

Review

Ubiquitin-Dependent Protein Quality Control in Polyglutamine Diseases

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ABSTRACT: Polyglutamine diseases comprise a family of nine age-dependent disorders caused by CAG triplet-repeat expansions that produce misfolded proteins with elongated glutamine tracts. Although these diseases share proteotoxic stress and engagement of protein quality control pathways as responses to their presence and disruptive activities, they differ in protein context, normal function, localization, interactomes and selective vulnerability. Here, we review how expanded polyglutamine proteins engage ubiquitin-dependent protein quality control across Huntington's disease, dentatorubral-pallidoluysian atrophy, spinal and bulbar muscular atrophy, and spinocerebellar ataxias 1, 2, 3, 6, 7 and 17. Rather than treating protein quality control as a uniform response, we emphasize pathway selectivity. A central theme arises across these diseases: mutant polyglutamine proteins are recognized by ubiquitin-related machinery, but recognition does not necessarily produce productive degradation. Instead, disease-specific outcomes are shaped by tissue context, subcellular localization, aggregate state, disease protein fragmentation, normal protein function, compensatory pathway activation and local proteostasis capacity over time. The information synthesized in this review may help the field develop a more comparative and granular understanding of processes and pathways that are shared or divergent among polyglutamine diseases and may also inform more targeted therapeutic strategies for this family of incurable disorders.

Keywords: Ataxia, Autophagy, Cerebellum, Chaperone, Dentatorubral-Pallidoluysian Atrophy, Huntington's disease, Kennedy's disease, Mitochondria, Neurodegeneration, Proteasome, Proteostasis, RNA, Spinal and Bulbar Muscular Atrophy

Introduction

Polyglutamine (polyQ) diseases comprise nine disorders linked by a common pathogenic mechanism in which misfolded proteins interact with and stress the cell's protein quality control (PQC) machinery (Fig. 1; Table 1; Table 2 lists all of the abbreviations used in this review) [1, 2]. The resulting proteotoxic stress engages coordinated PQC pathways, including chaperone-mediated folding, degradation through the ubiquitin-proteasome system (UPS) and autophagy. Despite this shared overarching mechanism, the polyQ diseases produce distinct phenotypes and selectively affect different neuronal populations, raising a

central and therapeutically relevant question: which differences in PQC engagement are relevant to these divergent cellular outcomes?

PolyQ diseases arise from CAG repeat expansions within the coding regions of largely unrelated genes, producing misfolded proteins with abnormally long glutamine tracts. The disorders include Huntington's disease (HD), dentatorubral-pallidoluysian atrophy (DRPLA), spinal and bulbar muscular atrophy (SBMA), and spinocerebellar ataxia (SCA) 1, 2, 3, 6, 7 and 17 [2, 3]. Although these proteins share a polyQ expansion, they differ in normal function and interactomes. Together with evidence that pure CAG repeat models can be highly toxic because the repeat lacks native protein structure through

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which normal interactors can engage, these differences indicate that protein context strongly shapes disease pathology [4]. Recent experimental work further supports the importance of protein context: the position of a polyQ

tract within a protein can influence the pathogenic expression threshold and its association with the proteasome, reinforcing the notion that repeat length alone does not determine proteotoxic behavior [5].

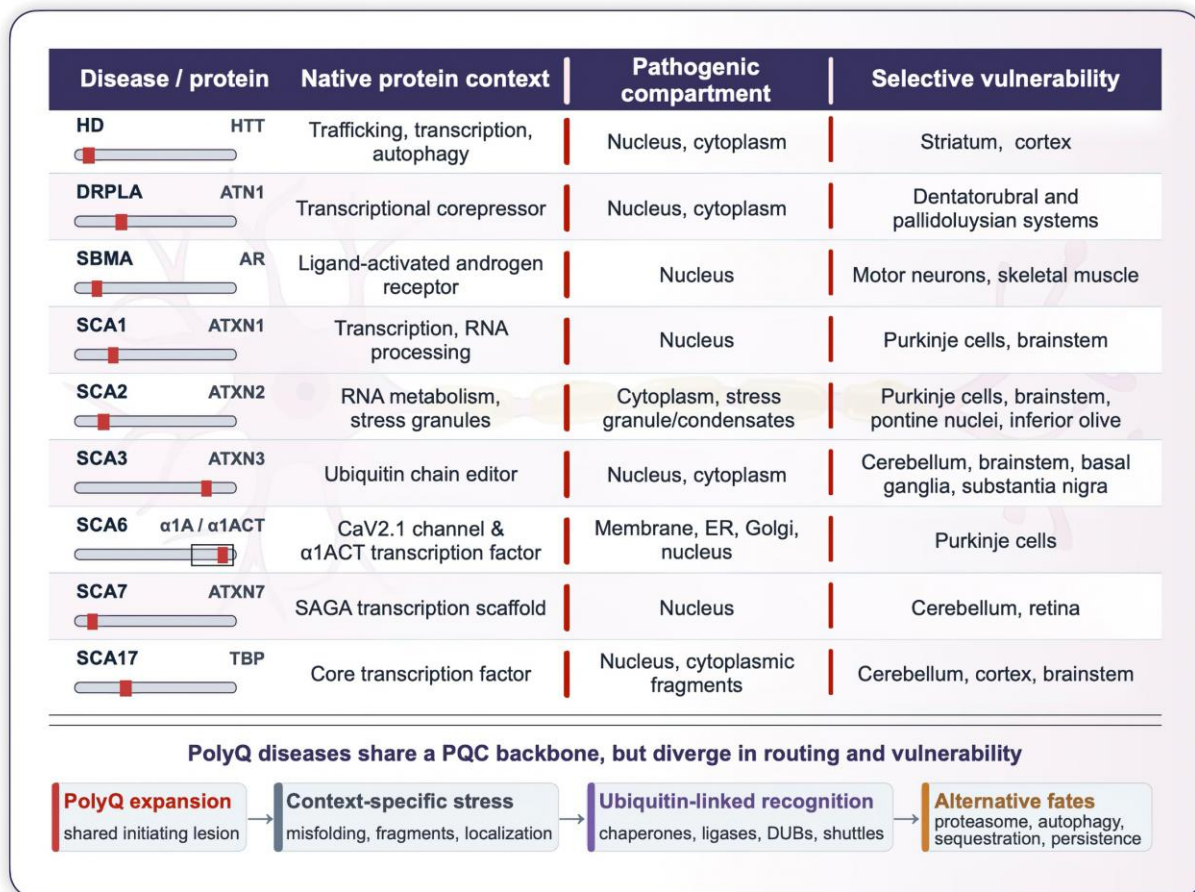


Figure 1. The polyQ diseases. Protein cartoons are not to scale. Red boxes indicate the relative positions of polyQ tracts. The additional box in the SCA6 schematic denotes the C-terminal region that encodes α 1ACT.

PQC is an interconnected network that maintains proteostasis during normal cellular function and under stresses such as those imposed by aggregation-prone polyQ proteins [1, 6]. Its major branches include chaperone-mediated folding systems, which fold newly synthesized proteins or refold and stabilize misfolded proteins; the UPS, which generally targets soluble and short-lived substrates for degradation; and autophagy-related pathways, which are well suited to degrading larger protein assemblies, damaged organelles and aggregated species. Cytosolic, mitochondrial, lysosomal and other compartment-specific proteases also contribute to protein homeostasis. The polyQ proteins engage distinct cellular partners and PQC components; consequently, cellular responses are not uniform [3].

Within the PQC network, the UPS is especially important because ubiquitination is one indication that a

polyQ protein has been recognized as abnormal [7]. Ubiquitination is an ATP-dependent post-translational process in which ubiquitin is covalently attached to a substrate, altering its interactions, localization, activity, or stability. This process depends on the action of three groups of proteins: E1 enzymes activate ubiquitin, E2 enzymes carry it, and E3 ligases facilitate its transfer to a substrate lysine through an isopeptide bond. Acceptor proteins may receive one ubiquitin, multiple individual ubiquitins, or polyubiquitin chains. Chains form through ubiquitin's own seven lysines (K6, K11, K27, K29, K33, K48, K63) or its N-terminal methionine, yielding structurally distinct homotypic, mixed, or branched linkages. K48 and K11 chains principally target proteins for proteasomal degradation, whereas K63 chains commonly support signaling, protein trafficking, DNA repair, autophagy and lysosomal targeting. The other chains are associated with mitochondrial quality control and DNA-damage responses (K6),

DNA-damage, immune signaling and membrane trafficking (K27, K29, K33). M1-linked linear chains primarily function in inflammatory and NF- κ B signaling. Mixed-

and branched-chain architectures further expand these outcomes and can create especially potent degradation or signaling platforms [8].

Table 1. Details and characteristics of each polyQ disease.

Disease, gene & protein	Inheritance	Normal/Intermediate polyQ range	Pathogenic polyQ range	Normal function of affected protein	Pathological features
Huntington's disease (HD) HTT Huntingtin	Autosomal dominant	6–26 normal; 27–35 intermediate	36–39 reduced penetrance; 40–121 full penetrance	Vesicular and axonal transport; transcriptional regulation; selective autophagy; DNA damage repair; nervous system development; scaffold and anti-apoptotic functions.	Widespread neurodegeneration, especially in the striatum and cortex; chorea and impaired voluntary movement; gait, balance and coordination deficits; cognitive decline and dementia; psychiatric symptoms; seizures (particularly in juvenile HD); skeletal muscle atrophy; metabolic and autonomic dysfunction.
Dentatorubral–pallidolusian atrophy (DRPLA) ATN1 Atrophin11	Autosomal dominant	3–38 normal; 39–48 intermediate	≥ 49 repeats	Transcriptional corepressor; roles in nervous system development (normal functions remain incompletely defined).	Degeneration of dentatorubral and pallidolusian systems; cerebellar ataxia; myoclonus and epilepsy/seizures; choreoathetosis; psychiatric changes; progressive cognitive decline and dementia.
Spinal and bulbar muscular atrophy (SBMA; Kennedy's disease) AR Androgen receptor	X-linked recessive (primarily affects males)	6–37	≥ 38 repeats	Ligand-activated steroid hormone receptor; transcription factor and DNA-binding protein; cell differentiation and androgen signaling.	Ligand-dependent toxicity; degeneration of lower motor neurons and skeletal muscle pathology; progressive bulbar, facial and limb weakness and atrophy; dysphagia; tremor and fasciculations; muscle cramps; hyporeflexia; mild androgen-insensitivity features.
Spinocerebellar ataxia type 1 (SCA1) ATXN1 Ataxin-1	Autosomal dominant	6–38	39–88; repeat interruption status modifies pathogenicity near the threshold	Transcriptional regulation; RNA processing, including splicing and mRNA stability/transport; chromatin-associated protein interactions.	Progressive cerebellar ataxia with gait and limb incoordination; dysarthria; oculomotor abnormalities; pyramidal signs and hyperreflexia; dysphagia; distal amyotrophy; cognitive impairment in some patients; degeneration of Purkinje cells and brainstem.
Spinocerebellar ataxia type 2 (SCA2) ATXN2 Ataxin-2	Autosomal dominant	14–26 normal; 27–34 intermediate (27–33 associated with increased risk of Amyotrophic Lateral Sclerosis)	≥ 35 repeats	Cytoplasmic RNA binding and handling; RNA metabolism and stability; RNA transport and translation; transcriptional regulation; stress-granule biology.	Degeneration of Purkinje cells, brainstem, pontine, inferior olive; progressive cerebellar ataxia; dysarthria; markedly slow saccadic eye movements; hyporeflexia; peripheral neuropathy and amyotrophy; postural tremor; rigidity or spasticity; cognitive impairment in some patients; parkinsonism.
Spinocerebellar ataxia type 3 (SCA3; Machado–Joseph disease) ATXN3 Ataxin-3	Autosomal dominant	12–54	≥ 55 repeats (commonly 60–87)	Deubiquitinating enzyme; protein homeostasis; transcription; cytoskeleton regulation; cell signaling.	Degeneration of the dentate nucleus, substantia nigra, brainstem, basal ganglia and spinocerebellar pathways; progressive cerebellar ataxia; dystonia; limb and truncal ataxia; autonomic dysfunction; cognitive impairment; parkinsonism; abnormal eye movements.

Spinocerebellar ataxia type 6 (SCA6) CACNA1A CaV2.1 α1A channel subunit and polyQ-bearing α1ACT transcription factor (bicistronic CACNA1A products)	Autosomal dominant	4-18	≥ 19 repeats	P/Q-type voltage-gated Ca^{2+} channel activity; neurotransmitter release; cerebellar signaling; α 1ACT-dependent transcriptional regulation.	Late-onset, slowly progressive cerebellar ataxia; gait instability; dysarthria; nystagmus; limb incoordination; cerebellum-restricted degeneration, especially of Purkinje cells.
Spinocerebellar Ataxia 7 (SCA7) ATXN7 Ataxin-7	Autosomal dominant	4-27 normal; 28-33 mutable/intermediate; 34-36 reduced penetrance	≥ 37 fully penetrant (reported up to ~460)	Core component of the SAGA transcriptional co-activator complex; regulates transcription, histone acetylation and histone H2B deubiquitination; chromatin and retinal homeostasis.	Progressive cerebellar ataxia; retinal and macular degeneration; dysarthria; dysphagia; hyperreflexia; orofacial dyskinesia.
Spinocerebellar ataxia type 17 (SCA17) TBP TATA-binding protein	Autosomal dominant	25-40 normal; 41-48 intermediate/variable penetrance	≥ 49 usually fully penetrant (lower-repeat disease can occur with genetic modifiers)	TATA-box DNA binding; general transcription initiation and regulation.	Cerebral, cerebellar and brainstem atrophy; progressive ataxia; cognitive decline and dementia-like features; psychiatric symptoms; variable movement disorders, including chorea, dystonia and parkinsonism.

Much of the UPS literature on polyQ diseases has examined individual proteins, UPS factors, or disorders. This approach has identified important disease-specific mechanisms, but the growing depth of the literature also permits a comparative view of how the UPS handles different polyQ disease proteins in different contexts. Expanded polyQ proteins are not processed uniformly. Their fate depends on the expanded glutamine tract as well as where and how they are ubiquitinated, how deubiquitinases (DUBs) edit those signals, whether they can be extracted from complexes or compartments, whether they are transferred to proteasome- or autophagy-associated shuttle factors and whether they ultimately reach and can engage the proteasome or autophagy. Here, we integrate foundational and recent studies to compare how polyQ proteins engage the UPS and autophagy, how these interactions vary by protein context and model system and how disease-specific routing may help explain distinct cellular and clinical outcomes. Table 3 summarizes these factors and identifies select regulators characterized outside the polyQ-disease literature when those studies provide relevant mechanistic context. Table 4 provides a comparative view across the polyQ diseases.

We begin with HD, the most extensively studied polyQ disease, to introduce concepts that recur throughout the review; we then discuss the remaining diseases alphabetically. Each disease-specific section summarizes the relevant published evidence, followed by a comprehensive synthesis across the polyQ diseases. As will become clear, research attention has been distributed unevenly across this disease family, with some disorders studied

more extensively than others. We hope that future efforts will increasingly focus on these understudied disorders as the broader field strives toward a comprehensive understanding of their distinct etiologies and more equitable therapeutic development.

Huntington's disease

HD is an autosomal dominant polyQ disorder caused by CAG repeat expansion in the huntingtin (HTT) gene. Alleles with 36-39 repeats show reduced penetrance, whereas alleles with at least 40 repeats are generally fully penetrant [9] (Fig. 1; Table 1). Clinically, HD is characterized by progressive motor dysfunction, chorea and impaired voluntary movement, along with cognitive decline and psychiatric symptoms [10, 11]. Although HTT is expressed ubiquitously and neurodegeneration is widespread, pathology is severe in the striatum and cortex, suggesting that tissue and region-specific cellular responses play a role in which neurons succumb to death alongside the intrinsic toxicity of mutant HTT itself [12, 13].

At the molecular level, polyQ expansion promotes the aggregation propensity of HTT, abnormal proteolytic fragmentation, altered protein interactions and accumulation in both cytoplasmic and nuclear inclusions [14-16]. Normally, HTT participates in vesicle trafficking, transcriptional regulation, autophagy and other cellular processes, indicating that HD likely reflects both toxic gain-of-function (GOF) and disruption of normal HTT activity, particularly in the context of impaired autophagy [17-21]. Together, these features place sustained pressure on PQC

systems including the UPS, autophagy-lysosome pathway and molecular chaperone network.

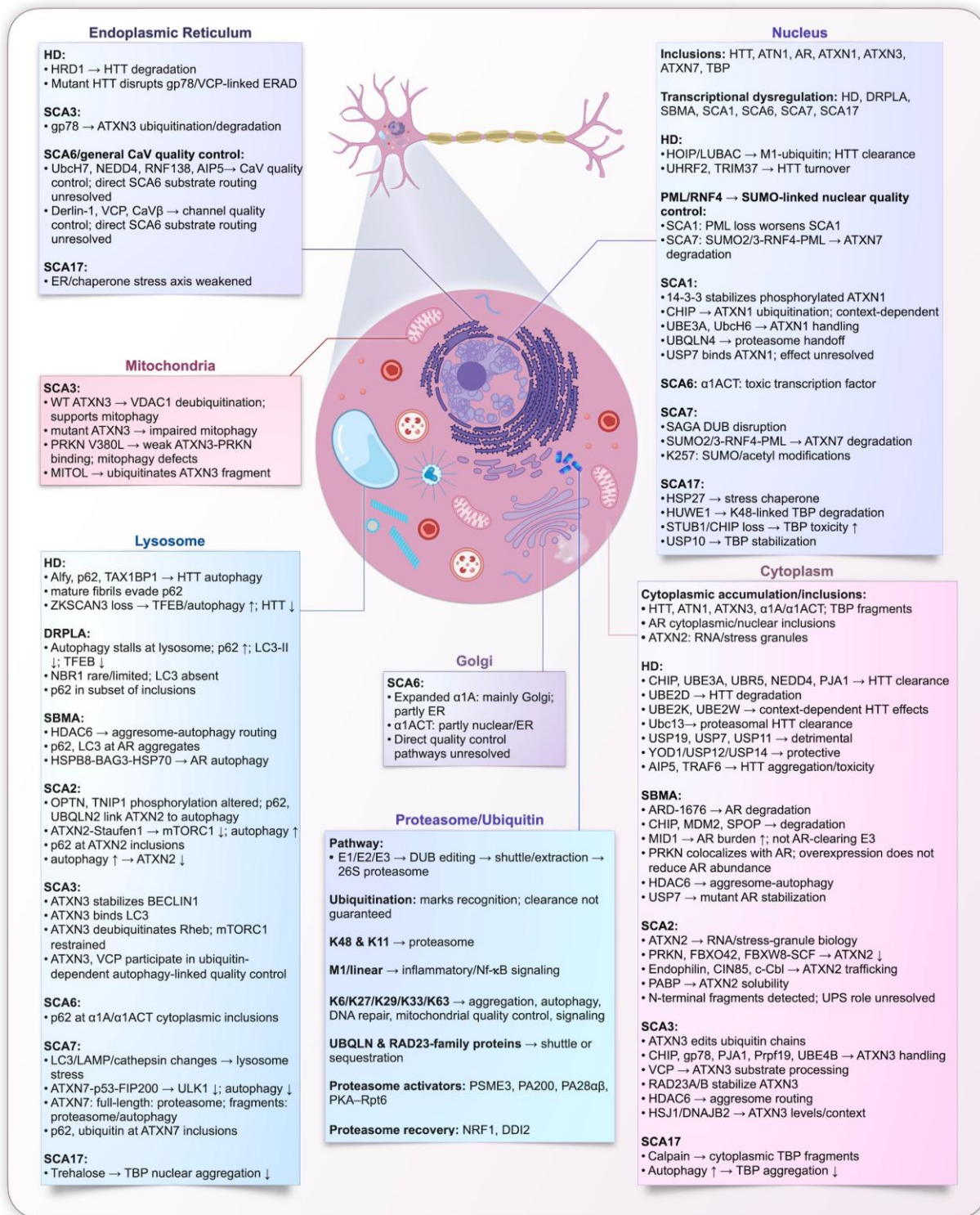


Figure 2. Visual summary of PQC engagement throughout the polyQ diseases. The cartoon of the prototypical neuron represents the various cells of the nervous system, including glia.

Ubiquitin-dependent quality control in HD

The extensive HD-related UPS literature is perhaps best understood not simply as proteasomal failure, but as failure of ubiquitin-dependent quality control at multiple levels. Expanded HTT is recognized by ubiquitin-related PQC systems, but ubiquitination does not always lead to productive degradation [22, 23]. HTT's fate depends on the ubiquitin chain type, the lysine site modified, the solubility and subcellular location of the substrate, the chaperones and deubiquitinases (DUBs) that edit the signals and whether the ubiquitinated protein is successfully extracted and shuttled to the proteasome and/or autophagy machinery (Fig. 2; Table 4). Before proceeding, we clarify our nomenclature. For genes and proteins reported to modify polyQ disease protein toxicity, we provide both the historical names or symbols used in the literature and the corresponding standardized human symbols (Table 2).

PolyQ expansion changes the proteins that bind HTT in vulnerable striatal tissue. HTT interaction maps place ubiquitin-mediated proteolysis and proteasome pathways within the larger HTT interaction network. In striatal HD mouse tissue, polyQ expansion remodeled HTT protein interactions early in disease and most polyQ expansion-dependent protein-protein interactions increased association with mutant HTT; many of these interaction changes occurred independently of changes in overall HTT protein abundance [14]. Within this remodeled interactome, ubiquitin-adjacent factors such as UBQLN2, RPS27A and SKP1 emerged as members of the remodeled interactome [14]. Another broad, curated HTT interactome analysis reached a similar conclusion at the pathway level by identifying protein modification as one of the major HTT interactor clusters and highlighting UPS within that network

[24]. A complementary dataset used APEX2 proximity proteomics to map wild-type and mutant HTT interactomes in living cells and their remodeling under proteasome inhibition, again placing UPS components among HTT's dynamic neighbors [25]. A conceptually distinct study added that HTT itself contains a ubiquitin-binding domain and may help route ubiquitinated mitochondrial and RNA-binding proteins to the lysosome, raising the possibility that HTT is not only a substrate of the ubiquitin system but also a reader of ubiquitin within its own interactome [26].

At the level of the ubiquitin signaling language, degradation-associated chains such as K48 and K11 generally favor proteasomal turnover, whereas K63 and atypical K6, K27 and K29 linkages are more often associated with signaling, aggregation or autophagy-linked handling [27, 28]. HTT is ubiquitinated at several lysine residues, including K6, K9, K15, K132, K337, K631, K804, K837 and K2097. K6 and K9 were detected on mutant HTT; K132, K804 and K837 were detected on wild-type HTT [29-31]. These observations indicate that polyQ expansion alters site-specific ubiquitination in addition to global HTT ubiquitination. The N-terminal K6/K9/K15 region of HTT is also important because these residues accept competing ubiquitin and SUMO modifications [31]. A recent study reported that preventing K6/K9 ubiquitination in mutant HTT knock-in mice worsened disease pathology [32]. This site-specific logic is not confined to the HTT protein itself. A proteomic survey mapped site-specific ubiquitination events on heat shock proteins in response to mutant HTT and found region-specific changes across the HD brain, linking the chaperone machinery to the ubiquitin code [33].

Table 2. Abbreviations.

Abbreviation or symbol	Name or explanation
11S; 19S; 20S; 26S	Proteasome activator; regulatory particle; core particle; and holoenzyme (respectively)
14-3-3 ϵ	14-3-3 protein epsilon
α 1ACT	C-terminal fragment of the α 1A subunit (CACNA1A-derived transcription factor)
AIP1/MAGI2	Atrophin-1-interacting protein 1 / membrane-associated guanylate kinase, WW and PDZ domain-containing 2
AIP2/WWP2	Atrophin-1-interacting protein 2 / WW domain-containing E3 ubiquitin-protein ligase 2
AIP3/WWP3	Atrophin-1-interacting protein 3 / WW domain-containing protein 3
AIP4/ITCH	Atrophin-1-interacting protein 4 / itchy E3 ubiquitin-protein ligase
AIP5/WWP1	Atrophin-1-interacting protein 5 / WW domain-containing E3 ubiquitin-protein ligase 1
Alfy/WDFY3	Autophagy-linked FYVE protein / WD repeat and FYVE domain-containing protein 3
APC/C-Cdh1	Anaphase-promoting complex / cyclosome with Cdh1/FZR1 co-activator
APEX2	Ascorbate peroxidase 2, used for proximity labeling
AR	Androgen receptor
ARD-1676	Androgen receptor-targeting proteolysis-targeting chimera
AR113Q	Knock-in mouse carrying 113 CAG repeats in the androgen receptor
ASC-JM17	Small molecule proteostasis activator
ATN1	Atrophin-1
ATXN1	Ataxin-1
ATXN1L	Ataxin-1-like protein
ATXN2	Ataxin-2

ATXN3	Ataxin-3
ATXN7	Ataxin-7
AXH	Ataxin-1 / HBP1 domain
BACHD; R6/1; R6/2; N171-82Q; Q140; Q175	Huntington's disease mouse models referenced in the text
BAG3/BAG1	BCL2-associated athanogene 3 (with BAG1) co-chaperone
BECLIN1/BECN1	Beclin-1
c-Cbl/CBL	Cbl proto-oncogene
CACNA1A	Gene encoding the $\alpha 1A$ subunit of the P/Q-type voltage-gated calcium channel CaV2.1 and the transcription factor $\alpha 1ACT$
CAG	Cytosine-adenine-guanine trinucleotide repeat encoding glutamine
CAPN1	Calpain 1
CAPN2	Calpain 2
CaV2.1	P/Q-type voltage-gated calcium channel (CACNA1A product)
CaV2.1-CTF	CaV2.1 C-terminal fragment
CaV β /CACNB	Voltage-gated calcium channel auxiliary beta subunit
CBP/CREBBP	CREB-binding protein
CCT2	Chaperonin-containing TCP1 subunit 2
CDK5	Cyclin-dependent kinase 5
CHIP/STUB1	C-terminus of Hsc70-interacting protein; encoded by STUB1
CIN85/SH3KBP1	SH3 domain-containing kinase-binding protein 1
COS-1; HeLa; HEK293(T); Neuro2a; PC12; SH-SY5Y	Cultured cell lines used in the cited studies
CRL3-SPOP	Cullin 3-SPOP E3 ubiquitin ligase complex
CUL1	Cullin 1
CUL7	Cullin 7
DDB2	Damage-specific DNA-binding protein 2
DDI2	DNA damage-inducible 1 homolog 2
Derlin-1/DERL1	Derlin 1
DHT	Dihydrotestosterone
DNAJB12	DnaJ heat shock protein family member B12
DNAJB6	DnaJ heat shock protein family member B6
DRPLA	Dentatorubral-pallidoluysian atrophy
DUB	Deubiquitinating enzyme
Endophilin A1/SH3GL2	SH3 domain-containing GRB2-like protein 2
ERAD	Endoplasmic reticulum-associated degradation
FBXO30	F-box protein 30
FBXO32	F-box protein 32
FBXO42	F-box protein 42
FBXW8	F-box and WD repeat domain-containing 8
Exoc7	Exocyst complex component 7
ETO/MTG8	Eight-twenty-one protein / myeloid translocation gene 8
FIP200	FAK family kinase-interacting protein of 200 kDa / RB1-inducible coiled-coil 1
GABARAP	GABA type A receptor-associated protein
GFI-1/Senseless	Growth factor independent 1 / Senseless
GOF	Gain of function
gp78/AMFR	Glycoprotein 78, encoded by AMFR
H2B	Histone H2B
HACE1	HECT domain and ankyrin repeat-containing E3 ubiquitin-protein ligase 1
HAP1	Huntingtin-associated protein 1
HD	Huntington's disease
HDAC1/2	Histone deacetylases 1 and 2
HDAC3	Histone deacetylase 3
HDAC6	Histone deacetylase 6
HDJ-2/DNAJA1	Human DnaJ homolog 2
HECTD1	HECT domain E3 ubiquitin-protein ligase 1
HMGB1	High-mobility group box 1
HOIP	HOIL-1-interacting protein (also known as RNF31)
HRD1/SYVN1	HMG-CoA reductase degradation protein 1 / synoviolin 1
HSF1	Heat shock factor 1
HSC70/HSPA8	Heat shock cognate 71 kDa protein
HSJ1/DNAJB2	DnaJ heat shock protein family member B2
HSP110	Heat shock protein 110 family
HSP27/HSPB1	Heat shock protein 27 / heat shock protein beta-1
HSP40/DNAJB1	Heat-shock protein 40 / DnaJ heat shock protein family (HSP40) member B1
HSP70/HSP90	Heat shock protein 70 and heat shock protein 90 families
HSPA5/BiP/GRP78	Heat shock protein family A member 5 / Binding immunoglobulin protein / Glucose-regulated protein 78

HSPB8	Heat shock protein family B (small) member 8 / HSP22
HTT	Huntingtin
HUWE1	HECT, UBA and WWE domain-containing E3 ubiquitin-protein ligase 1
iPSC	Induced pluripotent stem cell
IRSp53/BAIAP2	Insulin receptor substrate protein of 53 kDa / brain-specific angiogenesis inhibitor 1-associated protein 2
IκBα/NFKBIA	NF-κB inhibitor alpha
K6, K11, K27, K29, K33, K48, K63	Lysine residues defining ubiquitin chain linkage types
KLHL15	Kelch-like family member 15
LaminB1/LMNB1	Lamin B1
LAMP1/2	Lysosome-associated membrane proteins 1 and 2
LC3/MAP1LC3	Microtubule-associated protein 1A/1B light chain 3
LC3C/MAP1LC3C	Microtubule-associated protein 1 light chain 3 gamma
LOF	Loss of function
LUBAC	Linear ubiquitin chain assembly complex
MAGUK	Membrane-associated guanylate kinase proteins
MDM2	Mouse double minute 2 homolog
MG132	Proteasome inhibitor
MID1/TRIM18	Midline 1 / tripartite motif-containing 18
MITOL/MARCH5	Mitochondrial ubiquitin ligase / membrane-associated ring-CH-type finger 5
mTORC1	Mechanistic target of rapamycin complex 1
NBR1	Neighbor of BRCA1 gene 1
NC009-1	Pharmacological inducer of HSP27/HSPB1
NEDD4	Neural precursor cell expressed, developmentally downregulated 4
NEDD8	Neural precursor cell expressed, developmentally downregulated 8
NF-κB	Nuclear factor kappa B
NF-YA	Nuclear transcription factor Y subunit alpha
NRF1/NFE2L1	Nuclear factor erythroid 2-related factor 1
NRF2	Nuclear factor erythroid 2-related factor 2
OPTN	Optineurin
p53/TP53	Cellular tumor antigen p53
p62/SQSTM1	Sequestosome 1
PA200/PSME4	Proteasome activator subunit 4
PA28αβ/PSME1-PSME2	11S proteasome activator PA28 alpha/beta
PABP/PABPC1	Poly(A)-binding protein cytoplasmic 1
Parkin/PRKN	Parkin RBR E3 ubiquitin-protein ligase
Pin1	Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1
PJA1	Praja ring finger ubiquitin ligase 1
PJA2	Praja ring finger ubiquitin ligase 2
PKA	Protein kinase A
PML	Promyelocytic leukemia protein
polyQ	Polyglutamine
PQC	Protein quality control
PROTAC	Proteolysis Targeting Chimeras
Prpf19	Pre-mRNA-processing factor 19
PSMA7	Proteasome 20S subunit alpha 7
PSMD6	Proteasome 26S subunit, non-ATPase 6
PSME3/PA28γ	Proteasome activator subunit 3
RAD23A/HR23A	RAD23 homolog A
RAD23B/HR23B	RAD23 homolog B
Raptor/RPTOR	Regulatory-associated protein of mTOR complex 1
RBX1	RING-box 1
RERE	Arginine-glutamic acid dipeptide repeats protein
RFP2/TRIM13	Ret finger protein 2 / tripartite motif-containing 13
Rheb	Ras homolog enriched in brain
RING	Really interesting new gene E3 ubiquitin ligase class
RNF138	Ring finger protein 138
RNF4	Ring finger protein 4
RNF6	Ring finger protein 6
RNF8	Ring finger protein 8
Rpn10/PSMD4	26S proteasome non-ATPase regulatory subunit 4
Rpn11/PSMD14	26S proteasome non-ATPase regulatory subunit 14
Rpn13/ADRM1	Proteasome ubiquitin receptor Rpn13 / Adhesion-regulating molecule 1
RPS27A	Ribosomal protein S27a
Rpt6/PSMC5	26S proteasome regulatory subunit 8
S4/PSMC1	Proteasome 26S subunit ATPase 1
S7/PSMC2	Proteasome 26S subunit ATPase 2

SAGA	Spt-Ada-Gcn5 acetyltransferase complex
SBMA	Spinal and bulbar muscular atrophy
SCA	Spinocerebellar ataxia
SCF/FBXW7	SCF E3 ubiquitin ligase complex containing F-box / WD repeat-containing protein 7
Sgf73	Yeast orthologue of ATXN7
SIAH2	Siah E3 ubiquitin protein ligase 2
SKP1	S-phase kinase-associated protein 1
SKP2	S-phase kinase-associated protein 2
Staufen1/STAU1	Staufen double-stranded RNA-binding protein 1
SUMO	Small ubiquitin-like modifier
SUMO2/3	Small ubiquitin-like modifier 2/3
TAX1BP1	Tax1-binding protein 1
TBP	TATA-binding protein
TFEB	Transcription factor EB
TNIP1	TNFAIP3-interacting protein 1
TPR	Tetratricopeptide repeat domain
TRAF4	TNF receptor-associated factor 4
TRAF6	TNF receptor-associated factor 6
TRIM37	Tripartite motif-containing 37
Ubc13/UBE2N	Ubiquitin-conjugating enzyme 13 / Ubiquitin-conjugating enzyme E2 N
UbcH6/UBE2E1	Ubiquitin-conjugating enzyme H6 / Ubiquitin-conjugating enzyme E2 E1
UbcH7/UBE2L3	Ubiquitin-conjugating enzyme H7 / Ubiquitin-conjugating enzyme E2 L3
Ube1/UBA1	Ubiquitin-activating enzyme 1
UBE2D/eff	Ubiquitin-conjugating enzyme E2 D / effete
UBE2J1	Ubiquitin-conjugating enzyme E2 J1
UBE2K/E2-25K	Ubiquitin-conjugating enzyme E2 K
UBE2Q1	Ubiquitin-conjugating enzyme E2 Q1
UBE2T	Ubiquitin-conjugating enzyme E2 T
UBE2W	Ubiquitin-conjugating enzyme E2 W
UBE3A/E6-AP	Ubiquitin-protein ligase E3A / E6-associated protein
UBE4B/E4B	Ubiquitination factor E4B
UBQLN2	Ubiquilin 2
UBQLN4/A1Up	Ubiquilin 4 / Ataxin-1 ubiquitin-like-interacting protein
UBR5/EDD1	Ubiquitin-protein ligase E3 component n-recognin 5 / EDD1
UFM1	Ubiquitin-fold modifier 1
UHRF2	Ubiquitin-like with PHD and ring finger domains 2
UIM	Ubiquitin-interacting motif
ULK1	Unc-51-like autophagy-activating kinase 1
UPS	Ubiquitin-proteasome system
USP10	Ubiquitin-specific peptidase 10
USP11	Ubiquitin-specific peptidase 11
USP12	Ubiquitin-specific peptidase 12
USP13	Ubiquitin-specific peptidase 13
USP14	Ubiquitin-specific peptidase 14
USP19	Ubiquitin-specific peptidase 19
USP22	Ubiquitin-specific peptidase 22
USP26	Ubiquitin-specific peptidase 26
USP36	Ubiquitin-specific peptidase 36
USP54	Ubiquitin-specific peptidase 54
USP7/HAUSP	Ubiquitin-specific peptidase 7
USP9X	Ubiquitin-specific peptidase 9, X-linked
VCP/p97	Valosin-containing protein
VDAC1	Voltage-dependent anion channel 1
WDR5	WD repeat-containing protein 5
YOD1	YOD1 deubiquitinase
ZKSCAN3	Zinc finger with KRAB and SCAN domains 3

At the level of the ubiquitin signaling language, degradation-associated chains such as K48 and K11 generally favor proteasomal turnover, whereas K63 and atypical K6, K27 and K29 linkages are more often associated with signaling, aggregation or autophagy-linked handling [27, 28]. HTT is ubiquitinated at several lysine residues, including K6, K9, K15, K132, K337, K631, K804, K837

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Table 3. Summary of PQC components, cellular complexes and chemicals described in the text and the polyQ diseases with which they have been associated. For AR, the table also includes factors linked to AR abundance, stability, or signaling in cancer-related studies but not yet established in SBMA: USP9X [309], USP13 [310], USP36 [311] and USP54 [312].

Component	Name	Function	PolyQ disease(s) with which it has been associated
14-3-3ε	14-3-3 protein epsilon	Phospho-binding adaptor proteins that bind and stabilize ATXN1, increasing the soluble nuclear pool that must be managed by PQC.	SCA1
AIP1/MAGI2	Atrophin-1 interacting protein 1 / membrane associated guanylate kinase, WW and PDZ domain-containing 2	MAGUK-like scaffold protein; binds ATN1 near the polyQ tract and helps organize protein complexes through WW and PDZ domains.	DRPLA
AIP2/WWP2	Atrophin-1-interacting protein 2 / WW domain-containing E3 ubiquitin protein ligase 2	NEDD4-family HECT E3 ubiquitin ligase; identified as a WW-domain protein that binds ATN1 near the polyQ tract; direct ATN1 ubiquitination/clearance not established.	DRPLA
AIP3/WWP3	Atrophin-1-interacting protein 3 / WW domain-containing protein	WW-domain scaffold protein identified by yeast two-hybrid as an ATN1 interactor near the polyQ tract.	DRPLA
AIP4/ITCH	Atrophin-1-interacting protein 4 / itchy E3 ubiquitin protein ligase	NEDD4-family HECT E3 ubiquitin ligase; binds ATN1 through WW domains; direct ATN1 ubiquitination/clearance not established.	DRPLA
AIP5/WWP1	Atrophin-1-interacting protein 5 / WW domain-containing E3 ubiquitin-protein ligase 1	HECT E3 ubiquitin ligase; ubiquitinates signaling and regulatory proteins to control protein turnover, trafficking and stress responses. Promotes K63-linked ubiquitination of mutant HTT associated with aggregation/toxicity; binds ATN1 near the polyQ tract without direct ATN1 ubiquitination evidence; clears CaV2/UNC-2 in <i>C. elegans</i> as candidate calcium-channel quality control; direct SCA6 connection not established.	HD; DRPLA; SCA6
Alfy/WDFY3	Autophagy-linked FYVE protein / WD repeat and FYVE domain-containing protein 3	p62-partnered selective-autophagy scaffold; lower levels accelerate HTT accumulation and disease onset, whereas increased levels delay pathology in HD models.	HD
APC/C-Cdh1	Anaphase-promoting complex / Cyclosome with Cdh1/FZR1 co-activator	Multi-subunit RING E3 ubiquitin ligase complex; helps recruit substrates for ubiquitination and proteasomal degradation, especially in cell-cycle control and neuronal protein homeostasis; mutant AR binds complex and inhibits its activity.	SBMA
ARD-1676	Androgen receptor-targeting proteolysis-targeting chimera	Promotes ubiquitin-dependent proteasomal degradation of polyQ-expanded AR and reduces mutant AR in overexpression systems, patient-derived cells and AR113Q mice.	SBMA
ASC-JM17	Small-molecule proteostasis activator	Activates NRF1-, NRF2- and HSF1-linked stress programs, increasing proteasome subunits, antioxidant enzymes and molecular chaperones.	SBMA
ATXN1L	Ataxin-1-like protein	Competes with expanded ATXN1 for incorporation into native complexes; increasing ATXN1L displaces mutant ATXN1 and suppresses neuropathology in SCA1 mice.	SCA1
BAG3/BAG1	BAG cochaperone 3 (with BAG1)	HSP70 co-chaperones; the BAG1/BAG3 balance routes HSP70 clients between proteasomal degradation (BAG1) and selective autophagy (BAG3), shaping mutant AR handling.	SBMA

BE-CLIN1/BECN1	Beclin-1	Autophagy-initiation regulator. PolyQ-expanded proteins can sequester ATXN3 away from Beclin-1, increasing Beclin-1 ubiquitination and impairing autophagy; Beclin-1-related autophagy also influences mutant ATXN3 clearance.	DRPLA; SCA3; SBMA; SCA17
C-Cbl	Cbl proto-oncogene	RING E3 ubiquitin ligase; ubiquitinates activated receptors such as EGFR to promote endocytosis and receptor downregulation; ATXN2 can bind it and modifies its function. PolyQ untested.	SCA2
CAPN1	Calpain 1	Calcium-activated cysteine protease; cleaves selected proteins during calcium stress and can generate TBP proteolytic fragments that alter localization or toxicity.	SCA17
CAPN2	Calpain 2	Calcium-activated cysteine protease; works in calcium-dependent proteolysis and stress signaling, including cleavage of disease proteins in some neurodegenerative models.	SCA17
Caspase-3	Caspase 3	Cysteine protease; detected in subset of SCA7 inclusions.	SCA7
Caspase-7	Caspase 7	Executioner caspase associated with mutant ATXN7 inclusions; cleaves ATXN7 at Asp266 and Asp344 to generate aggregation-prone, toxic N-terminal fragments.	SCA7
Cathepsin D	Cathepsin D	Aspartic protease that is altered in SCA7.	SCA7
CaVβ/CACNB	Voltage-gated calcium channel auxiliary beta subunit	Auxiliary calcium-channel subunit; stabilizes calcium channels and protects them from ERAD; not directly linked to SCA6.	SCA6
CBP/CREBBP	CREB-binding protein	Acetyltransferase that acetylates ATXN7 K257, blocking autophagic turnover of a toxic cleavage fragment and promoting its accumulation.	SCA7
CCT2	Chaperonin-containing TCP1 subunit 2	Aggrephagy receptor that clears HTT aggregates.	HD
CDK5	Cyclin-dependent kinase 5	Phosphorylates ATXN2 and promotes its proteasomal degradation, reducing toxic polyQ-expanded ATXN2 in cell models.	SCA2
CHIP/STUB1	C terminus of Hsc70 interacting protein; encoded by STUB1	HSP70/HSP90 co-chaperone and U-box E3 ubiquitin ligase; promotes ubiquitination and degradation of misfolded client proteins.	HD; SBMA; SCA1; SCA3; SCA17
CIN85/SH3KB P1	SH3 domain containing kinase binding protein 1	Endocytic scaffold protein; links receptors, SH3 domain interactions and ubiquitin linked trafficking complexes.	SCA2
CRL3-SPOP	Cullin 3-SPOP E3 ubiquitin ligase complex / Speckle type BTB/POZ protein	CUL3-based E3 ubiquitin ligase complex in which SPOP acts as the substrate adaptor, recruiting selected proteins for ubiquitination and proteasomal degradation; evidence from AR/prostate-cancer studies. PolyQ untested.	SBMA
CUL1	Cullin 1	Scaffold of SCF E3 ubiquitin ligase complexes; helps assemble SKP1, F-box proteins and RBX1 for ubiquitin transfer; impacts HTT and ATXN2 stability and toxicity.	HD; SCA2
CUL7	Cullin 7	Cullin scaffold protein; forms SCF-like E3 ligase complexes with SKP1, FBXW8 and RBX1 to support substrate ubiquitination; facilitates ATXN2 degradation.	SCA2
DDB2	Damage specific DNA binding protein 2	Substrate receptor in the CUL4-DDB1 E3 ubiquitin ligase complex; enhances AR degradation; evidence from AR/prostate-cancer studies.	SBMA
DDI2	DNA-damage inducible 1 homolog 2	Aspartic protease that activates the proteasome-bounce-back factor NRF1; NRF1/DDI2-dependent proteasome recovery is impaired in SBMA muscle.	SBMA

Derlin-1/DERL1	Derlin 1	ER membrane retrotranslocation factor; helps move misfolded ER proteins into the cytosol for ERAD and proteasomal degradation; not directly linked to SCA6.	SCA6
DNAJB12	DnaJ heat shock protein family member B12	ER membrane HSP40/DNAJ co-chaperone; assists HSP70 in ER-associated protein quality control and degradation.	DRPLA
DNAJB6	DnaJ heat shock protein family member B6	HSP40/DNAJ co-chaperone; works with HSP70 to suppress protein aggregation and help manage misfolded proteins.	DRPLA
Endophilin A1/SH3GL2	SH3 domain containing GRB2 like 2	Endocytic adaptor protein; helps shape membranes and regulate synaptic vesicle and receptor internalization; ATXN2 can bind it and impacts function.	SCA2
ETO/MTG8	Eight-twenty-one protein / myeloid translocation gene 8	Transcriptional corepressor that associates with ATN1 in the nuclear matrix; whether it influences ATN1 turnover remains untested.	DRPLA
Exoc7	Exocyst complex component 7	Interactor that restrains Prpf19-dependent polyubiquitination and degradation of expanded ATXN3; the Prpf19-Exoc7 balance influences aggregate clearance.	SCA3
FBXO30	F-box protein 30	F-box protein; likely substrate receptor for SCF E3 ubiquitin ligase complexes; indirectly linked to SCA1.	SCA1
FBXO32	F-box protein 32	Muscle-enriched F-box E3 adaptor; promotes ubiquitin-dependent degradation during muscle atrophy and stress; indirectly linked to SCA1.	SCA1
FBXO42	F-box protein 42	F-box protein; substrate receptor for SCF E3 ubiquitin ligase complexes, linking selected proteins to ubiquitination and proteasomal degradation; enhances degradation of ATXN2.	SCA2
FBXW8	F-box and WD repeat domain-containing 8	Substrate-recognition F-box subunit of an SCF-type E3 ligase (with SKP1, CUL1/CUL7, RBX1) that promotes ATXN2 ubiquitination and proteasome-dependent degradation.	SCA2
FIP200/RB1CC1	FAK family kinase-interacting protein of 200 kDa / RB1-inducible coiled-coil 1	Autophagy-initiation scaffold sequestered with p53 into mutant ATXN7 inclusions, reducing soluble FIP200 and destabilizing ULK1.	SCA7
GABARAP	GABA type A receptor-associated protein	ATG8-family protein bound by ATXN3 LC3-interacting regions to support efficient autophagic flux.	SCA3
Gfi-1/Senseless	Growth factor independent 1 / Senseless	Zinc finger transcriptional repressor; regulates cell fate, differentiation and neuronal or sensory development programs; ATXN1 can impact its stability.	SCA1
gp78/AMFR	Glycoprotein 78; encoded by AMFR	ER membrane RING E3 ubiquitin ligase; promotes ERAD by ubiquitinating misfolded proteins for proteasomal degradation.	HD; SCA3
HACE1	HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1	HECT E3 ubiquitin ligase; regulates oxidative stress, RAC1 signaling and proteostasis linked stress responses. HACE1 levels are reduced in HD patient striatum; HACE1 expression protects cells from expanded HTT.	HD
HAP1	Huntingtin-associated protein 1	Neuronal scaffolding and trafficking protein; binds the conserved core domain of TBP and can sequester TBP into cytoplasmic inclusions.	SCA17
HDAC1/2	Histone deacetylases 1 and 2	Chromatin-regulating corepressors that form nuclear-receptor corepressor complexes with ATN1 and RERE; effects on ATN1 turnover remain untested.	DRPLA
HDAC3	Histone deacetylase 3	Class I histone deacetylase; binds normal and expanded ataxin-7, increases its post-translational modification and level and modifies polyQ-dependent toxicity.	SCA7

HDAC6	Histone deacetylase 6	Cytoplasmic deacetylase. HDAC6 binds ubiquitinated cargo and routes it toward autophagic clearance when proteasome capacity is limiting.	SCA3; SBMA
HDJ-2/DNAJA1	Human DnaJ homolog 2 / DNAJA1	HSP40/DNAJ co-chaperone; stimulates HSP70 activity and helps manage protein folding, refolding and aggregation control.	SBMA; SCA1; SCA7
HECTD1	HECT domain E3 ubiquitin protein ligase 1	HECT E3 ubiquitin ligase; regulates ubiquitination linked to development, signaling and protein turnover; indirectly linked to SCA1.	SCA1
HMGB1	High-mobility group box 1	Chromatin-associated transcriptional cofactor; sequestered by mutant TBP into aggregates, weakening HSPA5 transcription and starvation-induced autophagy.	SCA17
HOIP/LUBAC	HOIL-1 interacting protein, encoded by RNF31; catalytic subunit of LUBAC	E3 ubiquitin ligase within LUBAC; generates linear ubiquitin chains involved in NF- κ B signaling, inflammation and aggregate-associated ubiquitin regulation; recruited to HTT aggregates.	HD
HRD1/SYVN1	Synoviolin 1	ER membrane RING E3 ubiquitin ligase; promotes ER-associated degradation of misfolded proteins.	HD; SCA3
HSC70/HSPA8	Heat shock cognate 71 kDa protein	Constitutive HSP70 chaperone; supports basal protein folding, trafficking and proteostasis.	DRPLA; SCA3; SCA7; SCA17
HSF1	Heat shock factor 1	Transcriptional regulator of molecular chaperone and proteostasis stress responses; activated in SCA1 models; engaged by ASC-JM17 in SBMA models.	SBMA; SCA1
HSJ1/DNAJB2	DnaJ heat shock protein family member B2	Co-chaperone whose J-domain promotes HSP70-mediated proteasomal degradation of ATXN3, while its ubiquitin-interacting motifs can stabilize ubiquitinated ATXN3; it can also be sequestered by expanded ATXN7.	SCA3; SCA7
HSP110	Heat shock protein 110 family	Cooperates with HSP70 as a disaggregase system; together with UBQLN2, selectively lowers aggregated mutant HTT in HD mouse models.	HD
HSP27/HSPB1	Heat shock protein 27 / heat shock protein beta-1	Small heat shock chaperone; helps limit protein misfolding and aggregation during stress.	SCA17
HSP40/DNAJB1	Heat-shock protein 40 / DnaJ heat shock protein family (HSP40) member B1	A chaperone protein that stimulates the activity of HSP70.	DRPLA; SBMA; SCA7
HSP70/HSP90	Heat shock protein 70 and heat shock protein 90 families	Molecular chaperones; assist protein folding, stabilize client proteins and help route damaged proteins toward refolding or degradation.	HD; SBMA; SCA1; SCA3; SCA6; SCA7; SCA17
HSPA5/BiP/GRP78	Heat shock protein family A member 5 / Binding immunoglobulin protein / Glucose-regulated protein 78	ER-resident HSP70 chaperone; helps fold newly synthesized proteins, responds to ER stress and supports unfolded protein response signaling.	SCA17
HSPB8	Heat shock protein family B (small) member 8 / HSP22	Small heat shock protein; promotes clearance of mutant AR through autophagy-linked mechanisms.	SBMA
HUWE1	HECT, UBA and WWE domain-containing E3 ubiquitin-protein ligase 1	HECT E3 ligase that promotes K48-linked ubiquitination and proteasomal degradation of TBP. PolyQ untested.	SCA17
IRSp53/BAIAP2	Insulin receptor substrate protein of 53 kDa / brain-specific angiogenesis inhibitor 1-associated protein 2	SH3-domain-containing ATN1 interactor that binds a proline-rich region adjacent to the polyQ tract; its effect on ATN1 turnover is untested.	DRPLA

IκBα/NFKBIA	NF-κB inhibitor alpha	Proteasome substrate that accumulates when mutant ATXN7 impairs proteasome activity, contributing to disrupted NF-κB signaling.	SCA7
KLHL15	Kelch like family member 15	BTB-kelch protein; substrate adaptor for CUL3 E3 ubiquitin ligase complexes; indirectly linked to SCA1.	SCA1
Lam-inB1/LMNB1	Lamin B1	Nuclear lamina protein degraded and excreted through a nucleophagy-based route when canonical autophagy stalls in DRPLA models.	DRPLA
LAMP1/2	Lysosome-associated membrane proteins 1 and 2	Lysosomal membrane proteins reported as abnormal in SCA7 models, consistent with disrupted autophagy-lysosome handling.	SCA7
LC3/MAP1LC3	Microtubule-associated protein 1A/1B light chain 3	Autophagosome membrane marker used to assess autophagy engagement; mutant AR aggregates colocalize with LC3, and LC3/autophagy-lysosome handling is altered in SCA7; increased LC3-II enhances autophagic degradation of insoluble TBP.	SBMA; SCA7; DRPLA (LC3 absent from intranuclear inclusions); SCA17
LC3C/MAP1LC3C	Microtubule-associated protein 1 light chain 3 gamma	ATG8-family protein bound by ATXN3 LC3-interacting regions to support autophagic flux.	SCA3
MDM2	Mouse double minute 2 homolog	RING E3 ubiquitin ligase best known for ubiquitinating p53 and regulating stress-response pathways, apoptosis and protein stability. Forced proximity between AR and MDM2 promoted AR ubiquitination and proteasomal degradation in cultured cells.	SBMA
MID1/TRIM18	Midline 1 / tripartite motif-containing 18	Microtubule-associated RING E3 ubiquitin ligase; regulates protein ubiquitination, PP2A-associated signaling and cytoskeletal/proteostasis pathways. Binds CAG-repeat-containing AR mRNA, increases production of pathogenic AR and promotes androgen-dependent motor-neuron vulnerability.	SBMA
MITOL/MARCH5	Mitochondrial ubiquitin ligase / membrane associated ring-CH-type finger 5	Mitochondrial outer membrane E3 ubiquitin ligase; regulates mitochondrial dynamics, stress responses and turnover of mitochondrial proteins; promotes degradation of truncated ATXN3.	SCA3
mTORC1	Mechanistic target of rapamycin complex 1	Nutrient-sensing complex suppressed when polyQ-expanded ATXN2 sequesters Raptor; ATXN3 also restrains mTORC1 by deubiquitinating Rheb during starvation.	SCA2; SCA3
NBR1	Neighbor of BRCA1 gene 1	Ubiquitin-binding selective autophagy receptor; detected (inconsistently) in DRPLA intranuclear inclusions.	DRPLA
NEDD4/NEDD4-1	Neural precursor cell expressed, developmentally downregulated 4	HECT E3 ubiquitin ligase that promotes mutant HTT ubiquitination and clearance. Broader calcium-channel studies also implicate NEDD4 in channel degradation, but direct SCA6 regulation remains unestablished.	HD; SCA6
NEDD8	Neural precursor cell expressed, developmentally downregulated 8	Ubiquitin-like modifier recruited with 19S proteasome cap components to polyQ-expanded AR aggregates in SBMA cell models.	SBMA
NF-YA	Nuclear transcription factor Y subunit alpha	DNA-binding subunit of the NF-Y transcription factor complex; helps regulate NF-Y target genes; sequestered by mutant TBP into aggregates, weakening NF-Y-dependent HSPA5 expression.	SCA17
NF-κB	Nuclear factor kappa B	Stress-responsive transcription pathway disrupted when mutant ATXN7 reduces proteasome activity and causes accumulation of IκBα.	SCA7
NRF1/NFE2L1	Nuclear factor erythroid 2-related factor 1	Transcription factor whose DDI2-dependent activation supports proteasome recovery; NRF1/DDI2-dependent recovery is impaired in SBMA muscle.	SBMA

NRF2	Nuclear factor erythroid 2 related factor 2	Oxidative-stress transcription factor enhanced by HACE1 in HD striatal neuronal progenitor cells and engaged by ASC-JM17 in SBMA models.	HD; SBMA
OPTN	Optineurin	Ubiquitin-dependent selective-autophagy receptor with altered phosphorylation in SCA2 mouse spinal cord.	SCA2
p53/TP53	Cellular tumor antigen p53	Stress-responsive transcription factor; stabilized by ATXN3 deubiquitination and co-aggregates with mutant ataxin-7 (with FIP200), disrupting autophagy initiation.	SCA3; SCA7
p62/SQSTM1	Sequestosome 1	Ubiquitin binding autophagy adaptor; links ubiquitinated proteins or aggregates to autophagy and stress signaling pathways.	HD; DRPLA; SBMA; SCA1; SCA2; SCA3; SCA6; SCA7
PA200/PSME4	Proteasome activator subunit 4	Proteasome activator; regulates 20S proteasome activity, especially for nuclear protein turnover and stress-related proteolysis.	HD
PA28$\alpha$$\beta$/PSME1-PSME2	11S proteasome activator PA28 α /beta	Proteasome activator; regulates 20S proteasome activity, especially for nuclear protein turnover and stress related proteolysis.	HD
PABP/PABPC1	Poly(A)-binding protein cytoplasmic 1	Poly(A)-binding protein; RNA-dependent chaperone that binds ATXN2 and helps maintain ATXN2 solubility; loss promotes ATXN2 aggregation.	SCA2
Parkin/PRKN	Parkin RBR E3 ubiquitin protein ligase	RBR E3 ubiquitin ligase; promotes ubiquitination of mitochondrial and PQC substrates, especially during mitophagy and stress responses.	HD; SBMA; SCA2; SCA3
Pin1	Peptidylprolyl cis/trans isomerase NIMA-interacting 1	Phospho-proline isomerase; changes protein conformation after phosphorylation to regulate stability, localization and signaling; promotes α 1A degradation; connection to SCA6 unclear.	SCA6
PJA1	Praja ring finger ubiquitin ligase 1	Brain-enriched RING-H2 E3 ubiquitin ligase; promotes ubiquitination and proteasomal degradation of polyQ-expanded mutant HTT and ATXN3, reducing aggregation and toxicity.	HD; SCA3
PJA2	Praja ring finger ubiquitin ligase 2	RING E3 ubiquitin ligase; regulates signaling proteins through ubiquitination, including stress and kinase-linked pathways; indirectly linked to SCA1.	SCA1
PKA	Protein kinase A	Can regulate proteasome activity in HD models.	HD
PML	Promyelocytic leukemia protein	Nuclear scaffold protein; forms PML nuclear bodies that organize stress responses, SUMO signaling, transcriptional regulation and nuclear protein quality control.	SCA1; SCA7
Prpf19	Pre-mRNA-processing factor 19	Nuclear U-box ligase that promotes degradation of expanded ATXN3; Exoc7 restrains this activity, thus Prpf19-Exoc7 balance affects aggregate clearance.	SCA3
PSMA7	Proteasome 20S subunit alpha 7	20S proteasome alpha subunit; expression is reduced in AR113Q SBMA muscle.	SBMA
PSMD6	Proteasome 26S subunit, non-ATPase 6	19S regulatory proteasome subunit; expression reduced in AR113Q SBMA muscle.	SBMA
PSME3/PA28γ	Proteasome activator subunit 3	Nuclear proteasome activator; regulates 20S proteasome activity and promotes degradation of selected nuclear proteins.	HD; SBMA
RAD23A/HR23A	RAD23 homolog A	UBL-UBA proteasome shuttle factor; helps deliver ubiquitinated proteins to the proteasome and also functions in nucleotide excision repair; protects ATXN3 from degradation.	SCA3
RAD23B/HR23B	RAD23 homolog B	UBL-UBA proteasome shuttle factor; delivers ubiquitinated proteins to the proteasome and also functions in nucleotide excision repair; localizes with HTT inclusions; protects ATXN3 from degradation; impacts ATXN3 physical state.	HD; SCA3

Raptor/RPTOR	Regulatory-associated protein of mTOR complex 1	mTORC1 component sequestered by polyQ-expanded ATXN2, contributing to suppression of mTORC1 and autophagic engagement.	SCA2
RBX1	Ring-box 1	RING component of cullin E3 ligases; recruits E2 enzymes and supports ubiquitin transfer to substrates; helps facilitate ATXN2 turnover.	SCA2
RERE	Arginine-glutamic acid dipeptide repeats protein	ATN1 paralog that forms nuclear-receptor corepressor complexes with HDAC1/2; whether it influences ATN1 turnover remains untested.	DRPLA
RFP2/TRIM13	Ret finger protein 2 / tripartite motif containing 13	ER membrane RING E3 ubiquitin ligase; promotes ubiquitination linked to ER associated degradation and stress signaling; no direct link to SCA6.	SCA6
Rheb	Ras homolog enriched in brain	Lysosomal small GTPase deubiquitinated by ATXN3 to restrain mTORC1 during starvation.	SCA3
RNF138	Ring finger protein 138	RING E3 ubiquitin ligase; regulates ubiquitination linked to DNA damage repair, protein stability and stress response pathways; helps degradation of α 1A; connection to SCA6 unclear.	SCA6
RNF4	Ring finger protein 4	SUMO-targeted RING E3 ubiquitin ligase; recognizes SUMOylated proteins and promotes their ubiquitination for nuclear protein quality control.	SCA1; SCA7
RNF6	Ring finger protein 6	RING E3 ubiquitin ligase; modulates AR ubiquitination and transcriptional activity; evidence from AR/prostate-cancer studies.	SBMA
RNF8	Ring finger protein 8	RING E3 ubiquitin ligase; promotes ubiquitin signaling at DNA damage sites and helps coordinate repair pathways; not directly linked to SCA1.	SCA1
Rpn10/PSMD4	26S proteasome non-ATPase regulatory subunit 4	Proteasome ubiquitin receptor; helps recognize ubiquitinated substrates and deliver them for degradation.	SCA1; SCA7
Rpn11/PSMD14	26S proteasome non-ATPase regulatory subunit 14	Proteasome associated deubiquitinase; removes ubiquitin chains from substrates before their degradation by the proteasome.	DRPLA
Rpn13/ADRM1	Proteasome ubiquitin receptor Rpn13 / Adhesion-regulating molecule 1	26S proteasome ubiquitin receptor; becomes ubiquitinated in SBMA muscle, marking stalled proteasome handling.	SBMA
RPS27A	Ribosomal protein S27a	Encodes a ubiquitin-fused ribosomal protein that contributes to ribosome function and supplies ubiquitin for protein turnover and stress responses; connection to HD unclear.	HD
Rpt6/PSMC5	26S proteasome regulatory subunit 5	AAA ATPase subunit of the 19S proteasome; helps unfold and translocate ubiquitinated substrates into the 20S core for degradation.	HD; SCA3
S4/PSMC1	Proteasome 26S subunit ATPase 1	19S proteasome ATPase; helps unfold and translocate ubiquitinated substrates into the 20S core.	SCA7
S7/PSMC2	Proteasome 26S subunit ATPase 2	19S proteasome ATPase; supports substrate unfolding, proteasome function and ATP dependent degradation.	SCA7
SCF/FBXW7	SKP1-CUL1-F-box complex / F-box and WD repeat domain containing 7	SCF E3 ubiquitin ligase substrate receptor; recruits phosphorylated substrates for ubiquitination and proteasomal degradation.	HD
SIAH2	Siah E3 ubiquitin protein ligase 2	RING E3 ubiquitin ligase; targets an NCOR1-bound, transcriptionally inactive AR pool; evidence from AR/prostate-cancer studies.	SBMA

SKP1	S-phase kinase associated protein 1	Adaptor of SCF E3 ubiquitin ligase complexes; helps recruit F-box proteins for substrate ubiquitination and proteasomal degradation.	HD; SCA2
SKP2	S-phase kinase-associated protein 2	F-box substrate receptor of an SCF E3 ligase; influences AR ubiquitination/turnover; evidence from AR/prostate-cancer studies.	SBMA
Staufen1/STAU1	Staufen double-stranded RNA-binding protein 1	ATXN2 interactor whose overabundance contributes to Raptor sequestration, mTORC1 suppression and autophagic engagement in SCA2 models.	SCA2
SUMO2/3	Small ubiquitin like modifier 2/3	Ubiquitin-like modifier; attaches to proteins to regulate localization, stability, stress responses and SUMO-targeted ubiquitin degradation; SCA1 (indirect nuclear quality-control pathway); SCA7 (direct SUMO-targeted ATXN7 routing)	SCA1, SCA7
TAX1BP1	Tax1-binding protein 1	Ubiquitin-binding selective-autophagy receptor; helps target HTT to autophagy.	HD
TFEB	Transcription factor EB	Transcription factor that regulates lysosomal/autophagy programs; ZKSCAN3 disruption activates TFEB-linked lysosomal/autophagy programs in HD; TFEB is lowered in DRPLA models; and TFEB-driven autophagy promotes mutant ATXN1 clearance.	HD; DRPLA; SCA1
TNIP1	TNFAIP3-interacting protein 1	Ubiquitin-binding regulator with altered phosphorylation in SCA2 mouse spinal cord, linking ATXN2 pathology to selective-autophagy signaling.	SCA2
TRAF4	TNF receptor associated factor 4	RING domain ubiquitin ligase/adaptor protein; regulates signaling and can mediate nonproteolytic ubiquitination of substrates, including AR in prostate cancer models.	SBMA
TRAF6	TNF receptor associated factor 6	RING E3 ubiquitin ligase and signaling adaptor; builds mainly K63 linked ubiquitin chains that regulate NF- κ B, immune signaling and stress responses.	HD
Trehalose	Induces autophagy independently of mTOR	Reduces nuclear mutant TBP aggregation in culture and improves motor performance in SCA17 mice.	SCA17
TRIM37	Tripartite motif containing 37	TRIM family RING E3 ubiquitin ligase; regulates ubiquitination, development and proteostasis-related stress pathways; promotes atypical ubiquitination of HTT.	HD
Ubc13/UBE2N	Ubiquitin-conjugating enzyme 13 / Ubiquitin-conjugating enzyme E2 N	E2 ubiquitin-conjugating enzyme; its inhibition reduces mutant HTT levels through proteasome and improves phenotypes.	HD
UbcH6/UBE2E1	Ubiquitin-conjugating enzyme H6 / Ubiquitin-conjugating enzyme E2 E1	E2 ubiquitin conjugating enzyme; works with E3 ligases to transfer ubiquitin to substrates for degradation or signaling; promotes ATXN1 ubiquitination.	SCA1
UbcH7/UBE2L3	Ubiquitin-conjugating enzyme H7 / Ubiquitin-conjugating enzyme E2 L3	E2 ubiquitin-conjugating enzyme; affects androgen-dependent AR transcriptional activity (evidence from AR/prostate-cancer studies); drives ubiquitin-dependent degradation of CaV2.2 channels (not directly linked to SCA6).	SBMA; SCA6
Ube1/UBA1	Ubiquitin-activating enzyme 1	Main E1 ubiquitin activating enzyme; initiates ubiquitination by activating ubiquitin before transfer to E2 enzymes.	HD
UBE2Q1	Ubiquitin-conjugating enzyme E2 Q1	E2 ubiquitin-conjugating enzyme; increased in symptomatic SBMA mouse muscle.	SBMA
UBE2D/eff	Ubiquitin-conjugating enzyme E2 D family / effete	E2 ubiquitin-conjugating enzyme family required for proteasome activity and polyQ handling; loss of <i>Drosophila</i> eff increases HTT aggregates, whereas human UBE2D2 rescues the phenotype.	HD

UBE2J1	Ubiquitin conjugating enzyme E2 J1	ER membrane-associated E2 ubiquitin-conjugating enzyme; works with E3 ligases in ubiquitination, ERAD and protein turnover; evidence from AR/prostate-cancer studies.	SBMA
UBE2K/HIP2/E2-25K	Ubiquitin conjugating enzyme E2 K	E2 ubiquitin conjugating enzyme; promotes ubiquitin chain formation and has been linked to HTT ubiquitination and aggregate handling.	HD
UBE2T	Ubiquitin-conjugating enzyme E2 T	E2 ubiquitin-conjugating enzyme; downregulated in SBMA mouse model muscle.	SBMA
UBE2W	Ubiquitin conjugating enzyme E2 W	E2 ubiquitin conjugating enzyme; promotes N-terminal ubiquitination and helps mark selected proteins for degradation or quality control.	HD; SCA1; SCA3
UBE3A/E6-AP	Ubiquitin protein ligase E3A / E6-associated protein	HECT E3 ubiquitin ligase; ubiquitinates selected substrates for proteasomal degradation and is linked to neuronal protein quality control.	HD; SBMA; SCA1
UBE4B/E4B	Ubiquitination factor E4B	E4 ubiquitin chain elongation factor; extends pre existing ubiquitin chains to promote proteasomal degradation of selected substrates; promotes ATXN3 ubiquitination and degradation.	SCA3
UBQLN2	Ubiquilin 2	Ubiquitin adaptor; helps shuttle misfolded or ubiquitinated proteins to proteasomal or autophagy linked degradation.	HD; SCA2
UBQLN4/A1Up	Ubiquilin 4	UBL-UBA ubiquitin adaptor; links ubiquitinated or misfolded proteins to proteasomal degradation and DNA damage/proteostasis pathways; ATXN1 impacts its binding to proteasome.	SCA1
UBR5/EDD1	Ubiquitin protein ligase E3 component n-recognin 5 / E3 identified by differential display	HECT E3 ubiquitin ligase; regulates protein turnover, DNA damage responses and cellular stress pathways; helps HTT turnover.	HD
UFM1	Ubiquitin-fold modifier 1; leads to protein UFMylation	UFMylation of p62/SQSTM1 enhances autophagic clearance of mutant HTT.	HD
UHRF2	Ubiquitin like with PHD and ring finger domains 2	RING E3 ubiquitin ligase and chromatin reader; links ubiquitination with cell cycle and epigenetic regulation; helps degrade HTT.	HD
ULK1	Unc-51-like autophagy-activating kinase 1	Autophagy-initiation kinase destabilized when mutant ATXN7 co-aggregates p53 and FIP200, impairing autophagy initiation.	SCA7
USP10	Ubiquitin-specific peptidase 10	Deubiquitinating enzyme; can influence AR stability/activity; stabilizes TBP.	SBMA; SCA17
USP11	Ubiquitin-specific peptidase 11	Age-dependently upregulated in the striatum of R6/1 mice; striatal knockdown reduces mitochondrial dysfunction and neuronal damage through a PTEN-AKT axis.	HD
USP12	Ubiquitin specific peptidase 12	Deubiquitinating enzyme; removes ubiquitin from selected substrates and regulates protein stability, signaling and stress responses; protects from HTT; binds to AR (effects unclear).	HD; SBMA
USP13	Ubiquitin-specific peptidase 13	AR-stabilizing deubiquitinase; evidence from AR/prostate-cancer studies.	SBMA
USP14	Ubiquitin specific peptidase 14	Proteasome associated deubiquitinating enzyme; trims ubiquitin chains and regulates substrate degradation by the proteasome; protects in HD models; binds to AR (effects unclear).	HD; SBMA
USP19	Ubiquitin specific peptidase 19	Deubiquitinating enzyme; edits ubiquitin signals and regulates ER-associated degradation, stress responses and misfolded protein handling; stabilizes HTT fragments.	HD
USP22	Ubiquitin specific peptidase 22	SAGA complex deubiquitinase; removes ubiquitin from histone H2B and helps regulate chromatin and transcription. AR information comes from cancer-related studies.	SBMA; SCA7

USP26	Ubiquitin-specific peptidase 26	Deubiquitinating enzyme; can influence AR ubiquitination/activity; evidence from AR/prostate-cancer studies.	SBMA
USP36	Ubiquitin-specific peptidase 36	AR-stabilizing deubiquitinase identified in prostate-cancer studies.	SBMA
USP54	Ubiquitin-specific peptidase 54	AR-stabilizing deubiquitinase identified in prostate-cancer studies.	SBMA
USP7	Ubiquitin-specific peptidase 7 (HAUSP)	Deubiquitinating enzyme; interacts with ATXN1 (downstream fate unresolved); in SBMA, preferentially binds polyQ-expanded AR and reduces its ubiquitination; lowering USP7 is protective.	SCA1; SCA3; SBMA; HD
USP9X	Ubiquitin-specific peptidase 9 X-linked	AR-stabilizing deubiquitinase identified in prostate-cancer studies.	SBMA
VCP/p97	Valosin-containing protein	AAA+ ATPase; extracts ubiquitinated proteins from complexes, membranes or aggregates for proteasomal degradation or remodeling.	HD; DRPLA; SBMA; SCA3; SCA6; SCA17
VDAC1	Voltage-dependent anion channel 1	Outer mitochondrial membrane channel; deubiquitinated by wild-type ATXN3 to support PRKN-dependent mitophagy.	SCA3
WDR5	WD repeat-containing protein 5	Chromatin-associated WD40 protein; with TBP, recruits the APC/C complex to transcription start sites for histone ubiquitination; not established as TBP-clearing pathway.	SCA17
YOD1	YOD1 deubiquitinase	Deubiquitinating enzyme; edits ubiquitin chains during ERAD and helps regulate p97/VCP dependent protein extraction; helps protect against HTT.	HD
ZKSCAN3	Zinc finger with KRAB and SCAN domains 3	Transcriptional repressor of TFEB-linked lysosomal and autophagy programs; disruption increases lysosomal activity and reduces mutant HTT burden.	HD

At the molecular level, polyQ expansion promotes the aggregation propensity of HTT, abnormal proteolytic fragmentation, altered protein interactions and accumulation in both cytoplasmic and nuclear inclusions [14-16]. Normally, HTT participates in vesicle trafficking, transcriptional regulation, autophagy and other cellular processes, indicating that HD likely reflects both toxic gain-of-function (GOF) and disruption of normal HTT activity, particularly in the context of impaired autophagy [17-21]. Together, these features place sustained pressure on PQC systems including the UPS, autophagy-lysosome pathway and molecular chaperone network.

Comprehensive surveys of E3 ubiquitin ligases in neurodegenerative disease underscore how ligase identity and substrate selectivity shape disease-specific proteostasis outcomes [34]. Several E3 ligases favor clearance-associated outcomes in HTT. CHIP/STUB1 (an E3 ligase that we will encounter repeatedly; Fig. 3; Table 3) linked HSP70/HSP90 chaperone triage to ubiquitin-dependent quality control and reduced polyQ-expanded HTT accumulation, aggregation and toxicity in cellular, neuronal,

zebrafish and mouse models of HD [35-37]. Additional ligases (UBE3A/E6-AP, UBR5/EDD1, HRD1/SYVN1, NEDD4, UHRF2, TRIM37 and HOIP with LUBAC) also fit into this broader clearance-or-routing framework, although the strength and model specificity of the evidence vary. UBE3A promotes K48-linked ubiquitination and proteasomal degradation of mutant HTT fragments. In HD knock-in mouse brain, UBE3A levels declined with age and restoration of UBE3A protein reduced mutant HTT accumulation and aggregation, suggesting a protective role for UBE3A-linked ubiquitination in HD [38, 39]. UBR5 also appears protective. In HD patient-derived induced pluripotent stem cells (iPSCs), UBR5 knockdown increased HTT levels and triggered mutant HTT aggregation, UBR5 overexpression promoted polyubiquitin- and proteasome-dependent degradation of Q100 HTT, whereas a ligase-dead version failed to produce the same effect. Consistent with these findings, the loss of the *C. elegans* UBR5 ortholog increased aggregation and motility defects in a neuronal Q67 yellow fluorescent protein model [40].

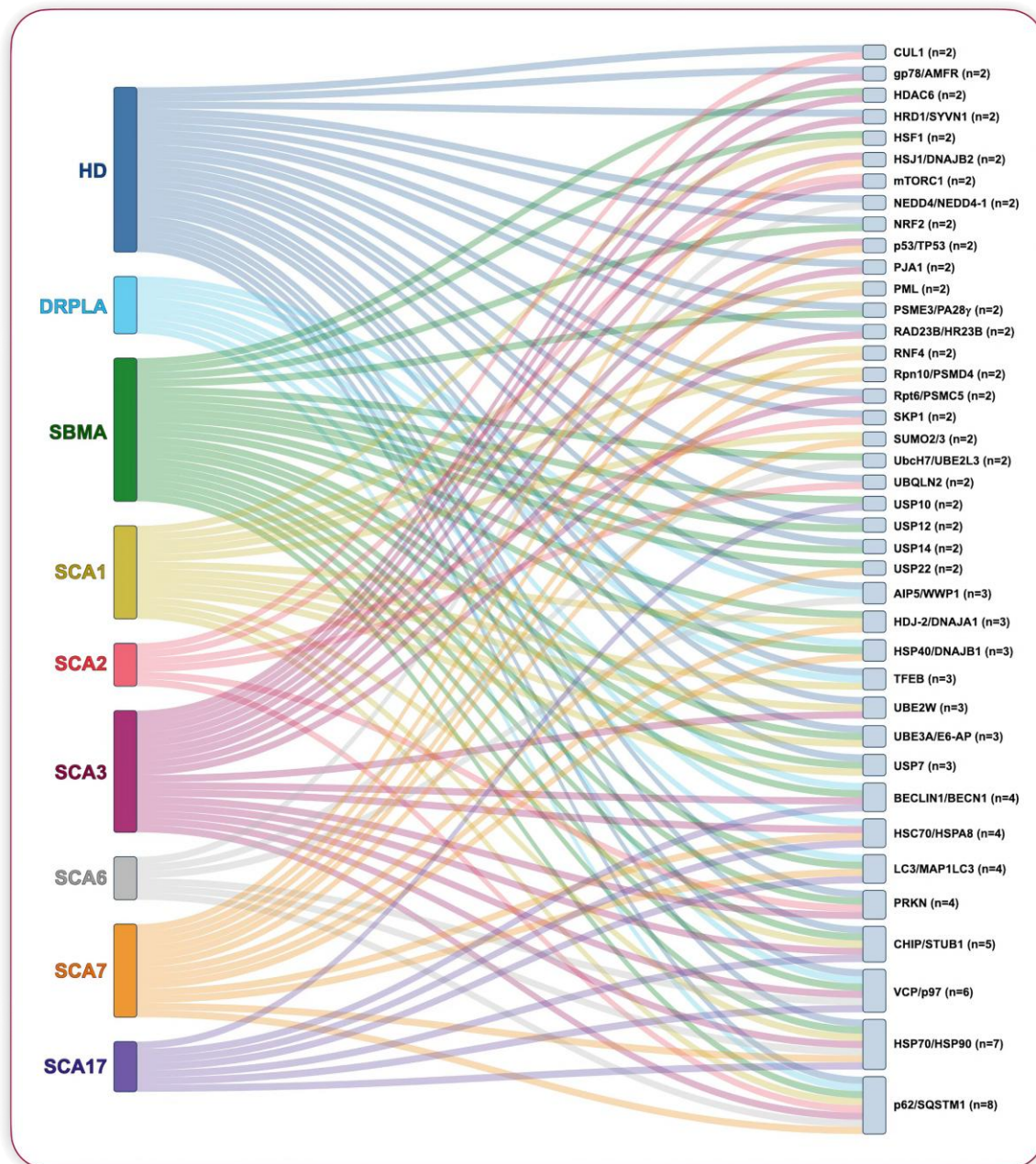


Figure 3. Alluvial diagram of covered factors that are involved in 2 or more polyQ diseases.

HRD1/SYVN1 may link mutant HTT to ER-associated degradation (ERAD), since HRD1 enhanced degradation and reduced toxicity of polyQ HTT in cell models [41]. In ERAD, mutant HTT interacts with gp78/AMFR and can interfere with gp78 binding to ubiquitin and the AAA-ATPase VCP/p97 [42]. A recent study added another protective E3 to this group: NEDD4. NEDD4 ubiquitinated mutant HTT and promoted its clearance; furthermore, NEDD4 loss increased HTT aggregation and toxicity in mouse primary neurons and a *Drosophila* HD model [43]. This study also found reduced NEDD4 in

polyQ-HTT-expressing neurons as well as in HD mouse brains [43], suggesting mutant HTT weakens one of the pathways that help clear it.

Another E3 ligase, Parkin (PRKN), promoted the ubiquitination and elimination of expanded polyQ proteins in cultured cells. In R6/1 HD mice, partial PRKN suppression worsened behavioral and striatal apoptotic phenotypes (R6/1, like the R6/2 model that we will encounter further below, expresses the isolated first exon of HTT and presents with a milder phenotype than R6/2;

[44]), suggesting a role for PRKN in HTT-dependent toxicity, potentially linked to its turnover.

The brain-enriched E3 ligase Praja1 (PJA1) binds polyQ-expanded proteins and promotes their ubiquitination and proteasomal degradation, reducing aggregate formation [45]. In cultured cell, yeast and *Drosophila* models, depleting PJA1 raised polyQ protein levels and toxicity, whereas restoring it was protective; these effects were observed for both mutant HTT and ataxin-3 (ATXN3; [45]). A follow-up study positioned PJA1 as a common suppressor of neurodegeneration-associated aggregation acting downstream of HSF1 [46]. An additional E3 ligase with potential protective effects in HD is HACE1. In HD patient striatal tissue, HACE1 levels were reduced and experimental HACE1 expression protected striatal neuronal progenitor cells from expanded-HTT-induced redox imbalance and oxidative stress by enhancing NRF2 activity in cells [47].

Nuclear localization is a hallmark of pathology in several polyQ diseases, including HD. Although nuclear UPS machinery can support stress-responsive turnover, nuclear localization does not always ensure productive clearance [2, 3]. UHRF2 is a nuclear RING E3 ligase that colocalized with nuclear mutant HTT and promoted HTT ubiquitination and turnover in mouse and cell models [48]. TRIM37 is another E3 ligase relevant to the HD UPS framework. A recent primate study identified TRIM37 as an HTT-interacting E3 ligase that promotes mutant HTT ubiquitination and degradation. Because TRIM37 is selectively lower in primate striatum, the authors proposed that reduced TRIM37-dependent HTT clearance may contribute to regional HTT accumulation and striatal vulnerability [49].

LUBAC provides a distinct form of ubiquitin-dependent post-translational modification through M1-linked linear ubiquitination [50]. In HD models, the HOIP/LUBAC complex was recruited to misfolded HTT species and HTT aggregates, with M1-linked ubiquitin detected at cytoplasmic and nuclear aggregates in cells, R6/2 mouse brain and human HD cortex. HOIP recruitment depended in part on VCP/p97 and linear ubiquitination could remodel the surface of misfolded HTT and promote its proteasome-dependent clearance [51].

Some E3 ligases can modify HTT in ways that, under certain circumstances, can promote its aggregation or toxicity. One example comprises SCF components: CUL1, SKP1 and FBXW7, which connect ubiquitin signaling to proteostasis and heat-shock regulation. On the one hand, reduced CUL1 or SKP1 activity increased mutant-HTT aggregation and toxicity in mice brain and cultured models [52, 53]. A recent striatal interactome investigation also identified SKP1 among HTT-associated proteins [14]. On the other hand, another study noted that FBXW7

(the substrate-recognition F-box protein of the SCF complex), stabilized the checkpoint kinase CHK2 in HD cells; lowering FBXW7 reduced susceptibility to DNA damage and improved cellular stability [54]. These findings suggest that, at least through the CHK2-linked DNA-damage arm, FBXW7 activity contributes to HD-associated stress rather than protective HTT clearance.

Another E3 ligase that may have harmful effects in HD is AIP5/WWP1, a NEDD4 family HECT ligase, which was recruited to mutant HTT and promoted K63-linked ubiquitination; this outcome was associated with increased aggregation and toxicity rather than HTT degradation [55]. TRAF6, also an E3 ligase, interacted with HTT and promoted atypical K6-, K27- and K29-linked ubiquitination associated with aggregate formation [56]. Thus, not all E3 ligases engage mutant HTT for the purposes of elimination or to reduce its toxicity under all cellular contexts.

As noted in the “Introduction,” E1 and E2 enzymes are critical to ubiquitination. Inhibition of the E1 Ube1/UBA1-dependent ubiquitin activation limited mutant HTT handling, leading to higher levels of aggregated HTT species. Additionally, lower UBE1 levels were observed in brain tissue from HD mouse models than in peripheral tissues [57], suggesting a broader relationship between ubiquitination and HD – a relationship that reflects cellular abnormalities arising from HD-like stress rather than a direct HTT-dependent effect. Among E2 enzymes, UBE2K/E2-25K was identified as an HTT-interacting ubiquitin-conjugating enzyme and was also highlighted in the curated HTT interactome literature [24, 58, 59]. UBE2K can catalyze K48-linked ubiquitin-chain assembly and, beyond its original identification as an HTT-interacting E2, was implicated in expanded polyQ aggregation and toxicity. In cell models, UBE2K increased aggregate formation and polyQ-induced cell death, whereas a dominant-negative version or lowered levels of UBE2K muted these effects [58, 59].

Recent studies have suggested that additional E2 enzymes can influence HTT proteostasis in distinct ways. In *Drosophila* retina, loss of UBE2D (effete or eff in *Drosophila*) increased GFP-tagged HTTQ72 aggregates and high-molecular-weight HTT species without increasing transgene expression; human UBE2D2 suppressed this phenotype, consistent with a conserved role for UBE2D in polyQ degradation [60]. Mechanistically, this may relate to the broader requirement for UBE2D in maintaining proteasome activity [60]; direct ubiquitination of HTT was not reported and UBE2D was not detected as an HTT interactor. Another E2, UBE2W, regulated mutant HTT solubility and aggregation in cellular, neuronal and mouse models, but whether it directly N-terminally ubiquitinated HTT or acted indirectly through other substrates remains

unclear [61]. Ubc13/UBE2N adds another context-dependent E2 mechanism. In HD mice and complementary models, inhibition of Ubc13/UBE2N promoted clearance of mutant HTT through a K48-linked UPS pathway rather than detectable enhancement of autophagy [62].

Within ubiquitin signaling, ubiquitin removal is as important as ubiquitin addition; this process is mediated by DUBs. Among them, USP19 was reported to stabilize N-terminal HTT fragments and increase the aggregation and toxicity of polyQ-expanded HTT species in cell models [63]. Mechanistically, USP19 interacts with HSP90, associates with polyQ substrates through this chaperone system and reduces ubiquitination of HTT N552-100Q. The available data support a model in which USP19 stabilizes the expanded HTT fragment by opposing ubiquitin-dependent degradation, thereby increasing the pool of aggregation-prone protein.

Two further DUBs appear to act in the same, potentially negative, direction as USP19. USP7 preferentially interacted with polyQ-expanded proteins and regulated their aggregation and/or stability; although this work was carried out mainly in SBMA and SCA3 models, the same study also reported that USP7 differentially interacted with mutant HTT in the striatum and frontal cortex of an HD knock-in mouse [64]. A comparable, HD-specific pattern was reported for USP11: it was upregulated in an age-dependent manner in the striatum of R6/1 mice, and striatal USP11 knockdown reduced mitochondrial dysfunction and neuronal damage through a PTEN-AKT axis, slowing disease progression [65].

In contrast, the DUBs YOD1 and USP12 appear protective in HD models, but they do so through apparently different and still incompletely understood mechanisms. In *Drosophila*, YOD1 overexpression improved several polyQ HTT phenotypes, including retinal degeneration, viability, lifespan and motor activity [66]. This protection did not result from a clear reduction in aggregate number, although YOD1 modestly shifted aggregates toward larger species [66]. USP12 also suppressed mutant HTT toxicity in rodent neurons, HD patient-derived neurons and flies. In neuronal models, this effect was mainly linked to ATG7-dependent autophagy and did not require USP12 catalytic activity, with no clear change in soluble mutant HTT or inclusion formation [66, 67].

Ubiquitin conjugation is only one step in mutant HTT clearance. Productive degradation also requires delivery to the proteasome, engagement with proteasomal receptors, substrate commitment and adequate proteasomal activity. VCP/p97, which, among its many functions helps to extract and route ubiquitinated substrates to the proteasome, was linked directly to HD and more broadly to polyQ proteostasis through studies in cultured cells, primary neurons, human patient tissue, *Drosophila* and

mouse models. Consistent with evidence of VCP/p97 involvement in polyQ disease, in vitro/biochemical and HeLa cell-based assays suggested that VCP/p97 can directly engage HTT exon 1 aggregates and can reduce preformed HTT97Q aggregates in an ATP-dependent manner [68, 69]. However, VCP/p97-mediated protection in vivo may not depend only on aggregate clearance, because VCP/p97 also rescued polyQ phenotypes and improved DNA-damage markers without clearly altering inclusion formation [68, 69]. The proteasome-associated shuttle proteins UBQLN2 and RAD23B/HR23B were reported in relation to HD. PolyQ HTT can reportedly sequester these ubiquitin-binding shuttle factors into aggregates, likely impeding overall proteostasis in the impacted cells [70]. However, UBQLN2 was not only sequestered. Acting together with the HSP70-HSP110 disaggregase, this ubiquitin-associated protein selectively lowered levels of aggregated mutant HTT, but not ATXN3, pointing to a substrate-selective clearance role alongside its capture into aggregates [71].

Proteasome-associated regulators additionally help shape mutant HTT handling: PSME3 and PA200, both proteasome activators, were connected to HTT. PSME3 improved proteasome function and survival in HD cell models and PA200 enhanced the degradation of N-terminal HTT [72, 73]. The related 11S activator, PA28 $\alpha\beta$ was additionally tied to HTT handling: its activation was reduced in HD mouse brain and this reduction correlated with increased mutant HTT aggregation in cell models [29]. USP14 also fits in this group as a proteasome-associated DUB. In mutant HTT cell models, USP14 lowered SDS-insoluble HTT aggregates and reduced caspase-3 activation and cell death in a manner dependent on its catalytic activity and proteasome function. The mechanism is probably not just general cell health, because USP14 could interact with HTT, but the study did not establish a direct pathway where USP14 deubiquitinated HTT. Its protection also involved reduced IRE1 α activation and ER stress signaling [74]. Lastly, studies in HD models highlight a PKA (protein kinase A)-Rpt6 (a.k.a. PSMC5; component of the 19S proteasome) axis as an important regulator of proteasome function in HD. In mutant HTT-expressing striatal cells as well as in the R6/2 and N171-82Q mouse models, proteasome impairment was associated with weakened PKA signaling. Restoring PKA activity increased phosphorylation of the proteasomal ATPase subunit Rpt6 at S120, enhanced proteasome function, reduced mutant HTT aggregation and improved motor outcomes [75].

Therapeutic studies support coordinated activation of complementary clearance systems in the cell in response to mutant HTT. Not only is the UPS involved; autophagy is an additional, key component of the cellular engage-

ment of the HD protein. Evidence that proteasomal processing and autophagy can be interdependent comes from yeast. Impaired proteasomal degradation of soluble mutant HTT exon 1 disrupted selective autophagic removal of HTT inclusion bodies and implicated VCP/p97-associated cofactors in coordinating the two pathways [76]. The importance of autophagy in HD is exemplified by studies in Q175 mice, where mTOR inhibition enhanced neuronal autophagy and facilitated mutant HTT clearance [77]. Genetic disruption of ZKSCAN3, a transcriptional repressor of TFEB-linked lysosomal and autophagy programs, similarly increased lysosomal activity and reduced mutant HTT burden in an HD animal model and patient-derived 3D neural cultures [78]. Additional studies report that neuronal responses to autophagy manipulation can vary by circuit and sex in *Drosophila* [79], while *cnm-5* (a magnesium transport protein) knockdown in *C. elegans* improved mutant HTT proteostasis alongside increased UPS and autophagy activity [80].

Efficiency of disposal depends on which selective-autophagy receptors recognize mutant HTT. That recognition is largely determined by ubiquitin. In situ cryo-electron tomography of cultured cells expressing an HTT exon 1 polyQ model observed that the ubiquitin-binding receptor p62/SQSTM1 engaged the non-fibrillar aggregate phase (the fraction autophagosomes clear most readily) while amyloid fibrils shut p62/SQSTM1 out and largely escaped [81]. A second ubiquitin-binding receptor, TAX1BP1, protected against HTT aggregate toxicity when overexpressed in iPSC-derived neurons and its loss permitted aggregates to accumulate in mouse brain [82]. The p62/SQSTM1-partnered scaffold Alf1 (also known as WDFY3) organized the same selective autophagy: lowering Alf1 in BACHD mice accelerated HTT accumulation and disease onset [83], whereas a rare Alf1 variant, which raised its levels and was associated with delayed HD onset by up to two decades in patients, decelerated pathology when introduced into two HD mouse models [84]. Ubiquitin-dependent routing has a limit, though: in Q140 knock-in mouse brain, the chaperonin subunit CCT2, which bridges aggregation-prone proteins with autophagy-related components, cleared the more solid aggregates without any ubiquitin signal [85], suggesting that once HTT is fully fibrillar, its physical state rather than its ubiquitination may determine how it is cleared.

Overall, the HD literature supports a model of multi-layered failure in ubiquitin-dependent protein quality control rather than simple collapse of proteasomal activity. Mutant HTT is recognized and ubiquitinated, but its fate depends on the modified lysine, ubiquitin-chain architecture, E2 and E3 enzymes, DUBs, chaperones, shuttle factors and receptors that write, edit, interpret and route those signals. Clearance further depends on HTT fragment

length, conformation, solubility, subcellular compartment, extraction by factors such as VCP/p97, delivery to the proteasome or selective-autophagy machinery and the functional capacity of those downstream systems. Accordingly, ubiquitination can promote proteasomal degradation, nuclear quality control or autophagy-linked disposal, but it can also stabilize mutant HTT, favor aggregation, sequester PQC components or amplify toxicity when signal interpretation or substrate processing is incomplete. These outcomes are further shaped by non-canonical ubiquitin-like signaling. For example, the conjugation of the small protein modifier, UFM1 onto p62/SQSTM1 regulates its autophagy-related functions and enhances HTT clearance in primary neuronal cultures and HD mouse striatum [86].

HD provides the most developed example of a polyQ protein acting not merely as a defective degradation substrate, but as an active remodeler of the ubiquitin-proteasome and autophagy systems responsible for its disposal. This framework also defines the central therapeutic challenge: effective intervention will require selective restoration of productive routing and clearance without reinforcing ubiquitin-dependent pathways that instead stabilize, aggregate or misdirect mutant HTT.

Dentatorubral-pallidoluysian atrophy

DRPLA is also autosomal dominant and is caused by CAG repeat expansion in atrophin-1 (ATN1). Pathogenic alleles are typically ≥ 49 repeats and repeat length strongly influences age of onset and disease severity (Fig. 1; Table 1). Clinically, DRPLA can present with a combination of motor, cognitive and seizure-related symptoms, including ataxia, epilepsy, psychiatric changes and progressive cognitive decline. The major affected systems include the dentatorubral and pallidoluysian pathways, helping to explain the combination of cerebellar, basal ganglia and cognitive features [87, 88].

At the molecular level, ATN1 is best understood as a transcriptional corepressor. PolyQ expansion alters normal ATN1 behavior and promotes accumulation in both the nucleus and cytoplasm, with intranuclear inclusions being a major pathological feature [89, 90]. Protein fragmentation is an important aspect of DRPLA, since truncated ATN1 species can accumulate in the nucleus and appear to be more toxic than the full-length protein. Caspase cleavage of ATN1 at Asp109 increased cytotoxicity and aggregate formation; transgenic DRPLA mice expressing full-length mutant ATN1 accumulated truncated ATN1 fragments in neuronal nuclei [91, 92].

DRPLA's UPS story is less developed than HD, SBMA or some of the SCAs. The existing literature suggests that mutant ATN1 engages ubiquitin-related pathways, autophagy and chaperone-linked mechanisms, but

the specific machinery that decides whether ATN1 is degraded, sequestered or allowed to persist remains undefined.

Ubiquitin-dependent quality control in DRPLA

In human DRPLA tissue, mutant ATN1 predominantly accumulates in neuronal intranuclear inclusions, many of which are ubiquitin-immunoreactive; less frequently, ATN1-positive intracytoplasmic filamentous inclusions have also been reported [90, 93, 94]. As in other polyQ disorders, the persistence of these inclusions and their decoration by ubiquitin suggest that ubiquitination does not necessarily result in productive degradation. Instead, ubiquitination may reflect recognition without clearance or sequestration that helps preserve cellular homeostasis.

An early connection between ATN1 and ubiquitin signaling came from yeast two-hybrid work reporting that ATN1 bound WW domain-containing proteins through a region near the polyQ tract [95]. The interacting proteins included the NEDD4-family HECT E3-ligase-related proteins AIP2/WWP2, AIP4/ITCH and AIP5/WWP1, as well as the MAGUK-like scaffolds AIP1 and AIP3/WWP3 [95]. These data place ATN1 near a ubiquitin ligase scaffolding network, although these studies did not establish whether ATN1 was ubiquitinated by any of them. Beyond the WW-domain network, ATN1 interacted with nuclear and cytoplasmic partners that help define its normal transcriptional and scaffolding context: ETO/MTG8 in the nuclear matrix [89], IRSp53/BAIAP2 through a proline-rich region adjacent to the polyQ tract [96] and, together with RERE, with HDAC1/2-containing nuclear-receptor corepressor complexes [97]. Whether these interactions influence ATN1 turnover is unknown.

Recent *Drosophila* models of DRPLA implicated VCP/p97 and the proteasome-associated DUB Rpn11 (PSMD14) as modifiers of ATN1 toxicity in a tissue-dependent manner [98]. Furthermore, expanded or truncated ATN1 can form nuclear and cytoplasmic aggregates in cell models and proteasome inhibition increased full-length ATN1 accumulation [90, 99]. Conversely, pharmacological enhancement of clearance can lower expanded ATN1, as Rho-kinase inhibition reduced aggregation of expanded ATN1 alongside mutant HTT and ATXN3 in cell models, an effect attributed to increased proteasomal and macroautophagic degradation [100]. A study of human DRPLA tissue identified p62/SQSTM1 in a subset of intranuclear inclusions. In contrast, NBR1, a related selective autophagy receptor, was much less consistently detected. LC3, a marker of autophagosomes, was absent from these tissues, perhaps because autophagy-linked recognition did not progress to autophagosome recruitment [101].

Additional studies reinforce the idea that recognition may not progress to effective clearance. In DRPLA transgenic mice and patient-derived fibroblasts, canonical autophagy was impaired at the lysosomal stage, as indicated by p62/SQSTM1 accumulation, as well as reduced conversion of LC3-I to LC3-II and lower TFEB levels. Together, these defects appeared to redirect cells toward a nucleophagy-based pathway that degraded and expelled LaminB1 [102]. *Drosophila* ATN1 models point the same way, with autophagic organelles accumulating because clearance was blocked after autophagosome-lysosome fusion and, unusually among polyQ models, further induction of autophagy failing to reduce ATN1 toxicity [103, 104].

A complementary mechanism links ATN1 to autophagy through the ubiquitin system. Soluble polyQ tracts, including those in mutant ATN1, sequestered ATXN3 away from BECLIN1. This event led to increased K48-linked ubiquitination of BECLIN1 and reduced autophagy initiation; the defect was also observed in DRPLA patient fibroblasts [105]. These findings suggest that some ATN1 inclusions recruit ubiquitin-binding quality control proteins, but the evidence for productive clearance is not substantial. Cleaved ATN1 species may exacerbate this problem, since caspase cleavage at Asp109 and other truncation events can generate fragments with altered localization, greater aggregation and increased toxicity [91, 106].

In addition, cell and fly models of DRPLA implicate chaperone and proteostasis modifiers in this disease. In mammalian cells stably overexpressing expanded ATN1, heat-shock protein 40 (HSP40/DNAJB1) and the co-chaperones DNAJB6 and DNAJB12 were transcriptionally downregulated, suggesting impaired chaperone activity [107]. Studies using full-length human ATN1 *Drosophila* models have also identified Hsc70-3 and select HSP40 proteins as tissue-dependent modifiers of toxicity [98].

Together with VCP/p97 and Rpn11 modifier data, these findings hint that DRPLA toxicity may depend less on whether ATN1 is recognized by PQC systems and more on whether fragmented, ubiquitinated, or nuclear ATN1 can be extracted and committed to degradation, similar to what has been observed in models of HD. Overall, understanding of ubiquitin-dependent quality control in DRPLA remains limited and warrants detailed investigation.

Spinal and bulbar muscular atrophy

SBMA, or Kennedy's disease, is an X-linked adult-onset neuromuscular disorder caused by a CAG-repeat expansion in the androgen receptor gene (AR); pathogenic alleles generally contain at least 38 repeats [3, 108] (Fig. 1; Table 1). Toxicity is mostly ligand-dependent: testosterone or dihydrotestosterone binding promotes nuclear

translocation and accumulation of polyQ-expanded AR, helping explain the male predominance [109, 110]. Clinically, SBMA presents with progressive limb and bulbar muscle weakness, accompanied by endocrine-related abnormalities due to disrupted AR signaling. Although widely considered a toxic GOF disorder, partial loss of AR transcriptional activity likely contributes to loss-of-function (LOF) disease manifestations. At the cellular level, mutant AR accumulates especially in the nucleus, forming inclusions in both motor neurons and muscle [2, 3, 111].

Ubiquitin-dependent quality control in SBMA

Across human tissue, animal models and cell systems, mutant AR is repeatedly engaged by the UPS. AR inclusions stain for ubiquitin and proteasome-associated components, indicating that the cell recognizes mutant AR as a potential PQC problem [112-114]. In SBMA, mutant AR is tagged by ubiquitin and handled by the UPS, but what happens next depends on ligand state, chaperone engagement, E3 ligase activity, DUB editing, proteasome capacity and whether the protein is routed toward degradation, sequestration or autophagy.

Within this system, CHIP/STUB1 is one of the strongest regulators of both wild-type and mutant AR turnover. As mentioned in the “HD” section, CHIP/STUB1 collaborates with the chaperones HSP70/HSP90 and represents a direct bridge between chaperone recognition and ubiquitin-mediated degradation. In SBMA models, increased CHIP/STUB1 lowered mutant AR accumulation and aggregation and improved disease phenotypes, while reduced CHIP/STUB1 made cells and tissues more vulnerable to proteotoxic stress [36, 115]. Other E3 ligases, including MDM2 and CRL3-SPOP, also regulated AR ubiquitination and clearance, with their activity shaped by ligand binding and AR post-translational modifications [116]. In the broader AR literature, CRL3-SPOP promoted ubiquitination and proteasomal degradation of full-length WT AR, although this mechanism has not been directly established for polyQ expanded AR in SBMA models [116]. An early PROTAC (proteolysis targeting chimeras) study reported that forced proximity between AR and MDM2 promoted AR ubiquitination and proteasomal degradation in cultured cells [117]. However, these experiments did not use polyQ-expanded AR; rather, they were conducted in the context of AR-related cancer. This finding supports the point that AR degradation can be redirected by changing which E3 ligase the receptor engages. PRKN may also participate in this network during proteotoxic stress, as both PRKN and CHIP/STUB1 colocalized with mutant AR aggregates in SBMA cell models and skeletal muscle from AR113Q knock-in mice and PRKN co-immunoprecipitated with

polyQ-expanded AR [118]. Although PRKN overexpression did not reduce mutant AR abundance, these findings suggest partial functional overlap among E3 ligases involved in polyQ protein quality control.

Not every ubiquitin-linked factor that interacts with expanded AR is protective or promotes its clearance. MID1/TRIM18, a microtubule-associated RING E3 ligase, is relevant to SBMA but appears to act differently from CHIP/STUB1. Rather than targeting mutant AR for degradation, MID1 bound CAG-repeat-containing AR mRNA, increased production of the pathogenic protein and promoted androgen-dependent motor neuron vulnerability [119]. MID1 is therefore perhaps better viewed as a ubiquitin-linked regulator of mutant AR burden than as a confirmed AR-related E3 ligase.

PolyQ-expanded AR can disrupt the function of ubiquitin ligases. In SBMA models, mutant AR interacted with the APC/C-Cdh1 complex without being degraded and instead inhibited APC/C-Cdh1 activity [120]. Several additional ubiquitin ligases directly regulate AR, although most of the supporting evidence comes from prostate cancer or steroid receptor biology rather than SBMA models. DDB2 promoted AR ubiquitination and degradation and SIAH2 selectively targeted an NCOR1-bound, transcriptionally inactive pool of AR [121, 122].

Additional work further illustrates the mechanistic diversity of AR ubiquitin regulation. In prostate cancer models, TRAF4 led to nonproteolytic K27-linked ubiquitination that altered AR transcriptional activity rather than promoting receptor turnover [123]. Other AR regulators, including SKP2, RNF6 and UBE3A/E6-AP were also studied largely in prostate cancer or broader AR signaling contexts rather than SBMA models. These factors can alter AR ubiquitination, stability, or transcriptional activity, but they do not uniformly direct the receptor toward degradation [124-126]. Although these findings have not yet been established for polyQ-expanded AR in SBMA, they reinforce the broader principle that the consequences of AR ubiquitination depend on the enzymes involved, the linkage assembled, the site modified and the functional state of the receptor.

In AR113Q knock-in muscle, transcriptomic analysis showed reduced expression of E2 enzymes and proteasome subunits. Reduced ubiquitin-proteasome gene expression was accompanied by impaired NRF1- and DDI2-dependent proteasome recovery, diminished proteasome activity and ubiquitination of the proteasome receptor Rpn13/ADRM1 [111]. A separate AR113Q muscle study found increased UBE2Q1 expression in symptomatic male mice [127], suggesting that SBMA muscle involves selective remodeling of ubiquitin pathway components rather than one global direction of UPS change.

Proteasome regulators also matter in SBMA, but the details depend on the disease model. In transfected cell

systems, polyQ-expanded AR aggregates recruited UPS-associated machinery, including the 19S proteasome cap and NEDD8 (ubiquitin-like modifier), along with chaperones such as HSP70, HSP90 and HDJ-2/DNAJA1 [113]. The proteasomal activator, PSME3, adds another component to this relationship, because it modified polyQ AR aggregation and motor neuron viability in SBMA models [128]. The effects of PSME3 on mutant AR appear to depend on cell type. In PC12 cells, PSME3 increased mutant AR aggregation and toxicity, likely in part through reduced MDM2-associated polyubiquitination rather than simple activation of proteasome activity. In contrast, PSME3 rescued toxicity in SBMA motor neurons in a proteasome-binding-dependent manner [128]. Together, these findings suggest that mutant AR handling is shaped not only by ubiquitin tagging and canonical proteasome activity, but also by proteasome regulators. Substrate extraction may be similarly relevant. PolyQ-expanded AR bound VCP/p97 through its polyQ tract and mutant AR sequestered nuclear VCP/p97 away from sites of DNA repair, linking the receptor to the extraction machinery that helps commit ubiquitinated substrates to the proteasome [68].

Therapeutic studies support the idea that SBMA is not only a problem of insufficient AR ubiquitination. Instead, it appears to involve a broader failure of coordinated proteostasis recovery. ASC-JM17, a small-molecule activator of NRF1, NRF2 and HSF1-linked stress programs, mitigated polyQ AR toxicity in SBMA cell, fly and mouse models by increasing proteasome subunits, antioxidant enzymes and molecular chaperones [129]. These findings corroborate the previously mentioned AR113Q muscle studies that reported impaired NRF1- and DDI2-dependent proteasome recovery, reduced proteasome activity and stalled proteasome handling marked by ubiquitinated Rpn13/ADRM1 [111]. Therefore, improving SBMA phenotypes may require coordinated increases in proteasome capacity, oxidative stress resistance and broader chaperone-mediated triage rather than targeting one UPS node in isolation.

Newer AR degradation strategies suggest that efficient degradation of mutant AR may still be beneficial. The AR PROTAC degrader ARD-1676 promoted ubiquitin-dependent proteasomal degradation of polyQ-expanded AR and reduced mutant AR in overexpression systems, patient iPSC-derived motor neurons, skeletal muscle cells and AR113Q mice [130]. Thus, mutant AR can be cleared when the UPS is forced onto the right substrate, even if endogenous handling is insufficient in diseased tissue.

Relatively little is known about E2 enzymes in SBMA. As this field develops, some prostate cancer studies focusing on wild-type AR suggest that UBE2J1 and UbcH7/UBE2L3 may be relevant to AR regulation.

UBE2J1 promoted AR ubiquitination and degradation, while UbcH7/UBE2L3 affected androgen-dependent AR transcriptional activity [131, 132]. Their potential involvement in polyQ-expanded AR regulation requires investigation.

Given their central role in ubiquitin-dependent processes, DUBs provide additional regulatory points in SBMA. USP7 is the clearest SBMA-related DUB reported so far. USP7 preferentially interacted with polyQ-expanded AR and reduced mutant AR ubiquitination. Lowering USP7 reduced mutant AR aggregation and toxicity in SBMA cell and fly models and improved motor phenotypes in SBMA mice. Thus, mutant AR fate is controlled not only by which ubiquitin chains are added, but also by which ones are edited and/or removed [64]. In non-SBMA contexts, USP12, USP14, USP26, USP10 and USP22 have been linked to AR stability or transcriptional activity [133-137]. Their roles in polyQ-expanded AR remain unclear.

Beyond direct degradation via the proteasome, mutant AR is shaped by chaperone-linked routing decisions that connect the UPS to autophagy. PolyQ-expanded AR is handled by HSP90, HSP70 and HSP40 systems, with HSP90 helping to maintain ligand-responsive AR and HSP70/HSP40 promoting proteasomal degradation of the polyQ receptor [113, 138, 139]. At a mechanistic level, HSP70 and HSP40 bound the AR N-terminal “FQNLF” motif and held the receptor in an inactive conformation that was released upon ligand binding, tying the same chaperones that govern polyQ-AR triage to the receptor’s conformational and ligand state [140]. This finding makes mutant AR especially dependent on chaperone-guided triage, where the same machinery can either stabilize the receptor, move it forward to CHIP/STUB1-mediated ubiquitination and degradation, or help route misfolded species toward other clearance pathways [115, 141]. HSP90 helped stabilize ligand-responsive mutant AR, while HSP90 inhibition destabilized the mutant receptor and promoted proteasomal degradation [142]. Separately, CHIP/STUB1 provides a chaperone-linked E3 route that can ubiquitinate mutant AR and promote its proteasomal clearance [115]. Thus, mutant AR fate depends less on one linear degradation pathway and more on how chaperone systems decide whether the receptor is stabilized, handed to the UPS or redirected toward alternative clearance routes.

Mutant AR can additionally be redirected toward selective autophagy. AR aggregates colocalized with p62/SQSTM1 and LC3 and p62/SQSTM1 helped eliminate mutant AR through autophagy [143]. HSPB8, BAG3 and HSP70 add another regulatory layer to this system, where HSPB8 promoted mutant AR clearance through autophagy-linked mechanisms and BAG3 helped to shift HSP70-bound clients between proteasomal degradation

and selective autophagy [127, 144]. In SBMA muscle, this shift toward selective autophagy was accompanied by increased p62/SQSTM1, BECLIN1 and LC3, along with greater activation of the HSPB8-BAG3 chaperone-assisted autophagy machinery [127]. The HDAC6-dependent aggresome pathway also links the UPS to autophagy in this disease: HDAC6 bound ubiquitinated cargo and routed it toward autophagic clearance when proteasome function was limiting and HDAC6 expression rescued polyQ-AR degeneration in a *Drosophila* SBMA model [145].

Overall, the SBMA literature supports a model in which mutant AR toxicity reflects failure of an integrated ubiquitin-dependent proteostasis network rather than a single defect in proteasomal degradation. Ubiquitination can promote mutant AR clearance, alter its transcriptional activity, increase its production, or favor sequestration. Downstream factors then determine whether mutant AR is stabilized, extracted, degraded, sequestered, or redirected toward selective autophagy. At the same time, mutant AR actively remodels this system by altering expression of ubiquitin-related enzymes and proteasome subunits and reducing proteasome capacity in at least some affected tissues. SBMA is therefore not simply a disease in which mutant AR escapes degradation; it is one in which the substrate and the clearance machinery progressively compromise one another. A recent review synthesizes strategies for targeting androgen receptor stability and degradation through proteasomal, chaperone, autophagy and degrader-based approaches as therapeutic avenues for SBMA [146].

Spinocerebellar Ataxia Type 1

SCA1 is an autosomal dominant polyQ disorder caused by a CAG-repeat expansion in ataxin-1 (ATXN1; [147]). Disease-associated alleles generally contain at least 39 repeats and repeat interruption status modifies pathogenicity near the threshold [148] (Fig. 1; Table 1). ATXN1 is a nuclear protein involved in transcriptional regulation and RNA processing. SCA1 prominently affects cerebellar Purkinje cells and brainstem pathways, producing progressive ataxia, dysarthria and oculomotor abnormalities, with cognitive features in some patients [149].

Molecularly, SCA1 is marked by nuclear accumulation of polyQ-expanded ATXN1 and widespread transcriptional dysregulation [150, 151]. Mutant ATXN1 remains a nuclear protein and can continue to engage transcriptional and regulatory complexes, even as the expanded polyQ tract alters its folding, stability and interaction profile [152, 153]. This makes SCA1 a useful example of how polyQ toxicity can arise from the intersection of impaired proteostasis, altered protein interactions and

transcriptional dysregulation, rather than from visible inclusions alone.

Ubiquitin-dependent quality control in SCA1

The SCA1 literature points to a similar theme as the aforementioned diseases: mutant ATXN1 is recognized by PQC systems, but recognition alone does not necessarily lead to its elimination. ATXN1 can be ubiquitinated and routed to the proteasome, yet the expanded protein may remain stabilized, especially in the nucleus, where it continues to engage transcriptional and regulatory complexes [154-156].

Unbiased proteomics observed that mutant ATXN1 interacts with a broad network of proteostasis factors. Proximity-labeling and affinity-based analyses identified heat-shock proteins, ubiquitination machinery, ubiquitin and established ATXN1 partners, while also linking mutant ATXN1 to disrupted nuclear transport [157, 158]. Within the ubiquitination machinery, UBE3A, CHIP/STUB1 and UbcH6/UBE2E1 emerged as key players. UBE3A is one of the best-supported UPS links in SCA1. In SCA1 mice, loss of UBE3A reduced nuclear inclusion frequency but worsened Purkinje cell pathology, indicating that visible inclusions are not required for neurodegeneration and that impaired proteasomal handling of mutant ATXN1 can aggravate disease [154]. CHIP/STUB1 added a chaperone-related UPS route in this disease. In cell culture and in vitro biochemical assays, CHIP/STUB1 interacted with ATXN1 and promoted ubiquitination of both expanded and unexpanded ATXN1, with HSP70 enhancing CHIP/STUB1-mediated ATXN1 ubiquitination in vitro. In *Drosophila*, CHIP/STUB1 overexpression lowered steady-state levels of expanded and unexpanded ATXN1, further supporting a role for CHIP/STUB1 in ATXN1 protein clearance, and also colocalized with ATXN1 nuclear inclusions in SCA1 postmortem tissue [159]. CHIP/STUB1's effect on ATXN1 may not be uniformly clearance-promoting, however. A separate, cell-based study observed that CHIP/STUB1 overexpression reduced ATXN1 solubility and increased aggregate formation in a manner dependent on Ser776 phosphorylation and the CHIP/STUB1 TPR domain [160].

The E2 enzyme UbcH6/UBE2E1 has been implicated in SCA1 through cell-based and in vitro biochemical assays. UbcH6/UBE2E1 colocalized with ATXN1 in the nucleus, bound ATXN1 through the AXH domain and promoted its ubiquitination, likely toward proteasomal degradation [161]. In addition, UbcH6/UBE2E1 overexpression reduced both wild-type and polyQ-expanded ATXN1-mediated transcriptional repression in HEK293T and SH-SY5Y cells, reduced ATXN1 half-life in HeLa cells and reduced nuclear aggregation of both ATXN1

forms [162]. Follow-up work from the same group localized this ubiquitination on K589 within the AXH domain; a K589R mutant that cannot be modified at this site led to enhanced aggregation, tying a defined ubiquitination site to ATXN1 protein levels [163].

Among DUBs, USP7 is the main enzyme with direct evidence for involvement with ATXN1 in SCA1. It was identified as an ATXN1-interacting ubiquitin protease, with the ATXN1 C-terminal region required for binding [164]. However, unlike CHIP/STUB1, UBE3A and UbcH6/UBE2E1, the downstream effect of USP7 on ATXN1 degradation, aggregation or toxicity is unresolved.

Human tissue profiling adds an indirect UPS angle to SCA1. In patient brain, altered small noncoding (nc) RNAs were predicted to target ubiquitin pathway genes, including HECTD1, RNF8, PJA2, FBXO30, FBXO32, KLHL15, UBE2W and several USP DUBs. HECTD1 was the strongest candidate altered in SCA1 brain, because ncRNAs suppressed its expression and HECTD1 inhibition by siRNA worsened ATXN1 82Q cytotoxicity in HEK293T cells [165]. Still, these factors remain indirectly connected to ATXN1.

While CHIP/STUB1 and its association with heat-shock proteins links this class of proteins to SCA1, chaperones are connected to this disease in additional ways as well. In SCA1 patient brainstem neurons, mouse Purkinje cells and mutant ATXN1-transfected cells, nuclear ATXN1 inclusions colocalized with HDJ-2/DNAJA1 and 20S proteasome components. In HeLa cells expressing expanded ATXN1, HDJ-2/DNAJA1 overexpression reduced nuclear aggregation [166]. When chaperone activity was manipulated pharmacologically, the HSP90 inhibitor BIIB021 activated HSF1 and promoted degradation of mutant ATXN1 in cell models, consistent with the notion that HSP90 can stabilize the mutant protein and its inhibition favors clearance [167]. The exact role of these chaperones in SCA1 remains to be determined. Similarly in need of additional investigation is the role of substrate delivery to the proteasome in SCA1. UBQLN4/A1UP is an ATXN1-interacting protein that binds the proteasomal receptor Rpn10/PSMD4 while also binding polyubiquitin chains [168]. In COS-1 cells, ATXN1 altered the association of UBQLN4/A1UP with the proteasome, suggesting disrupted proteasome-associated handling in SCA1 [169].

Autophagy is another clearance route for ATXN1, although it has been probed less extensively in SCA1 than in other polyQ diseases. Autophagic markers colocalized with cytoplasmic ATXN1 inclusions and knockdown of autophagy genes increased cytoplasmic ATXN1 aggregation, positioning autophagy alongside the UPS in ATXN1 degradation [170]. Consistent with these findings, induction of Mitf (the *Drosophila* ortholog of TFEB) and the

Mitf-driven lysosomal-autophagy program cleared expanded ATXN1 [171]. In a *Drosophila* SCA1 model, neuroprotection that optimized selective autophagy lowered levels of ubiquitinated proteins and the receptor p62/SQSTM1 [172]. Pharmacological autophagy enhancers were also reported to improve phenotypes in *Drosophila* SCA1 models, supporting autophagy induction as a candidate therapeutic route [173].

We should mention SUMO-dependent nuclear quality control as an additional factor in SCA1-related UPS. PML (a scaffold protein) and the SUMO ubiquitin ligase RNF4 can promote degradation of misfolded nuclear proteins through sequential SUMOylation and PML loss worsened disease in SCA1 model mice [174]. ATXN1 may also disrupt UPS handling of other nuclear proteins, because its AXH domain promotes proteasomal degradation of Gfi-1/Senseless (a transcription regulator linked to oncogenesis, cell death, proliferation, as well as cell fate specification and differentiation), linking SCA1 toxicity to changed stability of DNA transcription control [175].

14-3-3 proteins are important examples of interactor-mediated ATXN1 stabilization in SCA1. Although they are not UPS factors, their binding to ATXN1 stabilizes the protein and increases the pool of soluble nuclear species that PQC must manage. In cell studies, 14-3-3 proteins bound phosphorylated, polyQ-expanded ATXN1 and increased its stability; *Drosophila* and mouse SCA1 models indicated that this interaction can modify ATXN1 toxicity and regional disease phenotypes [176, 177]. This form of interactor-mediated stabilization may also be relevant to other polyQ proteins, for which binding partners can influence whether disease proteins persist long enough to be cleared or instead accumulate.

Lastly, a related form of interactor-dependent handling comes from the ATXN1 paralog ataxin-1-like (ATXN1L), which competes with expanded ATXN1 for incorporation into native complexes. Increasing ATXN1L displaced mutant ATXN1 from these complexes and suppressed neuropathology in SCA1 mice, illustrating how partitioning between binding partners can determine how much mutant protein persists in a toxic form [178].

Based on the SCA1 literature covered here, mutant ATXN1 is recognized by ubiquitin-dependent quality-control machinery, yet a pathogenic pool persists, perhaps most consequentially within the nucleus, where it can continue to perturb transcriptional and regulatory complexes. Disease outcome is determined not simply by whether ATXN1 is ubiquitinated, but by whether ubiquitin tagging results in efficient degradation, altered sequestration or prolonged residence within toxic soluble complexes. SCA1 therefore reinforces the broader polyQ principle that UPS engagement is not synonymous with successful clearance. Rather, disease may emerge from an imbalance

between recognition and productive disposal, compounded by interaction-dependent stabilization, nuclear retention and disruption of the turnover of other regulatory proteins.

Spinocerebellar Ataxia Type 2

SCA2 is an autosomal dominant polyQ disorder caused by a CAG-repeat expansion in ataxin-2 (ATXN2; [179-181]). Pathogenic SCA2 alleles generally contain at least 35 repeats. Intermediate alleles in the 27-34-repeat range are associated with increased Amyotrophic lateral sclerosis risk and repeat interruptions can modify phenotype [182, 183] (Fig. 1; Table 1).

Clinically, SCA2 presents with worsening gait imbalance, limb incoordination and dysarthria. One of the more interesting and recognizable features is slowed saccadic eye movements; patients can also develop broader neurologic symptoms such as tremor, cognitive changes and sometimes parkinsonism [180, 184, 185]. ATXN2 is predominantly a cytoplasmic, RNA-associated protein. Its normal functions include RNA metabolism and stability, transcriptional regulation and stress-granule biology [186, 187]. Unlike SCA1, SCA7 and SCA17, for example, SCA2 is less a disorder of transcription-factor function than of cytoplasmic RNA handling, translation and stress-granule biology. The cerebellum, especially Purkinje cells, is a major site of vulnerability; other affected regions include the brainstem, pontine nuclei and inferior olive [188].

Ubiquitin-dependent quality control in SCA2

At the broadest level, ATXN2 appears to be regulated by ubiquitination in a proteasome-sensitive manner. PRKN was reported to ubiquitinate both normal and polyQ-expanded ATXN2, providing evidence that ATXN2 can be recognized by ubiquitin-dependent quality-control machinery [189]. More recent *Drosophila* studies observed that the proteasome inhibitor MG132 stabilized ATXN2 during cycloheximide-chase experiments and that FBXO42 promoted its proteasome-dependent degradation [190]. These findings implicate SCF-related ubiquitin ligase machinery in ATXN2 turnover. One other SCF-associated example is FBXW8, which functions as the substrate-recognition component of an SCF E3 complex that, alongside catalytic partners SKP1, CUL1 or CUL7 and RBX1, assembles the ubiquitin-transfer machinery and facilitates ATXN2 degradation [191, 192]. ATXN2 abundance is additionally regulated upstream of these ligases by phosphorylation. CDK5 phosphorylated ATXN2 and promoted its proteasomal degradation, clearing toxic polyQ-expanded ATXN2 in cell models and suggesting

CDK5 activity as a further modulator of ATXN2 levels [193].

The E3 ligase C-CBL helps traffick activated EGFR into the endocytic pathway by recruiting CIN85 and EN-DOPHILIN A, which supports receptor internalization and lysosomal degradation. ATXN2 can bind these SH3-domain proteins through its proline-rich regions and was found in mouse brain complexes containing EN-DOPHILIN A1, CIN85 and C-CBL. Functional studies also showed that ATXN2 slowed EGFR internalization, linking it to C-CBL-associated endocytic trafficking [194]. However, this study did not detect clear differences between wild-type and expanded ATXN2 in binding to these endocytic partners or in effects on EGFR internalization, leaving the relevance of this pathway to polyQ-dependent SCA2 pathogenesis in need of further clarification.

ATXN2 turnover may also intersect with SCA2 disease through proteolytic processing. N-terminal cleavage can generate polyQ-containing ATXN2 fragments and such fragments were detected in human brain tissue [195]. Their presence raises the possibility that incomplete degradation or altered processing produces species with distinct stability, localization or toxicity. Nevertheless, the relationship among ATXN2 fragmentation, proteasome function and neuronal injury remains insufficiently defined.

Whether ATXN2 is cleared or allowed to accumulate also depends on chaperones that govern its solubility, most notably poly(A)-binding protein PABP/PABPC1. This is an unconventional, RNA-dependent chaperone that bound a short linear motif in ATXN2 and emulsified its condensates to keep the protein soluble [196]. Loss of this chaperoning activity appears to promote ATXN2 aggregation [196].

Autophagy provides an additional potential clearance route for pathogenic ATXN2. In SCA2 patient striatum and cerebellum as well as in disease models, p62/SQSTM1 was abnormally accumulated and pharmacological autophagy induction reduced mutant ATXN2 aggregate load and was neuroprotective in vivo [197]; this autophagic engagement was likely driven in part by polyQ-expanded ATXN2 sequestering Raptor to suppress mTORC1, aided by the over-abundant ATXN2 interactor Staufen1 [198, 199]. Phosphoproteomic profiling of SCA2 mouse spinal cord reinforced this crossover, reporting altered phosphorylation of the ubiquitin-dependent selective-autophagy receptors p62/SQSTM1, OPTN and UBQLN2 (together with the ubiquitin-binding regulator TNIP1) and positioning ATXN2 pathology at the interface of the proteasome, ubiquitin-binding shuttle factors and selective autophagy [200].

Evidence reported thus far does not yet support classifying SCA2 as a generalized disorder of the UPS. Instead, it points to a more selective disturbance involving cytoplasmic ATXN2 turnover, RNA- and stress-granule biology and ubiquitin-dependent trafficking. Within this framework, PRKN, FBXW8-containing ligase complexes and FBXO42 connect ubiquitination and proteasome-sensitive degradation to the abundance and cellular behavior of ATXN2, while the trafficking and fragmentation findings broaden the potential consequences of altered ATXN2 handling.

Spinocerebellar Ataxia Type 3

SCA3, also known as Machado-Joseph disease, is autosomal dominant and is caused by CAG expansion in ATXN3, which encodes the DUB ATXN3 [201] (Fig. 1; Table 1). Pathogenic alleles generally contain at least approximately 55 repeats, although commonly reported disease alleles are longer [2]. ATXN3 is unique among polyQ disease proteins because it participates directly in ubiquitin-dependent protein quality control: as a DUB, it edits and removes ubiquitin chains from substrates [202–205].

SCA3 affects multiple nervous-system regions, including the brainstem, basal ganglia, substantia nigra and cerebellum [206]. Clinical features include progressive ataxia, abnormal eye movements, dystonia and gait instability, among others. Expanded ATXN3 localizes to both the cytoplasm and nucleus, with nuclear accumulation being particularly relevant to toxicity. Mutant ATXN3 can also undergo proteolytic cleavage, generating shorter fragments with increased aggregation propensity and altered intracellular behavior [2, 3, 207].

Ubiquitin-dependent quality control in SCA3

The catalytic Josephin domain, ubiquitin-interacting motifs and additional protein-interaction surfaces that comprise ATXN3 allow it to bind and edit ubiquitin chains [204, 207]. ATXN3 can also interact with proteasome-associated proteins such as RAD23A/HR23A, RAD23B/HR23B and VCP/p97 [208]. Importantly, this interaction does not appear to function simply as a route for ATXN3 degradation. Instead, ATXN3 bound directly to RAD23A/HR23A and RAD23B/HR23B and these interactions stabilized ATXN3 by protecting it from proteasomal turnover [209, 210]. Proteasomal adaptors may therefore play an unexpected role in SCA3 by preserving ATXN3 rather than promoting its clearance. Not all proteasome-associated factors preserve ATXN3, however: the 19S regulatory-particle ATPase Rpt6 bound ATXN3 and promoted its proteasomal degradation with substrate

specificity, offering a route for committing ATXN3 to the proteasome [211].

RAD23B/HR23B may also influence the physical state of ATXN3. In vitro biochemical and cell-based work indicated that RAD23B/HR23B can delay the liquid-to-solid phase transition of ATXN3 through heterotypic buffering [212]. Thus, RAD23/HR23 proteins may both stabilize ATXN3 against proteasomal turnover and slow its maturation into less dynamic assemblies, making their net effect on disease-associated ATXN3 dependent on concentration, interaction state and cellular context. Biochemical work with another ATXN3 interactor, VCP/p97, identified wild-type ATXN3 and other VCP/p97-associated proteins as readers and debranching enzymes for K48-K63-branched ubiquitin chains [213]. This activity expands our understanding of the functions of normal ATXN3 beyond removal or trimming of simple chains and places it within the processing of branched ubiquitin architectures that can coordinate proteasomal and organelle-quality-control decisions. How polyQ expansion impacts these activities and their implications in SCA3 remain to be clarified.

Beyond ubiquitin-chain architecture, a growing set of physiological substrates provide examples of how ATXN3's DUB activity contributes directly to quality-control decisions. Wild-type ATXN3 uses its polyQ domain to bind BECLIN1 and deubiquitinate it, protecting BECLIN1 from proteasomal degradation and thereby enabling starvation-induced autophagy; critically, soluble polyQ-expanded proteins, including mutant ATXN3 itself, competitively titrated wild-type ATXN3 away from BECLIN1 in a repeat-length-dependent manner, providing a direct route by which polyQ expansion can impair autophagy [105]. ATXN3 also contains LC3-interacting regions that can bind LC3C and GABARAP to support efficient autophagic flux [214], deubiquitinate Rheb at the lysosome to restrain mTORC1 during starvation [215] and stabilize p53 by removing its ubiquitin; polyQ-expanded ATXN3 retained an enhanced p53-directed activity that drove neurodegeneration in zebrafish and mouse models [216]. In a mitochondrial arm, wild-type ATXN3 deubiquitinated voltage-dependent anion channel 1 (VDAC1) to support PRKN-dependent mitophagy, an activity impaired in SCA3 patient fibroblasts [217]. Together, these substrates reframe ATXN3 not only as a chain-editing enzyme, but as a DUB whose loss or misdirection upon polyQ expansion can compromise autophagy and mitophagy.

Several E3 ligases and E2 enzymes have been linked to ATXN3 handling. CHIP/STUB1 provides a chaperone-associated quality-control route. Cell-based studies reported that CHIP/STUB1 reduced expanded-ATXN3 abundance [35]. In SCA3 mice, CHIP/STUB1 loss wors-

ened disease and increased SDS-resistant ATXN3 microaggregates that partitioned in the soluble brain fraction [37]. This pathway also intersects directly with the DUB activity of ATXN3. UBE2W monoubiquitinated CHIP/STUB1, strengthening its binding to ATXN3. Within this complex, ATXN3 trimmed or limited the extension of ubiquitin chains on CHIP/STUB1 substrates and deubiquitinated CHIP/STUB1, thereby helping to terminate or reset the complex for another reaction [37, 205]. Two further E3 ligases sit on the ATXN3-clearance side. The brain-enriched RING ligase PJA1 directly ubiquitinated polyQ-expanded ATXN3, promoted its proteasomal degradation and reduced aggregation and toxicity in a *Drosophila* SCA3 model [45]. In the nucleus, the U-box ligase Prpf19 promoted polyubiquitination and degradation of expanded ATXN3 and reduced neurodegeneration in cell and fly SCA3 models; this activity was restrained by its interactor, Exoc7, such that the balance between Prpf19 and Exoc7 set how effectively aggregated ATXN3 was cleared [218].

E4 enzymes act after initial ubiquitin attachment by extending existing ubiquitin chains, helping to improve substrate recognition by the proteasome. In SCA3, UBE4B was identified as an E4 factor that promotes ATXN3 polyubiquitination and degradation. In cell-based studies, UBE4B lowered levels of ATXN3 13Q and 79Q, while dominant-negative UBE4B delayed ATXN3 degradation and increased intracellular aggregation. UBE4B also suppressed degeneration in a *Drosophila* eye model expressing truncated ATXN3 Q78. This distinction is important because truncated ATXN3 is more aggregation-prone than the full-length protein, meaning the fly data support UBE4B as a modifier of pathogenic ATXN3 fragment toxicity but do not by themselves prove identical handling of full-length mutant ATXN3 in an organism [219].

The ER-associated E3 ligase gp78 has likewise been observed to regulate ATXN3 levels in cultured cells. In HEK293 cell models, gp78 interacted with both wild-type and polyQ-expanded ATXN3, increased their ubiquitination and promoted their proteasomal degradation. gp78 knockdown produced the opposite effect, whereas HRD1, another ERAD ligase mentioned earlier, did not display the same ATXN3-clearing activity [220]. MITOL, a mitochondrial outer-membrane RING E3 ligase [221], ubiquitinated and promoted proteasomal degradation of a mitochondria-localized, N-terminally truncated ATXN3-Q71 construct in cultured cells [222]. This latter study did not establish clearance of full-length ATXN3 in SCA3.

More recent studies have added VCP/p97-dependent protein handling to this UPS framework. In *Drosophila* SCA3 models, targeting the ATXN3 VCP/p97-binding motif with an N-terminal VCP/p97 decoy, or mutating ATXN3 so that it could no longer bind VCP/p97 directly,

reduced pathogenic ATXN3 aggregation and improved disease phenotypes [223, 224]. A complementary study linked the ATXN3-VCP/p97 axis to lysosomal quality control. ATXN3 can process K48-K63-branched ubiquitin conjugates during lysosome recovery after membrane damage, facilitating turnover of lysosomal membrane proteins and restoration of degradative capacity [225]. This establishes a mechanistic connection among ATXN3, VCP/p97, branched ubiquitin, lysophagy and lysosome regeneration. The study primarily defined normal ATXN3 function; whether polyQ expansion diminishes, preserves or aberrantly redirects this activity in SCA3 remains to be established.

Earlier work showed that mutant ATXN3 can alter PRKN ubiquitination and stability, establishing a biochemical connection between the two proteins before PRKN was identified as a genetic modifier of SCA3 [226]. In a SCA3 patient cohort study, the PRKN V380L variant was identified as a genetic modifier that lowers the age of onset in homozygous carriers [227]. In a cell model, PRKN-V380L did not alter the soluble or aggregated levels of ATXN3, but it weakened the physical interaction between PRKN and ATXN3 (seen with both wild-type ATXN3-15Q and expanded ATXN3-77Q). Its disease-relevant effect was observable on mitochondria: in cells expressing expanded ATXN3-148Q, PRKN-V380L caused excessive loss of mitochondrial proteins and reduced viability relative to wild-type ATXN3, impairing mitophagy. These findings link the ATXN3-PRKN axis to mitochondrial quality control rather than to ATXN3 degradation per se [227].

In addition to participating in proteasomal regulation, ATXN3 can help route misfolded proteins into sequestration pathways and can itself be sequestered through related mechanisms. Regardless of polyQ length, ATXN3 associated with ubiquitinated aggregates and used its DUB activity to generate exposed ubiquitin C termini. These termini were recognized by HDAC6, which promoted dynein-dependent transport of aggregates toward the aggresome [228, 229]. Chaperone-linked mechanisms provide an additional level of regulation. In *Drosophila* SCA3 models, the ubiquitin-interacting motifs (UIMs) of ATXN3 enhanced aggregation and toxicity partly through interactions with Hsc70-4, suggesting that the same ubiquitin-binding regions that support normal ATXN3 function can also shape pathogenic chaperone engagement [230]. The co-chaperone HSJ1/DNAJB2 adds a bidirectional layer to this chaperone regulation, since its J-domain drove HSP70-mediated proteasomal degradation of ATXN3, whereas its UIMs stabilized ubiquitinated ATXN3 [231]; moreover, polyQ-expanded proteins could sequester HSJ1/DNAJB2 into aggregates in a UIM-dependent manner, depleting functional HSJ1/DNAJB2 and impairing ATXN3 proteostasis [232].

These aggregate-routing pathways also intersect with autophagy-dependent clearance. In SCA3 models, mutant ATXN3 is associated with altered p62/SQSTM1 recruitment and impaired autophagic flux. Conversely, increasing autophagy through BECLIN1 or related pathways can reduce mutant ATXN3 levels, decrease aggregation and improve disease phenotypes [233-235]. ATXN3 therefore occupies a junction among ubiquitin-dependent proteasomal triage, aggregate transport and autophagy-lysosome clearance, with the autophagy findings best viewed here as evidence of crosstalk with the UPS. Allosteric studies further reported that pathological ATXN3 aggregation can be modified by targeting conformational states outside the polyQ tract [236]. Although this work is not itself a direct UPS mechanism, it is relevant to protein quality control because the conformation and material state of ATXN3 are likely to influence recognition, extraction, ubiquitin-chain editing and access to proteasomal or autophagic machinery.

SCA3 is best understood as a disease in which UPS dysfunction lies both upstream and downstream of mutant ATXN3. PQC must recognize and clear expanded ATXN3, yet the expanded protein can simultaneously perturb the ubiquitin-dependent machinery in which ATXN3 normally functions. This creates a complex proteostasis problem: disease may arise not only from inefficient disposal of a toxic polyQ protein, but also from altered ubiquitin-chain editing, proteasomal handoff, VCP/p97-associated processing, aggresome routing and coordination with autophagy. The same domains and interactions that normally allow ATXN3 to regulate substrate fate may therefore become liabilities when the polyQ tract expands. SCA3 consequently illustrates how a pathogenic protein can be both a target and a regulator of quality control, amplifying toxicity through the combined effects of protein accumulation and disruption of the systems required to manage it.

Spinocerebellar Ataxia Type 6

SCA6, which is also dominantly inherited, is caused by CAG expansion in CACNA1A, a gene that encodes the $\alpha 1A$ subunit of the P/Q-type voltage-gated calcium channel, CaV2.1 [237, 238] (Fig. 1; Table 1). At ≥ 19 repeats, pathogenic expansions are shorter than in most other polyQ diseases. $\alpha 1A$ plays central roles in calcium entry, synaptic transmission and cerebellar signaling [239]. SCA6 is not simply a channelopathy. CACNA1A is bicistronic, producing both the $\alpha 1A$ channel subunit and the C-terminal $\alpha 1ACT$ transcription factor, which contains the SCA6 polyQ tract, linking the disease to both transcriptional and calcium-signaling mechanisms [240].

Clinically, SCA6 is usually a late-onset, slowly progressive cerebellar ataxia, with gait instability, dysarthria,

nystagmus and limb incoordination as major features [241]. The main vulnerable region is the cerebellum, especially Purkinje cells, making SCA6 more cerebellum-restricted than broader polyQ diseases like HD or SCA3 [242].

At the pathological level, polyQ-containing C-terminal CACNA1A products accumulate in SCA6 Purkinje cells. The proteolytic CaV2.1 C-terminal fragment (CaV2.1-CTF) and the independently translated $\alpha 1ACT$ protein overlap in sequence but should not be treated as synonymous. CaV2.1-CTF preferentially accumulated in the cytoplasm of human SCA6 Purkinje cells [242] and cytoplasmic expression of CaV2.1-CTF was cytotoxic in model systems [243]. p62/SQSTM1 immunostaining revealed abundant cytoplasmic inclusions in SCA6, of which only a subset were also ubiquitin-immunopositive, in contrast to the strongly ubiquitin-positive inclusions of other polyQ diseases [244]. A unique challenge is presented to the PQC in SCA6: the bicistronic nature of its causative gene likely leads to different needs to handle each resulting protein, such that processes important for CaV2.1 turnover are different from those that control the fate of $\alpha 1ACT$.

Ubiquitin-dependent quality control in SCA6

The best characterized UPS interactor of $\alpha 1A$ is RNF138, an E3 ubiquitin ligase that bound CaV2.1 and promoted its polyubiquitination and proteasomal degradation [245]. RNF138 overexpression lowered CaV2.1 protein levels, increased CaV2.1 polyubiquitination and shortened its protein half-life, while proteasome inhibition, dominant-negative RNF138 or RNF138 knockdown increased CaV2.1 stability. The disease-focused experiments used the Episodic Ataxia Type 2-associated CACNA1A mutants R1281X and F1406C, which led to accelerated turnover through RNF138-dependent degradation. Thus, RNF138 provides strong evidence for proteasome-sensitive $\alpha 1A$ quality control [245]. Pin1 adds a phosphorylation-dependent layer to this pathway. This prolyl isomerase bound phosphorylated Ser/Thr-Pro motifs and altered the conformation of target proteins. In CaV2.1/ $\alpha 1A$ models, Pin1 promoted $\alpha 1A$ polyubiquitination and proteasomal degradation through an RNF138-linked mechanism [246]. These studies, however, were not conducted in SCA6 models [245, 246]. It therefore remains unknown whether RNF138 or Pin1 regulate polyQ-expanded $\alpha 1A$, the $\alpha 1ACT$ transcription factor or other disease-associated $\alpha 1A/\alpha 1ACT$ species.

Recent work in a SCA6 knock-in mouse provided evidence for proteostasis failure. Proteotoxicity from misfolded mutant CaV2.1 was buffered by an HSP90-dependent unfolded-protein response; age-related decline of this resilience component contributed to the late-onset of

Purkinje-cell dysfunction [247]. Mitochondrial quality control and endolysosomal trafficking are also disrupted: in a SCA6 knock-in model, mitochondrial damage accumulated with disease and mitophagy became impaired at late stages, exacerbating mitochondrial dysfunction, with corroborating metabolic changes in postmortem SCA6 patient cerebellum [248], while a complementary study reported endo-lysosomal trafficking dysfunction [249]. These findings connect SCA6 to chaperone, autophagy-lysosome and mitophagy quality-control arms, although a direct link to ubiquitin-dependent clearance of the expanded $\alpha 1A/\alpha 1ACT$ species is currently lacking.

SCA6 also has an important ER- and Golgi-associated quality-control dimension. In SCA6 model mice and Neuro2a cells, polyQ-expanded $\alpha 1A$ localized predominantly to the Golgi, whereas partial nuclear localization was observed for expanded $\alpha 1ACT$. Both species also localized partially to the ER and were associated with ER stress and apoptosis [250]. These findings suggest that CACNA1A-derived disease proteins generate cellular stress through mislocalization and impaired organelle handling, in addition to altered calcium-channel function or transcriptional dysregulation. The UPS factors responsible for recognizing, extracting or degrading these expanded species, however, have not yet been reported.

Studies of broader calcium-channel quality control provide potentially relevant context, although these factors should not be considered established SCA6 regulators. NEDD4, which is implicated in other polyQ disorders, may regulate the degradation of newly synthesized voltage-gated calcium channels through proteasome- and lysosome-linked pathways [251]. Two enzyme-level mechanisms extended this general calcium-channel quality-control picture. The E2 ubiquitin-conjugating enzyme UbcH7/UBE2L3, recruited by the MAP1B light chain LC1, drove ubiquitin-dependent degradation of surface CaV2.2 channels, a mechanism the authors proposed might be also conserved for CaV2.1 [252]. Separately, a genetic screen in *C. elegans* identified the HECT E3 ligase AIP5/WWP1 as ubiquitinating and clearing the CaV2 channel UNC-2, the invertebrate ortholog of CaV2.1, from the presynaptic active zone [253]. None of these factors was tested on polyQ-expanded $\alpha 1A$ or $\alpha 1ACT$, but they nominate additional candidate machinery for disease protein turnover in SCA6.

Additional ER quality-control components have been linked to calcium-channel handling outside SCA6, particularly in studies of CACNA1C. These include the E3 ubiquitin ligase RFP2, the ER membrane translocation factor Derlin-1 and the extraction factor VCP/p97. CaV β subunits may also contribute by stabilizing calcium channels and protecting them from ERAD and proteasomal turnover [254, 255]. Although these findings define plausible

machinery through which misfolded calcium-channel proteins might be handled, their relevance to expanded $\alpha 1A$ or $\alpha 1ACT$ in SCA6 is untested.

Altogether, the available evidence supports the broader principle that voltage-gated calcium channels are monitored by ER quality-control and UPS-linked degradation pathways. For SCA6 specifically, however, the mechanistic bridge between general $\alpha 1A$ quality control and clearance of polyQ-expanded $\alpha 1A$ - or $\alpha 1ACT$ -derived species remains incomplete. Establishing which factors recognize these disease-associated proteins, where they are processed and whether they are routed toward proteasomal or alternative clearance pathways remains an important, unresolved question.

Spinocerebellar Ataxia Type 7

SCA7 is an autosomal dominant disorder caused by a CAG-repeat expansion in ataxin-7 (ATXN7; [256]). Alleles with 34-36 repeats show reduced penetrance, whereas alleles with at least 37 repeats are generally fully penetrant; 28-33 repeats are considered mutable or intermediate [257] (Fig. 1; Table 1). SCA7 is uniquely distinguished from other ataxias by the combination of progressive cerebellar ataxia and cone-rod dystrophy leading to vision loss [258]. ATXN7 is a nuclear core component of the Spt-Ada-Gcn5 acetyltransferase (SAGA) transcriptional coactivator complex. This characteristic places SCA7 at an intersection of polyQ aggregation, transcriptional dysregulation, chromatin regulation and PQC.

Like other polyQ proteins, mutant ATXN7 misfolds and accumulates in nuclear inclusions, but in SCA7 these inclusions are especially important because they can sequester SAGA components, transcriptional regulators, chaperones and proteasome-linked proteins [259], making SCA7 a useful example of how polyQ aggregation can disrupt both nuclear transcriptional machinery and PQC at the same time.

Ubiquitin-dependent quality control in SCA7

ATXN7 normally functions as a scaffold within the SAGA transcriptional coactivator complex, where the USP22-containing deubiquitinase module regulates histone H2B ubiquitination [259]. In SCA7, polyQ-expanded ATXN7 altered SAGA function and sequestered SAGA components within nuclear inclusions, linking mutant ATXN7 accumulation to disrupted histone ubiquitination and transcriptional dysregulation [260-263]. *Drosophila* studies further support a loss-of-SAGA-function model. When ATXN7 was displaced from SAGA, the DUB module was released but remained stabilized, increasing deubiquitination of downstream chromatin substrates and

thereby affecting transcriptional regulation [264]. The released USP22 also gained deubiquitinase activity toward non-histone substrates [264, 265]. Thus, the DUB module can be dysregulated in either direction depending on ATXN7 anchoring. The consequences of mutant ATXN7 extend to disruption of a ubiquitin-regulated transcriptional complex in which the normal protein serves an essential structural role. More recent work extended this loss-of-DUB-function picture in mice. In SCA7 knock-in mouse cerebella, monoubiquitinated histone H2B was increased, consistent with impaired SAGA-DUB-module activity during disease progression [266]. Beyond its structural role, ATXN7 is itself a substrate of the UPS: in yeast and in human cells, the ATXN7 orthologue (Sgf73) and human ATXN7 were ubiquitinated and degraded by the proteasome and this turnover fine-tuned ATXN7 abundance to preserve the assembly and DUB activity of SAGA [267].

Mutant ATXN7 is recognized by nuclear protein quality-control machinery. Across SCA7 patient brains, knock-in and transgenic mice, *Drosophila* models and mammalian cell systems, mutant ATXN7 accumulated in nuclear inclusions containing ubiquitin, SUMO-associated proteins, chaperones, transcriptional regulators, RNA-binding proteins and proteasome components [268-276]. Proteasome-associated factors included 19S regulatory-particle components S4/PSMC1, S7/PSMC2 and Rpn10/PSMD4, as well as 20S core-particle components. Activated caspase-3 was detected in a subset of inclusions [277]. Separately, caspase-7 cleaved ATXN7 at Asp266 and Asp344 to generate an N-terminal polyQ fragment with increased aggregation propensity and toxicity [278]. Functionally, this recruitment coincided with proteasome impairment: polyQ-expanded ATXN7 reduced proteasome proteolytic activity in cultured cerebellar neurons, leading to accumulation of proteasome substrates such as I κ B α , disrupted NF- κ B signaling and caspase-9-dependent death [279]. Mutant ATXN7 may therefore overwhelm the proteasomal machinery recruited to clear it.

A well-defined degradation pathway for mutant ATXN7 is nuclear-localized and SUMO-dependent. Evidence centers on SUMO2/3 modification, the SUMO-targeted ubiquitin ligase RNF4 and PML clastosomes. Mutant ATXN7 is more extensively modified by SUMO2/3 than wild-type ATXN7, with K257 identified as a major site. RNF4 recognized poly-SUMOylated mutant ATXN7, promoted its ubiquitination and facilitated its proteasomal degradation [275]. K257 also sits at the center of a competing set of modifications that determine the fate of a toxic ATXN7 fragment. As noted above, caspase-7 can cleave ATXN7 at Asp266 and Asp344 to generate an N-terminal polyQ fragment that is more aggregation-

prone and toxic than the full-length protein [278]; acetylation of K257 within this fragment by CBP blocked its autophagy-mediated turnover and promoted its accumulation, whereas deacetylation favored fragment clearance [280]. Because K257 can undergo both acetylation and SUMOylation, findings from separate studies suggest that alternative modification at this residue influences ATXN7 accumulation or clearance; a direct competition between these modifications has not been tested. Interferon- β supports this clearance option by increasing SUMO-pathway activity and PML clastosome formation, improving mutant ATXN7 clearance and reducing aggregation in SCA7 models. SUMOylation attenuated the aggregation and toxicity of polyQ-expanded ATXN7 in cell models [273] and in SCA7 knock-in mice interferon- β induced PML-dependent clearance of mutant ATXN7 and improved motor function and Purkinje cell survival [281]. Thus, enhancing SUMO-dependent nuclear clearance can improve mutant ATXN7 handling and disease-relevant phenotypes.

Chaperone recruitment provides an additional layer of quality-control engagement. HDJ-2/DNAJA1, HSC70 and HSP70-family proteins colocalized with mutant ATXN7 inclusions, supporting recognition of the misfolded protein by the chaperone network. Yet, overexpression of HSP40 and HSP70 did not prevent the retinal phenotype in SCA7 mice [277, 282]. The chaperone relationship is not only one of recognition but also of sequestration: the N-terminal fragment of polyQ-expanded ataxin-7 trapped the HSP40 co-chaperone HSP40/DNAJB2 into aggregates, depleting the functional co-chaperone pool and further burdening proteostasis [232]. ATXN7 stability is additionally shaped by HDAC3, which bound wild-type and expanded ATXN7, increased its post-translational modification and levels and modified polyQ-dependent toxicity [283].

Autophagy-related findings indicate a p62/SQSTM1 ubiquitin-dependent bridge to selective autophagy in SCA7. Mutant ATXN7 inclusions in knock-in mice were immunoreactive for p62/SQSTM1, ubiquitin, LC3, LAMP1, LAMP2, and cathepsin D [274]. In inducible SCA7 cell models, full-length ATXN7 was cleared largely by the proteasome, whereas cleaved fragments were handled by both the proteasome and autophagy and pharmacological autophagy induction reduced aggregates and improved viability [284]. However, mutant ATXN7 co-aggregated p53 and FIP200 into inclusions, depleting soluble FIP200 and destabilizing ULK1, thereby disrupting autophagy initiation through a p53-dependent route [285]. These results position autophagy as a failure because of mutant ATXN7, not simply as an incomplete response to it.

Overall, current evidence suggests that SCA7 is a nuclear proteostasis disorder in which mutant ATXN7 disrupts ubiquitin-regulated transcription while simultaneously becoming a substrate for nuclear quality-control machinery. Mutant ATXN7 perturbs the SAGA DUB module, accumulates in ubiquitin- and SUMO-positive inclusions and recruits proteasomes, chaperones, and autophagy-associated factors, yet these responses remain insufficient to prevent its persistence and toxicity. The disease likely reflects the combined effects of incomplete mutant ATXN7 disposal, sequestration of nuclear regulatory machinery, altered chromatin-associated ubiquitin signaling and progressive failure to coordinate proteasomal and autophagy-linked responses.

Spinocerebellar Ataxia Type 17

SCA17 is an autosomal dominant disorder caused by a CAG-repeat expansion in the TATA-binding protein (TBP) gene [286-288]. Alleles with 25-40 repeats are generally considered normal, 41-48 repeats show variable penetrance, and alleles with at least 49 repeats are usually fully penetrant; lower-repeat disease can occur in the presence of genetic modifiers such as pathogenic STUB1 variants [289] (Fig. 1; Table 1). The central role of TBP in SCA17 makes it mechanistically distinct from many other polyQ diseases because the mutated protein is a core component of the cellular transcriptional machinery.

Clinically, SCA17 presents with progressive ataxia, cognitive decline, psychiatric symptoms and variable movement disorders, including chorea, dystonia and parkinsonism [289]. Impacted areas include the cerebellum, cerebrum and brainstem [290]. Because some patients develop prominent chorea and dementia-like features, SCA17 can overlap clinically with HD. Pathologically, mutant TBP accumulates predominantly in ubiquitin-associated nuclear inclusions. Recent evidence indicates that cytoplasmic TBP fragments can also contribute to toxicity, placing SCA17 at the intersection of nuclear aggregation, transcriptional dysregulation and cytoplasmic PQC stress [291].

Ubiquitin-dependent quality control in SCA17

CHIP/STUB1 is the clearest UPS factor linked to SCA17. Human genetic studies showed that pathogenic STUB1 variants, which impair the CHIP protein, can occur with intermediate TBP expansions and contribute to TBP-associated disease [292, 293]. Intermediate TBP alleles and LOF STUB1 variants can produce a digenic phenotype with features of SCA17 and SCA48 [294]. Clinical-genetic analysis further reinforces the frequent CHIP/STUB1 SCA17 association and supports a lower

pathogenicity threshold for intermediate expanded TBP alleles [295].

In patient tissue, mutant TBP formed neuronal intranuclear inclusions that were immunoreactive for ubiquitin, while cell and rat model studies suggested that TBP aggregation can also involve proteolytic TBP fragments, transcriptional regulators such as NF-YA and, more recently, cytoplasmic TBP fragments generated by calpain cleavage [288, 291, 296-298]. The machinery that normally controls TBP levels was defined biochemically: the HECT E3 ligase HUWE1 promoted K48-linked ubiquitination and proteasomal degradation of TBP, while the deubiquitinase USP10 opposed this to stabilize TBP [299]. TBP is additionally connected to a chromatin-associated ubiquitin axis, where TBP together with WDR5 recruited the anaphase-promoting complex to transcription start sites, where it ubiquitinated histones and recruited VCP/p97 and the proteasome [300]. Although neither pathway has yet been reported for polyQ-expanded TBP, together they identify enzymes and routes through which TBP can be normally handled by the UPS. Beyond these degradative routes, the HTT-associated protein, HAP1 bound the conserved core domain of TBP away from its polyQ and sequestered a subset of TBP into cytoplasmic inclusions, a mechanism whose relevance to SCA17 remains unclear [301].

The chaperone-linked UPS axis may be important to SCA17. Patient-derived lymphoblastoid cells had altered HSPA8 expression and inducible SCA17 mice linked age-dependent loss of HSC70 and broader chaperone activity to mutant TBP accumulation and worsening Purkinje cell pathology [302, 303]. Smaller stress chaperones also participate in this response. In primary cerebellar granule neurons from SCA17 transgenic mice, HSP27/HSPB1 did not colocalize with mutant TBP aggregates like HSP70 does, but it still modified mutant TBP-linked transcriptional stress. HSP27/HSPB1 is perhaps better conceptualized as a stress-response chaperone rather than a direct UPS enzyme [304]. Consistent with a protective role for this small heat-shock chaperone, pharmacological enhancement of HSP27/HSPB1 with the indole compound NC009-1 reduced mutant TBP aggregation in SCA17 cell models and ameliorated behavioral deficits in TBP transgenic mice [305].

HSPA5 (BiP/GRP78) adds a broader chaperone stress angle to SCA17. Studies with patient-derived SCA17 lymphoblastoid cells reported altered HSPA5 and HSPA8/HSC70 expression, while HEK293 and SH-SY5Y cellular models suggested that mutant TBP can sequester NF-YA (the regulatory DNA binding subunit of the transcription factor NF-Y) into aggregates and weaken NF-Y-dependent HSPA5 expression [298, 302]. The consequence is a reduced ability to sustain HSPA5-mediated ER chaperone buffering, which may make cells less able

to manage mutant TBP misfolding and aggregation. This chaperone-buffering defect is compounded by the loss of another HSPA5 regulator: mutant TBP sequestered the transcriptional cofactor HMGB1 into aggregates, reducing soluble HMGB1 and thereby both weakening HSPA5 transcription and impairing starvation-induced autophagy [306]. HMGB1 sequestration thus links the HSPA5 chaperone axis to autophagic clearance in SCA17.

CAPN1 and CAPN2, both calcium-activated proteases, have been implicated in mutant TBP cleavage. In vitro assays and SCA17 cell models determined that calpains can cleave TBP to generate C-terminal fragments that contain the DNA-binding core but become enriched in the cytoplasm rather than the nucleus. Similar C-terminal fragments and increased calpain activation markers were detected in TBP-Q64 rat cerebellum, supporting this pathway in vivo [291]. Direct evidence for calpain-mediated TBP cleavage in SCA17 patient tissue has not yet been reported.

Autophagy induction has emerged as a route to reduce mutant TBP. In SCA17 transgenic mice, the mTOR-independent autophagy inducer trehalose reduced nuclear mutant TBP aggregation and improved gait ataxia and gliosis [307]. Pre-symptomatic administration of granulocyte colony-stimulating factor also prevented motor deficits while raising HSP70, BECLIN1 and LC3-II and lowering insoluble mutant TBP, coupling chaperone induction to autophagic clearance in vivo [308]. These findings indicate that enhancing autophagy can improve mutant TBP handling, complementing the proteasomal and chaperone routes noted above.

Overall, the SCA17 UPS story is less about degradation pathways and more about a stressed nuclear proteostasis environment. Mutant TBP is recognized by ubiquitin-linked quality control systems, forms ubiquitin-positive nuclear inclusions and engages the HSP70/HSC70 axis, but the available evidence does not conform to a simple model in which the UPS efficiently clears mutant

TBP. Instead, SCA17 seems to involve several overlapping bottlenecks: weakened CHIP/STUB1 function may lower the threshold for TBP toxicity, loss of chaperone activity may reduce the ability to manage mutant TBP and calpain cleavage may generate smaller TBP fragments that add to aggregation stress.

Cross-disease synthesis: shared nodes, disease-specific routing and therapeutic opportunities

Across the polyQ diseases, each mutant protein is commonly recognized by ubiquitin-dependent PQC, but its recognition does not ensure clearance. Despite differences in normal function, interaction partners and localization, these proteins, like most others in the eukaryotic cellular environment, converge on a limited set of possibilities: chaperone-assisted stabilization or refolding, ubiquitination, extraction, proteasomal degradation, autophagic disposal, sequestration into inclusions, or persistence within toxic soluble complexes. Several outcomes may occur simultaneously without restoring proteostasis. The question is therefore not whether a mutant protein is ubiquitinated, but whether that signal is translated into productive disposal in the relevant compartment and vulnerable tissue.

The machinery engaged is also not identical across diseases. This distinction separates a shared quality-control architecture from disease-specific substrate routing (Fig. 2, 3; Table 3). Chaperones assess folding and influence whether a client is stabilized, refolded or committed to degradation. E2 and E3 enzymes write ubiquitin signals, DUBs edit them, extraction factors mobilize substrates and shuttle proteins and receptors direct them toward the proteasome or autophagy. Some components recur across diseases, but their outcomes depend on the disease protein's normal biology, localization, fragmentation, aggregation state, interaction network and tissue-specific proteostasis capacity (Table 4).

Table 4. Summary of PQC components described in the text, organized by polyQ disease.

Disease / protein & location	Key E2/E3 regulators	DUBs & other regulators	PQC routing	Other features & evidence level
HD / HTT Cytoplasm and nucleus; soluble fragments and cytoplasmic/nuclear inclusions.	E2s: UBE2D (supports degradation; loss increases aggregates); Ubc13/UBE2N (proteasome-linked clearance); UBE2K (increases aggregation/toxicity); UBE2W (controls solubility/aggregation). E3s: CHIP/STUB1 (decreases accumulation/aggregation/toxicity); HACE1 (NRF2-mediated oxidative-stress protection); HOIP/LUBAC (M1 ubiquitination; proteasomal clearance);	USP19 (stabilizes HTT; increases aggregation/toxicity); USP7 and USP11 (detrimental in HD models); YOD1 (protective; aggregate clearance not required); USP12 (autophagy-dependent, DUB-independent protection); USP14 (decreases insoluble aggregates/ER stress; neuroprotective); PSME3, PA200 and PKA-Rpt6 (enhance proteasome function); p62/SQSTM1 UFMylation;	Site- and chain-specific ubiquitin routing; VCP/p97 extraction; UBQLN2/RAD23B shuttling and sequestration; UBQLN2-HSP70/HSP110 disaggregation; p62/SQSTM1, TAX1BP1 and Alf1/WDFY3 selective autophagy; CCT2 acts as an aggregate receptor for solid HTT aggregates without requiring a ubiquitin signal.	Most developed polyQ UPS model; HTT is both ubiquitin substrate and reader; striatal interactome remodeling; fragments, compartment, solubility and aggregate state determine routing; fibrils can exclude p62/SQSTM1. Highest evidence level; extensive cell, fly, worm, zebrafish, mouse, primate,

	HRD1/SYVN1 (increases degradation; decreases toxicity); NEDD4 (increases clearance; decreases aggregation/toxicity); PRKN (ubiquitination/elimination; protective); PJA1 (proteasomal degradation; decreases aggregation); SCF/FBXW7 (aggregation/stress regulation); TRAF6 (atypical ubiquitination; increases aggregation); TRIM37 (increases ubiquitination/degradation); UBE3A/E6-AP (K48 ubiquitination; proteasomal degradation); UBR5/EDD1 (proteasomal degradation; suppresses aggregation); UHRF2 (nuclear turnover); AIP5/WWP1 (K63 ubiquitination; increases aggregation/toxicity).	ZKSCAN3–TFEB lysosomal regulation.		patient tissue and iPSC evidence.
DRPLA / ATN1 Nucleus and cytoplasm; predominantly ubiquitin-positive neuronal intranuclear inclusions; occasional cytoplasmic filamentous inclusions.	WW-domain/NEDD4-family associations: AIP2/WWP2, AIP4/ITCH and AIP5/WWP1; direct ATN1 ubiquitination or degradation by these ligases not established.	Rpn11/PSMD14 and VCP/p97 (tissue-dependent toxicity modifiers); p62/SQSTM1 in a subset of inclusions; NBR1 uncommon and LC3 absent in patient tissue; reduced TFEB, impaired LC3 conversion and LaminB1-linked nucleophagy.	Proteasome inhibition increases full-length ATN1; canonical autophagy stalls after autophagosome–lysosome fusion at the lysosomal step; nucleophagy may compensate	Caspase-generated fragments show greater nuclear accumulation, aggregation and toxicity; recognition is evident, but no defined ATN1-targeting E2/E3/DUB clearance pathway; autophagy induction may fail to reduce toxicity. Limited evidence; mainly patient tissue, cell, fly and transgenic-mouse studies.
SBMA / AR Cytoplasm and nucleus; androgen binding drives nuclear translocation and accumulation; inclusions occur in motor neurons and muscle.	CHIP/STUB1 (ubiquitination/proteasomal clearance; decreases aggregation/toxicity); MDM2 and CRL3-SPOP (WT AR ubiquitination/clearance, polyQ untested); PRKN (binds/colocalizes with mutant AR; overexpression does not lower abundance); MID1/TRIM18 (increases mutant AR production; not a clearing E3). Non-SBMA AR regulators: DDB2 and SIAH2 (degradation); TRAF4 (K27 signaling); SKP2, RNF6 and UBE3A/E6-AP (stability/activity regulation).	USP7 (deubiquitinates mutant AR; inhibition protective); USP12, USP14, USP26, USP10 and USP22 (AR regulators; polyQ-expanded AR roles largely untested); HSP90 stabilizes ligand-responsive AR; HSP70/HSP40 and CHIP promote degradation; HSPB8–BAG3–HSP70, p62/SQSTM1 and HDAC6 route cargo to autophagy; PSME3 effects are cell-type dependent.	Ligand- and chaperone-dependent triage between stabilization, proteasomal degradation and selective autophagy; VCP/p97 is sequestered from DNA repair; muscle shows reduced proteasome recovery/capacity and ubiquitinated Rpn13; ARD-1676 forces ubiquitin-dependent proteasomal degradation.	Toxicity depends on androgen activation; mutant AR remodels E2/proteasome expression; UPS and autophagy are tightly coupled in muscle; endogenous clearance is inadequate but degrader-enforced routing is effective. Established evidence level; strong cell, fly, mouse, patient-derived neuron and muscle and patient-based evidence.
SCA1 / ATXN1 Predominantly nuclear; mutant ATXN1 persists in soluble nuclear complexes and nuclear inclusions.	UbcH6/UBE2E1 (E2; K589 ubiquitination, shorter half-life and decreases aggregation); UBE3A/E6-AP (proteasomal handling; loss worsens pathology despite fewer inclusions); CHIP/STUB1 (ubiquitination/clearance, but context-dependent aggregation); RNF4 (SUMO2/3-targeted nuclear quality control; direct ATXN1 targeting remains unestablished).	USP7 (interacts with ATXN1; downstream effect unresolved); UBQLN4/A1Up (proteasome-shuttle handoff); PML/SUMO–RNF4 pathway; 14-3-3 stabilizes phospho-Ser776 ATXN1; HSP90 inhibition/HSF1 activation and TFEB-driven autophagy promote clearance; ATXN1L displaces mutant ATXN1 from native complexes.	Nuclear ubiquitination and proteasomal delivery; SUMO-targeted PML-associated routing; chaperone state, Ser776 phosphorylation and native-complex binding determine persistence versus clearance.	Inclusions do not directly predict toxicity; UBE3A loss reduces inclusions but worsens Purkinje pathology; CHIP effects depend on phosphorylation and chaperone context. Moderate evidence level; cell, fly, mouse, iPSC and human postmortem evidence.
SCA2 / ATXN2 Predominantly cytoplasmic and RNA-associated; stress-granule linked; toxic	PRKN (ubiquitin-dependent ATXN2 turnover); FBXW8-containing SCF complex and <i>Drosophila</i> Fbxo42 (promote degradation/limit toxicity).	No ATXN2-directed DUB established; CDK5 promotes proteasomal degradation; PABP/PABPC1 maintains solubility; p62/SQSTM1, OPTN, UBQLN2 and TNIP1 connect ATXN2 to selective autophagy;	Proteasome-sensitive cytoplasmic turnover; E3-dependent handling competes with RNA-granule persistence; p62-linked autophagy provides an alternate route when ATXN2 accumulates.	Links RNA metabolism and stress-granule biology to PQC; fragment production and granule state may shape clearance.

N-terminal fragments may accumulate.		Raptor/mTORC1 sequestration alters autophagy signaling.		Moderate evidence level; primarily cell, fly, mouse, patient tissue and human genetic evidence.
SCA3 / ATXN3 Cytoplasm and nucleus; soluble species and cytoplasmic/nuclear inclusions; nuclear accumulation is especially toxic.	CHIP/STUB1 (ubiquitination/clearance); gp78/AMFR (ER-associated handling); MITOL (ubiquitination and degradation of a mitochondria-localized, N-terminally truncated ATXN3-Q71 construct); PJA1 (proteasomal degradation; decreases aggregation); Prpf19 (ubiquitination, restrained by Exoc7); UBE4B/E4B (ubiquitin-chain extension); PRKN (mitophagy modifier).	ATXN3 is itself a DUB; RAD23A/B stabilize ATXN3; Rad23B influences phase behavior; VCP/p97 and HDAC6 regulate extraction/aggresome routing; Rpt6 promotes degradation; Beclin-1, LC3C/GABARAP, Rheb and VDAC1 link ATXN3 to autophagy, mTORC1 and mitophagy; HSP70/HSC70/HSP90 chaperone axis; CAPN1/CAPN2 cleavage; HSPA5/HSPA8 stress responses; HAP1 sequesters cytoplasmic TBP; HMGB1 sequestration weakens HSPA5-dependent chaperone buffering and autophagy; trehalose promotes autophagic clearance.	Ubiquitin editing, VCP/p97-dependent aggregation, proteasome shuttling, aggresome formation, selective autophagy and mitophagy jointly determine ATXN3 fate.	Disease protein is a DUB; polyQ expansion perturbs ATXN3 clearance and its normal ubiquitin-editing functions; ubiquitin-binding surfaces, cleavage and nuclear entry shape toxicity. Established evidence level; extensive biochemical, cell, fly, iPSC, mouse and patient tissue evidence.
SCA6 / α1A; α1ACT Expanded CaV2.1 α 1A mainly Golgi/ER associated; α 1ACT is partly nuclear; polyQ-containing C-terminal fragments preferentially form cytoplasmic aggregates in Purkinje cells.	RNF138 (CaV2.1 quality control in non-SCA6 channel models); UbcH7/UBE2L3 (E2; tested on CaV2.2); NEDD4-1 (tested on CaV1.2); AIP5/WWP1 (tested on the <i>C. elegans</i> CaV2 ortholog UNC-2); direct effects on polyQ-expanded α 1A or α 1ACT remain unproven.	CaV β subunits can protect CaV channels from ERAD; HSP90-dependent unfolded-protein response buffers misfolded CaV2.1 but declines with age; Pin1 involvement in SCA6 remains undefined.	ER/Golgi channel quality control and ERAD are plausible routes; direct ubiquitin-dependent routing of expanded α 1A, α 1ACT, or toxic C-terminal fragments has not been established.	Bicistronic CACNA1A produces a membrane channel and the α 1ACT transcription factor; pathogenic species occupy different compartments, complicating assignment of a single clearance pathway. Limited evidence level; largely inferred from general CaV2.1 quality-control studies plus SCA6 localization/pathology.
SCA7 / ATXN7 Nuclear; mutant ATXN7 forms nuclear inclusions; full-length and caspase-cleaved fragments are handled differently.	RNF4 (SUMO-targeted E3; proteasomal routing through PML clastosomes).	USP22-containing SAGA DUB module; SUMO2/3 and PML clastosomes enhance clearance; p62/SQSTM1; caspase-7 cleavage and CBP-dependent K257 acetylation regulate fragment accumulation; caspase-3 in subset of inclusions; HDAC3 stabilizes ATXN7; HSP70/HSC70/HSP90 chaperone axis; CAPN1/CAPN2 cleavage; HSPA5/HSPA8 stress responses; HAP1 sequesters cytoplasmic TBP; HMGB1 sequestration weakens HSPA5-dependent chaperone buffering and autophagy; trehalose promotes autophagic clearance.	SUMO2/3–RNF4–PML-clastosome proteasomal routing; full-length ATXN7 is cleared mainly by the proteasome, whereas cleaved fragments use both proteasomal and autophagic routes; inclusions sequester PQC and SAGA components.	Retinal and cerebellar vulnerability; SAGA/chromatin dysfunction converges with impaired autophagy initiation; cleavage state determines routing. Moderate evidence level; cell, fly, mouse, iPSC and human tissue evidence.
SCA17 / TBP Predominantly nuclear; calpain-generated C-terminal fragments can mislocalize to the cytoplasm and aggregate.	Pathogenic STUB1 variants that impair CHIP can worsen proteostasis; HUWE1 (K48-linked TBP ubiquitination/degradation); WDR5–APC/C regulates normal TBP-linked histone ubiquitination but is not established as an SCA17 TBP-clearance pathway.	USP10 (stabilizes TBP); HSP70/HSC70/HSP90 chaperone axis; CAPN1/CAPN2 cleavage; HSPA5/HSPA8 stress responses; HAP1 sequesters cytoplasmic TBP; HMGB1 sequestration weakens HSPA5-dependent chaperone buffering and autophagy; trehalose promotes autophagic clearance.	No single efficient disposal pathway; HUWE1-mediated proteasomal degradation, chaperone buffering and autophagy oppose accumulation, while calpain cleavage generates toxic cytoplasmic fragments.	TBP is an essential basal transcription factor; nuclear transcriptional dysfunction coexists with cytoplasmic fragment toxicity; intermediate TBP expansions can interact genetically with pathogenic STUB1 variants that impair CHIP. Limited to moderate evidence level; cell, mouse, rat, patient-derived and human genetic evidence.

Shared and distinct PQC components

The HSP70/HSP90–CHIP/STUB1 axis is one of the clearest shared decision points. CHIP/STUB1 links chaperone recognition to ubiquitination and influences mutant

HTT in HD, ATXN1 in SCA1, ATXN3-associated phenotypes in SCA3, mutant AR in SBMA and TBP-associated disease in SCA17. Its recurrence places CHIP/STUB1 at a conserved junction among stabilization, refolding and degradation (Fig. 3 summarizes the shared nodes as an alluvial diagram). Its benefit, however, depends on whether downstream extraction, delivery and degradation remain functional. Other recurring factors act later in the pathway. VCP/p97 helps extract and mobilize ubiquitinated proteins and is implicated in HD, DRPLA, SBMA, SCA3 and SCA17. UBQLN and RAD23 proteins and p62/SQSTM1 further determine whether ubiquitinated substrates reach the proteasome, accumulate in aggresome-like compartments or are redirected toward autophagy. Thus, an apparently appropriate ubiquitin signal may still fail because extraction, handoff, proteasome engagement, or autophagic assistance and/or completion is defective.

Set against this shared backbone, polyQ diseases also engage a distinctive complement of factors that, within the literature reviewed here, were reported in one disorder or only a small subset; table 3 is particularly helpful in highlighting such cases. In HD, examples include M1-linked ubiquitination by HOIP/LUBAC, the proteasome activators PA200 and PA28 $\alpha\beta$ and the PKA-Rpt6 axis. SCA2 includes the RNA-dependent chaperone PABP/PABPC1 and Staufen1-facilitated sequestration of Raptor by expanded ATXN2. SCA7 includes altered function of the SAGA USP22-containing deubiquitinase module. HUWE1 and USP10 regulate normal TBP abundance, but their roles in SCA17 are unclear. Other factors occur in a subset of diseases: gp78 is linked to HD and SCA3, PJA1 promotes clearance of mutant HTT and ATXN3, and HSP70/DNAJB2 participates in ATXN3 proteostasis and is sequestered by expanded ATXN7 fragments. PML/RNF4-dependent nuclear quality control is implicated in SCA1, whereas a direct SUMO2/3–RNF4 pathway for the disease protein is established for ATXN7 in SCA7. In some cases, these differences may reflect genuine disease selectivity dictated by the normal function of each protein and the complexes in which it participates (e.g., ATXN2 and Staufen, ATXN7 and SAGA). In other cases, they may well reflect incomplete investigation across the entire polyQ family.

The polyQ diseases appear to differ primarily in where the routing of the mutant protein becomes incomplete or maladaptive. HD provides the most extensively defined example, spanning ubiquitin-chain architecture, E2 and E3 enzymes, DUBs, VCP/p97-dependent extraction, shuttle-mediated delivery, proteasome regulation, selective autophagy and aggregate sequestration (Table 4). Mutant HTT accumulation reflects disruption at several interconnected stages rather than proteasome failure alone. DRPLA remains comparatively underdeveloped:

VCP/p97 and Rpn11 modify ATN1 toxicity, and ATN1 interacts with a WW-domain network and transcription-linked partners. However, the enzymes that directly write and edit ATN1 ubiquitin signals remain poorly defined. SBMA is distinguished by ligand-dependent AR activation and nuclear entry and by marked tissue specificity. Androgen state, chaperone engagement, AR-directed ubiquitination, proteasome capacity and muscle-specific remodeling jointly determine whether mutant AR is stabilized, degraded, sequestered or routed toward autophagy. SCA1 is dominated by the nuclear and transcriptional context of ATXN1. SCA2 centers more narrowly on cytoplasmic ATXN2 turnover, RNA and stress-granule biology and SCF-related machinery. SCA3 is distinctive because ATXN3 is itself a native component of the UPS, where it functions as a DUB. Expanded ATXN3 must be cleared while it simultaneously participates in ubiquitin-dependent quality control processes. The mutant protein therefore functions both as a degradation substrate and as a regulator of substrate fate. Evidence in SCA6 is very limited; how the broader range of toxic α 1A- and α 1ACT-derived species is handled is unresolved. SCA7 and SCA17 are both nuclear, transcription-centered disorders, but their quality-control pressures differ. As noted in the “Introduction,” much work needs to be conducted to level the playing field for the polyQ disease family members to enable more comprehensive, comparative analyses.

The effect of polyQ aggregates on proteasomal and autophagic clearance

PolyQ inclusions commonly contain ubiquitin, chaperones, proteasome subunits and autophagy receptors. Their presence, however, cannot by itself establish whether an aggregate is being cleared or is obstructing the pathway recruited to it. For the proteasome, recruitment can remain dynamic and potentially productive. Mutant HTT inclusion bodies incorporated newly supplied ubiquitin into conjugates and recruited catalytically active ligases and DUBs, indicating ongoing ubiquitin-dependent processing rather than irreversible immobilization of the entire ubiquitin system [23]. Nuclear polyQ aggregates are not necessarily terminal deposits either. In cultured cell and neuronal models, the nuclear ubiquitin ligase UHRF2 promoted ubiquitination and UPS-dependent turnover of nuclear polyQ HTT, reduced aggregate burden and protected against toxicity [48]. Active ubiquitin chemistry at an inclusion does not by itself prove proteasomal degradation of that inclusion; taken together, however, these reports indicate that UPS machinery can engage at least some aggregated or aggregation-prone pools productively.

Other observations support non-productive capture and secondary loss of proteasome capacity. PolyQ-expanded AR aggregates recruited the 19S proteasome cap but contained relatively little 20S core particle, creating an altered subunit ratio that was determined to be unlikely to constitute functional 26S proteasomes [113]. Mutant HTT and ATXN3 aggregates also sequestered the ubiquitin-binding shuttle factors RAD23B/HR23B and UBQLN2 through interactions with conjugated ubiquitin and led to reduced levels of proteins stabilized by RAD23B/HR23B [70]. Thus, aggregates can behave as sinks for substrate-delivery and quality-control factors, compromising the handling of other proteins even without physically blocking the proteasome core. Consistent with reduced system capacity, mutant HTT-expressing striatal cells and HD mouse brain displayed reduced proteasome activity [72, 75]. A reciprocal relationship may exist between aggregate burden and proteasome capacity, but available evidence does not fully support the notion that aggregates universally “clog” the proteasome.

Autophagy investigations led to similar observations of a distinction between productive engagement and pathway failure. In SBMA mice, loss of p62/SQSTM1 impaired autophagic degradation and increased both monomeric and high-molecular-weight mutant AR, whereas p62 overexpression was protective and promoted cytoprotective inclusion formation [143]. In this setting, inclusion formation was compatible with protection rather than being evidence that autophagy had failed. Compartment also imposes a major limit. Cytoplasmic aggregates can be engulfed by autophagosomes, whereas nuclear aggregates are not directly accessible to this machinery; in HTT models, autophagy contributed to cytoplasmic aggregate removal but not nuclear polyQ clearance, which depended on the UPS [48].

PolyQ proteins may also hamper autophagy at several downstream steps. In neurons, mutant HTT disrupted the HTT-HAP1 motor-scaffolding function required for processive retrograde transport of autophagosomes. Autophagosomes still formed and cargo was loaded into them, but impaired transport was associated with defective maturation and inefficient content degradation [20]. In SCA7, full-length mutant ATXN7 impaired autophagic flux in overexpressing cells; knock-in mice and patient tissue showed abnormal accumulation of autophagy/lysosome markers and mice had reduced soluble levels of various autophagy components [274]. Symptomatic SBMA muscle likewise had a robust induction of autophagy-related markers with a shift toward autophagic rather than proteasomal routing [127].

The overall conclusion is therefore a qualified one: polyQ aggregates can hamper both the proteasome and autophagy, but engagement with an aggregate is not intrinsically inhibitory. Persistent aggregates may become

poorly accessible substrates, sequester shuttle factors or incomplete proteasome assemblies, disturb autophagosome transport and maturation, or exceed lysosomal capacity. Conversely, inclusions can recruit active ubiquitin chemistry, remain susceptible to nuclear UPS pathways and protect cells by sequestering toxic species or enabling autophagy-dependent disposal. Direct aggregate-induced inhibition needs to be distinguished from pathway impairment that develops upstream, downstream or in parallel. Mechanistic studies that combine aggregate-state and compartment measurements with proteasome catalytic assays, turnover of defined substrates and complete autophagic-flux measurements can help discern among these possibilities and also identify other options.

The role of context and aging in ubiquitin-dependent PQC

Ubiquitin-dependent PQC is not a fixed program deployed uniformly across the nervous system or life course; it performs routine proteome maintenance while adapting to substrate load and specialized cellular function. Consequently, the same component can exert different effects across cellular settings. For example, in SBMA, PSME3 increased polyQ-expanded AR aggregation and toxicity in PC12 cells, yet protected motor neurons through a proteasome-binding-dependent mechanism [128]. Regional differences also occur within a disease. Lowering 14-3-3 ϵ in SCA1 mice reduced mutant ATXN1 levels and its incorporation into large toxic complexes in the cerebellum, rescuing cerebellar pathology and motor performance; but it did not rescue weight loss, respiratory dysfunction or premature lethality; ATXN1 levels and toxic-complex incorporation were unchanged in the brainstem [177]. Thus, activity measured in one cell type or region cannot be generalized to another.

Proteostasis requirements also change with organismal age and disease stage. One example comes from inducible SCA17 mice, where initiating mutant TBP expression in older animals produced more rapid symptom onset, greater Purkinje-cell degeneration and more TBP accumulation, consistent with an age-dependent decline in brain chaperone activity measured in separate wild-type cohorts [303]. In SBMA muscle, age-, hormone- and polyQ-length-dependent repression of UPS genes was accompanied by reduced active NRF1, reduced DDI2 and diminished proteasome activity; autophagy-marker elevations reported in prior SBMA studies were thus considered to be possible compensatory response to this proteasomal failure [111]. Similarly, UBE2D/eff declined with age in *Drosophila* skeletal muscle, where muscle-specific knockdown reduced proteasome activity and ac-

celerated insoluble polyubiquitinated-protein accumulation; in a fruit fly retinal polyQ HTT model, eff knock-down impaired HTT-polyQ degradation [60].

The relative contributions of chaperone triage, the UPS and autophagy are therefore likely to shift across development and maturation, aging and symptomatic progression. Early in disease, soluble or newly misfolded species may remain accessible to chaperone-assisted refolding or proteasomal degradation; later, fragmentation, aggregation, organelle damage and declining clearance capacity may increase reliance on selective autophagy while limiting its completion. An important question, therefore, is which PQC arm is carrying the burden, where and when and whether it can complete disposal.

Mitochondrial consequences of ubiquitin-dependent PQC dysfunction

Mitochondrial turnover provides an additional example of how disease-specific changes in the PQC network can affect overall proteostasis. In HD neurons, mutant HTT disrupted the normal HTT-HAP1 scaffold that coordinates motor-driven autophagosome transport; although autophagosomes formed and were able to acquire cargo, their impaired transport and maturation were associated with inefficient degradation of engulfed mitochondrial fragments, linking altered polyQ-protein handling to defective mitophagic completion [20].

This connection is perhaps more directly coupled to ubiquitin signaling in SCA3. The mitochondrial outer-membrane E3 ligase MITOL ubiquitinated an N-terminally truncated ATXN3-71Q species that partially localized to mitochondria and promoted its proteasome-dependent degradation, whereas MITOL depletion increased the mitochondrial accumulation, aggregation and toxicity of this species [222]. ATXN3 also deubiquitinated PRKN and regulated its stability [226]; correspondingly, SCA3 patient-derived fibroblasts showed impaired VDAC1 deubiquitination, reduced PRKN recruitment to depolarized mitochondria and increased p62-linked mitophagy [217].

A distinct late-stage mitophagy defect has also been observed in SCA6 mice, in which damaged mitochondria accumulated while lysosome-mitochondrion colocalization and LC3 levels declined in Purkinje cells; metabolic signatures consistent with mitochondrial dysfunction were also detected in human SCA6 cerebellum [248]. Together, these reports suggest that polyQ-associated PQC failure extends beyond disposal of the disease protein to mitochondrial surveillance itself and that mitochondrial localization of disease proteins and PQC factors creates compartment-specific points of vulnerability.

Therapeutic considerations

A primary reason to understand the biology of the polyQ disorders and the manner in which cells respond to and handle mutant proteins has been the possibility of successful therapeutic interventions based on this knowledge. The comparisons made here can be helpful to identify therapeutic opportunities, but caution against treating any shared node as uniformly protective. Enhancing degradation-competent HSP70/HSP90–CHIP/STUB1 triage may improve handling across several diseases, but only when downstream pathways remain competent. Restoring proteasome capacity may be particularly relevant in HD and SBMA, the latter through recovery of the NRF1- and DDI2-dependent program in muscle, whereas improving VCP/p97-dependent extraction or shuttle-mediated delivery may help convert ubiquitination into degradation. Coordinating proteasomal processing with p62/SQSTM1-mediated autophagy may be necessary for larger or aggregated species that are poorly suited to direct proteasomal degradation, and, in HD specifically, ubiquitin-independent routes may be required once HTT is fully fibrillar. Other strategies may require closer matching to subcellular context. SUMO-targeted nuclear quality control is supported in SCA1 and is well defined in SCA7. Disease-protein-directed degraders, exemplified by the AR PROTAC ARD-1676 in SBMA, may bypass weak endogenous recognition by forcing the substrate into a degradation-competent complex. Even these approaches remain dependent on downstream pathway capacity and could generate harmful intermediates if extraction, delivery, proteasome engagement, or autophagic completion remains impaired. The therapeutic objective should therefore not be indiscriminate activation of the UPS, but improved fidelity, selectivity and completion of ubiquitin-dependent routing. This requires identifying the dominant bottleneck in each disease and matching intervention to the disease protein's biology, localization, fragment and aggregate state and vulnerable tissue. The recurrence of CHIP/STUB1, VCP/p97, SCF-related machinery, RAD23, UBQLN, p62/SQSTM1, LC3, PML and RNF4 suggests that a limited set of proteostasis nodes may be leveraged across polyQ disorders (Fig. 3), but their manipulation will require disease-, compartment- and tissue-specific implementation.

Conclusions

Across the family of polyQ diseases, disease-causing proteins are frequently recognized by ubiquitin-linked quality-control systems, but recognition does not dictate a single outcome. Their eventual fate reflects the combined actions of E2 and E3 enzymes, DUBs, chaperones, extraction factors, shuttle proteins, proteasome regulators and autophagy receptors operating within protein-specific,

subcellular, tissue and temporal contexts. This comparison also reveals that the depth and type of evidence remain markedly uneven across diseases, leaving unresolved why particular cell types and brain regions succumb while others remain comparatively functional.

Several developing areas of proteostasis research broaden this framework, including organelle-selective quality control, RNA-binding-protein homeostasis, translational control and the dynamics of stress granules and other biomolecular condensates. ATXN2 best exemplifies the convergence between protein and RNA homeostasis. Evidence that HTT can direct ubiquitinated RNA-binding proteins toward lysosomal degradation suggests that this proteostasis-RNA interface extends beyond SCA2. Important questions therefore include how ubiquitin-dependent PQC components regulate the assembly, material state, disassembly and clearance of aggregates and condensates and conversely whether persistent RNA-protein assemblies or sequestration of RNA-binding proteins reduces the availability or fidelity of PQC machinery.

Addressing these emerging layers will be important for translating PQC biology into therapy. Successful strategies will require identifying which ubiquitin signals and routing decisions are protective for each disease protein, where the dominant bottleneck lies, whether downstream machinery remains competent in the affected tissue and how these relationships change with age and disease stage. Clarifying the reciprocal interactions among protein clearance, organelle surveillance, RNA metabolism and condensate dynamics will help explain selective cellular vulnerability and enable interventions that restore productive clearance without disrupting adaptive stress responses, or the normal functions of the affected proteins.

Note: Although we aimed to cite all relevant publications, some studies may have been inadvertently omitted. We apologize for any omissions.

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Declaration of interests

The authors do not have any conflicts of interest to declare

Author Contributions

MVP: Conceptualization; data curation; investigation; methodology; writing – original draft; writing – review and editing; visualization. KR: Data curation; investigation; writing – review and editing; visualization. SVT:

Data curation; funding acquisition; investigation; methodology; writing – original draft; writing – review and editing; visualization.

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