

A multi-layer functional genomic analysis to understand noncoding genetic variation in lipids

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In this study, we present a multi-layer framework to combine the largest multi-ancestry GWAS to date on lipid levels with both transcriptomic and epigenomic datasets to prioritize regulatory variants, effector genes, cell types, and tissues with strong functional relevance to lipid biology.

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A multi-layer functional genomic analysis to understand noncoding genetic variation in lipids

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Summary

A major challenge of genome-wide association studies (GWAS) is to translate phenotypic associations into biological insights. Here, we integrate a large GWAS on blood lipids involving 1.6 million individuals from five ancestries with a wide array of functional genomic datasets to discover regulatory mechanisms underlying lipid associations. We first prioritize lipid-associated genes with expression quantitative trait locus (eQTL) colocalizations and then add chromatin interaction data to narrow the search for functional genes. Polygenic enrichment analysis across 697 annotations from a host of tissues and cell types confirms the central role of the liver in lipid levels and highlights the selective enrichment of adipose-specific chromatin marks in high-density lipoprotein cholesterol and triglycerides. Overlapping transcription factor (TF) binding sites with lipid-associated loci identifies TFs relevant in lipid biology. In addition, we present an integrative framework to prioritize causal variants at GWAS loci, producing a comprehensive list of candidate causal genes and variants with multiple layers of functional evidence. We highlight two of the prioritized genes, *CREBRF* and *RRBP1*, which show convergent evidence across functional datasets supporting their roles in lipid biology.

Introduction

Most GWAS findings have not directly led to mechanistic interpretations, largely because approximately 90% of GWAS associations map to noncoding sequences.^{1,2} Mech-

anistic interpretations in GWAS have proven challenging because the strongest signals identified in GWAS typically contain many variants in strong linkage disequilibrium (LD)³ and functional mechanisms including genes of action are often not clear from GWAS data alone.^{4,5}

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Linking trait-associated variants to genome function has emerged as a promising model for mechanistic interpretation of noncoding findings in GWAS. This “variant-to-function” model is premised on recent observations that noncoding variants often affect a trait of interest through the regulation of genes and processes in trait-relevant cell types or tissues.^{2,6} Implementing this functional model in GWASs has become more feasible as large-scale functional genomic resources, such as epigenomic⁷ and transcriptomic⁸ catalogs, have been systematically generated across a wide range of human cell types and tissues. The integration of functional genomics with GWASs has identified regulatory mechanisms in variants associated with some flagship disorders such as obesity⁹ and schizophrenia,¹⁰ yielding important functional insights into the genetic architecture of human complex traits.

The history of the human genetics of lipids mirrors the successes and challenges of GWASs. Increasing sample size and genetic diversity has significantly boosted the power of discovery: the first lipid GWAS in 2008 with 8,816 European-descent individuals identified 29 lipid-associated loci;¹¹ the latest study of 1.6 million individuals across five ancestries¹² found 941. Despite the dramatic increase in the number of associations, our biological understanding of many of these genetic discoveries remains limited. The causal gene has been confidently assigned at only a small fraction of these loci,² and the regulatory mechanism connecting variant to phenotype has been conclusively characterized for only a handful of genes.⁵ Furthermore, systematic mapping of lipid-associated variants to their biological functions has been missing in the literature at the time of this study.

Here we conduct a genome-scale integrative analysis on the largest published GWAS to date of five lipid phenotypes (LDL, or low-density lipoprotein; HDL, or high-den-

sity lipoprotein; TC, or total cholesterol; nonHDL, or non-high density lipoprotein; and TG, or triglycerides)¹² involving 1.65 million individuals from five ancestries.¹² Combining the lipid GWAS with a wide array of functional genomic resources in diverse human tissues and cell types, we identify regulatory mechanisms of noncoding genetic variation in lipids with a full suite of computational approaches. Further, we develop a generalizable framework to understand how tissue-specific gene regulation can explain GWAS findings and we demonstrate its real-world value on lipid-associated loci.

Material and methods

GWAS

We used the recently published GWAS data from the Global Lipids Genetics Consortium (GLGC) for five blood lipid traits (LDL, HDL, TC, TG, and nonHDL) in 1.65 million individuals from five ancestry groups¹² (African and African-admixed, East Asian, European, Hispanic, South Asian) at 91 million variants imputed primarily from the Haplotype Reference Consortium¹³ or 1,000 Genomes Phase 3.¹⁴ GWASs of individual cohorts were based on the hg19 version of the human reference genome. MR-MEGA¹⁵ was used for meta-analysis across cohorts.

We defined “sentinel variants” as the most significant variant at independent trait-associated loci in the genome. The windows are the greater of 500 kb or 0.25 cM around the sentinel variant; genetic distances were defined using reference maps from HapMap 3.¹⁶ We performed a second round of conditional analysis, conditioning on the sentinel variants to identify and remove any significant windows that are shadow signals of (or dependent on) a neighboring locus to enforce independence of associated loci.

For each sentinel variant, we defined credible sets of potentially causal variants within ± 500 kb region around the sentinel variant representing the set of variants harboring the causal variant with

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a 95% posterior probability. Full details of the credible set construction are reported in our recent GWAS publication.¹² The credible sets are freely available ([web resources](#)).

Colocalization of GWAS associations with eQTLs

We performed statistical colocalization of lipid GWASs with eQTLs obtained from GTEx v8 across 49 tissues.⁸ For each of the five lipid traits, we used the same sentinel variants defined in the previous section to represent approximately independent GWAS-associated windows (also removing shadow signals as described before). For each such window, we ran eQTL colocalization with GTEx v8 single-tissue *cis*-eQTL summary statistics.⁸ For each of 49 GTEx tissues, we first identified all genes within 1 Mb of the sentinel SNP, and then restricted analysis to those genes with significant eQTLs (i.e., eGenes as defined by GTEx) in that tissue (FDR < 0.05). We used the R package *coloc* (R v.3.4.3, *coloc* v.3.2.1)¹⁷ with default parameters to run colocalization between the GWAS signal and the eQTL signal for each of these *cis*-eGenes, using as input those SNPs in the defined window (greater than 500 kb or 0.25 cM on either side of the lead variant) that are present in both datasets. Because eQTL summary statistics were in GRCh38, we lifted over the GWAS summary statistics from hg19 to GRCh38 using *liftOver*.¹⁸ As in previous studies,¹⁹ we used a colocalization posterior probability of (PP3+PP4) > 0.8 to identify loci with enough colocalization power, and PP4/PP3 > 0.9 to define those loci that show significant colocalization, where PP4 represents posterior probability of a single shared signal, and PP3 represents posterior probability of two unique signals in the GWAS and eQTL datasets.

Overlap with promoter Capture-C data

We used four promoter-focused Capture-C (henceforth Capture-C) datasets from three human cell types ([web resources](#)) to capture physical interactions between gene promoters and their regulatory elements. The four Capture-C datasets are (1) three biological replicates of HepG2 liver carcinoma cells (HepG2.1),²⁰ (2) another HepG2 dataset described in Selvarajan et al. (HepG2.2),²¹ (3) hepatocyte-like cells (HLC) produced by differentiating three biological replicates of iPSCs (which in turn were generated from peripheral blood mononuclear cells using a previously published protocol²²), and (4) an adipose dataset obtained from Pan et al.²³ that was produced using primary human white adipocytes. Across the four datasets, the number of significant interactions on the same chromosome ranges from 67,819 (adipose) to 126,565 (HLC). The bait end has a median size of 2,141 (HepG2.1) to 6,567 (HepG2.2) bases. The interacting end has a median size of 2,100 (HepG2.1) to 3,243 base pairs (HepG2.2) for all datasets. The median distance between the bait and interacting ends for all interactions on the same chromosome ranges from 71,722 (HLC) to 285,140 base pairs (adipose).

The detailed protocol to prepare HepG2 or HLC cells for the Capture-C experiment is described in Chesi et al.²⁰ Briefly, for each dataset, 10 million cells were used for promoter Capture-C library generation. Custom capture baits were designed using an Agilent SureSelect library design targeting both ends of DpnII restriction fragments encompassing promoters (including alternative promoters) of all human coding genes, noncoding RNA, antisense RNA, snRNA, miRNA, snoRNA, and lincRNA transcripts, totalling 36,691 RNA baited fragments. Each library was then sequenced on an Illumina HiSeq 4,000 (HepG2) or Illumina NovaSeq (HLC), generating 1.6 billion read pairs per sample (50

base pair read length). We used HiCUP v0.7.2²⁴ to process the raw FASTQ files into loop calls and CHiCAGO v1.6.0²⁵ to define significant looping interactions; we defined a CHiCAGO score of 5 as significant, as specified in the default parameters.

Starting with Capture-C maps processed as described above, we re-annotated the baits to gene IDs from Gencode v.19²⁶ to ensure uniformity of gene annotations with the rest of our pipeline. For each bait, we identified any gene whose transcription start site (TSS) from any transcript in Gencode v.19 was within 175 base pair distance from the bait (to account for differing bait designs for external datasets which may not directly overlap the canonical TSS). We filtered all datasets to only include interactions in which the interacting end was not another bait. Enrichment with colocalized genes was robust to our choice of distance between bait and gene (enrichment with eQTL colocalized genes ranging from 2.94 to 2.96 for bait distances from 0 to 350 base pairs).

To identify genetic variants associated with any of the five lipid traits that physically interact with locations in the genome, we used the R package *Genomic Ranges* v.1.30.3²⁷ to find overlap between credible sets for each trait's GWAS and the previously annotated promoter Capture-C data. Given the bait end of a gene, we defined a GWAS locus as interacting with this gene if a variant in the credible set for this GWAS locus fell inside the interacting end.

Presence of gene-variant pairs in same topologically associated domains

To assess the frequency of colocalized gene-sentinel variant pairs in the same topologically associated domain (TAD), we used a list of 2,499 publicly available TADs from human liver²⁸ ([web resources](#)). We computed as a fraction the number of colocalizations with the sentinel variant and colocalized gene in the same TAD divided by all colocalizations in which the sentinel variant lies in a TAD. To test whether this fraction was statistically significant, we generated random TAD boundaries (using *bedtools shuffle*) 1,000 times and calculated the same fraction for these randomly generated TAD boundaries.

Pathway enrichment

We used *ClusterProfiler* v3.6.0²⁹ to look for pathways over-represented in each gene list: genes with eQTL colocalization and genes interacting with variants in GWAS credible sets. We used the *enrichKEGG* function to look for enriched pathways in the latest version of the KEGG database.³⁰ We first re-mapped Gencode IDs to gene symbols using the Gencode v.24 annotation and then used the *biomaRt* R package v2.34.2³¹ to convert gene symbols to Entrez IDs. We ran *enrichKEGG* to identify enriched pathways that were significant at a Benjamini-Hochberg threshold of 0.05.

Enrichment in known lipid-associated genes

We calculated enrichment odds ratio of genes identified in our analysis with four known sets of lipid-associated genes using the Fisher exact test (R function *fisher.test*). First, we identified 33 Mendelian genes from ClinVar³² with lipidemia-associated ICD10 codes (E78). Second, we used 35 genes with rare-coding variants associated with lipid levels.³³ Third, we extracted 1,115 genes associated with "cholesterol" or "lipidemia" phenotypes in mouse knockouts from the Mouse Genome Informatics (MGI) database.³⁴ Fourth, we identified 4,008 genes from a transcriptome-wide association study (TWAS) on the same GWAS and GTEx v8 summary

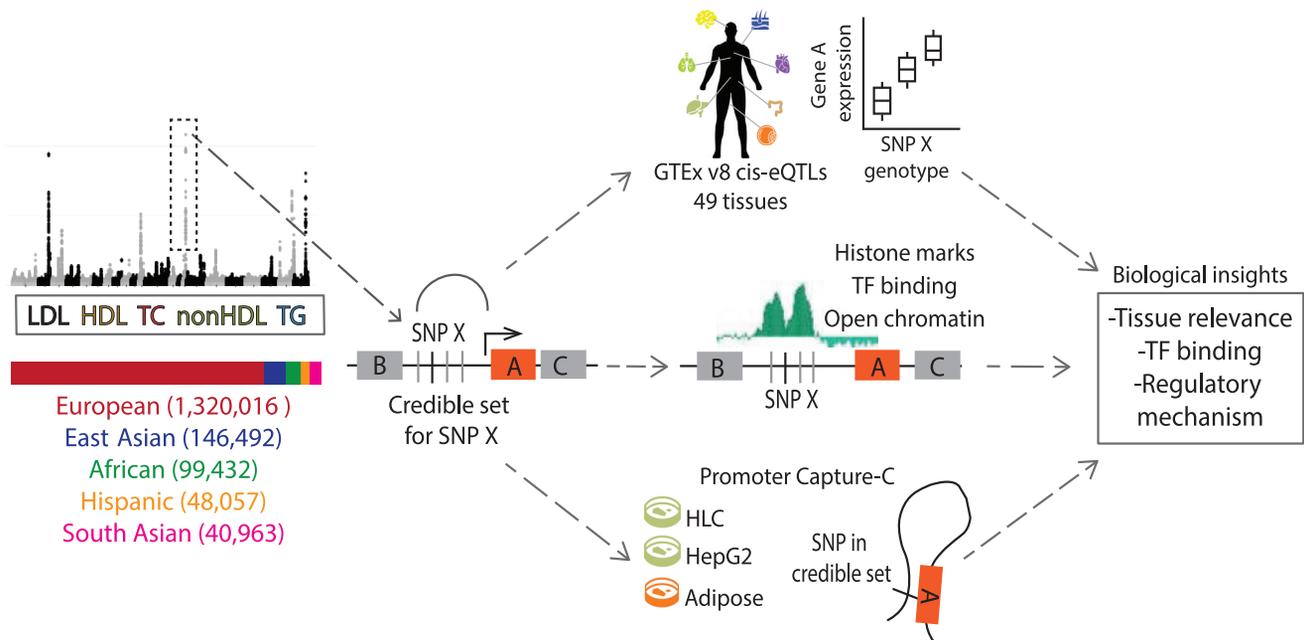


Figure 1. Schematic overview of the multi-layer functional genomic analysis

We integrate GWAS summary statistics for five lipid phenotypes with eQTL and chromatin interaction data to identify potential genes mediating the GWAS loci, and use epigenomic annotations to identify regulatory mechanisms at these loci. For a GWAS locus indexed by a lead variant X, A, B, and C represent nearby eGenes across tissues, and SNPs around SNP X represent variants in the credible set for this locus.

statistics using the S-PrediXcan software³⁵ default setup. The TWAS method accounts for allelic heterogeneity and thus complements the eQTL colocalization approach that assumes one causal variant per locus.

TF binding sites

We extracted TF binding sites from ChIP-seq data of 161 TFs in 91 cell types from the ENCODE project⁷ ([web resources](#)). We included all cell types in our primary analysis because TFs were not comprehensively assayed in most cell lines. We also performed a secondary analysis using TF binding sites from HepG2 only. All TF binding sites were aligned to the hg19 version of human reference genome (https://www.encodeproject.org/chip-seq/transcription_factor/).

Stratified LD score (S-LDSC) regression analysis

We used LDSC version 1.0.1³⁶ to estimate the enrichment of heritability explained using GWAS summary statistics in different epigenetic and transcriptomic annotations, including gene expression, chromatin marks, and TF binding sites. The gene expression and chromatin mark annotations across 205 datasets from more than 170 tissues and cell types and the corresponding LD scores were provided as Multitissuegeneexpr1000Gv3 and Multitissuechromatin1000Gv3 databases in LDSC software ([web resources](#)). The LD scores for binding sites of each TF were estimated from 1,000 Genomes Phase 3 European samples using `ldsc.py -l2`. We first converted the summary statistics for each phenotype to LDSC-formatted summary statistics using `munge_sumstats.py`. Second, we ran `ldsc.py` using the `baseline_v1.2` model on each annotation to estimate enrichment of heritability. For primary analyses, we used multi-ancestry GWAS summary statistics and LD scores estimated from 1,000 Genomes Phase 3 European samples. For secondary analyses on East Asian

(EAS) GWAS alone, we obtained EAS-specific LD scores for the same functional annotations.³⁷

Genomic regulatory elements and GWAS overlap algorithm (GREGOR) analysis

We used GREGOR³⁸ to estimate enrichment of sentinel variants for each lipid phenotype in TF binding sites for 161 TFs from ENCODE compared to a null distribution of variants matched for allele frequency. We ran GREGOR with default parameters, specifying 0.8 as the R^2 threshold, window size of 1 Mb, and 'EUR' as the population. Annotations with enrichment >2 and FDR-adjusted p value < 0.05 were considered significant.

Enrichment in single-cell expression data

We overlapped our list of colocalized genes with publicly available single-cell RNA-sequencing data of 8,444 cells from liver³⁹ and 38,408 cells from adipose ([web resources](#)) in humans. For both datasets, we downloaded normalized TPM data and existing tSNE cluster annotations for each cell. For each cluster, we defined median expression for each gene across all cells in that cluster. Then for each cluster, we quantified the overrepresentation of our gene list in ranked genes for this cluster via an enrichment p value computed by the `fgsea`⁴⁰ R package v.1.4.1 implemented in R 3.4.3.

Results

We systematically integrated lipid GWAS results¹² with multiple layers of functional genomic data from diverse tissues and cell types to understand regulatory mechanisms at lipid-associated loci ([Figure 1](#)). Specifically, we overlaid GWAS loci with eQTL and chromatin-chromatin

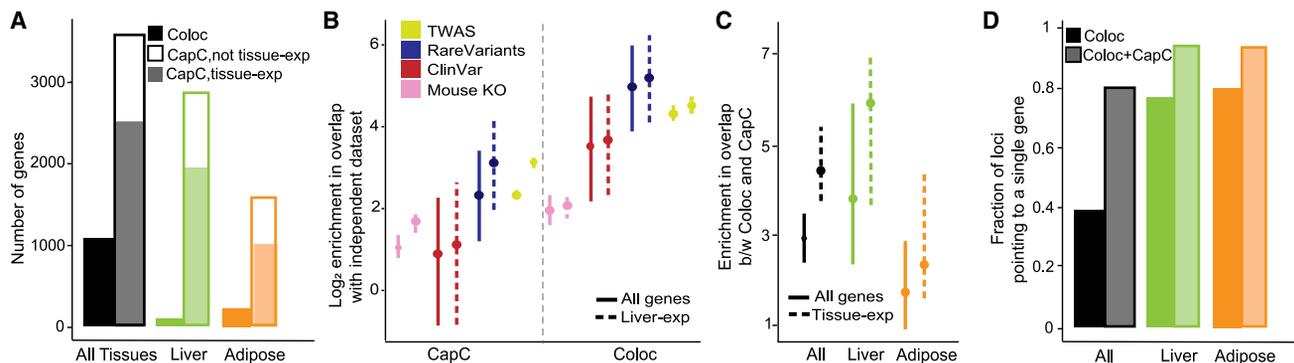


Figure 2. Overlap between eQTL colocalized genes and Capture-C prioritized genes, and their enrichments in known lipid-associated genes

(A) Numbers of genes identified by two approaches: eQTL colocalization (Coloc) and promoter Capture-C interaction (CapC). Capture-C interactions restricted to genes expressed in the tissue of interest (or in the union of adipose and liver for “all tissues”) are shaded.

(B) Overlap between two list of prioritized genes (left: Capture-C prioritized genes; right: eQTL colocalized genes) with four external sets of genes previously associated with lipid biology (MGI knockout genes, ClinVar lipidemia-associated genes, genes implicated in rare burden of lipids, and genes from a lipid TWAS). Dashed lines represent enrichments using only genes expressed in the liver.

(C) Enrichment in overlap between eQTL colocalized genes and Capture-C prioritized genes against what is expected by chance, assuming both gene sets are independent.

Dashed lines represent genes expressed in the tissue of interest (or in the union of adipose or liver for “all”). Enrichment estimates and 95% confidence intervals shown in (B) and (C) are based on the Fisher exact test.

(D) Fraction of colocalized loci that point to a single candidate gene when using eQTL data alone or using both eQTL and Capture-C data.

interactions to identify causal genes. We assessed polygenic enrichments of tissue-specific histone marks to prioritize relevant tissues and examined GWAS loci at transcription factor (TF) binding sites to detect lipid-relevant TFs. Finally, we combined all these layers to prioritize functional variants at GWAS loci, providing a holistic view of gene regulation at lipid loci in relevant tissue and cell types.

Colocalization with eQTLs identifies candidate lipid-relevant genes

First, we identified shared association signals between lipid levels and expression of nearby genes, since most GWAS signals are presumed to influence complex traits through impact on gene expression.⁴¹ To do so, we tested for colocalization of each significant lipid GWAS signal with significant *cis*-eQTL data across 49 human tissues from the GTEx consortium.⁸ The significant GWAS signals were 1,750 loci reaching genome-wide significance and corrected for shadow signals in our multi-ancestry meta-analysis for at least one of five lipid traits. Credible set sizes ranged from 1 to 417 variants at the 1,750 examined loci, with a median size of 5 variants per credible set.

Second, we restricted our analysis to loci most likely mediated through regulatory mechanisms as opposed to coding variation. Specifically, we excluded all loci with credible sets containing at least one missense variant (369 of 1,750 loci, 21% of credible sets). Of the remaining 1,381 GWAS loci, 696 significantly colocalized with eQTLs (the ratio of posterior probability of a shared signal to the posterior probability of two signals being >0.9 ¹⁹) in at least one of 49 tissues for at least one lipid phenotype. This resulted in 1,076 colocalized eGenes ranging from 1 to 16

genes per locus (Figure 2A and Table S1). Since with eQTL data alone it is difficult to disentangle a single functional gene from multiple functional (and likely coregulated) genes at a locus,⁴² we performed all downstream analyses with all 1,076 colocalized genes, to further prioritize functional genes at loci with multiple eGenes.

Since lipid-associated genetic variants are often enriched in the liver and adipose,^{43,44} we repeated the colocalization analysis on eQTLs only from liver or adipose. Compared to the 1,076 colocalized eGenes identified from all 49 tissues, the liver- and adipose-only analysis identified 119 and 225, respectively (Figure 2A). The reduced discovery of colocalized eGenes in the liver- and adipose-only analysis is likely due to the small sample sizes of liver ($n = 208$) and adipose ($n = 581$) in GTEx v8 (Figure S1). Leveraging the large degree of tissue sharing in eQTLs,^{19,45} our cross-tissue colocalization analysis enhanced the discovery power through the collectively large sample size across all 49 tissues ($n = 15,201$). For example, several well-documented lipid-relevant genes such as *PPARA*⁴⁶ and *LPL*⁴⁷ were not identified in the liver- or adipose-only analysis but were identified as significant in our cross-tissue analysis.

To acquire additional functional insights into the 1,076 colocalized genes, we assessed their enrichments across existing biological and clinical gene sets (Figure 2B, Tables S2 and S3). Colocalized genes showed enrichments in (1) 20 KEGG pathways³⁰ at FDR 5%, including known lipid-related processes such as cholesterol metabolism, PPAR signaling, and bile secretion; (2) 33 Mendelian genes from ClinVar³² associated with lipid-related ICD10 codes (11.61-fold enrichment, $p = 2.08 \times 10^{-6}$, including *APOB*, *LPL*, and *APOE*), suggesting the shared genetic basis of Mendelian and complex lipid phenotypes;⁴⁸ (3) 35

genes with rare-variant burden for lipid phenotypes in a recent multi-ancestry analysis³³ (30.82-fold enrichment, $p = 1.77 \times 10^{-16}$, including *APOB*, *LPL*, *LIPG*, and *ANGPTL4*), confirming shared mechanisms of rare and common variation underlying lipid traits;⁴⁹ (4) genes implicated by cholesterol or lipidemia phenotypes in mouse knockouts (3.92-fold enrichment, $p = 2.18 \times 10^{-20}$), suggesting the shared genetic basis of lipid traits between human and mouse.⁵⁰ Colocalized genes also showed enrichment with genes implicated in TWAS (Table S4) run on the same GWAS and eQTL summary statistics (20.14-fold enrichment, $p < 2.22 \times 10^{-308}$). These enrichment results demonstrate the biological relevance of candidate functional genes prioritized by our approach.

Chromatin-chromatin interactions shortlist eQTL-based colocalization

Our eQTL-based colocalization analysis uses a linear sequence of DNA and ignores physical interaction between non-adjacent DNA segments, another regulatory layer underlying complex human traits.⁵¹ To add this layer to our analysis, we generated Capture-C data from HepG2 liver carcinoma cells (HepG2.1) and hepatocyte-like cells (HLC) derived from differentiating iPSCs,²² as well as publicly available Capture-C datasets from HepG2²¹ (HepG2.2) and white adipocytes.²³ Based on the Capture-C data, we defined an interaction between a GWAS locus and a gene as a significant interaction between the bait end (promoter) for this gene and the interacting end that contains a variant in the credible set for this GWAS locus. In total, 1,079 of 1,750 GWAS loci had at least one variant in the credible set with a physical interaction with a gene promoter and 3,543 of 26,621 genes with promoter-interactions had promoters physically interacting with at least one GWAS credible set variant (Figure 2A and Table S5).

Unlike eQTL-colocalized genes, genes interacting with GWAS credible sets were not significantly enriched in lipid-relevant KEGG pathways (Table S2) and lipid-related genes from ClinVar (Figure 2B and Table S3). These genes were significantly enriched in genes with rare-variant lipid associations (5.36-fold enrichment, $p = 2.8 \times 10^{-5}$), genes with lipid-related mouse knockouts (1.43-fold enrichment, $p = 2.8 \times 10^{-4}$), and TWAS-prioritized genes (5.05-fold enrichment, $p = 2.5 \times 10^{-288}$), but their enrichments were consistently lower than enrichments of eQTL-colocalized genes nonetheless (Figure 2B and Table S3).

Since genes expressed in the liver are most likely to harbor genuine lipid-relevant variant-gene interactions, we repeated the enrichment analyses above restricting both eQTL colocalization and Capture-C interactions to genes expressed in the liver (>0.1 TPM and ≥ 6 reads in at least 20% of GTEx liver samples). Reassuringly, we observed higher enrichments for each combination of two methods (eQTL, Capture-C) and four databases (ClinVar, Rare Variant, Mouse Knockout, TWAS) when we restricted our analyses to genes expressed in the liver (Figure 2B and Table S3). For the same database, we observed higher en-

richments in eQTL colocalized genes than Capture-C prioritized genes, consistent with the results based on all genes.

Genes physically interacting with GWAS loci significantly overlapped with eQTL colocalized genes despite their reduced enrichments in lipid-related gene sets. Of 1,079 credible sets with promoter interactions, 224 also colocalized with eQTLs for the same gene. Across 49 eQTL tissues and four Capture-C cell lines, 233 genes were implicated in both eQTL colocalizations and Capture-C interactions (Table S6), representing an enrichment of 3-fold compared to random chance (Figure 2C, $p = 3.11 \times 10^{-38}$). Because our Capture-C data came from liver and adipose only, we observed a stronger enrichment in overlap when restricting genes expressed in the liver or adipose (4.5-fold enrichment, $p = 2.89 \times 10^{-65}$). We observed similar enrichment patterns when analyzing liver and adipose Capture-C data separately (Figure 2C). Together, the enrichments in overlap suggest that, despite a large number of genes identified by Capture-C (Figure 2A), many of them are likely to harbor functional interactions with GWAS loci.

Chromatin-chromatin interactions helped shortlist functional genes from eQTL colocalization. Among 224 loci with concordant eQTL colocalizations and Capture-C interactions across all tissues, only 39% (88) mapped to a single gene using eQTL data alone, whereas adding Capture-C information increased this fraction to 80% (180). We observed the same trend in the adipose-only and liver-only analysis: 80% (12/15) and 79% (26/33) of loci mapped to a single gene using adipose and liver eQTLs alone, compared to 93% (14/15) and 97% (32/33) after the integration of adipose-only and liver-only Capture-C data, respectively (Figure 2D). These results showcase the potential value of combining eQTLs with physical chromatin interactions to prioritize functional genes at GWAS loci.

Since eQTLs are likely to reside in the same topologically associated domain (TAD) as the genes they regulate,⁵² we examined TADs from an independent human liver dataset²⁸ at lipid GWAS loci with eQTL colocalizations to confirm GWAS variant-target gene colocalization within the same TAD. Of eQTL-GWAS colocalizations in which the sentinel variant resided within a TAD, 84.8% (1,040 out of 1,235) had the colocalized gene residing in the same TAD ($p < 0.001$ with 1,000 permutations). When we restricted to all colocalizations concordant with Capture-C data in any cell type, 96.9% (252 out of 260) of gene-variant pairs fell in the same TAD. This fraction further increased to 100% (33 out of 33) when we repeated the analysis using liver eQTLs and liver Capture-C interactions only. These results add to the existing evidence for TAD boundaries being regulatory insulators in the cell⁵³ and confirm our integration of chromatin interactions with eQTL colocalizations as an effective strategy to hone in on functional genes.

Tissue-specific enrichment of GWAS signals differentiates lipid traits

Regulatory variants often affect complex traits in a tissue-specific manner,⁶ as shown in our eQTL colocalization

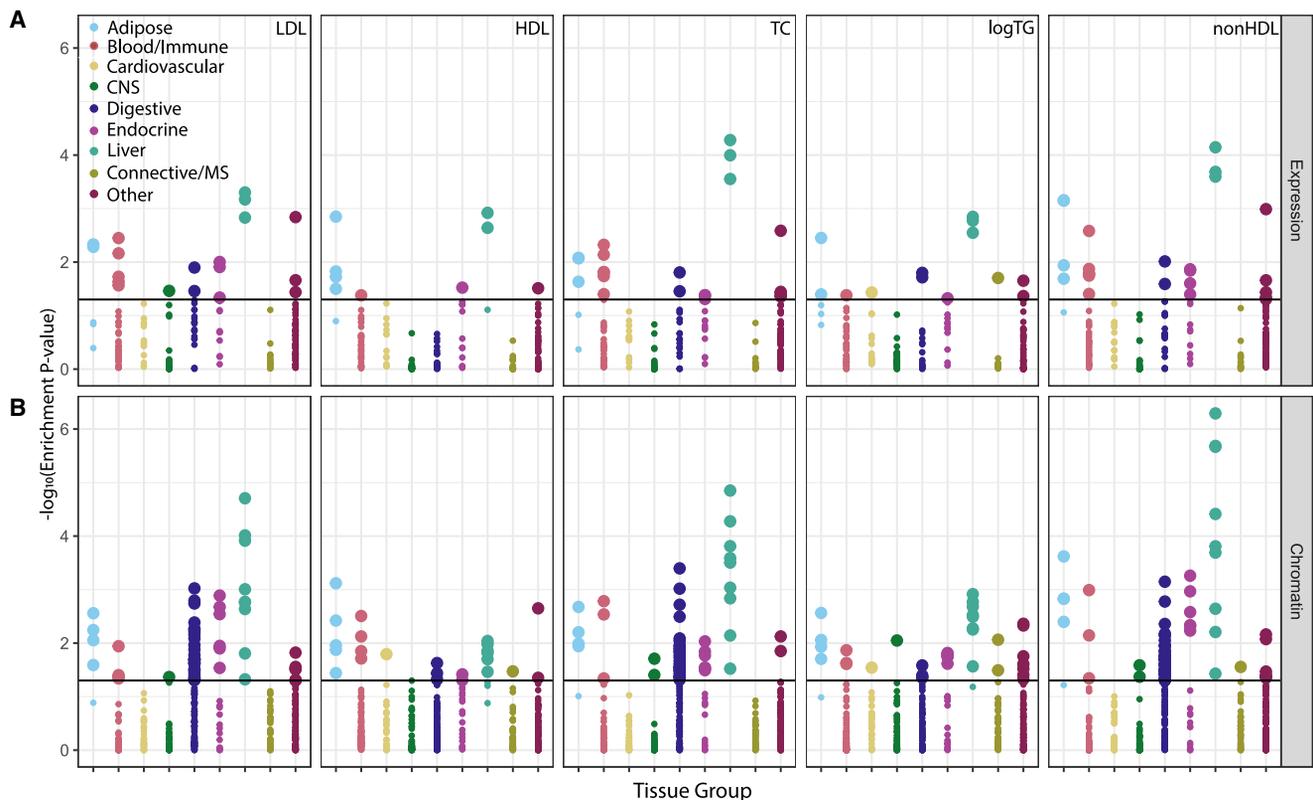


Figure 3. Tissue relevance of lipid-associated loci

Partitioning heritability of lipid GWAS summary statistics on gene expression (A) and active chromatin marks (B) across tissues. Each plotted point represents a tested dataset for enrichment of heritability, with larger dots representing datasets with enrichment p value < 0.05 . Each color represents a tissue group (Table S7), and the y-axis represents $-\log_{10}$ p value for enrichment of heritability.

analysis. Specifically, by computing the ratio of the number of colocalizations in a tissue to eQTL sample size in that tissue, we found that the liver was universally enriched for colocalized eGenes with respect to sample size across all lipid traits whereas adipose was selectively enriched in HDL and TG only (Figure S1). Motivated by these findings, we leveraged systematic approaches and additional data to identify relevant tissues and cell types for each lipid trait.

We implemented stratified LD score regression (S-LDSC),³⁶ a polygenic approach not restricted to genome-wide significant variants, on tissue-specific transcriptomic and epigenomic annotations across 205 datasets from more than 170 tissues and cell types, to identify relevant tissues for each lipid trait. Consistent with previous studies^{43,44} and our eQTL-based analysis, liver-related tissues (Tables S7 and S8) showed strong enrichments across all lipid traits (S-LDSC enrichment p values ranging from 0.001 in TG to 0.0001 in TC), for both expression (Figure 3A) and chromatin annotations (Figure 3B). This result was confirmed by analysis using two other approaches: DEPICT⁵⁴ (Figure S2 and Table S9) and RSS-NET⁵⁵ (Table S10). To assess the robustness of our S-LDSC results based on multi-ancestry GWASs, we applied S-LDSC to population-specific GWASs in European and East Asian ancestry participants together with popula-

tion-specific LD scores and obtained similar results (Table S11, Figures S3 and S4).

The S-LDSC results also highlighted tissues selectively enriched in certain lipid traits as shown in the eQTL-based analysis. The most enriched category for HDL using chromatin annotation is adipose H3K4me3 ($p = 7.6 \times 10^{-4}$); for TG, enrichment in liver-related tissues ($p = 1.2 \times 10^{-3}$) is similar to enrichment in adipose ($p = 2.7 \times 10^{-3}$). For LDL, TC, and nonHDL, enrichment p values for the liver were much more significant than for all other tissues including adipose (Figure 3B). We observed the same pattern in S-LDSC results based on gene expression (Figure 3A). This finding is consistent with the known influence of adipose on plasma HDL levels,⁵⁶ and the role of adipose as TG deposits.⁵⁷ These results were corroborated by eQTL colocalizations stratified by phenotype (Figure S1) and DEPICT analysis on gene expression⁵⁴ (Figure S2 and Table S9). Together, these results confirm the liver as a tissue of action for all five lipid traits and highlight the additional role of adipose primarily in HDL and TG.

Given the importance of the liver and adipose in modulating lipid levels, we further identified the relevant cell types within these tissues. Using existing single-cell data from adipose and liver,³⁹ we performed gene set enrichment analysis⁵⁸ to identify cell-type clusters enriched for genes with eQTL colocalizations for any lipid trait. Out

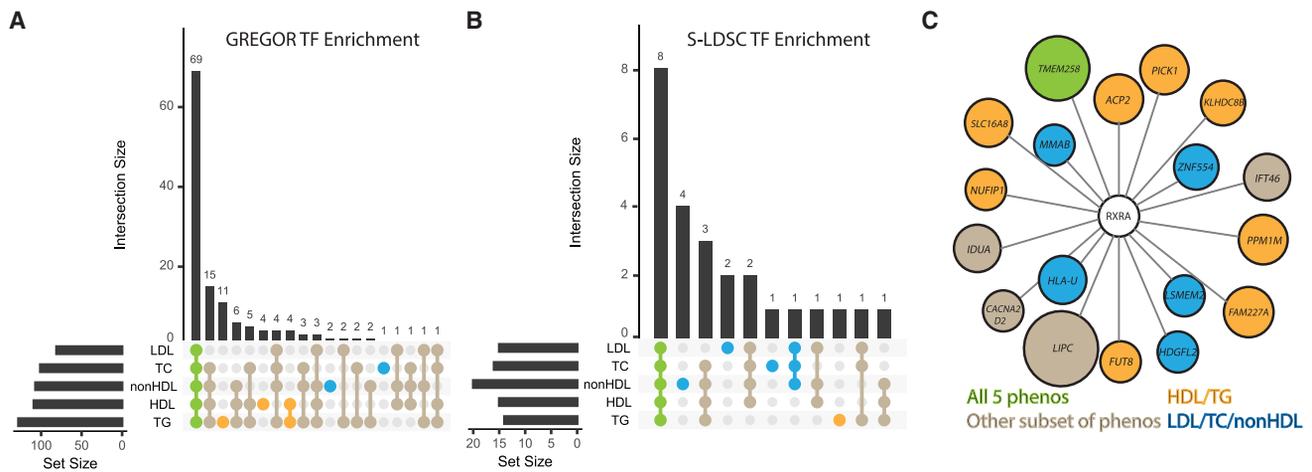


Figure 4. TF enrichment identified by GREGOR and S-LDSC

(A) Number of TFs enriched in the GREGOR analysis on GWAS loci for each of the five lipid traits.

(B) Number of TFs enriched in S-LDSC analysis on each of the five lipid traits.

(C) TF RXRA binds to the promoters of 26 colocalized genes (18 protein-coding). Colors represent the subsets of lipid phenotypes with colocalization. Larger node sizes represent smaller GWAS *p* values of colocalized loci.

of 11 identified cell types in 20 clusters in the liver, only hepatocytes were enriched at FDR-adjusted $p < 0.05$ (Figure S5 and Table S12), consistent with previous results.²¹ In adipose, only adipocyte clusters and macrophage-monocyte clusters showed suggestive enrichment (nominal $p < 0.05$) in colocalized genes (Figure S6 and Table S12). Of note, the enrichment in adipocytes was significant when we restricted this analysis to genes that were colocalized with HDL and TG (FDR-corrected $p < 0.05$), consistent with the selective enrichments of adipose in HDL and TG (but not the other lipid traits) from our S-LDSC analysis. Evaluations at cellular resolution are required to understand the cell-type-specific mechanisms underlying lipid GWAS loci, but our results could form a useful basis for future studies.

Overlapping GWAS signals with binding sites highlights lipid-relevant TFs

TFs have been implicated as a key mediator of linking genetic variation to complex traits.⁵⁹ To understand lipid GWASs in the context of TF activity, we assessed enrichment of genome-wide significant variants at TF binding sites using GREGOR³⁸ and performed polygenic enrichment analysis of TF binding sites using S-LDSC. Because TFs were not comprehensively assayed in most cell lines (Figure S7), we used all cell types in our primary analysis presented below.

Using ChIP-seq data from 161 TFs across 91 cell types from the ENCODE project,⁷ 70.7% of lipid credible sets overlapped with at least one TF binding site. Using GREGOR,³⁸ we identified 137 TFs whose binding sites were significantly enriched in GWAS lead SNPs for at least one lipid phenotype (enrichment >2 ; FDR adjusted p value < 0.05 ; Figure 4A and Table S13). We obtained similar results when repeating the GREGOR analysis on TF binding sites derived from HepG2 only (Table S14). To

assess the impact of GWAS power on TF enrichments, we repeated the GREGOR analysis on the same TF binding sites using a previous version of lipid GWAS, and we identified 54 enriched TFs (Table S15). Between the two versions of lipid GWASs, the total sample size and number of GWAS loci increased 8.7-fold (from 188,577 to 1,650,000) and 11-fold (from 156 to 1,750), respectively, but the number of enriched TFs only increased 2.5-fold (from 54 to 137), suggesting that the large number of enriched TFs is unlikely driven by the GWAS power alone.

Among these 137 enriched TFs, 69 of them (50%) showed significant enrichments across all five lipid phenotypes, suggesting a potential core regulatory circuit shared by all lipid traits (Figure 4A and Table S13). The TF with the strongest enrichment in all phenotypes was ESRRA (estrogen-related receptor alpha), a nuclear receptor active in metabolic tissues;⁶⁰ ESRRA has been implicated in adipogenesis and lipid metabolism, and ESRRA-null mice display an increase in fat mass and obesity.⁶⁰

The GREGOR analysis also highlighted 68 TFs significantly enriched in specific subsets of (but not all five) lipid phenotypes (Figure 4A and Table S13). For example, we found 4 TFs (FOXM1, PBX3, ZKSCAN1, ZEB1) enriched in HDL and TG only, 4 TFs (EZH2, NFE2, NFATC1, KDM5A) enriched in HDL only, and 11 TFs (FOSL1, IRF3, JUN, MEF2C, NANOG, PRDM1, RUNX3, SIRT6, SMC3, STAT3, ZNF217) enriched in TG only. Of these TFs, the central role of ZEB1 in adiposity⁶¹ and fat cell differentiation has been demonstrated.⁶² These TF-centric findings corroborate the selective enrichments of adipose in HDL and TG (but not the other lipid traits) identified in our previous tissue prioritization analyses.

We also performed polygenic enrichment analysis of TF binding sites using S-LDSC (Figure 4B and Table S16), which differed from GREGOR analysis by looking at not only the genome-wide significant associations but also

the polygenic signal without GWAS p value cutoff. On the same 161 ENCODE TFs, this polygenic analysis identified 25 TFs whose binding sites were significantly enriched in heritability explained (nominal $p < 0.05$) for at least one lipid phenotype; reassuringly, 24 of 25 TFs were also significant in the GREGOR analysis. As a sensitivity check, we repeated the S-LDSC analysis on TF binding sites derived from HepG2 only, and we obtained similar results (Table S17).

Among 24 enriched TFs identified by both GREGOR and S-LDSC, eight were significantly enriched in all five lipid traits (CEBPB, CEBPD, FOXA2, HDAC2, HNF4G, NFYA, RXRA, SP1). RXRA (retinoid X receptor alpha) is encoded by a colocalized gene (*RXRA*) near a GWAS hit (chr9:137,268,682). RXRA is a ligand-activated transcription factor that forms heterodimers with other receptors (including PPARG) and is involved in lipid metabolism.⁶³ Moreover, 145 lipid GWAS loci overlap RXRA binding peaks, and RXRA binds to the promoters of 26 colocalized genes (18 of which are protein-coding) (Figure 4C and Table S18), suggesting that the GWAS variants might affect lipids (partially) through affecting the binding activity of RXRA. While *RXRA* has been previously implicated,⁶⁴ our study demonstrates its role in lipid biology through its regulatory influence on other lipid-associated genes.

Multi-layer functional integration reveals regulatory mechanisms at GWAS loci

Motivated by our finding that integrating chromatin interaction shortlisted eQTL colocalizations, we further brought together multiple lines of functional evidence at each GWAS locus for mechanistic inference. We started with the list of genes with evidence for both eQTL colocalization and Capture-C interactions in the liver or adipose. We next annotated each variant in the 95% credible set with various indicators of regulatory function, including its open chromatin status in liver²⁰ or adipose-related cell types,⁶⁵ its proximity to a promoter or an enhancer,⁶⁶ and its RegulomeDB regulation probability;⁶⁷ see Table S19 for the complete list of annotations used. To account for complexities of regulatory mechanisms and limitations of functional datasets, we combined evidence across these datasets to prioritize variants at GWAS loci (Figure 5A). Specifically, we prioritized variants with at least three independent lines of functional evidence (chromatin openness, physically interaction with target genes, and promoter/enhancer status) in the liver or adipose, with at least two being in the same tissue with colocalization with the target gene, and with a RegulomeDB score >0.5 . Applying this simple procedure to lipid GWASs we prioritized 28 candidate loci with the strongest multi-layer evidence, 13 of which point to a single functional variant (Table 1). We have also made the full results of variant prioritization freely available (web resources). Below we describe two examples to highlight key features of this multi-layer integration framework.

RRBP1 (ribosomal binding protein 1) could be identified from eQTL colocalization alone, but our multi-layer integration approach strengthened the conclusion via convergent evidence from various sources (Figure 5B). The *RRBP1* eQTL signals in the liver colocalize with LDL, TC, and nonHDL GWAS signals. The credible set at this locus contains a single lead variant (chr20:17,844,684). The “T” allele of this lead variant decreases *RRBP1* expression levels and increases LDL, TC, and nonHDL levels. This lead variant is in open chromatin in HLC and adipose and physically interacts with the *RRBP1* promoter (250 kb away) in adipose. All these data consistently point to *RRBP1* as the functional gene underlying this locus. *RRBP1* specifically tethers the endoplasmic reticulum to the mitochondria in the liver (an interaction that is enriched in hepatocytes) and regulates very low-density lipoprotein levels.⁶⁸ Rare variants in *RRBP1* are associated with LDL in humans⁶⁹ and silencing *RRBP1* in liver affects lipid homeostasis in mice.⁶⁸

CREBRF (CREB3 regulatory factor) further demonstrates the power of our multi-layer integration framework in prioritizing functional variants (Figure 5C). The eQTL signals of *CREBRF* colocalized with a GWAS locus for HDL with 30 candidate variants. In contrast, our multi-layer approach identified a single candidate variant (chr5:172,566,698) at this locus that physically interacts with the *CREBRF* promoter in adipose and is predicted to be a regulatory element (RegulomeDB score = 0.91). Consistent with the index variant (chr5:172,591,337), the allele “A” at this functional variant increased HDL levels and increased *CREBRF* expression in adipose. Missense variants in *CREBRF* have been linked to body mass index, and the gene has been linked to obesity risk in Samoans.⁷⁰

Finally, to compare the power of functional fine-mapping with multi-ancestry fine-mapping, we applied our prioritization rule to credible sets derived from European-only meta-analysis. The 111 variants prioritized by our rule described above (including multiple variants in the same credible set) were all found in the multi-ancestry credible sets, representing a 3.7-fold enrichment ($p < 1 \times 10^{-4}$ based on 10,000 permutations randomly sampling variants from the European-only credible sets). This convergence of complementary approaches to the same smaller set of fine-mapped variants highlights the power of multi-ancestry datasets as an approach to narrow in on functional variants.

Discussion

Here we integrate the largest multi-ancestry lipid GWAS to date with a wide array of functional genomic resources to understand how noncoding genetic variation affects lipids through gene regulation. Specifically, we identify 1,076 genes whose eQTL signals colocalize with lipid GWAS signals and demonstrate how physical chromatin interaction can improve standard eQTL-based colocalization. We

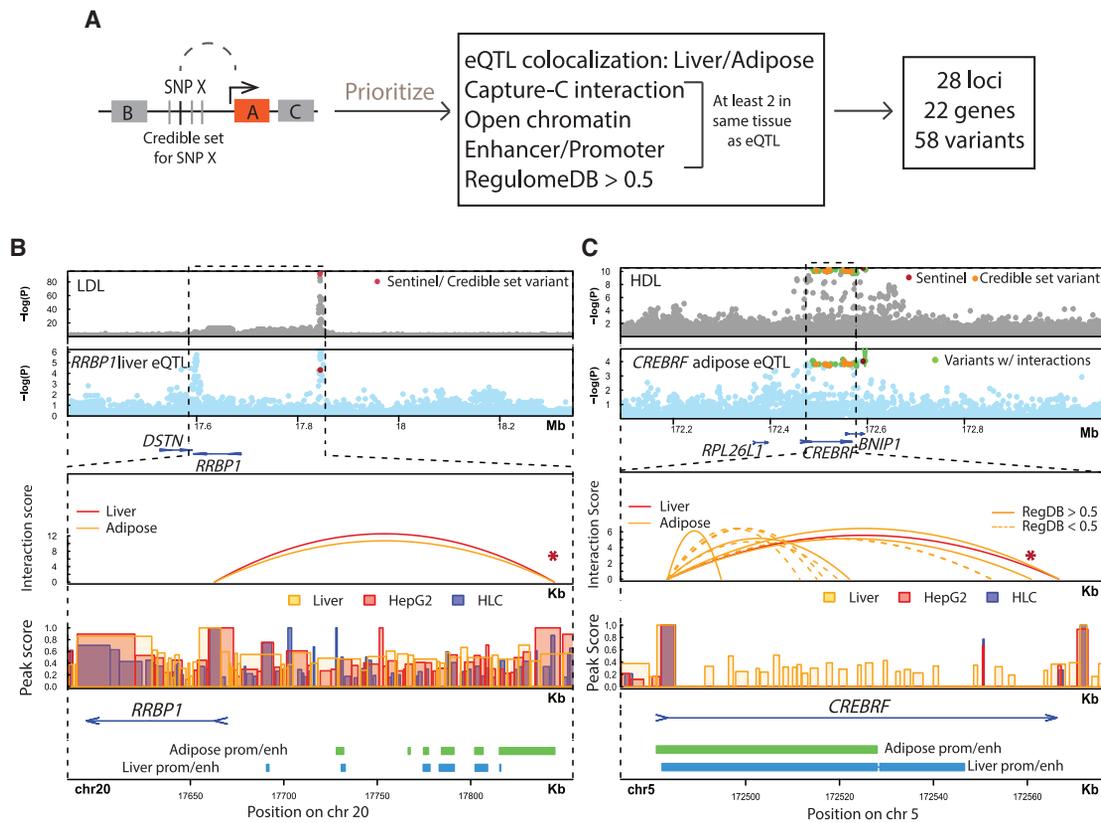


Figure 5. Multi-layer functional integration to prioritize variants at GWAS loci

(A) Variant annotation and prioritization scheme at each GWAS credible set.

(B) Evidence for *RRBP1* from functional genomics data. The LDL GWAS locus at this region (first row) is an eQTL for *RRBP1* in the liver (second row). Variants in the credible set of this locus interact with the gene promoter in both adipose and HepG2 Capture-C data (third row). The interacting variant is also in an open chromatin peak in three liver-related cell types (fourth row).

(C) Multiple sources of functional genomics data support *CREBRF* as a gene contributing to HDL levels. The HDL GWAS locus at this region (first row) is an eQTL for *CREBRF* in adipose (second row). Variants in the credible set at this locus interact with the *CREBRF* promoter in adipose (third row). The interacting variant is also in open chromatin in liver-related cell types (fourth row).

assess tissue-specific enrichments of lipid GWAS signals and demonstrate the selective importance of adipose in HDL and triglyceride biology. We examine binding site enrichments of 161 TFs in lipid GWASs and expand our understanding of lipid GWAS loci (e.g., *RXRRA*) in the context of TF activity. Finally, we build a simple and interpretable prioritization framework that automatically combines multiple lines of evidence from orthogonal datasets, pinpointing a single functional variant at each of 13 lipid-associated loci (e.g., *RRBP1* and *CREBRF*). While there are studies that interpret lipid GWAS associations,^{21,71,72} the size of our multi-ancestry GWAS and multi-layer functional integration represent a comprehensive effort and an important step forward in this direction.

Our multi-layer analysis has two key strengths. First, despite a large array of functional genomic resources being embedded, our analysis produces results with high consistency. For example, the selective enrichment of adipose in HDL and TG identified by S-LDSC is confirmed by our eQTL-based colocalization and TF binding site overlap. Another example of consistency is the multi-layer prioritization of *RRBP1*, which can be identified from eQTL-based

colocalization alone and it is further validated by chromatin accessibility and interaction. Such convergent evidence from various sources improves the confidence of our findings. Second, our analysis highlights that combining multiple layers of regulatory information can improve sensitivity to prioritize functional genes and variants. For example, we refined eQTL colocalized genes (1,076) to a smaller set of functional genes (233) through integration with promoter Capture-C data. Another example of sensitivity is *CREBRF*, where eQTL-based colocalization implicates 30 candidate variants and adding other regulatory layers points to a single functional variant. Moving forward, we expect these two features will serve as useful guidelines for future integrative genomic analyses of other traits.

Our results rely on the breadth and accuracy of functional genomic datasets used in our analyses. First, unlike our lipid GWASs, current functional datasets⁷³ are limited both in sample size and ancestral diversity, which can affect discovery and replication of regulatory mechanisms in diverse populations. Second, some functional datasets are generated at limited resolution. For example, our colocalizations

Table 1. Thirteen prioritized loci with highest confidence of a single functional variant in the credible set

Gene Name	Tissue	Sentinel	Prioritized Var	Open	CapC	Enhancer	Prom-oter	RegDB
<i>CEP68</i>	adipose	2:65284231	65279414	liver	liver	none	ad	0.5896
<i>TIPARP</i>	adipose	3:156797941	156795408	both	both	ad	liver	0.705
<i>CREBRF</i>	adipose	5:172591337	172566698	liver	ad	none	both	0.9124
<i>PALM2</i>	adipose	9:112556911	112556911	both	ad	both	none	0.6091
<i>MEGF9</i>	adipose	9:123481206	123421556	liver	ad	none	liver	0.9933
<i>GBF1</i>	liver	10:104142294	104107191	ad	ad	none	both	0.705
<i>MICAL2</i>	liver	11:12071855	12221016	liver	liver	none	liver	0.6018
<i>ACP2</i>	liver	11:47278917	47276350	ad	liver	liver	ad	0.6091
<i>PTPRJ</i>	adipose	11:48021778	48011180	liver	ad	liver	ad	0.8797
<i>NFATC2IP</i>	adipose	16:28899411	28883327	liver	liver	none	both	0.6091
<i>HELZ</i>	liver	17:65109591	65156919	liver	liver	none	both	0.60906
<i>FAM210A</i>	liver	18:13725674	13725674	liver	liver	none	both	0.7571
<i>RRBP1</i>	liver	20:17844684	17844684	both	ad	both	none	0.6091

The “sentinel” column represents the lead variant at the locus. The “prioritized var” column represents the prioritized variant in the credible set. Columns 5–8 represent overlap of the functional variant with open chromatin (“open”), capture-C (“CapC”) interactions with the candidate gene, enhancer and promoter marks from Roadmap in liver (“liver”), adipose (“ad”), both, or none of these tissues. The “RegDB” column represents the RegulomeDB score of the prioritized variant.

are based on eQTLs from bulk tissue RNA-seq,^{8,74} which may miss detailed cell types and biological processes in which lipid-associated SNPs regulate gene expression. Third, some functional datasets are not available across the full spectrum of human tissues and cell types. One example is that our chromatin-chromatin interaction analysis examines only a few cell types in two known lipid-related tissues (liver and adipose), producing results that may be biased toward known lipid biology. Another example is that ENCODE TF ChIP-seq data are not available in adipose-related cell lines. Fourth, our results are validated computationally but not experimentally. That said, our results provide a high-confidence list of regulatory mechanisms at lipid GWAS loci, forming a useful basis for future experiments. As more comprehensive and accurate functional genomic resources are becoming publicly available in diverse cellular contexts and ancestry groups, the resolution and power of integrative analyses like ours will be markedly increased.

Other limitations of this study stem from computational methods embedded in our framework. First, the colocalization approach coloc assumes one causal variant per locus, whereas recent studies suggest extensive allelic heterogeneity⁷⁵ consistent with a model of a milieu of related transcription factors binding within a single locus. Accounting for allelic heterogeneity in summary statistics-based colocalization typically requires modeling multiple correlated SNPs through LD matrix,⁷⁶ which is computationally intensive in large-scale analyses derived from many cohorts with diverse ancestries, like the multi-ancestry GWASs examined here. Second, due to restricted access to individual genotypes of 201 cohorts, we cannot produce multi-ancestry LD scores within GLGC but have to use European-based LD scores in all S-LDSC analyses. This

approach, though less rigorous in principle, provides robust results in practice (as confirmed by our ancestry-specific analysis), largely because 79% of cohorts in GLGC are of European descent.¹² That said, we caution that the same approach might fall short in ancestrally diverse studies with few European individuals.⁷⁷ Third, our multi-layer variant prioritization framework is built on a series of simple rules that are easy to implement on large datasets. This approach could possibly be formalized as statistical models (e.g., priors in Bayesian methods⁵⁵), but our approach simplifies computation and allows for scalability of the underlying framework. Despite the technical limitations, our approach here can serve as a useful benchmark for future development of methods with improved statistical rigor and computation efficiency.

In summary, mapping noncoding genetic variation of complex traits to biological functions can benefit greatly from thorough integration of multiple layers of functional genomics, as demonstrated in the present study. Although tested on lipids only, our integrative framework is straightforward to implement more broadly on many other phenotypes, yielding functional insights of heritable traits and diseases in humans.

Data and code availability

The accession number for the HLC Capture-C data reported in this paper is <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE189026>.

Supplemental information

Supplemental information can be found online at <https://doi.org/10.1016/j.ajhg.2022.06.012>

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Declaration of interests

G.C.-P. is currently an employee of 23andMe Inc. M.J.C. is the Chief Scientist for Genomics England, a UK Government company. B.M. Psaty serves on the steering committee of the Yale Open Data Access Project funded by Johnson & Johnson. G. Thorleifsson, A.H., D.F.G., H. Holm, U.T., and K.S. are employees of deCODE/Amgen Inc. V.S. has received honoraria for consultations from Novo Nordisk and Sanofi and has an ongoing research collaboration with Bayer Ltd. M. McCarthy has served on advisory panels for Pfizer, NovoNordisk, and Zoe Global and has received honoraria from Merck, Pfizer, Novo Nordisk, and Eli Lilly and research funding from Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, NovoNordisk, Pfizer, Roche, Sanofi Aventis, Servier, and Takeda. M. McCarthy and A. Mahajan are employees of Genentech and holders of Roche stock. M.S. receives funding from Pfizer Inc. for a project unrelated to this work. M.E.K. is employed by SYNLAB MVZ Mannheim GmbH. W.M. has received grants from Siemens Healthineers, grants and personal fees from Aegerion Pharmaceuticals, grants and personal fees from AMGEN, grants from Astrazeneca, grants and personal fees from Sanofi, grants and personal fees from Alexion Pharmaceuticals, grants and personal fees from BASE, grants and personal fees from Abbott Diagnostics, grants and personal fees from Numares AG, grants and personal fees from Berlin-Chemie, grants and personal fees from Akzea Therapeutics, grants from Bayer Vital GmbH, grants from bestbion dx GmbH, grants from Boehringer Ingelheim Pharma GmbH Co KG, grants from Immundiagnostik GmbH, grants from Merck Chemicals GmbH, grants from MSD Sharp and Dohme GmbH, grants from Novartis Pharma GmbH, grants from Olink Proteomics, and other from Synlab Holding Deutschland GmbH, all outside the submitted work. A.V.K. has served as a consultant to Sanofi, Medicines Company, Maze Pharmaceuticals, Navitor Pharmaceuticals, Verve Therapeutics, Amgen, and Color Genomics; received speaking fees from Illumina and the Novartis Institute for Biomedical Research; received sponsored research agreements from the Novartis Institute for Biomedical Research and IBM Research, and reports a patent related to a genetic risk predictor (20190017119). S. Kathiresan is an employee of Verve Therapeutics and holds equity in Verve Therapeutics, Maze Therapeutics, Catabasis, and San Therapeutics. He is a member of the scientific advisory boards for Regeneron Genetics Center and Corvidia Therapeutics; he has served as a consultant for Acceleron, Eli Lilly, Novartis, Merck, Novo Nordisk, Novo Ventures, Ionis, Alnylam, Aegerion, Haug Partners, Noble Insights,

Leerink Partners, Bayer Healthcare, Illumina, Color Genomics, MedGenome, Quest, and Medscape; and he reports patents related to a method of identifying and treating a person having a predisposition to or afflicted with cardiometabolic disease (20180010185) and a genetics risk predictor (20190017119). D.K. accepts consulting fees from Regeneron Pharmaceuticals. D.O.M.-K. is a part-time clinical research consultant for Metabolon, Inc. D. Saleheen has received support from the British Heart Foundation, Pfizer, Regeneron, Genentech, and Eli Lilly pharmaceuticals. P.N. reports investigator-initiated grants from Amgen, Apple, AstraZeneca, Boston Scientific, and Novartis, personal fees from Apple, AstraZeneca, Blackstone Life Sciences, Foresite Labs, Novartis, Roche / Genentech, is a co-founder of TenSixteen Bio, is a scientific advisory board member of Esperion Therapeutics, geneXwell, and TenSixteen Bio, and spousal employment at Vertex, all unrelated to the present work. The spouse of C.J.W. is employed by Regeneron.

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Web resources

Adipose single-cell data, https://singlecell.broadinstitute.org/single_cell/study/SCP133/human-adipose-svf-single-cell
bedtools, <https://bedtools.readthedocs.io/en/latest/>
biomaRt, <https://bioconductor.org/packages/release/bioc/html/biomaRt.html>
Browser of noncoding variant prioritization, http://csg.sph.umich.edu/willer/public/glgc-lipids2021/variant_prioritization.html
CHiCAGO, <https://www.bioconductor.org/packages/release/bioc/html/Chicago.html>
ClinVar, <https://www.ncbi.nlm.nih.gov/clinvar/>
ClusterProfiler, <https://guangchuangyu.github.io/clusterProfiler>
coloc, <https://cran.r-project.org/web/packages/coloc>
DEPICT, <https://data.broadinstitute.org/mpg/depict>
East Asian LD scores and related annotations, <http://jenger.riken.jp/en/data>
ENCODE ChIP-Seq data, <https://hgdownload.cse.ucsc.edu/goldenpath/hg19/encodeDCC/wgEncodeRegTfbsClustered/wgEncodeRegTfbsClusteredWithCellsV3.bed.gz>
European LD scores and related annotations, <https://data.broadinstitute.org/alkesgroup/LDSCORE/>
fgsea, <http://bioconductor.org/packages/release/bioc/html/fgsea.html>
GenomicRanges, <https://bioconductor.org/packages/release/bioc/html/GenomicRanges.html>
GLGC GWAS summary statistics and credible sets, <http://csg.sph.umich.edu/willer/public/glgc-lipids2021/>
GREGOR, <https://genome.sph.umich.edu/wiki/GREGOR>
GTEx v8 summary statistics, <https://www.gtexportal.org/home/datasets>
HepG2 Capture-C data (Chesi et al.²⁰), <https://www.ebi.ac.uk/arrayexpress/experiments/E-MTAB-7144/>
HepG2 Capture-C data (Selvarajan et al.²¹), <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE157306>
HiCUP, <https://www.bioinformatics.babraham.ac.uk/projects/hicup/>
Human liver Hi-C data, <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE58752>

Human white adipocyte Capture-C data, <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE110619>
 LDSC software, <https://github.com/bulik/ldsc>
 liftOver, <https://genome.ucsc.edu/cgi-bin/hgLiftOver>
 Liver single-cell data, <http://shiny.baderlab.org/HumanLiverAtlas/MGI>, <http://www.informatics.jax.org/downloads/reports/index.html#pheno>
 Open chromatin data from HepG2, <https://www.omicsdi.org/dataset/arrayexpress-repository/E-MTAB-7543>
 Open chromatin data from adipose, <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE110734>
 Roadmap epigenomic data (promoters and enhancer annotation), <https://egg2.wustl.edu/roadmap/data/byFileType/chromhmmSegmentations/ChmmModels/coreMarks/jointModel/final/>
 RegulomeDB, <https://regulomedb.org/regulome-search/>
 RSS-NET, <https://github.com/SUwonglab/rss-net>
 S-PrediXcan, <https://github.com/hakyimlab/MetaXcan>

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Supplemental information

A multi-layer functional genomic analysis

to understand noncoding genetic variation in lipids

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Supplemental figures and legends

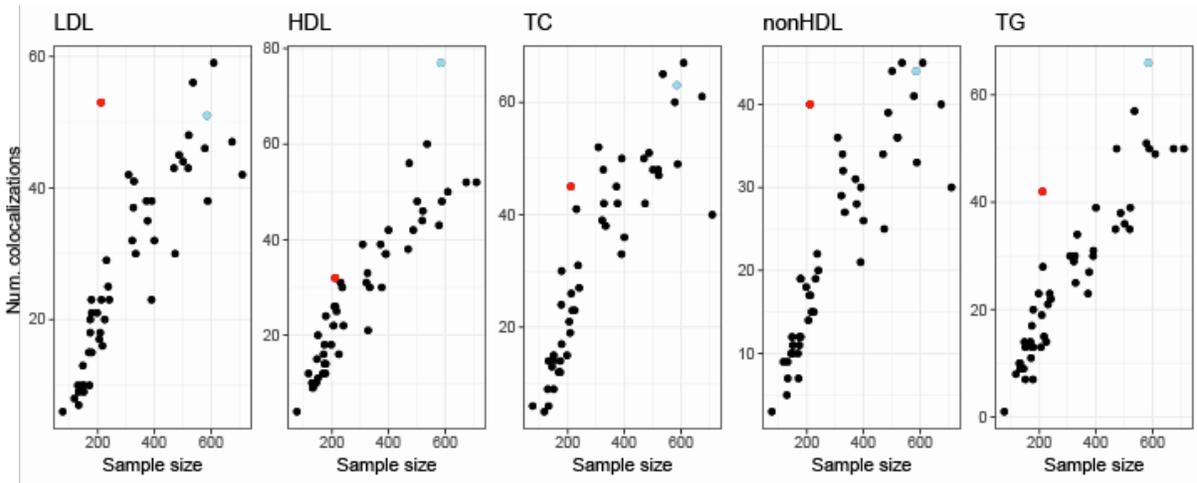


Figure S1. Number of colocalizations per tissue (Y axis) is directly proportional to the eQTL sample size (X axis) for that tissue. The red dot is the liver, the blue dot is adipose subcutaneous.

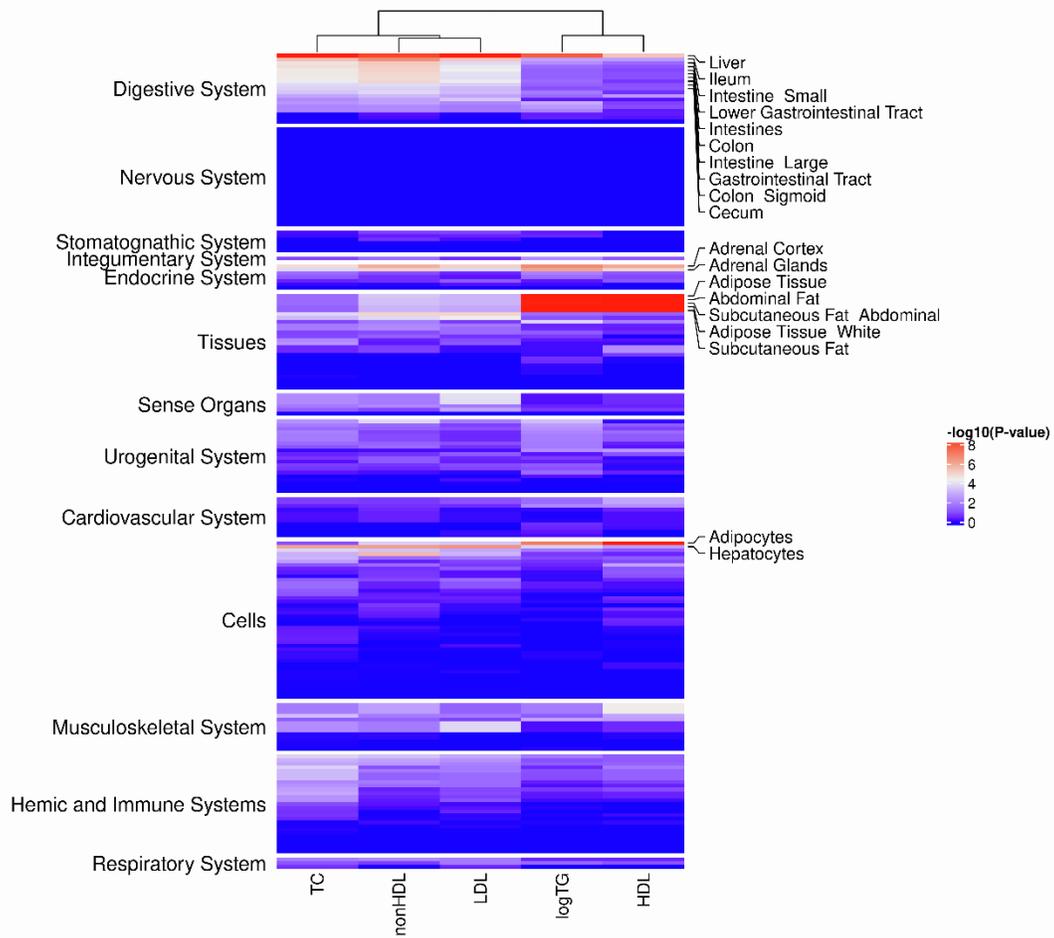


Figure S2. DEPICT analysis on GWAS summary statistics shows different tissues enriched for each lipid phenotype. Adipose-related tissues are particularly enriched in HDL and logTG compared to the liver, which is enriched for all phenotypes.

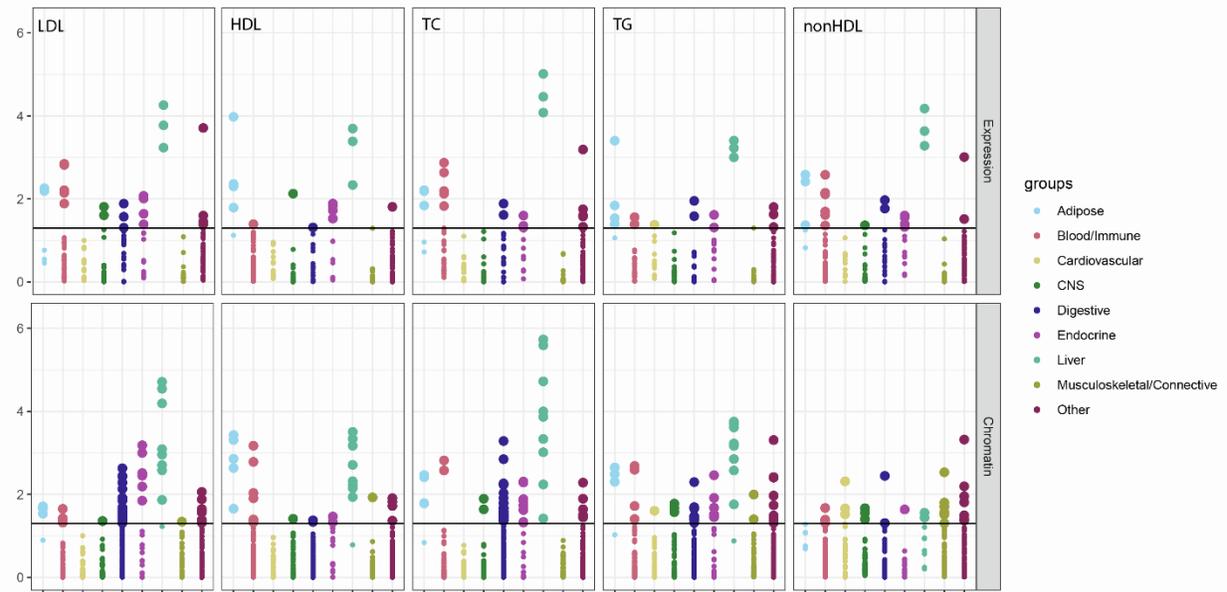


Figure S3. S-LDSC results based on EUR-only GWAS data. The legend is the same as the Figure 3 in the article.

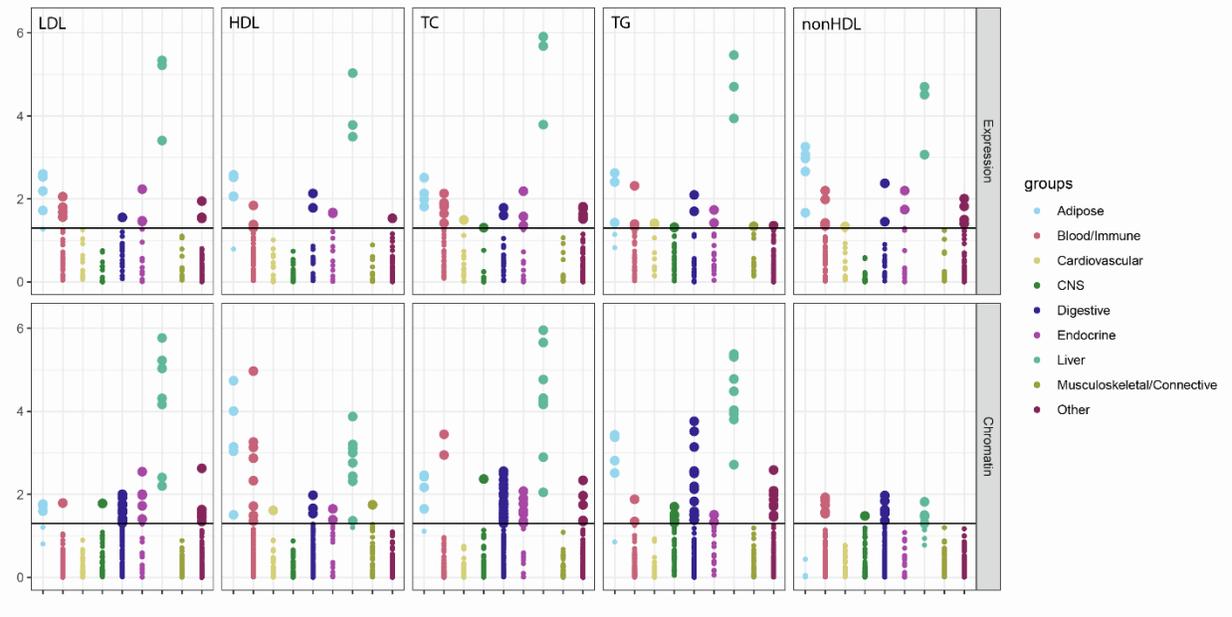


Figure S4. S-LDSC results based on EAS-only GWAS data. The legend is the same as the Figure 3 in the article.

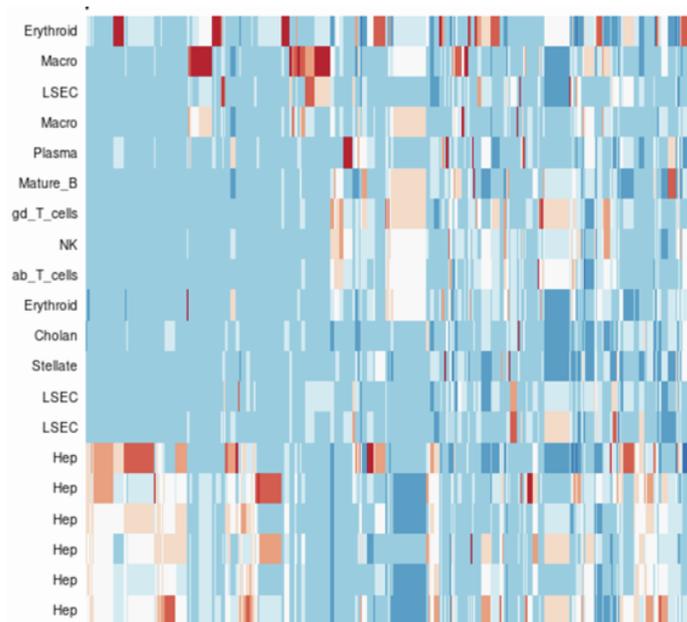


Figure S5. Hierarchical clustering of normalized gene expression for colocalized genes in hepatic cell types (10 cell types organized into 20 single-cell clusters). Hepatocytes (labeled ‘Hep’) are most strongly enriched in gene expression (red shows stronger expression and blue shows weaker). Cell types are labeled as in MacPharland et al, 2018 (Reference 39 in the article; <https://doi.org/10.1038/s41467-018-06318-7>).

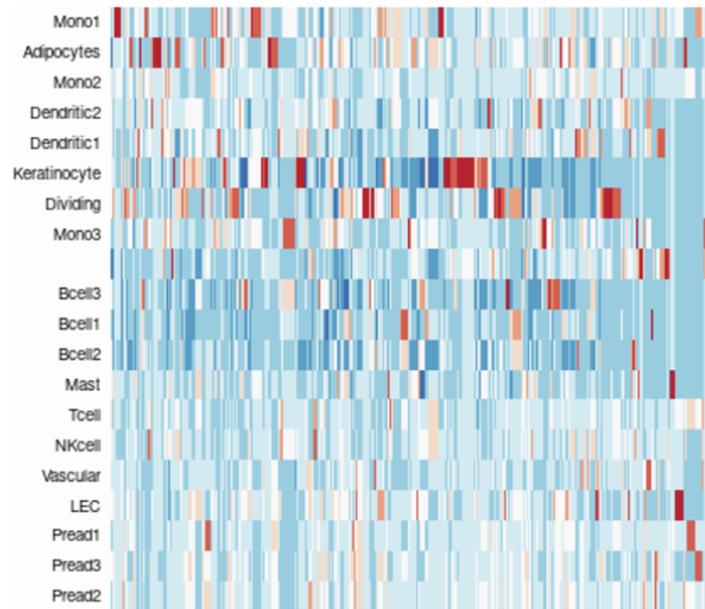


Figure S6. Heatmap of normalized gene expression for colocalized genes in adipose cell types (10 cell types organized into 20 single-cell clusters). Cell type names are monocytes, adipocytes, dendritic, keratinocytes, B cells, mast cells, T-cells, NK cells, vascular cells, lymphatic endothelial cells, preadipocytes.

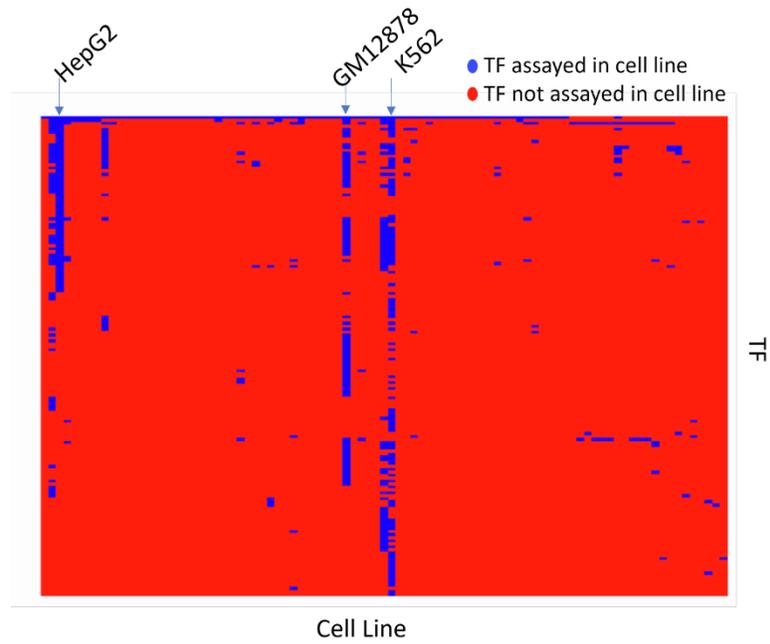


Figure S7. Heatmap of TFs (rows) assayed in ENCODE cell types (columns). Well-assayed cell types are highlighted.

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Genetic Regulation of Arterial Pressure In humans in the Community

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Multi-Ethnic Study of Atherosclerosis

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- VA Northeast Ohio Healthcare System (Frank Jacono, M.D.)
10701 East Boulevard, Cleveland, OH 44106
- Durham VA Medical Center (Jean Beckham, Ph.D.)
508 Fulton Street, Durham, NC 27705
- Edith Nourse Rogers Memorial Veterans Hospital (John Wells., Ph.D.)
200 Springs Road, Bedford, MA 01730
- Edward Hines, Jr. VA Medical Center (Salvador Gutierrez, M.D.)
5000 South 5th Avenue, Hines, IL 60141
- Veterans Health Care System of the Ozarks (Gretchen Gibson, D.D.S., M.P.H.)
1100 North College Avenue, Fayetteville, AR 72703
- Fargo VA Health Care System (Kimberly Hammer, Ph.D.)
2101 N. Elm, Fargo, ND 58102
- VA Health Care Upstate New York (Laurence Kaminsky, Ph.D.)
113 Holland Avenue, Albany, NY 12208
- New Mexico VA Health Care System (Gerardo Villareal, M.D.)
1501 San Pedro Drive, S.E. Albuquerque, NM 87108

- VA Boston Healthcare System (Scott Kinlay, M.B.B.S., Ph.D.)
150 S. Huntington Avenue, Boston, MA 02130
- VA Western New York Healthcare System (Junzhe Xu, M.D.)
3495 Bailey Avenue, Buffalo, NY 14215-1199
- Ralph H. Johnson VA Medical Center (Mark Hamner, M.D.)
109 Bee Street, Mental Health Research, Charleston, SC 29401
- Columbia VA Health Care System (Roy Mathew, M.D.)
6439 Garners Ferry Road, Columbia, SC 29209
- VA North Texas Health Care System (Sujata Bhushan, M.D.)
4500 S. Lancaster Road, Dallas, TX 75216
- Hampton VA Medical Center (Pran Iruvanti, D.O., Ph.D.)
100 Emancipation Drive, Hampton, VA 23667
- Richmond VA Medical Center (Michael Godschalk, M.D.)
1201 Broad Rock Blvd., Richmond, VA 23249
- Iowa City VA Health Care System (Zuhair Ballas, M.D.)
601 Highway 6 West, Iowa City, IA 52246-2208
- Eastern Oklahoma VA Health Care System (Douglas Ivins, M.D.)
1011 Honor Heights Drive, Muskogee, OK 74401
- James A. Haley Veterans' Hospital (Stephen Mastorides, M.D.)
13000 Bruce B. Downs Blvd, Tampa, FL 33612
- James H. Quillen VA Medical Center (Jonathan Moorman, M.D., Ph.D.)
Corner of Lamont & Veterans Way, Mountain Home, TN 37684
- John D. Dingell VA Medical Center (Saib Gappy, M.D.)
4646 John R Street, Detroit, MI 48201
- Louisville VA Medical Center (Jon Klein, M.D., Ph.D.)
800 Zorn Avenue, Louisville, KY 40206
- Manchester VA Medical Center (Nora Ratcliffe, M.D.)
718 Smyth Road, Manchester, NH 03104

- Miami VA Health Care System (Hermes Florez, M.D., Ph.D.)
1201 NW 16th Street, 11 GRC, Miami FL 33125
- Michael E. DeBakey VA Medical Center (Olaoluwa Okusaga, M.D.)
2002 Holcombe Blvd, Houston, TX 77030
- Minneapolis VA Health Care System (Maureen Murdoch, M.D., M.P.H.)
One Veterans Drive, Minneapolis, MN 55417
- N. FL/S. GA Veterans Health System (Peruvemba Sriram, M.D.)
1601 SW Archer Road, Gainesville, FL 32608
- Northport VA Medical Center (Shing Shing Yeh, Ph.D., M.D.)
79 Middleville Road, Northport, NY 11768
- Overton Brooks VA Medical Center (Neeraj Tandon, M.D.)
510 East Stoner Ave, Shreveport, LA 71101
- Philadelphia VA Medical Center (Darshana Jhala, M.D.)
3900 Woodland Avenue, Philadelphia, PA 19104
- Phoenix VA Health Care System (Samuel Aguayo, M.D.)
650 E. Indian School Road, Phoenix, AZ 85012
- Portland VA Medical Center (David Cohen, M.D.)
3710 SW U.S. Veterans Hospital Road, Portland, OR 97239
- Providence VA Medical Center (Satish Sharma, M.D.)
830 Chalkstone Avenue, Providence, RI 02908
- Richard Roudebush VA Medical Center (Suthat Liangpunsakul, M.D., M.P.H.)
1481 West 10th Street, Indianapolis, IN 46202
- Salem VA Medical Center (Kris Ann Oursler, M.D.)
1970 Roanoke Blvd, Salem, VA 24153
- San Francisco VA Health Care System (Mary Whooley, M.D.)
4150 Clement Street, San Francisco, CA 94121
- South Texas Veterans Health Care System (Sunil Ahuja, M.D.)
7400 Merton Minter Boulevard, San Antonio, TX 78229

- Southeast Louisiana Veterans Health Care System (Joseph Constans, Ph.D.)
2400 Canal Street, New Orleans, LA 70119
- Southern Arizona VA Health Care System (Paul Meyer, M.D., Ph.D.)
3601 S 6th Avenue, Tucson, AZ 85723
- Sioux Falls VA Health Care System (Jennifer Greco, M.D.)
2501 W 22nd Street, Sioux Falls, SD 57105
- St. Louis VA Health Care System (Michael Rauchman, M.D.)
915 North Grand Blvd, St. Louis, MO 63106
- Syracuse VA Medical Center (Richard Servatius, Ph.D.)
800 Irving Avenue, Syracuse, NY 13210
- VA Eastern Kansas Health Care System (Melinda Gaddy, Ph.D.)
4101 S 4th Street Trafficway, Leavenworth, KS 66048
- VA Greater Los Angeles Health Care System (Agnes Wallbom, M.D., M.S.)
11301 Wilshire Blvd, Los Angeles, CA 90073
- VA Long Beach Healthcare System (Timothy Morgan, M.D.)
5901 East 7th Street Long Beach, CA 90822
- VA Maine Healthcare System (Todd Stapley, D.O.)
1 VA Center, Augusta, ME 04330
- VA New York Harbor Healthcare System (Scott Sherman, M.D., M.P.H.)
423 East 23rd Street, New York, NY 10010
- VA Pacific Islands Health Care System (George Ross, M.D.)
459 Patterson Rd, Honolulu, HI 96819
- VA Palo Alto Health Care System (Philip Tsao, Ph.D.)
3801 Miranda Avenue, Palo Alto, CA 94304-1290
- VA Pittsburgh Health Care System (Patrick Strollo, Jr., M.D.)
University Drive, Pittsburgh, PA 15240
- VA Puget Sound Health Care System (Edward Boyko, M.D.)
1660 S. Columbian Way, Seattle, WA 98108-1597

- VA Salt Lake City Health Care System (Laurence Meyer, M.D., Ph.D.)
500 Foothill Drive, Salt Lake City, UT 84148
- VA San Diego Healthcare System (Samir Gupta, M.D., M.S.C.S.)
3350 La Jolla Village Drive, San Diego, CA 92161
- VA Sierra Nevada Health Care System (Mostaqul Huq, Pharm.D., Ph.D.)
975 Kirman Avenue, Reno, NV 89502
- VA Southern Nevada Healthcare System (Joseph Fayad, M.D.)
6900 North Pecos Road, North Las Vegas, NV 89086
- VA Tennessee Valley Healthcare System (Adriana Hung, M.D., M.P.H.)
1310 24th Avenue, South Nashville, TN 37212
- Washington DC VA Medical Center (Jack Lichy, M.D., Ph.D.)
50 Irving St, Washington, D. C. 20422
- W.G. (Bill) Hefner VA Medical Center (Robin Hurley, M.D.)
1601 Brenner Ave, Salisbury, NC 28144
- White River Junction VA Medical Center (Brooks Robey, M.D.)
163 Veterans Drive, White River Junction, VT 05009
- William S. Middleton Memorial Veterans Hospital (Robert Striker, M.D., Ph.D.)
2500 Overlook Terrace, Madison, WI 53705