Quantitative genetics

2. Gene identification approaches

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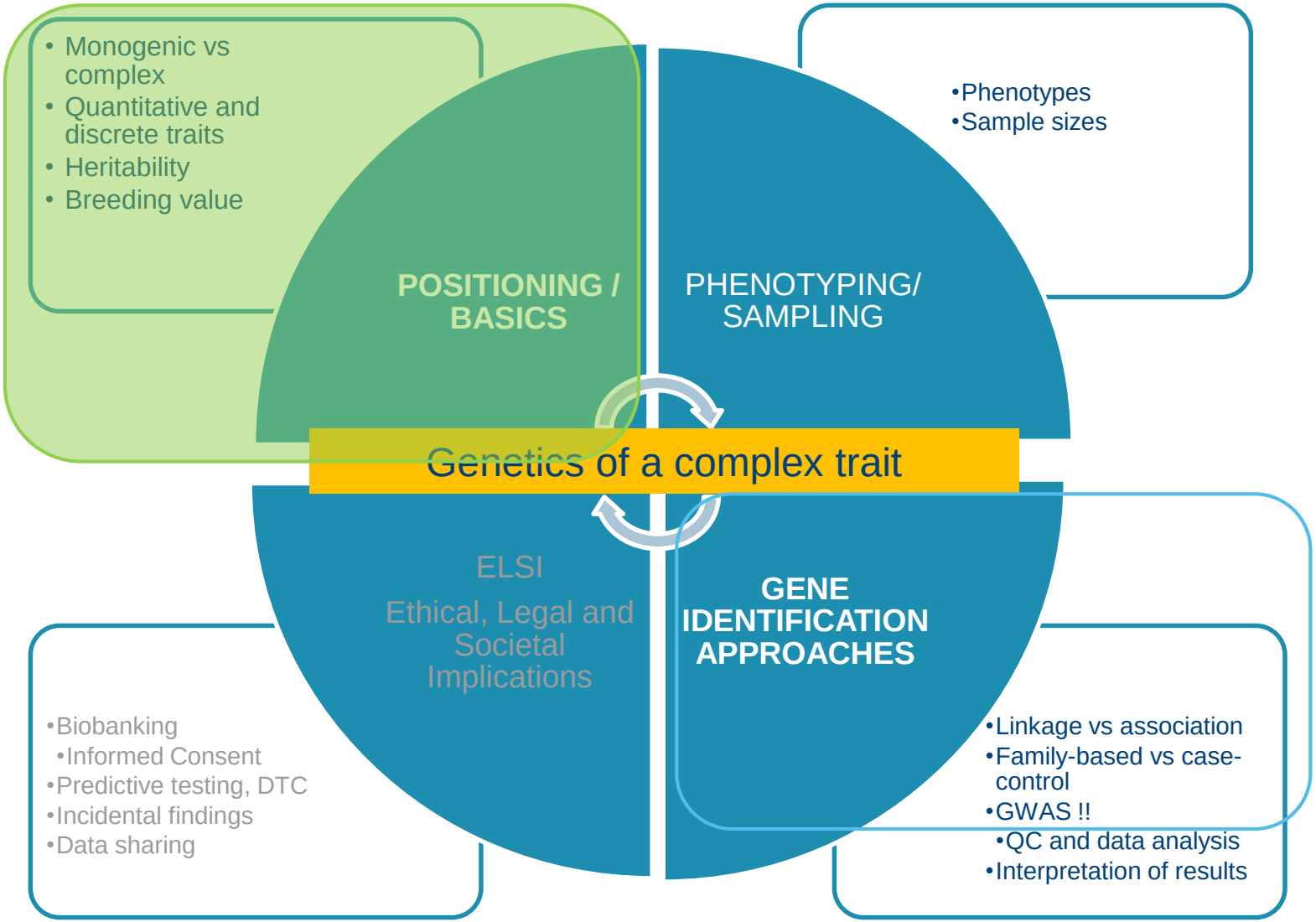
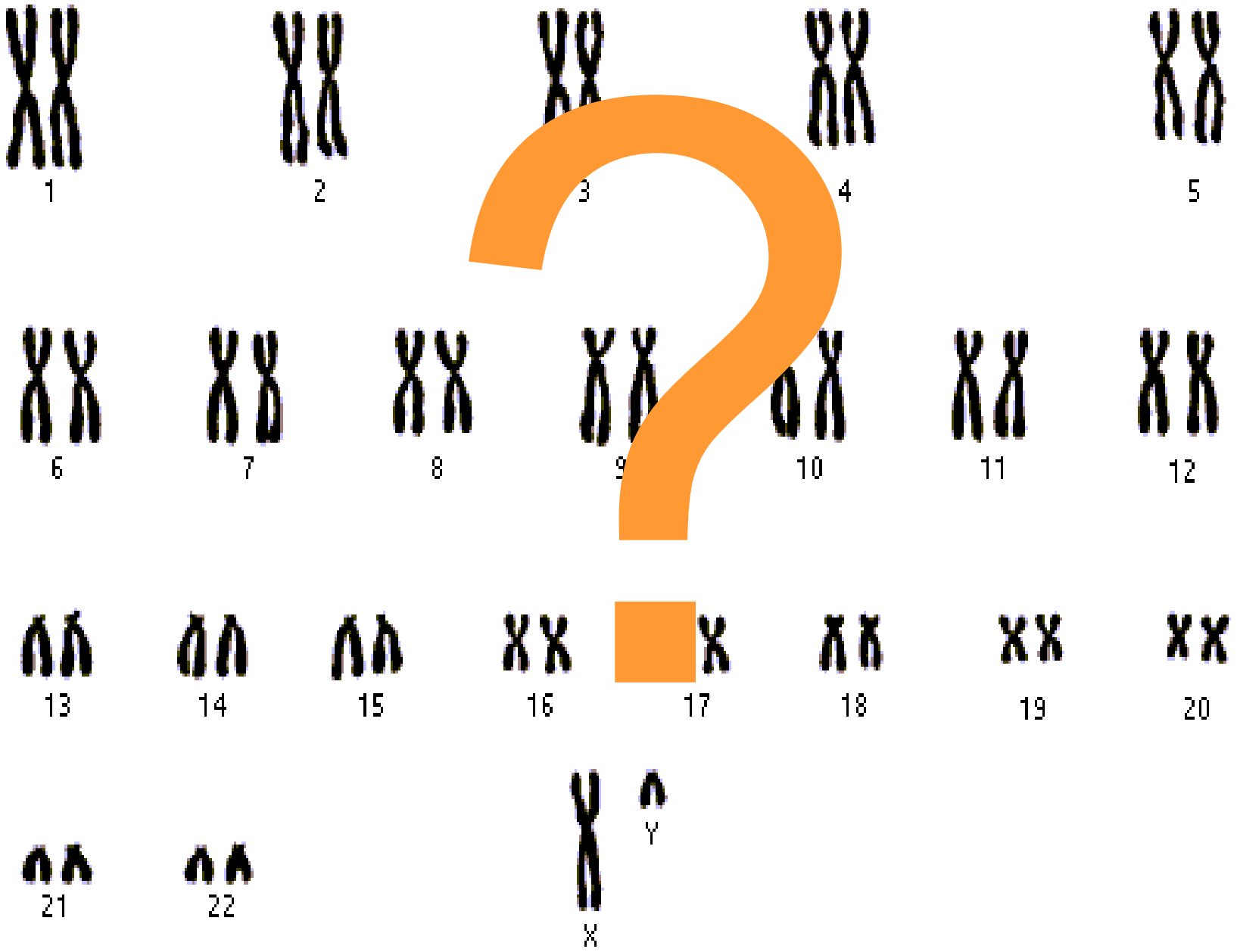

• Monogenic vs complex
• Quantitative and discrete traits
• Heritability
• Breeding value
POSITIONING / BASICS
•Phenotypes
•Sample sizes
PHENOTYPING/ SAMPLING
Genetics of a complex trait
ELSI
Ethical, Legal and Societal Implications
GENE IDENTIFICATION APPROACHES
•Biobanking
•Informed Consent
•Predictive testing, DTC
•Incidental findings
•Data sharing
•Linkage vs association
•Family-based vs case-control
•GWAS !!
•QC and data analysis
•Interpretation of results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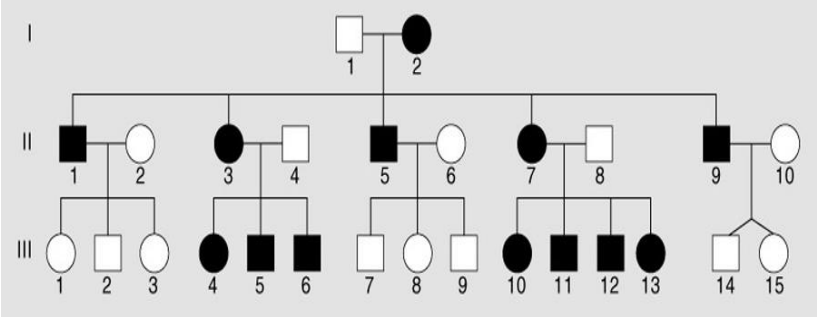
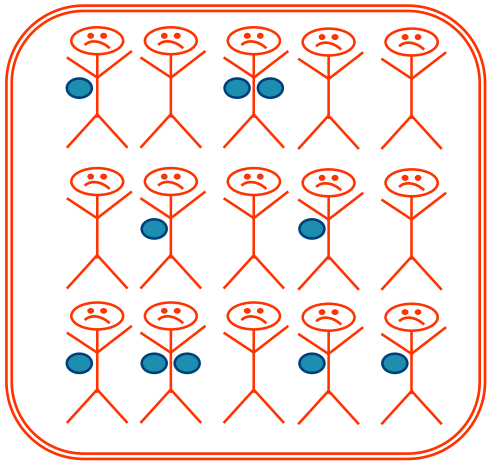
Linkage versus association

- Linkage studies

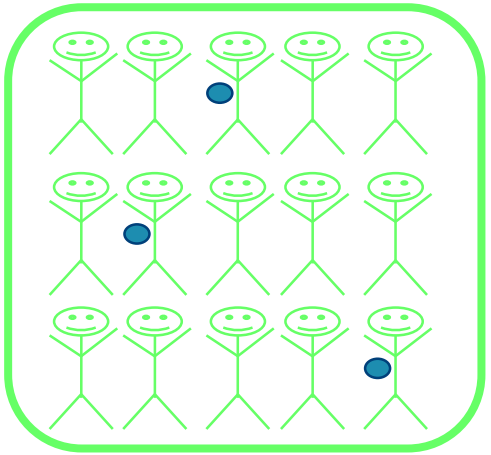


- Association studies

cases



controls



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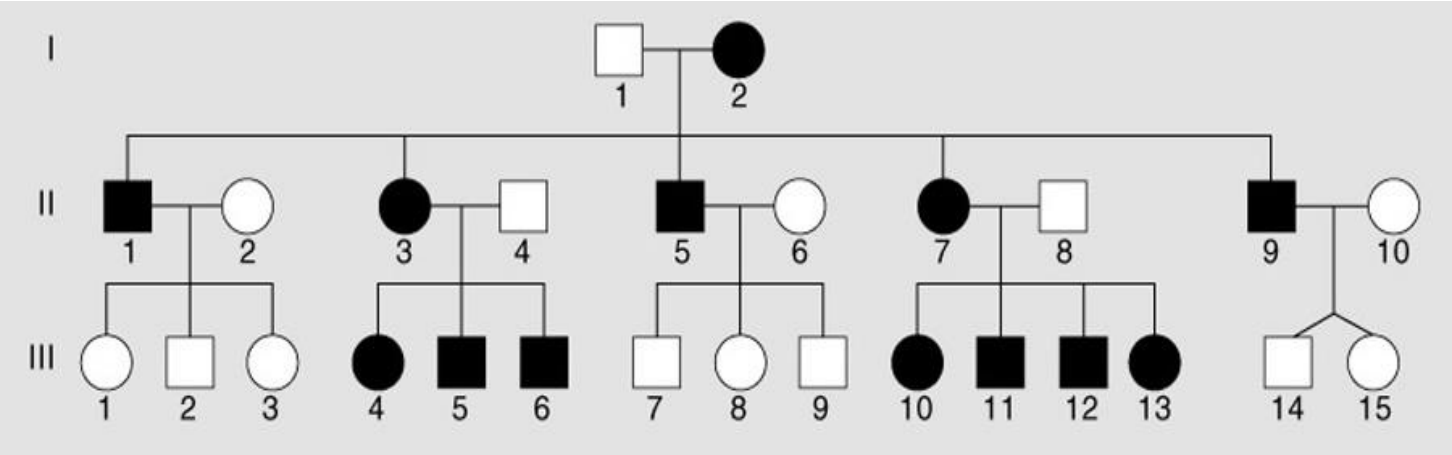
Linkage analysis

- co-segregation of genetic marker(s) and disease in a family

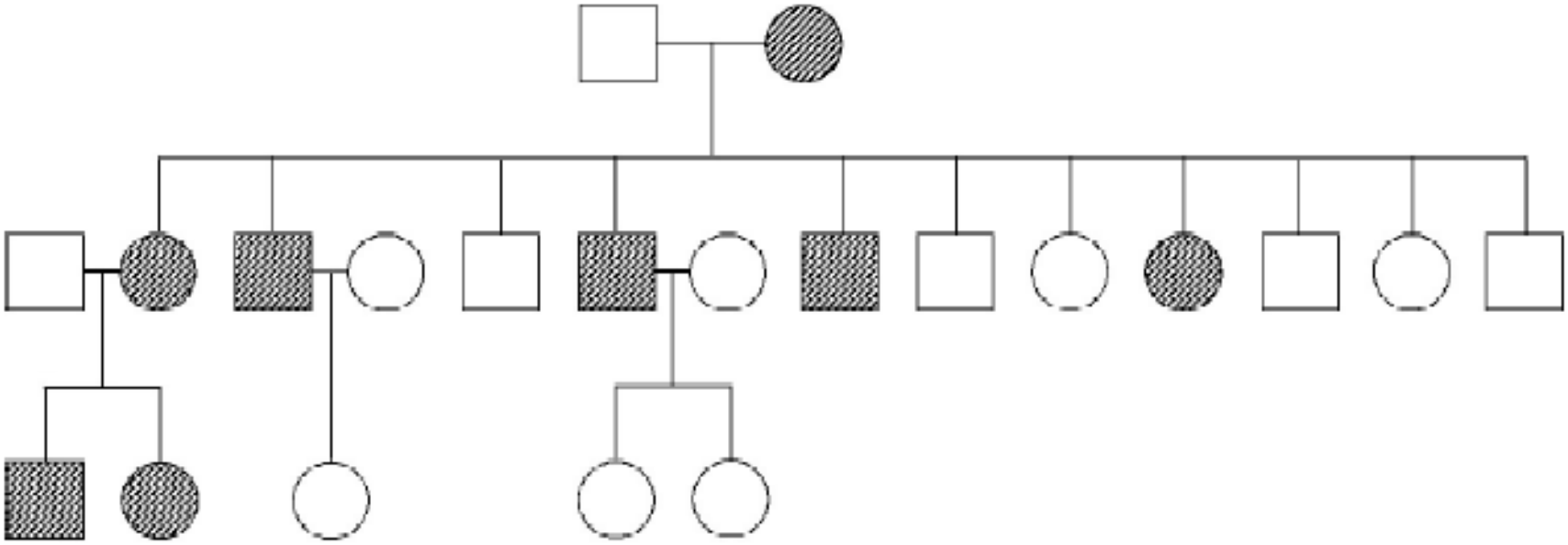


- Goal:
  - identify chromosomal region with risk gene
  - map traits of interest to particular chromosomal region

- What is linkage?
- How to quantify?
- How to use it to identify chromosomal region(s) with disease gene(s)?

Example – nail patella syndrome (NPS)

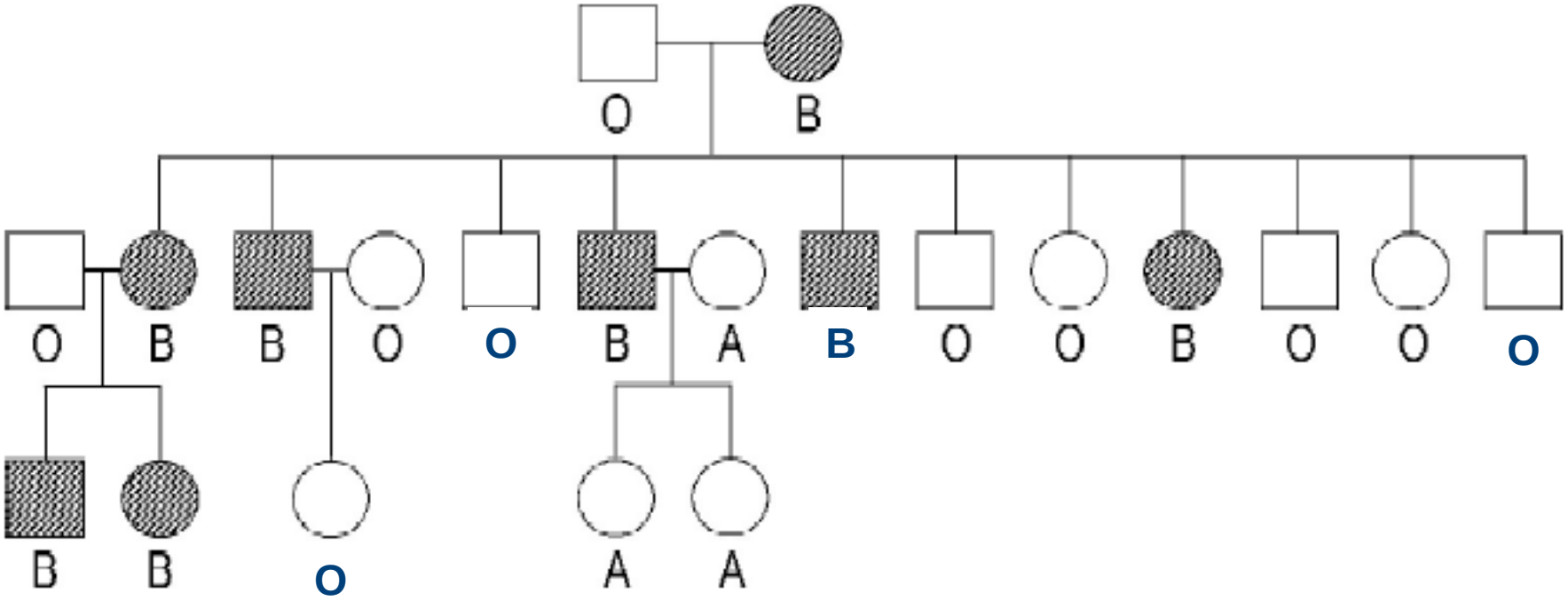
Example – Nail patella syndrome



Autosomal dominant

Example – Nail patella syndrome

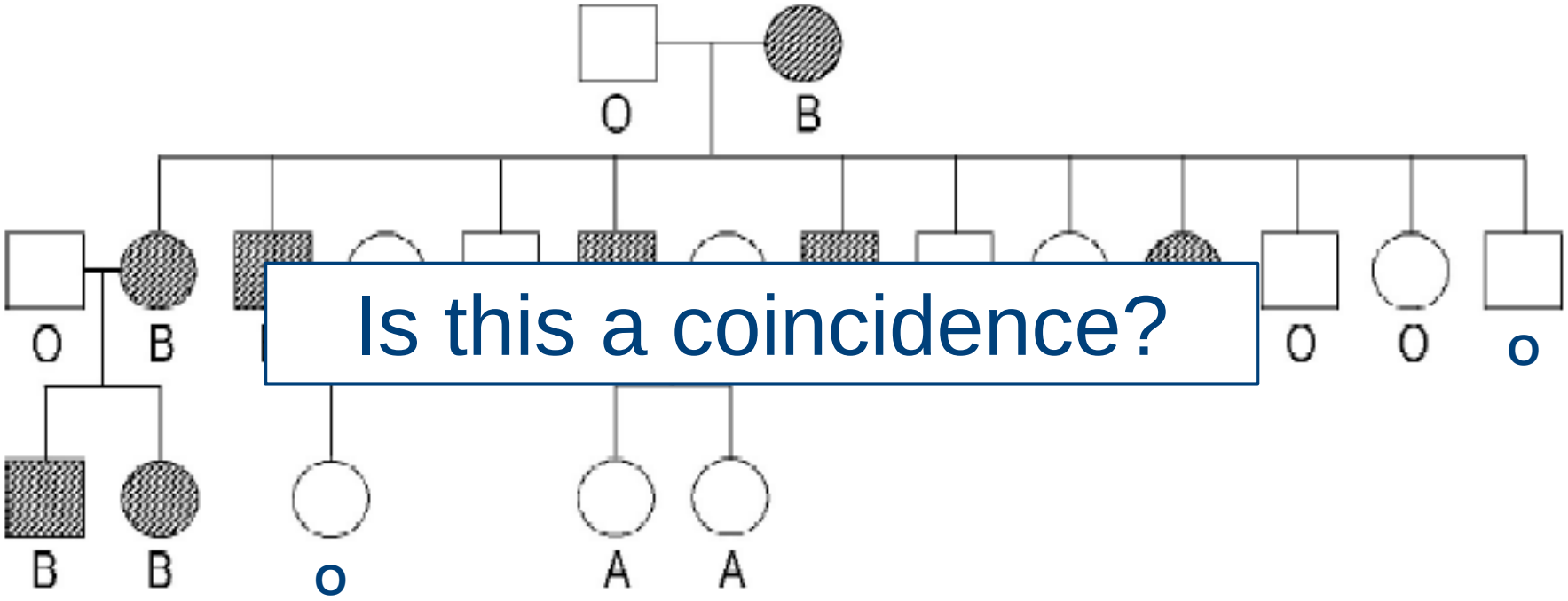
ABO-blood type



All individuals with NPS in this family have the same blood type

Example – Nail patella syndrome

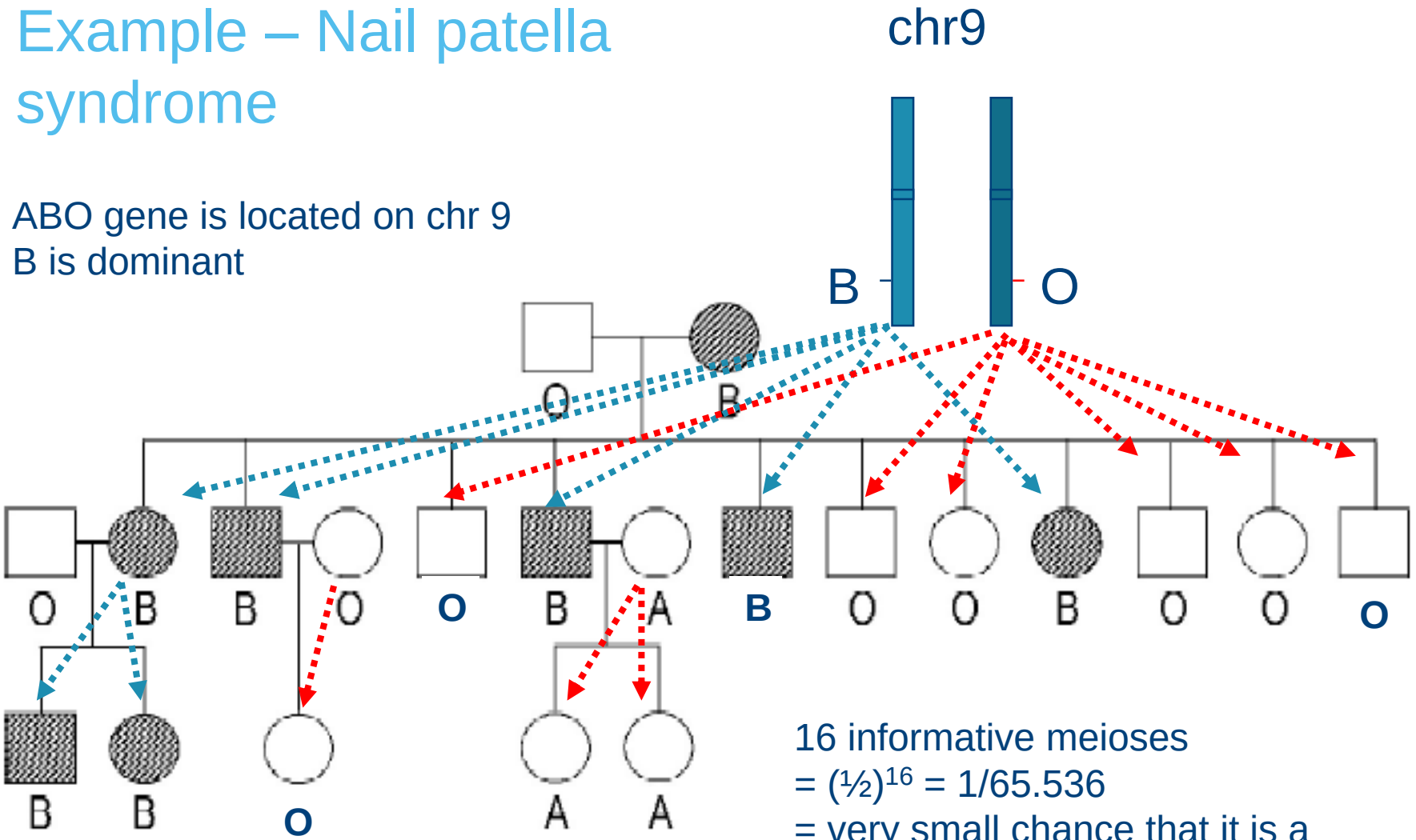
ABO-blood type



All individuals with NPS in this family have the same blood type

Example – Nail patella syndrome

- ABO gene is located on chr 9
- B is dominant



16 informative meioses
= $(½)^{16}$ = 1/65.536
= very small chance that it is a coincidence that NPS is always co-inherited with blood type

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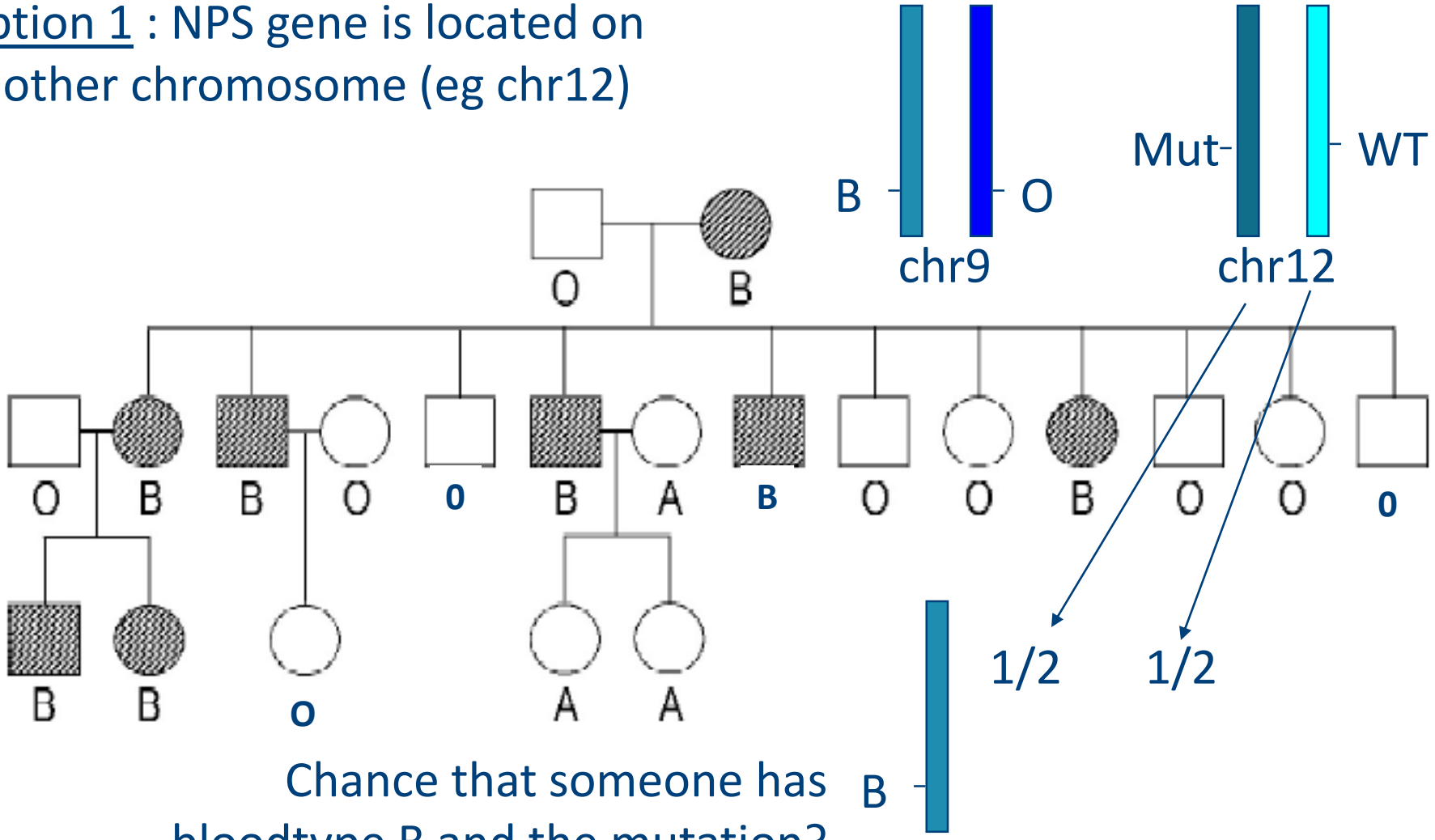
Where is the NPS gene located?

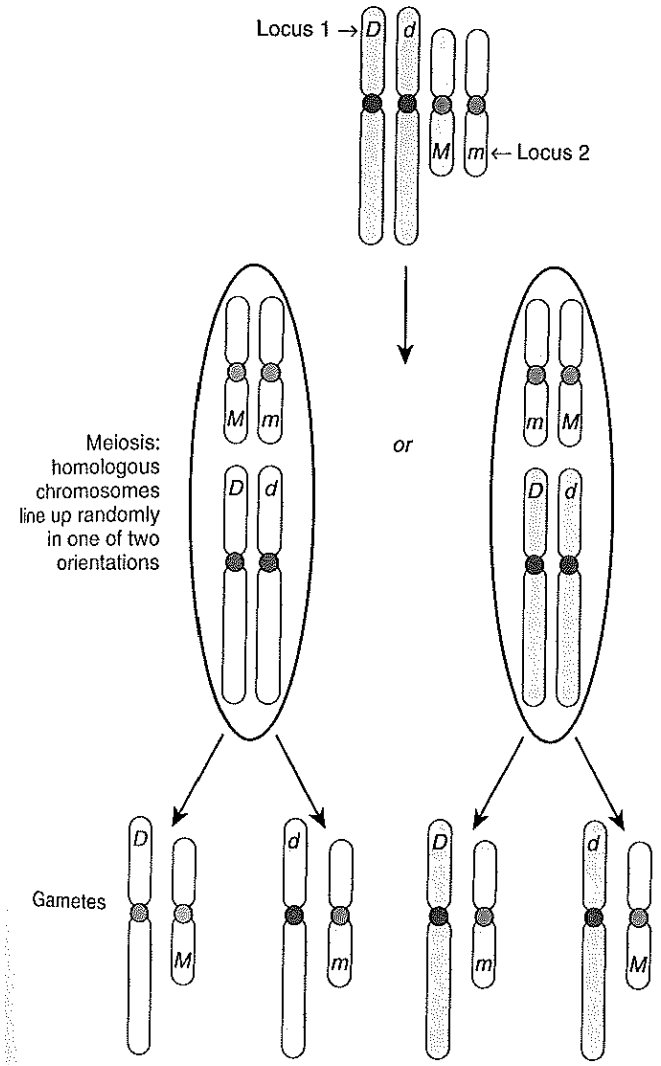
Option 1 : NPS gene is located on another chromosome (eg chr12)



Chance that someone has bloodtype B and the mutation?

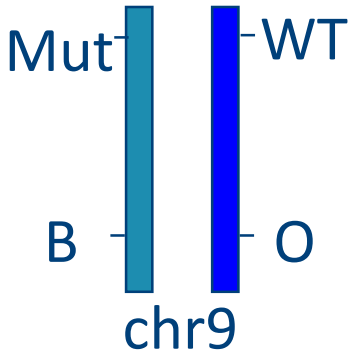
Law of independent assortment (Mendel)

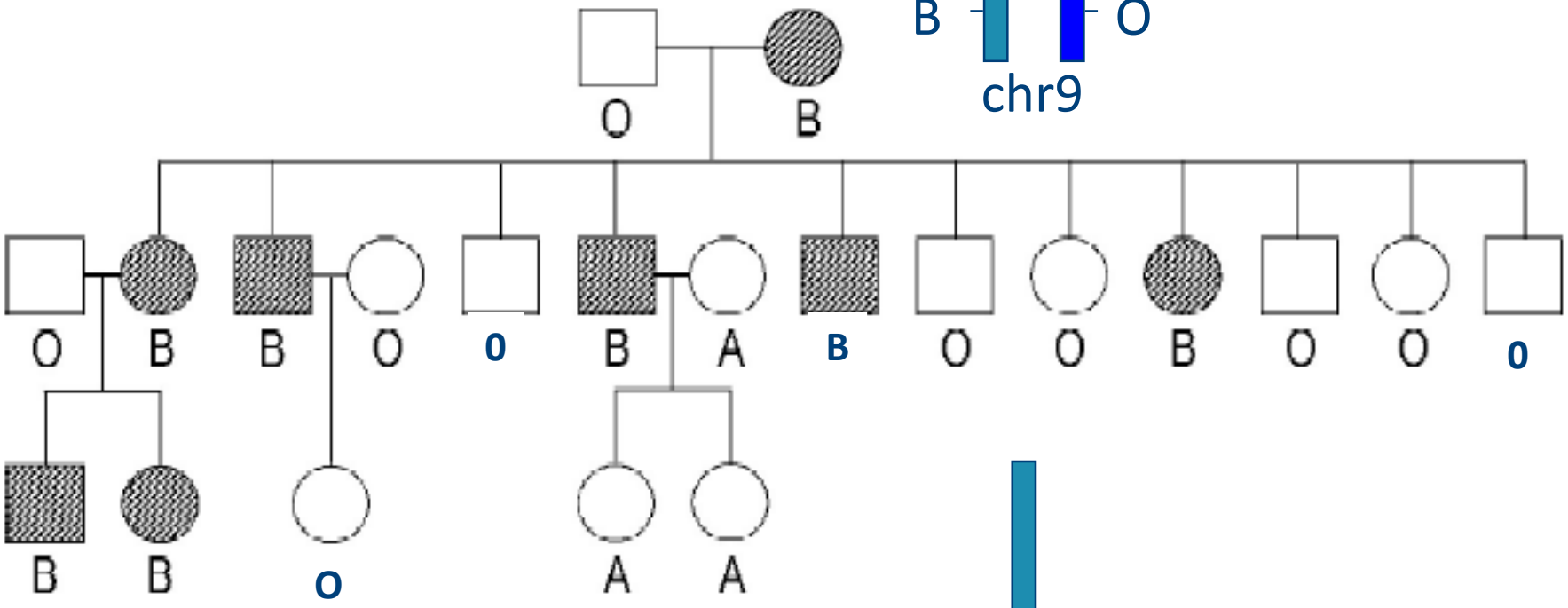
Alleles at loci on different chromosomes assort independently



Where is the NPS gene located?

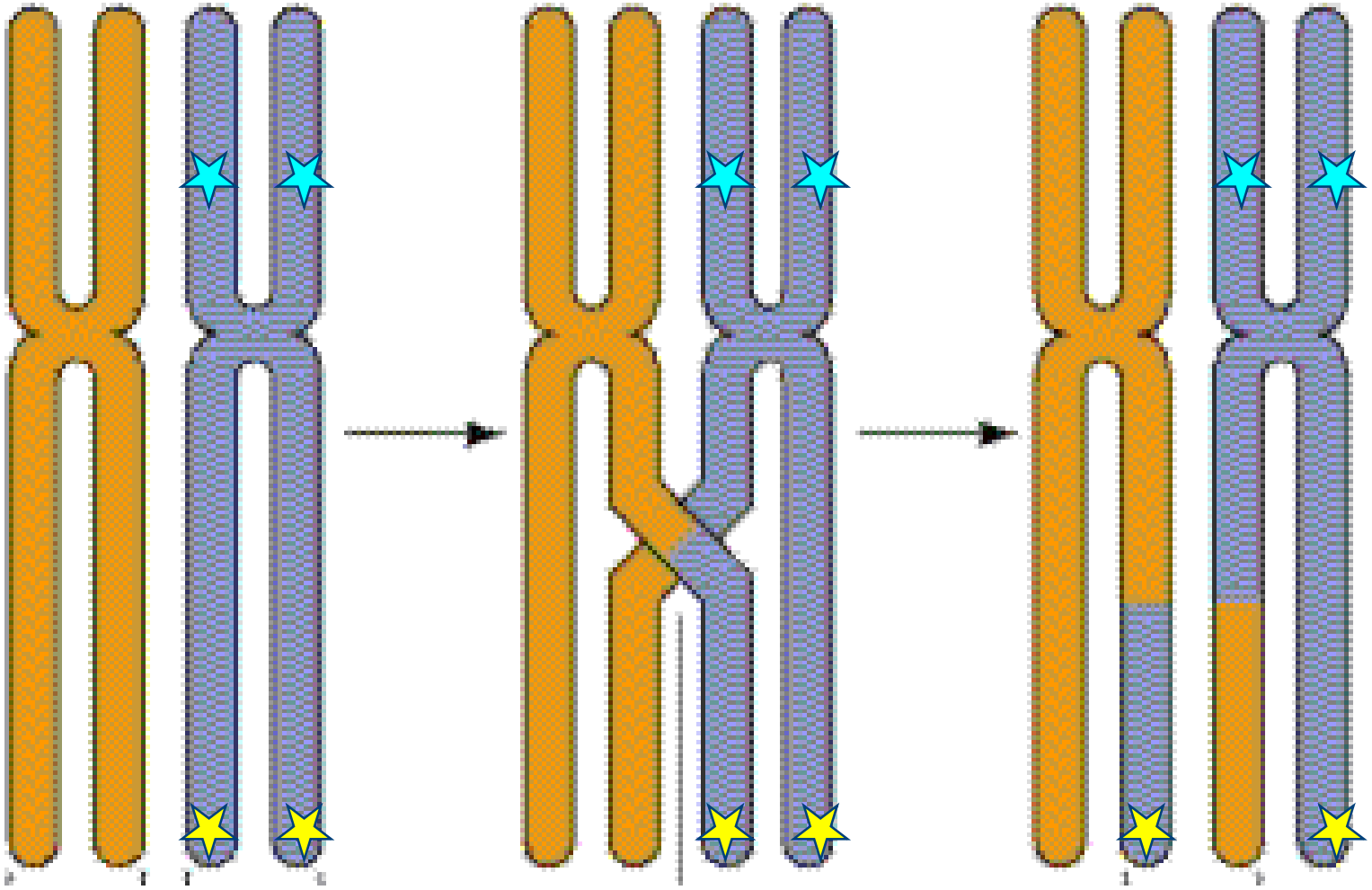
Option 1 : NPS gene is located on same chromosome, far from ABO gene





Chance that someone has bloodtype B and the mutation?

50%



CROSSING-OVER
=> are not co-inherited

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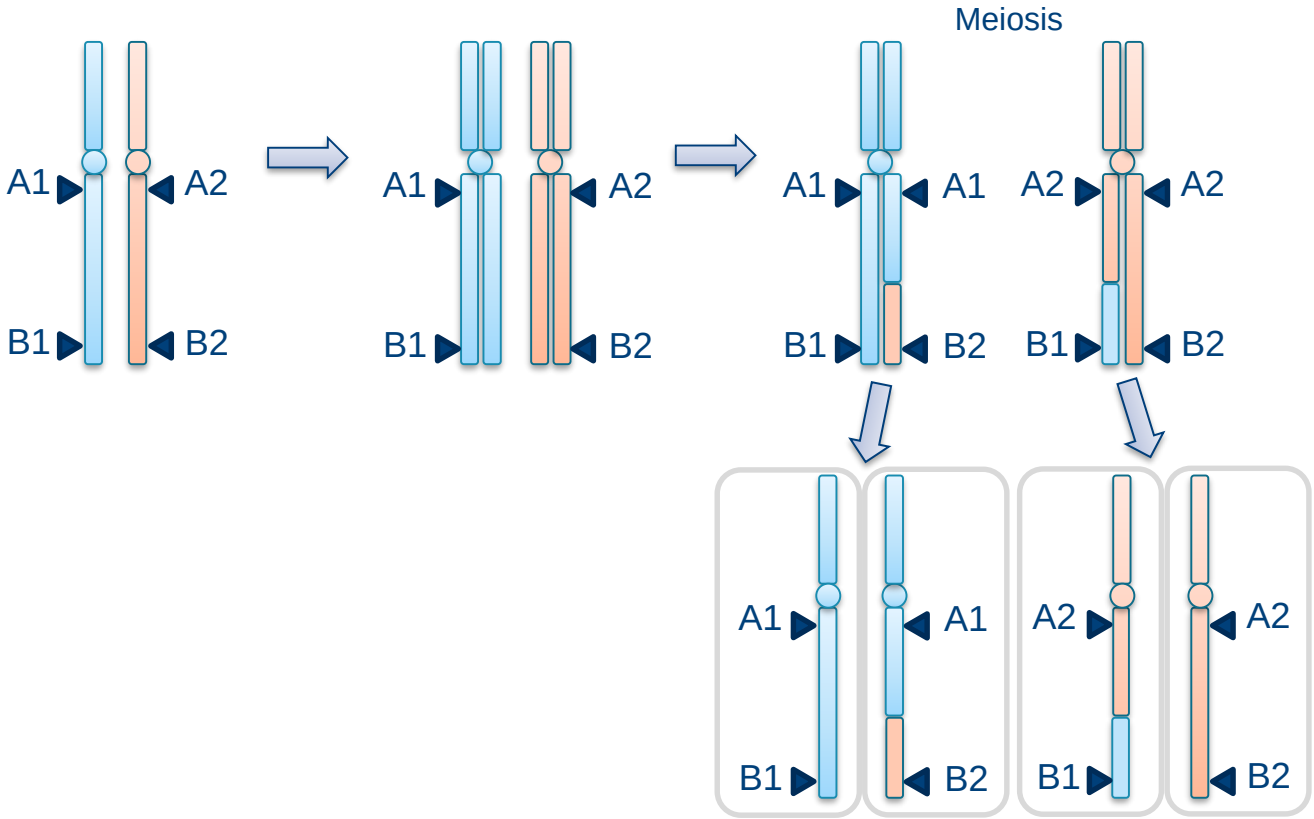
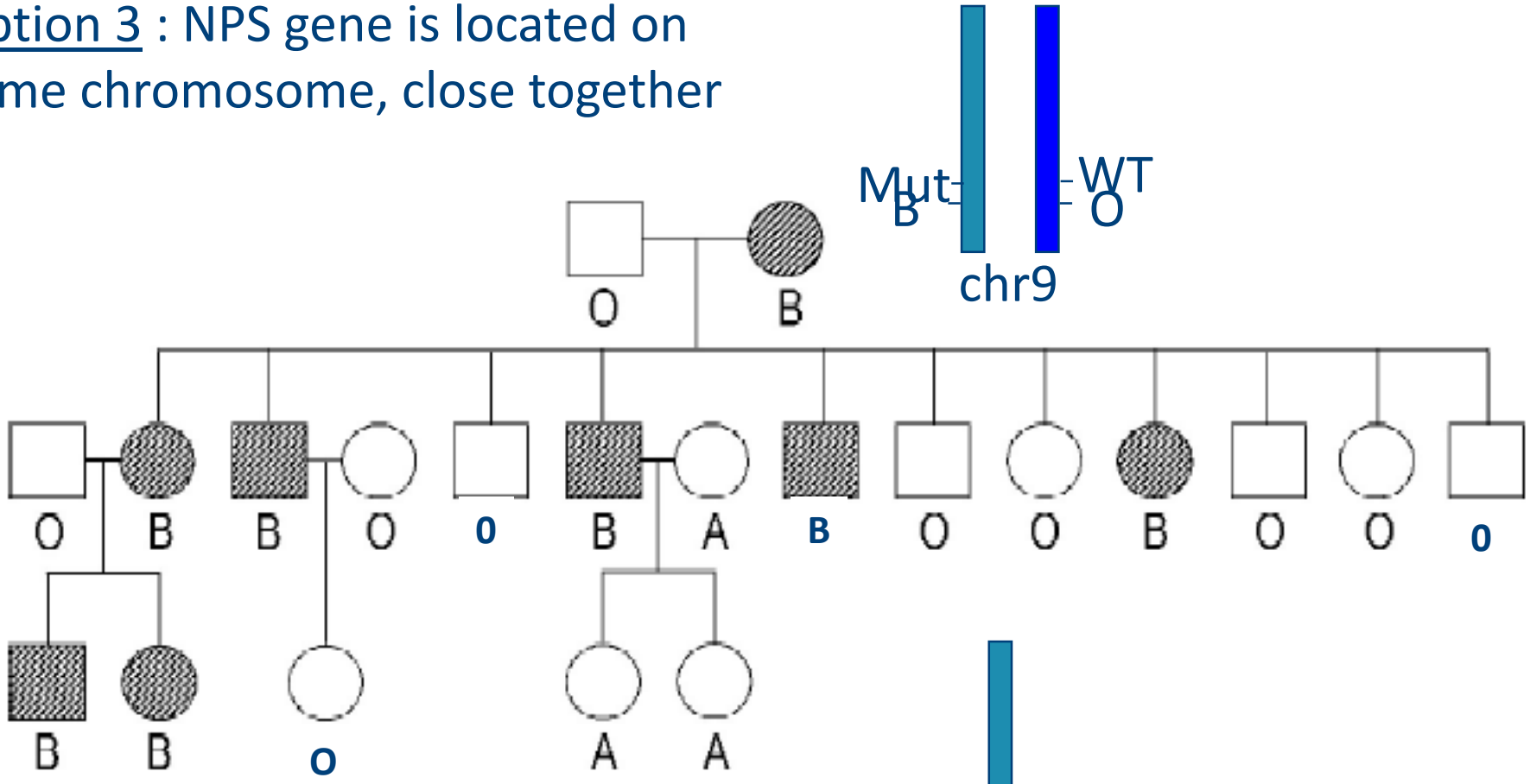
Recombination during meiosis



Where is the NPS gene located?

Option 3 : NPS gene is located on same chromosome, close together



Chance that someone has bloodtype B and the mutation?

> 50%

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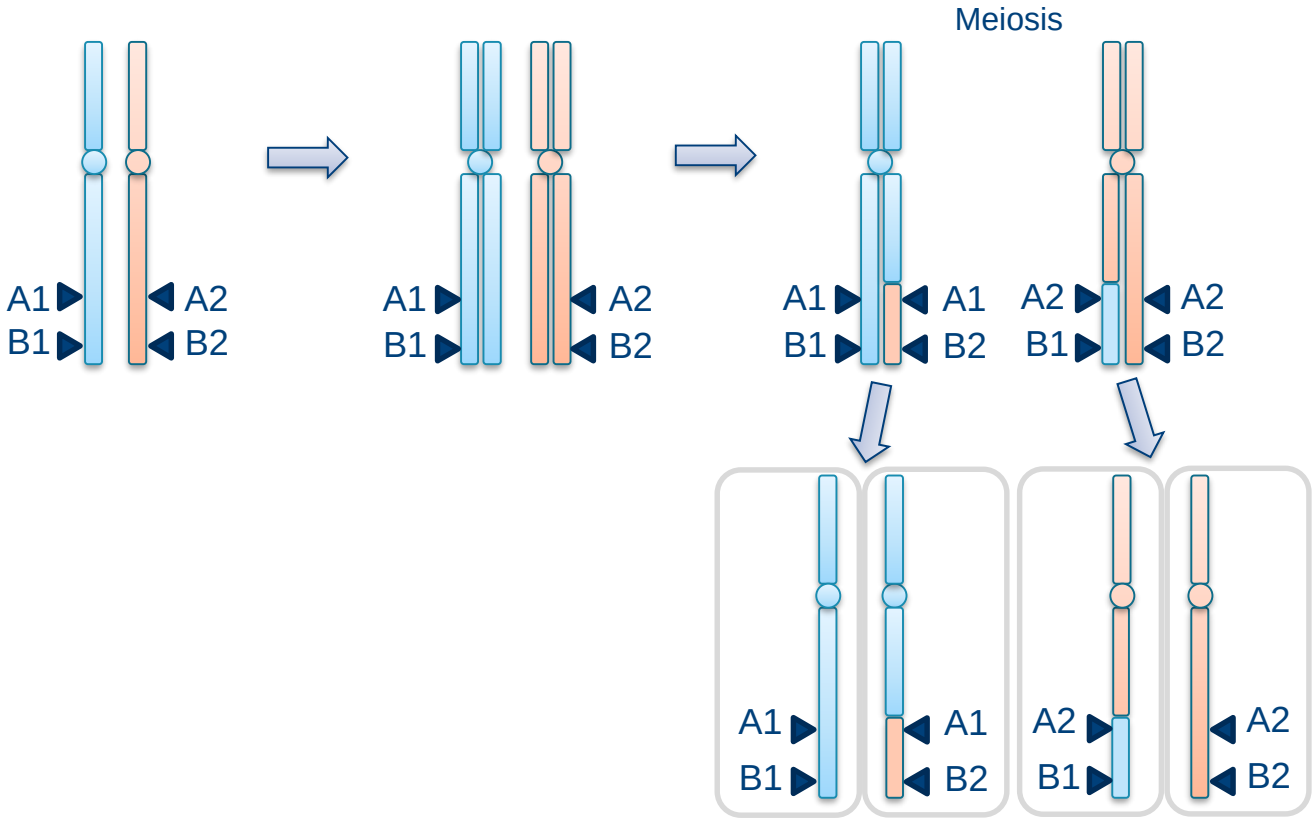
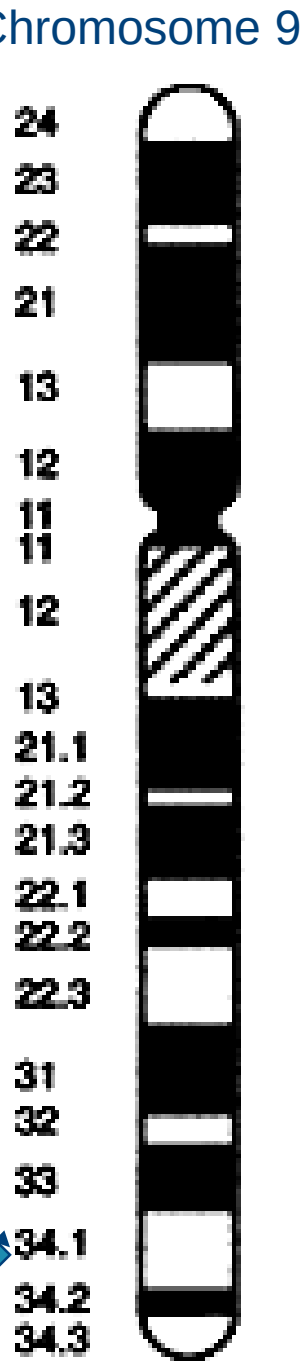
Recombination during meiosis



Where is the NPS gene located?



ABO blood type gene

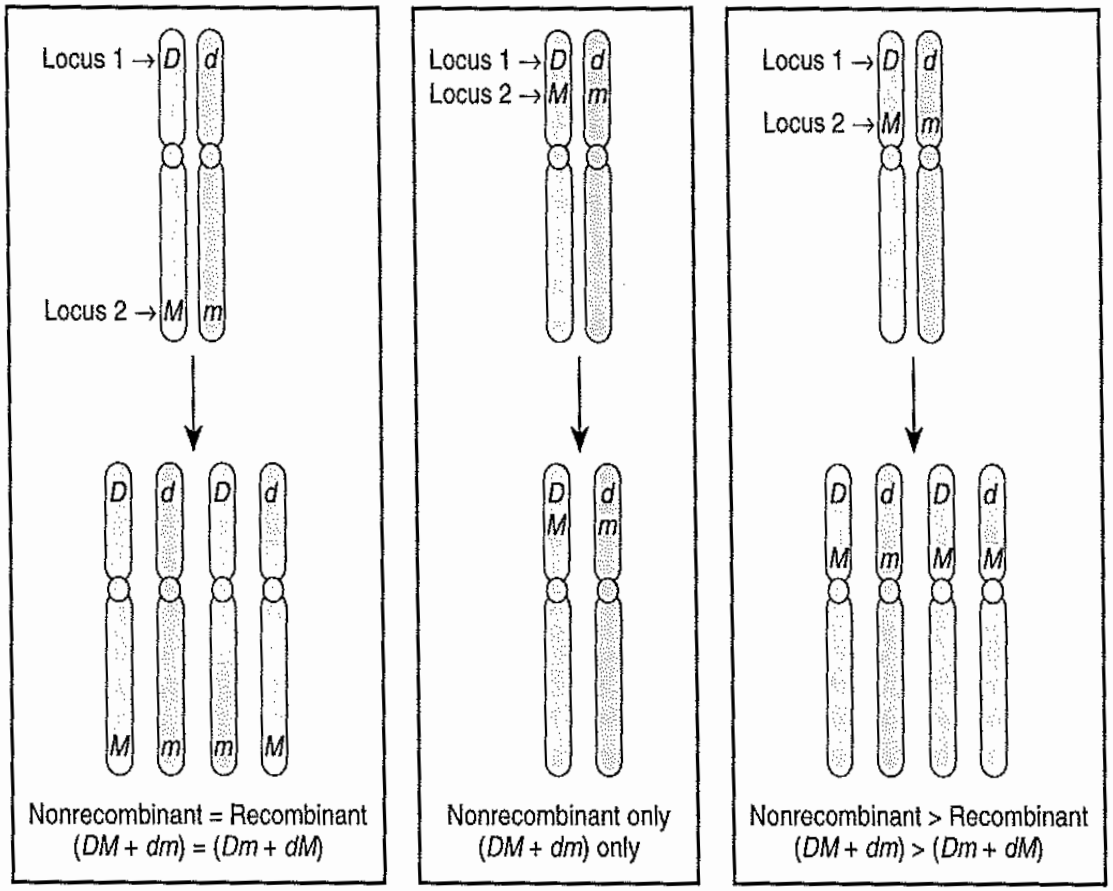
Nail Patella Syndrome gene

Linkage

- When genes are found on different chromosomes or far apart on the same chromosome, they assort independently = **unlinked**
- When genes are close together on the same chromosome, the alleles, or gene versions, will be inherited as a unit more frequently than not = **linked**

- How can we measure this?

Recombination during meiosis



50% 0% 0%<θ<50% Recombination fraction

The recombination fraction (θ) between two loci is a measure for the distance between these two loci

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Linkage

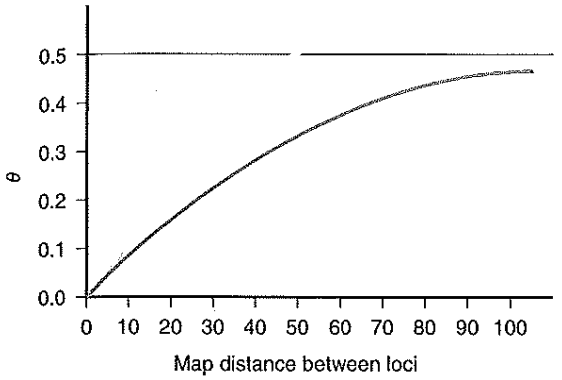
- When genes are found on different chromosomes or far apart on the same chromosome, they assort independently = **unlinked**
- When genes are close together on the same chromosome, the alleles, or gene versions, will be inherited as a unit more frequently than not = **linked**

- How can we measure this?
  - use data from genetic crosses (‘meiotic mapping’) to calculate the **recombination fraction (θ)**
  - If you do this for many gene/marker pairs, we can make **linkage maps** that show the relative distances of the genes on the chromosome

Recombination fraction θ

$$\theta = \frac{number\ of\ recombined\ gametes\ (r)}{number\ of\ gametes\ transmitted\ (n)}$$

Parent	Gametes	θ
	50% non-rec and 50% rec	0.5
	90% non-rec and 10% rec	0.1
	99% non-rec and 1% rec	0.01
	100% non-rec	0



Genetic distance

- Chromosomal position: physical vs. genetic
  - physical: base pair position (bp)
  - genetic: recombination fraction (Morgan)

- Mapping function

Kosambi (1943): $W = \frac{1}{4}\ln\left(\frac{1+2\theta}{1-2\theta}\right)$

- Globally: 1cM = 1Mb = 1% recombination
  - recombination deserts: 0.3 cM/Mb
  - recombination jungles: 3 cM/Mb

Recombination fraction θ

$$\theta = \frac{number\ of\ recombined\ gametes\ (r)}{number\ of\ gametes\ transmitted\ (n)}$$

- Recombination fraction (θ) as a measure for linkage
- $0 \leq \theta < \frac{1}{2}$?

50% chance of recombination when completely unlinked

- What is linkage?
- How to quantify?
- **How to use it to identify chromosomal region(s) with disease gene(s)?**

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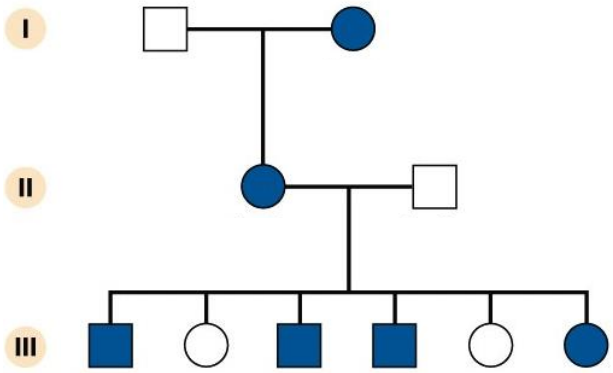
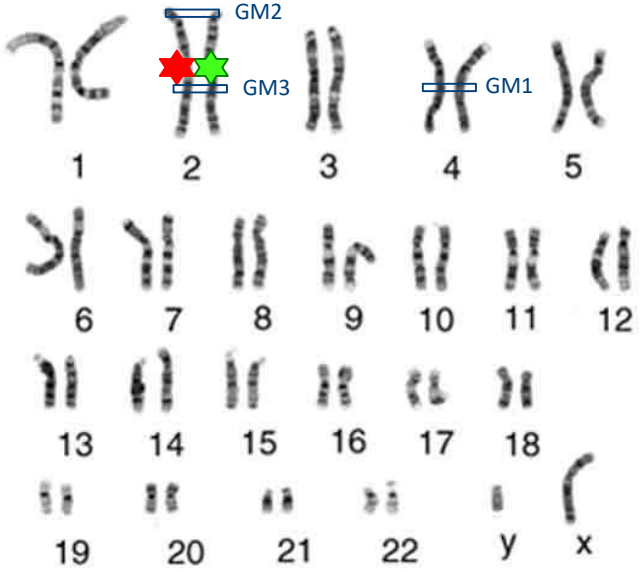
Linkage analysis

- Linkage analysis is a method that is used to decide if two loci, or a genetic marker (GM) and a disease gene, are linked :
  - Ascertain whether the recombination fraction θ between the two loci deviates significantly from 0.5





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Linkage analysis – how?

1. Collect familie(s)
2. Choose a genetic marker (eg microsatellite, SNP) for linkage analysis
3. Genotype this marker in all individuals of the familie(s)
4. Identify informative meioses (R vs NR → between heterozygous GM and heterozygous disease locus)
   - Based on the phenotype you know the disease locus genotype (affected vs unaffected)
   - Is phase known?
5. Determine whether there is linkage between the GM locus and the disease locus
   - Determine recombination fraction θ

$$log_{10}\left[\frac{Likelihood\ of\ linkage\ (\theta)}{Likelihood\ that\ loci\ are\ unlinked\ \left(\theta=\frac{1}{2}\right)}\right] = log_{10}\left[\frac{L\ (\theta)}{L\left(\theta=\frac{1}{2}\right)}\right] = log_{10}\left[\frac{(1-\theta)^{NR} * \theta^{R}}{0.5^{(R+NR)}}\right]$$ = max

   - Is this recombination significantly different from 0.5?

     (= null hypothesis; no linkage between GM and disease locus)

$$log_{10}\left[\frac{Likelihood\ of\ linkage\ (\theta)}{Likelihood\ that\ loci\ are\ unlinked\ \left(\theta=\frac{1}{2}\right)}\right] = log_{10}\left[\frac{L\ (\theta)}{L\left(\theta=\frac{1}{2}\right)}\right] = log_{10}\left[\frac{(1-\theta)^{NR} * \theta^{R}}{0.5^{(R+NR)}}\right]$$ ≥ 3 ?

6. Do we need more informative meioses / families?

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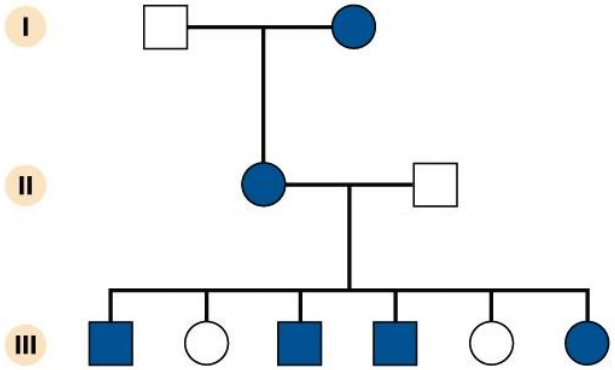
Collect families



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6. Do we need more informative meioses / families?

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Linkage analysis: genetic markers

- Requirements
  - polymorphic
  - informative = high mean heterozygosity

- Types: RFLPs, microsatellites & SNPs

- Advantages
  - easy to detect
  - relatively inexpensive to test easily available material

Linkage analysis – how?

1. Collect familie(s)
2. Choose a genetic marker (eg microsatellite, SNP) for linkage analysis
3. Genotype this marker in all individuals of the familie(s)
4. Identify informative meioses (R vs NR → between heterozygous GM and heterozygous disease locus)
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6. Do we need more informative meioses / families?

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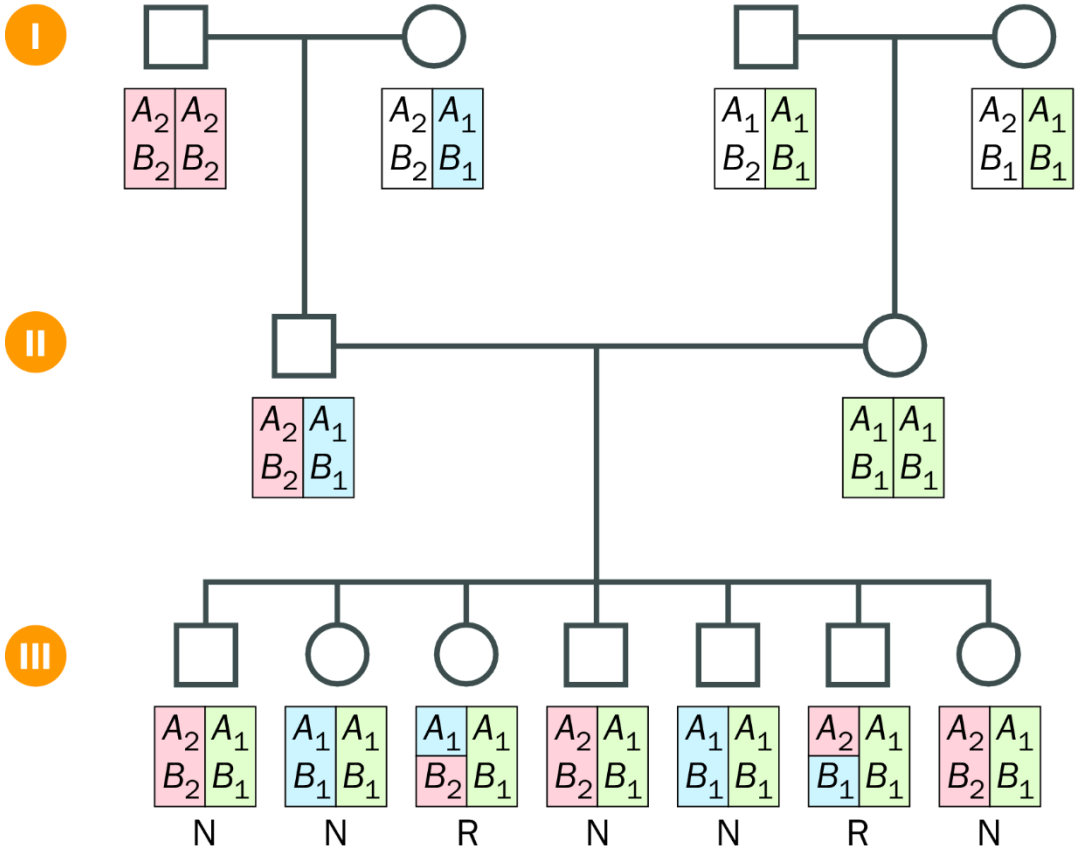
Recombinants vs non-recombinants



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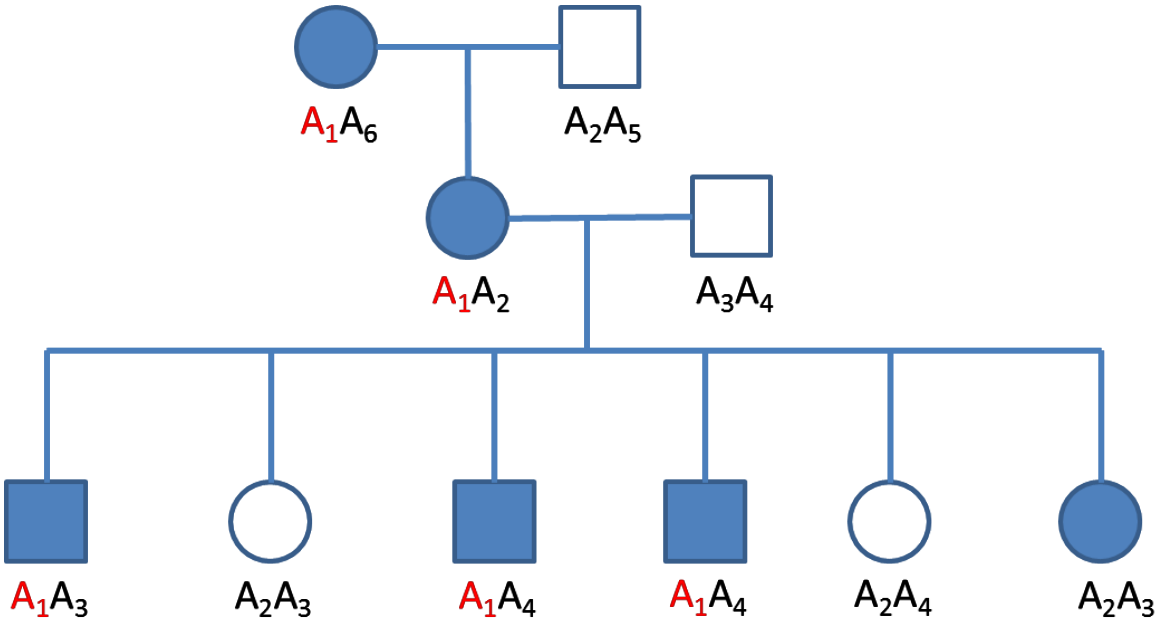
Recombinants vs non-recombinants

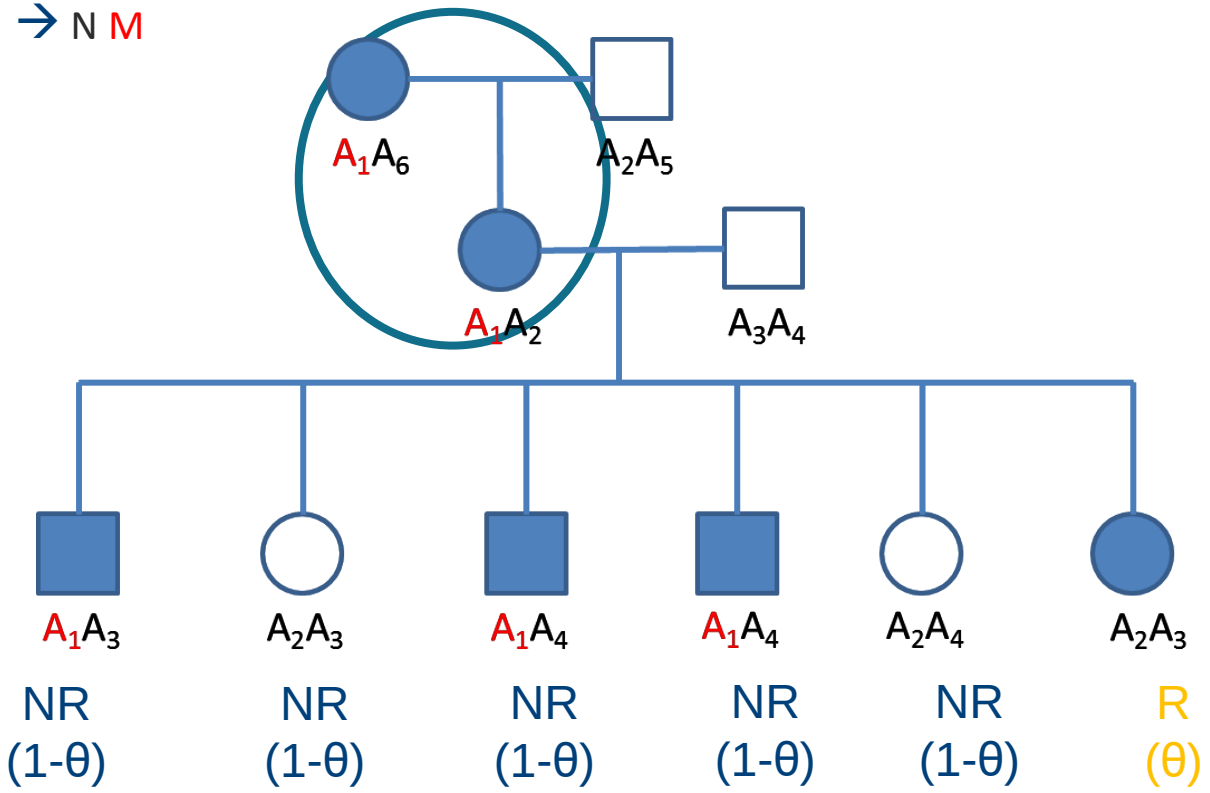
Phase known?



Based on Strachan & Read (2004)

Recombinants vs non-recombinants

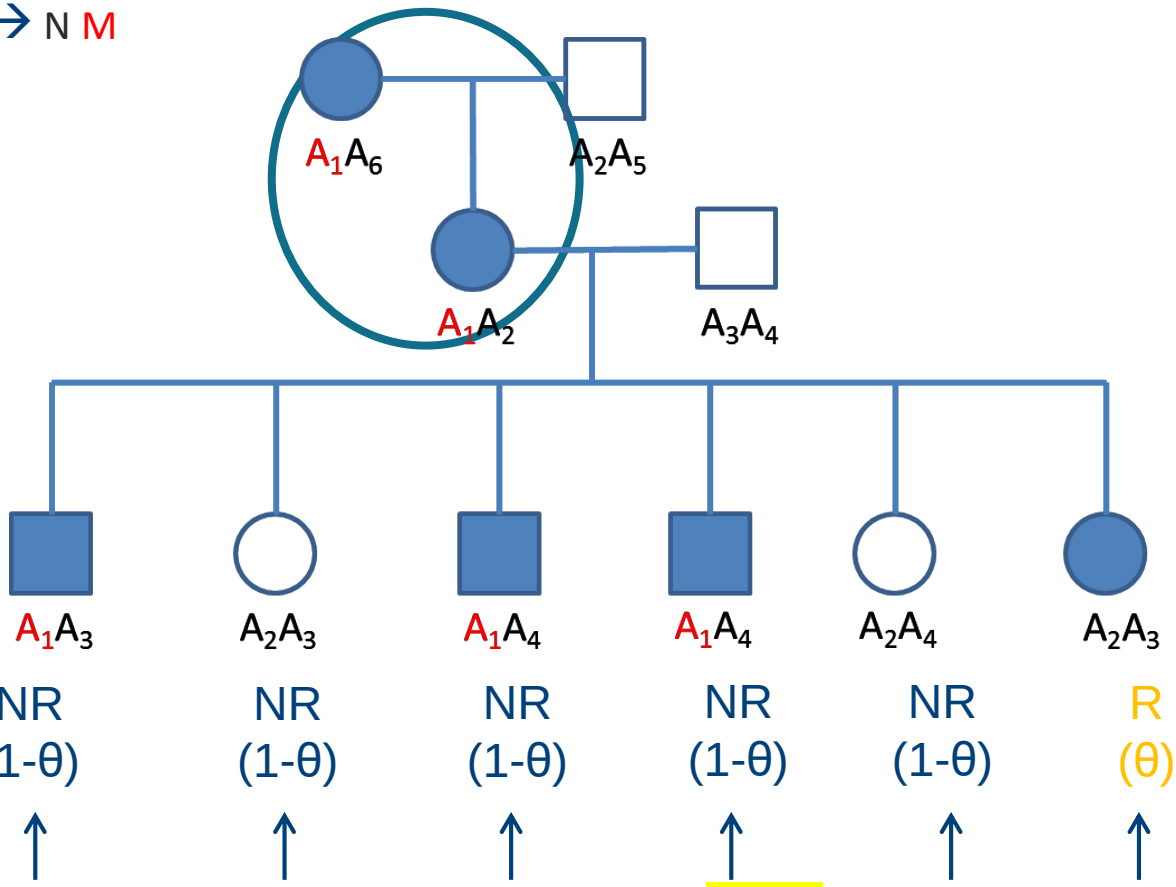
Phase known → N M



Based on Strachan & Read (2004)

Recombinants vs non-recombinants

Phase known → N M



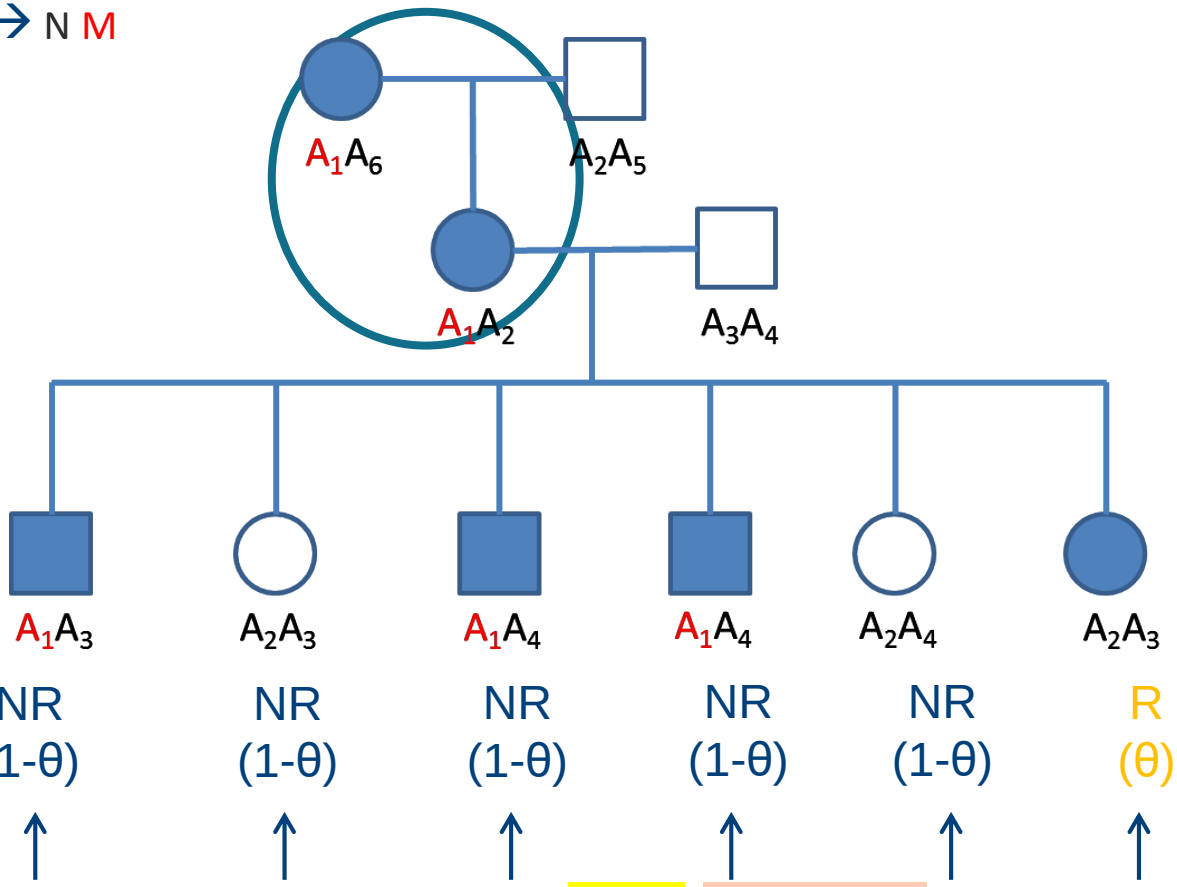
Chance for this observation when marker locus is linked with disease locus via θ?

$$L(\theta) = (1 - \theta)^5 * \theta^1$$

Based on Strachan & Read (2004)

Recombinants vs non-recombinants

Phase known → N M



Chance for this observation when marker locus is linked/NOT linked with disease locus via θ?

$L(\theta) = (1 - \theta)^5 * \theta^1$

$(1 - 0.5)^5 * 0.5 = 0.5^6$

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Based on Strachan & Read (2004)

Linkage analysis – LOD score

- $Odds = \frac{Likelihood\ of\ linkage\ (\theta)}{Likelihood\ that\ loci\ are\ unlinked\ \left(\theta=\frac{1}{2}\right)} = \frac{L\ (\theta)}{L\left(\theta=\frac{1}{2}\right)} = \frac{(1-\theta)^5 * \theta^1}{0.5^6}$

- $Logarithm\ of\ odds = LOD\ score\ (Z) = log_{10}\left[\frac{L\ (\theta)}{L\left(\theta=\frac{1}{2}\right)}\right]$

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Linkage analysis – LOD score

- $Odds = \frac{Likelihood\ of\ linkage\ (\theta)}{Likelihood\ that\ loci\ are\ unlinked\ \left(\theta=\frac{1}{2}\right)} = \frac{L\ (\theta)}{L\left(\theta=\frac{1}{2}\right)} = \frac{(1-\theta)^5 * \theta^1}{0.5^6}$

>1

What is most likely θ?

- $Logarithm\ of\ odds = LOD\ score\ (Z) = log_{10}\left[\frac{L\ (\theta)}{L\left(\theta=\frac{1}{2}\right)}\right]$

>0

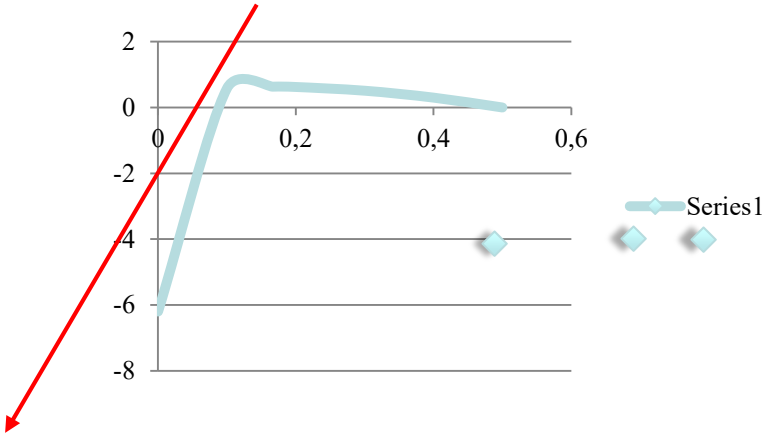
Most likely θ ?

$$\log_{10}\left[\frac{\Theta^{R} \times (1-\Theta)^{NR}}{0.5^{(R+NR)}}\right]$$

R = # rec. = 1

NR = # non-rec. = 5

teta	0.00000001	0.1	0.16666667	0.2	0.3	0.4	0.5
lod score	-6.19382	0.57739252	0.63212249	0.6226599	0.50879143	0.29899622	0



Is this significantly different from 0.5 ?

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Linkage analysis – LOD score

- $Odds = \frac{Likelihood\ of\ linkage\ (\theta)}{Likelihood\ that\ loci\ are\ unlinked\ \left(\theta=\frac{1}{2}\right)} = \frac{L\ (\theta)}{L\left(\theta=\frac{1}{2}\right)} = \frac{(1-\theta)^5 * \theta^1}{0.5^6}$

  >1

- $Logarithm\ of\ odds = LOD\ score\ (Z) = log_{10}\left[\frac{L\ (\theta)}{L\left(\theta=\frac{1}{2}\right)}\right]$

  >0 → ≥3 ?

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Z=3.0 threshold for accepting linkage with a 5% chance of a type1 error (falsely rejecting the null hypothesis)

Hypothesis	**Loci are linked** (recombination fraction = θ)	**Loci are not linked** (recombination fraction = 0.5)
Prior probability	1/50	49/50
Conditional likelihood: 1000:1 odds of linkage [lod score $Z(\theta) = 3.0$]	1000	1
Joint probability (prior × conditional)	20	~1

Box 14.3 Human Molecular Genetics, 4ed. (© Garland Science)

Most likely θ ?

$$\log_{10}\left[\frac{\Theta^{R} \times (1-\Theta)^{NR}}{0.5^{(R+NR)}}\right]$$

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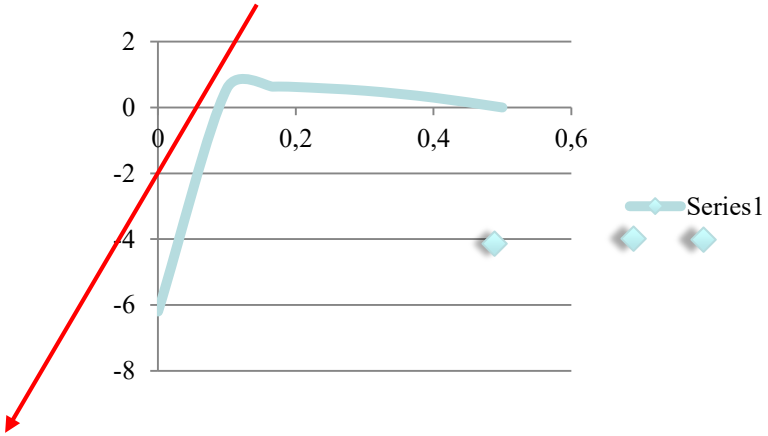

Is this significantly different from 0.5 ? → ≥3 ?

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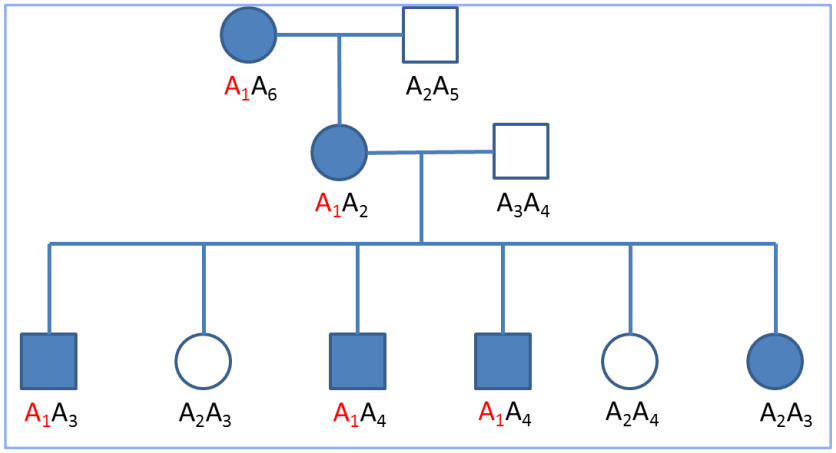
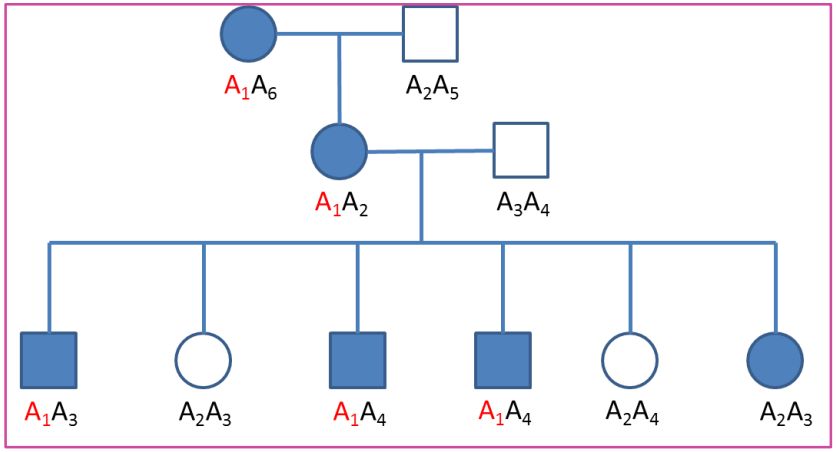
More families…





$$\log_{10}\left[\frac{\Theta^{(R1+R2)} \times (1-\Theta)^{(NR1+NR2)}}{0.5^{(R1+NR1)+(R2+NR2)}}\right]$$

Family 1
R1 = # rec.
NR1 = # non-rec.

Family 2
R2 = # rec.
NR2 = # non-rec.

$$\log_{10}\left[\frac{\Theta^{R1} \times (1-\Theta)^{NR1}}{0.5^{(R1+NR1)}}\right]$$

$$+ \log_{10}\left[\frac{\Theta^{R2} \times (1-\Theta)^{NR2}}{0.5^{(R2+NR2)}}\right]$$

SUM ≥ 3 ?

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Potential LOD score curves

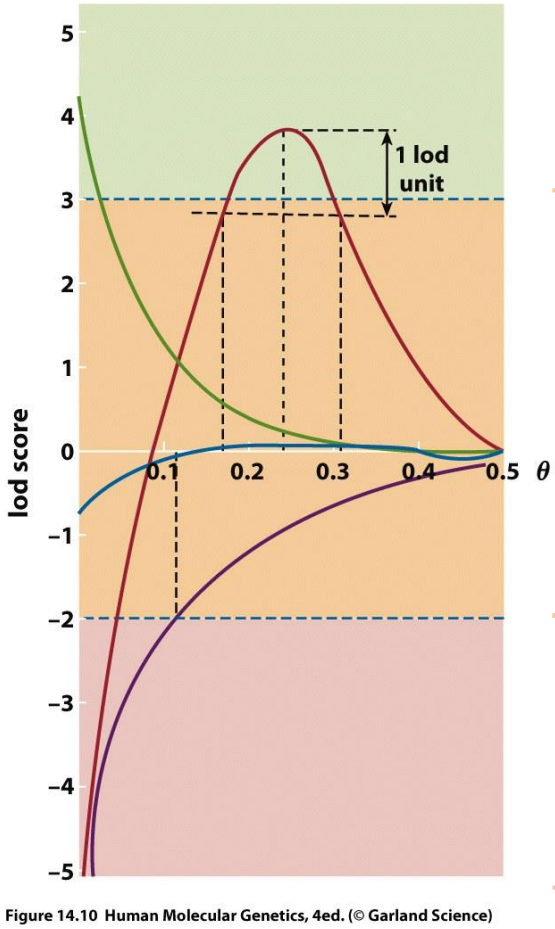
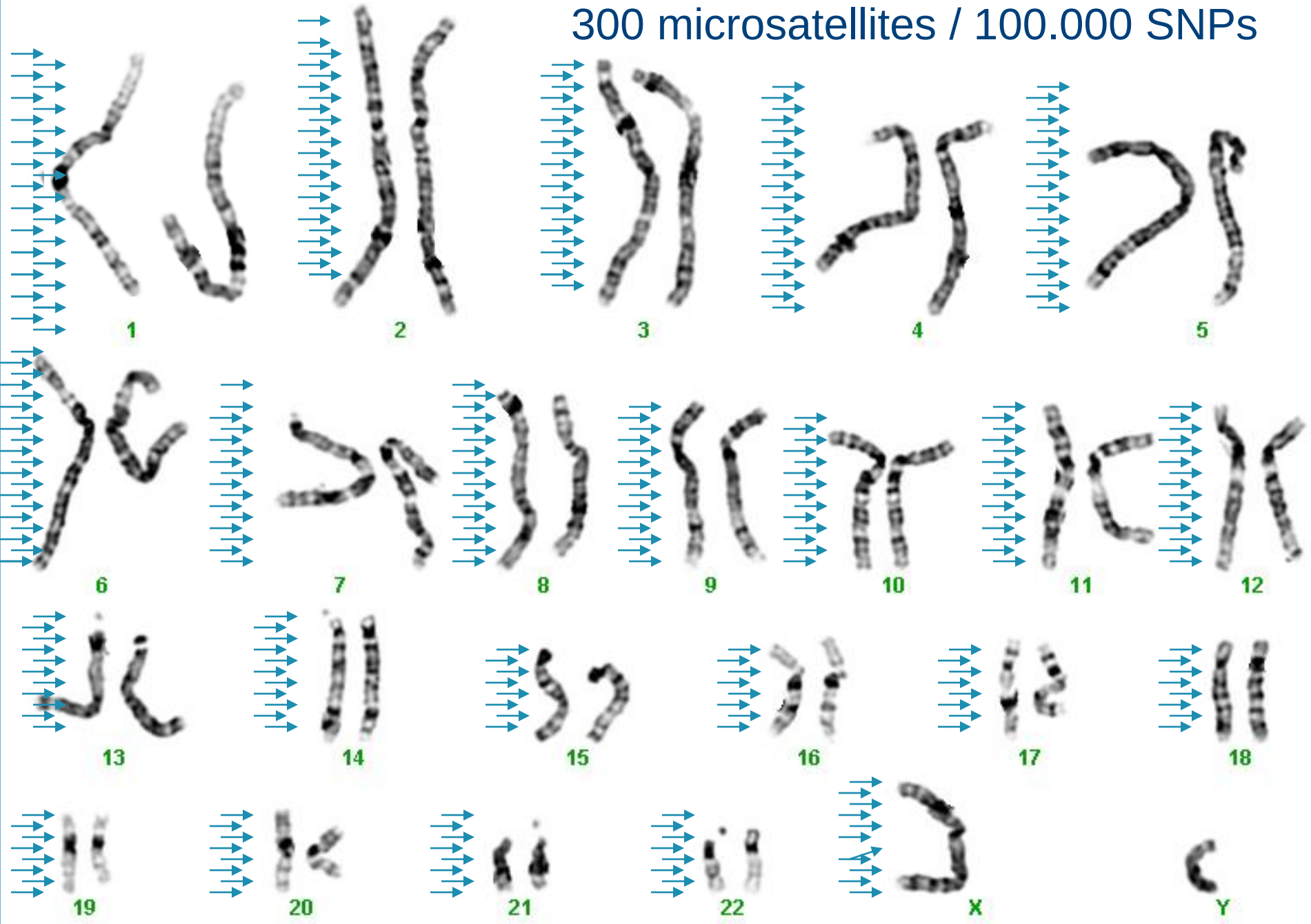


Figure 14.10 Human Molecular Genetics, 4ed. (© Garland Science)

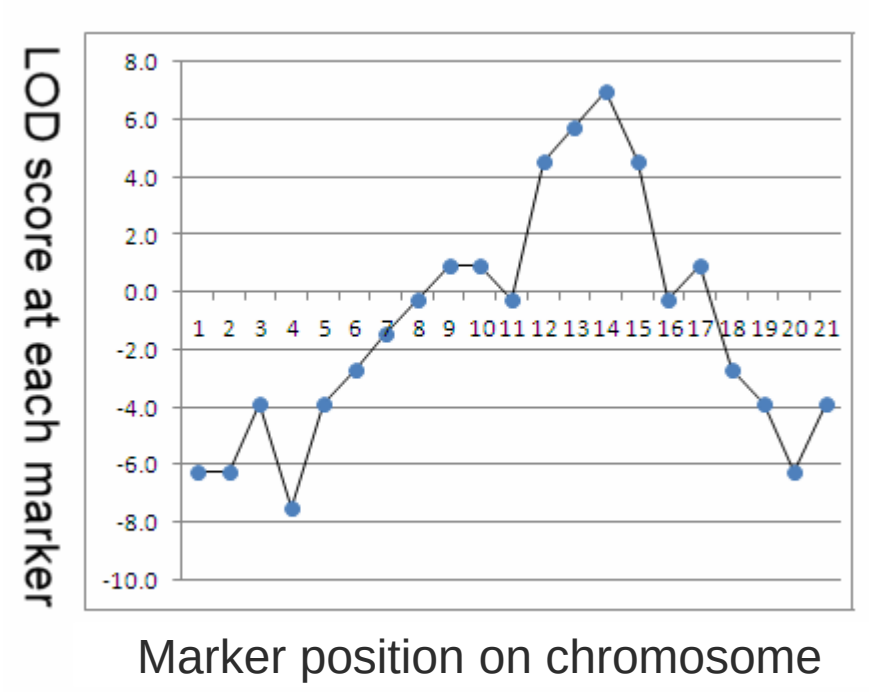
inconclusive

Exclusion mapping

300 microsatellites / 100.000 SNPs

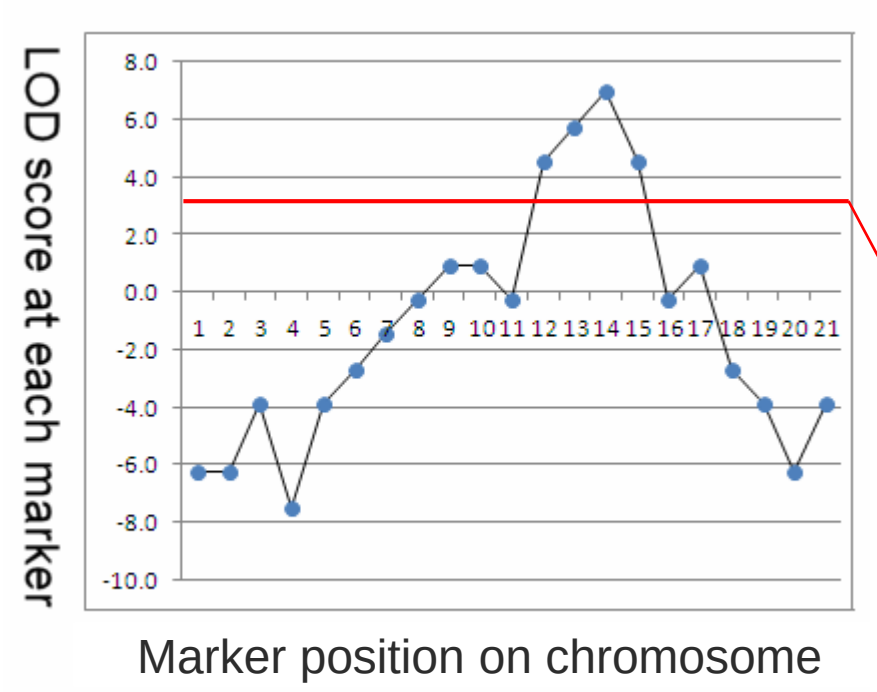


LOD score - visualization



- θ between genetic markers & disease locus
  - LOD score plotted against chromosomal positions
  - highest peak = most likely locus

LOD score - visualization



- θ between genetic markers & disease locus
  - LOD score plotted against chromosomal positions
  - highest peak = most likely locus
- LOD score = 3
  - ➢ 1 / 10^3 chance that the observed concordance is due to chance

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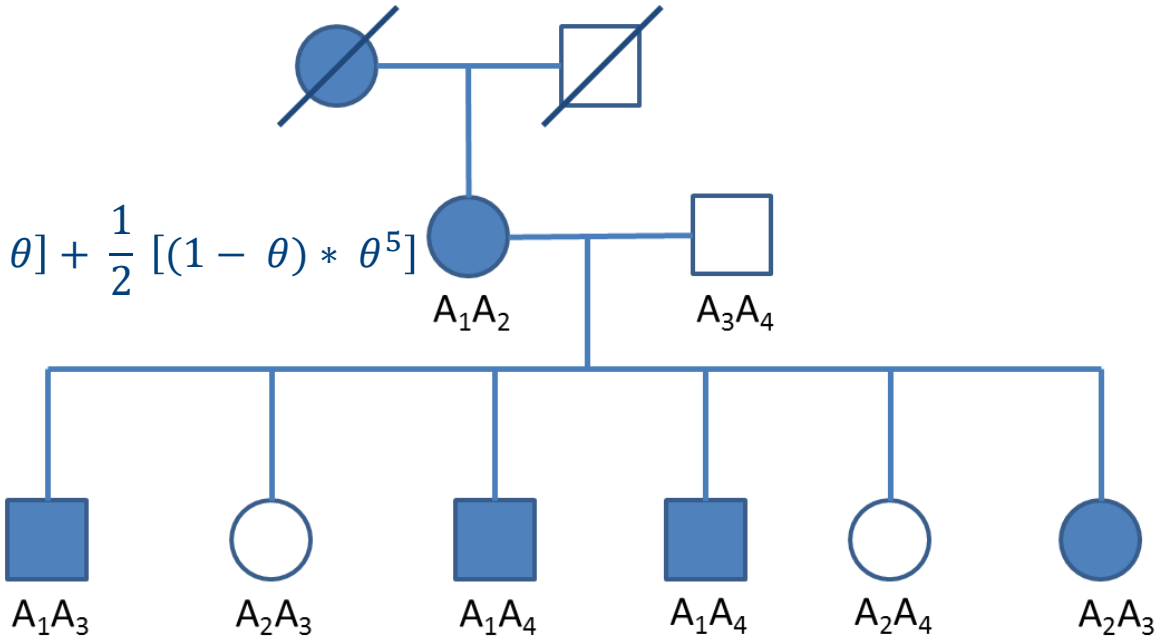
Recombinants vs non-recombinants

Phase unknown

$$L(\theta) = \frac{1}{2}\left[(1-\theta)^5 * \theta\right] + \frac{1}{2}\left[(1-\theta) * \theta^5\right]$$



Linkage analysis – how?

1. Collect familie(s)
2. Choose a genetic marker (eg microsatellite, SNP) for linkage analysis
3. Genotype this marker in all individuals of the familie(s)
4. Identify informative meioses (R vs NR → between heterozygous GM and heterozygous disease locus)
   - Based on the phenotype you know the disease locus genotype (affected vs unaffected)
   - Is phase known?
5. Determine whether there is linkage between the GM locus and the disease locus
   - Determine recombination fraction θ

$$log_{10}\left[\frac{Likelihood\ of\ linkage\ (\theta)}{Likelihood\ that\ loci\ are\ unlinked\ \left(\theta=\frac{1}{2}\right)}\right] = log_{10}\left[\frac{L\ (\theta)}{L\left(\theta=\frac{1}{2}\right)}\right] = log_{10}\left[\frac{(1-\theta)^{NR} * \theta^{R}}{0.5^{(R+NR)}}\right]$$

= max

   - Is this recombination significantly different from 0.5?

     (= null hypothesis; no linkage between GM and disease locus)

$$log_{10}\left[\frac{Likelihood\ of\ linkage\ (\theta)}{Likelihood\ that\ loci\ are\ unlinked\ \left(\theta=\frac{1}{2}\right)}\right] = log_{10}\left[\frac{L\ (\theta)}{L\left(\theta=\frac{1}{2}\right)}\right] = log_{10}\left[\frac{(1-\theta)^{NR} * \theta^{R}}{0.5^{(R+NR)}}\right]$$

≥ 3 ?

6. Do we need more informative meioses / families?

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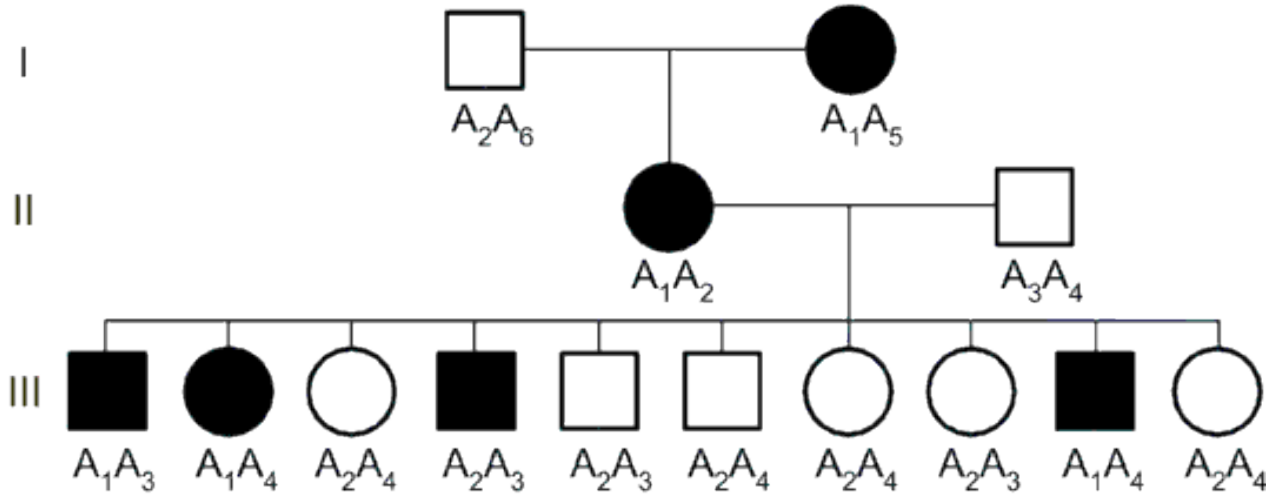
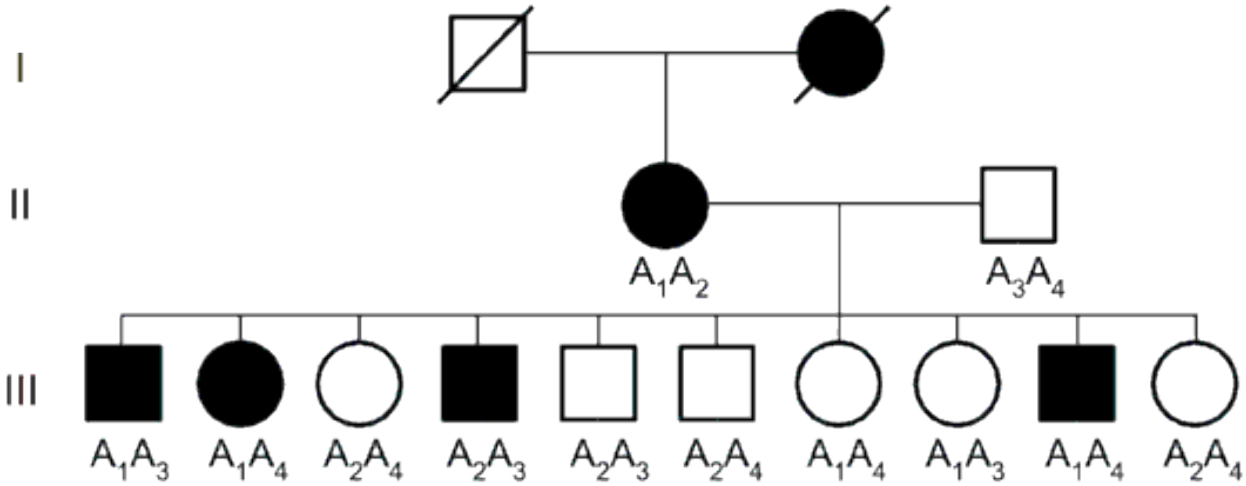
Linkage analysis – homework → assignment 2



θ = ?

LOD = ?

Linkage analysis – homework → assignment 2



θ = ?

LOD = ?

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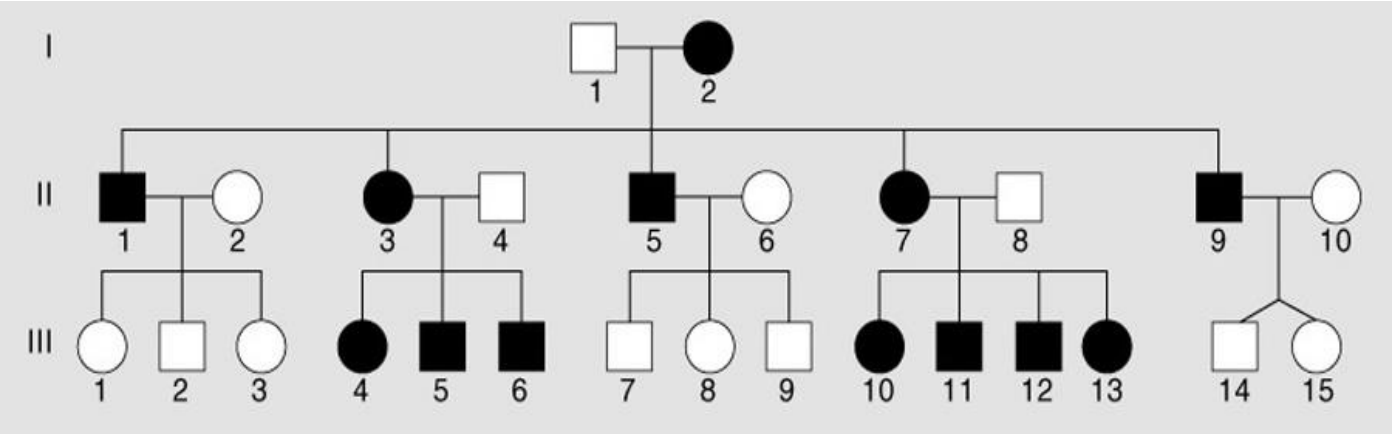
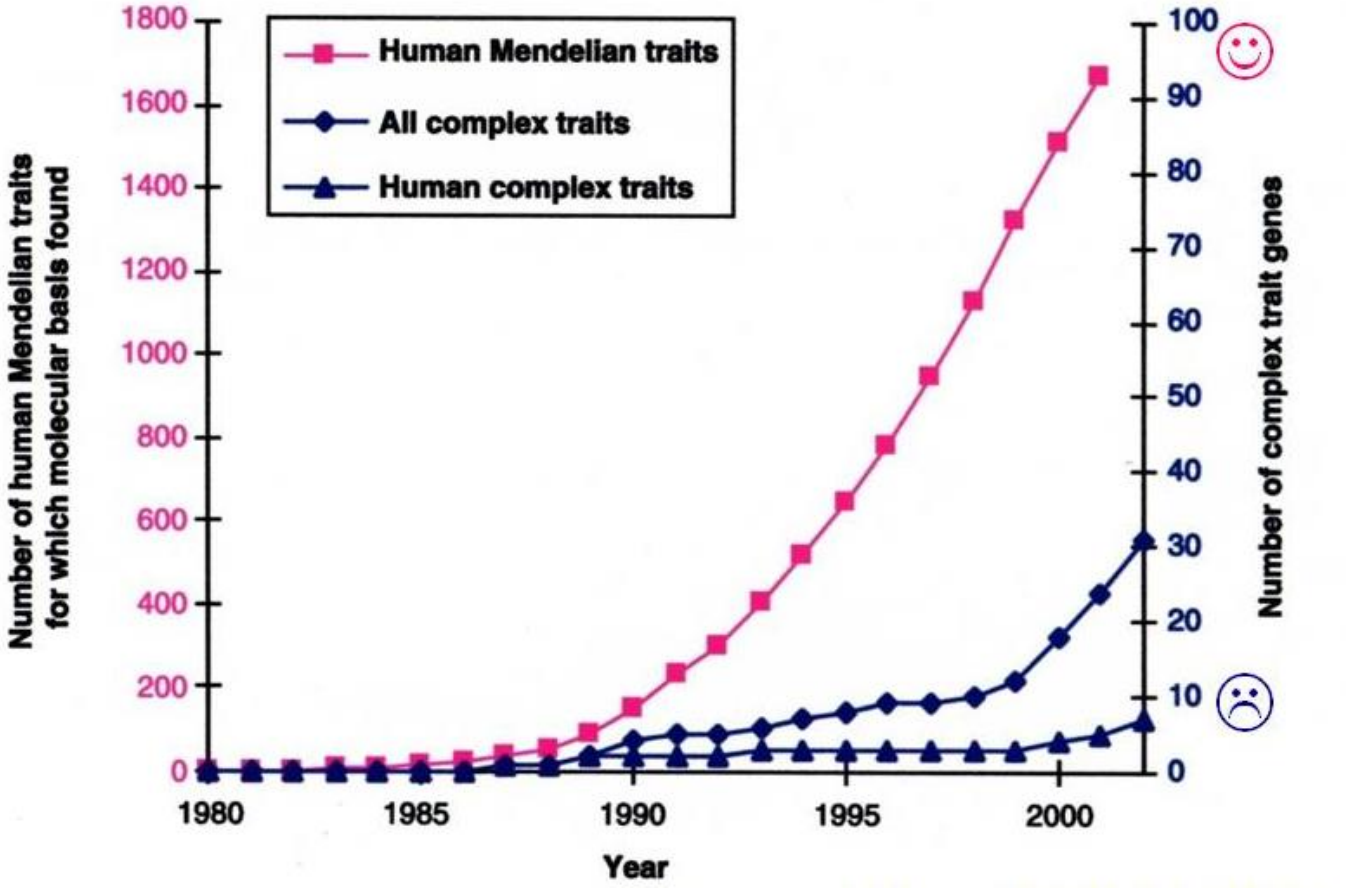
Linkage analysis

- co-segregation of genetic marker(s) and disease in a family



- Goal: identify chromosomal region with risk gene
- Limits :
  - good for detection of highly penetrant variant (ie extremely likely to cause the disease when present)
  - Hard to get big enough pedigrees with enough informative individuals

Genetic successes in Mendelian >< complex disorders



Glazier et al, Science 298: 2345-9,2002

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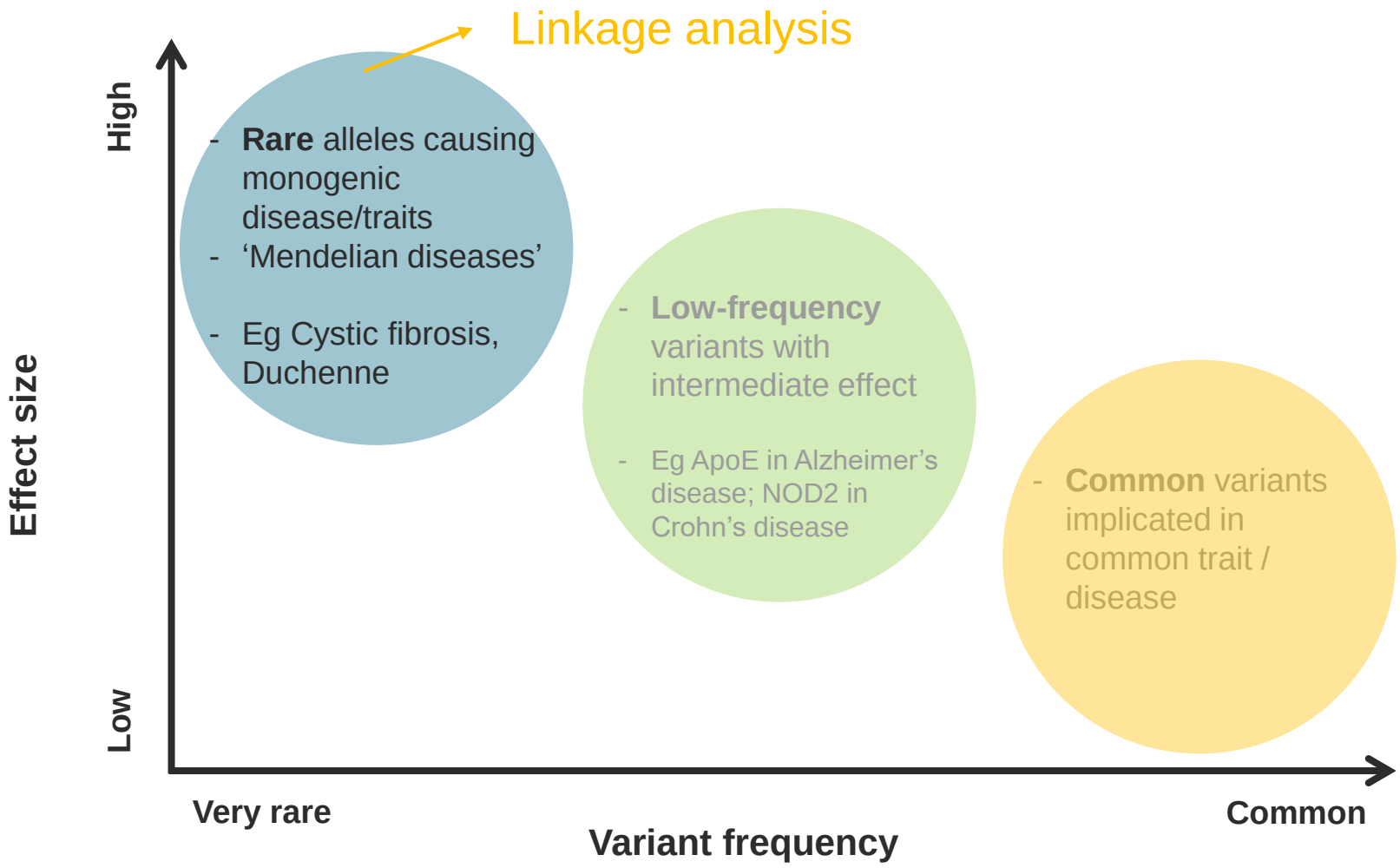
The genetic spectrum



Adapted from Manolio TA et al, Nature Reviews, 2009

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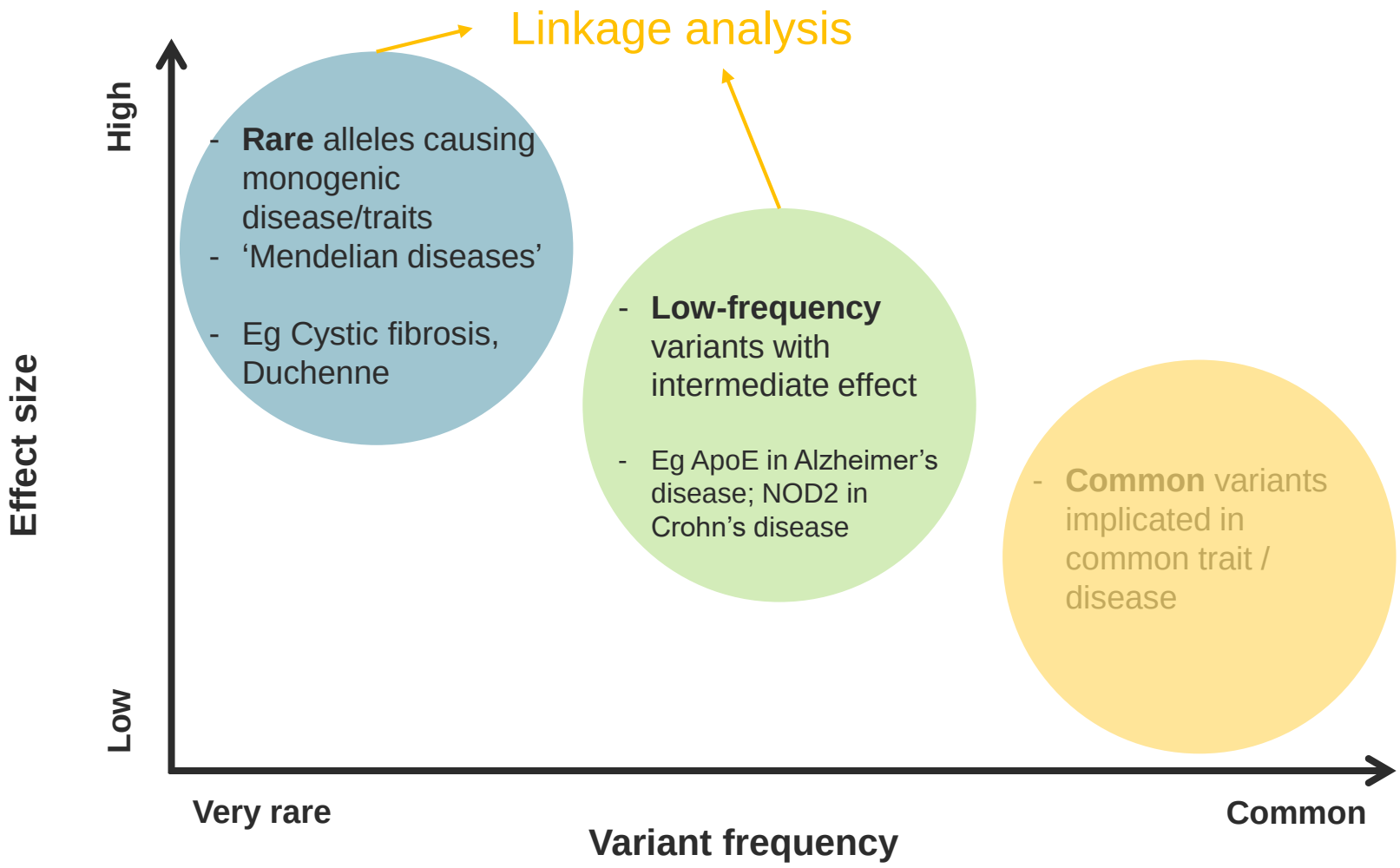
The genetic spectrum



Adapted from Manolio TA et al, Nature Reviews, 2009

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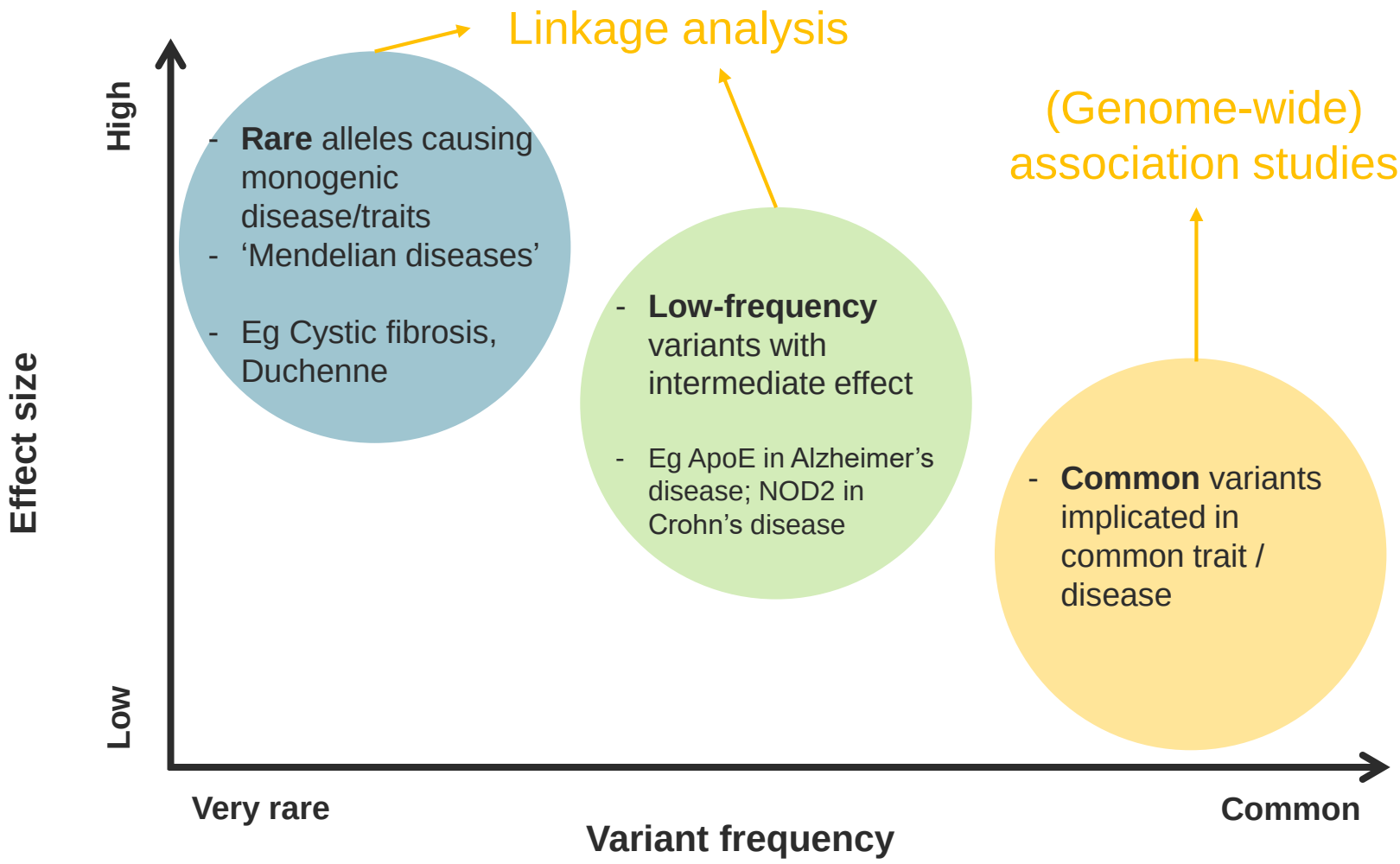
The genetic spectrum



Adapted from Manolio TA et al, Nature Reviews, 2009

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