Case File 5: Familial Hypercholesterolemia

Sophie and Stephan Grosfeuille are the parents of two young girls, Isabelle and Claire. Sadly, 14 year old Isabelle recently died from a heart attack. Sophie and Stephan knew that many members of each of their families had suffered heart attacks but they never thought it would happen to someone so young. Devastated by their loss, and fearful for the health of their other daughter Claire, the Grosfeuille’s had an appointment with a doctor at a genetics clinic. The family history (pictured below) was reviewed.

The doctor suspected a condition called Familial Hypercholesterolemia (FH) was being passed down on both sides of the family. FH is a genetic condition where individuals have heart attacks at early ages because they have extremely high levels of the ‘bad’ cholesterol (fat) called low-density-lipoprotein (LDL) in their body. Individuals with this condition may also have waxy plaques (cholesterol deposits) on their eyelids, knees, buttocks and elbows. There are 3 different phenotypes of FH depending on the individual’s genotype as shown below:

- Let ‘D’ represent the non-functioning (mutant) allele
- Let ‘d’ represent the functional (normal) allele

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>dd (homozygous normal)</td>
<td>Healthy. No increased risk for heart attacks.</td>
</tr>
<tr>
<td>Dd (heterozygous for mutation)</td>
<td>Heart attacks in middle age (~40-50s)</td>
</tr>
<tr>
<td>DD (homozygous for mutation)</td>
<td>Heart attacks in childhood</td>
</tr>
</tbody>
</table>

1) What type of inheritance pattern do the heart attacks have in this family? Dominant, Recessive or X-linked?
2) What are the likely genotypes of Stephan, Sophie, Isabelle and Claire?
3) How would you describe the alleles involved in FH: co-dominant, completely dominant, incompletely dominant? Explain your answer.

Genetic testing on 12 year old Claire found that she is heterozygous for the nonfunctional mutation (Dd).

4) What is Claire’s risk of a heart attack?

As an adult Claire decides to have children.

5) If her partner is a healthy, homozygous normal man, what are the possible genotypes and phenotypes of their children?
6) If her partner is known to be heterozygous for the nonfunctional allele, what are the possible genotypes and phenotypes of their children?

Stephan’s brother Louie had genetic testing. His genotype is dd.

7) What is his chance of having a heart attack?
   a. He has no chance of having a heart attack.
   b. He has an increased risk of heart attacks compared to other men his age.
c. He has the same chance of having a heart attack as any other man his age.

Case File 5: Answers

Question 1
ANSWER: Dominant inheritance

EXPLANATION:
- X-linked inheritance can be ruled out because both males and females are affected.
- Recessive inheritance is unlikely because there are many affected individuals in the family.
- Dominant inheritance is the best fit (see below for features of this type of inheritance).

Key points about classic Dominant inheritance:
- Many individuals affected across many generations
- Both males and females may be affected
- Affected individuals have affected parents

Question 2
ANSWER:
Stephan: Dd
Sophie: Dd
Isabelle: DD
Claire: Dd or DD or dd

EXPLANATION:
- Isabelle’s genotype is most likely ‘DD’ because she was very young when she had a heart attack. She most likely inherited one ‘D’ allele from each parent.
- Taking into consideration that Stephan and Sophie have not yet had heart attacks and their family histories, Stephan and Sophie are most likely ‘Dd’. Further, Sophie was noted to have skin plaques which provide more evidence that her genotype is ‘Dd’. Stephan not having plaques shows the variability of this disorder.
- Claire could be Dd, DD or dd. There is not enough information to pinpoint her genotype further.

Question 3
ANSWER: Incompletely dominant

EXPLANATION:
- Incomplete dominance is when there is the partial expression of each allele. In other words, the expression of each allele is different to that of each homozygous allele. Using the example of FH, heterozygous individuals are a ‘blending’ or midway point between the homozygous normal individuals (dd) and the homozygous individuals for the mutant allele (DD). The heterozygous (Dd) phenotype is more severe than the normal (dd) phenotype, but less severe than the phenotype seen in ‘DD’ individuals.
- Note that co-dominance is when there is the complete expression of each allele at the same time.
- Complete dominance is when the phenotype from one allele is always expressed and the phenotype of the second (recessive) allele is always hidden. In this situation, it wouldn’t matter if an individual had a ‘Dd’ or ‘DD’ genotype – the phenotype would be the same. With most dominant conditions we assume that the ‘DD’ genotype is very rare, so in fact the phenotype of ‘DD’ individuals for most dominant conditions is not well understood.

Question 4
ANSWER: Claire is at increased risk for having heart attacks in middle age.
Question 5

**Answer:**

Genotypes: Dd, dd

Phenotypes: ½ children will be at increased risk for heart attacks in middle age. The other ½ will not be at increased risk for heart attacks.

**Explanation:**
- Claire's genotype is 'Dd'
- Her partner's genotype is 'dd'
- Claire's partner will always pass down a functioning 'd' allele. Claire will either pass down her functioning 'd' allele OR pass down her non-functioning 'D' allele. See the diagram below

**Heterozygous female x Homozygous normal male: Dd x dd**

<table>
<thead>
<tr>
<th>D</th>
<th>d</th>
<th>½ children are at increased risk for heart attacks in middle age (Dd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>d</td>
<td>Dd</td>
<td>½ children are not at increased risk for heart attacks (dd)</td>
</tr>
<tr>
<td>d</td>
<td>Dd</td>
<td>½ children are not at increased risk for heart attacks (dd)</td>
</tr>
</tbody>
</table>

Question 6

**Answer:**

Genotypes: DD, dd, Dd

Phenotypes: ¼ of the children will not be at increased risk for heart attacks. ½ will be at increased risk for heart attacks in middle age. ¼ will have heart attacks in childhood.

**Explanation:**
- Claire is Dd.
- Her partner is Dd.
- Each Claire and her partner may pass down either their functional 'd' allele or their non-functional 'D' allele.

**Heterozygous female x Heterozygous male: Dd x Dd**

<table>
<thead>
<tr>
<th>D</th>
<th>d</th>
<th>¼ children are not at increased risk for heart attacks (dd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>DD</td>
<td>2/4 (½) are at increased risk for heart attacks in middle age (Dd)</td>
</tr>
<tr>
<td>d</td>
<td>Dd</td>
<td>¼ are at increased risk for heart attacks in childhood (DD)</td>
</tr>
</tbody>
</table>

Question 7

**Answer: C**

**Explanation:**

Having a homozygous normal genotype of 'dd' does not protect against heart attacks. While an individual with a 'dd' genotype is not at increased risk of having heart attacks at an early age, there remains a baseline risk for the individual to have a heart attack. Of course we all know that we should eat well and exercise to be healthier, but we don't always do what is best for us. A low fat, low cholesterol diet along with regular exercise and keeping a healthy body weight helps to reduce the risk of heart attacks both in predisposed individuals as well as for people in the general population.

**References:**

2) Emedicine: [www.emedicine.com](http://www.emedicine.com)

Saunders.