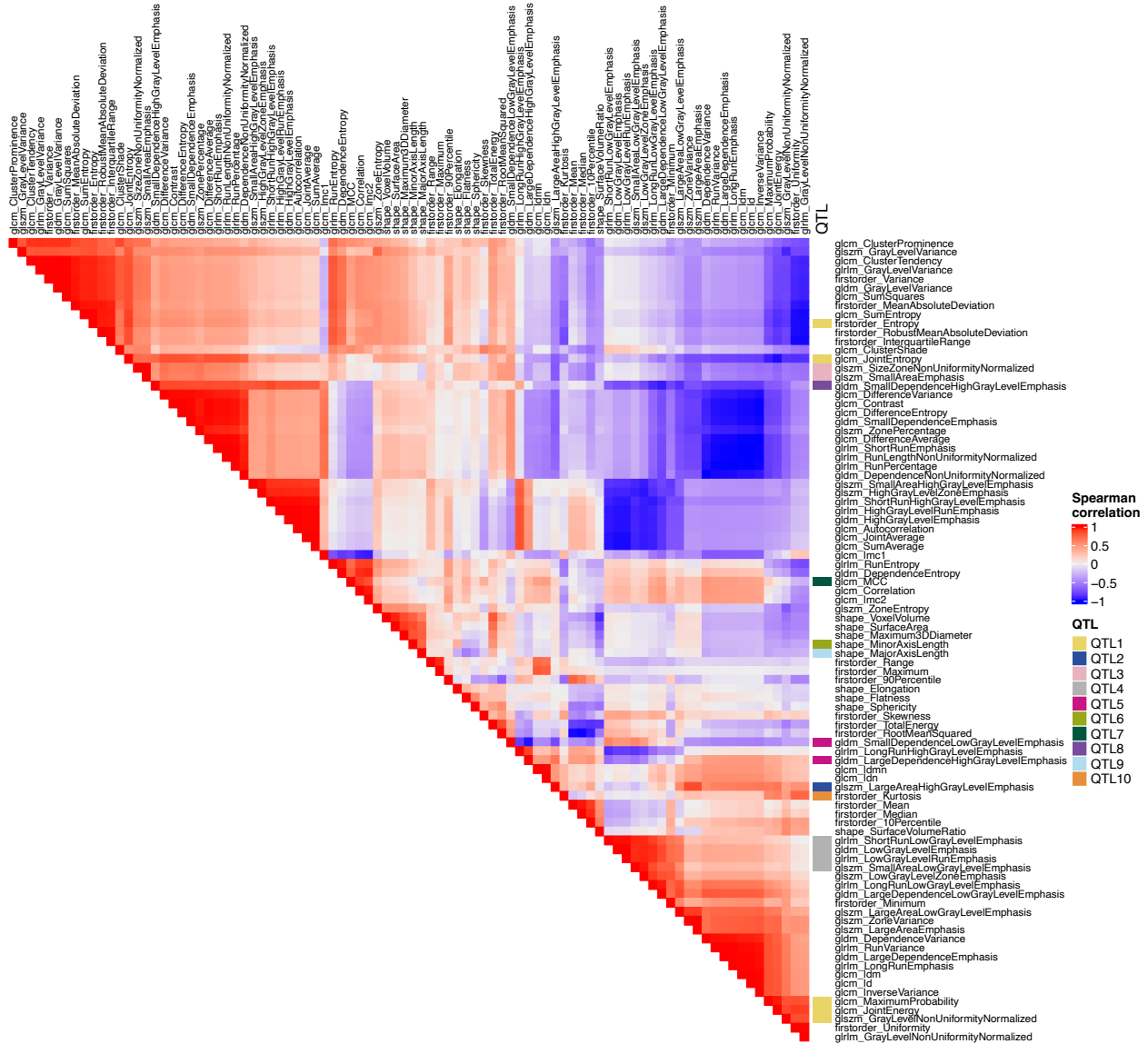
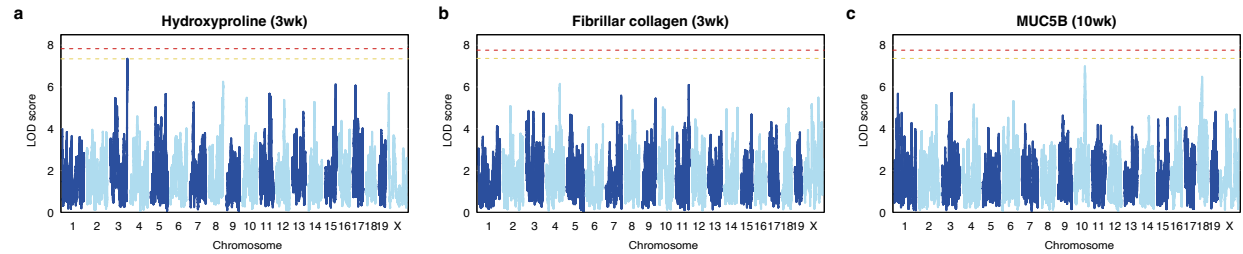
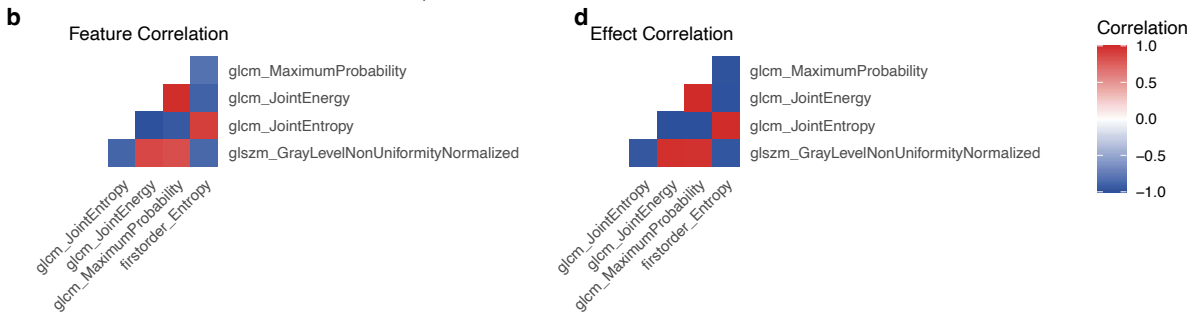
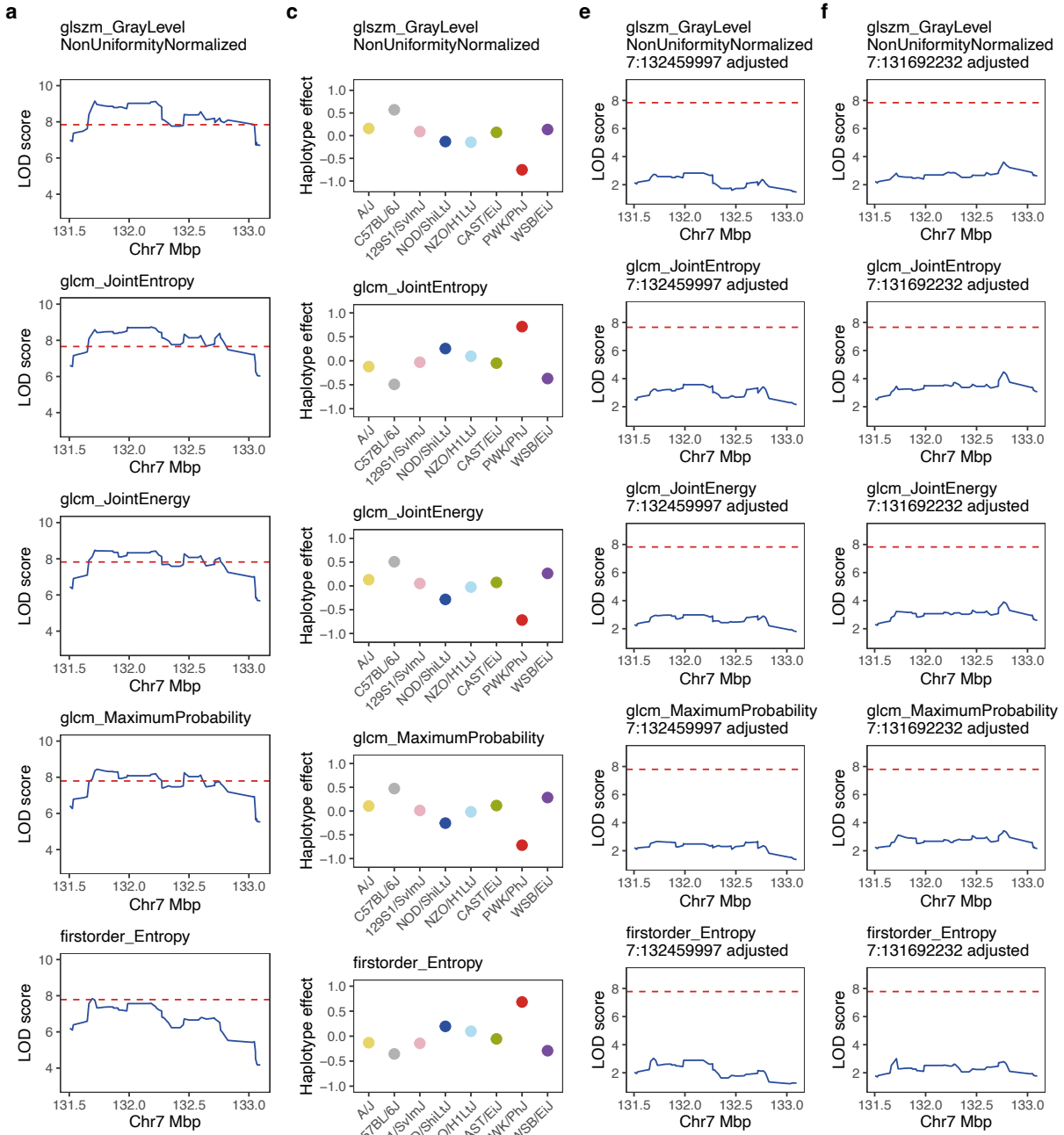




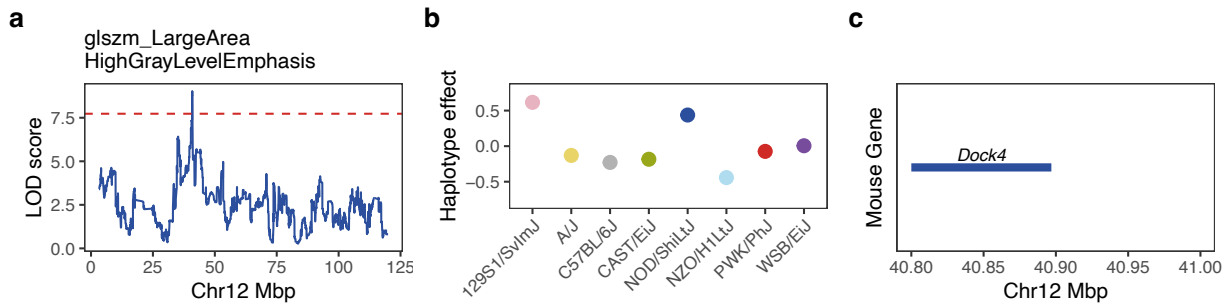
Supplementary Figure 1. Correlation matrix of radiomic features. Spearman correlations among 90 radiomic features reveal that 45.8% are weakly correlated ($|\rho| < 0.3$), 37.6% demonstrate moderate correlation ($0.3 < |\rho| < 0.7$), and 16.6% show high correlations ($|\rho| > 0.7$). Features mapping to the same QTL tend to be highly correlated, whereas features mapping to different QTLs are more independent.



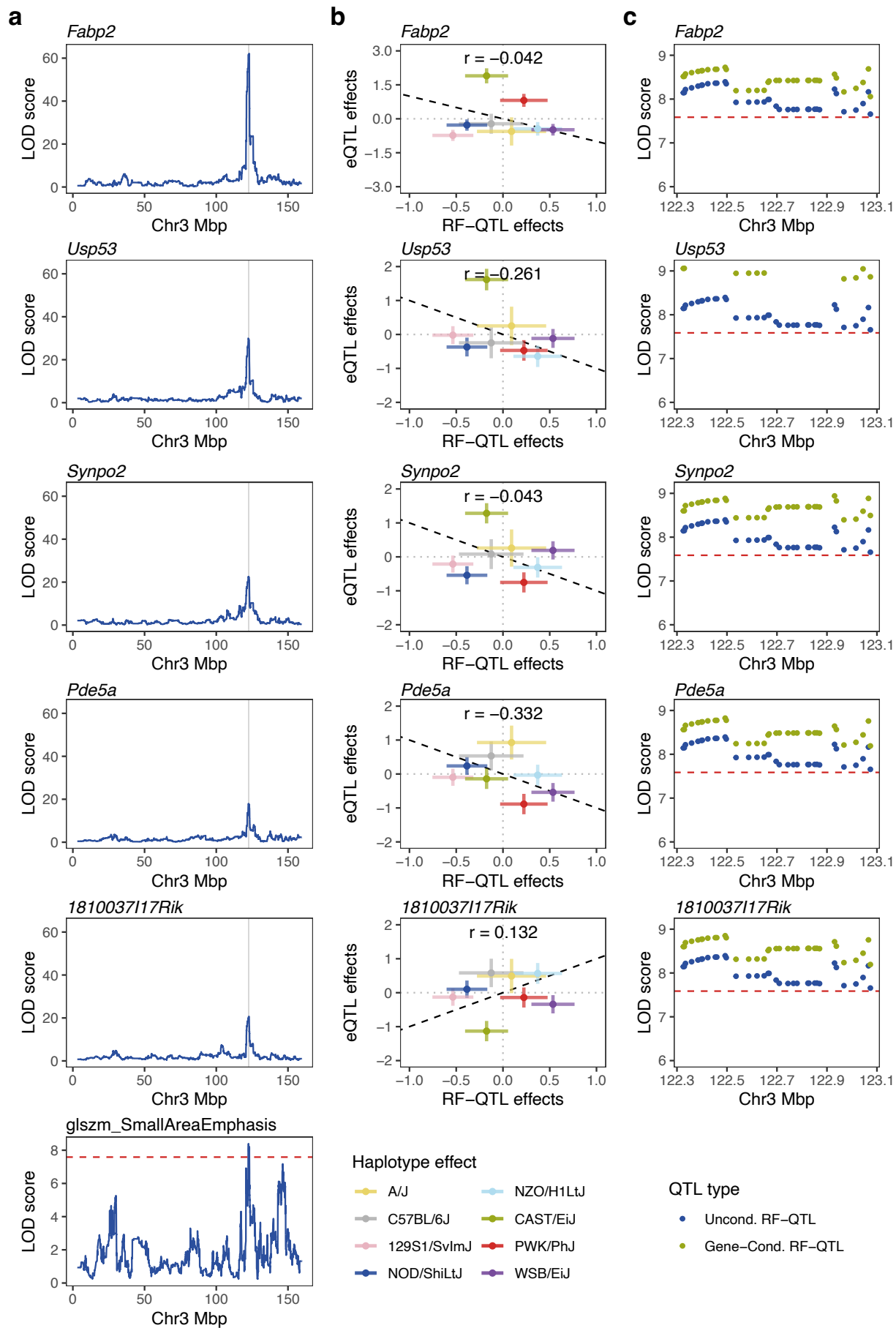
Supplementary Figure 2. 3-week fibrosis endpoints and 10-week MUC5B protein abundance do not show detectable genetic regulation in this cohort. Genome-wide quantitative trait locus (QTL) scans for **a** hydroxyproline content after 3 weeks of bleomycin challenge, **b** fibrillar collagen content after 3 weeks, and **c** MUC5B concentration after 10 weeks. The red dashed line indicates the genome-wide significance logarithm of odds (LOD) score threshold ($p = 0.05$), and the yellow dashed line indicates the suggestive threshold ($p = 0.1$), both determined by 1,000 permutation tests. No loci exceeded either threshold for any of these traits.



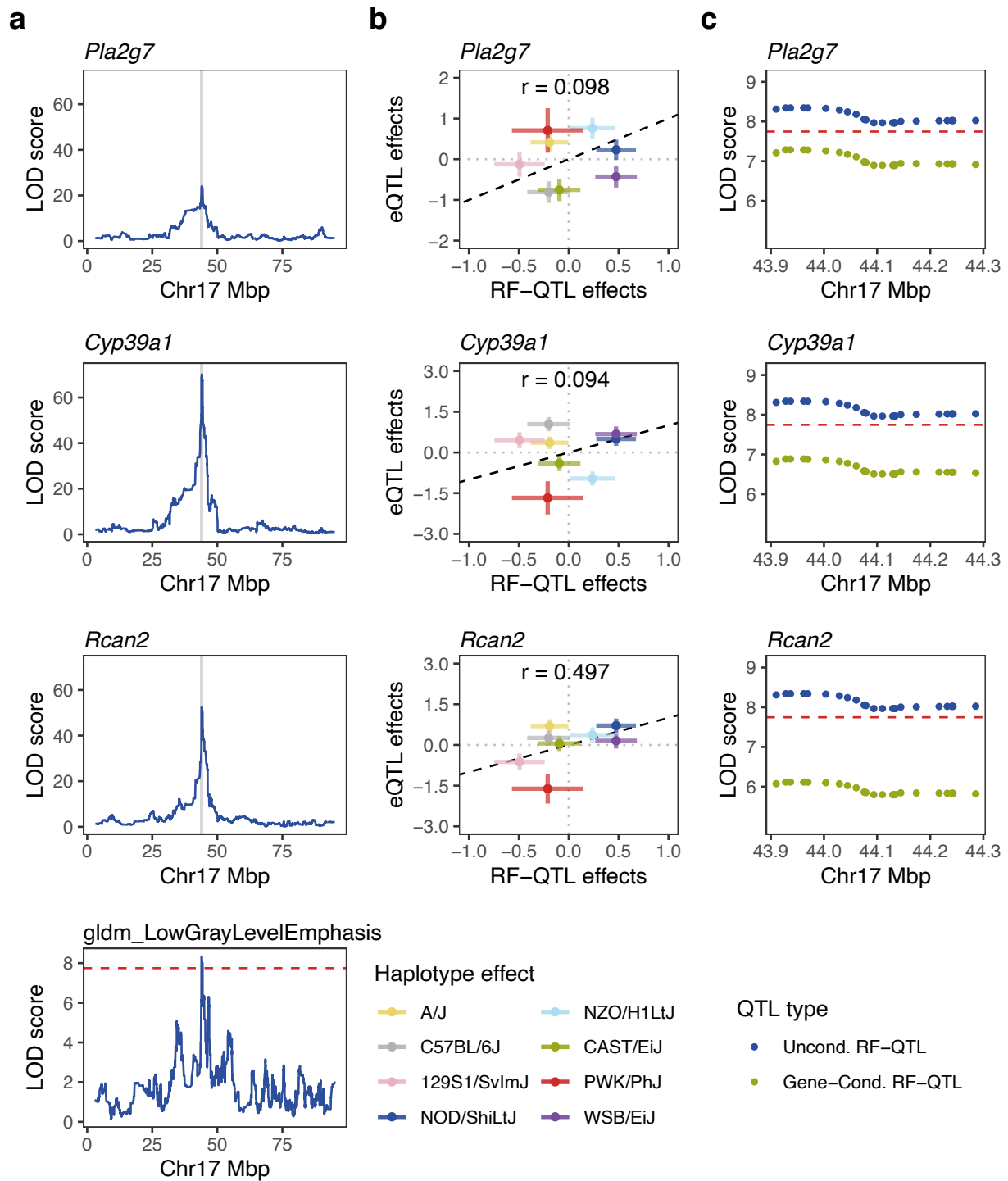
Supplementary Figure 3. Multiple correlated radiomic features share a common genetic locus on chromosome 7 (Chr7). **a** Five radiomic features (RFs) map to Chr7:131.5–133.1 Mbp, with two distinct peaks. Four features (glszm_GrayLevelNonUniformityNormalized, glcm_JointEnergy, glcm_MaximumProbability, and firstorder_Entropy) peak at 131.7 Mbp, while glcm_JointEntropy peaks at 132.2 Mbp. **b** Five RFs mapping to the same locus are highly correlated with each other. **c** Haplotype effects of each RF-QTL reveal a consistent genetic pattern across traits, with the strain PWK/PhJ shows the strongest effect. **d** Haplotype effects for five RF-QTLs are highly correlated with each other. **e, f** Conditioning on the allele frequency of either of the two distinct top SNPs eliminates the original QTL signal. In all panels, the red dashed line represents the significance threshold LOD (corresponding to $p < 0.05$) from 1,000 permutation tests.



Supplementary Figure 4. Radiomic feature (RF) quantitative trait locus (QTL) on Chromosome 12. **a** Genome-wide QTL mapping identifies a locus on Chromosome 12 associated with the radiomic feature glszm_LargeAreaHighGrayLevelEmphasis. The red dashed line indicates the significance threshold logarithm of the odds (LOD) (corresponding to $p < 0.05$) determined from 1,000 permutation tests. **b** Haplotype effects at this locus reveal strain 129S1/SvImJ exhibiting the strongest effect on glszm_LargeAreaHighGrayLevelEmphasis. **c** The protein-coding gene *Dock4* is located within the RF-QTL but is not regulated by a local eQTL, indicating that this RF-QTL is not mediated by detectable transcriptional variation of nearby genes.

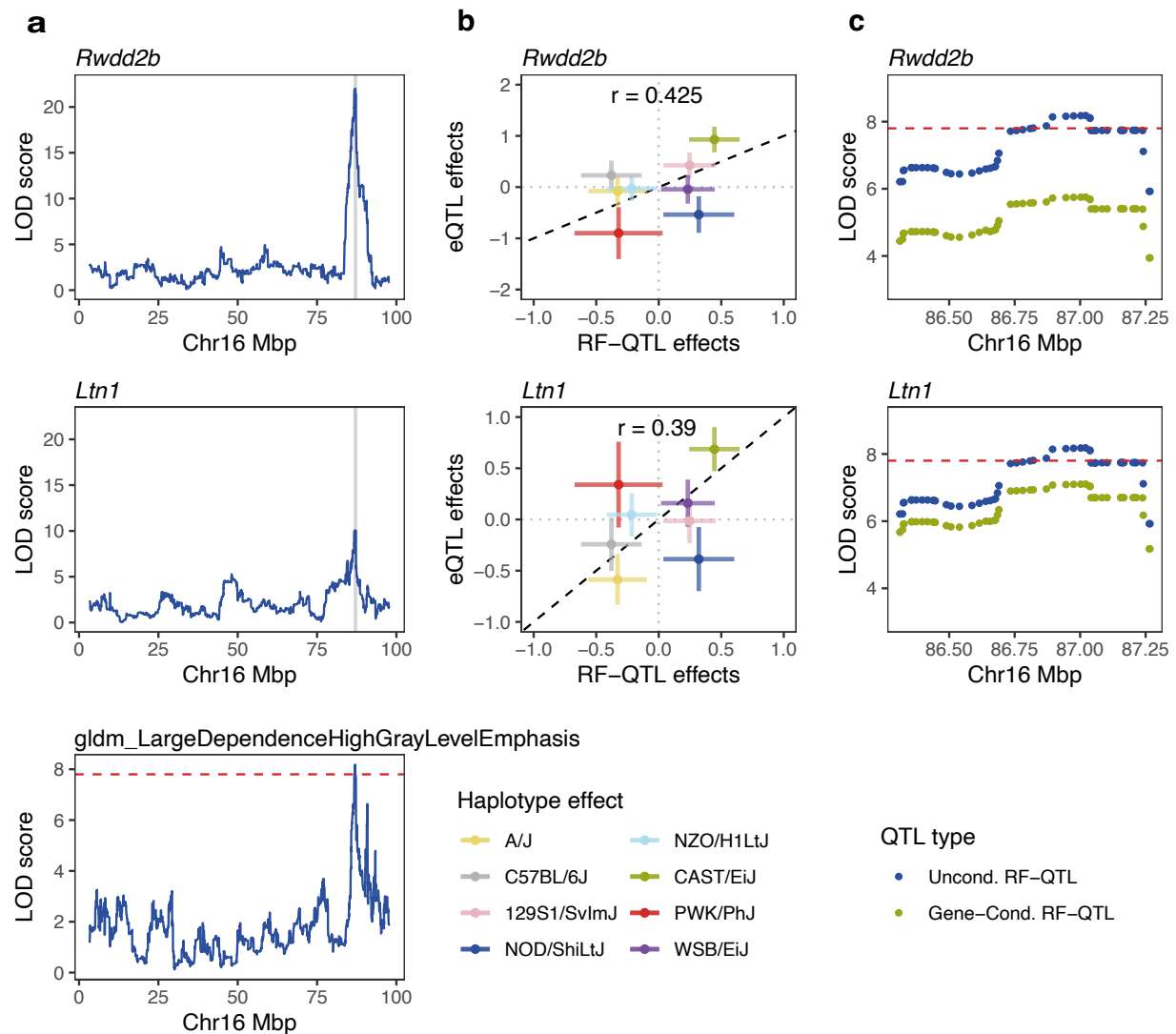


Supplementary Figure 5. A radiomic feature (RF) quantitative trait locus (QTL) on Chromosome 3 co-localizes with multiple cis-eQTLs but is not explained by local gene expression. **a** QTL mapping identifies a locus on chromosome 3 associated with the radiomic feature *glszm_SmallAreaEmphasis*. Within this interval, several local genes (*Fabp2*, *Usp53*, *Synpo2*, *Pde5a*, and *1810037117Rik*) exhibit local expression QTLs (eQTLs) whose eQTL peaks co-localize with the RF-QTL. **b** Haplotype effects of the RF-QTL are not correlated with the corresponding eQTL haplotype effects for any of the local genes across the eight founder strains. **c** Conditioning the RF-QTL on the expression levels of each candidate gene fails to attenuate the original RF-QTL signal, indicating that none of these local gene expression traits account for the genetic effect on this RF.

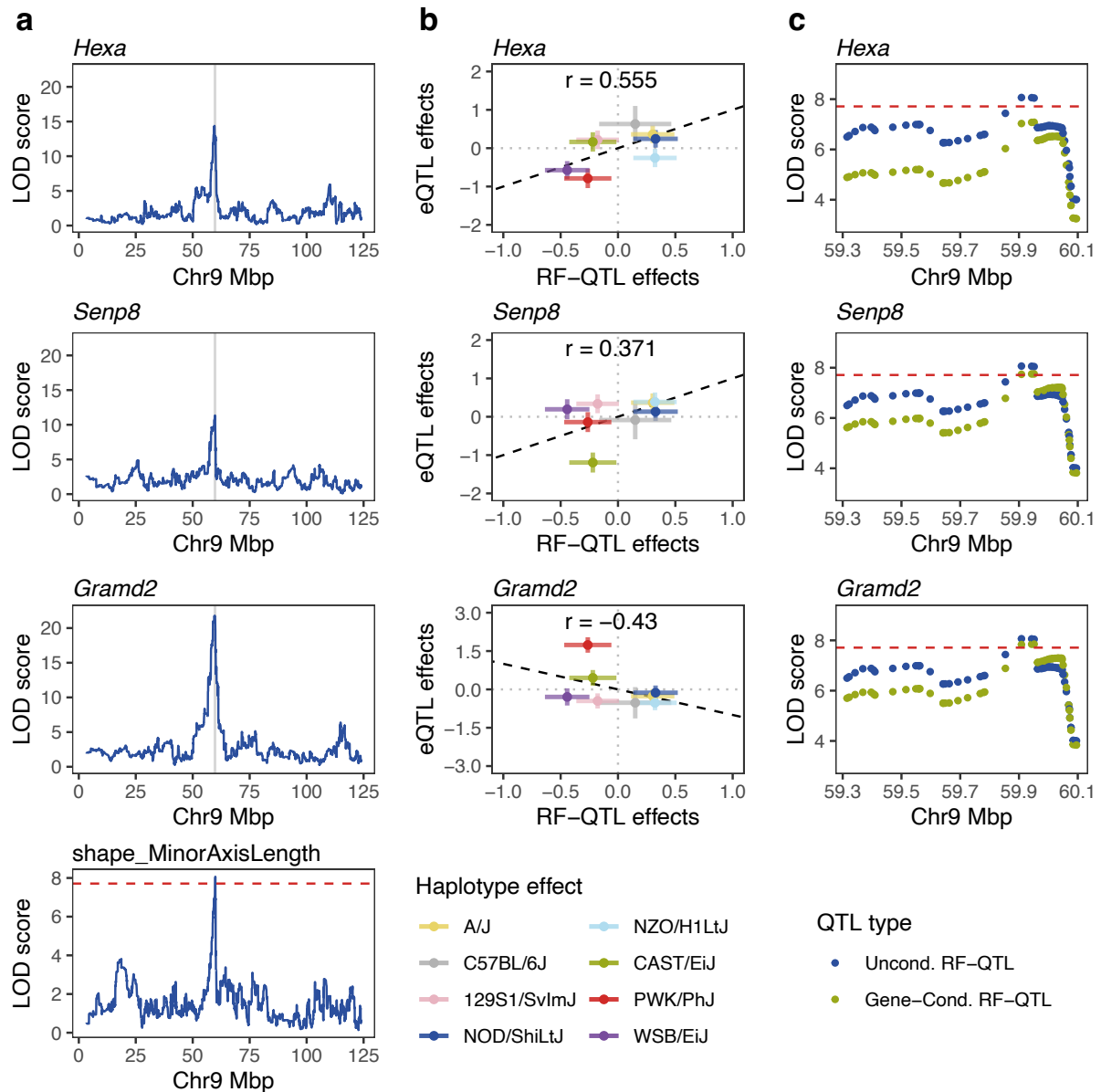


Supplementary Figure 6. *Rcan2* expression mediates a radiomic feature (RF) quantitative trait locus (QTL) on Chromosome 17. a QTL mapping identifies a locus on chromosome 17 associated with the radiomic feature *gldm_LowGrayLevelEmphasis*.

Within this interval, local expression QTLs (eQTLs) are detected for *Pla2g7*, *Cyp39a1* and *Rcan2*, with eQTL peaks co-localizing with the RF-QTL. **b** Haplotype effects of the RF-QTL shows a moderate correlation with the eQTL haplotype effects of *Rcan2*, but not with those of *Pla2g7* or *Cyp39a1*, across the eight founder strains. **c** Conditioning the RF-QTL on *Rcan2* expression abolishes the original RF-QTL signal, indicating that variation in *Rcan2* expression mediates the genetic effect on this RF.



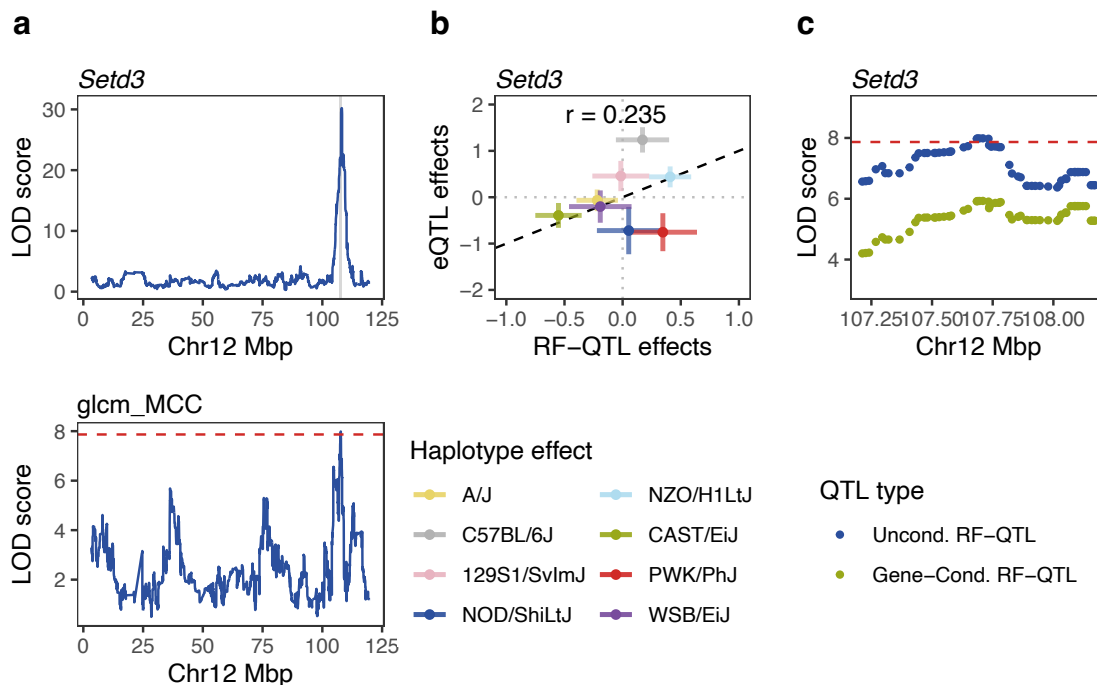
Supplementary Figure 7. *Rwd2b* expression mediates a radiomic features (RF) quantitative trait locus (QTL) on Chromosome 16. **a** QTL mapping identifies a locus on chromosome 16 associated with the radiomic feature *gldm_LargeDependenceHighGrayLevelEmphasis*. Within this interval, local expression QTLs (eQTLs) are detected for *Rwd2b*, *Ltn1*, with eQTL peaks co-localizing with the RF-QTL. **b** Haplotype effects of the RF-QTL show a moderate correlation with the eQTL haplotype effects of *Rwd2b*, but not with those of *Ltn1*, across the eight founder strains. **c** Conditioning the RF-QTL on *Rwd2b* expression abolishes the original RF-QTL signal, indicating that variation in *Rwd2b* expression mediates the genetic effect on this RF.



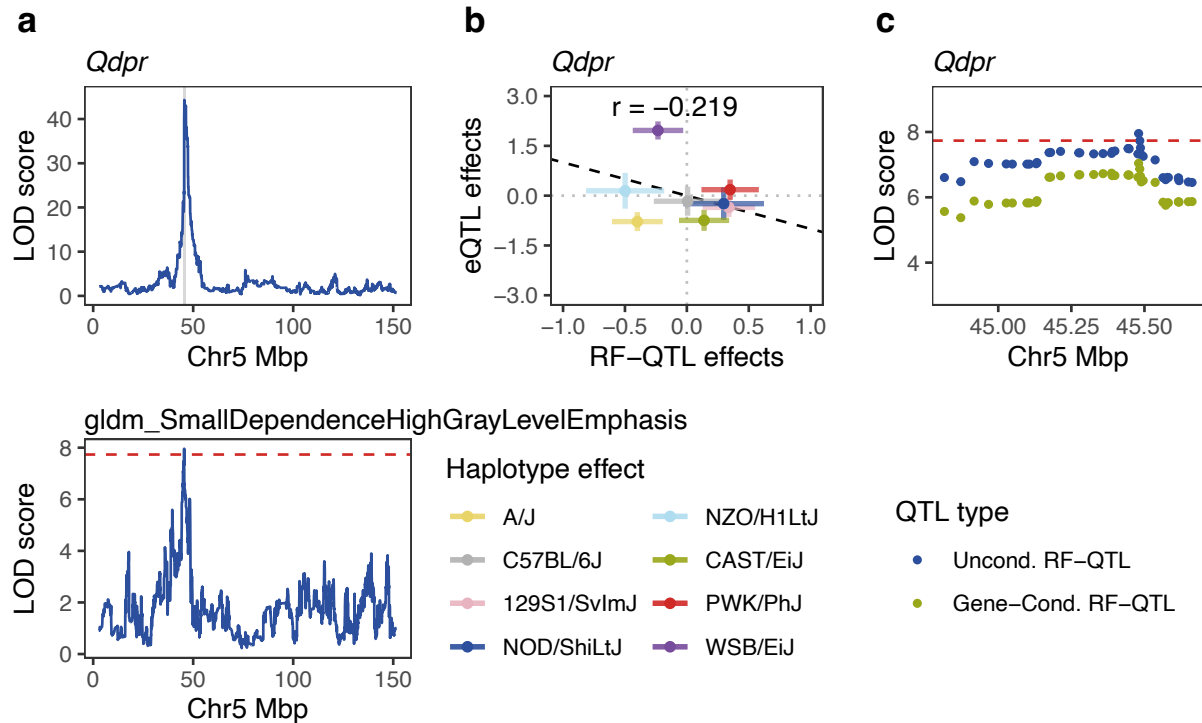
Supplementary Figure 8. *Hexa* expression mediates a radiomic feature (RF)

quantitative trait locus (QTL) on Chromosome 9. **a** QTL mapping identifies a locus on chromosome 9 associated with the radiomic feature shape_MinorAxisLength. Within this interval, local expression QTLs (eQTLs) are detected for *Hexa*, *Senp8*, and *Gramd2*, with eQTL peaks co-localizing with the RF-QTL. **b** Haplotype effects of the RF-QTL moderately correlate with the eQTL haplotype effects of *Hexa* and *Gramd2* across the eight founder strains. **c** Conditioning the RF-QTL on *Hexa* expression abolishes the

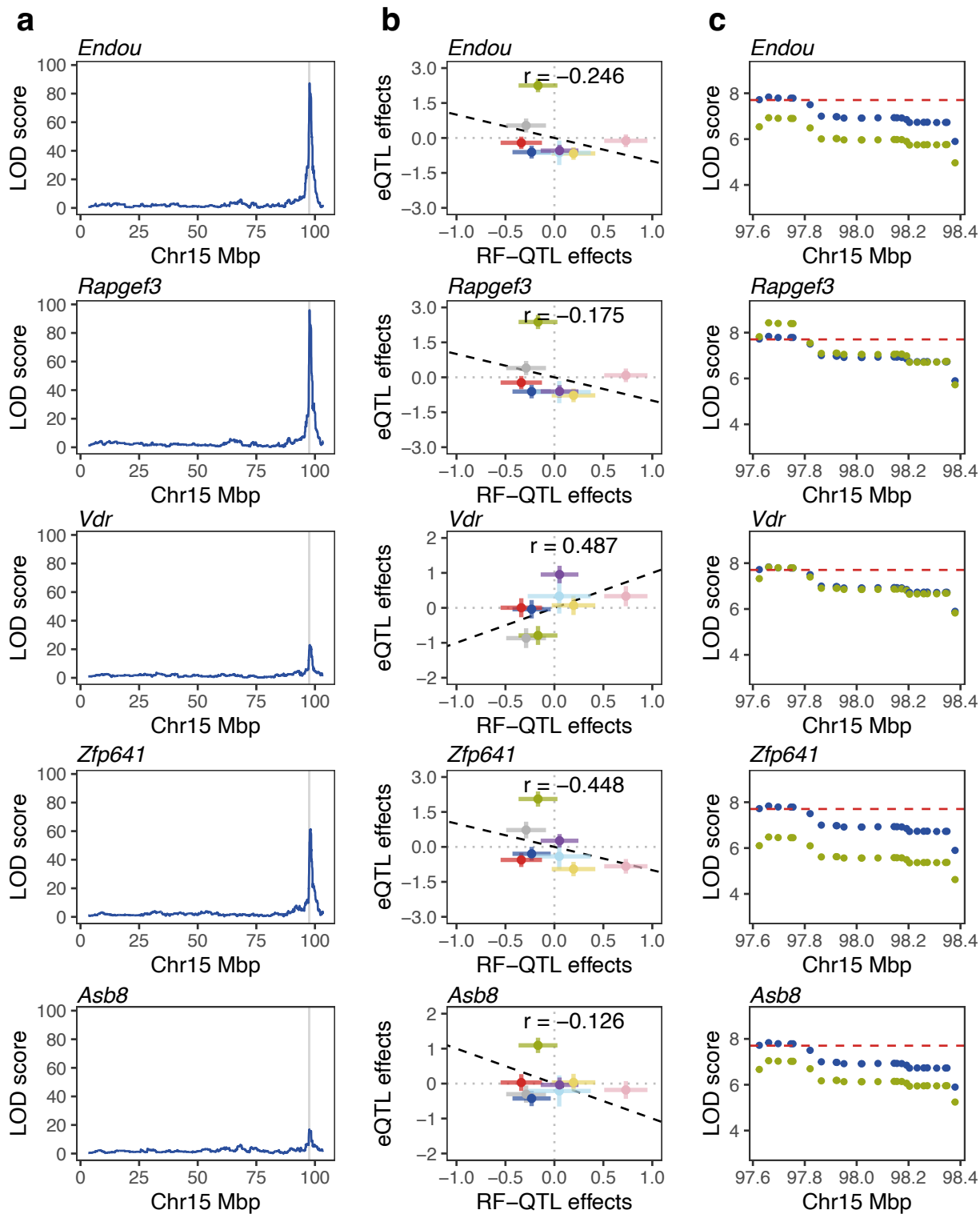
original RF-QTL signal, indicating that variation in *Setd3* expression mediates the genetic effect on this RF.

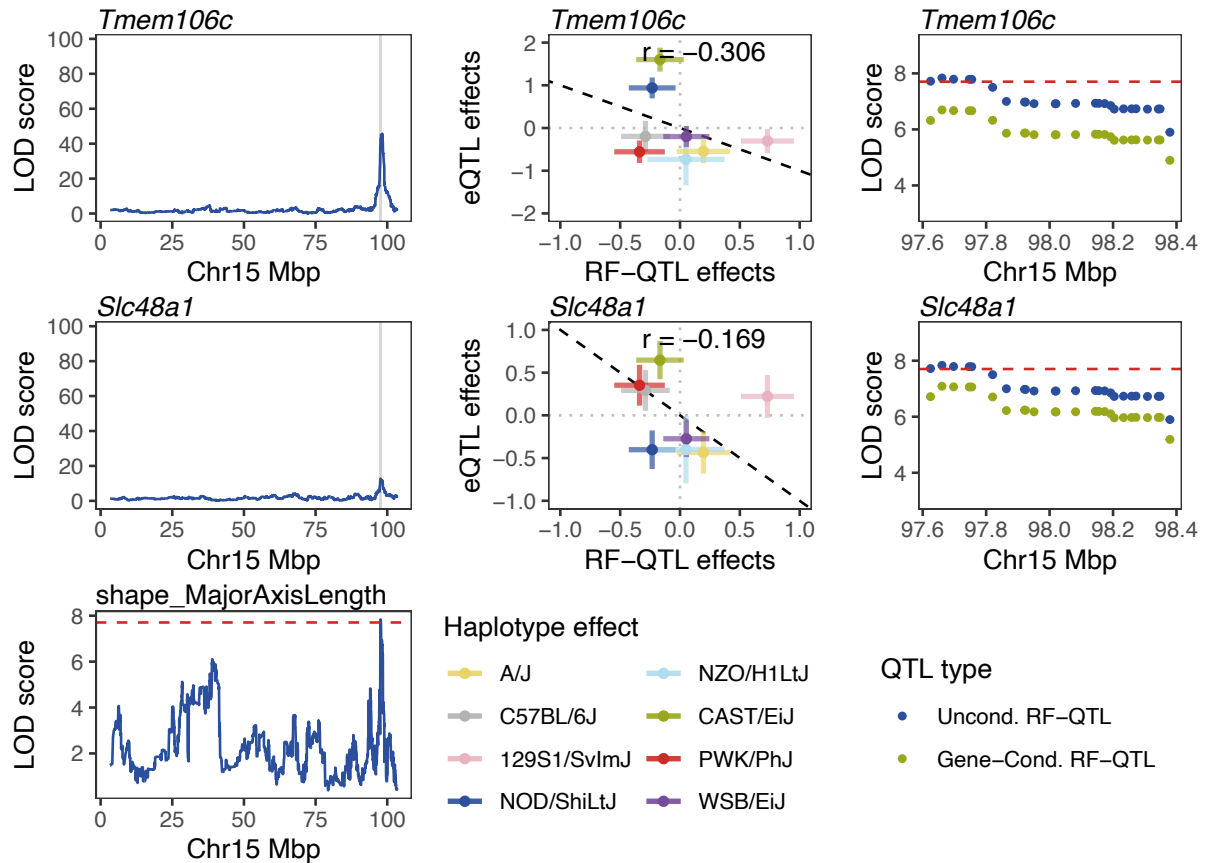


Supplementary Figure 9. A radiomic feature (RF) quantitative trait locus (QTL) on Chromosome 12 was identified, without evidence for mediation by local gene expression. a QTL mapping identifies a locus on chromosome 12 associated with the radiomic feature *glcm_MCC*. Within this interval, a local expression QTL (eQTL) is detected for *Setd3*, with its eQTL peak co-localizing with the RF-QTL. **b** Haplotype effects of the RF-QTL show low correlation with the eQTL haplotype effects of *Setd3* across the eight founder strains. **c** Conditioning the RF-QTL on *Setd3* expression does not attenuate the original QTL signal, indicating that local *Setd3* expression does not mediate the genetic effect on this RF.



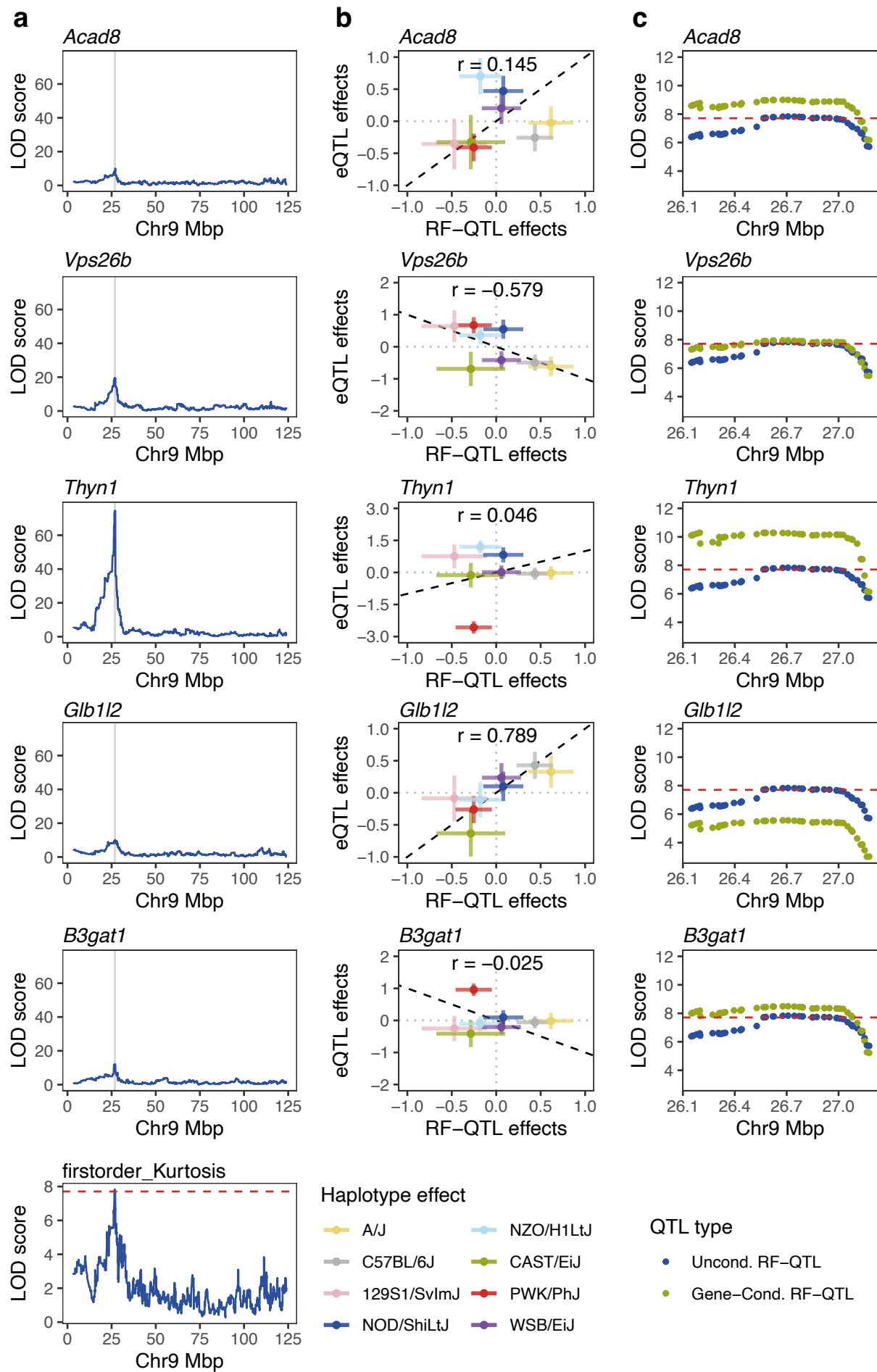
Supplementary Figure 10. A chromosome 5 radiomic feature (RF) quantitative trait locus (QTL) was identified, without evidence for mediation by local gene expression. **a** QTL mapping identifies a locus on chromosome 5 associated with the radiomic feature *gldm_SmallDependenceHighGrayLevelEmphasis*. Within this interval, a local expression QTL (eQTL) is detected for *Qdpr*, with its eQTL peak co-localizing with the RF-QTL. **b** Haplotype effects of the RF-QTL show low correlation with the eQTL haplotype effects of *Qdpr* across the eight founder strains. **c** Conditioning the RF-QTL on *Qdpr* expression does not attenuate the original QTL signal, indicating that local *Qdpr* expression does not mediate the genetic effect on this RF.



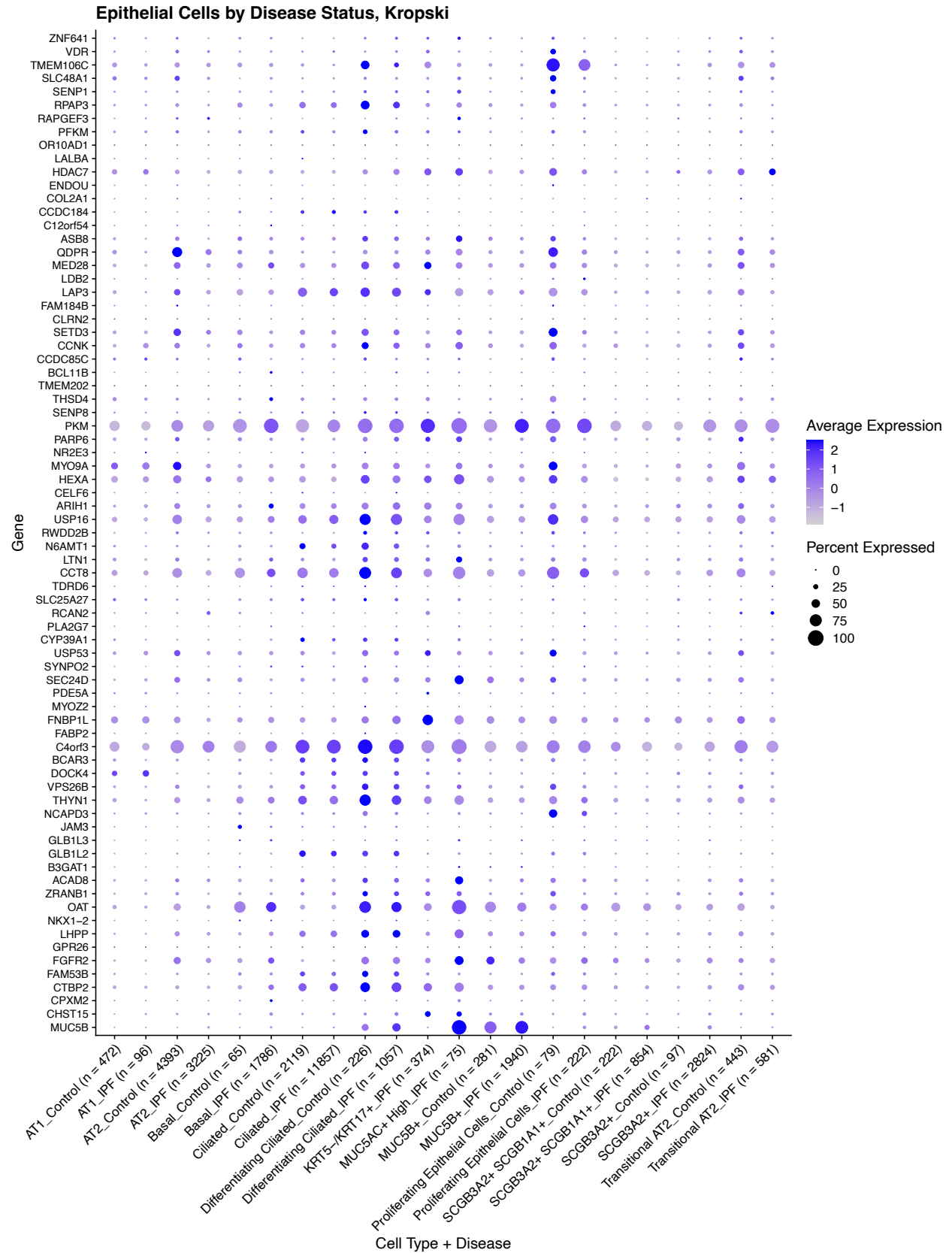


Supplementary Figure 11 (continued).

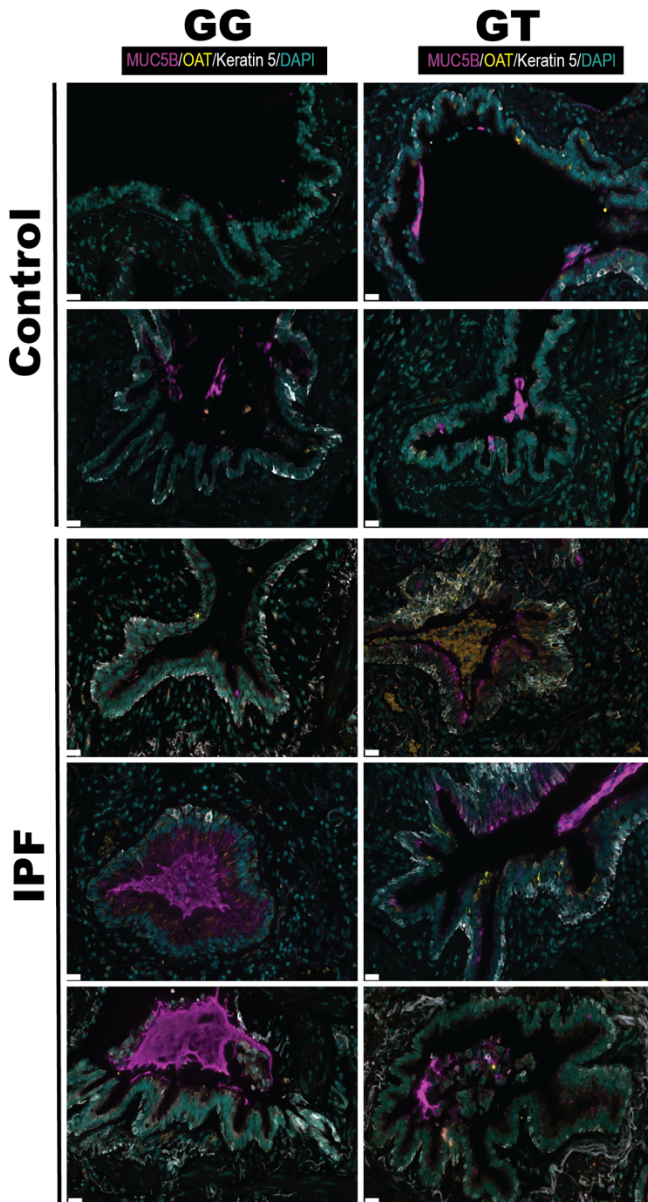
Supplementary Figure 11. *Zfp461* mediates a radiomic features (RF) quantitative trait locus (QTL) on chromosome 15. a A RF-QTL for the radiomic feature *shape_MajorAxisLength* was detected on chromosome 15. Within this interval, multiple local genes (*Endou*, *Rapgef3*, *Vdr*, *Zfp641*, *Asb8*, *Tmem106c* and *Slc48a1*) have colocalizing expression QTLs (eQTLs). **b** Haplotype effects of the RF-QTL show moderate correlation with the eQTL haplotype effects of *Zfp461* across the eight founder strains, but not with other local genes. **c** Conditioning the RF-QTL on *Zfp461* expression abolishes the original QTL signal, indicating that variation in *Zfp461* expression mediates the genetic effect on this RF.



Supplementary Figure 12. *Glb1/2* expression mediates a radiomic feature (RF) quantitative trait locus (QTL) on Chromosome 9. **a** A RF-QTL for the radiomic feature *firstorder_Kurtosis* was detected on chromosome 9. Within this interval, multiple local genes (*Acad8*, *Vps26b*, *Thyn1*, *Glb1/2* and *B3gat1*) have co-localizing eQTLs. **b** Haplotype effects of the RF-QTL show moderate correlation with the eQTL haplotype effects of *Glb1/2* across the eight founder strains, but not with the other local genes. **c** Conditioning the RF-QTL on *Glb1/2* expression abolishes the original QTL signal, indicating that variation in *Glb1/2* expression mediates the genetic effect on this RF.



Supplementary Figure 13. Human orthologs of mouse quantitative trait loci genes show cell type- and disease-specific expression patterns. Dot plot showing the expression of human orthologs of genes located within mouse quantitative trait loci across epithelial cell subtypes annotated by disease status. Each dot represents the average scaled expression (color) and proportion of expressing cells (size) for a given gene in each epithelial cell type–disease group. Data are from Kropski et al., Sci Adv 2020. The plot illustrates cell type and disease-specific transcriptional patterns of orthologous mouse QTL genes in the context of pulmonary fibrosis.



Supplemental figure 14. OAT and MUC5B alterations in IPF small airways.

Immunofluorescent staining for MUC5B, OAT and Keratin 5 in lung tissues obtained for small airways in control (4 donors) and IPF (6 donors) stratified by MUC5B genotype. Increased OAT signal (yellow) is observed in epithelial cells, with higher increase in Keratin 5+ basal cells and MUC5B- cells in IPF airways compared to control lungs. MUC5B signal (purple) in the lumens of airways depicts accumulated mucus with trapped cells. Scale bar is 20um.