2018

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HHS Public Access

Author manuscript

Hum Hered. Author manuscript; available in PMC 2019 November 02.

Published in final edited form as:

Hum Hered. 2018 ; 83(2): 92–99. doi:10.1159/000492830.

Contribution of Inbred Singletons to Variance Component Estimation of Heritability and Linkage

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Abstract

Objectives: An interesting consequence of consanguinity is that the inbred singleton becomes informative for genetic variance. We determine the contribution of an inbred singleton to variance component analysis of heritability and linkage.

Methods: Statistical theory for the power of variance component analysis of quantitative traits is used to determine the expected contribution of an inbred singleton to likelihood-ratio tests of heritability and linkage.

Results: In variance component models an inbred singleton contributes relatively little to a test of heritability, but can contribute substantively to a test of linkage. For small to moderate QTL effects and a level of inbreeding comparable to matings between first cousins (the preferred form of union in many human populations), an inbred singleton can carry nearly 25% the information of a non-inbred sibpair. In more highly inbred contexts available with experimental animal populations, nonhuman primate colonies, and some human subpopulations, the contribution of an inbred singleton relative to a sibpair can exceed 50%.

Conclusions: Inbred individuals, even in isolation from other members of a sample, can contribute to variance component estimation and tests of heritability and linkage. Under certain conditions the informativeness of the inbred singleton can approach that of non-inbred sibpair.

Keywords

Inbreeding; Heritability; Linkage analysis; Statistical genetics; Variance component analysis

Introduction

A simplification often made in quantitative genetic theory and analysis is the assumption that the parents of an individual are unrelated. The assumption implies that any offspring of the parents are not inbred, and a corollary implication is that a single individual cannot be informative for linkage. The assumption is frequently plausible, such as for most

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Conflicts of Interests

The authors declare no conflicts of interest.

westernized human populations, but may often be purely expedient, e.g., when applied to the founding members of a pedigree.

Consanguinity, however, carries additional information regarding the inheritance of alleles that can be exploited to increase the power of statistical genetic methods based on allele sharing [1]. A curious consequence of parental relatedness is the nonzero probability for both alleles at a locus in the inbred offspring to be identical by descent (IBD). Therefore, even in isolation from a larger pedigree structure, inbred singletons are inherently informative for genetic linkage.

Here the approach presented in [2] (see also [3, 4, 5]), for variance component analysis of quantitative traits is extended to the case of an inbred singleton. The contribution of the inbred singleton to the likelihood-ratio statistic is determined for models of polygenic variation and linkage, and the informativeness of the inbred individual is compared with that for the conventional minimal unit of analysis, the sibpair. Under certain conditions, an inbred singleton can contribute a significant fraction of the information of a non-inbred sibpair.

Definitions

To introduce concepts and fix notation it is helpful to review the following definitions [6, 7, 8, 9, 10].

An individual is said to be inbred (at a given locus) if the individual has (at that locus) two copies of a given ancestral allele. This condition generally obtains only if the parents share an allele identical by descent (IBD), i.e., are themselves related through some common ancestor. offspring of related parents need not inherit two copies of an ancestral allele, but without knowledge of the relatedness of the parents it is only the presence in the offspring of two copies of an ancestral allele that provides unequivocal evidence of inbreeding.

The *coefficient of kinship* ϕ_{ij} between individuals i and j is the probability that an allele chosen at random from individual i is IBD with an allele chosen randomly from the same locus in individual j. If i and j are unrelated, $\phi_{ij} = 0$.

The *inbreeding coefficient* f of an individual is the probability that the two parental alleles transmitted to the individual are IBD. If parents are unrelated, $f = 0$, otherwise f is equal to the coefficient of kinship between the parents.

The coefficient of kinship of an inbred individual with itself can be understood as the inbreeding coefficient of the progeny that would be produced by self-mating. To see this, suppose individuals i and j are genetically identical with genotype $\gamma_1\ \gamma_2$ at a locus and probability f that γ_1 and γ_2 are IBD. In random sampling their coefficient of kinship must therefore be

$$\begin{aligned}\phi_{ij} &= Pr\left(\gamma_1\gamma_1 \cup \gamma_2\gamma_2\right) + Pr\left(\gamma_1\gamma_2\right) Pr\left(\gamma_1 \equiv \gamma_2\right) \\ &= \frac{1}{2} + \frac{1}{2}f = \frac{1}{2}(1+f)\,.\end{aligned}$$

Finally, the *coefficient of relationship*, $r_{ij} = 2\phi_{ij}$, is the coefficient of the additive genetic contribution to the covariance between relatives [9, 10].

Contribution To Likelihood Ratio

In variance component analysis the significance of a modeled effect is typically evaluated using a likelihood-ratio test [11]. To evaluate the contribution of an inbred singleton to a test of heritability or linkage, we follow the approach presented by others [3, 4, 5, 2] for computing the expected likelihood ratio in variance component tests of polygenic and QTL effects for a quantitative trait. For more extensive theoretical development of this approach, including applications, discussion, and simulation results, the reader is referred to [3, 4, 5, 2] and references therein.

Let $\boldsymbol{\theta}_0$ and $\boldsymbol{\theta}_1$, respectively, be the vector of variance components (i.e., the model parameters) under the null H_0 and alternative H_1 hypotheses. The likelihood-ratio statistic for the test of H_0: $\boldsymbol{\theta} = \boldsymbol{\theta}_0$ vs H_1: $\boldsymbol{\theta} = \boldsymbol{\theta}_1$ is distributed asymptotically as a noncentral χ^2 with noncentrality parameter

$$\Lambda = (\boldsymbol{\theta}_1 - \boldsymbol{\theta}_0)'\mathbf{T}(\boldsymbol{\theta}_1 - \boldsymbol{\theta}_0)$$

where **T** is the information matrix of the parameters [11]. The *i,j*-th element of **T** is given by

$$\{\mathbf{T}\}_{ij} = \frac{1}{2} Tr\left(\boldsymbol{\Omega}^{-1}\frac{\partial \boldsymbol{\Omega}}{\partial \theta_i}\boldsymbol{\Omega}^{-1}\frac{\partial \boldsymbol{\Omega}}{\partial \theta_j}\right)$$

where θ_k is the *k*-th element of the parameter vector $\boldsymbol{\theta}_0$ [2, 5]. For a specific hypothesis test, the quantity Λ completely specifies the distribution of the likelihood ratio under H_1 and can be used to determine the power of the likelihood-ratio test or, as is done here, as a figure of merit for comparing different sampling units.

Results

When considering the influence of an individual, much of the matrix formulation implicit in the general case becomes unnecessary. For a singleton, assumed unrelated to the other members of a pedigree, the structuring matrices for the phenotypic covariance, and the covariance matrix itself, reduce to scalar quantities and most of the analytical effort is devoted to computing the information matrix for the model parameters.

Polygenic Model

In a variance component model of polygenic inheritance, the phenotypic covariance matrix is structured as

$$\boldsymbol{\Omega} = 2\boldsymbol{\Phi}\sigma_a^2 + \mathbf{I}\sigma_e^2,$$

where $\mathbf{\Phi}$ is the kinship matrix, I is the identity matrix, $\sigma_a^2 = a^2\sigma^2$ is the variance due to additive genetic effects, $\sigma_e^2 = e^2\sigma^2$ is the variance due to random, individual-specific environmental effects, and $\sigma^2 = \sigma_a^2 + \sigma_e^2$ is the total phenotypic variance. In the case of a singleton $2\mathbf{\Phi} \equiv 2\boldsymbol{\varphi} = \{1 + f\}$, $\mathrm{I} \equiv \{1\}$, and $\mathbf{\Omega} \equiv \omega = (1 + f)\sigma_a^2 + \sigma_e^2 = \sigma^2 + f\sigma_a^2$ illustrating that the additive genetic contribution to the phenotypic variance is inflated by inbreeding in proportion to the relatedness of the parents.

Information Matrix—Under the null hypothesis $H_0{:}\sigma_a^2 = 0$, there is no (additive) genetic variation and all phenotypic variation is purely environmental. The phenotypic covariance is therefore $\mathbf{\Omega}|H_0 \equiv \omega_0 = \sigma_e^2 \equiv \sigma^2$. Elements t_{ij} of the information matrix $\mathbf{T}$ are found by straightforward evaluation of standard results [3, 4,2].

$$\begin{aligned}\{t_{11}\} &= \frac{1}{2}\,\mathrm{Tr}\left(\mathbf{\Omega}^{-1}2\mathbf{\Phi}\mathbf{\Omega}^{-1}2\mathbf{\Phi}\right)\\ &= \frac{1}{2}\left[\omega_0^{-1}(1+f)\omega_0^{-1}(1+f)\right] = \frac{1}{2}\left(\frac{1}{\sigma^2}\right)^2(1+f)^2,\\ \{t_{12}\} &= \frac{1}{2}\,\mathrm{Tr}\left(\mathbf{\Omega}^{-1}2\mathbf{\Phi}\mathbf{\Omega}^{-1}\mathbf{I}\right)\\ &= \frac{1}{2}\left[\omega_0^{-1}(1+f)\omega_0^{-1}(1)\right] = \frac{1}{2}\left(\frac{1}{\sigma^2}\right)^2(1+f),\end{aligned}$$

and

$$\begin{aligned}\{t_{22}\} &= \frac{1}{2}\,\mathrm{Tr}\left(\mathbf{\Omega}^{-1}\mathbf{I}\mathbf{\Omega}^{-1}\mathbf{I}\right)\\ &= \frac{1}{2}\left[\omega_0^{-1}(1)\omega_0^{-1}(1)\right] = \frac{1}{2}\left(\frac{1}{\sigma^2}\right)^2.\end{aligned}$$

The complete information matrix for the polygenic model in the case of an inbred singleton is then

$$\mathbf{T} = \frac{1}{2}\left(\frac{1}{\sigma^2}\right)^2\begin{bmatrix}(1+f)^2 & 1+f\\ 1+f & 1\end{bmatrix}.$$

Likelihood-Ratio Statistic—The utility of the singleton in a test of additive genetic effects is ultimately determined by its contribution to the total likelihood-ratio statistic. For the polygenic model, with parameters σ_a^2 and σ_e^2, the parameter vectors under the null and alternative hypotheses, respectively, are $\hat{\boldsymbol{\theta}}_0 = \left(0, \sigma_a^2 + \sigma_e^2\right)'$ and $\hat{\boldsymbol{\theta}}_1 = \left(\sigma_a^2, \sigma_e^2\right)'$. The singleton-specific likelihood ratio is then

$$\begin{aligned}\Lambda_1 &= \left(\hat{\boldsymbol{\theta}}_1 - \hat{\boldsymbol{\theta}}_0\right)' \mathbf{T} \left(\hat{\boldsymbol{\theta}}_1 - \hat{\boldsymbol{\theta}}_0\right) \\ &= \frac{1}{2}\left(\frac{1}{\sigma^2}\right)^2 \left(\sigma_a^2, -\sigma_a^2\right)' \begin{bmatrix} (1+f)^2 & 1+f \\ 1+f & 1 \end{bmatrix} \begin{pmatrix} \sigma_a^2 \\ -\sigma_a^2 \end{pmatrix} \\ &= \frac{1}{2}\left(\frac{\sigma_a^2}{\sigma^2} f\right)^2 = \frac{1}{2}\left(a^2 f\right)^2,\end{aligned}$$

where $a^2 = \sigma_a^2/\sigma^2 \equiv h^2$ is the proportion of the phenotypic variance due to additive genetic effects. (In this polygenic model, a^2 is equivalent to the trait heritability h^2.) For a given additive effect a^2, an inbred singleton contributes to estimation of heritability in proportion to the square of the inbreeding coefficient. If the singleton is not inbred, then $f = 0$ and the individual contributes nothing to the overall likelihood-ratio statistic.

From [2] the corresponding expected likelihood-ratio statistic for a test of the polygenic model in sibpairs is

$$\Lambda_{\mathrm{SP}} = \frac{1}{4}\left(\frac{\sigma_a^2}{\sigma^2}\right)^2 = \frac{1}{4}\left(a^2\right)^2.$$

These likelihood-ratio statistics for the inbred singleton and the sibpair are illustrated in Figure 1. Even for relatively large genetic effects, the singleton contributes little information to a test of heritability. As a unit of analysis, the efficiency of an inbred singleton relative to a sibpair is

$$\Lambda_1 / \Lambda_{\mathrm{SP}} = 2f^2.$$

This comparison is illustrated in Figure 2. The relative efficiency is independent of the effect size a^2 and strictly a function of the inbreeding coefficient, and is therefore constant for a given level of inbreeding. Typically $f \ll 1$ even for moderately high levels of inbreeding, so the efficiency of the single-efficiency of the singleton for heritability estimation is never large. For example, with $f \sim 1/10$, an inbred singleton contributes about 1/50-th the information of a sibpair.

For levels of inbreeding exceeding $f = 1/\sqrt{2} \approx 0.71$, the singleton becomes more informative than a non-inbred sibpair. Such high levels of inbreeding are not to be expected in human populations, but could easily be achieved in experimental settings, e.g., after two generations of selfing, or after six generations of sib-sib matings [9].

Linkage Model

To evaluate the contribution of an inbred singleton to a test of linkage, the additive genetic effect of a major gene is modeled by introducing a QTL-specific variance component. The model for the phenotypic covariance matrix becomes

$$\mathbf{\Omega} = \widehat{\mathbf{\Pi}}\sigma_q^2 + 2\mathbf{\Phi}\sigma_a^2 + \mathbf{I}\sigma_e^2.$$

where $\widehat{\mathbf{\Pi}}$ is a matrix of (estimated) allele sharing between individuals at a locus linked to the QTL, $\sigma_q^2 = q^2\sigma^2$ is the QTL-specific additive genetic variation, and the other quantities are as defined for the polygenic model.

Information Matrix—Under the null hypothesis for linkage, $H_0{:}\sigma_q^2 = 0$, there is no effect due to a QTL and all (additive) genetic variation can be ascribed to polygenic effects. The phenotypic covariance is therefore $\mathbf{\Omega}|H_0 \equiv \omega_0 = 2\varphi\sigma_a^2 + \sigma_e^2 = \left(1 + fh^2\right)\sigma^2$, where h^2 is trait heritability. The elements t_{ij} of the information matrix $\mathbf{T}$ are

$$\left\{t_{11}\right\} = \frac{1}{2}\left[\omega_0^{-1}\hat{\pi}\omega_0^{-1}\hat{\pi}\right] = \frac{1}{2}\omega_0^{-2}\hat{\pi}^2$$

$$\left\{t_{12}\right\} = \frac{1}{2}\left[\omega_0^{-1}\hat{\pi}\omega_0^{-1}(1+f)\right] = \frac{1}{2}\omega_0^{-2}\hat{\pi}(1+f)$$

$$\left\{t_{13}\right\} = \frac{1}{2}\left[\omega_0^{-1}\hat{\pi}\omega_0^{-1}(1)\right] = \frac{1}{2}\omega_0^{-2}\hat{\pi}$$

$$\left\{t_{22}\right\} = \frac{1}{2}\left[\omega_0^{-1}(1+f)\omega_0^{-1}(1+f)\right] = \frac{1}{2}\omega_0^{-2}(1+f)^2$$

$$\left\{t_{23}\right\} = \frac{1}{2}\left[\omega_0^{-1}(1+f)\omega_0^{-1}(1)\right] = \frac{1}{2}\omega_0^{-2}(1+f)$$

$$\left\{t_{33}\right\} = \frac{1}{2}\left[\omega_0^{-1}(1)\omega_0^{-1}(1)\right] = \frac{1}{2}\omega_0^{-2},$$

and the complete information matrix for the linkage model is

$$\mathbf{T} = \frac{1}{2}\omega_0^{-2}\begin{bmatrix} \hat{\pi}^2 & \hat{\pi}(1+f) & \hat{\pi} \\ \hat{\pi}(1+f) & (1+f)^2 & 1+f \\ \hat{\pi} & 1+f & 1 \end{bmatrix}.$$

Likelihood-Ratio Statistic—For the linkage model parameterized by σ_q^2, σ_a^2, and σ_e^2, the parameter vectors under the null and alternative hypotheses are, respectively, $\hat{\boldsymbol{\theta}}_0 = \left(0, \sigma_q^2 + \sigma_a^2, \sigma_e^2\right)'$ and $\hat{\boldsymbol{\theta}}_1 = \left(\sigma_q^2, \sigma_a^2, \sigma_e^2\right)'$. The singleton-specific likelihood ratio is then

$$\begin{aligned}\Lambda_1 &= \left(\boldsymbol{\theta}_1 - \boldsymbol{\theta}_0\right)' \mathbf{T} \left(\boldsymbol{\theta}_1 - \boldsymbol{\theta}_0\right) \\ &= \frac{1}{2}\omega_0^{-2}\left(\sigma_q^2, -\sigma_q^2, 0\right)' \begin{bmatrix} \hat{\pi}^2 & \hat{\pi}(1+f) & \hat{\pi} \\ \hat{\pi}(1+f) & (1+f)^2 & 1+f \\ \hat{\pi} & 1+f & 1 \end{bmatrix} \begin{pmatrix} \sigma_q^2 \\ -\sigma_q^2 \\ 0 \end{pmatrix} \\ &= \frac{1}{2}\left(\frac{q^2}{1+fh^2}\right)^2 (1+f-\hat{\pi})^2,\end{aligned}$$

where the quantity $(1+f) - \hat{\pi}$ is seen to be the difference in allele sharing at the locus under null and alternative models.

For an inbred singleton there are only two possible IBD states at a given locus,

$$\hat{\pi} = \begin{cases} 2 & \text{with probability } f \\ 1 & \text{with probability } 1-f \end{cases}$$

with expectations $E[\hat{\pi}] = 1+f$ and $E\left[\hat{\pi}^2\right] = 1+3f$. The corresponding expectation for the likelihood-ratio statistic in a test of linkage is therefore

$$\Lambda_1 = \frac{1}{2} f(1-f)\left(\frac{q^2}{1+fh^2}\right)^2.$$

Again, in the absence of inbreeding ($f = 0$), the likelihood ratio is identically zero and the singleton does not contribute to the estimation of linkage.

From [2] the corresponding expected likelihood-ratio statistic for a test of the linkage model in sibpairs is

$$\Lambda_{\mathrm{SP}} = \frac{1}{2}\frac{h^4+4}{\left(h^4-4\right)^2} q^4.$$

These expressions for inbred singleton and sibpair are illustrated in Figure 3 for various values of the inbreeding coefficient. The curves have qualitatively the same appearance, with the likelihood ratio (and therefore the power of a test of linkage) increasing with the QTL effect q^2. When q^2 exceeds about0.4–0.5 the power of the sibpair begins to increase markedly faster than for the inbred individual.

Relative to the sibpair, the efficiency for linkage of the inbred singleton is

$$\frac{\Lambda_1}{\Lambda_{SP}} = \frac{f(1-f)}{1+fh^2}\frac{\left(h^4-4\right)^2}{h^4+4}.$$

This ratio is illustrated in Figure 4. Note that the efficiency is independent of the QTL-specific effect, and depends only on the trait heritability. For low to moderate levels of inbreeding an inbred singleton can contribute a signifficant proportion of the linkage information of the sibpair. In extreme cases (unlikely to be found with human populations, but easily encountered or contrived with animal populations), an inbred individual can carry more than half of the linkage content of a sibpair.

Dominance Variance

The foregoing models have considered only additive genetic variation. However, since an inbred individual has a nonzero probability of having both alleles IBD at a locus, the individual can also be informative for dominance variance. The effect of dominance variance can be incorporated into a variance component model by introducing the term $\mathbf{\Delta}_7\,\sigma_d^2$, where $\mathbf{\Delta}_7$ specifies the (expected) probability of sharing both alleles IBD and σ_d^2 is the variance due to dominance interactions [2].

Dominance variance is generally ignored in variance component models, however, because only certain kinds of relative pair can share both alleles IBD (MZ twins, full sibs, double first cousins, etc). Even with large extended pedigrees containing many contributing relationships, the effect of dominance is inconsequential against the additive genetic effect and di cult to estimate accurately. Inclusion of dominance variance in the statistical model also introduces an additional degree of freedom for an effect that is primarily of academic interest.

Discussion

The ability to collect and analyze large extended human and nonhuman pedigrees significantly increases the probability of encountering pedigree loops, consanguinity, and inbred individuals [12]. When these features are present, statistical methods that avoid simplifying assumptions regarding relatedness will recover more of the available inheritance information, leading to more precise parameter estimates and more secure inferences. Penetrance-based approaches to linkage analysis often accommodate consanguinity and inbreeding with little if any additional effort, and approaches based on variance component models require only that the algorithms for computing the relevant structuring matrices (e.g., the kinship and QTL-specific sharing matrices) are written to handle correctly any consanguinity loops.

In quantitative genetic studies of large, pedigreed, human and nonhuman populations, the inclusion of isolated but inbred individuals can materially increase the power of statistical analysis. The realized benefit depends greatly on the number of such individuals and the expected level of consanguinity in the population under study, but even in populations

having a low mean coefficient of inbreeding, the linkage information contributed by isolated inbred individuals can accumulate to useful levels.

In human populations, the average inbreeding coefficient is typically less than 1/1000 [13, 14]. For genetic studies of many westernized populations the assumption of an outbred study sample is met to a greater or lesser degree, and ignoring inbreeding will have minimal impact on statistical power. For many of the world's populations, however, endogamy and consanguineous marriages are favored, and the mean level of inbreeding can become significant [15, 16, 17]. In many Asian and African populations, for example, first cousin marriages are the preferred form of consanguineous union [18, 19, 20,21]. Across the world's populations, inbreeding coefficients f near 1/30 are not uncommon, and in many groups f exceeds 1/10. An extreme case is found in the well-known Jicaque pedigree [22, 7] in which the kinship coefficient $\phi = 0.3710$ for the terminal pair of sibs implies $f > 1/3$ for their hypothetical offspring.

In wild primate populations, behavioral and demographic patterns (e.g., dispersal of males from their natal groups) act to reduce matings between close relatives, and lead to population mean inbreeding coefficients that are nearly zero or even slightly negative [23]. In captive or experimental populations, however, controlled breeding for colony management—even if new founders are introduced to maintain genetic diversity—can eventually raise the overall inbreeding coefficient to well over 1/8 [24, 25], and experimental selection for extreme phenotypes can generate many individuals having an inbreeding coefficient approaching 1/4.

With any inbred population, inclusion of inbred singletons is relatively most advantageous for smaller QTL effects. Not only is the linkage information content of the individual relatively greater in such cases, but the additional information compensates somewhat for the inherently reduced power of linkage analysis to detect smaller QTL effects. Ultimately, any increase in statistical power is desirable, particularly in the case of discrete phenotypes which, in variance component models, are markedly less informative than their quantitative counterparts [26].

Acknowledgements

The authors gratefully acknowledge helpful discussions with Thomas Dyer, and the constructive comments of two anonymous reviewers. This research was supported in part by National Institutes of Health grants DK099051 (to HHHG) and MH059490 (to JB), and conducted in part in facilities constructed with the support of NIH grant 1C06RR020547.

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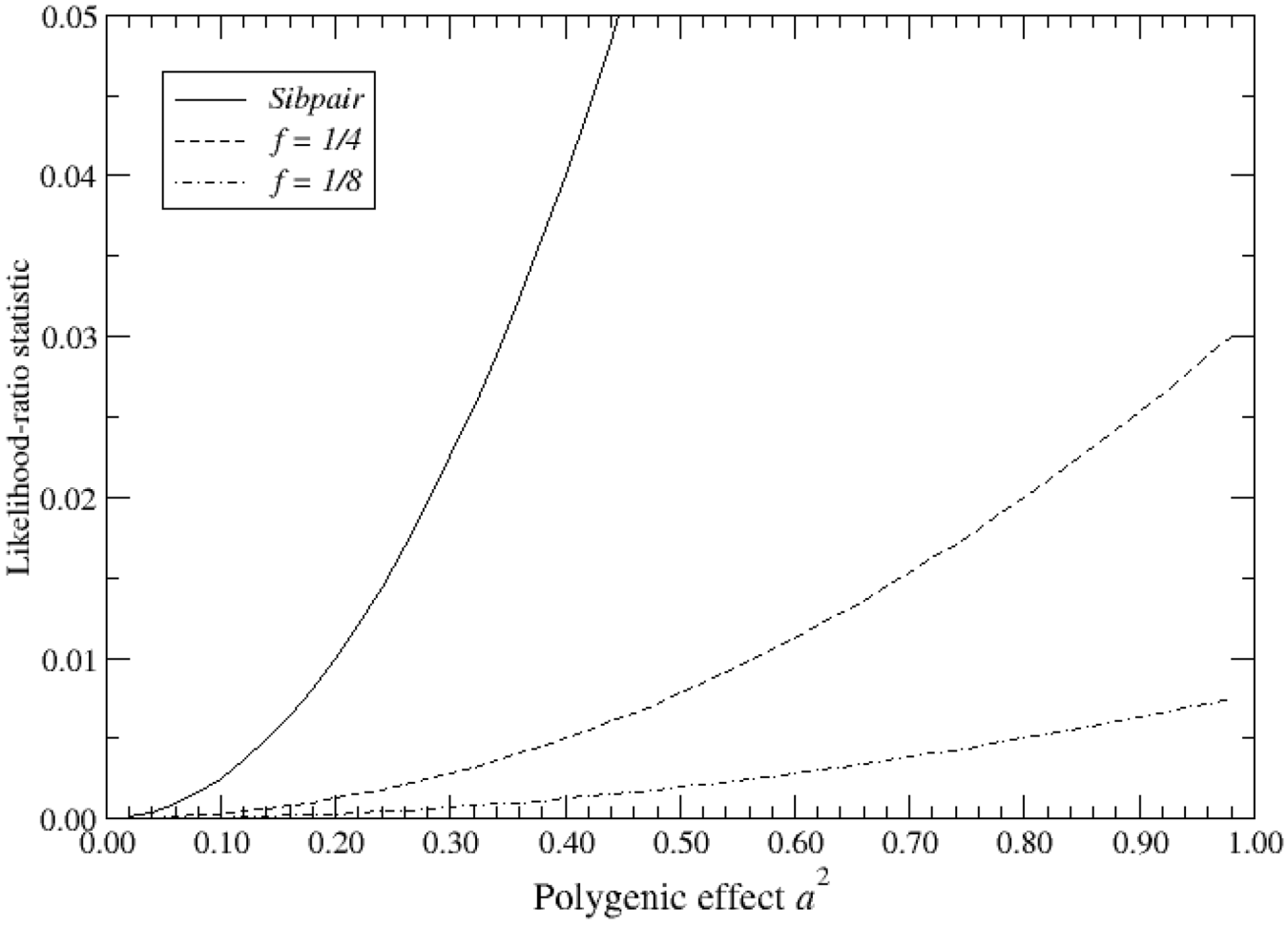

Figure 1.

Likelihood-ratio statistic for an inbred singleton and a (non-inbred) sibpair in variance component estimation of heritability. Curves are shown for inbreeding coefficients $f = 1/4$ (e.g., matings between full sibs, or parent and offspring) and 1/8 (e.g., half-sib, double first cousin, or offspring-grandparent matings).

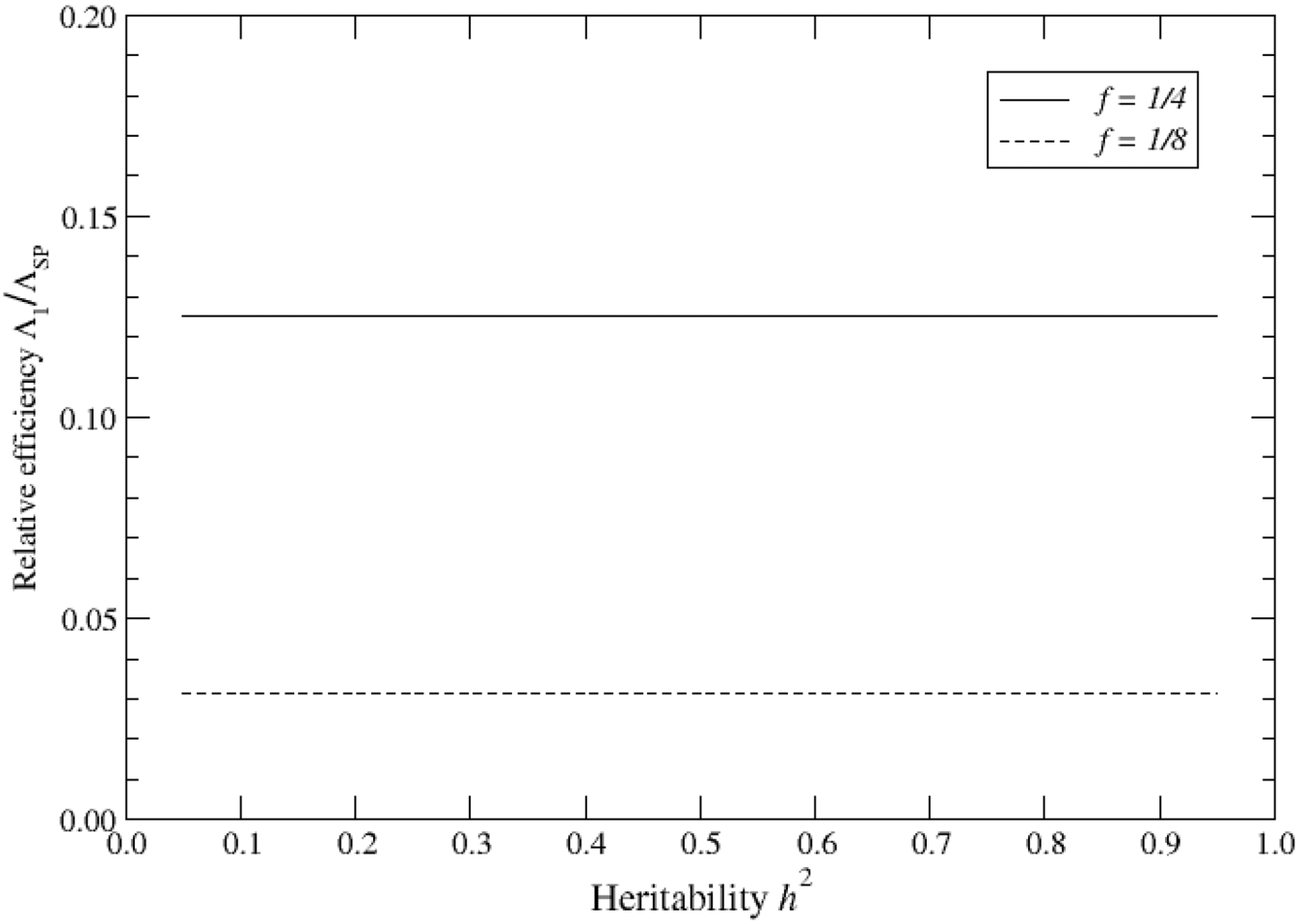

Figure 2.

The contribution of an inbred singleton relative to a (non-inbred) sibpair in variance component estimation of heritability. See Figure 1 for description of the inbreeding coefficients.

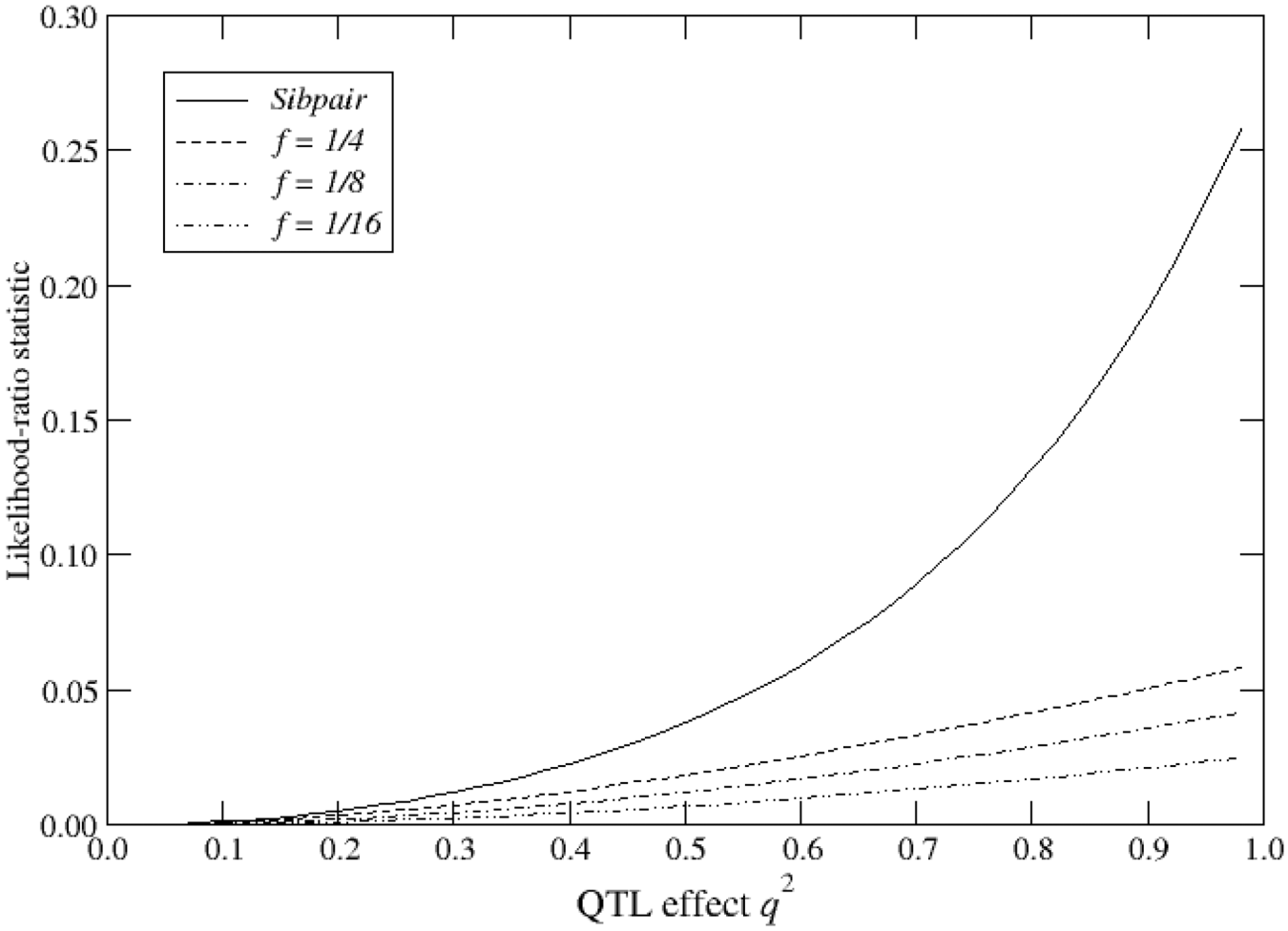

Figure 3.

Likelihood-ratio statistic for an inbred singleton and a (non-inbred) sibpair in variance component linkage analysis. Data are shown for inbreeding coefficients $f = 1/4$ (e.g., matings between full sibs, or parent and offspring), 1/8 (e.g., matings between half-sibs, double first-cousins, or grandparent and offspring), and 1/16 (e.g., matings between single first-cousins).

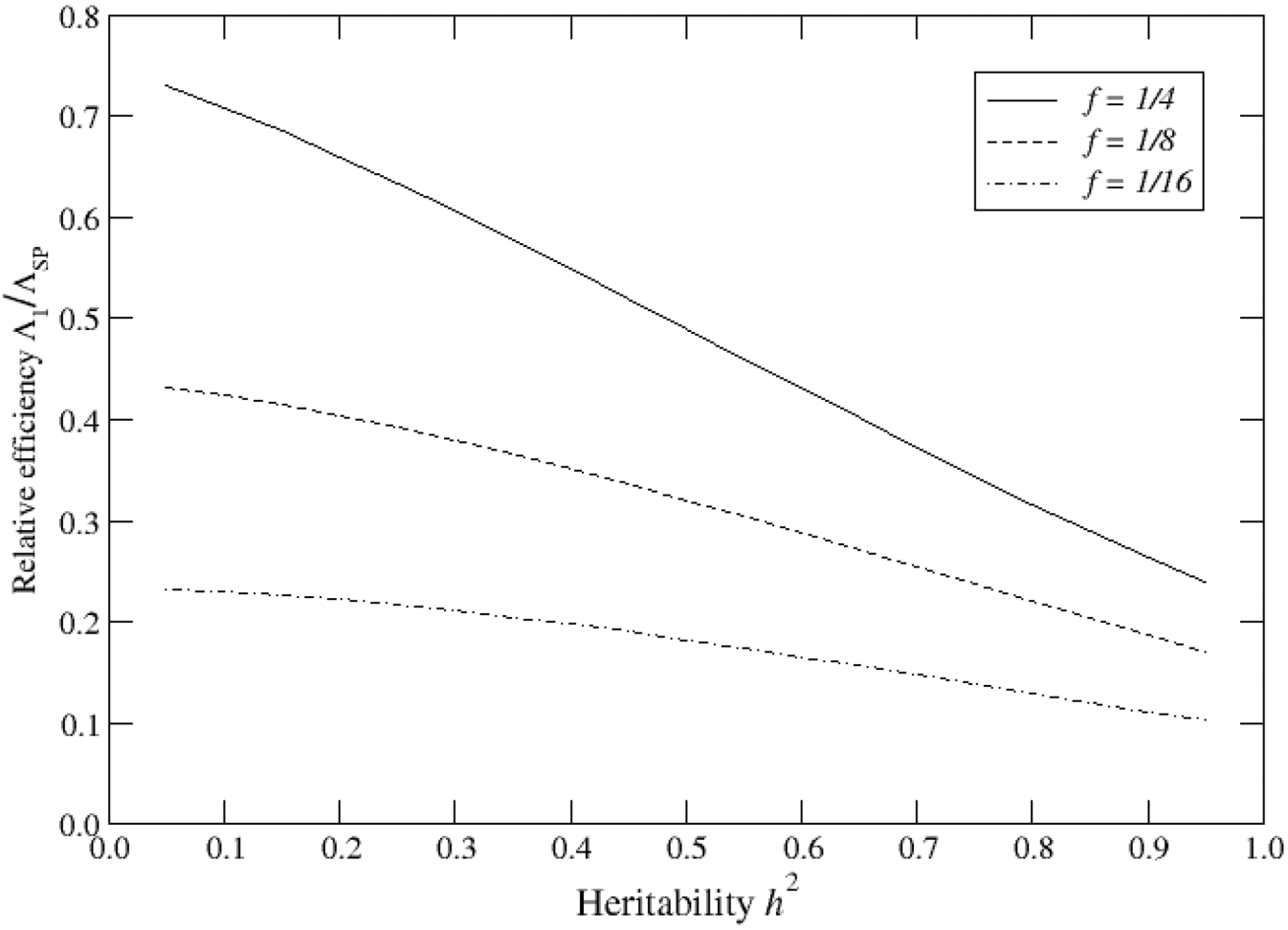

Figure 4.

The contribution of an inbred singleton relative to a (non-inbred) sibpair in variance component linkage analysis. See Figure 3 for description of the inbreeding coefficients.