

Huntington Disease (HD)

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Key Points

- Huntington disease (HD) is a progressive neurological disorder that typically has its onset in the early 40s.
- HD is an autosomal dominant disorder. Genetic testing can determine whether a person has inherited HD prior to the onset of symptoms.
- Because of the lack of treatment for HD, the decision of an asymptomatic at-risk individual to undergo genetic testing is a personal one, based on the value of the information to the individual.
- Identification of the genetic change that causes HD in an individual at 25% risk (for example, the grandchild of an affected person) also reveals information about the genetic status of that individual's parent.
- The current standard of care calls for the provision of genetic counseling prior to genetic testing for HD. Genetic counselors are trained to help individuals who are considering testing to cope with the emotional, psychological, and ethical issues associated with the testing decision.

Learning Objectives

Participants will be able to:

- Identify social and ethical issues that may arise when predictive genetic testing for HD is used within a family;
- Identify resources for genetic counseling related to HD;
- Interpret the results for HD genetic testing in terms of the number of CAG repeats.

Family History Issues

Huntington disease is inherited in an autosomal dominant manner. For each offspring of an affected individual, there is a 50% risk of inheriting the genetic change that causes HD. Most affected individuals can identify an affected parent, but occasionally there is no history of HD in the family. Non-medical explanations for lack of an affected parent include misassigned paternity, adoption, or early death of a parent before symptoms of HD are

evident. Medical reasons for lack of an affected parent are failure to recognize symptoms of HD, late-onset disease in a parent, or the presence of an intermediate or reduced penetrance allele in a parent.

Red Flags



Early symptoms of HD may include subtle changes in coordination, minor involuntary movements, difficulty in mental planning, and a depressed or irritable mood.

Case 24. Patient Worried Because his Grandfather Died of Huntington Disease

Mr. J is a 20-year-old male concerned about his family history of HD. He was raised by his mother after his parents divorced when he was ten years old. He has had only intermittent contact with his father, who is now 51 years old. As far as he knows, his father is in good health. However, his father's father (his paternal grandfather) is said to have died of HD at age 58 after 15 years of illness, the last ten years of which were spent in a nursing home. Mr. J understands that HD is genetic. The last time he talked with his father, about a year ago, his father assured him that Mr. J need have no concern about the disease because he, himself, was unaffected.

Clinical Care Issues

Natural history of Huntington disease (HD)

HD is a progressive neurologic disorder with typical onset in the early 40s, although about 10% of at-risk individuals have onset of symptoms before age 20 years, and about 25% have onset of symptoms after age 50 years. HD is manifested by progressive uncontrolled movements (chorea) and problems with coordination. Mental disabilities may include both cognitive decline and psychiatric symptoms. There is usually a 15- to 20-year progressive neurological decline before death. The disease course tends to be more severe if the symptom onset is at a young age compared to symptom onset after age 50.

No preventive treatment or effective therapy exists for HD. As a result, genetic testing of family members can clarify their genetic status, but testing does not provide a means to prevent or delay the onset of the disease.

Implications of genetic testing for Huntington disease

Because of the lack of treatment for HD, the decision to undergo genetic testing is a personal one, based on the value of the information to the individual considering testing. Often decisions center around making reproductive decisions, career choices, financial planning, or other major life decisions. If Mr. J were to proceed with testing and have a normal test result, he could be reassured that he did not inherit the genetic change associated with HD, and therefore would not develop HD or pass it on to his children. However, he needs to consider the possibility that he might receive a positive test result, indicating that he had inherited HD, and that the information could be stigmatizing or cause discrimination or psychological distress. Once the knowledge is known, it cannot be "unknown."

An additional consideration for Mr. J is that if his test result is positive, his father's genetic status will also be known. A positive test result would indicate that Mr. J had inherited HD from his father, and would therefore also reveal that his father had inherited HD.

It may be important for Mr. J to discuss testing with his father prior to proceeding, to ensure that his father's wishes regarding information about the test results can be anticipated and respected. An ethical dilemma could result if Mr. J is found to have the genetic change associated with HD and his father does not want the information. Also, if Mr. J has a positive test result, it would have implications for siblings; if his test indicates he has inherited HD, his siblings would be at 50% risk of having inherited HD.

Risk Assessment

Role of family history and age of onset in assessing risk

Before Mr. J undergoes genetic counseling or testing, Mr. J's grandfather's diagnosis of HD should be documented, ideally with molecular genetic test results. In some instances, what appears to be HD turns out to be another disorder. Without medical records confirming that Mr. J's grandfather had the genetic change associated with HD, other causes of chorea, dementia, or psychological disturbances might explain his medical course. Potential etiologies include both genetic disorders with symptom profiles overlapping

with HD and non-genetic causes of chorea or dementia, such as cerebrovascular disease (see [GeneReview: Huntington Disease, Differential Diagnosis](#)).

Once the grandfather's diagnosis is confirmed, risks for Mr. J and other family members can be calculated based on the pattern of autosomal dominant inheritance, e.g., siblings and children at 50% risk, grandchildren at 25% risk.

Although Mr. J's father feels confident that he is unaffected, we do not know the basis for this belief. Even though he feels healthy, he could have mild symptoms of HD and be unaware of them, or he could have inherited HD but not yet be manifesting the disease. Unless he has undergone testing himself, and has been found NOT to have the genetic change associated with HD, his clinical status is still uncertain.

Because HD is inherited in an autosomal dominant manner, the risk that Mr. J's father inherited HD from his own father is 50%. He may be basing his belief that he is unaffected on the fact that he is still healthy several years after the age at which his father began to show symptoms of HD (43 years old). It is true that his risk of inheriting HD diminishes as his age progressively exceeds his father's age of onset. However, variability in age of onset is observed in family members, and he still has significant risk at age 51. Nevertheless, advancing age reduces risk. If he had inherited HD, he would eventually be expected to show signs of the disease; therefore, the longer he remains asymptomatic, the lower the likelihood that he inherited HD.

Based on the Mendelian principles of autosomal dominant inheritance, Mr. J's likelihood of developing HD is half of his father's risk. However, if his father develops symptoms of HD, Mr. J's risk then becomes 50%. On the other hand, if his father had HD genetic testing and the testing was negative, Mr. J's risk of inheriting HD is 0%.

Genetic Counseling and Testing

Are there genetic testing options?

Genetic testing is clinically available and is performed by analyzing the number of CAG trinucleotide repeats in both copies (alleles) of the *HD* gene.

- The number of CAG repeats in normal alleles ranges from ten to 26.

- Intermediate alleles range from 27 to 35 CAG repeats and are not associated with developing symptoms of HD. However, the CAG repeats are unstable during meiosis and individuals (particularly males) with intermediate alleles may be at risk of having a child with HD as a result of an increase in CAG repeats occurring during sperm production. This seems to be a rare occurrence, but explains how a person can be the first affected person in the family.
- Alleles with CAG repeat number between 36 and 39 are considered to be alleles with reduced penetrance. In this range, the age of onset tends to be later, and some individuals have not developed HD.
- Individuals with CAG repeats of 40 or more are predicted to develop symptoms of HD in their lifetime.

There is an inverse correlation between the number of CAG repeats and the age of onset of HD; persons with a higher number of repeats tend to have symptoms at younger ages. For example, individuals with 60 or more repeats have juvenile HD, with onset before age 21 (see [GeneReview: Huntington Disease, Juvenile HD](#)). However, the correlation is not exact, and it is impossible to predict the precise age of symptom onset, the course of the disease, or the degree of disability based on the size of the CAG repeat.

What is the optimal testing strategy for the family?

Ideally, the testing process would be initiated by testing Mr. J's father. It is possible that Mr. J's father has already undergone testing, or would be willing to be tested.

- If Mr. J's father had HD testing and the result was negative, no additional testing would be necessary, because his children (including Mr. J) would not be at risk.
- If Mr. J's father had HD testing and an *HD* allele was detected, Mr. J and his siblings would then know they are at risk for HD, and could proceed with testing to determine their own status if they wished.

If Mr. J's father does not wish to be tested, or Mr. J does not want to involve his father, the test could be offered directly to Mr. J. If this course is chosen, Mr. J should be encouraged to give careful consideration to how or whether he will disclose his test results to any other family members.

Genetic counseling prior to genetic testing

Because of the lack of treatment for HD and severe nature of the disease,

the personal impact of positive or negative test results may be significant. Therefore, testing protocols have been developed to "minimize" or "anticipate" potential psychological harm from the genetic testing process. These protocols represent the current standard of care with respect to HD genetic testing, and are usually conducted by genetic counseling and testing centers. Most centers follow the comprehensive testing protocol developed by the [International Huntington Association](#). Before testing is initiated, there are extensive pre-test discussions in which the reasons for requesting the test, the individual's knowledge of HD, and the possible psychosocial impact of test results are explored in detail. [Bennett et al 1993] Genetic counseling, a neurological exam, DNA testing, and results disclosure are usually offered over a period of two to four visits. Additional follow-up may be offered. A listing of genetic testing centers nationwide is maintained by the [Huntington's Disease Society of America](#). Resources for finding a genetic counselors can be found through the [National Society of Genetic Counselors](#).

Interventions

Preventive care. No therapy is available to prevent or retard disease progression in HD.

Other clinical management. Pharmacologic therapy is limited to symptomatic treatment. Choreic movements can be partially suppressed by neuroleptics. Anti-Parkinsonian agents may ameliorate hypokinesia and rigidity. Psychiatric disturbances such as depression, psychotic symptoms, and outbursts of aggression may respond to psychotropic drugs. Cognitive impairment is not amenable to treatment.

Supportive care with attention to nursing, speech and swallowing, diet, ambulation, special equipment, environmental adaptations, social services, and eligibility for state and federal benefits is important for individuals with HD and their families. Referral to a regional HD support group (see [Resources](#)) or a Huntington Disease Center of Excellence is helpful to provide education material, medical resources, and psychosocial support.

Ethical/Legal/Social/Cultural Issues

Genetic testing has potential to reveal information about others. In some situations, genetic testing in one family member can reveal the genetic status of another family member who does not want to know his status. For example, if Mr. J's father indicates that he does not want to know his genetic

status, but Mr. J decides to proceed with testing, the presence of an *HD* allele in Mr. J will reveal his father's genetic status. In pre-test genetic counseling, Mr. J should be encouraged to explore the consequences of genetic testing for his father as well as himself. These consequences may include family communication issues as well as financial and social supports.

Discussion with Mr. J's father. Mr. J should be encouraged to have a conversation about genetic testing for HD with his father. For example, it could be that the father has already been tested; the father could have tested negative and not shared his results, or he could have tested positive and be worried about how his family will react to this information. However, a more likely scenario is that Mr. J's father assumes that his lack of symptoms at age 51 indicates that he did not inherit HD. Having witnessed the effects of HD in his own father, he may not even want to consider the possibility that he could still develop the condition. Therefore, Mr. J may find a discussion with his father about the possibility of HD exceedingly difficult. Given the lack of a close relationship, Mr. J may ultimately decide against pursuing this discussion with his father.

Feelings of guilt. Parents may feel guilty about passing a genetic disorder to their children. As a result, parents may be reluctant to discuss results of genetic tests with their children. In general when considering the effects of genetic disease, physicians should be attentive to the patient's feelings. Patients may be helped by discussions prior to testing of implications of positive results for members of their family.

Resources

- **Huntington's Disease Society of America**
505 Eighth Avenue, Suite 902
New York, NY 10018
Phone: 212-242-196; 800-345-HDSA
Fax: 212-239-3430
Email: hdsainfo@hdsa.org
- **Caring for People with Huntington's Disease**
- **The Hereditary Disease Foundation**
11400 West Olympic Blvd, Suite 855

Los Angeles, CA 90064-1560

Phone: 310-575-9656

Fax: 310-575-9156

Email: cures@hdfoundation.org

- **International Huntington Association**

Callunahof 8

7217 St Harfsen

The Netherlands

Phone: +31-573-431595

Fax: +31-573-431595

Email: iha@huntington-assoc.com

- **NCBI Genes and Disease Webpage:** [Huntington disease](#)

- **National Library of Medicine Genetics Home Reference**
[Huntington disease](#)

- **Testing for Huntington Disease: Making an Informed Choice**
Booklet providing information about Huntington disease and genetic testing; Acrobat reader required

- **GeneReview: Huntington Disease**

- **GeneTests Resources for Huntington Disease** 

- **GeneTests Online Medical Genetics Information Resource**

References

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