Role of Genetic Analyses in Cardiology
Part II: Heritability Estimation for Gene Searching in Multifactorial Diseases

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“Those who know only their own present surroundings think that it is not important to know which conditions of life. How much we do not know of it to attribute to the accumulative action of natural selection, and how much to the conditions of life.” Charles Darwin, *The Origin of Species*, Chapter 5: Laws of Variation, 1859

Genetic testing is a growing discipline in clinical practice, and it is being used to make treatment decisions and to counsel patients. Before genetic testing can be done, reliable information needs to be available on which genes are involved in a disease. Research into genetic determinants of disease is often based on articles reporting the magnitude of the heritability of disease. Here, we address limitations in the use of heritability as a point of departure, such as a basis for power calculations, for genetic studies.

**What Is Heritability?**
Familial aggregation of diseases generally is taken as evidence for a role of genetic factors in the origin of a disorder or trait. A commonly used measure to quantify the extent to which this familial aggregation of diseases is due to genetic factors is the heritability. Heritability estimates were first used by plant and animal breeders to predict the effectiveness of their selection of a desired phenotype such as an increase in milk production or resistance to yeast infections. In human studies, heritability has the intuitive appeal of quantifying genetic effects without necessarily knowing the mode of inheritance of a trait. Heritability is frequently estimated for complex diseases or traits such as diabetes mellitus, coronary artery disease, and serum lipid levels, which are phenotypes reflecting the interplay of genetic and environmental factors.

Continuous traits or phenotypes (height, body mass index, serum lipid levels, etc) in a population usually have an approximately normal distribution characterized by a mean and a variance. The total variance can be partitioned mathematically into components: a genetic component and an environmental component. Heritability is defined as the proportion of the total phenotypic variation within a population that can be attributed to the genetic variance. In analysis of variance (ANOVA), a commonly used method to compute heritability, the shared variance is attributed to genetic variance, and the nonshared variance is attributed to error, environment, or both.

Originally, the purpose of plant and animal breeders was (and still is) to reduce heritability by reducing genetic variability and to “produce” 100% (genetically) identical plants or animals with the desired phenotype. In medical literature, the purpose of calculating heritability is to estimate the likelihood that genes are involved in the origin of a disease or trait and whether a search for genes through linkage and candidate gene studies is warranted. Higher heritability is generally interpreted as a larger contribution of genes in the origin of the disease (or trait). As has been noted,1,2 heritability estimates cannot be used to assess the magnitude of the contribution by genes for several reasons.

**Used Methods Are Insufficient**
First, the components of the variance, genes and environment, are in most cases not independent. Specific differences in environment (eg, nutrition, smoking, infections) may modify a genetic effect in different ways. This is called interaction. In many situations, it is not known how genotypes or gene products interact with environmental factors or with other gene (product)s. This has consequences for the statistical models (linear, multiplicative log models, or others) used to estimate heritability. Statistically significant gene-environment interactions are difficult to find, but this does not imply that they are not important. Especially for complex diseases, it is incorrect to assume that main genetic or main environmental effects explain most of the phenotypic variation, neglecting important interactions. Causes of phenotypic variation cannot be separated into genes and environment.3 The different components genetic and environment cannot be summed to 100%.

For example, thrombotic disease has a heritable component such as carrierrship of factor V Leiden.4,5 Women taking oral contraceptives also have an increased risk of thrombosis.6 However, women who are carriers of factor V Leiden and...
Heritability: Is There a Simple Truth?

Heritability estimates are specific for a particular population at a specific point in time. They are not generalizable to other populations, and there is not a singular truth to challenge even in the presence of a proper model and capture of all environmental factors.

It is crucial to realize that heritability is a ratio, a relative measure. A more uniform environment will increase the heritability, even if the variance in disease occurrence resulting from genetic factors remains the same. A clear illustration, given by Hirsch in 1981, relates to the number of legs that humans have, of which all the variation is determined by environment (amputations, thalidomide). Although the number of legs is clearly determined by genes, because of the absence of genetic variation between humans, the heritability estimate is 0%.

Alternatively, a heritability of 100% does not imply that environmental factors are nonexistent or not important. It only implies that in the studied population, the variation of the trait was not caused by environmental variation or that the relevant environmental variables were not measured. This may be caused by a lack of variation in the environment, although it remains very possible that a change in the environment causes large differences in disease occurrence.

It is not meaningful to compare heritabilities of different traits in the same population to assess which traits are more strongly determined by genetic factors. Moreover, comparison of heritabilities of the same trait between populations does not help to decide whether the observed differences are due to genetic factors. Uncertainty about the genetic basis of menopausal age can serve as an example. Many different heritability estimates of menopausal age have been reported, varying between 30% and 80%. Still, the genetic contribution is likely to be more or less equal across populations because the distribution of menopausal age does not differ much between populations. Rather, the range in heritability estimates reflects the difficulty in measuring menopausal age, which is due to different proportions of use of postmenopausal hormonal therapy, women undergoing surgical menopause, and the fact that it is commonly assessed in retrospect.

Heritability studies on cardiovascular disease may serve as another example. Most cases of myocardial infarction and stroke result from interactions of multiple genetic and environmental factors, none of which can fully cause disease by itself. Studies have indicated that family history is a very important risk factor.

For carotid intima-media thickness, a measure of generalized atherosclerosis, studies show heritabilities of 12% to 40%. In a genome scan, heritability is estimated by markers, and recently unadjusted estimates of heritability of intima-media thickness of 68% have been found, adjusted 43% to 40%. These differences in heritabilities are due to the different study designs. In a study in twins, there is by definition less genetic variation than in studies in sibpairs. Furthermore, heritability estimates differ by the number of environmental factors that are adjusted for; adjustment can reduce a crude heritability estimate from 68% to 40%. Although it is not true that one heritability is more valid than another, it shows that estimates calculated in different populations, or ruling out more environmental variation, yield different heritabilities.

Several reports have been published on other correlates of atherosclerosis. Flow-mediated dilation is a measure of endothelial dysfunction believed to be a contributing factor to atherosclerosis. Its heritability is estimated at $\approx 12\%$ to 14%. Calcification of arteries occurs during atherosclerotic development; it can be detected in the abdominal aorta on radiographs. The heritability was estimated to be 49% in the Framingham population. These different estimates probably show difficulties in the measurement of the correlates rather than different genetic or gene-environment contribution to atherosclerosis in general.

Heritabilities for risk factors for coronary artery disease have repeatedly been studied, notably for body mass index, blood pressure, and lipid levels. Apart from the obvious differences in heritability estimates across populations, these studies do not show which risk factor is most strongly controlled by genes. Environmental factors that influence the phenotype are different for each parameter within and across populations; therefore, the genetic variance is not comparable.

The above leads to the conclusion that there is no single true heritability estimate for a particular phenotype.

A High Heritability Does Not Predict Successful Mapping of Genes

In studies to identify relevant genes in disease origin, 2 study designs are commonly used, ie, association studies and linkage studies. The first method is used when a candidate gene is known from, for example, pathophysiological insight. The allele frequency of the candidate gene is compared between cases and controls.

Second, if no prior hypothesis of possible genes involved in a trait or disease is available, a genome-wide linkage
analysis may be applied. The aim of such a study is to identify genomic loci that are involved in the trait under study without prior assumptions about the underlying mechanism. Linkage analysis is based on the number of alleles that are shared at a chromosomal locus among family members and the phenotypic similarity between these family members. Because this method detects the loci and not necessarily the genes itself, these regions can subsequently be subjected to a search for possible genes, the positional candidate genes.

Linkage studies have been very successful for mapping genes of mendelian diseases characterized by single major gene defects like cystic fibrosis or Huntington’s disease. Detecting genes in complex diseases, however, is highly problematic. The lack of a simple correspondence between genotype and phenotype and the involvement of multiple genes cause difficulties in identifying each single contributing locus. The chance of mapping relevant genes in linkage studies depends not only on the number of loci but also on the relative contribution of each locus, which is not reflected in the magnitude of the heritability estimate. In addition, it is possible that different genotypes cause the same phenotype, called heterogeneity. Heterogeneity complicates gene mapping and similarly is not reflected in the heritability estimate.

It should be noted that subjects included in a linkage study are generally others than those included in a preceding heritability study. Even if they are from the same population, they are often from different families; therefore, the heritability will not reliably reflect the variance attributable to genes.

A further complication in linkage studies is that heritability estimates are used to calculate the statistical power or to determine the sample size. Besides the fact that heritability is not stable across populations and time, power calculations require assumptions for other parameters that are usually unknown such as the number of loci that play a role and the frequency with which these loci occur in the population. These assumptions highly limit the meaning of power calculations performed before linkage analysis.

To increase the power in linkage studies of complex diseases, restricting the study population to family members with extreme phenotypic expression of the trait has been suggested. This would result in reduced genetic variation within siblings with extreme concordant trait values and maximize the genetic variation between siblings with opposite extremes. Under those circumstances, heritability estimates are not useful at all.

Major questions regarding the likelihood that genetic involvement in a disease are how many genes are involved, their individual impact, and the potential to map these genes by linkage analyses. Efforts to measure heritability do not answer these questions. A trait influenced by a few loci is the best candidate for linkage. A high heritability of a trait in a certain population only leads to successful mapping in case of a few important loci. A high heritability resulting from a cumulative effect of many minor genetic effects will therefore not lead to success. If all environmental factors are known and measured, a linkage study could successfully detect the genes involved even for a trait with a low heritability, as long as the (main) genetic variance is due to a limited number of genes.

Conclusions

Estimates of heritability to evaluate the genetic contributions to traits must be interpreted with great caution. In general, heritability is not a reliable measure to compare the relative importance of genes to explain differences in disease occurrence between different populations or to compare the genetic contribution to different traits. Neither does it provide a reliable parameter for estimating the statistical power of a linkage study. Heritability estimates in human studies have serious limitations as a valid quantitative measure, in contrast to animal and plant studies that involve large numbers of progeny with a relatively fixed or constant environment.

As a consequence, the results from heritability studies in humans cannot be used with confidence. Absence of an alternative does not justify the continued estimation and publication of heritability estimates. Currently, the role of heritability in human studies may be better considered qualitatively with a judgment on whether detectable genetic variance is present and not its magnitude. To accept a quantitative heritability estimate from any study as a fact of nature is but an illusion.

Disclosures

None.

References


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