Modeling functional enrichment improves polygenic prediction accuracy in UK Biobank and 23andMe data sets

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Abstract

Genetic variants in functional regions of the genome are enriched for complex trait heritability. Here, we introduce a new method for polygenic prediction, LDpred-funct, that leverages trait-specific functional enrichments to increase prediction accuracy. We fit priors using the recently developed baseline-LD model, which includes coding, conserved, regulatory and LD-related annotations. We analytically estimate posterior mean causal effect sizes and then use cross-validation to regularize these estimates, improving prediction accuracy for sparse architectures. LDpred-funct attained higher prediction accuracy than other polygenic prediction methods in simulations using real genotypes. We applied LDpred-funct to predict 21 highly heritable traits in the UK Biobank. We used association statistics from British-ancestry samples as training data (avg N=365K) and samples of other European ancestries as validation data (avg N=22K), to minimize confounding. LDpred-funct attained a +9% relative improvement in average prediction accuracy (avg prediction R^2=0.145; highest R^2=0.413 for height) compared to LDpred (the best method that does not incorporate functional information), consistent with simulations. For height, meta-analyzing training data from UK Biobank and 23andMe cohorts (total N=1107K;

higher heritability in UK Biobank cohort) increased prediction R^2 to 0.429. Our results show that modeling functional enrichment improves polygenic prediction accuracy, consistent with the functional architecture of complex traits.

Introduction

Genetic variants in functional regions of the genome are enriched for complex trait heritability[1–6]. In this study, we aim to leverage functional enrichment to improve polygenic prediction[7,8]. Several studies have shown that incorporating prior distributions on causal effect sizes can improve prediction accuracy[9–12], compared to standard Best Linear Unbiased Prediction (BLUP) or Pruning+Thresholding methods[13–15]. Recent efforts to incorporate functional information have produced promising results[16,17], but may be limited by dichotomizing between functional and non-functional variants[16] or restricting their analyses to genotyped variants[17].

Here, we introduce a new method, LDpred-funct, for leveraging trait-specific functional enrichments to increase polygenic prediction accuracy. We fit functional priors using our recently developed baseline-LD model[18], which includes coding, conserved, regulatory and LD-related annotations. LDpred-funct first analytically estimates posterior mean causal effect sizes, accounting for functional priors and LD between variants. LDpred-funct then uses cross-validation within validation samples to regularize causal effect size estimates in bins of different magnitude, improving prediction accuracy for sparse architectures. We show that LDpred-funct attains higher polygenic prediction accuracy than other methods in simulations with real genotypes, analyses of 21 highly heritable UK Biobank traits, and meta-analyses of height using training data from UK Biobank and 23andMe cohorts.

Methods

Polygenic prediction methods

We compared 5 main prediction methods: Pruning+Thresholding[14,15] (P+T), LDpred[12], P+T with functionally informed LASSO shrinkage[16] (P+T-funct-LASSO), our new LDpred-funct-inf method, and our new LDpred-funct method; we also included LDpred-inf[12], which is known to attain lower prediction accuracy than LDpred[12], in some of our secondary analyses. P+T, LDpred-inf and LDpred are polygenic prediction methods that do not use functional annotations. P+T-funct-LASSO is a modification of P+T that corrects marginal effect sizes for winner's curse, accounting for functional annotations. LDpred-funct-inf is an improvement of LDpred-inf that incorporates functionally informed priors on causal effect sizes. LDpred-funct is an improvement of LDpred-funct-inf that uses cross-validation to regularize posterior mean causal effect size estimates, improving prediction accuracy for sparse architectures. Each method is described in greater detail below. In both simulations and analyses of real traits, we used squared correlation (R^2) between predicted phenotype and true phenotype in a held-out set of samples as our primary measure of prediction accuracy.

P+T. The P+T method builds a polygenic risk score (PRS) using a subset of independent SNPs obtained via informed LD-pruning [15] (also known as LD-clumping) followed by P-value thresholding [14]. Specifically, the method has two parameters, R^2_{LD} and P_T, and proceeds as follows. First, the method prunes SNPs based on a pairwise threshold R^2_{LD}, removing the less significant SNP in each pair. Second, the method restricts to SNPs with an association P-value below the significance threshold P_T. Letting M be the number of SNPs remaining after LD-clumping, polygenic risk scores (PRS) are computed as

$$PRS(P_T) = \sum_{i=1}^{M} \mathbb{1}_{\{P_i < P_T\}} \tilde{\beta}_i g_i, \tag{1}$$

where $\tilde{\beta}_i$ are normalized marginal effect size estimates and g_i is a vector of normalized genotypes for SNP i. The parameters R^2_{LD} and P_T are commonly tuned using validation data to optimize prediction accuracy [14,15]. While in theory this procedure is susceptible to overfitting, in practice, validation sample sizes are typically large, and R^2_{LD} and P_T are selected from a small discrete set of parameter choices, so that overfitting is considered to have a negligible effect [7,14,15,19]. Accordingly, in this work, we consider $R^2_{LD} \in \{0.1, 0.2, 0.5, 0.8\}$ and $P_T \in \{1, 0.3, 0.1, 0.03, 0.01, 0.003, 0.001, 3 * 10^{-4}, 10^{-4}, 3 * 10^{-5}, 10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}\}$, and we always report results corresponding to the best choices of these parameters. The P+T method is implemented in the PLINK software (see Web Resources).

LDpred-inf. The LDpred-inf method estimates posterior mean causal effect sizes under an infinitesimal model, accounting for LD [12]. The infinitesimal model assumes that normalized causal effect sizes have prior distribution $\beta_i \sim N(0, \sigma^2)$, where $\sigma^2 = h^2_g/M$, h^2_g is the SNP-heritability, and M is the number of SNPs. The posterior mean causal effect sizes are

$$E(\boldsymbol{\beta}|\tilde{\boldsymbol{\beta}}, \mathbf{D}) = (\frac{N}{1 - h^2_l} * \mathbf{D} + \frac{1}{\sigma^2}\mathbf{I})^{-1} N * \tilde{\boldsymbol{\beta}}, \tag{2}$$

where $\mathbf{D}$ is the LD matrix between markers, $\mathbf{I}$ is the identity matrix, N is the training sample size, $\tilde{\boldsymbol{\beta}}$ is the vector of marginal association statistics, and $h^2_l \approx kh^2/M$ is the heritability of the k SNPs in the region of LD; following ref. 12 we use the approximation $1 - h^2_l \approx 1$, which is appropriate when $M >> k$. $\mathbf{D}$ is typically estimated using validation data, restricting to non-overlapping LD windows. We used the default LD window size, which is M/3000. h^2_g can be estimated from raw genotype/phenotype data [20,21] (the approach that we use here; see below), or can be estimated from summary statistics using the aggregate estimator as described in ref. 12. To approximate the normalized marginal effect size ref. 12 uses the p-values to obtain absolute Z scores and then multiplies absolute Z scores by the sign of the estimated effect size. When sample sizes are very large, p-values may be rounded to zero, in which case we approximate normalized marginal effect sizes $\widehat{\beta}_i$ by

$\widehat{b_i}\frac{\sqrt{2*p_i*(1-p_i)}}{\sqrt{\sigma_Y^2}}$, where $\widehat{b_i}$ is the per-allele marginal effect size estimate, p_i is the minor allele frequency of SNP i, and σ_Y^2 is the phenotypic variance in the training data. This applies to all the methods that use normalized effect sizes. Although the published version of LDpred requires a matrix inversion (Equation 2), we have implemented a computational speedup that computes the posterior mean causal effect sizes by efficiently solving[22] the system of linear equations $(\frac{1}{\sigma^2}\mathbf{I}+N*\mathbf{D})E(\boldsymbol{\beta}|\tilde{\boldsymbol{\beta}},\mathbf{D}) = N\tilde{\boldsymbol{\beta}}$.

LDpred. The LDpred method is an extension of LDpred-inf that uses a point-normal prior to estimate posterior mean effect sizes via Markov Chain Monte Carlo (MCMC)[12]. It assumes a Gaussian mixture prior: $\beta_i \sim N(0, h_g^2/M*p)$ with probability p, and $\beta_i \sim 0$ with probability $1-p$, where p is the proportion of causal SNPs. The method is optimized by considering different values of p (1E-4, 3E-4, 1E-3, 3E-3, 0.01,0.03,0.1,0.3,1). We excluded SNPs from long-range LD regions (reported in ref. 23), as our secondary analyses showed that including these regions was suboptimal, consistent with ref. 24.

P+T-funct-LASSO. Ref. 16 proposed an extension of P+T that corrects the marginal effect sizes of SNPs for winner's curse and incorporates external functional annotation data (P+T-funct-LASSO). The winner's curse correction is performed by applying a LASSO shrinkage to the marginal association statistics of the PRS:

$$PRS_{LASSO}(P_T) = \sum_{i=1}^{M} sign(\tilde{\beta}_i)|\tilde{\beta}_i| - \lambda(P_T)|\mathbb{1}_{\{P_i<P_T\}}g_i, \quad (3)$$

where $\lambda(P_T) = \Phi^{-1}(1-\frac{P_T}{2})sd(\tilde{\beta}_i)$, where Φ^{-1} is the inverse standard normal CDF. Functional annotations are incorporated via two disjoint SNPs sets, representing "high-prior" SNPs (HP) and "low-prior" SNPs (LP), respectively. We define the HP SNP set for P+T-funct-LASSO as the set of SNPs in the top 10% of expected per-SNP heritability under the baseline-LD model[18], which includes coding, conserved, regulatory and LD-related annotations, whose enrichments are jointly estimated using stratified LD score regression[5,18] (see Baseline-LD model annotations section). We also performed secondary analyses using the top 5% (P+T-funct-LASSO-top5%). We define $PRS_{LASSO,HP}(P_{HP})$ to be the PRS restricted to the HP SNP set, and $PRS_{LASSO,LP}(P_{LP})$ to be the PRS restricted to the LP SNP set, where P_{HP} and P_{LP} are the optimal significance thresholds for the HP and LP SNP sets, respectively. We define $PRS_{LASSO}(P_{HP},P_{LP}) = PRS_{LASSO,HP}(P_{HP}) + PRS_{LASSO,LP}(P_{LP})$. We also performed secondary analyses were we allow an additional regularization to the two PRS: $PRS_{LASSO}(P_{HP},P_{LP}) = \alpha_1 PRS_{LASSO,HP}(P_{HP}) + \alpha_2 PRS_{LASSO,LP}(P_{LP})$; we refer to this method as P+T-funct-LASSO-weighted.

LDpred-funct-inf. We modify LDpred-inf to incorporate functionally informed priors on causal

effect sizes using the baseline-LD model[18], which includes coding, conserved, regulatory and LD-related annotations, whose enrichments are jointly estimated using stratified LD score regression[5,18]. Specifically, we assume that normalized causal effect sizes have prior distribution $\beta_i \sim N(0, c * \sigma_i^2)$, where σ_i^2 is the expected per-SNP heritability under the baseline-LD model (fit using training data only) and c is a normalizing constant such that $\sum_{i=1}^{M} \mathbb{1}_{\{\sigma_i^2>0\}} c\sigma_i^2 = h_g^2$; SNPs with $\sigma_i^2 \leq 0$ are removed, which is equivalent to setting $\sigma_i^2 = 0$. The posterior mean causal effect sizes are

$$E[\boldsymbol{\beta}|\tilde{\boldsymbol{\beta}}, \mathbf{D}, \sigma_1^2, \ldots, \sigma_{M_+}^2] = \mathbf{W}^{-1} N * \tilde{\boldsymbol{\beta}} = \left[N * \mathbf{D} + \frac{1}{c} \begin{pmatrix} \frac{1}{\sigma_1^2} & \ldots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \ldots & \frac{1}{\sigma_{M_+}^2} \end{pmatrix} \right]^{-1} N * \tilde{\boldsymbol{\beta}}, \qquad (4)$$

where M_+ is the number of SNPs with $\sigma_i^2 > 0$. The posterior mean causal effect sizes are computed by solving the system of linear equations $\mathbf{W} E[\boldsymbol{\beta}|\tilde{\boldsymbol{\beta}}, \mathbf{D}, \sigma_1^2, \ldots, \sigma_M^2] = N * \tilde{\boldsymbol{\beta}}$. h_g^2 is estimated as described above (see LDpred-inf). $\mathbf{D}$ is estimated using validation data, restricting to windows of size $0.15\% M_+$.

LDpred-funct. We modify LDpred-funct-inf to regularize posterior mean causal effect sizes using cross-validation. We rank the SNPs by their (absolute) posterior mean causal effect sizes, partition the SNPs into K bins (analogous to ref. 25) where each bin has roughly the same sum of squared posterior mean effect sizes, and determine the relative weights of each bin based on predictive value in the validation data. Intuitively if a bin is dominated by non-causal SNPs, the inferred relative weight will be lower than for a bin with a high proportion of causal SNPs. This non-parametric shrinkage approach can optimize prediction accuracy regardless of the genetic architecture. In detail, let $S = \sum_i E[\beta_i|\tilde{\beta}_i]^2$. To define each bin, we first rank the posterior mean effect sizes based on their squared values $E[\beta_i|\tilde{\beta}_i]^2$. We define bin b_1 as the smallest set of top SNPs with $\sum_{i \in b_1} E[\beta_i|\tilde{\beta}_i]^2 \geq \frac{S}{K}$, and iteratively define bin b_k as the smallest set of additional top SNPs with $\sum_{i \in b_1, \ldots, b_k} E[\beta_i|\tilde{\beta}_i]^2 \geq \frac{kS}{K}$. Let $PRS(k) = \sum_{i \in b_k} E[\beta_i|\tilde{\beta}_i] g_i$. We define

$$PRS_{LDpred-funct} = \sum_{k=1}^{K} \alpha_k PRS(k), \qquad (5)$$

where the bin-specific weights α_k are optimized using validation data via 10-fold cross-validation. For each held-out fold in turn, we split the data so we estimate the weights α_k using the samples from the other nine folds (90% of the validation) and compute PRS on the held-out fold using these weights (10% of the validation). We then compute the average prediction R^2 across the 10 held-out folds. To avoid overfitting when K is very close to N, we set the number of bins (K) to be between 1 and 100, such that it is proportional to h_g^2 and the number of samples used to estimate the K weights in each

fold is at least 100 times larger than K:

$$K = \min(100, \lceil \frac{0.9N * h_g^2}{100} \rceil), \quad (6)$$

where N is the number of validation samples. For highly heritable traits ($h_g^2 \sim 0.5$), LDpred-funct reduces to the LDpred-funct-inf method if there are ∼200 validation samples or fewer; for less heritable traits ($h_g^2 \sim 0.1$), LDpred-funct reduces to the LDpred-funct-inf method if there are ∼1,000 validation samples or fewer. In simulations, we set K to 40 (based on 7,585 validation samples; see below), approximately concordant with Equation 6. The value of 100 in the denominator of Equation 6 was coarsely optimized in simulations, but was not optimized using real trait data.

Standard errors. Standard errors for the prediction R^2 of each method and the difference in prediction R^2 between two methods were computed via block-jackknife using 200 genomic jackknife blocks[5]; this is more conservative than computing standard errors based on the number of validation samples, which does not account for variation across a finite number of SNPs. For each method, we first optimized any relevant tuning parameters using the entire genome and then analyzed each jackknife block using those tuning parameters.

Simulations

We simulated quantitative phenotypes using real genotypes from the UK Biobank interim release (see below). We used up to 50,000 unrelated British-ancestry samples as training samples, and 7,585 samples of other European ancestries as validation samples (see below). We made these choices to minimize confounding due to shared population stratification or cryptic relatedness between training and validation samples (which, if present, could overstate the prediction accuracy that could be obtained in independent samples[26]), while preserving a large number of training samples. We restricted our simulations to 459,284 imputed SNPs on chromosome 1 (see below), fixed the number of causal SNPs at 2,000 or 5,000 (we also performed secondary simulations with 1,000 or 10,000 causal variants), and fixed the SNP-heritability h_g^2 at 0.5. We sampled normalized causal effect sizes β_i for causal SNPs from a normal distribution with variance equal to $\frac{\sigma_i^2}{p}$, where p is the proportion of causal SNPs and σ_i^2 is the expected causal per-SNP heritability under the baseline-LD model[18], fit using stratified LD score regression (S-LDSC)[5,18] applied to height summary statistics computed from unrelated British-ancestry samples from the UK Biobank interim release (N=113,660). We computed per-allele effect sizes b_i as $b_i = \frac{\beta_i}{\sqrt{2p_i(1-p_i)}}$, where p_i is the minor allele frequency for SNP i estimated using the validation genotypes. We simulated phenotypes as $Y_j = \sum_i^M b_i g_{ij} + \epsilon_j$, where $\epsilon_j \sim N(0, 1 - h_g^2)$. We set the training sample size to either 10,000, 20,000 or 50,000. The motivation to perform simulations using one chromosome is to be able to extrapolate performance at larger sample sizes[12] according to

the ratio N/M, where N is the training sample size. We compared each of the five methods described above. For LDpred-funct-inf and LDpred-funct, for each simulated trait we used S-LDSC (applied to training data only) to estimate baseline-LD model parameters. For LDpred-funct, we report R^2 as the average prediction R^2 across the 10 held-out folds.

Full UK Biobank data set

The full UK Biobank data set includes 459,327 European-ancestry samples and ∼20 million imputed SNPs[23] (after filtering as in ref. 20, excluding indels and structural variants). We selected 21 UK Biobank traits (14 quantitative traits and 7 binary traits) with phenotyping rate > 80% (> 80% of females for age at menarche, > 80% of males for balding), SNP-heritability $h_g^2 > 0.2$ for quantitative traits, observed-scale SNP-heritability $h_g^2 > 0.1$ for binary traits, and low correlation between traits (as described in ref. 20). We restricted training samples to 409,728 British-ancestry samples[23], including related individuals (avg N=365K phenotyped training samples; see Table S1 for quantitative traits and Table S2 for binary traits). We computed association statistics from training samples using BOLT-LMM v2.3[20]. We have made these association statistics publicly available (see Web Resources). We restricted validation samples to 25,112 samples of non-British European ancestry, after removing validation samples that were related (> 0.05) to training samples and/or other validation samples (avg N=22K phenotyped validation samples; see Table S1 and S2). As in our simulations, we made these choices to minimize confounding due to shared population stratification or cryptic relatedness between training and validation samples (which, if present, could overstate the prediction accuracy that could be obtained in independent samples[26]), while preserving a large number of training samples. We analyzed 6,334,603 genome-wide imputed SNPs, after removing SNPs with minor allele frequency < 1%, removing SNPs with imputation accuracy < 0.9, and removing A/T and C/G SNPs to eliminate potential strand ambiguity. We used h_g^2 estimates from BOLT-LMM v2.3[20] as input to LDpred, LDpred-funct-inf and LDpred-funct.

UK Biobank interim release

The UK Biobank interim release includes 145,416 European-ancestry samples[27]. We used the UK Biobank interim release both in simulations using real genotypes, and in a subset of analyses of height phenotypes (to investigate how prediction accuracy varies with training sample size).

In our analyses of height phenotypes, we restricted training samples to 113,660 unrelated (≤ 0.05) British-ancestry samples for which height phenotypes were available. We computed association statistics by adjusting for 10 PCs[28], estimated using FastPCA[29] (see Web Resources). For consistency, we used the same set of 25,030 validation samples of non-British European ancestry with height phenotypes as defined above. We analyzed 5,957,957 genome-wide SNPs, after removing SNPs with

minor allele frequency $< 1\%$, removing SNPs with imputation accuracy < 0.9, removing SNPs that were not present in the 23andMe height data set (see below), and removing A/T and C/G SNPs to eliminate potential strand ambiguity. .

In our simulations, we restricted training samples to up to 50,000 of the 113,660 unrelated British-ancestry samples, and restricted validation samples to 8,441 samples of non-British European ancestry, after removing validation samples that were related (> 0.05) to training samples and/or other validation samples. We restricted the 5,957,957 genome-wide SNPs (see above) to chromosome 1, yielding 459,284 SNPs after QC.

23andMe height summary statistics

The 23andMe data set consists of summary statistics computed from 698,430 European-ancestry samples (23andMe customers who consented to participate in research) at 9,898,287 imputed SNPs, after removing SNPs with minor allele frequency $< 1\%$ and that passed QC filters (which include filters on imputation quality, avg.rsq< 0.5 or min.rsq< 0.3 in any imputation batch, and imputation batch effects). Analyses were restricted to the set of individuals with $> 97\%$ European ancestry, as determined via an analysis of local ancestry[30]. Summary association statistics were computed using linear regression adjusting for age, gender, genotyping platform, and the top five principal components to account for residual population structure. The summary association statistics will be made available to qualified researchers (see Web Resources).

We analyzed 5,957,935 genome-wide SNPs, after removing SNPs with minor allele frequency $< 1\%$, removing SNPs with imputation accuracy < 0.9, removing SNPs that were not present in the full UK Biobank data set (see above), and removing A/T and C/G SNPs to eliminate potential strand ambiguity.

Meta-analysis of full UK Biobank and 23andMe height data sets

We meta-analyzed height summary statistics from the full UK Biobank and 23andMe data sets. We define

$$PRS_{meta} = \gamma_1 PRS_1 + \gamma_2 PRS_2, \tag{7}$$

where PRS_i is the PRS obtained using training data from cohort i. The PRS can be obtained using P+T, P+T-funct-LASSO, LDpred-inf or LDpred-funct. The meta-analysis weights γ_i can either be specified via fixed-effect meta-analysis (e.g. $\gamma_i = \frac{N_i}{\sum N_i}$) or optimized using validation data[19]. We use the latter approach, which can improve prediction accuracy (e.g. if the cohorts differ in their heritability as well as their sample size). In our primary analyses, we fit the weights γ_i in-sample and report prediction accuracy using adjusted R^2 to account for in-sample fitting[19]. We also report

results using 10-fold cross-validation: for each held-out fold in turn, we estimate the weights γ_i using the other nine folds and compute PRS on the held-out fold using these weights. We then compute the average prediction R^2 across the 10 held-out folds.

When using LDpred-funct as the prediction method, we perform the meta-analysis as follows. First, we use LDpred-funct-inf to fit meta-analysis weights γ_i. Then, we use γ_i to compute (meta-analysis) weighted posterior mean causal effect sizes (PMCES) via $PMCES = \gamma_1 PMCES_1 + \gamma_2 PMCES_2$, which are binned into k bins. Then, we estimate bin-specific weights α_k (used to compute (meta-analysis + bin-specific) weighted posterior mean causal effect sizes $\sum_{k=1}^{K} \alpha_k PMCES(k)$) using validation data via 10-fold cross validation.

Baseline-LD model annotations

The baseline-LD model (v1.1) contains a broad set of 75 functional annotations (including coding, conserved, regulatory and LD-related annotations), whose enrichments are jointly estimated using stratified LD score regression[5,18]. For each trait, we used the τ_c values estimated for that trait to compute σ_i^2, the expected per-SNP heritability of SNP i under the baseline-LD model, as

$$\sigma_i^2 = \sum_c a_c(i)\tau_c, \tag{8}$$

where $a_c(i)$ is the value of annotation c at SNP i.

Joint effect sizes τ_c for each annotation c are estimated via

$$E[\chi_i^2] = N \sum_c \tau_c l(i,c) + 1, \tag{9}$$

where $l(i,c)$ is the LD score of SNP i with respect to annotation a_c and χ_i^2 is the chi-square statistic for SNP i. We note that τ_c quantifies effects that are unique to annotation c. In all analyses of real phenotypes, τ_c and σ_i^2 were estimated using training samples only.

In our primary analyses, we used 489 unrelated European samples from phase 3 of the 1000 Genomes Project[31] as the reference data set to compute LD scores, as in ref. 18.

To verify that our 1000 Genomes reference data set produces reliable LD estimates, we repeated our LDpred-funct analyses using S-LDSC with 3,567 unrelated individuals from UK10K[32] as the reference data set (as in ref. 33), ensuring a closer ancestry match with British-ancestry UK Biobank samples. We also repeated our LDpred-funct analyses using S-LDSC with the baseline-LD+LDAK model (instead of the baseline-LD model), with UK10K as the reference data set. The baseline-LD+LDAK model (introduced in ref. 33) consists of the baseline-LD model plus one additional continuous annotation constructed using LDAK weights[34], which has values $(p_j(1-p_j))^{1+\alpha} w_j$,

where $\alpha = -0.25$, p_j is the allele frequency of SNP j, and w_j is the LDAK weight of SNP j computed using UK10K data.

Results

Simulations

We performed simulations using real genotypes from the UK Biobank interim release and simulated phenotypes (see Methods). We simulated quantitative phenotypes with SNP-heritability $h_g^2 = 0.5$, using 476,613 imputed SNPs from chromosome 1. We selected either 2,000 or 5,000 variants to be causal; we refer to these as "sparse" and "polygenic" architectures, respectively. We sampled normalized causal effect sizes from normal distributions with variances based on expected causal per-SNP heritabilities under the baseline-LD model[18], fit using stratified LD score regression (S-LDSC)[5,18] applied to height summary statistics from British-ancestry samples from the UK Biobank interim release. We randomly selected 10,000, 20,000 or 50,000 unrelated British-ancestry samples as training samples, and we used 7,585 unrelated samples of non-British European ancestry as validation samples. By restricting simulations to chromosome 1 ($\approx 1/10$ of SNPs), we can extrapolate results to larger sample sizes ($\approx$ 10x larger; see Application to 21 UK Biobank traits), analogous to previous work[12].

We compared prediction accuracies (R^2) for five main methods: P+T[14,15], LDpred[12], P+T-funct-LASSO[16], LDpred-funct-inf and LDpred-funct (see Methods). Results are reported in Figure 1 (main simulations) and Figure S1 (additional values of number of causal variants); numerical results are reported in Table S3 and Table S4. Among methods that do not use functional information, the prediction accuracy of LDpred was higher than P+T (particularly for the polygenic architecture), consistent with previous work[8,12] (see Table S5 and Table S6 for optimal tuning parameters).

Incorporating functional information via LDpred-funct-inf (a method that does not model sparsity) produced improvements that varied with sample size (+4.7% relative improvement for sparse architecture and +4.8% relative improvement for polygenic architecture at N=50K training samples, compared to LDpred; smaller improvements at smaller sample sizes). These results are consistent with the fact that LDpred is known to be sensitive to model assumptions at large sample sizes[12]. Accounting for sparsity using LDpred-funct further improved prediction accuracy, particularly for the sparse architecture (+7.3% relative improvement for sparse architecture and +5.4% relative improvement for polygenic architecture at N=50K training samples, compared to LDpred; smaller improvements at smaller sample sizes). LDpred-funct attained substantially higher prediction accuracy than P+T-funct-LASSO in most settings (+11% relative improvement for sparse architecture

and +18% relative improvement for polygenic architecture at N=50K training samples; smaller improvements at smaller sample sizes). The difference in prediction accuracy between LDpred and each other method, as well as the difference in prediction accuracy between LDpred-funct and each other method, was statistically significant in most cases (see Table S4). Simulations with 1,000 or 10,000 causal variants generally recapitulated these findings, although P+T-funct-LASSO performed better than LDpred-funct for the extremely sparse architecture (Table S3).

We performed three secondary analyses. First, we assessed the calibration of each method by checking whether a regression of true vs. predicted phenotype yielded a slope of 1. We determined that LDpred-funct was well-calibrated (regression slope 0.98-0.99), LDpred was fairly well-calibrated (regression slope 0.85-1.00), and other methods were not well-calibrated (Table S7). Second, we assessed the sensitivity of LDpred-funct to the choice of K=40 posterior mean causal effect size bins to regularize effect sizes in our main simulations. We determined that results were not sensitive to this parameter (Table S8); slightly higher values of K performed slightly better, but we did not finely optimize this parameter. Third, we evaluated a "cheating" version of LDpred-funct that utilized the true baseline-LD model parameters used to simulate the data, instead of estimating these parameters from the data (LDpred-funct-cheat). LDpred-funct-cheat performed only slightly better than LDpred-funct, indicating that LDpred-funct is not sensitive to imperfect estimation of functional enrichment parameters (see Table S9).

Application to 21 UK Biobank traits

We applied P+T, LDpred, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct to 21 UK Biobank traits (14 quantitative traits and 7 binary traits; Table S1 and Table S2). We analyzed training samples of British ancestry (avg N=365K) and validation samples of non-British European ancestry (avg N=22K). We included 6,334,603 imputed SNPs in our analyses (see Methods). We computed summary statistics and h_g^2 estimates from training samples using BOLT-LMM v2.3[20] (see Table S10). We estimated trait-specific functional enrichment parameters for the baseline-LD model[18] by running S-LDSC[5,18] on these summary statistics. Results for quantitative traits are reported in Figure 2 and Table S11, and results for binary traits are reported in Figure 3 and Table S12. Differences between each main prediction method and LDpred (and block-jackknife standard errors on these differences) are reported in Table S13, and averages across all 21 traits for main and secondary prediction methods are reported in Table S14.

Among methods that do not use functional information, LDpred outperformed P+T (+18% relative improvement in avg prediction R^2), consistent with simulations under a polygenic architecture (see Table S15 and Table S16 for optimal tuning parameters) and with previous work[8,12]. LDpred also outperformed LDpred-inf, a method that does not model sparsity (see Table S14). The exclusion of

long-range LD regions (see Methods) was critical to LDpred performance, as running LDpred without excluding long-range LD regions (as implemented in a previous version of this paper[35]) performed much worse (see Table S14).

Incorporating functional information via LDpred-funct-inf (a method that does not model sparsity) performed only slightly better than LDpred (+0.9% relative improvement in avg prediction R^2). Accounting for sparsity using LDpred-funct substantially improved prediction accuracy (+8.7% relative improvement in avg prediction R^2 vs. LDpred, $P = 0.006$ for difference using one-sided z-test based on block-jackknife standard error in Table S13; avg prediction R^2=0.145; highest R^2=0.413 for height), consistent with simulations. The relative improvement in avg prediction R^2 for LDpred-funct vs. LDpred was larger for quantitative traits (+9.2%; higher prediction R^2 for 14/14 traits) than for binary traits (+6.6%; higher prediction R^2 for 2/7 traits), consistent with the higher average h_g^2 for quantitative traits (0.33) than for binary traits (0.19; observed scale), which corresponds to higher effective sample size (see simulation results in Figure 1) and higher absolute prediction R^2 (Figure 2 vs. Figure 3). Accordingly, the improvement of LDpred-funct vs. LDpred across all 21 traits was smaller when averaging relative improvements in prediction R^2 for each trait individually (+6.3%), a computation that more heavily weights traits with low prediction R^2. LDpred-funct also performed substantially better than P+T-funct-LASSO (+19% relative improvement in avg prediction R^2), consistent with simulations under a polygenic architecture.

We performed several secondary analyses. First, we assessed the calibration of each method by checking whether a regression of true vs. predicted phenotype yielded a slope of 1. As in our simulations, we determined that LDpred-funct was well-calibrated (average regression slope: 0.98), LDpred was fairly well-calibrated (average regression slope: 0.89), and other methods were not well-calibrated (Table S17). Second, we assessed the sensitivity of LDpred-funct to the average value of $K = 58$ posterior mean causal effect size bins to regularize effect sizes in these analyses (see Equation 6 and Table S10). We determined that results were not sensitive to the number of bins (Table S18). Third, we assessed the sensitivity of LDpred-funct to validation sample size; we note that our main analyses involved very large validation sample sizes (up to 25,032; Table S1 and Table S2), which aids the regularization step of LDpred-funct. We determined that results were little changed when restricting to smaller validation sample sizes (as low as 1,000; see Table S19). Fourth, we determined that functional enrichment information is far less useful when restricting to genotyped variants (e.g. −6.9% relative change in avg prediction R^2 for LDpred-funct vs. LDpred when both methods are restricted to typed variants; Table S14), likely because tagging variants may not belong to enriched functional annotations. Fifth, we evaluated a modification of P+T-funct-LASSO in which different weights were allowed for the two predictors (P+T-funct-LASSO-weighted; see Methods), but results were little changed (+1.1% relative improvement in avg prediction R^2 vs. P+T-funct-LASSO; Table

S14). Sixth, we obtained similar results for P+T-funct-LASSO when defining the "high-prior" (HP) SNP set using the top 5% of SNPs with the highest per-SNP heritability, instead of the top 10% (see Table S14). Seventh, we determined that incorporating baseline-LD model functional enrichments that were meta-analyzed across traits (31 traits from ref. 18), instead of the trait-specific functional enrichments used in our primary analyses, slightly reduced the prediction accuracy of LDpred-funct-inf (Table S14). Eighth, we determined that using our previous baseline model[5], instead of the baseline-LD model[18], slightly reduced the prediction accuracy of LDpred-funct-inf and LDpred-funct (Table S14). Ninth, we determined that inferring functional enrichments using only the SNPs that passed QC filters and were used for prediction had no impact on the prediction accuracy of LDpred-funct-inf (Table S14). Tenth, we determined that using UK10K (instead of 1000 Genomes) as the LD reference panel had virtually no impact on prediction accuracy (Table S14).

Application to height in meta-analysis of UK Biobank and 23andMe cohorts

We applied P+T, LDpred-inf, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct to predict height in a meta-analysis of UK Biobank and 23andMe cohorts (see Methods). Training sample sizes were equal to 408,092 for UK Biobank and 698,430 for 23andMe, for a total of 1,106,522 training samples. For comparison purposes, we also computed predictions using the UK Biobank and 23andMe training data sets individually, as well as a training data set consisting of 113,660 British-ancestry samples from the UK Biobank interim release. (The analysis using the 408,092 UK Biobank training samples was nearly identical to the analysis of Figure 2, except that we used a different set of 5,957,935 SNPs, for consistency throughout this set of comparisons; see Methods.) We used 25,030 UK Biobank samples of non-British European ancestry as validation samples in all analyses.

Results are reported in Figure 4 and Table S20. The relative improvements attained by LDpred-funct-inf and LDpred-funct were broadly similar across all four training data sets (also see Figure 2), implying that these improvements are not specific to the UK Biobank data set. Interestingly, compared to the full UK Biobank training data set (R^2=0.413 for LDpred-funct), prediction accuracies were only slightly higher for the meta-analysis training data set (R^2=0.429 for LDpred-funct), and were lower for the 23andMe training data set (R^2=0.328 for LDpred-funct), consistent with the $\approx$ 30% higher heritability in UK Biobank as compared to 23andMe and other large cohorts[18,20,21]; the higher heritability in UK Biobank could potentially be explained by lower environmental heterogeneity. We note that in the meta-analysis, we optimized the meta-analysis weights using validation data (similar to ref. 19), instead of performing a fixed-effect meta-analysis. This approach accounts for differences in heritability as well as sample size, and attained a +5.9% relative improvement in prediction R^2 compared to fixed-effects meta-analysis (see Table S20).

Discussion

We have shown that leveraging trait-specific functional enrichments inferred by S-LDSC with the baseline-LD model[18] substantially improves polygenic prediction accuracy. Across 21 UK Biobank traits, we attained a +9% relative improvement in average prediction R^2 using a method that leverages functional enrichment and performs an additional regularization step to account for sparsity (LDpred-funct), compared to the most accurate method that does not model functional enrichment (LDpred). We note that our main analyses used baseline-LD model v1.1, but using the updated baseline-LD model v2.1 yields slightly higher prediction R^2 for LDpred-funct-inf and LDpred-funct (Table S14).

Previous work has highlighted the potential advantages of leveraging functional enrichment to improve prediction accuracy[16,17]. We included one such method[16] (which we call P+T-funct-LASSO) in our analyses, determining that LDpred-funct attains a +19% average relative improvement vs. P+T-funct-LASSO across 21 UK Biobank traits. More recently, ref. 17 introduced AnnoPred, which uses a Bayesian framework to incorporate functional annotations. However, ref. 17 considered only genotyped variants and binary annotations. As noted above, functional enrichment information is far less useful when restricting to genotyped variants (Table S14), likely because tagging variants may not belong to enriched functional annotations; thus, the utility of AnnoPred in more general settings is currently unknown. To assess this, we applied AnnoPred to the 21 UK Biobank traits (see Table S14 and Table S21. We determined that AnnoPred performed slightly but non-significantly worse than LDpred-funct (−2.3% relative change in avg prediction R^2 for AnnoPred vs. LDpred-funct, $P = 0.17$ for difference using one-sided z-test based on block-jackknife standard error in Table S21). We emphasize that our study is, to our knowledge, the first study that combines binary and continuous-valued functional annotations to improve polygenic risk prediction using imputed variants.

Our work has several limitations. First, LDpred-funct analyzes summary statistic training data (which are publicly available for a broad set of diseases and traits[36]), but methods that use raw genotypes/phenotypes as training data have the potential to attain higher accuracy[20]; incorporating functional enrichment information into prediction methods that use raw genotypes/phenotypes as training data remains a direction for future research. Second, the regularization step employed by LDpred-funct to account for sparsity relies on heuristic cross-validation instead of inferring posterior mean causal effect sizes under a prior sparse functional model; we made this choice because the appropriate choice of sparse functional model is unclear, and because inference of posterior means via MCMC may be subject to convergence issues. As a consequence, the improvement of LDpred-funct over LDpred-funct-inf may be contingent on the number of validation samples available for cross-validation; in particular, for very small validation samples, the number of cross-validation bins is equal to 1 (Equation 6) and LDpred-funct is identical to LDpred-funct-inf. However, we determined

that results of LDpred-funct were little changed when restricting to smaller validation sample sizes (as low as 1,000; see Table S19). Third, we have considered only single-trait analyses, but leveraging genetic correlations among traits has considerable potential to improve prediction accuracy[37,38]. Fourth, we have not considered how to leverage functional enrichment for polygenic prediction in related individuals[39]. Fifth, we have not investigated the application of our methods to polygenic prediction in diverse populations[19,40,41], for which very similar functional enrichments have been reported[42,43]. Finally, the improvements in prediction accuracy that we reported are a function of the baseline-LD model[18], but there are many possible ways to improve this model, e.g. by incorporating tissue-specific enrichments[1–6,44–47], modeling MAF-dependent architectures[48–50], and/or employing alternative approaches to modeling LD-dependent effects[34]; we anticipate that future improvements to the baseline-LD model will yield even larger improvements in prediction accuracy. As an initial step to explore alternative approaches to modeling LD-dependent effects, we repeated our analyses using the baseline-LD+LDAK model (introduced in ref. 33), which consists of the baseline-LD model plus one additional continuous annotation constructed using LDAK weights[34]. (Recent work has shown that incorporating LDAK weights increases polygenic prediction accuracy in analyses that do not include the baseline-LD model[51].) We determined that results were virtually unchanged (avg prediction R^2=0.1350 for baseline-LD+LDAK vs. 0.1354 for baseline-LD using LDpred-funct-inf with UK10K SNPs; see Table S14 and Table S22). Despite these limitations and open directions for future research, our work demonstrates that leveraging functional enrichment using the baseline-LD model substantially improves polygenic prediction accuracy.

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Author contributions

C.M.L. and A.L.P. designed experiments. C.M.L. performed experiments. C.M.L., S.G., P.R.L., S.S.K., N.F. and A.A. analyzed data. C.M.L. and A.L.P. wrote the manscript with assistance from S.G., P.R.L. S.S.K., N.F. and A.L.P.

Web Resources

Software implementing the LDpred-funct-inf and LDpred-funct: `https://www.hsph.harvard.edu/alkes-price/software`

LDscore regression software: `https://github.com/bulik/ldsc`

UK Biobank Resource: `http://www.ukbiobank.ac.uk/`

BOLT-LMM v2.3 software `http://data.broadinstitute.org/alkesgroup/BOLT-LMM/`

BOLT-LMM v2.3 association statistics: `https://data.broadinstitute.org/alkesgroup/UKBB/UKBB_409K/`

23andMe height association statistics: The full summary statistics for the 23andMe height GWAS will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Please visit `https://research.23andme.com/collaborate/#publication` for more information and to apply to access the data.

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Figures

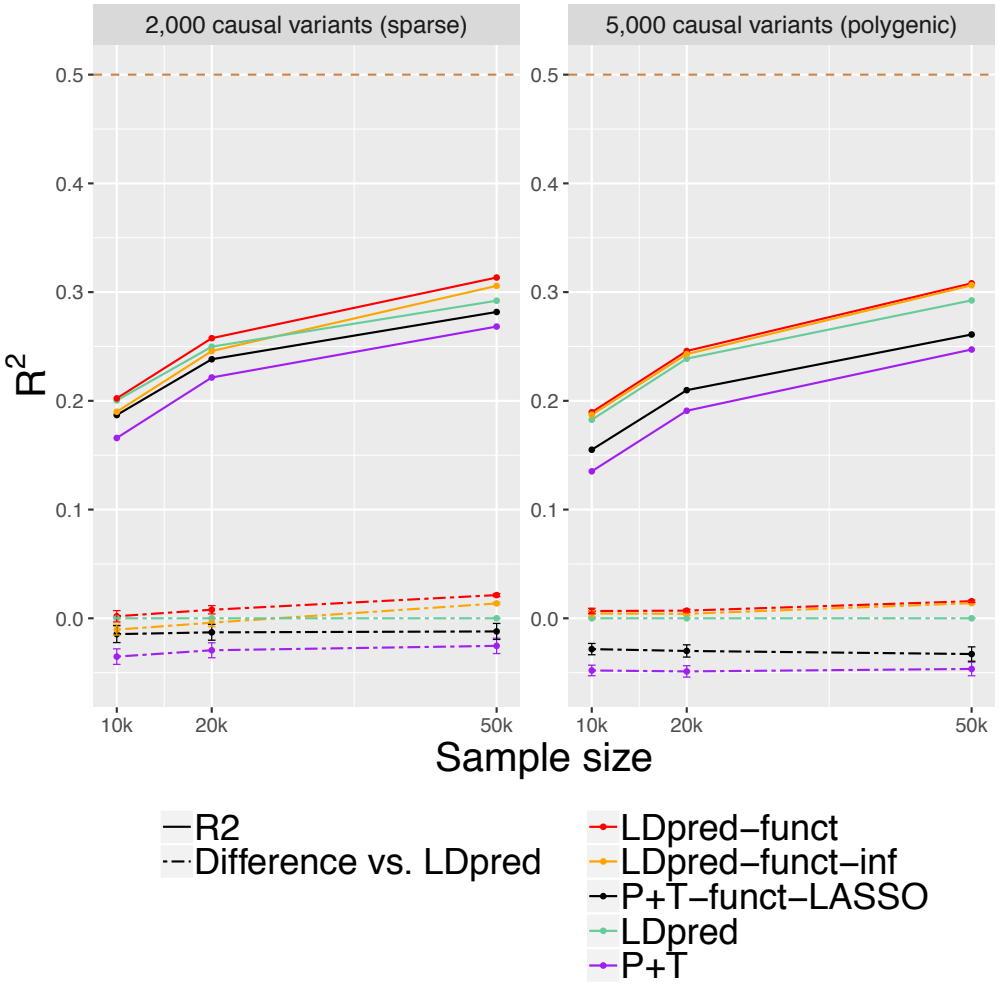

Figure 1: Accuracy of 5 polygenic prediction methods in simulations using UK Biobank genotypes. We report results for P+T, LDpred, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct in chromosome 1 simulations with 2,000 causal variants (sparse architecture) and 5,000 causal variants (polygenic architecture). Results are averaged across 100 simulations. Top dashed line denotes simulated SNP-heritability of 0.5. Bottom dashed lines denote differences vs. LDpred; error bars represent 95% confidence intervals. Results for other values of the number of causal variants are reported in Figure S1, and numerical results are reported in Table S3 and Table S4.

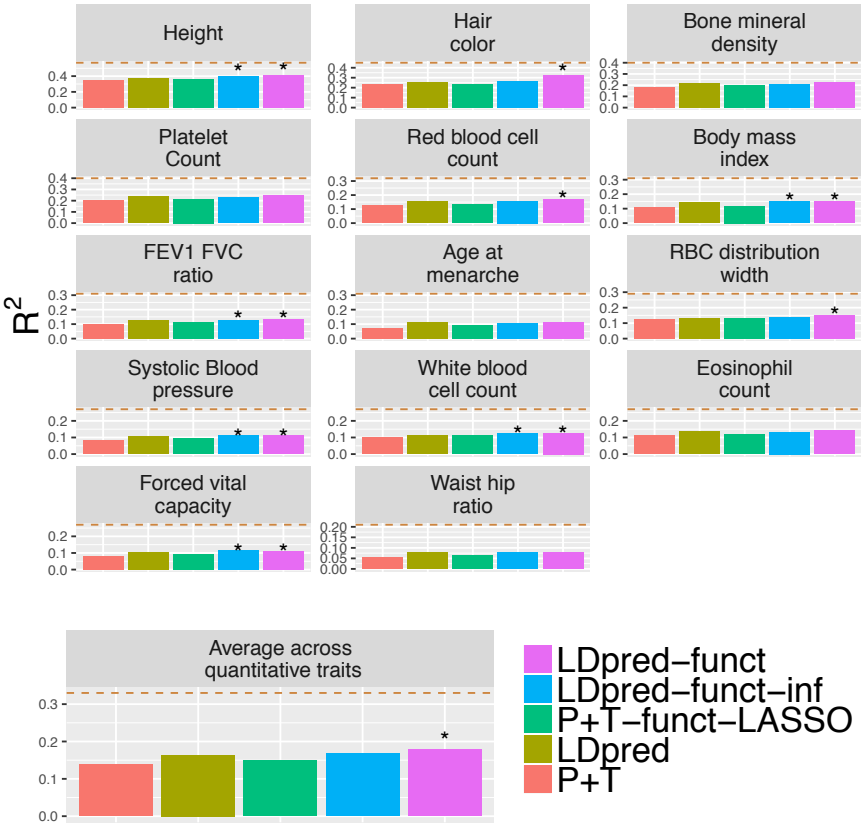

Figure 2: Accuracy of 5 polygenic prediction methods across 14 UK Biobank quantitative traits. We report results for P+T, LDpred, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct. Dashed lines denote estimates of SNP-heritability. Numerical results are reported in Table S11. $*$ denotes methods that significantly outperform LDpred ($P < 0.05$ for difference using one-sided z-test based on block-jackknife standard error in Table S13).

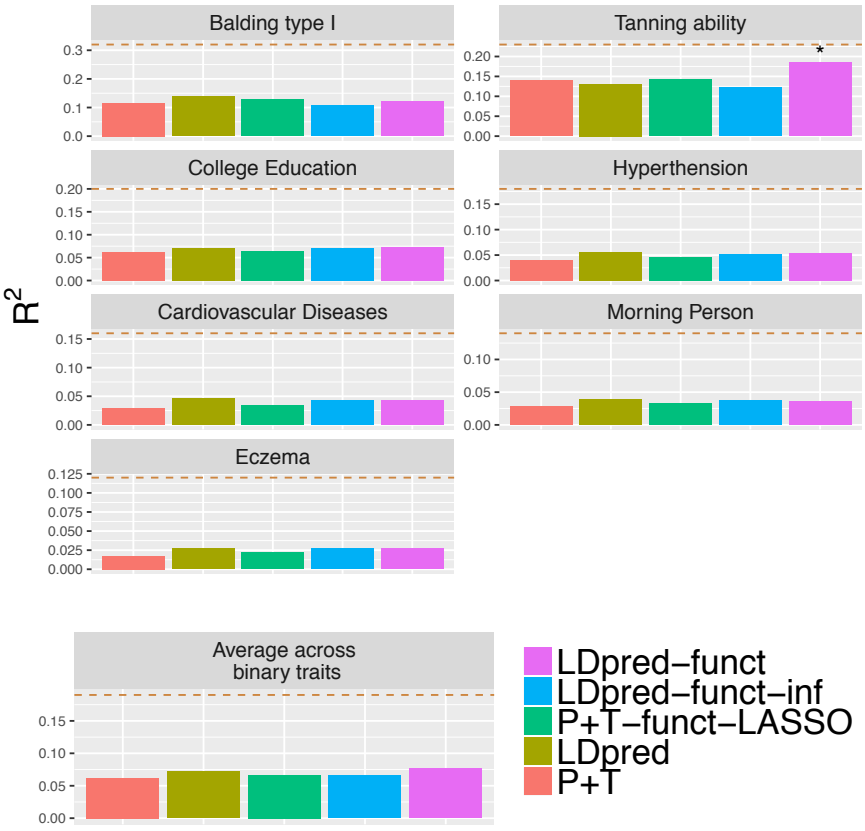

Figure 3: Accuracy of 5 polygenic prediction methods across 7 UK Biobank binary traits. We report results for P+T, LDpred, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct. Dashed lines denote estimates of SNP-heritability. Numerical results are reported in Table S12. $*$ denotes methods that significantly outperform LDpred ($P < 0.05$ for difference using one-sided z-test based on block-jackknife standard error in Table S13).

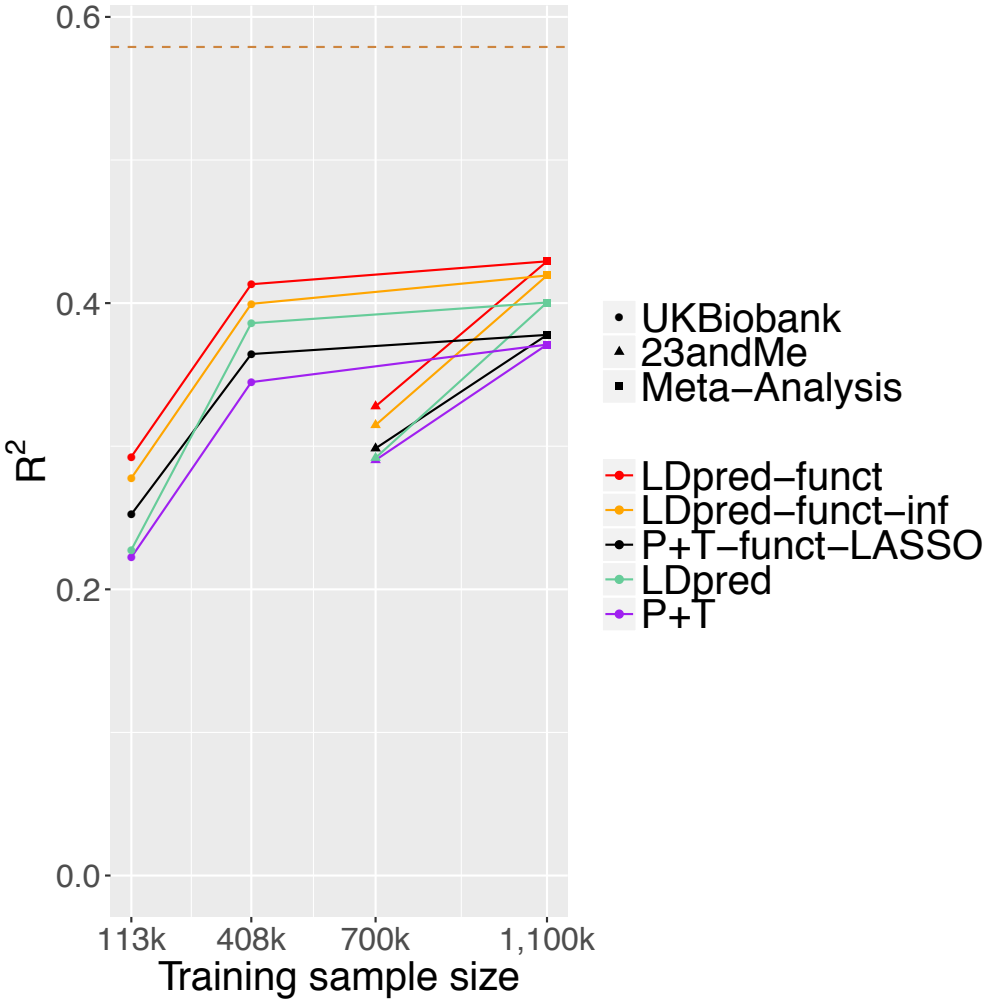

Figure 4: Accuracy of 5 prediction methods in height meta-analysis of UK Biobank and 23andMe cohorts. We report results for P+T, LDpred, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct, for each of 4 training data sets: UK Biobank interim release (113,660 training samples), UK Biobank (408,092 training samples), 23andMe (698,430 training samples) and meta-analysis of UK Biobank and 23andMe (1,107,430 training samples). Nested training data sets are connected by solid lines (e.g. UK Biobank (408k) and 23andMe are both connected to Meta-Analysis, but not to each other). Dashed line denotes estimate of SNP-heritability in UK Biobank. Numerical results are reported in Table S20.

Supplementary Figures

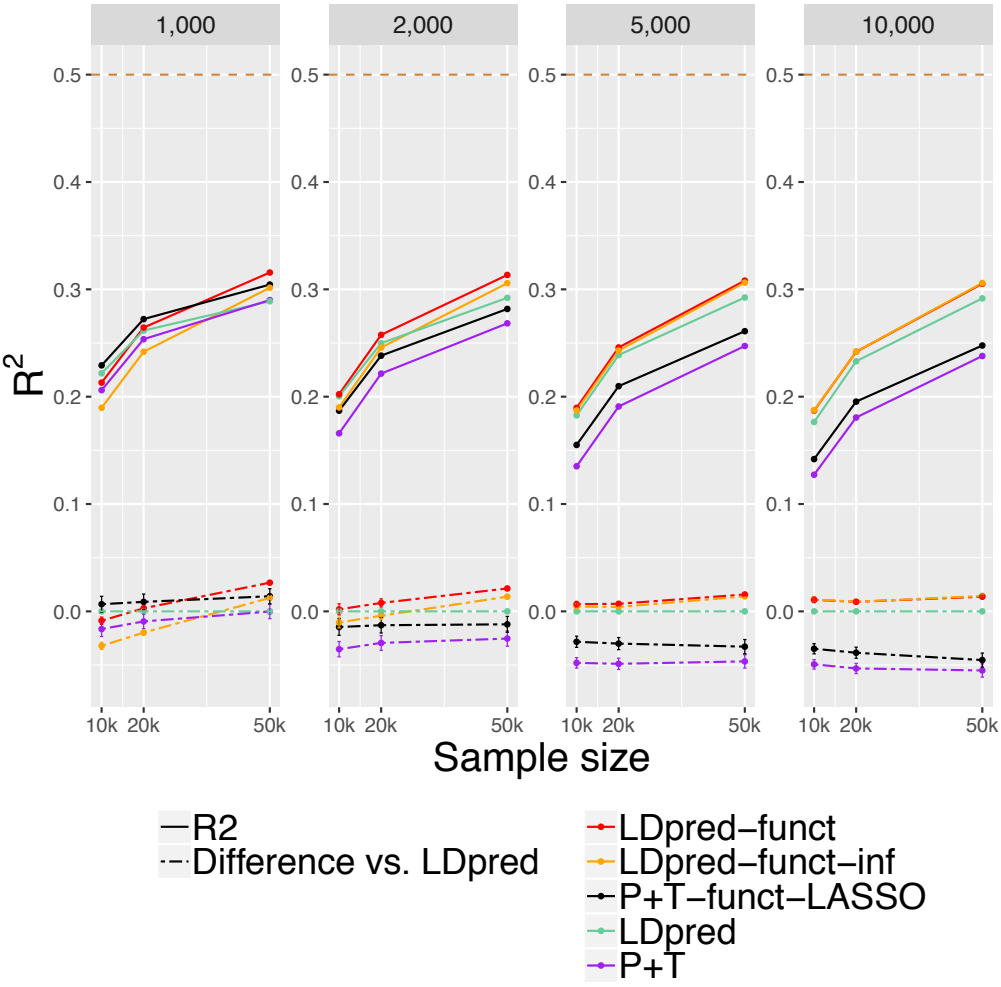

Figure S1: Accuracy of 5 polygenic prediction methods in simulations using UK Biobank genotypes, for 4 values of the number of causal variants. We report results for P+T, LDpred, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct in chromosome 1 simulations with 1,000 causal variants (extremely sparse architecture), 2,000 causal variants (sparse architecture), 5,000 causal variants (polygenic architecture) and 10,000 causal variants (extremely polygenic architecture). Results are averaged across 100 simulations. Top dashed line denotes simulated SNP-heritability of 0.5. Bottom dashed lines denote differences vs. LDpred-inf; error bars represent 95% confidence intervals. Numerical results are reported in Table S3 and Table S4.

Supplementary Tables

	Trait	h_g^2	Training N	Validation N (ancestry distribution)
1	Height	0.57	408092	25030 (43.5% Irish,56.5% Other)
2	Hair color	0.45	403024	24773 (43.5% Irish,56.5% Other)
3	Platelet count	0.40	395747	24277 (43.5% Irish,56.5% Other)
4	Bone mineral density	0.40	397274	24167 (43.6% Irish,56.4% Other)
5	Red blood cell count	0.32	396464	24305 (43.5% Irish,56.5% Other)
6	Age at menarche	0.31	214860	13999 (39.7% Irish,60.3% Other)
7	FEV1 FVC ratio	0.31	331786	19929 (42.5% Irish,57.5% Other)
8	Body mass index	0.31	407667	25000 (43.5% Irish,56.5% Other)
9	RBC distribution width	0.29	394258	24175 (43.5% Irish,56.5% Other)
10	Forced vital capacity	0.27	331786	19929 (42.5% Irish,57.5% Other)
11	Eosinophil count	0.27	391787	24030 (43.4% Irish,56.6% Other)
12	White blood cell count	0.27	395835	24293 (43.5% Irish,56.5% Other)
13	Systolic Blood pressure	0.27	376437	23127 (43.2% Irish,56.8% Other)
14	Waist hip ratio	0.21	408196	25032 (43.5% Irish,56.5% Other)

Table S1: List of 14 UK Biobank quantitative traits. We list the training sample size and validation sample size for each trait. h_g^2 estimates are obtained using BOLT-LMM v2.3 using the training data set.

	Trait	h_g^2	Training		Validation	
			N	Prevalence	N (ancestry distribution)	Prevalence
1	Balding Type I	0.32	186506	0.32	10578 (48.9% Irish,51.1% Other)	0.34
2	Tanning	0.23	400721	0.61	24608 (43.5% Irish,56.5% Other)	0.60
3	College Education	0.20	405140	0.31	24749 (43.5% Irish,56.5% Other)	0.49
4	Hyperthension	0.18	408323	0.27	25041 (43.5% Irish,56.5% Other)	0.25
5	Cardiovascular Diseases	0.16	408963	0.32	25111 (43.5% Irish,56.5% Other)	0.29
6	Morning Person	0.14	365245	0.63	22768 (43.4% Irish,56.6% Other)	0.58
7	Eczema	0.12	408454	0.23	25052 (43.5% Irish,56.5% Other)	0.23

Table S2: List of 7 UK Biobank binary traits. We list the training sample size, validation sample size and prevalence for each trait. h_g^2 estimates are obtained using BOLT-LMM v2.3 using the training data set.

# Causal variants	Model	Training sample size 10,000 Average $R^2(s.e.)$	20,000 Average $R^2(s.e.)$	50,000 Average $R^2(s.e.)$
1,000	P+T	0.2061 (0.0022)	0.2536 (0.0021)	0.2900 (0.0019)
	LDpred	0.2218 (0.0024)	0.2616 (0.0021)	0.2889 (0.0018)
	P+T-funct-LASSO	0.2292 (0.0024)	0.2723 (0.0024)	0.3044 (0.002)
	LDpred-funct-inf	0.1896 (0.0018)	0.2419 (0.0019)	0.3015 (0.0019)
	LDpred-funct	0.2131 (0.002)	0.2644 (0.0021)	0.3157 (0.002)
2,000	P+T	0.1658 (0.0022)	0.2215 (0.0026)	0.2683 (0.0029)
	LDpred	0.2004 (0.0028)	0.2498 (0.0023)	0.2921 (0.0015)
	P+T-funct-LASSO	0.1869 (0.0026)	0.2383 (0.0028)	0.2817 (0.0031)
	LDpred-funct-inf	0.1900 (0.0015)	0.2458 (0.0015)	0.3057 (0.0016)
	LDpred-funct	0.2023 (0.0016)	0.2576 (0.0016)	0.3134 (0.0017)
5,000	P+T	0.1352 (0.0016)	0.1909 (0.002)	0.2472 (0.0024)
	LDpred	0.1826 (0.0017)	0.2388 (0.0013)	0.2924 (0.0013)
	P+T-funct-LASSO	0.1550 (0.0018)	0.2098 (0.0021)	0.261 (0.0026)
	LDpred-funct-inf	0.1872 (0.0012)	0.243 (0.0013)	0.3063 (0.0014)
	LDpred-funct	0.1895 (0.0012)	0.2458 (0.0013)	0.3081 (0.0014)
10,000	P+T	0.1273 (0.0015)	0.1806 (0.002)	0.2379 (0.0024)
	LDpred	0.1764 (0.0016)	0.233 (0.0012)	0.2916 (0.0012)
	P+T-funct-LASSO	0.1419 (0.0017)	0.1954 (0.0022)	0.2477 (0.0026)
	LDpred-funct-inf	0.1873 (0.0012)	0.2419 (0.0012)	0.3059 (0.0013)
	LDpred-funct	0.1870 (0.0013)	0.2418 (0.0012)	0.3053 (0.0012)

Table S3: Accuracy of 5 polygenic prediction methods in simulations using UK Biobank genotypes, for 4 values of the number of causal variants. We report results for P+T, LDpred, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct in chromosome 1 simulations with 1,000 causal variants (extremely sparse architecture), 2,000 causal variants (sparse architecture), 5,000 causal variants (polygenic architecture) and 10,000 causal variants (extremely polygenic architecture). Results are averaged across 100 simulations. We report standard errors in parentheses.

(a)

# Causal variants	Model	Training sample size 10,000 Diff. R^2 $(s.e.)$	20,000 Diff. R^2 $(s.e.)$	50,000 Diff. R^2 $(s.e.)$
1,000	P+T	0.0069 (0.0018)	0.0106 (0.0016)	0.0254 (0.0015)
	P+T-funct-LASSO	-0.0162 (0.002)	-0.0081 (0.0018)	0.011 (0.0016)
	LDpred	-0.0087 (0.0017)	0.0028 (0.0013)	0.0267 (8e-04)
	LDpred-funct-inf	0.0235 (8e-04)	0.0225 (6e-04)	0.0142 (6e-04)
	LDpred-funct	0	0	0
2,000	P+T	0.0365 (0.0019)	0.0361 (0.0022)	0.0451 (0.0026)
	P+T-funct-LASSO	0.0153 (0.0023)	0.0194 (0.0024)	0.0317 (0.0027)
	LDpred	0.0019 (0.0026)	0.0078 (0.0019)	0.0213 (7e-04)
	LDpred-funct-inf	0.0123 (5e-04)	0.0118 (5e-04)	0.0077 (4e-04)
	LDpred-funct	0	0	0
5,000	P+T	0.0544 (0.0016)	0.055 (0.0018)	0.0609 (0.0021)
	P+T-funct-LASSO	0.0345 (0.0017)	0.036 (0.0019)	0.0471 (0.0023)
	LDpred	0.0067 (0.0013)	0.007 (7e-04)	0.0157 (5e-04)
	LDpred-funct-inf	0.0023 (3e-04)	0.0029 (3e-04)	0.0018 (2e-04)
	LDpred-funct	0	0	0
10,000	P+T	0.0597 (0.0016)	0.0612 (0.002)	0.0674 (0.0024)
	P+T-funct-LASSO	0.0451 (0.0017)	0.0464 (0.0022)	0.0576 (0.0026)
	LDpred	0.0107 (0.0013)	0.0089 (5e-04)	0.0136 (5e-04)
	LDpred-funct-inf	-4e-04 (2e-04)	-1e-04 (2e-04)	-7e-04 (2e-04)
	LDpred-funct	0	0	0

(b)

# Causal variants	Model	Training sample size 10,000 Diff. R^2 $(s.e.)$	20,000 Diff. R^2 $(s.e.)$	50,000 Diff. R^2 $(s.e.)$
1,000	P+T	-0.0165 (0.0035)	-0.0094 (0.0034)	-2e-04 (0.0033)
	LDpred	0	0	0
	P+T-funct-LASSO	0.0067 (0.0037)	0.0088 (0.0037)	0.0141 (0.0035)
	LDpred-funct-inf	-0.0321 (0.0017)	-0.0198 (0.0012)	0.0125 (6e-04)
	LDpred-funct	-0.0087 (0.0017)	0.0028 (0.0013)	0.0267 (8e-04)
2,000	P+T	-0.0352 (0.0036)	-0.0294 (0.0035)	-0.0254 (0.0036)
	LDpred	0	0	0
	P+T-funct-LASSO	-0.0146 (0.0039)	-0.0129 (0.0036)	-0.0121 (0.0037)
	LDpred-funct-inf	-0.0104 (0.0025)	-0.004 (0.0019)	0.0137 (5e-04)
	LDpred-funct	0.0019 (0.0026)	0.0078 (0.0019)	0.0213 (7e-04)
5,000	P+T	-0.048 (0.0024)	-0.0488 (0.0026)	-0.0466 (0.0031)
	LDpred	0	0	0
	P+T-funct-LASSO	-0.0283 (0.0026)	-0.03 (0.0028)	-0.0329 (0.0033)
	LDpred-funct-inf	0.0044 (0.0013)	0.0041 (7e-04)	0.0139 (4e-04)
	LDpred-funct	0.0067 (0.0013)	0.007 (7e-04)	0.0157 (5e-04)
10,000	P+T	-0.0493 (0.0022)	-0.0532 (0.0024)	-0.0551 (0.0031)
	LDpred	0	0	0
	P+T-funct-LASSO	-0.0348 (0.0024)	-0.0386 (0.0026)	-0.0454 (0.0033)
	LDpred-funct-inf	0.0111 (0.0012)	0.009 (4e-04)	0.0143 (5e-04)
	LDpred-funct	0.0107 (0.0013)	0.0089 (5e-04)	0.0136 (5e-04)

Table S4: Differences between polygenic prediction methods in simulations using UK Biobank genotypes, for 4 values of the number of causal variants. We report results for P+T, LDpred, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct in chromosome 1 simulations with 1,000 causal variants (extremely sparse architecture), 2,000 causal variants (sparse architecture), 5,000 causal variants (polygenic architecture) and 10,000 causal variants (extremely polygenic architecture). Results are averaged across 100 simulations. We report standard errors in parentheses. (a) Difference between R^2 for LDpred-funct vs. R^2 for each method. (b) Difference between R^2 for each method vs. R^2 for LDpred.

	Training sample size		
# Causal	10,000	20,000	50,000
1,000	0.03	0.1	1
2,000	0.03	0.1	1
5,000	0.03	0.1	1
10,000	0.1	0.3	1

Table S5: Model parameter values for LDpred in simulations. We report the optimal value of p which is the fraction of non-zero effects in the prior, and LD-radious assumed was 2000 SNPs. The analyses from LDpred exclude long-range LD regions reported in ref. 23.

# Causal		Training sample size 10,000	20,000	50,000
1,000	P+T	0.0001	0.0001	0.0001
	P+T-funct-LASSO HP SNP Set	0.1000	0.1000	0.3000
	P+T-funct-LASSO LP SNP Set	0.0100	0.0100	0.0100
2,000	P+T	0.0010	0.0010	0.0010
	P+T-funct-LASSO HP SNP Set	0.1000	0.1000	0.3000
	P+T-funct-LASSO LP SNP Set	0.0100	0.0100	0.0100
5,000	P+T	0.0100	0.0100	0.0100
	P+T-funct-LASSO HP SNP Set	0.3000	0.3000	0.3000
	P+T-funct-LASSO LP SNP Set	0.1000	0.1000	0.1000
10,000	P+T	0.1000	0.1000	0.0100
	P+T-funct-LASSO HP SNP Set	0.3000	0.3000	1.0000
	P+T-funct-LASSO LP SNP Set	0.1000	0.1000	0.1000

Table S6: Model parameter values for P+T and P+T-funct-LASSO in simulated traits. We report the optimal p-value threshold for Pruning + Thresholding (P+T), optimal p-value threshold for P+T-funct-LASSO high prior SNP (HP) set and optimal p-value threshold for P+T-funct-LASSO low prior SNP (LP) set. Optimal R^2_{LD} values was 0.1.

# Causal variants	Model	Training sample size 10,000 Average $R^2(s.e.)$	20,000 Average $R^2(s.e.)$	50,000 Average $R^2(s.e.)$
1,000	P+T	0.9371 (0.0282)	0.9806 (0.0294)	0.8189 (0.0486)
	LDpred	0.992 (0.0146)	0.947 (0.0083)	0.8521 (0.004)
	P+T-funct-LASSO	1.5051 (0.0589)	1.3703 (0.0386)	1.0151 (0.075)
	LDpred-funct-inf	0.4708 (0.0025)	0.454 (0.002)	0.4345 (0.0024)
	LDpred-funct	0.9803 (6e-04)	0.9847 (4e-04)	0.9877 (4e-04)
2,000	P+T	0.7644 (0.0309)	0.791 (0.0257)	0.7976 (0.0209)
	LDpred	0.9688 (0.037)	0.9346 (0.0257)	0.8483 (0.0044)
	P+T-funct-LASSO	1.3572 (0.0382)	1.2138 (0.0544)	1.0448 (0.0284)
	LDpred-funct-inf	0.4656 (0.004)	0.457 (0.0028)	0.4396 (0.0021)
	LDpred-funct	0.9787 (0.001)	0.9837 (7e-04)	0.9882 (4e-04)
5,000	P+T	0.4546 (0.0207)	0.5954 (0.0172)	0.6728 (0.0158)
	LDpred	0.9984 (0.0067)	0.9671 (0.0071)	0.8538 (0.0044)
	P+T-funct-LASSO	0.8085 (0.0267)	0.8994 (0.012)	0.909 (0.0213)
	LDpred-funct-inf	0.47 (0.0035)	0.4584 (0.0023)	0.4424 (0.0015)
	LDpred-funct	0.9776 (9e-04)	0.9839 (5e-04)	0.9881 (4e-04)
10,000	P+T	0.3196 (0.0136)	0.4655 (0.016)	0.586 (0.0116)
	LDpred	0.9903 (0.0156)	0.9449 (0.0059)	0.847 (0.0041)
	P+T-funct-LASSO	0.6824 (0.0182)	0.8142 (0.0182)	0.8178 (0.017)
	LDpred-funct-inf	0.4654 (0.0028)	0.4528 (0.0025)	0.4365 (0.0024)
	LDpred-funct	0.9761 (7e-04)	0.9824 (6e-04)	0.9874 (4e-04)

Table S7: Calibration of 5 polygenic prediction methods in simulations using UK Biobank genotypes, for 4 values of the number of causal variants. We report calibration slopes for P+T, LDpred, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct in chromosome 1 simulations with 1,000 causal variants (extremely sparse architecture), 2,000 causal variants (sparse architecture), 5,000 causal variants (polygenic architecture) and 10,000 causal variants (extremely polygenic architecture). Results are averaged across 100 simulations.

# Causal variants	Model	Training sample size 10,000 Average $R^2(s.e.)$	20,000 Average $R^2(s.e.)$	50,000 Average $R^2(s.e.)$
1,000	LDpred-funct-inf	0.1896 (0.0018)	0.2419 (0.0019)	0.3015 (0.0019)
	LDpred-funct-inf-5	0.208 (0.002)	0.2585 (0.002)	0.3104 (0.0019)
	LDpred-funct-inf-10	0.2101 (0.002)	0.261 (0.002)	0.3124 (0.002)
	LDpred-funct-inf-20	0.2116 (0.002)	0.263 (0.002)	0.314 (0.002)
	LDpred-funct-inf-30	0.2126 (0.002)	0.2638 (0.002)	0.315 (0.002)
	LDpred-funct-inf-40	0.2131 (0.002)	0.2644 (0.0021)	0.3157 (0.002)
	LDpred-funct-inf-50	0.2141 (0.002)	0.2652 (0.0021)	0.3161 (0.002)
	LDpred-funct-inf-60	0.2145 (0.0021)	0.2655 (0.0021)	0.3172 (0.002)
	LDpred-funct-inf-70	0.2157 (0.0021)	0.266 (0.0021)	0.317 (0.0021)
	LDpred-funct-inf-80	0.216 (0.002)	0.2665 (0.0021)	0.3173 (0.0021)
	LDpred-funct-inf-90	0.2164 (0.0021)	0.2667 (0.0021)	0.3176 (0.0021)
	LDpred-funct-inf-100	0.2165 (0.0021)	0.267 (0.0021)	0.3174 (0.0021)
2,000	LDpred-funct-inf	0.1900 (0.0015)	0.2458 (0.0015)	0.3057 (0.0016)
	LDpred-funct-inf-5	0.1994 (0.0016)	0.254 (0.0016)	0.3101 (0.0016)
	LDpred-funct-inf-10	0.2005 (0.0016)	0.2554 (0.0016)	0.3113 (0.0017)
	LDpred-funct-inf-20	0.2016 (0.0016)	0.2566 (0.0016)	0.3124 (0.0017)
	LDpred-funct-inf-30	0.2018 (0.0016)	0.2572 (0.0016)	0.3129 (0.0017)
	LDpred-funct-inf-40	0.2023 (0.0016)	0.2576 (0.0016)	0.3134 (0.0017)
	LDpred-funct-inf-50	0.2023 (0.0016)	0.2575 (0.0016)	0.3136 (0.0017)
	LDpred-funct-inf-60	0.2025 (0.0016)	0.258 (0.0017)	0.3137 (0.0017)
	LDpred-funct-inf-70	0.2027 (0.0016)	0.2579 (0.0017)	0.3135 (0.0017)
	LDpred-funct-inf-80	0.2031 (0.0016)	0.2583 (0.0017)	0.3133 (0.0017)
	LDpred-funct-inf-90	0.2028 (0.0016)	0.2579 (0.0017)	0.3134 (0.0018)
	LDpred-funct-inf-100	0.2031 (0.0016)	0.2582 (0.0017)	0.313 (0.0018)
5,000	LDpred-funct-inf	0.1872 (0.0012)	0.243 (0.0013)	0.3063 (0.0014)
	LDpred-funct-inf-5	0.1895 (0.0012)	0.2451 (0.0013)	0.3075 (0.0014)
	LDpred-funct-inf-10	0.1898 (0.0012)	0.2456 (0.0013)	0.3079 (0.0014)
	LDpred-funct-inf-20	0.1897 (0.0012)	0.2461 (0.0013)	0.3083 (0.0014)
	LDpred-funct-inf-30	0.1898 (0.0012)	0.2461 (0.0013)	0.3084 (0.0014)
	LDpred-funct-inf-40	0.1895 (0.0012)	0.2458 (0.0013)	0.3081 (0.0014)
	LDpred-funct-inf-50	0.1894 (0.0012)	0.2457 (0.0013)	0.3081 (0.0014)
	LDpred-funct-inf-60	0.1893 (0.0012)	0.2454 (0.0013)	0.3077 (0.0014)
	LDpred-funct-inf-70	0.1891 (0.0012)	0.245 (0.0013)	0.3073 (0.0014)
	LDpred-funct-inf-80	0.1888 (0.0012)	0.2447 (0.0013)	0.3071 (0.0014)
	LDpred-funct-inf-90	0.1885 (0.0012)	0.2444 (0.0013)	0.3066 (0.0014)
	LDpred-funct-inf-100	0.188 (0.0012)	0.244 (0.0013)	0.3062 (0.0014)
10,000	LDpred-funct-inf	0.1873 (0.0012)	0.2419 (0.0012)	0.3059 (0.0013)
	LDpred-funct-inf-5	0.1883 (0.0012)	0.2428 (0.0012)	0.3064 (0.0013)
	LDpred-funct-inf-10	0.1882 (0.0012)	0.2428 (0.0012)	0.3064 (0.0012)
	LDpred-funct-inf-20	0.1878 (0.0012)	0.2427 (0.0012)	0.3061 (0.0012)
	LDpred-funct-inf-30	0.1873 (0.0013)	0.2422 (0.0012)	0.3056 (0.0013)
	LDpred-funct-inf-40	0.187 (0.0013)	0.2418 (0.0012)	0.3053 (0.0012)
	LDpred-funct-inf-50	0.1865 (0.0012)	0.2414 (0.0012)	0.3049 (0.0013)
	LDpred-funct-inf-60	0.186 (0.0013)	0.2409 (0.0012)	0.3043 (0.0013)
	LDpred-funct-inf-70	0.1855 (0.0013)	0.2406 (0.0012)	0.3039 (0.0013)
	LDpred-funct-inf-80	0.1851 (0.0012)	0.2399 (0.0012)	0.3036 (0.0012)
	LDpred-funct-inf-90	0.1846 (0.0013)	0.2393 (0.0012)	0.3027 (0.0013)
	LDpred-funct-inf-100	0.1841 (0.0013)	0.2387 (0.0012)	0.3027 (0.0013)

Table S8: Sensitivity of LDpred-funct results to number of bins used for regularization in simulations using UK Biobank genotypes. We report results with the number of posterior mean causal effect size bins used for regularization (K) set to 10, 20, 50 or 100. LDpred-funct-K denotes each respective value of K. We also report results for LDpred-funct-inf, which is identical to LDpred-funct with K set to 1. Results are averaged across 100 simulations. We report standard errors in parentheses.

# Causal variants	Model	Training sample size 10,000 Average $R^2(s.e.)$	20,000 Average $R^2(s.e.)$	50,000 Average $R^2(s.e.)$
1,000	LDpred-funct-inf	0.1896 (0.0018)	0.2419 (0.0019)	0.3015 (0.0019)
	LDpred-funct	0.2131 (0.002)	0.2644 (0.0021)	0.3157 (0.002)
	LDpred-funct-inf-cheat	0.1926 (0.0018)	0.2456 (0.0019)	0.3074 (0.002)
	LDpred-funct-cheat	0.2221 (0.0021)	0.2714 (0.0022)	0.3228 (0.0021)
2,000	LDpred-funct-inf	0.1900 (0.0015)	0.2458 (0.0015)	0.3057 (0.0016)
	LDpred-funct	0.2023 (0.0016)	0.2576 (0.0016)	0.3134 (0.0017)
	LDpred-funct-inf-cheat	0.1943 (0.0015)	0.2498 (0.0016)	0.3108 (0.0016)
	LDpred-funct-cheat	0.2109 (0.0016)	0.2646 (0.0017)	0.3193 (0.0017)
5,000	LDpred-funct-inf	0.1872 (0.0012)	0.243 (0.0013)	0.3063 (0.0014)
	LDpred-funct	0.1895 (0.0012)	0.2458 (0.0013)	0.3081 (0.0014)
	LDpred-funct-inf-cheat	0.1928 (0.0013)	0.2479 (0.0013)	0.3102 (0.0014)
	LDpred-funct-cheat	0.1972 (0.0014)	0.252 (0.0013)	0.3121 (0.0014)
10,000	LDpred-funct-inf	0.1873 (0.0012)	0.2419 (0.0012)	0.3059 (0.0013)
	LDpred-funct	0.1870 (0.0013)	0.2418 (0.0012)	0.3053 (0.0012)
	LDpred-funct-inf-cheat	0.1937 (0.0012)	0.2474 (0.0012)	0.3097 (0.0012)
	LDpred-funct-cheat	0.194 (0.0013)	0.2482 (0.0013)	0.3096 (0.0013)

Table S9: Accuracy of LDpred-funct method in simulations using UK Biobank genotypes under different BaselineLD estimates, for 4 values of the number of causal variants. LDpred-funct-cheat refers to a "cheating" version of LDpred-funct that utilized the true baseline-LD model parameters used to simulate the data. Results are averaged across 100 simulations.

	Trait	Training N	h_g^2	c	bins
1	Height	408092	0.57	0.45	100
2	Hair color	403024	0.45	0.22	100
3	Platelet count	395747	0.40	0.29	88
4	Bone mineral density	397274	0.40	0.26	87
5	Red blood cell count	396464	0.32	0.21	70
6	Age at menarche	214860	0.31	0.20	40
7	FEV1 FVC ratio	331786	0.31	0.24	56
8	Body mass index	407667	0.31	0.27	70
9	RBC distribution width	394258	0.29	0.20	63
10	Eosinophil count	391787	0.27	0.18	60
11	Forced vital capacity	331786	0.27	0.22	50
12	White blood cell count	395835	0.27	0.21	60
13	Systolic Blood pressure	376437	0.27	0.21	56
14	Waist hip ratio	408196	0.21	0.15	48
1	Balding type I	186506	0.32	0.11	31
2	Tanning ability	400721	0.23	0.09	53
3	College Education	405140	0.20	0.15	45
4	Hyperthension	408323	0.18	0.14	41
5	Cardiovascular Diseases	408963	0.16	0.12	37
6	Morning Person	365245	0.14	0.11	29
7	Eczema	408454	0.12	0.09	27

Table S10: Parameter values for 21 UK Biobank traits. The 14 quantitative traits are listed first, followed by the 7 binary traits. For each trait, we list the training sample size, h_g^2 estimate (from BOLT-LMM v2.3; used by LDpred, LDpred-funct-inf and LDpred-funct), the c parameter (used by LDpred-funct-inf and LDpred-funct) and number of bins for LDpred-funct.

	Trait	h2g	P+T	LDpred	P+T-funct-LASSO	LDpred -funct-inf	LDpred -funct
1	Height	0.57	0.3462 (0.0164)	0.3763 (0.0193)	0.3667 (0.0167)	0.4003 (0.0194)	0.4128 (0.0261)
2	Hair color	0.45	0.2339 (0.086)	0.2519 (0.1072)	0.2389 (0.0844)	0.2624 (0.1096)	0.329 (0.1358)
3	Platelet count	0.40	0.1994 (0.0192)	0.2392 (0.024)	0.215 (0.0203)	0.2315 (0.0201)	0.246 (0.0269)
4	Bone mineral density	0.40	0.1871 (0.0177)	0.2188 (0.0219)	0.1993 (0.0178)	0.2137 (0.0188)	0.2256 (0.025)
5	Red blood cell count	0.32	0.1247 (0.0117)	0.1526 (0.0159)	0.1326 (0.0123)	0.1571 (0.0139)	0.1659 (0.0202)
6	Age at menarche	0.31	0.0747 (0.0076)	0.1108 (0.0098)	0.0899 (0.0087)	0.1079 (0.0089)	0.1122 (0.0183)
7	FEV1 FVC ratio	0.31	0.1029 (0.0083)	0.125 (0.0099)	0.1142 (0.0089)	0.1311 (0.0091)	0.133 (0.017)
8	Body mass index	0.31	0.1087 (0.0057)	0.1446 (0.0074)	0.1189 (0.0064)	0.1508 (0.0071)	0.1499 (0.0151)
9	RBC distribution width	0.29	0.1237 (0.0123)	0.1324 (0.0151)	0.1346 (0.013)	0.1421 (0.0147)	0.1533 (0.0202)
10	Forced vital capacity	0.27	0.0817 (0.0059)	0.1072 (0.0071)	0.0935 (0.0062)	0.1145 (0.0067)	0.1134 (0.0148)
11	Eosinophil count	0.27	0.1131 (0.0097)	0.1359 (0.0239)	0.1189 (0.0103)	0.1335 (0.0126)	0.1409 (0.0191)
12	White blood cell count	0.27	0.0994 (0.0078)	0.1143 (0.0095)	0.1109 (0.0085)	0.1239 (0.0093)	0.127 (0.0161)
13	Systolic Blood pressure	0.27	0.0802 (0.0061)	0.1049 (0.0067)	0.0919 (0.0066)	0.1114 (0.0064)	0.1112 (0.0133)
14	Waist hip ratio	0.21	0.0567 (0.0045)	0.0762 (0.007)	0.0645 (0.0049)	0.0793 (0.005)	0.0806 (0.0116)
15	Average across quantitative traits	0.33	0.1380 (0.0107)	0.1636 (0.0105)	0.1493 (0.0082)	0.1685 (0.0101)	0.1786 (0.0117)

Table S11: Accuracy of 5 polygenic prediction methods across 14 UK Biobank quantitative traits. We report results for P+T, LDpred, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct. Optimal parameters for each method are reported in Table S16, Table S15 and Table S10. We report block jackknife standard error over 200 equally sized blocks of adjacent SNPs.

	Trait	h2g	P+T	LDpred	P+T-funct-LASSO	LDpred -funct-inf	LDpred -funct
1	Balding type I	0.32	0.1158 (0.015)	0.138 (0.0653)	0.1269 (0.0157)	0.1075 (0.0132)	0.1221 (0.0235)
2	Tanning ability	0.23	0.1405 (0.0516)	0.1308 (0.0678)	0.143 (0.0446)	0.1229 (0.0631)	0.1842 (0.0784)
3	College Education	0.20	0.0612 (0.0057)	0.0699 (0.0086)	0.0637 (0.006)	0.0716 (0.0059)	0.0728 (0.0109)
4	Hyperthension	0.18	0.0403 (0.0038)	0.0551 (0.0054)	0.0458 (0.0044)	0.0523 (0.0043)	0.0534 (0.0094)
5	Cardiovascular Diseases	0.16	0.0282 (0.0028)	0.0457 (0.0078)	0.0333 (0.0034)	0.0423 (0.0037)	0.0427 (0.0084)
6	Morning Person	0.14	0.0289 (0.0027)	0.0385 (0.0046)	0.0333 (0.0029)	0.0372 (0.0032)	0.0365 (0.008)
7	Eczema	0.12	0.0172 (0.0023)	0.0273 (0.0121)	0.0222 (0.0029)	0.0274 (0.0026)	0.0272 (0.0064)
8	Average across binary traits	0.19	0.0617 (0.0104)	0.0722 (0.0139)	0.0669 (0.0075)	0.0659 (0.0096)	0.0770 (0.0119)

Table S12: Accuracy of 5 polygenic prediction methods across 7 UK Biobank binary traits. We report results for P+T, LDpred, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct. Optimal parameters for each method are reported in Table S16, Table S15 and Table S10. We report block jackknife standard error over 200 equally sized blocks of adjacent SNPs.

	Trait	h_g^2	P+T	P+T-funct-LASSO	LDpred	LDpred-funct-inf	LDpred-funct
1	Height	0.575	-0.029 (0.0075)	-0.0077 (0.0073)	0	0.0238 (0.0066)	0.036 (0.0069)
2	Hair color	0.446	-0.0107 (0.0252)	-0.0099 (0.0298)	0	0.0103 (0.0127)	0.0756 (0.0378)
3	Platelet count	0.401	-0.0381 (0.007)	-0.0204 (0.0071)	0	-0.0077 (0.0062)	0.0058 (0.0059)
4	Bone mineral density	0.398	-0.0294 (0.0106)	-0.0163 (0.0085)	0	-0.005 (0.0077)	0.0066 (0.007)
5	Balding type I	0.323	-0.0245 (0.0561)	-0.0101 (0.0575)	0	-0.0296 (0.0574)	-0.0151 (0.0568)
6	Red blood cell count	0.319	-0.0294 (0.0105)	-0.0216 (0.0066)	0	0.0045 (0.0047)	0.0135 (0.0043)
7	Age at menarche	0.313	-0.0396 (0.0047)	-0.0233 (0.0038)	0	-0.0025 (0.0035)	7e-04 (0.0035)
8	FEV1 FVC ratio	0.309	-0.0254 (0.0089)	-0.0125 (0.0037)	0	0.0061 (0.0036)	0.0082 (0.004)
9	Body mass index	0.307	-0.0375 (0.0034)	-0.0259 (0.003)	0	0.0062 (0.0023)	0.005 (0.0025)
10	RBC distribution width	0.286	-0.0144 (0.007)	-0.0024 (0.005)	0	0.0098 (0.0076)	0.0209 (0.0075)
11	Forced vital capacity	0.274	-0.0308 (0.0044)	-0.0178 (0.0033)	0	0.0073 (0.0027)	0.0061 (0.0027)
12	Eosinophil count	0.274	-0.026 (0.0174)	-0.0188 (0.0179)	0	-0.0023 (0.0184)	0.0053 (0.0181)
13	White blood cell count	0.273	-0.0184 (0.0044)	-0.0058 (0.0032)	0	0.0095 (0.0034)	0.0126 (0.0043)
14	Systolic Blood pressure	0.267	-0.023 (0.0038)	-0.0082 (0.0027)	0	0.0064 (0.0021)	0.0057 (0.0021)
15	Tanning ability	0.235	-0.0026 (0.0194)	-9e-04 (0.0283)	0	-0.0078 (0.014)	0.0534 (0.0297)
16	Waist hip ratio	0.21	-0.0197 (0.0049)	-0.0115 (0.0045)	0	0.0032 (0.0042)	0.0044 (0.0043)
17	College Education	0.198	-0.0086 (0.0063)	-0.006 (0.0062)	0	0.0019 (0.0059)	0.0031 (0.0061)
18	Hyperthension	0.179	-0.0148 (0.0026)	-0.0082 (0.0021)	0	-0.0027 (0.0021)	-0.0016 (0.0022)
19	Cardiovascular Diseases	0.16	-0.0181 (0.0066)	-0.0121 (0.0061)	0	-0.0034 (0.0063)	-0.0029 (0.0062)
20	Morning Person	0.137	-0.0123 (0.0032)	-0.0077 (0.0028)	0	-0.0013 (0.0027)	-0.002 (0.0028)
21	Eczema	0.118	-0.0124 (0.0112)	-0.0061 (0.0109)	0	-0.0015 (0.0111)	-0.001 (0.011)
22	Average across traits	0.286	-0.0221 (0.0042)	-0.0121 (0.0045)	0	0.0012 (0.0037)	0.0114 (0.0045)

Table S13: Absolute differences between polygenic prediction methods across 21 UK Biobank traits. We report results for P+T, LDpred, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct. We report the difference between prediction R^2 for each method vs. prediction R^2 for LDpred. Block-jackknife standard errors are reported in parentheses.

	Method	Average R^2
1	P+T	0.1126
2	LDpred	0.1331
3	P+T-funct-LASSO	0.1218
4	LDpred-funct-inf	0.1343
5	LDpred-funct	0.1447
6	LDpred-inf	0.1133
7	LDpred (without excluding long-range LD regions)	0.0839
8	LDpred (typed SNPs only)	0.1299
9	LDpred-funct-inf (typed SNPs only)	0.1135
10	LDpred-funct (typed SNPs only)	0.1209
11	P+T-funct-LASSO-weighted	0.1231
12	P+T-funct-LASSO (5%)	0.1219
13	LDpred-funct-inf (meta31)	0.1303
14	LDpred-funct-inf (baseline)	0.1313
15	LDpred-funct (baseline)	0.1411
16	LDpred-funct-inf(QCfilters)	0.1339
17	LDpred-funct-inf(UK10K)	0.1354
18	LDpred-funct-inf(UK10K, baseline-LD+LDAK)	0.1350
19	AnnoPred	0.1413
20	LDpred-funct-inf (Baseline-LD v2.1)	0.1360
21	LDpred-funct (Baseline-LD v2.1)	0.1469

Table S14: Accuracy of secondary polygenic prediction methods across 21 UK Biobank traits. For each method, we report the average prediction R^2 across 21 UK Biobank traits. Rows 1-5 correspond to the "Average across traits" panel of Figure 2. Row 6 correspond to the average prediction R^2 from LDpred-inf. Row 7 correspond to the average prediction R^2 from LDpred that includes SNPs from long-range LD regions. Rows 8-10 are methods that analyze only genotyped SNPs (601,728 genotyped SNPs after QC). Rows 11-12 are slightly modified versions of P+T-funct-LASSO. Row 13 uses baseline-LD model functional enrichments that were meta-analyzed across 31 traits. Row 14-15 uses the baseline model, instead of the baseline-LD model. Row 16 restricts the baseline-LD model to the 6,334,603 SNPs that passed QC filters and were used for prediction. Row 17 infers baseline-LD model parameters using UK10K SNPs, instead of 1000 Genomes SNPs. Row 18 uses UK10K SNPs and uses the baseline-LD+LDAK model, instead of the baseline-LD model. Row 19 corresponds to the average prediction R^2 from AnnoPred. Row 20 corresponds to the average prediction R^2 for LDpred-funct-inf using baseline-LD model v2.1 (instead of baseline-LD model v1.1, which is used in our main analyses). Row 21 corresponds to the average prediction R^2 for LDpred-funct using baseline-LD model v2.1 (instead of baseline-LD model v1.1, which is used in our main analyses).

	Trait	h_g^2	p
1	Height	0.57	0.3000
2	Hair color	0.45	0.3000
3	Platelet count	0.40	0.1000
4	Bone mineral density	0.40	0.1000
5	Balding type I	0.32	0.0100
6	Red blood cell count	0.32	0.1000
7	Age at menarche	0.31	0.0300
8	FEV1 FVC ratio	0.31	0.1000
9	Body mass index	0.31	0.1000
10	RBC distribution width	0.29	0.1000
11	Forced vital capacity	0.27	0.0300
12	Eosinophil count	0.27	0.0300
13	White blood cell count	0.27	0.1000
14	Systolic Blood pressure	0.27	0.1000
15	Tanning ability	0.23	0.1000
16	Waist hip ratio	0.21	0.0300
17	College Education	0.20	0.0300
18	Hyperthension	0.18	0.0300
19	Cardiovascular Diseases	0.16	0.0100
20	Morning Person	0.14	0.0100
21	Eczema	0.12	0.0030

Table S15: Model parameter values for LDpred applied to 21 UK Biobank traits. h_g^2 estimate (from BOLT-LMM v2.3), p is the fraction of non-zero effects in the prior, and LD-radious assumed was 2000 SNPs. The main analyses from LDpred exclude long-range LD regions reported in ref. 23, given that including these regions proved to be sub-optimal (see Table S14).

	Phenotype	h_g^2	P-values threshold for P+T	P-values threshold for P+T-funct-LASSO HP SNP set	P-values threshold for P+T-funct-LASSO LP SNP set
1	Height	0.57	0.0100	0.30	0.10
2	Hair color	0.45	0.0010	0.10	0.01
3	Platelet count	0.40	0.0100	0.10	0.10
4	Bone mineral density	0.40	0.0010	0.10	0.10
5	Balding type I	0.32	0.0001	0.10	0.01
6	Red blood cell count	0.32	0.0010	0.10	0.10
7	Age at menarche	0.31	0.0100	0.10	0.10
8	FEV1 FVC ratio	0.31	0.0010	0.10	0.10
9	Body mass index	0.31	0.1000	0.30	0.10
10	RBC distribution width	0.29	0.0010	0.10	0.01
11	Forced vital capacity	0.27	0.0100	0.10	0.10
12	Eosinophil count	0.27	0.0010	0.10	0.10
13	White blood cell count	0.27	0.0100	0.10	0.10
14	Systolic Blood pressure	0.27	0.0100	0.10	0.10
15	Tanning ability	0.23	0.0010	0.10	0.01
16	Waist hip ratio	0.21	0.0100	0.10	0.10
17	College Education	0.20	1.0000	0.30	0.30
18	Hyperthension	0.18	0.0100	0.10	0.10
19	Cardiovascular Diseases	0.16	0.1000	0.10	0.10
20	Morning Person	0.14	0.0100	0.10	0.10
21	Eczema	0.12	0.0100	0.10	0.01

Table S16: Model parameter values for P+T and P+T-funct-LASSO in 21 UK Biobank traits. We report the optimal p-value threshold for Pruning + Thresholding (P+T), optimal p-value threshold for P+T-funct-LASSO high prior SNP (HP) set and optimal p-value threshold for P+T-funct-LASSO low prior SNP (LP) set. Optimal R^2_{LD} values was 0.1.

	Phenotype	h_g^2	P+T	P+T-funct-LASSO	LDpred	LDpred-funct-inf	LDpred-funct
1	Height	0.575	0.2228	0.3034	0.7595	0.7367	0.9938
2	Hair color	0.446	0.2505	0.3058	0.7254	0.7182	0.9920
3	Platelet count	0.401	0.2429	0.3423	0.8451	0.8115	0.9895
4	Bone mineral density	0.398	0.2871	0.3477	0.8192	0.8246	0.9865
5	Balding type I	0.323	0.3693	0.5050	0.8994	0.8781	0.9776
6	Red blood cell count	0.319	0.2898	0.3458	0.8583	0.8202	0.9822
7	Age at menarche	0.313	0.1990	0.3430	1.0227	0.8706	0.9782
8	FEV1 FVC ratio	0.309	0.3021	0.3593	0.8843	0.8527	0.9740
9	Body mass index	0.307	0.1687	0.3541	0.9138	0.8599	0.9813
10	RBC distribution width	0.286	0.2839	0.4189	0.8399	0.8123	0.9833
11	Forced vital capacity	0.274	0.2237	0.3783	0.9085	0.8665	0.9770
12	Eosinophil count	0.274	0.2781	0.3298	0.9082	0.8518	0.9830
13	White blood cell count	0.273	0.2352	0.3707	0.9033	0.8538	0.9793
14	Systolic Blood pressure	0.267	0.2200	0.3637	0.9050	0.8453	0.9808
15	Tanning ability	0.235	0.2437	0.2873	0.8312	0.8292	0.9905
16	Waist hip ratio	0.210	0.2057	0.3344	0.8453	0.8500	0.9758
17	College Education	0.198	0.1345	0.2610	1.0159	0.8520	0.9728
18	Hyperthension	0.179	0.2140	0.3557	0.9817	0.8077	0.9710
19	Cardiovascular Diseases	0.160	0.1213	0.3296	0.9376	0.7953	0.9643
20	Morning Person	0.137	0.2158	0.3720	1.0803	0.8751	0.9651
21	Eczema	0.118	0.1752	0.4971	0.7496	0.7611	0.9634
22	Average across traits	0.286	0.2325	0.3574	0.8873	0.8273	0.9791

Table S17: Calibration comparison for the 5 methods applied to 21 UK Biobank traits. We report calibration slopes for each method, where a value close to 1 respresents a well calibrated prediction.

	Trait	LDpred-funct-inf	LDpred-funct-10	LDpred-funct-20	LDpred-funct-50	LDpred-funct-75	LDpred-funct-100
1	Height	0.4003	0.4113	0.4116	0.4126	0.4127	0.4128
2	Hair color	0.2624	0.2998	0.3059	0.3174	0.3199	0.3290
3	Platelet count	0.2315	0.2445	0.2453	0.2445	0.2446	0.2448
4	Bone mineral density	0.2137	0.2266	0.2266	0.2271	0.2265	0.2256
5	Balding type I	0.1075	0.1217	0.1235	0.1220	0.1198	0.1185
6	Red blood cell count	0.1571	0.1651	0.1655	0.1660	0.1660	0.1649
7	Age at menarche	0.1082	0.1118	0.1116	0.1122	0.1112	0.1070
8	FEV1 FVC ratio	0.1311	0.1353	0.1348	0.1343	0.1336	0.1315
9	Body mass index	0.1508	0.1501	0.1504	0.1494	0.1481	0.1473
10	RBC distribution width	0.1421	0.1527	0.1535	0.1535	0.1530	0.1517
11	Forced vital capacity	0.1145	0.1160	0.1155	0.1145	0.1128	0.1118
12	Eosinophil count	0.1335	0.1425	0.1422	0.1415	0.1406	0.1395
13	White blood cell count	0.1239	0.1278	0.1284	0.1276	0.1266	0.1261
14	Systolic Blood pressure	0.1114	0.1129	0.1119	0.1118	0.1108	0.1105
15	Tanning ability	0.1229	0.1716	0.1794	0.1818	0.1873	0.1892
16	Waist hip ratio	0.0793	0.0818	0.0810	0.0804	0.0798	0.0782
17	College Education	0.0716	0.0720	0.0731	0.0731	0.0748	0.0739
18	Hyperthension	0.0523	0.0542	0.0541	0.0528	0.0521	0.0519
19	Cardiovascular Diseases	0.0423	0.0437	0.0433	0.0421	0.0410	0.0410
20	Morning Person	0.0372	0.0372	0.0366	0.0359	0.0349	0.0340
21	Eczema	0.0274	0.0278	0.0275	0.0271	0.0274	0.0258
22	Average across traits	0.1343	0.1432	0.1439	0.1442	0.1440	0.1436

Table S18: Sensitivity of LDpred-funct results to number of bins used for regularization across 21 UK Biobank traits. We report results with the number of posterior mean causal effect size bins used for regularization (K) set to 10, 20, 50, 75 or 100. LDpred-funct-K denotes each respective value of K. We also report results for LDpred-funct-inf, which is identical to LDpred-funct with K set to 1.

				Validation sample size					
	Trait	h_g^2	LDpred-funct-inf	1000	2000	5000	10000	ALL
1	Height	0.57	0.4003	0.4105	0.4097	0.4100	0.4106	0.4128
2	Hair color	0.45	0.2624	0.2998	0.3005	0.3018	0.3076	0.3290
3	Platelet count	0.40	0.2315	0.2475	0.2443	0.2437	0.2435	0.2460
4	Bone mineral density	0.40	0.2137	0.2296	0.2260	0.2266	0.2256	0.2256
5	Balding type I	0.32	0.1075	0.1257	0.1227	0.1219	0.1237	0.1221
6	Red blood cell count	0.32	0.1571	0.1665	0.1657	0.1643	0.1638	0.1659
7	Age at menarche	0.31	0.1079	0.1161	0.1124	0.1115	0.1108	0.1122
8	FEV1 FVC ratio	0.31	0.1311	0.1408	0.1372	0.1345	0.1347	0.1330
9	Body mass index	0.31	0.1508	0.1549	0.1511	0.1512	0.1503	0.1499
10	RBC distribution width	0.29	0.1421	0.1550	0.1519	0.1515	0.1529	0.1533
11	Forced vital capacity	0.27	0.1145	0.1211	0.1172	0.1143	0.1136	0.1134
12	Eosinophil count	0.27	0.1335	0.1469	0.1434	0.1412	0.1414	0.1409
13	White blood cell count	0.27	0.1239	0.1315	0.1291	0.1278	0.1276	0.1270
14	Systolic Blood pressure	0.27	0.1114	0.1162	0.1138	0.1119	0.1107	0.1112
15	Tanning ability	0.23	0.1229	0.1524	0.1568	0.1769	0.1805	0.1842
16	Waist hip ratio	0.21	0.0793	0.0899	0.0841	0.0825	0.0812	0.0806
17	College Education	0.20	0.0716	0.0794	0.0751	0.0726	0.0727	0.0728
18	Hyperthension	0.18	0.0523	0.0604	0.0557	0.0543	0.0537	0.0534
19	Cardiovascular Diseases	0.16	0.0423	0.0504	0.0459	0.0446	0.0435	0.0427
20	Morning Person	0.14	0.0372	0.0439	0.0407	0.0380	0.0369	0.0365
21	Eczema	0.12	0.0274	0.0354	0.0317	0.0288	0.0277	0.0272
	Average across traits	0.29	0.1343	0.1464	0.1436	0.1433	0.1435	0.1447

Table S19: Sensitivity of LDpred-funct results to number of validation samples across 21 UK Biobank traits. We report results with the number of validation samples set to 1,000, 2,000, 5,000, 10,000 (the number of regularization bins is proportional to the number of validation samples; see Equation 6. Results are averaged across 100 random subsets of each size. ALL denotes results of LDpred-funct using the total number of validation samples (reported in Table S1). We also report results for LDpred-funct-inf, which is equivalent to LDpred-funct in the limit of a very small number of validation samples.

Data Set	Training N	P+T	LDpred	P+T-funct -LASSO	LDpred-funct-inf	LDpred-funct
UK Biobank interim release	113,660	0.2223	0.2276	0.2524	0.2777	0.2926
UK Biobank	408,092	0.3448	0.3860	0.3644	0.3995	0.4132
23andMe	698,430	0.2903	0.2919	0.2985	0.3148	0.3279
Meta-analysis of UK Biobank and 23andMe	1,107,430	0.3710	0.4004	0.3778	0.4193	0.4292
Fixed-effect meta-analysis	1,107,430	0.3687	0.3675	0.3663	0.3965	0.4051

Table S20: Accuracy of 5 prediction methods in height meta-analysis of UK Biobank and 23andMe cohorts. We report results for P+T, LDpred, P+T-funct-LASSO, LDpred-funct-inf and LDpred-funct, for each of 4 training data sets: UK Biobank interim release (113,660 training samples), UK Biobank (408,092 training samples), 23andMe (698,430 training samples) and meta-analysis of UK Biobank and 23andMe (1,107,430 training samples). We also report results for a fixed-effect meta-analysis of UK Biobank and 23andMe.

	Phenotype	h_g^2	LDpred-funct	AnnoPred	Difference
1	Height	0.57	0.4128 (0.0261)	0.4078 (0.0268)	-0.0046 (0.0186)
2	Hair color	0.45	0.3290 (0.1358)	0.2591 (0.1124)	-0.0683 (0.0284)
3	Platelet count	0.40	0.2460 (0.0269)	0.2351 (0.0221)	-0.0099 (0.0095)
4	Bone mineral density	0.40	0.2256 (0.025)	0.2316 (0.0211)	0.0062 (0.0042)
5	Balding type I	0.32	0.1221 (0.0235)	0.1452 (0.0207)	0.0230 (0.0131)
6	Red blood cell count	0.32	0.1659 (0.0202)	0.1680 (0.0155)	0.0018 (0.0034)
7	Age at menarche	0.31	0.1122 (0.0183)	0.1144 (0.0102)	0.003 (0.0028)
8	FEV1 FVC ratio	0.31	0.1330 (0.017)	0.1445 (0.0102)	0.0112 (0.0034)
9	Body mass index	0.31	0.1499 (0.0151)	0.1539 (0.0079)	0.0042 (0.0029)
10	RBC distribution width	0.29	0.1533 (0.0202)	0.1487 (0.0149)	-0.0046 (0.007)
11	Forced vital capacity	0.27	0.1134 (0.0148)	0.1190 (0.0071)	0.0056 (0.0021)
12	Eosinophil count	0.27	0.1409 (0.0191)	0.1386 (0.014)	-0.0025 (0.0108)
13	White blood cell count	0.27	0.1270 (0.0161)	0.1320 (0.0096)	0.0049 (0.0067)
14	Systolic Blood pressure	0.27	0.1112 (0.0133)	0.1173 (0.0069)	0.0067 (0.0019)
15	Tanning ability	0.23	0.1842 (0.0784)	0.1226 (0.0645)	-0.0616 (0.028)
16	Waist hip ratio	0.21	0.0806 (0.0116)	0.0853 (0.0071)	0.0047 (0.0039)
17	College Education	0.20	0.0728 (0.0109)	0.0707 (0.0066)	-0.0022 (0.0027)
18	Hyperthension	0.18	0.0534 (0.0094)	0.0575 (0.0048)	0.0041 (0.0019)
19	Cardiovascular Diseases	0.16	0.0427 (0.0084)	0.0468 (0.004)	0.0040 (0.0012)
20	Morning Person	0.14	0.0365 (0.008)	0.0390 (0.0032)	0.0025 (0.0013)
21	Eczema	0.12	0.0272 (0.0064)	0.0306 (0.0034)	0.0044 (0.0014)
	Average across traits	0.29	0.1439 (0.0112)	0.1407 (0.0098)	-0.0032 (0.0034)

Table S21: Accuracy of LDpred-funct and AnnoPred across 21 UK Biobank traits. We report prediction R^2 for LDpred-funct and AnnoPred, and difference in prediction R^2 between AnnoPred and LDpred-funct. Block-jackknife standard errors are reported in parentheses. When running AnnoPred, we excluded SNPs from long-range LD regions (analogous to LDpred). We note that AnnoPred employs either (i) a prior in which the probability of being causal is the same for each SNP and the causal effect size variance varies across SNPs, or (ii) a prior in which the probability of being causal varies across SNPs and the causal effect size variance is the same for each SNPs. We considered only the first prior, as the second prior constructs categories of SNPs that share the same annotation values; in the case of continuous-valued annotations this would lead to an infinite number of categories.

	Trait	h_g^2	LDpred-funct-inf under different priors: baselineLD (1000G)	baselineLD (UK10K)	baselineLD + LDAK (UK10K)
1	Eosinophil count	0.274	0.1335	0.1335	0.1342
2	Platelet count	0.401	0.2315	0.2327	0.2298
3	RBC distribution width	0.286	0.1421	0.1432	0.1451
4	Red blood cell count	0.319	0.1571	0.1566	0.1544
5	White blood cell count	0.273	0.1239	0.1246	0.1251
6	Bone mineral density	0.398	0.2137	0.2122	0.2117
7	Balding type I	0.323	0.1075	0.1040	0.1070
8	Body mass index	0.307	0.1508	0.1503	0.1502
9	Height	0.575	0.4003	0.4031	0.4033
10	Waist hip ratio	0.210	0.0793	0.0793	0.0785
11	Systolic Blood pressure	0.267	0.1114	0.1113	0.1136
12	College Education	0.198	0.0716	0.0788	0.0790
13	Eczema	0.118	0.0274	0.0283	0.0277
14	Cardiovascular Diseases	0.160	0.0423	0.0446	0.0449
15	Hyperthension	0.179	0.0523	0.0548	0.0555
16	FEV1 FVC ratio	0.309	0.1311	0.1309	0.1323
17	Forced vital capacity	0.274	0.1145	0.1147	0.1140
18	Morning Person	0.137	0.0372	0.0404	0.0404
19	Hair color	0.446	0.2624	0.2749	0.2723
20	Tanning ability	0.235	0.1229	0.1254	0.1232
21	Age at menarche	0.313	0.1079	0.0995	0.0930

Table S22: Accuracy of LDpred-funct-inf(1000G), LDpred-funct-inf(UK10K) and LDpred-funct-inf(UK10K, baseline-LD+LDAK) across 21 UK Biobank traits. We report results for each trait. Results for Average across traits are reported in Table S14.