The biological function of the Huntingtin protein and its relevance to Huntington's Disease pathology

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Abstract

Huntington's Disease is an adult-onset dominant heritable disorder characterized by progressive psychiatric disruption, cognitive deficits, and loss of motor coordination. It is caused by expansion of a polyglutamine tract within the N-terminal domain of the Huntingtin protein. The mutation confers a toxic gain-of-function phenotype, resulting in neurodegeneration that is most severe in the striatum. Increasing experimental evidence from genetic model systems such as mice, zebrafish, and *Drosophila* suggest that polyglutamine expansion within the Huntingtin protein also disrupts its normal biological function. Huntingtin is widely expressed during development and has a complex and dynamic distribution within cells. It is predicted to be a protein of pleiotropic function, interacting with a large number of effector proteins to mediate a host of physiological processes. In this review, we highlight the wildtype function of Huntingtin, focusing on its postdevelopmental roles in axonal trafficking, regulation of gene transcription, and cell survival. We then discuss how potential loss-of-function phenotypes resulting in polyglutamine expansion within Huntingtin may have direct relevance to the underlying pathophysiology of Huntington's Disease.

Keywords

Huntingtin; Huntington's Disease; neurodegeneration; polyglutamine; axonal transport

INTRODUCTION

Huntington's Disease (HD) is a progressive and disabling neurodegenerative disorder of the central nervous system, affecting approximately 1 in 10,000 individuals [1]. Patients suffer from motor, cognitive, and behavioural disturbances arising at a mean age of 35 years. There is currently no cure, and the disease is fatal approximately 15 to 20 years after the age of onset. HD is caused by inheritance of an autosomal dominant mutation in the Huntingtin (Htt) protein (Figure 1). In HD, the polyglutamine (polyQ) domain of the protein is expanded beyond a threshold of 36 glutamines [2]. The length of mutant polyQ expansion strongly correlates in an inverse manner to disease age of onset, with 40-50 repeats leading to adult-onset HD, and 50-120 repeats leading to a juvenile form of the disease which presents with Parkinsonian rigidity characteristics [3]. While 70% of the variance of the age of onset can be attributed to polyQ length, environmental and individual genetic backgrounds account for the remainder [4-10].

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HD pathology is defined principally by death of the medium-sized spiny neurons of the striatum that utilize γ-aminobutyric acid (GABA). Cortical pyramidal neurons that project to the striatum degenerate, and striatal neurons projecting to the substantia nigra also show degeneration in presymptomatic patients [11, 12]. Numerous lines of evidence suggest a glial component of HD pathogenesis. Reactive microglia, which can contribute to cell death in neurodegenerative diseases, appear in the striatum and cortex in both early and late stages of the disease, but not in control post-mortem brains [13]. Activated microglia are also found in the globus pallidus and adjoining white matter of HD brains. In addition, there is an increase in activated astrocyes and oligodendroglia in the striatum [14-16]. An overall loss of brain volume is reported in HD patients, with different brain compartments showing different rates of loss [17, 18]. Below average brain volumes have also been reported in HD individuals before disease symptoms appear [18-20]. Post-mortem morphometric analysis of HD patients revealed a 21-29% area loss of the cerebral cortex, 29-34% loss of telencephalic white matter, 64% loss in the putamen, and 57% loss in the caudate nucleus, compared to control same age individuals [21].

Within brain cells, mutant polyQ Htt is misfolded and forms aggregates with toxic properties [22], in contrast to diffuse localization in unaffected individuals. The rate of aggregation is proportional to the length of polyQ expansion [23]. Misfolding of polyQ Htt overloads the ubiquitin-proteasomal degradation system, which is needed for cellular homeostasis of protein recycling and energetics [24-26]. Mutant Htt also co-aggregates with other proteins, including CREB binding protein, which can effectively deplete a number of different proteins available to the cell [27, 28]. From analysis of human disease tissue, multiple animal and *in vitro* models, there is substantial evidence that the polyQ expansion in Htt results in a toxic gain-of-function phenotype [29]. However, additional studies that include gene knockouts and knockdowns demonstrate that polyQ expansion within Htt can also cause loss-of-function effects. Therefore therapeutic interventions must take into account the role of the wildtype non-polyQ-expanded Htt protein.

Structural clues for Huntingtin function

Htt is a large, 350 kDa protein found in metazoans, with the highest degree of conservation among vertebrates [30-33]. It is predicted to form an elongated superhelical solenoid [34], and thought to have a flexible structure that can alter its activity [35]. All Htt orthologs are of similar size and contain HEAT (Huntingtin, Elongator factor3, PR65/A regulatory subunit of PP2A, and Tor1) repeats (Figure 1). While there is variation amongst species, the HEAT repeats are very similar in terms of number, sequence similarity, and distribution along the length of the protein [33, 36]. HEAT repeats are thought to mediate protein-protein interactions. Within the Htt protein, their distribution could confer a scaffolding role for protein complex formation [32]. Other conserved proteins with many HEAT repeats are PP2A, PR65/A subunit and β-importin, which also form solenoid-like structures for protein-protein interactions [37-42]. These domains are thought to be elastic and undergo deformation with pushing/pulling forces which could modulate substrate specificity [43].

Interestingly, the N-terminal polyQ domain starting at amino acid 18 of Htt is not found in all organisms bearing a homolog. *Drosophila* does not have any glutamine in or around this position, while the honeybee *Apis mellifera* has a single glutamine. All vertebrates have at least four repeated glutamines, which is regarded as the smallest 'true' polyQ tract. The number of glutamines increases with higher species, with the longest known polyQ tract found in humans [33].

A normal length polyQ tract forms a polar zipper which mediates the binding of other factors bearing polar residues [44-46]. Neurological disruption in a polyQ-deleted knockin mouse suggests that the polyQ tract confers significant neuronal function in vertebrates [47].

PolyQ tracts can reduce the solubility of the protein [48]. Htt is unusual for its solubility, given its large size and long polyQ tract. Flanking the polyQ tract in higher vertebrates is a polyproline (polyP) domain, which is thought to help maintain solubility of the protein [49]. The polyP tract is also reported to mediate interactions with vesicle-associated proteins [50].

A number of features suggest that Htt may traffic between the nucleus and cytoplasm. The Htt C-terminus has an active nuclear export signal (NES). In addition, the 18 amino acid N-terminus region interacts with TPR, a nuclear pore protein that has nuclear translocation activity [51, 52]. This N-terminus domain forms an amphipathic alpha helical membrane-binding domain that reversibly mediates association with the endoplasmic reticulum (ER), endosomes, and autophagic vesicles [52]. Point mutation and deletion of this region results in accumulation of Htt within the nucleus and cellular toxicity [51, 52].

Htt also contains conserved caspase and calpain cleavage sites among higher vertebrates [53-57]. Cleaved fragments of Htt are observed in the nucleus, yet their activity is unclear. Cellular status can affect proteolysis, as increased proteolysis has been reported in diseased brain, and increased selectivity for N- and C-terminal cleavage fragments has been observed particularly in the striatum [58]. N-terminal fragments are also generated through lysosomal degredation pathways by Cathepsin proteases [59]. Htt N-terminal region may also be modified via ubiquitination and sumoylation, and subject to phosphorylation via kinases such as Akt, ERK1, and Cdk5 [60-64]. Modulation of Htt's phosphorylation state is primarily regulated by S/T phosphatases PP1 and PP2A [65]. Finally, Htt can be modified via palmitoylation in its N-terminal region through interaction with Huntingtin-Interacting Protein 14 (HIP 14) [66]. Palmitoylation allows proteins to maintain close apposition to the plasma membrane, and is a feature of many proteins that control vesicle trafficking.

Huntingtin is expressed ubiquitously throughout the body, and observed at its highest levels in the brain and testes [67-70]. Within the brain, it is found in all neurons, as well as glial cells [67-69, 71-76]. The subcellular localization of Htt is complex and dynamic. Htt may change conformation depending on its compartmental localization, as different anti-Htt antisera recognizing different epitopes within the protein show distinct subcellular labeling profiles [77]. Htt colocalizes with many organelles, including the nucleus, endoplasmic reticulum, Gogli complex, and endosomes [70, 78, 79]. It is observed in axonal processes and at synapses, in association with microtubules, clathrin-coated vesicles, caveolae, and synaptosomes [70, 80].

Evidence that loss of Huntington function contributes to HD pathology

Increasing lines of evidence suggest that a component of HD pathology is due to loss-of-function effects. However, the extent of loss-of-function effects versus the more prominent gain-of-function phenotype remains unclear. In higher vertebrates, *huntingtin* is an essential gene.

Homozygous Htt knockout mice (*Hdh*−/−) are embryonic lethal at the pre-gastrulation stage [81-83]. Even animals heterozygous for *Hdh* knockout show physical defects in the brain, as well as behavioural changes [81, 84, 85]. Partial reduction of Htt levels in zebrafish via morpholino knockdown at the one-cell stage has also provided insight into the varying sensitivities of neurons to loss of Htt. Neurodevelopmental defects are observed in the anterior-most brain regions, while mid- and hindbrain regions are not as sensitive to knockdown [86]. Interestingly, humans homozygous for mutant expanded polyQ Htt develop to adulthood with no obvious enhancement in pathology other than a small reduction in brain volume [87, 88]. Therefore, Htt loss-of-function effects conferred by polyQ expansion may preferentially manifest during the aging process, while preserving some developmental roles.

Within multiple genetic degeneration models, the benefit of a fully functioning Htt protein in a disease context is highlighted. Loss of wild type Htt in mice expressing polyQ-expanded Htt show reduced striatal size, motor performance, and shortened longevity compared to those with wildtype Htt [89, 90]. This is also observed in *Drosophila*, even though its Htt ortholog, *dhtt*, is not required for early development. Removal of the *dhtt* gene from the genetic background of flies expressing a human polyQ Htt exon 1 fragment exacerbates the age-related neuronal degeneration phenotype [36]. Given these observations, potential therapies aimed at translational repression of Htt should ideally target the disease transcript only.

Huntingtin mediated trafficking of vesicles and organelles

Htt, with its large number of protein-protein interaction domains, has been found to interact so far with over 200 other proteins [45, 46, 91, 92]. A large number of Htt protein interactors function in microtubule-based axon trafficking. Huntingtin-associated protein 1 (HAP1) helps mediate the interaction between Htt, microtubule motor proteins and their co-factors, including kinesin, dynactin, and dynein [93-97]. Kinesin and dynein are plus- and minus-end molecular motors respectively, suggesting that Htt is involved in both antero- and retrograde axon transport. Its role in axon transport has been well confirmed in mammalian culture, as well as in *Drosophila* and mouse models [97-101]. In conditional Htt knock-out mice, vesicular and mitochondrial trafficking is impaired in both directions, and progressive brain degeneration is observed [101, 102]. The bidirectional switching of axon transport is thought to be controlled at least in part by the phosphorylation of Htt at Serine 421 (Ser421) at its C-terminus. This phosphorylation changes the net directional movement of vesicles from retrograde to anterograde, possibly via the recruitment of more kinesin to the Htt microtubule-associated complexes, or the stabilization of kinesin-dynactin interactions [103].

Htt may also mediate short-range transport along the actin cytoskeleton at the cell cortex as a component of the endocytic pathway. Htt associates with the endocytosis proteins clathrin and dynamin, as well as endocytic organelle trafficking proteins such as Endophilin 3, α-Adaptin, HIP-14, HAP1, and Huntingtin-associated protein 40 (HAP40) [45, 46, 92, 104]. The tethering of Htt-associated endosomes with the actin cytoskeleton is promoted by the interactor HAP40. Optineurin, a myosin VI linker protein, associates with Htt-HAP40 [105]. This interaction is thought to allow Htt-associated early endocytic vesicles to move along actin filaments [106, 107]. The early endosomal trafficking effector, Rab5 GTPase forms a complex with Htt [100]. In polyQ mutant Htt cells, Rab5-GFP-tagged endosomes accumulate along actin filaments, and there is a deficit of Rab-GFP positive vesicles associated with microtubules [100]. Loss of Htt in Zebrafish leads to a dysregulation of iron and hemoglobin production, where neurons are capable of endocytosing iron, yet cannot properly traffic iron-containing vesicles [108]. These observations have led to the hypothesis that the Htt protein may act as a scaffold that links transport cargo with motor proteins, and may regulate factors that coordinate trafficking and transferring of cellular material along and between actin and microtubule cytokeletons in a bidirectional manner over both short and long distances [105].

Since Htt functions in vesicle and organelle transport along axons, the biological processes associated with Htt-linked cargos may be affected by the loss of Htt function and thus impact disease pathogenesis. Brain-Derived Neurotrophic Factor (BDNF) is produced by cortical cells and is transported from Golgi secretory vesicles by complexes containing Htt, HAP1, and dynactin [97, 109-111]. BDNF is an important factor in HD, since the transfer of BDNF from cortical afferents to striatal cells promotes striatal survival and activity of cortico-striatal synapses [112-116]. BDNF colocalizes with Htt, and RNAi knockdown of Htt leads to reduced axonal transport of BDNF in neuroblastoma cells [98]. Green

Fluorescence Protein-tagged BDNF (GFP-BDNF) vesicle motility is increased in response to ectopic Htt. GFP-BDNF vesicle transport is also improved if wild type Htt is expressed in polyQ Htt expressing cells [98]. However, overexpression of polyQ Htt does not increase the motility of BDNF-containing vesicles. Thus deficits in trafficking of BDNF observed in HD models probably represent a loss-of-function feature of polyQ Htt. Since Htt also stimulates the trafficking of Yellow Fluorescence Protein-tagged Amyloid Precursor Protein (APP-YFP) and GFP-tagged epidermal growth factor receptor (GFP-EGFR), it is likely that Htt-mediated vesicle trafficking may extend to a large number of proteins [98, 99, 117].

Htt is also associated with the movement of mitochondria along neurites. In conditional Htt mouse knockouts expressing less than 50% of normal Htt, mitochondrial movement along neurites show a decrease in speed, pause more often, and travel less distance between pauses compared to controls in both the antero- and retrograde directions [101]. Similar delays in mitochondrial trafficking are observed in mouse primary neurons and with *in vivo* mice expressing polyQ Htt, with greater loss of motility associated with longer polyQ expansion [101]. Disrupted mitochondrial trafficking is detected in asymptomatic polyQ mutant Htt mouse primary neurons [101]. In HD neurons bearing protein aggregates, mitochondrial trafficking loss-of-function effects are also compounded further, since the aggregates physically impair the passage of mitochondria and other cargo [118, 119]. Striatal neurons may be more susceptible to trafficking dysfunction than other neuronal types such as cortical neurons. Striatal mitochondria have trafficking defects even in regions without Htt protein aggregates. In addition, in resting wildtype neurons, striatal mitochondria traffic is slower than in cortical neurons [118, 120].

The specific cellular consequences of early disruption of mitochondrial trafficking are unclear, yet it is likely that if mitochondria are not found at essential subcellular locations in correct numbers and at appropriate times, then neurons may encounter stress during energy-demanding stimuli. Neurons require high levels of ATP synthesis from mitochondria to maintain membrane polarization and are thus sensitive to mitochondrial disruption. Mitochondrial dysfunction is a component of HD, as revealed from postmortem analysis [121, 122]. Early stage HD patients show no deficits in mitochondrial oxygen metabolism compared to age-matched controls, thus respiratory disruption is suggested to be a late, non-causal event of the disease [123-126]. It is thought that aberrant mitochondrial trafficking affects key upstream events of altered Ca^{2+} homeostasis and ATP synthesis along neurites during HD pathogenesis [118, 125, 127]. The later stages of mitochondrial dysfunction are also more likely to be a cause of polyQ gain-of-function effects in mutant Htt. For example, ATP/ADP synthesis decreases as polyQ expansion increases [128]. The many deleterious primary and secondary effects of polyQ Htt have been previously described [125, 127]. Since both axonal trafficking and mitochondrial dysfunction are common to a number of neurodegenerative diseases involving protein aggregation, including Alzheimer's Disease and Parkinson's Diseases, the links between these two processes during disease pathogenesis may be important considerations for therapeutic intervention.

Huntingtin transcriptional regulation and protein handling at the ER-Golgi

A large number of genes show similar patterns of transcriptional dysregulation in HD brains, mouse models and *in vitro* HD systems [129-133]. In R6/2 Htt mutant mice, ~1.5% of all genes show dysregulation during both pre-symptomatic and early symptomatic stages, with 75% showing downregulation [133]. Importantly, dysregulation is seen in both aggregate and non-aggregate bearing neurons of different types [131, 134]. PolyQ tracts are known to mediate the interaction between transcription factors and transcriptional regulators. These interactions can be disrupted with polyQ expansion, a molecular phenotype reported for a number of polyQ disorders [28, 44, 135]. Wild type Htt binds to transcriptional regulators, most notably Repressor Element-1 Transcription Factor/Neuron Restrictive Factor (REST/

NRSF) and cAMP Response Element Binding Protein (CBP). CBP is a transcriptional co-activator that regulates histone acetylation/deacetylation to control the expression of neuronal survival signals [136, 137]. Its glutamine-rich C-terminal interacts with the polyQ-polyP region of mutant Htt, leading to sequestration of CBP in the cytoplasm in aggregates [27, 28, 138, 139]. The CBP histone acetyltransferase activity enables transcription factors to bind DNA [27]. PolyQ Htt binding interferes with the acetyltransferase activity of CBP, as well as other acetyltransferase proteins, and the resultant changes in DNA transcription may be a significant pathophysiology in HD [139]. In support of hypothesis, studies in *Drosophila* and mouse HD disease models have shown that histone deacetylase (HDAC) inhibitors reduce neurodegeneration phenotypes [139-142].

An important factor in neuronal survival is controlled by the interaction of wild type Htt with REST/NRSF to allow BDNF transcription to occur. BDNF is a key neurotrophic factor [112-115, 143] that is synthesized in cortical neurons and provided to striatal neurons for their activity and survival [110, 116, 144, 145]. Htt sequesters REST/NRSF in the cytoplasm, preventing it from binding neuron-restrictive silencer elements (NRSE) which are found at 1,892 sites in the human genome, including *BDNF* and many other genes required for neuronal development and function [146, 147]. PolyQ-expanded Htt is not able to effectively bind to REST/NRSF, thus increased amounts of the repressor locate to the nucleus and suppress *BNDF* expression and other genes regulated by NRSEs [146]. Since striatal neurons require BDNF to be synthesized and trafficked over long range by cortical cells, it is likely that the combined effects of reduced transcription and protein trafficking may be responsible in part for the striatal sensitivity in HD.

Although wild type Htt is primarily cytoplasmic, recent work has found that Htt can interact with nuclear receptors. Long-range signals can activate nuclear receptors that are important for regulation of homeostasis, and 94% of all nuclear receptor genes are expressed in the brain [148, 149]. Htt binds to a number of nuclear receptors, including the vitamin D receptor (VDR), thyroid hormone receptor-α1 (TRα1), and the cholesterol metabolism regulators LXRα and LXRβ [150]. LXRs are critical for brain function, since knockout of LXRα and LXRβ leads to cholesterol dysregulation and subsequent neurodegeneration [151]. From *in vitro* reporter assays, wild type Htt acts as a co-factor for LXR-mediated gene transcription, while polyQ expansion reduces this activity [150]. Zebrafish LXR knockdown results in downregulation of LXR target genes and causes morphological phenotypes which can be partially rescued by an LXR agonist [150]. Cholesterol homeostasis is also disrupted in HD mouse models, and reduced activity of LXRs may be a contributing factor [152, 153].

Antiapoptotic activity

Wild type Htt has neuroprotective functions during numerous proapoptotic challenges [89, 154-157]. In Htt conditional knockouts, neuronal reduction of Htt leads to apoptotic cell death in the striatum, cortex, and hippocampus [102]. In contrast, ectopic expression of wildtype Htt protects against ischaemia and excitotoxicity in a dose-dependent manner [84, 158-160]. Specific neuroprotective mechanisms of Htt are now linked to apoptosis signaling pathways. Htt physically interacts with caspase-3 to inhibit its activity [157]. Knockdown of Htt in zebrafish results in strong activation of caspase-3 and cell death [161]. The polyQ expansion in Htt reduces the inhibitory interaction with caspase-3 and may contribute to neuronal loss in HD brains [157]. p21-activated serine-threonine kinase Pak2 is ubiquitously expressed in the brain and linked to apoptosis [162, 163]. Pak2 is cleaved by caspases to generate an active C-terminal fragment (Pak2p34) that is a mediator of cell death from Fas-related signals [164, 165]. Htt interacts *in vitro* with Pak2 to prevent its cleavage by caspase-3 and caspase-8, thus protecting neurons from Fas-signal-induced apoptosis [166]. The interaction with Pak2 is weaker with polyQ Htt, thus the protective effect is attenuated

[166]. Htt also reduces the activity of HIP1, a pro-apoptotic protein that can activate pro-caspase-8, by sequestering it in a complex together with HIP 1 Protein Interactor (HIPPI) [167]. In HD, the interaction between Htt and HIP1 is reduced [168], thus a greater pool of HIP1-HIPPI may result in increased apoptosis via caspase-8 activation [169].

FUTURE DIRECTIONS

While Huntington's Disease is caused by a toxic gain of function due to polyQ expansion, multiple models suggest that a loss-of-function of the wildtype Htt protein may contribute significantly to several components of disease pathology (as summarized in Figure 2). Htt interacts with a large number of effector proteins, and also functions in transcription and trafficking processes that can alter the processing and localization of many others. Thus, loss of normal Htt function may have even wider ranging impacts on cell physiology than currently appreciated. Although these disruptions can be diverse, it is likely that neurons tolerate some better than others. For therapeutic intervention, it will be important to determine which of the altered physiological processes have the greatest impact on disease progression. It will also be important to gain a better understanding of how much of a loss of normal Htt expression can be tolerated by cells, since some of the therapeutic approaches being developed target reduction of Htt levels [170].

There are also many more questions to be addressed with respect to the normal function of Htt, which may be important for understanding the disease. There is evidence that striatal neurons die in HD as a result of excitotoxicity [171, 172], and Htt is found at synapses with synaptic vesicle trafficking proteins [104, 173]. However, the precise function of normal Htt at the synapse is poorly understood. Also, given the important role of endosomal signaling in neuronal development and function [174], detailed characterization of the role of Htt in endosomal biology may provide further insights into critical mechanisms that may be disrupted in HD neurons. By further characterizing the normal roles of Huntingtin, a more comprehensive understanding of HD and potential therapeutic approaches will be uncovered.

Acknowledgments

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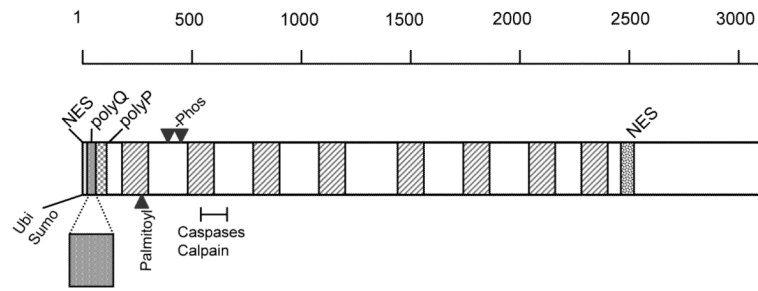
Figure 1. Huntingtin domains and posttranslational modifications

Htt has Ubiquitination (Ubi), Sumoylation (Sumo) and nuclear export signal (NES) at its N-terminal region, followed by polyglutamine (polyQ) and poly proline (polyP) tract. The expansion of polyQ in Huntington's Disease is shown below, connected by dotted lines. HEAT repeats (diagonal stripes) are present throughout the protein. Htt is also palmityolated, phosphorylated, and subject to cleavage by caspases and calpains. A NES is located at the C-terminal region of the protein. The amino acid number is indicated at the top.
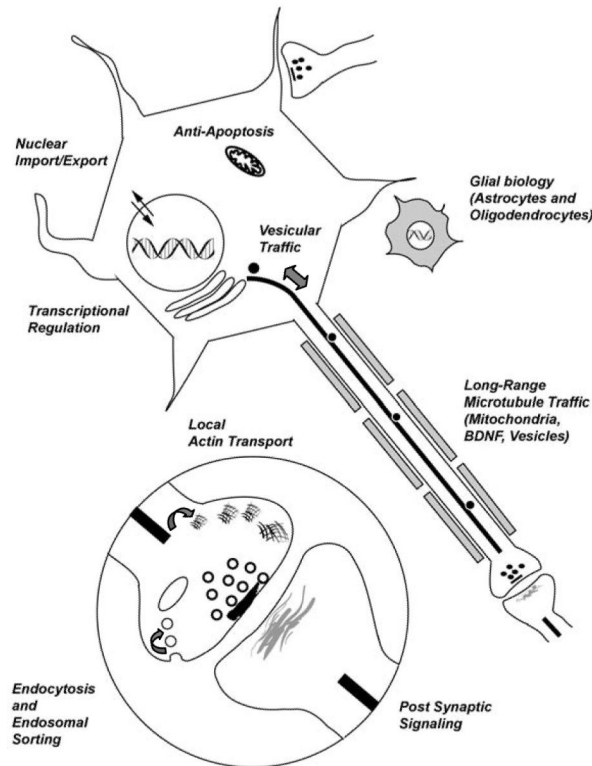
Figure 2. Schematic illustrating the biological functions of wildtype Huntingtin
Illustration shows a generic neuron with an ensheathed axon (grey boxes represent oligodendrocyte wrapping) and an astrocyte (grey stellate shape). Enlarged circle is a magnified view of a synapse. The Htt protein has been suggested to regulate both neuronal and glial function. Within neurons, Htt has been implicated in nuclear import and transcriptional regulation. In addition, Htt regulates apoptotic signaling and axonal transport. At the synapse, Htt has been suggested to have both pre- and post-synatpic roles.