EXERCISES
Session 4a

Exercise 1

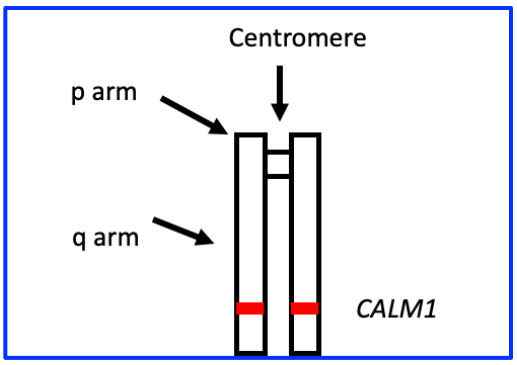
CPVT is a rare genetic condition that causes life-threatening arrhythmias. It follows an autosomal dominant inheritance pattern and is caused by mutations in the CALM1 gene, with at least 76 different mutations identified globally. Individuals carrying a pathogenic mutation are advised to receive an implantable cardioverter-defibrillator.

A. What type of genetic heterogeneity do we see for CPVT?
Allele heterogeneity (there is also locus heterogeneity, but this information is not present in the text).

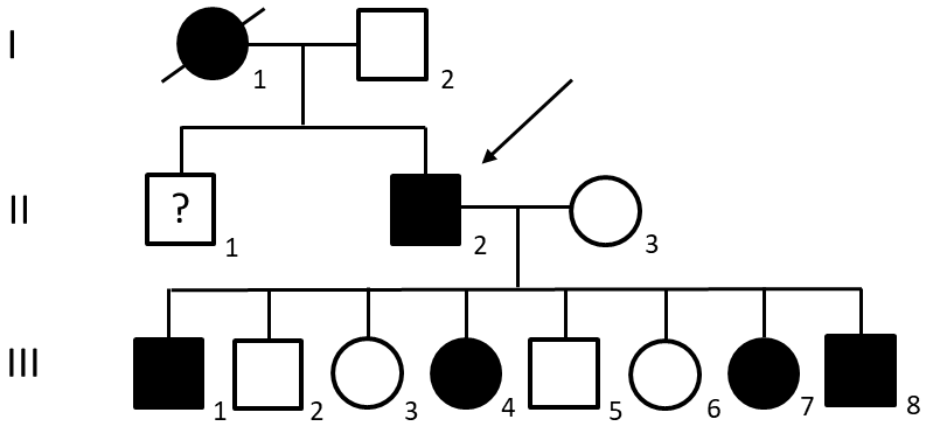
The *CALM1* gene is located on chromosome 14q32. Chromosome 14 is acrocentric.

B. Draw chromosome 14 in the metaphase and indicate p arm, q arm, centromere, and the approximate location of the *CALM1* locus.

Drawing:



Below is the pedigree of Carl's family, and Carl is indicated by an arrow.



C. How can you see from the pedigree that CPVT is an autosomal dominant disease?
Individuals with disease present in all generations.
Both males and females are affected.

A marker analysis is performed for the linked marker D19S584 located 0cM from the *CALM1* gene. The genotypes found in the marker analysis are shown in the table below.

Individual	**Carl's mother I-1**	**Carl's father I-2**	**Carl II-2**	**Carl's wife II-3**	**Child 1 III-1**	**Child 2 III-2**	**Child 3 III-3**	**Child 4 III-4**	**Child 5 III-5**	**Child 6 III-6**	**Child 7 III-7**	**Child 8 III-8**
D19S584	**1,1**	**1,2**	**1,2**	**1,3**	**1,3**	**1,2**	**2,3**	**1,1**	**1,2**	**2,3**	**1,1**	**1,3**

D. What is the disease-linked allele in this family?
1 – the 1 allele present in Carl (he has inherited 2 from his healthy father, so 1 must be the disease-linked allele)

E. Why does Carl's father not have CPVT despite having the exact same genotype for the linked marker as Carl?
This is because Carl has the disease-linked allele 1, which he inherited from his father. The mother does not have the disease-linked 1. Remember it is not allele 1 that is causing disease. Allele 1 is a normal allele in the population and can appear on both chromosome carrying the mutation and chromosomes not carrying the mutation.

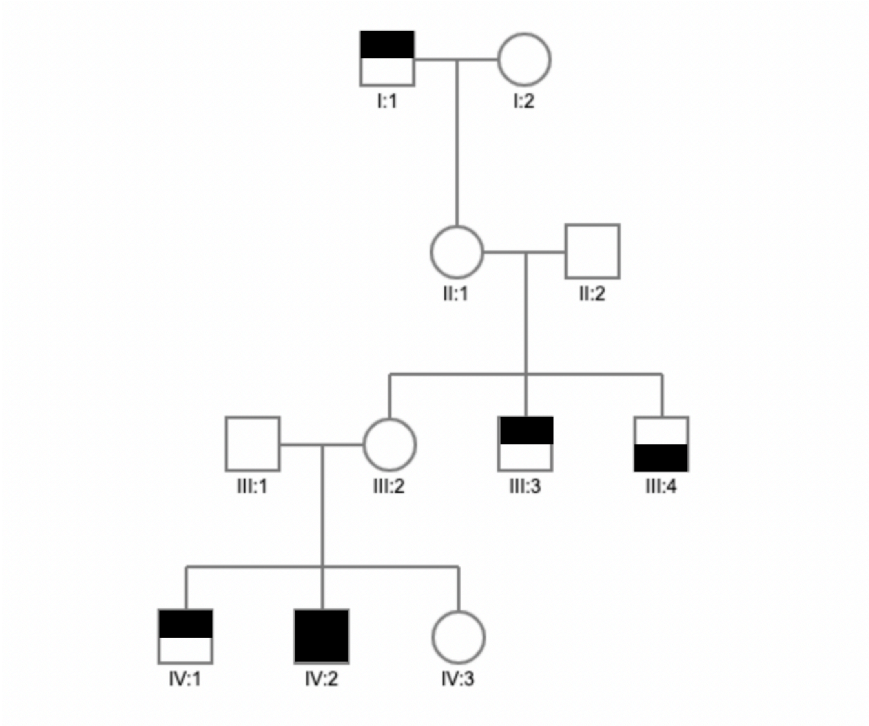
II-I was given up for adoption and now lives in Spain. The family has no contact with him. His phenotype is unknown.

F. Without knowing his genotype, what is the risk that Carl's brother (II-1) has the disease allele?
½ (risk that I-1 has passed on the disease allele to him)

G. If Carl's brother's genotype is 1,1 do we then know for sure if he has inherited the disease?
No. The mother is homozygous for the marker allele, so the marker analysis does not show if Carl's brother has inherited the disease allele or the other allele.

Exercise 9

In the pedigree below people suffering from ichtyosis are illustrated by  , and persons suffering from ocular albinism are illustrated by  . The disorders are both rare with monogenic inheritance. The disease loci are linked and the distance between the two loci can be set to 15cM. The possible occurrence of new mutations can be disregarded.



A. What mode of inheritance explains the pedigree better? Why?

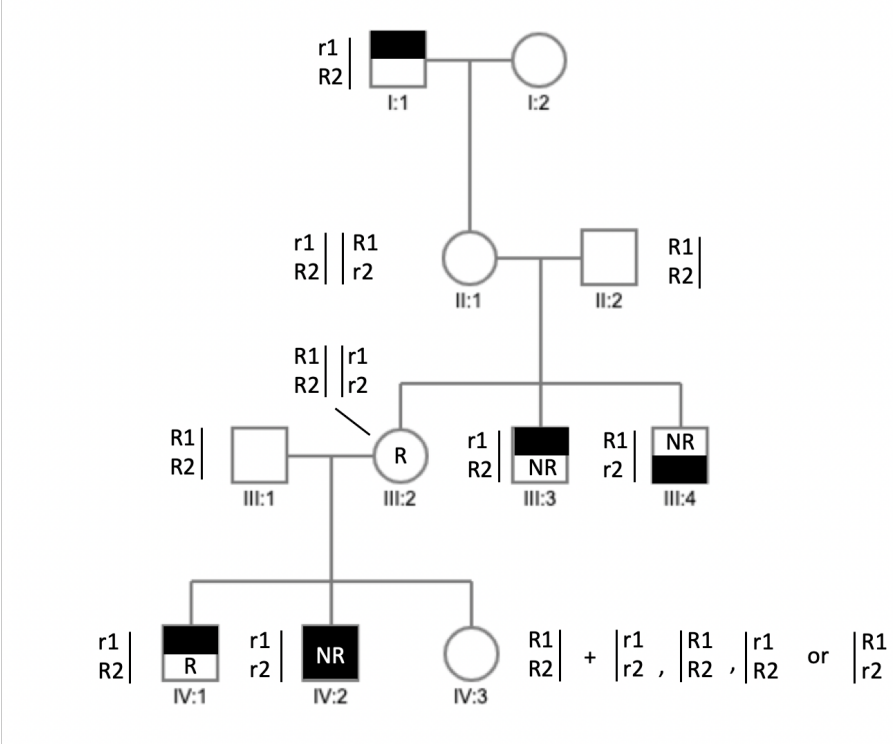
X-linked recessive – the disease is transmitted from healthy mothers to their sons. Autosomal recessive is unlikely because it would require that II:2 and III:1 (married into the family) are both carriers. Also because the gender ratio is skewed.

B. Draw the pedigree on a piece of paper (large pedigree) including all relevant chromosomes and indicate the possible haplotypes for all the individuals in generation III and IV.

Genotypes of males can be identified directly from their phenotypes!
Ichtyosis: locus 1, alleles R1/r1 (r1 is disease allele)
Ocular albinism (OA): locus 2, alleles R2/r2 (r2 is disease allele)

I. I:1 (male) has the genotype r1R2 (identified directly from the phenotype)
II. II:1 inherits r1R2 from his father. She is not sick (-> R1) and transmits OA to one of her sons (-> r2). II:2 is a healthy male = R1R2.

III:2 inherits R1R2 from her father and transmits both ichtyosis and OA -> r1r2.



C. Which of the individuals in generation III and IV can with certainty be identified as recombinants and which can with certainty be identified as non-recombinants?

We can identify these individuals by comparing the haplotypes in the children to those in their parents.

III. Recombinants: III:2 and IV:4
IV. Non-recombinants: III:3, III:4, and IV:2