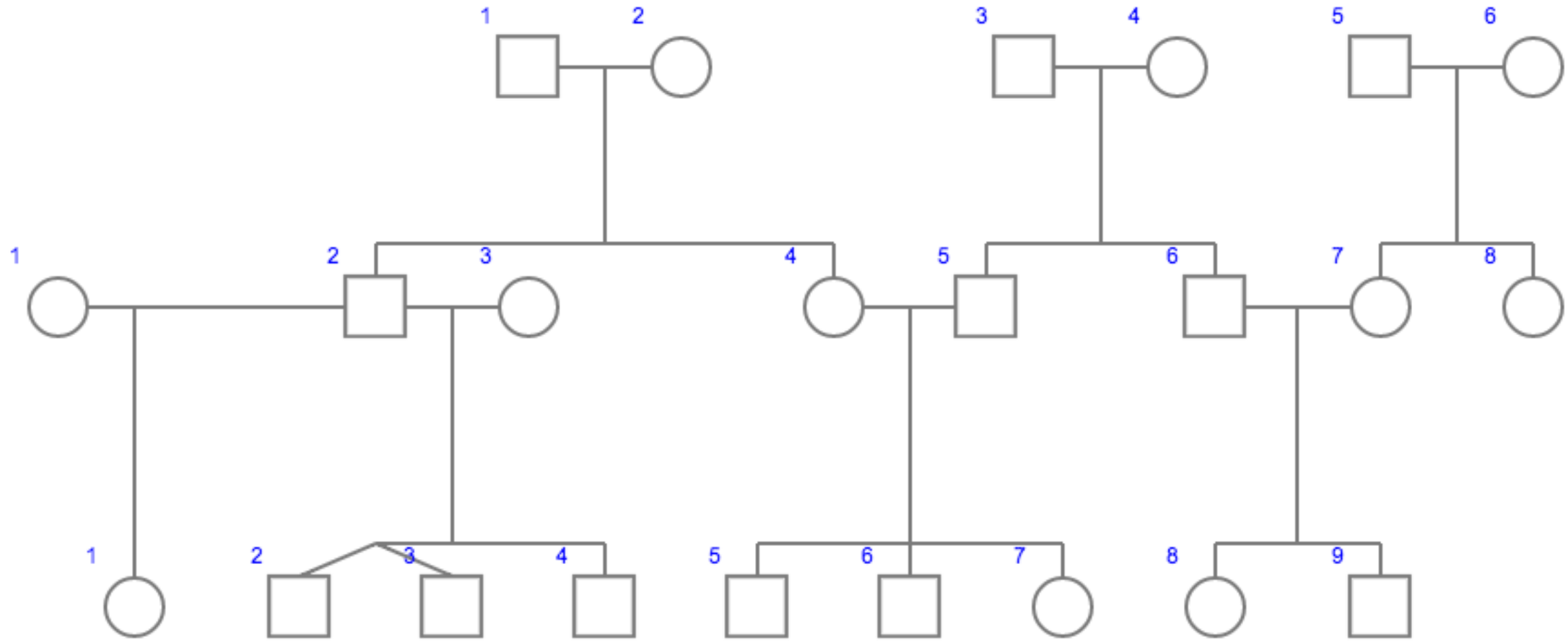
Bio393: Genetic Analysis

Linkage mapping in families



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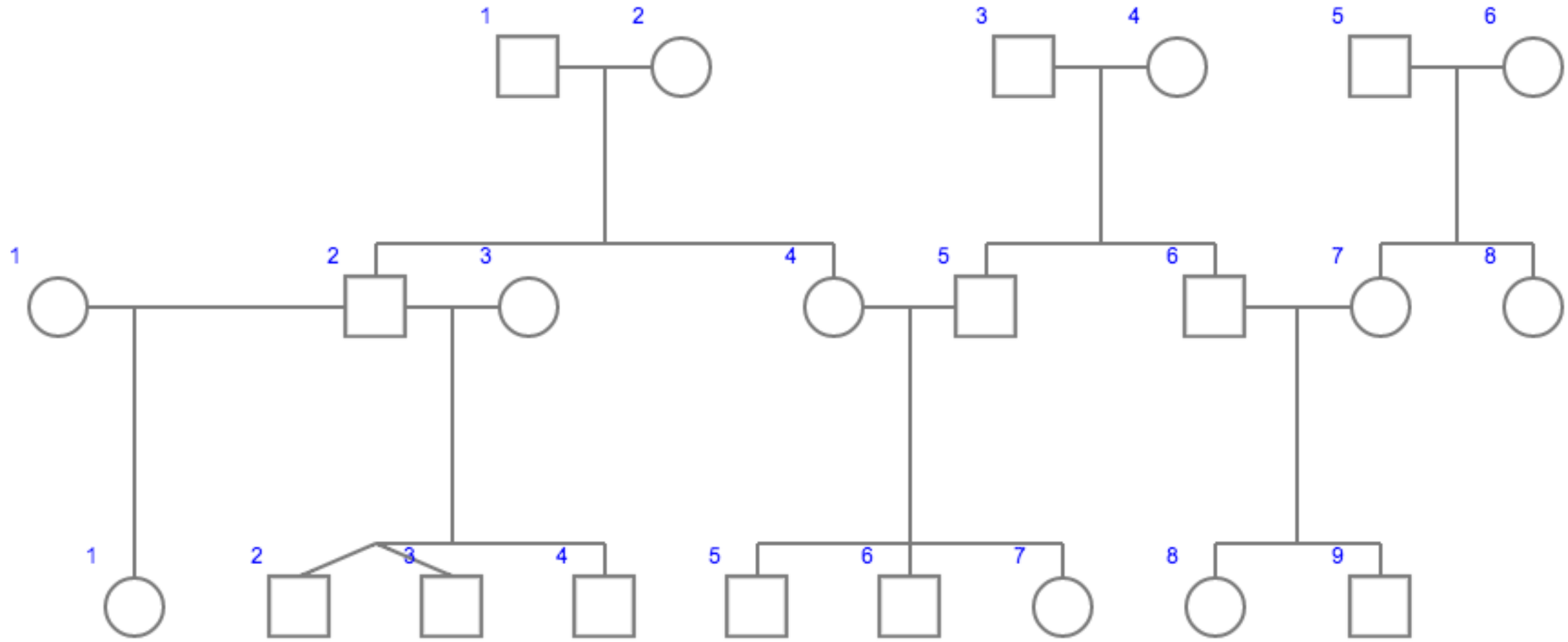


Dominant human disorders are caused mostly by haploinsufficient loci

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

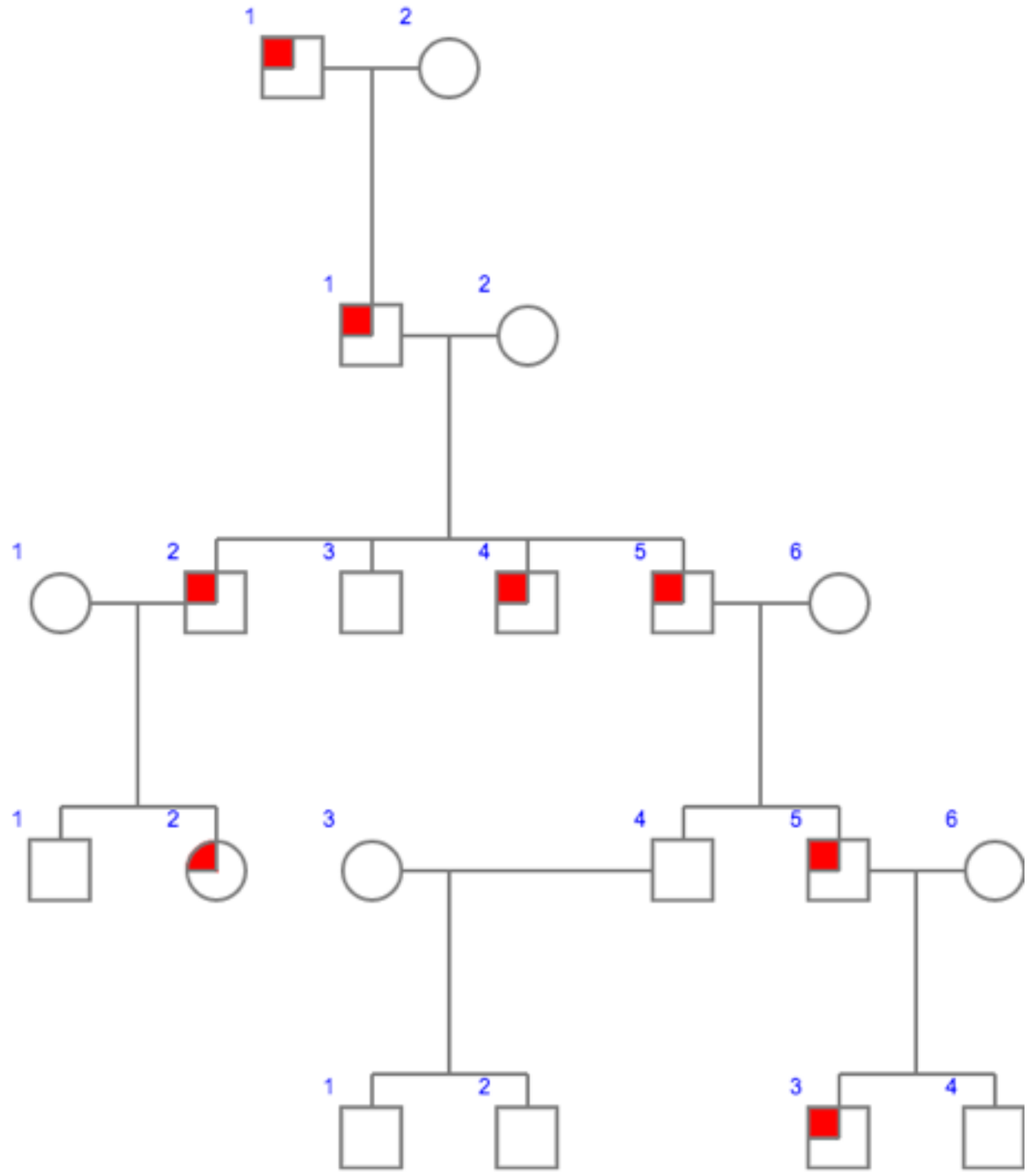
Friday, May 29 - Complex traits and GWAS, Quiz make-up

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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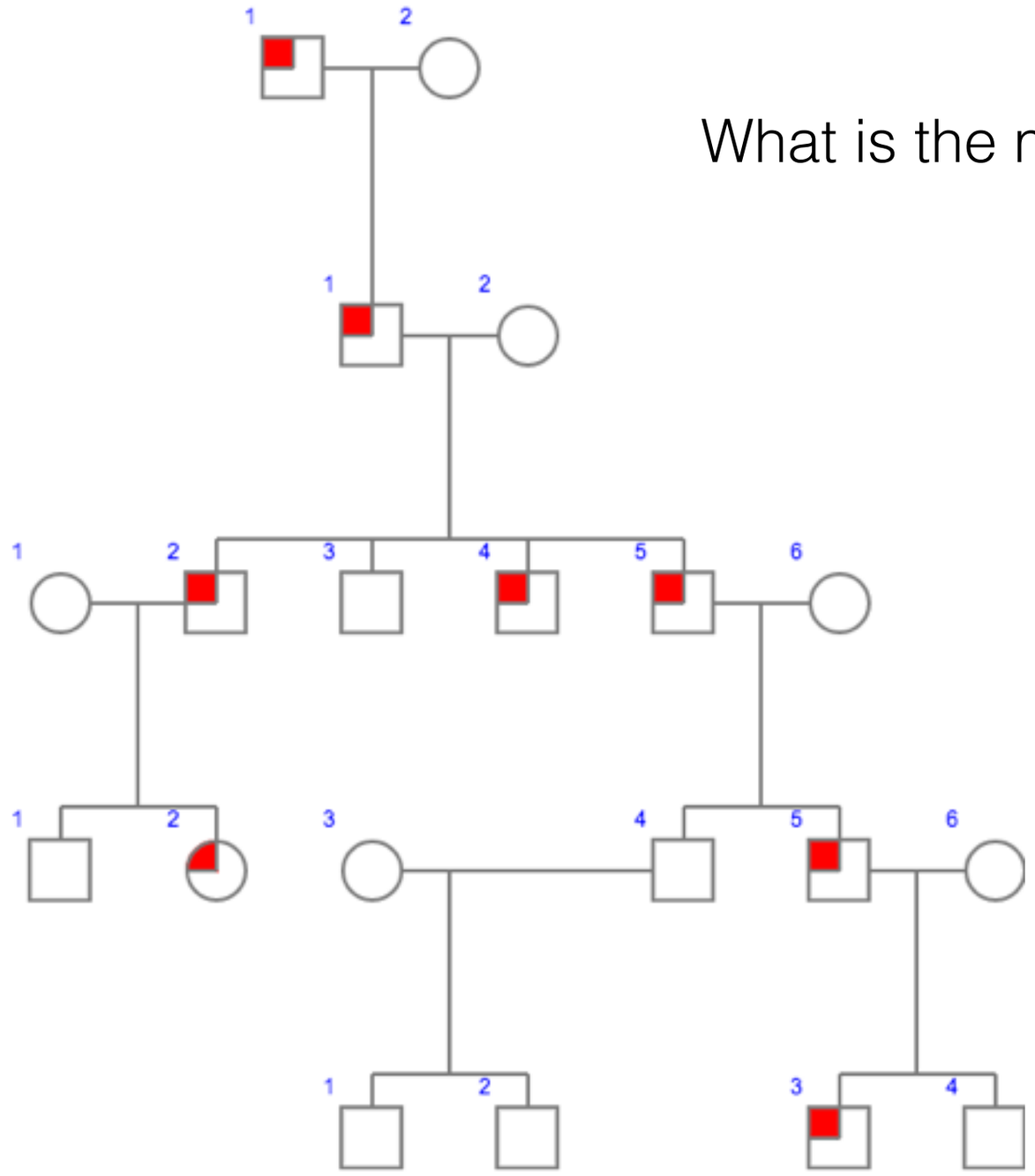
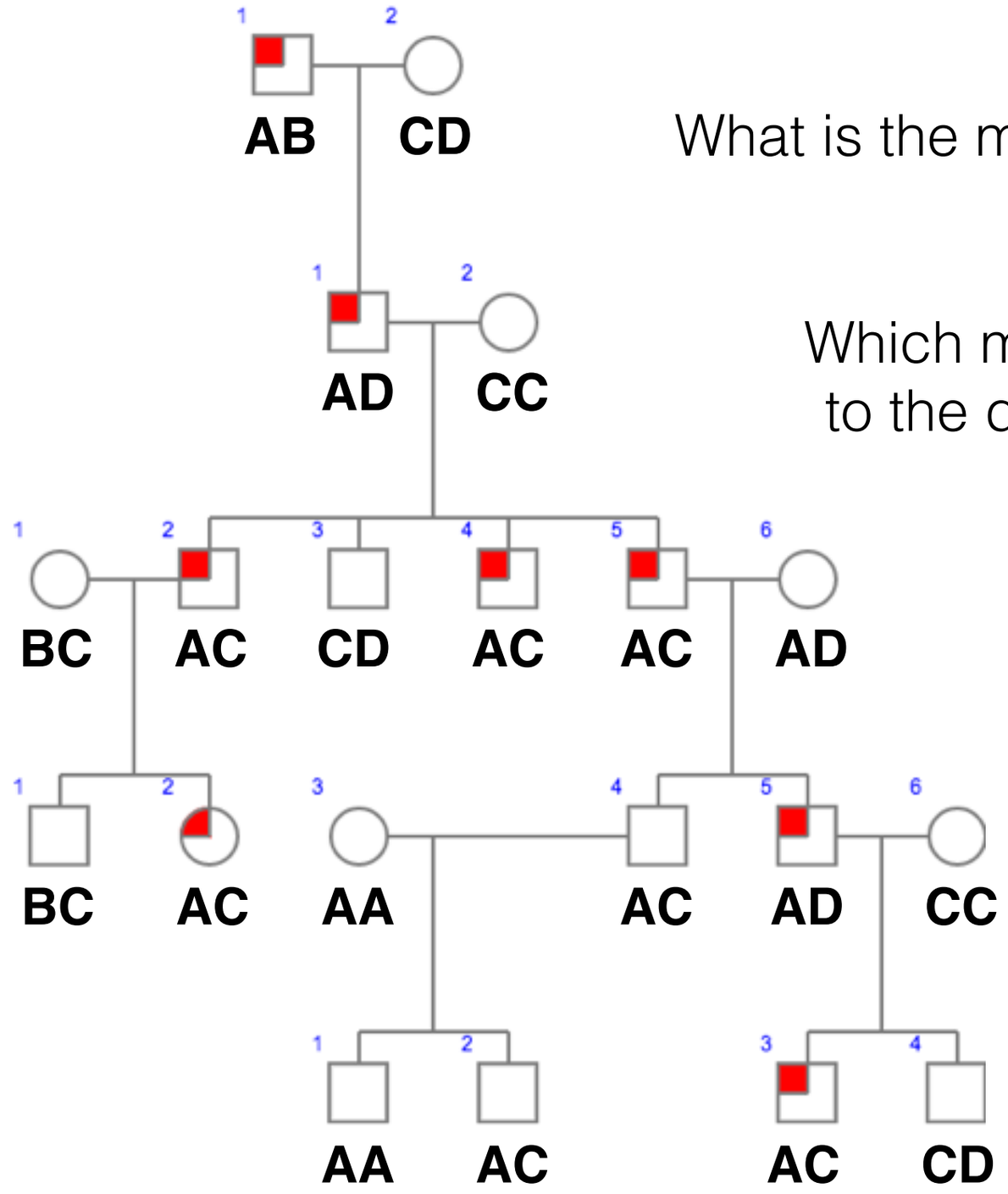


What is the mode of inheritance?

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

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

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

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.

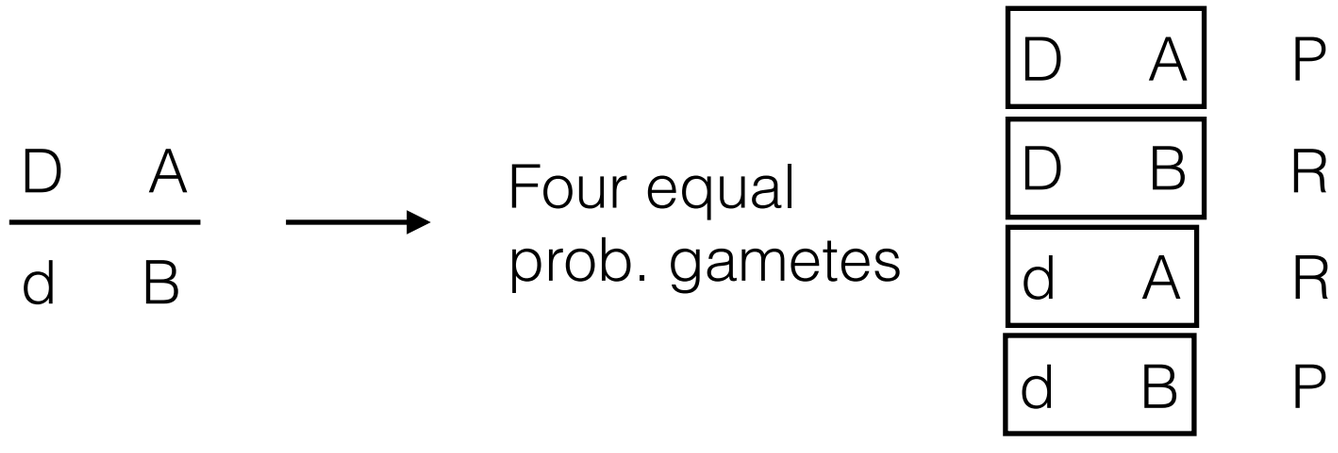
Linkage is reported as a log of the odds ratio or LOD

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

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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Probability of pedigree under linkage versus no linkage

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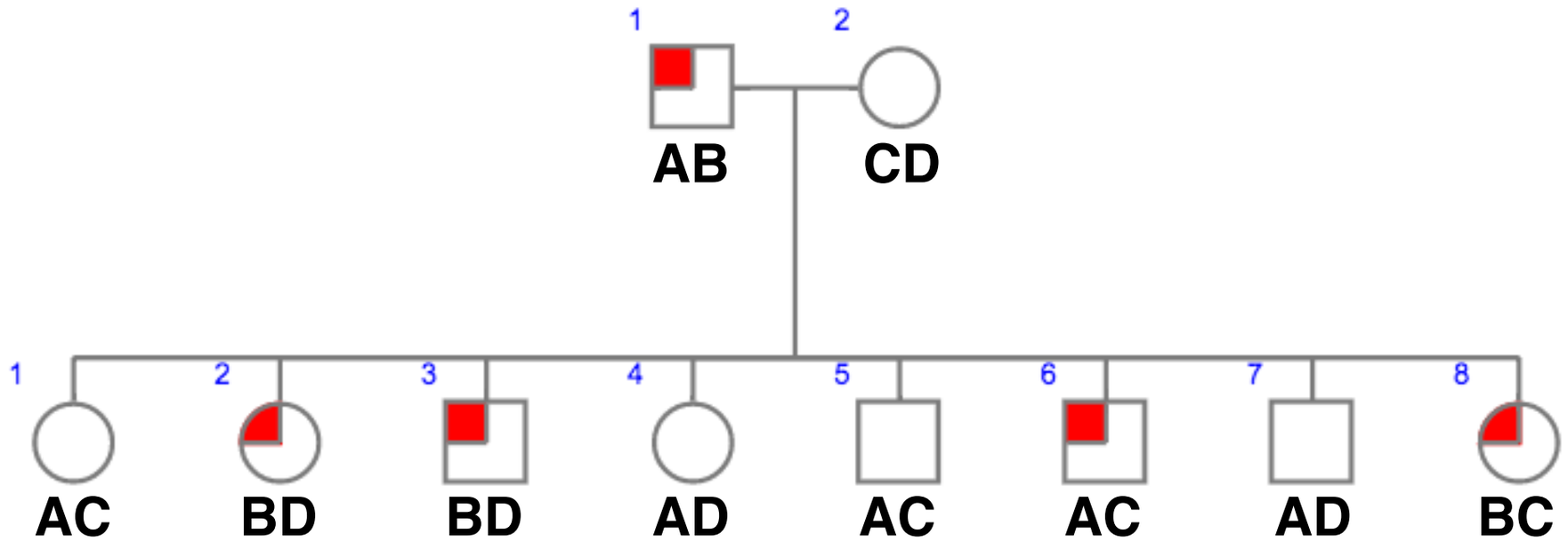
$$LOD = \log_{10} \frac{P(data \mid \theta)}{P(data \mid \theta = 0.5)}$$

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

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

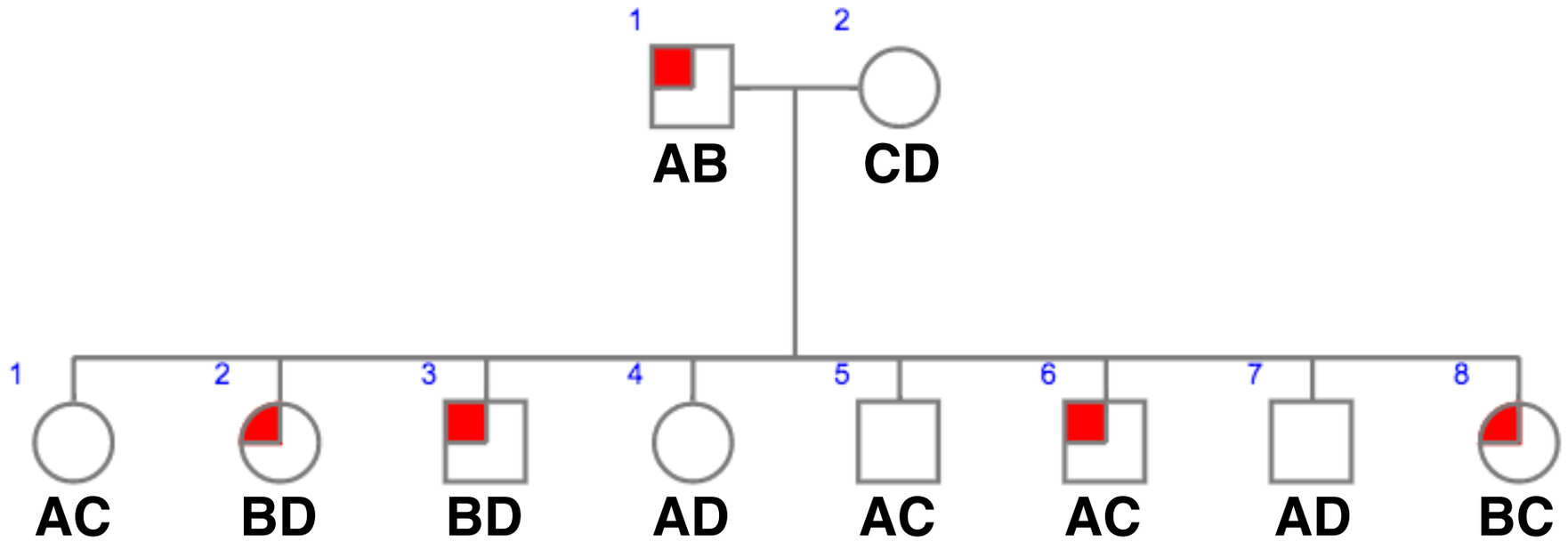
This equation for when we know phase.

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

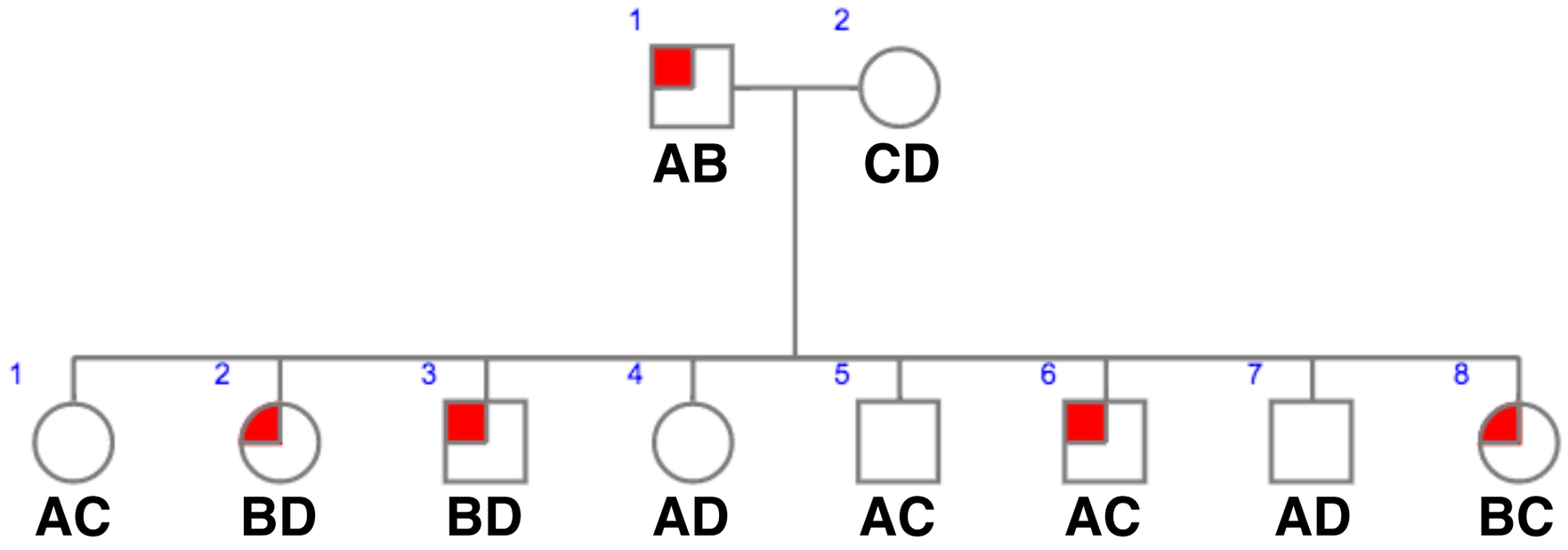


Do we know the phase of I-1?

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?

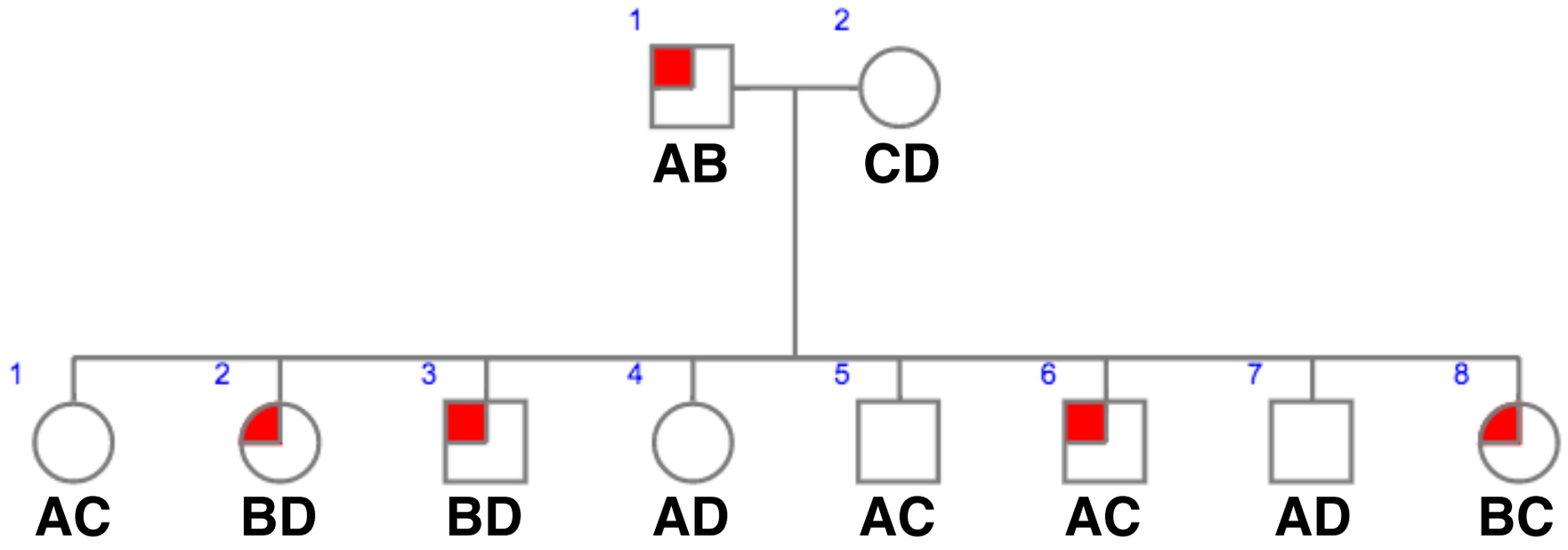
NO

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…

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

½ chance for each phase

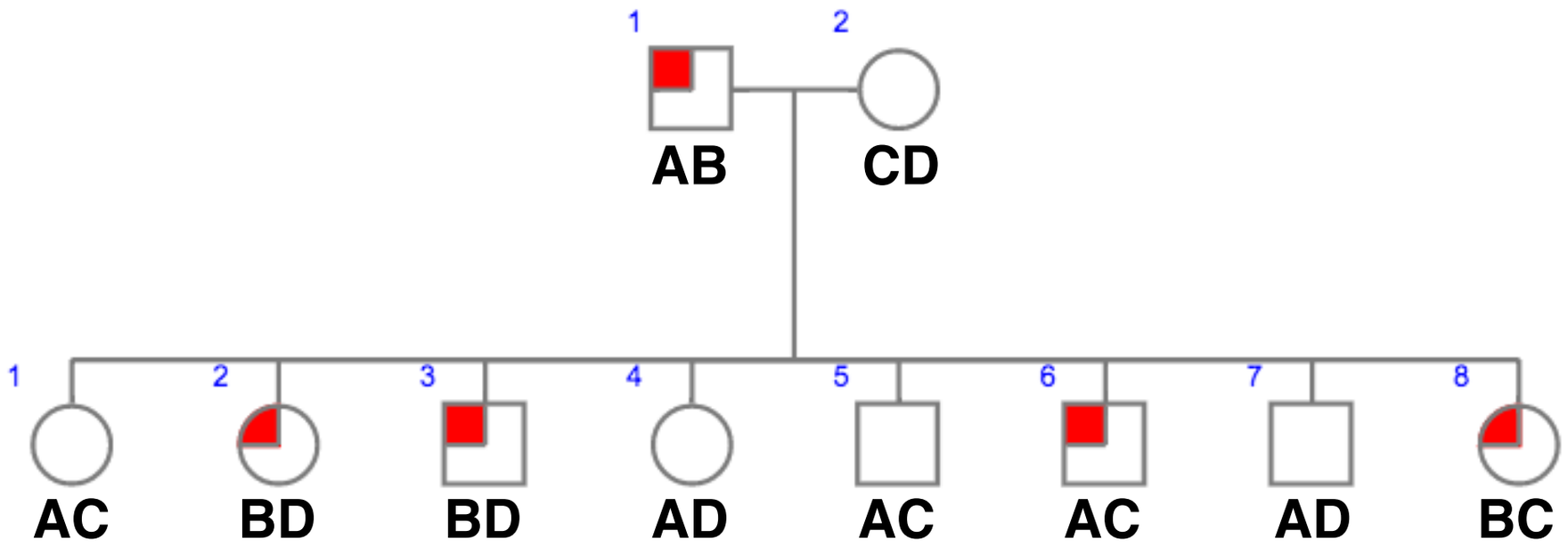
Phase 1

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

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

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

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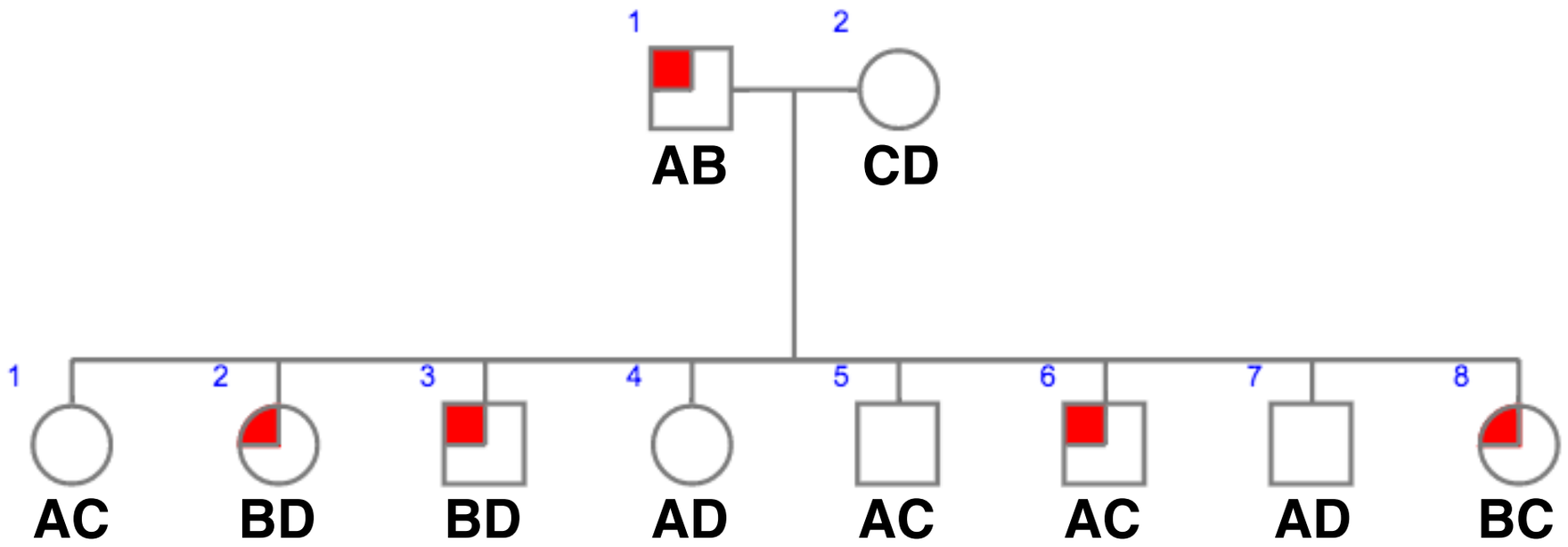

Phase 1	P	P	P	P	P	R	P	P

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

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Phase 1

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

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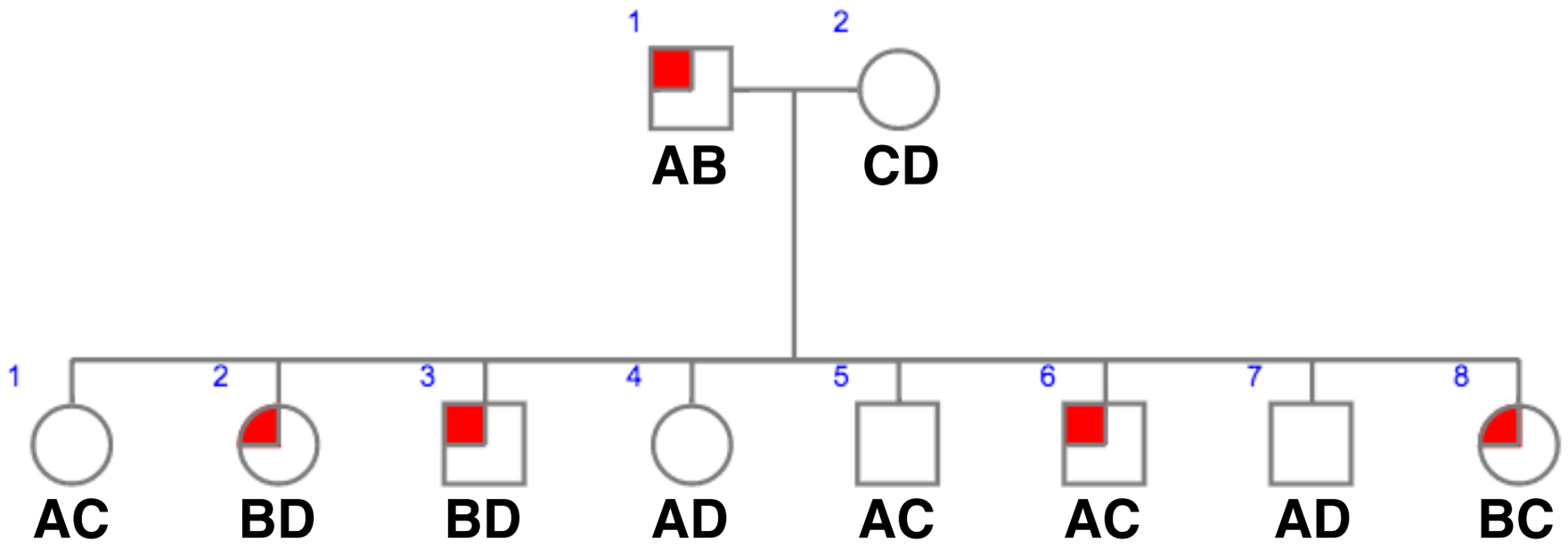


Phase 2	R	R	R	R	R	P	R	R

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

½ chance for each phase

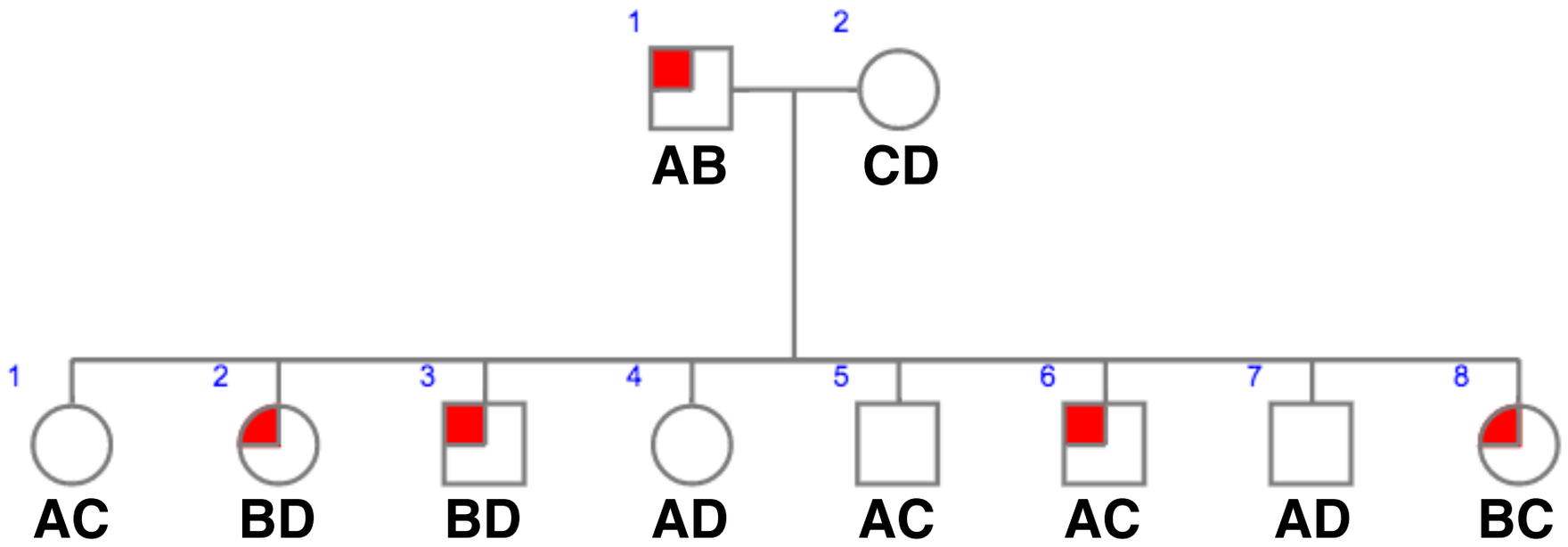
Phase 1

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

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

$$LOD = \log_{10} \frac{\frac{1}{2}(1 - 0.125)^{7} \times 0.125^{1}}{\frac{1}{2}\ 0.5^{(7+1)}} + \frac{\frac{1}{2}(1 - 0.125)^{1} \times 0.125^{7}}{\frac{1}{2}\ 0.5^{(1+7)}}$$

½ chance for each phase

$\theta = 0.125$

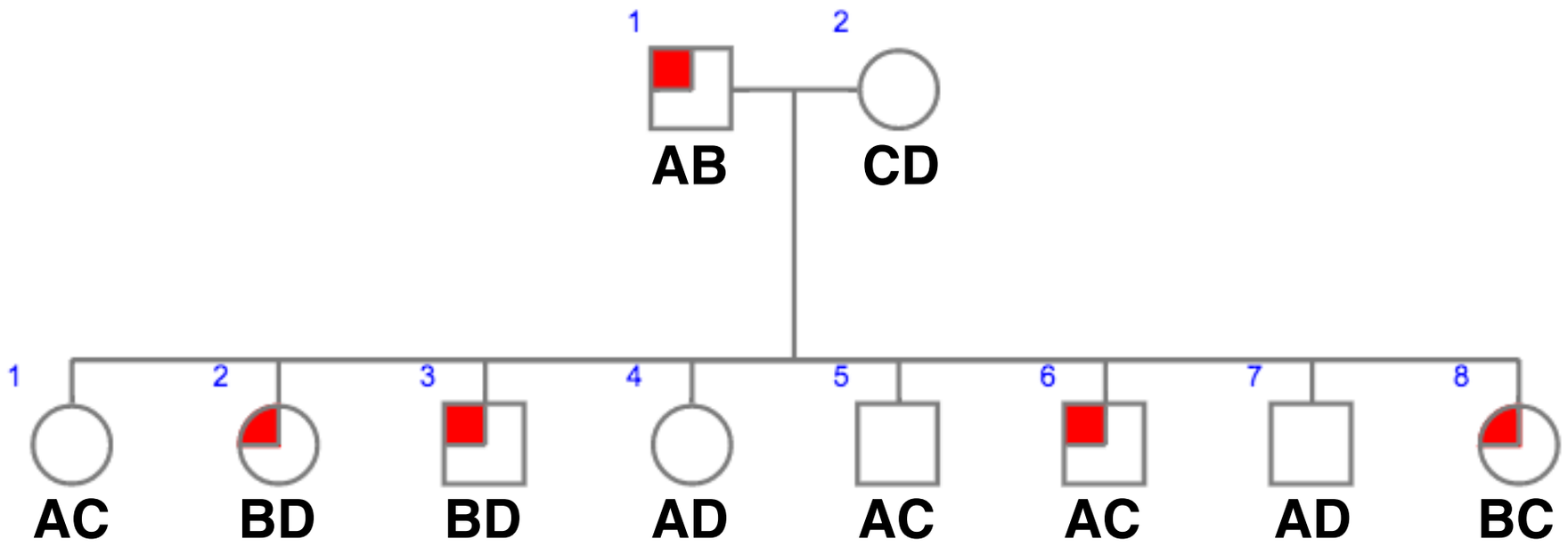
Phase 1

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

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

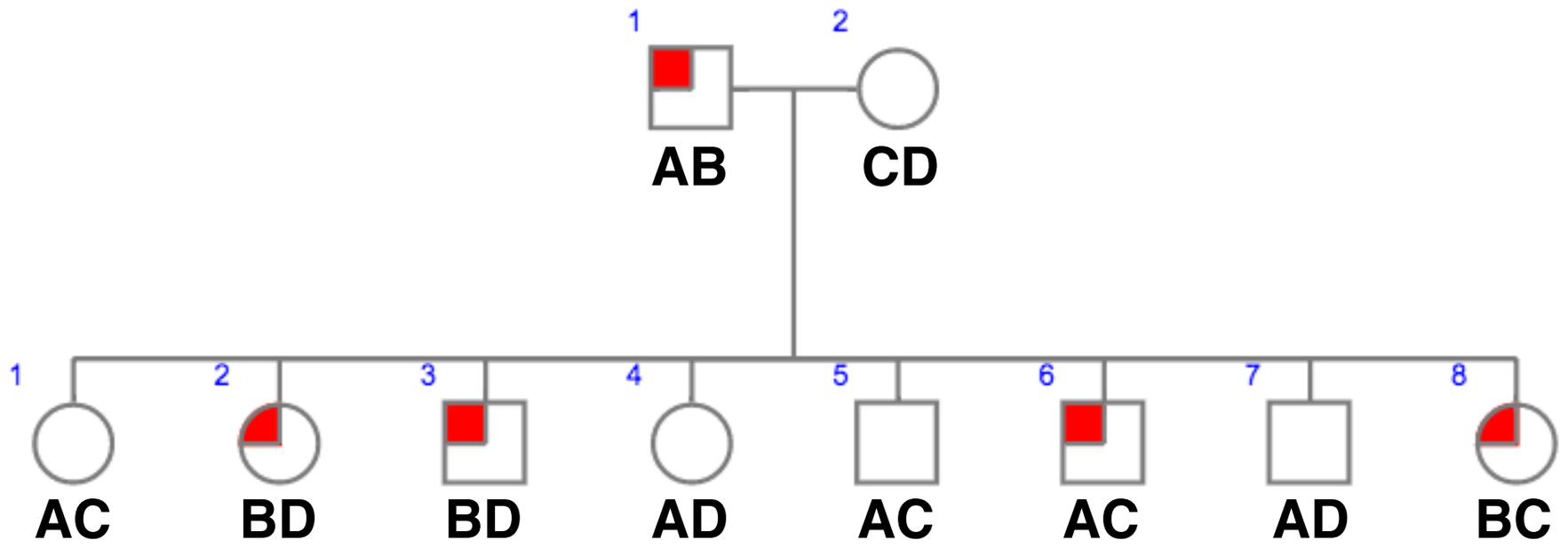
LOD = 0.79 $\theta = 0.125$

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?



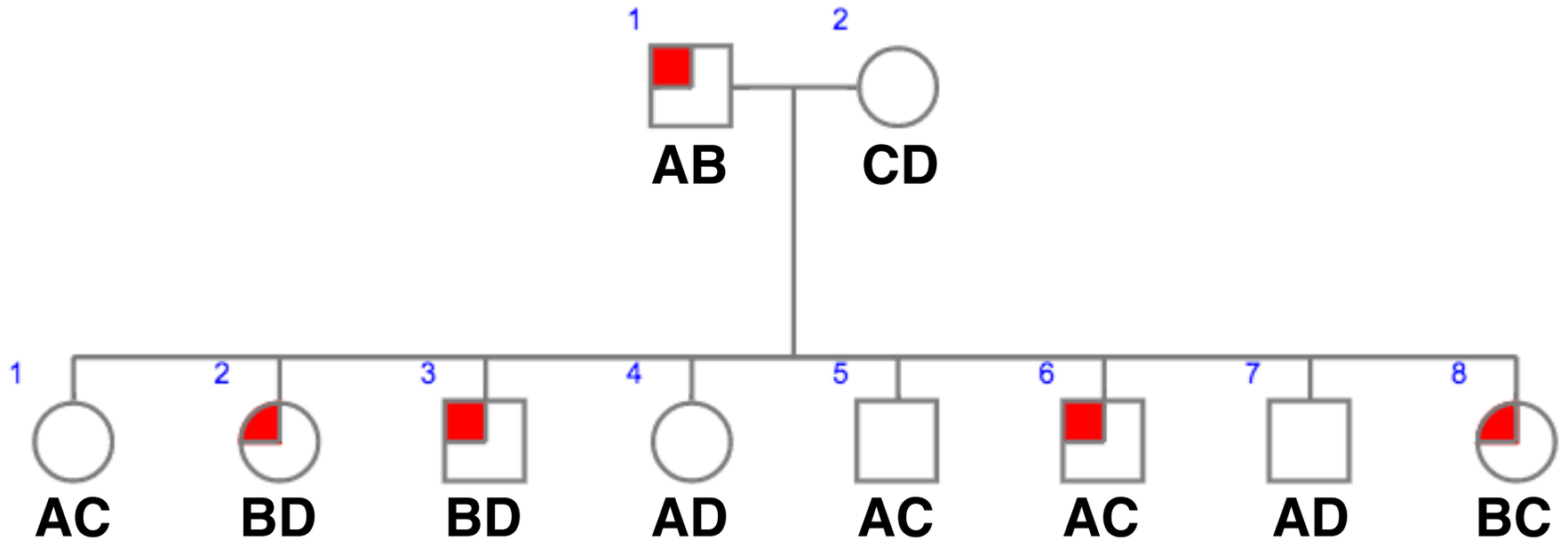
Phase 1	P	P	P	P	P	R	P	P

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

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

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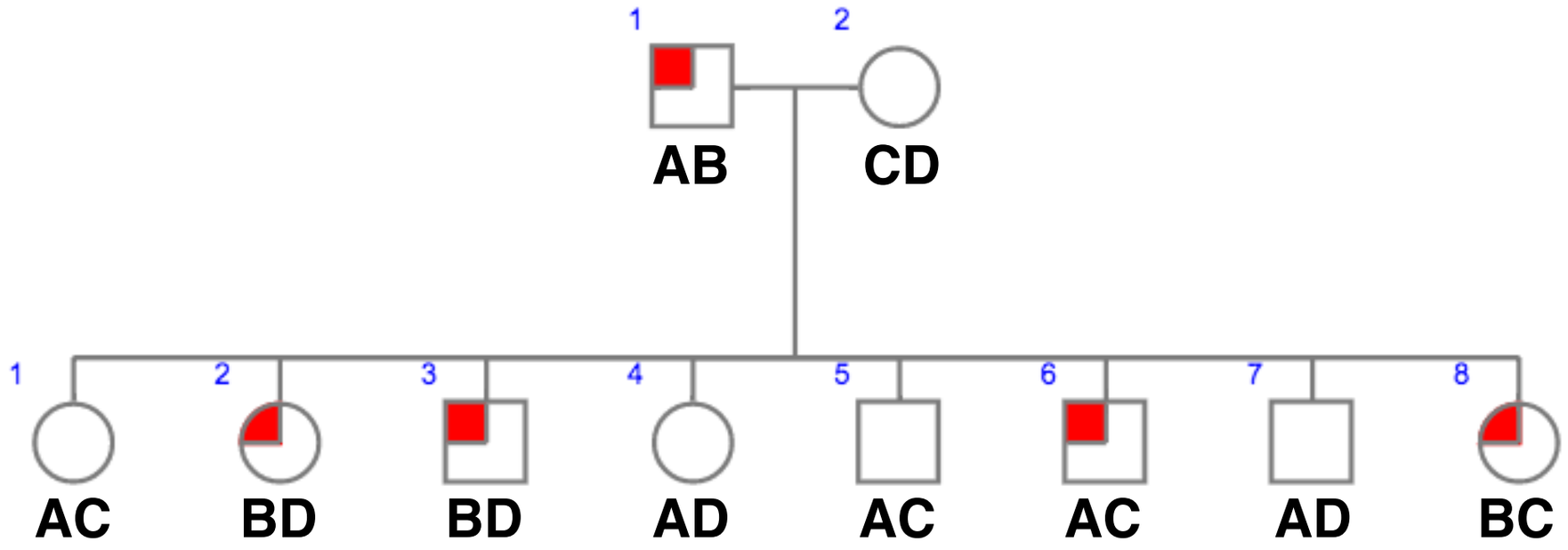
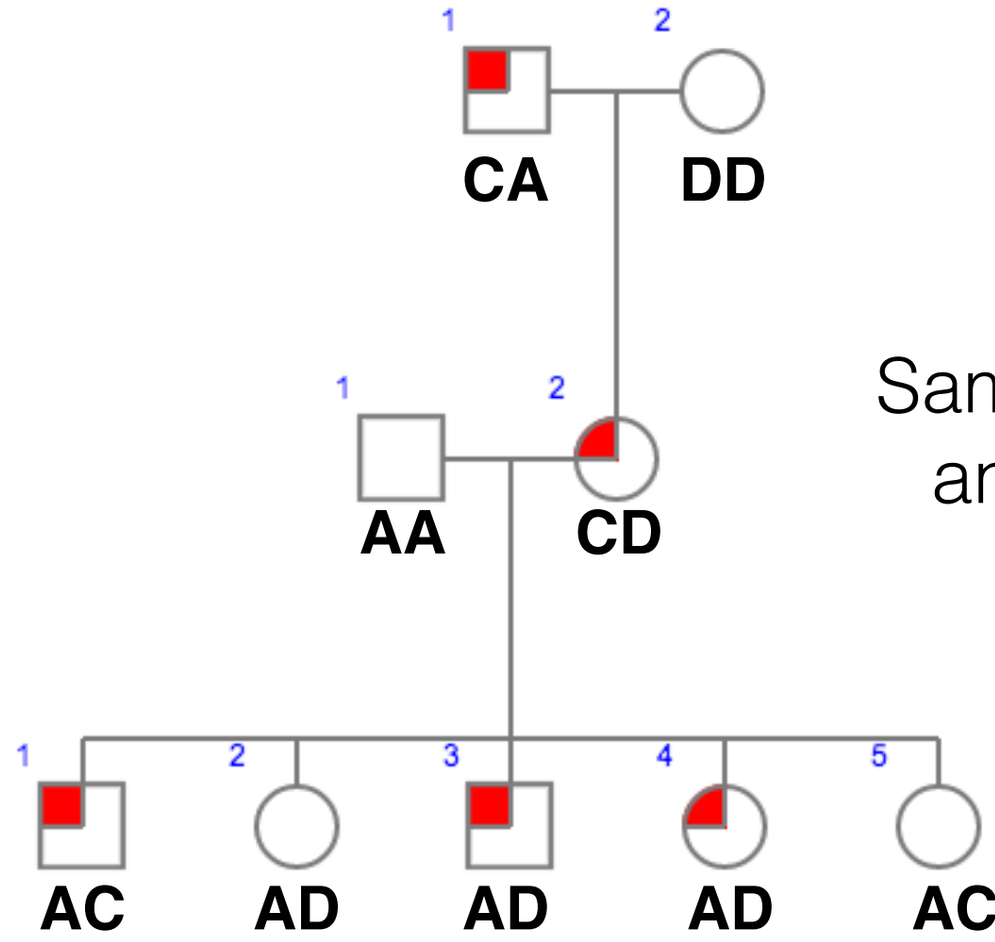
What happens when we know phase?



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

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

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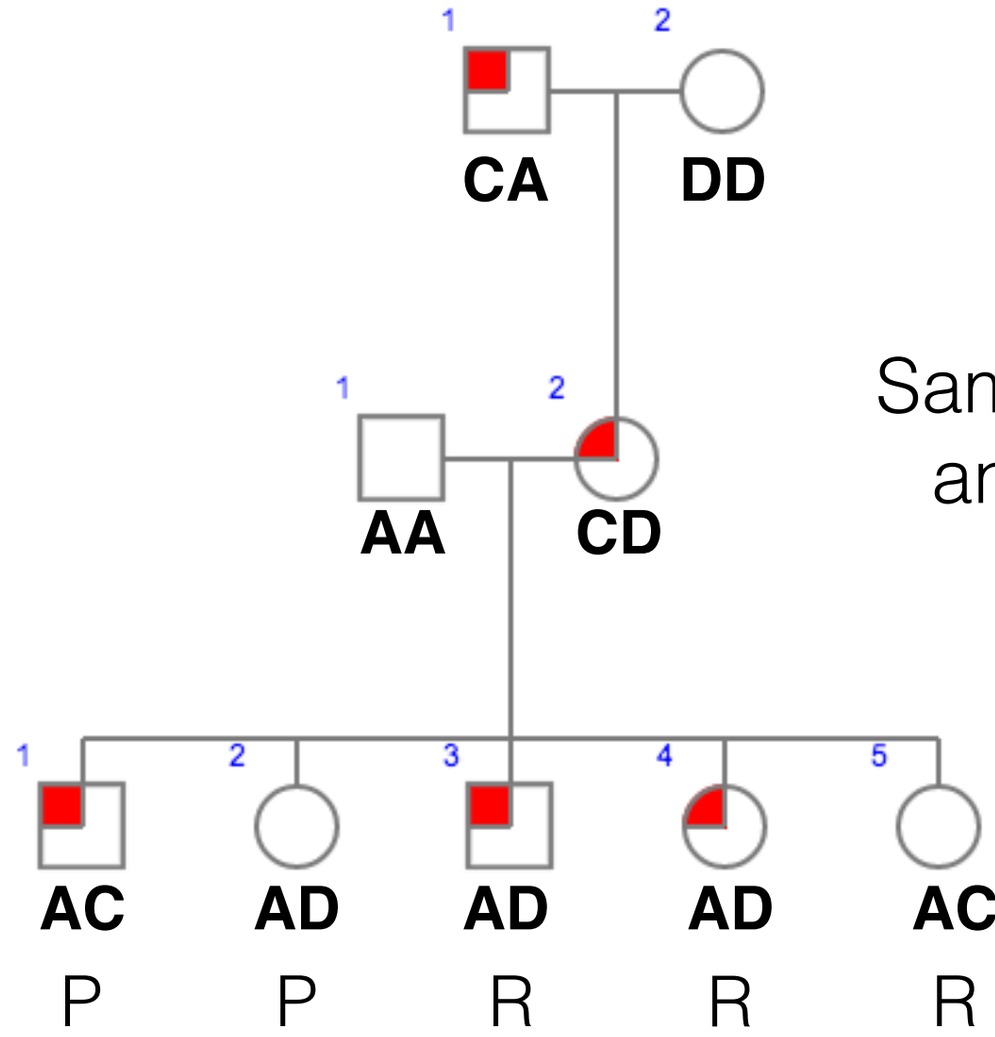

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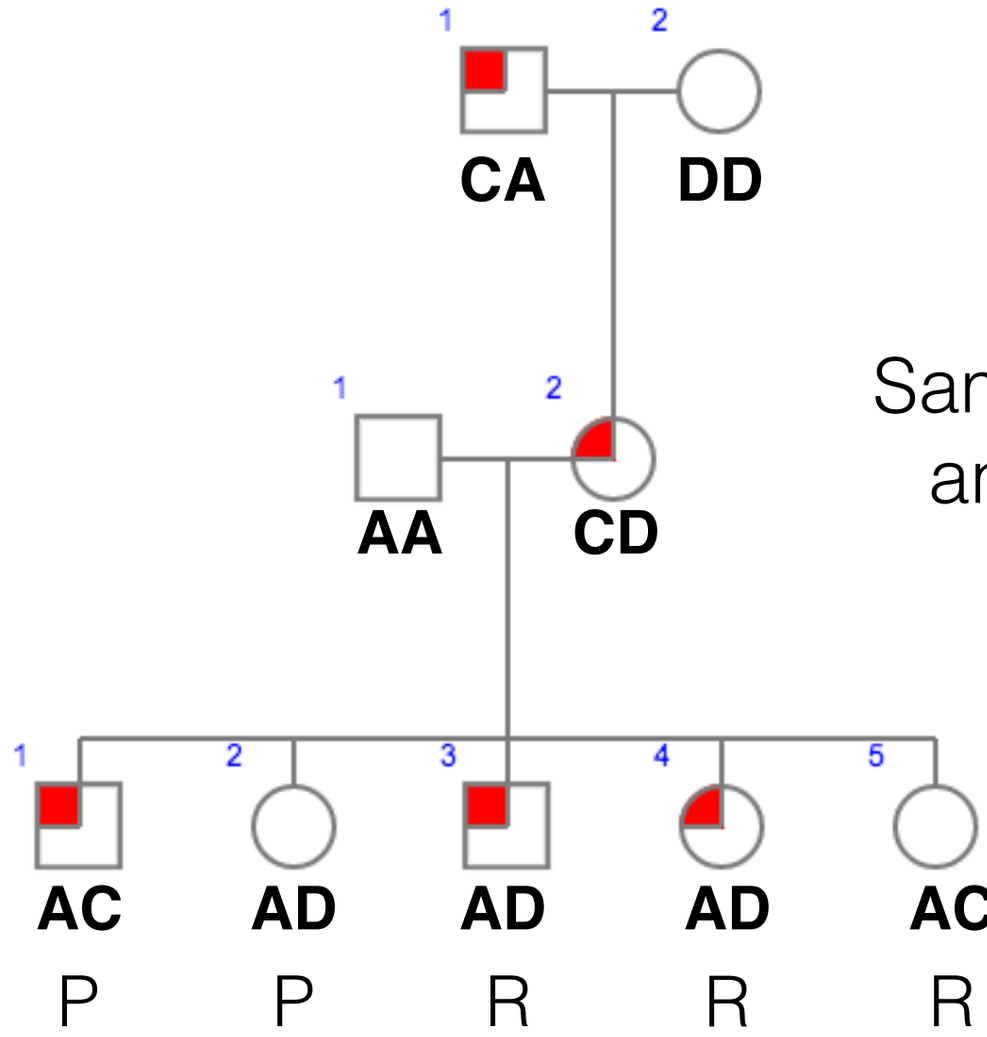
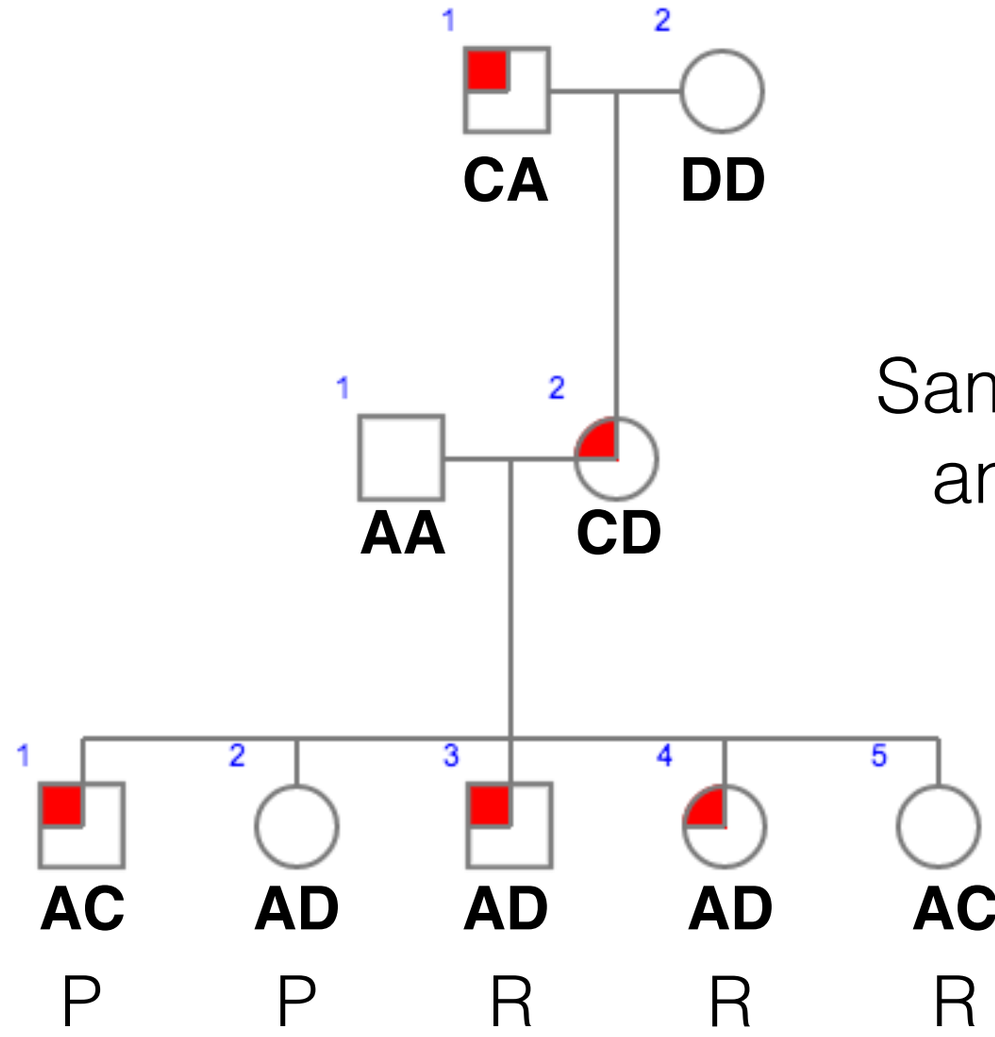


Same marker as before and we know phase

$$LOD = \log_{10} \frac{½\,(1 - \mathbf{0.125})^2 \times \mathbf{0.125}^{\,3}}{½\;0.5^{(2+3)}}$$

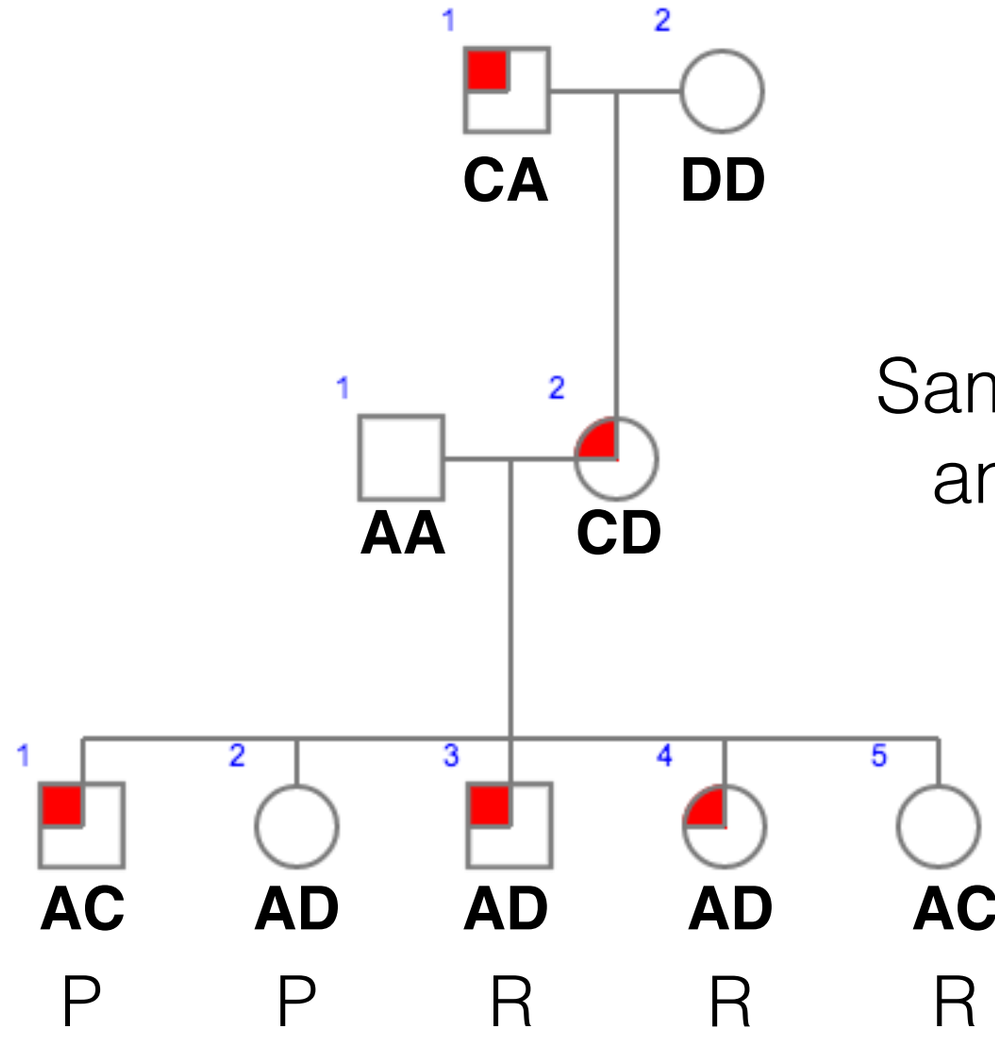
Let’s add another family



Same marker as before and we know phase

LOD = - Infinity $\theta = 0.125$

Let’s add another family

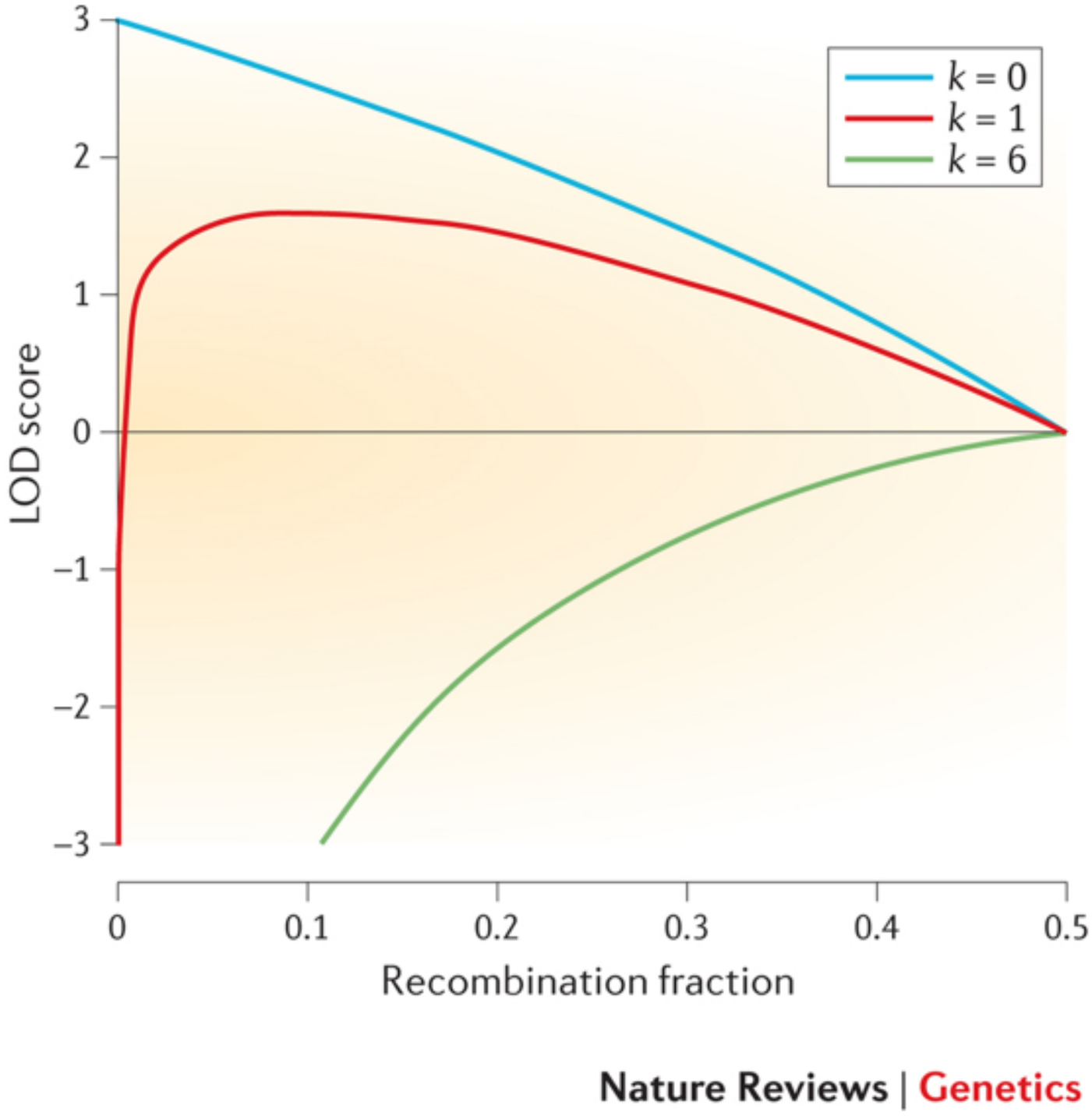


Same marker as before and we know phase

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?



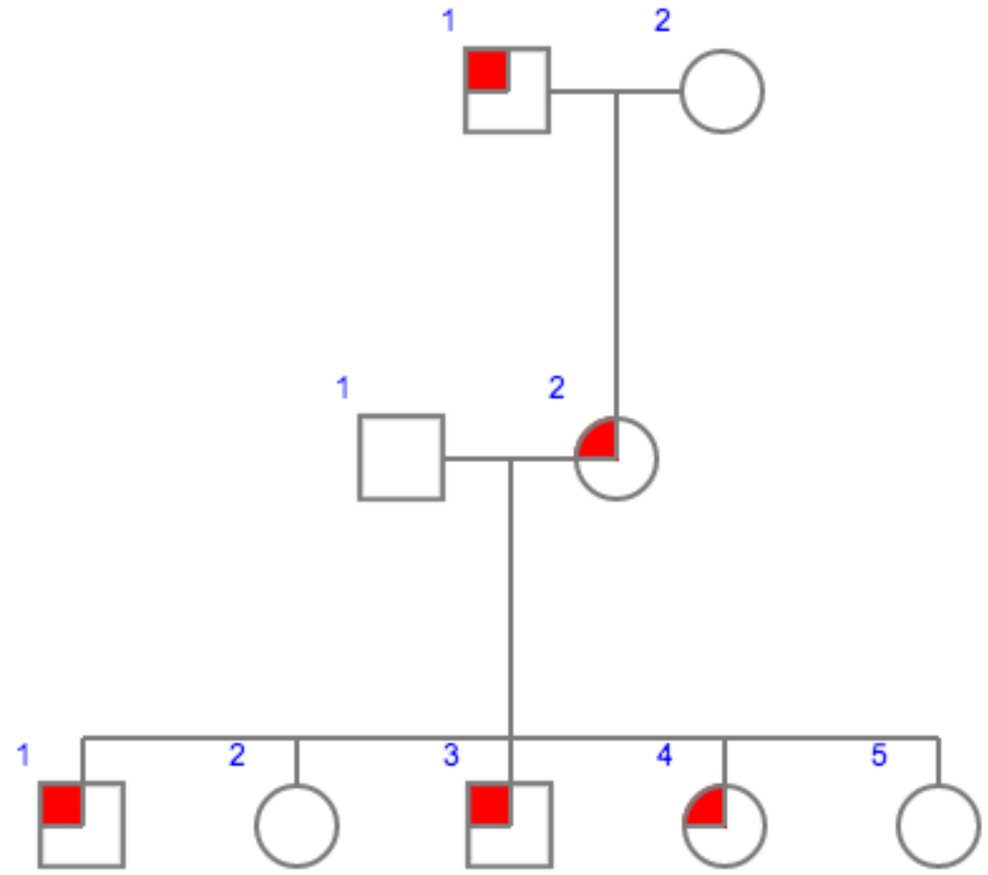
k = # of recombinants
out of 10 individuals

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

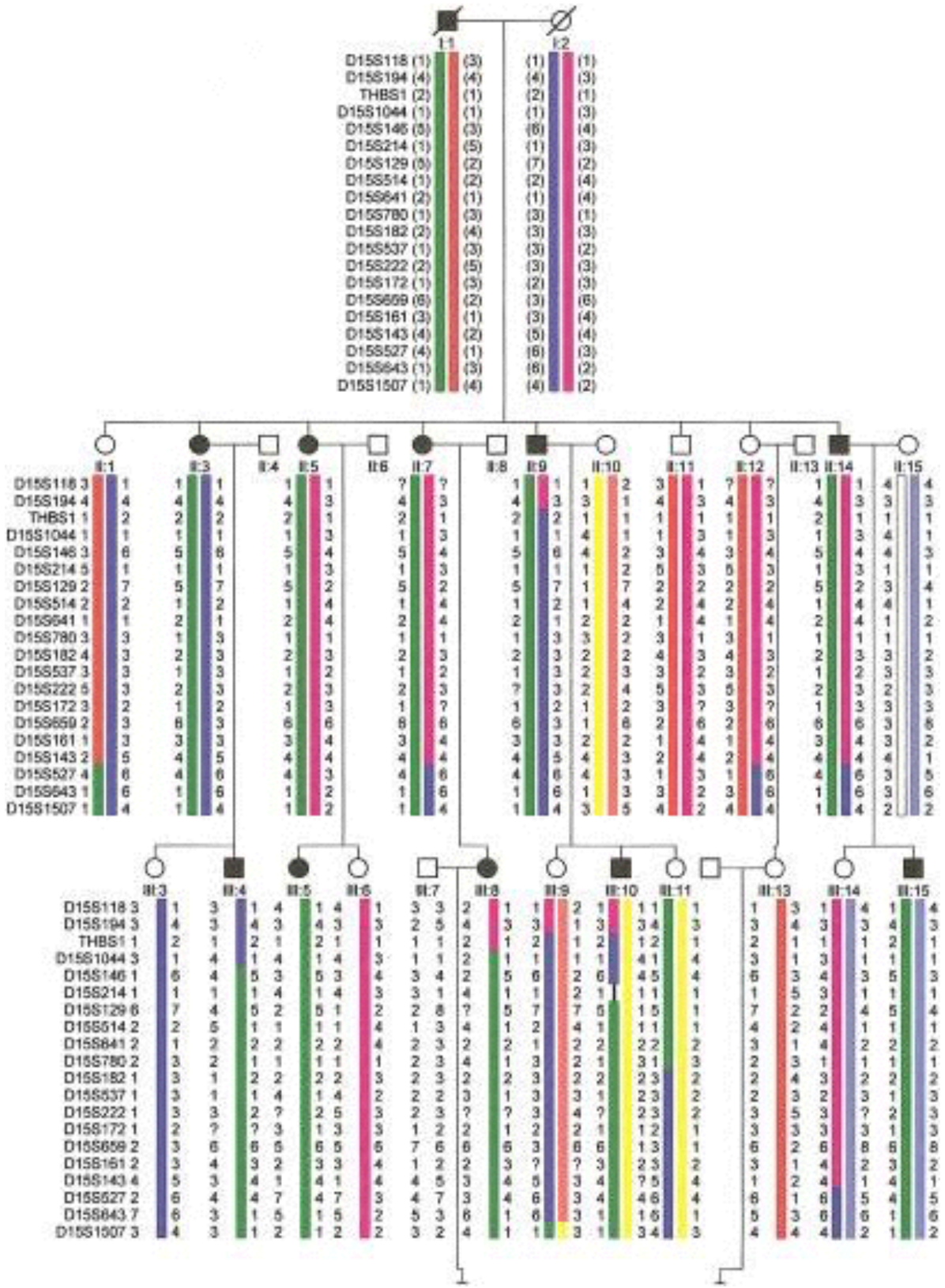
Negatives:
- Large families are rare
- Different families with the “same” disease could have different genetic causes
- Mapping resolution is 5 cM or 5 megabase pairs
- Difficult for late-onset diseases

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



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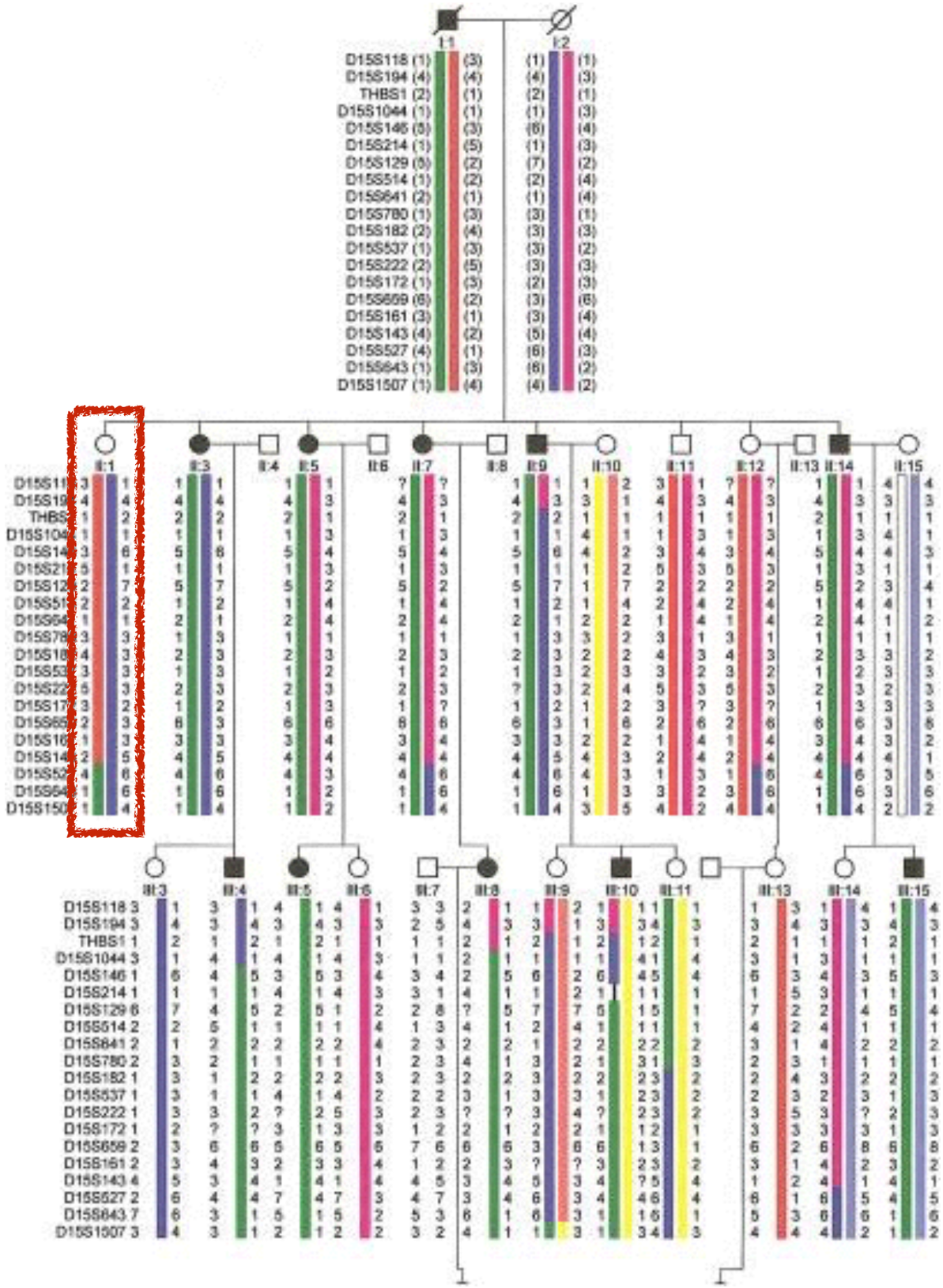

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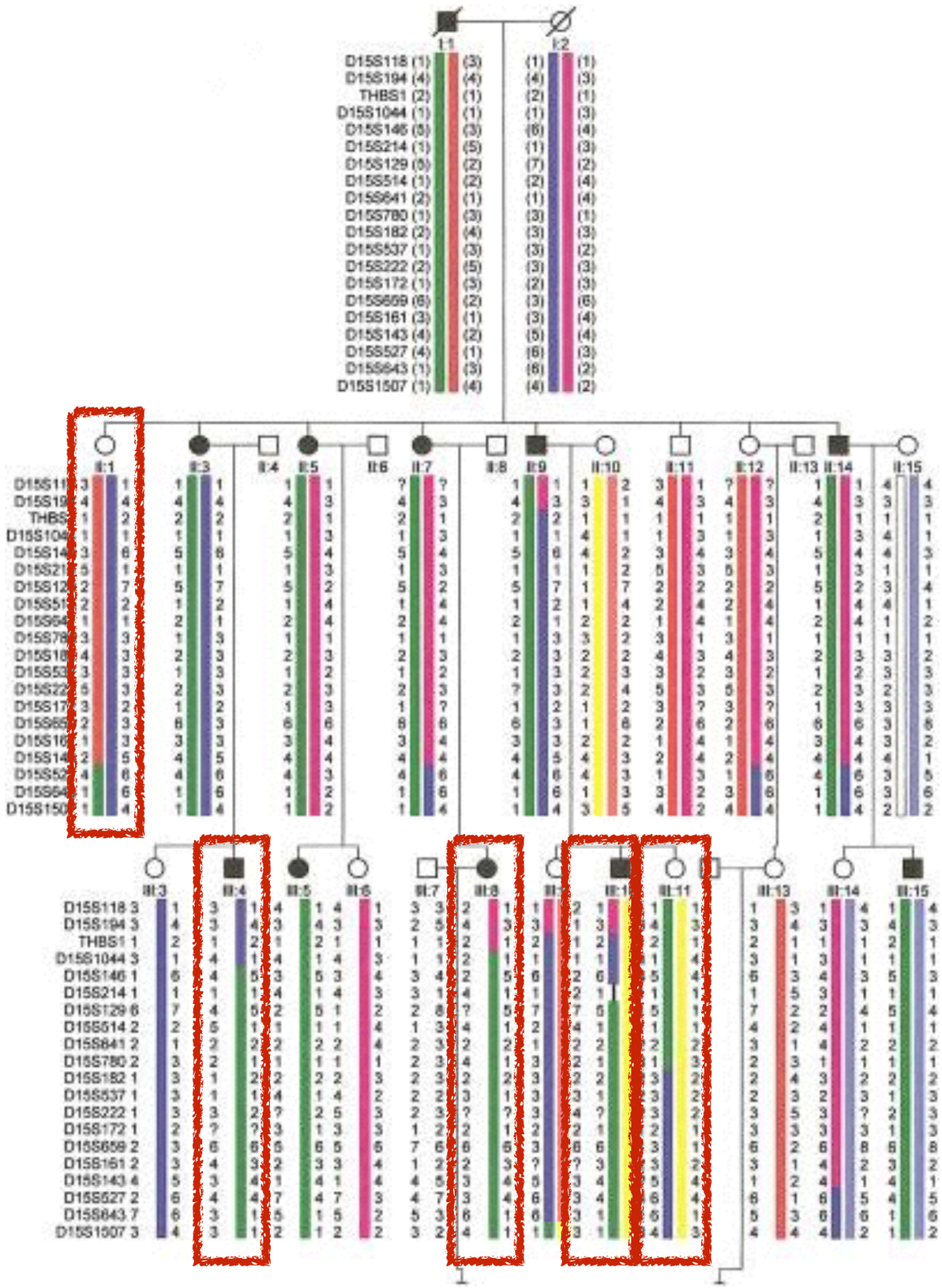
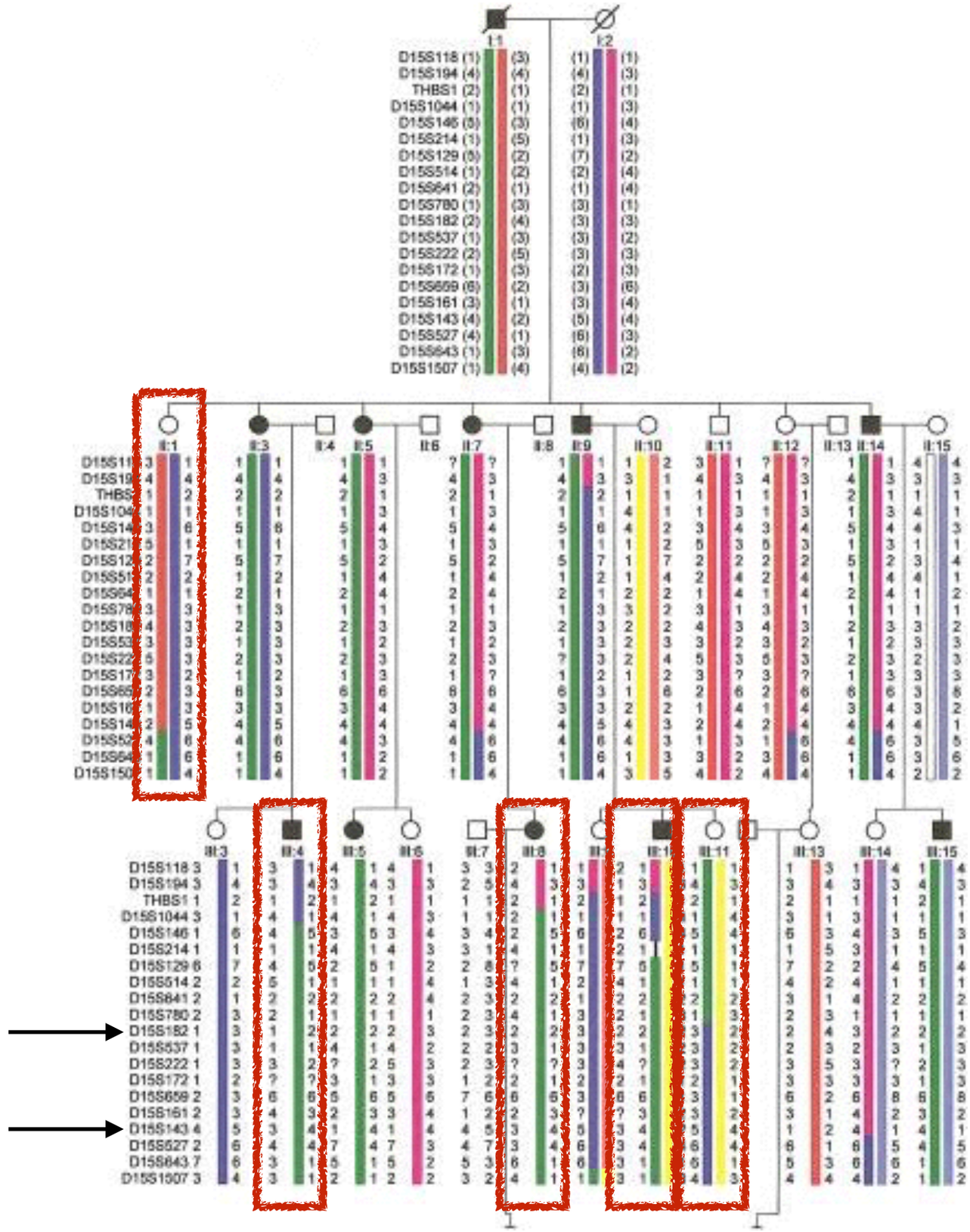
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