Genetik komplexer Merkmale

HHR, 20.05.03

Kopplungsuntersuchungen,
Lod score (wdh.);
Kopplungsungleichgewicht,
Assoziationsstudien,
Transmission Disequilibrim Test,
polygene und multifaktorielle Vererbung,
multifaktorielle Vererbung mit Schwellenwert

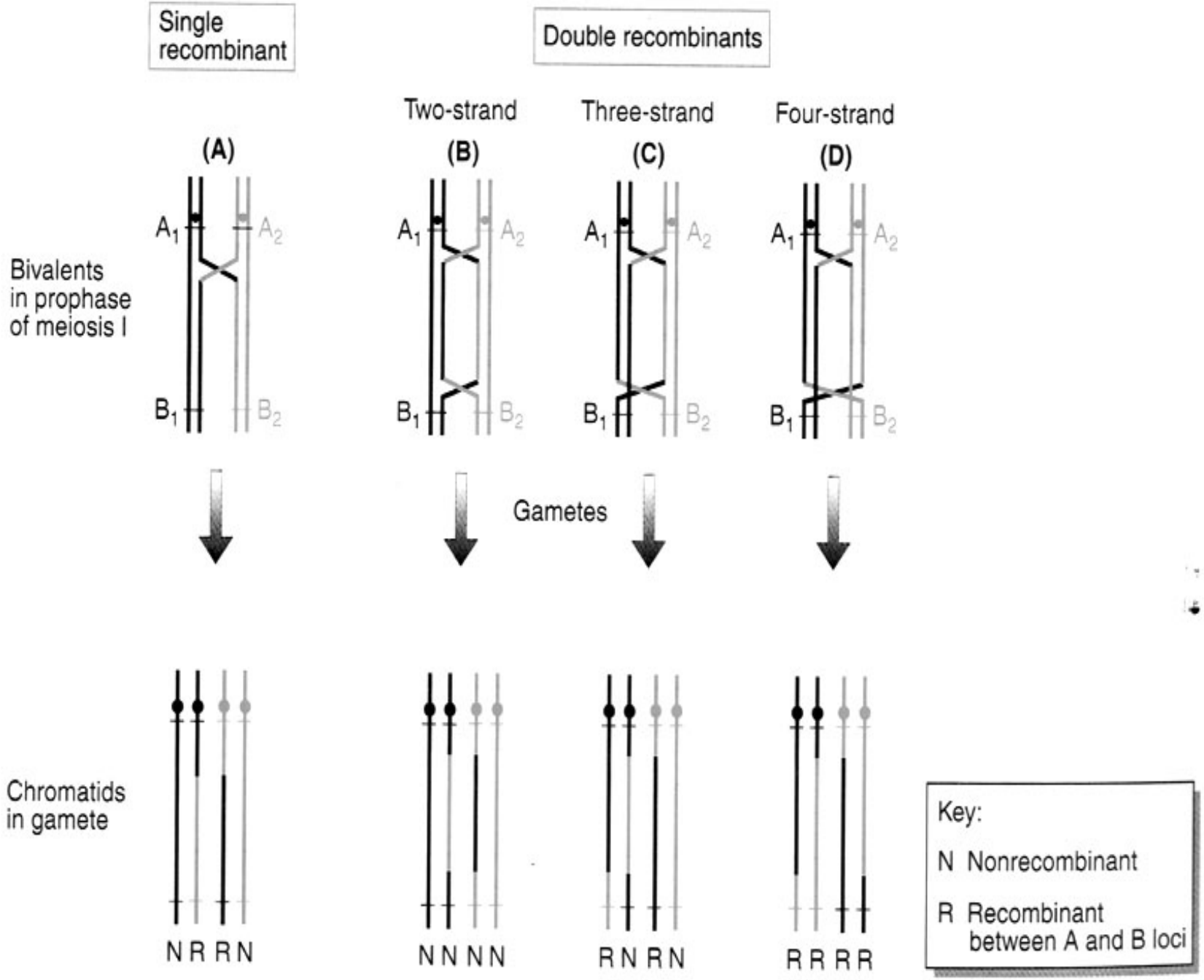


Figure 11.2: Single and double recombinants.

There are about 60 chiasmata in each male meiosis, corresponding to 30 crossovers per male germ cell

1 Morgan (M) is the genetic interval corresponding to 1 crossover in the genome; thus, the genetic length of the male genome is about 30 Morgans (or 3000 cM)

Gene (or marker) loci on the same chromosome are linked if their alleles stay together during transmission from parent to offspring significantly more often than not (i.e., if their recombination frequency theta (Θ) is < 0.5).

For small values of Θ (e.g., < 0.10), the recombination fraction in % is equivalent to the genetic distance in cM (5 % rec. --> 5 cM)

... but for Θ --> 0.5 , the genetic distance approaches ∞

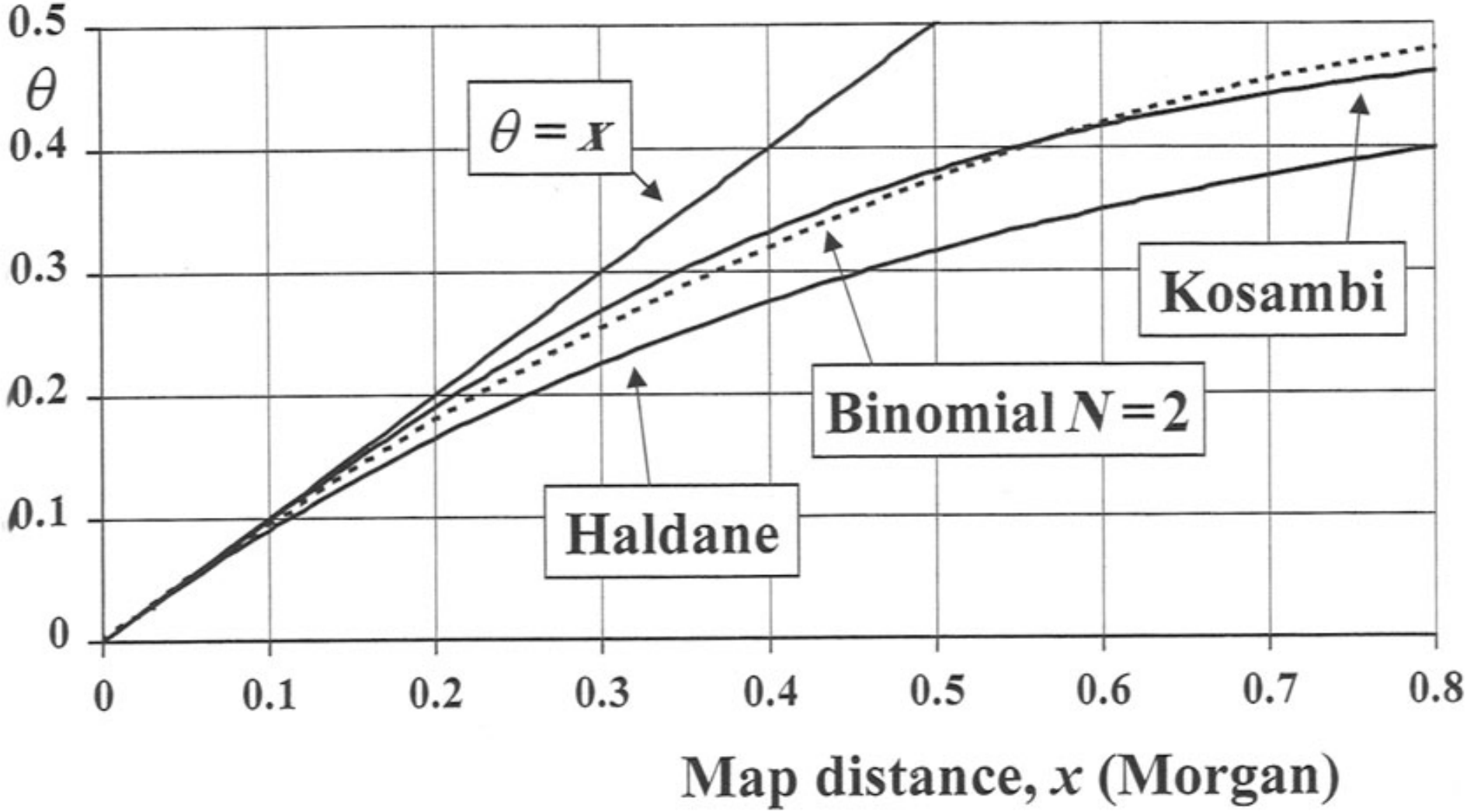


Figure 1.4. Graphs of several map functions.

The LOD (= log of odds) score:

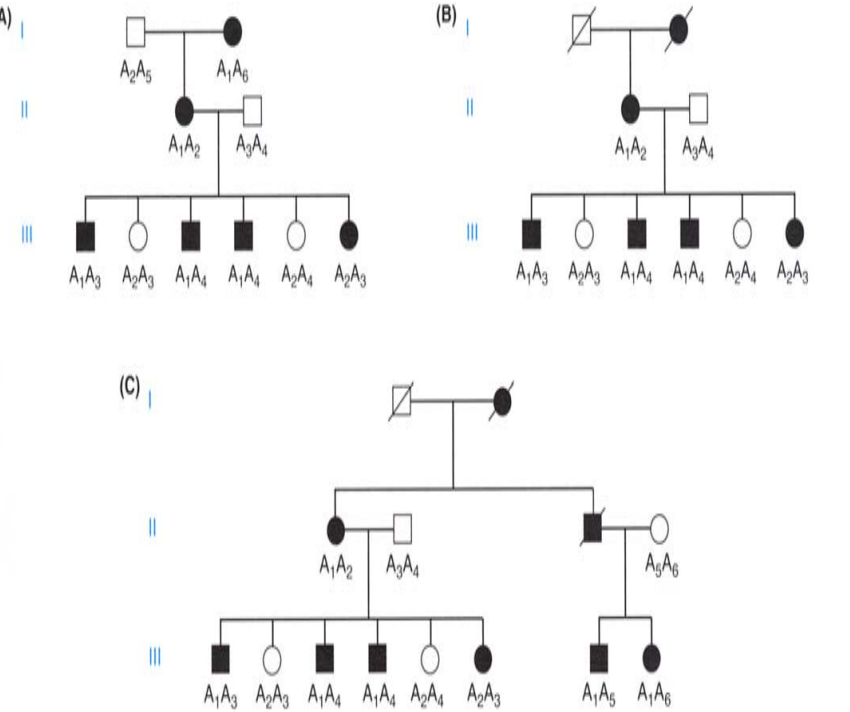
a tool for the quantitiative assessment of linkage between disease genes and (other) genetic marker loci in families

Principle:

a) calculation of the likelihood that disease and marker allele co-segregate in the pattern observed in a family under the assumption that the two are linked (i.e., assuming that their true recombination frequency theta is < 0.5; e.g. 0.0, 0.1, 0.2, 0.3,....)

b) calculation of the likelihood of the segregation pattern under the assumption that the two loci are unlinked (theta = 0.5)

c) calculation of the log of (a/b) for any value of theta between 0.0 and 0.5 (where it becomes zero) --> **the LOD score curve**



Recognizing recombinants: three versions of a family with an autosomal dominant disease, typed for a marker A.

Calculation of lod scores for the families in *Figure 11.4*

- Given that the loci are truly linked, with recombination fraction θ, the likelihood of a meiosis being non-recombinant is $1 - \theta$ and the likelihood of it being recombinant is θ.
- If the loci are in fact unlinked, the likelihood of a meiosis being either recombinant or nonrecombinant is 1/2.

Family A

There are five recombinants and one nonrecombinant.
The overall likelihood, given linkage, is $(1 - \theta)^5.\theta$
The likelihood given no linkage is $(1/2)^6$
The likelihood ratio is $(1 - \theta)^5.\theta / (1/2)^6$
The lod score, Z, is the logarithm of the likelihood ratio.

θ	0	0.1	0.2	0.3	0.4	0.5
Z	− infinity	0.577	0.623	0.509	0.299	0

Family B

II_1 is phase-unknown.
If she inherited A_1 with the disease, there are five non-recombinants and one recombinant.
If she inherited A_2 with the disease, there are five recombinants and one nonrecombinant.
The overall likelihood is $\frac{1}{2}[(1 - \theta)^5.\theta / (1/2)^6] + \frac{1}{2}[(1 - \theta).\theta^5 / (1/2)^6]$. This allows for either possible phase, with equal prior probability.
The lod score, Z, is the logarithm of the likelihood ratio.

θ	0	0.1	0.2	0.3	0.4	0.5
Z	− infinity	0.276	0.323	0.222	0.076	0

Family C

At this point nonmasochists turn to the computer.

Pedigree sizes (no. of informative meioses) required to 'prove' linkage:

co-segregation of two markers at one meiosis increases the likelihood ratio (odds) for linkage by a factor of 2, or the log of odds (LOD score) by 0.301

thus, co-segregation of two X-chromosomal markers from a grandfather to 2 daughters and to their 7 grandsons (7 informative meioses) yields a LOD score of 2.107

10 informative meioses are required to obtain statistically significant evidence for linkage between two autosomal loci (LOD score > 3)

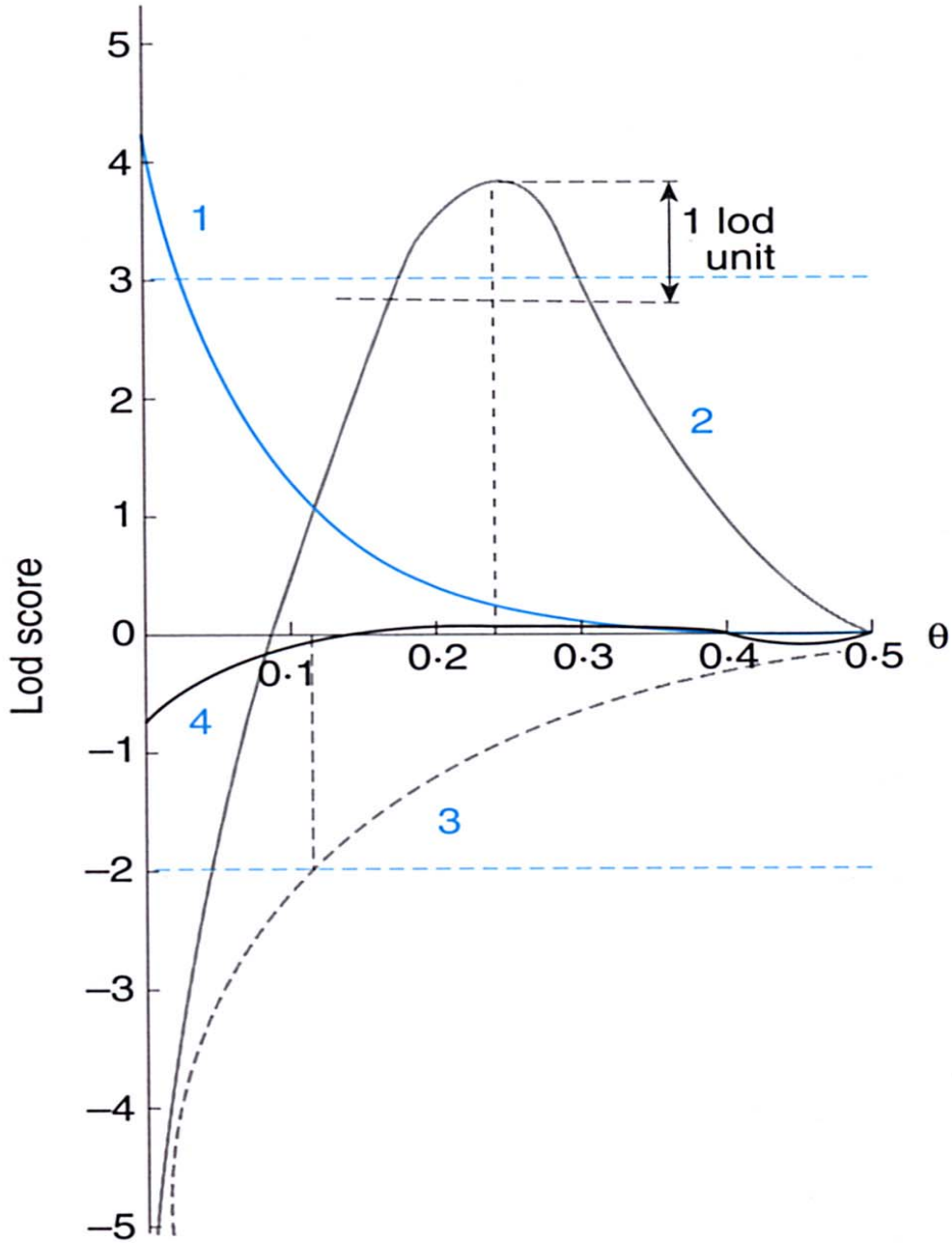


Figure 11.5: Lod score curves.

A LOD score of > 3 is considered as significant for linkage between autosomal genes and markers (for X-linked markers: LOD score > 2 !), and for a given recombination fraction Θ, linkage is excluded if the LOD score is < - 2

Rule of thumb for the relation between genetic and physical distances in the human genome:

1 centiMorgan (cM) = 10^6 basepairs (1 Megabase = 1 Mb)

(because the physical map of the human genome is roughly 3 billion bp long and its genetic length is about 3000 cM)

but: - does not apply everywhere in the genome
- in female meiosis, genetic map is larger (chiasmata are more frequent)

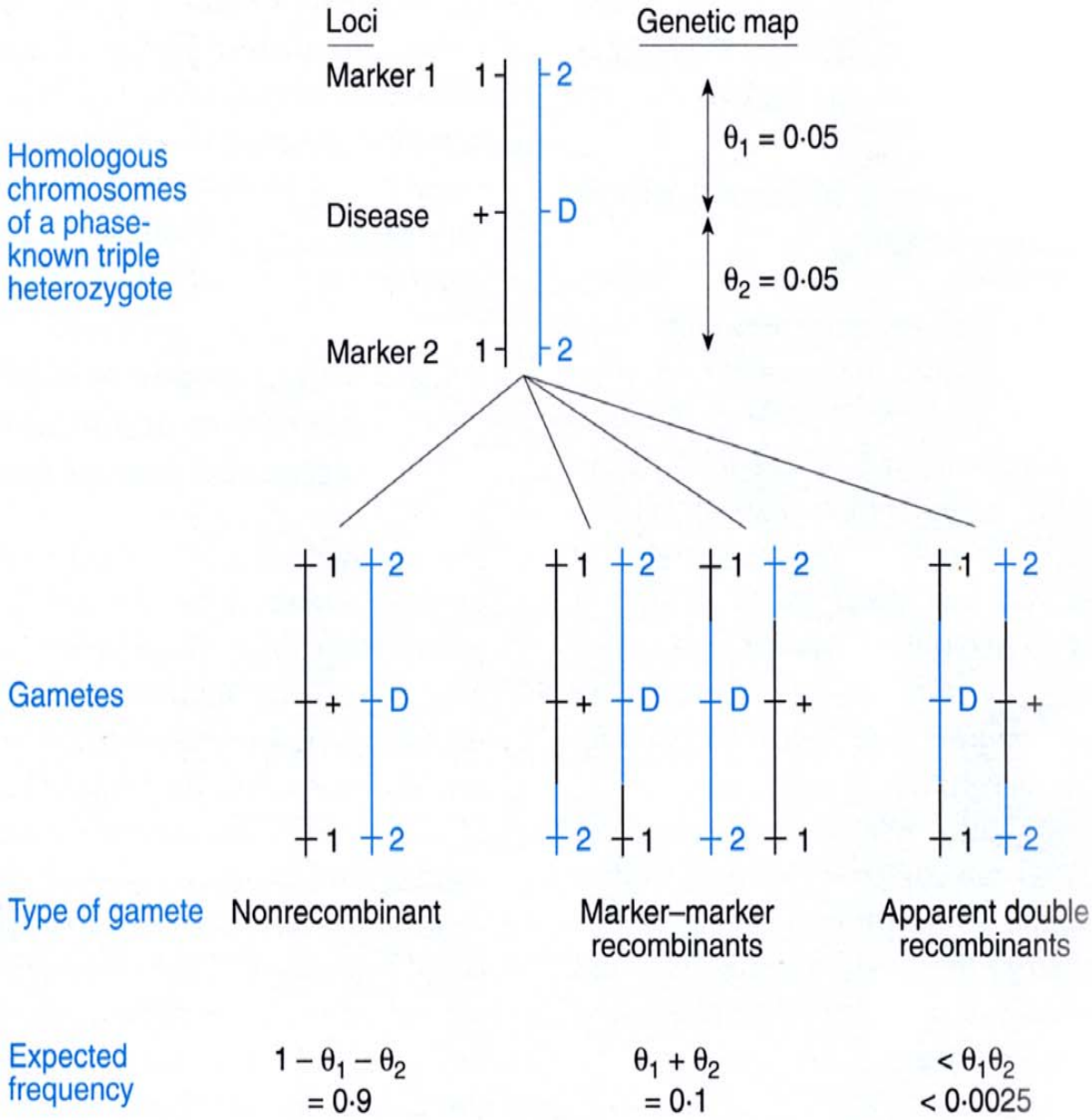


Figure 11.7: Apparent double recombinants suggest errors in the data.

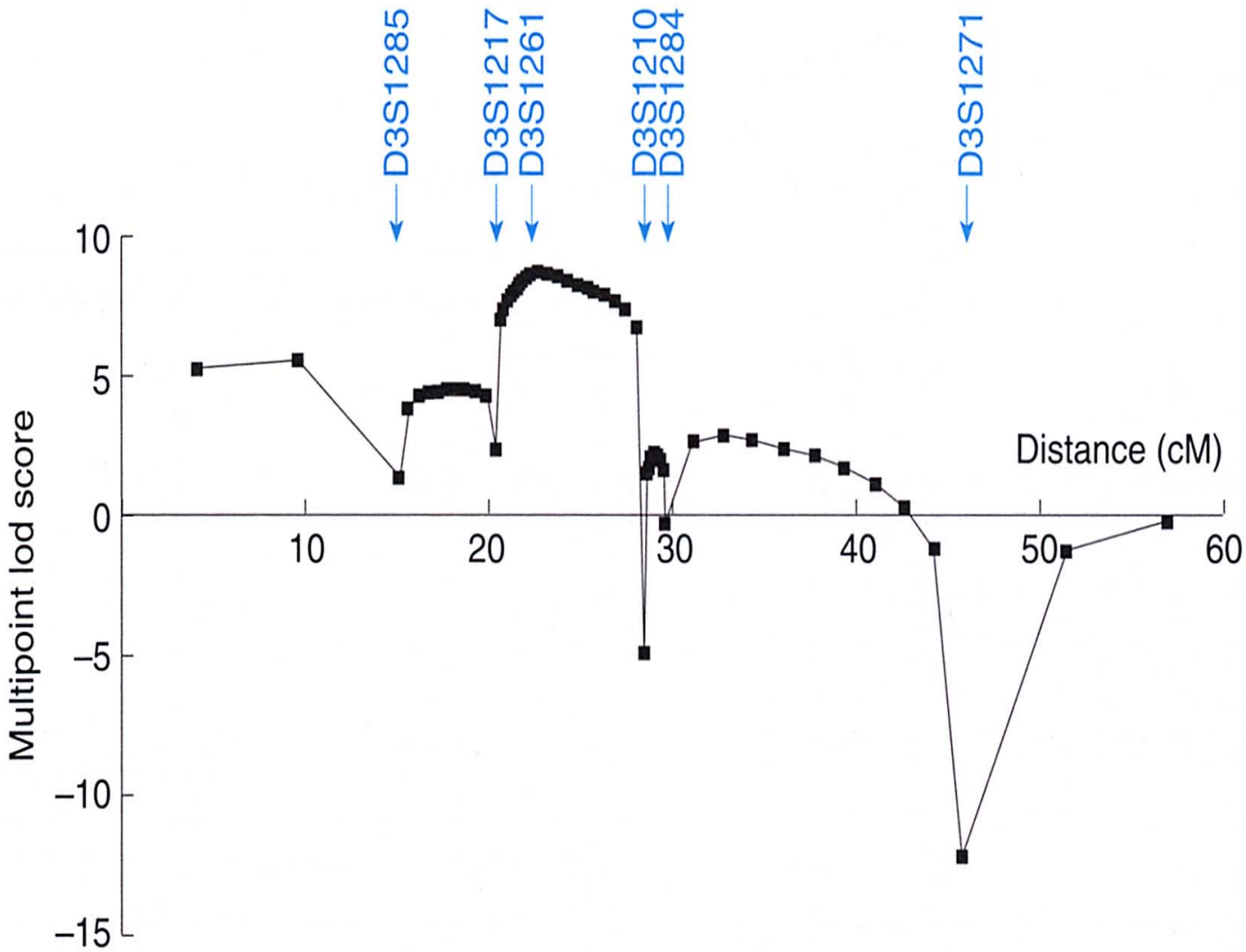


Figure 11.6: Multipoint mapping in man.

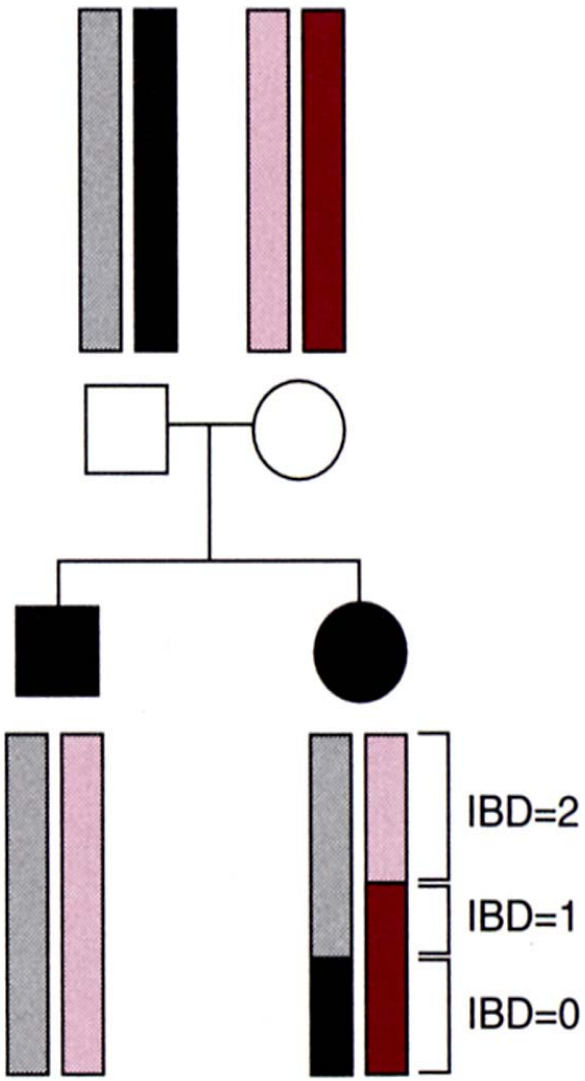


Figure 4.11. Sharing of alleles identical-by-descent in affected siblings. The parental chromosomes can be marked by the study of highly polymorphic markers at defined intervals; this leads to the unique identification of each homologous pair of parental chromosomes and to the identification of which segments were inherited by each offspring from a specific parent. Comparison of the offspring chromosomes identifies which segments are shared identical-by-descent (IBD) by the siblings. This sharing can be for both parental copies (2), one parental copy (1), or no sharing (0). By quantitating the degree of sharing at each chromosomal (genomic) site in many families one can identify those regions in which sharing is greater than expected, and thus likely to harbor a susceptibility allele. (Courtesy of Professor Aravinda Chakravarti, Department of Genetics, Case Western Reserve University.)

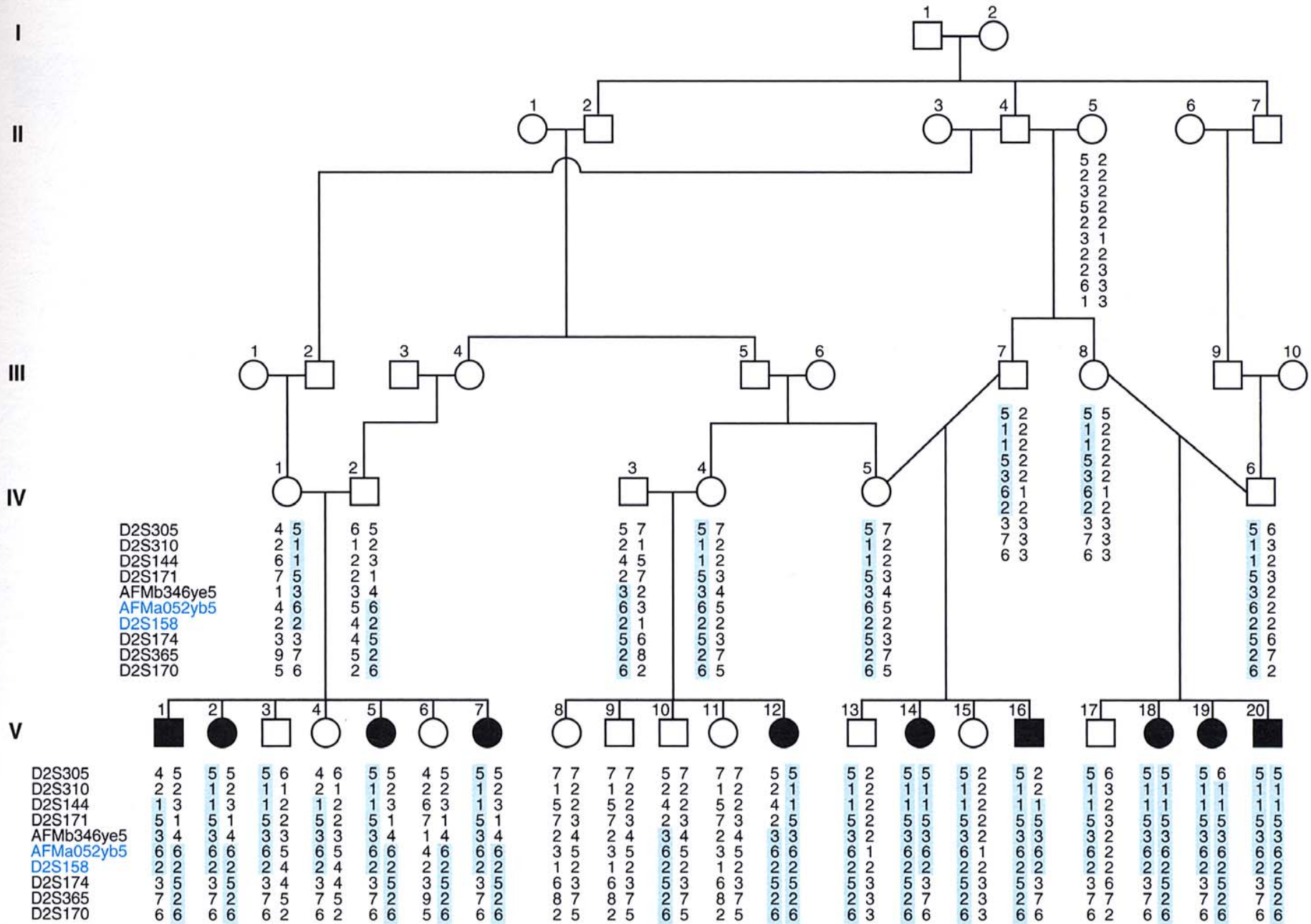


Figure 11.8 Autozygosity mapping.

Linkage disequilibrium ('Kopplungsungleichgewicht'):

genetic markers or gene defects are inherited as parts of chromosome segments which are limited by crossovers

if Θ is the probability of recombination separating two neighboring loci during one meiosis, $(1-\Theta)$ is their chance to stay together

For two descendants of the same common ancestor living n generations ago, this probability will be $(1-\Theta)^{2n}$

If this ancestor lived around 1550 (i.e., 22 generations ago), the chance of two closely linked markers ($\Theta = 0.01$) to stay together in both descendants would be $0.99^{44} = 64\%$!

Length of such evolutionarily conserved 'haplotypes' showing allelic associations depends on population history

Table 12.1: Allelic association in cystic fibrosis

Marker alleles	CF chromosomes	Normal chromosomes
X_1, K_1	3	49
X_1, K_2	147	19
X_2, K_1	8	70
X_2, K_2	8	25

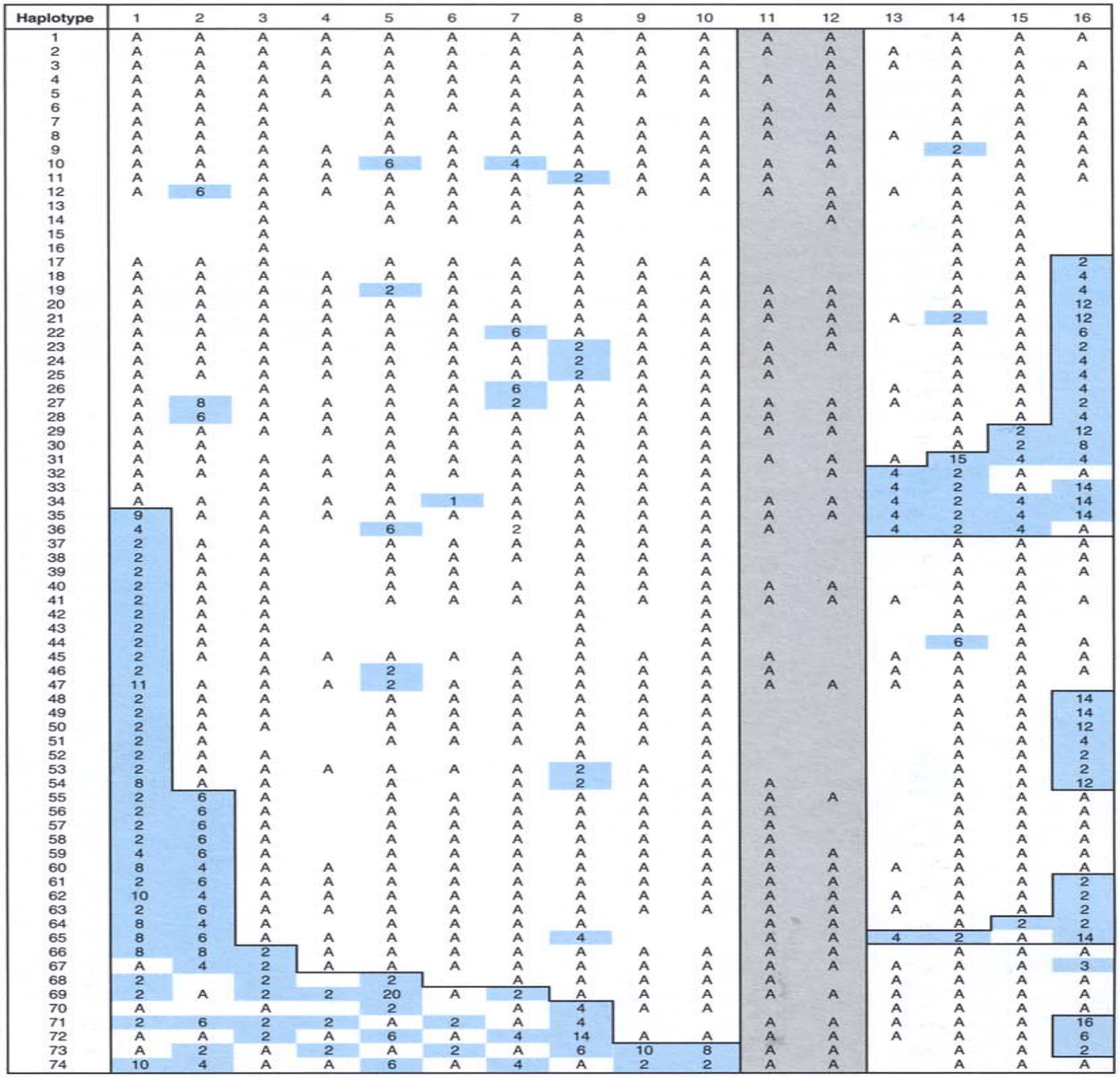


Figure 12.5: An ancestral haplotype in European patients with Nijmegen breakage syndrome.

Association is not necessarily due to linkage disequilibrium:

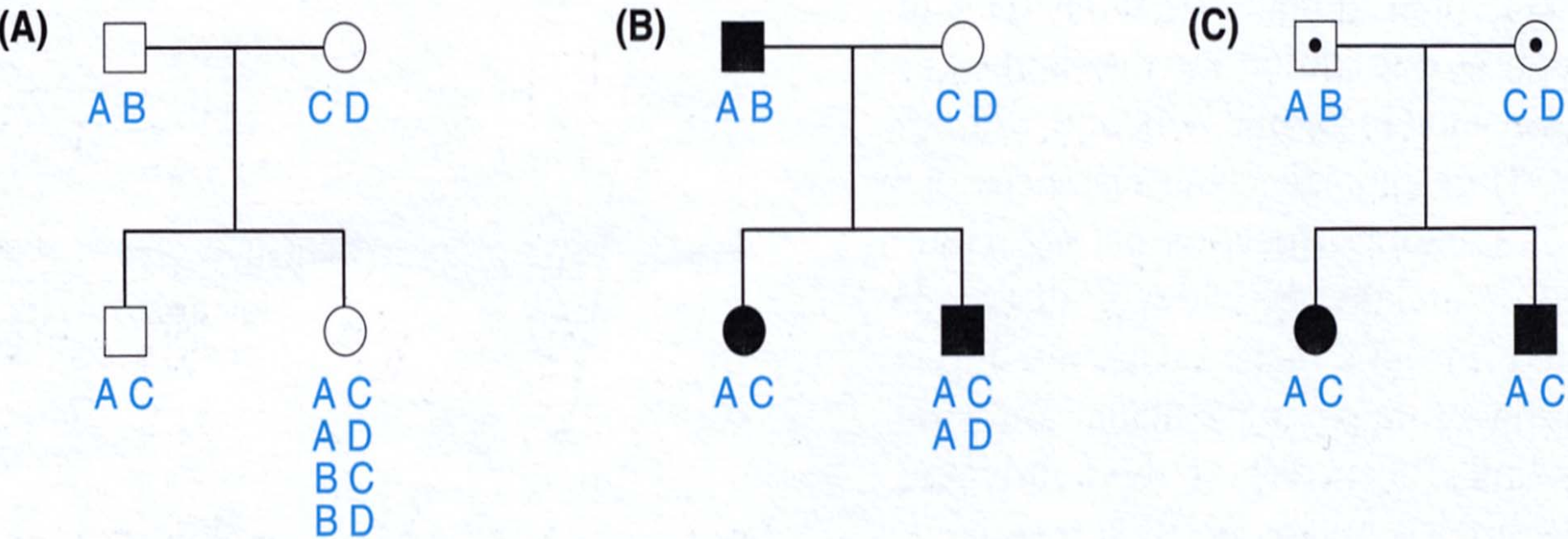
- marker could be directly responsible for the disease

- presence of associated factor might confer selective advantage to carrier of unlinked gene defect

- gene defect and associated marker might be confined to subset of the population (and be rare outside this subset) ('population stratification')

- association might be a statistical artefact (e.g., if n loci are tested, significance levels have to be raised accordingly)

- association due to linkage disequilibrium will only be observed if most disease-predisposing chromosomes are derived from common ancestor



Sib pair analysis.

Box 12.1

The TDT test to determine whether marker allele M_1 is associated with a disease

(i) Affected probands are ascertained.

(ii) The probands and their parents are typed for the marker.

(iii) Those parents who are heterozygous for marker allele M_1 are selected. They may or may not themselves be affected.

(iv) Let a be the number of times a heterozygous parent transmits M_1 to the affected offspring, and b be the number of times the other allele is transmitted. The TDT test statistic is $(a-b)^2/(a+b)$. This has a χ^2 distribution with 1 degree of freedom, provided the numbers are reasonably large.

(v) Other alleles at the M locus can be tested using the same set of families. If n marker alleles are tested, each individual p value must be corrected by multiplying by $(n-1)$.

Table 12.3: Sample sizes for 80% power to detect significant linkage or association in a genome-wide search.

		ASP analysis		TDT analysis	
γ	p	Y	N-ASP	P(trA)	N-TDT
5	0.01	0.534	2530	0.830	747
	0.1	0.634	161	0.830	108
	0.5	0.591	355	0.830	83
3	0.01	0.509	33797	0.750	1960
	0.1	0.556	953	0.750	251
	0.5	0.556	953	0.750	150
2	0.1	0.518	9167	0.667	696
	0.5	0.526	4254	0.667	340
1.5	0.1	0.505	115537	0.600	2219
	0.5	0.510	30660	0.600	950
1.2	0.1	0.501	3951997	0.545	11868
	0.5	0.502	696099	0.545	4606

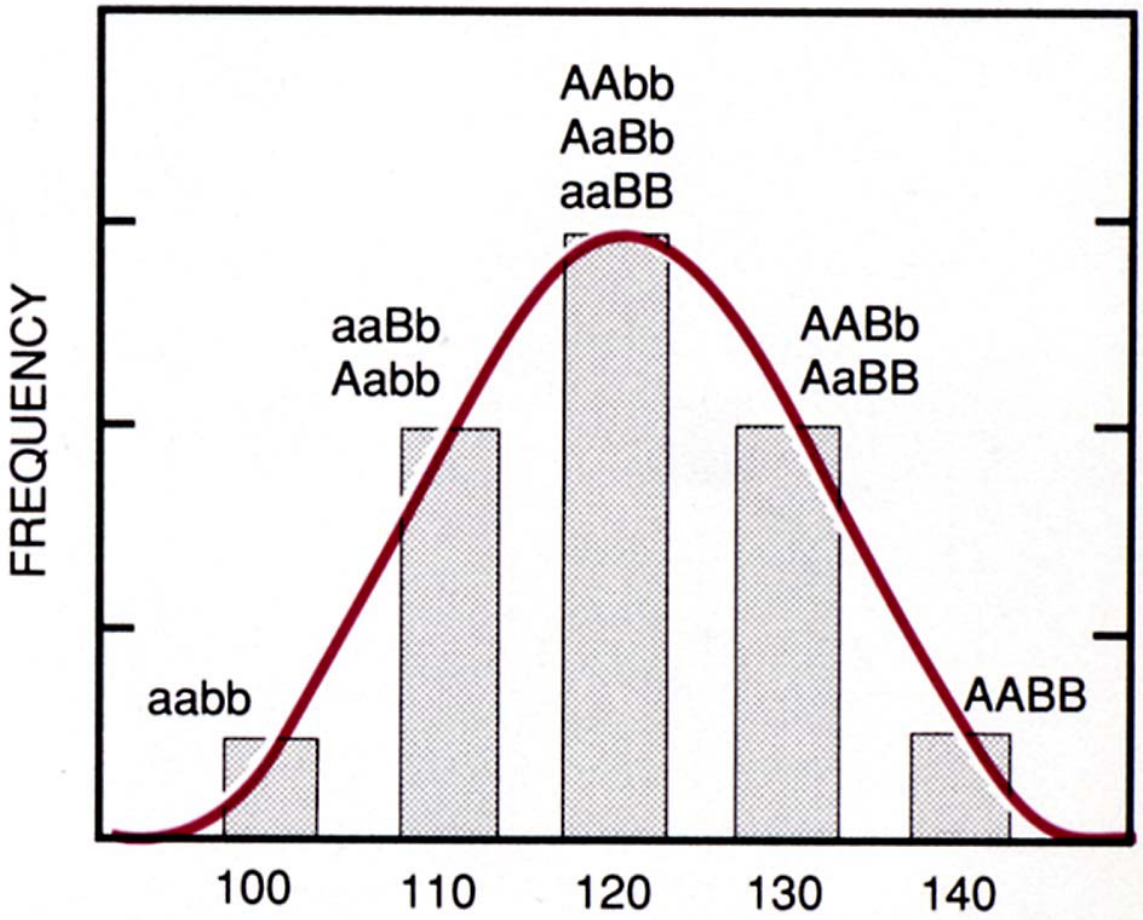


Figure 4.3. Frequency distribution of systolic blood pressure determined by a two-locus two-allele model. See text for explanation.

Table 4.6. Frequency Distribution of Systolic Blood Pressure Determined by a Two-Locus Two-Allele Model[a]

	AA *1/4*	*Aa* *1/2*	*aa* *1/4*
BB 1/4	1/16 (*40*)	2/16 (*30*)	1/16 (*20*)
Bb 1/2	2/16 (*30*)	4/16 (*20*)	1/16 (*10*)
bb 1/4	1/16 (*20*)	2/16 (*10*)	1/16 (*0*)

[a] The numbers in parentheses indicate the increment (in mm Hg pressure) to the systolic blood pressure above a basal level of 100 mm Hg contributed by each genotype.

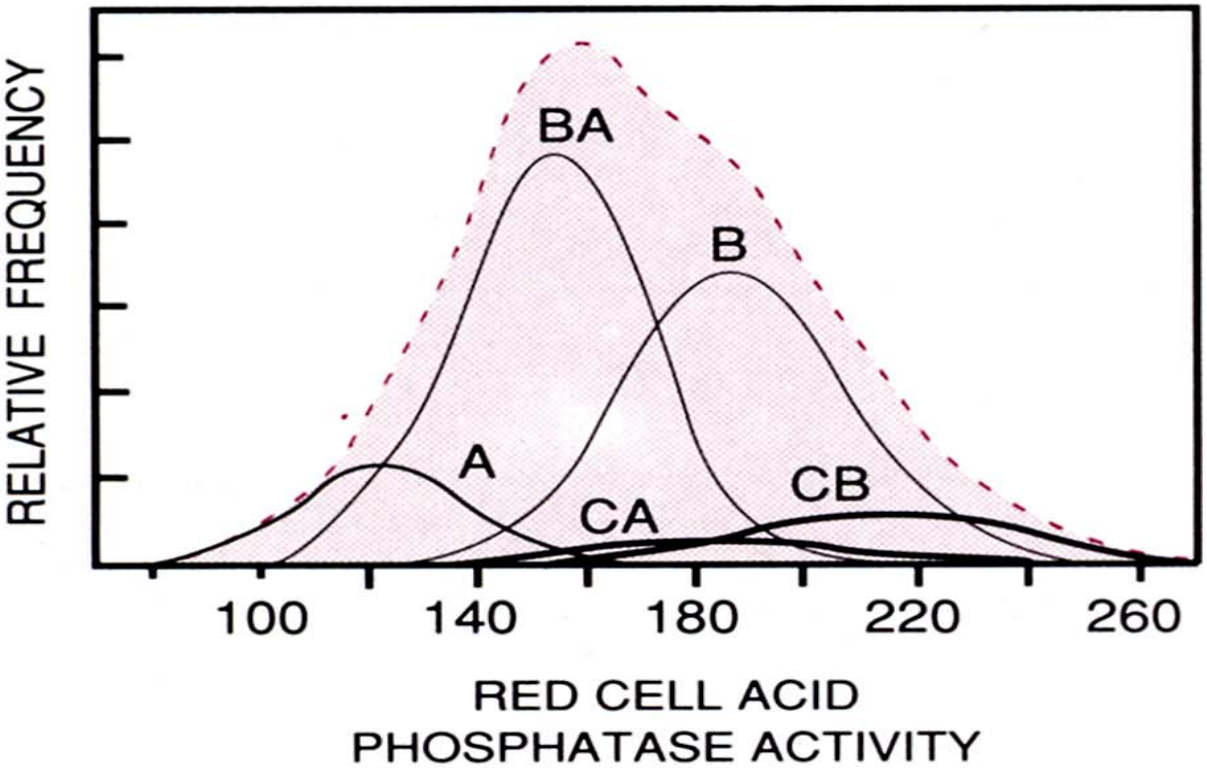


Figure 4.4. Distribution of red cell acid phosphatase activities in the general population (*broken red line*) and in individuals with the separate phenotypes. The *solid* curves are constructed from the data on the different phenotypes as found in the British population. (From Harris H. The principles of human biochemical genetics. 3rd ed. Amsterdam: Elsevier/North-Holland, 1980:186.)

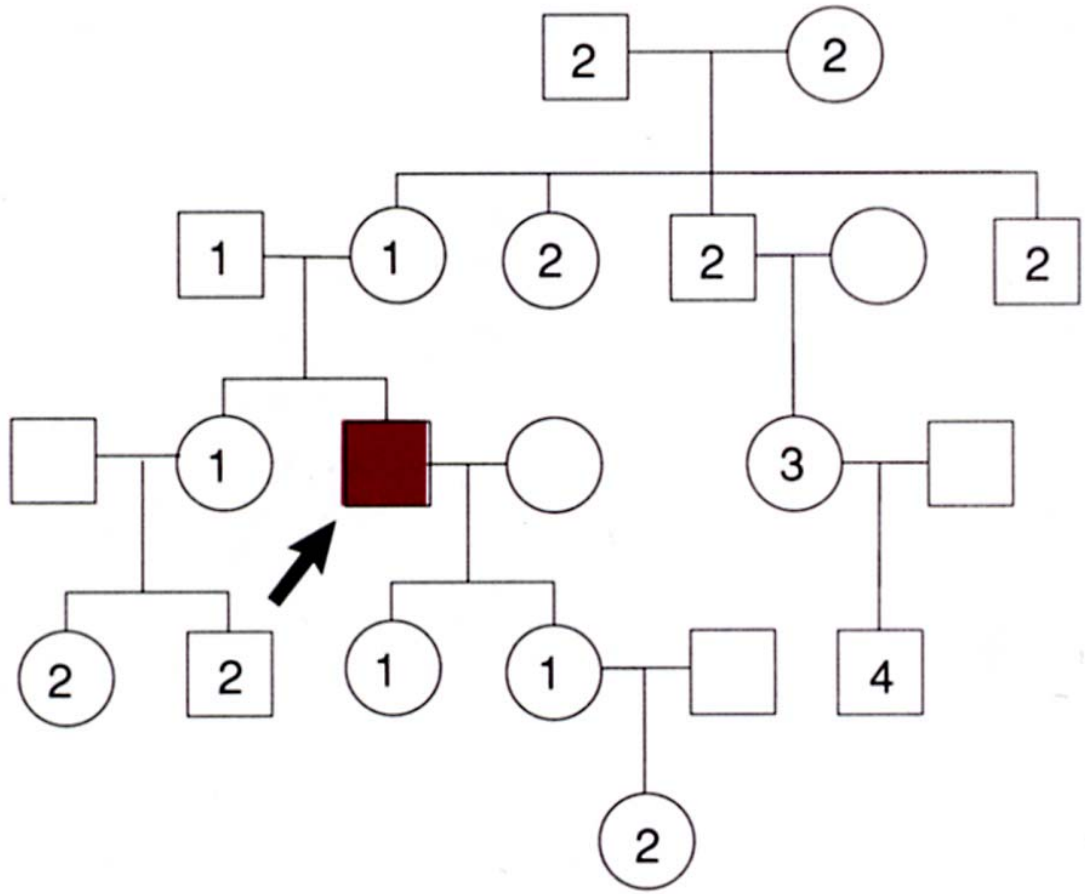


Figure 4.5. Pedigree showing degree of relationship. In this figure, the *numbers inside the symbols* indicate the degree of relationship to the proband (*red symbol*).

Table 4.7. Correlation of Fingertip Ridge Counts among Relatives Compared with Expectations Based on the Proportion of Shared Genes[a]

Relationship	*Observed Correlation*	*Expected Correlation*
Monozygotic twins	0.95 ± 0.07	1.00
Dizygotic twins	0.49 ± 0.08	0.50
Siblings	0.50 ± 0.04	0.50
Parent-child	0.48 ± 0.04	0.50
Spouses	0.05 ± 0.07	0.00

[a] From Carter CO: Genetics of common disorders. Br Med Bull 25:52–57, 1969.

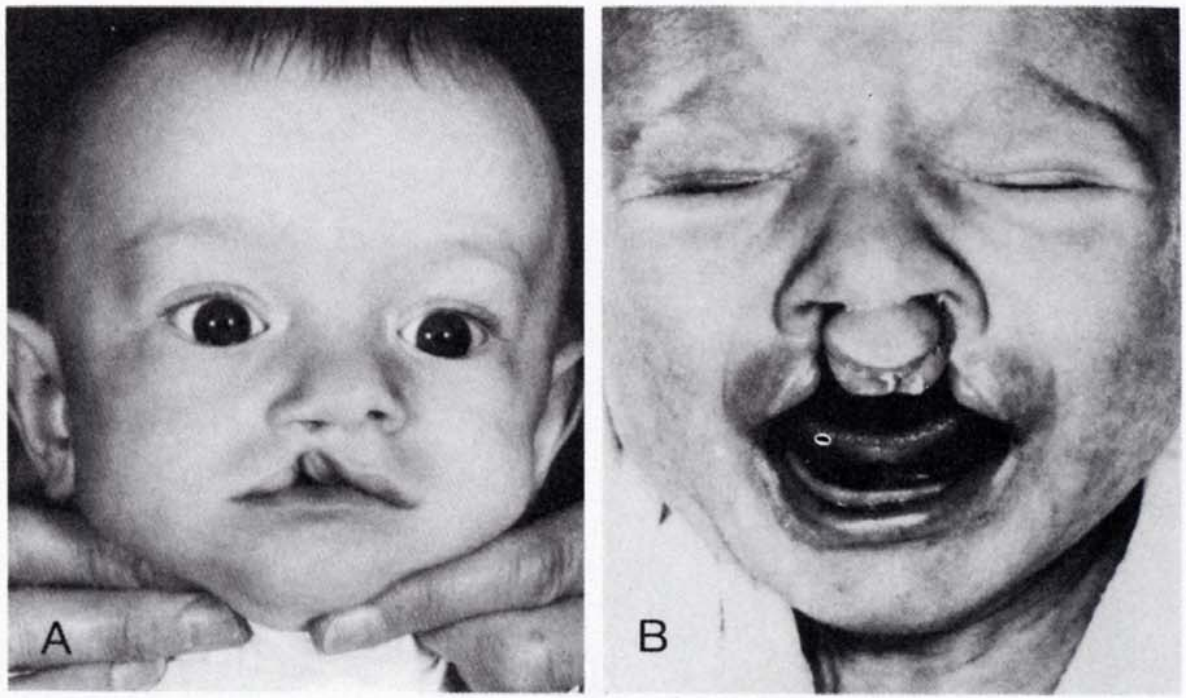


Figure 4.6. Children with cleft lip ± cleft palate. **A.** Child with unilateral cleft lip; **B.** Child with bilateral cleft lip and cleft palate. (From Ross RB, Johnson MC. Cleft lip and palate. Baltimore: Williams & Wilkins, 1972:131, 141.)

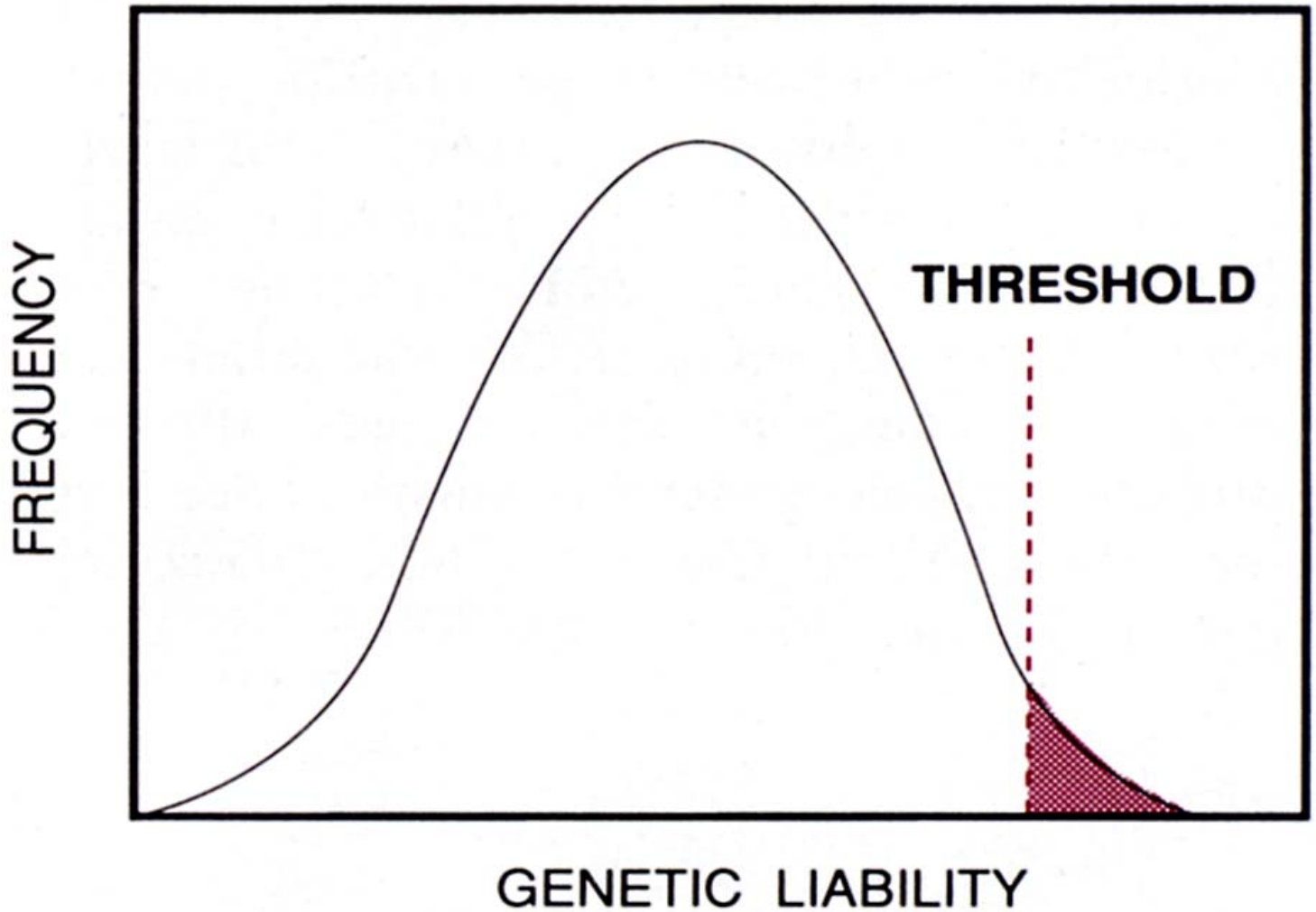
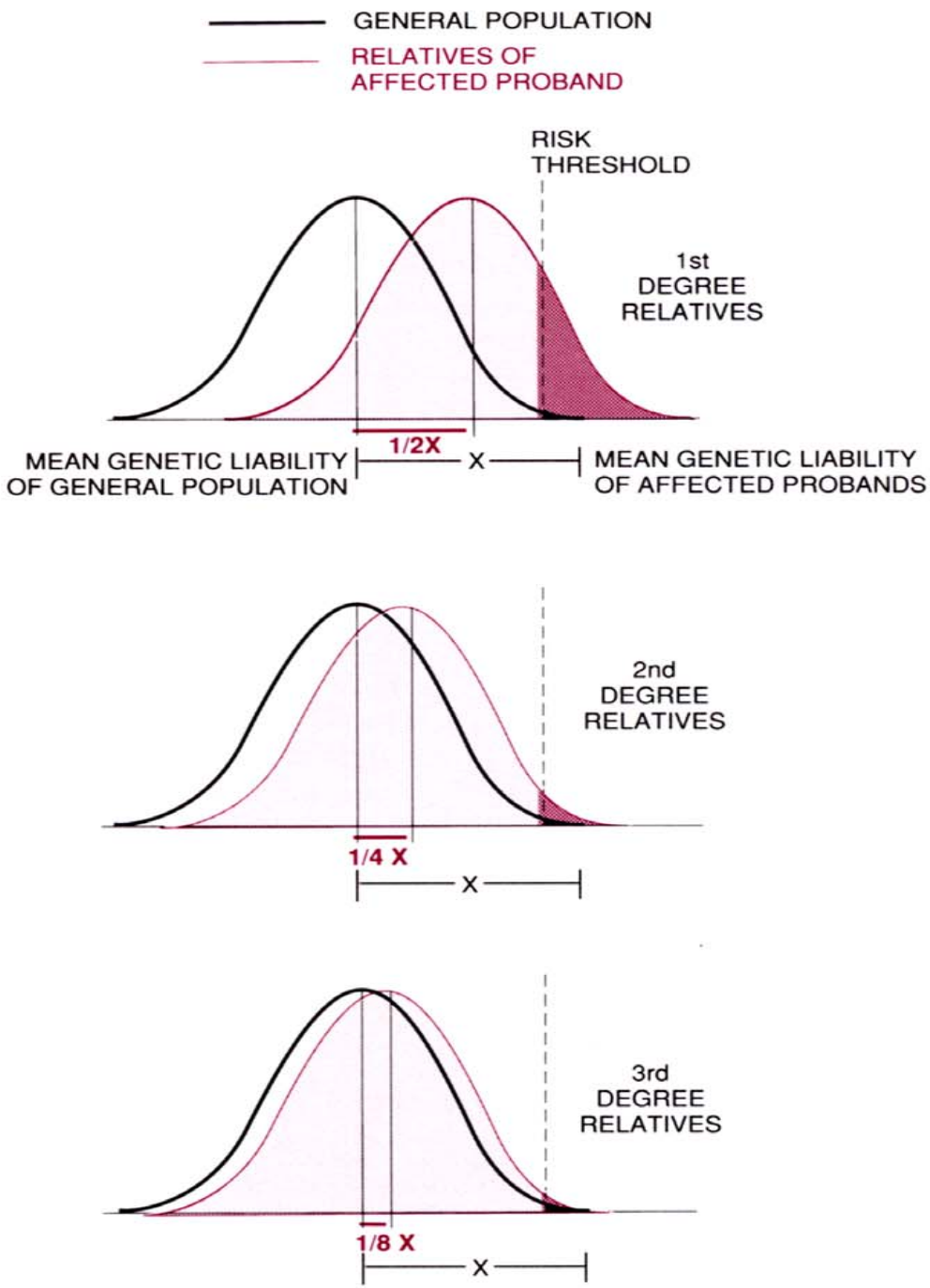


Figure 4.7. Threshold model of multifactorial inheritance. See text for details.

Figure 4.8. Multifactorial threshold model: distribution of genetically determined liability among relatives. The distribution of genetic liability in relatives of an affected proband is indicated by the *lightly shaded red area below* the *red curve*. *X* is the difference in mean genetic liability between affected probands and the general population. See text for details. (From Carter CO. Multifactorial genetic disease. Hosp Pract 1970;5:45–59.)



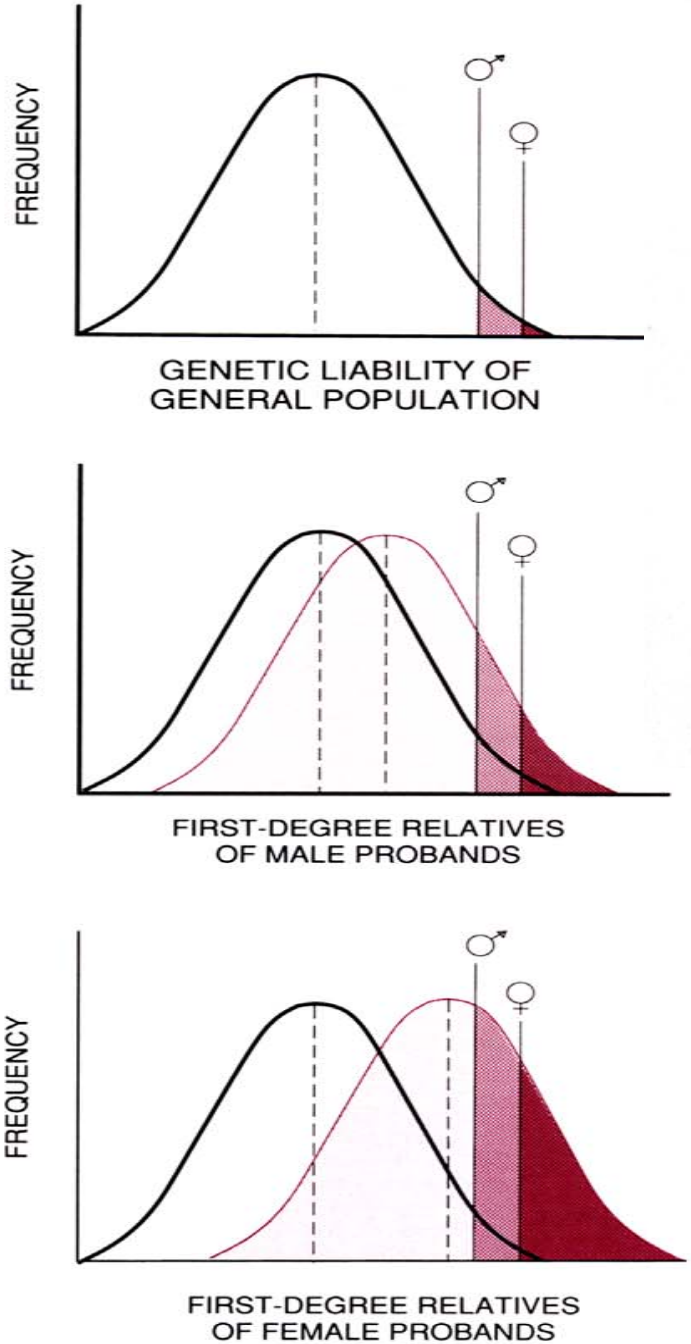


Figure 4.10. Multifactorial threshold model: explanation for sex differences in incidence of pyloric stenosis in probands and their relatives. The risk thresholds for males and females are indicated by the *solid vertical lines*. The distribution of genetic liability in relatives of male and female probands is indicated by the *red shaded areas below* the *red curve*. Affected individuals are indicated by the *darker red areas*. See text for details. (Redrawn from Thompson M. Genetics in medicine. 4th ed. Philadelphia: WB Saunders, 1986:217.)

Table 4.11. Proportion of Children Affected with Pyloric Stenosis[a]

Proband	Children	
	Sons	Daughters
	%	
Father	5.5	2.4
Mother	19.4	7.3
Population incidence	0.5	0.1

[a] From Carter CO: Genetics of common disorders. Br Med Bull 25:52–57, 1969.

Table 4.10. Family Patterns in Some Common Congenital Malformations[a]

Malformation	Incidence in General Population	Incidence Relative to General Population			
		Monozygotic Twins	First Degree Relatives	Second Degree Relatives	Third Degree Relatives
Cleft lip (± cleft palate)	0.001	×400	×40	×7	×3
Club foot	0.001	×300	×25	×5	×2
Neural tube defects	0.002		×8		×2
Congenital dislocation of hip (females only)	0.002	×200	×25	×3	×2
Congenital pyloric stenosis (males only)	0.005	×80	×10	×5	×1.5

[a] From Carter CO: Genetics of common disorders. Br Med Bull 25:52–57, 1969 and Smith DW, Aase JM: Polygenic inheritance of certain common malformations. J Pediatr 76:653–659, 1970.

Table 4.8. Family Studies of the Incidence of Cleft Lip (± Cleft Palate)[a]

Relatives	*Pecentage of Relatives Affected*	*Incidence Relative to General Population*
First degree		
Sibs	4.1	× 40
Children	3.5	× 35
Second degree		
Aunts and uncles	0.7	× 7
Nephews and nieces	0.8	× 8
Third degree		
First cousins	0.3	× 3

[a] From Carter CO: Genetics of common disorders. Br Med Bull 25:52–57, 1969.

Table 4.9. Concordance among Monozygotic and Dizygotic Twins for Common Malformations and Diseases

	Concordance	
Trait	*MZ*	*DZ*
	%	
Cleft lip ± cleft palate	40	4
Pyloric stenosis	22	2
Schizophrenia	46	14
Insulin-dependent diabetes mellitus	30	6

Table 19.2: Twin studies in schizophrenia

Study	Concordant MZ pairs	Concordant DZ pairs
Kringlen, 1968	14/55 (21/55)	4–10%
Fischer *et al.*, 1969	5/21 (10/21)	10–19%
Tienari, 1975	3/20 (5/16)	3/42
Farmer, 1987	6/16 (10/20)	1/21 (4/31)
Onstad *et al.*, 1991	8/24	1/28

Box 19.1

Genetic differences between identical twins

All individuals, even monozygotic twins, differ in:

- their repertoire of antibodies and T-cell receptors (because of epigenetic rearrangements and somatic cell mutations);
- somatic mutations in general (*Chapter 18*);
- the numbers of mitochondrial DNA molecules (epigenetic partitioning);
- the pattern of X inactivation, if female.

Table 19.3: An adoption study in schizophrenia

	Schizophrenia cases among biological relatives	Schizophrenia cases among adoptive relatives
Index cases (chronic schizophrenic adoptees)	44/279 (15.8%)	2/111 (1.8%)
Control adoptees (matched for age, sex, social status of adoptive family and number of years institutionalized)	5/234 (2.1%)	2/117 (1.7%)

Table 19.8: Type 1 diabetes susceptibility loci suggested by affected sib pair (ASP) or transmission disequilibrium (TDT) analysis.

Locus	MIM no.	Location	Status
IDDM1	222100	6p21	λ_s = 3.1; determinant is HLA-DQB
IDDM2	125852	11p15	λ_s = 1.3; determinant is a VNTR upstream of INS gene
IDDM3	600318	15q26	λ_s = 1.4; detected in two studies
IDDM4	600319	11q13	λ_s = 1.6; confirmed in three screens
IDDM5	600320	6q24–q27	λ_s = 1.2; confirmed in two studies; homolog of mouse *idd5*?
IDDM6	601941	18q21	ASP and TDT evidence in one very large study.
IDDM7	600321	2q31–q33	λ_s = 1.3; seen in three ASP studies and TDT shows association
IDDM8	600883	6q25–q27	λ_s = 1.8; confirmed in two studies
IDDM10	601942	10p11–q11	ASP and TDT data in two studies from one group
IDDM11	601208	14q24–q31	Seen in one study
IDDM12	600388	2q33	Confirmed. Linkage disequilibrium with CTLA4
IDDM13	601318	2q34	Seen in one study. Same as *IDDM7* and/or *12*?
IDDM15	601666	6q21	Yet another 6q locus, seen in one study
IDDM17	603266	10q25	In one large Bedouin family

Data from the OMIM entries and papers cited therein; λ_s values are from Luo *et al*. (1995).

Table 19.9: Results of three whole-genome searches for susceptibility loci for multiple sclerosis

	Cambridge series	US / French series	Canadian series
Stage 1 screen	143 ASPs 311 markers	52 families including 81 ASPs; 443 markers	100ASPs 257 markers
MLS > 1*	1p36, 2p13, 3p14–p21 4q35, 14q32, 19q13	5q13–q23, 7q32–q34, 11p15, 12q24–qter, 19q13	2p16, 3q21–q24, 11q22.3, Xp21–p11.4
Suggestive linkage	1cen, 5cen, 7p21–p15, 12p13–p12, 17q22, 22q13	7q21–q22	5p (D5S406)
Stage 2 screen	108 ASP 6 regions of suggestive linkage tested	23 families including 45 ASP; data reported only for 6p21	(a) 44 ASP (b) 78 ASP Tested for 5p and 6p21
Overall result	MLS 2.8 for 6p21 MLS 2.7 for 17q22	MLS 3.6 for 6p21	MLS 0.65 for 6p21 MLS 1.6 for 5p

* The US–French study used three different statistical tests; loci in the 'MLS >1' row passed two tests and those shown as 'suggestive' passed all three tests. See text for details.