Evaluating and improving heritability models using summary statistics

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There is currently much debate regarding the best way to model how heritability varies across the genome. The authors of GCTA recommend the GCTA-LDMS-I Model, the authors of LD Score Regression recommend the Baseline LD Model, while we have instead recommended the LDAK Model. Here we provide a statistical framework for assessing heritability models using summary statistics from genome-wide association studies. Using data from studies of 31 complex human traits (average sample size 136,000), we show that the Baseline LD Model is the most realistic of the existing heritability models, but that it can be significantly improved by incorporating features from the LDAK Model. Our framework also provides a method for estimating the selection-related parameter α from summary statistics, finding strong evidence (P<1e-6) of negative selection for traits including height, systolic blood pressure and college education.

Previously,[1] we explained how the softwares GCTA[2] and LD Score Regression[3] (LDSC) derive their estimates from an underlying heritability model, and demonstrated how changing this model can lead to very different estimates of SNP heritability, confounding bias and heritability enrichments.[4] Originally, both GCTA and LDSC assumed that each SNP is expected to contribute equal heritability, which we refer to as the GCTA Model.[5] We showed that it is more realistic to assume the LDAK Model, where expected heritability varies with both linkage disequilibrium (LD) and minor allele frequency (MAF).[1,6] Now the authors of GCTA recommend using the GCTA-LDMS-I Model,[7,8] which partitions the GCTA Model based on MAF and LD, while the authors of LDSC recommend using the Baseline LD Model,[9,10] which adds to the GCTA Model 74 SNP annotations based on LD, MAF and functional classifications (when used with this model, LDSC is referred to as S-LDSC).

Our earlier work[1] compared the GCTA and LDAK Models based on the likelihood from restricted maximum likelihood[11] (REML). However, this approach requires access to individual-level data and is only feasible for relatively simple heritability models. We now propose an approximate model likelihood that can be computed from genome-wide association study (GWAS) summary statistics and for highly complex heritability models.

Results

For our main analysis, we use summary statistics from 31 GWAS to compare twelve heritability models (Table 1). Here we briefly describe the heritability models, our proposed model likelihood and the data we use; for full details see Online Methods.

Heritability models. The heritability model specifies how $E[h^2_j]$, the expected heritability contributed by SNP j, varies across the genome. We consider nine existing heritability models. The one-parameter GCTA Model[5] assumes $E[h^2_j]$ is constant. The 20-parameter GCTA-LDMS-R[7] and GCTA-LDMS-I[8] Models both partition the genome based on MAF and LD, then assume $E[h^2_j]$ is constant within each bin. The 53-parameter Baseline Model[9] extends the GCTA Model by adding 52 functional annotations; these include 24 function indicators that can be used to estimate functional enrichments (the heritability enrichments of functional categories of SNPs). The 75-parameter Baseline LD Model[10] adds to the GCTA Model six LD-related annotations, ten MAF indicators and 58 functional annotations (including the 52 functional annotations of the Baseline Model). The two-parameter GCTA+1Fun Model[12] adds to the GCTA Model one function indicator from the Baseline LD Model (there are 24 versions of this model, depending on which indicator is added). The one-parameter LDAK Model[1,6] assumes $E[h^2_j]$ is proportional to $w_j[f_j(1-f_j)]^{0.75}$, where w_j is the LDAK weighting of SNP j (w_j tends to be higher for SNPs in low-LD regions) and f_j is its MAF. The two-parameter LDAK+1Fun[1] and 25-parameter LDAK+24Fun[4] Models extend the LDAK Model by adding either one or all 24 function indicators of the Baseline Model.

We construct three novel heritability models. The 66-parameter BLD-LDAK Model combines features of the Baseline LD and LDAK Models: first we add to the Baseline LD Model the LDAK weighting w_j, then we remove the ten MAF indicators and scale the remaining 66 annotations by $[f_j(1-f_j)]^{0.75}$. The 67-parameter BLD-LDAK+Alpha Model is the same, except it scales the annotations by $[f_j(1-f_j)]^{1+\alpha}$, where α is estimated from the data.

The one-parameter LDAK-Thin Model is a simplified version of the LDAK Model, obtained by setting the LDAK weightings to either one or zero.

Measuring model fit. Suppose we have summary statistics from a GWAS; let S_j denote the $\chi^2(1)$ test statistic from regressing the phenotype on SNP j. Suppose also we have genotype data from an ancestrally-matched reference panel, from which we can estimate r^2_{jl}, the squared correlation between SNPs j and l. The authors of LDSC[3] derived that the marginal distribution of each S_j is approximately gamma with shape ½ and scale $2E[S_j]$, where $E[S_j]$ is the expectation of S_j (a function of the parameters of the chosen heritability model). Based on this, we propose the approximate joint log likelihood

$$\text{logl} = \sum_j \frac{1}{u_j} \log\left(\Gamma\left(S_j \middle| \frac{1}{2}, 2E[S_j]\right)\right)$$

where

$$u_j = \sum_{l \text{ near } j} r^2_{jl},$$

and $\Gamma(X|a,b)$ is the probability density function of a gamma distribution with shape a and scale b. The weights $1/u_j$ are the same as those used by LDSC when regressing S_j onto $E[S_j]$, and are included to allow for correlations between local SNPs.[3]

We perform three analyses to support the use of logl to compare heritability models. Firstly, Supplementary Fig. 1 shows that for scenarios where both logl and the REML likelihood can be computed, they are concordant. Secondly, Supplementary Fig. 2 shows that when we add a non-informative annotation to a heritability model, twice the increase in logl is approximately $\chi^2(1)$ distributed (the distribution were logl an exact likelihood). Thirdly, Table 1 shows that the ranking of heritability models based on logl is consistent with the ranking based on leave-one-chromosome-out prediction of test statistics. Additionally, Supplementary Table 1 shows that the ranking of models is unchanged if we instead compute an unweighted version of logl (using only SNPs in approximate linkage equilibrium and u_j=1).

Data. We use summary statistics from two sets of GWAS. The first set are 14 traits from UK Biobank (UKBb):[13,14] eight continuous (body mass index, forced vital capacity, height, impedance, neuroticism score, pulse rate, reaction time and systolic blood pressure), four binary (college education, ever smoked, hypertension and snorer) and two ordinal (difficulty falling asleep and preference for evenings). We performed these GWAS ourselves; after stringent quality control, 130k samples and 4.7M SNPs remained. We additionally use summary statistics from 17 Public GWAS:[4,15] ten continuous (including anthropometric measures and psychiatric scores) and seven binary (mostly complex diseases). The average sample size is 141k (range 21-329k). As a reference panel, we use 479 European individuals from the 1000 Genome Project,[16] recorded for 10.0M SNPs (MAF>0.005).

Performance of heritability models. Table 1 reports logl for the twelve heritability model, averaged across either the 14 UKBb or 17 Public GWAS (values for individual GWAS are in Supplementary Table 2). We rank models based on the Akaike Information Criterion[17] (AIC), equal to 2K-2logl, where K is the number of parameters.

When we restrict to the nine existing heritability models, the Baseline LD Model performs best; it has average AIC 236 lower than the next best model and is the top-ranked model for 28 of the 31 GWAS. However, when we consider all twelve heritability models, the BLD-LDAK and BLD-LDAK+Alpha Models are the best; they both have average AIC 109 lower than the Baseline LD Model, and now these are the top two models for 28 of the 31 GWAS. These two models would remain the best if instead of the AIC, we ranked models based on -2logl or 4K-2logl (i.e., either removed or doubled the penalty on parameters). Although the LDAK-Thin Model ranks poorly overall, it is the best one-parameter model (we explain the utility of this model in the Discussion).

		14 UKBb GWAS		17 Public GWAS	
Existing Models	**K**	**Average logl**	**Average ρ**	**Average logl**	**Average ρ**
GCTA	1	0	0.059	0	0.038
GCTA-LDMS-R	20	174	0.072	162	0.051
GCTA-LDMS-I	20	179	0.070	146	0.048
GCTA+1Fun	2	257	0.068	215	0.056
Baseline	53	430	0.074	428	0.061
Baseline LD	75	562	0.084	576	0.071
LDAK	1	56	0.066	37	0.048
LDAK+1Fun	2	145	0.067	127	0.055
LDAK+24Fun	25	220	0.068	224	0.057
Novel Models	**K**	**Average logl**	**Average ρ**	**Average logl**	**Average ρ**
BLD-LDAK	66	611	0.085	618	0.071
BLD-LDAK+Alpha	67	612	0.085	619	0.071
LDAK-Thin	1	174	0.073	136	0.056

Table 1 | Performance of heritability models. K is the number of parameters. logl is the approximate model likelihood (relative to that for the GCTA Model) and ρ is the weighted correlation between observed and predicted test statistics from leave-one-chromosome-out prediction; values are averaged across either the 14 UKBb or 17 Public GWAS. The s.d. of average ρ is always 0.001. There are 24 versions of the GCTA+1Fun and LDAK+1Fun Models (one for each function indicator); values here correspond to the versions with highest average logl.

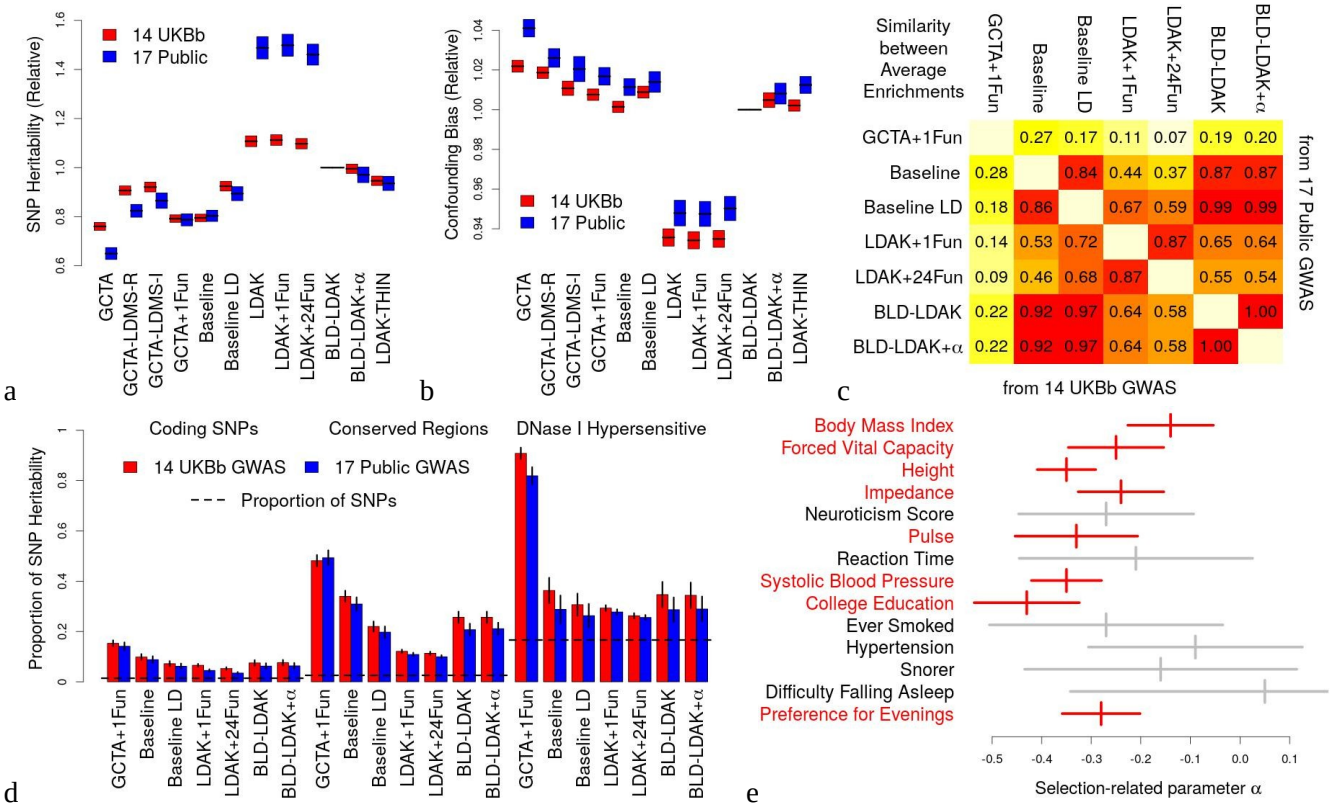

Fig. 1 | Genetic architecture estimates from different heritability models. a & **b**, Average estimates of SNP heritability and confounding bias from twelve heritability models; values are relative to those from the BLD-LDAK Model, and calculated using either the 14 UKBb or 17 Public GWAS (bar heights indicate 95% confidence intervals). There are 24 versions of the GCTA+1Fun and LDAK+1Fun Models (one for each function indicator); values here correspond to the versions with highest average logl. **c**, Concordance correlation coefficient between average estimates of functional enrichments from seven heritability models; values are calculated using either the 14 UKBb or 17 Public GWAS. **d**, Average estimates of the proportion of SNP heritability contributed by coding SNPs, conserved regions and DNase I hypersensitive sites (three of the 24 functional categories of SNPs) from seven heritability models; values are calculated using either the 14 UKBb or 17 Public GWAS (vertical segments indicate 95% confidence intervals). The estimates of functional enrichments are obtained by dividing these estimates by the proportion of SNPs in each category (dashed horizontal lines). **e**, Estimates of α for the 14 UKBb GWAS, obtained using the BLD-LDAK+Alpha Model (horizontal lines indicate 95% confidence intervals). α is significantly negative ($P<0.05/31$) for the eight red traits. See main text for details of the heritability models.

Genetic architecture estimates. Figures 1a-d, Supplementary Fig. 3 and Supplementary Tables 3-6 compare estimates of SNP heritability, confounding bias, and functional enrichments from the twelve heritability models (note that only the seven models that include function indicators can be used to estimate functional enrichments). As heritability models have become more sophisticated, estimates have tended to converge (the more complex models produce estimates of SNP heritability and confounding bias intermediate between those from the GCTA and LDAK Models, and estimates of functional enrichments intermediate between those from the GCTA+1Fun and LDAK+1Fun Models). Based on model fit (Table 1), we consider the BLD-LDAK and BLD-LDAK+Alpha Models to be most reliable; their estimates of confounding bias and functional enrichments are close to those from the Baseline LD Model, while their estimates of SNP heritability tend to be between those from the Baseline LD and GCTA-LDMS-I Models and those from the LDAK Model.

Figure 1e and Supplementary Table 7 report estimates of α in the BLD-LDAK+Alpha Model. This parameter specifies the assumed relationship between heritability and MAF,[1,6] and has been used to measure selection[10,18] (negative α indicates that less-common SNPs tend to have larger effect sizes than more-common SNPs, and vice versa). Across the 31 GWAS, the average estimate of α is -0.26 (s.d. 0.01). Estimates of α are significantly negative ($P<0.05/31$) for eight of the 14 UKBb GWAS and two of the 17 Public GWAS; the three most significant are for height (α=-0.35, s.d. 0.03), systolic blood pressure (α=-0.35, s.d. 0.04) and college education (α=-0.43, s.d. 0.05).

Discussion

When software for estimating SNP heritability were first developed, little attention was given to the heritability model, and instead it was standard to assume that all SNPs are expected to contribute equal heritability.[2,3] It is now recognized that this assumption is sub-optimal,[1,4] and the best way to model how heritability varies across the genome has become a topic of debate.[7,8,10,19,20] Heritability models have previously been compared based on REML likelihood,[1,20] prediction accuracy[4,20] and performance on simulated data,[7,8] however, all three approaches have shortcomings; the REML likelihood requires individual-level data and can not be computed for complex heritability models, to measure prediction accuracy requires two independent datasets for each trait (one for training and one for testing) and there is no consensus regarding the best prediction method, while comparisons of heritability models based on simulated data are sensitive to the assumptions of the simulation model.[1]

We have proposed logl, an approximate model likelihood that can be computed from summary statistics and for complex heritability models. Using logl, we showed that the Baseline LD Model is the best of the existing heritability models, but that it can be substantially improved by incorporating the SNP weightings and MAF scaling used by the LDAK Model. Estimates of confounding bias and functional enrichments from the resulting BLD-LDAK Model are close to those from the Baseline LD Model, while its estimates of SNP heritability are between those of the Baseline LD, GCTA-LDMS-I and LDAK Models.

Our results support those of Gazal et al.,[20] who argued that estimates of functional enrichments from the Baseline LD Model are more accurate than those from the LDAK+1Fun Model. They provide partial support for Evans et al.,[8] who argued that the GCTA-LDMS-I Model produces the most accurate estimates of SNP heritability (although we found that the GCTA-LDMS-I Model performs well compared to the other existing models, our analysis indicates that the BLD-LDAK Model should now be preferred). Our results support our previous finding[4] that the LDAK Model is more realistic than the GCTA Model, but not that estimates of functional enrichments from the LDAK+24Fun Model should be preferred to those from the Baseline and Baseline LD Models. We discuss these three papers in detail in the Supplementary Note.

Recently, Hou et al.[21] proposed GRE, a method for estimating SNP heritability without specifying a heritability model. While we agree with the benefits of performing heritability analysis without requiring a heritability model, this is not feasible for most analyses. For example, GRE can not be used on our Public GWAS, because it requires individual-level data, nor can it be used on our UKBb GWAS, because it requires that the number of samples is larger than the number of SNPs on the largest chromosome (at least 600k). Nonetheless, it is reassuring to see that for analyses where GRE is feasible (Hou et al. considered 22 UK Biobank traits, restricting to 480k directly-genotyped SNPs), its estimates of SNP heritability qualitatively match those from the BLD-LDAK Model (they likewise tend to be intermediate between those from the Baseline LD and LDAK Models).[21]

The BLD-LDAK+Alpha Model is a generalization of the BLD-LDAK Model. The two models have similar fit and produce similar estimates of SNP heritability, confounding bias and heritability enrichments. For computational reasons, we generally recommend the BLD-LDAK Model. However, the advantage of the BLD-LDAK+Alpha is that it provides estimates of the selection-related parameter α. Our results broadly agree with those of Zeng et al.;[18] using the software BayesS, they found significantly negative α for 23 out of 28 UK Biobank traits, while their average estimate of α was -0.38 (s.d. 0.01). To our knowledge, SumHer is the only software to estimate α from

summary statistics, and therefore can be viewed as a more computationally-efficient alternative to BayesS (for a full comparison of the two methods and their results, see Supplementary Fig. 4).

Although its shortcomings have been well-documented, the GCTA Model continues to be widely used in statistical genetics. It remains the default model of both the GCTA and LDSC software, and is the model used by LD Hub[22] (a web interface for performing LDSC analyses). More widely, the GCTA Model is implicitly assumed by any penalized or Bayesian regression method that standardizes genotypes then assigns the same penalty or prior distribution to each SNP, or in simulations when causal SNPs are picked at random then their standardized effects sizes drawn from the same distribution. Ideally, the GCTA Model should be replaced by the BLD-LDAK or BLD-LDAK+Alpha Model whenever it occurs. However, we recognize that for many methods, introducing a multi-parameter heritability model would require substantial algorithmic changes and dramatically increase computational demands. When this is the case, we instead recommend using the Lis is a one-parameter model, so computation demands should not be affected, which can be incorporated in any existing method simply by changing which predictors are included in the regression and how these are standardized.

We finish by highlighting three areas for future work. Firstly, we have only considered common SNPs; with the increasing availability of sequence data, it will be necessary to examine whether the BLD-LDAK and BLD-LDAK+Alpha Models remain the best performing model when rare SNPs are included. Secondly, the ability to measure model fit for very large sample sizes means that we now have sufficient power to construct heritability models specific to either individual traits or groups of traits (Supplementary Table 2). Thirdly, we have only considered the genomic annotations contained within the Baseline LD Model. We expect it will be possible to find new annotations predictive of how heritability varies across the genome (i.e., whose inclusion in the heritability model significantly increases logl). Identifying these will both improve the performance of the heritability model and our understanding of the genetic architecture of complex traits.

Online Methods

Let h^2_j denote the heritability (uniquely) contributed by SNP j. Suppose we have summary statistics from a GWAS of n individuals; let S_j denote the $\chi^2(1)$ test statistic from regressing the phenotype on SNP j. Suppose also we have access to an ancestrally-matched reference panel, from which we can estimate r^2_{jl}, the squared correlation between SNPs j and l (genotypes coded additively).

Linear heritability models. The heritability model describes how the expectation of h^2_j varies across the genome. We first assume the model takes the form

$$E[h_j^2]=\sum_k a_{jk}\tau_k$$

where the a_{jk} are pre-specified SNP annotations and the parameters τ_k are estimated in the analysis. Assuming no confounding bias[3]

$$E[S_j]\approx 1+\sum_k \left(n\sum_{l\in \mathrm{Ref}\ j} r_{jl}^2 a_{jk}\right)\tau_k \qquad (1)$$

where Ref j indexes the reference panel SNPs 'near' SNP j (a working definition of near is within 1 cM[4]). The term within the parentheses is known, and thus we can estimate the τ_k by regressing S_j on $E[S_j]$ (details below). To allow for confounding bias, the authors of LDSC[3] recommend increasing each $E[S_j]$ by A, the average amount each test statistic is inflated additively (it is standard to then report 1+A, referred to as the intercept), while we[4] instead recommended scaling each $E[S_j]$ by C, the average amount each test statistic is inflated multiplicatively. Allowing for confounding bias (whether additive or multiplicative) results in a revised form for Eq. (1), but it remains that $E[S_j]$ can be expressed as a linear combination of the model parameters[4] (now the τ_k plus either A or C), and so we can continue to estimate the parameters by regressing S_j on $E[S_j]$.

Approximate model likelihood. The authors of LDSC[3] derived that each S_j approximately follows a scaled $\chi^2(1)$ distribution with scale factor $E[S_j]$ (or equivalently, a gamma distribution with shape ½ and scale $2E[S_j]$). Let

$$u_j=\sum_{l\in \mathrm{Reg}\ j} r_{jl}^2,$$

where Reg j indexes the regression SNPs (those used when regressing S_j on $E[S_j]$) near SNP j. We propose the approximate log likelihood

$$\text{logl} = \sum_j \frac{1}{u_j}\left(-\frac{S_j}{2E[S_j]} - \frac{1}{2}\log(S_j) - \frac{1}{2}\log(2E[S_j]) - \frac{1}{2}\log(\pi)\right).$$

To ensure logl can be computed, we replace non-positive $E[S_j]$ with 10^{-6} (this is rarely an issue, because $E[S_j]$ generally remains positive even if some $E[h^2_j]$ are negative). The term within the large parentheses is the log likelihood for a single SNP; therefore logl computes a weighted sum of these, where the weights $1/u_j$ reflect local correlations. Supplementary Fig. 1 & 2 show that logl is concordant with the exact likelihood computed from REML and can validly be used for likelihood ratio testing.

Estimating parameters. LDSC estimates the parameters using weighted least-squares regression,[3] with regression weights $1/u_j$ x $1/(2E[S_j]^2)$; weighting by $1/u_j$ allows for correlations between nearby SNPs (motivating our use of $1/u_j$ in the definition of logl), while weighting by $1/(2E[S_j]^2)$ allows for heteroskedasticity ($2E[S_j]^2$ is the variance of a gamma distribution with shape ½ and scale $2E[S_j]$).

When we proposed SumHer, we also estimated parameters using weighted least-squares regression.[4] However, now that we have an expression for the model likelihood, we can instead use maximum likelihood estimation. To identify the values that maximize logl, we use (multi-dimensional) Newton-Raphson.[23] Let θ denote the vector of parameters (the τ_k and, if allowing for confounding, either A or C). Starting from the null model (τ_k=0, A=0, C=1), we update θ iteratively until convergence using $\theta_{n+1}=\theta_n-(C_n)^{-1}B_n$, where the vector B_n and matrix C_n contain, respectively, the first and second derivatives of logl evaluated at $\theta=\theta_n$ (the required derivatives can be computed using the chain rule; for example, $\delta\text{logl}/\delta\theta_k = \delta\text{logl}/\delta E[S_j] \times \delta E[S_j]/\delta\theta_k$). Occasionally, a move causes a substantial reduction in logl. When this happens, we cancel the move, then for the next iteration (only) update each parameter once individually using (one-dimensional) Newton-Raphson.

Supplementary Fig. 5 shows that for simple heritability models, the weighted least-squares and maximum likelihood solver result in identical logl, but that for complex models, the maximum likelihood solver often results in substantially higher logl.

Non-linear heritability models. To date LDSC and SumHer have required that the heritability model is linear (this ensures that $E[S_j]$ can be expressed as a linear combination of the model parameters). However, SumHer can now accommodate (a small number of) non-linear parameters. We first crudely estimate the non-linear parameters using a grid-search, selecting the values that result in highest logl; we then increase resolution and obtain standard deviations by fitting a Gaussian likelihood to the realizations of logl. For full details, see Supplementary Fig. 6.

Leave-one-chromosome-out prediction of test statistics. For each SNP we compute $E[S_j]$ in Eq. (1) using parameter estimates obtained from the other 21 chromosomes. In Table 1 we report a weighted correlation between predicted and observed test statistics

$$\rho = \frac{C(S_j, E[S_j])}{\sqrt{C(S_j, S_j)}\sqrt{C(E[S_j], E[S_j])}},$$

where

$$C(a_j, b_j) = \left(\sum_j \frac{a_j b_j}{u_j}\right)\left(\sum_j \frac{1}{u_j}\right) - \left(\sum_j \frac{a_j}{u_j}\right)\left(\sum_j \frac{b_j}{u_j}\right)$$

We estimate the standard deviation of ρ using block jackknifing with 200 blocks.[3,24] We consider it appropriate to include the weights $1/u_j$, as otherwise ρ will overweight high-LD regions, however, Supplementary Table 1 shows that the ranking of models is the same if we instead compare unweighted correlations.

GWAS. We accessed UK Biobank[13,14] (UKBb) data via Project 21432. In total we identified 20 phenotypes that were recorded for the majority of individuals: the 14 we retained were body mass index (data field 21001), forced vital capacity (3062), height (50), impedance (23106), neuroticism score (20127), pulse rate (102), reaction time (20023), systolic blood pressure (4080), college education (6138), ever smoked (20160), hypertension (20002), snorer (1210), difficulty falling asleep (1200) and preference for evenings (1180); the six we discarded were asthma, wears glasses, handedness, any mouth problem, basal metabolic rate and diastolic blood pressure (each either had estimated heritability less than 0.1 or was highly correlated with one of the retained phenotypes). The imputed

dataset contains 487k individuals recorded for 93M SNPs. However, after quality control, which included filtering individuals based on ancestry and relatedness, and excluding SNPs with MAF<0.01, info score <0.99 or within the major histocompatibility complex (Chr6:25-34Mb), only 130,080 individuals and 4,725,151 SNPs remained.[5,6,25] With access to individual-level data, we were able to confirm that confounding due to residual population structure, relatedness or genotyping errors was slight.[1] For the association analysis, we tested each SNP using linear regression (regardless of whether the phenotype was continuous, categorical or binary), having first regressed the phenotype on 13 covariates: age (data field 21022), sex (31), Townsend Deprivation Index (189) and ten principal components. For more details, see Supplementary Fig. 7.

The 17 Public GWAS are coronary artery disease,[26] Crohn's Disease,[27] ever smoked,[28] inflammatory bowel disease,[27] rheumatoid arthritis,[29] schizophrenia,[30] type 2 diabetes,[31] bone mineral density,[32] body mass index,[33] depressive symptoms,[34] height,[35] menarche age,[36] menopause age,[37] neuroticism,[34] subjective well-being,[34] waist-hip ratio[38] and years education.[39] These are a subset of the 24 GWAS we considered previously;[4] we excluded the remaining seven GWAS as the authors of LDSC[9,40] recommend only using traits with a heritability Z-score above seven. For these GWAS we have to rely on the quality control choices of the original authors (Supplementary Table 8), which are generally less strict than ours, and without access to individual-level data, we can not test for confounding due to population structure, relatedness or genotyping errors.

Software settings. When running an analysis using LDSC or SumHer it is necessary to choose the heritability and confounding models, provide a reference panel, select the regression and heritability SNPs, and if estimating enrichments, specify the expected proportion of SNP heritability contributed by each category (for an explanation of each option, see Supplementary Table 9). We describe the different heritability models we consider below. For the other options, our main analysis follows the recommendations of LDSC.[3,9] When analyzing the UKBb GWAS, we assume there is no confounding bias (the exception is for Figure 1b, when we allow for additive confounding bias, then report the estimate of 1+A); when analyzing the Public GWAS, we always allow for additive confounding bias. Our reference panel is the 1000 Genome Project[16] dataset provided on the LDSC website (see URLs), which contains 489 European individuals recorded for 10.0M autosomal SNPs with MAF>0.005. When analyzing the UKBb GWAS, the regression SNPs are all 4.7M GWAS SNPs; when analyzing the Public GWAS, the regression SNPs are the GWAS SNPs present in HapMap3[41] but not in the major histocompatibility complex (on average 1.1M SNPs per GWAS). The heritability SNPs are the 6.0M reference panel SNPs with MAF≥0.05. When computing estimates of enrichments, we divide the estimated proportion of SNP heritability contributed by a category by the proportion of SNPs it contains.

Sensitivity analyses. Supplementary Table 1 shows that the ranking of heritability models is the same if we use a UK Biobank[13,14] reference panel (instead of the 1000 Genomes Project panel), if we reduce the reference panel to the 4.7M SNPs in our UKBb GWAS, or if we reduce the regression SNPs to a subset in approximate linkage equilibrium. Supplementary Table 10 shows that enrichment estimates from the BLD-LDAK Model are similar if the heritability SNPs are all 10.0M reference panel SNPs (rather than just the 6.0M with MAF≥0.05).

Existing heritability models. Full details of all heritability models are provided in Supplementary Tables 11 & 12. The one-parameter GCTA Model[5] (the default model of both the GCTA and LDSC software) assumes $E[h^2_j]=\tau_1$. The GCTA-LDMS-R[7] and GCTA-LDMS-I[8] Models assume

$$E[h_j^2]=\sum_k I_{jk}\tau_k$$

where I_{jk} indicates whether SNP j is in Bin k. The bins are obtained by first dividing the genome four-ways based on LD, then M-ways based on MAF, (when dividing based on LD, the GCTA-LDMS-R Model ranks SNPs based on regional LD scores, while the GCTA-LDMS-I Model ranks based on per-SNP LD scores). We opt for M=5, with the boundaries at 0.1, 0.2, 0.3 and 0.4 (in total 20 bins); this choice is based on the first application of GCTA-LDMS-R,[7] which used seven MAF tranches with boundaries at 0.001, 0.01, 0.1, 0.2, 0.3 and 0.4 (we exclude the bottom two tranches as we only consider common SNPs). Supplementary Table 13 shows that this version performs better than using M=2, with the boundary at 0.05 (in total 8 bins), a choice based on the first application of GCTA-LDMS-I,[8] which used four MAF tranches with boundaries at 0.0025, 0.01 and 0.05.

The 53-parameter Baseline Model[9] adds to the GCTA Model 52 functional annotations; 24 of these are function indicators (e.g., which SNPs are within coding regions), while 28 are 'buffer' indicators (e.g., which SNPs are within 500bp of a coding region). The 75-parameter Baseline LD Model[10] adds to the GCTA Model 74 SNP annotations: six are LD-related annotations (e.g., estimated allele age), ten are MAF indicators (e.g., which SNPs have 0.05 ≤ MAF < 0.07) and 58 are functional annotations (including the 52 used in the Baseline Model). The two-

parameter GCTA+1Fun Model[12] adds to the GCTA Model one function indicator from the Baseline Model (there are 24 versions of this model, one for each indicator).

The one-parameter LDAK Model[1,6] assumes $E[h^2_j]=w_j p_j^{0.75}\tau_1$, where w_j is the LDAK weighting of SNP j, f_j is its MAF and $p_j=f_j(1-f_j)$. We recommend that the weightings are only computed over high-quality SNPs[1,6] (so low- and moderate-quality SNPs automatically get $w_j=0$). We do not have SNP info scores for the 1000 Genome Project reference panel, so when computing weightings, we restrict to the 4.7M SNPs in our UKBb GWAS (i.e., we assume that SNPs well-genotyped in the UK Biobank are well-genotyped in the 1000 Genome Project). The two-parameter LDAK+1Fun Model[1] assumes $E[h^2_j]=w_j p_j^{0.75}(\tau_1+b_{ji}\tau_2)$, where b_{ji} is the ith function indicator from the Baseline LD Model (there are 24 versions of this model, one for each indicator), while the 25-parameter LDAK+24Fun Model[4] assumes

$$E[h_j^2]=w_j p_j^{0.75}\left(\tau_1+\sum_{k=2}^{25} b_{j(k-1)}\tau_k\right).$$

Novel heritability models. The 66-parameter BLD-LDAK and 67-parameter BLD-LDAK+Alpha Model both take the form

$$E[h_j^2]=p_j^{1+\alpha}\tau_1+\sum_{k=2}^{65} c_{jk}\, p_j^{1+\alpha}\tau_k+w_j\, p_j^{1+\alpha}\tau_{66}$$

where the c_{jk} are the 64 LD-related and functional annotations from the Baseline LD Model;[10] the BLD-LDAK Model fixes $\alpha=-0.25$, while the BLD-LDAK+Alpha estimates α from the data. To construct the BLD-LDAK Model we first added the LDAK weighting to the Baseline LD Model (this increased average logl by 11), then scaled all annotations by $p_j^{0.75}$ (this increased average logl by a further 44). At this point we noted that the 10 MAF indicators had limited value (excluding them reduced average logl by only 9) so we removed them. We were unable to improve the model further by adding features from the GCTA-LDMS-R and GCTA-LDMS-I Models (for example, if we incorporated the 4 LD or the 20 MAF-LD bins from the GCTA-LDMS-I Model, this increased the number of parameters by 3 and 19, respectively, but increased average logl by only 2 and 13). For more details, see Supplementary Table 14.

Considering that the functional classifications are both approximate and incomplete, it would be concerning if genetic architecture estimates were sensitive to which functional annotations were included in the heritability model. In Supplementary Fig. 8, we construct reduced versions of the BLD-LDAK and BLD-LDAK+Alpha Models by excluding the 57 binary functional annotations (retaining only the continuous functional annotation, GERP-NS, a measure of conservation); reassuringly, estimates from the reduced versions of the models are consistent with those from the full versions.

When computing the LDAK weightings, the first step is to thin SNPs so that no pair remains within 100kb with $r^2_{jl}>0.98$ (excluding duplicate SNPs substantially improves the efficiency of the solver used to compute the weightings[1]). The LDAK-Thin Model assumes $E[h^2_j]=I_j p_j^{0.75}\tau_1$, where I_j indicates whether SNP j remains after the thinning. To implement the LDAK-Thin Model within an existing penalized or Bayesian regression method requires two changes: firstly, thin the SNPs (for the UKBb data, this reduced the number from 4.7M to 1.4M); secondly, center and scale the genotypes so that SNP j has variance $p_j^{0.75}$.

URLs. LDAK, http://www.ldak.org; LDSC, http://www.github.com/bulik/ldsc; UK Biobank https://www.ukbiobank.ac.uk

Acknowledgements
We thank A. Price, S. Gazal and H. Finucane for helpful discussions. D.S. is funded by the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie grant agreement no. 754513, by Aarhus University Research Foundation (AUFF) and by the Independent Research Fund Denmark under Project no. 7025-00094B. D.J.B. is funded by the Australian Research Council under the Discovery Project 'Improved models to understand the genomic architecture of complex traits'.

Author contributions
D.S. and J.H. performed the analysis, D.S. and D.J.B. wrote the manuscript.

Competing interests
The authors declare no competing interests.

Data availability
We performed the UKBb GWAS using data applied for and downloaded via the UK Biobank website (see URLs). We obtained summary statistics for the Public GWAS from the websites of the corresponding studies. We downloaded the 1000 Genome Project data from the LDSC website (see URLs).

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