Some Epistatic Two-Locus Models of Disease.
I. Relative Risks and Identity-by-Descent Distributions in Affected Sib Pairs

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SUMMARY

A two-locus disease model is presented in which a marker locus interacts epistatically with another *unlinked* trait to cause the disease. Such a model can lead to disease-marker associations and distortions in the sharing of marker types among affected family members. These effects are quantified. In the case of HLA-disease associations, this model is presented as an alternative to the "hitchhiking" theory of tight linkage leading to linkage disequilibrium.

INTRODUCTION

Disease-marker associations, particularly those involving the HLA complex, are currently attracting much interest [1, 2]. Often a disease or trait is found more frequently in conjunction with certain allele(s) at the marker locus than would be expected from population figures. Simultaneously, it is observed that within families, affected members tend to share marker types "in common" (identical by descent) more often than expected by random segregation. Among the diseases of particular interest are (juvenile) insulin-dependent diabetes [3], multiple sclerosis [4], ankylosing spondylitis [5], psoriasis [6], coeliac disease [7], and idiopathic hemochromatosis [8], all found in association with certain antigens of the major histocompatibility system, HLA.

One plausible explanation for these phenomena is that a disease or disease-susceptibility locus exists tightly linked to and in linkage disequilibrium with the

marker locus. This hypothesis has been proposed by McDevitt and Bodmer [9] for several diseases in connection with the HLA marker system. Inherent in this hypothesis is the idea that the associated marker allele(s) are not causally involved in occurrence of the disease. Rather, the association is thought to be merely the result of the linkage disequilibrium ("hitchhiking effect") [10]. Several studies, for example, [11, 12], have concluded that this is in fact the correct explanation for the disease in question.

An alternative explanation is that the marker locus may itself be causally implicated in expression of the disease, in epistatic interaction with one or more additional *unlinked* loci; that is, genes of the marker system may have pleiotropic effects. Such a model would explain both the observed disease-marker association and the increased sharing of haplotypes within families (among affected individuals), without recourse to linkage disequilibrium. If the marker allele increases susceptibility to the disease but is not alone either necessary or sufficient for its manifestation, then "loose associations" will result, as observed for a number of diseases in connection with HLA.

This second explanation involving two loci has been suggested by a number of investigators (for example, [5, 13]), but the quantitative details of such a model have not previously been reported. This paper quantifies the implications of such an epistatic system (1) for the sharing of marker types identical by descent in pairs of affected siblings and (2) for disease-marker associations. The study of affected sib pairs represents a relatively easy way to examine the sharing of marker types within families [14–17], and methods of analysis of affected sib pairs have generated much interest [18–21]. A second paper [22] will address the broader issue of how disease-marker associations may affect linkage analyses performed between the disease and the marker.

MODEL

Consider two unlinked autosomal loci interacting epistatically. They are denoted, respectively, the "trait" and "marker" loci. The trait locus has two alleles, A and a, occurring with frequencies p and q, respectively. The marker locus has an allele M with frequency r; all other marker allele(s) are denoted m and have a (collective) frequency $s = 1 - r$.

Thus, there are nine genotypes of interest. One fairly general restriction is imposed: the penetrance structure must be multiplicative. The reasons for placing this restriction will be discussed later. Table 1 shows the structure of the model. The α_i and v_i represent penetrance contributions from the trait and marker loci, respectively. (The standard notation of f for penetrance is reserved for the more general two-locus formulation, in the APPENDIX.) Neither all α_i nor all v_i can be zero.

Table 2 shows some numerical examples of potential biological interest. For example, consider the dominant-dominant model illustrated in the table. The name dominant-dominant implies three statements: (1) One allele, A, at the trait locus is dominant, in the classical sense that A must be present for the disease to occur and A has equal action in either single or double dose. (2) One allele, M, at the marker locus increases susceptibility in a dominant fashion, but the disease can occur in the absence of this allele. Thus the chance of manifesting the disease is low if M is not simultaneously present with A and is much higher if M is present, in either single or double dose. Note that the term "dominant" is being used in a different sense for the trait and marker loci. (3) The two loci interact multiplicatively.

When gene action is neither dominant nor recessive, it is termed intermediate.

TABLE 1

PENETRANCES OF THE TWO-LOCUS EPISTATIC MODEL

GENOTYPE AT TRAIT LOCUS	GENOTYPE AT MARKER LOCUS		
	$MM(r^2)$*	$Mm(2rs)$	$mm(s^2)$
$AA(p^2)$*	$\alpha_1 v_1$	$\alpha_1 v_2$	$\alpha_1 v_3$
$Aa(2pq)$	$\alpha_2 v_1$	$\alpha_2 v_2$	$\alpha_2 v_3$
$aa(q^2)$	$\alpha_3 v_1$	$\alpha_3 v_2$	$\alpha_3 v_3$

* Figures in parentheses represent population genotype frequencies, assuming Hardy-Weinberg equilibrium.

A disease in which transmission is governed by this model will exhibit both an association with the marker allele M and a preponderance of marker types shared identical by descent, that is, a high rate of marker concordance among affected family members, pairs of affected siblings in particular. The details of these two properties will be elucidated in what follows.

METHODS

In this section, (1) the desired identity-by-descent (IBD) distribution at the marker in affected sib pairs is given in terms of stochastic relationship matrices. Under random segregation, two affected sibs share 2, 1, or 0 marker types or haplotypes with probabilities ¼, ½, and ¼, respectively. The general formulas for IBD in all two-locus (unlinked) models are derived (in the APPENDIX), and it is shown that when penetrances are multiplicative, this distribution reduces to a one-locus case and depends only on the marker parameters r and the v_i. (2) The expression for the cross-product relative risk, a standard measure of association between the disease and the marker, is given. (3) Finally, the calculations are illustrated with an example.

TABLE 2

SOME EXAMPLES OF THE GENERAL MODEL IN TABLE 1

	DOMINANT-DOMINANT (TRAIT DOMINANT, MARKER DOMINANT)				RECESSIVE-RECESSIVE		
	MM	Mm	mm		MM	Mm	mm
AA	.75	.75	.05	AA	0	0	0
Aa	.75	.75	.05	Aa	0	0	0
aa	0	0	0	aa	.50	.05	.05
	$\alpha_1 = \alpha_2 = 1$, $\alpha_3 = 0$				$\alpha_1 = \alpha_2 = 0$, $\alpha_3 = 1$		
	$v_1 = v_2 = .75$, $v_3 = .05$				$v_1 = .50$, $v_2 = v_3 = .05$		

	DOMINANT-RECESSIVE				RECESSIVE-INTERMEDIATE		
	MM	Mm	mm		MM	Mm	mm
AA	.50	.05	.05	AA	0	0	0
Aa	.50	.05	.05	Aa	0	0	0
aa	0	0	0	aa	1.0	.5	0
	$\alpha_1 = \alpha_2 = 1$, $\alpha_3 = 0$				$\alpha_1 = \alpha_2 = 0$, $\alpha_3 = 1$		
	$v_1 = .50$, $v_2 = v_3 = .05$				$v_1 = 1.0$, $v_2 = .5$, $v_3 = 0$		

IBD Distribution in Affected Sib Pairs

Use the $\underset{\sim}{I}$-$\underset{\sim}{T}$-$\underset{\sim}{Q}$ matrices of [23, 24]. They are shown here for the marker locus M:

$$\underset{\sim}{I} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}, \quad \underset{\sim}{T} = \begin{bmatrix} r & s & 0 \\ \frac{1}{2}r & \frac{1}{2} & \frac{1}{2}s \\ 0 & r & s \end{bmatrix}, \quad Q = \begin{bmatrix} r^2 & 2rs & s^2 \\ r^2 & 2rs & s^2 \\ r^2 & 2rs & s^2 \end{bmatrix}. \quad (1)$$

The three genotypes are ordered $1 = MM$, $2 = Mm$, $3 = mm$. The ijth element of each matrix gives the probability that a person has genotype j, given a relative has genotype i, conditioned on the two relatives sharing 2, 1, or 0 genes IBD, for $\underset{\sim}{I}$, $\underset{\sim}{T}$, or $\underset{\sim}{Q}$, respectively. For example, for a parent-child pair, who always share one gene IBD, the probability of a child being MM, given the parent is Mm, is $\frac{1}{2}r$, from $\underset{\sim}{T}$. For two siblings, the overall relationship matrix is $\underset{\sim}{W} = \frac{1}{4}\underset{\sim}{I} + \frac{1}{2}\underset{\sim}{T} + \frac{1}{4}\underset{\sim}{Q}$, since the probabilities of their sharing 2, 1, or 0 genes IBD are $\frac{1}{4}$, $\frac{1}{2}$, and $\frac{1}{4}$, respectively. Thus

$$\underset{\sim}{W} = \begin{bmatrix} \frac{1}{4}(1 + r)^2 & \frac{1}{2}s(1 + r) & \frac{1}{4}s^2 \\ \frac{1}{4}r(1 + r) & \frac{1}{2}(1 + rs) & \frac{1}{4}s(1 + s) \\ \frac{1}{4}r^2 & \frac{1}{2}r(1 + s) & \frac{1}{4}(1 + s)^2 \end{bmatrix}, \quad (2)$$

that is, the ijth element of W represents the probability that an individual has genotype j, given his sib has genotype i.

Define a penetrance vector

$$\underset{\sim}{v}' = (v_1, v_2, v_3), \quad (3)$$

the ith element of which gives the probability that a person is affected, given he has marker genotype i. Also define the vector

$$\underset{\sim}{u}' = (r^2 v_1, \quad 2rs v_2, \quad s^2 v_3), \quad (4)$$

the ith element of which is proportional to the probability that a person has genotype i, given he is affected.

Define $P(l) = \mathrm{Pr}$ (2 sibs share l genes IBD at the marker locus|both sibs are affected), $l = 2, 1, 0$. Then from the APPENDIX, equation (A-12),

$$\begin{aligned} P(2) &= (\tfrac{1}{4}) \, \underset{\sim}{u}' \, \underset{\sim}{I} \, \underset{\sim}{v} / (\underset{\sim}{u}' \, \underset{\sim}{W} \, \underset{\sim}{v}) \\ P(1) &= (\tfrac{1}{2}) \, \underset{\sim}{u}' \, \underset{\sim}{T} \, \underset{\sim}{v} / (\underset{\sim}{u}' \, \underset{\sim}{W} \, \underset{\sim}{v}). \\ P(0) &= (\tfrac{1}{4}) \, \underset{\sim}{u}' \, \underset{\sim}{Q} \, \underset{\sim}{v} / (\underset{\sim}{u}' \, \underset{\sim}{W} \, \underset{\sim}{v}) \end{aligned} \quad (5)$$

Written out, the APPENDIX shows the following: when the penetrance matrix in a two-locus epistatic model has a multiplicative structure, as in table 1—that is, when the two loci are independent—then the IBD distribution in pairs of affected siblings at either locus depends only on the allele frequency and penetrance contributions at that locus. Thus, the marker IBD distribution depends only on $\underset{\sim}{r}$ and the three $\underset{\sim}{v}_i$. Moreover, this distribution is computed exactly as if the marker were the only locus, that is, exactly the same as for a one-locus model.

For example, both the recessive-recessive and dominant-recessive models illustrated in table 2 have the same marker IBD distribution since both are marker-recessive with $\underset{\sim}{v} = (.50, .05, .05)$. Moreover, the following model would also be equivalent:

$$\begin{bmatrix} .10 & .01 & .01 \\ .20 & .02 & .02 \\ .45 & .045 & .045 \end{bmatrix},$$

since v is still the same, if we take $\alpha_1 = .2, \alpha_2 = .4, \alpha_3 = .9$. In other words, the 10:1:1 ratio is preserved in each row. In all three of these cases, the IBD distribution in affected sib pairs is found by inserting v, together with the selected value of r, into equation (5). Also see the numerical example below.

Thus, only three types of models need to be considered for the IBD distribution in affected sib pairs: marker-dominant, where $v_1 = v_2 > v_3$; marker-recessive, where $v_1 > v_2 = v_3$; and, more generally, marker intermediate, where $v_1 > v_2 > v_3$.

Relative Risk

The relative risk Q denotes the cross-product or odds ratio from a 2×2 table, as shown in table 3:

$$Q = \frac{(r^2v_1 + 2rsv_2)(1 - v_3G)}{[r^2(1 - v_1G) + 2rs(1 - v_2G)]v_3} , \tag{6}$$

where $G = p^2\alpha_1 + 2pq\alpha_2 + q^2\alpha_3$. Q can be interpreted as the *relative odds*, that is, the ratio of the odds for patients to have the marker allele M to the odds for controls to have it. If the 2×2 table is of this form

	M Present	M Absent
Patients	a	b
Controls	c	d

,

then $Q = (a/b)/(c/d)$. Some properties of the relative risk and the rationale for its use are discussed in [25, 26].

From equation (6), Q depends on the trait-locus parameters only through the quantity G. It is straightforward to show, by algebraic manipulations, that Q is a strictly increasing function of G. Thus for any given set of *marker*-locus parameters r and v_i, lower (Q_L) and upper (Q_U) bounds on Q can be obtained by substituting $G = 0$ and $G = 1$, respectively, into equation (6):

$$Q_L = \frac{r^2v_1 + 2rsv_2}{v_3} \times \frac{1}{r^2 + 2rs}$$

$$Q_U = \frac{r^2v_1 + 2rsv_2}{v_3} \times \frac{1 - v_3}{r^2(1 - v_1) + 2rs(1 - v_2)} .$$

In a marker-dominant model, where $v_1 = v_2$, these bounds simplify to

$$\begin{aligned} Q_L &= v_1/v_3 \\ Q_U &= v_1(1 - v_3)/[v_3(1 - v_1)] . \end{aligned} \tag{7}$$

TABLE 3

2×2 TABLE OF PATIENTS VS. CONTROLS IN PRESENCE OR ABSENCE OF MARKER ALLELE M

	M Present	M Absent	Marginal totals
Patients..............	$(r^2v_1 + 2rsv_2)G$	s^2v_3G	$(r^2v_1 + 2rsv_2 + s^2v_3)G$
Controls..............	$r^2 + 2rs - (r^2v_1 + 2rsv_2)G$	$s^2 - (s^2v_3G)$	$1 - (r^2v_1 + 2rsv_2 + s^2v_3)G$
Marginal totals....	$r^2 + 2rs$	s^2	1

NOTE: $G = p^2\alpha_1 + 2pq\alpha_2 + q^2\alpha_3$; $(r^2v_1 + 2rsv_2 + s^2v_3)G$ gives the population prevalence K of the trait.

Example

It has recently been proposed [27], based on clinical and immunologic evidence, that coeliac disease, or gluten-sensitive enteropathy (GSE), is controlled by alleles at two unlinked loci: a GSE-associated B-cell antigen, of which a double dose is needed, and HLA-DR3, of which only a single dose is needed. Gene frequencies are given as $q = .09 =$ frequency of the B-cell antigen and $r = .19 =$ frequency of DR3. Assume for the sake of illustration that the penetrances are as shown:

	MM (.0361)	*Mm* (.3078)	*mm* (.6561)
AA (.8281).........	0	0	0
Aa (.1638).........	0	0	0
aa (.0081).........	.100	.100	.004

Here a denotes the B-cell antigen, and M, DR3. This model would yield a disease prevalence of $2.998 \times 10^{-4} = .000300$ or about three in 10,000. The model is a recessive-dominant one, with $\alpha_1 = \alpha_2 = 0$, $\alpha_3 = 1$. To obtain the IBD distribution, first substitute $r = .19$ and $s = .81$ into equations (1) and (2). Vector v' in equation (3) is (.1, .1, .004), and u' in equation (4) is (.003610, .030780, .002624). Then equation (5) yields $P(2) = (\frac{1}{4}) (3.449496 \times 10^{-3})/ (2.355211 \times 10^{-3}) = .366$, and similarly $P(1) = .488$, $P(0) = .145$. From equation (6), the predicted relative risk is $Q = 25.02$, or approximately v_1/v_3. However, if the DR3 antigen in fact acts recessively, as proposed by [28], then Q will be much lower, and the IBD distribution will be further distorted from the expected values of $P(2) = .25$, $P(1) = .50$, $P(0) = .25$.

RESULTS

IBD Distribution

Tables 4, 5, and 6 show the predicted marker IBD distributions in affected sib pairs, that is, the $P(l)$ values in equation (5), for marker-dominant, marker-recessive, and marker-intermediate models. The $P(l)$ are given as a function of the three-way ratio $v_1:v_2:v_3$ and of the frequency r of the marker allele M. Results are shown for $r = .20, .10, .05$, and $.01$.

In both marker-dominant and marker-recessive models, the greatest distortion from the expected $P(l)$ values of (.25, .50, .25) occurs when there is complete or near-complete penetrance at the marker, that is, as the ratio $v_1:v_3$ approaches 1:0. At

TABLE 4

MARKER IBD DISTRIBUTION $P(2)$, $P(1)$, AND $P(0)$ IN AFFECTED SIB PAIRS. MARKER-DOMINANT MODELS, WITH MARKER PENETRANCES $v_1 = v_2 > v_3$

	MARKER GENE FREQUENCY r			
$v_1:v_3$	.20	.10	.05	.01
3:1	.286, .496, .218	.286, .498, .216	.278, .499, .223	.259, .500, .241
5:1	.313, .493, .193	.323, .496, .180	.318, .498, .184	.280, .500, .220
10:1	.342, .490, .168	.369, .494, .137	.378, .497, .125	.341, .499, .160
15:1	.353, .489, .158	.388, .493, .119	.405, .496, .099	.385, .499, .115
20:1	.359, .488, .152	.398, .492, .110	.419, .496, .085	.413, .499, .088
25:1	.362, .488, .149	.403, .492, .104	.427, .495, .077	.431, .499, .070
50:1	.370, .487, .143	.416, .491, .093	.444, .495, .061	.465, .499, .036
1:0	.377, .487, .136	.428, .491, .081	.460, .495, .045	.491, .499, .010

TABLE 5

MARKER IBD DISTRIBUTION $P(2)$, $P(1)$, AND $P(0)$ IN AFFECTED SIB PAIRS.
MARKER-RECESSIVE MODELS, WITH MARKER PENETRANCES $v_1 > v_2 = v_3$

	MARKER GENE FREQUENCY r			
v_1:v_3	.20	.10	.05	.01
3:1	.271, .489, .239	.257, .496, .247	.252, .499, .249	.250, .500, .250
5:1	.316, .467, .217	.275, .486, .240	.257, .496, .247	.250, .500, .250
10:1	.430, .410, .160	.349, .442, .208	.283, .479, .237	.251, .499, .249
15:1	.504, .373, .123	.432, .394, .173	.324, .454, .222	.254, .498, .249
20:1	.549, .350, .100	.505, .352, .143	.372, .424, .204	.257, .496, .248
25:1	.579, .336, .086	.562, .319, .119	.422, .393, .185	.260, .493, .246
50:1	.639, .305, .055	.703, .237, .060	.625, .266, .109	.292, .472, .236
100:1	.668, .291, .041	.774, .196, .030	.788, .165, .047	.394, .405, .201
200:1	.682, .284, .034	.803, .179, .018	.862, .119, .019	.610, .263, .127
500:1	.689, .280, .030	.818, .170, .012	.894, .099, .007	.872, .090, .037
1:0	.694, .278, .028	.826, .165, .008	.907, .091, .002	.980, .020, .000

low values of r, the distribution of IBD values approaches (.25, .50, .25) when v_1:v_3 is low; when v_1:v_3 is high, the distribution approaches (.5, .5, 0) for dominant and (1, 0, 0) for recessive models. As r increases, the spread of possible IBD distributions becomes less broad. In the marker-dominant models, $P(1)$ never deviates very far from 0.5. Also, the marker-recessive models are particularly sensitive to the presence of sporadics, most notably at low values of r. Thus for $r = .05$, the IBD distribution for a v_1:v_3 ratio of 50:1 or 100:1 is still quite different from that when v_1:v_3 is 1.0. This effect is even more pronounced when $r = .01$.

It is more difficult to generalize the results under the marker-intermediate model, since they are a function of two ratios, v_1:v_2 and v_2:v_3, not just one. The simplest case is 2:1:0, that is, linear dose effect. Under this model, $P(1)$ is always .50, whereas $P(2)$ is distorted upward from .25, and $P(0)$, downward from .25. Again, the distortion is more pronounced for low values of marker frequency r.

TABLE 6

MARKER IBD DISTRIBUTION $P(2)$, $P(1)$, AND $P(0)$ IN AFFECTED SIB PAIRS.
MARKER-INTERMEDIATE MODELS, WITH MARKER PENETRANCES $v_1 > v_2 > v_3$

	MARKER GENE FREQUENCY r			
v_1:v_2:v_3	.20	.10	.05	.01
3:2:1	.269, .500, .231	.265, .500, .235	.259, .500, .241	.252, .500, .248
5:2:1	.289, .495, .216	.274, .497, .229	.262, .499, .238	.252, .500, .247
10:3:1	.336, .486, .179	.316, .491, .194	.291, .496, .213	.260, .500, .241
15:4.5:1	.364, .480, .156	.349, .485, .166	.321, .492, .187	.270, .499, .230
20:4.5:1	.391, .469, .140	.378, .474, .148	.344, .485, .171	.277, .499, .224
25:5:1	.412, .460, .128	.402, .464, .134	.365, .478, .156	.285, .498, .217
2:1:0	.375, .500, .125	.423, .500, .077	.456, .500, .043	.490, .500, .010
5:4:0	.373, .493, .134	.424, .495, .080	.458, .497, .045	.491, .499, .010
5:1:0	.447, .461, .092	.482, .459, .059	.496, .468, .036	.501, .490, .009

Relative Risk

In marker-dominant models, the relative risk Q depends only on the penetrances v_i and not on the gene frequency r. For a given $v_1{:}v_3$ ratio, the lower bound Q_L is simply the ratio v_1/v_3, from equation (7). The upper bound varies with the actual value of v_1, approaching infinity or v_1/v_3 as v_1 approaches 1 or 0, respectively.

In marker-recessive and -intermediate models, Q depends on gene frequency. When r is small, Q is not much greater than 1, and the upper and lower bounds Q_L and Q_U are close together. For all cases, the lower bound does not depend on the absolute values of the v_i but only on their ratios. Tables 7, 8, and 9 show Q_L and Q_U for selected marker-dominant, -recessive, and -intermediate models.

In summary, the marker IBD distribution in affected sib pairs is the same, whether one tightly linked susceptibility locus is involved in the disease, or a disease locus and the marker locus are both causally involved. (This fact has also been demonstrated by [29], in a different context, in the special case of dominant or recessive inheritance and no sporadics.) Thus the IBD distribution alone cannot distinguish between these two hypotheses. Similarly, the fact of a disease-marker association, whether weak or strong, cannot make this distinction either.

DISCUSSION

Distorted marker IBD distributions in affected sib pairs and disease-marker associations have been reported for a variety of traits. Such observations have often been adduced as evidence in favor of a disease susceptibility gene tightly linked to the HLA complex. However, as illustrated above, these two observations are equally compatible with the model examined here, in which the marker gene is itself causally involved in the trait (pleiotropy) and interacts epistatically with another unlinked gene. Based on IBD observations and association data alone, it is not possible to determine whether a disease susceptibility locus is *tightly linked* to a marker locus or *is* in fact the marker locus. Nor is it possible to determine whether this susceptibility locus represents a *major* contribution to disease pathogenesis or merely increases susceptibility, as primarily determined by another gene altogether.

Epistatic systems are well documented in animals [30, 31] and for the Bombay phenotype in humans [32]. Evidence for the action of two or more epistatic loci in

TABLE 7

RANGE OF RELATIVE RISKS, MARKER-DOMINANT MODELS

$v_1{:}v_3$	(v_1, v_2, v_3)	(Q_L, Q_U)
3:1	(.9, .9, .3)	(3.00, 21.00)
	(.3, .3, .1)	(3.00, 3.86)
	(.09, .09, .03)	(3.00, 3.20)
25:1	(.9, .9, .036)	(25.00, 241.00)
	(.25, .25, .01)	(25.00, 33.00)
	(.10, .10, .004)	(25.00, 27.67)

NOTE: The v_i's are the marker penetrances, Q_L and Q_U are the lower and upper bounds on the relative risk.

TABLE 8

RANGE OF RELATIVE RISKS, MARKER-RECESSIVE MODELS

$v_1{:}v_3$	(v_1, v_2, v_3)	$r = .2$ (Q_L, Q_U)	$r = .01$ (Q_L, Q_U)
3:1	(.9, .3, .3)	(1.22, 1.35)	(1.01, 1.01)
	(.09, .03, .03)	(1.22, .123)	(1.01, 1.01)
25:1	(.9, .036, .036)	(3.67, 4.07)	(1.12, 1.13)
	(.1, .004, .004)	(3.67, 3.71)	(1.12, 1.12)
100:1	(.9, .009, .009)	(12.00, 13.33)	(1.50, 1.50)
	(.1, .001, .001)	(12.00, 12.13)	(1.50, 1.50)
200:1	(.9, .0045, .0045)	(23.11, 25.68)	(2.00, 2.01)
	(.1, .0005, .0005)	(23.11, 23.37)	(2.00, 2.01)

NOTE: The v_i's are the marker penetrances, Q_L and Q_U are the lower and upper bounds on the relative risk, r = marker gene frequency.

other human traits, including diseases, is highly suggestive [27, 33, 34]. A number of the classical models of epistasis [35] can be viewed as special cases of the multiplicative model considered here. Thus, the assumption of multiplicative penetrances was made because it appears biologically reasonable and simplifies the mathematics of the model. Other equally reasonable models are not being considered here.

Two HLA-associated diseases currently attracting great interest are juvenile-type diabetes and multiple sclerosis. Recently, careful linkage studies of both these diseases (using lod scores) have demonstrated that if a single locus with two alleles is assumed, under a wide variety of penetrance values, the evidence favors loose, not tight linkage, with θ between 10% and 20% [4, 13, 36]. These findings are not conclusive [14]. Nonetheless, they argue against a *single*-locus "hitchhiking" theory, which requires tight linkage. In the case of juvenile diabetes, alternative models are also being proposed [37, 38].

The following sets of $P(l)$ values illustrate some IBD distributions in affected sib pairs reported in the literature. For juvenile-type diabetes, Spielman et al. [14], combining their data with three other reports, give $P(2) = .57$, $P(1) = .41$, and $P(0) = .02$. Christy et al. [39] gives .58, .37, and .04, respectively, for the same disease. Smeraldi et al. [15] give .52, .38, and .09, respectively, for "primary affective

TABLE 9

RANGE OF RELATIVE RISKS, MARKER-INTERMEDIATE MODELS

$v_1{:}v_2{:}v_3$	(v_1, v_2, v_3)	$r = .2$ (Q_L, Q_U)	$r = .01$ (Q_L, Q_U)
3:2:1	(.9, .6, .3)	(2.11, 4.03)	(2.01, 3.52)
	(.09, .06, .03)	(2.11, 2.15)	(2.01, 2.03)
25:5:1	(.90, .18, .036)	(7.22, 9.41)	(5.10, 6.02)
	(.10, .02, .004)	(7.22, 7.41)	(5.10, 5.19)

NOTE: The v_i's are the marker penetrances, Q_L and Q_U are the lower and upper bounds on the relative risk, r = marker gene frequency.

disorder." Tabulating sibships with exactly two definite cases of multiple sclerosis from six sets of published pedigrees [16, 40–44] yields 19, 12, and 4 affected sib pairs sharing 2, 1, or 0 HLA haplotypes IBD, for frequencies of .54, .34, and .11. These $P(I)$ values were estimated from small and/or pooled data sets, and the standard errors and possible heterogeneity are not known. For purposes of illustration, note that they all correspond approximately to those given for a marker-recessive model with marker gene frequency r = .20 and a marker penetrance ratio $v_1{:}v_3$ around 15:1 to 25:1 (table 5).

Examples of reported disease-marker associations include relative risks Q of 2.4 for juvenile-type insulin-dependent diabetes with HLA-B8 [45], 4.2 for multiple sclerosis with Dw2 [46], and 13.8 for idiopathic hemochromatosis with the A3-B14 haplotype [47]. These values are represented in both marker-dominant and marker-recessive models (tables 7 and 8).

The IBD distributions given in tables 4 and 5 for the ratio 1:0 correspond to those given in [10], where only dominant and recessive cases with no sporadics are considered.

Equation (5) gives the IBD distribution in pairs of affected siblings for any one-locus model and for any two-locus model whose penetrances are multiplicative in the sense defined here. Equation (A-8) in the APPENDIX gives the corresponding distribution for *any* two-locus autosomal unlinked model. Thus, researchers investigating one- or two-locus models can use one of these two formulas to determine the expected IBD distribution in affected sib pairs.

The cross-product relative risk Q has been criticized, and alternative measures of relative risk have been proposed [48, 49]. Q was examined here because it is widely used in the literature. The qualitative effects discussed in this study should be the same for alternative measures as well.

It should be clear that it is only the *IBD distribution* (at one locus) that is independent of gene frequency and penetrance at the other locus. Other quantities of interest, such as the segregation ratio, the monozygotic twin and sib concordance rates, and the population prevalence of the disease, depend on the parameters of both loci. However, the marker IBD distribution in affected sib pairs and the fact of a disease-marker association alone can only point out that the marker locus is in some way involved with the trait. They cannot draw the important distinction as to whether this involvement is causal, as in the two-locus model, or merely accidental, as in the case of linkage disequilibrium and tight linkage.

APPENDIX

THE COMPLETE TWO-LOCUS SYSTEM

As noted in the text, the contributions of $\underset{\sim}{I}$, $\underset{\sim}{T}$, and $\underset{\sim}{Q}$ are weighted by the probabilities that the two relatives share, respectively, 2, 1, or 0 genes IBD. In the case of two siblings, the weighted relationship matrix is $\underset{\sim}{W}$ = ¼$\underset{\sim}{I}$ + ½$\underset{\sim}{T}$ + ¼$\underset{\sim}{Q}$, as in equation (2).

In a two-locus system, there are nine possible genotypes. For unlinked loci, the appropriate 9 × 9 matrices are found by taking Kronecker products of the individual matrices for each locus [24]. [See equation (A-9) for an illustration of how Kronecker multiplication works.] For two siblings, the two-locus relationship matrix is simply

$$\Omega = W_1 \otimes W_2$$
$$= W_1 \otimes (\tfrac{1}{4}I_2 + \tfrac{1}{2}T_2 + \tfrac{1}{4}Q_2) , \tag{A-1}$$

where subscripts 1 and 2 denote the trait and marker loci, respectively. The order of the genotypes is: *AAMM, AAMm, AAmm, AaMM, AaMm, Aamm, aaMM, aaMm, aamm.*

The 9 × 1 penetrance vector f, corresponding to v in equation (3), is simply an "elongation" of the penetrances in table 1. When the penetrance structure is multiplicative, f can be partitioned as follows:

$$f = (\alpha_1 v', \alpha_2 v', \alpha_3 v') , \tag{A-2}$$

where $v' = (v_1, v_2, v_3)$ as in equation (3). Finally, q is the 9 × 1 vector whose ith element is the conditional probability that a random affected individual has genotype i. Note that q corresponds to u in equation (4), except that q has been normalized by the population prevalence of the trait. Let K represent the population prevalence of the trait. When the penetrance structure is multiplicative, then $K = (p^2\alpha_1 + 2pq\alpha_2 + q^2\alpha_3) \cdot (r^2v_1 + 2rsv_2 + s^2v_3)$ and the vector q can be partitioned as follows:

$$q' = (1/K) (\alpha_1 p^2 u', \alpha_2 (2pq) u', \alpha_3 q^2 u') , \tag{A-3}$$

where $u' = (r^2v_1, 2rsv_2, s^2v_3)$, as in equation (4).

Derivation of IBD Distribution at Marker Locus in Affected Sib Pairs

Let Y and Z denote two sibs. "Y aff." indicates that Y is affected, and "IBD = l" indicates that Y and Z share l genes IBD at the *marker* locus. The marker IBD distribution in affected sib pairs is denoted by $P(l)$, l = 2, 1, or 0; that is, by definition $P(l) = \Pr(\text{IBD} = l | Y \text{ aff.}, Z \text{ aff.})$. Applying Bayes' rule to the events "IBD = l" and "Y aff." and conditioning on "Z aff." yields

$$P(l) = \frac{\Pr(Y \text{ aff.} | Z \text{ aff.}, \text{IBD} = l) \cdot \Pr(\text{IBD} = l | Z \text{ aff.})}{\Pr(Y \text{ aff.} | Z \text{ aff.})} . \tag{A-4}$$

The first term in the numerator is:

$$q' \cdot (W_1 \otimes I_2) \cdot f \text{ for } l = 2$$
$$q' \cdot (W_1 \otimes T_2) \cdot f \text{ for } l = 1 \tag{A-5}$$
$$q' \cdot (W_1 \otimes Q_2) \cdot f \text{ for } l = 0 ,$$

since the Kronecker product of W with I_2, T_2, or Q_2 is the relationship matrix for two siblings who share an unspecified number of genes IBD at the trait locus and share 2, 1, or 0 genes, respectively, at the marker locus.

The second term in the numerator of equation (A-4) reduces to $\Pr(\text{IBD} = l)$, since the affectational status of *one* sib cannot affect the IBD value of the *pair*:

$$\Pr(\text{IBD} = l) = \begin{cases} \tfrac{1}{4} \text{ for } l = 2, 0 \\ \tfrac{1}{2} \text{ for } l = 1 \end{cases} . \tag{A-6}$$

The denominator of equation (A-4) is given by

$$q' \Omega f , \tag{A-7}$$

since now the number of genes shared IBD is not specified for either locus, and hence Ω in equation (A-1) is the appropriate relationship matrix for the two siblings. Inserting equations (A-5)–(A-7) into equation (A-4) yields

$$P(2) = (\tfrac{1}{4}) \, [\underset{\sim}{q}' \, (\underset{\sim}{W}_1 \otimes \underset{\sim}{I}_2) \, \underset{\sim}{f}] \, / \, (\underset{\sim}{q}' \, \Omega \, \underset{\sim}{f})$$
$$P(1) = (\tfrac{1}{2}) \, [\underset{\sim}{q}' \, (\underset{\sim}{W}_1 \otimes \underset{\sim}{T}_2) \, \underset{\sim}{f}] \, / \, (\underset{\sim}{q}' \, \Omega \, \underset{\sim}{f}) \ . \tag{A-8}$$
$$P(0) = (\tfrac{1}{4}) \, [\underset{\sim}{q}' \, (\underset{\sim}{W}_1 \otimes \underset{\sim}{Q}_2) \, \underset{\sim}{f}] \, / \, (\underset{\sim}{q}' \, \Omega \, \underset{\sim}{f})$$

These formulas apply for any two-locus unlinked model, whether or not it fulfills the assumption of multiplicative penetrances. [If the penetrances are *not* multiplicative, then the vectors $\underset{\sim}{q}$ and $\underset{\sim}{f}$ in equation (A-8) must be written out with all nine terms; they cannot be partitioned as in equations (A-2) and (A-3).]

Independence of IBD Distribution from Trait-Locus Parameters

In this section, denote the matrices $\underset{\sim}{I}_2$, $\underset{\sim}{T}_2$, and $\underset{\sim}{Q}_2$ by $\underset{\sim}{N}(2)$, $\underset{\sim}{N}(1)$, and $\underset{\sim}{N}(0)$. That is, $\underset{\sim}{N}(l)$ denotes the relationship matrix for the marker locus when l genes are shared IBD at that locus. Consider the matrix product $\underset{\sim}{q} \, [\underset{\sim}{W}_1 \otimes \underset{\sim}{N}(l)] \underset{\sim}{f}$ in the numerators of equations (A-8). Partitioning $\underset{\sim}{W}_1 \otimes \underset{\sim}{N}(l)$ in that numerator according to the definition of the Kronecker product:

$$\underset{\sim}{W}_1 \otimes \underset{\sim}{N}_2(l) = \begin{bmatrix} w_{11} \, \underset{\sim}{N}(l) & w_{12} \, \underset{\sim}{N}(l) & w_{13} \, \underset{\sim}{N}(l) \\ w_{21} \, \underset{\sim}{N}(l) & w_{22} \, \underset{\sim}{N}(l) & w_{23} \, \underset{\sim}{N}(l) \\ w_{31} \, \underset{\sim}{N}(l) & w_{32} \, \underset{\sim}{N}(l) & w_{33} \, \underset{\sim}{N}(l) \end{bmatrix} . \tag{A-9}$$

Premultiplying equation (A-9) by the partitioned form of $\underset{\sim}{q}'$ in equation (A-3) and postmultiplying by f in equation (A-2) yields a product of the form:

$$\begin{aligned} \underset{\sim}{q}' \, [\underset{\sim}{W}_1 \otimes \underset{\sim}{N}(l)] \underset{\sim}{f} = (1/K) \, [&\alpha_1 p^2 (\alpha_1 w_{11} + \alpha_2 w_{12} + \alpha_3 w_{13}) \\ &+ \alpha_2 (2pq)(\alpha_1 w_{21} + \alpha_2 w_{22} + \alpha_3 w_{23}) \\ &+ \alpha_3 q^2 (\alpha_1 w_{31} + \alpha_2 w_{32} + \alpha_3 w_{33})] \cdot \underset{\sim}{u}' \underset{\sim}{N}(l) \underset{\sim}{v} \\ = H \cdot \underset{\sim}{u}' \, \underset{\sim}{N}(l) \, \underset{\sim}{v} \ . \end{aligned} \tag{A-10}$$

The $(1/K)$ and the expression in square brackets do not depend on l; combine them under the name "H." The term $\underset{\sim}{u}' \underset{\sim}{N}(l) \underset{\sim}{v}$ is a function only of the marker-locus parameters r and v_i and does not depend on the trait-locus parameters p and α_i. Similarly for the denominators of equations (A-8): using equation (A-1), $\underset{\sim}{q}' \, \Omega \, \underset{\sim}{f}$ can be written as:

$$\begin{aligned} \underset{\sim}{q}' \, \Omega \, \underset{\sim}{f} &= \tfrac{1}{4} \underset{\sim}{q}' \, (\underset{\sim}{W}_1 \otimes \underset{\sim}{I}_2) \underset{\sim}{f} + \tfrac{1}{2} \underset{\sim}{q}' \, (\underset{\sim}{W}_1 \otimes \underset{\sim}{T}_2) \underset{\sim}{f} + \tfrac{1}{4} \underset{\sim}{q}' \, (\underset{\sim}{W}_1 \otimes \underset{\sim}{Q}_2) \underset{\sim}{f} \\ &= H \, \underset{\sim}{u}' \, (\tfrac{1}{4} \underset{\sim}{I}_2 + \tfrac{1}{2} \underset{\sim}{T}_2 + \tfrac{1}{4} \underset{\sim}{Q}_2) \, \underset{\sim}{v} \\ &= H \, \underset{\sim}{u}' \, \underset{\sim}{W}_2 \, \underset{\sim}{v} \ . \end{aligned} \tag{A-11}$$

Inserting equations (A-10) and (A-11) into equation (A-8) yields

$$P(2) = (\tfrac{1}{4}) \, \underset{\sim}{u}' \underset{\sim}{I}_2 \, \underset{\sim}{v} \, / \, \underset{\sim}{u}' \, \underset{\sim}{W} \, \underset{\sim}{v}$$
$$P(1) = (\tfrac{1}{2}) \, \underset{\sim}{u}' \, \underset{\sim}{T}_2 \, \underset{\sim}{v} \, / \, \underset{\sim}{u}' \, \underset{\sim}{W} \, \underset{\sim}{v} \tag{A-12}$$
$$P(0) = (\tfrac{1}{4}) \, \underset{\sim}{u}' \, \underset{\sim}{Q}_2 \, \underset{\sim}{v} \, / \, \underset{\sim}{u}' \, \underset{\sim}{W} \, \underset{\sim}{v}$$

All trait-locus parameters appear only in H in both the numerator and denominator, and thus they cancel out. Clearly, the result requires the assumption of multiplicative penetrances, for if f and q cannot be partitioned as in equations (A-2) and (A-3), the trait-locus parameters will not all go into the scalar term "H" in equations (A-10) and (A-11).

Thus it has been shown that when the penetrance matrix in a two-locus epistatic model has a multiplicative structure, as in table 1, then the IBD distribution in pairs of affected siblings at either locus depends only on the allele frequency and penetrance contributions at that locus.

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