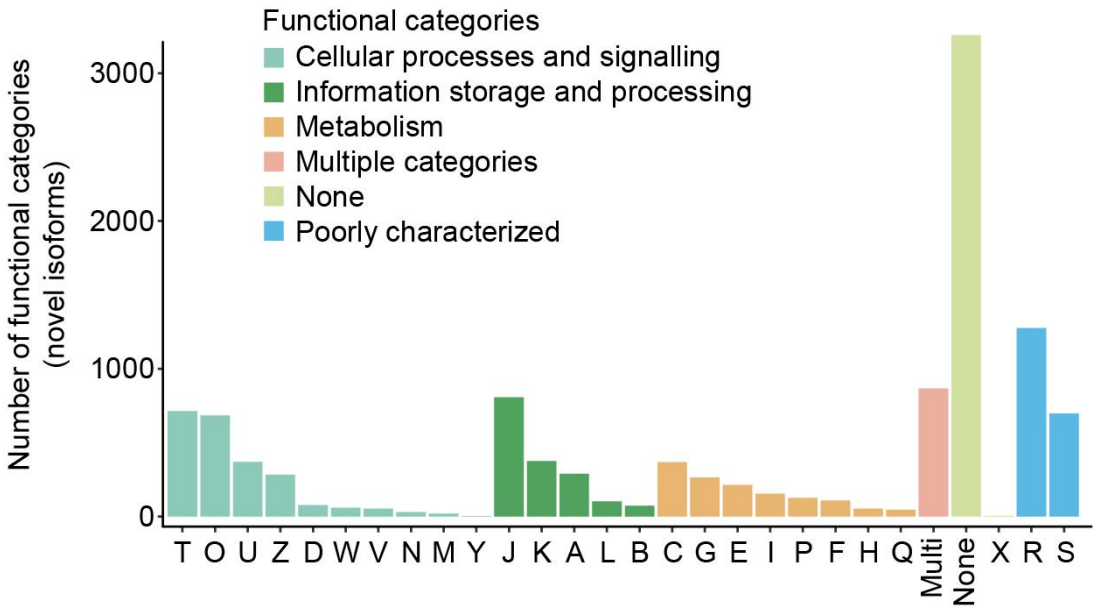
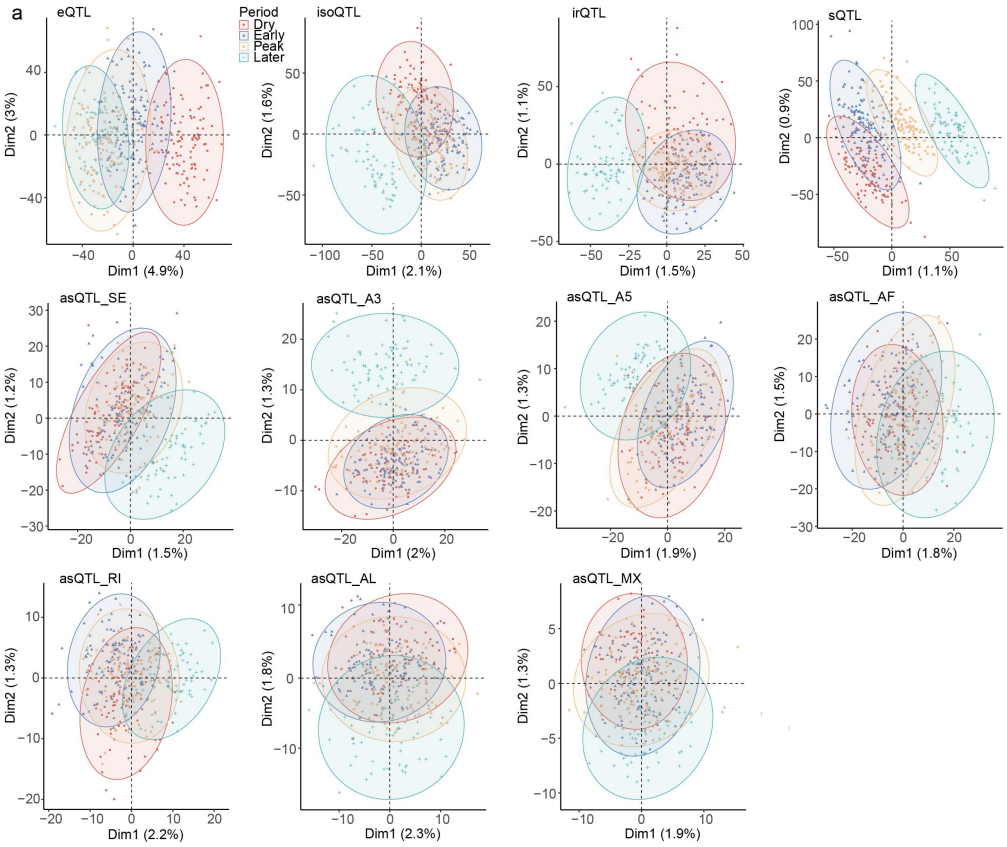
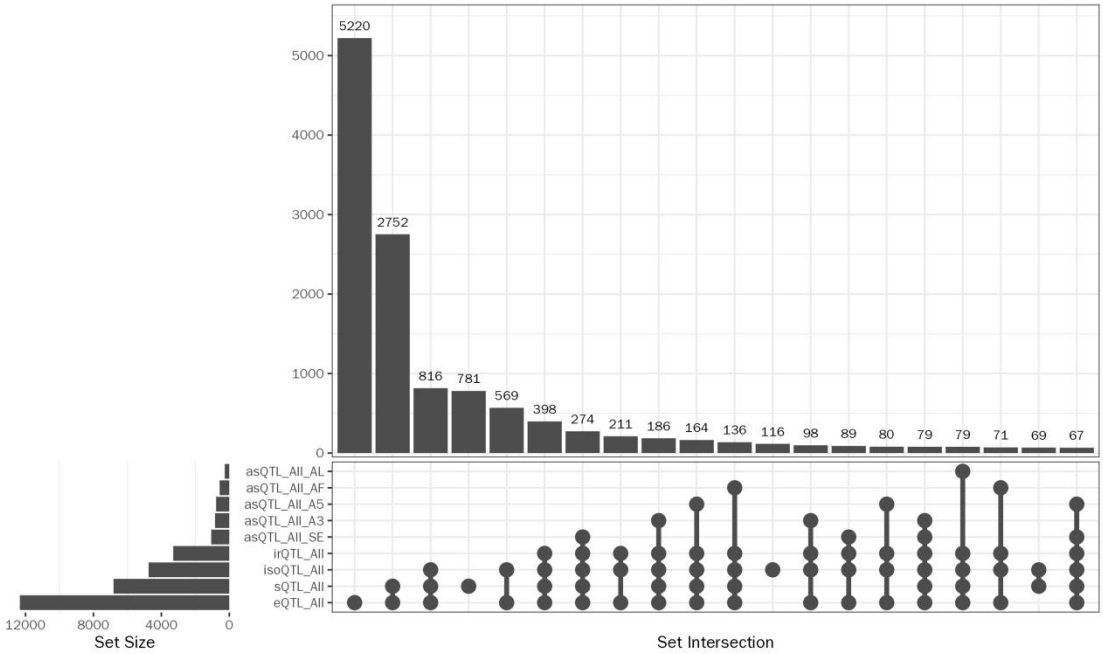


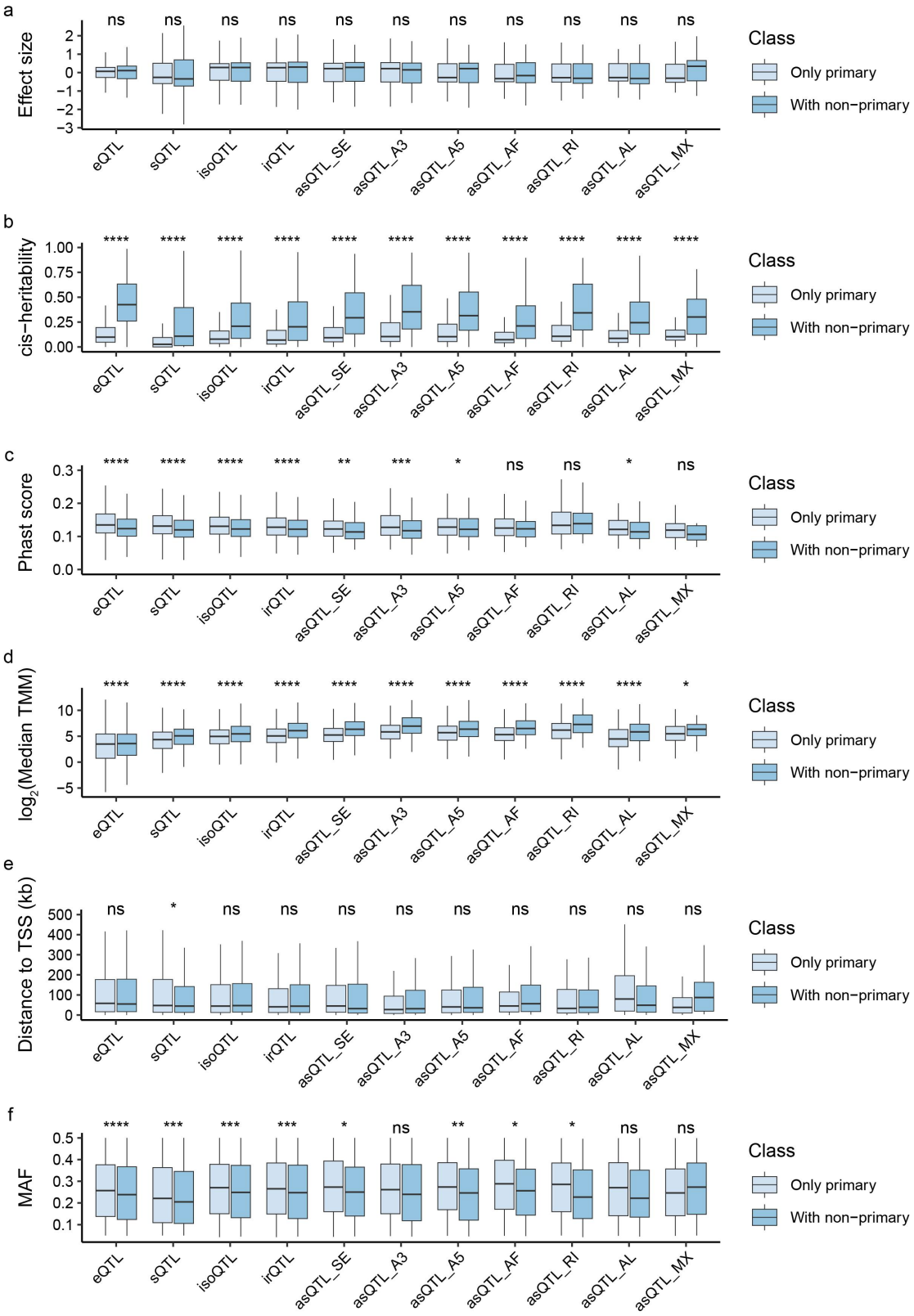
Supplementary Fig. 1 | Functional annotation of novel isoforms. Novel isoforms were functionally annotated using the COG database.



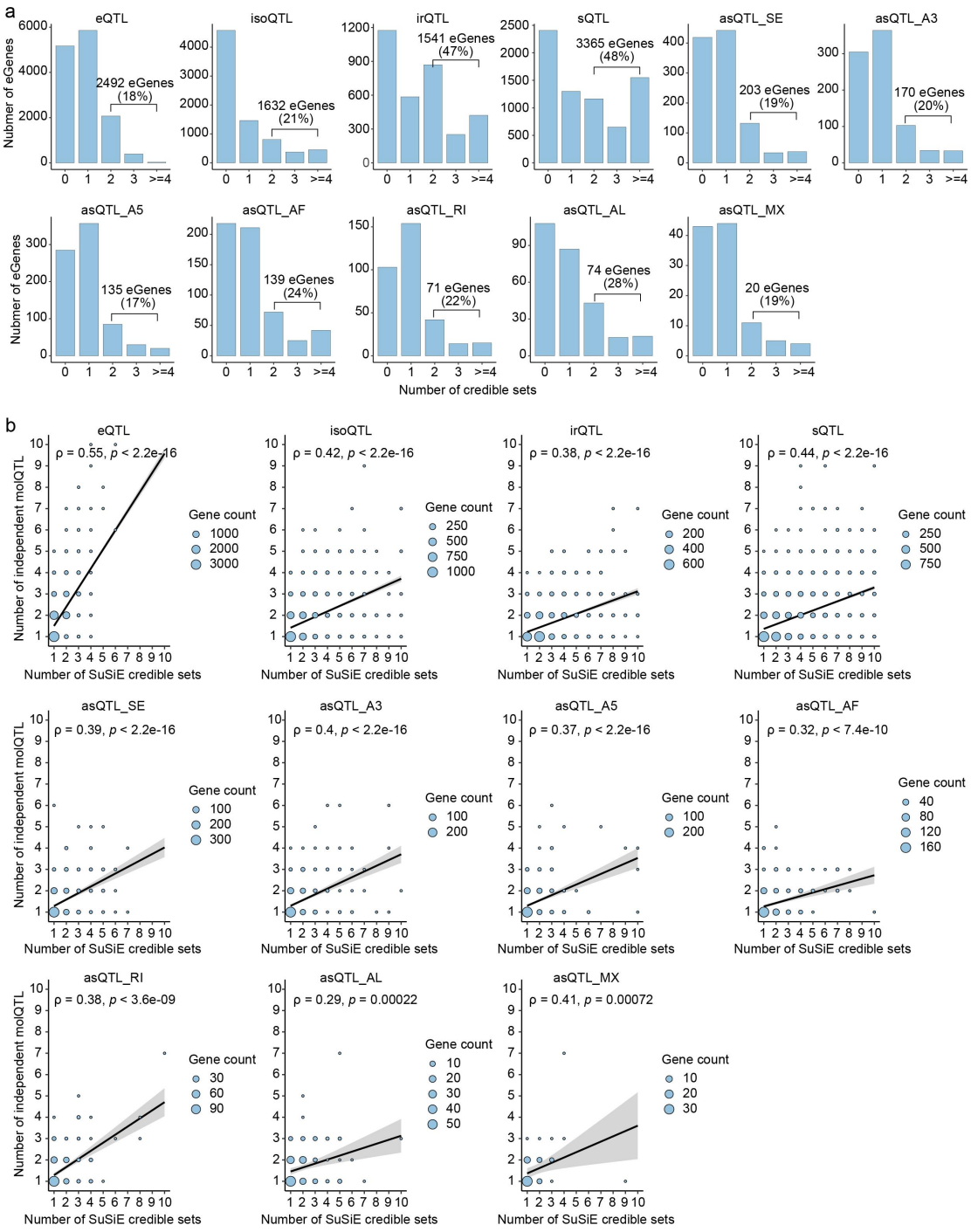
Supplementary Fig. 2 | PCA clustering of 11 molecular phenotypes.



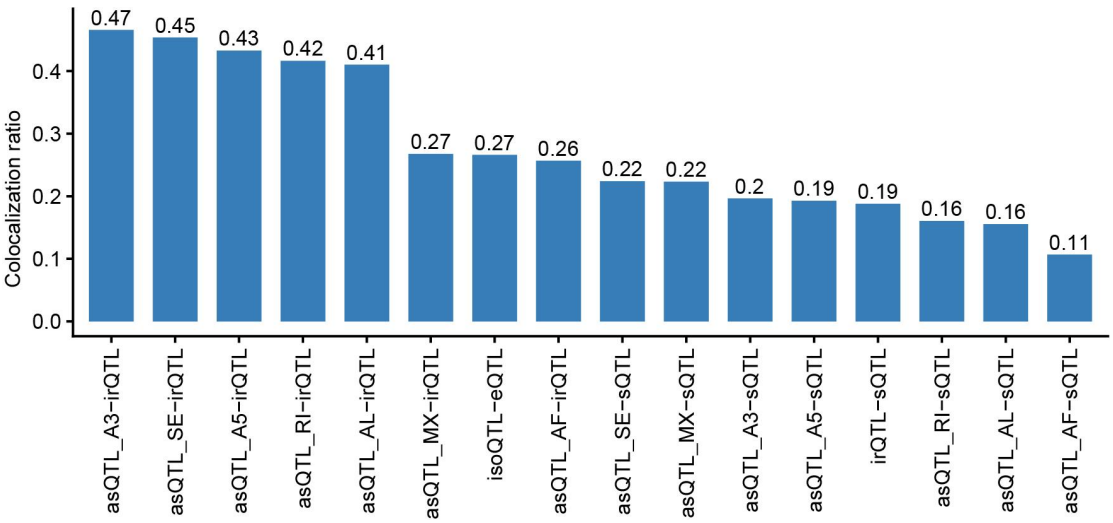
Supplementary Fig. 3 | Intersection of molGenes across 11 molecular phenotypes. UpSet plot showing the overlap of molGenes identified for the 11 molecular phenotypes.



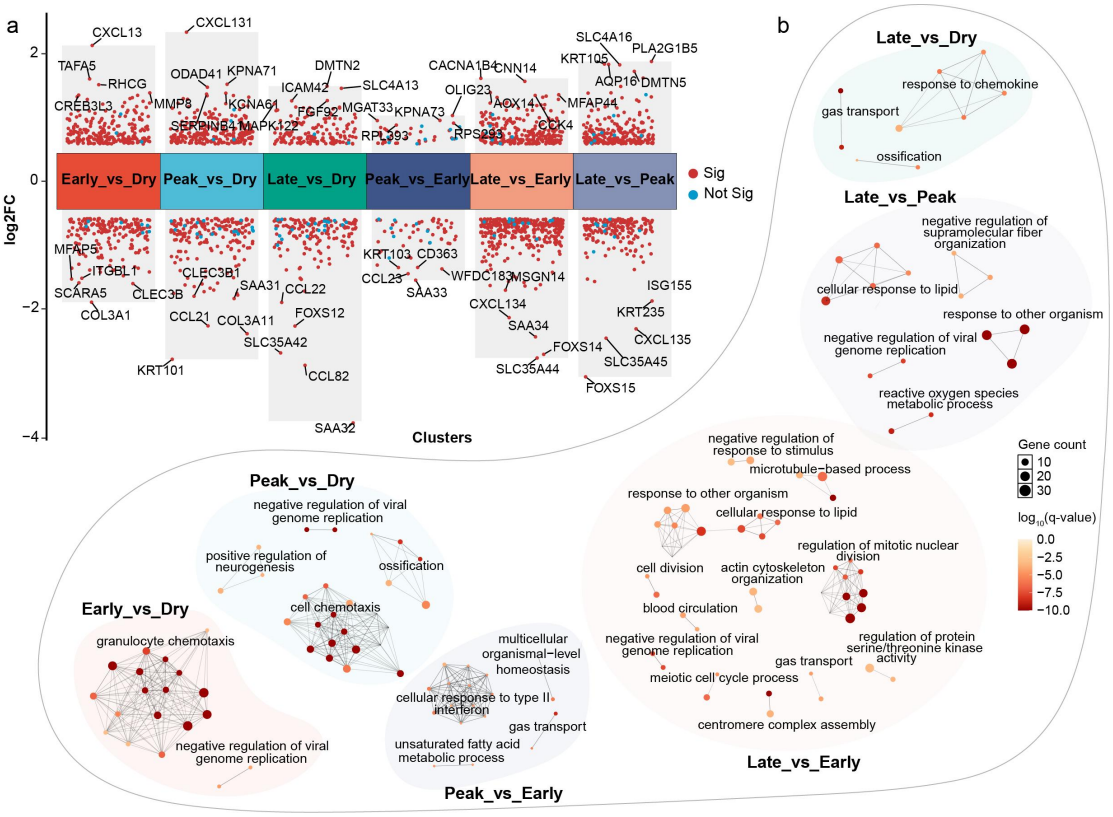
Supplementary Fig. 4 | Comparison of characteristics between primary and non-primary molQTL. a-f, The comparison of |β| **(a)**, *cis-h*^{2} **(b)**, PhastCons score **(c)**, molecular phenotype expression **(d)**, distance to TSS **(e)**, and MAF **(f)** between primary and with non-primary across molQTL. P values were calculated using two-sided paired Wilcoxon signed-rank tests. ns, not significant; *, P < 0.05; **, P < 0.01; ***, P < 0.001.



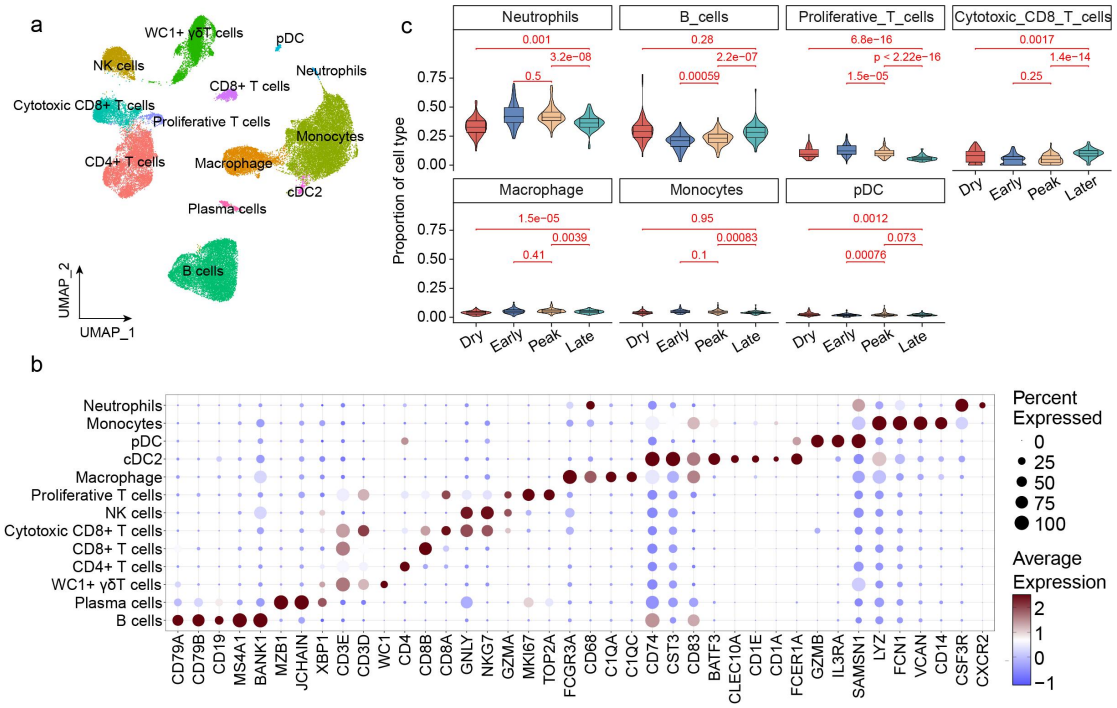
Supplementary Fig. 5 | Fine-mapped *cis*-molQTL. a, Distribution of molGenes by the number of fine-mapped credible sets. **b**, Spearman's correlation between the number of fine-mapped credible sets and the number of conditionally independent molQTL per gene. Dot size reflects the number of genes, and two-sided P values were obtained using Spearman correlation tests.



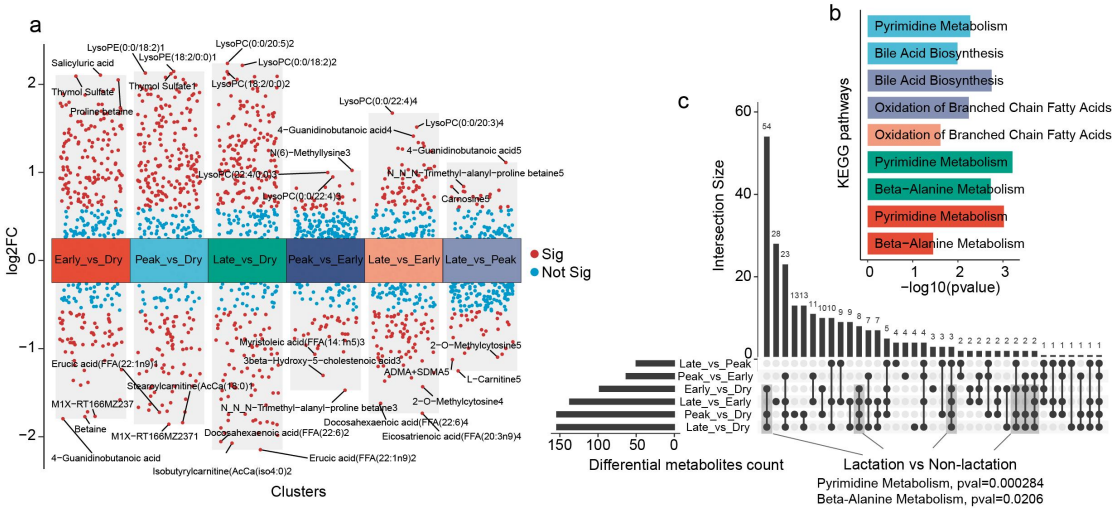
Supplementary Fig. 6 | Colocalization between molQTLs. Colocalization was defined as PP.H4 > 0.8, and the proportion was calculated as the number of colocalized molQTL divided by the total number of tested molQTL.



Supplementary Fig. 7 | Transcriptional dynamics associated with lactation. a, Differential gene analysis for pairwise comparisons across four lactation stages.Each point represents a metabolite. Points above the horizontal axis indicate higher expression in the case group, whereas points below indicate higher expression in the control group. Red points denote significantly differentially expression genes (FDR < 0.05 and $|\log_2 FC| > 0.58$). **b**, GO enrichment analysis of differentially expressed genes (DEGs).

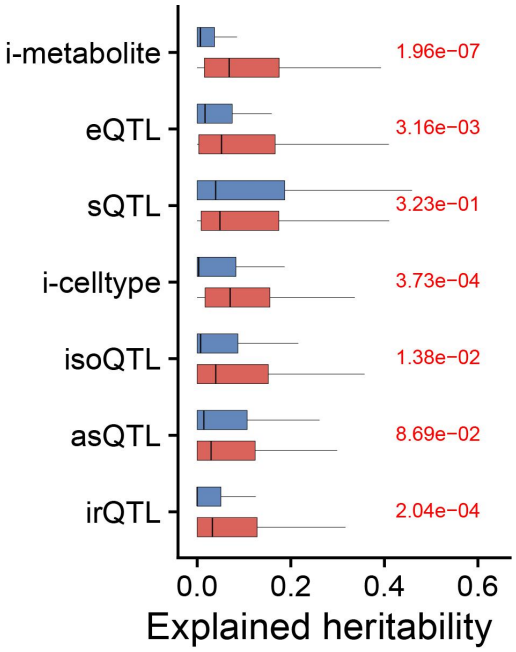


Supplementary Fig. 8 | Single-cell transcriptomic profiling of bovine blood. a, UMAP visualization of 46,078 cells from bovine blood, clustered into 13 distinct cell types. **b**, Dot plot showing marker gene expression for each cell type. Dot size represents the proportion of cells expressing the gene, and color indicates scaled average expression. **c**, Box plots of cell type proportions across different lactation stages. *P* values were calculated using two-sided paired Wilcoxon signed-rank tests.

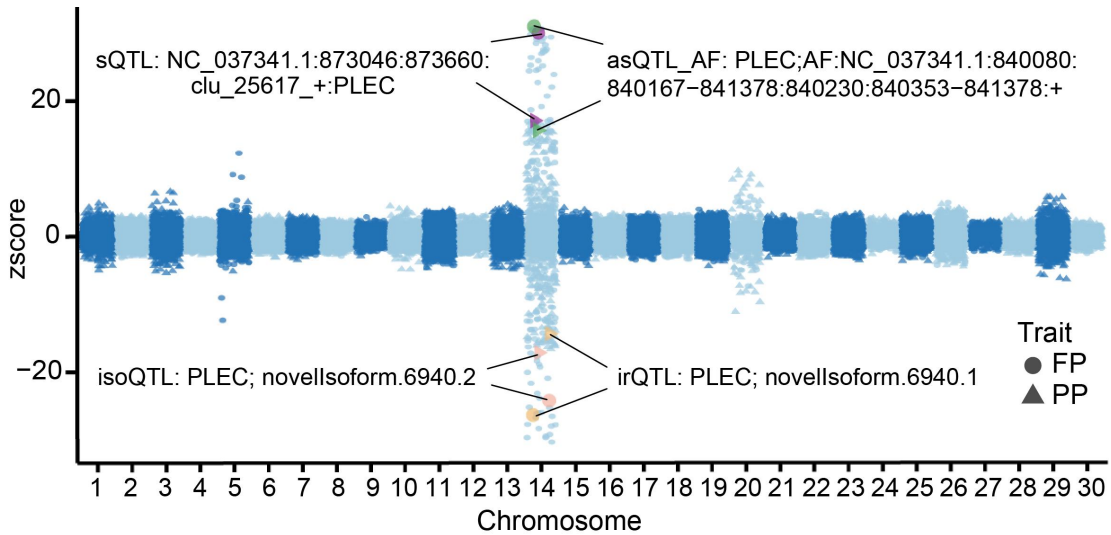


Supplementary Fig. 9 | Metabolic reprogramming related to lactation. a, Pairwise differential metabolite analyses among the four lactation stages. Each point represents a metabolite. Points above the horizontal axis indicate higher abundance in the case group, whereas points below indicate higher abundance in the control group. Red points denote significantly differentially abundant metabolites (FDR < 0.05 and $|\log_2 FC| > 0.58$). **b**, KEGG pathway enrichment analysis of

differentially abundant metabolites, with colors indicating different pairwise comparisons. **c**, UpSet plot showing the overlap of differentially abundant metabolites across comparisons; highlighted intersections indicate KEGG pathways enriched among metabolites differentially expressed between lactation and dry stages.



Supplementary Fig. 10 | Contribution of molQTL to the heritability of complex traits in dairy cattle. Proportion of heritability explained for 90 cattle traits by independent molQTL versus MAF-matched random SNPs. *P* values were calculated using two-sided paired Wilcoxon signed-rank tests.



Supplementary Fig. 11 | TWAS results of *PLEC*. TWAS z-score of PP and FP traits using isoQTL, irQTL, sQTL, and asQTL_AF.