Narrow-sense heritability estimation of complex traits using identity-by-descent information.

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ABSTRACT

Heritability is a fundamental parameter in genetics. Traditional estimates based on family or twin studies can be biased due to shared environmental or non-additive genetic variance. Alternatively, those based on genotyped or imputed variants typically underestimate narrow-sense heritability contributed by rare or otherwise poorly-tagged causal variants. Identical-by-descent (IBD) segments of the genome share all variants between pairs of chromosomes except new mutations that have arisen since the last common ancestor. Therefore, relating phenotypic similarity to degree of IBD sharing among classically unrelated individuals is an appealing approach to estimating the near full additive genetic variance while avoiding biases that can occur when modeling close relatives. We applied an IBD-based approach (GREML-IBD) to estimate heritability in unrelated individuals using phenotypic simulation with thousands of whole genome sequences across a range of stratification, polygenicity levels, and the minor allele frequencies of causal variants (CVs). IBD-based heritability estimates were unbiased when using unrelated individuals, even for traits with extremely rare CVs, but stratification led to strong biases in IBD-based heritability estimates with poor precision. We used data on two traits in ~120,000 people from the UK Biobank to demonstrate that, depending on the trait and possible confounding environmental effects, GREML-IBD can be applied successfully to very large genetic datasets to infer the contribution of very rare variants lost using other methods. However, we observed apparent biases in this real data that were not predicted from our simulation, suggesting that more work may be required to understand factors that influence IBD-based estimates.

KEYWORDS

Identical-by-descent, IBD, heritability, missing heritability, GCTA, shared haplotype

INTRODUCTION

The proportion of phenotypic variance due to additive genetic variation, termed narrow-sense heritability (h^2), is perhaps the most fundamental aspect of a trait's genetic architecture and has both medical and evolutionary significance (Visscher *et al.*, 2008; Tenesa and Haley, 2013). Traditionally, h^2 has been estimated from family-based studies (h^2_{FAM}), which have suggested that for many complex traits, much of the phenotypic variance is due to additive genetic variance (Polderman *et al.*, 2015). However, h^2_{FAM} estimates may be biased by factors shared by close relatives, such as non-additive genetic and common environmental effects (Eaves *et al.*, 1978; Coventry and Keller, 2005; Yang *et al.*, 2010; Zuk *et al.*, 2012; Tenesa and Haley, 2013). Alternatively, the variance explained by genetic markers in unrelated individuals, for instance from genome-wide association studies (GWAS), may avoid many of the possible confounding factors of family-based studies. However, the thousands of variants associated with complex traits (Visscher *et al.*, 2012; Ripke *et al.*, 2014; Wood *et al.*, 2014) often explain only a fraction of trait heritability, with the difference often called the "missing heritability." This missing heritability may result from causal variants (CVs) that are rare or otherwise poorly tagged by commercial genotyping arrays, insufficient sample sizes to detect small effect variants that do not reach genome-wide significance, and biases that inflate h^2_{FAM}.

Recently, methods have been developed to estimate the phenotypic variance explained by all genotyped markers simultaneously in unrelated individuals, h^2_{SNP} (Yang *et al.*, 2010; Speed *et al.*, 2012; Bulik-Sullivan *et al.*, 2015). Most of these approaches

generally use a genetic relatedness matrix (GRM) that reflects allele sharing or the average correlation between individuals *i* and *j* across genotyped SNPs with entries:

$$A_{ij} = \frac{1}{m}\sum_{k}^{m}\frac{(x_{ik}-2p_k)(x_{jk}-2p_k)}{2p_k(1-p_k)} \quad (1)$$

where *m* is the number of SNPs, x_{jk} is the genotype (coded as 0, 1, or 2) of individual *j* at the k^{th} locus, and p_k is the minor allele frequency (MAF) of the k^{th} locus. The variance-covariance of the phenotype is

$$var(\boldsymbol{y}) = \boldsymbol{A}\sigma_v^2 + \boldsymbol{I}\sigma_e^2 \quad (2)$$

where the variance explained by the SNPs (σ^2_v) and error variance (σ^2_e) are estimated using restricted maximum likelihood (REML). The method, termed GREML, is implemented in packages such as GCTA (Yang, *et al.*, 2011). We refer to matrix **A** (of dimension *n* x *n* and with elements A_{ij}) as the "SNP-GRM." The proportion of the variance explained by all SNPs is an estimate of "SNP-based heritability" ($h^2_{SNP} = \sigma^2_v / (\sigma^2_v + \sigma^2_e)$). By using unrelated individuals, these approaches avoid the confounding of non-additive genetic and environmental effects that can occur in family or twin-based studies, and by estimating all marker effects jointly, the contribution from variants with small effect sizes is captured. Using marker-based approaches, h^2_{SNP} estimates for some complex traits, such as height, have approached h^2_{FAM}, suggesting that little of the heritability remains missing (Yang *et al.*, 2015). For other traits, such as BMI, schizophrenia and neuroticism, h^2_{FAM} estimates remain larger than h^2_{SNP}, and a substantial amount of the heritability remains "still missing" (Lee *et al.*, 2012; Yang *et al.*, 2015).

Advances on the original approach by Yang *et al.* (2010) have better captured the effects of rare CVs and account for linkage disequilibrium (LD) of markers across

the genome, leading to increased h^2_{SNP} estimates (Yang *et al.*, 2015). However, even with the best-performing methods such as MAF- and LD-stratified GREML (GREML-LDMS) and large imputation reference panels, downward bias is likely. Imputation quality declines at low MAF, resulting in a downward bias when causal variants are very rare (MAF<0.0025) and for diverse populations underrepresented in sequencing panels (Evans *et al.*, 2017). The underestimation of variance due to rare CVs may partly explain why h^2_{SNP} remains below h^2_{FAM} for many traits. Thus, developing alternative methods to estimate the variation caused by very rare variants is an important goal.

One such alternative is to leverage information on the proportion of the genome shared identical-by-descent (IBD) between pairs of individuals in a sample (Visscher *et al.*, 2006; Hayes *et al.*, 2009; Zuk *et al.*, 2012; Browning and Browning, 2013), and use a GRM whose elements are the estimated proportions of IBD between all pairs of individuals (IBD-GRM) to estimate heritability (h^2_{IBD}). This is in some ways similar to classical family-based estimates of heritability, which are based on the expected proportion of the genome shared IBD between close relatives (Falconer and Mackay, 1996; Lynch and Walsh, 1998; Visscher *et al.*, 2006). However, rather than using close relatives, an appealing alternative is to estimate pairwise IBD segments directly between all pairs of unrelated (or technically, distantly related) individuals in a sample and use these estimated relationship values to estimate the additive genetic variation. Such an IBD-based approach should capture additive genetic variation due to all but the rarest variants and, so long as close relatives have been removed from the sample, the IBD-based h^2 estimate should be uncontaminated by confounding factors shared by close relatives. Note that we use “IBD” to denote two homologous chromosomal

segments that came from the same common ancestor without intervening recombination, such that the sequence identity of the two segments is identical except at sites where new mutations arose since the last common ancestor. The probability that such mutations arose is a function of the time since the last common ancestor, and therefore a function of the length of the shared IBD segment (Wakeley, 2009). Very long segments are therefore more likely to be identical at all sequence sites, whereas shorter ones are more likely to have occasional differences at sites harboring typically very rare variants. Thus, IBD-GRMs calculated from increasingly long IBD thresholds should capture sharing at increasingly rare CVs.

Such IBD-based GRMs have been used in several instances to estimate heritability. Price *et al.* (2011) and Zaitlen *et al.* (2013) used IBD segments in an Icelandic dataset with close relatives to estimate heritability in quantitative and disease traits, leveraging the known familial relationships within the Icelandic cohort to identify IBD segments. While they demonstrated that IBD could be used for heritability estimation, using close relatives leads to possible confounding of shared environmental or non-additive genetic effects, as noted above. Indeed, Zaitlen *et al.* (2013) found higher heritability estimates using closer relatives, consistent with confounding from non-additive genetic and/or shared environment effects. Using simulated data, Zuk *et al.* (2012) demonstrated that the slope estimated from regressing phenotypic similarity (defined as the standardized phenotypic product of individuals *i* and *j,* $Z_i \times Z_j$) on the IBD-GRM elements from long IBD segments—known as Haseman-Elston (H-E) regression—provides an unbiased estimate of the additive genetic variance in isolated founder populations. Browning and Browning (2013) estimated IBD tracts in a Finnish

cohort of 5,400 individuals, and used the resulting IBD GRM in both H-E regression and GREML to estimate h^2_{IBD} for nine quantitative metabolic traits. h^2_{IBD} was higher than h^2_{SNP} for only five of the nine traits, and never significantly so. The most notable result of their study was the over two-fold higher standard errors for h^2_{IBD} (~0.17) compared to h^2_{SNP} (~0.07), due to the lower variation in the off-diagonal elements of the IBD-GRM compared to the SNP-GRM, suggesting that very large sample sizes will be required to obtain meaningful results in non-founder populations.

Several important questions about IBD-based heritability estimation remain in light of these findings. First, can an IBD-based approach account for very rare CVs? Previous studies (e.g., Browning and Browning, 2013) have simulated CVs from SNPs present on genotyping arrays, which are more common, have generally higher LD than most variants throughout the genome, and are shared across ancestry groups, and therefore do not provide an accurate picture of how h^2 estimation methods perform when CVs do not share these same properties. Thus, it is unclear whether h^2_{IBD} estimates are unbiased estimates of h^2 in the presence of rare CVs. Second, the studies mentioned above utilized isolated founder populations that were both more homogeneous and more related than non-founder populations. To what extent does genetic stratification bias h^2_{IBD}, and how feasible are such IBD-based method in samples from non-founder populations, which are much more readily available?

To address these questions, we used thousands of recently sequenced whole genomes from the Haplotype Reference Consortium (McCarthy *et al.*, 2016) to simulate phenotypes under a range of conditions, including various genetic architectures and levels of stratification, then estimated narrow-sense heritability (h^2_{IBD}) using the an IBD-

GRM, either alone or in combination with various SNP-based GRMs. By simulating CVs from whole genome sequences rather than commercial array SNPs, our study was able to examine the role of all but the rarest frequency classes of CVs in the genome under realistic genomic conditions. We then estimated h^2_{IBD} for height and BMI in the UK Biobank with over 120,000 individuals.

MATERIALS AND METHODS

Samples and Population Structure

We tested the h^2_{IBD} estimation method using simulated phenotypes derived from Haplotype Reference Consortium (HRC) whole genome sequence data (McCarthy *et al.*, 2016). Full details of the HRC can be found in McCarthy *et al.* (2016). Briefly, this resource comprises roughly 32,500 individual whole genome sequences from multiple sequencing studies, with phased genotypes with a minor allele count of at least 5 at all sites. This large sequence dataset allowed us to simulate CVs across all MAF classes down to ~.0003 with real patterns of LD (within and among chromosomes). It also allowed us to simulate SNP markers available on existing commercial genotyping arrays in order to mimic the process of IBD detection in SNP data. We obtained permission to access the following HRC cohorts (recruitment region & sample size): AMD (Europe & worldwide; 3,189), BIPOLAR (European ancestry; 2,487), GECCO (European ancestry; 1,112), GOT2D (Europe, 2,709), HUNT (Norway; 1,023), SARDINIA (Sardinia; 3,445), TWINS (Minnesota; 1,325), 1000 Genomes (worldwide; 2,495), UK10K (UK; 3,715) (see (McCarthy *et al.*, 2016) for additional details of the HRC). This set of cohorts, which included isolated subpopulations of European descent, allowed investigation into the

effects of stratification on estimates. The subset totaled 21,500 whole genome sequences comprising 38,913,048 biallelic SNPs. This is the same set of individuals and simulated phenotypes used in Evans *et al.* (2017) to compare SNP-based heritability methods. Below, we briefly describe our approach.

Our goal was to assess the accuracy and potential bias of the h^2_{IBD} estimation method using data similar to those collected for a typical GWAS analysis and h^2_{SNP} estimation. In order to mimic this kind of data, we first extracted variant positions corresponding to a widely-used commercially available genotyping array, the UK Biobank Affymetrix Axiom array. We then identified individuals of primarily European ancestry, using principal components analysis with 133,603 MAF- and LD-pruned markers (plink2 (Chang *et al.*, 2015) command: --maf 0.05 --indep-pairwise 1000 400 0.2) to identify a grouping associated with the 1000 Genomes European individuals in the HRC. This dataset comprised 19,478 individuals including Finnish and Sardinian samples (Fig. S1).

From within this European ancestry dataset, we identified clusters that contained different levels of genetic heterogeneity within them (Fig. S2). The most structured group contained all samples (N=19,478). The somewhat structured group excluded Sardinian and Finnish samples (N=14,424). The low structure group contained northern/western European samples (N=11,243), and the least structured was a subset of mainly British Isles samples (N=8,506). We used GCTA (Yang, *et al.*, 2011) with LD- and MAF-pruned SNPs to estimate relatedness and remove the minimal number of individuals from pairs with relatedness > 0.1 within each of the four samples. In the most homogeneous and smallest sample with no genetic structure, this left 8,201 individuals.

In order to eliminate the influence of varying sample size in our comparison across the range of stratification, we randomly chose 8,201 of the unrelated individuals from within each of the other three stratification subsamples. We similarly tested a lower relatedness cutoff of 0.05 within each group (leaving 7,792; 8,115; 8,129; and 8,186 individuals for the four subsamples), and used both subsets later to examine how a 0.1 or 0.05 relatedness cutoff influences h^2_{IBD} estimates.

Simulated Phenotypes Using Whole Genome Sequencing Data

To test how h^2_{IBD} estimation our method performed on a range of genetic architectures, we simulated phenotypes from CVs drawn randomly from five MAF ranges: common (MAF>0.05), uncommon (0.01<MAF<0.05), rare (0.0025<MAF<0.01), very rare (0.0003<MAF<0.0025), and all variants randomly drawn with MAF>0.0003. Phenotypes were generated with 1,000 or 10,000 CVs from the model $y_i = g_i + e_i$, where $g_i = \sum w_{ik}\beta_k$, w_{ik} is the genotype (coded as 0, 1, or 2) of individual i at the k^{th} CV, and β_k is the k^{th} allelic effect size, drawn from ~N(0,1/[2p_k(1-p_k)]), where p_k is the MAF of allele k within each of the four samples, which assumes larger additive effects for rarer variants. The g_i's were standardized and residual error was added as ~N(0,(1- h^2)/h^2) for a simulated h^2 of 0.5. A total of 400 replications were performed for each CV MAF range and for each of the four stratification subsets.

Mixed Models for Heritability Estimation

We estimated heritability for each simulation using GCTA (Yang, Lee, *et al.*, 2011). We tested different models to assess our IBD-based GREML method (GREML-

IBD). First, we used the single IBD-GRM with GREML to estimate h^2_{IBD}. Second, to partition the genetic variance into that tagged by common SNPs and that tagged by haplotype sharing, presumably from rarer CVs, we used a two GRM model (GREML-IBD+SNPs) with the IBD-GRM (h^2_{IBD}) and a common SNP-GRM derived from Axiom array positions with MAF>0.01 (h^2_{SNP}). Last, we estimated genetic variances due to LD- and MAF-stratified imputed variant SNP-GRMs (h^2_{SNP}) as well as the IBD-GRM (h^2_{IBD}) as a comparison to the GREML-LDMS method, which we term GREML-IBD+LDMS. From previous work, we knew that GREML-LDMS underestimates variance attributable to the rarest CVs when using imputed data. We therefore wished to determine if the IBD-GRM could capture that missing heritability. To do this, we estimated 16 SNP-GRMs stratified into the above 4 MAF categories and 4 LD score quartiles using imputed genome-wide variants, and included these plus the IBD GRM in the model (17 GRMs total). To determine if the IBD-GRM captured the genetic variance due to the rarest CVs, we also tested a model with 12 SNP-GRMs, removing the rarest MAF category described above, for a total of 13 GRMs in the analysis (three MAF categories X four LD score quartiles + 1 IBD-GRM). To impute, we first phased SNP data using SHAPEIT2 (Delaneau *et al.*, 2013), imputed using minimac3 (Das *et al.*, 2016), and retained variants with imputation $R^2 \geq 0.3$ (Yang *et al.*, 2015). We used the HRC sequence data as our imputation reference panel after removing all target (8201 unrelated + relatives) individuals in the HRC reference panel, thereby assuring ~independence (no relatedness) between the target and reference panels. Additional details of the imputation procedure can be found in Evans *et al.* (2017). We estimated LD scores for the LD stratification using GCTA. In all cases we used the –reml-no-

256 constrain option of GCTA, and included 20 principal components (PCs; 10 from
257 worldwide PC analysis and 10 from the specific subsample PC analysis) as continuous
258 covariates, with sequencing cohort as a categorical covariate.
259
260 *Estimating IBD-GRMs*
261 To mimic computationally phased SNP data with realistic phase errors, we first
262 un-phased the sequence data for each data subset and then re-phased the Axiom array
263 positions using SHAPEIT2 (Delaneau *et al.*, 2013). We then used FISHR2 (Bjelland *et*
264 *al.*, 2017) to identify shared haplotype segments that are putatively IBD across all pairs
265 of individuals within each of our four structure samples. FISHR2 first uses a modified
266 version of GERMLINE (Gusev *et al.*, 2009) to find candidate IBD segments. It then
267 improves the accuracy of the segment endpoints by comparing an observed moving
268 average of haplotype mismatches (potential phase or SNP call errors) for a given
269 candidate IBD segment to (a) the distribution of haplotype mismatches in segments that
270 are almost certainly IBD (the middlemost sections of very long IBD segments) and (b)
271 the distribution of haplotype mismatches in segments that are almost certainly non-IBD
272 (between random pairs of individuals at matched locations). FISHR2 truncates
273 candidate segments when this moving average becomes more consistent with non-IBD
274 than IBD. FISHR2 is more accurate than leading competitors at detecting long (> 3 cM)
275 IBD segments and is the only software that gives unbiased estimates of the true length
276 of IBD segments. The parameters we used for FISHR2 were stringent (command line -
277 err_hom 4 -err_het 1 –min_snp 128 –min_cm_initial 1 –min_cm_final 1 –window 50 –
278 gap 100 -h_extend -w_extend –homoz -emp-ma-threshold 0.06 -emp-pie-threshold

0.015 -count.gap.errors TRUE), chosen to minimize false positive IBD detection (Bjelland *et al.*, 2017). We used an initial length threshold of 1 cM, but because longer IBD segments are more likely to share rare variants, we also identified segments of length greater than 2, 3, 4, 6, 9, and 12 cM. The FISHR2 parameters we used should lead to consistently low false positive rates (<.05) at all threshold lengths, and should lead to a sensitivity that increases as a function of the length of the true IBD segments, and should be >.90 for IBD segments >3cM (Bjelland *et al.*, 2017). To reduce the influence of low recombination regions artificially extending segments (e.g., due to one or a few matching IBS SNPs that are far from the termini of true IBD segments), we windsorized genetic map positions by setting the maximum distance between adjacent markers to 0.2 cM, and used an initial 1 cM minimum IBD segment length threshold.

We then summed the length in Mb of all segments shared between each pair of individuals and divided by twice the length of the genome. This IBD-GRM then represents the estimated proportion of the genome, D_{ij}, shared IBD between individuals *i* and *j* in the sample, similar to the A_{ij} elements of the SNP-GRM. We created IBD-GRMs for each minimum segment cM length threshold. As recombination rate varies throughout the genome, in two of the subsamples we also tested whether an IBD-GRM based on the summed cM length of segments influences heritability estimates.

Stratification Effects

We performed four additional analyses to further determine the influence of stratification on h^2_{IBD} estimates. First, to test whether bias observed in stratified samples was due to inadequate control of structure, we ran K-means clustering on the somewhat

stratified subsample for K=2 clusters, then ran PC analysis within each of the two clusters. We included the first 35 PCs within each cluster, for a total of 90 PCs (the original 20 plus 35 from each cluster). Because PC analysis was run within each cluster separately, we set the PC scores for the alternate cluster to 0 (the mean).

Second, we tested, within the stratified subsample, whether including 10 additional PCs from very rare variants could correct for the upward bias (Mathieson and McVean, 2012). We used 150,000 randomly selected very rare SNPs from the WGS data and pruned for LD (plink2 command: --indep-pairwise 1000 400 0.2), leaving 129,710 variants for the PCA. As a comparison, we also estimated heritability with no covariates included.

Third, we estimated h^2_{IBD} for phenotypes in which all CVs were drawn from odd chromosomes using IBD-GRMs estimated only from the even chromosomes. The presence of uncontrolled cryptic relatedness or population structure can lead to cross-chromosome LD that inflates h^2 estimates (Yang *et al.*, 2011). We estimated the correlation of off-diagonal GRM elements between the IBD-GRMs from even chromosomes and those from odd chromosomes. We also examined the correlation between the off-diagonal elements from IBD-GRMs and the off-diagonal elements from GRMs built from very rare (0.0003<MAF<0.0025) and common (MAF>0.05) sequence variants. This tested whether correlations between even and odd chromosome IBD-GRMs were stronger in more stratified subsamples, and whether the correlation with very rare variants was stronger with increasing minimum cM length of the IBD-GRM.

Last, simultaneously fitting GRMs derived from each chromosome protects against cross chromosome correlations induced by stratification or cryptic relatedness

because the estimates of variance explained by one GRM are conditional on the other GRMs (Yang *et al.*, 2011). However, because the variances of the off-diagonal elements in the IBD-GRMs were so small, models with 22 IBD-GRMs would not converge. Instead, we tested a two GRM model with one IBD-GRM estimated from the odd numbered chromosomes and a second from the even numbered chromosomes, which should partially address the effects of long-range LD (Speed *et al.*, 2012).

Heritability of Complex Traits in the UK Biobank

We applied the IBD-based approaches to height and body mass index (BMI) data in the UK Biobank, a very large resource of ~500K adults from the UK, genotyped using the Affymetrix Axiom array (Sudlow *et al.*, 2015). The current release includes ~150K genotyped individuals, imputed using the combined UK10K/1000 Genomes reference panels. We used this resource previously, and full details on quality control can be found in Evans *et al.* (2017). We identified putative IBD segments as described above using FISHR2 and then calculating IBD-GRMs with minimum cM thresholds of 2, 3, 4, 6, 9, and 12cM. We applied a relatedness cutoff of 0.05, and used individuals of European ancestry, resulting in a final sample size of ~120K individuals included in the analysis (Fig. S2). We used GCTA to estimate variance components and included sex, UK Biobank assessment centre, genotype measurement batch, and qualification (highest level of educational attainment) as categorical covariates, and the Townsend deprivation index, age at assessment, age at assessment squared, and the 15 PC scores from the UK Biobank as quantitative covariates. We compared these models using Akaike information criterion with sample size correction (AICc) (Burnham and

348 Anderson, 2002), and used this to determine if additional information was added by
349 using an IBD-GRM.
350
351 **RESULTS**
352 *Simulated Phenotypes – GREML-IBD*
353 Using a single IBD-GRM, h^2_{IBD} estimates varied greatly depending on the MAF
354 range of the CVs in simulated phenotypes and the amount of stratification in the
355 subsample (Fig. 1). In the two more homogeneous subsamples, h^2_{IBD} increased then
356 stabilized with increasing IBD segment length threshold. The 95% CI overlapped the
357 true heritability (0.5) for all IBD thresholds > 4 cM and for all CV MAF classes,
358 suggesting that GREML-IBD produces unbiased estimates of h^2 in relatively
359 homogeneous samples. For phenotypes simulated from common CVs, unbiased
360 estimates of h^2_{IBD} were also obtained using shorter cM thresholds. Results were similar
361 for different relatedness thresholds (Figs S3 & S4) and for larger numbers of CVs (Fig.
362 S5), although h^2_{IBD} appeared to be biased upwards in phenotypes with 10,000 common
363 CVs and long IBD length thresholds in the low stratification subsample (Fig. S5).
364 In the two most stratified samples, we observed upward biases at long cM IBD
365 thresholds, particularly for the rarest CVs (h^2_{IBD} > 1). This bias remained when using
366 higher or lower relatedness thresholds (Figs. S3-4), and with 10,000 CVs (Fig S5).
367 Controlling for 70 additional PCs or with additional PCs from very rare variants did not
368 correct for the upward bias in very rare CV phenotypes, though inclusion of PCs did
369 correct for bias in common CV phenotypes (Fig. S6). Furthermore, this bias was not
370 mitigated by summing genetic length (cM) of IBD segments for calculating the GRM

371 rather than physical length (Fig. S7) nor when using a two-GRM model, with one IBD-
372 GRM calculated from even-numbered chromosomes and the second from odd-
373 numbered chromosomes (Fig. S8-S9). Fitting a larger number of IBD-GRMs (e.g., one
374 per chromosome) would better capture all the long-range correlations and might better
375 mitigate the bias, but this approach is impractical for GREML-IBD in real data because
376 the low variance of D_{ij} creates estimation problems. Thus, stratification has strong
377 impacts on GREML-IBD estimates of heritability that we were unable to control for.
378 To explore why stratification had such strong influences on h^2_{IBD}, we first
379 examined the correlations of off-diagonal GRM elements between the odd chromosome
380 GRMs and even chromosome GRMs. Stratification clearly led to stronger long-range
381 correlations, as did, in most subsamples, longer IBD thresholds for the GRM (Fig. S10).
382 In the two least stratified subsamples, the correlation of even chromosome IBD-GRMs
383 with odd chromosome WGS SNP-GRMs, estimated from either common or very rare
384 WGS variants, was weak, and did not change drastically with increasing cM thresholds.
385 There were stronger correlations overall in the two most stratified subsamples,
386 especially between even chromosome IBD-GRMs and odd chromosome GRMs built
387 from either IBD segments or from very rare WGS variants. Thus, stratification induced
388 long-range correlations, such that D_{ij} for a pair of individuals at one chromosome
389 predicted rare variant sharing at other chromosomes, which can presumably lead to
390 over-estimation of h^2_{IBD} due to rare CVs being redundantly tagged by IBD sharing.
391 In simulations with odd chromosome CVs and IBD-GRMs calculated from even
392 chromosomes only, we observed upward biases in h^2_{IBD} estimates for long IBD
393 thresholds that were particularly severe in stratified samples with rare odd-chromosome

CVs (Fig. S11). This pattern of results was similar to the pattern observed in our primary simulations (Fig. 1), consistent with the explanation that the upward biases in h^2_{IBD} for rare CVs we observed at long IBD thresholds was due to long-range, redundant tagging of CVs in stratified samples. Note that the simulated h^2 for the even chromosomes was 0. Because there is more recent common ancestry within than between subpopulations, there is more sharing of long IBD segments—and importantly more sharing of rare (recently arisen) causal variants. Consequently, due to stratification, long, shared IBD segments at one genomic location weakly predict not only sharing of long IBD segments, but also sharing of rare variants and shorter IBD segments, at other genomic locations. This redundant tagging of rare causal variants across the genome in stratified samples presumably leads to inflated h^2_{IBD} estimates. The same phenomenon has been described h^2_{SNP} in the context of stratification (Yang *et al.*, 2011; Speed *et al.*, 2012), although the bias is less extreme and, because the variance of A_{ij} elements is much greater than the variance of D_{ij}, is more easily alleviated by fitting multiple GRM models.

Simulated Phenotypes – GREML-SNPs+IBD

The second model we tested was GREML-SNPs+IBD, which included a common SNP-GRM and the IBD-GRM. For phenotypes with 1,000 or 10,000 CVs, the total heritability ($h^2_{IBD}+h^2_{SNP}=h^2_{Total}$) was unbiased in the two least stratified subsamples regardless of the CV MAF range (Fig. S12, S13). However, h^2_{Total} was again increasingly over-estimated in the two most stratified samples for very rare CV phenotypes. As expected, partitioning the variance to each of the GRMs, GREML-SNPs+IBD attributed more of the phenotypic variance to the common SNP-GRM when

the CVs were common, and more of the variance to the IBD-GRM when the CVs were rarer (Figs. S14-S15). For common CV phenotypes, the variance attributable to the common SNP-GRM was overestimated by ~20%, which is consistent with previous findings for a common SNP-GRM based on the Axiom array positions and occurs because CVs in the common bin have higher average MAF than the SNPs on the Axiom array (Evans *et al.*, 2017). Interestingly, this overestimate was balanced by a negative variance estimate attributed to the IBD-GRM, such that the total estimated heritability was unbiased at ~0.5 (Figs. S12-S15). Nevertheless, h^2_{IBD} continued to be overestimated for very rare CV phenotypes in structured samples.

Simulated Phenotypes – GREML-LDMS+IBD

Our third model included 16 imputed variant GRMs that were MAF- and LD-stratified, and the IBD-GRM. We found that across subsamples, GREML-LDMS+IBD produced unbiased h^2_{Total} estimates with either 1,000 CVs or 10,000 CVs across all CV MAF ranges (Figs. S16-S17). Partitioning the variance among GRMs revealed that for the rare and very rare CV phenotypes, the IBD-GRM explained a small amount of the variance, but was near-zero otherwise (Figs. S18-S19).

When we excluded the rarest MAF bin from the model, leaving 12 imputed variant GRMs plus the IBD-GRM, GREML-LDMS+IBD produced unbiased h^2_{Total} estimates with either 1,000 CVs or 10,000 CVs across all CV MAF ranges in subsamples with little or no stratification (Figs. 2, S20). However, with increased stratification, h^2_{Total} estimates were again overestimated for very rare CV phenotypes in the context of stratification. Partitioning the variance into that attributable to the LDMS

imputed-variant GRMs and the IBD-GRM showed that, in unstratified samples, most of the genetic variance was attributable to the LDMS GRMs for CV MAF ranges > 0.0025 while the IBD-GRM captured the genetic variance for very rare CV MAF ranges (0.0003-0.0025) (Figs. 3, S21). While the variance attributed to the LDMS GRMs was never overestimated, that attributed to the IBD-GRMs at longer IBD thresholds was overestimated, resulting in total heritability estimates > 1 for the rarest CV phenotypes in the presence of stratification.

Real Phenotypes from the UK Biobank

Using GREML-IBD, h^2_{IBD} for height (but not for BMI) increased with longer minimum shared haplotype length, did not stabilize at longer segment thresholds, and appeared upwardly biased, similar to what we observed in stratified samples in our simulations (Fig. 4a, Table S1). The 95% CIs increased with longer minimum IBD length, as expected given the lower variance in D_{ij} at longer segment thresholds. For comparison, h^2_{SNP} estimates from approaches using only SNPs are also presented in Table S1.

Using either GREML-SNPs+IBD or GREML-LDMS+IBD, we found similar patterns of increasing h^2_{IBD} estimates with longer minimum IBD length for height, but the pattern was less extreme, and 95% CIs were generally smaller (Fig. 4b, Table S1). Results for GREML-LDMS+IBD either including the rarest MAF category or excluding it were similar: height h^2_{IBD} estimates increased from 0.75 to 1.1 across the range of minimum IBD lengths we examined. This increase in h^2_{IBD} was due to increasing estimates of variance attributable to the IBD-GRM rather than to the imputed variant

SNP-GRMs (Fig. S22, Table S1). BMI h^2_{IBD} estimates were again ~0.2-0.3, though at longer minimum IBD length thresholds the standard errors were large, and the 95% CI overlapped 0 (Table S1).

Interestingly, inclusion of the IBD-GRM in addition to the SNP-GRM or LDMS-GRMs often improved model fit and resulted in a lower AICc (Table S1). Often the lowest AICc was found with shorter IBD minimum length thresholds. For instance, for height, the minimum AICc was found when using all LD- and MAF-stratified imputed variant GRMs and the IBD-GRM with a 3cM minimum IBD length threshold (Table S1), while AICc increased with longer length thresholds. Thus, while increasing the minimum length threshold led to unreasonable and uninterpretable total heritability estimates, at shorter IBD length thresholds, the inclusion of the IBD-GRM was preferred. This indicates that some additional variance remains to be explained over using only imputed-variant GREML-LDMS and that inclusion of the IBD-GRM led to models that better explained the observed phenotypic similarity, perhaps reflecting the effect of CVs that are not well captured by imputed variants.

DISCUSSION

We present here the most thorough assessment to-date of an IBD-based heritability estimation approach. The interest in using IBD information in classically unrelated samples to estimate heritability arises from the potential to estimate the full narrow-sense heritability without the confounding of effects shared within families that can bias estimates when close relatives are used, and without the downward bias in estimation when CVs are rare or poorly tagged by SNPs. We demonstrated that

GREML-IBD can produce unbiased heritability estimates in realistic whole-genome SNP data so long as there is little genetic stratification in the sample. Moreover, although we showed only marginal improvement, at best, over imputed variant-based approaches, IBD-based approaches should do increasingly better than ones based on imputed SNPs in estimating heritability if CVs are even rarer (MAF < .0003) than we could simulate here. That said, no estimation based on genomic sharing can capture variation due to CVs that occur only once in the sample.

While IBD-based approaches are appealing in principle, our study highlights two important drawbacks. First, stratification can bias heritability estimates upward, depending on the allele frequencies of CVs. The effect of stratification is strong when CVs are very rare, and is not controlled by inclusion of a large number of PC covariates, the typical approach to controlling such effects (Price *et al.*, 2010), or even PCs derived from very rare variants (Mathieson and McVean, 2012). Similar overestimates have been observed in a related method that used sharing at predefined, segregating haplotypes (Bhatia *et al.*, 2016). Overestimates appear to stem from redundant tagging by long IBD segments of very rare CVs as well as shorter IBD segments, particularly in stratified samples. Previous studies using IBD-based approaches (Zuk *et al.*, 2012; Browning and Browning, 2013) used isolated, homogeneous populations, which should mitigate this source of bias. Our simulation results suggest somewhat less homogenous samples, such as those of general northern/western European ancestry, can be used to derive unbiased heritability estimates so long as there are no additional confounding factors.

Second, the standard error (SE) of the h^2_{IBD} estimate is large due to the very low variance in IBD sharing among unrelated individuals in large, non-founder populations. For example, for height in the UK Biobank when using GREML-LDMS+IBD, total heritability SE≥0.053 for minimum IBD lengths ≥ 6cM, largely due to the IBD-GRM variance component SE. However, using just the imputed variant GREML-LDMS approach SE=0.015. Thus, while the GREML-LDMS+IBD may have accounted for more of the genetic variance, it did so with substantially lower precision. Very large sample sizes will be required to reach high levels of precision. Taken together, it is not clear whether the increased variance explained, arising from capturing rare CVs with IBD-based GRMs, outweighs the very large increase in standard errors and the increased potential for bias due to stratification or other factors we did not model here.

Heritability of Real Complex Traits

Our results from real UK Biobank data for height demonstrate the potential for additional biases of an IBD-based approach that were not captured in our simulation. The estimates of total heritability for height increased with minimum IBD cM length, and were much greater than other reported estimates (e.g., Yang *et al.*, 2015; Evans *et al.*, 2017). This was unexpected given that the UK Biobank sample was similar to simulated data with respect to stratification. It is possible that the CVs, particularly rare CVs, underlying height are more geographically stratified than those that influence BMI. Indeed, evidence suggests that across Europe, genetic variance in height is more geographically structured than BMI, though both traits are more genetically structured than a neutral, drift-only model (Robinson *et al.*, 2015). However, environmental

variation in BMI across Europe appears to be stronger than genetic differentiation (Robinson *et al.*, 2015). Thus, for height, neutral structure (shared long IBD segments) may covary with geographical variation in the CVs themselves, and lead to inflation of h^2_{IBD}. While consistent with our observed likely upward bias in height h^2_{IBD} but not BMI h^2_{IBD}, we cannot be certain that divergent selection is driving these patterns.

Vertically-transmitted non-genetic effects, shared common environmental effects, and assortative mating may also confound estimates of h^2_{IBD}. Estimates of h^2_{FAM} using close relatives can be altered by these factors (Eaves *et al.*, 1978; Martin *et al.*, 1978; Coventry and Keller, 2005; Zuk *et al.*, 2012). It is currently unknown how GREML-based estimates, and IBD-based approaches in particular, are affected by assortative mating. Common environmental effects, which can induce similarity across highly extended pedigrees, would be confounded with IBD sharing, and are therefore a potential source of bias in IBD-based estimates. Such extended pedigree environmental similarity would be difficult to simulate using our simulation method, and so we did not explore how such an effect might bias h^2_{IBD}. Our results in the UK Biobank data suggest that our assumption that removing close relatives (relatedness < 0.05) would mitigate shared environment confounding may require further investigation. The use of lower relatedness thresholds may alleviate the problem, but lower relatedness thresholds decrease the sample size and variance of IBD sharing and therefore further exacerbate the already high standard errors of these estimates. Rare variants are more differentially confounded by stratification than common variants, and typical approaches using PCA may not fully correct for such confounding (Mathieson and McVean, 2012). Extremely rare SNPs, as with long IBD segments, will co-segregate along extended pedigrees,

554 and future work must focus on the role of confounding between familial and
555 environmental effects and rare variants or long IBD segments.

556 While we cannot conclude with certainty which factors led to the apparent bias in
557 height h^2_{IBD}, estimates of h^2_{IBD} for BMI were more stable and also in line with previous
558 reports. They suggest that BMI h^2 is roughly 0.25-0.3, with up to 5% of the total
559 phenotypic variance due to very rare or otherwise poorly-imputed variants that are
560 captured by the IBD-GRM (see Table S1). As estimates from classical twin design
561 studies range from 0.4-0.8, this suggests that much of the family-based estimates are
562 due to shared environment, assortative mating, or non-additive genetic variance,
563 supported by extended twin design variance estimates (Coventry and Keller, 2005;
564 Keller and Coventry, 2005). This also suggests that little unexplained variance remains
565 for BMI, as estimates of BMI h^2_{SNP} from recent studies range from 0.21 (Locke *et al.*,
566 2015) to 0.27 (Yang *et al.*, 2015).

567 Our findings may also offer context to the observed heritability estimates reported
568 by several other studies that used haplotype-based approaches. Browning and
569 Browning (2013) reported h^2_{IBD} for BMI of 0, with standard error of 0.16 (height was not
570 measured), although their upper 95% CI estimate is not inconsistent with a true h^2 of
571 0.25-0.3. This low estimate may simply be due to sampling variance, arising from the
572 small number of individuals (5,402) in the Finnish sample they used. Zaitlen et al.
573 (2013) used IBD among close relatives to derive estimates of h^2_{IBD} of 0.69 for height
574 and 0.42 for BMI. As discussed by the authors, these estimates may be upwardly
575 biased due to common environmental and non-additive genetic effects.
576

577 *Conclusions*

578 Identical-by-descent haplotypes in common between a pair of chromosomes
579 capture sharing at all variants that existed along their length in the last common
580 ancestor. The ability to estimate such IBD segments using SNP data means that there
581 is potential to estimate narrow-sense heritability of traits in a way that should be
582 unbiased by factors that bias SNP or family-based estimates. We conclude that IBD-
583 based estimates can be used to obtain estimates of the near full narrow-sense
584 heritability. However, IBD-based estimates are imprecise and very sensitive to
585 stratification. Moreover, when we estimated h^2_{IBD} in real data, we observed unexpected
586 biases that appeared similar to those that we had observed in more stratified samples in
587 our simulation, which suggests that there are biases in real data that we were not able
588 to adequately capture in our simulation. Taken together, these factors diminish the
589 appeal of IBD-based approaches for estimating heritability, especially when compared
590 to approaches that use imputed variants, such as GREML-LDMS. Nevertheless, until
591 whole genome sequence data is feasible for the large sample sizes required for h^2
592 estimation from genotype data, IBD-based estimates may be able to capture the rarest
593 CVs better than imputation. In particular, though larger and more diverse reference
594 panels are becoming available, isolated populations may not be well-represented. IBD-
595 based approaches offer a method to capture rare genome-wide variants not
596 represented in imputation reference panels, and these isolated, homogeneous
597 populations may also be the most advantageous for IBD-based heritability estimation
598 due to the larger variance in IBD sharing.
599

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DATA ARCHIVING: Data are from the Haplotype Reference Consortium and the UK Biobank and can be accessed through those resources.

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FIGURE LEGENDS

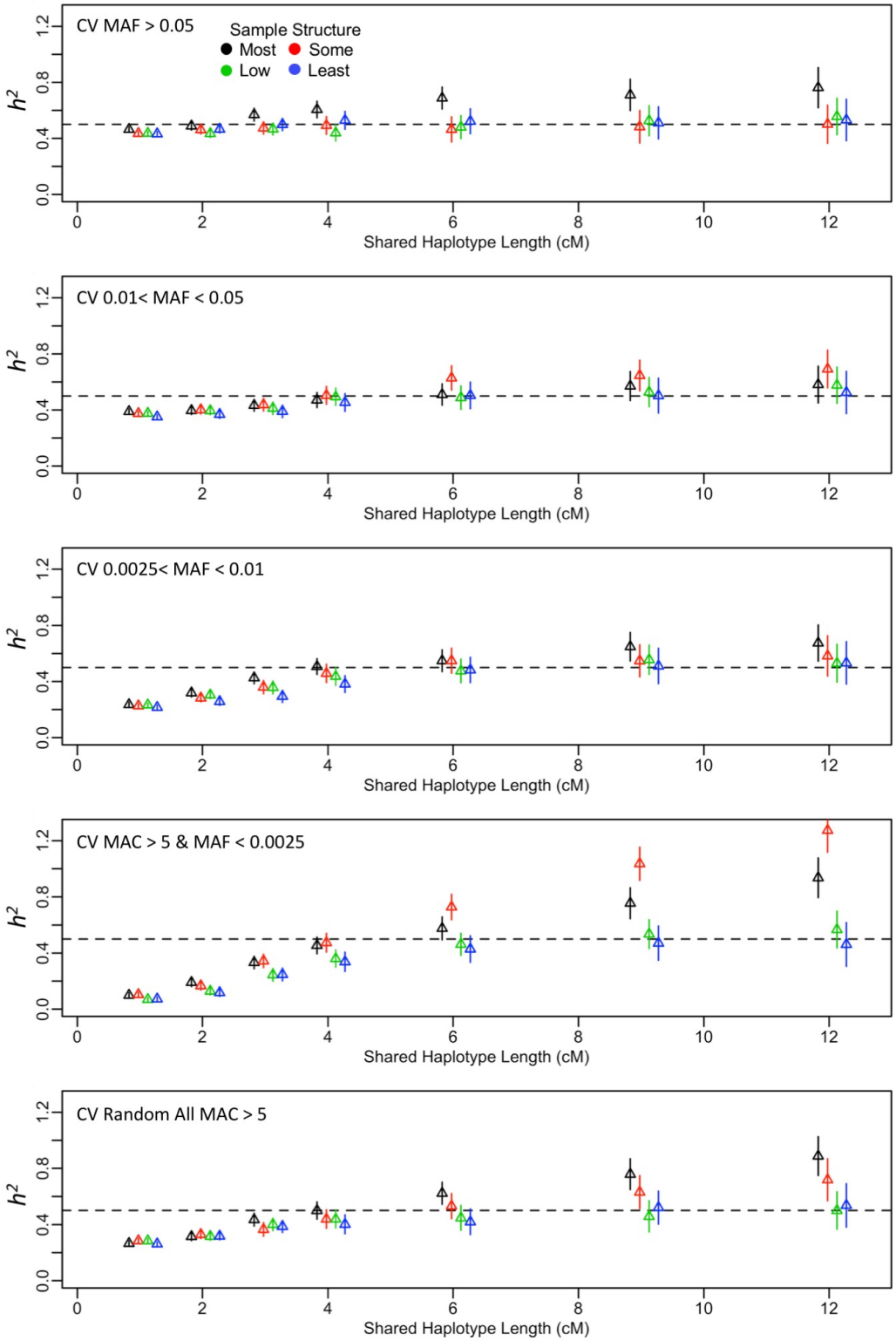


Figure 1. GREML-SC using an IBD-GRM. h^2_{IBD} estimates (mean ± 95% CI from 400 replicates). X axis indicates the IBD shared haplotype length threshold for the IBD-GRM. Phenotypes with 1,000 CVs randomly drawn from the MAF range specified in

each panel. Different colors indicate degree of stratification in the sample. Relatedness cutoff of 0.05 used.

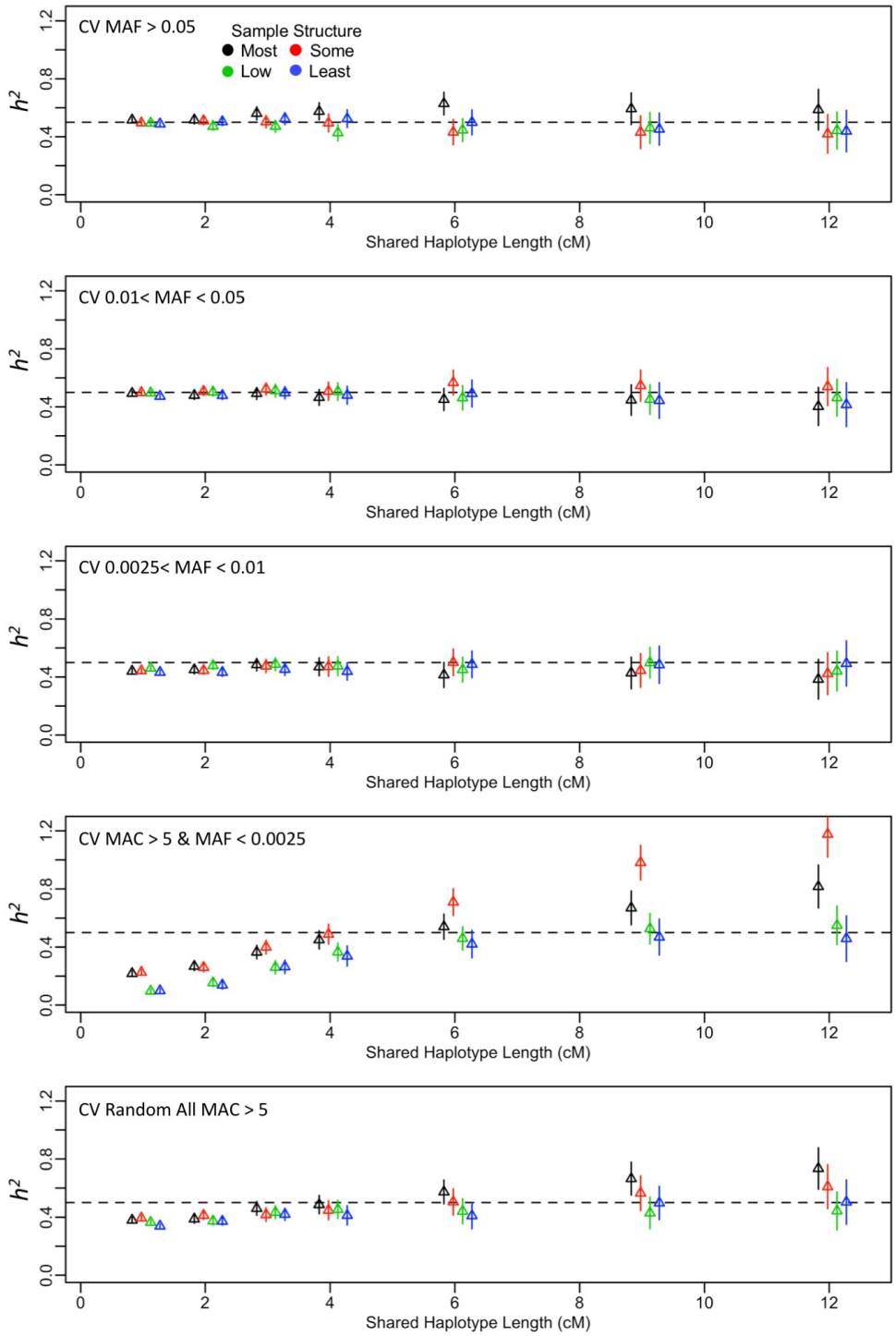
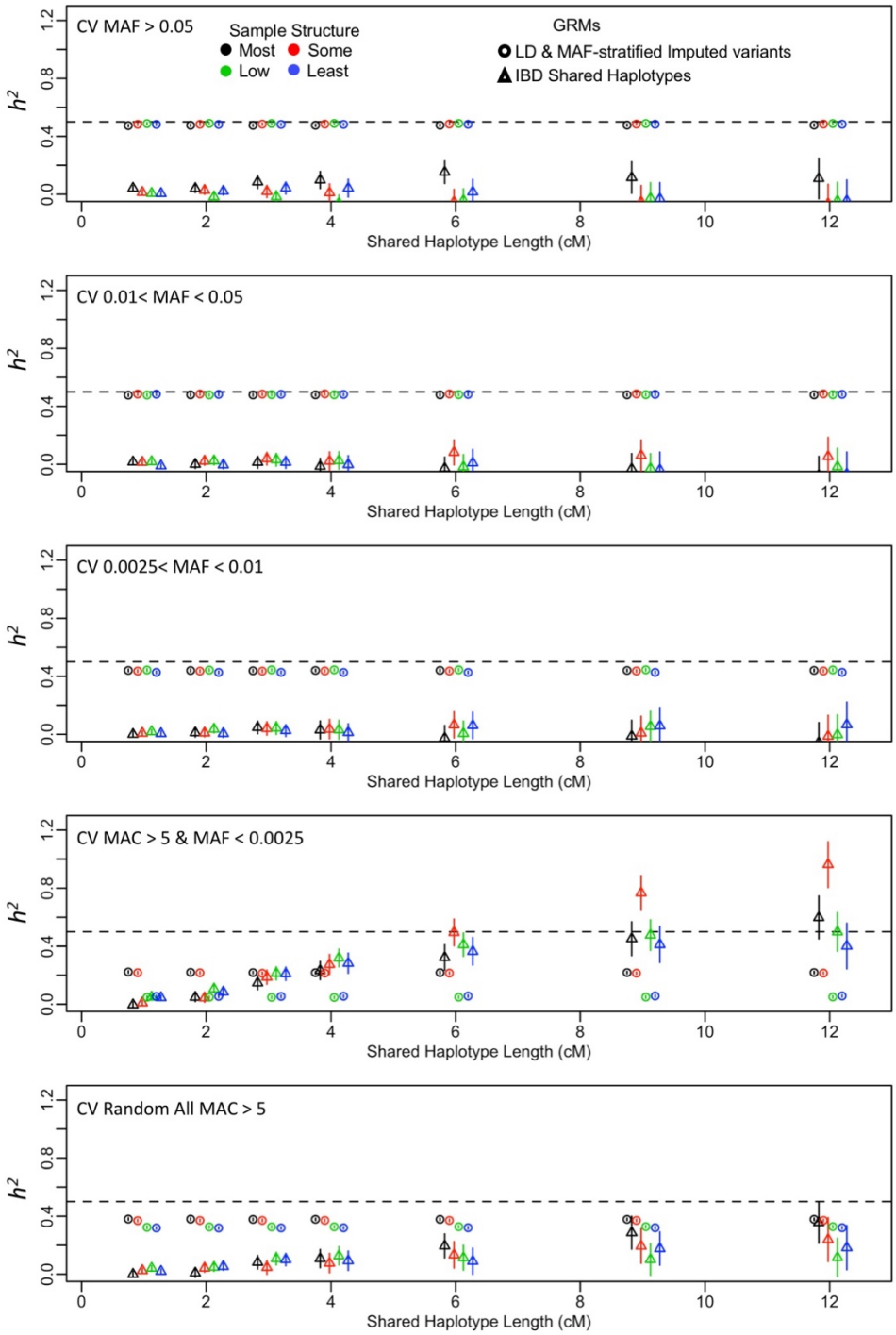


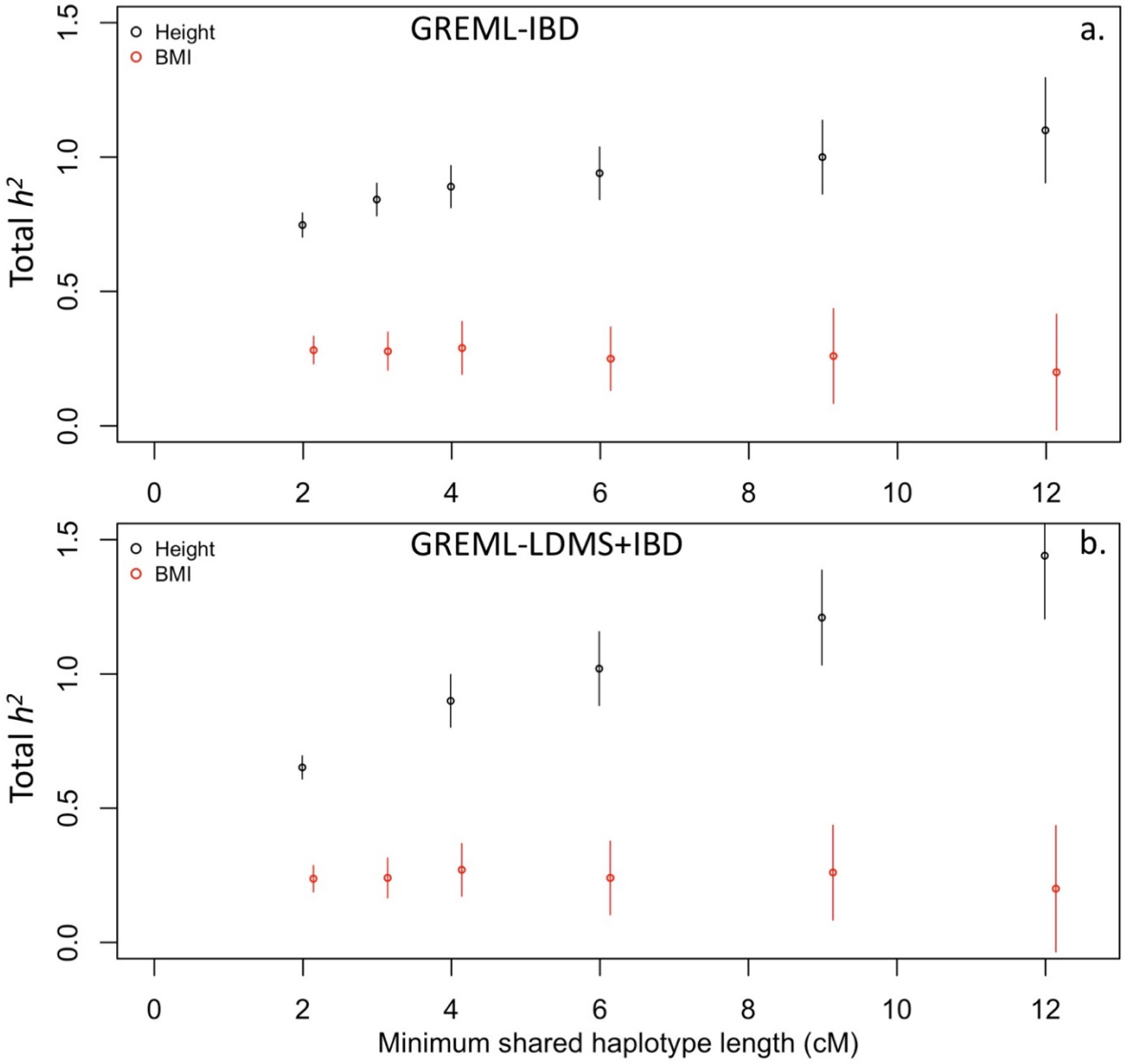
Figure 2. GREML-LDMS+IBD model. This had 13 components, 12 LD & MAF-stratified GRMs using imputed genome-wide variants, and one GRM from IBD shared haplotypes. Total h^2 estimates are shown (mean ± 95% CI from 400 replicates). X axis indicates the different IBD shared haplotype length thresholds for the IBD-GRM. Phenotypes with 1,000 CVs randomly drawn from the MAF range specified in each

770 panel. Different colors indicate degree of stratification in the sample. Relatedness cutoff
771 of 0.05 used.



772
773 **Figure 3.** GREML-LDMS+IBD. This model had 13 components, 12 LD & MAF-stratified
774 GRMs using imputed genome-wide variants, and one GRM from IBD shared
775 haplotypes. Separate h^2 estimates for each component are given by the symbols (mean
776 ± 95% CI from 400 replicates). Note that the "Imputed LDMS" symbol represents the
777 sum of the imputed LDMS GRM variance estimates. X axis indicates the different IBD
778 shared haplotype length thresholds for the IBD-GRM. Phenotypes with 1,000 CVs

779 randomly drawn from the MAF range specified in each panel. Different colors indicate
780 degree of stratification in the sample. Relatedness cutoff of 0.05 used.



781
782 **Figure 4.** Total heritability estimates for three continuous traits in the UK Biobank. (a)
783 GREML-IBD, which had a single IBD-GRM. (b) GREML-LDMS+IBD for three
784 continuous traits in the UK Biobank. This model had 13 components, 12 LD & MAF-
785 stratified GRMs using imputed genome-wide variants, and one GRM from IBD shared
786 haplotypes. Total h^2 estimates are shown (± 95% CI). X axis indicates the different IBD
787 shared haplotype length thresholds for the IBD-GRM. Relatedness cutoff of 0.05 used.
788