

*IBS Methods for  
Affected Pairs Linkage*

**Biostatistics 666**

**Lecture 14**

## Genetic Mapping

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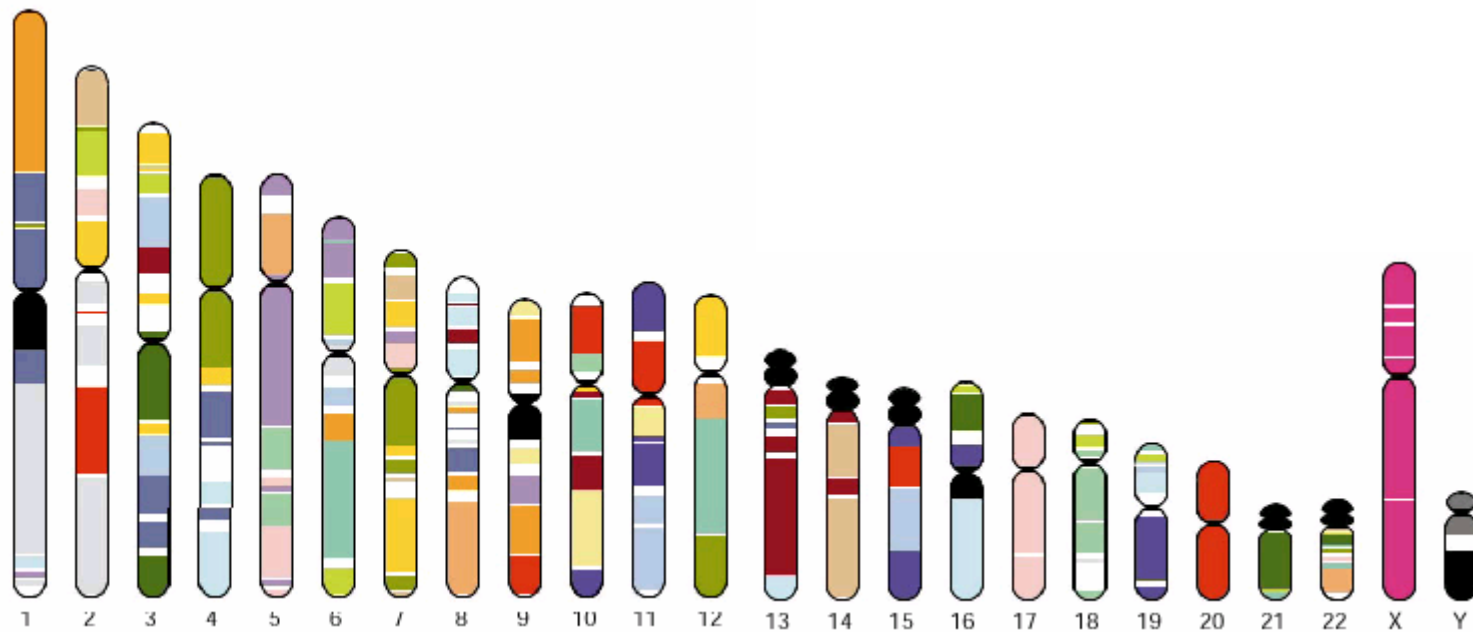
“Compares the inheritance pattern of a trait with the inheritance pattern of chromosomal regions”

## Positional Cloning

“Allows one to find where a gene is, without knowing what it is.”

Where are the genes influencing  
a particular trait?

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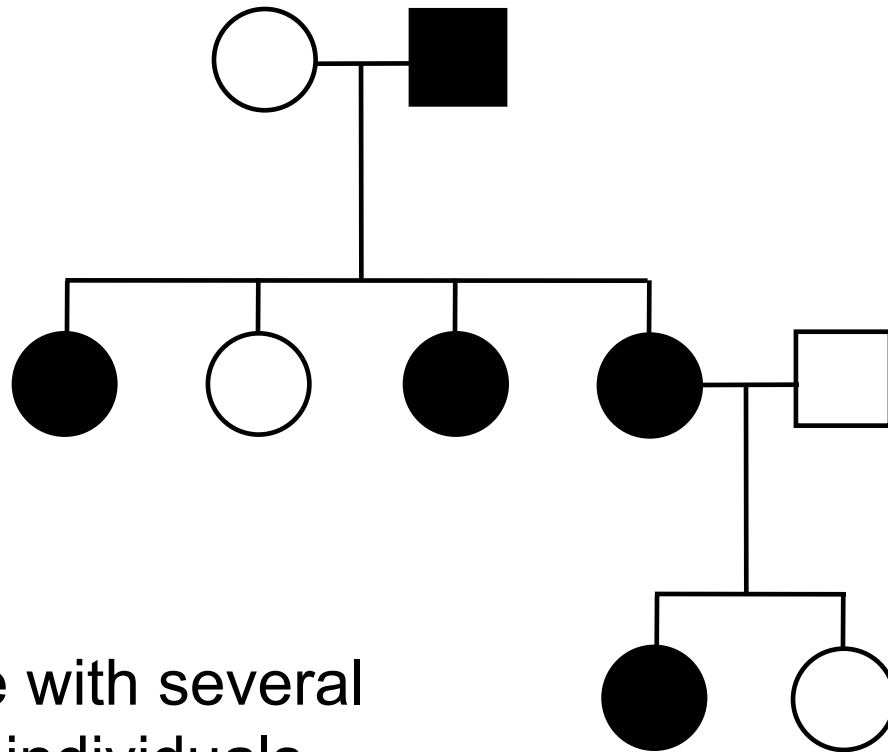
# Intuition for Linkage Analysis

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- Millions of variations could potentially be involved
  - Costly to investigate each individually
- Within families, variation is organized into a limited number of haplotypes
  - Sample modest number of markers to determine whether each stretch of chromosome is shared

# Tracing Chromosomes

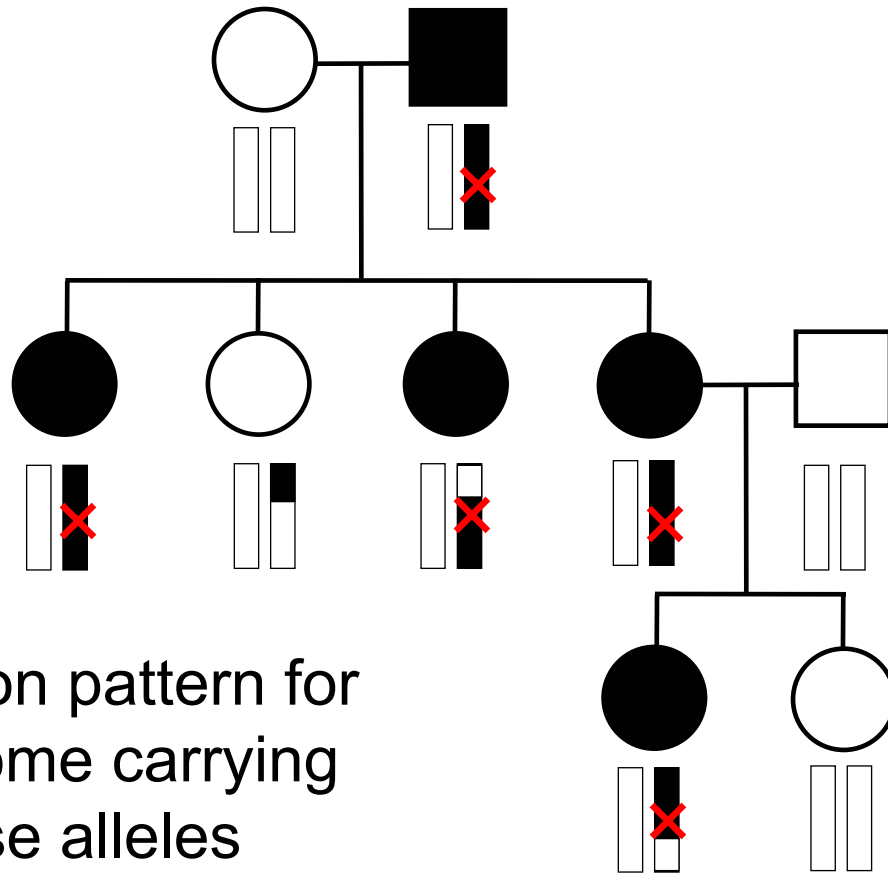
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A pedigree with several affected individuals

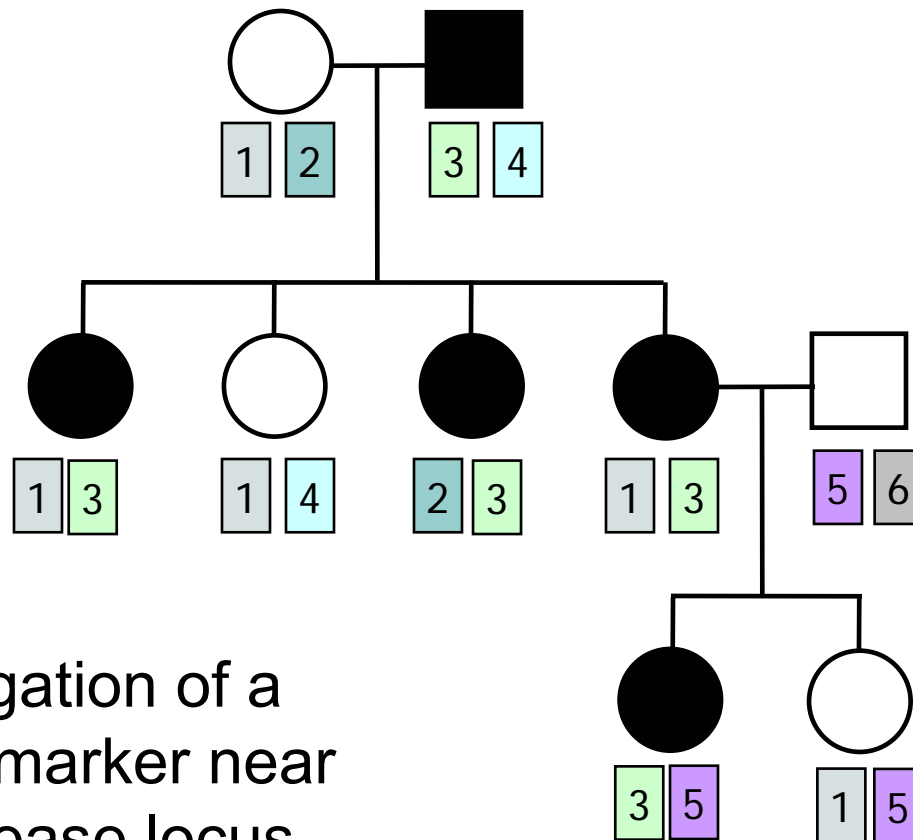
# Tracing Chromosomes

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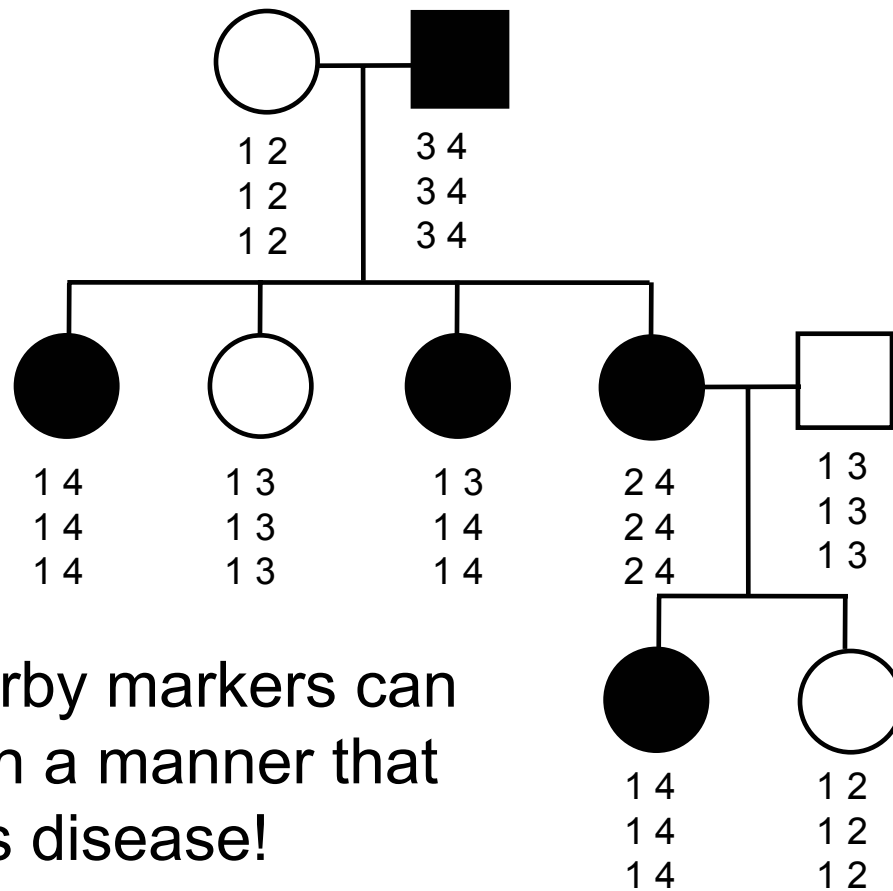
Segregation pattern for  
chromosome carrying  
disease alleles

# Tracing Chromosomes



Segregation of a  
specific marker near  
the disease locus

# Tracing Chromosomes



Multiple nearby markers can segregate in a manner that tracks disease!



## Today ...

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- Linkage analysis with sibling pairs
  - Identity-by-State (IBS) based method
- Find markers that are near disease locus
  - Near means recombination fraction  $\theta < \frac{1}{2}$
- Minimalist approach ...

## Reference for Today...

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- Power of IBS Methods for Linkage Analysis
- Bishop DT and Williamson JA (1990)  
*Am J Hum Genet* **46**:254-265
- Recommended Reading

# Bishop and Williamson (1990)

## Opening Line

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"The availability of a large number of DNA markers has made possible mapping projects with the certainty that if:

- (a) a major gene exists for a trait;
- (b) the trait is reasonably homogeneous;
- (c) there is sufficient family material available;

then a linked marker can be found."

# Data for a Linkage Study

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- Pedigree
  - Set of individuals of known relationship
- Observed marker genotypes
  - SNPs, VNTRs, microsatellites
- Phenotype data for individuals

# Minimalist Approach

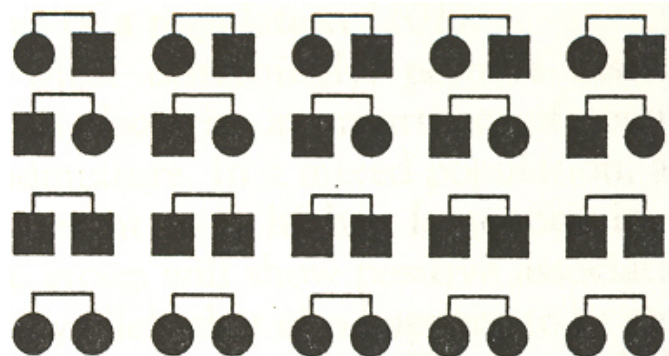
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- Pedigree
  - Two individuals of known relationship
- Observed Marker Genotypes
  - A single marker
- Phenotypes
  - Both individuals are affected

# Allele Sharing Analysis

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- Reject random sharing at a particular region
- Less powerful than classic methods
  - When disease model is known
- More robust than classic methods
  - When disease model is unknown



## Consider Autosomal Recessive Locus ...

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- For a collection of sibling pairs...
- What patterns of sharing do you expect at the disease locus?
- What patterns of sharing do you expect as you move away from the disease locus?

# Historical References

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- Penrose (1953) suggested comparing IBD distributions for affected siblings.
  - Possible for highly informative markers (eg. HLA)
- Thomson (1986) suggested discarding partially informative families.
- Lange (1986) proposed using IBS information instead of IBD.



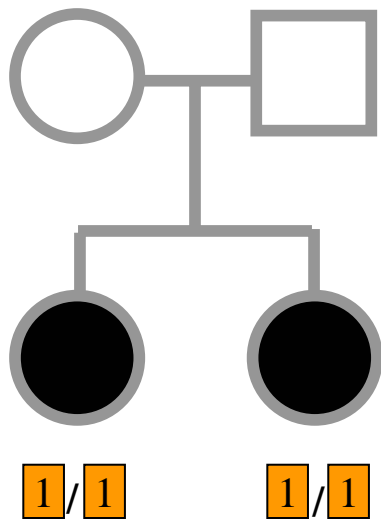
## IBS Based Methods

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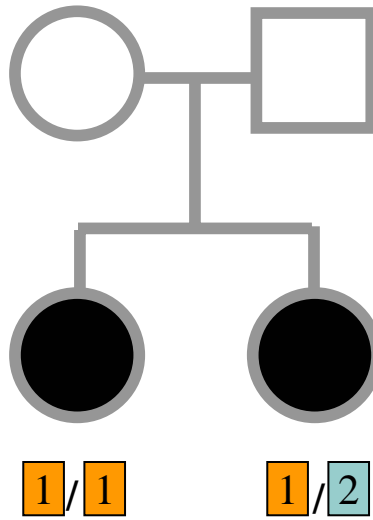
- Sample of affected relative pairs
- Examine a marker of interest
- Count alleles shared for each pair
  - This includes both ...
  - Chromosomes that are identical-by-descent
  - Chromosomes that simply carry identical alleles

# Examples of IBS States

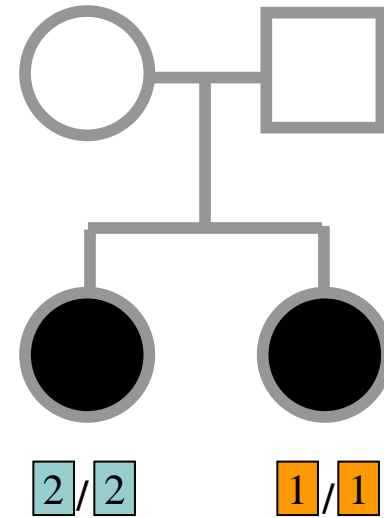
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IBS = 2



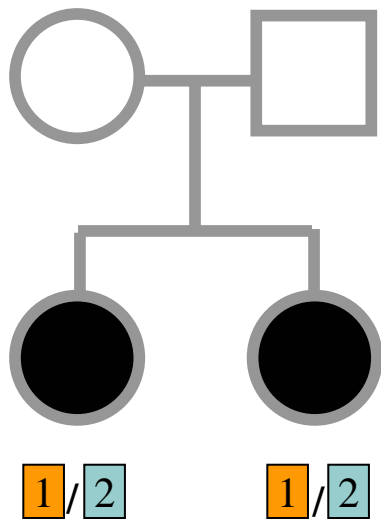
IBS = 1



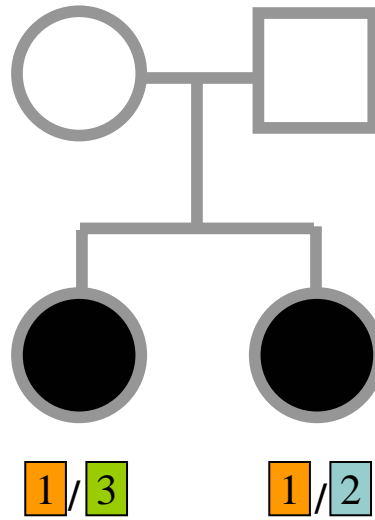
IBS = 0

# Examples of IBS States

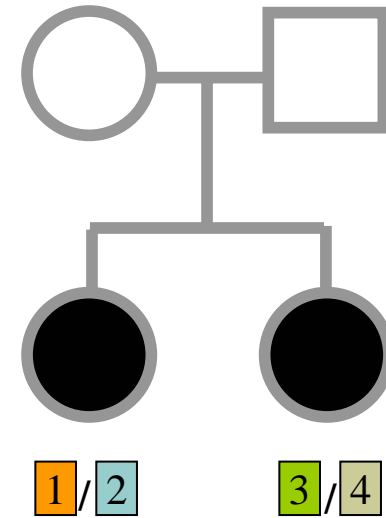
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**IBS = 2**



**IBS = 1**



**IBS = 0**

## Evidence for Linkage

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- Increased similarity in affected pairs
- Compared to:
  - Unselected pairs
  - Unaffected pairs
  - Discordant pairs
  - Expectations derived from allele frequencies

# Test for Independence

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$$\chi^2_{2df} = \sum_i \frac{[N_{IBS=i} - E(N_{IBS=i})]^2}{E(N_{IBS=i})} \quad \text{(general test, for sibling pairs)}$$

$$\chi^2_{1df} = \frac{[N_{IBS=0} - E(N_{IBS=0})]^2}{E(N_{IBS=0})} + \frac{[N_{IBS>0} - E(N_{IBS>0})]^2}{E(N_{IBS>0})} \quad \text{(grouping often preferable for other relatives)}$$

- Assuming all counts are relatively large
- If counts are small, use binomial or trinomial distribution

# Modeling IBS Sharing

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- For any relative pair, calculate:
  - Probability of IBD sharing
    - 0, 1 or 2 alleles
  - Conditional probability of IBS sharing
    - 0, 1, 2 alleles
  - IBS sharing  $\geq$  IBD sharing
    - Why?

# IBD

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- The underlying sharing of chromosomes segregating within a family
- Siblings share 0, 1 or 2 alleles
  - Probabilities  $\frac{1}{4}$ ,  $\frac{1}{2}$  and  $\frac{1}{4}$
- Unilineal relatives share 0 or 1 alleles
  - Probability of sharing is kinship coefficient  $\phi * 4$

# P(Marker Genotype|IBD State)

Relative		IBD		
I	II	0	1	2
(a,b)	(c,d)	$4p_a p_b p_c p_d$	0	0
(a,a)	(b,c)	$2p_a^2 p_b p_c$	0	0
(a,a)	(b,b)	$p_a^2 p_b^2$	0	0
(a,b)	(a,c)	$4p_a^2 p_b p_c$	$p_a p_b p_c$	0
(a,a)	(a,b)	$2p_a^3 p_b$	$p_a^2 p_b$	0
(a,b)	(a,b)	$4p_a^2 p_b^2$	$(p_a p_b^2 + p_a^2 p_b)$	$2p_a p_b$
(a,a)	(a,a)	$p_a^4$	$p_a^3$	$p_a^2$
Prior Probability		$1/4$	$1/2$	$1/4$

Note: Assuming alleles unordered within genotypes



## $P(\text{IBS} = i \mid \text{IBD} = j)$

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$$P(\text{IBS} = 2 \mid \text{IBD} = 0) = 2 \sum_{i \neq j} p_i^2 p_j^2 + \sum_i p_i^4$$

$$P(\text{IBS} = 1 \mid \text{IBD} = 0) = 4 \sum_{i \neq j} p_i^2 p_j (1 - p_i - p_j) + 4 \sum_i p_i^3 (1 - p_i)$$

$$P(\text{IBS} = 0 \mid \text{IBD} = 0) = \sum_{i \neq j} p_i p_j (1 - p_i - p_j)^2 + \sum_i p_i^2 (1 - p_i)^2$$

$$P(\text{IBS} = i \mid \text{IBD} = j)$$

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$$P(\text{IBS} = 2 \mid \text{IBD} = 2) = 1$$

$$P(\text{IBS} = 1 \mid \text{IBD} = 2) = 0$$

$$P(\text{IBS} = 0 \mid \text{IBD} = 2) = 0$$

$$P(\text{IBS} = 2 \mid \text{IBD} = 1) = \sum_i p_i^2$$

$$P(\text{IBS} = 1 \mid \text{IBD} = 1) = \sum_{i \neq j} p_i p_j$$

$$P(\text{IBS} = 0 \mid \text{IBD} = 1) = 0$$

Example,  
Assuming Equal Allele Frequencies

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	P(IBS=0)	P(IBS=1)	P(IBS=2)
2 alleles, IBD=0	.125	.500	.375
2 alleles, IBD=1	.000	.500	.500
3 alleles, IBD=0	.222	.592	.185
3 alleles, IBD=1	.000	.666	.333

## Inference from Example

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- IBS approaches IBD as number of alleles increases
- If linkage is being tested with chi-square test, how does the number of alleles (and marker informativeness) affect these two tests:
  - A test of whether  $N_{IBS \geq 1}$  increases?
  - A test of whether  $N_{IBS > 1}$  increases?

## IBS Probabilities

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No. of Alleles	P(IBS=0)	P(IBS=1)	P(IBS=2)
2	.03	.37	.60
3	.05	.48	.47
4	.08	.51	.40
20	.21	.52	.27
$\infty$	.25	.50	.25

Sibling IBS as a function of allele count, for marker with equally frequent alleles

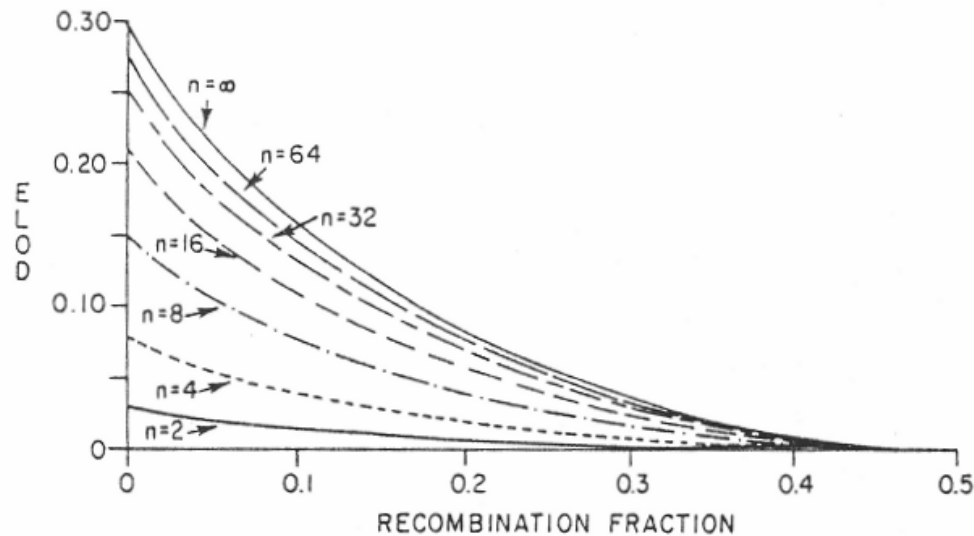
## Results of Bishop and Williamson (1990)

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- Effect size,  $P(\text{IBS} \mid \text{Affected pair})$
- Number of alleles at marker
- Different relationships
- Recombination fraction

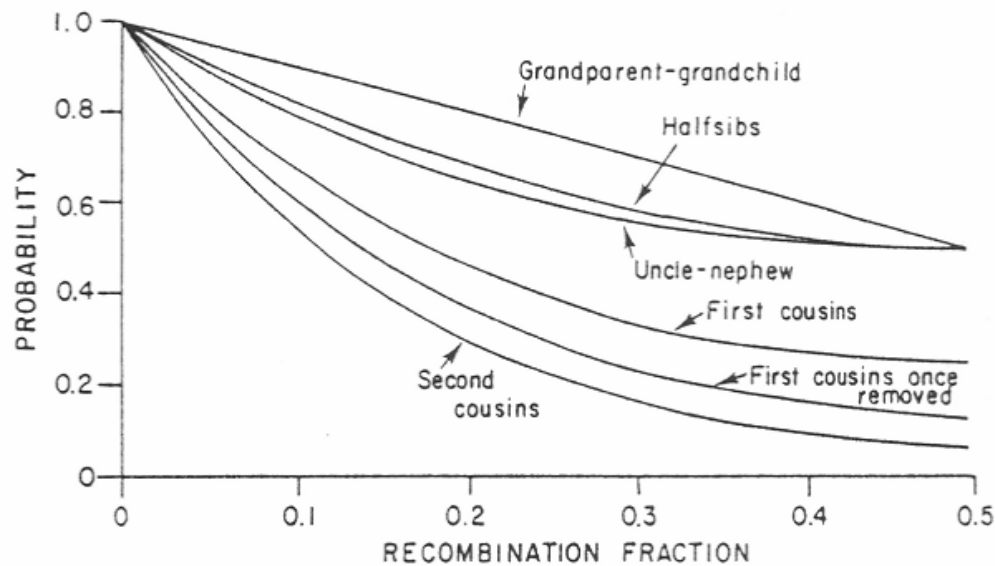
# More Alleles Increase Power

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**Figure 3** Variation in ELOD as a function of  $n$ , the number of alleles at the marker locus. All alleles are assumed to have frequency  $1/n$ . This calculation is performed for the grandparent-grandchild relationship with a rare trait allele frequency.

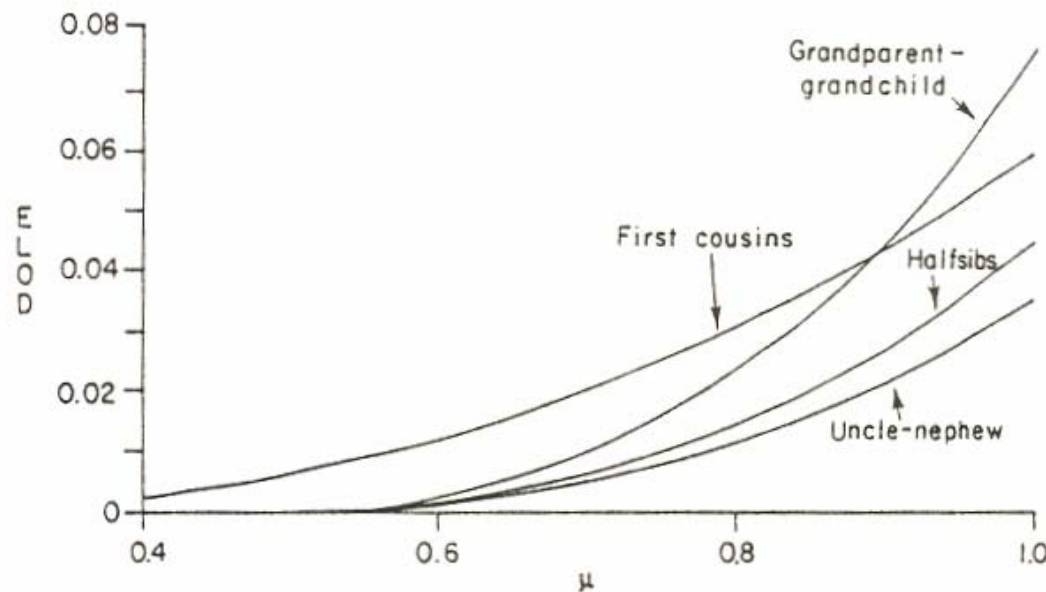
# Effect of Recombination Varies According to Relationship



**Figure 2** Probability of i.b.d. at a second linked locus conditional on i.b.d. at an index locus, as a function of the recombination fraction  $r$  between the loci, for specific genetic relationships. This function is  $d_{11}(r)$  in the notation of table 1.



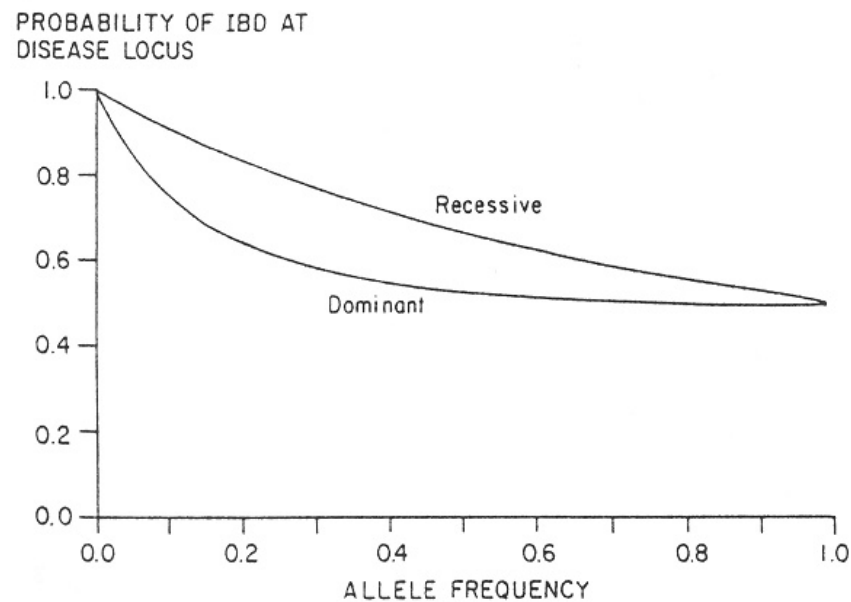
# Power vs. $P(\text{IBS} \mid \text{Affected Pair})$



**Figure 4** ELOD as a function of  $\mu$  for an eight-allele marker system for a range of relationships. The recombination fraction between the trait and marker locus is .1.

# With no phenocopies, rare alleles are easier to map

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**Figure 1** Probability of i.b.d. at a trait locus for two affected related individuals, as a function of the mode of inheritance of the trait. This figure is computed for the relationships with  $\phi = .125$ .

# In general, phenocopies decrease power

**Table 2**

**Average Informativeness for Mapping a Partially Penetrant Dominant Trait with Phenocopies**

$p$ and $x$	$\mu^a$	Phenocopy Rate	Relative Information Content (%)
<b>.01:</b>			
.000 . . . .	.96	.00	100
.001 . . . .	.96	.05	98
.01 . . . . .	.92	.33	81
.02 . . . . .	.88	.50	61
.05 . . . . .	.74	.71	23
.10 . . . . .	.61	.83	5
<b>.10:</b>			
.000 . . . .	.75	.00	100
.001 . . . .	.75	.00	99
.01 . . . . .	.74	.04	89
.02 . . . . .	.73	.08	80
.05 . . . . .	.69	.18	56
.10 . . . . .	.64	.30	31

NOTE.—The recombination fraction is .1, and the marker system has eight equally frequent alleles.

<sup>a</sup> For a grandparent-grandchild affected pair.

## Shortcomings of IBS Method

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- All sharing is weighted equally
  - Sharing a rare allele
  - Sharing a common allele
  - Sharing homozygous genotype
  - Sharing heterozygous genotype
- Inefficient.

## Recommended Reading

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- Bishop DT and Williamson JA (1990)  
*Am J Hum Genet* **46**:254-265
- Good introduction to linkage analysis in affected relative pairs, discusses
  - Marker choice
  - Recombination fraction
  - Disease model
  - Type of relative pair