

Academic Biology Chapter 11 Genetics Lab
“It’s Those Annoying CAG Repeats”
Huntington Disease Pedigree Using Direct Genetic Testing

HUNTINGTON'S DISEASE BACKGROUND

Huntington's disease is a progressive disorder of the central nervous system. Intellectual impairment and severe mental disturbances are also a part of the disease. Initial symptoms include irritability, clumsiness, depression and forgetfulness. Mood, personality change and uncontrollable movements may begin ten years before diagnosis of the disease. (folksinger Woody Guthrie, who died of the disease, was first thought to be an alcoholic and later schizophrenic, before he was properly diagnosed.)

The arrival of the gene in the New World can be traced to the 17th century. It is believed that symptoms of the disorder may have been responsible for charges made against some persons of consorting with the devil and of being witches. In 1630, three men whose families had been persecuted for witchcraft immigrated to America. One of the men settled in East Hampton, Long Island, New York. His offspring were notorious for a strange and frightening disease and it is one of them who was described in a paper first reporting the disease.

The gene for Huntington's Disease (HD) is dominant. If a person has the gene, that person will have the disease. The average age of onset is 40, though there is a wide range. The illness is progressive, with no remission, and is always fatal. Persons with the disease usually live about 20 years after first showing symptoms. It has recently been found that HD is caused by a mutation that brings about an increase in the number of repeats of three nucleotide bases, CAG, found at the end of the number 4 chromosome. The normal version of the HD gene has between 11 and 34 copies of CAG. The mutation which causes Huntington's increases the number of repeats to 37 or more. The HD repeat size rarely stays the same from one generation to the next and tends to increase. When passed on from fathers the increase is sometimes dramatic. Small increases, or sometimes decreases, have been seen when transmitted from mothers. There seems to be some relationship between the number of CAG repeats and the age at which the disease first appears. When there are more than 52 repeats, age of onset is usually much younger than the forties. One child who was diagnosed by age 3 had 86 copies of the repeat. Most persons with adult onset HD have between 37 and 52 repeats. In a few cases of new mutations to HD, repeats between 33 and 38 units have been identified. These people are unaffected, but the risk for HD in their children or grandchildren may be increased. The exact size range of repeats has not been definitely established, so repeats between 31 and 39 are considered uncertain.

The direct genetic test for the HD gene is expected to be in place within a few months (from mid 1994), will be relatively fast (a few days), and will cost several hundred dollars. A blood sample will be taken and a polymerase chain reaction assay will be carried out. Presently testing for HD is possible only when a person at risk has living relatives with the disease, involves linkage analysis and costs several thousand dollars.

REFERENCES:

- Myers, Richard H. "Direct testing for Huntington's Disease". **The Genetic Resource**. Vol. 8, No. 1 1994.
- Wynbrandt, James and M.D. Ludman. **The Encyclopedia of Genetic Disorders and Birth Defects**. New York: Facts on File. 1991.
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HUNTINGTON'S DISEASE, A Family History

John became interested in finding out more about genetic testing when he learned that his great grandfather had died of a disease that no one wanted to talk about. He also knew that his great-great grandfather, Jedediah, had come to Louisiana in 1895 from Long Island and that there were stories about his ancestors involving witchcraft. After reading the background on Huntington's disease, John became very concerned about his own family and was told that his great-grandfather had died, after suffering for 17 years, of Huntington's disease. Some members of his family agreed to volunteer for experimental screening using the new PCR test for the CAG repeats. Your job is to analyze the findings and determine if there is a possibility that John might be at risk for this disease.

A. Make a pedigree of John's family using the information given below. The numbers indicate how many uninterrupted CAG repeats there are on each of the two number 4 chromosomes. Write the name of the person and the number of CAG repeats beside or underneath them. (Hint: Begin the pedigree with John and work backwards.)

*Joshua's parents: great-great grandmother Dovie (not tested) and great great- grandfather Jedediah (not tested)

*Osco's parents: great-grandmother Ophelia (not tested) and great grandfather Joshua (died of Huntington's, not tested)

*Maternal grandmother Maudie: 12, 32

*Maternal grandfather Osco: 18, 37

*Mother's brother Dink: 12, 53 (HD symptoms appeared at age 22)

*Mother's sister Emma: 18, 12

*Mother's sister Barbara: refused to have the test

*Mother, Lucretia: 48, 12

*Father, Randolph: 35, 14

*John (is under age 18, cannot be tested)

Name _____

B. Answer the following questions using the Pedigree that you made and Background information on Huntington's

1. Using general probability, what are the chances of a parent with HD passing with HD passing the gene on to any one of his or her children?

2. Write the number of CAG repeats for each of the following situations:

a. Normal Gene

b. Huntington's disease

c. Early onset HD

d. New mutations, unaffected, but children or grandchildren may be affected

e. Uncertain

3. Thinking of all the ways in which the number of repeats may be passed on to children, discuss the possibility that John may get an HD gene

- a. from his mother

- b. from his father

4. From which parent did Dink get the gene for HD? Explain how you can tell.

5. Do you expect John's mother to show symptoms of HD? Why or why not.

6. John's Aunt Barbara refused to have the test for HD.

a. Discuss some reasons that she may have had for coming to that decision.

b. When she applied for a job as an airline pilot, the company, knowing of the occurrence of HD in the family, insisted that she be tested. Does the company have the right to require the test? Explain why or why not.

7. When John reaches the age of 18, he may make the decision of whether or not to be tested for the HD gene.

a. Explain to John why he should have the test done.

b. Explain to John why he should not have the test done.