Gene-free quantitative genetics: A thought experiment

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**Abstract**

Quantitative genetics is the analysis of variation in traits of humans, other animals, or plants in ways that take account of the genealogical relatedness of the individuals whose traits are observed. The standard methods of quantitative genetic analysis are based on mathematical models of hypothetical genes with simple Mendelian inheritance and direct contributions to the trait under consideration. This article introduces an alternative form of analysis of trait variation, which takes into account degrees of relatedness but makes no reference to hypothetical genes. Empirical parameters take the place of unreliable heuristics about the similarity of relatives (e.g., all other things being equal, fraternal twins should be half as similar as identical twins for any given trait because the former share only half of the genes that vary in the population). In the case of data from human twins raised together, the alternative shows the interaction variance fraction is discounted when the standard methods are used. The alternative form of analysis also helps counter the common conceptual slippage from analysis of observations of a trait to claims about differences in the genetic and environmental factors that influence it. Additional theoretical and empirical issues that invite investigation are noted.

Keywords: Data analysis; Gene-free model; Heritability; Quantitative genetics; Statistical interaction

Quantitative genetics (QG) is the analysis of variation in traits of humans, other animals, or plants in ways that take account of the genealogical relatedness of the individuals whose traits are observed. The variation in traits, such as IQ test scores, height, litter size, yield, etc., is analyzed for three primary purposes: to interpret outcomes of artificial and natural selection and guide further selective breeding; to assess the relative influence of yet-to-be identified genetic and environmental entities or "factors" underlying the development of the trait in question; and to decide whether to investigate what those specific factors are. (What constitutes a "factor" will be spelled out shortly.) Since QG emerged in the first part of the twentieth century, its methods of analysis have been based on mathematical models of hypothetical genes with simple Mendelian inheritance and direct contributions to the trait (Falconer and Mackay 1996; Lynch and Walsh 1998). However, the data analysed in QG are of traits, not genes, so it must be possible to analyze the variation without making reference to hypothetical genes. What would that possibility look like? Would a gene-free analysis make a difference? This article takes up these questions as a thought experiment.

## Preliminaries

Conventional terminology obscures some distinctions that are important to the thought experiment, so some non-standard terms need to be employed. "Factor" is used in this article in a non-technical sense simply to refer to something whose presence or absence can, at least in principle, be observed or whose level can be measured. Measurable genetic factors include the presence of pairs of alleles (variant forms of a single gene) at a specific locus on paired (diploid) chromosomes, repeated DNA sequences, reversed sections of chromosomes, etc. Measurable environmental factors include income level of the family of upbringing, maltreatment when a child, amount of fertilizer applied per hectare, etc. Recent QG analysis has begun to employ information about genetic factors (Plomin et al. 2003, Moffitt et al. 2005). However, this article concerns primarily what will be refered to as "classical" QG, meaning that no data on measurable genetic or environmental factors are involved.

In genetics a genotype is the set of genetic factors an individual possesses (or at least the subset held to be related to some given trait). In QG, however, the label "genotype" is applied to groups of individuals that are genetically identical ("pure lines") or whose mix of genetic factors can be replicated (such as an open pollinated plant variety), or to groups whose relatedness by genealogy can be characterized (such as human twins). No knowledge of actual genotypes is entailed in the QG use of the term. Similarly, the label "environment" is applied in QG to the situations or places in which the genotypes are raised without knowledge of the relevant environmental factors. In this article, the agricultural terms "variety" and "location" are used instead. A human variety consists of the offspring of a pair of parents; being raised within a family becomes an instance of a location.

In adopting the terms factor, variety, and location, the intention is to counter any conceptual slippage from analysis of observations of a given trait to claims about "genetic" and "environmental" differences, given that such claims suggest misleadingly that QG analyses of variation in traits address the measurable genetic and environmental factors involved in the development of the trait. (For a similar reason, phenotype is not used here to refer to the traits.) When the terms "genetic" and "environmental" are used, often the distinction between traits and underlying measurable factors is not clearly made or is not consistently maintained. This is the case in most accounts of classical QG (e.g., Falconer and Mackay 1996, Lynch and Walsh 1998) and human QG (e.g., Plomin et al 1997, Rijsdijk and Sham 2002), as well as in accounts critical, to various degrees, of human QG (e.g., Layzer 1974, Jacquard 1983, Otto et al. 1995, Turkheimer 1998, Kamin and Goldberger 2002). Most notably, heritability, which is calculated in QG without reference to measurements on genetic (or environmental) factors, is commonly described in terms like the "contribution of genetic differences to observed differences among individuals" (Plomin et al. 1997, 83) or "fraction of the variance of a phenotypic trait in a given population caused by (or attributable to) genetic differences" (Layzer 1974, 1259). The terminology in this article is intended to remind readers that classical QG looks at differences among variety (or "genotypic") averages (for the trait averaged across locations and replicates), not at differences in genes or genetic factors. Translation from descriptive

QG analyses to hypotheses about causal factors is far from direct and depends on assumptions of interpretation discussed elsewhere (Taylor 2009).

The thought experiment concerns classical QG as it applies to data from any species, but the kind of genealogical relatedness used for purposes of illustraton is primarily that of twins. This choice is made to allow the discussion to speak to issues in human QG. The article does not, however, address many contentious issues in human QG, which include correct ascertainment and representative sampling of zygosity of twins; definition of traits such as IQ and schizophrenia; and the size of "genotype-environment" [here: variety-location] correlations. These have been debated extensively elsewhere (for accessible reviews, see Nuffield Council on Bioethics 2002, Parens 2004).

## The basic case of gene-free QG

The thought experiment begins by considering the general case of an agricultural evaluation trial, where it is possible to observe a set of animal or plant varieties in each of a set of locations, and to raise replicates for each variety-location combination. If the trait is recorded in all replicates, the data can be fitted to an additive ("linear") model that connects the values of the trait for an individual to the summation of several contributions:

$$y_{ijk} = m + v_i + l_j + vl_{ij} + e_{ijk} \quad (1)$$

where $y_{ijk}$ denotes the measured trait y for the $i^{th}$ variety in the $j^{th}$ location and $k^{th}$ replication;

m is a base level for the trait;

$v_i$ is the additional contribution of the $i^{th}$ variety;

$l_j$ is the additional contribution of the $j^{th}$ location;

$vl_{ij}$ is the additional contribution from the $i,j^{th}$ variety-location combination—in statistical terms, the "variety-location-interaction" contribution; and

$e_{ijk}$ is an unsystematic or "noise" contribution adding to the trait measurement.

Such an additive model can be converted to a model that adds up variances related to these contributions, or reciprocally, to partition the variance of the trait into these component variances (i.e., the "analysis of variance" or ANOVA). The conversion of

equation 1 to variances is made as follows: If each kind of contribution is uncorrelated with any of the others, and m is set at the average of the trait over all varieties, locations, and replicates, then the average of each of the other contributions is zero. If m is subtracted from both sides of equation 1, which are then squared and divided by the total number of individuals to arrive at the average of these squared contributions, the result is the following partitioning of variance:

$$Y = V + L + VL + E \quad (2)$$

where

Y denotes the variance of the $y_{ijk}$ observations as a whole,

V denotes the variance of the $v_i$ terms, etc.

When the observations are fitted to this model and the right hand side of equation 2 is divided by Y, the result is the fractions of the overall variance for, respectively, among-variety averages—which is another name for heritability—, among-location averages (referred to in human QG as "shared environmental effect"), among-variety-location-interaction averages, and noise (often called error or residual effects).

If observations are made only in a subset of all the variety-location combinations, it is still possible to estimate the variances in the previous paragraph. The smaller the subset the less uniformity there will be in the variance estimated from observations on one subset to the next. Nevertheless, if the subset is randomly chosen from the full data set, it is possible to estimate V, L, VL and E (except in some special cases, such as, when each variety replicated only in one of the locations).

As in any such partitioning of variance, the results of fitting observations to an additive model are conditional on the specific set of varieties and set of locations observed—the results are not an indication of causes or properties of the varieties that apply more generally (Taylor 2006). One way to keep this conditionality in mind is to consider how $v_i$ is fitted to the data. To use the simplest case, when the number of replicates observed for every variety-location combination is the same, the value of $v_i$ will be the average of $y_{ijk}$'s for variety i <u>across all the observed locations</u> and replicates minus the average over all varieties, locations, and replicates. In other words, the contribution $v_i$ is not a property of the variety i on its own. Similarly, for any location contribution, the

values that fit the data involve an average across all varieties. (Although partitioning of variance is often conducted without making explicit the original additive model, such as equation 1, or estimating the values of the various contributions that fit the data, the partitioning can always be related to such a model.)

Suppose now that the observations are divided into classes in various ways. For example, a class might be defined by all observations in which the variety is the same. In that case, equation 1 shows that, within the class of $i^{th}$ variety, m and $v_i$ are constant, but the other terms vary. The expected average for the trait in question for the class is $m + v_i$ (because the average in the class of each of the other contributions is zero), and the variance of those averages across classes is V. Similarly, for classes defined by all observations in which the location is the same, the variance of the averages for the classes is L, and for classes defined by all observations in which both the variety and the location are the same, the variance of the averages for the classes is V + L + VL. When these variances (i.e., variances of the contributions that do not vary within the class and are thus included in the class averages) are compared to the overall variance, Y, this is called the "intraclass correlation." (The name makes sense when it is noted that for classes of size two this quantity is mathematically equivalent to the usual linear correlation of the two values when the order in each pair is arbitrary, as would be the case if one wanted to know the correlation, say, of heights in same sex couples; Howell 2002.) Finally, if the sum of the first two intraclass correlations are subtracted from the third, the result would be VL, and if the last intraclass correlation is subtracted from 1, the result would be E.

It is possible to estimate the correlations in the previous paragraph even if observations are made only in a subset of all the variety-location combinations, just as it is possible to partition the variance in the trait according to equation 2 in such subsets. If the subsets are randomly chosen from the full data set, so that there are no systematic differences among classes in the contributions from varieties, locations, variety-location combinations and noise, then the three intraclass correlations can be used to estimate V, L, and by subtraction, VL and E.

Gene-free genealogical relatedness

The genealogical relatedness among varieties has not, up to now, been taken into account in estimation of the fractions of the overall variance using equation 2 or using intraclass correlations. Consider now a special case of the agricultural situation in which the varieties are replicated as identical, monzygotic (MZ) or fraternal, dizygotic (DZ) twins—choosing here the simplest case of genealogical relatedness. Equation 1 becomes:

$$y_{ijk} = m + v^{-}_{i} + t_{ik} + l_j + vl^{-}_{ij} + tl_{ijk} + e_{ijk} \quad (3)$$

where $y_{ijk}$, m, $l_j$, $e_{ijk}$ are as before;

$t_{ik}$ denotes an additional contribution from the $k^{th}$ twin (replicate) in the $i^{th}$ variety;

$tl_{ijk}$ is an additional contribution from the $k^{th}$ twin in the $i,j^{th}$ variety-location combination;

$v^{-}_{i}$ and $vl^{-}_{ij}$ replace the $v_i$ and $vl_{ij}$ contributions in equation 1. (The superscript indicates that the new contributions would tend to be smaller given the contributions of $t_{ik}$ and $tl_{ijk}$ to differences among twins [replicates].)

Note that for MZ twins $t_{i1} = t_{i2}$ and $tl_{ij1} = tl_{ij2}$. Assume for simplicity that the variance of the trait over all individuals is the same as in the general case, namely, Y. The partitioning of variance in equation 10 then becomes:

$$Y = V^{-} + T + L + VL^{-} + TL + E \quad (4)$$

where $V^{-}$ denotes the overall variance of the $v_i^{-}$ terms, etc.

The formulas for intraclass correlations in the situation of the agricultural trial with twins as replicates can be derived by identifying the contributions that do not vary within the twin pairs (and are thus included in the twin-pair averages), summing the variance of these contributions, and dividing by the overall variance. In the case where both twins in a pair are raised in the same location (family):

$$I_{MZ} = (V^{-} + T + L + VL^{-} + TL) / Y \quad (5)$$

$$I_{DZ} = (V^{-} + L + VL^{-}) / Y \quad (6)$$

where I denotes intraclass correlation and the subscript the kind of twin in the replicate.

(The difference between the formulas for MZ twins and DZ twins can be understood by recognizing that the equal $t_{ik}$ and equal $tl_{ijk}$ values for MZ twins means that these components do not vary within MZ twin pairs.)

If it is assumed that no systematic differences between the varieties and locations in which MZ pairs are observed and those in which DZ pairs are observed, so that variances with the same symbol refer to the same quantity in equations 4-6, these equations can be rearranged to yield the following:

$$2 ( \quad T \quad + TL) / Y \quad = 2 (I_{MZ} - I_{DZ}) \tag{7}$$

$$(V^{-} - T + L + VL^{-} - TL) / Y \quad = 2 I_{DZ} – I_{MZ} \tag{8}$$

$$E /Y \quad = 1 - I_{MZ} \tag{9}$$

Equation 9 can be used to estimate E, but equations 8 and 9 do not resemble any formulas given in QG texts. Suppose, however, that the data meet the following empirical condition:

$$V^{-} + VL^{-} \quad = T + TL \quad = .5 (V +VL) \tag{10}$$

Under this condition, equations 7 and 8 simplify to:

$$(V + VL) / Y \quad = 2 (I_{MZ} - I_{DZ} ) \tag{11}$$

$$L / Y \quad = 2 I_{DZ} – I_{MZ} \tag{12}$$

Equations 11 and 12 are the formulas used in twin studies for heritability and among-location-average variance fraction (Rijsdijk and Sham 2002), with one adjustment: V + VL takes the place of V.

In due course the V versus V +VL discrepancy and the empirical condition in equation 10 will be made sense of. What is important to note at this stage, however, is that equations 11 and 12 allow observations to be analyzed in a way that takes into account the genealogical relatedness yet makes no reference to or assumptions about hypothetical genes. No models of the contribution of such genes to the trait are needed in this derivation of the formulas that use intraclass correlations to estimate heritability and the fraction of the total variance made up by the among-location-average variance, L. Moreover, gene-free derivations of analyses for comparing relatives of other degrees (e.g., full sibs versus half-sibs) can be derived by the same approach, each derivation having its own equivalent of the empirical equality condition (equation 10).

Finally, in place of the agricultural case, consider the restricted circumstances of human twin studies, where each variety is observed only in a single, randomly chosen location (one location for each variety) and the twins are the two replicates for each of those variety-location combinations. (Non-random assignment of varieties to locations ["genotype-environment correlation"] is possible, but will not be considered here; Jacquard 1983.) Instead of partitioning the variance based on equation 3, a variant of equation 3 needs to be employed that replaces the subscript j with the subscript i. Provided the locations are randomly chosen, the expected estimates of the variances in equation 4 remain the same, and, given this, the expected results of the formulas based on intraclass correlations (equations 11 and 12) are the same. In short, the alternative, gene-free derivation for analysis of the agricultural case still holds for human twin studies.

Elaboration of the gene-free model and estimation of values

Is there empirical support for the equality condition in equation 10? (Recall that this condition arises from the move from the basic agricultural model in equation 1 to the situation in which replicates are twins in equation 3, where the overall variety variance (V) and variety-location-interaction variance (VL) are both split into two parts in equation 4.) To address this question it could be assumed that the terms are not equal and develop a method to estimate the ratio between them. Suppose then that the data meet the following empirical condition:

$$(V^{-} + VL^{-}) / f = T + TL = (V + VL) / (f + 1) \quad (13)$$

where f is a positive number (not necessarily equal to 1; i.e., the two parts are not necessarily equal).

The standard twin studies formulas for heritability and among-location-average variance fraction can then be estimated using observations across a number of locations:

$$(V + VL)/Y * 2 / (f+1) = 2 (I_{MZ} - I_{DZ}) \quad (14)$$

$$L/Y + (V + VL)/Y * (f-1)/(f+1) = 2 I_{DZ} - I_{MZ} \quad (15)$$

If f > 1, the left hand side of Eq. 14 is smaller than the left hand side of Eq. 11 (which assumes f =1); similarly, the left hand side of Eq. 15 is larger than the left hand side of Eq.

12. Conversely, if f < 1. These discrepancies disappear, however, if equations 11 and 12 are replaced by the following generalized forms:

$$(V + VL)/ Y = (f + 1) (I_{MZ} – I_{DZ}) \quad (16)$$

$$L / Y = I_{DZ} - f (I_{MZ} – I_{DZ}) \quad (17)$$

If equations 16 and 17 are used, the empirical question of whether the equality condition (equation 10) is met is superseded by the empirical question of what value f takes. The presence of V + VL, where V is expected from standard QG analysis of twins, remains.

To estimate f requires an additional kind of observation (providing three equations for three unknowns); to separate V from VL requires yet another kind of observation. To this end it is possible to make use of the studies of twins raised together with two other kinds of study: twins raised apart in randomly chosen locations; and groups of individuals from different varieties raised together, that is, each group in one randomly chosen location. Making use of the twins-raised-apart studies requires that the choice of locations of twins raised apart is truly random, that is, they are no more similar to each other on average than any two of the possible locations. Making use of the three kinds of studies together also requires the "equal environment assumption," that is, the treatment or experience of the twins or unrelated individuals within a location (for humans: family) is unaffected by whether they are MZ or DZ twins, non-twinned siblings, or unrelated. (This is a plausible assumption for agricultural and laboratory studies; a contested assumption for human QG; see Richardson and Norgate 2005.) Under these conditions, it becomes possible to use intraclass correlations to estimate values, as a fraction of Y, for $V^-$, T, L, $VL^-$, and TL. If subscripts MZ, DZ, MZA, DZA, UVT stand for, respectively, MZ and DZ twins raised together, MZ and DZ twins raised apart, and unrelated varieties raised together, then

$$I_{MZA} = (V^- + T) / Y \quad (18)$$

$$I_{DZA} = V^- / Y \quad (19)$$

$$I_{UVT} = L / Y \quad (20)$$

Together with equations 5 and 6, these equations can be rearranged to yield:

$$V^- /Y = I_{DZA} \quad (21)$$

$$T /Y = I_{MZA} – I_{DZA} \quad (22)$$

$$L /Y = I_{UVT} \quad (23)$$

$$VL^{-}/Y = I_{DZ} - I_{UVT} - I_{DZA} \quad (24)$$

$$TL/Y = I_{MZ} - I_{MZA} - I_{DZ} + I_{DZA} \quad (25)$$

From these equations, the following can also be derived:

$$V/Y = I_{MZA} \quad (26)$$

$$VL/Y = I_{MZ} - I_{MZA} - I_{UVT} \quad (27)$$

$$f = (I_{DZ} - I_{UVT})/(I_{MZ} - I_{DZ}) \quad (28)$$

Equations 20, 26, and 27 show that, in principle, the partitioning of variance under equation 2 can be completed in a way that takes into account the genealogical relatedness but makes no reference to or assumptions about hypothetical genes. (As before, gene-free derivations of analyses for comparing relatives of other degrees can be derived by the same approach, each derivation this time having its own equivalent of f and yielding a set of equations for estimation of the values of interest.)

Table 1. Three approaches to estimation of values in gene-free model

| **Data Set*** | **Conditions** | **Assumptions** | **Values that can be estimated** |
|---|---|---|---|
| 1 & 2. MZ, DZ in the same location (family) | | 1. Set value of f (not necessarily = 1) | V + VL, L, E can be estimated as fractions of Y |
| | | 2. Value of f unknown | E and composites of V + VL, L and f can be estimated as fractions of Y |
| 3. MZ, DZ, MZA, DZA, UVT in the same population | randomly chosen locations; equal environments | | V, L, VL, E can be estimated as fractions of Y; f can be estimated |

* MZ, DZ, MZA, DZA, UVT stand for, respectively, MZ and DZ twins raised together, MZ and DZ twins raised apart, and unrelated varieties raised together

A summary of the three approaches to estimation of f and variances as fractions of Y is given in Table 1. Using the third approach, the empirical value of f can be ascertained. The author has not been able to locate a data set for MZ, DZ, MZA, DZA, UVT in the same population, let alone a set that meets the conditions of randomly chosen locations and equal environments (discussed above). The approach can, at least, be illustrated by using the average intraclass correlations from human data assembled by Bouchard and McGue (1981) regarding IQ test scores. They do not report a value for DZA, but, if their figure for sibs raised apart is used in its place, then the data yield estimates, as a fraction of Y, of V, .72; L, .34; VL, -.20; and E, .14; which translates to f, 1.0. If the negative variance estimate for TL of -.22 (which is the cause of the negative estimate of VL) is replaced by zero and the other estimates adjusted so that their total is still 1, then, as a fraction of Y, V is .59; L, .28; VL, .02; E, .11; and f , .56. (All calculations available from the author on request. Ideally, the estimates should be accompanied by confidence intervals, but these cannot be determined using the data as assembled by Bouchard and McGue.) It is hard to judge what weight to give to the value of f not equal to 1 from these two alternative sets of estimates; in any case, they were included for illustration only.

In the absence of data sets that allow the third approach to be used, the first approach might be used, provided some value for f is set. Equations 16 and 17 allow the estimation, as a fraction of Y, of V + VL, L, and E. This approach provides no basis for separating V/Y from VL/Y, so one might as well divide any estimate made using equation 16 into two equal halves. In other words, the best estimate—albeit a crude one—of V/Y (i.e., heritability) would be only half of the estimate using the standard formulas from twin studies (Rijsdijk and Sham 2002). In fact, in agricultural plant evaluation trials, VL is typically as large as V. It is not known whether this is also the case for traits in animal or human populations observed in a typical range of locations. Yet, the size of the interaction variance has to be estimated by human QG researcher wanting to claim that variation among locations (families) is of small importance (or of smaller importance than had been believed) (Turkheimer 2000). To support such a claim entails showing not only that the among-location-averages variance is a small fraction of the total variance, but so also is the variety-location-interaction variance.

A note of clarification of the term "interaction": "Genotype-environment interaction" is used in range of ways, including cases in which "genotype" denotes a value of a measured genetic factor and/or "environment" denotes a value of a measured environmental factor (e.g., Plomin et al. 1977, Moffitt et al. 2005). The term "variety-location interaction" is used here to refer only to the analysis of trait variation made without reference to measured factors (see equation 1). In everyday terms, a high degree of variety-location interaction means that the responses of the observed varieties across the range of the observed locations do not parallel one another, that is, one variety may be highest for the trait in one location, but another variety may be highest in another location—or, at least, the difference between any two varieties may change location to location.

In the absence of a data set that allows the third approach to be used, and if a value for f is not set, only the second approach to gene-free QG summarized in Table 1 remains. That approach yields a clear estimate only of E as a fraction of Y.

Taking a fresh look at standard QG analysis

How does classical QG avoid the limitations that emerge in gene-free QG? For example, the standard formulas used in twin studies to estimate heritability and among-location-average variance fraction require only two intraclass correlations, $I_{MZ}$ and $I_{DZ}$ , in two equations (Rijsdijk and Sham 2002). One might suspect that some additional assumptions have been made. After all, for a given Y in equation 2, there are three independent variances, so some assumption must be required to eliminate the need for a third equation. To expose the assumptions, it is necessary reexamine, using the terminology of this article, the sequence of steps through which the standard models of QG are derived (Falconer and Mackay 1996; Lynch and Walsh 1998).

The first step is to consider the case of a trait governed by a pair of alleles of a single gene (i.e., at a single locus) where all the individuals are raised in a single location. In that location, the genes contribute directly to the trait in the sense that the presence or level of such a trait depends only on whether the individual has two copies of one allele (i.e., is “homozygote” for that allele), two of the other, or one of each (“heterozygote”).

For example, phenylketonuria (PKU) in humans is associated with having two copies of a non-functioning allele for the enzyme phenylalanine hydroxylase (PAH). The development of such individuals is extremely impaired by the level of phenylalanine present in normal diets. In this "normal-diet" location relatives will resemble each other more than unrelated individuals because if, say, a twin has PKU, both parents have at least one copy of the non-functioning PAH allele so the other twin is more likely to have two non-functioning PAH alleles than is an unrelated individual (i.e., one chosen at random from the population).

Intraclass correlation quantifies the resemblance of relatives for the given trait. For a trait governed by alleles at a single locus, the intraclass correlation for MZ twins is 1—there is no variation within the pairs—and for DZ twins is .5. (Recent research shows discordance between MZ twins at the genetic level, e.g., Bruder et al. 2008, but the simplication of an intraclass correlation of 1 for MZ twins is preserved in this article. Note also that the DZ intraclass correlation value is independent of the frequency in the population of the two alleles and of the degree of "dominance," which refers to degree that heterozygote individuals depart from the intermediate between the other two homozygote forms. The algebra is available from the author on request.)

Few traits are dictated only by alleles at a single locus, so the standard models of QG envisage the influence of alleles at many loci adding up to shape the traits to be observed and analyzed. If each pair of alleles is assumed to add a small direct contribution to the trait in the sense that each contribution is independent of the others, then the ratio of the variation among twin-pair averages to the total variance is unchanged and the intraclass correlations for MZ and DZ pairs remain the same. (Note that, because these intraclass correlations incorporate no environmental or unsystematic influences, they have been termed "genetic similarity" or "genetic correlation." However, to avoid any risk of implying that similarity in traits as analyzed in classical QG has a direct relation with similarity in genetic factors, the ambiguous adjective "genetic" is not used in this article's discussion of similarity.)

Next, the models allow for some noise (from measurement error or unsystematic variation among the replicates of the variety), which, in the case of twins, is assumed to be equal for both kinds of twins, that is:

$$Y = V^{+} + E \quad (29)$$

where

Y is the total variance for the trait across all replicates,

E is the noise contribution, and

$V^{+}$ refers both to the variance among the MZ twin-pair averages and to the variance among the DZ twin-pair averages combined with the average variance within the DZ twin pairs. (The superscript will be explained in due course.)

The intraclass correlations in the single location are no longer 1 and .5, but are given by:

$$I_{MZ} = V^{+} / Y \quad (30)$$

$$I_{DZ} = .5\ V^{+} / Y \quad (31)$$

Finally, to allow for the variety to be raised in a number of locations, the standard models of QG incorporate into the equations a term for variance across locations of the average value of the trait in each location. Again, the models assume that this term, L, is equal for both kinds of twins, that is:

$$Y = V^{+} + L + E \quad (32)$$

and

$$I_{MZ} = (V^{+} + L) / Y \quad (33)$$

$$I_{DZ} = (.5\ V^{+} + L) / Y \quad (34)$$

Now, if the intraclass correlations for the trait (in conventional terms: the "phenotypic correlations") are calculated from observations for a number of MZ and DZ twin pairs, then the fractions of the total variance made up by $V^{+}$ and L can be estimated using the following algebraic rearrangements of equations 33 and 34:

$$V^{+}/ Y = 2 (I_{MZ} - I_{DZ}) \quad (35)$$

$$L/ Y = 2 I_{DZ} - I_{MZ} \quad (36)$$

Equations 35 and 36 are identical to formulas used in twin studies for heritability and among-location-average variance fraction (Rijsdijk and Sham 2002), with one adjustment: $V^{+}$ takes the place of V. In other words, they are identical to equations 16 and 17, except that $V^{+}/ Y$ takes the place of (V+VL)/Y, that is, $V^{+}/ Y$ is an inflated estimate of V/ Y. What is not clear yet is why this inflation should be the case and where the equivalent of f comes into this derivation. The second issue will be taken first.

As noted above, for a trait observed at a single location and governed only by alleles at a single locus, the intraclass correlation for MZ twins is 1 and for DZ twins is .5. In this case, DZ twins are half as similar as MZ twins. Extrapolating from this fact and can it be concluded that the same ratio holds for other kinds of traits? The answer might be yes if there were evidence for the assumptions built into the subsequent steps in the derivation of the standard QG formulas (e.g., each pair of alleles adds a small contribution independently of the others). Such evidence is lacking, which is not surprising given the problems inherent in trying to discriminate among the contributions of many different loci (Lewontin 1974). In the absence of such evidence, QG researchers invoke a heuristic that connects the set of genes as a whole to similarities in the trait, namely, all other things being equal, DZ twins are half as similar as MZ twins <u>because</u> DZ twins share half the genes that vary in the population, while MZ twins share them all (e.g., Kendler and Prescott 2006, 42). (The common statement that DZ twins share half of their genes is not correct; it fails to acknowledge the large proportion of genes shared by all individuals in the given species.)

The heuristic is not reliable. It is straightforward to invent plausible models of the contributions of multiple genes to a trait that result in ratios of DZ: MZ similarity that are not .5 and that vary considerably around their average. Consider, for example, a disease trait modeled in the following way: The trait occurs when the combined "dosage" from many loci exceeds a threshold, where each pair of alleles contributes a full, zero, or half dose according to whether the alleles are, respectively, both the same for one variant, same for the other, or one of each. In this case, the intraclass correlation varies according to the frequency of alleles, level of dominance, and so on, and the varying values are predominantly well above .5. (The calculations are available from the author on request.) Of course, more complicated models of the interaction of genes and the timing of their contributions during development are possible. However, the point here does not depend on the validity of the model just mentioned or of any particular model of multiple hypothetical genes contributing to the trait. The reason that the heuristic is unreliable is that the relevant correlations need to be based on observed <u>traits</u> and, as such, cannot be directly given by the proportion of shared <u>genes</u> involved in the development of those traits. (For the same reason, heuristic values of the similarity of relatives of other degrees,

which are ubiquitous in QG path analyses and structural equation modeling, are also unreliable.)

Suppose the standard Mendelian derivation of twin studies described above is adjusted so it begins with an unknown intraclass correlation of $\gamma$ for DZ twins for a trait governed by a single locus observed in a single location. That is, equation 31 is replaced by:

$$I_{DZ} = \gamma V^{+} / Y \quad (37)$$

The same steps as above yield, in place of equations 35 and 36:

$$V^{+}/ Y = (I_{MZ} - I_{DZ})/(1- \gamma) \quad (38)$$

$$L / Y = I_{DZ} - \gamma (I_{MZ} - I_{DZ})/(1- \gamma) \quad (39)$$

If f is set to $\gamma / (1- \gamma)$, these equations become:

$$V^{+}/ Y = (f + 1) (I_{MZ} - I_{DZ}) \quad (40)$$

$$L / Y = I_{DZ} - f (I_{MZ} - I_{DZ}) \quad (41)$$

Equations 40 and 41 are identical to equations 16 and 17, except, again, that $V^{+}/ Y$ has taken the place of $(V + VL)/ Y$. Allowing for the unknown intraclass correlation of $\gamma$ for DZ twins brings the standard and gene-free models closer together. (However, the justification for a value of $\gamma$ other than .5 in the single-locus, single-location case is not obvious, so $\gamma$ might best be viewed as a value, like f, that has to be estimated in order to estimate the variances from data drawn from different forms of relatives.)

It still remains to understand where VL becomes incorporated into $V^{+}$ during the standard derivation. Consider equation 1 in some fixed location, say, J:

$$y_{iJk} = m + v_i + l_J + vl_{iJ} + e_{iJk} \quad (42)$$

Collecting the terms that are constant and the terms that vary from one variety to the next,

$$y_{iJk} = (m + l_J) + (v_i + vl_{iJ}) + e_{iJk} \quad (43)$$

and

$$Y = (V +VL) + E \quad (44)$$

Equation 44 serves as a reminder that, in equation 29, which refers to a single location, the variance for the trait among the MZ twin pairs, $V^{+}$, combines variance that is specific to that location with variance that would, if the varieties were raised across all locations, show up as differences among the averages for the varieties. The combination of location-specific (i.e., the variety-location-interaction variance) and across-location (i.e., the

variance among variety averages)—in short, the summation of VL and V—is preserved through the subsequent steps of the derivation of the standard models of twin studies (and into equations 36 and 37). The combination of VL and V in human QG should not be surprising. In the case of agricultural evaluation trials, in which a set of varieties is observed in each of a set of locations, it is possible to estimate V and VL separately (equation 2; see above). In studies of human twins raised together, in contrast, when each variety is observed in one location with two replicates (twins) for each of those variety-location combinations, there is no way to ascertain how much the variation among varieties would change if the varieties were observed in locations (families) other than the ones in which they were actually observed.

In summary, classical QG has not avoided the limitations that emerge in gene-free QG; both methods need data on MZ, DZ, MZA, DZA, and UVT in the same population in order to estimate the values properly. The standard formulas in QG for estimating heritability and from data on MZ and DZ twins raised in the same locations (families) require an unreliable heuristic about the similarity of relatives and a discounting of the fraction of variance from among variety-location-interaction averages (Table 2).

Table 2. Comparison of Standard QG and gene-free QG

| | **Standard QG** | **Gene-free QG** |
|---|---|---|
| General assumptions | Variation in the trait = sum of independent influences of many loci,<br>plus two added variances that are equal for different kinds of relatives: a) noise; and b) variance across locations of the average value of the trait in each location | No assumptions about genes<br><br>No systematic differences between the varieties, locations, and noise in which different kinds of relatives are observed |
| MZ, DZ in the same location (family) | If $\gamma = .5$, $V^+$, L, E can be estimated as fractions of Y | If $f = 1$, V + VL, L, E can be estimated as fractions of Y |

| | | |
|---|---|---|
| | When $V^+/Y$ is taken as an estimate of heritability, this discounts VL | Heritability, V/Y, cannot be separately estimated from VL/Y |
| | $\gamma = .5$ based on theoretical heuristic that is unreliable | Value of f needs empirical determination |
| MZ, DZ, MZA, DZA, UVT in the same population; randomly chosen locations (i.e., "equal environments") | Models with more than two variance fractions and values can be fitted to the data (see text to follow). | V, L, VL, E can be estimated as fractions of Y; f can be estimated |

Further steps

The gene-free QG thought experiment opens up additional theoretical and empirical issues for investigation:

1. The models on which classical QG is based, namely, of genes with simple Mendelian inheritance and direct contributions to the trait, have been elaborated by allowing dominance interactions among alleles at separate loci, epistatic interactions among loci, narrow versus broad heritability, and so on (Falconer and Mackay 1996; Lynch and Walsh 1998). If a sufficient number of different kinds of relatives are observed and comparisons among them are justified (i.e., required conditions, such as same population and randomly chosen locations, are met), the values of these models can be estimated. Can such elaborations be translated into gene-free QG? If so, does the translation result in an empirical rather than theoretical interpretation for the values (analogous to $\gamma$ versus f in the twins case)? How, moreover, do competing models from classical QG (Otto et al. 1995) compare when all of them are translated into gene-free QG?

2. If the proportionality that is used heuristically to link similarity of variety contributions to fraction of variable genes that relatives share is replaced by an empirically determined value (f or $\gamma$ for twin studies), what average value and range do these values

take in agricultural and laboratory populations, where empirical estimation is not difficult? In studies of twins in such populations, is the value of $\gamma$ generally close to .5 and how widely do the values vary? If the average value and ranges are extrapolated to human QG, what difference does it make to previously reported results from comparing MZ versus DZ twins raised together? The same questions could be asked of the equivalent values that arise in gene-free derivations of analyses for comparing relatives of other degrees (e.g., full sibs and half-sibs). Is there a linear relation between the empirically determined values for relatives of various degrees and the fraction of variable genes that each kind of relative shares? What difference do these empirical values make to the results of path analysis and structural equation modeling that makes use of the theoretical, heuristic values.

3. Can sets of data be found for twins raised together and apart and non-related individuals raised together be used to generate estimates for the variety-location-interaction ("genotype-environment interaction") fraction of variance for animal and human QG? Is the variety-location-interaction variance (and thus the amount of inflation involved in using $V^+$ as an estimate of V) generally negligible? How sensitive are the estimates to the special conditions required for the analyses of twins raised apart?

## Conclusion

How big a difference would a gene-free QG make? In two senses, this is an empirical matter beyond the scope of this article. Firstly, it depends on the results of the further investigations laid out but not pursued above. Secondly, it remains to be seen whether anyone puts in the work to produce gene-free derivations to compare relatives other than twins. It is unreasonable to expect researchers to jettison the highly elaborated analytic infrastructure of classical QG (Falconer and Mackay 1996; Lynch and Walsh 1998; Holland et al. 2003) simply on the basis of an article showing that an alternative form of analysis of trait variation is possible.

In advance of empirical outcomes on the preceeding issues, the thought experiment has potential implications for how descriptive QG analyses are translated into hypotheses about causal factors. Recall the preliminary remark that the terms factor, variety, and location were being adopted here in order to "counter any conceptual slippage from

analysis of observations of a given trait to claims about 'genetic' and 'environmental' differences." By showing that analysis of observations of trait variation is possible without reference to genes, the thought experiment further resists that conceptual slippage. Is there then any scientific necessity to interpret the results of classical QG in terms of differences in the genes and environmental factors that underlie those traits? That seems to be something worth thinking more about, even as QG analysis has now begun to employ direct information about genetic factors.

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**References**

Bouchard, T., and McGue, M., 1981. Familial studies of intelligence: a review. Science 212, 1055-1059.

Bruder, C.E.G., Piotrowski, A., Gijsbers, A.A.C.J., Andersson, R., Erickson, S., Ståhl, T.D.d., Menzel, U., Sandgren, J., Tell, D.v., Poplawski, A., Crowley, M., Crasto, C., Partridge, E.C., Tiwari, H., Allison, D.B., Komorowski, J., Ommen, G.-J.B.v., Boomsma, D.I., Pedersen, N.L., Dunnen, J.T.d., Wirdefeldt, K., and Dumanski, J.P., 2008. Phenotypically Concordant and Discordant Monozygotic Twins Display Different DNA Copy-Number-Variation Profiles American Journal of Human Genetics 82, 763-771.

Falconer, D.S., and Mackay, T.F.C., 1996. Introduction to Quantitative Genetics. Longman, Harlow.

Freedman, D.A., Linear statistical models for causation: A critical review, in: Everitt, B. and Howell, D., Eds.), Encyclopedia of Statistics in the Behavioral Sciences, Wiley, Chichester 2005.

Holland, J.B., Nyquist, W.E., and Cervantes-Martínez, C.T., 2003. Estimating and interpreting heritability for plant breeding: An update. Plant Breeding Reviews 22, 9-112.

Howell, D.C., 2002. Intraclass Correlation: For Unordered Pairs. http://www.uvm.edu/~dhowell/StatPages/More_Stuff/icc/icc.html (viewed 10 January 2007).

Jacquard, A., 1983. Heritability: One word, Three concepts. Biometrics 39, 465-477.

Kamin, L.J., and Goldberger, A.S., 2002. Twin studies in behavioral research: A skeptical view. Theoretical Population Biology 61, 83-95.

Kendler, K.S., and Prescott, C.A., 2006. Genes, Environment, and Psychopathology: Understanding the Causes of Psychiatric and Substance Abuse Disorders. The Guilford Press, New York.

Layzer, D., 1974. Heritability Analyses of IQ Scores: Science or Numerology? Science 183, 1259 - 1266.

Lewontin, R.C., 1974. The Genetic Basis of Evolutionary Change. Columbia University Press, New York.

Lynch, M., and Walsh, B., 1998. Genetics and Analysis of Quantitative Traits. Sinauer, Sunderland, MA.

Moffitt, T.E., Caspi, A., and Rutter, M., 2005. Strategy for investigating interactions between measured genes and measured environments. Archives of General Psychiatry 62, 473-481.

Nuffield Council on Bioethics, 2002. Genetics and Human Behavior: The Ethical Context. http://www.nuffieldbioethics.org (viewed 22 June 2007).

Otto, S.P., Christiansen, F.B., and Feldman, M.W., 1995. Genetic and cultural inheritance of continuous traits. Stanford University Morrison Institute for Population and Resource Studies Working Paper Series #64. http://www.stanford.edu/group/morrinst/pdf/64.pdf (viewed 29 March 2009)

Parens, E., 2004. Genetic differences and human identities: On why talking about behavioral genetics is important and difficult. Hastings Center Report, S1-S36.

Plomin, R., Defries, J.C., Craig, I.W., and McGuffi, P. (Eds.), 2003. Behavioral Genetics in the Postgenomic Era. American Psychological Association, Washington, DC.

Plomin, R., DeFries, J.C., and Loehlin, J.C., 1977. Genotype-environment interaction correlation in analysis of human behavior. Psychological Bulletin 84, 309-322.

Plomin, R., Defries, J.C., McClearn, G.E., and Rutter, M., 1997. Behavioral Genetics. Freeman, New York.

Richardson, K., and Norgate, S., 2005. The equal environments assumption of classical twin studies may not hold. British Journal Educational Psychology 75, 339-350.

Rijsdijk, F.V., and Sham, P.C., 2002. Analytic approaches to twin data using structural equation

models. Briefings In Bioinformatics 3, 119–133.

Taylor, P.J., 2006. Heritability and heterogeneity: On the limited relevance of heritability in investigating genetic and environmental factors. Biological Theory: Integrating Development, Evolution and Cognition 1, 150-164.

Taylor, P.J., 2009. Nothing Reliable about Genes or Environment: New Perspectives on Analysis of Similarity Among Relatives in Light of the Possibility of Underlying Heterogeneity. Studies in History and Philosophy of Biological and Biomedical Sciences.

Turkheimer, E., 1998. Heritability and Biological Explanation. Psychological Review 105, 782-791.

Turkheimer, E., 2000. Three laws of behavior genetics and what they mean. Current Directions in Psychological Science 9, 160-164.