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SUPPLEMENTARY INFORMATION

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Genetic evidence of assortative mating in humans

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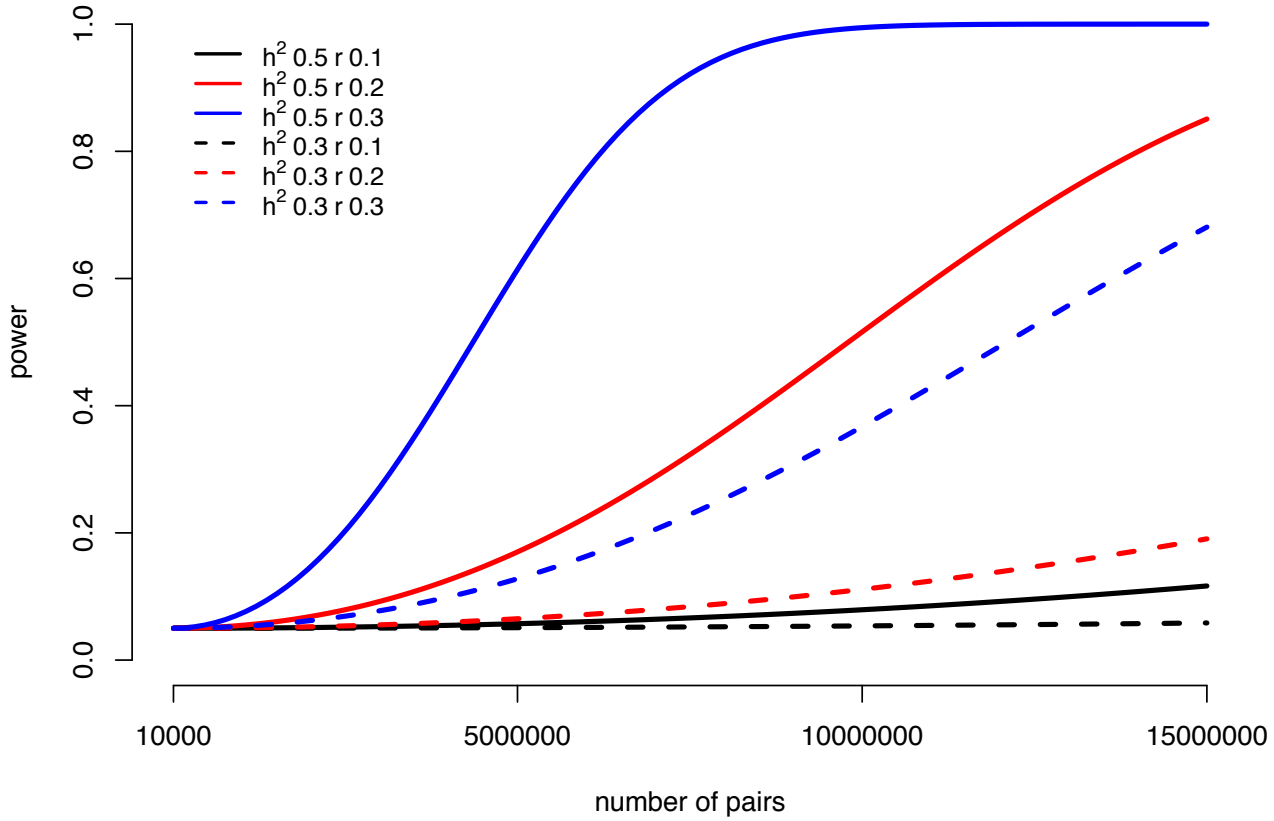
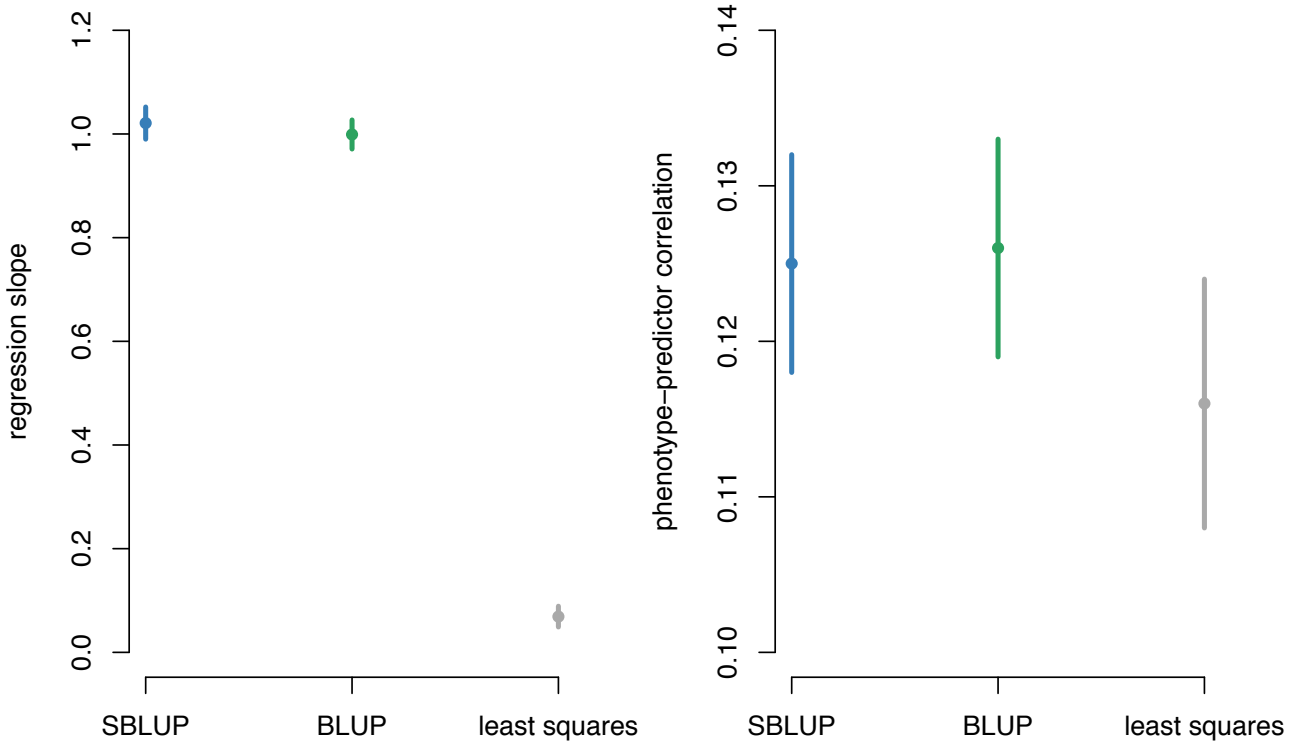
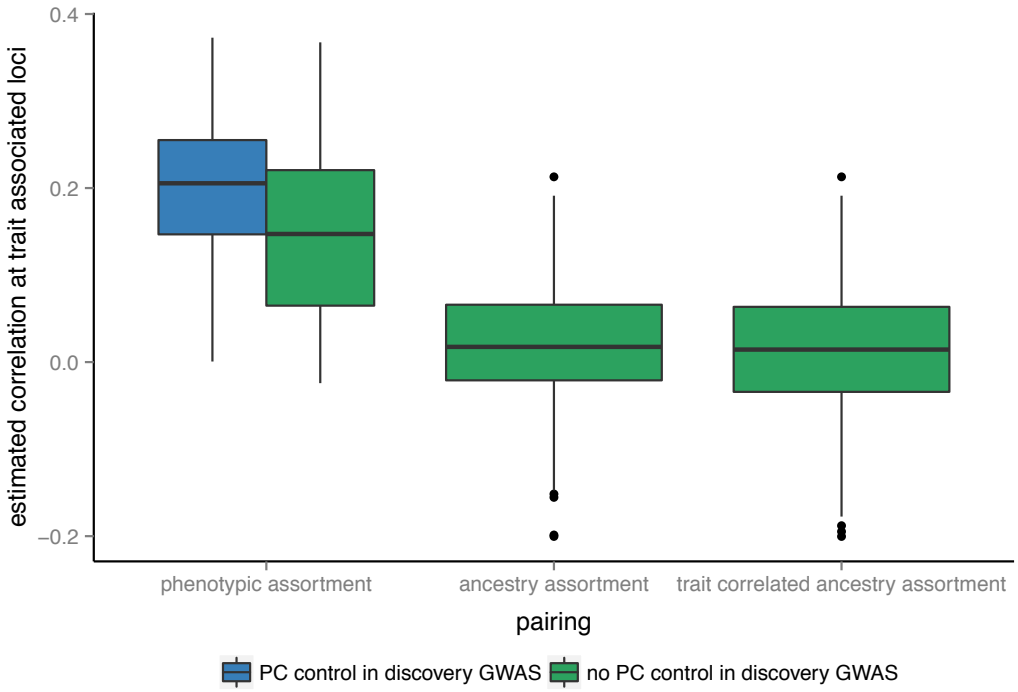
SUPPLEMENTARY FIGURES



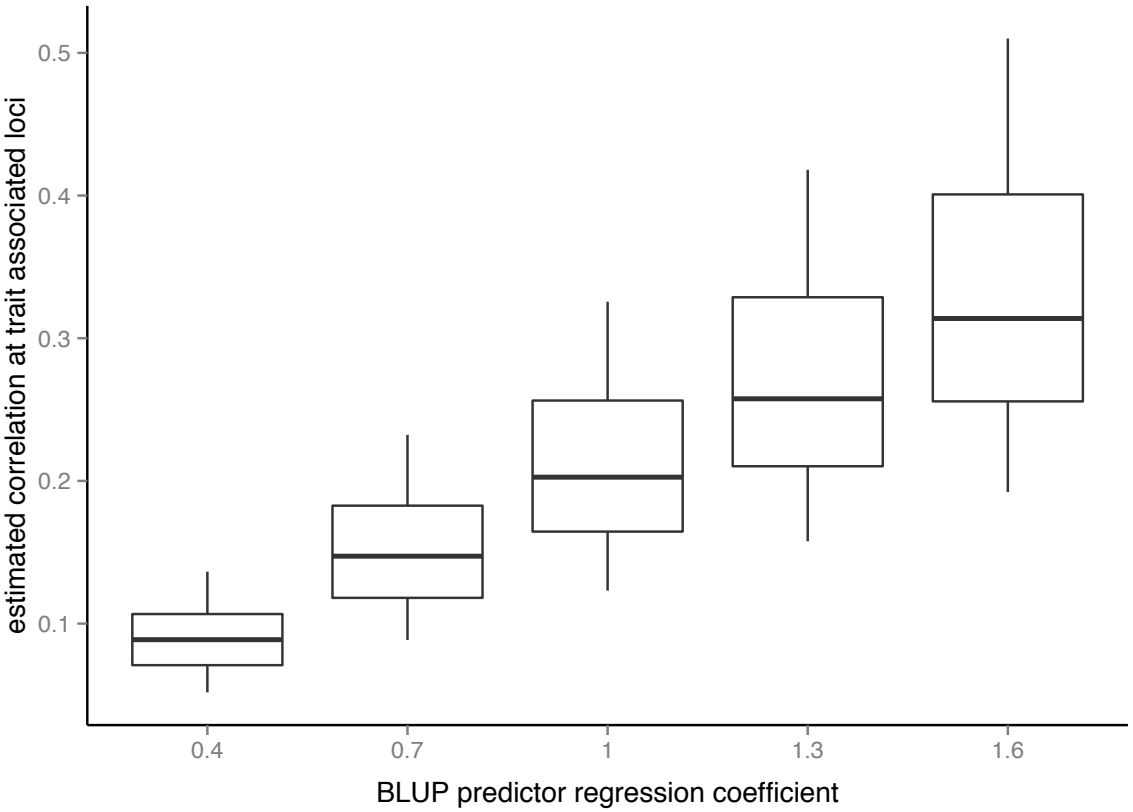
Supplementary Figure 1. Power to test whether the observed correlation among partners is greater than expected in the population for estimated genome-wide sharing of single nucleotide polymorphisms (SNPs). We assume 50,000 independent common SNP markers in the genome and a type-I error rate of 0.05. h^2 is the simulated heritability captured by common loci, and r is the phenotypic correlation. Genome-wide sharing statistic between any two individuals j and l is $\pi_{jl} = \left(\frac{1}{k}\right)\sum_{i=1}^{k}\left(w_{ij}w_{il}\right)$ where $w_i = \frac{x_i - 2p_i}{\sqrt{2p_i(1-p_i)}}$ with x_i the SNP dosage score and p_i the frequency of the i^{th} SNP.



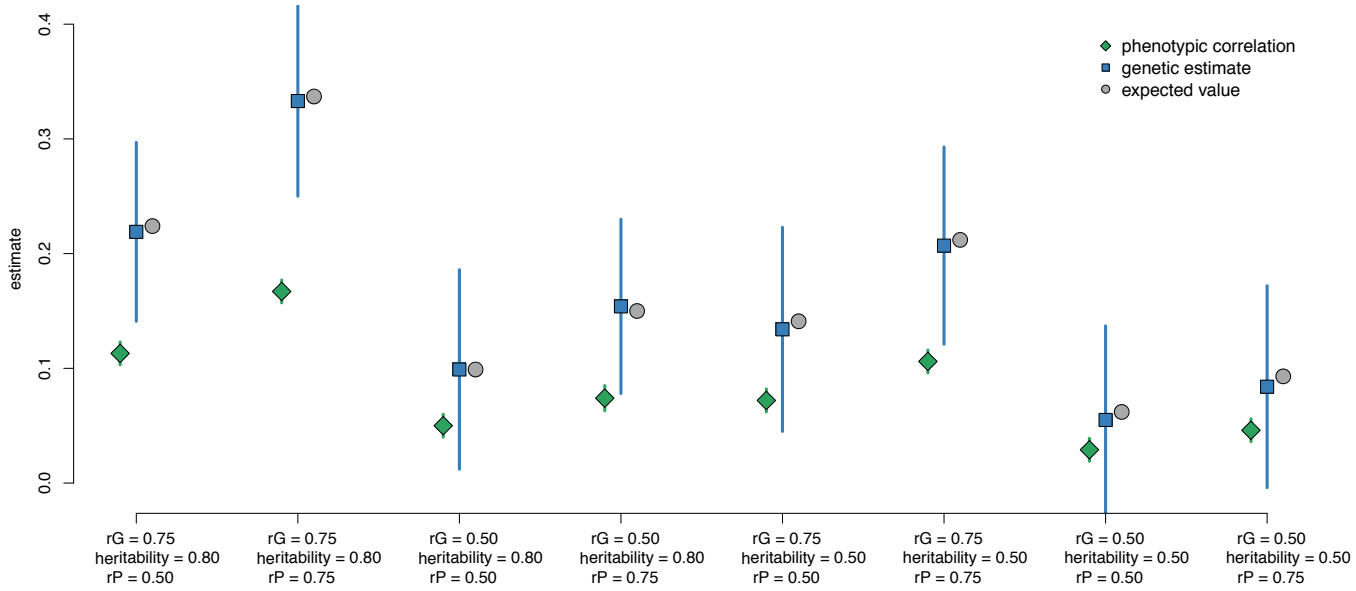
Supplementary Figure 2. Approximate summary statistic best linear unbiased genetic predictor (SBLUP). In our simulation study, 5000 SNPs were randomly selected as causal variants and effect sizes were allocated to these markers from a standard normal distribution. For each of 50 replicates, a phenotype was generated for all individuals, a genome-wide association study (GWAS) of the phenotype was conducted in a randomly selected set of 20,000 individuals at 1.2 Million HapMap3 SNPs, the SNP effect estimates were converted to approximate best linear unbiased predictor (SBLUP) SNP effects using a reference set of 10,000 randomly selected individuals, the BLUP SNP effects were used to create an approximate BLUP genetic predictor in 19,000 randomly selected individuals. We compare the SBLUP predictor (blue circles) to a predictor made from directly estimated BLUP SNP effects in an individual-level REML model (BLUP; green circles), and to a predictor made from the GWAS least squares SNP estimates (least squares; grey circles). The left-hand panel shows the slope of a regression where the phenotype is the dependent variable and the genetic predictor is the independent variable. The right-hand panel shows the correlation of the phenotype with the genetic predictor. The SBLUP approach has the same regression slope and correlation with the phenotype as the individual-level BLUP, and has improved prediction accuracy over a genetic predictor made from least squares estimates of the SNP effects.



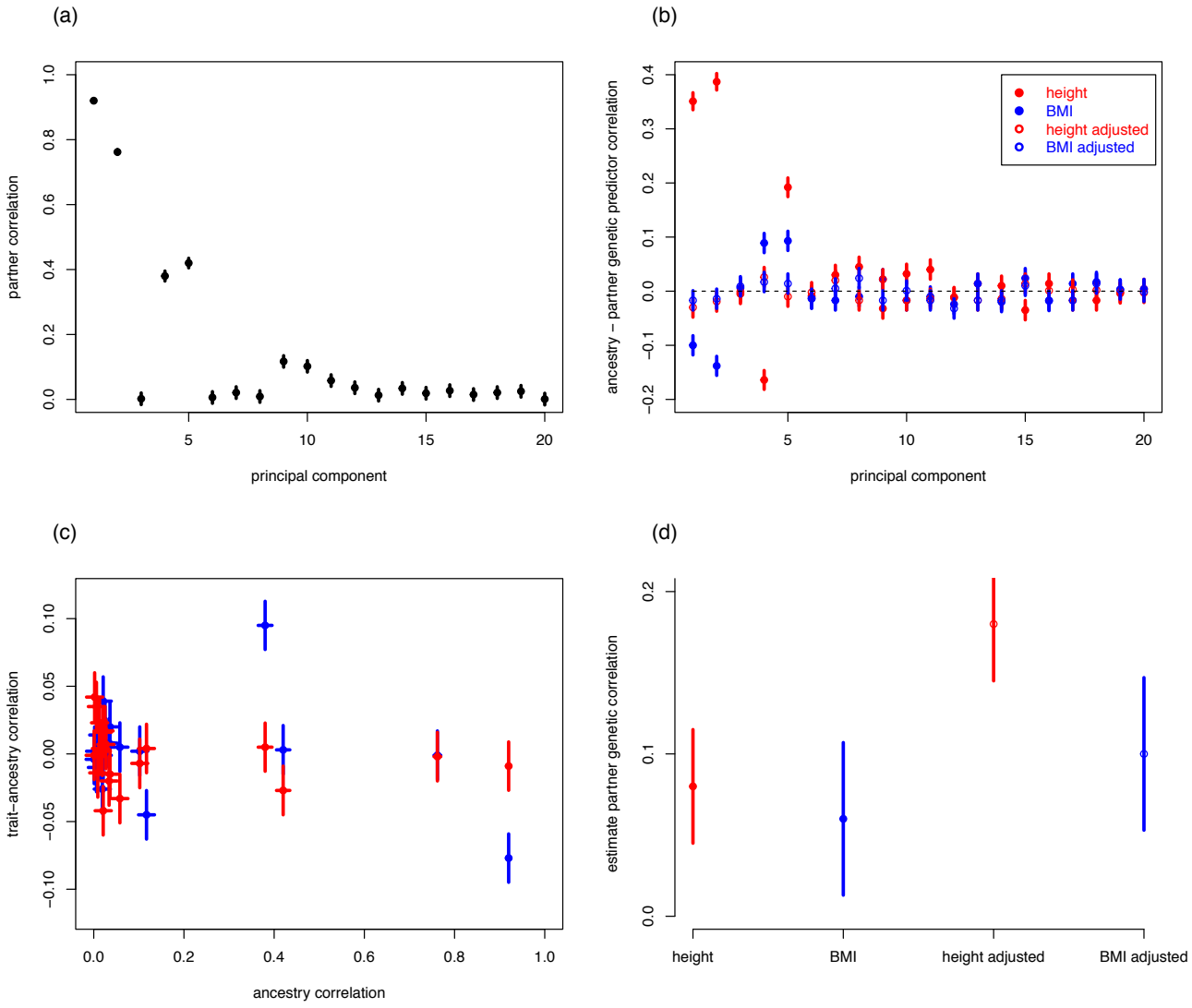
Supplementary Figure 3. Predicting phenotype of an individual from the genotype of their partner to estimate the degree to which assortative mating creates a genetic correlation at trait-associated loci among partners. We conducted a simulation study using real genotype data from 60,000 unrelated individuals. For each of 50 replicates, a phenotype was generated for all individuals, a genome-wide association study (GWAS) of the phenotype was conducted in a randomly selected set of 20,000 individuals at 1.2 Million HapMap3 SNPs, the SNP effect estimates were converted to approximate best linear unbiased predictor (BLUP) SNP effects using a reference set of 10,000 randomly selected individuals, the BLUP SNP effects were used to create a genetic predictor in 19,000 randomly selected individuals that were assigned to 9500 pairs, and finally we estimated the genetic assortative mating correlation for the phenotype using our framework (see Methods). We simulated three scenarios. In the first scenario (phenotypic assortment), individuals were paired based on their phenotype, with a spousal phenotypic correlation of 0.2. In the second scenario (ancestry assortment), individuals were paired based on their ancestry, defined as an individual's cumulative sum of the first 10 eigenvector values calculated from the SNP data, with a spousal correlation of 0.8. In the third scenario (trait correlated ancestry assortment), individuals were paired on their ancestry with a spousal correlation of 0.8 and the first 10 eigenvectors explained 5% of the phenotypic variance, which creates a genotype-environment correlation for the phenotype. The genetic assortative mating correlation for the phenotype is shown across 50 replicates for each pairing scenario, divided into different analysis approaches depending upon whether population stratification was controlled for in the discovery analysis. In the first scenario (phenotypic assortment), our approach returns the correct simulated value when population stratification is controlled for in the discovery analysis (shown in blue) and is only slightly reduced toward zero when population stratification is not accounted for in the discovery analysis (shown in green). In the second scenario (ancestry assortment) the spouse pair correlation is 0 for the phenotype and we found that the genetic assortative mating correlation for the trait was never significantly different from zero under the extreme scenario of no control for population stratification in the discovery analysis. In the third scenario (trait correlated ancestry assortment) there is genotype-environment correlation for the phenotype and again we found that the genetic assortative mating correlation for the trait was never significantly different from zero under the extreme scenario of no control for population stratification in the discovery analysis. Therefore, our approach is unbiased provided that principal components of the genotypic data capture the stratification that occurs.



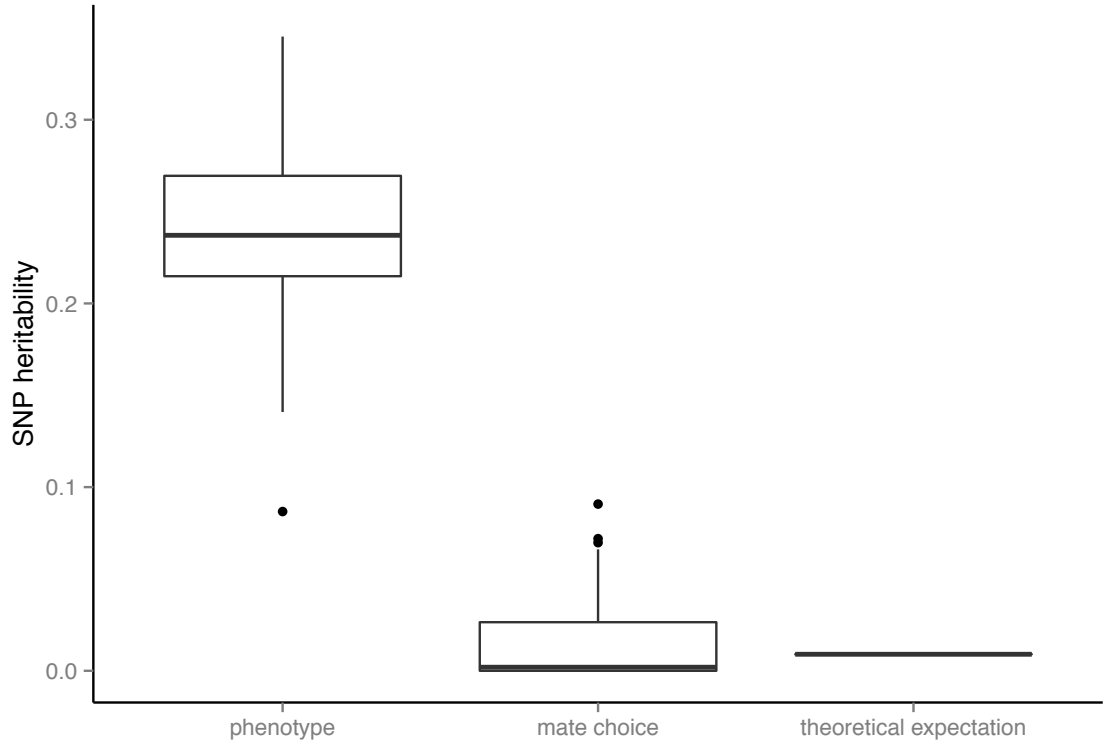
Supplementary Figure 4. BLUP properties of the SBLUP predictor. In our simulation study, we altered the lambda parameter across simulations in the approximate summary statistic BLUP (SBLUP) analysis, and then re-estimated the genetic correlation at trait-associated loci. Across all simulations the phenotypic correlation among partners was 0.2. When the genetic predictor has BLUP properties of a regression coefficient of phenotype on predictor of 1, and there is direct assortative mating on the phenotype, then the estimated correlation at trait-associated loci equals the phenotypic correlation. When the genetic predictor does not have BLUP properties then the estimate changes in proportion to the phenotypic correlation multiplied by the slope of the genetic predictor.



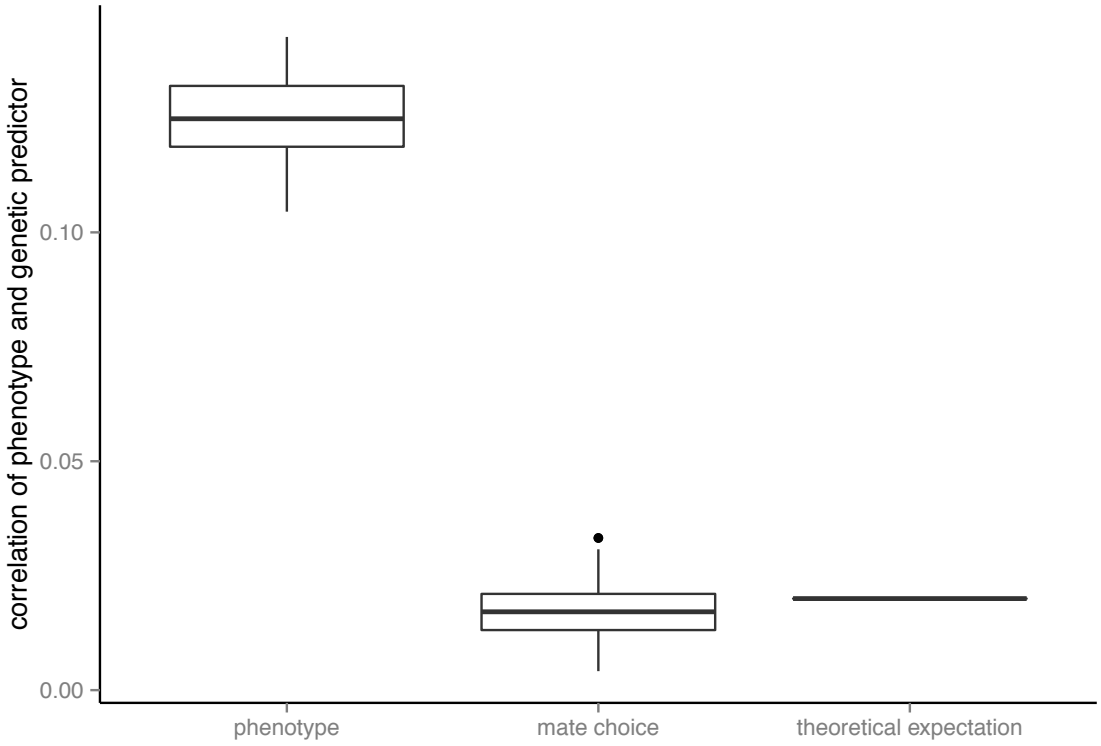
Supplementary Figure 5. Simulation study of assortative mating on a correlated trait. We extended our simulation study using real genotype data from 60,000 unrelated individuals, to simulate assortative mating for a correlated trait. For each of 50 replicates, we paired individuals on the basis of an unobserved genetically correlated trait (genetic correlation, rG, either 0.5 or 0.75, and heritability either 0.5 and 0.8), with a partner correlation, rP, of either 0.75 or 0.5. We then re-estimated Eq. 7 in each simulation scenario (blue square) for a focal trait that was measured and we compare the estimates gained to their expectation under Eq. 7.10 (grey circles). The phenotypic correlation among partners for the measured focal trait is shown by green diamonds. Error bars give the SD of the estimates across 50 replicates.



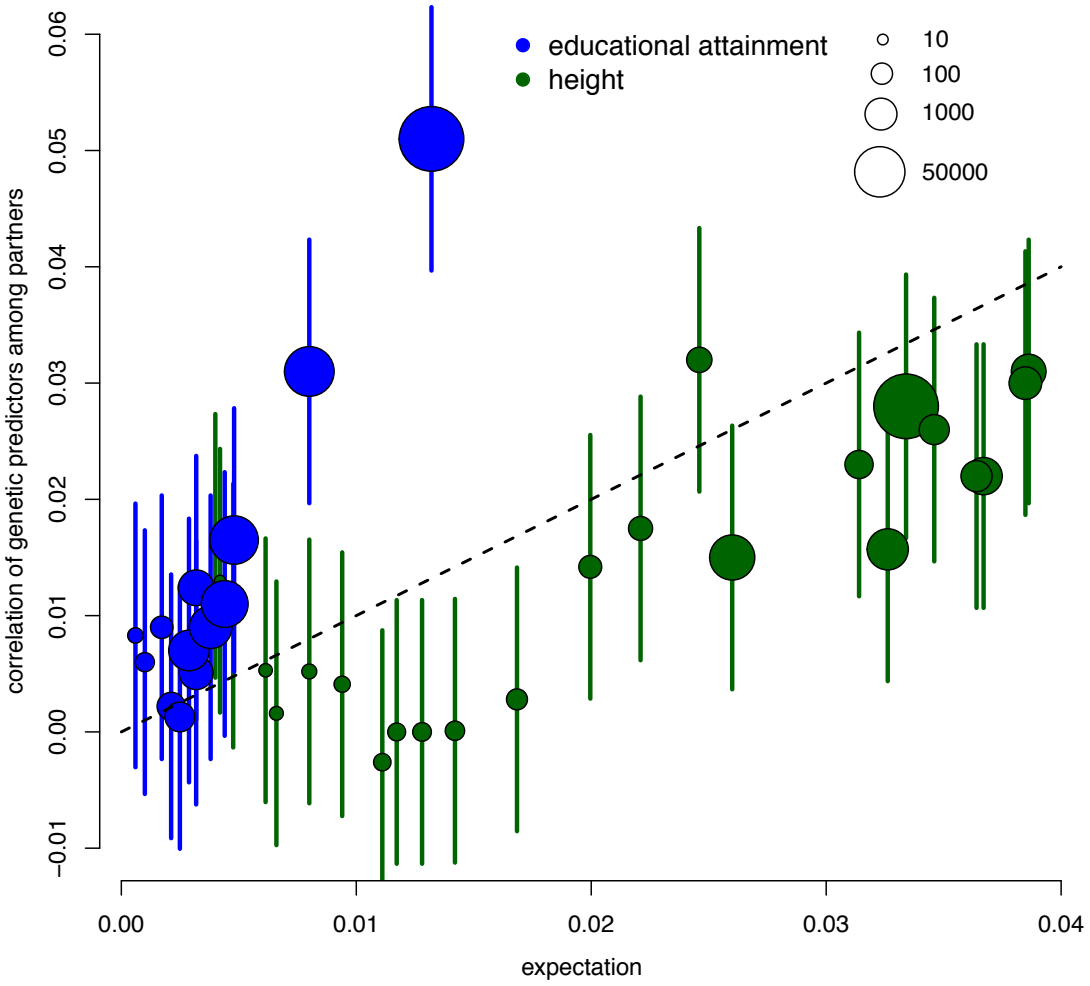
Supplementary Figure 6. Association between ancestry, phenotype, and genetic predictors of height and body mass index (BMI) among partners. (a) In the combined sample there is a high correlation at the leading principal components (PCs) of the genetic data among partners because pairing occurs within each study and within ethnicities. (b) Without correction for PCs, a genetic predictor of height and BMI for an individual is correlated with the leading PC values of their partner both positively and negatively. (c) Phenotypically, when height and BMI are converted to a z-score within each cohort, the PCs for which there is a high correlation among partners do not show a consistent directional correlation with either trait. (d) Therefore without correction for PCs, the estimate of the degree to which partners share trait associated loci is underestimated because there is no consistent directional match between ancestry sharing and the correlation between ancestry and trait value. Error bars give the SE of the estimates.



Supplementary Figure 7. SNP heritability of differences among individuals in their partner phenotype. In our simulation study, we estimated the SNP heritability of the simulated phenotype using REML, from which a theoretical expectation of the SNP heritability of differences among individuals in their partner phenotype can be derived (theoretical expectation). This theoretical expectation was then compared to the estimates gained from the analysis of the simulated data. Values shown are the point estimates across the 50 simulation replicates.



Supplementary Figure 8. Predicting phenotype from associations of an individual's phenotype with their partner's genotype. In our simulation study, we estimated the correlation of the simulated phenotype and a BLUP genetic predictor, from which a theoretical expectation can be derived of the correlation of an individual's phenotype with a genetic predictor created from the SNP effects gained in a mixed-linear model association analysis using their partners genotype as a trait (theoretical expectation). This theoretical expectation was then compared to the estimates gained from the analyses of the simulated data. Values shown are the point estimates across the 50 simulation replicates.



Supplementary Figure 9. Correlation of genetic predictors among partners for height (green) and educational attainment (blue) in 7,780 couples from the UK Biobank study, estimated using different subsets of SNP markers. Using summary statistics from recent GWAS studies and the clumping procedure in the software PLINK, we selected subsets of SNPs in linkage equilibrium (LD correlation < 0.01 within 1MB) that were associated with each trait across a wide range of significance thresholds. For each significance threshold, the SNPs selected were used to create a genetic predictor directly from the ordinary least squares estimates of the SNP effects, and we estimated the proportion of phenotypic variance explained and the correlation among partners. The expectation of the correlation in genetic predictors among partners is the product of the phenotypic correlation among partners (0.2 for height and 0.4 for educational attainment) and the phenotypic variance explained by the genetic predictor, and this is given on the x-axis. The y-axis then gives the estimate of the correlation of genetic predictors among partners. Each point represents the expectation and the estimate obtained using a predictor that contains SNPs selected at different clumping thresholds, with the size of the point reflecting the number of SNPs used in the genetic predictor. Error bars show the SE of the estimate.

SUPPLEMENTARY TABLES

Analysis	Cohort	Sample size	Number of SNP Markers
Spousal pair analyses	**Composite sample (ARIC, HRS, LL, MCTFR)**		
	Atherosclerosis Risk in Communities Study (ARIC)	*2,245 pairs*	*1,171,654*
	Health and Retirement Study (HRS)	*1,195 pairs*	*1,337,895*
	LifeLines Study (LL)	*818 pairs*	*1,170,052*
	Minnesota Center for Twin and Family Research Study (MCTFR)	*786 pairs*	*1,195,036*
	Total	**5,044 pairs**	**1,135,785**
	Sample from 23andMe research participant cohort	**11,908 pairs**	**1,134,501**
	Sample from the UK Biobank	**7,780 pairs**	**1,162,900**
Approximate BLUP genetic prediction	**Reference SNP marker set from TwinGene study**	**10,729 individuals**	**1,121,023**
	Ridge regression prediction in individuals from the combined sample (ARIC, HRS, LL, MCTFR) that are not part of, or related to, spousal pairs	**18,134 individuals**	**1,135,785**
Simulation study	**Unrelated European individuals from Kaiser Permanente study (GERA)**	**10,729 individuals**	**1,121,023**

Table S1. Cohorts used at each stage of analysis with their sample size and number of imputed HapMap3 SNP markers passing QC.

SUPPLEMENTARY NOTE

Expected genome-wide SNP sharing conditional on phenotypic similarity

Consider a phenotype as $y_j = \sum_{i=1}^{k} w_{ij} b_i + e_j$, where $w_{ij} = \frac{(x_{ij} - 2p_i)}{\sqrt{2p_i(1-p_i)}}$, with x_{ij} the SNP dosage score of the j^{th} individual, b_i the allelic effect of the i^{th} causal variant with allele frequency p_i, and e_j the residual (environmental effect) with y having mean zero and variance 1, and k the number of SNP markers. If $a_j = \sum_{i=1}^{k} w_{ij} b_i$, then $\sigma_a^2 = \sum_{i=1}^{k} (b_i{}^2) = h^2$, with h^2 the heritability of the phenotype.

For genome-wide sharing, the best-case scenario for detection is to consider the causal variants directly and to assume that all causal variants are independent. For any two individuals j and l, the sharing statistic π_{jl} can be considered as a random variable $\pi_{jl} = (\frac{1}{k}) \sum_{i=1}^{k} (w_{ij} w_{il})$. At the population-level, $\mathbb{E}(w_{ij} w_{il}) = 0$ and $\sigma^2_{w_{ij} w_{il}} = 1$ and hence $\mathbb{E}(\pi_{jl}) = 0$ and $\sigma^2_{\pi_{jl}} = 1/k$.

The relationship between phenotypic and genomic sharing is $y_j y_l | \pi_{jl} = h^2 \pi_{jl} + e$, which for a randomly selected pair of individuals in a population $\mathbb{E}(y_j y_l) = 0$ and $\sigma^2_{y_j y_l} = 1$. Previous work on assortative mating has focussed on the genomic sharing at SNP loci conditional on phenotypic sharing which is $\pi_{jl} | y_j y_l = \mu + \beta y_j y_l + e$, where $\beta = \frac{\sigma(\pi_{jl}, y_j y_l)}{\sigma^2_{y_j y_l}} = h^2 \sigma_\pi^2$ and μ is an intercept with $\mathbb{E}(\mu) = 0$.

Hence,

$$\pi_{jl} | y_j y_l = h^2 \sigma_\pi^2 y_j y_l + e = \left(\frac{h^2}{k}\right) y_j y_l + e \qquad [1]$$

If the phenotypes for the pairs j and l are ascertained as is the case when selecting partners, then we can express the expected value of their product as their phenotypic correlation, $\mathbb{E}(y_j y_l | ascertainment) = r$, with r the phenotypic correlation.

The expectation of Eq. [1] then becomes:

$$\mathbb{E}(\pi_{jl} | y_j y_l) = r h^2 / k, \qquad [2]$$

with variance:

$$\sigma^2_{\pi_{jl} | y_j y_l} = \sigma^2_{\pi_{jl}} - \sigma^2_{(h^2/k) y_j y_l} = \left(\frac{1}{k}\right) - \left((h^2/k) y_j y_l\right)^2 = (\frac{1}{k})(1 - \frac{h^4}{k})$$

Hence for detection using a statistical test, the non-centrality parameter (NCP) of a test for mean sharing among N selected pairs against a population-level value of zero is:

$$NCP = \frac{N(r^2 h^4 / k^2)}{(\frac{1}{k})(1 - \frac{h^4}{k})} = \frac{N r^2 h^4}{k - h^4} \qquad [3]$$

If the heritability is ~1 and if pairs are selected with identical phenotypes (r = 1) then $NCP = N/(k\text{-}1)$, and thus the power depends on the number of causal variants relative to the sample size (N pairs). Evidence suggests that for a complex phenotype like height, k>>1000 and thus even in the scenario where all causal variants are known and pairs

are selected with identical phenotypes, ~8000 pairs would be required to detect a significant deviation from the null at p<0.05 if we assume k=2000.

In reality, the phenotypic correlation among partners for height is $r \sim 0.2$, the h^2 captured by SNP loci ~ 0.5, and k is the effective number of common independent markers in the genome ~50,000[1]. Placing these numbers into Eq. [3] reveals that 7 million couples would be required in order to detect a deviation from expectation in genome-wide sharing. Power calculations from Eq. [3] are presented in Supplementary Figure 1 assuming a type-I error rate of 0.05.

These results demonstrate that very large sample size is required to detect whether couples share more SNP marker alleles than randomly selected pairs of individuals from the population and thus we devised a novel approach to estimating the genetic basis of phenotypic assortment.

Genetic (co)variance of phenotype and mate choice in related individuals

A recent study[32], presents a variance components approach for examining the genetic basis of assortative mating for a phenotype. They present a bivariate linear mixed effects model, where the first phenotype is the phenotype of the individual and the second is the phenotype of their chosen partner. In this model, the phenotypic (co)variance is partitioned into two components, genetic (co)variance using a relationship matrix estimated from SNP data, and residual (co)variance. The study uses data that is a mixture of unrelated and related individuals and as a result, like all family designs, it does not allow for a complete separation of genetic effects from common environment effects. This is because genetic and common environment effects, while being uncorrelated, may be confounded as close relatives share both genes and their environment to a greater extent than to other individuals.

Consider a phenotype as $y_j = a_j + c_j + e_j$, where $a_j$is the additive genetic value for the j^{th} individual, c_j are cultural or common environment effects that are shared among close relatives who come from the same family background, and e_j the residual (environmental effect). We assume $\sigma(c, e) = \sigma(a, e) = 0$ and a phenotypic variance of 1, giving $\sigma_p^2 = h^2 + c^2 + e^2$, with h^2 the heritability. One approach to estimating the heritability of a trait is to determine the covariance amongst full siblings, with $h^2 = 2\sigma(y_j, y_k)$, where y_j and y_k are the phenotypes of sibling j and k respectively.

The covariance between full siblings is $\sigma(y_j, y_k) = \sigma(a_j, a_k) + \sigma(c_j, c_k) + \sigma(e_j, e_k)$. We can then consider the covariance between a sibling and their partner which is $\sigma\left(y_j, y_{s_j}\right) = \sigma\left(a_j, a_{s_j}\right) + \sigma\left(c_j, c_{s_j}\right) + \sigma\left(e_j, e_{s_j}\right)$, and the covariance between the partners of the full siblings is then $\sigma\left(y_{s_j}, y_{s_k}\right) = \sigma\left(a_{s_j}, a_{s_k}\right) + \sigma\left(c_{s_j}, c_{s_k}\right) + \sigma\left(e_{s_j}, e_{s_k}\right)$. The expected value of the estimate of heritability of mate choice from this full sibling design is $h^2_{choice} = 2\sigma\left(y_{s_j}, y_{s_k}\right)$.

The covariance terms depend on the assumptions as to the mechanism of assortment and the assumptions on how the shared / common environment effects, c, covary between the full siblings and their spouses. In an extreme case, where all mate assortment is due to shared common environment effects and these are fully shared between full siblings then, $\sigma(y_1, y_2) = \frac{1}{2}h^2 + c^2$ and $\sigma\left(y_j, y_{s_j}\right) = r\left(c_j, c_{s_j}\right)c^2 = m$, with the correlation in the non-genetic shared environment effects among partners and m is the phenotypic correlation among partners. In this scenario, the only covariance between the spouses of the full siblings is through sharing of family background, with $\sigma\left(y_{s_j}, y_{s_k}\right) = \sigma\left(c_{s_j}, c_{s_k}\right) = r\left(c_{s_j}, c_{s_k}\right)c^2 = r\left(c_j, c_{s_j}\right)r(c_j, c_k)r(c_k, c_{s_k})c^2 =$

$r\left(c_j, c_{s_j}\right)^2 c^2 = r\left(c_j, c_{s_j}\right) m$. With these assumptions, the expected value of the estimate of heritability of realized mate choice is $h^2_{choice} = 2\sigma\left(y_{s_j}, y_{s_k}\right) = 2r\left(c_j, c_{s_j}\right) m$.

If we assume values of $r\left(c_j, c_{s_j}\right)$ from 0.1 to 0.5 and c^2 from 0.1 to 0.2 then h^2_{choice}ranges from 0.2% to 10% and m ranges from 0.01 to 0.1. For height, m has been characterized in the human population as ~0.2, common environment effects of ~0.1 have been reported[54], there is evidence for pairing on family background with correlation, $r\left(c_{s_1}, c_{s_2}\right) = 0.5$[54] and a recent study finds h^2_{choice}~0.04[32], meaning that the model described here is not consistent with current findings for height. However, the contribution of shared environment to phenotypic variance, and the degree to which individuals assort based on environmental effects such as family similarity will vary depending upon the phenotype. It is clear that under this model and these assumptions, covariance of the phenotypes of the spouses of relatives can contain an environmental component. Therefore, when using data on relatives mate choice based on family background can make it appear as though attraction to a mate of similar phenotype can be explained by a person's genotype with a high 'genetic' correlation between the phenotype and choice of the phenotype.

In this study, we use unrelated individuals when estimating h^2_{choice}. Although the estimates of h^2_{choice} for unrelated individuals will be unbiased by shared environment effects, partitioning the phenotypic covariance of spousal pairs into genetic and environmental components in a bivariate mixed model will likely always yield a significant estimate of both genetic and environmental covariance, even under direct mate choice. Therefore, conclusions as to the relative contributions of different mechanisms are difficult and hence we take the approach of predicting the phenotype of an individual from the genotype of their partner, enabling a direct comparison of the degree to which phenotypic assortment among partners creates a correlation at trait-associated loci, that is free of environmental confounding.

Correlation of effect size estimates made using the same individuals

Another approach to assessing whether the genetic basis of a phenotype and mate choice of phenotype are the same, is to estimate the correlation between (i) GWAS summary statistics for the trait, and (ii) GWAS summary statistics when the partner's phenotype is treated as the choice of an individual. However, when these two association studies are conducted on identical samples in the same population (in (i) and (ii) the same genetic markers are used), this analysis can result in a significant correlation in the estimated regression coefficients even when no genetic correlation exists between the trait and choice of the trait.

Consider a scenario where two phenotypes measured on the same individuals, $y1_j = \sum_{i=1}^{k} w_{ij} b1_i + e1_j$, and $y2_j = \sum_{i=1}^{k} w_{ij} b2_i + e2_j$, the allelic effects $b1$ and $b2$ arise from a multivariate normal distribution with $\sigma^2_{b1} = h^2_1/m$, $\sigma^2_{b2} = h^2_2/m$ and $\sigma_{b1,b2} = 0$, giving a genetic correlation between the two phenotypes of 0. The environmental effects $e1$ and $e2$ also arise from a multivariate normal distribution with $\sigma^2_{e1} = 1 - h^2_1$, $\sigma^2_{e2} = 1 - h^2_2$ and $\sigma_{e1,e2}$ the environmental covariance, which will be high when the phenotype is measured on identical individuals. For example, it is likely that family background is correlated with the environment experienced during development, the developmental environment influences variation of many phenotypes, and family background influences mate choice, which together create an environmental covariance between an individual's trait value and their choice of partner.

Following[55], if $b1_i$ and $b2_i$ are estimated in linear regressions on identical samples then the covariance in the estimated effects is $cov(\hat{b}1_i, \hat{b}2_i) = m\sqrt{\frac{\sigma^2_{y1}}{N}\frac{\sigma^2_{y2}}{N}}$, which reflects the phenotypic correlation m, a correlation that may be both genetic and environmental. To demonstrate this we use the same simulation approach described above, to generate two phenotypes ($h^2_1 = 0.7$; $h^2_2 = 0.04$) with a genetic correlation of zero and an environmental correlation of 0.2. Across 50 simulation replicates, the estimated SNP effect sizes were correlated at 0.203 (0.01 SD). Therefore in this study, we took the approach of conducting the discovery and then prediction in independent samples to avoid the potential for environmentally induced covariance in SNP effect sizes estimates.

SUPPLEMENTARY METHODS

Approximate BLUP genetic predictor (SBLUP)

Genome-wide association studies (GWAS) analyze one SNP at a time using the model $\boldsymbol{y} = \mathbf{X_i}\beta_i + \boldsymbol{e}$, where $\mathbf{y}$ is a $N \times 1$ vector of the phenotype, $\mathbf{X_i}$ is a $N \times 1$ vector of genotypes for each SNP i = 1, …, k (coded as 0, 1, or 2 defining the number of reference alleles), with k the number of SNP markers, and $\boldsymbol{e}$ is an $N \times 1$ vector of residuals. The computed least-squares estimates of the effect size, $\hat{\beta}_i$, of this model can be written as $\text{diag}(\mathbf{X}^T\mathbf{X})\widehat{\boldsymbol{\beta}} = \mathbf{X}^T\boldsymbol{y}$.

We re-estimated these SNP estimates in a random effects model that converts the least squares estimates, $\hat{\beta}$, into approximate best linear unbiased predictors (BLUP). The motivation behind this is that prediction power is maximized and the genetic predictor gained has BLUP properties which include of a regression slope of 1 on the phenotype[2,3]. To obtain the BLUP estimates of SNP effects, the effects of all SNPs are fitted jointly in a random effect model as $\mathbf{y} = \mathbf{Xb} + \mathbf{e}$ with $\mathbf{b} \sim N(0, \sigma_b^2)$ and $\mathbf{e} \sim N(\mathbf{0}, \sigma_e^2)$, and the BLUP solution is $\hat{\mathbf{b}} = (\mathbf{X}^T\mathbf{X} + \mathbf{I}\lambda)^{-1}\mathbf{X}^T\boldsymbol{y}$, with $\lambda = \sigma_e^2/\sigma_b^2$. Although $\mathbf{X}$ and $\mathbf{y}$ in the discovery set are not available when using summary statistics, we can approximate the covariance matrix of SNP genotypes, $\mathbf{X}^T\mathbf{X}$, by that from a reference cohort, $\mathbf{W}^T\mathbf{W}$, that is independent from the prediction population as $\mathbf{X}^T\mathbf{X} \approx \frac{\mathbf{W}^T\mathbf{W}n_d}{n_r} = \boldsymbol{B}$ with n_d and n_r being the samples sizes of the discovery set and reference sample, respectively. This assumes that the allele frequencies and linkage disequilibrium (LD) between SNPs in the discovery set are similar to those in a reference sample. We can also approximate $\mathbf{X}^T\boldsymbol{y} = \text{diag}(\boldsymbol{B})\widehat{\boldsymbol{\beta}}$. We therefore have $\hat{\mathbf{b}} = (\mathbf{B} + \mathbf{I}\lambda)^{-1}\text{diag}(\boldsymbol{B})\widehat{\boldsymbol{\beta}}$.

Since the random effect model assumes every SNP has an effect on the trait, the proportion of phenotypic variance explained by all SNPs is $h_g^2 = k\sigma_b^2/\sigma_P^2$ with k being the total number of SNPs used in the analysis and σ_P^2 being the phenotypic variance (which is ~1 if the discovery GWAS was based on standardised phenotype). We then have $\lambda = k\left[1 - h_g^2\right]/h_g^2$.

For each individual, the BLUP SNP effects can be used to create a genetic predictor as $\widehat{\boldsymbol{g}} = \sum_{i=1}^{k} x_i \hat{\text{b}}_i$, where x_i the number of SNP minor alleles at SNP i (again coded 0, 1, or 2), $\hat{\text{b}}_i$ the BLUP effects estimate at SNP i, which is then summed over k SNPs to give a $N \times 1$ vector of predicted genetic effects, $\widehat{\boldsymbol{g}}$. This predictor has the expected property $\sigma(g, \hat{g}) = \sigma_{\hat{g}}^2$ where g is the genetic predictor gained if the true SNP effects were known. This follows a recent study[4] and is implemented within the software package GCTA[5] under the term SBLUP (--cojo-sblup).

We used the meta-analysis SNP effect size estimates and gained BLUP approximations of the SNP effects using the TwinGene cohort (Supplementary Table 1) as a reference. Our theory and empirical analyses outlined below rely on the assumption that the slope of the regression of the BLUP predictor on the phenotype is ~1. We therefore conducted a ridge regression to find the value of λ that gives a predictor with these BLUP properties of a regression slope of 1 on the phenotype. We selected individuals from the cohorts listed in Supplementary Table 1 that had genotypic and phenotypic data, but were not part of a spouse pair or related to the spouse pairs, and we devised an algorithm to grid search the value of lambda that gave a regression slope of 1 within this data. Data access restrictions prevented a ridge regression tailored specifically to the 23andMe data.

Predicting the phenotype of an individual from the genotype of their partner

To estimate the degree to which assortative mating creates a genetic correlation at trait-associated loci, we first determined the relationship between the genetic predictor of males and the phenotype of their female partner, and vice versa as:

$$\boldsymbol{y}_m = \mu_m + \hat{\boldsymbol{g}}_{p_f} + \boldsymbol{u}_m + \boldsymbol{e_m}, \qquad [4]$$
$$\boldsymbol{y}_f = \mu_f + \hat{\boldsymbol{g}}_{p_m} + \boldsymbol{u}_f + \boldsymbol{e_f}$$

where u is a $N \times 1$ vector of the total genetic effects of the individuals, with $u = N(0, \mathbf{A}\sigma_G^2)$, $\mathbf{A}$ is the genetic relationship matrix (GRM) between either males (when estimating $\boldsymbol{u}_m$), or females (when estimating $\boldsymbol{u}_f$) with its jl^{th} element being $A_{jl} = \frac{1}{N}\sum_{i=1}^{N}\frac{(x_{ij}-2p_i)(x_{il}-2p_i)}{2p_i(1-p_i)}$ where p_i is the frequency of the minor allele of the imputed HapMap3 common SNP *i*. and *x* is the SNP genotype (best guess for the combined cohort and rounded imputed diploid dosage for the 23andMe cohort). The GRM accounts for population stratification in the phenotype, as it is equivalent to fitting all the principal components within the model. Eq. [4] was estimated using the GREML function in GCTA v1.25.

The expectation of the regression coefficient from a linear regression of the phenotype of males on the genetic predictor of their female partners and vice versa can be derived under different types of assortative mating. Under direct assortment on a quantitative trait in Eq. [4]:

$$\mathbb{E}[\sigma(y_m, \hat{g}_f)] = b_{y_m,y_f}\sigma(y_f, \hat{g}_f), \text{ with } b_{y_m,y_f} = \frac{\sigma(y_m,y_f)}{\sigma^2(y_f)} \qquad [5]$$

If y_m and y_f are standardized to a z-score with mean = 0 and variance = 1 then:

$$\mathbb{E}[b_{y_m,y_f}] = r(y_m, y_f) \qquad [6]$$

where r is the correlation. Under the BLUP assumptions of $\sigma(g, \hat{g}) = \sigma_{\hat{g}}^2$ then:

$$\mathbb{E}[\sigma(y_f, \hat{g}_f)] = \sigma(g_f, \hat{g}_f) = \sigma_{\hat{g}_f}^2 \qquad [7]$$

and in Eq. [4] the slope of the regression of y_m on $\hat{g}_f$ is:

$$\mathbb{E}[b_{y_m\hat{g}_f}] = \frac{\sigma(y_m,\hat{g}_f)}{\sigma_{\hat{g}_f}^2} = \frac{r(y_m,y_f)\sigma(y_f,\hat{g}_f)}{\sigma(y_f,\hat{g}_f)} = r(y_1, y_2) \qquad [8]$$

An alternative scenario is where assortment occurs on a trait that is correlated to the observed trait. If y is the trait upon which assortment occurs, but z is the trait that is measured then the observed correlation among couples for trait z will be:

$$r(z_1, z_2) = r(y, z)^2 r(y_1, y_2) \qquad [9]$$

If we assume both traits have unit variance, we can consider the phenotypic regression of z on y:

$$z = r(y, z)y + e \qquad [10]$$

and the genetic regression of z on y assuming that the true genetic value is known:

$$g_z = \left(r(g_y, g_z)h_z/h_y\right)g_y + e \qquad [11]$$

with h_z^2 and h_y^2 the heritability of trait z and y respectively. Then the expectation of the covariance of trait z in males and the genetic value of their female partners is:

$$\mathbb{E}\left[\sigma\left(z_m, g_{z_f}\right)\right] = \sigma\left(r(y,z)y_m, \left(r(g_y,g_z)h_z/h_y\right)g_y\right)$$
$$= r(y,z)\, r(g_y,g_z)h_z/h_y\, \sigma\left(y_m, g_{y_f}\right)$$

$$= r(y,z)\, r\left(g_y, g_z\right) h_z / h_y \left(r(y_1, y_2) h_y^2\right)$$
$$= r(y,z) r(y_1, y_2) r\left(g_y, g_z\right) h_z h_y \quad [12]$$

So then the regression of trait z in males on the genetic value of their female partners, g_{z_f}, is:

$$\mathbb{E}[b_{z_m g_{z_f}}] = \frac{r(y,z) r(y_1,y_2) r(g_y,g_z) h_z h_y}{h_z^2} = r(y,z) r(y_1, y_2)\, r\left(g_y, g_z\right) h_y / h_z \quad [13]$$

If both traits are the same, $y = z$, then $r(y,z) = 1$, $r\left(g_y, g_z\right) h_y / h_z = 1$ and thus Eq. [13] reverts to Eq. [8]. Using Eq. [9] the ratio, d, of the expectation under assortment on a correlated trait, relative to the expectation under direct assortment is:

$$\mathbb{E}[d] = \frac{r(y,z) r(y_1,y_2)\, r(g_y,g_z) h_y}{r(z_1,z_2) h_z} = \frac{r(g_y,g_z) h_y}{r(y,z) h_z} \quad [14]$$

meaning that under assortment on a correlated trait the estimate from Eq. [4] can either be higher or lower than the expectation given by Eq. [8] depending upon (i) the magnitude of the genetic correlation as compared to the phenotypic correlation of z and y, and (ii) the heritability of y as compared to that of z.

Under both direct assortment on a phenotype and assortment on correlated traits, a correlation among partners at trait associated loci is expected, with Eq. [8] providing the expectation under direct assortment, and Eq. [13] providing the expectation under secondary assortment. Therefore, our approach provides an estimate of the correlation among couples at trait associated loci but cannot differentiate between direct assortment on a phenotype and assortment on a genetically correlated trait. However, our approach does differentiate between assortative mating based on selection of phenotypic characteristics and assortative mating based on shared social/environmental factors, because under only social/environmental homogamy we would not expect an association between genetic predictors of phenotype within the mixed effect model of Eq. [4] as it accounts for population stratification, by both regressing PCs from the genetic predictor, and by fitting a relationship matrix estimated from the SNP markers.

We estimated Eq. [4] in the combined set of data, and we then repeated the estimation in the 23andMe and then the UK Biobank data. The estimates gained were adjusted by the regression coefficient gained from regressing the phenotypic values onto the adjusted genetic predictors. This was done to ensure that the genetic predictor has the expected BLUP properties. We then compared our estimates from Eq. [4] to the phenotypic correlation between partners in z-scores of their phenotype.

Common SNP heritability of realized mate choice

We estimated the heritability associated with common SNPs (h^2_{SNP}) for realized mate choice of height and body mass index as:

$$\boldsymbol{y}_m = \mu_m + \mathbf{Z}\boldsymbol{\beta_m} + \boldsymbol{u}_f + \boldsymbol{e_m}, \quad [15]$$
$$\boldsymbol{y}_f = \mu_f + \mathbf{Z}\boldsymbol{\beta_f} + \boldsymbol{u}_m + \boldsymbol{e_f}$$

with notation the same as above. Eq. [15] controls for population stratification by fitting the effects of the first 20 principal components estimated within the 23andMe data before then estimating the effects $u = N(0, \mathbf{A}\sigma^2_G)$. We selected Hapmap3 common SNPs from the best-guess imputed SNP data to estimate $\mathbf{A}$ and thus σ^2_G is the variance explained by those SNPs. Eq. [15] was estimated using the GREML function in GCTA v 1.25.

The expectation of h^2_{SNP} estimated in Eq. [15] can be derived if we consider Eq. [15] as the regression

$$\boldsymbol{y}_{m_j}\boldsymbol{y}_{m_l} = \mu + \beta \boldsymbol{p}_{\boldsymbol{i}_{f_j,f_l}} + \boldsymbol{e}\,, \qquad [16]$$

with $\boldsymbol{y}_{m1}\boldsymbol{y}_{m2}$ an $N \times 1$ vector of the phenotypes of the males of the jl^{th} couple multiplied together, $\boldsymbol{p}_{\boldsymbol{i}_{f_j,f_l}}$ an $N \times 1$ vector the genetic relationship between the females of the jl^{th} couple taken from $\boldsymbol{A}$, and β is the regression coefficient.

The expectation of β can be derived by first considering the regression

$$\boldsymbol{y}_{m_j}\boldsymbol{y}_{m_l} = \mu + \beta_1 \left(\boldsymbol{y}_{f_j}\boldsymbol{y}_{f_l}\right) + e, \qquad [17]$$

with $\boldsymbol{y}_{f_j}\boldsymbol{y}_{f_l}$ an $N \times 1$ vector of the phenotypes of the females of the jl^{th} couple multiplied together.

$$\mathbb{E}[\beta_1] = \frac{\sigma\left(\boldsymbol{y}_{m_j}\boldsymbol{y}_{m_l},\ \boldsymbol{y}_{f_j}\boldsymbol{y}_{f_l}\right)}{\sigma^2{}_{\boldsymbol{y}_{f_j}\boldsymbol{y}_{f_l}}} = \sigma\left(\boldsymbol{y}_{m_j}\boldsymbol{y}_{m_l}\boldsymbol{y}_{f_j}\boldsymbol{y}_{f_l}\right), \qquad [18]$$

when all phenotypes are standardised to z-score where $y = N(0,1)$. Then:

$$\begin{aligned}\sigma\left(\boldsymbol{y}_{m_j}\boldsymbol{y}_{m_l}\boldsymbol{y}_{f_j}\boldsymbol{y}_{f_l}\right) &= \mathbb{E}\left[\boldsymbol{y}_{m_j}\boldsymbol{y}_{m_l}\boldsymbol{y}_{f_j}\boldsymbol{y}_{f_l}\right] - \mathbb{E}\left[\boldsymbol{y}_{m_j}\boldsymbol{y}_{m_l}\right]\mathbb{E}\left[\boldsymbol{y}_{f_j}\boldsymbol{y}_{f_l}\right] \\ &= \mathbb{E}\left[\boldsymbol{y}_{m_j}\boldsymbol{y}_{f_j}\right]\mathbb{E}\left[\boldsymbol{y}_{m_l}\boldsymbol{y}_{f_l}\right], \qquad [19]\end{aligned}$$

and thus we have $\mathbb{E}[\beta_1] = r\left(y_m, y_f\right)^2$.

Hence, we can then write Eq. [16] as:

$$\beta_1\boldsymbol{y}_{f_j}\boldsymbol{y}_{f_l} = \mu + \beta_2\boldsymbol{p}_{\boldsymbol{i}_{f_j,f_l}} + e, \qquad [20]$$

Thus, as the regression of $\boldsymbol{y}_{f_j}\boldsymbol{y}_{f_l}$ on $\boldsymbol{p}_{\boldsymbol{i}_{f_j,f_l}}$ provides an estimate of h^2_{SNP} [6,7] then the expectation of β is:

$$\mathbb{E}[\beta] = h^2_{SNP} r\left(y_m, y_f\right)^2 \qquad [21]$$

Under the assumption of h^2_{SNP} ~0.5 for height and ~ 0.2 BMI, and a phenotypic correlation among partners of ~0.3[8–10], our expectation in Eq. [21] is ~0.05 for height and ~0.018 for BMI. With N ~10,000 the standard error of these estimates will be ~0.04 and thus we are only interested in determining the magnitude of the point estimate rather than assessing whether the estimate is significantly greater than zero. If the estimates conform to the expectation, then this provides further evidence for a correlation at trait associated loci among couples.

Mixed linear model association analysis of realized mate choice

To identify the genomic regions associated with realized mate choice and test for a single genetic basis of the trait and mate choice, which implies direct assortment on phenotype, we conducted a mixed linear model association analysis[11] as:

$$\begin{aligned}\boldsymbol{y}_m &= \mu_m + \mathbf{X}_{\boldsymbol{f}_i}\beta_i + \boldsymbol{u}_m + \boldsymbol{e}_{\boldsymbol{m}}, \qquad [22] \\ \boldsymbol{y}_f &= \mu_f + \mathbf{X}_{\boldsymbol{m}_i}\beta_i + \boldsymbol{u}_f + \boldsymbol{e}_{\boldsymbol{f}}\end{aligned}$$

with notation the same as above, where β_i is the regression coefficient, $\mathbf{X}_{\boldsymbol{m}_i}$ and $\mathbf{X}_{\boldsymbol{f}_i}$ is a $N \times 1$ vector of genotypes for each SNP i = 1, …, k (coded as 0, 1, or 2 defining the number of reference alleles), for males and females respectively, and $\boldsymbol{u}_m$ and $\boldsymbol{u}_f$ are the polygenic effect (random effect) for males and females respectively, and $\boldsymbol{e}$ is the

residual. We selected HapMap3 common SNPs (MAF >= 0.01) from the best-guess imputed SNP data in Eq. [22] as we did for Eq. [4] and [15]. Eq. [22] was estimated using the MLMA function in GCTA v1.25.

The variance explained by a SNP for a phenotype $y = N(0,1)$, has the expectation $\mathbb{E}[h^2_{SNP_k}] = 2p(1-p)\hat{\beta}_i^2$ and thus the expectation of the phenotypic variance explained by a SNP in Eq. [22] is $\mathbb{E}[h^2_{SNP_k}] = 2p(1-p)\hat{\beta}_i^2 r(y_m, y_f)^2$. For height, genome-wide significant SNPs cumulatively account for ~16% of the phenotypic variance, and thus the expectation is that they should cumulatively account for ~1.4% of the phenotypic variance when using $\hat{\beta}_i$ from Eq. [22]. For BMI, the expectation is only ~0.6% and data sharing restrictions of 23andMe prohibited this analysis in their dataset. Therefore, in this section we only focus on height.

We used the $\hat{\beta}_i$ from Eq. [22] and gained BLUP approximations of the SNP effects using the TwinGene cohort (Supplementary Table 1) as a reference. We used these approximate BLUP SNP effects to create a genetic predictor $\hat{\boldsymbol{g}} = \sum_{i=1}^{k} x_i \hat{\beta}_i$ for each trait within an independent prediction cohort. We used the individuals from the combined cohorts that had genotypic and phenotypic data, but were not part of a spouse pair or related to the spousal pairs. We estimated principal components (PCs) of the HapMap 3 best-guess imputed SNPs in the prediction cohort. We selected the top 20 PCs to create a $N \times P$ matrix $\mathbf{Z}$, of eigenvectors across the P selected PCs. For each trait, we then regressed the estimated genetic predictor onto the eigenvectors as $\hat{\boldsymbol{g}} = \mu + \mathbf{Z}\boldsymbol{\beta} + \boldsymbol{e}$ where μ is the mean and $\boldsymbol{\beta}$ is a $P \times 1$ vector of the regression coefficients, and $\mathbf{e}$ is the residual error. We then adjusted the predictor of each trait as $\hat{\boldsymbol{g}}_p = \hat{\boldsymbol{g}} - \mathbf{Z}\hat{\boldsymbol{\beta}}$. For each trait, we then regressed the phenotypic values onto the adjusted genetic predictor as $\boldsymbol{y} = \mu + \hat{\boldsymbol{g}}_p + \boldsymbol{e}$ to determine whether phenotypic variance in the prediction set can be explained by a genetic predictor created using $\hat{\beta}_i$ from Eq. [22].

Simulation study

To support our results we conducted a simulation study using real genotype data. We used SNP data from the Kaiser Permanente study (GERA cohort, Supplementary Table 1), where we conducted identical imputation and QC steps described above to select autosomal HapMap3 loci. We selected 60,000 individuals of European ancestry.
We conducted 50 simulation replicates. In each simulation replicate, we:

1. Randomly selected 5000 SNPs that were in approximate linkage equilibrium (LD $r^2 < 0.05$).
2. Simulated a phenotype across all individuals from these loci as: $y_j = \sum_{i=1}^{k} w_{ij} b_i + e_j$, where $w_{ij} = \frac{(x_{ij} - 2p_i)}{\sqrt{2p_i(1-p_i)}}$, with b_i the allelic effect of the i^{th} causal variant and e_j the residual (environmental effect). b_i was simulated from $N(0,1)$ and e_j was simulated from $N\left(0, \left[\sigma^2_{\sum_{i=1}^{k} w_{ij} b_i} \times (1/h^2 - 1)\right]\right)$, where h^2 is the heritability of the trait which we set as 0.5.
3. Estimated the effects of each HapMap3 locus in 20,000 randomly selected individuals in a GWAS, controlling for the first 10 PCs that were estimated in the discovery sample.
4. Gained BLUP approximations of the SNP effects, using a randomly selected set of 10,000 reference individuals.
5. Randomly selected 20,000 individuals and paired them on the basis of their phenotypic values. To do this, we used the phenotypic values of the first half of the sample, and created a new linear variable that was correlated with the

phenotype at r = 0.2. We then (i) ordered the first half of the sample based on the new linear variable; (ii) ordered the second half of the sample based on their phenotypic values; (iii) paired the ordered first and second half of the samples. This creates pairs of individuals that are phenotypically assorted with a partner correlation of r = 0.2.

6. Estimated Eq. [7.1], [8.1] and [9.1] in the 10,000 pairs of individuals and compared these to our theoretical predictions given r = 0.2 among partner phenotypes and $h^2 = 0.5$ for the trait.

Second, we then repeated another 50 simulation replicates, but we did not control for population stratification in the GWAS in step 3.

Third, we then repeated another 50 simulation replicates, where we did not control for population stratification in the GWAS in step 3, and the pairing in step 5 was based upon the cumulative value of the first 10 principal components and not on the phenotype with a spousal pair correlation of r = 0.8.

Fourth, after creating the phenotype, y, in step 2 above, we created an association between y and the first 10 principal components so that the first 10 PCs explained ~20% of the phenotypic variance. The pairing in step 5 was based upon the cumulative value of the first 10 principal components and not on the phenotype with a spousal pair correlation of r = 0.8. As the first 10 PCs influence the phenotype, this results in a spousal correlation for the phenotype that is due to cultural homogamy rather than assortative mating. Therefore, this final set of simulations tests whether our approach can differentiate cultural homogamy, as captured by principal components of the genetic data, from assortative mating.

Finally, we extended our simulations to support our results under assortative mating for a correlated trait (Eq. 7.6 to 7.11), where assortment occurs for an unobserved trait that is genetically correlated to a trait that is measured. We repeated step 5 above, but we paired individuals on the basis of the 'unobserved' genetically correlated trait (genetic correlation either 0.5 or 0.75, and heritability either 0.5 and 0.8), with a partner correlation of either 0.75 or 0.5. We then re-estimated Eq. 7.1 for the focal measured trait across 50 replicates in each of 8 simulation scenarios and we compare the estimates gained to their expectation under Eq. 7.10.

Web resources

We used the following programs and documentation:

UK Biobank documentation
http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UKBiobank_genotyping_QC_documentation-web.pdf
http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/imputation_documentation_May2015.pdf
R 3.2.3 https://www.r-project.org/
GCTA http://cnsgenomics.com/software/gcta/
HapMap3 ftp://ftp.ncbi.nlm.nih.gov/hapmap/
Imputation https://github.com/CNSGenomics/impute-pipe.
HAPI-UR https://code.google.com/p/hapi-ur/
Impute2 https://mathgen.stats.ox.ac.uk/impute/impute_v2.html
Plink1.9 https://www.cog-genomics.org/plink2
BEAGLE https://faculty.washington.edu/browning/beagle/b3.html
Minimac http://genome.sph.umich.edu/wiki/Minimac

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