PBL. Human Genetic Disorders

Huntington's Disease Case

PROBLEM:

Kelly and Marco are newlyweds. They are eager to start a family and plan on having lots of children. One day Kelly gest a phone call from and adoption agency. Kelly's parents were always open with her that she was adopted, so the phone call was no surprise but what they had to share with her was. The adoption agency was recently contacted by Kelly's biological mother who wanted some family history information passed on to Kelly. Kelly is told that Huntington's disease (HD) runs in her biological father's family. Her father is affected and there is a chance that Kelly may have inherited this condition from him. The agency told Kelly that her father (He has an older brother and sister, respectively) is affected with HD and so is his older sister. Kelly's grandfather died due to the disease as well. Kelly is shocked by the news and she is gone to you for genetic counseling.

1. Draw the pedigree for this case.
2. What pattern of inheritance can you identify in the pedigree?
3. You find out that Kelly's mother does not have HD and no family history of HD. What are the possible genotypes that Kelly could have?
4. What is the chance that Kelly inherited the faulty HD gene from her father?
5. You explain to Kelly that HD is a degenerative disease with a late age of on-set (symptoms usually start between 30-50 years of age) produced by the mutation shown in the following picture. What type of mutation is it?

6. Although she is 29 years old she can have a predictive test for HD that can identify the mutation in individuals who do not show signs or symptoms of HD yet and tell if they can develop the condition in the future. She decides to have the test done to her and the results of her electrophoresis are shown in the following picture. What can you infer from this gel?

Lane 1: genotype with 10 repeats; Lane 2: genotype with 26 repeats; Lane 3: Kelly's genotype.

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7. Kelly tells you that she is 6 weeks pregnant, you test Marco and he is not affected with HD. What is the chance of Kelly's developing baby inherited the faulty HD gene?
8. What possibilities of family planning can you offer to her?
9. Would you want to have your developing baby tested? Explain your answer. What would you do if it was affected?
10. Kelly wonders if she declines testing in her pregnancy, can she have her baby tested in childhood. Would you want to test your child for HD? Explain your answer.
11. What are some possible issues with testing a child for a condition that does not show up until adulthood and that cannot be prevented or treated?

CASE:

Huntington's disease (HD) is a neurodegenerative genetic disorder which affects in the muscle coordination of the person and leads to dementia. Symptoms of HD can begin at any stage of life of a person, even in childhood but usually start between 30-50 years of age (Wikipedia, 2012).This is called a "late-onset disorder" because the disease does not express itself until later in life, well beyond the reproductive years (Tissot, 2001).Some mental symptoms of HD are: change in personality, loss of memory, reduced concentration, depression and delusion. Some neurological symptoms are: involuntary flicking movements, gait disturbances, and speech and language problems (Jones, 2009). These symptoms are presented because the disease destroys cells in the basal ganglia, which is the part of the brain that controls movement, emotion, and cognitive ability. (TUOU, n.d.)

Huntington disease is caused by a dominantly transmitted CAG gross lesionrepeat expansion mutation which becomes worst in each generation, meaning that the CAG repetitions usually increase in the offspring of a person with HD. A repeat expansion mutation is the one that repeats the same codon several times.In HD, the sequence may be duplicated many times, up to 26 times in the general population. The duplication of this segment is called a "trinucleotide repeat". Individuals with HD may have from 40 to over 100 repeated CAG segments (Collins, 1999). In Huntington's disease the size of

the expansion that has been inherited correlates to the age of onset or the severity of disease, but is not absolutely predictable. One cannot sequence the gene and precisely predict the age of onset of Huntington's disease (Tissot, 2001).

The pattern of inheritancefor HD is autosomal dominant, this means that the gene involved is on an autosomal chromosome (not one of the sex chromosomes); therefore, both male and female can be affected and also they have the same chance of having affected children. Recently it has been found the HD gene on the fourth autosomal chromosome pair. The HD gene is dominant because it is expressing itself more strongly and "dominates" the other working gene. Hence, there are not carriers of the disease becauseeveryone who has the HD allele is going to be affected in any stage of their life (Collins, 1999). Since people who have those repeats always suffer from the disease, it is known that the mutation possibly causes a gain of function, in which the messenger RNA (mRNA) or protein takes on a new property or is expressed inappropriately (NCBI, 2009).

It is known that HD must be heterozygous at all times, this means that every person who has the disease must have the genotype "Aa" having the HD dominant allele "A" and the normal allele "a". There are rare patients with homozygous mutant alleles "AA" and most of them die when conceived not soon after because the disease is very strong and the fetus becomes greatly disabled. (Janho, 2010; Squitieriti, 2002)

By knowing Kelly's case the following pedigree is presented:

KE

I KELLY

II

III

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Figure1. Pedigree showing Kelly's case

As it can be seen in the pedigree every generation has been affected by HD beginning with her grandfather, so there is a big possibility that Kelly also inherited the disease. The proband in Kelly is her father because of him is the reason why Kelly is going for genetic consul. By knowing that Kelly's biological mother does not have HD and no family history of HD, the possible genotypes for Kelly could be "Aa" (affected) or "aa" (not affected). The chance that Kelly has to inherit the faulty HD gene from her father was 50% (Janho, 2010). This percentage can be demonstrated in the following punnet square:

	A	a
a	Aa	aa
a	Aa	aa

Figure 2. Punnet square for Kelly's case The genotype "Aa" is for the father and "aa" for the mother.

Kelly's electrophoresis results show that she is affected with the HD mutant allele because she has more than 26 repeats of the CAG codon. Therefore, she has a 50% of probability of having her baby being affected with the disease because her husband is not affected. By knowing that Kelly is six weeks pregnant what it can be recommended is a Chorionic Villus Sampling (CVS) which consist in taking a sample of the placenta for the diagnose of chromosomal abnormalities (Wikipedia, 2012). However she will need to wait four weeks more because this test can only be used between weeks ten and thirteen of the pregnancy. In the other hand, this type of sampling has a one to two percent risk of miscarriage and also infections and the baby having limb defects can occur.

Figure 3. Actualized Kelly's pedigree

This type of diagnosis can help the couple to be mentally prepared to any situation that could be presented. Also they are a time to decide whether continue with the pregnancy or performing a medical abortion. This is a difficult decision but is an option that can be presented to the parents according to their location because it is not legal in every country or state (WOW, 2010). Furthermore, it is important to mention the fact that this type of mutations suffers from “anticipation” which is a phenomenon that makes that the expansion increase from one generation to the next worsening the disease, so the Kelly’s baby may be more affected than she is.

For their next pregnancy the preimplantation diagnosis could be presented as a good option for this couple. This process analyses cells of embryos conceived by in vitro fertilization to transfer to the mother’s uterus only those embryos which are found healthy of HD. (GHR, 2011).

If Kelly decides not having the test during her pregnancy, she can have her baby tested in childhood. The genetic test for HD consists of a blood test and then observing the number of CAG repeats. This process is made first by something called polymerase chain reaction in which a pieces of DNA are amplified in a very short time generating thousands of millions of copies of a particular DNA sequence (Wikipedia, 2012). Then gel electrophoresis is performed which is a technique that separates the DNA fragments by size with the help of electric current. The smaller fragments migrate faster and further to the positive pole of the gel and this create a band patter that can be analyzed. (Biggs *et al*, 2009). It is not considered a diagnosis when having a positive result because it may be obtained many years before the symptoms start appearing. Nevertheless, a negative test means that the individual does not carry the repeat expansion mutation and will not develop HD.

It is important to mention that having her baby tested in childhood, if it is affected with the disease, it can be a trigger for depression and frustration for both parents and the child. Being aware that this disease cannot be cured or treated and that the symptoms do not appear in a specified age could bring much frustration for the parents and also the future child, adolescent and adult. This is an issue that should be treated with delicacy and is something that both parents and child must be mentally prepared to face.

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