

HUNTINGTON'S DISEASE

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“Nurture may be as important as nature in complex diseases such as hypertension, but sometimes a single stuttering gene is enough to kill you.” says The Economist magazine(7). Huntington's disease(HD) is a fatal brain disorder caused by an autosomal dominant mutation. This simply means that there is a fault which is not to be found in the sex determining chromosomes. The location of the mutated gene has recently been identified along with discovery of Huntingtin-associated protein(HAP-1). Although the function of in huntingtin protein is not known, researchers continue to study the effects of HD and the methods to detect the disease. With all the discoveries and findings concerning HD, there is still no cure for the disease.(7)

Mutations that cause HD occur at the unstable segment of DNA in a previously unknown gene. This gene codes for a protein called “huntingtin.” When this gene was discovered it was labeled IT15 for interesting transcript number 15. Researchers observed that the stuttering, a section of a gene that repeats itself, occurs in the gene IT15 of the HD patients. The stuttering part is comprised of CAG bases. Since CAG codes for glutamine, HD patients have a gene IT15 product contains an elongated chain of glutamine residues.(5) In normal people the protein contains six to thirty seven glutamine residues. However, the HD gene product has forty to one hundred glutamines on the N-terminus. It was determined that the number of these repeating units is inversely related to the time of onset. The greater the number of CAG repeats, the earlier the disease begins. With forty repeating units of CAG, the onset of the disease is likely to be delayed until middle age. However, with fifty or more repeating units of CAG, symptoms can appear in a person's teens or even in infancy.(3)

Although patients with a high number of CAG repeats may exhibit symptoms early, HD usually appears during middle age with mood and personality changes. Patients with HD can progressively suffer from wild movements of the limbs and mental retardation. The progressive declining cognition and worsening of the movement disorder can lead to death. Usually, death results 18 years from the time of onset.(1)

HD is a dominantly inherited disease. The inheritance of chromosome 4 from either the mother or the father is likely to be damaging because chromosome 4 is where excess repeats of CAG occurs. It has been observed that each successive generation of HD patients has a reduced age of onset and an increased severity of the disease. This is due to the fact that the CAG repeats increase with each successive generation of HD patients, (1)

Knowing that the increase of CAG units contributes to the severity of HD does not explain how the elongation CAG affects the severity of HD. The explanation of CAG expansion is not readily available due to the fact that the function of huntingtin protein is still unknown. Therefore, it is difficult to explain the effect of the expansion of the CAG units. However, there are three possible explanations for how the excess of CAG units causes HD. The first possible explanation is that the elongation of CAG unit might increase the activity of huntingtin protein above its normal level, with harmful consequences. The second possible explanation is the huntingtin protein in HD might have a dominant negative effect. This means that the stretch of CAG units inactivates its normal counterpart and thereby reduces or eliminates the normal activity of the protein. The third possibility is that the huntingtin protein in HD might interact with another cellular component to cause other activity different from the normal activity of the huntingtin protein. (1)

The first and second possibilities require the knowledge of the normal of huntingtin protein and its crucial role to particular neurons. The third possibility does not require on the knowledge of the normal function of the HD gene product. The new interaction caused by the change in huntingtin might be one that can occur only in the target neurons. This could be completely unrelated to the normal activity of huntingtin protein. It is possible that the huntingtin proteins in HD patients may still carry out its normal function while the new function or functions created by the expansion of CAG repeats. The new funtions of HD huntingtin may interfere with or alter some unrelated cellular process in selective cells or during some special stage of development.(1)

A hypothesis suggests that the elongation of CAG units HD gene induces a toxic gain of function. This toxic gain of function is perhaps a result of interactions with other cellular proteins. Mduyo et al studied the inactivation of the Hdh gen in a mouse with HD. The Hdh gene is a homolog to the human HD gene. This study is called "Inactivation of the Mouse Huntington's Disease Gene."(4)

In order to differentiate between the loss of function and the gain of function, the study mentioned above generated an inactivating mutation of the mouse Hdh gene. The study proposed that if HD involves in the loss of function, the heterozygous(one HD carrying allele and one normal allele) gene for Hdh to be phenotypically normal and the mice homozygous(both alleles are mutated) of huntingtin gene to mature and manifest HD-like neuropathology.

Alternatively, if HD is caused by the gain of function, neither the heterozygous nor the homozygous Hdh would exhibit HD-like neuropathology. The gain of function may produce a entirely different phenotype(expressed traits) controlled by huntingtin's normal physiological role. The study shows that mice heterozygous for Hdh were phenotypically

normal whereas the mice homozygous for Hdh died. However, the study also reports that Hdh inactivation does not closely resemble adult HD neuropathology. From this, the study suggests that the human disease involves a gain of function.(6)

The gain of function is caused by the elongation of CAG repeats in HD results in neural loss. Although huntingtin protein is produced in other tissues, the damage is done in two parts of the brain, the basal ganglia and the cortex. Since the huntingtin protein is produced everywhere on the body, why does the mutation only affect the brain? One of the possible answers can be explained with a discovery of protein that binds specifically to huntingtin in rats. This protein is called HAP-1 for Huntingtin-associated protein. The studies of rHAP-1 (rat huntingtin-associated protein1) suggest that only the brain tissue makes HAP-1.(4)

A group of researchers led by Christopher A. Ross of the John Hopkins University School of Medicine in Baltimore discovered rHAP-1. They experimented with the rat brain and found that the rHAP1 binds to huntingtin protein of rats. In addition, they discovered that the rHAP1 binds tighter to the mutated huntingtin protein with many repeating units of glutamine residues. The researchers speculated that the human version of HAP-1 would act in similar manner.(6)

Another advance in the study of HD is the discovery of an antibody that seems to bind only to forms of huntingtin that have 40 or more glutamines. This antibody was identified by a French group headed by Frederic Saudou of the University of Strasbourg. Saudou suggested that “at a certain threshold of glutamine repeats, huntingtin and the two other proteins undergo a change in shape.” This transformation allows the antibody to bind to the mutant proteins and this binding may provide a clue as to why it causes HD.(4)

Another irregularity that HD patient may possess is the invariable repeat of CCG. CCG is another unit of the sequence of huntingtin protein. CCG, which codes for the amino acid

proline, is the trinucleotide repeat that immediately follows after the CAG repeats in the huntingtin gene. The number of repeats of CCG varies in normal people. This variability is called polymorphism. A study done by the University of British Columbia shows that in normal people the huntingtin gene can contain 7,9,10,11 or 12 CCG repeats. The study showed that the majority of HD patients invariably had 7 CCG units. The report suggests that polymorphism of the CCG repeat helps to determine the stability in the CAG repeat.(3)

In the past, a CCG repeat was used along with CAG repeat for primers for CAG trinucleotide assessment. These prior estimates of CAG size were determined based on the assumption that the CCG repeat invariably had 7 triplets. It was recently shown, as previously mentioned that CCG repeats are polymorphic, ranging from 7 to 12 triplets. This variability in the CCG repeats would have particular significance in the assessment of persons estimated to have 36 to 42 CAG repeats.(4)

This method of determining the CAG repeats in HD patients was initially used in Berry Kremer's study of worldwide of Huntington's Disease Mutation and the sensitive and specificity of measuring CAG repeats. After determining that the assumption of the invariability of CCG repeats was invalid, the study did a more precise assessment of the number of CAG repeats by excluding the CCG repeats from the primer.(1)

The worldwide study of HD mutations reports on 1007 patients who had signs and symptoms HD. Of these HD patients, 995 had excessive CAG repeats. These HD patients belonged to 565 pedigrees and 43 different national or ethnic groups. The study also mentions that there are no observed differences in allele size in different national or ethnic groups. However, the statistics in this study show that the median number of CAG repeats in affected black South Africans, Chinese, Japanese, Saudi Arabian, Native American

descent decreases respectively. This statistical analysis did not include a large enough sample size to absolutely determine the pattern of CAG repeats of different ethnicities.(2) Regardless of race, the “stuttering” gene strikes at people whose parents are or were carrying HD or potential HD gene. The understanding of HD has been advanced by the discovery of the location of the chromosome 4 in 1983. Further advancement has been successful in 1993 with the discovery of the CAG repeats on the gene IT15. With these two discoveries, the study of HD is more promising than before.(1,3)

In addition to the known location of the affected gene, researchers also found that the gene codes for the huntingtin protein. Although the function of the normal huntingtin protein is unknown, researchers have studied affected huntingtin in mice and found that HAP-1 binds more tightly to mutated huntingtin protein than in normal protein. A different study of mice suggests that HD is a result of a gain in function when excess CAG repeating unit occurs. Since other body tissues also produce huntingtin besides the brain, it is difficult to explain why the expansion of CAG repeats in huntingtin only affects the brain. Because of the discovery that HAP-1 is only produced in the brain in the mice study, it helps explain why HD is a neurodegenerative disease. As of now, there is no cure for HD. Jean-Louis Mandel of the INSERM laboratory at Illkirch, France said, “Any drug will have to work by knocking out the dysfunctional huntingtins while leaving the functional ones alone.”(7)

References

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