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Huntington disease

How many repeats does it take?

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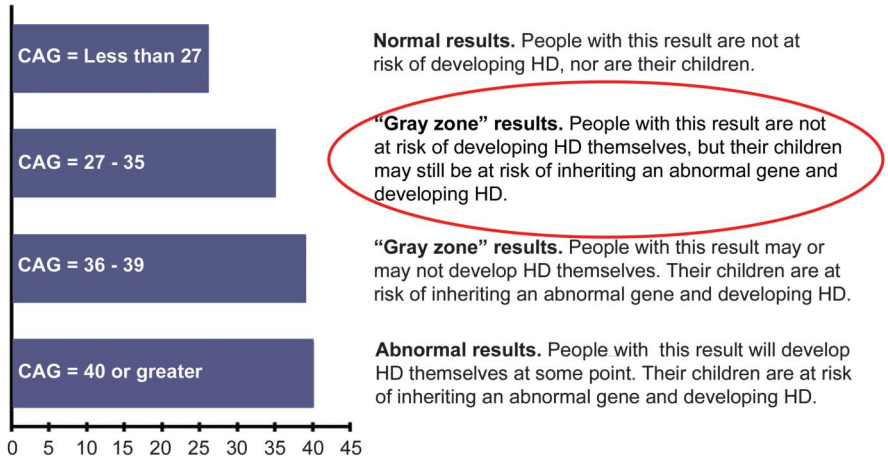
In this issue of *Neurology*®, Dr. Killoran and colleagues[1] report new findings in people at risk for Huntington disease (HD). HD is an inherited illness that causes problems with movement, mood, behavior, and thinking.

THE HD GENE AND GENETIC TESTING HD is a genetic disease (see About HD page). In order to understand the article by Dr. Killoran et al., it is helpful to have a little background on the genetics of HD. Every human being has 23 pairs of chromosomes. Human genes are located on the chromosomes. The HD gene sits on chromosome 4. Part of the gene is made up of repeating units of DNA abbreviated C-A-G. Different people have different numbers of CAG repeats. Having up to 26 CAG copies is considered normal. In people with HD, the number of CAG copies is higher than it should be. The gene test for HD counts the number of CAG repeats. This allows adult children of a person with HD to find out whether they have inherited from their parent the genetic abnormality (called a mutation) that causes the disease.

As shown in the figure, a test result showing 40 or more CAG repeats means that the person will develop signs of HD at some point in his or her lifetime. A result showing 26 or fewer repeats means that the person and his or her children will be free of the disease. People with 36 to 39 CAG repeats may or may not develop HD during a normal lifespan. Some of these people live a long life without developing any signs of illness, yet others develop HD in midlife.

THE HD "GRAY ZONE" What about CAG repeats between 27 and 35? The research by Dr. Killoran et al. focused on people in this "gray zone" who were participating in a larger study. We tell people with HD test results in this range that they are not at risk of developing HD, but that their children may still be at risk. This study confirmed our current thinking. The people in this group did not show movement or thinking problems, at least during 4 years of study. However, the study did find that the group in the gray zone (with 27–35 CAG repeats) was more likely to experience trouble with motivation or to have thoughts of suicide than those in the normal range. The research also showed that this group generally reported more mood and behavior problems. You might wonder whether just knowing that you carry the HD genetic abnormality might make you think

Figure CAG repeat length and risk of Huntington disease



Our current understanding of the effects of abnormal CAG repeats in the Huntington disease (HD) gene. The red oval shows the size of mutation that was studied by Dr. Killoran and colleagues. Although we still think people with 27–35 CAG repeats in their HD gene will not develop HD, the results by Dr. Killoran et al. suggest that they may be at risk for psychological difficulties such as thoughts of suicide or trouble with motivation. Adapted from Hogarth P, Shoulson I. Huntington's disease. In: Neurogenetics. Conneally PM, ed. Continuum 2000;6:100–119.

more about suicide or feel less motivated, but none of the people in the study knew whether they had inherited the abnormal gene or not, so the results were not influenced by this.

So—what does this mean for families with HD? Reasonably, Dr. Killoran and coauthors suggested that people with 27–35 CAG repeats in the HD gene be watched for psychiatric problems. The research group also made a more controversial conclusion. They suggested that the mood and behavior problems of those individuals in the gray zone may represent a kind of "pre-HD" state that might develop into full HD if followed into late life. This suggestion is supported by single case reports in the medical literature, but it is not yet widely agreed upon in the medical genetics community. More research following larger numbers of these "CAG gray zone" individuals for longer periods of time is required before we can change the genetic counseling recommendations for people undergoing testing for HD.

REFERENCE

1. Killoran A, Biglan KM, Jankovic J, et al. Characterization of the Huntington intermediate CAG repeat expansion phenotype in PHAROS. Neurology 2013;80:2022–2027.

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About Huntington disease

WHAT IS HUNTINGTON DISEASE? Huntington disease is a progressive neurologic disorder that causes involuntary fidgety movements called "chorea" (a term that comes from the Greek word for "dance") as well as poor balance and coordination. In addition to the movement disorder, people with HD may have mood and behavioral problems, as well as difficulties with planning, organization, and memory. Rarely, the illness can start to show symptoms in childhood or late in life, but usually it begins in midlife.

WHAT CAUSES IT? HD is a genetic disorder, meaning it is inherited, or passed down from one generation to the next. If a parent has the disease, each child has a 50/50 chance of inheriting the disease gene. The risk of inheriting the gene from an affected parent is the same for men and women.

HOW IS HUNTINGTON DISEASE DIAGNOSED? A neurologic examination showing the typical signs of HD, combined with a family history of the illness, is usually enough to make the diagnosis. A blood test may also be done to confirm the presence of the abnormal gene. The same blood test can also be done before the onset of symptoms to predict whether an individual from an HD family will develop the illness later in life. This type of "predictive" testing is best done with the involvement of a provider and genetic counselor experienced in inherited disorders.

CAN HUNTINGTON DISEASE BE TREATED? There are medications available to help manage the movement and mood symptoms of HD. However, there is no proven treatment to slow progress of the illness or prevent it. Support can be very helpful. This includes physical, occupational, and speech rehabilitation treatments, monitored exercise programs, nutritional counseling and management, and the use of cognitive tools and techniques.

WHAT RESEARCH IS BEING DONE IN HUNTINGTON DISEASE? In addition to research into treatments for the symptoms of HD, there are active research efforts under way to slow the illness's progression and maybe even prevent its onset. Some of these approaches use genetic techniques to try to correct the underlying problem. These include silencing the abnormal genetic message using a technique called "RNA interference." Other researchers are using growth factors to protect vulnerable brain cells. Still others are using approaches to halt the HD gene's many damaging effects on brain cells. Researchers have made models of HD using genetically altered mice and flies. This allows them to test new therapies before moving them into human patients with HD. These models also help to understand the biological basis of the disease.

FOR MORE INFORMATION

AAN Patients and Caregivers site
http://patients.aan.com/go/home

Hereditary Disease Foundation
http://www.hdfoundation.org

Huntington's Disease Society of America
http://www.hdsa.org

HD Buzz
http://en.hdbuzz.net/

Huntington Society of Canada
http://www.huntingtonsociety.ca/english/index.asp

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