Huntington’s disease

Huntington’s disease (HD), also known as Huntington’s chorea, was first described in 1872 by the New York physician George Huntington. It is an inherited neurodegenerative disorder characterized by clinically progressive motor impairment, reduction in cognitive abilities and psychopathologic deficits.

Epidemiology

HD does not usually begin to manifest in an affected individual until the third to fourth decade of life and then symptoms typically progress over a period of 10 to 25 years (1). It is estimated that 1 in every 10,000 people in the United States has HD. In addition, at least 150,000 others have a 50% risk of developing HD due to the fact that a parent suffers from HD. Although HD is found in every country of the world, it is more prevalent in people of Western European descent affecting 1 per 10,000 people whereas it affects 1 per 1,000,000 people of Asian or African descent.

Clinical Significance

Early signs can vary greatly from person to person, but may include symptoms that are physical, cognitive or psychopathologic. Early physical symptoms may begin as involuntary movements of the fingers, feet, face or trunk as well as mild problems with balance and clumsiness. Overtime, they may progress to slurred speech, difficulty swallowing, eating, speaking and walking. Although most sufferers will exhibit chorea, or random uncontrollable movements, some may instead experience stiffness and slowed movement.

Cognitive symptoms may include forgetfulness and impaired judgment. These symptoms may eventually affect the person’s ability to drive, learn new skills, answer questions or make decisions.

Psychopathological symptoms such as irritability, mood swings and depression often occur early in the course of the disease and may be the first noticeable symptoms, although, some may not experience these symptoms at all. In other patients, they may lessen overtime or continue to progress into deepened bouts of depression and hostile outbursts as the severity of the disease progresses.

One common thought is that the earlier symptoms first begin to appear, the more aggressive the progression of the disease. Therefore, in the less than 10% of cases of HD that are diagnosed prior to age 20, referred to as Juvenile Huntington’s disease (JHD), the typical 10 to 25 year course may be shortened by a number of years. In individuals with JHD, death will often occur within 10 years of the onset of disease (2).

Inheritance

Until recently, very little was known about HD and therefore no diagnostic tests were available. In 1983, a team of scientists discovered the first genetic marker for HD and this discovery led researchers to the location of the HD gene in 1993 (2). The gene defective in individuals with HD is located on the short arm of chromosome 4, which is one of the non-sex-linked, or autosomal, pairs of chromosomes. HD is considered an autosomal dominant disorder because one only needs to inherit a single defective copy of the gene from either parent to be affected (Figure 1). This autosomal based inheritance makes men and women equally susceptible. Although possible, it is very rare for people to develop HD if neither parent is affected.

![Figure 1](image)

**Figure 1**: Autosomal dominant inheritance pattern in HD.
Pathophysiology

In HD, there is a trinucleotide repeat in which the CAG triplet (cytosine-adenine-guanine) repeats itself \((3, 4)\). In the general population, this CAG pattern may repeat up to 26 times \((4)\). The series of CAG triplets codes for the amino acid glutamine, therefore a series of repeats forms what is referred to as polyglutamine, also known as polyQ. When the polyQ length is less than 26 glutamines, the HD protein Huntingtin is produced. Repeats of the amino acid glutamine beyond 40, results in mutant Huntingtin. The presence of this abnormal form of the protein results in Huntington’s disease.

The protein Huntingtin is ubiquitous in the cytoplasm of cells of the brain and body. Although, the function of this protein is still not completely understood, some research reports indicate that it is involved in coordinating proteins to signal various processes and intracellular transport \((5)\). The presence of mutant Huntingtin protein causes selective neurodegeneration in neurons of the striatum and deeper layers of the cortex of the brain early in the course of the disease. As the disease progresses, other areas of the brain are affected such as the hippocampus, hypothalamus, cerebellum, amygdala and some thalamic nuclei \((5)\). Additional findings include gliosis, or the presence of scars of dense fibrous neuroglia, in the affected areas of the brain of HD patients.

Diagnosis

In patients who have not yet exhibited symptoms but have a family history of HD, presymptomatic testing can be used. The child of a parent with HD has a 50% chance of acquiring the increased number of CAG repeats and developing this disorder.

The MDL’s Huntington’s disease test provides a simple, non-invasive diagnostic test for the trinucleotide repeat expansion status in the Huntington’s disease gene \(IT-15\). This test uses conventional polymerase chain reaction (PCR) in conjunction with capillary electrophoresis to determine PCR amplification fragment lengths and assign the number of allelic CAG repeats in the \(IT-15\) gene. While most HD genetic tests are based on analysis of DNA extracted from blood, our unique \textit{OneSwab}® technology utilizes a non-invasive collection method that provides sufficient DNA quantities from a cervicovaginal swab. Genetic material can be collected during a routine gynecological exam without subjecting the patient to an additional specimen collection procedure. Upon arrival at MDL, samples are processed for genomic DNA extraction using an automated robotic platform. This extracted DNA serves as a template for enhanced PCR capable of amplification of expanded trinucleotide repeat-containing loci \textit{within the IT-15 gene}. Capillary electrophoresis possesses high resolution power in the separation of PCR fragments. Their sizing and corresponding trinucleotide repeat number assignment is performed automatically by fragment analysis software (Figure 2).

Based on the interpretive criteria recommended by the American College of Medical Genetics (ACMG), CAG triplets occurring 27 times or more are indicative of a positive result and genetic counseling is recommended (Figure 3).

MDL’s Huntington’s disease test can be used as a diagnostic test in patients suspected of having HD and currently exhibiting symptoms as well as a predictive or presymptomatic test to determine one’s status prior to onset of the disease.

References: