This fact sheet describes a condition known as **Huntington disease** and includes the symptoms, causes, and any treatment or testing that is available.

In summary

- Huntington disease (HD) is a progressive neurological condition characterised by involuntary movements known as chorea, as well as personality changes
- HD is caused by an expanded CAG repeat length on the *HTT* gene, which codes for an important protein in brain cells called *huntingtin*
- Diagnostic genetic testing is available for symptomatic individuals
- Predictive genetic testing is available for currently healthy individuals with a family history of Huntington disease.

WHAT IS HUNTINGTON DISEASE?

Huntington disease (HD) is a progressive neurodegenerative condition characterised by involuntary movements known as **chorea** and personality changes. Symptoms typically develop between the ages of 30 to 50 years and become progressively more severe, with survival often between 15 to 20 years after first symptoms appear. Symptoms may include:

- Restlessness, clumsiness, and minor twitching that become progressively worse over time leading to involuntary jerks or twitches of the head and limbs. Some people with HD may have rigid muscles rather than twitches.
- Subtle intellectual or emotional signs such as short-term memory loss, irritability, loss of organisational skills, and depression which may become more pronounced over time.

As symptoms progress everyday tasks such as walking, talking, and eating become more difficult and individuals require full time care. Five (flexible) stages of progression of HD have been described:

- **Early Stage –** able to maintain full function both at home and in the workplace
- **Early Intermediate Stage** – reduced capacity at work and in daily tasks, but able to manage despite some difficulties
- **Late Intermediate Stage** – no longer able to work and capacity to manage household affairs is reduced. Support in daily activities is increasingly required
- **Early Advanced Stage** – permanent family or professional carer is required to support daily activities
- **Advanced Stage** – dependent on full-time care and professional nursing care is often required.

Cause of death arises from complications of the bodies weakened state including aspiration pneumonia, infections or heart failure as opposed to the disease itself.

WHAT CAUSES HUNTINGTON DISEASE?

HD is caused by mutations in the ***HTT*** gene, which produces a protein called ***huntingtin***. This protein is important in brain cells known as **neurons**, with mutations causing the gradual destruction of neurons in particular areas of the brain known as the cerebral cortex and basal ganglia.

If we look very closely at our genetic material we can see that it is made up of four molecules called **nucleotides**. These are adenine (A), cytosine (C), thymine (T), and guanine (G). These four molecules combine as triplets to form the code of a gene. The *HTT* gene has an area of repeating CAG triplets, with up to 26 repeats being normal. Increasing size of this repeat region to over 40 results in Huntington disease. 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.

Our body is made up of millions of cells, and in each cell there are instructions, called genes, that make all the necessary structural components and chemicals for the body to function. These genes are packaged onto little long strands known as chromosomes.

We all have 46 chromosomes arranged into 23 pairs. One copy of each pair is inherited from our mother and the other from our father. The first 22 chromosome pairs are numbered and are known as autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Males have an X and a Y chromosome and females have two copies of the X chromosome.

Since all our chromosomes come in pairs, all our genes also come in pairs. Sometimes, a gene may have a variation in the instruction that causes the gene to no longer function properly. This variation is called a **mutation** or **pathogenic variant**, and means that the product produced by the gene, called a protein, is impaired or even absent.

Gene mutations may be inherited from a parent, or occur for the first time in an individual. Once you have a gene mutation however, it may be passed on to future generations. This is referred to as genetic inheritance.

The increased length of CAG repeats means that the *huntingtin* protein also becomes longer and this appears to interfere with its function, therefore a copy of the *HTT* gene with an expanded CAG repeat length can be considered faulty. The number of CAG repeats can increase when the *HTT* gene is passed from a parent to a child, this is known as **anticipation**, and means that subsequent generations may be more severely affected or develop symptoms at an earlier age as the CAG repeat length increases.

It can also explain why some people don't know Huntington disease is in their family as their parent may have had an intermediate CAG repeat length that expanded when they passed it on (See Figure 55.1).

HOW IS HUNTINGTON DISEASE INHERITED?

Huntington disease is inherited in an autosomal dominant pattern, meaning that a mutation in only one copy of the *HTT* gene is sufficient to cause disease despite the other copy working properly. For every pregnancy in this situation there is:

- 50% chance that a child, either male or female, will inherit only working copies of a gene from their parents and be healthy
- 50% chance that they will inherit one copy of the faulty gene, and one working copy and be predisposed to developing a cardiomyopathy

A mother or a father can pass on an autosomal dominant condition and both male and female children may be affected (See Figure 55.2).

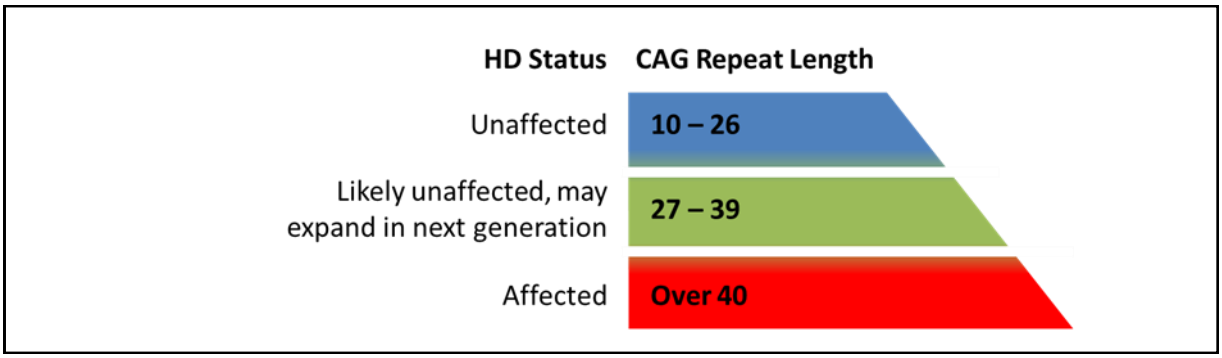

Figure 55.1: *CAG repeat length and Huntington disease status*

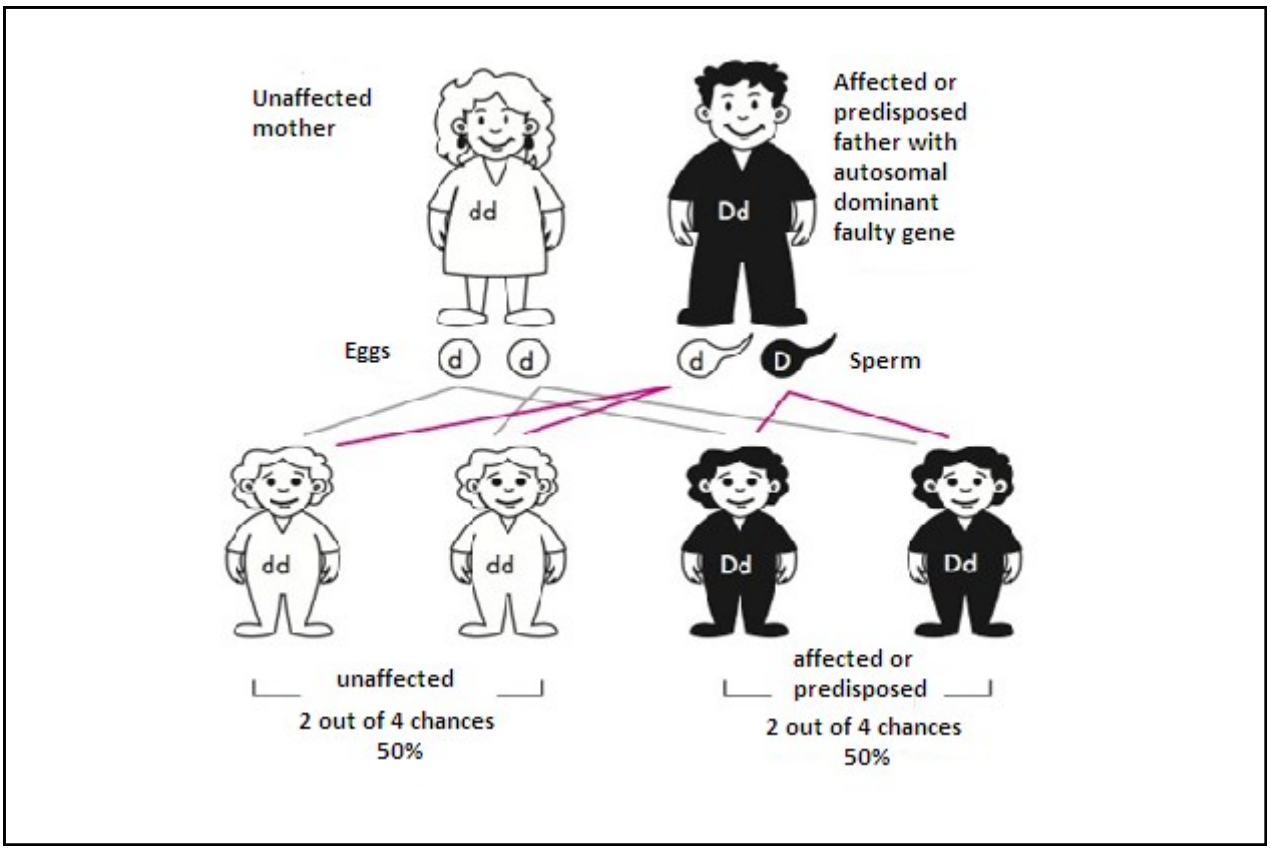

Figure 55.2: *Autosomal dominant inheritance when one parent carries the autosomal dominant faulty gene copy. The autosomal dominant faulty gene copy is represented by 'D'; the working copy of the gene by 'd'.*

IS THERE ANY TESTING OR TREATMENT AVAILABLE FOR HUNTINGTON DISEASE?

In a person who has symptoms, genetic testing may be used to confirm the diagnosis of Huntington disease. 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. All the advantages and disadvantages of having the presymptomatic test need to be considered **before** having testing.

Prenatal testing and PGD

For couples where there is a known family history of Huntington disease testing may be available during a pregnancy to determine whether or not the baby has inherited the faulty *HTT* gene. It may also be possible to undergo **pre-implantation genetic diagnosis** (PGD) on an embryo created using in vitro fertilisation (IVF). These options are best discussed and considered before pregnancy, when possible, in order to ensure all possible risks, benefits and outcomes are explored.

Treatment options

Currently Huntington disease is incurable; however some treatment is available to manage symptoms. Various therapies including medication, speech therapy, and physical therapy, are all available and should be discussed with a relevant health professional.