GENE MESSENGER

☆ **Topic:** Huntington Disease

☆ **Summary:** Informative genetic testing is currently available to individuals with clinical symptoms suggestive of Huntington disease (HD) and family members of individuals diagnosed with HD. Current research is focused on understanding the cellular basis of HD to inform future treatments and provide the basis for a possible cure.

☆ **Bottom line:** The benefits of genetic testing for HD are limited and mainly relate to the individual's perception of the psychological advantages of knowing whether he or she is predisposed to developing HD. There remains no cure or effective preventive therapy for the disease.

✓ The Disease

- A hereditary neurodegenerative disorder that affects 1 in 10,000 Canadians
- Characterized by progressive deterioration of cognitive and motor functions
- Symptoms usually begin between 35 and 44 years of age; however, the range is from childhood to over 80 years of age.
- The median survival is 15 to 18 years after onset of symptoms.
- Although HD is incurable, psychiatric and motor symptoms can be managed with pharmacological therapy.
- Inherited in an autosomal dominant manner.

✓ The Gene

- The HD gene on chromosome 4 was discovered in 1993.
- The protein produced by this gene is called "huntingtin".
- The gene contains a region of "CAG trinucleotide repeats" in which the three DNA nucleotides, Cytosine, Adenine and Guanine (CAG), are repeated over and over again.
- Each CAG trinucleotide repeat codes for a specific amino acid (glutamine) contained in the huntingtin protein.
- The CAG repeat length is highly variable in the population and the normal repeat size is usually less than 27 (median 18).
- The abnormal HD gene contains an 'expanded' number of CAG repeats (36 or more) leading to an abnormal huntingtin protein with a polyglutamine expansion (lots of extra glutamines).
- Exactly how the mutated huntingtin protein causes the symptoms of HD is unknown; however, Caspase-6 normally cleaves the huntingtin protein and evidence is accumulating that the resulting fragments of huntingtin protein containing expanded polyglutamine tracts may be toxic to nerve cells.

✓ Consequences of having a faulty gene / CAG expansion

- A man or woman with HD has a 50% chance of passing the gene with the expanded number of CAG repeats to a child.
- **> 36 CAG repeats**: these individuals will most likely develop the features of HD such as involuntary movements, abnormal gait, dysphagia, changes in coordination, cognitive decline and psychiatric disturbances (36-39 repeats causes reduced penetrance of HD features, 40 repeats and above causes full penetrance of HD features).
  - A well-established inverse correlation between CAG repeat length and age of onset exists (ie. the greater the repeat length, the earlier the age of onset); however this cannot be used to predict the exact age of onset in any one individual.
  - Adult-onset HD usually occurs when the CAG expansion is between 40 and 55 repeats whereas HD may show itself in adolescence or early adult life when the CAG expansion is above 50 repeats.

- **Between 27 and 35 CAG repeats**: These individuals are unlikely to develop any symptoms of HD (referred to as an "intermediate allele") but are at greater risk for passing on an expanded number (> 36) of CAG repeats to their offspring, particularly if the individual with this intermediate repeat number is male.
- Anticipation, the phenomenon in which increasing disease severity or decreasing age of onset is observed in successive generations, is known to occur in HD and occurs more commonly when the genetic mutation is inherited from the father because the number of CAG repeats can increase significantly when the gene is passed through a male.

✓ Who should be offered referral for genetic counselling/testing?

- Individuals with clinical symptoms suggestive of HD
- Family members of individuals diagnosed with HD

✓ Testing - for the faulty gene

- Testing of the HD gene is available in Canada for individuals showing symptoms suggestive of HD or relatives of individuals diagnosed with HD.
- As part of the genetic testing process for HD, a consultation with a neuropsychiatrist is often recommended.

✓ Benefits of genetic testing

- Assist with life planning (eg. decisions about having children, career, retirement and long-term care issues)
- Relief from uncertainty
- Increased feeling of control
- For those who test negative, relief from worry that they will develop the disease in the future and knowing that their children are not at risk of inheriting the disease

✓ Harms/limitations of genetic testing

- Currently, no medical benefit to knowing one has the HD gene mutation (ie. no cure, no early treatment)
- Adverse psychological reaction, family issues/distress
- Insurance/job discrimination, confidentiality issues
- Survivor guilt for family members who did not inherit the gene mutation

☆ **Web Resources:** **www.hsc-ca.org (Huntington Society of Canada)**
www.genetests.org (GeneTests website)

☆ **Review Article:** **Warby SC, et al. Phosphorylation of huntingtin reduces the accumulation of its nuclear fragments. *Mol Cell Neurosci* 2009;40(2):121-7.**
Mestre T, et al. Therapeutic interventions for symptomatic treatment in Huntington's disease. *Cochrane Database Syst Rev* 2009;(3):CD006456.

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GenetiKit KNOWLEDGE IN TRANSLATION

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