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Quantitative genetic dissection of complex traits in a QTL-mapping pedigree

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Abstract This paper summarizes and modifies quantitative genetic analyses on a pedigree used to map genetic factors (i.e., QTLs) underlying a complex trait. The total genetic variance can be exactly estimated based on the F_2 family derived from two homozygous parents for alternative alleles at all QTLs of interest. The parents, F_1 hybrids, and two backcrosses are combined to each parent, and the total number of QTLs and the number of dominant QTLs are estimated under the assumptions of gene association with the two parents, equal gene effect, no linkage, and no epistasis among QTLs. Further relaxation for each of the assumptions are made in detail. The biometric estimator for the QTL number and action mode averaged over the entire genome could provide some basic and complementary information to QTL mapping designed to detect the effect and location of specific genetic factors.

Key words QTL mapping · Genetic variance · The number of QTLs · Complex traits

Introduction

The dissection of quantitative traits into their Mendelian factors (*Q*uantitative *T*rait *L*oci, QTLs) may date back to Sax's (1923) work in which he related seed-coat pattern and pigmentation to seed size differences in *Phaseolus vulgaris*. The efforts to detect QTLs using morphological mutations as markers were subsequently extended by Rasmusson (1933) and Everson and Schaller (1955). However, until recently when DNA polymorphism can be produced in large supply for a number of organisms, Sax's idea did not prove promising for the genetic study of quantitative variation. The use of molecular markers to identify, locate, and manipulate QTLs has been reported in various context of biology, including plant (Paterson et al. 1991; Stuber et al. 1992; Groover et al. 1994; Bradshaw and Stettler 1995) and animal improvement (Anderson et al. 1994; Bishop et al. 1994), evolution (Doebley et al. 1990; Doebley and Stec 1991, 1993; Postlethwait et al. 1994), and biomedicine (Jacob et al. 1991; Dietrich et al. 1994). Meanwhile, theoretical analyses for high-resolution mapping of QTLs have been extensively developed in the recent literature (Lander and Botstein 1989; Jansen 1993; Moreno-Gonzalez 1993; Rodolphe and Lefort 1993; Zeng 1993; Haley et al. 1994; Jansen and Stam 1994; Kruglyak and Lander 1995).

However, none of these theoretical or experimental studies has explored the benefit from a joint analysis by molecular genetic and traditional biometrical genetic methods. Clearly, the quantitative method can provide some complementary information to the molecular analysis, since its estimates for genetic parameters are averaged across the entire genome. The overall knowledge from the quantitative method, such as the number of QTLs affecting a quantitative trait, can help to design the molecular experiments and determine their sample sizes. For current QTL mapping methods, a prerequisite is that two parents generating the F_2 or backcrosses are homozygous for the alternative alleles at each QTL of interest associated with known homozygous markers (Edwards et al. 1987; Lander and Botstein 1989; Zeng 1993). The generations derived from such inbred parents have received considerable analyses by quantitative geneticists (Mather 1949; Hayman and Mather 1955; Jinks and Jones 1958; Eberhart and Gardner 1966; Mather 1967; Wright 1968; Mather and Jinks 1982).

In this paper, I will show how much information we can gain from the quantitative genetic analysis of a QTL-mapping pedigree initiated with inbred lines. The total genetic variance and broad-sense heritability for a

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quantitative trait can be exactly estimated using the F_2 generation. Exact estimates for these two parameters are necessary to assess the contribution of a marker-associated QTL to the total phenotypic variance. By combining the backcross of the F_1 to each parent, we can also estimate the number of QTLs affecting the trait and their mode of gene action. The estimate for the number of QTLs underlying the quantitative variation of a trait was proposed originally by Wright (in Castle 1921) and has been a debatable issue for a long time (Serebrovsky 1928; Dempster and Snyder 1950; Wright 1968; Lande 1980; Vega and Frey 1980; Comstock and Enfield 1981; Carson and Lande 1984; Zeng et al. 1990; Zeng 1992; Ollivier and Janss 1993). This estimate is based on several simplifying assumptions, such as complete gene association, equal gene effect, no linkage, and no allelic interactions among loci (Wright 1968). Recently, Ollivier and Janss (1993) proposed a method to estimate both the total number of QTLs and the number of dominant QTLs by relaxing the assumption of gene additivity. The influences of linkage and unequality of gene effect on the QTL numeration have been examined by Zeng et al. (1990) and further modified by Zeng (1992). Here, the relaxation for each of the assumptions will be discussed in a different way.

Genetic variance and heritability

Consider a cross by two parents that are selected from a random-mating population at Hardy-Weinberg equilibrium with two alleles at each of n quantitative trait loci (QTLs) of interest. Assume that the two parents are homozygous for the alternative alleles at each of the QTLs affecting a quantitative trait. Thus, the F_1 hybrids between the two parents must be heterozygous at these loci n_d of which are assumed to express dominant effects. The F_1 individuals are mutually mated to generate an F_2 family that has three genotypes at each of the n QTLs. At the same time, the F_1 individuals are backcrossed to both parents, which leads to two backcross (B_1) families each with two genotypes at each of the n QTLs. All these generations build up a QTL-mapping pedigree and are grown in a common environment.

The variation of the F_1 must be exclusively nonheritable, but the heritable component of varition is present in the F_2 because of segregation. Consider a QTL, i, with two alleles, A and a. The value of three genotypes at the locus are denoted as a_i(AA), d_i(Aa), and $-a_i$(aa). It is not difficult to derive the genetic variance in the F_2, contributed by the QTL, as

$$V_{F2} = \tfrac{1}{2}a_i^2 + \tfrac{1}{4}d_i^2$$

If the n QTLs for the trait are not linked, the genetic variance of the F_2 is written as

$$V_{F2} = V_A + V_D + V_{AA} + V_{AD} + V_{DD} + \dots \quad (1)$$

where $V_A(=1/2\Sigma a_i^2)$ is the additive variance, $V_D=(1/4\Sigma d_i^2)$ is the dominant variance, and V_{AA}, V_{AD}, and V_{DD} are the epistatic variances due to additive × additive, additive × dominant, and dominant × dominant interactions in a random-mating population at equilibrium with equal allele frequencies. Thus, the genetic variance in the F_2, V_{F2}, is an unbiased estimate for the total genetic variance of a trait in a random-mating population when the two parents are homozygous for the alternative alleles at each of the n QTLs affecting the trait. If clonal replicates are available, V_{F2} may be estimated by subtracting the environmental variance, estimated with three homogeneous generations P_1, P_2, and F_1, from the phenotypic variance of F_2 (Wright 1968; Cockerham 1986). Given a group of genetically identical individuals, the phenotypic variance of a trait among them can be regarded as the environmental variance of their genotype. If environment is strictly additive, this variance is determined only by the variance of environmental contribution and hence, it is the same for any genotype (Gimelfarb 1994). This is not true, however, if environment is not additive. In this case, the genetic variance of the F_2 can be more accurately estimated using the analysis of variance method based on a randomized complete block design (e.g., Wu and Stettler 1994). The linear regression model for the analysis of variance is

$$y_{ijk} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + \varepsilon_{ijk} \quad (2)$$

where y_{ijk} is the observed value of the k-th tree of the i-th clone in the j-th replicate, μ is the overall mean; α_i is the effect due to the i-th clone; β_j is the effect due to the j-th replicate; $(\alpha\beta)_{ij}$ is the effect due to the interaction between the i-th clone and the j-th replicate; and ε_{ijk} is the residual term. If the assumption is made that the clone is random and replicate fixed, or both clone and replicate are random, broad-sense heritabilities on a clonal mean basis (H^2) and broad-sense genetic correlations (r_g) can be calculated according to their definitions (Falconer 1989).

The derivation of the genetic variance in the two backcrosses requires the following assumption: all increasing alleles in that trait come from one parent (high-value parent, P_1) and all decreasing alleles from the other (low-value parent, P_2). The genetic variances of the two backcross can be derived as

$$V_{B11} = \tfrac{1}{2}V_A + V_D - \tfrac{1}{2}W_{AD} + \tfrac{1}{4}V_{AA} + \tfrac{1}{2}V_{AD} + V_{DD} + \dots \quad (3a)$$

$$V_{B12} = \tfrac{1}{2}V_A + V_D + \tfrac{1}{2}W_{AD} + \tfrac{1}{4}V_{AA} + \tfrac{1}{2}V_{AD} + V_{DD} + \dots \quad (3b)$$

where B_{11} is the backcross to the P_1; B_{12} that to the P_2; and W_{AD} is the summation of the products of the

additive and dominant effects over all QTLs. W_{AD} becomes zero if the variances of the two backcrosses to the P_1 on P_2 are summed. On the basis of Eq. 3a and 3b, the total genetic variance for a trait cannot be estimated by a backcross since the genetic variance in the backcross underestimates the total genetic variance by $1/2\,V_A$, $3/4\,V_{AA}$, $1/2\,V_{AD}$,... and is also contaminated by $-1/2\,W_{AD}$ or $+1/2\,W_{AD}$. Furthermore, neither the summation nor the mean of genetic variance over the two backcrosses can provide an exact estimate for the total genetic variance in a random-mating population at equilibrium, although the term W_{AD} is eliminated:

$$V_{B11} + V_{B12} = V_A + 2V_D + \tfrac{1}{2}V_{AA} + V_{AD} + 2V_{DD} + \ldots \quad (3c)$$

$$\frac{V_{B11} + V_{B12}}{2} = \frac{1}{2}V_A + V_D + \frac{1}{4}V_{AA} + \frac{1}{2}V_{AD} + V_{DD} + \ldots \quad (3d)$$

Therefore, the estimates of broad-sense heritability and genetic correlation from the backcross families are only *approximate*. Also, because an exact estimate for the total genetic variance cannot be obtained from the B_1 families, it is not informative to use the B_1 generations to estimate the contribution of a marker-linked QTL to the heritability of a trait.

It should be pointed out that the total genetic variance can also be exactly estimated based on the F_2 from a cross in which both parents are heterozygous. However, the accuracy for estimating the variance from the F_2 generation will be affected in the two following cases:

1) AA × AA or aa × aa – both parents are homozygous but have the same genotypes. The genetic variance in the F_2 from this combination is zero.

2) Aa × aa or AA × Aa – one parent is homozygous and the other is heterozygous. The genetic variance in the F_2 from this combination is $5/8V_A + 15/16V_D \pm 3/8W_{AD} + 25/64V_{AA} + 75/128V_{AD} + 225/256V_{DD}$, where in the case of the double sign the upper one applies with Aa × aa and the lower one with AA × Aa. It can be seen that such a cross would lead to an underestimate of the total genetic variance.

The number and action of QTLs

Additive-dominant model

Wright's original method for estimating the number of QTLs relied on four assumptions, viz., (1) the P_1 and P_2 contain all increasing and decreasing alleles, respectively; (2) gene effects are equal; (3) linkage is absent; and (4) gene action is strictly additive among the QTLs. Here, I will summarize the results when each of these assumptions is relaxed. Some of the results are not new, whereas the other are the modification or extension of earlier work by quantitative geneticists. If the first three assumptions are kept but dominant gene action is allowed, one can obtain the equations as follows:

$$A = P_1 - P_2 = 2\sum_{i=1}^{n} a_i \quad (4)$$

which is the difference in the trait value between the two parents, and

$$D = F_1 - \frac{P_1 + P_2}{2} = \sum_{i=1}^{n_d} d_i \quad (5)$$

which is the deviation of the F_1 from the mid-parental value. The genetic variances in the F_2 and backcrosses are

$$V_{F2} = \frac{1}{2}\sum_{i=1}^{n} a_i^2 + \frac{1}{4}\sum_{i=1}^{n_d} d_i^2 \quad (6)$$

$$V_{B11} = \frac{1}{4}\sum_{i=1}^{n} a_i^2 + \frac{1}{4}\sum_{i=1}^{n_d} d_i^2 - \frac{1}{2}\sum_{i=1}^{n_d} a_i d_i \quad (7a)$$

$$V_{B11} = \frac{1}{4}\sum_{i=1}^{n} a_i^2 + \frac{1}{4}\sum_{i=1}^{n_d} d_i^2 + \frac{1}{2}\sum_{i=1}^{n_d} a_i d_i \quad (7b)$$

$$V_{B11} + V_{B12} = \frac{1}{2}\sum_{i=1}^{n} a_i^2 + \frac{1}{2}\sum_{i=1}^{n_d} d_i^2 \quad (7c)$$

Since it is assumed that a_i has the same value and that d_i has the same value and direction among all loci, the total number of QTLs, n, and the number of dominant QTLs, n_d, can be solved combining Eqs. 4–6 and 7c:

$$\tilde{n} = \frac{A^2}{8(2V_{F2} - V_{B11} - V_{B12})} \quad (8)$$

$$\tilde{n}_d = \frac{D^2}{4(V_{B11} + V_{B12} - V_{F2})}. \quad (9)$$

In addition, these two variables can be estimated by solving the three other equation groups composed of Eqs. 4–6 and 7a, Eqs. 4–6 and 7b, and Eqs. 4, 5, 7a, and 7b, respectively. Given Eqs. 8 and 9, a and d can be estimated as $a = A/2\tilde{n}$ and $d = D/\tilde{n}_d$. Thus, the additive and dominant components of genetic variance, narrow-sense heritability (h^2), and the degree of dominance may be estimated according to their definitions (Falconer 1989).

As shown in Lande (1980), the sampling variance of $\tilde{n}$ can be approximated by using the Taylor expansion on a ratio estimate (Stuart and Ord 1987) and retaining the

first-order terms:

$$\mathrm{VAR}(\tilde{n}) \approx \tilde{n}^2 \left[\frac{4\mathrm{VAR(A)}}{\mathrm{A}^2} + \frac{4\mathrm{VAR}(\mathrm{V_{F2}}) + \mathrm{VAR}(\mathrm{V_{B11}}) + \mathrm{VAR}(\mathrm{V_{B12}})}{(2\mathrm{V_{F2}} - \mathrm{V_{B11}} - \mathrm{V_{B12}})^2} \right]$$

where $\mathrm{VAR(A)} = \mathrm{V_{P1}}/\mathrm{N_{P1}} + \mathrm{V_{P2}}/\mathrm{N_{P2}}$ in which $\mathrm{V_{P1}}$ and $\mathrm{V_{P2}}$ are the environmental variances of the $\mathrm{P_1}$ and $\mathrm{P_2}$ parents and $\mathrm{N_{P1}}$ and $\mathrm{N_{P2}}$ are the respective sample sizes; $\mathrm{VAR}(\mathrm{V_{F2}})$, $\mathrm{VAR}(\mathrm{V_{B11}})$, and $\mathrm{VAR}(\mathrm{V_{B12}})$ are the sampling variances of the genetic variances in the $\mathrm{F_2}$, $\mathrm{B_{11}}$, and $\mathrm{B_{12}}$, respectively, and they can be estimated from the analysis of variance model if a clonally replicated trial is used. Similarly, the sampling variance of the number of dominant QTLs may be approximated as

$$\mathrm{VAR}(\tilde{n}_d) \approx \tilde{n}^2{}_d \left[\frac{4\mathrm{VAR(D)}}{\mathrm{D}^2} + \frac{\mathrm{VAR}(\mathrm{V_{B11}}) + \mathrm{VAR}(\mathrm{V_{B12}}) + \mathrm{VAR}(\mathrm{V_{F2}})}{(\mathrm{V_{B11}} + \mathrm{V_{B12}} - \mathrm{V_{F2}})^2} \right]$$

where $\mathrm{VAR(D)} = \mathrm{V_{F1}}/\mathrm{N_{F1}} + \mathrm{V_{P1}}/4\mathrm{N_{P1}} + \mathrm{V_{P2}}/4\mathrm{N_{P2}}$ in which $\mathrm{V_{F1}}$ and $\mathrm{N_{F1}}$ are the environmental variance and sample size of the $\mathrm{F_1}$. The sampling variances of a and d are also approximated as

$$\mathrm{VAR}(a) = a^2 \left[\frac{\mathrm{VAR(A)}}{\mathrm{A}^2} + \frac{\mathrm{VAR}(\tilde{n})}{\tilde{n}^2} \right]$$

$$\mathrm{VAR}(d) = d^2 \left[\frac{\mathrm{VAR(D)}}{\mathrm{D}^2} + \frac{\mathrm{VAR}(\tilde{n})}{\tilde{n}^2} \right]$$

Gene dispersion

In general, of the n QTLs for which the two parents differ, n' loci of increasing effects may be present in the $\mathrm{P_1}$ along with $n - n'$ loci of decreasing effects, and *vice versa* for the $\mathrm{P_2}$ parent. If we assume a similar additive effects and ignore epistatic effects among the n QTLs, the difference between the two parents becomes

$$\mathrm{P_1} - \mathrm{P_2} = -2(n - 2n')a \tag{10}$$

The $\mathrm{F_1}$ between the two parents must still be heterozygous for all n QTLs, irrespective of their distribution in the parents. When grown under the same condition, the mean of the $\mathrm{F_1}$ will be derived from the mid-parent by

$$\mathrm{F_1} - \frac{\mathrm{P_1} + \mathrm{P_2}}{2} = n_d d \tag{11}$$

where the degree and direction of dominance are assumed the same among all n_d QTLs. Since no linkage among the QTLs is assumed, the genetic variance of the $\mathrm{F_2}$ will be kept unchanged, as described by Eq. 6, regardless of gene dispersion. However, in backcrossing the $\mathrm{F_1}$ to either of its parents, the genetic variance in the backcross cannot be described by Eq. 7a or 7b. Consider first the $\mathrm{B_{11}}$ to the $\mathrm{P_1}$ in which there are a total of 2^n genotypes. The number of genotypes (m) that contain n, $n-1$, $n-2, \ldots, n', \ldots, 1, 0$ QTLs of increasing effects are $C_n^n, C_n^{n-1}, C_n^{n-2}, \ldots, C_n^{n'}, \ldots, C_n^1, C_n^0$, respectively. A combination of QTLs of increasing effects in the $\mathrm{B_{11}}$ has two cases: (1) all QTLs of increasing effects are homozygous (only when $m \geq n'$), and (2) only some QTLs of increasing effects are homozygous (for both $m < n'$ and $m \geq n'$). The mean value of the $\mathrm{B_{11}}$ can be calculated as

$$\begin{aligned}
\mu_{\mathrm{B11}} = \frac{1}{2^n} \{ & C_n^n [2n'a + (n-n')d] \\
& + C_n^{n-1} [\{2(n'-1)a + (n-n'-1)d\} C_{n-n'}^1 \\
& + \{2(n'-1)a + (n-n'+1)d\} C_{n'}^1] \\
& + C_n^{n-2} [\{2(n'-2)a + (n-n'-2)d\} C_{n-n'}^2 \\
& + \{2(n'-2)a + (n-n')d\} C_{n'}^1 \\
& + \{2(n'-2)a + (n-n'+2)d\} C_{n'}^2] \\
& + \ldots \\
& + C_n^{n'} [2(2n'-n)a C_{n-n'}^{n-n'} \\
& + \{2(2n'-n+1)a + 2d\} C_{n'}^1 \\
& + \{2(2n'-n+2)a + 4d\} C_{n'}^2 + \ldots \\
& + \{2(2n'-n)a + 2(n-n')d\} C_n^{n-n'}] \\
& + \ldots \\
& + C_n^1 [\{2(n'+1-n)a + (n'-1)d\} C_{n'}^1 \\
& + \{2(n'+1-n)a + (n'+1)d\} C_{n-n'}^1] \\
& + C_n^0 [2(n'-n)a + n'd] \}
\end{aligned}$$

The genetic variance of the $\mathrm{B_{11}}$ can be calculated as

$$\begin{aligned}
\mathrm{V_{B11}} = \frac{1}{2^n} \{ & C_n^n [2n'a + (n-n')d]^2 \\
& + C_n^{n-1} [\{2(n'-1)a + (n-n'-1)d\}^2 C_{n-n'}^1 \\
& + \{2(n'-1)a + (n-n'+1)d\}^2 C_{n'}^1] \\
& + C_n^{n-2} [\{2(n'-2)a + (n-n'-2)d\}^2 C_{n-n'}^2 \\
& + \{2(n'-2)a + (n-n')d\}^2 C_{n'}^1 \\
& + \{2(n'-2)a + (n-n'+2)d\}^2 C_{n'}^2] \\
& + \ldots
\end{aligned}$$

$$+ C_n^{n'}[\{2(2n'-n)a\}^2 C_{n-n'}^{n-n'} + \{2(2n'-n+1)a + 2d\}^2 C_{n'}^1 + \{2(2n'-n+2)a+4d\}^2 C_{n'}^2 + \ldots + \{2(2n'-n)a + 2(n-n')d\}^2 C_n^{n-n'}]$$

$$+ \ldots$$

$$+ C_n^1[\{2(n'+1-n)a + (n'-1)d\}^2 C_{n'}^1 + \{2(n'+1-n)a + (n'+1)d\}^2 C_{n-n'}^1] + C_n^0[2(n'-n)a + n'd]^2\} - \mu_{B11}^2$$

It can be shown that the summation of genetic variances over the two backcrosses will be unchanged, as described by Eq. 7c. By combining Eqs. 6, 7c, 10, and 11, we can estimate the number of dominant QTLs as:

$$\tilde{n}_d = \frac{D^2}{4(V_{B11} + V_{B12} - V_{F2})}$$

which gives the same expression as Eq. 9. Thus, the estimate for the dominant-QTL number is not affected by gene dispersion between the two parents. Although we cannot solve the total number of QTLs (n) and the number of QTLs with increasing effects in the P_1(n') because of inadequate degrees of freedom, the relationship between these two variables can be given as:

$$n' = \frac{n}{2} - \frac{A}{2}\sqrt{\frac{n}{2(2V_{F2} - V_{B11} - V_{B12})}}$$

In fact, n and n' are solvable if we use Eqs. 10 and 11 and the genetic variances of the F_2, along with the genetic variance of each backcross, to build up a equation group. However, we note that it is very difficult to derive the mathematical expressions of n and n' just like Eqs. 8 and 9, although the numerical solutions of these two variables can be obtained by simulating all their possible combinations. This is not difficult with the aid of computer simulation. Once n and n' are estimated, the degree of association of genes of like effect may be calculated with $\theta = (\tilde{n} - 2\tilde{n}')/\tilde{n}$, $0 \le \theta \le 1$ (Mather and Jinks 1982). If all genes of increasing effects are present in one parent, then $\theta = 1$; if they are equally shared between the two parents, in other words, they are dispersed, then $\theta = 0$.

A similar analysis can also be performed for heterozygous loci. Assuming that all QTLs are associated in the two parents, i.e., $\theta = 1$, the direction of dominance can be examined by letting n_d' and $(n_d - n_d')$ = the numbers of dominant loci from the P_1 to P_2 and from the P_2 to P_1, respectively. At this time, Eq. 4 is kept unchanged, but Eq. 11 is changed as:

$$D = -(n_d - 2n_d')d \tag{12}$$

The genetic variance of the F_2 and the summed genetic variance of the two backcrosses are not affected by the direction of dominant loci. Combining Eqs. 4, 6, 7c, and 12 solves the total number of additive-dominant QTLs (n) and the relationship between the n_d and n_d':

$$\tilde{n} = \frac{A^2}{8(2V_{F2} - V_{B11} - V_{B12})}$$

$$n_d' = \frac{n_d}{2} - \frac{D}{4}\sqrt{\frac{n_d}{V_{B11} + V_{B12} - V_{F2}}}$$

Clearly, different directions of dominant loci do not affect the estimate for the total number of QTLs. Unknown parameters, n and n_d, can be estimated by considering the genetic variances of the two backcrosses separately.

Unequal allelic effect

Consider the case in which additive and dominant genetic effects are different among the n QTLs segregating in the F_2 and backcross families. Assume that additive (a) and dominant effect (d) at a locus in the hybrid population follow a gamma distribution (i.e., Kimura 1979; Hill and Rasbash 1986), whose density functions, respectively, are

$$f(a) = \frac{\alpha^\beta e^{-\alpha a} a^{\beta-1}}{\Gamma(\beta)} \quad 0 \le a < \infty, 0 < \alpha, \beta < \infty$$

$$f(d) = \frac{\gamma^\lambda e^{-\gamma d} d^{\lambda-1}}{\Gamma(\lambda)} \quad 0 \le d < \infty, 0 < \gamma, \lambda < \infty$$

where α and γ are the scale parameters of the gamma distribution of additive and dominant effects, respectively, and β and λ are the corresponding shape parameters. The moments for this distribution are: $\mathscr{E}(a) = \beta/\alpha$, $\mathscr{E}(a^2) = \beta(1+\beta)/\alpha^2$, and $V(a) = \beta/\alpha^2$ for a and $\mathscr{E}(d) = \lambda/\gamma$, $\mathscr{E}(d^2) = \lambda(1+\lambda)/\gamma^2$, and $V(d) = \lambda/\gamma^2$ for d where $\mathscr{E}$ denotes expectation. The parameters β and λ can be used to measure the equality of additive and dominant effects at various QTLs (see Hill and Rasbash 1986). When $\beta, \lambda \to \infty$, the distribution converges to the case of equal allelic effects (Hill 1982; Zeng 1992). According to the above moments, the following two expressions can be obtained:

$$\frac{\sum_{i=1}^{n} a_i^2}{n} = \overline{a^2} = \mathscr{E}(a^2) = \frac{1+\beta}{\beta}[\mathscr{E}(a)]^2$$

$$\frac{\sum_{i=1}^{nd} d_i^2}{n_d} = \overline{d^2} = \mathscr{E}(d^2) = \frac{1+\lambda}{\lambda}[\mathscr{E}(d)]^2$$

where $\bar{a}$ and $\overline{a^2}$ are the average values of additive effects and of squared additive effects across all relevant QTLs, respectively, and $\bar{d}$ and $\overline{d^2}$ are the average values of dominant effects and of squared dominant effects across

all relevant QTLs, respectively. Because of unequal allelic effects, Eqs. 4 and 5 need to be rewritten as:

$$P_1 - P_2 = 2n\bar{a}$$

$$F_1 - \frac{P_1 + P_2}{2} = n\bar{d}.$$

The genetic variance of the F_2 and the summed genetic variance of the two backcrosses can be expressed as:

$$V_{F2} = \frac{1}{2}n\mathscr{E}(a^2) + \frac{1}{4}n\mathscr{E}(d^2) = \frac{1}{2}n\left(\frac{1+\beta}{\beta}\right)\{\bar{a}\}^2 + \frac{1}{4}n\left(\frac{1+\lambda}{\lambda}\right)\{\bar{d}\}^2$$

$$V_{B11} + V_{B12} = \frac{1}{2}n\mathscr{E}(a^2) + \frac{1}{2}n\mathscr{E}(d^2) = \frac{1}{2}n\left(\frac{1+\beta}{\beta}\right)\{\bar{a}\}^2 + \frac{1}{2}n\left(\frac{1+\lambda}{\lambda}\right)\{\bar{d}\}^2$$

Based on the four equations above, the QTL numbers, n and n_d, can be estimated as:

$$\tilde{n}^* = \frac{A^2}{8(2V_{F2} - V_{B11} - V_{B12})}\left(\frac{1+\beta}{\beta}\right) = \tilde{n}\left(\frac{1+\beta}{\beta}\right) \quad (13)$$

$$\tilde{n}_d^* = \frac{D^2}{4(V_{B11} + V_{B12} - V_{F2})}\left(\frac{\lambda}{1+\lambda}\right) = \tilde{n}_d\left(\frac{\lambda}{1+\lambda}\right) \quad (14)$$

where * denotes the estimators when allelic effects are different, and $\tilde{n}$ and $\tilde{n}_d$ are the estimators when allelic effects are equal among the QTLs (see Eqs. 8 and 9). Thus, the estimate for the total number of QTLs is affected only by the difference of additive effect but not by the difference of dominant effect among the QTLs. The inverse pattern is true for the estimate of the number of dominant QTLs. Denoting $z_1 = (1+\beta)/\beta$ and $z_2 = (1+\lambda)/\lambda$, we can express different patterns of distribution of allelic effects in terms of z_1 and z_2 (Zeng et al. 1990; Zeng 1992). If individual additive allelic effects (a) are normally distributed, then $z_1 = \pi/2 = 1.57$. However, a highly leptokurtic distribution can lead to a z_1 value larger than $\pi/2$ (Mackay et al. 1992). The value of z_1 may be further increased when alleles are not fixed in two parents (see Zeng 1992). Therefore, unequal allelic effects among loci always result in an underestimate for the QTL numbers (see Eqs. 13 and 14).

In practice, the value of z_1 or z_2 cannot be obtained without detailed molecular genetic analyses (Zeng 1992). We should find other ways to estimate the numbers of QTLs when allelic effects are not identical among the loci. Most quantitative traits are influenced by numerous QTLs (Wright 1968; Lande 1980), and typically a few loci have relatively large effects with many others having smaller effects (Spickett and Thoday 1966; Gregory 1965, 1966; Thompson 1975; Edwards et al. 1987; Paterson et al. 1988, 1991; Shrimpton and Robertson 1988; Doebley and Stec 1991, 1993). This suggests that the distribution of QTL effects may often be approximated by a geometric series (Lande and Thompson 1990):

$a, ar, ar^2, ar^3, \ldots, ar^n, r \neq 1$ for additive effects
$d, dw, dw^2, dw^3, \ldots, dw^n, w \neq 1$ for dominant effects

where r and w are the ratios determining the relative magnitude of the additive and dominant effects of each QTL, respectively. If gene association is assumed between the two parents, and no linkage and epistasis, Eqs. 3, 4, 6, and 7c can be rewritten as

$$A = 2a\frac{1-r^n}{1-r}$$

$$D = d\frac{1-w^n}{1-w}$$

$$V_{F2} = \frac{a^2}{2}\frac{1-r^{2n}}{1-r^2} + \frac{d^2}{4}\frac{1-w^{2n}}{1-w^2}$$

$$V_{B11} + V_{B12} = \frac{a^2}{2}\frac{1-r^{2n}}{1-r^2} + \frac{d^2}{2}\frac{1-w^{2n}}{1-w^2}$$

Based on the four equations above, we obtain:

$$\frac{A^2}{8(2V_{F2} - V_{B11} - V_{B12})} = \frac{1-r^n}{1+r^n}\frac{1+r}{1-r} \quad (13)$$

$$\frac{D^2}{4(V_{B11} + V_{B12} - V_{F2})} = \frac{1-w^n}{1+w^n}\frac{1+w}{1-w} \quad (14)$$

The left sides of Eqs. 13 and 14 are just the expressions of estimating n and n_d in the case where allelic effects are identical among the QTLs (see Eqs. 8 and 9). By analyzing the right sides of Eqs. 13 and 14, we find that the estimators of n and n_d, described by Eqs. 8 and 9, are determined more largely by the values of r and w than by their respective real values. When the differences in allelic effect are very large, i.e., r and $w \to \infty$, or $\to 0$, only a single QTL can be estimated from these two estimators. Letting $(1+r^n)/(1-r^n) = u$ and $(1+w^n)/(1-w^n) = v$, we derive the expressions of r and w as:

$$r = \frac{uA^2 - 8[2V_{F2} - (V_{B11} + V_{B12})]}{uA^2 + 8[2V_{F2} - (V_{B11} + V_{B12})]}$$

$$w = \frac{vD^2 - 4[(V_{B11} + V_{B12}) - V_{F2}]}{vD^2 + 4[(V_{B11} + V_{B12}) - V_{F2})]}$$

In any case, $|u|$, $|v| > 1$, unless r or $w = 0$. However, because most quantitative traits are controlled by many QTLs (n or n_d is large) and also because only a few have large effects (i.e., r or w is far different from one) (see above for references), it is possible to assume $|u|$, $|v| \approx 1$. Thus, the two ratios, r and w, are approximated by

$$r^* = \frac{A^2 - 8[2V_{F2} - (V_{B11} + V_{B12})]}{A^2 + 8[2V_{F2} - (V_{B11} + V_{B12})]}$$

$$w^* = \frac{D^2 - 4[(V_{B11} + V_{B12}) - V_{F2}]}{D^2 + 4[(V_{B11} + V_{B12}) - V_{F2})]}$$

These two estimators are viewed as upper bounds of the two ratios since $|u|$ and $|v|$ are always greater than one. The total number of QTLs (n) and the number of dominant QTLs (n_d) are approximately estimated, in terms of r^* and w^*, as

$$\tilde{n}^* = \log_{r^*}[8(2V_{F2} - V_{B11} - V_{B12})(1 + r^*) - A^2(1 - r^*)] - \log_{r^*}[8(2V_{F2} - V_{B11} - V_{B12})(1 + r^*) + A^2(1 - r^*)]$$

$$\tilde{n}_d^* = \log_{r^*}[4(V_{B11} + V_{B12} - V_{F2})(1 + w^*) - D^2(1 - w^*)] - \log_{r^*}[4(V_{B11} + V_{B12} - V_{F2})(1 + w^*) + A^2(1 - w^*)]$$

Linkage

Consider two homozygous parents which differ for n QTLs, each with the same effect. Assume no gene dispersion between the two parents, i.e., $\theta = 1$. Linkage between the QTLs does not affect the differences between the two parents or between the F_1 and the midparent, as described by Eqs. 4 and 5. However, it has an effect on the variance and covariance of the segregating generations. If all dominant loci are reinforcing one another by acting in the same direction and there is no espistasis among the QTLs, the genetic variance of the F_2 and the summed genetic variance of the backcrosses to the two parents are

$$V_{F2} = \frac{1}{2}[n + 2\sum_{i \neq j}^{n}\sum^{n} (1 - 2\rho_{ij})]a^2 + \frac{1}{4}[n_d + 2\sum_{i \neq j}^{n_d}\sum^{n_d} (1 - 2\rho_{ij})^2]d^2$$

$$V_{B1} + V_{B2} = \frac{1}{2}[n + 2\sum_{i \neq j}^{n}\sum^{n} (1 - 2\rho_{ij})]a^2 + \frac{1}{2}[n_d + 2\sum_{i \neq j}^{n_d}\sum^{n_d} (1 - 2\rho_{ij})]d^2$$

where ρ_{ij} is the recombination frequency between the ith and jth QTL. If we further assume that all QTLs are uniformly distributed on a chromosome, linkage relationships can be divided into $n - 1$ types: $(n - 1)$ pairs between the two neighboring QTLs; $(n - 2)$ pairs between the two QTLs flanking a QTL; $(n - 3)$ pairs between the two QTLs flanking two QTLs,...; 1 pair between the two QTLs in the end. In the case of no double crossover, the recombination frequency between the two QTLs flanking $t\,(0 \leq t \leq n - 2)$ QTLs equals $(t + 1)\rho$ where $\rho \leq 1/[2(n - 1)]$ is the recombination frequency between the two neighboring QTLs. Thus, the genetic variances in the F_2 and backcrosses are expressed as:

$$\begin{aligned} V_{F2} &= \tfrac{1}{2}\{n + 2(n-1)(1-2\rho) + 2(n-2)(1-4\rho) \\ &\quad + 2(n-3)(1-6\rho) + \ldots + 2[1 - 2(n-1)\rho]\}a^2 \\ &\quad + \tfrac{1}{4}\{n + 2(n-1)(1-2\rho)^2 + 2(n-2)(1-4\rho)^2 \\ &\quad + 2(n-3)(1-6\rho)^2 + \ldots + 2[1 - 2(n-1)\rho]^2\}d^2 \\ &= \tfrac{1}{2}Xa^2 + \tfrac{1}{4}Yd^2 \end{aligned} \tag{15}$$

$$\begin{aligned} V_{B11} + V_{B12} &= \tfrac{1}{2}\{n + 2(n-1)(1-2\rho) \\ &\quad + 2(n-2)(1-4\rho) + 2(n-3)(1-6\rho) \\ &\quad + \ldots + 2[1 - 2(n-1)\rho]\}a^2 \\ &\quad + \tfrac{1}{2}\{n_d + 2(n_d-1)(1-2\rho) \\ &\quad + 2(n_d-2)(1-4\rho) \\ &\quad + 2(n_d-3)(1-6\rho) + \ldots \\ &\quad + 2[1 - 2(n_d-1)\rho]\}d^2 = \tfrac{1}{2}Xa^2 + \tfrac{1}{2}Y'd^2 \end{aligned} \tag{16}$$

where $X = n[n - \frac{2}{3}(n-1)(n+1)\rho]$

$$\begin{aligned} Y = \{&n_d^2 - \tfrac{4}{3}(n_d - 1)n_d(n_d + 1)\rho + \tfrac{4}{3}(n_d - 1) \\ &\times \{(2n_d - 1)n_d^2 - \sqrt{(n_d - 1)}[(n_d - 1)\sqrt{(n_d - 1)} + 1] \\ &\times [2(n_d - 1)\sqrt{(n_d - 1)} + 1]\}\rho^2\} \end{aligned}$$

$$Y' = n_d[n_d - \tfrac{2}{3}(n_d - 1)(n_d + 1)\rho].$$

If the mean recombination frequency between the neighboring QTLs, ρ, is calculated from a marker-based genetic map, we can obtain the expression for estimating the number of dominant QTLs, n_d, based on

Eqs. 4, 5, 15, and 16:

$$\tilde{n}''_d = \sqrt{\tilde{n}_d(2Y' - Y)}$$

where $''$ denotes the estimators for the QTL numbers when linkage is considered and $\tilde{n}_d$ is expressed by Eq. 9. The total number of QTLs, n, can be estimated using

$$\tilde{n}'' = \tilde{n}''_d \sqrt{\frac{\tilde{n}X}{(\tilde{n}''_d)^2 + 2\tilde{n}_d(Y' - Y)}}$$

where $\tilde{n}$ is expressed by Eq. 8.

Epistasis

The n QTLs segregating in the hybrid populations may show the effects of non-allelic interaction (epistasis) on the phenotype of a trait. For simplicity, only digenic epistasis will be taken into account. Assume that the n QTLs are associated between the two parents, $\theta = 1$, and have the same effect and no linkage. Digenic epistasis does not affect the differences between the two parents described by Eq. 4, but does affect the difference between the F_1 and mid-parent described by Eq. 5. Consider the case in which all pairs of QTLs have similar interactions. Thus, Eq. 5 is changed as:

$$F_1 - \frac{P_1 + P_2}{2} = n_d d - \frac{1}{2}n(n-1)i + \frac{1}{2}n(n-1)l \qquad (17)$$

where i is the interaction of a pair of a (homozygous × homozygous); l is the interaction of a pair of d (heterozygous × heterozygous). The mean expression of a trait in the F_2 departs from the mid-parent value by:

$$F_2 - \frac{P_1 + P_2}{2} = \frac{1}{2}n_d d - \frac{1}{2}n(n-1)i + \frac{1}{8}n(n-1)l \qquad (18)$$

The genetic variance of the F_2 is derived as (Mather and Jinks 1982)

$$V_{F2} = \tfrac{1}{2}n[a + \tfrac{1}{2}(n-1)j]^2 + \tfrac{1}{4}n_d[d + \tfrac{1}{2}(n-1)l]^2 + \tfrac{1}{8}n(n-1)i^2 + \tfrac{1}{8}n(n-1)j^2 + \tfrac{1}{32}n(n-1)l^2 \qquad (19)$$

where j is the interaction of a and d (homozygous × heterozygous). The summed genetic variance of two backcrosses of the F_1 to the parents is

$$V_{B11} + V_{B12} = \tfrac{1}{2}na^2 + \tfrac{1}{2}n_d[d - \tfrac{1}{2}(n-1)i + \tfrac{1}{2}(n-1)l]^2 + \tfrac{1}{8}n(n-1)j^2 + \tfrac{1}{16}n(n-1)(i+l)^2 \qquad (20)$$

Digenic interactions involve a number of different types, depending on the values of interactions to be taken (Mather 1967). However, I will concern with the two most important types, which are called complementary and duplicate gene interactions.

At first, let $a = d = i = j = l$. This virtually corresponds to the 9:7 ratio in the F_2 that is characteristic of the classical complementary gene relationship. Similarly, if we set $a = d = -i = -j = -l$, then we find the 15:1 F_2 ratio of the classical duplicate gene relationship. We can generalize the two relationships by assuming $a = d$ and $i = j = l = \kappa a$ where κ is a measure of the intensity of the interaction (Mather 1967). At $|\kappa| = 1$, interaction is complete and a pair of QTLs show a classic complementary or duplicate relationship. $0 < |\kappa| < 1$ implies partial interaction and $|\kappa| > 1$ a super-interaction. There is no epistasis when $\kappa = 0$. The sign of κ reflects the two different gene interactions, i.e., "+" for complementary and "−" for duplicate.

For the solution of possible epistatic interactions between pairs of QTLs, we derive the following equations:

$$A = 2na$$

$$D = n_d a$$

$$F_2 - \frac{P_1 + P_2}{2} = \frac{1}{2}n_d\bar{a} + \frac{3}{8}n(n-1)\kappa a$$

$$V_{F2} = \tfrac{3}{4}n[a \pm \tfrac{1}{2}(n-1)\kappa a]^2 + \tfrac{9}{32}n(n-1)\kappa^2 a^2$$

$$V_{B11} + V_{B12} = \tfrac{1}{2}(n + n_d)a^2 + \tfrac{3}{8}n(n-1)\kappa^2 a^2$$

where in the case of double signs the upper one is associated with a complementary gene relationship and the lower one with a duplicate gene relationship. Four unknown parameters, a, n, n_d and κ, can be solved using a least squares method.

For a more general case, we should have no restrictions of $a = d$ and $i = j = l$. If we add more equations to the equation group composed of Eqs. 17–21, unknown parameters, n, n_d, a, d, i, j, and l can be solved. The two new equations are:

$$B_{11} - P_1 - F_1 = -\tfrac{1}{4}n(n-1)i + n(n-1)j - \tfrac{1}{4}n(n-1)l$$

$$B_{12} - P_2 - F_1 = -\tfrac{1}{4}n(n-1)i - n(n-1)j - \tfrac{1}{4}n(n-1)l$$

Discussion

QTL mapping is an important approach for dissecting the genetic factors affecting a quantitative trait of economical and biological importance. Rapid progress in the development of DNA-based genetic linkage maps has

made QTL mapping a practical and widely used approach. Parameteric interval mapping allows the detection and location of individual QTLs for quantitative traits through the use of molecular marker genotypes. The accuracy and power to detect QTLs can be improved if experimentalists combine quantitative genetic analyses of their mapping pedigrees. A robust QTL experiment relies on many factors, such as heritability, parental difference, and sample size (Lander and Botstein 1989). Information about these factors in a QTL-mapping pedigree can be provided by classical quantitative genetic analyses (Mather 1949; Hayman and Mather 1955; Eberhart and Gardner 1966; Mather 1967; Mather and Jinks 1982). In addition, the reliability of QTL mapping for a particular pedigree can be tested by comparing results from both the molecular and quantitative methods. If there is no agreement between the two methods, one should examine the reasons for the differences, which could further lead to a better understanding of the study material.

The method based on a three-generation pedigree itself may be an alternative to the previous quantitative genetic analyses commonly used in outcrossing species, such as forest trees. While a long generation cycle, an outcrossing mating system, and a high genetic load limit the application of the generation mean method to forest trees, a method to use a mating design with known family structure was developed for these species (Cockerham 1963; Foster and Shaw 1988; Mullin and Park 1992; Mullin et al. 1992; Wu 1996). However, this method can also be limited due to biological and economical constraints on the number of crosses and on family size (Stettler et al. 1980) relative to those desired for estimating genetic parameters (Namkoong and Roberds 1974). Furthermore, the estimation accuracy of genetic parameters is affected by the form of mating design used, especially in unbalanced cases (Namkoong and Roberds 1974). An appropriate QTL pedigree is derived from two parents that are homozygous for the alternative alleles at each QTL and its associated markers. In this paper, it has been shown that the genetic variance in the F_2 of such a pedigree provides an unbiased estimate for the total genetic variance in a random-mating population at Hardy-Weinberg equilibrium. More importantly, many additional genetic parameters, such as the number of QTLs affecting a trait and their association, effect, mode of action, and linkage, can be approximately estimated from the quantitative analyses of the mapping pedigree.

In practice, it is difficult to determine the accuracy of selecting homozygous parents. However, it can be increased through molecular genetic studies of the populations (reviewed in Libby 1992). Based on these studies, one can understand the genetic basis of a trait and selection type acting on it in the populations. Currently, two genetic models are used to explain the maintenance of quantitative variation in populations. The first is the multivariate normal model analyzed by Lande (1975) in which selection directly affects the quantitative trait of interest. Another one, termed the pleiotropic model, assumes that the trait itself is neutral but its value is determined by the pleiotropic effects of alleles at loci that are themselves selected (Hill and Keightley 1988; Barton 1990). If Lande's multivariate normal model is assumed, it is possible to select two homozygous parents with different genotypes by phenotypic and molecular analyses.

Cloning plays a critical role in the quantitative genetic analysis of a mapping pedigree. The advantages of cloning are to provide unbiased estimates for genetic variance and for the differences between the two parents and the F_1 vs mid-parent that are necessary for the QTL enumeration. However, non-genetic effects produced by cloning (C-effects) may bias estimations of generation means and the genetic variances in the F_2 (Libby and Jund 1962).

All current analytical methods used for outcrossing species, including the one suggested here, are hampered by multiple alleles (≥ 3) at a locus (see Groover et al. 1994). The segregation of multiple alleles at a QTL is more likely when interspecific crosses are made. Multiple alleles present a greater opportunity to generate hybrid vigor owing to increased interaction relationships (e.g., dominant, overdominant, and epistasis), but they also complicate our analyses. Further work in both QTL mapping and quantitative genetics of outcrossing species is required.

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