Lecture 1

Introduction I:
Pedigrees, genetics and probabilities

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Statistical methods in genetic relatedness and pedigree analysis

NORBIS course, 6th – 10th of January 2020, Oslo

Outline

- Part I: *Pedigrees*
  - Pedigree symbols and terminology
  - Some common relationships
- Part II: *Genetics*
  - Terminology
    - Locus, allele, genotype, marker
  - Mendelian inheritance
    - Autosomal, X, Y
- Part III: *Pedigree likelihoods*
  - Motivation: Real-life problems
  - Ingredients:
    - Hardy-Weinberg equilibrium
    - Mendelian transition probabilities
  - Likelihoods by hand
  - Computer algorithms

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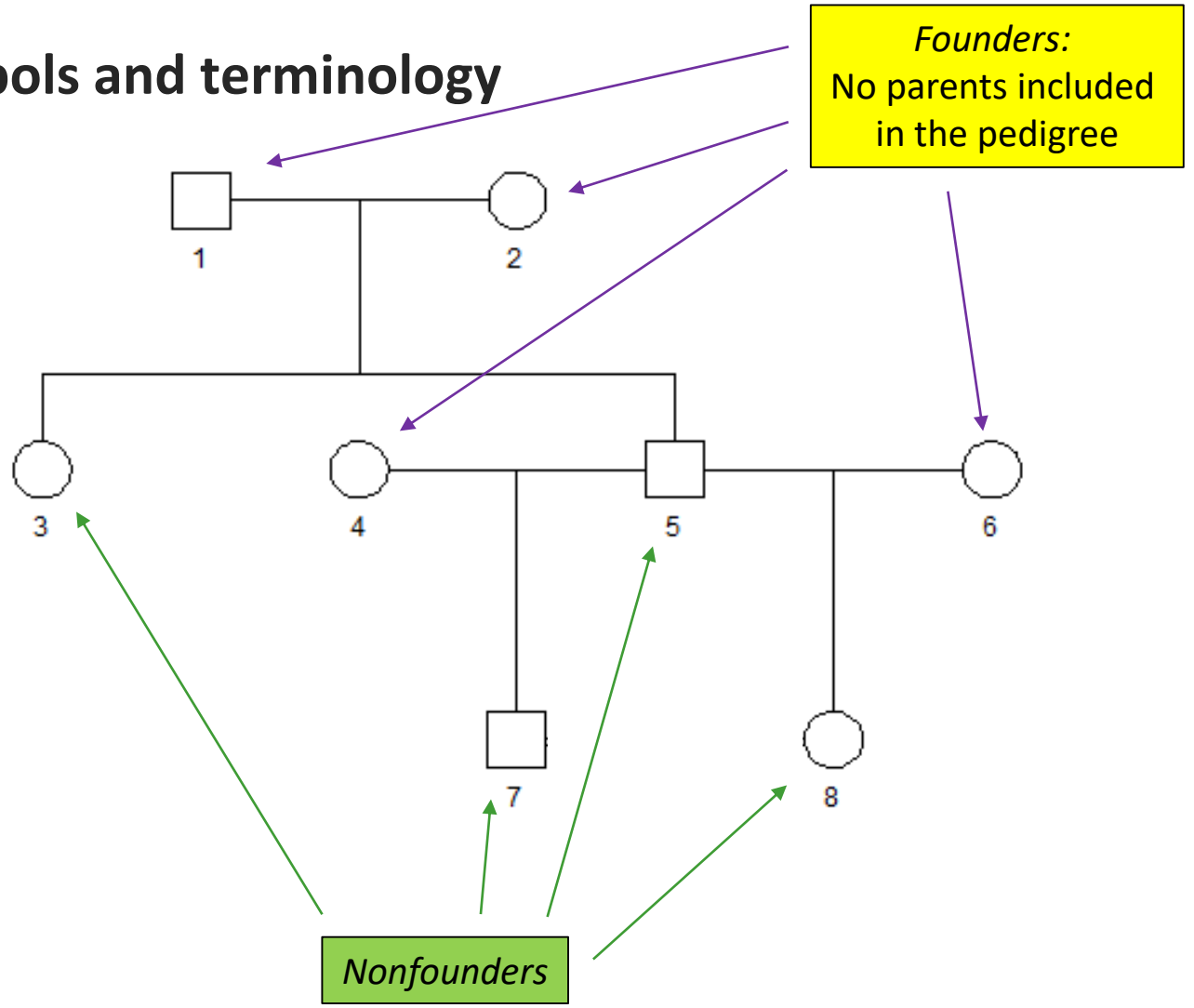
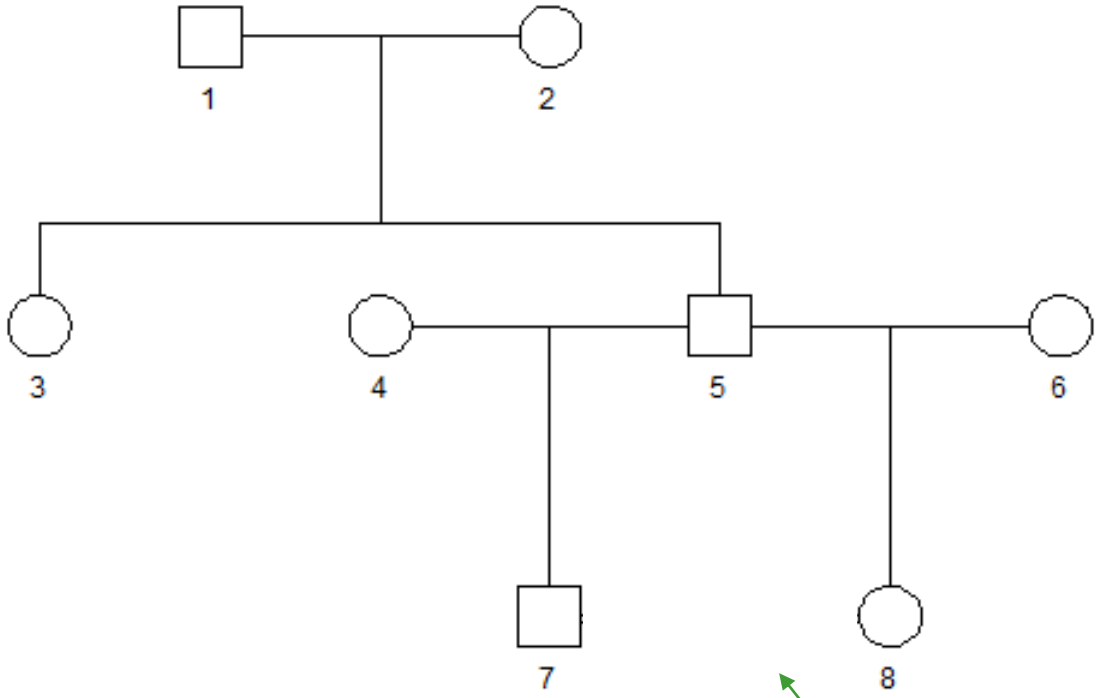
Pedigrees: Symbols and terminology



Pedigrees: Symbols and terminology

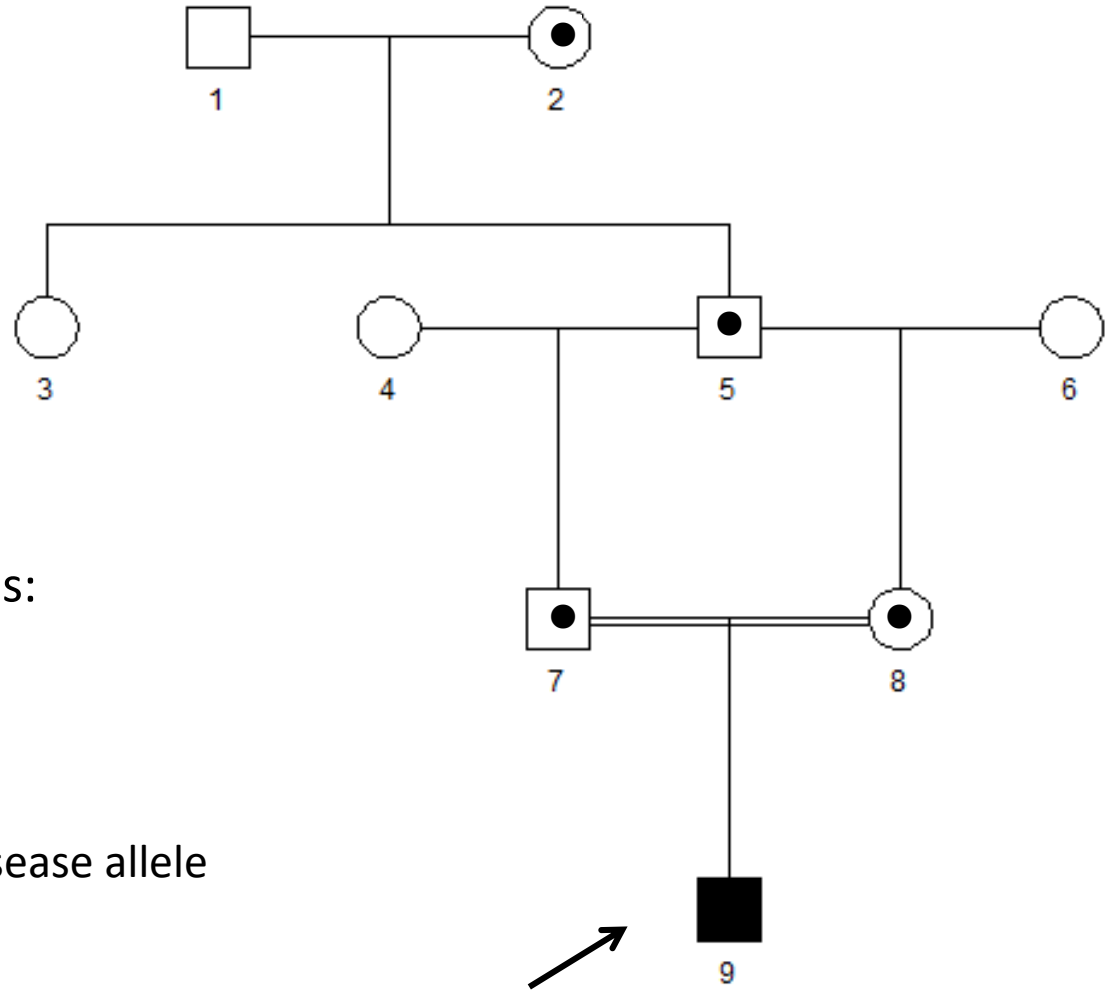


= male

= female

Consanguineous marriage

Pedigrees: Symbols and terminology



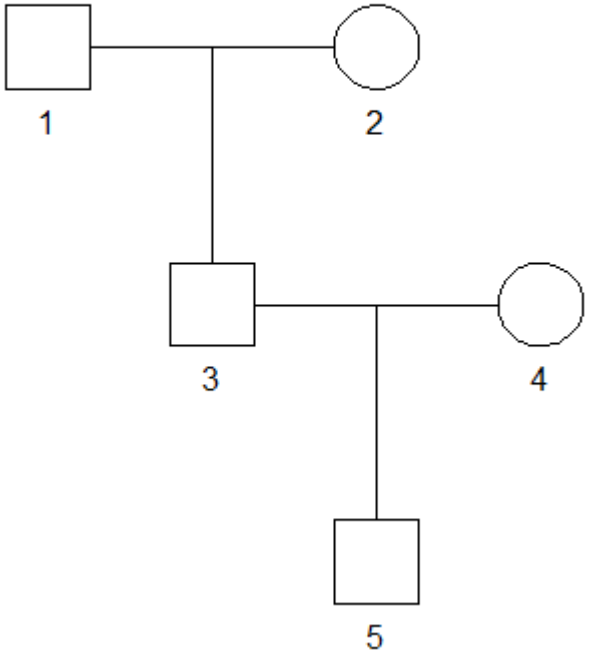
Medical pedigrees:

= affected

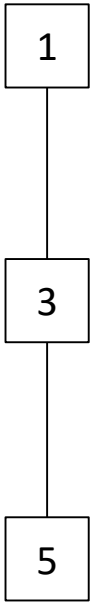
= unaffected

= carrier of disease allele

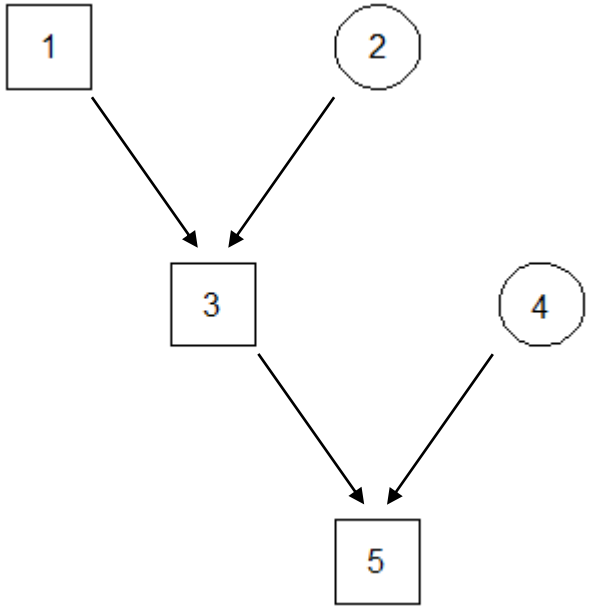
Alternative ways of drawing pedigrees



Standard



Simplified

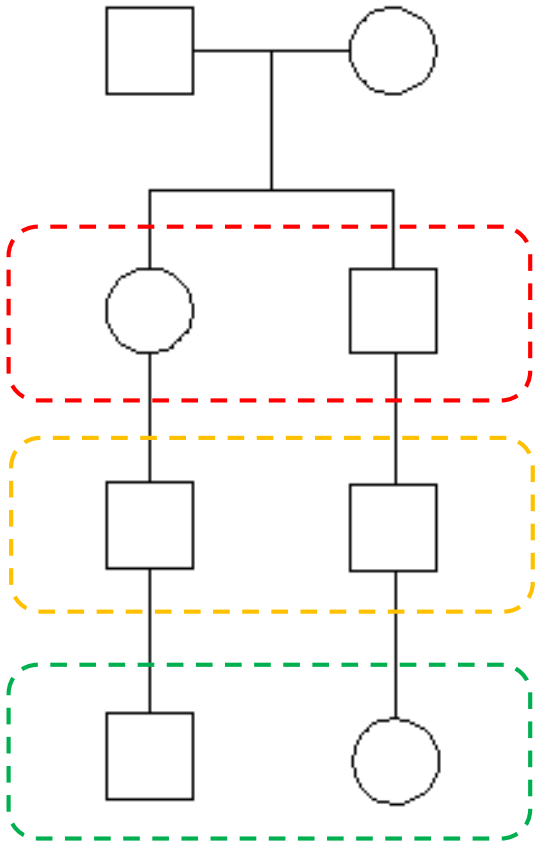


Directed acyclic graph

Some common relationships

(and some less common...)

Cousin relationships

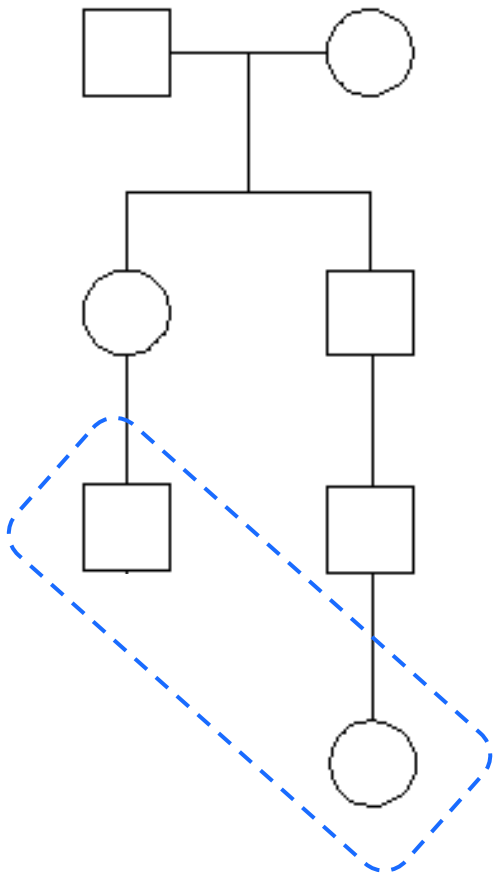


Full siblings

First cousins

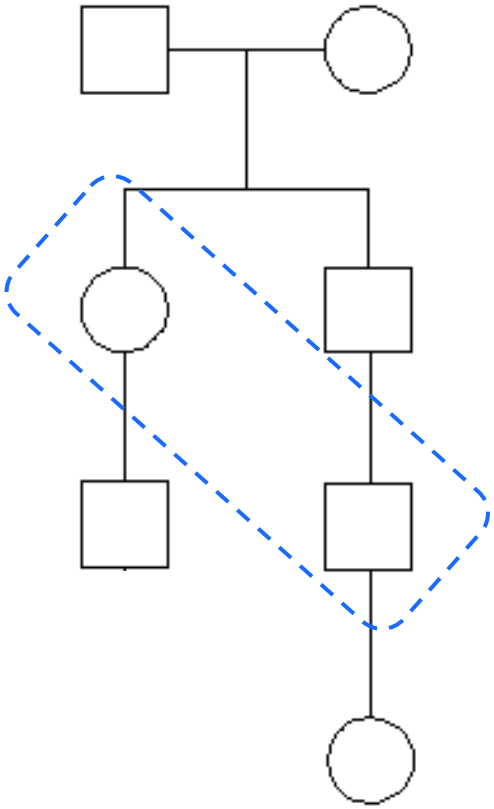
Second cousins

Cousin relationships



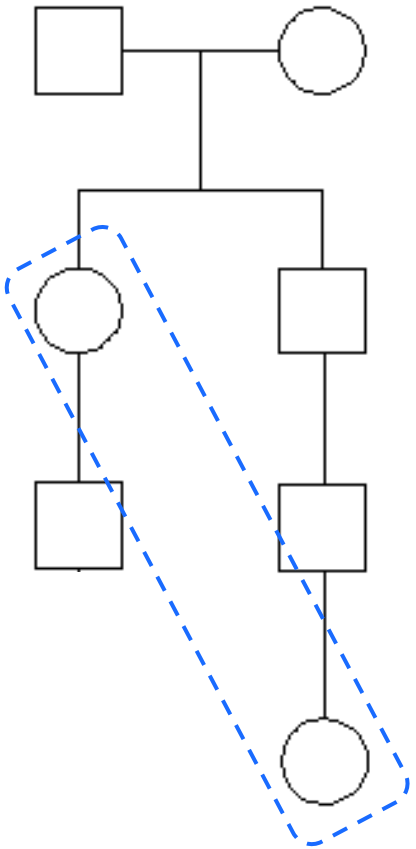
First cousins
once removed

Cousin relationships



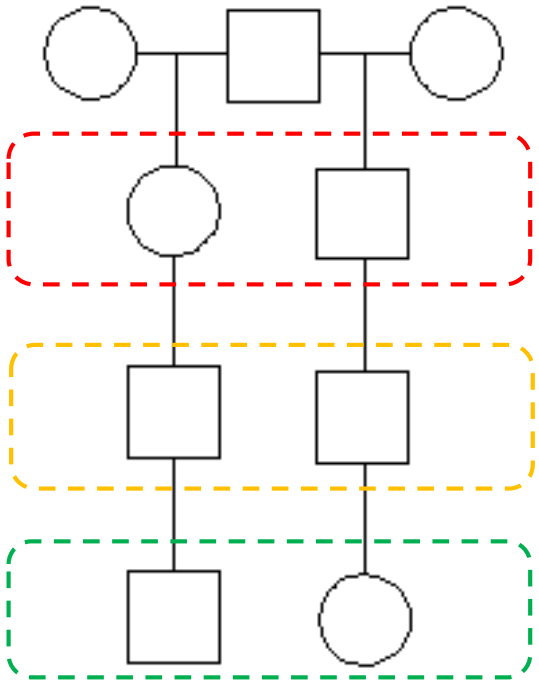
Aunt - nephew

Cousin relationships



Grandaunt

Half cousin relationships

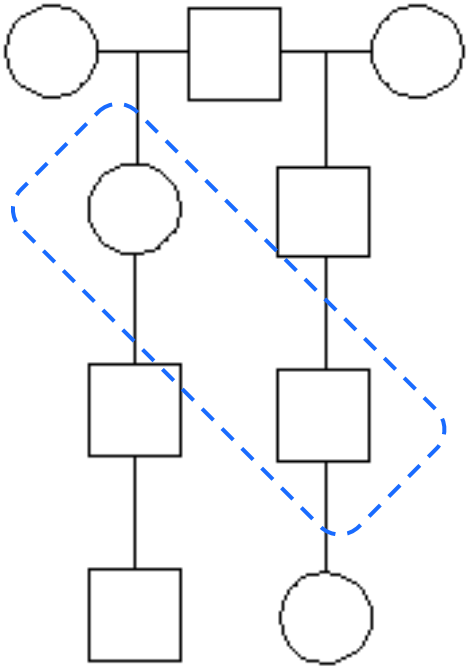


Half siblings (paternal)

Half first cousins

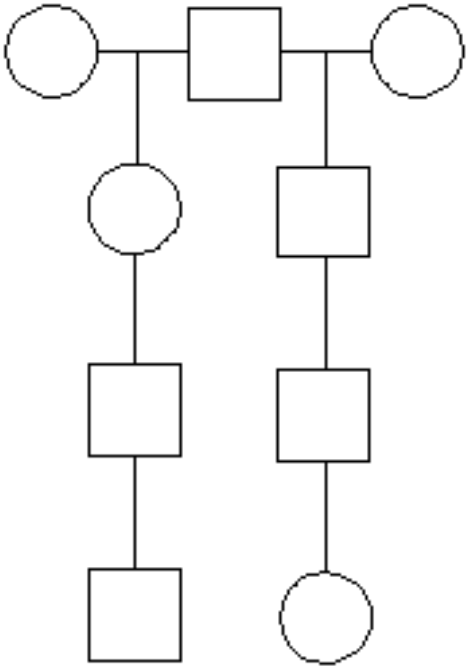
Half second cousins

Half cousin relationships

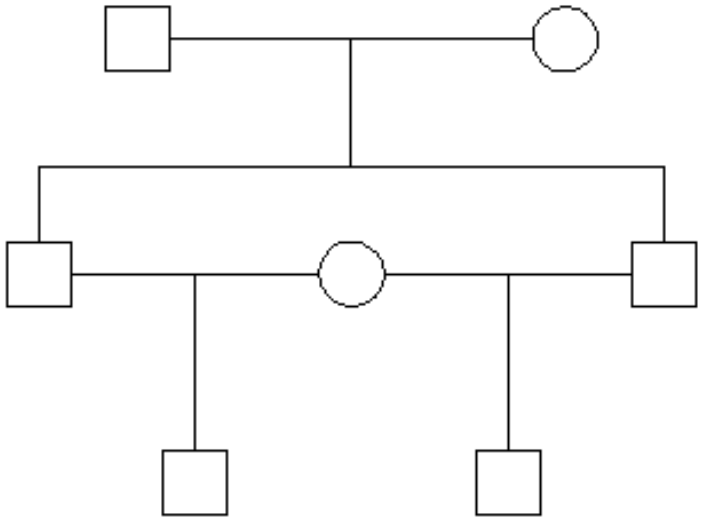


Half aunt /
half nephew

Half cousin relationships

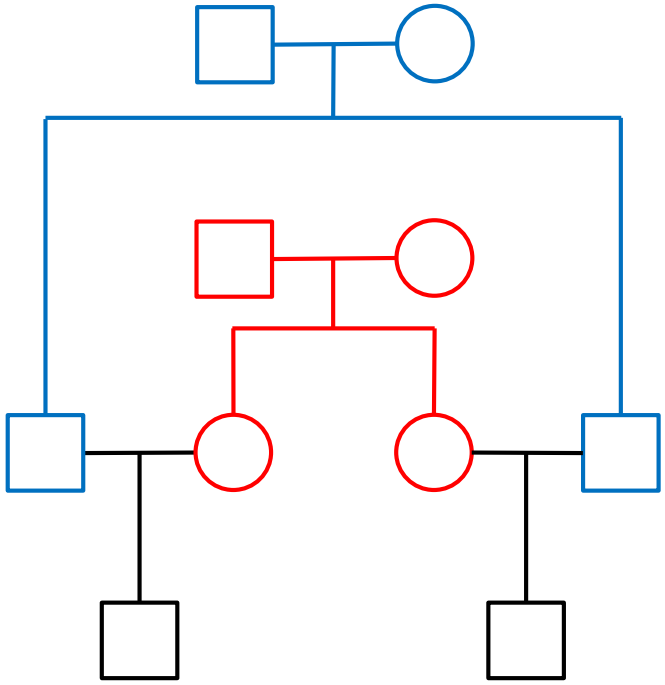


More complicated relationships



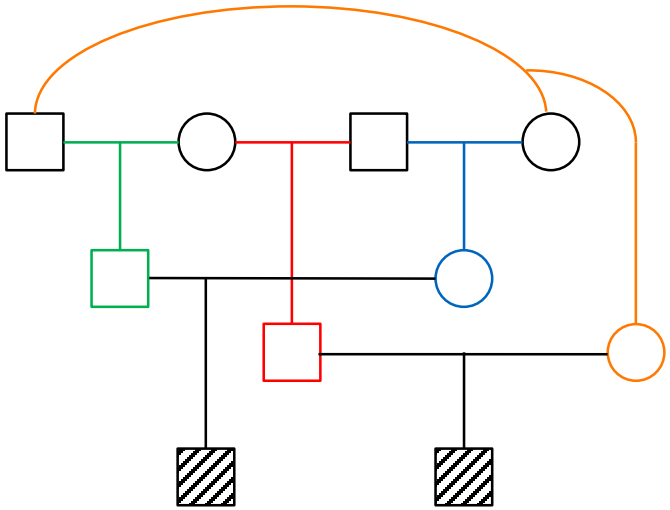
3/4 siblings

What about this?



Double first cousins

The connoisseur's favourite!



Quadruple half first cousins!

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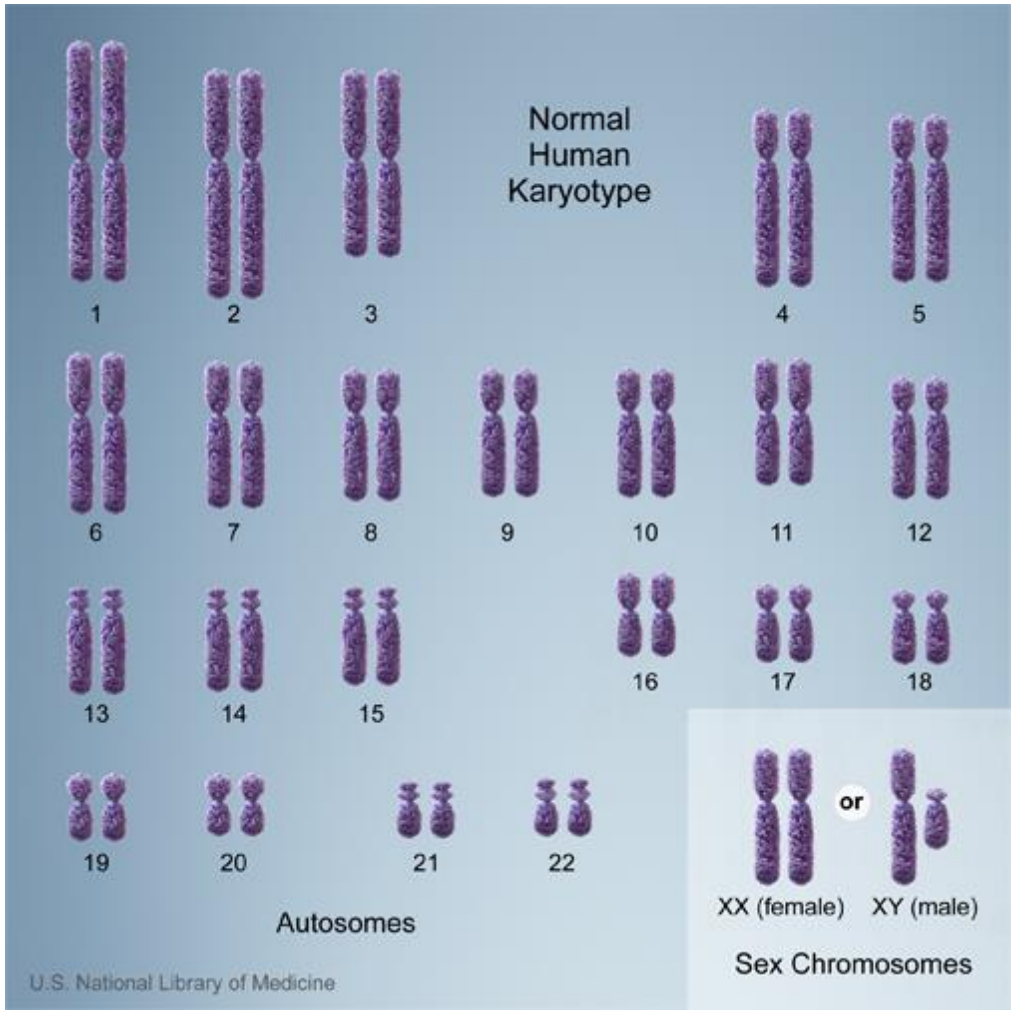
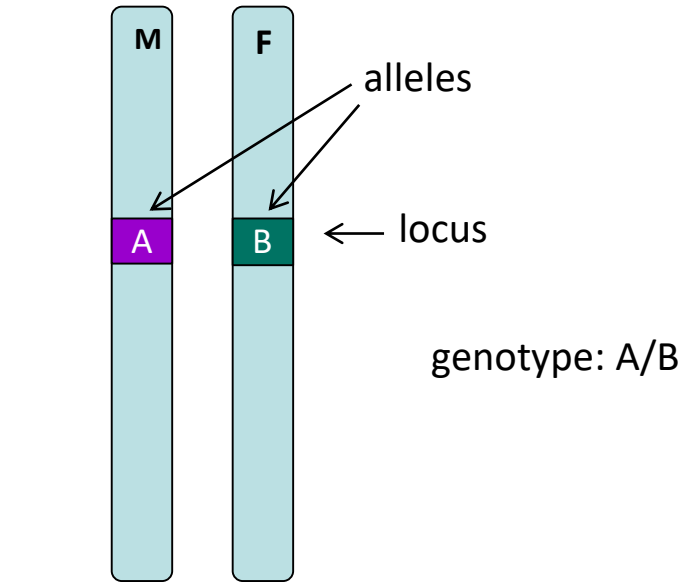
Genetics

- Human genome:
  - Diploid
  - 22 pairs of autosomes
  - Sex chroms: X and Y

- Some important terms
  - Locus
  - Allele
  - Genotype
  - Genetic markers
    - SNPs
    - microsatellites



Locus, allele, genotype



- **LOCUS** = a specific place in the genome, e.g. a base pair, a gene or a region
- **ALLELE** = any of the alternative forms of a locus
- **GENOTYPE** = the set of alleles carried by an individual at a given locus

Genetic markers

- Small parts of the genome which ...
  - have known position
  - vary in the population
  - are easy to genotype

- SNPs (single nucleotide polymorphisms)
  - two alleles
  - usual requirement: MAF > 1% = minor allele frequency
  - very common in the genome (millions!)
  - used in medical genetics +++

...CCGTTATATGGGC...
...CCGTTAGATGGGC...
...CCGTTATATGGGC...
...CCGTTATATGGGC...
...CCGTTAGATGGGC...

- STRs (short tandem repeats) = microsatellites
  - consecutive repeats of 2-5 bases
  - multiallelic: 5 - 50 alleles
  - allele names: # repeats
  - used in forensics

...ACG TTAG TTAG TTAG TTAG AAC..
...ACG TTAG TTAG AAC..
...ACG TTAG TTAG TTAG TTAG TTAG AAC..

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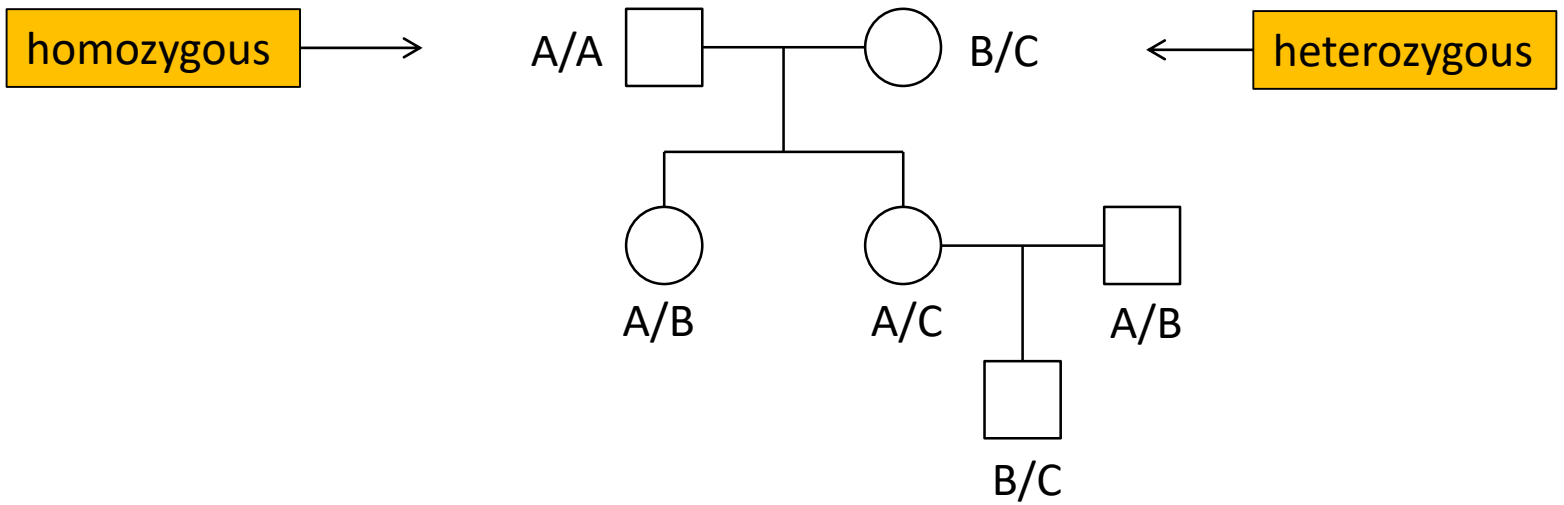
Mendelian inheritance: Autosomal (chromosomes 1-22)

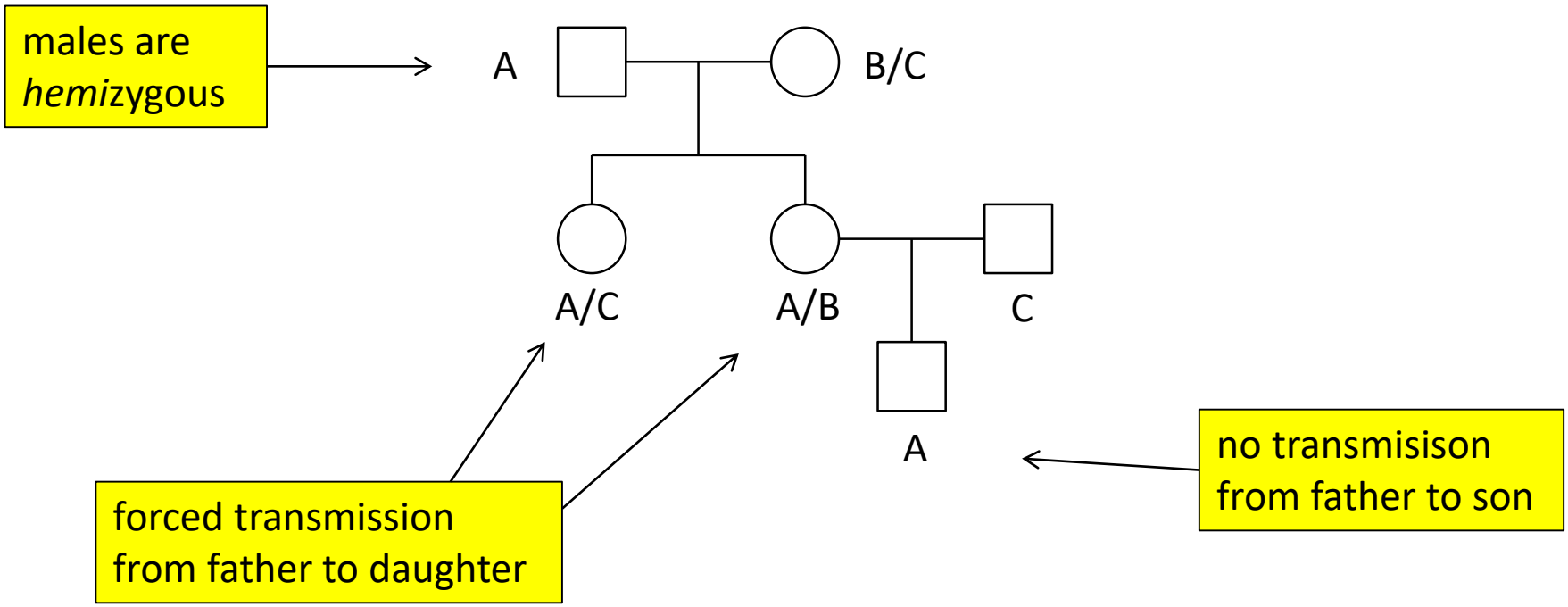
Example: autosomal marker with 3 alleles: A, B, C



Probability of transmitting either allele: **always 50%**

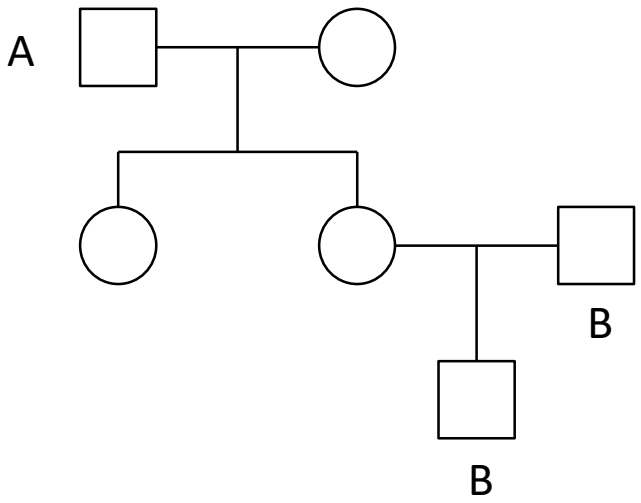
Mendelian inheritance: X-linked

Example: X-linked marker with 3 alleles: A, B, C



Mendelian inheritance: Y-linked

Example: Y-linked marker with 2 alleles: A, B



- no transmission involving females
- father-son forced

Assumptions throughout (most of) this course

- Diploid species
- No cytogenetic abnormalitites
- No *de novo* mutations

COFFEE BREAK!

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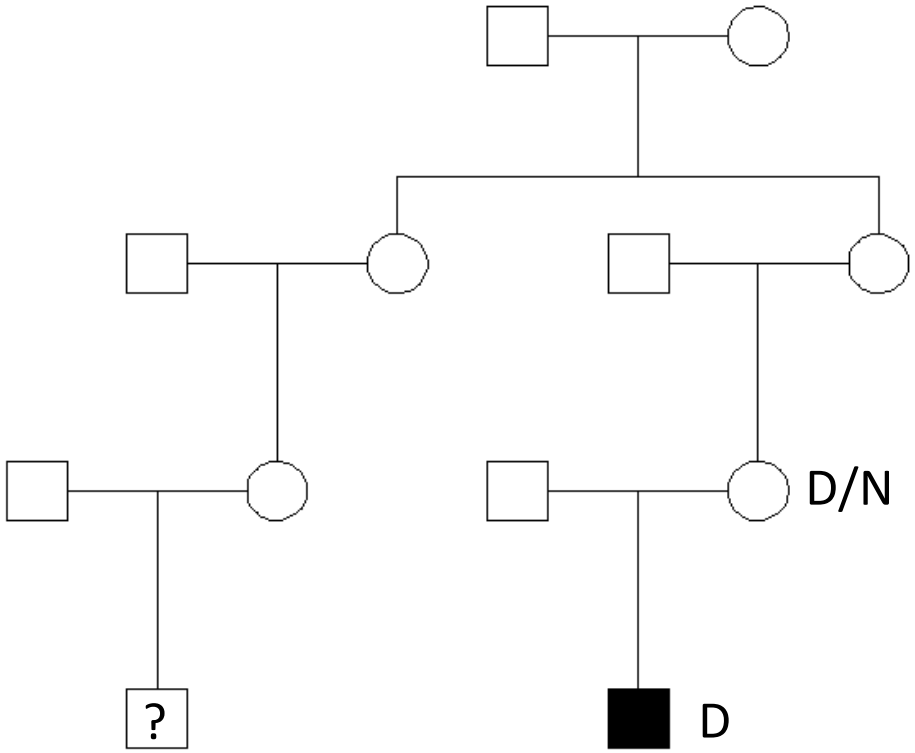
Questions related to pedigrees with genotypes

- Will my child have the disease?
- Is NN the true father?
- Brothers or half brothers?
- Is NN related to this family? How?
- Predict the missing genotype?

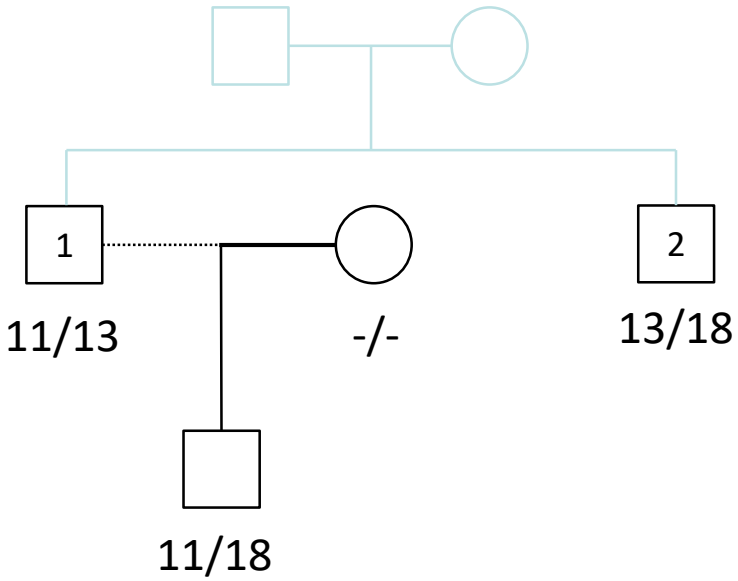
Questions related to pedigrees with genotypes



Disease locus:
alleles D and N

Will my child have the disease?

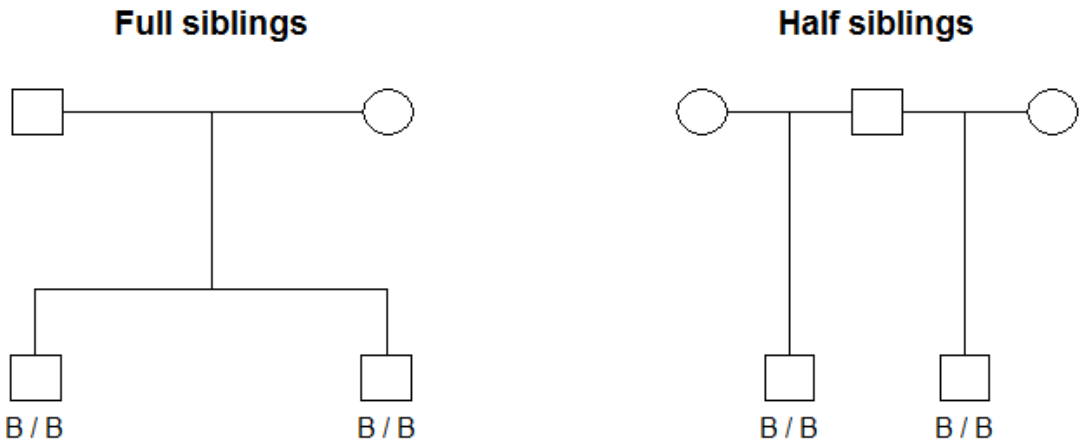
Questions related to pedigrees with genotypes



Suppose:
- 11 is common
- 18 is rare

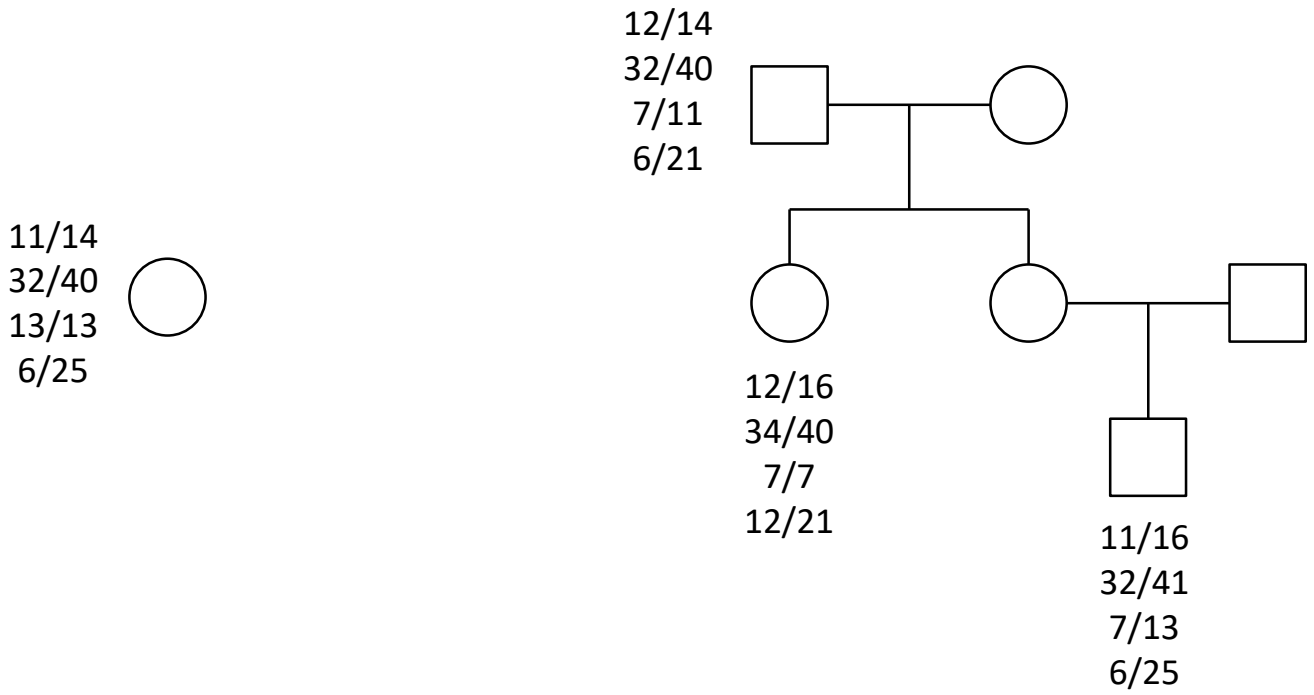
Who is the true father?

Questions related to pedigrees with genotypes



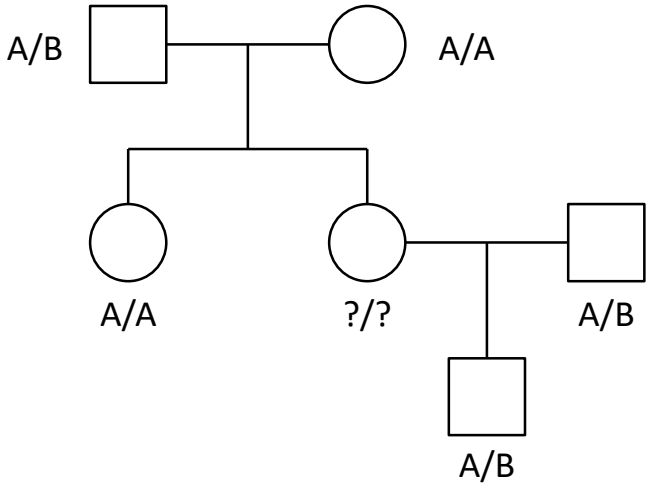
Brothers or half brothers?

Questions related to pedigrees with genotypes



Is this woman related to the family?

Questions related to pedigrees with genotypes



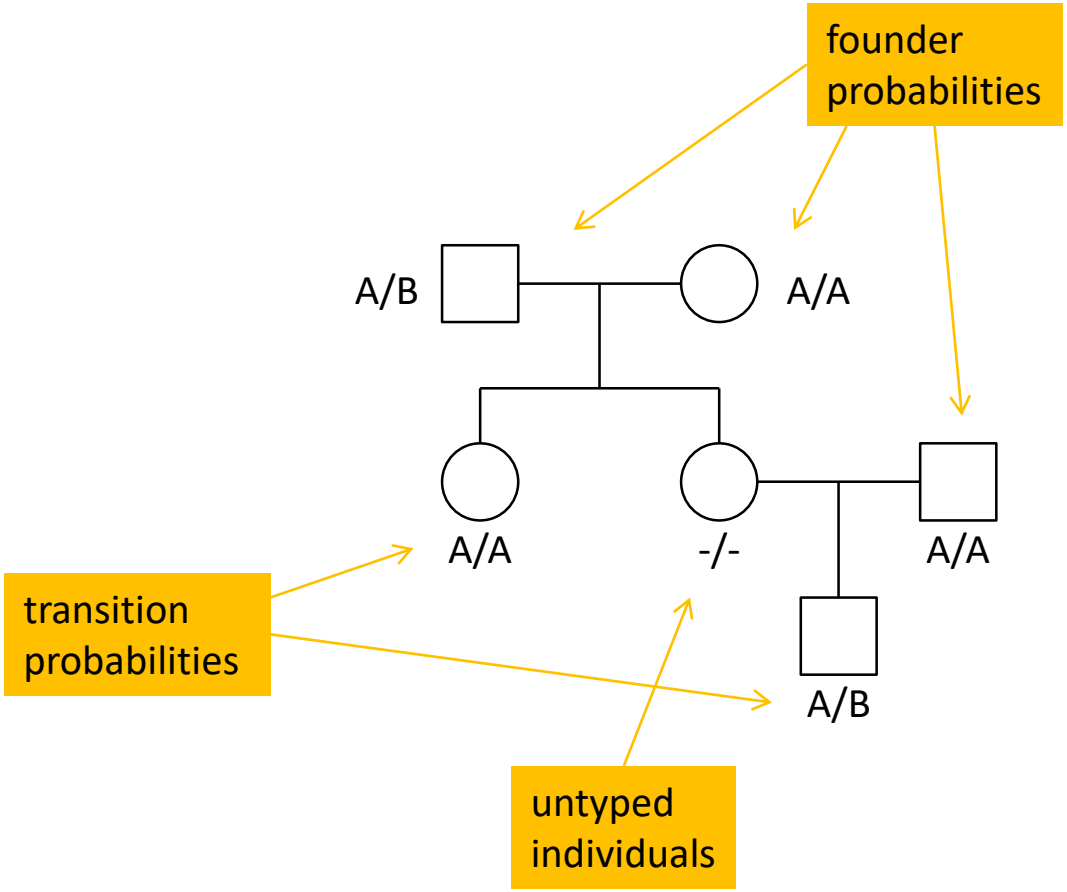
Can we predict the missing genotype?

- Common to all of these: The need to calculate probabilities

$$P(\text{ genotypes } \mid \text{ pedigree, marker info, allele freqs, .. })$$

- Called the *likelihood* of the pedigree.

Ingredients for likelihood computations



Ingredient 1: Founder probabilities

- Suppose the allele frequencies are:

$$P(A) = p$$
$$P(B) = q$$

- What are the frequencies of the genotypes *AA*, *AB*, *BB*?
- Under certain assumptions, the alleles can be treated as independent:

$$P(AA) = P(A) * P(A) = p^2$$

$$P(BB) = P(B) * P(B) = q^2$$

$$P(AB) = P(AB\ or\ BA) = pq + qp = 2pq$$

↑

two possible orderings!

The Hardy-Weinberg principle

Assumptions:

- infinite population
- random mating
- no selection
- no mutations
- no migration

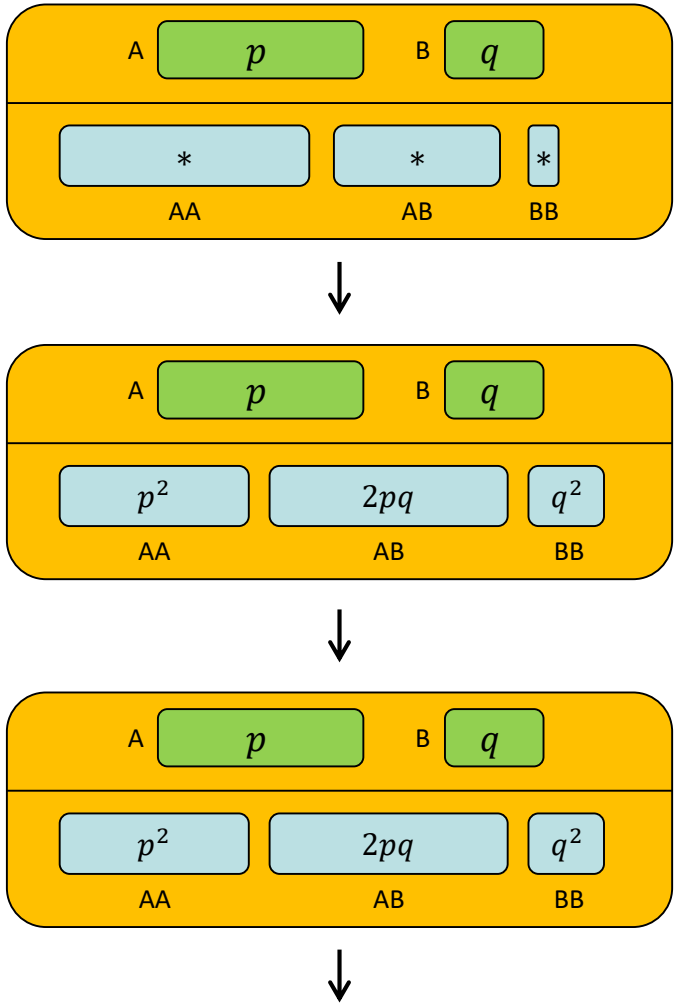
Hardy (1908): Shows

«... *using a little mathemathics of the multiplication table kind*»:

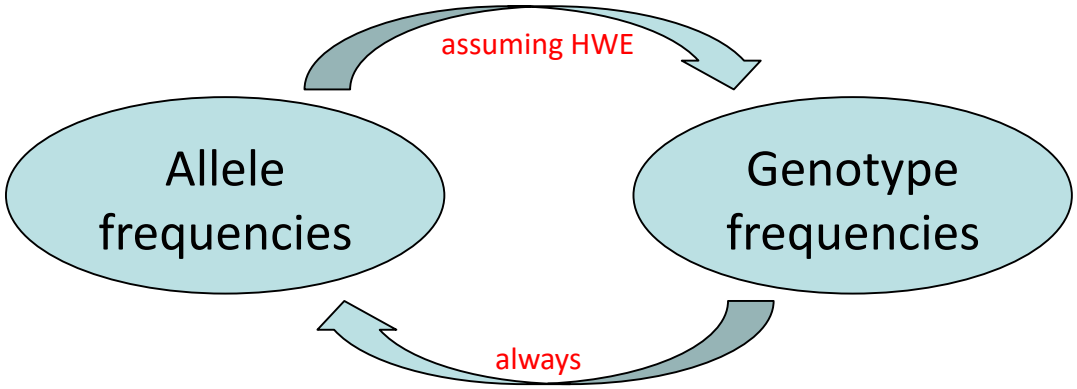
- allele freqs are unchanged from generation to generation
- after 1 generation the genotype freqs stay unchanged

$$P(AA) = p^2$$
$$P(AB) = 2pq$$
$$P(BB) = q^2$$

HW equilibrium



$$p_{AA} = p^2$$
$$p_{AB} = 2pq$$
$$p_{BB} = q^2$$

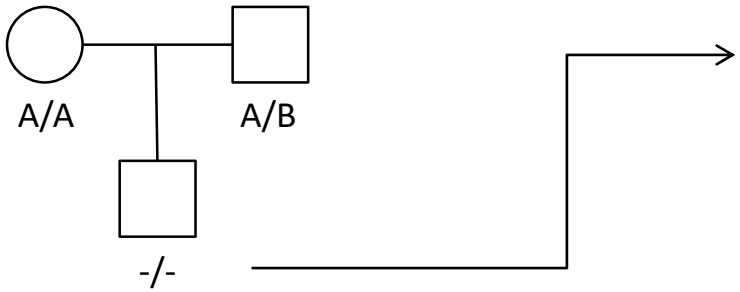


$$p = p_{AA} + 0.5\, p_{AB}$$
$$q = p_{BB} + 0.5\, p_{AB}$$

Ingredient 2: Transition probabilities

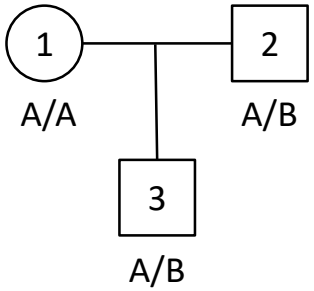
$$P(g_{child} \mid g_{parents})$$

- Easy - follows directly from Mendel's laws!



child / parents	A/A	AB	BB
AA × AA	1	0	0
AA × AB	0.5	0.5	0
AA × BB	0	1	0
AB × AA	0.5	0.5	0
AB × AB	0.25	0.5	0.25
AB × BB	0	0.5	0.5
BB × AA	0	1	0
BB × AB	0	0.5	0.5
BB × BB	0	0	1

Example



$$L = P(g_1, g_2, g_3)$$

$$= P(g_1) \cdot P(g_2) \cdot P(g_3 \mid g_1, g_2)$$

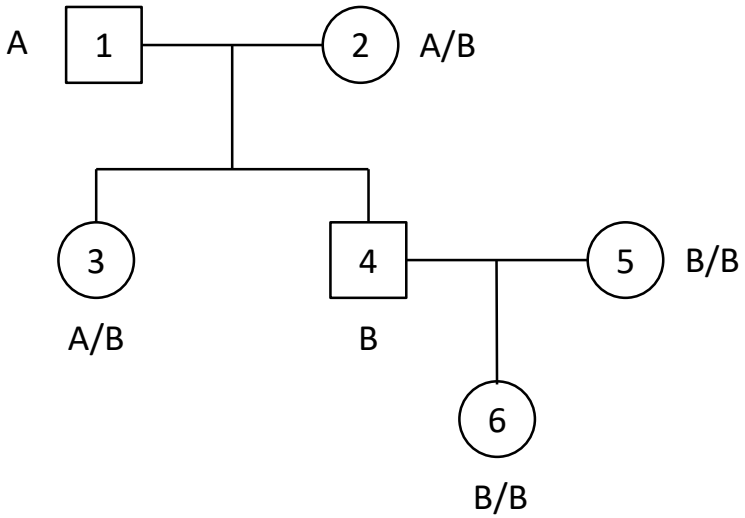
$$= P(AA) \cdot P(AB) \cdot P(AB \mid \text{parents} = AA \times AB)$$

$$= p^2 \cdot 2pq \cdot 0.5$$

$$= p^3 q$$

assuming HWE!

Example on X



$$L = P(genotypes \mid pedigree, p, q)$$

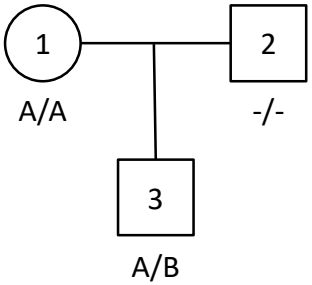
$$= \overset{1}{p} \cdot \overset{2}{2pq} \cdot \overset{3}{0.5} \cdot \overset{4}{0.5} \cdot \overset{5}{q^2} \cdot \overset{6}{1}$$

contribution from each individual

$$= 0.5\, p^2\, q^3$$

Ingredient 3: How to deal with untyped individuals

Solution: Sum of all possible genotypes for the untyped



$$P(g_1, g_3) = \sum_{g_2} P(g_1, g_2, g_3) = \sum_{g_2} P(g_1) \cdot P(g_2) \cdot P(g_3 | g_1, g_2)$$

$$= P(AA) \cdot P(AA) \cdot P(AB | AA \times AA) \; + \; P(AA) \cdot P(AB) \cdot P(AB | AA \times AB) \; + \; P(AA) \cdot P(BB) \cdot P(AB | AA \times BB)$$

$$= \; p^2 \cdot p^2 \cdot 0 \qquad + \; p^2 \cdot 2pq \cdot 0.5 \qquad + \; p^2 \cdot q^2 \cdot 1$$

$$= p^3 q + p^2 q^2 = p^2 q (p + q) = p^2 q$$

Pedigree likelihood: General formula

- Given:
  - pedigree with *n* individuals
  - *k* members are genotyped: $g_1, g_2, \ldots, g_k$

- Then:

founders non-founders

$$P(g_1, \ldots, g_k) = \sum_{G_1} \sum_{G_2} \ldots \sum_{G_n} P(g_1) \cdots P(g_j) \cdot P(g_{j+1}|par) \cdots P(g_n|par)$$

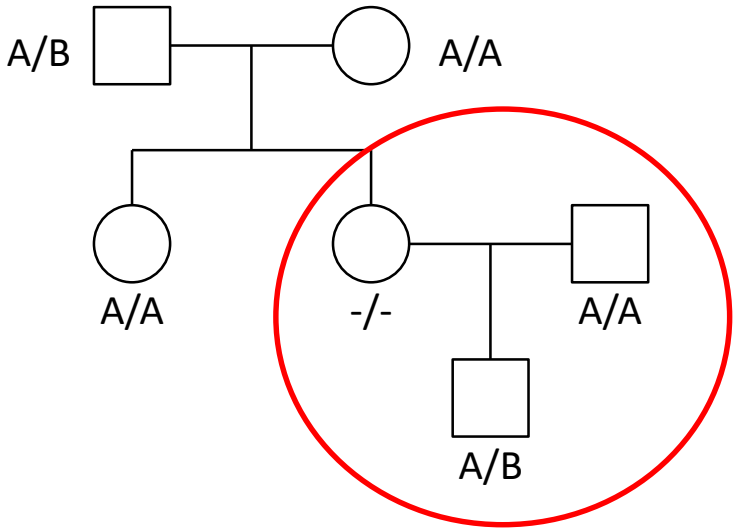
G_i = set of possible genotypes for individual *i*

- If everyone is typed: Only one term → easy

- Number of terms grows exponentially in #(untyped)
  - but clever algorithms exist!

Computer algorithms for pedigree likelihoods

- Elston-Stewart algorithm
  - a *peeling* algorithm
  - linear in pedigree size!



- Lander-Green
  - based on inheritance vectors
  - hidden Markov model
  - best choice with many *linked* markers
  - small/medium pedigrees only

Software

- R/pedprobr
  - Part of the *ped suite*
  - Elston-Stewart
  - general likelihoods, inbreeding, genotype distributions ++
- Familias
  - GUI for forensic applications
  - Elston-Stewart
  - handles mutations, HW deviations, ++
- MERLIN
  - command line program
  - Lander-Green
  - medical applications: multipoint linkage