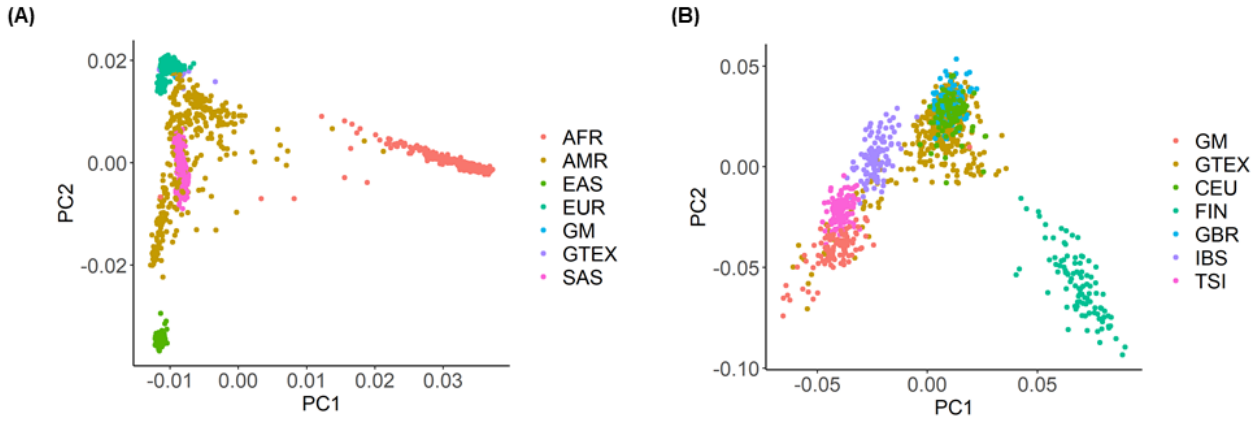
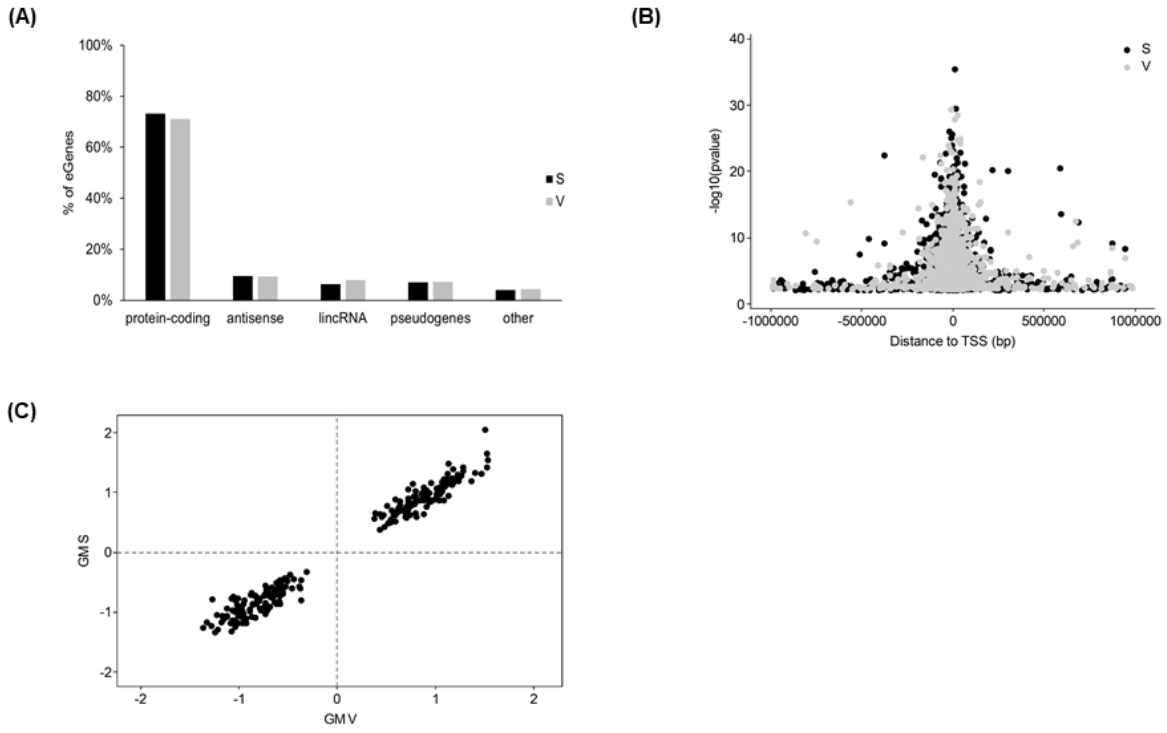
Additional File 1 (Supplementary Figures S1-S16)



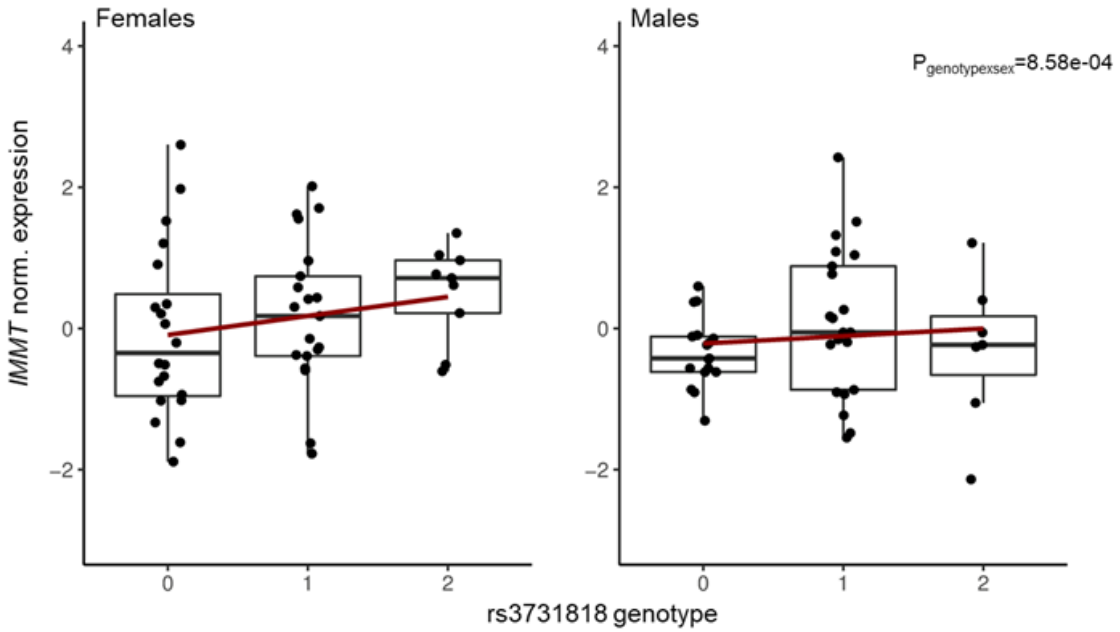
Supplementary Figure S1. GM individuals map close to Italian and Spanish populations.

Principal component analysis (PCA) of genotype data (MAF≥0.05) reveals that GM individuals map close to: (A) the 1KG EUR superpopulation, and (B) the IBS and TSI 1Kg populations. Abbreviations: GM, Greek Metabolic study; GTEX, GTEx-ancestry-matched; CEU, Central European; FIN, Finnish; GBR, British; IBS, Iberian; TSI, Tuscan, AFR, African; AMR, Admixed American; EAS, East Asian; EUR, European; SAS, South Asian.



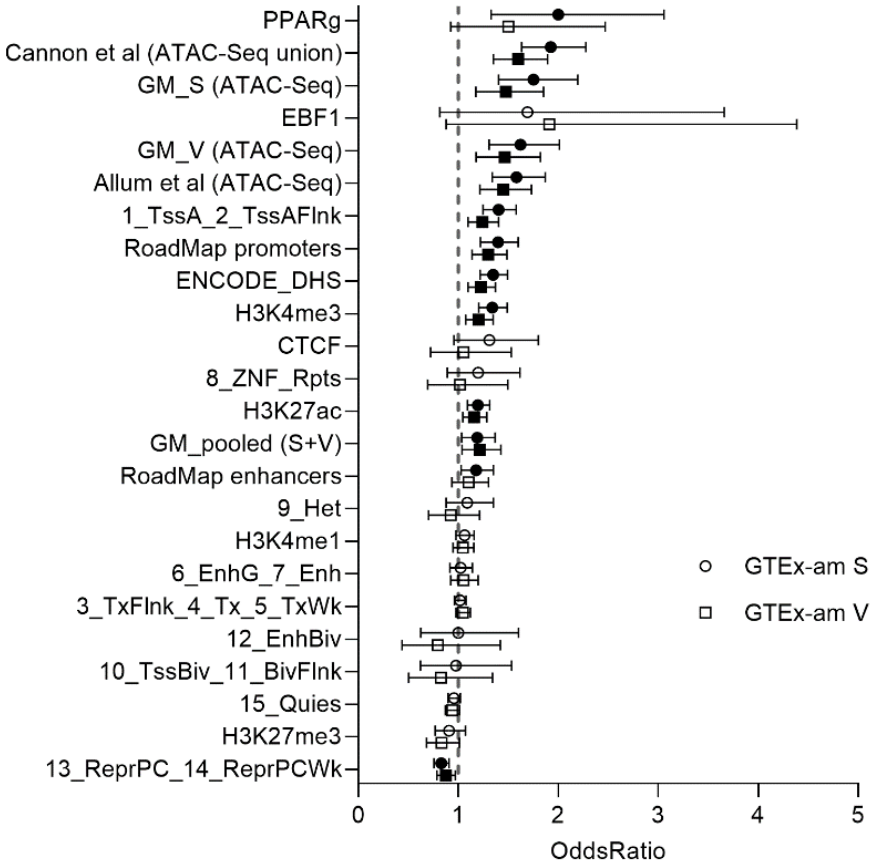
Supplementary Figure S2. Overview of eQTL mapping results in GM

(A) Distribution of biotypes for eGenes detected in GM tissues. (B) Clustering of eQTLs around TSS. (C) Direction of effect of shared eQTLs between S and V adipose tissue (R=0.988, P<1e-04).



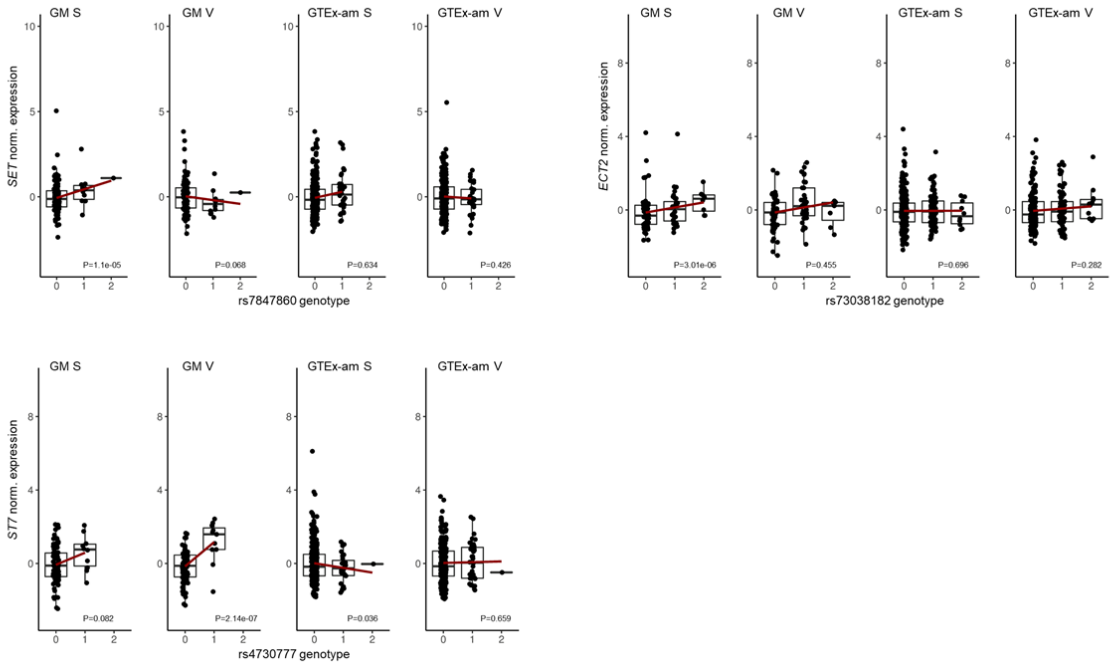
Supplementary Figure S3. An example of a Genotype×Sex regulatory interaction in *IMMT* gene in GM S

IMMT; Inner Membrane Mitochondrial Protein. This association did not pass FDR 5% threshold.



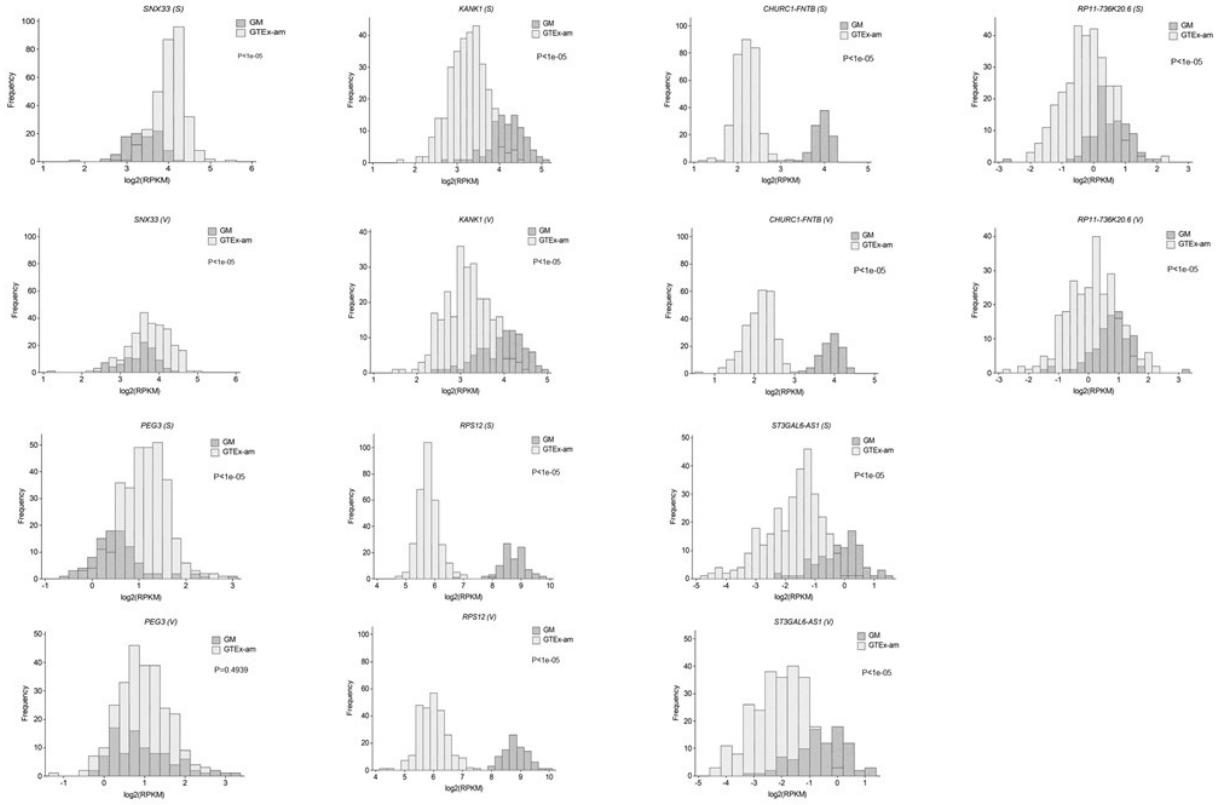
Supplementary Figure S4. Enrichment of GTEx-am eQTLs in adipose tissue functional annotations

Enrichment of GTEx-am eQTLs in adipose tissue functional annotations is shown as estimated odds ratios and 95% confidence intervals on the x axis for each annotation category on the y axis. Odds ratios greater than 1 indicate an enrichment of QTL variants in the given functional annotations, while odds ratios less than 1 indicate a depletion. Significant odds ratios are shown as filled circles or squares ($P < 0.05$). References Allum et al and Cannon et al are reported in the manuscript text.



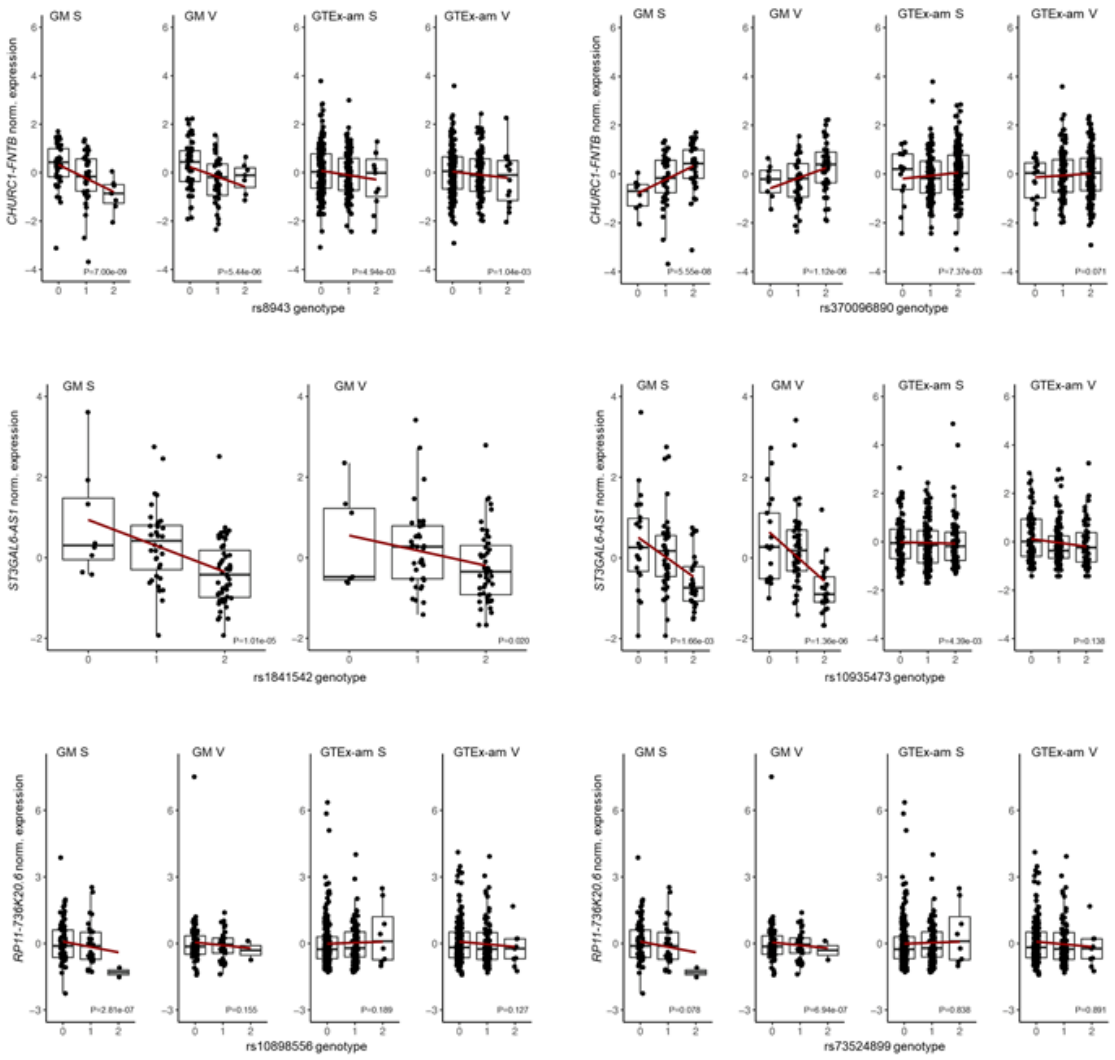
Supplementary Figure S5. eQTL plots for the oncogenes *SET, ECT2 and ST7*, showing population-specific regulatory effects

These eQTLs were found in GM only based on pi1 analysis. P-values represent association nominal p-values.



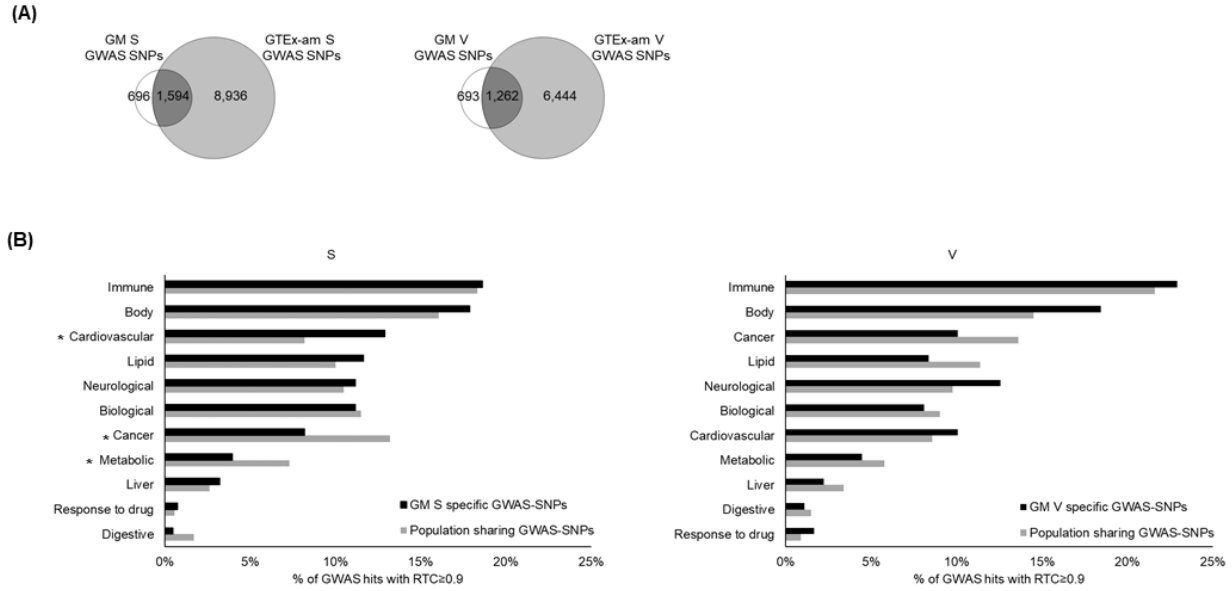
Supplementary Figure S6. Differences in expression patterns of eGenes detected in GM, but not in GTEx-am

We hypothesize that the observed differences may arise in part due to environmental factors. Histogram p-values are derived from M-W test.



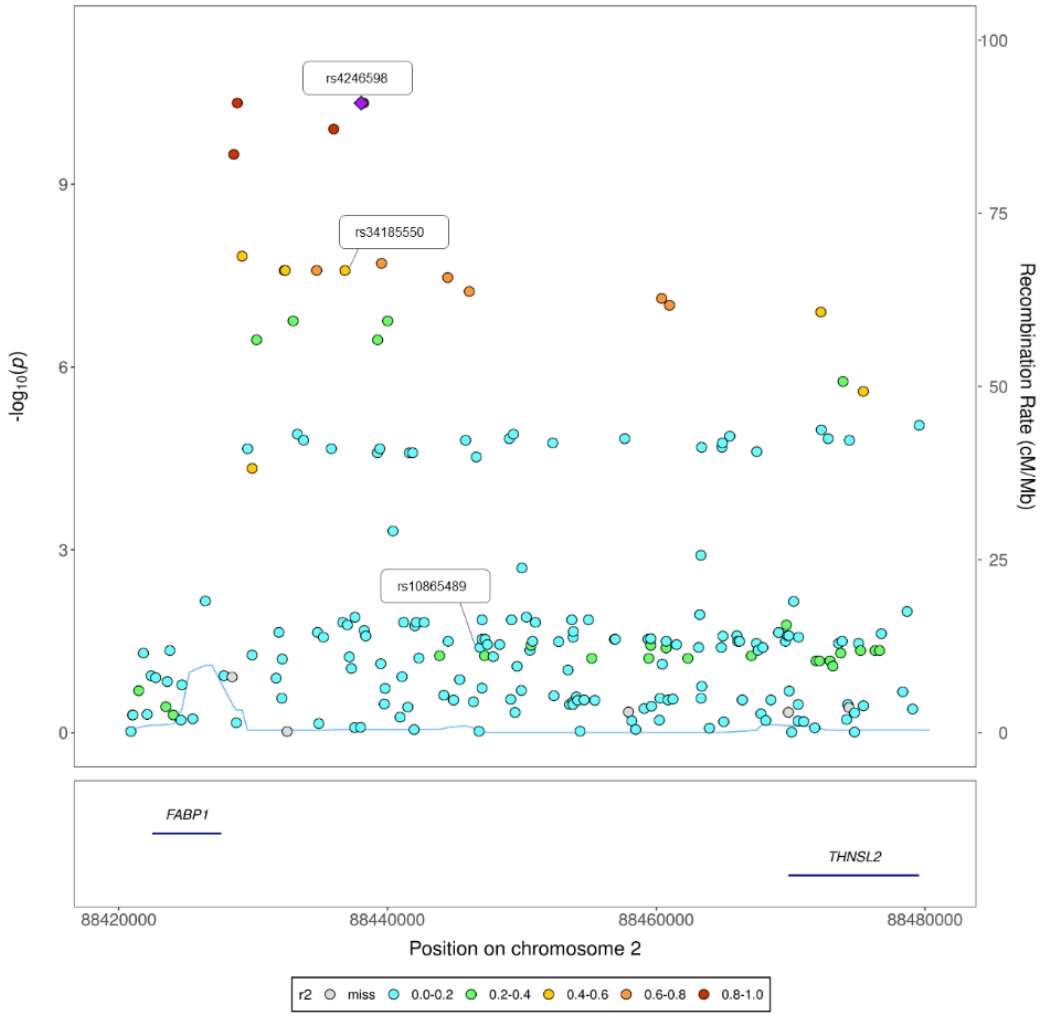
Supplementary Figure S7. eQTL plots for non protein-coding eGenes detected in GM only, displaying distinct expression patterns across populations

Genes were identified as eGenes in GM, but not GTEx-am. The associated eQTLs differ between S and V tissue of GM. P-values represent association nominal p-values.



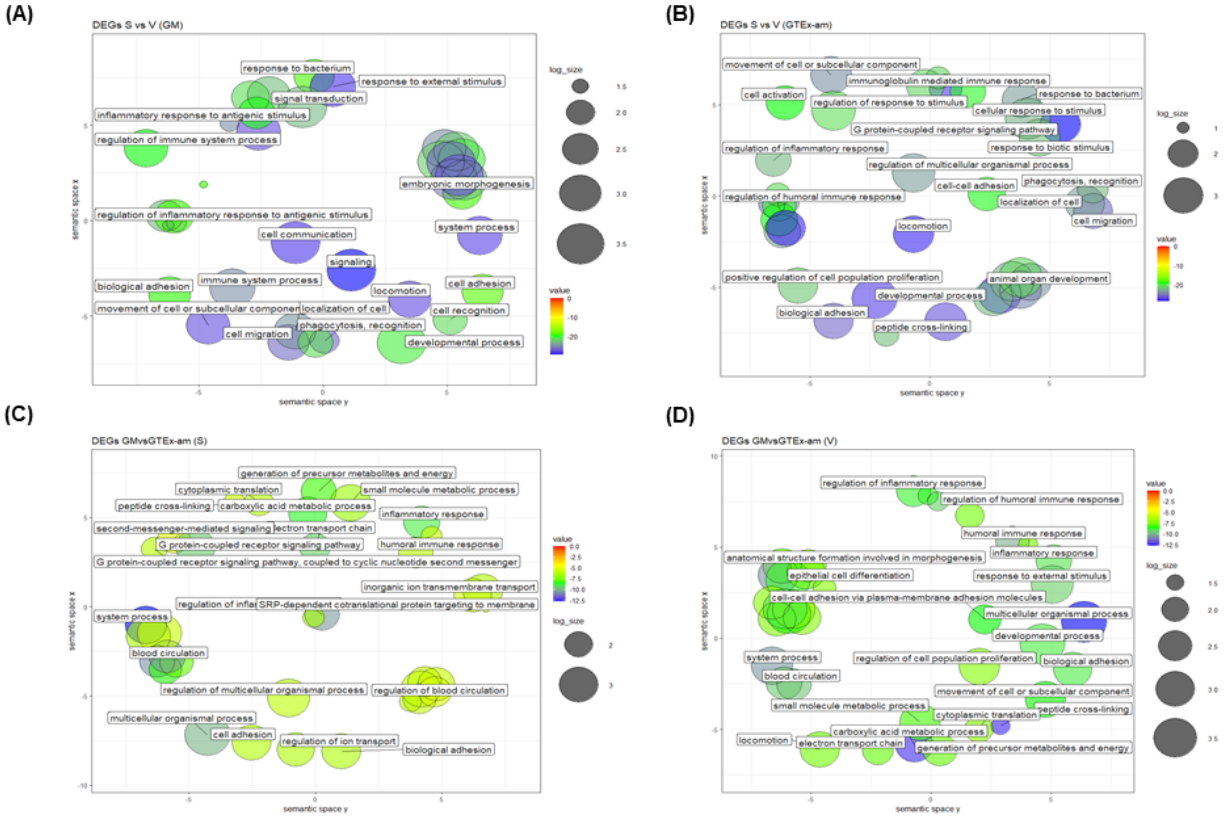
Supplementary Figure S8. Overlap of colocalizing GWAS SNPs between GM and GTEx-am

(A) Venn diagram of GWAS SNPs across GM and GTEx-am for each tissue. (B) Frequency in % of EFO categories related to GWAS signals that are specific to GM or population sharing. Statistical significance was tested using Fisher's test (* for P<0.05).



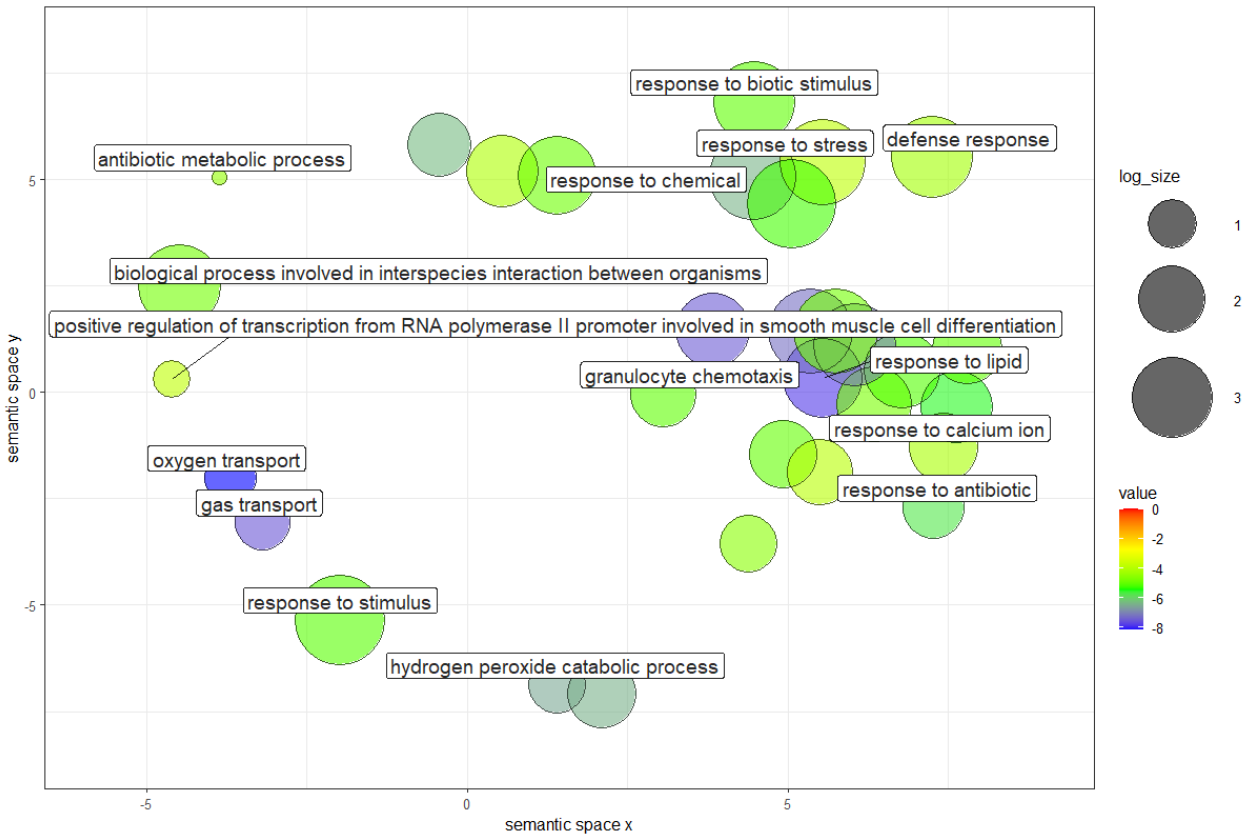
Supplementary Figure S9. Secondary eQTL for *THNSL2* in GM S colocalizes with a GWAS signal associated with CRP levels

A regional association plot is presented. The GWAS variant associated with CRP levels, rs4246598 (top), colocalizes with the secondary eQTL rs34185550 (middle), but not with the primary eQTL rs10865489 (bottom). Variants are colored by the strength of their LD with the GWAS variant (diamond), with darker colors indicating stronger LD. T*HNSL2:* Threonine Synthase Like 2.



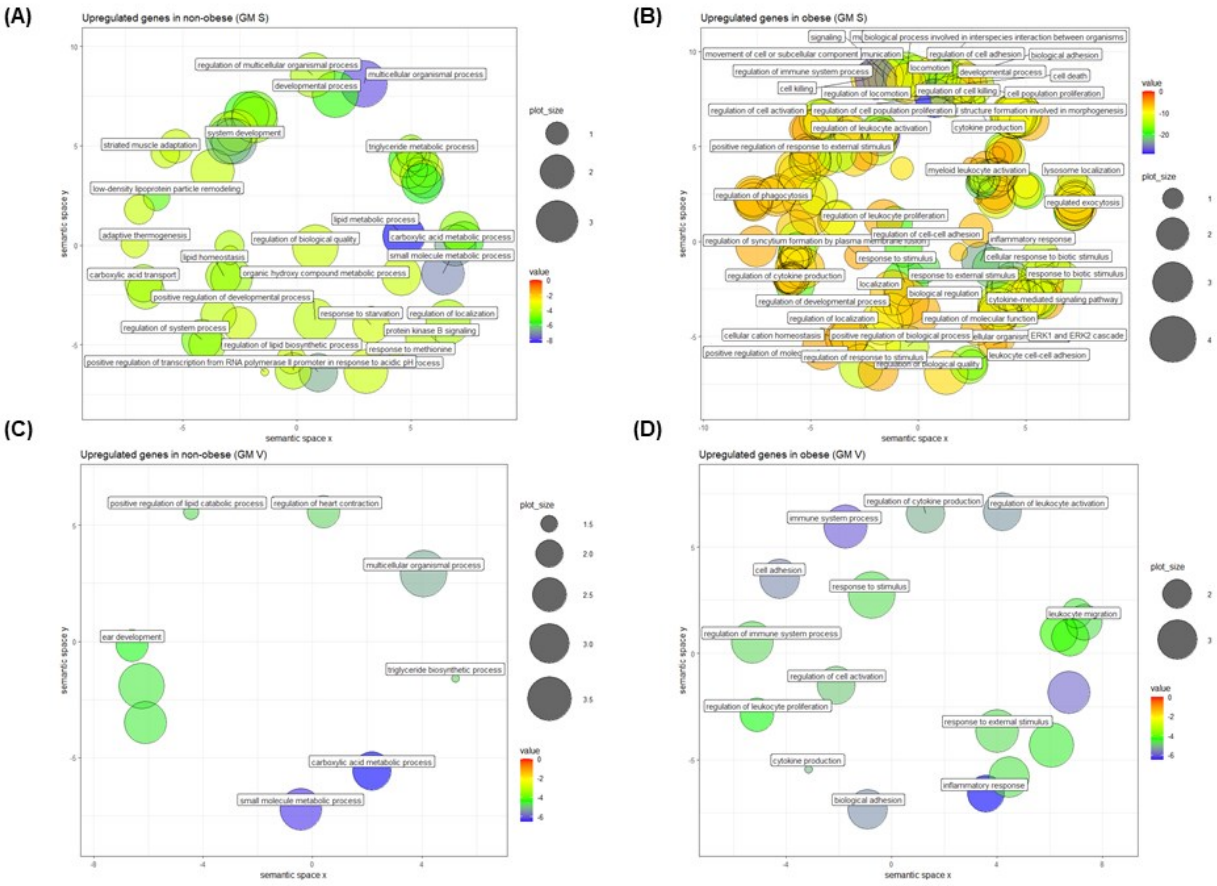
Supplementary Figure S10. REVIGO summary for DEGs by tissue and population

(A) 2,979 S vs V DEGs in GM. (B) 5,320 S vs V DEGs in GTEx-am. (C) 12,459 GM vs GTEx-am DEGs in S. (D) 11,652 GM vs GTEx-am DEGs in V. Top 50 statistically significant GO BP terms were used as input for REVIGO.



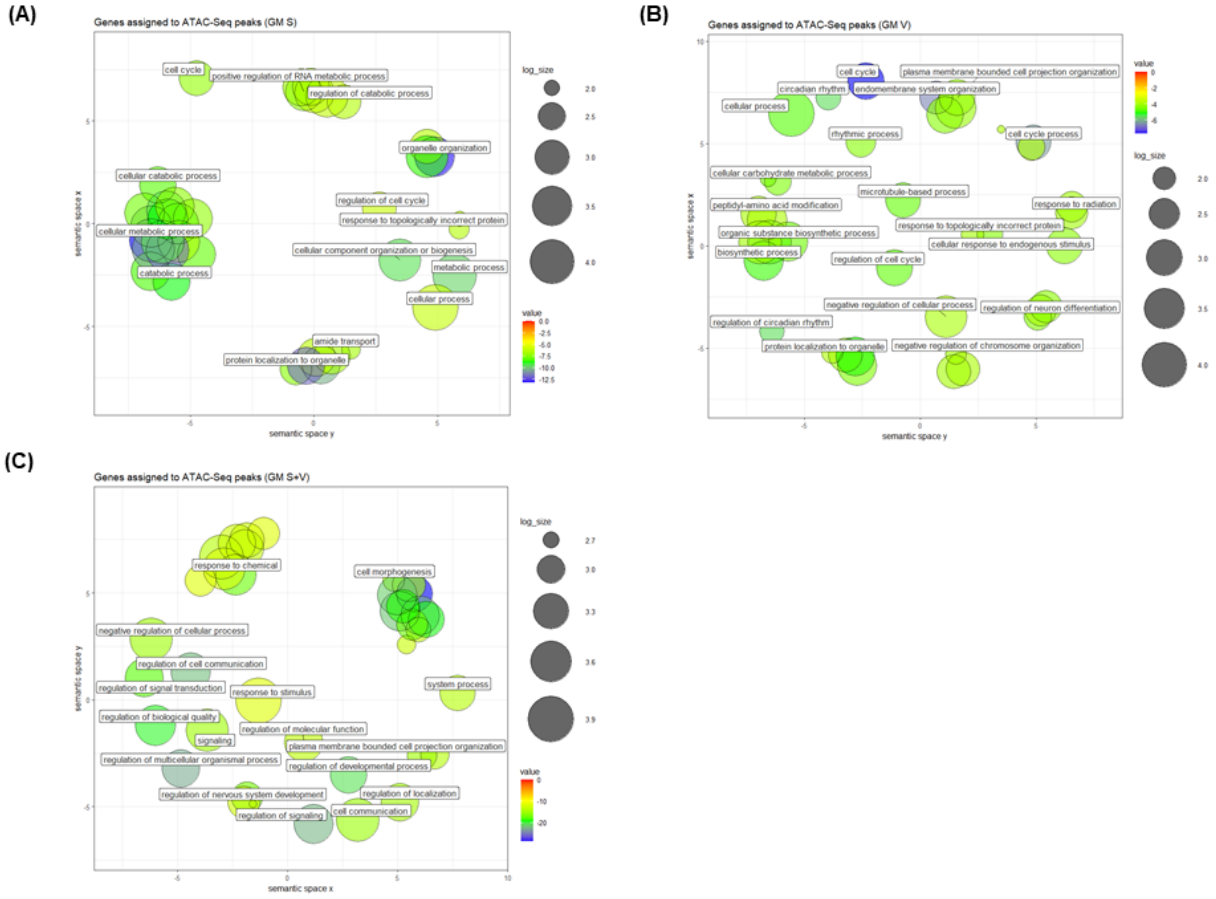
Supplementary Figure S11. REVIGO summary for 151 S vs V DEGs detected in both GM and GTEX-am, showing discordant direction of gene expression

Top 50 statistically significant GO BP terms were used as input for REVIGO.



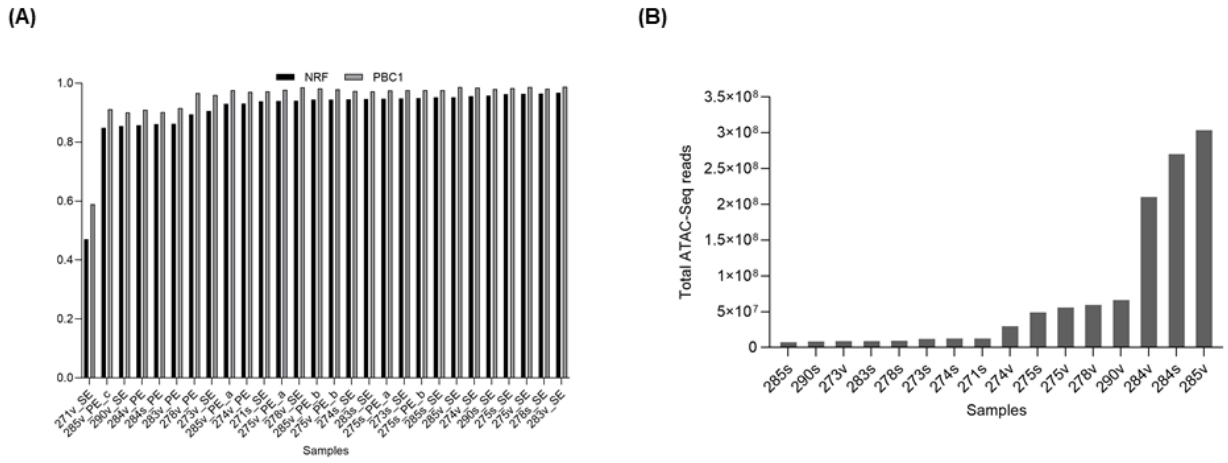
Supplementary Figure S12. REVIGO summary for DEGs by obesity status in GM

In GM S, (A) 352 upregulated genes in non-obese and (B) 702 upregulated genes in obese individuals. In GM V, (C) 166 upregulated genes in non-obese and (D) 263 upregulated genes in obese individuals. Top 50 statistically significant GO BP terms were used as input for REVIGO.



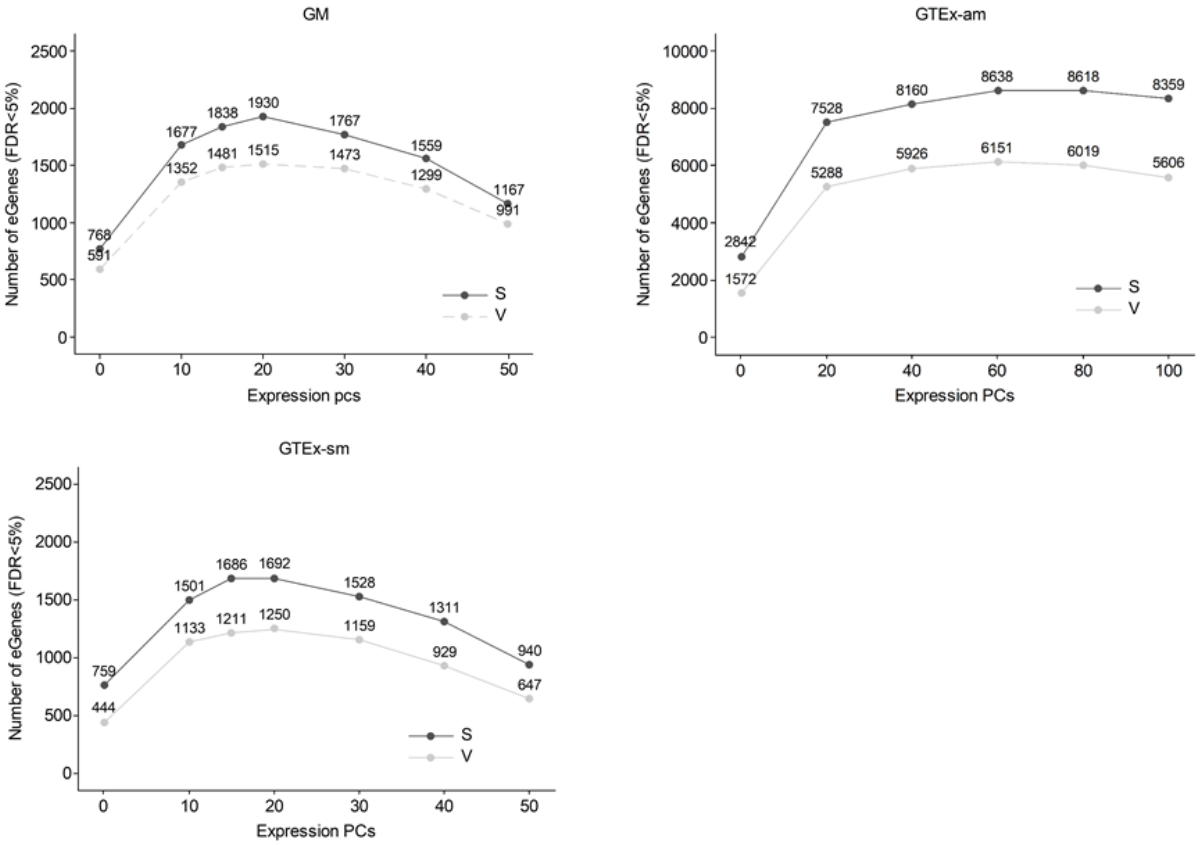
Supplementary Figure S13. Chromatin accessibility landscape in GM based on ATAC-Seq data

REVIGO summary of GO_BP terms for genes assigned to (A) 16,907 ATAC-Seq peaks in S, (B) 14,700 ATAC-Seq peaks in V and (C) 121,673 global (S+V) adipose peaks. Top 50 statistically significant GO BP terms were used as input for REVIGO.



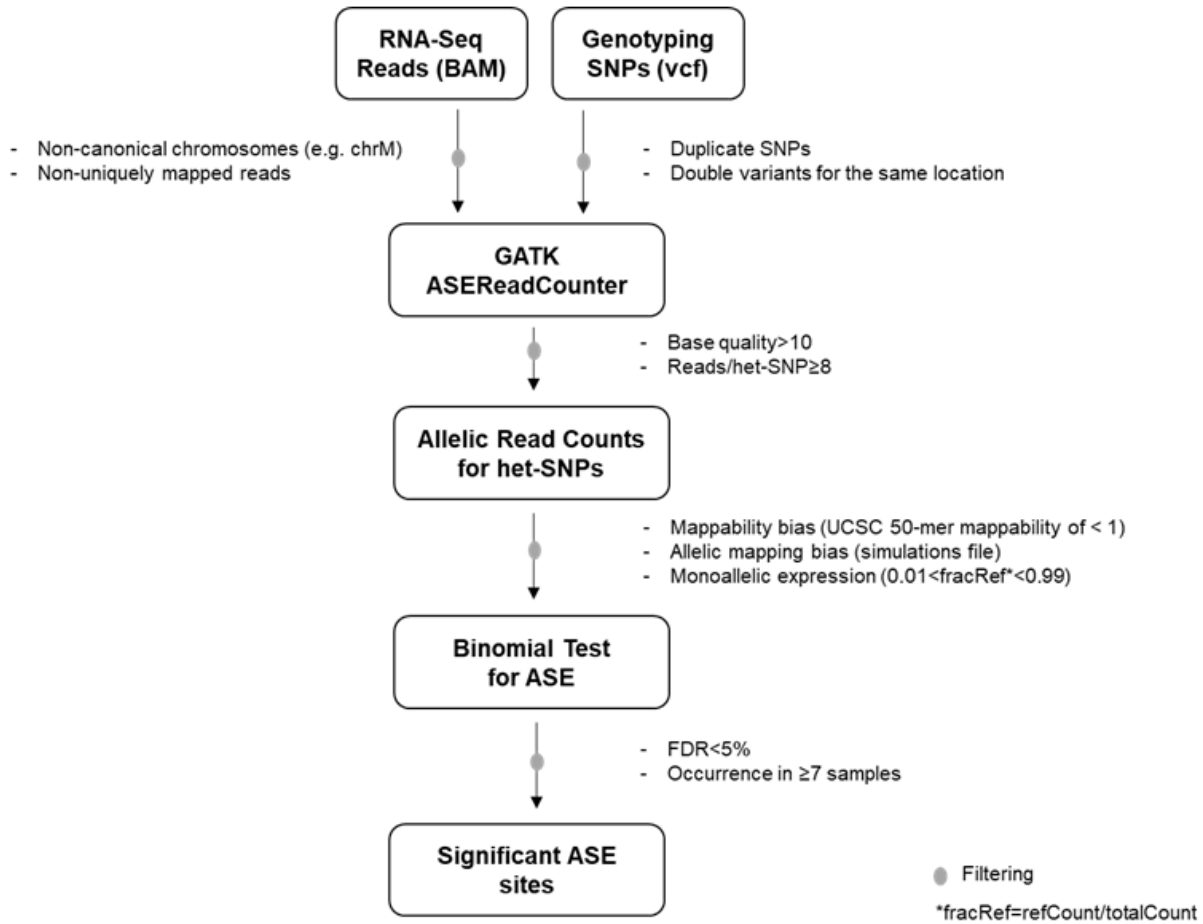
Supplementary Figure S14. Quality control (QC) of ATAC-Seq data

(A) NRF (non-redundant fraction) and PBC1 (PCR Bottlenecking Coefficient 1) were tested for measuring library complexity (values >0.7, based on ENCODE standards, are considered acceptable). (B) Number of total reads for 16 libraries retained after QC.



Supplementary Figure S15. Plot of detected eGenes depending on number of expression PCs added to eQTL mapping model

We tested different numbers of expression PCs as covariates in eQTL mapping in order to maximize power for eGene discovery. Using the threshold of FDR<5%, we found that 20, 60 and 20 expression PCs in GM, GTEx-am and GTEx-sm respectively, maximized eGene discovery and were used for eQTL mapping in each group accordingly. GM, Greek Metabolic study. GTEx-am, GTEx-ancestry-matched. GTEx-sm, GTEx-size-matched.



Supplementary Figure S16. Allele-specific expression (ASE) workflow in GM

Additional File 2

Supplementary Text S1

Analysis of the GTEx-sm population sample

To match for ancestry, size and phenotypic characteristics (age, sex ratio, % obesity), we performed all eQTL analyses in the GTEx-sm population sample. For the eQTL mapping, we retained variants with MAF≥0.05 in GTEx-sm (~6.2M) accounting for differences in sample size (compared to MAF>=0.01 in GTEX-am). Cis-eQTLs were mapped in S and V for 95 and 93 samples respectively. We detected similar levels of eGenes (1,692 in S and 1,250 in V; 807 shared) as in GM (**Additional File 2: Supplementary Table S20**). Comparison of GM to GTEx-sm eQTLs yielded replication rates of 82% in S and 86% in V. Similar to GM levels of GWAS-eQTL colocalization were observed in GTEx-sm (~48%) (**Additional File 2: Supplementary Table S21**). We also performed differential expression in GTEx-sm and found similar to GTEx-am number of DEGs (5,283 genes) (**Additional File 2: Supplementary Table S14**).

Additional File 3

Supplementary Text S2

Open chromatin profiling (ATAC-Seq) and QC

We performed ATAC-Seq on paired samples of S and V from nine individuals (18 samples) on the Illumina HiSeq2000 by using single-end 50bp sequencing mode (SEx50). We also sequenced a subset of samples with paired-end mode (PEx100), resulting in 28 sequenced samples. After trimming 100bp to 50bp reads and mapping to hg19 using BWA, we applied QC analysis. We excluded two samples that had low library complexity, as indicated by NRF (non-redundant fraction) and PBC1 (PCR Bottlenecking Coefficient 1) or low signal-to-noise ratio. For the 14 samples sequenced in both single- or paired-end mode, BAM files were merged, resulting in a total number of 16 samples (seven individuals with paired samples and two individuals only from S), retained for further analysis.