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Review

Zebrafish as an Alternative Animal Model of Huntington's Disease: Challenges and Future Directions

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Abstract

Huntington's disease (HD) is a lethal autosomal dominant neurodegenerative disorder characterized by progressing cognitive, motor, and other behavioral deficits. Animal models, especially rodent-based, are a valuable tool to study brain disorders, including HD. Given the existence of multiple valid and predictive models of HD and other brain disorders, we are now entering a phase of mechanistic discovery, as research shifts towards phenotype-based screening and multi-omic validation. In addition to rodent models, zebrafish (*Danio rerio*) are rapidly becoming a promising model organism for translational HD research. With considerable genetic homology to humans, embryonic transparency for real-time pathology tracking, physiological similarity to mammals, and high-throughput drug screening potential, zebrafish have become a valuable alternative model organism in translational HD research. Here, we discuss zebrafish HD models, their advantages and limitations, and future directions of translational research in this field.

Keywords: Huntington's disease; animal model; cross-taxon analyses; translational research; zebrafish

1. Introduction

Huntington's disease (HD, Huntington's chorea) is a serious, severely debilitating and lethal neurodegenerative disorder which represents a common cause of disability and mortality [1], with global prevalence of 0.38–2.71 per 100,000 people [2]. HD involves a wide range of motor and psychiatric symptoms [3,4,5] and presents a major economic, societal, and public health burden [6,7,8]. Typical clinical symptoms of HD include progressive chorea and hypokinesia which progress [9], accompanied by various other motor and mental deficits (Table 1 and Fig. 1). HD is frequently comorbid with other brain illnesses, including epilepsy, Alzheimer's disease, depression, and sleep disorders [10,11,12].

Unlike other major neurodegenerative illnesses, HD is a monogenic autosomal dominant disorder caused by the abnormal cytosine, adenine, and guanine (CAG) nucleotide repeat length in the huntingtin (*HTT*) gene (4p16.3). Resulting in mutant huntingtin (mHTT) protein with an enlarged polyglutamine chain, this mutation causes protein fragmentation, abnormal folding and accumulation that disrupt brain tissue and causes HD-related neurological deficits [9,13]. HD has racial differences in CAG repeat length, with Europeans and North Americans showing higher prevalence of the disorder than Asians [14,15]. Although HD impacts men and women relatively equally, female patients present more symptoms with a faster progression, impairing functional ability, independence and mood to a greater extent [16,17,18,19].

Currently, there are no effective treatments for HD, besides alternative management and quality of life/palliative support therapies [13]. HD is usually treated with supportive and symptomatic therapies using vesicular monoamine transporter 2 (VMAT2) inhibitors (e.g., tetrabenazine and deutetrabenazine) and antipsychotics to control motor symptoms, as well as selective serotonin reuptake inhibitors (SSRIs) to improve psychiatric symptoms, such as depression [20,21]. Potential disease-modifying therapies currently considered for HD involve modulating autophagy, increasing neurotrophic support, and epigenetic regulation [22,23,24]. Gene therapy (e.g., antisense oligonucleotides and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology) and stem cell transplantation have also entered clinical trials to treat HD [15,25,26].

HD symptoms show a typical progressive age-dependent pattern [27] (Fig. 1). At the preclinical stage (10–15 years before the motor symptoms), patients may show subtle neuropsychiatric and cognitive changes, in-

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Table 1. Major clinical symptoms of Huntington's disease (HD), including associated underlying mechanisms (also see Fig. 1).

Category	Symptoms	Mechanisms
Motor	Chorea Bradykinesia (slow movement) Dystonia (involuntary muscle spasms) Impaired gait/balance	Degradation and dysregulation of medium spiny neurons (MSNs) in striatum, basal ganglia-thalamocortical circuits. Reduced gamma-aminobutyric acid (GABA) and dopaminergic signaling
Cognitive	Memory decline Slow cognitive processing Severe dementia at late HD stages	Frontal and temporal lobe atrophy, due to synaptic dysfunction by mutant huntingtin (mHTT) aggregate toxicity, hence disturbing the brain-derived neurotrophic factor (BDNF) signaling
Psychiatric	Mood swings Anxiety Depression Irritability and aggression	mHTT aggregate toxicity in the limbic system (e.g., amygdala and the hippocampus); imbalance of serotonin and dopamine levels
Systemic	Weight loss Insomnia, chronobiology disorder Deficits in visuospatial processing	mHTT aggregate accumulation in peripheral tissues causes metabolic dysfunction (affects mitochondrial functions)

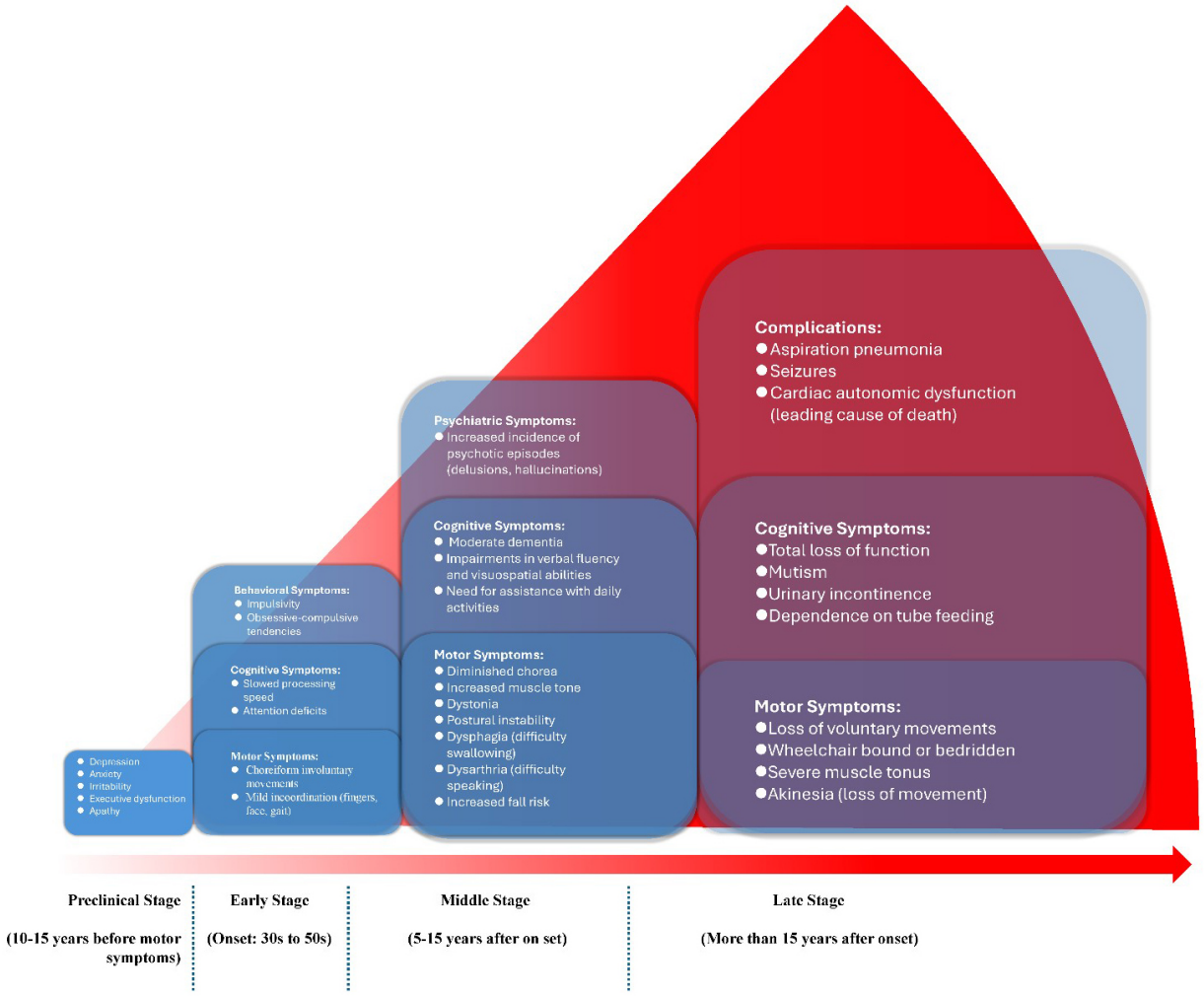


Fig. 1. Progression of clinical Huntington's disease (HD) symptoms and complications, as well as phases across the disease. Note the present lack of zebrafish models that clearly recapitulate this progression (also see Table 1 for details).

cluding depression, anxiety, irritability, apathy, and executive dysfunction, which are often misdiagnosed as primary psychiatric disorders [28,29]. Motor symptom onset (usually in the 30–50s) is marked by involuntary movements, initially characterized by mild incoordination of the fingers, face, or gait, progressing to generalized chorea [30,31,32,33,34]. This stage is often accompanied by pronounced cognitive decline and behavioral abnormalities [1,35]. In the middle of the disease (i.e., 5–15 years after its onset), motor symptoms can become more complicated, as chorea may diminish, while muscle tone, dystonia, and postural instability become dominant, leading to dysphagia, dysarthria, and falls [36]. Cognitive functioning deteriorates to moderate dementia, with impaired verbal fluency, visuospatial abilities, and the need for assistance with daily living [37]. Other psychiatric symptoms, such as psychotic episodes (e.g., delusions and hallucinations), are also increasingly seen during this HD phase [38]. In the later HD stages (>15 years after onset of the disease), patients lose the ability to make voluntary movements and become wheelchair bound or bedridden. Their chorea also largely disappears and is replaced by muteness, urinary incontinence, dependence on tube feeding, and various complications (e.g., pneumonia or seizures) that become the leading cause of death [39,40,41,42,43].

2. Experimental Animal Models of Huntington's Disease

In addition to extensive clinical studies of HD, animal models of this disorder generate important translational insights into its molecular pathology and potential therapies [44]. Commonly used animal models of HD include mammals (especially rodents and primates) and non-vertebrate species, such as worms and fruit flies (Table 2, Ref. [45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68]) [44,45]. Mice and rats have long served as model species of this disorder due to their genetic and physiological similarity to humans as well as experimental convenience [69]. Although the rodent cerebral cortex is far less complex than that of humans, their overall neuroanatomy is highly similar [70,71].

Because targeting HTT represents the most logical and rational strategy to model HD, transgenic mice (developed by introducing a genomic fragment with exon 1 of human *HTT*), predictably exhibit progressive neurological phenotype [64]. Multiple other genetic mouse models with expanded CAG repeats produce an HD-like profile with early onset age, alertness, altered exploration, hyper-responsive to sensory stimuli, and reduced lifespan [64,71]. More specific motor deficits have also been detected in these mice, including resting tremors, stereotypicity, involuntary movement, and occasional ataxia [64]. Other transgenic mouse HD models include N171-82Q and N586-82Q constructing 171 and 586 N-terminal amino acids of human *HTT* cDNA, respectively – both showing weight loss, reduced life span, progressive motor and cognitive decline, and several other HD-like symptoms, including depression-like behavior [59,60].

The two most studied transgenic mouse HD models are the transgenic animals engineered using yeast artificial chromosomes (YAC) - the YAC128 mice, and using bacterial artificial chromosomes (BAC) to model HD - BACHD mice, expressing a full-length human HTT construct with 128 and 97 repeats, respectively [63,68] (Table 2). Both strains display weight gain, brain atrophy, as well as progressive motor and gait decline, whereas YAC128 mice present early hyperactivity followed by later hypoactivity, and BACHD mice display reduced exploration [72]. Both models also exhibit depression-like and anxiety-like phenotypes, as well as cognitive deficits, including progressive motor learning deficit and novel recognition deficit, which are especially robust in YAC128 mice [63,68,71]. Genetic knock-in mice have also been established to investigate HD. For example, HdhQ111 mice, created with 111 CAG repeat units in the first exon of the endogenous *Htt* gene [73], help study the abnormal development of striatal neurons during the embryonic stage of HD [74,75]. CAG140 mice, in which 140 repeats of a pure CAG tract replace the mouse *Htt* exon 1 [76], target HD-related emotional symptoms and abnormal striatal gene expression [77,78]. The zQ175 mouse model originates from the spontaneous amplification of the CAG repeat sequence in the CAG140 knock-in mouse strain and is widely used in studying early HD pathogenesis and evaluating therapeutic drugs [79]. HdhQ150 mice, carrying a mutant knock-in with a 150 CAG/polyglutamine (polyQ) repeat mutation, help study the pathogenic mechanisms of the mHTT exon 1 protein [77,80], whereas HdhQ200 mice, carrying a mutant allele with a 200 CAG/polyQ repeat mutation, present an earlier appearance of aggregate pathology and more rapidly progressing HD-like motor deficits [81].

In addition to rodents, there are also other mammalian models of HD, including transgenic sheep with an inserted full-length human *mHTT* gene, recapitulating presymptomatic HD with no overt motor or cognitive deficits, but nerve fiber aggregation in cortical areas, reduction of striatal gamma-aminobutyric acid (GABA) receptors, and circadian rhythm dysregulation [82]. Transgenic monkeys exhibit progressive symptoms and pathologic features similar to those of human HD, including cognitive and motor dysfunction, loss of striatal neurons, aggregation of mHTT, decreased NAA, and astrocyte proliferation. They provide a reliable animal model for the study of the pathogenesis of HD and its treatment. However, traditional mammalian models are constrained by limitations related to scalability, cost, regulatory restrictions, and real-time pathological observation [9,25,83]. Collectively, this calls for the development of new models and the use of novel model organisms, in translational HD research.

Table 2. Selected genetic animal models of Huntington's disease (HD), including *C. elegans*, *Drosophila*, rodent, and primate models along with their corresponding genetic mutation/manipulation.

Models	Construct	CAG repeat	References
Caenorhabditis elegans			
HtnQ95, HtnQ15	79 and 171 amino acids of N-terminal fragment	95, 50	[46]
Htt57Q88, Htt57Q128	57 amino acids of N-terminal fragment	88, 128	[47]
Drosophila			
Httex1pQ93	65 amino acids of N-terminal fragment	93, 97	[48,49]
HttQ75, HttQ120	132 amino acids of N-terminal fragment	75, 120	[50]
N-term HttQ128	208 amino acids of N-terminal fragment	128	[51,52]
Htt128Q	548 amino acids of N-terminal fragment	128	[53]
Htt128QFL	Full-length human *HTT* cDNA	128	[54]
Rodents			
HD 51 rats	N-terminal fragment (22% of rat *Htt* gene)	51	[55,56,57]
BACHD rats	Full-length human *HTT*	97	[58]
N586-82Q mice	586 amino acids of N-terminal fragment	82	[59]
N171-Q82 mice	171 amino acids of N-terminal fragment	82	[60]
HD94 mice	67 amino acids of N-terminal fragment	94	[61]
YAC72 mice	Full-length human *HTT*	77	[62]
YAC128 mice	Full-length human *HTT*	125*	[63]
BACHD mice	Full-length human *HTT*	97	[68]
R6/1 mice	67 amino acids of N-terminal fragment	115	[64]
R6/2 mice	67 amino acids of N-terminal fragment	145	[64]
Other mammals			
Sheep	Full-length human *HTT* cDNA encoding 73 polyglutamine repeats	73	[65]
Tibetan miniature pig	First 208 amino acids of human *HTT* with 105Q (N208-105Q)	105	[66]
Primates			
Macaques	Htt171-82Q injection	82	[67]
Rhesus monkey	human *HTT* exon 1	84	[45]

* interrupted by CAACAACAACAGCAA at positions 24–28 and 109–113. HTT, huntingtin; BAC, bacterial artificial chromosome (related to HD modeling); YAC, yeast artificial chromosome.

Complementing mammalian models, HD research clearly benefits from invertebrate models, such as the fruit fly *Drosophila melanogaster* and the round worm *Caenorhabditis elegans*. Widely used in genetics research [84], *Drosophila* has been genetically modified to express *mHTT* [50], whose polyQ expansion induces the degeneration of photoreceptor neurons. Although powerful genetic tools (e.g., the galactose-responsive transcription factor GAL4/upstream activating sequence (UAS) system, P-element transgenic technology, and CRISPR/Cas9 gene editing) have been commonly used in *Drosophila* [85], this model has clear limitations for modeling HD. For example, as an invertebrate, it lacks the core area damaged in human HD [85], does not possess the necessary nervous system complexity, has far fewer neurons than humans, and does not have HD-specific neuronal subtypes such as striatal medium spiny neurons [86]. Their morphological development and movement patterns are also markedly different from those of humans [50,87,88,89,90,91,92,93], and the N-terminal domain of *HTT* does not have an extended polyglutamine sequence, unlike human *HTT* [94]. Likewise, *C. elegans* models of HD have been established by transgenic expression of *mHTT* fragments, thereby helping to explore the toxic mechanisms related to polyQ expansion [47]. Yet while such models (e.g., HtnQ95 and Htt57Q128) have provided useful tools for basic molecular pathological research of HD [46], these worms share multiple limitations with *Drosophila*. Lacking homologues, human *mHTT* fragments need to be induced by transgenic expression to simulate HD pathology, making it impossible to study neither the normal physiological functions of HTT nor the mechanisms of its dysfunction [95]. With only 302 neurons, *C. elegans* also lacks complex brain regions, such as the striatum and cerebral cortex of humans [96]. Moreover, *C. elegans* lacks a blood-brain barrier as well as circulatory and adaptive immune systems, and thus cannot adequately model the mechanism of drug delivery, systemic spread of disease, or the role of immune response [95]. Unable to model selective neuronal death [96], these worms also lack many typical neuropathological features of HD [97], and cannot simulate the temporal characteristics of its progression [98].

Table 3. Behavioral assays targeting key zebrafish phenotypes relevant to clinical and rodent models of Huntington's disease (HD, see Table 1 for clinical details).

Clinical HD symptoms	Rodent assays	Zebrafish assays*	Comments
Chorea	Observation cages	Observation tanks	Recording 2/3D behaviors
Bradykinesia	Observation cages	Observation tanks	Recording 2/3D behaviors
Dystonia	Observation cages	Observation tanks	
Impaired gait/balance	Observation cages	Observation tanks	
Memory decline	Y/T- and other mazes, habituation assays, recognition tasks	Y/T- and other mazes, habituation assays, recognition tasks	Assess spatial and working memory
Anxiety	Novelty-based assays	Novelty-based assays	
Depression	Despair- and anhedonia assays	Despair- and anhedonia assays	
Irritability and aggression	Aggression assays	Aggression assays	Mirror exposure test, dyadic confrontation assay
Insomnia, chronobiology disorder	Homecage observation	Hometank observation	Assessing sleep-related behaviors
Obstacles in visuospatial processing	Observation cages	Observation tanks	

*Clinical symptoms are compared to traditional rodent paradigms along with emerging zebrafish assays, where applicable.

3. Zebrafish Models of Huntington's Disease

In addition to mammalian and invertebrate models, zebrafish (*Danio rerio*) are rapidly becoming a critically important model organism in neuroscience research [99,100,101,102,103,104,105,106]. Both larval and adult zebrafish express robust, well-described behaviors, including motor, affective, cognitive, and neurological phenotypes [104,105,107] assessed in a wide range of tests, often adapted from rodents [104,108,109,110,111,112]. For example, zebrafish memory can be recorded in various mazes, conditioned place preference (CPP) tasks, dark-avoidance test, and shuttle box (Table 3), revealing multiple cognitive phenotypes similar to those in rodents [104]. A wide range of well-established molecular biology and neuroscience techniques have also been developed, including functional magnetic resonance imaging (fMRI) and quantitative gene expression analysis that have greatly advanced whole-brain imaging research [113,114,115]. Moreover, the transparency of embryos and juvenile zebrafish, as well as of some of their adult strains (e.g., *casper*) provide possibility to perform *in vivo* imaging and real time genetic manipulation [116,117,118,119].

Recognizing the growing importance of zebrafish for modeling HD and its pathobiology (Table 4, Ref. [20,45,83,120,121,122,123,124,125,126,127]), here we discuss various zebrafish-based genetic, pharmacological, and behavioral models relevant to this disorder, aiming to provide translational insights into its genetic and environmental determinants. Animal models of human brain or mental disorders are usually validated and accessed by three types of criteria: face validity (symptomatic similarity to human disease), predictive validity (the ability to predict and validate the therapeutic effects) and construct validity (the similarity of pathology) [128,129]. As we discuss the validity of zebrafish models of HD, we also critically evaluate the advantages and limitations of these models and outline future lines of research in this field.

Importantly, zebrafish display high (70%) genetic homology with humans, including the main HD risk gene *HTT*/*htt*, and show amenability to genetic manipulations, as well as strong reproductive capacity, low maintenance cost, and potential for large-scale screening [116,117,118,119]. Zebrafish share 72% homology with human *HTT* and HTT, as assessed by the Basic Local Alignment Search Tool (BLAST) database (https://blast.ncbi.nlm.nih.gov/Blast.cgi, accessed December 2025), but their *htt* encodes only for 4 glutamines (vs. 7 in mice and 35 in humans) [83]. While mice and humans share 84% and 91% homology of their HTT and its gene, respectively, zebrafish share 72% and 70% with mice. Zebrafish HTT is crucial in the formation of telencephalic progenitor cells, and the anatomy of the fish telencephalon is similar to those in mammals [83]. Zebrafish also possess all key neurotransmitters involved in HD pathogenesis (e.g., monoamines, GABA, glutamate, and acetylcholine) and show complex individual and group behavior relevant to HD symptoms.

In zebrafish, HTT levels peak during late embryonic development, and maintain moderate levels throughout adulthood, ubiquitously expressed in hippocampus, cortex, and cerebellum [120,130]. While normal HTT is predominantly localized in cytoplasm, mHTT tends to accumulate in the nucleus and mitochondria [131,132]. The loss of *htt*/HTT function in zebrafish leads to altered development of telencephalic progenitor cells and preplacodal cells [120,133].

A zebrafish HD model of HTT loss-of-function was generated via series of morpholino oligonucleotide (MO) injections, specifically inhibiting the expression of endogenous *htt* genes in zebrafish and interfering with HTT protein synthesis [120]. In this HD model, embryonic stages

Table 4. Selected zebrafish models of Huntington's disease (HD) and associated phenotypes.

Method	Phenotype	Validity	References
Genetic models			
HTT loss-of-function			
MOs mediated knockdown	Neuronal loss, morphological deformities, brain maldevelopment	P? F+ C+	[120]
19Q, 35Q, 56Q, and 80Q polyQ expansion	Neuronal loss (only from 56Q expansion), morphological deformities and increased mortality (56Q expansion).	P? F+ C+	[83,121]
4Q, 25Q, and 102Q polyQ expansion	Neuronal loss only in 102Q, morphological deformities and increased mortality (102Q expansion).	P? F+ C+	[83,122]
CRISPR/Cas9 deletion	Neuronal loss not detected; reduced fitness and survival in adulthood.	P? F+ C+	[83,123]
HTT gain-of-function			
Rhodopsin promoter with EGFP and mHTT containing a 71Q expansion	Accumulation of mHTT aggregates, loss of rhodopsin expression, consequential rod photoreceptor degeneration	P? F+ C+	[83,124]
Pharmacological			
N′-benzylidene-benzohydrazide (NBB)	Inhibited polyQ aggregation, neuronal loss and morphological deformity	P+ F+ C+	[83,122]
GPX4 activator	Improved mHTT-mediated iron accumulation and lipid peroxidation	P+ F+ C+	[125]
VMAT2 inhibitor	Regulated dopaminergic signals to improve abnormal movement in zebrafish	P+F+C+	[20]
Pharmacogenetic			
Cre-loxP inducible 97Q expansion – in relation to N17 domain	Increased mHTT aggregation, brain atrophy (mHTT without N17 domain), accelerated development of HD phenotype (stage 1 symptoms at week 5, death by 10-12 weeks).	P? F+ C+	[126]
Other models			
Organoid-zebrafish hybrid models	Reproduce the conserved circuit-level dysfunction of HD	P? F? C+	[45,123,127]

Validity criteria for the models include predictive (P), face (F) and construct (C) validity. Predictive validity reflects similarity of model's responses to clinically efficient treatments, construct validity reflects similar pathogenesis of the model and the disorder, and face validity is based on model's similarity to clinical manifestations. The + signs denote high validity, and the ? signs unclear validity of the model. MOs, morpholino oligonucleotides; polyQ, polyglutamine; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; Cas9, CRISPR-associated protein 9; mHTT, mutant huntingtin; EGFP, enhanced green fluorescent protein; GPX4, glutathione peroxidase 4; VMAT2, vesicular monoamine transporter 2.

presented with neuronal loss (apoptosis of telencephalic and spinal neurons), brain maldevelopment (impaired formation of telencephalic progenitor cells), and morphological deformities (curved body axis, shortened interocular distance) [120]. Furthermore, the downregulation of the brain-derived neurotrophic factor (BDNF) expression and activation of caspase-3 triggered apoptotic pathways, in this model resemble aberrant BDNF signaling and neuronal apoptosis in human HD [120,132]. In contrast, anti-HD drugs treatment (e.g., with butylphthalide and rasagiline) in zebrafish reduces the mHTT aggregates, rescues motor function, and decrease oxidative stress [122]. The 56Q/80Q transgenic zebrafish that express HTT fragments with different polyQ lengths present selective loss of telencephalic and retinal neurons, morphological deformities (curved body axis), and increased mortality [83,121]. Notably, selective damage of telencephalic neurons (the zebrafish homolog of the mammalian striatum) parallels the vulnerability of striatal neurons in human HD [127]. Importantly, zebrafish screens have successfully identified some compounds that are relevant for the potential treatment of HD, such as autophagy inducers [134,135]. Zebrafish research into selective autophagy processes has also highlighted the importance of using *in vivo* models to validate new *in vitro* findings and discover the physiologically relevant mechanisms [135]. Overall, zebrafish seem to possess considerable face and construct validity as HD models, and their predictive validity, albeit already reported to some drugs, remains to be confirmed with a wide range of prospective anti-HD agents.

In summary, given the high utility of zebrafish in translational neuroscience in modeling multiple neurological disorders, they have further emerged as a predictive model of HD. Their physiological and genetic homology to

both humans and rodents render zebrafish particularly well suited for studying the HD pathobiology, with several zebrafish HD models having already been established.

4. General Discussion: Problems, Challenges and Future Research

Overall, zebrafish appear increasingly relevant and appealing for modeling HD. First, they share high genetic homology with humans and replicate various core mechanisms and phenotypes related to this disorder [83,116]. Their optical transparency enables real-time tracking of neuronal degeneration and aggregate dynamics during development, which is impractical in mammals, but can be easily done in fish models of HD [116,117,118]. Zebrafish also excel in CNS drug screening, as multiple compounds dissolved directly in water can be tested in large numbers in high-throughput drug assays [136]. Notably, unlike mammals, zebrafish survive without HTT [83], making them an indispensable *complementary* tool to study genetic manipulations of this key HD gene by reducing or ablating its activity. Rescue studies using zebrafish models can also be useful to probe HD pathogenesis. For instance, *t*metal response element binding transcription factor 1 (MTF1) has been linked to reduced HTT activity [137] and reduces mHTT toxicity in zebrafish [122], paralleling similar neuroprotective effects in mammalian models [138]. Collectively, this further supports the therapeutic relevance of zebrafish models, establishing them as a powerful, cost-effective way of dissecting central HD mechanisms, accelerating drug discovery, and facilitating the identification of cross-species (hence, evolutionarily conserved and 'core') therapeutic targets.

However, like with any other experimental animal models, zebrafish also have various inherent limitations that impact their translatability and utility for studying HD. Some of these challenges are rather general, and others are species-specific, hence meriting further considerations. First, HD is a complex brain disorder with multiple overlapping clinical symptoms, ranging from motor to more complex behavioral, cognitive, and personality deficits (Table 1). Mimicking each of these symptoms, let alone their constellation, in any animal model becomes a major translational challenge. The fact that zebrafish are a relative newcomer to the field of behavioral research [106] makes mimicking such symptoms in fish rather problematic, both conceptually and practically. Second, despite their shared, evolutionarily conserved neuroanatomy, zebrafish lack a cortex [139,140], a critical structure impacted by HD [127]. Thus, modeling clinically *key* cortical HD-related processes in zebrafish becomes difficult, if not impossible. Likewise, the corpus callosum presents microstructural degeneration and white matter breakdown in HD, often appearing years before clinical symptoms. In contrast, the zebrafish lacks the corpus callosum, and therefore may not be suitable to study its specific roles (and the impact of inter-hemispheric communication in general), in HD pathogenesis. Moreover, while zebrafish possess striatal-analogous regions, their neural circuitry in general seems to lack mammalian complexity, hence broadly obscuring circuit-level dysfunction seen in human HD [83]. However, such characteristics offer specific utility, allowing for the dissection of disease mechanisms in ways that are confounded by other systems. For example, while lacking a neocortex, the zebrafish subpallium can nevertheless serve as a high-fidelity, reductionist model to isolate striatal vulnerability from cortical excitotoxicity.

The HTT gene and protein also differ between fish and humans. For example, zebrafish exhibit substantially shorter polyQ lengths compared to humans, potentially underrepresenting human-like polyQ toxicity mechanisms [83,122]. Zebrafish models also lack a human-specific HTT exon 1 structure, which may lead to changes in mHTT aggregation patterns. Compared to human mHTT, the lack of N17 domain of this protein (that regulates aggregation dynamics) in zebrafish also presents a translational challenge [126]. Thus, even if the structural differences in HTT are relatively minor, they may lead to inconsistent toxicity characteristics, thereby influencing the interpretation of HD and other polyQ-mediated neurodegenerative diseases.

Likewise, probing the association of HD with age is also translationally challenged in zebrafish, as humans become elderly in the last third of their lifespan, whereas laboratory zebrafish spend more than a half of their 4–5-year lifespan in advanced age. As such, the brain aging per se, as well as the progressive trajectory of HD in zebrafish and humans may differ markedly, with key implications for the model's construct, face and likely, predictive validity. However, this too presents an opportunity unique to zebrafish, as their rapid larval development can serve as a chronobiological stress test that could potentially unmask cellular fragility, allowing for high-throughput longitudinal studies of the entire disease trajectory. Another species-specific difference from mammals is higher neuroregeneration- and adult neurogenesis potential of zebrafish, which may counterbalance or mask the development of HD-like symptoms and biomarkers. For example, drug-induced HD models, such as injections with the neurotoxin quinolinic acid, can only trigger transient symptoms due to the rapid recovery of zebrafish, hence limiting their utility for chronic HD studies [116] and compromising therapeutic assessments [118].

Moreover, zebrafish underwent whole-genome duplication during their evolution, resulting in the existence of multiple copies of many, but not all, genes. While zebrafish express only one ortholog of human *HTT* (*htt*), this makes the study of functions of other HD-related genes relatively complex, as knocking out a single gene of interest may not lead to obvious phenotype changes [83,119]. Yet this may also be an advantage of the zebrafish model since while the knockout of certain key genes may lead to embryonic lethal-

ity in mammals, in zebrafish the same manipulation is non-lethal [83,119]. This notion is particularly true for zebrafish models of HD, since the genetic ablation of *htt* is indeed not lethal in these fish [123,130].

Another clinical aspect of HD that is difficult to model experimentally in any animal model is its complex temporal dynamics, which presents with a long pre-symptomatic phase and rapidly progressing symptomatic phase (Fig. 1). Currently, zebrafish models of HD rely on relatively simple behavioral and cognitive symptoms (e.g., motor deficits, cognitive impairment) but lack effective analyses of complex HD-related phenotypes, hence limiting its application to generalize the complete clinical spectrum of this illness [106]. In addition, zebrafish swimming is tightly regulated by the neural circuity of the spinal cord, thereby 'diluting' the cerebral involvement of their motor control and making it difficult to target clinically relevant HD-related central (i.e., basal ganglio-thalamocortical) circuits [141]. Again, given their lack of a neocortex (which is severely affected in human HD), zebrafish as naturally *acortical* organisms cannot replicate cortical-related HD pathologies, compromising the translational relevance of studies focusing on circuit-level dysfunction that involves cortex [127,139]. Furthermore, although zebrafish embryos and larvae are transparent for real-time imaging, most adult zebrafish strains lack such transparency, which has hindered the study of the dynamics of neurodegeneration and mHTT aggregation in the mature brain at middle and late stages [113]. It also remains technically challenging to optimize zebrafish tissue-specific and inducible mHTT expression systems, which are essential for replicating the spatiotemporal patterns of HD pathogenesis [136].

Importantly, the progression of HD is determined not only by genetic but also environmental factors. Due to different living environments of humans and zebrafish, the responses to key environmental risk factors in the development of diseases may also differ [142]. For example, distinct exposure scenarios and dimensions of environmental pathogenic factors, as well as the exposure pathways, may lead to different intensities of toxic reactions and priorities of targeted organs [143]. Although some environmental factors influencing human HD progression, such as lifestyle, cannot be accurately mirrored in zebrafish aquatic habitats, hence creating a divergence in disease manifestation [118], the use of environmental enrichment in such models can be relevant to the latter problem.

The regenerative capacity of the central nervous system (CNS) also factors into zebrafish difference from mammalian HD models. For example, unlike mammals, zebrafish exposed to the same environmental toxin (e.g., 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP), can repair dopaminergic neuron damage through autophagy activation, such as the upregulation of autophagy-related protein 5 (ATG5), essential for the formation of autophagosomes [144]. Since zebrafish are aquatic, and humans are terrestrial organisms, there are also differences in environmental adaptability and metabolism [145], meriting further scrutiny in the context of HD models [146,147,148]. For instance, compared with humans, zebrafish have a stronger iron metabolism [130], which can affect symptoms related to HTT deficiency. At the same time, the homeostasis of iron metabolism is disrupted in zebrafish lacking HTT, while iron accumulation in human HD patients is relatively stable from the early stage of the disease [130].

HD pathogenesis is closely related to imbalances in iron homeostasis, oxidative stress, and lipid peroxidation [149,150,151,152]. Ferroptosis is an iron-dependent form of programmed cell death characterized by lipid peroxidation that has been confirmed to play a role in the neuronal injury process of HD [153,154]. Abnormal aggregation of mHTT in HD disrupts iron homeostasis and the antioxidant system through multiple pathways, ultimately triggering ferroptosis [151,155]. On the one hand, mHTT can interfere with the storage and transport of iron within cells by interfering with ferritin activity (e.g., via iron regulatory proteins 1 and 2 (IRP1 and IRP2)) and inhibiting its synthesis, leading to the further accumulation of free iron within cells [120]. On the other hand, mHTT promotes the expression of the transferrin receptor (TfR1) and enhances the uptake of iron by cells [156]. In clinical HD, the brain has a higher content of free iron (vs. healthy controls), with its levels positively correlated with neuronal loss [151]. The glutathione (GSH)-glutathione peroxidase 4 (GPX4) axis is a key defense line against ferroptosis within cells, and mHTT disrupts this axis by inhibiting the cystine/glutamate transporter (xCT, SLC7A11) or directly binding to GPX4, suppressing its enzymatic activity and further weakening its ability to scavenge lipid peroxides [157]. Additionally, mHTT interferes with lipid metabolism pathways, increasing sensitivity to ferroptosis [158] and promoting lipoxygenase (LOX) expression, hence accelerating lipid peroxidation [155]. In the cerebrospinal fluid of human HD patients, lipid peroxidation products are elevated and positively correlate with the disease stage, thus linking lipid metabolism deficits to ferroptosis and HD [159,160,161].

Yet there are some further differences between zebrafish and humans in terms of iron metabolism regulation in the brain and pathological manifestations of HD [83,154,162,163,164,165]. The pathological localization of ferroptosis in HD patients and mammalian models mainly occurs in medium-sized striatal multispinous neurons (MSNs), the most vulnerable cell type in HD. As the disease progresses clinically, it spreads to the cortex and hippocampus [166,167]. Unlike mammals, zebrafish do not have a 'striatum' in the mammalian sense, and possess a telencephalon as a homologous structure instead [168,169]. In the zebrafish HD model, the disease mainly impacts telencephalic neurons and retinal cells, without obvious regional specificity [170]. Likewise, in clinical HD and its mammalian models, ferroptosis is a core mechanism caus-

ing neuronal loss in the middle and late stages of the disease, directly related to the progression of motor and cognitive decline [125]. In contrast, zebrafish HD models present defects in early embryonic development [120] and the impact of ferroptosis on fish motor function is relatively weak, since it more strongly depends on the spinal cord neural circuits and less on cerebral function [141].

To unravel the complex molecular mechanisms of HD and bridge the gap between zebrafish models and clinical translation, future research is needed to address integrative aspects of its pathogenesis by harnessing modern tools and technologies. For example, whole-brain spatial transcriptome mapping of zebrafish HD models, both in larval and adult stages, and wild-types can be performed by using ExSeq (extended *in situ* sequencing) technology. This may focus in-depth on the telencephalon region (similar to the mammalian striatum most strongly affected in HD), and spinal neural circuits [141,162]. The spatial distribution and expression levels of HD-related genes (e.g., HTT and its known direct molecular interactors) can be compared in HD vs. control cohorts, after which RNA sequencing (RNA-seq) can be performed on isolated neural tissues to construct a neural transcriptome map and screen for differentially expressed genes (DEGs) related to HD pathogenesis, and verified by real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR) [171]. With over 10 direct immediate protein interactors currently listed for both human and zebrafish HTT in the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (https://string-db.org/, accessed December 2025), such analyses can indeed be useful.

Building on this transcriptional map, future research can also focus on the epigenetic regulatory landscape of HD progression. Key epigenetic modification markers related to DNA methylation and histone acetylation/deacetylation can be detected in zebrafish HD models via the chromatin immunoprecipitation sequencing (ChIP-seq) and bisulfite sequencing (BSP). These methods can focus on the promoter regions of selected HD-related genes (e.g., *ascl1b,* a zebrafish proneural gene ortholog of the mammalian gene *ASCL1* encoding the achaete-scute family basic helix-loop-helix transcription factor 1, a master controller of neuronal development and fate), and the levels of epigenetic regulatory factors (e.g., histone deacetylase 1, *hdac1)* [130,172]. Finally, high-throughput zebrafish embryo bioassay systems developed via fish embryo toxicity tests (FET) can be used to screen chemical compounds which modulate these epigenomic markers [173], likely able not only to identify epigenetic modulators of HD but also candidate regulators to reverse disease phenotypes.

Another direction of research can focus on the epitranscriptomic regulation of HD using zebrafish models. For example, different RNA modifications (e.g., m6A, m5C) in the brain of HD zebrafish models and wild-type zebrafish can be identified by methylated RNA immunoprecipitation sequencing (MeRIP-seq, [174]) and the expression and modification levels of key RNAs can be verified using qRT-PCR and *in situ* hybridization – helping to probe the regulatory role of RNA modification in the stability of HTT homologous transcripts, subcellular localization, and translation efficiency [126].

Paralleling molecular analyses, a high-resolution microscopic image sequence database of zebrafish HD models could be constructed, spanning from embryonic to adult stages while including all useful models (e.g., genetically and chemically induced), as well as temporal characteristics of HD-related symptoms, such as early embryonic morphological abnormalities, intermittent swimming disorders, and decreased motor coordination [106,141]. To empower this approach further, the artificial intelligence (AI) tools can be developed for (i) the automatic detection and classification of HD-like symptoms in zebrafish, and (ii) for multimodal integration of behavioral, physiological, and omics data collected in such models (e.g., see [175]), hence bridging molecular and behavioral changes both in real time, and within the lifespan. For example, AI-driven analyses have already been used to detect neurological abnormalities in a conceptually similar modeling of another neurodegenerative disorder, Parkinson's disease [176], and putatively HD-relevant phenotypes, such as thigmotaxis (anxiety) and acoustic startle habituation (cognitive integrity) [177,178]. Additionally, AI-powered deep phenotyping applies neural networks to screen large datasets of compounds active on human receptors when tested prospectively *in vitro*, clustering diverse neuroactive compounds in a way that highly corresponds with known neuroactive biology, while phenotypically linking structurally distinct compounds in zebrafish – an approach potentially relevant for screening novel therapeutic drugs for HD [179,180].

Furthermore, whole-genome sequencing (WGS) can be applied to identify HD-associated genetic and copy number variations [162], while spatial transcriptomics and RNA-seq can help reveal complex patterns of gene expression and co-expression [171]. In addition, future research can combine zebrafish *in vivo* models with organoid *in vitro* models (Table 4). For instance, co-culturing neurons expressing mHTT in zebrafish with human cortical organs can demonstrate conservative circuit level dysfunction, combining the genetic processability of zebrafish with the structural reality of organoids [45]. Additionally, increased genetic precision in experimental manipulations will further advance efficiency and high-throughput capability – such as the current field shift from the utilization of morpholinos to the CRISPR F0 (crispants), bypassing the extensive process of breeding F1–F3 generations to isolate stable mutants [181,182]. Indeed, transient gene knockdown often has off-target effects and toxicities that mimic disease phenotypes [183,184], raising the logical question: if a morpholino phenotype is not replicated in a CRISPR mutant, can it be due to 'genetic compensation' (transcriptional adaption)? Thus,

it is critical to cross-verify prior morpholino results with CRISPR knockouts to ensure accuracy and rule out compensatory mechanisms [184]. Moreover, advances in spatial omics will also allow for the integration of scRNA-seq and spatial transcriptomics to identify 'first-responder' cell types and autonomous toxicity within the anatomical context of the fish brain [185]. Given the clinical heterogeneity of HD, including both individual variation in CAG repeat length and the disease progression itself [186,187], zebrafish could be used to create patient-specific models via injecting constructs mimicking specific patient mutations to predict individual disease trajectories. Together, these strategies will accelerate our understanding of HD pathogenesis and guide the development of targeted therapies.

Overall, zebrafish provide a high-throughput model for studying HD, paralleling mammalian observations in several contexts. Yet while certain cross-species differences exist at the physiological and genetic levels, this may actually provide a beneficial complementary approach, such as in examining key gene manipulations. Indeed, zebrafish-specific traits such as the lack of a neocortex and rapid development, may provide unique experimental advantages for mechanistic analyses of HD to bridge the clinical and pre-clinical translational gap.

5. Conclusion

Despite the relatively simple *monogenic* nature of HD pathogenesis, establishing reliable and valid zebrafish HD models faces multiple challenges. Thus, further improving the validity of zebrafish HD models (Table 4) relies on the precision of simulating complex clinical symptoms of this disorder [106,141]. For example, while zebrafish *htt* is different (4Q) compared to humans, models often express human exon 1 – presenting high construct validity for the mutation but low validity for the genomic context. Species differences in neuroanatomy [127,139], HTT genes and proteins [126,132,162], temporal bias of disease progression and biomarkers [27,29], genome replication history [123], and distinct physiological (e.g., metabolic) processes [125,130,142] must also be addressed. Elucidating the precise molecular mechanisms linking extreme CAG expansions to rapid neuronal death remains critical, leveraging zebrafish real-time imaging to track neurotoxicity dynamics [25,45,137]. Furthermore, as their transparency is limited to early stages [116], capitalizing on *adult* zebrafish HD models and their respective imaging can help study late-stage neurodegeneration. Exploring additional HTT protein roles in non-neuronal aspects, such as in glial cells, as well as for iron metabolism dysregulation and metabolic dysfunction, can provide further mechanistic insights into HD pathophysiology [83,117].

In summary, the zebrafish is emerging as a powerful complementary model organism for studying HD and bridging critical gaps between cellular mechanisms and therapeutic discovery [83,116,117]. Zebrafish models have successfully recapitulated core HD pathologies, including mHTT aggregation, striatal neuronal loss, motor/cognitive deficits, and conserved mechanisms of neurotoxicity [83,122]. Although inherent limitations of such models remain (e.g., including the underrepresentation of human toxicity due to shorter polyQ lengths, robust neurogenesis masking progressive degeneration, and simplified neural circuitry [83,122]), future research is expected to optimize imaging techniques, elucidate CAG expansion mechanisms, validate non-neuronal HTT roles in metabolic dysfunction [25,83,137], and develop novel HD-related motor and molecular biomarkers for both early- and late-stage disease. Finally, deeper integration of zebrafish with rodent, *in vitro*, and computational (*in silico*) models has the potential to accelerate translational HD research, offering a cost-effective sensitive platform for the dissection of its pathogenesis and the advancement of therapeutic interventions.

Author Contributions

Study Concept and Design: AVK; Analysis and Interpretation of Literature: JC, ZY, ZF, VP, EK, YP, YW, YX, MA, LY, VNP, AMS, AVK; Drafting of the Manuscript: JC, ZY, ZF; Supervision: AVK; Procurement of funding: AVK. All authors contributed to editorial changes in the manuscript. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

Allan V. Kalueff is an Editorial Board member of this journal. He had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Bettina Platt.

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