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## Supplemental information

# Partitioning gene-level contributions to complex-trait heritability by allele frequency identifies disease-relevant genes

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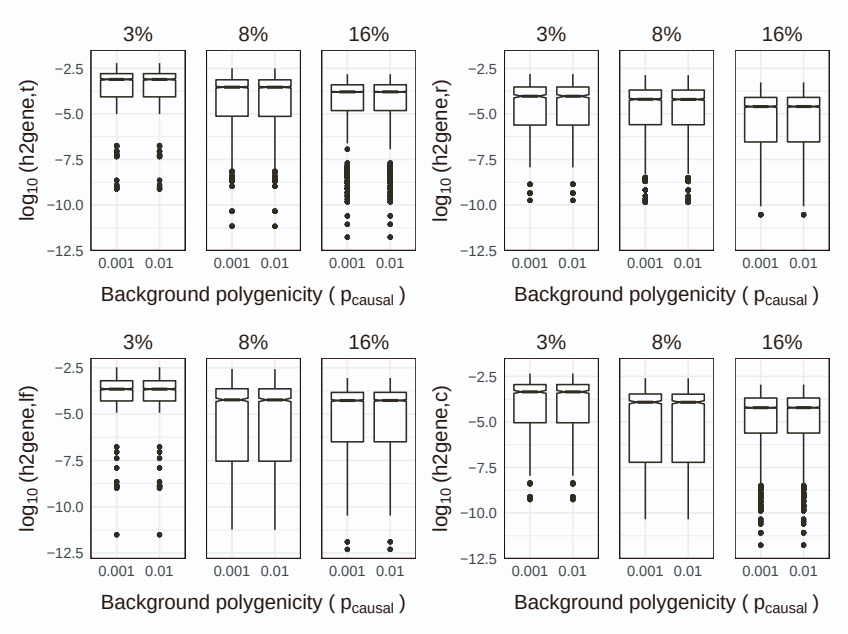
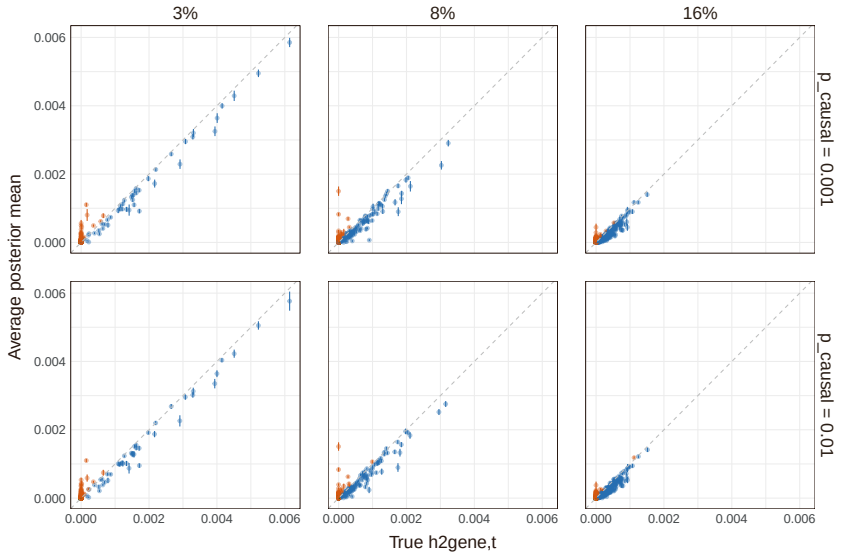
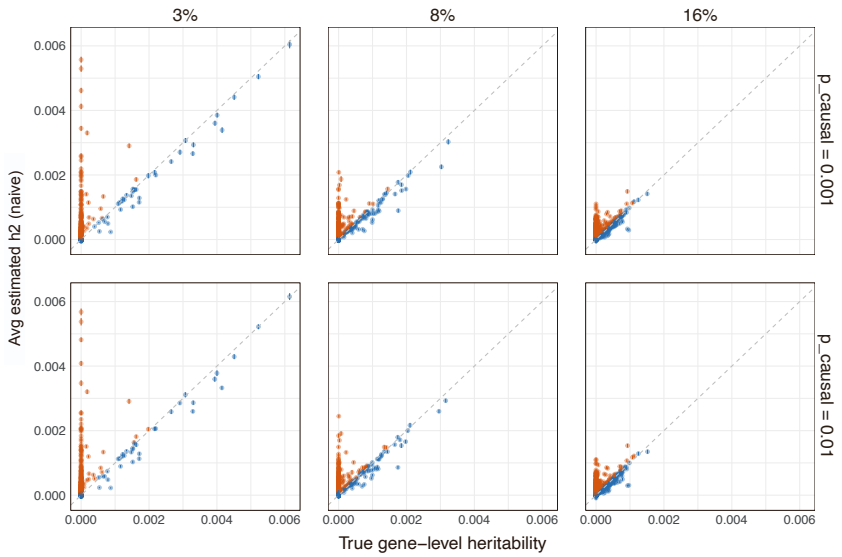


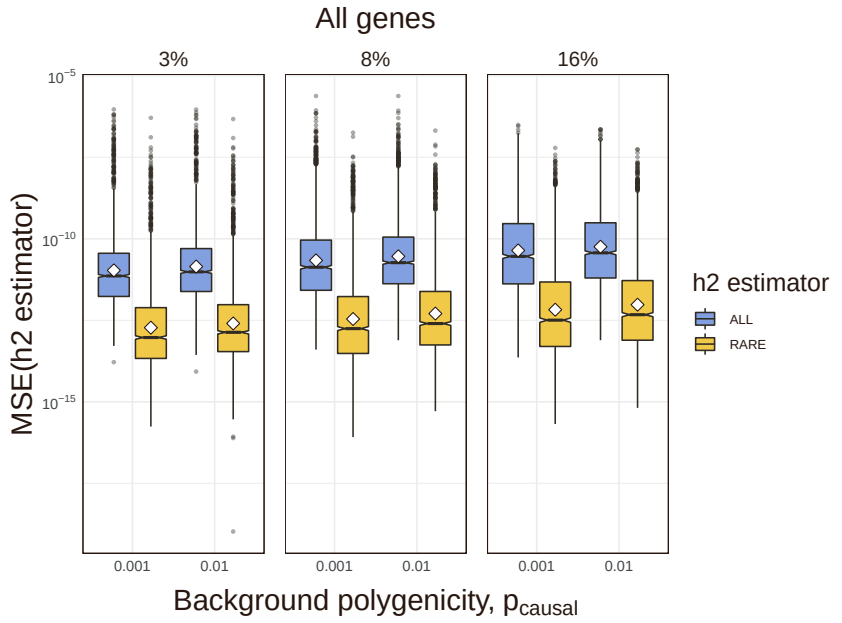

**Supplementary Figure 1**: Distributions of simulated values of $h^2_{\text{gene,t}}$, $h^2_{\text{gene,r}}$, $h^2_{\text{gene,lf}}$, and $h^2_{\text{gene,c}}$ in simulations on chromosome 1. Total $h^2_G = 0.05$. Cumulative $h^2_{\text{gene,t}} = 0.03$. 30 simulation replicates, MAF $>$ 0.005, N=291K. The proportion of causal genes (out of 1,083 genes on chr1) was set to 3%, 8%, or 16%. Background polygenicity was set to $p_{\text{causal}} = \{0.001, 0.01\}$.



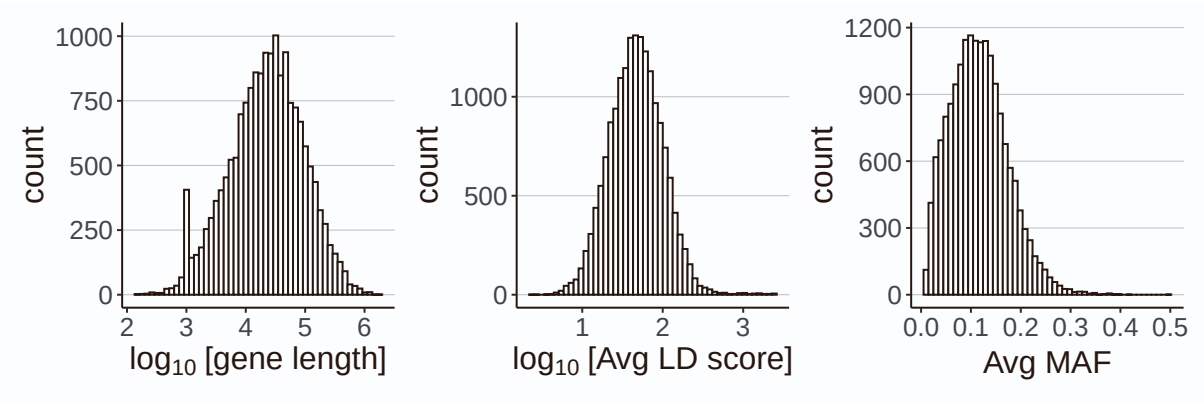

**Supplementary Figure 2**: Average $\hat{h}^2_{\text{gene,t}}$ vs. true $h^2_{\text{gene,t}}$ in simulations on chromosome 1 where 3% (left), 8% (middle), or 16% (right) of genes are causal. Orange points are genes with significantly upward-biased $\hat{h}^2_{\text{gene,t}}$, where bias is estimated as the average error, $(\hat{h}^2_{\text{gene}} - h^2_{\text{gene}})$, from 30 simulation replicates, and is considered "significant" if the error bars ($\pm 1.96$ s.e.m.) do not overlap true value of $h^2_{\text{gene,t}}$. Total $h^2_G = 0.05$. Cumulative $h^2_{\text{gene,t}} = 0.03$. MAF $>$ 0.005, N=291K.



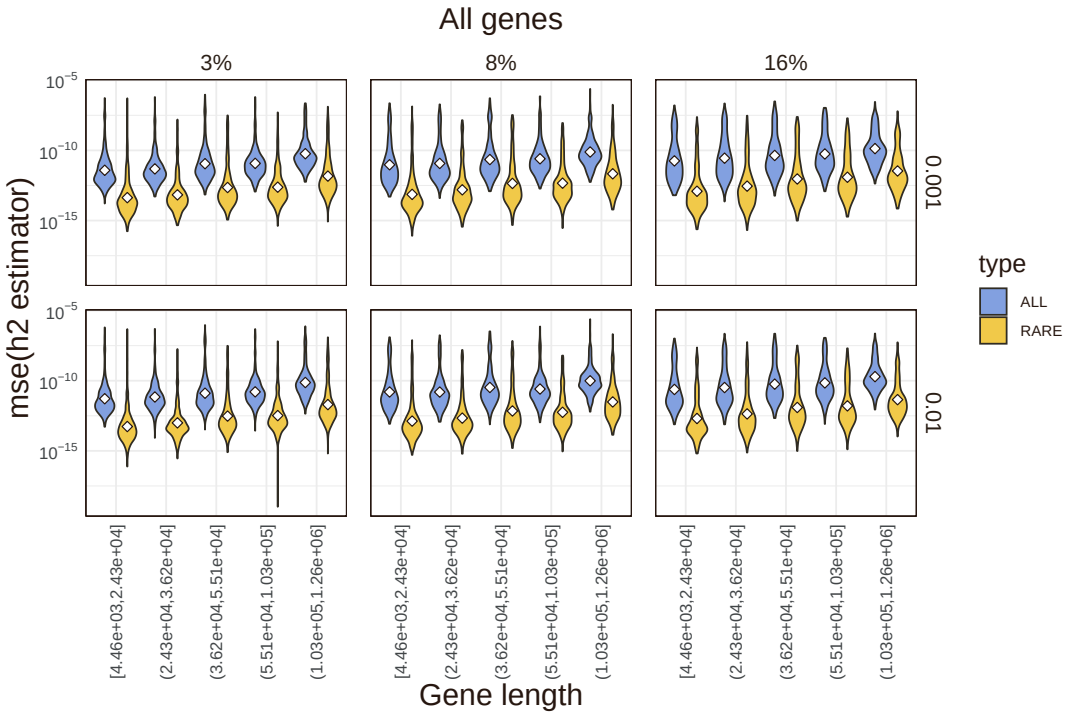

**Supplementary Figure 3**: Average estimated $h^2_{\text{gene,t}}$ from "naive method" vs. true value of $h^2_{\text{gene,t}}$ in simulations on chromosome 1 where 3%, 8%, or 16% of genes are causal. Orange points are genes with significantly upward-biased $\hat{h}^2_{\text{gene,t}}$, where bias is estimated as the average error, $(\hat{h}^2_{\text{gene}} - h^2_{\text{gene}})$, from 30 simulation replicates, and is considered "significant" if the error bars ($\pm 1.96$ s.e.m.) do not overlap true value of $h^2_{\text{gene,t}}$. Total $h^2_G = 0.05$, cumulative $h^2_{\text{gene,t}} = 0.03$, MAF $>$ 0.005, N=291K.



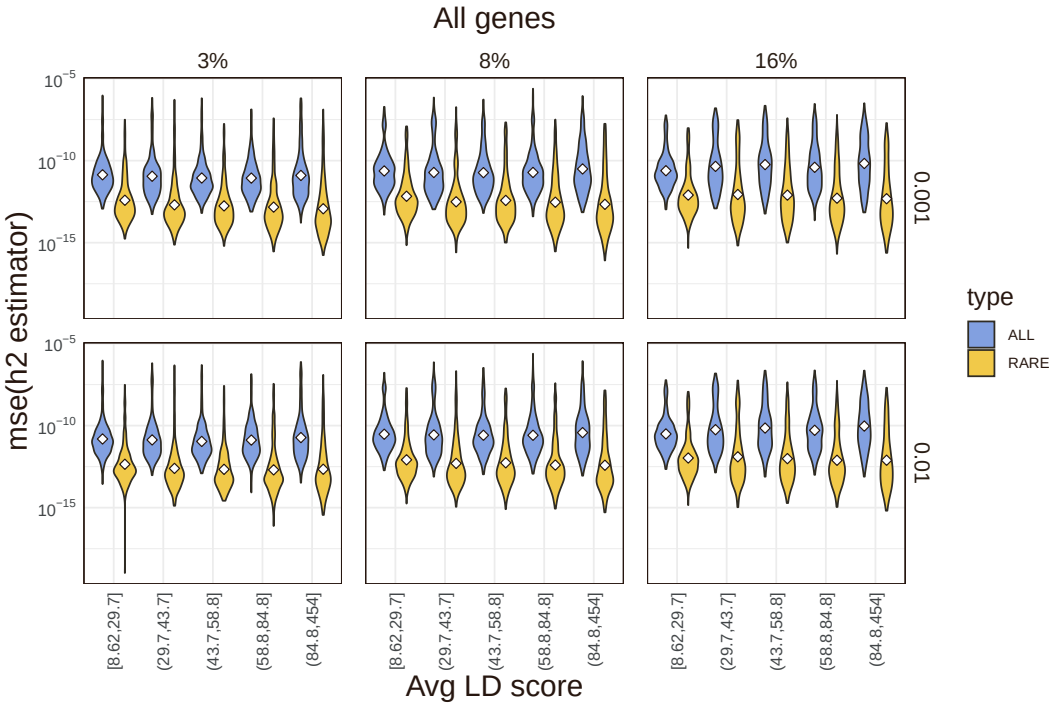

**Supplementary Figure 4**: MSE of $\hat{h}^2_{\text{gene,t}}$ (blue) and $\hat{h}^2_{\text{gene,r}}$ (yellow) for all 1,083 genes with respect to $p_{\text{causal}}$ (x-axis) in simulations on chromosome 1 where either 3%, 8%, or 16% of genes are causal. Each point in each boxplot is the MSE for a single gene estimated from 30 simulation replicates. Total $h^2_G = 0.05$. Cumulative $h^2_{\text{gene,t}} = 0.03$, MAF $>$ 0.005, $N = 291K$.



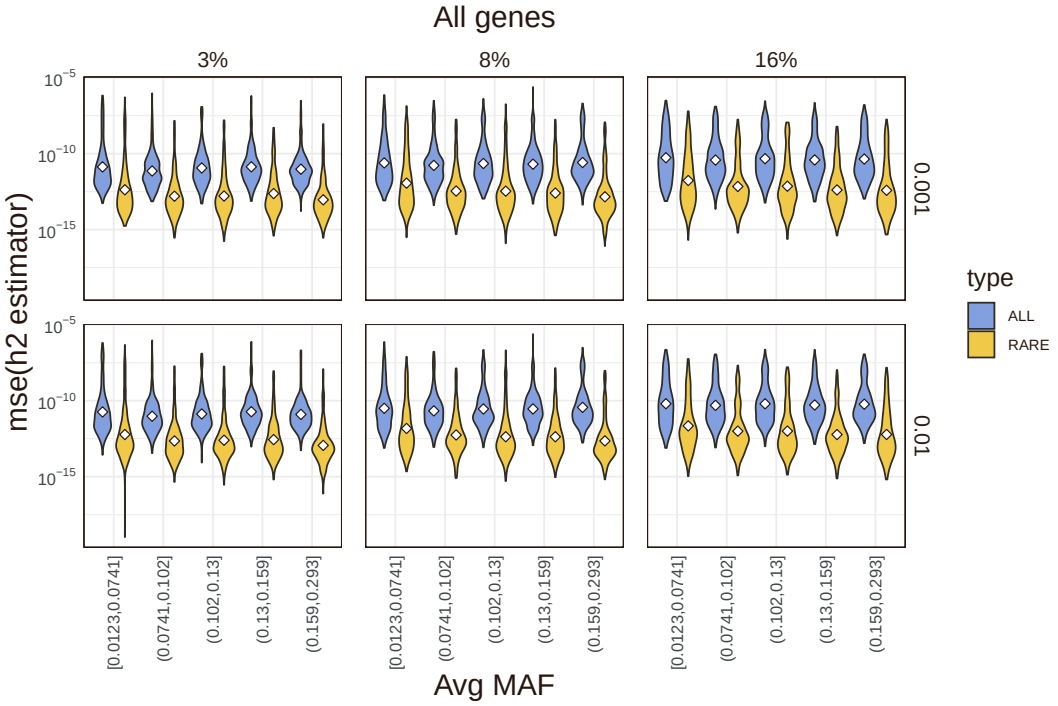

**Supplementary Figure 5**: Distribution of gene lengths (left), average LD score of variants assigned to gene (middle), and average MAF of variants assigned to gene (right) for 17,437 genes.



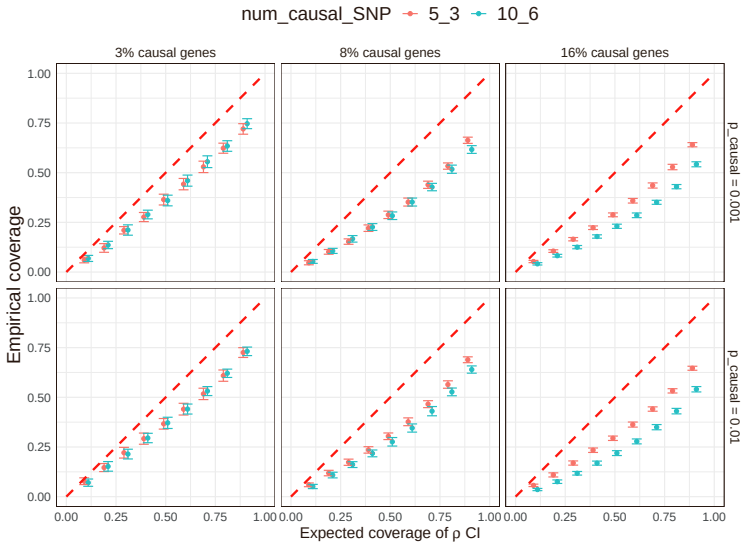

**Supplementary Figure 6**: MSE of $\hat{h}^2_{\text{gene,t}}$ (blue) and $\hat{h}^2_{\text{gene,r}}$ (yellow) with respect to gene length in simulations on chr1. Total $h^2_G = 0.05$. Cumulative $h^2_{\text{gene,t}} = 0.03$, MAF $> 0.005$, $N = 291K$, 30 simulation replicates.



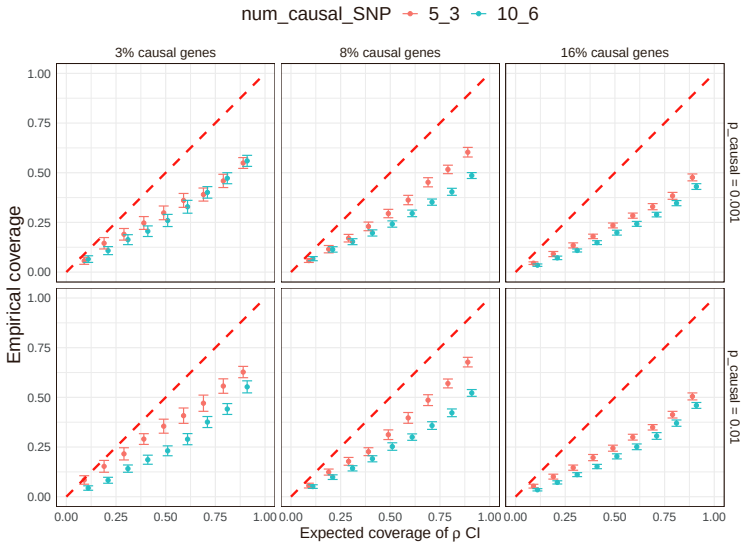

**Supplementary Figure 7**: MSE of $\hat{h}^2_{\text{gene,t}}$ (blue) and $\hat{h}^2_{\text{gene,r}}$ (yellow) with respect to average LD score of variants assigned to gene in simulations on chr1. Total $h^2_G = 0.05$. Cumulative $h^2_{\text{gene,t}} = 0.03$, MAF $>$ 0.005, $N = 291K$, 30 simulation replicates.



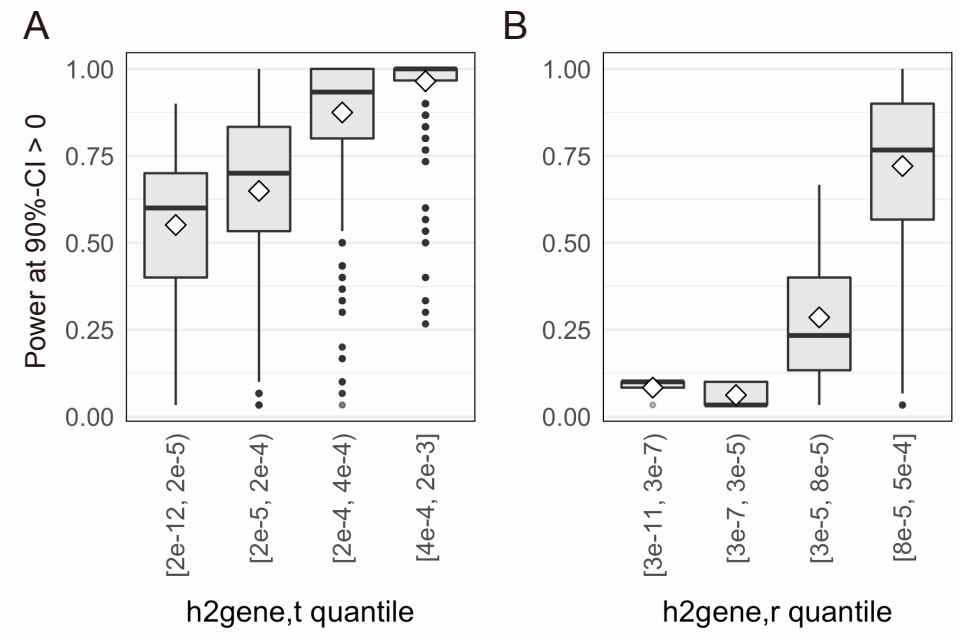

**Supplementary Figure 8**: MSE of $\hat{h}^2_{\text{gene,t}}$ (blue) and $\hat{h}^2_{\text{gene,r}}$ (yellow) with respect to average MAF of variants assigned to gene in simulations on chr1. Total $h^2_G = 0.05$. Cumulative $h^2_{\text{gene,t}} = 0.03$, MAF $>$ 0.005, $N = 291K$, 30 simulation replicates.



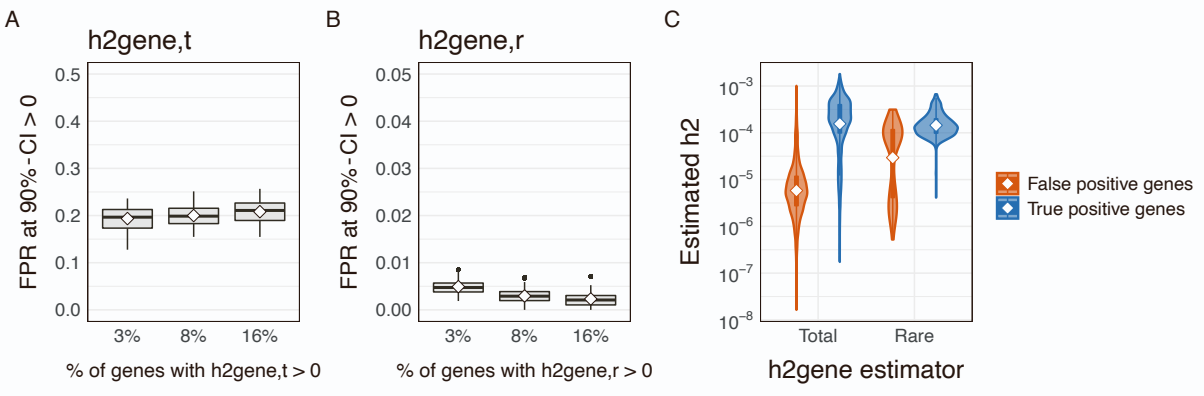

**Supplementary Figure 9**: Calibration of total $h^2_{\text{gene,t}}$ $\rho$-CIs for $\rho \in \{0.1, 0.2, ..., 0.9\}$. Empirical coverage for a given gene is the proportion of simulation replicates (out of 30) in which $\rho$-CI overlaps the true value of $h^2_{\text{gene,t}}$. Nonzero-$h^2$ genes contain either 5 (red) or 10 (blue) causal variants; their respective TSSs contain either 3 (red) or 6 (blue) causal variants (Material and Methods). Chromosome 1, MAF $>$ 0.005, N=291K, 1,083 genes.



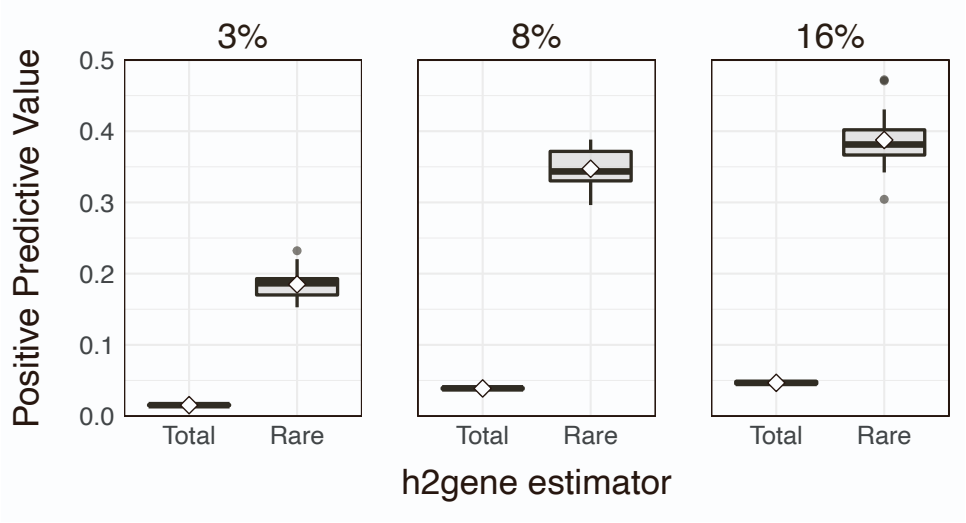

**Supplementary Figure 10**: Calibration of $h^2_{\text{gene,r}}$ $\rho$-CIs for $\rho \in \{0.1, 0.2, ..., 0.9\}$. Empirical coverage for a given gene is the proportion of simulation replicates (out of 30) in which $\rho$-CI overlaps the true value of $h^2_{\text{gene,r}}$. Nonzero-$h^2$ genes contain either 5 (red) or 10 (blue) causal variants; their respective TSSs contain either 3 (red) or 6 (blue) causal variants (Material and Methods). Chromosome 1, MAF $>$ 0.005, N=291K, 1,083 genes.



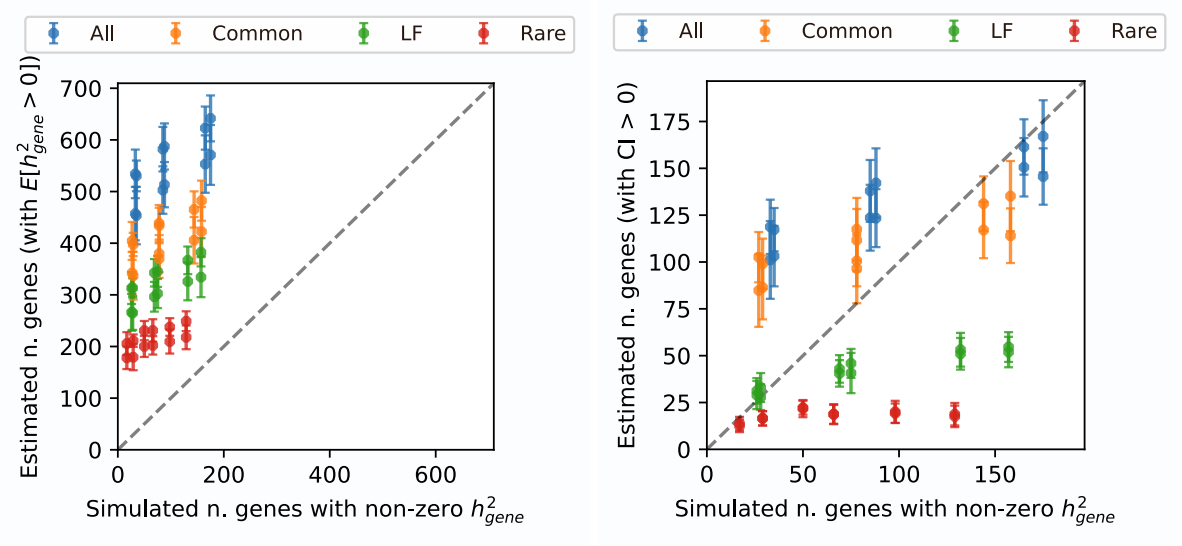

**Supplementary Figure 11**: Power to identify genes with (A) $h^2_{\text{gene,t}} > 0$ and (B) $h^2_{\text{gene,r}} > 0$ at the threshold 90%-CI $> 0$ in simulations where 16% of genes have nonzero heritability.




**Supplementary Figure 12**: False positive rate (FPR) of 90%-CI $> 0$ estimated from 30 simulation replicates for (A) $h^2_{\text{gene,t}}$ and (B) $h^2_{\text{gene,r}}$. (C) Distributions of estimates of $h^2_{\text{gene,t}}$ and $h^2_{\text{gene,r}}$ for true positive and false positive genes identified at 90%-CI $> 0$ in simulations where 16% of genes are causal. $h^2_G = 0.05$, cumulative $h^2_{\text{gene,t}} = 0.03$, MAF $> 0.005$, N=291K, 1,083 genes.



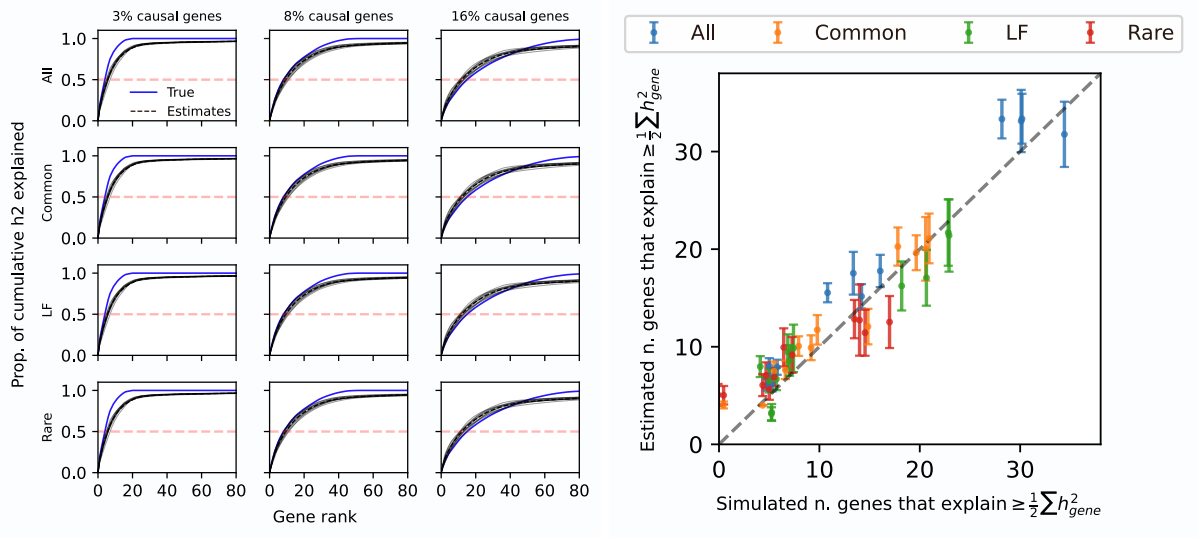

**Supplementary Figure 13**: Positive predictive value (PPV) for identifying genes with $(h^2_{\text{gene,r}}/h^2_{\text{gene,t}}) \geq 0.5$, using $h^2_{\text{gene,t}}$ 90%-CI $> 0$ or $h^2_{\text{gene,r}}$ 90%-CI $> 0$ as the significance threshold. For all plots: $h^2_G = 0.05$, cumulative $h^2_{\text{gene,t}} = 0.03$, MAF $> 0.005$, N=291K, chr1, 30 simulation replicates; white diamonds mark the mean.




(A) Sum of per-gene posterior probabilities

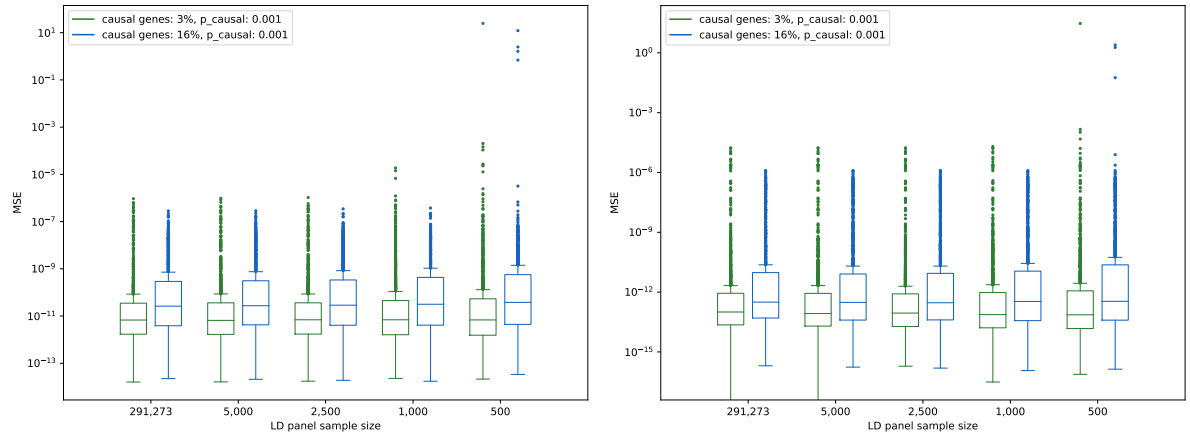
(B) Number of $h^2_{\text{gene}}$ 90%-CI $> 0$ genes

**Supplementary Figure 14**: Estimated vs. true number of nonzero-$h^2$ genes in simulations on chr1 ($h^2_G = 0.05$, $\sum h^2_{\text{gene,t}} = 0.03$, MAF $> 0.5\%$, N=290K). (A) For each gene, we compute the posterior probability that it has nonzero-$h^2$ from 500 posterior samples. The total number of nonzero-$h^2$ genes is then estimated by summing the posterior probabilities across genes. (B) Estimator is the number of genes with $\hat{h}^2_{\text{gene}}$ 90%-CI $> 0$. For both plots, each point is the average estimate from 30 simulation replicates. Error bars mark $\pm 1.96\times$SEM.

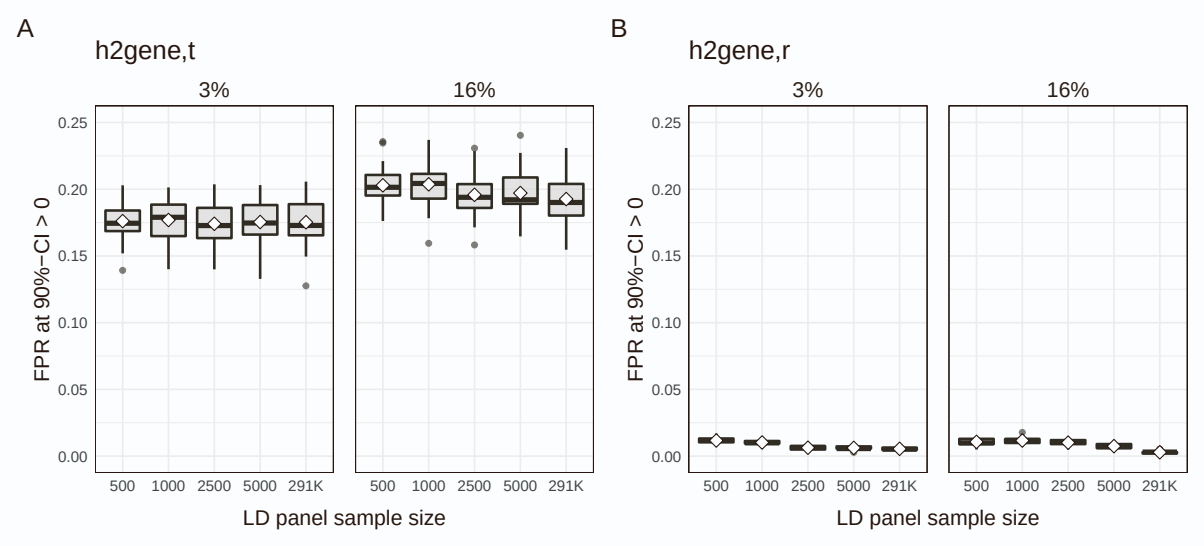



(A) (B)

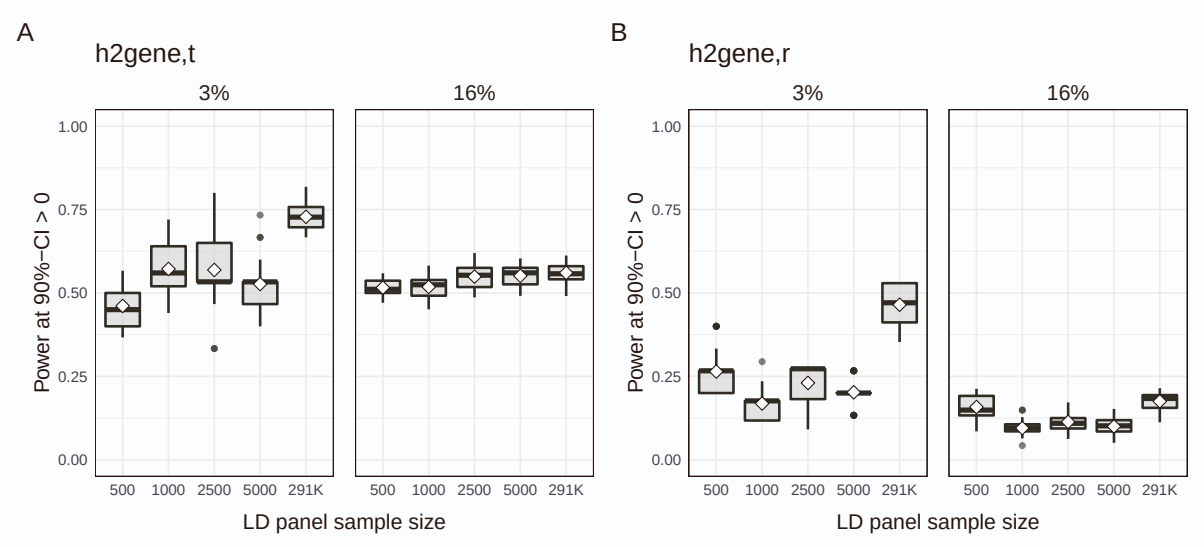
**Supplementary Figure 15**: (A) Cumulative distributions of $h^2_{\text{gene,t}}$, $h^2_{\text{gene,c}}$, $h^2_{\text{gene,lf}}$, and $h^2_{\text{gene,r}}$ for 90%-CI $> 0$ genes in simulations on chr1. Each plot can be read as "top X genes with 90%-CI $> 0$, rank ordered by $\hat{h}^2_{\text{gene}}$ from largest to smallest, that explain Y of cumulative $h^2_{\text{gene}}$." (B) Estimated vs. true number of genes that explain 50% of cumulative $h^2_{\text{gene,t}}$, $h^2_{\text{gene,c}}$, $h^2_{\text{gene,lf}}$, or $h^2_{\text{gene,r}}$ in simulations. Each point is the number of genes, rank ordered by $\hat{h}_{\text{gene}}$ from largest to smallest, that explain at least 50% of cumulative gene-level $h^2$, averaged across 30 simulation replicates. Error bars mark $\pm 1.96\times$SEM. Simulation parameters: $h^2_G = 0.05$, $\sum h^2_{\text{gene,t}} = 0.03$, MAF $> 0.5\%$, N=290K.



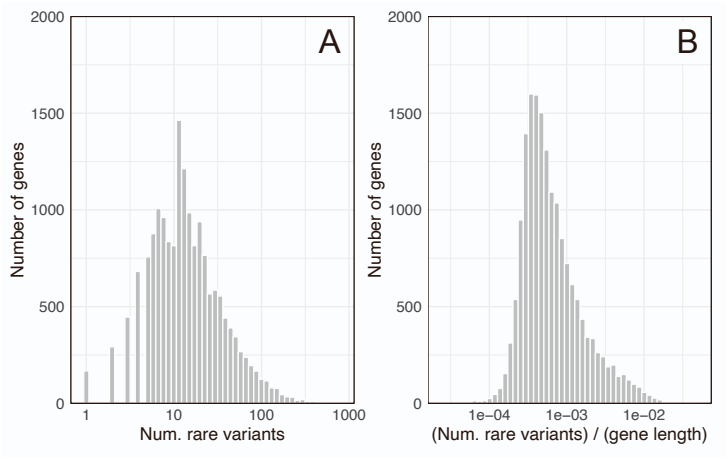

**Supplementary Figure 16**: MSE of $\hat{h}^2_{\text{gene,t}}$ (left) and $\hat{h}^2_{\text{gene,r}}$ (right) with respect to LD panel sample size (x-axis) in simulations (chromosome 1, MAF $> 0.005$, N=290K, 1,083 genes, 30 simulation replicates). Note: y-axes are different.



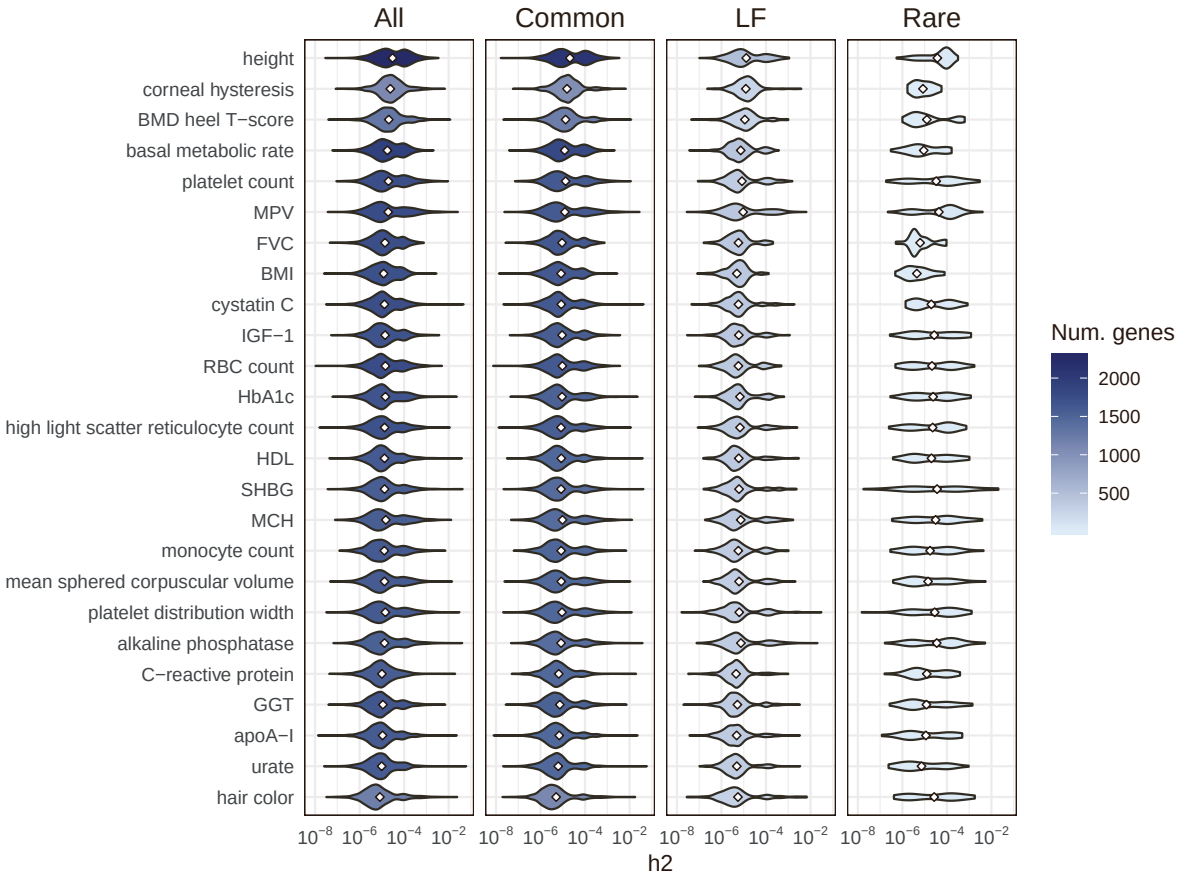

**Supplementary Figure 17**: False positive rate (FPR) of 90%-CI $> 0$ for (A) $h^2_{\text{gene,t}}$ and (B) $h^2_{\text{gene,r}}$ with respect to LD panel sample size (x-axis) in simulations (chromosome 1, MAF $> 0.005$, N=290K, 1,083 genes). Here, FPR is estimated as the proportion of zero-heritability genes that incorrectly pass the cutoff 90%-CI $> 0$ in a given simulation replicate. LD panels were generated by sampling individuals from the GWAS cohort.



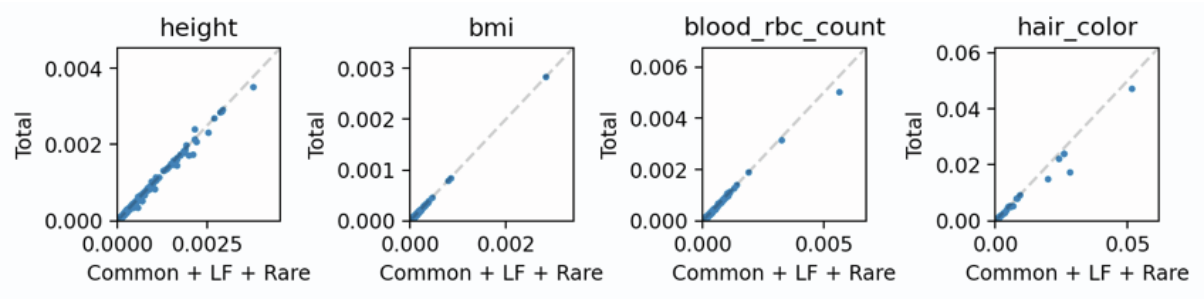

**Supplementary Figure 18**: Power of 90%-CI $> 0$ for (A) $h^2_{\text{gene,t}}$ and (B) $h^2_{\text{gene,r}}$ with respect to LD panel sample size (x-axis) in simulations (chromosome 1, MAF $> 0.005$, N=290K, 1,083 genes, 30 simulation replicates). Power is estimated per simulation replicate as the proportion of true nonzero-heritability genes that are correctly identified at the cutoff 90%-CI $> 0$. LD panels were generated by sampling individuals from the GWAS cohort.



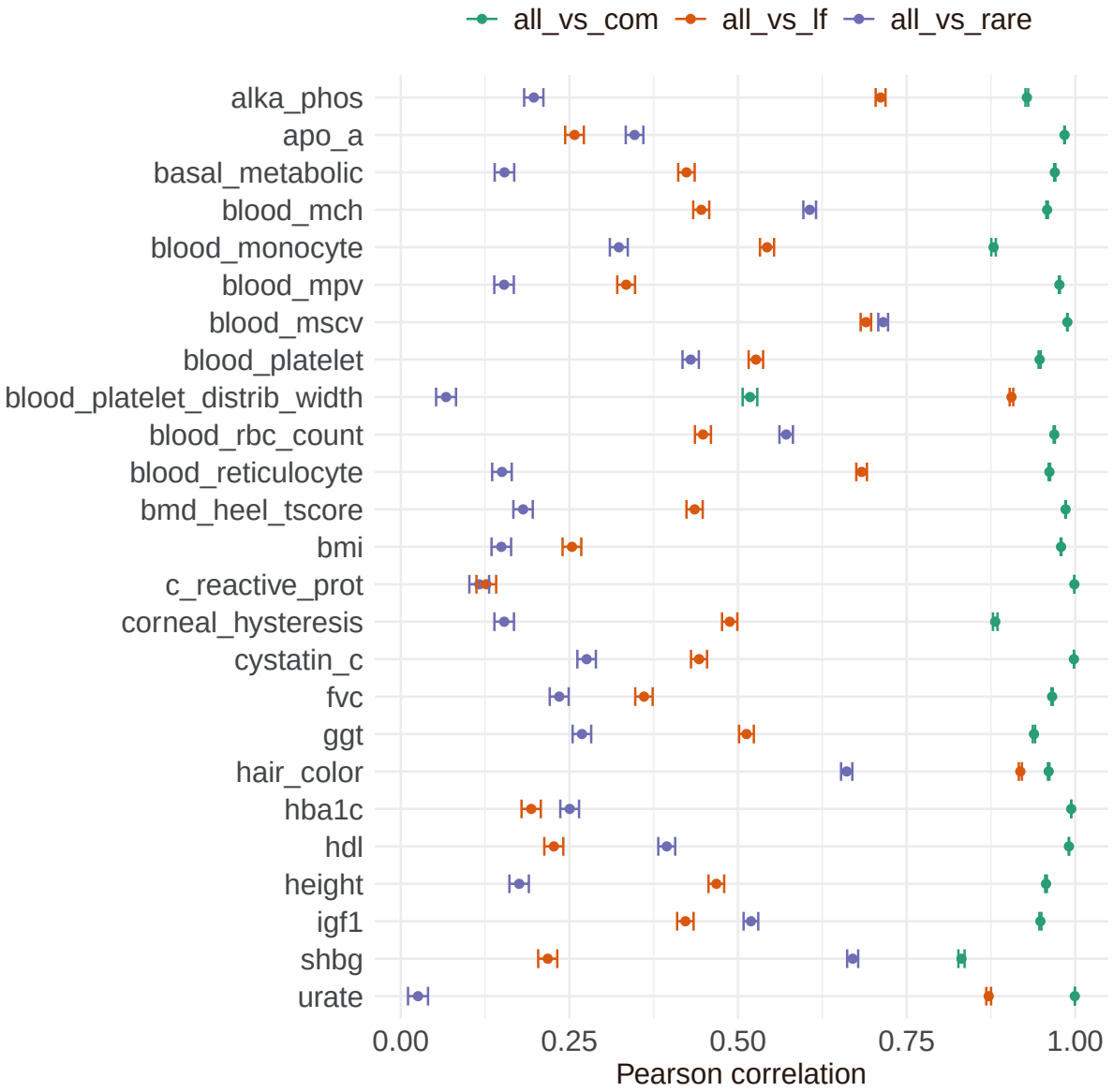

**Supplementary Figure 19**: Distributions of the (A) number and (B) rate of rare variants per gene body $\pm$ 10-kb upstream/downstream across 17,437 protein-coding genes.



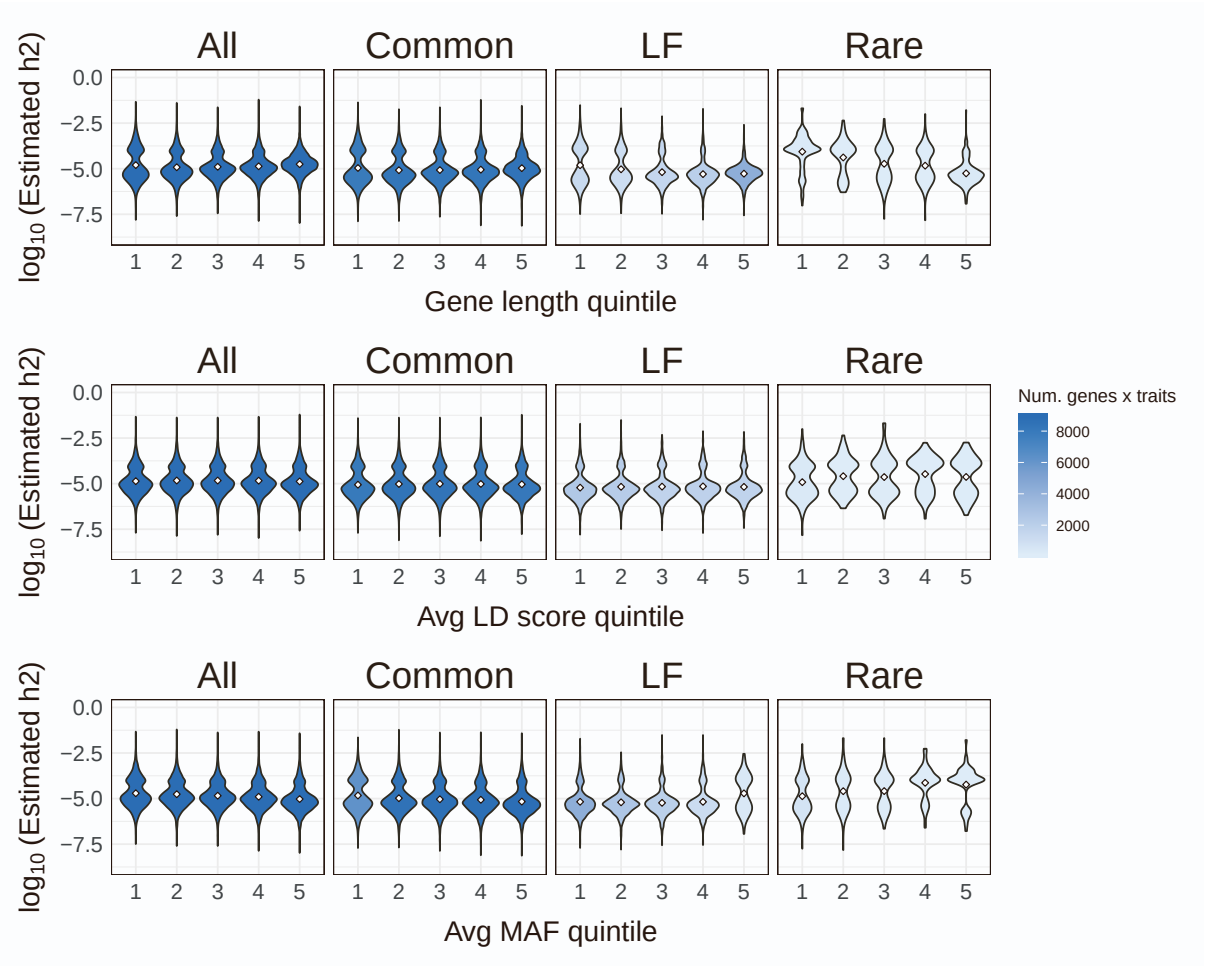

**Supplementary Figure 20**: Distributions of $\hat{h}^2_{\text{gene}}$ for 25 traits ($N = 290K$ "white British" individuals, UK Biobank). Each violin plot is the distribution of posterior mean estimates for genes with 90%-CI $> 0$ for one trait. The shading scales with the number of genes in the violin plot.



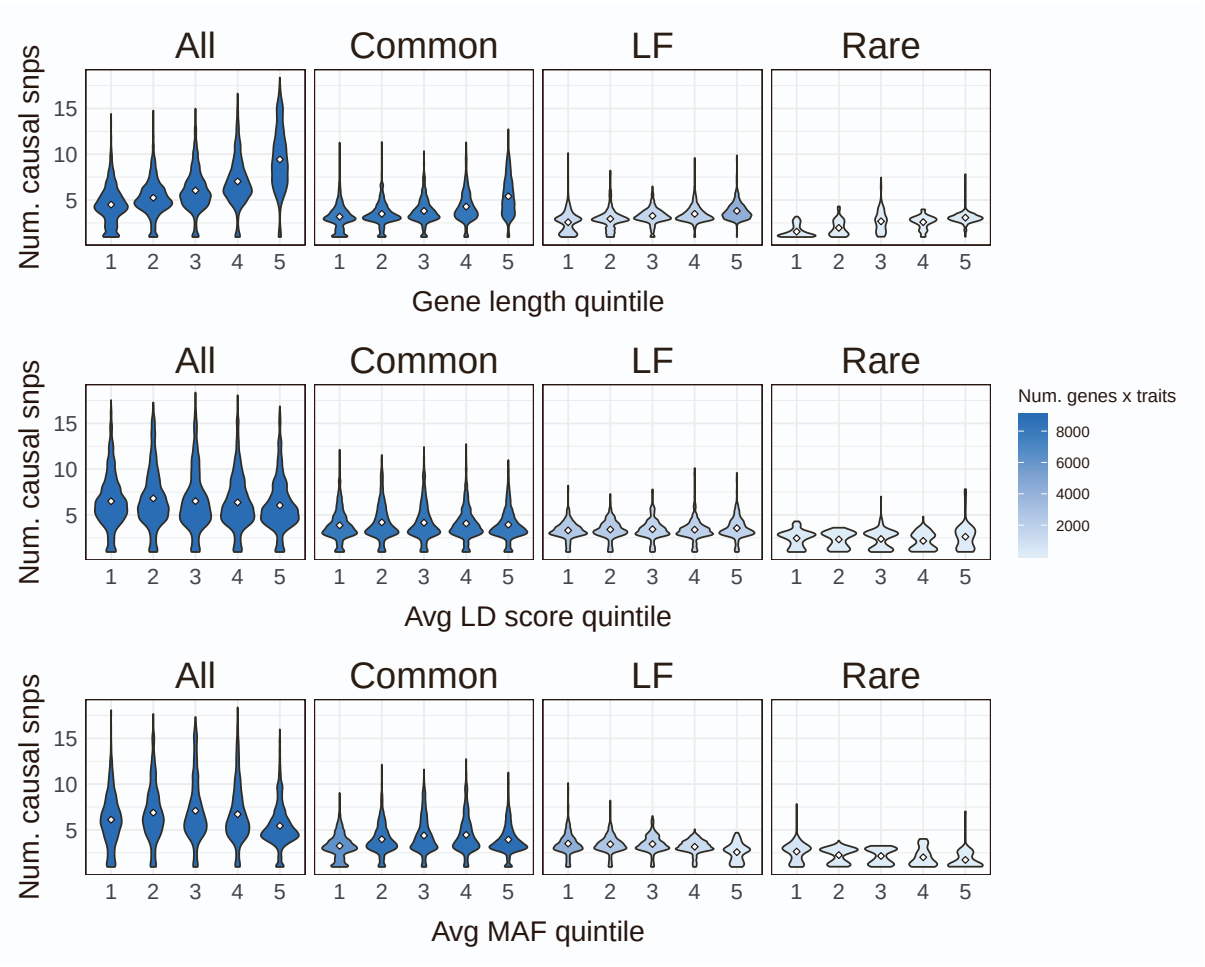

**Supplementary Figure 21**: $\hat{h}^2_{\text{gene,t}}$ (y-axis) vs. $\hat{h}^2_{\text{gene,c}} + \hat{h}^2_{\text{gene,lf}} + \hat{h}^2_{\text{gene,r}}$ (x-axis) across 90%-CI $> 0$ genes for height, BMI, red blood cell count, and hair color (N=290K, "white British," UK Biobank).



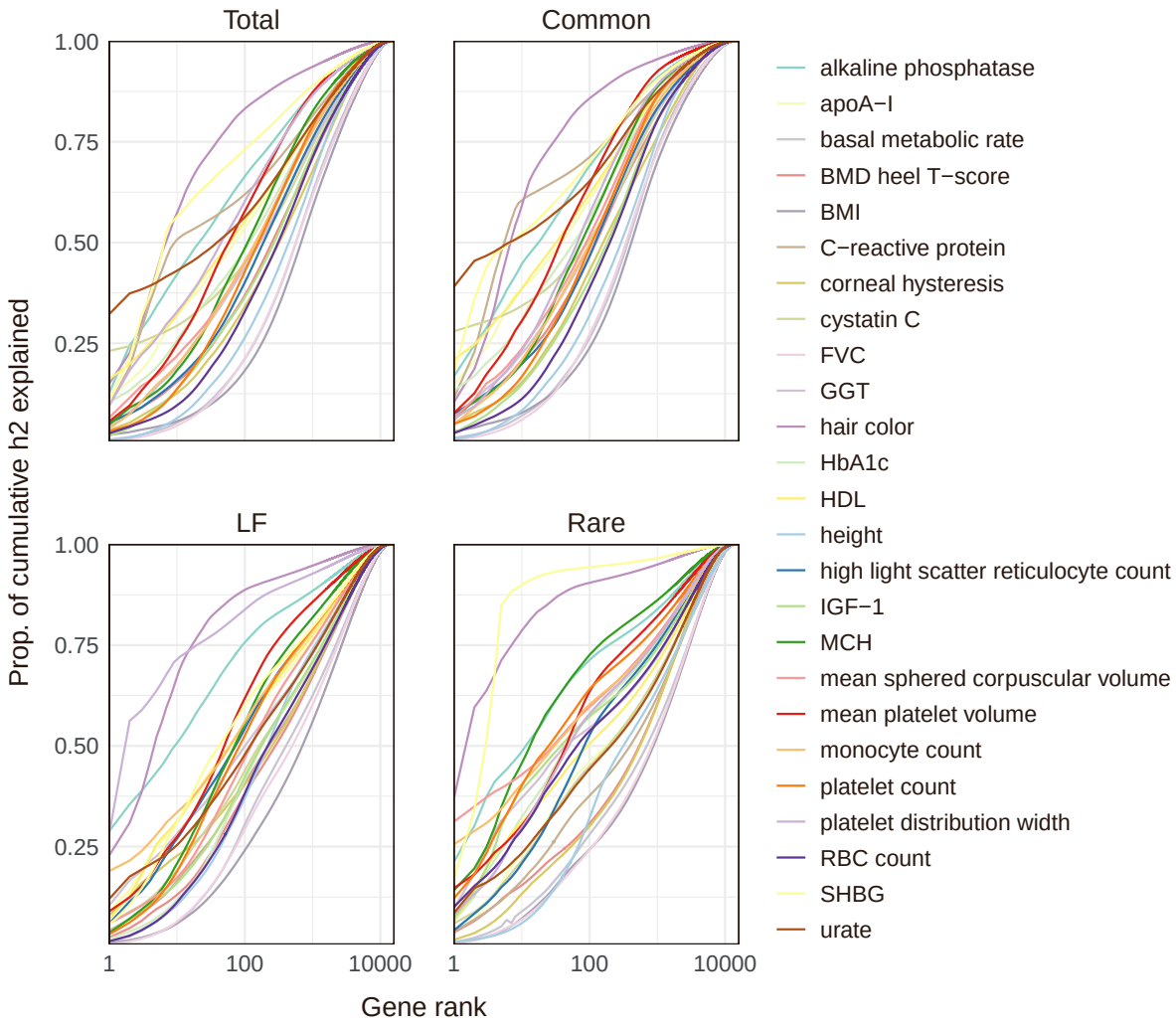

**Supplementary Figure 22**: Correlation of $\hat{h}^2_{\text{gene,t}}$ with $\hat{h}^2_{\text{gene,c}}$ (green), $\hat{h}^2_{\text{gene,lf}}$ (orange), and $\hat{h}^2_{\text{gene,r}}$ (purple) for 25 UK Biobank traits. Error bars mark 95% confidence intervals.




**Supplementary Figure 23**: Distributions of $\hat{h}^2$ for nonzero-heritability genes with respect to gene length (top), average LD score of variants assigned to gene (middle), average MAF of variants assigned to gene (bottom). Each point in each violin plot is an estimate for a unique gene-trait pair (25 traits in total). Violin plots are shaded to indicate the number of data points in the distribution. Diamonds mark the means of the distributions.




**Supplementary Figure 24**: Distributions of estimated number of causal variants in nonzero-heritability genes with respect to gene length (top), average LD score of variants assigned to gene (middle), and average MAF of variants assigned to gene (bottom). Violin plots are shaded to indicate the number of data points in the distribution. Each point in each violin plot is an estimate for a unique gene-trait pair (25 traits in total). Diamonds mark the means of the distributions.




**Supplementary Figure 25**: Empirical cumulative distribution cumulative heritability for 25 traits. Each curve can be read as, "the top X genes explain Y% of the cumulative gene-level heritability for a given trait." Cumulative heritability is estimated as the summation of posterior mean estimates for nonzero-heritability genes (90%-CI $> 0$). Clockwise from the top left: $\hat{h}^{\text{“2}}_{\text{gene,t}}$, $\hat{h}^2_{\text{gene,c}}$, $\hat{h}^2_{\text{gene,r}}$, and $\hat{h}^2_{\text{gene,lf}}$.

| % causal genes | $p_{\text{causal}}$ | $\rho$ | Underestimated | | Overestimated | |
|---|---|---|---|---|---|---|
| | | | Avg num genes | Avg % | Avg num genes | Avg % |
| 3% | 0.001 | 0.90 | 6.55 (0.28) | 19.29 (0.82) | 2.50 (0.13) | 7.37 (0.40) |
| 3% | 0.001 | 0.95 | 4.82 (0.26) | 14.17 (0.78) | 1.88 (0.13) | 5.58 (0.40) |
| 3% | 0.01 | 0.90 | 6.25 (0.26) | 18.42 (0.79) | 2.98 (0.17) | 8.74 (0.48) |
| 3% | 0.01 | 0.95 | 4.68 (0.23) | 13.80 (0.68) | 2.18 (0.14) | 6.43 (0.41) |
| 8% | 0.001 | 0.90 | 25.47 (0.64) | 29.39 (0.70) | 5.72 (0.24) | 6.62 (0.28) |
| 8% | 0.001 | 0.95 | 19.77 (0.63) | 22.80 (0.70) | 4.40 (0.20) | 5.09 (0.23) |
| 8% | 0.01 | 0.90 | 23.13 (0.64) | 26.70 (0.70) | 5.93 (0.23) | 6.86 (0.27) |
| 8% | 0.01 | 0.95 | 17.60 (0.58) | 20.30 (0.65) | 4.48 (0.24) | 5.18 (0.27) |
| 16% | 0.001 | 0.90 | 61.82 (1.43) | 36.22 (0.71) | 7.87 (0.28) | 4.62 (0.16) |
| 16% | 0.001 | 0.95 | 49.62 (1.38) | 29.05 (0.71) | 5.55 (0.27) | 3.26 (0.15) |
| 16% | 0.01 | 0.90 | 60.55 (1.58) | 35.46 (0.81) | 8.83 (0.31) | 5.20 (0.18) |
| 16% | 0.01 | 0.95 | 48.95 (1.47) | 28.64 (0.76) | 6.20 (0.27) | 3.66 (0.16) |

**Supplementary Table 1.** Calibration of h2gene $\rho$-CIs with respect to the number of causal genes, proportion of causal variants ($p_{\text{causal}}$), and $\rho \in \{0.90, 0.95\}$ in simulations (chromosome 1, MAF > 0.5%, 1,083 protein-coding genes, cumulative $h^2_{\text{gene}} = 0.03$ ). "Underestimated" and "overestimated" refer to genes whose $\rho$-CIs lie below and above their true gene-level heritability, respectively. For each simulation setup, we report the average (and s.e.m.) of the number and percentage of underestimated/overestimated genes in 30 simulation replicates.

| % causal genes | $p_{\text{causal}}$ | $\rho$ | Underestimated | | Overestimated | |
|---|---|---|---|---|---|---|
| | | | Avg num genes | Avg % | Avg num genes | Avg % |
| 3% | 0.001 | 0.90 | 9.70 (0.38) | 42.41 (0.93) | 0.52 (0.09) | 2.15 (0.38) |
| 3% | 0.001 | 0.95 | 8.67 (0.35) | 37.88 (0.95) | 0.35 (0.08) | 1.45 (0.31) |
| 3% | 0.01 | 0.90 | 8.98 (0.44) | 38.40 (0.97) | 0.67 (0.11) | 2.58 (0.40) |
| 3% | 0.01 | 0.95 | 7.80 (0.40) | 33.31 (1.00) | 0.43 (0.09) | 1.66 (0.34) |
| 8% | 0.001 | 0.90 | 25.82 (0.95) | 43.76 (0.98) | 1.07 (0.15) | 1.78 (0.25) |
| 8% | 0.001 | 0.95 | 22.73 (0.87) | 38.51 (0.95) | 0.52 (0.10) | 0.85 (0.16) |
| 8% | 0.01 | 0.90 | 22.97 (1.09) | 38.49 (1.26) | 0.87 (0.11) | 1.53 (0.21) |
| 8% | 0.01 | 0.95 | 19.52 (0.95) | 32.65 (1.12) | 0.55 (0.09) | 0.97 (0.16) |
| 16% | 0.001 | 0.90 | 61.03 (1.63) | 53.38 (0.65) | 1.35 (0.17) | 1.27 (0.16) |
| 16% | 0.001 | 0.95 | 53.90 (1.41) | 47.20 (0.60) | 0.68 (0.12) | 0.65 (0.12) |
| 16% | 0.01 | 0.90 | 57.87 (1.57) | 50.60 (0.65) | 1.27 (0.16) | 1.19 (0.16) |
| 16% | 0.01 | 0.95 | 51.08 (1.36) | 44.73 (0.59) | 0.78 (0.12) | 0.75 (0.12) |

**Supplementary Table 2.** Calibration of h2rare $\rho$-CIs with respect to the number of causal genes, proportion of causal variants ($p_{\text{causal}}$), and $\rho \in \{0.90, 0.95\}$ in simulations (chromosome 1, MAF > 0.5%, 1,083 protein-coding genes, cumulative $h^2_{\text{gene}} = 0.03$ ). "Underestimated" and "overestimated" refer to genes whose $\rho$-CIs lie below and above their true gene-level heritability, respectively. For each simulation setup, we report the average (and s.e.m.) of the number and percentage of underestimated/overestimated genes in 30 simulation replicates.