HUNTINGTON'S DISEASE
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Huntington's disease is a progressive neurodegenerative disorder which affects 5-8 people per 100,000 worldwide. It is a fatal, inherited disorder caused by a genetic error in the *Huntingtin* gene. The *Huntingtin* gene contains a repeated section, which is expanded in individuals affected with Huntington's disease. This section contains a cytosine-adenine-guanine (CAG) repeat, which may be repeated up to 34 times in normal healthy individuals. An expansion in this section of the gene produces a mutant protein that causes deleterious effects in the brain and also throughout the body. When this CAG section is repeated 35-39 times, individuals may develop Huntington's disease (incomplete penetrance), although this tends to onset later in life. However, when an individual has $\geq$40 repeats, they will develop symptoms of Huntington's disease (complete penetrance), and are usually diagnosed with the disease in the fourth-fifth decade of life. A child of a person with Huntington's disease has a 50% risk of inheriting the mutated gene - if the mutation is passed from one parent to a child, the child will ultimately develop the disease.

Individuals with Huntington's disease experience a debilitating 10-25 year mental, behavioural and physical deterioration prior to death. Currently, the disease is diagnosed due to the presence of involuntary muscle control deficits. People with Huntington's disease have problems with involuntary movements, because regions of the brain that control these movements become impaired, due to the dysfunction and subsequent death of neurons within these regions that control movement. As these cells stop working effectively and eventually die, this interferes with the circuitry in the brain, and messages involving movements don't occur as normal. Eventually, individuals will also have problems initiating voluntary movements. Muscle control continues to decline to the point that it affects performance of everyday activities, and will eventually render the individual incontinent and unable to swallow, speak or walk. Individuals will become totally incapacitated, confined to a wheelchair and unable to function independently. At this stage, they may be placed in an end-stage care facility, until death.

Although currently diagnosed by the presence of muscle control deficits, a wealth of emerging research, primarily from brain imaging studies, is revealing that cells in the brain may be dysfunctional and subsequently die a long time before the disease is clinically diagnosed ($>$15 years). The death of these cells underlies the mental and psychiatric components of the disease. An individual with Huntington's disease will ultimately suffer dementia. Initially, they may start to have problems with memory, and planning and organising their daily activities. They may have difficulty performing a task in the correct sequence, making appointments or paying bills. Psychiatric or behavioural symptoms include depression, apathy, lack of motivation or insight (they often don't realise that they can't do something as well as they used to), they may hallucinate or suffer from delusions and anxiety, and may exhibit impulsive, obsessive-compulsive or aggressive behaviour.

Despite the discovery of the gene responsible for Huntington's disease in 1993, which raised much hope for the Huntington's community, there is no cure for Huntington's disease and no demonstrated method to slow the progression of the disease. Patients are currently managed with pharmacological therapy to control their symptoms, however this does not stop the disease from progressing, and often these drugs produce unwanted side-effects.

It is therefore of critical importance that research continues to look for treatments that can slow the degenerative process, as well as searching for a cure, and to identify tools or methods to monitor therapeutic benefits of interventions. Brain imaging modalities are proving very informative, and have progressed our understanding of the disease process by allowing us to look inside the brain at changes that are occurring in people with Huntington's disease, even before they present with

symptoms of the disease. Interestingly, the loss of neurons in the brain more than a decade before clinical diagnosis of the disease indicates that the brain has a certain level of tolerance to this process, known as cognitive or brain reserve. It is crucial that this process is researched in Huntington's disease to help us to understand what silent processes are occurring which contribute to the disease, and when these processes start to occur. By understanding when a process of deterioration is or starts occurring, the underlying mechanisms that cause it can be explored with a view to providing therapeutic interventions capable of altering the disease course at the earliest possible stages, before the degenerative process occurs, or by limiting it before it gets too bad. Similarly, brain imaging can also be used to detect subtle neurological changes to the disease process due to therapeutic intervention.

Some promising research currently underway targets interfering with the gene to reduce production of the mutant Huntingtin protein. Drug therapies look at ameliorating biochemical pathways that are altered due to the disease, to prevent degeneration of cells or symptoms of the disease. Another very promising potential strategy to slow the disease progression and to produce neurological changes is to enhance brain stimulation via increased physical, mental and social activity. Interventions such as this that target slowing the disease will have important implications for future research, as they may maintain an individual at the best possible level should a cure be forthcoming.

Most importantly, therapies that can interfere with the disease process and slow or halt progression of the disease will provide patients with Huntington's disease and their families with dignity, hope, and a much needed improvement in their quality of life.