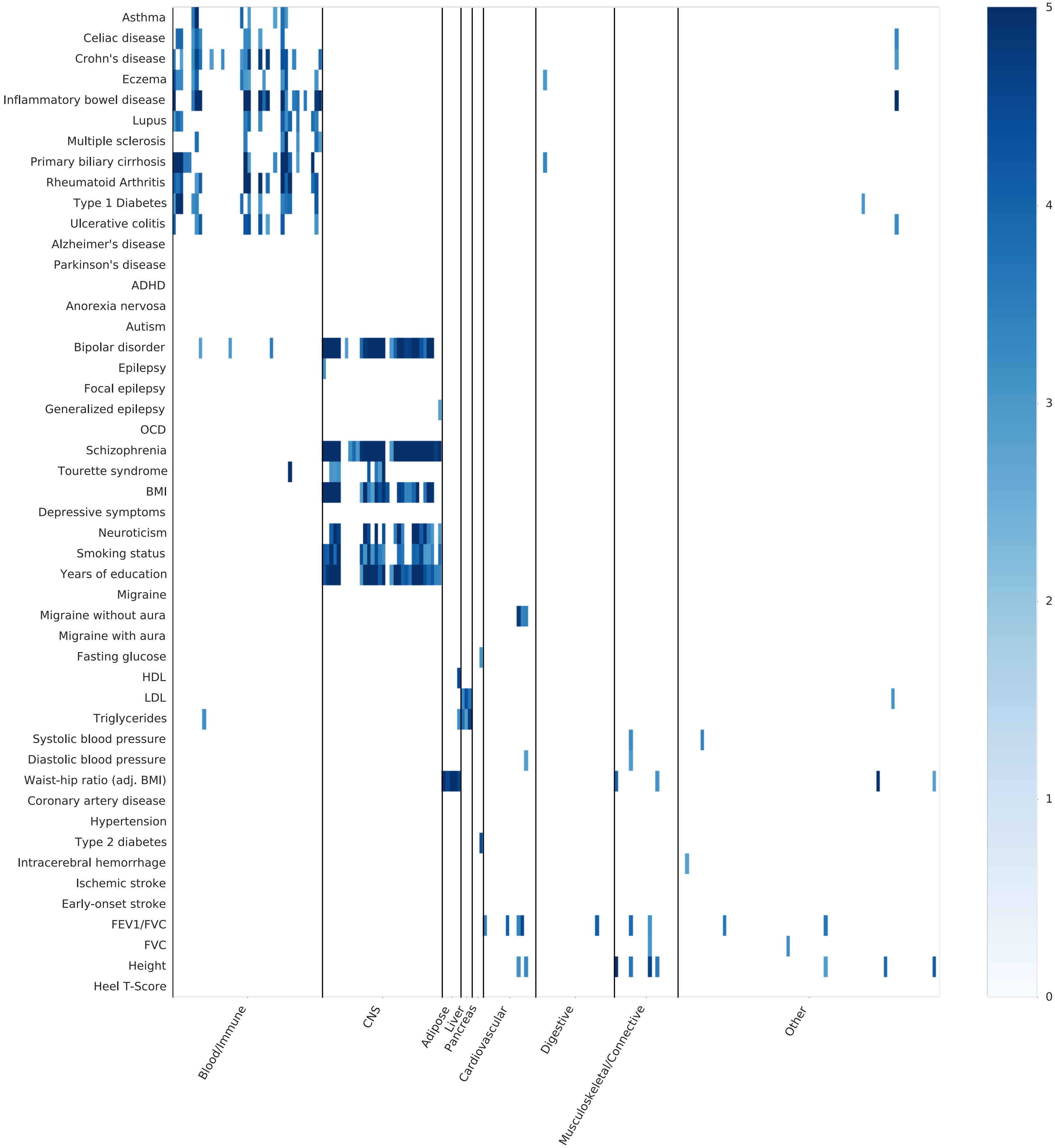


Figure S2a. Results of the multiple-tissue analysis for all traits, for comparison with **Figures S2b-e** and **Figures S12-S15.** –log_10(P) is displayed, truncated at 5, for results that pass the FDR < 5% threshold of $-\log_{10}(P)=2.75$. GWAS data is described in **Table S4**, gene expression data is described in the Online Methods and **Tables S2-3**, and the statistical method is described in the Overview of Methods and the Online Methods. Numerical results are reported in **Table S6.**

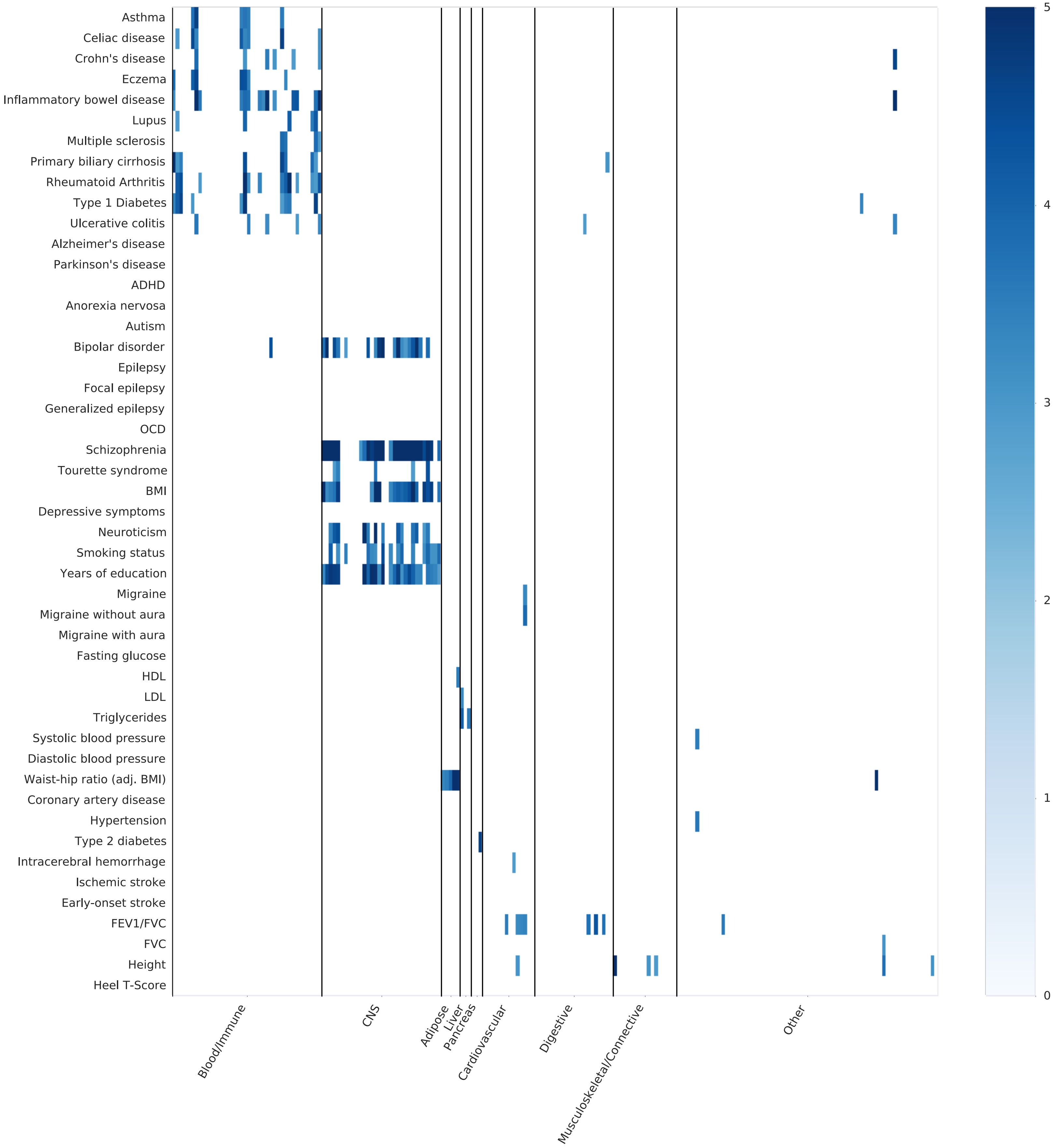


Figure S2b. Results of the multiple-tissue analysis with proportion of genes changed from 10% to 5%. –log_10(P) is displayed, truncated at 5, for results that pass the FDR < 5% threshold of $-\log_{10}(P)=2.91$. GWAS data is described in **Table S4**, gene expression data is described in the Online Methods and **Tables S2-3**, and the statistical method is described in the Overview of Methods and the Online Methods.

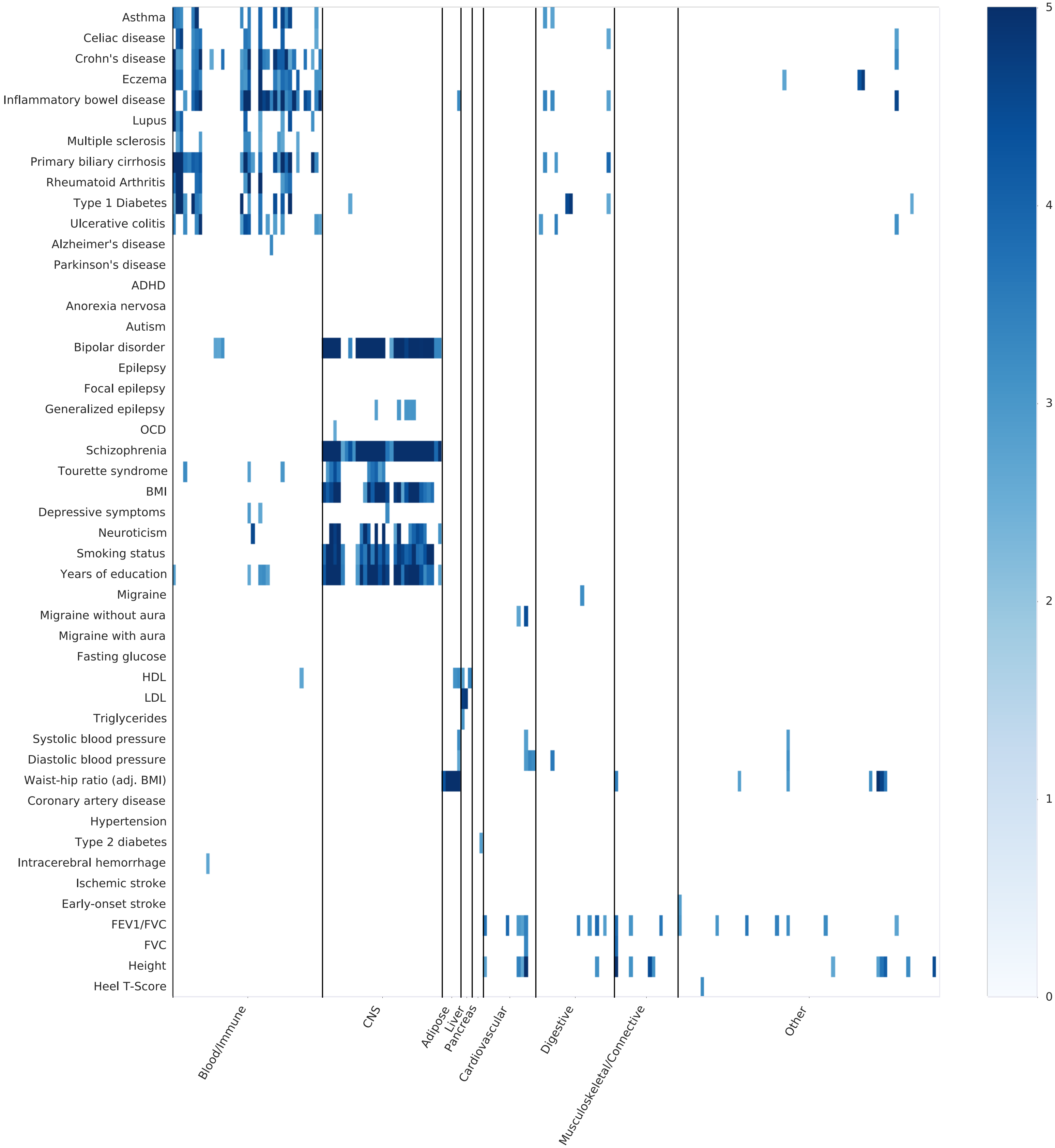


Figure S2c. Results of the multiple-tissue analysis with proportion of genes changed from 10% to 20%**.** –log_10(P) is displayed, truncated at 5, for results that pass the FDR < 5% threshold of $-\log_{10}(P)=2.84$. GWAS data is described in **Table S4**, gene expression data is described in the Online Methods and **Tables S2-3**, and the statistical method is described in the Overview of Methods and the Online Methods.

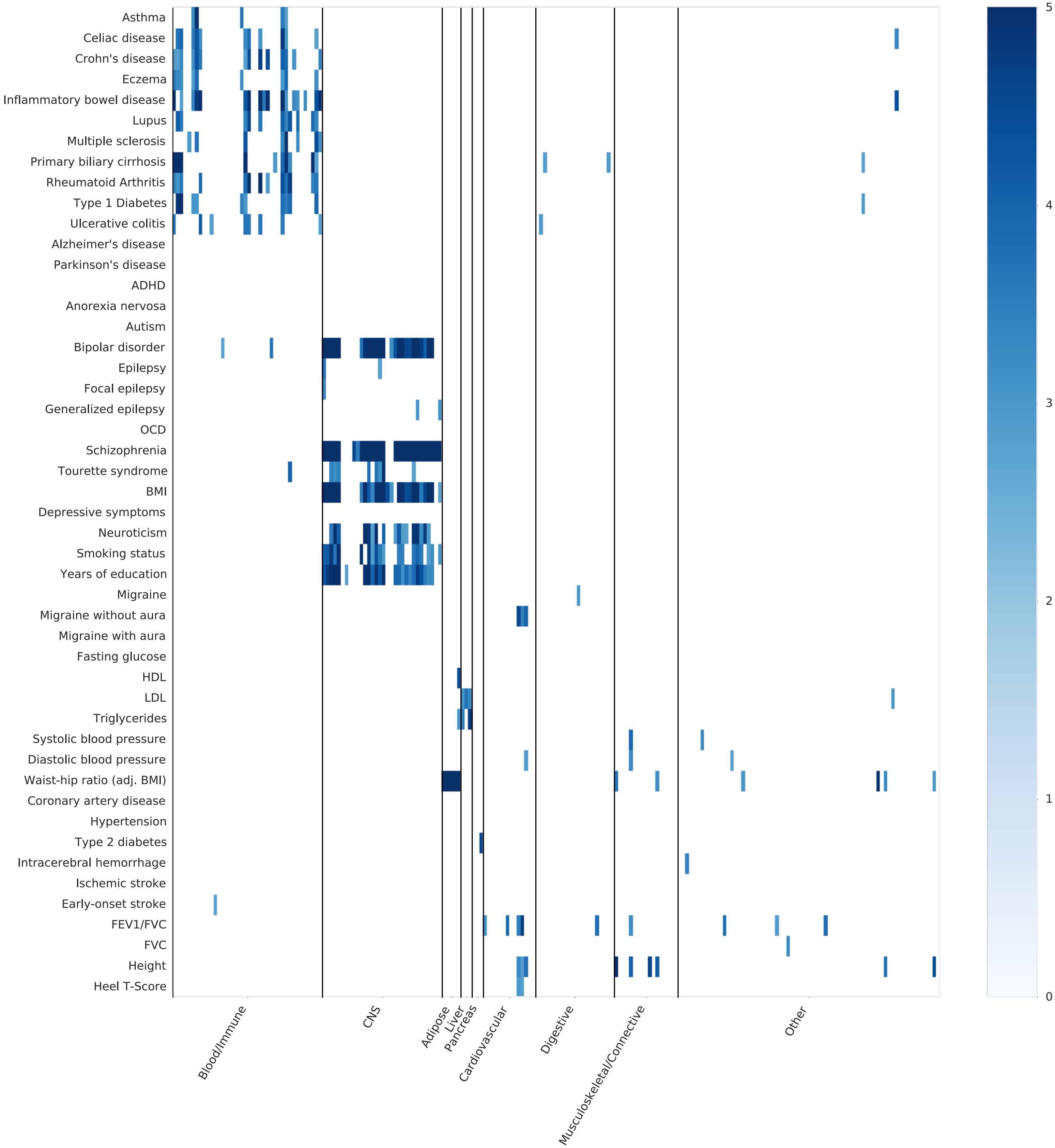


Figure S2d. Results of the multiple-tissue analysis with the window size changed from 100kb to 50kb. –log_10(P) is displayed, truncated at 5, for results that pass the FDR < 5% threshold of –$\log_{10}$(P)=2.78. GWAS data is described in **Table S4**, gene expression data is described in the Online Methods and **Tables S2-3**, and the statistical method is described in the Overview of Methods and the Online Methods.

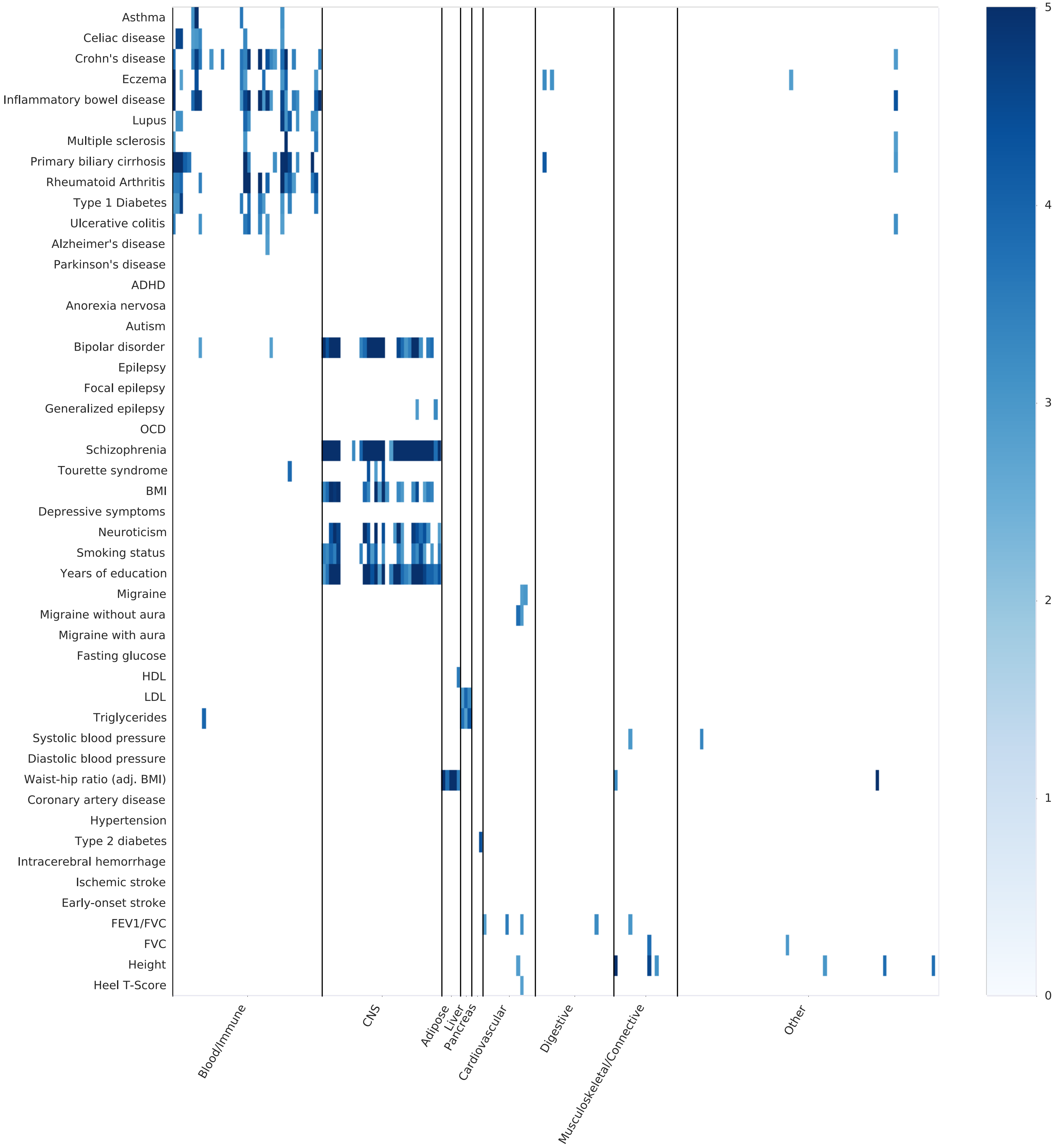


Figure S2e. Results of the multiple-tissue analysis with the window size changed from 100kb to 200kb. –log_10(P) is displayed, truncated at 5, for results that pass the FDR < 5% threshold of –log$_{10}$(P)=2.83. GWAS data is described in **Table S4**, gene expression data is described in the Online Methods and **Tables S2-3**, and the statistical method is described in the Overview of Methods and the Online Methods.

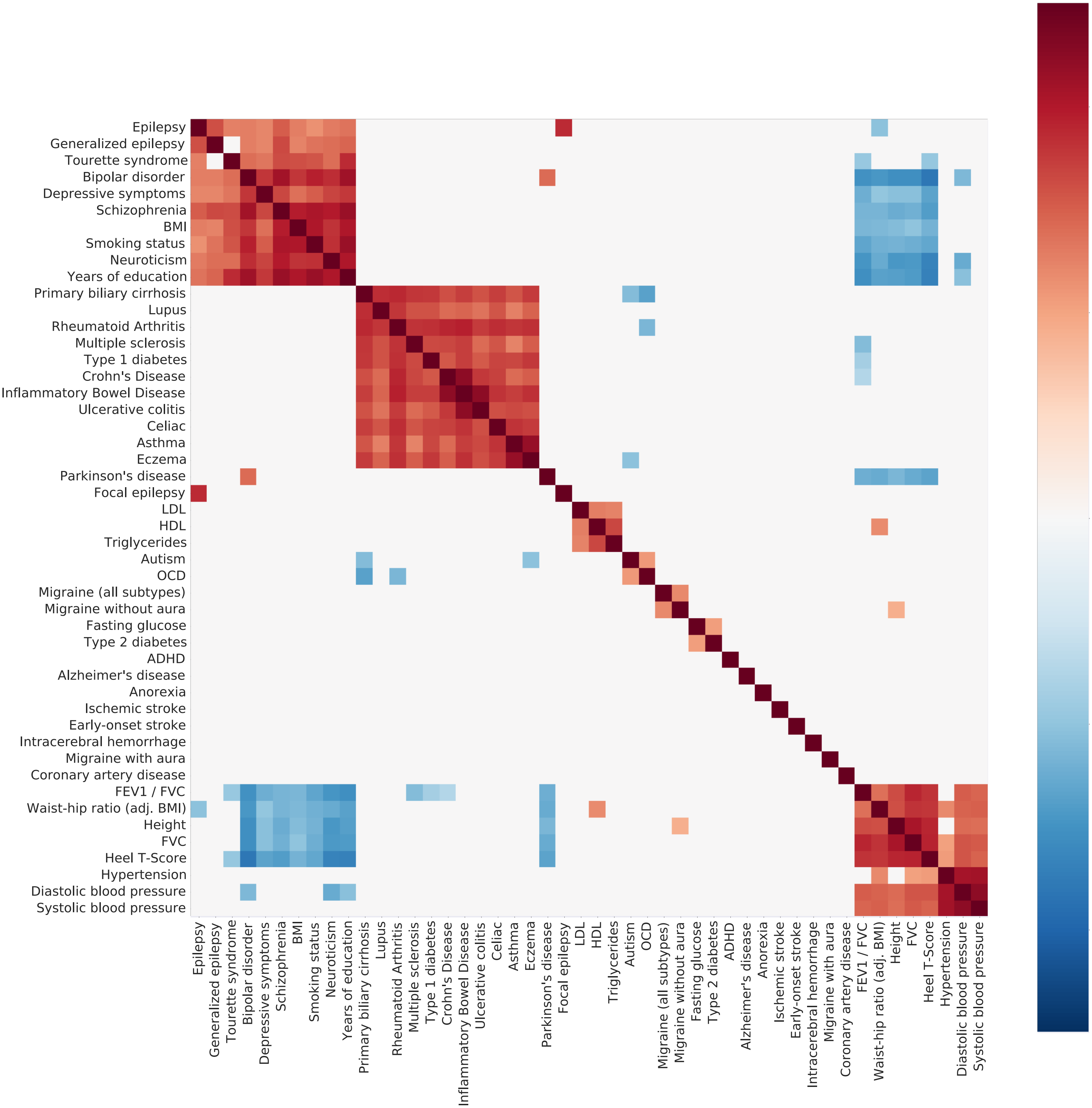


Figure S3. Estimates of enrichment correlations from the multiple-tissue analysis. Enrichment correlation estimates that pass the FDR<5% cutoff (two-sided test for difference from 0) are displayed. GWAS data is described in **Table S4**, gene expression data is described in the Online Methods and **Tables S2-3**, and the statistical method is described in the Online Methods.

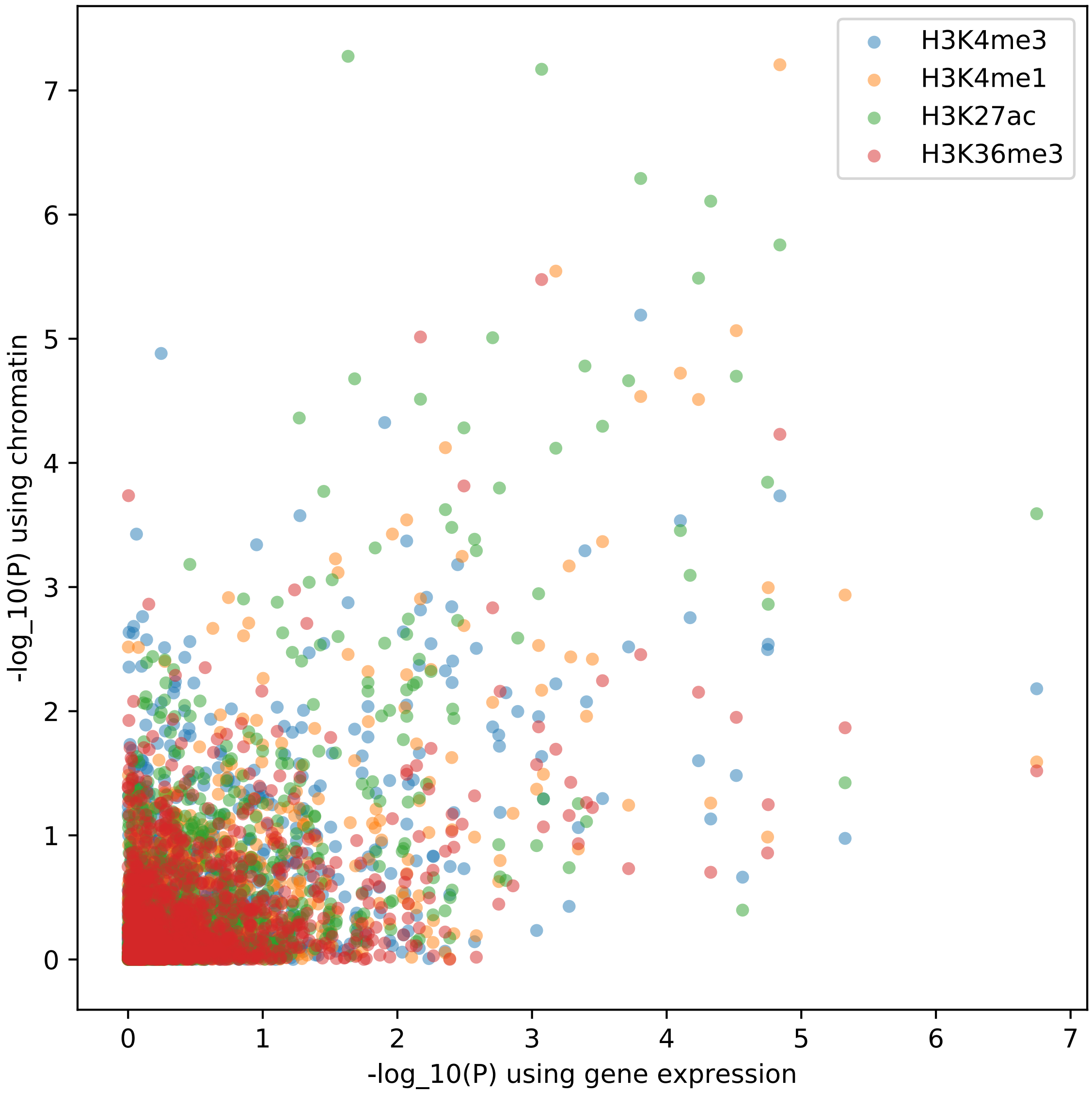


Figure S4. Comparison of GTEx and EN-TEx P-values. For each of 48 phenotypes, for each of 24 tissues shared between GTEx and EN-TEx, significance levels from the analysis using gene expression-based annotations are plotted against significance levels from the analysis using chromatin peaks.

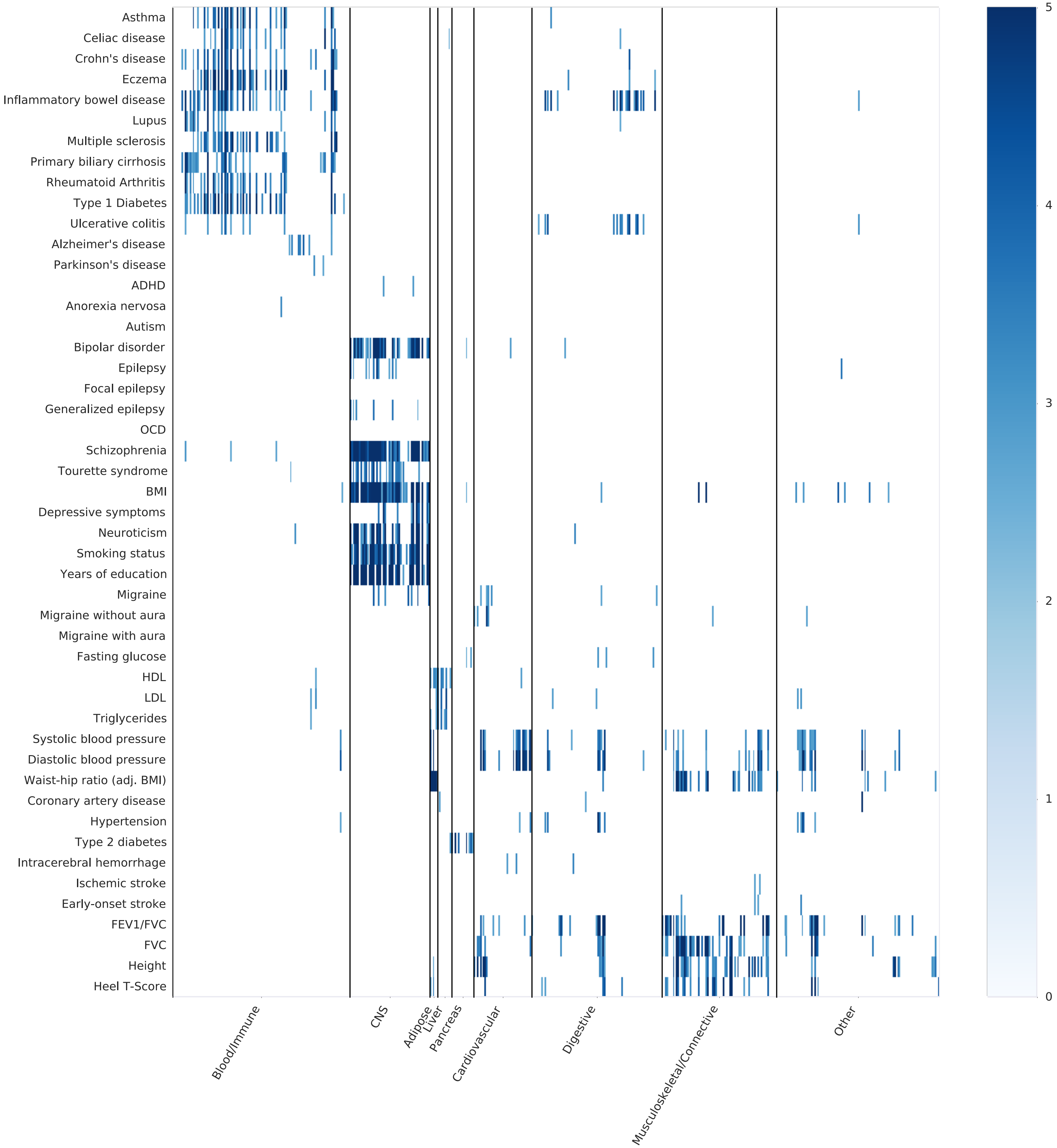


Figure S5. A heatmap of results from the analysis of 48 traits using chromatin data from the Roadmap Epigenomics project and ENCODE. –log_10(P) is displayed, truncated at 5, for results that pass the FDR < 5% threshold of –log_10(P) = 2.66. Numerical results are reported in **Table S7**. GWAS data is described in **Table S4**, chromatin data is described in the Online Methods and **Table S7**, and the statistical method is described in the Online Methods.

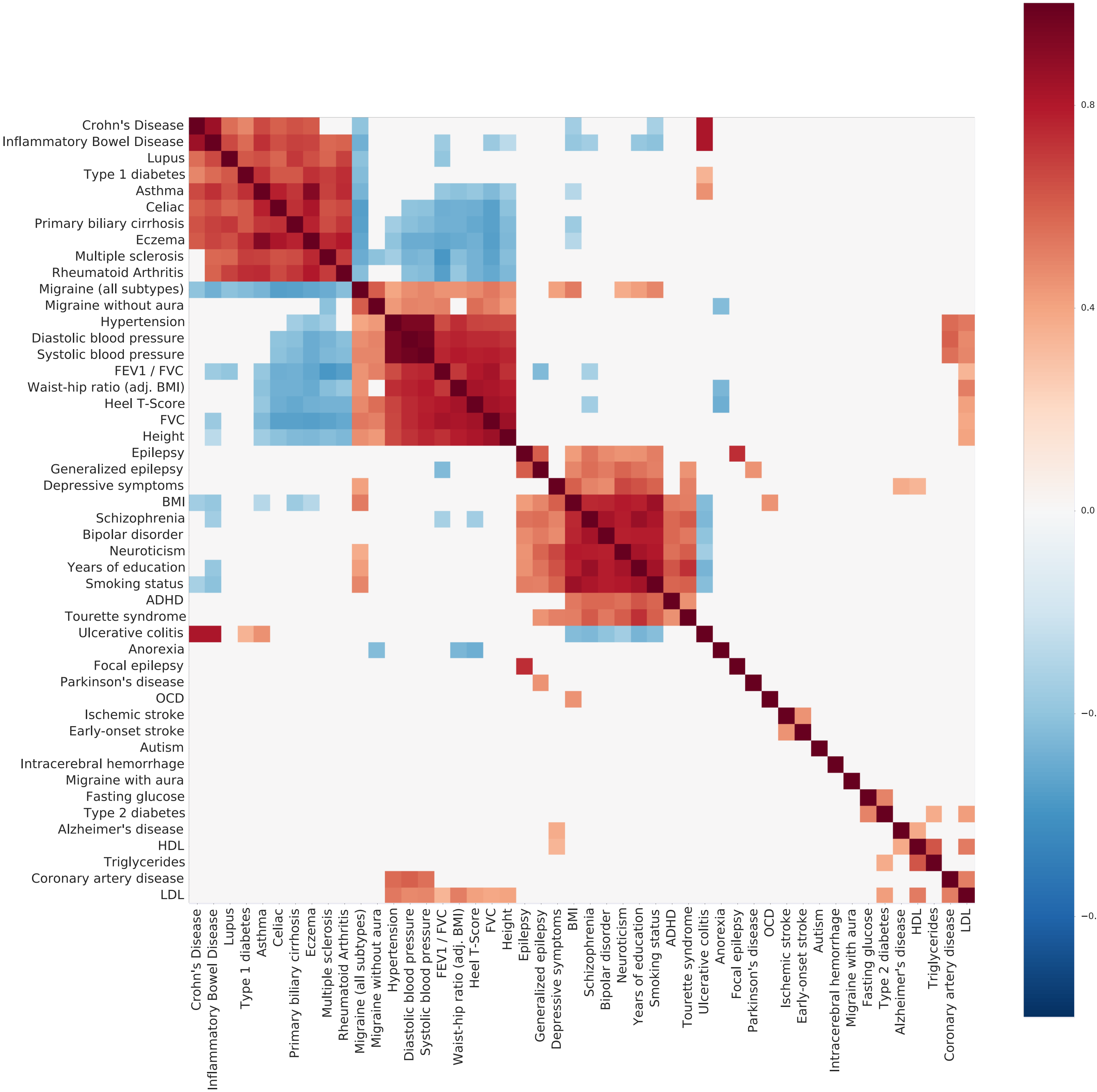


Figure S6. Estimates of enrichment correlations from the chromatin analysis. Enrichment correlation estimates that pass the FDR<5% cutoff (two-sided test for difference from 0) are displayed. GWAS data is described in **Table S4**, chromatin data is described in the Online Methods and **Table S7**, and the statistical method is described in the Online Methods.

Figure S7. (a) A heatmap of Jaccard indices among gene sets for the 13 brain regions in GTEx, in the multiple-tissue analysis. **(b)** A heatmap of Jaccard indices among gene sets for the 13 brain regions in GTEx, in the analysis of GTEx brain regions only. The data is described in the Online Methods and **Table S2** and the statistical method is described in the Overview of Methods and Online Methods.

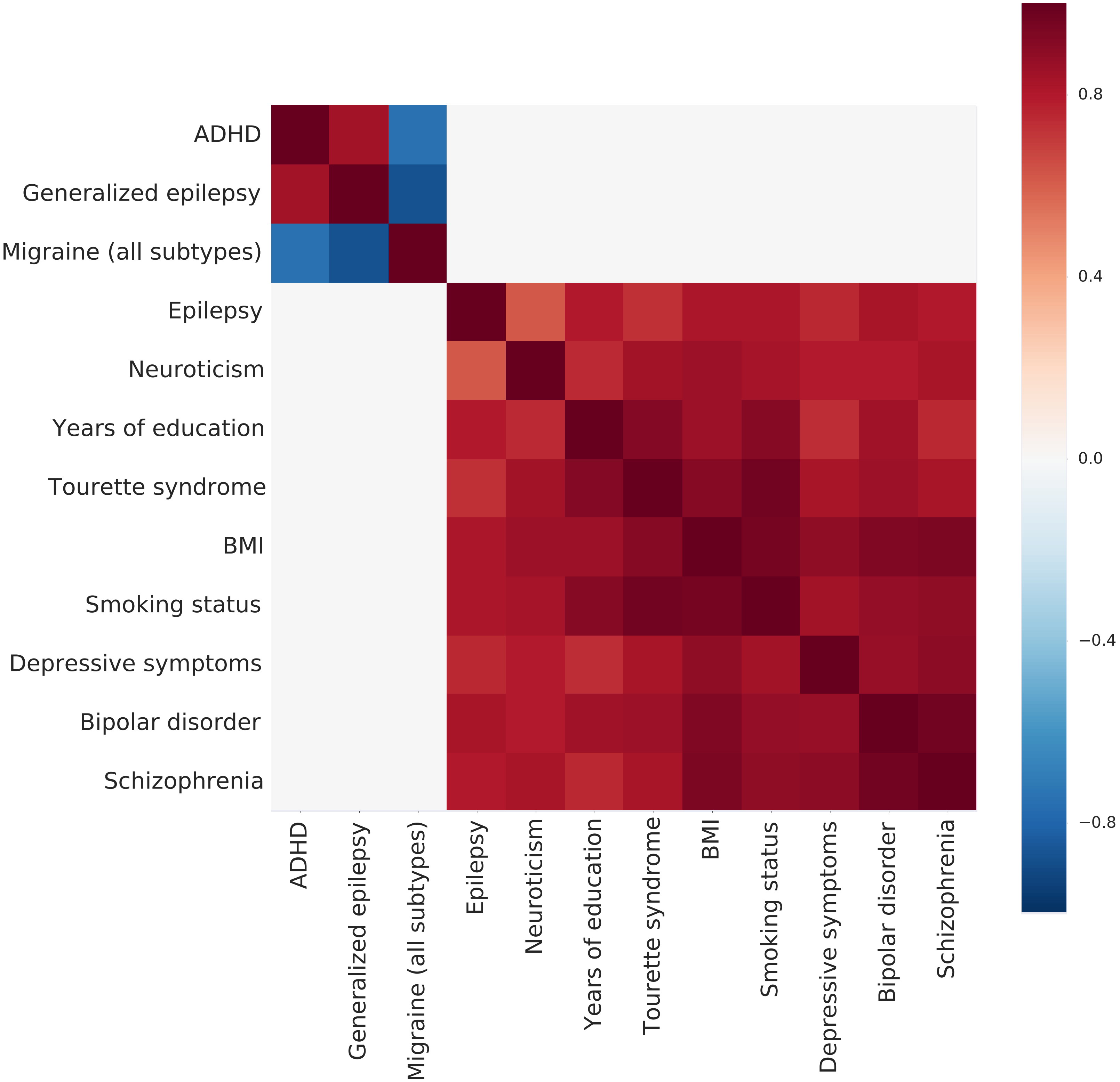


Figure S8. Estimates of enrichment correlations from the analysis of brain regions. Enrichment correlation estimates that pass the FDR<5% cutoff (two-sided test for difference from 0) are displayed. GWAS data is described in **Table S4**, gene expression data is described in the Online Methods and **Tables S2**, and the statistical method is described in the Online Methods.

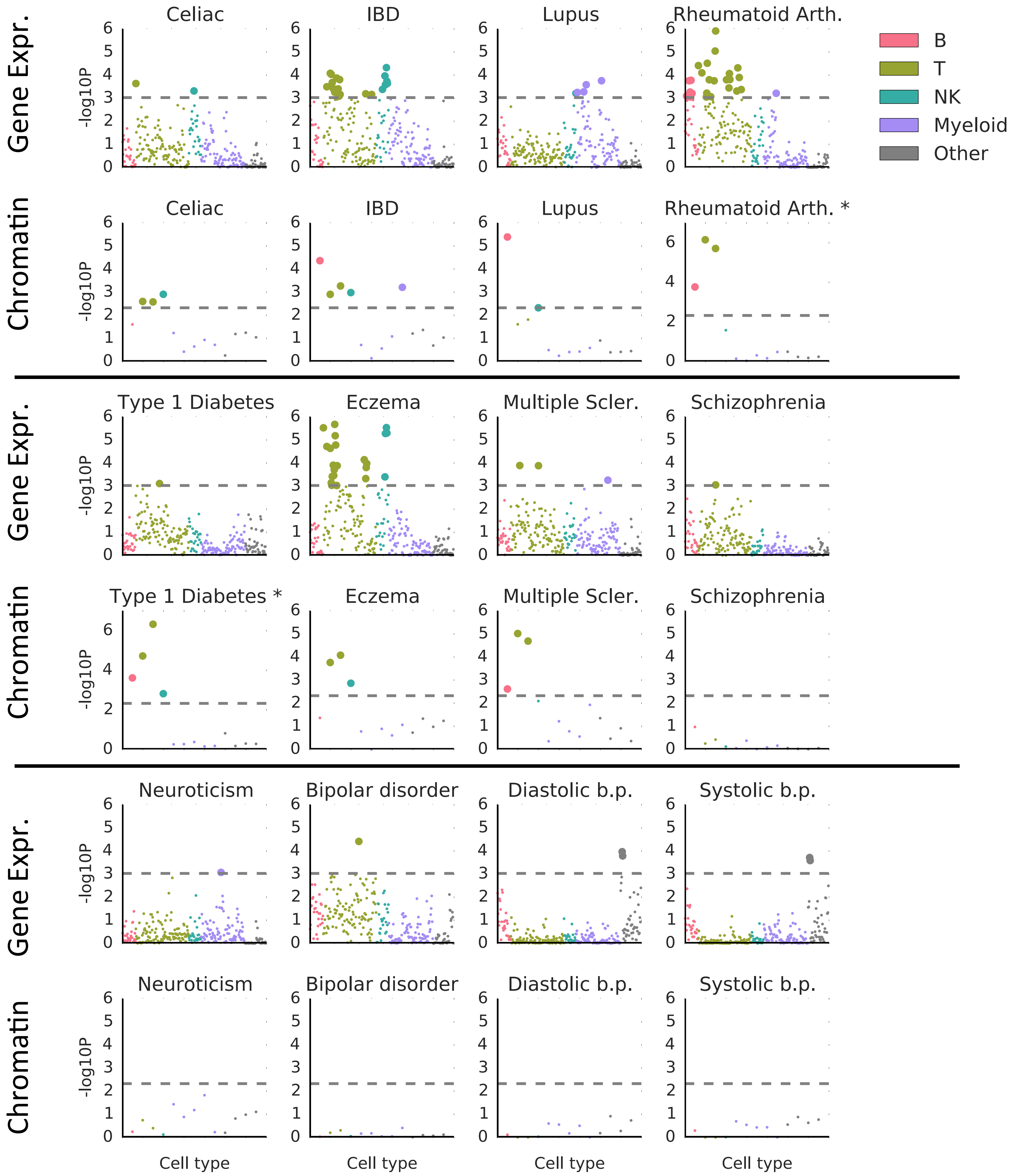


Figure S9. Results of the analysis of ImmGen gene expression data and hematopoiesis ATAC-seq data for traits with at least one ImmGen cell type passing FDR<5% not appearing in Figure 5. Large points passed the FDR<5% cutoff, $-\log_{10}(P)=3.03$ (ImmGen) or –log10(P)=2.32 (hematopoiesis). GWAS data is described in **Table S4**, gene expression and chromatin data is described in the Online Methods and **Table S10**, and the statistical method is described in the Overview of Methods and the Online Methods. Numerical results for all traits are reported in **Table S10**.

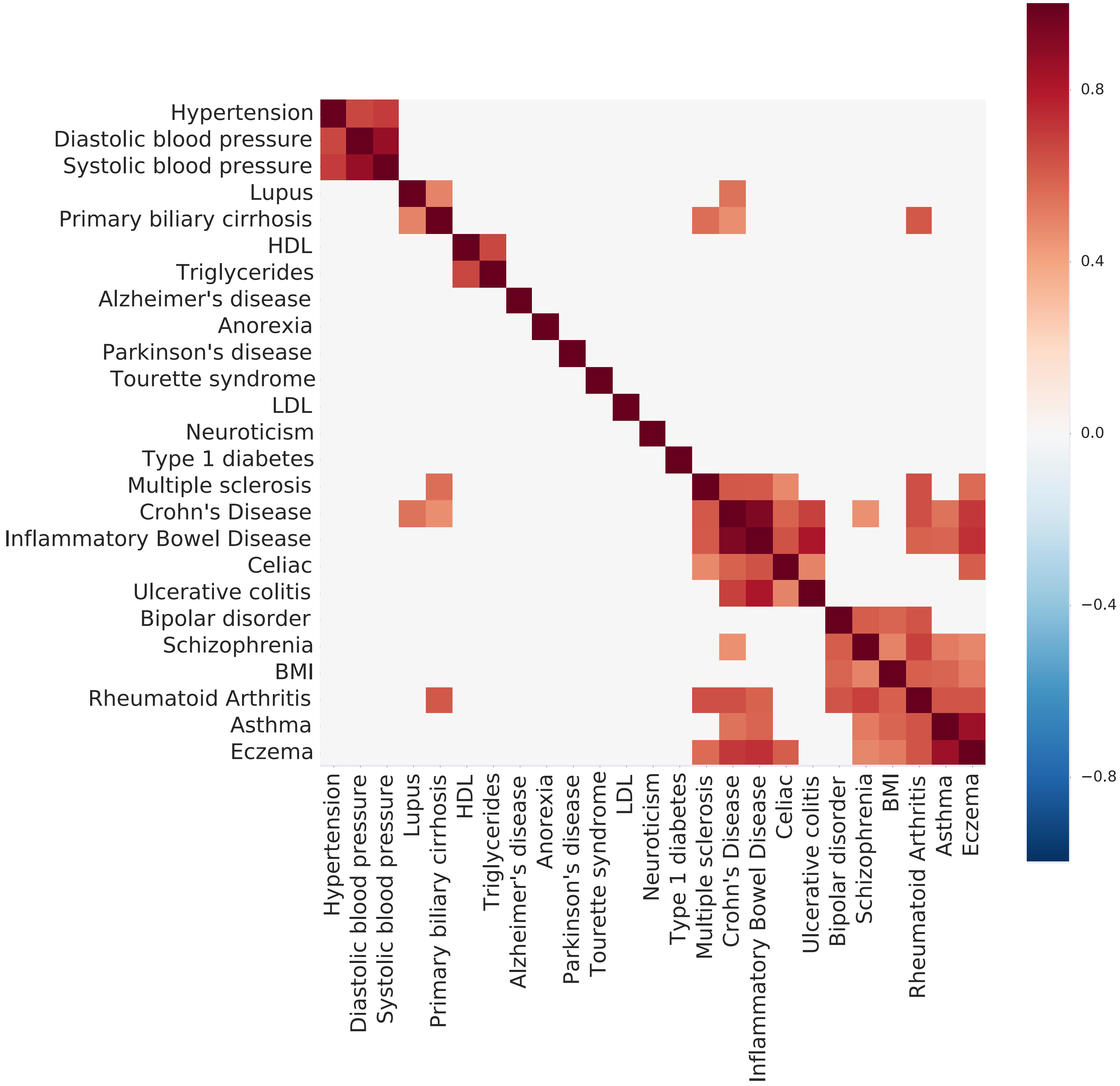


Figure S10. Estimates of enrichment correlations from the analysis of ImmGen data. Enrichment correlation estimates that pass the FDR<5% cutoff (two-sided test for difference from 0) are displayed. GWAS data is described in **Table S4**, gene expression and chromatin data is described in the Online Methods and **Table S10**, and the statistical method is described in the Online Methods.

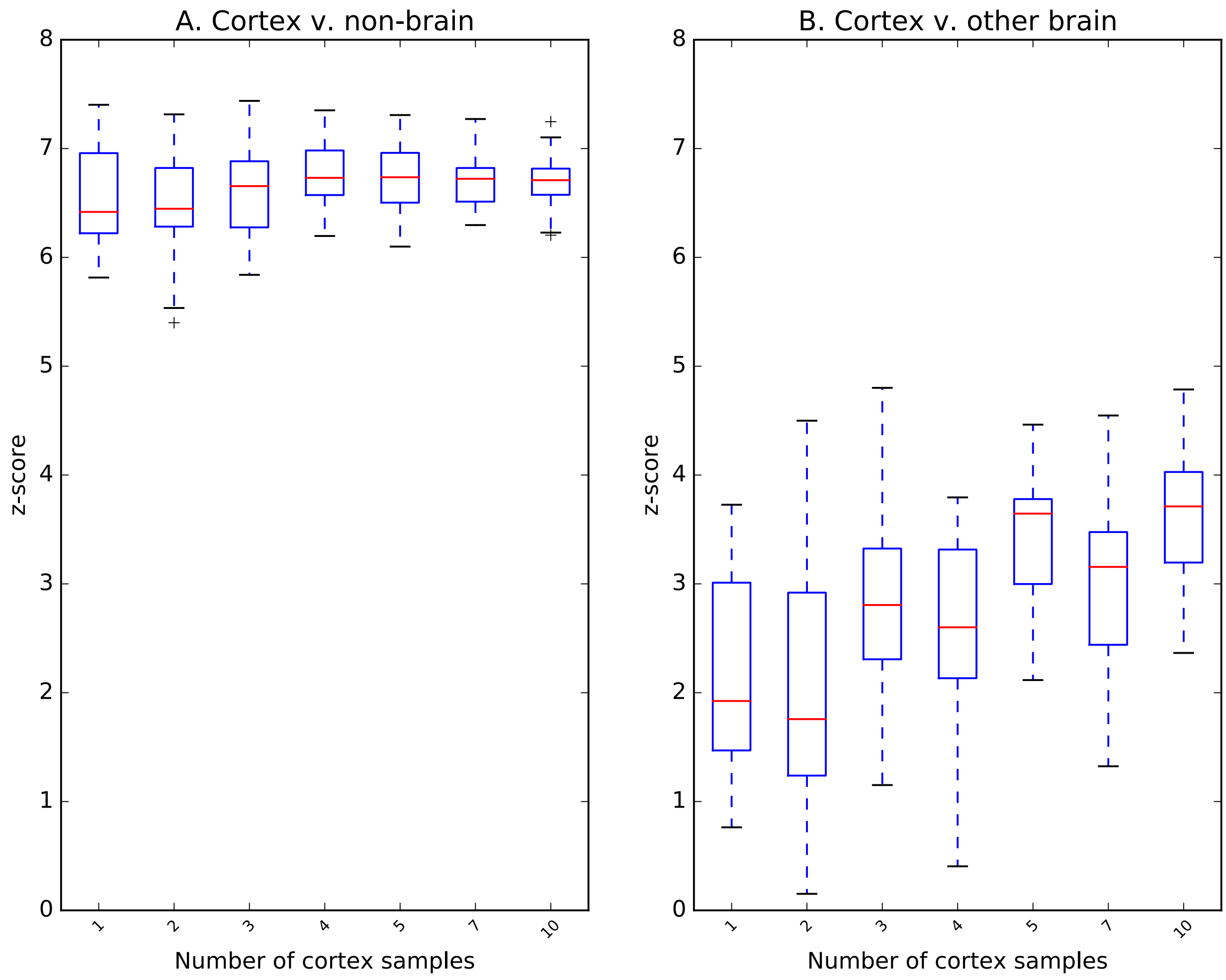


Figure S11. We repeatedly sub-sampled our dataset to a variety of sample sizes and ran our approach on the sub-sampled dataset. Each box plot represents the z-scores of 25 randomly sub-sampled datasets (center line, median; box limits, upper and lower quartiles; whiskers, max and min or 1.5x interquartile range; pluses, outliers). **(A)** We assessed cortex enrichment for schizophrenia in the multiple-tissue analysis, in which cortex was compared to all non-brain samples. We kept the ratio of cortex samples to non-brain samples constant as we downsampled. **(B)** We assessed cortex enrichment for schizophrenia in the analysis of GTEx brain regions, in which cortex was compared to all other brain samples. We kept the ratio of cortex samples to other brain samples constant as we downsampled.

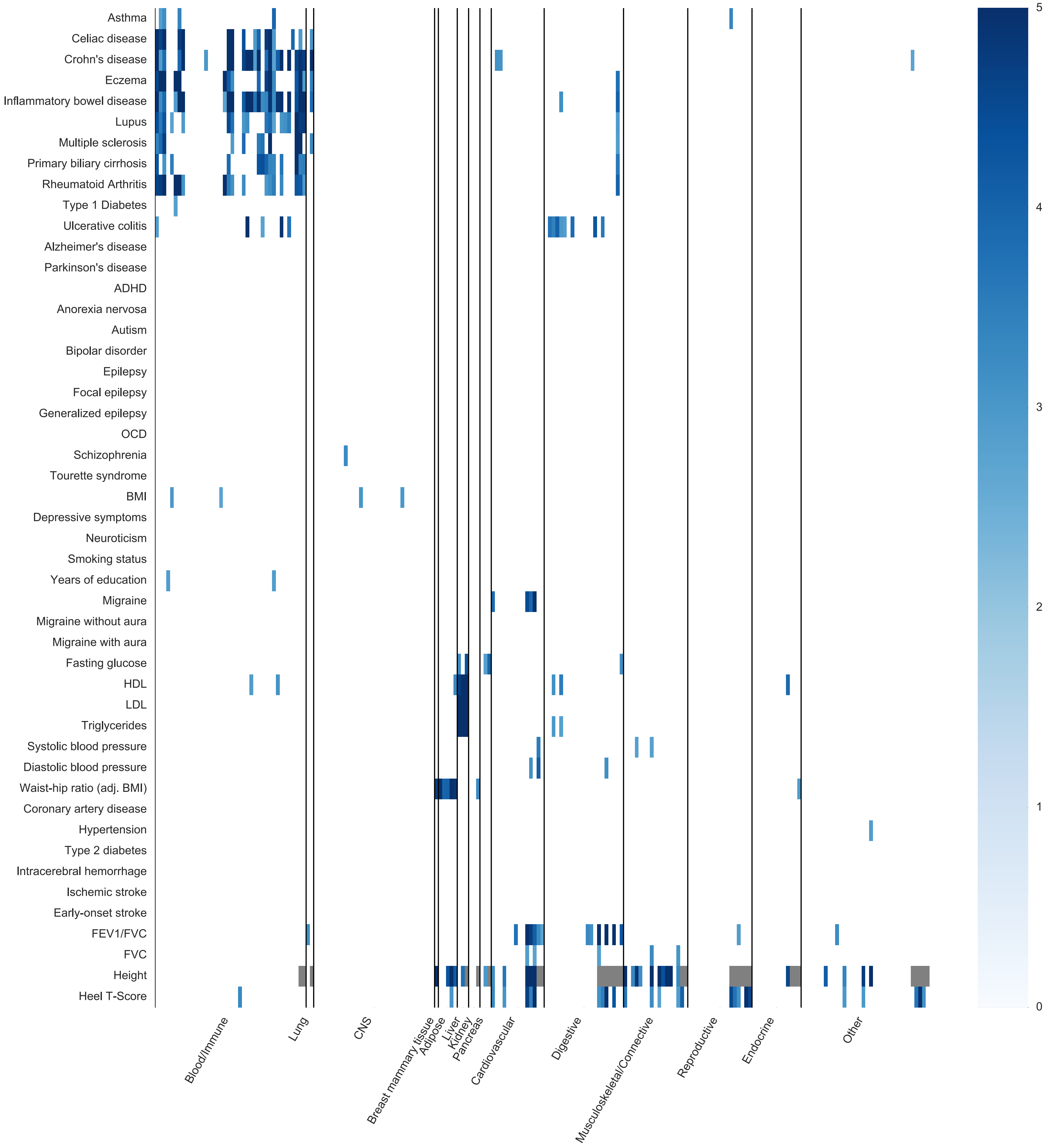


Figure S12. A heatmap of results from applying the SNPsea method to the gene expression data from the multiple-tissue analysis. –log_10(P) is displayed, truncated at 5, for results that pass the FDR<5% cutoff of $-\log_{10}(P)=2.74$. Grey boxes denote analyses that did not complete successfully at 8GB of RAM. GWAS data is described in **Table S4** and gene expression data is described in the Online Methods and **Tables S2-3**. Numerical results are reported in **Table S12**. SNPsea did not detect many of the CNS enrichments for brain-related traits identified by LDSC-SEG (see **Figure S2a** for comparison).

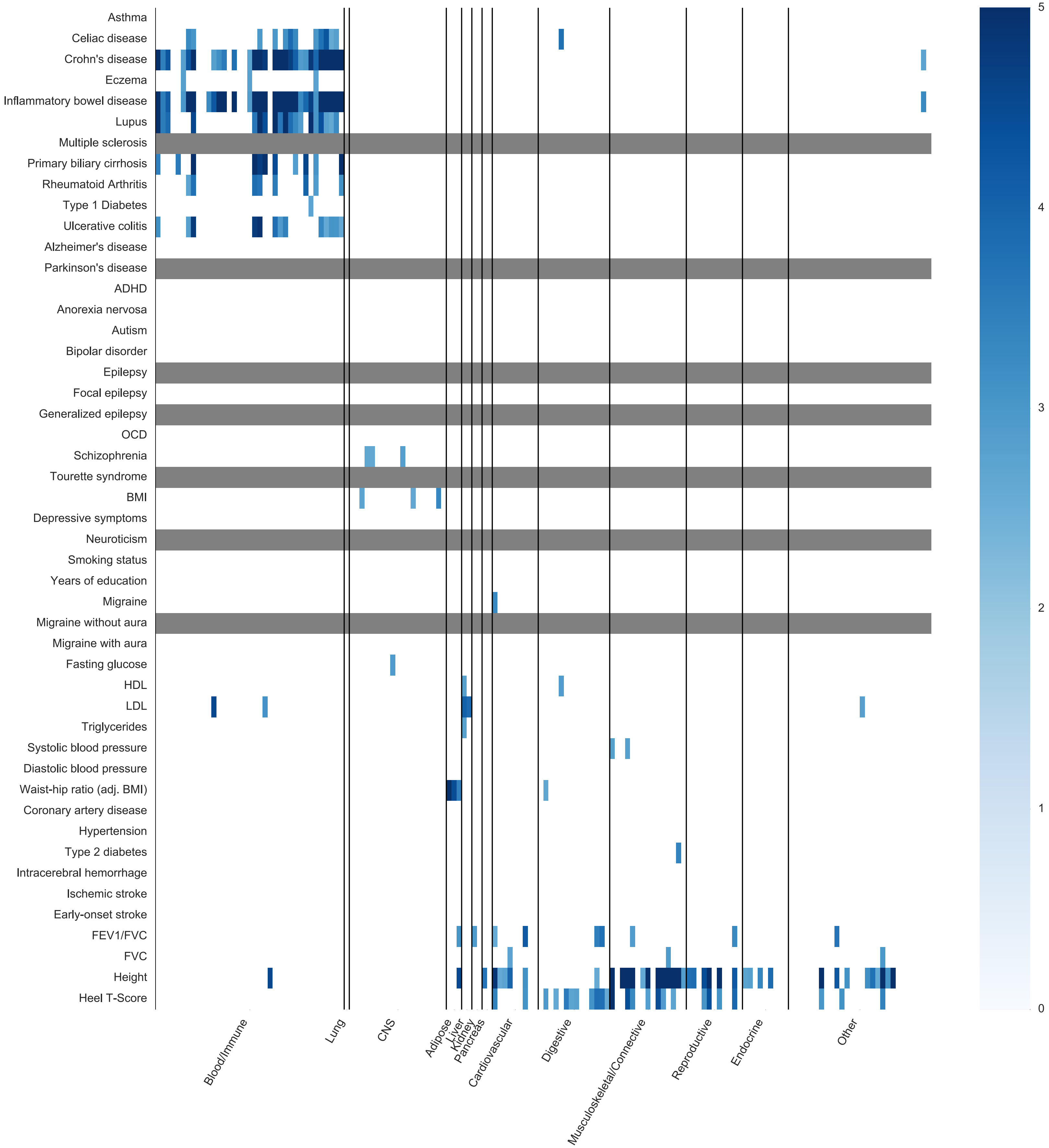


Figure S13. A heatmap of results from applying the DEPICT method with a P-value threshold of 5e-8 to the gene expression data from the multiple-tissue analysis. –log_10(P) is displayed, truncated at 5, for results that pass the FDR<5% cutoff of –log$_{10}$(P)=2.60. Grey boxes denote analyses that did not complete successfully. GWAS data is described in **Table S4** and gene expression data is described in the Online Methods and **Tables S3**. Numerical results are reported in **Table S13**. DEPICT with a threshold of 5e-8 did not detect many of the CNS enrichments for brain-related traits identified by LDSC-SEG (see **Figure S2a** for comparison).

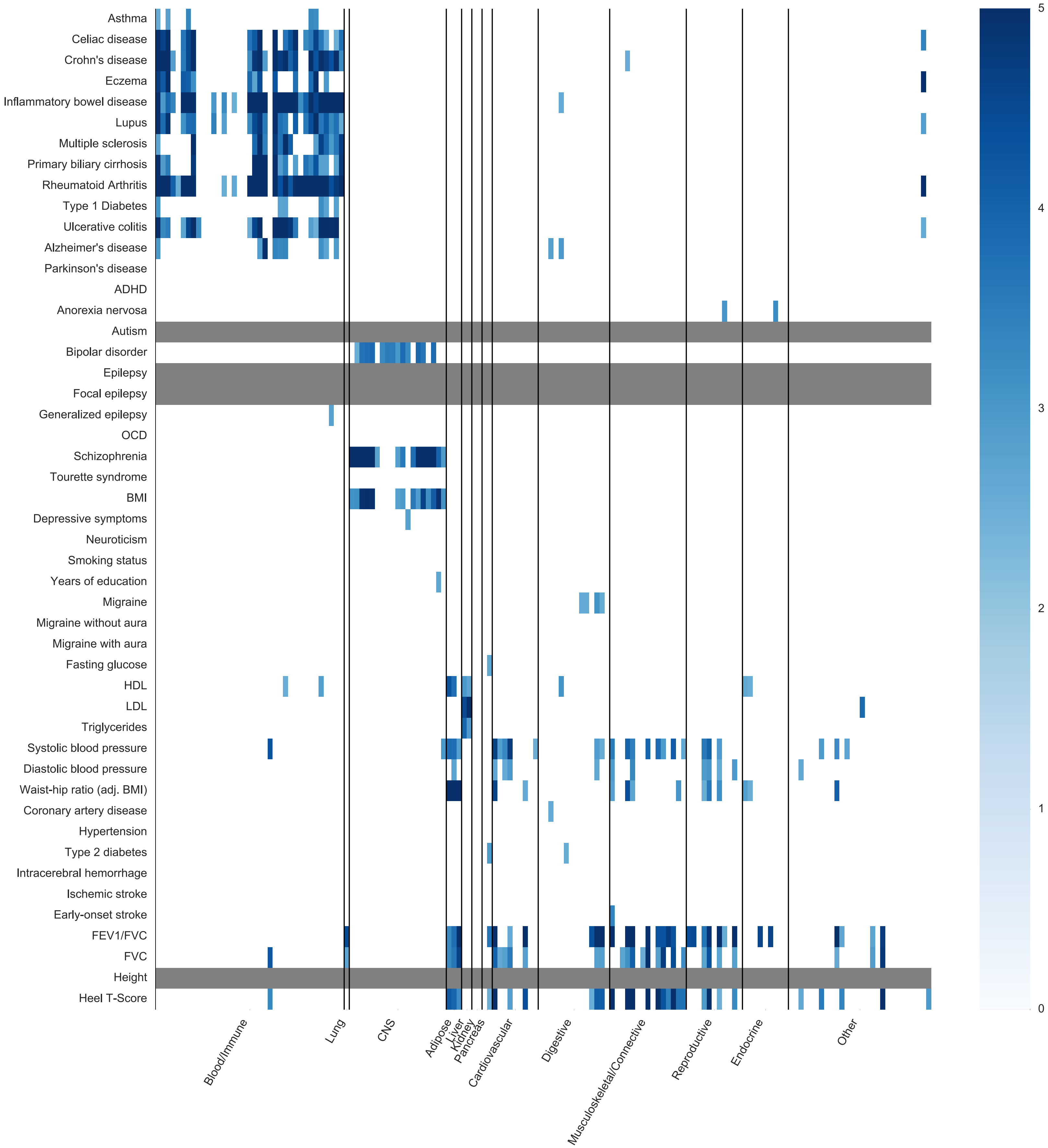


Figure S14. A heatmap of results from applying the DEPICT method with a P-value threshold of 1e-5 to the gene expression data from the multiple-tissue analysis. –log_10(P) is displayed, truncated at 5, for results that pass the FDR<5% cutoff of $-\log_{10}(P)=2.48$. Grey boxes denote analyses that did not complete successfully. GWAS data is described in **Table S4** and gene expression data is described in the Online Methods and **Tables S3**. Numerical results are reported in **Table S14**. DEPICT with a threshold of 1e-5 identified many enrichments, but in simulations did not have well-calibrated type I error (see **Figure S2a**).

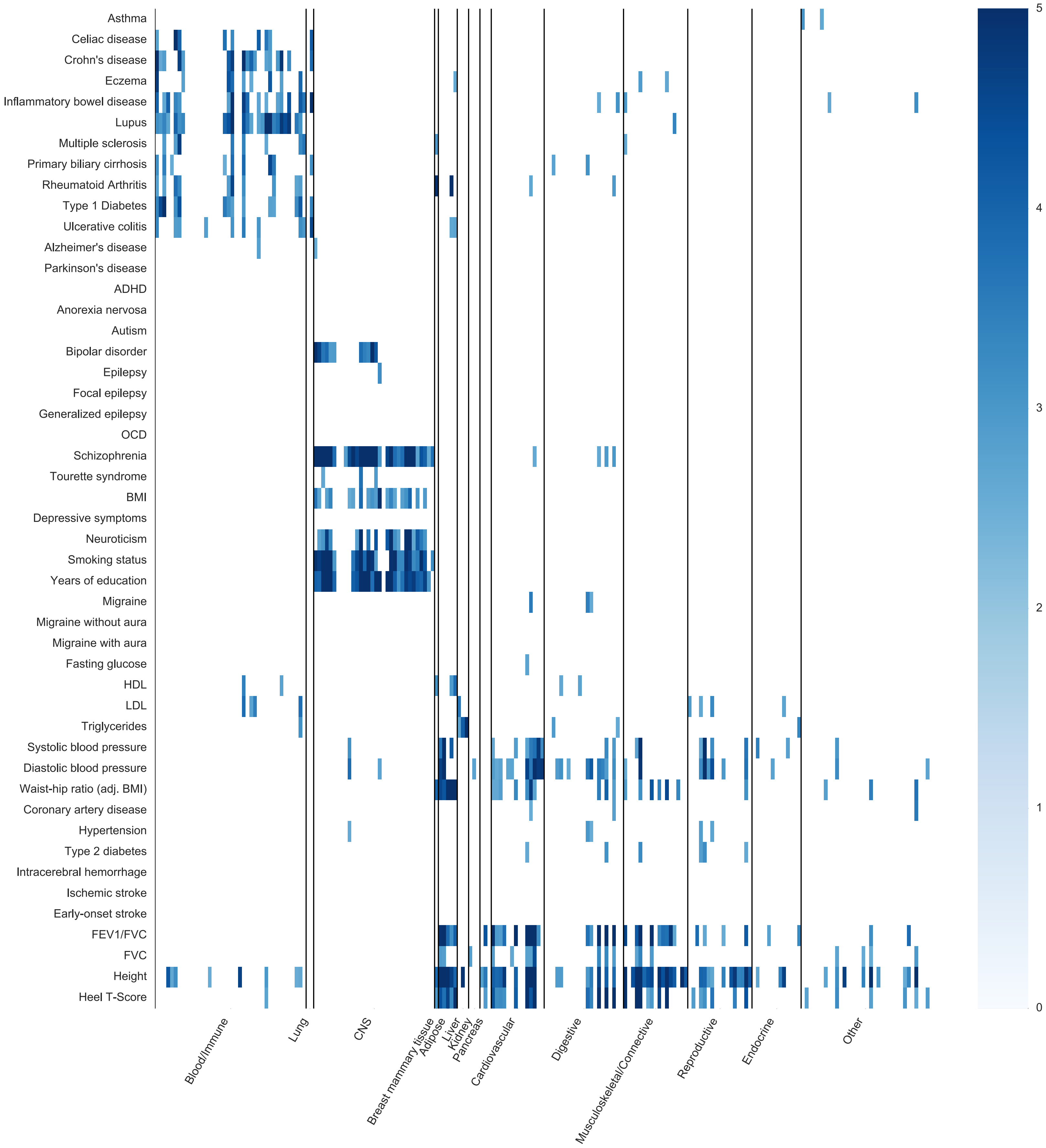


Figure S15. A heatmap of results from applying MAGMA to the specifically expressed gene sets from the multiple-tissue analysis. –log_10(P) is displayed, truncated at 5, for results that pass the FDR<5% cutoff of $-\log_{10}(P)=2.54$. GWAS data is described in **Table S4** and gene expression data is described in the Online Methods and **Tables S2-3**. Numerical results are reported in **Table S15**. MAGMA-SEG identified many enrichments, but in simulations did not have well-calibrated type I error (see **Figure S2a**).

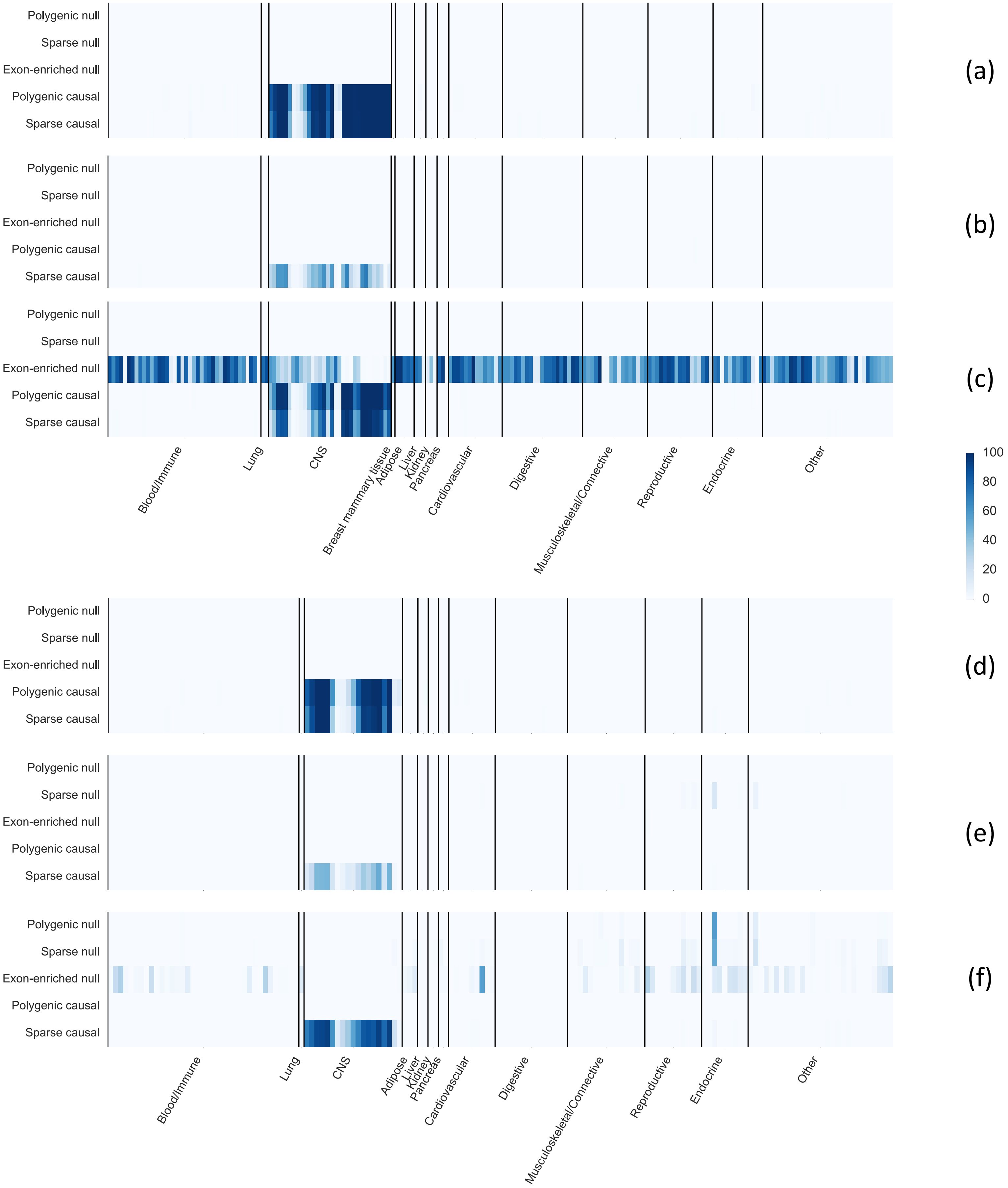
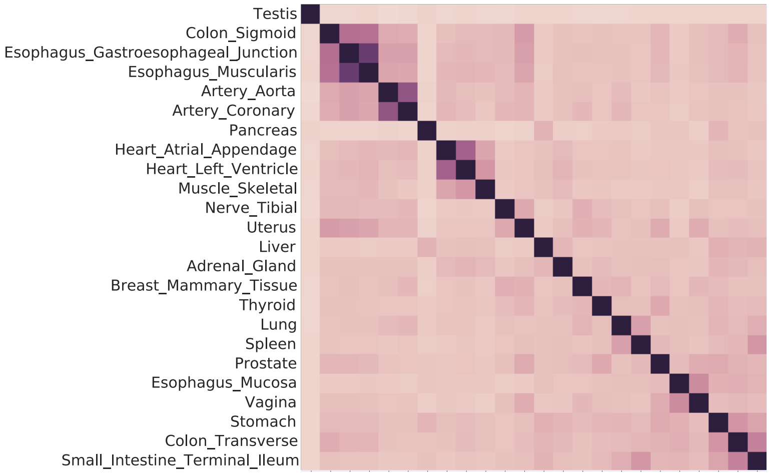


Figure S16. Number of the 100 simulated phenotypes that passed FDR < 5% for each method. Simulations are described in the Supplementary note, and have a sample size of n=47,360 individuals. (a) LDSC-SEG, (b) SNPsea, (c) MAGMA-SEG, (d)LDSC-SEG (Franke lab dataset only, included so that the comparison to DEPICT can be on the same set tissues/cell types), (e) DEPICT with 5e-8 cutoff, (f) DEPICT with 1e-5 cutoff. Numerical results are reported in **Table S16**.

(a) H3K27ac

(b) Gene expression - top 10% of genes by total expression



(c) Gene expression - top 10% of genes by specific expression

Figure S17. The Jaccard index between pairs of annotations. **(a)** Annotations are H3K27ac peaks from EN-TEx. **(b)** Annotations are 100kb windows around the top 10% of genes by total average expression in GTEx. **(c)** Annotations are 100kb windows around the top 10% of genes by specific expression in GTEx.