

Important points

- Huntington disease (HD) is a neurodegenerative genetic condition where the symptoms of involuntary movements and changes in personality usually appear slowly between the ages of 30 and 50 in both men and women
- In individuals with HD, the important brain protein (*huntingtin*) is abnormal due to a faulty gene
- People with HD, or those who will develop HD, have (from birth) a faulty copy of the *huntingtin* gene and a working *huntingtin* gene copy
- The change in the information in the *huntingtin* gene that has made it faulty is an increase in the number of times that one of the 'code words' (made up of the letters CAG) is repeated in a sequence in the gene
- A working '*huntingtin*' gene copy has up to 26 CAG repeats; when the gene is faulty, the CAG triplet is repeated 40 times or more and those who have the faulty gene copy will develop HD during their lifetime (if they live long enough); CAG triplet repeats between 27 and 39 in number, are in the 'intermediate range' and careful interpretation of the meaning of this result for the individual and their family is required
- The number of repeats of the CAG code word can increase when the *huntingtin* gene is passed from a parent to a child
- The pattern of inheritance in families of the faulty gene causing HD is described as **autosomal dominant inheritance**
- When one of the parents has the faulty *huntingtin* gene copy ie. has HD or will develop HD, they have 1 chance in 2 (or 50% chance) **in every pregnancy** of having a child who will develop HD
- In a person who has symptoms, genetic testing may be used to confirm the diagnosis
- Where a person has no symptoms of HD, genetic testing is available if a person has a family history of the condition. Any person utilising genetic testing before the onset of any signs of HD (called **presymptomatic genetic testing**) should only do so in the context of specialised counselling and with the help of a multidisciplinary team including geneticists, genetic counsellors, neurologists and supportive professionals such as social workers (see Genetics Fact Sheet 3). All the advantages and disadvantages of having the presymptomatic test need to be considered **before** having testing
- Genetic testing for changes in the *huntingtin* gene can be helpful in some situations such as life-planning. Testing a baby in pregnancy or an embryo before pregnancy may be available (see Genetics Fact Sheets 17C & 18). It is strongly recommended that testing be carried out in the context of genetic counselling (see Genetics Fact Sheet 3)

Huntington disease (HD) is a neurodegenerative condition that was formerly called Huntington's chorea. It was first recognised as an inherited condition in an American family of English descent by Dr Huntington in 1872.

HD affects about 1 in 10,000 Australians.

The symptoms usually appear slowly between the ages of 30 and 50 in both men and women and are often unnoticed by the affected individual. Symptoms include involuntary movements in the body and limbs as well as personality changes such as being easily irritated, having poor insight, depression, withdrawal, euphoria and difficulty with organisation.

As the condition develops, the individual's speech becomes slurred, swallowing becomes difficult and unsteadiness in walking increases. Reasoning and judgement become impaired.

Individuals usually live for 15 to 20 years after developing the first symptoms but eventually succumb to pneumonia or complications from falls.

What causes Huntington disease (HD)?

The cells of the body contain information, in the form of genes, for the body to make all the necessary structural components and chemicals to ensure normal function.

If a gene is changed so that it does not work properly, the gene is described as being faulty. The information contained in the

faulty gene, and its product, is impaired (see Genetics Fact Sheets 4 & 5).

The information for our nerve cells to make huntingtin, a protein that is thought to be important for brain function, is contained in a gene on chromosome number 4 (see Genetics Fact Sheet 1).

There are two copies of chromosome number 4 in every body cell and therefore two copies of the gene that codes for the huntingtin protein. This gene is called the *huntingtin* gene.

- Everyone has two copies of the *huntingtin* gene in their body cells
- People with HD, or those who will develop HD, have one working copy of the *huntingtin* gene and one copy of the gene in which a change has made it faulty.

The change (mutation) in the *huntingtin* gene is present at birth (inherited) but the symptoms typically do not appear until 30 to 50 years later.

What is the change that makes the huntingtin gene faulty and causes HD?

Genes are made up of DNA. The information in the genes is in the form of chemical 'code words' each made up of three out of a possible four 'letters': A, T, C or G. The letters represent four basic

chemicals in the DNA: they are arranged in a group of three and so the 'code words' are called *triplets*.

In some genes, these triplets are repeated many times over in a sequence, and are therefore referred to as 'triplet repeats' (see Genetics Fact Sheets 4 & 5). The number of times that the triplets are repeated in a sequence in the gene can be critical.

- The two copies of the *huntingtin* gene that everyone has usually each contain the triplet code word made up of the letters CAG repeated in a sequence up to 26 times
- In individuals with HD, or in those who will develop HD during their lifetime (if they live long enough), **one** of their two *huntingtin* gene copies is faulty because the CAG triplet is repeated 40 times or more. The other *huntingtin* gene copy on the partner chromosome usually contains the working number of triplet repeats (up to 26 times)
- Some people have the CAG triplet in one of their *huntingtin* gene copies repeated between 27 and 39 times.
 - Doctors call this the '**intermediate range**' of repeats and careful interpretation is required when assessing the meaning of this result for the individual and their family
- A complicating factor is that the triplet repeat gene change is 'dynamic'; ie. the number of repeats of the CAG code word can increase when the *huntingtin* gene is passed from a parent to a child. Larger increases in the number of CAG repeats can occur when the *huntingtin* gene passes to a child through the sperm from the father

When will the symptoms of HD start if a person has the faulty *huntingtin* gene?

It is still not possible to predict at what time in life the symptoms will appear in an individual who has inherited a faulty *huntingtin* gene.

Research suggests, however, that there is an association between age of onset and the number of repeats in the faulty gene. The age of onset is similar within families.

The information in other genes appear to modify the age of onset, although exactly which genes are important and how they influence this is still under investigation

What effect does the faulty gene have in the brain cells of people with HD?

Even though the individuals who will develop HD are born with a faulty copy of the *huntingtin* gene, the effects of the faulty gene do not appear for many years, most often not until 30-50 years later.

The faulty gene then leads to the production of huntingtin protein that does not work properly.

The exact relationship between the huntingtin protein not working properly, and the death of the brain cells in individuals affected with HD is still not clear but an understanding of this process is crucial to determining the basis of the condition. This research is facilitating the development of new treatments for individuals with HD.

What is the pattern of inheritance of HD in families?

HD is a genetic condition (see Genetics Fact Sheet 2). Therefore it is passed from parents to children in their genes.

Two factors influence the pattern of inheritance of the faulty *huntingtin* gene causing HD in families.

1. The *huntingtin* gene is located on chromosome 4, an autosome (one of the numbered chromosomes)
2. The effect of the change in the *huntingtin* gene is 'dominant' over the information in the working copy of the gene on the partner chromosome 4 (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance in families of the faulty gene causing HD is therefore described as **autosomal dominant inheritance** (see Genetics Fact Sheet 9).

In *Figure 44.1*, where the faulty *huntingtin* gene copy causing HD is represented by 'D' and the working copy by 'd', when one of the parents has HD, or is presymptomatic because they have the faulty gene copy, there are four possible combinations of the genetic information that is passed on by the parents.

This means that, **in every pregnancy**, there is

- 1 chance in 2 (ie. 2 chances in 4) or 50% chance that their child will inherit a copy of the faulty *huntingtin* gene and will therefore be affected by HD at some time in their life (if they live long enough)
- An equal chance (ie. 2 chances in 4) or 50% chance of not having inherited the faulty gene copy. Children who have not inherited it are not at risk of developing HD. Importantly, they cannot pass the faulty gene copy on to their children.

While *Figure 44.1* shows the father as the parent carrying the faulty *huntingtin* gene, the same situation would arise if it was the mother.

HD affects males and females equally.

What does understanding the faulty *huntingtin* gene mean for people with a family history of HD?

In the immediate future, there will be no changes. The methods for the treatment and diagnosis of HD will essentially remain the same for some time, although research is leading to new treatments. Analysis of the gene can be used to support a clinical diagnosis of HD.

Research has determined that the huntingtin protein has an effect on certain chemical pathways in the brain. It inhibits the action of several other proteins that are essential for normal brain function.

Substances that have been shown to delay the onset of symptoms in mice that have had a faulty copy of the human *huntingtin* gene inserted (*transgenic mice*), are being tested in humans. It is important that any drug testing is done in a careful, controlled manner in order to be sure that the treatment is effective.

Can a person determine if they have inherited the faulty gene for HD?

In some situations genetic testing may be used to confirm a diagnosis of HD in someone who has symptoms.

An individual with a parent affected with HD has 1 chance in 2, or 50% chance, that they will also develop the condition. Genetic testing gives individuals the choice to accurately determine if they have inherited a change in the information in their *huntingtin* gene.

Presymptomatic genetic testing is a general term applied to testing which determines whether a person carries a mutation for a condition that will arise later in life (see Genetics Fact Sheet 21).

Any person utilising genetic testing before the onset of any signs of HD (*presymptomatic genetic testing*) should do so in the context of specialised counselling and with the help of a multidisciplinary team including geneticists, genetic counsellors, neurologists and social workers. Clinical genetic testing programs are offered in conjunction with genetic counselling (see Genetics Fact Sheet 3). It is highly recommended that the advantages and disadvantages of having the presymptomatic test be considered **before** having testing.

Genetic testing for changes in the *huntingtin* gene can be helpful in some situations such as life-planning. Testing a baby in pregnancy or an embryo before pregnancy may also be possible (see Genetics Fact Sheets 17C & 18).

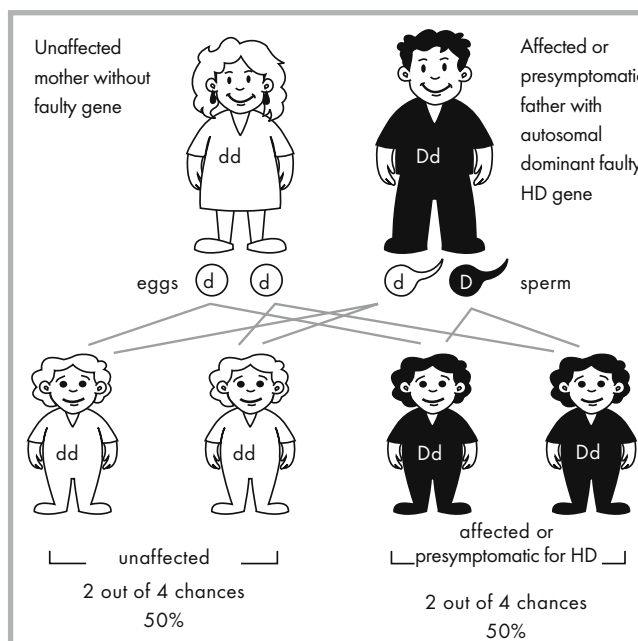


Figure 44.1: Autosomal dominant inheritance when one parent has a faulty *huntingtin* gene copy. The faulty *huntingtin* gene copy is represented by 'D'; the working copy by 'd'.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 2, 3, 4, 5, 9, 17C, 18

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