



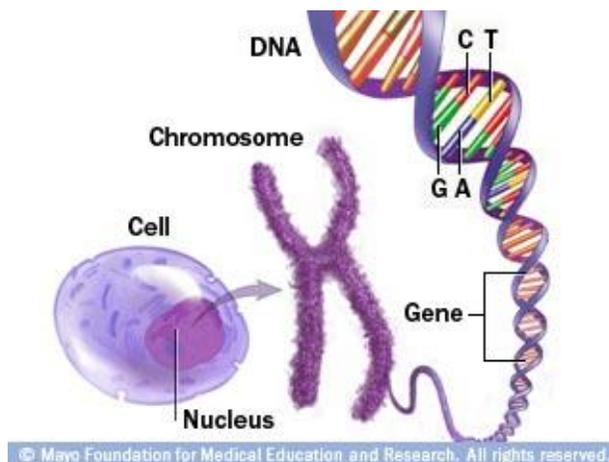
# Genetic Issues in Huntington's Disease

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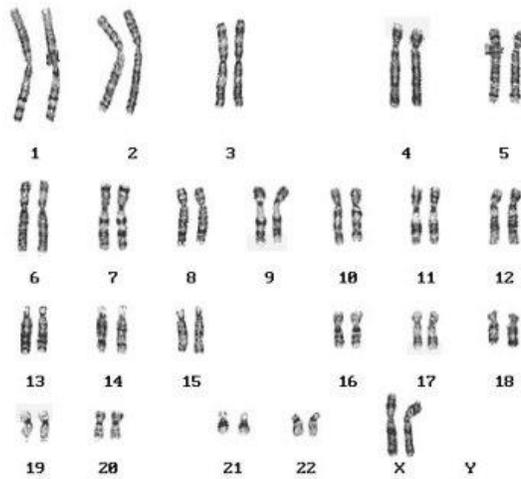
**Huntington's Disease** (HD) is a genetic condition of the brain where symptoms usually occur in adults between 30-50 years of life, although symptoms can begin in people who are younger or older as well. Even within the same family, the age of onset and symptoms can vary.

## To understand the genetics of HD, it helps to know some Basic Genetics.

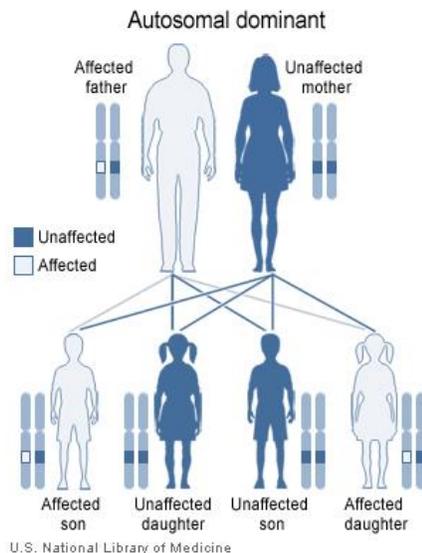
Our bodies are made of cells and in each cell (except red blood cells) we carry our genetic material in the nucleus. This genetic material is the "recipe" or "blueprint" about how to make each of us. Our DNA contains all of our genes and our genes make proteins that create and determine everything about our bodies from the chemicals that help us digest our food, our hair color, skin color, and yes, whether or not we will get HD in our lifetime. The DNA is packaged into structures called chromosomes that we can see under the microscope.



We all have 46 chromosomes which come in pairs; one of each pair comes from each parent. This means that 23 chromosomes are from the mother, and 23 chromosomes are from the father.



We know that the gene which causes HD is on chromosome 4 and the gene for HD makes a protein called "huntingtin". In people who have HD, one gene of the pair is not functioning correctly and expresses itself more strongly, or 'dominates', the other normally functioning gene.

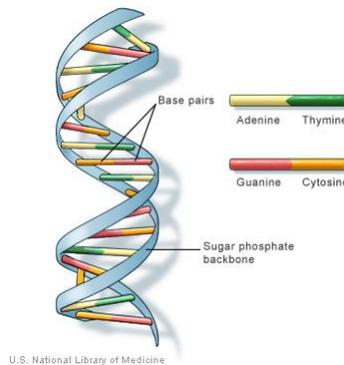


Huntington's disease is **dominantly inherited**. This means that if a person has HD they have a 50% risk of passing on this condition to each of their children. Although this

illustration shows the 50% risk, it doesn't mean if a person with HD has 4 children, that 2 will inherit the condition and 2 won't. The 50% risk is for each child. So in this same example (although not this illustration), all 4 children could inherit the gene, or 3, or 2, or 1, or none. It's like flipping a coin each time a person with HD has a child. Males and females have the same 50% risk of inheriting the condition from a parent who has HD.

### What is the genetic change in HD?

The HD gene is on chromosome 4. Remember that genes are made up of DNA.



DNA is a twisted double helix. You can imagine this molecule as a twisted ladder. The DNA is made up of a sugar phosphate backbone (the sides of the ladder) and then bases that hold the 2 sides together (the rungs of the ladder). These bases have names (**A**denine, **T**hymine, **G**uanine, **C**ytosine). The HD gene contains a series of **CAG repeats** (**C**ytosine- **A**denine- **G**uanine). A gene is made up of a series of three bases so we all have CAG repeats but people with HD have more copies of this CAG repeat in one copy of their genes that codes for the huntingtin protein.

Although the numbers vary slightly here is an explanation of the CAG repeat numbers amended from a well-respected Genetics website called GeneTests:

**Normal:** 26 or fewer CAG repeats

**Intermediate:** 27-35 CAG repeats. Not at risk of developing symptoms of HD, but because of instability in the CAG repeats, a person with a CAG number in this range may be at risk of having a child with an expansion of the CAG repeats into the HD-causing range.

**Reduced Penetrance:** 36-39 CAG repeats. People who have 36-39 CAG repeats may or may not develop symptoms of HD. This size repeat is also considered unstable so that future generations could be at risk.

**Affected:** If you have 40 copies of the CAG repeats on one of your HD genes, you will develop symptoms of HD over the course of a natural lifespan. If a person has 60 or more CAG repeats this would result in Juvenile onset HD.

An individual's number of CAG repeats is determined at conception and we wouldn't expect it to change over time.

**Paternal Inheritance:** There's an interesting phenomenon that occurs in HD where the gender of the parent you inherit an HD expansion from plays a role. If you inherit the HD causing gene from your father the number of the CAG repeats may increase where as if you inherit it from your mother, the number usually remains stable. This is important since we know that the number of these CAG repeats plays a role in the age of onset. In general, the higher the number of CAG repeats, the earlier the onset although exceptions are seen pretty regularly and we just use this as a general guideline. There are clearly other genetic and non-genetic variables that contribute to the complex issues around age of onset and severity of symptoms.

## **TESTING ISSUES IN HUNTINGTON'S DISEASE:**

### **Genetic Testing**

**Genetic Counseling** is a process where a person or family chooses to talk about genetic information and its impact. Genetic Counselors are non-directive, non-judgmental, and supportive of autonomous decision making around these very emotional and personal testing decisions.

The actual DNA test for HD itself is a fairly straightforward laboratory process, but the implications and emotional aftermath of the results are usually anything but straightforward. Since this is such a serious, degenerative brain disease and there is currently no cure for HD the emotional burden of results can be very high.

There are different types of genetic testing when we think about HD:

- 1) Diagnostic testing
- 2) Pre-symptomatic testing
- 3) Prenatal diagnosis
- 4) Pre-implantation diagnosis

**1) Diagnostic testing** is very similar to the model most people are used to when going to see a doctor. You have a symptom and you want to know why. You may or may not have a family history of HD but a person may show up at the doctor's office with symptoms of HD. A blood test is done to determine if you have HD or not. The result will be the number of CAG repeats in the HD genes.

**2) Pre-symptomatic testing** is more complicated. Pre-symptomatic testing is if a person who is at risk for HD but does NOT have symptoms wants genetic testing to find out if they are going to get HD in their lifetime. The majority of people who are at risk for HD do not seek pre-symptomatic testing, preferring not to know their future. However, for those who choose to have testing, research has shown that getting results after going through a pre-symptomatic testing protocol allows for better coping than not going

through the protocol. The pre-symptomatic testing protocol isn't in place to make it difficult for people to get the information they desire, but rather to provide support and encourage thought and discussion around important issues to help people feel supported and ready to get this very important information.

Some of the issues we explore/discuss are:

What is their life experience with HD?

Are they testing for themselves and not feeling pressured by others to do so?

How would the results change a person's life? Would they do things differently? (For example issues around education, marriage, having children, setting life priorities, etc.)

How does their family feel about them getting tested?

How do they feel they would react if the results are positive? Negative?

Are there any other major life stressors going on at the same time they are seeking this information? (For example, death of loved one, divorce, pregnancy, or other major life changes)

Why are they interested in getting this information now?

There are many, many reasons people choose to test or not test. Just a few reasons people choose to test can include: alleviating anxiety of "needing to know", planning for the future (marriage, children, and education), creating a support system, and living your life to the fullest. Some reasons people choose not to test can include: there's no cure, not emotionally prepared for results or testing process, not wanting to know the future, conflicts with loved ones about testing, and concerns about discrimination. Of course this is just a partial list and everyone comes with their own personal set of issues which can be explored as part of the genetic counseling process.

The **pre-symptomatic testing protocol** involves meeting with a Genetic Counselor, Neurologist, and also somebody who can provide emotional counseling and support

(Therapist, Social Worker, etc) before testing is performed. It may involve 3-4 visits and results are given in person.

This process also allows time to think through the issues thoroughly and some people do change their mind once they start the process, choosing to delay the test or not have it done at all. We remind people seeking this testing that once you we give you those results about your HD gene status, you can never “not know” your status again. There are studies suggesting a higher rate of depression in people who know their positive gene status but there are also many amazing people who have used their knowledge that they will develop HD in positive and inspirational ways.

This is obviously a very emotionally charged issue that everyone handles differently. If you'd like to read more about pre-symptomatic testing here are some articles and more information:

<https://www.hdsa.org/living-with-huntingtons/family-care/living-at-risk.html>

<http://news.blogs.nytimes.com/2007/03/18/facing-life-with-a-lethal-gene/>

You can also read more by entering Katharine (Katie) Moser into your search engine.

**Testing Children:** At this time the HDSA and the National Society of Genetic Counselors in conjunction with researchers and clinicians involved in caring for people and families with Huntington's disease, do not support the testing of anyone under 18 who is at risk for developing Huntington's disease unless they have symptoms of the condition that require medical treatment.

**Insurance Discrimination** is a major concern for many people considering pre-symptomatic testing for HD. There are several laws that protect against insurance discrimination.

First, all medical information is protected by HIPAA (Health Insurance Portability and Accountability Act of 1996). In general, HIPAA doesn't allow group health insurance issuers to create any rule of eligibility for a person or his/her dependents that discriminates against that person based on any health factor. The term “health factor” includes genetic information.

Secondly, a law has been passed called G.I.N.A. (**G**enetic **I**nformation **N**on-discrimination **A**ct) which provides some security against employment and medical insurance discrimination. GINA does not yet cover life, disability, or long term care insurances which are often of some concern to people in families with HD. GINA protects against discrimination based on positive gene status in healthy individuals who are gene positive but do not have HD. Once a person actually has signs or symptoms of the disease the protection disappears. GINA doesn't apply to the military and Indian reservations.

Genetics and Public Policy Center – More detailed information about GINA  
<http://www.dnapolicy.org/gina/>

Lastly, there are also California laws that provide some protection for those who are gene positive but do not yet have the diagnosis of HD.

State of California: Laws and Regulations – California Health and Safety Code  
<http://www.ca.gov/Health/LawsAndRegs.html>

State of California: Department of Managed Health Care - Knox-Keene Health Care Service Plan Act of 1975  
<http://www.healthconsumer.org/cs016knoxkeene.pdf>

California Insurance Code  
[http://www.leginfo.ca.gov/.html/ins\\_table\\_of\\_contents.html](http://www.leginfo.ca.gov/.html/ins_table_of_contents.html)

### **Other resources if you choose to read more about these issues:**

Genetic discrimination and GINA  
<http://www.genome.gov/10002328>

Database of Federal and State laws/statutes related to genetics  
<http://www.genome.gov/PolicyEthics/LegDatabase/pubsearch.cfm>

Genetic Home Reference-Overview of genetic discrimination  
<http://ghr.nlm.nih.gov/handbook/testing/discrimination>

National Institute of Health – Office of Legislative Policy and Analysis

<http://olpa.od.nih.gov>

Council for Responsible Genetics – A non-profit, non-governmental organization that fosters public debate about the social, ethical and environmental implications of genetic technologies.

<http://www.councilforresponsiblegenetics.org>

**3) Prenatal Diagnosis** is the process of testing a baby while in the pregnant uterus to determine if the baby has inherited HD or not. This can be done two different ways:

CVS (Chorionic Villus Sampling) is done typically between 10-13 weeks of pregnancy. A piece of the developing placenta is removed either through a woman's cervix or abdomen using a catheter or needle. This tissue is 99% genetically identical to the fetus so DNA testing can be done for HD status and a result given. CVS carries a risk for miscarriage that can vary slightly from center to center but is usually in the range of 1/100-1/500.

Amniocentesis is typically performed between 15-20 weeks of pregnancy. Amniotic fluid that surrounds the baby is removed from the uterus using a thin needle. This fluid contains cells from the baby that can be isolated, grown in the lab, and tested for HD status. Again, amniocentesis carries a risk for miscarriage that can vary slightly from center to center but is usually in the range of 1/200-1/500.

Prenatal diagnosis can be done in a way as to not disclose the at risk parent's HD status. A genetic counselor can help you understand these testing options in more detail.

**4) Pre-implantation diagnosis (PGD)** is a way to test an embryo before it's implanted in a woman's uterus. Using IVF (In Vitro Fertilization) techniques, the egg and sperm are combined outside the body. Once the embryo reaches a certain level of development it can be tested to see if it carries the gene causing HD. Only

embryos that are unaffected with HD are implanted in the woman's uterus. PGD can also be done in a way that doesn't disclose the at risk parent's status if that's how the couple outlines the process with the lab.

For more information on PGD and to read an inspiring story of hope, please refer to the following website:

<http://www.hdfreewithpgd.com/>

**Concluding thoughts:**

The diagnosis of HD in an individual or family member can have an immediate or eventual impact on a person's perceptions of themselves, day to day life, and their plans for the future, just to mention a few. Making these adjustments is different for everyone but we here at the UCD HD Center of Excellence are committed to helping you in this important aspect of your life-bringing hope, meaning, and purpose to your life with HD. We remain available to you at any time. Please do not hesitate to contact us if you have questions or would like to discuss these issues further.