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Estimation and Partitioning of Heritability in Human Populations using Whole Genome Analysis Methods

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Abstract

Understanding genetic variation of complex traits in human populations has moved from the quantification of the resemblance between close relatives to the dissection of genetic variation into the contributions of individual genomic loci. But major questions remain unanswered: how much phenotypic variation is genetic, how much of the genetic variation is additive and what is the joint distribution of effect size and allele frequency at causal variants? We review and compare three whole-genome analysis methods that use mixed linear models (MLM) to estimate genetic variation, using the relationship between close or distant relatives based on pedigree or SNPs. We discuss theory, estimation procedures, bias and precision of each method and review recent advances in the dissection of additive genetic variation of complex traits in human populations that are based upon the application of MLM. Using genome wide data, SNPs account for far more of the genetic variation than the highly significant SNPs associated with a trait, but they do not account for all of the genetic variance estimated by pedigree based methods. We explain possible reasons for this 'missing' heritability.

Keywords

Quantitative traits; whole genome methods; additive variance; genomic relationship; mixed linear model; genetic architecture

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1. Introduction

The discipline of quantitative genetics, or the genetics of complex traits, aims to understand and exploit genetic variation in continuously varying traits such as height (stature), blood pressure and cognitive ability in humans. The inheritance of these traits did not seem to follow Mendel's rules but Fisher (1918) (20) showed how this could be explained by a model in which many genes and environmental factors affected the trait. Following Fisher's model, genetic variance can be estimated from phenotypic similarity between relatives (19; 25; 55; 64). However, relatives often share both genes and a similar environment and so it is difficult to completely separate the genetic variance from the variance due to the environment shared by members of a family.

Technological advances now allow individuals to be assayed for 100,000s of genetic markers (usually single nucleotide polymorphisms: SNPs) covering DNA variation in the whole genome. These SNP data can be used in two ways – to map genes that affect a complex trait and to estimate the relationship between individuals more accurately than can be done from their known pedigree. Estimating genetic relationships between individuals from SNP data allows us to estimate genetic variance from supposedly unrelated individuals without confounding by shared environment and to dissect the genetic architecture of complex traits. Genetic architecture refers to the combination of the number, frequencies and effect sizes, and mode of gene action of causal variants.

Our focus here is on the theory and application of whole-genome analysis methods aiming to estimate genetic variance in human populations and to elucidate the genetic architecture of complex traits. In all analysis methods we review, mixed linear models (MLM) form the basis of the analysis. Large genetic data sets are available for humans, allowing accurate empirical validation of new genomic analysis methods. In the discussion of the analysis methods, we focus on analyses of quantitative traits, variations of these

methods have been developed to allow application to discrete traits, these will be discussed briefly.

We start with a concise history to place quantitative genetics and whole genome methods in context. We then review and compare three different designs and methods for estimation of genetic variance and discuss precision and potential sources of bias of the estimates. The three designs are referred to as the pedigree design, the within-family design, and the population design. Briefly, to estimate heritability the pedigree design utilizes observed and expected similarity of identical (MZ) and non-identical (DZ) twin pairs, the within-family design utilizes realized variation around expected genetic similarity for full-sibling pairs, and the population design utilizes realized genetic similarity between distant relatives. There are other pedigree designs that can be used to estimate genetic variance, for example parents and offspring or extended pedigrees, but here we focus on the twin design. Similarly, there are other within-family designs that could be used, for example families with half-siblings, but in this review we focus on families with full siblings. For each method we will summarize an example study on the model trait ‘human height’. We chose to select

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examples for human height because it is highly (~80%) heritable (e.g., 65; 81), has been studied for more than century (21), and has large empirical datasets are available to demonstrate analysis methods and statistical inference. Finally, we discuss to what extent the whole genome methods have contributed to a better understanding of the genetic architecture of complex traits in human populations and how developments in analysis methods and DNA sequencing technology can contribute further.

2. A brief history of complex trait genetics in human populations

Quantitative genetic methods build on the principles of genetics described by Mendel and on statistical methods developed initially by Galton. Whereas Mendel in his experiments

with peas focused on discrete traits, Galton pioneered statistical methods to study the resemblance between relatives and introduced concepts of regression and correlation to study continuous variation in a population. In his book Hereditary Genius (1869), Galton stated that if a trait is heritable, the closer the familial relatedness of two individuals, the more these people are thought to resemble each other. There was no genetic theory to explain the observations on the quantitative traits until RA Fisher's landmark paper "The correlation between relatives on the supposition of Mendelian inheritance" was published in 1918(20). Fisher showed that the seemingly contradictory hereditary properties of discrete traits (e.g., Mendel's peas) and continuous traits (e.g., Galton's height) were consistent if quantitative trait variation is caused by a combination of many genetic loci, each with a small effect and inherited in a Mendelian manner, together with environmental effects. The article by Fisher marks the beginning of the discipline of quantitative genetics. According to Fisher's "infinitesimal model", many segregating genes, each with very small (infinitesimal) effect on the trait, lead to a normal distribution of genetic values and, provided environmental effects are normally distributed, a normal distribution of phenotypes in the population. The theory implied that genetic and non-genetic sources of variation can be estimated by quantifying the correlation between relatives, without any knowledge of specific genes affecting the trait. Further important theoretical developments on the genetics, selection and evolution of quantitative traits were made by Wright (86), Crow and Kimura (8) and many others.

With the advent of molecular genetics, quantitative genetics, like many other disciplines in biology, has become a more empirical data-driven science. New data can be used to answer old questions about the genetic architecture of complex traits. Where, for example, in the past expected values of genetic similarity were used to estimate heritability from relatives it is now possible to estimate empirically the realized genetic similarity between close or distant relatives and to estimate heritability exploiting that information.

3. The mixed linear model

A cornerstone of the theory and applications of quantitative genetics is the linear mixed model (14) of the form

$$y=f+a+e. \quad \text{Equation 1}$$

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In this model,represents the measured quantitative trait or phenotype, *f* represents known fixed non-genetic variables (such as overall mean, sex and age) and *a* and *e* represent the random additive genetic and residual effects, respectively. Residual effects refer to effects that are not accounted for by the fixed and random effects specified in the model, e.g., measurement error. The model is called mixed because it jointly accounts for and fixed(*f*) and random (*a* and *e*) effects and linear because the various terms are additive in their effect on the trait.

In matrix notation, the linear mixed model represented in Equation (1) can be generalized as:

$$\mathbf{y}=\mathbf{X}\mathbf{f}+\mathbf{Z}\mathbf{a}+\mathbf{e}, \quad \text{Equation 2}$$

where **y** is a vector containing the phenotypic values, **f** is a vector of fixed effects with incidence matrix **X**, **a** is a vector of random additive genetic effects with incidence matrix **Z**, and **e** is a vector of residuals. The elements in the incidence matrices are either zero or one, depending on whether the relevant effect is present in the individual.

Crucially, elements in the vector **a** are correlated because individuals share genes by descent from a common ancestor. We define the covariance matrix for the vector **a** of genetic effects as **G** and the covariance matrix for the vector **e** of residuals as **R**. The covariance matrix for the vector phenotypic values **y** is then:

$$\mathbf{V}=\mathbf{Z}\mathbf{G}\mathbf{Z}^{T}+\mathbf{R}, \quad \text{Equation 3}$$

where the term $\mathbf{ZGZ}^{T}$ represents the variance-covariance matrix attributed to the random genetic effects and **R** represents the variance-covariance attributed to the residual effects. If we assume that the residual effects are independent and have constant variance, **R** is a diagonal matrix $\mathbf{R} = \sigma_E^2\mathbf{I}$. However, this assumption does not hold if there are shared environmental effects between subsets of individuals such as families. Then the general form **R** must be used or an equivalent model that includes the shared environmental effect.

The statistical and computational analysis of more advanced versions of Equation (2) for large datasets was facilitated by CR Henderson (31; 32), who developed efficient algorithms to obtain estimators of the fixed effects (Best Linear Unbiased Estimator, BLUE) and predictors (Best Linear Unbiased Predictor, BLUP) of the random effects simultaneously. In animal and plant breeding, BLUP is widely used to predict the breeding value of individuals in selection programs (22), whereas in human genetics BLUP could be used to make predictions on disease susceptibility (52).

The main objective of the applications reviewed here is to estimate and partition genetic and environmental variance. When variances are known, the mixed linear model allows the simultaneous estimation of the fixed effects (BLUE) and prediction of the random effects (BLUP). In practice, the variance components are usually estimated using Restricted Maximum Likelihood (REML, 54) and the estimates are subsequently used to obtain the BLUE and BLUP estimators of the fixed and random effects.

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The genetic effect (*a*) for an individual person is the sum of all effects at causal loci in the genome and is assumed to be drawn from a specified distribution, usually a normal distribution. We define *a* as the additive genetic value of the individual and hence its variance as the additive genetic variance. The heritability, sometimes called the narrow sense heritability, is the additive genetic variance as a proportion of the phenotypic variance. Non-additive effects due to dominance and epistasis occur but the variance due to them is hard to estimate. In this review we will ignore non-additive effects except as a source of bias in the estimation of additive genetic variance.

The differences in the three methods we discuss are reflected in the genetic relationship matrix **G** used in the MLM to estimate genetic variance [Equation (3)]. In pedigree designs without genetic marker data, elements **G** of are the coefficients of expected genetic relatedness between relatives, derived from the probabilities of identity-by-descent (IBD) based on the recorded pedigree, for example in the classical twin design, 1 for monozygotic (MZ) twins, ½ for dizygotic (DZ) twins, and 0 for unrelated individuals. In the within-family design, where the pedigree is known and genetic marker data are available, elements of **G** are the realized or actual coefficients of relatedness, and these coefficients vary around ½ for full siblings and are zero for individuals from different families. In the population design where the pedigree is unknown but genetic marker data are available, **G** contains estimates of coefficients of additive genetic covariance between pairs of individuals that is captured by the markers used to construct **G**, these coefficients are scaled to vary around zero for pairs of not-knowingly related individuals. See Figure 1B for graphical representation of matrix **G** for the three designs.

In all the designs we review, the sampling variance of the estimate of heritability is a function of sample size and the variation among the elements of **G** – more variation implies smaller sampling variance (see Figure 1A for a graphical representation of the distribution of elements in matrix **G**). In extended or complex pedigrees, the coefficients in matrix **G** are $½^k$ for individuals and descendants who are *k* generations apart. Hence, sampling variation in a (human) pedigree design using close relatives is small relative to designs using more distant relatives. Bias, however, is more likely to come with analyses of close relatives and is generally of more concern than precision. To obtain tractable and comparable approximations, we have assumed that the population value of heritability is small. When the true population value is large (as it is for height for example), the actual sampling variance will be smaller than our approximation. Table 1 summarizes precision of the estimates of genetic parameters for all methods.

4. Estimating heritability from expected genetic relatedness of relatives in a pedigree design

Design

In pedigree studies, genetic parameters are estimated from phenotypic similarity between known relatives (19; 45). Twin studies are a special case of pedigree studies and have been used to estimate heritability for a wide variety of traits, including disease susceptibility, anthropometric traits, and behavioural phenotypes (6). Heritability estimates vary widely (0

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to 0.8) but for many traits heritability is estimated as moderate to high (in the range of 0.4-0.8).

In the twin design, the phenotypic resemblance [often denoted as the intra-class correlation (t)] of MZ and DZ twins is utilized to estimate the contribution of genetic and environmental variation to phenotypic variation of a trait. MZ twins share 100% of their genomic variation IBD whereas DZ twins share on average 50% of their genomic variation IBD. Hence the matrix **G** has pairwise coefficients of 1 (MZ twins), ½ (DZ twins) and 0 (individuals from different families). Assuming that the common environmental variance is equal for MZ and DZ twins, heritability can be estimated as twice the difference in phenotypic correlations for MZ and DZ twin pairs (19). In practice, maximum likelihood methods are used to estimate (co)variance components (e.g., 50) and the MLM (Equation 2) is augmented with additional random effects, for example the effect of a shared environment.

Precision

An approximate asymptotic expression for the sampling variance of the estimate of narrow sense heritability from the classical twin design assuming an equal number (m) of MZ and DZ twin pairs is $4(1/m + 1/m) = 32/N$ (Table 1) (76) with N the total number of individuals with a measured phenotype ($N = 4m$). For example, for 200 MZ and 200 DZ pairs (800 samples in total), the approximate standard error of the estimate of heritability is (32/800) = 0.2.

Limitation and potential bias

A limitation of the classical twin design (with MZ and DZ twin pairs) is that it only allows estimation of 3 variance components (including residual variation) since there are only two estimates of correlation (one for MZ pairs and one for DZ pairs) from which variance components are estimated. Consequently, if the true population variance contains more than 3 sources of variance they cannot all be estimated simultaneously in the model. For instance, if MZ twins share a more similar environment than DZ twins, this effect cannot be separated from the increased genetic similarity between MZ twins compared to DZ twins. Similarly, non-additive genetic effects will inflate the correlation for MZ twins relative to the correlation of DZ twins and therefore may lead to over estimation of the heritability. Limitations of this design lead to strong assumptions about causes of family resemblance, for example absence of non-additive genetic variance (92). Extending the classical twin design with other relatives, such as parents, spouses, and offspring of the twins, and adopted children allows a wider range of models to be fitted and allows testing of some assumptions, but not all (e.g., 38; 47; 75) and collection of large cohorts is difficult.

Example for human height

In a comparative study on human height measured in Caucasian twin cohorts from eight different countries Silventoinen et al. (65) estimated heritability

from MZ and DZ twin pair resemblance. Data were available for 30,111 complete pairs. MZ twin correlations ranged from .87 to .94 in both men and women whereas same sex DZ twin

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correlations ranged from .42 to .57 in men and from .49 to .56 in women. Opposite sex DZ twin correlations ranged from .30 to .50 but were not included in the modelling. Maximum likelihood was used to estimate contribution of genetic and environmental effects. Contribution of shared environmental factors was generally low and non-significant in most cohorts. Heritability estimates ranged from .70 to .87 in men and from .68 to .93 in women. Although substantial variation was observed in mean body height across different cohorts, the relative contribution of genetic factors was very similar between populations. Both the observed resemblance between close relatives and the inference on heritability for human height have been consistent for over a century (80). These all suggest that most phenotypic variation in human height in the population is genetic, and that most genetic variation is additive.

5. Estimation of heritability from actual genetic relatedness in a within-family design

Design—In pedigree studies (e.g., twin- and other family studies), additive genetic variance is estimated from expected genome-wide IBD sharing between relatives. These studies are based on strong assumptions about the covariance between individuals within and between families. For the estimation of additive genetic variation, these assumptions can be by- passed by utilising only within-family information if very large data sets are available.

Through Mendelian segregation, full siblings of non-inbred parents share no, one, or two copies of the alleles at each autosomal locus with probabilities ¼ ½, and ½, respectively. The total expectation of IBD in a population then becomes ½ with variance of $\frac{1}{8}$ for a single locus. The variance becomes smaller when the number of loci increases (28; 34; 59) with the expected proportion of IBD sharing being equal to the actual proportion of

IBD sharing if genetic variance were due to an infinite number of independent loci. The number of loci is however limited and genetic linkage causes dependent segregation of loci in the pedigree, maintaining variation around the expected genetic similarity for all pairs of relatives, apart from MZ twin pairs (who always share both alleles IBD) and parents and offspring (who always share one allele IBD). Using genetic marker data we can estimate precisely the amount of the genome shared by a pair of relatives and can estimate heritability by simply regressing phenotypic similarity on their genome-wide genetic similarity.

Using information from exactly two full siblings per family, the matrix **G** in this design is block-diagonal and contains off-diagonals that are estimates of the realized or actual proportion of the genome that is shared IBD (π_G) for a pair of siblings. Elements for individuals from different families are zero (Figure 1A). Estimates of locus or genome-wide IBD is obtained from genetic marker data and efficient algorithms exist to calculate probabilities of IBD, in particular for small pedigrees (e.g., 1; 15; 40).

For analysis of the full sibling design, Equation (1) is augmented by a random effect that models the covariance between full siblings that is the same for all pairs, irrespective of how much of their genome they share IBD. This effect is included because the objective of the analysis is to estimate additive genetic variation from the deviation of the expected value of IBD, which is ½ for all pairs. The covariance between sibling pairs i and j is $cov(y_i, y_j) =$

$\pi_{Gij}\sigma_A{}^2 + \sigma_A{}^2$ where is the additive genetic variance and $\sigma_C{}^2$ represents the sibling covariance not explained by additive genetic effects such as the shared family environment. Because the heritability in this design (81) is estimated solely from segregation within families without any assumptions regarding underlying factors causing between-family variance, the estimate of additive genetic variance is free of confounding by environmental differences between families.

Precision

The sampling variance of the estimate of narrow sense heritability of this design is approximately $2/(m^*\text{var}(\pi_G))$, with m the number of full sibling pairs and $\text{var}(\pi_G)$ the variance in pairwise realized genetic relationships between the siblings. Theoretical studies provide an approximation of variation in realized relationships of full sibling pairs: $\text{var}(\pi_G) \approx 1/(16L) - 1/(3L^2)$, where L is the total length of the genetic map (in Morgans) (27; 28; 33; 69). For, humans, the total map length from the 22 autosomes is $L \approx 35$ (39) and so $\text{var}((\pi_G)) \approx 0.039^2$, which is close to what has been reported empirically (60; 79; 81). Hence around the expected proportion of sharing of 50% IBD there is a standard deviation of about 4%. Because the number of recombination events per chromosome is small (24), genome wide IBD sharing between full siblings can be estimated with only few markers per chromosome. The approximate sampling variance of the estimate of heritability of the full sibling design is $2667/N$ given a number of assumptions, with N the total number of individuals with a phenotype (Table 1).

Limitation and potential bias

The limitation of the within-family design is the large sample size required to estimate parameters with sufficient precision. For the same number of people with a phenotype, this design is about 80 times less efficient than a twin design with equal number of MZ pairs as DZ pairs. For 10,000 full sibling pairs (20,000 phenotypes), the approximate standard error is 0.37. Potential bias may come from non-additive genetic effects that are not modelled because limited sample size does not allow reliable distinction between additive and non-additive effects. Both additive and non-additive genetic variance are estimated from variation around the expected coefficient of relatedness, for full siblings, this is .5 for additive genetic variance and .25 for non-additive genetic variance (19). In theory, this design allows estimation of genetic dominance deviation but because the coefficients for additive variance and dominance variance are highly correlated (theoretical value is .89 (81)), a strong sampling correlation between the estimates is expected which implies that even larger sample sizes are required to reliably distinguish non-additive from additive genetic variance.

Example for human height

In a study on human height measured in 3375 quasi independent sibling pairs, Visscher et al. (81) estimated heritability by correlating phenotypic similarity and genome wide IBD sharing between siblings. Actual genome wide IBD for full siblings ranged from 0.374 to 0.617 with a mean of 0.498 (SE 0.0005). Two models were fitted, a full model including a genome-wide additive effect, a shared environmental effect and a residual effect, and a

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reduced model excluding the genome-wide additive effect. Maximum likelihood was used to estimate contribution of genetic and environmental effects using the MLM as described previously. Heritability was estimated at .80 (95% confidence interval 0.46-0.85) with the remaining variance completely attributable to the residual effect, very similar to estimates and inference from twin- and family studies (65). The within-family design, however, facilitated a complete separation of genetic and environmental factors and can therefore be seen as an independent validation study for estimating the heritability of human height from pedigree studies. A subsequent study with over 10,000 full sibling pairs reported a similar value and also partitioned additive genetic variation into contributions from individual chromosomes (79). It concluded that additive genetic variation explained by a chromosome was proportional to the length of that chromosome.

6.Estimating heritability from population-based estimates of genetic relatedness

Design—Advances in genotyping technologies have led to arrays of single-nucleotide-polymorphisms (SNPs) that can genotype 100,000s to millions of markers in a single assay (3). These 'SNP chips' form the basis of genome-wide association studies (GWAS), which have revolutionized human genetics in the last six years (e.g., 83). Table 2 shows GWAS results for a selection of quantitative traits.

GWAS test for association between the SNP and trait and the paradigm is based upon the existence of linkage disequilibrium (LD) between ungenotyped causal variants and SNPs in the analysis. LD refers to non-random assortment of alleles at two loci and occurs in a finite, random mating population because chromosomal segments are descended from a common ancestor without any recombination. Consequently, chromosomes that carry the same allele at a locus that affects a complex trait are also likely to carry the same allele at a nearby SNP generating an association between the SNP alleles and the trait (51).

Because of the large number of tests conducted in a genome-wide survey, very stringent type-I error rates are used ($\sim 7.2 \times 10^{-8}$, (12; 23)) to avoid false positives and to ensure that reported associations are robust and replicate in other samples from the same population. This stringent threshold minimises false positives but leads to many false negatives because a causal variant with a small effect or weak LD with SNPs on the chip will not generate an association between any one SNP and the trait that is large enough to be declared significant. In practice, the effect of these false negatives has been found to be dramatic. For most traits the SNPs that are declared significant explain in total 10% or less of the genetic variance. This has been referred to as the 'missing heritability' paradox (48).

Instead of testing the effect of each SNP on the trait independently, it is possible to estimate the variance explained by fitting all the SNPs simultaneously. This is equivalent to estimating the relationship between individuals from the SNPs and using this relationship matrix to estimate the genetic variance (22; 70; 73). A method described by Yang et al. (87; 88) utilizes LD between genotyped SNPs and unknown causal variants to capture additive genetic variation underlying phenotypic variation in a random sample of unrelated individuals in the population. In this design, matrix **G** represents genetic similarity between j and j from m genotyped SNPs:

$$G_{jk}=\frac{1}{m}\sum_{i=1}^{m}\frac{(x_{ij}-2p_i)(x_{ik}-2p_i)}{2p_i(1-p_i)}, \quad \text{Equation 4}$$

where p is the frequency of the reference allele and x_i is the genotype indicator of the ith SNP (x_i = 0, 1, or 2). Estimates of genetic similarity are the genetic relationships expressed relative to a base population; in this method the study sample is the base (whereas in pedigree studies the base is the set of founders with no recorded or inferred relationships to older individuals). In the equation above, the average similarity is zero if the allele frequencies (p) are estimated from the sample, because the expected value of x is $2p$. This is also the matrix that is used for principal component analysis to infer population structure from SNP data (57).

The basic idea behind this method is to estimate additive genetic variance by including all the SNPs in the model without focussing on individual SNPs. In other words, it is an estimation rather than a hypothesis testing paradigm. Variance explained by causal variants that are in LD with genotyped SNPs but whose effect sizes are too small to reach genome-wide significance in conventional GWAS will be included in the heritability estimate derived through this method.

Yang et al. (87) showed that estimates of additive genetic variation using this method directly address the perceived problem of 'missing heritability' (48; 49). Estimates of additive genetic variation quantifies how much variation is captured by all SNPs simultaneously, and therefore how much variation would be explained by GWAS when the sample size is so large that all variants that are associated would be statistically significant (82; 87; 88).

Precision

As mentioned above, sampling variance increases with decreasing variation among the coefficients of **G**, assuming all else equal. With expected coefficients being $½^k$ (for k^{th} degree relatives) the population design with only distant relatives yields only little variation. However, where **G** in the pedigree design is block diagonal with coefficients of expected or realized IBD for within family pairs and zeros for all other elements representing pairs of unrelated individuals, **G** in the population design is filled with estimates for all pairs of individuals. The number of pairs in the population design is (N^2 -N)/2 which is a multiple of the number of pairs in the pedigree design (= ½N for pairs of twins). The precision in the population design comes from the very precise estimate of genetic similarity and the large number of pairwise comparisons in the sample.

Theory borrowed from linkage analysis of quantitative traits (63; 78) predicts that the sampling variance of the estimate of heritability from the mixed model analysis is approximately 100,000/N^2 (Table 1), hence a standard error of 315/N. We validated this by simulations using GWAS data of the Atherosclerosis Risk in Communities Study (ARIC) cohort (58; 91), the simulation results are provided in the online material.

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Limitation and potential bias

A limitation of this design is that genetic variance contributed by causal variants that are not in sufficient LD with the genotyped SNPs will not be included in the heritability estimate. If LD between the genotyped SNPs and the causal variants is incomplete, the genetic similarity between individuals *j* and *k* at the causal variants will be different from the genetic similarity between those individuals estimated from the genotyped SNPs (85). Consequently, genetic variance from 'untagged' causal variants is not accounted for by the genetic similarity calculated from genotyped SNPs. This is where the matrix **G** differs from the previous applications. In the pedigree and within-family designs, the coefficients of relationships are based upon IBD, and blind to allele frequencies of casual variants (if DNA segments in a pair of individuals are IBD then any variant in that segment, common or rare, will be shared). In contrast, the population-based estimate of SNP sharing relies on LD and is sensitive to allele frequencies. In the extreme case that all causal variants in the genome are at low allele frequency in the population, and therefore not in LD with common variants (85), the pedigree and within-family design would estimate total heritability whereas the SNP-based estimates would be zero (and GWAS would not work either). Recently, Speed et al. (67) proposed a method in which matrix **G** is modified according to local LD. In this method, the contribution of the SNPs to the estimate of genetic similarity between a pair of individuals is weighted according to the LD with their neighbouring SNPs. Estimating heritability using LD adjusted genetic similarity reduces potential bias and increases the precision of the heritability estimate. Bias may come from ungenotyped causal variants in regions of high or low LD. Contributions to the estimated heritability of causal variants that are in high LD with the genotyped variants may be overestimated whereas contributions of causal variants in low LD with the genotyped variants may be underestimated. This bias can be avoided by adjusting for incomplete LD between the causal variants and the genotyped SNPs, but only when the MAF spectrum of the causal variants is known (which is generally not the case) (87).

Bias may also come from shared environment that is not modelled in this design. If individuals who share SNP genotypes more often than the average, also tend to share a common environment, then the heritability explained by the SNPs will be over-estimated. This would be expected if closely related people were included in the sample. However, if closely related people are avoided this source of bias should be small because, among "unrelated" people, genomic similarity is poorly correlated with pedigree relationship and it is only the pedigree relationship that might be correlated with environmental similarity.

Another possible source of bias is if the population consists of sub-populations who differ both genetically and environmentally. This bias is usually avoided by testing for

population structure and eliminating it from the data or correcting for it in the analysis (e.g., by including the first few principal components of the relationship matrix as fixed effects in the MLM). Biases attributable to population structure and genotyping artefacts such as plate and batch effects are more likely to be a problem in case-control rather than quantitative trait analyses, because confounding with the binary phenotype is not uncommon (42; 43).

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Example for human height

Yang et al. (87) estimated the heritability of human height from 294,831 SNPs genotyped on 3,925 'unrelated' individuals. The data were fitted in an MLM and REML was used to estimate the variance explained by the SNPs. All the SNPs were considered simultaneously in the model and the proportion of phenotypic variance explained by the SNPs was .45 (s.e. .08) with remaining variance due to non-familial environmental factors and possible measurement error. This estimate of genetic variance forms the lower boundary of total narrow sense heritability since only genetic variation due to causal variants that are in sufficient LD with the genotyped SNPs is included in the estimate. Using simulated data, the authors show that incomplete LD between the causal variants and the genotyped SNPs can explain all of the remaining heritability. This study showed that the so-called 'missing heritability' (48) for height is not missing, but hidden. The finding that common variants, together, explain a substantial proportion of the heritability proves that GWAS to date have been underpowered to detect individual SNPs with small effects. Results from this study indicate that much larger sample sizes are required to detect those individual SNP effects in GWAS. The observed strong relationship between experimental sample size of GWAS and the number of significant loci detected (77) is consistent with that conclusion.

7. A summary and comparison of the methods

We have reviewed three different methods to estimate heritability from genetic similarity between pairs of relatives. The methods differ in the parameters estimated. The use of the twin (pedigree design) and full sibling (within-family design) data leads to an estimate of total heritability whereas the use of SNPs to construct a relationship matrix (population design) estimates the genetic variance (and therefore heritability) explained by the SNPs. The proportion of genetic variance explained by the SNPs depends on the structure of the data. In a population of 'unrelated' individuals this proportion depends on the LD between SNPs and causal variants. Although individuals are not known to be related, they could share distant ancestors and therefore some chromosome segments that are IBD. Thus the estimate of genetic variance from all SNPs can be considered as driven by LD or by distant realized relationships: the two descriptions are equivalent. In fact, the variance of the SNP-based relationship is equal to the LD averaged over all pairs of SNPs. The within-family design, which uses variation in realized relationship between pairs of SNPs, can be described as using LD within a family, generated by the inheritance of large chromosome segments from parents to offspring. Consequently, this design estimates the full heritability because in this design the SNPs track all causal variants.

Heritability estimates derived through these designs differ in precision and possible bias. Generally, close relatives give more precision but potentially more bias whereas distant relatives give less precision and less bias. Bias in analyses of close relatives may come from environmental variation that is confounded with additive genetic variation within families, or in case of siblings, confounding with non-additive genetic effects. Precision in parameter estimates depends on the total number of individuals with a phenotype and the variation in relationship (pedigree, realized or population-based).

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The heritability estimated in the pedigree design has generally small sampling variance as much variation exists among the coefficients of relatedness. In this design,

however, potential bias is of greater concern and generally has larger impact on the estimate than precision. The heritability estimated from variation around the expected genetic similarity of full-siblings in a within-family design is free of assumptions about variation between families, but relative to the classical twin design, the sampling variance is large. Inflation of the estimate of narrow-sense heritability by non-additive genetic variation is a concern in both the pedigree and the within-family design. In the pedigree design this is caused by confounding with environmental factors and in the within-family design by a strong correlation of sampling variance between additive and non-additive genetic variation, and thus the power to estimate non-additive genetic variance is insufficient. Heritability estimated in the population design is unbiased: distant relatives are unlikely to share variation due to environmental factors or variation due to non-additive effects. Sampling variance is relatively small due to large number of pairwise comparisons that can be achieved with large sample sizes available to date. The population design is as efficient as a twin design when 10,000s of individuals with phenotypic and SNP data are available. Estimating heritability from genetic similarity of distant relatives requires smaller sample sizes compared to the within-family design to obtain similar precision. However, a much larger number of genetic markers are required to accurately estimate the genetic similarity of distant relatives in the population design. SNP chips available to date are adequately designed to ensure sufficient LD between genotyped variants and ungenotyped causal variants. Hence heritability can be estimated from distant relatives without much error, especially when heritability is high.

8. Genetic architecture

Numerous pedigree studies have revealed moderate to large heritability estimates for a wide variety of complex traits in human populations. After the completion of the Human

Genome Project, considerable success of GWAS was anticipated. After six years of GWAS discovery, however, much of the genetic variance estimated from pedigree studies has not been accounted for by the genetic variants discovered from GWAS. For complex traits, typically less than 10% of the genetic variation is explained by SNPs, although there are exceptions: for age-related-macular degeneration, an eye disease, approximately 50% of genetic variation has been accounted for by only 5 loci (29) and for Crohn's Disease and ulcerative colitis, two inflammatory bowel diseases, very large experimental sample sizes (~15,000 cases) have led to the discovery of hundreds of loci by GWAS which together with known less common variants explain about 20% of genetic variation (37).

Several explanations have been raised to answer the ‘case of the missing heritability’ (48). Possible explanations are that (i) pedigree studies have overestimated the heritability by e.g., bias due to non-additive and/or environmental effects, (ii) causal variants individually explain such a tiny amount of variation that their effects do not reach statistical significance in GWAS to date and/or (iii) causal variants are not in sufficient LD with the genotyped SNPs and therefore their effects are not fully captured by the genotyped SNPs in GWAS.

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Quantifying the difference between (ii) and (iii) is informative with respect to the allelic spectrum of causal variants, that is, the frequency of risk alleles in the population. Causal variants that are in low frequency in the population are not in high LD with genotyped SNPs. Consequently, variation caused by variants that are not in sufficient LD with SNPs cannot be captured and therefore remains undetected in GWAS.

Whole genome methods utilizing expected or realized genetic relationship between individuals have given us many clues about the genetic variation underlying complex traits. A short recapitulation for human height, pedigree studies using data from MZ and DZ twin pairs have repeatedly reported heritability estimates around 80% (e.g., 46; 65), an estimate confirmed by Visscher et al. (79; 81) utilizing empirical genome-wide IBD sharing of full

sibling pairs. Using realized genetic similarity between unrelated individuals, Yang et al (87; 91) have demonstrated that 45-55% of the phenotypic variance can be explained by common SNPs when taking the individual SNP effects together. The largest GWAS on height to date (41) has identified 180 genetic loci that together explain ~10% of the phenotypic variation. Together, these results show that for human height the genetic variance is additive and involves many loci of small effect. The difference between ~50% and 10% is due to SNP associations with height that are too small to reach the stringent significance level used in GWAS. Individual loci do not explain much of the genetic variation each because otherwise these effects would have been identified by GWAS to date. The variance unaccounted for (80%-50% = 30%) is likely due to the segregation of causal variants at low frequency. Bias due to non-additive genetic effects or environmental variation is unlikely for human height given the similar heritability estimates derived from different study designs and additive genetic models that fit the data well in all three study designs.

We summarise the proportion of variance explained from pedigree analyses, genome-wide significant SNPs and population based analyses using estimated pairwise genomic relationships for a selection of quantitative traits in Table 2. Traits other than height, such as body-mass-index and cognitive ability, follow the same trend, i.e., the estimates of heritability from pedigree designs is large, genome-wide significant loci explain zero to a small proportion of phenotypic variation but using genomic relationships capture one third to two thirds of pedigree heritability. For height, heritability estimates derived from pedigree studies have been confirmed by other study designs and biased estimates are unlikely. For other traits, however, inflated estimates from pedigree studies are a possible cause of part of the missing heritability (92).

9. Discussion

One of the aims of quantitative genetics has been to quantify the amount of variation in complex traits that is due to genetic variation and the amount due to environmental variation. This is difficult in humans because people who share genes also tend to share the similar environments. Traditional designs, such as the pedigree designs, at least partly overcome this problem. The availability of genome-wide SNP data has allowed the use of new designs, such as within-family variation in relationship, through which have overcome the confounding of genes and environment. Within-family studies have tended to confirm

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traditional estimates for height but their low power means that the standard errors on estimated heritability have been high. Consequently, this design was unfeasible for many traits for which sample sizes were too small. Designs based on a population sample of unrelated people can also overcome the confounding of genes and environment but only estimate the proportion of genetic variance explained by the SNPs which is typically 33-66% of the traditional estimate.

Population designs to estimate genetic variation in a two-stage procedure, by first estimating relatedness from genetic markers and then estimate heritability by contrasting genetic similarity to phenotypic similarity, are not new. Ritland (61) proposed this for studies in natural populations where obtaining pedigree information may be impossible. The idea was to detect IBD between close relatives (e.g., full siblings and half siblings) from a small number of markers and then correlate estimated relatedness with phenotypic covariance. Conceptually this approach is more similar to pedigree design, whereby the pedigree is inferred from IBD sharing of large chromosome segments, than the within-family or population design we have discussed. However, there is no fixed point at which an inferred pedigree design becomes a population design that relies on LD: increasing marker density allows the estimation of more distant relationships at the expense of a potential loss of information due to imperfect LD between the markers used to infer relatedness and causal variants for the trait.

The new (population based) whole genome methods have shown that large numbers of genetic variants with small effect explain a substantial proportion of the heritability for complex traits. These common variants account for the difference between the heritability explained by GWAS hits and the heritability estimated from all the SNPs in the population design (see Table 2). From this we can conclude that large sample sizes will lead to detection of more individually significant SNPs. Augmenting SNP genotypes with genome sequence data should help to find the remaining missing heritability, that is, the difference between the heritability estimates from pedigree studies and the heritability estimated from SNPs. In particular, sequence data should be more powerful where causal variants are rare and hence not in high LD with any SNPs on the SNP chip. However, each of these rare variants are expected to explain a small amount of variance, simply because they are rare.

Another goal of research on the genetics of complex traits is to identify individual causal variants and to elucidate their biological mechanisms. GWAS have identified many genes and even some causal sites within these genes causing variation in particular traits (e.g., 13; 26; 35).

Further research will no doubt identify more causal variants. However, since the variance explained by many individual causal variants is so small, it may never be possible to identify all of them. A slightly different aim is to describe the properties of causal variants as a class rather than to identify them all individually. For example, we would like to know the joint distribution of allelic effects and allele frequencies and to infer this relationship not all causal variants need to be known. This joint distribution is of interest because it reflects the evolutionary processes under complex trait variation, including natural selection, the distribution of effect sizes of new mutations and past and present population size.

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Moreover, understanding the allelic spectrum of causal variants allows us to provide realistic predictions of the number of genetic variants that are present in the genome and their effect sizes and hence the sample size that is required to detect the variants. That is, knowledge on the joint distribution of effect size and allele frequency leads to useful information on experimental designs to further dissect complex trait variation. The whole genome methods reviewed here will bring us closer to this goal and will help in the identification of individual causal variants.

Sidebar

Estimating heritability for disease

Categorical traits (e.g., disease traits) are sometimes inherited in a simple Mendelian manner but often they behave like continuous traits in that they are influenced by many genes and environmental factors. Unlike quantitative traits, the phenotypic variance of a disease trait depends on the population mean, i.e., the disease prevalence. To facilitate comparison of estimates across studies, heritability of disease is generally estimated for the liability underlying the disease (44). The disease status (measured on a 0/1 scale) is superimposed onto a distribution of liability in which a threshold of liability for disease is determined that bisects the distribution to reflect the proportion of affected and unaffected individuals in the population (18).

Estimates derived from linear mixed model analysis can be transformed to a liability scale by adjusting both for scale and for ascertainment of the data. Estimation methods for heritability of disease have recently been reviewed by Tenesa and Haley (71) and a detailed description of estimating heritability for disease traits in a population design is provided by Lee et al. (43).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary points

1. Expected or realized genetic similarity between relatives (either close or distant) can be used to estimate heritability of complex traits in human populations. Estimates based on close relatives generally yield high precision but may come with bias due to strong assumptions that are violated. Estimates based on distant relatives generally have less bias but lower precision.
2. Whole genome methods increase our understanding of genetic variation underlying complex traits in humans. These methods have shown that a substantial proportion of genetic variation is additive and that 1/3 to 2/3 of additive genetic variation is captured by common SNPs.
3. Whole genome methods have shown that the postulated genetic architectures involving only rare variants are not consistent with the data for many complex traits (see also Table 2).

Future issues

1. For many complex traits most of the heritability is hidden rather than missing. Empirical data analyses and simulation studies suggest that future gene-mapping endeavours should focus on both common and rare variants.
2. Whole genome methods utilizing realized genetic relationship as reviewed here could be exploited for the use of whole genome sequencing data to unravel the combined effects of rare variants underlying complex traits.
3. GWAS data that are widely available to date allow investigation of genetic pleiotropy between different traits (and/or diseases). Where the pedigree design required the two correlated traits to be measured in the same individuals, the population design allows estimation of genetic correlation also when the two traits measured in different individuals.

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Key terms

1. Complex trait

Traits for which variation is a result of multiple genes and multiple environmental factors (quantitative and categorical).

Genetic relationship

The expected or actual proportion of DNA variants identical by descent (pedigree or within-family design) or by state (population design).

3. Genetic architecture

Combination of the number of genetic variants, allelic frequencies and effect sizes variants of affecting a trait and their mode of gene action.

4. Whole-genome analysis methods

Methods that utilize information from the whole genome to estimate genetic parameters.

5. Mixed linear model (MLM)

A linear model that jointly accounts for fixed and random effects.

6. Breeding value

The sum of the additive effects of an individual's genes.

7. Identity-by-descent

Situation in which two alleles are inherited from a common ancestor.

8. Intra-class correlation

The correlation between measures within a group.

9. Single-nucleotide-polymorphisms (SNPs)

A DNA sequence variation occurring from a single nucleotide (A, C, T, or G)

10. Genome Wide Association Study (GWAS)

A study design in which hundreds of thousands of genetic variants in the genome (usually SNPs) are test for association with the trait.

11. Linkage-disequilibrium (LD)

Non-random assortment of alleles at two loci

12. Type-1 error

Rejection of the null hypothesis when the null hypothesis is true.

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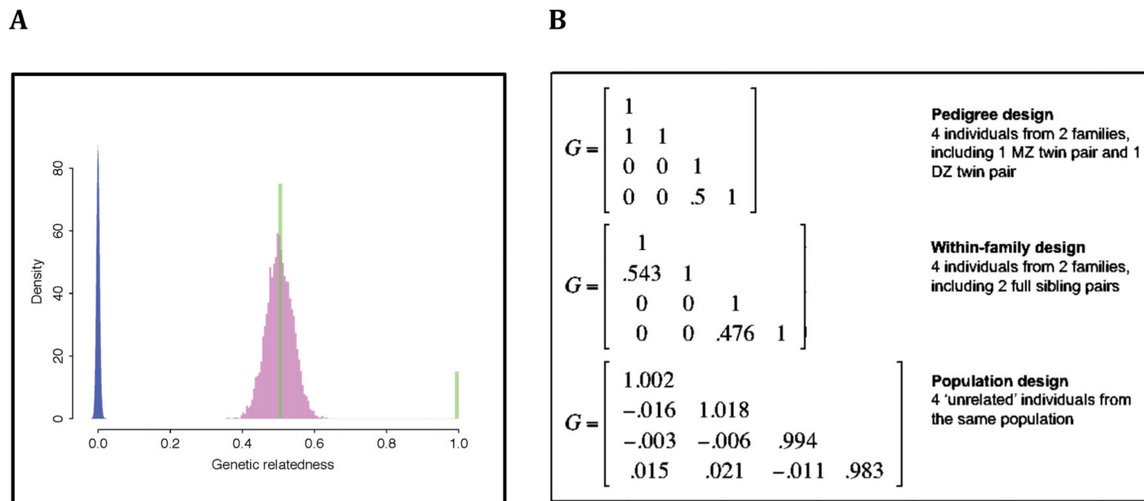

Figure 1.

A. Distributions of the off-diagonal elements for the genetic relationship matrix **G** in the pedigree design using MZ and DZ twin pairs (green), the within-family design using full sibling pairs (pink), and the population using 'unrelated' individuals (blue). **B.** Examples of the genetic relationship matrix **G** for 4 individuals in the pedigree design (upper matrix), the within-family design(middle matrix), and the population design (lower matrix).

Notes Figure 1:

A. The distribution of off-diagonal elements for the genetic relationship matrix **G** for the pedigree design represents the expected proportion of genome wide IBD for MZ (=1) and DZ (= 0.5) twin pairs. The distribution of actual proportion of the genome that is shared IBD within full sibling pairs in the within the family design varies around 0.5 whereas the distribution of the actual proportion of the genome that is shared IBS for individuals not knowingly related to each other varies around zero. IBD and IBS estimates for the within-family design and the population design, respectively, are derived from data from the Framingham Heart Study (FHS).

Mean IBD was estimated at .5028 with a standard deviation of 0.0368 for full siblings. Mean IBS was estimated at −.0002 with a standard deviation of 0.0046 for pairs of unrelated individuals.

Only full sibling pairs were selected for the IBD estimation in the within-family design while for the IBS estimation in the population design only one sibling per family was selected and one member of each of the remaining pairs of individuals that had an estimated genetic relationship of more than 0.025 was removed.

Estimates of IBS are relative to an arbitrary base population with an average relationship between all pairs of individuals of zero. In this analysis, the sample under study is used as the base population, consequently the average relationship between all pairs of individuals is zero and the average relationship of an individual with him- or herself is one. **B.** Diagonal elements in matrix **G** represent an individual's estimated genetic relatedness with him- or herself. Off-diagonal elements in matrix **G** represent genetic similarity between individuals. Note that matrix **G** is symmetrical and that for clarity only elements in the lower triangular are provided.

In the pedigree design, off-diagonal elements represent expected genome wide IBD sharing for 4 individuals (one MZ pair and one DZ pair) from two independent families in which parents are assumed to be unrelated.

In the within-family design, the off-diagonal elements represent actual variation around the expected genome wide IBD sharing [$E(\hat{\pi}) = 0.5 = 0.5$] for two independent full sibling pairs.

In the population design, the off-diagonal elements represent actual genome wide IBS for 6 pairs of not knowingly related individuals. An individual's genetic relatednes with him- or herself (diagonal elements) is an estimate of $1+F$, with F being the inbreeding coefficient relative to the base population.

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Table 1

Precision of estimates of heritability from whole genome methods

Design	Sampling variance of estimate
Pedigree design including an equal number of MZ and DZ twin pairs	$\text{var}(\hat{h}^2) \approx 4\left(\frac{1}{m}+\frac{1}{m}\right)=4\left(\frac{2}{m}=\frac{8}{m}=\frac{32}{N}\right)$
Within-family design including full sibling pairs	$\text{var}(\hat{h}^2) \approx \frac{2}{m * \text{var}(\hat{\pi})}$ $\text{var}(\hat{h}^2) \approx 4\left(\frac{1}{m}+\frac{1}{m}\right)=4\left(\frac{2}{m}=\frac{8}{m}=\frac{32}{N}\right)$(refs. 60; 79; 81) $\text{var}\hat{h}^2 \approx 4\left(\frac{1}{m}+\frac{1}{m}\right)=4\left(\frac{2}{m}=\frac{8}{m}=\frac{32}{N}\right)$
Population design including not knowingly related individuals	$\text{var}(\hat{h}^2) \approx 4\left(\frac{1}{m}+\frac{1}{m}\right)=4\left(\frac{2}{m}=\frac{8}{m}=\frac{32}{N}\right)$ (refs. 63; 78) $\text{var}(\hat{h}^2) \approx 4\left(\frac{1}{m}+\frac{1}{m}\right)=4\left(\frac{2}{m}=\frac{8}{m}=\frac{32}{N}\right)$ (ref. 22) $\text{var}(\hat{h}2) = 1 \times 10^5 / N^2$

Table notes: MZ = monozygotic; DZ = dizygotic; h^2 = heritability estimate; var = variance; m = number of MZ, DZ, or full sibling pairs; N = number individuals; n = number of pairwise comparisons [$n = N(N - 1)/2$, when N is large $n \approx N^2/2$], $var\left(\hat{h}^2\right) \approx 4\left(\frac{1}{m}+\frac{1}{m}\right)=4\left(\frac{2}{m}=\frac{8}{m}=\frac{32}{N}\right)$ estimated proportion of genome-wide IBD; L = total map length over all autosomes (L=35) (39), N_e = effective population size and equals 10,000.

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Table 2

Proportion of variance explained by genetic factors for a number of selected quantitative traits

Trait	h^2 pedigree design	h^2 GWAS hits	h^2 population design
Height	0.80 (65)	0.10 (41; 90)	0.45 (87; 91)
Body mass index	0.45 - 0.80 (62)	0.02 (68)	0.17 (91)
von Willebrand factor	0.66 - 0.75 (10; 53)	0.13 (66)	0.25 (91)
Bone mineral density	0.61 (2)	0.06 (16)	0.16 (89)
General intelligence			
-Children (~12 years)	0.40 - 0.60 (4; 30)	0 (5)	0.22 - 0.64 (5)
-Adults	0.80 (30; 56)	0 (7)	0.40 - 0.50 (9)
Red blood cell phenotypes			
-Haemoglobin concentration	0.84 (17)	0.02 (72)	
-Sodium	0.50 (84)	0.02 (89)	0.16 (89)
Personality			
-Neuroticism	0.13 - 0.58 (36)	0 (11)	0.06 (74)
-Extraversion	0.34 - 0.57 (36)	0 (11)	0.12 (74)

Table notes: heritability in the pedigree design is estimated by comparing expected and observed MZ and DZ twin pair resemblance; heritability from GWAS hits represents the total variation explained by all the SNPs that individually reached genome-wide significance in GWAS; heritability in the population design is estimated from the SNP-derived genetic similarity between pairs of not knowingly related individuals.