# Supplementary Figures

**Figure S1. Individual trait analysis of coding and DHS variants.** Forest plot of % $h^2_g$ inferred for each trait over coding SNPs (top) and DHS SNPs (bottom). Total $h^2_g$ shown for each trait and SNP platform in second column.

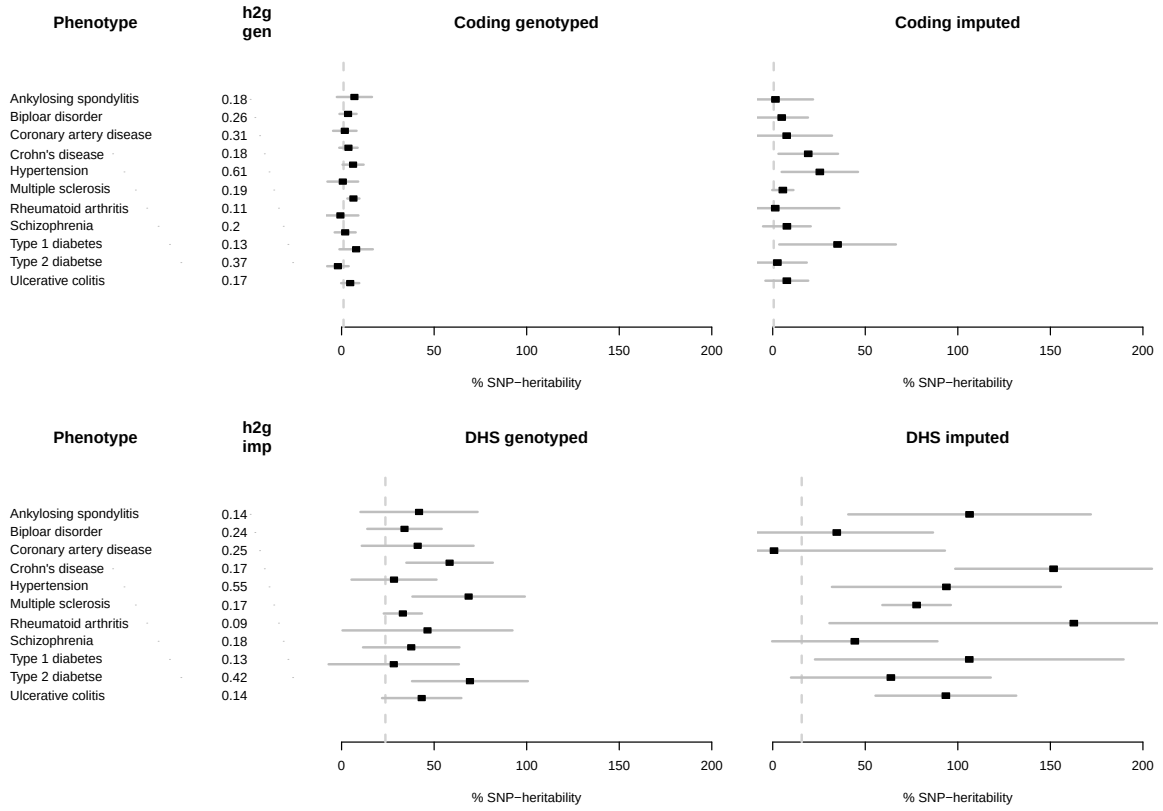


**Figure S2. Observed enrichment from simulated null architecture.** Distribution of enrichment estimate over 1000 simulations with three different disease architectures performed in genotyped SNPs (top) and imputed SNPs (bottom). All phenotypes simulated without category-specific enrichment, red line showing expected enrichment of 1.0×. Red asterisk indicates significant difference from expectation (by z-test, accounting for 36 comparisons).

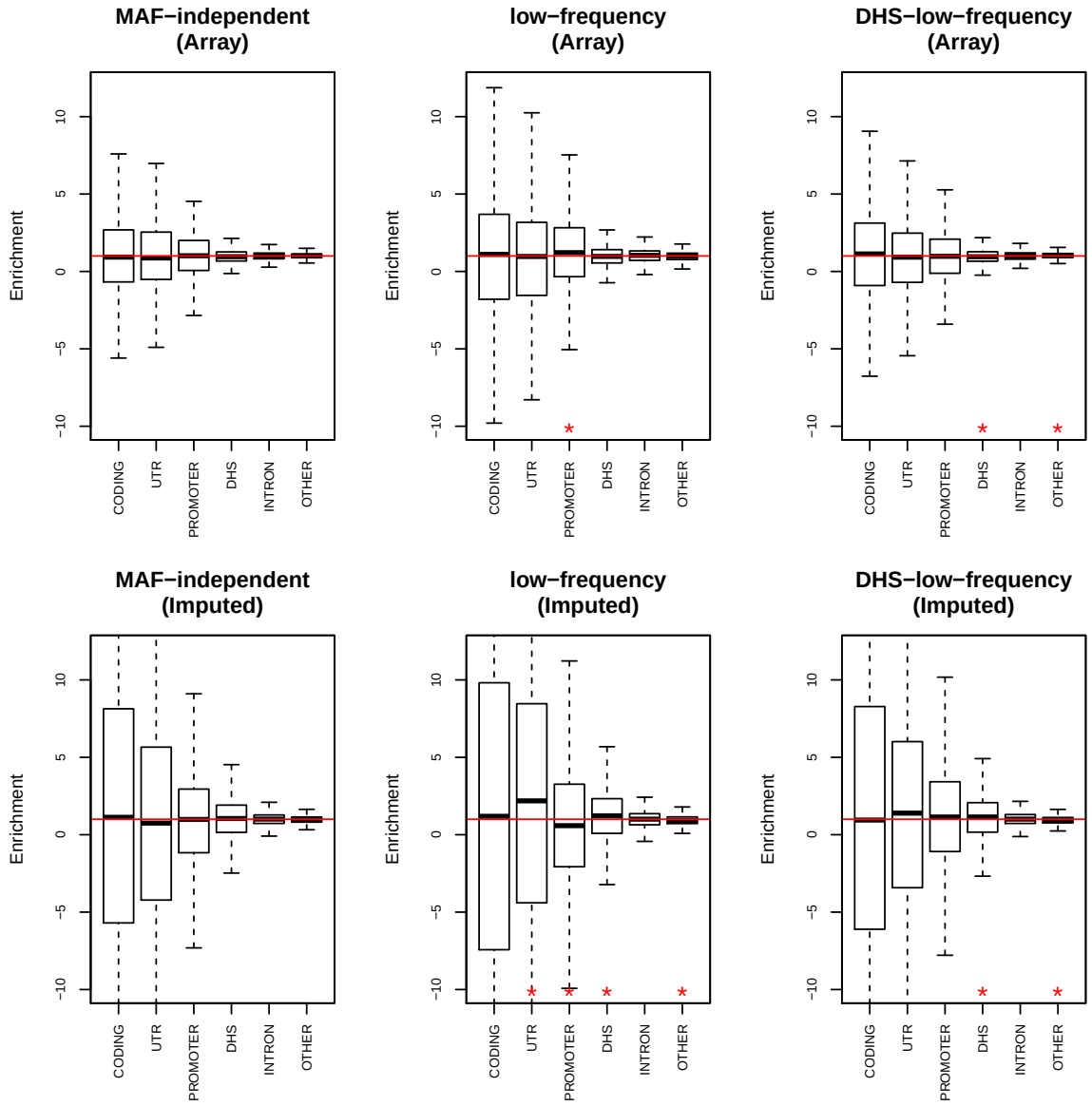


**Figure S3. Partitioning of $h^2_{\mathbf{g}}$ with imputed SNPs and MAF-independent causals.** Estimate of $h^2_{\mathrm{g}}$ from imputed SNPs in each functional category for phenotypes simulated from imputed SNPs with any frequency. Each section of the figure describes results from 200 simulations where all $h^2_{\mathrm{g}}$ was induced in the titular functional category (highlighted in blue).

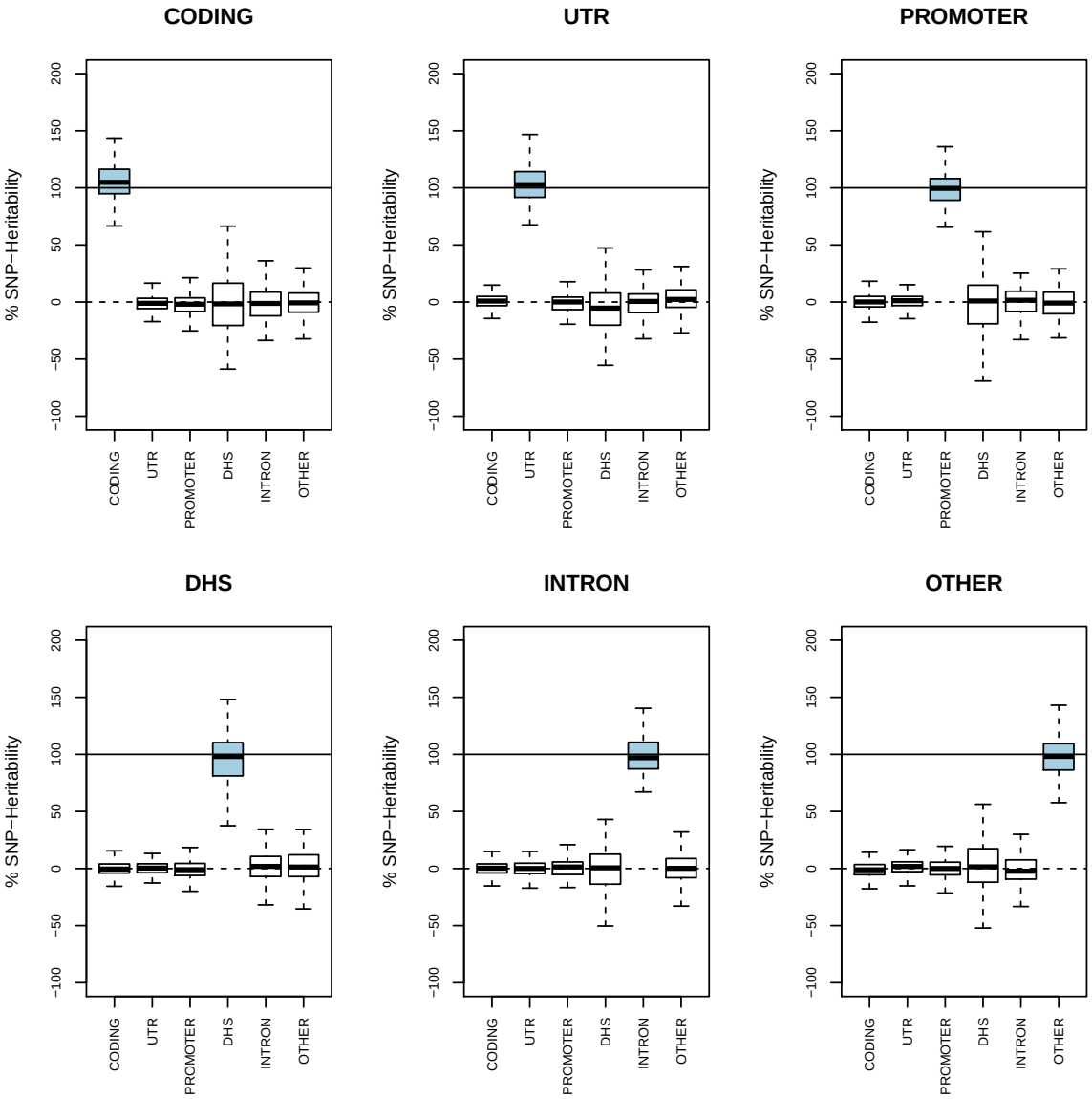


**Figure S4. Partitioning of $h^2_{\mathbf{g}}$ with true DHS and coding enrichment.** Inferred $h^2_{\mathrm{g}}$ enrichment from disease architecture mimicking observed DHS and coding enrichment in real data. Due to computational restrictions, enrichment was estimated from a random 15,000 samples of the 33,000 sample simulated GWAS cohort. Colored bars show the induced enrichment. Boxplots show the distribution of inferred enrichment over 50 trials.

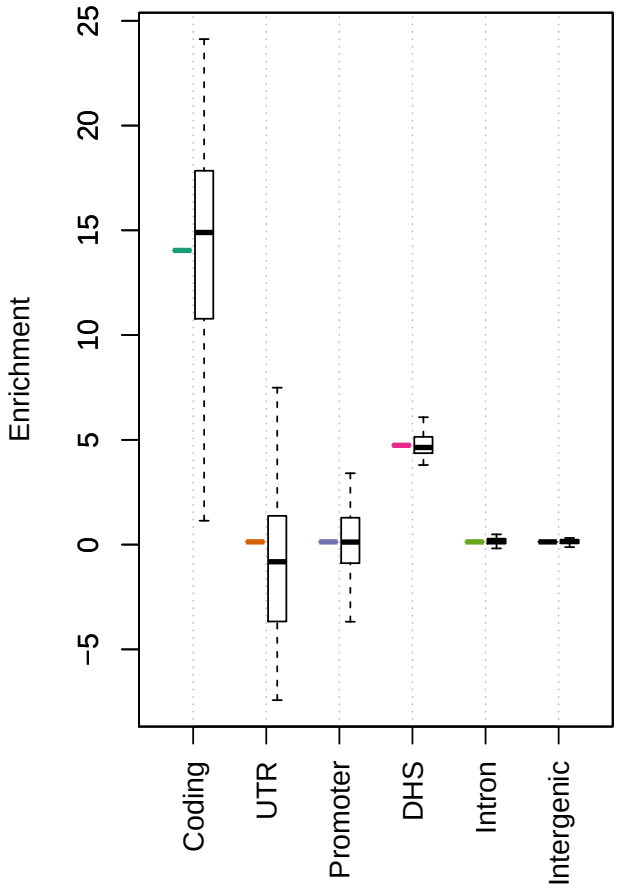


**Figure S5. Partitioning of $h^2_{\mathbf{g}}$ with imputed SNPs and low-frequency causals.** Estimate of $h^2_{\mathrm{g}}$ from imputed SNPs in each functional category for phenotypes simulated from imputed SNPs with MAF $< 0.05$. Each section of the figure describes results from 200 simulations where all $h^2_{\mathrm{g}}$ was induced in the titular functional category (highlighted in blue).

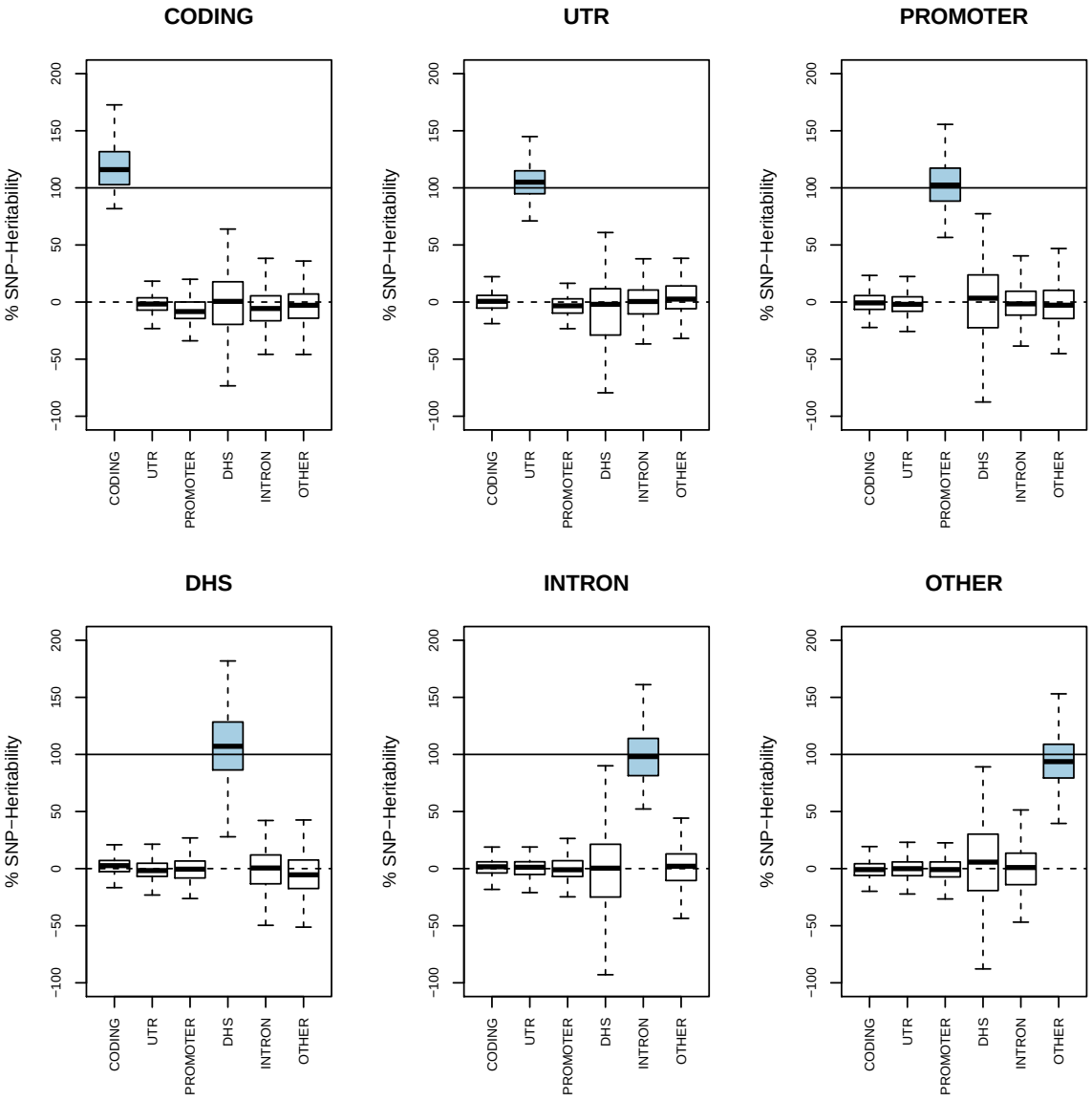


**Figure S6. Partitioning of $h_{\mathbf{g}}^2$ from causal variants at the DHS boundary.** Causal variants were sampled from non-DHS intronic and intergenic regions within 500bp (left) and 1000bp (right) of any DHS region boundary. Box-plots shown over 200 simulations with MAF-independent causal variants.

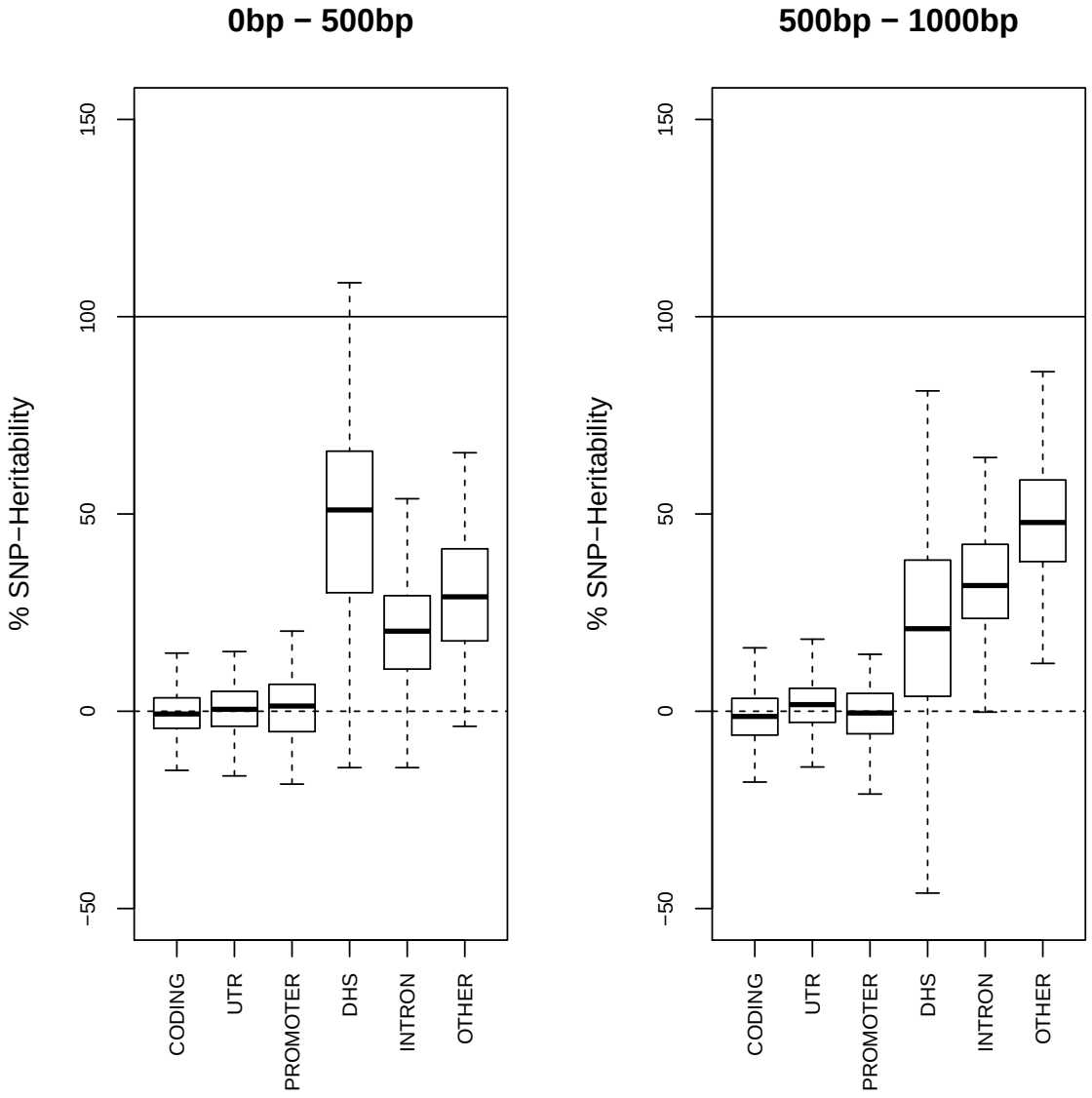


**Figure S7. P-value enrichment in 11 traits.** Fold-enrichment of p-values meeting a given significance threshold in each functional category. Enrichment plotted for all thresholds that contain at least 100 SNPs. Average over 11 traits shown in top-left for thresholds observed in all traits, with shaded region corresponding to standard error.

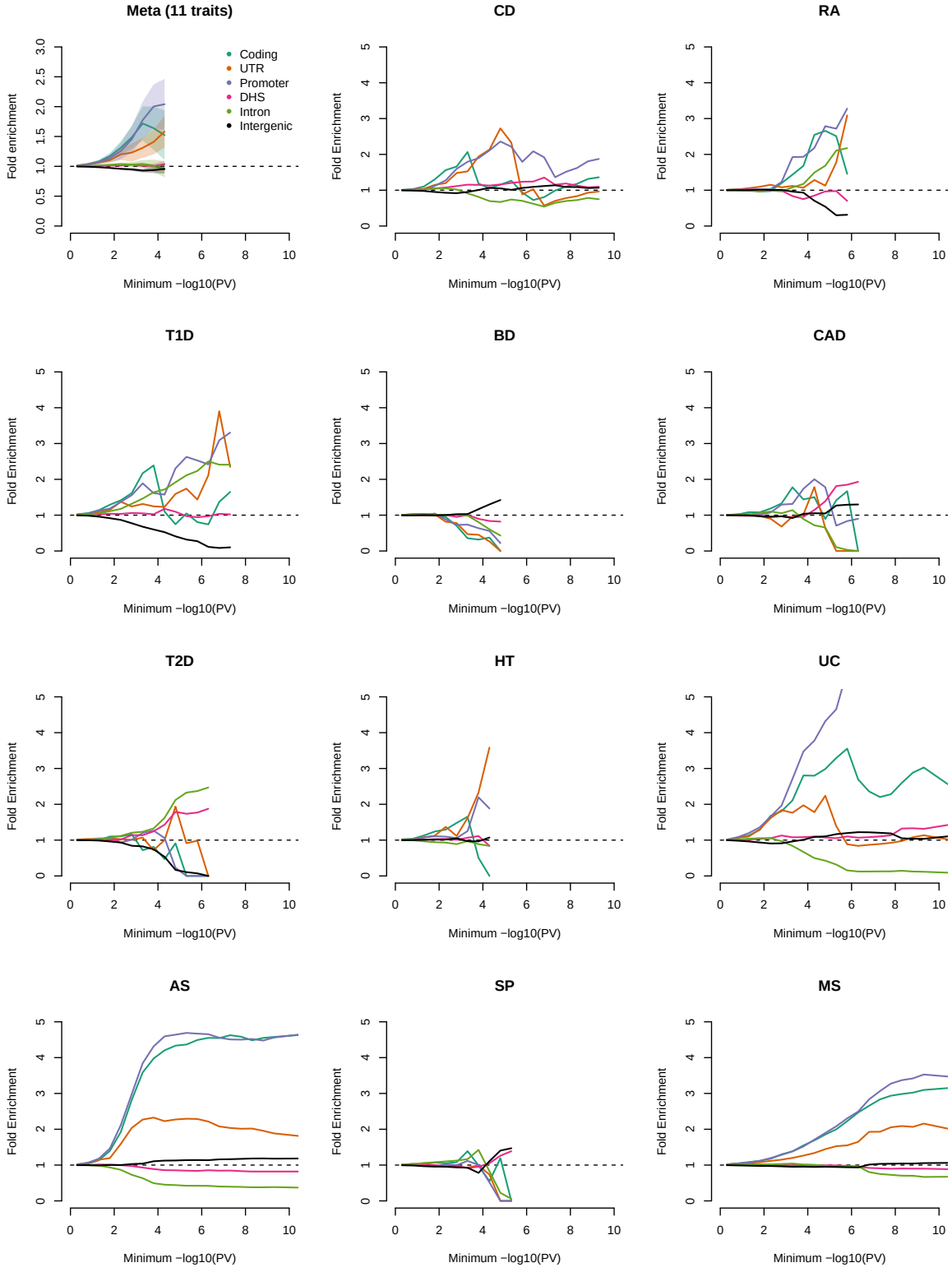


**Figure S8. Functional enrichment of SNP-heritability in DHS regions.** The ratio of observed % heritability over corresponding % of SNPs is reported as meta-analysis over all traits for four locus types. Light blue bars detail analysis of typed SNPs and dark blue bars detail analysis of typed and 1,000 Genomes imputed SNPs. "Known Loci" categories corespond to analysis restricted to regions around published genome-wide significant loci for the corresponding trait. SP, HT, and BD had too few known loci or could not converge in the local analyses and were excluded from all computations, resulting in slightly different overall values from Figure 1. Error bars define 95% confidence interval.

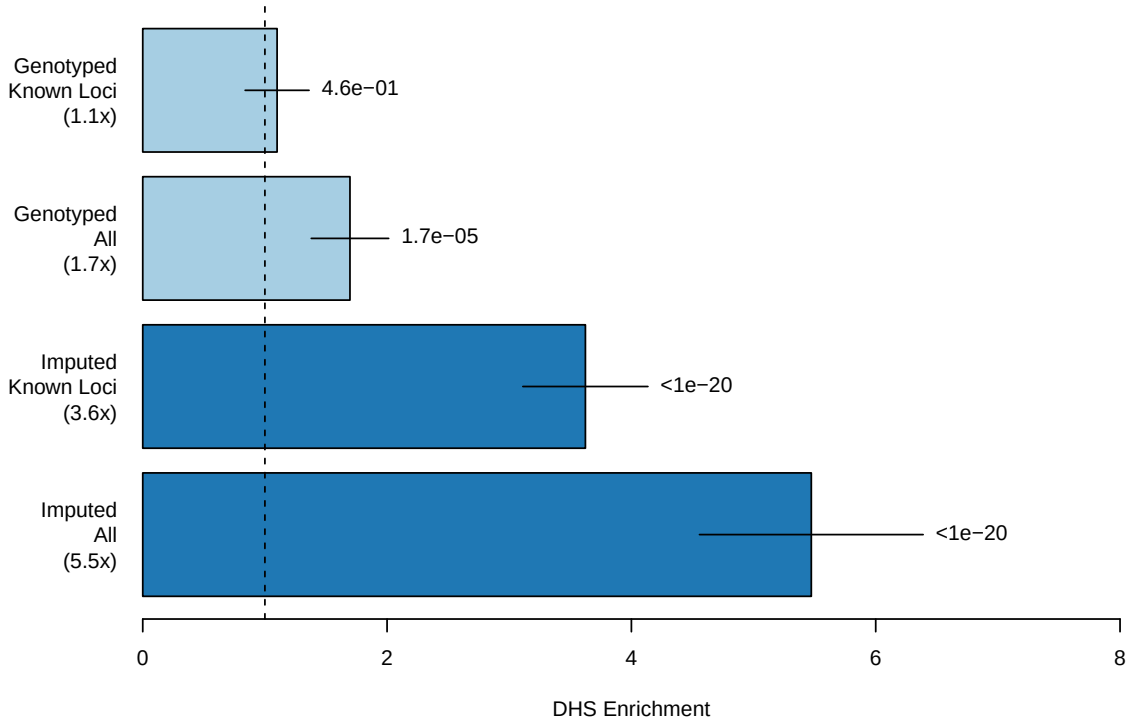


**Figure S9. Power to detect significant $h^2_{\mathbf{g}}$ enrichment.** Phenotypes werer simulated with DHS and coding enrichment matching the observed meta-analysis values in a 33,000 sample cohort. Power was then inferred as the fraction of 100 simulations where enrichment was significant at $P < 0.05$ over increasing sample sizes.

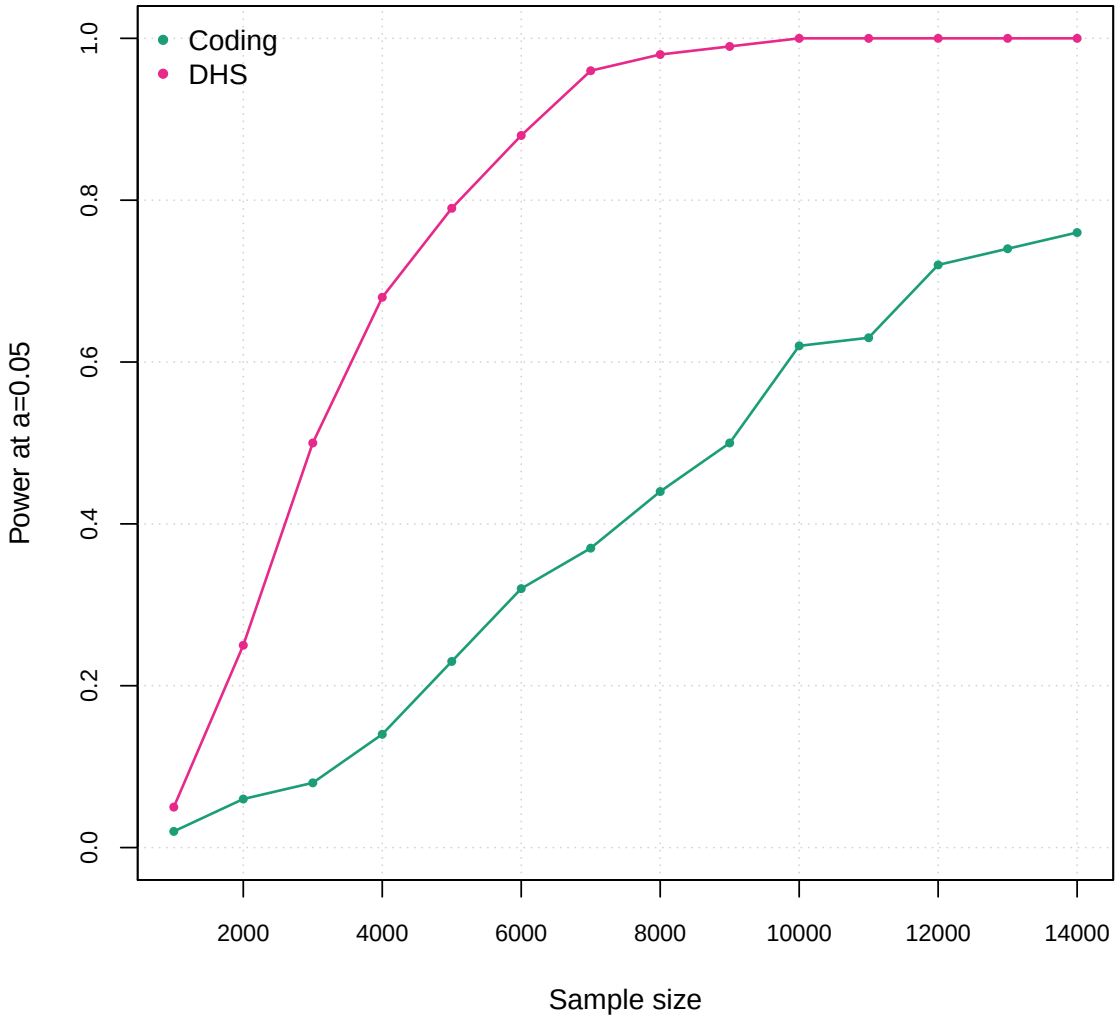


**Figure S10. Partitioning of $h^2_{\mathbf{g}}$ simulated in low-frequency imputed data.** Estimate of $h^2_{\mathrm{g}}$ from genotyped SNPs in each functional category for phenotypes simulated from imputed SNPs with MAF $< 0.05$. Each section of the figure describes average results from simulations where all $h^2_{\mathrm{g}}$ was induced in the titular functional category (highlighted in blue). Estimate $h^2_{\mathrm{g}}$ is spread across multiple functional categories due to incomplete tagging. Error-bars indicate standard error from 200 simulations.

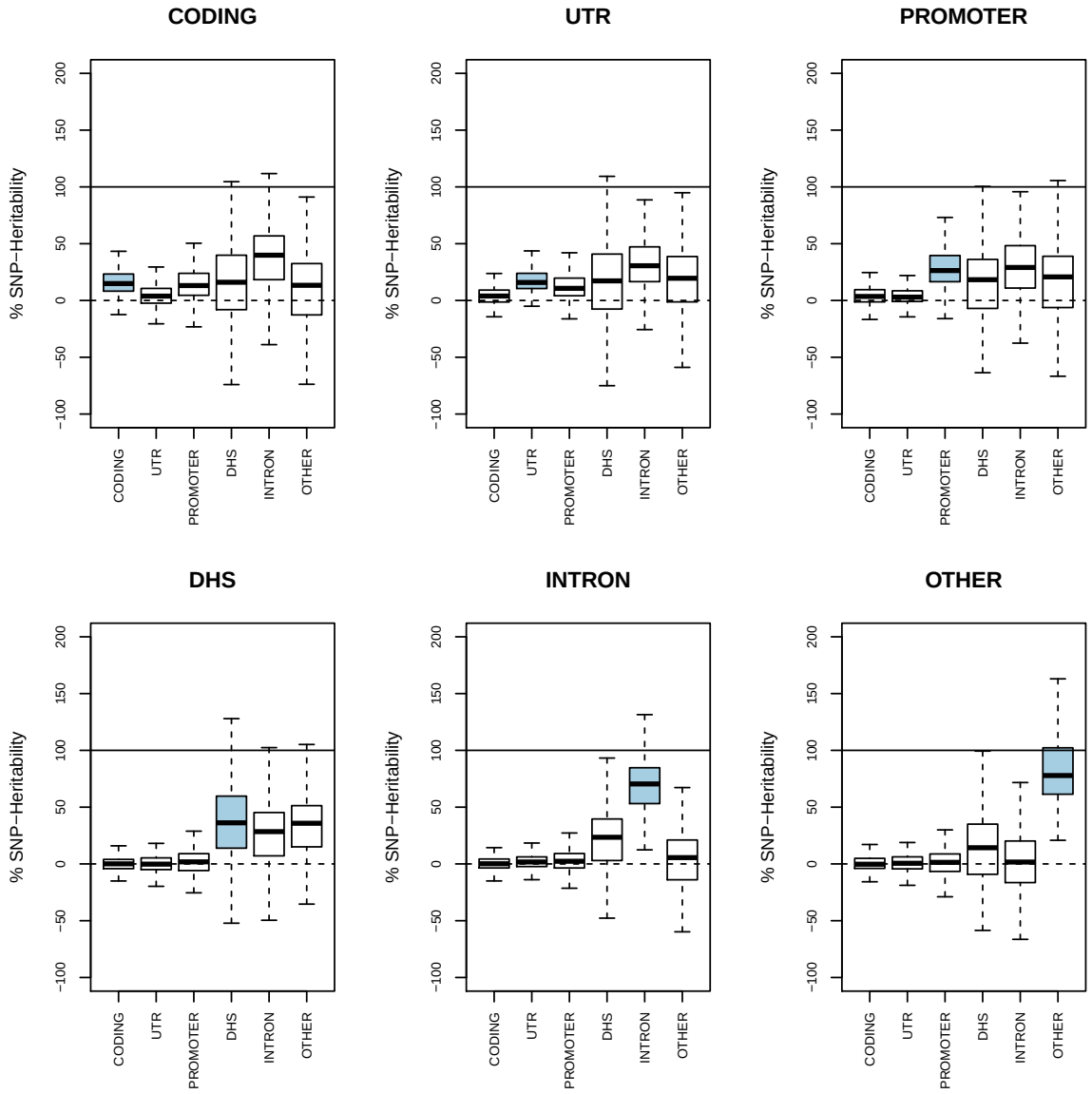


**Figure S11. Principal components analysis of Swedish samples.** Two main principal components are shown for analysis of GWAS data from the full Swedish Schizophrenia cohort. Homogenous Swedish samples are highlighted in blue.

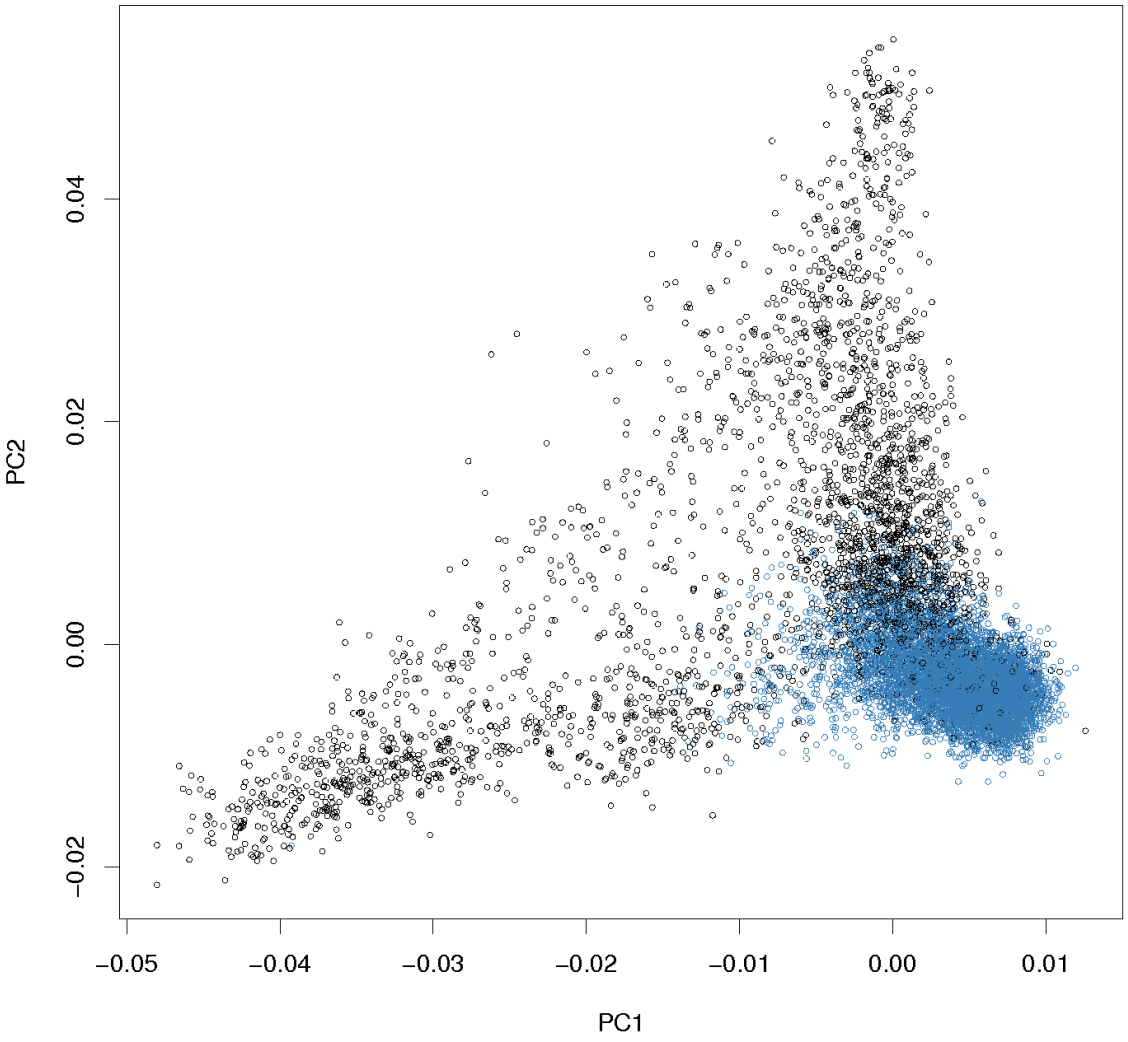


**Figure S12. Heritability estimates in simulation with normalized allelic effect-sizes.** Distribution $h^2_g$ inferred by four variance-component models is shown over a range of disease architectures. Additive phenotypes with $h^2 = 0.5$ were simulated from 1,000 randomly selected causal variants with maximum allele frequency from 0.01 to 0.1 (x-axis). Normalized SNP effect-sizes were drawn from the standard normal such that each SNP explains equal variance in expectation. Box-plots show inferred $h^2_g$ over 40 random simulations. For the joint component model the sum of both inferred $h^2_g$ values is reported. A red asterisk indicates significant difference from 0.5 by z-test after correcting for ten architectures tested.

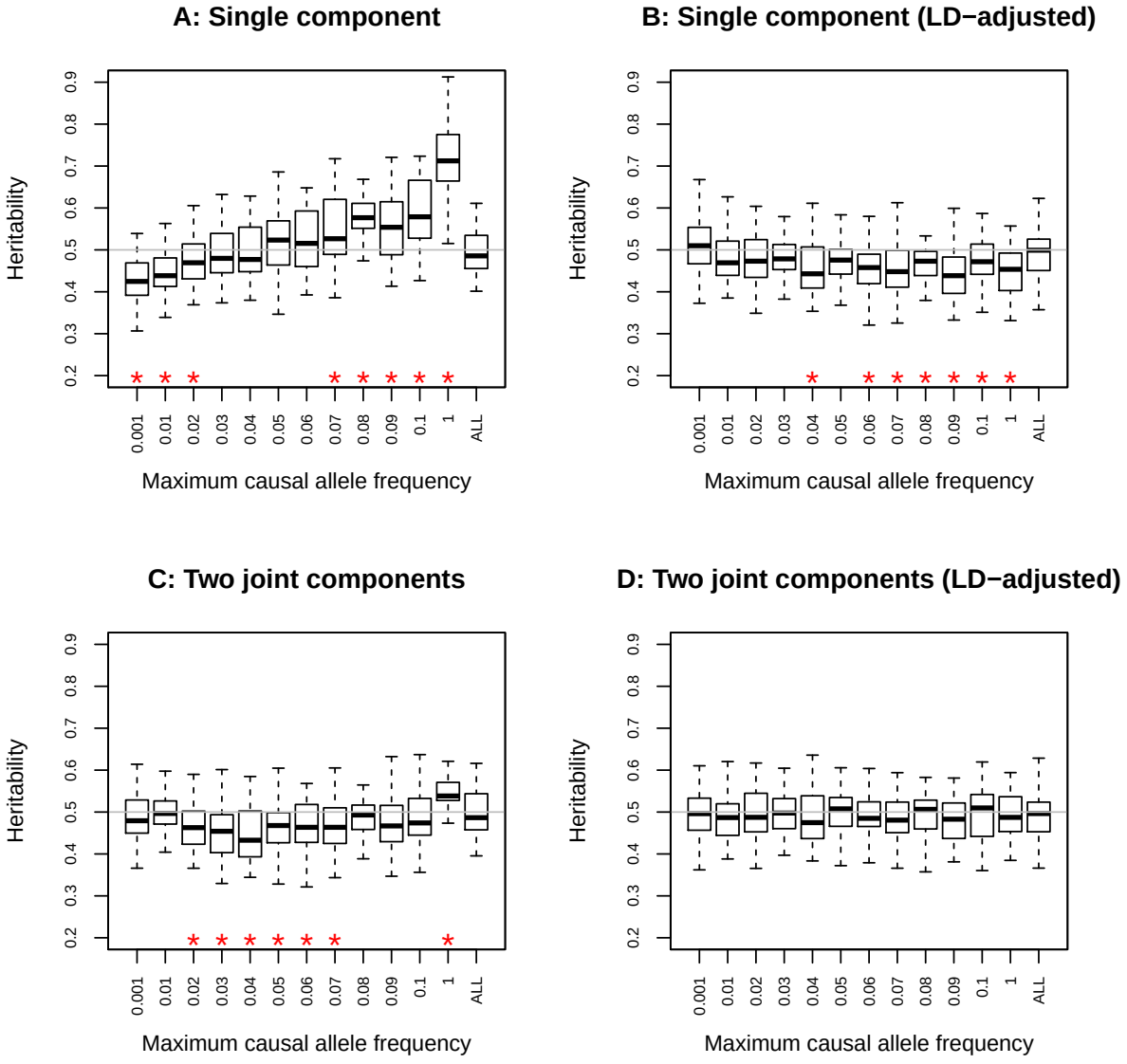
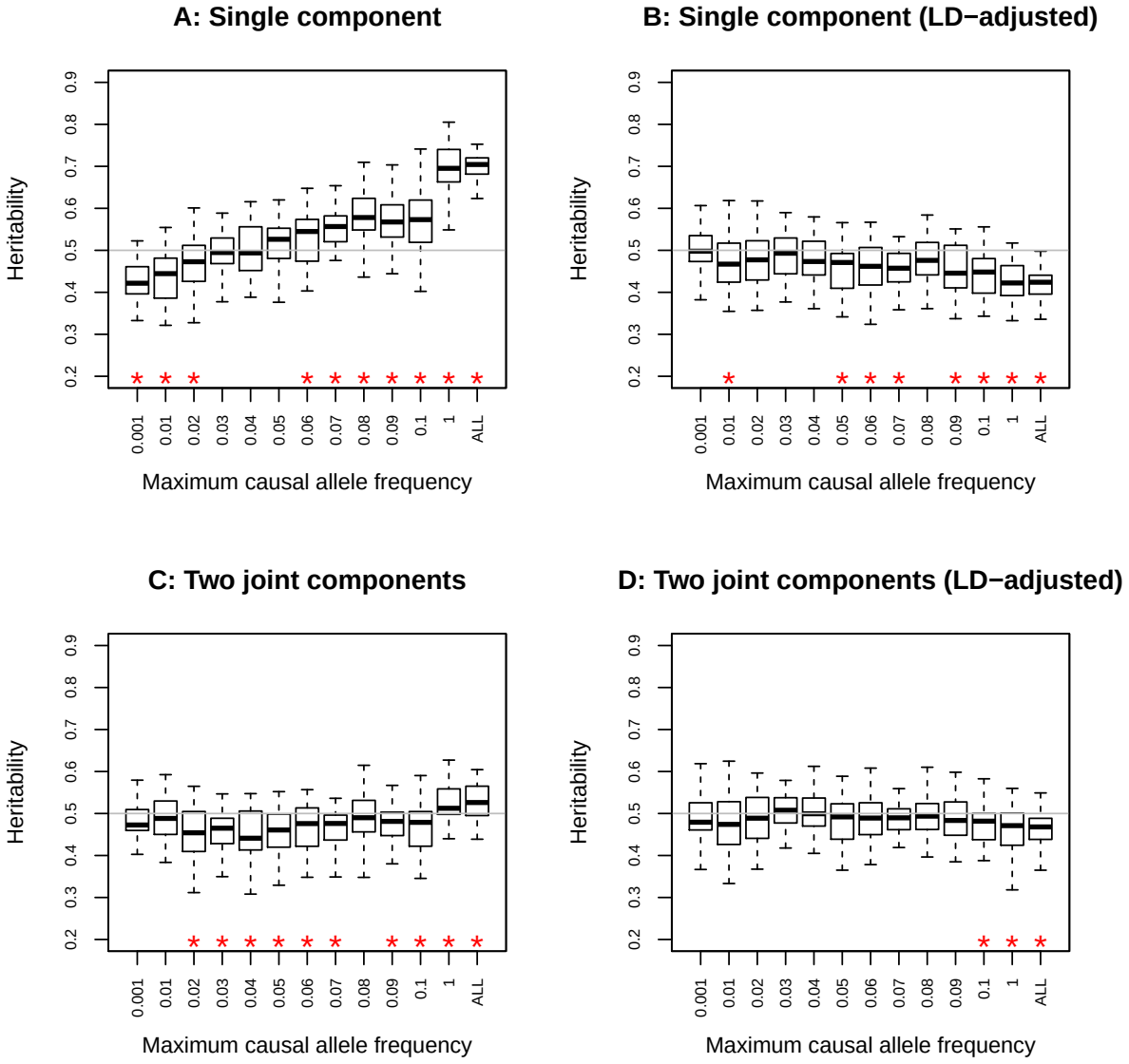


**Figure S13. Heritability estimates in simulation with standard allelic effect-sizes.** Distribution $h^2_g$ inferred by four variance-component models is shown over a range of disease architectures. Additive phenotypes with $h^2 = 0.5$ were simulated from 1,000 randomly selected causal variants with maximum allele frequency from 0.01 to 0.1 (x-axis). Allelic effect-sizes were drawn from the standard normal such that common SNPs explain more variance in expectation. Box-plots show inferred $h^2_g$ over 40 random simulations. For the joint component model the sum of both inferred $h^2_g$ values is reported. A red asterisk indicates significant difference from 0.5 by z-test after correcting for ten architectures tested.



# Supplementary Tables

**Table S1. Coding and regulatory annotation categories.** Description of functional categories and fraction occupied, respectively, by physical genome; all 1000 Genomes SNPs; average array SNPs; average imputed 1000G SNPs.

| Category | Description | % physical | % 1000G | % array | % imputed |
|---|---|---|---|---|---|
| Coding (non-UTR) | Overlaps a coding exon. | 1.1% | 0.9% | 0.9% | 0.5% |
| UTR | Overlaps a 5' or 3' untranslated region. | 1.0% | 0.9% | 1.0% | 0.8% |
| Promoter | Within 2kbp of a transcription start site. | 2.5% | 2.6% | 2.2% | 2.2% |
| DHS | Overlaps DHS region observed in any cell-type. | 14.6% | 16.4% | 23.3% | 15.7% |
| Intron | Overlaps an intron. | 29.1% | 28.6% | 26.8% | 28.8% |
| Intergenic | All other intergenic variants. | 51.8% | 50.5% | 44.8% | 52.0% |

**Table S2. Functional category features.** For each genotyping platform and functional category, the following features are reported: minor allele frequency (MAF), imputation quality (INFO), average number of LD partners (LD score), and GERP conservation score (Cons).

| WTCCC1 Genotyped: Affymetrix | | | | |
|---|---|---|---|---|
| Annotation | MAF | INFO | LD score | Cons |
| Coding | 0.2330 | NA | 116.4 | 1.076 |
| UTR | 0.2388 | NA | 104.1 | 0.560 |
| Promoter | 0.2435 | NA | 118.6 | 0.231 |
| DHS | 0.2462 | NA | 92.6 | 0.346 |
| Intron | 0.2450 | NA | 111.0 | 0.177 |
| Intergenic | 0.2489 | NA | 116.9 | 0.135 |
| WTCCC2 Imputed: Affymetrix | | | | |
| Annotation | MAF | INFO | LD score | Cons |
| Coding | 0.1700 | 0.9730 | 111.0 | 1.191 |
| UTR | 0.1773 | 0.9749 | 100.2 | 0.620 |
| Promoter | 0.1780 | 0.9739 | 114.5 | 0.266 |
| DHS | 0.1836 | 0.9775 | 89.0 | 0.388 |
| Intron | 0.1817 | 0.9776 | 108.2 | 0.194 |
| Intergenic | 0.1846 | 0.9773 | 111.6 | 0.148 |
| WTCCC2 Imputed: Illumina | | | | |
| Annotation | MAF | INFO | LD score | Cons |
| Coding | 0.1672 | 0.9745 | 91.7 | 1.525 |
| UTR | 0.1735 | 0.9758 | 85.8 | 0.816 |
| Promoter | 0.1749 | 0.9751 | 97.1 | 0.358 |
| DHS | 0.1798 | 0.9778 | 79.2 | 0.498 |
| Intron | 0.1780 | 0.9791 | 94.7 | 0.254 |
| Intergenic | 0.1810 | 0.9780 | 101.3 | 0.188 |

**Table S3. Datasets analyzed.** Number of samples and markers for each dataset analyzed.

| Phenotype | Label | Prevalence | Cases | Controls | Genotyped SNPs | Imputed SNPs |
|---|---|---|---|---|---|---|
| WTCCC2: | | | | | | |
| Schizophrenia | SP | 0.010 | 2698 | 5458 | 394992 | 4345606 |
| Ankylosing spondylitis | AS | 0.003 | 1783 | 5239 | 408616 | 6162624 |
| Multiple sclerosis | MS | 0.001 | 9315 | 5211 | 396469 | 5795523 |
| Ulcerative colitis | UC | 0.001 | 2495 | 5428 | 447905 | 4620390 |
| WTCCC: | | | | | | |
| Bipolar disorder | BD | 0.005 | 1550 | 2666 | 143054 | 4192374 |
| Coronary artery disease | CAD | 0.060 | 1746 | 2668 | 139567 | 4190156 |
| Crohns disease | CD | 0.001 | 1542 | 2662 | 146952 | 4199232 |
| Hypertension | HT | 0.260 | 1730 | 2669 | 139541 | 4185735 |
| Rheumatoid arthritis | RA | 0.005 | 1664 | 2664 | 143732 | 4190217 |
| Type 1 diabetes | T1D | 0.005 | 1746 | 2668 | 139206 | 4184291 |
| Type 2 diabetes | T2D | 0.080 | 1641 | 2671 | 142027 | 4195404 |
| Other: | | | | | | |
| Schizophrenia | PGC | 0.010 | 5073 | 6605 | NA | 4463775 |

**Table S4. Components of heritability from regulatory elements in GWAS data (meta-analysis).**

| | Genotyped | | | Imputed | | |
|---|---|---|---|---|---|---|
| Annotation | % $h_g^2$ (s.e.) | Enrichment (s.e) | P-value | % $h_g^2$ (s.e.) | Enrichment (s.e.) | P-value |
| Coding | 4% (1%) | 4.12 (0.85) | 2.59e-04 | 8% (2%) | 13.84 (3.67) | 4.74e-04 |
| DHS | 38% (3%) | 1.63 (0.14) | 7.98e-06 | 79% (7%) | 5.07 (0.42) | 3.64e-22 |
| Promoter | 5% (1%) | 2.19 (0.51) | 1.94e-0 | 6% (3%) | 2.79 (1.17) | 1.25e-01 |
| UTR | 4% (1%) | 3.51 (0.82) | 2.21e-03 | 7% (2%) | 8.42 (2.60) | 4.28e-03 |
| Intron | 23% (2%) | 0.83 (0.09) | 6.40e-02 | 2% (4%) | 0.05 (0.14) | 5.48e-12 |
| Intergenic | 25% (3%) | 0.56 (0.06) | 4.11e-13 | -3% (4%) | -0.06 (0.08) | 2.84e-42 |

**Table S5. Components of heritability from regulatory elements in GWAS data.** Family-based $h^2$ (from literature), total $h^2_g$, and function-specific $h^2_g$ of liability is reported for eleven traits. Enrichment computed over the % of SNPs in each category and P-value computed from Z-score. For auto-immune traits (CD,RA,T1D,MS,AS,UC) the well-studied MHC locus was removed from analyses.

| Bipolar disorder ($h^2$ = 0.6-0.7) | Genotyped $h^2_g$ = 0.26 (0.032) | | | | Imputed $h^2_g$ = 0.24 (0.035) | | | |
|---|---|---|---|---|---|---|---|---|
| Function | % $h^2_g$ | (s.e.) | Enrichment | P-value | % $h^2_g$ | (s.e.) | Enrichment | P-value |
| Coding | 3.5% | (2.4%) | 4.2 | 2.6e-01 | 4.9% | (7.2%) | 9.0 | 5.5e-01 |
| UTR | 3.6% | (2.5%) | 3.8 | 2.8e-01 | 11.6% | (7.6%) | 15.3 | 1.5e-01 |
| Promoter | -1.0% | (3.3%) | -0.5 | 3.4e-01 | -11.0% | (9.4%) | -5.1 | 1.6e-01 |
| DHS | 34.0% | (10.3%) | 1.4 | 3.1e-01 | 34.6% | (26.5%) | 2.2 | 4.7e-01 |
| Intron | 22.9% | (8.0%) | 0.9 | 6.2e-01 | 27.0% | (15.3%) | 0.9 | 9.2e-01 |
| Intergenic | 37.0% | (8.9%) | 0.8 | 3.3e-01 | 33.0% | (16.2%) | 0.6 | 2.3e-01 |
| Coronary artery disease ($h^2$ = 0.3-0.6) | Genotyped $h^2_g$ = 0.31 (0.057) | | | | Imputed $h^2_g$ = 0.25 (0.062) | | | |
| Function | % $h^2_g$ | (s.e.) | Enrichment | P-value | % $h^2_g$ | (s.e.) | Enrichment | P-value |
| Coding | 1.7% | (3.2%) | 2.2 | 7.7e-01 | 7.5% | (12.5%) | 14.0 | 5.7e-01 |
| UTR | 5.6% | (3.7%) | 5.9 | 2.1e-01 | 10.5% | (13.0%) | 13.8 | 4.6e-01 |
| Promoter | 4.5% | (5.1%) | 2.0 | 6.6e-01 | 2.8% | (16.0%) | 1.3 | 9.7e-01 |
| DHS | 41.1% | (15.4%) | 1.8 | 2.5e-01 | 0.7% | (47.1%) | 0.0 | 7.5e-01 |
| Intron | 24.5% | (12.0%) | 0.9 | 8.4e-01 | 44.4% | (27.5%) | 1.5 | 5.7e-01 |
| Intergenic | 22.6% | (13.8%) | 0.5 | 9.3e-02 | 34.1% | (27.2%) | 0.7 | 5.0e-01 |
| Crohn's disease ($h^2$ = 0.6-0.8) | Genotyped $h^2_g$ = 0.18 (0.024) | | | | Imputed $h^2_g$ = 0.17 (0.025) | | | |
| Function | % $h^2_g$ | (s.e.) | Enrichment | P-value | % $h^2_g$ | (s.e.) | Enrichment | P-value |
| Coding | 3.7% | (2.5%) | 4.6 | 2.5e-01 | 19.2% | (8.2%) | 35.9 | 2.3e-02 |
| UTR | -0.8% | (2.5%) | -0.8 | 4.8e-01 | 3.1% | (7.6%) | 4.1 | 7.6e-01 |
| Promoter | 7.3% | (4.0%) | 3.3 | 2.0e-01 | -3.6% | (9.5%) | -1.7 | 5.4e-01 |
| DHS | 58.4% | (11.9%) | 2.5 | 3.4e-03 | 151.7% | (27.1%) | 9.7 | 5.2e-07 |
| Intron | 14.9% | (8.8%) | 0.6 | 1.7e-01 | -30.9% | (15.6%) | -1.1 | 1.3e-04 |
| Intergenic | 16.5% | (10.3%) | 0.4 | 4.9e-03 | -39.5% | (17.3%) | -0.8 | 1.1e-07 |
| Hypertension ($h^2$ = 0.3-0.7) | Genotyped $h^2_g$ = 0.61 (0.089) | | | | Imputed $h^2_g$ = 0.55 (0.098) | | | |
| Function | % $h^2_g$ | (s.e.) | Enrichment | P-value | % $h^2_g$ | (s.e.) | Enrichment | P-value |
| Coding | 6.2% | (2.9%) | 7.6 | 6.4e-02 | 25.4% | (10.5%) | 47.2 | 1.8e-02 |
| UTR | 5.5% | (3.0%) | 5.6 | 1.3e-01 | 12.7% | (9.5%) | 16.7 | 2.1e-01 |
| Promoter | 4.9% | (4.2%) | 2.2 | 5.1e-01 | -3.0% | (11.7%) | -1.4 | 6.6e-01 |
| DHS | 28.3% | (11.7%) | 1.2 | 6.8e-01 | 93.8% | (31.6%) | 6.0 | 1.3e-02 |
| Intron | 19.4% | (9.4%) | 0.7 | 4.2e-01 | -32.4% | (18.6%) | -1.1 | 1.1e-03 |
| Intergenic | 35.6% | (10.5%) | 0.8 | 3.4e-01 | 3.4% | (19.8%) | 0.1 | 1.3e-02 |
| Rheumatoid arthritis ($h^2$ = 0.6) | Genotyped $h^2_g$ = 0.11 (0.031) | | | | Imputed $h^2_g$ = 0.09 (0.033) | | | |
| Function | % $h^2_g$ | (s.e.) | Enrichment | P-value | % $h^2_g$ | (s.e.) | Enrichment | P-value |
| Coding | -0.6% | (5.0%) | -0.8 | 7.7e-01 | 1.4% | (17.7%) | 2.6 | 9.6e-01 |
| UTR | 7.1% | (5.7%) | 7.3 | 2.9e-01 | 21.1% | (19.3%) | 27.9 | 2.9e-01 |
| Promoter | 1.9% | (7.5%) | 0.9 | 9.8e-01 | 28.3% | (24.6%) | 13.2 | 2.9e-01 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| DHS | 46.4% | (23.4%) | 2.0 | 3.3e-01 | 162.7% | (67.4%) | 10.4 | 2.9e-02 |
| Intron | 6.5% | (18.9%) | 0.2 | 2.8e-01 | -78.9% | (45.1%) | -2.8 | 1.7e-02 |
| Intergenic | 38.8% | (20.1%) | 0.8 | 7.3e-01 | -34.6% | (42.0%) | -0.7 | 3.8e-02 |
| Type 1 diabetes ($h^2$ =0.9) | Genotyped $h_g^2 = 0.13$ (0.030) | | | | Imputed $h_g^2 = 0.13$ (0.032) | | | |
| Function | % $h_g^2$ | (s.e.) | Enrichment | P-value | % $h_g^2$ | (s.e.) | Enrichment | P-value |
| Coding | 7.9% | (4.6%) | 9.5 | 1.3e-01 | 35.0% | (16.1%) | 65.3 | 3.2e-02 |
| UTR | 5.1% | (4.4%) | 5.2 | 3.5e-01 | -1.8% | (12.9%) | -2.4 | 8.4e-01 |
| Promoter | 11.0% | (6.7%) | 5.0 | 1.9e-01 | 28.8% | (18.3%) | 13.5 | 1.4e-01 |
| DHS | 28.2% | (18.0%) | 1.2 | 7.9e-01 | 106.2% | (42.5%) | 6.8 | 3.3e-02 |
| Intron | 36.7% | (14.7%) | 1.4 | 5.1e-01 | -8.3% | (26.0%) | -0.3 | 1.5e-01 |
| Intergenic | 11.2% | (17.1%) | 0.2 | 4.4e-02 | -59.9% | (30.8%) | -1.1 | 2.7e-04 |
| Type 2 diabetes ($h^2$ = 0.3-0.6) | Genotyped $h_g^2 = 0.37$ (0.065) | | | | Imputed $h_g^2 = 0.42$ (0.070) | | | |
| Function | % $h_g^2$ | (s.e.) | Enrichment | P-value | % $h_g^2$ | (s.e.) | Enrichment | P-value |
| Coding | -2.0% | (3.0%) | -2.4 | 3.5e-01 | 2.5% | (8.1%) | 4.7 | 8.1e-01 |
| UTR | -0.7% | (3.2%) | -0.7 | 6.0e-01 | 8.7% | (8.5%) | 11.4 | 3.5e-01 |
| Promoter | -3.5% | (4.7%) | -1.6 | 2.3e-01 | -3.3% | (10.3%) | -1.5 | 6.0e-01 |
| DHS | 69.3% | (16.0%) | 3.0 | 4.0e-03 | 63.8% | (27.5%) | 4.1 | 8.0e-02 |
| Intron | 26.1% | (11.4%) | 1.0 | 9.4e-01 | 17.1% | (17.4%) | 0.6 | 5.1e-01 |
| Intergenic | 10.7% | (13.6%) | 0.2 | 1.0e-02 | 11.1% | (17.2%) | 0.2 | 1.7e-02 |
| Multiple sclerosis ($h^2$ = 0.3-0.8) | Genotyped $h_g^2 = 0.19$ (0.009) | | | | Imputed $h_g^2 = 0.17$ (0.009) | | | |
| Function | % $h_g^2$ | (s.e.) | Enrichment | P-value | % $h_g^2$ | (s.e.) | Enrichment | P-value |
| Coding | 6.4% | (1.7%) | 3.6 | 6.2e-03 | 5.5% | (2.9%) | 9.4 | 9.5e-02 |
| UTR | 3.9% | (1.4%) | 3.2 | 6.3e-02 | 8.1% | (3.1%) | 9.4 | 1.9e-02 |
| Promoter | 6.1% | (2.0%) | 2.4 | 7.4e-02 | 11.7% | (4.0%) | 5.0 | 1.8e-02 |
| DHS | 33.1% | (5.3%) | 1.3 | 1.1e-01 | 77.7% | (9.4%) | 4.9 | 5.5e-11 |
| Intron | 24.1% | (4.0%) | 0.9 | 3.1e-01 | 1.5% | (5.7%) | 0.1 | 9.1e-07 |
| Intergenic | 26.4% | (4.2%) | 0.6 | 3.2e-04 | -4.5% | (5.7%) | -0.1 | 1.0e-16 |
| Ankylosing spondylitis ($h^2 > 0.90$) | Genotyped $h_g^2 = 0.18$ (0.028) | | | | Imputed $h_g^2 = 0.14$ (0.027) | | | |
| Function | % $h_g^2$ | (s.e.) | Enrichment | P-value | % $h_g^2$ | (s.e.) | Enrichment | P-value |
| Coding | 6.9% | (4.8%) | 3.9 | 2.9e-01 | 1.5% | (10.4%) | 2.6 | 9.3e-01 |
| UTR | 11.4% | (4.6%) | 9.2 | 2.7e-02 | 20.9% | (12.0%) | 24.5 | 9.6e-02 |
| Promoter | 5.2% | (5.7%) | 2.0 | 6.5e-01 | 7.5% | (13.5%) | 3.2 | 7.1e-01 |
| DHS | 41.8% | (16.1%) | 1.7 | 2.8e-01 | 106.3% | (33.4%) | 6.7 | 6.8e-03 |
| Intron | 14.9% | (11.7%) | 0.5 | 2.6e-01 | -23.6% | (20.6%) | -0.8 | 1.1e-02 |
| Intergenic | 19.8% | (12.7%) | 0.5 | 8.6e-02 | -12.6% | (20.2%) | -0.2 | 1.5e-03 |
| Schizophrenia ($h^2$ = 0.7-0.8) | Genotyped $h_g^2 = 0.20$ (0.025) | | | | Imputed $h_g^2 = 0.18$ (0.024) | | | |
| Function | % $h_g^2$ | (s.e.) | Enrichment | P-value | % $h_g^2$ | (s.e.) | Enrichment | P-value |
| Coding | 1.9% | (2.9%) | 2.6 | 6.8e-01 | 7.7% | (6.6%) | 14.2 | 2.8e-01 |
| UTR | 2.5% | (3.1%) | 2.6 | 6.2e-01 | 0.8% | (6.3%) | 1.0 | 1.0e 00 |
| Promoter | 7.4% | (4.4%) | 3.4 | 2.4e-01 | -9.7% | (7.7%) | -4.2 | 1.2e-01 |
| DHS | 37.6% | (13.3%) | 1.6 | 2.7e-01 | 44.4% | (22.8%) | 2.8 | 2.1e-01 |
| Intron | 26.6% | (9.4%) | 1.0 | 9.8e-01 | 37.3% | (14.0%) | 1.3 | 5.3e-01 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Intergenic | 23.9% | (10.6%) | 0.5 | 3.5e-02 | 19.6% | (14.1%) | 0.4 | 2.2e-02 |
| Ulcerative colitis ($h^2 = 0.5$) | Genotyped $h_g^2 = 0.17$ (0.017) | | | | Imputed $h_g^2 = 0.14$ (0.016) | | | |
| Function | % $h_g^2$ | (s.e.) | Enrichment | P-value | % $h_g^2$ | (s.e.) | Enrichment | P-value |
| Coding | 4.7% | (2.5%) | 6.2 | 1.2e-01 | 7.6% | (5.9%) | 14.5 | 2.3e-01 |
| UTR | 4.3% | (2.6%) | 4.5 | 2.1e-01 | -1.4% | (5.7%) | -1.7 | 7.0e-01 |
| Promoter | 8.7% | (3.7%) | 4.0 | 7.3e-02 | 23.8% | (7.9%) | 10.6 | 6.5e-03 |
| DHS | 43.3% | (10.9%) | 1.9 | 6.5e-02 | 93.5% | (19.4%) | 6.0 | 6.0e-05 |
| Intron | 21.2% | (7.6%) | 0.8 | 4.5e-01 | -5.6% | (11.5%) | -0.2 | 2.8e-03 |
| Intergenic | 17.9% | (8.7%) | 0.4 | 1.1e-03 | -18.0% | (12.4%) | -0.3 | 1.5e-08 |

**Table S6. $h^2_{\mathbf{g}}$ from narrowed DHS regions.** DHS regions were narrowed (to the center of the region) to achieve set % of genome, and $h^2_g$ estimates are reported from a single DHS component (univar) as well as jointly with the five other main components.

| | | Joint with main categories | | |
|---|---|---|---|---|
| % genome | % $h^2_g$ univar | % $h^2_g$ (se) | enrichment (se) | P-value |
| 1% | 0.610 | 0.198 (0.040) | 18.094 (3.655) | 2.91e-06 |
| 5% | 0.853 | 0.415 (0.070) | 7.971 (1.335) | 1.76e-07 |
| 10% | 0.948 | 0.704 (0.073) | 6.884 (0.717) | 2.35e-16 |
| 16% (all DHS) | 0.985 | 0.795 (0.066) | 5.072 (0.421) | 3.64e-22 |

**Table S7. Constrained REML estimate of $h^2_{\mathbf{g}}$.** Comparison of constrained analysis (where components estimating $h^2_{\mathrm{g}}$ below zero are dropped from the analysis) and the standard un-constrained results. All values computed from meta-analysis over 11 traits.

| | Constrained | | | Standard | | |
|---|---|---|---|---|---|---|
| Category | fraction $h^2_{\mathrm{g}}$ (se) | enrichment (se) | PV | fraction $h^2_{\mathrm{g}}$ (se) | enrichment (se) | PV |
| Coding | 0.052 (0.019) | 9.521 (3.418) | 1.27e-02 | 0.075 (0.020) | 13.838 (3.673) | 4.74e-04 |
| UTR | 0.053 (0.019) | 6.801 (2.443) | 1.76e-02 | 0.066 (0.020) | 8.417 (2.596) | 4.28e-03 |
| Promoter | 0.069 (0.025) | 3.126 (1.109) | 5.52e-02 | 0.062 (0.026) | 2.792 (1.168) | 1.25e-01 |
| DHS | 0.710 (0.064) | 4.532 (0.407) | 3.82e-18 | 0.795 (0.066) | 5.072 (0.421) | 3.64e-22 |
| Intron | 0.061 (0.038) | 0.211 (0.131) | 1.74e-09 | 0.015 (0.039) | 0.053 (0.137) | 5.48e-12 |
| Intergenic | 0.046 (0.039) | 0.088 (0.075) | 9.68e-34 | -0.031 (0.040) | -0.059 (0.078) | 2.84e-42 |

**Table S8. Comparison of analytical and jack-knife % $h^2_{\mathbf{g}}$ from genotyped SNPs.** For each trait and functional category, the % $h^2_{\mathrm{g}}$ and standard error (in parentheses) is shown from a the standard REML and a weighted block-jackknife dropping each chromosome in turn. Results from meta-analysis for each method shown at the bottom, with p-values for inrichment below each entry.

| Phenotype | Coding | DHS | Promoter | UTR | Intron | Intergenic |
|---|---|---|---|---|---|---|
| SP (REML) | 0.020 (0.029) | 0.376 (0.133) | 0.074 (0.044) | 0.025 (0.031) | 0.266 (0.094) | 0.239 (0.106) |
| SP (jknife) | 0.024 (0.027) | 0.368 (0.168) | 0.085 (0.047) | 0.022 (0.019) | 0.258 (0.143) | 0.244 (0.088) |
| AS (REML) | 0.069 (0.048) | 0.418 (0.161) | 0.052 (0.057) | 0.114 (0.046) | 0.149 (0.117) | 0.198 (0.127) |
| AS (jknife) | 0.086 (0.048) | 0.419 (0.188) | 0.040 (0.057) | 0.102 (0.052) | 0.115 (0.149) | 0.238 (0.112) |
| MS (REML) | 0.064 (0.017) | 0.331 (0.053) | 0.061 (0.020) | 0.039 (0.014) | 0.242 (0.040) | 0.264 (0.042) |
| MS (jknife) | 0.073 (0.023) | 0.339 (0.076) | 0.050 (0.021) | 0.046 (0.012) | 0.235 (0.034) | 0.258 (0.068) |
| UC (REML) | 0.047 (0.025) | 0.433 (0.109) | 0.087 (0.037) | 0.043 (0.026) | 0.212 (0.076) | 0.179 (0.086) |
| UC (jknife) | 0.045 (0.027) | 0.425 (0.105) | 0.085 (0.039) | 0.045 (0.028) | 0.223 (0.069) | 0.177 (0.077) |
| BD (REML) | 0.035 (0.024) | 0.340 (0.103) | -0.010 (0.033) | 0.036 (0.025) | 0.229 (0.080) | 0.370 (0.089) |
| BD (jknife) | 0.030 (0.027) | 0.321 (0.129) | -0.021 (0.035) | 0.047 (0.022) | 0.245 (0.088) | 0.377 (0.093) |
| CAD (REML) | 0.017 (0.032) | 0.411 (0.154) | 0.045 (0.052) | 0.056 (0.037) | 0.245 (0.120) | 0.226 (0.138) |
| CAD (jknife) | 0.018 (0.025) | 0.432 (0.137) | 0.048 (0.054) | 0.058 (0.039) | 0.225 (0.105) | 0.220 (0.134) |
| CD (REML) | 0.037 (0.025) | 0.584 (0.119) | 0.073 (0.040) | -0.008 (0.025) | 0.149 (0.088) | 0.165 (0.103) |
| CD (jknife) | 0.036 (0.025) | 0.619 (0.113) | 0.071 (0.050) | 0.005 (0.029) | 0.134 (0.107) | 0.133 (0.117) |
| HT (REML) | 0.062 (0.029) | 0.283 (0.117) | 0.049 (0.042) | 0.055 (0.030) | 0.194 (0.094) | 0.356 (0.105) |
| HT (jknife) | 0.062 (0.027) | 0.319 (0.110) | 0.058 (0.052) | 0.057 (0.026) | 0.210 (0.083) | 0.293 (0.116) |
| RA (REML) | -0.006 (0.049) | 0.464 (0.234) | 0.019 (0.076) | 0.071 (0.057) | 0.065 (0.189) | 0.388 (0.201) |
| RA (jknife) | -0.017 (0.037) | 0.444 (0.325) | -0.007 (0.085) | 0.069 (0.063) | 0.063 (0.193) | 0.443 (0.241) |
| T1D (REML) | 0.079 (0.046) | 0.282 (0.180) | 0.110 (0.067) | 0.051 (0.044) | 0.367 (0.147) | 0.112 (0.171) |
| T1D (jknife) | 0.077 (0.050) | 0.301 (0.158) | 0.114 (0.076) | 0.061 (0.054) | 0.361 (0.103) | 0.088 (0.161) |
| T2D (REML) | -0.020 (0.030) | 0.694 (0.160) | -0.035 (0.047) | -0.007 (0.032) | 0.261 (0.114) | 0.107 (0.136) |
| T2D (jknife) | -0.020 (0.041) | 0.769 (0.146) | -0.030 (0.048) | -0.019 (0.040) | 0.208 (0.160) | 0.096 (0.180) |
| meta (REML) | 0.040 (0.008) | 0.384 (0.033) | 0.050 (0.012) | 0.035 (0.008) | 0.226 (0.025) | 0.250 (0.028) |
| | 2.59e-04 | 7.98e-06 | 1.94e-02 | 2.21e-03 | 6.40e-02 | 4.11e-13 |
| meta (jknife) | 0.039 (0.009) | 0.418 (0.038) | 0.043 (0.013) | 0.040 (0.008) | 0.228 (0.024) | 0.238 (0.032) |
| | 1.10e-03 | 1.50e-06 | 1.07e-01 | 6.45e-05 | 6.72e-02 | 1.78e-11 |

**Table S9. Comparison of analytical and jack-knife % $h^2_g$ from imputed SNPs.** For each trait and functional category, the % $h^2_g$ and standard error (in parentheses) is shown from a the standard REML and a weighted block-jackknife dropping each chromosome in turn. Results from meta-analysis for each method shown at the bottom, with p-values for inrichment below each entry.

| Phenotype | Coding | DHS | Promoter | UTR | Intron | Intergenic |
|---|---|---|---|---|---|---|
| BD (REML) | 0.049 (0.072) | 0.346 (0.265) | -0.110 (0.093) | 0.116 (0.076) | 0.270 (0.153) | 0.330 (0.162) |
| BD (jknife) | 0.029 (0.079) | 0.244 (0.294) | -0.110 (0.119) | 0.155 (0.086) | 0.338 (0.173) | 0.345 (0.172) |
| CAD (REML) | 0.075 (0.125) | 0.007 (0.468) | 0.028 (0.160) | 0.105 (0.130) | 0.444 (0.275) | 0.341 (0.272) |
| CAD (jknife) | 0.052 (0.113) | 0.058 (0.598) | 0.024 (0.163) | 0.125 (0.103) | 0.449 (0.352) | 0.301 (0.307) |
| CD (REML) | 0.192 (0.082) | 1.517 (0.271) | -0.036 (0.095) | 0.031 (0.076) | -0.309 (0.156) | -0.395 (0.173) |
| CD (jknife) | 0.201 (0.090) | 1.506 (0.367) | -0.042 (0.106) | 0.044 (0.088) | -0.289 (0.196) | -0.417 (0.176) |
| HT (REML) | 0.255 (0.105) | 0.938 (0.316) | -0.030 (0.118) | 0.127 (0.095) | -0.324 (0.186) | 0.034 (0.198) |
| HT (jknife) | 0.253 (0.096) | 0.902 (0.431) | -0.020 (0.181) | 0.122 (0.086) | -0.266 (0.169) | 0.008 (0.261) |
| RA (REML) | 0.014 (0.176) | 1.627 (0.674) | 0.283 (0.246) | 0.212 (0.193) | -0.789 (0.451) | -0.346 (0.420) |
| RA (jknife) | 0.026 (0.213) | 1.592 (0.952) | 0.285 (0.218) | 0.250 (0.204) | -0.826 (0.347) | -0.340 (0.460) |
| T1D (REML) | 0.350 (0.161) | 1.062 (0.425) | 0.288 (0.183) | -0.018 (0.129) | -0.083 (0.260) | -0.599 (0.308) |
| T1D (jknife) | 0.370 (0.165) | 0.992 (0.509) | 0.290 (0.194) | 0.004 (0.121) | -0.126 (0.314) | -0.528 (0.287) |
| T2D (REML) | 0.025 (0.081) | 0.638 (0.275) | -0.033 (0.102) | 0.087 (0.085) | 0.171 (0.174) | 0.111 (0.172) |
| T2D (jknife) | 0.022 (0.063) | 0.668 (0.164) | -0.048 (0.064) | 0.084 (0.094) | 0.165 (0.186) | 0.110 (0.095) |
| SP (REML) | 0.077 (0.066) | 0.443 (0.228) | -0.097 (0.077) | 0.008 (0.063) | 0.373 (0.140) | 0.196 (0.141) |
| SP (jknife) | 0.077 (0.067) | 0.401 (0.186) | -0.063 (0.090) | 0.007 (0.052) | 0.373 (0.130) | 0.206 (0.134) |
| MS (REML) | 0.055 (0.029) | 0.777 (0.094) | 0.117 (0.040) | 0.080 (0.031) | 0.015 (0.057) | -0.045 (0.057) |
| MS (jknife) | 0.058 (0.026) | 0.782 (0.144) | 0.115 (0.052) | 0.089 (0.039) | 0.002 (0.080) | -0.048 (0.071) |
| AS (REML) | 0.015 (0.104) | 1.063 (0.334) | 0.075 (0.135) | 0.209 (0.120) | -0.236 (0.206) | -0.126 (0.202) |
| AS (jknife) | 0.019 (0.107) | 1.065 (0.437) | 0.073 (0.118) | 0.193 (0.178) | -0.232 (0.265) | -0.120 (0.235) |
| UC (REML) | 0.076 (0.059) | 0.935 (0.194) | 0.238 (0.079) | -0.014 (0.057) | -0.056 (0.115) | -0.180 (0.124) |
| UC (jknife) | 0.079 (0.058) | 0.897 (0.235) | 0.250 (0.100) | -0.043 (0.052) | -0.023 (0.123) | -0.161 (0.157) |
| meta (REML) | 0.075 (0.020) | 0.795 (0.066) | 0.062 (0.026) | 0.066 (0.020) | 0.015 (0.039) | -0.031 (0.040) |
| | 4.74e-04 | 3.64e-22 | 1.25e-01 | 4.28e-03 | 5.48e-12 | 2.84e-42 |
| meta (jknife) | 0.073 (0.019) | 0.710 (0.077) | 0.047 (0.029) | 0.057 (0.022) | 0.028 (0.047) | -0.002 (0.043) |
| | 3.35e-04 | 5.45e-13 | 3.98e-01 | 2.25e-02 | 4.17e-08 | 3.18e-33 |

**Table S10. Meta-analysis adjusted for shared controls.** For each functional category, the emperical inflation due to shared controls ($\lambda_{GC}$) was estimated from random sampling. The raw meta-analysis estimate of $h^2_g$, standard error, and enrichment p-value is shown; followed by the corresponding $\lambda_{GC}$ adjusted estimates.

| Category | $\lambda_{GC}$ | % $h^2_g$ | se | p-value | adjusted se | adjusted p-value |
|---|---|---|---|---|---|---|
| Coding | 1.26 | 7.5% | 2.0% | 4.74e-04 | 2.2% | 1.83e-03 |
| UTR | 1.34 | 6.6% | 2.0% | 4.28e-03 | 2.4% | 1.36e-02 |
| Promoter | 1.45 | 6.2% | 2.6% | 1.25e-01 | 3.1% | 2.02e-01 |
| DHS | 1.32 | 79.5% | 6.6% | 3.64e-22 | 7.6% | 3.74e-17 |
| Intron | 1.39 | 1.5% | 3.9% | 5.48e-12 | 4.7% | 4.89e-09 |
| Intergenic | 1.70 | -3.1% | 4.0% | 2.84e-42 | 5.3% | 1.53e-25 |

**Table S11. Total liability-scale $h^2_{\mathbf{g}}$ from four inference methods.** For each trait, the total estimate of $h^2_{\mathrm{g}}$ is shown from the standard REML method and Haseman-Elston regression with and without included fixed-effects. Estimates were transformed to liability-scale using the given prevalence.

| | | No fixed-effects | | PCs as fixed-effects | |
|---|---|---|---|---|---|
| Phenotype | Prevalence | REML (se) | Regression (se) | REML (se) | Regression (se) |
| BD | 0.005 | 0.31 (0.033) | 0.40 (0.034) | 0.24 (0.035) | 0.24 (0.035) |
| CAD | 0.060 | 0.27 (0.061) | 0.28 (0.059) | 0.25 (0.062) | 0.22 (0.059) |
| CD | 0.001 | 0.18 (0.025) | 0.22 (0.025) | 0.17 (0.025) | 0.20 (0.025) |
| HT | 0.260 | 0.58 (0.097) | 0.59 (0.093) | 0.55 (0.098) | 0.50 (0.093) |
| RA | 0.005 | 0.10 (0.033) | 0.11 (0.032) | 0.09 (0.033) | 0.08 (0.032) |
| T1D | 0.005 | 0.14 (0.032) | 0.15 (0.031) | 0.13 (0.032) | 0.13 (0.032) |
| T2D | 0.080 | 0.50 (0.068) | 0.62 (0.067) | 0.42 (0.070) | 0.43 (0.067) |
| SP | 0.010 | 0.75 (0.013) | 10.00 (0.021) | 0.18 (0.024) | 0.25 (0.055) |
| MS | 0.001 | 0.29 (0.007) | 2.91 (0.008) | 0.17 (0.009) | 0.21 (0.013) |
| AS | 0.003 | 0.15 (0.027) | 0.16 (0.026) | 0.14 (0.027) | 0.14 (0.026) |
| UC | 0.001 | 0.15 (0.016) | 0.15 (0.015) | 0.14 (0.016) | 0.14 (0.015) |

**Table S12. Fraction of DHS $h^2_{\mathbf{g}}$ from four inference methods.** For each trait, the total estimate of $h^2_{\mathrm{g}}$ is shown from the standard REML method and Haseman-Elston regression with and without included fixed-effects.

| | | No fixed-effects | | PCs as fixed-effects | |
|---|---|---|---|---|---|
| Phenotype | Prevalence | REML | Regression | REML | Regression |
| BD | 0.005 | 0.48 (0.20) | 0.63 (0.14) | 0.35 (0.27) | 0.43 (0.24) |
| CAD | 0.060 | -0.08 (0.44) | -0.05 (0.39) | 0.01 (0.47) | -0.10 (0.49) |
| CD | 0.001 | 1.46 (0.26) | 1.49 (0.21) | 1.52 (0.27) | 1.58 (0.24) |
| HT | 0.260 | 0.91 (0.29) | 1.06 (0.26) | 0.94 (0.32) | 1.12 (0.31) |
| RA | 0.005 | 1.37 (0.57) | 1.38 (0.52) | 1.63 (0.67) | 1.76 (0.75) |
| T1D | 0.005 | 1.21 (0.40) | 1.35 (0.36) | 1.06 (0.43) | 1.27 (0.43) |
| T2D | 0.080 | 0.70 (0.24) | 0.70 (0.18) | 0.64 (0.28) | 0.52 (0.26) |
| SP | 0.010 | 0.56 (0.06) | 0.75 (0.00) | 0.44 (0.23) | 0.09 (0.39) |
| MS | 0.001 | 0.72 (0.06) | 0.79 (0.00) | 0.78 (0.09) | 0.91 (0.11) |
| AS | 0.003 | 1.09 (0.31) | 1.09 (0.28) | 1.06 (0.33) | 1.07 (0.33) |
| UC | 0.001 | 0.91 (0.18) | 1.00 (0.16) | 0.94 (0.19) | 1.03 (0.18) |

**Table S13. Functional enrichment of main categories within DHS category.** The extended DHS category was sub-partitioned into five annotations, and $h_g^2$ reported. % category reports the percent of main category covered by DHS. The remaining non-DHS category was significantly negative ($P = 0.002$), likely due to underestimating standard errors.

| Category | % category | % $h_g^2$ | % DHS $h_g^2$ (se) | % DHS SNP | enrichment to DHS (se) | PV |
|---|---|---|---|---|---|---|
| DHS-Coding | 27.4% | 5% (1%) | 5% (1%) | 0.9% | 5.30 (1.34) | 1.35e-03 |
| DHS-UTR | 31.2% | 5% (1%) | 4% (1%) | 1.4% | 2.62 (0.93) | 8.16e-02 |
| DHS-Promoter | 29.8% | 9% (2%) | 9% (2%) | 3.9% | 2.25 (0.47) | 7.90e-03 |
| DHS-Intron | NA | 40% (3%) | 35% (2%) | 39.6% | 0.87 (0.06) | 3.74e-02 |
| DHS-Intergenic | NA | 51% (4%) | 48% (2%) | 54.2% | 0.89 (0.04) | 1.05e-02 |
| non-DHS | NA | -16% (5%) | NA | NA | NA | NA |

**Table S14. Cell-type and phenotype specific DHS enrichment.** Fold-enrichment of $h^2_g$ relative to SNPs reported for cell-types DHSs observed as significant (without adjusting for 83 cell-types tested). Enrichment was measured in comparison to $h^2_g$ at DHS regions, accounting for the background DHS enrichment. Results shown separately from meta-analysis of 6 autoimmune traits and 5 non-autoimmune traits.

| Tissue type | Cell type | Autoimmune traits | Non-autoimmune traits |
|---|---|---|---|
| Fetal Kidney | Fetal Left Renal Cortex Cell | 6.5 (7.2e-04) | 1.0 (9.9e-01) |
| Blood | T Cell | 5.8 (1.4e-05) | 1.8 (3.5e-01) |
| Fetal Muscle | Fetal Back Muscle Cell | 5.5 (1.0e-02) | 2.3 (4.6e-01) |
| Fetal Kidney | Fetal Right Renal Pelvis | 5.4 (4.3e-04) | 0.9 (8.2e-01) |
| Bone Marrow | Blast Cell | 5.1 (9.2e-04) | 2.1 (2.9e-01) |
| Liver | Hliver Cell | 4.5 (1.6e-03) | -0.6 (6.0e-02) |
| Bone Marrow | Monocyte CD14 | 4.3 (4.3e-04) | 1.1 (8.2e-01) |
| Blood | CD8 Primary Cell | 4.0 (1.7e-04) | 0.9 (7.9e-01) |
| Bone Marrow | Erythroleukemic Cell | 3.7 (1.9e-02) | 0.5 (2.6e-01) |
| Blood | Leukemia Cells | 3.5 (5.9e-05) | 0.9 (4.5e-01) |
| Blood | Lymphoblastoid Cell | 3.4 (3.1e-05) | 1.2 (8.9e-01) |
| Blood | CD14 Primary Cell | 2.3 (6.5e-03) | 0.8 (9.7e-01) |
| Blood | CD4 Primary Cell | 2.3 (3.2e-03) | 1.0 (5.8e-01) |
| Fetal Thymus | Fetal Thymus Cell | 2.3 (2.8e-03) | 0.9 (6.7e-01) |
| Blood | Lymphocyte | 1.9 (4.9e-02) | 0.4 (9.2e-02) |
| Endothelium | Endothelial Cell | 1.8 (2.8e-01) | -0.8 (7.1e-03) |
| Blood | CD34 Primary Cell | 1.7 (1.7e-02) | 0.3 (6.4e-02) |
| Kidney | Endothelial Cell | 1.6 (3.1e-01) | -0.7 (8.6e-03) |
| Blood | Endothelial Cell | 1.5 (2.3e-01) | 0.1 (3.7e-02) |
| Embryo | Embryonic Stem Cells | -0.4 (3.2e-02) | 1.1 (9.4e-01) |

**Table S15. Components of heritability from regulatory elements in schizophrenia.**

| A: GWAS chip + Exome chip | | | | | |
|---|---|---|---|---|---|
| Annotation | $h_g^2$ (se) | % $h_g^2$ (se) | % Non-coding SNPs | Enrichment (se) | P-Value |
| Coding (common) | 0.049 (0.015) | NA | NA | NA | NA |
| Coding (rare) | 0.037 (0.028) | NA | NA | NA | NA |
| UTR | 0.003 (0.007) | 1.1% (2.4%) | 1.9% | 0.59 (1.24) | 7.4e-01 |
| Promoter | 0.006 (0.008) | 2.2% (3.0%) | 3.0% | 0.73 (1.00) | 7.8e-01 |
| DHS | 0.114 (0.023) | 41.2% (8.0%) | 25.7% | 1.60 (0.31) | 5.3e-02 |
| Intron | 0.083 (0.019) | 30.2% (6.4%) | 26.2% | 1.15 (0.25) | 5.3e-01 |
| Intergenic | 0.070 (0.023) | 25.3% (7.4%) | 43.2% | 0.59 (0.17) | 1.6e-02 |
| B: GWAS chip | | | | | |
| Annotation | $h_g^2$ (se) | % $h_g^2$ (se) | % SNPs | Enrichment (se) | P-Value |
| Coding | 0.014 (0.007) | 4.3% (2.3%) | 2.0% | 2.15 (1.13) | 3.1e-01 |
| UTR | 0.005 (0.007) | 1.6% (2.1%) | 1.9% | 0.84 (1.12) | 8.9e-01 |
| Promoter | 0.009 (0.008) | 2.8% (2.6%) | 2.9% | 0.95 (0.90) | 9.5e-01 |
| DHS | 0.118 (0.023) | 37.8% (7.1%) | 25.2% | 1.50 (0.28) | 7.3e-02 |
| Intron | 0.092 (0.019) | 29.5% (5.8%) | 25.7% | 1.15 (0.22) | 5.1e-01 |
| Intergenic | 0.075 (0.023) | 24.0% (6.6%) | 42.4% | 0.57 (0.16) | 5.7e-03 |
| C: 1000G imputed + Exome chip | | | | | |
| Annotation | $h_g^2$ (se) | % $h_g^2$ (se) | % Non-coding SNPs | Enrichment (se) | P-Value |
| Coding (common) | 0.050 (0.016) | NA | NA | NA | NA |
| Coding (rare) | 0.035 (0.028) | NA | NA | NA | NA |
| UTR | 0.030 (0.016) | 11.0% (5.9%) | 0.8% | 13.26 (7.08) | 8.3e-02 |
| Promoter | -0.017 (0.019) | -6.1% (7.0%) | 2.3% | -2.63 (2.99) | 2.3e-01 |
| DHS | 0.144 (0.059) | 53.0% (20.4%) | 16.9% | 3.13 (1.21) | 7.7e-02 |
| Intron | 0.044 (0.032) | 16.0% (11.8%) | 28.7% | 0.56 (0.41) | 2.8e-01 |
| Intergenic | 0.071 (0.035) | 26.1% (12.6%) | 51.2% | 0.51 (0.25) | 4.7e-02 |
| D: 1000G imputed | | | | | |
| Annotation | $h_g^2$ (se) | % $h_g^2$ (se) | % SNPs | Enrichment (se) | P-Value |
| Coding | 0.056 (0.014) | 17.6% (4.8%) | 0.4% | 45.89 (12.43) | 3.1e-04 |
| UTR | 0.023 (0.015) | 7.2% (4.7%) | 0.8% | 8.66 (5.68) | 1.8e-01 |
| Promoter | -0.024 (0.018) | -7.7% (5.7%) | 2.3% | -3.31 (2.47) | 8.2e-02 |
| DHS | 0.169 (0.055) | 53.6% (16.4%) | 16.9% | 3.18 (0.97) | 2.5e-02 |
| Intron | 0.025 (0.030) | 7.8% (9.5%) | 28.6% | 0.27 (0.33) | 2.8e-02 |
| Intergenic | 0.068 (0.032) | 21.6% (10.1%) | 51.0% | 0.42 (0.20) | 3.7e-03 |

**Table S16. Functional enrichment from GWAS hits.** The single top genome-wide significant SNP from each corresponding 1MB locus in the analyzed cohorts was identified, and category enrichment relative to total number of SNPs in the category was computed (over all traits).

| Category | % top SNPs | % SNPs | enrichment |
|---|---|---|---|
| Coding | 1.7% | 0.5% | 3.16 |
| UTR | 1.7% | 0.8% | 2.20 |
| Promoter | 2.3% | 2.2% | 1.04 |
| DHS | 14.3% | 15.7% | 0.91 |
| Intron | 30.7% | 28.8% | 1.07 |
| Intergenic | 49.3% | 52.0% | 0.95 |

**Table S17. BLUP prediction accuracy in PGC.** Prediction $R^2$ and significance is reported for GBLUPs estimated from six functional categories jointly in 10-fold cross-validation. Univariate $R^2$ column reports the accuracy of a 1-dof predictor from each of the component individually. Step-wise $R^2$ column reports the accuracy of a multiple-dof prediction with each component added as an additional predictor in turn. Step-wise PV column reports p-value from the newly added predictor. Multivariate PV reports p-value from each predictor in the final 6-dof prediction model. In all instances, principal components were included as additional fixed-effects and subtracted from prediction $R^2$.

| Component | Univariate $R^2$ | Step-wise $R^2$ | Step-wise PV | Multivariate PV |
|---|---|---|---|---|
| DHS | 0.055 | 0.055 | 4.24e-104 | 7.49e-12 |
| Intron | 0.034 | 0.056 | 1.60e-03 | 2.83e-04 |
| Intergenic | 0.031 | 0.059 | 8.50e-07 | 6.22e-07 |
| UTR | 0.021 | 0.062 | 1.05e-07 | 7.34e-07 |
| Promoter | 0.016 | 0.062 | 3.46e-01 | 2.42e-01 |
| Coding | 0.009 | 0.062 | 2.24e-01 | 2.24e-01 |

**Table S18. Summary of exome-chip data.** Number of polymorphic variants by coding class and sub-cohort in the Swedish schizophrenia samples.

| Variant class | Homogenous | All |
|---|---|---|
| All coding | 104,240 | 110,331 |
| Singleton coding | 19,860 | 19,329 |
| Rare coding (MAF $< 0.01$, non-singleton) | 64,040 | 70,569 |
| Common coding (MAF $\geq 0.01$) | 20,340 | 20,433 |

**Table S19. Components of heritability of Schizophrenia from exome chip.** Estimates of $h^2_g$ are reported from variance components in the homogenous Swedish sub-population as well as all samples. Top panel shows estimates (without accounting for shared variance due to LD between classes) in All samples, homogenous Swedish sub-population, and LD-adjusted estimates from the homogenous Swedish sub-population. Bottom panel shows corresponding joint estimates accounting for shared variance due to LD. In bottom panel, P-Values from a likelihood ratio test on the corresponding component are shown below each row.

| Variant class (and SNPs in LD) | All $h^2_g$ (se) | Hom. $h^2_g$ (se) | Hom. $h^2_{gLD}$ (se) |
|---|---|---|---|
| All | 0.307 (0.027) | 0.366 (0.038) | 0.370 (0.040) |
| GWAS chip | 0.273 (0.020) | 0.314 (0.028) | 0.317 (0.042) |
| Exome chip | 0.116 (0.022) | 0.157 (0.032) | 0.158 (0.034) |
| Variant class (exclusive) | All $h^2_g$ (se)<br>P-Value | Hom. $h^2_g$ (se)<br>P-Value | Hom. $h^2_{gLD}$ (se)<br>P-Value |
| GWAS chip | 0.242 (0.020) | 0.282 (0.029) | 0.291 (0.028) |
| Exome chip | 0.065 (0.021)<br>$2.0 \times 10^{-06}$ | 0.084 (0.031)<br>$2.0 \times 10^{-03}$ | 0.079 (0.034)<br>$1.2 \times 10^{-02}$ |
| Exome chip (rare) | 0.014 (0.019)<br>$2.1 \times 10^{-01}$ | 0.040 (0.028)<br>$7.7 \times 10^{-02}$ | 0.037 (0.029)<br>$1.0 \times 10^{-01}$ |
| Exome chip (common) | 0.051 (0.011)<br>$5.2 \times 10^{-07}$ | 0.044 (0.015)<br>$1.3 \times 10^{-03}$ | 0.042 (0.017)<br>$7.7 \times 10^{-03}$ |

**Table S20. Theoretical entropy of functional partitions.** Normalized probability of a SNP being causal, as well as the resulting entropy is reported for five enrichment types observed in the real data.

| Enrichment | Coding | DHS | Promoter | UTR | Intron | Intergenic | Entropy (H) |
|---|---|---|---|---|---|---|---|
| Promoter (imputed) | 0.00% | 2.35% | 0.14% | 0.01% | 7.94% | 25.98% | 0.65 |
| Coding (imputed) | 0.04% | 2.28% | 0.05% | 0.01% | 7.69% | 25.17% | 0.64 |
| All categories (genotyped) | 0.02% | 6.02% | 0.11% | 0.03% | 6.49% | 13.03% | 0.62 |
| DHS (imputed) | 0.00% | 12.45% | 0.01% | 0.00% | 2.02% | 6.60% | 0.52 |
| All categories (imputed) | 0.04% | 12.45% | 0.14% | 0.05% | 0.44% | -1.59% | 0.30 |

**Table S21. Empirical and analytical standard error of partitioned $h^2_{\mathbf{g}}$.** Over 1,000 simulations for each of three disease architectures, the emperical standard deviation and average REML analytical standard error is reported for each functional category.

| Genotyped: | | | | | | |
|---|---|---|---|---|---|---|
| | causal MAF$< 0.50$ | | causal MAF$< 0.05$ | | causal MAF$_{\text{DHS}} < 0.05$ | |
| Category | empirical sd | REML se | empirical sd | REML se | empirical sd | REML se |
| Coding | 0.009 | 0.008 | 0.011 | 0.010 | 0.011 | 0.010 |
| UTR | 0.009 | 0.009 | 0.011 | 0.011 | 0.011 | 0.011 |
| Promoter | 0.015 | 0.015 | 0.017 | 0.016 | 0.016 | 0.016 |
| DHS | 0.059 | 0.053 | 0.050 | 0.051 | 0.051 | 0.051 |
| Intron | 0.047 | 0.047 | 0.041 | 0.042 | 0.042 | 0.042 |
| Intergenic | 0.058 | 0.058 | 0.050 | 0.050 | 0.051 | 0.050 |
| Imputed: | | | | | | |
| | causal MAF$< 0.50$ | | causal MAF$< 0.05$ | | causal MAF$_{\text{DHS}} < 0.05$ | |
| Category | empirical sd | REML se | empirical sd | REML se | empirical sd | REML se |
| Coding | 0.033 | 0.032 | 0.033 | 0.032 | 0.032 | 0.032 |
| UTR | 0.033 | 0.033 | 0.033 | 0.033 | 0.032 | 0.033 |
| Promoter | 0.042 | 0.041 | 0.042 | 0.041 | 0.044 | 0.041 |
| DHS | 0.124 | 0.124 | 0.125 | 0.124 | 0.126 | 0.124 |
| Intron | 0.069 | 0.068 | 0.069 | 0.068 | 0.067 | 0.069 |
| Intergenic | 0.077 | 0.075 | 0.073 | 0.075 | 0.077 | 0.075 |

**Table S22. Fraction of simulated common non-coding heritability inferred by coding variants.** Phenotypes were simulated using 5,000 randomly selected causal variants from GWAS-chip non-coding SNPs with $h_g^2 = 0.5$ and inferred using variance-components from exome coding SNPs only. Bottom panel shows results when a third variance-component corresponding to non-coding variants is estimated jointly in the model. Values reported represent the fraction of simulated heritability inferred averaged over 50 trials (with standard error in parenthesis).

| Joint GRM | $\hat{h}_g^2$ (se) | $\hat{h}_{\text{gLD}}^2$ (se) |
|---|---|---|
| Common coding | 10.7% (0.7%) | 11.8% (0.9%) |
| Rare coding (non-singleton) | 1.7% (1.6%) | 0.7% (2.0%) |
| **Joint GRM + non-coding** | $\hat{h}_g^2$ (se) | $\hat{h}_{\text{gLD}}^2$ (se) |
| Common coding | -1.2% (0.7%) | -1.1% (0.9%) |
| Rare coding (non-singleton) | -0.6% (1.7%) | -2.3% (2.1%) |

**Table S23. $\hat{h}_g^2$ of phenotypes simulated from coding variants.** Quasi-infinitesimal phenotypes were simulated from either rare coding ($f \leq 0.01$) or common coding ($f > 0.01$) variants. $\hat{h}_g^2$ inferred from different classes of GRMs is shown, with standard error over 10 trials in parenthesis. Lower panel shows results from multiple GRMs fit jointly, with bolded GRM corresponding to the reported variance-component estimate.

| | Causal variants | |
|---|---|---|
| GRM genotypes | Rare coding | Common coding |
| non-coding | 0.051 (0.012) | 0.426 (0.006) |
| rare coding | 0.509 (0.011) | 0.043 (0.015) |
| common coding | 0.024 (0.003) | 0.514 (0.008) |
| | Causal Variants | |
| Joint GRM genotypes | Rare coding | Common coding |
| rare coding + non-coding | 0.486 (0.003) | 0.002 (0.001) |
| common coding + non-coding | 0.025 (0.002) | 0.485 (0.003) |
| rare coding + common coding | 0.486 (0.004) | 0.001 (0.001) |
| rare coding + common coding | 0.000 (0.001) | 0.482 (0.004) |

**Table S24. Joint $h^2_{\mathbf{g}}$ from simulated phenotype in Swedish schizophrenia cohort**.

| Simulated $h^2_{\mathrm{g}}$ | | | Jointly inferred $\hat{h}^2_g$ (se) | | |
|---|---|---|---|---|---|
| rare coding | common coding | all non-coding | rare coding | common coding | all non-coding |
| 0.25 | 0.25 | 0.25 | 0.247 (0.003) | 0.262 (0.002) | 0.256 (0.003) |

**Table S25. Collapsed $\hat{h}_g^2$ of phenotypes simulated from non-coding variants.** An infinitesimal trait with $h_g^2 = 0.50$ was simulated from non-coding variants and $\hat{h}_g^2$ was inferred from coding variants collapsed below designated minor allele frequency $f_{\max}$. Mean and standard error are reported over 50 random trials.

| | $f_{\max}$ | | | | |
|---|---|---|---|---|---|
| GRM | Singleton | 0.001 | 0.005 | 0.010 | 0.050 |
| Collapsed | -0.009 (0.002) | -0.002 (0.002) | -0.002 (0.003) | -0.000 (0.003) | 0.009 (0.004) |
| Collapsed + non-coding | -0.007 (0.002) | -0.004 (0.002) | -0.004 (0.003) | -0.004 (0.003) | 0.001 (0.003) |

**Table S26. Collapsed $\hat{h}_g^2$ of phenotypes simulated from rare coding variants.** A quasi-infinitesimal trait was simulated from specified exome-wide causal fraction of coding variants and varying $f_{\max}$ and total $h_g^2 = 0.5$. Effect-sizes were sampled from a standard normal distribution on the normalized-variant scale or the allelic-variant scale, and forced to be uni-directional within each gene. The collapsed $\hat{h}_g^2$ was then estimated from coding variants at the given $f_{\max}$. No more than half of the true $h_g^2$ can be recovered from collapsing under any disease architecture.

| | | Fraction causal | | | |
|---|---|---|---|---|---|
| $f_{\max}$ | Effect distribution | 100% | 50% | 10% | 1% |
| 0.001 | Uniform | 0.49 (0.002) | 0.33 (0.003) | 0.21 (0.002) | 0.17 (0.005) |
| 0.001 | Allelic | 0.39 (0.003) | 0.28 (0.003) | 0.20 (0.003) | 0.17 (0.007) |
| 0.001 | Normalized | 0.33 (0.002) | 0.22 (0.003) | 0.16 (0.002) | 0.16 (0.006) |
| 0.005 | Uniform | 0.47 (0.002) | 0.33 (0.005) | 0.22 (0.002) | 0.19 (0.006) |
| 0.005 | Allelic | 0.37 (0.003) | 0.28 (0.004) | 0.21 (0.004) | 0.18 (0.007) |
| 0.005 | Normalized | 0.28 (0.003) | 0.19 (0.004) | 0.14 (0.002) | 0.14 (0.006) |
| 0.010 | Uniform | 0.47 (0.003) | 0.34 (0.005) | 0.24 (0.002) | 0.20 (0.006) |
| 0.010 | Allelic | 0.38 (0.002) | 0.29 (0.006) | 0.22 (0.003) | 0.20 (0.007) |
| 0.010 | Normalized | 0.24 (0.004) | 0.17 (0.003) | 0.13 (0.002) | 0.15 (0.007) |
| 0.050 | Uniform | 0.42 (0.003) | 0.35 (0.006) | 0.27 (0.003) | 0.23 (0.008) |
| 0.050 | Allelic | 0.35 (0.003) | 0.30 (0.006) | 0.28 (0.003) | 0.23 (0.010) |
| 0.050 | Normalized | 0.22 (0.003) | 0.16 (0.005) | 0.12 (0.002) | 0.14 (0.006) |

**Table S27. Likelihood ratio of collapsed vs. non-collapsed $\hat{h}_g^2$ for phenotypes simulated from rare coding variants.**

| | | Fraction causal | | | |
|---|---|---|---|---|---|
| $f_{\max}$ | Effect distribution | 100% | 50% | 10% | 1% |
| 0.001 | Uniform | 1.51 | 0.80 | 0.40 | 0.31 |
| 0.001 | Allelic | 1.00 | 0.63 | 0.38 | 0.31 |
| 0.001 | Normalized | 0.77 | 0.44 | 0.27 | 0.26 |
| 0.005 | Uniform | 1.54 | 0.92 | 0.49 | 0.42 |
| 0.005 | Allelic | 1.12 | 0.70 | 0.46 | 0.39 |
| 0.005 | Normalized | 0.72 | 0.41 | 0.24 | 0.26 |
| 0.010 | Uniform | 1.58 | 0.97 | 0.56 | 0.45 |
| 0.010 | Allelic | 1.14 | 0.76 | 0.51 | 0.46 |
| 0.010 | Normalized | 0.57 | 0.34 | 0.22 | 0.29 |
| 0.050 | Uniform | 1.31 | 0.96 | 0.72 | 0.59 |
| 0.050 | Allelic | 0.97 | 0.80 | 0.73 | 0.62 |
| 0.050 | Normalized | 0.48 | 0.31 | 0.20 | 0.26 |

**Table S28. Collapsed-variant $\hat{h}_g^2$ of Schizophrenia from exome chip.** Estimates of heritability from gene-based collapsed variants computed in two sub-groups of Swedish samples with increasing allele frequency thresholds. Analytical standard error reported in parenthesis.

| Coding $f_{\max}$ | Homogenous | All |
|---|---|---|
| Singleton | 0.000 (0.007) | 0.000 (0.004) |
| 0.001 | 0.000 (0.009) | 0.000 (0.006) |
| 0.005 | 0.000 (0.010) | 0.004 (0.007) |
| 0.010 | 0.000 (0.011) | 0.006 (0.008) |
| 0.050 | 0.025 (0.013) | 0.031 (0.009) |

**Table S29. Components of heritability for known Schizophrenia loci.** $h^2_g$ for multiple joint estimates at known schizophrenia loci are reported for the underlined component in the homogenous Swedish cohort.

| Joint GRM: | $h^2_g$ (se) |
|---|---|
| known,non-coding + non-coding | 0.018 (0.004) |
| known,non-coding + non-coding | 0.287 (0.028) |
| known,coding + known,non-coding + non-coding | 0.006 (0.004) |
| known,coding + known,non-coding + non-coding | 0.018 (0.004) |
| known,coding + known,non-coding + non-coding | 0.286 (0.028) |