GeneticTesting for Huntington Disease

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Huntington Society of Canada
HUNTINGTON
Société Huntington du Canada

Foreword

The first edition of this brochure, published in 1993, was the product of a collaborative effort led by Ralph Walker, as Executive Director of the Huntington Society of Canada, Dr. Michael Hayden, and members of Dr. Hayden's group at the University of British Columbia.

In presenting an updated and extensively revised new edition, the Huntington Society would like to extend our warm appreciation to Ralph Walker; Dr. Michael Hayden; Elizabeth Almqvist of the University of British Columbia; Dr. Wendy Meschino of the North York General Hospital; Mary Lou Klimek of the Starr Center for Human Genetics at The Rockefeller University; and Mary Shea of the Huntington Society of Canada.

Special thanks are due to Robin Bennett of the University of Washington Medical Center, for permission to reprint extensive portions of her booklet Testing for Huntington Disease: Making an Informed Choice.

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– October 1998

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Genetic Testing for Huntington Disease

Introduction

In 1983, genetic markers closely linked to the Huntington disease (HD) gene were identified. This discovery, together with the identification of additional genetic markers, led to the development of predictive testing programs for HD. Problems with this approach included some inaccuracy as it was not possible to test directly for the presence or absence of the genetic defect underlying HD.

In March, 1993, the gene causing Huntington disease was identified. This means that individuals at risk for HD can now be directly tested to "predict" who will develop this disease. The same test may be used to confirm the presence of the gene that causes HD in individuals already exhibiting clinical symptoms of the disease, especially when the family history is sketchy or unknown.

The decision about whether or not to have testing for HD is a very complex and personal one. Each individual in a family with HD will feel differently about testing. For some, this test will provide much desired information about their future. Others will choose not to undergo testing. There are no right or wrong choices. It is important, however, that the person who is thinking about being tested make an informed choice.

This booklet is intended to help the individual considering testing for HD reflect on some of the issues involved in testing and in dealing with the test results. Family, friends and professional support people may also find this material useful in supporting those considering testing.

What Is Huntington Disease?

Huntington disease is a degenerative disease of the central nervous system. The symptoms usually include a movement disorder, personality changes and intellectual decline. Men and women are affected equally.

Symptoms of HD usually begin between 30 and 50 years of age, although they may begin at any age, and progressively worsen over a period of 10 to 25 years. At present, there is no cure for HD, but research is advancing at a rapid pace and offers much hope for the future.

Transmission of Huntington Disease

Huntington disease is inherited in an autosomal dominant pattern. This means a man or woman with HD has a 50:50 chance of passing the genetic change or mutation that causes HD to *each* son or daughter. A person who has *not* inherited this genetic change will not develop HD and cannot pass HD on to a child.

In each cell of our body we have 46 chromosomes, which are arranged in 23 pairs. One chromosome from each pair is inherited from our mother, and the other from our father. Chromosomes are made up of small units of genetic material called *genes*. The gene for HD is located on chromosome 4.

Genes are made up of deoxyribonucleic acid, or DNA. DNA molecules consist of chains of four small elements called bases. There are four bases: A (adenine), T (thymine), G (guanine) and C (cytosine) (Figure 1). Their order constitutes a code which determines the type of protein that a particular gene produces. Any change in the sequence of bases may cause a problem in the functioning of that protein.

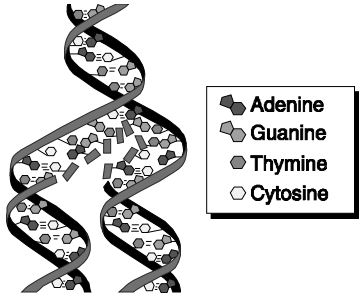

Figure 1

The gene causing HD has been shown to have a region in which three of the bases (CAG) are repeated many times (Figure 2).

Figure 2

The CAG repeat sequence with 5 repeats

/C-A-G/C-A-G/C-A-G/C-A-G/C-A-G/

Recently published "Laboratory Guidelines for Huntington Disease Genetic Testing" indicate that the normal gene contains 35 or fewer CAG repeats, while the disease-causing version has 36 or more repeats. A gene with 36–39 repeats falls into a "reduced penetrance"

range, which may or may not be associated with the onset of HD symptoms.[1] Further advances in genetic studies of HD may provide additional or revised information in the future.

Parents both pass one copy of each of their genes on to their child. Because our genes come in pairs, each person will have a certain number of CAG repeats in one HD gene and another number of repeats in the other gene. The CAG repeat sizes can be the same (such as 18 in both genes) or different (such as 18 repeats in one gene and 42 in the other). Analyzing the number of repeats in this region on each gene can be done on very small samples of DNA—this DNA can be obtained most easily from blood samples, but may sometimes be obtained from other tissue samples.

On the basis of DNA analysis, three test results are possible:

1. **A "negative" test result means that the individual has not inherited DNA changes associated with HD:**

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1 The American College of Medical Genetics/American Society of Human Genetics, Huntington Disease Genetic Testing Working Group, "ACMG/ASHG Statement: Laboratory Guidelines for Huntington Disease Genetic Testing", Am J Hum Genet 62:1243–1247 (1998). See also, Brinkman RR, Mezei MM, Thielman J, Almqvist E, Hayden MR. "The likelihood of being affected by Huntington disease by a particular age for a specific CAG size", Am J Hum Genet 60:1202–1210 (1997).

This individual will not develop HD.

- Both genes contain a CAG repeat in the normal range (usually 35 repeats or fewer depending on the specific laboratory values).
- The accuracy of this result is almost 100% if a parent or other affected relative is known to have a CAG expansion within the affected range (i.e., 40 or more).
- Rarely, a person with a CAG repeat in the normal range seems to have physical signs of HD. This requires further medical investigation.
- There is an intermediate range in which instability occasionally occurs. Specifically, individuals with 27–35 repeats on one of their two genes will *not* develop Huntington disease, but in rare instances can pass an expanded number (i.e., 36 or more) of CAG repeats to their offspring, who will then be at higher risk for HD. The number of CAG repeats usually remains stable on transmission through the mother, but in approximately 4% of cases can expand on transmission through the father.

2. **A "positive" test result means that the individual has inherited DNA changes associated with HD:**

   This individual is at high risk for HD.

- The CAG repeat on one gene is expanded, usually 36 or more repeats. Except in extremely rare cases, the other gene has a normal number of repeats.

- The accuracy of this result is close to 100%, indicating that the person has DNA changes usually associated with the clinical presentation of HD.
- The test does *not* tell:
  - if a person has physical signs of HD *or*
  - at exactly what age a person will start to have symptoms *or*
  - what those symptoms will be.

A positive result means that at some point in life this person will in all likelihood begin to have symptoms of HD. The number of CAG repeats is thought to be related to when the disease develops. However, there is a great deal of variability in the symptoms, their severity and the age of onset, even within the same family.

3. **Reduced penetrance:**

Some individuals with 36–39 CAG repeats may not manifest signs and symptoms of HD even if they live into old age (i.e., approximately 75 years).[2] About 1% of people who are tested fall into this reduced penetrance category.

Individuals with symptoms of HD should be examined by a neurologist who can confirm the diagnosis and provide continuing medical support and care.

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2 The ACMG/ASHG Laboratory Guidelines identify 36–39 CAG repeats as the reduced penetrance range. Other studies suggest 41 repeats as the upper limit. See Brinkman *et al*, Am J Hum Genet 60:1202-1210 (1997).

How Is the Actual Test Done?

The following example (Figure 3) illustrates how predictive testing may be done in a family. Mary has requested predictive testing. Her father, John, has Huntington disease. A sample of her father's DNA is analyzed and it is determined that he has 15 repeats on one chromosome and 45 repeats on the other. The fact that he has a gene with 45 repeats supports the clinical diagnosis of HD. Her mother does not have HD, and each of her chromosomes contain 10 repeats.

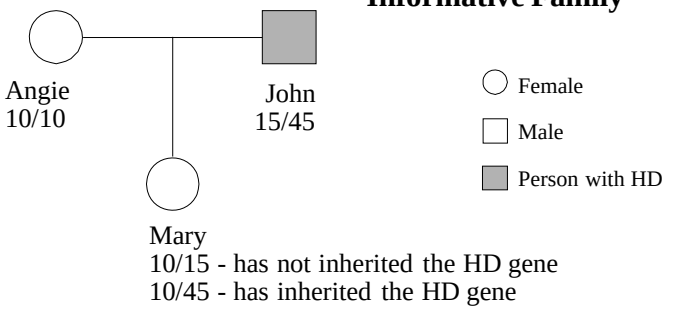
Mary's DNA can then be assessed. If she has received 10 repeats and 45 repeats, the 10 must have come from her mother and the 45 repeats must have been inherited from her father. This indicates that she has also inherited the disease-causing version of the HD gene. If, on the other hand, she has inherited 10 repeats and 15 repeats, she received the gene containing the 15 repeats from her father. This version of the gene will not cause HD.

Predictive testing is most informative and accurate when blood from an affected family member is available. However, Mary could still have been tested if blood from either parent was unavailable, and her DNA analysed to see if the number of repeats falls into the normal range.

Predictive testing provides virtually a 100% certain answer as to whether Mary has or has not inherited the gene causing HD. It does not, however, say anything about her current health with respect to Huntington disease.

Predictive testing may not be possible in a small number of families. This may occur if the clinical diagnosis in the family is HD, but none of the affected individuals in the family demonstrates the increased number of repeats found in the HD gene. This is most likely because the family has been misdiagnosed with HD but could be because there is another change in the gene causing HD that we do not yet know how to detect. It is also possible that the individual at risk may have repeats which fall into the intermediate range. In this case, clearer results may be possible after the laboratory has had the opportunity to do some further testing or to obtain more blood samples from additional family members.

Figure 3



The Process of Testing

The process of testing for HD involves much more than the analysis just described.

Confirming the diagnosis of HD in the family

It is important to make sure the diagnosis of HD is correct in the family. Often medical records on affected family members are requested. It is useful to perform the DNA blood test on an affected family member in order to confirm the presence of a CAG expansion.

Individuals may also wish to discuss with a genetic counsellor or medical geneticist the advisability and implications of banking samples for possible future testing of other family members.

Education and counselling

Testing involves education and counselling about the implications of the test by someone with appropriate expertise, such as a genetic counsellor or medical geneticist. A neurological examination may also be performed. Individuals with symptoms may discuss testing with a neurologist. A person with depression, changes in behaviour, or psychiatric illness should also be seen by a psychologist or psychiatrist.

The Huntington Society of Canada can provide a list of HD testing centres as well as local support groups and contacts.

A support person

The decision about whether or not to have testing for HD can be stressful. Waiting for the results can also place strain on the individual. The results, even "good news", can take time for adjustment. Having a support person, such as a friend or spouse, who is present at all appointments is useful. This person can act, not only as a second set of ears, but can also be a sounding board to talk through feelings about testing, and provide support after the test results are given.

Costs

There is little or no cost if the testing is done at one of the Genetic Centres across Canada, frequently located in a university-affiliated hospital, or at special outreach clinics.

Should I Be Tested?

The decision to be tested is very personal, and may be one of the most important decisions you ever face. Members of the same family will have different feelings about testing. It is important to respect each person's feelings. For individuals without symptoms of HD, the main benefit of "predictive" or "presymptomatic" testing is psychological and relate to life planning, since currently there is no medical benefit (for example, early treatment, specific diet, or lifestyle changes), that can slow or prevent Huntington disease. The test results have important implications for many life decisions. The following are just some of the issues to consider:

Relationship with spouse or significant other

- Is this person supportive of your decision to be tested or does he/she have a conflict with your decision?
- Have you discussed decisions that affect you as a couple that you might make differently depending on your test results: for example, decisions about having children, retirement and long-term care issues?
- Many people who are at risk for HD fear abandonment by their spouse or significant other should they develop HD. Have you discussed this fear or other fears with your partner?

Relationship with children

- Do your children know about HD?
- Are they pushing you to have testing or are you involving them in your decision-making?
- Will you tell them your results? If so, how will you tell them?

Relationships with extended family

- How do you think the test results will affect your interactions with your brothers and sisters, your parents and extended family?
- If the results show you have inherited the HD mutation, will this affect how you feel about your affected relatives: for example, feeling closer to or more distant from them?
- If you do not have the HD mutation you may experience "survival guilt", meaning that you wonder why you have "escaped" this disease whereas others in your family have been less fortunate. A person given a normal (negative) result may also experience a new feeling of responsibility for affected family members.
- Who, if anyone, in your family do you plan to tell of your results? How would you tell each of them: for example, by phone, by letter, at a family meeting?

Relationships with friends

- Are there people in your life that you feel you can talk to about HD and about your decision regarding testing?
- Have you been through difficult periods in your life with them before?
- In what ways were they supportive to you?

Seeking professional support

If you have used professional support services (for example, a therapist, psychologist, religious advisor, psychiatrist) through difficult times in the past, it may be helpful to discuss your decision to be tested with this person. This is particularly important if you have had problems with depression, anxiety or thoughts of suicide.

Career decisions and telling colleagues at work

- Will your test results affect your decisions about the type of work you are doing now or plan to do in the future? Do you plan to tell the people you work with about your decision to be tested or test results?
- Many people at risk for HD fear they will be treated differently at work if they tell anyone about HD. Some people fear they will not be considered for

promotion, or that they may even lose their job. Some companies have confidential employee services where you can discuss these concerns.

What about insurance and other financial planning?

You may wish to arrange adequate insurance coverage, if possible, before beginning testing, as individuals who have tested positive for the HD gene will be very unlikely to obtain new insurance coverage. Some people may feel locked into a certain job to maintain insurance coverage. Please inform the Huntington Society of Canada of any problems you encounter in this regard.

Do you think you have inherited Huntington disease?

Honestly considering your feelings about whether or not you believe you have or will develop HD is important. It can be more difficult to deal with the test results if the results are the opposite of your inner feelings.

Assessing your own coping strategies

- How have you dealt with difficult situations in the past? What things do you do to get out of a slump: for example, call a friend or family member, go for a walk, work out, work in the garden?

- What strategies work well to help you out in the short term versus those that work over a longer term?
- How do you ask for help when you need it?

Recognizing what resources have worked for you in the past is helpful because you can start using them again when you need help in the future.

Timing of testing

The process of being tested for HD and dealing with the results will be stressful and is often disruptive to dealing with everyday problems. It is good to choose a time to be tested when complicating factors from the outside are at a minimum. For example, in the middle of a divorce or break-up of a relationship, or at a stressful time at school or work is not a good time to be tested. Testing at a time of celebration may not be optimal: for example, directly before or after marriage or in the middle of important holidays.

It is easy to become "obsessed" thinking about testing for HD. It is useful to make a decision about whether or not to be tested even if the decision is not an absolute yes or no answer. For example, deciding not to be tested for a certain period of time (for example, "not until next year, after I turn 30"), can help you put this aspect of HD aside for a period of time until you are ready to readdress testing issues in the future.

The Decision to Be Tested

If you decide to be tested it is important to plan who you will tell. Will you tell them on the same day you are given your results? Exactly how and when will you plan to tell them? What if you change your mind and do not want them to know quite yet or at all? (One strategy is to tell them the results were uncertain.) Planning what you will do the day you are given the results can be helpful. Will you go directly home and who will be there? Will you take some time off work or from family responsibilities?

You will most likely have strong emotional feelings when the results are given, regardless of the outcome. Many people feel relief at having an answer and disbelief that the answer is accurate. Often people express a feeling of "loss of identity", particularly if the result is different from the one they expected. Frequently people go through a period of regretting past decisions which they might have made differently if they had known their status with regards to HD. This is particularly true if those decisions were permanent: for example, decisions about whether or not to have children, or about career paths. Some other feelings specific to the test result may be as follows:

Increased risk test result in a person with no symptoms

Many people express a sense of isolation, feeling that there are few other people who can relate to their feelings. Participating with an HD support group or continued support from their HD testing centre can help them feel they are not alone. Some people have difficulty with not knowing when they will first develop symptoms of HD. They, their friends and relatives may wonder if the occasional clumsiness, jerk or emotional outburst is the beginning of HD. An appointment in the HD testing centre or with a neurologist may help to sort through some of these fears. Feelings such as depression, anger, loss of hope, despair and severe stress can occur. If these feelings occur, talking to a psychologist, psychiatrist or counsellor can be very helpful. The sense of "riding an emotional roller coaster" with good days and bad days is normal. Most people eventually come to terms with their results and use the information to help them make plans for the future.

Increased risk test result in a person with symptoms

For some people it is a relief to have an explanation for some of the problems they may have been experiencing. Sometimes this information can reduce stress in the work environment. The person with HD may be

eligible for job reclassification or benefits. Stress in the family may also be reduced. As with the diagnosis of any chronic illness, the diagnosis of HD can also bring feelings of shock, grief, anger, disbelief, depression and loss of control. Professional support and support from friends and family can help someone with HD continue to lead a productive and satisfying life.

Normal result

Most people feel extreme joy and relief with a negative result but a small proportion may experience a low period following the testing. They may be disappointed that the "good news" did not bring as many positive changes in their life as anticipated. It must be remembered that the problems that existed before the HD testing are most likely still there.

Huntington disease will continue to be a part of their life. Often there may be a feeling of increased responsibility for caring for affected family members. Often people who have lived their lives feeling they would not live a long life because they would someday develop HD have a hard time dealing with the concept of "having a future". They may feel a new pressure to "make something of themselves". They may also feel guilty that they will not develop HD when other close family members will, particularly if they are the only family member who has "escaped".

Coping with results

Most people eventually adjust well to their test resultswith time. This can take several weeks or months, therefore if is important to draw on the support of professionals, family and friends.

Can Children Be Tested?

Testing is not offered to children under the age of legal consent (often age 18). There is no medical reason to test a child without symptoms of HD. When children become adults, they can make informed personal decisions about whether or not to undergo testing. Children with possible symptoms of HD should be evaluated by a neurologist.

Prenatal Testing

Prenatal testing is one of a range of options which may be of interest to couples who are at risk of passing the disease-causing version of the HD gene to a child. Testing options may vary from centre to centre, and may include amniocentesis and/or CVS. A genetic counsellor can help individuals and couples identify which option is most suitable to their circumstances and perspective.

The purpose of prenatal testing is to determine whether a fetus has the HD gene. This information can be used by the parents to make an informed decision about whether to continue the pregnancy.

Points to consider

It is important to understand that prenatal testing involves considering the possibility of termination of the pregnancy if the fetus is found to have the HD mutation. Thus, it is a good idea to think very carefully about prenatal testing for HD and how you feel about pregnancy termination, **well in advance of a pregnancy.**

You may wish to consider alternative reproductive techniques, such as donor insemination, or in vitro fertilization (IVF) with preimplantation genetic diagnosis may enable you to have a child, without the risk of passing on the HD mutation.

Once a pregnancy has occurred, there is very little time in which to absorb the information about the prenatal test and to make such important decisions.

Where prenatal testing is positive for the HD mutation and the pregnancy is continued, there are potential difficulties of having a child identified from birth as one who has the HD mutation and who will develop HD later in life.

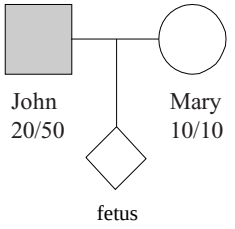
Ideally, all aspects and implications of prenatal testing for HD should be discussed with a genetic counsellor **prior to a pregnancy**, in order that the future parents and the counsellor have sufficient time to address all the important technical and emotional issues involved.

There are three different situations in which prenatal testing for HD may be done:

a) *The expectant parent has HD.* This type of testing is called *definitive prenatal testing*, because the status of the parent with respect to HD is *definite*. In Figure 4, Mary is pregnant and her husband John has HD. What needs to be determined is whether the fetus has inherited the disease-causing version of the HD gene from John. John's DNA has been analyzed and it is known that he has inherited genes with 20 and 50 repeats. If the fetus inherited the gene with the 20 repeats, it has not inherited the HD gene alteration. If the fetus inherited the gene with the 50 repeats, then it has inherited the DNA mutation underlying HD.

Figure 4

Definitive Prenatal Testing



10/20 has not inherited the HD gene
10/50 has inherited the HD gene

b) *The expectant parent has had predictive testing and has been shown to have inherited the gene mutation which causes HD*. This is also considered definitive testing since the status of the parent is known (i.e. he or he or she has inherited the HD gene mutation, although symptoms of the disease are not yet present). Testing is done as in Figure 4, except that John is not yet affected with HD, although he has the gene. The outcome is also similar — the fetus has inherited from John either the gene with 20 repeats (not the HD gene) or the gene with 50 repeats (the HD-causing gene).

c) *The expectant parent has no symptoms of HD, and does not wish to have predictive testing for herself/ himself*. This type of testing is called *exclusion prenatal testing*, and is performed only under very rare circumstances. Additional information on exclusion prenatal testing may be obtained from a genetics centre.

Chorionic Villus Sampling (CVS)

This test is usually done at 10–12 weeks after the first day of the mother's last menstrual period. Thus it is important to see your doctor as soon as you realize you are pregnant.

The test is done by looking at cells taken from the developing placenta, called the chorionic villi. A thin catheter, or flexible tube, is inserted through the vagina and cervix, and small amounts of the chorionic villi are sampled. Alternatively, the test is occasionally done by inserting a needle through the mother's abdomen to obtain chorionic villi. In either case, the cells are tested in the laboratory for the presence of the HD mutation.

No anaesthetic is required for this procedure. When the test is carried out by an obstetrician experienced in the technique, the risk of miscarriage related to the test is about 1% (1 in 100 pregnancies).

Amniocentesis

This test is done at 14–18 weeks of pregnancy. The fluid surrounding the fetus, called amniotic fluid, contains skin cells from the developing fetus. A sample of this fluid is taken by inserting a needle through the abdomen into the uterus, and then sent to a laboratory to be studied for the presence of the HD mutation in the fetal cells.

No anaesthetic is required. When the test is carried out by an obstetrician experienced in this technique, the risk of a miscarriage related to the test is about 0.5% (1 in 200 pregnancies).

Resources

For additional copies of this booklet or other information, please contact:

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519 749 8965 (fax)
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The Society has a network of Resource Centres, staffed by a trained professional, as well as support (social) workers, in locations across the country. The Society's national office will be happy to provide local names and telephone numbers, if you are having difficulty locating them.

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References and Suggested Reading

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