



Medical Genetics

Sheet: 11 - Risk Assessment

Writer: Reham badayneh

Scientific: Mothana Olimat

Final: Lina Abdelhadi

Doctor: Bilal Azab

Risk assessment

In this sheet, we are going to solve questions that will demonstrate the idea of risk assessment, take a minute to solve the question by your own and then look at the answer.

Question 1: what is the probability that if a couple has 4 children all will be males?

Answer :-

[Probability of Male = $1/2$]

All males means (the first child is male, the second child is male, the third child is male and the fourth child is male).

Probability (all males) = $1/2 \times 1/2 \times 1/2 \times 1/2 = 1/16$

For the same question: what Is the probability that the 4 children all will be females?

Answer :-

[Probability of female = $1/2$]

All females means (the first child is female, the second child is female, the third child is female and the fourth child is female).

Probability (all females) = $1/2 \times 1/2 \times 1/2 \times 1/2 = 1/16$

Again, for the same question: what Is the probability that the 4 children all will be the same gender?

Answer :-

The same gender means that the 4 children are Either (4 females OR 4 males)

Probability (same gender) = $1/2 \times 1/2 \times 1/2 \times 1/2 + 1/2 \times 1/2 \times 1/2 \times 1/2 = 2/16=1/8$

***note : when we use AND ; It means that we multiply the probabilities, whereas when we use OR we add the probabilities .**

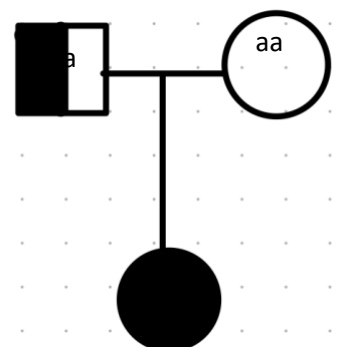
Question 2: A women has a father who died of Huntington's disease, what Is the probability that she will develop the symptoms of the disease?

(For these kinds of questions draw a pedigree)

Answer :-

* Remember Huntington's disease is Autosomal dominant disease.

* Use **A = Dominant allele, a = Recessive allele** for the disease.



-Regarding the pedigree

Remember that we assume that the affected father is heterozygous (**Aa**), also we assume that the partner (the mother here) is not affected unless stated otherwise (**aa**).

-Using Punnett square :-

Dad Mom	A	a
a	Aa	aa
a	Aa	aa

Probability (that the female child will develop the symptoms of the disease) = 2/4 = 1/2

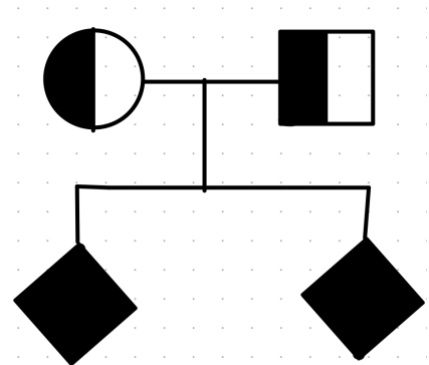
Question 3: A couple are both tested and found to be carriers of the cystic fibrosis gene, If they have 2 children :-

A- what is the chance that both children will be affected by cystic fibrosis?

Answer :-

- * Remember that cystic fibrosis is an autosomal recessive disease.
- * Use **A= dominant allele, a = recessive allele.**

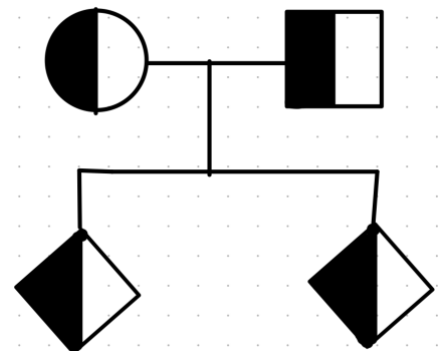
Dad Mom	A	a
A	AA	Aa
a	Aa	aa



Probability (that both children will be affected by cystic fibrosis, the first child is affected AND the second child is affected) = 1/4 x 1/4 = 1/16

B-what is the chance that both will be carriers of cystic fibrosis?

Dad Mom	A	a
A	AA	Aa
a	Aa	aa

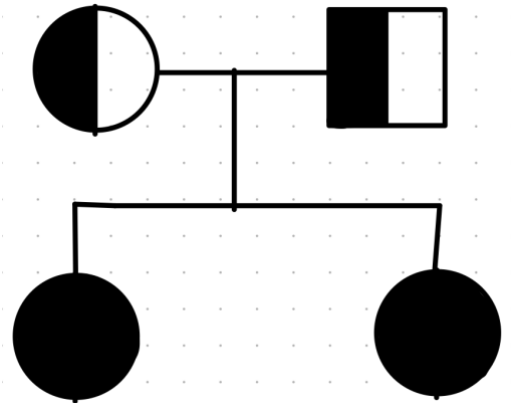


A	AA	Aa
a	Aa	aa

Probability (that both children are carriers of cystic fibrosis, the first child is a carrier AND the second child is a carrier) = $1/2 \times 1/2 = 1/4$

C- what is the chance that they will have 2 girls that are both affected by cystic fibrosis?

Dad Mom	A	a
A	AA	Aa
a	Aa	aa



Probability (that both children are affected girls, the first child is an affected girl AND the second child is an affected girl) = $1/4 \times 1/2 \times 1/2 \times 1/4 = 1/64$

* Note we multiply the probability to have an affected child (1/4) by (1/2) because the question has specified the gender.

Question 4: The ability to taste the chemical (PTC) is determined by a single gene in humans with the ability to taste given by the dominant allele (T) and inability to taste by the recessive allele (t). Suppose two heterozygous tasters (Tt) have a large family.

A- Predict the proportion of their children who will be tasters and non-tasters. Use a Punnett square to illustrate how you make these predictions.

Dad Mom	T	t
T	TT	Tt
t	Tt	tt

Proportion of their children who will be tasters = $3/4$ (75%)

Proportion of their children who will be non-tasters = $1/4$ (25%)

B- what is the likelihood that their first child will be a taster? What is the likelihood that their fourth child will be a taster?

Dad Mom	<i>T</i>	<i>t</i>
<i>T</i>	<i>TT</i>	<i>Tt</i>
<i>t</i>	<i>Tt</i>	<i>tt</i>

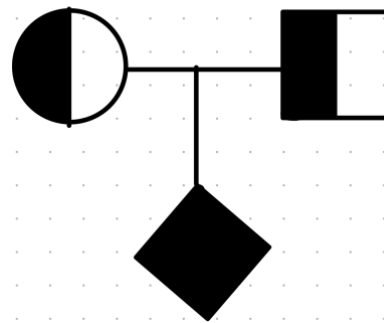
Probability (that their first child will be a taster) = 3/4

Probability (that their 4th child will be a taster) = 3/4

* Remember that the probabilities of each pregnancy is **Independent** from the probabilities of the previous pregnancies.

Question 5: For a Caucasian couple with no family history, what is the chance they will have a child with CF (Cystic fibrosis)? Knowing that caucasian population carrier frequency is 1/25.

Dad Mom	<i>A</i>	<i>a</i>
<i>A</i>	<i>AA</i>	<i>Aa</i>
<i>a</i>	<i>Aa</i>	<i>aa</i>



Answer :-

* Remember that Cystic fibrosis is an autosomal recessive disease.

* use **A= Dominant allele, a = recessive allele.**

- In this question it doesn't tell us that the couple tested for CF neither if one or both of them are affected, but the red note mentioned in the question gives us a clue (carrier frequency of 1/25; means that out of 25 people one will be carrier).

-Remember that we assume that the couple aren't affected unless otherwise indicated, so for these unaffected couple to have an affected child (**aa**) they must be at least both heterozygous (**Aa,Aa**), to pass on the affected allele.

So, now we have three probabilities =

Probability for the mom to be a carrier AND Probability for the dad to be a carrier AND Probability to have an affected child = 1/25 x 1/25 x 1/4 = 1/ 2500

Question 6: Couple with diagnosis of Cystic fibrosis in mother's nephew, what is risk to fetus (to be affected by CF)? Carrier frequency is 1/25

* Remember that Cystic fibrosis is an autosomal recessive disease.

*Use **A= dominant, a= recessive.**

- Here, when there is a family history (In the mother's side) we discard the carrier frequency for her.

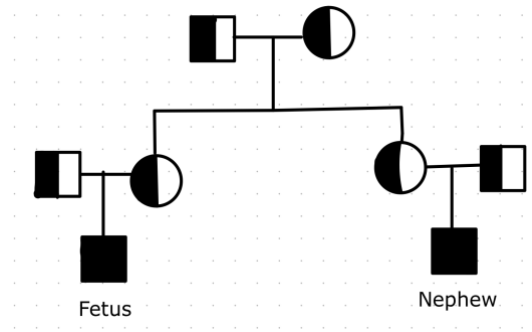
-So let's draw the pedigree first :-

1-Regarding the nephew (nephew means: a son of one's brother or sister) :-

-He is an affected child (aa), each of his parents must have the affected allele (a).

- Regarding his father, we assume he is heterozygous (Aa)

-Regarding his mother (the sister of the Fetus's mother) we assume she is heterozygous not affected; because it is not mentioned in the question that she is affected (Aa).



2- Regarding the grandparents, the affected allele (a) present in the nephew's mother must be passed on from **one** of her parents (Either the mom or the dad but not from both), so the probability that the grandfather will be a carrier is $1/2$ and the probability that the grandmother will be a carrier is $1/2$.

3-Regarding the Fetus :-

-He is an affected child (aa), each of his parents must have the affected allele.

-Regarding his father, we assume that he is heterozygous (Aa).

-Regarding his mother we assume that she is heterozygous (Aa), now the probability that she will be a carrier is = (the probability that she inherited the mutant allele from her father **OR** from her mother) $1/2$ (the odds that the father is a carrier) $\times 1/2$ (the odds to pass the mutant allele from the father to his daughter) + $1/2$ (the odds that the mother is a carrier) $\times 1/2$ (the odds to pass the mutant allele from the mother to her daughter) = $1/2$

* NOTE: if my niece or nephew are affected with a recessive disease the odds that I will be a carrier is $1/2$.

So, what is the probability that the fetus is affected (the probability that the mother is a carrier AND the probability that the father is a carrier AND the probability that the fetus is affected) = $1/2 \times 1/25 \times 1/4 = 1/200$

Good luck

Risk Assessment 2

In this sheet, we'll discuss risk assessment regarding autosomal recessive disorders only. Assume "A" is the normal allele and "a" is the mutant recessive one for all questions.

General tips before we get started:

- Use carrier frequency when the individual has no family history of the disease.
- Use Punnett square when there is only one possible genotype for each parent.

Q1. If someone has an affected nephew with CF (Cystic fibrosis), what is the probability that he is a carrier?

1-Draw the pedigree.

2-Determine the pattern of inheritance and what the question is asking for.

- ⇒ CF is inherited in an autosomal recessive fashion.
- ⇒ The question is asking for the probability that individual II-1 is a carrier.... $P(\text{II-1 genotype} = "Aa") = ??$

3- Analyze the pedigree starting from the affected individual.

- ⇒ Starting from individual III-1
 - ✓ His genotype must be "aa", as CF is an autosomal recessive disease.
 - ✓ the only way III-1 can be affected is that both of his parents are carriers.
 - ✓ so, II-2 and II-3 are obligate carriers "Aa".
 - ✓ Individual II-2 must have inherited the mutant allele from one of her parents.
 - ✓ So, either I-1 is a carrier or I-2 is a carrier.
 - ✓ There are 2 possible scenarios:

(I-1 genotype= "Aa", I-2 genotype= "AA") or (I-1 genotype= "AA", I-2 genotype= "Aa")

4- Write the equation for calculating the wanted probability.

- ⇒ It is easier than doing Punnett square as there are more than one possible genotype for each parent (I-1, I-2).

In order for II-1 to be a carrier:

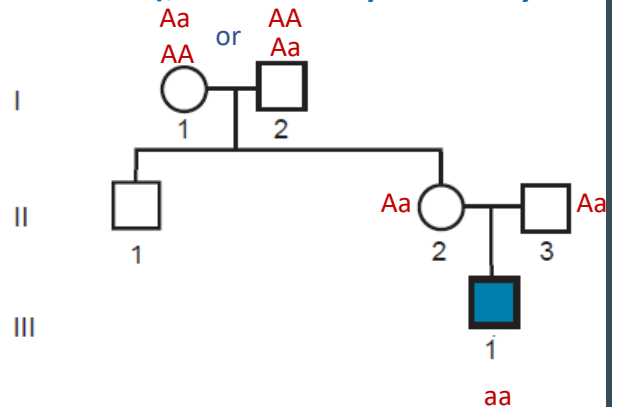
I-1 is carrier and passed on the mutant allele or I-2 is a carrier and passed on the mutant allele.

$P(\text{II-1 carrier}) = p(\text{I-1 is a carrier}) \times p(\text{passing "a"}) \oplus p(\text{I-2 is a carrier}) \times p(\text{passing "a"})$

Its either Aa or AA
So $p(\text{being "Aa"}) = \frac{1}{2}$

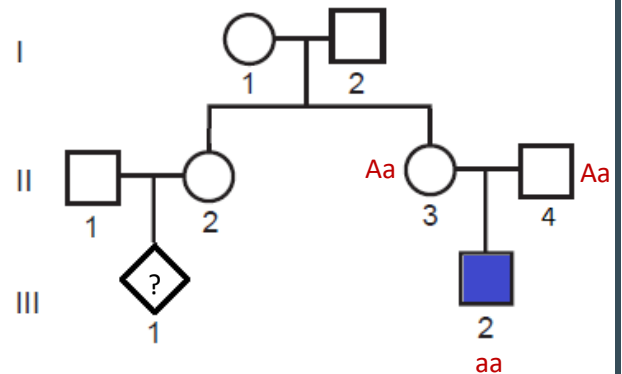
2 diff alleles for Aa genotype {A,a}
So $p(\text{"a" is the inherited}) = \frac{1}{2}$

$$\left(\frac{1}{2} \times \frac{1}{2}\right) + \left(\frac{1}{2} \times \frac{1}{2}\right) = \frac{1}{2}$$



**Q2. Assume a couple with diagnosis of CF in mother's nephew. What is risk to fetus?
Carrier frequency is 1/25.**

- 1- Draw the pedigree.
- 2- Determine the pattern of inheritance and what the question is asking for.
 - ⇒ autosomal recessive
 - ⇒ $p(\text{III-1 genotype} = "aa") = ??$
- 3- Analyze the pedigree starting from the affected individual.
 - ⇒ Using the same analysis of the previous question:
 $P(\text{II-2 carrier}) = \frac{1}{2}$
- 4- Write the equation for calculating the wanted probability.



In order for III-1 to be affected:

II-1 is a carrier **and** passed on the mutant allele **and** II-2 is a carrier **and** passed on the mutant allele.

$$P(\text{III-1 affected}) = p(\text{II-1 carrier}) \times p(\text{passing "a"}) \times p(\text{II-2 carrier}) \times p(\text{passing "a"})$$

No family history
Use carrier freq

From the previous question it is 1/2

$$(1/25 \times \frac{1}{2}) \times (\frac{1}{2} \times \frac{1}{2}) = 1/200$$

Q3. Assume a couple in which the father is tested to be a carrier for CF while the mother hasn't been tested. What is the probability that they'll have:

a- An affected child?

In order for the child to be affected:

The father is a carrier and passed on the mutant allele and the mother is a carrier and passed on the mutant allele

$$= p(\text{carrier father}) \times p(\text{passing "a"}) \times p(\text{carrier mother}) \times p(\text{passing "a"})$$

100% he is carrier according to the question

No family history, use carrier freq

$$(1 \times \frac{1}{2}) \times (1/25 \times \frac{1}{2}) = 1/100$$

b- Two affected children?

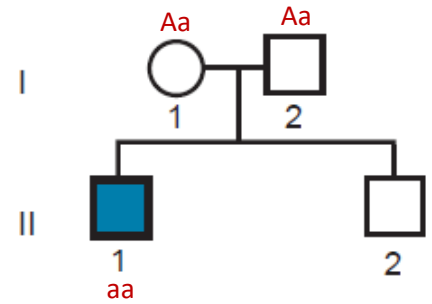
One affected child **and** another affected child = $1/100 \times 1/100 = 1/10000$

c- An affected girl?

Girl **and** affected = $\frac{1}{2} \times 1/100 = 1/200$

Q4. If someone has an affected brother with CF, what is the probability that he is a carrier?

- 1- Draw the pedigree.
- 2- Determine the pattern of inheritance and what the question is asking for.
 - ⇒ autosomal recessive
 - ⇒ $p(\text{II-2 genotype} = "Aa") = ??$
- 3- Analyze the pedigree starting from the affected individual.



- 4- Do a Punnett square (one possible genotype for each parent, so it is easier to do Punnett square).
- 5- Take a look at the results you got from the Punnett square and rule out the impossible ones.
 - ⇒ Is it possible for II-2 genotype to be "AA"? Sure, as he doesn't show the trait.
 - ⇒ Is it possible for II-2 genotype to be "Aa"? Sure, being heterozygous for a recessive disease doesn't show the trait.
 - ⇒ Is it possible for II-2 genotype to be "aa"? No way, if his genotype was "aa", he would be affected (show the trait). so, this result must be ruled out.

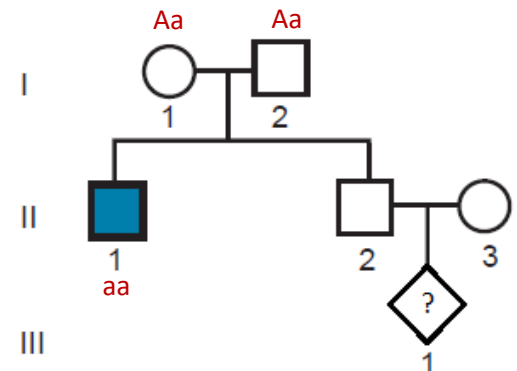
Cross: Aa x Aa

	A	a
A	AA	Aa
a	Aa	aa

$$\therefore p(\text{II-2 genotype} = "Aa") = 2/3$$

Q5. Assume a couple with diagnosis of CF in father's brother. What's the risk to the fetus?

- 1- Draw the pedigree.
- 2- Determine the pattern of inheritance and what the question is asking for.
 - ⇒ autosomal recessive
 - ⇒ $p(\text{III-1 genotype} = "aa") = ??$
- 3- Analyze the pedigree starting from the affected individual.
 - ⇒ The same analysis of the previous question
 - $P(\text{II-2} = \text{carrier}) = 2/3$



- 4- Write the equation for calculating the wanted probability. In order for III-1 to be affected:

II-2 is a carrier and passed on the mutant allele and II-3 is a carrier and passed on the mutant allele

$$p(\text{III-1 affected}) = p(\text{II-2 carrier}) \times p(\text{passing "a"}) \times p(\text{II-3 carrier}) \times p(\text{passing "a"})$$

From the previous question = 2/3

No family history, use carrier freq

$$(2/3 \times 1/2) \times (1/25 \times 1/2) = 1/150$$

To sum up:

For a given autosomal recessive disorder:

- If someone has an affected nephew/niece, the probability he is a carrier = $\frac{1}{2}$
- If someone has an affected sibling, the probability he is a carrier = $\frac{2}{3}$

In all patterns of inheritance:

- If there is family history for a given disease, disregard carrier frequency.
- If there is only one possible genotype for each parent, it is easier to do Punnett square. Otherwise, write the desired equation.
- After doing a Punnett square, check the results and rule out the impossible ones.
- If you write an equation (not Punnett square), don't worry about ruling out any results, as they are ruled out automatically.

*Best of
Luck!*