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Repeat expansion and autosomal dominant neurodegenerative disorders: consensus and controversy

Dobrila D. Rudnicki and Russell L. Margolis

Repeat-expansion mutations cause 13 autosomal dominant neurodegenerative disorders falling into three groups. Huntington's disease (HD), dentatorubral pallidoluysian atrophy (DRPLA), spinal and bulbar muscular atrophy (SBMA), and spinocerebellar ataxias (SCAs) types 1, 2, 3, 7 and 17 are each caused by a CAG repeat expansion that encodes polyglutamine. Convergent lines of evidence demonstrate that neurodegeneration in these diseases is a consequence of the neurotoxic effects of abnormally long stretches of glutamines. How polyglutamine induces neurodegeneration, and why neurodegeneration occurs in only select neuronal populations, remains a matter of intense investigation. SCA6 is caused by a CAG repeat expansion in *CACNA1A*, a gene that encodes a subunit of the P/Q-type calcium channel. The threshold length at which the repeat causes disease is much shorter than in the other polyglutamine diseases, and neurodegeneration may arise from expansion-induced change of function in the calcium channel. Huntington's disease-like 2 (HDL2) and SCAs 8, 10 and 12 are rare disorders in which the repeats (CAG, CTG or ATTCT) are not in protein-coding regions. Investigation into these diseases is still at an early stage, but it is now reasonable to hypothesise that the net effect of each expansion is to alter gene expression. The different pathogenic mechanisms in these three groups of diseases have important implications for the development of rational therapeutics.

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Since the discovery of the first repeat-expansion mutation disease (spinal and bulbar muscular atrophy; SBMA) by La Spada and Fischbeck and colleagues in 1991 (Ref. 1), repeat expansions as a cause of neurodegeneration have captured the attention of geneticists, molecular and structural biologists, neurologists, cell biologists, neuroscientists, neuropathologists and even psychiatrists. What explains the fascination of these diseases? In part, it is the concept that a disease can simultaneously have both mendelian and nonmendelian – simple and complex – modes of inheritance. In part, it is nosological – the confusing array of overlapping phenotypes of adult-onset neurodegenerative disorders can be placed into a simple classification that is satisfying for the theoretician, practical for the clinician, and tangible for the patient. Most importantly, perhaps, the discovery of expansion mutations has generated new insight into the pathogenesis of neurodegeneration, with implications for the relatively uncommon repeat-expansion diseases themselves and for their more common cousins, especially Parkinson's disease and Alzheimer's disease.

In this article we focus on the dominant neurodegenerative repeat-expansion disorders. Our aim is not to be comprehensive, as more than a paper each day has been published about this group of disorders over the past ten years. For instance, we do not discuss intriguing new evidence about the role of polyglutamine expansion in the regulation of internal calcium (Ca^{2+}) stores (Ref. 213). Instead, our goal is to highlight the aspects of the pathogenesis of these diseases with the most promise for therapeutic intervention, with a particular emphasis on points of active controversy. The diseases are split into three types based on presumed modes of pathogenesis: (1) the diseases in which CAG repeat expansions result in long polyglutamine tracts; (2) the so far single disease in which a small repeat expansion alters normal protein function; and (3) those diseases in which repeat expansion may interfere with gene expression.

The polyglutamine diseases: HD, DRPLA, SBMA, SCAs 1, 2, 3, 7 and 17

Nine neurodegenerative diseases result from CAG repeat expansions in-frame to encode polyglutamine: Huntington's disease (HD), dentatorubral pallidoluysian atrophy (DRPLA), SBMA, and spinocerebellar ataxia (SCA) types 1, 2, 3, 7 and 17. (SCA6, although also a 'polyglutamine' disease, is both genetically and pathogenically distinct, and is considered below.) Each disorder is caused by a mutation at a different locus and in genes that have no similarity to each other except for the presence of the CAG repeat (Table 1). Nonetheless, several common features are characteristic for the group. Clinically, each disease is typically of adult onset, progressive, and confined to the nervous system, with signs and symptoms reflective of the specific regions of the nervous system affected (Table 1). Pathologically, these diseases are characterised by the loss of specific neuronal populations. Although the areas affected differ in each disease, there is considerable overlap between them (Ref. 2; see also Table 1). Microscopically, inclusion bodies that stain with antibodies against expanded polyglutamine or ubiquitin are typically found within nuclei of multiple brain regions in each disease. Genetically, the threshold for repeat length to cause disease is typically in the range of 35 to 40 triplets. Anticipation (decreasing age of onset in successive generations) is present in these disorders, a phenomenon now understood as the result of an inverse relationship between repeat length and age of disease onset combined with a tendency for repeats in the pathological range to expand further during paternal transmission.

The striking similarities in clinical, pathological and genetic features of the polyglutamine disorders suggest that they share a common mechanism of pathogenesis. Finding this mechanism has become one of the 'hottest' topics in medical science, with some areas of agreement and much that remains controversial. Here we address the following issues, chosen because of their potential relevance for the development of rational therapeutics. Does the expansion result in a new and toxic property, or does it interfere with normal protein function? What is the structural abnormality conferred by polyglutamine expansion? What is the structure and contents of the protein aggregates that can be detected in these disorders, and how (if at all) do these aggregates relate to disease pathogenesis? Does polyglutamine expansion confer toxicity by disruption of the ubiquitin–proteasome pathway? Are the proteins with polyglutamine expansions subject to proteolysis and, if so, where and by what enzymes? Is the proteolysis critical for pathogenesis? What is the

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Table 1. Summary of clinical findings and neuropathology for characterised dominant repeat disorders[a] (tab001rmb)

Disease; gene; triplet expansion	Clinical findings	Neuropathology
Polyglutamine (gain of toxic function)		
HD; huntingtin; 6–35 vs 36–>200	Motor impairment, involving both voluntary and involuntary movements. Chorea is the classic symptom, but rigidity and dystonia are occasionally more prominent, especially in juvenile-onset cases. Abnormal eye movements, ataxia and dysphagia are common. Cognitive decline is universal, and psychiatric syndromes are common (Ref. 192)	Marked neuronal loss and gliosis of the striatium and cerebral cortex. Less consistent loss in thalamus, substantia nigra, olive, hypothalmus, and deep cerebellar nuclei (Ref. 193)
SBMA; androgen receptor; 9–36 vs 38–62	Males only. Proximal muscle weakness, muscle atrophy, and fasciculations. Patients often show gynecomastia, testicular atrophy, and reduced fertility due to androgen insensitivity (Ref. 194)	Selective degeneration of lower motor neurons in the anterior horn, bulbar region, and dorsal root ganglia (Ref. 195)
DRPLA; atrophin-1; 3–35 vs 49–88	Ataxia, choreoathetosis, dementia, and psychiatric disorders in adults; ataxia myoclonus, epilepsy, and dementia in children (Ref. 196)	Degeneration of cerebral cortex, cerebellar cortex, globus palidus, striatum, dentate, subthalamic and red nuclei. Intense gliosis and severe demyelination at sites of neuronal degeneration; occasionally calcification of the basal ganglia (Ref. 197)
SCA1; SCA1/ ATX-1; 6–38 vs 39–83	Universal gait and limb ataxia, dysarthria, and bulbar dysfunction. With progression, some have vibration and proprioception loss, abnormal saccades, nystagmus, ophthalmoparesis, mild optic atrophy, hypertonia (usually early), hypotonia (later), and decreased deep tendon reflexes. Late-stage findings include facial weakness, difficulties with swallowing or breathing, and extrapyramidal signs including dystonia and chorea (Ref. 198)	Degeneration of Purkinje cells, dentate, inferior olive, red nucleus, cranial nerve nuclei (especially 3rd, 10th and 12th), and sometimes substantia nigra, putamen, pallidum, and subthalamic nucleus (Ref. 199)
SCA2; SCA2; 14–31 vs 32–77	Near-universal gait and limb ataxia, dysarthria, and abnormal eye movements. Neuropathy, chorea or dystonia, and dementia are frequently present, and pyramidal signs are occasionally present (Refs 200, 201)	Degeneration of Purkinje and granule neurons, inferior olive, pontocerebellar nuclei, substantia nigra, striatum, Clarke's column of the spinal cord, and spinal ganglia; demyelination of the posterior columns and spinocerebellar tracts; sometimes cerebral cortex; dentate is spared (Ref. 202)
SCA3 (MJD); MJD; 12–40 vs 54–86	Wide spectrum, arbitrarily divided into four types: Type 1, with long repeats, young onset, dystonia and rigidity; Type 2 (the most common form), with onset age 20–45 years, and cerebellar and pyramidal signs; Type 3, with onset age 40–60 years, slow progression, and predominance of cerebellar signs and peripheral neuropathy; and possibly Type 4, with prominent parkinsonism (Ref. 203)	Degeneration of subthalamic nucleus, substantia nigra, dentate nucleus, pontine and cranial nerve nuclei (3rd, 4th, 6th, 7th, 8th and 10th) and spinal neurons. Occasional sensory and motor peripheral neuropathy. Relative sparing of cerebellar and cerebral cortex, inferior olive, caudate and putamen (Ref. 203)

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Table 1. Summary of clinical findings and neuropathology for characterised dominant repeat disorders (tab001rmb) *(continued)*

Disease; gene; triplet expansion	Clinical findings	Neuropathology
SCA7; SCA7; 4–35 vs 37–200	Near-universal visual loss, accompanied by gait and limb ataxia and dysarthria. Relatively common pyramidal signs, decreased vibration sense, dysphagia, ophthalmoplegia, sphincter dysregulation, and hearing impairment. Extrapyramidal signs relatively uncommon (Ref. 204)	Degeneration of retina, cerebellar Purkinje and granule cells, dentate nucleus, inferior olive, subthalamic nucleus, and spinal motor neurons (Ref. 205)
SCA17; TBP; 29–42 vs 47–63	Gait and limb ataxia, dementia, with later pyramidal and extrapyramidal signs, often including parkinsonism and either chorea or dystonia. Eye movements are normal. Seizures develop in many individuals at varying stages of the disease (Refs 55, 206)	Degeneration of small neurons in the caudate and putamen, Purkinje cells, thalamus, and frontal and temporal cortex (Refs 55, 214)
Alteration of normal protein function		
SCA6; CACNA1A; 4–19 vs 20–30	Cerebellar findings dominate the illness, particularly in the first ten years or so, although mild noncerebellar signs including ophthalmoplegia, spasticity, peripheral neuropathy, dysphagia and parkinsonism sometimes develop later in the course of the disease. The course is slowly progressive, and wheelchair use may not be required for 15 years (Refs 161, 207, 208)	Cerebellar degeneration with loss of Purkinje cells more severe than loss of granule neurons or neurons in the dentate nucleus; some neuronal loss in the inferior olive but only minimal brainstem atrophy (Ref. 209)
Alteration of gene expression		
SCA8; SCA8; 16–91? vs 107–127?	Clinical findings include limb and gait ataxia, dysarthria, spasticity, oculomotor abnormalities, and decreased vibration sensation. Progression is slow, such that mobility aids are not required for >20 years of illness duration (Ref. 210). Other case series noted similar findings, with the addition of tremor and frequent cognitive complications in a Finnish series (Ref.178) and a case of infantile onset in a Portuguese series (Ref.181)	MRI scans show cerebellar atrophy (Ref. 210)
SCA10; SCA10; 10–22 vs 750–4500	Progressive cerebellar ataxia and dysarthria, usually accompanied by seizures and psychiatric disturbances (depression and/or aggression). Nearly half of the affected individuals had pyramidal signs, and most had evidence of polyneuropathy and abnormal eye movements. Liver, cardiac and haematological abnormalities have been detected in a few pedigrees (Ref. 185)	MRI scans show cerebellar atrophy with little or no cortical or brain stem atrophy (Ref. 185)
SCA12; PPP2R2B; 7–28 vs 66–78	Begins with action tremor of the head and upper extremities and progresses to include a wide range of signs and symptoms, including mild cerebellar dysfunction, hyper-reflexia, subtle parkinsonian features, psychiatric symptoms, and, in some of the oldest subjects, dementia. Symptoms in most individuals begin in the fourth decade, and the disease is slowly progressive thereafter (Refs 187, 188, 191)	One brain examined: generalised atrophy of the CNS, predominantly affecting the cerebral cortex and cerebellum; marked Purkinje cell loss (Ref. 211)

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Table 1. Summary of clinical findings and neuropathology for characterised dominant repeat disorders (tab001rmb) *(continued)*

Disease; gene; triplet expansion	Clinical findings	Neuropathology
HDL2; junctophilin-3; 7–26 vs 41–57	Variable, but within broad HD phenotype. In some, prominent early weight loss, followed by rigidity, bradykinesia, dystonia, mild chorea, psychiatric syndromes, dementia and rapid decline; others with prominent chorea and slower course (Refs 173, 175)	Three brains examined: neuronal loss in striatum, cortex and other regions indistinguishable from HD (Refs 175, 176)

[a] Table based partly on Ref. 212, with permission from Current Medicine.
Abbreviations: ATX-1, ataxin-1; CACNA1A, voltage-dependent P/Q-type Ca^{2+} channel alpha A1 subunit; CNS, central nervous system; DRPLA, dentatorubral pallidoluysian atrophy; HD, Huntington's disease; HDL2, Huntington's disease-like 2; MJD, Machado-Joseph disease; MRI, magnetic resonance imaging; PPP2R2B, 55 kDa β subunit of protein phosphatase 2A; SBMA, spinal and bulbar muscular atrophy; SCA, spinocerebellar ataxia; TBP, TATA-binding protein.

role of nuclear localisation? Does polyglutamine expansion initiate apoptotic pathways via mitochondrial toxicity? Can polyglutamine toxicity be reversed? Although much of the data that we cite derives from studies of HD, the most intensely investigated of the polyglutamine disorders, we also include pertinent results from the other polyglutamine diseases. We recognise that this approach blurs the distinctions among these diseases, but our goal is to emphasise common themes and controversies. HD is covered in more detail in *Expert Reviews in Molecular Medicine* in Ref. 3.

The toxic gain-of-function hypothesis

The discovery of the polyglutamine-expansion diseases immediately suggested a loss-of-function hypothesis – that is, repeat expansion interfering with gene expression and resulting in haploinsufficiency, as it does in fragile X. It rapidly became clear that this supposition was wrong, and that pathogenesis most likely arises from a toxic gain-of-function mutation. First, very early data demonstrated that the CAG repeat expansions were both transcribed and translated, with equal levels of normal and mutant protein expression (Refs 4, 5). Overexpression of polyglutamine repeats (with various flanking sequences) in neuronal and non-neuronal cultured cells (Refs 6, 7, 8), transgenic mice (Refs 9, 10, 11, 12, 13, 14, 15, 16, 17), knock-in mice (Refs 18, 19, 20, 21, 22, 23, 24), *Drosophila* (Refs 25, 26, 27, 28, 29, 30) and *Caenorhabditis elegans* (Refs 31, 32, 33) typically results in cell toxicity, movement abnormalities, or aspects of neuropathology (see below) that reflect the human diseases. On the contrary, most knock-out mice with heterozygous deletions of *huntingtin* or *Sca1* do not show behavioural or neuropathological alterations (Refs 34, 35), and homozygotes have severe developmental deficits that do not resemble the deficits observed in polyglutamine-expansion diseases (Refs 34, 36, 37). This toxic gain of function is consistent with the clinical finding that rare patients homozygous for HD do not phenotypically differ from heterozygotes (Refs 38, 39). However, homozygosity might lead to a more severe phenotype in SCA3 (Ref. 40). In addition, patients and rodents with complete loss of the androgen receptor (the gene with the CAG repeat expansion in SBMA) develop an androgen insensitivity syndrome but not other features of SBMA (Refs 41, 42).

The possibility that a loss of huntingtin function might contribute to HD pathogenesis has recently re-entered the debate. It now appears that huntingtin might be necessary for proper neuronal function in adult mouse brain, with huntingtin expression necessary for normal nuclear and perinuclear membrane organelles, RNA biogenesis, iron homeostasis (Ref. 43) and vesicular transport (Refs 44, 45). The complete absence of huntingtin results in embryonic lethality (Refs 34, 36, 37), and elimination of huntingtin expression in adult mouse forebrain results in progressive neurodegeneration (Ref. 46). Of particular interest, polyglutamine expansion was shown to reduce the capacity of huntingtin

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to stimulate brain-derived neurotrophic factor (BDNF) in cortical neurons derived from transgenic mice overexpressing mutant huntingtin (Ref. 47). Loss of BDNF was also detected in human HD brain. This series of experiments suggests that loss of BDNF trophic support to striatal neurons may substantially contribute to the death of these neurons. Huntingtin with an expansion appears to recruit the normal huntingtin protein into aggregates, which might further potentiate the loss of huntingtin function (Ref. 48). Loss of huntingtin function might also contribute to pathogenesis by a novel nonreceptor-mediated pathway that activates caspase-8 and results in apoptosis (Ref. 49). It has also been suggested, at least in HD, that translation of expanded repeats could begin from an alternative site, shifting the reading frame so that the repeat would encode polyalanine (Ref. 50). Although polyalanine expansions may be toxic (Ref. 51), there is little other support for this mechanism.

Additional evidence that loss of function may contribute to aspects of the polyglutamine disease phenotype derives from the androgen insensitivity or testicular feminisation observed in SBMA, a consequence of loss of androgen receptor function (Refs 52, 53, 54). Polyglutamine-expansion-dependent loss of function of TATA-binding protein (TBP) might also contribute to the SCA17 phenotype (Ref. 55).

Structure of elongated polyglutamine tracts

Perutz originally suggested that normal protein conformation is destabilised by the presence of expanded polyglutamine tracts, which lead to abnormal protein–protein interactions and formation of β-sheet structures held together by hydrogen bonds (polar zippers) between their main-chain and side-chain amides (Refs 56, 57). In vitro experiments have shown that truncated huntingtin fragments with an expanded polyglutamine tract form amyloid-like protein aggregates with a fibrillar or ribbon-like morphology (Ref. 58). Recent evidence suggests that polyglutamine aggregation is an ordered process, resembling amyloid fibril formation in both assembly kinetics and aggregate structure, and might involve intermediaries similar to the protofibrils observed in amyloid fibril formation (Refs 59, 60).

Alternatively, the abnormal structure of polyglutamine expansions has been proposed to stem from transglutaminases, which crosslink glutamine repeats with lysine residues in other proteins through isopeptide bonds (Ref. 61). Although in vitro evidence has confirmed the potential for transglutaminase crosslinkage of protein with long tracts of polyglutamine (Refs 62, 63, 64, 65), transglutaminase activity has no effect on aggregation of a truncated huntingtin fragment containing an expanded polyglutamine tract in an HD cell model (Ref. 66). Evidence for the presence of γ-glutaminyl–lysyl bonds colocalising with expanded glutamine tracts within neuronal intranuclear inclusions would strengthen the transglutaminase hypothesis. It is possible that both polar zipper and enzymatic crosslinking contribute to aggregate formation.

Inclusions: cause or consequence?

The potential relevance of protein aggregates to polyglutamine disease was brought to the forefront when intranuclear inclusions containing the appropriate disease protein (ataxin-1, ataxin-3 or huntingtin) and ubiquitin were identified in neurons of SCA1, SCA3 and HD patients and HD transgenic mice (Refs 10, 67, 68, 69). Inclusions have since been found in SCA7 and DRPLA patient brain and transgenic mice modelling SCA7, DRPLA and SBMA (Refs 14, 70, 71, 72, 73), but are completely absent from the cerebellum of SCA2 patients, a key site of neurodegeneration (Refs 74, 75, 76). The distribution of aggregates is generally nuclear in brain regions most affected by the diseases, but can also be cytoplasmic and extranuclear (dystrophic neurites and neuropil aggregates). Aggregates have been detected in glia (Ref. 68) and tissue outside of the central nervous system (CNS) (Ref. 77). Immunohistochemical evaluations have shown that these inclusions not only contain the mutant protein (with long polyglutamine stretches stained by one of several antibodies relatively specific for expanded, but not normal, polyglutamine), but also ubiquitin, components of proteasomes, chaperones and transcription factors (see below).

The potential role of inclusions in pathogenesis has been addressed directly and indirectly using several model systems and by semiquantitative analysis of pathological samples (Ref. 78). However, it is now becoming clear that aggregations themselves are probably not an essential part of the pathogenic pathway. For example, in a well-characterised SCA1 transgenic mouse model in which ataxin-1 with an expanded glutamine is driven by the PcP2 promoter, the

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formation of intranuclear inclusions was dependent on the presence of the ataxin-1 self-association domain. Purkinje cell loss and abnormal behaviour was present whether or not this domain was part of the overexpressed ataxin-1 construct (Ref. 79), although Perutz suggested later that removal of the self-assocciation domain could itself result in abnormal folding of the protein and ataxic phenotype (Ref. 80). In a striatal cell model, transfection of an N-terminal huntingtin fragment under conditions that inhibited the formation of inclusions (blockade of ubiquitination) increased cell death (Ref. 81). Similarly, aggregations were not associated with cell death in primary neurons from a mouse model conditionally expressing mutant huntingtin (Ref. 16).

The observation that nuclear inclusions exist, and might even be more dense, in neuronal types that show little degeneration in a given disease also supports a dissociation of inclusion formation from neuronal toxicity. In HD patients, aggregates are primarily present in brain regions with little or no cell loss (Ref. 82). Lack of inclusions in affected neurons and their more frequent presence in neurons more resistant to neurodegeneration has also been reported for SCA2 and SCA7 (Refs 67, 75, 82, 83), although this relationship may be somewhat different in SBMA (Ref. 83). A similar dissociation has been detected in mouse models of HD (Ref. 84). In other mouse models, neuronal intranuclear inclusions occur only after the development of pathological and behavioural changes (Refs 16, 23, 85).

One possible explanation for the apparent lack of a direct association between inclusions and pathogenesis is that intermediates that arise during the process of aggregation are more toxic than the final resulting inclusions. This line of investigation has been in part motivated by the complex biochemical process leading to amyloid generation, which involves the step-wise accumulation of several intermediate species, including oligomers and protofibrils (Ref. 86). Intermediates have recently been reported in an in vitro model of huntingtin aggregation (Ref. 60) and 'microaggregates' have been detected in a SBMA transgenic mouse (Ref. 87). The toxicity of an intermediate stage of aggregation might explain the results of the experiment in which blockade of formation of large aggregates led to increased toxicity. Aggregate intermediates might be more accessible to other proteins (Ref. 80), and this could explain some of the effects of polyglutamine expansions on transcription described below. Recently, it was reported that the azo-dye Congo Red promotes the clearance of expanded polyglutamine in vitro and in a transgenic mouse model of HD (Ref. 88). Congo Red has the ability to bind to β-sheets containing amyloid fibrils (Ref. 89) and can inhibit oligomerisation (Ref. 90). In the infused animals, a protective effect of the chemical on weight loss, survival and motor performance was observed, suggesting a viable therapeutic approach.

Formation of insoluble aggregates might also represent a cellular mechanism to diminish toxicity of intermediate products of aggregation. Aggresomes are pericentrosomal cytoplasmic structures into which aggregated, ubiquitinated, misfolded proteins are sequestered via active transport by the cytoskeletal microtubular system, potentially representing a protective cellular response to excess amounts of misfolded proteins (Refs 91, 92). Evidence that cytoplasmic inclusions formed of polyglutamine protein resemble aggresomes derives in part from similarities of these inclusions to the aggregates observed in a cell model of familial amyotrophic lateral sclerosis. A potential role for aggresomes in polyglutamine pathogenesis is also supported by perinuclear accumulations of mutant huntingtin in human HD brain samples (Ref. 93), and the demonstration that microtubule disruption in yeast overexpressing mutant huntingtin results in decreased huntingtin aggregation but increased cytoxicity (Ref. 94).

Ubiquitin, proteasomes and chaperones

The observation that polyglutamine-disease aggregates stained for ubiquitin (Refs 10, 68, 69) raised the possibility that the ubiquitin-mediated proteolytic pathway might be affected by polyglutamine expansions. In this pathway, ubiquitin, a 76 amino acid peptide, is attached to a target protein at one or more lysine residues by a ubiquitin-conjugating enzyme (Ubc E2). Proteins can become mono- or polyubiquitinated. The polyubiquitinated proteins are transported to the 26S proteasome, a complex cytosolic and nuclear protease with an active 20S multicatalytic proteolytic core (Refs 95, 96). This system is one of the key mechanisms for clearing unneeded proteins from the cell, and disabling the system results in cell toxicity (Ref. 97). Detection by immunohistochemical methods of both ubiquitin

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and 20S proteasomes within Purkinje cell aggregates in brain from SCA1 transgenic mice and SCA1 patients provided further evidence that this system might be impaired in polyglutamine disease (Ref. 98). A later experiment demonstrated that ataxin-1 containing only two glutamines and ataxin-1 containing an expanded repeat with 92 glutamines become polyubiquinated to an equal extent, but ataxin-1 with an expanded polyglutamine tract was more resistant to proteasomal degradation (Ref. 99). Together, these findings led to the more specific hypothesis that proteins with expanded polyglutamines are misfolded and targeted for proteolysis, but are resistant to degradation. In support of this hypothesis, inhibition of proteasomal function in several different cell lines transfected with a truncated ataxin-3 fragment led to increased aggregation of mutant ataxin-3 (Ref. 100). In addition, clearance of aggregates in primary neurons derived from a reversible mouse model of HD (Ref. 16) is dependent on proteasomal activity (Ref. 101).

If misfolding of proteins with expanded polyglutamine stretches is indeed relevant to polyglutamine disease pathogenesis, as suggested by both structural analyses and the involvement of the ubiquitin–proteasome system, then molecular chaperones, which facilitate normal protein folding, should modify the pathogenic process (Ref. 102). Indeed, overexpression of molecular chaperones diminishes the toxicity of glutamine expansions in a number of in vitro, invertebrate and mouse model systems without necessarily reducing polyglutamine aggregation (Refs 103, 104). The HSP40 and HSP70 families of chaperones, which refold misfolded proteins (Refs 105, 106) and play a role in ubiquitin-dependent protein degradation (Refs 107, 108), appear to be of particular relevance. For instance, both the constitutive (Hsc70) and inducible (Hsp70) forms of HSP70 decrease aggregation of huntingtin and androgen receptor protein with expanded polyglutamine (Refs 109, 110), and overexpression of Hsp40/HDJ-1 and Hsc70/Hsp70 reduced toxicity in cell culture models of SBMA and HD (Refs 111, 112). In a *Drosophila* model of polyglutamine toxicity, Hsp70 suppresses neuronal degeneration with little effect on aggregates (Ref. 113). Similar results were observed in a mouse model of SCA1 (Refs 109, 110, 114, 115). Pharmacologically increasing the levels of certain chaperones might be of potential therapeutic value, as shown in an experiment in which geldanamycin-induced expression of Hsp40, Hsp70 and Hsp90 inhibited aggregation of a truncated huntingtin protein (Ref. 116).

Endosomal–lysosomal pathway

In addition to the ubiquitin–proteasome pathway, at least some processing of proteins with polyglutamine expansions might occur through the endosomal–lysosomal pathway (Ref. 117). Electron microscopic immunohistochemistry of DRPLA and SCA3 brain revealed the presence of neuronal intracytoplasmic granules containing expanded polyglutamine stretches. The granules corresponded predominantly to lysosomes of a primitive type. This is consistent with earlier data demonstrating the presence of lysosome-related structures containing mutant huntingtin in HD brain (Ref. 93). The endosomal–lysosomal–vacuolar pathway has also been linked to autophagy, a form of cell death characterised by the degradation of cytoplasmic proteins or organelles in lysosomes (Ref. 118). It has been suggested that autophagy might be induced by the accumulation of mutant huntingtin via stimulation of the endosomal–lysosomal system, leading to huntingtin proteolysis and autophagic cell death (Ref. 45). However, exactly the opposite could be the case: inhibition of the sequestration stage of autophagy was reported to increase aggregate formation and cell death in COS-7 cells overexpressing mutant huntingtin exon 1, suggesting agents that stimulate autophagy might have therapeutic potential (Ref. 119).

Proteolytic cleavage

The possibility of pharmacological intervention through inhibition of proteases has generated considerable interest in the role of proteolytic cleavage in polyglutamine pathogenesis. In human HD and SBMA tissue (Refs 71, 77), in an HD mouse model (Ref. 23) and in cell models (Ref. 7), polyglutamine inclusions stained with antibodies directed against N-terminal, but not C-terminal, huntingtin or androgen receptor epitopes, suggesting that the inclusions were composed of truncated huntingtin and androgen receptor. In transiently transfected 293T cells and an inducible NG108-15 cell model of HD, the length of the transfected mutant huntingtin, holding repeat length constant, correlated inversely with its potential to aggregate and

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trigger cell death (Refs 7, 120). Processed fragments of mutant protein have been detected in human SCA2 brain (Ref. 74), DRPLA transgenic mice and human brain (Ref. 14), SCA7 transgenic mice (Refs 72, 121), and a stable inducible HD cell model (Ref. 122). Recently, several transiently transfected neuronal (X57, X58, NG108-15) and non-neuronal (293T) cell models were used to detect a cleavage site in huntingtin that results in a fragment of similar size to that observed in HD human brain. Cleavage appears to be dependent upon the length of the polyglutamine repeat (Ref. 123). However, there is also evidence that cleavage might not be critical to polyglutamine pathogenesis. For instance, wild-type full-length huntingtin is more susceptible to cleavage than full-length mutant huntingtin in affected brain tissue (Ref. 124), and nuclear localisation appears to involve full-length huntingtin in a knock-in mouse model of HD (Ref. 23).

If cleavage occurs, what enzymes are responsible? Caspase activity has been suggested in numerous studies. Huntingtin has been shown to be a substrate of caspase-1 and caspase-3 (Refs 125, 126). Lymphoblasts derived from HD patients have previously been reported to exhibit increased stress-induced apoptotic cell death associated with caspase-3 activation (Ref. 127). Inhibition of caspase-1 and caspase-3 by minocycline delayed mortality in an HD transgenic mouse model (Ref. 128). Inhibiting caspase-3 and caspase-6 cleavage of huntingtin reduced toxicity and aggregate formation in neuronal and non-neuronal cells (Ref. 129). Caspases that do not cleave huntingtin directly might also play a role in HD. For example, caspase-8 is recruited to and activated by polyglutamine-containing aggregates, including aggregates in HD brains (Ref. 130). Mutation of caspase cleavage sites within the androgen receptor and atrophin 1 proteins renders them less toxic when expressed in cells exposed to an exogenous toxic stimulus, and prevents the formation of intracellular aggregates (Ref. 131). Evidence from human HD tissue and rat primary cortical neurons suggests a role for calpains (Ca^{2+}-dependent noncaspase cysteine proteases) in HD proteolysis (Refs 129, 132), and the possibility of sequential proteolysis of huntingtin by caspase-3 and calpain has been raised (Ref. 133). Most recently, evidence has emerged suggesting a role for pepstatin-sensitive aspartic endopeptidases in huntingtin cleavage (Ref. 122). The opportunity to block particular proteolytic enzymes pharmacologically is an intriguing approach to the prevention of polyglutamine toxicity, tempered by concern for nonspecific effects of such inhibition.

Toxicity within the nucleus and transcriptional dysregulation

Although, as discussed above, cytoplasmic processes such as protein misfolding, proteasomal processing, and aggresome formation may be important to polyglutamine disease pathogenesis, other lines of evidence suggest the possibility that nuclear events are central to pathogenesis. Manipulation of huntingtin by adding or removing nuclear localisation or export signals has generally suggested that nuclear localisation corresponds best to toxicity of polyglutamine tracts (Refs 81, 134). Use of truncated forms of polyglutamine-containing proteins in cell culture has focused attention on the mechanisms for nuclear entry, including the potential role of active transport and protein cleavage in nuclear translocation. The other issue is how entry into the nucleus might prove toxic. One potential mechanism is through disruption of transcription regulation. For instance, polyglutamine aggregates, or protoaggregates, might sequester transcription factors, including CREB-binding protein (CBP; an acetyl transferase) (Refs 135, 136) and Sp1 (Refs 137, 138), through their glutamine-rich domains, and impede transcription of genes dependent on these factors. Other transcription factors that might be similarly affected include TBP-associated factor ($TAF_{II}130$) (Refs 139, 140), the co-repressors N-Cor and mSin3a (Ref. 141), and the co-activators CA150 (Ref. 141) and p53 (Refs 135, 142). Interestingly, the proteins with polyglutamine expansions that cause SCA17 (TATA-binding protein) and SBMA (the androgen receptor) are themselves transcription factors (Ref. 55).

Transcriptional dysregulation might also provide a clue for the regional differences in neuronal degeneration among the polyglutamine disorders. The retinal degeneration that is characteristic of SCA7, for instance, might be at least partially accounted for by a specific interaction between ataxin-7 and the cone-rod homeobox protein (CRX), a transcription factor containing a polyglutamine reach region (Ref. 143). Polyglutamine (Q)-tract-binding protein 1 (PQBP-1), a repressive transcription cofactor of the neuronal transcription factor Brn-2 that is

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predominantly expressed in the cerebellum, interacts with ataxin-1 in a polyglutamine-dependent manner, resulting in the induction of cell death via apoptosis (Ref. 144). However, some mechanisms of transcriptional dysregulation might be common to multiple polyglutamine-repeat disorders. For instance, a large number of overlapping gene expression changes were detected in the cerebella of huntingtin and atrophin-1 transgenic mouse (Ref. 145). A subset of the changes was also observed in the cerebella of mice expressing mutant ataxin-7 and androgen receptor.

Another promising line of investigation, consistent with polyglutamine-induced dysregulation of transcription, focuses on the modulatory role of histone deacetylase inhibitors (Ref. 146). Polyglutamine toxicity in neuronal cell culture correlates with a deficiency in histone acetylation, an effect that can be reversed by treatment with histone deacetylase inhibitors (Ref. 30). HDAC inhibitors also ameliorated polyglutamine-induced neurodegeneration in *Drosophila* (Ref. 30) and motor deficits in the R6/2 line of HD transgenic mice (Ref. 147).

Mitochondria and polyglutamine toxicity

Mitochondria dysfunction has been implicated in the pathogenesis of multiple neurodegenerative diseases (Ref. 148), and pathways through which mitochondrial dysfunction leads to cell death have been partially elucidated (Ref. 149). The possibility that mitochondrial dysfunction could play a role in the pathogenesis of HD emerged with animal models developed prior to the discovery of the HD gene. 3-Nitropropionic acid (3-NP) and malonate inhibit succinate dehydrogenase, disrupting mitochondrial transmembrane potential with consequent generation of superoxide radicals, secondary excitotoxicity, and apoptosis. Systemic delivery of these agents to rodents results in selective neuronal loss in the striatum that mimics the pathology observed in HD (Refs 150, 151). Evidence that the HD mutation can disrupt mitochondria derives from analysis of lymphoblasts from HD patients (Ref. 127), which exhibited lower membrane potential and depolarisation at lower Ca^{2+} loads than control mitochondria. The same mitochondrial defect was detected prior to the onset of behavioural or neuropathological abnormalities in a yeast artificial chromosome (YAC)-transgenic mouse model expressing full-length mutant huntingtin (Ref. 152).

Polyglutamine diseases: pathways and therapeutics

As illustrated in Figure 1, the various pathogenic pathways discussed above suggest multiple approaches to therapeutic intervention. Each model system developed to explore these pathways has unique strengths and limitations as a method of screening for therapeutic agents (Ref. 153). The experience of the CARE-HD study (Ref. 154), the largest clinical treatment trial of a polyglutamine disease, demonstrated that the resources for performing high-quality patient trials are insufficient for launching more than a few such trials at any one time. It will therefore be important to test potential agents carefully in a variety of models before moving to work in patients.

Biochemical models, such as a system developed for screening aggregation formation (Refs 116, 155), can be extremely efficient, but are useful only to the extent that the particular process under study proves to be fundamental to disease pathogenesis. Cell models are easy to manipulate, and allow for assays of several outcomes, including aggregate formation, cell death, and biochemical processes such as protein cleavage. The idiosyncracies of the particular cell type under investigation must be carefully considered. Also, cell models might not reflect nonautonomous mechanisms of pathogenesis, such as the impact of glutamatergic cortical projection neurons on striatal neurons (Ref. 156). Slice models have recently been developed that keep intact such projections, although biochemical analysis of slices is more problematic than that of typical cell culture assays.

Mice present complexity approaching that of the human patient, but at the cost of slower speed of analysis and greater expense than other systems. Each mouse line has its own particular idiosyncracies. The R6/2 transgenic mouse line (Ref. 9) that overexpresses a short huntingtin fragment with an expanded polyglutamine tract is useful for assaying aggregate formation and behavioural responses, but the potential benefits of inhibition of huntingtin cleavage cannot be assessed. The mice might also have a latent diabetes (Ref. 157), and do not show clear neurodegeneration. Mice expressing YACs containing the full human huntingtin gene

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(Ref. 11), or mice in which an expanded repeat is inserted into the mouse huntingtin gene system (Ref. 158) nicely recapitulate the HD phenotype, but pathology develops only very slowly. The short time span for development of pathology in *Drosophila* or *C. elegans* lines that overexpress expanded polyglutamine, and the large number of animals that can be rapidly screened for genetic or pharmacological modifying factors, vastly increases efficiency over murine models, at the cost of a loss of system complexity. A recently developed rat transgenic model of HD may prove of value in neuroanatomic studies (Ref. 159).

None of the mouse HD models yet devised exhibits substantial loss of spiny medium neurons (the striatal cell type most profoundly affected in patients), and aberrant quantitative and spatial expression of huntingtin transgenes introduces additional variables that might be difficult to control. In partial answer to these problems, a new HD model has been developed based on lentiviral-mediated delivery of mutant huntingtin to rat striatum (Ref. 160). Rats injected with truncated huntingtin containing 82 glutamines developed intranuclear inclusions, then neuronal dysfunction. The phenotype progresses over three months, with drastic and dose-dependent degeneration of striatal neurons. The relative distribution of aggregates between nucleus and cell processes varied with the strength of the promoter used. In addition to recapitulating HD pathology, lentiviral models also can be tested across species, facilitating development of nonhuman primate models of polyglutamine pathogenesis. An alternative rodent model, employing a conditionally expressed truncated form of mutant huntingtin, was used to show that protein aggregation and behavioural abnormalities reverse when expression of the mutant protein is turned off (Ref. 16). This experiment suggests that removal or inactivation of the mutant protein might be an effective therapeutic strategy, even after the onset of clinical disease.

SCA6: repeat expansion and altered normal protein function

SCA6, a slowly progressive disease primarily involving the cerebellum, is caused by relatively small expansions in the CAG repeat within *CACNA1A*, the gene encoding the alpha(1)2.1 subunit of P/Q-type Ca^{2+} channel located on chromosome 19p13 (Ref. 161). Normal repeat length ranges from 4 to 19 triplets, whereas the disease range (overlapping with normal) is 19 to 30 triplets, well within the normal range for the other polyglutamine disorders and many other proteins (Ref. 162). The mean onset age is about 50 years, with longer expansions associated with early onset age. Repeat length is typically, although not universally, stable during vertical transmission. In SCA6 Purkinje cells, cytoplasmic and intranuclear inclusions were detected using 1C2, an antibody specific for expanded tracts of polyglutamine (Ref. 163), while antibodies specific to ataxin-6 recognised densely immunoreactive, oval or rod-shaped structures in the cytoplasm, but not nucleus (Ref. 164). Although a direct role of polyglutamine toxicity in SCA6 pathogenesis cannot be excluded, the relatively short size of the expansion makes such an explanation less likely. By contrast, there is evidence that the CAG expansion increases the density of the alpha1A voltage-dependent Ca^{2+} channel in the cell membrane, with a consequent overall increase in inward Ca^{2+} flux following channel activation (Ref. 165). The toxicity of the polyglutamine expansion is therefore most likely to be a result of an alteration of normal Ca^{2+}-channel function.

Additional support for this mode of pathogenesis derives from the existence of two disorders allelic to SCA6. Episodic ataxia type 2 (EA2) is characterised by constant and progressive cerebellar signs complicated by attacks of vertigo, visual disturbance, dysarthria, and ataxia responsive to acetazolamide (Refs 166, 167). Familial hemiplegic migraine (FHM) is characterised by migraine headaches, at times with accompanying ictal hemiparesis and in some families with progressive cerebellar degeneration (Ref. 168). The cause of these disorders are point mutations in *CACNA1A* (Ref. 169). The extensive phenotypical overlap among EA2, FHM and SCA6 (Refs 170, 171, 172) supports the notion that it is abnormalities within the alpha(1)2.1 subunit of P/Q-type Ca^{2+} channel that are essential to SCA6, rather than direct toxicity of the polyglutamine repeat. The relationship of disease to Ca^{2+} flux suggests that therapeutic strategies aimed at restoring normal Ca^{2+} homeostasis might be of value to all members of this disease class.

Repeat expansion and loss of gene expression

The common feature of the third class of autosomal dominant repeat-expansion

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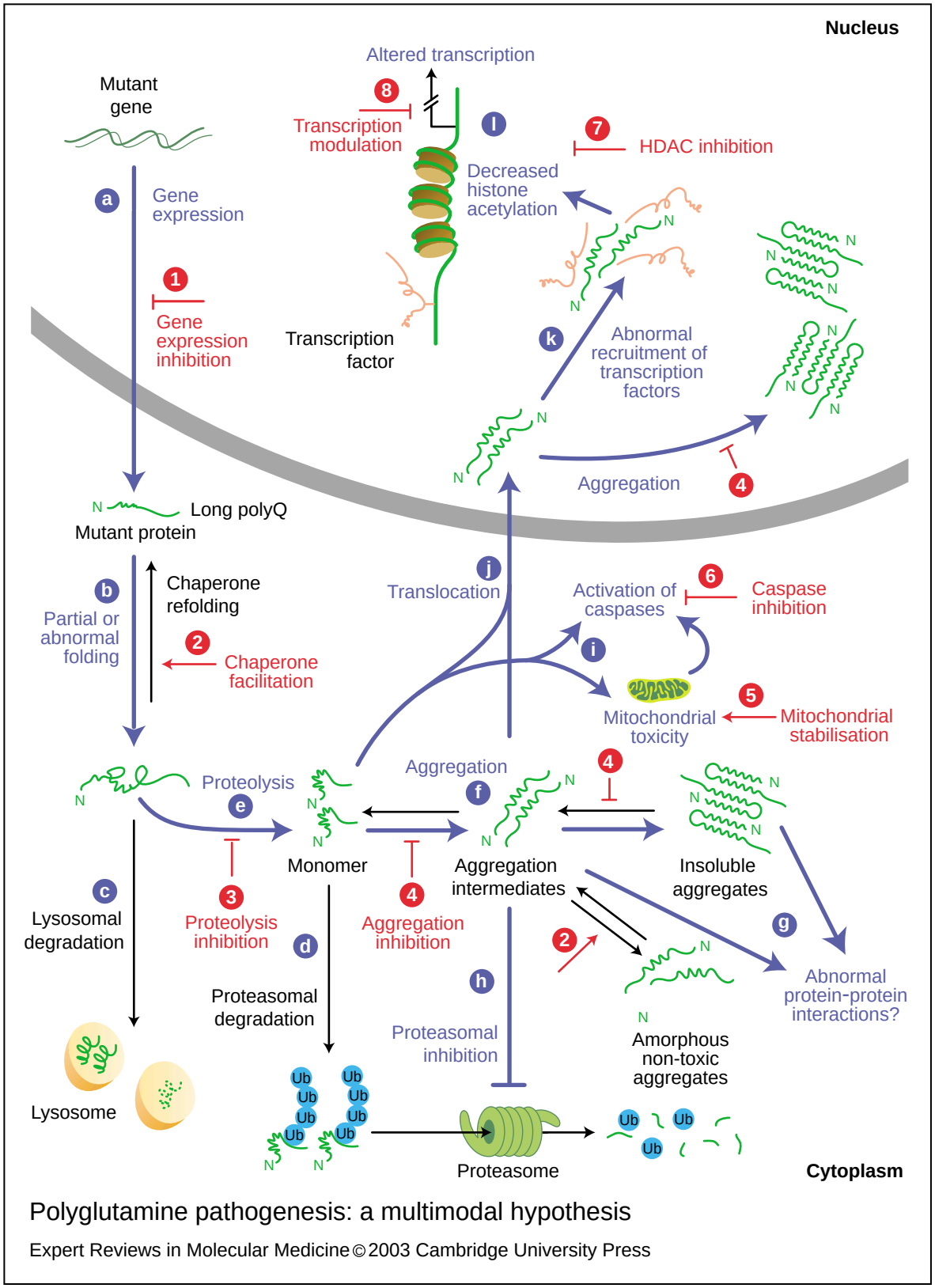

Polyglutamine pathogenesis: a multimodal hypothesis

Figure 1. Polyglutamine pathogenesis: a multimodal hypothesis (fig001rmb) *(see next page for legend).*

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Figure 1. Polyglutamine pathogenesis: a multimodal hypothesis *(legend; see previous page for figure).* Various pathogenic pathways have been suggested. As a simplification, they are depicted here as originating in the cytoplasm, although some of the disease proteins, including huntingtin, might also be located in the nucleus or cycle between the cytoplasm and nucleus. (a) The pathogenic process (blue arrows) begins with the synthesis of a protein with an expanded polyglutamine (polyQ) tract. (b) The expanded polyglutamine tract alters the native conformation of the protein, modulated by the presence of molecular chaperones. (c) At least a fraction of the abnormally folded protein is subjected to lysosomal-dependent proteolysis, and (d) another portion of the abnormal protein is ubiquitinated (Ub) and degraded via the proteasome. (e) Cleavage of the abnormally folded mutant protein produces an N-terminal fragment that favours the aggregation process. (f) The mutant proteins shift, in part, from a monomeric random coil or β-sheet into oligomeric β-sheets and eventually into insoluble aggregates (amyloid fibrils). (g) These might contribute to pathology through abnormal interactions with cellular proteins, or might represent a mechanism for reducing the toxicity of aggregation intermediates. (h) Aggregation intermediates inhibit proteasomal processing. (i) The monomers or oligomers directly activate caspases or disrupt mitochondrial function, leading to indirect activation of caspases. (j) Proto-aggregates translocate into the nucleus (by an unknown mechanism) and (k) recruit specific nuclear factors, co-activators and co-repressors, inhibiting their normal activities and (l) resulting in altered gene transcription (an example is the loss of function of proteins with histone acetyltransferase activity). The pathogenic pathways depicted here suggest a number of potential sites for therapeutic intervention (indicated in red). These include: (1) inhibition of expression of the mutant protein at the level of transcription or translation; (2) facilitation of chaperone function; (3) inhibition of proteolysis; (4) inhibition of aggregation (by enhancement of chaperones or by pharmacological agents such as Congo Red that suppress formation of intermediates or protofibrillar assembly into insoluble aggregates); (5) mitochondrial stabilisation (agents such as creatine that protect against bioenergetic dysfunction); (6) caspase inhibition; (7) inhibition of histone deacetylase (HDAC) activity; and (8) modulation of transcription that is adversely affected by mutant huntingtin. This model is most representative of HD pathogenesis, but also pertains, in part, to other polyglutamine diseases **(fig001rmb).**

neurodegenerative disorders (HDL2, and SCAs 8, 10 and 12) is that the causative repeat expansion is not in an open reading frame. The effect of the expansion on each gene appears to be different, but it is possible that the net effect of the expansion in all four diseases is a change in gene expression. The consequences of the expansion mutation would be expected to vary based on the function of each gene. One therapeutic strategy for these diseases might consist of restoring gene expression to normal, either through preventing the mutation from affecting gene expression, or by increasing or decreasing gene expression to compensate for the effect of the mutation. However, downstream approaches to blocking neurodenegeration might be more feasible, especially since each of the following diseases is quite rare.

HDL2: loss of function and dysregulation of Ca^{2+} flux?

HDL2, currently reported in 18 pedigrees of African ethnicity and one Mexican pedigree, is strongly associated with a CTG repeat expansion in the junctophilin 3 (*JPH3*) gene on chromosome 16q23.4 (Ref. 173). The junctophilins are a family of proteins that form a component of the junctional complex between the plasma membrane and the endoplasmic or sarcoplasmic reticulum. This physical coupling might facilitate the functional coupling between cell-surface voltage sensors and intracellular Ca^{2+} channels (Ref. 174). The CTG repeat is 760 nucleotides 3' to exon 1 of*JPH3*. Exon 2A, containing the repeat, is not expressed as part of the normal full-length *JPH3* mRNA. However, alternative splice products exist in which *JPH3* exon 1 is spliced to alternative splice acceptor sites in exon 2A (which then becomes the terminal exon), such that the repeat is variably in a 3' untranslated region, in frame to encode polyalanine, or in frame to encode polyleucine. There is little evidence of a transcript on the reverse strand. Intranuclear inclusions that stain with the 1C2 antibody that is allegedly specific for expanded polyglutamine expansions have been reported in the three HDL2 brains that have come to autopsy (Refs 175, 176; R. Margolis, unpublished), but the presence of 1C2-positive inclusions in SCA6 brain suggests that the antibody may detect epitopes other than very long polyglutamine tracts. Given the putative function of JPH3 as a modulator of Ca^{2+} flux, a mutation-induced loss of function of this allele in HDL2 is an attractive but as yet unproven hypothesis.

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SCA8: expansion in an untranslated gene

SCA8 remains the most controversial of the SCAs. The disease was initially defined in 1999 when a CTG/CTA repeat expansion in an untranslated gene on chromosome 13q21 was found to segregate with SCA in a large Minnesota pedigree (Ref. 177). Repeat length in affected individuals ranged from 107 to 127 triplets, whereas unaffected expansion carriers had repeat lengths of 71 to 101 CTG triplets. Almost all expanded alleles were maternally inherited, with paternal transmissions usually resulting in a marked repeat contraction. The mean onset age of disease in this family is 39 years (range 13 to 65). SCA8 might account for as many as 3–6% of cases of autosomal dominant cerebellar ataxia and some sporadic cases, but the calculation is impeded by the potentially high rate of nonpenetrance of the SCA8 expansion. Expansions (defined as repeats of 100 or more triplets) have been detected in 1–3% of many (Refs 178, 179, 180), but not all (Refs 177, 181), control populations. Even if the worldwide prevalence of the expansion is only 0.1%, the number of individuals with nonpenetrant expansions would exceed the total number of all dominant cerebellar ataxia cases by a factor of between 10- and 100-fold, creating considerable difficulties in interpreting SCA8 genetic test results. The debate continues about whether the SCA8 mutation is causative but of low penetrance, or is in linkage disequilibrium with another mutation. The likelihood of the latter possibility increased with the recent finding that a point mutation in fibroblast growth factor 14, on chromosome 13q34, results in a dominant cerebellar ataxia (Ref. 182).

The proposed mechanism of SCA8 pathogenesis is unique among neurodegenerative disorders. The *SCA8* gene itself is not translated into protein, but overlaps the transcription and translation start sites and the first splice junction of *KLHL-1*, a gene on the antisense DNA strand from *SCA8* (Ref. 183). *KLHL-1* encodes a 748 amino acid protein, expressed in multiple brain regions and in some tissues outside the CNS, with structural similarities to a family of proteins involved in the organisation of the cytoskeletal protein actin. The working hypothesis is that *SCA8* normally regulates expression of *KLHL-1* through an RNA–RNA interaction, and that an *SCA8* repeat expansion alters this regulatory activity. However, it is possible that the repeat expansion has other effects at the RNA level or alters expression of other nearby genes.

SCA10: the first pentameric-repeat-expansion disease

SCA10, found in five pedigrees from Mexico (Refs 185, 186), is caused by an expansion of an ATTCT pentanucleotide repeat located within intron 9 of *SCA10*, a gene of unknown function located on chromosome 22q13-qter. The normal length of the repeat is 10 to 22 pentamers, whereas affected individuals carry an expanded allele varying in length from ~800 to 4500 pentamers. There is marginal correlation between age of onset and repeat length. The mode of pathogenesis remains unknown, although it seems plausible that the repeat expansion disrupts *SCA10* expression. The precedent for this type of pathogenesis is in Friedreich's ataxia, a recessive disorder usually caused by a long intronic GAA repeat that blocks expression of the frataxin gene.

SCA12: altered phosphatase activity?

SCA12 was initially identified in a large American pedigree of German descent and has been subsequently identified in multiple Indian pedigrees (Refs 187, 188), perhaps accounting for 6% of all dominant SCA cases in India. SCA12 is caused by a CAG repeat expansion in the gene encoding PPP2R2B (Ref. 189), a brain-specific regulatory subunit of a ubiquitous enzyme, protein phosphatase PP2A, which is involved in multiple cellular functions. Normal repeat length in the population is 7 to 32 triplets, whereas expanded repeats range from 55 to 78 triplets (Ref. 190). There is no clear association between repeat length and age of SCA12 onset, although repeat length is modestly unstable during vertical transmission. Preliminary analysis of the single SCA12 brain that has come to autopsy revealed diffuse atrophy, including loss of cerebellar Purkinje cells, with no evidence of abnormal tau accumulation (Ref. 191). Preliminary findings suggest that the repeat occurs in a functional promoter region, and that the SCA12 mutation alters the expression of PPP2R2B (Ref. 190), which could in turn shift the substrate preference for PP2A, with potentially lethal consequences.

Outstanding questions and clinical implications

The available evidence suggests that repeat expansion leads to dominant neurodegenerative

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diseases by one of three mechanisms: polyglutamine toxicity, altered normal protein function, and altered gene expression. Why is repeat expansion mutation frequently the aetiology of neurodegenerative processes, yet rarely of other diseases? For the polyglutamine diseases, the answer appears to lie in the realm of specific neuronal vulnerability to long stretches of glutamine, and the frequency with which polyglutamine-containing proteins are expressed in the CNS. For the other two classes of disorder, the answer is less clear. Part of the explanation is probably a bias towards searching for repeat expansions in rare dominant disorders of the CNS, and perhaps the frequency with which rare dominant disorders occur in the CNS relative to other organ systems.

Many questions with important clinical implications remain only partially answered. Polyglutamine expansion is clearly toxic, but is loss of function of normal polyglutamine-containing proteins a contributing factor? If this loss is important, can it be reversed by blocking aggregation? Is polyglutamine aggregation directly toxic? Much evidence now suggests that the aggregates reflect the end-product of more-toxic intermediates. What is the relative importance and interrelationship of pathways that involve proteolysis, proteasomal degradation, mitochondrial toxicity, oxidative stress, and transcriptional dysregulation? Is blocking one pathway sufficient to stop the phenotype? What other pathways may be involved? For the non-polyglutamine-repeat diseases, the key questions involve how the expansion alters gene expression, and what the effect of altered expression may be.

More importantly, what is the most feasible therapeutic approach to these disorders? The early pathogenic stages that may be common to all (or most) of the polyglutamine disorders, such as the early stages of aggregate formation, proteolysis, or nuclear import, make intriguing targets (Fig. 1). While the rarity of the other repeat-expansion diseases might preclude development of specific therapies, strategies designed to block common final pathways of neurodegeneration might be universally beneficial.

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Further reading, resources and contacts

The following websites provide general information and other links about Huntington's disease and related disorders:

National Ataxia Foundation

http://www.ataxia.org/

Hereditary Disease Foundation

http://www.hdfoundation.org/

Huntington's Disease Society of America

http://www.hdsa.org/

Division of Neurobiology, Department of Psychiatry, Johns Hopkins University School of Medicine

http://www.hopkinsmedicine.org/bhdc/

Features associated with this article

Figure
Figure 1. Polyglutamine pathogenesis: a multimodal hypothesis (fig001rmb).

Table
Table 1. Summary of clinical findings and neuropathology for characterised dominant repeat disorders (tab001rmb).

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