

## What is the cause of Huntington disease?

Huntington disease (HD) is caused by a genetic mutation. This genetic mutation involves an increase in the number of CAG repeats in the Huntingtin (HTT) gene on chromosome 4. While everyone has the HTT gene, it is the number of CAG repeats in the gene that will determine whether or not someone will develop the disease at some point in their lifetime. Individuals who will develop HD in their lifetime have 36 or more CAG repeats in their HTT gene. In this case doctors and scientists say the individual is mutation-positive. Persons with 26 CAG repeats or less will not develop HD. These individuals are considered mutation-negative.

## What is the inheritance pattern of HD?

HD follows an autosomal dominant inheritance pattern. This means that children, or offspring, of persons with 36 or more CAG repeats have a 50 per cent chance to develop HD when they are adults. Conversely, offspring of persons who have 26 CAG repeats or less are not at-risk to develop the disease during their lifetime.

## What are intermediate alleles?

Intermediate alleles (IA) are a unique category of Huntingtin genes that have between 27-35 CAG repeats. This is a range that falls just below the threshold of 36 CAG repeats required to develop the disease.

## What are the clinical implications of an IA?

Individuals with an IA will likely not develop the disease, however, there is a possibility that their offspring may develop HD. The next generation is at-risk of developing HD because the number of CAG repeats may increase when the IA is passed from parent to child. If the number of CAG repeats increases to 36 or more, the offspring will develop HD in their lifetime.

Scientists call this increase in the number of CAG repeats, **“CAG repeat expansion”**.

## What causes CAG repeat expansion?

Scientists do not know why CAG repeat expansion occurs, but they do know factors that influence whether or not it will occur.

The gender of the parent is the most important factor – CAG repeat expansion most often occurs when the IA is passed down from a father (male). The number of CAG repeats will most likely stay the same when the IA is passed down from a mother (female). The gender of the offspring does not impact the likelihood of CAG repeat expansion. Therefore, offspring of males with an IA have the greatest risk of developing HD in the future.

Another factor that influences CAG repeat expansion is the number of CAG repeats in the IA. The larger the CAG size of the IA, the more likely it will expand into HD range when passed from parent to child. This means that a male with an IA with 35 CAG repeats has a greater chance to expand into the disease range than an IA with 27 CAG repeats.

## How common are IAs?

One study determined that about 7 per cent of individuals in the general population that have no known association to someone with HD have an IA. Scientists have determined that approximately 1 out of every 17 individuals undergoing predictive testing for HD will receive an IA genetic test result (sources noted in bibliography, available by request).

## What are the potential influences on IAs to expand beyond 36 CAG repeats when passed from parent to child?

This is not an easy question to answer as scientists do not understand why CAG repeat expansion occurs. What we have learned through research is that the higher the IA CAG repeat, the higher the chances of expansion in the transmission of the IA from one generation to the next (Apollinaro, Paiva and Agostinho, 2017). Research has started to explore the role of the environment and other genetic factors (other than CAG repeats) on IAs and is ongoing. If you are interested in participating in research, discuss the options with your HD clinic team, as observational studies such as EnrollHD may be recruiting individuals within the IA range.

## How are IAs identified?

IAs are identified in two different family histories – in families that have a long-standing history and in families with no previous history of the disease, but in which a case of HD has unexpectedly occurred.

- **NO FAMILY HISTORY:** For decades, HD has been described as an inherited condition that is passed down in families from generation to generation. While this is most often the case, scientists have now determined that in some families, HD has not been present for generations; instead the disease appears in the family unexpectedly. Scientists call this single case of HD in a family with no previous history a new mutation. Research has shown that new mutations are caused by CAG repeat expansion of IAs. In this case, the unaffected parent, most likely the father, had an IA that underwent CAG repeat expansion beyond 36 CAG repeats when passed down to the individual affected with HD.
- **LONG-STANDING FAMILY HISTORY:** IAs are also found in families that have a traditional long-standing family history. In this case, the IA is often inherited from the unaffected parent. In other words, the IA is passed down from the non-HD side of the family. As mentioned previously, IAs have been identified in persons in the general population that have no known association to someone with HD. These IAs are identified when an individual from the general population becomes part of an HD family (e.g. has children with someone who has a family history of HD).

## Confused about IAs?

IAs have introduced an added layer of complexity to the genetics of HD, especially given that they conflict with many common beliefs about HD inheritance (e.g. children are only at-risk to develop HD if the parent is affected, only persons with a family history are at-risk to develop HD). Many individuals are shocked when they receive an IA predictive test result and have difficulty understanding IAs and their clinical implications. Therefore, it is not uncommon to need extra support, education, or counselling.

## Would you like more information?

If you would like more information please contact your local medical genetics clinic or HSC resource centre. Scientists are continuing to learn about the clinical implications of IAs, therefore you may also wish to stay in contact with your medical genetics clinic or HSC resource centre for updates on the latest research findings.

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