Supplementary Note

1 Proofs and derivations

1.1 Derivation of the regression equation

Regression equation:

$$\mathbb{E}\left[Z_i^2\right] = \sum_{c=1}^{C} Nl(i,c)\tau_c + \sum_{k=1}^{K} Nd(i,k)\omega_k + r_{ii}\sigma_e^2, \tag{1}$$

where $l(i,c) = \sum_{j=1}^{M} a_c(j) r_{ij}^2$ and $d(i,k) = \sum_{j=1}^{M}\sum_{j'=1}^{M} G_k(j,j') r_{ij} r_{ij'}$.

Proof. Let $\mathbf{X}_i = [X_{1i}, \cdots, X_{Ni}]^T$ be the i-th column of $\mathbf{X}$. The summary association statistic for SNP i satisfies

$$Z_i^2 = \frac{1}{N}\left(\sum_{n=1}^{N} y_n X_{ni}\right)^2 = \frac{1}{N}\left(\mathbf{X}_i^T\mathbf{y}\right)^2 = \frac{1}{N}\left[\mathbf{X}_i^T(\mathbf{X}\boldsymbol{\beta}+\mathbf{e})\right]^2 = \frac{1}{N}\left(\mathbf{X}_i^T\mathbf{X}\boldsymbol{\beta}+\mathbf{X}_i^T\mathbf{e}\right)^2. \tag{2}$$

Next, the expectation of Z_i^2 can be written as

$$\mathbb{E}\left[Z_i^2\right] = \mathbb{E}\left[\frac{1}{N}\left(\mathbf{X}_i^T\mathbf{X}\boldsymbol{\beta}+\mathbf{X}_i^T\mathbf{e}\right)^2\right] \tag{3}$$

$$\overset{\boldsymbol{\beta},\mathbf{e}\ \text{indpt.}}{=} \mathbb{E}\left[\frac{1}{N}\left(\mathbf{X}_i^T\mathbf{X}\boldsymbol{\beta}\right)^2 + \frac{1}{N}\left(\mathbf{X}_i^T\mathbf{e}\right)^2\right] \tag{4}$$

$$= \mathbb{E}\left[\frac{1}{N}\mathbf{X}_i^T\mathbf{X}\boldsymbol{\beta}\boldsymbol{\beta}^T\mathbf{X}^T\mathbf{X}_i + \frac{1}{N}\mathbf{X}_i^T\mathbf{e}\mathbf{e}^T\mathbf{X}_i\right] \tag{5}$$

$$\overset{\text{linearity of expectation}}{=} \frac{1}{N}\mathbf{X}_i^T\mathbf{X}\mathbb{E}\left[\boldsymbol{\beta}\boldsymbol{\beta}^T\right]\mathbf{X}^T\mathbf{X}_i + \frac{1}{N}\mathbf{X}_i^T\mathbb{E}\left[\mathbf{e}\mathbf{e}^T\right]\mathbf{X}_i \tag{6}$$

$$\overset{Eq.\ (3)}{=} \frac{1}{N}\mathbf{X}_i^T\mathbf{X}\boldsymbol{\Sigma}\mathbf{X}^T\mathbf{X}_i + \frac{1}{N}\mathbf{X}_i^T\mathbf{X}_i\sigma_e^2. \tag{7}$$

Let $\mathbf{r}_i = \frac{1}{N}\mathbf{X}^T\mathbf{X}_i = [r_{i1}, \cdots, r_{iM}]^T$ be the signed LD between SNP i and other SNPs. We have

$$\mathbb{E}\left[Z_i^2\right] = N\mathbf{r}_i^T\boldsymbol{\Sigma}\mathbf{r}_i + r_{ii}\sigma_e^2. \tag{8}$$

Define the vector form of single-SNP annotation $\mathbf{a}_c = [a_c(1), \cdots, a_c(M)]^T$ and the matrix form of SNP-pair annotation $\mathbf{G}_k : [\mathbf{G}_k]_{ij} = G_k(i,j)$. Taking Eq. (4) into the above equation to have

$$\mathbb{E}\left[Z_i^2\right] = N\mathbf{r}_i^T\left(\sum_{c=1}^{C}\mathrm{diag}(\mathbf{a}_c)\tau_c + \sum_{k=1}^{K}\mathbf{G}_k\omega_k\right)\mathbf{r}_i + r_{ii}\sigma_e^2 \tag{9}$$

$$= \sum_{c=1}^{C} N\mathbf{r}_i^T\mathrm{diag}(\mathbf{a}_c)\mathbf{r}_i\tau_c + \sum_{k=1}^{K} N\mathbf{r}_i^T\mathbf{G}_k\mathbf{r}_i\omega_k + r_{ii}\sigma_e^2 \tag{10}$$

$$= \sum_{c=1}^{C} N\left(\sum_{j=1}^{M} a_c(j) r_{ij}^2\right)\tau_c + \sum_{k=1}^{K} N\left(\sum_{j=1}^{M}\sum_{j'=1}^{M} G_k(j,j') r_{ij} r_{ij'}\right)\omega_k + r_{ii}\sigma_e^2 \tag{11}$$

$$= \sum_{c=1}^{C} Nl(i,c)\tau_c + \sum_{k=1}^{K} Nd(i,k)\omega_k + r_{ii}\sigma_e^2 \tag{12}$$

□

1.2 Derivation of heritability

Heritability for binary single-SNP annotation c:

$$h^2(c) = \frac{1}{N}\sum_{n=1}^{N}\mathrm{Var}\left[\sum_{i\in a_c} X_{ni}\beta_i\right] = \sum_{i\in a_c}\sum_{c'=1}^{C} a_{c'}(i)\tau_{c'} + \sum_{i\in a_c}\sum_{j\in a_c}\sum_{k'=1}^{K} G_{k'}(i,j) r_{ij}\omega_{k'}. \tag{13}$$

Proof. Let $\mathbf{X}_n = [X_{n1}, \cdots, X_{nM}]^T$ be the n-th row of $\mathbf{X}$. Let $[\cdot]_{a_c}$ denote restricting the corresponding vector/matrix to elements in a_c.

$$h^2(c) = \frac{1}{N}\sum_{n=1}^{N} \mathrm{Var}\left[\sum_{i\in a_c} X_{ni}\beta_i\right] \tag{14}$$

$$= \frac{1}{N}\sum_{n=1}^{N} \mathrm{Var}\left[[\mathbf{X}_n]_{a_c}^T [\boldsymbol{\beta}]_{a_c}\right] \tag{15}$$

$$\overset{[\mathbf{X}_n]_{a_c}^T[\boldsymbol{\beta}]_{a_c} \text{is zero-mean}}{=} \frac{1}{N}\sum_{n=1}^{N} \mathbb{E}\left[[\mathbf{X}_n]_{a_c}^T [\boldsymbol{\beta}]_{a_c}[\boldsymbol{\beta}]_{a_c}^T [\mathbf{X}_n]_{a_c}\right] \tag{16}$$

$$= \frac{1}{N}\sum_{n=1}^{N} [\mathbf{X}_n]_{a_c}^T \mathbb{E}\left[[\boldsymbol{\beta}]_{a_c}[\boldsymbol{\beta}]_{a_c}^T\right][\mathbf{X}_n]_{a_c} \tag{17}$$

$$= \frac{1}{N}\sum_{n=1}^{N} [\mathbf{X}_n]_{a_c}^T [\boldsymbol{\Sigma}]_{a_c}[\mathbf{X}_n]_{a_c} \tag{18}$$

$$= \frac{1}{N}\sum_{n=1}^{N} \mathrm{tr}\left([\mathbf{X}_n]_{a_c}^T [\boldsymbol{\Sigma}]_{a_c}[\mathbf{X}_n]_{a_c}\right) \tag{19}$$

$$\overset{\text{cyclic property of trace}}{=} \frac{1}{N}\sum_{n=1}^{N} \mathrm{tr}\left([\boldsymbol{\Sigma}]_{a_c}[\mathbf{X}_n]_{a_c}[\mathbf{X}_n]_{a_c}^T\right) \tag{20}$$

$$\overset{\text{linearity of trace}}{=} \mathrm{tr}\left(\frac{1}{N}\sum_{n=1}^{N} [\boldsymbol{\Sigma}]_{a_c}[\mathbf{X}_n]_{a_c}[\mathbf{X}_n]_{a_c}^T\right) \tag{21}$$

$$\overset{\text{linearity of dot product}}{=} \mathrm{tr}\left([\boldsymbol{\Sigma}]_{a_c}\left(\frac{1}{N}\sum_{n=1}^{N} [\mathbf{X}_n]_{a_c}[\mathbf{X}_n]_{a_c}^T\right)\right) \tag{22}$$

$$= \mathrm{tr}\left([\boldsymbol{\Sigma}]_{a_c}[\mathbf{R}]_{a_c}\right), \tag{23}$$

where for the last equation, we note that $\frac{1}{N}\sum_{n=1}^{N}\mathbf{X}_n\mathbf{X}_n^T = \mathbf{R}$, the LD matrix whose ij-th element is equal to r_{ij}.

Define the vector form of single-SNP annotation $\mathbf{a}_c = [a_c(1), \cdots, a_c(M)]^T$ and the matrix form of SNP-pair annotation $\mathbf{G}_k : [\mathbf{G}_k]_{ij} = G_k(i,j)$. Furthermore,

$$h^2(c) = \mathrm{tr}\left([\boldsymbol{\Sigma}]_{a_c}[\mathbf{R}]_{a_c}\right) \tag{24}$$

$$\overset{\boldsymbol{\Sigma} \text{ is symmetric}}{=} \mathrm{tr}\left([\boldsymbol{\Sigma}]_{a_c}^T[\mathbf{R}]_{a_c}\right) \tag{25}$$

$$\overset{\text{Eq. (4)}}{=} \mathrm{tr}\left(\left[\sum_{c'=1}^{C}\mathrm{diag}(\mathbf{a}_{c'})\tau_{c'} + \sum_{k'=1}^{K}\mathbf{G}_{k'}\omega_{k'}\right]_{a_c}^T [\mathbf{R}]_{a_c}\right) \tag{26}$$

$$\overset{\text{linearity}}{=} \sum_{c'=1}^{C}\mathrm{tr}\left([\mathrm{diag}(\mathbf{a}_{c'})\tau_{c'}]_{a_c}^T[\mathbf{R}]_{a_c}\right) + \sum_{k'=1}^{K}\mathrm{tr}\left([\mathbf{G}_{k'}\omega_{k'}]_{a_c}^T[\mathbf{R}]_{a_c}\right) \tag{27}$$

$$\overset{r_{ii}=1}{=} \sum_{i\in a_c}\sum_{c'=1}^{C} a_{c'}(i)\tau_{c'} + \sum_{i\in a_c}\sum_{j\in a_c}\sum_{k'=1}^{K} G_{k'}(i,j)r_{ij}\omega_{k'} \tag{28}$$

□

References

1. Hilary K Finucane, Brendan Bulik-Sullivan, Alexander Gusev, Gosia Trynka, Yakir Reshef, Po-Ru Loh, Verneri Anttila, Han Xu, Chongzhi Zang, Kyle Farh, et al. Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nature genetics*, 47(11):1228, 2015.

Supplementary Tables

See Supplementary Excel file

Supplementary Table 1. GWAS diseases and complex traits. We report the name, identifier, indication of 29 independent traits, and number of samples for 70 diseases/traits analyzed in the paper. For each disease/trait, we also report estimates of heritability, heritability SE, and z-score for nonzero heritability from LDSPEC with the baseline-SP model.

See Supplementary Excel file

Supplementary Table 2. Main single-SNP annotations. We report the name, identifier, type, number of common SNPs (MAF$\geq$5%), number of low-frequency SNPs (0.5%$\leq$MAF$<$5%), reference, source, and version of baseline model for main 45 single-SNP annotations in the baseline-SP model.

See Supplementary Excel file

Supplementary Table 3. Single-SNP annotations in baseline-SP. We report the name, type, and number of SNPs for the 165 single-SNP annotations in the baseline-SP model.

See Supplementary Excel file

Supplementary Table 4. Main SNP-pair annotations. We report the name, identifier, type, and description for 34 main SNP-pair annotations in the baseline-SP model. For each SNP-pair annotation, we also report number of SNP pairs and average distance (combined across common negative-LD, low-frequency negative-LD, common positive-LD, low-frequency positive-LD), and we report average LD (for common negative-LD, low-frequency negative-LD, common positive-LD, low-frequency positive-LD, separately).

See Supplementary Excel file

Supplementary Table 5. SNP-pair annotations in baseline-SP. We report the name and number of SNP pairs for the 136 SNP-pair annotations in the baseline-SP model.

See Supplementary Excel file

Supplementary Table 6. Correlation of LD and directional LD scores. We report the correlation across 14,820,648 SNPs between 165 single-SNP annotations and 136 SNP-pair annotations in the baseline-SP model.

See Supplementary Excel file

Supplementary Table 7. Simulation parameters. We report the simulation name, term, and values for all simulations performed in the paper. "h2g" denotes target SCV (may be different from heritability in causal simulations), "p_causal" denotes proportion of causal SNPs, and "alpha" denotes the MAF-dependent genetic architecture, i.e., scaling the per-SNP heritability by $[\mathrm{MAF}(1-\mathrm{MAF})]^{(1+\alpha)}$.

See Supplementary Excel file

Supplementary Table 8. Numerical results for null simulations in Figure 1a. We report the annotation name, term, term identifier, and true value for all estimates across the 165 single-SNP annotations and 136 SNP-pair annotations in the baseline-SP model. For each term and each annotation, we report LDSPEC estimates aggregated across the 50 simulation replicates: jackknife SE ($\sqrt{\frac{1}{50}\sum_{i=1}^{50}\text{JNSE}_i^2}/\sqrt{50}$), empirical mean (mean across 50 estimates), empirical SE (SD across 50 estimates divided by $\sqrt{50}$), empirical p-value (assuming normal distribution), and empirical FWER (P<0.05/165 for single-SNP annotations and P<0.05/136 for SNP-pair annotations).

See Supplementary Excel file

Supplementary Table 9. Numerical results for causal simulations in Figure 1b. We report the annotation name, term, term identifier, and true value for all estimates across the 165 single-SNP annotations and 136 SNP-pair annotations in the baseline-SP model. For each term and each annotation, we report LDSPEC estimates aggregated across the 50 simulation replicates: jackknife SE ($\sqrt{\frac{1}{50}\sum_{i=1}^{50}\text{JNSE}_i^2}/\sqrt{50}$), empirical mean (mean across 50 estimates), empirical SE (SD across 50 estimates divided by $\sqrt{50}$), empirical p-value (assuming normal distribution), and empirical FWER (P<0.05/165 for single-SNP annotations and P<0.05/136 for SNP-pair annotations).

See Supplementary Excel file

Supplementary Table 10. LDSPEC results for single-SNP annotations and 70 diseases/traits. We report trait identifier, annotation identifier, annotation type, and number of SNPs for 165 single-SNP annotations. We report point estimates, SE, and p-values of τ, heritability, SCV, heritability enrichment, and heritability shrinkage for 165 single-SNP annotations and 70 diseases/traits.

See Supplementary Excel file

Supplementary Table 11. LDSPEC results for SNP-pair annotations and 70 diseases/traits. We report trait identifier, annotation identifier, and number of SNP pairs for 136 SNP-pair annotations. We report point estimates, SE, and p-values of ω, total SNP-pair effect covariance, ξ, total excess SNP-pair effect covariance, and ξ^* for 70 diseases/traits and 136 SNP-pair annotations.

See Supplementary Excel file

Supplementary Table 12. Meta-analyzed LDSPEC results for single-SNP annotations. We report meta-analyzed point estimates, SE, and p-values of τ, heritability, SCV, heritability enrichment, and heritability shrinkage for 165 single-SNP annotations. The meta-analysis was performed across 29 independent diseases/traits.

See Supplementary Excel file

Supplementary Table 13. Meta-analyzed LDSPEC results for SNP-pair annotations. We report meta-analyzed point estimates, SE, and p-values of ω, total SNP-pair effect covariance, ξ, total excess SNP-pair effect covariance, and ξ^* for 136 SNP-pair annotations. The meta-analysis was performed across 29 independent diseases/traits.

See Supplementary Excel file

Supplementary Table 14. Numerical results for Figure 2. We report annotation name, ξ estimate, SE of ξ estimate, p-value of ξ estimate, and FWER of ξ estimate for low-frequency negative-LD, common negative-LD, low-frequency positive-LD, and common positive-LD SNP-pair annotations in Figure 2, respectively.

See Supplementary Excel file

Supplementary Table 15. Jacknife-estimated differences for comparisons in Figure 2. We report annotation name, first stratum, second stratum, estimated difference, SE, p-value, and FWER for each comparison.

See Supplementary Excel file

Supplementary Table 16. Numerical results for Figure 3. We report annotation name, ξ^* estimate, SE of ξ^* estimate, p-value of ξ^* estimate, and FWER of ξ estimate for the 0-100bp and 0-1kb common positive-LD, low-frequency positive-LD, common negative-LD, and low-frequency negative-LD SNP-pair annotations, respectively.

See Supplementary Excel file

Supplementary Table 17. Jacknife-estimated differences for comparisons in Figure 3. We report annotation name, first stratum, second stratum, estimated difference, SE, p-value, and FWER for each comparison.

See Supplementary Excel file

Supplementary Table 18. Numerical results for Figure 4. We report the annotation name, heritability enrichment estimate, SE of heritability enrichment estimate, ξ^* estimate, and SE of ξ^* estimate for SNP-pair annotations in Figure 4.

See Supplementary Excel file

Supplementary Table 19. Heterogeneity across traits. We report the chi-square statistic, p-value, within-trait variance, between-trait variance, variance ratio (within over between), FWER (across 136 SNP-pair annotations tested), and FDR (across 136 SNP-pair annotations tested).

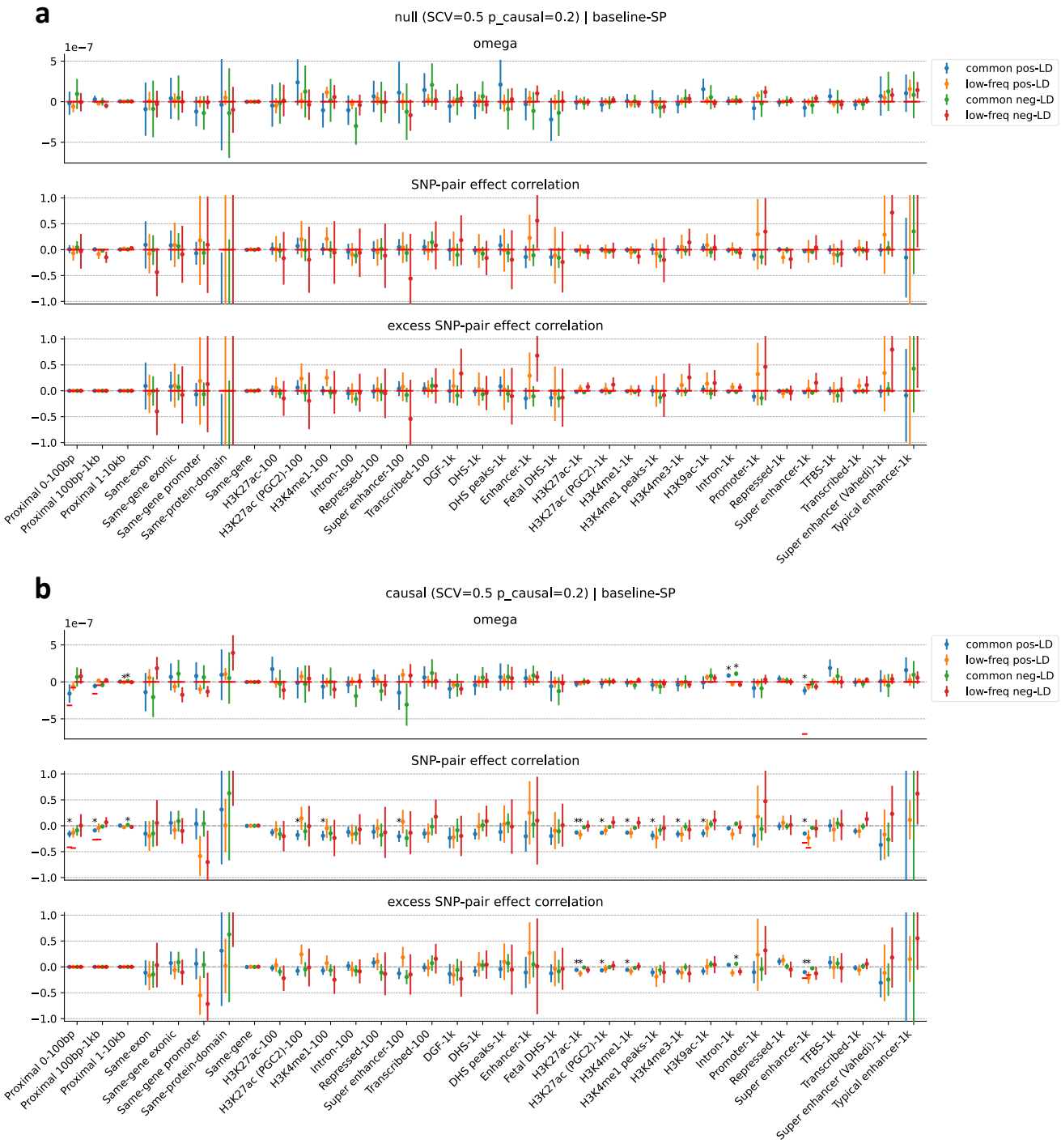
See Supplementary Excel file

Supplementary Table 20. Numerical results for Figure 5. We report the trait name, heritability estimate, SE of heritability estimate, SCV estimate, SE of SCV estimate, heritability shrinkage estimate, and SE of heritability shrinkage estimate for 70 diseases/traits.

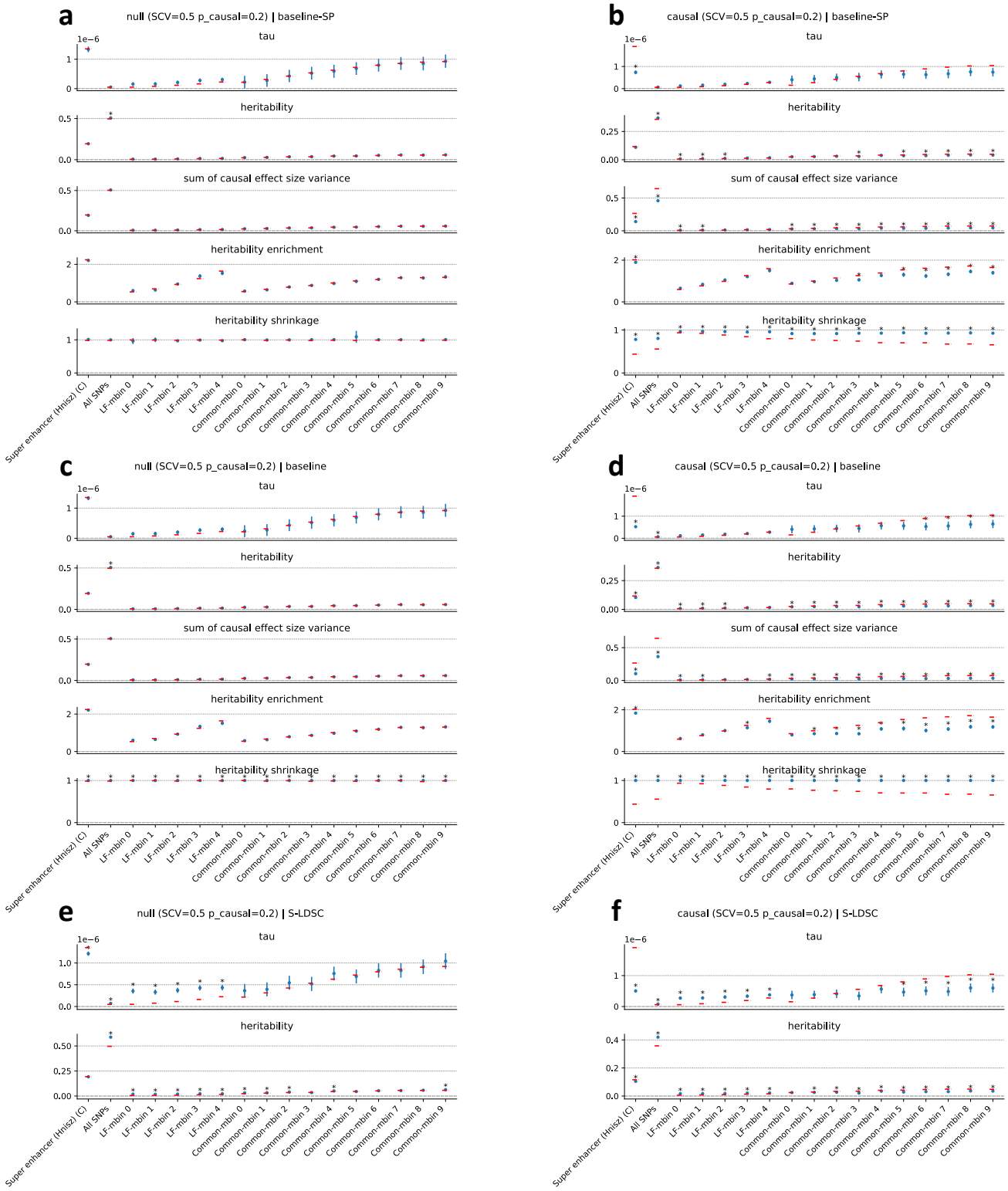
See Supplementary Excel file

Supplementary Table 21. Numerical results for Figure 6. We report the distance bin, MAF bin, LD bin, ξ estimate, and SE of ξ estimate for SNP-pair categories in Figure 6.

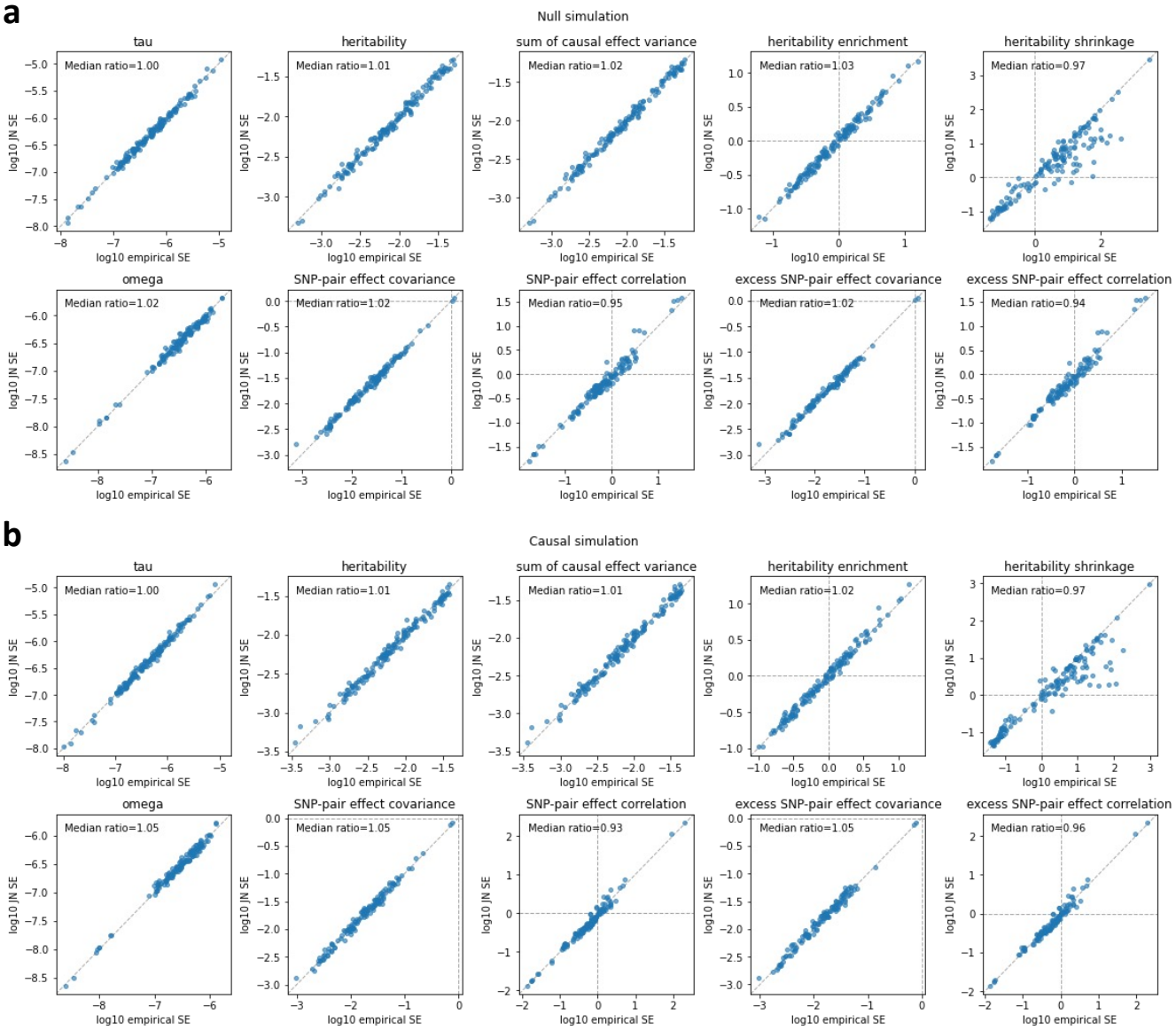
Supplementary Figures



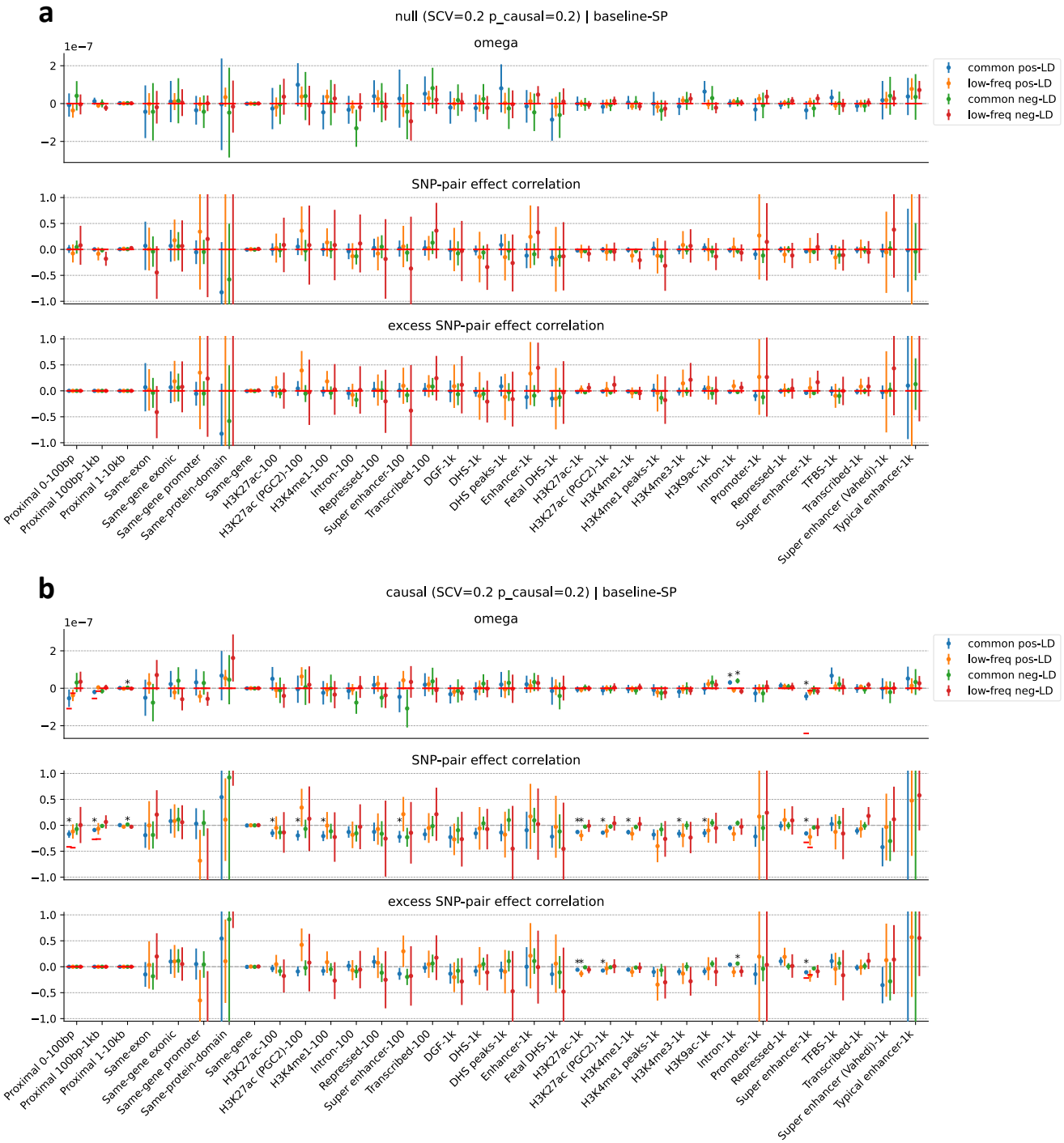
Supplementary Figure 1. Additional results of estimates for SNP-pair annotations in null and casual simulations in Figure 1. We report estimates of ω, ξ, and ξ^* for 136 SNP-pair annotations in the baseline-SP model. **(a)** for null simulations and **(b)** for causal simulations. Error bars denote 95% confidence intervals around the mean of 50 simulation replicates; "*" denotes statistical significance after multiple testing correction (P<0.05/136). Red horizontal lines represent the true simulated values for SNP-pair annotations whose true values are available.



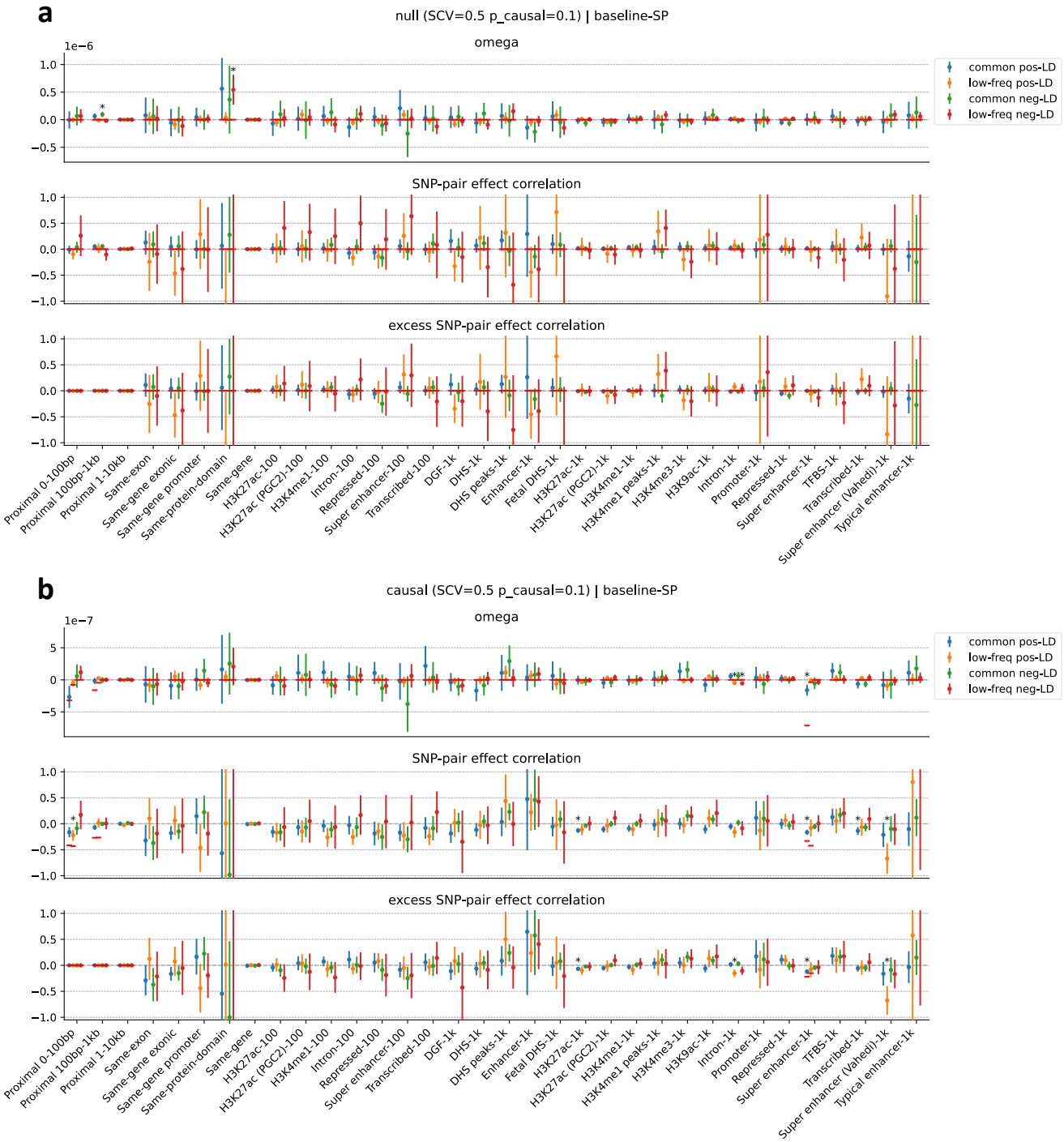
Supplementary Figure 2. Additional results of estimates for single-SNP annotations in null and casual simulations in Figure 1. We report estimates of τ, heritability, SCV, heritability enrichment, and heritability shrinkage for 17 binary single-SNP annotations whose true values for all 5 terms are available. **(a)** for null simulations and **(b)** for causal simulations. We also report the corresponding estimates using LDSPEC + baseline (without SNP-pair annotations) in panels c,d, and corresponding estimates (τ and heritability) using S-LDSC[1] + baseline (without SNP-pair annotations) in panels e,f. Error bars denote 95% confidence intervals around the mean of 50 simulation replicates; "*" denotes statistically significantly different from the true values after multiple testing correction (P<0.05/165). Red horizontal lines represent the true values.



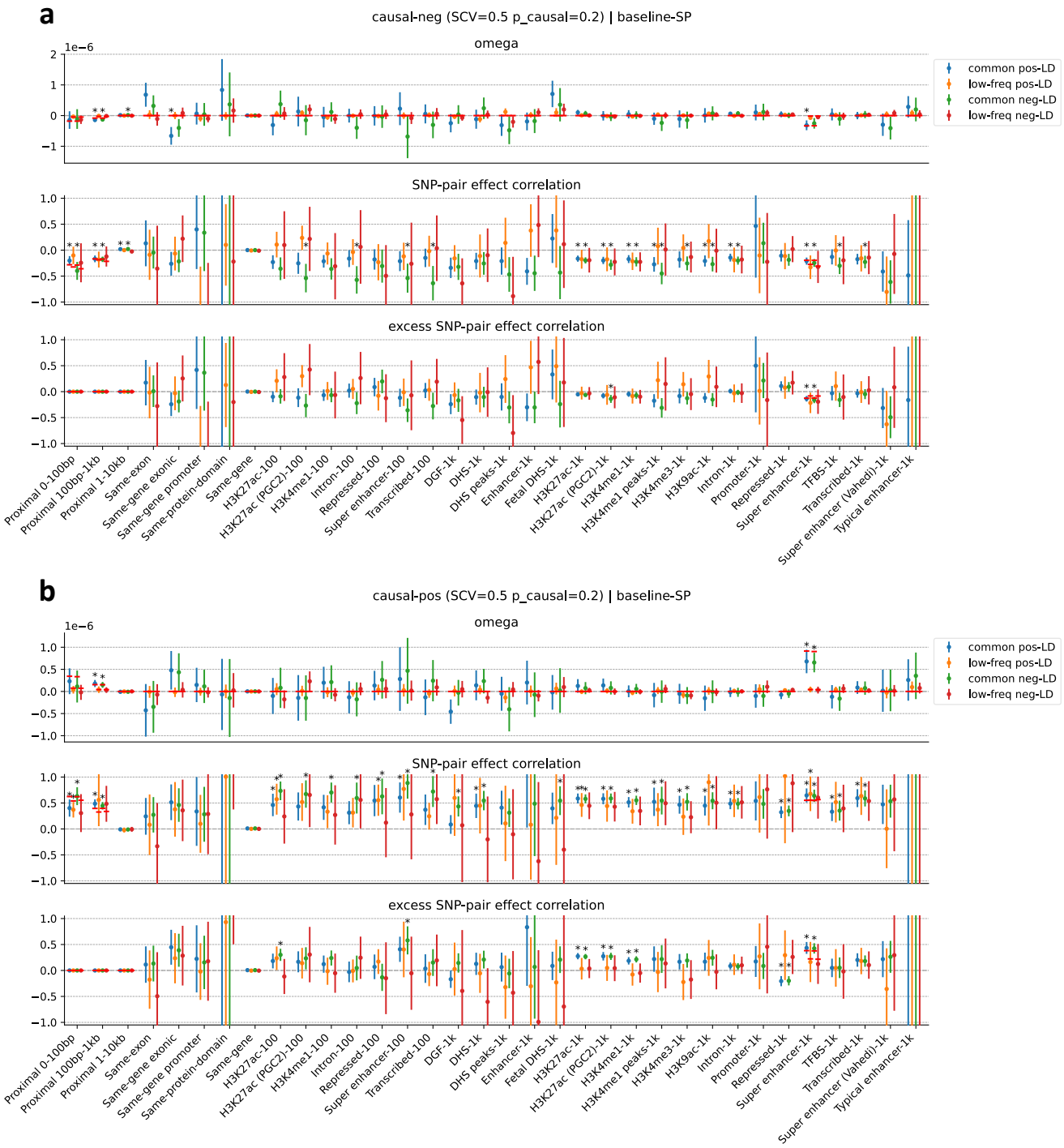
Supplementary Figure 3. Calibration of CIs for null and causal simulations in Figure 1. Results are shown for estimates of τ, heritability, SCV, heritability enrichment, heritability shrinkage, ω, SNP-pair effect covariance, ξ, excess SNP-pair effect covariance, and ξ^*, respectively. **(a)** for null simulations and **(b)** for causal simulations. Each point represents an annotation, x-axis represents the $\log 10$ empirical SE (SD of estimates across simulation replicates), and y-axis represents the $\log 10$ jackknife SE ($\sqrt{\frac{1}{50}\sum_{i=1}^{50} \mathrm{JNSE}_i^2}$). The median of ratios between jackknife SE and empirical SE across annotations is provided in the figure annotation. We note that the p-value of ξ is based on estimates of SNP-pair effect covariance, and the p-value of ξ^* is based on estimates of excess SNP-pair effect covariance (Methods).



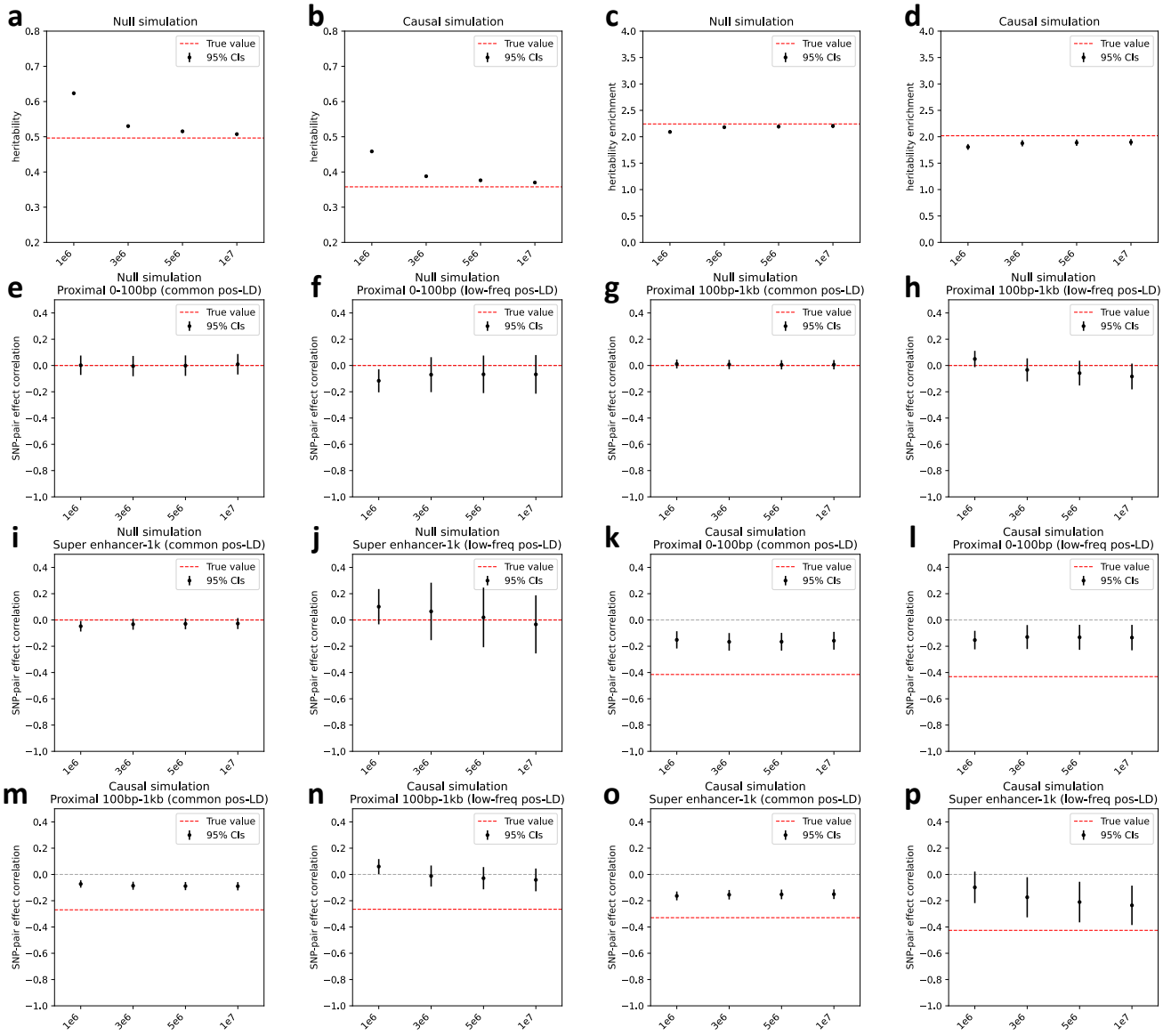
Supplementary Figure 4. Null and causal simulations with a lower value of SCV. (a) Null simulations with SCV of 0.2 (instead of 0.5) and causal SNP proportion of 0.2. **(b)** Causal simulations with SCV of 0.2 (instead of 0.5) and causal SNP proportion of 0.2. We report estimates of ω, ξ, and ξ^* for 136 SNP-pair annotations in the baseline-SP model. Error bars denote 95% confidence intervals around the mean of 50 simulation replicates; "*" denotes statistical significance after multiple testing correction (P<0.05/136). Red horizontal lines represent the true simulated values for SNP-pair annotations whose true values are available.



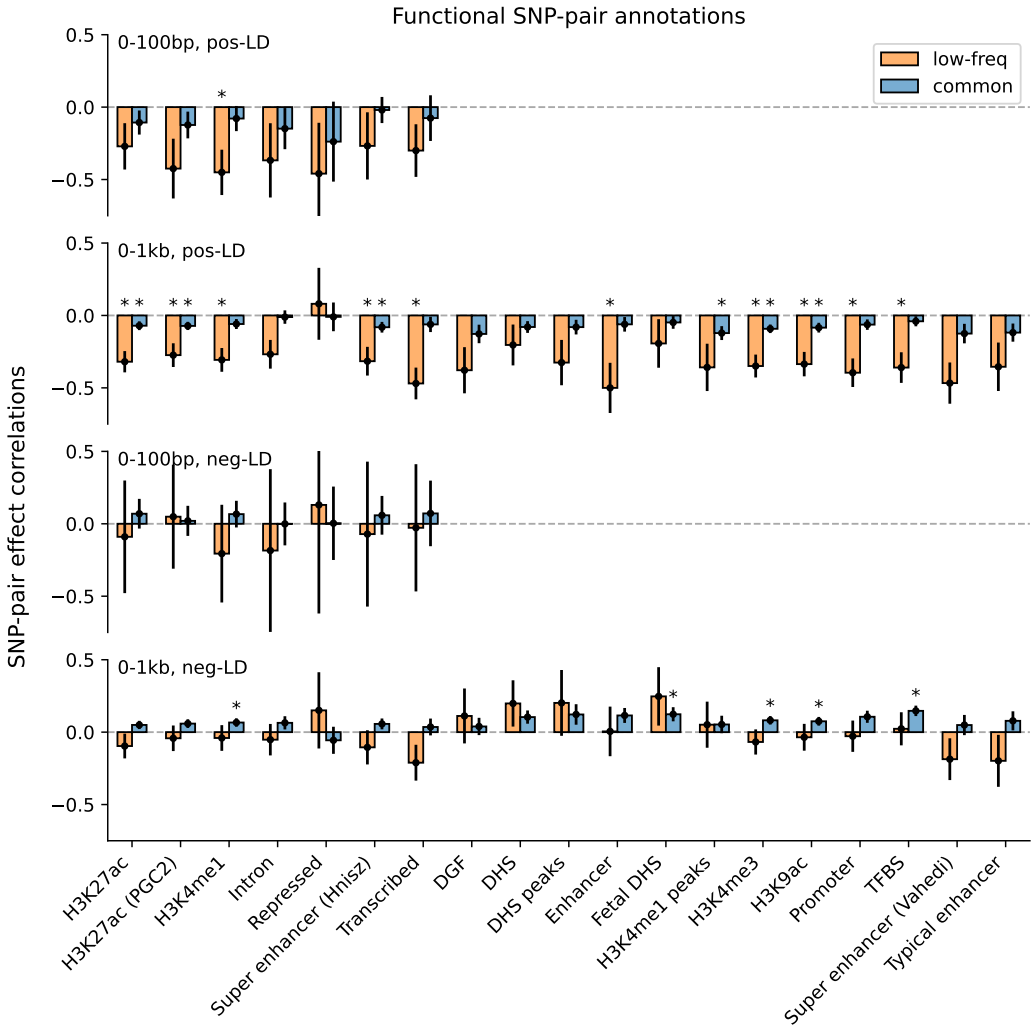
Supplementary Figure 5. Null and causal simulations with a lower value of causal SNP proportion. **(a)** Null simulations with SCV of 0.5 and causal SNP proportion of 0.1 (instead of 0.2). **(b)** Causal simulations with SCV of 0.5 and causal SNP proportion of 0.1 (instead of 0.2). We report estimates of ω, ξ, and ξ^* for 136 SNP-pair annotations in the baseline-SP model. Error bars denote 95% confidence intervals around the mean of 50 simulation replicates; "*" denotes statistical significance after multiple testing correction (P<0.05/136). Red horizontal lines represent the true simulated values for SNP-pair annotations whose true values are available.



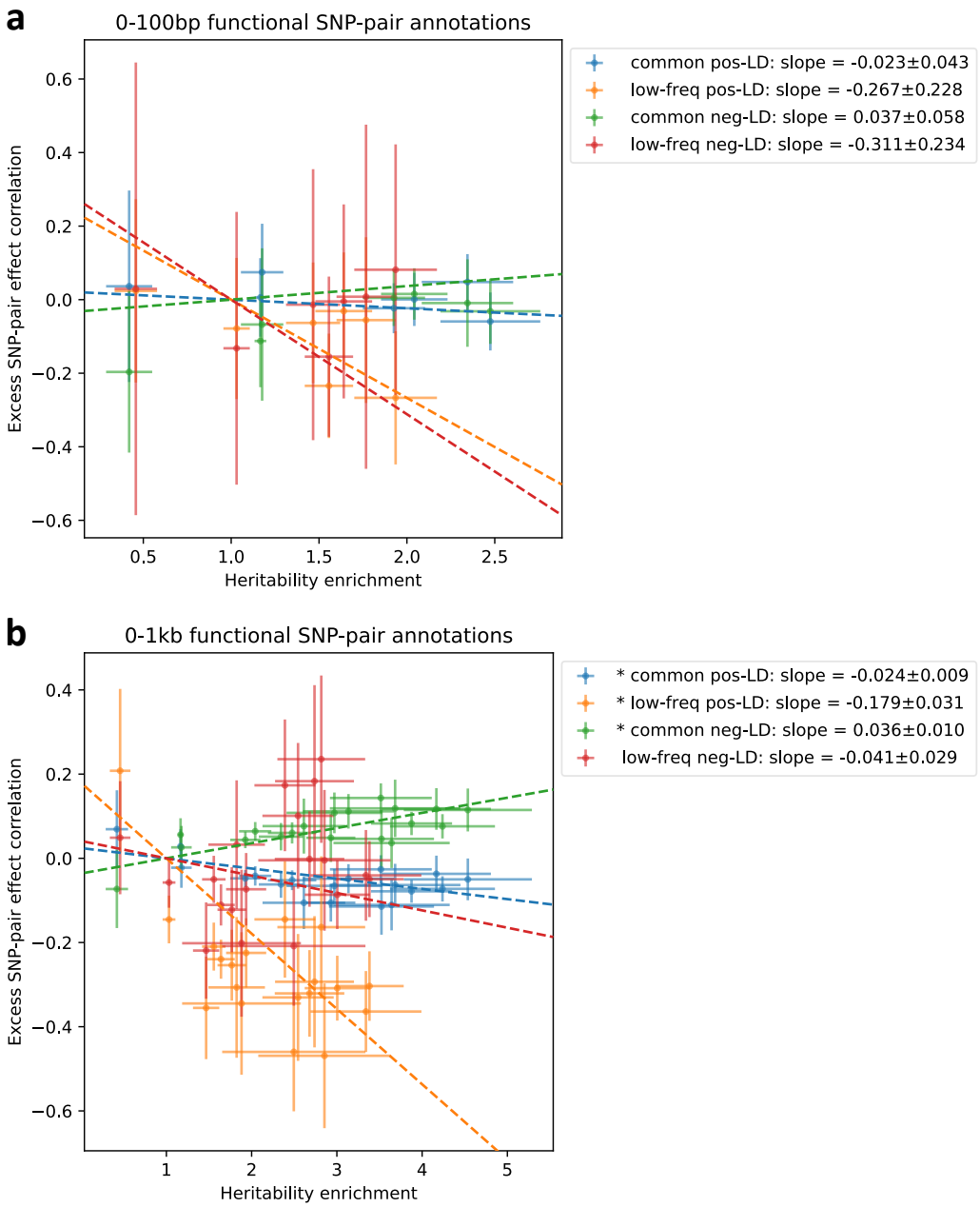
Supplementary Figure 6. Non-LD-stratified causal simulations. **(a)** Causal simulations with negative ω for both positive-LD and negative-LD SNP-pair annotations (vs. negative ω for only positive-LD SNP-pair annotations in primary simulations), SCV of 0.5, and causal SNP proportion of 0.2. **(b)** Causal simulations with positive ω for both positive-LD and negative-LD SNP-pair annotations (vs. negative ω for only positive-LD SNP-pair annotations in primary simulations), SCV of 0.5, and causal SNP proportion of 0.2. We report estimates of ω, ξ, and ξ^* for 136 SNP-pair annotations in the baseline-SP model. Error bars denote 95% confidence intervals around the mean of 50 simulation replicates; "*" denotes statistical significance after multiple testing correction (P<0.05/136). Red horizontal lines represent the true values for SNP-pair annotations whose true values are available.



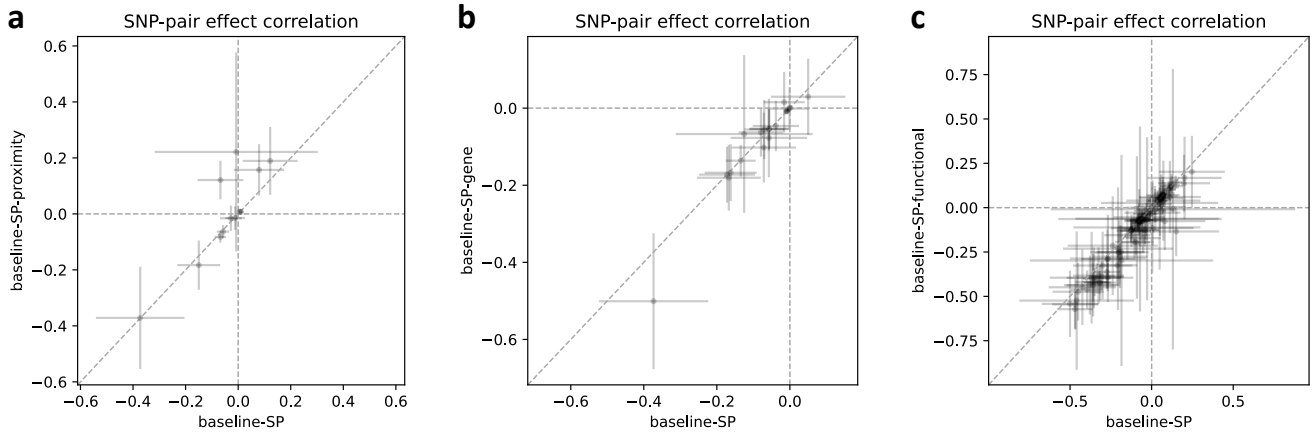
Supplementary Figure 7. Results for applying LDSPEC to the primary null and causal simulation data with LD and directional LD scores computed with smaller window sizes. We considered 3 smaller window sizes: 1Mb, 3Mb, 5Mb (instead of 10Mb). **(a-b)** Estimates of heritability in null and causal simulations. **(c-d)** Estimates of heritability enrichment for the common Super enhancer (Hnisz) annotation in null and causal simulations (simulated to have a positive τ in both null and causal simulations). **(e-p)** Estimates of ξ in null and causal simulations for the 6 SNP-pair annotations simulated to have negative ω in the causal simulation. Error bars denote 95% confidence intervals around the mean of 50 simulation replicates. Red horizontal lines represent the true simulated values.



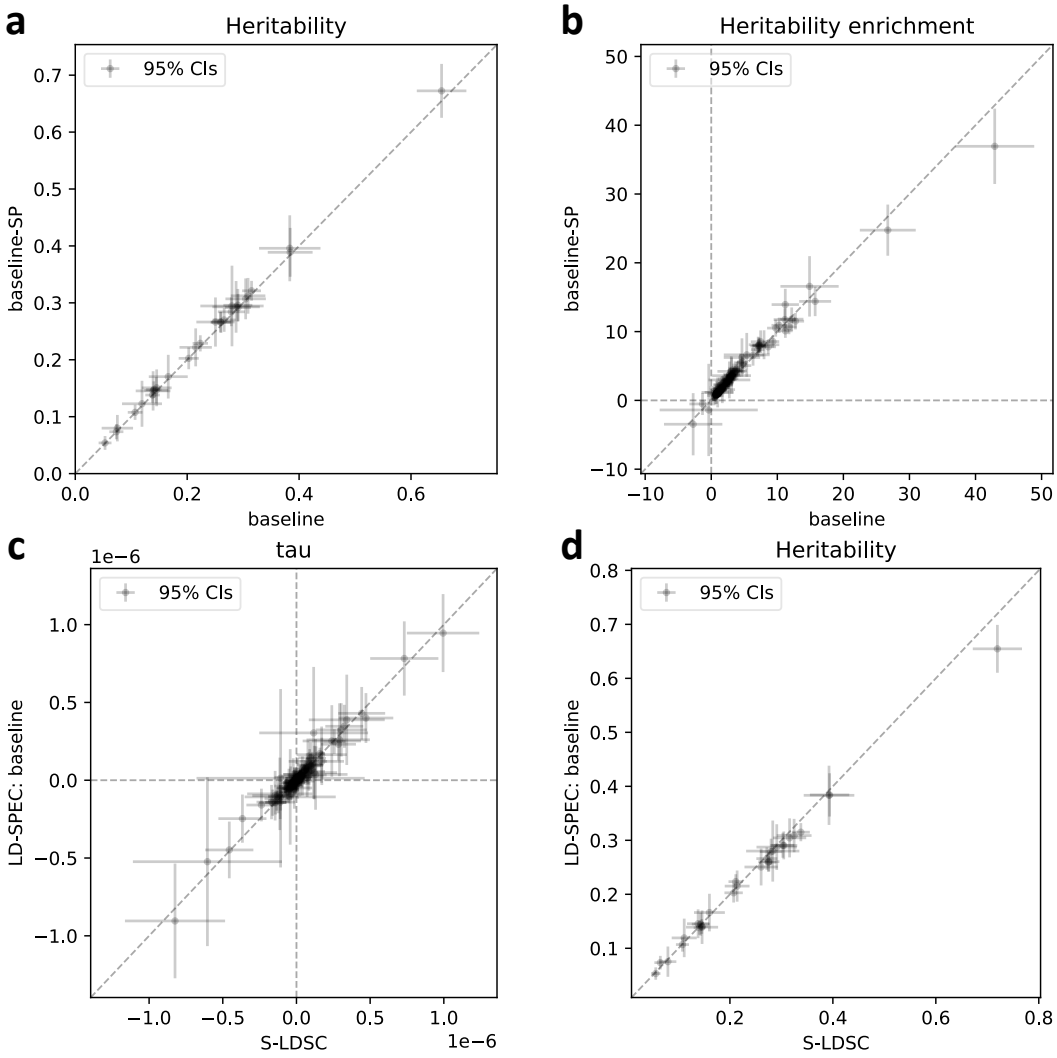
Supplementary Figure 8. Estimates of SNP-pair effect correlation (ξ) across 29 independent diseases and complex traits for functional SNP-pair annotations. We report meta-analyzed ξ estimates across 29 independent diseases for 7 functional 0-100bp and 19 functional 0-1kb SNP-pair annotations. Results are shown for the positive-LD 0-100bp, positive-LD 0-1kb, negative-LD 0-100bp, and negative-LD 0-1kb SNP-pair annotations in the 4 panels, respectively, and are stratified by MAF in each panel. Error bars denote 95% confidence intervals. "*" denotes statistical significance after multiple testing correction across estimates on the figure (P<0.05/136).



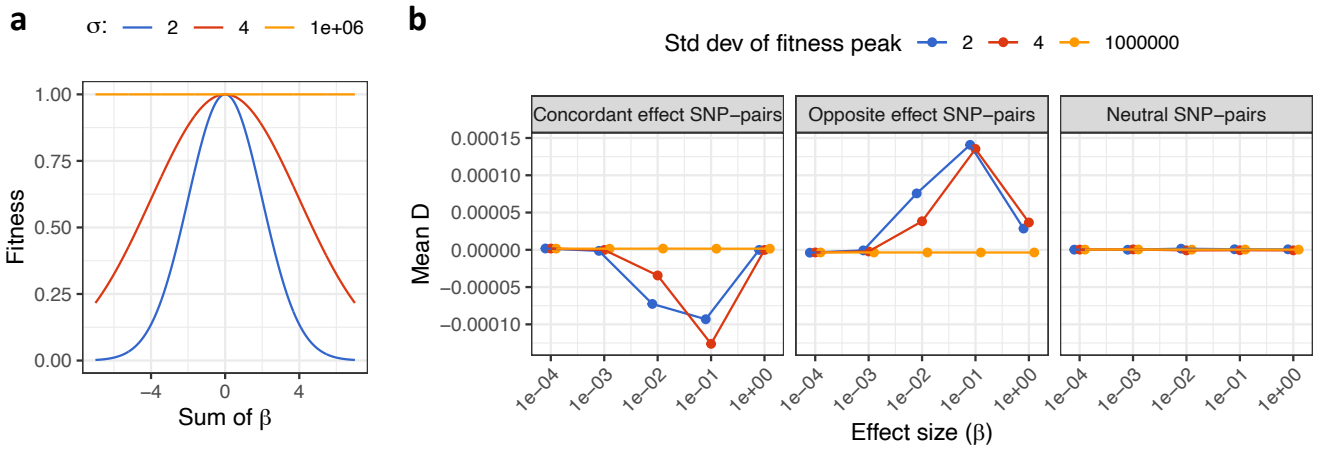
Supplementary Figure 9. Comparison between estimates of heritability enrichment and estimates of excess SNP-pair effect correlation estimate (ξ^*) across functional SNP-pair annotations. Panels a and b show results for functional 0-100bp and functional 0-1kb SNP-pair annotations, respectively. Each dot represents a SNP-pair annotation, x-axis represents the meta-analyzed estimate of heritability enrichment, and y-axis represents the meta-analyzed estimate of ξ^* (across 29 independent diseases/traits). In each panel, results are shown for the common positive-LD, low-frequency positive-LD, common negative-LD, and low-frequency positive-LD SNP-pair annotations separately. Error bars denote 95% confidence intervals. Regression slopes are provided with SEs in the figure legend; "*" denotes statistical significance after multiple testing correction (P<0.05/4).



Supplementary Figure 10. Comparison of ξ estimates of LDSPEC with alternative heritability models. (a) Comparison of meta-analyzed ξ estimates between the baseline-SP model (x-axis) and the baseline-SP-proximity model for 12 proximity-based SNP-pair annotations shared between the two models. **(b)** Comparison of meta-analyzed ξ estimates between the baseline-SP model (x-axis) and the baseline-SP-gene model for 20 gene-based SNP-pair annotations shared between the two models. **(c)** Comparison of meta-analyzed ξ estimates between the baseline-SP model (x-axis) and the baseline-SP-functional model for 104 functional SNP-pair annotations shared between the two models. Each dot represents a SNP-pair annotation. No difference between the x-value and y-value is statistically significant (P>0.05/136).



Supplementary Figure 11. Comparison of estimates for single-SNP annotations. **(a)** Comparison of heritability estimates using LDSPEC with the baseline model (x-axis) and the baseline-SP model (y-axis) for 29 independent diseases/traits. **(b)** Comparison of meta-analyzed heritability enrichment estimates using LDSPEC with the baseline model (x-axis) and the baseline-SP model (y-axis) for 165 single-SNP annotations. **(c)** Comparison of meta-analyzed τ estimates between S-LDSC[1] (x-axis) and LDSPEC (y-axis) (both using the baseline model) for 165 single-SNP annotations. **(d)** Comparison of heritability estimates between S-LDSC[1] (x-axis) and LDSPEC (y-axis) (both using the baseline model) for 29 independent diseases/traits. No difference between the x-value and y-value is statistically significant (P>0.05/29 for panels a,d, P>0.05/165 for panels b,c).



Supplementary Figure 12. Additional results for forward evolutionary simulations. (a) Fitness as a function of sum of causal effects (aggregate SNP effect on trait) under a stabilizing selection model. The 3 curves correspond to strong selection (width $\sigma = 2$), moderate selection (width $\sigma = 4$), and no selection (width $\sigma = 1 \times 10^6$). **(b)** LD measured by D as a function of effect size (β) for concordant-effect SNP pairs (left), opposite-effect SNP pairs (middle), and neutral SNP pairs (right, at least one zero-effect SNP in the SNP pair). Error bars denote 95% CIs.