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# Mechanisms of transcriptional dysregulation in Huntington's disease

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## Abstract

Recent studies have provided strong evidence for transcription-related deficits in Huntington's disease (HD). These discoveries include consistent changes in steady-state mRNA levels, direct interactions between huntingtin and known transcription factor proteins, sequestration of transcription-related factors into polyglutamine aggregates, and inhibition of enzymes involved in chromatin remodeling. Also, there is increasing evidence that huntingtin itself may be a transcriptional regulator. This review discusses the cumulative body of evidence for transcriptional dysregulation as a mechanism of HD pathogenesis and possible implications for disease progression and treatment.

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## 1. Introduction

Accumulating evidence points to transcriptional dysregulation as a central mechanism in the pathogenesis of Huntington's disease (HD) [1]. Specific alterations in mRNA expression have been documented in human HD post-mortem brain and in cellular and transgenic mouse models of HD. Messenger RNA expression profiling using DNA microarrays has provided a detailed account of the alterations in gene expression that occur as a result of the mutant huntingtin (htt) protein. In tandem, much has been learned about huntingtin's protein–protein interactions and its potential to disrupt the function of particular transcriptional regulators.

The idea that transcription might be an early pathogenic mechanism in HD came from several independent observations. In considering a normal function for huntingtin, investigators recognized that many polyglutamine-containing proteins are transcription factors [2,3]. In these proteins, the polyglutamine domain is critical for transcriptional activation. Scientists also appreciated that polyglutamine domains were potential sites of protein–protein interactions, and discovered that other proteins—including polyglutamine-bearing transcription factors—could be recruited into mutant polyglutamine aggregates [4–8]. In addition, it was discovered that both wild-type and mutant

huntingtin, and especially N-terminal huntingtin fragments, accumulated abnormally in the nuclear compartment in HD brain and HD model systems at an early point in the disease process [9–11]. Moreover, characteristic changes in mRNA levels have been observed in both HD patients and in mice expressing a mutant N-terminal huntingtin fragment [12–15]. This review will summarize the existing evidence for transcriptional dysregulation in HD. In addition, we highlight recent findings concerning which genes are targeted, the potential mechanisms underlying gene dysregulation, and the neuronal functions that may be affected by transcriptional abnormalities.

### 1.1. Changes in steady-state mRNA levels

In situ histochemical data from post-mortem human brain tissue together with results of in vivo positron emission tomography (PET) studies in human subjects suggested that losses in D1 and D2 dopamine receptor densities in the caudate nucleus were among the earliest signs of HD neuropathology [13,16]. The extent to which these changes might simply represent neuronal loss was unclear, however. The recent development of a variety of HD model systems has permitted more detailed investigation. Evidence from early studies of mice carrying a transgene encoding a mutant N-terminal huntingtin fragment (R6/2 line [17]) showed that changes at the mRNA level preceded changes in the corresponding proteins or

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113 frank neuronal death, and thus gave support for the idea that  
114 such changes arose from deficits in transcription [14,18].

115 The first studies of gene expression in mouse models of  
116 HD were guided by data from human studies which  
117 suggested that neurotransmitter receptors were early targets  
118 of HD pathology. Thus, several receptor types were  
119 analyzed in the newly available R6/2 mouse [14,18]. The  
120 R6/2 mouse was a model well-suited to examining  
121 huntingtin-related changes in cellular function that precede  
122 cell death because neuronal loss in this model is minimal  
123 during the first 12 weeks of life [17,19]. In R6/2 mouse  
124 brain, early losses of dopamine D1 and D2 receptor mRNAs  
125 account for the decreases of corresponding receptor proteins  
126 [14]. In addition, specific changes in mRNAs encoding  
127 other cAMP-coupled receptors, such as adenosine A2a  
128 [14,18] and cannabinoid CB1 receptors [20], were detected  
129 at an early point in the disease process. The mRNA  
130 alterations observed in the R6/2 lines did not result from  
131 disruption of a gene within the host mouse genome, since  
132 two other transgenic lines with distinct chromosomal  
133 insertion sites (R6/1 and R6/5 lines [17]) demonstrated  
134 mRNA decreases similar to those observed in the R6/2  
135 mice. Moreover, decreases in mRNA levels were an effect  
136 of the polyglutamine expansion, since transgenic mice  
137 carrying a non-expanded transgene (Hdex6 and Hdex27  
138 lines [17]), did not exhibit mRNA alterations [18]. In  
139 contrast to the decreases in mRNAs encoding certain  
140 receptors, no changes in NMDA receptor NR1 subunit or  
141  $\beta$ -actin mRNA were detected. Thus, mRNA alterations  
142 observed in transgenic HD mice appeared to result from  
143 polyglutamine length-dependent dysregulation of particular  
144 genes and could not simply be attributed to neuronal death.

145 In parallel with the development of huntingtin transgenic  
146 mice came the discovery that both the mutant and wild-type  
147 forms of the huntingtin protein were associated with  
148 synaptic vesicles [21–24]. Morton and colleagues explored  
149 whether the composition of these vesicles might be  
150 disrupted in HD, and discovered an early and progressive  
151 diminution in the expression of complexin II in R6/2 mice  
152 and human HD brain [25]. The diminution in the expression  
153 of this protein also appears to be controlled at the mRNA  
154 level. Similarly, Kusakabe et al. have observed a loss of  
155 mRNA encoding the extracellular matrix glycoprotein  
156 tenascin-C in R6/2 mice [26].

157 With growing evidence for HD-related perturbations in  
158 transcription, the search for other genes targeted by mutant  
159 huntingtin was expanded using discovery-based gene  
160 expression assays including high-density oligonucleotide  
161 microarrays. These studies revealed that expression of  
162 multiple components of the neuronal second messenger  
163 signaling cascade was affected in the R6/2 striatum,  
164 including regulators of intracellular calcium concentrations,  
165 and protein kinase A- and protein kinase C-related proteins  
166 [15,27–32]. Also, array studies in the R6/2 and sister line  
167 R6/1 mice uncovered several new potential pathways of  
168 HD-related pathology. These included decreases in mRNAs

169 transcribed from retinoid-, cAMP-, and Sp1-inducible genes  
170 [15,29,33], increases in molecular chaperones [34], cell  
171 death-related [27,35], and inflammation-related [15,27]  
172 mRNAs. A partial list of specific mRNA changes found in  
173 HD brain and HD model systems is found in Table 1.

174 While studies of R6 mice had generated interest in  
175 transcriptional changes, it was unclear whether such  
176 changes were model-specific. In order to address this  
177 question, studies of gene expression were conducted in  
178 other mouse models of HD. Interestingly, two independ-  
179 ently derived mouse lines also expressing a mutant N-  
180 terminal huntingtin fragment (HD-N171-82Q and HD94)  
181 showed changes similar to those observed in the R6 models  
182 [15,36,37]. Furthermore, some mRNA changes observed in  
183 both the R6/2 and N171 lines were also observed in mouse  
184 models of other polyglutamine diseases [37].

185 In addition, comparison of gene expression changes in  
186 R6/2 and N171 HD mice to those in mice carrying longer or  
187 full-length huntingtin transgenes suggests that at least some  
188 HD-related changes in transcription are dependent on the  
189 formation of a huntingtin N-terminal fragment [38].  
190 Whereas many mRNA changes previously observed in  
191 HD are recapitulated in R6/2 and N171 mice, only two of  
192 these (decreases in D2 dopamine receptor and A2a  
193 adenosine receptor) are observed in HD100 mice (carrying  
194 approximately one-third of an htt cDNA with 100 repeats),  
195 and none were observed in HD46 or YAC72 mice (which  
196 express approximately one-third of an htt with 46 repeats, or  
197 full-length htt with 72 repeats, respectively; Table 1).  
198 Possible explanations for increased transcriptional disruption  
199 by the N-terminal fragment include an enhanced  
200 nuclear localization and/or a difference in its protein-  
201 protein interactions. An alternative interpretation of these  
202 findings is that transcriptional dysregulation is a secondary,  
203 rather than a primary, pathogenic event (see Discussion).

204 Differential gene expression has also been examined in  
205 cell models of HD. Relative to brain tissues, cellular models  
206 provide a more homogeneous system in which steady-state  
207 mRNA changes may be examined. Also, these assays focus  
208 on cell autonomous effects, e.g. those effects that are  
209 independent of neuronal circuitry. Stably transfected cells  
210 expressing an N-terminal fragment of mutant huntingtin  
211 demonstrated deficits in neurite outgrowth and decreased  
212 expression of nerve growth factor receptor subunits trkA  
213 and p75 [39]. In two other lines of PC12 cells in which the  
214 expression of mutant huntingtin is controlled by an  
215 inducible promoter, changes in steady-state mRNA popu-  
216 lations can be observed within 16–18 h [29,40]. The  
217 specific changes in one of these cell lines included several  
218 that mirrored changes observed in R6/2 mouse striatum  
219 including a decrease in retinol-binding protein, an increase  
220 in the G-protein subunit  $G_{\gamma 3}$ , and the decreased expression  
221 of several cAMP-regulated genes [29]. Novel changes in  
222 other molecules, including several transcription factors,  
223 were also observed. In a second PC12 cell line, increases in  
224 the expression of four tyrosine phosphatase mRNAs were

mRNA	Proposed function of encoded polypeptide	Change detected	
Table 1 mRNA changes in HD brain or model systems (partial list)			
D2 dopamine receptor	G-protein-coupled receptor (activation decreases cAMP)	Decreased in human HD dorsal caudate; grade $\geq 1$ [13] Decreased in R6/2 mouse striatum $\geq 4$ weeks [14,18] Decreased protein (binding) in R6/1 mouse striatum $\geq 3$ months + [18] Decreased in HD-N171-82Q mouse striatum $\geq 4$ months [15] Decreased in HD-N171-82Q cultured primary striatal neurons [47] Decreased binding in HD100 at 10–13 months [38] No change in HD46 at 10–13 months [38] No change in YAC72 at 12 months [38]	281 282 283 284 285 286 287 288 289 290 291 292 293
Preproenkephalin	Neuropeptide	Decreased in human HD caudate and putamen; grade $\geq 0$ [12] Decreased in R6/2 mouse striatum $\geq 6$ weeks + [15,84] Decreased in CAG71, CAG94 knock-in mouse striatum 4 months [84] Decreased in HD94 mouse striatum 4–5 months [87] No change in HD46, HD100 at 10–13 months [38] No change in YAC72 at 12 months [38]	294 295 296 297 298 299
CB1 cannabinoid receptor	G-protein-coupled receptor (activation decreases cAMP)	Decreased in R6/2 mouse striatum $\geq 6$ weeks [15,20] Decreased in HD94 mouse striatum 4–5 months [87]	300 301
Adenosine A2a receptor	G-protein-coupled receptor (activation increases cAMP)	Decreased in R6/2 mouse striatum $\geq 4$ weeks [18] Decreased binding in human HD [88] Decreased mRNA in HD100 at 10–13 months [38] No change in HD46 at 10–13 months [38] No change in YAC72 at 12 months [38]	302 303 304 305
DARPP32	Modulates cAMP signaling cascade	Decreased in R6/2 mouse striatum $\geq 6$ weeks [15,28]	306
PCP4/PEP-19	Modulation of calmodulin-mediated signaling	Decreased in R6/2 mouse striatum 6 weeks + [33] Decreased immunoreactivity in human HD caudate, putamen and globus pallidus [83]	307 308
Protein kinase C $\beta$ II	Second messenger-regulated protein phosphorylation	Decreased in R6/2 mouse striatum 10 weeks [15,30]	309
Hippocalcin	Calcium-activated signaling processes	Decreased in R6/2 mouse striatum 6 weeks + [15,33]	310
Retinol-binding protein (RBP)	Retinoid signaling	Decreased in R6/2 mouse striatum 6 weeks [15] Decreased in HD-Q74 cell line 18 h [29]	311 312
Rrs1	Ribosomal protein	Increased in Hdh <sup>Q50</sup> , Hdh <sup>Q91</sup> and Hdh <sup>Q111</sup> mice [89] Increased in human HD patients [89]	313 314
Brain-derived neurotrophic factor (BDNF)	Neuronal differentiation and survival	Decreased in Flmu cells [72] Decreased in YAC72 cortex and hippocampus [72] Decreased in human HD frontoparietal cortex; grade 2 + [72] Decreased in R6/2 mouse cerebellum 8 weeks + and cortex 12 weeks [33]	315 316 317 318
Tenascin-C	Extracellular matrix protein	Decreased in R6/2 cortex and thalamus [26]	319
SNF-1 related kinase (SNRK)	Chromatin remodeling	Decreased in R6/2 cerebellum 6 weeks + [33]	320
HMG Co-A reductase, stearyl-CoA desaturase 2	Lipid metabolism	Decreased in Q105 and Q118 N-548 ST14A cells 48 h [41]	321
Neurotrophin receptor subunits TrkA, p75 <sup>NTR</sup>	Nerve growth factor signaling	Decreased in 150Q PC12 cells [39]	322
Proteasome activator subunit PA28 alpha	Regulation of proteasome activity	Increased in R6/2 striatum, cortex and cerebellum 12 weeks [15,33]	323 324
RNA polymerase II large subunit	Component of basal transcription machinery	Increased in R6/2 striatum, cortex and cerebellum 12 weeks [33]	325
Myristoylated alanine-rich C-kinase substrate (MARCKS)	Protein kinase C-mediated regulation of actin cytoskeleton	Increased in R6/2 cerebellum $\geq 6$ weeks [33]	326
Tetrapeptide-2	Molecular chaperone	Increased in human HD cortex; grade 3 [34]	327
Protein phosphatases MKP1, MKP3, CPG21	Dephosphorylation of tyrosine/serine/threonine residues	Increased in PC12 118Q cell line $\geq 16$ h [40]	328 329
G-protein subunit G $\gamma$ 3	G-protein-coupled receptor signaling	Increased in R6/2 mouse striatum 12 weeks [15] Increased in HD-Q74 cell line $\geq 18$ h [29]	330 331
Neuroleukin	Neuronal survival	Increased in R6/1 brain 7 months [27]	332
Abbreviations: PCP4, Purkinje cell protein 4; PEP-19, brain-specific polypeptide 19; MAP, mitogen-activated kinase; MKP1, MAP kinase phosphatase 1; MKP3, MAP kinase phosphatase 3; CPG21, candidate plasticity-related gene 1. Original characterizations of model systems not found in the above cited reports: R6/1, R6/1 mice [17]; HD-N171-82Q mice [90]; YAC72 mice [91]; CAG71, CAG94 knock-in mice [92].			

discovered [40]. Changes in another inducible cell model derived from ST14A cells, which have a striatal neuron-like phenotype, included the decreased expression of mRNAs encoding enzymes involved in sterol metabolism [41].

### 1.2. Interactions between htt and transcriptional regulatory proteins

Interactions between huntingtin and known transcriptional regulatory proteins have been identified by several different mechanisms. The first transcription factors identified to be huntingtin interactors were discovered in unbiased yeast two-hybrid screens [42,43]. Other studies have explored potential interactions between the polyglutamine domain of huntingtin and those of polyglutamine-rich transcription factors [7,8,44,45]. Additional associations have been detected based on different theoretical interaction domains or non-polyglutamine homologies to transcriptional regulators [44,46]. Most recently, microarray studies of mRNA expression have identified candidates based on their regulation of particular gene promoters [15,29,33,47].

The ability of huntingtin to disrupt transcription by interacting with specific transcriptional regulators is likely to be dependent, at least in part, on its ability to enter the nucleus. Recent evidence indicates that while only a small fraction of huntingtin is present in the nucleus under normal conditions [46], huntingtin accumulates in the nucleus with the disease state [9,10]. With increased nuclear localization, the possibility of huntingtin interacting with transcriptionally active proteins becomes more likely. Nuclear localization of huntingtin is covered in another review in this issue (Truant, this volume).

The transcriptome is composed of four general sets of activities (Fig. 1). Binding of transcriptionally active proteins to specific DNA sequences increases or decreases transcription of a particular gene, and thus these proteins are

known as *transcriptional activators or repressors*, respectively. Another group of molecules mediate interactions between transcriptional activators or repressors and the basal transcriptional machinery without binding directly to DNA, and these are known as *co-activators or co-repressors*. An additional category of important transcriptional regulators is the set of enzymes that govern the access of the basal transcriptional machinery to the gene promoter, and these are known as *chromatin remodeling factors*. Manufacture of mRNA precursors (heteronuclear RNAs) is carried out by the *basal transcriptional machinery* associated with RNA polymerase II (RNA pol II). Huntingtin interacts with, and may influence the functions of, multiple types of transcriptionally active molecules (Fig. 1 and Table 2). Most of the mechanisms proposed for huntingtin-mediated disruptions in transcription involve mitigating a particular factor's ability to maintain its normal protein–protein or protein–DNA interactions. The functional impact of these changes will be covered in a subsequent section of this review.

#### 1.2.1. Transcriptional activators and repressors

Htt has been found to bind to a number of transcriptional activators (Table 2). Huntingtin yeast partner B (HYPB), otherwise known as p231BP (the 231 kDa Huntingtin Binding protein), was among the first huntingtin interactors to be discovered [42]. This protein is one of several huntingtin interactors known to possess a WW domain motif. Other members of this set appear to be spliceosome components, giving huntingtin another possible link to mRNA biogenesis. HYPB/p231BP is thought to be a transcriptional activator based on its binding to a previously characterized motif within the adenovirus 12 *E1A* oncogene promoter [48].

Recently, an intriguing interaction between huntingtin and the transcription factor Sp1 has been described [47,49].

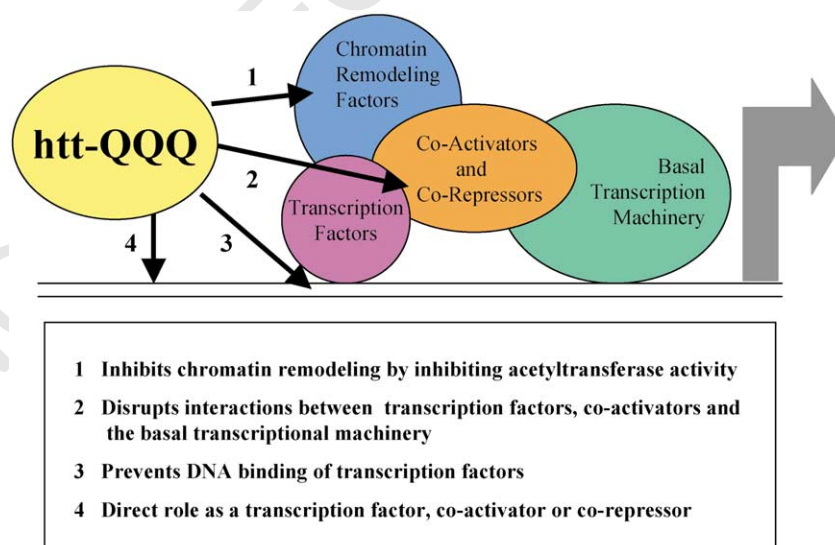


Fig. 1. Possible roles of mutant huntingtin in transcriptional dysregulation.

Table 2  
Transcriptionally active huntingtin interactors

Interactor	Reference	Likely function(s)	Differential interactions with wt and mutant polyQ	Detected in polyQ inclusions?
HYPB/p231HBP	[42]	Transcriptional activator	mut $\approx$ wt	N <sup>a</sup>
NCoR	[43,56]	Co-repressor	mut $\geq$ wt	N
CBP <sup>b</sup>	[7,44,45]	Co-activator, chromatin remodeling (AT)	mut > wt	Y
PQBP-1/Npw38	[65,67]	Co-repressor/activator, spliceosomal factor	mut > wt	Y
mSin3a	[43,44]	Chromatin remodeling	mut $\approx$ wt	Y
p53	[44]	Transcriptional activator	mut $\approx$ wt	Y
TAF <sub>II</sub> 130	[47,51]	Co-activator, chromatin remodeling (AT)	mut $\geq$ wt	Y
CA150	[93,94]	Inhibitor of transcriptional elongation	wt > mut	Y
Sp1	[47,49]	Transcriptional activator	mut > wt	Y
CtBP	[46]	Co-repressor	wt > mut	?
NF- $\kappa$ B	[44,95]	Transcriptional activator	?	Y
TBP <sup>c</sup>	[54,68]	Basal transcription machinery	?	Y
RXR $\alpha$ <sup>c</sup>	[44]	Transcriptional activator	?	Y
RNA pol II large subunit <sup>c</sup>	[33]	Basal transcription machinery	?	Y

Abbreviations: PQBP-1, polyglutamine(Q) tract binding protein-1; NCoR, nuclear co-repressor; AT, acetyltransferase.

<sup>a</sup> Detected in HD-related autofluorescent bodies but not in ubiquitinated inclusions.

<sup>b</sup> Also binds to related factor P/CAF in a polyglutamine-independent manner.

<sup>c</sup> Soluble interaction with htt has not been determined. Acetyltransferases may be involved in chromatin remodeling or transcription factor acetylation.

Sp1 was the first human transcription factor to be isolated [50], and it also contains a polyglutamine motif. Many genes downregulated in R6/2 mice are Sp1-driven [14,15,18]. Huntingtin interacts with Sp1 via sequences present in htt's N-terminus [47,49]. Mutant htt interferes with Sp1-dependent transcription, and Sp1 overexpression rescues htt-induced toxicity in some systems [49]. In another study, co-expression of Sp1 and its co-activator TAF<sub>II</sub>130 were required to rescue the toxicity and dopamine D2 receptor deficits caused by mutant htt in transfected cells [47]. While Sp1 has been co-localized with aggregates, the more relevant interaction appears to be Sp1 binding to soluble huntingtin [47,49]. While overall levels of Sp1 do not appear to be decreased in HD brain, both the association between Sp1 and TAF<sub>II</sub>130, as well as Sp1 binding to DNA, appear to be disrupted by mutant huntingtin [47].

In cell and mouse models of polyglutamine disease, there are decreases in the expression of cyclic AMP-responsive genes [15,29,51]. Intriguingly, mice with targeted disruptions of CREB and the related factor CREM demonstrate regionally specific neurodegeneration that is reminiscent of HD [52]. Biochemical data also point to a connection between huntingtin and cAMP-regulated gene expression. Huntingtin binds at least two of CREB's co-activators, CBP and TAF<sub>II</sub>130, in a polyglutamine-dependent manner [47]. Interestingly, TAF<sub>II</sub>130 is also a critical co-activator for another one of huntingtin's interactors, Sp1 (see above).

p53 is another transcriptional activator that binds to htt [44]. Huntingtin appears to decrease the activity of p53 at its target promoters. Both p53 and one of its regulators, mdm2, have been found within intracellular polyQ aggregates [53,54]. Other transcriptional activators can also be

recruited into polyglutamine aggregates, including the retinoid receptor RXR $\alpha$ .

### 1.2.2. Co-regulators

Huntingtin has also been found to bind to a number of co-regulators. Nuclear co-repressor (NCoR) was one of the co-regulators identified to interact with huntingtin [43]. In a yeast two-hybrid system, NCoR was found to interact with the N-terminal portion of huntingtin, with a higher affinity for the polyglutamine-expanded version. Nuclear hormone receptors such as thyroid hormone receptor (TR) and retinoic acid receptor function as transcriptional activators when bound to their cognate ligands. NCoR is a 270 kDa protein that acts in concert with other DNA-binding transcriptional proteins to repress transcriptional activation of the nuclear hormone receptors [55]. Boutell et al. found decreased nuclear immunodetection of NCoR in human HD brain, compared to control tissues [43]. Recently, we have found that mutant huntingtin not only increases NCoR-mediated repression but also enhances ligand-dependent nuclear hormone activation [56]. The ability of mutant huntingtin to increase the expression of a TR-responsive reporter construct suggests that huntingtin itself may possess co-activator activity. Indeed, we found that mutant huntingtin could interact directly with labeled thyroid hormone receptor [56].

Huntingtin and other polyglutamine proteins have been found to interact with CREB-binding protein (CBP), which itself contains a polyglutamine domain [44,45,57]. CBP is also a co-activator that interacts with Sp1. These observations have led to the hypothesis that CBP might be sequestered into polyglutamine aggregates, thus limiting

the available CBP within the cell [7,44,45,57]. Interestingly, in an inducible cell model of HD, there is decreased expression of cyclic AMP response element- (CRE-) dependent transcription [29]. In hippocampal cell lines transfected with mutant huntingtin constructs, cell death involves degradation of CBP [58].

### 1.2.3. Chromatin remodeling factors

Proper control of gene expression is also dependent on chromatin remodeling, a major component of which occurs through covalent histone modification [59]. Gene regulation is dependent on post-translational histone modifications including acetylation, phosphorylation, methylation, ubiquitination, and SUMOylation. Huntingtin has not yet been shown to interact with any proteins with dedicated histone-modifying activity. However, many huntingtin interactors also possess histone-modifying capability, such as CBP, which has histone acetyltransferase (HAT) activity, and mSin3a, which can recruit histone deacetylase (HDAC) activity [44]. Recent evidence also suggests that SUMOylation is increased in polyglutamine diseases, including HD [60].

Another mechanism by which huntingtin may disrupt transcription involves its ability to inhibit the post-translational modifying activity of HATs. Huntingtin inhibits the acetyltransferase activity of the CREB-binding protein–protein (CBP) and the related transcriptional co-activators P/CAF and p300 [61]. Inhibition of acetyltransferase activity corresponds with decreased histone acetylation that has been observed in transgenic models of HD [61,62]. This hypoacetylation of histones may be pathologically crucial, as HDAC inhibitors can ameliorate the disease phenotype in these models. Acetyltransferase activity is thought to be a critical step in chromatin remodeling by acetylating histone tails and may also be important for transcription factor acetylation [59,63]. It is unknown whether mutant huntingtin may also inhibit the acetyltransferase activities of other transcription-related proteins. Recently, mutant huntingtin aggregates have been found to contain histones H3 and H4 as well as heterogenous nuclear ribonucleoproteins (hnRNP) [64]. Immunohistochemical staining for hnRNP and histone H3 demonstrated redistribution of these proteins into aggregates, suggesting that mutant huntingtin can perturb the normal intranuclear distribution of these transcriptionally important molecules.

### 1.2.4. Basal transcriptional machinery

The coordinated assembly of transcriptional co-activators, co-regulators, and chromatin modifying factors is thought to culminate in recruitment of the basal transcriptional machinery including the enzymatic complex that synthesizes mRNA.

Huntingtin and other polyglutamine-containing proteins have been found to interact with polyglutamine binding protein-1 (PQBP) [65]. PQBP-1 was initially discovered as

a molecule that downregulates Brn-2-dependent transcription; PQBP-1's binding interaction was dependent on the polyglutamine region of Brn-2 [65]. Localized primarily in the nucleus, PQBP-1 binds to all polyQ-containing proteins [66]. The WW domain of the PQBP-1 can bind the C-terminal region of RNA pol II large subunit, which regulates RNA termination, splicing and degradation of the RNA pol II [66]. The mutated form of ataxin-1, another polyglutamine disease-causing protein, interacts with a complex containing both PQBP and RNA pol II, resulting in a cooperative repression of basal transcription [67]. Huntingtin has also been shown to repress transcription from a minimal promoter [46], but it is unclear whether this occurs through modulation of the interaction between PQBP and RNA pol II. Intriguingly, RNA pol II large subunit can be recruited to polyglutamine inclusions in cell lines expressing mutant huntingtin [33].

Another connection between huntingtin and the basal transcription machinery may be through its interaction with TAF<sub>II</sub>130 [47,51], which binds to the TATA-binding protein (TBP). Like RNA pol II large subunit, TBP can be detected in huntingtin aggregates [54,68]. Interestingly, TBP is itself a polyglutamine-containing protein, and polyglutamine expansion of TBP causes spinocerebellar ataxia 17 (SCA17 [69]).

With regard to promoter specificity, an effect of huntingtin on any one of its known transcription-related interactors is insufficient to explain the observed set of dysregulated genes, or the unique pattern of neurodegeneration in HD. Thus, it is possible that the effects of huntingtin are exerted on promoters which require specific combinations of these factors with which it interacts. Alternatively, the key to regional specificity might be the manner in which particular transcriptional deficits interrelate with other pathogenic mechanisms, such as huntingtin proteolysis or aggregation.

### 1.3. Promoter analyses

The discovery of protein–protein interactions between huntingtin and a number of transcriptional regulatory proteins prompted functional studies of candidate target genes. These include model promoter sequences and native promoters, both cloned and endogenous. Despite a number of differences in the systems utilized for these studies, some unifying conclusions have emerged. There is a good deal of consensus in these data that a polyglutamine mutation is more likely to cause repression than activation, and particularly in promoters that are positively regulated by CREB, CBP, Sp1 and p53. The mechanism(s) for this repression are a matter of debate, however. Whereas some invoke a normal transcriptional regulatory function of huntingtin that is changed by the mutation, others favor a gain-of-function model that invokes transcriptional repression as a consequence of abnormal protein–protein

interactions. A detailed account of huntingtin's effects on various promoters is provided in Table 3.

#### 1.4. Models of huntingtin-mediated dysregulation of gene expression

Several models have been developed to explain the mechanism(s) of huntingtin-related disruption of transcriptional processes. These models are not mutually exclusive, and provide a framework for continued testing of huntingtin's role as a transcriptional activator or repressor. One major hypothesis involves the sequestration of particular transcription factors in polyglutamine aggregates

(Fig. 2, panel A). Data from several studies support this model. Housman, Thompson, Ross and colleagues observed that polyglutamine transcription factors and factors to which they bound could be recruited into polyglutamine aggregates, causing them to disappear from the cytoplasmic and nuclear compartments [7,8,44,45,70]. Other classes of transcriptional regulators, such as NCoR, mSin3, RAR-alpha and p53 have also been shown to interact with huntingtin or to be present in polyglutamine aggregates (Table 2).

A second potential model for transcriptional dysregulation by mutant huntingtin involves soluble interactions between mutant huntingtin and various transcriptional

Table 3  
Promoter analysis of huntingtin-induced altered gene expression

Promoter class*	Assay	Reference	Huntingtin effect	Suspected binding partner(s)
Sp1-activated	Reporter assay of native D2 receptor promoter	[47]	Expression decreased by N-terminal fragment of mutant htt	Sp1, TAF <sub>II</sub> 130
	Binding to Sp1 consensus sequence from D2 promoter		DNA-binding ability is decreased by mutant htt	Sp1, TAF <sub>II</sub> 130
	Reporter assay of nerve growth factor receptor (p75) promoter	[49]	Decreased in cells overexpressing an N-terminal fragment of mutant htt	Sp1
cAMP-responsive	Binding to Sp1 consensus sequence		DNA-binding ability is decreased by mutant htt	Sp1
	mRNAs from genes with Sp consensus sequences in the proximal promoter	[33]	Decreased by co-expression of N-terminal fragment of mutant htt	Sp1 or other Sp-like factors
	mRNAs from genes with functional cAMP-responsive elements	[15]	Decreased by co-expression of N-terminal fragment of mutant htt	NC
	Transcriptional activation from experimental promoter by GAL4-CREB	[51]	Decreased by non-pathogenic polyQ and further decreased by mutant polyQ	TAF <sub>II</sub> 130
	Reporter assay with cAMP-responsive elements in an experimental promoter	[45]	No change with N-terminal fragment of wt htt, decrease with N-terminal fragment of mutant htt	CBP
	mRNAs from genes with functional cAMP-responsive elements	[29]	Decreased by co-expression of N-terminal fragment of mutant htt	CBP, TAF <sub>II</sub> 130
	Reporter assay with cAMP-responsive element inserted into a minimal SV40 promoter	[29]	Decreased by co-expression of N-terminal fragment of mutant htt	CBP, TAF <sub>II</sub> 130
CBP-dependent	KCl-stimulated transcriptional activation from experimental promoter by GAL4-CBP	[45]	No change with N-terminal fragment of wt htt, decrease with N-terminal fragment of mutant htt	CBP
	Acetyltransferase activity	[61]	CBP, p300 and P/CAF acetyltransferase activities inhibited by N-terminal fragments of wt and mutant htt	CBP, P/CAF
p53-activated	Reporter assay of native p21 <sup>WAF1/CIP1</sup> promoter	[61]	No change with N-terminal fragment of wt htt, decrease with N-terminal fragment of mutant htt	p53, CBP, mSin3A
Nuclear hormone receptor-regulated	mRNAs from genes with functional retinoic acid-responsive elements	[15]	Decreased by co-expression of N-terminal fragment of htt in transgenic mice	NC
	Reporter assay with thyroid hormone- and retinoic acid-responsive promoter constructs	[56]	Enhanced repression and derepression of thyroid hormone receptor-dependent transcription	NcoR
CtBP-regulated	Repression of experimental promoter (derived from TK promoter) by GAL4-htt	[46]	Repressed by full-length wt htt and full-length mutant htt; repressed by N-terminal fragment of mutant htt	CtBP, NCoR
BDNF	BDNF gene reporter constructs	[72]	WT htt increases transcription from exon II promoter, mutant htt represses transcription from exon II–IV promoters	NC
	Total BDNF mRNA levels	[72]	WT htt increases total BDNF mRNA, mutant htt decreases total BDNF mRNA	NC
	BDNF mRNA levels	[33]	Decreased by co-expression of N-terminal fragment of htt in transgenic mice	NC

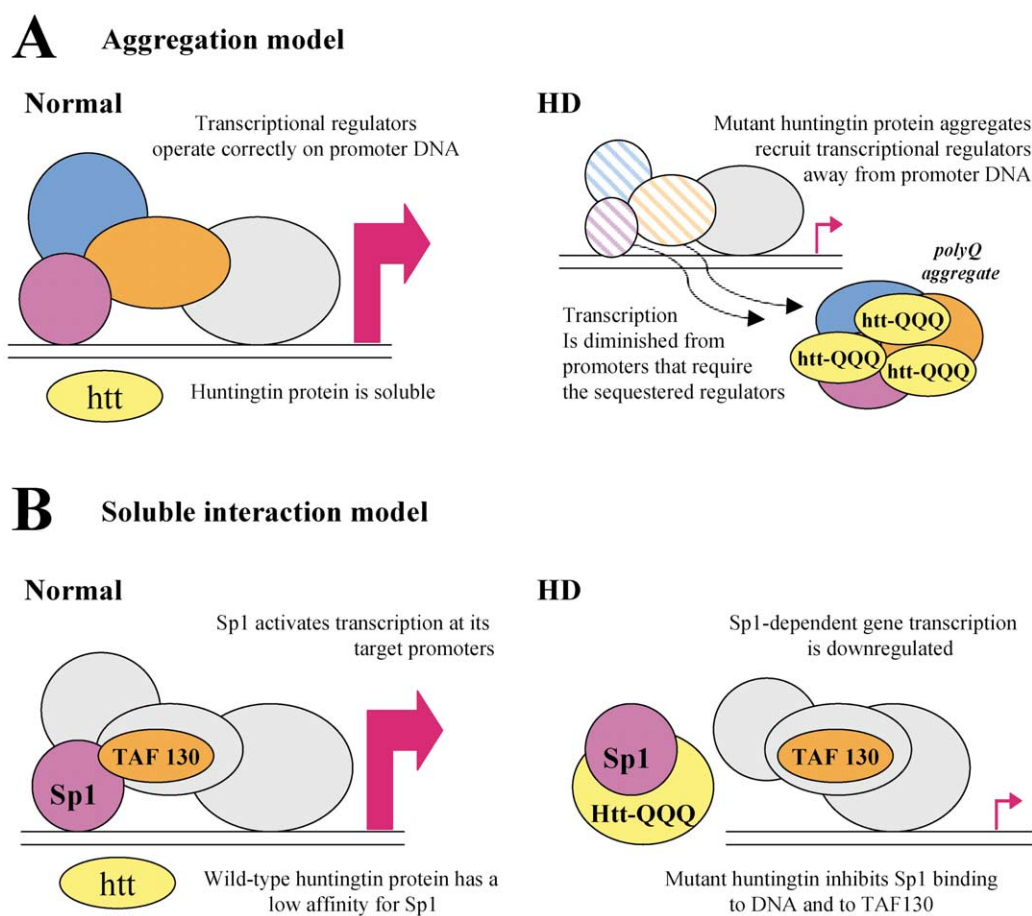


Fig. 2. Potential mechanisms by which mutant huntingtin may decrease the function of transcriptional regulators. Mutant huntingtin may interfere with transcription indirectly through the inactivation of transcriptional regulators through their sequestration into aggregates (A) or through abnormal protein–protein interactions (B).

regulators. In this model, the mutant form of the disease protein has a different effect than the normal protein by virtue of their differential affinities for a particular factor (Fig. 1, panel B). This is the mechanism proposed by Krainc and colleagues for the disruption of the functions of Sp1 and TAF<sub>II</sub>130 by mutant huntingtin [47]. In this model, the enhanced affinity of mutant huntingtin for Sp1 is shown to disrupt the binding of Sp1 to both TAF<sub>II</sub>130 and to its DNA targets. This model is further supported by the independent findings of Li and colleagues that also demonstrate polyglutamine-dependent interactions between soluble Sp1 and huntingtin [49,71].

Other proposed models are predicated on evidence that huntingtin has direct transcriptional regulatory actions. DiFiglia and colleagues have shown that, as full-length proteins, both wild-type and mutant huntingtin are capable of transcriptional repression when recruited to DNA [46]. Kegel et al. hypothesize that these effects may be due to interactions of both forms of huntingtin with the C-terminal binding protein (CtBP; Fig. 3, panel B). This effect is proposed to be a physiologically regulated, normal function of huntingtin. By contrast, N-terminal fragments of

wild-type and mutant huntingtin have differential abilities to repress transcription, with the mutant protein showing such activity while the wild-type does not. Given that the identified binding site for CtBP is not contained in this fragment, the authors suggest that these effects may be due to mutant huntingtin's recruiting NCoR or some other regulator, and represent a potential abnormal gain-of-function property of mutant huntingtin.

Another huntingtin-mediated effect on gene expression has been observed by Cattaneo and colleagues. Zuccato et al. observed differential regulation of BDNF expression by its four possible promoters whereby wild-type huntingtin increased the mRNA produced from transcription of exon II, while mutant huntingtin downregulated transcription from exon II, III and IV promoters resulting in decreased BDNF mRNA and protein [72]. These authors interpreted the transcriptional activation of the BDNF gene to be a normal function of wild-type huntingtin; mutant huntingtin interferes with this activity (Fig. 3, panel A). It is not yet known whether these effects of huntingtin on transcription occur through direct or indirect mechanisms.

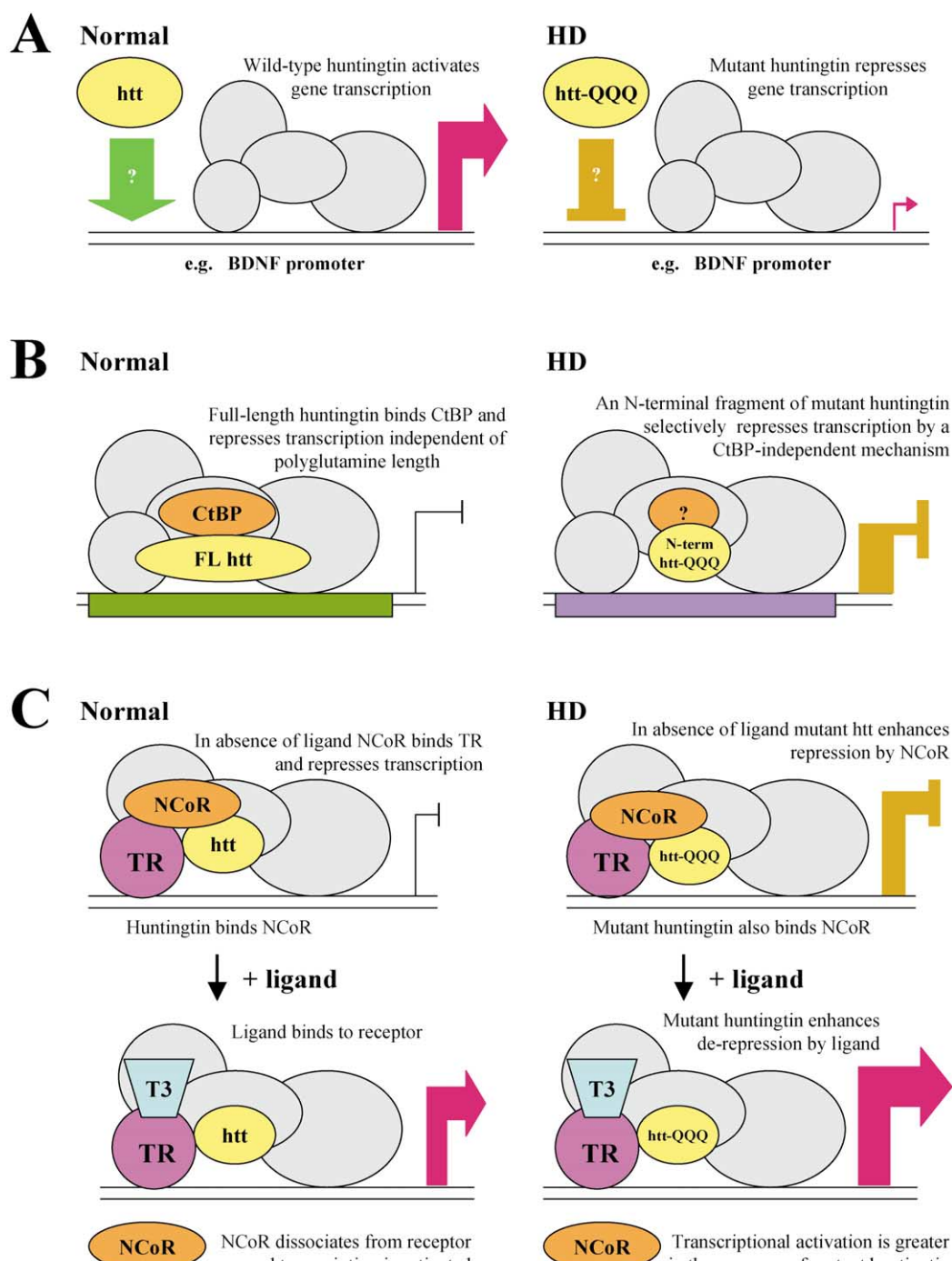


Fig. 3. Evidence for regulation of transcription by huntingtin. These diagrams represent mechanisms by which huntingtin may influence transcription in polyglutamine-dependent and polyglutamine-independent ways. In model A, proposed by Zuccato et al. [72], positive regulation of the BDNF promoter by wild-type huntingtin is inhibited in a dominant-negative fashion by its mutant counterpart. As indicated by question marks, it is not clear whether changes in BDNF expression occur through direct or indirect actions of huntingtin. In model B, which represents data from Kegel et al. [46], full-length forms of wild-type or mutant huntingtin can bind to CtBP and can repress transcription. By contrast, N-terminal fragments of huntingtin fail to bind CtBP and show a polyglutamine-dependent repression of transcription through a CtBP-independent mechanism. In model C, which schematizes data from Yohrling et al. [56], huntingtin shows polyglutamine-dependent effects on the transcription of thyroid hormone-receptor (TR) target genes. In the absence of ligand (T3), polyglutamine expansion enhances NCoR-dependent repression of TR-regulated promoters by huntingtin. In addition, huntingtin enhances TR-dependent transcription in the presence of T3 in a polyglutamine length-dependent fashion.

Most recently, the effect of huntingtin on nuclear hormone receptor function has been examined. In testing possible effects of huntingtin on these receptor transcription factors by NCoR, Yohrling et al. discovered that huntingtin

enhances NCoR-mediated repression and ligand-dependent derepression of the thyroid hormone in a polyglutamine-dependent manner [56]. These results suggest that mutant huntingtin may have enhanced repressor or co-activator

1009 activities relative to its wild-type counterpart  
1010 (Fig. 3, panel C).

1011  
1012 *1.5. Functional consequences to neuronal signaling*  
1013 *and homeostasis in HD*

1014  
1015 *1.5.1. What changes in cell function would be predicted*  
1016 *by changes in this particular set mRNAs/proteins?*

1017 Although we cannot yet determine which transcription  
1018 factor abnormalities play the lead role(s) in the pathogenesis  
1019 of HD, we may predict some of their downstream  
1020 consequences by virtue of the known functions served by  
1021 the molecules whose expression is altered in the disease.  
1022 Decreases in neurotransmitter receptors are the best-  
1023 characterized HD-related changes in gene expression.  
1024 While the effect of these decreases might seem obvious at  
1025 first glance, the regulation of neurotransmitter systems in HD  
1026 brain may actually be more complex. Despite the diminution  
1027 of dopamine receptors and components of their second  
1028 messenger systems [13–16,18,28,73–76], both increases  
1029 and decreases in dopaminergic responses have been observed  
1030 in R6 mice [77–79]. A similarly paradoxical enhancement of  
1031 adenosine A2a receptor function has also been observed in a  
1032 cell model of HD [80]. Recent studies of glutamatergic  
1033 systems suggest that aberrant control of neuronal responses  
1034 may be a biphasic phenomenon during the disease process,  
1035 with an early phase of enhanced response that may contribute  
1036 to neurodegeneration, and a later phase that may reflect  
1037 severe neuronal dysfunction [81].

1038 The influences of losses in trophic and differentiation  
1039 factors may be more clear. Deficiencies in trophic factor  
1040 signaling would be expected to impair neurite outgrowth  
1041 and maintenance and to make neurons more vulnerable to  
1042 apoptosis. BDNF and retinoic acid are known to play major  
1043 roles in differentiation of striatal neurons, and both of these  
1044 show downregulation in HD. It is not surprising, then, that  
1045 some of the first changes detected in medium spiny neurons  
1046 are the decreased expression of their phenotypic  
1047 markers such as enkephalin, DARPP-32 and PCP4/pep19  
1048 [28,82–84].

1049 There is also specific evidence from R6/2 striatal gene  
1050 expression profiles that ionic signaling and homeostasis are  
1051 disrupted by changes in gene expression. These data predict  
1052 an impaired capacity to sequester free calcium, and  
1053 diminished calcium-induced calcium responses [15]. Con-  
1054 sistent with these predictions, Deckel et al. have observed  
1055 biphasic changes in the functions of calcium-dependent  
1056 proteins [32]. Also, decreased expression of inwardly  
1057 rectifying potassium channel subunits may account for the  
1058 altered firing properties of R6/2 neurons [81].

1059  
1060 *1.5.2. How do transcriptional changes relate to other*  
1061 *pathogenic mechanisms?*

1062 There is currently much debate about whether transcrip-  
1063 tional disruption is an early phenomenon in HD. In cultured  
1064 cells, changes in mRNA levels are observed relatively early,

1065 whereas mice show mRNA changes only after inclusions  
1066 are observed and the first behavioral signs are noted. One  
1067 factor that may regulate the rate of mRNA changes in these  
1068 experimental systems is the level of huntingtin expression,  
1069 which is much higher in cellular models than in the mice.  
1070 Alternatively, compensatory mechanisms may exist in the  
1071 intact brain that are not present in cultured cells.

1072 There are several other variables that may cause impact  
1073 on the development and/or detection of transcriptional  
1074 changes in vivo. One major contributor to huntingtin-  
1075 induced transcriptional changes may be the requisite  
1076 proteolysis of huntingtin to an N-terminal fragment [85].  
1077 Whether this is due to the resultant accumulation and/or  
1078 aggregation of huntingtin protein, its enhanced nuclear  
1079 localization, or changes in its protein–protein interactions,  
1080 is unclear.

1081 Data from human HD provide little clarification of where  
1082 transcription fits into the scheme of HD pathogenesis. One  
1083 notable observation is that the DNA-binding abilities of the  
1084 transcription factor Sp1 and its cofactor TAF<sub>II</sub>130 are  
1085 inhibited in tissue from presymptomatic HD-gene positive  
1086 cases [47]. In addition, changes in steady-state mRNA  
1087 populations have been observed in human grade 3 HD  
1088 cortex [34]. Future studies of the human disease are needed  
1089 to define more precisely the temporal course of transcrip-  
1090 tional and other pathogenic events.

1091  
1092 *1.6. Transcriptionally active therapeutics*

1093  
1094 The recent development of sequence-selective DNA-  
1095 binding drugs has opened the door to utilizing gene- and  
1096 transcription factor-directed pharmacotherapies. These  
1097 efforts are further complemented by efforts to understand  
1098 and manipulate the enzymes involved in chromatin  
1099 remodeling. For example, drugs that inhibit histone  
1100 deacetylation also reverse the abnormal phenotype in cell  
1101 and transgenic animal models of polyglutamine disease  
1102 [61,62,86]. Continued efforts to discover new and combine  
1103 existing transcription-targeted therapeutics may hold prom-  
1104 ise in correcting multiple aspects of the transcription-related  
1105 deficits in HD.

1106  
1107 *1.7. Summary*

1108  
1109 Ongoing study of the interactions between transcrip-  
1110 tional regulatory proteins, their DNA targets, and huntingtin  
1111 may eventually explain many of the specific molecular  
1112 changes that occur in HD. These future studies will need to  
1113 account for the interplay between transcriptional dysregula-  
1114 tion and other disease mechanisms, such as polyglutamine  
1115 aggregation. The availability of transcriptionally active  
1116 pharmacologic agents may allow for transcriptional deficits  
1117 to be targeted therapeutically, either alone or as components  
1118 of a combinatorial approach.

## References

- 1121  
1122  
1123 [1] Cha J-HJ. Transcriptional dysregulation in Huntington's disease. Trends Neurosci 2000;23:387–92. 1177  
1124 [2] Gerber H-P, Seipel K, Georgiev O, et al. Transcriptional activation 1178  
1125 modulated by homopolymeric glutamine and proline stretches. Science 1994;263:808–11. 1179  
1126 [3] Karlin S, Burge C. Trinucleotide repeats and long homopeptides in 1180  
1127 genes and proteins associated with nervous system disease and 1181  
1128 development. Proc Natl Acad Sci U S A 1996;93:1560–5. 1182  
1129 [4] Perutz MF. Glutamine repeats and inherited neurodegenerative 1183  
1130 diseases: molecular aspects. Curr Opin Struct Biol 1996;6:848–58. 1184  
1131 [5] Imafuku I, Waragai M, Takeuchi S, et al. Polar amino acid-rich 1185  
1132 sequences bind to polyglutamine tracts. Biochem Biophys Res 1186  
1133 Commun 1998;253:16–20. 1187  
1134 [6] Davies SW, Turmaine M, Cozens BA, et al. From neuronal inclusions 1188  
1135 to neurodegeneration: neuropathological investigation of a transgenic 1189  
1136 mouse model of Huntington's disease. Philos Trans R Soc Lond B 1190  
1137 Biol Sci 1999;354:981–9. 1191  
1138 [7] Kazantsev A, Preisinger E, Dranovsky A, Goldgaber D, Housman D. 1192  
1139 Insoluble detergent-resistant aggregates form between pathological 1193  
1140 and nonpathological lengths of polyglutamine in mammalian cells. 1194  
1141 Proc Natl Acad Sci U S A 1999;96:11404–9. 1195  
1142 [8] Preisinger E, Jordan BM, Kazantsev A, Housman D. Evidence for a 1196  
1143 recruitment and sequestration mechanism in Huntington's disease. 1197  
1144 Philos Trans R Soc Lond B Biol Sci 1999;354:1029–34. 1198  
1145 [9] Davies SW, Turmaine M, Cozens BA, et al. Formation of neuronal 1199  
1146 intranuclear inclusions underlies the neurological dysfunction in mice 1200  
1147 transgenic for the HD mutation. Cell 1997;90:537–48. 1201  
1148 [10] DiFiglia M, Sapp E, Chase KO, et al. Aggregation of huntingtin in 1202  
1149 neuronal intranuclear inclusions and dystrophic neurites in brain. 1203  
1150 Science 1997;277:1990–3. 1204  
1151 [11] Ross CA. Intranuclear neuronal inclusions: a common pathogenic 1205  
1152 mechanism for glutamine-repeat neurodegenerative diseases? Neuron 1206  
1153 1997;19:1147–50. 1207  
1154 [12] Augood SJ, Faull RLM, Love DR, Emson PC. Reduction in 1208  
1155 enkephalin and substance P messenger RNA in the striatum of early 1209  
1156 grade Huntington's disease: a detailed cellular *in situ* hybridization 1210  
1157 study. Neuroscience 1996;72:1023–36. 1211  
1158 [13] Augood SJ, Faull RLM, Emson PC. Dopamine D1 and D2 receptor 1212  
1159 gene expression in the striatum in Huntington's disease. Ann Neurol 1213  
1997;42:215–21. 1214  
1160 [14] Cha J-HJ, Kosinski CM, Kerner JA, et al. Altered brain neuro- 1215  
1161 transmitter receptors in transgenic mice expressing a portion of an 1216  
1162 abnormal human Huntington disease gene. Proc Natl Acad Sci U S A 1217  
1998;95:6480–5. 1218  
1163 [15] Luthi-Carter R, Strand A, Peters NL, et al. Decreased expression of 1219  
1164 striatal signaling genes in a mouse model of Huntington's disease. 1220  
Hum Mol Genet 2000;9:1259–71. 1221  
1165 [16] Weeks RA, Piccini P, Harding AE, Brooks DJ. Striatal D1 and D2 1222  
1166 dopamine receptor loss in asymptomatic mutation carriers of 1223  
1167 Huntington's disease. Ann Neurol 1996;40:49–54. 1224  
1168 [17] Mangiarini L, Sathasivam K, Seller M, et al. Exon 1 of the HD gene 1225  
1169 with an expanded CAG repeat is sufficient to cause a progressive 1226  
1170 neurological phenotype in transgenic mice. Cell 1996;87:493–506. 1227  
1171 [18] Cha J-HJ, Frey AS, Alsdorf SA, et al. Altered neurotransmitter 1228  
1172 receptor expression in transgenic mouse models of Huntington's 1229  
1173 disease. Philos Trans R Soc Lond B Biol Sci 1999;354:981–9. 1230  
1174 [19] Turmaine M, Raza A, Mahal A, Mangiarini L, Bates GP, Davies 1231  
1175 SW. Nonapoptotic neurodegeneration in a transgenic mouse model 1232  
1176 of Huntington's disease. Proc Natl Acad Sci U S A 2000;97: 1233  
8093–7. 1234  
1177 [20] Denovan-Wright EM, Robertson HA. Cannabinoid receptor messen- 1235  
1178 ger RNA levels decrease in a subset of neurons of the lateral striatum, 1236  
1179 cortex and hippocampus of transgenic Huntington's disease mice. 1237  
Neuroscience 2000;98:705–13. 1238  
1180 [21] DiFiglia M, Sapp E, Chase K, et al. Huntingtin is a cytoplasmic 1239  
1181 protein associated with vesicles in human and rat brain neurons. 1240  
Neuron 1995;14:1075–81. 1241  
1182 [22] Gutekunst CA, Levey AI, Heilman CJ, et al. Identification and 1242  
1183 localization of huntingtin in brain and human lymphoblastoid cell 1243  
1184 lines with anti-fusion protein antibodies. Proc Natl Acad Sci U S A 1244  
1995;92:8710–4. 1245  
1185 [23] Wood JD, MacMillan JC, Harper PS, Lowenstein PR, Jones AL. 1246  
1186 Partial characterisation of murine huntingtin and apparent variations 1247  
1187 in the subcellular localisation of huntingtin in human, mouse and rat 1248  
1188 brain. Hum Mol Genet 1996;5:481–7. 1249  
1189 [24] Velier J, Kim M, Schwarz C, et al. Wild-type and mutant huntingtins 1250  
1190 function in vesicle trafficking in the secretory and endocytic 1251  
1191 pathways. Exp Neurol 1998;152:34–40. 1252  
1192 [25] Morton AJ, Edwardson JM. Progressive depletion of complexin II in a 1253  
1193 transgenic mouse model of Huntington's disease. J Neurochem 2001; 1254  
76:166–72. 1255  
1194 [26] Kusakabe M, Mangiarini L, Laywell ED, et al. Loss of cortical and 1256  
1195 thalamic neuronal tenascin-C expression in a transgenic mouse 1257  
1196 expressing exon 1 of the human Huntington disease gene. J Comp 1258  
1197 Neurol 2001;430:485–500. 1259  
1198 [27] Iannicola C, Moreno S, Oliverio S, Nardacci R, Ciofi-Luzzatto A, 1260  
1199 Piacentini M. Early alterations in gene expression and cell 1261  
1200 morphology in a mouse model of Huntington's disease. 1262  
J Neurochem 2000;75:830–9. 1263  
1201 [28] Bibb JA, Yan Z, Svenningsson P, et al. Severe deficiencies in 1264  
1202 dopamine signaling in presymptomatic Huntington's disease mice. 1265  
Proc Natl Acad Sci U S A 2000;97:6809–14. 1266  
1203 [29] Wytenbach A, Swartz J, Kita H, et al. Polyglutamine expansions 1267  
1204 cause decreased CRE-mediated transcription and early gene 1268  
1205 expression changes prior to cell death in an inducible cell model of 1269  
1206 Huntington's disease. Hum Mol Genet 2001;10:1829–45. 1270  
1207 [30] Harris AS, Denovan-Wright EM, Hamilton LC, Robertson HA. 1271  
1208 Protein kinase C beta II mRNA levels decrease in the striatum and 1272  
1209 cortex of transgenic Huntington's disease mice. J Psychiatry Neurosci 1273  
2001;26:117–22. 1274  
1210 [31] Deckel AW, Tang V, Nuttal D, Gary K, Elder R. Altered neuronal 1275  
1211 nitric oxide synthase expression contributes to disease progression in 1276  
1212 Huntington's disease transgenic mice. Brain Res 2002;939:76–86. 1277  
1213 [32] Deckel AW, Elder R, Fuhrer G. Biphasic developmental changes in 1278  
1214 Ca<sup>2+</sup> /calmodulin-dependent proteins in R6/2 Huntington's disease 1279  
1215 mice. NeuroReport 2002;13:707–11. 1280  
1216 [33] Luthi-Carter R, Hanson SA, Strand AD, et al. Dysregulation of gene 1281  
1217 expression in the R6/2 model of polyglutamine disease: parallel 1282  
1218 changes in muscle and brain. Hum Mol Genet 2002;11:1911–26. 1283  
1219 [34] Karpuj MV, Becher MW, Springer JE, et al. Prolonged survival and 1284  
1220 decreased abnormal movements in transgenic model of Huntington 1285  
1221 disease, with administration of the transglutaminase inhibitor 1286  
1222 cystamine. Nat Med 2002;8:143–9. 1287  
1223 [35] Kita H, Carmichael J, Swartz J, et al. Modulation of polyglutamine- 1288  
1224 induced cell death by genes identified by expression profiling. Hum 1289  
1225 Mol Genet 2002;11:2279–87. 1290  
1226 [36] Lastres-Becker I, Hansen HH, Berrendero F, et al. Alleviation of 1291  
1227 motor hyperactivity and neurochemical deficits by endocannabinoid 1292  
1228 uptake inhibition in a rat model of Huntington's disease. Synapse 1293  
2002;44:23–35. 1294  
1229 [37] Luthi-Carter R, Strand AD, Hanson SA, et al. Polyglutamine and 1295  
1230 transcription: gene expression changes shared by DRPLA and 1296  
1231 Huntington's disease mouse models reveal context-independent 1297  
1232 effects. Hum Mol Genet 2002;11:1927–37. 1298  
1233 [38] Chan EYW, Luthi-Carter R, Strand A, et al. Increased huntingtin 1299  
1234 protein length reduces the severity of polyglutamine-induced gene 1300  
1235 expression changes in mouse models of huntingtin disease. Hum Mol 1301  
1236 Genet 2002;11:1939–51. 1302  
1237 [39] Li SH, Cheng AL, Li H, Li XJ. Cellular defects and altered gene 1303  
1238 expression in PC12 cells stably expressing mutant huntingtin. 1304  
J Neurosci 1999;19:5159–72. 1305

- 1233 [40] Wu ZL, O’Kane TM, Scott RW, Savage MJ, Bozyczko-Coyne D. Protein tyrosine phosphatases are up-regulated and participate in cell  
1234 death induced by polyglutamine expansion. *J Biol Chem* 2002;277:  
1235 44208–13.
- 1236 [41] Sipione S, Rigamonti D, Valenza M, et al. Early transcriptional  
1237 profiles in huntingtin-inducible striatal cells by microarray analyses.  
1238 *Hum Mol Genet* 2002;11:1953–65.
- 1239 [42] Faber PW, Barnes GT, Srinidhi J, Chen J, Gusella JF, MacDonald  
1240 ME. Huntingtin interacts with a family of WW domain proteins. *Hum*  
1241 *Mol Genet* 1998;7:1463–74.
- 1242 [43] Boutell JM, Thomas P, Neal JW, et al. Aberrant interactions of  
1243 transcriptional repressor proteins with the Huntington’s disease gene  
1244 product, huntingtin. *Hum Mol Genet* 1999;8:1647–55.
- 1245 [44] Steffan JS, Kazantsev A, Spasic-Boskovic O, et al. The Huntington’s  
1246 disease protein interacts with p53 and CBP and represses transcrip-  
1247 tion. *Proc Natl Acad Sci U S A* 2000;97:6763–8.
- 1248 [45] Nucifora Jr. FC, Sasaki M, Peters MF, et al. Interference by huntingtin  
1249 and atrophin-1 with cbp-mediated transcription leading to cellular  
1250 toxicity. *Science* 2001;291:2423–8.
- 1251 [46] Kegel KB, Meloni AR, Yi Y, et al. Huntingtin is present in the  
1252 nucleus, interacts with the transcriptional corepressor C-terminal  
1253 binding protein, and represses transcription. *J Biol Chem* 2002;277:  
1254 7466–76.
- 1255 [47] Dunah AW, Jeong H, Griffin A, et al. Sp1 and TAFII130  
1256 transcriptional activity disrupted in early Huntington’s disease.  
1257 *Science* 2002;296:2238–43.
- 1258 [48] Rega S, Stiewe T, Chang DI, et al. Identification of the full-length  
1259 huntingtin-interacting protein p231HBP/HYPB as a DNA-binding  
1260 factor. *Mol Cell Neurosci* 2001;18:68–79.
- 1261 [49] Li S-H, Cheng AL, Zhou H, et al. Interaction of Huntington disease  
1262 protein with transcriptional activator Sp1. *Mol Cell Biol* 2002;22:  
1263 1277–87. [Abstract] [Full Text].
- 1264 [50] Kadonaga JT, Carner KR, Masiarz FR, Tjian R. Isolation of cDNA  
1265 encoding transcription factor Sp1 and functional analysis of the DNA  
1266 binding domain. *Cell* 1987;51:1079–90.
- 1267 [51] Shimohata T, Nakajima T, Yamada M, et al. Expanded polyglutamine  
1268 stretches interact with TAFII130, interfering with CREB-dependent  
1269 transcription. *Nat Genet* 2000;26:29–36.
- 1270 [52] Mantamadiotis T, Lemberger T, Bleckmann SC, et al. Disruption of  
1271 CREB function in brain leads to neurodegeneration. *Nat Genet* 2002;  
1272 31:47–54.
- 1273 [53] Freedman DA, Wu L, Levine AJ. Functions of the MDM2  
1274 oncoprotein. *Cell Mol Life Sci* 1999;55:96–107.
- 1275 [54] Suhr ST, Senut MC, Whiteledge JP, Faull KF, Cuizon DB, Gage FH.  
1276 Identities of sequestered proteins in aggregates from cells with  
1277 induced polyglutamine expression. *J Cell Biol* 2001;153:283–94.
- 1278 [55] Hollenberg AN. Thyroid hormone receptor isoforms, nuclear  
1279 corepressors and coactivators: new insights into thyroid hormone  
1280 action. *Curr Opin Endocrinol Diabetes* 1998;5:314–20.
- 1281 [56] Yohrling GJ, Farrell LA, Hollenberg AN, Cha J-HJ. Mutant  
1282 huntingtin increases nuclear corepressor function and enhances  
1283 ligand-dependent nuclear hormone receptor activation. *Mol Cell*  
1284 *Neurosci*, in press.
- 1285 [57] McCampbell A, Taylor JP, Taye AA, et al. CREB-binding protein  
1286 sequestration by expanded polyglutamine. *Hum Mol Genet* 2000;9:  
1287 2197–202.
- 1288 [58] Jiang H, Nucifora Jr. FC, Ross CA, DeFranco DB. Cell death  
1289 triggered by polyglutamine-expanded huntingtin in a neuronal cell  
1290 line is associated with degradation of CREB-binding protein. *Hum*  
1291 *Mol Genet* 2003;12:1–12.
- 1292 [59] Jenuwein T, Allis CD. Translating the histone code. *Science* 2001;  
1293 293:1074–80.
- 1294 [60] Ueda H, Goto J, Hashida H, et al. Enhanced SUMOylation in polyglut-  
1295 amine diseases. *Biochem Biophys Res Commun* 2002;293:307–13.
- 1296 [61] Steffan JS, Bodai L, Pallos J, et al. Histone deacetylase inhibitors  
1297 arrest polyglutamine-dependent neurodegeneration in *Drosophila*.  
1298 *Nature* 2001;413:739–43.
- 1299 [62] Hockly E, Richon VM, Woodman B, et al. Suberoylanilide  
1300 hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor  
1301 deficits in a mouse model of Huntington’s disease. *Proc Natl Acad Sci*  
1302 *U S A* 2003;100:2041–6.
- 1303 [63] Chen H, Lin RJ, Xie W, Wilpitz D, Evans RM. Regulation of  
1304 hormone-induced histone hyperacetylation and gene activation via  
1305 acetylation of an acetylase. *Cell* 1999;98:675–86.
- 1306 [64] Hazeki N, Tsukamoto T, Yazawa I, et al. Ultrastructure of nuclear  
1307 aggregates formed by expressing an expanded polyglutamine.  
1308 *Biochem Biophys Res Commun* 2002;294:429–40.
- 1309 [65] Waragai M, Lammers CH, Takeuchi S, et al. PQBP-1, a novel  
1310 polyglutamine tract-binding protein, inhibits transcription activation  
1311 by Brn-2 and affects cell survival. *Hum Mol Genet* 1999;8:977–87.
- 1312 [66] Okazawa H, Sudol M, Rich T. PQBP-1 (Np/PQ): a polyglutamine  
1313 tract-binding and nuclear inclusion-forming protein. *Brain Res Bull*  
1314 2001;56:273–80.
- 1315 [67] Okazawa H, Rich T, Chang A, et al. Interaction between mutant  
1316 ataxin-1 and PQBP-1 affects transcription and cell death. *Neuron*  
1317 2002;34:701–13.
- 1318 [68] Huang CC, Faber PW, Persichetti F, et al. Amyloid formation by  
1319 mutant huntingtin: threshold, progressivity and recruitment of normal  
1320 polyglutamine proteins. *Somat Cell Mol Genet* 1998;24:217–33.
- 1321 [69] Nakamura K, Jeong SY, Uchihara T, et al. SCA17, a novel autosomal  
1322 dominant cerebellar ataxia caused by an expanded polyglutamine in  
1323 TATA-binding protein. *Hum Mol Genet* 2001;10:1441–8.
- 1324 [70] Kazantsev A, Walker HA, Slepko N, et al. A bivalent Huntingtin  
1325 binding peptide suppresses polyglutamine aggregation and pathogen-  
1326 esis in *Drosophila*. *Nat Genet* 2002;30:367–76.
- 1327 [71] Yu ZX, Li SH, Nguyen HP, Li XJ. Huntingtin inclusions do not  
1328 deplete polyglutamine-containing transcription factors in HD mice.  
1329 *Hum Mol Genet* 2002;11:905–14.
- 1330 [72] Zuccato C, Ciammola A, Rigamonti D, et al. Loss of huntingtin-  
1331 mediated BDNF gene transcription in Huntington’s disease. *Science*  
1332 2001;293:493–8.
- 1333 [73] Reisine TD, Fields JZ, Stern LZ, Johnson PC, Bird ED, Yamamura  
1334 HI. Alterations in dopaminergic receptors in Huntington’s disease.  
1335 *Life Sci* 1977;21:1123–8.
- 1336 [74] Richfield EK, O’Brien CF, Eskin T, Shoulson I. Heterogeneous  
1337 dopamine receptor changes in early and late Huntington’s disease.  
1338 *Neurosci Lett* 1991;132:121–6.
- 1339 [75] Turjanski N, Weeks R, Dolan R, Harding AE, Brooks DJ. Striatal D1  
1340 and D2 receptor binding in patients with Huntington’s disease and  
1341 other choreas. A PET study. *Brain* 1995;118:689–96.
- 1342 [76] Andrews TC, Weeks RA, Turjanski N, et al. Huntington’s disease  
1343 progression. PET and clinical observations. *Brain* 1999;122:2353–63.
- 1344 [77] Spektor BS, Miller DW, Hollingsworth ZR, et al. Differential D<sub>1</sub> and  
1345 D<sub>2</sub> receptor-mediated effects on immediate early gene induction in a  
1346 transgenic mouse model of Huntington’s disease. *Mol Brain Res*  
1347 2002;102.
- 1348 [78] MacGibbon GA, Hamilton LC, Crocker SF, et al. Immediate-early  
1349 gene response to methamphetamine, haloperidol, and quinolinic acid  
1350 is not impaired in Huntington’s disease transgenic mice. *J Neurosci*  
1351 *Res* 2002;67:372–8.
- 1352 [79] Ariano MA, Aronin N, Difiglia M, et al. Striatal neurochemical  
1353 changes in transgenic models of Huntington’s disease. *J Neurosci Res*  
1354 2002;68:716–29.
- 1355 [80] Varani K, Rigamonti D, Sipione S, et al. Aberrant amplification of  
1356 A2A receptor signaling in striatal cells expressing mutant huntingtin.  
1357 *FASEB J* 2001;15:1245–7.
- 1358 [81] Cepeda C, Hurst RS, Calvert CR, et al. Transient and progressive  
1359 electrophysiological alterations in the corticostriatal pathway in a  
1360 mouse model of Huntington’s disease. *J Neurosci* 2003;23:961–9.
- 1361 [82] Reiner A, Albin RL, Anderson KD, D’Amato CJ, Penney JB, Young  
1362 AB. Differential loss of striatal projection neurons in Huntington  
1363 disease. *Proc Natl Acad Sci U S A* 1988;85:5733–7.
- 1364 [83] Utal AK, Stopka AL, Roy M, Coleman PD. PEP-19 immunohisto-  
1365 chemistry defines the basal ganglia and associated structures in

- 1345 the adult human brain, and is dramatically reduced in Huntington's  
1346 disease. *Neuroscience* 1998;86:1055–63.
- 1347 [84] Menalled L, Zanjani H, MacKenzie L, et al. Decrease in striatal  
1348 enkephalin mRNA in mouse models of Huntington's disease. *Exp*  
1349 *Neurol* 2000;162:328–42.
- 1350 [85] Wellington C, Leavitt B, Hayden MEA. Huntington disease: new  
1351 insights on the role of huntingtin cleavage. *J Neural Transm Suppl*  
1352 2000;58.
- 1353 [86] McCampbell A, Taye AA, Whitty L, Penney E, Steffan JS, Fischbeck  
1354 KH. Histone deacetylase inhibitors reduce polyglutamine toxicity.  
1355 *Proc Natl Acad Sci U S A* 2001;98:15179–84.
- 1356 [87] Lastres-Becker I, Berrendero F, Lucas JJ, et al. Loss of mRNA levels,  
1357 binding and activation of GTP-binding proteins for cannabinoid  
1358 CB(1) receptors in the basal ganglia of a transgenic model of  
1359 Huntington's disease. *Brain Res* 2002;929:236–42.
- 1360 [88] Glass M, Dragunow M, Faull RL. The pattern of neurodegeneration  
1361 in Huntington's disease: a comparative study of cannabinoid,  
1362 dopamine, adenosine and GABA(A) receptor alterations in the  
1363 human basal ganglia in Huntington's disease. *Neuroscience* 2000;  
1364 97:505–19.
- 1365 [89] Fossale E, Wheeler VC, Vrbanac V, et al. Identification of a  
1366 presymptomatic molecular phenotype in Hdh CAG knock-in mice.  
1367 *Hum Mol Genet* 2002;11:2233–41.
- 1368 [90] Schilling G, Becher MW, Sharp AH, et al. Intranuclear inclusions and  
1369 neuritic aggregates in transgenic mice expressing a mutant N-terminal  
1370 fragment of huntingtin. *Hum Mol Genet* 1999;8:397–407.
- 1371 [91] Hodgson JG, Agopyan N, Gutekunst CA, et al. A YAC mouse model  
1372 for Huntington's disease with full-length mutant huntingtin, cyto-  
1373 plasmic toxicity, and selective striatal neurodegeneration. *Neuron*  
1374 1999;23:181–92.
- 1375 [92] Levine MS, Klapstein GJ, Koppel A, et al. Enhanced sensitivity to N-  
1376 methyl-D-aspartate receptor activation in transgenic and knockin  
1377 mouse models of Huntington's disease. *J Neurosci Res* 1999;58:  
1378 515–32.
- 1379 [93] Holbert S, Denghien I, Kiechle T, et al. The Gln-Ala repeat  
1380 transcriptional activator CA150 interacts with huntingtin: neuro-  
1381 pathologic and genetic evidence for a role in Huntington's disease  
1382 pathogenesis. *Proc Natl Acad Sci U S A* 2001;98:1811–6.
- 1383 [94] Goldstrohm AC, Albrecht TR, Sune C, Bedford MT, Garcia-Blanco  
1384 MA. The transcription elongation factor CA150 interacts with RNA  
1385 polymerase II and the pre-mRNA splicing factor SF1. *Mol Cell Biol*  
1386 2001;21:7617–28.
- 1387 [95] Takano H, Gusella JF. The predominantly HEAT-like motif structure  
1388 of huntingtin and its association and coincident nuclear entry with  
1389 dorsal, an NF-kB/Rel/dorsal family transcription factor. *BMC*  
1390 *Neurosci* 2002;3:15.
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