Medical Genetics

Sheet: Risk assessment - 12

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Risk Assessment 2

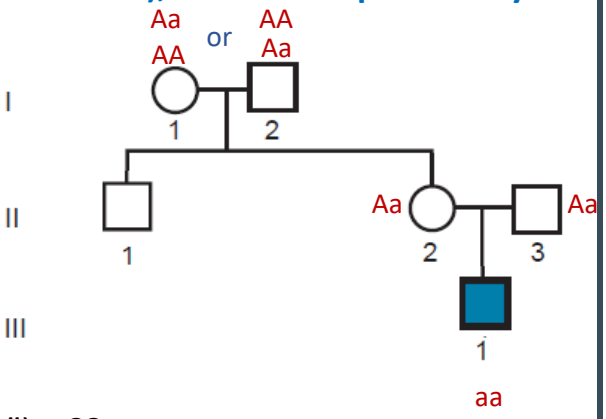
In this sheet, we'll discuss risk assessment regarding autosomal recessive disorders only.

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(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(II-1 carrier)= p(I-1 is a carrier) × p(passing "a") ⊕ p(I-2 is a carrier) × p(passing"a")

Its either Aa or AA

So p(being "Aa") = ½

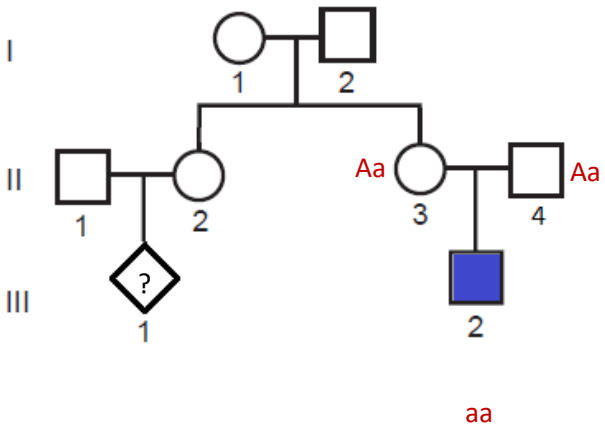
2 diff alleles for Aa genotype {A,a}

So p("a" is the inherited)= ½

$(½ \times ½) + (½ \times ½) = ½$

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(III-1 genotype="aa")=??
3- Analyze the pedigree starting from the affected individual.
   ⇨ Using the same analysis of the previous question:
   P(II-2 carrier) = ½
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(III-1 affected)= p(II-1 carrier) × p(passing "a") × p(II-2 carrier) × p(passing "a")

No family history
Use carrier freq

From the previous question it is 1/2

(1/25 × ½) × (½ × ½) = 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(carrier father) × p(passing "a") × p(carrier mother) × p(passing "a")

100% he is carrier according to the question

No family history, use carrier freq

(1 × ½) × (1/25 × ½)= 1/100

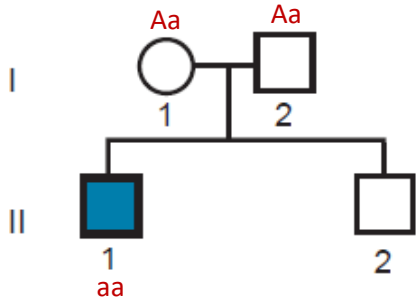
b- Two affected children?

One affected child and another affected child= 1/100 × 1/100=1/10000

c- An affected girl?

Girl and affected = ½ ×1/100 =1/200

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



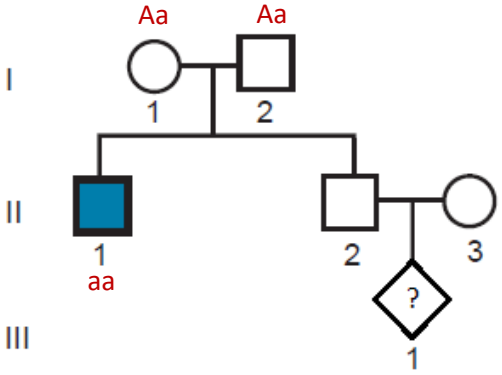
1- Draw the pedigree.
2- Determine the pattern of inheritance and what the question is asking for.
   - ⇨ autosomal recessive
   - ⇨ p(II-2 genotype="Aa")=??
3- Analyze the pedigree starting from the affected individual.
   - ⇨ II-1 genotype= aa
   - ⇨ I-1 and I-2 are obligate carriers "Aa"
4- Do a Punnett 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

∴ p(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(III-1 genotype="aa")=??
3- Analyze the pedigree starting from the affected individual.
   - ⇨ The same analysis of the previous question P(II-2 =carrier) = 2/3
4- Write the equation for calculating the wanted probability.

In order for III-3 to be affected:

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

p(III-3 affected)= p(II-2 carrier)×p(passing "a") × p(II-3 carrier)×p(passing "a")

From the previous question=2/3

No family history, use carrier freq

(2/3 × ½) × (1/25 × ½)=1/150

To sum up:

For a given autosomal recessive disorder:

- If someone has an affected nephew/niece, the probability he is a carrier = ½
- If someone has an affected sibling, the probability he is a carrier = 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.