**RESEARCH ARTICLE SUMMARY**

**HUMAN GENOMICS**

**Analysis of genetic dominance in the UK Biobank**

Duncan S. Palmer¹, Wei Zhou, Liam Abbott, Emilie M. Wigod, Nikolas Baya, Claire Churchhouse, Cotton Seed, Tim Poterba, Daniel King, Masahiro Kanai, Alex Bloemendal†, Benjamin M. Neale*†

**INTRODUCTION:** In statistical genetics, dominance is a deviation from an additive genetic effect on a trait and is well documented in model organisms, particularly in the context of measures of “fitness,” and in plant and animal breeding. In humans, however, evidence of nonadditive genetic effects on complex, polygenic traits is sparse. We looked for evidence of nonadditive effects in more than 1000 phenotypes in the UK Biobank population cohort (N = 361,194). To test for “dominance heritability,” or the aggregate contribution of nonadditive genetic effects to trait variance genome-wide, we introduce dominance linkage disequilibrium (LD) score regression (d-LDSC). Our method builds upon existing software to include nonadditive effects site by site.

**RATIONALE:** Identifying nonadditive genetic effects on traits allows us to better understand their underlying biology. Although nonadditive effects are commonly tested in Mendelian disorders, they are rarely tested in human complex traits. Population biobanks allow us to explore questions of genetic architecture at scale and to detect small effect sizes. We sought to test for evidence of nonadditive effects in the UK Biobank. We also investigated whether the less-correlated nature of dominance associations among sites at a locus relative to their additive counterparts can help pinpoint causal variants.

**RESULTS:** We identified 183 phenotype-locus pairs at genome-wide significance (P < 4.7 × 10⁻¹⁰). We replicated known associations for phenotypes with dominant and recessive patterns of inheritance, for example, hair color at the MC1R locus. Qualitatively, we observed stronger nonadditive effects in instances where additive effects are large or the underlying genetic architecture is concentrated in a few loci. The power to detect nonadditive loci was low: We estimate that around a 20- to 30-fold increase in sample size is necessary to capture evidence of dominance effects similar to that observed at additive loci. Applying LDSC and d-LDSC to 1060 traits, we confirmed strong evidence of additive heritability (700 traits, P < 4.7 × 10⁻⁶). Despite analyzing a much larger collection of traits with increased power over existing studies, we found little evidence of dominance heritability. We introduced dominance fine-mapping to pinpoint causal variants in the presence of a dominance signal. Gains in fine-mapping resolution due to the rapid decay of dominance LD compared with additive LD are generally outweighed by weaker association signals.

**CONCLUSION:** We evaluated the contribution of nonadditive genetic effects on trait variation across 1060 traits in the UK Biobank. We identified a modest number of loci and confirmed that heritability explained by dominance is small, in line with previous analyses. Our results support the robustness of the additive model when modeling human complex traits, consistent with the view that most common variants induce small perturbations of continuous latent biological processes aggregated by a mean-field approximation. Furthermore, the additive model typically captures much of the trait variance at a population level, even under classical dominant or recessive patterns. We estimate that for most complex traits, minimum sample sizes of millions are required to detect nonadditive effects at the same strength of association as those reported for additive effects. 🌟

The list of author affiliations is available in the full article.

*Corresponding author: Email: duncan.stuart.palmer@gmail.com (D.S.P.); breake@broadinstitute.org (B.M.N.)
†These authors contributed equally to this work.

READ THE FULL ARTICLE AT
https://doi.org/10.1126/science.abn8455
Classical statistical genetics theory defines dominance as any deviation from a purely additive, or dosage, effect of a genotype on a trait, which is known as the dominance deviation. Dominance is well documented in plant and animal breeding. Outside of rare monogenic traits, however, evidence in humans is limited. We systematically examined common genetic variation across 1060 traits in a large population cohort (UK Biobank, N = 361,194 samples analyzed) for evidence of dominance effects. We then developed a computationally efficient method to rapidly assess the aggregate contribution of dominance deviations to heritability. Lastly, observing that dominance associations are inherently less correlated between sites at a genomic locus than their additive counterparts, we explored whether they may be leveraged to identify causal variants more confidently.

These authors contributed equally to this work.

Palmer et al., Science 379, 1341–1349 (2023) 31 March 2023
enabling rapid estimation of the dominance contribution to phenotypic variance across thousands of phenotypes.

**Testing for dominance effects at each variant**

We tested variants for evidence of dominance deviation beyond a purely additive model (Fig. 1A) (32). This is a pertinent area of study because the extent of nonadditive contribution to complex traits has yet to be thoroughly examined. Further, such effects may point to relevant biological insights about the nature of variant effects. The phenotypic variance contributions explained by this model are split into two parts in quantitative genetics theory (32, 46): (i) the variance explained by the average effect of allelic substitution (captured by a purely additive model), known as the additive variance, and (ii) the remaining variance (captured by the dominance deviation), known as the dominance variance. We use the terms “nonadditive” and “dominance” interchangeably to refer to effects captured by within-locus interactions that are not explained by the additive model. We refer to the unique recoding of allele counts (up to a linear re-scaling) that allows us to test for a dominance deviation directly as the “dominance encoding” (36, 38, 39, 42, 47). This is not the same as recoding allele counts according to canonical biological dominance, in which the presence of at least one copy of the dominant allele explains the variation in the trait at the site ([0, 1, 2] → [0, 1, 1], as illustrated in Fig. 1B). Nor is it the same as an encoding where the heterozygote displays a more pronounced phenotype than either homozygote, known as overdominance (an example of overdominance, [0, 1, 2] → [0, 1, 0], is illustrated in Fig. 1C). In the biological dominance case (Fig. 1B), even if a variant is present in half the population [a minor allele frequency (MAF) of 0.5], the additive model captures most of the variance explained by the locus (88.8%). Furthermore, if a dominance deviation truly exists at a particular genetic variant, then the additional contribution to variance that is explained by the dominance deviation depends on how common that variant is within the population (its MAF). This can be seen by contrasting the top and bottom rows of Fig. 1. Finally, we note that when dominance effects at a locus are considered in GWASs, they are often incorporated by adding a term that encodes the genotypes as [0, 1, 1] or [0, 1, 0] in a joint model with the additive encoding [0, 1, 2] (48). The motivation for the dominance encoding chosen here is largely mathematical because it imposes orthogonality on the two components of variance, meaning that we can run the association test in parallel rather than jointly and that the dominance effects estimates will not be contaminated by additive genetic effect spillover (36).

Under Hardy-Weinberg equilibrium (HWE), the standardized dominance encoding maps allele counts from [0, 1, 2] to \(-p/(1 - p), 1 - (1 - p)/p\) for each variant, where \(p\) is the MAF of the variant (36, 38, 39, 42, 47). Using this dominance encoding, we assessed within-locus nonadditive effects using dominance GWASs and estimated the relative contribution of additive and nonadditive genetic variation to phenotypic variance in regions that display the strongest signals of association. Figure 1 displays examples of inheritance patterns. In each panel, the variance in the phenotype that is captured by deviations from the best linear fit (shown by the dashed purple line) is exactly the genetic effect that the dominance encoding will estimate. The largest contributions to nonadditive variation in a trait occur when the deviation from additivity is large and the genetic variant is common in the population. Dominance heritability, the variance in phenotype explained by the sum of all of these nonadditive effects, will manifest if biological dominance and overdominance inheritance patterns are widespread at sites that are highly

---

**Fig. 1. Examples of inheritance patterns at different MAFs.** The effect sizes under a collection of genetic architectures are shown by the black lines. The expected proportions of individuals with each of the three genotypes are shown by a green circle above the alternative allelic dosage (0, 1, or 2); the area of the circle scales with the expected proportion of samples with that genotype. The extra variance captured by deviations from the additive fit (dashed purple line) is the nonadditive or dominance contribution to phenotypic variance. (A) Purely additive genetic architecture at the SNP, with no deviation of the truth (black line) from the additive fit (dashed purple line), so no extra variance is explained by nonadditive effects, independent of MAF (top, \(p = 0.5\); bottom, \(p = 0.3\); the variance contribution for both MAFs is entirely blue, representing 100% additive variance contribution at this site). (B) Biological dominance architecture at a very common SNP (top, \(p = 0.5\)) and at a common SNP (bottom, \(p = 0.3\)). Despite being the canonical dominance architecture, additivity explains a large portion of the variance (the dashed purple line is not horizontal, and the variance contribution of additive effects is high; see the length of the blue bar relative to the red bar), but there is an appreciable amount of variation that cannot be explained by a purely additive model. The allele frequency of the SNP matters: The nonadditive variance contribution decreases as MAF decreases from 0.5. Because of the rarity of the homozygous alternate genotype (shown by a smaller green circle beneath the black line at “2” in the bottom graph), the additive model explains a larger portion of the total variance at the SNP. The variance contribution of the recessive contribution is equivalent to the biological dominance encoding of the other allele and amounts to swapping the alternative allele. (C) Overdominance at a very common SNP (top, \(p = 0.5\)) and at a common SNP (bottom, \(p = 0.3\)). When \(p = 0.5\) (top), half the sample is expected to be heterozygous, which completely balances the homozygous individuals so that the additive model explains none of the variance (the dashed purple line is horizontal, and the variance contribution is entirely red) for this genetic architecture at a SNP with \(p = 0.5\). However, overdominance architecture with any other MAF will contain an additive contribution, for example, the bottom graph, where \(p = 0.3\).
variable in the population. See fig. S1 for examples of the additive and dominance encoding at varying allele frequency and effect size and how they combine to represent any inheritance pattern at a single-nucleotide polymorphism (SNP).

The dominance encoding may facilitate the identification of causal variants at regions with nonadditive effects. Because DNA is inherited in long tracts from one generation to the next, the pairwise correlation between variants, and how they combine to represent any inherited nature of the genome can be represented by the correlated nature of dominance effects to more readily refine marginal dominance signals of association to likely causal variants, a process known as fine-mapping. We explored this idea by developing a modification to existing fine-mapping software (SuSiE) (50) to “dominance fine-map” putative dominance associations.

**Association studies in the UK Biobank**

After quality control and curating the phenotypic and genotypic data (361,194 samples, 13.7 million variants, 1060 phenotypes), we ran additive and dominance GWASs [(42, 51, 52); figs. S3 and S4 and table S1]. Binary traits were chosen such that at least eight samples in both categories were expected to be homozygous down to an allele frequency of 5% (42). For continuous traits, we analyzed the inverse-rank normal transformation of the raw phenotype to guard against spurious dominance associations [(42); figs. S5 to S7 and tables S2 and S3].

After removing variants out of HWE ($P < 10^{-6}$) and restricting to common variants (MAF > 0.05 for binary traits, and MAF > 0.01 for continuous traits), we identified independent signals of association for each phenotype by defining significant regions, known as loci, as 500-kb windows around nominally significant dominance associations ($P < 5.0 \times 10^{-8}$). After merging loci where windows overlapped, we found 183 phenotype-locus pairs that harbored genome-wide significant associations between dominance-encoded genotypes and phenotypes (using a conservative Bonferroni cutoff: $P < 5 \times 10^{-6}/1060 = 4.7 \times 10^{-9}$), hereafter referred to as “genome-wide significant loci.” Examples include 10 blood cell traits at the **RHD** locus, hair color before graying at the **MCIR** locus, and four bone mineral–density phenotypes upstream of **WNT16**. Among the phenotype-locus pairs, 137 were associations with continuous traits and 46 were association with binary traits. To check for potential artifacts that influenced genotype calling, we examined a collection of variant quality metrics.
(42) (figs. S8 to S10). Dominance loci were more confidently genotyped and imputed than random allele frequency–matched loci. A summary of our dominance and additive GWAS results is shown in Fig. 2 and fig. S11. We verified that these results were not due to deviations from HWE (42) (figs. S12 to S18). We performed additional dominance GWASs in 30 biomarkers without assuming HWE (53, 54) and found highly concordant P values of dominance association strength (figs. S17 and S18). Of the reported biomarker dominance loci, 53 of 54 remained significant (P < 4.7 × 10^{-11}), and the remaining phenotype-locus pair was nominally significant (P = 1.5 × 10^{-9}). At lead variants in dominance loci, estimates of the underlying genetic architecture were enriched for monotonic functions of allele count (141/183 = 77.0%).

We replicated known nonadditive effects, including rs1805007 in MCIR for hair color (55, 56) (P < 1 × 10^{-5000} for red hair; fig. S19), an intronic variant of HERC2 that functions as an enhancer that regulates OCA2 expression for hair and skin color (57, 58) (rs12913832, P = 2.87 × 10^{-56} and P = 5.33 × 10^{-10} for blond hair and skin color, respectively; figs. S20 and S21), and a nonadditive signal-tagging ILDR1 for hearing difficulty that is stronger than the additive signal at the locus (additive P = 4.26 × 10^{-8}, dominance P = 5.79 × 10^{-13}; fig. S22). ILDR1 is a known Mendelian hearing-loss gene (59–61). The stronger dominance signal reflects the high MAF and putative overdominant contribution to the phenotype. We also observed a genome-wide significant nonadditive association with red blood cell distribution width (rs67002563, P = 2.99 × 10^{-13}; fig. S23) in tight LD with ITPA. Notably, this locus did not reach genome-wide significance under additivity (P = 0.000152; fig. S23). ITPA has been implicated in red blood cell disorders through an autosomal recessive mode of inheritance (62–65). A strong nonadditive association was also observed for the distribution width of platelets at an intronic variant that is associated with increased expression of ARHGEF3 (rs1354034, P = 5.80 × 10^{-90}; fig. S24) in platelets (66). ARHGEF3 displays a regulatory role in myeloid cell differentiation in zebrafish (67). Although this locus harbors a highly significant additive association for platelet count (P = 2.23 × 10^{-748}; fig. S25) and volume (P = 1.98 × 10^{-2042}; fig. S26), the additive signal was completely ablated for platelet distribution width (P = 0.825; fig. S24).

The relative contribution of additive and dominance effects to trait variation at top loci
To probe the relative variance explained by the additive and nonadditive contributions, we first examined their relative contributions across the top loci. We extracted the top-five additive and dominance associations across unique cytobands for each phenotype and assessed the relative contribution of additive to nonadditive effects. The median ratio of the two variance contributions was 20.9 (Fig. 3A). When restricting to additive and dominance associations with P < 1 × 10^{-6}, the median ratio of the variance components increased to 28.9 (Fig. 3B). Therefore, we estimate that millions of samples (~7,500,000) are required to be powered to detect nonadditive effects at the same strength of association as those currently reported for additive effects (68).

This estimate is a best-case scenario: On average, there is much less dominance variance than additive variance at any particular locus. As a result, the expected amount of statistical noise in the dominance effect-size estimate is greater than that in the additive effect-size estimate. Furthermore, given the reduced power in dominance GWASs, effect-size estimates at dominance loci are more susceptible to “winner’s curse” than estimates at additive loci.

Fine-mapping dominance loci
Given that not all dominance GWASs were null (Fig. 2) and that the dominance LD decays at the square of additive LD (fig. S2 and [36, 42, 49]), we investigated whether we could fine-map nonadditive signals of association. To do this, we simply took the dominance LD matrix and dominance GWAS associations as input into existing fine-mapping software (42, 69) instead of their additive counterparts.

We used SuSiE (50) to fine-map the dominance signal at nominally significant (P < 5.0 × 10^{-8}) dominance loci. We then fine-mapped any additive effects at these loci and compared the results. A summary is displayed in Fig. 4. While acknowledging the likelihood of winner’s curse in these results (because we restricted to nominally significant dominance loci (P < 5.0 × 10^{-8})), we observed differences in fine-mapping. Of the additively fine-mapped variant-phenotype pairs with more evidence of being causal under the additive model (n = 690; yellow shaded area of Fig. 4), 431 reside in genes (70). Of these, 23.6% are additive signals without a dominance component [posterior inclusion probability (PIP) < 0.01] that lie in the same gene as a fine-mapped dominance association (PIP > 0.2). Of particular interest were putatively causal variants that were more confidently fine-mapped by their dominance association (n = 314; gray shaded area of Fig. 4) because they represent potentially causal association candidates that are not as confidently implicated through additive fine-mapping. Table S4 summarizes the collection of exonic variants that are more confidently dominance fine-mapped. The nonadditive signal in the ITPA locus that is associated with red blood cell distribution width was fine-mapped to rs127354, a nonsynonymous single-nucleotide variant that predicts drug-induced anemia among patients with chronic hepatitis C virus infection (71–75). The genome-wide significant nonadditive association (P = 5.79 × 10^{-13}; fig. S22) with hearing difficulty was partially fine-mapped to rs2877561, a synonymous change in ILDR1 that is associated with age-related hearing impairment (76), but did not reach genome-wide significance in that study. We note that rs2877561 is a variant associated with changes in expression and splicing for a large number of genes and tissues (77).

Genome-wide dominance
After our dominance scans, we also investigated what proportion of phenotypic variance can be explained by dominance effects. Previous papers have suggested, both through theory and empirically, that dominance heritability is likely small in human complex traits.
(33, 36). More recently, additional methods to estimate dominance heritability were developed and applied to 50 (38) and 70 (39) continuous phenotypes in the UK Biobank. These works found zero or marginal evidence that nonadditive effects contribute meaningfully to phenotypic variance genome-wide.

We estimated dominance heritability by extending LDSC. LDSC is a statistical genetics approach that enables computationally efficient estimation of the additive heritability of a trait by relating effect-size estimates of SNPs from GWASs to the extent to which these SNPs tag other SNPs in the genome through LD (their so-called LD score). By generalizing the additive model on which the original LDSC software is based to include dominance effects at each variant, we were able to estimate the dominance heritability of traits rapidly, which enabled analysis of thousands of binary and continuous traits within a few minutes (42).

Indeed, after a dominance GWAS and generation of “dominance LD scores,” dominance SNP heritability estimates can be obtained as quickly as additive SNP heritability estimates (78). This efficiency allowed us to estimate the nonadditive variance contribution to all 1060 curated phenotypes at low time and economic cost. We performed extensive simulation studies with varying genetic architecture and case-control ascertainment: Dominance heritability estimates were unbiased and well calibrated under all simulation scenarios [(42); figs. S27 to S35 and tables S5 and S6].

**Dominance heritability of traits in the UK Biobank**

Applying additive LDSC and d-LDSC to the 1060 traits, we found strong evidence of significant additive heritability (700 traits with \( P < 4.7 \times 10^{-5} \)) as expected but little evidence of dominance heritability (Fig. 5 and tables S7 and S8). These findings were robust to the assumed allele frequency dependence on effect size (42) (fig. S36). This contrast was present in both continuous and binary traits. For binary phenotypes, we see increased evidence of trait variance that is explained by additive effects at common variants (MAF > 0.05) as case count increases. This trend was not apparent for dominance heritability tagged by common variation. Our results support existing evidence for the modest additional contributions of a nonadditive model to phenotypic variance tagged by common variation over a purely additive model (36, 38, 39). Across all 1060 curated phenotypes, we found marginal evidence of a small nonzero relative contribution of dominance heritability estimates to additive heritability estimates (York regression; gradient = 0.0023, \( P = 0.050 \); Fig. 5A). We observed similar results when using a denser set of SNPs down to a MAF of 0.01 to estimate additive and dominance heritability (York regression; gradient = 0.0028, \( P = 0.0017 \); fig. S37).

Although the relative contribution of dominance heritability to additive heritability is low, this does not preclude the possibility that nonadditivities are present or even widespread throughout the genome (Fig. 1) or suggest that nonadditive effects should be disregarded. Nonadditive loci may have large effects on an individual level but may not contribute greatly to the heritability of a trait in the population. Finally, the power to detect deviations from additivity is weakest precisely where we expect the largest nonadditive effects: rarer variation.

**Discussion**

We performed a large and comprehensive dominance scan and heritability analysis of 1060 phenotypes in the UK Biobank and identified 183 phenotype-locus pairs at genome-wide significance (\( P < 5 \times 10^{-8} \approx 4.7 \times 10^{-11} \)). These loci consisted of many well-known associations in phenotypes with dominant and recessive patterns of inheritance (for example, hair color). Qualitatively, we observed stronger nonadditive effects in instances where additive effects are large or the underlying genetic architecture is concentrated in a few loci; examples include blood traits, hair color, and biomarkers. For most traits, far more samples are likely necessary to capture evidence of dominance effects. Extrapolating from the top-five loci in each trait, we estimated that millions of samples would be required to obtain marginal dominance effect-size estimates with strengths of association similar to those now observed in additive GWASs. Despite analyzing a much larger collection of traits with increased power over existing studies (36, 38–40), we found limited evidence of a dominance contribution to phenotypic variance. Across the analyzed traits, the mean additive and dominance heritabilities (averaged on the liability scale for binary traits) were 0.088 and 0.00076, respectively. A dominance contribution of around 1/120 of the additive contribution is broadly in line with recent...

---

**Fig. 4. Fine-mapping dominance loci using SuSiE.** We took the collection of genome-wide significant dominance loci (\( P < 5.0 \times 10^{-8} \)) tagged by SNPs with MAF > 0.05 and fine-mapped using SuSiE (42, 50). This amounted to passing dominance effect sizes and within-sample dominance LD. We then plotted the additive and dominance posterior inclusion probabilities against each other for all dominance loci across all phenotypes. Red points are in the exome, and blue points are intronic or intergenic. The yellow shaded region is the space where additive PIP > dominance PIP and additive PIP > 0.2. The gray shaded region is the space where dominance PIP > additive PIP and dominance PIP > 0.2. Black lines are included to delineate regions. Frequency distributions of additive and dominance PIP are displayed in the margins of the plot.
estimates of 1/200 for the traits analyzed by Pazokitoroudi et al. (38) and Hivert et al. (39). We hypothesize that nonsignificant estimates of dominance heritability are due to limited power, owing to the low relative magnitude of dominance variance to additive variance under the most biologically plausible genetic architectures (Fig. 1) (79). Our results provide further evidence to support the robustness of the linear model when modeling human complex traits, which reflects that most common variant effects are largely small perturbations of continuous latent biological processes aggregated by a mean-field approximation.

Yengo et al. (17) introduced a complementary but distinct summary statistic–based approach to ours to estimate inbreeding depression, in which a mean dominance effect size across genetic markers is estimated within an LDSC framework. The authors found enrichment of inbreeding depression within genomic regions with low LD, regions conserved across species, regulatory elements, and regions with an increased contribution to additive heritability. Note that this is a distinct estimator in which the mean nonadditive effect size is estimated, whereas we, as in Pazokitoroudi et al. (38), constructed an estimator of the average variance contribution of nonadditive effect across the genome assuming a mean effect size of zero.

We introduce dominance fine-mapping to attempt to pinpoint causal variants in the presence of a dominance signal. With the same strength of association as an additive signal, a dominance signal will fine-map more easily. However, gains in fine-mapping accuracy due to the far-more-rapid decay of dominance LD compared with additive LD are generally outweighed by a larger additive signal of association at the locus. A natural extension of this work would be to explore the use of both additive and dominance association signals jointly to increase fine-mapping precision.

There are caveats and limitations to this work. First, throughout this study, we have assumed HWE in the determination of the dominance encoding and subsequent evaluation of dominance effect sizes and heritability. If this assumption is violated, additive effects will be partially captured by the dominance encoding and manifest as nonzero dominance effect sizes. To counter this effect, we imposed a stringent filter to remove variants out of HWE ($P < 1.0 \times 10^{-6}$). In doing so, we may have removed a subset of SNPs under selection with putatively large effects, which we would have been most well-powered to detect. However, we expect that common variants that exhibit this behavior are far more likely to be due to genotyping errors than to true effects of selection. To check the robustness of the HWE assumption, we ran further dominance scans in 30 biomarkers without assuming HWE (53, 54).

**Fig. 5. Summary of heritability analysis.** (A) Contrasting estimates of additive and dominance heritability for 1060 traits in the UK Biobank. The first column displays histograms of LD score–based estimates of additive and dominance SNP heritability, which are shown in blue and red, respectively. Mean heritability estimates are shown by the gray lines. The second column displays the paired results for each phenotype, colored according to the key. The York regression best-fit line is displayed in black (intercept = 0.00025, gradient = 0.0023). (B) Contrasting the statistical evidence for additive and dominance heritability across 1060 traits in the UK Biobank. The first and second columns display quantile-quantile (Q-Q) plots of observed against expected $P$ values evaluated using block jackknife standard errors to test if $h^2_A \neq 0$ and $h^2_D \neq 0$, respectively. The top row includes all traits with more than 50,000 data points if continuous or ordinal and more than 3000 cases if binary. In the middle row, we restrict to the continuous and ordinal traits. Finally, in the bottom row, we restrict to the binary traits.
and found highly concordant $P$ values of dominance association strength.

Second, in our dominance scans, we assumed the same cutoff for genome-wide significance as for additive GWASs ($P < 5.0 \times 10^{-8}$). However, given the increased number of effectively independent sites in the genome implied by the less-correlated nature of dominance LD, this assumption should be challenged. The benefit that dominance LD provides for fine-mapping is a drawback for GWASs and the detection of phenotypic variance explained by nonadditive effects genome-wide: Dominance LD tagging does not extend as far in the genome as additive LD tagging. Future studies should investigate bottlenecked populations such as those of Finland and Iceland, because many globally rare variants (where we expect the largest dominance effects) will be more common and thus more easily detectable. Moreover, longer haplotypes (i.e., less decay in LD) in these populations may offer enhanced power to detect nonadditive effects at a locus. Third, as we concentrate our analyses of non-additive effects to common genetic variation, our results do not capture the full spectrum of genetic variation in humans. Finally, the entirety of our analysis was applied to samples within the UK Biobank of British and Irish ancestry. We made this restriction for two reasons. First, filtering to an ancestry group avoids deviations from HWE that would be induced through sampling from a mixture of ancestry groups. Second, the British and Irish ancestry subset is by far the largest among the homogeneous ancestry groups within the UK Biobank. The generation of increasingly large genetic datasets from non-European ancestry groups will allow us to explore the nonadditive genetic contribution to phenotypes of interest. However, based on our and others’ results (36, 38, 39), cohorts with orders-of-magnitude-larger sample sizes than are now available are necessary to robustly identify dominance associations in non-European populations, with the exception of consanguineous and bottlenecked populations. In this work, we estimated dominance heritability tagged by common SNPs genome-wide and did not consider partitions of the genome due to the general paucity of variance explained by nonadditive effects. However, given a nonzero dominance variance, the entirety of the LD score toolkit, including partitioned heritability estimation (45) and genetic correlation estimation (43), can be applied to dominance effects. In addition to site-by-site dominance effects, LDSC is readily extendable to test gene-by-environment interactions.

We systematically evaluated the contribution of nonadditive genetic effects on trait variation across 1060 traits in the UK Biobank. We found a modest number of individually significant loci and broadly confirmed that heritability explained by dominance is small, in line with previous analyses.

### Materials and methods summary

#### Parametrization of nonadditivity at a locus

The dominance encoding maps the genotypes $[0, 1, 2]$ to $[p(1 - p), 1, -(1 - p)p]$ for each variant (36, 38, 39, 42, 47). The model we assume, which incorporates an additive effect and dominance deviation, is

$$y = X_A\beta_A + X_D\beta_D + \varepsilon$$

(1)

where $y$ is a phenotype vector across samples; $X_A$ and $X_D$ are matrices of the standardized additive and dominance encoding of the genotypes; $\beta_A$ and $\beta_D$ are vectors of causal effect sizes with entries sampled independently from distributions with mean 0 and variance $h^2_A/m$ and $h^2_D/m$, respectively, where $h^2_A$ and $h^2_D$ are the additive and dominance heritabilities, respectively, and $m$ is the number of variants; and $\varepsilon$ is a noise term $\sim N(0, 1 - \beta^2)$. For association tests, we regressed $y$ on both $X_A$ and $X_D$, separately, for each variant $j$.

### Deviations from HWE

We assumed HWE in the dominance encoding. If this is not the case at a variant, then the additive and dominance encoding of that variant becomes correlated and an additive signal bleeds into the dominance contribution. We tested the impact of deviations from HWE at a variant, $j$, on dominance associations by varying genotype proportions through an inbreeding coefficient: $F(AA) = (1 - Fp^2 + pF, F(Aa) = 2pq(1 - F),$ and $F(aa) = (1 - Fp^2 + qF,$ where $F$ is the inbreeding coefficient. We then simulated phenotypes: $y = \beta_A x_0 + \varepsilon, \varepsilon \sim N(0, 1 - \beta^2)$, where $x_0$ is the standardized additively encoded variant $j$. We then applied the dominance encoding assuming HWE and determined the strength of the dominance association in a sample size of 50,000 with a variant whose additive effects explain 5% of the trait variance. We varied the MAF from 0.05 to 0.5 and the inbreeding coefficient from 0 to 0.05. Similarly, we simulated genotyping error and its impact on dominance associations by varying genotype proportions using a genotyping error parameter $\phi$: $P(AA) = p^2 + 2pq\phi, P(Aa) = 2pq(1 - \phi),$ and $P(aa) = q^2, \phi$ denotes the proportion of heterozygous calls that we incorrectly called as homozygous. We reran the same procedure as above, varying $\phi$ from 0 to 0.05. The results are displayed in figs. S12 and S13. To determine if such a phenomenon is present in our results, we examined the distribution of $\beta_D$ in the MAF and $F$ bins (figs. S14 to S16).

### Similarity of logistic and linear regression with small effect sizes

We assessed whether our choice to run logistic regression through association testing materially affected our results by running logistic regression at significant ($P < 5.0 \times 10^{-8}$, using linear regression) dominance loci. $P$ values of association were highly correlated between linear and logistic regression at dominance loci (mean Pearson correlation of 0.993).

### Fine-mapping

We ran SuSiE (50) on summary statistics to perform dominance fine-mapping by passing
in-sample LD matrices and loci variable summary statistics to the software. Loci were defined by merging 1.5-Mb neighborhoods around significant ($P < 5.0 \times 10^{-8}$) associations. Lead SNPs that were used to define a locus for fine-mapping had to have a MAF > 0.05, but we passed variants within respective loci with less stringent HWE $P > 1 \times 10^{-10}$ and no MAF cutoff. We evaluated LD matrices at each locus using LDStoe (86). We allowed up to 10 causal variants per locus and a uniform prior for variant causality. Resultant fine-mapped variants with MAF < 0.01 were removed. We excluded the human leukocyte antigen (HLA) region from fine-mapping.

**LD score dominance extension**

To estimate SNP-based dominance heritability, $h^2_D$, we constructed a d-LDSC model in which we regressed the chi-squared statistics of dominance GWASs on dominance LD scores. The dominance encoding provides a new flavor of LD ($36, 40$), $p^DD := \frac{1}{2}X^2_y X_D$. We can derive a dominance LD score equation relating dominance summary statistics to dominance LD scores, $l^D_j := \sum_{m \neq j} p^D_m p^D_j$. Assuming HWE yields a simple, decomposed analog of the additive LDSC ($44$, then

$$E \left[ \hat{n}^D_m \hat{n}^D_j \right] = \frac{n h^2_D}{m} p^D_j + 1$$

(2)

where $n$ is the number of samples, $m$ is the number of SNPs, $h^2_D$ is the dominance heritability, and $\hat{n}^D_j$ is the marginal nonadditive effect of SNP $j$ on phenotype $y$. See (42) for full details. As in the original LDSC, we may estimate dominance LD scores using an ancestry-matched reference panel. With access to dominant summary statistics and LD scores, we can estimate $h^2_D$ by the gradient of the linear model in Eq. 2. We used a block jackknife (44) to obtain standard errors on our estimates. We filtered to HapMap3 SNPs (87) and evaluated additive and dominance LD scores within a 1-centimorgan window.

**d-LDSC simulation studies**

To ensure that d-LDSC is an appropriately conditioned statistical model, we performed an extensive collection of simulation studies. We considered two simulation scenarios: (i) Fully simulated genotypes and phenotypes. We simulated genotype data using msprime (88) from 10 million sites in 10 independent chromosomes, sampled 50,000 individuals, and subsetted to variants with MAF > 5%, which was ~250,000 variants. (ii) Real genotypes and simulated phenotypes. We randomly sampled a subset of samples from the quality-controlled UK Biobank data (10,000, 50,000, and 100,000).

We then simulated phenotype data according to Eq. 1, varying $h^2_D$ and $h^2_D$ (0, 0.05, 0.2), genetic architecture (100% variant causal, 10% causal via spike and slab), and trait type (continuous, liability threshold generated binary trait with 6% in population prevalence, 18% in sample prevalence) and without case ascertainment (6% population prevalence). Estimates were unbiased and well calibrated (figs. S27 to S35 and tables S5 and S6). See (42) for full details.

**REFERENCES AND NOTES**

1. M. E. Wolak, L. F. Keller, in Quantitative Genetics in the Wild, A. Charmantier, D. Garant, Ed. (Oxford Univ. Press, 2014).
2. J. S. Bloom, I. M. Ehrenreich, W. T. Loo, T.-L. V. Lite, L. Kruglyak, Nature 494, 234–237 (2013).
3. J. P. R. dos Santos, R. C. C. Vanconcellos, L. P. M. Pres, M. Balestria, R. G. Von Prino, PLOS ONE 11, e0152045 (2016).
4. W. Huang et al., Proc. Natl. Acad. Sci. U.S.A. 109, 15553–15559 (2012).
5. M. S. Lopes, J. W. M. Baslaarans, L. Janes, E. F. Knol, H. Bovenhuis, Genet. Sel. Evol. 40, 2629–2637 (2008).
6. M. M. Monir, J. Zhu, Front. Plant. Sci. 9, 627 (2018).
7. E. C. Park, H. R. Horvitz, Genetics 113, 821–852 (1986).
8. M. Pettersson, F. Besnier, P. B. Siegel, D. Carlborg, PLOS Genet. 7, e1001380 (2011).
9. F. Manna, G. Martin, T. Lenormand, Genetics 189, 923–937 (2011).
10. A. Garcia-Dorado, A. Caballero, Genetics 155, 1991–2001 (2000).
11. D. Chavarrias, C. Lopez-Fanjul, A. Garcia-Dorado, Genetics 158, 681–693 (2001).
12. D. Houle, K. H. Hughes, A. Sasimacopoulous, B. Charlesworth, Genet. Res. 70, 27–34 (1997).
13. K. Szarvasiecz, D. M. Wloch, P. SiIka, R. H. Borts, R. Korana, Genet. Res. 82, 19–31 (2003).
14. L. L. Vassilieva, A. M. Hook, M. Lynch, Evolution 54, 1234–1246 (2000).
15. C. D. Huber, A. Durvasula, A. M. Hancock, K. E. Lohmueller, Nat. Commun. 9, 2790 (2018).
16. L. Yingo, N. R. Way, P. M. Vischer, Nat. Commun. 10, 3719 (2019).
17. L. Yingo et al., Am. J. Hum. Genet. 108, 1488–1501 (2021).
18. S. Wright, Am. Nat. 68, 24–53 (1934).
19. R. A. Vellia, J. Theor. Biol. 220, 10–25 (2003).
20. S. Bottari, R. A. Vellia, Biol. Rev. Camb. Philos. Soc. 92, 953–963 (2017).
21. A. H. Porter, N. A. Johnson, A. Y. Tulchinlys, Genetics 205, 101–112 (2017).
22. S. Billard, V. Castric, V. Laurens, Biol. Rev. Camb. Philos. Soc. 96, 2925–2942 (2021).
23. R. Blows, J. Genet. 3, 299–315 (1914).
24. J. B. S. Haldane, E. B. Ford, Proc. R. Soc. London Ser. B 145, 303–306 (1956).
25. A. E. van’t Hof et al., Nature 534, 102–105 (2016).
26. Z. G. McArthur et al., Science 335, 823–828 (2012).
27. J. D. Ooi et al., Nature 545, 243–247 (2017).
28. T. Lappalainen et al., Nature 501, 506–513 (2013).
29. J. J. Crowley et al., Nat. Genet. 47, 353–360 (2015).
30. Welcome Trust Case Control Consortium, Nature 447, 661–676 (2007).
31. R. J. F. Los, Nat. Commun. 6, 1990 (2015).
32. D. A. Fisher, Trans. R. Soc. Edinb. 52, 399–433 (1919).
33. W. G. Hill, M. E. Goddard, P. M. Vischer, PLOS Genet. 4, e1000008 (2008).
34. C. E. G. Amorim et al., PLOS Genet. 13, e1006915 (2017).
35. J. C. Chong et al., Am. J. Hum. Genet. 97, 199–215 (2015).
36. Z. Hu et al., Am. J. Hum. Genet. 96, 377–385 (2015).
37. C. Bicort et al., Nature 562, 203–209 (2018).
38. A. Pazoki-Kordouei, A. M. Chiu, K. S. Burch, B. Pasinucci, S. Sangaraman, Am. J. Hum. Genet. 108, 799–808 (2021).
39. V. Hvisert et al., Am. J. Hum. Genet. 108, 786–798 (2021).
40. X. Chen et al., Am. J. Hum. Genet. 97, 708–714 (2015).
41. T. J. C. Polderman et al., Nat. Genet. 47, 702–703 (2015).
42. Materials and methods.
43. B. bulk-Sullivan et al., Nat. Genet. 47, 1236–1241 (2015).
44. A. bulk-Sullivan et al., Nat. Genet. 47, 291–295 (2015).
45. H. K. Finucane et al., Nat. Genet. 50, 621–629 (2018).
46. D. S. Falconer, T. F. C. Mackay, Introduction to Quantitative Genetics (Pearson Education, 1996).
47. Z. G. Vitseiza, L. Varona, A. Legaria, Genetics 195, 1233–1230 (2013).
Therapeutics, Takeda Pharmaceutical, and Biogen. D.S.P. was an employee of Genomics plc. All the analyses reported in this paper were performed as part of D.S.P.’s employment at the Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA, and Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA. All other authors declare no competing interests. Data and materials availability: Dominance summary statistics and heritability estimates are available for download from Amazon web services at https://broad-ukb-sumstats-us-east-1.s3.amazonaws.com/round2/dominance-tsvs/{file}, where each {file} download link can be extracted from the manifest file at https://bit.ly/dominance-GWAS. We also performed sex-specific analyses, curating phenotypes according to the same pipeline (42); table S1, fig. S3, and the associated summary statistics files are also available at https://broad-ukb-sumstats-us-east-1.s3.amazonaws.com/round2/additive-tsvs/ {file}, where each {file} download link can be extracted from the manifest file at https://bit.ly/additive-GWAS (68). Code implementing the d-LDSC framework is available at https://github.com/astheeggeggs/d-ldsc and Zenodo (78). Code to reproduce our analyses is available at https://github.com/astheeggeggs/d-ldsc-paper. License information: Copyright © 2023 the authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original US government works. https://www.sciencemag.org/about/science-licenses-journal-article-reuse Materials and methods and references cited therein can be found in the main article online.

SUPPLEMENTARY MATERIALS

science.org/doi/10.1126/science.abn8455

Materials and Methods
Figs. S1 to S37
Tables S1 to S8
References (89–98)
MDAR Reproducibility Checklist

View/request a protocol for this paper from Bio-protocol.

Submitted 12 January 2022; accepted 15 February 2023