

Huntington's Disease 10 Years Later

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Uncontrollable movements, memory problems, depression, decrease in mental acuity, and behavioral disturbances are just some of the symptoms associated with Huntington's disease. Huntington's disease is a progressive neurodegenerative disorder which is caused by a defect in the gene that codes for the protein huntingtin. Tests are now available to detect the trait before symptoms develop, but complex social issues still surround testing. Questions still remain about who should be tested (Riordan and Loescher 2006), why and when they should be tested (Decruyenaere et al.1995), and how to handle the results (Mennie, Holloway, and Brock 1990). To gain insight into these questions, I will be analyzing trends in interviews with individuals who decided to undergo direct testing for Huntington's disease 10 years ago.

BACKGROUND

Huntington's disease is caused by a defect in the huntingtin protein. The defective huntingtin protein induces apoptosis, or programmed cell death, of brain cells called neurons in multiple parts of the brain affecting speech, memory, motor activity, and even personality (Bano, Zanetti, Mende, & Nicotera 2011).

The damage caused by the abnormal protein starts early in life, but symptoms may not appear until the fifth decade of life. The most common age of onset for the disease is age thirty-seven, but the incipient manifestation of the disorder varies widely based on the severity of the mutation and environmental factors (Hockly et al. 2002, Wexler 2004).



The human brain, showing the impact of HD on brain structure in the basal ganglia region of a person with HD (top) and a normal brain (bottom).

<http://kobiljak.msu.edu>

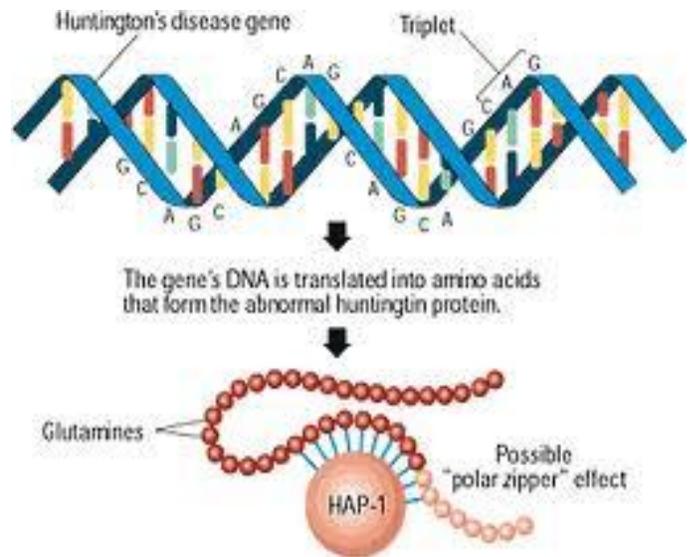
The disease is largely hereditary, but in some rare cases can occur randomly. For this study we will focus on the hereditary form which passed through families in an autosomal dominant pattern. This means that if a person's mother or father had the condition, that person stands a 50% chance of developing the condition.

The coupling of the late onset and strong hereditary pattern left families who knew they carried the trait with a great deal of uncertainty. Because the disease normally shows no symptoms until after many people have their children, individuals who knew they were at risk for the disease would have to decide whether to have children and risk

passing the disease on to them or forego childbearing. Additionally, many people would choose not to marry believing that they carried the disease. Career and educational choices also had to be made based on a person's best guess as to whether or not they had the condition. Many people would live in fear of the disease only to never develop symptoms. Others would build their lives as if they were not at risk only to begin having symptoms. This was the reality of life for those at risk for Huntington's disease until linkage analysis was invented in 1983 (Meiser & Dunn 2000).

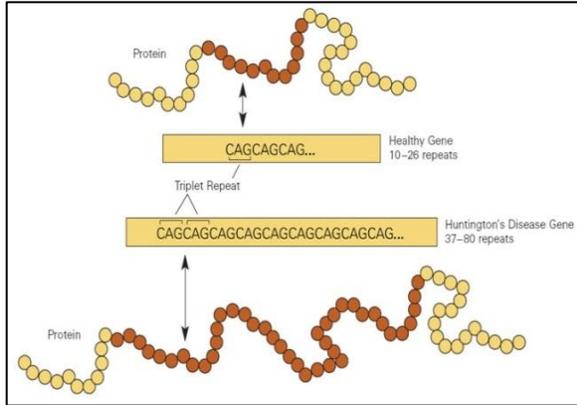
Linkage analysis is by no means a perfect test, but it did give persons at risk for Huntington's disease a better idea of whether or not they would develop the condition. By linkage analysis, a person who had previously only known she had a 50/50 chance of inheriting the gene responsible for Huntington's disease would be able to learn if she would develop the condition with as much as 98% certainty. This was a huge breakthrough, and for many people it alleviated the torture of trying to plan their lives in the face of uncertainty. Although the test was not 100% certain, they could at least make their decisions in a better informed manner.

In 1993 the uncertainty was completely eliminated when the gene mutation that causes Huntington's disease was isolated. The protein huntingtin had been mapped to the short arm of the fourth chromosome, which meant it could be tested for with 100% certainty by DNA sequencing. Additionally, the severity of the mutation could be analyzed and an approximate age of onset calculated based on the individual's number of "CAG" repeats.



From: <http://www.javeriana.edu>.

In humans, and all species that use DNA as their genetic code, there are four nucleotides that are arranged in a specific order to form out DNA. These nucleotides are Adenine (A), Guanine (G), Cytosine (C), and Thymine (T). Together they form long and complex codes, called genes, which are translated into the infinite number of proteins required by the body to function. One such protein is huntingtin, which is necessary in the human brain and elsewhere. In Huntington's disease patients, there is a defect in this gene. The gene has an elevated number of "CAG" repeats. Within the human genome there are areas where the number of time a given DNA sequence is repeated has little or no effect, but in others it can cause a disease state. This is the case in Huntington's disease.



A normal person, one who will not develop Huntington's disease, would have fewer than 27 CAG repeats at the 4p16.3 locus. An "intermediate" person would have 27-35 repeats (Meiser & Dunn 2000, Bhattacharyya 2008). Anything above 35 repeats is considered diagnostic for Huntington's disease. The most severely affected people have over 50 repeats and can have an onset of symptoms before the age of 20. This is called Juvenile Huntington's disease and is much rarer than the common form, which has an onset between the ages of 30 and 50.

By sequencing a person's DNA, the number of CAG repeats a person has can be counted and analyzed for Huntington disease trait. Persons who have more than 35 repeats will know without doubt that they will develop the disease. Individuals who have less than 27 repeats can rest assured that they will be asymptomatic. A person with an intermediate amount of repeats will have a higher tendency to develop dementia but will not develop full symptoms of the disease (Bhattacharyya 2008).

METHODS

Taking interviews of patients who elected to undergo testing for Huntington's disease 10 years ago, which were conducted by Rachel Koff, a graduate student in the California State University Stanislaus Masters in Genetic Counseling Program, and

a few of her colleagues, I will search for trends in the attitudes of the interviewees. Rachel and I will be searching for trends in the data using "coding." "Coding" is defined as the process of identifying similar trends in interviews and filing them under general phrases. The frequency of these phrases are then taken and compared to others in a statistical manner. This is done in order to achieve a clearer understanding of the interviewees' attitudes by eliminating researcher bias. Our goal is to find whether it has proven to be a positive or negative experience for those who have chosen to undergo genetic testing for Huntington's disease and how the test result has changed their lives.

SIGNIFICANCE

A definitive answer as to whether and individual will develop Huntington's disease might seem solely beneficial for the families affected by Huntington's disease, but psychological concerns must also be taken into account. For at risk individuals, being unsure if they will develop a neurodegenerative condition can cause a great deal of stress. However, a new set of stressors may come with a diagnosis or, for that matter, a lack of one.

Of patients who are diagnosed with Huntington's disease, 11%-33% report considering suicide as an option for their future rather than waiting for the disease to set in (Lawson et al. 1996). In fact, the second leading cause of death amongst Huntington disease patients is suicide (Roos 2010). However, the diagnosis alone may not be to blame.

There is shown to be a higher correlation of previous psychological adjustment than test result in determining depression in patients after testing (Lawson et al. 1996). This means that depression after testing is more strongly linked to depressive behavior prior to the test than the test result. It was also found that patients who undergo

direct testing rather than linkage analysis, regardless of result, are more likely to become depressed (Codori, et al. 1997). This might be explained by the dueling consequences of “survivor’s remorse” if negative and a sense of being trapped by the disease if positive.

Not surprisingly, it also found that patients who had a previous history of depression were more likely to have a major psychological crisis (suicide attempts, new drug abused, loss of regard for responsibilities or major relationships, etc.) after testing. Patients who had a positive result were more likely to have a psychological crisis in the months following receiving their results; however, over the long run there was no significant difference in the mental health of those who tested positive and those who tested negative (Duisterhof et al. 2001). However, in a five year study patients who tested positive for Huntington’s disease tended to have fewer positive thoughts than those who were cleared. They also were less willing to speak about Huntington’s disease and practiced more avoidance behaviors when questioned than those who tested negative. They also were shown to be considerably more “hopeless” using the Beck Hopelessness scale. Higher levels of hopelessness were correlated with marriage and lower levels with parenthood. The mechanism behind these trends is not understood. (Codori 1997).

Many studies have been conducted on the psychological events after Huntington’s disease testing, but very few have asked patients about their experiences. Speaking

directly to patients about their experiences might give researchers a better understanding of why these trends are seen and perhaps help find solutions.

PROJECTED FINDINGS

Coding data is only in its initial stages, but it appears that the majority of people are viewing their decision to be tested for Huntington’s disease as a positive choice. Very little data exist on patients’ attitudes toward testing after having been tested, but it is found that patients tend to have an interest in predictive testing (Kreuz 1996).

For patients who tested positive in our study, most interviews had to be obtained from caregivers rather than the patient due to the disease’s progression. This may pose a serious limitation because, as revealed in surveys taken before predictive testing was made available, the partners of people at risk for Huntington’s disease tend to have more positive feelings toward predictive testing than the patients themselves (Evers-kiebooms, Cassiman, and Van Den Berghe 1987). Most caregivers of patients who tested positive for the disease said that testing was a positive experience despite the result because it helped them to prepare for the future.

Of individuals who tested negative for the trait, many sight a sense of relief at finding negative results, but a few also acknowledged a sense of guilt when other members of their family proved to be positive. These are only preliminary trends. New trends may surface as the remainder of the data is analyzed.

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