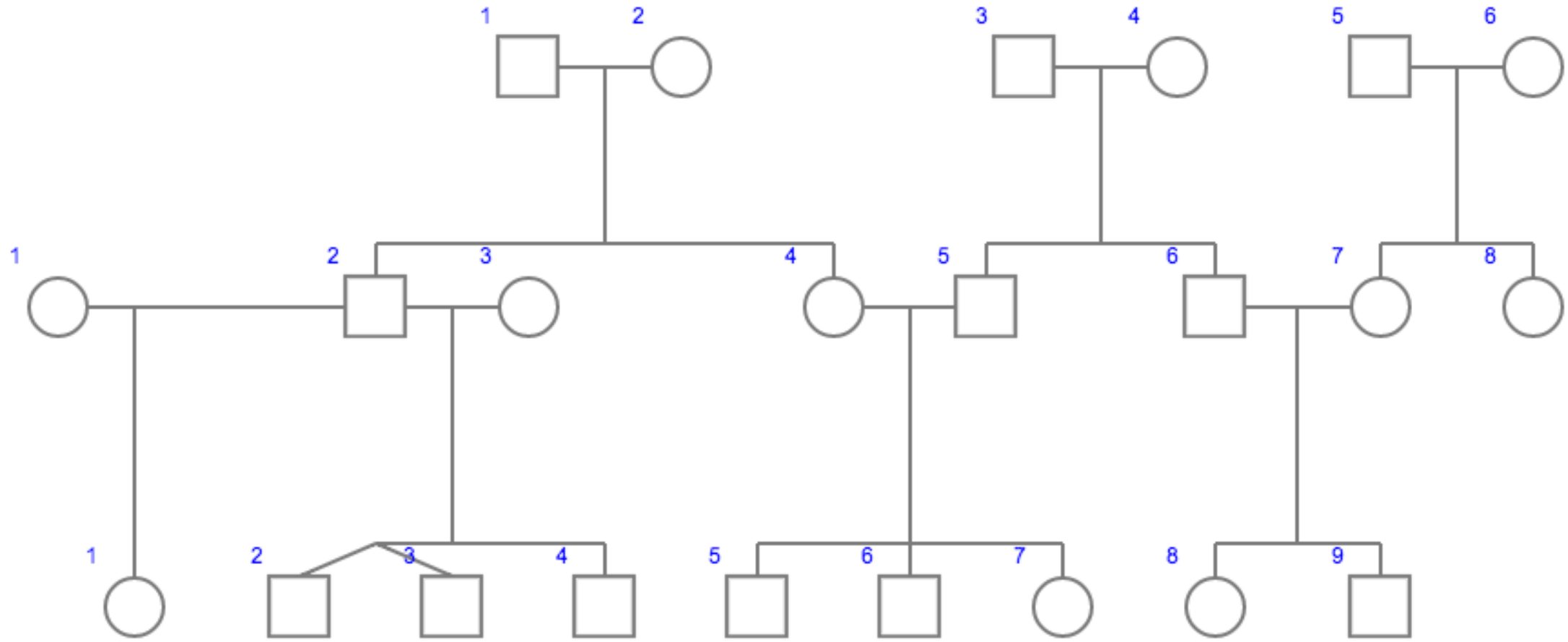
Bio393: Genetic Analysis

Linkage mapping in families



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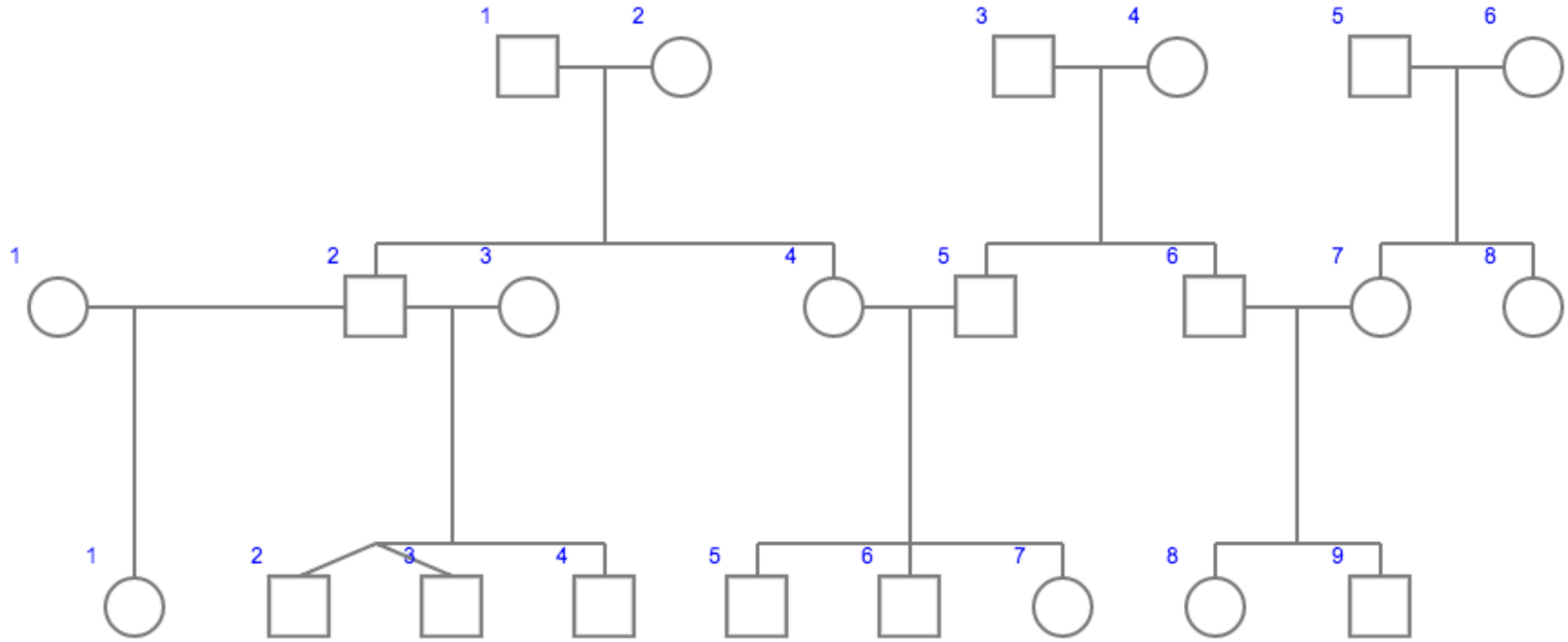


Dominant human disorders are caused mostly by haploinsufficient loci

Changes to syllabus

Friday, May 22 - Review PS#3, Quiz#4

Monday, May 25 - NO CLASS, PS#4 goes out

Wednesday, May 27 - Linkage disequilibrium and population structure

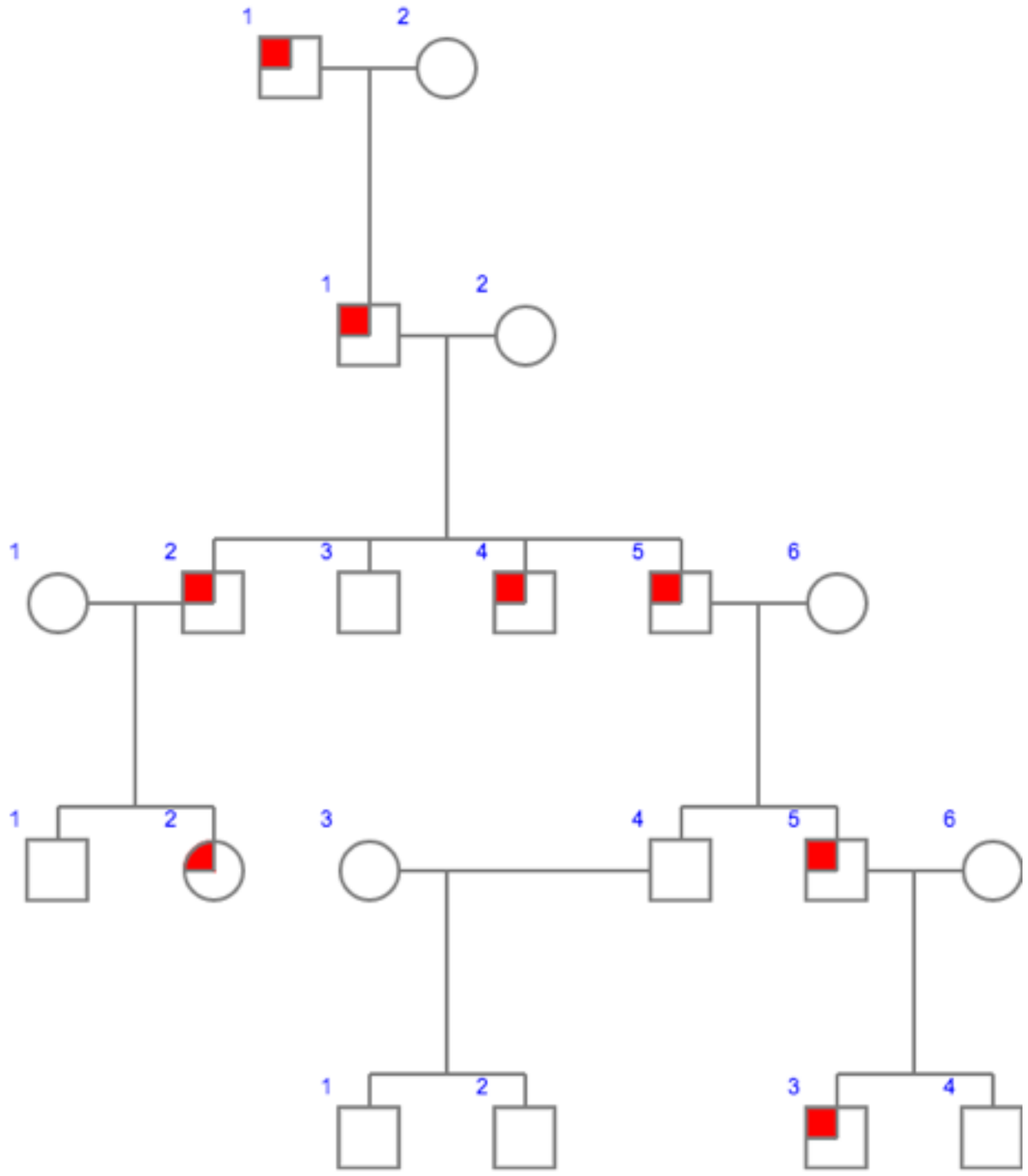
Friday, May 29 - Complex traits and GWAS, Quiz make-up

Monday, June 1 - PS#4

Wednesday, June 3 - review questions?

Wednesday, June 10, Final 3-5 PM

The goal of linkage analysis is to identify a marker nearby the disease-causing allele



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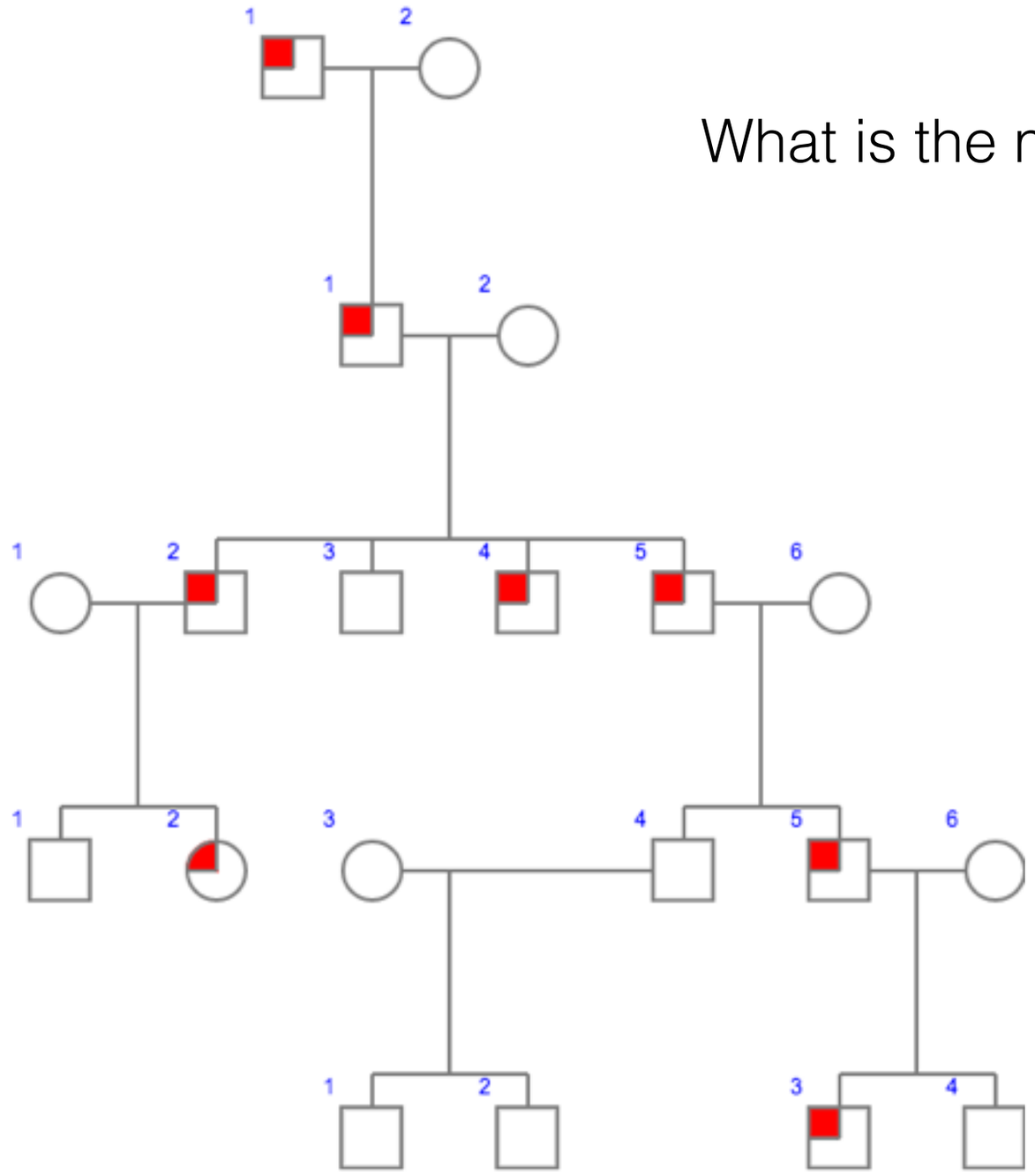
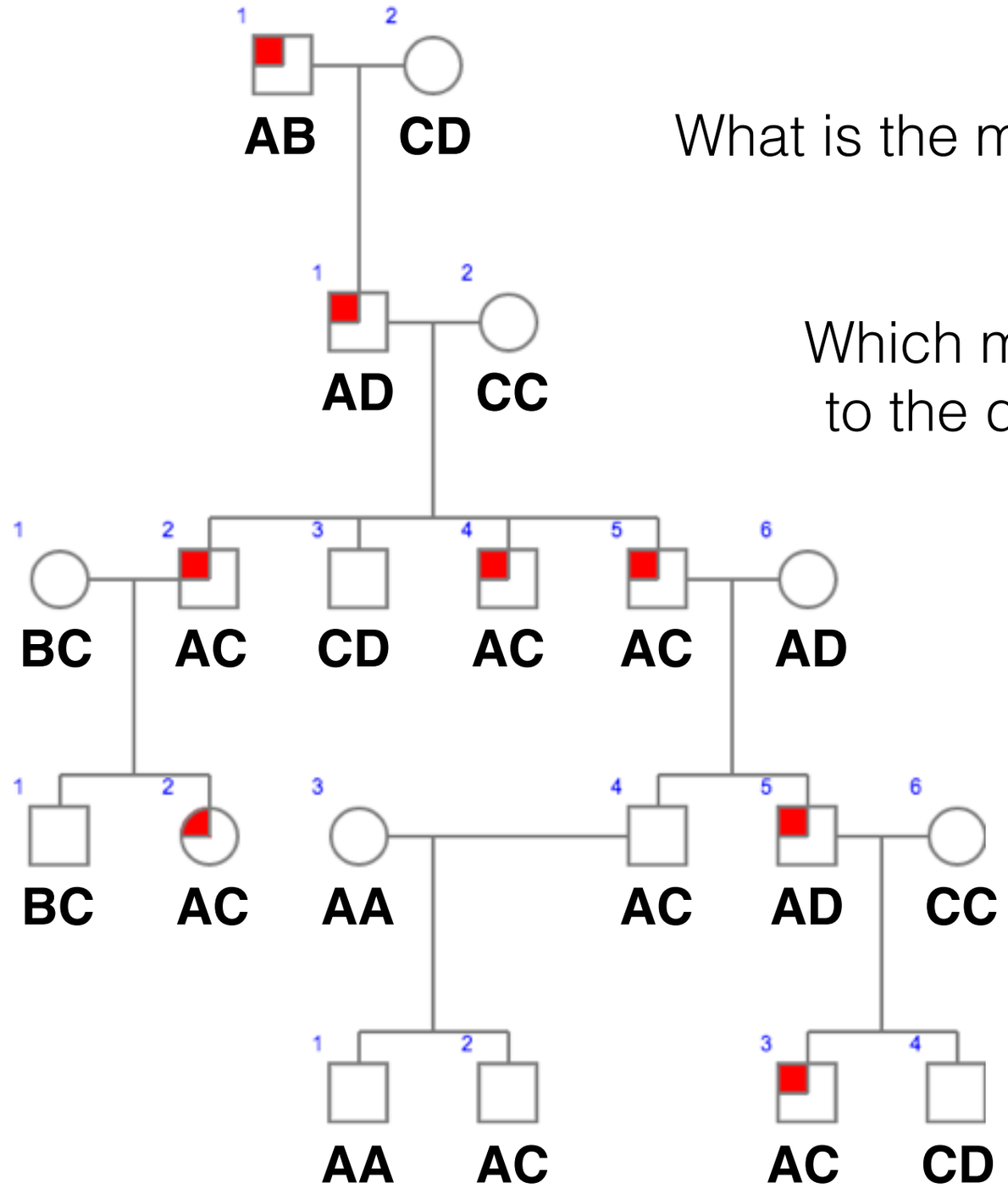


What is the mode of inheritance?

The goal of linkage analysis is to identify a marker nearby the disease-causing allele



What is the mode of inheritance?

Which marker is linked to the disease allele?

Linkage is reported as a log of the odds ratio or LOD

The odds ratio is a statistical method to measure association of some attribute with the presence or absence of another attribute.

Probability of pedigree under linkage versus no linkage

$$\text{LOD} = \log_{10} \frac{\text{P(pedigree with linkage)}}{\text{P(pedigree with no linkage)}}$$

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Probability of pedigree under linkage versus no linkage

$$\text{LOD} = \log_{10} \frac{\text{P(pedigree with linkage)}}{\text{P(pedigree with no linkage)}}$$

LOD > 3 is good evidence of linkage
1 in 1,000 chance of data by chance

LOD < 0 means data are more likely by chance

How linked is our marker to the disease-causing allele? Recombination frequency

Recombination frequency is written as θ

Percentage of recombinant gametes passed down

θ = 0 is perfect linkage

θ = 0.5 is no linkage

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Probability of pedigree under linkage versus no linkage

$$\text{LOD} = \log_{10} \frac{\text{P(pedigree with linkage)}}{\text{P(pedigree with no linkage)}}$$

$$\text{LOD} = \log_{10} \frac{\text{P(data} \mid \theta)}{\text{P(data} \mid \theta = 0.5)}$$

P(data) = probability that a particular gamete was inherited

Linkage is reported as a log of the odds ratio or LOD

$$LOD = \log_{10} \frac{P(data \mid \theta)}{P(data \mid \theta = 0.5)}$$

P(data) = probability that a particular gamete was inherited

$P(data \mid \theta)$ =

Probability that recombination did not occur for parental 1 - θ

Probability that recombination did occur for recombinant θ

Probability that recombinant or parental gamete passed down ½

Probability of phase of parent

Each individual is independent.
Use product rule to multiply probabilities.

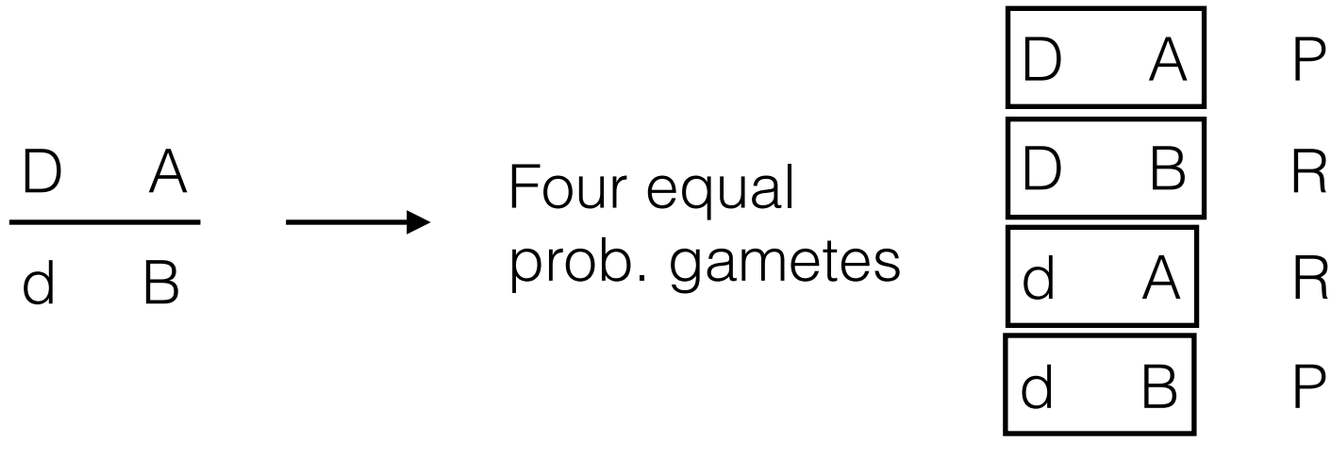
Linkage is reported as a log of the odds ratio or LOD

$$LOD = \log_{10} \frac{P(data \mid \theta)}{P(data \mid \theta = 0.5)}$$

P(data) = probability that a particular gamete was inherited

$$P(data \mid \theta = 0.5)$$

Equal probability of two loci independently assorting and one gamete being passed down



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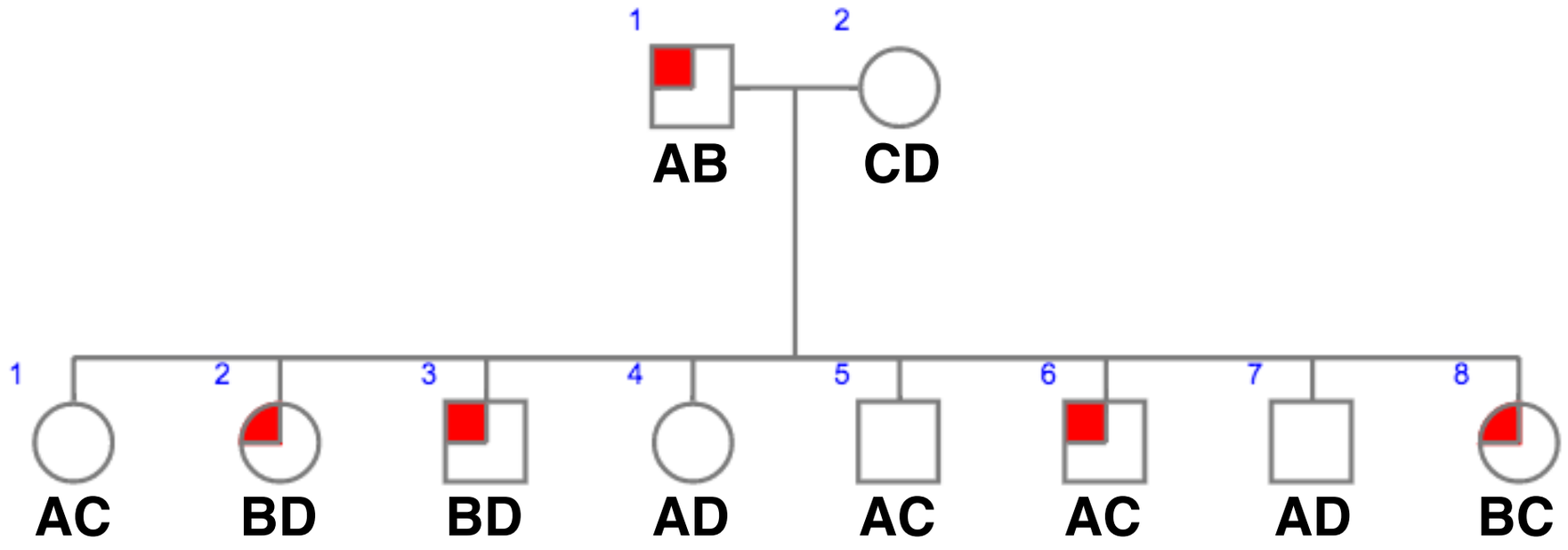
$$LOD = \log_{10} \frac{P(data \mid \theta)}{P(data \mid \theta = 0.5)}$$

P(data) = probability that a particular gamete was inherited

$$LOD = \log_{10} \frac{\frac{1}{2}(1 - \theta)^{NR} \times \theta^{R}}{\frac{1}{2}\, 0.5^{(NR + R)}}$$

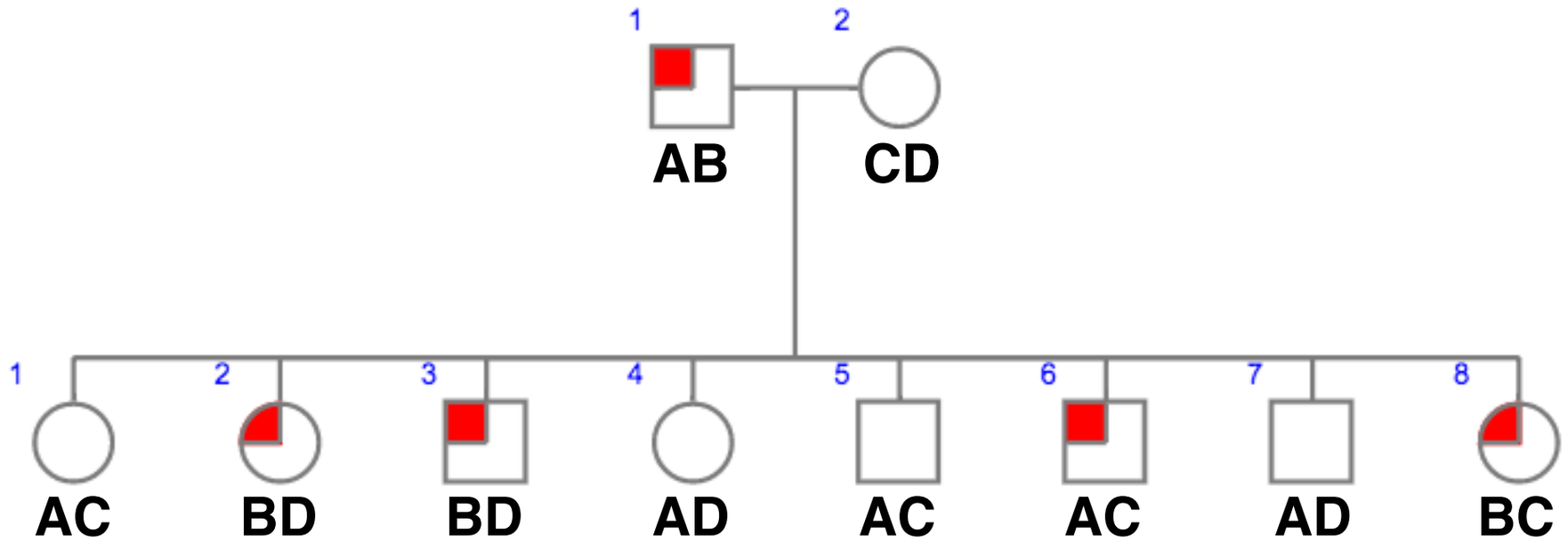
This equation for when we know phase.

Linkage is reported as a log of the odds ratio or LOD



Do we know the phase of I-1?

Linkage is reported as a log of the odds ratio or LOD

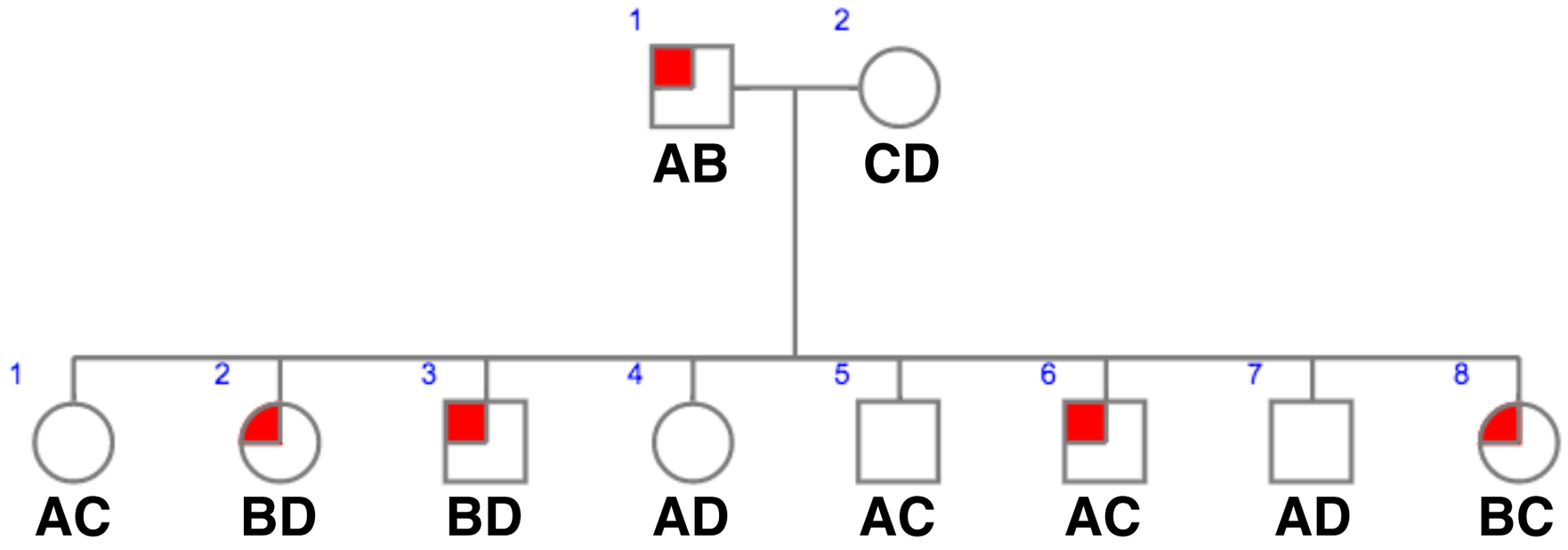


Do we know the phase of I-1?

NO

Every child has an equal chance of being a recombinant or parental

Linkage is reported as a log of the odds ratio or LOD



Do we know the phase of I-1?

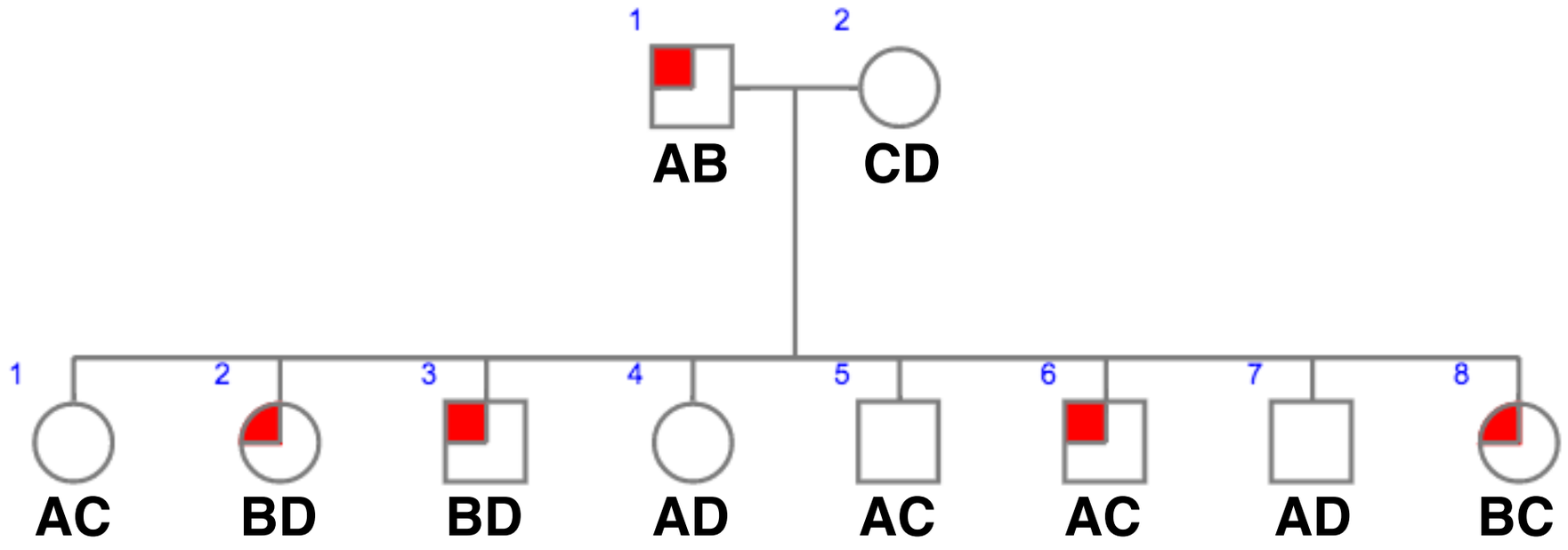
NO

Every child has an equal chance of being a recombinant or parental

Difference between being informative and knowing phase

Informative = Parent heterozygous at each of two loci

Linkage is reported as a log of the odds ratio or LOD



With unknown phase of parent, the LOD equation is…

$$LOD = \log_{10} \frac{\frac{1}{2}((1 - \theta)^{NR} \times \theta^{R}) + \frac{1}{2}((1 - \theta)^{NR} \times \theta^{R})}{\frac{1}{2}(0.5^{(NR + R)})}$$

½ chance for each phase

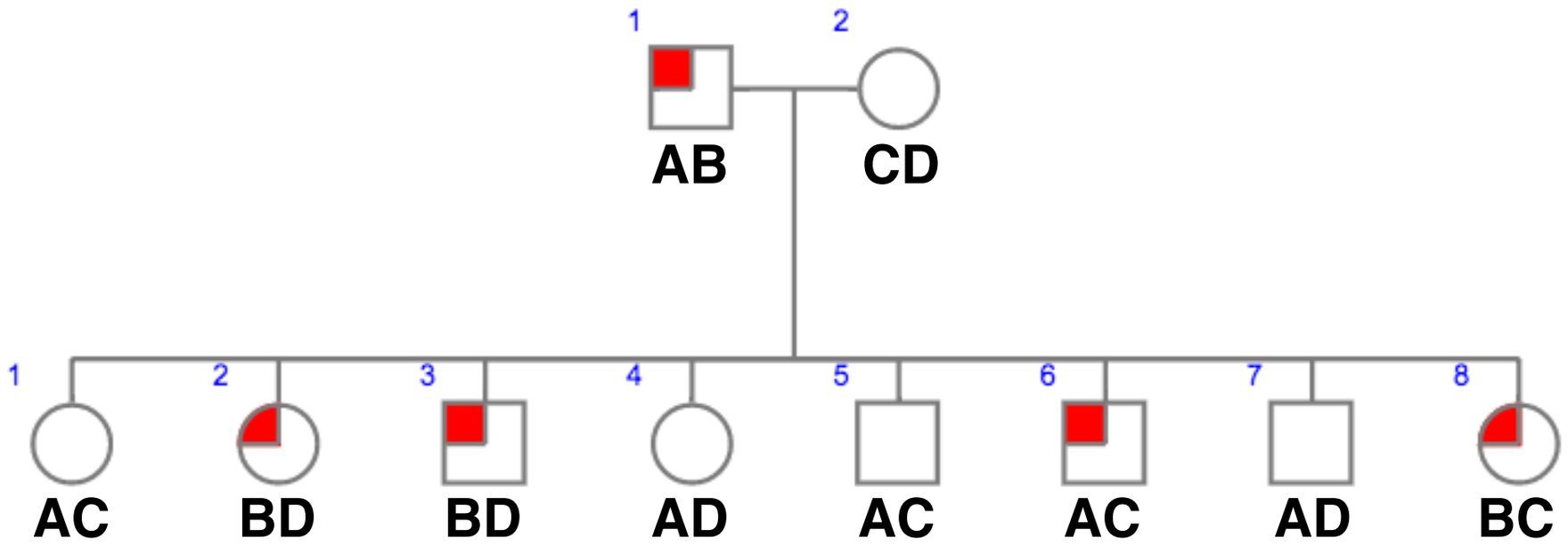
Phase 1

$$\frac{D \quad B}{d \quad A}$$

Phase 2

$$\frac{D \quad A}{d \quad B}$$

Linkage is reported as a log of the odds ratio or LOD



Phase 1	P	P	P	P	P	R	P	P

$$LOD = \log_{10} \frac{\frac{1}{2}((1 - \theta)^{NR} \times \theta^{R}) + \frac{1}{2}((1 - \theta)^{NR} \times \theta^{R})}{\frac{1}{2}(0.5^{(NR + R)})}$$

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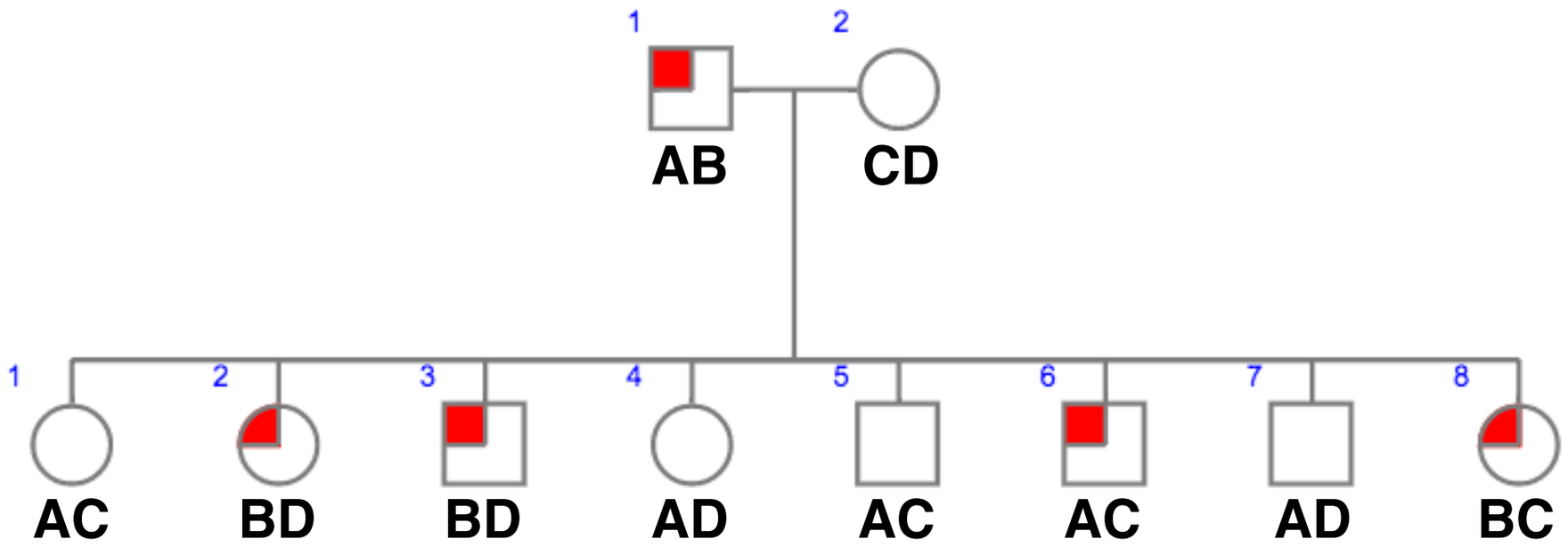


Phase 1	P	P	P	P	P	R	P	P

$$LOD = \log_{10} \frac{\frac{1}{2}((1-\theta)^{7} \times \theta^{1}) + \frac{1}{2}((1-\theta)^{NR} \times \theta^{R})}{\frac{1}{2}(0.5^{(8)})}$$

½ chance for each phase

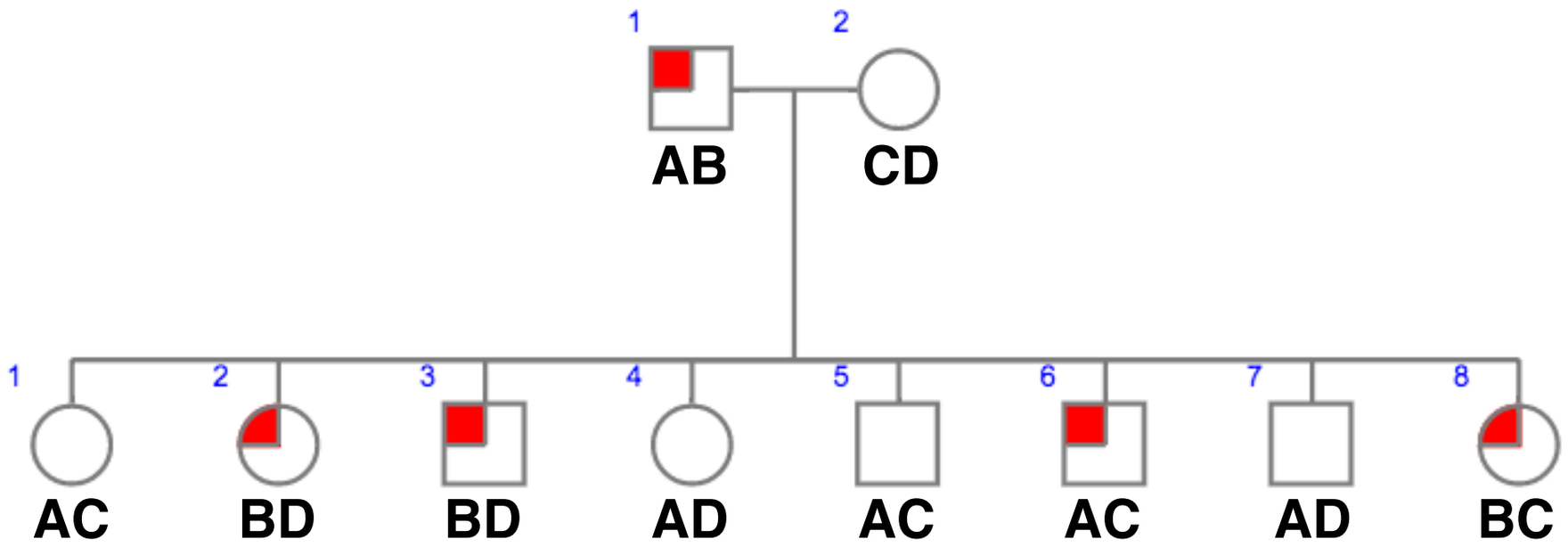
Phase 1

$$\frac{D \quad B}{d \quad A}$$

Phase 2

$$\frac{D \quad A}{d \quad B}$$

Linkage is reported as a log of the odds ratio or LOD



Phase 2	R	R	R	R	R	P	R	R

$$LOD = \log_{10} \frac{\frac{1}{2}((1-\theta)^7 \times \theta^1) + \frac{1}{2}((1-\theta)^1 \times \theta^7)}{\frac{1}{2}(0.5^{(8)})}$$

½ chance for each phase

Phase 1

$$\frac{D \quad B}{d \quad A}$$

Phase 2

$$\frac{D \quad A}{d \quad B}$$

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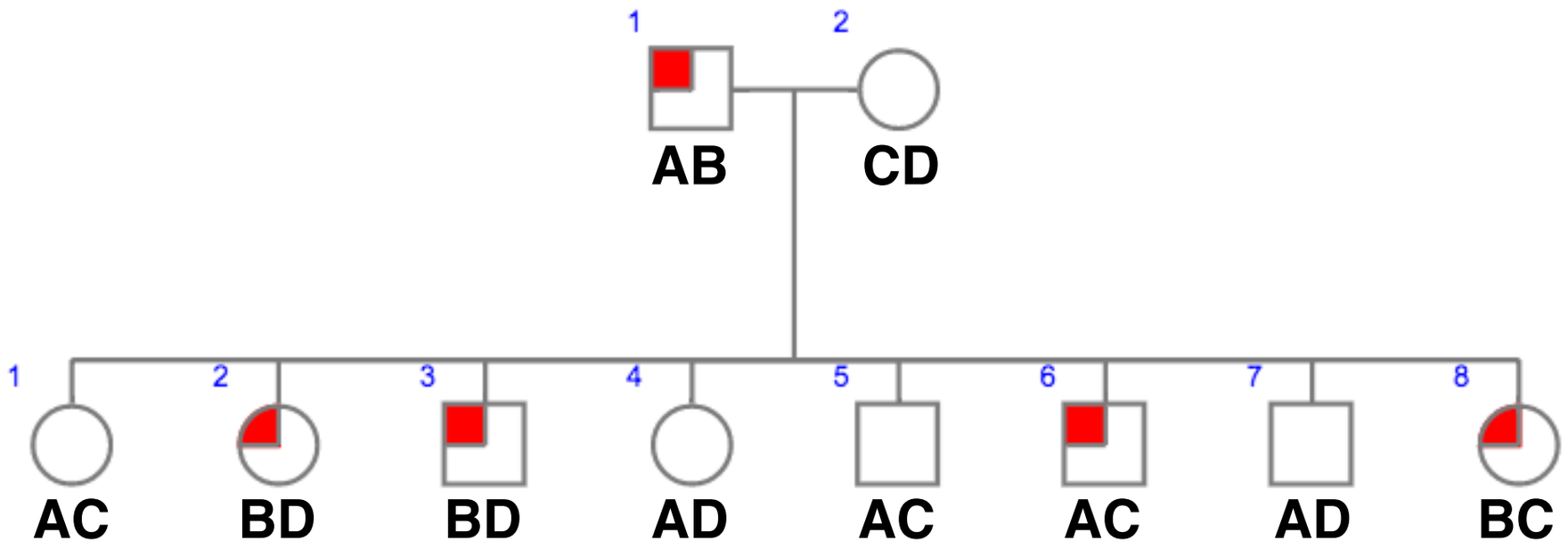


Phase 2	R	R	R	R	R	P	R	R

$$LOD = \log_{10} \frac{½((1 - 0.125)^7 \times 0.125^1) + ½((1 - 0.125)^1 \times 0.125^7)}{½(0.5^{(8)})}$$

½ chance for each phase

$\theta = 0.125$

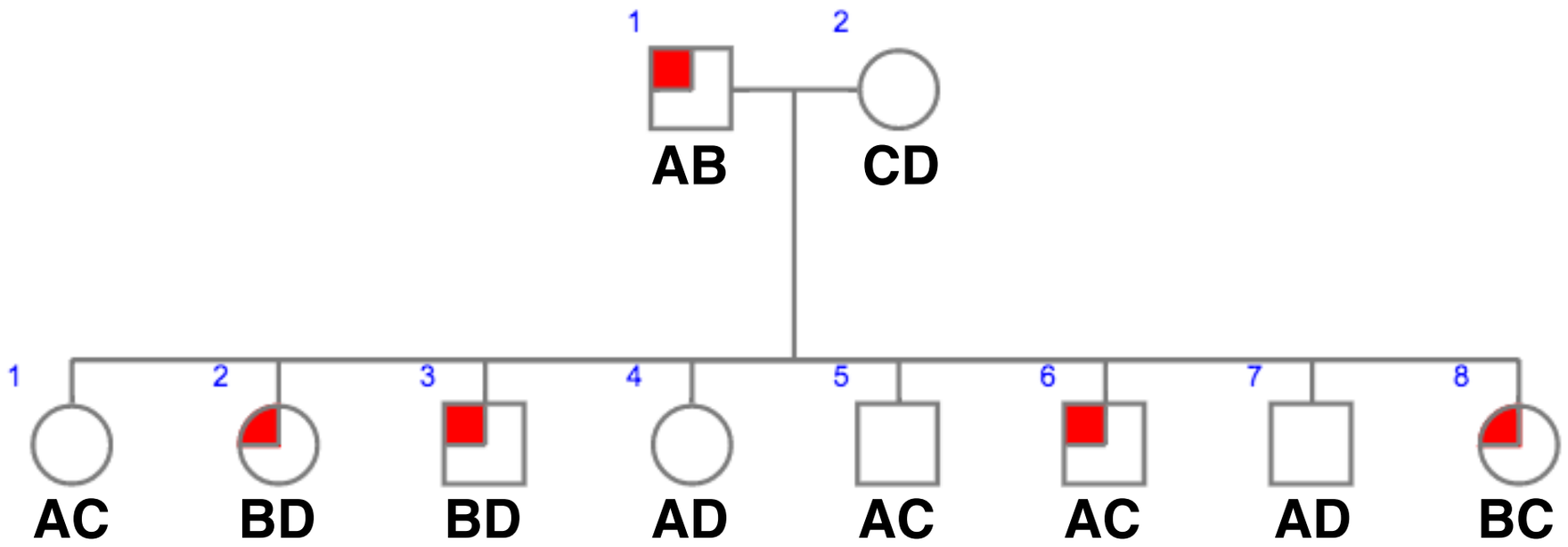
Phase 1

$$\frac{D \quad B}{d \quad A}$$

Phase 2

$$\frac{D \quad A}{d \quad B}$$

Linkage is reported as a log of the odds ratio or LOD



Phase 2	R	R	R	R	R	P	R	R

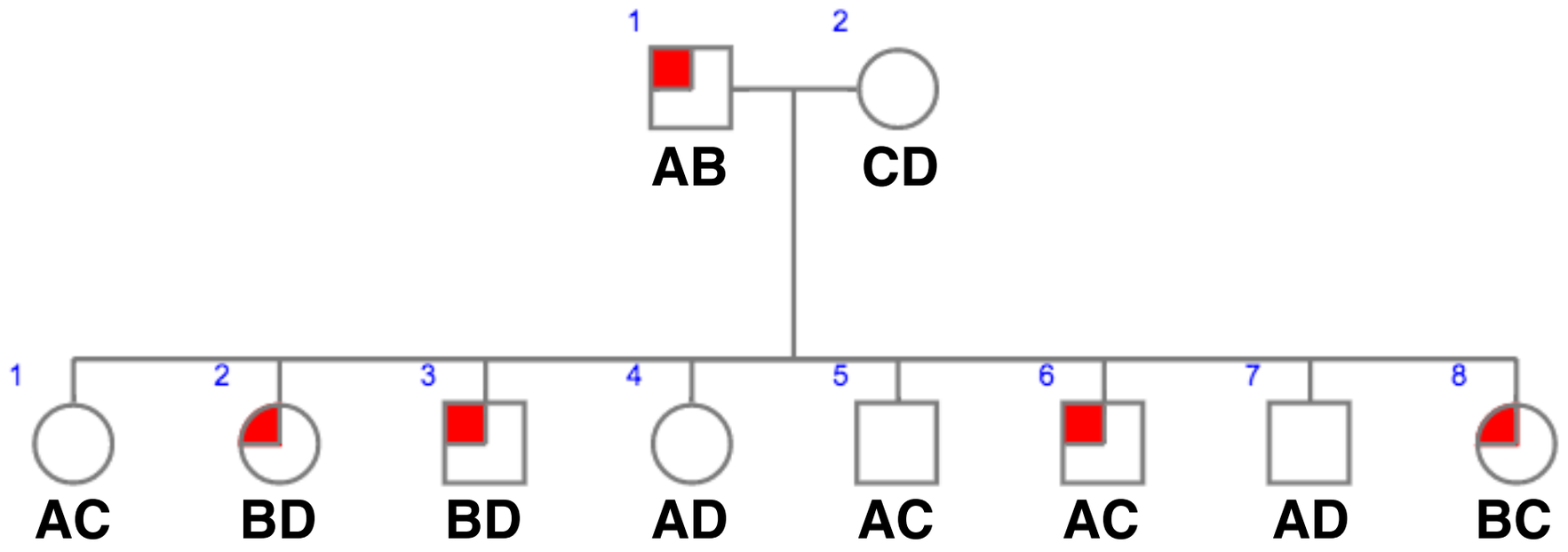
LOD = 0.79 $\theta = 0.125$

Some properties of LOD scores

LOD scores from independent families can be added
(product rule with logarithms)

Determining phase increases the LOD score

What happens when we know phase?



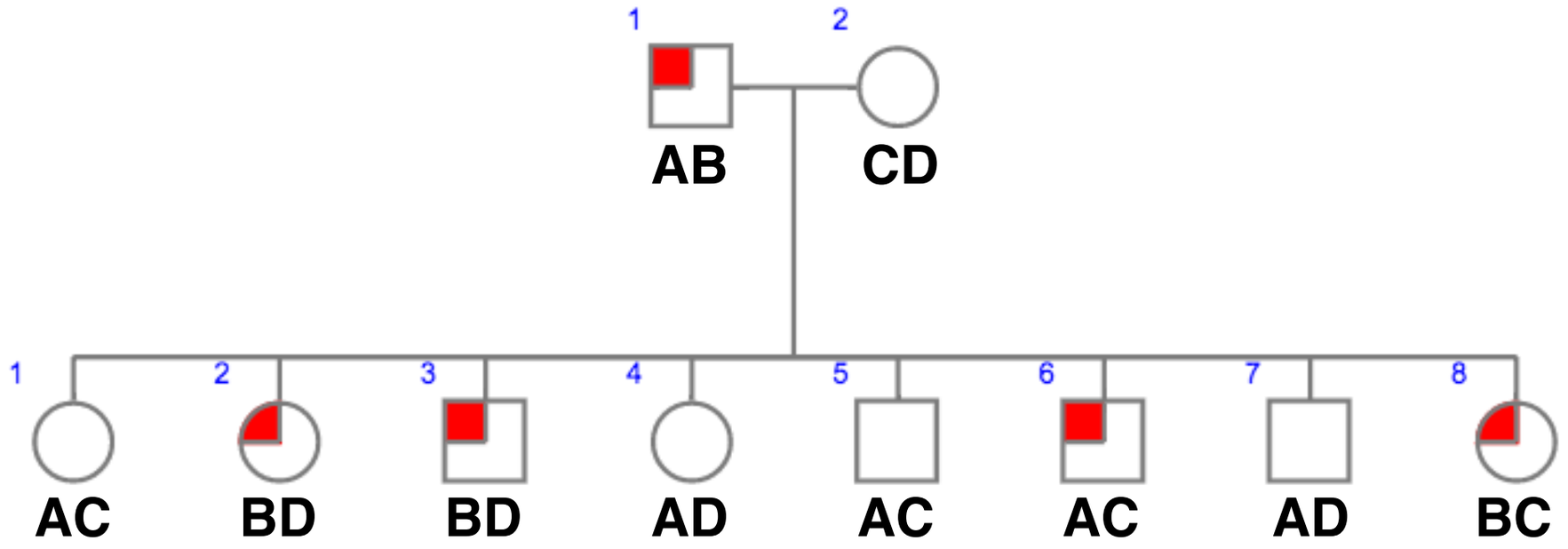
Phase 1	P	P	P	P	P	R	P	P

The paternal grandmother had the disease and her genotype was BD. Her husband's genotype was AA and he was not affected

$$LOD = \log_{10} \frac{½\,(1 - \theta)^{NR} \times \theta^{R}}{½\,0.5^{(NR + R)}}$$

½ chance for each phase and second phase probability go away!

What happens when we know phase?

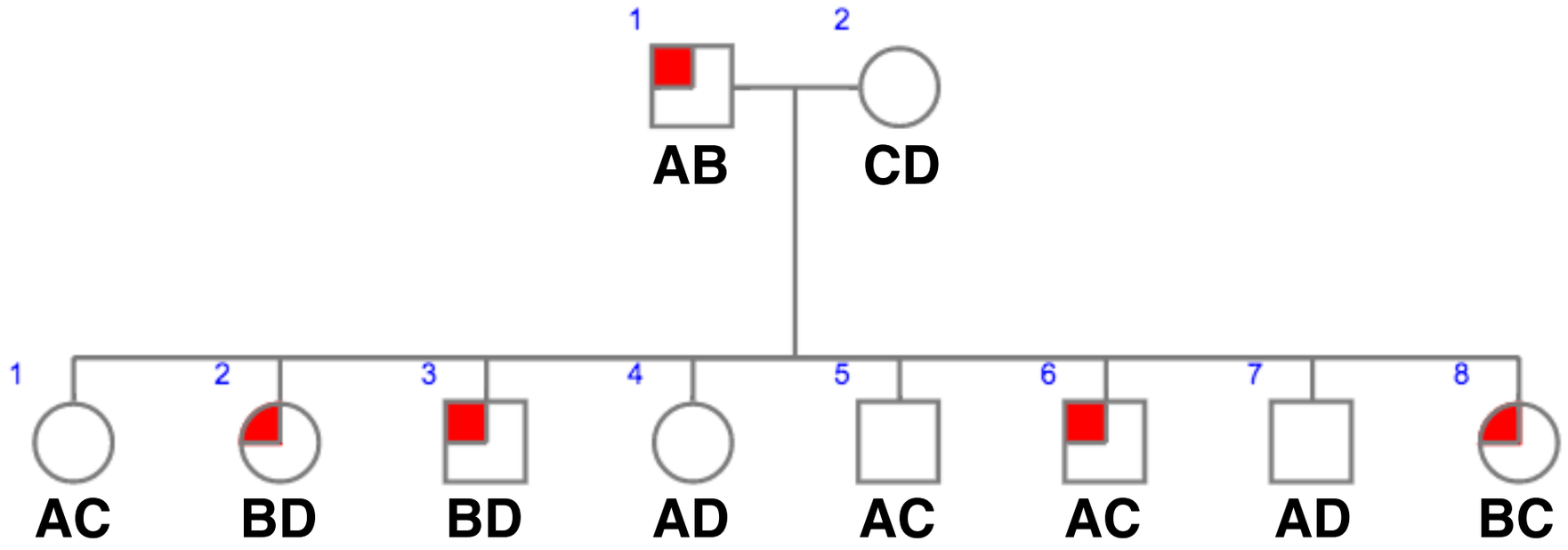


Phase 1	P	P	P	P	P	R	P	P

$$LOD = \log_{10} \frac{½\,(1 - 0.125)^{7} \times 0.125^{1}}{½\;0.5^{(7+1)}}$$

½ chance for each phase
and second phase probability
go away!

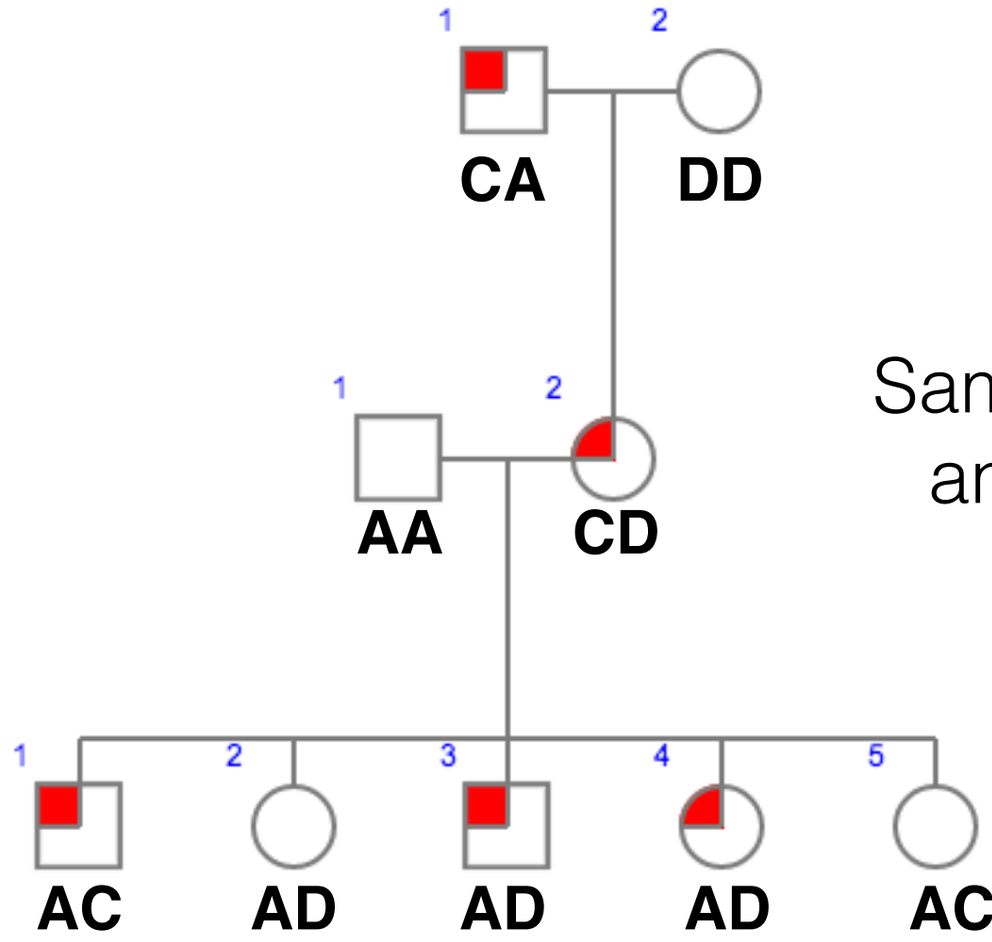
What happens when we know phase?



LOD = 1.1 $\theta = 0.125$

½ chance for each phase
and second phase probability
go away!

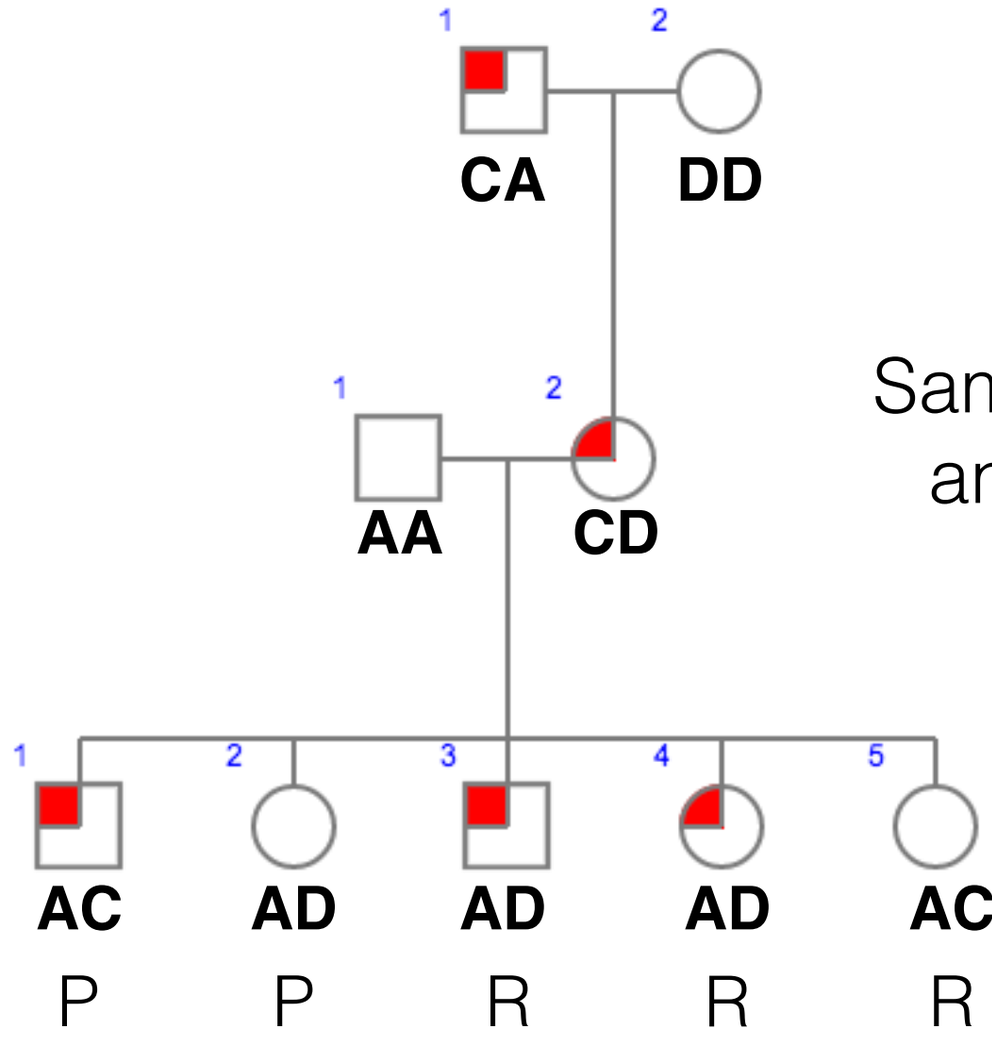
Let’s add another family



Same marker as before and we know phase

$$LOD = \log_{10} \frac{½\,(1 - \theta)^{NR} \times \theta^{R}}{½\,0.5^{(NR + R)}}$$

Let’s add another family



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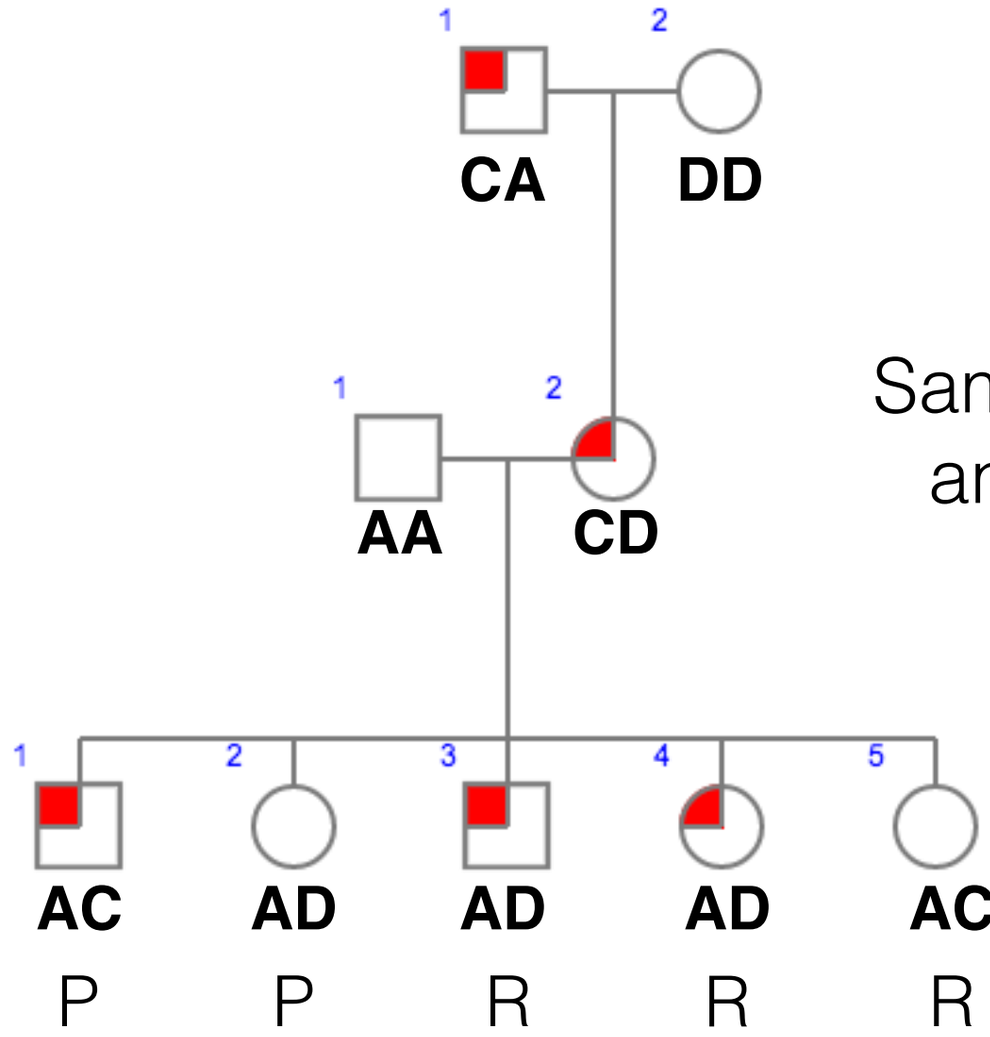
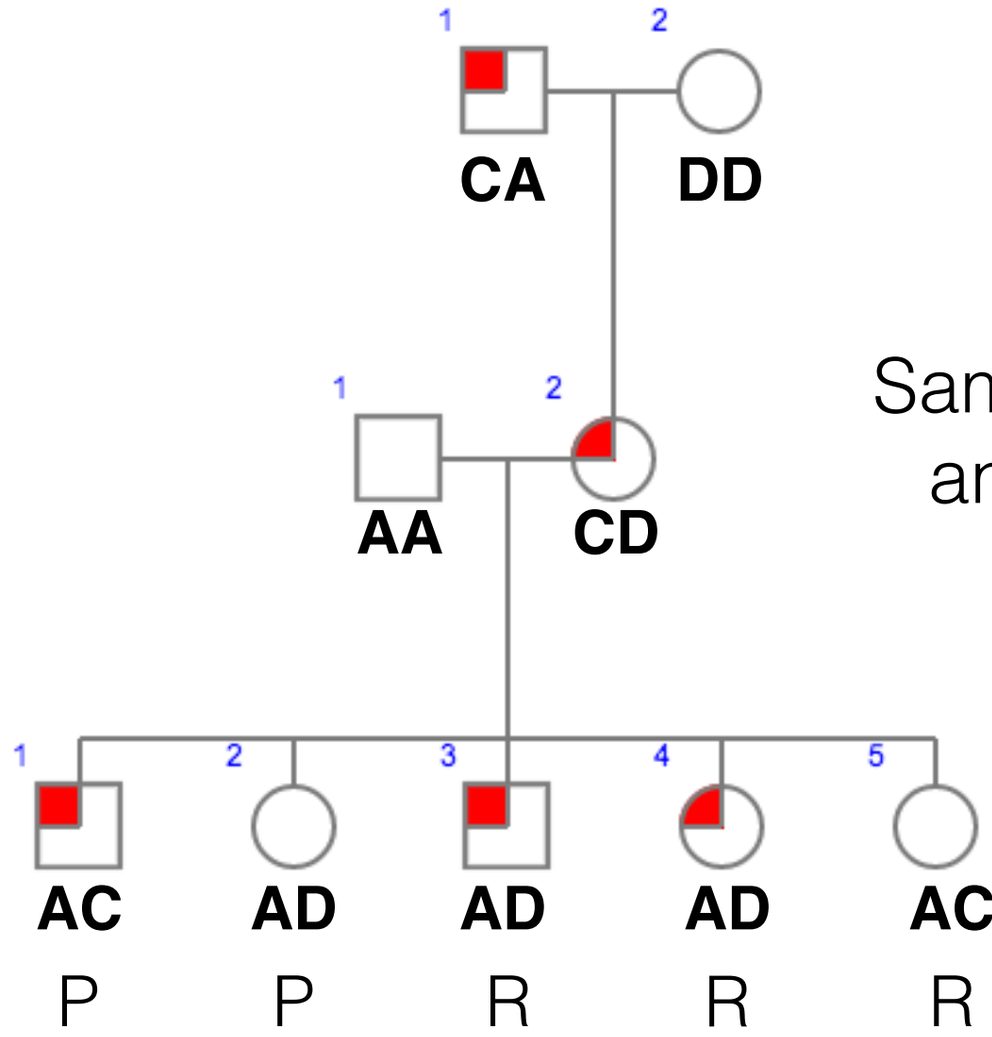


Same marker as before and we know phase

$$\text{LOD} = \log_{10} \frac{\frac{1}{2}(1 - \mathbf{0.125})^2 \times \mathbf{0.125}^{3}}{\frac{1}{2}\ 0.5^{(2+3)}}$$

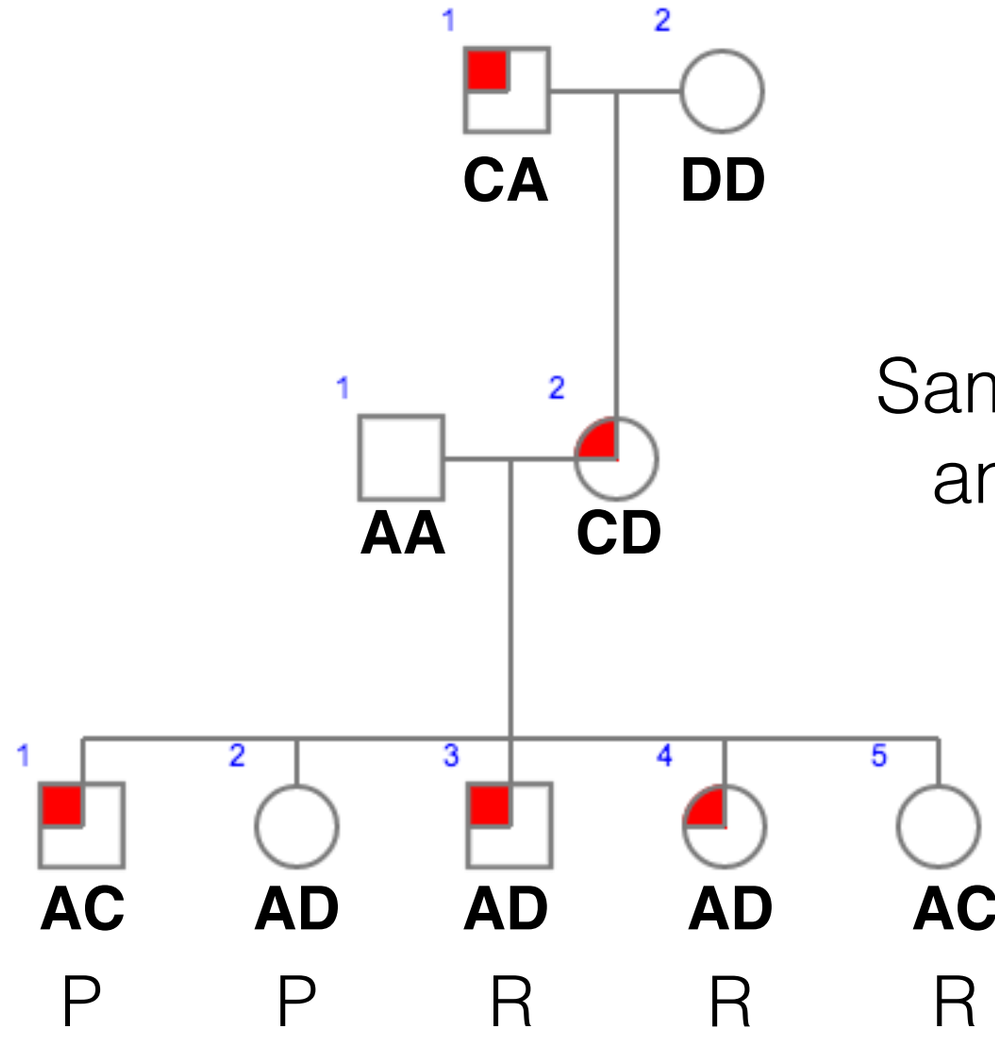
Let’s add another family



Same marker as before and we know phase

LOD = - Infinity $\theta = 0.125$

Let’s add another family

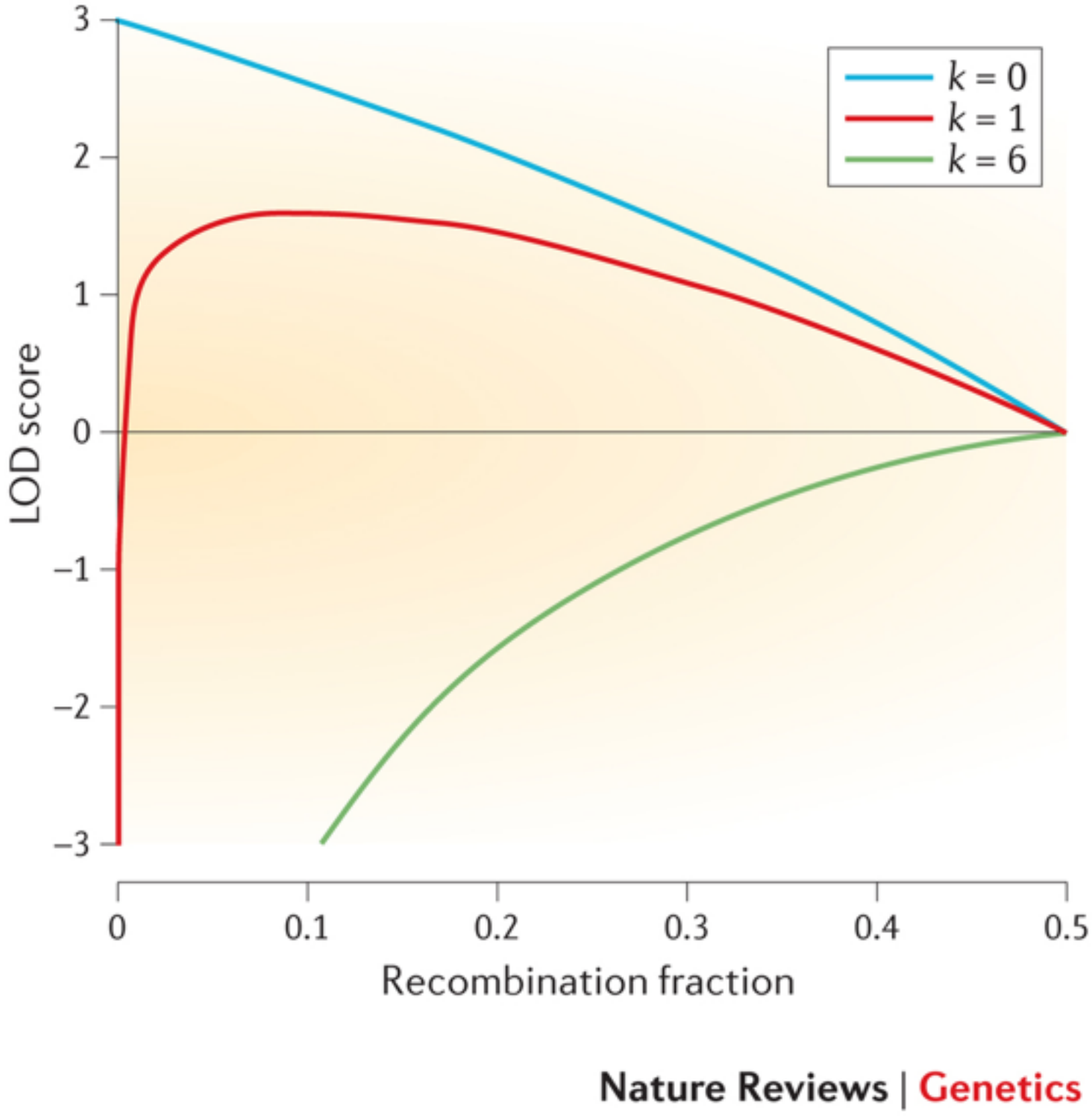


Same marker as before and we know phase

LOD = - Infinity $\theta = 0.125$

Change theta to 0.6? No, 0.5 is unlinked

What if we try all possible thetas between 0 and 0.5?



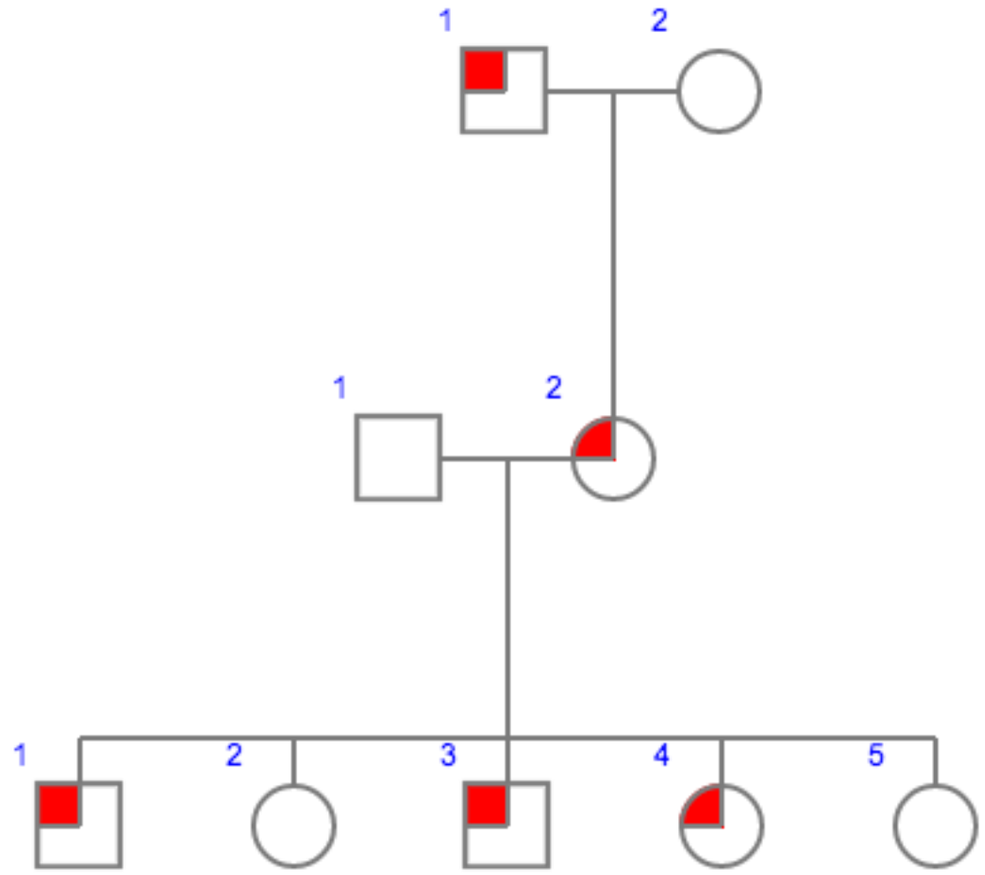
k = # of recombinants
out of 10 individuals

The good and the bad of family-based linkage analysis

Positives:
- Less allelic heterogeneity in families
- Clearly tell recombination events
- Powerful method to find rare variant effects

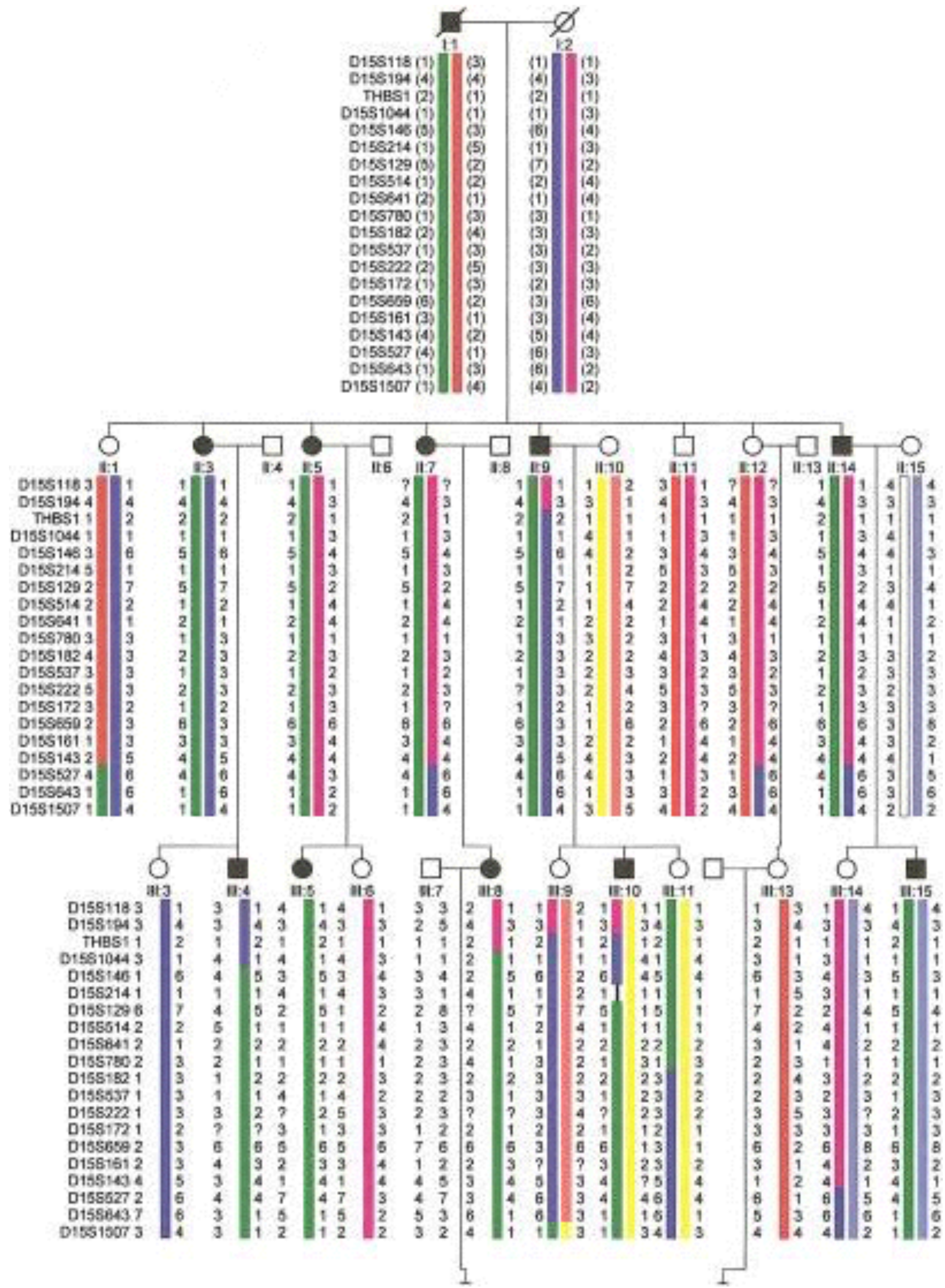
Negatives:
- Large families are rare
- Different families with the “same” disease could have different genetic causes
- Mapping resolution is 5 cM or 5 megabase pairs
- Difficult for late-onset diseases

With whole-exome and whole-genome sequencing, family linkage analysis gets even more powerful

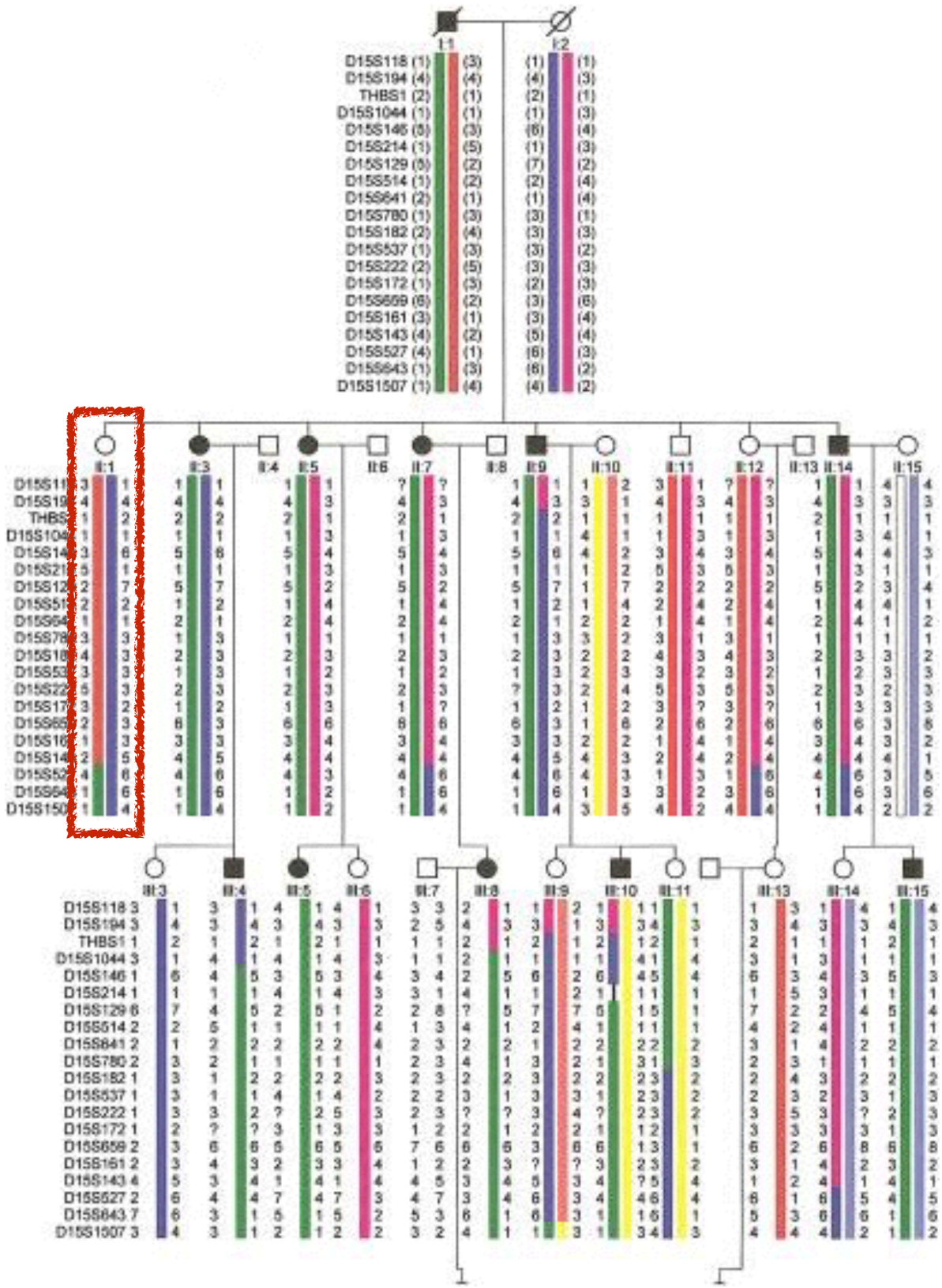


- Look at “all” markers in the genome simultaneously
- Dominant disorders mean look for heterozygous mutations linked to shared blocks of variants (haplotypes)
- X-linked lets you focus on the X chromosome
- Variants should be private to the family and deleterious

Linked markers on chromosomes allow for haplotype mapping

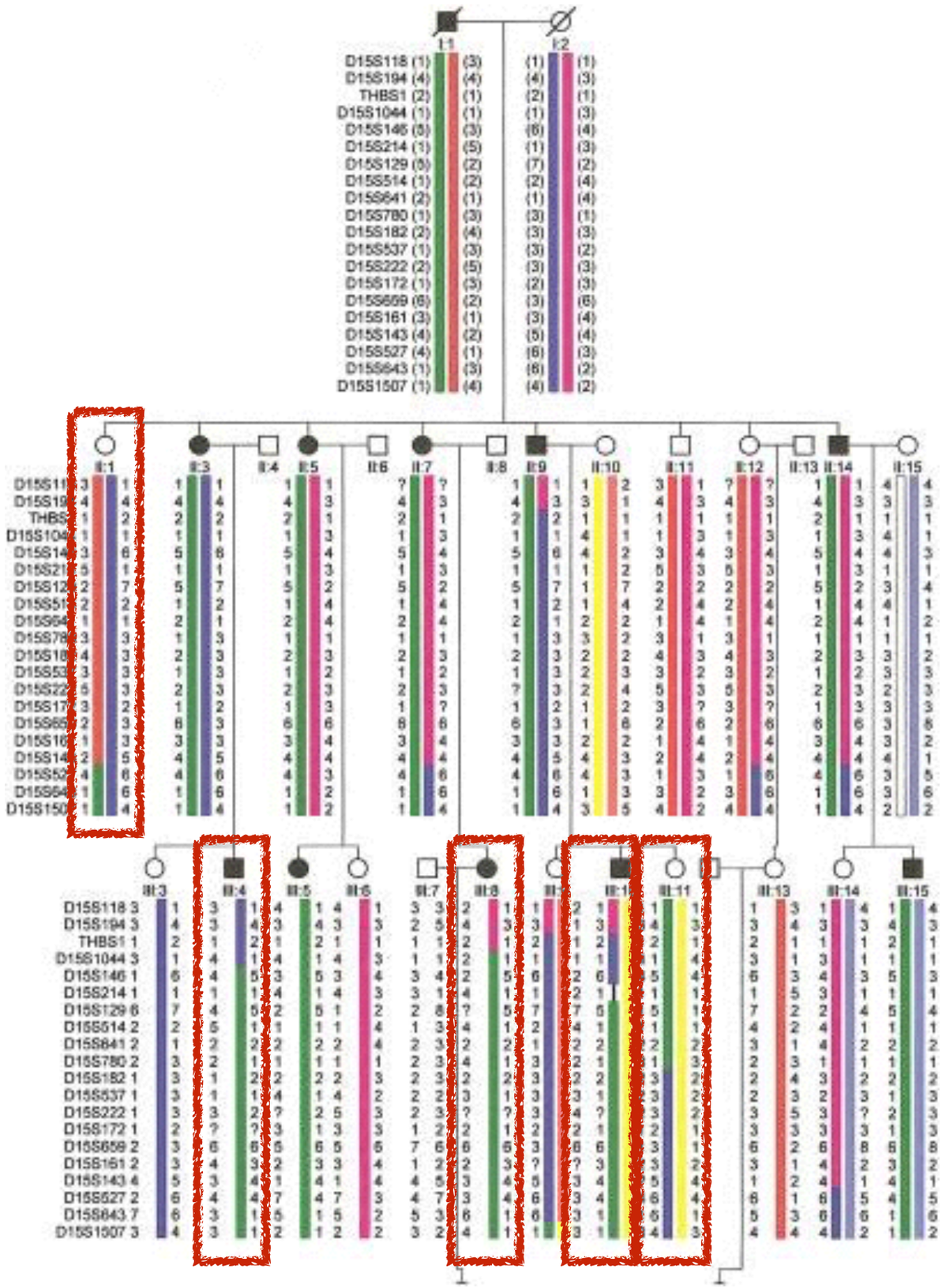


Linked markers on chromosomes allow for haplotype mapping



Lecture 16

Linked markers on chromosomes allow for haplotype mapping



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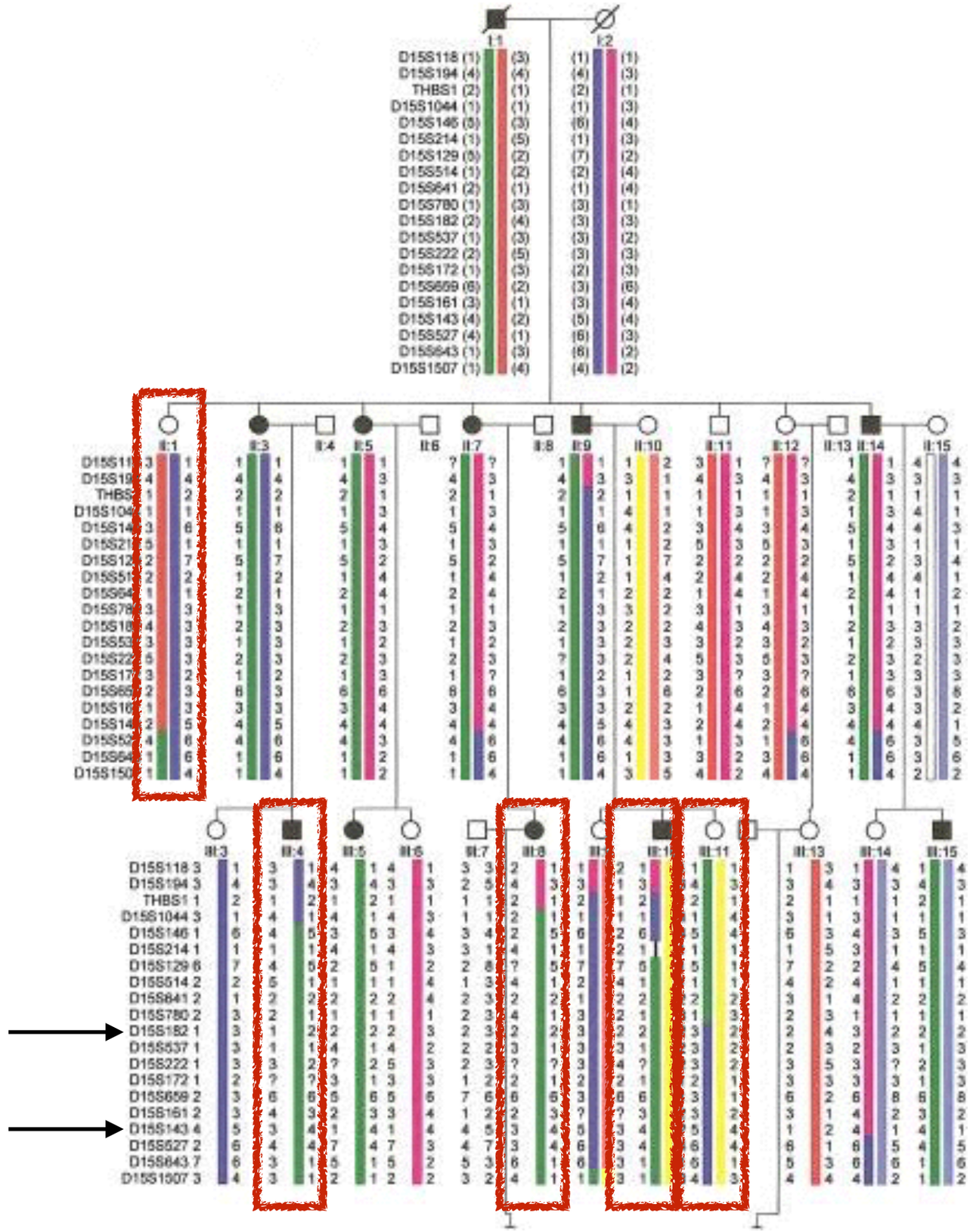
Linked markers on chromosomes allow for haplotype mapping



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