



Huntington's
Disease
Association



Genetics and genetic testing in Huntington's disease



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Introduction: The genetics of Huntington's disease

The gene that is important to Huntington's disease is HTT, which provides the instruction for a protein called Huntingtin. The gene is located on chromosome 4. All humans have two copies of the HTT gene – one inherited from each parent. It is only when one copy of the gene is altered in a particular way that a person will be at risk of developing Huntington's disease.

In the first coding region (exon) of the HTT gene, there is a section of the genetic instruction where CAG (the genomic instruction to produce an amino acid called glutamine) is repeated many times. This is called a CAG triplet repeat and it codes for several glutamines in a row (polyglutamine).

It is normal to have a CAG triplet repeat in the HTT gene and the number of repeats can be variable between different people. As well as having two copies of the HTT gene, humans also have two numbers for the CAG repeat length.





If a person has two copies of the HTT gene which both contain 26 or fewer CAG repeats they will not be at risk of developing Huntington's disease and neither will their children.

If a person has Huntington's disease, they have an expansion of the CAG repeat length in one copy of their HTT gene. This is called a CAG triplet repeat expansion. If there are too many CAG repeats on one copy of the

gene, the protein that is produced has too many glutamines. This CAG repeat expansion is present from the time of conception. The CAG repeat expansion affects the normal function of the protein, can build up in cells and, over time, damage nerve cells in the brain.

The onset of symptoms of Huntington's disease is variable even between members of the same family. It is not possible to predict when symptoms will begin based on the size of the CAG repeat. However, in general, the larger the size of the CAG repeat, the earlier the age of onset of symptoms tends to be. For example, Juvenile Huntington's disease is rare but causes symptoms in childhood and occurs with large CAG repeat expansions (above 60 CAGs). The relationship between CAG repeats and Huntington's disease is explained below:

- **Up to 26 CAG repeats:** Is not associated with Huntington's disease.
- **A CAG repeat of 27-35 (intermediate allele):** People with an intermediate allele will not develop Huntington's disease. Approximately 6-8% of the general population carry an intermediate allele. They are usually identified incidentally. However, there is a small chance that the child of someone who carries an intermediate allele could inherit a reduced or full penetrance CAG-repeat expansion.
- **36 and 39 CAG repeats (reduced penetrance):** Some people in this range will develop symptoms of Huntington's disease within their lifetime, but others will not develop symptoms at all. If symptoms do develop, the age at which they start tends to be much later and the likelihood of them occurring increases if there are a higher number of repeats. The child of someone with a CAG repeat in the 'reduced penetrance' range has a 50% risk of inheriting a gene within the 'reduced penetrance' range. However, occasionally, this 'reduced penetrance' CAG repeat can expand between generations and so a child could inherit a full expansion of more than 40 repeats.
- **40 or more CAG repeats (full expansion):** An expansion of more than 40 CAG repeats is associated with a definite risk of developing Huntington's disease.

| Huntington's status | | CAG repeat length | |
|---------------------|---------------------|--|--|
| Unaffected | Normal |  10-26 | |
| | Intermediate allele |  27-35 | |
| Affected | Reduced penetrance |  36-39 | |
| | Full penetrance |  40+ | |

How is Huntington's disease inherited?

Huntington's disease is an 'autosomal dominant disorder'.

Every child conceived naturally to a parent who has a CAG triplet expansion has a 50% chance of inheriting the expanded copy of the gene and therefore the risk of developing Huntington's disease.

If both parents have a CAG triplet repeat expansion, the child has a 75% chance of inheriting Huntington's disease.

In rare cases where one parent has two expanded copies of the gene, all of their children inherit Huntington's disease.

Cases without a family history arise if:

- A person is adopted or does not know their family history for some other reason, or if their parent who carried the altered gene died early, before symptoms had developed.
- A new diagnosis of Huntington's disease in a family can occur if one parent carried a reduced penetrance or intermediate allele.

Genetic testing

A genetic test for Huntington's disease is usually just a blood test to collect a sample of DNA that is then analysed to count the number of CAG repeats on each copy of the gene. There are two types of genetic testing - diagnostic

testing and predictive testing.

Diagnostic testing

Whilst a diagnosis of Huntington's disease is based on a collection of clinical features, it can be helpful to confirm the diagnosis with genetic testing. Diagnostic genetic testing is carried out when a person of any age has symptoms of Huntington's disease.

Doctors who think their patient may have Huntington's disease or Juvenile Huntington's disease undertake diagnostic tests, with the appropriate consent. This is usually a targeted test of the HTT gene alone. However, if the diagnosis is not certain or if there is no existing family history of Huntington's disease, a broader genetic test, such as whole genome sequencing, might be arranged.

The time scale for results from these two types of testing can vary. A targeted HTT genetic testing will take approximately 2-3 months for a result, and whole genome sequencing results can take up to a year.

A lack of insight is a symptom for some people with Huntington's disease. Therefore, a patient who is presenting with symptoms may not be aware of them. This needs to be handled sensitively.

Be aware that people who are receiving a diagnostic test result will need support around what this test means, not just in relation to symptom management, but also from a genetic perspective (impact on the wider family) and the effect the result may have on other areas of their life.

For information on differential diagnosis and mimics, please see Stoker et al's 2022 review of the diagnosis and management of Huntington's disease (see 'references' below).

Predictive testing

If somebody knows they are at risk of Huntington's disease due to their family history, but has no symptoms of the condition, it is possible to arrange predictive genetic testing. This will mean the person will then know whether they have inherited a CAG triplet repeat expansion.

The test itself is a blood test where DNA is extracted and analysed. The results take approximately a month to 6 weeks to return. Due to the potential implications of the result, testing should be offered alongside

predictive test counselling with a Clinical Geneticist or Genetic Counsellor.

There are a number of complex scenarios that can arise, which require careful support from a genetic counselling team. For example, where the person who would like predictive testing is a twin, or where the person who wishes to know if they carry an expanded copy of the Huntington's disease gene has a parent who has chosen not to find out this information.

Be aware that someone living at risk of Huntington's disease may need support regardless of whether they would like to have a predictive test. Living 'at risk' can have a huge impact on a person's life, and they may need support from counselling, psychological or psychiatric services. They may also want to know more about the disease and meet others impacted in a similar way – the Huntington's Disease Association offers a wide range of peer support and education opportunities.

The predictive testing process

Predictive testing is available through Regional Genetics Clinics, which are located throughout England and Wales. A referral from a GP is usually required to access these services. Referrals to Clinical Genetics can be for discussion only and do not oblige someone to proceed with genetic testing.

Each clinic should follow an internationally agreed set of predictive test counselling recommendations (MacLeod et al, 2013 – see 'references' below). This usually means that genetic testing will occur over a number of appointments.

A person under 18 years old who is considering a predictive test should be able to discuss their risk of Huntington's disease and seek advice from their local genetics team, but testing would not usually be recommended until they are an adult.

Once the decision to proceed with genetic testing has been taken, the results should be available within a month to six weeks. Understandably, this can be a stressful time for the person who is waiting for their results.

The results are usually delivered in person or via a video consultation. Follow-up appointments should be available, regardless of the testing outcome.

Genetic counselling and the impact of having a predictive test

Genetic counselling can help people to make their decision on whether to have a predictive test.

If a person does choose to have the test, in addition to the emotional impact the result may have on them and their family, they should also consider how the result could affect other parts of their life. A gene positive result may have an impact on life insurance and job opportunities. There are certain occupations, such as the armed forces, where being at risk of Huntington's disease may act as an obstacle to recruitment.

A predictive test cannot show when a person will begin to develop symptoms, or what those symptoms may be, but it can usually confirm whether that person is going to develop Huntington's disease.

The genetic test result, regardless of the outcome, can affect people differently. Some people find relief in knowing that they will go on to develop the disease rather than continuing at 50% risk, allowing them to plan ahead. Many people use the result as their motivation to live their lives, raise awareness of the disease, or take part in research opportunities.

There are people who have lived at risk and have mentally prepared themselves for a gene-positive test result and a life with Huntington's disease, who can find it difficult to adapt to the news that they will not go on to develop the condition. If someone has received a gene-negative test result, they may experience feelings of guilt if close family members have Huntington's disease.

Options for starting a family

Many people at risk of Huntington's disease, or who have had a positive predictive test, do not alter their family planning decisions. However, others consider certain family planning options (discussed below) that could mean that they would have a child who is not at risk of Huntington's disease.

People at risk of Huntington's disease, or who have had a gene-positive predictive test for Huntington's disease, should be able to discuss their options on starting a family with a genetic counsellor.

Pregnant women should receive an urgent referral to their genetics team from their antenatal clinic to discuss their options.



Preimplantation Genetic testing (PGT-M)

PGT-M (formerly known as pre-implantation genetic diagnosis - PGD) uses In vitro fertilisation (IVF), a procedure where a woman's ovaries are stimulated with medications to enhance egg production. The eggs are removed from the ovaries and then fertilised with sperm to create embryos. These can then be re-implanted into the woman's womb with the aim of achieving a successful pregnancy.

For genetic conditions like Huntington's disease, which are caused by a single gene or are 'monogenic', PGT-M can be undertaken alongside IVF. In the case of PGT-M, after the fertilised embryos have developed for a few days, some cells are removed from each one for genetic testing. Only unaffected embryos would then be available for transfer. If the pregnancy is successful, the baby will not be at risk of Huntington's disease.

Whilst PGT-M is a good option for many couples, like all IVF, it is a physically and emotionally demanding process, and it may not result in a successful pregnancy. Unlike IVF, only a few clinics are licensed to carry out PGT-M.

The NHS in England and Wales will fund up to three cycles of PGT-M until there is a successful pregnancy. However, people have to meet certain criteria in order to be eligible for NHS treatment, and the waiting times can be long.

More information about clinics, PGT-M and other assisted conception techniques can be found by visiting the Human Fertilisation and Embryology Authority website. Information is also available on the Genetic Alliance UK website (see 'resources' below).

Prenatal testing

Prenatal testing can be done early in a pregnancy, from around 11 weeks gestation. It is carried out using a needle, which is inserted through the pregnant woman's womb and into the placenta (Chorionic villus sample, CVS), or the fluid which surrounds the foetus (amniocentesis), to collect a sample of DNA which matches the developing foetus. Genetic testing on this sample can see if the foetus has inherited a CAG repeat expansion. The

results usually return within 10 days. In most cases, this test is only carried out if the person would consider ending the pregnancy if the foetus is found to be at risk of Huntington's disease.

Both PGT-M and prenatal testing might be considered for someone who has had predictive testing, which has shown that they carry an expanded copy of the HTT gene. They may also be an option if someone has chosen not to have predictive testing. This is called exclusion testing. Exclusion testing is not appropriate or possible for everyone, but it can be discussed with a genetics team.

Alternative options

Other options include the use of donated eggs, sperm or embryos. This would result in a pregnancy, which is not genetically related to the parent with the CAG repeat expansion.

Juvenile Huntington's disease

A diagnosis of Juvenile Huntington's disease is based on clinical presentation and family history.

Children are likely to present to the GP and / or paediatrics with symptoms rather than a professional with a specific knowledge of Huntington's disease. This means there is an increased risk of misdiagnosis or diagnostic delay.

Symptoms (e.g. challenges at school) can be confused with other disorders. There may be a challenging family situation, which can affect behaviour.

A child or young person who has Juvenile Huntington's disease is likely to have a family history of the disease, though this may not be known if a child or young person has been adopted. There are also cases where a child or young person presents with clinical symptoms before a parent.

Genetic testing is used to confirm a diagnosis if there is complete confidence that the clinical presentation is that of Juvenile Huntington's disease. It is necessary to have this confidence, as otherwise the child or young person could, despite having a positive test result, be displaying symptoms that are not related to Huntington's. Instead, they could have the genetic make-up for adult-onset disease. If this is the case, then the opportunity for them to make their own decision about testing as an adult has been removed and this can cause significant distress.



Resources

Huntington's Disease Association resources

For professionals

The Huntington's Disease Association offers a range of resources to support professionals working with people affected by Huntington's disease.

You can find our resources at www.hda.org.uk

Explore the professionals webpage using the search bar to find specific resources. Search "resources".

Stay informed

Join our professional-only mailing list to receive updates on events, webinars, and new resources tailored to your needs. You can sign up at <https://www.hda.org.uk/professionals-and-training/>

Support for families, children, and young people

Find information on our Huntington's Disease Youth Engagement Service (HDYES) by searching for "HDYES" on the website.

Huntington's disease: A genetic testing guide

Our guide for families on genetic testing is available at <https://www.hda.org.uk/seecmsfile/?id=99>

Other useful resources for families

Genetic Alliance UK. Guide to pre-implantation genetic testing. Available [here](#).

HD Buzz. March 2024. Making babies: having a family, the HD way. Available [here](#).

Other useful resources for professionals

NHS England. Presentation: Clinical suspicion of Huntington disease. Available [here](#).

Human Fertilisation and Embryology Authority. Information about IVF, clinics and other fertility treatments. Available [here](#).

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Notes

Notes

Get in touch

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Registered charity no. 296453

A company limited by guarantee.
Registered in England no. 2021975

Design and print by the Huntington's Disease Association. Published February
2026. First edition

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