EFFECTS OF LINKAGE ON THE COVARIANCES BETWEEN RELATIVES[1]

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W ITH two alleles per locus, partitioning of the hereditary variance of diploid populations factorially into additive, dominance, additive by additive and higher order components depends only on the assumption that genotypic frequencies are proportional to the marginal frequencies of the phases (*AA*, *Aa* or *aa*) of each locus (COCKERHAM 1954). This assumption, in effect, specifies linkage equilibrium. When an arbitrary number of alleles at each locus is considered, the variance can be broken into the same framework of partitions at least when an additional assumption of Hardy-Weinberg equilibrium of marginal frequencies is met (KEMPTHORNE 1954). Thus, in randomly mating populations linkages do not affect the hereditary variance nor its partitions as long as the population is in linkage equilibrium. Even so, linkages do affect the covariances between some relatives. Covariances between relatives are the sources from which components of hereditary variance are estimated. While the breeder or geneticist may be willing to assume linkage equilibrium in his population, he is certainly not willing to assume that none of the loci are linked. The purpose of this paper is to elucidate some of these linkage effects on the covariances and to indicate relatives whose covariances will be affected. Linkage is used in the sense of lack of free recombination at meiosis. Position effects are assumed to be absent. Only relatives in randomly mating populations that are in linkage equilibrium will be considered.

The method of obtaining the covariance between relatives makes use of MALE-COT's (1948) probabilities of genes being identical by descent which were employed by KEMPTHORNE (1954). The basic result, as given by KEMPTHORNE, is that the coefficients of the various types of components of variance in the covariances between relatives are a function of, and can be computed from, the probabilities of genes having descended from the same gene. For example, consider two half sibs which have descended from a sire with the following genotype,

$$\frac{x_1 \; \rho_{12} \; y_1 \; \rho_{23} \; z_1}{x_2 \qquad y_2 \qquad z_2},$$

where x_1 and x_2, y_1 and y_2, and z_1 and z_2 are alleles at the x, y and z locus, respectively, and ρ_{12} and ρ_{23} are recombination frequencies. Now in the covariance between half sibs, the coefficient of the additive component of variance arising from any locus, the x locus in this example, is

$$\frac{\phi}{2} = \frac{P(s, \; s' \; = \; x_1) \; + \; P(s, \; s' \; = \; x_2)}{2} = \frac{1}{4}.$$

$P(s,s' = x_1) = \frac{1}{4}$ is the probability that both half sibs, s and s', inherited the allele, x_1, and so on. Thus ϕ is the total probability that both half sibs inherited the same gene from their sire. No components involving dominance enter into the covariance between half sibs because dominance components enter into covariances between relatives only when they have common dominance elements; that is, the two genes at a locus of one relative are identical by descent with the two genes at the same locus of the other relative.

With free recombination, $\rho_{12} = \rho_{23} =$ etc. $= \frac{1}{2}$, the coefficient of the two-factor additive component arising from any pair of loci in the covariance between half sibs is $(\phi/2)^2$. However, to include linkage the appropriate coefficient is

$$\frac{\phi_{12}}{4} = \frac{P(s, s' = x_1 y_1) + P(s, s' = x_2 y_2) + P(s, s' = x_1 y_2) + P(s, s' = x_2 y_1)}{4}$$

These probabilities are, in their respective order,

$$\phi_{12} = \left(\frac{1 - \rho_{12}}{2}\right)^2 + \left(\frac{1 - \rho_{12}}{2}\right)^2 + \left(\frac{\rho_{12}}{2}\right)^2 + \left(\frac{\rho_{12}}{2}\right)^2$$

$$= \frac{1}{4} + \frac{(1 - 2\rho_{12})^2}{4} = \frac{1 + \delta_{12}}{4}$$

Thus $\phi_{12} = \phi^2$ only if there is no linkage. The coefficient of the two-factor additive component, $\sigma^2_{a_1 a_2}$ for the x and y loci in this case, in the covariance between half sibs is $(1 + \delta_{12})/16$. Linkage causes a positive bias in the amount of $\delta_{12}\sigma^2_{a_1 a_2}/16$. This bias is summed over all pairs of linked loci, $\Sigma\delta_{ij}\sigma^2_{a_i a_j}$.

For the triple additive components the coefficients in the covariance between half sibs are $(1 + \delta_{ij})(1 + \delta_{jk})/64$, where the loci are in the linear order of i, j and k, and provided interference is absent, i.e., $\rho_{ik} = \rho_{ij} + \rho_{jk} - 2\rho_{ij}\rho_{jk}$ or $\delta_{ik} = \delta_{ij}\delta_{jk}$. Less than free recombination of only two of the loci still causes a positive bias. This observation can be generalized further to say that less than free recombination of two loci will bias the coefficients of all the additive epistatic components in which they are involved. For example, the coefficients for quadruple additive components are $(1 + \delta_{ij})(1 + \delta_{jk})(1 + \delta_{kl})/256$ and so on for the higher order components.

In the covariance between full sibs the coefficients of all types of epistatic components are affected by lack of free recombination. The coefficients of the various components are set out in table 1 for components up to 3 factors. The loci are considered to be in the linear order i, j and k, and interference is assumed to be absent. No simple method by which one could ascertain any desired coefficient was found. Again, the coefficient of any epistatic component is affected by linkage of any of the loci involved in the component, and the effect is always to increase the coefficient.

If position effects are absent, as assumed throughout, the covariance between parent and offspring is unaffected by linkage. This can be seen for two loci by noting that the coupling and repulsion parents have identical genotypic values and that the distribution (and consequently the mean) of their offspring as a group does not depend on linkage so that the average product or covariance between parent and

TABLE 1

Coefficients of components of hereditary variance in the covariance between full sibs

Type of component	Coefficients		
	Unspecified recombination	No recombination	Free recombination
a_i	$1/2$	$1/2$	$1/2$
d_i	$1/4$	$1/4$	$1/4$
$a_i \times a_j$	$[1 + (1 + \delta_{ij})]/8$	$3/8$	$1/4$
$a_i \times d_j$	$(1 + \delta_{ij})/8$	$1/4$	$1/8$
$d_i \times d_j$	$(1 + \delta_{ij})^2/16$	$1/4$	$1/16$
$a_i \times a_j \times a_k$	$[1 + (1 + \delta_{ij}) (1 + \delta_{jk})]/16$	$5/16$	$1/8$
$a_i \times a_j \times d_k$	$[(1 + \delta_{ij})(1 + \delta_{jk}) + (1 + \delta_{ik})(1 + \delta_{jk})]/32$	$1/4$	$1/16$
$a_i \times d_j \times a_k$	$(1 + \delta_{ij})(1 + \delta_{jk})/16$	$1/4$	$1/16$
$d_i \times a_j \times a_k$	$[(1 + \delta_{ij})(1 + \delta_{jk}) + (1 + \delta_{ij})(1 + \delta_{ik})]/32$	$1/4$	$1/16$
$a_i \times d_j \times d_k$	$(1 + \delta_{ij})(1 + \delta_{jk})^2/32$	$1/4$	$1/32$
$d_i \times a_j \times d_k$	$(1 + \delta_{ij})(1 + \delta_{ik})(1 + \delta_{jk})/32$	$1/4$	$1/32$
$d_i \times d_j \times a_k$	$(1 + \delta_{ij})^2(1 + \delta_{jk})/32$	$1/4$	$1/32$
$d_i \times d_j \times d_k$	$(1 + \delta_{ij})^2(1 + \delta_{jk})^2/64$	$1/4$	$1/64$

offspring remains the same. The lack of repulsion types from the coupling parent is supplied by an excess of repulsion types from the repulsion parent, and so on. This same condition holds for all other sets of relatives where one relative is an ancestor of the other. Thus in randomly mating diploid populations where genotypic frequencies are in linkage equilibrium, the covariances between parent and offspring, grandparent and grand offspring, great grandparent and great grand offspring and so on are unaffected by linkage.

Sets of relatives whose covariances are affected by linkage are those in which one is not a common ancestor of the other, e.g., half sibs, full sibs, cousins, uncle and nephew. As the number of generations from one relative through the common ancestor to the other relative increases the amount of bias due to linkage decreases. At the same time, however, the ratio of the amount of bias to the variance found without linkage increases. For example, these ratios are δ_{12}, $3\delta_{12}$ and $6\delta_{12} + \delta_{12}^2$ for the two factor additive components in the covariances of half sibs, uncle and nephew and half first cousins, respectively.

The contribution of linkage to the covariances between relatives can not be generally foretold of course. Of the covariances which are subject to linkage bias only the epistatic components are affected and these only if they involve loci which have a recombination frequency less than one half. Agencies which limit recombination, such as localization of chiasmata, crossover suppressors and inversions could cause considerable bias in the covariances.

Methods of estimating various components of hereditary variance must necessarily involve covariances between relatives. If linkage effects are not accounted for directly in the analysis or avoided by choosing relatives whose covariances are unaffected, then they must at least be regarded as a probable source of bias in the results.

SUMMARY

In randomly mating diploid populations whose genotypic frequencies are in linkage equilibrium, the covariances between relatives of which one is an ancestor of the other are not affected by linkages, provided position effects are absent. In contrast, covariances between relatives where one is not an ancestor of the other are affected by recombination frequencies less than one half. The lower the recombination frequency, the higher the covariance, and the bias is in the amount of the epistatic components that appears in the covariances and not in the amount of additive genetic and dominance components. Explicit expressions are given for full sibs and half sibs up to and including three factor epistatic components.

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