Review Article: Huntington Disease: Mechanism of Pathogenesis and Recent Developments in Its Therapeutic Strategies- A Short Review

Ozoemena Emmanuel Eje[1,*], Chimeremnma Victory Ogbonna[2], Chinekwu Samson Onoyima[1], Florence Obiageli Nduka[1, 3]

[1]*Department of Biochemistry, University of Nigeria, Nsukka, Enugu, Nigeria*
[2]*Department of Community Health Extension, School of Public Health/Nursing Technology, Nsukka, Enugu, Nigeria*
[3]*Department of Applied Sciences, Federal College of Dental Technology and Therapy, Enugu, Nigeria*

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ABSTRACT

One of the leading causes of death apart from cancer is a neurodegenerative disease. Huntington's disease (HD) is such that affects the neurons resulting from the programmed degeneration of the nerve cells. It is expressed throughout the brain, most striking within the striatum and the cortex. The misfolded HD protein interrupts the other interacting proteins' activity resulting in the abnormal functioning of the nerve cells leading to the uncontrolled movements, loss of intellectual faculties, emotional disturbances categorizing motor dysfunctions, and behavioural and cognitive deficits. The genomic origin of the disease can be traced to the amplification of a cysteine-adenosine-guanine repeat that encodes a polyglutamine region in the huntingtin's amino terminal end. However, the mechanism and modality in which cysteine-adenosine-guanine expansion leads to a poisonous effect on the neuron are yet to be clearly understood. However, studies have recently revealed that change in the blueprint (mRNA) of the protein gives rise to misfolded protein and the fragments accumulate, by making interaction with the other elements in cells resulting in the problems associated with HD. Hence, as opposed to the traditional and controversial protein misfolding hypothesis, amyloid formation is the result rather than the HD cause. Although, the N-terminal fragments of mutant huntingtin (mHtt) misfolded into amyloid-like fibrils as a key signature of HD pathology. Currently, no effective remedy has been found for HD. This review highlights the possible cause, pathogenesis, and recent therapy aiming at down-regulating the expression of huntingtin (Htt), lowering the misfolding, and aggregation of the huntingtin protein.

***Corresponding Author: Ozoemena Emmanuel Eje** (ozoemena.eje.pg01794@unn.edu.ng)*

Ozoemena Emmanuel Eje: He is a graduate Research Assistant at the University of Nigeria, Nsukka, Enugu, Nigeria. He completed his BSc and MSc from the department of Biochemistry, University of Nigeria. He has a strong research interest in the following areas: Enzymology, Protein Chemistry, Computational Biology, Phytochemistry, Bioinformatics, and Nanotechnology, Biopolymer synthesis, Additive manufacturing and he also engages multidisciplinary research areas.

Chimeremnma Victory Ogbonna: She has completed a degree in Community Health at the School of Public Health Nursing/Technology, Nsukka, Enugu, Nigeria and is currently taking higher national diploma (HND) in Public Health in the same School.

Chinekwu Samson Onoyima: He is graduate of Biochemistry University of Nigeria Nsukka and currently a postgraduate program (MSc) student in the same school with specialization on Enzymology. He's a Graduate Research Assistant, a Computational Biologist with special interest in Bioinformatics, Drug Discovery, designing and targeting. A hard working and results-oriented young scientist.

Florence Obiageli Nduka: She is a lecturer in the Department of Applied Sciences, Federal College of Dental Technology and Therapy, Enugu, Nigeria. She holds master's degrees in Pharmacological Biochemistry and Environmental Biochemistry from the Department of Biochemistry, University of Nigeria and is currently a PhD student at the same department. Her research interests are Environmental Management, Nanotechnology and Green Synthesis and has published research articles in a reputable journals.

Content

1. Introduction

In the early times, HD's nature was originally sketched by the Renaissance alchemist; Paraclesus dates back to the 16th century and is termed the most prominent motor feature of the disease "chorea naturalis". Until 1872, George Huntington delivered a lecture describing the disease as Huntington's chorea. This neurodegenerative disorder is genetic, i.e. it passes from one generation to the other within families. The disease onset occurs often among the middle-aged individuals with a characteristic triad of dancing movements, cognitive impairment, mental illness, and dementedness are the common features [1],[2]. Until the 1980s, the name remained unchanged for many decades when the full awareness of the widespread slowness of movement indication was unveiled; HD became the acceptable name to date. A connection of the causative gene on chromosome 4 was well-known in 1983, and the HD gene was discovered and sequenced in 1993 [3],[4]. Huntingtin protein is highly connected to some cytoplasmic and nucleus-related cellular activities including several other proteins linked that play crucial roles in the expression of a gene, intra-cell signalling, transport, and metabolic function. Studies provide multiple lines of evidence that Htt is associated with neurogenesis and with DNA repair [5]. Although the array of gene mutations due to the irregular CAG enlargement is clear to have existed in the huntingtin genome, 4p16.3, its modality of apoptosis and the reason why the stratum of the brain is the major target remains vague [6],[7], The finding of the root cause of HD was striking as it opened more doors for research on the other neurodegenerative ailments. The real pre-manifest diagnoses of the other trinucleotide repeats-based disease conditions such as Spinobulbar muscular atrophy (SBMA), Spinocerebellar ataxias (SCA), and Dentatorubralpllidoluysian (DRPLA) were found for the first time during the period. Over time, HD has been a template and blueprint of research on neurodegeneration among neurologists and neurosurgeons. These diseases have similar mutations coupled with the fact that they are all dominant except SBMA which is X-linked. In each of these diseases, the protein-carrying mutation, and also distribution of the neuronal loss are different which are likely to be responsible for the difference in the patterns of neurodegeneration [8].

The HD prevalence occurs in the ratio of 3-7:100,000 among people from the western European. It is most common among the Japanese, Chinese, and the people in Finland including the black even though in terms of populations, people of Western European origin reported major cases of HD of 15 per 100,000 [9]. The identity of this monogenic alteration accountable for HD was described at first among Venezuela's Lake Maracaibo region dwellers and is thought to be the highest predominance of HD worldwide [10]. In particular, influenced allomorphs with haploid genotype event in the usual population of these groups of people enhance clarification perhaps in part of the uneven spreading of this disease. According to the European Huntington's Disease Network, it was reported that 15-20% of HD occurrences happened in ten years among people from Australia, North America,

and Western Europe. Whether these specific haplotypes' proclivity for CAG expansion is due to the size of the CAG tract, or the cis-agent content of the haploid genotype that confers the tendency for variability is debated [4],[11].

1.1. Hereditary foundation of Huntington's chorea

As previously mentioned, HD leads to an inheritable defective gene from a single mutant huntingtin. The Htt gene codes for a protein known as huntingtin, which plays a crucial role in brain neurons [5],[8],[10],[11]. The Htt mutation involves a DNA segment that is repeated within the gene 10 to 35 times. Individuals who have ≥40 repeats are definite, 36 -39 repeats are at high risk, CAG repeats of 27 to 35 in Htt gene are at low or no risk; children of affected parents are at risk of development while ≤26 is normal repeats length, no risk of disease development in parent or offspring, as displayed in **Figure 1** [6]. The extended protein molecules are split into the smaller fragments. These fragments are toxic when bound together and accumulate in the neurons, and thus interfering with their normal functions [12]. This physiological interruption and dysfunction could eventually lead to the nerve cell apoptosis in the brain region triggering the manifestations seen in HD [5],[13].

Despite the single gene origin of HD, the signature of its pathology is extremely complicated. The normal huntingtin has crucial roles in DNA transcription, and preservation, monitoring cell division, arrangement of cell components, shuttling of macromolecules, catabolic and anabolic roles, synaptic communication, and polypeptide pool balance. Having seen the different forms of existence among molecules, mHtt can cause the widespread proteome destabilization and successive interruption occurs during various intra- and inter-cell metabolism [14]. Human genetics revealed that the restoration pathways in DNA particularly during mismatch repair (MMR), serve a key function during the initiation, and then progression of CAG repeat diseases [15-17]. Several genes possessing the disease-causing CAG expansion tract encrypt the other macromolecules involving the repair of a gene. DNA damage accumulation in the neurons leads to an extra increase in a triad repeat location, thereby establishing a pathological cascade trend if not intervened [16]. It is noteworthy that this disorder is an inheritable autosomal dominant pattern since the inheritance of a single mutant allele can be responsible for an array of cell dysfunction [18, 19]. Modality of inheritance of this mutant gene is achieved through an infected person and more seldom, some affected individuals do not have parents that originally had the disorder. The amount of this poly repeat tends to increase exponentially with the number of mutant huntingtin genes which are inheritable in nature. This rise in expansion has been

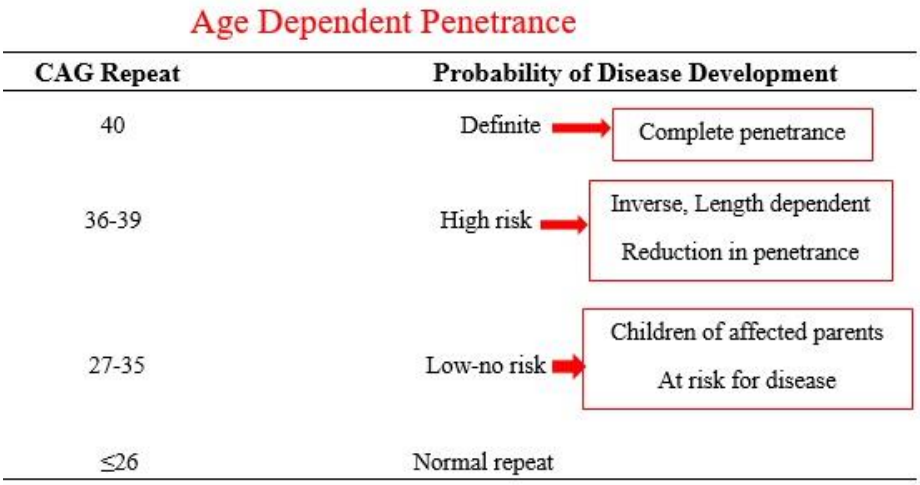

Figure 1. Age-dependent penetrance of HD

linked to the genesis of its manifestations and this is wholly referred to “Anticipation”. Among aged individuals and children, 40-50, and above 60 repeats of the trinucleotide repetition of the glutamine tract in the misfolded gene results to the disease’s signs and symptoms.

As early stated, this brain-related disorder exhibits some movement disorder, psychological impairment, and attitude instability [12]-[14],[20]. The disease-causing genetic mutation was revealed for over 2.5 decades, and studies on the experimental rats showed irregular cell stacking during peptide conversion of the message into protein, post-processing, and purification [21]. The pathology entails timely and unresolved deterioration of the striatal part of the brain and sooner or later greater substantial dearth of cerebral matters [5], [20-23]. They can be detected using blood tests and this gene is responsible for this enlargement of the mutant gene leading to the brain deterioration within a decade and half before the indication of its pathophysiology [24, 25].

The coordinators of movement, thinking, or even talking progressively fail as neurons have been destroyed and apoptosis occurred, especially within the striatum, which is maximally stricken by HD. As this continues, the other part of the brain, the cortex gets also affected making mental retardation more complicated [26].

1.2. Causes of Huntington’s diseases

A lengthened CAG replication at the first exon HD gene located at chromosome 4p16.3 is the root cause of HD [14],[16],[27]. Just one mutant copy causes progressive neuro-degeneration, which typically begins in person's forties. This mutant protein disrupts the activity of other interacting proteins, resulting in abnormal nerve cell function [28]. Even though the Htt allele had been revealed several years ago, the neurobiological nature of the protein was only recently discovered. This expansion of CAG starts from the root sequence of DNA tribase coding from glutamic acid that produces the misfolded protein, as depicted in **Figure 2** [26],[29],[30].

2. Pathogenic Mechanism of Polyglutamine Diseases

Molecular studies revealed that the diverse CAG found in animal mutant huntingtin all codes for glutamine near the amino acid end. The native huntingtin is a structural protein that anchors diverse macromolecules which plays crucial roles in cell metabolism. However, when Htt misfolding exists, there is loss of normal function due to protein breakdown of the mutant form leaving the fragments and gaining harmful features which interrupt many cell functionalities (**Figure 3**) [31]-[33]. Likewise, splicing mistakes are produced when small polyadenylated mRNAs code for the mutant pieces, short polyadenylated mRNAs, indicating that the small disease-generating fragments as not the cause, but the results of proteolytic dysfunction or impairment [34],[35].

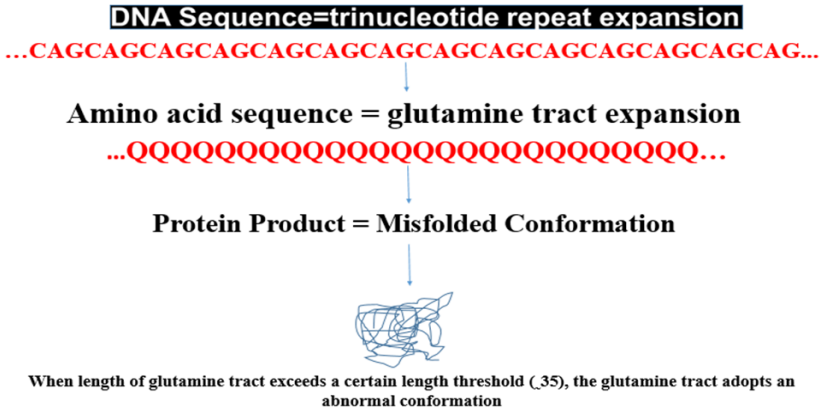

Figure 2. Trinucleotide expansion

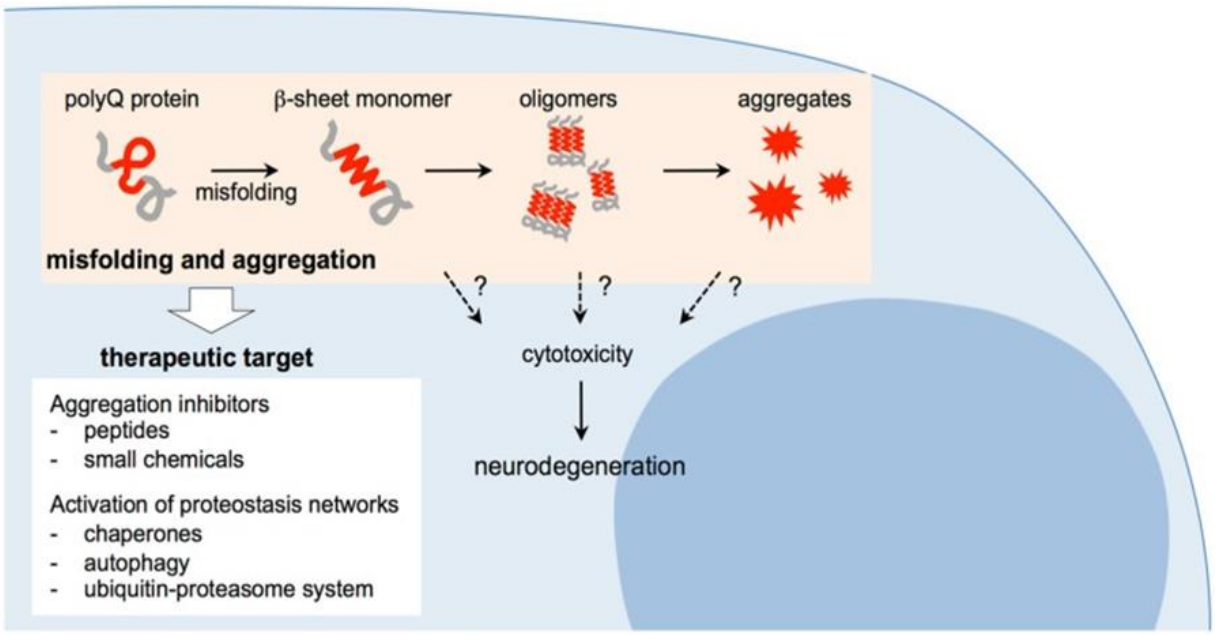

Figure 3. Amplification of CAG tract enlarged polyQ

Some other abnormal polypeptides such as polyalanine, polyserine, polyleucine, and polycysteine have been presented to amass in the HD patients which also cause neurone breakdown [36, 37]. Notwithstanding this scientific proof, there appears to be a correlation between the number and position of inclusions, and HD-degenerate brain regions. Furthermore, research using animal subjects has revealed that neurodegeneration can occur without the presence of observable aggregates and granules can be the pioneer in the epilepsy of neuronal impairment or degenerative changes. The toxic species in HD, on the other hand, have been recognized as decipherable repeating units of the misfolded protein, mHtt [38]. Furthermore, research showed that altered Htt ribonucleic acid stable hairpins are poisonous [36]. These submit the existence of several toxic Htt species, each, which may function differently during the onset of Huntington's disease. These suggest the involvement of the toxic feature mechanism in the etiology of polyglutamine infection [39]. Certainly, it has been reported that knocking off the huntingtin gene has no drastic effect on the physical appearance [8],[40]. On the other hand, knock-out experimental mice HD gene revealed that huntingtin allele distortion leads to serious damage and/or death of the embryo. This further supported the aforementioned crucial role of the protein, since it is highly conserved in several organisms [8],[12]. Polyglutamine abnormal enlargement resulting in disease condition is due to a gain in function mechanism ascribed to a monogenic change in the CAG reiteration growth and HD is not an exception [1],[11],[41].

2.1. Pathophysiology of HD

The advance symptoms sometimes appear as a negligible physiological, cognitive, or emotive change. Many disorders seem to be much more dominant and possess a larger impact on the features and roles as the disease continues [18]. Physiologic indications of HD include "nervous" activity, squirming, extreme exhaustion, and tiredness, or anxiety at the onset. Clumsiness, uncontrolled scripting, or difficulty in carrying out house chores, corporal skills, and dynamical activities are usually the experiences [1],[42]. The early abnormality in movement signs often graduates further to some unconscious movements such as shaking and shuddering of several body parts including the head, collar, arms, and legs, which may interfere with walking, speaking, and swallowing. Although some patients' experiences in moving their

body parts are minimal, this spontaneous move rise with the conscious activity, stress, anxiety, excitement, and drops at individual resting state, however, while it becomes infinitesimal when asleep. The HD manifestations make the individual vulnerable to problems of thinking, moving, balance and falls, losing weight, and sleeplessness [8],[19],[23].

The medical manifestation of HD carrier parent stands as one among the other diagnostic tools to detect possible individuals with HD through DNA analysis i.e. a double barrel approach of engaging clinical measures with genetics for examination. There should be no signs nor symptoms detected, but the individual is at the risk of having the disease, and then a predictive examination of the gene or DNA will be a determinant of the possibility of CAG extension beyond normal or not [7],[43],[44].

3. Therapeutic Strategies and Approaches

One aspect of disease diagnosis is to unravel the possible treatment approach. Unfortunately, at present, no efficient cure has been elucidated to handle the principal cause(s) of HD, even though some strategies that aim at reducing the HD manifestation for the affected patients have been discovered, it is cloned with multifaceted drawbacks [2]. Recently developed disease-modifying strategies aimed at reducing Htt expression are being investigated as a potential treatment for HD [45],[46], as indicated in **Figure 4**. Among these therapeutic approaches include the use of ribonucleic acid interference (RNAi) for gene silencing, clustered regularly interspaced short palindromic repeats (CRISPR-Cas9) for molecular scissoring, Ionis's drug, and antisense oligonucleotide (ASO)] also known as lowering therapies targeting misfolded and clustering huntingtin and its mutant form. Further targeting the "RNA" which is an intermediate between the information in the HD gene and the huntingtin protein have given the promising results. However, more efficient HD therapeutics are needed to better improve the life of an affected person. Histone deacetylase (HDAC) inhibitors possess therapeutic value except for their toxic effects [47],[48]. Flavonoids have also been proven to be used as therapeutic molecules for HD [13]. RNAi or ASO reduces wild-type or mHtt appearance, which has shown valuable in different experimental models with a mouse. The zinc finger nucleases (ZFNs) are another strategic tool for editing the entire gene responsible for CAG zone enlargement [6], [49]. CRISPR/Cas9 system (molecular scissors) represents a genome editing tool enabling clear-cut alteration along DNA sequences and serve as options for the treatment of HD [17], [50]. Nevertheless, despite how helpful these tools are, they suffer shortcomings. Since an efficient alternative is yet to be announced, these approaches are currently employed to save the life of a dying HD individual. Some tools are the nuclease-oriented gene re-writing equipment which are the single-stranded oligodeoxynucleotides, transcription activator-like effector nucleases (TALENs), ZFNs, CRISPR-Cas9, and RNA-guided nucleases [17],[49]. In the CRISPR Cas9 system, the expression of the 160 kDa protein (Htt) with the single guide RNA molecule (sgRNA) is the key to the efficient role of the system in genome re-writing for therapeutic intervention. As a result of this co-expression, the binding of the sgRNA molecules triggers the recruitment of the Cas9 protein to target a specific sequence of interest in the gene ladder initiating the breakage of the double-stranded DNA, hence activating the control system for the dsDNA break repair pathway [49],[51] (**Figure 4**). The response of the cell to the collapse of the DNA ladder can be explained using two mechanisms: non-homologs end joining (NHEJ) and (b) homology-directed repair (HDR) mechanisms. The former is responsible for frameshift, insertion, and deletion while the latter gives a DNA blueprint serving as the donor homologous re-joining processes [49], [52], [53]. The deletion of the target gene by NHEJ is achieved when the complex, sgRNA-Cas9 is tightly bound to the target region causing the unwinding of the double-stranded gene. The DNA-oriented therapies for lowering HD are pre-clinical levels with some ethical concerns because of the attempt to tamper the germline DNA. However, other therapeutics such as stem cell, antibody, and small molecule therapies (the first two are administered through the vein and the latter orally) show less invasive and are still under scrutiny [41],[54]. It is noteworthy that each of

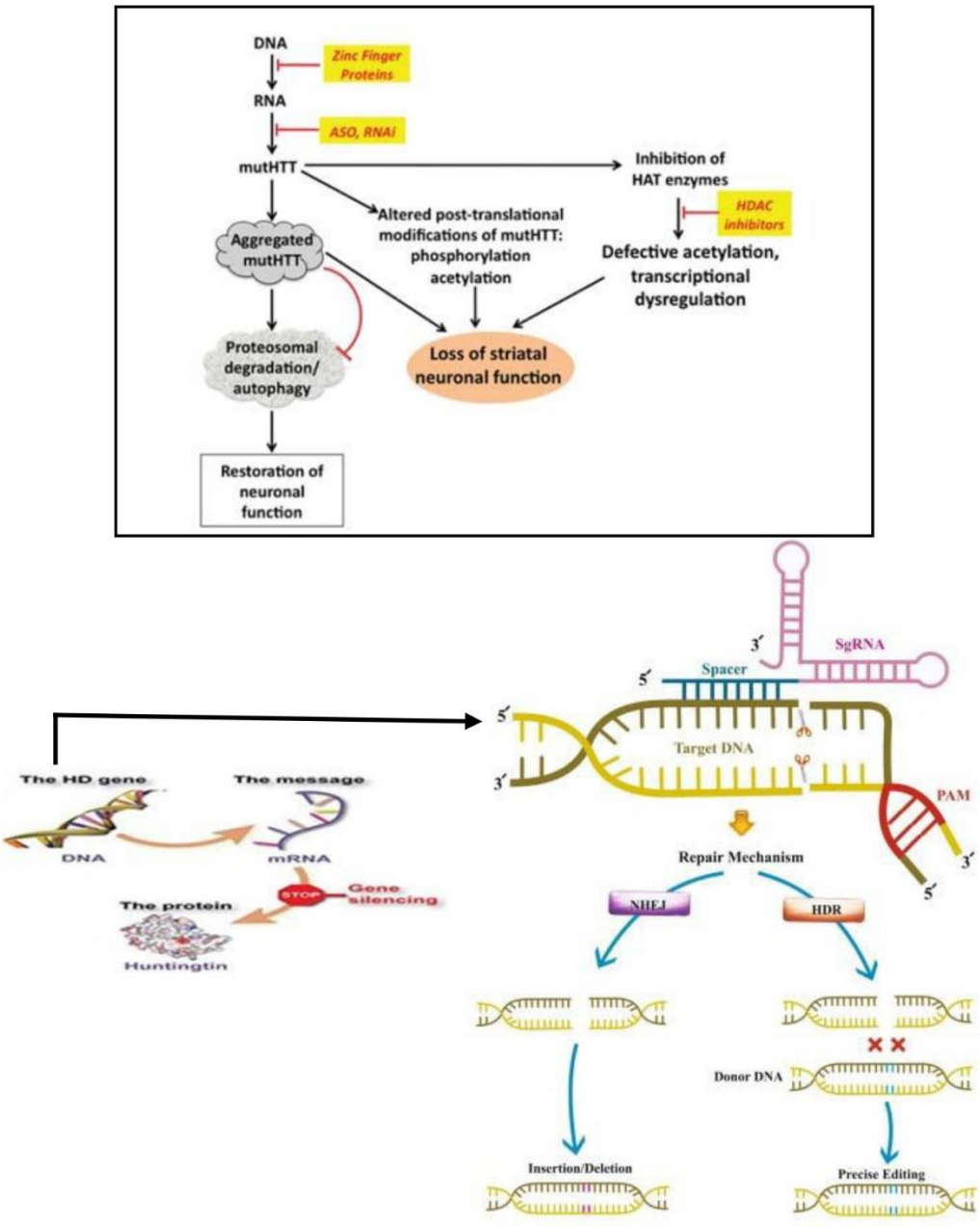

Figure 4. HD Therapeutic targets

the aforementioned treatments has strengths and weaknesses, even though, these drugs are of great benefit to ameliorate the HD symptoms until novel and efficient ones are discovered, approved and made accessible to HD patients [20],[55]. Of all these genome editing tools including the CRISPR-Cas9 which is considered the utmost, cost-effective, robust, and flexible tool, notwithstanding their numerous benefits have some limitations. These drawback are off-targets, unwanted deletion, and insertion, production of gRNA, and efficient delivery system [53].

The TALENs are protein motifs, and specific endonucleases recognizing DNA and are produced by unique polypeptides, the TALE

proteins commonly found in Xanthomonas, the invasive bacterium affecting plants. These proteins can be engineered by combining a DNA-binding region effector, TAL with a nuclease cutting at the DNA exact point, practically at any desired DNA sequence. One TALE motif has the capacity to identify a nucleotide and its collection can assemble with an extended sequence [17], [41], [60]-[63], [42], [48], [49], [53], [56]-[59]. Hence, the role of each TALE region is constrained to a single nucleotide that doesn't influence the binding of other nearby TALEs making TALENS engineering more simple and easy compared to ZFN.

It is important to acknowledge that ZFNs are a group of proteins playing crucial roles during transcription, hence called transcription factors (TF). When this protein combines with an endonuclease *FokI,* it induces the recognition of trinucleotide sequence providing on-target specificity. The *FokI* endonuclease works as a dimer, since the double-strand DNA cutting takes place at the exact site where two ZFNs bind to the opposite DNA strands. In the ZFNs system, zinc finger motifs are arranged in a manner that the neighbouring protein-nucleases would be influenced for a specific action, making the construction and selection of this arrangement of modified zinc fingers more tasking and time-consuming. This is because it is a jaw-breaking task to predict the specificity of the final and functional arrangement. As mentioned before, the system relies on two ZFNs fashioned to spot various closely allied arrangements of nucleotide in the target site, and it needs both ZFNs to recognize and bind at the same time, limiting off-target effects [17],[41],[60]-[63],[42],[48],[49],[53],[56-59].

Both TALENS and ZNF envelop the FoKI nuclease and need them to carry out their functions in gene-editing technology.

The CRISPR system of genome editing comprises Cas9 nuclease and RNAs isoform, trans-activating crRNA (tracrRNA), and sgRNA identifies target sequence by base pairing and replication model of Watson-Crick. The Cas9 houses motif of DNA referred to the protospacer adjacent motif (PAM) e.g., 5'-NGG-3' is a normal Cas9 [59]-[62]. Cas9 nuclease cleaves DNA, which can result in a collapse of the DNA double-stranded ladder in the enzyme or a collapse of a single strand in mutant Cas9 variants known as nickases. RNA-DNA interactions govern the recognition of DNA sites in the genome editing system of CRISPR-Cas9. This has many benefits compared to ZFNs and TALENs, due to the easy design approach for any targeted gene of interest, the likelihood of detecting off-target sites, and at the same time the ability to modify multiple genomic sites (multiplexing) [53], [56-58], [62].

Scientists are yet to uncover the entire functions of this protein, huntingtin which is argued to be responsible for many metabolic activities in the entire cell environment besides the brains [15], [29]. However, Dr. Kochanek has unraveled its nature, and also elucidated the modality of interaction with other biomolecules bringing to light the diverse roles of the wild-type. This observation at the time was mind-blowing as shooting in the dark to comprehend huntingtin's role was a history of the past [64-66]. His innovative finding was a big relief and fired up the zeal for the discovery of an effective treatment for HD, since a clear distinction between the native and mutant Htt has been made [8], [27], [65].

Moreover, in July 2018, McMaster University led a team of scientists who lay bare new signalling from damaged DNA. The signals were considered huntingtin activity markers in DNA repair and are impaired in HD, the research in forming the claim was published in the National Academy of Sciences Proceedings (PNAS). The outcome of that research with a mouse model (according to Laura Bowie, a Ph.D. student in McMaster's Department of Biochemistry and Biomedical Sciences) showed that the excess application of the signalling molecule even orally tends to restore signalling HD [66]. Consequently, the alteration of the wild-type was not observed in the mutant form, by this claim a novel compound, N6-furfuryladenine obtained from the repair of DNA damage improved the defect in mHtt, restoring it to normalcy-a recent turn in the hunt for HD antidote". Shannon and Fraint [21] had reported the use of tetrabenazine (**Figure 5**) as an approved drug in the US for the abnormal movement in HD patient due to its ability to not

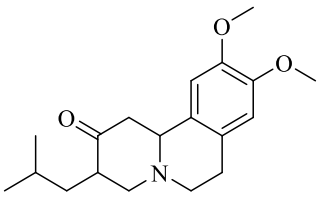

Figure 5. Tetrabenazine structure for chorea treatment

only inhibit the vesicular monoamine transporter type 2 (VMAT2), and also reduces the neurotransmitters, dopamine, noradrenaline, and 5-hydroxyl tryptamine (serotonin) [50],[54]. Most of the treatment approach targets the DNA or/ RNA to lower the toxic effects resulting from huntingtin misfolding [54].

More insight kept precipitating as Bowie [67] posited that amyloid-protein aggregation and deposition were not the cause but the consequence of the disease case. That was a ground-breaking era that opened up a novel way and claims into asking critical questions. Although the observations and claims were not equal to an effective drug or a cure, this hypothesis brought hope for HD in 25 years since its structure elucidation, as it annuls the amyloid claim which has failed in drug development not just for HD but other diseases [63],[64], [66]. Noticeably, the clinical studies for a number of these therapeutic agents are either underway or will begin soon, making this an interesting time for HD drug continued development. In the future, the application of throughput molecular imaging, and digital biomarkers for therapeutic would improve the clinical trial strategy. Besides, regulatory agencies amplified-flexibility amplified flexibility in discussing refined effectiveness endpoints will enable clinical trial progression.

4. Conclusion

In conclusion, this review indicated that knowing the cause of the disease and its manifestation does not always guarantee efficient treatment in real-life, since every progress in life is dependent on work and collaboration, developing a proper drug for Huntington's patients' needs a hands-on deck. The HD carrier always feels time exhaustion for being alive due to the rapid expansion of CAG. Although better insight into the pathogenesis has led to the development of drugs in experimental animals, it is unclear whether targeting just one of these downstream pathogenicity would be acceptable, and whether all of them should be targeted. Regardless of the previous failures, the future appears bright to find potential treatments for HD.

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Conflicts of interest

None declared.

Orcid:

Ozoemena Emmanuel Eje
https://orcid.org/0000-0001-8680-6117
Chinekwu Samson Onoyima
https://orcid.org/0000-0002-3137-6356
Florence Obiageli Nduka
https://orcid.org/0000-0001-9912-9290

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