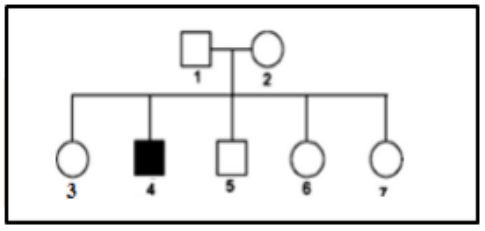
Calculation of the Risk

Hereditary diseases are caused by mutated alleles that are transmitted from parents to children. The risk of the parents to have a child with an inherited disease can be determined. This risk varies according to the conditions of the parents and to the mode of transmission of the disease (recessive or dominant, autosomal or sex linked).

1. Autosomal recessive disease

(Let N be the symbol of the dominant normal allele and d that of the mutated recessive allele)

1.1. Two heterozygous parents:



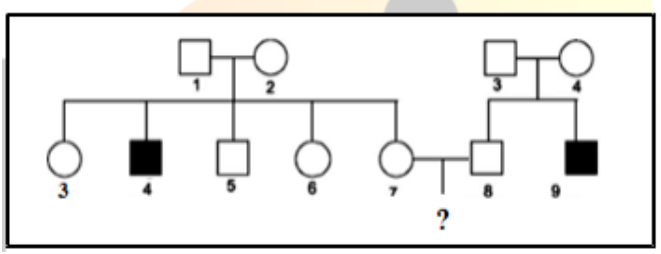
Calculation of the risk of the two parents (1) and (2) to have an affected fetus:

Probability of the fetus to be affected= P(mother to be heterozygous)xP(father to be heterozygous)x P(heterozygous parents to have an affected fetus)

The two parents (1) and (2) are normal having an affected child (4), so the probability for both to be heterozygous of genotype Nd=1. Each one of them produces 2 types of gametes of equal probability: ½ N and ½ d. To be affected, the fetus must take an allele (d) from each of the parents. Each one of the parents has a risk of ½ to give an allele (d) if they are heterozygous so the risk of having an affected fetus if they are heterozygous is of ¼.

Therefore, The risk of the child to be affected is: 1x1x 1/4 = ¼.

1.2. Two parents with affected siblings



Calculation of the risk of the two parents (7) and (8) to have an affected fetus:

The risk for (7) to be of genotype Nd is 2/3 because she has an affected brother (4), her parents (1) and (2) are heterozygous.

The risk for 8 to be of genotype Nd is 2/3 because he has an affected brother (9), his parents (3) and (4) are heterozygous.

To be affected, the fetus must take an allele (d) from each of the parents.

Each one of the parents has a risk of ½ to give an allele (d) if they are heterozygous so the risk of having an affected fetus if they are heterozygous is of ¼.

The risk for the two parents (7) and (8) to have an affected child = Risk for the father to be heterozygous × risk for the mother to be heterozygous × risk of the heterozygous parents to have an affected child = 2/3 × 2/3 × ¼ = 1/9.

1.3. Two parents with no family history of the disease

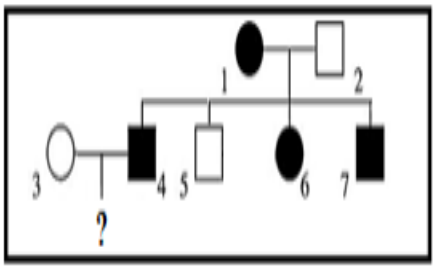
Given that the proportion of heterozygotes in the population of parents is 1/20.

Calculation of the risk of the two parents (1) and (2) to have an affected fetus:

Since the two parents have no family history,the risk for each of the two parents (1) and (2) to be heterozygous is equal to the proportion of heterozygotes in the population which is 1/20.

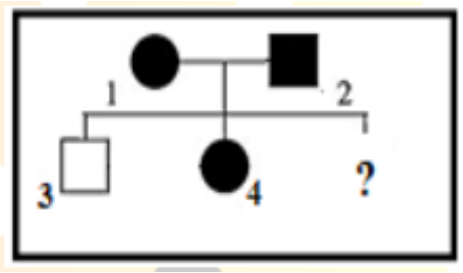
To be affected, the child must take an allele (d) from each of the parents. Each of the parents has a risk of ½ to give an allele (d) if they are heterozygous.
The risk for the two parents (1) and (2) to have an affected child = Risk for the father to be heterozygous × risk for the mother to be heterozygous × risk of the heterozygous parents to have an affected child = 1/20 × 1/20 × ¼ = 1/1600.

2. **Case of an autosomal dominant disease:**
(Let n be the symbol of the recessive normal allele and D that of the dominant mutated allele)



2.1. One of the parents is affected
Calculation of the risk of the two parents (3) and (4) to have an affected fetus:
Mother (3) is normal of genotype nn because the normal allele is recessive and is expressed only in the homozygous state.She can transmit only one allele n.
Father (4) has the genotype Dn because he is affected and has a normal father from whom he had taken an allele n.Since the father is heterozygous,the probability to produce a gamete carrying the allele D is 1/2 ; Father 4 can transmit 2 alleles:1/2 allele D and ½ allele n.
To be affected, the child only needs to take an allele D from the father; the risk of the child to take D from father is ½.
Therefore, the risk for the fetus to be affected is ½.

2.2. The two parents are affected

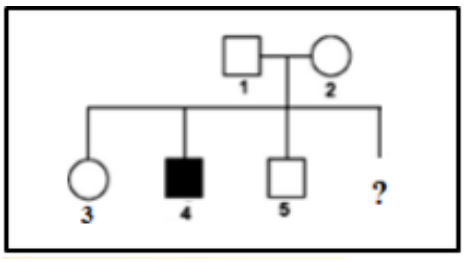


Calculation of the risk of the two parents (1) and (2) to have an affected child:

(1) and (2) are of genotype Dn because they are affected and have a normal child (3) of genotype nn. Each parent produces 2 types of gametes of equal probability: ½ D and ½ n
If the child takes n from each of them, he will be normal, his chance of doing so is ½ × ½ = ¼.
The risk for the child to be affected is therefore 1 - ¼ = ¾.

3. **Case of a recessive sex-linked disease:**
Remark: we can calculate the risk for the child to be affected regardless of the sex or we can calculate the risk for a girl to be affected and for a boy to be affected. (Let N be the symbol of the dominant normal allele and d that of the mutated recessive allele)

3.1. A heterozygous mother



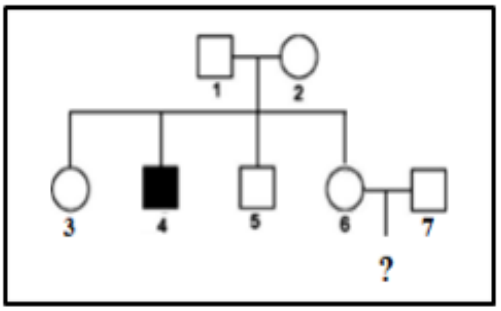
Calculation of the risk of the two parents (1) and (2) to have an affected child:

Father 1 is of genotype X^NY because he's phenotypically normal and the normal allele is dominant and located on X chromosome,

Mother 2 is of genotype X^NX^d because she is normal and the normal allele is dominant and has an affected son 4 to whom she had given an X^d .So the probability to give gamete carrying X^d is ½.Therefore she produces 2 types of gametes of equal probability: X^N ½ and X^d 1/2

- If the child is a boy, he would have taken Y from the father. The risk for the mother to give an X^d is ½, then the risk for the child to be affected is ½.
- If the child is a girl she would have taken X^N from the father and she will be normal whatever she will take from her mother, her risk to be affected is null.

3.2. A mother with an affected brother



Calculation of the risk of the two parents (6) and (7) to have an affected fetus:

Mother (2)is of genotype X^NX^d because she's normal and has an affected son (4) to whom she had given an X^d.

Mother(6) has a ½ risk of taking an X^d from her mother to be heterozygous of genotype X^NX^d .

Father(7) is of genotype X^NY

- If the fetus is a boy, he will take Y from the father. The risk for the mother to give an X^d is ½ if she is heterozygous. Then the risk for the fetus to be affected = risk for the mother to be heterozygous × risk for fetus to take X^d from his mother = ½ × ½ = 1/4.

- If the fetus is a girl, she would take X^N from the father and she will be normal whatever she will take from her mother since the normal allele is dominant and is expressed in homozygous and heterozygous state;therefore, her risk to be affected is null.

4. Case of a dominant sex linked disease:

Remark: we can calculate the risk for the child to be affected regardless the sex or we can calculate the risk for a girl to be affected and for a boy to be affected.

(Let n be the symbol of the recessive normal allele and D that of the dominant mutated allele)

4.1. An affected heterozygous mother and a normal father

The mother is heterozygous with genotype $X^D X^n$;so she can give X^D1/2 and X^n ½ (so the probability to produce gamete carrying the allele X^D is ½). The father is normal with the genotype $X^n Y$.

If the fetus is a boy, he would take Y from his father and has a ½ risk of taking X^D from his mother and being affected; then its risk of being affected is 1/2.

If the child is a girl, she would take X^n from her father and has ½ the risk to take X^D from her mother to become affected; thus her risk to be affected is of 1/2.

4.2. A normal mother and an affected father

The father has the genotype $X^D Y$. The mother is normal of genotype X^nX^nwho produces only gametes carrying X^n .

If the fetus is a boy, he would have taken Y from his father and X^n from his mother and he will surely be normal, thus his risk to be affected is zero.

If the fetus is a girl, she would have taken X^D from her father and she will be affected because the allele of the disease is dominant. Her risk to be affected is therefore 1.

4.3. An affected heterozygous mother and an affected father

The mother is heterozygous of genotype $X^D X^n$ so she produces gametes carrying X^D ½ and gametes carrying X^n 1/2 , the father has the genotype X^DY.

- If the fetus is a boy, he would have taken Y from his father and has a risk of ½ to take X^D from his mother and be affected; then his risk to be affected is 1/2.
- If the fetus is a girl, she would have taken X^D from her father and she will be surely affected because the disease allele is dominant. Her risk to be affected is therefore 1.