

Purpose of analysis

Just as the objects of analysis are different when we analyze causes and when we analyze variance, so the purposes of these analyses are different. The analysis of causes in human genetics is meant to provide us with the basic knowledge we require for correct schemes of environmental modification and intervention. Together with a knowledge of the relative frequencies of different human genotypes, a knowledge of norms of reaction can also predict the demographic and public health consequences of certain massive environmental changes. Analysis of variance can do neither of these because its results are a unique function of the present distribution of environment and genotypes.

The legitimate purposes of the analysis of variance in human genetics are to predict the rate at which selection may alter the genotypic composition of human populations and to reconstruct, in some cases, the past selective history of the species. Neither of these seems to be a pressing problem since both are academic. Changes in the genotypic composition of the species take place so slowly as compared to the extraordinary rate of human social and cultural evolution, that human activity and welfare are unlikely to depend upon such genetic change. The reconstruction of man's genetic past, while fascinating, is an activity of leisure rather than of necessity. At any rate, both these objectives require not simply the analysis into genetic and environmental components of variation, but require absolutely

a finer analysis of genetic variance into its additive and nonadditive components. The simple analysis of variance is useless for these purposes and indeed it has no use at all. In view of the terrible mischief that has been done by confusing the spatiotemporally local analysis of variance with the global analysis of causes, I suggest that we stop the endless search for better methods of estimating useless quantities. There are plenty of real problems.

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Commentary: Heritability estimates—long past their sell-by date

Steven P R Rose

Heritability then

It might seem—it probably is—presumptuous for a neuroscientist to comment on a theoretical text in population genetics, especially when the paper in question is by one of the prominent figures in the field. However, it is relevant to recall the context in which Lewontin's 1974 article in *The American Journal of Human Genetics*¹ appeared. Symbolized by the publication, in 1969, of Arthur Jensen's article: *How much can we boost IQ and scholastic achievement?*,² there had been a resurgence of claims as to the heritability of human traits. Jensen had argued that, as IQ scores had a high heritability (~80%), it followed that the consistent difference in IQ scores between black and white citizens of the US was too great to be

accounted for by 'environmental' factors. Instead, he concluded, the on average lower IQ of blacks compared with whites must reflect genetic differences between the two populations.

Jensen's contention raised a firestorm of political and scientific responses (e.g. Kamin,³ Gould,⁴ Rose *et al.*⁵). Some of these focussed on empirical inadequacy, others on the theoretical limitations of the IQ theory and of heritability calculations. It is with the latter two that Lewontin's article is concerned. His intent is, first to clarify common misconceptions over the meaning of the term, and second, to emphasize its inutility outside the very narrow range of circumstances for which it was originally derived. To summarize:

- (i) Heritability is *not* a measure of the contributions of genes and environments to any *individual* phenotype, a fruitless enterprise as both are subsumed within the processes of development.

- (ii) Heritability is an estimate of the genetic and environmental contributions to the *variance* of any phenotypic measure around the mean for a given population.
- (iii) The measure cannot say anything about the causes of differences *between* populations (Jensen's earlier error).
- (iv) Heritability refers to the genetic contribution to variance *within a population and in a specific environment* (it was originally introduced for use in breeding experiments intended to improve crop yield); if the environment changes, the heritability measure changes.
- (v) Implicit in the measure is the assumption that the contributions of genes and environment are additive, although a fudge factor for small interactions is included. To demonstrate the problems with this assumption, Lewontin draws extensively on the concept, originally introduced by Schmalhausen in the USSR and developed in the US by Dobzhansky, of *norm of reaction*, which means that the phenotypic effect of any gene may vary continuously but non-linearly and often unpredictably across a range of environments. The various figures in the paper are intended to demonstrate some of these possibilities.

Beyond this important ground-clearing exercise, essential in the field of human genetics and especially human behavioural genetics, where the heritability concept was (and sometimes still is) persistently misused, or at least misunderstood, Lewontin goes on to make a much more profound point, expanded in his many subsequent books and essays (e.g. Levins and Lewontin^{6,7}). As scientists, we are interested in the causes of the phenomena we study. In genetics, this may refer to the supposed causal effects of specific genes or combinations of genes on phenotypic expression. The heritability equation, however, shifts attention away from the attempt to understand the relationship between gene, genome, and phenotype towards a statistical formalism, the *variance* of phenotypes from the mean. In a world where there are real biological phenomena to be studied, he concludes, heritability is a 'useless quantity'.

Heritability now

More than 3 decades after Lewontin's paper appeared, the face of genetics has been transformed beyond recognition, in part as a consequence of some of his own early discoveries about the extent of apparently selectively neutral protein polymorphisms in wild-type populations. For molecular geneticists and developmental biologists, 'genes' are no longer theoretical constructs, Mendel's 'hidden determinants', inferred from statistical manipulation of pedigrees. The Human Genome Project revealed a genome over 98% of which is non-coding DNA, interspersed with short lengths of coding DNA that are regulated, spliced, edited, and transcribed in a huge number of different ways, enabling humans with our hundred-thousand or so different proteins and 250-odd different cell types to construct ourselves with the help of not many more 'genes' as does the fruit fly. Indeed, for many purposes, except perhaps those of theoretical evolutionary modelling, the term 'gene' has outlived its shelf-life (Rose,⁸ Keller⁹). It is a figment; what exists, as the molecular geneticist

Alberto Ferrus (personal communication) has put it, is the genome.

In the laboratory, interest focuses on identifying the ways in which during development the expression of particular DNA sequences is regulated and the consequent cellular pattern of proteins—so called proteomics. (As a biochemist by training I have problems with that term too, as it misses the dynamics that is the essential property of living organisms, reducing it to a smattering of spots of a two-dimensional gel). Population genetics too has been transformed. DNA databases are mined to reveal either mutations in coding regions or single nucleotide polymorphisms in non-coding regions, which might be correlated with particular disease or behavioural susceptibilities. Interest has shifted from single gene disorders, often transmitted in semi-Mendelian ways, to the attempt to identify genetic risk factors—conditions influenced by many genes of small effect. In this more modern context it is no longer necessary to invoke norms of reaction, as it is abundantly clear that gene expression cannot be considered in the abstract but is a contingent feature of the developmental process, a process that engages the entire genome and multiple environmental levels.⁸ It is in these approaches that Lewontin's call for the analysis of causes is being pursued.

Under these circumstances, one might imagine that the 'useless quantity' of heritability would have been discarded. Even if not repudiated, as in chemistry phlogiston was replaced by oxygen, the laborious calculation of heritability estimates should at least have been given an honourable pension. In many areas of genetic research this is indeed the case. However, in one field in particular, that of psychometry and 'behaviour', researchers cling to the concept as if afraid of letting go the hand of the nurse. Heritability estimates are compiled for everything from sexual orientation to political tendency and 'compulsive shopping'. And the emphasis on the heritability of 'intelligence' (or more precisely, IQ) persists, witness the reprise of Jensen in Herrnstein and Murray's book *The Bell Curve*.¹⁰ From Minneapolis to the Maudsley, the fascination with trawling national twin registers persists and routinely makes newspaper headlines. It is true that the mathematics has become a little more sophisticated, and attempts are made to identify quantitative trait loci (QTLs)—. However, it is not generally recognized that QTL analysis itself relies on a prior assumption of significant heritability.

The reasons for the persistence of heritability estimates are worth some discussion. One is the intractability of most forms of behaviour to genetic analysis. Except in the case of relatively clear-cut Mendelian disorders such as Huntington's Disease the search for identifiable genes unequivocally associated even with conditions such as depression and schizophrenia has proved elusive. When it comes to the more elusive characters beloved of behaviour genetics ('anti-social behaviour', alcoholism, etc.) where one may question the reification of complex human interactions into presumed phenotypes with a biological locus in the individual, the hunt for 'genes for' this or that behaviour becomes even more embarrassingly vacuous. Heritability estimates become a way of applying a useless quantity to a socially constructed phenotype and thus apparently scientizing it—a clear-cut case of Garbage In, Garbage Out. And even if the estimate did indeed refer to a

material reality rather than a statistical artefact one might question its utility. The practical relevance of claiming that some character in some environment is 80% heritable provides no guidance for how to respond—except in a purely ideological way, by arguing as first Jensen and later Herrnstein and Murray did that the measure indicates that there is a permanent genetically inferior underclass and that no amount of social engineering—to say nothing of social justice—will improve its lot.

Biological systems are complex, non-linear, and non-additive. Heritability estimates are attempts to impose a simplistic and reified dichotomy (nature/nurture) on non-dichotomous processes. Real progress in genetics, developmental and behavioural biology will come from paying attention to Lewontin's insistence that we attempt to analyse causes, not variances.

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Commentary: The analysis of variance is an analysis of causes (of a very circumscribed kind)

Peter Taylor

1974—Two publications

The year 1974 saw the publication of two influential works by Richard Lewontin. In different ways, both addressed the measurement and characterization of genetic variation and asked whether this is interesting—what could we explain or do with the resulting knowledge?

*The Genetic Basis of Evolutionary Change*¹ was firmly positioned within the population genetic tradition of viewing evolution as a change of gene frequencies in a population over time. In this light it was obviously important to characterize the amount of genetic variation and account for its maintenance. Lewontin masterfully synthesized research on genetic diversity in laboratory and natural populations in relation to models of selection or its absence. At the same time he drew attention to some troublesome themes for evolutionary biology. It was not variation as such that should count, but variation that resulted

in differential fitness among the variants. Yet measurements of the components of fitness—survival and reproduction—were possible only when the phenotypic effect of a single allelic substitution was large not when the effects of gene substitutions make only small differences. This led Lewontin to remark that: 'What we can measure is by definition uninteresting and what we are interested in is by definition unmeasurable.' [p. 23 in Ref. (1)]. The problems of relating models of selection to observations become astronomically worse when there are multiple, linked loci [p. 317 in Ref. (1)]. He concluded that population genetics should shift its attention to the fitness effects of long segments of chromosomes; such effects could be measured.

The idea that many genes may contribute small effects to a trait derives from a different research tradition, quantitative genetics, which is the subject of the other publication, 'The Analysis of Variance and the Analysis of Causes' (hereon, AVAC).² Quantitative genetics concerns itself not with any specific genes having discrete (qualitative) effects but with the statistical analysis of continuous (quantitative) traits varying