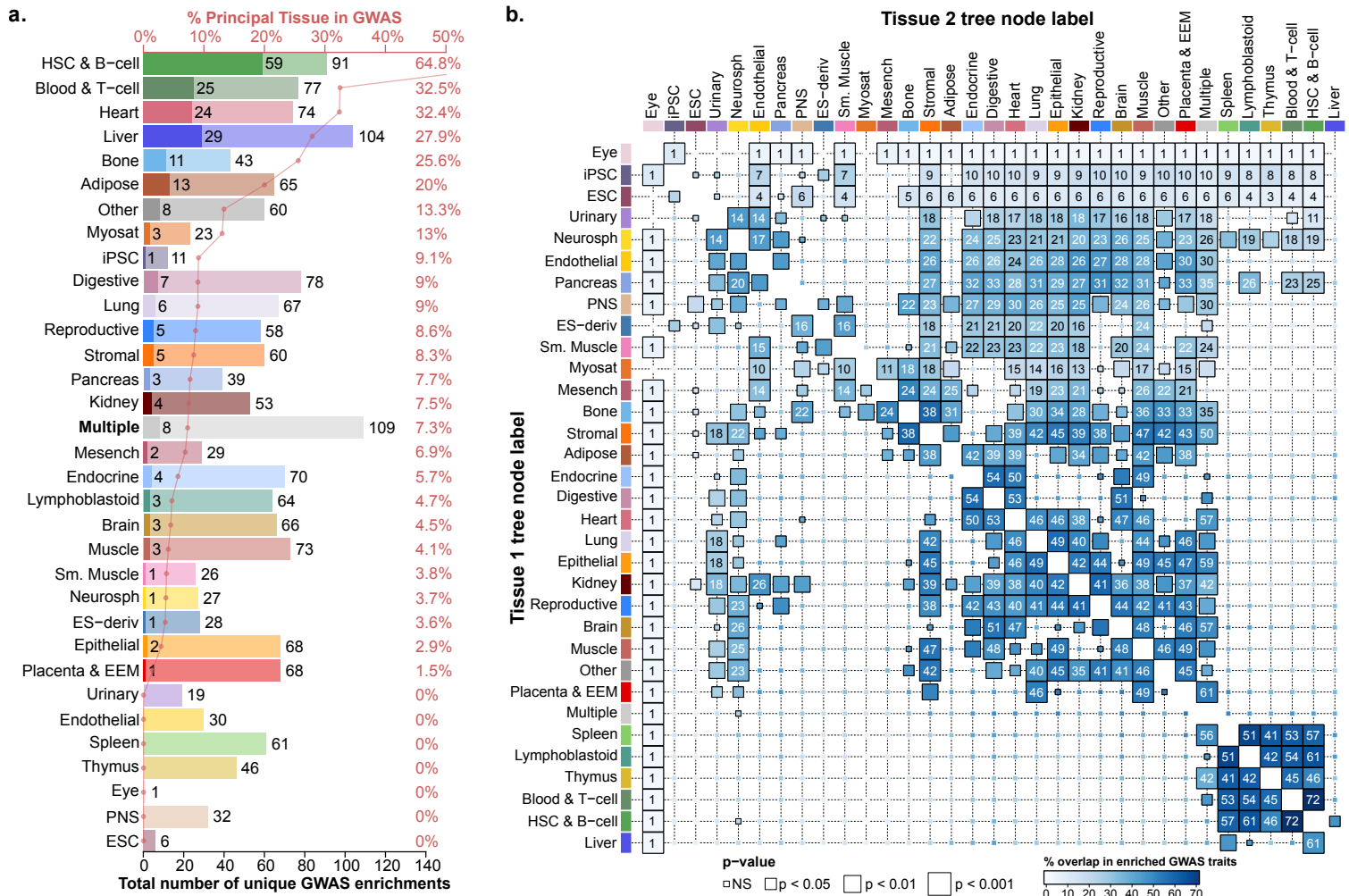


Extended Data Fig. 9 | GWAS tissue-prioritization. a, Trait-tissue enrichment (centre, heat map) between reported lead single-nucleotide polymorphisms (SNPs) from 226 genome-wide association studies (rows) and accessible active enhancers across 833 biosamples (columns) (FDR <1%). Enriched tissue groups (left) and number of enriched biosamples (right) shown for each trait. Only 83 representative traits labelled, using a bag-of-words approach (full list of traits in Supplementary Fig. 19). Traits coloured by sample with maximal trait-tissue enrichment. **b**, Contribution of each project to the maximum GWAS trait-tissue enrichment for the 226 traits with significant enrichments.



c.

T1	T2	Traits enriched in both tissues (tree node labels)
Liver	Adipose	HDL cholesterol (100%), HDL cholesterol (100%), Triglycerides (100%), HDL cholesterol (100%), HDL cholesterol (100%)
	Digestive	Liver enzyme levels (gamma-glutamyl transferase) (100%), C-reactive protein or LDL-cholesterol levels (pleiotropy) (100%), Total chol. levels (100%), HDL chol. (100%), HDL chol. (81.8%)
Liver	HSC & B-cell	C-reactive protein levels (100%), Mean corpuscular volume (100%), Platelet count (100%), Red cell distribution width (96.6%), Mean corpuscular hemoglobin concentration (96%)
	Blood & T-cell	Platelet count (47.5%), Hypothyroidism (41.2%), Rheumatoid arthritis (ACPA-positive) (39.6%)
Heart	Pancreas	Estimated glomerular filtration rate (33.3%), Hematocrit (16.7%), Cardiovascular disease (11.5%), Hemoglobin concentration (11.2%), Gamma glutamyl transferase levels (9.1%)
	Bone	Pulse pressure (32.1%), Systolic blood pressure (26.9%), Systolic blood pressure (25.5%), Body fat distribution (leg fat ratio) (15%), Body fat distribution (trunk fat ratio) (15%)
Heart	Adipose	Pulse pressure (64.5%), Pulse pressure (32.1%)
	Muscle	Atrial fibrillation (84.1%), Atrial fibrillation (81.2%), Systolic blood pressure (76.9%), Body fat distribution (trunk fat ratio) (45%), Heel bone mineral density (43%)
Adipose	Endocrine	PR interval (86.3%), Resting heart rate (81%), Atrial fibrillation (73.9%), Atrial fibrillation (67.5%), P wave duration (66.7%)
	Endothelial	Coronary artery disease (13.7%), Plateletcrit (4.9%), Platelet distribution width (4.6%), Platelet count (4.4%), Waist-hip ratio (4.2%)
Adipose	Stromal	WHR adj. for BMI (smoking interaction) (100%), WHR adj. for BMI (57.1%), WHR adj. for BMI (48.3%), Balding type 1 (44.7%), Waist circumference adj. for BMI (33.6%)
	Heart	Pulse pressure (64.5%), Pulse pressure (32.1%)
Adipose	Heart	WHR adj. for BMI (adj. for smoking) (62.5%), WHR adj. for BMI (57.1%), Heel bone mineral density (41.1%), WHR adj. for BMI (physical activity interaction) (40%), WHR adj. for BMI x sex x age interaction (4df test) (39.8%)
	Muscle	WHR adj. for BMI (adj. for smoking) (62.5%), WHR adj. for BMI (57.1%), Heel bone mineral density (41.1%), WHR adj. for BMI (physical activity interaction) (40%), WHR adj. for BMI x sex x age interaction (4df test) (39.8%)

Extended Data Fig. 11 | Tissue-tissue GWAS relationships. Principal and partner tissue enrichments. **a.** For each tree node label (rows), the number of GWAS traits (black x-axis, bottom) showing maximum enrichment in that tree node (dark bars, principal tissue) or any enrichment in that tree node (light bars, partner tissue), and the percentage of tissue-enriched traits for which the tissue shows the maximal enrichment (red x-axis, top) across 232 traits. **b.** Overlap in enriched GWAS traits between pairs of tissues with maximal enrichment in the trait (principal tissue, rows) and lower enrichment in the same trait (partner tissue, columns), using tree node labels. **c.** Top traits in significant interactions for selected tissue pairs (liver, endocrine, muscle, heart, adipose, PNS). For each pair of co-enriched tissue groups we reported the top 5 GWAS by their per cent of significant enrichments coming from either group.

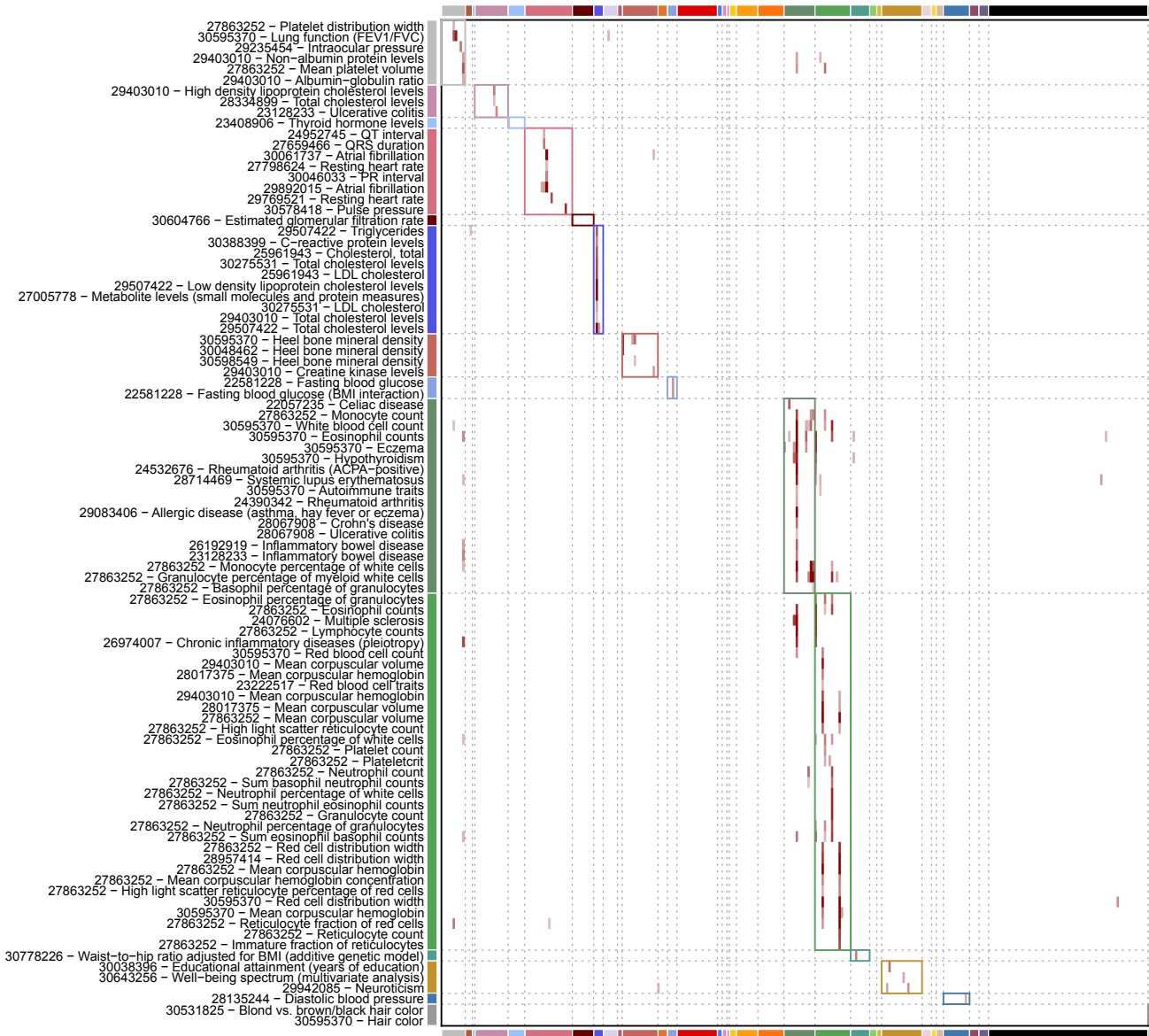


Figure S20: All module trait enrichments at FDR of 1%, for 93 traits (rows) and 300 modules (columns). Modules are ordered as in Figure 2a.

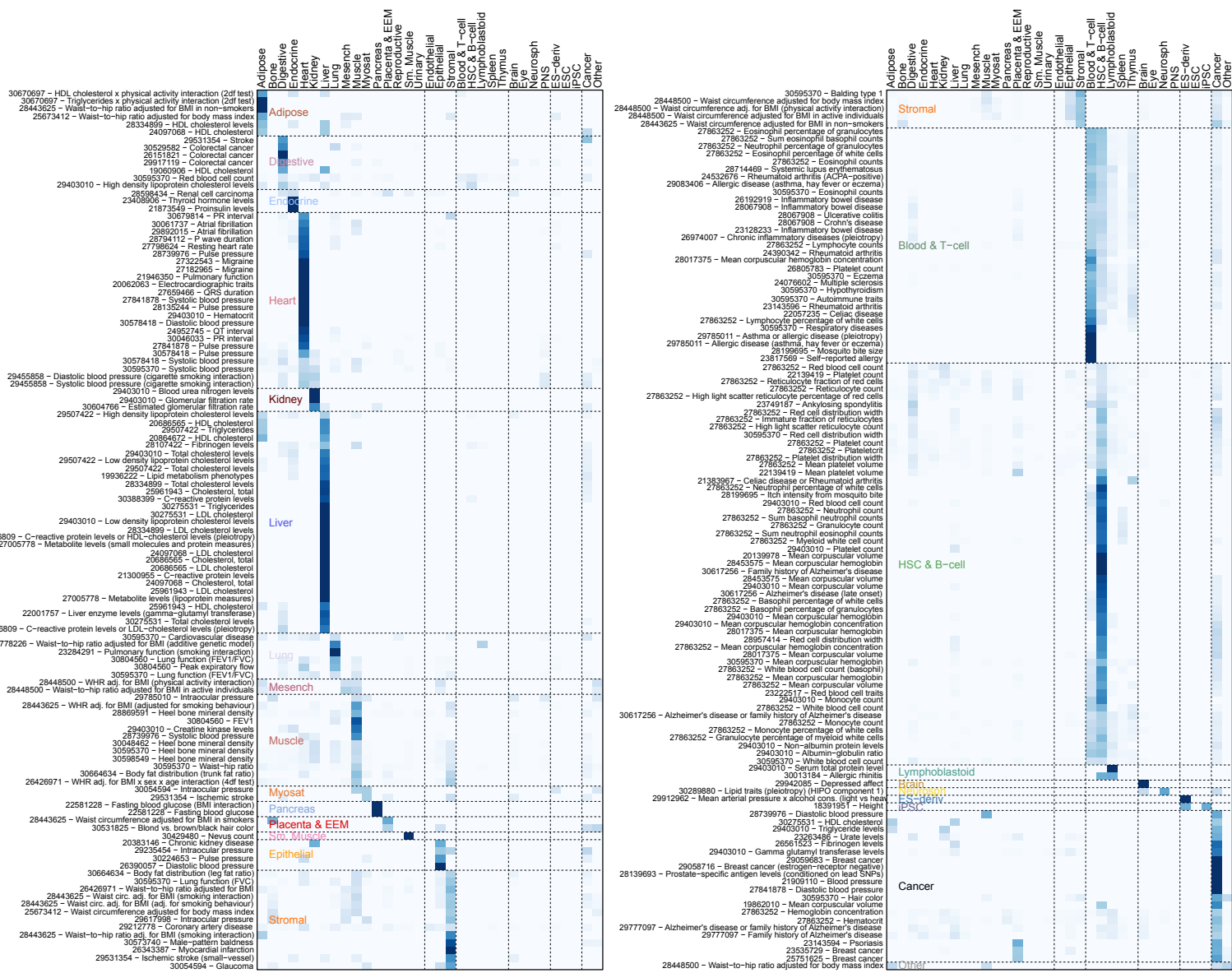


Figure S21: Overall tissue-level prioritization of 230 traits at FDR of 1%. Heatmap represents trait (rows) vs. tissue matrix and is split for visibility. Traits are diagonalized according to their top tissue enrichment, and values are the trait-normalized and tissue aggregated $-\log_{10}$ p-values.

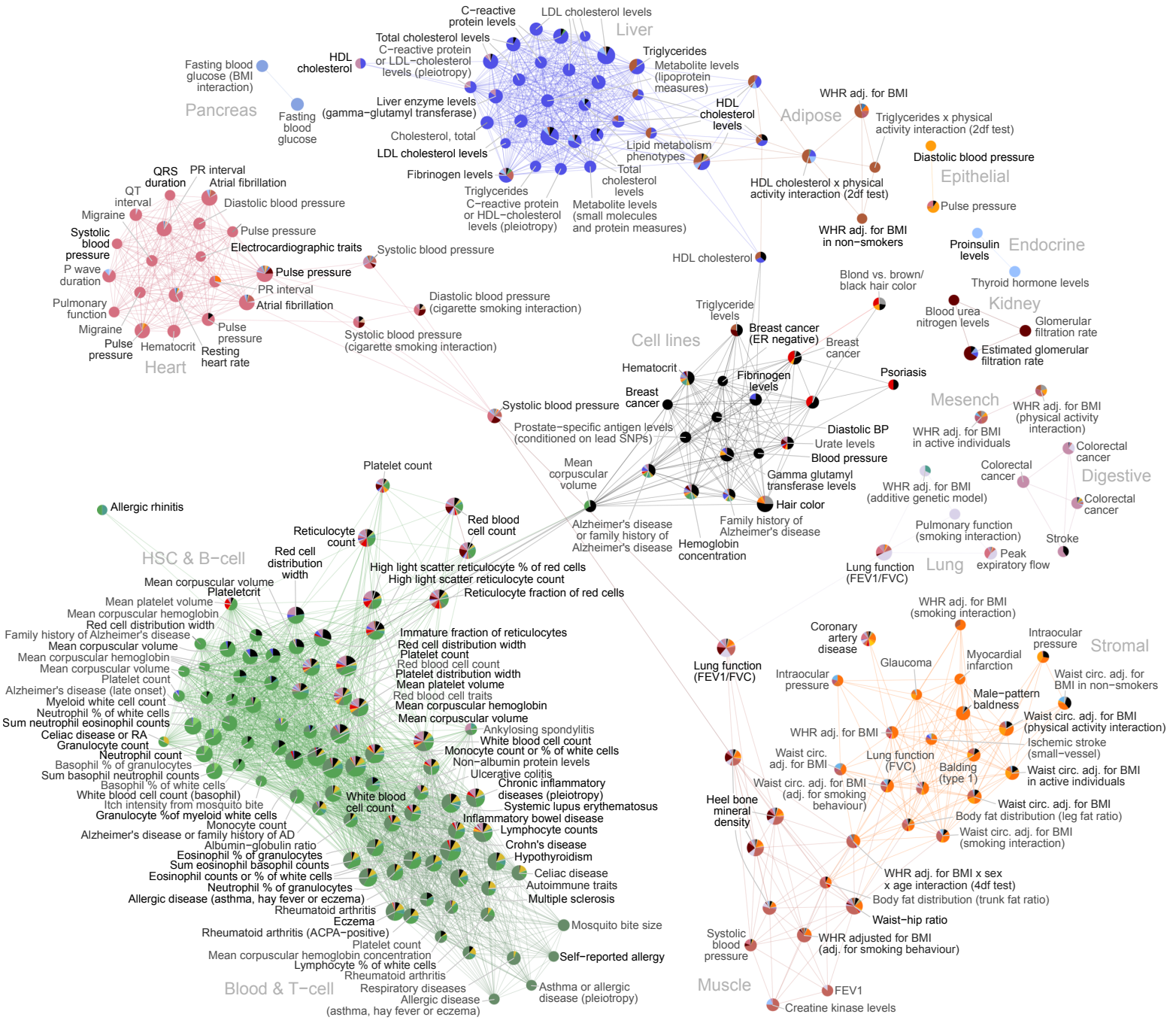
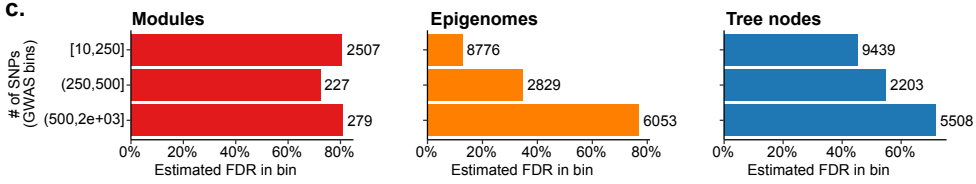
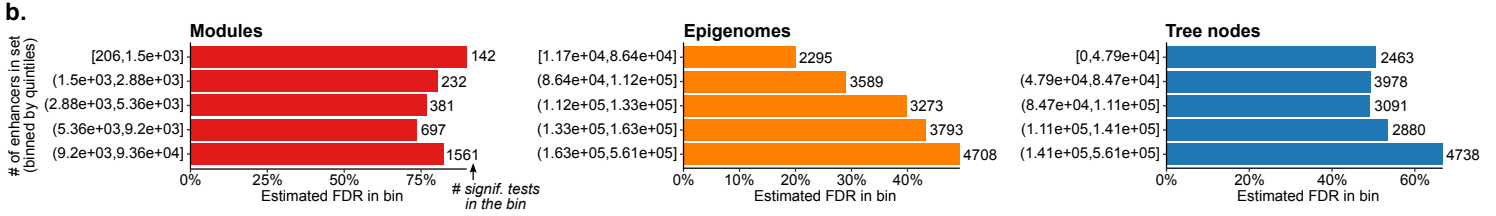
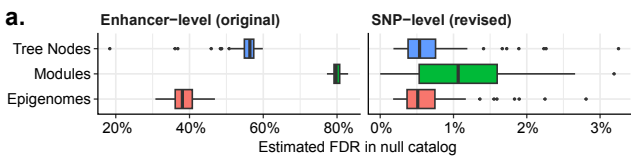


Figure S22: Trait-trait network (as Figure 3) across 215 traits by similarity of epigenetic enrichments (cosine similarity ≥ 0.75), laid out using the Fruchterman-Reingold algorithm. Traits (nodes) are colored by contributing groups (pie chart by fraction of $-\log_{10}p$, size by maximal $-\log_{10}p$) and interactions (edges) by the group with maximal dot product of enrichments between two traits. All 215 traits labeled.



Empirical FDR for original and revised EpiMap GWAS enrichment analyses. **a.** Empirical FDR estimates for three GWAS enrichments analyses (on epigenomes, modules, and tree nodes) for original and revised methodologies. **b.** Empirical FDR estimates for enhancer sets, binned by number of enhancers in the set for each of the original three analyses. Numbers are the number of original enrichments in each bin. **c.** Empirical FDR estimates for GWAS, binned by number of SNPs in each GWAS for each of the original three analyses. Numbers are the number of original enrichments in each bin.