Published in final edited form as:
Prog Neurobiol. 2007 November ; 83(4): 228–248.

Transcriptional Signatures in Huntington's Disease

Jang-Ho J. Cha, MD, PhD
MassGeneral Institute for Neurodegenerative Disease, 114 16th Street/B114-2000, Charlestown, MA 02129-4404, USA, Tel: 617-724-1481, Fax: 617-724-1480, Email: cha@helix.mgh.harvard.edu

Abstract

While selective neuronal death has been an influential theme in Huntington's disease (HD), there is now a preponderance of evidence that significant neuronal dysfunction precedes frank neuronal death. The best evidence for neuronal dysfunction is the observation that gene expression is altered in HD brain, suggesting that transcriptional dysregulation is a central mechanism. Studies of altered gene expression began with careful observations of post-mortem human HD brain and subsequently were accelerated by the development of transgenic mouse models. The application of DNA microarray technology has spurred tremendous progress with respect to the altered transcriptional processes that occur in HD, through gene expression studies of both transgenic mouse models as well as cellular models of HD. Gene expression profiles are remarkably comparable across these models, bolstering the idea that transcriptional signatures reflect an essential feature of disease pathogenesis. Finally, gene expression studies have been applied to human HD, thus not only validating the approach of using model systems, but also solidifying the idea that altered transcription is a key mechanism in HD pathogenesis. In the future, gene expression profiling will be used as a readout in clinical trials aimed at correcting transcriptional dysregulation in Huntington's disease.

Keywords

Huntington's disease; transcription; gene expression; transgenic mouse; mRNA; microarray

1. Introduction

1.1 The cycle of discovery

The ‘cycle of discovery’ is well-demonstrated in considering Huntington's disease (Wexler et al., 1991). In this cycle, fundamental observations about a disease are made in human patients. These clinical and pathologic observations form the foundation from which scientific hypotheses can be constructed. These hypotheses in turn lead to identification of defective genes or environmental causes, development of animal models, and preclinical testing. *In vitro* models, particularly those involving cell biology, as well as transgenic animal models provide additional insight into mechanisms of disease pathogenesis. The cycle is completed when these advances are brought to bear upon the initial human malady. In the example of Huntington's disease, fundamental observations including field studies in Venezuela led ultimately to the discovery of the *HD* gene in 1993 (Huntington's Disease Collaborative Research Group, 1993). Discovery of the molecular defect then led to the development of transgenic HD mice, followed subsequently by model systems including yeast, *Drosophila*, *C.*

Correspondence to: Jang-Ho J. Cha.

elegans, and transgenic rats. Preclinical therapeutics which have been screened on transgenic animal models have now been introduced into human clinical trials, thus completing the cycle of discovery.

1.2 Transcriptional dysregulation as an example of the cycle of discovery

The idea of transcriptional dysregulation in Huntington's disease thus follows a similar trajectory. Starting from initial observations in post-mortem human HD brain, subsequent observations were first confirmed and then expanded in transgenic mouse models, and finally, the human HD brain has been re-interrogated. Along the way, we have gained significant perspective on how the mutant form of the huntingtin (Htt) protein causes selective neuronal death in the brain. In addition, these transcriptional studies have fundamentally revolutionized our view of the role of normal huntingtin. These steps through the cycle of discovery confirm that transcriptional dysregulation is a key central feature of HD pathogenesis, and may therefore serve as a target for rational therapy. In this review, I focus on the transcriptional signatures, those studies that have detailed the alteration of mRNA expression in Huntington's disease.

2. Early evidence of altered gene expression

2.1 Neurodegeneration of Huntington's disease is region- and cell-specific: human studies

The pathologic hallmark of Huntington's disease is a regionally distinct pattern of cell loss, with the caudate and putamen (nuclei of the basal ganglia, collectively called the striatum in non-human mammals) showing the highest degree of cell loss (Vonsattel et al., 1985). The basal ganglia are a set of subcortical gray matter structures which are involved in various aspects of motor control, cognition, and sensory pathways (Graybiel, 1990). Pathologic changes have also been described in cortex, thalamus, and subthalamic nucleus (Hedreen et al., 1991). Recently, there has been increasing recognition that there is progressive cortical atrophy, and that cortex may be affected in an important way (Cudkowicz and Kowall, 1990; Rosas et al., 2005; Rosas et al., 2003; Rosas et al., 2002). The recognition that cortex is involved has given rise to the idea that striatal neurons are in part susceptible because they receive glutamatergic input from corticostriatal afferents, a model of non-cell-autonomous cell death (Gu et al., 2005).

A major conceptual advance was the idea that cell loss was not indiscriminate, but rather that there was selective neuronal vulnerability. Within the caudate-putamen, medium spiny neurons —neurons that send projections to other nuclei—were preferentially lost, while interneurons were relatively spared (Ferrante et al., 1985). Moreover, this pattern of death of medium spiny projection neurons with relative sparing of NADPH-diaphorase-containing interneurons could be reproduced with intrastriatal injections of glutamate receptor agonists (Beal et al., 1986; Coyle and Schwarcz, 1976; McGeer and McGeer, 1976). This seminal observation gave rise to the idea that certain neuronal populations were especially sensitive to toxicity in Huntington's disease. Moreover, it was these observations in the context of Huntington's disease that gave rise to the notion that a neurotransmitter—namely, glutamate—could have toxic effects if its actions were abnormally regulated.

2.1.1 Neurotransmitter receptors in human HD caudate—Around this time, there were numerous observations of altered neurochemical measures in HD (reviewed in Yohrling and Cha, 2002). Most of these decreases in neurotransmitter levels, neurotransmitter metabolites, or neurotransmitter receptors were interpreted as a consequence of loss of medium spiny projection neurons. For example, Young and colleagues postulated that loss of NMDA receptors in the caudate-putamen of HD patients resulted from excitotoxic cell death, with NMDA-receptor-bearing cells being preferentially targeted (Young et al., 1988). This observation was in keeping with the idea that NMDA receptor mediated toxicity was a primary

etiologic factor in HD pathogenesis. A subsequent study from the same group actually refuted the idea that there was preferential involvement of NMDA receptors, as Dure and colleagues found evidence of decreased receptor binding not only to NMDA receptors but also to quisqualate and kainate subtypes of glutamate receptors (Dure et al., 1991). Using receptor binding autoradiography, Dure et al. found that measures of NMDA receptors (NMDA-displaceable [^{3}H]glutamate, [^{3}H]glycine and [^{3}H]MK-801 binding) were decreased to a similar extent (50-60%) as measures of other non-NMDA ionotropic receptors ([^{3}H]kainate and [^{3}H] AMPA binding). However, binding to metabotropic glutamate receptors was decreased to a lesser extent (26-31%), suggesting that glutamate receptors were not all affected to the same degree. Also, Dure et al. noted that the binding pattern of all of these glutamatergic ligands was different from the patterns seen in normal human caudate, with more patchiness observed in the HD samples. There was no clear relationship between the matrix/patch compartments that had been described by acetylcholinesterase histochemistry (Graybiel, 1983). Even so, there were indications that neurochemical alterations were not simply explained by cell loss. These observations helped form the basis for the idea that there was selective impact on neurotransmitter systems in the HD brain.

2.1.2 Early human *in situ* hybridization studies—There were early reports that certain mRNA species were specifically decreased. Augood *et al.* applied the then-new technique of *in situ* hybridization to measure messenger RNA (mRNA) encoding the signaling neuropeptides enkephalin and substance P (Augood et al., 1996). In the neuropathological grading scheme derived by Vonsattel and colleagues, grade 0 refers to brains that have no recognizable neuropathologic abnormality, whereas grade 1 implies that neuropathological abnormalities are only apparent microscopically (Vonsattel et al., 1985). Even in early grade 0/1 HD brains, there was decreased expression of preproenkephalin and substance P mRNA, suggesting that one could not invoke cell loss as a cause. Further, within the caudate-putamen, there was a heterogeneous distribution of mRNA loss, reinforcing the idea of selective neuronal susceptibility. However, the susceptibility here applies not to the phenomenon of cell death but of downregulation of target genes. Reminiscent of the receptor binding studies, there were regions of caudate that were preferentially affected, with the dorsal regions demonstrating more decreases of these mRNA species. This finding seemed to presage the observation that neuropathological damage, as assessed by immunoreactivity for glial fibrillary acidic protein (GFAP), seems to progress in a dorsal to ventral direction, affecting the striosomal compartment first (Hedreen and Folstein, 1995). There was also decreased numbers of substance P and preproenkephalin mRNA on a per-cell basis.

Augood and colleagues followed up with a similar study showing that dopamine receptors were altered in early HD brain (Augood et al., 1997). In this study, the authors studied mRNA encoding dopamine D1 receptor (D1) and dopamine D2 receptor (D2) in the caudates of HD brains of different pathological grade. For the dopamine D1 receptor mRNA, in early stage cases, they observed decreased numbers of cell expressing the message, although those cells expressing the dopamine D1 receptor message did so at normal levels (as assessed by number of mRNA molecules per cell). In later grade brains, they actually observed *increased* D1 message per cell, which they attributed to a shift in cell populations. As medium spiny projection neurons disappear, there are relatively more interneurons, which contain high levels of D1 mRNA. Dopamine D2 receptor mRNA, in contrast, was apparently regulated in a different way. In early grade cases, there were not only fewer cells expressing D2 mRNA but also the number of D2 messages per cell was decreasing. This finding suggested that cell loss alone was insufficient to account for the decrease in D2 message. Importantly, given the difference between D1 and D2, this study indicated that mRNA molecules are altered differentially in HD brain.

Norris et al. investigated the interneurons of the caudate-putamen (Norris et al., 1996). These authors found levels of mRNA encoding neuronal nitric oxide synthase (nNOS) and somatostatin were decreased on a per-cell basis, despite survival of neurons containing neuropeptide Y, nNOS, NADPH diaphorase, and somatostatin. These authors concluded that these striatal neurons survive, but are damaged, and they inferred a progressive downregulation of nNOS messenger RNA.

Arzberger et al. studied mRNA encoding NMDA subunits of the glutamate receptor in human HD brain (Arzberger et al., 1997). Again, these authors used *in situ* hybridization with radioactive oligonucleotides in order to obtain quantitative results. Messenger RNA encoding the NR1 and NR2B subunits were decreased in accordance with disease severity, as was mRNA encoding the glutamate transporter GLT1. Decreases in mRNA were more prominent in the putamen than the caudate, even though there was more gross atrophy in the caudate, again suggesting that decreases in mRNA levels did not simply mirror cell loss.

Analyzing mRNA in human brain samples is notoriously difficult, as RNA is rapidly degraded, and post-mortem intervals can vary widely, the problem being magnified if the number of cases interrogated is small. However, these early mRNA studies were reinforced by a number of measures of neurotransmitter receptor proteins, neurotransmitters, and neurotransmitter metabolites (reviewed in Yohrling and Cha, 2002). In general, these studies focused on specific decreases in particular markers, with relative sparing of other markers. Again, these studies pointed out the possibility that there were regional- or cell-specific decreases in expression of these important signaling molecules. All of these studies were confounded by the issue of cell death. That is, if one observed a decrease in a particular marker, how could one be sure that this decrease was not simply a reflection of loss of cells? The arguments that there were relative decreases in certain markers over others were less than convincing. More informative were the studies of Augood and colleagues (Augood et al., 1997; Augood et al., 1996), in that they looked at early stage brains and measured mRNA levels on a per-cell basis, but the confounding issue of cell death still lingered.

2.2 Transgenic mice: a window into transcriptional dysregulation

A major breakthrough in the HD field was the creation of a mouse model by Gillian Bates and colleagues (Mangiarini et al., 1996). These mice, named R6 lines, were created by inserting exon 1 of the human *HD* gene, under the control of the human *HD* promoter, into mouse embryonic stem cells. The human *HD* gene is comprised of 67 exons, but the polymorphic CAG region that encodes the polyglutamine moiety in the huntingtin protein is contained within exon 1. Moreover, since Bates and colleagues were interested in studying trans-generational CAG repeat instability, they engineered an extremely high number of repeats. The most common abnormal CAG repeat number among HD patients is 44; R6 mouse lines were created with up to 150 repeats. Surprisingly, despite expressing a construct encoding only about 3% of the full-length huntingtin protein, R6 mice displayed an abnormal phenotype that was, in many respects, reminiscent of human Huntington's disease. R6 mice appear normal at birth, but then develop progressive problems in movement as well as defects in learning and memory (Carter et al., 1999; Lione et al., 1999; Mangiarini et al., 1996). In addition, R6 mice lose brain weight and body weight, which is again reminiscent of human patients with HD (Mangiarini et al., 1996). R6/2 mice died at 12 weeks of age, at which time, their brains were significantly atrophied. Thus, the amino terminus of the huntingtin protein with expanded polyglutamine is sufficient to cause many HD-like abnormalities.

In their initial report, Mangiarini et al. failed to demonstrate any significant neuroanatomical abnormalities in brains of R6/2 mice, as assessed by immunohistochemistry for glial fibrillary acidic protein (GFAP) or the mouse macrophage and microglial marker F4/80, Nissl staining, and thionin staining (Mangiarini et al., 1996). Surprisingly, although the brain size was smaller

than wild-type littermates, there were apparently normal numbers of striatal neurons and no clearly degenerating neurons were seen. Subsequently, a subset of neurons have been identified that undergo so-called dark cell degeneration, but these cells are not numerous and they are most detectable in the anterior cingulate (Turmaine et al., 2000). Thus, while some degenerating neurons have been detected in these mice, it is fair to say that widespread neuronal death is not a predominant neuropathological feature of R6 transgenic mice. These mice thus put front and center the controversy between neuronal death versus neuronal dysfunction. Despite expressing a very short piece of the *HD* gene, R6 mice recapitulate many of the features of HD, including apparently normal development, progressive neurologic abnormalities, and premature death. These findings, however, could not be explained by invoking large-scale neuronal death, and, moreover, there was not an obvious clue as to any neurochemical derangements.

Other lines of transgenic mice have also been created, and important lessons have been gleaned by comparing different mouse models. In general, mouse lines that contain a truncated form of the *HD* gene tend to show abnormal symptoms before lines containing full-length huntingtin (Menalled and Chesselet, 2002). The N171-82Q transgenic mouse contains a truncated human *HD* gene under the control of the mouse prion promoter, with a longer transgene than was used in the R6 lines. N171-82Q mice express a transprotein of 171 amino acids and 82 glutamines, show an abnormal neurological phenotype, accumulate ubiquitinated inclusions, and have shortened lifespan, although they survive longer than R6 mice. HD94 is another line of exon1 mice, but in this case, the transgene, which has 94 glutamines, is tetracycline-regulatable (Yamamoto et al., 2000). In HD94 mice, turning off transgene expression resulted in reversal of neuropathological and behavioral measures, suggesting that some of the pathology in HD is potentially reversible.

Mouse models expressing full-length versions of huntingtin have also been created, both as transgenics (Hodgson et al., 1999; Reddy et al., 1998; Slow et al., 2003) and as knock-in models in which extra CAG repeats are inserted into the endogenous mouse locus (Menalled et al., 2002; Shelbourne et al., 1999; Wheeler et al., 2000). Full-length models have the conceptual advantage of more faithfully replicating the genetic mutation in human HD, but these mice have much slower onset of abnormal behavioral and neuropathologic abnormalities, compared to mice expressing truncated versions of huntingtin.

2.2.1 Altered mRNA expression in transgenic mice: single gene studies

2.2.1.1 Initial studies in R6 mouse lines: Despite apparently normal numbers of neurons, the R6/2 mice clearly had an abnormal phenotype. Moreover, the preliminary survey of neurochemical markers had been unrevealing. Cha et al. embarked on an investigation of glutamate receptors in these mice, as glutamate excitotoxicity had historically been a leading idea regarding HD pathogenesis (Albin and Greenamyre, 1992; Beal et al., 1991; Bruyn and Stoof, 1990; Coyle and Schwarcz, 1976; DiFiglia, 1990). The strongest evidence for the involvement of the neurotransmitter glutamate was the observation that injection of glutamate analogues into the striatum of rodents or primates could reproduce the pattern of neuropathological damage seen in HD, namely, death of medium spiny projection neurons with relative sparing of interneurons. Indeed, many were surprised upon the discovery of the gene to find that the *IT-15* transcript, subsequently renamed the *HD* gene, was not a glutamate receptor subunit or another molecule clearly related to glutamatergic neurotransmission. Nonetheless, in the absence of a clear neuropathological abnormality in R6 mice, measuring glutamate receptors was a reasonable initial step.

In R6/2 mice, glutamate receptors, as well as other neurotransmitter receptors, were altered in a fashion that was remarkably similar to that seen in human HD caudate-putamen (Cha et al., 1998). That is, certain neurotransmitter receptors seemed to be quite selectively downregulated

—for example, dopamine D1 and D2 receptors. Receptor binding autoradiography also revealed decreases in AMPA and metabotropic glutamate receptors, with relative preservation of NMDA receptor binding. Muscarinic cholinergic receptors were also decreased, but there was not difference in GABA receptor binding. Interestingly, decreases in D1 dopamine receptor binding and expression could be observed by just four weeks of age, well before the onset of behavioral and motor symptoms in these mice. These findings indicated that mouse models of HD replicated the pattern of receptor alterations that have been observed in human HD. In addition, receptor alterations were specific, in that certain receptors were altered while others were not. The reminiscent pattern of neurotransmitter receptor losses in R6/2 mice argued that receptor downregulation was not simply reflective of neuronal loss, since there was not widespread striatal cell death in these mice.

Receptor binding autoradiography is a measure of the amount of receptor protein, and decreased protein could result from a number of mechanisms, including disrupted trafficking or accelerated protein degradation. An alternate explanation was that the decreased protein levels actually reflected a failure to generate adequate amounts of the corresponding mRNA. In order to discriminate between these possibilities, Cha and colleagues measured levels of mRNA encoding neurotransmitter receptors, and found that those receptors that had decreased proteins levels had decreased mRNA levels as well (Cha et al., 1999; Cha et al., 1998). For example, there were decreased mRNA encoding the mGluR1, mGluR2, and mGluR3 subtypes of the metabotropic glutamate receptors, as well as dopamine D1 and D2 receptors. In contrast, mRNA encoding the NR1 subunit of the NMDA receptor and β-actin were expressed at normal levels. These studies confirmed that there was selective alteration of certain mRNA molecules in R6/2 mice, thereby implicating a transcriptional problem in HD.

One could argue that decreases in mRNA encoding neurotransmitter receptors were a developmental effect, as the mutant transgene is expressed throughout development. Indeed, deletion of the huntingtin-encoding gene in mice results in embryonic lethality (White et al., 1997; Zeitlin et al., 1995). However, the observation that young R6/2 mice were phenotypically indistinguishable from wild-type littermates argues against the notion of a developmental defect. In addition, time course experiments demonstrate that 4-week-old transgenic mice start off with nearly normal levels of neurotransmitter mRNA, with levels decreasing when measured at 8 or 12 weeks of age (Cha et al., 1999). This situation parallels what occurs in human subjects. Positron emission tomography (PET) scanning reveals decreases in dopamine D2 receptor binding potential in HD gene-positive human subjects who are clinically asymptomatic, supporting the notion that functional changes can occur before overt clinical symptoms develop (Andrews et al., 1999). These studies suggest that levels of key molecules decline over time in the HD brain.

Similar studies were performed to characterize the neurotransmitter changes in different lines of R6 mice (Cha et al., 1999). Decreases in adenosine A2a, dopamine D1 and dopamine D2 receptor binding were observed in the R6/1, R6/2 and R6/5 HD mouse lines. All of the lines develop an abnormal phenotype, albeit at different time points (Mangiarini et al., 1996). Transgenic mice expressing exon 1 of the human HD gene with 18 CAG repeats did not show any significant changes in neurotransmitters, indicating that receptor alterations were caused by the presence of the abnormally expanded CAG repeats present in the R6 lines. Receptor binding decreases were preceded by selective decreases in the corresponding mRNA species; significant decreases in D1 mRNA were observed in 4-week-old R6/2 mice without a corresponding decrease in D1 binding. Thus, mRNA changes may not always be accompanied by changes in protein levels, which appear to follow later. Again, this early-stage decrease in dopamine receptor mRNA is reminiscent to what has been reported for human HD cases (Augood et al., 1997). These observations suggested that the altered transcription of specific

genes might contribute to the development of clinical symptoms in HD, and that transcriptional dysregulation may be a key pathological mechanism in HD (Cha, 2000).

2.2.2 Categories of downregulated genes—Following these initial studies, there were a number of genes that were shown to be aberrantly expressed in transgenic R6/2 mice as well as other lines of transgenic HD mice. Interestingly, the first genes to be identified as being downregulated fell into several distinct categories including neurotransmitter receptors, intracellular signaling molecules, and cytoskeletal proteins. The first sets of genes that were identified as being altered in transgenic HD mice were informed by prior observations of neurochemical changes in postmortem human HD brain, and thus focused heavily on molecules involved in neurotransmission. In addition, second messengers and synaptic proteins have been found to be altered in transgenic R6 mice.

2.2.2.1 Neurotransmitter receptors: Other neurotransmitter receptors were found to be decreased in transgenic mouse models. For example, decreases have been found in CB1 receptors in R6/1 and R6/2 mice (Denovan-Wright and Robertson, 2000; McCaw et al., 2004), as well as in HD94 mice (Lastres-Becker et al., 2002), reminiscent of what had been found in human HD brain (Glass et al., 2000; Glass et al., 1993; Richfield and Herkenham, 1994).

Glutamate receptors have historically been important in the field of HD (DiFiglia, 1990). In addition to the metabotropic glutamate receptors, other subtypes of glutamate receptors have been identified as downregulated in R6 mouse lines, including AMPA receptors (Cha et al., 1998) and the NR2a and NR2b subunits of the NMDA receptor (Luthi-Carter et al., 2003). Interestingly, in terms of NMDA receptors, there was more downregulation in the hippocampus as opposed to the striatum. This observation calls into question whether the striatum is uniquely affected in HD. One of the most puzzling realizations has been that the huntingtin protein is expressed throughout the brain, and not primarily in the striatum. Clearly, the striatum is the brain region that demonstrates the most severe neuronal loss, but at least in terms of downregulation of NMDA receptors, other areas are affected to a greater degree. One possibility that emerges is that the hippocampus, by virtue of downregulation of NMDA receptors, is actually relatively protected from glutamate excitotoxicity compared to the striatum, and as a result manifests less atrophy. Alteration of glutamate receptor mRNA is not limited to the striatum, as the cortex of R6/2 also demonstrates selective decreases of certain mRNA (Cha et al., 1998; Luthi-Carter et al., 2003).

2.2.2.2 Neurotransmitters: The GABAergic projection neurons of the striatum are further classified into two groups, one group co-containing substance P and projecting to the internal globus pallidus and the substantia nigra (striatonigral neurons) and the second group co-containing enkephalin and projecting to the external globus pallidus (striatopallidal neurons) (Albin et al., 1989). Of these, there seems to be preferential impact on the enkephalinergic striatopallidal neurons (Reiner et al., 1988). The expression of several neurotransmitters, neuropeptides, and GAD has also been examined in the R6/2 and CAG71 and CAG94 HD mice (Menalled et al., 2000). Both types of mice showed significant decreases in enkephalin mRNA in the striatum with quantitative *in situ* hybridization. Immunohistochemistry, itself not a quantative approach, did not reveal any significant protein changes for enkephalin, substance P, GAD_{65}, GAD_{67}, somatostatin or ChAT, indicating that the distribution and number of cells expressing these proteins are not altered in transgenic mice.

Reynolds and colleagues characterized the levels of many neurotransmitters in the R6/2 mice (Reynolds et al., 1999). The concentrations of GABA, glutamate, and the monoamine neurotransmitters were measured by HPLC in four brain regions, at times before and after the emergence of a HD-like phenotype. When compared to the human post-mortem findings,

several noteworthy disparities were observed. Striatal GABA in the R6/2 mice was normal. This finding suggests that loss of GABA-containing neurons is not an important early pathogenic event in the transgenic mice, and that the GABA decreases described in human HD are likely simply reflective of cell loss. This disparity between R6/2 and human HD brain suggests that such comparisons can be informative in terms of being able to ascribe certain alterations as a *consequence* of neuronal loss, as opposed to being a *cause* of neuronal loss. In the striatum of 12 week old R6/2 mice, there were significant decreases in dopamine and serotonin. A significant drop in striatal 5-hydoxyindolacetic acid (5-HIAA) levels, the major metabolite of serotonin, was seen in 4-, 8-, and 12-week-old animals. Similar decreases were observed at 8 and 12 weeks of age only in the hippocampus and brain stem of the R6/2 mice. Norepinephrine levels were decreased only in the hippocampus and brain stem. These data appear to indicate that the R6/2 model of HD has severely disrupted serotonergic and dopaminergic systems. This study did not look specifically at mRNA levels of neurotransmitter synthetic enzymes, focusing rather on measurements of the actual neurotransmitters themselves.

A particular story has emerged regarding brain-derived neurotrophic factor (BDNF). This peptide neurotrophic factor is decreased in the brains of HD mice and human HD brains (Zuccato et al., 2001). Striatal BDNF is actually produced in cortical neurons and transported through cortical efferents into the striatum. This group has found that wild-type Htt is a positive regulator of BDNF transcription in neurons, a function that is impaired in mutant Htt (Zuccato et al., 2001). In addition, there is reduced expression of trkB, which forms part of the cell surface receptor for BDNF (Gines et al., 2006). In all, these findings predict a defect in BDNF function, including consequences for dopaminergic neurotransmission (Pineda et al., 2005).

While the strtiatum has been the best-studied region, gene expression is altered in other brain regions. In the hypothalamus of transgenic mice expressing N-terminal huntingtin with expanded polyQ fused to eGFP, there was decreased expression of a number of hypothalamic neuropeptides, including oxytocin, vasopressin and cocaine-amphetamine-regulated transcript (Kotliarova et al., 2005), indicating that transcriptional dysregulation induced by exon 1 huntingtin can produce brain region-specific effects, again, affecting also non-striatal regions.

2.2.2.3 Neurotransmitter synthesis: In addition to receptors, neurotransmitters themselves as well as their synthetic enzymes have been identified as being downregulated. Tyrosine hydroxylase is the rate-limiting enzyme for catecholamine synthesis, and both transgenic HD mice and human HD brain demonstrate decreases in TH mRNA (Yohrling et al., 2002). *In situ* hybridization revealed decreased tyrosine hydroxylase mRNA in human HD substantia nigra neurons. In addition, mutant Htt disrupted transcription of tyrosine hydroxylase and dopamine beta-hydroxylase promoter constructs, pointing to a direct repressive role of mutant Htt. Dopamine content is reduced in the R6/2 brain by about 9 weeks of age, but long-term replacement of dopamine worsened motor function in these mice (Hickey et al., 2002).

2.2.2.4 Intracellular signaling: Also affected were molecules involved in intracellular signaling, particularly molecules involved in calcium signaling. Harris et al. identified protein kinase C beta II as downregulated in R6/2 mice (Harris et al., 2001). Bibb et al. identified severe reductions of dopamine- and cAMP-regulated phosphoprotein, M(r) 32 kDA (DARPP-32) in the brains of R6/2 mice (Bibb et al., 2000), and van Dellen et al. identified similar decreases in R6/1 mice (van Dellen et al., 2000). At 4 weeks of age, the R6/2 mice displayed severe deficiencies in dopamine signaling in the striatum. Neurochemical changes included selective reductions in striatal dopamine- and cAMP-regulated phosphoprotein, DARPP-32, as well as other dopamine-regulated phosphoprotein markers of medium spiny neurons (Bibb et al., 2000). At 6 weeks of age, the R6/2 mice resembled DARPP32 knockout mice, which also have abnormal dopamine signaling (Greengard et al., 1999). Dopamine

signaling is known to regulate gene transcription (Berke et al., 1998). The DARPP-32 defect also appears to be region-specific, in that R6 mice show decreased expression in the striatum, but normal levels in the kidney (Gomez et al., 2006).

2.2.2.5 Synaptic, cytoskeletal and structural proteins: Structural proteins comprise another important group of downregulated molecules. Tenascin-C is an extracellular matrix glycoprotein involved in cell migration, which is downregulated in R6/2 mouse brain (Kusakabe et al., 2001). These authors found normal expression of tenascin-C in astrocytes, but reduced expression in the cortex and thalamus. At later ages (12 weeks), neuronal expression of tenascin-C disappeared in several thalamic nuclei (e.g., the ventromedial, parafascicular, lateral posterior, and posterior thalamic groups) as well as in frontal cortex. At this age, there was an accompanying astrogliosis within the thalamus. These observations suggest that neurons are more susceptible to mRNA downregulation than astrocytes.

Another important category of downregulated molecules includes those involved in synaptic function. PSD-95 is a major organizing protein at the postsynaptic density, functioning as a scaffolding protein (Kennedy, 1997). Huntingtin binds directly to PSD-95 (Sun et al., 2001), and PSD-95 levels decreased in R6/2 mice (Luthi-Carter et al., 2003). Citron is a protein that binds to PSD-95 that is involved in dendritic spine formation (Zhang et al., 1999). Citron expression is decreased in the brains of N171-82Q mice (Jarabek et al., 2004). In addition, another glutamate receptor anchoring protein, alpha-actinin-2, is decreased in R6/2 mouse brain (Luthi-Carter et al., 2003). These observations of altered expression of postsynaptic proteins imply dysfunctional postsynaptic responses, particularly at excitatory NMDA receptor synapses, with important implications in terms of NMDA-receptor-mediated excitotoxicity (Jarabek et al., 2004; Luthi-Carter et al., 2003; Sun et al., 2001).

Complexin II is a component of the SNARE complex, and is likely to be involved in the control of exocytosis. Complexin II levels are progressively decreased in the brains of R6/2 mice (Morton and Edwardson, 2001). Complexin II was also found to co-aggregate with huntingtin to form intranuclear inclusions. This observation suggests that mutant huntingtin may disrupt neurotransmitter release by sequestering complexin II into aggregates and rendering the presynaptic vesicles unable to release neurotransmitter. Alpha-SNAP and complexin I are also decreased in R6/2 brain, but these changes lag behind the decrease in complexin II. Rabphilin 3A, another protein involved in exocytosis, is decreased in the brains of R6/2 mice (Smith et al., 2005). Taken together, these decreases predict abnormal exocytotic function in R6/2 mice, a prediction that has been confirmed electrophysiologically (Cepeda et al., 2003).

2.2.2.6 Other molecules: Other molecules aside from neurotransmitters, receptors, and cytoskeletal proteins have been shown to have decreased expression at the mRNA level in transgenic HD mice. de Chaldee et al. used Serial Analysis of Gene Expression (SAGE) to identify capucin (caudate-and putamen-enriched sequence) (de Chaldee et al., 2006). Capucin mRNA distribution exhibits a strikingly restricted pattern, detectable only in brain and, to a lesser extent, in testis, and essentially confined to the striatum. Capucin expression was decreased not only in R6/2 brain but also in rat striatal neurons infected with a lentiviral mutant Htt construct.

One of the surprising findings has been the lack of change in mRNA levels encoding mitochondrial proteins or proteins involved in apoptosis. There have been some reports of mRNA encoding mitochondrial proteins being affected. In striatal neurons transduced with a mutant huntingtin-containing lentivirus, there is decreased expression of Ip and Fp, two components of the mitochondrial electron transport chain (Benchoua et al., 2006). However, overall, the mRNA encoding mitochondrial proteins are expressed at normal levels. Similarly, there is a lack of changes for caspases, the apoptotic proteases that have been implicated in

HD neuronal death processes (Friedlander, 2003). Lack of mRNA expression changes does not mean that these processes are unimportant in HD pathogenesis, however. For example, much of the regulation of caspases occurs post-translationally, either through proteolytic cleavage or through intracellular trafficking (Sanchez et al., 2003).

Htt-induced transcriptional dysregulation is not limited to brain. Many lines of transgenic mice develop diabetes (Hurlbert et al., 1999), and in the pancreatic beta cells, there is diminished expression of key regulators of insulin gene transcription, including the pancreatic homeoprotein PDX-1, E2A proteins, and the coactivators CBP and p300 (Andreassen et al., 2002). Decreased expression of these key pancreatic transcription factors may lead to insulin deficiency and diabetes in these mice.

2.2.3 Summary of single gene studies in transgenic mice—Informed by neurochemical changes that had been previously observed in postmortem human HD brain, researchers have been able to confirm that many of these same changes also occur in the brain of transgenic HD mice. The implication of these neurochemical studies is that numerous neurotransmitter systems are impacted, affecting other regions in addition to the striatum. Widespread derangement of neurotransmitter systems contributes to the neuronal dysfunction that precedes neuronal death. Since many of these changes were observable in transgenic mice that expressed only exon 1 of the human *HD* gene, these studies also focused more attention to the polyglutamine moiety of the huntingtin protein. One of the implications is that such transcriptional changes may be related to polyglutamine, and, as such, may be applicable to other polyglutamine diseases (Ross, 2002). However, these ‘candidate gene’ approaches suffer from the bias of ascertainment, in that one can only measure what one sets out to detect. The possibility is that other sets of genes aside from those involved in neurotransmission might be similarly affected, but that these genes had yet to be investigated.

3. Microarray analysis of gene expression

While single-gene studies offered a tantalizing insight into how mutant huntingtin perturbed the normal functioning of neurons, these experiments could not measure all of the gene changes that occur. A logical extension of early single-gene studies was to harness the power of recently developed DNA microarray technology. Using nanolithography techniques originally developed for computer chip, manufacturers, notably Affymetrix, developed high-density arrays in which oligonucleotides corresponding to thousands of transcripts were arrayed onto a single ‘gene chip’ or glass slide. In contrast to the candidate gene approach, the use of DNA microarrays is an unbiased approach that promises a more comprehensive reckoning of all gene expression changes. By fluorescently labeling mRNA derived from tissues of interest, one could simultaneously assess expression levels of thousands of genes, thus permitting an instantaneous snapshot of all transcripts. Huntington's disease was the first human neurologic disease to which DNA microarray technology was applied (Luthi-Carter et al., 2000). Subsequently, gene expression abnormalities have been found in a number of neurodegenerative diseases, including Alzheimer's Disease (Wu et al., 2006), amyotrophic lateral sclerosis (Dangond et al., 2004), Parkinson's disease (Grunblatt et al., 2004; Miller et al., 2004; Noureddine et al., 2005), prion diseases (Xiang et al., 2004), frontotemporal dementia and progressive supranuclear palsy (Hauser et al., 2005), and multiple sclerosis (Steinman and Zamvil, 2003), suggesting that impacting the genome is another common feature of these disorders. The use of DNA microarray has proved especially powerful in the study of Huntington's disease pathogenesis. A special issue of *Human Molecular Genetics* was devoted largely to expression profiling studies of HD models (Orr, 2002). This collection of papers was remarkable in that researchers around the world freely joined the Huntington's Disease Array Group (HDAG), agreeing to perform experiments on a common platform, analyze data using similar tools, and share data.

The power of such high-throughput analysis brings with it some considerations. Strict statistical methodologies must be employed to account for the huge number of comparisons that are being made (Kooperberg et al., 2002). For example, in the current generation of DNA microarrays, one could easily compare expression levels for 11,000 genes simultaneously. The 'false discovery rate' thus becomes an indispensable measure in performing these studies (Pan, 2002). Certain types of statistical corrections can be introduced, but these corrections also suffer from the assumption that each gene is an independent entity, an assumption that is clearly not true. An obvious example is the case in which a particular transcription factor has an altered expression levels; one would expect that the genomic targets of this transcription factor may be altered as well, but not as independent occurrences. The statistics that have been applied to analyze these data continue to undergo an evolution to address these issues. There is general agreement that critical results obtained from microarray datasets ought to be confirmed by more traditional single gene methods, such as quantitative RT-PCR, Northern blot or *in situ* hybridization.

3.1 Microarray studies in transgenic mouse models of HD

Luthi-Carter and colleagues published the first study using DNA microarrays to measure gene expression in the striatum of R6/2 mice (Luthi-Carter et al., 2000). In this study, these authors used first-generation mouse chips, measuring the expression of 6,000 genes. Remarkably, only a small number were decreased, and these were restricted to genes encoding neurotransmitter, calcium and retinoid signaling pathway components. Overall, 1.7% of transcripts were altered at 6 weeks of age, and 1.2% at 12 weeks of age. Decreases outnumbered increases by a ratio of 3:1. Again, this study pointed to disruptions of gene transcription that would prove especially deleterious to the functioning of medium spiny striatal neurons. As suggested by previous studies, this study indicated that decreases in the expression of neuronal signaling genes was not due to large shifts in striatal cell populations, as some mRNAs known to be expressed in medium spiny neurons (e.g., preprotachykinin) were unchanged. Decreases in mRNAs predominated; at 12 weeks of age, only 21 were increased in R6/2 striatum. Many of the increased genes were related to inflammation, and these were likely compensatory changes. This pioneering study not only demonstrated the power of using DNA microarrays, but also produced a comprehensive survey of all gene changes that occur in the R6/2 striatum. In short, numerous genes were affected, but there was a measure of selectivity, in that fewer than 2% of the transcripts had altered expression. Downregulation of genes appeared to be a more important mechanism in that gene decreases predominated, and decreases in expression could be detected at earlier time points. This study thus gave rise to the notion that mutant huntingtin could produce a progressive downregulation of susceptible genes. While certain groups of genes seemed to be affected, the rule determining which genes would be downregulated was not immediately apparent.

3.1.1 Microarray studies of other R6 mice—Benn et al. created lines of transgenic mice which were modifications of the original R6/2 mouse line (Benn et al., 2005). In order to determine the importance of nuclear localization of polyglutamine-expanded exon 1 huntingtin, Benn and colleagues made versions of R6/2 mice, modified in that they expressed transgenes bearing either a nuclear localization signal (NLS) or a nuclear export signal (NES). These mice have distinct transgene genomic integration sites, and yet the expression profiling of these lines, as assessed by DNA microarray, were quite similar, arguing that the transcriptional profile seen in R6/2 mice is not simply the result of the genomic locus of integration. Interestingly, directing expanded polyglutamine to the nucleus reliably worsens phenotype in transgenic mice, whereas excluding polyglutamine from the nucleus delays the phenotype (Benn et al., 2005; Jackson et al., 2003; Schilling et al., 2004). These observations bolster the argument that disruption of transcription is a critical pathogenic event in polyglutamine diseases.

3.1.2 Microarray studies: other lines of transgenic mice—Other diseases share the same causative mechanisms as HD: expansion of a CAG trinucleotide repeat encoding an abnormally large polyglutamine moiety within the host protein (Paulson and Fischbeck, 1996). Expression profiling studies have shown that many of these transgenic mouse models show mRNA expression changes, including other transgenic mouse models of HD (Chan et al., 2002; Kotliarova et al., 2005), dentatorubropallidal luysian atrophy (DRPLA, Luthi-Carter et al., 2002b), and spinocerebellar ataxia type 7 (SCA-7 Abou-Sleymane et al., 2006; La Spada et al., 2001). These studies suggest that altered gene expression is a common feature of these polyglutamine diseases. Certain genes changes were common to numerous of these diseases. For example, 6 of the gene expression changes common to both huntingtin and atrophin-1 transgenic mice were also observed in the cerebella of mouse models expressing full-length mutant ataxin-7 or the androgen receptor (Luthi-Carter et al., 2002b). However, most of the particular genes that are affected differ between disease models. The longer the polyglutamine portion, the more marked the gene changes, and conversely, the longer the fragment of huntingtin, the less severe the gene changes (Chan et al., 2002).

Fossale and colleagues hybridized mRNA from *Hdh* knock-in mice to a filter array containing human genes, in order to detect altered expression of conserved genes (Fossale et al., 2002). They identified increased expression of *Rrs1*, a ribosomal protein. While this result is interesting, the use of human gene filter arrays raises the possibility that some of the expression changes in these mice were missed.

3.2 Expression profiling studies of cell models

Cellular models have been created that express different portions of the Htt molecule. Some cellular models express a truncated transgene, sometimes with inducible expression. ‘Knock-in’ models that express a full length version of mouse huntingtin have also been developed. Some of these cell models have been subjected to gene expression analysis. In comparison to intact brain, the signal to noise ratio that can be achieved in cultured cells is much higher. However, cells in culture lack the appropriate synaptic and neurochemical environment that neurons *in vivo* experience. Nevertheless, the use of cellular models has been tremendously helpful. As an example, use of the inducible models allows one to detect the earliest changes that occur, something that is not practically achievable with transgenic mice.

Wyttenbach et al. performed expression profiling on PC-12 cells that inducibly express exon 1 of the human *HD* gene containing either 23 or 74 glutamines (Wyttenbach et al., 2001). These authors observed a pattern of gene expression that was consistent with impaired cyclic AMP response element (CRE) signaling, which they confirmed using a CRE reporter construct. A subsequent report from the same group also identified altered expression of molecules in pathways regulated by retinoic acid response element, and nuclear factor kappaB (Sugars et al., 2004). Apostol et al. also performed expression profiling on another PC-12 cell model, again expressing human exon 1 containing either 18 or 103 glutamines (Apostol et al., 2006). In this study, there were more gene increases than decreases, and impairment of the mitagen-activated protein kinase (MAPK) pathway was identified. In their expression profiling study of PC-12 cells expressing either 23 or 74 glutamines, Kita identified 5 genes with altered expression that could suppress neuronal death, implying that some of these gene changes are compensatory and possibly relevant to polyglutamine pathogenesis (Kita et al., 2002).

Sipione et al. performed expression profiling on ST14A cells, immortalized striatal cell lines that stably express a relatively long piece of huntingtin, 548 amino acids (Sipione et al., 2002). These authors found genes involved in cell signaling, transcription, lipid metabolism and vesicle trafficking, with some genes being altered within 12 hours of mutant protein induction. A novel target in HD pathology also emerged from this work, as this report identified genes involved in cholesterol biogenesis as being downregulated. This group has gone on to

confirm alteration of the cholesterol biosynthetic pathway in human HD samples (Valenza et al., 2005). Cholesterol, or the molecules that are involved in cholesterol biosynthesis, such as the master transcriptional activator SREBP, may serve both as a biomarker and as a novel target in HD therapeutics.

4. Mechanisms of transcriptional dysregulation

Now that mRNA expression abnormalities have been demonstrated across several types of HD models, the questions remain as to how exactly these changed expression profiles come about. Numerous mechanisms have been proposed for the mechanisms by which mutant Htt alters the pattern of gene expression (reviewed in Luthi-Carter and Cha, 2003). Not all mRNA decreases reflect a transcriptional mechanism. For example, in R6 mice several of the chaperone proteins, including Hdj1, Hdj2, Hsp70, alphaSGT and betaSGT, are decreased at the protein levels, with no difference in corresponding mRNA levels (Hay et al., 2004).

4.1 mRNA changes reflect neuronal pathology

Most of the decreases in mRNA measured in the R6/2 striatum likely reflect neuronal, as opposed to glial, expression changes, as neuronal populations obtained through laser capture microdissection (LCM) recapitulate the findings found for striatal homogenates (Sadri-Vakili et al., 2006; Zucker et al., 2005). Other data arguing that mRNA changes represent primarily neuronal pathology includes the expression profiling studies of neuronal and neuronal-like cell lines (Apostol et al., 2006; Kita et al., 2002; Sipione et al., 2002; Sugars et al., 2004; Wyttenbach et al., 2001). These findings do not obviate the possibility that glial cells also can manifest altered mRNA expression. For example, R6/2 mice demonstrate decreased mRNA levels of GLT-1, the major astroglial glutamate transporter (Lievens et al., 2001).

4.2 Nuclear inclusions do not cause mRNA downregulation

The role of neuronal intranuclear inclusions (NII) has been hotly debated in HD pathogenesis. Although NII have been identified in the brains of R6/2 transgenic HD mice (Davies et al., 1997) as well as in human HD brain (DiFiglia et al., 1997), their role in HD pathogenesis is controversial. NII appear before the onset of symptoms and neurodegeneration in R6/2 mice, suggesting that aggregation of mutant Htt into NII is a requisite step in neuropathogenesis (Davies et al., 1998; Ross, 1997). Others have proposed a protective role, arguing that NII may represent the cellular response to polyglutamine-induced toxicity (Arrasate et al., 2004; Kim et al., 1999; Saudou et al., 1998). Sadri-Vakili et al. have recently analyzed NII-positive and NII-negative striatal neurons from R6/2 mice, and found that there was no difference in the degree of mRNA downregulation between these two cell populations (Sadri-Vakili et al., 2006). Although techniques such as double-label *in situ* hybridization and immunohistochemistry, or laser capture microdissection, cannot eliminate the possibility that “NII-negative” cells actually contain small microaggregates or oligomers, these findings indicate that visible NII do not account for downregulation of mRNA. These findings also argue against the idea that NII are protective with respect to transcription. As visible aggregates have been shown to be protective in an *in vitro* transient transfection model (Arrasate et al., 2004), one possibility is that mRNA downregulation lies in a different pathogenic pathway than cell death *in vitro*.

4.3 Htt interactions with transcription factors

Huntingtin, in both normal and polyglutamine-expanded forms, can interact with a number of transcription factors (reviewed in Luthi-Carter and Cha, 2003). Htt binding interactors include CREB-binding protein (CBP) (Nucifora et al., 2001; Steffan et al., 2000), TATA-binding protein (TBP) (Huang et al., 1998), p53 (Steffan et al., 2000), Sp1 (Dunah et al., 2002), and p53 (Bae et al., 2005; Steffan et al., 2000), raising the possibility that NII cause transcriptional

dysregulation by sequestering transcription factors. However, Yu et al. reported no change in transcription or sequestration of transcription factors by mutant Htt aggregates (Yu et al., 2002). More recent studies report the idea that soluble Htt can interfere with transcription factor activity (Schaffar et al., 2004), or may function to disrupt coactivator complexes on susceptible gene promoters (Zhai et al., 2005). Several transcription factors have been studied in detail.

4.3.1 CBP—CREB Binding Protein (CBP) is a transcription factor that contains a stretch of 19 glutamines. In 1999, it was recognized that aggregates of polyglutamine-containing proteins could recruit CBP into aggregates (Kazantsev et al., 1999; McCampbell et al., 2000; McCampbell et al., 1999). Steffan et al. showed that mutant huntingtin could interact with CBP and mSin3a, raising the possibility that huntingtin orchestrated abnormal transcriptional complexes at the promoters of susceptible genes (Steffan et al., 2000). Sequestration of CBP may be a common feature of polyglutamine diseases, as interaction with CBP has been demonstrated not only with huntingtin (Nucifora et al., 2001; Steffan et al., 2000), atrophin-1, the protein mutated in dentatorubropallidoluysian atrophy (Nucifora et al., 2001), ataxin-3, the protein mutated in spinocerebellar ataxia type 3 or Machado-Joseph disease (McCampbell et al., 2000), and androgen receptor, the protein mutated in spinobulbar muscular atrophy (McCampbell et al., 2000). As CBP possesses histone acetyl transferase (HAT) activity, one possibility is that mutant polyglutamine proteins alter the landscape of histone modifications by aberrantly interacting with HATs such as CBP (Sadri-Vakili and Cha, 2006).

4.3.2 Sp1—Sp1 (‘specificity protein 1’) was the first human transcription factor to be isolated (Kadonaga et al., 1987). Inspection of gene expression profiling studies of R6/2 mice suggested that Sp1-dependent genes were especially impacted (Luthi-Carter et al., 2000). Mutant huntingtin interacts with Sp1 *in vitro*, with mutant huntingtin binding more avidly than wild-type huntingtin (Dunah et al., 2002; Li et al., 2002). Mutant huntingtin interferes with Sp1-dependent transcription (Dunah et al., 2002; Li et al., 2002), and co-expression of Sp1 and the transcriptional mediator TAFII130 inhibits huntingtin toxicity (Dunah et al., 2002). Genes that have decreased expression levels have decreased Sp1 bound to their promoters, whereas normally-expressed genes had normal Sp1 association, as assessed using chromatin immunoprecipitation (ChIP) (Chen-Plotkin et al., 2006). While these data suggest Sp1 hypofunction, exactly how Sp1 is involved in HD is still not clear. It is worth noting that many Sp1-driven genes have normal levels of expression. Decreasing Sp1 using RNA interference or crossing R6/2 mice with Sp1 heterozygote knockout mice actually improves the abnormal neurologic phenotype (Qiu et al., 2006).

4.3.3 NCoR—One of the first binding interactors of huntingtin that was identified was nuclear co-repressor (NCoR) (Boutell et al., 1999). NCoR is a protein that serves as a transcriptional co-repressor (Hollenberg, 1998). Mutant huntingtin enhances the transcriptional repression effect of NCoR, raising the possibility that aberrant huntingtin-NCoR binding could occasion inappropriate gene repression (Yohrling et al., 2003). However, while some studies have shown increased binding by mutant huntingtin (Boutell et al., 1999), others have shown a similar extent of binding between wild-type and mutant huntingtin (Yohrling et al., 2003).

4.3.4 p53—p53 is a tumor suppressor that functions within the cell to integrate stress signals. The N-terminal portion of huntingtin resembles p53 in that both molecules possess a transcriptional activation domain flanked by a polyproline moiety (Steffan et al., 2000). Exon 1 of the huntingtin protein containing the polyproline regions (httex1p) was found to interact with p53 *in vitro* and *in vivo*, and p53 was found to be recruited into polyglutamine aggregates. In addition, expanded httex1p repressed transcription of p53-responsive promoters (Steffan et al., 2000). Both p53 and one of its regulators, mdm2, have been found within intracellular polyQ aggregates (Steffan et al., 2000; Suhr et al., 2001). Again, while these observations

suggest that there is hypofunction of p53 in HD, the relationship may be more complex. A recent study shows that p53 levels are increased in HD tissues, and that decreasing p53 protects against Htt toxicity (Bae et al., 2005). The *HD* promoter itself has multiple p53 response elements, and activation of p53 leads to increased expression of huntingtin (Feng et al., 2006).

4.3.1 REST/NRSF—Brain-derived neurotrophic factor (BDNF) is a pro-survival factor. A particular link has been made to repression of BDNF expression (Zuccato et al., 2001; Zuccato et al., 2003). In the cytoplasm, wild-type Htt binds the transcriptional repressor element-1 transcription factor/neuron restrictive silencer factor (REST/NRSF), which is less bound by mutant huntingtin. The theory is that, due to a loss of cytoplasmic sequestration of REST, there is inappropriate nuclear entry of REST in the presence of mutant huntingtin. Zuccato and colleagues have argued that this loss-of-function results in inappropriate repression of BDNF expression, as unbound REST is liberated to travel into the nucleus and repress the BDNF promoter. Consistent with this view is the observation of decreased transcription of REST-controlled genes in the presence of mutant huntingtin (Zuccato et al., 2003). Importantly, this schema postulates a loss of function of mutant huntingtin—failure to sequester REST in the cytoplasm—as an additional mechanism by which huntingtin disrupts transcription.

4.3.6 Core Transcriptional Machinery—There are numerous interactions between mutant huntingtin and components of the basal transcriptional machinery. Huntingtin binds TAFII130 (Dunah et al., 2002; Shimohata et al., 2000), which binds to the TATA-binding protein (TBP). Both RNA polymerase II large subunit and TBP can be detected in Htt aggregates (Huang et al., 1998; Suhr et al., 2001). TBP is itself a polyglutamine-containing protein, and polyglutamine expansion of TBP causes spinocerebellar ataxia 17 (SCA17) (Nakamura et al., 2001). Zhai et al. identified TFIID and TFIIF, components of the core transcriptional meachinery, as direct targets of mutant Htt (Zhai et al., 2005). Specifically, these authors found that the RAP30 subunit of the TFIIF complex can specifically interact with mutant Htt, and overexpression of RAP30 protects against Htt toxicity. Huntingtin's effect on the core transcriptional machinery may also involve RNA polymerases. RNA pol II large subunit can be recruited to polyglutamine inclusions in cell lines expressing mutant Htt (Luthi-Carter et al., 2002b). These observations suggest that mutant Htt can disrupt the core transcriptional machinery, but they do not explain the regional specificity that is seen in gene expression profiles (Desplats et al., 2006; Hodges et al., 2006).

4.3.7 PGC-1α—There may be links to huntingtin-induced transcriptional dysregulation and mitochondrial dysfunction. Peroxisome proliferator activated receptor γ (PPAR©) coactivator 1α (PGC-1α) is considered a master regulator of mitochondrial biogenesis and function. Weydt et al. observed that HD transgenic mice had impaired thermoregulation and had lower levels of PGC-1α (Weydt et al., 2006). Cui et al. found that mutant huntingtin inhibits expression of PGC-1α by associating at the promoter and interfering with CREB/TAf4-mediated expression of PGC-1α (Cui et al., 2006). Expression of PGC-1α protects against mutant Htt-induced toxicity and crossing HD knock-in mice with PGC-1α knockout mice exacerbates striatal degeneration (Cui et al., 2006). These findings suggest that mutant Htt interferes with energy production by inhibiting the expression of PGC-1α.

4.4 Decreased transcription or accelerated degradation?

Most measures of mRNA levels represent stead-state levels. Hence, decreased levels could reflect either decreased rates of transcription or accelerated rates of degradation. However, where it has been studied, decreases in mRNA stability appear to reflect decreased transcription, as opposed to accelerated degradation (McCaw et al., 2004). In addition, mutant Htt appears to disrupt transcriptional machinery at the promoters of susceptible genes,

suggesting that the primary locus of mutant's transcriptional effects is at specific gene promoters (Chen-Plotkin et al., 2006; Cui et al., 2006; Dunah et al., 2002; Zhai et al., 2005). Accelerated degradation has not been excluded as a potential mechanism. Interestingly, many of the genes whose expression is altered are concerned with RNA metabolism, including elongation factors and factors involved in splicing.

5. Microarray analysis of gene expression in human HD brain

The study of altered mRNA expression found its beginnings in the observations from human post-mortem HD brain. Recently, Hodges et al. completed the scientific cycle of discovery by applying DNA microarray techniques to human HD brain (Hodges et al., 2006). In this *tour de force*, 44 human HD brains were compared to 36 unaffected controls. Of note, this effort also represents a collaboration among several groups, reminiscent of the first wave of DNA microarray profiling studies performed on transgenic mouse models. As the number of available human HD brains is limited, combining available samples greatly increases the statistical power of such a study. Four brain regions were analyzed: caudate nucleus, cerebellum, prefrontal association cortex, and motor cortex. The caudate and motor cortex manifested the greatest number of changes, followed in number by the cerebellum, with the prefrontal association cortex showing no changes. This pattern of gene changes parallels the pattern of neuropathology. It should be emphasized that this regional pattern of altered gene expression cannot be adequately explained simply by the regional expression of Htt; both the cerebellum and prefrontal association cortex express Htt. Recent studies from transgenic mouse models suggest that there are striatal-specific factors which may render the striatum more susceptible to transcriptional dysregulation (Desplats et al., 2006; Gomez et al., 2006).

Of interest, in the Hodges et al. study there were many genes among those showing the greatest downregulation that had also been identified in expression profiling studies of transgenic mice, including cannabinoid CB1 receptor, dopamine D1 receptor and enkephalin. A considerable number of Ca^{2+}-binding protein and Ca^{2+}, K^+ and Na^+ channel mRNAs are downregulated, consistent with previously published studies of R6/2 mice (Luthi-Carter et al., 2002a; Luthi-Carter et al., 2000; Luthi-Carter et al., 2002b). The similarity between human HD brain and a transgenic mouse model that bears such an extremely truncated portion of the *HD* gene is nothing short of remarkable and argues strongly that polyglutamine-expanded exon 1 accounts for a significant portion of the transcriptional changes seen in HD. Undoubtedly, other portions of the Htt molecule could also produce transcriptional changes. For example, Hodges et al. also identified novel changes in vacuolar proton channel complex subunits, and they postulate that these changes could affect a number of neuronal processes, including synaptic vesicle release.

6. Expression profiling as a therapeutic readout

Expression profiling of mRNA also provides a rich phenotype which may be used to monitor therapy. Transcriptionally active therapies would be predicted to normalize the aberrant transcriptional profiles found in HD tissues. Clearly, expression profiling with current methodologies would not be practical for the human HD brain. However, if altered mRNA expression were present in more accessible tissues, one could then measure expression profiles in these tissues as a biomarker. An ideal biomarker reflects a critical aspect of disease pathology, such as serum cholesterol in the study of heart disease. Additionally, such a biomarker, in the presence of a treatment, may serve as a measure of therapeutic efficacy, such as one is able to assess the effect cholesterol-lowering effects of statin drugs.

6.1 Accessible tissues

One exciting possibility is tissues other than brain may yield fundamental information that mirrors what is going on in brain. For years, a metabolic abnormality has been identified in HD skeletal muscle (Jenkins et al., 1993; Koroshetz et al., 1997). R6/2 mice manifest gene expression changes not only in brain, but also in muscle (Luthi-Carter et al., 2002a). Strand et al. compared gene expression profiles from skeletal muscle of R6/2 mice, Hdh(CAG150) knock-in mice and human HD patients (Strand et al., 2005). These authors observed an HD-related expression phenotype that was consistent with a transition from fast-twitch to slow-twitch muscle fiber types. Gene expression changes reflected disease progression. One can imagine that punch biopsy of muscle might be used as a biomarker for clinical trials.

Even a punch biopsy of muscle is not without discomfort to patients. Borovecki et al. used peripheral blood samples to measure mRNA expression in blood samples from human HD patients (Borovecki et al., 2005). These authors identified 322 mRNAs with altered expression in HD blood samples, compared with controls. Most of the genes that were changed were different than those that had been identified as changed in previous expression profiling studies of brain. This disparity is not surprising in that neurons and peripheral blood cells express distinct sets of genes; one would not *a priori* that the same genes would be affected by mutant Htt. A subset of up-regulated mRNAs selected from this group was able to distinguish controls, presymptomatic individuals carrying the HD mutation, and symptomatic HD patients. Early presymptomatic subjects showed gene expression profiles similar to those of controls, whereas late presymptomatic subjects showed altered expression that resembled that of symptomatic HD patients. These findings suggested that expression profiles of peripheral blood had a relationship with disease severity, and that these profiles might be a useful measure in both measuring disease severity as well as response to therapy. Importantly, many of the genes that were upregulated in peripheral blood were found to have increased expression in human HD caudate, indicating that examination of the blood could reflect some of what was going on in the central nervous system.

6.2 Does treatment improve expression profiles?

Decreasing expression of the mutant transgene ameliorates behavioral and neuropathologic measures in a transgenic mouse model of HD, attesting to the regenerative potential of the HD brain (Yamamoto et al., 2000). Targeting expression of the mutant *HD* gene is thus an area of active interest, with potential approaches including antisense oligonucleotides, intrabodies and RNA interference. An important issue is whether decreasing the levels of mutant Htt will correct transcriptional abnormalities. Indeed, decreasing Htt expression using an siRNA approach reversed gene expression abnormalities of enkephalin and DARPP-32 and improved a paw-clasping phenotype (Rodriguez-Lebron et al., 2005).

Treatment may be reflected in improved expression profiles. A multidrug regimen (tacrine, moclobemide and creatine) partially corrected gene expression abnormalities in R6/2 mice, although some other genes were further dysregulated (Morton et al., 2005a). The effect of HDAC inhibitors on gene expression profiles has also been examined (Ferrante et al., 2003). Microarray analysis showed increased expression of alpha- and beta-globins and MAP kinase phosphatase-1 in sodium butyrate-treated R6/2 mice, indicative of improved oxidative phosphorylation and transcriptional regulation. This study suggests that the benefits of HDAC inhibitors lies not only in correcting the expression of aberrantly dysregulated genes, but also in increasing the expression of other salutary genes.

In human patients, in a small dose-finding study, treatment with the histone deacetylase (HDAC) inhibitor phenyl butyrate was able to decrease expression of some genes that were abnormally increased in peripheral blood cells of human HD samples (Borovecki et al.,

2005). In human HD subjects dosed with the nutritional supplement creatine, there is an overall decrease in levels of 8-hydroxydeoxyguanosine, a measure of oxidative damage to DNA (Hersch et al., 2006). The relationship between oxidative DNA damage to altered gene expression has not been elucidated in Huntington's disease, although there does seem to be a direct relationship in the aging brain (Lu et al., 2004).

7. Future directions

Measuring transcriptional dysregulation has been tremendously useful in a number of ways. First, the remarkable similarity between expression profiling changes between human HD brain and transgenic mice largely validates the utility of these valuable models in understanding transcriptional dysregulation in HD. Certain features of human HD, notably selective striatal neuronal death, are not well-replicated by transgenic mice expressing truncated forms of human huntingtin. These mice may thus be most useful for learning more about the transcriptional phenotype in HD. Expression profiling has also generated novel targets, molecules that were not previously suspected in HD pathogenesis, such as the cholesterol biosynthetic pathway and PGC-1α. The use of microarrays has already demonstrated potential as a therapeutic readout for clinical trials.

Important issues remain, however. Even though DNA microarray studies demonstrate a measure of selectivity in which genes are affected, it is clear that many genes are affected. Focusing on any single protein may therefore be a short-sighted strategy, and one ought to think of more upstream mechanisms.

The mechanisms producing these transcriptional signatures are largely unknown, although they certainly emanate from a single molecule: polyglutamine-expanded versions of the huntingtin protein. Several inroads have been advanced. Using a comparative approach Chen-Plotkin et al. found that downregulated genes have decreased binding of the transcription factor Sp1 to their promoters, compared to genes expressed at wild-type levels (Chen-Plotkin et al., 2006). Similarly, at the promoters of susceptible genes, mutant Htt disrupts the assembly of transcriptional complexes (Zhai et al., 2005). A systematic investigation of transcription factors and histone proteins will undoubtedly shed light on the causative mechanisms. Histones associated with downregulated genes are hypo-acetylated compared to histones associated with normally expressed genes (G. Sadri-Vakili and J.-H.J. Cha, unpublished data).

A looming issue is one of causality. While altered transcription is clearly a phenotype, it is not clear if these gene changes are causative or epiphenomenal. The critical test will be to see if correcting this abnormal phenotype produces clinical benefit. In this regard, recent experience with HDAC inhibitors has been instructive (reviewed in Sadri-Vakili and Cha, 2006). Transgenic HD mice are improved when treated with HDAC inhibitors (Ferrante et al., 2003; Gardian et al., 2005; Hockly et al., 2003), and some of these compounds are now being tested in human HD patients.

Overall, transcriptional signatures illustrate the cycles of discovery in Huntington's disease, in which initial observation from postmortem human brain informs preliminary experiments in animal and cellular models. Additional insights developed in these models, fueled by biotechnological innovation such as the development of DNA microarrays, can then be brought to bear on the human patient. The ultimate progress of this cycle will be measured not only in new ideas and new targets but, ultimately, in new therapies.

References

Abou-Sleymane G, Chalmel F, Helmlinger D, Lardenois A, Thibault C, Weber C, Merienne K, Mandel JL, Poch O, Devys D, Trottier Y. Polyglutamine expansion causes neurodegeneration by altering the neuronal differentiation program. Hum Mol Genet 2006;15:691–703. [PubMed: 16434483]

Albin RL, Greenamyre JT. Alternative excitotoxic hypotheses. Neurology 1992;42:733–738. [PubMed: 1314341]

Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends in Neurosciences 1989;12:366–375. [PubMed: 2479133]

Andreassen OA, Dedeoglu A, Stanojevic V, Hughes DB, Browne SE, Leech CA, Ferrante RJ, Habener JF, Beal MF, Thomas MK. Huntington's disease of the endocrine pancreas: insulin deficiency and diabetes mellitus due to impaired insulin gene expression. Neurobiol Dis 2002;11:410–424. [PubMed: 12586550]

Andrews TC, Weeks RA, Turjanski N, Gunn RN, Watkins LH, Sahakian B, Hodges JR, Rosser AE, Wood NW, Brooks DJ. Huntington's disease progression. PET and clinical observations. Brain 1999;122:2353–2363. [PubMed: 10581228]

Apostol BL, Illes K, Pallos J, Bodai L, Wu J, Strand A, Schweitzer ES, Olson JM, Kazantsev A, Marsh JL, Thompson LM. Mutant huntingtin alters MAPK signaling pathways in PC12 and striatal cells: ERK1/2 protects against mutant huntingtin-associated toxicity. Hum Mol Genet 2006;15:273–285. [PubMed: 16330479]

Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. Nature 2004;431:805–810. [PubMed: 15483602]

Arzberger T, Krampfl K, Leimgruber S, Weindl Aw. Changes of NMDA receptor subunit (NR1, NR2B) and glutamate transporter (GLT1) mRNA expression in Huntington's disease - An in situ hybridization study. J Neuropathol Exp Neurol 1997;56:440–454. [PubMed: 9100675]

Augood SJ, Faull RLM, Emson PC. Dopamine D1 and D2 receptor gene expression in the striatum in Huntington's disease. Ann Neurol 1997;42:215–221. [PubMed: 9266732]

Augood SJ, Faull RLM, Love DR, Emson PC. Reduction in enkephalin and substance P messenger RNA in the striatum of early grade Huntington's disease: a detailed cellular *in situ* hybridization study. Neuroscience 1996;72:1023–1036. [PubMed: 8735227]

Bae BI, Xu H, Igarashi S, Fujimuro M, Agrawal N, Taya Y, Hayward SD, Moran TH, Montell C, Ross CA, Snyder SH, Sawa A. p53 mediates cellular dysfunction and behavioral abnormalities in Huntington's disease. Neuron 2005;47:29–41. [PubMed: 15996546]

Beal MF, Ferrante RJ, Swartz KJ, Kowall NW. Chronic quinolinic acid lesions in rats closely resemble Huntington's disease. J Neurosci 1991;11:1649–1659. [PubMed: 1710657]

Beal MF, Kowall NW, Ellison DW, Mazurek MF, Swartz KJ, Martin JB. Replication of the neurochemical characteristics of Huntington's disease by quinolinic acid. Nature 1986;321:168–171. [PubMed: 2422561]

Benchoua A, Trioulier Y, Zala D, Gaillard MC, Lefort N, Dufour N, Saudou F, Elalouf JM, Hirsch E, Hantraye P, Deglon N, Brouillet E. Involvement of mitochondrial complex II defects in neuronal death produced by N-terminus fragment of mutated huntingtin. Mol Biol Cell 2006;17:1652–1663. [PubMed: 16452635]

Benn CL, Landles C, Li H, Strand AD, Woodman B, Sathasivam K, Li SH, Ghazi-Noori S, Hockly E, Faruque SM, Cha JH, Sharpe PT, Olson JM, Li XJ, Bates GP. Contribution of nuclear and extranuclear polyQ to neurological phenotypes in mouse models of Huntington's disease. Hum Mol Genet 2005;14:3065–3078. [PubMed: 16183657]

Berke JD, Paletzki RF, Aronson GJ, Hyman SE, Gerfen CR. A complex program of striatal gene expression induced by dopaminergic stimulation. J Neurosci 1998;18:5301–5310. [PubMed: 9651213]

Bibb JA, Yan Z, Svenningsson P, Snyder GL, Pieribone VA, Horiuchi A, Nairn AC, Messer A, Greengard P. Severe deficiencies in dopamine signaling in presymptomatic Huntington's disease mice. Proc Natl Acad Sci U S A 2000;97:6809–6814. [PubMed: 10829080]

Borovecki F, Lovrecic L, Zhou J, Jeong H, Then F, Rosas HD, Hersch SM, Hogarth P, Bouzou B, Jensen RV, Krainc D. Genome-wide expression profiling of human blood reveals biomarkers for Huntington's disease. Proc Natl Acad Sci U S A 2005;102:11023–11028. [PubMed: 16043692]

Boutell JM, Thomas P, Neal JW, Weston VJ, Duce J, Harper PS, Jones AL. Aberrant interactions of transcriptional repressor proteins with the Huntington's disease gene product, huntingtin. Hum Mol Genet 1999;8:1647–1655. [PubMed: 10441327]

Bruyn RP, Stoof JC. The quinolinic acid hypothesis in Huntington's chorea. J Neurol Sci 1990;95:29–38. [PubMed: 2159984]

Carter RJ, Lione LA, Humby T, Mangiarini L, Mahal A, Bates GP, Dunnett SB, Morton AJ. Characterization of progressive motor deficits in mice transgenic for the human Huntington's disease mutation. J Neurosci 1999;19:3248–3257. [PubMed: 10191337]

Cepeda C, Hurst RS, Calvert CR, Hernandez-Echeagaray E, Nguyen OK, Jocoy E, Christian LJ, Ariano MA, Levine MS. Transient and progressive electrophysiological alterations in the corticostriatal pathway in a mouse model of Huntington's disease. J Neurosci 2003;23:961–969. [PubMed: 12574425]

Cha JHJ. Transcriptional dysregulation in Huntington's disease. Trends in Neurosciences 2000;23:387–392. [PubMed: 10941183]

Cha JHJ, Frey AS, Alsdorf SA, Kerner JA, Kosinski CM, Mangiarini L, Penney JB Jr, Davies SW, Bates GP, Young AB. Altered neurotransmitter receptor expression in transgenic mouse models of Huntington's disease. Philos Trans R Soc Lond B Biol Sci 1999;354:981–989. [PubMed: 10434296]

Cha JHJ, Kosinski CM, Kerner JA, Alsdorf SA, Mangiarini L, Davies SW, Penney JB, Bates GP, Young AB. Altered brain neurotransmitter receptors in transgenic mice expressing a portion of an abnormal human Huntington disease gene. Proceedings of the National Academy of Sciences, USA 1998;95:6480–6485.

Chan EYW, Luthi-Carter R, Strand A, Solano SM, Hanson SA, DeJohn MM, Kooperberg C, Chase KO, DiFiglia M, Young AB, Leavitt BR, Cha JHJ, Aronin N, Hayden MR, Olson JM. Increased huntingin protein length reduces the severity of polyglutamine-induced gene expression changes in mouse models of Huntington disease. Human Molecular Genetics 2002;11:1939–1951. [PubMed: 12165556]

Chen-Plotkin AS, Sadri-Vakili G, Yohrling GJ, Braveman MW, Benn CL, Glajch KE, DiRocco DP, Farrell LA, Krainc D, Gines S, MacDonald ME, Cha JH. Decreased association of the transcription factor Sp1 with genes downregulated in Huntington's disease. Neurobiol Dis 2006;22:233–241. [PubMed: 16442295]

Coyle JT, Schwarcz R. Lesion of striatal neurones with kainic acid provides a model for Huntington's chorea. Nature 1976;263:244–246. [PubMed: 8731]

Crocker SF, Costain WJ, Robertson HA. DNA microarray analysis of striatal gene expression in symptomatic transgenic Huntington's mice (R6/2) reveals neuroinflammation and insulin associations. Brain Res 2006;1088:176–186. [PubMed: 16626669]

Cudkowicz M, Kowall NW. Degeneration of pyramidal projection neurons in Huntington's disease cortex. Ann Neurol 1990;27:200–204. [PubMed: 2138444]

Cui L, Jeong H, Borovecki F, Parkhurst CN, Tanese N, Krainc D. Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. Cell 2006;127:59–69. [PubMed: 17018277]

Dangond F, Hwang D, Camelo S, Pasinelli P, Frosch MP, Stephanopoulos G, Brown RH Jr, Gullans SR. Molecular signature of late-stage human ALS revealed by expression profiling of postmortem spinal cord gray matter. Physiol Genomics 2004;16:229–239. [PubMed: 14645737]

Davies SW, Beardsall K, Turmaine M, DiFiglia M, Aronin N, Bates GP. Are neuronal intranuclear inclusions the common neuropathology of triplet-repeat disorders with polyglutamine-repeat expansions? Lancet 1998;351:131–133. [PubMed: 9439509]

Davies SW, Turmaine M, Cozens BA, DiFiglia M, Sharp AH, Ross CA, Scherzinger E, Wanker EE, Mangiarini L, Bates GP. Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. Cell 1997;90:537–548. [PubMed: 9267033]

de Chaldee M, Brochier C, Van de Vel A, Caudy N, Luthi-Carter R, Gaillard MC, Elalouf JM. Capucin: a novel striatal marker down-regulated in rodent models of Huntington disease. Genomics 2006;87:200–207. [PubMed: 16359841]

Deckel AW, Tang V, Nuttal D, Gary K, Elder R. Altered neuronal nitric oxide synthase expression contributes to disease progression in Huntington's disease transgenic mice. Brain Res 2002;939:76–86. [PubMed: 12020853]

Denovan-Wright EM, Robertson HA. Cannabinoid receptor messenger RNA levels decrease in a subset of neurons of the lateral striatum, cortex and hippocampus of transgenic Huntington's disease mice. Neuroscience 2000;98:705–713. [PubMed: 10891614]

Desplats PA, Kass KE, Gilmartin T, Stanwood GD, Woodward EL, Head SR, Sutcliffe JG, Thomas EA. Selective deficits in the expression of striatal-enriched mRNAs in Huntington's disease. J Neurochem 2006;96:743–757. [PubMed: 16405510]

DiFiglia M. Excitotoxic injury of the neostriatum: a model for Huntington's disease. Trends in Neurosciences 1990;13:286–289. [PubMed: 1695405]

DiFiglia M, Sapp E, Chase KO, Davies SW, Bates GP, Vonsattel JP, Aronin N. Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. Science 1997;277:1990–1993. [PubMed: 9302293]

Dunah AW, Jeong H, Griffin A, Kim YM, Standaert DG, Hersch SM, Mouradian MM, Young AB, Tanese N, Krainc D. Sp1 and TAFII130 transcriptional activity disrupted in early Huntington's disease. Science 2002;296:2238–2243. [PubMed: 11988536]

Dure LS, Young AB, Penney JB. Excitatory amino acid binding sites in the caudate nucleus and frontal cortex of Huntington's disease. Ann Neurol 1991;30:785–793. [PubMed: 1665055]

Feng Z, Jin S, Zupnick A, Hoh J, de Stanchina E, Lowe S, Prives C, Levine AJ. p53 tumor suppressor protein regulates the levels of huntingtin gene expression. Oncogene 2006;25:1–7. [PubMed: 16278683]

Ferrante RJ, Kowall NW, Beal MF, Richardson EP Jr, Bird ED, Martin JB. Selective sparing of a class of striatal neurons in Huntington's disease. Science 1985;230:561–564. [PubMed: 2931802]

Ferrante RJ, Kubilus JK, Lee J, Ryu H, Beesen A, Zucker B, Smith K, Kowall NW, Ratan RR, Luthi-Carter R, Hersch SM. Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice. J Neurosci 2003;23:9418–9427. [PubMed: 14561870]

Fossale E, Wheeler VC, Vrbanac V, Lebel LA, Teed A, Mysore JS, Gusella JF, MacDonald ME, Persichetti F. Identification of a presymptomatic molecular phenotype in Hdh CAG knock-in mice. Hum Mol Genet 2002;11:2233–2241. [PubMed: 12217951]

Freeman W, Morton AJ. Regional and progressive changes in brain expression of complexin II in a mouse transgenic for the Huntington's disease mutation. Brain Res Bull 2004;63:45–55. [PubMed: 15121238]

Friedlander RM. Apoptosis and caspases in neurodegenerative diseases. N Engl J Med 2003;348:1365–1375. [PubMed: 12672865]

Gardian G, Browne SE, Choi DK, Klivenyi P, Gregorio J, Kubilus JK, Ryu H, Langley B, Ratan RR, Ferrante RJ, Beal MF. Neuroprotective effects of phenylbutyrate in the N171-82Q transgenic mouse model of Huntington's disease. J Biol Chem 2005;280:556–563. [PubMed: 15494404]

Gines S, Bosch M, Marco S, Gavalda N, Diaz-Hernandez M, Lucas JJ, Canals JM, Alberch J. Reduced expression of the TrkB receptor in Huntington's disease mouse models and in human brain. Eur J Neurosci 2006;23:649–658. [PubMed: 16487146]

Glass M, Dragunow M, Faull RL. The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and GABA(A) receptor alterations in the human basal ganglia in Huntington's disease. Neuroscience 2000;97:505–519. [PubMed: 10828533]

Glass M, Faull RLM, Dragunow M. Loss of cannabinoid receptors in the substantia nigra in Huntington's disease. Neuroscience 1993;56:523–527. [PubMed: 8255419]

Gomez GT, Hu H, McCaw EA, Denovan-Wright EM. Brain-specific factors in combination with mutant huntingtin induce gene-specific transcriptional dysregulation. Mol Cell Neurosci 2006;31:661–675. [PubMed: 16446101]

Gourfinkel-An I, Parain K, Hartmann A, Mangiarini L, Brice A, Bates G, Hirsch EC. Changes in GAD67 mRNA expression evidenced by in situ hybridization in the brain of R6/2 transgenic mice. J Neurochem 2003;86:1369–1378. [PubMed: 12950446]

Gray M, Shirasaki D, Cepeda C, Wilburn B, Wu H, Li X, Li S, Yang XW, Sun YE, Levine MS. BAC transgenic models of Huntington's disease recapitulate phenotypic features of adult onset HD. Society for Neuroscience 2006:219–217.

Graybiel AM. Compartmental organization of the mammalian striatum. Prog Brain Res 1983;58:247–256. [PubMed: 6635191]

Graybiel AM. Neurotransmitters and neuromodulators in the basal ganglia. Trends Neurosci 1990;13:244–254. [PubMed: 1695398]

Greengard P, Allen PB, Nairn AC. Beyond the dopamine receptor: the DARPP-32/protein phosphatase-1 cascade. Neuron 1999;23:435–447. [PubMed: 10433257]

Grunblatt E, Mandel S, Jacob-Hirsch J, Zeligson S, Amariglo N, Rechavi G, Li J, Ravid R, Roggendorf W, Riederer P, Youdim MB. Gene expression profiling of parkinsonian substantia nigra pars compacta; alterations in ubiquitin-proteasome, heat shock protein, iron and oxidative stress regulated proteins, cell adhesion/cellular matrix and vesicle trafficking genes. J Neural Transm 2004;111:1543–1573. [PubMed: 15455214]

Gu X, Li C, Wei W, Lo V, Gong S, Li SH, Iwasato T, Itohara S, Li XJ, Mody I, Heintz N, Yang XW. Pathological cell-cell interactions elicited by a neuropathogenic form of mutant huntingtin contribute to cortical pathogenesis in HD mice. Neuron 2005;46:433–444. [PubMed: 15882643]

Harris AS, Denovan-Wright EM, Hamilton LC, Robertson HA. Protein kinase C beta II mRNA levels decrease in the striatum and cortex of transgenic Huntington's disease mice. J Psychiatry Neurosci 2001;26:117–122. [PubMed: 11291528]

Hauser MA, Li YJ, Xu H, Noureddine MA, Shao YS, Gullans SR, Scherzer CR, Jensen RV, McLaurin AC, Gibson JR, Scott BL, Jewett RM, Stenger JE, Schmechel DE, Hulette CM, Vance JM. Expression profiling of substantia nigra in Parkinson disease, progressive supranuclear palsy, and frontotemporal dementia with parkinsonism. Arch Neurol 2005;62:917–921. [PubMed: 15956162]

Hay DG, Sathasivam K, Tobaben S, Stahl B, Marber M, Mestril R, Mahal A, Smith DL, Woodman B, Bates GP. Progressive decrease in chaperone protein levels in a mouse model of Huntington's disease and induction of stress proteins as a therapeutic approach. Hum Mol Genet 2004;13:1389–1405. [PubMed: 15115766]

Hebb AL, Robertson HA, Denovan-Wright EM. Striatal phosphodiesterase mRNA and protein levels are reduced in Huntington's disease transgenic mice prior to the onset of motor symptoms. Neuroscience 2004;123:967–981. [PubMed: 14751289]

Hedreen JC, Folstein SE. Early loss of neostriatal striosome neurons in Huntington's disease. J Neuropathol Exp Neurol 1995;54:105–120. [PubMed: 7815073]

Hedreen JC, Peyser CE, Folstein SE, Ross CA. Neuronal loss in layers V and VI of cerebral cortex in Huntington's disease. Neuroscience Letters 1991;133:257–261. [PubMed: 1840078]

Hermel E, Gafni J, Propp SS, Leavitt BR, Wellington CL, Young JE, Hackam AS, Logvinova AV, Peel AL, Chen SF, Hook V, Singaraja R, Krajewski S, Goldsmith PC, Ellerby HM, Hayden MR, Bredesen DE, Ellerby LM. Specific caspase interactions and amplification are involved in selective neuronal vulnerability in Huntington's disease. Cell Death Differ 2004;11:424–438. [PubMed: 14713958]

Hersch SM, Gevorkian S, Marder K, Moskowitz C, Feigin A, Cox M, Como P, Zimmerman C, Lin M, Zhang L, Ulug AM, Beal MF, Matson W, Bogdanov M, Ebbel E, Zaleta A, Kaneko Y, Jenkins B, Hevelone N, Zhang H, Yu H, Schoenfeld D, Ferrante R, Rosas HD. Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG. Neurology 2006;66:250–252. [PubMed: 16434666]

Hickey MA, Reynolds GP, Morton AJ. The role of dopamine in motor symptoms in the R6/2 transgenic mouse model of Huntington's disease. J Neurochem 2002;81:46–59. [PubMed: 12067237]

Hockly E, Richon VM, Woodman B, Smith DL, Zhou X, Rosa E, Sathasivam K, Ghazi-Noori S, Mahal A, Lowden PAS, Steffan JS, Marsh JL, Thompson LM, Lewis CM, Marks PA, Bates GP. Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. PNAS 2003;100:2041–2046. [PubMed: 12576549]

Hodges A, Strand AD, Aragaki AK, Kuhn A, Sengstag T, Hughes G, Elliston LA, Hartog C, Goldstein DR, Thu D, Hollingsworth ZR, Collin F, Synek B, Holmans PA, Young AB, Wexler NS, Delorenzi M, Kooperberg C, Augood SJ, Faull RL, Olson JM, Jones L, Luthi-Carter R. Regional and cellular gene expression changes in human Huntington's disease brain. Hum Mol Genet 2006;15:965–977. [PubMed: 16467349]

Hodgson JG, Agopyan N, Gutekunst CA, Leavitt BR, LePiane F, Singaraja R, Smith DJ, Bissada N, McCutcheon K, Nasir J, Jamot L, Li XJ, Stevens ME, Rosemond E, Roder JC, Phillips AG, Rubin EM, Hersch SM, Hayden MR. A YAC mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration. Neuron 1999;23:181–192. [PubMed: 10402204]

Hollenberg AN. Thyroid hormone receptor isoforms, nuclear corepressors and coactivators: New insights into thyroid hormone action. Current Opinion in Endocrinology and Diabetes 1998;5:314–320.

Hu H, McCaw EA, Hebb AL, Gomez GT, Denovan-Wright EM. Mutant huntingtin affects the rate of transcription of striatum-specific isoforms of phosphodiesterase 10A. Eur J Neurosci 2004;20:3351–3363. [PubMed: 15610167]

Huang CC, Faber PW, Persichetti F, Mittal V, Vonsattel JP, MacDonald ME, Gusella JF. Amyloid formation by mutant huntingtin: Threshold, progressivity and recruitment of normal polyglutamine proteins. Somat Cell Mol Genet 1998;24:217–233. [PubMed: 10410676]

Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is unstable in Huntington's disease chromosomes. Cell 1993;72:971–983. [PubMed: 8458085]

Hurlbert MS, Zhou W, Wasmeier C, Kaddis FG, Hutton JC, Freed CR. Mice transgenic for an expanded CAG repeat in the Huntington's disese gene develop diabetes meelitus. Diabetes 1999;48:649–651. [PubMed: 10078572]

Iannicola C, Moreno S, Oliverio S, Nardacci R, Ciofi-Luzzatto A, Piacentini M. Early alterations in gene expression and cell morphology in a mouse model of Huntington's disease. J Neurochem 2000;75:830–839. [PubMed: 10899961]

Jackson WS, Tallaksen-Greene SJ, Albin RL, Detloff PJ. Nucleocytoplasmic transport signals affect the age at onset of abnormalities in knock-in mice expressing polyglutamine within an ectopic protein context. Hum Mol Genet 2003;12:1621–1629. [PubMed: 12812988]

Jarabek BR, Yasuda RP, Wolfe BB. Regulation of proteins affecting NMDA receptor-induced excitotoxicity in a Huntington's mouse model. Brain 2004;127:505–516. [PubMed: 14662521]

Jenkins BG, Koroshetz WJ, Beal MF, Rosen BR. Evidence for impairment of energy metabolisn in vivo in Huntington's disease using localized 1H NMR spectroscopy. Neurology 1993;43:2689–2695. [PubMed: 8255479]

Kadonaga JT, Carner KR, Masiarz FR, Tjian R. Isolation of cDNA encoding transcription factor Sp1 and functional analysis of the DNA binding domain. Cell 1987;51:1079–1090. [PubMed: 3319186]

Kazantsev A, Preisinger E, Dranovsky A, Goldgaber D, Housman D. Insoluble detergent-resistant aggregates form between pathological and nonpathological lengths of polyglutamine in mammalian cells. Proc Natl Acad Sci U S A 1999;96:11404–11409. [PubMed: 10500189]

Kennedy MB. The postsynaptic density at glutamatergic synapses. Trends Neurosci 1997;20:264–268. [PubMed: 9185308]

Kim M, Lee HS, LaForet G, McIntyre C, Martin EJ, Chang P, Kim TW, Williams M, Reddy PH, Tagle D, Boyce FM, Won L, Heller A, Aronin N, DiFiglia M. Mutant huntingtin expression in clonal striatal cells: dissociation of inclusion formation and neuronal survival by caspase inhibition. J Neurosci 1999;19:964–973. [PubMed: 9920660]

Kita H, Carmichael J, Swartz J, Muro S, Wyttenbach A, Matsubara K, Rubinsztein DC, Kato K. Modulation of polyglutamine-induced cell death by genes identified by expression profiling. Hum Mol Genet 2002;11:2279–2287. [PubMed: 12217956]

Kooperberg C, Sipione S, LeBlanc M, Strand AD, Cattaneo E, Olson JM. Evaluating test statistics to select interesting genes in microarray experiments. Hum Mol Genet 2002;11:2223–2232. [PubMed: 12217950]

Koroshetz WJ, Jenkins BG, Rosen BR, Beal MF. Energy metabolism defects in Huntington's disease and effects of coenzyme Q_{10}. Ann Neurol 1997;41:160–165. [PubMed: 9029064]

Kotliarova S, Jana NR, Sakamoto N, Kurosawa M, Miyazaki H, Nekooki M, Doi H, Machida Y, Wong HK, Suzuki T, Uchikawa C, Kotliarov Y, Uchida K, Nagao Y, Nagaoka U, Tamaoka A, Oyanagi K, Oyama F, Nukina N. Decreased expression of hypothalamic neuropeptides in Huntington disease transgenic mice with expanded polyglutamine-EGFP fluorescent aggregates. J Neurochem 2005;93:641–653. [PubMed: 15836623]

Kusakabe M, Mangiarini L, Laywell ED, Bates GP, Yoshiki A, Hiraiwa N, Inoue J, Steindler DA. Loss of cortical and thalamic neuronal tenascin-C expression in a transgenic mouse expressing exon 1 of the human Huntington disease gene. J Comp Neurol 2001;430:485–500. [PubMed: 11169482]

La Spada AR, Fu YH, Sopher BL, Libby RT, Wang X, Li LY, Einum DD, Huang J, Possin DE, Smith AC, Martinez RA, Koszdin KL, Treuting PM, Ware CB, Hurley JB, Ptacek LJ, Chen S. Polyglutamine-expanded ataxin-7 antagonizes CRX function and induces cone-rod dystrophy in a mouse model of SCA7. Neuron 2001;31:913–927. [PubMed: 11580893]

Lastres-Becker I, Berrendero F, Lucas JJ, Martin-Aparicio E, Yamamoto A, Ramos JA, Fernandez-Ruiz JJ. Loss of mRNA levels, binding and activation of GTP-binding proteins for cannabinoid CB(1) receptors in the basal ganglia of a transgenic model of Huntington's disease. Brain Res 2002;929:236–242. [PubMed: 11864629]

Li SH, Cheng AL, Zhou H, Lam S, Rao M, Li H, Li XJ. Interaction of Huntington disease protein with transcriptional activator Sp1. Molecular and Cellular Biology 2002;22:1277–1287. [PubMed: 11839795]

Lievens JC, Woodman B, Mahal A, Spasic-Boscovic O, Samuel D, Kerkerian-Le Goff L, Bates GP. Impaired glutamate uptake in the R6 Huntington's disease transgenic mice. Neurobiol Dis 2001;8:807–821. [PubMed: 11592850]

Lione LA, Carter RJ, Hunt MJ, Bates GP, Morton AJ, Dunnett SB. Selective discrimination learning impairments in mice expressing the human Huntington's disease mutation. J Neurosci 1999;19:10428–10437. [PubMed: 10575040]

Lu T, Pan Y, Kao SY, Li C, Kohane I, Chan J, Yankner BA. Gene regulation and DNA damage in the ageing human brain. Nature 2004;429:883–891. [PubMed: 15190254]

Luthi-Carter R, Apostol BL, Dunah AW, DeJohn MM, Farrell LA, Bates GP, Young AB, Standaert DG, Thompson LM, Cha JHJ. Complex alteration of NMDA receptors in transgenic Huntington's disease mouse brain: analysis of mRNA expression levels, protein abundance, interacting proteins and phosphorylation. Neurobiology of Disease 2003;14:624–636. [PubMed: 14678777]

Luthi-Carter R, Cha JHJ. Mechanisms of transcriptional dysregulation in Huntington's disease. Clinical Neuroscience Research 2003;3:165–177.

Luthi-Carter R, Hanson SA, Strand AD, Bergstrom DA, Chun W, Peters NL, Woods AM, Chan EY, Kooperberg C, Krainc D, Young AB, Tapscott SJ, Olson JM. Dysregulation of gene expression in the R6/2 model of polyglutamine disease: parallel changes in muscle and brain. Human Molecular Genetics 2002a;11:1911–1926. [PubMed: 12165554]

Luthi-Carter R, Strand A, Peters NL, Solano SM, Hollingsworth ZR, Menon AS, Frey AS, Spektor BS, Penney EB, Schilling G, Ross CA, Borchelt DR, Tapscott SJ, Young AB, Cha JHJ, Olson JM. Decreased expression of striatal signaling genes in a mouse model of Huntington's disease. Hum Mol Genet 2000;9:1259–1271. [PubMed: 10814708]

Luthi-Carter R, Strand AD, Hanson SA, Kooperberg C, Schilling G, La Spada AR, Merry DE, Young AB, Ross CA, Borchelt DR, Olson JM. Polyglutamine and transcription: gene expression changes chared by DRPLA and Huntington's disease mouse models reveal context-independent effects. Human Molecular Genetics 2002b;11:1927–1937. [PubMed: 12165555]

Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, Lawton M, Trottier Y, Lehrach H, Davies SW, Bates GP. Exon 1 of the *HD* gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. Cell 1996;87:493–506. [PubMed: 8898202]

McCampbell A, Taylor JP, Taye AA, Robitschek J, Li M, Walcott J, Merry D, Chai Y, Paulson H, Sobue G, Fischbeck KH. CREB-binding protein sequestration by expanded polyglutamine. Hum Mol Genet 2000;9:2197–2202. [PubMed: 10958659]

McCampbell ARV, Taye AA, Walcott JL, Merry DE, Fischbeck KH. Co-localization of CBP with expanded polyglutamine containing androgen receptor. American Journal of Human Genetics 1999;65(Suppl):A106–A106.

McCaw EA, Hu H, Gomez GT, Hebb AL, Kelly ME, Denovan-Wright EM. Structure, expression and regulation of the cannabinoid receptor gene (CB1) in Huntington's disease transgenic mice. Eur J Biochem 2004;271:4909–4920. [PubMed: 15606779]

McGeer EG, McGeer PL. Duplication of biochemical changes of Huntington's chorea by intrastriatal injections of glutamic acid and kainic acids. Nature 1976;263:517–519. [PubMed: 9592]

Menalled L, Zanjani H, MacKenzie L, Koppel A, Carpenter E, Zeitlin S, Chesselet MF. Decrease in striatal enkephalin mRNA in mouse models of Huntington's disease. Exp Neurol 2000;162:328–342. [PubMed: 10739639]

Menalled LB, Chesselet MF. Mouse models of Huntington's disease. Trends Pharmacol Sci 2002;23:32–39. [PubMed: 11804649]

Menalled LB, Sison JD, Wu Y, Olivieri M, Li XJ, Li H, Zeitlin S, Chesselet MF. Early motor dysfunction and striosomal distribution of huntingtin microaggregates in Huntington's disease knock-in mice. J Neurosci 2002;22:8266–8276. [PubMed: 12223581]

Miller RM, Callahan LM, Casaceli C, Chen L, Kiser GL, Chui B, Kaysser-Kranich TM, Sendera TJ, Palaniappan C, Federoff HJ. Dysregulation of gene expression in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse substantia nigra. J Neurosci 2004;24:7445–7454. [PubMed: 15329391]

Morton AJ, Edwardson JM. Progressive depletion of complexin II in a transgenic mouse model of Huntington's disease. J Neurochem 2001;76:166–172. [PubMed: 11145989]

Morton AJ, Hunt MJ, Hodges AK, Lewis PD, Redfern AJ, Dunnett SB, Jones L. A combination drug therapy improves cognition and reverses gene expression changes in a mouse model of Huntington's disease. Eur J Neurosci 2005a;21:855–870. [PubMed: 15787692]

Morton AJ, Wood NI, Hastings MH, Hurelbrink C, Barker RA, Maywood ES. Disintegration of the sleep-wake cycle and circadian timing in Huntington's disease. J Neurosci 2005b;25:157–163. [PubMed: 15634777]

Nakamura K, Jeong SY, Uchihara T, Anno M, Nagashima K, Nagashima T, Ikeda S, Tsuji S, Kanazawa I. SCA17, a novel autosomal dominant cerebellar ataxia caused by an expanded polyglutamine in TATA-binding protein. Hum Mol Genet 2001;10:1441–1448. [PubMed: 11448935]

Norris PJ, Waldvogel HJ, Faull RL, Love DR, Emson PC. Decreased neuronal nitric oxide synthase messenger RNA and somatostatin messenger RNA in the striatum of Huntington's disease. Neuroscience 1996;72:1037–1047. [PubMed: 8735228]

Noureddine MA, Li YJ, van der Walt JM, Walters R, Jewett RM, Xu H, Wang T, Walter JW, Scott BL, Hulette C, Schmechel D, Stenger JE, Dietrich F, Vance JM, Hauser MA. Genomic convergence to identify candidate genes for Parkinson disease: SAGE analysis of the substantia nigra. Mov Disord 2005;20:1299–1309. [PubMed: 15966006]

Nucifora FC Jr, Sasaki M, Peters MF, Huang H, Cooper JK, Yamada M, Takahashi H, Tsuji S, Troncoso J, Dawson VL, Dawson TM, Ross CA. Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. Science 2001;291:2423–2428. [PubMed: 11264541]

Orr HT. Microarrays and polyglutamine disorders: reports from the Hereditary Disease Array Group. Hum Mol Genet 2002;11:1909–1910. [PubMed: 12165553]

Oyama F, Miyazaki H, Sakamoto N, Becquet C, Machida Y, Kaneko K, Uchikawa C, Suzuki T, Kurosawa M, Ikeda T, Tamaoka A, Sakurai T, Nukina N. Sodium channel beta4 subunit: down-regulation and possible involvement in neuritic degeneration in Huntington's disease transgenic mice. J Neurochem 2006;98:518–529. [PubMed: 16805843]

Pan W. A comparative review of statistical methods for discovering differentially expressed genes in replicated microarray experiments. Bioinformatics 2002;18:546–554. [PubMed: 12016052]

Pang TY, Stam NC, Nithianantharajah J, Howard ML, Hannan AJ. Differential effects of voluntary physical exercise on behavioral and brain-derived neurotrophic factor expression deficits in Huntington's disease transgenic mice. Neuroscience 2006;141:569–584. [PubMed: 16716524]

Paulson HL, Fischbeck KH. Trinucleotide repeats in neurogenetic disorders. Annu Rev Neurosci 1996;19:79–107. [PubMed: 8833437]

Perez-Severiano F, Escalante B, Vergara P, Rios C, Segovia J. Age-dependent changes in nitric oxide synthase activity and protein expression in striata of mice transgenic for the Huntington's disease mutation. Brain Res 2002;951:36–42. [PubMed: 12231454]

Petrasch-Parwez E, Habbes HW, Weickert S, Lobbecke-Schumacher M, Striedinger K, Wieczorek S, Dermietzel R, Epplen JT. Fine-structural analysis and connexin expression in the retina of a transgenic model of Huntington's disease. J Comp Neurol 2004;479:181–197. [PubMed: 15452853]

Pineda JR, Canals JM, Bosch M, Adell A, Mengod G, Artigas F, Ernfors P, Alberch J. Brain-derived neurotrophic factor modulates dopaminergic deficits in a transgenic mouse model of Huntington's disease. J Neurochem 2005;93:1057–1068. [PubMed: 15934928]

Qiu Z, Norflus F, Singh B, Swindell MK, Buzescu R, Bejarano M, Chopra R, Zucker B, Benn CL, DiRocco DP, Cha JH, Ferrante RJ, Hersch SM. Sp1 is up-regulated in cellular and transgenic models of Huntington disease, and its reduction is neuroprotective. J Biol Chem 2006;281:16672–16680. [PubMed: 16595660]

Reddy PH, Williams M, Charles V, Garrett L, Pike-Buchanan L, Whetsell WO Jr, Miller G, Tagle DA. Behavioural abnormalities and selective neuronal loss in HD transgenic mice expressing mutated full-length HD cDNA. Nat Genet 1998;20:198–202. [PubMed: 9771716]

Reiner A, Albin RL, Anderson KD, D'Amato CJ, Penney JB, Young AB. Differential loss of striatal projection neurons in Huntington disease. Proceedings of the National Academy of Sciences, USA 1988;85:5733–5737.

Reynolds GP, Dalton CF, Tillery CL, Mangiarini L, Davies SW, Bates GP. Brain neurotransmitter deficits in mice transgenic for the Huntington's disease mutation. J Neurochem 1999;72:1773–1776. [PubMed: 10098889]

Richfield EK, Herkenham M. Selective vulnerability in Huntington's disease: preferential loss of cannabinoid receptors in lateral globus pallidus. Ann Neurol 1994;36:577–584. [PubMed: 7944290]

Rodriguez-Lebron E, Denovan-Wright EM, Nash K, Lewin AS, Mandel RJ. Intrastriatal rAAV-mediated delivery of anti-huntingtin shRNAs induces partial reversal of disease progression in R6/1 Huntington's disease transgenic mice. Mol Ther 2005;12:618–633. [PubMed: 16019264]

Rosas HD, Hevelone ND, Zaleta AK, Greve DN, Salat DH, Fischl B. Regional cortical thinning in preclinical Huntington disease and its relationship to cognition. Neurology 2005;65:745–747. [PubMed: 16157910]

Rosas HD, Koroshetz WJ, Chen YI, Skeuse C, Vangel M, Cudkowicz ME, Caplan K, Marek K, Seidman LJ, Makris N, Jenkins BG, Goldstein JM. Evidence for more widespread cerebral pathology in early HD: an MRI-based morphometric analysis. Neurology 2003;60:1615–1620. [PubMed: 12771251]

Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, van der Kouwe A, Jenkins BG, Dale AM, Fischl B. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 2002;58:695–701. [PubMed: 11889230]

Ross CA. Intranuclear neuronal inclusions: a common pathogenic mechanism for glutamine-repeat neurodegenerative diseases? Neuron 1997;19:1147–1150. [PubMed: 9427237]

Ross CA. Polyglutamine pathogenesis: emergence of unifying mechanisms for Huntington's disease and related disorders. Neuron 2002;35:819–822. [PubMed: 12372277]

Sadri-Vakili G, Cha JH. Mechanisms of disease: Histone modifications in Huntington's disease. Nat Clin Pract Neurol 2006;2:330–338. [PubMed: 16932577]

Sadri-Vakili G, Menon AS, Farrell LA, Keller-McGandy CE, Cantuti-Castelvetri I, Standaert DG, Augood SJ, Yohrling GJ, Cha JH. Huntingtin inclusions do not down-regulate specific genes in the R6/2 Huntington's disease mouse. Eur J Neurosci 2006;23:3171–3175. [PubMed: 16820007]

Sanchez I, Mahlke C, Yuan J. Pivotal role of oligomerization in expanded polyglutamine neurodegenerative disorders. Nature 2003;421:373–379. [PubMed: 12540902]

Saudou F, Finkbeiner S, Devys D, Greenberg ME. Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. Cell 1998;95:55–66. [PubMed: 9778247]

Schaffar G, Breuer P, Boteva R, Behrends C, Tzvetkov N, Strippel N, Sakahira H, Siegers K, Hayer-Hartl M, Hartl FU. Cellular toxicity of polyglutamine expansion proteins: mechanism of transcription factor deactivation. Mol Cell 2004;15:95–105. [PubMed: 15225551]

Schilling G, Savonenko AV, Klevytska A, Morton JL, Tucker SM, Poirier M, Gale A, Chan N, Gonzales V, Slunt HH, Coonfield ML, Jenkins NA, Copeland NG, Ross CA, Borchelt DR. Nuclear-targeting of mutant huntingtin fragments produces Huntington's disease-like phenotypes in transgenic mice. Hum Mol Genet 2004;13:1599–1610. [PubMed: 15190011]

Shelbourne PF, Killeen N, Hevner RF, Johnston HM, Tecott L, Lewandoski M, Ennis M, Ramirez L, Li Z, Iannicola C, Littman DR, Myers RM. A Huntington's disease CAG expansion at the murine Hdh locus is unstable and associated with behavioural abnormalities in mice. Hum Mol Genet 1999;8:763–774. [PubMed: 10196365]

Shimohata T, Nakajima T, Yamada M, Uchida C, Onodera O, Naruse S, Kimura T, Koide R, Nozaki K, Sano Y, Ishiguro H, Sakoe K, Ooshima T, Sato A, Ikeuchi T, Oyake M, Sato T, Aoyagi Y, Hozumi I, Nagatsu T, Takiyama Y, Nishizawa M, Goto J, Kanazawa I, Davidson I, Tanese N, Takahashi H, Tsuji S. Expanded polyglutamine stretches interact with TAFII130, interfering with CREB-dependent transcription. Nat Genet 2000;26:29–36. [PubMed: 10973244]

Sipione S, Rigamonti D, Valenza M, Zuccato C, Conti L, Pritchard J, Kooperberg C, Olson JM, Cattaneo E. Early transcriptional profiles in huntingtin-inducible striatal cells by microarray analyses. Hum Mol Genet 2002;11:1953–1965. [PubMed: 12165557]

Slow EJ, van Raamsdonk J, Rogers D, Coleman SH, Graham RK, Deng Y, Oh R, Bissada N, Hossain SM, Yang YZ, Li XJ, Simpson EM, Gutekunst CA, Leavitt BR, Hayden MR. Selective striatal neuronal loss in a YAC128 mouse model of Huntington disease. Hum Mol Genet 2003;12:1555–1567. [PubMed: 12812983]

Smith R, Petersen A, Bates GP, Brundin P, Li JY. Depletion of rabphilin 3A in a transgenic mouse model (R6/1) of Huntington's disease, a possible culprit in synaptic dysfunction. Neurobiol Dis 2005;20:673–684. [PubMed: 15967669]

Steffan JS, Kazantsev A, Spasic-Boskovic O, Greenwald M, Zhu YZ, Gohler H, Wanker E, Bates GP, Housman DE, Thompson LM. The Huntington's disease protein interacts with p53 and CBP and represses transcription. Proceedings of the National Academy of Sciences, USA 2000;97:6763–6768.

Steinman L, Zamvil S. Transcriptional analysis of targets in multiple sclerosis. Nat Rev Immunol 2003;3:483–492. [PubMed: 12776208]

Strand AD, Aragaki AK, Shaw D, Bird T, Holton J, Turner C, Tapscott SJ, Tabrizi SJ, Schapira AH, Kooperberg C, Olson JM. Gene expression in Huntington's disease skeletal muscle: a potential biomarker. Hum Mol Genet 2005;14:1863–1876. [PubMed: 15888475]

Sugars KL, Brown R, Cook LJ, Swartz J, Rubinsztein DC. Decreased cAMP response element-mediated transcription: an early event in exon 1 and full-length cell models of Huntington's disease that contributes to polyglutamine pathogenesis. J Biol Chem 2004;279:4988–4999. [PubMed: 14627700]

Suhr ST, Senut MC, Whitelegge JP, Faull KF, Cuizon DB, Gage FH. Identities of sequestered proteins in aggregates from cells with induced polyglutamine expression. J Cell Biol 2001;153:283–294. [PubMed: 11309410]

Sun Y, Savanenin A, Reddy PH, Liu YF. Polyglutamine-expanded huntingtin promotes sensitization of N-Methyl-D-aspartate receptors via post-synaptic density 95. J Biol Chem 2001;276:24713–24718. [PubMed: 11319238]

Turmaine M, Raza A, Mahal A, Mangiarini L, Bates GP, Davies SW. Nonapoptotic neurodegeneration in a transgenic mouse model of Huntington's disease. Proc Natl Acad Sci U S A 2000;97:8093–8097. [PubMed: 10869421]

Valenza M, Rigamonti D, Goffredo D, Zuccato C, Fenu S, Jamot L, Strand A, Tarditi A, Woodman B, Racchi M, Mariotti C, Di Donato S, Corsini A, Bates G, Pruss R, Olson JM, Sipione S, Tartari M, Cattaneo E. Dysfunction of the cholesterol biosynthetic pathway in Huntington's disease. J Neurosci 2005;25:9932–9939. [PubMed: 16251441]

van Dellen A, Welch J, Dixon RM, Cordery P, York D, Styles P, Blakemore C, Hannan AJ. N-Acetylaspartate and DARPP-32 levels decrease in the corpus striatum of Huntington's disease mice. Neuroreport 2000;11:3751–3757. [PubMed: 11117485]

Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP. Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol 1985;44:559–577. [PubMed: 2932539]

Wexler NS, Rose EA, Housman DE. Molecular approaches to hereditary diseases of the nervous system: Huntington's disease as a paradigm. Annu Rev Neurosci 1991;14:503–529. [PubMed: 1827708]

Weydt P, Pineda VV, Torrence AE, Libby RT, Satterfield TF, Lazarowski ER, Gilbert ML, Morton GJ, Bammler TK, Strand AD, Cui L, Beyer RP, Easley CN, Smith AC, Krainc D, Luquet S, Sweet IR, Schwartz MW, La Spada AR. Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1alpha in Huntington's disease neurodegeneration. Cell Metab 2006;4:349–362. [PubMed: 17055784]

Wheeler VC, White JK, Gutenkunst CA, Vrbanac V, Weaver M, Li XJ, Li SH, Yi H, Vonsattel JP, Gusella JF, Hersch S, Auerbach W, Joyner AL, MacDonald ME. Long glutamine tracts cause nuclear localization of a novel form of huntingtin in medium spiny striatal neurons in *Hdh*^{Q92} and *Hdh*^{Q111} knock-in mice. Hum Mol Genet 2000;9:503–513. [PubMed: 10699173]

White JK, Auerbach W, Duyao MP, Vonsattel JP, Gusella JF, Joyner AL, MacDonald ME. Huntingtin is required for neurogenesis and is not impaired by the Huntington's disease CAG expansion. Nature Genet 1997;17:404–410. [PubMed: 9398841]

Wu ZL, Ciallella JR, Flood DG, O'Kane TM, Bozyczko-Coyne D, Savage MJ. Comparative analysis of cortical gene expression in mouse models of Alzheimer's disease. Neurobiol Aging 2006;27:377–386. [PubMed: 15927307]

Wyttenbach A, Swartz J, Kita H, Thykjaer T, Carmichael J, Bradley J, Brown R, Maxwell M, Schapira A, Orntoft TF, Kato K, Rubinsztein DC. Polyglutamine expansions cause decreased CRE-mediated transcription and early gene expression changes prior to cell death in an inducible cell model of Huntington's disease. Hum Mol Genet 2001;10:1829–1845. [PubMed: 11532992]

Xiang W, Windl O, Wunsch G, Dugas M, Kohlmann A, Dierkes N, Westner IM, Kretzschmar HA. Identification of differentially expressed genes in scrapie-infected mouse brains by using global gene expression technology. J Virol 2004;78:11051–11060. [PubMed: 15452225]

Yamamoto A, Lucas JJ, Hen R. Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. Cell 2000;101:57–66. [PubMed: 10778856]

Yohrling, GJ.; Cha, JHJ. Neurochemistry of Huntington's disease. In: Bates, GP.; Harper, PS.; Jones, AL., editors. Huntington's Disease. Oxford Medical Publications; London: 2002. p. 276-308.

Yohrling GJ, Farrell LA, Hollenberg AN, Cha JHJ. Mutant huntingtin increases nuclear corepressor function and enhances ligand-dependent nuclear hormone receptor activation. Molecular and Cellular Neuroscience 2003;23:28–38. [PubMed: 12799135]

Yohrling GJ IV, Jiang GCT, DeJohn MM, Robertson DJ, Vrana KE, Cha JHJ. Inhibition of tryptophan hydroxylase activity and decreased 5-HT1A receptor binding in a mouse model of Huntington's disease. J Neurochem 2002;82:1416–1423. [PubMed: 12354289]

Young AB, Greenamyre JT, Hollingsworth Z, Albin R, D'Amato C, Shoulson I, Penney JB. NMDA receptor losses in putamen from patients with Huntington's disease. Science 1988;241:981–983. [PubMed: 2841762]

Yu ZX, Li SH, Nguyen HP, Li XJ. Huntingtin inclusions do not deplete polyglutamine-containing transcription factors in HD mice. Hum Mol Genet 2002;11:905–914. [PubMed: 11971872]

Zeitlin S, Liu JP, Chapman DL, Papaioannou VE, Efstratiadis A. Increased apoptosis and early embryonic lethality in mice nullizygous for the Huntington's disease gene homologue. Nature Genetics 1995;11:155–163. [PubMed: 7550343]

Zhai W, Jeong H, Cui L, Krainc D, Tjian R. In vitro analysis of huntingtin-mediated transcriptional repression reveals multiple transcription factor targets. Cell 2005;123:1241–1253. [PubMed: 16377565]

Zhang W, Vazquez L, Apperson M, Kennedy MB. Citron binds to PSD-95 at glutamatergic synapses on inhibitory neurons in the hippocampus. J Neurosci 1999;19:96–108. [PubMed: 9870942]

Zuccato C, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L, MacDonald ME, Friedlander RM, Silani V, Hayden MR, Timmusk T, Sipione S, Cattaneo E. Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. Science 2001;293:493–498. [PubMed: 11408619]

Zuccato C, Liber D, Ramos C, Tarditi A, Rigamonti D, Tartari M, Valenza M, Cattaneo E. Progressive loss of BDNF in a mouse model of Huntington's disease and rescue by BDNF delivery. Pharmacol Res 2005;52:133–139. [PubMed: 15967378]

Zuccato C, Tartari M, Crotti A, Goffredo D, Valenza M, Conti L, Cataudella T, Leavitt BR, Hayden MR, Timmusk T, Rigamonti D, Cattaneo E. Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. Nat Genet 2003;35:76–83. [PubMed: 12881722]

Zucker B, Luthi-Carter R, Kama JA, Dunah AW, Stern EA, Fox JH, Standaert DG, Young AB, Augood SJ. Transcriptional dysregulation in striatal projection- and interneurons in a mouse model of Huntington's disease: neuronal selectivity and potential neuroprotective role of HAP1. Hum Mol Genet 2005;14:179–189. [PubMed: 15548548]

Abbreviations

BDNF
brain-derived neurotrophic factor

CBP
CREB binding protein

CRE
cyclic AMP response element

DARPP-32
dopamine- and cAMP-regulated phosphoprotein, M(r) 32 kDA

HAT
histone acetyl transferase

HD
Huntington's disease

HDAC
histone deacetylase

Htt
huntingtin

httex1p
huntingtin exon1 containing polyproline region

mRNA
messenger RNA

NCoR
nuclear co-repressor

NII
neuronal intranuclear inclusion

NMDA
N-methyl-D-aspartate

PGC-1α
peroxisome proliferator activated receptor γ (PPAR©) coactivator 1α

Sp1
specificity protein 1

TBP
TATA-binding protein

Table 1

Specific mRNA alterations in transgenic mouse models of HD

Neurotransmitters, Neurotransmitter synthesis, Intracellular Signaling:		
Gene	**Transgenic Mouse**	**Comment**
BDNF	YAC72 (Hermel et al., 2004; Zuccato et al., 2001) R6/2(Zuccato et al., 2005) R6/1 (Pang et al., 2006) BACHD (Gray et al., 2006)	Decreased BDNF contributes to dopamine function (Pineda et al., 2005)
Enkephalin	R6/2, (Menalled et al., 2000) (Luthi-Carter et al., 2000) CAG71, CAG94 (Menalled et al., 2000) N171-82Q (Luthi-Carter et al., 2000)	
oxytocin, vasopressin and cocaine-amphetamine-regulated transcript	Inducible HD transgenic line (Kotliarova et al., 2005)	
GAD67	R6/2 (Gourfinkel-An et al., 2003)	Synthetic enzyme for GABA
Tyrosine hydroxylase	R6/2 (Yohrling et al., 2002)	Synthetic enzyme for catecholamines including dopamine
Adenosine A2a receptor	R6/1, R6/2 and R6/2 (Cha et al., 1999) N171-82Q (Luthi-Carter et al., 2000)	
CB1 receptors	HD94 (Lastres-Becker et al., 2002) R6/1, R6/2 (Denovan-Wright and Robertson, 2000) (McCaw et al., 2004)	
Dopamine D1 receptor	R6/2 (Cha et al., 1998) (Cha et al., 1999) R6/1, R6/5 (Cha et al., 1999) N171-82Q (Jarabek et al., 2004)	
Dopamine D2 receptor	R6/2 (Cha et al., 1998) N171-82Q (Luthi-Carter et al., 2000)	
mGluR1 glutamate receptor	R6/2 (Cha et al., 1998)	
mGluR2 glutamate receptor	R6/2 (Cha et al., 1998)	Striatal mGluR2 protein actually resides on corticostriatal terminals; decreased mRNA detected in cortical pyramidal neurons.
mGluR3 glutamate receptor	R6/2 (Cha et al., 1998)	
NMDA NR2a subunit	R6/2 (Luthi-Carter et al., 2003)	Decreases more prominent in hippocampus than striatum
NMDA NR2b subunit	R6/2 (Luthi-Carter et al., 2003)	Decreases more prominent in hippocampus than striatum
Kainate receptors	R6/2 (Cha et al., 1998)	
AMPA receptors	R6/2 (Cha et al., 1998)	
Muscarinic cholinergic receptors	R6/2 (Cha et al., 1998)	
TrkB receptor	R6/1 (Gines et al., 2006)	TrkB decrease not simply a consequence of decreased BDNF
GLT glutamate transporter	R6/2 (Lievens et al., 2001)	Glutamate transporter that is primarily astrocytic; other glutamate transporters expressed at normallevels
Protein kinase beta II	R6/2 (Harris et al., 2001)	
dopamine- and cAMP-regulated phosphoprotein, M(r) 32 kDA (DARPP-32)	R6/2 (Bibb et al., 2000) R6/1 (van Dellen et al., 2000) N171-82Q (Luthi-Carter et al., 2000)	
Phosphodiesterase 10A	R6/1, R6/2(Hu et al., 2004) (Hebb et al., 2004)	Htt decreases transcription of PDE10A transcripts, a striatum-specific PDE
Phosphodiesterase 1B	R6/1, R6/2 (Hebb et al., 2004)	
nNOS	R6/1 (Perez-Severiano et al., 2002) R6/2 (Deckel et al., 2002)	
mBmal1	(Morton et al., 2005b)	Clock protein whose altered expression may underlie disrupted sleep in HD
Adenylate cyclase	R6/2, N171-82Q (Luthi-Carter et al., 2000)	
Synaptic, cytoskeletal and structural proteins:		
Gene	**Transgenice Mouse**	**Comment**
Tenascin C	R6/2 (Kusakabe et al., 2001)	Extracellular matrix protein
Rabphilin 3a	R6/1 (Smith et al., 2005)	rabphilin 3A, a protein involved in exocytosis, is substantially decreased in R6/1 synapses
Alpha-actinin-2	R6/2 (Luthi-Carter et al., 2003)	Involved in clustering of NMDA receptors
Connexin 36 and Connexin 45	R6/2 retina (Petrasch-Parwez et al., 2004)	
PSD-95	R6/2 (Luthi-Carter et al., 2003) N171-82Q (Jarabek et al., 2004)	Involved in clustering of NMDA receptors
Citron	N171-82Q (Jarabek et al., 2004)	PSD-95 binding partner involved in dendritic spine formation
alpha-SNAP	R6/2 (Freeman and Morton, 2004)	Component of SNARE complex. Decrease in alpha-SNAP lags behind decrease in Complexin II

Neurotransmitters, Neurotransmitter synthesis, Intracellular Signaling:		
Gene	**Transgenic Mouse**	**Comment**
Complexin I	R6/2 (Freeman and Morton, 2004)	Component of SNARE complex. Decrease in alpha-SNAP lags behind decrease in Complexin II
Complexin II	R6/2 (Freeman and Morton, 2004; Morton and Edwardson, 2001)	
Other:		
Gene	**Transgenice Mouse**	**Comment**
Ip and Fp subunits of mitochondrial complex II	Striatal neurons transfected with Lentiviral injection of N171-82Q (Benchoua et al., 2006)	
Capucin	R6/2 (de Chaldee et al., 2006)	Novel striatal specific gene downregulated in HD
PDX-1, E2A proteins, and the coactivators CBP and p300	R6/2 and N171-82Q (Andreassen et al., 2002)	Altered gene expression may account for diabetes phenotype in transgenic mice

Table 2

Summary of Microarray Profiling Studies

Transgenic Mouse Models:			
Study	**Tissue Profiled**	**Form of mutant huntingtin**	**Comment**
(Luthi-Carter et al., 2000)	R6/2 mouse striatum	Transgenic expression of human exon 1 with ~150Q	1.7% of genes are changed, with decreases outnumbering increases by 3:1. Decreased genes include: neurotransmitters and receptors, second messengers, calcium homeostasis and nuclear receptors.
(Iannicola et al., 2000)	R6/1 whole brain	Transgenic expression of human exon 1 with ~115Q	Whole brain mRNA hybridized to filters containing cDNA for 588 genes. 7 genes increased; 2 decreased.
(Chan et al., 2002)	Striatum from R6/2, N171-82Q, HD46, YAC72 transgenic mice	Transgenic mice expressing different lengths of human Htt	Mice with shorter fragments demonstrate more pronounced gene expression changes. Strength of conclusions undermined by the many differences in the models used.
(Luthi-Carter et al., 2002b)	Striatum of mouse models of HD, SCA-7, DRPLA, and SBMA	Different polyglutamine disease transgenes	Many shared gene changes bolster the idea that polyglutamine moiety is responsible for gene changes
(Ferrante et al., 2003)	R6/2 striatum	Transgenic expression of human exon 1 with ~150Q	Treatment with the HDAC inhibitor sodium butyrate partially reverses transcriptional dysregulation
(Benn et al., 2005)	Striatum of NLS- and NES versions of R6 mouse lines	Transgenic expression of human exon 1 with ~140Q	Nuclear localization produces more mor pronounced changes. R6/2 and R6/2 mice chare similar transcriptional profiles.
(Oyama et al., 2006)	Transgenic HD190QG mice	Transgenic expression of human exon 1 with 190Q, fused to eGFP	Overall pattern similar to that seen in R6/2 mice, additional ESTs identified. Identifies sodium channel beta4 subunit as downregulated, possible involvement in neurite retraction
(Morton et al., 2005a)	R6/2 mouse striatum	Transgenic expression of human exon 1 with ~150Q	Treatment of with a combination of tacrine, moclobemide and creatine partially reverses gene expression abnormalities
(Desplats et al., 2006)	R6/1 mouse striatum	Transgenic expression of human exon 1 with ~140Q	Pattern of downregulated genes explains striatal specificity
(Crocker et al., 2006)	R6/2 mouse striatum	Transgenic expression of human exon 1 with ~150Q	170/15000 (1.1%) genes changed. More genes upregulated than downregulated.
Cell Models:			
Study	**Tissue Profiled**	**Form of mutant huntingtin**	**Comment**
(Wyttenbach et al., 2001)	PC12 cells	Human exon 1, inducible expression, 23Q, or 74Q	Evidence of compromised CRE-mediated transcription, partially resuced by cAMP or forskolin.
(Sipione et al., 2002)	ST14a immortalized striatal cells	N-terminal 548-amino-acid huntingtin fragments with 26, 67, 105 or 118 glutamines	Inducible system allows for temporal resolution of gene changes. More genes decreased than increased. Cholesterol metabolism implicated.
(Kita et al., 2002)	PC12 cells	Stable Human exon 1 with 23Q or 74Q	126/1824 (6.9%) genes changed. Some of the genes with identified changes involved with cell death.
(Sugars et al., 2004)	PC12 cells	Exon 1, inducible	Disrupted pathways controlled by cAMP response element (CRE), retinoic acid response element, and nuclear factor kappaB.
(Apostol et al., 2006)	PC12 cells	Truncated form of human exon 1	85 genes increased, 53 genes decreased. Suggests activation of MAP kinase pathway.
Human:			
Study	**Tissue Profiled**	**Form of mutant huntingtin**	**Comment**
(Borovecki et al., 2005)	Human peripheral blood cells	Mutant human *HD* alleles	More genes increased than decreased. Sets of genes could discriminate control, presymptomatic and symptomatic patients.
(Hodges et al., 2006)	Human HD brain	Mutant human *HD* alleles	Results remarkably similar to that seen in truncated transgenic mouse models. Gene changes most prominent in striatum and motor cortex, with few changes in cerebellum and none in frontal association cortex.