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Inference in Linkage Analysis of Multifactorial Traits Using Recombinant Inbred Strains of Mice

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Recombinant inbred strains have been shown to be important tools for segregation and linkage analysis of multifactorial traits. Tests of association have been used as robust methods of linkage detection, however, guidelines for forming inferences from significance levels have not been generally available. In this paper, lessons learned from a Bayesian statistical approach to linkage analysis of Mendelian traits have been applied to studies of multifactorial traits. Criteria for detection of linkage based on Bonferroni's correction for multiple testing are also discussed.

KEY WORDS: linkage analysis; multifactorial traits; mice; recombinant inbred strains.

INTRODUCTION

The use of recombinant inbred (RI) strains in genetic studies of complex phenotypes has recently received increased attention (McClearn *et al.*, 1991; Plomin *et al.*, 1991). An RI strain is an inbred strain derived from a cross of two other inbred strains, known as the progenitor strains, by brother × sister matings of randomly selected offspring for 20 or more generations (Bailey, 1971). A set of RI strains that were independently derived from the same original cross of progenitor strains constitutes a very valuable genetic resource. RI strains have been used primarily to determine the mode of inheritance of phenotypes (i.e., Mendelian or multifactorial) and to map Mendelian traits and single major loci influencing complex phenotypes by detecting linkage to previously mapped marker loci. Several reviews of the use of RI strains, including analysis

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of correlated phenotypic traits, are available (Taylor, 1978; Oliverio, 1979; Bailey, 1981; Vadasz *et al.*, 1982).

One of the traditional strengths of the use of RI strains is the ability to perform transmission (or segregation) analysis of genetic traits. If variation between the progenitor strains is influenced by only a single locus, each of the RI strains will resemble one or the other progenitor strain. On the other hand, if one or more subsets of RI strains is distinguishable from both progenitors, an estimate of the number of effective loci can be calculated from an analysis of variance (Taylor, 1976). This estimate may not be robust because it makes several assumptions that are unlikely to be correct. Alternatively, an estimate of the minimum number of loci influencing variation can be derived from the number of phenotypic groups within an RI strain set (Baran *et al.*, 1975; Bailey, 1981). Larger sample sizes in each of the RI strains help reduce standard errors so that smaller differences between strains can be detected.

Linkage analysis utilizing RI strains has a great advantage. A large number of marker loci typings for each of the RI strains have been published, so that association between a trait and these marker loci can be tested after a set of RI strains is characterized for this trait. [Comprehensive tables listing published genotype data are given by Taylor (1989) and in the yearly reports of each of the Mouse Chromosome committees that are published in *Mammalian Genome*.] In the case of a Mendelian (single-locus) trait, linkage analysis is quite simple. Each of the RI strains is typed to determine which allele was inherited and then the strain distribution pattern (SDP) of alleles at that locus is compared to those of all known marker loci in an attempt to detect linkage. Because there are several chances for meiotic recombination between linked loci during the development of an RI strain, only tightly linked loci will remain associated in a comparison of SDPs. A maximum-likelihood estimate of recombination frequency between linked loci can be calculated from the proportion of discordances in the comparison of SDPs (Haldane and Waddington, 1931; Taylor, 1978). Upper and lower 95 and 99% confidence limits for this estimate can be calculated as proposed by Silver (1985).

The statistical support for inferences based on linkage data is more difficult to calculate. Alternative approaches include Monte Carlo simulations and Markov processes, however, Bayes' theorem is computationally simpler. In two previous papers, I presented a Bayesian statistical approach to determining the probability of linkage given a set of experimental results. The first paper (Neumann, 1990) reported a method of computing the probability of linkage given i mismatches between the SDPs for a pair of loci in a set of N RI strains and included simple

reference tables of critical values. The second paper (Neumann, 1991) presented a method of computing the probability of linkage and each of the three alternative gene orders given a set of linkage data for a test locus and a pair of linked marker loci. Although these studies indicated that previous guidelines for acceptance of linkage from RI strain data were not sufficiently stringent, Bailey (1981) and others have suggested that linkage assignments be confirmed by typing backcrosses, intercrosses, other RI strain sets, and bilineal congenic inbred strains. In the present paper, we consider linkage analysis of multifactorial traits using RI strains.

MULTIFACTORIAL TRAITS

Multifactorial traits can be divided into two types. The first is that in which phenotypic variation displays a bimodal distribution in a set of RI strains, suggesting the influence of a single major gene. The second displays a more complicated phenotypic distribution.

If analysis of a set of RI strains indicates the effect of a single major gene, that gene can be mapped using RI strains (Klein, 1978; Bailey, 1981), as demonstrated by Seyfried *et al.* (1980). Their detection of linkage between *Ias* (Inhibition of audiogenic seizures, now known as *Asp-1*, Audiogenic seizure prone-1) and *Ah* (aromatic hydrocarbon responsiveness) was confirmed by analysis of backcrosses and congenic strains (Seyfried and Glaser, 1981). Although it was later demonstrated that susceptibility to audiogenic seizures was influenced by three major genes and that the SDP assigned to *Ias* included some errors in genotype assignment, linkage of *Asp-1* to *Ah* on chromosome 12 has been demonstrated beyond reasonable doubt (Neumann and Seyfried, 1990; Neumann and Collins, 1991).

Linkage analysis is more complicated when phenotypic variation is not bimodal. Two approaches have been reported: genetic dissection and simultaneous search. In each case, RI strains are used to detect possible linkage assignments of QTLs (quantitative *and qualitative* trait loci) for confirmation in backcrosses and intercrosses. The first approach attempts to construct oligogenic models of phenotypic variation and potential SDPs for these loci for comparison to SDPs of marker loci. *Asp-2* and *Asp-3*, two additional major loci that influence susceptibility to audiogenic seizures, were mapped by separating RI strains into different phenotypic classes and then confirming proposed locations with backcrosses (Neumann and Seyfried, 1990; Neumann and Collins, 1991; 1992). A major component of the stringency of this method is the low probability of randomly constructing a strain distribution pattern that is either identical

to a known SDP or a plausible intermediate between a pair of known SDPs. A digression on probability may make the point clearer. For a set of 26 RI strains (as are available in the BXD set), there are 2^{26} (or 6.7×10^7) possible distinct SDPs, but the number of distinct SDPs that actually exist, discovered or not, is much lower. Assuming that the mouse genome has a length of 1600 cM and that the maximum-likelihood estimate of recombination frequency between loci that have a single discordant strain in this set is 1.02%, it is likely that fewer than 1600 distinct SDPs exist. Thus, the odds against randomly generating a SDP that matches one of these SDPs are approximately 40000:1. Further modifications of this estimate can be made that account for the fact that the majority of these SDPs is still undiscovered at this time (for an example, see Neumann and Collins, 1991).

The goal of a simultaneous search approach is to map several QTLs influencing a trait in a single analytical procedure. This entails independent, "simultaneous" attempts to detect linkage between loci influencing the trait of interest and multiple marker loci distributed over as much of the genome as possible, without a preliminary modeling of the effects of individual loci or the mode of inheritance. Lander and Botstein (1986, 1989) have convincingly argued that simultaneous search approaches to linkage detection are efficient. Several examples of the use of this approach to analysis of backcrosses and intercrosses have been published. The availability of a very large number of published SDPs for sets of RI strains has led to the proposal that the simultaneous search approach be applied to RI strain data. Klein (1978) proposed the use of multiple regression analysis of phenotypic variation, and more recently, McClearn, Plomin, and their colleagues have advocated the use of Pearson product–moment correlations (McClearn *et al.*, 1991; Plomin *et al.*, 1991). Tests of association between multifactorial traits and marker loci may be preferable to other statistical treatments because tests of association are computationally simple and statistically robust (Haseman and Elston, 1972; Blackwelder and Elston, 1982). In the next two sections, the significance of various degrees of associations to inferences about QTL detection in RI strains is investigated both within a Bayesian framework and from a more traditional viewpoint using Bonferroni's correction for multiple testing.

BAYESIAN STATISTICAL APPROACH TO LINKAGE DETECTION IN RI STRAINS

Five percent of pairs of unlinked loci will show random association at the .05 confidence level, but the significance of this p value to the

question of linkage detection is not straight forward. Knowing that the probability of obtaining the data, if the null hypothesis (nonlinkage) is true, is less than 5% does not provide an estimate of the probability that the null hypothesis is false. Bayesian analysis provides just such an estimate for use in statistical inference. Calculation of the probability of an event given a specific data set, that is, the posterior probability of that event, requires reasonable estimates of the prior and conditional probabilities of each of the alternative events. These requirements are fulfilled in the case of linkage analysis in mice. The prior probability of linkage is low, therefore very stringent criteria are required for acceptance of linkage with a high degree of certainty.

Figure 1 illustrates the relationship between p associated with a χ^2 (1 df) test and the posterior probability of linkage of a Mendelian trait to a marker locus in a set of RI strains. This figure is derived from a table of computed probabilities of linkage (Table 1 of Neumann, 1990).

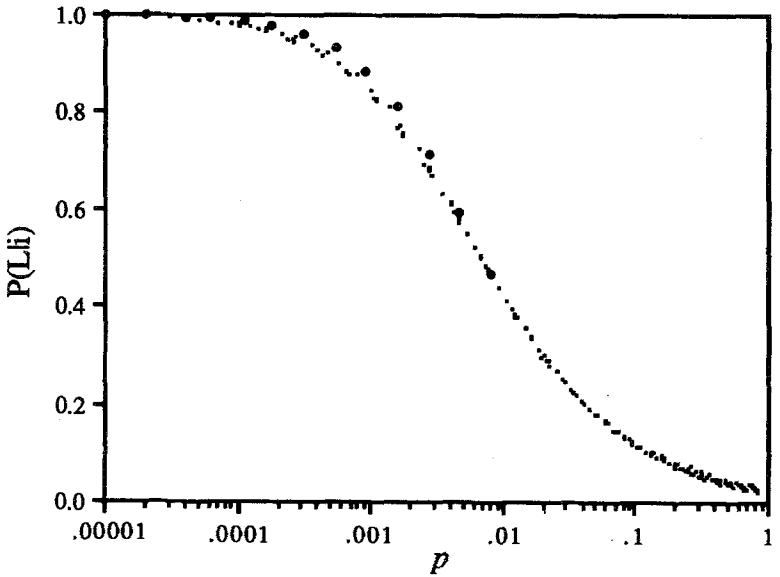

Fig. 1. The relationship between probability, p, values for χ^2 tests of association and the posterior probability of linkage, $P(L|i)$, of a Mendelian trait and a marker locus in a set of recombinant inbred strains as determined by a Bayesian statistical analysis. The posterior probabilities were taken from Table 1 of Neumann (1990). The corresponding χ^2 values were calculated from the number of RI strains (N) and recombinants (i). p values were obtained from the STAT-SAK (Gerard E. Dallel, Malden, MA) program. The larger points represent the cases where $i = 0$.

From Fig. 1, one can see that the criterion for 95% probability of linkage is equivalent to a test statistic p value in the range of .00025 to .0003 and that a p value of .05 is equivalent to approximately 18% probability of linkage. For illustrative purposes let us imagine that in a series of tests of association between a trait and a set of marker loci, five or six independent tests are "significant" at the $p = .05$ level. If each of these p values is close to .05, on average only one of these will represent linkage. The relationship between p values and probability of linkage depicted in Fig. 1 can serve as a guide for mapping loci involved in multifactorial traits, but it must be remembered that these calculations were derived for Mendelian traits rather than multifactorial traits and that the p values are taken from a χ^2 distribution rather than the Student t distribution. To the best of my knowledge, a reasonable argument for making the requirements for detection of a locus involved in a multifactorial trait less stringent than the criteria for acceptance of linkage detection for Mendelian traits has not been presented.

A severe limitation to RI analysis of multifactorial traits caused by the relatively small number of RI strains available in each set is demonstrated in Table I. For a QTL to be detected with 95% probability of linkage, the proportion of the variance explained by the QTL, which can be estimated from the square of r (R^2), must be quite high. For example, in a set of 21 RI strains, half of the between-strains variance must be explained (that is, the correlation coefficient, r, must be greater than .7) if an appropriately high probability of linkage is required before acceptance as a provisional QTL. Even in a set of 30 RI strains, the critical value of r is .61. Therefore, a set of 21–30 RI strains probably only rarely provides strong evidence for more than two linkage associations for a multifactorial trait. However, QTL analysis in RI strains will become more powerful as the number of known, distinct strain distribution patterns (SDPs) increases because recombinations between QTLs and marker loci will tend to obscure associations.

ESTIMATION OF BONFERRONI t STATISTIC FOR RI STRAINS

An alternative method of determining the appropriate significance level is the Bonferroni t statistic (Alt, 1982; Kotz and Johnson, 1982), which corrects for the effect of multiple testing. In other words, the Bonferroni t statistic maintains the confidence level in simultaneous inference. Typically, when multiple independent tests of association are simultaneously conducted with a variable, the confidence level for an individual test is set at a value equal to the desired confidence level for

Table I. Critical Values of the Correlation Coefficient and the Associated Estimate of the Proportion of Variance Explained[a]

N	*df*	*r*	R^2
13	11	.838	.702
14	12	.819	.671
15	13	.800	.64
16	14	.782	.612
17	15	.765	.585
18	16	.749	.561
19	17	.734	.539
20	18	.720	.518
21	19	.706	.498
22	20	.693	.480
23	21	.681	.464
24	22	.670	.449
25	23	.659	.434
26	24	.648	.420
27	25	.638	.407
28	26	.628	.394
29	27	.619	.383
30	28	.610	.372

[a] For sets of 13 to 30 RI strains the minimal correlation coefficient (r) that is associated with a p value of .0003 was obtained using the STAT-SAK program. This value is proposed as a threshold for provisional acceptance of linkage in analysis of RI strain data because p values of .0003 in the χ^2 distribution are equivalent to 95% probability of linkage (Neumann, 1990; see Fig. 1). The table begins with 13 RI strains because this is the smallest set in which linkage can be detected with a probability of 95%. An estimate of the proportion of the between-strains variance explained by a provisional QTL can be calculated from the square of r (called R^2). *N*, number of RI strains; df, degrees of freedom in the two-tailed t test.

the set of tests divided by the number of comparisons (α/k). A more stringent, and arguably more appropriate, test would be to set the value of k to the number of possible independent tests, which can be estimated because the genome has a finite length.

The number of independent tests can be considered a function of a marker locus' "swept radius." Carter and Falconer (1951) defined the swept radius as the genetic distance equivalent to the largest recombination frequency two standard deviations below 50%. For a Mendelian trait, k can be approximated by $h + G/2s$, where h is the number of chromosomes in a haploid genome (20 in mice), G is the length of the haploid genome (estimated to be 1600 cM in mice), and s is the swept radius, which is a function of sample size. Thus, in a set of 21 RI strains of mice, where the swept radius is 12.5 cM, an estimate of k would be 84. If the significance level for the set of comparisons is set at .05, the individual significance level would be .0006. This correction for multiple

testing is slightly less stringent than the effect of the Bayesian analysis but has the same order of magnitude. Because the swept radius increases with the number (N) of RI strains, there is an inverse relationship between k and N.

Alternatively, a more stringent option might be justifiable for QTL detection because multifactorial traits display lower associations than Mendelian traits when recombination frequencies are the same. For example, the number of independent tests could be considered a function of the size of the portion of the chromosome in which linkage to a marker locus can be demonstrated with a probability greater than or equal to 95%. Because this "radius swept" is very small relative to chromosome length, k can be estimated simply by dividing G by twice the radius swept. For example, in a set of 21 RI strains, the maximum permissible recombinants is 2 (Neumann, 1990) for a maximal-likelihood estimate of 2.77% recombination. The estimate of k is 1600/(5.54) or 289. If the significance level for the set of comparisons is set at .05, the individual significance level is .00017. Estimates of Bonferroni t statistics for sets of 21 to 30 RI strains vary from .00016 to .00028 (calculations not shown), which are similar to the Bayesian estimates for the critical value of p for demonstrating that there is a 95% probability of linkage. As above, there is an inverse relationship between k and N.

CANDIDATE GENE APPROACH

One way in which power of RI strains can be increased is through a candidate gene approach. If hypotheses of relationships between known loci and multifactorial traits can be generated prior to performance of studies using RI strains, criteria for linkage detection can be reduced. Significance levels in tests of association must be stringent in exploratory data analysis, however, criteria for acceptance of linkage are relaxed to traditional levels (e.g., $p = .05$) in confirmatory experiments and in planned comparisons. If multiple planned comparisons are made, the appropriate value of k is simply the number of planned comparisons. One-tailed tests of association can be justified if previous studies of candidate genes suggest that direction of the expected effect of allelic variation, however, one-tailed tests are not justified by the direction of the parental phenotypic difference.

RANDOM ASSOCIATION OF UNLINKED LOCI

Correction for random association of unlinked loci is particularly important in studies with small sample sizes. Estimates of allelic effects

on multifactorial traits can be increased or decreased by deviations from the expected independent assortment of unlinked loci, which can obscure true linkage associations and lead to false linkage detection and incorrect mapping of loci influencing multifactorial traits relative to linked marker loci. For example, Neumann and Collins (1991) described a three-locus model based on 23 RI strains. Theoretically there could have been as many as eight distinct phenotypic classes, however, only seven genotypic classes were identified and one of those consisted of a single strain. In the analysis of a multifactorial trait, absence of one or more genotypic classes in a set of RI strains is common (Demant and Hart, 1986). Although *Asp-2* and *Asp-3* are not linked, their proposed SDPs show a positive correlation ($r = .46$). Failure to correct for random association is equivalent to assuming that all eight genotypic classes are equally represented or, in other words, that the three allelic variations are distributed uniformly and independently. As a result, in these RI strains, the marker locus *Ifa* (Interferon α) is associated with a smaller AGS susceptibility difference than *b* (Brown coat color) (Neumann and Seyfried, 1990), even though *Asp-2* is closer to *Ifa* (Neumann and Collins, 1991).

SEQUENTIAL SEARCH

In a study of cerebellar folial pattern (Neumann, Garretson, Skabardonis, and Mueller, submitted for publication), we have employed another approach to RI strain analysis, which we call sequential search. The strategy is an extension of the simultaneous search approach that incorporates correction for random association of unlinked loci. After the first major locus has been mapped by RI strain analysis and confirmed by a classical cross, the effect of that locus on the trait under examination is estimated. The unexplained residuals for the trait in each RI strain are estimated by factoring out the effect of the mapped locus. Then the unexplained residuals are subjected to another simultaneous search for QTLs. The process is repeated until potential QTLs can no longer be detected in RI strain analysis or until potential QTLs identified by the residuals cannot be confirmed.

CONCLUDING REMARKS

The use of appropriately low significance levels in tests of association is critical for avoidance of spurious linkage detection. Rough guidelines for forming inferences from significance levels generated from analyses of RI strain data have been discussed in the preceding para-

graphs. Although two calculations of a Bonferroni correction factor are presented, the guidelines based on the Bayesian analysis are recommended.

Two possible causes of biased tests of association that should be avoided are inclusion of progenitor strain data and assumption of equal variances. It is my practice to use an F test to determine whether the variances are significantly different so that appropriate t tests can be employed. Inclusion of "parents" in tests of association will tend to increase random associations between unlinked loci, shifting all correlations in the direction of the parental difference. This will also obscure QTLs that have directional effects opposite to the parental difference and all QTLs when there are no parental differences.

All statistical treatments of linkage in RI strains depend on the assumptions of the Haldane and Waddington (1931) equation for the probability of recombination between linked loci after inbreeding by sequential brother × sister matings. One of these assumptions is that there is no resistance to inbreeding, that is, that the rate of fixation of genotypes in developing inbred strains is not retarded by "inbreeding depression" (the converse of hybrid vigor) or the effects of a limited number of loci. The effect of such a reduction in the rate of inbreeding would be to increase the number of opportunities for meiotic recombination. This, in turn, leads to increased estimates of recombination between linked loci and of the radius swept. Therefore, the use of the critical p values generated by Bayesian linkage analyses of Mendelian traits in RI strains for analyses of multifactorial traits in RI strains is reasonable, although this method may be slightly less stringent than it should be.

Examination of Table I may be discouraging to many potential users of RI strains. The conclusion that a QTL would have to account for 40–50% of the between-strains variance to be detected with 95% probability of linkage to a marker locus in a set of 20–30 RI strains should not be interpreted as a powerful argument against the use of RI strains for the analysis of multifactorial traits. First, RI strains are very valuable for analyses of the genetic component of the variance and mode of transmission. Second, although linkage analyses utilizing RI strains have limited power, they complement similar studies of classical crosses. It should be considered good experimental practice, rather than a burden, to conduct independent tests of all linkage assignments that are not proved beyond a reasonable doubt. Finally, the value of a series of RI strains for the analysis of multifactorial traits can be increased by production of a set of F_1 hybrid populations from crosses of these RI strains with one or both of the progenitor strains or from crosses between RI strains

(Neumann and Seyfried, 1990; Neumann and Collins, 1991; Plomin *et al.*, 1991).

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