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Outbred animal stock quantitative trait loci may be finely mapped using this approach.

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ABSTRACT
Because of the huge effect sizes seen in crosses between inbred strains, high-resolution mapping of quantitative trait loci (QTL) in animals has proven to be problematic. Each has a little impact. We've discovered that mice are more scared than previously thought. small-effect QTLs may be fine-mapped in a genetically diverse population the stock market (HS). This is a great overall technique for fine-tuning. given that QTLs are found in crosses between inbreds, the mapping process The HS may be used to identify the strains that generated theHS. Weshow Only two of the five candidates are found in this study using a single-marker association analysis. In the HS, QTLs are predicted to be segregated, which presumably restricts the number of QTLs. For precise mapping, strategy is crucial. With this issue, we come up with a novel solution. allele descent probabilities may be calculated using multipoint analysis. from each of the HS's ancestors. Pedigrees are not used in the study. but instead calls for data on the haplotypes of the HS's founding fathers. We were able to locate all three previously unidentified loci using this strategy. Chr. 1 logP 4.9, Chr. 10 logP 6.0, and Chr. 15 logP 4.0 [chromosomes]. Wesingle-marker association fails because of this reason its inability to discriminate between the phenotypic impacts of competing QTLs when both markers are found on the same allele of the gene We've created a new product. QTL mapping in genetically diverse populations using a robust technique genetic testing on animals and claim that it is now cost-effective simultaneous, high-resolution examination of several complicated characteristics a group of mice

INTRODUCTION
Most phenotypes of medical importance can be measured quantitatively, and in many cases the genetic contribution is substantial, accounting for 40% or more of the phenotypic variance. Considerable efforts have been made to isolate the genes responsible for quantitative genetic variation in human populations, but with little success, mostly because genetic loci contributing to quantitative traits (quantitative trait loci, QTL) have only a small effect on the phenotype (1). Association studies have been proposed as the most appropriate method for finding the genes that influence complex traits (2). However, family- based studies may not provide the resolution needed for posi- tional cloning, unless they are very large, whereas environmental or genetic differences between cases and controls may confound population-based association studies (3) These difficulties have led to the study of animal models of human traits. Studies using experimental crosses between inbred animal strains have been successful in mapping QTLs with effects on a number of different phenotypes, including behavior, but attempts to fine map QTLs in animals often have foundered on the discovery that a single QTL of large effect was in fact caused by multiple loci of small effect positioned within the same In an attempt to circumvent the difficulties encountered with inbred crosses, we have been using a genetically heterogeneous stock (HS) of mice for which the ancestry is known. The hetero- geneous stock was established from an eight-way cross of C57BL,BALB/c, RIII, AKR, DBA/2, I, A, and C3H/2 inbred strains (5).

Since its foundation 30 years ago, the stock has been maintained by breeding from 40 pairs and, at the time of this experiment, was in its 60th generation. Thus each chromosome from an HS animal is a fine-grained genetic mosaic of the founder strains, with an average distance between recombinants of 1/60 or 1.7 cM.

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Theoretically, the HS offers at least a 30-fold increase in resolution for QTL mapping compared with an F_2 intercross (6, 7). The high level of recombination means that fine mapping is possible by using a relatively small number of animals; for QTLs of small to moderate effect, mapping to under 0.5 cM is possible with fewer than 2,000 animals. The large number of founders increases the genetic heterogeneity, and in theory one can map all QTLs that account for progenitor strain genetic differences. Potentially, the use of the HS offers a substantial improvement over current methods for QTL mapping.

However, for HS mapping to achieve widespread use, we need to establish its limitations and provide a robust statistical method of analysis. In this paper we describe a multipoint method capable of detecting small-effect QTLs in the HS; we evaluate both its power of QTL detection and the expected degree of QTL resolution. The utility of the method is demonstrated by fine mapping five QTLs for fearfulness in HS mice, only two of which were detectable by single-marker (SM) association.

Statistical Theory

Failure of SM Association Analysis. It has been noted in association studies in human populations that SM association analysis may fail to detect QTLs expected to be segregating (1). We encountered the same problem in a study (8) of open-field behaviors of HS mice, a validated animal model of susceptibility to anxiety (9). We typed a total of 67 markers approximately 1 cM apart on 750 HS mice, over five regions where previous F2 intercrosses had detected QTLs (refs. 10 and 11; Table 1). We expected to

Table 1. QTLs detected in F_2 intercrosses and corresponding SM ANOVA logP of HS mice

Closest marker	Position, cM	LOD	% var.	Cross	SM logP
D1Mit150	84.4	13.4	9.2	b	0.5
D1Mit116	80.2	7.1	6.3	a	6.8
D10Mit237	76.0	8.8	8.3	a	1.8
D12Mit47	31.5	4.3	4.4	b	4.5
D15Mit63	44.0	11.0	8.1	b	1.4

The inbred crosses are: (a) A/J X C57BL/6 (11), (b) BALBc/J X C57BL/6 (10).
LOD, logarithm of odds.

confirm QTLs in all five regions because the strains that were used in the F2 detection experiments were among the founders of the HS. We used SM analysis of variance to map the QTLs. At each marker the animals were grouped according to their genotype and one-way ANOVA was used to test for significant differences between the group means. Marker-QTL association was indicated by a significant *F*-statistic in the ANOVA. We confirmed and fine mapped QTLs in only two of the five regions (Table 1). On chromosome 1 a QTL accounting for 6% of the phenotypic

variance was mapped into an interval of 0.8 cM, so in some

circumstances SM association works well. We therefore sought

an explanation for the three failures.

A Multipoint Model Using Progenitors. To incorporate information

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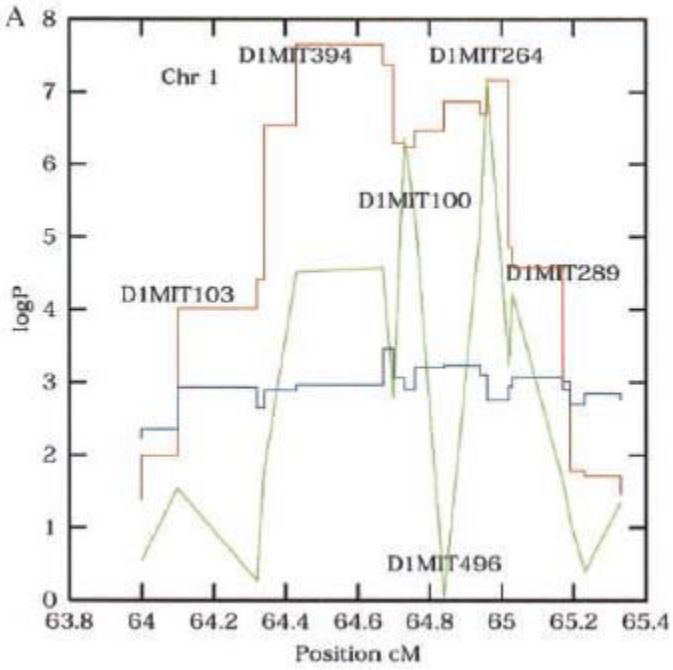
from flanking markers and the progenitor haplotypes, we developed a multipoint method that determines the probability of each founder strain being the ancestor of a given allele in the HS. QTLs then are detected by testing for differences between the genetic effects of the progenitor haplotypes rather than by association at each locus. Note that it would not help to reconstruct the haplotypes of the HS at the generation we tested, as this would not determine whether (in the example) an allele at D1Mit496 was derived from RIII or from one of the other strains. The critical issue is to calculate the probability that an allele is descended from one of the eight progenitors, which is different from standard interval mapping (12) or interval mapping with marker cofactors (13–15).



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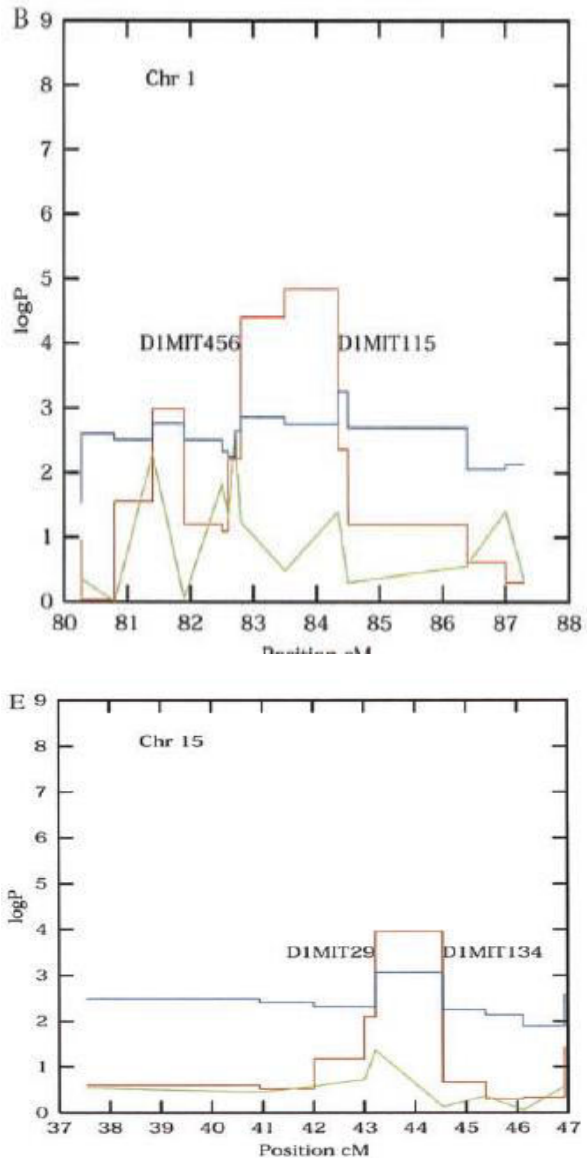

Fig. 1. SM(green) andDP(red) analyses of regions of chromosomes (Chr) 1 (*A* and *B*), chromosome 10 (*C*), chromosome 12 (*D*), and chromosome 15 (*E*). Distances along each chromosome are given in cM (*x* axis). The *y* axis measures logP values. DP thresholds (blue) are the empirical 0.1% logP thresholds

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derived by permuting the genotypes 1,000 times. Selected markers are labeled.

Table 2. Bootstrap estimates of QTL locations compared with positions determined by RIST analysis of BALBc/J X C57BL/6 (17)

Chromosome	DP range	Bootstrap probability	RIST range
Chr1	64.0–65.0	0.92	
	82.3–83.8	0.96	80.0–84.3
Chr10	69.5–70.0	0.99	
Chr12	31.0–32.0	0.80	
	32.5–33.0	0.20	
Chr15	42.0–43.5	0.91	43.0–47.2

The bootstrap probability is the proportion of times the highest logP value in the neighborhood of the QTL fell in the specified DP range. RIST, recombinant inbred segregation test.

locus $m + 1$ is in state s, t given all information from markers $m+ 1$ through M by running the algorithm backward from the terminal marker. Analysis of N individuals, M markers, and Sstrains requires space proportional to NMS^2 and time propor- tional to NMS^4.

Results

Significance Levels and Resolution. We examined a 10-cM region around each of the five QTLs identified in the F2 intercrosses (Table 1), placing markers on the radiation hybrid map and, where possible, the European Collaborative Interspecific Backensi genetic map to provide accurate marker positions necessary for the method. The results are shown in Fig. 1.

To check the accuracy of the tabulated ANOVA significance levels, we permuted the phenotypes between animals and repeated the ANOVA 1,000 times, thereby taking into account the large number of markers, the fact that the tests are no longer independent, and that the phenotypes may not be normally distributed. At each marker interval the logP values were ranked, and the 5%, 1%, and 0.1% significance levels were defined as the corresponding percentiles. They are slightly less than their theoretical values, so the use of logP derived from a tabulated F distribution is reliable and conservative. Fig. 1 shows the 0.1% significance levels. Additionally, the most significant permuted logP in each region was close to the reciprocal of the number of intervals, so the tests may be treated as independent. Therefore, to establish significance levels appropriate for any mapping experiment, we need only divide the individual regression Pvalue by the number of intervals. We analyzed a total of 63

intervals, so the 1.0% and 0.1% logP thresholds are 3.8 and 4.8, respectively. All of the QTLs we have detected exceed the 1% level, and only one (near D15Mit134, logP 3.95) fails to exceed

the 0.1% level.

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