

Huntington's disease and testing for it

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Huntington's disease is an autosomal dominant (Harper et al, 1991) neurodegenerative disorder characterized by involuntary movements, cognitive loss, and psychiatric problems as described by Martin and Gusella (1986). These symptoms are related to the death of medium spiny projection neurons in the caudate nucleus, putamen, and the cortex (Reiner et al, 1988). In later stages of the disease, even areas such as the hippocampus and hypothalamus gets affected as well (Kassubek et al, 2004). Huntington's disease has a prevalence rate of approximately 1 in 10, 000 Caucasian populations (Harper et al, 1991).

Patients with Huntington's disease most typically display a choreic movement disorder involving involuntary writhing movements observed by George Huntington himself. The age of onset of Huntington's disease seem to be normally distributed around the average age of 35 to 42, with small number of cases developing in patients younger than 20 years of age or older than 60 years of age (Andrew et al, 1993). The majority of juvenile patients, whose disease onset are at age 20 years or less, have inherited the paternally defected gene (Andrew et al, 1993).

Patients usually died within 15 to 20 years of disease onset. Gusella et al (1983) first determined the location of the genetic mutation in Huntington's disease to be the short arm of chromosome 4. It was after another 10 years did the researchers of The Huntington's Disease Collaborative Research Group (1993) able to discover that a gene in chromosome 4 containing a trinucleotide repeat of CAG was abnormally expanded in diseased individuals. The IT15 (interesting transcript 15) gene, dubbed the huntingtin gene by the group, codes for the huntingtin gene.

This CAG repeat, which translates into a poly-glutamine stretch, is highly polymorphic among the population ranging from 11 to 34 copies on normal individuals. However, in individuals with Huntington's disease it expanded to more than 42 repeats and increasing to upwards of 100 (The Huntington's Disease Collaborative Research Group, 1993). This provides evidence showing that the mutant huntingtin protein seems to be toxic to its native cells and confers a disease state to individuals with an extended length of repeats. There is also a correlation between the CAG length and disease onset as shown by Andrew et al (1993).

The mutated elongated huntingtin protein is cut by enzymes into fragments and the fragments begin to form abnormal clusters, neuronal intranuclear inclusions (NIIs), inside cells. These clusters can also act to recruit normal proteins to adhere together as well (Davies et al, 1997). This was originally thought to cause the pathogenesis of Huntington's disease. However, more recent studies have shown that the presence of NIIs is actually a coping response to the toxicity of mutant huntingtin proteins and acts to prolong the life of the cells and reduce intracellular mutant huntingtin in neighbouring neurons (Arrasate et al, 2004).

The exact function of the wild-type huntingtin protein are unclear, however many efforts have been made in understanding its native functions. Nasir et al (1995) showed that homozygous huntingtin homologs in mice died before embryogenesis could occur and that heterozygotes displayed similar deficits as diseased human patients. Wild-type huntingtin is also crucial for establishing and maintaining neuronal identity, especially in cortex and striatum (Reiner et al, 2001).

Current data can provide the conclusion that normal huntingtin protein has actions important for development in mammals. In vitro, wild-type huntingtin have been shown to act to protect brain cells from apoptotic stimuli, such as serum deprivation, mitochondrial toxins, or the transfection of death genes (Cattaneo et al, 2005). Wild-type huntingtin protein, not mutated, stimulates brain-derived neurotrophic factor (BDNF) production by acting at level of Bdnf transcription. BDNF is very important for survival of striatal neurons (Cattaneo et al, 2005).

Intracellularly, huntingtin protein has been found to associate with various organelles such as the nucleus, endoplasmic reticulum, and Golgi complex (Cattaneo et al, 2005). It has also been found in neurites and at synapses, where it associates with vesicular structures and microtubules (Li et al, 2003). This characteristic has been shown to enhance vesicular transport of BDNF along microtubules (Gauthier et al, 2004). On a similar note, huntingtin interacts with a number of cytoskeletal and synaptic vesicle proteins that are essential for exo- and endocytosis at synaptic terminals.

Wild-type huntingtin binds directly to the Src homology 3 domain of postsynaptic density protein 95, which binds NMDA and kainite receptors. This activity is decreased in mutant proteins and can lead to overactivation or sensitization of NMDA receptors (Cattaneo et al, 2005). Aside from the toxicity of the mutated huntingtin protein, the loss of normal huntingtin protein also seems to add to the pathogenesis of Huntington's disease. Presence of only mutant huntingtin protein results in massive apoptotic cell death in the testes of male mice (Leavitt, 2001).

However, no apoptosis can be seen in testes of mice expressing human mutant huntingtin when wild-type huntingtin is expressed as well (Leavitt, 2001). It was also seen that in mice, the absence of wild-type huntingtin protein led to a worsening of striatal atrophy and neuronal loss, and a significant decrease in neuronal cross-sectional area compared to mice that had wild-type huntingtin present (Cattaneo et al, 2005). Huntington's disease still remains incurable to this day. However, many treatments are available for treatments of its symptoms.

Chorea, the hallmark of the disease is a major target for many treatments. Such drugs include dopamine-depleting agents, dopamine antagonists, benzodiazepines, glutamate antagonists, acetylcholinesterase inhibitors, dopamine agonists, antiseizure medications, cannabinoids, lithium, deep brain stimulation and fetal cell transplantation (Frank and Jankovic, 2010). One notable drug currently in use is Tetrabenazine, which is the only US FDA-approved drug for treatment of Huntington's disease (Frank and Jankovic, 2010).

The drug acts by reversibly inhibiting the central vesicular monoamine transporter type 2, this cause a depletion of dopamine (Bagchi, 1983). The main area of effect for tetrabenazine is in the caudate nucleus, putamen, and the nucleus accumbens, all areas known to be responsible for the major pathology of the disease. The Huntington Study Group (2006) was able to demonstrate the efficacy of tetrabenazine in a double-blind, placebo-controlled trial. Subjects who received tetrabenazine showed a change from the baseline in the maximal chorea score of the UHDRS.

Compared to the baseline, treatment resulted in a reduction of 5.0 units in chorea compared with a 1.5 unit reduction for the placebo group. A second symptom targeted for treatment to allow patients to function normally is the psychiatric problems. Dopamine receptor blocking agents are commonly used as anti-psychotics in order to treat psychosis associated with Huntington's disease (Frank and Jankovic, 2010). There are many ethical issues that have been associated with Huntington's disease patients, in particular pertaining to the application of genetic testing.

The expanded CAG repeats associated with Huntington's disease (Gusella et al, 1983) are used as a predictive testing to determine the risk of a person for developing inherited HD gene. The debate of ethics with respect to genetic testing for Huntington's disease seems to lie on several major factors including: autonomy, beneficence, confidentiality, and justice (Huggins et al, 1990). The question remains whether or not the current use of genetic predictive testing is ethical. Autonomy refers to the respect for the individual's right to make an informed decision about an action that may have a profound effect on his or her life.

The patients should feel no pressure from physicians or institutions with regards to their decision for genetic testing. Also, they should also have a full understanding of the consequences and implications of their decisions. This would require physicians to provide all the necessary information to the patients so that they are informed about the testing. If a woman refuses to get tests done for her baby even though her relatives are with her insisting on getting it performed, the physician cannot allow the testing to be performed.

Beneficence is summarized by the phrase “first do no harm” (Huggins et al, 1990). This is an important factor when the results of the test may reveal genetic information about oneself. This implies not only avoiding harm to patient but also preventing harm to other individuals, which may include family members of patients. Due to the genetic characteristics of Huntington's disease, family members can be both directly and indirectly influenced by the results of the test.

If for example a pregnant woman decides to get an ultrasound for her baby in order to find out if the baby has spina bifida, and upon confirmation by the physician decides that she wants to give birth at home as opposed to in a hospital where the baby could be treated correctly in order to minimize the risk of the disease. The physician should take any action he can in order to avoid any risk to the health of the baby. Confidentiality with genetic tests applies the same as with any other form of personal information. It should not be disclosed to any other third parties, which includes family members as well.

For example, if two siblings were to go and receive a CAG repeat test at the same time and one sibling asks the physician about the results of the other sibling. The physician cannot disclose any information or they will violate the confidentiality of the patient. Justice simply means equal access to health services and information to all. This also includes long-term support and guidelines for testing as a medical service so that the service is not difficult to obtain if needed. For example, even though Cystic Fibrosis is mostly only prominent in Caucasians, the testing should still be offered to pregnant women of other ethnicities as well. Other ethical dilemmas still exist with

current genetic testing technologies. One particularly pertaining to Huntington's disease is whether or not the information is obtained even though there is no cure for the disease. In diseases such as phenylketonuria (PKU), after newborn screening, dietary interventions will allow the individuals with the condition to lead healthy and normal lives (Lea et al, 2005). However, for Huntington's disease, even after knowing that the disease will affect the individual what can be done?

Therefore, would it be better to not know at all? By testing and finding out that an individual has the mutation that will eventually lead to the development of Huntington's disease, the individual can attend to the initial development of symptoms and as a result may be treated much earlier. This can result in a more favourable prognosis. Similarly, the individual can live more cautiously as to prevent further exacerbation of their condition. On a more subjective level, the individual may use the knowledge to live a more fulfilling life knowing that he or she may not live as long as the rest of the population.

Conversely, the information can also be used negatively. There can be a lot of discrimination in terms of applying for employment and health insurance. This information would also impact the ambition and life goals of the individual, the amount of psychological harm that comes with eventually developing an incurable and lethal neurodegenerative disease is extremely large. Similarly, would they still pursue to have a family and children if they knew that they had a very high risk of dying at a young age? This particular issue should be resolved by following the ethical factors listed before.

As long as the individual is informed, are being prevented from harm, information not shared with any third party members, and has access to healthcare services, then being tested for Huntington's disease will be ethically correct. This knowledge will give them insight on how to live the rest of their life.

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