FUNDAMENTAL CONCEPTS IN GENETICS

Heritability in the genomics era — concepts and misconceptions

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Abstract | Heritability allows a comparison of the relative importance of genes and environment to the variation of traits within and across populations. The concept of heritability and its definition as an estimable, dimensionless population parameter was introduced by Sewall Wright and Ronald Fisher nearly a century ago. Despite continuous misunderstandings and controversies over its use and application, heritability remains key to the response to selection in evolutionary biology and agriculture, and to the prediction of disease risk in medicine. Recent reports of substantial heritability for gene expression and new estimation methods using marker data highlight the relevance of heritability in the genomics era.

A central question in biology is whether observed variation in a particular trait is due to environmental factors or biological factors — sometimes expressed as the nature–nurture debate. Heritability is a concept which summarizes how heritable a phenotype of interest is, in particular with reference to the resemblance of offspring and parents. Heritability is both a word that is used in common speech and a technical term in genetics, thereby causing confusion[1]. In common language it loosely means 'the quality of being heritable', but as a technical term in genetics it is a population parameter with specific definitions (see BOX 1). In this Review we address the multiple technical definitions of heritability, discuss commonly held misconceptions (BOX 2) and show the manifold applications of heritability in evolutionary biology, medicine and agriculture. A brief historical background to the origin of the term heritability is given in BOX 3.

Estimation of heritability in populations depends on the partitioning of observed variation into unobserved genetic and environmental factors. Statistical methodology to partition variation and to estimate heritability is well developed and has more or less converged across species and disciplines[2]. However, strong and often untestable assumptions about the analysis model remain, which make statistical inference difficult and sometimes controversial, in particular for behavioural phenotypes in humans. We show the circumstances under which heritability can change, and conclude with a section about the usefulness of heritability in the genomics era. We argue that in this era the importance of heritability remains central and that the new opportunities it provides (for example, in measuring gene expression, methylation and metabolites) will enable the dissection of phenotypic variation and the interplay between genes and environment to be unravelled more clearly.

Definitions

Heritability is formally defined as a ratio of variances, specifically as the proportion of total variance in a population for a particular measurement, taken at a particular time or age, that is attributable to variation in additive genetic or total genetic values — termed the narrow-sense heritability (or just heritability, h^2) and the broad-sense heritability (H^2), respectively (BOX 1). It measures with a single number the fraction of variation between individuals in a population that is due to their genotypes. Because individuals transmit only one copy of each gene to their offspring, most relatives share only single or no copies that are identical by descent (IBD) (the most important exceptions are identical twins and full siblings (sibs)), and dominance and other non-additive genetic effects that are based on sharing two copies do not contribute to their phenotypic resemblance. This is why the selection response and correlation of most relatives depend on h^2 and not H^2, and why h^2 is the usual parameter.

Because heritability is a ratio of variances, both the numerator and denominator need close scrutiny. The denominator contains the total observed variation, usually excluding variation that is due to known fixed factors and covariates such as sex, age and cohort. The numerator of h^2 contains variation that is due to additive genetic values in the population. These values, called

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'breeding values' in the literature[3], are defined as the sum of the average effects of parents' genes that give rise to the mean genotypic value of their progeny. Breeding values can be measured even when the average effects of individual genes cannot. For example, the breeding value for milk production of a dairy sire can be estimated with great accuracy, even though milk production is a female sex-limited trait, because he can have many thousands of milking daughters by artificial insemination. His breeding value is twice the deviation from the population average of the mean milk yield of his progeny.

A consequence of the definition of heritability is that it depends on the population, because both the variation in additive and non-additive genetic factors, and the environmental variance, are population specific. Genetic variance depends on segregation in a population of the alleles that influence the trait, the allele frequencies, the effect sizes of the variants and the mode of gene actions. All these variables can differ across populations. Similarly, environmental variance can vary across populations. Therefore, the heritability in one population does not, in theory, predict the heritability of the same trait in another population. We say 'in theory' because in practice, heritabilities of similar traits are often remarkably similar in other populations of the same species, or even across species. For example, heritabilities are higher for morphometric traits than for fitness traits; the former are often higher in more favourable environments (FIG. 1). Heritability can also differ between sexes, and heritability of the same trait can differ early and late in life. For example, the heritabilities of weaning weight and market weight in beef cattle are approximately 0.3 and 0.4, respectively[4].

Estimation of heritability

Heritabilities and the variances that contribute to them are parameters of a population. In reality, the only understanding that we have about these parameters are estimates, although often the distinction between parameter and estimate is not made, which has led to some confusion[5]. Heritability can be estimated from empirical data of the observed and expected resemblance between relatives. The expected resemblance between relatives depends on assumptions regarding its underlying environmental and genetic causes. Sometimes these assumptions are straightforward (as in the dairy sire example above), but sometimes they are not (see BOX 4).

When selection is applied, the ratio of the observed selection response (R, the change in the mean phenotype between generations) to the observed selection differential (S, the difference in mean phenotype between the parents selected for breeding and the overall mean in their generation) can be used to estimate heritability. This relationship is summarized in the breeder's equation[2], $R = h^2S$. For an experiment that runs over several generations, the realized heritability has been defined as the ratio, or regression, of cumulative selection response (the sum of all responses) to cumulative selection differential (the sum of all selection differentials)[3].

Traditionally, heritability was estimated from simple and often balanced designs, such as simple functions of the regression of offspring on parental phenotypes, the correlation of full or half sibs, and the difference in the correlation of monozygotic (MZ) and dizygotic (DZ) twin pairs[3]. In FIG. 2 an example is given of the

Box 1 | Heritability and the partitioning of total variance

Population parameters

Observed phenotypes (P) of a trait of interest can be partitioned, according to biologically plausible nature–nurture models, into a statistical model representing the contribution of the unobserved genotype (G) and unobserved environmental factors (E):

$$\text{Phenotype (P)} = \text{Genotype (G)} + \text{Environment (E)} \quad (1)$$

The variance of the observable phenotypes (σ^2_P) can be expressed as a sum of unobserved underlying variances (σ^2_G and σ^2_E):

$$\sigma^2_P = \sigma^2_G + \sigma^2_E \quad (2)$$

Heritability is defined as a ratio of variances, by expressing the proportion of the phenotypic variance that can be attributed to variance of genotypic values:

$$\text{Heritability (broad sense)} = H^2 = \frac{\sigma^2_G}{\sigma^2_P}$$

The genetic variance can be partitioned into the variance of additive genetic effects (breeding values; σ^2_A), of dominance (interactions between alleles at the same locus) genetic effects (σ^2_D), and of epistatic (interactions between alleles at different loci) genetic effects (σ^2_I):

$$\sigma^2_G = \sigma^2_A + \sigma^2_D + \sigma^2_I$$

$$\text{and heritability (narrow or strict sense)} = h^2 = \frac{\sigma^2_A}{\sigma^2_P}$$

In general, σ^2_E can be broken down into any number of identifiable, but random, contributing factors that can be specific to the phenotype. Examples include the environmental variance that is common to specified groups, for example, siblings and litters (σ^2_{CE}), and the non-genetic variance that is common to repeated measures of individuals (σ^2_{PE}).

We define the remainder of the environmental variance, which cannot be attributed to other factors, as the environmental residual variance, which includes individual stochastic error variance and measurement error (σ^2_{RE}):

$$\sigma^2_E = \sigma^2_{CE} + \sigma^2_{PE} + \sigma^2_{RE}$$

In the simplest partitioning, no specific factors that contribute to σ^2_E are identified and $\sigma^2_{RE} = \sigma^2_E$. Both the genetic and environmental variances can be partitioned further for a trait such as birth weight of the offspring to include genetic and environmental maternal effects that are attributable to the mother[75].

The partitioning of the phenotypic variance (equation 2) assumes the absence of genotype by environment covariance ($\sigma_{G,E}$). Examples leading to a positive covariance are parents with a high intelligence quotient (IQ) providing an IQ-stimulating environment for their children, and dairy cattle being fed according to production. A further term that is ignored in equations 1 and 2 is the interaction between genotype and environment (G*E), when the effect of the genotype depends on the environment. The most studied, yet still controversial, example of G*E in humans is the interaction between stressful life events (the environment) and the length polymorphism of the serotonin transporter gene (the genotype) and their effects on major depression (the phenotype)[76]. If G*E exists, P = G + E + G*E, so a more complete partitioning of phenotypic variance is:

$$\sigma^2_P = \sigma^2_G + \sigma^2_E + 2\sigma_{G,E} + \sigma^2_{G*E}$$

Both G and E covariation and G*E interaction are often ignored, usually because they cannot be estimated. If either is present, ignoring the former will inflate estimates of σ^2_G and ignoring the latter will inflate estimates of σ^2_E (REF. 3).

Box 2 | **Misconceptions regarding heritability**

Heritability is the proportion of a phenotype that is passed on to the next generation
This is a commonly held misconception; phenotypes are not passed on but genes are. The definition of narrow-sense heritability (BOX 1) contains the variation in additive genetic effects (A). Half of these effects are passed on from each parent, but the actual half is unique to each offspring.

High heritability implies genetic determination
A high heritability means that most of the variation that is observed in the present population is caused by variation in genotypes. It means that, in the current population, the phenotype of an individual is a good predictor of the genotype. However, it does not mean that the phenotype is determined once we know the genotype, because the environment can change or can be manipulated to alter the phenotype. For example, the well-documented secular rise in height in many human populations[77,78] is not at odds with reported heritabilities of about 0.8, but is likely to reflect changes in the environment resulting from improved nutrition and medical care. Genetic determination is sometimes implied when making predictions about the phenotype of offspring given the parental phenotypes for traits with a high heritability. What this ignores is the segregation of genes within families: in a non-inbred population, half of the additive genetic variance is between families and half is within families. This implies that for a trait such as adult height in human populations, with a heritability of 0.8 and a standard deviation of approximately 7 cm in the population, the standard deviation of height in adult offspring around the mean value of the parents is 5.4 cm (=√[7^2 (1 – ½*0.8)]), which is not much smaller than the standard deviation in the entire population. Hence, tall parents have on average tall children, but with a considerable variation around the parental mean.

Low heritability implies no additive genetic variance
A low heritability means that of all observed variation, a small proportion is caused by variation in genotypes. It does not mean that the additive genetic variance is small. This difference matters because the response to natural or artificial selection depends on the amount of genetic variation in the population. Many phenotypes relating to fitness in natural populations have a large amount of additive genetic variation relative to the mean[79–81]. Egg number in farmed chickens has responded dramatically to artificial selection[82]. These observations are surprising because theory predicts that additive variation for fitness should be small because of natural selection. These observations led Houle to propose the additive genetic coefficient of variation ($CV_A = \sigma_A$/mean) to measure 'evolvability'[79]. He showed that, for natural populations, fitness-related traits tend to have a larger value of CV_A than morphological traits. Nevertheless, the response to natural or artificial directional selection on the phenotype is proportional to $h\sigma_A$, so both the heritability and genetic variance are important. In addition, a coefficient of variance (CV) can only be used to compare traits if the mean has an intrinsic biological meaning. Many traits in human populations have an artificial scale (for example, intelligence quotient (IQ)), so their CV is not informative.

Heritability is informative about the nature of between-group differences
This misconception comes in two forms, and in both cases height and IQ in human populations are good examples. The first misconception is that when the heritability is high, groups that differ greatly in the mean of the trait in question must do so because of genetic differences. The second misconception is that the observation of a shift in the mean of a character over time (when we can discount changes in gene frequencies) for a trait with high heritability is a paradox. For IQ, a large increase in the mean has been observed in numerous populations, and this phenomenon is called the Flynn effect, after its discoverer[83]. The problem with this suggested paradox is that heritability should not be used to make predictions about mean changes in the population over time or about differences between groups, because in each individual calculation the heritability is defined for a particular population and says nothing about environments in other populations. White males born in the United States were the tallest in the world in the mid-19th century and about 9 cm taller than Dutch males[78]. At the end of the 20th century, although the height of males in the United States had increased, many European countries had overtaken them and Dutch males are now approximately 5 cm taller than white US males[78], a trend that is likely to be environmental rather than genetic in origin.

A large heritability implies genes of large effect
In many gene-mapping experiments, the probability of detecting a gene of large effect increases with heritability. However, this does not by itself imply that there is a relationship between heritability and the number or size of genes affecting the trait. Mendelian single-gene traits have a broad-sense heritability of 1.0 but these seem to be exceptions. Morphological traits usually have high heritability, but are polygenic, for although a few individual genes have been identified that have a large effect[84,85], these do not explain a high proportion of the genetic variance[86].

Linear mixed model
A statistical model in which the dependent variable is a linear function of both fixed and random independent variables. Fixed effects are constant following the taking of repeated samples, whereas random effects are a sample from a distribution of effects.

Sampling variance
The variation of a parameter estimate across repeated samples due to finite sample size.

estimate of heritability from offspring–parent regression for traits with either a low or high heritability. When phenotypic measures are available for individuals with a mixture of relationships — both within and across multiple generations — or in general when the design is unbalanced, estimates of additive genetic variance and environmental components are most efficiently estimated from a linear mixed model. In particular, the 'animal model' has become the model of choice in livestock genetics[2], evolutionary genetics[7] and in some applications in human genetics[8]. The animal model was originally derived for livestock genetics applications[6] and a random additive genetic effect (breeding value[2,3]) is fitted for each individual in the pedigree. In this model, all pairwise additive genetic relationships in the entire pedigree are used and, for analysis, all sources of information are appropriately weighted by their sampling variance. Estimation methods that are based on the animal model are iterative and are therefore computationally more intensive than estimates of heritability

Box 3 | **Historical background**

It has become standard to use the symbol h^2 for heritability because Sewall Wright[87] used h (for heredity) to denote the correlation between genotype and phenotype in his path coefficient model[87]. The square of that correlation (that is, h^2) is, per definition, the proportion of variation in the phenotype that is attributable to the path from genotype to phenotype. Ronald Fisher, in his classical 1918 paper, parameterized the resemblance between relatives in terms of correlation and regression coefficients, but also gives an example of the percentage of the total variance in stature in humans that can be ascribed to genotypes and to 'essential genotypes'[88]. These percentages correspond to what we now call broad-sense and narrow-sense heritability (BOX 1). It is thought that J. L. Lush was the first to formally use the term 'heritability' to describe the proportion of variation that is due to hereditary factors[89].

that are based on regression or correlation coefficients. Residual maximum likelihood[9] is the standard method for estimating genetic variance components in complex pedigrees and it is used in livestock, natural populations and human populations[2,10–14], and Markov chain Monte Carlo methods are also being developed that are flexible and allow Bayesian estimation[15].

The accuracy of a heritability estimate depends on its sampling error, which is a function of the sample size and pedigree structure, and on bias, which can come from confounding. Bias can occur, for example, through assortative mating and selection. The sampling variance of the estimate of heritability is inversely proportional to the relationship of individuals squared, the number of families and, to a lesser extent, the number of individuals in a family[3]. Therefore, hundreds of observations are needed to obtain a standard error less than 0.1, and thousands are needed to attain very precise estimates.

Estimability refers to the number of parameters that can be estimated from data and depends on the extent to which the experiment to estimate heritability enables partitioning of the total observed variance into putative causal sources. Sometimes, a number of these sources are unavoidably confounded in the experimental design, so that their contribution to the overall variance cannot be separated. For example, estimates of dominance variance and common environmental variance are confounded when partitioning of the variance is carried out using observations on full sibs. In the classical twin design of MZ and DZ twin pairs, there are only three essential statistics that can be estimated from their phenotypes, namely the MZ resemblance (for example, covariance or correlation), the DZ resemblance and the overall phenotypic variation in the sample. Therefore, only three variance components can be estimated, although many more genetic and non-genetic causal components of variance can be postulated to influence MZ and DZ resemblance[2,3]. Confounding might lead to severe bias in the estimate of heritability. For example, if the resemblance of parents and offspring is partly due to common environmental effects, then an estimate of heritability that is based on their resemblance will be biased upwards. Although correlations of distant relatives are less likely to be biased by non-genetic factors, their relationship is so small that heritability estimates that are based on distant relatives have a high sampling error.

The denominator of heritability is the total phenotypic variance, which is estimated as the variance of the trait after correcting for known fixed effects such as sex, age or cohort. If identifiers for these factors are unknown then estimates of phenotypic variance will be greater (and the estimate of heritability less). For example, in humans, if the average difference in height of 15 cm between males and females was ignored, the estimate of heritability would be reduced to 0.6 compared with 0.8 when this difference is taken into account. Should the total phenotypic variance be adjusted for known fixed effects when estimating the fraction of variance that is due to genetic factors? Plant and animal breeders would say yes, because they obtain the best prediction of future performance by working with the amount of variation that is not accounted for by known effects. Similarly, human geneticists would say yes, because heritability is used to understand the genetic component of risk to disease, independently of known environmental risk factors. Evolutionary geneticists might say no, because the raw material of natural selection is the total variation between individuals. Prediction of the response to natural selection depends on whether selection takes place within or across the factors that cause variation. For example, if year-to-year fluctuations in climate have a large effect on the mean viability of an annual plant but natural selection operates within years, then the best prediction of response would be based on a heritability that is estimated by adjusting for between-year variation.

Heritability and repeated measures

Repeated measurements of an individual can be taken for some traits either temporally, for example, body weight at different ages, or spatially, for example, the number of bristles on the left and right side of *Drosophila melanogaster*. The resulting variation can be partitioned between and within individuals. If it is assumed that these repeated measures are expressions of the same genotype, then the variation within individuals is caused by measurement errors and other random environmental factors. The correlation is then called the repeatability, and it is an upper bound for the broad-sense heritability[3]. Heritability can be lower than the repeatability because the correlation of repeated measures of an individual can be environmental as well as genetic in origin. If the phenotype for a trait is estimated from the mean of several observations we need to be careful defining heritability, because heritability depends on how many records were used, and is not the same as the heritability of an individual observation. The heritability of the mean can be much larger if the heritability of a single observation and the repeatability are small, for example, when the heritability of any single observation is 0.10 and the correlation of repeated measures has no environmental component, the heritability of the mean of 10 observations is approximately 0.53. However, for the same heritability of 0.10 and a large correlation of repeated measures of 0.8, the heritability of the mean of 10 observations is only 0.125. In artificial-selection programmes the availability of repeated measures is useful, because the additive genetic values of individuals can be predicted with higher accuracy so that a larger response to selection can be achieved.

Bayesian estimation
An estimation method that combines prior information and observed data to draw statistical inference.

Confounding
The impossibility of separating the effect of two or more causal factors on an observed variable.

Assortative mating
The tendency of mates to resemble each other in phenotype.

Applications

The parameter of heritability is so enduring and useful because it allows the meaningful comparison of traits within and across populations, it enables predictions about the response to both artificial and natural selection, it determines the efficiency of gene-mapping studies and it is a key parameter in determining the efficiency of prediction of the genetic risk of disease. Heritability is a simple dimensionless measure of the importance of genetic factors in explaining the differences between individuals, and it allows an immediate comparison of the same trait across populations and of different traits within a population. Such comparisons can lead to insights into the biology of the phenotype, or can have practical consequences for plant and animal breeding programmes. For example, the heritability of body size (or stature) is generally high across a wide range of species (FIG. 1), signifying developmental processes that seem to be robust to environmental insults.

In medicine and human genetics, estimates of heritability can be compared across diseases to gauge the relative influence of genetic and environmental factors. Because disease is usually measured on an all-or-none scale, allowance has to be made for the incidence of disease when making comparisons. Heritability for such categorical traits can be defined on the observed discontinuous scale or on an unobserved continuous 'liability' scale[16]. The continuous scale is more general because it is independent of the incidence of each category (see BOX 5). For example, consider the psychiatric disorders schizophrenia and major depression, which differ considerably in the relative risks to first-degree relatives of affected individuals: 9 for schizophrenia[17] but only 3 for major depression[18]. However, the lower incidence of schizophrenia of 1%[17] compared with 3%[18] for major depression results in similar estimates of heritability on the observed scale of 0.16 and 0.12, respectively. Conversely, heritabilities that are estimated on the underlying liability scale[19] are quite different at 0.81 and 0.37, respectively. For risk prediction that is based on family history or measured genotypes, it is the heritability on the observed 0–1 risk scale, however, that is most important[20].

In artificial-selection programmes, heritability has a crucial role because it determines the precision with which the genetic value can be predicted from phenotypic information, and therefore determines the design of breeding schemes. The correlation between the observed phenotype and unobserved breeding value is h, the square root of the heritability[3]. Therefore, for a trait with a high heritability, the phenotype of an individual is highly informative for its breeding value. So for traits that are easy to measure and have a high heritability (for example, growth or weight traits (FIG. 1)) an easy and effective breeding scheme is to choose the best individuals for further breeding on the basis of their phenotypes. For traits with a low heritability (for example, litter size) information from many relatives is needed to predict breeding values accurately, but the accuracy of prediction of breeding values remains a function of the heritability. Hence, heritability is central in predicting the response to selection.

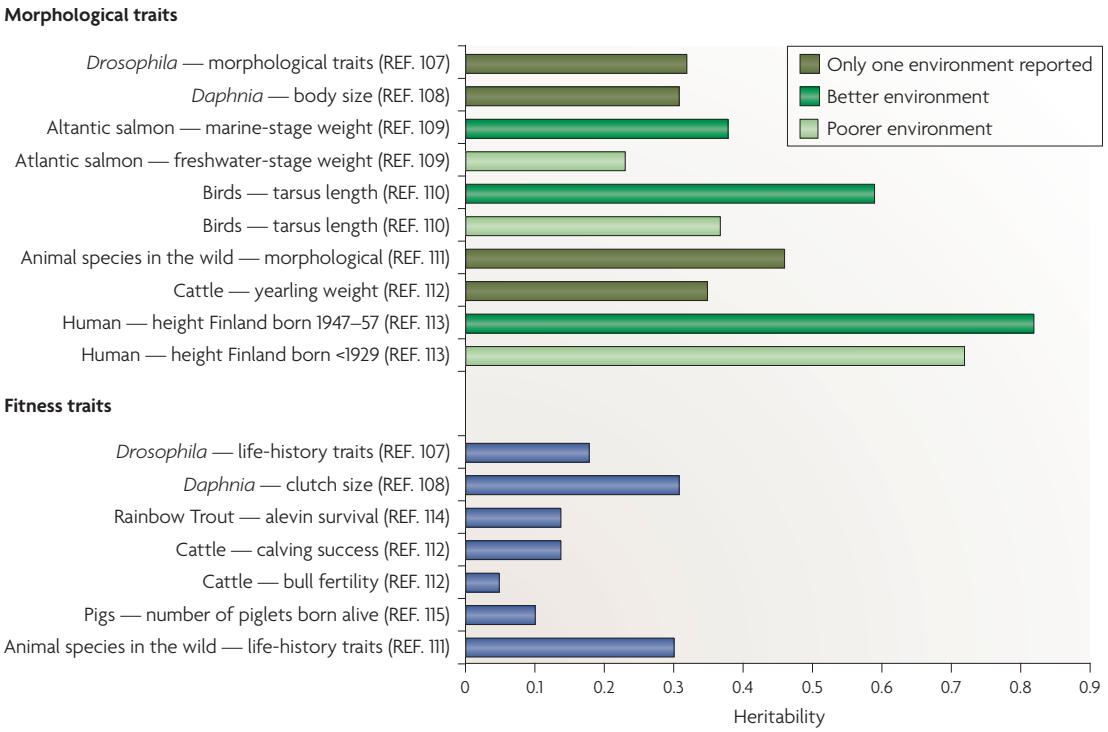

Figure 1 | **Examples of estimates of heritabilities of morphological and fitness traits.** Where possible, the estimates of heritability were taken from Reviews, and are the mean across a number of studies. The examples show that, on average, heritability estimates are larger for morphological traits than for fitness-related traits, and that heritability tends to be larger in better environments when compared with poorer environments.

Heritability is an important parameter that determines statistical power in gene-mapping studies that use pedigree information. A large heritability implies a strong correlation between phenotype and genotype, so that loci with an effect on the trait can be more easily detected. However, heritability by itself does not provide information about the genetic architecture of the traits, for example, how many loci contribute to genetic variation (BOX 2). In principle, a trait with a low heritability can have a single locus that causes variation and a trait with a high heritability can have hundreds of contributing loci.

Box 4 | **The heritability of IQ controversy**

Nowhere has the debate about nature and nurture been so controversial as in the study of mental ability in humans[5,90,91]. Controversies about the concept and use of intelligence quotient (IQ), a phenotypic measurement of relative performance on a series of mental ability tests, are manifold. They include: its definition ('intelligence is what intelligence tests measure'[90]); documented historical abuse relating to eugenics; inference about the cause of observed differences between ethnic groups (see BOX 2); incorrect statistical inference from observational studies[90]; and disputed implications of IQ differences between individuals and groups on social and economic interventions[92,93]. We will not discuss the uses and abuses of measures of cognitive ability, but we will point out that there is abundant empirical evidence that shows that IQ is a good predictor of outcomes in life, including educational attainment, income and health[94]. Controversy about IQ is by and large because of social, not scientific, reasons. Here, we focus on one point of controversy about IQ: its heritability.

Twins have been used in the majority of studies to estimate the heritability of IQ. These studies include twins that were separated at birth (adoption studies), monozygotic (MZ) and dizygotic (DZ) twins that were raised together, and a combination of these designs with additional siblings. There have also been numerous studies involving other relatives[94]. The empirical results are clear: MZ twins are substantially more similar in IQ than DZ twins, whether they are raised together or apart. Reported estimates of heritability for IQ from twin studies are remarkably consistent in the range of 0.5–0.8, across many age groups. The reported estimate of heritability for young (preschool) children is lower[95] and estimates of heritability at old age are approximately 0.6–0.8 (REF. 96).

A recurring criticism of estimates of heritability for IQ is that it is too high. A large heritability for IQ can be controversial because of the perceived implications that a person's or group's 'intelligence' cannot be changed by intervention strategies (this is an incorrect perception, see BOX 2). Nevertheless, it is valid to question the correctness of all those twin and family studies. The issue is one of statistical inference. The reported resemblance between relatives for IQ, measured, for example, by correlation coefficients, is unequivocal. For example, across many studies, the average MZ and DZ correlation was 0.86 and 0.60, respectively, based on 4,672 MZ and 5,546 DZ twin pairs[94]. To estimate a narrow-sense or broad-sense heritability from these correlations (or directly from the raw data), assumptions have to be made about models of genetic and non-genetic causes of family resemblance. Some of these assumptions can be tested empirically, others cannot. For example, there is likely to be a correlation between genes and environments for IQ so that estimates of heritability might be overestimated[5,90]. Another example is that if there are strong maternal (for example, *in utero*) effects on the IQ of twins, and these are larger for MZ twins than for DZ twins or siblings, then the estimate of heritability would be biased upwards because it is assumed (in common practice) that the resemblance due to common environmental factors are equal[97]. In one meta-analysis of a number of twin studies the modelling of maternal effects implied a narrow-sense heritability of only 0.3 and an estimate of broad-sense heritability of 0.5 (REF. 98). Although much lower than 0.8, these estimates are still moderate to large when compared with measures of behavioural and other phenotypes in livestock species and natural populations. Therefore, we can conclude from the wealth of empirical data currently available that the resemblance between relatives is large and consistent with the hypothesis that a large proportion of the variation in IQ between individuals within a population is associated with additive genetic factors.

Heritability and evolutionary genetics

In selection experiments and plant and animal breeding programmes, the phenotype that is under selection is known and h^2 is sufficient for predicting the response to selection using the breeder's equation. If selection is on multiple traits simultaneously, prediction of response to selection is possible using a multivariate version of the equation that accounts for the known or estimable genetic correlations between traits, the phenotypic correlations between traits and the relative weight attached to each trait in a selection index[3]. However, in natural populations, selection acts through differences in 'relative fitness', which is difficult if not impossible to measure in the field. If we could measure relative fitness then the breeder's equation for fitness would be $R_F = h^2_F S_F$, with the subscript F representing relative fitness. However, the weighted selection differential for relative fitness (S_F) is equal to the phenotypic variance of fitness[3,21], and so the breeder's equation becomes $R_F = \sigma^2_{A(F)}$, the additive genetic variance of fitness. This result, that the response to natural selection in fitness equals the additive genetic variance of fitness, is known as Fisher's fundamental theorem of natural selection[21].

Functional characteristics, such as morphological and life-history traits, can be measured in natural populations and can be correlated with fitness. If a trait is phenotypically, but not necessarily genetically, correlated with fitness, then we would observe an apparent selection differential because the mean phenotypic value of the selected individuals differs from the mean in the population[3]. However, it would be wrong to apply the breeder's equation to this apparent selection differential[22,23]. Response to natural selection of a trait (Y) that is correlated with fitness is $R_Y = r_g h_Y h_F \sigma_Y \sigma_F$, with r_g the additive genetic correlation coefficient of the trait and fitness, and σ_Y and σ_F the phenotypic standard deviations[3]. This correlated response can also be expressed as $R_Y = \mathrm{cov}_A(Y,F)$, the additive genetic covariance between fitness and the trait (cov represents covariance). This is sometimes known as the Robertson–Price identity, and was first derived by Alan Robertson in a paper on selection in dairy cows[3,24].

The important consequence from these predictions is that to predict the response to selection in any one trait, the heritability of that trait, the heritability of the trait under selection (in this case, fitness) and the genetic correlation between them need to be known. With many traits under selection the prediction becomes more complicated and, in addition to heritabilities, all genetic and phenotypic correlations need to be known[3,22,23]. What practical implications do these theoretical results have? The main one is that if we consider one trait at a time, the breeder's equation is unlikely to work in natural populations. For example, antler size in deer is phenotypically correlated with male reproductive fitness (males with bigger antlers have more progeny) and it is heritable, but no response over time is observed[25]. The likely explanation is that there is no genetic correlation between antler size and fitness, so that the observed phenotypic

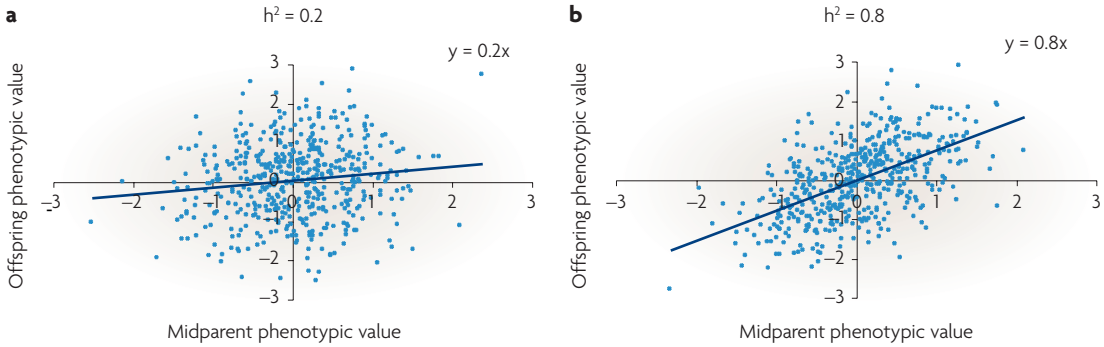

Figure 2 | **Estimation of heritability from the regression of offspring phenotype on the average phenotype of the parents.** The slope of the regression line is an estimate of the narrow-sense heritability for traits with a heritability of 0.2 (**a**) and 0.8 (**b**) and phenotypic variance of 1. The variances of the observations about the regression line are 0.98 (**a**) and 0.68 (**b**), demonstrating that the average phenotypic value of the parents (midparent phenotypic value) is a better predictor of the offspring phenotypic value if heritability is high.

correlation and the apparent selection differential are induced by the environment, for example, nutritional status[25]. Predicting the response to multivariate selection in natural populations is an active area of research with new methodological developments[26] but it could be constrained by the lack of data that is needed to accurately estimate genetic correlations and selection gradients[27]. We conclude that in order to predict the response to natural selection, knowledge of heritabilities is necessary but usually not sufficient.

Heritability is not necessarily constant

Heritabilities can change. For example, estimates of heritability for first-lactation milk yield in dairy cattle nearly doubled from ~25% in the 1970s[28] to ~40% in recent times[29]. From the population-specific definition of heritability (BOX 1), it is easy to see how heritability can change over time: the variance in genetic values can change, variation owing to environmental factors can change or the correlation between genes and environments can change. Genetic variance can change if allele frequencies change (for example, owing to selection or inbreeding), if new variants come into the population (for example, by migration or mutation) or if existing variants only contribute to the genetic variance following a change in genetic background or in the environment. The same trait measured over an individual's lifetime can have different genetic and environmental effects influencing it, so that the variances become a function of age. For example, variance in weight at birth is influenced by maternal uterine environment, variance in weight at weaning depends on maternal milk production, but variance of mature adult weight is unlikely to be influenced by maternal factors, which themselves have both a genetic and environmental component.

Heritabilities can be manipulated by changing the variance contributed by the environment. This can be as simple as changing the method of measurement, for example replacing a self-reported measure of height by a clinical one[12]. In unfavourable environmental conditions, different hypotheses have proposed a decrease, an increase or unpredictable changes in genetic variance[30], with the impact on heritability being unpredictable in each scenario. Empirical evidence for morphometric traits suggests lower heritabilities in poorer environments[31], but not for traits that are more closely related to fitness[31]. Testing these hypotheses is difficult, but in an experiment using the cricket (*Gryllus pennsylvanicus*), in which one half of each family was raised in laboratory conditions and the other half was raised in cages in a field location, the heritabilities of wing dimorphism were found to be 0.71 in the laboratory but only 0.21 in the field samples. There was an increased total variance in the laboratory, but a genetic correlation close to 1 between the two environments[32].

Understanding how heritability changes with environmental stressors is important for understanding evolutionary forces in natural populations[31]. In livestock, the heritability of economically important traits is generally higher in good husbandry environments than in bad environments[33]. Interestingly, the reason for this observation is not only because there are more random environmental effects in low-production systems that cause the environmental variance to increase. In good husbandry environments, as measured by mean performance or output, there is typically increased genetic and environmental variance[34], which is only partly explained by the mean-variance scale relationship that is often observed in nature. A similar observation (that the proportion of phenotypic variation due to additive and maternal genetic factors increases with a better environment) was recently made for a population of wild sheep[35]. In humans, the estimate of the heritability of intelligence quotient (IQ) increases with increasing socio-economic status[36], which might be viewed as a measure of quality of the environment.

Effect of selection and inbreeding on heritability

Quantitative genetic theory predicts that selection and/or inbreeding will alter additive genetic variance and, as a consequence, will also alter heritability. With truncation selection used in animal and plant breeding or with stabilizing selection in natural populations, the variance

Truncation selection
Selection of individuals with trait values equal to or greater than some threshold as parents of the next generation.

Stabilizing selection
Selection, either natural or artificial, of individuals with trait values in the middle of the distribution as parents of the next generation.

Box 5 | **Heritability of categorical traits**

The heritability of all-or-none (0/1) traits, such as disease status, twinning rate or survival, can be defined in the usual way, that is, by the proportion of variation on an observed scale, for example, 0 and 1, that is due to additive genetic factors, and can be estimated as for continuous traits by, for example, parent–offspring regression or sibling correlation. However, variances and heritabilities calculated on this observed scale (h^2_O) are a function of the incidence of the trait in the population[2,3]. For example, the phenotypic variance on the observed scale for a 0/1 trait with an incidence of K is K(1–K), with a maximum at K = 0.5. This relationship between mean and variance obscures the comparison of the importance of genetic factors in different environments or in different populations that differ in incidence.

Because most quantitative traits follow a normal bell-shaped distribution, it is reasonable to assume that all-or-none traits can be represented by an underlying normally distributed liability trait, which, as for other traits, is the sum of independent normally distributed genetic and environmental components[16,19]. This assumption implies that liability to disease is multifactorial and that contributions from individual genetic or environmental risk factors are small. If the score on the liability scale exceeds a threshold then the individual has a phenotypic value of 1, otherwise it is 0, with the proportion of the normal distribution that exceeds the threshold being equal to the trait incidence. The relationship between h^2_O and the narrow-sense heritability on the underlying continuous liability scale (h^2) is:

$$h^2_O = h^2 z^2/[K(1–K)]$$

where z is the height of the standard normal curve at the threshold that truncates the proportion K (REF. 99). Heritability on the observed scale is always smaller than that on the liability scale because information is lost by the grouping into two categories, and the maximum value for h^2_O is 0.64 when K = 0.5 and $h^2 = 1$. For categorical traits with more than two classes, heritability can be estimated by assuming that the categories relate to multiple thresholds across an underlying liability scale[2,3]. Estimation of heritability for susceptibility to disease in human populations is often based on the threshold liability model.

of the parents (the between-family variance in their offspring) is reduced below that of the parental generation as a whole. The level of this reduction depends on the intensity of selection and on heritability. Under the infinitesimal model of a large number of loci that are each of small effect contributing to genetic variance, changes in allele frequencies at each locus are infinitesimally small yet genetic variance is reduced. This change in genetic variance resulting from selection, which is due to gametic disequilibrium, was explained by Bulmer[37] and is commonly known as the Bulmer effect. However, if selection stops then the genetic and phenotypic variances and heritability return to their pre-selection values after a few generations, but the change in the mean is permanent[37]. The results from this limiting model of an infinite number of loci imply that permanent changes to the genetic variance and heritability as a result of selection are likely to be small when the number of loci contributing to the genetic variance is finite but large. Individual loci of large effect can, however, be fixed by selection with a consequent reduction in variance.

Genetic variance is also expected to be reduced by inbreeding. The rate of inbreeding is a function of the number of individuals who are parents to the next generation and of the variation in family size, which can be expressed as the effective population size[3]. If a parent is inbred then a proportion of its genome is IBD from a common ancestor so that the variance of the genic values of the gametes it produces is less than if it were not inbred. The variance within families is therefore reduced by inbreeding — the reduction is linear if the gene effects are additive. Furthermore, inbreeding is higher in a population that is undergoing selection compared with an unselected population of the same number of breeding parents. This is because the best individuals will tend to come from the same families and be more related than when parents are randomly selected[38]. Continued inbreeding is expected to reduce genetic variance slowly but relentlessly, eventually depleting all genetic variance as the population becomes completely inbred unless new genetic variants are introduced, for example, by migration or mutation. Certainly, extreme selection intensity and close inbreeding can result in total loss of genetic variance, as seen in inbred lines. These predictions of quantitative genetic theory have been tested in model species and have generally been upheld, although with considerable variation between replication lines, for morphological traits in mice[39], *D. melanogaster*[40] and *Tribolium castaneum*[41].

For fitness traits, in which non-additive variance is important, genetic variance has been shown to increase as a result of inbreeding[41]. Theory for changes in non-additive genetic variation as a result of selection and inbreeding has been proposed[42–44] but is difficult to verify empirically, even in species in which mating designs can be planned in an attempt to disentangle estimates of higher order non-additive-variance components. Moreover, environmental variance has been observed to increase as a result of selection[39] and/or inbreeding[45]. The Illinois long-term selection experiments of maize have completed more than 100 generations of truncation selection (selecting for the top 20%). These experiments have generated responses in both the oil percentage and protein percentage selection lines of more than 20 standard deviations from the original population mean, yet significant genetic variance remains, despite a maximum effective population size of 96. This observation is explained, in part, by new mutations[46,47], which are estimated to be in the order of 0.1–1% of heritability per generation[48].

Heritability in the genomics era

The genomics era has brought new tools and resources to study the relationship between phenotype and genotype. Polymorphisms are abundant in the genome of outbred populations, and efficient high-density array technology has been developed to measure thousands to hundreds of thousands of SNPs in humans, model organisms and livestock. Similarly, arrays have been developed to measure mRNA transcript levels at many genes simultaneously, and new high-density platforms have been developed to measure gene methylation intensities and to perform large-scale proteomics studies. These developments offer new research avenues to estimate heritabilities in unpedigreed populations and to estimate heritability for medically important traits in human populations.

Gametic disequilibrium
The non-random association of alleles at different loci (also termed linkage disequilibrium).

Box 6 | **Heritability of new phenotypes**

The estimation of heritability for new phenotypes — those that can be measured with recently developed technologies — provides knowledge about the nature of between-individual differences in core biological processes. Such knowledge is important for intervention strategies to create phenotypic change, for example drug development in medicine and artificial selection in plant and animal breeding programmes. There are many new phenotypes for which heritability estimation has been an important step towards a better understanding of individual differences; here, we give a few examples of exciting developments.

In humans, brain scanning using magnetic resonance imaging techniques can measure the volume of whole-brain grey and white matter. Posthuma *et al.*[100], using a twin study, reported heritabilities of 0.82 and 0.87 for grey- and white-matter volume, respectively, implying that most of the between-person variation is due to genetic differences.

Shortening in the length of the telomeres of chromosomes, which is observed as individuals age, has been implicated in cell ageing and disease[101,102]. Telomere length can be measured from blood samples using restriction enzymes, because they consist of a repeat nucleotide motif. In humans, age-corrected heritabilities in the range of 0.4 to 0.8 have been reported from twin and family studies[103–105]. These findings are important because they quantify to what extent cellular ageing is under genetic control. They pave the way for gene-mapping studies to identify pathways and detect mutations that cause differences between individuals, increasing our understanding of cell death and ageing.

Plants are rich in biochemical compounds called metabolites, but their regulation, interaction and function is not fully understood. Using high-density mass spectrometry, the genetic basis of natural variation in the metabolite composition in 14 accessions of *Arabidopsis thaliana* was recently investigated[106]. The authors detected 2,475 different mass peaks and estimated for most masses a surprisingly high broad-sense heritability, many larger than 0.5 (REF. 106). The large heritability and subsequent genetic mapping of the loci responsible for the difference between two divergent accessions[106] imply that natural variation in metabolite composition can be exploited in plant breeding programmes.

Heritability with unknown pedigrees. Genetic markers can help to estimate heritability in novel ways. When phenotypes are collected on a sample of individuals whose relatedness is partially or wholly unknown, genetic markers can be used to infer relatedness between pairs of individuals, because related individuals tend to share more marker alleles than unrelated individuals. The inferred relatedness can then be correlated with phenotypic similarity, and quantitative genetic parameters, including heritability, can be estimated[49–52]. This method has been applied in evolutionary studies to estimate heritability for quantitative traits when phenotypes and DNA samples are available but pedigree information is not, for example in fish[53], plants[54] and mammals[55]. A disadvantage of this method is that many polymorphic markers, typically hundreds, are needed to estimate relatedness accurately, for distant relatives in particular. Generally, the closer the relatives the fewer markers are needed. Offspring–parent pairs can be easily identified with only a few polymorphic markers because they always share at least one allele at all marker loci. Funding, rather than the availability of large numbers of polymorphic markers, could be the only limiting factor in the near future, given the rapid discovery of new markers in many species and the development and application of high-density array technology.

Exploiting variation in relatedness. Genetic markers can also be used to estimate heritability when the pedigree is known, by estimating the actual or realized relationship between relatives[56]. Apart from offspring–parent pairs (who always share 50% of their genes IBD) and monozygotic twins (who share 100% IBD), the proportion of the genome that is shared IBD varies around its expectation for pairs of relatives because of the stochastic nature of segregation and recombination. A parent has one chromosome from each of its parents, and which parts of these two grandparental chromosomes are passed on to an offspring is a chance event (random segregation). This segregation causes variation in the actual number of alleles shared IBD between relatives. For example, for full sib pairs at a single locus, 25% of all the sib pairs share no alleles IBD (they are 'unrelated' at that locus), 25% share two alleles IBD (they are 'clones' at that locus) and the remaining 50% share one allele IBD. Recombination events during the formation of gametes reduce the variation in the proportion of a chromosome (or genome) that is shared IBD between relatives, by creating more segregating segments: the larger the number of segregating units, the smaller the variation in the proportion of segments shared. The measuring of multiple genetic markers in relatives allows the estimation of the total proportion of the genome that is shared, using multiple-marker IBD estimation procedures[57].

The amount of variation around the expectation is modest, but measurable. For example, for sib pairs the average proportion shared is 50%, with a standard deviation of approximately 4%[58–60]. For half sibs the mean and standard deviation are 25% and 3%, respectively[58,59]. Visscher *et al.*[56] estimated heritability for height from the correlation between phenotypic similarity and the estimated proportion of the genome shared IBD, and found that sibs sharing a high proportion of their genome IBD were indeed more similar in height than those sharing less. The estimated heritability for height from this study was 0.8, in line with reports from twin and family studies[56]. The significance of this new approach is that heritability can be estimated without strong assumptions about the causes of family resemblance, because it is estimated from data within families[61,62]. In the future, with sufficient data, this will allow unbiased estimation of heritability of contentious phenotypes such as IQ in humans, unbiased estimation of the genetic contribution to concordance for disease in relatives, and unbiased estimation of additive and non-additive variance that is not affected by confounding factors.

Heritability of gene expression. Recently, an exciting combination of genetic data and genome-wide gene expression analysis has been used to try to understand the genetic basis of gene expression. In these studies, mRNA levels are the phenotypes of interest and are subject to experimental, environmental and genetic sources of variation that can be estimated. It was first demonstrated in experimental populations that there is substantial genetic variation among genotypes [63,64] and that within a population, statistically significant estimates of heritability were found for gene expression in a much larger proportion of genes than would be expected by chance[64,65]. The average broad-sense heritability of gene expression levels estimated from monozygotic twin pairs

was approximately 0.3 (REF. 13). These demonstrations of significant heritability for gene expression are important because the statistical power to detect gene variants that affect gene expression depends on heritability. The combination of genetics and gene expression, called genetical genomics[66], has been used successfully to map genes and pathways to causal polymorphisms in a number of species, including yeast, mice, maize, rats, *Eucalyptus globulus* and *Arabidopsis thaliana*[67,68]. Evidence is emerging that genetic variation for complex traits is caused by mutations that alter the amount of gene expression. Two recent studies that used genome-wide association studies in humans on Crohn disease[69] and asthma[70] reported that the most significant disease-associated SNP was also associated with gene expression levels at a nearby gene. In BOX 6 we give further examples of the heritability of new phenotypes.

Why are heritabilities so large?

Observations about the values of heritability for which we do not have adequate answers at present and that need further research include: why so much of the genetic variance is additive by nature, and what determines the relative amounts of genetic and environmental variances so that heritabilities have a particular value? Empirically, we observe substantial amounts of additive genetic variation, measured either as the proportion of total variation (heritability, approximately 0.8 for height in humans; FIG. 1) or as a proportion of the mean (evolvability; see BOX 2). However, theory predicts that additive genetic variance should be depleted because of natural selection, and biology tells us that genes work in interactive pathways, which implies non-additive interaction variance. Fortunately, the existence of additive genetic variance is not incompatible with strong interactions at the gene level[2,3], in particular if gene frequencies are near 0 or 1 (as a number of theories predict), which might be a partial answer to the question of why so much genetic variance is additive[71]. The question about the relative magnitudes of genetic and non-genetic variances is more difficult to answer. Why is heritability for bristle number in *D. melanogaster*, for which most genetic variance is additive, approximately 0.5 and not, for example, 0.1 or 0.9? These observations suggest that there is some genetic control of environmental (and hence phenotypic) variance[72,73]. There is empirical evidence that environmental variance for morphological traits increases following inbreeding or a bottleneck[40], which is compatible with developmental homeostasis. Selection experiments also tend to show that, despite a predicted reduction in additive genetic variance owing to selection and inbreeding, the total phenotypic variance usually increases in the lines that are selected for an increase in the mean[3]. There is currently no consensus theory that explains these observations.

Conclusions and further research

Heritability is, and will continue to be, an important parameter in genetics. It allows a comparison of the relative importance of genetic and non-genetic factors across species, traits and identified environments, and is a key parameter for predicting the response to artificial and natural selection. However, as with all other parameters, it is limited. For example, because heritability is a ratio of variances it does not tell us about the magnitude of each component; it refers to a particular population and environment and not their differences. Furthermore, because it is a composite measure, it tells us nothing about the actions and interactions of individual genes. Within the constraints of this short Review we have tried to bring together studies from a broad range of situations, touching on many active areas of research in quantitative, population and evolutionary genetics, including the maintenance of genetic variance in natural populations, the magnitude of additive and non-additive variation, the nature and amount of mutational variance, and the genetic control of phenotypic variance.

Estimates of heritability have produced new scientific questions that researchers have hardly started to address. For example, why is the heritability of, for example, body size so similar across species[72]? Why does the heritability not change much after long periods of artificial selection (for example, in poultry[10,74] and corn[47]), when existing theory implies that it should? These are fundamental questions about the nature and scale of mutational variance and the interplay between genes and environment, in particular the question of whether and how environmental variation might be under genetic control. It is a sobering thought that after nearly a century of research in genetics that has used the concept of heritability we still do not fully understand why heritabilities, both broad sense and narrow sense, have the values that they do. Fortunately, the incredible pace of gene–phenotype discoveries in many species will allow new insights to these questions in the near future.

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