

A Complete Enumeration and Classification of Two-Locus Disease Models

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Two-locus model · Epistasis · Identity by descent · Correlation

Abstract

There are 512 two-locus, two-allele, two-phenotype, fully penetrant disease models. Using the permutation between two alleles, between two loci, and between being affected and unaffected, one model can be considered to be equivalent to another model under the corresponding permutation. These permutations greatly reduce the number of two-locus models in the analysis of complex diseases. This paper determines the number of nonredundant two-locus models (which can be 102, 100, 96, 51, 50, or 58, depending on which permutations are used, and depending on whether zero-locus and single-locus models are excluded). Whenever possible, these nonredundant two-locus models are classified by their property. Besides the familiar features of multiplicative models (logical AND), heterogeneity models (logical OR), and threshold models, new classifications are added or expanded: modifying-effect models, logical XOR models, interference and negative interference models (neither dominant nor recessive), conditionally dominant/recessive models, missing lethal genotype models, and highly symmetric models. The following aspects of two-locus models are studied: the marginal penetrance tables at both loci, the expected joint identity-by-descent

(IBD) probabilities, and the correlation between marginal IBD probabilities at the two loci. These studies are useful for linkage analyses using single-locus models while the underlying disease model is two-locus, and for correlation analyses using the linkage signals at different locations obtained by a single-locus model.

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Introduction

Disease models involving two genes, usually called ‘two-locus models’ [e.g. ref. 41, 64], have been widely used in the study of complex diseases, including likelihood-based linkage analysis [34, 48, 61, 77], allele-sharing-based linkage analysis [9, 17, 24, 39, 46, 75], marker-association-segregation method [4, 14], weighted-pairwise correlation method [94], variance component analysis [84–86], recurrence risk of relatives [67, 74, 88], and segregation analysis [16, 18, 19, 31, 32, 35]. Besides human genetics, two-locus models have also been used in the study of evolution, as well as in genetic studies of inbreeding animals and plants.

Using two-locus models is a natural choice if the underlying disease mechanism indeed involves two or more genes, though there have been extensive discussions on the power of using single-locus models for linkage analysis in that situation [15, 29, 30, 33, 36, 40, 69, 78, 79, 87, 89, 90]. Also, two-locus models have frequently been used in

generating simulated datasets for testing various linkage methods and strategies [2, 11, 12, 21, 23, 27, 28, 37, 59, 82, 87]. Although segregation analysis based on two-locus models is common [22, 43, 70, 76, 93], linkage analysis based on two-locus models is relatively rare, due to the large number of combinations of two markers out of as many as 300 markers in the whole genome, due to the cost of a time-consuming calculation of the pedigree likelihood, and due to a large number of possible interactions between two genes.

One would naturally ask: how many possible types of two-locus models exist? Complete enumerations and classifications of systems have been used in many other fields as a starting point of a study; for example, two-person two-move games in the study of game theory [73], two-state three-input cellular automata in the study of dynamical systems [55], and two-symbol 3-by-3 lattice models in the study of protein folding [53]. These types of studies lay out the space of all possibilities with nothing missing. This paper follows a similar path in completely enumerating all two-locus two-allele two-phenotype disease models.

Strickberger [83] listed a few types of two-locus models encountered in experimental systems, though the number of phenotypes is multiple (such as being a smooth, partly rough and fully rough Mendelian pea), instead of binary (such as affected and unaffected). De-frise-Gussenhoven [6] listed five types of two-locus models, which were followed up by a study by Greenberger [31]. Neuman and Rice [67] listed six two-locus models. Nevertheless, nobody provided a complete list of all possible two-locus models.

This complete enumeration of all two-locus models can be useful when a linkage signal is observed in two separated regions, or if two candidate genes with known locations are studied. In these situations, it is of interest to determine the nature of the interaction between the two disease genes [e.g. ref. 14]. Without knowing all possible forms of interaction, such determination is not complete.

A list of all two-locus models is perhaps useful for likelihood-based linkage analysis, but may not be essential. In such a linkage analysis, parameters in the two-locus model can be determined by a maximum likelihood method, and the fitted values are generally continuous rather than discrete. The enumeration of two-locus models in this paper, however, uses discrete parameter values. Nevertheless, during the stage of interpretation of the result, the classification of two-locus models discussed in the 'Classifying Two-Locus Models' section can be useful.

Since most likelihood-based linkage analyses still use single-locus disease models, it is of interest to know how

closely a single-locus model approximates a two-locus model. For this purpose, we examine the marginal penetrance (on both loci) of all two-locus models, which should be the optimal parameter value if a single-locus model is used for the linkage analysis [79]. The question of which two-locus models can be reasonably approximated by single-locus models, or which two-locus interaction can be detected by single-locus linkage analysis, can be easily answered by this marginal penetrance information. This topic will be discussed in the 'Marginal Penetrance Tables' section.

Allele-sharing-based linkage analysis requires a calculation of the expected allele sharing between a relative pair under a certain disease model [9, 17, 24, 46, 75]. We provide a new formulation for this calculation which is an extension of the classical Li-Sacks method, which in turn is based on Bayes' theorem. This topic will be discussed in the 'IBD Probabilities in Two-Locus Models' section.

It has been suggested that interaction or epistasis between two regions can be detected by calculating the correlation between two linkage signals, each determined by a single-locus linkage analysis [10, 60]. A positive correlation may suggest interaction (epistasis), and a negative correlation may suggest heterogeneity [10, 60]. We examine such a correlation for all two-locus models, which not only confirms this simple rule-of-thumb, but also generalizes to other two-locus models. This topic will be discussed in the 'Correlation between IBD Sharings at Two Loci' section.

Enumeration of Two-Locus Models

A two-locus model is typically represented by a 3-by-3 penetrance table. The row label gives the three possible genotypes of the first disease locus (i.e. aa , aA , AA , where A might be considered as the disease allele at locus 1), and the column label gives the genotypes for the second locus (i.e. bb , bB , BB , where B is the disease allele at locus 2):

	bb	bB	BB	
f_{ij}	f_{11}	f_{12}	f_{13}	(1)
aA	f_{21}	f_{22}	f_{23}	
AA	f_{31}	f_{32}	f_{33}	

The table element f_{ij} ('penetrance') is the probability of being affected with the disease when the genotype at the first locus is i , and that of the second locus is j . In the most general case, f_{ij} s range from 0 to 1. Models defined on con-

tinuously varying parameters are hard to be classified to a few discrete categories. On the other hand, if the allowed values of f_{ij} s are 0 and 1 only ('fully penetrant'), we can categorize the nine-parameter space to $2^9 = 512$ distinct points. We use the following notation to label each of these 512 fully penetrant two-locus models:

$$\text{'model number'}_{10} = (f_{11}, f_{12}, f_{13}, f_{21}, f_{22}, f_{23}, f_{31}, f_{32}, f_{33})_2, \quad (2)$$

where the subscript of 2 or 10 indicates whether the number is represented as binary or decimal. For example, if a model has $f_{13} = 1$ and other f_{ij} s are zero, the binary representation of the penetrance table is $(001000000)_2$, which is 64 in decimal notation, or model M64. Model numbers range from 0 to 511.

The number of nonredundant two-locus models is less than 512 due to the following considerations: (1) if all f_{ij} s are 0 (or 1), the model is a zero-locus model; (2) if the elements of the penetrance table do not change with row (or with column), it is a single-locus model; the nature of the model should not change (3) if the first and second locus are exchanged, (4) if the two alleles in the first (or second) locus are exchanged, or (5) if the affection status is exchanged. We will show below that when the symmetries implied by permutation (3) and (4) are imposed, the number of nonredundant two-locus model (N_1) is 102; when (3), (4), (5) are considered, the number (N_2) is 51. Subtracting zero-locus and/or single-locus models, we get $N_1 - 2 = 100$, $N_1 - 6 = 96$, $N_2 - 3 = 48$.

This result of the number of nonredundant two-locus models is based on the counting theorem by Pólya [71] and de Bruijn [13]. Cotterman [5] pioneered combinatorial genetics, but he only enumerated single-locus multiple-allele models. Although Hartle and Maruyama [38] had already applied the counting theorem to enumerate genetic models, we would like to repeat and simplify the derivation to focus on our particular case, i.e., the two-locus two-allele models.

To do so, it is necessary to review the concept of 'cycle index' below. If a permutation is applied to a set of m elements, some elements are invariant under this permutation (b_1 of them), some form cycles of length 2 (b_2 of them), some form cycles of length 3 (b_3 of them), etc. For each permutation, construct a polynomial with m variables:

$$x_1^{b_1} x_2^{b_2} x_3^{b_3} \dots x_m^{b_m}.$$

Going through all permutations p 's that are part of the permutation group P (suppose the number of permutations is $|P|$), the cycle index is defined as the polynomial:

$$C(x_1, x_2, \dots, x_m) \equiv \frac{1}{|P|} \sum_{p \in P} x_1^{b_1} x_2^{b_2} x_3^{b_3} \dots x_m^{b_m}.$$

For two-locus models, there are 9 genotypes, and 8 permutations can be considered on this set of genotypes: (1) the identity operation; (2) exchange alleles a and A ; (3) exchange alleles b and B ; (4) exchange the first and the second locus; (5) is (2) plus (3); (6) is (2) plus (4); (7) is (3) plus (4); (8) is (5) plus (4). The cycle index for this group of 8 permutations on the 9 genotypes is:

$$C_{\text{geno}}(x_1, x_2, \dots, x_9) = \frac{x_1^9 + 4x_1^3x_2^3 + x_1x_2^4 + 2x_1x_4^2}{8}.$$

By Pólya's counting theorem [theorem 5.1 in ref. 13], the number of nonredundant two-locus models, without considering permutations in phenotype, is equal to the cycle index of the permutation group on the genotype evaluated by replacing all variables by the number of phenotypes (which is 2), i.e.:

$$N_1 = \frac{2^9 + 2^8 + 2^5 + 2^4}{8} = 102.$$

When all 0's in the penetrance table are switched to 1 and 1's switched to 0, one two-locus model becomes another two-locus model. If we consider these two models as equivalent, the number of non-redundant models is

$$N_2 = \frac{N_1}{2} = 51.$$

Actually, the same conclusion can be obtained by considering not only the cycle index of the permutation group on the genotype, but also that of a permutation group on the phenotype, then using de Bruijn's generalization of Pólya's theorem (see Appendix 1). The advantage of this approach is that if a more complicated permutation group applied to phenotype is considered, the method to get N_2 by a simple division of N_1 would not work.

Classifying Two-Locus Models

This section discusses some possible classification schemes of two-locus models. No attempt is made to exhaustively classify all models, considering the fact that some 'exotic' models can never be classified using familiar terms. What we have here is a collection of classification schemes, each selecting a subset of models by a special property they possess. As a comparison, out of the 50 models listed in this paper, Defrise-Gussenhoven studied M1, M3, M11, M15, M27 [6]; Greenberg studied M1, M3, M27 [31]; and Neuman and Rice studied M1, M3, M11, M15, M27, M78 [67]. All $N_2 - 1 = 50$ models are listed in table 1. The $N_1 - N_2 - 1 = 50$ models generated by switching affecteds and unaffecteds (plus possibly other

Table 1. The penetrance tables of all $N_2 - 1 =$ two-locus models

M1(RR) 0 0 0 0 0 0 0 0 1	M2 0 0 0 0 0 0 0 1 0	M3(RD) 0 0 0 0 0 0 0 1 1	M5 0 0 0 0 0 0 1 0 1	M7(1L:R) 0 0 0 0 0 0 1 1 1	M10 0 0 0 0 0 1 0 1 0	M11 (T) 0 0 0 0 0 1 0 1 1
M12 0 0 0 0 0 1 1 0 0	M13 0 0 0 0 0 1 1 0 1	M14 0 0 0 0 0 1 1 1 0	M15(Mod) 0 0 0 0 0 1 1 1 1	M16 0 0 0 0 1 0 0 0 0	M17 0 0 0 0 1 0 0 0 1	M18 0 0 0 0 1 0 0 1 0
M19 0 0 0 0 1 0 0 1 1	M21 0 0 0 0 1 0 1 0 1	M23 0 0 0 0 1 0 1 1 1	M26 0 0 0 0 1 1 0 1 0	M27 (DD) 0 0 0 0 1 1 0 1 1	M28 0 0 0 0 1 1 1 0 0	M29 0 0 0 0 1 1 1 0 1
M30 0 0 0 0 1 1 1 1 0	M40 0 0 0 1 0 1 0 0 0	M41 0 0 0 1 0 1 0 0 1	M42 0 0 0 1 0 1 0 1 0	M43 0 0 0 1 0 1 0 1 1	M45 0 0 0 1 0 1 1 0 1	M56(1L:I) 0 0 0 1 1 1 0 0 0
M57 0 0 0 1 1 1 0 0 1	M58 0 0 0 1 1 1 0 1 0	M59 0 0 0 1 1 1 0 1 1	M61 0 0 0 1 1 1 1 0 1	M68 0 0 1 0 0 0 1 0 0	M69 0 0 1 0 0 0 1 0 1	M70 0 0 1 0 0 0 1 1 0
M78(XOR) 0 0 1 0 0 1 1 1 0	M84 0 0 1 0 1 0 1 0 0	M85 0 0 1 0 1 0 1 0 1	M86 0 0 1 0 1 0 1 1 0	M94 0 0 1 0 1 1 1 1 0	M97 0 0 1 1 0 0 0 0 1	M98 0 0 1 1 0 0 0 1 0
M99 0 0 1 1 0 0 0 1 1	M101 0 0 1 1 0 0 1 0 1	M106 0 0 1 1 0 1 0 1 0	M108 0 0 1 1 0 1 1 0 0	M113 0 0 1 1 1 0 0 0 1	M114 0 0 1 1 1 0 0 1 0	M170 0 1 0 1 0 1 0 1 0
M186 0 1 0 1 1 1 0 1 0						

Each model represents a group of equivalent models under permutations. The representative model is the one with the smallest model number. The six models studied in Neuman and Rice [67] ('RR, RD, DD, T, Mod, XOR'), as well as two single-locus models ('1L' – the recessive (R) and the interference (I) model), are marked.

permutations between loci and allele) are listed in table 2 for convenience.

We first review the 6 models studied in Neuman and Rice [67]:

(1) *Jointly recessive-recessive model (RR)*: M1 requires two copies of the disease alleles from both loci to be affected. This model was studied as early as 1952 [50, 62, 81], and can also be called ‘recessive complementary’.

(2) *Jointly dominant-dominant model (DD)*: M27 requires at least one copy of the disease allele from both loci to be affected. This model can also be called ‘dominant complementary’.

(3) *Jointly recessive-dominant model (RD)*: M3 requires two copies of disease alleles from the first locus and at least one disease allele from the second locus to be affected.

Note that the Heterogeneity Models (logical OR models) discussed in Neuman and Rice [67] are equivalent to the above three RR, DD, RD models by the $0 \leftrightarrow 1$ permutation in the penetrance table plus possibly some permutations between two loci and/or two alleles. RR model becomes D + D model, DD model becomes R + R, and RD becomes D + R [20].

(4) *A modifying-effect model (Mod)*: M15 can be modified to a single-locus recessive model if the penetrance at the genotype aA-BB is changed from 1 to 0. This model is one of the ‘modifying-effect models’ and ‘almost single-locus models’ discussed below.

(5) *Threshold model (T)*: M11 requires at least three disease alleles, regardless of which locus the disease alleles are from, to be affected. M95, which is equivalent to M11, requires at least two disease alleles to be affected.

(6) *An exclusive OR model (XOR)*: M78 is almost the R + R model except for the two-locus genotype AA-BB. This model was used to model the genetics of handedness [49]. In fact, M78 is one of the ‘exclusive OR’ models to be discussed below.

There are also the following classification schemes:

Single-locus models (1L): M7 is a single-locus recessive model (it is also equivalent to a single-locus dominant model M63, by $0 \leftrightarrow 1$ permutation in the penetrance table, followed by a permutation between alleles *a* and *A*). M56 is a single-locus ‘interference’ (the term used by Johnson [42] is ‘metabolic interference’, or ‘maximum heterozygosity model’). As discussed in details by Johnson [2], in this hypothetical model, neither allele *a* nor *A* is really abnormal; only when the gene products interact, can there be harmful effects. M365 is equivalent to M56 by the $0 \leftrightarrow 1$ permutation (plus a permutation between two loci), which can be called a ‘negative interference model’ or a ‘maximum

homozygosity model’. Models similar to M56 and M365, which are neither dominant nor recessive, will be discussed more below. M7, M63, M56, M365 are labeled as *R, D, I, Ī*.

We can classify two-locus models which are one mutation away from single-locus models as *almost single-locus models*. The modifying-effect model M15 is actually an almost single-locus model. Others include M23, M57, M58 ($0 \rightarrow 1$ mutation in the penetrance table), M3, M5, M59, and M61 ($1 \rightarrow 0$ mutation in the penetrance table).

Logical AND (multiplicative) models: The logical AND operation on two binary variables is defined as: $0 \text{ AND } 0 = 0$, $0 \text{ AND } 1 = 0$, $1 \text{ AND } 0 = 0$, $1 \text{ AND } 1 = 1$. Imagine that the penetrance table receives a contribution from both loci, $\{g_{1i}\}$ and $\{g_{2j}\}$ ($i, j = 1, 2, 3$), and the penetrance value can be represented as a product of the two contributions [66]:

$$f_{ij} = g_{1i} \text{ AND } g_{2j},$$

This class of model includes M1(RR), M2(RI), M3(RD), M5(R \bar{I}), M16(II), M18(DI), M27(DD), M40(I \bar{I}), M45(D \bar{I}), and M325 ($\bar{I}\bar{I}$), where *R, D, I, Ī* are dominant, recessive, interference, and negative interference single-locus models. M325 is equivalent to M186 by the permutation in the affection status. Although M7 and M56 are also logical AND models, they are actually trivial single-locus models. One can see that for M45, for example, when the second and third columns in the penetrance table are switched, all non-zero elements form a rectangular block. It is true for any multiplicative model that such a rectangular block can be formed by switching columns and/or rows.

The special interest of multiplicative models lies in the fact that the probability of the value of identity by descent (IBD) at one locus is independent of the other locus [39]. In other words, if one uses the joint IBD between affected sibpairs to study a possible interaction between two locations, such an interaction cannot be detected. More on the calculation of the probability of IBD values will be discussed below.

Logical OR (heterogeneity) models: The logical OR operation on two binary variables is defined as: $0 \text{ OR } 0 = 0$, $0 \text{ OR } 1 = 1$, $1 \text{ OR } 0 = 1$, $1 \text{ OR } 1 = 1$. The $0 \leftrightarrow 1$ permutation in the penetrance table will transform a logical AND model to a *logical OR model*, or a *heterogeneity model*. Note that for fully-penetrant models, we cannot have an exact, but only approximate, *additive models* in the original sense, since $1 + 1 = 2$ is larger than what is allowed by a penetrance.

Logical XOR models: The logical XOR (exclusive OR) operation on two binary variables is defined as: $0 \text{ XOR } 0 = 0$, $0 \text{ XOR } 1 = 1$, $1 \text{ XOR } 0 = 1$, $1 \text{ XOR } 1 = 0$. The last equation makes XOR an extremely nonlinear operation.

Table 2. The penetrance tables of $N_1 - N_2$ 1 = 50 two-locus models

M31→15 (Mod)	M47→23	M63→7(1L:D)	M71→59	M79→27(R+R)	M87→46	M95→11(T)
0 0 0 0 1 1 1 1 1	0 0 0 1 0 1 1 1 1	0 0 0 1 1 1 1 1 1	0 0 1 0 0 0 1 1 1	0 0 1 0 0 1 1 1 1	0 0 1 0 1 0 1 1 1	0 0 1 0 1 1 1 1 1
M102→94	M103→30	M105→61	M107→29	M109→57	M110→86	M111→19
0 0 1 1 0 0 1 1 0	0 0 1 1 0 0 1 1 1	0 0 1 1 0 1 0 0 1	0 0 1 1 0 1 0 1 1	0 0 1 1 0 1 1 0 1	0 0 1 1 0 1 1 1 0	0 0 1 1 0 1 1 1 1
M115→99	M117→106	M118→78	M119→14	M121→45	M122→101	M123→13
0 0 1 1 1 0 0 1 1	0 0 1 1 1 0 1 0 1	0 0 1 1 1 0 1 1 0	0 0 1 1 1 0 1 1 1	0 0 1 1 1 1 0 0 1	0 0 1 1 1 1 0 1 0	0 0 1 1 1 1 0 1 1
M124→108	M125→41	M126→70	M127→3(D+R)	M171→85	M173→113	M175→21
0 0 1 1 1 1 1 0 0	0 0 1 1 1 1 1 0 1	0 0 1 1 1 1 1 1 0	0 0 1 1 1 1 1 1 1	0 1 0 1 0 1 0 1 1	0 1 0 1 0 1 1 0 1	0 1 0 1 0 1 1 1 1
M187→69	M189→97	M191→5	M229→114	M231→28	M238→84	M239→17
0 1 0 1 1 1 0 1 1	0 1 0 1 1 1 1 0 1	0 1 0 1 1 1 1 1 1	0 1 1 1 0 0 1 0 1	0 1 1 1 0 0 1 1 1	0 1 1 1 0 1 1 1 0	0 1 1 1 0 1 1 1 1
M245→98	M247→12	M254→68	M255→1(D+D)	M325→186	M327→58	M335→26
0 1 1 1 1 0 1 0 1	0 1 1 1 1 0 1 1 1	0 1 1 1 1 1 1 1 0	0 1 1 1 1 1 1 1 1	1 0 1 0 0 0 1 0 1	1 0 1 0 0 0 1 1 1	1 0 1 0 0 1 1 1 1
M341→170	M343→42	M351→10	M365→56(1L: \bar{I})	M367→18	M381→40	M383→2
1 0 1 0 1 0 1 0 1	1 0 1 0 1 0 1 1 1	1 0 1 0 1 1 1 1 1	1 0 1 1 0 1 1 0 1	1 0 1 1 0 1 1 1 1	1 0 1 1 1 1 1 0 1	1 0 1 1 1 1 1 1 1
M495→16						
1 1 1 1 0 1 1 1 1						

These models are equivalent to the models in table 1 by the $0 \leftrightarrow 1$ permutation plus possibly other permutations between two loci and between two alleles. The most familiar models, including the two single-locus models – the dominant (D) and the negative interference (\bar{I}) model, are marked.

Because of this property, XOR is a favorite function to illustrate the advantage of artificial neural networks over linear discrimination and linear regression [e.g. ref. 3]. Logical XOR two-locus models include M78 (as discussed earlier), M113, and M170.

Conditional dominant (recessive) models: These are models where the first (or the second) locus behaves like a dominant (or recessive) model if the second (or the first) locus takes a certain genotype. For example, the first locus in M11 behaves as a recessive model when the genotype at the second locus is bb , but as a dominant model when the

genotype at the second locus is BB . Models similar to M11 include: M1(RR), M2, M3(DR), M5, M13, M15(Mod), M18, M19, M23, and M45.

Interference models: neither dominant nor recessive: We can extend the single-locus ‘neither dominant nor recessive’ models M56 and M365 to two-locus models. In positive interferences, two otherwise normal proteins produced at two loci interact to lead to the disease. In negative interferences, two complementary proteins lead to a functional product and an unaffected person, whereas the lack of either complementary component leads to affection.

Table 3. 1L: single-locus models

Model	Classifications	Model	Classifications
M1	RR , C, AND, S_L , [3, 68] (M255 → D + D , OR)	M43	[11]
M2	L, C, AND, S_A , [3]	M45	C, AND, S_A
M3	L, RD , C, AND, [1, 7, 11] (M127 → D + R , OR)	M56	1L:I , $S_{A,AA}$ (M365 → 1L:I)
M5	C, AND, S_A , [1, 7]	M57	[56]
M7	1L:R , S_A , [3] (M63 → 1L:D)	M58	S_A , [56, 186]
M10	L , S_L , [11]	M59	[27] (M71 → [7])
M11	T , C, S_L , [3, 27]	M61	S_A (M105 → [7])
M12	L , [1]	M68	I , $S_{L,AA}$, [1] (M254 → L)
M13	C, [3]	M69	S_L , [68] (M187 → [186])
M14	L , [3]	M70	[3, 68] (M126 → L)
M15	C, [7, 11] (M31 → [27])	M78	L , XOR, S_L (M118 → [27])
M16	I , AND, $S_{L,A,AA}$	M84	L , $S_{L,AA}$, [68]
M17	S_L , [1, 16]	M85	S_L (M171 → [170])
M18	L , C, S_A , AND, [16, 56]	M86	L
M19	L , C, [3, 27]	M94	L , S_L (M102 → [11])
M21	S_A	M97	S_A
M23	C, S_A , [7]	M98	S_L
M26	S_L , [27]	M99	
M27	DD , C, AND, S_L , [11] (M79 → R + R , OR)	M101	
M28	L	M106	
M29		M108	S_{AA} (M124 → L)
M30	L	M113	XOR, S_A
M40	AND, $S_{A,AA}$, [56]	M114	S_L
M41	[3]	M170	I , XOR, $S_{L,A,AA}$, [186]
M42	S_A , [170]	M186	I , OR, $S_{L,A,AA}$, [170] (M325 → AND)

D = Dominant; **R** = recessive; **I**, \bar{I} = interference; **RR** = jointly recessive-recessive model; **DD** = jointly dominant-dominant model; **RD** = jointly recessive-dominant model; **T** = threshold model; **I** = interference models; **L** = missing lethal genotype models; C = conditionally dominant and/or conditionally recessive; AND = logical AND models (multiplicative); OR = logical OR models (heterogeneity models); XOR = logical XOR models; S = symmetric models (S_L = with respect to permutation of two loci; S_A = with respect to permutation of two alleles at one locus; S_{AA} = with respect to permutation of two alleles at both loci), [] = modifying-effect models. For example, [11] indicates a model that modifies M11 by one bit in the penetrance table.

These following models illustrate the situation: M68, M186, and M170.

In M68, the only two-locus genotypes that lead to the disease are *aa-BB* and *bb-AA*. Suppose an abnormal effect is caused by an interaction between the protein product generated from allele *a* and that from *B*, or between the protein products from *b* and *A*. Then only the above two two-locus genotypes lead to the maximum abnormal effect. This model was studied by Merry et al. [65].

For M325, which is equivalent to M186 by the 0 ↔ 1 permutation in the penetrance table, four two-locus genotypes lead to the disease: *aa-bb*, *aa-BB*, *AA-bb*, *AA-BB*. This is a situation where maximum doses of the protein produced at both loci lead to the disease. From this perspective, M325 is a 'maximum homozygosity' model (and M186 a 'maximum heterozygosity' model).

For M170, four two-locus genotypes lead to the disease: *aa-bB*, *aA-bb*, *aA-BB*, *AA-bB*. The difference between M170 and M186 is that the double-heterozygosity genotype *aA-bB* does not lead to the disease, whereas all other heterozygous genotypes lead to the disease. One might consider that there is another between-locus interference besides the within-locus interference, and the two interferences cancel out.

In *Drosophila* genetics, the phenomenon of metabolic interference is called 'negative complementation' [91, 92]. For example, the Notch gene has two types: 'enhancers' and 'suppressors'. The homozygotes for both types are viable, whereas the heterozygotes are lethal.

The phenomenon of 'maternal-fetal incompatibility' [68] is reminiscent of, but not identical to, the interference we discuss here. This incompatibility is between the

red blood cells in the mother and in the fetus, due to the inheritance of two different alleles from the mother and the father. This occurs only if the fetus' genotype is heterozygous.

More modifying-effect models: Just as M15 is a modified version of the single-locus recessive model, any model whose penetrance table is one mutation away from a classified model has a modifying-effect on the latter. For example, changing the penetrance value from 1 to 0 in M41 at the two-locus genotype $aA-bb$ makes it a single-locus dominant model. Other modifying-effect models are listed in table 3.

Missing lethal genotype models: We consider the following situation: a genetic disease requires a minimum number of disease alleles from either/both locus/loci (i.e. alleles A and B), which lead to models similar to the threshold model (M11 or its equivalent model M95). Nevertheless, if the disease is lethal, all individuals carrying a large number of disease alleles disappear from the population. Consequently, it is impossible to have the two-locus genotype with the maximum number of disease alleles (e.g. $AA-BB$, $AA-bB$, $aA-BB$). Although all possible two-locus genotypes are specified in the penetrance table, some genotypes never appear in the population. Effectively, we may replace the penetrances at these genotypes by 'not available' +s or 0s.

For example, in the penetrance table below, the $AA-BB$ genotype is missing from the population, thus its penetrance is replaced by a '+':

	bb	bB	BB
aa	0	0	0
aA	0	0	1
AA	0	1	+

(3)

Since we will never have a chance to use the penetrance represented by +, it might be replaced by a 0, and become model M10. The following models also belong to this class: M2, M12, M14, M18, M26, M28, M30, M78, M84, M86, M94, M124 (equivalent to M108), M126 (equivalent to M70), M254 (equivalent to M68) (the +s appear in the lower-right corner), M3, M19 (the +s appear in the upper-right corner). A model similar to M84 was discussed in Frankel and Schork [26].

The discussion presented here illustrates a general principle: even if two two-locus models may differ in their penetrance table, they can be effectively identical if the differing element appears with a very small probability.

Highly symmetric models: During the discussion of Pólya's theorem, eight permutations were listed including the identity operation and 7 other permutations. Whether a model is invariant or not under the seven permutations provides a measure of the degree of symmetry of the model. For example, M40 is invariant under three permutations: exchange of alleles a and A , exchange of alleles b and B , exchange of both a, A , and b, B . Other models which are invariant under a large number of permutations (indicated by the number in the parentheses) include: M16 (7), M40 (3), M68 (3), M84 (3), M170 (7), M186 (7). M56 is excluded because it is a single-locus model.

Models that are symmetric with respect to permutation of two loci need only one single-locus model to approximate both loci. Models that are symmetric with respect to permutation of two alleles might be more relevant to common diseases.

Admittedly, there are 'exotic' models which have yet to be classified. Although one can relax the definitions of modifying-effect and interference models to incorporate them, they are less likely to be useful in modeling the gene-gene interaction in real situations. Table 3 summarizes what we have discussed in this section.

Marginal-Penetrance Tables

One important question we ask is how a two-locus model differs from a single-locus model. This question has practical implications in linkage analyses because almost all current analyses are carried out by focusing on one susceptibility gene. We can use the marginal-penetrance table on each one of the two loci to represent the effective single-locus model as the effects of other interacting genes are averaged out. The marginal-penetrance table on the first locus is: $f_i^{eff1} = \sum_j P_j^2 f_{ij}$, where $\{P_j^2\}$ are the genotype frequencies at the second locus, and that on the second locus is $f_j^{eff2} = \sum_i P_i^1 f_{ij}$, where $\{P_i^1\}$ are the genotype frequencies at the first locus.

Take the modifying-effect model M15, for example. If p_1 and p_2 are disease allele frequencies at the two loci ($q_1 = 1 - p_1$, $q_2 = 1 - p_2$, and Hardy-Weinberg equilibrium is assumed), the corresponding genotype frequencies are:

	$bb(q_2^2)$	$bB(2p_2q_2)$	$BB(p_2^2)$
$aa(q_1^2)$	0	0	0
$aA(2p_1q_1)$	0	0	1
$AA(p_1^2)$	1	1	1

(4)

Table 4. Marginal-penetrance tables at both loci for all $N_2 - 1 = 50$ two-locus models assuming disease allele frequencies $p_1 = p_2 = 0.1$

Model No.	First locus				Second locus			
	aa	aA	AA	type	bb	bB	BB	type
M1	0	0	0.01	-	0	0	0.01	-
M2	0	0	0.18	R	0	0.01	0	-
M3	0	0	0.19	R	0	0.01	0.01	-
M5	0	0	0.82	R	0.01	0	0.01	-
M7	0	0	1	R	0.01	0.01	0.01	-
M10	0	0.01	0.18	R	0	0.01	0.18	R
M11	0	0.01	0.19	R	0	0.01	0.19	R
M12	0	0.01	0.81	R	0.01	0	0.18	R
M13	0	0.01	0.82	R	0.01	0	0.19	R
M14	0	0.01	0.99	R	0.01	0.01	0.18	R
M15	0	0.01	1	R	0.01	0.01	0.19	R
M16	0	0.18	0	I	0	0.18	0	I
M17	0	0.18	0.01	I	0	0.18	0.01	I
M18	0	0.18	0.18	D	0	0.19	0	I
M19	0	0.18	0.19	D	0	0.19	0.01	I
M21	0	0.18	0.82	R	0.01	0.18	0.01	I
M23	0	0.18	1	R	0.01	0.19	0.01	I
M26	0	0.19	0.18	D	0	0.19	0.18	D
M27	0	0.19	0.19	D	0	0.19	0.19	D
M28	0	0.19	0.81	R	0.01	0.18	0.18	D
M29	0	0.19	0.82	R	0.01	0.18	0.19	D
M30	0	0.19	0.99	R	0.01	0.19	0.18	D
M40	0	0.82	0	I	0.18	0	0.18	\bar{I}
M41	0	0.82	0.01	I	0.18	0	0.19	\bar{I}
M42	0	0.82	0.18	I	0.18	0.01	0.18	\bar{I}
M43	0	0.82	0.19	I	0.18	0.01	0.19	\bar{I}
M45	0	0.82	0.82	D	0.19	0	0.19	\bar{I}
M56	0	1	0	I	0.18	0.18	0.18	-
M57	0	1	0.01	I	0.18	0.18	0.19	-
M58	0	1	0.18	I	0.18	0.19	0.18	-
M59	0	1	0.19	I	0.18	0.19	0.18	-
M61	0	1	0.82	D	0.19	0.18	0.19	-
M68	0.01	0	0.81	R	0.01	0	0.81	R
M69	0.01	0	0.82	R	0.01	0	0.82	R
M70	0.01	0	0.99	R	0.01	0.01	0.81	R
M78	0.01	0.01	0.99	R	0.01	0.01	0.99	R
M84	0.01	0.18	0.81	R	0.01	0.18	0.81	R
M85	0.01	0.18	0.82	R	0.01	0.18	0.82	R
M86	0.01	0.18	0.99	R	0.01	0.19	0.81	R
M94	0.01	0.19	0.99	R	0.01	0.19	0.99	R
M97	0.01	0.81	0.01	I	0.18	0	0.82	R
M98	0.01	0.81	0.18	I	0.18	0.01	0.81	R
M99	0.01	0.81	0.19	I	0.18	0.01	0.82	R
M101	0.01	0.81	0.82	D	0.19	0	0.82	R
M106	0.01	0.82	0.18	I	0.18	0.01	0.99	R
M108	0.01	0.82	0.81	D	0.19	0	0.99	R
M113	0.01	0.99	0.01	I	0.18	0.18	0.82	R
M114	0.01	0.99	0.18	I	0.18	0.19	0.81	R
M170	0.18	0.82	0.18	I	0.18	0.82	0.18	I
M186	0.18	1	0.18	I	0.18	1	0.18	I

D, R, I, \bar{I} represents (approximately) dominant, recessive, interference, and negative interference. The symbol '-' represents the case where the penetrance is not very sensitive to changes in the genotype.

The three marginal penetrances at the first locus are $(0, p_2^2, 1)$. As expected, it is very similar to the recessive model except for a modifying effect on the heterozygote. Similarly, the three marginal penetrances at the second locus are $p_1^2, p_1^2, p_1^2 + 2p_1q_1$, which are almost zero when p_1 is small. If linkage analysis for markers near both disease genes is carried out, the marker near the first gene will provide a linkage signal under the recessive model with a modified (reduced) penetrance; the marker near the second gene will barely provide any linkage signal.

Assuming $p_1 = p_2 = 0.1$, table 4 lists the marginal penetrance at both loci for all $N_2 - 1 = 50$ two-locus models. Table 5 lists those for the remaining $N_1 - N_2 - 1 = 50$ models. Each marginal penetrance on a single locus is roughly classified as one of the four types: dominant (D), recessive (R), interference (I), and negative interference (\bar{I}). Note that this classification only provides crude guidance for marginal single-locus effect. For example, in table 4 the marginal penetrance table $(0, 0.2, 0.8)$ is classified as recessive, though it is only approximately recessive with some phenocopy probability. Also note that for models that are equivalent to the representative models listed in tables 3 and 4, the marginal penetrances need to be recalculated using the correct allele frequencies.

Marginal penetrance tables can provide insight into linkage analyses using a single-locus model when the underlying disease model involves two genes. For example, for M1 (RR), both genes behave like a recessive locus but with a highly reduced penetrance (0.01 if the disease allele frequency is 0.1). A single-locus-based linkage analysis might detect both loci but with difficulty because of the low penetrance. M78 (an XOR model) provides another example. It is almost identical to M79 (R + R) in that both genes behave as a recessive locus, but the marginal penetrance is reduced from 1 to 0.99. The almost negligible effect with the exclusive OR operation at the $AA-BB$ genotype is due to the fact that the population frequency of the $AA-BB$ genotype is very small. In practice, it might be very difficult to distinguish M78 from M79 in a single-locus-based linkage analysis.

It is important to know that tables 4 and 5 are derived with a particular disease allele frequency ($p_1 = p_2 = 0.1$). When the disease allele frequency is the same as the normal allele frequency ($p_1 = p_2 = 0.5$), the nature of the marginal single-locus model could be completely different. For example, the marginal effect of both loci in M84 is between recessive and dominant when $p_1 = p_2 = 0.1$. When $p_1 = p_2 = 0.5$, the marginal penetrance becomes $(0.25, 0.5, 0.25)$ at both loci, similar to an interference model. If the penetrance f_{22} is 0.5 instead of 1, the margin-

al penetrance is (0.25, 0.25, 0.25) [26]; in other words, there is no marginal linkage signal at all.

In a practical pedigree analysis, the genotype frequencies may not be taken from the population frequencies, but from the pedigrees one has [79, 89, 90]. It is thus possible that the penetrance table is specific to each individual in the pedigree. It is another way of saying that the risk of developing the disease for each family member is conditional on the affection status of other family members, and such conditional probability may differ from person to person.

IBD Probabilities in Two-Locus Models

There is a growing interest in using IBD sharing between affected sibpairs or affected relative pairs to test whether a marker is linked to a susceptibility gene. The premise behind the IBD test is that affected sib pairs or affected relative pairs should share more IBD near the region of the disease gene than expected from a random segregation. IBD sharing at one location is usually determined regardless of IBD sharing at other chromosomal locations, in other words, a single-locus model is implicitly assumed. To test for possible interactions between two regions, joint IBD sharing is needed [9, 17, 24, 46, 75].

The observed joint IBD sharing can be compared with expected IBD sharing under a certain model. There are at least three approaches in determining the expected joint IBD sharing probability at two loci between two affected sibs or affected relatives given a disease model. The first is to list all mating types, and count the number of each sharing situation among all possibilities. The second is to calculate the covariance of a quantitative trait between two relatives [8, 44, 45]. This covariance is decomposed into the sum of the products of 'coefficient of parentage' (or kinship coefficient) [63] and the variance components. The latter includes additive and dominant variance components by a linear regression of the quantitative trait to the number of alleles [25]. The conversion from the covariance of a quantitative trait to the IBD sharing between affected relatives can be accomplished by Bayes' theorem. The third, and perhaps the more elegant approach, is to use Bayes' theorem to convert the probability of IBD sharing, given that the two relatives are affected, to the probability of two relatives being affected, given the IBD sharing. This approach was first developed by Li and Sacks in 1954 [51, 52].

In Li-Sacks' original approach, a set of conditional probabilities, the probability that the second relative has a

Table 5. Similar to table 4, but for $N_1 - N_2 - 1 = 50$ two-locus models that are equivalent to the models in table 4 by switching the affection status and possibly other permutations between loci and alleles

Model No.	First locus				Second locus			
	aa	aA	AA	type	bb	bB	BB	type
M31	0	0.19	1	R	0.01	0.19	0.19	D
M47	0	0.82	1	D	0.19	0.01	0.19	\bar{I}
M63	0	1	1	D	0.19	0.19	0.19	-
M71	0.01	0	1	R	0.01	0.01	0.82	R
M79	0.01	0.01	1	R	0.01	0.01	1	R
M87	0.01	0.18	1	R	0.01	0.19	0.82	R
M95	0.01	0.19	1	R	0.01	0.19	1	R
M102	0.01	0.81	0.99	D	0.19	0.01	0.81	R
M103	0.01	0.81	1	D	0.19	0.01	0.82	R
M105	0.01	0.82	0.01	I	0.18	0	1	R
M107	0.01	0.82	0.19	I	0.18	0.01	1	R
M109	0.01	0.82	0.82	D	0.19	0	1	R
M110	0.01	0.82	0.99	D	0.19	0.01	0.99	R
M111	0.01	0.82	1	D	0.19	0.01	1	R
M115	0.01	0.99	0.19	I	0.18	0.19	0.82	R
M117	0.01	0.99	0.82	D	0.19	0.18	0.82	R
M118	0.01	0.99	0.99	D	0.19	0.19	0.81	R
M119	0.01	0.99	1	D	0.19	0.19	0.82	R
M121	0.01	1	0.01	I	0.18	0.18	1	R
M122	0.01	1	0.18	I	0.18	0.19	0.99	R
M123	0.01	1	0.19	I	0.18	0.19	1	R
M124	0.01	1	0.81	D	0.19	0.18	0.99	R
M125	0.01	1	0.82	D	0.19	0.18	1	R
M126	0.01	1	0.99	D	0.19	0.19	0.99	R
M127	0.01	1	1	D	0.19	0.19	1	R
M171	0.18	0.82	0.19	I	0.18	0.82	0.19	I
M173	0.18	0.82	0.82	D	0.19	0.81	0.19	I
M175	0.18	0.82	1	D	0.19	0.82	0.19	I
M187	0.18	1	0.19	I	0.18	1	0.19	I
M189	0.18	1	0.82	D	0.19	0.99	0.19	I
M191	0.18	1	1	D	0.19	1	0.19	I
M229	0.19	0.81	0.82	D	0.19	0.81	0.82	D
M231	0.19	0.81	1	D	0.19	0.82	0.82	D
M238	0.19	0.82	0.99	D	0.19	0.82	0.99	D
M239	0.19	0.82	1	D	0.19	0.82	1	D
M245	0.19	0.99	0.82	D	0.19	0.99	0.82	D
M247	0.19	0.99	1	D	0.19	1	0.82	D
M254	0.19	1	0.99	D	0.19	1	0.99	D
M255	0.19	1	1	D	0.19	1	1	D
M325	0.82	0	0.82	\bar{I}	0.82	0	0.82	\bar{I}
M327	0.82	0	1	\bar{I}	0.82	0.01	0.82	\bar{I}
M335	0.82	0.01	1	\bar{I}	0.82	0.01	1	\bar{I}
M341	0.82	0.18	0.82	\bar{I}	0.82	0.18	0.82	\bar{I}
M343	0.82	0.18	1	\bar{I}	0.82	0.19	0.82	\bar{I}
M351	0.82	0.19	1	\bar{I}	0.82	0.19	1	\bar{I}
M365	0.82	0.82	0.82	-	1	0	1	\bar{I}
M367	0.82	0.82	1	-	1	0.01	1	\bar{I}
M381	0.82	1	0.82	-	1	0.18	1	\bar{I}
M383	0.82	1	1	-	1	0.19	1	\bar{I}
M485	1	0.82	1	-	1	0.82	1	-

certain genotype given the first relative having a certain genotype, is conveniently written in three 3-by-3 matrices ('Li-Sacks matrices') or four 4-by-4 matrices [7]. These approaches were modified in [57] by using two 2-by-2 matrices, which are the conditional probabilities that the

second relative has a certain allele derived from one parent, given that the first relative has a certain allele derived from the same parent. In this formulation, the probability that the two affected sibs share $k1_m$ maternal alleles IBD and $k1_p$ paternal alleles IBD at the first locus, and $k2_m$ maternal alleles IBD and $k2_p$ paternal alleles IBD at the second locus is

$$p(k1_m, k1_p, k2_m, k2_p | \text{both sibs affected}) = \frac{\text{numerator N}}{\text{denominator D}},$$

with

$$N = \sum_{i1_m, i1_p, i2_m, i2_p, j1_m, j1_p, j2_m, j2_p} f_{j1_m j1_p j2_m j2_p} \cdot t_{i1_m j1_m}(k1_m) t_{i1_p j1_p}(k1_p) t_{i2_m j2_m}(k2_m) t_{i2_p j2_p}(k2_p) \cdot f_{i1_m i1_p i2_m i2_p} \cdot p(k1_m) p(k1_p) p(k2_m) p(k2_p)$$

$$D = (\text{sum of N over } k1_m, k1_p, k2_m, k2_p) \quad (5)$$

where

$i1_m$ is the index for the maternally derived allele (the paternally derived allele uses the label p), in the first sib (second sib uses the label j), at the first locus (second locus uses the label 2);

$f_{i1_m i1_p i2_m i2_p}$ and $f_{j1_m j1_p j2_m j2_p}$ are the penetrance tables of the two-locus model. Although it has 4 indices, it can be easily obtained from the 3-by-3 penetrance table as in (1);

$p_{i1_m}, p_{i1_p}, p_{i2_m}, p_{i2_p}$ are the allele frequencies, which take the value of either p_1 or $q_1 = 1 - p_1$;

$p(k1_m), p(k1_p), p(k2_m), p(k2_p)$ are the prior probabilities of sharing allele IBD at 4 places (maternally and paternally derived, first and second locus), which are 1/2s for sib-pairs, and

$t_{i1_m j1_m}(k1_m), t_{i1_p j1_p}(k1_p), t_{i2_m j2_m}(k2_m), t_{i2_p j2_p}(k2_p)$ are the revised 2-by-2 Li-Sacks matrices given by:

$$\{t_{ij}(1)\} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}, \quad \{t_{ij}(0)\} = \begin{pmatrix} p & q \\ q & q \end{pmatrix} \quad (6)$$

Despite the complicated indexing, the revised Li-Sacks approach is easier to implement in a computer code, and easier to generalize to other situations, such as unilineal relative pairs, multiple alleles, unaffected-unaffected and unaffected-affected pairs, the probability of identify-by-state, two markers instead of two disease genes, etc. [57]. More details will be discussed elsewhere [Li, in preparation].

There are two types of joint IBD measurements currently in use: the first is the addition of maternal and paternal IBDs, which take the values of 0, 1, 2:

$$P_{geno}(k1, k2) = \sum_{k1 = k1_m + k1_p, k2 = k2_m + k2_p} P(k1_m, k1_p, k2_m, k2_p). \quad (7)$$

The genotypic IBDs, $\{P_{geno}(k2, k2)\}$, form a 3-by-3 matrix. The second measurement focuses on maternal (or equivalently, paternal) IBD only:

$$P_{alle}(k1_m, k2_m) = \sum_{k1_p, k2_p} P(k1_m, k1_p, k2_m, k2_p). \quad (8)$$

The symmetry between the maternally derived and paternally derived alleles implies that $P(k1_p, k2_p) = P(k1_m, k2_m)$. The allelic IBDs, $P_{alle}(k1_m, k2_m)$, form a 2-by-2 matrix, which will be the joint IBD measurement we use. For example, for M15 at $p_1 = p_2 = 0.1$, the joint allelic IBD is:

	$k2_m = 0$	$k2_m = 1$	marginal $k1_m$
$k1_m = 0$	0.050549	0.072689	0.123238
$k1_m = 1$	0.413962	0.462800	0.876762
marginal $k2_m$	0.464511	0.535489	1

The marginal probabilities of IBD sharing in equation 9 confirms our intuition that there is a strong preference for the IBD sharing on the first locus to be 1 (probability of sharing 0.876762 versus nonsharing 0.123238), whereas the deviation from 0.5 at the second locus is very small (0.535489 versus 0.464511).

Correlation between IBD Sharings at Two Loci

For probabilities of joint IBD sharings at two loci as exemplified by equation 9, we ask the following question: can the joint probability be derived from the two marginal IBD sharing probabilities at the two separated loci? This question is motivated by the suggestion in MacLean et al. [60] and Cox et al. [10] that one might first detect marginal effects by single-locus linkage analysis, then detect interaction later using the correlation analysis. Such a correlation between two marginals exists only if the joint probability is not equal to the product of the two marginals. Statistical correlations can be measured in different ways, one of them being the mutual information, defined as [47, 54]:

$$M = \sum_{k1_m, k2_m} P(k1_m, k2_m) \log_2 \frac{P(k1_m, k2_m)}{P(k1_m, \cdot) P(\cdot, k2_m)} \quad (10)$$

where $P(k1_m, \cdot)$ and $P(\cdot, k2_m)$ are the two marginal IBD sharing probabilities at two loci. Mutual information has certain meaning in information theory, and is intrinsically related to the concept of entropy. Two is chosen as the base of the logarithm so that it is measured by the unit of 'bit', though base e and base 10 can also be used.

Table 6. Values of mutual information (with one significance digit) between the two marginal probabilities of IBD sharing for all $N_2 - 1 = 50$ two-locus models

Model No.	Disease allele frequency			
	0.001	0.01	0.1	0.1, 0.01
M1*	0	0	0	0
M2*	0	0	0	0
M3*	0	0	0	0
M5*	0	0	0	0
M7*	0	0	0	0
M10	0.02(N)	0.01(N)	2e-4(N)	2e-4(N)
M11	0.02(N)	0.01(N)	ie-4(N)	3e-4(N)
M12	4e-5(N)	3e-4(N)	e-3(N)	2e-7(N)
M13	4e-5(N)	3e-4(N)	2e-3(N)	3e-7(N)
M14	4e-5(N)	3e-4(N)	8e-4(N)	2e-7(N)
M15	4e-5(N)	3e-4(N)	e-3(N)	3e-7(N)
M16*	0	0	0	0
M17	2e-14(P)	2e-10(P)	2e-6(P)	2e-8(P)
M18*	0	0	0	0
M19	0.0(P)	7e-11(P)	2e-7(P)	3e-9(P)
M21	2e-3(N)	e-3(N)	2e-5(P)	e-3(N)
M23	2e-3(N)	2e-3(N)	7e-5(N)	2e-3(N)
M26	0.0(N)	2e-12(N)	5e-9(P)	3e-13(P)
M27*	0	0	0	0
M28	2e-3(N)	e-3(N)	3e-5(P)	e-3(N)
M29	2e-3(N)	e-3(N)	2e-5(P)	e-3(N)
M30	2e-3(N)	2e-3(N)	4e-5(N)	2e-3(N)
M40*	0	0	0	0
M41	0.0(P)	0.0(P)	8e-10(P)	e-13(P)
M42	9e-14(P)	9e-10(P)	8e-6(P)	8e-8(P)
M43	9e-14(P)	9e-10(P)	8e-6(P)	8e-8(P)
M45*	0	0	0	0
M56*	0	0	0	0
M57	0.0(P)	0.0(P)	e-9(P)	e-13(P)
M58	0.0(P)	4e-11(P)	2e-7(P)	4e-9(P)
M59	0.0(P)	4e-11(P)	2e-7(P)	4e-9(P)
M61	0.0(P)	3e-11(P)	2e-7(P)	3e-9(P)
M68	0.1(N)	0.1(N)	0.02(N)	5e-5(N)
M69	0.1(N)	0.1(N)	0.02(N)	5e-5(N)
M70	0.1(N)	0.1(N)	0.02(N)	4e-5(N)
M78	0.1(N)	0.1(N)	0.03(N)	9e-5(N)
M84	9e-3(N)	6e-3(N)	9e-6(N)	e-3(N)
M85	9e-3(N)	6e-3(N)	e-5(N)	e-3(N)
M86	9e-3(N)	7e-3(N)	2e-4(N)	2e-3(N)
M94	9e-3(N)	7e-3(N)	4e-4(N)	2e-3(N)
M97	e-8(N)	e-6(N)	e-5(N)	7e-10(N)
M98	e-8(N)	e-6(N)	5e-8(N)	6e-8(P)
M99	e-8(N)	e-6(N)	6e-8(N)	6e-8(P)
M101	e-8(N)	e-6(N)	5e-6(N)	3e-10(N)
M106	e-8(N)	e-6(N)	e-5(N)	5e-8(P)
M106	e-8(N)	e-6(N)	e-5(N)	5e-8(P)
M108	e-8(N)	e-6(N)	3e-5(N)	2e-9(N)
M113	e-8(N)	e-6(N)	5e-6(N)	6e-10(N)
M114	e-8(N)	e-6(N)	2e-6(N)	e-9(P)
M170	3e-3(N)	2e-3(N)	7e-5(P)	e-5(N)
M186	3e-3(N)	2e-3(N)	e-4(N)	7e-5(N)

The allele frequencies are chosen at four different values: $p_1 = p_2 = 0.001$, 0.01, 0.1; $p_1 = 0.1$ and $p_2 = 0.01$. Values lower than 10^{-14} are converted to 0. '4e-5' means to 4×10^{-5} , etc. Multiplicative models are marked by *.

We calculate the mutual information for the 2-by-2 joint probabilities of allelic IBD sharing at two loci for all 50 two-locus models, at 3 different allele frequency values: $p_1 = p_2 = 0.001$, 0.01, and 0.1. Also shown is an asymmetric situation when $p_1 = 0.1$ and $p_2 = 0.01$. The result is summarized in table 6 (and table 7 for the other 50 models). Only one significance digit is kept in tables 6 and 7.

Table 6 confirms the conclusion in Hodge [39] that for multiplicative models, the IBD sharing probability at one locus can be calculated as if there is no interaction with another locus: the correlation as measured by mutual information is 0 for all these models.

It should be of interest to examine which two-locus models exhibit the smallest correlation, and which the largest. Besides the zero correlation for multiplicative and single-locus models, all modifying-effect models as altered from a single-locus model or a multiplicative model should exhibit small correlations. Indeed, in table 6, we see that at $p_1 = p_2 = 0.001$, M19, M26, M41, M57, M58, M59, M61 all exhibit close-to-zero correlations.

From tables 6 and 7, it seems that missing lethal genotype models tend to have larger correlation values, although these values are derived from a limited choice of parameter settings. To some extent, this observation is not surprising. Missing lethal genotype models are typically 'nonlinear' in the sense that as the sum of the total number of disease alleles is increased, the change in phenotype is not monotonic (it can first change from unaffected to affected, then from affected to unaffected). For these models, using the joint IBD sharing probability to detect linkage should have the greatest increase of power over methods using marginal probability of IBD sharing.

Occasionally, not only would we like to know the 'strength' or 'magnitude' of the correlation between the marginal IBD sharing probabilities at two loci, but also the sign of the correlation. For example, in MacLean et al. [60] and Cox et al. [10], whether the statistical correlation between two linkage signals obtained at two loci is positive or negative provides an indication as to whether the two loci are 'interacting' or simply heterogeneous. We provide this piece of information for all two-locus models in tables 6 and 7. A '(P)' indicates that $P(k_{1_m} = 1, k_{2_m} = 1)$ is larger than the expected value from no correlation $P(k_{1_m} = 1) \cdot P(k_{2_m} = 1)$; similarly, an '(N)' indicates that the joint probability is smaller than the product of two marginals. As expected, all heterogeneity models (M79, M127, M255) have negative correlations.

Note that we measure the correlation by a probability-based quantity rather than a statistics-based one. This is because we start with a theoretical model, i.e. a two-locus

model, and investigate the consequence of the model. On the other hand, if we start with a sample of size N and the count of joint IBD status ij is N_{ij} ($\sum_{ij} N_{ij} = N$), we can use any one of statistics to test the significance of the correlation; for example, the likelihood ratio statistic,

$$G^2 = 2N \sum_{ij} \frac{N_{ij}}{N} \log \frac{N_{ij}N}{N_i N_j}, \quad (11)$$

and the Pearson χ^2 statistics,

$$X^2 = \sum_{ij} \frac{(N_{ij} - N_i N_j / N)^2}{N_i \times_j / N}, \quad (12)$$

where $N_i \equiv \sum_j N_{ij}$ and $N_j \equiv \sum_i N_{ij}$ are the two marginal counts. It can be shown (see Appendix 2) that G^2 and X^2 are approximately equal. Under the no-correlation null hypothesis, both G^2 and X^2 approximately follow the χ^2 distribution with 1 degree of freedom. The larger the G^2 and X^2 , the more likely that the null hypothesis is wrong.

It is important to note that if the null hypothesis is indeed incorrect, both G^2 and X^2 increase with the sample size N . Consequently, G^2 and X^2 do not measure the strength of the correlation, but the evidence that the no-correlation hypothesis is wrong. On the other hand, the normalized quantities such as $\sqrt{G^2/N}$ and $\sqrt{X^2/N}$ ('phi coefficient' [80, p. 741] or Cramer's V , [72, p. 631]) do measure the correlation strength. Compared with the mutual information defined in equation 10, we see that $G^2/N \approx 2 \log(2)M$.

Discussion

We present a complete enumeration and an attempt at classification of 512 two-locus two-allele fully-penetrant disease models. Excluding zero-locus and single-locus models, the minimum set of nonredundant two-locus models is 48, and with the two single-locus models included, 50. Even though the permutation of affection status does not change the 'nature' of the interaction between two genes, for many practical applications, it is helpful to keep 50 other models which are equivalent to the first 50 models by this permutation in the penetrance table (plus possibly other permutations between alleles and loci). For example, a logical OR model (heterogeneity model) is equivalent to a logical AND model (multiplicative model). Nevertheless, the special property for a multiplicative model, that the joint IBD sharing probability is equal to the product of two marginal IBD probabilities, does not hold for a heterogeneity model. Even with our total 100 nonredundant models, the permutations between

Table 7. Similar to table 6 but for the $N_1 - N_2 - 1 = 50$ models that are equivalent to the models in table 6 by switching affection status

Model No.	Disease allele frequency			
	0.001	0.01	0.1	0.1, 0.01
M31	2e-3(N)	2e-3(N)	4e-5(N)	2e-3(N)
M47	3e-14(P)	3e-10(P)	e-6(P)	e-8(P)
M63*	0	0	0	0
M71	0.1(N)	0.1(N)	0.03(N)	4e-5(N)
M79	0.1(N)	0.1(N)	0.03(N)	9e-5(N)
M87	9e-3(N)	7e-3(N)	2e-4(N)	2e-3(N)
M95	9e-3(N)	7e-3(N)	4e-4(N)	2e-3(N)
M102	e-8(N)	e-6(N)	e-6(N)	e-8(P)
M103	e-8(N)	e-6(N)	e-6(N)	e-8(P)
M105	e-8(N)	e-6(N)	5e-5(N)	4e-9(N)
M107	e-8(N)	e-6(N)	e-5(N)	5e-8(P)
M109	e-8(N)	e-6(N)	3e-5(N)	2e-9(N)
M110	e-8(N)	e-6(N)	2e-5(N)	6e-9(P)
M111	e-8(N)	e-6(N)	2e-5(N)	5e-9(P)
M115	e-8(N)	e-6(N)	2e-5(N)	e-9(P)
M117	e-8(N)	e-6(N)	1e-6(N)	2e-9(P)
M118	e-8(N)	e-6(N)	2e-6(N)	3e-10(N)
M119	e-8(N)	e-6(N)	2e-6(N)	3e-10(N)
M121	e-8(N)	e-6(N)	2e-5(N)	3e-9(N)
M122	e-8(N)	e-6(N)	2e-5(N)	3e-11(P)
M123	e-8(N)	e-6(N)	2e-5(N)	2e-11(P)
M124	e-8(N)	e-6(N)	e-5(N)	2e-10(P)
M125	e-8(N)	e-6(N)	e-5(N)	2e-10(P)
M126	e-8(N)	e-6(N)	e-5(N)	2e-9(N)
M127	e-8(N)	e-6(N)	7e-5(N)	2e-9(N)
M171	3e-3(N)	2e-3(N)	7e-5(P)	e-5(N)
M173	3e-3(N)	2e-3(N)	8e-5(P)	6e-6(N)
M175	3e-3(N)	2e-3(N)	7e-5(P)	6e-6(N)
M187	3e-3(N)	2e-3(N)	e-4(N)	7e-5(N)
M189	3e-3(N)	2e-3(N)	7e-5(N)	4e-5(N)
M191	3e-3(N)	2e-3(N)	8e-5(N)	4e-5(N)
M229	3e-3(N)	2e-3(N)	9e-5(P)	6e-6(N)
M231	3e-3(N)	2e-3(N)	8e-5(P)	6e-6(N)
M238	3e-3(N)	2e-3(N)	7e-5(P)	6e-6(N)
M239	3e-3(N)	2e-3(N)	7e-5(P)	6e-6(N)
M245	3e-3(N)	2e-3(N)	4e-5(N)	4e-5(N)
M247	3e-3(N)	2e-3(N)	5e-5(N)	4e-5(N)
M254	3e-3(N)	2e-3(N)	6e-5(N)	4e-5(N)
M255	3e-3(N)	2e-3(N)	7e-5(N)	4e-5(N)
M325*	0	0	0	0
M327	0(P)	e-14(P)	8e-9(P)	e-10(P)
M335	0(P)	4e-14(P)	3e-8(P)	e-10(P)
M341	4e-13(P)	4e-9(P)	4e-5(P)	4e-7(P)
M343	4e-13(P)	4e-9(P)	4e-5(P)	4e-7(P)
M351	4e-13(P)	4e-9(P)	4e-5(P)	4e-7(P)
M365*	0	0	0	0
M367	0(P)	e-14(P)	8e-9(P)	e-10(P)
M381	4e-14(P)	4e-10(P)	2e-6(P)	2e-8(P)
M383	4e-14(P)	4e-10(P)	2e-6(P)	3e-8(P)
M495	4e-14(P)	4e-10(P)	e-6(P)	2e-8(P)

alleles or loci require a corresponding change of allele frequencies in some calculations.

One of the main purposes of this paper is to point out that besides 6 two-locus disease models typically used in linkage analysis assuming two interacting genes, there are

many other types of gene-to-gene interactions. On the one hand, we admit that many of the two-locus models may not describe a real interaction between two gene products in a genetic disease; on the other hand, it is fairly straightforward to construct a biochemical system based on a two-locus model. A prototypical biochemical system consists of proteins formed by one peptide, dimer proteins formed by two complementary peptides, and dimer proteins formed by two identical peptides. By specifying the functional and nonfunctional proteins as well as the level of protein concentration required by a normal phenotype, it is possible to materialize any two-locus models.

The marginal-penetrance table we calculated in this paper is relevant to linkage analysis using only single-locus models. There have been discussions of whether single-locus models are sufficient to detect a linkage signal even if the underlying disease model may involve gene-to-gene interaction [15, 29, 30, 33, 36, 40, 69, 78, 79, 87, 89, 90]. Part of the answer can be predicted by the marginal-penetrance table: if the marginal-penetrance table is clearly dominant or recessive, it is possible that a single-locus model is able to detect linkage; otherwise, two-locus models should offer more power. Although it was mentioned that the gain of the logarithm of likelihood ratio (same as log-of-odd, or lod scores) by using two-locus models over those by single-locus models may be at most 17% [79], after removing the logarithm, the increase of the likelihood ratio can be much larger. For example, if the lod score equals to 2, or the likelihood ratio is equal to 100, an increase in lod of 17% is equivalent to an increase in likelihood ratio of 118%! What is considered as 'more' powerful versus 'slightly more' powerful is not specified.

As a compromise between detecting linkage signals using single-locus models and using two-locus models, it is suggested that a pairwise correlation between linkage signals obtained by single-locus models can be used to detect linkage for interacting genes [10, 60]. A similar idea for detecting higher-order correlations among linkage signals from different locations using artificial neural networks is discussed in Li et al. [58]. Our result on the sign and strength of correlation between two marginal IBD sharing probabilities (table 6, 7) is directly relevant to this approach. We observed that models modified from the multiplicative and single-locus models exhibit a very weak correlation, whereas missing lethal genotype models or 'nonlinear' models exhibit the strongest correlation. Since many two-locus models share similar correlation values, of sign and magnitude, we may not be able to distinguish them using this approach.

There are many topics on two-locus disease models that are not discussed here. Some classification schemes discussed in Li [56] are not included (e.g. models that are conditionally dominant or recessive with respect to two loci), as well as the idea of genotype-induced representation of joint IBD distributions [Reich, unpubl. results], and the idea of 'phase transition' in the two-locus model space [Li, unpubl. results]. The extension from fully penetrant models to reduced-penetrant models as well as models for quantitative traits is very important since many complex diseases are not dichotomous. Many calculations presented in this paper are implemented in a computer program: u2 for 'utility program for two-locus models'. More information on this program can be found at the web page <http://linkage.rockefeller.edu/soft/u2>.

Appendices

A Formal Derivation of the Value of N_2 by de Bruijn's Theorem

Let's consider two permutations applied on the phenotypes: the identity operation and the exchange permutation. The cycle index of this permutation group on the phenotype is:

$$C_{pheno}(x_1, x_2) = \frac{x_1^2 + x_2}{2}.$$

By de Bruijn's generalization of Pólya's theorem (theorem 5.4 in de Bruijn [13]), when the permutation group on phenotypes is considered, the number of equivalence two-locus models can be obtained by the following procedure: replacing x_1 in C_{geno} by the partial derivative $\partial/\partial x_1$, x_2 by $\partial/\partial x_2$, etc., and applying the partial derivative to C_{pheno} while replacing x_1 with $e^{(x_1+x_2+\dots)}$, x_2 with $e^{2(x_2+x_4+\dots)}$, etc., then evaluating the expression at $x_1 = x_2 = \dots = 0$:

$$\begin{aligned} N_2 &= \frac{1}{8} \left[\frac{\partial^9}{\partial x_1^9} + 4 \frac{\partial^3}{\partial x_1^3} \frac{\partial^3}{\partial x_1^3} + 2 \frac{\partial}{\partial x_1} \frac{\partial}{\partial x_4} \right] \\ &\quad \frac{1}{2} [e^{2(x_1+x_2+x_3+x_4)} + e^{2(x_2+x_4)}] |_{x_1=\dots=0} \\ &= 51. \end{aligned}$$

Since the permutation group on the phenotype considered here is particularly simple, N_2 is simply N_1 divided by 2.

Approximate Equivalence between G^2 and X^2

If we write $J_{ij} = N_{ij}/N$, $S_{ij} = N_i N_j / N^2$, and assume the difference between the two is small: $\Delta_{ij} \equiv J_{ij} - S_{ij}$, the following approximation by a Taylor expansion,

$$\begin{aligned} 2 \sum_{ij} J_{ij} \log \frac{J_{ij}}{S_{ij}} &\approx 2 \sum_{ij} (S_{ij} + \Delta_{ij}) \log \left(1 + \frac{\Delta_{ij}}{S_{ij}} \right) \\ &\approx 2 \sum_{ij} (S_{ij} + \Delta_{ij}) \left(\frac{\Delta_{ij}}{S_{ij}} - \frac{\Delta_{ij}^2}{2S_{ij}^2} \right) \\ &\approx 2 \sum_{ij} \Delta_{ij} + \sum_{ij} \frac{\Delta_{ij}^2}{S_{ij}} \approx \sum_{ij} \frac{\Delta_{ij}^2}{S_{ij}} = \sum_{ij} \frac{(J_{ij} - S_{ij})^2}{S_{ij}}, \end{aligned} \quad (13)$$

shows that G^2 and X^2 are approximately equal [1].

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Note Added in Proof

We noticed that the interference model has been suggested for human traits under the name 'heterosis', indicating a situation where the trait is greater in heterozygotes than in either homozygote. The negative-interference model is simply the case of negative heterosis. See, for example, Crocq MA, Mant R, Asherson P, et al.: Association between schizophrenia and homozygosity at the dopamine D3 receptor gene [J Med Genet 1992;29:858–860], Comings DE, Gade R, Wu S, et al.: Studies of the potential role of the dopamine D1 receptor gene in addictive behaviors [Mol Psychiatry 1997;2:44–56], and Comings DE: Molecular heterosis as the explanation for the controversy about the effect of the DRD2 gene on dopamine D2 receptor density [Mol Psychiatry 1999;4:213–215].