JEM Journal of Experimental Medicine

REVIEW

Pathogenesis of polyglutamine diseases: Piecing together a complex molecular puzzle

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Polyglutamine (polyQ) diseases, caused by a CAG repeat expansion encoding a glutamine tract in nine distinct proteins, present a complex molecular puzzle in which each piece contributes to neurodegeneration. While each of the causative proteins has a distinct function, the downstream consequences of polyQ toxicity are often similar, including protein accumulation, transcriptional dysregulation, somatic CAG repeat instability, disrupted energy homeostasis, compromised synaptic function, and selective neuronal death. This review summarizes emerging insights into how proteins with an expanded polyQ tract disrupt distinct cellular functions, and we examine a multitude of discoveries that are inspiring and reshaping novel therapeutic strategies.

Introduction

Polyglutamine (polyQ) diseases are a group of monogenic neurodegenerative disorders that share a mutational mechanism: a CAG trinucleotide expansion in the disease gene that encodes for an abnormally long glutamine tract. This expansion alters the function of the host protein and leads to neuronal dysfunction and degeneration. Nine polyQ disorders have been described to date: spinobulbar muscular atrophy (SBMA), Huntington's disease (HD), spinocerebellar ataxia (SCA) types 1, 2, 3, 6, 7, and 17, and dentatorubral-pallidoluysian atrophy (DRPLA) (Table 1).

These disorders share several characteristics. All, except for SBMA, are inherited in an autosomal dominant manner. SBMA is an X-linked recessive disorder, but the expanded polyQ tract exerts dominant effects at the cellular level. This cellular dominance would explain why some female carriers, despite reduced levels of circulating androgens and random X-inactivation protecting about half of their cells, occasionally manifest subclinical features of SBMA (Ishihara et al., 2001; Sobue et al., 1993; Schmidt et al., 2002). For all these disorders, longer CAG expansions are associated with earlier age of disease onset and more severe symptomatology. Typically, polyQ disorders strike in midlife and cause progressive degeneration over the next 10–20 years, eventually leading to death. Larger expansions in subsequent generations of affected individuals—a phenomenon known as genetic anticipation—lead to infantile and juvenile-onset cases. For the most part, the causative proteins are ubiquitously expressed, with the exception of CACNA1A, the protein involved in SCA6, which is primarily restricted to cerebellar Purkinje cells (PCs) (Westenbroek et al., 1995; Ishikawa et al., 1999). Finally, while the nine disorders share some overlapping clinical features, each disease is marked by a distinct pattern of neurodegeneration affecting specific brain regions and neurons.

Genetic mouse models of polyQ diseases have been instrumental in elucidating important aspects of pathogenesis, disease course, and therapeutic strategies. Given the shorter lifespan of mice compared with humans, most polyQ disease models carry transgenes or knock-in alleles with very large repeat sizes resembling juvenile forms of each disorder. While different models will be suitable for different research questions and approaches, knock-in models are ideal for pathogenesis studies because they maintain the mutation in its natural genetic landscape (endogenous promoters and enhancers) and full-length protein context. We have compiled a few widely used mouse models that faithfully reproduce each polyQ disease (Table 2). When drawing conclusions from experiments in the field, careful consideration of the models used (i.e., whether they are transgenic or knock-in, or express full-length versus truncated protein) is essential for contextualizing and interpreting their relevance to human disease.

The field of polyQ diseases has undergone remarkable progress in recent years, revealing new mechanistic and therapeutic insights. This review seeks to highlight the most recent advances in pathogenic mechanisms of polyQ disorders and discuss how they support or reshape long-standing hypotheses and ideas in the field. It concludes with an overview of the current therapeutic efforts, their potential, and challenges.

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Table 1. **Summary of molecular and clinical features of polyQ diseases**

Disease	Gene (locus)	Protein	Normal protein function	Normal (CAG)n	Pathogenic (CAG)n	Major clinical symptoms	Brain regions and cell types most affected	Essential literature
SBMA/ Kennedy's disease	*AR* (Xq11-q12)	Androgen receptor (AR)	Steroid hormone receptor and transcription factor	≤34	35–37: reduced penetrance[a], ≥38: pathogenic	Affects males; females can show very mild abnormalities. Progressive muscle weakness and atrophy, fasciculations, gynecomastia, testicular atrophy, and reduced fertility	Anterior horn of spinal cord (lower motor neurons) and brainstem	Arnold and Merry (2019)
HD	*HTT* (4p16.3)	Huntingtin (HTT)	Synaptic transmission, scaffolding protein for axonal transport	6–35	36–39: reduced penetrance, ≥40: pathogenic	Chorea, progressive motor impairment, dystonia, cognitive deficits, dysarthria, dysphagia, and psychiatric disturbances	Striatum (MSNs) and cerebral cortex	Bates et al. (2015), Bunting et al. (2022)
SCA1	*ATXN1* (6p23)	Ataxin 1 (ATXN1)	Transcriptional corepressor	4–39 uninterrupted or 39–44 if interrupted by CAT	>39 uninterrupted repeats, or ≥45 if interrupted by CAT: pathogenic	Progressive cerebellar ataxia, spasticity, dysarthria, and deterioration of bulbar functions	Cerebellum (PCs and dentate nucleus), brainstem, and spinocerebellar tracts	Tejwani and Lim (2020)
SCA2	*ATXN2* (12q24)	Ataxin 2 (ATXN2)	RNA metabolism, calcium regulation, and stress response	14–31	32–34: reduced penetrance[a], ≥35: pathogenic	Progressive cerebellar ataxia, dysarthria, nystagmus, slow saccadic eye movements, myoclonus, and parkinsonism	Cerebellum, brainstem, and spinal cord	Velázquez-Pérez et al. (2017), Egorova and Bezprozvanny (2019)
SCA3/ Machado–Joseph disease	*ATXN 3* (14q24.3-q31)	Ataxin 3 (ATXN3)	Deubiquitinase	12–44	45–55: reduced penetrance, ∼60[b]–87: pathogenic	Progressive cerebellar ataxia, dystonia, spasticity, dysarthria, dysphagia, ophthalmoplegia, bulging eyes, and faciolingual fasciculations	Cerebellum (dentate nucleus and PCs), brainstem (vestibular, pontine and motor nuclei), basal ganglia, and spinal cord	Paulson (2012), McLoughlin et al. (2020)
SCA6	*CACNA1A* (19p13)	CaV2.1	Calcium channel	4–18	19: reduced penetrance[a], 20–33: pathogenic	Progressive cerebellar ataxia, dysphagia, dysarthria, and nystagmus	Cerebellum (PCs and dentate nucleus)	Du and Gomez (2018)
SCA7	*ATXN7* (3p12-p21.1)	Ataxin 7 (ATXN7)	Subunit of the SAGA complex	4–33	34–36: reduced penetrance, ≥37: pathogenic	Progressive cerebellar ataxia, dysphagia, dysarthria, and retinal degeneration that leads to blindness	Cerebellum (PCs and dentate nucleus), brainstem, and retina (photoreceptors)	Niewiadomska-Cimicka and Trottier (2019)

Table 1. **Summary of molecular and clinical features of polyQ diseases (*Continued*)**

Disease	Gene (locus)	Protein	Normal protein function	Normal (CAG)n	Pathogenic (CAG)n	Major clinical symptoms	Brain regions and cell types most affected	Essential literature
SCA17	*TBP* (6q27)	TATA box-binding protein (TBP)	Transcription factor	25–40 CAG/CAA	41–48 CAG/CAA: reduced penetrance, ≥49 CAG/CAA: pathogenic	Progressive cerebellar ataxia, dystonia, parkinsonism, chorea, dementia, psychiatric abnormalities, and seizures	Cerebellum (PCs), cortex, and striatum	Liu et al. (2019), Toyoshima and Takahashi (2018)
DRPLA	*ATN1* (12p13)	Atrophin 1 (ATN1)	Transcriptional corepressor	6–35	35–47: reduced penetrance or milder phenotype, 48–93: pathogenic	Progressive cerebellar ataxia, myoclonus, epilepsy, chorea, intellectual deterioration (juvenile), dementia (adults), and psychiatric symptoms	Cerebellum (dentate nucleus), basal ganglia (globus pallidus and subthalamic nucleus), and brainstem	Nowak et al. (2023)

[a]These have also been described as alleles of uncertain clinical significance and should be interpreted within the context of family history and patient clinical presentation.
[b]Shortest full-penetrance allele is not well defined.

Pathogenesis

PolyQ diseases, despite their monogenic nature, exhibit complex pathogenic mechanisms that result in progressive neurodegeneration. The expanded polyQ tract initiates a cascade of cellular dysfunction that involves protein misfolding and accumulation, altered protein–protein interactions, transcriptional dysregulation, mitochondrial impairment, compromised protein quality control, and somatic instability. These pathogenic processes form an intricate network of interdependent mechanisms that amplify cellular damage (Fig. 1).

PolyQ diseases are proteinopathies

The term "proteinopathies" describes disorders characterized by the abnormal accumulation of proteins in the brain and peripheral tissues (Bayer, 2015). PolyQ diseases are part of this group, along with prominent neurodegenerative conditions like Alzheimer's disease and Parkinson's disease (Ross and Poirier, 2004; Golde et al., 2013). PolyQ diseases exhibit the main hallmarks of proteinopathies: misfolding and aggregation of specific proteins, alterations of the target protein function or gain of a toxic function, neuronal dysfunction, and neurodegeneration.

Protein misfolding and aggregation. One of the earliest histopathological observations in the field was that the proteins with an expanded polyQ tract are prone to misfolding and aggregation. Intranuclear ubiquitin-positive inclusions of the disease proteins were observed in selective neuronal populations in postmortem brains of human patients and some mouse models of HD (Davies et al., 1997; DiFiglia et al., 1997; Scherzinger et al., 1997), SCA3 (Paulson et al., 1997), SCA1 (Skinner et al., 1997), SBMA (Li et al., 1998), DRPLA (Hayashi et al., 1998), SCA2 (Koyano et al., 1999), SCA7 (Holmberg et al., 1998), and SCA17 (Nakamura et al., 2001). Inclusions are also present in SCA6, but they are ubiquitin-negative and are mostly cytoplasmic (Ishikawa et al., 1999).

Whether these inclusions are pathogenic, incidental, or protective has been resolved for some polyQ diseases, but not all. Early studies showed that polyQ inclusions increase with repeat size and display amyloid-like structures similar to those seen in Alzheimer's disease (DiFiglia et al., 1997). Critical cellular machinery, including molecular chaperones, proteasomal components, and transcription factors, colocalize with these inclusions (Cummings et al., 1998; Steffan et al., 2000). The redistribution of critical cellular factors initially emerged as a potential pathogenic mechanism. However, subsequent discoveries challenged the idea that inclusions were a source of toxicity, demonstrating that nuclear inclusions were not necessary for pathogenesis in SCA1 and SCA2 (Klement et al., 1998; Cummings et al., 1999; Huynh et al., 2000; Handler et al., 2023), did not correlate with cell death in HD (Saudou et al., 1998), and were virtually absent in the most vulnerable neurons in HD, medium spiny neurons (MSNs) (Gutekunst et al., 1999; Kuemmerle et al., 1999). Furthermore, inclusions were shown to reduce intracellular levels of the soluble mutant protein, reducing the risk of cell death (Arrasate et al., 2004). These findings shifted the consensus toward viewing inclusions as a protective cellular response to cope with misfolded proteins.

Table 2. **Some of the most accurate mouse models of PolyQ disease**

Disease	Mouse model name	Genetic approach and repeat number	Behavioral phenotypes	Prominent neuropathology	Major advantages or special features	References
SBMA	AR113Q	Knock-in of human *AR* exon 1 containing 113 CAG repeats into mouse *Ar* locus	Weight loss, neuromuscular weakness (~8 wk), testicular atrophy, reduced fertility, reduced survival (2–4 mo)	Myopathic and denervating changes in skeletal muscle, nuclear inclusions (NIs) in spinal neurons	Physiologically relevant expression of mutant protein. Pathology is androgen-dependent	Yu et al. (2006)
HD	CAG140	Knock-in of human *HTT* exon 1 containing 140 CAG repeats into mouse *Htt* locus, homozygote	Hyperactivity followed by hypoactivity, motor deficits (~4–6 mo), motor learning impairment, abnormal gait (>12 mo)	Selective striatal neuronal loss, reduced spine density of MSNs, cortical and striatal gliosis, NIs	Physiologically relevant expression of mutant protein. Slower progression is a more accurate representation of adult-onset HD progression	Menalled et al. (2003), Hickey et al. (2008)
	YAC128	Full-length human *HTT* transgene with 128 repeats (mostly pure CAG tract with some CAA interruptions), with all endogenous regulatory regions present	Motor learning deficits (~2 mo), depression-like behavior, abnormal gait (~8–12 mo), hyperactivity followed by hypoactivity	Selective striatal neuronal loss, cortical atrophy reduced brain weight, NIs, and reduced dopamine levels	Earlier and more robust phenotypes than the knock-in model. Exhibits psychiatric phenotypes too. Repeat number is stable	Slow et al. (2003), Van Raamsdonk et al. (2005)
	BAC-CAG HD	Full-length human *HTT* transgene encoding 131 glutamines, with an uninterrupted stretch of 120 CAGs. All endogenous regulatory regions present	Motor learning deficits (6 mo), hypoactivity, reduced grip strength, and sleep disruption	No overt brain atrophy. Loss of striatal MSNs synapses, NIs in striatum and cortex, astrogliosis, and microgliosis in the striatum	Somatic CAG instability in striatum, which correlates with behavioral impairment. The sequence also includes patient-associated SNPs	Gu et al. (2022)
SCA1	*Atxn1*$^{154Q/2Q}$	Knock-in of 154 CAG repeats into mouse *Atxn1* locus	Progressive motor deficits (onset ~5 wk), cognitive deficits (~7 wk), abnormal gait, weight loss, kyphosis, breathing deficits, and premature death (~48 wk)	NIs, gradual PC pathology, hippocampal neuronal dysfunction, reduced brain weight, and ventricle enlargement	Physiologically relevant expression of mutant protein. Extensively characterized; closely reproduces SCA1 phenotypes	Watase et al. (2002), Jafar-Nejad et al. (2011)
SCA2	Atxn2-CAG42	Knock-in of 42 CAG repeats into mouse *Atxn2* locus	Weight loss and late-onset cerebellar motor phenotypes (~12 mo)	Cytoplasmic inclusions in PCs	Physiologically relevant expression of mutant protein	Damrath et al. (2012)
	BAC-Q72	Full-length human *ATXN2* transgene with 72 CAG repeats, with all endogenous regulatory regions present	Motor deficits (onset ~16 wk) and reduced body weight	Gradual PC pathology	Ubiquitous expression of mutant protein	Dansithong et al. (2015)
SCA3	YAC84Q (MJD84.2)	Full-length human *ATXN3* transgene with 84 CAG repeats, with all endogenous regulatory regions present	Abnormal gait, late-onset motor deficits (~30 wk), hypoactivity, kyphosis, and reduced body weight	NIs, neuronal loss in pontine and dentate nuclei, and gliosis	Expression of all isoforms of ATXN3. Resembles adult-onset SCA3	Cemal et al. (2002)
SCA6	*Sca6*$^{84Q/84Q}$	Knock-in of human exon 47 containing 84 CAG repeats into mouse *Cacna1a* locus, homozygote	Progressive motor impairment (onset at ~7 mo) and abnormal gait	Cytoplasmic inclusions in PCs	Physiologically relevant expression of mutant protein. Resembles adult-onset disease	Watase et al. (2008)

Table 2. **Some of the most accurate mouse models of PolyQ disease (*Continued*)**

Disease	Mouse model name	Genetic approach and repeat number	Behavioral phenotypes	Prominent neuropathology	Major advantages or special features	References
SCA7	*Sca7*$^{266Q/5Q}$	Knock-in of 266 CAG repeats into mouse *Atxn7* locus	Ptosis, visual impairment, ataxia, muscle wasting, kyphosis and tremors (onset ∼5 wk), hypokinesia, and premature death (4–5 mo)	NIs in brain and retina, cone-rod dystrophy, and reduced brain size	Physiologically relevant expression of mutant protein. Rapid progression, resembles infantile SCA7	Yoo et al. (2003)
SCA17	Germline-TBP 105Q	Knock-in of human exon 2 containing 105 CAG repeats into *Tbp* mouse locus, flanked by loxP sites under the control of Ella-Cre (germline)	Progressive motor deficits (onset ∼3 mo), ataxia, kyphosis, reduced body weight, premature death (∼5–10 mo)	PC degeneration, muscle degeneration, and TBP aggregation in muscle and brain	Proper spatiotemporal expression of mutant protein and relatively rapid progression	Huang et al. (2011), Huang et al. (2015)
DRPLA	Q129	Full-length human *DRPLA* transgene with 129 CAG repeats, under the control of endogenous promoter	Myoclonus and ataxic gait (onset ∼3 wk), epileptic seizures (onset ∼9 wk), and premature death (by 16 wk)	NIs, reduced brain weight, and progressive cortical atrophy	Rapid onset of disease replicates juvenile-onset DRPLA	Sato et al. (2009)

In the following years, aggregation was shown to be a two-step process: initially, mutant proteins assemble into soluble oligomers rich in β-sheet structures, which later form larger insoluble inclusions (Ellisdon et al., 2006). Biochemical experiments in cells expressing polyQ peptides suggested that soluble oligomers, rather than insoluble inclusions, are the primary toxic species and that inhibiting their formation can improve cellular viability (Sánchez et al., 2003; Takahashi et al., 2008). In the *Atxn1*$^{154Q/2Q}$ mouse model of SCA1, oligomer levels correlated with motor impairment (Lasagna-Reeves et al., 2015a), and inhibiting internalization of ATXN1 oligomers by passive immunotherapy delayed disease progression (Lasagna-Reeves et al., 2015b). Additionally, Congo red, a dye that inhibits oligomer formation, resulted in amelioration of pathology in the R6/2 transgenic mouse model of HD (Sánchez et al., 2003).

A few more recent studies in mouse and cell models expressing mutant HTT exon 1 (Httex1) challenge the view that inclusions are purely cytoprotective, showing that perinuclear inclusions can damage the nuclear membrane (Liu et al., 2015), while cytoplasmic inclusions disrupt nuclear transport and alter endoplasmic reticulum dynamics (Woerner et al., 2016; Bäuerlein et al., 2017). Another Httex1 study proposed a model in which inclusions initially protect cells by sequestering toxic oligomers but later contribute to slow cell death by gradually trapping essential factors and inducing cellular quiescence (Ramdzan et al., 2017). While interesting, these findings may not fully reflect the behavior of full-length huntingtin, given that they are solely based on the expression of a truncated HTT fragment containing a long polyQ tract. Additional studies using patient-derived samples or full-length protein models are needed.

Mutant protein cleavage resulting in more toxic species. Proteins with expanded polyQ regions tend to misfold and undergo proteolytic cleavage, generating smaller fragments that are more prone to aggregation than the full-length proteins. Mutant HTT (mHTT), ATXN3, ATXN7, AR, and ATN1 are substrates of caspases, a family of cysteine proteases, and the resulting cleavage fragments are toxic to neurons (Wellington et al., 1998; Kim et al., 2001; Wellington et al., 2002; Shoesmith Berke et al., 2004; Ellerby et al., 1999b; Ellerby et al., 1999a; Young et al., 2007). Calpains, another family of cysteine proteases, also cleave mHTT, ATXN3, and TBP into pathogenic fragments (Gafni and Ellerby, 2002; Hübener et al., 2013; Weber et al., 2022). In addition, a *Drosophila* screen identified three enzymes of the matrix metalloproteinase family that cleave HTT (Miller et al., 2010). Proteolytic cleavage of HTT results in the release of toxic N-terminal fragments that accumulate and aggregate more readily, which helps explain why animal models expressing truncated HTT, such as the R6/2 mouse model, develop more severe pathology than full-length models (Wang et al., 2008; Landles et al., 2010). These findings suggest that blocking proteolytic cleavage could ameliorate polyQ toxicity. Supporting this, knockdown of matrix metalloproteinase homologs in a *Drosophila* model of HD rescues neuronal dysfunction (Miller et al., 2010), and mutation of caspase and calpain sites in several polyQ-expanded proteins prevents cell death *in vitro* and neurodegeneration *in vivo* (Ellerby et al., 1999a; Ellerby et al., 1999b; Graham et al., 2006; Young et al., 2007).

Recent experiments have provided more insight into how cleaved fragments disrupt cellular functions and lead to cell death. For instance, the expression of truncated forms of ATXN3 resulting from calpain cleavage caused disrupted mitochondrial dynamics and increased susceptibility to apoptosis (Harmuth et al., 2018). C-terminal fragments of HTT that do not contain the polyQ stretch have also been shown to cause cellular dysfunction. These fragments cause dilation of the endoplasmic reticulum and cell death by inactivating dynamin-1, an important player in membrane fission (El-Daher et al., 2015). However, while proteolytic cleavage appears to play a key role in the disruption of several cellular functions, it may not be essential

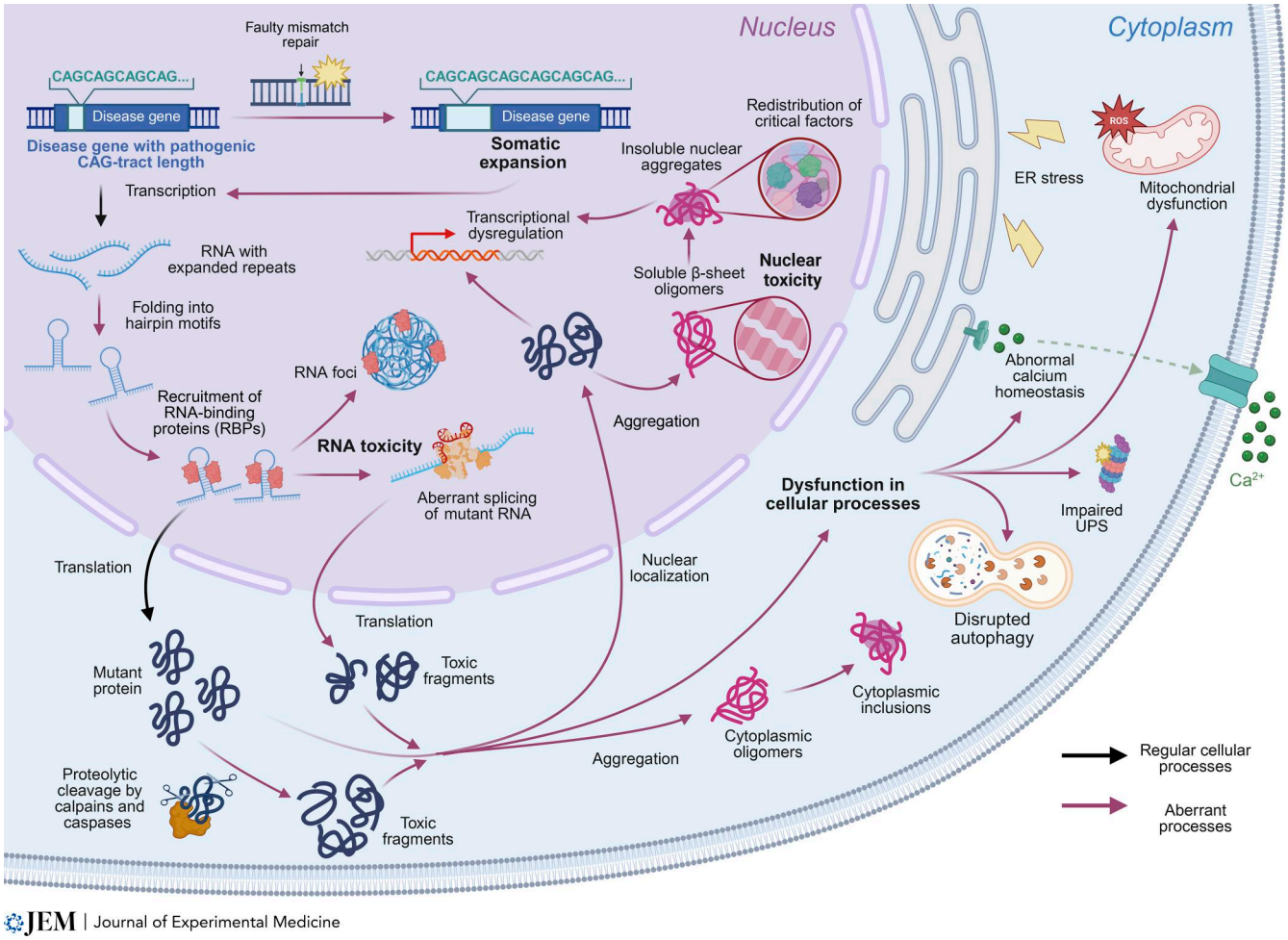

Figure 1. **Pathogenesis of polyQ diseases.** PolyQ pathogenesis involves the interplay of several disrupted cellular processes. The mutated gene is transcribed, producing RNA that can misfold, undergo aberrant splicing, and exert RNA toxicity. After translation takes place in the cytoplasm, the mutant protein is often cleaved by proteolytic enzymes into aggregation-prone fragments. Many aberrantly spliced transcripts are also translated into fragments that aggregate readily. Both full-length and fragmented proteins that contain a nuclear localization signal translocate into the nucleus, where they form toxic soluble oligomers and, eventually, insoluble aggregates. These aggregates deplete the host protein and other essential cellular factors from their native functions, leading to transcriptional dysregulation and widespread dysfunction. Additional cellular pathways including endoplasmic reticulum dynamics, mitochondrial bioenergetic pathways, protein clearance, and calcium signaling are disrupted. Moreover, the CAG tract is prone to somatic expansion due to failed MMR, resulting in the progressive lengthening of the tract and exacerbation of toxicity (created in BioRender, https://BioRender.com/r78karc).

for pathogenesis in all polyQ diseases. For instance, there is no evidence that ATXN1 undergoes cleavage, and the role of ATXN2 fragments in SCA2 remains poorly understood. Therefore, targeting protein cleavage may be a viable therapeutic avenue for some, but not all, polyQ diseases.

Alteration in function: Mixture of gain and loss of function. Pathogenesis in polyQ diseases is driven by a combination of gain- and loss-of-function effects. For all polyQ disorders, toxic gain-of-function effects are considered the primary drivers of disease and usually stem from changes in the mutated protein's stability, abnormal accumulation, transcriptional dysregulation, or altered interactions. Loss-of-function mechanisms are still significant and usually occur due to diversion of the protein away from its critical sites of action or normal functions.

There are multiple well-established examples of gain-of-function mechanisms across polyQ diseases. ATXN1 natively interacts with the transcription factor Capicua (CIC) to repress CIC target genes. When ATXN1 carries an expanded polyQ tract, the ATXN1-CIC complex acquires a toxic gain of function that results in enhanced repression of target genes (Lam et al., 2006; Fryer et al., 2011; Rousseaux et al., 2018). While there are some CIC targets that show derepression in the cerebellum of *Atxn1*$^{154Q/2Q}$ mice, reducing CIC levels in these mice relieves the strong repression and improves motor phenotypes, suggesting that a gain of CIC function drives cerebellar pathogenesis (Fryer et al., 2011). Interestingly, disrupting the polyQ-expanded ATXN1-CIC interaction rescues pathology in a PC-specific mouse model of SCA1, but it only partially rescues transcriptional defects and phenotypes in the rest of the cerebellum of *Atxn1*$^{154Q/2Q}$ mice (Rousseaux et al., 2018; Coffin et al., 2023). These findings suggest that ATXN1-CIC gain of function drives PC pathology but may not underlie dysfunction in other cerebellar cell types. This underscores an important feature of

polyQ diseases: different affected cell populations may exhibit distinct pathogenic mechanisms.

Loss-of-function effects are usually determined by comparing polyQ disease phenotypes with those seen in individuals carrying loss-of-function mutations in the same gene, or with knockout or knockdown experimental models. Androgen insensitivity, which manifests as undervirilization in males, is a phenotype seen in patients with loss-of-function mutations in AR (Brinkmann, 2001). SBMA patients show relatively mild androgen insensitivity phenotypes (manifested as gynecomastia, testicular atrophy, and infertility), which suggests that there is a partial loss of AR function contributing to non-degenerative phenotypes (Dejager et al., 2002). Consistent with this, key features of SBMA such as lower motor neuron degeneration and brainstem dysfunction are not seen in AR knockout mouse models or patients with severe AR loss-of-function mutations (Yeh et al., 2002; Batista et al., 2018). As another example, knockout of ATXN1 in mice results in a mild learning and memory phenotype (Matilla et al., 1998). This resembles the cognitive decline seen in juvenile-onset SCA1 patients and the knock-in mouse model, suggesting that this phenotype may be partly driven by loss of function of ATXN1 (Crespo-Barreto et al., 2010). Similar to SBMA, loss of function of ATXN1 does not reproduce the hallmark features of SCA1—cerebellar ataxia and brainstem dysfunction (Matilla et al., 1998). This suggests that while some phenotypes might be partially driven by loss of function of the respective protein, polyQ diseases are mainly driven by gain-of-function mechanisms.

The role of the wild-type allele. Aside from SBMA, polyQ diseases are autosomal dominant disorders, meaning that one mutant allele is sufficient to cause disease. To study pathogenesis in a comprehensive manner, it is necessary to determine how the wild-type allele influences disease progression in each disorder. Early studies suggested that the wild-type allele has a protective role. In a transgenic cellular model of HD, the overexpression of the full-length wild-type protein reduced cell death (Leavitt et al., 2006). Similarly, in a *Drosophila* model of SCA3, the co-expression of full-length wild-type and mutant ATXN3 ameliorated neurodegeneration phenotypes (Warrick et al., 2005). Conversely, experiments that depleted the wild-type host protein in the YAC72 mouse model of HD and in the *Atxn1*$^{154Q/2Q}$ model of SCA1 resulted in worsened phenotypes, supporting the idea of the wild-type allele conferring protection (Leavitt et al., 2001; Lim et al., 2008). Additionally, a cis regulatory variant that reduces *HTT* expression is associated with earlier age at onset when present in the wild-type allele in HD patients (~3.9 years earlier), suggesting that reduction of the wild-type protein is a modifier of disease (Bečanović et al., 2015).

More recent experiments have tested the effect of selectively reducing the levels of the mutant protein compared with reducing both mutant and wild-type protein levels. For instance, phosphorylation at serine 776 of ATXN1 increases its stability by preventing its degradation (Emamian et al., 2003; Chen et al., 2003). Mutating this critical phosphorylation site in the expanded allele of *Atxn1*$^{154Q/2Q}$ mice reduced polyQ-expanded protein levels and resulted in a significant phenotypic rescue. However, if wild-type protein levels were also reduced by mutating the S776 in the nonexpanded 2Q allele, the rescue was significantly reduced, further supporting the hypothesis that wild-type ATXN1 is neuroprotective (Nitschke et al., 2021).

Understanding the role of the wild-type allele in the disease state is critical for developing effective therapies. While loss of the wild-type protein in an otherwise healthy background could result in mild or no phenotypes, the disease background is sensitized, and hence, reduced expression could be detrimental. This is especially true if the wild-type protein competes with its polyQ-expanded counterpart for interactors, dampening its toxic effects. Thus, when studying protein reduction strategies and potential therapeutic avenues, it is crucial to consider the role of the wild-type protein in disease rather than extrapolating from loss-of-function studies that occur in the absence of the polyQ-expanded protein.

RNA toxicity

Some evidence suggests that the expression of the mutant RNA can itself be toxic independently of the protein. A genetic screen for modifiers of SCA3 toxicity in *Drosophila* revealed that upregulation of *muscleblind*, a gene involved in RNA toxicity of CUG expansion diseases, dramatically enhanced toxicity (Li et al., 2008). Mutation of the CAG repeat sequence to an interrupted CAACAG sequence (still coding the same number of glutamines) resulted in a much milder phenotype in a SCA3 fly model. Moreover, the expression of untranslated CAG repeats induced neurodegeneration in the retina and brain of flies, as well as muscle defects in mice, suggesting that the expanded CAG RNA can be toxic (Li et al., 2008; Hsu et al., 2011). There is also evidence that repeat-associated non-AUG (RAN) translation proteins (polyAla, polySer, polyLeu, and polyCys) accumulate in the brains of HD patients, particularly within regions most vulnerable to HD pathology, and they exhibit toxicity *in vitro* (Bañez-Coronel et al., 2015). To date, HD is the only polyQ disorder in which RAN translation has been clearly demonstrated, as conclusive evidence in other polyQ disorders is still lacking.

Several studies have attempted to find the mechanism behind potential RNA toxicity. Analysis of the RNA structure of expanded vs. wild-type HTT *in vitro* showed that mutant RNAs fold into hairpin motifs that aberrantly recruit RNA binding proteins. These RNAs form foci that colocalize with splicing factors such as muscleblind-like 1 and stall the transport of RNA to the cytoplasm for translation (De Mezer et al., 2011). Sequestration of these splicing factors results in aberrant splicing of other genes, which contributes to neuronal dysfunction in HD and SCA3 (Mykowska et al., 2011; Schilling et al., 2019). Another *in vitro* study suggested that CAG RNAs reduce ribosomal RNA, causing nucleolar stress (Tsoi et al., 2012). Finally, it has been proposed that expanded RNA is processed by Dicer, which produces short CAG-containing RNAs that cause toxicity by activating RNA interference (RNAi) (Krol et al., 2007; Bañez-Coronel et al., 2012), and that the amount of toxic short RNAs is dependent on the length of uninterrupted CAGs (Murmann et al., 2022).

There are, however, numerous successful rescue studies across various polyQ diseases that target mechanisms independent of the mutant RNA. Despite leaving the CAG RNA

unchanged, these interventions have demonstrated abrogation of toxicity, suggesting that protein-mediated toxicity is the main mechanism driving neurodegeneration. For example, in the AR113 knock-in mouse model of SBMA, surgical castration resulted in the rescue of phenotypes, suggesting that deprivation of androgens is enough to reduce toxicity (Yu et al., 2006). For SCA1, mutation of the nuclear localization signal rescues toxicity and improves lifespan (Klement et al., 1998; Handler et al., 2023), and mutation of phosphorylation site S776 in the mutant allele, which reduces protein stability, also rescues toxicity (Emamian et al., 2003; Nitschke et al., 2021). Similarly, mutation of a caspase-6 site in HTT prevents toxic proteolytic cleavage and allows YAC128 mice to maintain normal neuronal function without developing neurodegeneration (Graham et al., 2006). Furthermore, mimicking phosphorylation in serine 421 of HTT confers neuroprotection in induced pluripotent stem cells (iPSCs) derived from HD patients (Xu et al., 2020) and ameliorates behavioral phenotypes and neurodegeneration in BACHD mice (Kratter et al., 2016). These are only a few examples of experiments in which the CAG tract of the RNA stayed intact, but the phenotype was rescued. Finally, HD and SCA17 patients with CAA interruptions in the mutant CAG tract often exhibit delayed onset or reduced disease severity compared to those with uninterrupted repeats of the same length. While this is consistent with the idea of RNA toxicity, CAA interruptions may instead confer protection by stabilizing the repeat tract and limiting somatic expansion (Gao et al., 2007; Wright et al., 2019; Lee et al., 2019).

Taken together, some studies suggest that RNA from CAG-expanded transcripts can cause cytotoxicity through formation of RNA foci, sequestering of RNA binding proteins, activation of RNAi, and, in some cases, RAN translation. However, most evidence for toxicity comes from *in vitro* experiments or relies on artificial expression of untranslatable CAG constructs *in vivo* rather than the full-length construct, so further validation is needed. An extensive amount of evidence on protein-mediated toxicity strongly suggests that while RNA toxicity might be a contributor, it is not the main driver of pathogenesis.

Disrupted protein interactions and posttranslational modifications

The polyQ expansion alters protein conformation, affecting sites involved in native interactions and posttranslational modifications while potentially giving rise to novel pathogenic interactions or exposing new modification sites. These interactions can have widespread effects on cellular functions. Early studies, for example, identified huntingtin-associated protein 1 (HAP1) as a key interactor of huntingtin. HAP1 participates in intracellular trafficking, and it binds mHTT more tightly than wild-type HTT (Li et al., 1995). This enhanced binding to mHTT diverts HAP1 from other important complexes that are required for the transport and release of essential factors that participate in neurotrophic support and neurite outgrowth (Gauthier et al., 2004; Rong et al., 2006; Wu et al., 2010). HAP1 also regulates autophagosome dynamics, and this function is disrupted by mHTT binding, leading to defective cargo degradation (Wong and Holzbaur, 2014). Another more recently discovered interaction is the translation factor eIF5A, which preferentially interacts with mHTT *in vitro* and is sequestered in aggregates, altering translation dynamics (Aviner et al., 2024).

Importantly, each cell type provides a different molecular context for a specific protein. The levels of co-expression of interactors of a mutant protein in a specific cell will determine which interactions get disrupted most significantly and the effect they have on cellular function. A recent longitudinal single-cell study in the cerebellum of SCA1 knock-in mice found that cerebellar cell types that show similar patterns of expression of ATXN1 interactors also have similar general expression profiles, suggesting that the cell type–specific effects might be dependent on the co-expression of interactors (Tejwani et al., 2024). These data suggest a potential mechanism for cell-specific vulnerability.

In addition to binding partners, posttranslational modifications of the mutant protein also play a role in pathogenesis as they can influence stability, degradation, and cleavage. Ubiquitination of the mutant protein is generally protective in all polyQ diseases, as it promotes its degradation (Johnson et al., 2022). Thus, deubiquitination will have detrimental effects. For example, the deubiquitinase USP7 shows preferential interaction with polyQ-expanded AR and HTT, promoting their aggregation and toxicity in knock-in mouse models of SBMA and HD (Pluciennik et al., 2021). Other posttranslational modifications like phosphorylation, SUMOylation, and acetylation also have a role in protein toxicity, but their effects can vary depending on the protein and context. For example, SUMOylation can enhance toxicity in mouse models of SCA3 and SBMA, but can exert a protective effect in HD. Specifically, SUMOylation of lysine 166 in polyQ-expanded ATXN3 partially increases its stability, which in turn enhances apoptosis rate *in vitro* (Zhou et al., 2013). Disrupting SUMOylation sites in a knock-in model of SBMA rescues muscular phenotypes and prolongs survival (Chua et al., 2015). On the other hand, SUMOylation of mHTT reduces toxicity by decreasing soluble mutant protein *in vitro* (O'Rourke et al., 2013).

These and more studies show that alteration of normal protein interactions and posttranslational modifications has downstream effects on stability, aggregation propensity, transcriptional regulation, neuronal growth, autophagy, and many other cellular functions.

Aberrant transcription and gene regulation

Transcriptional dysregulation emerges as a central pathogenic mechanism in polyQ diseases, resulting from both the direct role of disease proteins in transcriptional regulation and their altered interactions with key regulatory factors. AR, ATN1, ATXN1, ATXN7, and TBP function as transcription factors or cofactors (Table 1). In SCA7, mutant ATXN7 disrupts the STAGA histone acetyltransferase complex, leading to widespread changes in chromatin accessibility and gene expression that result in photoreceptor dysfunction (Helmlinger et al., 2006). Similarly, in SBMA, polyQ-expanded AR shows altered interactions with nuclear receptor coregulators, disrupting hormone-dependent transcription (Nedelsky et al., 2010). As described earlier, in SCA1, mutant ATXN1's interaction with the transcriptional repressor CIC results in the hyper-repression of critical CIC target

genes (Lam et al., 2006). Recent work has revealed that ATXN1 also interacts with other transcription factors like RFX1, ZBTB5, and ZKSCAN1, and some of the SCA1 transcriptional changes could be attributed to these factors (Coffin et al., 2023). Another example is mHTT and the repressor element-1 silencing transcription factor (REST). Wild-type HTT interacts with REST in the cytoplasm, preventing it from repressing neuronal genes. This interaction is weaker with polyQ-expanded HTT, which results in greater inhibition of REST targets (Zuccato et al., 2003). Transcriptional dysregulation can also arise from aggregation and redistribution of proteins. For instance, both mutant AR and HTT form nuclear aggregates that recruit CREB binding protein, depleting it from its normal nuclear locations and disrupting its transcriptional activation function, which in turn affects neuronal survival (Nucifora et al., 2001; McCampbell et al., 2000).

Transcriptional dysregulation in polyQ diseases is widespread and progressive and has downstream consequences in almost every aspect of cellular function, including metabolism, autophagy pathways, cellular stress, and cell death.

Mitochondrial dysfunction

Mitochondrial dysfunction has been recognized as a critical feature of polyQ diseases since early studies identified energy metabolism deficits in patient tissues. Initial observation of HD patient postmortem tissue revealed reduced activity of mitochondrial complexes II, III, and IV in the putamen and caudate, and deficits in complex I in muscles, suggesting fundamental defects in energy production (Parker et al., 1990; Gu et al., 1996; Arenas et al., 1998). Similar bioenergetic deficits were subsequently identified across other polyQ disorders, pointing to shared pathogenic mechanisms involving compromised respiratory chain complexes and higher oxidative stress (Laço et al., 2012; Yu et al., 2009; Cornelius et al., 2017).

The molecular basis of these defects is gradually becoming clear. A study in iPSC-derived motor neuron-like cells from SBMA patients showed that polyQ-expanded AR leads to widespread repression of genes involved in oxidative phosphorylation and fatty acid metabolism. This transcriptional dysregulation results in reduced acetyl-CoA levels, low ATP production, and altered lipid metabolism (Pourshafie et al., 2020). Similarly, the top downregulated genes in the cerebellum of the *Sca6*$^{84Q/84Q}$ mouse model at disease onset were related to oxidative phosphorylation, cellular respiration, and mitochondrial function (Leung et al., 2024). These transcriptional changes preceded changes in function, but as mice aged, they showed more mitochondrial morphological defects and increases in oxidative stress in PCs. Additionally, late-stage mice showed insufficient mitophagy (Leung et al., 2024). Proteome analysis of the cerebellum of *Atxn1*$^{154Q/2Q}$ mice revealed significant downregulation of proteins related to mitochondrial function in PCs. In this model, treatment with the antioxidant MitoQ delayed mitochondrial deficits and improved motor performance (Stucki et al., 2016). In another study, SCA7 patient–derived iPSCs and the *Sca7*$^{266Q/5Q}$ mouse model showed severe mitochondrial dysfunction characterized by abnormal mitochondrial morphology and NAD+ depletion, which results in disrupted energy homeostasis (Ward et al., 2019). Direct protein interactions also contribute to mitochondrial pathology. In HD, mHTT shows enhanced binding to dynamin-related protein 1, a GTPase involved in mitochondrial fission, leading to excessive mitochondrial fragmentation and impaired organelle function (Cherubini et al., 2020). The current data suggest that mitochondrial dysfunction, oxidative stress, and insufficient mitophagy create a cycle of cellular stress that exacerbates pathogenesis. Treatment with antioxidants has a potential to delay disease-onset and subdue symptoms.

Disrupted proteasomal machinery and autophagy pathways

The ubiquitin–proteasome system (UPS) and autophagy are the two major pathways through which misfolded proteins are degraded. The UPS is functional in both the nucleus and cytoplasm, and it tags short-lived proteins for proteasomal degradation by ubiquitinating a lysine residue in the target protein through 3 enzymes: an activating (E1), a conjugating (E2), and a ligase (E3) enzyme (reviewed in Pickart [2001]). In contrast, autophagy is limited to the cytoplasm, and it involves the engulfment of long-lived proteins, aggregated proteins, damaged organelles, or pathogens into the autophagosome. This autophagosome then fuses with lysosomes, where the engulfed contents are degraded (reviewed in Khandia et al. [2019]).

Early on, studies suggested that aggregation and accumulation of polyQ proteins impaired the UPS (Cummings et al., 1998; Bence et al., 2001; Weinhofer et al., 2002; Venkatraman et al., 2004). It has been shown that inclusions sequester molecular chaperones such as Sisp1, an essential chaperone of heat-shock protein (Hsp) 40, which helps recognize and bind misfolded proteins for ubiquitination (Park et al., 2013). Given that the UPS is active in the nucleus, and this is an essential site of toxicity of polyQ proteins, enhancing the UPS has been shown to be neuroprotective. For example, the overexpression of C-terminus of heat-shock cognate protein 70–interacting protein, an E3 ligase, has resulted in the amelioration of phenotypes in several models of polyQ diseases, among them, a *Drosophila* model of SCA1 (Al-Ramahi et al., 2006), a transgenic mouse model of SBMA (Adachi et al., 2007), and cellular models of HD and SCA3 (Jana et al., 2005).

Autophagy is also significantly disrupted in these disorders, with impairments occurring at multiple steps, including initiation, cargo recognition, autophagosome transport, and degradation. One example is beclin-1 (BECN1), an autophagy-initiating protein. Wild-type ATXN3 natively interacts with BECN1 via its polyQ domain and deubiquitinates it, preventing its degradation and promoting autophagy. However, expanded polyQ tracts in disease-causing proteins can outcompete wild-type ATXN3 for this interaction, leading to reduced BECN1 levels and impaired autophagy initiation (Ashkenazi et al., 2017). Another example is the cargo receptor p62, which has been shown to aberrantly interact with mHTT, resulting in impaired cargo recognition *in vitro* (Martinez-Vicente et al., 2010). Moreover, HTT has been shown to natively bind dynein and HAP1 to regulate the axonal transport of autophagosomes, and this process is also defective in cells derived from HD knock-in mice, suggesting that the polyQ expansion in HTT

functionally disrupts this complex (Wong and Holzbaur, 2014). Consistent with this, neurons derived from HD patients exhibit significant autophagic deficits, particularly in neurites, where late autophagic structures accumulate and display defective transport (Pircs et al., 2022).

Rescuing autophagic activity through different methods has been shown to alleviate some of the pathology seen in different disease models. In reprogrammed MSNs from symptomatic HD patients, there is a significant downregulation of autophagy-related genes, as well as a reduction in autophagic activity. Enhancing autophagy, either by reducing levels of the autophagy inhibitor miR-29b-3p or by treatment with a chemical autophagy activator, ameliorated neurodegeneration phenotypes in these cells (Oh et al., 2022). HD neurons in both mouse and rat models showed a reduction in lysosomal density in dendrites, and optogenetic relocation of lysosomes was able to rescue long-term potentiation deficits, indicating that restoring lysosomal function can also mitigate some of the synaptic impairments associated with HD (Chen et al., 2023). Conversely, depleting autophagy-linked FYVE protein, a scaffolding protein with a role in selective autophagy of insoluble inclusions, accelerated aggregate accumulation and hastened phenotypic onset in BACHD mice, and increased aggregation (though not cell death) in HD patient–derived MSNs (Fox et al., 2020). Overall, these data suggest that modulation of autophagy can improve neuronal function and delay disease progression.

PolyQ-expanded proteins affect both autophagy and the UPS through various mechanisms, which results in impaired clearance of mutant proteins and exacerbated toxicity. As a result, improving autophagic and proteasomal responses could be protective against neurodegeneration and a viable therapeutic approach.

Other disrupted cellular functions

A substantial amount of data indicates that important cytoplasmic processes are disrupted in polyQ diseases. Fast axonal transport (FAT), for instance, has been shown to be dysfunctional in HD and SBMA (Szebenyi et al., 2003; Gunawardena et al., 2003). FAT is the process through which membrane-bound organelles like vesicles and mitochondria are transported within a neuron. Loss of function of a motor protein involved in FAT is sufficient to cause neurodegeneration, supporting the importance of this process for proper neuronal function (Reid et al., 2002). Mutant AR and HTT have been shown to inhibit FAT by activating c-Jun NH_2-terminal protein kinase 3, which in turn phosphorylates kinesin-1 and decreases its ability to move cargo (Morfini et al., 2006; Morfini et al., 2009). Additionally, mHTT's altered interaction with HAP1 disrupts HAP1's function in motor complexes and decreases the transport of vesicles carrying essential factors such as brain-derived neurotrophic factor (BDNF) (Gauthier et al., 2004; Wong and Holzbaur, 2014). This disruption is particularly significant because striatal cells depend on BDNF produced by cortical neurons for their survival (Mizuno et al., 1994; Ventimiglia et al., 1995), and lower BDNF levels have been seen in the striatum, but not in the cortex, of HD brains (Ferrer et al., 2000).

Perturbations in calcium signaling have also been observed in mouse models of HD, SCA2, SCA3, and SBMA (Tang et al., 2003; Bezprozvanny and Hayden, 2004; Chen et al., 2008; Liu et al., 2009; Marchioretti et al., 2023). Mutant ATXN2, ATXN3, and HTT have been shown to interact with inositol 1,4,5-trisphosphate receptor type 1, an intracellular calcium release channel (Tang et al., 2003; Chen et al., 2008; Liu et al., 2009). *In vitro* experiments showed that these interactions sensitize this receptor to activation, resulting in an increased efflux of calcium and thus an ionic imbalance within the neuron. This imbalance further sensitizes vulnerable neurons like PCs to glutamate-induced apoptosis *in vitro* (Chen et al., 2008; Liu et al., 2009). Treatment of transgenic HD, SCA2, and SCA3 models with dantrolene, a calcium ion stabilizer, reduced protein aggregation and ameliorated motor deficits, suggesting that defective calcium signaling contributes to pathogenesis in these disorders (Tang et al., 2003; Chen et al., 2008; Liu et al., 2009).

Transcriptional dysregulation, ionic imbalance, deficits in vesicle transport, and other disrupted pathways converge to cause early and progressive electrophysiological abnormalities that precede behavioral impairments and extensive neuronal loss. Studies in several HD mouse models have shown that cortical pyramidal neurons experience increased excitability, which sensitizes the neurons to excitotoxicity (Cepeda et al., 2003; Cummings et al., 2006; Cummings et al., 2009). The increased cortical activity also affects MSNs, which receive inputs from this region. In fact, studies in mice and postmortem patient tissue suggest there is a progressive disconnection of cortex and striatum networks in HD (Hong et al., 2012; Wilton et al., 2023). Additionally, mHTT reduces the expression of functional Kir4.1 K^+ channels in astrocytes, leading to impaired K^+ buffering, elevated extracellular K^+ in the striatum, and consequent hyperexcitability of MSNs (Tong et al., 2014). As MSNs degenerate in HD, their outputs to the external and internal pallidal segments are lost, resulting in chorea in early HD and akinesia in late HD (Reiner and Deng, 2018). In several transgenic models of SCA2, SCA3, and SCA6, firing of PCs is decreased and becomes irregular, which is hypothesized to contribute to ataxia (reviewed in Meera et al. [2016]). While the breadth and complexity of the electrophysiological disturbances in polyQ diseases are beyond the scope of this review, it is clear that these early and progressive disruptions set the stage for circuit failure and the onset of clinical phenotypes.

Genetic instability and somatic expansion

CAG repeats are highly unstable and tend to expand further in somatic cells over time. With the exception of SCA6, all polyQ disorders have shown somatic instability of the CAG tract (reviewed in Donaldson et al. [2021]). The expansion rate differs across tissues but is usually most pronounced in the striatum across different polyQ diseases (Kennedy et al., 2003; Watase et al., 2003; Kacher et al., 2021). Both the mechanisms of somatic mosaicism and its pathological contribution have been most extensively studied in HD.

Repeat expansions are believed to result from misaligned DNA secondary structures formed by the CAG repeats during replication, transcription, or repair (reviewed in Pearson et al.

[2005], Mirkin [2005]). In postmitotic neurons, where replication is absent, destabilization of CAG repeats is initiated by transcription, and subsequent errors in DNA repair result in repeat expansions (Lin et al., 2006; Nakamori et al., 2011). Initial studies in bacteria and yeast showed that deficiency in several genes involved in mismatch repair (MMR) destabilizes CAG repeats, highlighting this pathway's potential role in repeat instability (Jaworski et al., 1995; Schweitzer and Livingston, 1997). In the MMR pathway, mismatches in DNA are first identified and bound by either of two specialized MutS complexes: MutSα (MSH2-MSH6), which recognizes small insertion–deletion loops, or MutSβ (MSH2-MSH3), which recognizes large ones (Gupta et al., 2011). Once bound, they recruit another complex that usually has an endonuclease function, MutL. The MMR protein MLH1 is an obligate component of MutL complexes, which can be MutLα: MLH1-PMS2; MutLβ: MLH1-PMS1; or MutLγ: MLH1-MLH3 (reviewed in Kunkel and Erie [2005]).

Over the past 25 years, a substantial body of evidence has shown that genetic deficiency of specific MMR components can prevent somatic expansion and neuronal loss in HD models, and that variants in these genes are modifiers of disease in humans. Knockout of MMR genes *Msh2* and *Msh3* in transgenic and knock-in HD mouse models showed that the MutSβ complex was necessary for somatic expansion (Manley et al., 1999; Wheeler et al., 2003; Dragileva et al., 2009; Kovalenko et al., 2012). By leveraging linkage mapping in an HD mouse model (Hdh^{Q111}) with higher somatic expansion in a C57BL/6 genetic background compared with a 129 background, Pinto and colleagues found that variants in *Mlh1* are modifiers of somatic expansion. Additionally, they showed that genetic deletion of *Mlh1* or its binding partner *Mlh3* abolishes somatic expansion and slows disease progression in mice, demonstrating that the MutLγ complex is also involved in this process (Pinto et al., 2013). A few years later, a genome-wide association study identified several loci that influence age at onset in HD, and these loci harbor several MMR genes: MSH3, MLH1, PMS1, and PMS2, as well as the DNA repair genes FAN1 and LIG1 (Lee et al., 2015). The study found variants that delayed age at onset in *MSH3*, *FAN1*, *MLH1*, and *PMS2* by an average of 6.1, 1.3, and 0.8 years (for both *MLH1* and *PMS2*), respectively. Conversely, variants in *PMS1* and *LIG1* hastened age at onset by 0.9 and 0.6 years, respectively (Lee et al., 2019). Unlike MLH1 and MLH3, the DNA repair nuclease FAN1 appears to act as a suppressor of somatic expansion. Variants associated with lower FAN1 expression correlate with earlier age at onset (Goold et al., 2019). Knockdown of FAN1 in HD patient-derived iPSCs and striatal neurons resulted in increased CAG expansion rate (Goold et al., 2019). Deletion of *Fan1* in $Hdh^{Q111/+}$ mice causes accelerated CAG expansion. However, if both *Fan1* and *Mlh1* are knocked out, this effect is lost, suggesting the protective effect of FAN1 is mediated by MLH1 (Loupe et al., 2020). Overall, these data suggest that several MMR proteins are modifiers of age at onset of HD, likely due to their role in accelerating or delaying somatic instability.

While MMR has emerged as the main pathway driving expansions, other DNA repair mechanisms have also been implicated. In the R6/1 transgenic model of HD, somatic expansion correlates with oxidative DNA lesions, which are repaired by DNA glycosylases through the base excision repair (BER) pathway (Kovtun et al., 2007). Loss of OGG1, the main DNA glycosylase responsible for removing 8-oxoguanine bases, reduced expansions in both the R6/1 and Hdh^{Q150} models (Kovtun et al., 2007; Budworth et al., 2015). Similarly, loss of NEIL1, another glycosylase that removes pyrimidine-derived lesions, reduced expansions in R6/1 mice (Møllersen et al., 2012). While the stoichiometry of BER proteins, like OGG1 and FEN1, correlate with tissue vulnerability for expansion in R6 models (Goula et al., 2009), it remains to be determined whether this also holds in HD knock-in mouse models and human postmortem tissue.

A central question in the field is the extent to which somatic instability patterns account for the selective regional vulnerability in polyQ diseases. In both SCA1 and HD, somatic CAG expansion is most prominent in the striatum, which is the most vulnerable region in HD, and least prominent in the cerebellum, even though the cerebellum and brainstem are the primary sites of pathology in SCA1 (Kennedy et al., 2003; Watase et al., 2003; Pinto et al., 2020; Kacher et al., 2021). A recent study revealed the potential mechanism driving striatal repeat instability. Mätlik and colleagues studied postmortem brains of HD and SCA3 patients and found that the largest CAG expansions were predominantly observed in MSNs for both diseases, despite this population not being as vulnerable to cell death in SCA3 as they are in HD. The authors showed that MSNs express higher levels of MutSβ components MSH2 and MSH3, and that these proteins inhibit nucleolytic excision of CAG slip-outs by FAN1. This results in the retention of slip-outs as somatic expansions and can explain the higher vulnerability of MSNs to somatic instability (Mätlik et al., 2024). Interestingly, a study of SCA1, SCA2, SCA3, and SCA7 postmortem brain tissue showed that somatic instability was the lowest in the cerebellum (Kacher et al., 2024). This is particularly intriguing because the cerebellum is the most vulnerable region to neurodegeneration and cell death in SCAs, which would suggest that somatic expansion is not the mechanism driving cerebellar pathology. So far, these data suggest that the striatum is intrinsically vulnerable to CAG repeat expansion, and that patterns in somatic instability are not sufficient to explain region-specific vulnerability across polyQ diseases.

Beyond regional distribution, the relative contribution of somatic instability to pathogenesis remains contentious, with some arguing that it is necessary yet insufficient to independently cause neuronal death, while others contend that it functions as a primary disease driver. Current scientific consensus favors the former view. Two recent studies used fluorescence-activated nuclear sorting followed by RNA sequencing in the striatum, cerebellum, and cortex of postmortem brains from HD patients, and found that somatic CAG repeat expansions occur both in vulnerable populations (such as MSNs and layer 5a corticostriatal pyramidal neurons) and in populations that experience dysfunction but remain resilient against cell death (including cholinergic and layer 6 neurons) (Pressl et al., 2024; Mätlik et al., 2024). The fact that neuronal populations with divergent disease outcomes both show extensive CAG expansions led the researchers to conclude that while somatic expansion represents a necessary element in the pathogenic

cascade, it is not sufficient for neuronal loss. However, the techniques used in this study could detect up to 113 CAG repeats, and it is possible that MSNs present much longer repeats that are out of the limit of detection. Handsaker and colleagues recently developed a single-cell RNA-sequencing method based on long reads, which allows obtaining the transcriptional profile and the *HTT* CAG size from each cell. Using this method in the anterior caudate of postmortem HD brains, they found much longer repeat expansions in MSNs (up to 842 CAG) and observed that profound cell-autonomous transcriptional changes only occurred in cells that surpassed a threshold of 150 CAGs (Handsaker et al., 2025). With this, the authors proposed a model called "ELongATE" in which repeats become toxic only when they are very long (>150) and concluded that somatic expansion is necessary and sufficient for pathology. Nevertheless, several studies have shown that there are significant transcriptional and functional changes in iPSC-derived neurons derived from HD patients and HD organoids that have repeat sizes much lower than 150 and have not been in culture long enough for any of the neurons to reach that level of expansion (Victor et al., 2018; Mehta et al., 2018; Ooi et al., 2019; Galimberti et al., 2024). To resolve these contradictions, future long-read single-cell studies should examine whether the toxic threshold model holds across both resilient and vulnerable cell types in other brain regions affected by HD. Additionally, investigating somatic expansion in other polyQ diseases, where MSNs are not the primary vulnerable cell type, could provide valuable insights, as the inherent susceptibility of MSNs to expansion may confound HD-specific findings.

A few other studies have also explored the possibility of a pathogenic threshold of somatic expansion, after which repeat toxicity increases markedly. Wang and colleagues further dove into the molecular, transcriptional, and neuropathological effects of knocking out MMR proteins in the CAG140 mouse model of HD. The authors found that knockout of *Msh3* and *Pms1* strongly reversed disease-related transcriptional changes in striatal neurons and prevented mHTT protein aggregation. Homozygous knockout of *Msh3* in CAG140 mice stabilized the CAG repeat length and delayed the onset of transcriptional dysregulation. While many of the same genes were affected in control CAG140 mice, the changes in the *Msh3* knockout were significantly attenuated and had a later onset. This suggests that transcriptional dysregulation can occur without expansion beyond 140 CAG repeats, but expansion significantly exacerbates this process (Wang et al., 2025). Knocking out *Msh3* in an HD knock-in mouse model with a 185 CAG tract (zQ175) prevented somatic expansion but had no effect on aggregation and transcriptional dysregulation. This suggests that MMR proteins might only be modifiers of disease up to a certain toxic threshold of expansion, after which ultra-long repeats are inherently toxic regardless of additional expansion (Aldous et al., 2024). This supports a model in which MMR-driven somatic instability contributes to disease progression at intermediate repeat lengths, but ultra-long expansions impose intrinsic toxicity and accelerate degeneration. Additionally, it underscores that preventing somatic expansion might only help a small percentage of cells that have not crossed a toxic CAG length threshold, suggesting that therapies targeting this pathogenic mechanism need to be administered as early as possible.

Therapeutic strategies

Despite significant advances in understanding polyQ disease mechanisms, there are currently no effective disease-modifying therapies. However, multiple therapeutic approaches targeting different aspects of pathogenesis are under development (Fig. 2). Given the widespread cytotoxic effects of polyQ-expanded proteins, therapeutic approaches that reduce mutant protein levels or stabilize nontoxic conformations are likely to provide greater benefit than interventions targeting individual downstream pathways. In this section, we have summarized some of the therapeutic strategies that are being developed in the recent years.

Conformation stabilization and aggregation inhibitors

These types of approaches aim to prevent the misfolding and aggregation of the expanded proteins into toxic species such as β-sheet soluble oligomers. Intrabodies, which are recombinant antibodies that bind specific targets inside cells, initially emerged as promising aggregation inhibitors. Several intrabodies against different regions of the HTT protein have been developed, such as scFv-C4 (Lecerf et al., 2001), V(L)12.3 (Southwell et al., 2009), and INT41 (Amaro and Henderson, 2016). Treatment with these antibodies has resulted in reduction of mHTT aggregates and amelioration of phenotypes in the transgenic models of HD R6/1 and R6/2. However, intrabody-based therapies face two significant challenges: first, existing intrabodies have not demonstrated long-term efficacy in aggregate reduction; and second, the large molecular size of intrabodies restricts brain delivery options exclusively to viral vector systems.

More recently, small molecules that stabilize native protein conformations or prevent β-sheet formation have shown promise. An example of this is CLR01, a molecular tweezer that has been shown to inhibit self-aggregation of amyloid proteins by binding to lysine residues, disrupting interactions that are necessary for oligomerization (Sinha et al., 2011). While CLR01 has shown great promise in mouse models of Alzheimer's and Parkinson's disease (Di et al., 2021; Bengoa-Vergniory et al., 2020), its effect on polyQ diseases is currently being explored. So far, it has been shown to inhibit Httex1 aggregation *in vitro* (Vöpel et al., 2017) and is currently being tested in SCA3 models. However, no *in vivo* data have been published to date.

Additionally, arginine has been identified as another promising anti-aggregation compound for polyQ proteins. This chemical chaperone has been shown to prevent the conformational transition to toxic β-sheets, hindering oligomerization (Minakawa et al., 2020). Oral administration of arginine resulted in amelioration of molecular pathology and motor symptoms in the *Atxn1*$^{154Q/2Q}$ and AR-97Q mouse models of SCA1 and SBMA, respectively (Minakawa et al., 2020). Recently, the phase 2 clinical trial of arginine in SCA6 patients has been concluded (AJA030-002), and the results showed a mild, but nonstatistically significant, amelioration of ataxia symptoms in treated patients (Ishihara et al., 2024). A

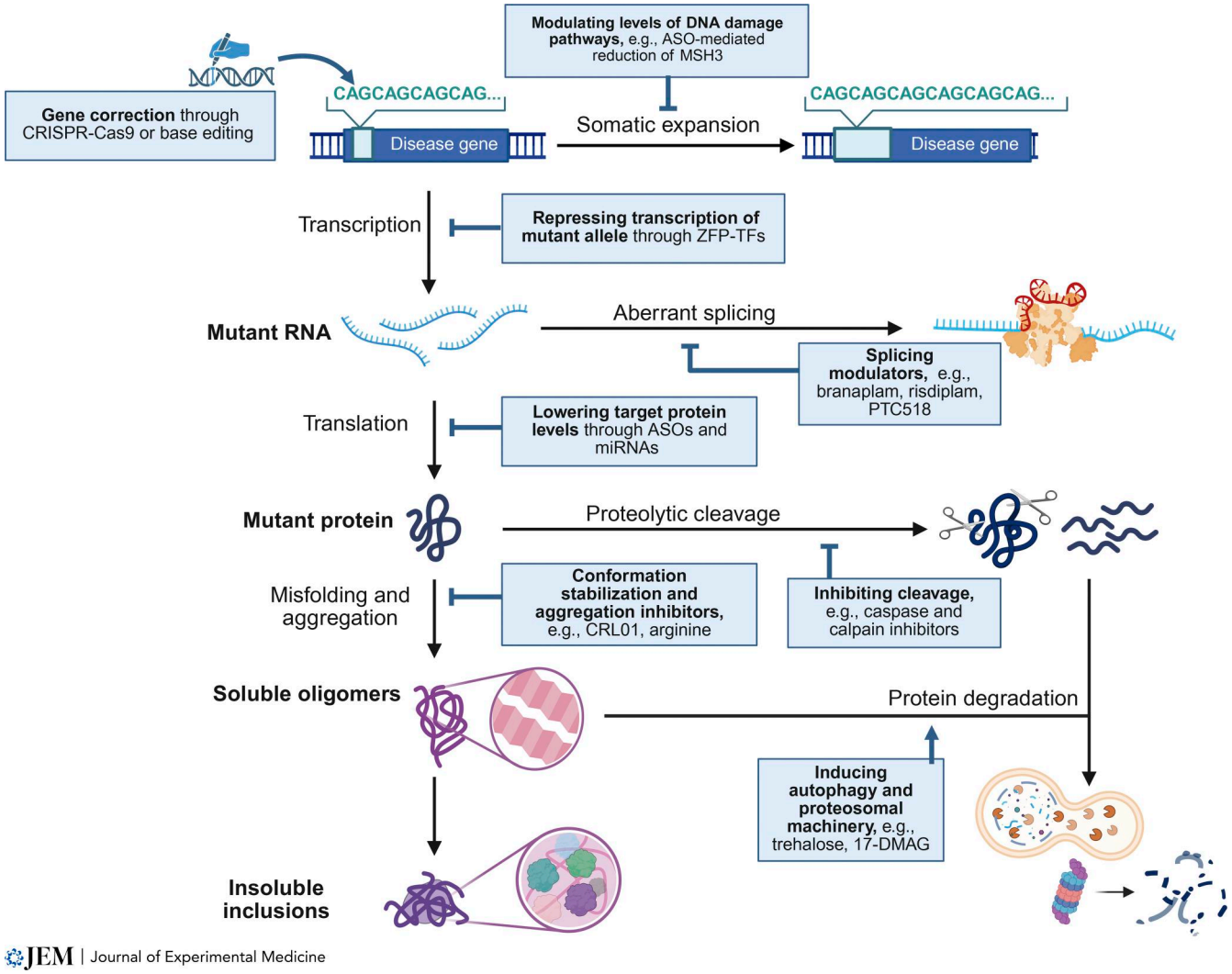

Figure 2. **Therapeutic approaches for polyQ diseases.** Although no effective disease-modifying therapies are currently available, several promising strategies are under development. These approaches target different levels of pathogenesis. At the DNA level, CRISPR/Cas9 and base editing approaches seek to correct the CAG-expanded tract or insert CAA interruptions. ZFP-TFs aim to reduce transcription of the disease gene. As the mutant RNA undergoes aberrant splicing, splicing modulators correct aberrant RNA processing. Additionally, RNA-based therapies such as ASOs and miRNAs target mutant transcripts for degradation or repress translation. At the protein level, conformation stabilizers and aggregation inhibitors help prevent protein misfolding and inclusion formation, while caspase and calpain inhibitors prevent cleavage of the mutant protein into toxic fragments. Finally, autophagy-inducing compounds enhance clearance of misfolded proteins (created in BioRender, https://BioRender.com/4l83pge).

potential phase 3 trial with a larger sample size has been discussed but not yet confirmed.

Enhancing protein degradation

The objective of this strategy is to reduce neurotoxicity by increasing the clearance of misfolded proteins through activation of the UPS, autophagy, or molecular chaperones. Extensive research has shown that modulating the levels of molecular chaperones can ameliorate neurodegeneration by inducing the heat-shock response. For example, pharmacological inhibition of Hsp90 with compounds like geldanamycin and 17-DMAG induces the proteasomal degradation of Hsp90 client proteins (Zou et al., 1998; Tokui et al., 2009; Silva-Fernandes et al., 2014). Treatment of transgenic mouse models of SBMA and SCA3 with 17-DMAG reduces levels of polyQ-expanded protein and ameliorates motor coordination deficits (Tokui et al., 2009; Silva-Fernandes et al., 2014).

Trehalose, an autophagy-inducing compound that also acts as a conformation stabilizer preventing oligomerization, has shown efficacy in alleviating phenotypes in transgenic mouse models that express N-terminal fragments of expanded HTT and ATXN3 (Tanaka et al., 2004; Santana et al., 2020). A clinical trial of trehalose in SCA3 patients (NCT04399265) is ongoing, and results are pending.

Reducing proteolytic cleavage

This approach seeks to prevent the generation of toxic fragments that result from proteolytic cleavage by caspases and calpains. Calpain inhibitors have resulted in amelioration of neuropathology and motor deficits in two animal models of SCA3: a

lentiviral mouse model and a zebrafish transgenic model (Simões et al., 2014; Watchon et al., 2017). Besides reducing proteolytic cleavage, the calpain inhibitor calpeptin increased autophagic flux, which was essential for the observed rescue (Watchon et al., 2017). Another group designed a peptide encompassing part of the human HTT sequence that competes for caspase-6 cleavage, functioning as a sink for this enzyme. BACHD mice treated with this peptide showed reduced motor deficits and alleviation of depression phenotypes (Aharony et al., 2015). However, caspase and calpain inhibitors and molecular sinks face the challenge of poor target specificity and therefore have struggled to progress to clinical trials.

The challenge of target specificity could be solved by strategies that target the cleavage site in the mutant gene. There is a naturally occurring isoform of HTT, HTTΔ12, that contains a truncated exon 12 and is resistant to caspase-6 cleavage. To mimic this isoform, Kim and colleagues designed an antisense oligonucleotide (ASO) QRX-704 to skip exon 12 of HTT, which reduced formation of toxic fragments and decreased aggregation in the YAC128 mouse model of HD (Kim et al., 2022). While no adverse effects were seen, more studies are needed to evaluate rescue of pathology and behavioral phenotypes.

Lowering mutant protein levels

DNA-based approaches. Advances in gene-editing technologies and biomolecular engineering have led to the development of allele-selective approaches that specifically target the expanded allele in polyQ diseases. Techniques such as engineered zinc finger protein transcription factors (ZFP-TFs) and CRISPR/Cas9 have been employed to selectively repress the expression of the mutant allele or to correct the CAG expansion. ZFP-TFs are DNA-binding sequences that can be engineered to target a specific gene and control its expression. Zeitler and colleagues designed poly-CAG targeting ZFP-TFs that successfully lowered mHTT levels in three different mouse models of HD: R6/2, Hdh50Q, and zQ175, and partially improved behavioral phenotypes (Zeitler et al., 2019). Although this has not yet been tested for these ZFP-TFs, any strategy that lowers transcription of the mutant allele could also help limit somatic instability by reducing transcription-dependent destabilization. Alternatively, CRISPR/Cas9 strategies seek to correct the expansion in the mutant allele by replacing it with a normal repeat length. This has been successfully achieved in HD and SCA3 patient–derived iPSCs, in which gene correction has rescued protein aggregation, mitochondrial dysfunction, and cell death (Xu et al., 2017; He et al., 2021). This strategy remains to be tested *in vivo*, and certain challenges still need to be overcome, such as optimized delivery methods and minimization of off-target effects.

Since studies have shown that the length of the uninterrupted CAG repeat is the main determinant of age at disease onset (Lee et al., 2019; Wright et al., 2019), emerging strategies have attempted to introduce interruptions in the CAG tract. To this end, base editing successfully introduced CAA interruptions in HEK293T cells, but it remains to be thoroughly tested in patient-derived cells and mouse models due to technical challenges (Choi et al., 2024). An approach of this type aims to delay age at onset by stabilizing repeat instability; however, it does not address downstream protein toxicity effects.

RNA-based approaches. There are diverse methods that aim to decrease translation of the mutant protein by targeting its mRNA for degradation using either small interfering RNA, ASOs, short hairpin RNA (shRNA), or microRNA (miRNA). These approaches can be designed in two ways: non–allele-specific, which reduce the levels of both wild-type and mutant mRNA; or allele-specific, which selectively target the mutant allele while preserving wild-type expression.

ASOs require repetitive intrathecal injections into the cerebrospinal fluid, and they have reached clinical trials with mixed results. The GENERATION HD1 study (NCT03761849; Roche), which investigated the use of the non–allele-specific ASO tominersen (Tabrizi et al., 2019), revealed significant challenges. Although initially promising by showing significantly reduced HTT levels, the study was halted due to adverse effects, including a transient increase in cerebrospinal fluid markers indicative of neuronal injury (Tabrizi et al., 2022). Despite this, post hoc analyses suggested that younger patients with lower disease burdens might benefit from treatment (McColgan et al., 2023), leading to the initiation of the GENERATION HD2 study (NCT05686551; Roche), which is currently underway. While it is possible that younger brains might be more resilient to the treatment, it is also important to explore the deleterious effects of lowering wild-type HTT in patients.

Other promising recent advances are the development of allele-specific ASOs targeting the CAG tract or regions proximal to it. Hauser and colleagues developed an ASO for SCA3 by leveraging a single nucleotide polymorphism (SNP) proximal to the CAG repeat stretch in ATXN3 (c.987G > C) that is frequent in SCA3 alleles but rare in wild-type ones. This ASO achieved significant reduction of mutant ATXN3 while sparing wild-type protein levels in patient-derived neurons (Hauser et al., 2021). While promising, further studies in animal models are required to explore its efficacy and safety. A different approach targets the CAG repeat tract directly using an ASO with the sequence $(CUG)_7$. This ASO, named VO659, has been tested in knock-in and transgenic mouse models of HD, as well as in SCA1 and SCA3 knock-in models (Evers et al., 2011; Datson et al., 2017; Kourkouta et al., 2019). Due to the length of the CUG sequence, VO659 binds both the wild-type and expanded transcripts, but it preferentially targets longer CAG tracts, causing a greater reduction of the mutant protein. It is currently in phase 1/2a clinical trials for HD, SCA1, and SCA3 patients (NCT05822908; VICO Therapeutics). By targeting the repeat itself, this approach offers a promising avenue for developing a single therapeutic strategy that is not only allele-preferential but applicable across multiple polyQ diseases.

Other RNA-based therapeutic strategies include approaches that utilize shRNA or miRNA to achieve gene silencing through RNAi. These therapies involve a single-dose treatment of an adeno-associated virus (AAV) or a lentiviral vector that allows continuous expression of the shRNA or miRNA. Currently, AAV5-miHTT/AMT-130, a non–allele-specific miRNA that showed promising results in HTT animal and cellular models (Miniarikova et al., 2017; Keskin et al., 2019; Thomson et al.,

2023), is undergoing two phase 1/2 clinical trials in early-stage HD patients (NCT04120493 and NCT05243017; uniQure Biopharma B.V.).

So far, the mixed clinical trial results highlight the complexity of translating polyQ protein-lowering strategies into effective treatments, though the approach remains promising with multiple ongoing trials testing both allele-specific and nonspecific RNA targeting methods.

Splicing modulators

A novel therapeutic approach targets disease-associated splicing events. Branaplam (Novartis), an orally active small molecule originally developed for spinal muscular atrophy, nonspecifically reduces both wild-type and mHTT levels while ameliorating splicing defects in HD models (Palacino et al., 2015; Keller et al., 2022; Krach et al., 2022). Recently, a study found that splicing modulators like branaplam and risdiplam also modify CAG instability *in vitro* by promoting inclusion of a pseudoexon in *PMS1*, a gene involved in MMR (McLean et al., 2024). The VIBRANT-HD trial of branaplam in adults (NCT05111249), however, was halted in phase 2 due to safety concerns. PTC518 (NCT05358717; PTC Therapeutics), another splicing modulator (Bhattacharyya et al., 2021; Gao et al., 2024), is advancing to phase 2A trials, showing HTT lowering without significant adverse effects so far. While there are currently promising splicing modulators, the data so far highlight that thorough investigation into the effect of these approaches is crucial, especially into off-target splicing modulation events that could cause toxicity.

Emerging approaches

A growing number of strategies aim to prevent, or even reverse, somatic CAG expansion. One example is naphthyridine-azaquinolone (NA), a small molecule that specifically binds slipped-DNA structures formed by long CAG repeats during transcription and interferes with the aberrant repair processes that lead to expansions. Treatment with NA induced repeat contractions in HD patient fibroblasts and in the striatum of the R6/2 transgenic model of HD (Nakamori et al., 2020). In a transgenic mouse model of DRPLA, NA induced small repeat contractions in the striatum and was associated with a mild motor improvement. While this treatment is allele-specific and potentially applicable across polyQ disorders, more data are needed in nontransgenic mouse models and patient neurons to evaluate whether it leads to measurable phenotypic improvements and whether its effects can extend beyond the striatum. Other strategies being explored are the modulation of levels of proteins like FAN1 and MSH3. For instance, ASO-mediated reduction of MSH3 levels effectively prevented somatic expansion in striatal neurons derived from HD patients (Bunting et al., 2025). *In vivo* work will need to demonstrate whether HD phenotypes are rescued, and whether MSH3 loss is well-tolerated in the long term. Moreover, it is important to consider recent evidence suggesting CAG repeats may be inherently toxic beyond a certain threshold (Aldous et al., 2024; Wang et al., 2025), which raises important concerns about optimal therapeutic timing and whether targeting DNA repair pathways might be only beneficial in early-stage patients.

Concluding remarks

The landscape of polyQ diseases is remarkably complex, challenging our initial quest for a single pathogenic trigger that explains all aspects of downstream dysfunction. The neurotoxicity caused by polyQ expansions is mainly protein-mediated, resulting in downstream consequences such as transcriptional dysregulation, impaired protein clearance and energy homeostasis, dysfunctional axonal transport, among others. Modern molecular tools have illuminated previously hidden disease mechanisms, yet fundamental questions persist about cellular and regional vulnerability. Recently, certain abnormal cellular processes such as somatic expansion have been debated as the drivers of toxicity and cell death; however, further work needs to be done to establish direct causality.

Although recent clinical trials have not yet achieved the expected outcomes, they have provided crucial insights, such as the importance of maintaining wild-type protein function and thoroughly testing off-target effects. Emerging approaches like allele-specific targeting and advanced delivery systems hold great promise. Looking ahead, success will likely come from integrating multiple strategies that address the various facets of disease pathogenesis, an approach made possible by our deeper appreciation of disease complexity rather than hindered by it.

Acknowledgments

This work was funded by the Howard Hughes Medical Institute (Huda Y. Zoghbi), and the National Institute of Neurological Disorders and Stroke/NIH grant 5R01NS027699 (Huda Y. Zoghbi).

Author contributions: Esmeralda Villavicencio Gonzalez: conceptualization, data curation, formal analysis, investigation, visualization, and writing—original draft, review, and editing. Huda Y. Zoghbi: conceptualization, funding acquisition, project administration, resources, supervision, and writing—review and editing.

Disclosures: H.Y. Zoghbi reported personal fees from Regeneron, Cajal Therapeutics, Lyterian, and The Column Group outside the submitted work. No other disclosures were reported.

Submitted: 10 June 2025
Revised: 25 September 2025
Accepted: 30 September 2025

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