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REVIEW ARTICLE

# Huntington's Chorea—a Rare Neurodegenerative Autosomal Dominant Disease: Insight into Molecular Genetics, Prognosis and Diagnosis

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**Abstract**
Huntington's disease is a neurodegenerative autosomal disease results due to expansion of polymorphic CAG repeats in the huntingtin gene. Phosphorylation of the translation initiation factor 4E-BP results in the alteration of the translation control leading to unwanted protein synthesis and neuronal function. Consequences of mutant huntington (mhtt) gene transcription are not well known. Variability of age of onset is an important factor of Huntington's disease separating adult and juvenile types. The factors which are taken into account are—genetic modifiers, maternal protection i.e excessive paternal transmission, superior ageing genes and environmental threshold. A major focus has been given to the molecular pathogenesis which includes—motor disturbance, cognitive disturbance and neuropsychiatric disturbance. The diagnosis part has also been taken care of. This includes genetic testing and both primary and secondary symptoms. The present review also focuses on the genetics and pathology of Huntington's disease.

**Keywords** Huntington · CAG repeats · Neurodegenerative · Pathogenesis · Aetiology

## Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by the expansion of polymorphic CAG repeats in huntington (Htt) gene. This disease is named after George Huntington as he was the first person to describe adult HD. Juvenile HD characteristics are different from that of adult HD. Mutations in the genes that code the transcription factors which regulate the expression of Htt gene lead to neuronal loss. It is hypothesised that expansion of glutamine (poly Q) repeats in huntingtin protein leads to the development of aggregates. Transcription factors (TFs) like p53, Sp1 and NFkB play important role in it. TFs

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are prevented from performing their assigned work which lead to the loss of function of TFs. Symptoms of Huntington's disease are—difficulty in concentrating and memory lapses, depression, stumbling, clumsiness, mood swings, personality changes and problem in moving. HD usually expresses itself between 30 to 45 years. Mutant Htt gene (mHtt) represses p53 activity resulting in a hypo function of p53 in HD [1]. But the level of p53 is increased in few models of HD as well as in infected tissues of HD patients; it may be due to post transcriptional and post translational modifications [2, 3]. A study showed that promoter of Htt gene and p53 interacts which harbours multiple p53 response elements [3].

Translation initiation factor 4F (eIF4F) controls the protein synthesis; it is composed of the cap binding protein eIF4E, RNA helicase eIF4A and the scaffolding protein eIF4G which recruits mRNA to the ribosome. The main regulator is 4E-BP (binding protein) which inactivates eIF4E. Phosphorylation of the binding protein blocks its association with eIF4E resulting in altered translational activities which leads to aberrant protein synthesis [3–6].

The function mutant Htt gene is not fully known. In order to understand it clearly, generally co-immunoprecipitation studies, analysis of components of Htt aggregates are done by Y2H assays. These studies enabled us to understand the cellular role of Htt which include vesicular transport, cytoskeletal organisation and post-synaptic signalling [7, 8].

## Aetiology of Huntington's Disease

One of the main causes of HD is CAG repeat mutations. CAG plays a very significant role in the evolution of the HD. There are various factors responsible for the progression of the disease such as CAG instability, CCG repeat polymorphism and CAG tract sequence.

## CAG Instability

CAG repeat mutation when passed from one generation to another is not stable over generations. This instability brings in a lot of variations in the pattern of progression of HD. There are numerous factors which affect CAG instability such as CAG repeat length, gender, age of the person having HD and CAG repeat size range.

### CAG Repeat Size:

Huntington's disease is caused due to mutations in the Htt gene (mHtt), which leads to the formation of an unstable CAG expansion in the huntingtin gene which is located in exon-1 on chromosome 4 (4p63) [9]. The number of CAG repeats varies between 6 and 35 in a normal individual, while in persons affected by HD, number repeats are usually more than 40. The Htt gene provides instructions for making a protein called huntingtin. People with 36 to 39 CAG repeats may or may not develop the signs and symptoms of HD, while people with 40 or more repeats usually develop the disorder. An increase in the size of the CAG segment leads to the production of an abnormally long version of the huntingtin protein. The elongated protein is divided into smaller fragments that bind together and accumulate in neurons, disrupting the normal functions of these cells. The dysfunction and eventual death of neurons in certain areas of the brain underlie the signs and symptoms of HD. Since it is autosomal dominant trait, one copy of the altered gene is sufficient to cause the disorder. Therefore, it is observed in both

heterozygous as well homozygous dominant traits. An affected person usually inherits the altered gene from one affected parent. As it is a dominant disorder, it never skips any generation. It has been observed that in a family any affected individual has more CAG repeats compared to the previous generation [10, 11]. A larger number of repeats are usually associated with an earlier onset of signs and symptoms. This phenomenon is called anticipation. In most cases, an intermediate number such as 36 to 40 of CAG repeats leads to a slower progression as a result of the incomplete penetrance of the mutant allele. Usually CAG repeat between 27 and 35 does not develop HD rather individual having these repeats are at risk for developing HD [12, 13]. As the gene is passed from parent to child, the size of the CAG trinucleotides repeat may lengthen into the range associated with HD. Either normal or affected ones, the CAG gene segment is inherited in mendelian fashion [14]. Most HD patients have expansions of trinucleotide ranging from 40 to 50 whereas expansions between 70 and 100 mainly occur in juvenile onset [15].

Most of the person having HD is heterozygous having one normal chromosome and one affected chromosome (with expanded CAG repeat) [16]. In a male suffering from HD larger than the repeat size, greater is the possibility of the occurrence and progression of the disease in the offspring. On the contrary, HD female or mother has no role in intergenerational CAG repeat size changes [16, 17]. From a study, it was concluded that if CAG alleles are more than 36, then there would be a greater degree of intergenerational CAG repeat expansion [17] (Table 1).

### Age of the Person Having HD:

Most of the studies showed there were no significant correlation between the age of the affected parent and the degree of disease transmission to the offspring [19, 20].

### Gender of the Affected Person:

It is observed that in case of affected male, the probability of expansion to occur is more likely whereas some studies showed that there is no such difference between paternal and maternal transmission. In paternal transmission, the average range is from 1 to 9 units whereas in maternal transmission average is from − 0.36 to 0.4 units [21–23].

### CCG Repeat Polymorphism:

This is located at exon1 of the Htt gene which codes for polyproline. Most abundant alleles are CCG7 and CCG10. In several studies, it was observed that CCG7 is the most common allele

**Table 1** Variation in average number of CAG repeats in HD patients from different regions of the world [18]

| Geographical origins | CAG repeats of HD patients |
|---|---|
| Japan (110 cases) | 36–95 |
| India (28 cases) | 41–59 |
| England (118 cases) | 38–63 |
| Germany (46 cases) | 40–65 |
| Italy (52 cases) | 39–54 |
| Australia (1 case) | - |
| Canada (35 cases) | 36–75 |
| Russia (22 cases) | 37–47 |
| The Mainland of China (28 cases) | 36–120 |

[24–29]. The frequencies of CCG 7 on affected and normal chromosome vary significantly [25].

### Medical History:

Several studies were conducted on the medical history of patients suffering from HD to find out if there is any correlation with other psychiatric diagnosis, depression, but no significant correlation was reported [30–33].

### Other Factors Associated with HD:

Few studies reported that patients consuming alcohol and tobacco were found to be more prone to progression of HD [16, 31, 34, 35] (Figs. 1 and 2).

## Epidemiology

### Comparison Between Age of onset (adult and juvenile)

The onset of symptoms can occur at any period of our life. It varies depending on the CAG repeat expansion in HD gene. The larger the CAG repeat, age of onset will be earlier. Juvenile

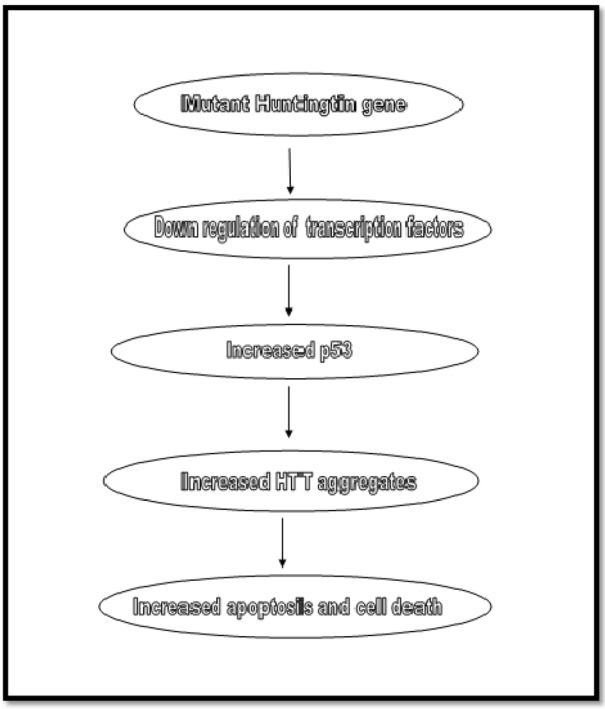


**Fig. 1** Genetic cause of Huntington's disease

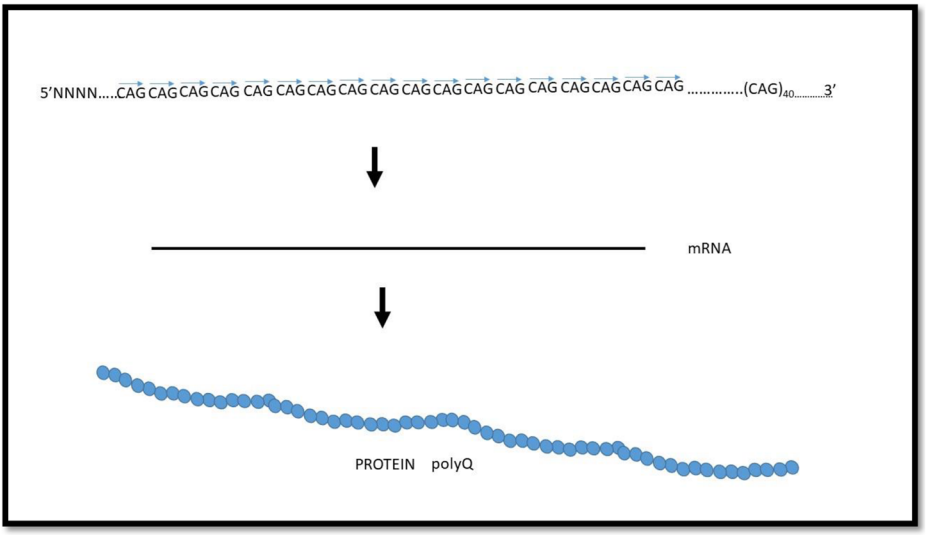


**Fig. 2** CAG repeats and its role in translation of huntingtin protein

and adult HD differs in clinical and neuropathological factors. In juvenile HD, a child's brain is affected more severely as compared to a person who is suffering from adult HD. Few symptoms of juvenile HD are- severe paucity of movement, parkinsonism, epilepsy, bradykinesia, rigidity and tremor whereas in adult HD, the symptoms are—chorea, the involuntary jerky, dance-like movements etc. [36, 37].

According to a study that up to 60 CAG repeats has a lesser influence on age of onset. After this, each new addition of CAG repeat has a different impact on the age of onset of HD disease. Depending on the age of onset, the severity of neurodegenerative disorder differs [38].

A study [39] suggested that the late onset of Huntington's disease may occur due to some random events like specific somatic gene mutations in stem cells of the central nervous system. This mutant stem cell gives rise to undesirable cells, and their products result in attacking target cells bearing complementary recognition macromolecules. When the threshold intensity of attack crosses, the symptoms of the disease appears.

Location of the mutant protein in the cell is also very important; Mutant Htt protein (mHtt) are mostly found in the nucleus of the neurons in juvenile HD whereas in adult HD, they are mostly found in perinuclear cytoplasm [39]. Juvenile and adult HD both are caused due to expansion of CAG repeat but they have different pathological mechanisms. In addition to CAG repeats, an increase in polyglutamic stretch takes place in adult HD.

Sex of the affected parents also plays an important role in the development of juvenile HD in child (before the age of 21). If the father is affected, child becomes more prone to develop juvenile HD. In males, average age of onset is 3.5 years earlier as compared to female [40].

## Environmental Factors:

Few environmental factors like hormones, climate [41, 42] and stress at work place [43] play important role in disease progression.

## Importance of Trinucleotide (CAG) Repeat lLength and Number

A person, who is a carrier of HD can be an ideal model for studying the preclinical phase of neurodegeneration if the person possesses mutation, which causes CAG repeats greater than 40. Reduced penetrance is seen between 36 and 39 repeats; on the other hand 27–35 is considered the intermediate range and below 27 is normal. CAG repeat length accounts for approximately 56% of the variability in age of onset [44]. It is also associated with progression of motor and cognitive deficits [45].

## Trinucleotide Repeats and Phenotype:

Huntington's disease leads to uncontrolled movements, emotional problems and loss of thinking ability and neurodegenerative disorders. Early signs and symptoms can include irritability, depression, small involuntary movements, poor coordination and trouble learning new information or making decisions. Many people with Huntington's disease develop involuntary jerking or twitching movements known as chorea [9]. As the disease progresses, these movements become more pronounced. Affected individuals may have trouble in walking, speaking and swallowing. Changes in personality and loss of thinking and reasoning abilities are also observed. Individuals with the adult-onset form of Huntington's disease usually live about 15 to 20 years after signs and symptoms begin. A less common form of Huntington's disease is known as the juvenile onset Huntington's disease that begins in childhood or adolescence. It also involves movement problems and mental and emotional changes, clumsiness, frequent falling, rigidity, slurred speech and drooling. Seizures occur in 30 percent to 50 percent of children with this condition. It has been observed that Juvenile Huntington's disease develop more quickly than the adult-onset form. Affected individuals usually live 10 to 15 years after manifestation of signs and symptoms [46].

## Transcriptional Alterations in Huntington Disease

The main gene that is mutated in HD is the Htt gene which interacts with several proteins that participate in different cellular pathways. HIP-1 is the mostly studied protein among almost 300 proteins that interact with Htt gene [15]. HIP-1 and its molecular partner HIPPI regulate apoptosis and transcription, the two processes that are affected in HD [47]. HIP-1 interacts with the wild type Htt strongly than the mutated form. Based on this observation, it has been suggested that the weaker interaction of HIP-1 with mutated Htt in HD may be the reason for increased amount of freely available HIP1 and enhance the tendency for the formation of HIP-1-HIPPI heterodimer. Recent studies suggest that the neural degeneration that occurs in HD is a combined effect of the gain of function of the mutated Htt gene (mHtt) and the loss of function of the wild type Htt gene [48]. The increased amount of HIPPI-HIP-1 can be the reason for increased cell death in HD. HIPPI is not known to have many domains except the 'pseudo' death effector domain and a myosin-like domain through which it interacts with the novel protein HIP-1 which also is known to have the 'pseudo' death effector domain. HIP-1 is associated with endocytosis, the evidence of which comes from HIP-1 knockout mice, which shows defects in assembly of endocytic protein complexes on liposomal membranes [49]. HD is caused by an expansion in CAG repeats that is translated abnormally into a long polyglutamine tract in the huntingtin protein, which causes increased apoptosis in a specific region of the brain. In individuals with $(CAG)_{40}$, the symptoms for the disease will develop in

normal lifespan but in individuals with $(CAG)_{70}$ or more will cause childhood onset [50]. It has been found that, crossing the normal threshold i.e., 35 copies of the CAG repeats lead to the transformation of α- helix to β-chains [51]. 30 miRNAs are upregulated and 24 downregulated among the 54 miRNAs that are expressed in HD brains [52]. These miRNAs are regulated by transcription factors and the host gene in which they reside. Through literature reviews, we came to know that the transcription factors TP53, E2F1, REST and GATA4 together could regulate expression of 26miRNAs in HD [52]. HIPPI is directly or indirectly related to gene alterations, the evidence of which comes from the fact that cells expressing exogenous HIPPI have increased expressions of caspase-1, caspase-3, caspase-7 and caspase-10. When apoptosis was studied in HeLa cells tagged with GFP, it was seen that nuclear fragmentation and caspases activation were increased significantly in HIPPI-expressing cells [53]. HIPPI interacts with the promoter of caspase-1 both in-vitro and in-vivo. Based on the in vitro interactions of the different mutants of the sequence 5′-AAAGACATG-3′, present on the caspase-1 upstream sequence where HIPPI can bind, it has been predicted that HIPPI will interact with AAAGA[GC][ATC][TG] [15].

## Increased Translation in Huntington's Disease

HD is a result of misfolded mutant protein (mHtt) aggregation and toxicity. The most vulnerable region is the striatum hence 4E-BP interaction has been studied. Cap-binding protein (eIF4E) is inactivated by eIF4E-binding protein (4E-BP). eIF4G is the initiation factor which is responsible for m-RNA recruitment to the ribosome. A study has been done by Aviner et al. 2014 where 4E-BP1 has been inactivated to study the phosphorylation of 4E-BP in the striatum of R6/1, R6/2 [54]. Results showed 4E-BP was hyper-phosphorylated as a result lead to inactivation of the binding protein in the striatum. Inactivation of 4E-BP leads to decrease in the interaction of the (4E-BP- eIF4E). If (4E-BP- eIF4E) interaction is reduced, then (eIF4E- eIF4G) would increase as a result cap-dependent translation is over-activated. Due to over translation, it is obvious that there would be many newly synthesised proteins. Due to over translation, many pathways were altered by differently translated peptides. It was observed that few proteins were increased and few were decreased. Few proteins which were associated with ribosomes, and oxidative phosphorylation were observed to be increased. Complex I of the respiratory chain was produced less but the production of reductase complex, ATPase was increased [3, 4, 6].

## Principles of Pathogenesis

Huntington mainly occurs due to the repeated units of around 50 consecutive glutamines (polyQ) in Htt [55]. There can be several key features of the pathogenesis of this disease. First can be the mutation of Htt which has the tendency to disturb the formation of proper conformations and β-sheet structures as well. But this is not one of the main reasons for the onset of this disease. There are several other reasons like the systems that handle abnormal proteins were found impaired in cells and tissues of patients with Huntington's disease. Also, truncated Htt gene can give rise to toxic N-terminal fragments. The post translational modification of the Htt gene can also trigger toxicity via changing the conformation of proteins [56]. Most of the efforts for understanding the pathogenesis of this disease have been influenced by the gain of function hypothesis of the Htt gene. Researchers have also attempted in determining the mechanisms by which the polyQ tract causes neurodegeneration [50]. Mutant Htt and polyQ disease proteins form insoluble aggregates in neuron, the role of which in the

pathogenesis of polyQ diseases remain argumentative [57]. This polyglutamine aggregate is prompted by the post-translational N-terminal proteolysis of the protein huntingtin by the caspases, endoproteases and calpains. The mutant polyglutamine tract in the truncated N-terminal protein is exposed to the surrounding substrates and hence, maximally aggressive [58]. Some researchers believe these aggregates to be toxic while others suggest these to be neural by-products that are neuroprotective [59]. A good number of researchers have suggested that unusually long polyQ tracts interfere with the normal functioning of the cellular proteins, causing the onset of the disease [59]. It has already been mentioned earlier that HD is a result of the pathological increase in the number of copies of the glutamine-encoding CAG repeats. If the number of copies crosses the threshold limit of 35, it causes the transformation of α- helix to β-folded chains. These chains get cross-linked by the mechanism of polar 'zippers' to form high molecular weight antiparallel strands [60]. The pathological signature of HD is the presence of intranuclear inclusion bodies that are large aggregates of the mutated Htt (mHtt) protein in the neuronal nuclei. Aggregates can also arise from other places of the cell, like the dendrites, cytoplasm and exon terminals [61]. HD can mainly be characterised by the degeneration of the central nervous system (CNS), but some of the features of the disease can be outside of the CNS [62]. These features include muscle degradation, weight loss, endocrine disturbances and metabolic dysfunction.

Another key feature in the pathogenesis of HD can be cell-cell interactions, both intracellular and intercellular interactions between the neurons and the glial cells [63]. From studies, it was found that in a yeast genetic model, the toxic effects of Htt can be modulated by kynurenine 3- monooxygenase (KMO); it is a very important microglial enzyme connected with the generation of reactive oxygen species and toxicity [64, 65]. Discovery of drugs associated with targeting the KMO pathway is still under investigation (Figs 3 and 4).

## Motor Disturbance

In accordance with the biphasic course, initial loss of medium spiny neurons (MSNs) of the indirect pathway, which is followed by loss of MSNs of the direct pathway, is associated with

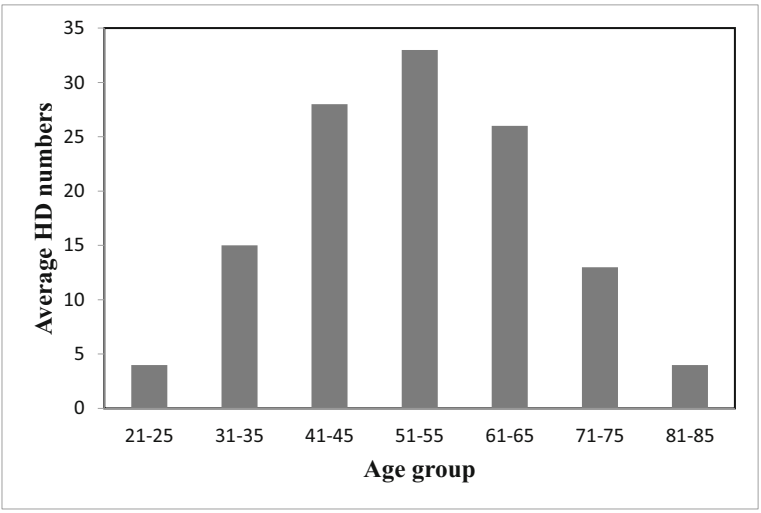


**Fig. 3** Graph showing prevalence of HD among various age groups [66]

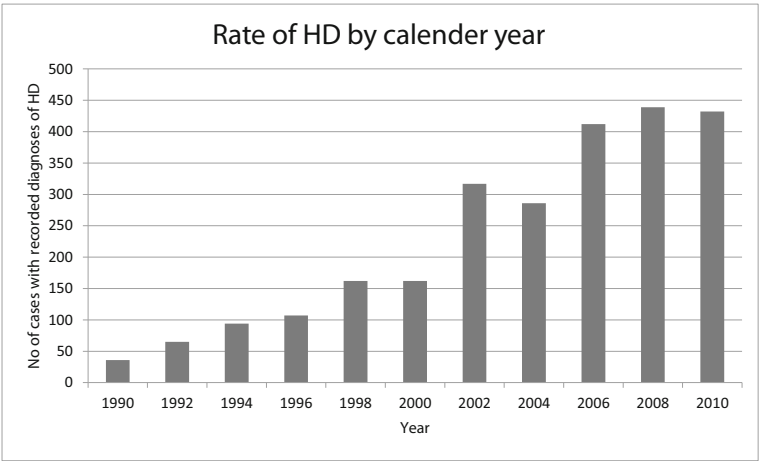


**Fig. 4** Number of recorded cases of HD from 1990 to 2010 [66].

striatal pathology [67]. Hyperkinetic phase of motor disturbance is associated with prominent chorea in the early stages of the disease [68]. The hypokinetic phase is widely classified into bradykinesia, dystonia and balance and gait disturbance [69]. Evaluation of motor disturbance is based on the Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS), which assesses speech, eye movements, dystonia, alternating hand movements, chorea and gait [70]. There are more quantitative methods such as the Qmotor battery, which includes tongue force variability, grip force, speeded and self-paced tapping [71, 72].

## Cognitive Disturbance

Cognitive disturbance might be seen many years before manifestation of symptom. It follows a subcortical pattern that is characterised by impaired emotion recognition, processing speed, visuospatial and executive function [73]. In early indication of the disease, longitudinal changes can be exhibited over 12 and 24 months [74]. This is done by performing the symbol digit modalities test, which evaluates psychomotor speed, word reading which determines executive function, indirect circle tracing which is used to perform to assess visuospatial performance and the emotion recognition test [70].

## Neuropsychiatric Disturbance

A wide variety of neuropsychiatric symptoms, which include anxiety, depression, irritability, apathy, obsessive-compulsive behaviour and psychosis, occur in Huntington disease. A study suggested psychiatric disturbance is common which can be manifested many years before the pre manifestation stage [70]. Neurological apathy is observed in 25 to 30% cases; however, irritability, depression and obsessive-compulsive behaviours occur in around 12 to 14% cases. A study suggested that psychosis is a rare disorder because it occurs in 1 to 2%. Other symptoms like apathy, irritability and depression involved in reducing function. Amongst them, apathy is the only neuropsychiatric symptom which progresses simultaneously with the disease [70].

### Diagnosis:

Diagnosis of Huntington's disease is carried out by analysing the confirmed history of the disease in the family. It can also be diagnosed by genetic test. The onset of motor disturbance is defined by the Unified HD Rating Scale (UHDRS). This score ranges from zero, refers to as no motor abnormalities, to four, which means greater than 90% to be due to HD, with a score of four defining motor onset or 'manifest' HD. However, cognitive, subtle motor and psychiatric deficits can be identified up to 10 to 15 years before the onset of symptoms of the disease [75].

### Genetic Modifiers

The largest genome wide association study (GWAS) in HD discovered a number of genes, which are involved in DNA repair system that can alter the age of motor onset [76]. There are two genes on chromosome 15 known as FAN1 (Fanconi anaemia FANC1/FANCD2-associated endonuclease) and MTMR10 (myotubularin-related protein 10) were identified. They have most significant role in gene modification [77]. A significant relation was identified with RRM2B, a subunit of DNA damage p53 inducible ribonucleotide reductase M2 B and URB5, an HECT domain E3 ubiquitin protein ligase on chromosome8 [78]. In addition, genetic pathway analysis insinuates gene pathways involved in DNA repair, mitochondrial fission and oxidoreductase activity [76]. Similarly, a recent GWAS has revealed the significant relationship between HD progression and a genetic variant in MSH3, a DNA repair gene that is associated with CAG somatic instability [79].

### Biomarkers

Almost 100 clinical trials have been conducted so far in Huntington's disease (HD), with a very low success rate [80]. There can be several types of biomarkers like clinical, pharmacodynamic and biofluid. Pharmacodynamic markers are used to detect whether or not the drug has engaged with its target and produce biological effect. Biofluid markers are present in body fluids and are capable of precise and reliable quantification. Some of the biomarkers that are newly identified include cholesterol metabolites [81]. These biomarkers require further investigation. Some of these biomarkers also include indirect markers of transcriptional dysregulation [82].

## Conclusion:

Huntington's chorea disease is a progressive and devastating disease. Throughout the last decade, there has been a rapid growth in our understanding of the natural history of HD and pathogenesis at both the cellular and macroscopic level. Till date, very few treatments are available and a number of clinical trials have failed. However, the development of therapeutic strategies capable of targeting mHTT directly heralds a new era for HD research. Now, more than ever, there is a real potential to modify and prevent HD.

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**Code Availability** Not applicable

## Declarations

**Ethics Approval** As this is a review article, there is no need of any ethical approval.

**Consent to Participate** Not applicable as this is a review article.

**Consent for Publication** The authors give the consent for publication.
Conflict of Interest/Competing Interests
The authors declare no competing interests.

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