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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 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 epigenomic [7] and transcriptomic [8] 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 obesity [9] 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 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 loci[11] ; the latest study of 1.6 million individuals across five ancestries [12] 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 only for 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 density lipoprotein; TC, or total cholesterol; nonHDL, or non-high density lipoprotein; and TG, or triglycerides) 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 demonstrate its real-world value on lipid-associated loci.

Material and methods

GWAS

We used the recently-published GWAS data for five blood lipid traits (LDL, HDL, TC, TG, and nonHDL) in 1.65 million individuals from five ancestry groups [12] (African and African-admixed, East Asian, European, Hispanic, South Asian) at 91 million variants imputed primarily from the Haplotype Reference Consortium [13] or 1000 Genomes Phase 3 [14]. GWAS

809 of individual cohorts were based on the hg19 version of the human reference genome. MR-
810 MEGA [15] was used for meta-analysis across cohorts.
811
812 We defined 'sentinel variants' as the most significant variant at independent trait-associated
813 loci in the genome. The windows are the greater of 500kb or 0.25cM around the sentinel
814 variant; genetic distances were defined using reference maps from HapMap 3 [16]. We
815 performed a second round of conditional analysis, conditioning on the sentinel variants to
816 identify and remove any significant windows that are shadow signals of (or dependent on) a
817 neighboring locus to enforce independence of associated loci.
818
819 For each sentinel variant, we defined credible sets of potentially causal variants within +-
820 500kb region around the sentinel variant representing the set of variants harboring the causal
821 variant with a 95% posterior probability. Full details of the credible set construction are
822 reported in our recent GWAS publication [12]. The credible sets are freely available (Web
823 resources).
824
825 *Colocalization of GWAS associations with eQTLs*
826
827 We performed statistical colocalization of lipid GWAS with eQTLs obtained from GTEx v8
828 across 49 tissues [8]. For each of the five lipid traits, we used the same sentinel variants defined
829 in the previous section to represent approximately independent GWAS-associated windows
830 (also removing shadow signals as described before). For each such window, we ran eQTL
831 colocalization with GTEx v8 single-tissue cis-eQTL summary statistics [8]. For each of 49
832 GTEx tissues, we first identified all genes within 1Mb of the sentinel SNP, and then restricted
833 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 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) that are present in both datasets. eQTL summary statistics were in GRCh38, so 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 protocol [22]); (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 4000 (HepG2) or Illumina NovoSeq (HLC), generating 1.6 billion read pairs per sample (50 base pair read length.) We used HiCUP v0.7.2 [24] to process the raw FASTQ files into loop calls and CHiCAGO v1.6.0 [25] 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 v19 [26] 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 v19 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 2.94-2.96 for bait distances from 0-350 base pairs).

884 To identify genetic variants associated with any of the five lipid traits that physically interact
885 with locations in the genome, we used the R package 'Genomic Ranges' version 1.30.3 [27] to
886 find overlap between credible sets for each trait's GWAS and the previously annotated
887 promoter Capture-C data. Given the bait end of a gene, we defined a GWAS locus as
888 interacting with this gene if a variant in the credible set for this GWAS locus fell inside the
889 interacting end.
890
891 *Presence of gene-variant pairs in same topologically associated domains*
892
893 To assess the frequency of colocalized gene-sentinel variant pairs in the same topologically
894 associated domain (TAD), we used a list of 2,499 publicly-available TADs from human liver
895 [28] (Web resources). We computed as a fraction the number of colocalizations with the
896 sentinel variant and colocalized gene in the same TAD divided by all colocalizations in which
897 the sentinel variant lies in a TAD. To test if this fraction was statistically significant, we
898 generated random TAD boundaries using 'bedtools shuffle' 1000 times and calculated the
899 same fraction for these randomly-generated TAD boundaries.
900
901 *Pathway enrichment*
902
903 We used ClusterProfiler v3.6.0 [29] to look for pathways over-represented in each gene list:
904 genes with eQTL colocalization and genes interacting with variants in GWAS credible sets.
905 We used the enrichKEGG function to look for enriched pathways in the latest version of the
906 KEGG database [30]. We first re-mapped gencode IDs to gene symbols using the Gencode v24
907 annotation and then used the biomaRt R package v2.34.2 [31] 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's exact test (R function 'fisher.test'). First, we identified 33 Mendelian genes from ClinVar [32] 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 database [34]. Fourth, we identified 4,008 genes from a transcriptome-wide association study (TWAS) on the same GWAS and GTEx v8 summary statistics using the S-PrediXcan software [35] 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 project [7] (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 1.0.1 [36] 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 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-ancestry GWAS summary statistics and LD scores estimated from 1000 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 GREGOR [38] 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 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 liver [39] 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 v1.4.1implemented in R 3.4.3.

Results

We systematically integrated lipid GWAS results [12] 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.

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, 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, Table S2, Table S3). Colocalized genes showed enrichments in (a) 20 KEGG pathways [30] at FDR 5%, including known lipid-related processes such as cholesterol metabolism, PPAR signaling, and bile secretion; (b) 33 Mendelian genes from ClinVar [32] associated with lipid-related ICD10 codes (11.61-fold enrichment, P=2.08e-06, including *APOB, LPL*, and *APOE*), suggesting the shared genetic basis of Mendelian and complex lipid phenotypes [48]; (c) 35 genes with rare-variant burden for lipid phenotypes in a recent multi-ancestry analysis [33] (30.82-fold enrichment, P=1.77e-16, including *APOB, LPL, LIPG* and *ANGPTL4*), confirming shared mechanisms of rare and common variation underlying lipid traits [48,49] ; (d) genes implicated by cholesterol or lipidemia phenotypes in mouse knockouts (3.92-fold enrichment, P=2.18e-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<2.22e-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 HepG2 [21] (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,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, Table S3).These genes were significantly enriched in genes with rare-variant lipid associations (5.36-fold enrichment, P=2.8e-05), genes with lipid-related mouse knockouts (1.43-fold enrichment, P=2.8e-04),and TWAS-prioritized genes (5.05-fold enrichment, P=2.5e-288), but their enrichments were consistently lower than enrichments of eQTL-colocalized genes nonetheless (Figure 2B, Table S3).

Since genes expressed in the liver are most likely to harbour 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, Table S3). For the same database, we observed higher enrichments 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 =3.11e-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=2.89e-65). We observed similar enrichment patterns when analysing 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 harbour 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 dataset [28] 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 1000 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 cell [53] 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 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 (Table S7, Table S8) 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: DEPICT [54] (Figure S2, Table S9) and RSS-NET [55] (Table S10). To assess the robustness of our S-LDSC results based on multi-ancestry GWAS, we applied S-LDSC to population-specific GWAS in European and East Asian ancestry participants together with population-specific LD scores and obtained similar results (Table S11, Figure S3, Figure 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=7.6e-04); for TG, enrichment in liver-related tissues (P=1.2e-03) is similar to enrichment in adipose (P=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 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

1131 analysis on gene expression [54] (Figure S2, Table S9). Together, these results confirm the
1132 liver as a tissue of action for all five lipid traits, and highlight the additional role of adipose
1133 primarily in HDL and TG.
1134
1135 Given the importance of the liver and adipose in modulating lipid levels, we further identified
1136 the relevant cell types within these tissues. Using existing single-cell data from adipose and
1137 liver [39], we performed gene-set enrichment analysis [58] to identify cell-type clusters enriched
1138 for genes with eQTL colocalizations for any lipid trait. Out of 11 identified cell types in 20
1139 clusters in the liver, only hepatocytes were enriched at FDR-adjusted $P < 0.05$ (Figure S5,
1140 Table S12), consistent with previous results[21]. In adipose, only adipocyte clusters and
1141 macrophage-monocyte clusters showed suggestive enrichment (nominal $P < 0.05$) in
1142 colocalized genes (Figure S6, Table S12). Of note, the enrichment in adipocytes was
1143 significant when we restricted this analysis to genes that were colocalized with HDL and TG
1144 (FDR-corrected $P < 0.05$), consistent with the selective enrichments of adipose in HDL and
1145 TG (but not the other lipid traits) from our S-LDSC analysis. Evaluations at cellular
1146 resolution are required to understand the cell-type specific mechanisms underlying lipid
1147 GWAS loci, but our results could form a useful basis for future studies.
1148
1149 *Overlapping GWAS signals with binding sites highlights lipid-relevant TFs*
1150
1151 TFs have been implicated as a key mediator of linking genetic variation to complex traits [59].
1152 To understand lipid GWAS in the context of TF activity, we assessed enrichment of genome-
1153 wide significant variants at TF binding sites using GREGOR [38] and performed polygenic
1154 enrichment analysis of TF binding sites using S-LDSC. Because TFs were not

1155 comprehensively assayed in most cell lines (Figure S7), we used all cell types in our primary
1156 analysis presented below.
1157
1158 Using ChIP-Seq data from 161 TFs across 91 cell types from the ENCODE project [7], 70.7%
1159 of lipid credible sets overlapped with at least one TF binding site. Using GREGOR [38], we
1160 identified 137 TFs whose binding sites were significantly enriched in GWAS lead SNPs for
1161 at least one lipid phenotype (enrichment > 2; FDR adjusted P-value < 0.05; Figure 4A, Table
1162 S13). We obtained similar results when repeating the GREGOR analysis on TF binding sites
1163 derived from HepG2 only (Table S14). To assess the impact of GWAS power on TF
1164 enrichments, we repeated the GREGOR analysis on the same TF binding sites using a
1165 previous version of lipid GWAS [11], and we identified 54 enriched TFs (Table S15). Between
1166 the two versions of lipid GWAS, the total sample size and number of GWAS loci increased
1167 8.7-fold (from 188,577 to 1,650,000) and 11-fold (from 156 to 1750) respectively, but the
1168 number of enriched TFs only increased 2.5-fold (from 54 to 137), suggesting that the large
1169 number of enriched TFs is unlikely driven by the GWAS power alone.
1170
1171 Among these 137 enriched TFs, 69 of them (50%) showed significant enrichments across all
1172 five lipid phenotypes, suggesting a potential core regulatory circuit shared by all lipid traits
1173 (Figure 4A, Table S13). The TF with the strongest enrichment in all phenotypes was ESRRA
1174 (estrogen-related receptor alpha), a nuclear receptor active in metabolic tissues [60]; ESRRA
1175 has been implicated in adipogenesis and lipid metabolism, and ESRRA-null mice display an
1176 increase in fat mass and obesity [60].
1177
1178 The GREGOR analysis also highlighted 68 TFs significantly enriched in specific subsets of
1179 (but not all five) lipid phenotypes (Figure 4A, 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 adiposity [61] 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, 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 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 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, Table S18), suggesting that the GWAS variants

might affect lipids (partially) through affecting the binding activity of RXRA. While *RXRA* has been previously implicated as a GWAS locus [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 liver [20] 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 GWAS 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 (250kb 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 humans [69] 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 ($P < 1e-04$ based on 10000 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 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 [21,71,72], 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 GWAS, current functional datasets [73] 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-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 only examines a few cell types in two known lipid-related tissues, producing results that may be biased towards 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 heterogeneity [75] 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 matrix [76], which is computationally intensive in large-scale analyses derived from many cohorts with diverse ancestries, like the multi-ancestry GWAS 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 methods [55]), 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.

Description of supplemental data

Supplemental data include seven figures and nineteen 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 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.M. has served on advisory panels for Pfizer, NovoNordisk and Zoe Global, 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.M. and A.M. are employees of Genentech and a 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 BASF, 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, 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, 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.K. 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; 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,

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Web resources

Browser of noncoding variant prioritization: http://csg.sph.umich.edu/willer/public/glgc-lipids2021/variant_prioritization.html

GLGC GWAS summary statistics and credible sets: http://csg.sph.umich.edu/willer/public/glgc-lipids2021/

GTEx v8 summary statistics: https://www.gtexportal.org/home/datasets

coloc: https://cran.r-project.org/web/packages/coloc

liftOver: https://genome.ucsc.edu/cgi-bin/hgLiftOver

HepG2 Capture-C data (Chesi et al): https://www.ebi.ac.uk/arrayexpress/experiments/E-MTAB-7144/

HepG2 Capture-C data (Selvarajan et al): https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE157306

Human white adipocyte Capture-C data: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE110619

HiCUP: https://www.bioinformatics.babraham.ac.uk/projects/hicup/

CHiCAGO: https://www.bioconductor.org/packages/release/bioc/html/Chicago.html

GenomicRanges: https://bioconductor.org/packages/release/bioc/html/GenomicRanges.html

Human liver Hi-C data: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE58752

bedtools: https://bedtools.readthedocs.io/en/latest/

ClusterProfiler: https://guangchuangyu.github.io/clusterProfiler

biomaRt: https://bioconductor.org/packages/release/bioc/html/biomaRt.html

ClinVar: https://www.ncbi.nlm.nih.gov/clinvar/

MGI: http://www.informatics.jax.org/downloads/reports/index.html#pheno

S-PrediXcan: https://github.com/hakyimlab/MetaXcan

ENCODE ChIP-Seq data:
https://hgdownload.cse.ucsc.edu/goldenpath/hg19/encodeDCC/wgEncodeRegTfbsClustered/wgEncodeRegTfbsClusteredWithCellsV3.bed.gz

LDSC software: https://github.com/bulik/ldsc

European LD scores and related annotations:
https://data.broadinstitute.org/alkesgroup/LDSCORE/

East Asian LD scores and related annotations: http://jenger.riken.jp/en/data

DEPICT: https://data.broadinstitute.org/mpg/depict

RSS-NET: https://github.com/SUwonglab/rss-net

Liver single-cell data: http://shiny.baderlab.org/HumanLiverAtlas/

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

fgsea: http://bioconductor.org/packages/release/bioc/html/fgsea.html

GREGOR: https://genome.sph.umich.edu/wiki/GREGOR

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/

Data and code availability

The HLC Capture-C data is available at

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

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Figure titles and legends

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.

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 and promoter *Capture*-C interaction. 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 confidence intervals shown in Panels B and C are based on the Fisher’s 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.

Figure 3. Tissue relevance of lipid-associated loci. Partitioning heritability of 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 P-value < 0.05. Each color represents a tissue group (Table S6), and the y-axis represents -log10 P-value of enrichment of heritability.

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 subset of lipid phenotypes with colocalization. Larger node sizes represent smaller GWAS P-value of colocalized loci.

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 gene *RRBP1* from functional genomics data. The LDL GWAS locus at this region (first row) is an eQTL for gene *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 gene *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).

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. 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.

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