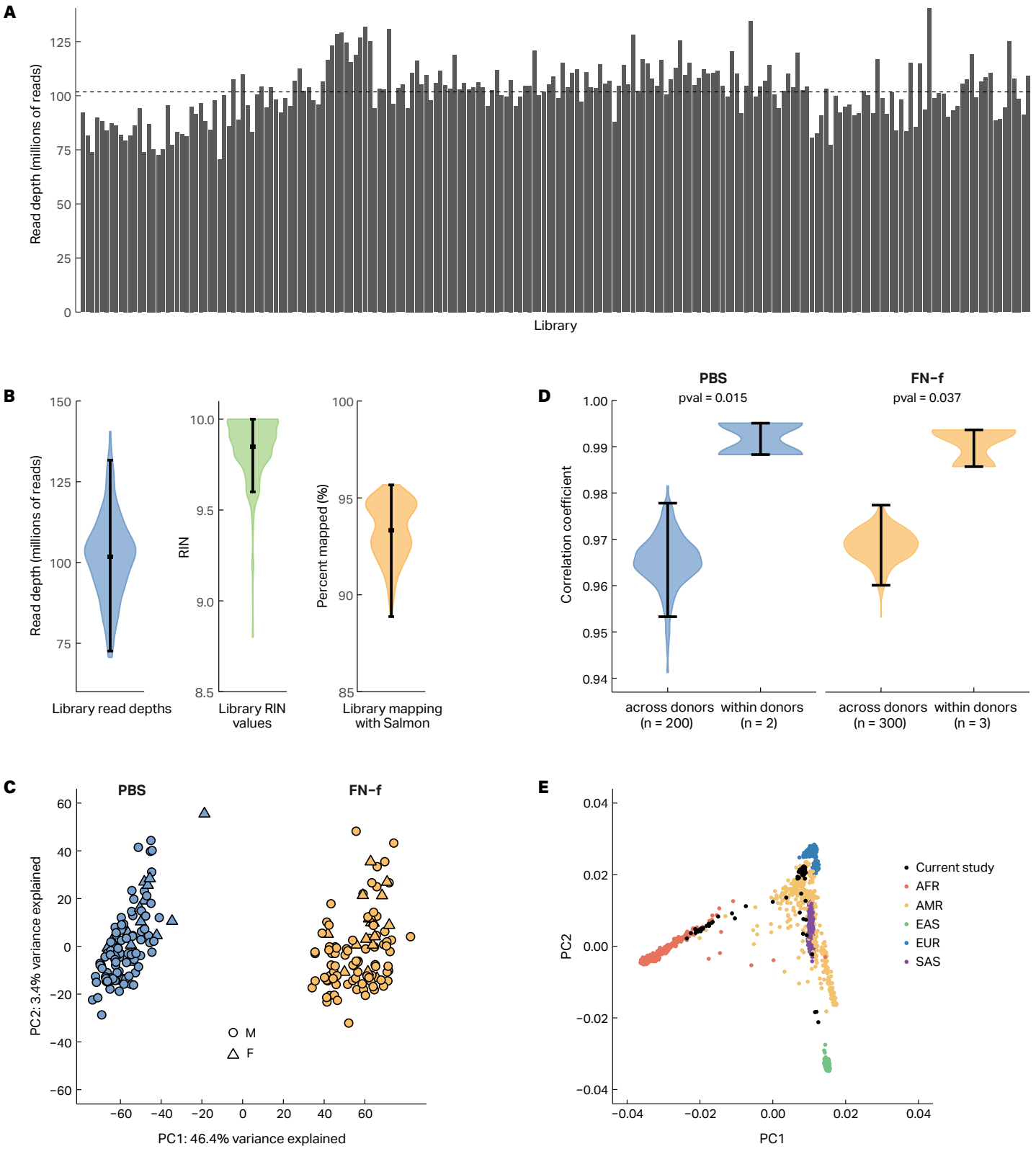
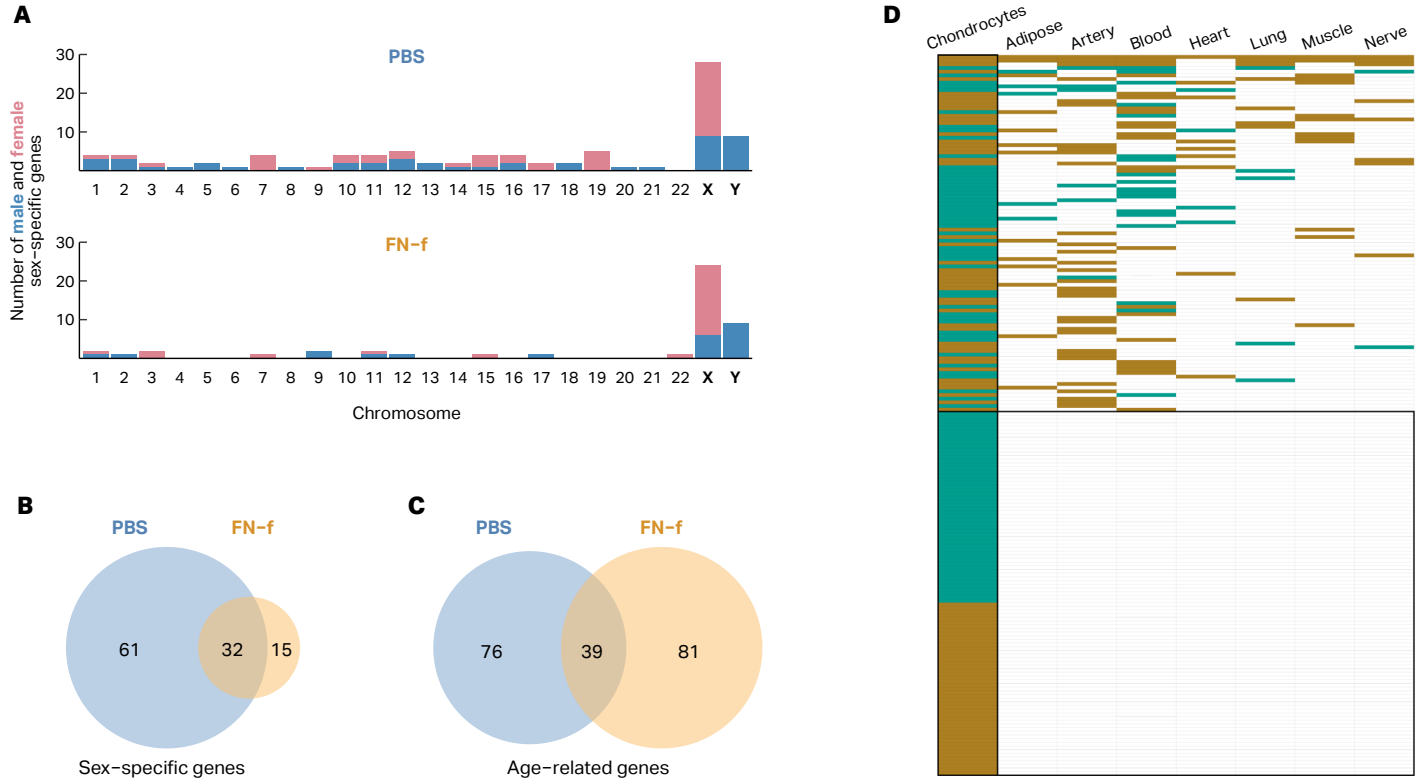
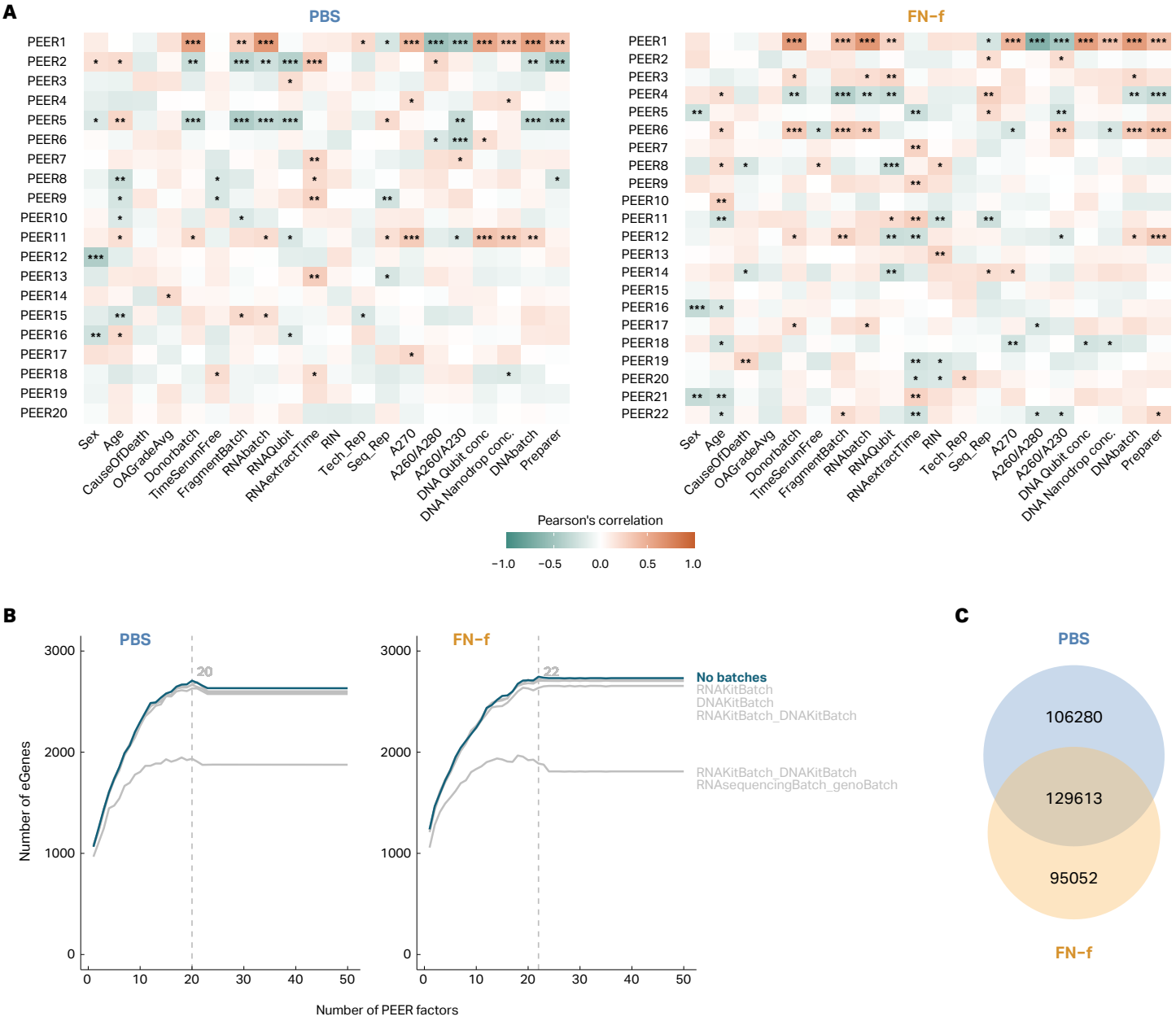
Supplemental Information



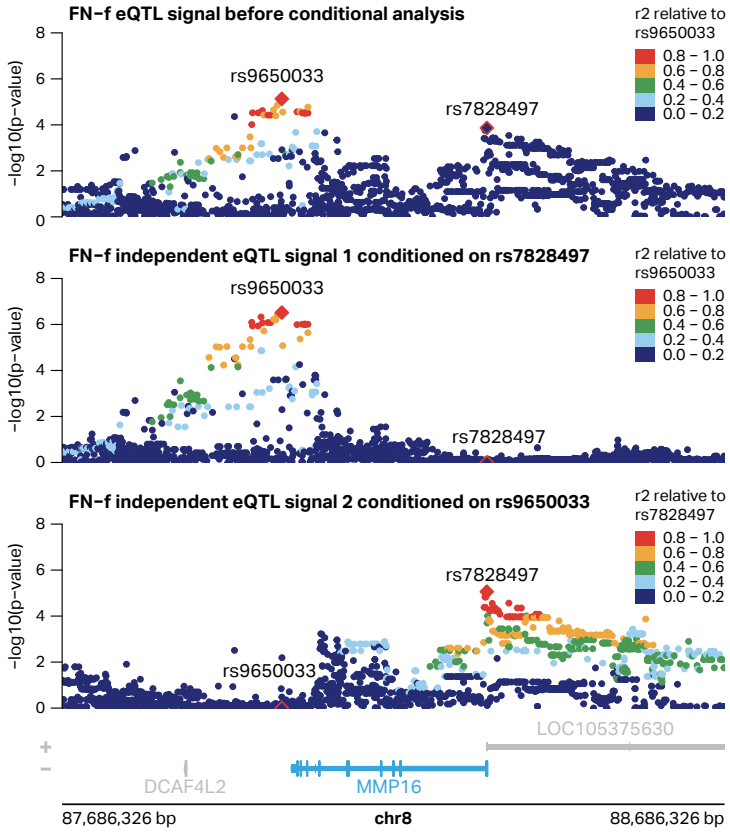
Supplemental Fig 1 | RNA-seq and eQTL QC analyses. (**A**) Barplot depicting read depths for all 202 RNA-seq data sets used in this study. The dashed line represents the mean library read depth (101.8 million reads). (**B**) Violin plots depicting the distributions of read depths (left), RIN scores (middle), and mappability (right) of RNA-seq data sets used in this study. (**C**) The correlation of gene expression between vs within donors for PBS and FN-f samples is visualized via violin plots. (**D**) PCA plots reveal that RNA-seq samples cluster largely by treatment. Samples are colored by treatment and shaped by donor sex. (**E**) Principal component analysis of donor genotyping data calculated with EIGENSTRAT. Study data, colored in black, is overlaid with 1000 Genomes data, which are colored by superpopulations as denoted by the 1000 Genomes Project. AFR: African, AMR: Admixed American, EAS: East Asian, EUR: European, SAS: South Asian.



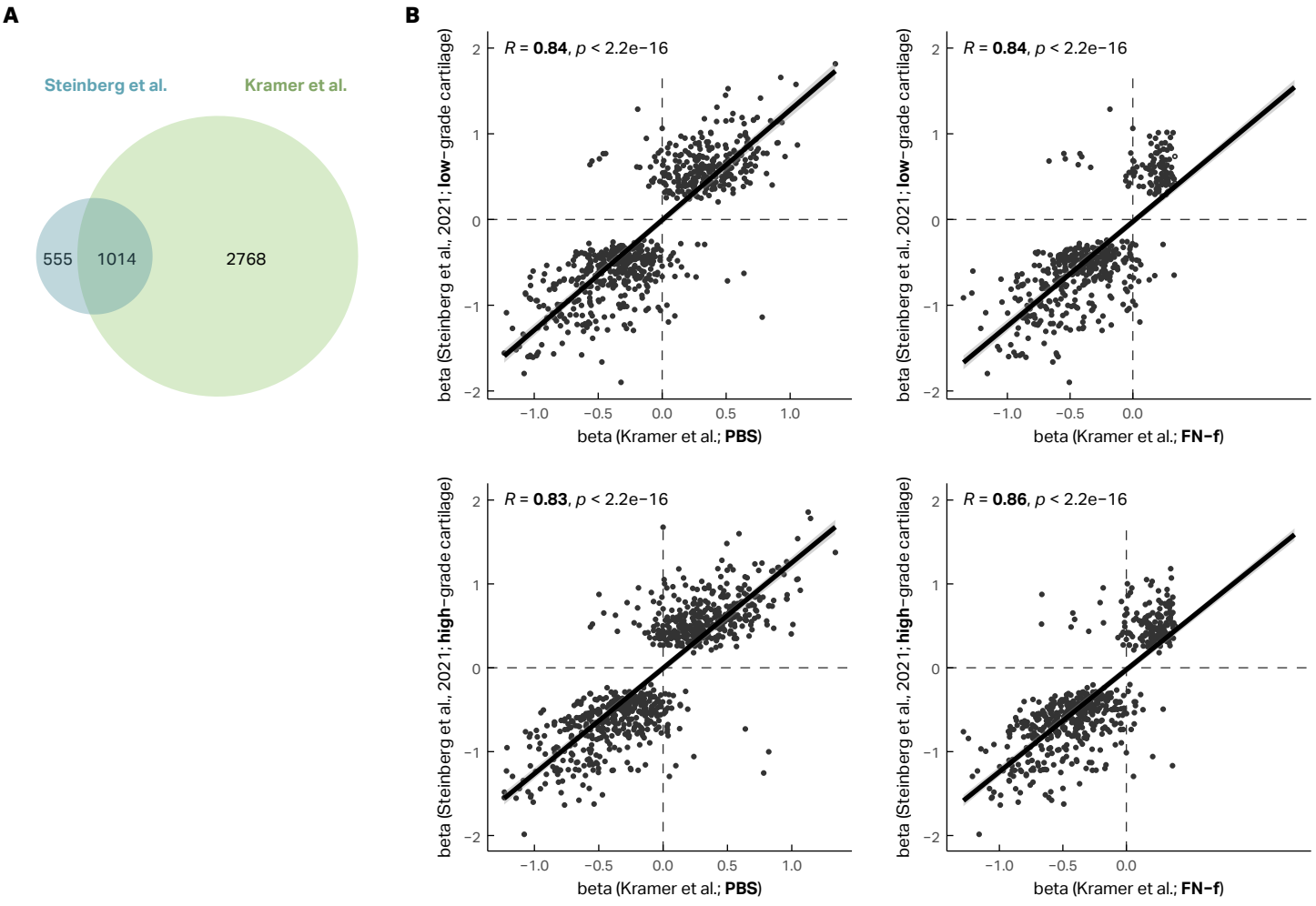
Supplemental Fig 2 | Overview of sex and age related gene expression differences. (**A**) A barplot showing that most, but not all, sex-biased genes in chondrocytes in both PBS and FN-f reside on X and Y chromosomes. Venn diagrams depicting the overlap of sex (**B**) and age (**C**) biased genes between conditions.



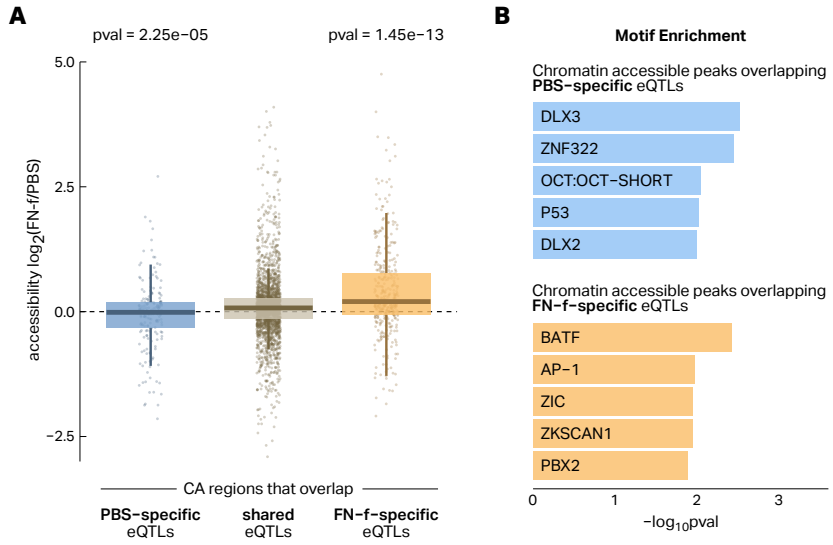
Supplemental Fig 3 | Optimization of eQTL discovery. (**A**) Heatmaps of Pearson's correlations between calculated PEER factors and known technical covariates in PBS (left) and FN-f (right) samples. * p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001. (**B**) Number of significant eGenes as a result of correcting for 1-50 PEER factors and including various additional batch covariates. 20 PEER factors with no additional batches and 22 PEER factors with no additional batches yielded the most significant eGenes in PBS (left) and FN-f (right) with eQTL mapping. (**C**) Venn diagram of all significant eQTL-eGene pairs identified in PBS and FN-f.



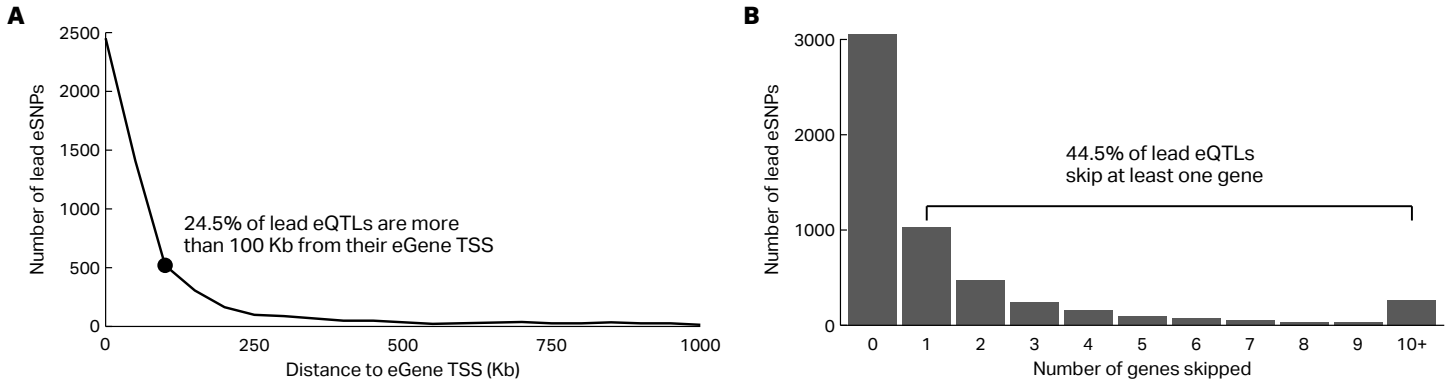
Supplemental Fig 4 | Conditional eQTL mapping identifies secondary signals. Locus zooms of the FN-f MMP16 eQTL signal before conditional analysis and after isolating independent signals. rs9650033 and rs7828497 are lead variants for the independent signals and are not in LD with each other. Each signal is colored by LD relative to the signal lead variant.



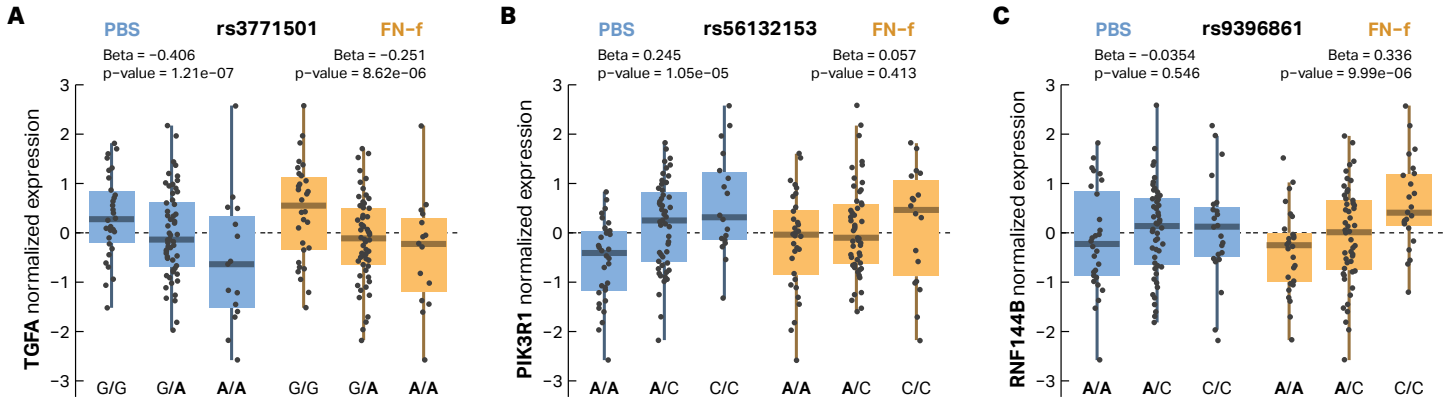
Supplemental Fig 5 | Comparison of chondrocyte eQTLs to those identified by Steinberg et al. (**A**) A Venn diagram shows the overlap of eGenes between our study (PBS and FN-f) and Steinberg et al. (low-grade and high-grade cartilage). (**B**) Scatterplots comparing the effect sizes (beta) of Steinberg et al. lead variants for shared eGenes between the current study and Steinberg et al. Effect sizes are shown comparing PBS to low-grade cartilage (top left), PBS to high-grade cartilage (bottom left), FN-f to low-grade cartilage (top right), and FN-f to high-grade cartilage (bottom right) eQTLs. R represents the Pearson correlation coefficient between beta values.



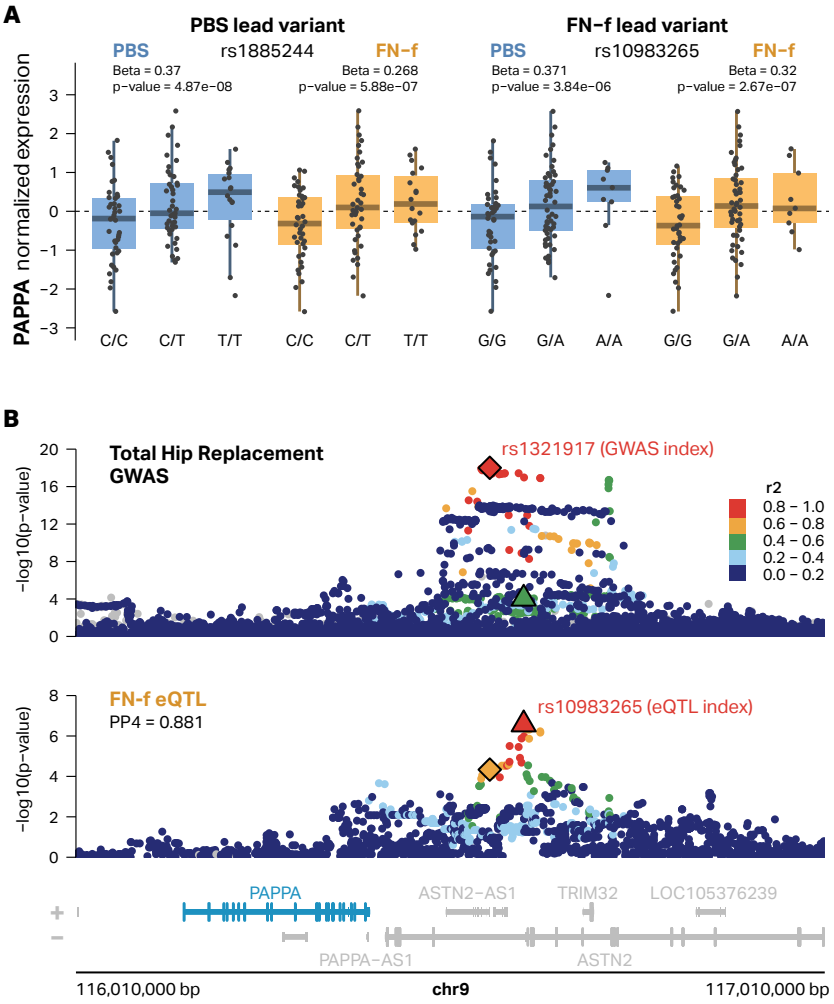
Supplemental Fig 6 | Chromatin accessibility supports condition-specific eQTLs. (**A**) Boxplots showing the log2 fold change in accessibility (FN-f/PBS) of chromatin-accessible (CA) regions overlapping high-confidence PBS-specific eQTLs (blue), shared eQTLs (tan), and high-confidence FN-f-specific eQTLs (yellow). Each set of eQTLs used to overlap with CAs contains the lead variant and any variants in high LD (> 0.8) with the lead. P-values are calculated from a Wilcox test. (**B**) Transcription factor motif enrichment for CAs overlapping PBS-specific (blue) or FN-f specific eQTLs (yellow).



Supplemental Fig 7 | Many lead eQTLs suggest distal regulatory contacts with their eGenes. (**A**) Kilobase distance of PBS and FN-f lead eSNPs to their eGene transcription start sites (TSS) as defined in methods. (**B**) Barplot showing the number of other genes skipped between the assignment of a lead eSNP to its eGene.



Supplemental Fig 8 | Effects of GWAS risk variants for examples of PBS-specific, FN-f-specific, and shared eQTL colocalizations. (**A**) The risk allele (A) of GWAS variant rs3771501 is associated with decreased expression of *TGFA* in both PBS and FN-f. (**B**) The risk allele (A) of GWAS variant rs56132153 is associated with decreased expression of *PIK3R1* only in PBS. (**C**) The risk allele (A) of GWAS variant rs9396861 is associated with decreased expression of *RNF144B* only after FN-f treatment. Boxplots depict donor genotypes at GWAS variants vs normalized gene expression with GWAS risk alleles bolded within labeled genotypes.



Supplemental Fig 9 | *PAPPA* eQTL variants in PBS and FN-f colocalize with OA GWAS. (**A**) Boxplots depicting the effects of the PBS lead eQTL rs1885244 (left) and FN-f lead eQTL rs10983265 (right) on *PAPPA* expression. Both lead variants show the same direction of effect in both PBS and FN-f. (**B**) Locus zoom depicting the colocalization between Total Hip Replacement GWAS and the eQTL signal identified in FN-f. Total Hip Replacement GWAS is colored by LD relative to the GWAS index rs1321917 according to the 1000 Genomes European reference panel.

Supplemental Fig 10 | eQTL signals for *NPC1* and *FAM53A* do not colocalize with OA GWAS. (**A**) An All OA GWAS signal that was previously identified as colocalized with *NPC1* eQTL is identified as an eQTL in our study but is no longer significant in updated OA GWAS from Boer et al. Association plots depict Boer et al. All OA GWAS (top) and PBS (middle) and FN-f (bottom) eQTL signals for *NPC1*. All OA GWAS is colored by LD relative to the GWAS index rs10502437 from Tachmazidou et al. according to the 1000 Genomes European reference panel. PBS eQTL is colored by LD relative to PBS lead variant rs8083301 and FN-f eQTL is colored by LD relative to FN-f lead variant rs6507716. The Steinberg et al. lead variant for NPC1 (highlighted blue) resided in an intron of *TMEM241* (highlighted light blue). (**B**) A previously identified eQTL signal for *FAM53A* that colocalized with KneeHip OA GWAS is not identified in the current study. A KneeHip OA GWAS signal identified by Tachmazidou et al. remains significant in Boer et al. with the lead variants from both studies in high LD (> 0.8) according to the 1000 Genomes European reference panel (top). *FAM53A* PBS eQTL (middle) and FN-f eQTL (bottom) signals are not significant. Association plots are all colored by LD relative to the Boer et al. GWAS index variant rs1530586 according to the 1000 Genomes European reference panel. The Steinberg et al. lead variant for *FAM53A* (highlighted blue) resided in an intron of *SLBP* (highlighted light blue).