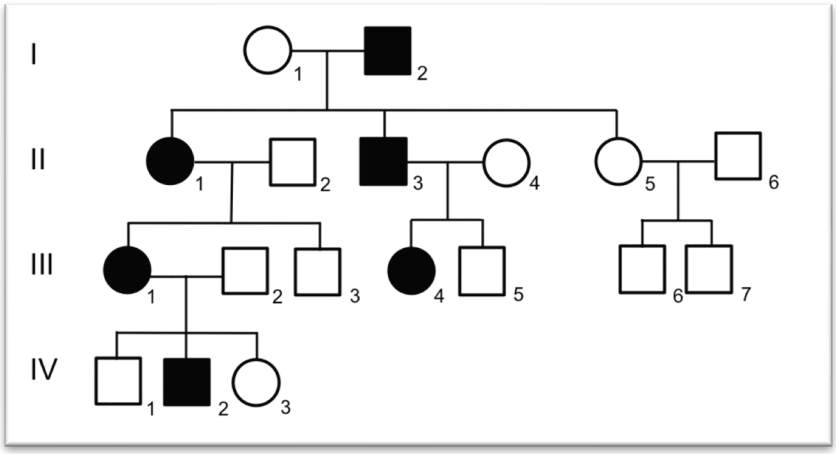
EXERCISES
Session 3

Exercise 1

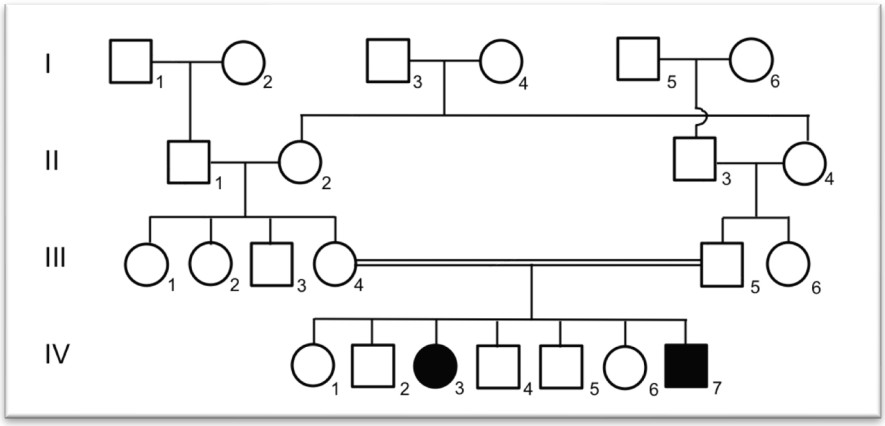
For each pedigree, indicate the most likely inheritance pattern. Assume monogenic inheritance and full penetrance in all pedigrees.

Pedigree 1



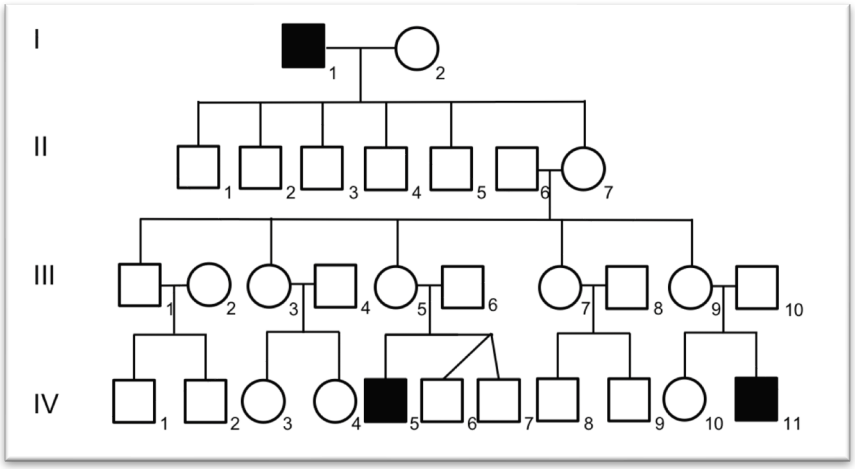
Autosomal dominant

Pedigree 2



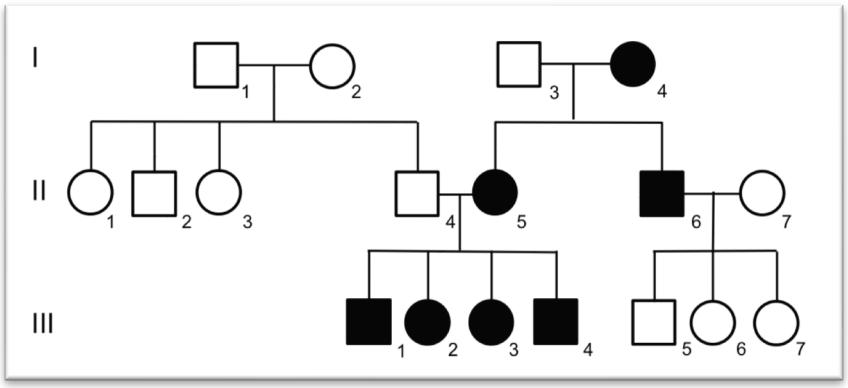
Autosomal recessive

Pedigree 3



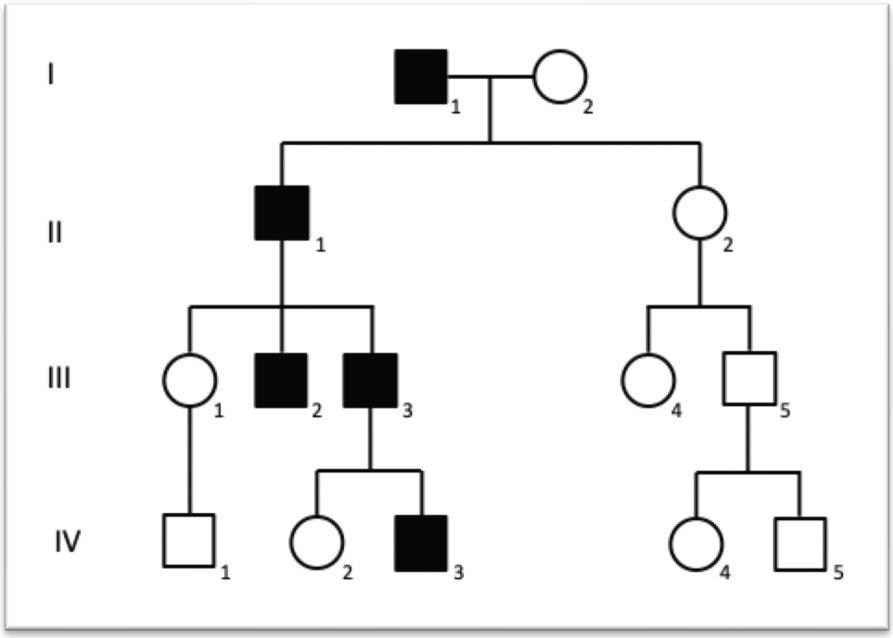
X-linked recessive

Pedigree 4



Mitochondrial inheritance

Pedigree 5



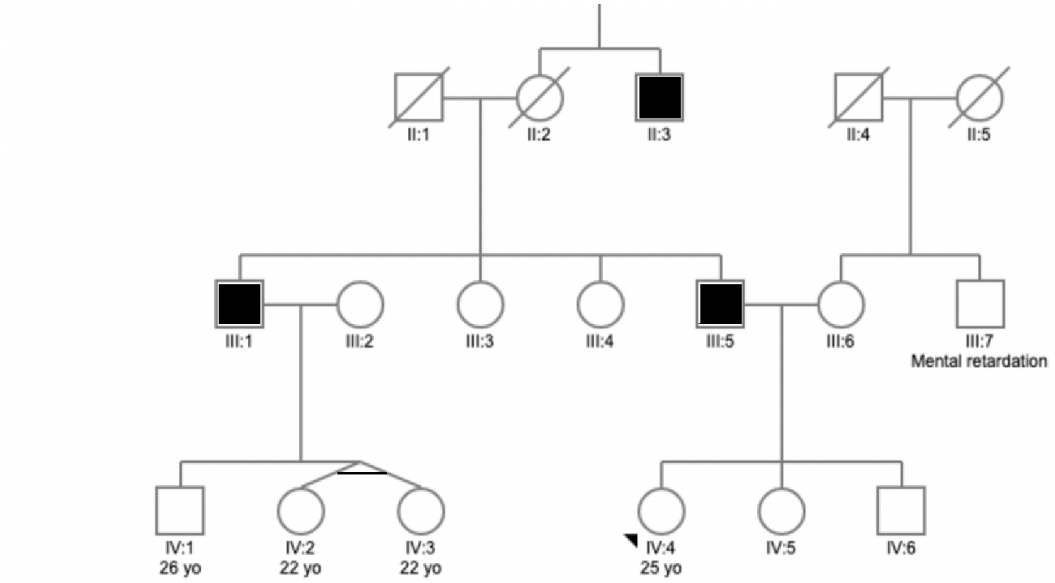
Y-linked

Exercise 2

A 25-year-old healthy woman comes in for genetic counselling on a hereditary skin disease that runs in her family. The disease – ichtyosis – causes dry and thickened "fish-scale" skin.
The woman has a healthy younger brother and sister.
Her father has the disease.
The father has an older brother, who also has the disease and two healthy older sisters.
The father's brother has three healthy children, a 26-year-old boy and two monozygotic, 22-year-old girls.
The woman's mother has a younger brother who has mental retardation, but normal skin.
Both the mother's and the father's parents are deceased but were not affected by the disease. The paternal grandmother had a brother with the disease.

1) Draw the pedigree for the family
2) What mode of inheritance does this disease have? Why?
3) The woman starts a relationship with her father's brother's son. If they decide to have children, what would their risk of having a child with ichtyosis be? (Hint: make a Punnett square)

Answers:
1) Pedigree:

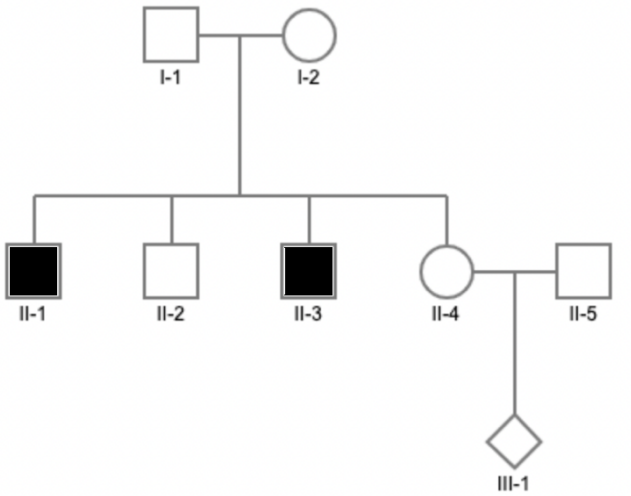


2) X-linked recessive. Only boys have the disease, and it is passed on by healthy female carriers. Present across generations.
3) 25% because the woman is an obligate carrier. 50% risk of disease if the child is a boy, and 50% risk of being a carrier if the child is a girl.

	X	Y
X	XX (Healthy girl)	XY (Healthy boy)
X	XX (Healthy carrier girl)	XY (Boy with disease)

Exercise 3

In the pedigree below, filled symbols represent individuals affected by chronic granulomatous disease.



A. Assuming the disease is X-linked recessive:
   a. Which individuals are obligate carriers of the disease-causing allele?
      I-2
   b. How should obligate carriers be indicated in the pedigree?
      With a dot inside the symbol
   c. What is the probability that individual II-4 is a carrier of the disease-causing allele?
      ½.
   d. What is the probability that individual III-1 will develop the disease?

      1/8. Risk = (II-4's risk of being carrier) x (risk of having a child with the disease if II-4 is carrier*) = ½ x 1/4 = 1/8.

      *Draw a Punnett square. Only boys will have the disease.

B. Assuming the disease is autosomal recessive, and individual II-5 is not a carrier:
   a. Which individuals are obligate carriers of the disease allele?
      I-1 and I-2.
   b. What is the probability that individual II-4 is a carrier?
      2/3. Draw a Punnett square. We can exclude aa because she does not have the disease.
   c. What is the probability that individual III-1 has inherited the disease-causing allele?
      1/3. Explanation: II-4 has 2/3 risk of being carrier and ½ risk of passing the disease allele on to III-1 if she is a carrier. 2/3 x ½ =1/3.

C. Assuming the disease is autosomal recessive, with a population disease frequency of 4 in 10,000:
   a. What is the probability that individual II-5 is a carrier?
      Disease freq = q^2 = 4/10,000

- ⇨ P(a) = q = 1/50 =0.02
- ⇨ P(A) = p = 1-q = 1-1/50 = 49/50 = 0.98

Carrier freq = 2pq = 2 x 0.02 x 0.98 = 0.0392 (ca. 4%)

b. If you take the above risk into consideration, what is then the risk that III-1 will get the disease?

P (disease child) = (carrier risk II-4) x (carrier risk II-5) x (risk of aa in child*)

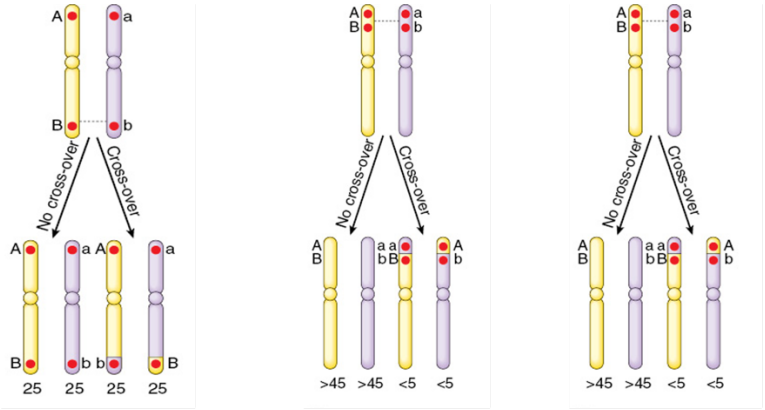
= 2/3 x 0,0392 x ¼

= 0.0065 (ca. 1/150)

*Make a Punnett square (Aa x Aa) – ¼ risk of aa.

Exercise 4

What is the genetic distance between locus A and B in the three examples below?



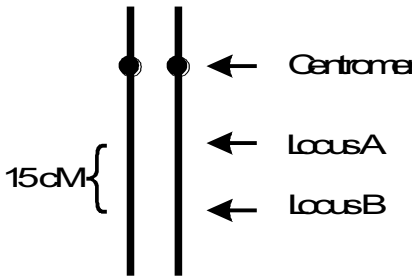
Genetic distance = (no of R / total no of chrom)

Exercise 5

The two genetic marker loci, A and B, are located on chromosome 9, with a genetic distance of 15 cM between them.

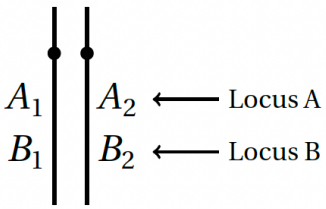
- Marker locus A has two alleles, A1 and A2
- Marker locus B has two alleles, B1 and B2

The father is heterozygous at both loci, carrying the haplotypes A1B1 and A2B2. The figure below illustrates chromosome 9, depicting both loci and their respective alleles.



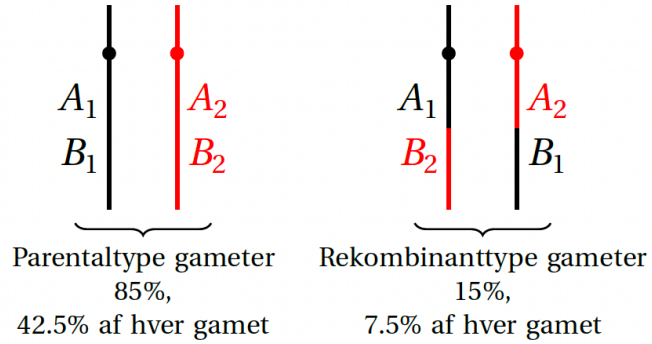
A. Draw a similar chromosome set and position the father's alleles.

Svar A:



B. Describe the different gametes that the father can produce and account for the frequencies of these gametes.

Svar B:

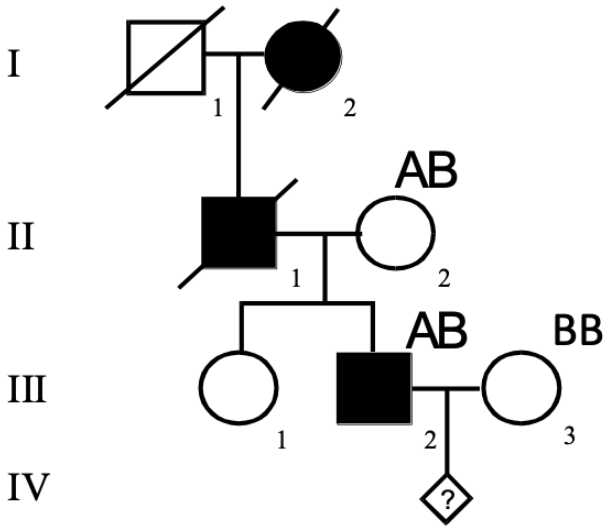


Parentaltype gameter
85%,
42.5% af hver gamet

Rekombinanttype gameter
15%,
7.5% af hver gamet

Exercise 6

A monogenic hereditary disease is present in the pedigree shown below. A marker locus located in the first intron of the disease gene has two alleles, A and B. The genotypes for this marker locus are provided for individuals II-2, III-2, and III-3 in the pedigree.



A. Based on the available genotype data, can we determine which marker allele (A or B) is linked to the disease allele? Justify your answer.

No. We don't know from this if III-2 received A or B from II-2, and therefore we cannot tell which allele the disease segregates with in this family.

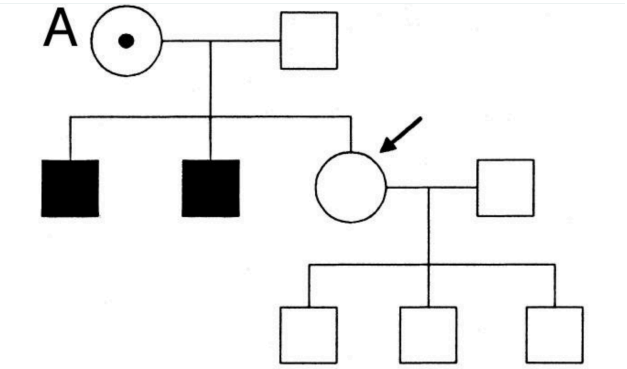
B. If we assume that II-1 has the genotype BB, does this allow us to conclusively determine which marker allele is linked to the disease allele?
We now know that III-2 has inherited A from his unaffected mother and B from his affected father.

C. If the fetus IV-1 has inherited the disease allele, what genotype is expected at the marker locus?
BB – B from the unaffected mother and B (disease allele) from the affected father.

Exercise 7

Assume an X-linked recessive monogenic disorder with full penetrance.

1. Based on all the information in the pedigree below, what is the probability that II.3 is a carrier of the monogenic disease-causing allele? (Hint: Use Bayes theorem)



Hypothesis	H: Is a carrier	H: Is not a carrier
Prior probability	$\frac{1}{2}$	$\frac{1}{2}$
Conditional probability (three normal sons)	$\frac{1^3}{2} = \frac{1}{8}$	1
Joint probability	$\frac{1}{16}$	$\frac{1}{2}$
Posterior probability	$\frac{\frac{1}{16}}{\frac{1}{16}+\frac{1}{2}} = \frac{1}{9}$	$\frac{\frac{1}{2}}{\frac{1}{16}+\frac{1}{2}} = \frac{8}{9}$

Exercise 8

Lise is of Danish origin and wants to know her risk of being a carrier of a pathogenic variant in BRCA1 and BRCA2. From previous screening (Sanger Seq.) no variant was found.

1. What is her risk of being a carrier?

Hypothesis	H: Is a carrier	H: Is not a carrier
Prior probability	0.03	0.97
Conditional probability (Sanger Seq neg)	0.2	1
Joint probability	0.006	0.97
Posterior probability	$\frac{0.006}{0.006 + 0.97} = 0.0061$	$\frac{0.97}{0.006 + 0.97} = 0.994$

- Prior probability: 3% (0.03) of Danish women with breast cancer carry a pathogenic variant.
- Test sensitivity: Sanger sequencing detects pathogenic variants 80% of the time (false-negative rate = 20%).

- Probability of a negative test result given that Lise is a carrier:
- P(\text{Negative Test} | \text{Carrier}) = 1 - 0.80 = 0.20
- Since non-carriers always test negative (100% specificity) the probability of a negative test given she is non-carrier is 1.