

# Huntington's Disease: A Neurodegenerative Curse

Indra Pratap Singh<sup>1</sup>, Yashwani Singh<sup>2</sup>

<sup>1</sup>Assistant Professor, Department of Biotechnology, KSVCEM, Bijnor, India

<sup>2</sup>Student, Department of Biotechnology, KSVCEM, Bijnor, India

**Abstract:** Huntington's disease: A fatal neurodegenerative disease. It was initially described by Dr. George Huntington. Huntington's disease is an autosomal dominant inherited disorder which means that it can be transferred from the parents to their children. Generally prevalent in the European populations unlike the Asians, it destroys the patient's motor, cognitive and psychological skills resulting in symptoms like memory loss, loss of control over muscles, jerky movements, depression and suicidal thoughts. Huntington's disease can be diagnosed though its diagnosis depends upon the symptoms, it can also be detected by genetic testing. The treatment of Huntington's disease include the treatment of symptoms related to it but its root cause is not yet curable, which is the mutation on chromosome number 4 as a result of which production of a toxic protein starts because of which the brain cells starts degrading. Some techniques such as gene therapy, gene editing, and stem cell therapy can be employed in the treatment of Huntington's disease.

**Keywords:** Huntington's disease Juvenile HD and Medical diagnosis

## 1. Introduction

The disease is named after him as HUNTINGTON'S DISEASE. HD affects specific brain areas, mainly the striatum and cerebral cortex resulting in disorders such as motor, cognitive, and psychiatric disorders. Huntington's disease is an Autosomal Dominant inherited disorder that means presence of only one copy of the defective gene in a person's genome causes HD. The mutation responsible for HD is on "chromosome number 4". People suffering from HD are born with the mutated gene but the symptoms are visible at 30-50 years of age, but in some cases, the symptoms start at an early age i.e. 17-20 years hence it is known as "Juvenile HD". Initially the symptoms are mild, but progressively become worse. The brain starts to accumulate protein that is toxic to the nerve cells and hence eventually leads to the degeneration of the nerve cells. Huntington's disease degenerates brain's neurons, it degenerates brain cells, reduces the ability to perform common activities such as walking, thinking, remembering etc. The progeny of a carrier parent would have the probability of inheriting the disease and the offspring with mutated gene would suffer from this disorder.

*Juvenile HD:* It can be defined as the early onset form of the fatal "neurodegenerative" Huntington's disease that is, it is the

HD, which have an onset during the early age of a patient (approximately 20 years of age). Juvenile HD begins either in the childhood or in the adolescence. This disease has a rapid progression once the symptoms begin to be visible.

### A. Cause

The gene responsible for HD is IT15 and is present on short arm of chromosome 4. The IT15 alleles have a section of CAG (Cytosine- Adenine-Guanine) repeats and these repeats codes for amino acid i.e. Glutamine. Huntington's disease is caused by the elongation of these CAG (trinucleotide) repeats. It is absolutely normal if the number of CAG repeats vary individual to individual. Usually the number of repeats is always less than 36, which is a normal case and HD is not caused in this case. But if the number of repeats is 36 or more than 36 on the short arm of chromosome 4 then HD is caused. If an allele contains between 10-35 CAG repeats then the allele is normal, whereas a mutated allele contains 36 or more than 36 CAG repeats. The longer the CAG repeats, the earlier will be the onset of the HUNTINGTON'S DISEASE. The mutation in the Huntington gene causes the production of a defective protein, this defective protein when gets accumulated results in degradation of brain cells. Huntington's disease is an autosomal dominant inherited disorder, thus the major cause of HD is inheriting the mutated gene from affected as well as from carrier parents. As it is an inherited disorder which means if either of the parents are carrier or affected by HD then there are 50% chances that the children of that parent would be affected by Huntington's disease. However, if neither of the parent is affected nor carrier of HD then the children would not be affected by HD also male and female both have equal chances of inheriting the disorder. Huntington's disease does not skip generations, which means that if the one of the parents is affected then there will be 50% chances that each offspring would inherit the gene of HD and if the offspring would not inherit the disorder then they will not pass it on to their coming generations. Thus, it can be concluding that the main causes of the HD are its hereditary prevalence and the geography and ethnicity of the affected population however, the onset of disease is caused by the presence of elongated CAG repeats and age of onset depending upon the length of the elongated CAG repeats.

### B. Symptoms

The symptoms of Huntington's disease arise between the ages of 30-50 years. The person suffering from HD dies at an average time span of 15-20 years after the symptoms are first observed. Huntington's disease causes undesirable alterations in the normal motor (movement), cognitive (processes involved in acquiring information) as well as psychiatric (mental) functions. The symptoms of HD are listed below:

- *The motor symptoms include:* Clumsiness, difficulty in maintaining body balance, tremor (jerk movements), chorea (writhing movements), muscle rigidity/dystonia (muscle contracture), abnormal eye movements, impaired posture, difficulty swallowing, difficulty with speech, and gait (manner of walking).
- *The cognitive symptoms include:* Difficulty in learning, slowness in generating thoughts, difficulty finding words, actions without thinking, lack of focus, problems with focus, and repetition of a particular gesture/perseveration.
- *The psychiatric symptoms include:* Social withdrawal, depression, altered sleep pattern, change in appetite, hopelessness, suicidal tendencies, irritability, feeling of worthlessness, anxiety, fatigue, loss of energy and insomnia.

### C. Diagnosis

Medical diagnosis of HD can be made by physical analysis, which includes analysis of the disorders associated with motor, cognitive, and psychiatric functions as a whole. The diagnosis can be made by observation of occurrence of the symptoms associated with HD. The physical symptoms are observed for the identification of HD. Genetic test is possible for counting the number of CAG repeats in each HUNTINGTON allele. The diagnosis of HD is generally based upon the observation of occurring symptoms associated with HD along with observing the family history of the individual suspected to be affected by HD and for confirmation Genetic testing can be performed. For identification of presence of HD in an embryo, prenatal testing through amniocentesis can be performed within 14-18 weeks of pregnancy, the amniotic fluid is tested for signs of HD mutation. The current standard for standard for diagnosing HD in a person is its DNA determination, which would give an account of presence of elongated CAG repeats on HD gene on chromosome number 4 in the particular person's genome.

### D. Cure

Currently there is no cure of HD as well as for reducing its effects. But treatments such as drugs, physiotherapy, and talk therapy can be useful in maintenance of the symptoms associated with HD. Counseling and physical therapy can be useful in improving the conditions as a cause of HD. Physical therapy can be useful in improving the muscle functions and muscle strength and counseling can be useful in improving the problem solving and decision making ability as well as aiding the behavioral changes but these treatments don't assure

extinction of HD in the individual suffering from it. The possible cures for HD are briefly discussed below:

## 2. Gene Therapy in the treatment of HD

What is Gene Therapy? Gene therapy is the introduction of normal genes into cells in place of missing or defective genes in order to correct genetic disorders.

*Gene therapy for HD:* The neurodegenerative disease HD does not have any cure yet but gene therapy can aid the treatment of HD.

### A. Current Research

#### 1) AMT-130 gene therapy product

uniQure a gene therapy company discovered in 1998 based in Amsterdam (Netherlands), is developing a gene therapy product AMT-130 for treatment of fatal neurodegenerative disorder HD. AMT-130 gene therapy product consists of a recombinant AAV5 (adeno-associated virus type 5) vector which are being investigated and employed in the gene transfer to central nervous system neuronal cells. AAV are members of the parvovirus family and they have in common a similar size, structure, and dependence on a helper virus for replication and gene expression. AMT-130 consists of a vector AAV5, which carries an artificial micro-RNA specifically, designed to silence the Huntington gene. The goal of this therapy is to inhibit the production of mutant Huntingtin protein (mHTT). A study was performed on animal models via uniQure, the results of which were that the mHTT was notably reduced by a median of 68% in the striatum and a median of 47% in the frontal cortex at 6 months after the administration of AMT-130. Thus the uniQure is going to become the first AAV gene therapy for the treatment of HD.

## 3. Gene editing in the treatment of HD

What is Gene editing?

It is a group of technologies that enables scientists to change an organism's DNA and for that, genetic material can be added, removed or altered at specific locations in the genome.

### A. CRISPR technology in HD treatment

CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats and is a family of sequences of DNA in the genome of prokaryotic organisms (such as bacteria and archaea). The therapies based on CRISPR technology have the ability to treat various ranges of diseases including HD. CRISPR can inactivate the defective gene resulting in inhibiting its products. Thus the CRISPR can be employed to add, remove or alter the Huntington gene thus resulting in the inhibition of accumulation of Huntington protein. The targeted DNA cutting capabilities of CRISPR along with short sequences of RNA (guide RNA) paired with a complementary DNA sequence can be used to target almost any kind of genetic sequence. Cas9 enzyme (RNA guided DNA endonuclease enzyme) possesses the ability to cut both strand of a DNA sequence of interest at a specific site. Thus the pair of guide RNA and complementary

DNA sequence coupled with Cas9 can be employed to edit the mutated gene of HD.

A study published in the Journal of Clinical investigation was performed on mice, these mice was a genetically engineered one to possess the HD. When these mice became 9 months old they started developing symptoms of HD, which were impaired movements. The team performing this study implemented CRISPR to alter the genes of the mice. However, the HD was not cured but it resulted in the improvement of the prevalent condition. The method of this study was the injection of the code for cure of HD in to the brain of the mouse (the part of the brain aimed was responsible for controlling movements) in the form of a virus (AAV- Adeno Associated Virus). This technique can prove to be one of the most effective cures for HD and many other genetic disorders. But to use this kind of genetically altering techniques it is necessary for the researchers to be cautious before employing these techniques as a slight alteration of a wrong gene can result in the development of undesirable birth defects.

#### 4. GENE silencing

Other measure that can be employed in treating HD on gene level is Gene silencing. Gene silencing can be used to switch off the mutant gene which is responsible for the production of huntingtin protein. Switching off the mutant gene can lower the production of huntingtin protein which would in turn result in lowering the effects of Huntingtin protein.

##### A. Stem cell therapy

For the treatment of HD by stem cell therapy, modified neural stem cells are required that are capable of resisting the progression and the treatment of the symptoms associated with HD. These modified neural stem cells are isolated from the human embryonic stem cells. The clinical trials for stem cell therapy in the treatment of HD are underway. The stem cell therapy can be useful in the development of the desired neural stem cells that can be used to replace the neural cells that are degraded by the onset of HD and can help in the treatment of defects being developed as a result of HD.

##### B. Epidemiology of huntington's disease

The epidemiology of HD depends on its cause that is the elongation of the CAG repeats thus making a difference in the prevalence of diseases among different individuals depending upon the number of CAG repeats. Prevalence of HD also depends upon the ancestry, geography and differences in the ethnicity of the populations varying from each other. HD can be detected by studying physical, mental and behavioral changes altogether with the studies at genetic level. The studies have found that the prevalence of HD is mostly found in the European populations because of their ancestry unlike the other living populations that is there is a significant difference in the commonness of HD in the European population and other populations. This could have been a result of ancestry. Molecular studies are being used to find out the causes of these

kinds of variations of presence of HD among the different populations. There is a lower chances of prevalence of HD in the Asian populations whereas in the Australian, American and European populations widespread of HD has subsequently increased in the past 50 years (according to studies). HD is rarely found in Japan whereas it shows a high commonness in the Eastern population i.e. 4-8 per 100,000 and HD is found to be common in Central Asia and India. In the Caucasian population widespread of HD is estimated at 1 per 20,000- 1 per 10,000. Common prevalence of HD is 1-9 per 100,000. HD affects approximately 1 per 10,000 people in the United States.

##### C. Future of HD treatment:

There is no direct treatment for the root cause of HD but the treatments available today are basically the cure of symptoms of Huntington's disease. The cure for HD is mainly focused on reducing the production of the mutant protein that is the cause of HD, to understand the cause that makes brain's nerve cells vulnerable to HD, and substitution of the damaged nerve cells. This can be done by;

*Gene therapy*- this can be done by introducing the gene responsible for producing normal Huntington protein.

*Stem cell therapy*- this can be useful in the replacement of the degraded nerve cells with those nerve cells that are produced by the process of stem cell therapy.

*Improving the survival of nerve cells*, this can be done by studying the causes and activities leading to the death of the nerve cells in the brains of the patients affected with HD.

*Development of drugs*- Clinical trials (of the drugs for HD) include the drugs, which can be helpful in the cure of the symptoms related to HD, and also in the resistance of the production of mutant protein (resulting in slowing down the advancement of HD).

The HD was initially characterized by the American physician George Huntington, however it was approximately 50 years ago came in to light and have become an area for research as it is found to be one of the most cruellest and fatal autosomal disorder which do not have any cure yet. But the researchers today not only focus on curing the symptoms but also on the treatment of the causes of HD basically on the gene level. The ways discussed above can prove to be the ways which can be used in the future to not only cure the symptoms but also the causes and hence can be helpful in resisting the prevalence of this fatal neurodegenerative disorder in the future generations. After several decades there is a ray of hope for the patients suffering by HD in the form of gene therapy, CRISPR, and stem cell therapy. And a clinical trial aiming the mutant gene responsible for HD is ongoing and it has shown lowering the amount of toxin protein produced by it as initial results.

#### 5. Conclusion

It can be concluded that though HD have been a prevalent fatal neurodegenerative disease with no known treatment, with the current work and research in genetic engineering prove to

be an aid in finding the cure for HD i.e. helpful in detection, early cure of not only symptoms but cause of HD. The discovery of the gene responsible for Huntington's disease in 1983 has resulted in the introduction of a new era in the history of Huntington's disease and has paved the way for the various researches in the field of developing a permanent cure for this fatal neurodegenerative disorder. If we consider the ongoing research work for the development of cure for Huntington's disease then we can say that we are quite near in finding ways to cure this fatal disorder. Various techniques developed for the probable treatments of Huntington's disease are undergoing trials (on the animal models) and the preliminary results obtained from them are quite satisfying but still researchers have to be cautious about practicing these techniques on the humans (patients) as the techniques generally work at genetic level so there are chances of undesired alterations in the gene that could result in birth defects. On a positive note, in the future we could be able to find the drugs and techniques that can be employed for permanent treatment of HD and can save the life of many.

#### Abbreviations

- HD: Huntington's Disease
- CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats
- AAV: Adeno Associated Virus

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