

Statistically and functionally fine-mapped blood eQTLs and pQTLs from 1,405 humans reveal distinct regulation patterns and disease relevance

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Wang et al. 2024

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Replication of pQTL fine-mapping in external datasets

Here we describe comparison of our pQTL fine-mapping results with datasets other than the UKB-PPP. First, we compared our pQTL fine-mapping results with a recent pQTL fine-mapping dataset from Zhang et al. ([PMID: 35501419](#)), where they tested 4,435 proteins measured in the SOMAscan platform for two populations (n=7,213 European population and n=1,871 African population) separately. Despite the differences in measurement platform, population background and additional technical details, our fine-mapping PIP was highly consistent with theirs. Nearly 60% of putative causal pQTLs in our study presented causal evidence ($0.5 \leq \text{PIP}$) in one of their two study populations, when tested (77 out of 130 = 59.2%; **Fig. 1c** and **Supplementary Fig. 6**). Further details comparing the fine-mapping results are described in the next section.

We also confirmed the concordance of variant effect sizes, although lower than that with the UKB-PPP dataset (**Supplementary Fig. 6a** and **b**; Pearson $r=0.81$ against European population and $r=0.64$ against African data, when filtering to $0.01 \leq \text{PIP}$), presumably reflecting the differences in the technological platform.

Investigating other pQTL data, effect size correlation was relatively higher when compared against the EPIC-Norfolk study results ([PMID: 36823471](#)) where Olink platform was used (**Supplementary Fig. 7a**; $r=0.95$ when filtered to $0.9 \leq \text{PIP}$ in our study and lead variant in independent credible sets in theirs), while remained moderate when compared against another pQTL dataset derived from east Asian population that utilized mass spectrometry techniques (Xu et al. [PMID: 36797296](#), **Supplementary Fig. 7b**; $r=0.72$ when filtered to n=40 replicated examples from their pQTL list). These comparisons together highlight the technological platform differences as the major source of discrepancy on top of population background and sample sizes.

Further details on replication of pQTL fine-mapping in the ARIC dataset

Here we describe further evaluation of differences in our pQTL fine-mapping and the one in the ARIC study (Zhang et al; [PMID: 35501419](#)).

First, we used SuSiE+FINEMAP and conservatively took the minimum PIP from the two, whereas they used SuSiE alone. We compared the case where we use SuSiE alone for fair comparison, but this has minimal effect on the result (**Supplementary Fig. 6d**). Other technical details, such as whether or not to use the in-sample linkage disequilibrium (LD) matrix adjusted for covariates could be contributing to the difference (we did not find a description about LD matrix in Zhang et al manuscript). Second is the population background difference. When comparing the PIP with European and African dataset separately, the concordance was slightly higher for European data, possibly thanks to their larger sample size potentially leading to less noisy PIP estimations, but they both showed high concordance (**Supplementary Fig. 6e,f**).

We also note that the overlap between our dataset and theirs is limited. For example, 86.6% of putative causal pQTLs in our dataset are missing (or fine-mapping was not applied due to non-significant p-value; **Supplementary Fig. 6g**) in theirs. In addition, only a fraction of putative causal pQTLs identified in their dataset was replicated in our analysis (e.g. only 7.5% showed $0.5 < \text{PIP}$ in our dataset, for their European dataset; **Supplementary Fig. 6h,i**), even after removing variants and genes missing in our analysis. To investigate this one-sided low replication rate, we investigated the functional annotations of the variant-genes stratified by the PIPs in different dataset. Although the number of variant-genes passing a certain PIP threshold was consistently larger for their dataset, we observed higher fraction of variant-genes with clear functional annotations (**Supplementary Fig. 6j**, and even after filtering missense variations; **Supplementary Fig. 6k,l**). For example, when filtering to $0.9 \leq \text{PIP}$, while 52.0% of variant-genes in our dataset contained major functional annotations, only 23.7% did in their EUR dataset. The 23.7% roughly corresponds to the threshold of $0.2 \leq \text{PIP}$ in our dataset (where the number is 25.3%), suggesting our PIP assignment is more stringent compared to Zhang et al.'s, highlighting possible tradeoff between sensitivity and specificity.

Further descriptions of eQTL fine-mapping improvement

Here we describe the improvement of fine-mapping results.

First, the updated, larger and population specific in-house reference panel for variant imputation (consisting of whole-genome sequencing data from $n=4,561$ Japanese) is likely to be contributing to the improved quality of fine-mapping. We compared the posterior inclusion probabilities (PIPs) before and after updating the imputation panel (while fixing everything else the same), and observed larger functional enrichment (as measured by the Expression Modifier Score = EMS; [PMID: 34099641](#)) as well as higher consistency with external data (GTEx v8) (e.g. 1.76 more chance of $\text{PIP} > 0.9$ in GTEx when the variant-gene is moved from low: $\text{PIP} < 0.5$ to high: $\text{PIP} > 0.9$ bin by imputation panel update, compared to the other way around, Fisher's exact test $p=0.016$; **Supplementary Fig. 1**).

Second, the improved sample size ($n=465$ to $n=1,019$) resulted in larger power without introducing major biases. When compared with the previous version of our fine-mapping call from 465 samples, the minimum association p-value per gene was correlated and lower overall thanks to the increased sample size (**Supplementary Fig. 2a**), contributing to the larger number of putative causal eQTLs (**Extended Fig. 2a**). The PIPs were also highly consistent (**Supplementary Fig. 2c,d**) when a variant existed in the previous call. For example, nearly half of the p-causal eQTLs had PIP larger than 0.5 in the previous version, when they existed (1,051 of 2,234 = 47.0%). Functional enrichment was also comparable (**Fig. 2b** and **Supplementary Fig. 2e,f**), and the replication with eQTLgen was also reasonable (**Supplementary Fig. 2g,h**).

These results validate the quality and quantity improvement of our eQTL fine-mapping call compared to the previous release.

Evaluating the quality of rare fine-mapped variants

Inclusion of rare (and low-quality) variants intuitively negatively affect the fine-mapping results by introducing false-positives. On the other hand, recent work in biobank-scale fine-mapping and simulations have shown that inclusion of rare variants, even with low quality, is beneficial (See. our [preprint](#)). Intuitively we can understand this since natural selection should shift the truly causal functional variants to the rarer end of allele frequency spectrums. In other words, rare variants are enriched for putative false-positives AND true-positives, and existing fine-mapping algorithms seem to benefit more from the latter.

To evaluate the quality of rare high-PIP variants, we investigated their functional annotation enrichments compared to common variants (We chose ± 500 bp proximity to the distance to transcription starting site for eQTLs, and missense annotation for pQTLs, as features that should be well-enriched in “Truly causal” variants). As shown in **Supplementary Fig. 2i,j**, we do see a certain amount of depletion of functional annotations for rare variants (the leftmost bin; $2 < \text{MAC} \leq 10$), which suggests that rare high-PIP variants are indeed somewhat enriched for errors. Especially, for missense enrichment in pQTLs, compared to the increasing trend down to $10 < \text{MAC} \leq 30$ presumably due to deleteriousness of some of missense variants, the depletion in the rarest bin seems problematic. On the other hand, the enrichment level for the highest PIP variants ($0.9 < \text{PIP}$; red dots) for the rarest bin is roughly equivalent to the common-variant average of the 2nd best PIP bin ($0.7 < \text{PIP} \leq 0.9$). These results suggest that the quality of “putative causal” rare variants ($0.9 < \text{PIP}$ and $\text{MAC} \leq 10$) is likely to be somewhere around that of common ($10 < \text{MAC}$) variants of $0.7 < \text{PIP} \leq 0.9$. We next investigated the number of rare variants, to confirm that rare-variants represent a sizable fraction across PIP bins (**Supplementary Fig. 2k,l**).

Even when assuming that, given these observations, only 70% of the rare-putative causal e/pQTLs ($0.9 < \text{PIP}$ and $\text{MAC} \leq 10$) are “true” positives,

- for eQTLs, out of $n=419$, roughly 293 are “true” positives and 126 are false positives,

- for pQTLs, out of $n=138$, roughly 96 are “true” positives and 42 are false positives

and thus we are getting near 300 (or 100) true positive eQTLs (or pQTLs) by the inclusion of rare variants. We note that these identifications of “true” rare causal e/pQTLs likely comes with the prevention of nominating “false” positive common variants that arise instead when we do not include rare variants.

We thus conclude that rare putative causal e/pQTLs are likely to have slightly higher false-positive rates, although our analysis nevertheless supports that inclusion of rare variants is indeed beneficial in our analysis, nominating a larger number of putative causal variants. Setting the exact threshold to maximize the quality of fine-mapping in a strict sense (in terms of number of discovery, calibration, precision-recall or any other measures) is an important future direction to be explored.

The unresolved ALDH2 locus

The ALDH2 locus is known to harbor an extremely pleiotropic, east asian-specific missense variant, rs671 (chr12_111803962_G_A_b38; the variant has been under selective pressure and has reported associations with various complex diseases and biomarkers [main article ref. 39-42]). Although the specific missense variation is often thought to explain the causal mechanism of the locus, our result was nuanced, reflecting the complex LD structure of the locus; rs671 presented the highest eQTL PIP (PIP=0.28) but very limited pQTL PIP (PIP=0.014). Another nearby variant, rs2074356 (chr12_112207597_G_A_b38) presented a much higher pQTL PIP (PIP=0.74). Notably, although the pQTL effect was significant in our dataset ($p < 1e-49$), it was not replicated in UKB east asian data ($p > 0.05$), suggesting complex environmental interactions specific to the Japanese population. MPRA experiment targeting 570 common variants around the ALDH2 locus centering rs671 (+0.5 Mb) also did not nominate rs671 as a significant expression modifier variant (FDR>0.1). Our results highlight the challenges of pinpointing the causal variant(s) in a pleiotropic locus even when combining multiple layers of analysis (**Supplementary Fig. 14** and **Supplementary Table 1**).

Exploring drug-target enrichment in different QTLs

Although exploratory, an analysis of druggability provided suggestive evidence that genes harboring protein-specifically regulated genes are more likely to be drug targets than other classes (**Supplementary Fig. 15f**). In the analysis, we downloaded the list of drug-targetable genes that are approved or in different phases of clinical trials were obtained from Opentarget Genetics web portal (<https://genetics-docs.opentargets.org/data-access/data-download>), removed the blacklisted drug-gene associations and computed the enrichment of genes with drug-target evidence in different clinical trial stage (the gene universe was restricted to 2,211 genes where both mRNA-specific and protein-specific QTL effects were evaluated, for fair comparison). As a result, 19.9% of protein-specifically regulated genes have approved or phase 1 to 3 drug-target evidence, versus 10.2% for colocalizing and 13.8% for mRNA-specifically regulated genes ($p = 3.6e-2$ compared to the other two categories combined). Although this result alone is insufficient in statistical power, it aligns with recent biobank scale studies suggesting the utility of pQTL study for drug target discovery and motivates us for further exploration of proteomics data in light of drug development.

Complication in comparing protein-specific QTLs with non-specific pQTLs

Although our analysis in the pQTLs may be more relevant to complex traits than eQTLs section suggested plasma protein-specific QTLs are more relevant to complex traits compared to blood mRNA-specific QTLs, the analyses do not fully uncover the relevance of (mRNA and protein) colocalizing QTLs (or non-specific pQTLs, that harbors not only high pQTL PIP but also high eQTL PIP). The main challenge is the differences in the unit. When comparing protein-specific

QTLs with mRNA-specific QTLs, the same unit, posterior inclusion probability (PIP) could be used, but the prioritization of colocalizing QTLs rely on the calculation of colocalization posterior probability (CLPP), limiting direct comparison with mRNA or protein-specific QTL PIPs. One alternative way is to take a matched control (i.e. for each of high pQTL PIP variant with high eQTL PIP, take a corresponding control with roughly the same pQTL PIP and near zero eQTL PIP), although this results in answering a slightly different question of “Given that we have pQTL evidence, does eQTL evidence further support complex trait relevance?”. Instead, we performed a rank-based comparison comparing the same number of variants prioritized by protein-specific QTL PIP or the CLPP (**Supplementary Fig. 15g**). The results were Inconsistent for UKB and BBJ in the rank-based enrichment comparison, complicating the interpretation. Further analysis is warranted to understand whether protein-specific QTLs (i.e. pQTLs not mediated by blood mRNA eQTLs) are even more relevant to complex traits than colocalizing pQTLs mediated by blood mRNA eQTLs. We again note that what the results in our main manuscript suggest is: “If we were to prioritize variants from either one of pQTL or eQTL information but not both, we would rather choose pQTL”, focusing on the ~3,000 gene set where we do have pQTL information. In real case scenario, utilizing as much information from different regulatory layers are of importance.

Cases where pQTL analysis explains variant-trait association

Here we present specific observations where pQTL information is useful in explaining trait-associated loci, continuing from the pQTLs may be more relevant to complex traits than eQTLs section in the main manuscript.

1. rs884205 on *TNFRSF11A* gene (**Fig. 4d**)

Rs884205 (chr18_62387624_A_C_b38) is a putative causal variant for negative effect on alkaline phosphatase value (ALP; PIP=1.0 in BBJ and UKB), as well as positive effect on estimated bone mineral density (eBMD; PIP>0.99). The variant, located on 3'UTR of the *TNFRSF11A* gene (involved in a number of bone-related diseases), is a putative causal pQTL lowering TNFRSF11A protein ($\beta=-0.15$ and PIP=1), but is not likely a causal eQTL on *TNFRSF11A* mRNA expression ($p=0.02$, PIP=0), thus possibly involved in post-transcriptional regulation without changing the mRNA expression level. Alternatively, although the variant is not a significant eQTL in any of GTEx tissues, it is also possible that the pQTL effect is a result of mRNA expression regulation in trait-relevant tissue(s) missing in GTEx.

2. rs429358 on *APOE* (**Fig. 4e**)

Rs429358 (chr19_44908684_T_C_b38), the well-known constituent of APOE- $\epsilon 4$ allele (PIP>0.99 for a number of traits such as increased total cholesterol, reduced C-reactive protein count in BBJ and UKB, and increased risk of Alzheimer disease in UKB), shows a clear pQTL signal (PIP=1), without being an eQTL (PIP=0). Notably, in previous studies using another platform (Zhang et al. [PMID: 35501419](https://pubmed.ncbi.nlm.nih.gov/35501419/), SOMAScan), the variant presented a positive effect on the protein expression level, while in our analysis the effect was clearly negative ($\beta=-0.97$;

Supplementary Fig. 16). This negative effect direction was consistent with UKB-PPP data which uses the same Olink platform as ours, across three populations ($\beta=-0.63$, -1.01 and -1.11 for EAS, EUR and AFR). Another recent study has also reported such inconsistency in the effect size of pQTL on APOE (Xu et al. [PMID: 36797296](#), and for other genes as well; e.g. Pietzner et al. [PMID: 34819519](#) reported a similar discrepancy of effect sizes between platforms for PILRA), exemplifying such difference can arise from changes in platform-specific aptamer binding affinity (epitope effect) introduced by missense variants.

3. rs13395911 on *EFHD1* (**Supplementary Fig. 15h**)

Rs13395911 (chr2_232655544_A_T_b38), a fine-mapped putative causal variant on hepatic traits such as increased alanine transaminase value (PIP=0.90 in BBJ, 0.87 in UKB), is a putative causal pQTL on EFHD1 protein expression (PIP=1). This intronic variant, although not likely to be a causal eQTL in whole blood (PIP=0), has been identified as a putative causal eQTL in liver tissue in GTEx (PIP>0.99; [PMID: 34099641](#)), suggesting an effect on protein expression in plasma through mRNA expression regulation in liver rather than in whole blood. Importantly, there is a distinct putative causal whole-blood eQTL in our dataset, rs73995831 (chr2_232636954_G_T_b38, relatively rare variant with MAF=0.003 in European population and thus are not called in GTEx) with PIP=0.916, with no notable complex trait associations.

4. rs28372783 on *CDH1* (**Supplementary Fig. 15i**)

Our fine-mapping analysis confirmed that rs28372783 is the putative causal variant (PIP=0.95 in SuSiE and 0.92 in FINEMAP) on CDH1 protein expression, without clear eQTL effect observed previously. We also note that the variant was missing in the UKB-PPP dataset (likely filtered out by allele frequency or other threshold in the joint population). The lead variant in UKB EUR dataset, rs2011779, is an intronic variant with a modest effect size ($\beta = -0.04$, in contrast to $\beta=0.26$ for rs28372783), suggesting that their lead variant, even if causal, has a much smaller effect on CDH1 expression compared to our proposed putative causal variant rs28372783. The variant could be nominated as a potential follow up study, as suggestive evidence of trait relevance of *CDH1* exists; in a meta-analysis of Biobank Japan and Korean Genome and Epidemiological Study, a near-genome wide significant association ($p=6.7e-8$) with γ -glutamyl transpeptidase level was observed <https://koges.leelabsq.org/variant/16-68771122-A-C>. Survival rate difference in gastric carcinoma patients was observed in a study in China [Zhang et al 2018 = [PMID: 29168119](#)].

As noted in the main manuscript, these examples each suggest scenario where plasma pQTL fine-mapping is beneficial in addition to eQTL fine-mapping in whole blood for complex trait-causal variant interpretation (1. a 3'UTR variant possibly involved in post-transcriptional regulation 2. a missense variant likely affecting protein stability and 3. 4. an mRNA expression regulation taking place in non-blood tissue).

Further notes on trans-e/pQTL analysis

The human leukocyte antigen (HLA) genes, located in the human major histocompatibility complex (MHC) region, is known to explain a large fraction of complex trait heritability, especially for immune related disorders, motivating us to focus on this specific region instead of testing all the variants genome-wide. Although the molecular interaction between KIR and class 1 HLA was well known, we deem our results as one of the first observations uncovering the genetic basis for the link between these two gene families. Further studies dissecting the genetically-determined versus environmentally driven mechanisms, as well as their interactions, are warranted.

Regarding the lack of overlap between trans e/pQTLs in HLA, the simple fact that the list of genes with protein expression measurement was much smaller than that of mRNA expression (2,932 vs 19,798; e.g. the T cell receptor variable families, of which six genes showed significant trans-mRNA- association, have only mRNA measurement) alone does not explain this low overlap, since the majority of trans-protein regulated genes were included in the eQTL analysis as well, although not showing significant trans-mRNA associations (15 out of 19; bold font in the lower half of **Fig. 5c**).

Further details on context (severe COVID-19) specific e/pQTL effects

Here we discuss details about the COVID-19 severity interaction e/pQTL analysis (ie and ipQTLs). Compared to our previous analysis of ieQTLs ([\[PMID: 35995775\]](#)), our current version is different in the sample size (previous version performed ieQTL analysis with 465 samples, where we utilized 998 samples in this research) and the QTL type (previous version did not have protein measurements). Consistent with our previous result, ieQTL analysis does not prioritize genes from COVID-19 susceptibility GWAS (**Supplementary Fig. 19**), presumably because interactions rather reflect the consequence of severe disease state. Nevertheless, increased sample size allowed us to call ieQTLs with higher statistical power (**Supplementary Fig. 20a**), where 20 genes passed the Bonferroni significance threshold ($p=5e-8$). On the other hand, for ipQTLs (pQTLs interacting with COVID-19 severity) called from the identical sample, none of the 20 genes reached significance (**Fig. 6c**, only two proteins including IL1RL1 passed the significance threshold; **Fig. 6d**). As an example, while the eQTL effect of rs11202918 on *FAS* mRNA expression monotonically decreases along with COVID-19 severity, the pQTL effect on *FAS* protein expression is constantly small and non-significant (ipQTL $p=4.5e-3$; **Fig. 6e**). Even for *CLEC4C*, where the ieQTL is the most significant ($p=4.1e-32$ for rs7302014), ipQTL effect does not reach significance threshold ($p=2.4e-7$; **Fig. 6f**).

We note that many of those ie-genes are highly expressed in lymphocytes compared to other tissues in GTEx (e.g. 5 genes including *FAS* have the highest expression in lymphocytes out of 54 tissues; yellow dots in **Fig. 6c**). Also, *CLEC4C* is almost exclusively expressed in blood, testis and lymphocytes in GTEx). Neither rs11202918 nor rs7302014 is annotated as significant eQTL in lymphocytes in GTEx, suggesting that the effect of ieQTLs are buffered by mRNA

expressions in lymphocyte that are presumably relatively stable against the genetic variations. Alternatively, there are also at least two possible simpler explanations; The results could reflect 1. the differences between whole blood and plasma (e.g. dynamics of solid components such as white blood cells in the blood is not captured by plasma pQTL analysis), or 2. the detection sensitivity difference of RNA-seq vs affinity based assay. Specifically for 2., we note that the percentage of samples falling below the limitation of detection (LOD) for *CLEC4C* increases along with the disease severity state (**Supplementary Fig. 21a**; 0% in asymptomatic to 9.3% in the most severe state), which could be limiting the quantification of *CLEC4C* protein expression in severe state and thus resulting in lower statistical power. Although existence of LOD is expected and is not likely to introduce significant biases (**Supplementary Fig. 21**), the results suggest that methodological improvements for more sensitive quantification of protein level would be beneficial. Further discussion about such LOD is in the next section.

Additional evaluation of protein measurements below the Limitation of Detection (LOD)

As recommended in the Olink webpage FAQ (<https://olink.com/faq/how-is-the-limit-of-detection-lod-estimated-and-handled/>) stating “*especially in large multiplate studies LOD is a conservative measurement. Using actual data may increase the statistical power and gives a more normal distribution of the data. Including data under LOD does commonly not increase false positives*”, we did not set any threshold to remove the measurement data based on percentage of samples below the LOD.

As visible in **Supplementary Fig. 21e,f**, although the majority of genes have near 0% of measurements below LOD, some genes indeed have high % of measurements below LOD (e.g. 20% of the measured genes have >40% of samples below LOD). While that sounds problematic, most of such genes do not appear to have significant pQTL associations (e.g. the right-end of **Supplementary Fig. 21g**, suggesting that over 90% of the genes with >75% samples below LOD do not have any variants below pQTL $p=5e-5$. Only $n=3$ genes with $p<5e-8$), suggesting that the existence of LOD is not introducing major false-positives, as it is not inflating the p-values (although it surely is decreasing our power to call pQTLs by rather deflating the p-values).

The potential power-loss by having non-zero percentage of LOD is exemplified in the case of COVID-19 interaction pQTL (ipQTL) effects of *CLEC4C* (**Supplementary Fig. 21a** and in the main text Buffering of context (COVID-19 severity) specific eQTL effects section). To further evaluate the overall influence of LOD in ipQTL call, we compared the %measurements below LOD for each gene with ie/ipQTL statistics (**Supplementary Fig. 21b**), and found that a few genes with significant ieQTL and non-significant ipQTL effects indeed have medium~high fraction of measurements below LOD. As in the example of *CLEC4C*, this is especially problematic when the %measurements below LOD itself correlates with the COVID-19 severity. To evaluate the potential impact of such correlations, we tested the linear model where

the %below LOD ~ COVID-19 severity, and found that CLEC4C is one of the two genes with significant ieQTL effects and a significant correlation between %LOD and severity (**Supplementary Fig. 21c,d**; RPA2 and CLEC4C, $p < 0.05/\#genes$). These results suggest that the existence of LOD and especially the correlation between LOD could partially explain the mild interaction-pQTL effects.

Overall we did not find strong evidence that inclusion of genes with high %samples below LOD affects the result in a negative way, and we deem that our decision to keep the values as is without adjustment of exclusion is one of the valid choices. We leave further discussion on whether or not and how to set a cutoff based on %samples below LOD as future directions.

Distinguishing age-driven QTL effect from COVID-19 interaction QTLs

Interaction between sample age and the mRNA expression QTL (eQTL) effects are well known (e.g. [\[PMID: 36192477\]](#)), and COVID-19 phenotype severity is correlated with sample age (i.e. older individuals are more likely to have severe COVID-19 phenotype). We thus aimed to control age-driven effects, by the inclusion of age as a covariate in the interaction QTL analysis (i.e. if the marginal effect scales linear with the age, it would be captured by the age term). To further validate that the potential age-driven effects that are in reality near-independent of COVID-19 severity itself are limited, we repeated interaction QTL analysis with following three additional patterns (2) to (4), totalling in four distinct patterns:

- (1) testing the interaction effect of **COVID-19 severity**, including age as a covariate (= our main analysis result in the manuscript)
- (2) testing the interaction effect of **COVID-19 severity**, excluding age from the covariates
- (3) testing the interaction effect of **age**, including COVID-19 severity as a covariate
- (4) testing the interaction effect of **age**, excluding COVID-19 severity from the covariates and compared the test statistics (**Supplementary Fig. 20b-d**).

The result suggests that, for both interaction eQTL and pQTLs, while the interaction effect with COVID-19 severity shows moderate correlation with the interaction effect of age (e.g. $r=0.44$ for the correlation between $-\log_{10}p$ of the interaction eQTL effects), the former is of higher statistical significance compared to the latter. The figure also shows that the inclusion of age as a covariate when testing interaction effect of COVID-19 severity (or vice versa) has little effect on the result (presumably because these factors are mostly captured by PEER factors, as discussed in our previous manuscript [\[PMID: 35995775\]](#)).

The top-significant genes for COVID-19 severity interaction partially intersects with that of age severity interaction (e.g. CLEC4C, the top for COVID-19 severity, is the 3rd top for age), but they each present some unique genes (e.g. PPIE is the 4th best in COVID-19 severity interaction with $p=7.9e-18$, but $p=3.8e-4$ in age interaction / ANXA11 is the 2nd best in age interaction with $p=2.3e-11$, but $p=2.3e-2$ in COVID-19 severity interaction), validating that the COVID-19 severity interaction we discover is not merely capturing age-interaction effects.

We also repeated the comparison of interaction eQTL vs interaction pQTL p-values and discovered that, the attenuation of interaction eQTL effect, as discussed in our main manuscript for COVID-19 severity, is present for age-interaction effect too, although with smaller magnitude (Lower panel of **Supplementary Fig. 20b**). In the plot, we additionally overlapped known age-interacting eQTL genes [PMID: 36192477] which does not necessarily overlap with our result (presumably due to age distribution differences and other study-specific factors), again validating that the COVID-19 severity interaction we discover is not merely capturing age-interaction effects.

While we do acknowledge that perfectly distinguishing the interaction effect of COVID-19 severity with age remains challenging (due to their correlation), we believe the added analysis above suggests that our main findings (e.g. COVID-19 interaction-eQTL effect on CLEC4C gene) are unlikely to be due to confounding of age-specific interaction.

Transcriptional activity estimation in massively parallel reporter assay (MPRA)

Our definition of transcriptional activity as measured by MPRA is primarily based on that presented in MPRAAnalyze package [Ashuach et al. 2019; PMID: 31477158], with a few simplified assumptions. Specifically, we assume that, within a cell type,

1. The transcription rate for a 200 bp oligo is a function of oligo sequence s alone: $\alpha_s = f(s)$
2. for each oligo sequence s , barcode i and replicate j , RNA count is a poisson draw with parameter $\lambda_{s,i,j} = \alpha_s \cdot DNA_{s,i,j}$. That is, $RNA_{s,i,j} \sim \text{poisson}(\lambda_{s,i,j})$.

We assume that the barcode, replicate and other specific factors affect RNA count only through DNA count, and not through the parameter α_s . Under this simplified model, the log-likelihood of an observed data given the translation rate α_s for an oligo sequence s given all measurements across barcode i and replicate j is given by:

$$\begin{aligned} LL(\alpha_s) &= \log\left\{ \prod_{i,j} \exp(-\lambda_{s,i,j}) \cdot \lambda_{s,i,j}^{RNA_{s,i,j}} \cdot (RNA_{s,i,j})^{-1} \right\} \\ &= -\sum_{i,j} \lambda_{s,i,j} + \sum_{i,j} RNA_{s,i,j} \log(\lambda_{s,i,j}) - \log(RNA_{s,i,j}) \\ &= -\alpha_s \sum_{i,j} DNA_{s,i,j} + \sum_{i,j} RNA_{s,i,j} \{ \log(\alpha_s) + \log(DNA_{s,i,j}) \} - \log(RNA_{s,i,j}) \end{aligned}$$

Thus to obtain the best estimation of α_s ,

$$\frac{d}{d\alpha_s} LL(\alpha_s) = -\sum_{i,j} DNA_{s,i,j} + \alpha_s^{-1} \cdot \sum_{i,j} RNA_{s,i,j} = 0$$

$$\text{i.e. } \alpha_s = \frac{\sum_{i,j} RNA_{s,i,j}}{\sum_{i,j} DNA_{s,i,j}}.$$

In other words, under our simplified model, we estimate the translation rate α_s simply as the aggregated ratio: the ratio of the sum of RNA counts divided by the sum of DNA counts, both aggregated across barcodes and replicates.

Variant effect quantification in massively parallel reporter assay (MPRA)

In our MPRA assay, our goal is to test the variant effect on transcriptional activity. In other words, most of the 200 oligos are coupled with the other one with single nucleotide variation (SNV) or short insertion, deletion (indels). For each of these pairs, which we call one oligo as reference = ref and the other as alternative = alt without loss of generality, we test the difference of the translation rate between the ref and alt oligos in a permutation based method as follows:

1. Given a pair of ref and alt sequences corresponding to a genomic variant v , we calculate the log fold change of the translation rate and let it be the test statistics:

$$LFC_v = \log_2\left(\frac{\alpha_{alt}}{\alpha_{ref}}\right)$$

2. To get null statistics, we shuffle the label of ref or alt for the barcodes associated with either the ref and alt sequences, across all the replicates. We then calculate the log fold change when these shuffled pseudo-label were assigned.
3. We iterate step 2. for 100,000 times to obtain the null distribution, as well as the p-value corresponding to the test statistics in step 1.
4. We perform 1~3 for all the variants, and apply Benjamini-Hochberg procedure to control for false-discovery rate (FDR). Variants passing the $FDR < 0.01$ threshold were defined as Tier 1 expression modifying variants (emvars), and other variants passing the $FDR < 0.1$ threshold were defined as Tier 2 emvars.

The null hypothesis is that, for each variant, the difference between the transcription rate in ref and alt sequences is not different from that between a shuffled random division (of the same numbers) of the associated barcodes. We applied these steps for two cell types (HepG2 and K562) separately to obtain lists of emvars for each cell type. We note that since we applied a non-parametric, permutation based method as in step 3, the resolution of p-values are capped at $1/100,000 = 1e-5$.

Supplementary Table

Supplementary Table 1. List of expression modifying variants in the ALDH2 locus prioritized by reporter assay

variant hg38	rsid	pval K562	$\log_2\left(\frac{\alpha_{alt}}{\alpha_{ref}}\right)$ K562	Tier K562	pval HepG2	$\log_2\left(\frac{\alpha_{alt}}{\alpha_{ref}}\right)$ HepG2	Tier HepG2
chr12_11 1394189_ A_G	rs457219 6	0	1.26	Tier 1	0.00053	0.89	Tier 2
chr12_11 1409936_ A_G	rs380317 0	8.0E-05	-0.29	Tier 1	0.40	-0.055	None
chr12_11 1834936_ G_A	rs577519 44	0.54	-0.07	None	1.0E-05	-0.49	Tier 1
chr12_11 2143468_ ACCT_A	rs344525 06	0.129	0.16	None	0	0.57	Tier 1

Supplementary Table 2. Properties of the major putative-causal eQTL and pQTL variants on the *ABO* gene

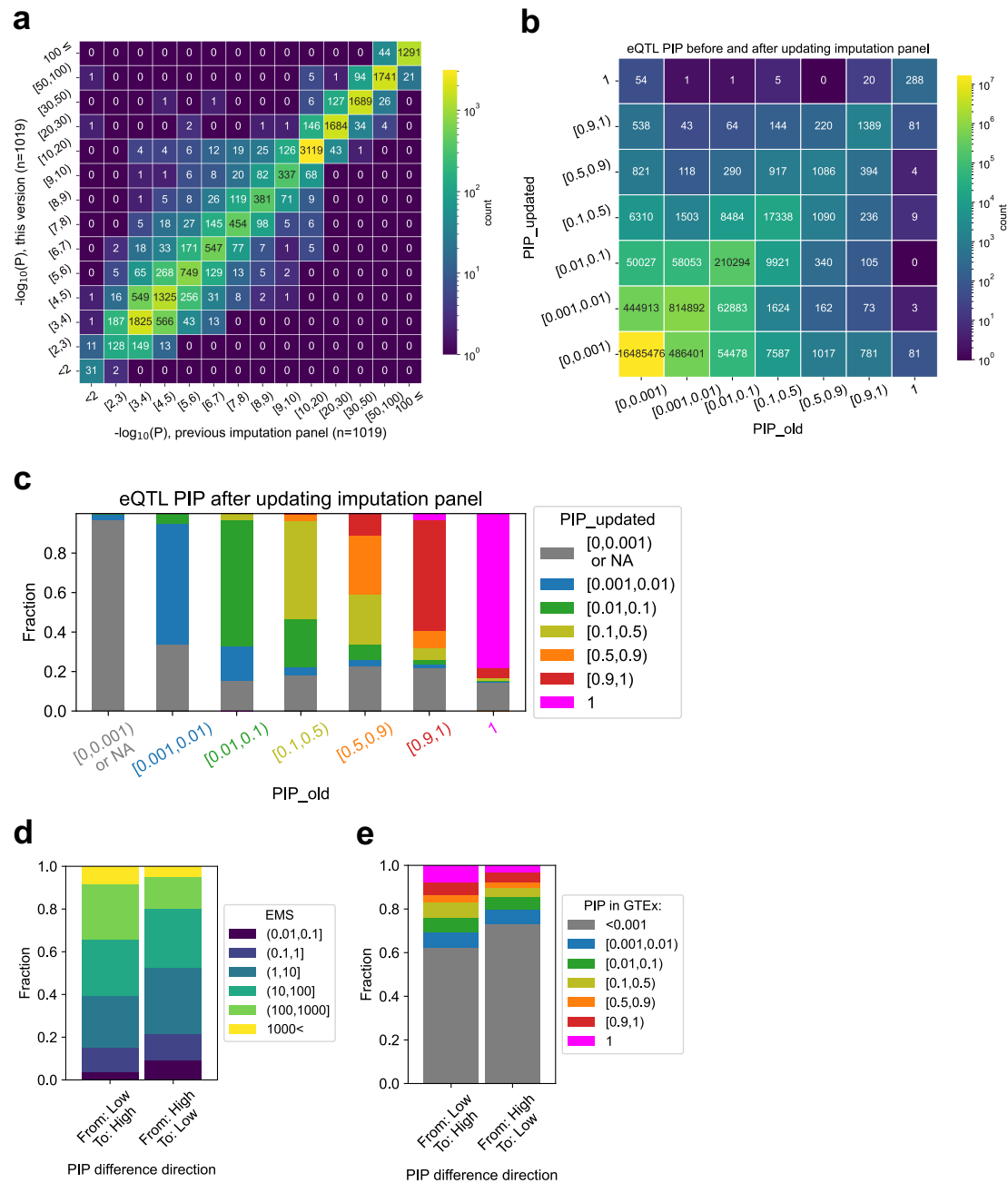
Abbreviation	variant_hg38	rsid	MAF	eQTL PIP	pQTL PIP	Annotation
e1	chr9_133252214_G_A	rs9411476	0.2780561	0.3	0	nc-transcript exon
e2	chr9_133301911_T_C	rs656105	0.3762525	0.28	0	upstream
e3	chr9_133302510_G_A	rs4962043	0.3757515	0.42	0	nc-transcript exon
p1	chr9_133257521_T_TC	rs8176719	0.498998	0	1	frameshift exon 6
p2	chr9_133261991_T_C	rs139669834	0.0506012	0	0.73	Intron

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Supplementary Figure 1. Evaluating the updated imputation panel with eQTL fine-mapping results

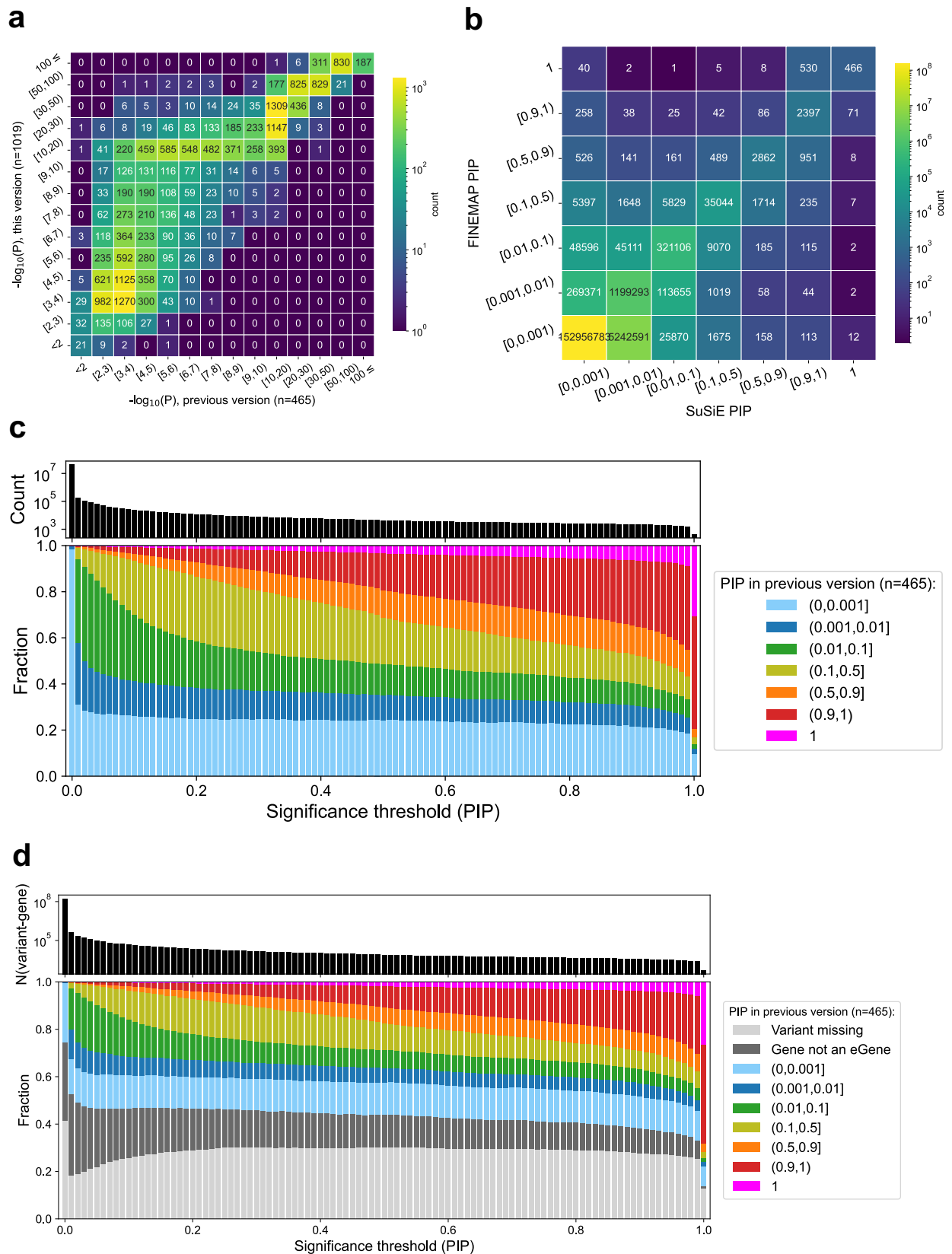


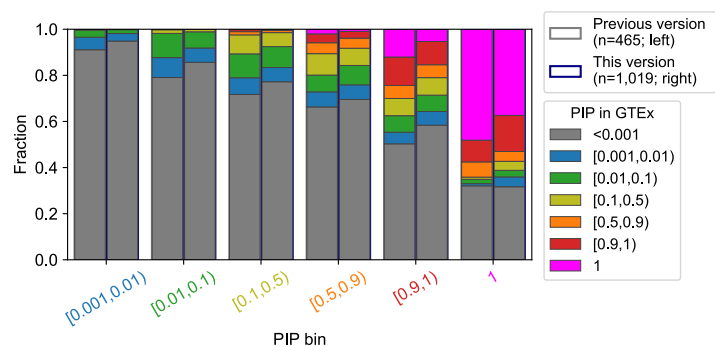
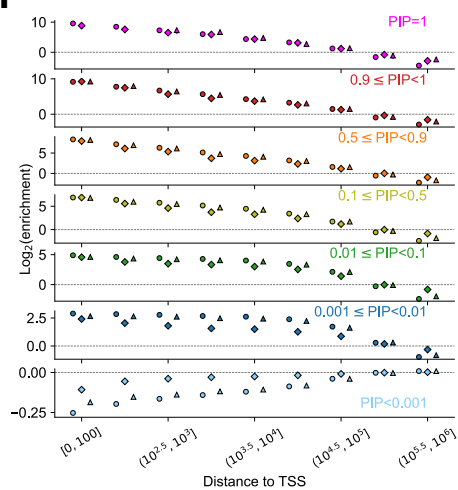
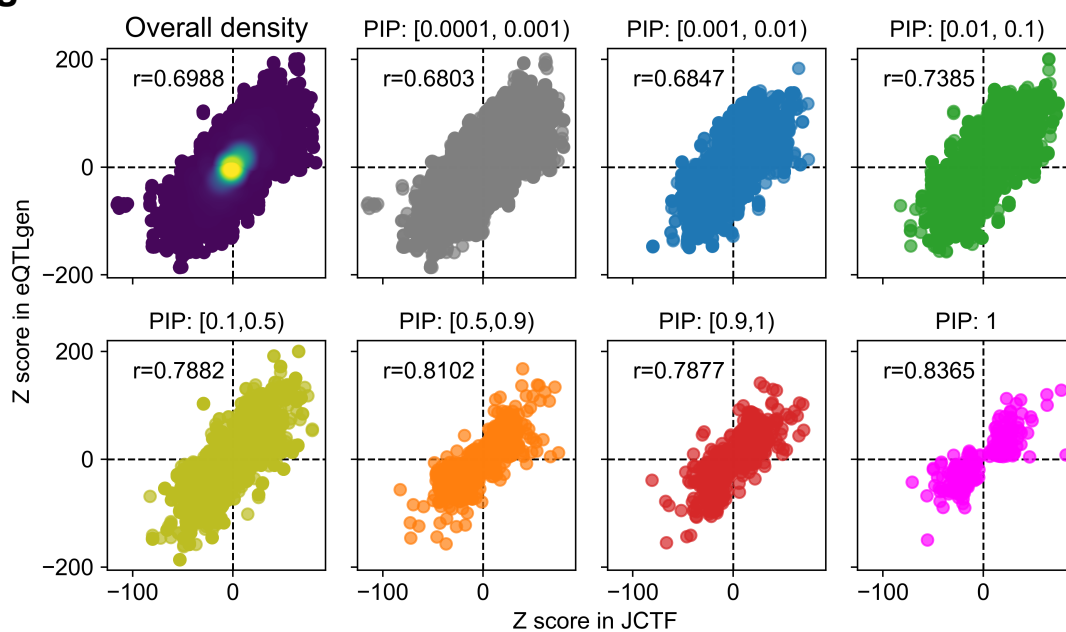
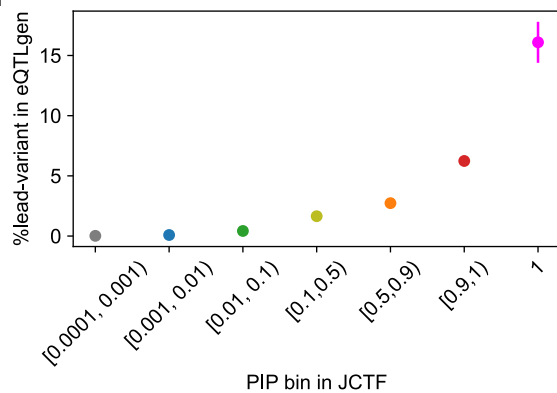
a. Comparison with the eQTL call using the previous imputation panel, in terms of the marginal association p-values (minimum per gene).

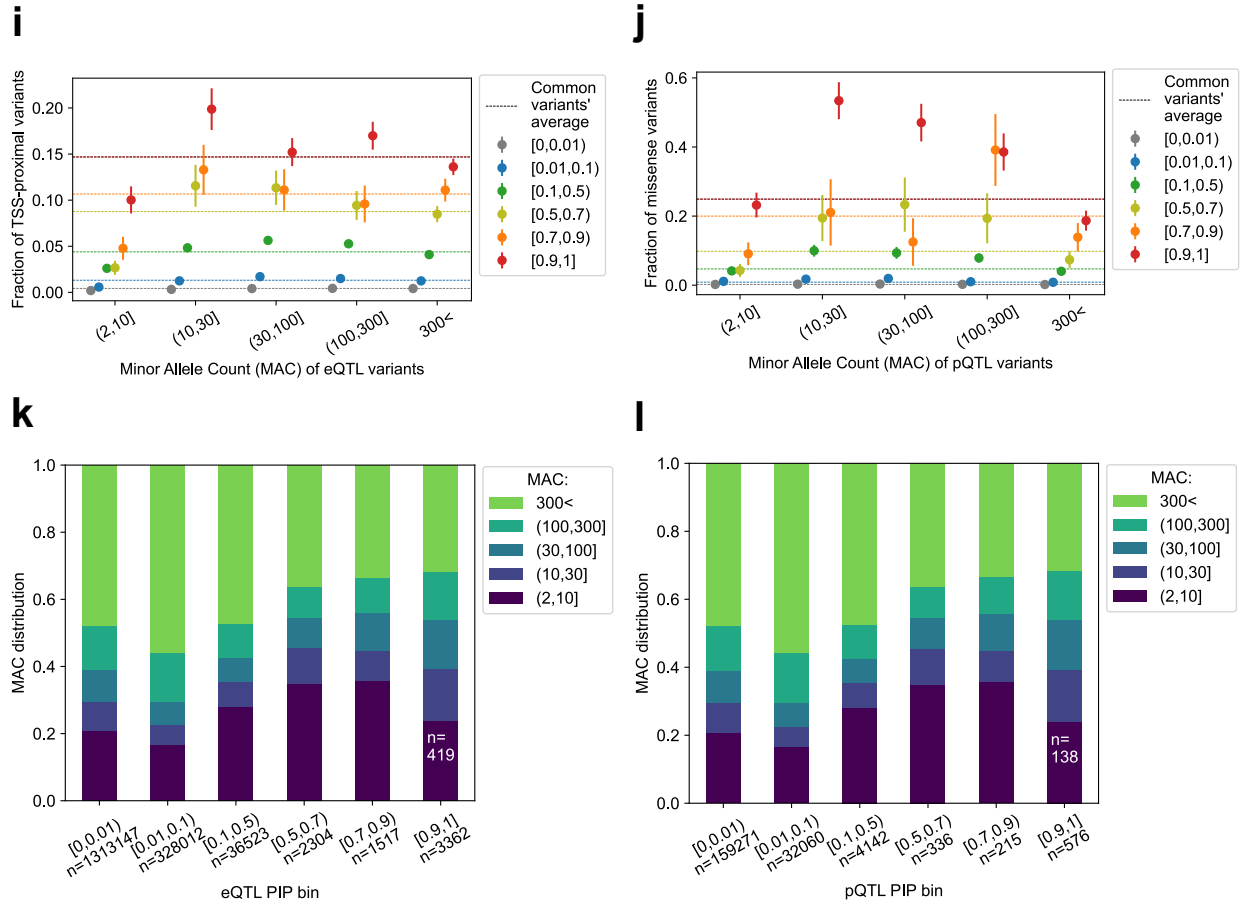
b.c. Comparison with the eQTL call using the previous imputation panel, in terms of posterior inclusion probability (PIP). **c.** is normalized and includes missing variants in the visualization

d.e. Comparison of the Expression Modifier Score (EMS) (**d**) or GTEx v8 whole blood eQTL PIP (**e**), for the ones resulted in significantly higher or lower PIP when using the updated imputation panel (low to high: PIP<0.5 to PIP>0.9, high to low: PIP>0.9 to PIP<0.5), together showing that the updated result has higher functional enrichment and replication rate.

Supplementary Figure 2. Quality check of eQTL fine-mapping results

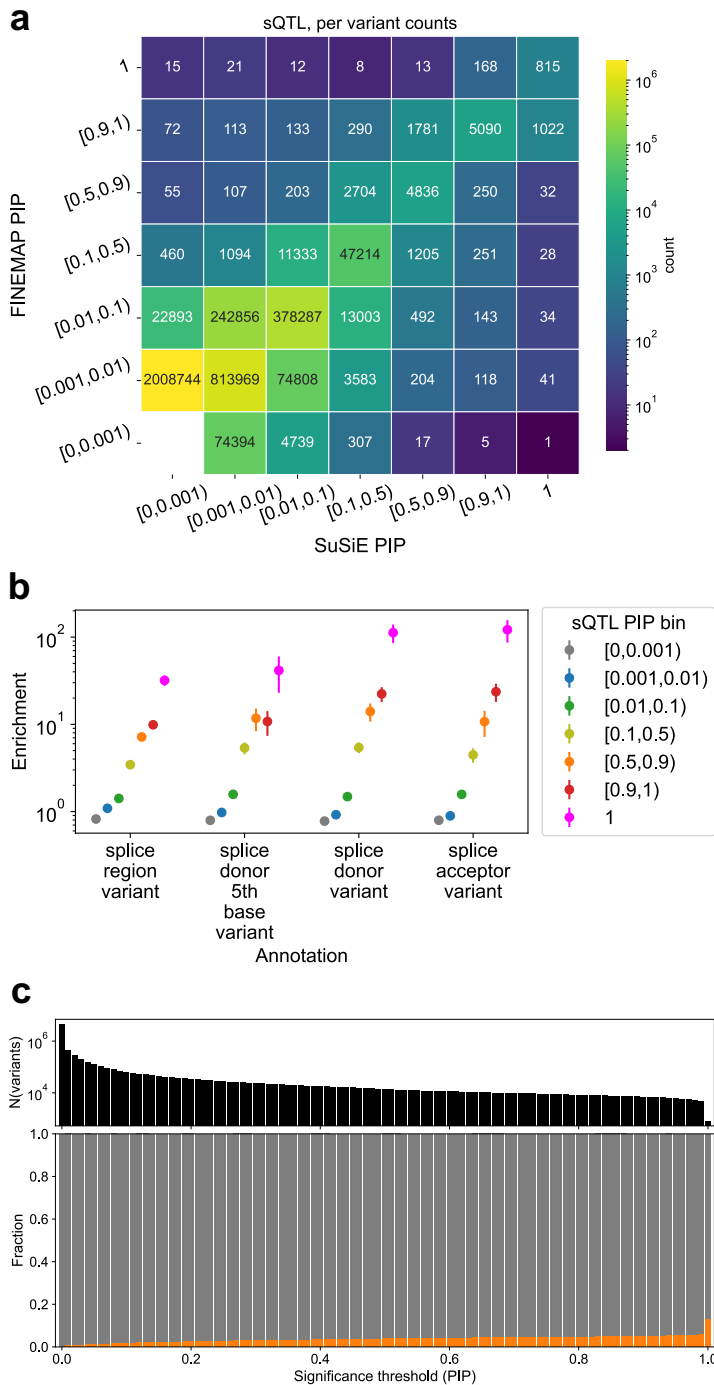


e**f****g****h**



- Comparison of minimum p-value per gene with our previous eQTL dataset (n=465).
 - Comparison of the eQTL PIPs for each variant-gene when using SuSiE or FINEMAP.
 - Comparison with the eQTL PIPs from the previous call set (n=465), when existing.
 - Comparison with the eQTL PIPs from the previous call set (n=465), including previously missing or uncharacterized variants.
 - Comparison by the concordance with PIPs from GTEx dataset.
 - Comparison by the distance to transcription starting site (TSS) distribution, in an enrichment scale.
 - Comparison of the z-scores with the eQTLgen dataset, stratified by the PIPs in our dataset.
 - Percentage of eQTLs appearing as lead variants (i.e. the variant with lowest p-value for a gene) in eQTLgen, stratified by the PIPs in our dataset.
 - Fraction of eQTLs within 500bp from the transcription starting site of the regulated gene (=TSS-proximal variants) as a proxy of the causal eQTL signal, stratified by the PIP and the minor allele count (MAC). Dashed lines are the average for common ($100 \leq \text{MAC}$) variants.
 - Fraction of missense pQTLs as a proxy of the causal pQTL signal, stratified by the PIP and the minor allele count (MAC). Dashed lines are the average for common ($100 \leq \text{MAC}$) variants.
 - i. Distribution of MAC per PIP, for eQTLs (**k**) and pQTLs (**l**).
- All the n=165,410,953 variant-gene are included in **h.**, where the number per PIP is available in e.g. **Supplementary Fig. 2b**. N in **i.** and **j.** are identical as those shown in **k.** and **l.**

Supplementary Figure 3. Splice QTL (sQTL) fine-mapping overview



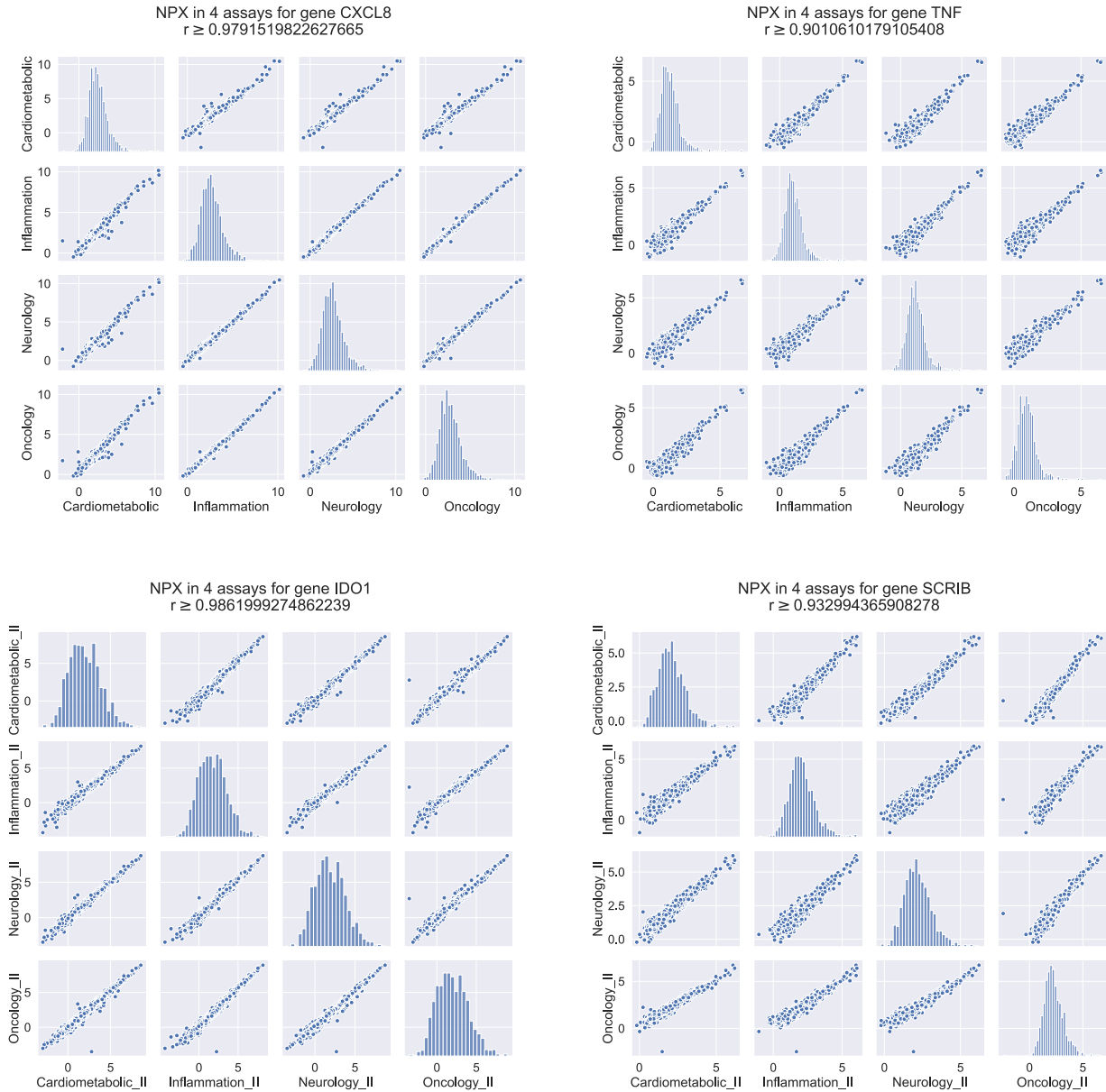
a. Comparison of sQTL PIPs for each variant-intron cluster when using SuSiE or FINEMAP. The lowest bin is intentionally removed for visualization purposes.

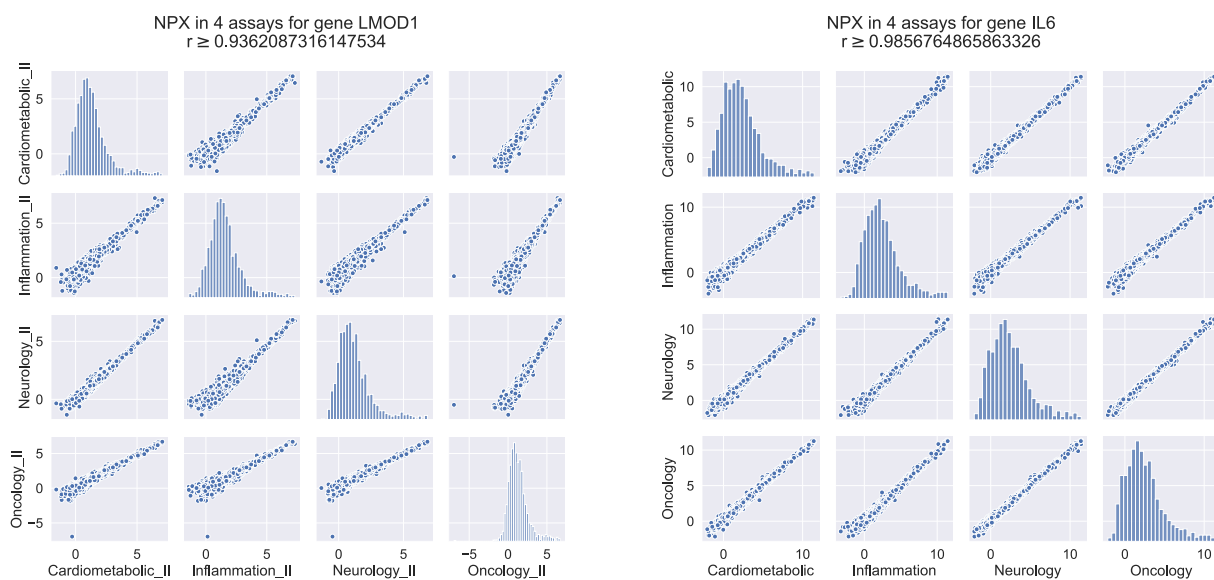
b. Enrichment of splice-related annotations in VEP for different PIP bins, validating the quality of our sQTL fine-mapping. $n=2,907,208$, $1,136,914$, $403,640$, $51,700$, $6,912$, $6,280$ and 815 variant-introns in each PIP bin.

c. The number of variant-genes, as well as the fraction of variant-genes with splice-related annotations in VEP.

Supplementary Figure 4. Quality control (QC) for pQTL call and fine-mapping

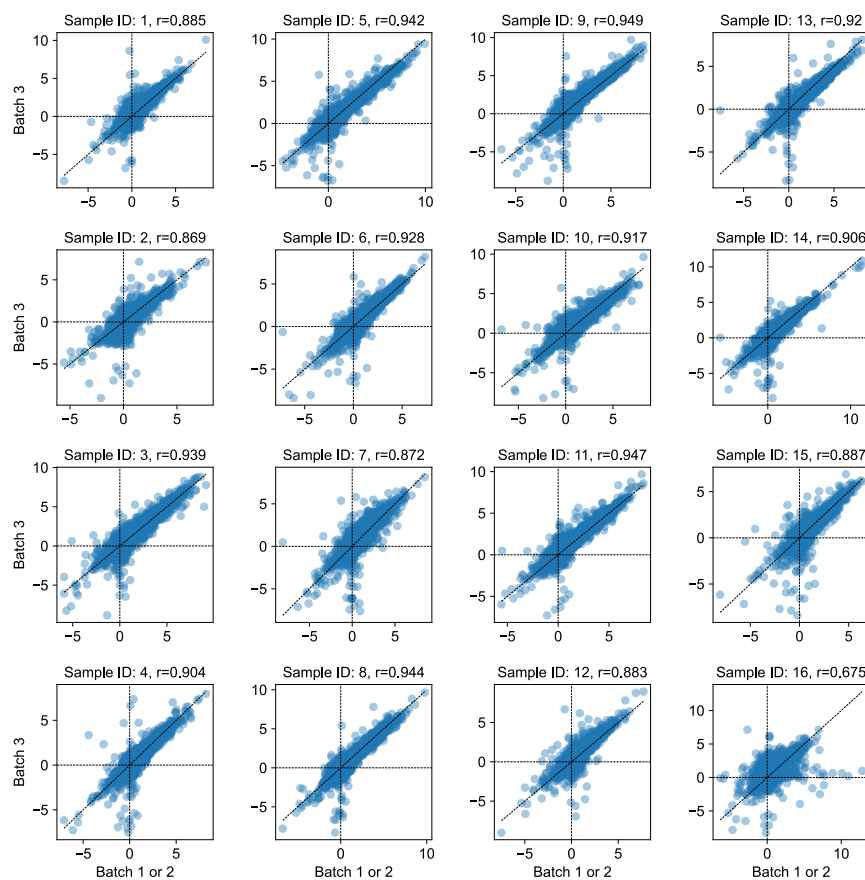
a

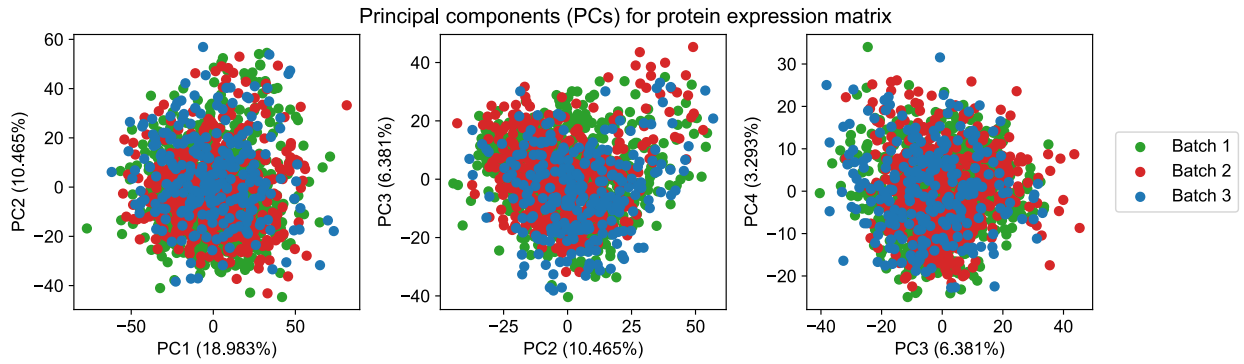
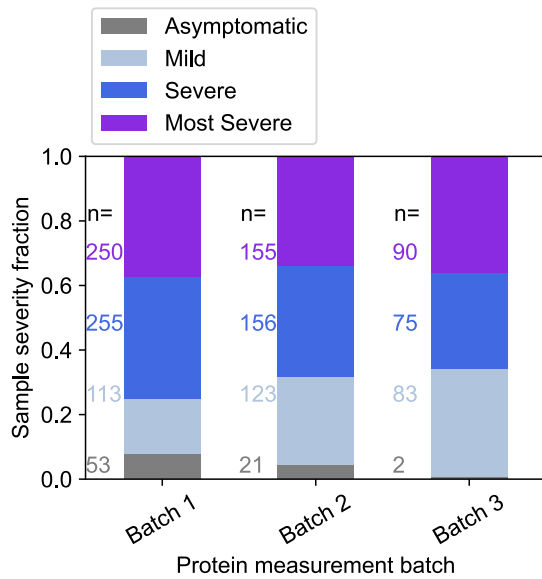
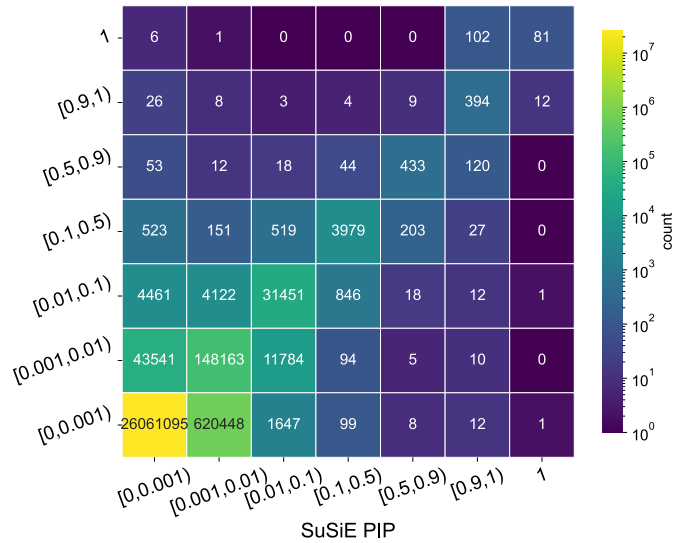




b

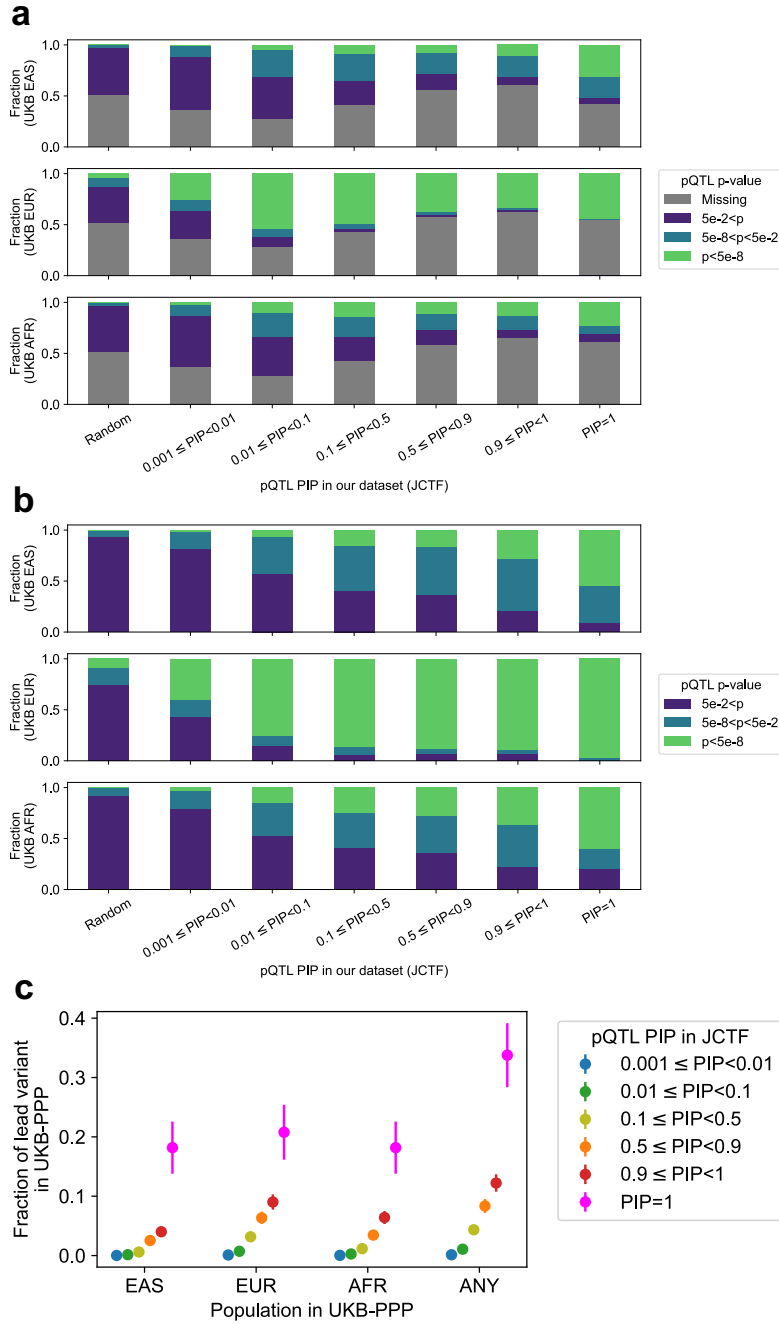
Correlation between duplicated samples in different batch



c**d****e**

- a.** Scatter plots comparing the NPX (Normalized Protein eXpression) of the six genes measured in four different panels.
- b.** Scatter plots comparing the NPX of all the measured genes for 16 samples that are included in two different batches.
- c.** Scatter plots showing the principal components calculated from bridge-normalized and inverse-normal transformed expression matrix, colored differently by different batches.
- d.** Sample COVID-19 severity status distribution per batch, suggesting no major differences between batches.
- e.** Comparison of the PIP from FINEMAP and SuSiE.

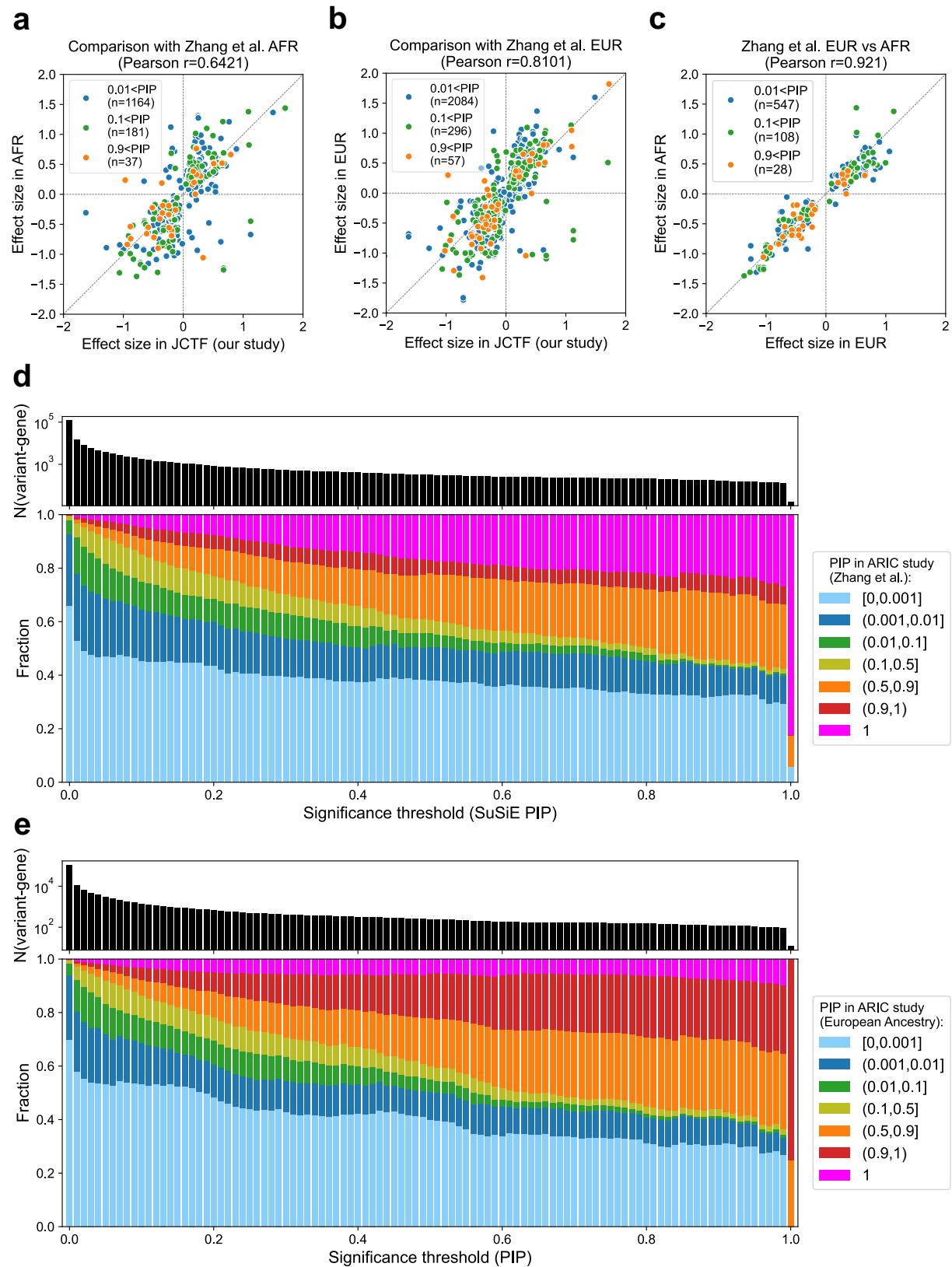
Supplementary Figure 5. Detailed evaluation of pQTL fine-mapping result with the UKB-PPP data

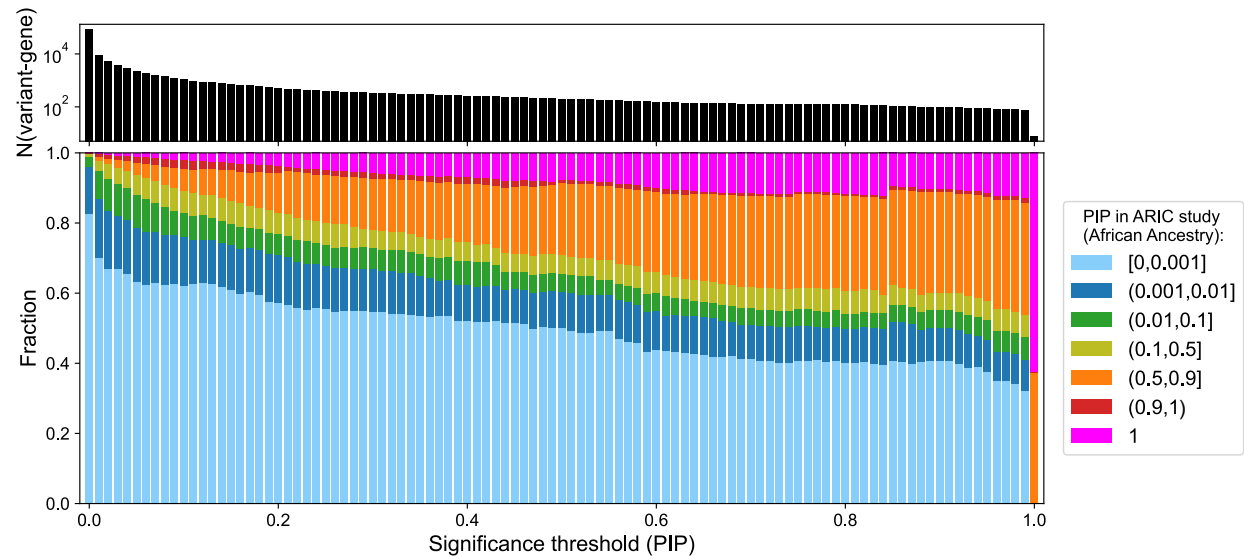
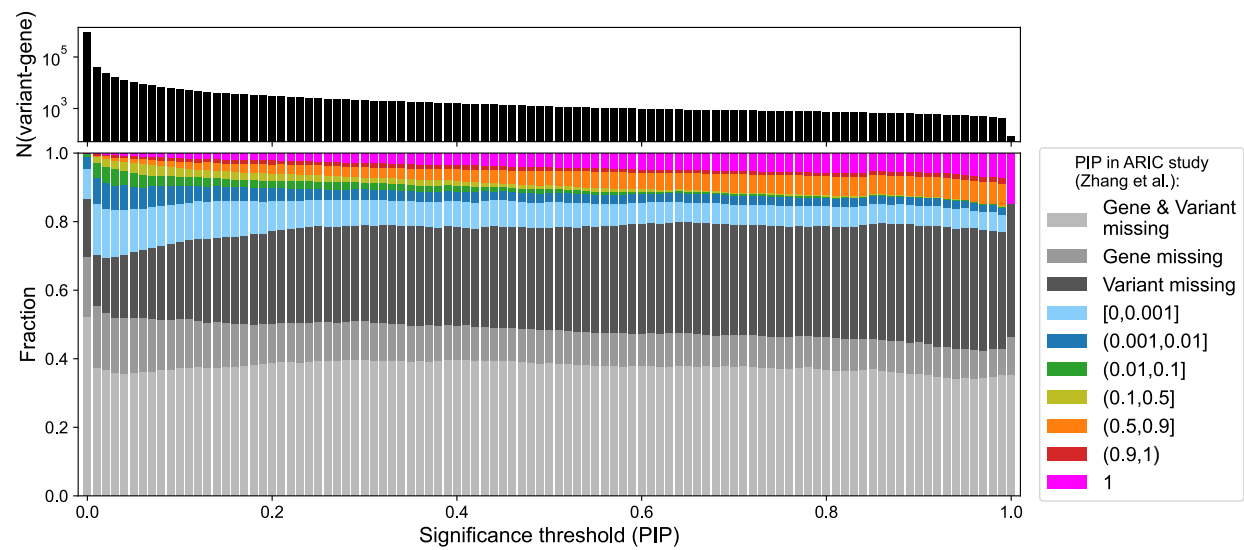


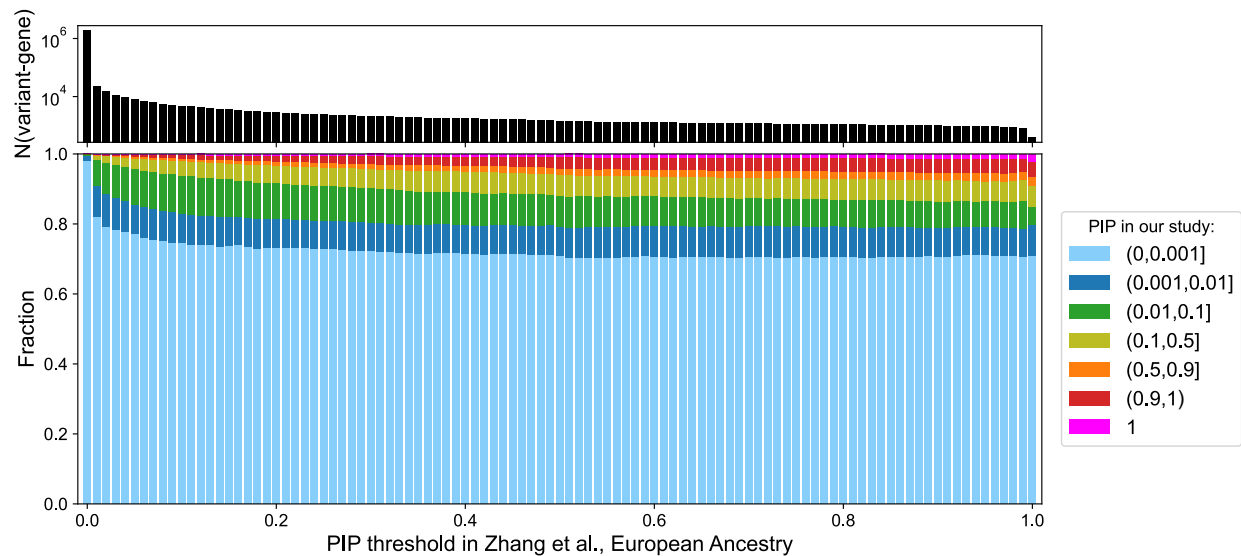
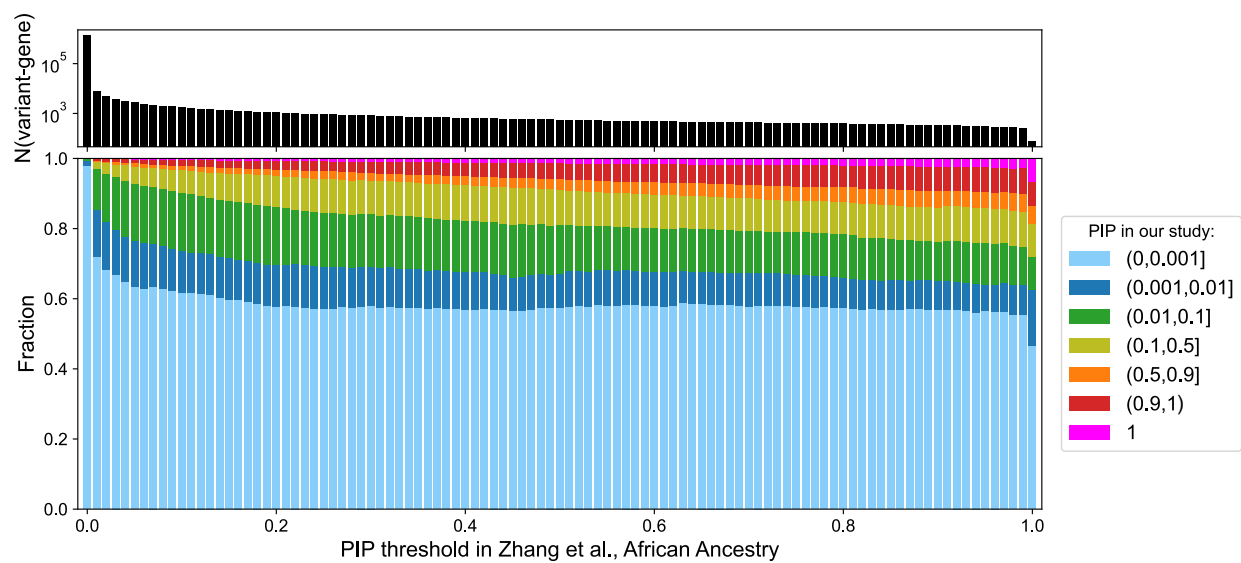
a.b. Distribution of pQTL association p-values in UKB, stratified by the population background in UKB-PPP (columns; EAS=East Asian, EUR=Europeans, and AFR=Africans) and the pQTL PIPs in our dataset (rows). Missing variants are included in (a) while excluded in (b). These results not only validate our pQTL fine-mapping but also suggest that only a small fraction of the variants passing canonical “genome-wide significance” $5e-8$ are causal in the size of UKB-PPP EUR dataset (assuming that the causal architectures are largely shared).

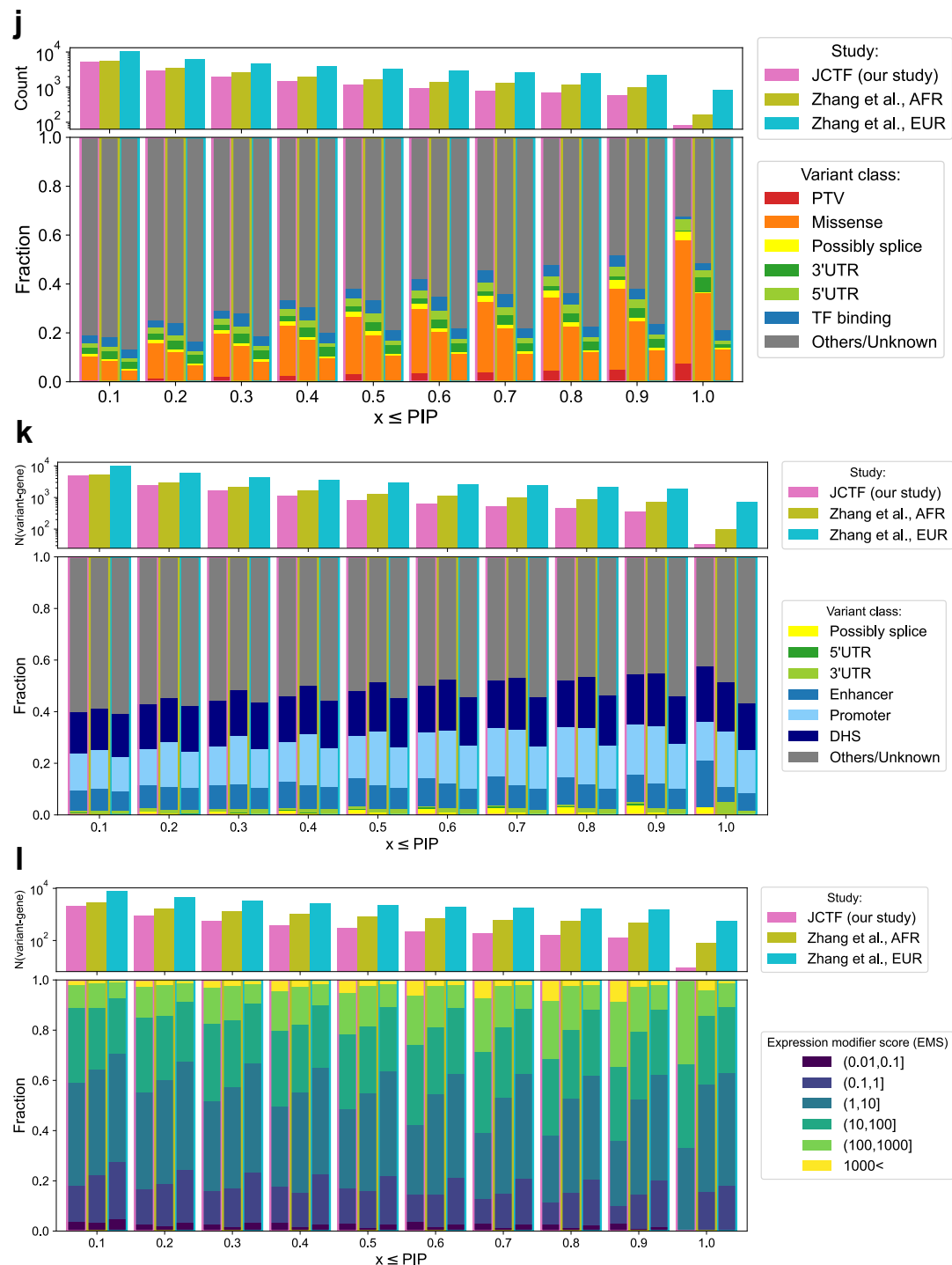
c. Fraction of lead-variants (variants with the lowest p-value for a gene) in UKB, stratified by the pQTL PIPs in our dataset. The same total 27,556,761 variant-genes as in **Fig. 2** are included.

Supplementary Figure 6. Detailed evaluation of pQTL fine-mapping result with the ARIC data



f**g**

h**i**



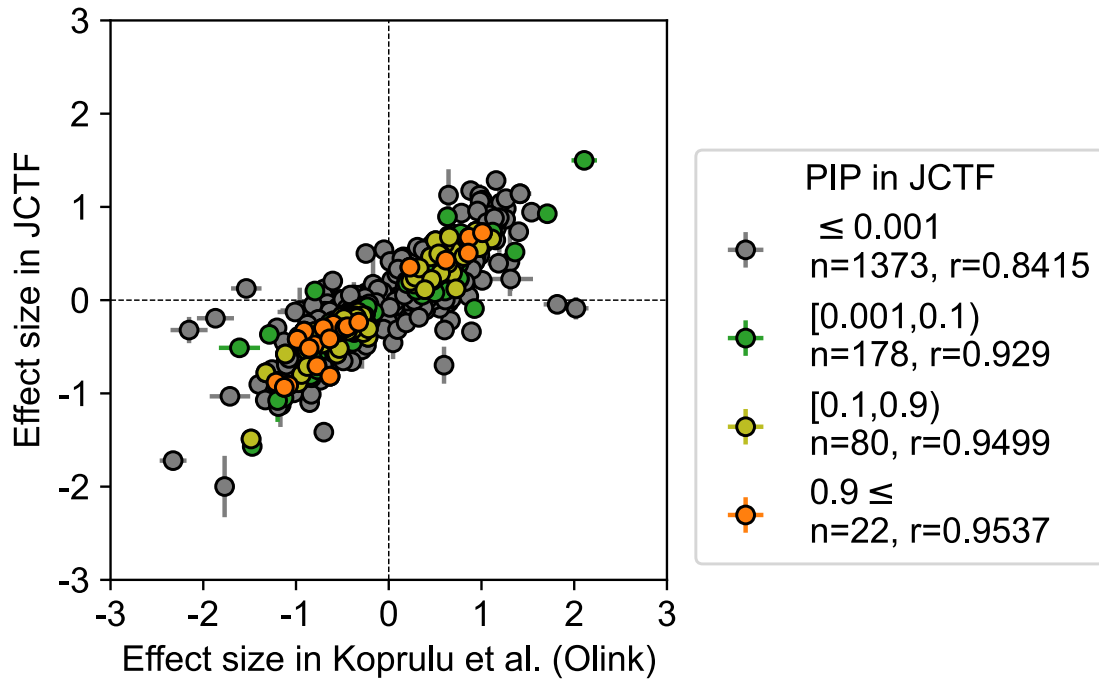
a-c. Comparison of (marginal) effect sizes between studies and cohorts within a study, stratified by PIPs in our pQTL fine-mapping (**a**: our study vs Zhang et al. [PMID: 35501419], African population, **b**: our study vs Zhang et al., European population, and **c**: Zhang et al., European vs African population).

d-i. Numbers and fraction of variant-genes with various PIP thresholds in different studies.

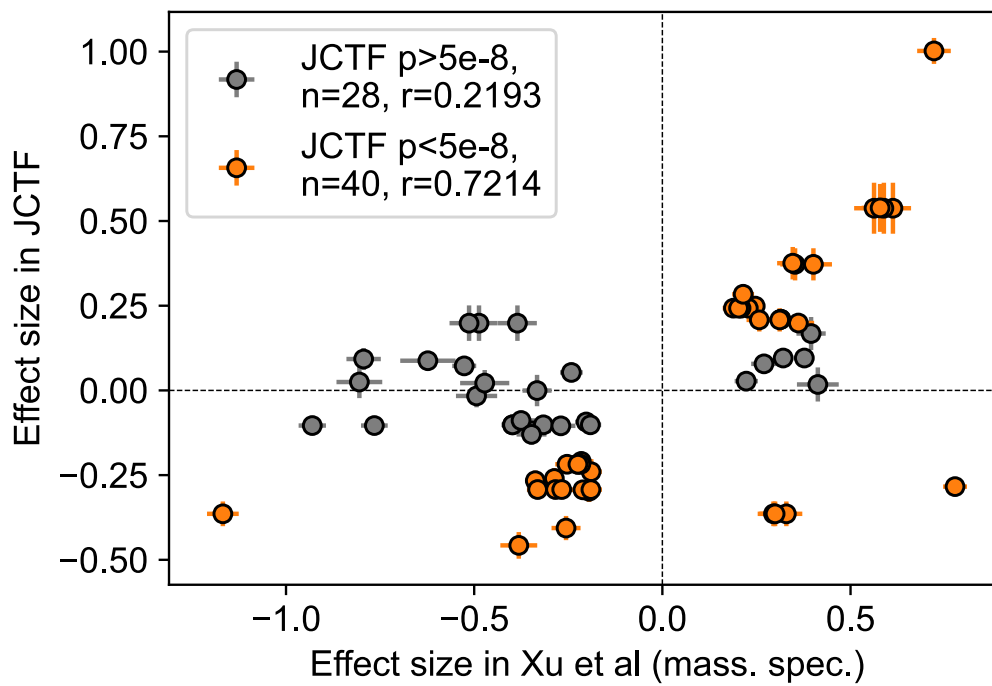
j-l. Comparison of the enrichment of canonical functional annotations and the expression modifier score (EMS) between datasets.

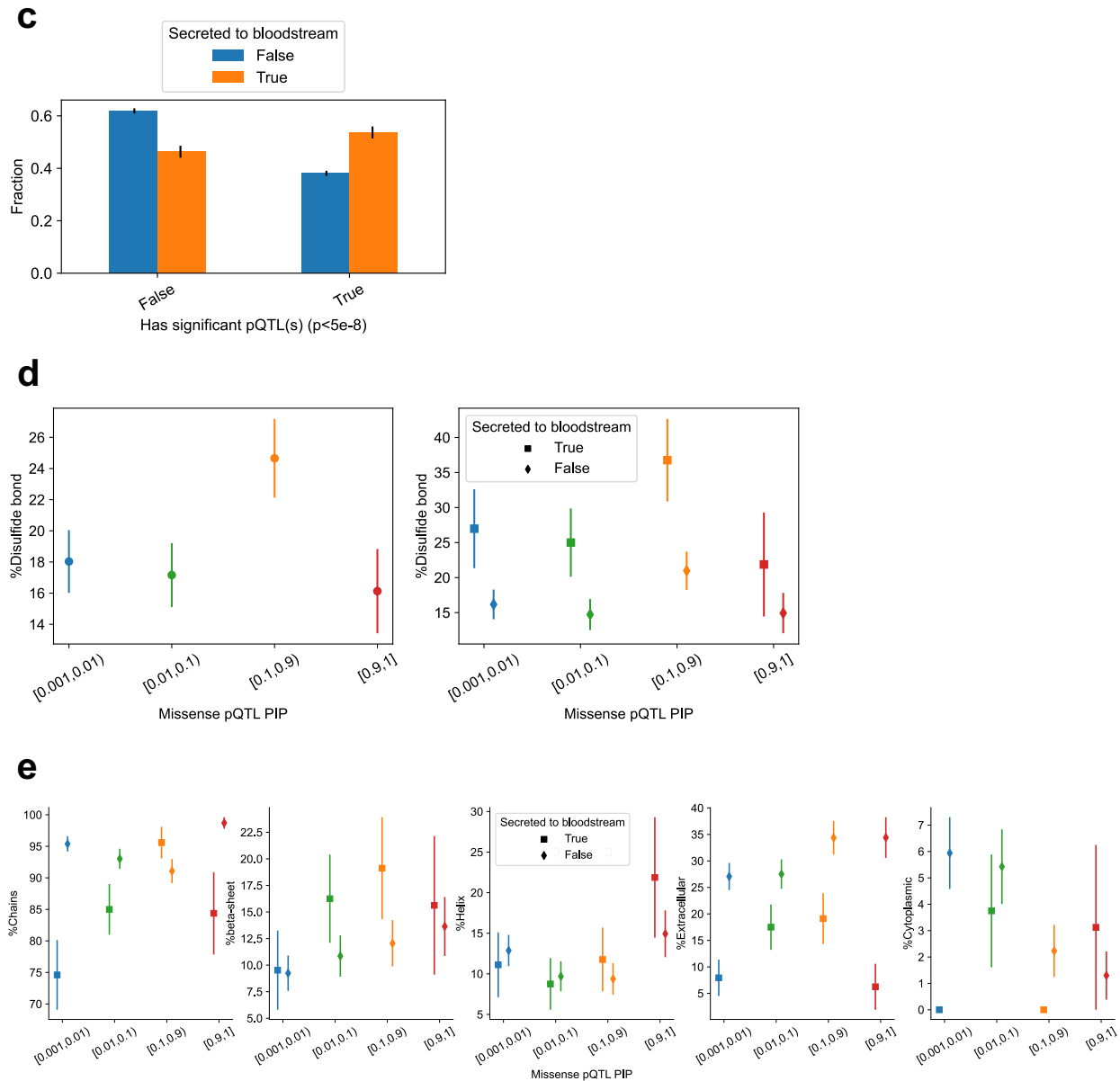
Supplementary Figure 7. Detailed evaluation of pQTL fine-mapping result with additional public data

a



b





a. Effect size comparison with the EPIC-Norfolk study (Koprulu et al 2023 [PMID: 36823471]), stratified by the PIPs in our study.

b. Effect size comparison with the Xu et al 2023 [PMID: 36797296] (where they used mass spectrometry technique), stratified by the PIPs in our study.

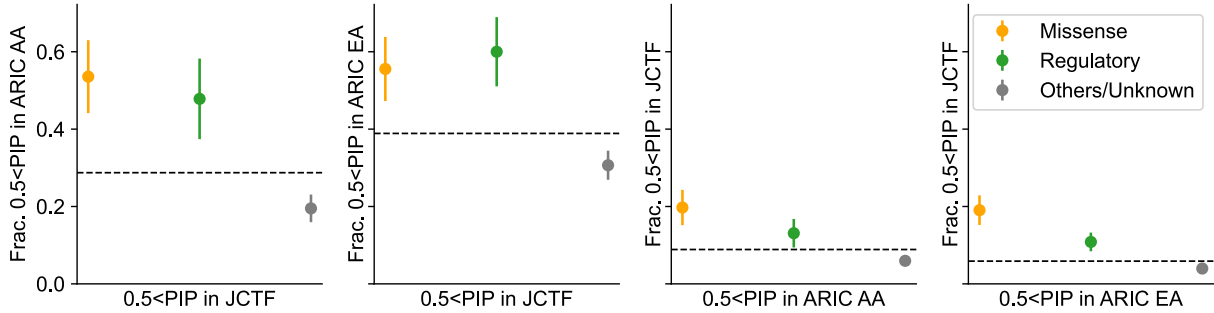
c. Proteins known to be actively secreted to the bloodstream are enriched for pQTLs, consistent with the observation in Koprulu et al. $n=1,520$, 221, 935 and 256 genes each, from left to right.

d. Percentage of pQTL variant falling on a disulfide bond domain, with or without stratification by protein secretion, suggesting that putative causal pQTLs (PIP>0.9) are not necessarily falling on the domain.

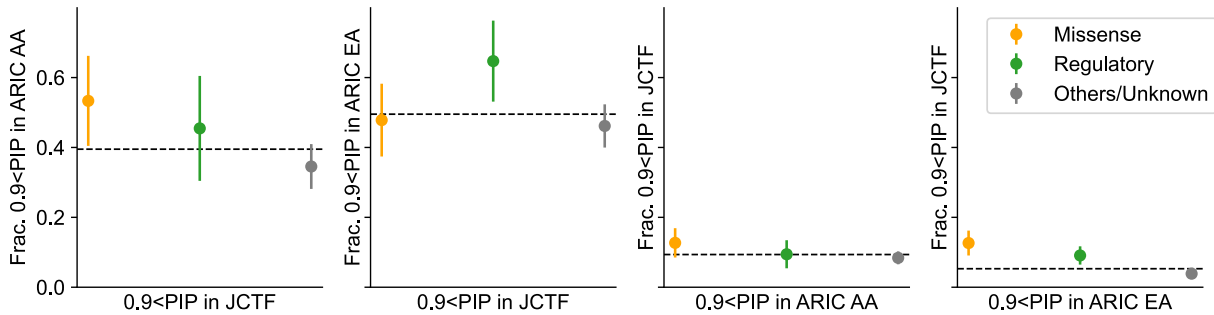
e. Percentage of putative causal pQTLs falling in various domain, stratified by the gene's secretion status. Total $N=366$, 338, 292 and 186 variant-genes in each PIP bin in **d.** and **e.**, and $n=(303, 63)$, (258,80), (224,68), (154,32) when stratified by the secretion status as in **d.**

Supplementary Figure 8. Replication rate of fine-mapped pQTLs stratified by functional annotations

a

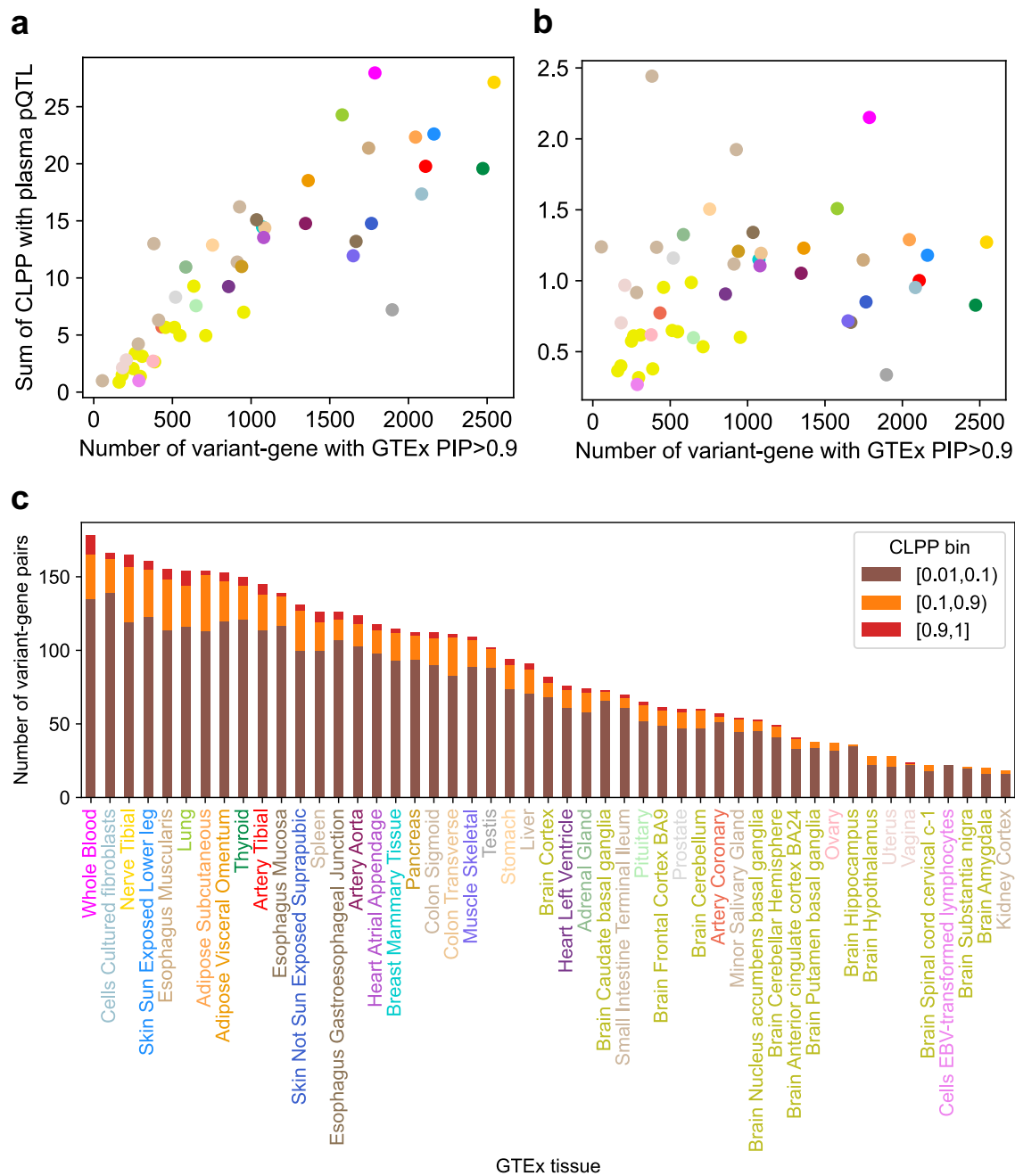


b



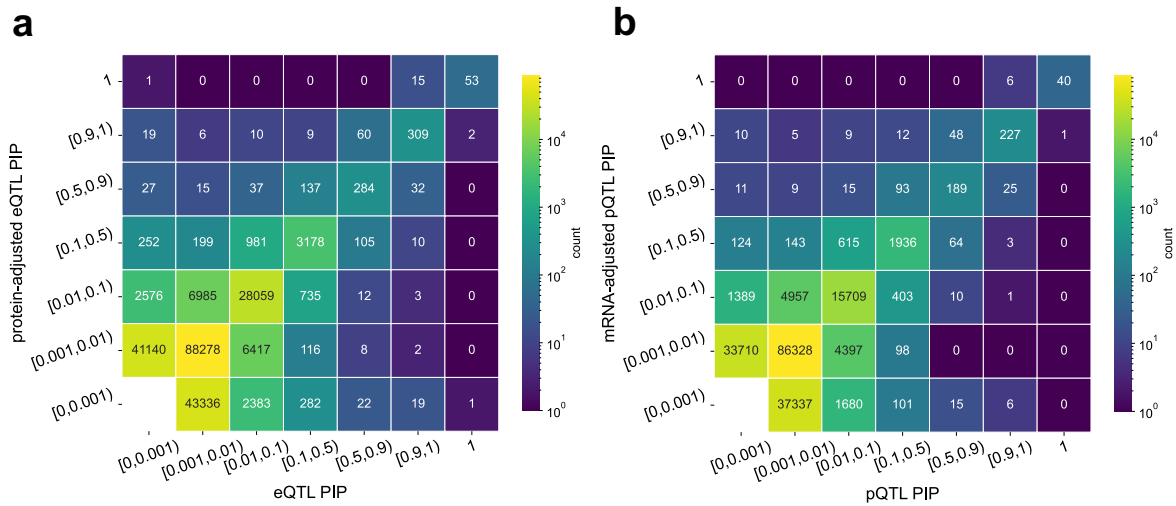
Concordance of pQTL fine-mapping PIPs in our dataset and the ARIC dataset, stratified by major functional annotations. PIP threshold = 0.5 for (a) and 0.9 for (b) (compared to the main Fig. 3c where we used PIP=0.1 threshold, we unionized all the major regulatory annotations to increase the power). For a., n=348, 432, 1,126 and 2,860 variant-genes are included in each panel. For b., n=162, 210, 684 and 1,964 variant-genes are included in each panel.

Supplementary Figure 9. Comparison of pQTL fine-mapping with eQTL in different tissues in GTEx v8



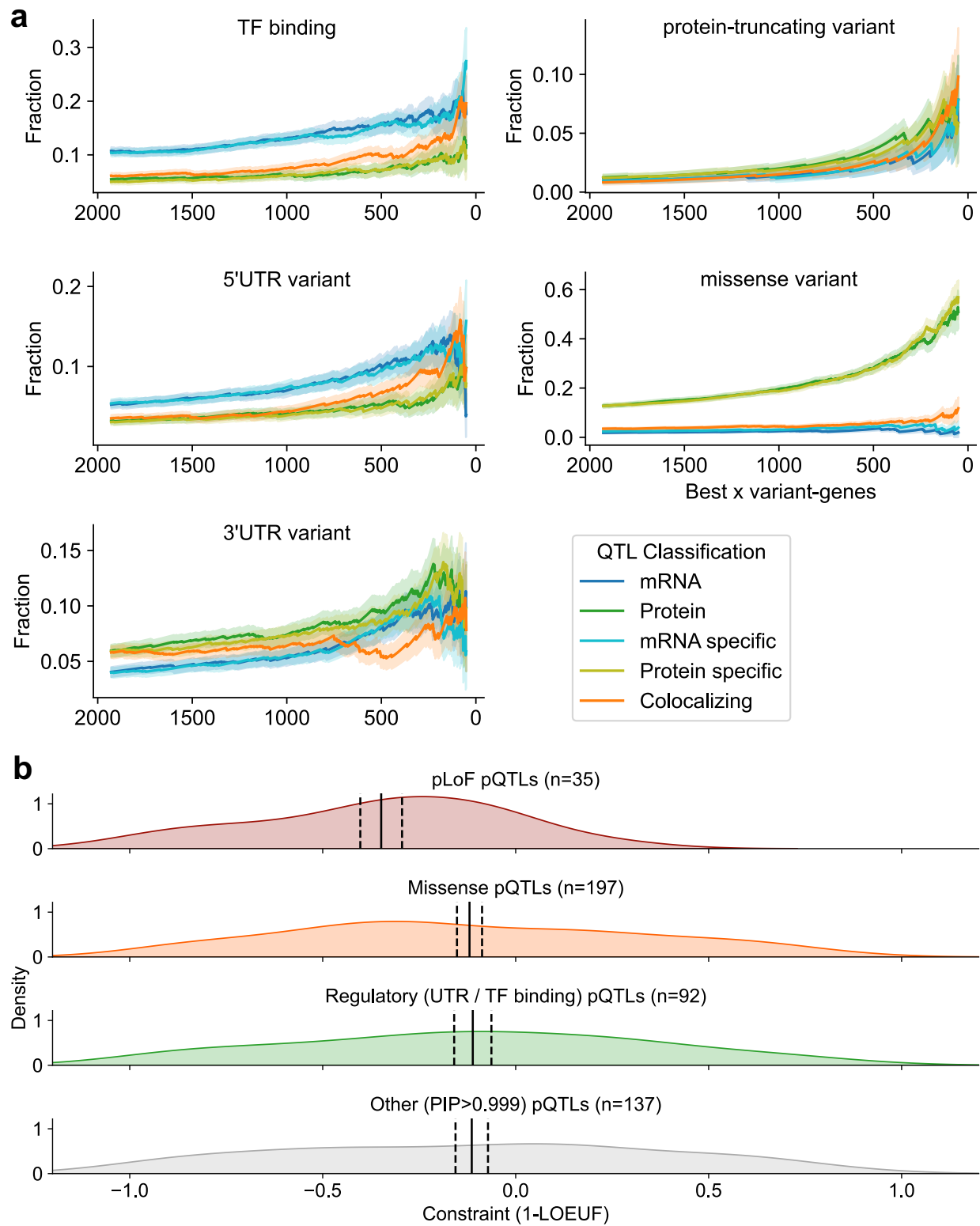
- a.** Number of variant-gene pairs with different levels of colocalization between pQTL causal evidence in our study and eQTL causal evidence in GTEx for 49 major tissues (as measured by the colocalization posterior probability = CLPP).
- b.** Scatter plot presenting correlation between the number of putative causal eQTLs in GTEx (x axis) and the sum of CLPP with our pQTL (y axis).
- c.** Scatter plot presenting low-correlation between the number of putative causal eQTLs in GTEx (x axis) and the colocalization enrichment score with our pQTL (y axis), suggesting that our score quantification successfully limits the bias due to sample sizes in GTEx.

Supplementary Figure 10. e/p specific QTL fine-mapping overview



Comparison of the eQTL versus protein-adjusted eQTL PIPs (**a**), as well as pQTL versus mRNA-adjusted pQTL PIPs (**b**). There were $n=446$ putative causal protein-adjusted eQTLs and $n=309$ putative causal mRNA-adjusted pQTLs, largely but not perfectly overlapping with simple eQTLs as well as pQTLs (68.8% and 69.7% agreement, respectively). The largely consistent results suggest that regressing out either protein or mRNA expression of the same gene has limited effect on QTL calls, presumably due to their low colocalization probability.

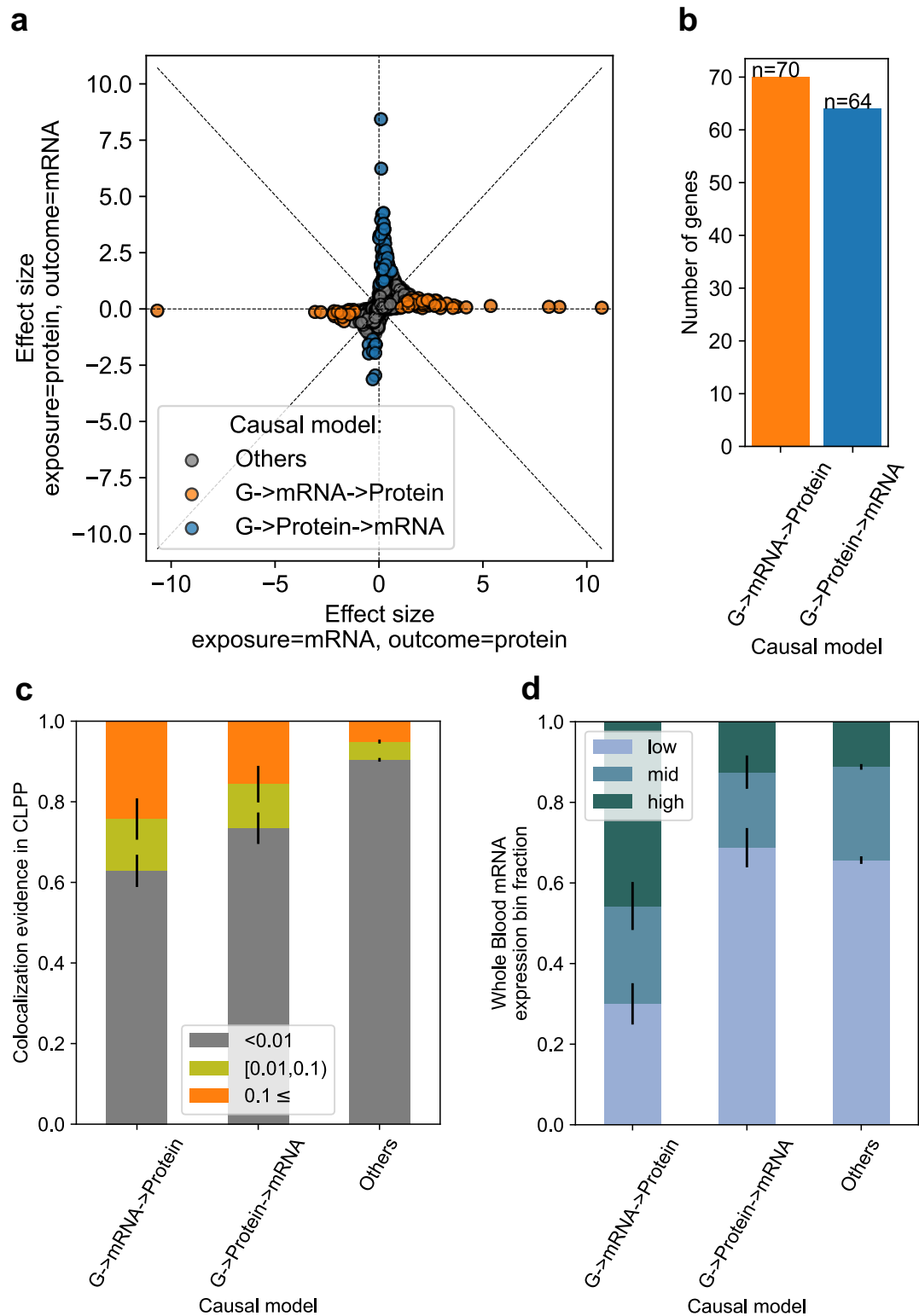
Supplementary Figure 11. Functional investigation of different QTL classes



a. For each of the major functional categories, the fraction of variant-genes belonging to the category is shown as a function of to x variant-genes ranked by different QTL PIPs.

b. Distribution of gene constraint for different classes of putative causal (PIP>0.9) pQTLs.

Supplementary Figure 12. A Mendelian Randomization (MR) analysis to investigate the causal relationship between QTL layers



a. Scatter plot showing the causal effect size estimates of the exposure variable on the outcome variable. On the x-axis is when the exposure is the mRNA expression and outcome is the

protein expression, and on the y-axis the exposure is the protein expression and the outcome is the mRNA expression. Those with $1 < \text{effect size difference}$ are colored based on the estimated direction of causality.

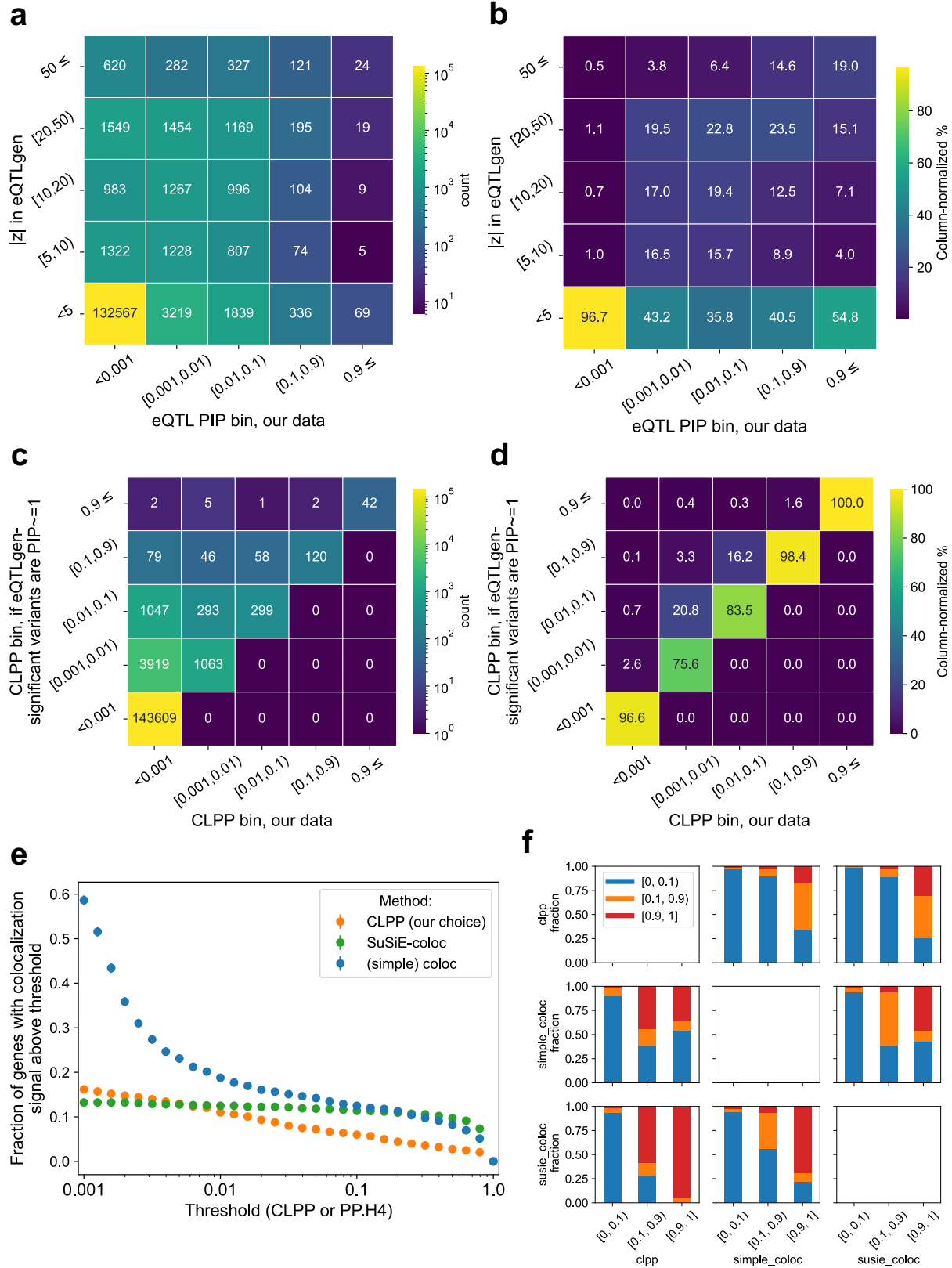
b. Number of genes with $1 < \text{effect size difference}$.

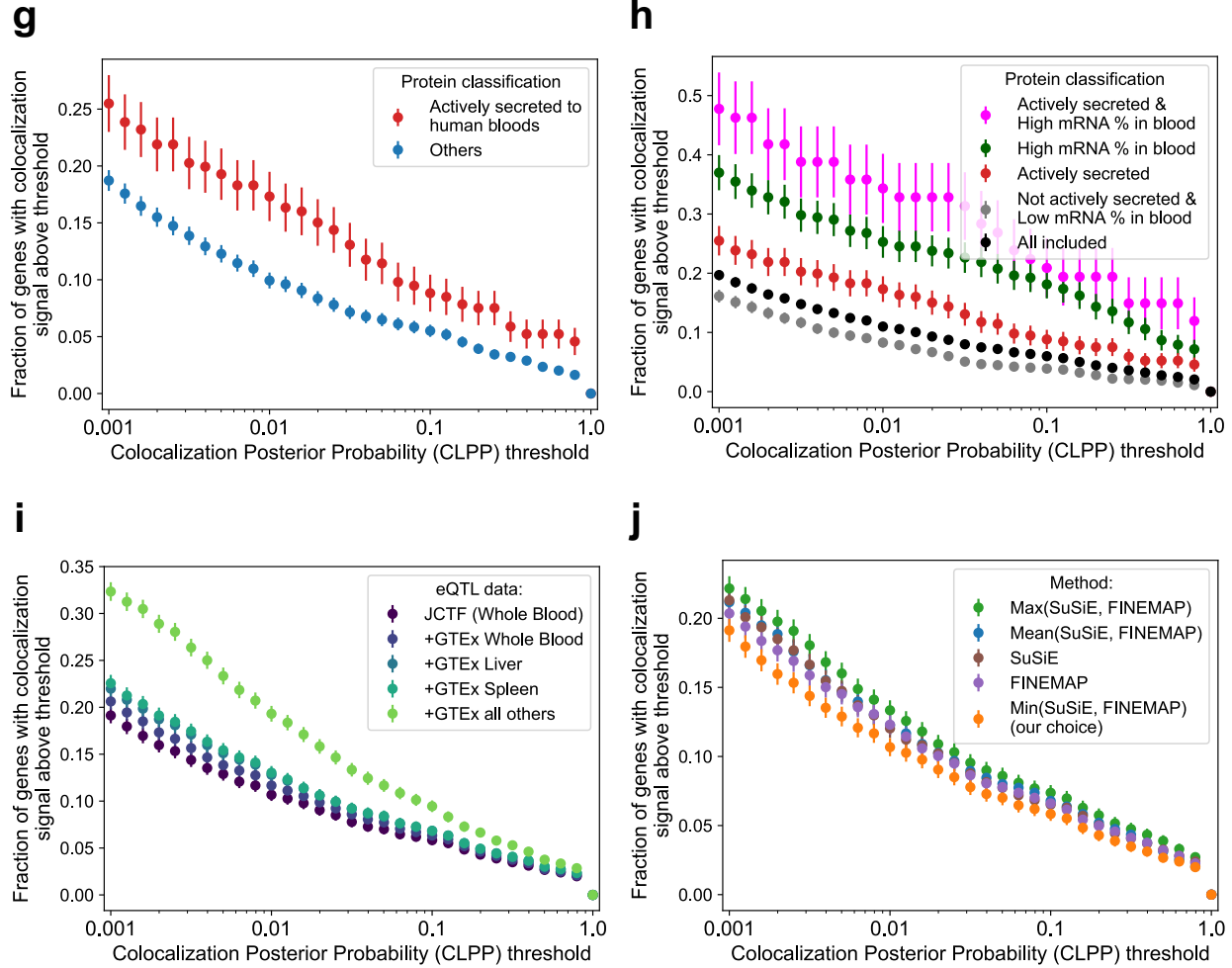
c,d. Distribution of **(c)** colocalization evidence quantified by colocalization posterior probability (CLPP) and **(d)** the mRNA expression fraction in the blood, for genes classified into different causal models by MR.

Two-sample MR was performed using the TwoSampleMR package

(<https://mrcieu.github.io/TwoSampleMR/>), including all the cis-variants for a gene (i.e. not pruning to independent set of variants. This could inflate the causal effect size estimate but the inflation should be equal for both causal direction since we are using the same $n=998$ samples). Output from the MR-egger was used, but the result was almost identical when other methods (e.g. Inverse-variance weighted) were used.

Supplementary Figure 13. Evaluation of colocalization evidence utilizing alternative methods and external resources





a,b. Distribution of z-scores in eQTLgen, stratified by the eQTL PIPs in our data (**a**; raw and **b**; column-normalized). The “<5” row includes variants missing in eQTLgen.

c,d. Heatmap visualizing the differences of the colocalization posterior probabilities (=CLPP; the product of eQTL and pQTL PIPs) in our dataset versus when updating the eQTL PIPs by optimistically assuming eQTLgen-significant variants as causal (i.e. PIP=0.5 when 5<z-score and PIP=1 when 10<z-score) (**c**; raw and **d**; column-normalized).

e, f. Fraction of genes with colocalization evidence in different stringency (x-axis; variant level colocalization posterior probability for CLPP / PP.H4 for coloc and SuSiE-coloc) when using different statistical methods (**e**), and the concordance between the methods (**f**).

g, h. Fraction of genes with colocalization evidence when considering the active secretion of the proteins to the bloodstream (**g**) and combined with the %mRNA expression in the blood (**h**).

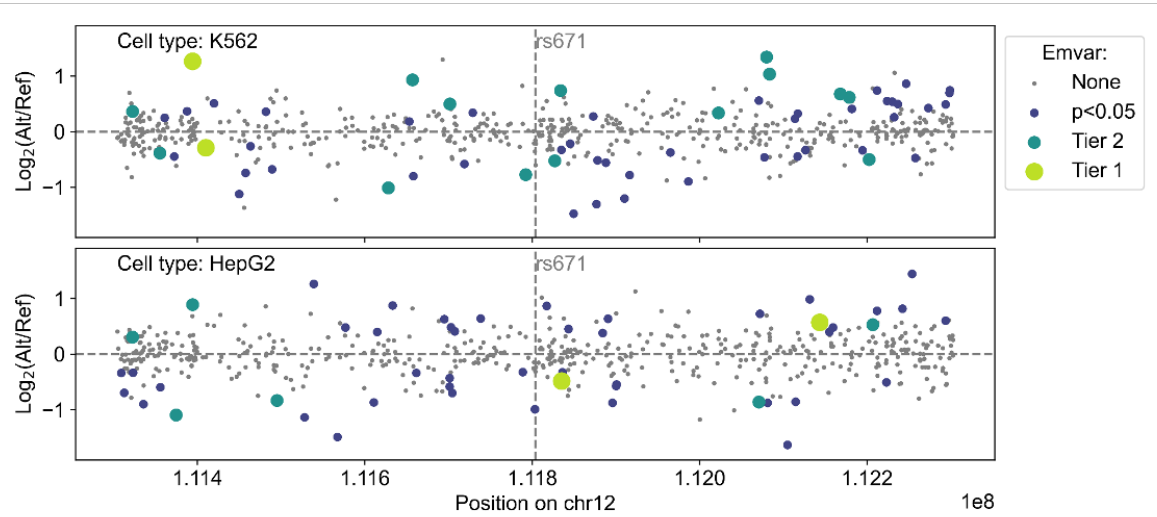
i. Fraction of genes with colocalization evidence with or without taking eQTL PIPs in various tissues in GTEx into account (x-axis; variant level colocalization posterior probability for CLPP, maximum across dataset and tissues when applicable).

j. Fraction of genes with colocalization evidence when changing the methods to combine the eQTL PIP estimates from FINEMAP and SuSiE.

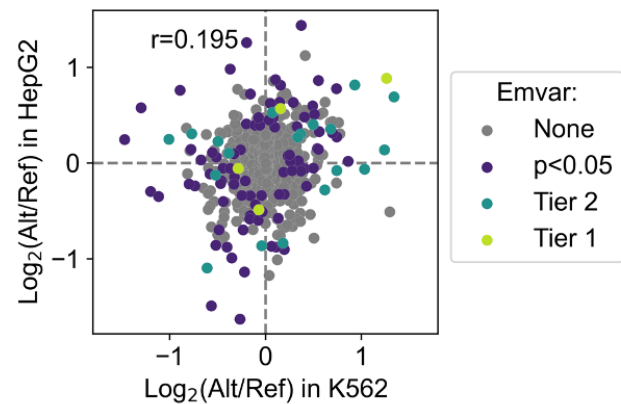
All n=2,211 genes where colocalization was tested are included in the analysis.

Supplementary Figure 14. Massively Parallel Reporter Assay (MPRA) of the ALDH2 locus

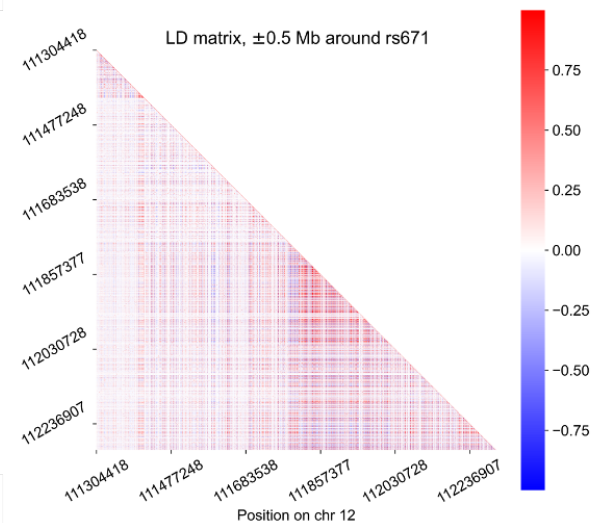
a



b



c

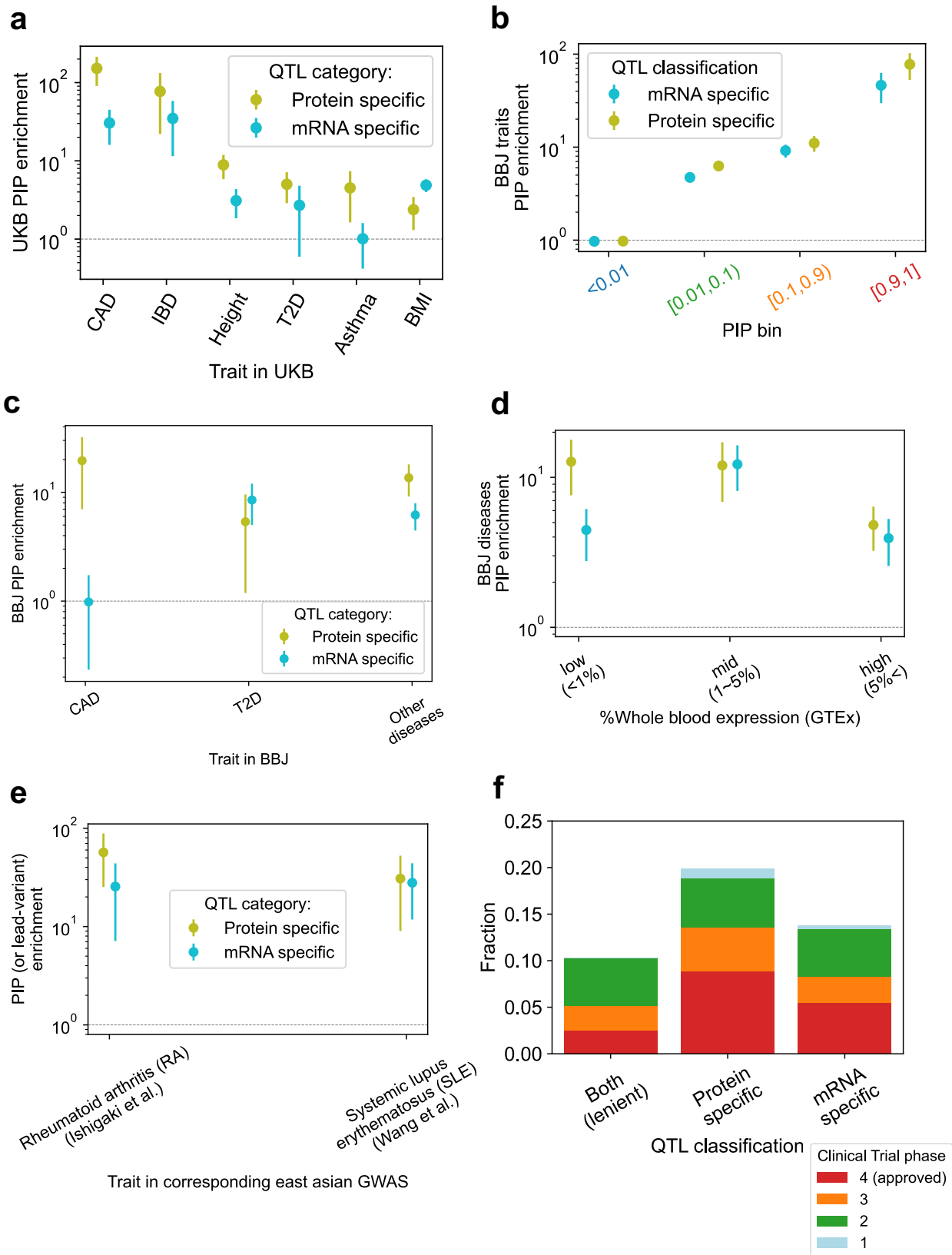


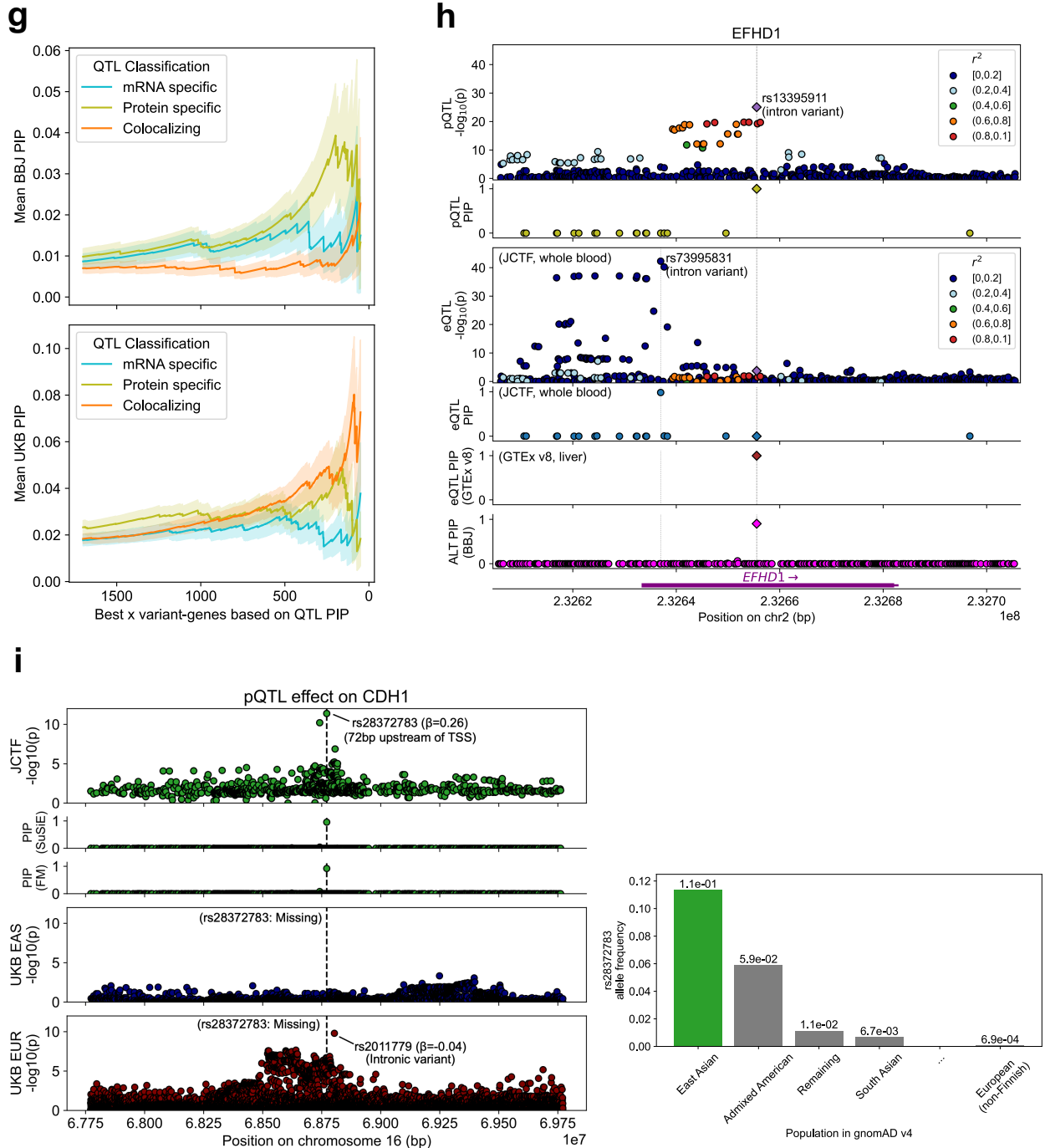
a. Variant activity for common variants in ± 0.5 Mb window of rs671.

b. Correlation between variant activities in two cell types.

c. The in-sample linkage disequilibrium (LD) matrix for common variants in ± 0.5 Mb window of rs671.

Supplementary Figure 15. Complex trait colocalization for different QTL classes

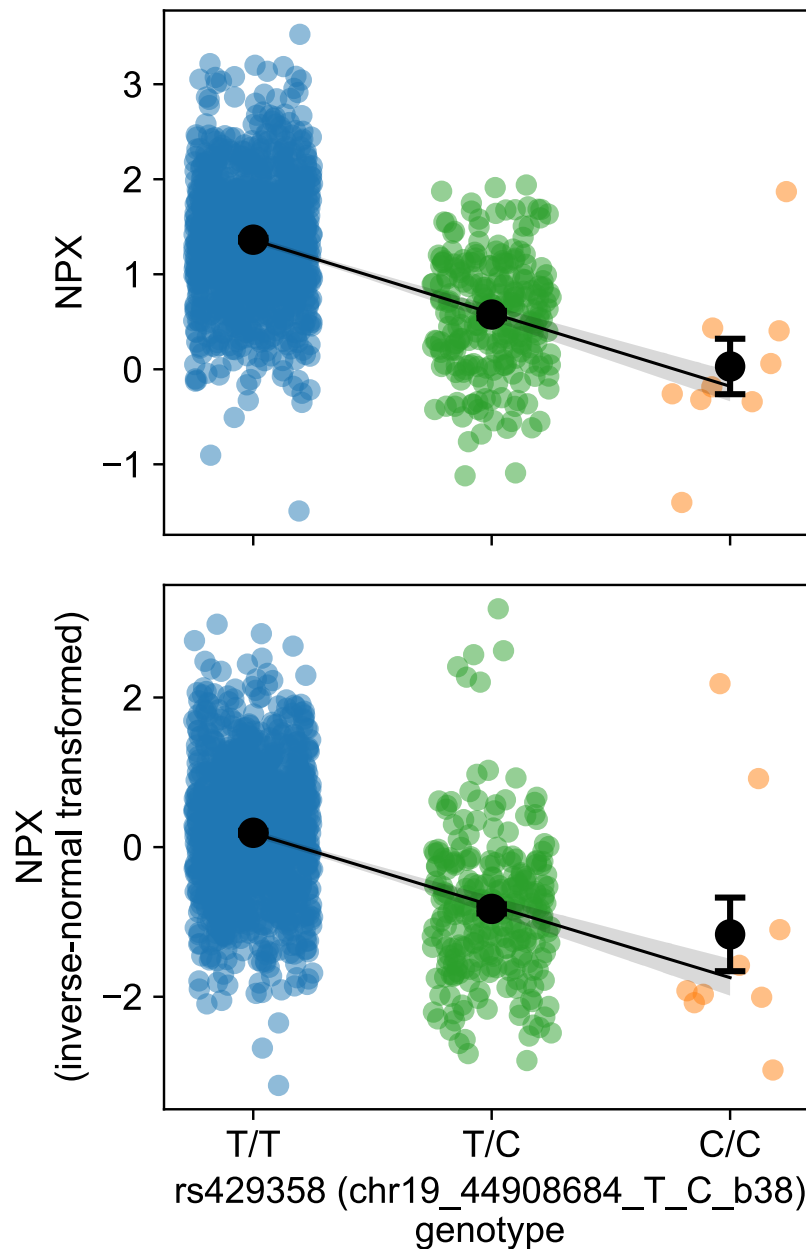




- a.** Enrichment of complex trait PIPs from UK Biobank (UKB) per trait category, for variants with putative mRNA or protein specific causal QTL effects, focusing on polygenic complex trait of disease.
- b.** Enrichment of complex trait PIPs from Biobank Japan (BBJ), along with mRNA or protein-specific QTL PIPs.
- c.** Enrichment of complex trait PIPs filtered to major complex diseases from BBJ per trait category, for variants with putative mRNA or protein specific causal QTL effects.

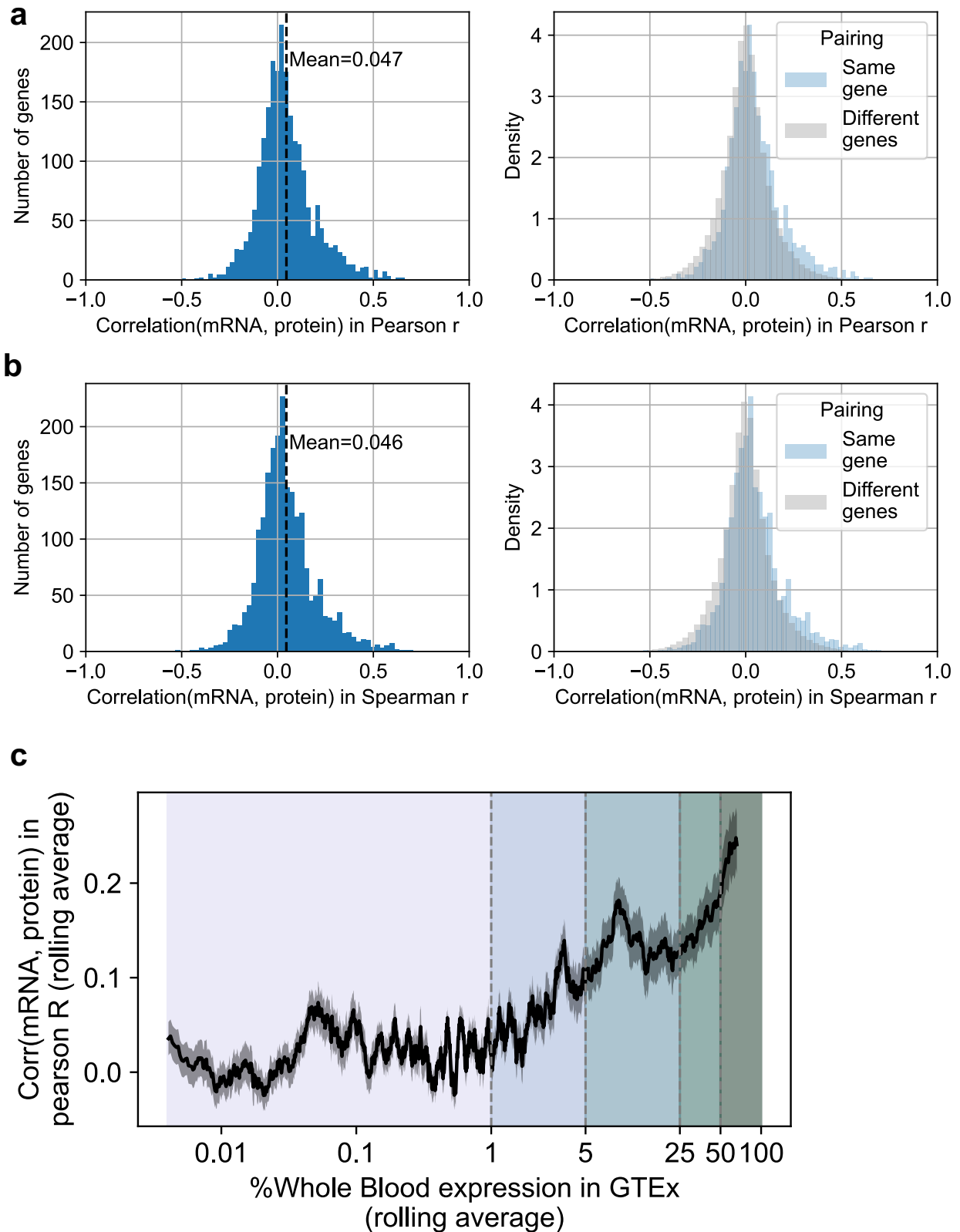
- d.** Enrichment of complex trait PIPs filtered to major complex diseases from BBJ per gene's mRNA expression fraction in whole-blood, for variants with putative mRNA or protein specific causal QTL effects.
 - e.** Enrichment of complex trait lead-variants (or PIP in Ishigaki et al) from major Japanese studies per trait category, for variants with putative mRNA or protein specific causal QTL effects.
 - f.** Fraction of genes with drug target evidence for different gene-level QTL categories.
 - g.** Rank based analysis of complex trait PIPs from BBJ (top) and UKB (bottom) for different classes of molecular QTLs. Error bands represent the standard error of mean.
 - h.** An additional example where pQTL colocalizes with complex trait causal variants (EFHD1, where eQTL effect is present in liver, but not in whole blood).
 - i.** Manhattan plot of the *CDH1* *cis* region and the allele frequency distribution of the putative causal variant in gnomAD v4.
- In **a-e**, $n=3,206$ protein-specific and $n=5,308$ mRNA expression-specific QTLs passing the $PIP>0.1$ threshold are included, as in **Fig. 5**.

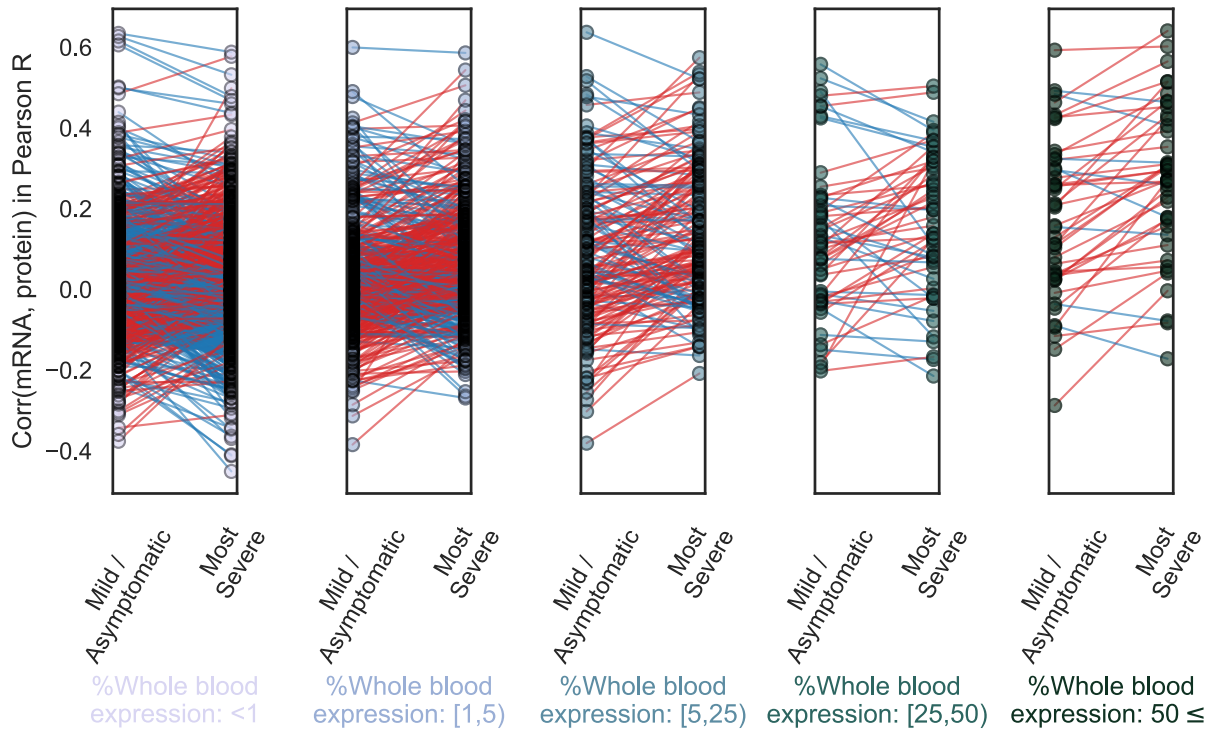
Supplementary Figure 16. The negative effect of rs429358 on APOE protein expression measurement in Olink platform



Raw **(a)** or inverse-normalized **(b)** protein expression (NPX) level of APOE protein is shown for different rs429358 genotypes, consistently presenting a negative effect size of the variant. Error bar represents the standard error of the mean, while the shaded line represents 95% confidence interval estimated via bootstrapping. n=1,114, 241 and 9 in each genotype. 20 samples with NA in the APOE expression measurements were removed.

Supplementary Figure 17. Detailed characterization of the correlation of blood mRNA and plasma protein expressions



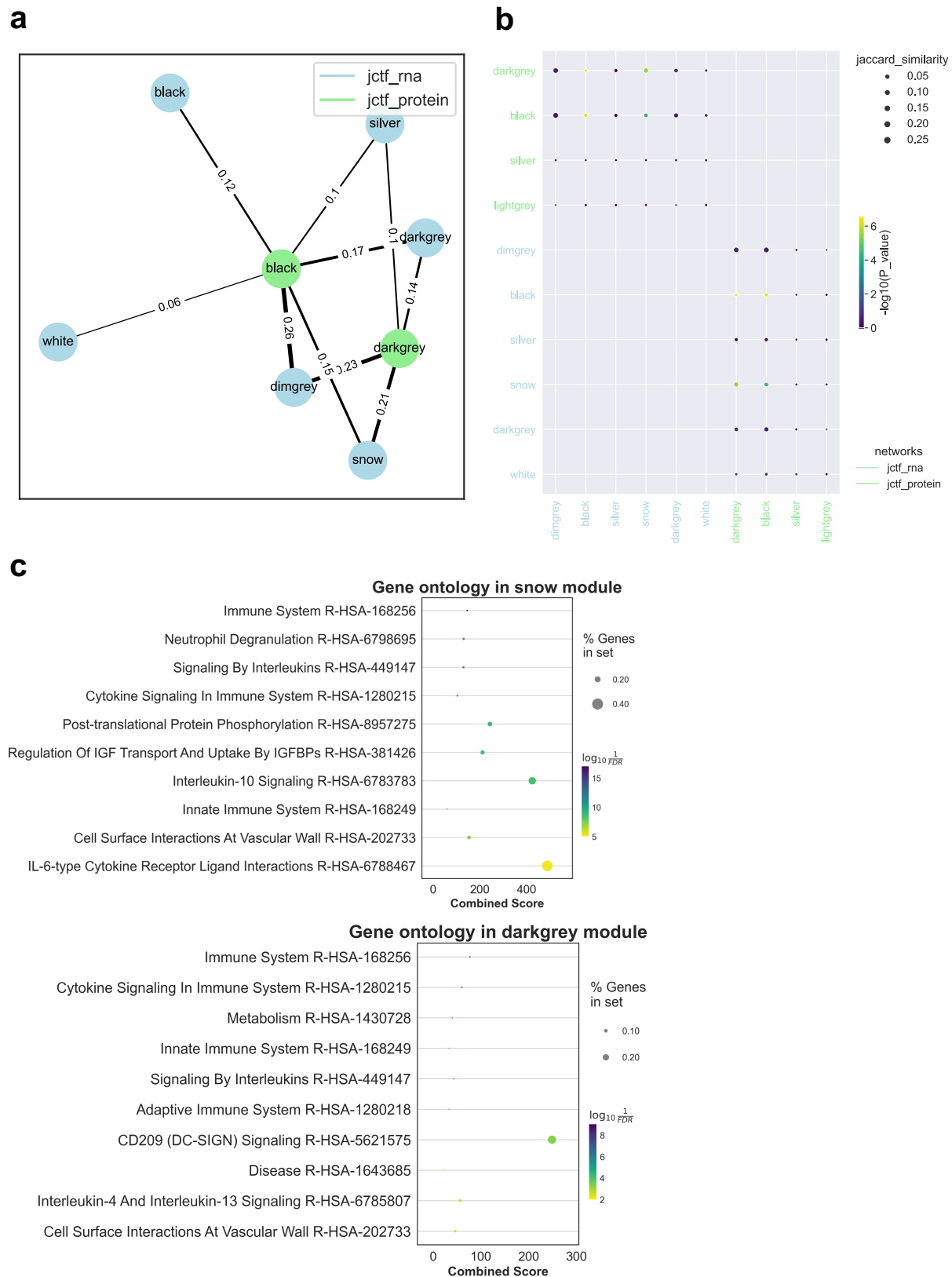
d

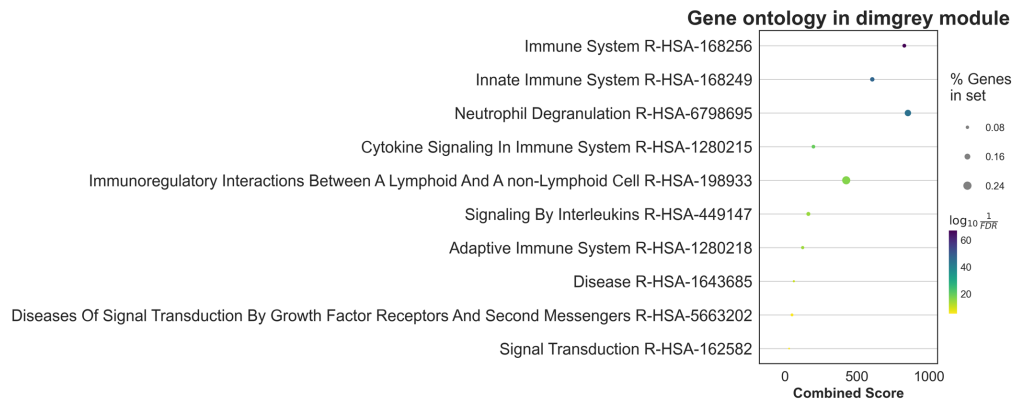
a,b. Histogram of the correlation between mRNA and protein expressions (**a**; Pearson, **b**; Spearman) in our dataset. Counts are on the left and densities are on the right. Densities for random mRNA-protein pairs are shown in grey for comparison. These together suggest that mRNA and protein expression correlations are limited, although higher than random pairs.

c. Correlation of mRNA and protein expression in pearson R, as a function of the percentage of mRNA expression in whole blood in GTEx (rolling average, window size=100 and stride size=50 genes), validating the stratification by the percentage. Error bands represent the standard error of mean.

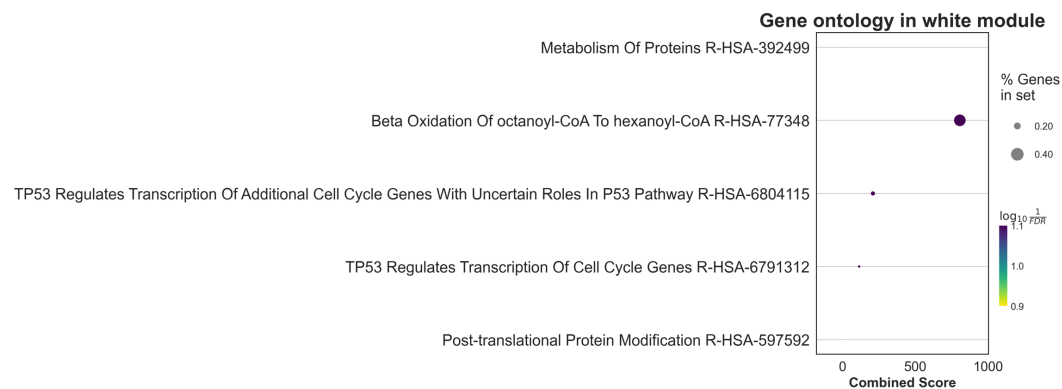
d. Correlation of mRNA and protein expression in pearson R within mild versus severe COVID-19 state, stratified by the percentage of mRNA expression in whole blood in GTEx. Each gene is connected by a line, red if the correlation has increased in the severe disease group and blue otherwise.

Supplementary Figure 18. The shared gene modules of blood mRNA and plasma protein expressions

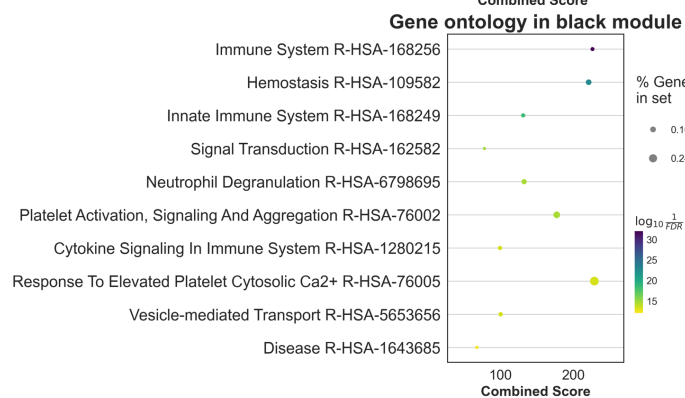
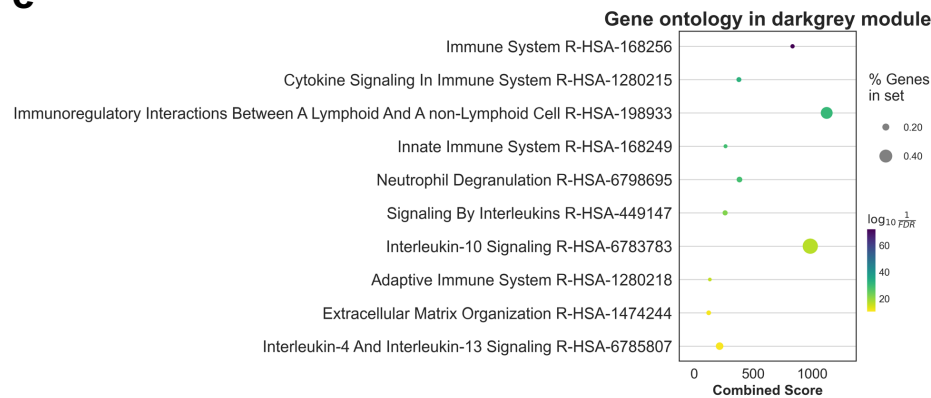


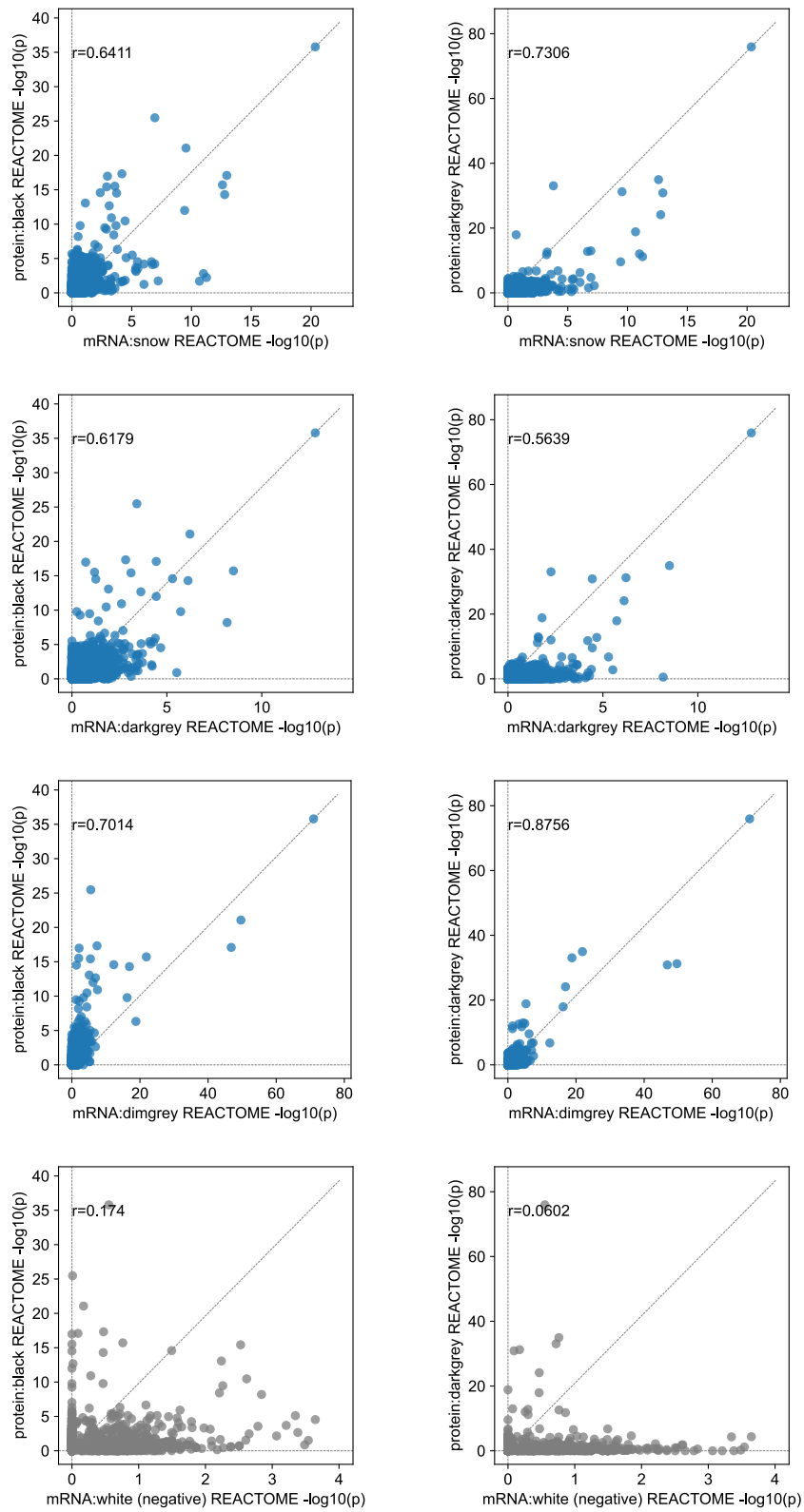


d

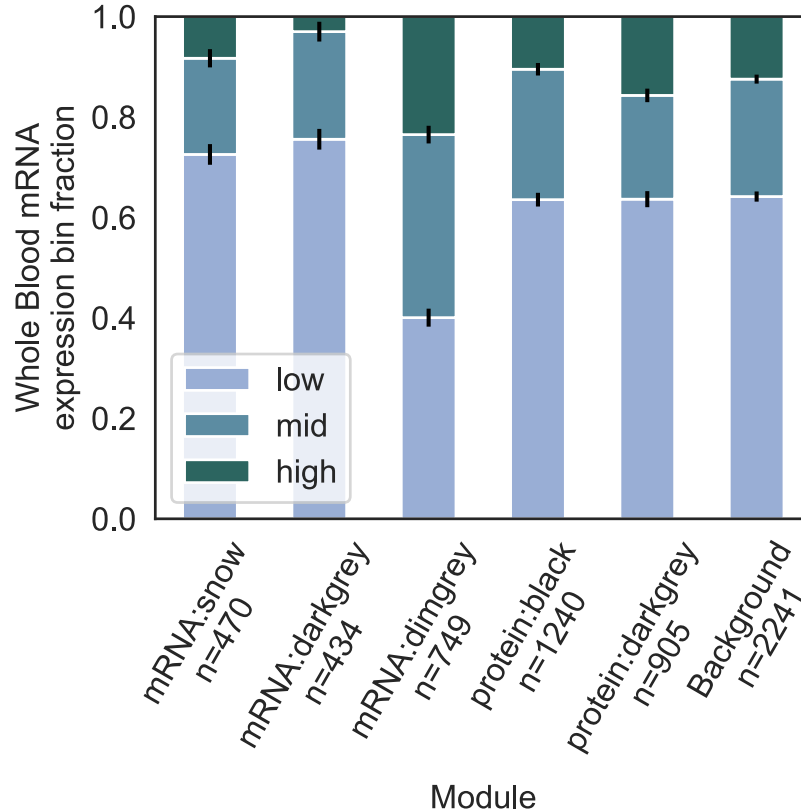


e



f

g



a,b. Visualization of the similarity between blood mRNA and plasma protein expression modules, as measured by the Jaccard similarity (**a**; in a graph and **b**; in a dotplot).

c. Reactome term enrichment for mRNA expression modules presenting significant similarities with protein expression modules (i.e. snow, darkgrey and dimgrey).

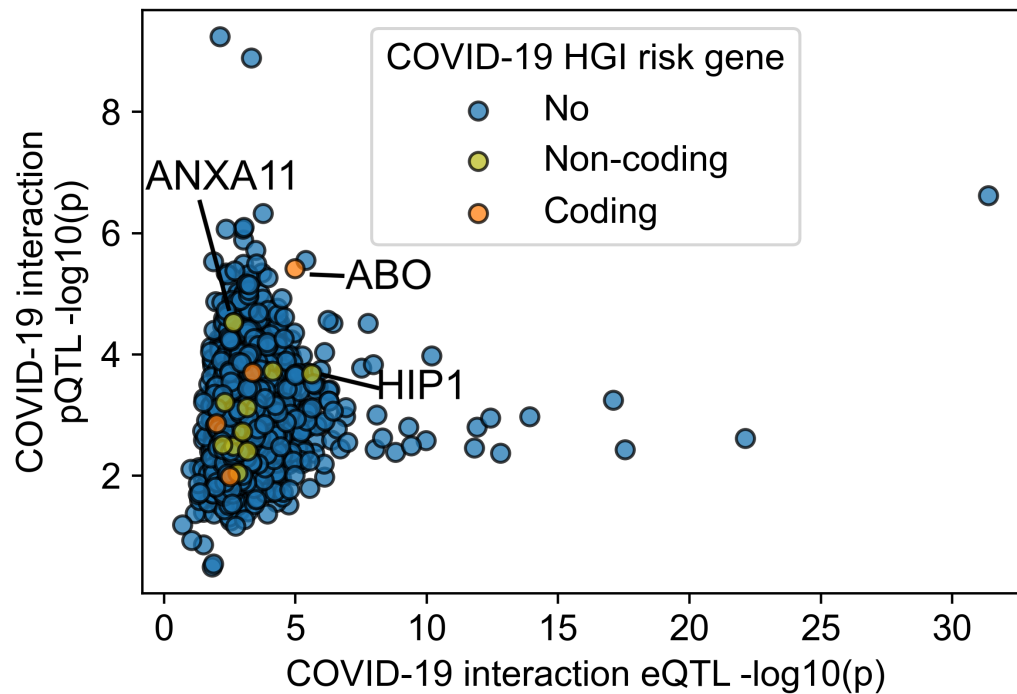
d. Reactome term enrichment for mRNA expression modules presenting no similarities with protein expression modules (i.e. white), as a negative control.

e. Reactome term enrichment for protein expression modules presenting significant similarities with mRNA expression modules (i.e. darkgrey and black).

f. Scatter plots comparing the $-\log_{10}(\text{p-value})$ for Reactome term enrichment in mRNA and protein modules.

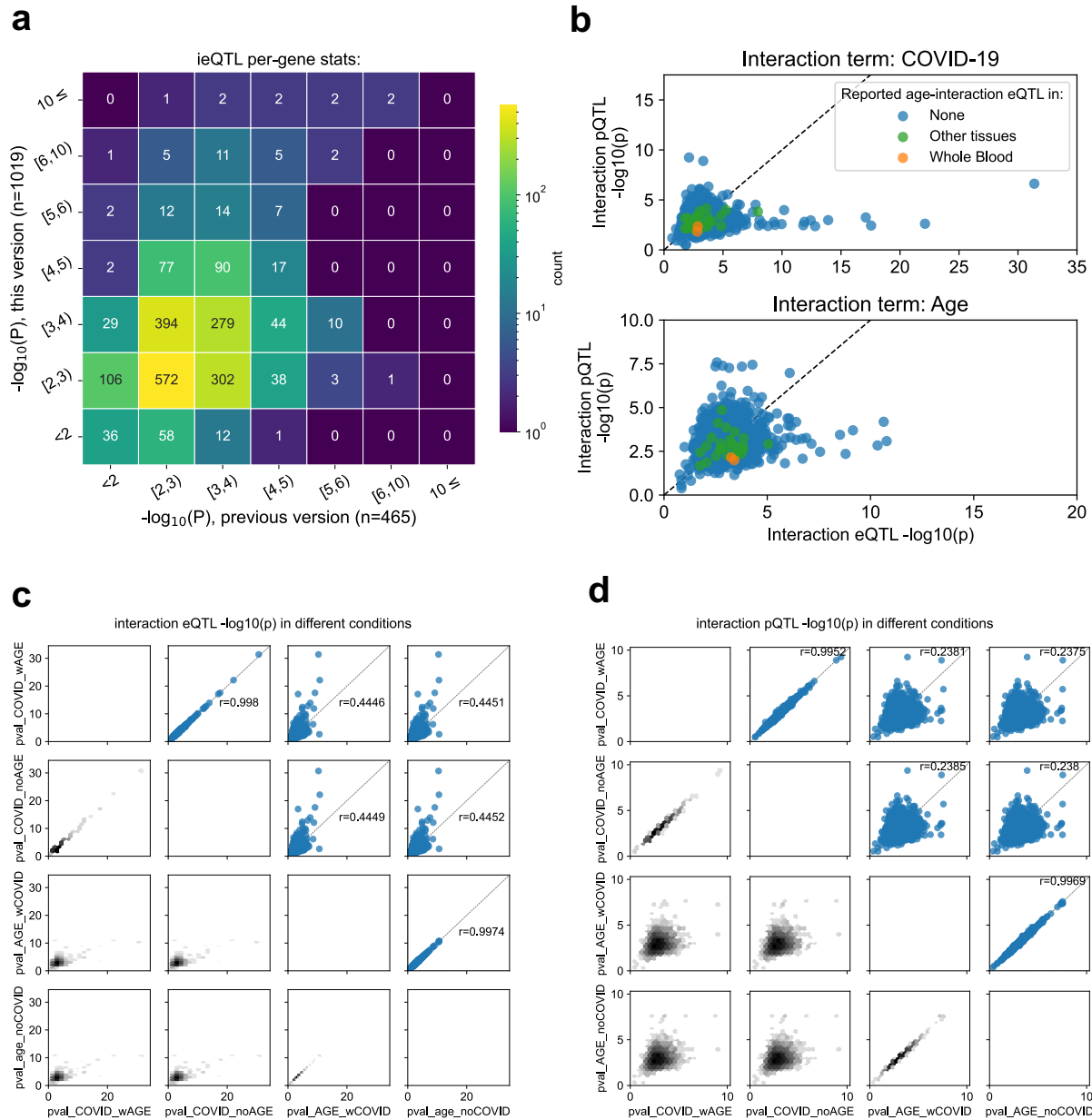
g. Distribution of the relative mRNA expression level in the whole blood in each gene modules. These results altogether suggest the shared dynamics of blood mRNA and plasma protein expression as modules, even though the gene-level expression correlation tends to be limited, and that the shared dynamics are not necessarily driven by genes predominantly mRNA-expressed in the blood. pyWGCNA (<https://github.com/mortazavilab/PyWGCNA>) was used to explore the shared modules.

Supplementary Figure 19. No major enrichment of COVID-19 GWAS hits in interaction QTLs (iQTLs)



Scatter plot comparing the significance ($-\log_{10}(p)$) of ieQTLs (x axis) and ipQTLs (y axis), colored in yellow (regulatory) or orange (coding) when the gene that is regulated has a variant significantly associated with COVID-19 susceptibility in a large-association study ([PMID: 37674002](https://pubmed.ncbi.nlm.nih.gov/37674002/)).

Supplementary Figure 20. Detailed evaluation of the interaction QTL call

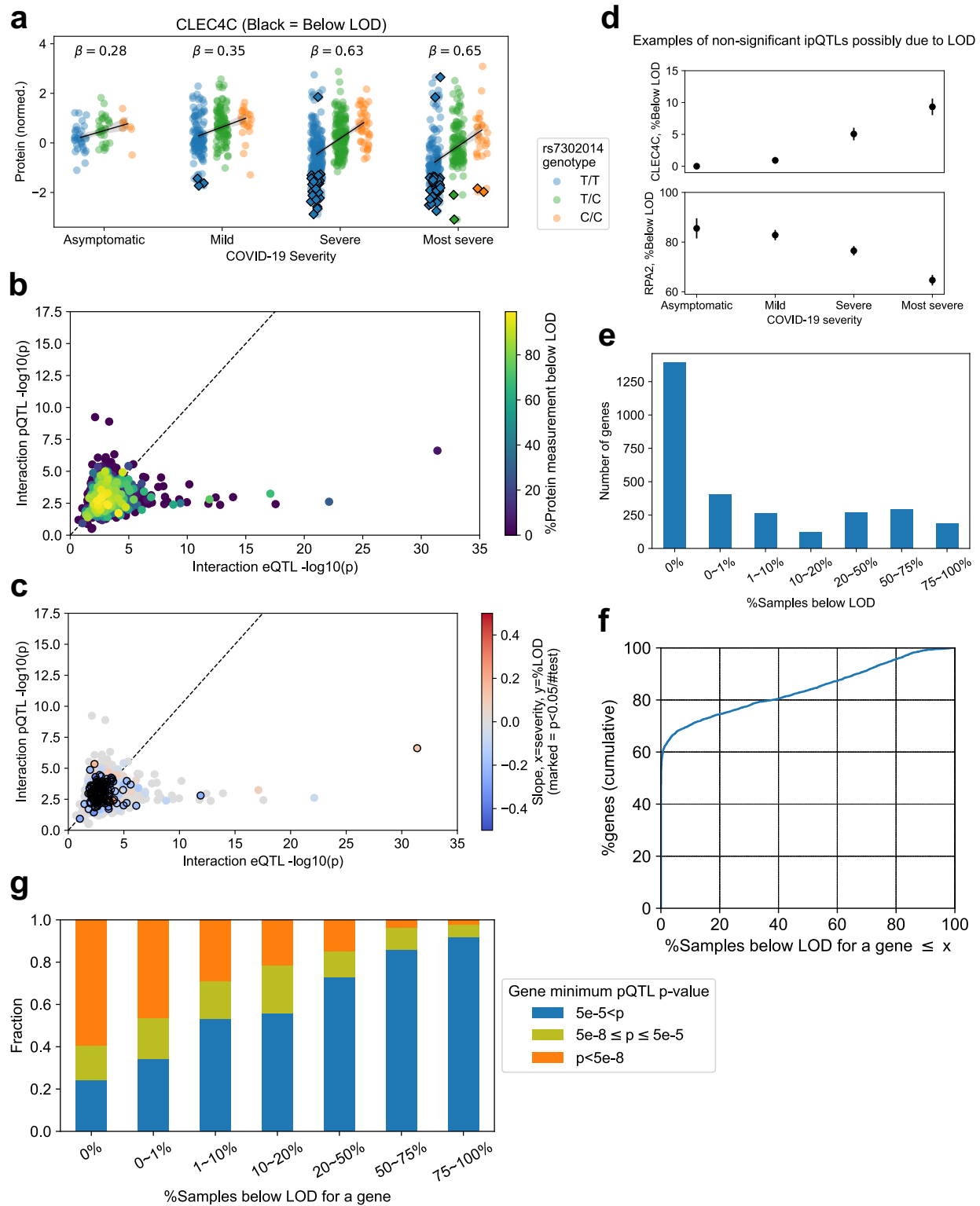


a. Comparison of minimum ieQTL p-value per gene with that from the previous call set ($n=465$), for the 2,211 genes.

b. Scatter plot comparing the significance ($-\log_{10}(p)$) of ieQTLs (x axis) and ipQTLs (y axis), when the interaction term is COVID-19 severity (top) or age (bottom). Colored in orange if the gene has known age-ieQTL evidence from a previous study ([PMID: 36192477](https://pubmed.ncbi.nlm.nih.gov/36192477/)) and green if in other tissue in GTEx).

c,d. Matrices of scatter and density plots showing the correlation of iQTL $-\log_{10}(p)$ tested in four different conditions (from the first to fourth row and columns; 1. interaction term = COVID-19 severity, including age as a covariate, 2. excluding age from the covariates, 3. interaction term = age, including COVID-19 severity as a covariate, and 4. excluding COVID-19 severity from the covariates). Density plots are in the lower triangle, **c.** for ieQTL and **d.** for ipQTL.

Supplementary Figure 21. Protein measurements below the Limitation of Detection (LOD)



a. Scatter plot showing the effect of rs1055602 on *CLEC4C* mRNA and protein expression (same as main Fig. 6f but), plotting protein measurements below the LOD in diamond shape.

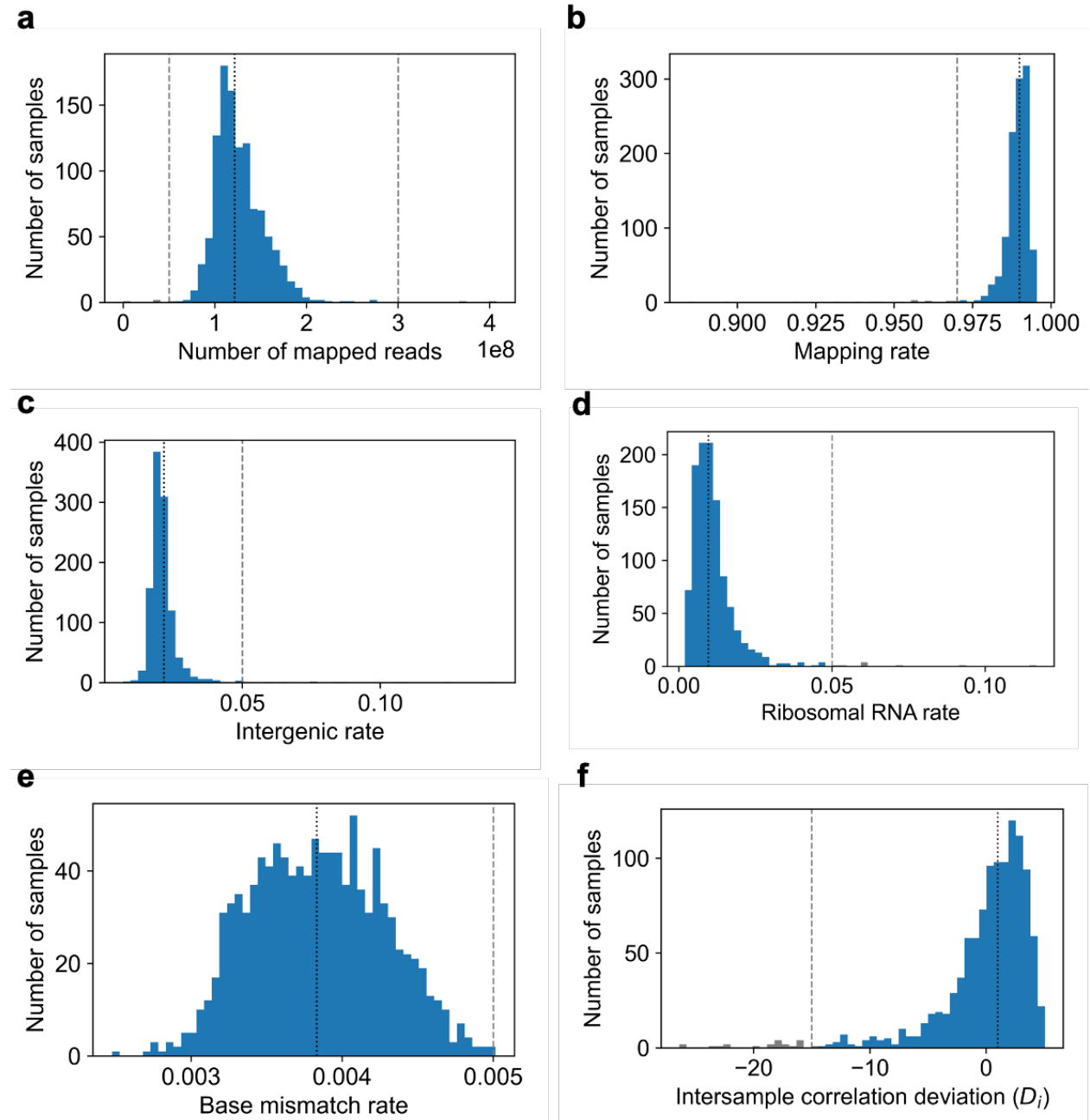
b,c. Scatter plot comparing the significance ($-\log_{10}(p)$) of COVID-19 severity ieQTLs (x axis) and ipQTLs (y axis), colored by the percentage of samples below the LOD in a gene (**b**), or the slope of the linear model where x =COVID-19 severity and y =percentage of samples below the LOD in each gene (**c**). Those passing Bonferroni significance are marked in **c**.

d. Percentage of samples below the LOD in CLEC4C and RPA2, the two genes passing significance threshold in (**c**).

e,f. Distribution of the percentage of samples below the LOD per gene, in a bar (**e**) or cumulative density plot (**f**).

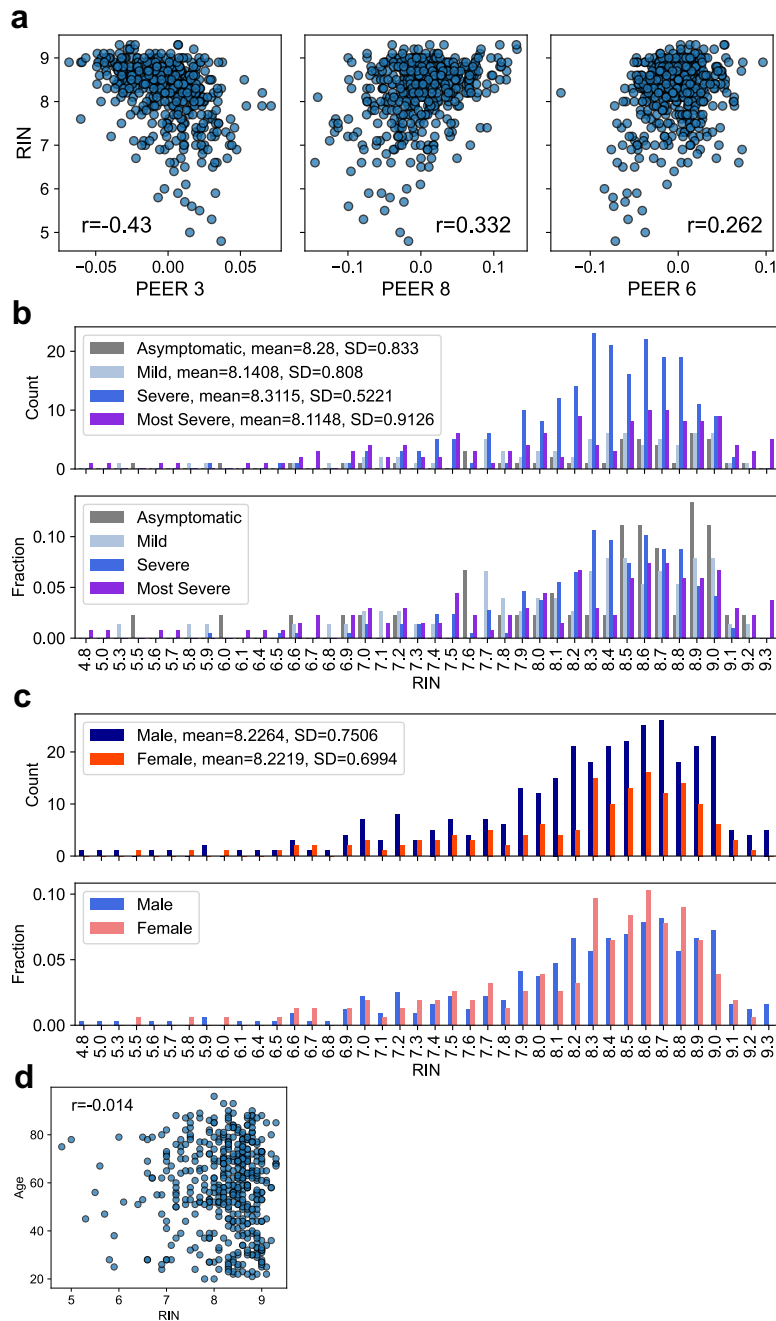
g. Distribution of pQTL p-value (minimum per gene) stratified by the percentage of samples below the LOD in a gene.

Supplementary Figure 22. Quality control (QC) for RNA-seq data



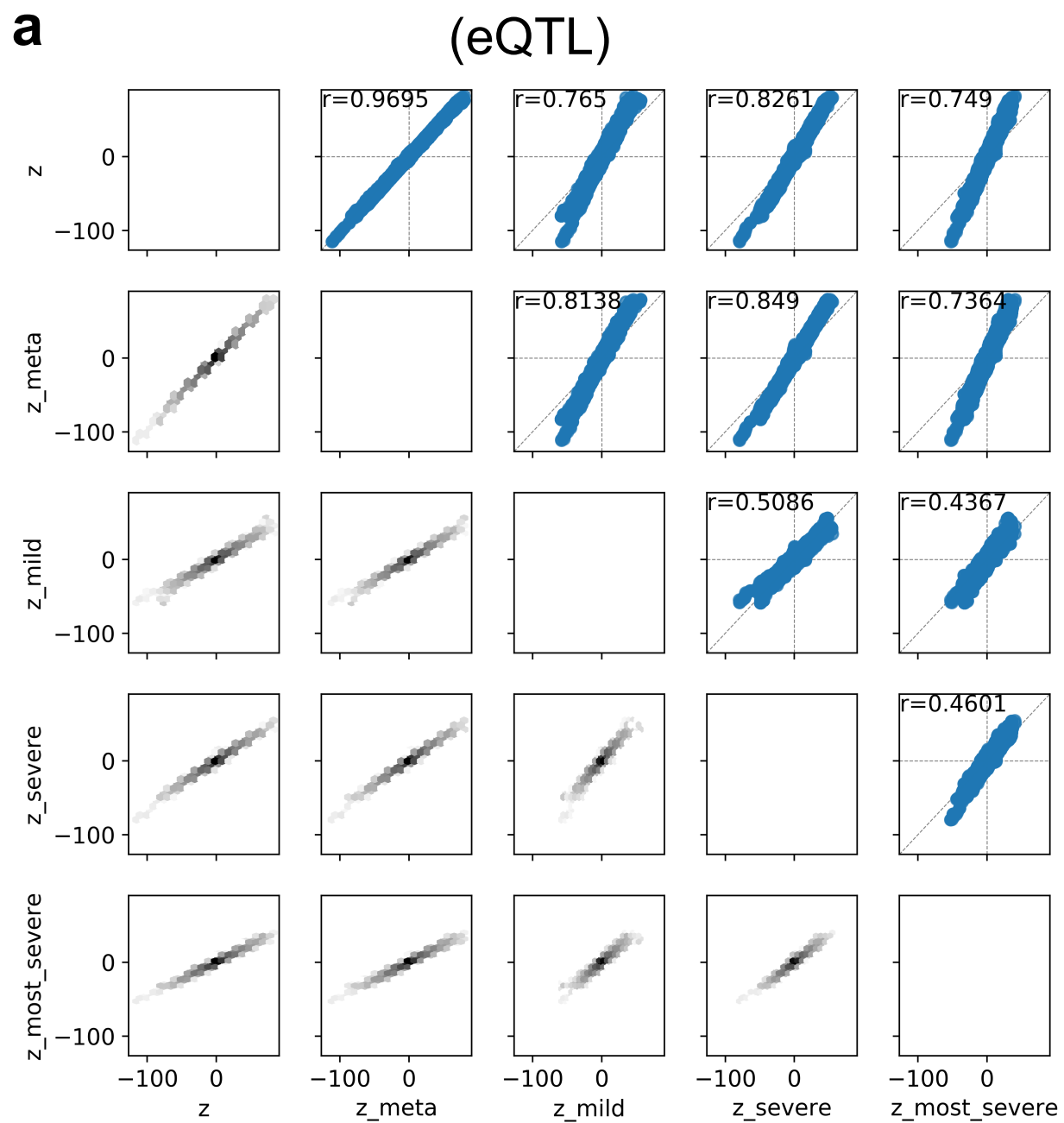
Black dotted line shows the median, and the gray dashed line shows the filtering threshold. Specifically, only samples satisfying **(a)** $0.5e8 < \text{number of mapped reads} < 3e8$, **(b)** $0.97 < \text{mapping rate}$, **(c)** $\text{intergenic rate} < 0.05$, **(d)** $\text{ribosomal RNA rate} < 0.05$, **(e)** $\text{base mismatch rate} < 0.005$, and **(f)** $-15 < \text{intersample correlation deviation measure}$ were kept for downstream analysis. Specifically, 1,045 samples out of 1,102 with RNA-seq data passed the QC criteria.

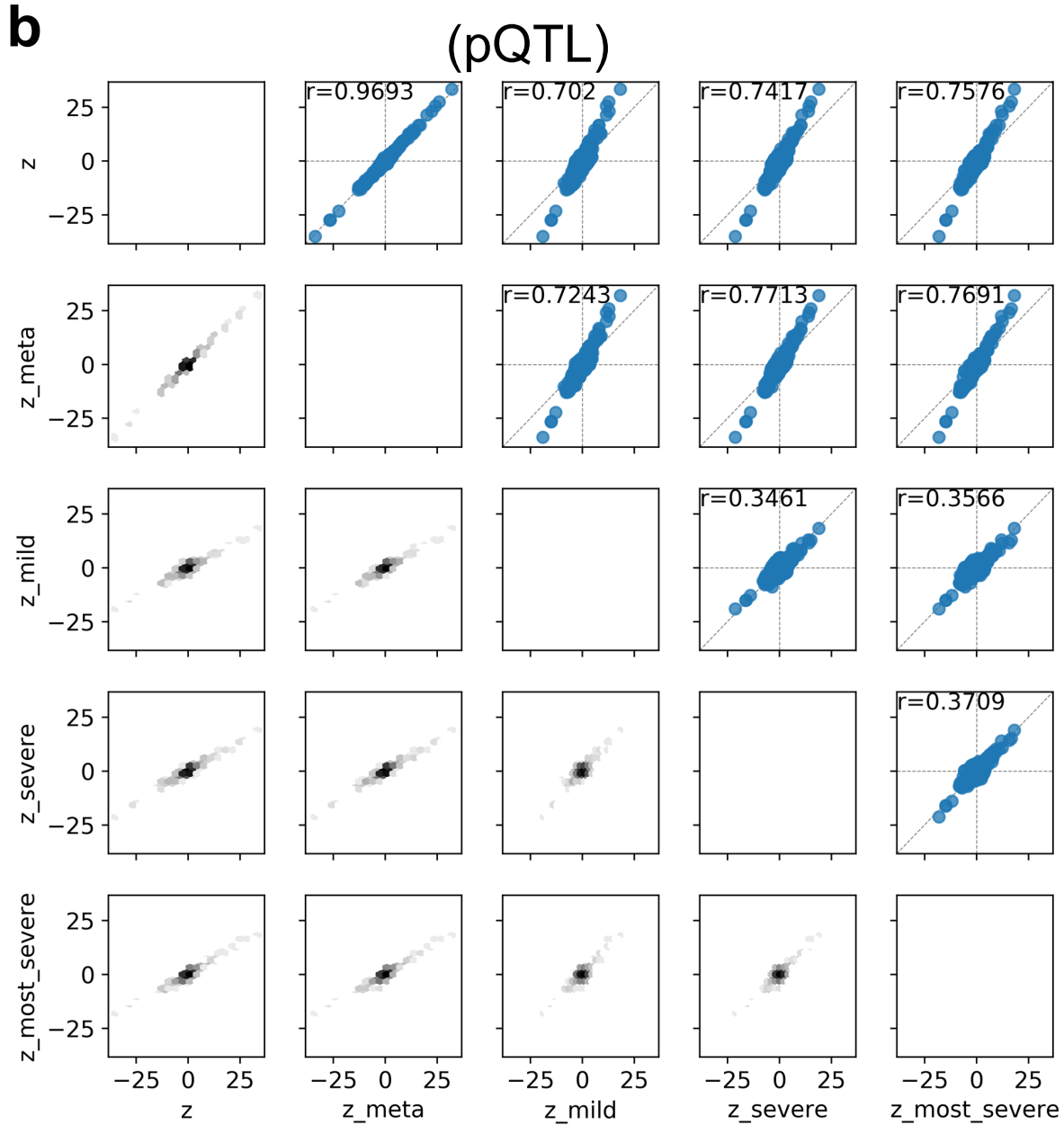
Supplementary Figure 23. Correlation between RNA Integrity Number (RIN) and major covariates



Sample RINs are correlated with a number of PEER factors that were included in the covariates to correct for unwanted sample variation (**a**; top three correlated PEER factors are shown). On the other hand, RINs distribution are not largely different between different COVID-19 disease status (**b**) or sex (**c**), and has no correlation with sample age (**d**), together suggesting that RINs are almost independent of sample's biological properties, and that the inclusion of PEER factors should largely account for sample-to-sample technical variation arising from RIN differences. Here we restricted to the $n=473$ samples that were part of our previous release ([[PMID: 35995775](https://pubmed.ncbi.nlm.nih.gov/35995775/)] re-QCed for this round) for this analysis for simplicity.

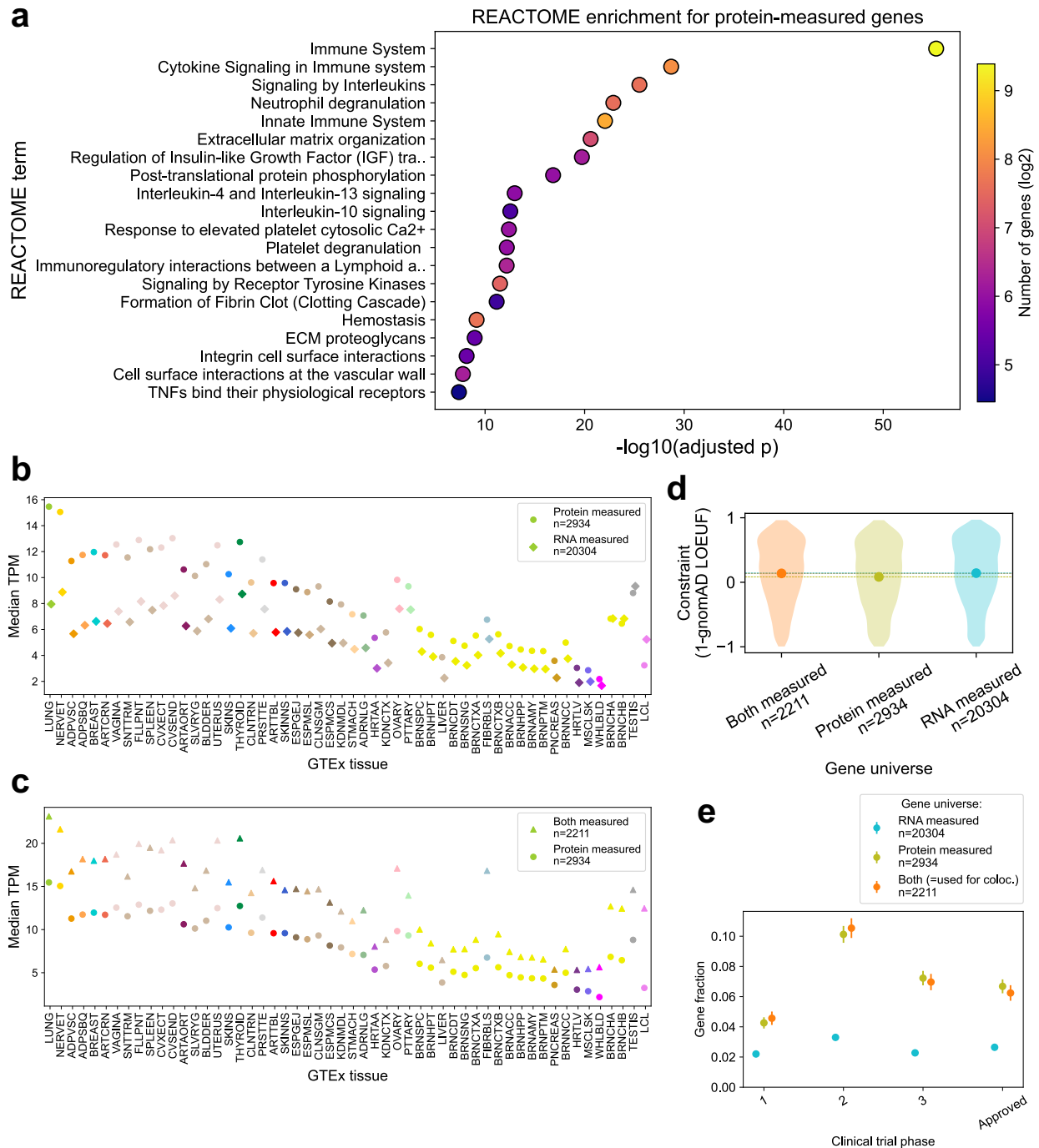
Supplementary Figure 24. Comparison between QTL calls for each COVID-19 severity group and combined





Matrices of scatter and density plots showing the correlation of z-scores tested in different sample stratification methods (from the first to fifth row and columns; 1. Our main method, jointly including all samples and accounting for COVID-19 severity differences with covariates, 2. Performing QTL calls in each disease severity strata and combining the statistics in a fixed-effect meta-analysis, 3. Performing QTL calls in asymptomatic or mild samples, 4. in severe samples, and 5. in most severe samples). Density plots are in the lower triangle, **a.** for ieQTL and **b.** for ipQTL.

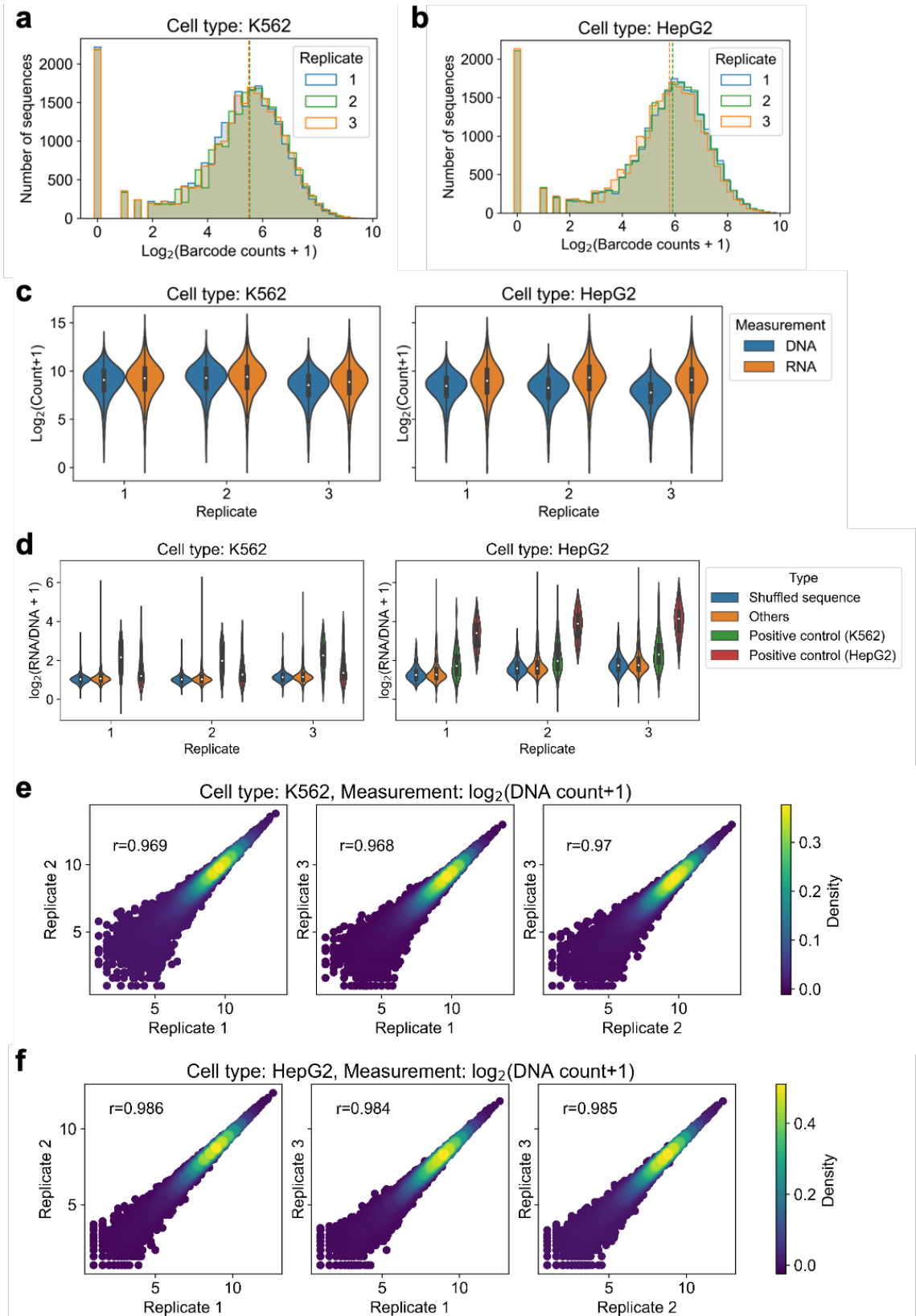
Supplementary Figure 25. Characterization of genes with mRNA, protein measurement or both

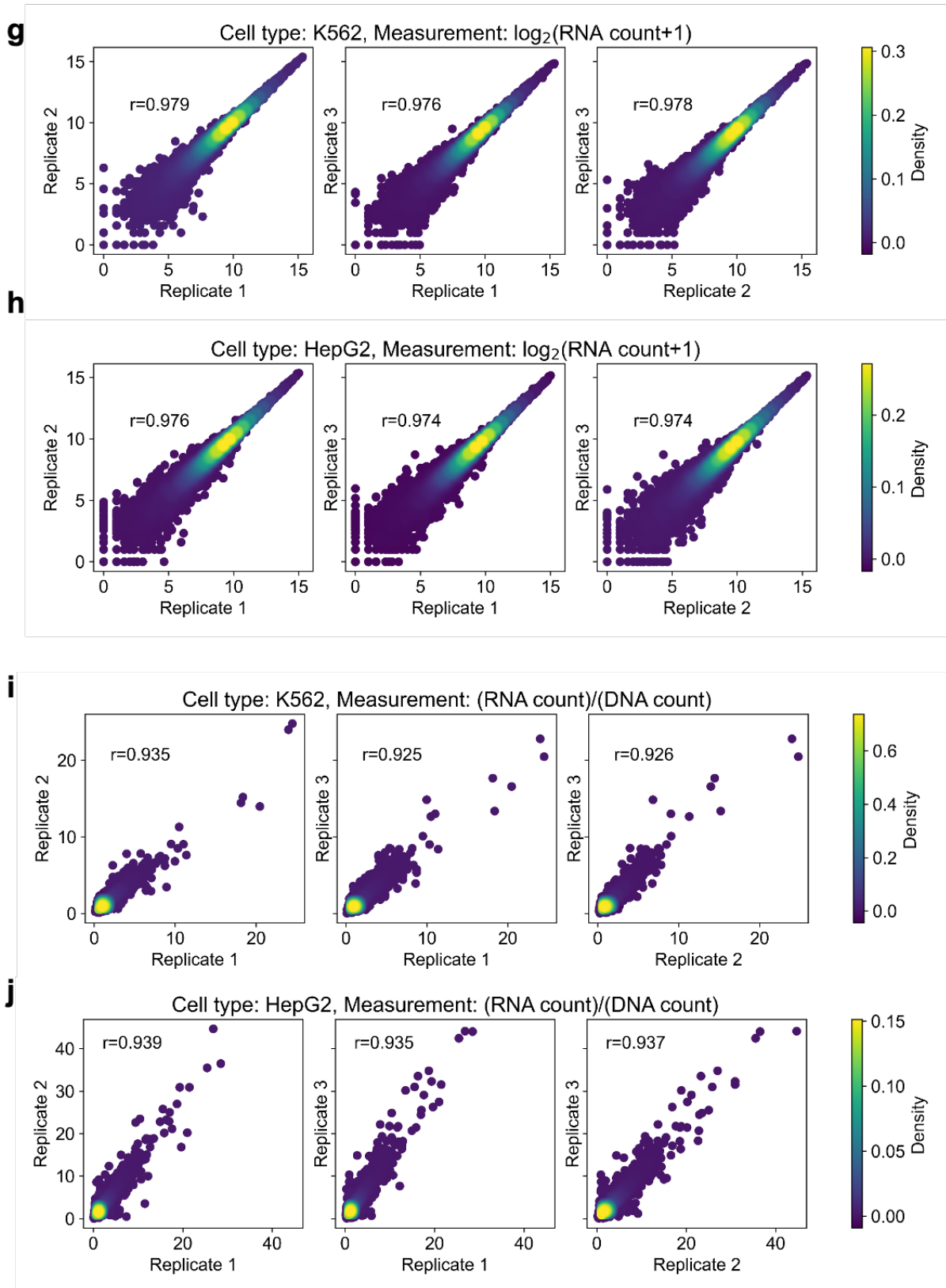


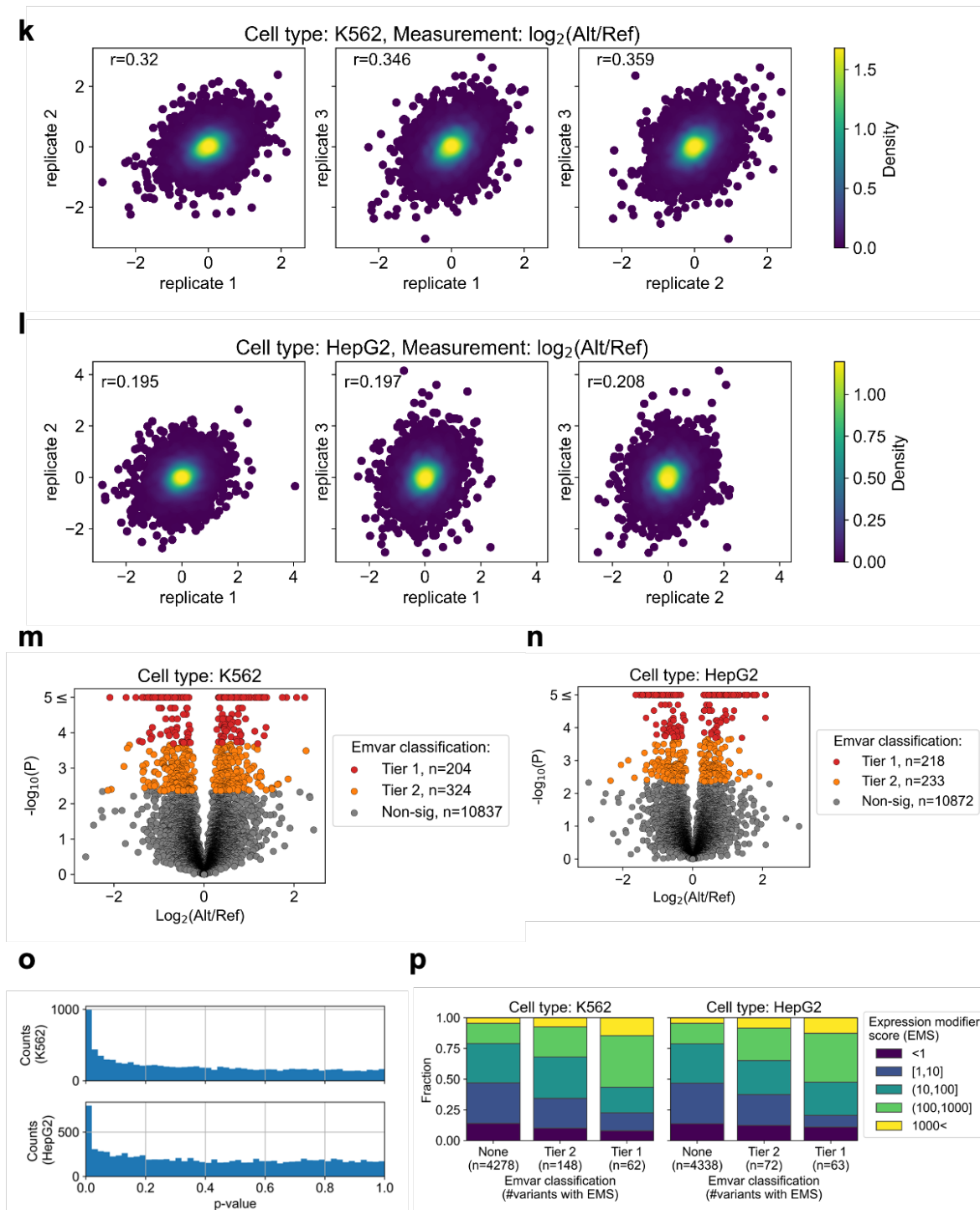
a. Reactome enrichment for 2,932 genes with proteomics measurements (analyzed with g:Profiler <https://biit.cs.ut.ee/gprofiler/gost>).

b-e. Median gene expression (TPM) in GTEx (**b,c**), gene constraint (**d**; 1-LOEUF) and drug-target evidence (**e**) for genes with transcriptomics measurements (n=20,234), proteomics measurements (n=2,932) and both (n=2,211).

Supplementary Figure 26. Details of Massively Parallel Reporter Assay (MPRA) experiments







a, b. Distribution of barcode counts per 200 bp sequence per replicate after filtering barcodes with 0 DNA count in a replicate (**a**: K562 and **b**: HepG2 cell type).

c. Distribution of DNA and RNA counts per replicate per cell type.

d. Distribution of RNA/DNA count for different control types.

In **c.** and **d.**, the boxes inside the violin plots show 25%, 50% and 75%-ile. $n=24,000$ oligos were included in each replicate. Within each replicate, $n=156$ shuffled negative controls, $n=50$

positive control for K562 and another n=50 for HepG2 (defined previously based on [[Gordon, M.G., Inoue, F., Martin, B. et al. PMID: 32641802](#)]) were included.

e-l. Correlation of DNA count (**e,f**), RNA count (**g,h**), RNA/DNA count (**i,j**), as well as allelic fold change (**k,l**) between replicates. Barcodes with <5 dna counts and sequences with <5 barcodes were removed in **i** to **l**.

m, n. Volcano plot displaying the allelic effect (fold change) and significance for each tested variant. Tier 1 corresponds to FDR<0.01 and tier 2 to FDR<0.1. Due to finite permutations (100,000 times), the p-values lower than 1e-5 are collapsed.

o. Distribution of p-values for allelic effects.

p. Distribution of expression modifier score (EMS, maximum for each variant over cis-genes), validating the enrichment of functional variants in Tier 1 and 2 emvars.