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1 **A multi-layer functional genomic analysis to understand noncoding genetic variation in**
2 **lipids**
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740 **Abstract**

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. Two prioritized genes, *CREBRF* and *RRBPI*, 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 90% of GWAS associations map to non-coding sequences^{1,2}. Mechanistic 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}.

Linking trait-associated variants to genome function has emerged as a promising model for mechanistic interpretation of non-coding findings in GWAS. This 'variant-to-function' model is premised on recent observations that non-coding 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 GWAS has become more feasible as large-scale functional genomic resources, such as epigenomic⁷ and transcriptomic⁸ catalogues, have been systematically generated across a wide range of human cell types and tissues. The integration of functional genomics with GWAS has identified regulatory mechanisms in variants associated with some flagship disorders such as obesity⁹ and schizophrenia¹⁰, 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 GWAS. 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 loci¹¹; 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 loci², and the regulatory mechanism connecting variant to phenotype has been conclusively characterized only for a handful of genes⁵. 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 GWAS to-date of five lipid phenotypes (LDL, or low density lipoprotein; HDL, or high density lipoprotein; TC, or total cholesterol; nonHDL, or non-high density lipoprotein; and TG, or triglycerides) involving 1.65 million individuals from five ancestries¹². 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 demonstrate its real-world value on lipid-associated loci.

Material and Methods

GWAS

We performed GWAS 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 1000 Genomes Phase 3¹⁴. The individual GWAS and meta-analyses were performed using the hg19 version of the human reference genome. We used MR-MEGA¹⁵ for meta-analysis across cohorts.

We defined 'sentinel variants' as lead variants representing independent trait-associated loci in the genome. These windows are the greater of 500kb or 0.25cM around the sentinel variant; genetic distances were defined using reference maps from HapMap 3¹⁶. We performed a second round of conditional analysis, conditioning on the sentinel variants to identify and remove any significant windows that are shadow signals (or dependent on) of a neighboring locus to enforce independence of associated loci.

Colocalization with eQTLs

We performed statistical colocalization of lipid GWAS with eQTLs obtained from GTEx v8 across 49 tissues⁸. 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 statistics⁸. For each of 49 GTEx tissues, we first identified all genes within 1Mb 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' (run on R version 3.4.3, coloc version 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 500kb or 0.25cM on either side of the lead variant), i.e. all SNPs present in both datasets. eQTL summary statistics were in GRCh38, so we first lifted over the GWAS summary statistics (in hg19) to GRCh38 using liftOver¹⁸. As in previous studies¹⁹, 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/tissue types to capture physical interactions between gene promoters and their regulatory elements. We used three biological replicates of HepG2 liver carcinoma cells²⁰, another HepG2 dataset described in Selvarajan et al²¹, 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 an adipose dataset obtained from Pan et al²³ that was produced using primary human white adipocytes.

The detailed protocol to prepare HepG2 or HLC cells for the Capture-C experiment is described in Chesi et al²⁰. 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, totaling 36,691 RNA baited fragments. Each library was then sequenced on an Illumina HiSeq 4000 (HepG2) or Illumina NovoSeq (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 v1.6.0^{24,25} to define significant looping interactions; we defined a CHiCAGO score of 5 as significant, as specified in the default parameters.

858

859 Starting with Capture-C maps processed as described above, we re-annotated the baits to
 860 gene IDs from Gencode v19²⁶ to ensure uniformity of gene annotations with the rest of our
 861 pipeline. For each bait, we identified any gene whose transcription start site (TSS) from any
 862 transcript in Gencode v19 was within 175 base pair distance from the bait (to account for
 863 differing bait designs for external datasets which may not directly overlap the canonical
 864 TSS). We filtered all datasets to only include interactions in which the interacting end was
 865 not another bait. Enrichment with colocalized genes was robust to our choice of distance
 866 between bait and gene (enrichment with eQTL colocalized genes ranging from 2.94-2.96 for
 867 bait distances from 0-350 base pairs).

868

869 To identify genetic variants associated with any of the five lipid traits that physically interact
 870 with locations in the genome, we used the R package 'Genomic Ranges' version 1.30.3²⁷ to
 871 find overlap between credible sets for each trait's GWAS and the previously annotated
 872 promoter Capture-C data; we refer to these as Capture-C/GWAS interactions. Each credible
 873 set was defined as the set of variants with a 95% posterior probability of being the causal
 874 variant. For all individual variants within all GWAS-associated loci for the five lipid traits,
 875 we identified which variants overlapped any interacting end of the four previously annotated
 876 promoter Capture-C data.

877

878 *Presence of gene-variant pairs in same topologically associated domains*

879

880 To estimate the frequency of colocalized gene-sentinel pairs in the same topologically
 881 associated domain (TAD), we used publicly-available TADs from human liver²⁸. We
 882 compared 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 if this ratio was statistically significant, we generated random TAD boundaries using ‘bedtools shuffle’ 1000 times, and calculated the same ratio 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 pathway enrichment in KEGG pathways (using the latest version of the KEGG database³⁰). We first re-mapped gencode IDs to gene symbols using the Gencode v24 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 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 three known sets of lipid-associated genes using the Fisher’s exact test (R function ‘fisher.test’). First, we identified a list of 33 Mendelian genes from ClinVar³² with lipidemia-associated ICD10 codes (E78). Second, we used the set of genes identified from a transcriptome-wide association study (TWAS) on the same GWAS and GTEx v8 summary statistics using the S-PrediXcan software³³ default setup. Third, we used 35 genes with rare-coding variants associated with lipid levels³⁴.

Stratified LD score regression

We used LDSC version 1.0.1³⁵ to estimate the enrichment of heritability 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 and the corresponding LD scores were provided as 'Multitissuegeneexpr1000Gv3' and 'Multitissuechromatin1000Gv3' databases in LDSC software. The TF binding site annotations were extracted from ChIP-seq data of 161 TFs from ENCODE, and their LD scores were estimated from 1000 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 baseline model on each annotation to estimate enrichment of heritability. For primary analyses, we used multi-population GWAS summary statistics and LD scores estimated from 1000 Genomes Phase 3 European samples. For secondary analyses on East Asian GWAS alone, we obtained EAS-specific LD scores for the same epigenomic annotations³⁶.

GREGOR analysis

We used GREGOR³⁷ 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 1Mb, and 'EUR' as the population. Annotations with 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 liver³⁸ 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 calculated the enrichment P-value for our list of colocalized genes using the ‘fgsea’ R package v1.4.1, which looks for overrepresentation of our gene list in ranked genes for each cluster³⁹, 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 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.

Figure 1: Schematic overview of the multi-layer functional genomic analysis. We first integrate GWAS summary statistics for five lipid phenotypes with eQTL and chromatin interaction data to identify potential genes mediating the GWAS association, and then

incorporate epigenomic annotations to identify regulatory mechanisms at these loci. For any lead variant 'X', A, B, and C represent nearby eGenes, and SNPs around SNP X represent variants in the credible set.

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 expression⁴⁰. To do so, we tested for colocalization of each of the 1,750 significant lipid GWAS association signals across the five traits examined with significant cis-eQTL data across 49 human tissues from the GTEx consortium⁸. Here, we defined significant GWAS signals as 1,750 loci reaching genome-wide significance and corrected for shadow signals (Methods) in our multi-population meta-analysis for at least one of five lipid traits.

Second, we restricted our analysis to those loci likely mediated through regulatory mechanisms as opposed to coding variation. In particular, 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; Methods) 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; 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 locus⁴¹ we performed all downstream analyses with all 1,076 colocalized genes, to further prioritize functional genes at loci with multiple eGenes.

To acquire additional functional insights into the 1,076 colocalized genes, we assessed their enrichments across existing biological and clinical gene sets. Colocalized genes showed enrichments in (a) 20 KEGG pathways³⁰ at FDR 5% (Table S2), including known lipid-related processes such as cholesterol metabolism, PPAR signaling, and bile secretion; (b) 33 Mendelian genes from ClinVar³² associated with lipid-related ICD10 codes, (11 fold enrichment at $P=2.08e-06$, including *APOB*, *LPL*, and *APOE*; Figure 2B), suggesting the shared genetic basis of Mendelian and complex lipid phenotypes⁴²; (c) 35 genes with rare-variant burden for lipid phenotypes in a recent multi-ancestry analysis³⁴ (30-fold enrichment, $P = 1.77e-16$, including *APOB*, *LPL*, *LIPG* and *ANGPTL4*), confirming shared mechanisms of rare and common variation underlying lipid traits^{42,43}. Colocalized genes also showed enrichment with genes implicated in TWAS run on the same GWAS and eQTL summary statistics (20-fold enrichment, $P<2.22e-308$). These enrichment results demonstrate the biological relevance of candidate functional genes prioritized by our approach.

Figure 2: Overlap between eQTL colocalized genes and capture-C prioritized genes, and their enrichment in known lipid-associated genes. A. Numbers of genes identified by two

approaches: *eQTL colocalization* (upper half) and *promoter capture-c interactions* (lower half) *B. Overlap between our list of prioritized genes* (left: *capture-C prioritized genes*; right: *eQTL colocalized genes*) *with three sets of genes previously associated with lipid biology* (*ClinVar lipidemia-associated genes*, *genes implicated in rare burden of lipids*, and *genes from a lipid TWAS*). *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. Enrichment estimates and confidence intervals shown in Panels B and C were obtained using Fisher's exact test.*

Chromatin-chromatin interactions improve 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 traits⁴⁴. To add this layer to our analysis, we generated Capture-C data from HepG2 liver carcinoma cells (denoted as HepG2.1) and hepatocyte-like cells (HLC) derived from differentiating iPSCs (the latter is described in²²), as well as publicly-available Capture-C datasets from HepG2^{21,43} (denoted as HepG2.2) and adipose tissue²³. We defined a GWAS-relevant interaction as any Capture-C interaction between any gene and a variant in the 95% credible set for a GWAS locus⁴⁵. 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. In total, 1,079 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; Table S3). Unlike eQTL-colocalized genes, these genes interacting with their credible sets showed limited enrichment in relevant KEGG pathways (Table S2) and lipid-related genes from ClinVar (Figure 2B), though we see 5-fold enrichment (compared to greater than 10-fold enrichment for eQTL-colocalized genes) in genes with rare-variant lipid associations ($P = 2.8 \times 10^{-5}$) and TWAS genes ($P = 2.5 \times 10^{-288}$).

Genes physically interacting with GWAS loci helped shortlist functional genes from eQTL colocalization despite their reduced enrichments in known gene sets. Of 1,079 credible sets with promoter interactions, 224 also colocalized with eQTLs for the same gene. At the gene level, 233 genes were implicated in both eQTL colocalization and Capture-C interactions (Figure 2C), representing an enrichment of 3-fold compared to random chance ($P = 3.11 \times 10^{-38}$). Among these loci with concordant eQTL colocalizations and Capture-C interactions, only 39% of them mapped to a single gene using eQTL data alone, whereas adding Capture-C information increased this fraction to 80%. 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 (TADs) as the genes they regulate⁴⁶, we examined TAD structure from independent datasets at lipid GWAS loci with eQTL colocalizations. Of eQTL-GWAS colocalizations in which the sentinel variant resided within a liver TAD²⁸, the colocalized gene resided in the same liver TAD

84.8% of the time ($P < 0.001$ with 1000 permutations; Methods). When we restricted colocalizations to those supported by Capture-C data in any cell type, 91.2% fall in the same TAD. These results add to the existing evidence for TAD boundaries being regulatory insulators in the cell⁴⁷ 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 manner⁶, as shown in our eQTL colocalization 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), a polygenic approach not restricted to genome-wide significant variants, on tissue-specific transcriptomic and epigenomic annotations across 204 datasets from more than 170 tissues and cell types, to identify relevant tissues for each lipid trait (Methods). Consistent with previous studies and our eQTL-based analysis, liver-related tissues (Table S4) showed strong enrichments across all lipid traits (S-LDSC enrichment p-values ranging from .001 in TG to .0001 in TC), for both expression (Figure 3A) and chromatin annotations (Figure 3B). This result was confirmed by analysis using two other approaches: DEPICT⁴⁸ (Figure S2) and RSS-NET⁴⁹ (Table S5). To assess the robustness of our S-LDSC results based on multi-population

GWAS, we applied S-LDSC to population-specific GWAS in European and East Asian ancestry participants together with population-specific LD scores (Methods) and obtained similar results (Table S6).

Figure 3: Tissue relevance based on lipid GWAS and functional annotations. Partitioning heritability of GWAS summary statistics for five lipid traits on gene expression (A) and chromatin mark (B) annotations across tissues. Each plotted point represents a tested dataset for enrichment of heritability, with larger dots representing datasets with P-value < 0.05; multiple annotation datasets are tested for the same tissue group. Each color represents a tissue group, and the y-axis represents -log₁₀ P-value of enrichment of heritability.

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-value 7.6e-04); for TG, enrichment in liver-related

tissues (P-value 1.2e-03) is similar to enrichment in adipose (P-value 2.7e-03). For LDL, TC, and non-HDL, 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 levels⁵⁰, and the role of adipose as TG deposits⁵¹. These results were corroborated by eQTL colocalizations stratified by phenotype (Figure S1) and DEPICT analysis on gene expression⁴⁸ (Figure S2). Together, these results confirm the liver as the tissue of action for all five lipid traits, and highlight the additional role of adipose in HDL and TG only.

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, we performed gene-set enrichment analysis⁵² to identify cell-type clusters enriched for genes colocalized with any lipid trait. Out of 11 identified cell types in 20 clusters in the liver, only hepatocytes were enriched at FDR-adjusted $P < 0.05$ (Figure S3), consistent with previous results²¹. In adipose, only adipocyte clusters and macrophage-monocyte clusters showed suggestive enrichment (nominal $P < 0.05$) in colocalized genes (Figure S4). Of note, the enrichment in adipocytes was significant when we restricted this analysis to genes that were colocalized only 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

1111

1112 TFs have been implicated as a key mediator of linking genetic variation to complex traits ⁵³.

1113 To understand lipid GWAS in the context of TF activity, we assessed enrichment of genome-

1114 wide significant variants at TF binding sites using GREGOR ³⁷ and performed polygenic

1115 enrichment analysis of TF binding sites using S-LDSC.

1116

1117 Using ChIP-Seq data from 161 TFs across 91 cell types from the ENCODE project ⁷, 70.7%

1118 of lipid credible sets overlapped with at least one TF binding site. Using GREGOR ³⁷, we

1119 identified 137 TFs whose binding sites were significantly enriched in GWAS lead SNPs for

1120 at least one lipid phenotype (enrichment > 2; FDR adjusted P-value < 0.05; Figure S5; Table

1121 S7). Among these 137 enriched TFs, 69 of them (50%) showed significant enrichments

1122 across all five lipid phenotypes, suggesting a potential core regulatory circuit shared by all

1123 lipid traits (Figure S5). The TF with the strongest enrichment in all phenotypes was ESRRA

1124 (estrogen-related receptor alpha), a nuclear receptor active in metabolic tissues ⁵⁴; ESRRA

1125 has been implicated in adipogenesis and lipid metabolism, and ESRRA-null mice display an

1126 increase in fat mass and obesity ⁵⁴.

1127

1128 The GREGOR analysis also highlighted 68 TFs significantly enriched in specific subsets of

1129 (but not all five) lipid phenotypes (Figure S8). For example, we found 4 TFs (FOXM1,

1130 PBX3, ZKSCAN1, ZEB1) enriched in HDL and TG only, 4 TFs (EZH2, NFE2, NFATC1,

1131 KDM5A) enriched in HDL only and 11 TFs (FOSL1, IRF3, JUN, MEF2C, NANOG,

1132 PRDM1, RUNX3, SIRT6, SMC3, STAT3, ZNF217) enriched in TG only. Of these TFs, the

1133 central role of ZEB1 in adiposity ⁵⁵ and fat cell differentiation has been demonstrated ⁵⁶.

1134 Taken together, 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.

Similar to tissue prioritization, we also performed polygenic enrichment analysis of TF binding sites using S-LDSC (Table S8), which differed from GREGOR analysis by looking at not only the genome-wide significant associations but also the polygenic signal irrespective of GWAS P-values. On the same 161 ENCODE TFs, this polygenic analysis identified 25 TFs whose binding sites were significantly enriched in heritability (nominal $P < 0.05$) for at least one lipid phenotype (Figure S6); reassuringly, 24 of 25 TFs were also significant in GREGOR analysis. Among these enriched TFs, eight (34%) were significantly enriched in all five lipid traits (CEBPB, CEBPD, FOXA2, HDAC2, HNF4G, NFYA, RXRA, SP1; $P < 0.05$). Of those TFs significant in both analyses, RXRA (retinoid X receptor alpha) is also 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 metabolism⁵⁷ and homeostasis. Moreover, 145 GWAS loci (Table S9) overlap RXRA binding peaks, suggesting that the GWAS variants might affect lipids (partially) through affecting the binding activity of RXRA. While the *RXRA*-associated variant has been previously implicated as a GWAS locus⁵⁸, 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 improved 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 in the liver or adipose and credible set physical interactions. We next annotated each variant in the 95% credible set with various indicators of regulatory function, including its open chromatin status in liver or adipose-related cell types, its proximity to a promoter or an enhancer, and its RegulomeDB regulation probability⁵⁹ (see Table S10 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 4A). 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 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 GWAS we identified 13 candidate loci, each with the strongest multi-layer evidence pointing to a single functional variant (Table 1). 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 4B). The *RRBP1* eQTL signals in the liver colocalize with LDL, TC, and nonHDL GWAS signals. The 'T' allele of the lead variant (chr20:17,844,684, hg19) decreases *RRBP1* expression levels and increases LDL, TC, and nonHDL levels. This lead variant is in open chromatin in HLC, and physically interacts with the *RRBP1* promoter (250kb away) in adipose and HepG2. 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

1184 very low density lipoprotein (vLDL) levels⁶⁰. Rare variants in *RRBP1* are associated with
 1185 LDL in humans⁶¹ and silencing *RRBP1* in liver affects lipid homeostasis in mice⁶⁰.
 1186
 1187 *Figure 4. An easy-to-implement multi-layer framework to prioritize functional variants at*
 1188 *GWAS loci. A. Variant annotation and prioritization scheme at each credible set. B. Evidence*
 1189 *for gene RRBPI from functional genomics data. The LDL GWAS locus at this region is an*
 1190 *eQTL for gene RRBPI in the liver (second row). Variants in the credible set of this locus*
 1191 *interact with the gene promoter in both adipose and HepG2 Capture-C data. The interacting*
 1192 *variant is also in an open chromatin peak in three liver-related cell types. C. Multiple*
 1193 *sources of functional genomics data support CREBRF as a gene contributing to HDL levels.*
 1194 *The HDL GWAS locus at this region is an eQTL for gene CREBRF in adipose (second row).*
 1195 *Variants in the credible set at this locus interact with the CREBRF promoter in adipose. The*
 1196 *interacting variant is also in open chromatin in liver-related cell types.*

1198

1199 *CREBRF* (CREB3 regulatory factor) demonstrates the power of our multi-layer integration
 1200 framework in prioritizing functional variants (Figure 4C). The eQTL signals of *CREBRF*
 1201 colocalized with a GWAS locus for HDL with 30 candidate variants. In contrast, our multi-
 1202 layer approach identified a single candidate variant (chr5:172,566,698) at this locus that
 1203 physically interacts with the *CREBRF* promoter in adipose, was predicted to be a regulatory
 1204 element (RegulomeDB score=0.91). Consistent with the index variant (chr5:172,591,337),
 1205 the allele 'A' at this functional variant increased HDL levels and increased *CREBRF*
 1206 expression in adipose. Missense variants in *CREBRF* have been linked to body mass index,
 1207 and the gene has been linked to obesity risk in Samoans ⁶².

1208

1209 Finally, to compare the power of functional fine-mapping with trans-ancestry fine-mapping,
 1210 we applied our prioritization rule to credible sets derived from European-only meta-analysis.
 1211 The 111 variants prioritized by our rule described above (including multiple variants in the
 1212 same credible set) were all found in the multi-ancestry credible sets, representing a 3.7 fold
 1213 enrichment ($P < 1e-04$ derived from 10000 permutations randomly sampling variants from
 1214 the European-only credible sets). This convergence of complementary approaches to the
 1215 same smaller set of variants highlights the power of multi-ancestry datasets as an approach to
 1216 narrow in on functional variants.

1217

1218 **Discussion**

1219

1220 Here we integrate the largest multi-population lipid GWAS to date with a wide array of
 1221 functional genomic resources to understand how noncoding genetic variation affects lipids
 1222 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 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 GWAS and expand our understanding of lipid GWAS loci (e.g., *RXRA*) 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^{21,63,64}, the size of our multi-population 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 openness 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 GWAS, current functional datasets⁶⁵ 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 are based on eQTLs from bulk tissue RNA-seq⁸, which may miss detailed cell types and biological processes in which lipid-associated SNPs regulate gene expression⁶⁶. Third, some functional datasets are not available across the full spectrum of human tissues and cell types. For example, our chromatin-chromatin interaction analysis only examines a few cell types in two known lipid-related tissues, producing results that may be biased towards known lipid biology. 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 heterogeneity⁶⁷ 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 modelling multiple correlated SNPs through LD matrix⁶⁸, which is computationally intensive in large-scale analyses derived from many cohorts with diverse ancestries, like the multi-population GWAS examined here. Second, due to restricted access to individual genotypes of 201

cohorts, we cannot produce multi-population 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 descent¹². That said, we caution that the same approach might fall short in ancestrally diverse studies with few European individuals⁶⁹. 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 methods⁴⁹), but certainly simplify computation and improve scalability of our 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.

Description of Supplemental Data

Supplemental data include seven figures and ten tables, and study-specific acknowledgements.

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.P. serves on the steering committee of the Yale Open Data Access Project funded by Johnson & Johnson. G.T., A.H., D.F.G., H.H., U.T., and

1295 K.S. are employees of deCODE/Amgen Inc. V.S. has received honoraria for consultations
1296 from Novo Nordisk and Sanofi and has an ongoing research collaboration with Bayer Ltd.
1297 M.M. has served on advisory panels for Pfizer, NovoNordisk and Zoe Global, has received
1298 honoraria from Merck, Pfizer, Novo Nordisk and Eli Lilly, and research funding from
1299 Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, NovoNordisk,
1300 Pfizer, Roche, Sanofi Aventis, Servier, and Takeda. M.M. and A.M. are employees of
1301 Genentech and a holders of Roche stock. M.S. receives funding from Pfizer Inc. for a project
1302 unrelated to this work. M.E.K. is employed by SYNLAB MVZ Mannheim GmbH. W.M. has
1303 received grants from Siemens Healthineers, grants and personal fees from Aegerion
1304 Pharmaceuticals, grants and personal fees from AMGEN, grants from Astrazeneca, grants
1305 and personal fees from Sanofi, grants and personal fees from Alexion Pharmaceuticals, grants
1306 and personal fees from BASF, grants and personal fees from Abbott Diagnostics, grants and
1307 personal fees from Numares AG, grants and personal fees from Berlin-Chemie, grants and
1308 personal fees from Akzea Therapeutics, grants from Bayer Vital GmbH , grants from
1309 bestbion dx GmbH, grants from Boehringer Ingelheim Pharma GmbH Co KG, grants from
1310 Immundiagnostik GmbH, grants from Merck Chemicals GmbH, grants from MSD Sharp and
1311 Dohme GmbH, grants from Novartis Pharma GmbH, grants from Olink Proteomics, other
1312 from Synlab Holding Deutschland GmbH, all outside the submitted work. A.V.K. has served
1313 as a consultant to Sanofi, Medicines Company, Maze Pharmaceuticals, Navitor
1314 Pharmaceuticals, Verve Therapeutics, Amgen, and Color Genomics; received speaking fees
1315 from Illumina, the Novartis Institute for Biomedical Research; received sponsored research
1316 agreements from the Novartis Institute for Biomedical Research and IBM Research, and
1317 reports a patent related to a genetic risk predictor (20190017119). S.K. is an employee of
1318 Verve Therapeutics, and holds equity in Verve Therapeutics, Maze Therapeutics, Catabasis,
1319 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; 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.S. has received support from the British Heart Foundation, Pfizer, Regeneron, Genentech, and Eli Lilly pharmaceuticals. The spouse of C.J.W. is employed by Regeneron.

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1367 **Web Resources**

- 1368 GLGC 2021 summary statistics: <http://csg.sph.umich.edu/willer/public/glgc-lipids2021/>
- 1369 GTEx v8 summary statistics: <https://www.gtexportal.org/home/datasets>
- 1370 coloc: <https://cran.r-project.org/web/packages/coloc>
- 1371 liftOver: <https://genome.ucsc.edu/cgi-bin/hgLiftOver>
- 1372 HiCUP: <https://www.bioinformatics.babraham.ac.uk/projects/hicup/>
- 1373 CHiCAGO: <https://www.bioconductor.org/packages/release/bioc/html/Chicago.html>
- 1374 GenomicRanges: <https://bioconductor.org/packages/release/bioc/html/GenomicRanges.html>
- 1375 bedtools: <https://bedtools.readthedocs.io/en/latest/>
- 1376 ClusterProfiler: <https://guangchuangyu.github.io/clusterProfiler>
- 1377 biomaRt: <https://bioconductor.org/packages/release/bioc/html/biomaRt.html>
- 1378 ClinVar: <https://www.ncbi.nlm.nih.gov/clinvar/>
- 1379 S-PrediXcan: <https://github.com/hakyimlab/MetaXcan>
- 1380 LDSC software: <https://github.com/bulik/ldsc>
- 1381 LD scores and related annotations: <https://data.broadinstitute.org/alkesgroup/LDSCORE/>
- 1382 DEPICT: <https://data.broadinstitute.org/mpg/depict>
- 1383 RSS-NET: <https://github.com/SUwonglab/rss-net>

1384 Adipose single cell data:

1385 https://singlecell.broadinstitute.org/single_cell/study/SCP133/human-adipose-svf-single-cell

1386 fgsea: <http://bioconductor.org/packages/release/bioc/html/fgsea.html>

1387 GREGOR: <https://genome.sph.umich.edu/wiki/GREGOR>

1388 RegulomeDB: <https://regulomedb.org/regulome-search/>

1389

1390 **Data and Code Availability**

1391 HLC Capture-C data is available at

1392 <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE189026>

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Tables

Table 1. Thirteen prioritized loci with highest confidence of a single functional variant in the credible set. The ‘sentinel’ column represents the lead variant at the locus. ‘Prioritized var’ 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 datasets. The ‘RegDB’ column represents the RegulomeDB score of the prioritized variant.

<i>Gene Name</i>	<i>Tissue</i>	<i>Sentinel</i>	<i>Prioritized Var</i>	<i>Open</i>	<i>CapC</i>	<i>Enhancer</i>	<i>Promoter</i>	<i>RegDB</i>
<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	Both	Ad	0.705
<i>MICAL2</i>	Liver	11:12071855	12221016	Liver	Liver	Liver	Ad	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	Both	Ad	0.60906
<i>FAM210A</i>	Liver	18:13725674	13725674	Liver	Liver	Both	Ad	0.7571
<i>RRBP1</i>	Liver	20:17844684	17844684	Both	Ad	Both	Ad	0.6091