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The expanding role for chromatin and transcription in polyglutamine disease

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Abstract

Nine genetic diseases arise from expansion of CAG repeats in seemingly unrelated genes. They are referred to as polyglutamine (polyQ) diseases due to the presence of elongated glutamine tracts in the corresponding proteins. The pathologic consequences of polyQ expansion include progressive spinal, cerebellar, and neural degeneration. These pathologies are not identical, however, suggesting that disruption of protein-specific functions is critical to establish and maintain each disease. A closer examination of protein function reveals that several act as regulators of gene expression. Here we examine the roles these proteins play in regulating gene expression, discuss how polyQ expansion may disrupt these functions to cause disease, and speculate on the neural specificity of perturbing ubiquitous gene regulators.

Keywords

polyglutamine; polyQ; spinocerebellar ataxia; trinucleotide expansion disease; transcription; RNA processing; gene expression; neurodegenerative disease; chromatin; histone modifications; acetyltransferase; deubiquitinase

Introduction

The search for causative mechanisms among polyQ diseases continues and, at this time, it remains unclear whether the associated genes impact different points within the same biological pathway, or whether they ultimately affect neurodegeneration via different routes. Many hypotheses regarding the mechanism of polyQ disease have been postulated, one being that dysregulation of transcription is causative. Our understanding, however, of the mechanisms underlying transcriptional and post-transcriptional deregulation in polyQ disease remains incomplete. Thus, we are unable to weigh the contribution of imbalanced gene expression to the corresponding pathology.

Previous studies comparing gene expression profiles among PolyQ disease models have found genes commonly misregulated between diseases, but none have revealed the genes or

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pathways responsible for neurodegeneration [1,2]. Additionally, it is not clear which changes in gene expression in these early studies reflected primary or secondary effects. Therefore, the questions remain: Is misregulation of critical genes causative in each polyglutamine disease? Is misregulation of these genes common to multiple diseases? Can we develop therapeutic interventions to alleviate the consequences of misregulated gene expression? Here we review the evidence for polyQ-mediated effects on transcriptional regulation and chromatin modification, and consequent transcriptional dysregulation in polyglutamine diseases.

Polyglutamine expansion diseases and regulation of gene expression

Nine inherited neurodegenerative diseases are a consequence of genetic instability that leads to expansion of CAG repeats in seemingly unrelated genes (Table 1). These CAG repeats cause expanded polyglutamine tracts (polyQ) in the corresponding proteins. Repeat length increases intergenerationally, and increased repeat length correlates with severity of disease and time to onset of disease symptoms. PolyQ diseases manifest as progressive degeneration of the spine, cerebellum, brain stem and, in the case of spinocerebellar ataxia 7 (SCA7), the retina and macula. Though they all lead to neural degeneration, different diseases are initially diagnosed by very specific symptoms and patterns of neuronal death. As these diseases progress, extensive neurodegeneration can lead to overlapping patterns of cell death [3]. Currently, no effective treatment for these fatal diseases is available [4].

Early histological and immunohistological analyses showed that polyglutamine-expanded proteins, or even a polyglutamine stretch alone, can form intranuclear aggregates that contain transcriptional regulatory proteins [5]. Titration of these factors seemed a likely cause of polyQ toxicity, but some studies have suggested that these inclusions may sometimes play a protective role [6]. Furthermore, inclusions are not observed in SCA2 [7,8], and intranuclear inclusions are not necessarily indicative or predictive of cell death in polyQ models and patient samples. In addition, although the essential lysine acetyltransferase (KAT) and transcriptional coactivator cAMP-response element-binding (CREB) binding protein (CBP) are sequestered in aggregates formed by mutant Ataxin-3 or huntingtin, they can move in and out of aggregates formed by Ataxin-1 [9]. Thus, localization of proteins to nuclear inclusions does not always reflect functional sequestration, and may not be a common cause of PolyQ toxicity.

Increasing evidence suggests that PolyQ proteins regulate gene expression and indeed, many of the 9 CAG-expanded genes are transcription factors, transcriptional coactivators, and regulators of RNA stability (Figure 1 and Table 1). Furthermore, analysis of gene expression profiles indicates that a large number of genes are deregulated in mouse models of polyQ disease [10]. We speculate that deregulation of the transcriptional program may be central to polyQ disease aetiology. Accordingly, we hypothesize that closer examination of the transcriptional basis for polyQ disease will yield new avenues for therapeutic intervention.

Huntington Disease

Huntington disease is caused by polyglutamine expansion of the Huntingtin (Htt) protein [11]. Nearly two decades ago, post-mortem brain samples with the initial histological signs

of Huntington disease showed deregulation of transcripts for enkephalin and substance P prior to onset of clinical symptoms [12]. These observations suggested that early changes in transcriptional regulation contributed to the onset of clinical symptoms. Subsequently, mouse models for Huntington disease showed altered expression of genes involved in neurotransmission, stress response, and axonal transport prior to the onset of disease symptoms, suggesting neural-specific deregulation of transcriptional control [13]. Among the many interacting partners of Htt are important transcriptional regulators such as specificity protein 1 (Sp1), TATA-box-binding protein-associated factor II, 130 kDa (TAFII130) [14], CREB, tumor protein p53 (TP53), SIN3 transcription regulator family member A (Sin3a) [15], K (lysine) acetyltransferase 2B (KAT2B/PCAF), CBP, and repressor element 1(RE1)-silencing transcription factor REST [16]. Although CBP and its close homolog E1A binding protein p300 (EP300/p300) are often functionally redundant, and commonly referred to as CBP/p300, polyQ expanded Huntingtin correlates with the degradation of only CBP [17]. CBP is associated with histone H3K27 acetylation, a potential marker for enhancers that are active but not inactive or poised [18]. Thus, perturbation of gene expression by Htt may occur through changes in epigenetic marks such as H3K27ac.

Studies suggest that polyQ Htt interferes with transcriptional activation by sequestering transcription factors. For example, overexpression of Sp1 and TAFII130 rescues polyQ Htt-mediated inhibition of the dopamine D2 receptor gene, protecting neurons from Htt-induced cellular toxicity [14]. PolyQ Htt can sequester CBP and PCAF, reducing histone acetylation and expression of CBP-regulated genes [15,19]. Accordingly, overexpression of CBP can rescue neuronal toxicity in a mouse model of Huntington disease [19]. PolyQ Htt also reduces WT Htt function. For example, Htt normally sequesters REST in the cytoplasm, preventing repression of the neuroprotective brain-derived neurotrophic factor (BDNF). PolyQ Htt disrupts this interaction, reducing BDNF expression and, consequently, causing loss of neurons [20]. Wild-type Htt can also interact with methyl CpG binding protein 2 (MeCP2), resulting in its localization to methylated gene promoters and reduced expression of the downstream genes. PolyQ expansion increases Htt's interaction with MeCP2 and its localization to the BDNF promoter, causing stronger repression of BDNF. SiRNA-mediated knock-down of MeCP2 alleviates this effect, restoring expression of BDNF [21]. Thus, PolyQ Htt reduces BDNF levels through a combination of sequestration of the REST transcription factor in the cytoplasm and stronger repression at the methylated BDNF gene.

Histone methylation is altered in Huntington disease patient brains through elevated levels of the H3K9 methyltransferase ERG-associated protein with SET domain (ESET). While the contribution of altered methylation and the consequent changes in transcription to polyQ disease are not clear, the reduction of H3K9 trimethylation by pharmacological treatments increases lifespan by 40% in a mouse model and suggests histone methylation as a potential therapeutic target in humans [22].

Spinal and bulbar muscular atrophy (SMBA), or Kennedy's disease

SBMA is caused by polyglutamine expansion in the transactivation domain of the androgen receptor (AR) [23]. AR is a steroid hormone-dependent transcription factor that binds to

androgen response elements in target genes when associated with testosterone or dihydrotestosterone. AR then recruits transcriptional co-activators and promotes gene expression. Polyglutamine expansion of its glutamine-rich transactivation domain interferes with AR binding to coactivators such as p160 and components of the basal transcription apparatus TFIIF and TBP. It remains to be determined whether H3R17 methylation, H3S10 phosphorylation, and H3K4 methylation, all of which are regulated dynamically during normal AR-mediated gene expression, are impacted by its PolyQ expansion [24].

Dentatorubral pallidoluysian atrophy (DRPLA)

DRPLA is caused by polyglutamine expansion of the gene encoding the atrophin-1 protein, which leads to significant degeneration in the brain and spinal cord [25]. Histologically, higher order chromatin architecture appears to be drastically altered in patient brain samples [26]. Atrophin-1 is a member of a small family of proteins that interact with nuclear receptors and function as co-repressors. The members of this family include Atrophin-1 and arginine glutamic acid repeats encoded protein (RERE, or Atrophin-2) in vertebrates, and Atrophin (Atro or Grunge) in *Drosophila* [27]. Atrophin-1 can repress transcription in reporter gene assays and sequesters transcriptional regulators into nuclear matrix-associated inclusions. Some of these regulators include Sin3A, histone deacetylases (HDACs), and runt-related transcription factor 1; translocated to, 1 (cyclin D-related) (RUNX1T1/ETO/MTG8) – a component of nuclear receptor co-repressor complexes [28]. Atrophin-1 contains five PY motifs (PPXY) proximal to the region susceptible to polyglutamine expansion. These motifs interact with Trp-Trp (WW) domain-containing proteins [29]. Accordingly, atrophin-1 interacting partners include WW domain containing members of the Nedd-4 family of E3 ubiquitin ligases. Nedd-4 proteins regulate ubiquitin-mediated trafficking, protein degradation, and nuclear translocation of various transcription factors [30,31].

In *Drosophila,* Atrophin binds to the histone methyltransferase G9a and mediates monoand di-methylation of H3K9. In humans, RERE also associates with G9a to methylate histones. *Drosophila* Atrophin and RERE interact with G9a through conserved SANT (switching-defective protein 3 (Swi3), adaptor 2 (Ada2), nuclear receptor co-repressor (N-CoR) and transcription factor (TF)IIIB) domains. Atrophin-1 does not contain a SANT domain but interacts with RERE, suggesting that Atrophin-1 and RERE might act together to regulate histone methylation [32].

Spinocerebellar ataxia 1 (SCA1)

SCA1 is caused by polyglutamine expansion of the *Ataxin-1* gene, which encodes two proteins – Ataxin-1 and alt-Ataxin-1. Alt-Ataxin-1 is produced by an out-of-reading-frame coding sequence within Ataxin-1. These gene products can interact with each other and with poly(A)(+) RNA [33]. An early screen performed in *Drosophila* to identify modifiers of SCA1-mediated neurodegeneration identified genes important for RNA processing and transcriptional regulation, [34]. Ataxin-1 also inhibits transcription from the Hey1 promoter, a critical gene in Notch signaling, where it is recruited through interaction with the recombination signal binding protein for immunoglobulin kappa J region (RBPJκ) transcription factor [35]. It has also been proposed that Ataxin-1 plays a general role in transcriptional repression. Polyglutamine expansion of Ataxin-1 increases its interaction

with poly-glutamine (Q) tract-binding protein-1 (PQBP-1) which, in turn, stimulates PQBP-1 binding to RNA polymerase II (Pol II) and reduces Pol II phosphorylation and transcription [36].

Ataxin-1 associates with protein phosphatase 2A (PP2A), and overexpression of Ataxin-1 in mice stimulates PP2A activity. However, whereas overexpression of wild-type Ataxin-1 led to a 59% increase in PP2A activity, overexpression of polyglutamine-expanded Ataxin-1 resulted in a 238% increase [37]. PP2A affects H3S10 phosphorylation, and its overexpression causes a genome-wide reduction in H3 phosphorylation [38]. The effect of Ataxin-1 PolyQ expansion on H3 phosphorylation has not been examined.

Spinocerebellar ataxia 2 (SCA2)

Polyglutamine expansion in the Ataxin-2 gene contributes to two diseases. SCA2 is caused by expansions of 32-200 CAGs, and intermediate expansions of 27-39 CAGs were identified as a genetic risk factor for amyotrophic lateral sclerosis (ALS) [39,40]. At this time, intermediate expansion of Ataxin-2 is the best-known predictor of ALS [39]. Ataxin-2 is an RNA binding protein and it regulates gene expression post-transcriptionally through interactions with mRNA and other RNA-binding proteins. Among these interactions is the RNA binding protein Ataxin-2 binding protein 1 (A2BP1),[41]. Ataxin-2 and A2BP1 interact and colocalize in vivo, but their functional relationship is unknown. Ataxin-2 also binds to the DEAD/H-box RNA helicase DDX6, and the poly(A) binding protein 1 (PABP-C1), both components of P-bodies and stress granules [42,43]. PABP-C1 also forms a protein-mRNA complex with Ataxin-2 in polyribosomes. In this complex, PABP-C1 and Ataxin-2 bind to each other and each maintain direct contact with RNA. Interestingly, polyglutamine expansion does not interfere with Ataxin-2 assembly with polyribosomes, suggesting that polyglutamine expansion of Ataxin-2 might interfere with translational regulation [43]. Interestingly, Ataxin-2-mediated regulation of PERIOD translation is required for maintaining circadian clock function in pacemaker neurons that set daily rhythms for behavior and synchronize transcriptional rhythms to the circadian clock organism-wide [44,45]. Sassone-Corsi and co-workers discuss this process further in this issue.

Spinocerebellar ataxia 3 (SCA3), or Machado-Joseph disease

SCA3 is caused by polyglutamine expansion of the Ataxin-3 gene and is the most common inherited cerebellar ataxia in some populations [46]. The Ataxin-3 protein is a transcription factor and can bind directly to gene promoters in chromatin [47]. It is also a Josephin domain-containing ubiquitin protease that binds to and deubiquitinates poly-ubiquitin chains on histone H2B [48]. Ataxin-3 normally interacts with numerous transcriptional regulators including the forkhead box O (FOXO)-4 transcription factor, TATA-binding protein-associated factor TAFII130 [56], CBP [57], nuclear co-repressor receptor NCoR [49], histone deacetylases [47], and DNA repair protein RAD23 [50]. Thus, it seems capable of recruiting transcriptional regulators to gene promoters through its interactions with both DNA binding proteins and non-DNA binding chromatin regulatory factors. Once there, it can function to deubiquitinate histone H2B. Accordingly, Ataxin-3 ubiquitin protease activity is indispensable for gene activation [47].

Upon oxidative stress, Ataxin-3 shuttles with the FOXO-4 transcription factor into the nucleus, where they bind and activate the manganese superoxide dismutase (SOD2) gene promoter. Polyglutamine expansion impairs Ataxin-3 transactivation function by preventing recruitment of co-activators, and SOD2 expression is reduced in the brains of SCA3 patients [51]. It is tempting to speculate that histone deubiquitination is disrupted in SCA3 and that a balance of H2B ubiquitination is important for maintenance of neural stability. Wild-type Ataxin-3 can also recruit histone deacetylase 3 (HDAC3) and nuclear receptor corepressor 1 (NCoR) to the matrix metalloproteinase-2 (MMP-2) promoter, resulting in histone deacetylation and transcriptional repression [47]. PolyQ Ataxin-3 binds chromatin but does not recruit HDAC3 or NCoR, reducing the HDAC activity of the Ataxin-3-containing complexes [47] and eliminating repression of genes such as MMP2. In addition, bulk H3 acetylation is higher in cells expressing PolyQ-expanded Ataxin-3 [47]. This intimate interplay between Ataxin-3, transcription factors and chromatin modifiers, along with the ability of Ataxin-3 to deubiquitinate histones, provides ample opportunity for misregulation of chromatin modifications in SCA3.

Spinocerebellar ataxia 6 (SCA6)

SCA6 is caused by polyglutamine expansion of the bicistronic calcium channel, voltage-dependent, P/Q type, alpha 1A subunit (CACNA1A) gene, which encodes two protein products – the α1A voltage-dependent calcium channel subunit and the α1ACT transcription factor [52]. Full-length CACNA1A mRNA produces the α1A ion channel subunit. The α1ACT transcription factor is produced from a cryptic internal ribosomal entry site (IRES) in the 3’ end of the transcript [52]. Polyglutamine expansion occurs in both gene products. This expansion does not perturb calcium channel gating in knock-in studies [53]. However, expression of the expanded α1ACT alone is sufficient to cause the SCA6 phenotype [54-57]. The α1ACT protein normally coordinates expression of many genes involved in neural and Purkinje cell development. PolyQ expanded α1ACT lacks transcription factor activity yet forms intra-nuclear inclusions that co-localize with the CREB transcription factor [52,58]. It is unclear whether the disease phenotype results from the lack of expression of normal α1ACT target genes or, perhaps, perturbed expression of CREB target genes.

Spinocerebellar ataxia 7 (SCA7)

SCA7 is the most prevalent SCA disease in Scandinavian populations and is caused by expansion of the *ATXN7* gene, which encodes the Ataxin-7 protein. Ataxin-7 is a subunit of the chromatin modifying Spt-Ada-Gcn5-Acetyltransferase (SAGA) complex. This highly conserved, multi-protein complex is comprised of approximately 20 subunits and is an essential transcriptional coactivator that regulates a large number of genes [59]. The complex bears two histone-modifying activities: the Gcn5/KAT2 acetyltransferase and the ubiquitin specific protease 22 (USP22) deubiquitinase. SAGA acetylates H3K9 and H3K14, as well as other residues in histone H3 and the linker histone H1. USP22 deubiquitinates histone H2Bub and H2Aub. which are important marks for transcription activation and elongation [60,61].

Within the SAGA complex, Ataxin-7 tethers the deubiquitinase and histone acetyltransferase (HAT) modules to each other. Crystal structures of the Saccharomyces cerevisiae deubiquitinase module have shown that the amino terminus of Ataxin-7 is embedded within the module [62,63]. Polyglutamine expansion occurs within the amino terminus, and the repeat length can be very large (Table 1) [64]. H3K9 acetylation is decreased upon polyglutamine expansion of Ataxin-7 [65-67], indicating that the expanded protein impairs the GCN5 activity within the SAGA HAT module. In some models, deubiquitinase activity is also impaired, and the level of ubiquitinated histones increases. The mechanism underlying perturbation of histone deubiquitination upon PolyQ expansion of Ataxin-7 is unknown [68], including whether the deubiquitinase module assembles and functions properly.

Spinocerebellar ataxia 17 (SCA17)

SCA17 is caused by polyglutamine expansion of the TATA box-binding protein (TBP), a general transcription factor at the core of the Transcription Factor II D (TFIID) complex [69]. TBP binds to the TATA box and facilitates assembly of the RNA polymerase II pre-initiation complex (PIC). Accordingly, TBP is responsible for regulation of a large number of genes. Polyglutamine expansion occurs in the TBP C-terminus and increases its association with transcription factors that include TFIIB and NFY [70]. However, DNA binding is reduced, slowing the rate of transcription complex formation and, consequently, transcription initiation [71].

Polyglutamine diseases: expanding possibilities?

It is apparent from the above discussion that these nine particular genes are expressed in many cell types and their gene products regulate the expression of a large number of genes. Intriguingly, the consequences of interfering with protein function by PolyQ expansion manifest as very specific disease pathologies. Even within the brain, different regions appear to be more susceptible than others. The mechanisms underlying this tissue specificity of polyglutamine diseases are of major interest and will be instrumental in developing therapeutic interventions.

Why do Polyglutamine-expansion diseases preferentially impact neural tissues? It is possible that the functions of the wild-type counterparts of the PolyQ expanded proteins are not as important in other tissues. It also possible that these proteins have similar biochemical behaviours in all cells but that the brain and neural tissues are simply more sensitive to global changes in gene regulation. Alternatively, these proteins may play a special role in the brain that is disrupted by polyQ expansion. One speculation is that neurons are simply more fragile and less resilient to perturbations than other tissues. It is also possible that defective neural function may be more apparent clinically, leading to a focus on neural tissues to exclusion of others. Thus, it is our view that closely examining the gene regulatory mechanisms disrupted by polyQ expansion may provide novel insights into causative events giving rise to disease and in disease progression.

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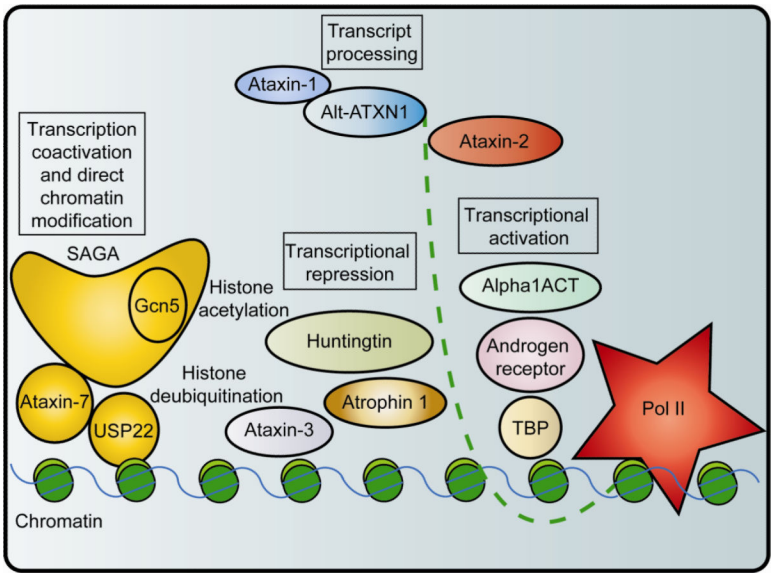

Figure 1.

PolyQ disease affects chromatin modification and usage. Chromatin events are central to polyQ disease. The polyglutamine expanded proteins Huntingtin, Androgen receptor, Atrophin 1, Ataxin-1, Ataxin-2, Ataxin-3, alpha-1a voltage-dependent calcium channel subunit, alpha1ACT, Ataxin-7, and TATA box binding protein (TBP) are all important regulators of gene expression and chromatin modification.

Table 1

Genes affected by polyglutamine expansion and the function of their protein products where known. In some cases repeat expansion affects more than one gene product.

Polyglutamine expansion diseases				
Disease name	**Products of expanded gene**	**Wild-type number of repeats (repeat sequence)**	**Repeat expansion in disease**	**Protein function**
Huntington disease (HD)	Huntingtin	6-34 (CAG)	36-121	Transcriptial repressor, membrane trafficking, endocytosis
Spinal and bulbar muscular atrophy (SBMA)/Kennedy's disease	Androgen receptor	9-36 (CAG)	38-62	Nuclear receptor, Androgen response
Dentatorubral-pallidoluysian atrophy	Atrophin 1	7-34 (CAG)	49-88	Nuclear receptor corepressor, Transcriptional corepressor
SCA1	Ataxin-1, alt-ATXN1	6-39 (CAG)	40-82	RNA processing, Transcription factor, Transcriptional corepressor, general repressor of transcription
SCA2 and amyotrophic lateral sclerosis (ALS)	Ataxin-2	15-24 (CAG)	27-33 for ALS, 32-200 for SCA2	RNA binding protein
SCA3, Machado-Joseph disease	Ataxin-3	13-36 (CAG)	61-84	Transcription factor, Transcriptional coactivator, Transcriptional repressor, Histone H2B deubiquitinase
SCA6	α1A voltage-dependent calcium channel subunit, and α1ACT	4-18 (CAG)	19-33	Voltage-gated calcium channel, Transcription factor
SCA7	Ataxin-7	4-35 (CAG)	36-460	Integral member of SAGA complex, regulation of histone acetylation and ubiquitination.
SCA17	TATA box binding protein (TBP)	25-42 (CAG)	47-63	General transcription factor, member of TFIID complex

Table 2

Summary of interactions with focus on known regulators of gene expression and associated chromatin modifications.

Polyglutamine expansion diseases			
Disease name	**Products of expanded gene**	**Associated regulators of gene expression**	**Chromatin modifications associated with wild-type and/or mutant protein**
Huntington disease (HD)	Huntingtin	PolyQ-expanded Huntingtin sequesters Sp1, TAFII130, CREB, p53, Sin3a, REST, PCAF, CBP	In HD, there is decreased CBP-dependent acetylation, decreased PCAF-associated acetylation, increased H3K9 methylation due to increased expression of ESET methyltransferase
Spinal and bulbar muscular atrophy (SBMA)/Kennedy's disease	Androgen receptor	The AR itself is a ligand-dependent transcription factor. Expanded AR is refractory to hormone signalling and is preferntially degraded. Like many TFs it can interact with coactivators such as p160 and CBP/p300, as well as the basal transcripton apparatus, including TFIIF and TBP.	In SBMA, histone acetylation is reduced. During normal AR-mediated gene expression H3R17 methylation, H3S10 phosphorylation, and H3K4 methylation are all regulated dynamically
Dentatorubral-pallidoluysian atrophy	Atrophin 1	Atrophin 1 interacts with Sin3A, HDACs, and the ETO/MTG8 corepressor complex subunit. Drosophila Atrophin interacts with histone methyltransferase G9a. Atrophin-1 also interacts with Nedd-4 E3 ubiquitin ligases, which regulate transcription factors from SMAD, p53, KLF, RUNX, and Jun families. Nedd-4 E3 ligases also regulate transcriptional regulators TGFbeta, EGF, IGF, VEGF, SDF-1, and TNFalpha.	Histone acetylation. Higher order chromatin structure appears abberant in DRPLA patients brain samples.
SCA1	Ataxin-1, alt-ATXN1	Ataxin-1 and alt-ATXN1 interact with each other and with poly(A) (+) RNA. Ataxin-1 is recruited to the Hey1 promoter by transcription factor RBPJ-kappa to repress transcription. PolyQ-expanded Ataxin-1 associates with PQBP-1 and stimulates its interaction with Pol II, reducing Pol II phosphorylation and transcription	Unknown
SCA2 and amyotrophic lateral sclerosis (ALS)	Ataxin-2	SCA2 regulates gene expression post-transcriptionally, by regulating RNA processing and translation. It interacts with RNA binding protein A2BP1, RNA helicase DDX6, and Poly(A) binding protein PABP-C1	Unknown
SCA3, Machado-Joseph disease	Ataxin-3	Ataxin-3 binds chromatin directly and can be found in gene promoters. It can activate and repress transactivation. It is a deubiquitinase and this activity is indespensible for transactivation function. Interacts with FOXO-4, TAFII130, CBP, NCoR, HDACs, RAD23. PolyQ expansion reduces Ataxin-3 transcrional repression function.	H2B poly-ubiquitination, H3ac
SCA6	α1A voltage-dependent calcium	The α1ACT transcription factor coordinates expression of many	Histone acetylation

Polyglutamine expansion diseases			
Disease name	**Products of expanded gene**	**Associated regulators of gene expression**	**Chromatin modifications associated with wild-type and/or mutant protein**
	channel subunit, and α1ACT trascription factor	genes involved in neural and Purkinje cell development. Upon polyglutamine expansion, α1ACT lacks transcription factor function yet forms intranuclear inclusions that colocalize with the CREB transcription factor [32,33].	
SCA7	Ataxin-7	Ataxin-7 is a subunit of the SAGA chromatin modifying complex, which interacts with many transcription factors, and also contains the histone acetyltransferase Gcn5/PCAF, as well as the histone deubiquitinase USP22.	In SCA7 H3K9ac and H3K14ac are reduced. The SAGA complex also regulates H2B ubiquitination and H2A ubiquitination.
SCA17	TATA box binding protein (TBP)	TBP is a general transcription factor involved in expression of a large number of genes. TBP interacts directly with chromatin and with other transcriptional regultors such as: TFIIB and NFY. PolyQ expansion has been shown to decrease interaction with chromatin, but increase interaction with TF's.	TBP is associated with transcriptional activation and therefore, chromatin modifications associated with a transcriptionally active state. The effect of PolyQ expansion of TBP on downstream chromatin marks is not clear.