

## Huntington's Disease

Huntington's Disease (HD) is an inherited disorder affecting cognition, behaviour and movement. HD was first described by George Huntington in 1872, a physician whose father and grandfather, also clinicians, had dealt with families presenting with the neurological symptoms over a number of decades. They realised that half of the children of each sufferer inherited the disease, and described the onset and progression.

In the 130 years since HD was first described, we have discovered much more about its causes and disease mechanisms. In 1993, an international consortium discovered the HD gene (by studying families in a part of Venezuela where around 1 in 4 people inherited the disease gene), and named the protein it encoded 'huntingtin'. It turned out that HD was one of the first human diseases found to be caused by an extraordinary 'genetic stutter', a repeating stretch of DNA that varies amongst healthy individuals and is longer in patients. In the case of HD the triplet of DNA bases, CAG, are present as a longer repetitive stretch, which in turn encodes a long tract of the amino acid glutamine in the huntingtin protein. It appears that this long repeat adds toxicity to the protein so that it gradually poisons specific cells in the brain (and other organs) over many years. New research from animal models of HD have suggested that the gene mutation and consequent toxic protein can disrupt the way neurons communicate at 'synapses', thus disrupting information processing in cerebral cortex, striatum and other brain areas, needed for normal cognition and movement.

This HD gene mutation is passed on to approximately 50% of children. Therefore, genetic counselling is sought by family members before non-symptomatic individuals decide to take the genetic test. Once an individual has been found to have the expanded DNA mutation in their genome, it is not possible to predict exactly when they will develop symptoms, due to both genetic and environmental factors. A role for specific environmental factors in HD was first demonstrated in a mouse model, and more recently via an epidemiological study from Australian researchers, indicating that those who are more active (including enhanced cognitive stimulation and physical activity) may have a later disease onset. However, the roles of specific environmental factors, and potential treatments, require more investigation and are being tested with ongoing clinical trials.

HD symptoms can present as a combination of the movement disorder, cognitive problems and psychiatric symptoms. The most distinctive motor symptom is chorea, writhing 'dance-like' symptoms. The onset of overt HD symptoms is usually in mid-life (for example the thirties or forties), however it is known that around 5% of patients (those with a very long genetic stutter which can expand between generations) have juvenile onset with onset as young as a few years of age. The cognitive symptoms can include problems with memory, planning, and judgement, culminating in dementia. Psychiatric symptoms also vary between patients, with depression being the most common psychiatric conditions experience by those with the HD gene mutation.

Following adult onset (approximately 95% of cases), HD progresses for 10-30 years, although much faster in those with the childhood onset form of the disease. Late-stage disease can include problems with swallowing, speaking and walking. While there are drug treatments used to alleviate specific symptoms, there is currently no treatment which slows or stops disease progression. A large amount of research is being done with animal models of HD, to understand disease mechanisms and develop and treatments. As there is a known genetic cause of the disease, there is hope that future clinical trials will be aimed not only at stopping progression in symptomatic patients, but also bringing hope to the many families suffering from this devastating disorder.

If you want to find out more about HD, the following sites are useful:

Huntington's Australia, with advice for families and links to state HD associations,

<http://huntingtonaustralia.asn.au/>

HD Buzz, an interactive website presenting the latest HD research news to the lay community,

<http://en.hdbuzz.net/>