

## Current Updates on Huntington Disease

Deepika Delsa Dean <sup>1</sup>, Ambreen Asim <sup>2</sup>, HariKrishnan S <sup>3</sup>, Poonam Tripathi <sup>4\*</sup>

<sup>1</sup>Department of Biotechnology, Isabella Thoburn College, Lucknow- 226007, UttarPradesh, India

<sup>2</sup>University of Texas Health Science Center at Houston, U.S.A.

<sup>3</sup>MedGenome Labs, Bangalore, India.

<sup>4\*</sup> PhD in Medical Genetics, Department of medical genetics, SGPGIMS, Lko.

### ARTICLE INFO

2024 Volume 1, Issue 1  
<https://www.doi.org/jeghg.2024.tgc.0270>

#### Article History:

Received: Feb 12, 2024

Accepted: Feb 15, 2024

Published: Feb 26, 2024

**Citation:** Poonam Tripathi. (2024). Current Updates on Huntington Disease. *Journal of Epidemiology, Global Health and Genomics, The Geek Chronicles.* 1(1): 1-13

**Copyright:** © 2024 Poonam Tripathi, this is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Keywords:** Huntington disorder (HD), CAG repeat, neurodegenerative disorder, HTT, mHTT

### ABSTRACT

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder and a common cause of mortality. It is characterized with a progressive loss in the motor, cognitive and behavioral abilities. The main cause of HD is expansion of CAG repeat in the HTT genes beyond the threshold size. Presently, there is no cure for HD and the current treatment include management of symptoms using antipsychotics and antidepressants. Thus, understanding the pathways and molecular pathophysiology might be helpful in designing the possible leads for drug discovery. The review focusses on current possible drug targets for HD and shed some lights on the use of NGS-based techniques to determine the etiology of HD that can be further used in the therapeutic design for HD.

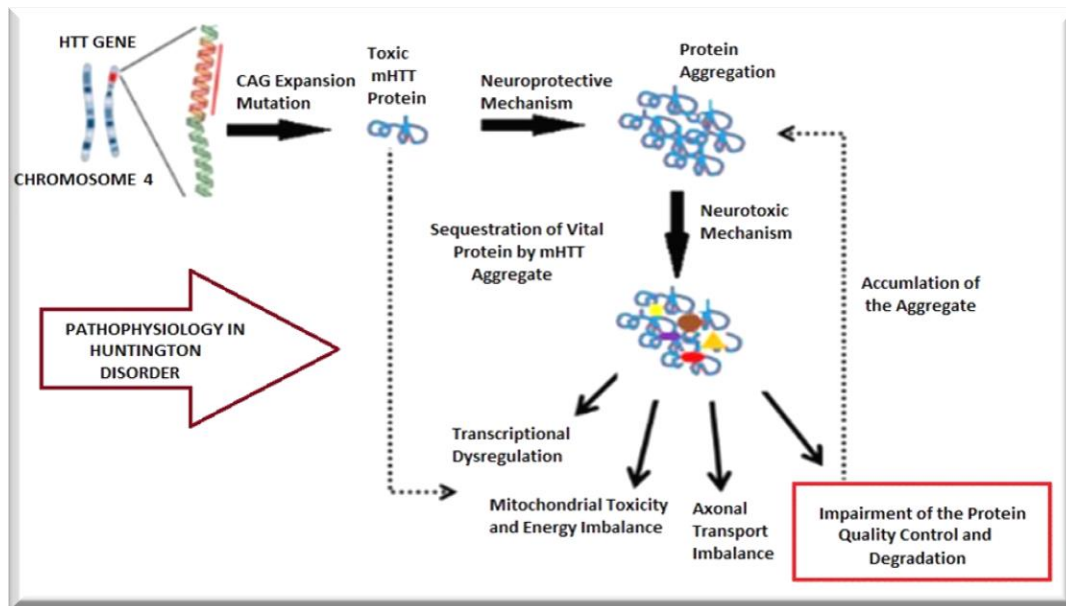
#### Background

Huntington Disease / Disorder (HD) is a fatal neurologic disorder that affects both the sexes in all the ethnic group and races worldwide. Onset of the disease is quite variable being most frequent between 30-40 years of age. However, symptoms may also start as early as 2 years of age or as late as 85 years. If the disease symptoms appear before 20 years it is known as Juvenile HD (JHD). The main clinical features associated with HD includes neurologic, Psychiatric and cognitive problems. and also, non- neurologic peripheral abnormalities.

HD is caused due to expansion of CAG repeat in exon 1 of *HTT* gene, beyond a threshold number. Depending upon the size of the CAG repeat there are 4 types of *HTT* allele - Normal *HTT* allele in the range 6- 26, intermediate alleles with 27–35 CAG repeats, reduced penetrance allele with CAG repeat ranging between 36-39 (may/may not cause HD) and disease-causing allele ( $\geq 39$  CAG repeats). These CAG repeats may be interrupted by glutamate encoding CAA repeats. Interestingly, recent evidences showed that patients with no CAA interruptions have early disease onset suggesting that the timing of onset is a property of the expanded CAG repeat rather than the length of polyglutamine, but the underlying mechanism of this toxicity is not clear. CAG repeat length is inversely correlated with the age of onset and age of death in affected individuals. The CAG repeat length show approximately 60% variation with the age of onset, this is thought to be due to presence of functional genetic differences (genetic modifiers) that may interact with the mHTT during different stages resulting in differences in onset, manifestation and progression of the disease in different individuals. Studying genetic modifiers in HD will aid in identifying pathways that are critical in disease manifestation and therefore could form ideal avenues for designing better drug targets to delay or prevent onset of HD.

The *HTT* gene encodes for huntingtin protein (HTT) which is important for the nervous system development. HTT protein is found to be involved in trafficking of various proteins, vesicular-transport, clathrin-mediated endocytosis; synaptic-signaling, transcriptional regulation, and anti-apoptotic function. The CAG repeats expansion mutation in *HTT* gene results in production of abnormally long stretch of poly-glutamine (Poly Q) tract in the mutated HTT (mHTT) protein that may have altered functionality. The loss of function of normal HTT or gain of toxic function of mHTT results in neural cell death. Toxic mHTT fragment could be generated either due to proteolytic cleavage of mHTT or as a result of alternative splicing during transcription that yielded mHTT fragment containing the exon 1, which is thought to be the most toxic. These fragments might interact with each other to form aggregates which is the hallmark for HD. It is suggested by some researchers that aggregate

formation is a way via which the cell attempts to sequester toxic HTT monomers that might be harmful for cellular function. In fact, large inclusion bodies (IBs) have shown to decrease cellular mHTT level and increase neural survival. However, many studies have shown implications of mHTT monomer and/or oligomers in neurotoxicity. The possible explanation could be that even if inclusions are not responsible for toxicity initially and is a way in which cell tries to cope with accumulating monomeric and oligomeric toxic HTT, but as they keep on accumulating, they sequester other vital proteins with important functions and disrupts the function of important cellular organelles in the cell like mitochondria. These aggregates cause impairment of the protein quality control and degradation machinery leading to disease pathogenesis (Figure 1).



**Figure:1** Pathophysiology of Huntington Disorder

In fact, the protein homeostasis is found to be impaired in HD as evident from the accumulation of ubiquitin positive inclusions in

the brain tissue of HD patient suggest that these aggregates are targeted

for proteolysis but are resistant to removal. Thus, targeting the growth of these aggregates and their maturation represents a potential therapeutic strategy.

Mitochondrial dysfunction has also been enormously studied in context with HD pathogenesis. mHTT interacts with the mitochondrial outer membrane and cause impairment of electron transport chain (ETC) complexes II and III, thereby decreasing intracellular ATP pool and increasing reactive oxygen species (ROS) [1]. Mitochondrial dynamics is also found to be perturbed with an excessive mitochondrial fission taking place in HD. and mHTT interacts with and impairs PPAR- $\gamma$  co-activator-1 $\alpha$  (PGC-1 $\alpha$ ) that regulates expression of gene in mitochondrial biogenesis [2].

Proper trafficking of mitochondria to neuronal ends are important as these are the places where synaptic connections take place and there is high energy demand. But in HD the axonal transport of mitochondria is also impaired either due to interaction of mHTT with HAP (Huntingtin associated protein) that is involved in intracellular trafficking or due to physical hindrance caused by mHTT aggregates in the narrow region of the neurons. These findings are in line with the compromised energy production and metabolism as observed in HD patient [3].

Gene expression profile in case of HD is highly altered such that expression of mHTT has global effect on the transcriptome. Soluble mHTT oligomers sequester and thus impede the function of important proteins that are important for general promoter accessibility and transcription initiation like specificity protein 1 (SP1), TATA box binding protein (TBP), the TFIID subunit TAFII130, the RAP30 subunit of the TFIIF complex, and the CAAT box transcription factor NF-Y [4]. Sequestration of CBP (CREB Binding Protein), that has a histone deacetylase domain, alleviates expression of many genes important for proper synapse development and memory [5]. mHTT also facilitates polycomb repressive complex 2 (PRC2), mediated methylation of histone H3 in

lysine 27 and causes transcriptional repression [6]. A decrease in expression of BDNF, an essential neurotrophin of Central Nervous System is also documented in tabHD. This is a result of incapability of mHTT in binding REST which is transcriptional co-repressor of BDNF. Usually, REST interacts with wild type HTT and stays in the cytosol. As mHTT fails to bind REST, it translocates to the nucleus and binds the Repressor-Element 1 (RE1) blocking BDNF gene transcription [7].

### **Current Priority: Therapeutic Targets Under Investigation for HD**

Despite of a plethora of scientific studies and review work done on HD and its pathogenesis not much progress has been made in direction of its treatment [11]. Till date no clinical trial successfully identified disease-modifying treatments for HD there is no cure for Huntington disease. A list of ongoing clinical drug trials for HD is given in Table 1. Current treatments are primarily symptomatic and include antipsychotics and antidepressants. An understanding of the various pathways and cellular events that are disrupted in HD might be helpful in designing possible drug targets. But this is quite challenging in case of HD owing to the fact that precise function of HTT is still not clear and it interacts with several proteins and is involved in many pathways. The question that has to be considered with care is that which of these pathways and molecular events have a pivotal role in the pathology and how many of these processes should be blocked to prevent HD pathology and what molecular tools can be used to test these possibilities?

### **Targeting Mitochondrial Dysfunction in HD**

Drug targeting mitochondrial dysfunction have been recently reported to hold promising results. Treatment with selective inhibitor (P110-TAT) of the mitochondrial fission protein DRP1[8] reduced mitochondrial dysfunction, motor deficits, neuropathology, and mortality in HD mouse model and fibroblasts and iPS cell-derived neurons from HD patients. The PPAR agonist rosiglitazone

(RSG) is reported to induce mitochondrial biogenesis and prevent mitochondrial dysfunction in cells expressing mHTT[9]. Similarly, KD3010 which has been previously used for diabetes trials have showed significant improvements in motor function, neurodegeneration, and survival in the HD mice and also reduced HTT-induced neurotoxicity *in* medium spiny-like neurons generated from human HD stem cells [10]. Mitochondrial accumulation of mHTT alters the electron transport chain and its nuclear accumulation alters the gene expression and translation of *HTT*. It was previously reported that N17 domain of HTT is the key regulator of its stability and localization and is implicated in the mHTT mediated pathogenic mechanism [11]. Interestingly, research in zebrafish depicted that mHTT without N17 domain showed an early onset of symptoms, whereas that with N17 domain showed a delayed onset of symptoms<sup>12</sup>. This emphasizes that the expression of N17 domain in mHTT alleviates Other approaches to clear off mHTT aggregates have also shown promising results. These include autophagy enhancement by inhibiting mTOR (mammalian target of rapamycin) that inhibits autophagy. Recently, two novel brain penetrant compounds - the mTORC1/2 inhibitor PQR620, and PQR530 were reported to induce autophagy without affecting cell viability and reduce mHTT levels in cell models of HD [16]. However, mTOR is involved in other important cellular pathways too, thus targeting mTOR may disturb normal cellular functioning. PolyQ aggregation was inhibited both *in vivo* and *in vitro* by treatment with a disaccharide trehalose. Poly (trehalose) nanoparticles depicted inhibition of polyQ aggregates under extra-/intracellular conditions, reduction of cytotoxicity, and prevented aggregation in a HD mouse brain [17]. A recent study depicted that allosteric activation of Hsp70 chaperone with a pharmacological mimetic of the Hsp70 co-chaperone Hip, YM-1, was able to reduce the N-terminal huntingtin clustering and nuclear aggregation and thus can modulate huntingtin

its accumulation and toxicity and hence N17 domain could serve as a viable target for the development of the new therapeutic strategy for HD [13].

### **Targeting Impaired Histone Acetylation in HD**

As stated, before mHTT disrupts histone acetylation by CBP and thus causes hypoacetylation and silencing of important neuronal genes. HDAC inhibitors have shown to ameliorate mHTT toxicity [14]. Also, treatment with HDAC inhibitor may indirectly help in mHTT aggregate clearance by enhancing expression of UPS related genes and by directly increasing acetylation of mHTT at lysine 444 that facilitates trafficking of mHTT into autophagosomes leading to protein clearance and reversing the mHTT toxicity in striatal and cortical neurons in HD model [ 15].

### **Targeting mHTT Aggregation in HD**

proteostasis [18]. The eukaryotic chaperonin TCP-1 Ring Complex [TRiC, also called to chaperonin containing TCP-1 (CCT)], a member of HSP60 family, have been proposed to protect against polyQ aggregation [19]. It was established that even exogenous apical domain of a single mammalian chaperonin TRiC/CCT subunit CCT1 (ApiCCT1) when delivered to striatal neuronal cells from full-length knock-in HD mice, can alleviate mHTT-mediated toxicity and can delay the onset of inclusion body formation by sequestering N17 portion of mHTT and thus not allowing it to form aggregates . TRiC/CCT is degraded by ubiquitin proteasome system and the kinase activity of vaccinia-related kinase 2 (VRK2) facilitates its degradation thus VRK2 inhibitors can also be utilized for HD therapy. For example, recently, it was reported that neuronal heterogeneous nuclear ribonucleoprotein Q (HNRNP Q) specifically binds to the 3'untranslated region of VRK2 mRNA in neuronal cells and reduces its stability, which in turn suppresses polyglutamine huntingtin aggregation in human neuroblastoma cells and

mouse cortical neurons, hence preventing HD [19].

### Targeting Excitotoxicity in HD

Perturbation in Kynurenine pathway (involved in tryptophan degradation in glial cells) is reported in HD model. The enzyme kynurenine monooxygenase (KMO) is a key branchpoint in KP (kynurenine pathway), and when its activity decreases Kynurenic acid (KA) is produced which is neuroprotective while neurotoxic quinolinic acid (QA) is produced when KMO is more active. The level of QA is comparatively high than KA levels in post-mortem HD patient brain. Researchers have observed that inhibition of KMO via CHDI-340246, increases the levels of KA in HD rodent models and in Cerebro spinal fluid (CSF) of nonhuman primates and thus appears promising to cure HD [20]. Of late a study has identified 19 new KMO inhibitors, one of them (named as **1**) is found to be neuroprotective in a *Drosophila* HD model however it is minimally brain penetrant in mice. The prodrug variant (named as **1b**) has shown to cross the blood–brain barrier and release KMO inhibitor **1** in the brain, thus lowers the levels of 3-hydroxykynurenine, a toxic KP metabolite associated with neurodegeneration. Prodrug **1b** will lead to advance development of targeted therapies against KP pathway related neurodegenerative diseases including HD [21]. The said excitotoxicity in HD may also be a result of excess amount of excitatory neurotransmitter glutamate at the synapse that cause NMDA receptor activation and hence raises intracellular calcium level. High intracellular calcium concentration leads to activation of cellular degradation processes causing cell death. As NMDA receptor currents is enhanced in both in vivo and in vitro HD models. Excitatory amino acid transporter 2 (EAAT-2) expression (for removing extracellular glutamate), is found to be compromised in HD mice and HD patient brains [22]. Therefore, drugs enhancing the activity/expression of EAAT-2 may be explored for controlling neural death in HD.

### Targeting Neural Cell Death

Neural cell survival is compromised in HD due to decrease in level of neurotrophin BDNF owing to its reduced expression and axonal transport. Numerous studies focusing on pharmacological interventions for increasing endogenous BDNF levels are done using in vivo HD models. These strategies would circumvent the problems related to the use of invasive methods of BDNF delivery while allowing for the correct dosage and stability of this neurotrophin. Recently, immunomodulators, like Laquinimod and Glatiramer acetate have shown to elevate BDNF levels and positively impact motor function in HD mouse model [23]. Targeting BDNF signaling might also improve non-motor deficits like long-term memory, depressive-like and anhedonic behaviors and cognition related features in HD mouse model [24]. Binding of BDNF to TrkB receptor mediates differentiation, proliferation, survival, migration and branching. Thus, in absence of BDNF alternative modalities that would activate TrkB receptors might be useful. Recently, monoclonal antibodies specific for TrkB resulted in protection of striatal neurons from mHTT-induced cell death in HD models [25].

### Targeting mHTT Expression in HD

An advancement in technology have led to emergence of treatment approaches that relies on lowering the expression of mHTT at the level of DNA (transcription) or RNA (translation) [26]. These include RNA interference (RNAi) using short interfering RNA (siRNA); (shRNA); translational repression using single-stranded DNA-based antisense oligonucleotides (ASOs); and transcriptional repression using zinc finger proteins (ZFPs). Nigrostriatal injection of Adeno-associated virus (AAV2) vector expressing HTT-silencing miRNA in YAC128 HD mouse model resulted in a transduction of approximately 80% of the striatum and approximately 50% reduction is noted in HTT mRNA and HTT protein and

mHTT aggregation. Though both wild type and mutant Huntington levels were found to be reduced still there was no evidence of inflammation or neurotoxicity reported, while the performance of treated mouse improved [27]. Intrastriatal administration of AMT-130 resulted in sustained suppression of HTT in Hu128/21 mice for at least 7 months post-injection and leads to behavioral and neuropathological improvements [28]. Furthermore, this gene therapy in induced-pluripotent stem cells (iPSC) derived from neurons and astrocytes from 2 patients carrying different HTT mutations showed that the level of HTT was lowered by 68% in a single dose, while there was no evidence of off-target effects [29].

Artificially synthesized ASO's are of lot of interest currently after the successful first phase 1 human trials of ASO targeting superoxide dismutase 1(SOD1) in familial amyotrophic lateral sclerosis in 2013 that was completed without significant safety issues. ASO-HTT-RX developed by Isis pharmaceuticals and Roche have shown successful results in animal models and in phase 1 clinical trial [30]. However, as the study was monitored in phase III clinical trial it was subsequently brought to halt in March 2021, as there were no recognizable clinical effectiveness of the drug and/or the drug appeared less safe than expected.

The main concern in application of these approaches is to specifically target HTT allele. A study on Caucasian 234 HD patients identified fifty HD-SNPs across the HTT gene that are significantly enriched on HD alleles compared to wild type alleles [31] and about 85% of HD patients can be covered by targeting as few as three SNPs. These basic sequence differences might be targeted to develop allele specific silencing methods for HD. siRNA are incapable of crossing the blood brain barrier thus limiting its therapeutic potential. However, this can be enhanced by methods, including viral vectors/ exosomes/cholesterol conjugation/convection-enhanced delivery/ovel conjugates of single-stranded siRNA compounds [32]. ASO can be delivered directly

in the CSF owing to its smaller size and chemical structure and can elicit therapeutic effect thus giving huntington holiday to brain [33]. Another type of small non coding RNA, short hairpin RNAs (shRNAs) which have have fewer "off-target" effects and a long-lasting effect can also be used . . . . Recently it was studied that short hairpin RNAs targeting repeat sequence alleviated mutant huntingtin, atrophin1, ataxin3, and ataxin7 proteins levels in patient-derived fibroblasts and can be utilized as a universal allele-selective reagents for polyglutamine (polyQ) diseases [34]. Once, the technical challenges related to shRNA based therapy could be solved, it may surely be used as a powerful approach to combat HD and other related neurodegenerative disorders [35].

ZFP, the artificially engineered proteins can specifically bind to the defective expanded *HTT* DNA sequences (but not the normal *HTT* sequences or other, unrelated sequences) and repress the synthesis of the toxic gene products. ZFP target the origin that is the defective gene rather than RNA. As mHTT RNA might also have certain deleterious effects which are not yet known thus by targeting the gene itself the production of toxic RNA can be avoided. Recently, a study depicted that virally delivered ZFP-Transcription factors selectively repressed >99% of HD-causing alleles (for at least 9 months in mouse brain) over a wide dose range in patient-derived fibroblasts and neurons, while the expression of >86% of normal alleles was preserved [36].

### Targeting Neural Stem Cells for HD

Stem cell transplantation strategy for HD treatments can be utilized for replacing the dysfunctional or lost neurons. For obtaining the optimal Neural stem cells (NSCs) are to be developed from brain, pluripotent stem cells (PSCs), and somatic cells of the HD patients. Stem cell-based therapy has been successfully applied in HD animal models and functional recovery has been reported by various studies [37]. Moreover, ntra-cerebral transplantation of BDNF-overexpressing human NSC (HB1.F3.BDNF) into the contra-

lateral side of unilateral quinolinic acid (QA)-lesioned striatum promoted migration, differentiation and functional restoration in HD rat model [38]. Similarly, Intranasal delivery of Bone Marrow-MSCs (Mesenchymal Stem Cells) (preconditioned with mood stabilizers) in a N171-82Q HD transgenic mice lead to functional improvements, reduction in neuropathological features, reduction in striatal neuronal loss and ameliorated huntingtin aggregates [39]. Transplanting MSCs derived from the umbilical cord (UC) are an attractive alternative as the latter is a non-controversial, inexhaustible source of stem cells and can be harvested at a relatively lower cost. UC-MSCs, isolated from day 15 gestation pups, were transplanted intrastratially into 5-week-old transgenic R6/2 mouse model of HD and a transient improvement in a spatial memory task was observed with the finding that, grafting of high-passaged UC MSCs provided greater behavioral and neuropathological sparing than low-passaged UC MSC [40]. Another study targeted SUPT4H1 gene, which selectively supports transcription of long trinucleotide repeats. SUPT4H1-edited HD-induced pluripotent stem cell-derived neural precursor cells (iPSC-NPCs) were transplanted into the YAC128 HD mouse leading to reduction in mHTT expression without compensating the wild-type HTT expression, and caused an improvement in the motor functionality in comparison to unedited HD iPSC-NPCs [41]. Stem cell-based therapies offer promising opportunities for the treatment of HD, but a more in-depth and comprehensive pre-clinical studies are required to confirm its therapeutic potential.

Advances in therapeutics for HD has been recently reviewed by Kim et.al., 2021 and has elaborated on approved treatment options and current clinical trials for HD [42]. With the development of first human genomic transgenic mouse model of HD with long uninterrupted CAG repeats which depicted selectivetoxicity to striatum via distinct toxic molecular mechanisms like somatic DNA repeat instability, RNA gain-of-function toxicities and

toxic protein products due to repeat-associated non-ATG translation (RAN translation), studies using this new model is matchless and can aid in entering into an era where HD would be curable or at least its onset and progression could be delayed [43].

### Role of NGS in HD Treatment

The Next Generation Sequencing technologies are no doubt unmatched for its potential of disease diagnosis and prognosis, but also it can explore the effect of pathogenic mutation on the genome and hence answer various mechanistic questions. In case of HD, by utilizing this robust and powerful technology, it was deduced that the damaging coding-variants in candidate modifier genes can alter HD onset or severity and hence, emerge as promising drug targets. Recently, a study assessed the candidate modifier genes from GeM-HD GWAS via exome sequencing and identified rare, coding variants in genes like: *FAN1*, *MSH3*, *PMS1*, *RRM2B*, *TCERG1*, *LIG1* etc. to be associated predominantly with early onset in HD [44]. Among them, recently FAN 1, a DNA repair nuclease was recently extensively reviewed to understand the effect of its variants on DNA damage response and subsequently on repeat instability [45]

Another promising NGS technology, the RNA-Seq on HD model mice showed extensive and progressive transcriptomic dysregulation in the striatum and cortex. Interestingly, RNA Seq identified a widespread mis-splicing was depicted in the muscle of HD mouse models. Moreover, a study found that the mutant huntingtin intron 1 mis-splicing is translated into a highly pathogenic exon 1 protein, thus the RNA at the 5' UTR or in exon 1 of HTT could be targeted via antisense oligonucleotides or RNAi technologies for reducing the levels of full-length as well as the short mis-spliced exon 1 *HTT* transcript [46]. Another recent study revealed through RNA-seq analysis that the gene expression signature was dysregulated for immune functions and inflammatory response, particularly the interferome, in HD cases as compared to controls [47]. Another recent

RNA seq based study deduced the connecting links among the differentially expressed genes, the transcripts, and the variants identified in HD. This study identified that the neuroinflammatory signaling pathways genes can be targeted for therapeutic interventions in HD [48]. Additionally, single nucleus RNA sequencing (snRNAseq) in rapidly progressing mouse model (R6/2) and human post-mortem brain revealed glucose and lipid metabolism

alteration to be linked to abnormal cell maturation. The Thiamine pyrophosphokinase 1 (TPK1) and Protein kinase C epsilon (PRKCE) genes were identified as key genes and suggests combined thiamine and biotin as potential treatment for HD patients, and is currently under clinical trial [49]. All these studies showed that NGS can provide a hope for development to target identification for planning treatment modalities in case of HD.

**Table 1: List of Current Drug Clinical Trials of Huntington Disorder**

1	Active, not recruiting	PRidopidine's Outcome on Function in <b>Huntington</b> , PROOF- HD	NCT04556656	Drug: Pridopidine Drug: Placebo
2	Active, not recruiting	Clinical Extension Study for Safety and Efficacy Evaluation of Cellavita-HD Administration in <b>Huntington</b> .	NCT04219241	Biological: Cellavita-HD
3	Active, not recruiting	Safety Evaluation of Cellavita HD Administered Intravenously in Participants with <b>Huntington</b>	NCT02728115	Biological: Cellavita HD Lower Dose & Higher dose
4	Recruiting	Study of WVE-003 in Patients with <b>Huntington</b>	NCT05032196	Drug: WVE-003
5	Recruiting	Impact of Deutetrabenazine on Functional Speech and Gait Dynamics in <b>Huntington</b> Disease	NCT04713982	Drug: Deutetrabenazine
6	Recruiting	Safety and Proof-of-Concept (POC) Study With AMT-130 in Adults with Early Manifest <b>Huntington</b> Disease	NCT04120493	Genetic: intra-striatal rAAV5-miHTT Other: Imitation (sham) surgery
7	Not yet recruiting	A Study to Evaluate the Effect of SAGE-718 on Cognitive Function in Participants with <b>Huntington</b>	NCT05107128	Drug: SAGE-718 Drug: Placebo
8	Not yet recruiting	Trial of the Combined Use of Thiamine and Biotin in Patients with <b>Huntington</b>	NCT04478734	Drug: Moderate and High doses of Thiamine y Biotin
9	Active, not recruiting	An Open Label Study of ANX005 in Subjects With, or at Risk for, Manifest <b>Huntington</b>	NCT04514367	Drug: ANX005
10	Recruiting	Symptomatic Therapy for Patients with <b>Huntington</b>	NCT04071639	Drug: Haloperidol 2Mg Tab Drug: Risperidone 1Mg Tab Drug: Zoloft 50Mg Tablet (and 2 more...)
11	Active, not recruiting	Safety and Efficacy of Fenofibrate as a Treatment for <b>Huntington</b>	NCT03515213	Drug: Fenofibrate Drug: Placebo
12	Active, not recruiting	An Open-Label Extension Study to Evaluate Long-Term Safety and Tolerability of RO7234292 (RG6042) in <b>Huntington</b> Participants Who Participated in Prior Roche and Genentech Sponsored Studies	NCT03842969	Drug: RO7234292 (RG6042)
13	Active, not recruiting	A Study to Evaluate the Efficacy and Safety of Intrathecally Administered RO7234292	NCT03761849	Drug: RO7234292 Drug: Placebo

		(RG6042) in Participants with Manifest <b>Huntington</b>		
14	Recruiting	A Dose Range Finding Study with Open-Label Extension to Evaluate the Safety of Oral LMI070/Branaplam in Early Manifest <b>Huntington</b>	NCT05111249	Drug: Branaplam Drug: Placebo
15	Recruiting	Open-Label Rollover Study for Continuing Valbenazine Administration for the Treatment of Chorea Associated with <b>Huntington</b> Disease	NCT04400331	Drug: Valbenazine
16	Recruiting	A Pilot Study Assessing Impulsivity in Patients with <b>Huntington</b> on Xenazine (Tetrabenazine)	NCT02509793	Drug: Tetrabenazine
17	Recruiting	Evaluating the Efficacy of Dextromethorphan/Quinidine in Treating Irritability in <b>Huntington</b>	NCT03854019	Drug: Dextromethorphan/ quinidine 20mg/10mg (DM/Q 20mg/10mg) Drug: Placebo
18	Not yet recruiting	TEsting METformin Against Cognitive Decline in HD	NCT04826692	Drug: Metformin Drug: Placebo
19	Recruiting	Risperidone for the Treatment of <b>Huntington</b> Involuntary Movements	NCT04201834	Drug: Risperidone Device: BioStamp nPoint device
20	Not yet recruiting	Efficacy of Deutetrabenazine to Control Symptoms of Dysphagia Associated With HD	NCT04301726	Drug: Deutetrabenazine Oral Tablet [Austedo] Drug: Placebo oral tablet

## Conclusion:

HD is a fatal condition that worsens with time and affects both the proband and their family. The pathogenesis and development of HD are influenced by a variety of factors. A lot of clinical trials have failed, and there are currently few medicines available. This mini review summarized the molecular underpinning of HD pathophysiology and described how these can be targeted in order to either reduce HD onset or its phenotype. With updated knowledge about molecular event taking place in HD, advent of newer genomic platforms and development of new HD study model we can look forward to precise treatment for HD in nearing future.

**Author Contribution:** Deepika Delsa Dean wrote the main manuscript; Ambreen Asim compiled the data and framed this manuscript; Harikrishnan S worked on the biomarkers portion and final editing of the manuscript, Poonam Tripathi contributed in critical review and formatting of the manuscript.

**Acknowledgements:** Not Applicable

**Funding:** None

**Conflict of Interest:** Authors have no conflict of interest.

## References

1. Cherubini M, Lopez-Molina L, Gines S. Mitochondrial fission in Huntington's disease mouse striatum disrupts ER-mitochondria contacts leading to disturbances in  $Ca^{2+}$  efflux and Reactive Oxygen Species (ROS) homeostasis. *Neurobiol Dis.* 2020 Mar; 136:104741.
2. Johri A, Chandra A, Flint Beal M. PGC-1 $\alpha$ , mitochondrial dysfunction, and Huntington's disease. *Free Radic Biol Med.* 2013; 62:37-46.
3. Covarrubias-Pinto A, Parra AV, Mayorga-Weber G, Papic E, Vicencio I, Ehrenfeld P, Rivera FJ, Castro MA. Impaired intracellular trafficking of sodium-dependent vitamin C transporter 2 contributes to the redox imbalance in Huntington's disease. *J Neurosci Res.* 2021 Jan;99(1):223-235.
4. Labbadia J, Morimoto RI. Huntington's disease: underlying molecular mechanisms and emerging concepts. *Trends Biochem Sci.* 2013;38(8):378-385.
5. Paldino E, Cardinale A, D'Angelo V, Sauve I, Giampà C, Fusco FR. Selective Sparring of Striatal Interneurons after Poly (ADP-Ribose) Polymerase 1 Inhibition in the R6/2 Mouse Model of Huntington's Disease. *Front Neuroanat.* 2017; 11:61. Published 2017 Aug 2.
6. Ferrari Bardile C, Garcia-Miralles M, Caron NS, et al. Intrinsic mutant HTT-mediated defects in oligodendroglia cause myelination deficits and behavioral abnormalities in Huntington disease. *Proc Natl Acad Sci U S A.* 2019;116(19):9622-9627.
7. Orozco-Díaz R, Sánchez-Álvarez A, Hernández-Hernández JM, Tapia-Ramírez J. The interaction between RE1-silencing transcription factor (REST) and heat shock protein 90 as new therapeutic target against Huntington's disease. *PLoS One.* 2019 Jul 30;14(7): e0220393.
8. Reddy PH. Inhibitors of mitochondrial fission as a therapeutic strategy for diseases with oxidative stress and mitochondrial dysfunction. *J Alzheimers Dis.* 2014;40(2):245-256.
9. Chiang MC, Cheng YC, Nicol CJ, Lin KH, Yen CH, Chen SJ, Huang RN. Rosiglitazone activation of PPAR $\gamma$ -dependent signaling is neuroprotective in mutant huntingtin expressing cells. *Exp Cell Res.* 2015 Nov 1;338(2):183-93.
10. Dickey AS, Pineda VV, Tsunemi T, et al. PPAR- $\delta$  is repressed in Huntington's disease, is required for normal neuronal function and can be targeted therapeutically. *Nat Med.* 2016;22(1):37-45.
11. Dhiraj Kumar, Gulam Mustafa Hasan, Asimul Islam, Md. Imtaiyaz Hassan, Therapeutic targeting of Huntington's disease: Molecular and clinical approaches, Biochemical and Biophysical Research Communications, Volume 655, 2023, Pages 18-24. Maiuri T, Woloshansky T, Xia J, Truant R. The huntingtin N17 domain is a multifunctional CRM1 and Ran-dependent nuclear and cilia export signal. *Hum Mol Genet.* 2013; 22:1383–1394.
12. Veldman MB, Rios-Galdamez Y, Lu X-H, Gu X, Qin W, Li S, et al. The N17 domain mitigates nuclear toxicity in a novel zebrafish Huntington's disease model. *Mol Neurodegener.* 2015; 10:16.
13. Kumar V, Singh A. Targeting N17 domain as a potential therapeutic target for the treatment of Huntington disease: An opinion. *EXCLI J.* 2021; 20:1086-1090. Published 2021 Jun 9.
14. ia H, Wang Y, Morris CD, Jacques V, Gottesfeld JM, Rusche JR, Thomas EA. The Effects of Pharmacological Inhibition of Histone Deacetylase 3 (HDAC3) in Huntington's Disease Mice. *PLoS One.* 2016 Mar 31;11(3): e0152498.
15. Son SM, Park SJ, Fernandez-Estevez M, Rubinsztein DC. Autophagy regulation by acetylation-implications for neurodegenerative diseases. *Exp Mol Med.* 2021;53(1):30-41.
16. Singer E, Walter C, Fabbro D, Rageot D, Beauvils F, Wymann MP, Rischert N, Riess O, Hillmann P, Nguyen HP. Brain-penetrant PQR620 mTOR and PQR530 PI3K/mTOR inhibitor reduce huntingtin levels in cell models of HD. *Neuropharmacology.* 2020 Jan 1; 162:107812.

17. Koushik Debnath, Nibedita Pradhan, Brijesh Kumar Singh, Nihar R. Jana, and Nikhil R. Jana. Poly(trehalose) Nanoparticles Prevent Amyloid Aggregation and Suppress Polyglutamine Aggregation in a Huntington's Disease Model Mouse. *ACS Applied Materials & Interfaces* 2017 9 (28), 24126-24139
18. Brígida R. Pinho, Liliana M. Almeida, Michael R. Duchon, Jorge M.A. Oliveira, Allosteric activation of Hsp70 reduces mutant huntingtin levels, the clustering of N-terminal fragments, and their nuclear accumulation, *Life Sciences*, Volume 285,2021,120009, ISSN 0024-3205,
19. Ryu HG, Kim S, Lee S, Lee E, Kim HJ, Kim DY, Kim KT. HNRNP Q suppresses polyglutamine huntingtin aggregation by post-transcriptional regulation of vaccinia-related kinase 2. *J Neurochem.* 2019 May;149(3):413-426.
20. Vahri Beaumont, Ladislav Mrzljak, Ulrike Dijkman, Robert Freije, Mariette Heins, Arash Rassoulpour, Geoffrey Tombaugh, Simon Gelman, Amyaouch Bradaia, Esther Steidl, Melanie Gleyzes, Taneli Heikkinen, Kimmo Lehtimäki, Jukka Puoliväli, Outi Kontkanen, Robyn M. Javier, Ioana Neagoe, Heike Deisemann, Dirk Winkler, Andreas Ebnet, Vinod Khetarpal, Leticia Toledo-Sherman, Celia Dominguez, Larry C. Park, Ignacio Munoz-Sanjuan, The novel KMO inhibitor CHDI-340246 leads to a restoration of electrophysiological alterations in mouse models of Huntington's disease, *Experimental Neurology*, Volume 282,2016,Pages 99-118,ISSN 0014-4886,
21. Zhang, S., Sakuma, M., Deora, G.S. *et al.* A brain-permeable inhibitor of the neurodegenerative disease target kynurenine 3-monooxygenase prevents accumulation of neurotoxic metabolites. *Commun Biol* 2, 271 2019.
22. Parsons MP, Vanni MP, Woodard CL, Kang R, Murphy TH, Raymond LA. Real-time imaging of glutamate clearance reveals normal striatal uptake in Huntington disease mouse models. *Nat Commun.* 2016 Apr 7; 7:11251.
23. Garcia-Miralles M, Yusof N.A.B.M., Tan J.Y., Radulescu C.I., Sidik H., Tan L.J., Belinson H., Zach N., Hayden M.R., Pouladi M.A. Laquinimod Treatment Improves Myelination Deficits at the Transcriptional and Ultrastructural Levels in the YAC128 Mouse Model of Huntington Disease. *Mol. Neurobiol.* 2019; 56:4464–4478.
24. Da Fonsêca V.S., da Silva Colla A.R., de Paula Nascimento-Castro C., Plácido E., Rosa J.M., Farina M., Gil-Mohapel J., Rodrigues A.L.S., Brocardo P.S. Brain-Derived Neurotrophic Factor Prevents Depressive-Like Behaviors in Early-Symptomatic YAC128 Huntington's Disease Mice. *Mol. Neurobiol.* 2018; 55:7201–7215.
25. Todd D, et al. A Monoclonal Antibody TrkB Receptor Agonist as a Potential Therapeutic for Huntington's Disease. Hetman M, ed. *PLoS ONE.* 2014 ;9(2): e87923.
26. Wild EJ, Tabrizi SJ. Therapies targeting DNA and RNA in Huntington's disease [published correction appears in *Lancet Neurol.* 2017 Dec;16(12):954]. *Lancet Neurol.* 2017;16(10):837-847.
27. Stanek LM, et al. Silencing mutant huntingtin by AAV-mediated RNAi ameliorates disease manifestations in the YAC128 mouse model of Huntington's disease. *Hum Gene Ther* 2014; 25:461-474.
28. Spronck, Lisa & Brouwers, Cynthia & Valles-Sanchez, Astrid & deHaan, Martin & Petry, Harald & van Deventer, Sander & Konstantinova, Pavlina & Evers, Melvin. (2019). AAV5-miHTT Gene Therapy Demonstrates Sustained Huntingtin Lowering and Functional Improvement in Huntington Disease Mouse Models. *Molecular Therapy - Methods & Clinical Development.* 13..
29. Chang CY, Ting HC, Liu CA, et al. Induced Pluripotent Stem Cell (iPSC)-Based Neurodegenerative Disease Models for Phenotype Recapitulation and Drug Screening. *Molecules.* 2020;25(8):2000. Published 2020 Apr 24.
30. Tabrizi SJ, Leavitt BR, Landwehrmeyer GB, Wild EJ, Saft C, Barker RA, Blair NF, Craufurd D, Priller J, Rickards H, Rosser A, Kordasiewicz HB, Czech C, Swayze EE, Norris DA, Baumann T,

- Gerlach I, Schobel SA, Paz E, Smith AV, Bennett CF, Lane RM; Phase 1–2a IONIS-HTTRx Study Site Teams. Targeting Huntingtin Expression in Patients with Huntington's Disease. *N Engl J Med*. 2019 Jun 13;380(24):2307-2316.
31. Skotte NH, et al. Allele-Specific Suppression of Mutant Huntingtin Using Antisense Oligonucleotides: Providing a Therapeutic Option for All Huntington Disease Patients. *PLoS ONE* 2014; 9(9): e107434.
  32. Zhang L, Wu T, Shan Y, et al. Therapeutic reversal of Huntington's disease by in vivo self-assembled siRNAs. *Brain*. 2021;144(11):3421-3435.
  33. Lu XH and Yang XW. “Huntingtin holiday”: progress toward an antisense therapy for Huntington’s disease. *Neuron* 2012; 74:964-966.
  34. Kotowska-Zimmer A, Ostrovska Y, Olejniczak M. Universal RNAi Triggers for the Specific Inhibition of Mutant Huntingtin, Atrophin-1, Ataxin-3, and Ataxin-7 Expression. *Mol Ther Nucleic Acids*. 2020 Mar 6; 19:562-571.
  35. Aguiar S, van der Gaag B, Cortese FAB. RNAi mechanisms in Huntington's disease therapy: siRNA versus shRNA. *Transl Neurodegener*. 2017 Nov 27; 6:30. doi: 10.1186/s40035-017-0101-9. PMID: 29209494; PMCID: PMC5702971.
  36. Zeitler B, Froelich S, Marlen K, Shivak DA, Yu Q, Li D, Pearl JR, Miller JC, Zhang L, Paschon DE, Hinkley SJ, Ankoudinova I, Lam S, Guschin D, Kopan L, Cherone JM, Nguyen HB, Qiao G, Ataei Y, Mendel MC, Amora R, Surosky R, Laganriere J, Vu BJ, Narayanan A, Sedaghat Y, Tillack K, Thiede C, Gärtner A, Kwak S, Bard J, Mrzljak L, Park L, Heikkinen T, Lehtimäki KK, Svedberg MM, Häggkvist J, Tari L, Tóth M, Varrone A, Halldin C, Kudwa AE, Ramboz S, Day M, Kondapalli J, Surmeier DJ, Urnov FD, Gregory PD, Rebar EJ, Muñoz-Sanjuán I, Zhang HS. Allele-selective transcriptional repression of mutant HTT for the treatment of Huntington's disease. *Nat Med*. 2019 Jul;25(7):1131-1142.
  37. Colpo GD, Furr Stimming E, Teixeira AL. Stem cells in animal models of Huntington disease: A systematic review. *Mol Cell Neurosci*. 2019 Mar; 95:43-50. doi: 10.1016/j.mcn.2019.01.006. Epub 2019 Jan 24. PMID: 30685323.
  38. Kim HS, Jeon I, Noh JE, et al. Intracerebral Transplantation of BDNF-overexpressing Human Neural Stem Cells (HB1.F3. BDNF) Promotes Migration, Differentiation and Functional Recovery in a Rodent Model of Huntington's Disease. *Exp Neurobiol*. 2020;29(2):130-137.
  39. Linares, G.R., Chiu, C.T., Scheuing, L., Leng, Y., Liao, H.M., Maric, D., et al., 2016. Preconditioning mesenchymal stem cells with the mood stabilizers lithium and valproic acid enhances therapeutic efficacy in a mouse model of Huntington's disease. *Exp. Neurol*. 281, 81–92.
  40. Fink K.D., Rossignol J., Crane A.T., Davis K.K., Bombard M.C., Bavar A.M., Clerc S., Lowrance S.A., Song C., Lescaudron L., et al. Transplantation of umbilical cord-derived mesenchymal stem cells into the striata of R6/2 mice: Behavioral and neuropathological analysis. *Stem Cell Res. Ther*. 2013; 4:130.
  41. Park, H.J., Han, A., Kim, J.Y. *et al.* *SUPT4H1*-edited stem cell therapy rescues neuronal dysfunction in a mouse model for Huntington’s disease. *npj Regen Med* 7, 8 (2022).
  42. Kim A, Lalonde K, Truesdell A, et al. New Avenues for the Treatment of Huntington's Disease. *Int J Mol Sci*. 2021;22(16):8363. Published 2021 Aug 4.
  43. Gu X., Richman J, Langfelder P. et. al. Uninterrupted CAG repeat drives striatum-selective transcriptionopathy and nuclear pathogenesis in human Huntingtin BAC mice. *Neuron*.
  44. McAllister B, Donaldson J, Binda CS, Powell S, Chughtai U, Edwards G, Stone J, Lobanov S, Ejlinton L, Schuhmacher LN, Rees E, Menzies G, Ciosi M, Maxwell A, Chao MJ, Hong EP, Lucente D, Wheeler V, Lee JM, MacDonald ME, Long JD, Aylward EH, Landwehrmeyer GB, Rosser AE; REGISTRY Investigators of the European Huntington’s disease network; Paulsen JS; PREDICT-

- HD Investigators of the Huntington Study Group; Williams NM, Gusella JF, Monckton DG, Allen ND, Holmans P, Jones L, Massey TH. Exome sequencing of individuals with Huntington's disease implicates FAN1 nuclease activity in slowing CAG expansion and disease onset. *Nat Neurosci.* 2022 Apr;25(4):446-457-
45. Deshmukh AL, Porro A, Mohiuddin M, Lanni S, Panigrahi GB, Caron MC, Masson JY, Sartori AA, Pearson CE. FAN1, a DNA Repair Nuclease, as a Modifier of Repeat Expansion Disorders. *J Huntingtons Dis.* 2021;10(1):95-122.
46. Theresa A Gipson, Andreas Neueder, Nancy S Wexler, Gillian P Bates & David Housman (2013) Aberrantly spliced *HTT*, a new player in Huntington's disease pathogenesis, *RNA Biology*, 10:11, 1647-1652.
47. Andrade-Navarro, Miguel A. and Mühlenberg, Katja and Spruth, Eike J. and Mah, Nancy and González-López, Adrián and Andreani, Tommaso and Russ, Jenny and Huska, Matthew R. and Muro, Enrique M. and Fontaine, Jean-Fred and Amstislavskiy, Vyacheslav and Soldatov, Alexei and Nietfeld, Wilfried and Wanker, Erich E. and Priller, Josef}. RNA Sequencing of Human Peripheral Blood Cells Indicates Upregulation of Immune-Related Genes in Huntington's Disease. *Frontiers in Neurology.* 11,2020 1664-2295.
48. Sneha, N.P.; Dharshini, S.A.P.; Taguchi, Y.-h.; Gromiha, M.M. Investigating Neuron Degeneration in Huntington's Disease Using RNA-Seq Based Transcriptome Study. *Genes* **2023**, 14, 1801.
49. Lim RG, Al-Dalahmah O, Wu J, Gold MP, Reidling JC, Tang G, Adam M, Dansu DK, Park HJ, Casaccia P, Miramontes R, Reyes-Ortiz AM, Lau A, Hickman RA, Khan F, Paryani F, Tang A, Ofori K, Miyoshi E, Michael N, McClure N, Flowers XE, Vonsattel JP, Davidson S, Menon V, Swarup V, Fraenkel E, Goldman JE, Thompson LM. Huntington disease oligodendrocyte maturation deficits revealed by single-nucleus RNAseq are rescued by thiamine-biotin supplementation. *Nat Commun.* 2022 Dec 21;13(1):7791.