Huntington’s disease (HD) is an inherited neurological disease, which results in progressive loss of neurons in specific regions of the brain. Its characteristic clinical feature is the presence of involuntary movements, sometimes referred to as chorea, (Roos 2010). The first accurate medical description of the disease was given by the American physician George Huntington in 1872. The worldwide prevalence of the disease is reported to be 2.7 per 100,000 with a significantly lower prevalence in Asia relative to Europe, North America and Australia (Pringsheim et al., 2012). Following diagnosis, the mean survival time is 17-20 years with pneumonia being the most common cause of death (Roos 2010).

Genetics:

The cause of the disease was first identified in 1993 as a mutation in a gene that codes for a protein called Huntintin (Burgunder., 2014). The mutation is a dominant mutation so that children of affected individuals have a 50% chance of inheriting the disease. The disease is one of a group of diseases called trinucleotide repeat disorders. This is when a short sequence of the DNA that codes for part of the gene becomes abnormally expanded and repeated. This changes the structure of the protein that the gene codes for. Other examples of trinucleotide repeat disorders are Myotonic dystrophy, Freidreich’s Ataxia and Spinal and Bulbar Muscular Atrophy (La Spada and Taylor 2010). The number of times the DNA is repeated and expanded is related to the age of onset of disease so that those with a high number of repeats (50-60 repeats) usually have a juvenile onset (Burgunder., 2014). As the gene is inherited through the generations the repeat sequence can get longer so that the offspring may have a younger onset of disease. This is known as genetic anticipation. Genetic testing is available for Huntington’s disease and genetic counselling is available for those who are at risk.

Symptoms of HD:

Although the disease can begin at any age, in most people the symptoms of the disease do not show until the 30’s or 40’s. Only about 10% cases are juvenile onset (Roos 2010). The mutation causes degeneration of nerve cells in the striatum and the cerebral cortex, which is the area of the brain responsible for our higher order function or cognitive ability. The loss of nerve cells in these areas of the brain causes cognitive, motor and psychiatric disturbances. Characteristic motor symptoms of HD involve involuntary, jerky unwanted movements, termed chorea. These start as small muscle twitches, for example in face muscles, fingers and toes, but progress to the...
main trunk of the body and can become more prolonged. Eventually walking, talking and swallowing become problematic. Psychiatric symptoms can be present from early in the disease, often before motor symptoms and can have a negative impact on family relations. These symptoms include depression, anxiety, apathy, obsessions and later in the disease psychosis and hallucinations. Cognitive decline or dementia can also be present long before motor symptoms. Patients may lose the ability to perform goal directed behaviour and the ability to make plans and organise their life. Memory may also be impaired. Additional less well-described symptoms include weight loss and sleep disturbance.

Pathology and Pathogenesis of HD:
The genetic mutation in HD causes the Huntingtin protein to have an extra region known at the polyglutamine expansion. These parts of the protein can become cleaved off the main protein and aggregate to form inclusions (Zuccato et al., 2010). Inclusions are present mainly in specific cell types in the striatum, the medium spiny neurons. These aggregates may be toxic to the cell. The medium spiny neurons that are preferentially lost in disease normally act to dampen down neuronal excitability and so loss of these neurons may result in a toxic increase in neuronal firing, termed excitotoxicity. In addition to this toxic ‘gain of function’, loss of function of the Huntingtin protein may also contribute to the disease. The exact function of the Huntingtin protein in the cell is not completely clear but there is a lot of ongoing research in this area (Zuccato et al., 2010, Bano et al., 2010). The protein is expressed in many parts of the neuron including the nucleus, mitochondria, vesicles, and at synapses and may have multiple roles within the cell. It is expressed during development, however as most people with Huntingtons’s disease do not develop symptoms of the disease until later in life it is likely that the role of the protein in mature neurons is important in disease. There is some evidence that the protein plays a role in controlling nerve cells connections and that loss of the protein may cause a breakdown in information processing.

Treatment for HD:
At the moment there is no cure for Huntington’s disease. Treatments are available to alleviate some of the symptoms of the disease. Tetrabenazine can be used to supress the involuntary movements associated with the disease. Antidepressants (eg fluoxetine), antipsychotics (eg. Haloperidol) and mood stabilizing drugs (eg lithium) may also be prescribed. Physical Therapy and occupational therapy may also be beneficial to manage mobility problems.

Future Research.
Current research is targeting the many potential mechanisms of disease caused by the Huntingtin mutation including protein aggregation, protein cleavage, excitotoxicity, synaptic stimulation, energy impairment and transcriptional dysregulation (Reviewed in Zuccato et al., 2010). Several mouse models have been developed that mimic aspects of the disease and these will help decipher
mechanisms of disease. Determining the cell type specific function of Huntingtin protein during aging will likely provide further clues to the pathogenesis of disease and aid in the development of novel therapeutics.

References: