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REVIEW ARTICLE

Huntington's disease: the coming of age

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Abstract. Huntington's disease (HD) is caused due to an abnormal expansion of polyglutamine repeats in the first exon of huntingtin gene. The mutation in huntingtin causes abnormalities in the functioning of protein, leading to deleterious effects ultimately to the demise of specific neuronal cells. The disease is inherited in an autosomal dominant manner and leads to a plethora of neuropsychiatric behaviour and neuronal cell death mainly in striatal and cortical regions of the brain, eventually leading to death of the individual. The discovery of the mutant gene led to a surge in molecular diagnostics of the disease and in making different transgenic models in different organisms to understand the function of wild-type and mutant proteins. Despite difficult challenges, there has been a significant increase in understanding the functioning of the protein in normal and other gain-of-function interactions in mutant form. However, there have been no significant improvements in treatments of the patients suffering from this ailment and most of the treatment is still symptomatic. HD warrants more attention towards better understanding and treatment as more advancement in molecular diagnostics and therapeutic interventions are available. Several different transgenic models are available in different organisms, ranging from fruit flies to primate monkeys, for studies on understanding the pathogenicity of the mutant gene. It is the right time to assess the advancement in the field and try new strategies for neuroprotection using key pathways as target. The present review highlights the key ingredients of pathology in the HD and discusses important studies for drug trials and future goals for therapeutic interventions.

Keywords. Huntington's disease; neurodegeneration; autosomal dominant disorder; huntingtin; pathophysiology; neurochemistry; therapeutic intervention.

Introduction

HD is a progressive neurodegenerative disorder which usually manifests in adulthood and is inherited in an autosomal-dominant manner. The disease has peculiar phenotypes with distinct motor defects, psychiatric symptoms and cognitive decline. The motor symptoms include chorea (bizarre dance like movements), dyskinesia (difficulty or distortion in performing voluntary movements) and dystonia (involuntary contraction of muscles). Psychiatric symptoms, that usually precede the motor symptoms, include depression, anxiety and sleep disorders (Spires and Hannan 2007). Cognitive decline is manifested as difficulties in concentration and retaining newly acquired information, decline in language skills, disorganized speech and perceptual impairments. As the disease progresses, motor rigidity and dementia predominate. Several areas in brain show signs of neuropathology in HD, with the maximum degeneration occurring in the caudate nucleus and putamen (Vonsattel *et al.* 1985).

The mutation in huntingtin (*htt*) gene was identified in 1993 as an unstable expansion of CAG (the trinucleotide coding for glutamine) repeats, which occurs within the first exon of the gene 'IT 15' (for 'Interesting Transcript 15') in HD patients (The Huntington's Disease Collaborative Research Group 1993). This gene on chromosome 4 (4p63) encodes the protein huntingtin. The discovery of mutant *htt* was one of the single most major events in the history of HD and genetics. It led to a hurricane of events starting from an efficient molecular diagnosis of HD to the development of mutant *htt* knock-in transgenic models of the disease.

The mutation in huntingtin gene produces an expanded stretch of the amino acid glutamine (denoted by the

letter Q) towards the amino terminal end of the protein. This causes the mutant protein to interact abnormally with other cell proteins, leading to changes in its function. The glutamine tract in htt is polymorphic, with 8 to 36 glutamine repeats in the normal population and 41 or more in HD. People with 38 or more glutamine repeats in htt can manifest HD but occasionally individual with up to 41 repeats in old age with no discernible symptoms have been reported (Rubinsztein *et al.* 1996). Several studies have pointed out a strong inverse correlation between the repeat number and the age at onset of HD (Zühlke *et al.* 1993; Nørremølle *et al.* 1993; Tabrizi *et al.* 2013).

Historical background of HD

A vivid account of the disease by George Huntington has subsequently borne his name and is considered to be the best report and landmark in the study of HD (Huntington 1872). All the cardinal features of HD are listed in the description: the adult onset, progressive course of the disease, choreiform movements, mental impairment, suicidal tendency and the pattern of inheritance. Such a vivid description of the disease was made possible because of the clinical observation of HD patients by Huntington, his father and grandfather. The clear study and documentation of the two older generations of the Huntingtons gave George Huntington a unique advantage in describing the disease fully.

In 1883, Westphal described juvenile symptoms resembling those seen in HD but he attributed it to a cause other than HD as the patients showed a predominance of hypokinesia and rigidity. The term 'Westphal variant' is often used to describe the clinical picture of juvenile HD. Although, there were several reports about the neuropathology of HD, it was not until the 1920s that there was an equivocal agreement that in HD the changes in brain are primarily degenerative and atrophic, and that the caudate nucleus is most affected (Harper 2002).

In 1993, the HD gene, huntingtin (*htt*) was discovered by the 10-year collective effort of six teams in the United States and Britain, the Huntington Disease Collaborative Research Group. Soon after, several genetic models were developed including several transgenic models in *Drosophila* (Krench and Littleton 2013), nematode *Caenorhabditis elegans* (Bates *et al.* 2006), minipigs (Baxa *et al.* 2013), primates (Yang *et al.* 2008), sheep (Jacobsen *et al.* 2010) and knock-in mouse models (Mangiarini *et al.* 1996; Reddy *et al.* 1998; Hodgson *et al.* 1999). Increasing evidence has converged to indicate that the normal protein functions in intracellular vesicular trafficking, endocytosis, synaptic functioning, autophagy and transcription, and that the mutant *htt* has been linked to disruption of transcription, oxidative stress, autophagy, aggregate formation and several other functions in the cellular homeostasis. The mutant *htt* acquires a toxic gain of function leading to abnormal functioning but the exact pathway of cell death is still elusive.

Epidemiology of HD

Epidemiological studies have now assumed a major role in the study of various neurological disorders like Parkinson's disease, multiple sclerosis and stroke where the information is used in determining the hypotheses about the societal causes, if any, of these diseases, as well as for simply documenting their frequency and variation in the society. In case of HD, the situation is different, because it is a monogenic Mendelian disorder. The route to understand the pathogenesis of the disease is principally molecular, not epidemiological. To study the frequency of the affected population, it involves careful study of complete families, rather than surveys restricted to primary cases, while those at risk are also mostly family members, rather than population at large.

Prevalence of HD in different countries

The incidence of HD is variable across the globe, with Japan, South Africa and Finland having very low rates of the disease among the population as depicted in table 1. Previous estimates of 4–10 per 100,000 people in Western Hemisphere were low (Harper 2002), as recent prevalence data from UK suggests higher prevalence of adult HD at 12.3 per 100,000 based on diagnoses recorded in general practice records (Evans *et al.* 2013). It is assumed that the disease spread across the globe due to migration of affected people from north-west Europe. While detailing about the prevalence of HD, one cannot leave aside the presence of sizeable population of HD patients in Venezuela. The remarkable concentration of HD patients living by the shores of Lake Maracaibo, Venezuela represents the single largest cluster derived from a single ancestor that has remained localized. The pedigree contains over 10,000 members with over 100 living subjects. The high frequency of the disorder in this region was first documented by Negrette (Okun and Thommi 2004). This particular population was recognized by Hereditary Disease Foundation to carry out a systematic study. It was easier to study the genealogy, pedigree analysis and homozygotes, as several families had both the parents affected, it was a landmark project in the history of HD which gave a new direction to HD research. The Venezuela project helped in mapping and isolation of HD gene, which led to the beginning of molecular research in HD (Wexler *et al.* 2004).

Pathophysiology of HD

The pathophysiology of HD contributed by mutant *HTT* is highly complex impacting various functional domains, as is evident from the behavioural expression, neuroanatomical topography and neurochemical profiles of affected individuals.

Table 1. Prevalence estimates of HD in different parts of the world.

Reference	Year of prevalence study	Region	Prevalence (per 100,000)
Reed and Chandler (1958)	1940	Michigan general / black population, USA	4.1/1.5
Folstein *et al.* (1987)	1980	Maryland general / black population, USA	5.5/6.4
Wright *et al.* (1981)	1980	South Carolina general / black population, USA	4.8/0.91
Kokmen *et al.* (1994)	1990	Minnesota, Olmsted county, USA	2
Almqvist *et al.* (2001)	1993–2000	British Columbia, Canada	0.69
Fisher and Hayden (2014)	2011	British Columbia, Canada	13.6
Shokeir (1975)	–	Manitoba and Saskatchewan, Canada	8.5
Pleydell (1955)	1954	Northamptonshire, UK	6.5
Harper *et al.* (1979)	1971	South Wales, UK	7.61
Simpson and Johnston (1989)	1984	Grampian region of Scotland, UK	10.0
Palo *et al.* (1987)	1986	Finland	0.5
Conneally (1984)	–	Tasmania, Australia	17.4
Pridmore (1990)	1990	Tasmania, Australia	12.1
McCusker *et al.* (2000)	1996	New South Wales, Australia	6.3
Adachi and Nakashima (1999)	1997	Western Japan	0.72
Shiwach and Lindenbaum (1990)	1990	Indian subcontinent	1.75
Chen and Lai (2010)	2007	Taiwan	0.42
Peterlin *et al.* (2009)	2009	Slovenia	5.16
Morrison *et al.* (1995)	1991	Northern Ireland	6.4

Behavioural symptoms

Behavioural symptoms are obvious from the impairment in motor, cognitive and psychiatric attributes. Although motor problems are the major phenotypes seen in HD patients, the psychiatric symptoms and cognitive deficits precede it, and they also cause significant burden on a patient's life and lead them to complete loss of independence.

Motor abnormalities

Clinically, the motor disturbances in HD is characterized by involuntary movements, i.e. chorea or dystonia, all of which impair initiation, or execution of movements (Kirkwood *et al.* 2002). Motor abnormalities like bradykinesia, chorea, dystonia and oculomotor symptoms have been shown to be progressive in HD patients (Andrich *et al.* 2007). HD patients also suffer from motor problem, which is more like an inability to maintain a voluntary muscle contraction at a constant level. As a result, they cannot maintain the constant pressure during a handshake and is treated as a characteristic of HD, known as milkmaid's grip (Walker 2007). As the disease progresses, hyperkinetic movements lessen and bradykinesia and rigidity become more prominent (Novak and Tabrizi 2010).

Psychiatric and cognitive changes

Cognitive decline, with progression from early changes in speed of information processing, cognitive inflexibility, and memory retrieval to more severe and widespread abnormalities later in the disease course has been demonstrated as part of the HD phenotype by researchers (Verny *et al.* 2007). Many investigators have noted that the pattern of cognitive deficits seen in HD is similar to neurological or psychiatric conditions that disrupt functioning in the frontal lobe or basal ganglia, or conditions such as lesions in the prefrontal cortex (Brown and Marsden 1988). Severe psychiatric and cognitive impairments have also been observed in juvenile HD patients (Ribaï *et al.* 2007). One of the salient features of George Huntington's description of patients suffering from the disease was 'a tendency to insanity and suicide'. HD patients have four to six times higher suicidal tendency than the general population (Di Maio *et al.* 1993). This rate is even higher for patients whose age is more than 50 years (Schoenfeld *et al.* 1984).

HD patients have been shown to suffer from depression, apathy and irritability when analysed on a Unified Huntington's Disease Rating Scale (UHDRS) (Kingma *et al.* 2008). Apathy is also common, which is characterized by loss of interest and passive behaviour. Working memory deficits have been found in HD patients, when event-related functional magnetic resonance imaging and a parametric verbal working memory task were used to investigate cerebral function (Wolf *et al.* 2009). Memory acquisition and ability to concentrate are poor in HD patients due to

subcortical degeneration (Zakzanis 1998). Sleep disturbance is a cause of significant distress in HD patients (Videnovic *et al.* 2009).

Anatomical features

The most striking neuropathological feature of the HD brain is the shrunken appearance of the neostriatum with gross atrophy of the caudate nucleus and putamen, with the caudate nucleus reduced to a rim of tissue. Reduction in size of the caudate is accompanied by the enlargement of ventricles. HD brains weigh less than brains of age-matched controls with the weight being reduced by 10–20%. Another notable feature is the loss of white matter in the subcortical zone. As a result, the brain is smaller than normal in the late stage of the disease (Vonsattel and DiFiglia 1998).

The striatum is composed of heterogeneous compartments that contain distinct neurochemicals and project to different target regions. These compartments are found in the form of patches termed as striosomes and matrix (Graybiel *et al.* 1990). Striosomes consist of discrete zones and mainly contain opioid receptors, substance P, met-enkephalin and cholecystokinin. The matrix is rich in somatostatin, neuropeptide Y, nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase, acetylcholinesterase, calbindin and cytochrome oxidase. Several conflicting reports associated with the neuropathology of these two compartments in HD exist in the literature. Some describe that the total area of matrix is changed but the total area of striosomes remains the same, as determined by the staining of acetylcholinesterase or calbindin (Ferrante *et al.* 1987; Seto-Ohshima *et al.* 1988). Other studies have suggested the involvement of striosomes in the early phases of the disease (Reiner *et al.* 1988; Hedreen and Folstein 1995). The atrophied striatum is characterized by marked neuronal loss and astrogliosis, which has been used to qualify the neuropathology (Vonsattel *et al.* 1985; Myers *et al.* 1988; Heinsen *et al.* 1994). Quantitative microscopic studies have revealed that there is a relative sparing of the large striatal neurons but severe loss of medium-sized striatal neurons. The majority of these medium-sized striatal neurons are gamma-aminobutyric acid (GABA)-ergic in nature. As these neurons degenerate, there is a corresponding loss of the neurochemicals they contain including glutamic acid decarboxylase (GAD), Substance P, enkephalin, calcineurin, calbindin and adenosine, together with failure of dopaminergic receptors in the striatum. According to their neurochemical differences and differential connectivity, the medium spiny neurons are of two kinds. Medium spiny neurons which express D1 dopamine receptors and Substance P project to internal segment of globus pallidus (globus pallidus interna, GPi) and substantia nigra pars compacta (SNpc), whereas those expressing D2 dopamine receptors and enkephalin project to external segment of globus pallidus (globus pallidus externa, GPe) (Gerfen 1992). One study of 17 early and middle grade HD cases found that the enkephalin containing neurons connecting to GPe were much more affected than the Substance P containing neurons projecting to GPi (Reiner *et al.* 1988). In two other studies, striatal neurons projecting to GPe showed evident loss, whereas the neurons projecting to GPi appeared relatively spared at presymptomatic or early stages of the disease (Albin *et al.* 1990, 1992).

In addition to the medium spiny neurons, the striatum has various interneurons which include the large cholinergic neurons and the sparse medium spiny neurons containing somatostatin, neuropeptide Y and NADPH diaphorase neurons. The striatal interneurons are relatively spared in HD (Ferrante *et al.* 1987; Cicchetti *et al.* 2000). In a major study on neuropathology of HD, 163 post-mortem HD brains were processed and evaluated for assigning a five-point grading scale for the severity of striatal neuropathological involvement in HD with 0 indicating no abnormality and 4 signifying very severe involvement (Vonsattel *et al.* 1985). The grading was based on the histopathological features of relative neuronal loss and relative gliosis in different areas of the brain, which included the cortical, subcortical, and brain stem. Other factors like clinical records of the 163 HD cases were reviewed which included the sex, age at death and a rating of physical disability. Grade 0 was assigned to those cases in which there was substantial evidence for the diagnosis of HD, yet no gross or microscopic abnormalities that could be related to HD neuropathology. In grade 1 brains, there were no macroscopically distinguishable alterations at the level of globus pallidus (GP) and caudate nucleus–nucleus accumbens septi-putamen (CAP). However, there was moderate fibrillary astrocytosis when observed microscopically. Further, the extent of neuronal loss was evident only after cell counting and the putamen showed slight astrocytosis throughout. Grade 2 brains had atrophied caudate nucleus (CN) at the head region at CAP level, which was visible macroscopically. Microscopically, neuronal loss was observed in CAP with concomitant fibrillary astrocytosis in CN and putamen. At GP level, the CN displayed a marked neuronal loss and astrocytosis. The globus pallidus showed minimal or no changes. Grade 3 brains had a shrunken CN at CAP level. At GP level, the CN was reduced to a thin strip. Both the putamen and globus pallidus were moderately decreased in size. Moderate neuronal loss with fibrillary astrocytosis involved the gray matter bridges between CN and putamen. Neuronal loss and gliosis is evident macroscopically in putamen. The lateral segment of the GP showed slight to moderate fibrillary astrocytosis adjacent to putamen. In grade 4 brains at the CAP level, the CN was extremely shrunken and yellow brown. The putamen was markedly atrophic with a concave medial outline. At GP level, the CN was reduced to a thin strip. The putamen was markedly reduced in size and showed widened perivascular spaces in its ventral portion. Microscopically, neuronal depletion and astrocytosis was

extremely severe and diffuse throughout the CN and putamen at both levels CAP and GP. The nucleus accumbens showed slight to moderate fibrillary astrocytosis dorsally. This grading system devised by Vonsattel *et al.* (1985) has been quite useful in HD research, as it remains the single largest study of the neuropathology of post-mortem HD brains.

Although, the loss of neurons from nucleus caudatus putamen (NCP) is the most conspicuous feature of HD brains, there are several reports of the involvement of other brain areas in HD neuropathology. Atrophy of the cerebral cortex has long been recognized as occurring in HD. In HD, the most affected regions in the cortex are layers III, V and VI. Previous studies have confirmed the thinning of the cerebral cortex and underlying white matter (Hedreen *et al.* 1991; Heinsen *et al.* 1994; Macdonald *et al.* 1997; Ciarmiello *et al.* 2006). Recent investigation using *in vivo* magnetic resonance imaging reveals that the behavioural deficits found in the HD patients are closely associated with discrete cortical degeneration in the brain (Rosas *et al.* 2008). Hippocampal CA3, CA4 and granule cell layer of dentate too show neuronal loss (Spargo *et al.* 1993). Neuronal loss has also been reported in ventrolateral thalamus (Dom *et al.* 1976) and in the centromedianparafascicular complex in thalamus in HD brains (Heinsen *et al.* 1996). Cerebellar atrophy has been reported in some cases of HD (Jeste *et al.* 1984; Rodda 1981) with loss of Purkinje cells in some cases (McCaughey 1961).

Microscopic examination of sections after staining them with different microglia markers also revealed reactive microglia is striatum, neocortex and internal capsule (Sapp *et al.* 2001). With the discovery of mutant *htt* and its study in transgenic models of mice helped to identify neuronal nuclear inclusion bodies in HD brains (Davies *et al.* 1997; Becher *et al.* 1998). These inclusion bodies stain positively for IC2 antibody raised against TATA-binding protein with 38 or more polyQ stretch. The inclusion bodies involve about 7% of neocortical neurons but are virtually absent in GP or cerebellum (Gutekunst *et al.* 1999).

Neurochemical alterations in HD

Neurochemical alterations may not only reflect changes in tissue pathology but also give insight into the cause of cell death in specific brain nuclei in HD.

GABA

The first neurotransmitter shown to be decreased in HD brain was GABA. Significant decrease in level of GABA and its synthetic enzyme GAD was shown in post-mortem HD brain (Perry *et al.* 1973; Bird and Iversen 1974). The striatal medium spiny neurons that are GABAergic in nature are most vulnerable neurons in HD and their demise is considered to be the neuropathological hallmark of HD (Vonsattel *et al.* 1985; DiFiglia 1990). Apart from striatum decreased levels of GABA have been found in hippocampus and cerebral cortex (Reynolds and Pearson 1987). Significant decrease in levels of GAD were observed throughout the brain, but most markedly in the striatum and GPe (Spokes 1980). GABA receptors were decreased in striatum but unchanged in the cortex (Lloyd *et al.* 1977).

Dopamine

Dopamine levels were found to be increased (Spokes 1980) or unchanged in striatum, nucleus accumbens, and SNpc (Reynolds and Garrett 1986). Treatment of primary cultures of striatal neurons with DA caused striatal neurodegeneration with reduction in mitochondrial complex-II activity (Benchoua *et al.* 2008). No significant alterations were found in the dopamine synthesizing enzyme tyrosine hydroxylase in post-mortem HD striatum (Bird and Iversen 1977). Deficit in vesicular monoamine transporter type 2 (VMAT2) expression was found in posterior putamen in post-mortem HD brains (Bohnen *et al.* 2000). *In vivo* D_2 receptor binding studies using positron emission tomography (PET) with the help of the specific receptor ligand, raclopiride in HD patients revealed a loss of the postsynaptic receptor in striatum and in temporal and frontal cortex (Pavese *et al.* 2003). Similar observations have been made for both D_1 and D_2 receptors in HD patient's striata using PET analysis (Turjanski *et al.* 1995).

Acetylcholine

Muscarinic cholinergic receptor expression and choline acetyltransferase enzyme activity were found to be significantly decreased in caudate nucleus of HD brain but not in the cortex (Enna *et al.* 1976). Vesicular acetylcholine transporter (VAChT) has been found to be reduced in post-mortem striatal HD brain (Smith *et al.* 2006). However, large cholinergic interneurons in striatum are spared in HD.

Serotonin

Serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were found to be increased in pallidum, cortex and basal ganglia in post-mortem HD brain (Reynolds and Pearson 1987; Kish *et al.* 1987).

Brain-derived neurotrophic factor

Among different trophic factors supporting neuronal cell growth and maintenance in the striatum, BDNF has been found to be consistently decreased in HD patients and different transgenic HD models (Ferrer *et al.* 2000; Baquet *et al.* 2004). Reduced BDNF induced TrkB receptor signalling has been observed in striatal cells of R6/2 transgenic mice model of HD (Nguyen *et al.* 2016).

Cysteine

Cystathione γ-lyase, an enzyme important for synthesis of the amino acid cysteine has been found to be depleted in HD patients brain, striatal cells, and transgenic mouse models, and cysteine supplementation in diet led to significant neuroprotection in HD models (Paul *et al.* 2014).

The biology of huntingtin: cellular basis of pathology

The discovery of the HD gene in 1993 made it possible to generate *in vitro* and *in vivo* genetic models to study the physiopathology of the mutant gene. Studies were designed to investigate the normal function of htt and its various interactions in normal and mutant forms to identify the pathways, which lead to cell death (figure 1). The HD gene contains 67 exons and extends across 170 kb of DNA (Baxendale *et al.* 1995). The CAG repeat that is expanded on HD chromosomes lies within exon 1 and is translated into a stretch of polyQ residues. The protein HTT expressed from the HD gene has over 3000 amino acids, giving a molecular mass of around 350 kDa and is well conserved from flies to mammals (Saudou and Humbert 2016). However, the amino terminal region has been extensively studied, as it contains an expandable polyQ stretch which is considered pathogenic. Several motifs have been identified including the polyglutamine and polyproline tracts close to the N-terminus and the several HEAT (Htt, Elongation factor 3, the PR65/A subunit of protein phosphatase 2A, and the lipid kinase TOR) repeats found just downstream of the proline-rich regions C-terminal to the glutamine tract (Andrade and Bork 1995). A HEAT repeat is a degenerate of a generally 50-amino acid motif consisting of two anti-parallel α-helices forming a helical hairpin. HEAT repeat proteins generally mediate important protein–protein interactions involved in cytoplasmic and nuclear transport, microtubule dynamics, and chromosome segregation (Neuwald and Hirano 2000). Using cross-species comparative analysis, Takano and Gusella (2002) predicted that vertebrate htt contains 28–36 HEAT repeats that span the entire protein. Human *htt* has rat and mouse homologues (Barnes *et al.* 1994; Schmitt *et al.* 1995). It also has recognizable orthologues with the Puffer fish, *Fugu rupribes* (Baxendale *et al.* 1995) and the Zebra fish, *Danio rerio* (Karlovich *et al.* 1998).

HTT gene has two mRNA transcripts of 10336 bp and 13711 bp (Lin *et al.* 1993) and the second transcript which has an additional 3' UTR sequence of 3360 bp seems to be enriched in the brain. HTT transcripts and protein are found to be expressed at different levels throughout the humans and murine tissue (Marques Sousa and Humbert 2013). Although htt expression is not restricted to brain regions which preferentially degenerate in HD, as htt is found to be expressed in several kinds of striatal projection neurons and interneurons as well as cortex, hippocampus and cerebellum. The expression of *htt* starts in embryonic stage and its knock-out is lethal on embryonic day 7.5 (Zeitlin *et al.* 1995) and persists in adulthood but the preferential toxicity in striatal cell death and the manifestation of the disease in adulthood adds a layer of complexity to the disease.

Mutant huntingtin and pathogenesis

Expansion of polyQ tract in htt to greater than 36Q causes the disease and it has been observed that as the number of polyQ repeat increases the earlier is the age of onset of symptoms of HD (Narain *et al.* 1999). It has been observed that ectopic expression of proteins containing polyQ expansion are toxic in cells, however, a loss of huntingtin function can also contribute towards the progression of the disease.

Mutant htt and inclusion bodies

Post-mortem HD brain samples and transgenic HD mice models expressing mutant htt with increased polyQ repeats revealed densely stained intraneuronal inclusions (Davies *et al.* 1997). Inclusion bodies have been reported from multiple regions of the brain including striatum, cerebral cortex, cerebellum, brain stem and spinal cord. Longer polyQ tracts of htt have been found to have increased propensity to form aggregates of mutant htt with ubiquitin positive proteins (Finkbeiner 2011). Immunostaining of inclusion bodies have revealed positive staining of huntingtin and ubiquitin proteasome degradation related proteins (Becher *et al.* 1998). Huntingtin protein is subjected to proteolysis by a variety of proteases. There is also an increase in protease activity in the brains of patients. It is possible that the disease specific enhancement of proteolysis is an important step, as it leads to the generation of small N terminal fragments that contain polyQ stretch and helps to translocate into the nucleus where they are toxic as depicted in figure 1 (Graham *et al.* 2005). Inclusion bodies have also been reported in cytosol and neuronal processes (Gutekunst *et al.* 1999). Initial reports of inclusion bodies containing mutant htt in post-mortem brain samples patients and HD mice models tempted researchers to conclude these are toxic to the host neurons. However, intense research has led to an argument about neuroprotective mechanisms of these aggregate proteins (Zuchner and Brundin 2008; Arrasate *et al.* 2004). A number of studies found that the localization of inclusion bodies and the vulnerability and demise of neurons in HD did not correlate well (Miller *et al.* 2010; Slow *et al.* 2005). The paradigms tested to arrive at this juncture also led some researchers to pharmacologically promote IBs formation as a possible therapeutic approach for HD (Chopra *et al.* 2007). However, recent reports suggest that soluble forms of mutant htt aggregates and insoluble forms may have different level of toxicities and may regulate cell survival and death in different ways (Xi *et al.* 2016). Another recent study suggests that although, soluble htt aggregates lead to apoptotic cell death but insoluble aggregates of mutant htt lead to a delayed necrotic cell death (Ramdzan *et al.* 2017). In yet another important study, it was found that soluble forms of mutant htt were severely toxic to cells by interacting with larger repertoire of proteins related to ribosome biogenesis, translation, transcription and vesicle transport as compared to the insoluble aggregates of mutant htt which had a smaller interactome which were related to quality control such as chaperons and ubiquitin-protease system (Kim *et al.* 2016).

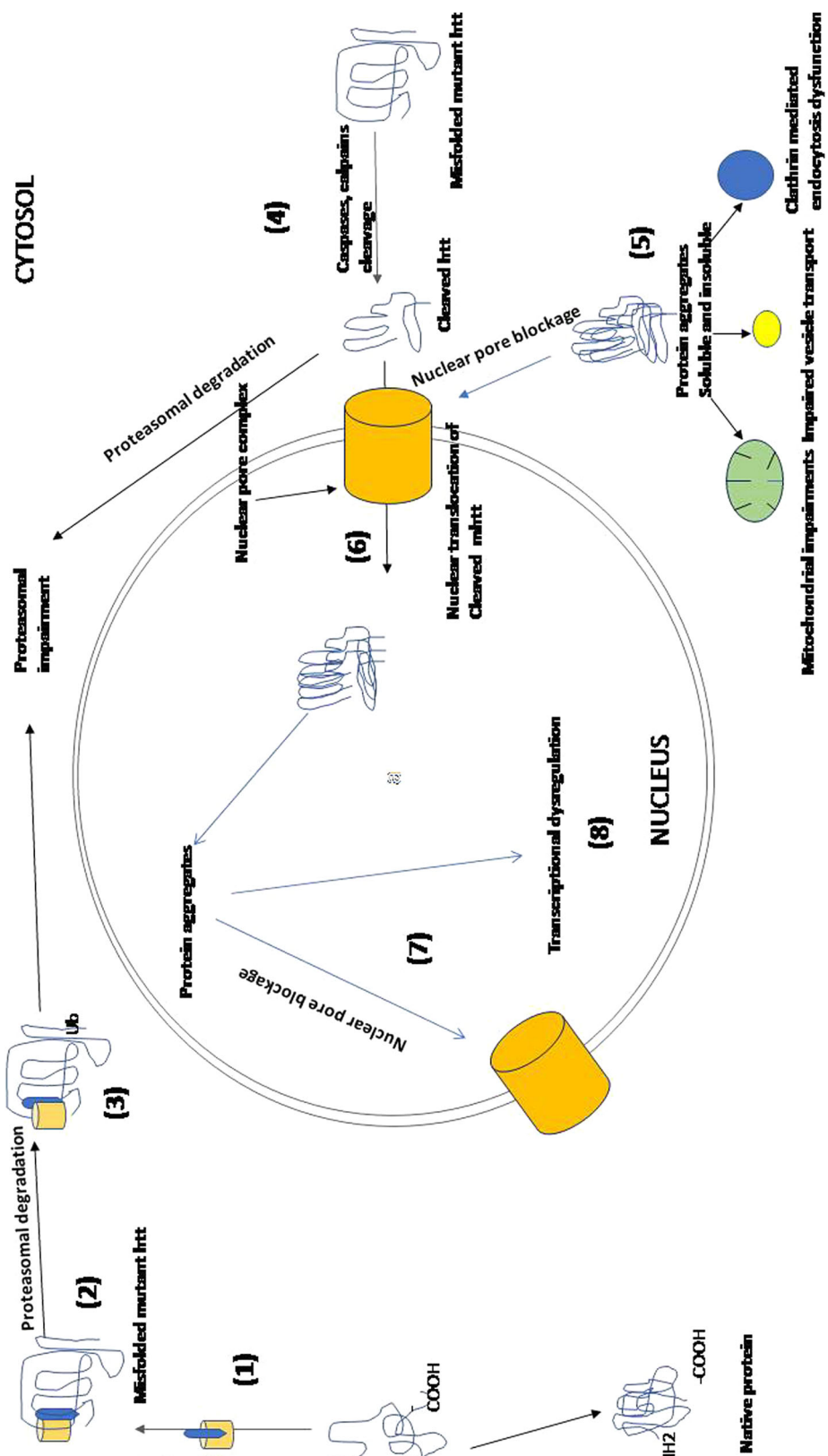

Figure 1. A diagrammatic representation of various known pathways through which mutant htt causes abnormal interactions leading to disruption of cellular homeostasis, ultimately resulting in cell demise. Mutant htt is misfolded abnormally (1) and is (2) bound to chaperones leading to (3) ubiquitination. The ubiquitinated misfolded huntingtin competes with other proteins for degradation. (4) Mutant htt is also cleaved by proteases which forms aggregates which causes (5) mitochondrial impairments, impaired autophagosome and other vesicle transport and dysfunctional endocytosis at presynaptic junctions. The cleaved N terminal mutant htt containing polyQ repeats also (6) translocates to nucleus and causes (7) nuclear pore blockage and (8) transcriptional dysregulation.

Mutant htt and aggregate formation

Studies on mutant htt aggregation have found that its aggregation can be affected by several intrinsic factors such as the length of polyQ stretch, the amino acid residues flanking the polyQ stretch and the conformation of mutant htt. Earlier, mutant htt with increased polyQ stretches showed aggregation pattern in budding yeast (Krobitsch and Lindquist 2000) and in primary striatal culture neurons (Miller *et al.* 2010). Besides the expandable polyQ repeat, the flanking proline rich domain towards the C-terminus and the 17-amino acid peptide towards the N- terminus have been found to influence the mutant htt's capacity to aggregate. In immortalized striatal cell culture, it has been observed that proline rich domain is necessary to form visible aggregates of mutant htt (Steffan *et al.* 2004). In contrast, attaching a proline rich sequence flanking the C-terminus of the polyQ domain decreased the rate of aggregation *in vitro* (Bhattacharyya *et al.* 2006). Similarly, mutant htt lacking the first 17 amino acid residues at the N-terminus showed delayed aggregation in cells (Thakur *et al.* 2009). It has also been observed that although, the N17 residues help the cleaved mutant htt to localize in the nucleus but it is helpful in mitigating the disease pathology in HD transgenic mice (Gu *et al.* 2015) and a HD transgenic zebra fish (Veldman *et al.* 2015). Besides, the 17 N terminus amino acids are also secondarily modified such as dephosphorylated (Branco-Santos *et al.* 2017) and phosphorylation (DiGiovanni *et al.* 2016) which regulates its aggregation, localization and toxicity. Mutant htt has also been found to disrupt the nuclear pore complex (figure 1), which is important for nuclear-cytoplasm transport of proteins and other molecules (Grima *et al.* 2017; Gasset-Rosa *et al.* 2017). However, proteolysis of wild-type *HTT* has not been reported in normal individuals. The proteolysis of wild-type *HTT* may inactivate some of its normal function (El-Daher *et al.* 2015).

Posttranslational modifications of mutant htt

HTT is subjected to multiple posttranslational modifications which include phosphorylation, acetylation, palmitoylation, ubiquitinylation and sumoylation. Most of these modifications have been studied in mutant *HTT* which could have therapeutic implications as they modify the interactions and functions of the protein. HTT interacts with HIP 14 and HIP14L that belong to the family of palmitoyl-acyl transferases (Yanai *et al.* 2006). HTT is palmitoylated at C214 and its polyQ expansion leads to a reduction in the enzymatic activity of HIP 14 and of its auto palmitoylation (Huang *et al.* 2011) leading to the enzymatic activity of HIP 14 on other substrates and therefore, regulate intracellular trafficking and synaptic localization of other neuronal proteins.

Mutant htt and autophagy

Autophagy is an important cellular process which is responsible for the removal of damaged organelles and aggregated proteins by delivering them to lysosomes for degradation. Autophagy defects have been consistently observed in HD (Steffan 2010; Martin *et al.* 2015). High amount of autophagosome formation a reduced capacity to degrade aggregated proteins and organelles has been found in HD models (Martin *et al.* 2015). Studies also suggest that wild-type htt may play a significant role in autophagy. Reducing HTT expression decreased optineurin interaction in Golgi apparatus hints that HTT may also regulate dynamics of autophagosome through its interaction with optineurin (Toro *et al.* 2009). Autophagosomes in neurons under basal conditions are generated at distal axons and are retrogradely trafficked to the cell body. Silencing of htt blocks the retrograde transport of autophagosomes along the axon (Wong and Holzbaur 2014). Similar defects were observed with mutant htt, which led to inefficient clearance of mutant htt, suggesting that htt may regulate its own clearance.

In human HD and transgenic HD rodent samples, mutant htt has been found to activate autophagy by sequestering and inactivating mTOR leading to an induction of autophagy (Ravikumar *et al.* 2004). The mechanistic defects in autophagy in HD are exaggerated by mutant htt. Mutant htt results in defective autophagy mediated degradation and aggregate formation, which leads to compensatory upregulation of autophagy and accumulation of mutant htt and neurotoxicity. Further due to decreased cargo movement of autophagosome to fuse with lysosomes leading to defective autophagy (Wong and Holzbaur 2014). Moreover, expression levels of autophagy genes have been observed in HD striatum (Hodges *et al.* 2006). In the caudate nucleus of HD patients, mRNA expression of LC3A, ULK2, and LAMP2 is significantly increased whereas; PINK1, WDFY3 and FK506 binding protein 1A are significantly decreased. These findings suggest that the increased expression of LC3A and ULK2 correlate to early autophagy induction and autophagosome formation in HD (Martinez-Vicente *et al.* 2010). A decrease in PINK1 expression induces mitochondrial fragmentation and mitophagy (Kamat *et al.* 2014). HD is associated with increased mitochondrial fragmentation and inefficient corporation of mitochondria into autophagosomes (Wong and Holzbaur 2014). Autophagy defects in HD may be a combined effect of loss of function of wild-type htt and a toxic gain of function by mutant htt.

Vesicular transport and mutant htt

HTT has been found to be involved in a variety of vesicular trafficking in neurons including synaptic precursor vesicles (Zala *et al.* 2013), autophagosomes (Wong and Holzbaur 2014), lysosomes (Liot *et al.* 2013), BDNF-containing vesicles (Gauthier *et al.* 2004) and GABA-containing vesicles (Twelvetrees *et al.* 2010). It is not clear whether htt also promotes mitochondrial transport in neurons (Trushina *et al.* 2004) but it has been observed that the mutant

HTT has an association with the fusion–fission machinery of the organelle (Costa *et al.* 2010; Song *et al.* 2011; Pandey *et al.* 2010). HTT is also found to interact with several proteins involved in clathrin-mediated endocytosis (Legendre-Guillemin *et al.* 2002). HTT also activated GTPase Rab11 that participates in vesicle recycling during endocytosis (Li *et al.* 2008).

Evidences suggest that *HTT* is required for ciliogenesis (Haremaki *et al.* 2015). HTT is found at the base of the cilia in neurons, photoreceptor cilia, and cilia in multiciliated cells (Keryer *et al.* 2011). Absence of HTT from mouse cells impairs the retrograde trafficking of the pericentriolar material 1 protein and the primary cilium is not formed.

Transcriptional dysregulation and mutant htt

Post-mortem samples from HD brain and transgenic mouse models show transcriptional dysregulation (Valor 2015). Wild-type *htt* binds to several transcription factors including CREB-binding protein (Steffan *et al.* 2000), p53 tumour suppressor, nuclear factor-κB (Takano and Gusella 2002), PPAR-γ, vitamin D receptor, thyroid hormone receptor-α1 (Futter *et al.* 2009). With these interactions, HTT can potentiate transcription factors which can have various outcomes (figure 1). Transcriptional studies in rat PC12 cells expressing doxycycline induced mutant htt with increasing polyQ repeats were done in early stage, aggregate formed stage and late toxic stage and compared. Two major clusters of gene expression changes were observed in aggregate and later stage which were related to mitochondrial dysfunction and developmental processes related to cellular homeostasis (van Hagen *et al.* 2017). Transcriptome analysis of HD when compared to normal brains revealed wide spread aberrant alternative splicing in the diseased brains (Lin *et al.* 2016). RNA seq data from myeloid cells of HD patients revealed increases in proinflammatory cytokines in resting stage which indicates abnormal basal activation to an exaggerated immune response to a stimulus (Miller *et al.* 2016). In another RNA seq study from HD brain samples, it was found that there was upregulation of developmental homeobox genes and neuroinflammatory genes (Labadorf *et al.* 2015). Multiple studies related to transcriptional dysregulation in HD samples reveal changes in inflammatory responses regulated by NF-kB, metabolic homeostasis related to mitochondrial oxidative phosphorylation and developmental genes related to neuronal growth and cell cycle regulation.

Altered proteostasis and mutant htt

Mutant htt is prone to aggregate formation whose soluble and insoluble forms are neurotoxic to cells. Such misfolded forms of proteins are regulated by different proteostasis mechanisms such as chaperone-mediated folding or degraded by ubiquitin-mediated degradation or by lysosomal-autophagy degradation (figure 1). However, the increasing load of chaperons found in inclusion bodies such Hsp70 and ubiquitin related protein degradation machinery or accumulation of autophagosome related target proteins lead to altered proteostasis. The expanded polyQ fibrils can deregulate proteostasis nodes by sequestering transcription factors (Suhr *et al.* 2001) or physically obstruct neuronal extensions (Gunawardena *et al.* 2003). Moreover, ageing is also a risk factor for altered proteostasis (Hartl 2016). Chaperone functions are known to be compromised in HD (Kakkar *et al.* 2014).

The differential ability of neurons to handle stress of altered proteosis could also explain the vulnerability of striatal neurons in HD. Cerebellar neurons have been observed to induce Hsp70 expression upon mutant htt expression. However, striatal neurons cannot upregulate their chaperone expression to overcome this proteostasis stress (Tagawa *et al.* 2007). It is also possible that distinct nodes of proteostasis may have unique ways of handling proteostatic stress in HD. Manipulation of different proteostasic nodes genetically or pharmacologically could be another way to handle the toxicity of mutant htt (Koyuncu *et al.* 2017).

Therapeutic interventions in HD

The cardinal features of HD like (i) movement disorder characterized initially by chorea and later by dystonia and parkinsonism, (ii) progressive cognitive decline and disordered behaviour, and (iii) depression and agitation appear mostly during adulthood and progress relentlessly leading to functional disability. Parkinsonism is frequently observed in the rare juvenile form, slowing saccadic movements of the eye and possible cerebellar dysfunction helps in differential diagnosis. Neuropsychiatric symptoms are common and do not show increased progression with disease severity. The multifaceted phenotype of HD makes it difficult to manage the patients. Clinical trials of drugs are being conducted in every possible ways for HD therapy. Both uncontrolled and open labelled treatment reports as well as controlled trials have been carried out, where the intervention studied is compared to an active or inactive (placebo) comparator. Most of the drugs are symptomatic in nature where they are targeted to improve the clinical features of illness but do not block the progressive nature of the disease. Presently, there is no internationally recognized standard care for HD. Therefore, throughout the world the therapeutic approaches widely vary, according to the license of the respective country.

Symptomatic drugs

Most of the symptomatic drugs are directed against chorea, which is the most conspicuous feature of the disease. These drugs either deplete dopamine reserves or block the dopaminergic receptors in the brain, thereby providing temporary relief to the patient. Reserpine, tetrabenazine (a short-acting reserpine analogue), phenothiazines (such as chlorpromazines) and butyrophenones

(such as haloperidol) have been used extensively for symptomatic relief in HD (Marsden 1973). In a double-blind crossover trial involving four treatments of haloperidol, haloperidol and lithium carbonate, lithium carbonate and placebo carried out for three weeks, none of the treatments provided effective relief from choreiform movements. Psychological variables like levels of irritability, outbursts of anger and depression did appear to have some effect due to these drugs. While three HD patients showed some relief in haloperidol and lithium carbonate combination, the other three did not show any significant relief. Haloperidol itself increased the levels of depression when compared to other combinations including placebo (Leonard *et al.* 1975). In another study, 18 patients with Huntington's chorea were examined before and after treatment with three neuroleptic drugs, pimozide, haloperidol and tiapride. Pimozide and haloperidol gave relief from hyperkinesias but none of the drug improved motor performance significantly (Girotti *et al.* 1984). In an interesting study, HD patients having gait abnormalities and choreiform movements were treated with haloperidol. Although, there was a decrease in choreiform movement, yet it did not correct gait abnormalities (Koller and Trimble 1985). Long-term treatment of haloperidol is known to cause aggravated parkinsonism, tardive dyskinesis, difficulties in swallowing and dysphasia (Emerich *et al.* 1991). Tetrabenazine, an inhibitor of vesicular monoamine transporter 2 (VMAT2) leading to depletion of dopamine and other monoamines like serotonin and norepinephrine in the central nervous system has been used extensively in hyperkinetic disorders, especially HD. In an open labelled study described by Kenney *et al.* (2007), over 400 patients suffering from hyperkinetic movement disorders including 98 HD patients were treated with tetrabenazine at the Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic. There was a marked improvement in patients with choreiform movements.

The Huntington Study Group (2006) recently completed a phase III study assessing the safety, efficacy, and dose-tolerability of tetrabenazine for ameliorating chorea in patients with HD. A total of 84 patients were randomly assigned to placebo ($n = 30$) or tetrabenazine ($n = 54$) up to 100 mg/day for 12 weeks. Based on the chorea score of the UHDRS, tetrabenazine was found to significantly reduce chorea. GABAergic strategies have included muscimol, a potent GABA mimetic agonist (Shoulson *et al.* 1978). In this double-blind study, muscimol treatment did not lead to any improvement in motor and cognitive deficits in 10 HD patients. However, administration of muscimol ameliorated chorea in the most severely affected hyperkinetic patients. It also heightened dystonia, particularly in the early onset patients who had predominant parkinsonism and dystonic features. For the treatment of depression in HD patients, standard antidepressant medication, including selective serotonin reuptake inhibitors (SSRIs) have been used. Fluoxetine, an SSRI that is widely used as an antidepressant has been shown to be effective in HD transgenic mice (Grote *et al.* 2005) but when administered in randomized, double-blind, placebo-controlled trial of this medication in depressed and nondepressed HD patients, no differences between the treatment groups were found in total functional capacity, neurological, or cognitive ratings (Como *et al.* 1997). Pridopidine, a dopamine D2 receptor antagonist was tested in three large multicentre clinical trials of HD which has been published (Lundin *et al.* 2010; de Yebenes *et al.* 2011; Huntington Study Group HART Investigators 2013). The MermaiHD study and the HART study found that the higher dose of 90 mg/day showed improvement in motor scores and gait balance as compared to placebo but did not reach statistical significance. Presently, a large, global, multicentre, double blind phase II trial with higher dose of pridopidine——PRIDE-HD is currently under progress to assess the drug tolerability and managing motor symptoms (Reilmann 2013).

Neuroprotective drugs

Neuroprotective therapy is targeted at the level of genetic aetiology to slow down the progressive nature of the disease. Most of the drugs tested in this case have been targeted at the level of oxidative metabolism or glutamate transmission because of the metabolic decrease in activity or increased excitotoxic mechanisms in HD.

Coenzyme Q_{10}, a principle mitochondrial cofactor involved in complex-I activity has been studied as a neuroprotective agent in HD animal models (Matthews *et al.* 1998). In a multicentre, parallel group, double blind, randomized clinical trial on coenzyme Q_{10} along with ramacemide (NMDA antagonist) in early HD patients, conducted by Huntington Study Group (2001), neither remacemide nor coenzyme Q_{10}, produced significant slowing in functional decline in early HD even after 30 months. To add to these negative data, there was an increased frequency of nausea, vomiting and dizziness with remacemide; and increased frequency of stomach upset with coenzyme Q_{10}.

Another drug that has been extensively used in HD neuroprotective therapy is creatine. Creatine is a naturally occurring compound that, through its intermediate phosphocreatine, provides a necessary cellular reserve of high energy phosphates. There is a strong evidence to suggest that a bioenergetic defect exists in HD as discussed earlier. Creatine supplementation is intended to augment cerebral reserves of phosphates and thereby reduce neuronal metabolic and oxidative stress, and to slow down neurodegeneration. While there have been several clinical trials of creatine in HD, none have been powered to detect significant slowing of progression or improvement in clinical symptoms. Verbessem and colleagues treated 26 HD patients with 5 mg/kg creatine and 15 patients with placebo for one year and found no significant differences in measures of strength, neurological status, or cognitive function

(Verbessem *et al.* 2003). In an interesting study, Bender and colleagues used magnetic resonance spectroscopy to examine the levels of glutamate in HD patients treated with 20 g/day for 5 days, followed by 6 g/day for 8–10 weeks. They demonstrated a significant reduction in glutamate levels in the parietooccipital cortex. This is of great significance because glutamate release and excitotoxicity are enhanced by energy deficiency and are considered to play an important role in the pathogenesis of HD (Bender *et al.* 2005). However, none of the studies are informative enough to show that creatine is neuroprotective in HD.

A small scale study of foetal transplantation with a long term follow up in HD subjects was reported in 2014 (Paganini *et al.* 2014). Twenty-six HD patients (10 subjects transplanted with foetal striatal tissue) were followed for median 11.2 years in transplanted subjects. Transplanted subjects showed a slower decline in motor and cognitive measures (Barker *et al.* 2013). Another small study of five transplanted and 12 control subjects followed over 3–10 years showed no significant benefit on clinical or cognitive features. Pathological studies have shown poor graft survival as well as aggregation of mutant htt in the grafted tissue (Cicchetti *et al.* 2014; Cisbani and Cicchetti 2014). Cell replacement therapy is considered to have great potential in degenerative diseases. In this context, HD makes an effective disease condition for such therapy as it is marked by striatal neurodegeneration (Precious *et al.* 2017).

Conclusions and future study

It has been almost 25 years since the discovery of the mutant gene *htt* responsible for causing HD, but there is still no cure available for the disease. In spite of the intense efforts to discover and find a cure for the disease most of the drugs provide palliative relief. However, the research has led to a better understanding of the protein's functions in its wild type and mutant state. The multifaceted role of the normal protein and its further anomalies in its gain of functions in mutant state makes the drug targeting more challenging. The advantage of studying this monogenic Mendelian neurodegenerative disorder has been in identifying presymptomatic biomarkers, which also be used for tracking the progression of the disease. This helps the clinicians to find more sensitive quantifiable biomarkers apart from mere behavioural phenotypes of patients, which are used for drug screening and tracking the progression of the disease. Identification of peripheral markers or neurochemical agents such as BDNF, 8-OHdG and interleukins or other molecules that could also help in finding the efficacy and tracking down the neuroprotective role of drugs in clinics (Ross and Tabrizi 2011). Brain imaging is also a very reliable and quantifiable tool to measure striatal volume, cortical thickness and ventricular volume to assess the damage in brain tissue.

Although, the transgenic knock-in mice models have helped us to understand the disease better but most of them do not express the disease pathology similar to humans. This has led to an increase in numbers of different mice models which correlate to different pathological phenotypes as seen in humans. Identifying protein targets of mutant *htt* interactions which lead to disease pathology could be an important strategy. With the advent of CRISPR-Cas9 technology, gene silencing of mutant *htt* in preferred areas of neurodegenerative regions could be also considered. Better animal models which exhibit pathology closer to humans would be helpful in understanding the pathology of the disease and very helpful for preclinical screening of drugs. Induced pluripotent stem cells could also be used for primary drug screening. A combination therapy of antipsychotics along with neuronal survival agent could also an effective strategy of looking at delaying the disease progression.

References

Adachi Y. and Nakashima K. 1999 Population genetic study of Huntington's disease-prevalence and founder's effect in the San-in area, western Japan. *Nippon Rinsho.* **57**, 900–904.

Albin R. L., Reiner A., Anderson K. D., Penney J. B. and Young A. B. 1990 Striatal and nigral neuron subpopulations in rigid Huntington's disease: implications for the functional anatomy of chorea and rigidity-akinesia. *Ann. Neurol.* **27**, 357–365.

Albin R. L., Reiner A., Anderson K. D., Dure L. S. 4th, Handelin B., Balfour R. *et al.* 1992 Preferential loss of striato-external pallidal projection neurons in presymptomatic Huntington's disease. *Ann. Neurol.* **31**, 425–430.

Almqvist E. W., Elterman D. S., MacLeod P. M. and Hayden M. R. 2001 High incidence rate and absent family histories in one quarter of patients newly diagnosed with Huntington disease in British Columbia. *Clin. Genet.* **60**, 198–205.

Andrade M. A. and Bork P. 1995 HEAT repeats in the Huntington's disease protein. *Nat. Genet.* **11**, 115–116.

Andrich J., Saft C., Ostholt N. and Müller T. 2007 Complex movement behaviour and progression of Huntington's disease. *Neurosci. Lett.* **416**, 272–274.

Arrasate M., Mitra S., Schweitzer E. S., Segal M. R. and Finkbeiner S. 2004 Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. *Nature* **431**, 805–810.

Baquet Z. C., Gorski J. A. and Jones K. R. 2004 Early striatal dendrite deficits followed by neuron loss with advanced age in the absence of anterograde cortical brain-derived neurotrophic factor. *J. Neurosci.* **24**, 4250–4258.

Barker R. A., Mason S. L., Harrower T. P., Swain R. A., Ho A. K., Sahakian B. J. *et al.* 2013 The long-term safety and efficacy of bilateraltransplantation of human fetal striatal tissue in patients with mild to moderate Huntington's disease. *J. Neurol. Neurosurg. Psychiatry* **84**, 657–665.

Barnes G. T., Duyao M. P., Ambrose C. M., McNeil S., Persichetti F., Srinidhi J. *et al.* 1994 Mouse Huntington's disease gene homolog (Hdh). *Somat. Cell Mol. Genet.* **20**, 87–97.

Bates E. A., Victor M., Jones A. K., Shi Y. and Hart A. C. 2006 Differential contributions of *Caenorhabditis elegans* histone deacetylases to huntingtin polyglutamine toxicity. *J. Neurosci.* **26**, 2830–2838.

Baxa M., Hruska-Plochan M., Juhas S., Vodicka P., Pavlok A., Juhasova J. *et al.* 2013 A transgenic minipig model of Huntington's disease. *J. Huntingtons Dis.* **2**, 47–68.

Baxendale S., Abdulla S., Elgar G., Buck D., Berks M., Micklem G. *et al.* 1995 Comparative sequence analysis of the human and pufferfish Huntington's disease genes. *Nat. Genet.* **10**, 67–76.

Becher M. W., Kotzuk J. A., Sharp A. H., Davies S. W., Bates G. P., Price D. L. *et al.* 1998 Intranuclear neuronal inclusions in Huntington's disease and dentatorubral and pallidoluysian atrophy: correlation between the density of inclusions and IT15 CAG triplet repeat length. *Neurobiol. Dis*. **4**, 387–397.

Benchoua A., Trioulier Y., Diguet E., Malgorn C., Gaillard M. C., Dufour N. *et al.* 2008 Dopamine determines the vulnerability of striatal neurons to the N-terminal fragment of mutant huntingtin through the regulation of mitochondrial complex II. *Hum. Mol. Genet.* **17**, 1446–1456.

Bender A., Auer D. P., Merl T., Reilmann R., Saemann P., Yassouridis A. *et al.* 2005 Creatine supplementation lowers brain glutamate levels in Huntington's disease. *J. Neurol.* **252**, 36–41.

Bhattacharyya A., Thakur A. K., Chellgren V. M., Thiagarajan G., Williams A. D., Chellgren B. W. *et al.* 2006 Oligoproline effects on polyglutamine conformation and aggregation. *J. Mol. Biol.* **355**, 524–535.

Bird E. D. and Iversen L. L. 1974 Huntington's chorea. Postmortem measurement of glutamic acid decarboxylase, choline acetyltransferase and dopamine in basal ganglia. *Brain* **97**, 457–472.

Bird E. D. and Iversen L. L. 1977 Neurochemical findings in Huntington's chorea. *Essays Neurochem. Neuropharmacol.* **1**, 177–195.

Bohnen N. I., Koeppe R. A., Meyer P., Ficaro E., Wernette K., Kilbourn M. R. *et al.* 2000 Decreased striatal monoaminergic terminals in Huntington disease. *Neurology* **54**, 1753–1759.

Branco-Santos J., Herrera F., Poças G. M., Pires-Afonso Y., Giorgini F., Domingos P. M. *et al.* 2017 Protein phosphatase 1 regulates huntingtin exon 1 aggregation and toxicity. *Hum. Mol. Genet.* **26**, 3763–3775.

Brown R. G. and Marsden C. D. 1988 Subcortical dementia': the neuropsychological evidence. *Neuroscience* **25**, 363–387.

Chen Y. Y. and Lai C. H. 2010 Nationwide population-based epidemiologic study of Huntington's disease in Taiwan. *Neuroepidemiology* **35**, 250–254.

Chopra V., Fox J. H., Lieberman G., Dorsey K., Matson W., Waldmeier P. *et al.* 2007 A small-molecule therapeutic lead for Huntington's disease: preclinical pharmacology and efficacy of C2-8 in the R6/2 transgenic mouse. *Proc. Natl. Acad. Sci. USA* **104**, 16685–16689.

Ciarmiello A., Cannella M., Lastoria S., Simonelli M., Frati L., Rubinsztein D. C. *et al.* 2006 Brain white-matter volume loss and glucose hypometabolism precede the clinical symptoms of Huntington's disease. *J. Nucl. Med.* **47**, 215–222.

Cicchetti F., Prensa L., Wu Y. and Parent A. 2000 Chemical anatomy of striatal interneurons in normal individuals and in patients with Huntington's disease. *Brain Res. Brain Res. Rev.* **34**, 80–101.

Cicchetti F., Lacroix S., Cisbani G., Vallières N., Saint-Pierre M., St-Amour I. *et al.* 2014 Mutanthuntingtin is present in neuronal grafts in Huntington disease patients. *Ann. Neurol.* **76**, 31–42.

Cisbani G. and Cicchetti F. 2014 The fate of cell grafts for the treatment of Huntington's disease: the post-mortem evidence. *Neuropathol. Appl. Neurobiol.* **40**, 71–90.

Como P. G., Rubin A. J., O'Brien C. F., Lawler K., Hickey C., Rubin A. E. *et al.* 1997 A controlled trial of fluoxetine in nondepressed patients with Huntington's disease. *Mov. Disord*. **12**, 397–401.

Conneally P. M. 1984 Huntington disease: genetics and epidemiology. *Am. J. Hum. Genet.* **36**, 506–526.

Costa V., Giacomello M., Hudec R., Lopreiato R., Ermak G., Lim D. *et al.* 2010 Mitochondrial fission and cristae disruption increase the response of cell models of Huntington's disease to apoptotic stimuli. *EMBO Mol. Med.* **2**, 490–503.

Davies S. W., Turmaine M., Cozens B. A., DiFiglia M., Sharp A. H., Ross C. A. *et al.* 1997 Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. *Cell* **90**, 537–548.

de Yebenes J. G., Landwehrmeyer B., Squitieri F., Reilmann R., Rosser A., Barker R. A. *et al.* 2011 Pridopidine for the treatment of motor function in patients with Huntington'sdisease (MermaiHD): a phase 3, randomised, double-blind, placebo-controlledtrial. *Lancet Neurol.* **10**, 1049–1057.

del Toro D., Alberch J., Lázaro-Diéguez F., Martín-Ibáñez R., Xifró X., Egea G. *et al.* 2009 Mutant huntingtin impairs post-Golgi trafficking to lysosomes bydelocalizing optineurin/Rab8 complex from the Golgi apparatus. *Mol. Biol. Cell.* **20**, 1478–1492.

Di Maio L., Squitieri F., Napolitano G., Campanella G. and Trofatter J. A. 1993 Conneally suicide risk in Huntington's disease *J. Med. Genet.* **30**, 293–295.

DiFiglia M. 1990 Excitotoxic injury of the neostriatum: a model for Huntington's disease. *Trends Neurosci.* **13**, 286–289.

DiGiovanni L. F., Mocle A. J., Xia J. and Truant R. 2016 Huntingtin N17 domain is a reactiveoxygen species sensor regulating huntingtin phosphorylation and localization. *Hum. Mol. Genet.* **25**, 3937–3945.

Dom R., Malfroid M. and Baro F. 1976. Neuropathology of Huntington's chorea. Studies of the ventrobasal complex of the thalamus. *Neurology* **26**, 64–68.

El-Daher M. T., Hangen E., Bruyère J., Poizat G., Al-Ramahi I., Pardo R. *et al.* 2015 Huntingtin proteolysis releases non-polyQ fragments that cause toxicity through dynamin 1 dysregulation. *EMBO J.* **34**, 2255–2271.

Emerich D. F., Norman A. B. and Sanberg P. R. 1991 Nicotine potentiates the behavioral effects of haloperidol. *Psychopharmacol. Bull.* **27**, 385–390.

Enna S. J., Bird E. D., Bennett Jr J. P., Bylund D. B., Yamamura H. I., Iversen L. L. *et al.* 1976 Huntington's chorea. Changes in neurotransmitter receptors in the brain. *N. Engl. J. Med.* **294**, 1305–1309.

Evans S. J., Douglas I., Rawlins M. D., Wexler N. S., Tabrizi S. J. and Smeeth L. 2013 Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. *J. Neurol. Neurosurg. Psychiatry* **84**, 1156–1160.

Ferrante R. J., Kowall N. W., Beal M. F., Martin J. B., Bird E. D. and Richardson Jr E. P. 1987 Morphologic and histochemical characteristics of a spared subset of striatal neurons in Huntington's disease. *J. Neuropathol. Exp. Neurol*. **46**, 12–27.

Ferrer I., Goutan E., Marín C., Rey M. J. and Ribalta T. 2000 Brain-derived neurotrophic factor in Huntington disease. *Brain Res.* **866**, 257–261.

Finkbeiner S. 2011 *Huntington's disease*. Cold Spring Harbor Laboratory Press, Cold Spring Harbor.

Fisher E. R. and Hayden M. R. 2014 Multisource ascertainment of Huntington disease in Canada: prevalence and population at risk. *Mov. Disord.* **29**, 105–114.

Folstein S. E., Chase G. A., Wahl W. E., McDonnell A. M. and Folstein M. F. 1987 Huntington disease in Maryland: clinical aspects of racial variation. *Am. J. Hum. Genet.* **41**, 168–179.

Futter M., Diekmann H., Schoenmakers E., Sadiq O., Chatterjee K. and Rubinsztein D. C. 2009 Wild-type but not mutant huntingtin modulates the transcriptional activity of liver X receptors. *J. Med. Genet*. **46**, 438–446.

Gasset-Rosa F., Chillon-Marinas C., Goginashvili A., Atwal R. S., Artates J. W., Tabet R *et al.* 2017 Polyglutamine-expanded Huntingtin exacerbates age-related disruption of nuclear integrity and nucleocytoplasmic transport. *Neuron* **94**, 48–57.

Gauthier L. R., Charrin B. C., Borrell-Pagès M., Dompierre J. P., Rangone H., Cordelières F. P. *et al.* 2004 Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. *Cell* **118**, 127–138.

Gerfen C. R. 1992 The neostriatal mosaic: multiple levels of compartmental organization. *J. Neural. Transm. Suppl*. **36**, 43–59.

Girotti F., Carella F., Scigliano G., Grassi M. P., Soliveri P., Giovannini P. *et al.* 1984 Effect of neuroleptic treatment on involuntary movements and motor performances in Huntington's disease. *J. Neurol. Neurosurg. Psychiatry* **47**, 848–852.

Graham R. K., Slow E. J., Deng Y., Bissada N., Lu G., Pearson J. *et al.* 2005 Levels of mutant huntingtin influence the phenotypic severity of Huntington disease in YAC128 mouse models. *Neurobiol. Dis.* **21**, 444–455.

Graybiel A. M., Ohta K. and Roffler-Tarlov S. 1990 Patterns of cell and fiber vulnerability in the mesostriatal system of the mutant mouse weaver. I. Gradients and compartments. *J. Neurosci.* **10**, 720–733.

Grima J. C., Daigle J. G., Arbez N., Cunningham K. C., Zhang K., Ochaba J. *et al*. 2017 Mutant Huntingtin disrupts the nuclear pore complex. *Neuron* **94**, 93–107.

Grote H. E., Bull N. D., Howard M. L., van Dellen A., Blakemore C., Bartlett P. F. *et al.* 2005 Cognitive disorders and neurogenesis deficits in Huntington's disease mice are rescued by fluoxetine. *Eur. J. Neurosci.* **22**, 2081–2088.

Gu X., Cantle J. P., Greiner E. R., Lee C. Y., Barth A. M., Gao F. *et al.* 2015 N17 Modifies mutant Huntingtin nuclear pathogenesis and severity of disease in HD BAC transgenic mice. *Neuron* **85**, 726–741.

Gunawardena S., Her L. S., Brusch R. G., Laymon R. A., Niesman I. R., Gordesky-Gold B. *et al.* 2003 Disruption of axonal transport by loss of huntingtin or expression of pathogenic polyQ proteins in Drosophila. *Neuron* **40**, 25–40.

Gutekunst C. A., Li S. H., Yi H., Mulroy J. S., Kuemmerle S., Jones R. *et al.* 1999 Nuclear and neuropil aggregates in Huntington's disease: relationship to neuropathology. *J. Neurosci.* **19**, 2522–2534.

Haremaki T., Deglincerti A. and Brivanlou A. H. 2015 Huntingtin is required forciliogenesis and neurogenesis during early Xenopus development. *Dev. Biol.* **408**, 305–315.

Harper P. S. 2002 Huntington's disease: a historical background in Huntington's disease (ed. G. Bates, P. S. Harper and L. Jones), pp. 3–37. Oxford University Press, Oxford.

Harper P. S., Walker D. A., Tyler A., Newcombe R. G. and Davies K. 1979 Huntington's chorea. The basis for long-term prevention. *Lancet* **2**, 346–349.

Hartl F. U. 2016 Cellular homeostasis and aging. *Ann. Rev. Biochem*. **85**, 1–4.

Hedreen J. C. and Folstein S. E. 1995 Early loss of neostriatal striosome neurons in Huntington's disease. *J. Neuropathol. Exp. Neurol.* **54**, 1051–1020.

Hedreen J. C., Peyser C. E., Folstein S. E. and Ross C. A. 1991 Neuronal loss in layers V and VI of cerebral cortex in Huntington's disease. *Neurosci. Lett.* **133**, 257–261.

Heinsen H., Strik M., Bauer M., Luther K., Ulmar G., Gangnus D. *et al.* 1994 Cortical and striatal neurone number in Huntington's disease *Acta. Neuropathol*. **88**, 320–333.

Heinsen H., Rüb U., Gangnus D., Jungkunz G., Bauer M., Ulmar G. *et al.* 1996 Nerve cell loss in the thalamic centromedian-parafascicular complex in patients with Huntington's disease. *Acta. Neuropathol.* **91**, 161–168.

Hodges A., Strand A. D., Aragaki A. K., Kuhn A., Sengstag T., Hughes G. *et al.* 2006 Regional and cellular gene expression changes in human Huntington's disease brain. *Hum. Mol. Genet*. **15**, 965–977.

Hodgson J. G., Agopyan N., Gutekunst C. A., Leavitt B. R., LePiane F., Singaraja R. *et al.* 1999 A YAC mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration. *Neuron* **23**, 181–192.

Huang K., Sanders S. S., Kang R., Carroll J. B., Sutton L., Wan J. *et al.* 2011 Wild-type HTT modulates the enzymatic activity of the neuronal palmitoyl transferase HIP14. *Hum. Mol. Genet.* **20**, 3356–3365.

Huntington G. 1872 On chorea. *Med. Surg. Rep*. **26**, 317–321.

Huntington Study Group 2001 A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. *Neurology* **14**, 397–404.

Huntington Study Group 2006 Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. *Neurology* **66**, 366 –372.

Huntington Study Group HART Investigators 2013 A randomized, double-blind, placebo-controlled trial of pridopidine in Huntington's disease. *Mov. Disord.* **28**, 1407–1415.

Jacobsen J. C., Bawden C. S., Rudiger S. R., McLaughlan C. J., Reid S. J., Waldvogel H. J. *et al.* 2010 An ovine transgenic Huntington's disease model. *Hum. Mol. Genet.* **19**, 1873–1882.

Jeste D. V., Barban L. and Parisi J. 1984 Reduced Purkinje cell density in Huntington's disease. *Exp. Neurol.* **85**, 78–86.

Kakkar V., Meister-Broekema M., Minoia M., Carra S. and Kampinga H. H. 2014 Barcoding heat shock proteins to human diseases: looking beyond the heat shock response. *Dis. Model Mech.* **7**, 421–434.

Kamat P. K., Kalani A., Kyles P., Tyagi S. C. and Tyagi N. 2014 Autophagy of mitochondria: a promising therapeutic target for neurodegenerative disease. *Cell Biochem. Biophys*. **70**, 707–719.

Karlovich C. A., John R. M., Ramirez L., Stainier D. Y. and Myers R. M. 1998 Characterization of the Huntington's disease (HD) gene homologue in the zebrafish *Danio rerio*. *Gene* **217**, 117–121.

Kenney C., Hunter C. and Jankovic J. 2007 Long-term tolerability of tetrabenazine in the treatment of hyperkinetic movement disorders. *Mov. Disord*. **15**, 193–197.

Keryer G., Pineda J. R., Liot G., Kim J., Dietrich P., Benstaali C. *et al.* 2011 Ciliogenesis is regulated by a huntingtin-HAP1-PCM1 pathway and is altered in Huntington disease. *J. Clin. Invest.* **121**, 4372–4382.

Kim Y. E., Hosp F., Frottin F., Ge H., Mann M., Hayer-Hartl M. *et al.* 2016 Soluble oligomers of PolyQ-expanded Huntingtin target a multiplicity of key cellular factors. *Mol. Cell* **63**, 951–964.

Kingma E. M., van Duijn E., Timman R., van der Mast R. C. and Roos R. A. 2008 Behavioural problems in Huntington's disease using the problem behaviours assessment. *Gen. Hosp. Psychiatry.* **30**, 155–161.

Kirkwood S. C., Siemers E., Viken R., Hodes M. E., Conneally P. M., Christian J. C. *et al.* 2002 Longitudinal personality changes among presymptomatic Huntington disease gene carriers. *Neuropsychiatry Neuropsychol. Behav. Neurol*. **15**, 192–197.

Kish S. J., Shannak K. and Hornykiewicz O. 1987 Elevated serotonin and reduced dopamine in subregionally divided Huntington's disease striatum. *Ann. Neurol.* **22**, 386–389.

Kokmen E., Ozekmekci F. S., Beard C. M., O'Brien P. C. and Kurland L. T. 1994 Incidence and prevalence of Huntington's disease in Olmsted County, Minnesota (1950 through 1989). *Arch. Neurol.* **51**, 696–698.

Koller W. C. and Trimble J. 1985 Gait abnormality of Huntington's disease. *Neurology* **35**, 1450–1454.

Koyuncu S., Fatima A., Gutierrez-Garcia R. and Vilchez D. 2017 Proteostasis of huntingtin in health and disease. *Int. J. Mol. Sci*. **19**, 18.

Krench M. and Littleton J. T. 2013 Modeling Huntington disease in Drosophila: Insights into axonal transport defects and modifiers of toxicity. *Fly (Austin)* **7**, 229–236.

Krobitsch S. and Lindquist S. 2000 Aggregation of huntingtin in yeast varies with the length of the polyglutamine expansion and the expression of chaperone proteins. *Proc. Natl. Acad. Sci. USA* **97**, 1589–1594.

Labadorf A., Hoss A. G., Lagomarsino V, Latourelle J. C., Hadzi T. C., Bregu J. 2015 RNA Sequence analysis of human Huntington disease brain reveals an extensive increase in inflammatory and developmental gene expression. *PLoS One* **10**, e0143563.

Legendre-Guillemin V., Metzler M., Charbonneau M., Gan L., Chopra V., Philie J. *et al.* 2002 HIP1 and HIP12 display differential binding to F-actin, AP2, and clathrin. Identification of a novel interaction with clathrin lightchain. *J. Biol. Chem.* **277**, 19897–19904.

Leonard D. P., Kidson M. A., Brown J. G., Shannon P. J. and Taryan S. 1975 A double blind trial of Lithium carbonate and haloperidol in Huntington's chorea. *Aust. N Z J*. **9**, 115–118.

Li X., Sapp E., Valencia A., Kegel K. B., Qin Z. H., Alexander J. *et al.* 2008 A function of huntingtin in guanine nucleotide exchange on Rab11. *Neuroreport* **19**, 1643–1647.

Lin B., Rommens J. M., Graham R. K., Kalchman M., MacDonald H., Nasir J. *et al.* 1993 Differential 3' polyadenylation of the Huntington disease gene results in two mRNA species with variable tissue expression. *Hum. Mol. Genet*. **2**, 1541–1545.

Lin L., Park J. W., Ramachandran S., Zhang Y., Tseng Y. T., Shen S. *et al.* 2016 Transcriptome sequencing reveals aberrant alternative splicing in Huntington's disease. *Hum. Mol. Genet*. **25**, 3454–3466.

Liot G., Zala D., Pla P., Mottet G., Piel M. and Saudou F. 2013 Mutant Huntingtin alters retrograde transport of TrkB receptors in striatal dendrites. *J. Neurosci.* **33**, 6298–6309.

Lloyd K. G., Dreksler S. and Bird E. D. 1977 Alterations in 3H-GABA binding in Huntington's chorea. *Life Sci.* **21**, 747–753.

Lundin A., Dietrichs E., Haghighi S., Göller M. L., Heiberg A., Loutfi G. *et al.* 2010 Efficacy and safety of the dopaminergic stabilizer Pridopidine (ACR16) inpatients with Huntington's disease. *Clin. Neuropharmacol.* **33**, 260–264.

Macdonald V., Halliday G. M., Trent R. J. and McCusker E. A. 1997 Significant loss of pyramidal neurons in the angular gyrus of patients with Huntington's disease. *Neuropathol. Appl. Neurobiol.* **23**, 492–495.

Mangiarini L., Sathasivam K., Seller M., Cozens B., Harper A., Hetherington C. *et al.* 1996 Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice *Cell* **87**, 493–506.

Marques Sousa C. and Humbert S. 2013 Huntingtin: here, there, everywhere! *J. Huntingtons Dis*. **2**, 395–403.

Marsden C. D. 1973 Drug treatment of diseases characterized by abnormal movements. *Proc. R. Soc. Med*. **66**, 871–873.

Martin D. D., Ladha S., Ehrnhoefer D. E. and Hayden M. R. 2015 Autophagy in Huntington disease and huntingtin in autophagy. *Trends Neurosci.* **38**, 26–35.

Martinez-Vicente M, Talloczy Z, Wong E, Tang G, Koga H, Kaushik S. *et al.* 2010 Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease. *Nat. Neurosci.* **13**, 567–576.

Matthews R. T., Yang L., Browne S., Baik M. and Beal M. F. 1998 Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. *Proc. Natl. Acad. Sci. USA* **95**, 8892–8897.

McCaughey W. T. E. 1961 The pathologic spectrum of Huntington's Chorea. *J. Nerv. Ment. Dis.* **133**, 91–103.

McCusker E. A., Casse R. F., Graham S. J., Williams D. B. and Lazarus R. 2000 Prevalence of Huntington disease in New South Wales in 1996. *Med. J. Aust*. **173**, 187–190.

Miller J., Arrasate M., Shaby B. A., Mitra S., Masliah E. and Finkbeiner S. 2010 Quantitative relationships between huntingtin levels, polyglutamine length, inclusion body formation, and neuronal death provide novel insight into Huntington's disease molecular pathogenesis. *J. Neurosci.* **30**, 10541–10550.

Miller J. R., Lo K. K., Andre R., Hensman Moss D. J., Träger U., Stone T. C. *et al.* 2016 RNA-Seq of Huntington's disease patient myeloid cells reveals innate transcriptional dysregulation associated with proinflammatory pathway activation. *Hum. Mol. Genet*. **25**, 2893–2904.

Morrison P. J., Johnston W. P. and Nevin N. C. 1995 The epidemiology of Huntington's disease in Northern Ireland. *J. Med. Genet.* **32**, 524–530.

Myers R. H., Vonsattel J. P., Stevens T. J., Cupples L. A., Richardson E. P., Martin J. B. *et al.* 1988 Clinical and neuropathologic assessment of severity in Huntington's disease. *Neurology* **38**, 341–347.

Narain Y., Wyttenbach A., Rankin J., Furlong R. A. and Rubinsztein D. C. 1999 A molecular investigation of true dominance in Huntington's disease. *J. Med. Genet.* **36**, 739–746.

Neuwald A. F. and Hirano T. 2000 HEAT repeats associated with condensins, cohesins, and other complexes involved in chromosome-related functions. *Genome Res*. **10**, 1445–1452.

Nguyen K. Q., Rymar V. V. and Sadikot A. F. 2016 Impaired TrkB Signaling Underlies reduced BDNF-mediated trophic support of striatal neurons in the R6/2 mouse model of Huntington's disease. *Front Cell Neurosci.* **9**, 37.

Nørremølle A., Riess O., Epplen J. T., Fenger K., Hasholt L. and Sørensen S. A. 1993 Trinucleotide repeat elongation in the Huntingtin gene in Huntington disease patients from 71 Danish families. *Hum. Mol. Genet*. **2**, 1475–1476.

Novak M. J. and Tabrizi S. J. 2010 Huntington's disease. *BMJ* **30**, 340.

Okun M. S. and Thommi N. 2004 Americo Negrette (1924 to 2003): diagnosing Huntington disease in Venezuela. *Neurology* **63**, 340–343.

Paganini M., Biggeri A., Romoli A. M., Mechi C., Ghelli E., Berti V. *et al.* 2014 Fetal striatal grafting slows motor and cognitive decline of Huntington's disease. *J. Neurol. Neurosurg. Psychiatry* **85**, 974–981.

Palo J., Somer H., Ikonen E., Karila L. and Peltonen L. 1987 Low prevalence of Huntington's disease in Finland. *Lancet* **2**, 805–806.

Pandey M., Mohanakumar K. P. and Usha R. 2010 Mitochondrial functional alterations in relation to pathophysiology of Huntington's disease. *J. Bioenerg. Biomembr.* **42**, 217–226.

Paul B. D., Sbodio J. I., Xu R., Vandiver M. S., Cha J. Y., Snowman A. M. *et al.* 2014 Cystathionine γ-lyase deficiency mediates neurodegeneration in Huntington's disease. *Nature* **509**, 96–100.

Pavese N., Andrews T. C., Brooks D. J., Ho A. K., Rosser A. E., Barker R. A. *et al.* 2003 Progressive striatal and cortical dopamine receptor dysfunction in Huntington's disease: a PET study. *Brain* **126**, 1127–1135.

Perry T. L., Hansen S. and Kloster M. 1973 Huntington's chorea. Deficiency of gamma-aminobutyric acid in brain. *N. Engl. J. Med*. **288**, 337–342.

Peterlin B., Kobal J., Teran N., Flisar D. and Lovrečić L. 2009 Epidemiology of Huntington's disease in Slovenia. *Acta. Neurol. Scand.* **119**, 371–375.

Pleydell M. J. 1955 Huntington's chorea in Northamptonshire. *Br. Med. J.* **2**, 889.

Precious S. V., Zietlow R, Dunnett S. B., Kelly C. M. and Rosser A. E. 2017 Is there a place for human fetal–derived stem cells

for cell replacement therapy in Huntington's disease? *Neurochem. Int.* **106**, 114–121.
Pridmore S. A. 1990 The prevalence of Huntington's disease in Tasmania. *Med. J. Aust.* **153**, 133–134.
Ramdzan Y. M., Trubetskov M. M., Ormsby A. R., Newcombe E. A., Sui X., Tobin M. J. *et al.* 2017 Huntingtin inclusions trigger cellular quiescence, deactivate apoptosis, and lead to delayed necrosis. *Cell Rep.* **19**, 919–927.
Ravikumar B., Vacher C., Berger Z., Davies J. E., Luo S., Oroz L. G. *et al.* 2004 Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nat. Genet*. **36**, 585–595.
Reddy P. H., Williams M., Charles V., Garrett L., Pike-Buchanan L., Whetsell W. O. Jr *et al.* 1998 Behavioural abnormalities and selective neuronal loss in HD transgenic mice expressing mutated full–length HD cDNA. *Nat. Genet.* **20**, 198–202.
Reed T. E. and Chandler J. H. 1958 Huntington's chorea in Michigan. I. Demography and genetics. *Am. J. Hum. Genet.* **10**, 201–225.
Reilmann R. 2013 The pridopidine paradox in Huntington's disease. *Mov. Disord.* **28**, 1321–1324.
Reiner A., Albin R. L., Anderson K. D., D'Amato C. J., Penney J. B. and Young A. B. 1988 Differential loss of striatal projection neurons in Huntington disease. *Proc. Natl. Acad. Sci. USA* **85**, 5733–5737.
Reynolds G. P. and Garrett N. J. 1986 Striatal dopamine and homovanillic acid in Huntington's disease. *J. Neural. Transm.* **65**, 151–155.
Reynolds G. P. and Pearson S. J. 1987 Decreased glutamic acid and increased 5-hydroxytryptamine in Huntington's disease brain. *Neurosci. Lett*. **78**, 233–238.
Ribaï P., Nguyen K., Hahn-Barma V., Gourfinkel-An I., Vidailhet M., Legout A. *et al.* 2007 Psychiatric and cognitive difficulties as indicators of juvenile Huntington disease onset in 29 patients. *Arch. Neurol.* **64**, 813–819.
Rodda R. A. 1981 Cerebellar atrophy in Huntington's disease. *J. Neurol. Sci.* **50**, 147–157.
Rosas H. D., Salat D. H., Lee S. Y., Zaleta A. K., Pappu V., Fischl B. *et al.* 2008 Cerebral cortex and the clinical expression of Huntington's disease: complexity and heterogeneity. *Brain* **131**, 1057–1068.
Ross C. A. and Tabrizi S. J. 2011 Huntington's disease: from molecular pathogenesis to clinical treatment. *Lancet Neurol.* **10**, 83–98.
Rubinsztein D. C., Leggo J., Coles R., Almqvist E., Biancalana V., Cassiman J. J. *et al.* 1996 Phenotypic characterization of individuals with 30–40 CAG repeats in the Huntington disease (HD) gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36–39 repeats. *Am. J. Hum. Genet.* **59**, 16–22.
Sapp E., Kegel K. B., Aronin N., Hashikawa T., Uchiyama Y., Tohyama K. *et al.* 2001 Early and progressive accumulation of reactive microglia in the Huntington disease brain. *J. Neuropathol. Exp. Neurol*. **60**, 161–172.
Saudou F. and Humbert S. 2016 The biology of Huntingtin. *Neuron* **89**, 910–926.
Schmitt I., Bächner D., Megow D., Henklein P., Hameister H., Epplen J. T. *et al.* 1995 Expression of the Huntington disease gene in rodents: cloning the rat homologue and evidence for downregulation in non-neuronal tissues during development. *Hum. Mol. Genet.* **4**, 1173–1182.
Schoenfeld M., Myers R. H., Cupples L. A., Berkman B., Sax D. S. and Clark E. 1984 Increased rate of suicide among patients with Huntington's disease. *J. Neurol. Neurosurg. Psychiatry* **47**, 1283–1287.
Seto-Ohshima A., Emson P. C., Lawson E., Mountjoy C. Q. and Carrasco L. H. 1988 Loss of matrix calcium-binding protein-containing neurons in Huntington's disease. *Lancet* **1**, 1252–1255.
Shiwach R. S. and Lindenbaum R. H. 1990 Prevalence of Huntington's disease among UK immigrants from the Indian subcontinent. *Br. J. Psychiatry* **157**, 598–599.
Shokeir M. H. 1975 Investigations on Huntington's disease in the Canadian Prairies. I. Prevalence. *Clin. Genet*. **7**, 345–348.
Shoulson I., Goldblatt D., Charlton M. and Joynt R. J. 1978 Huntington's disease: treatment with muscimol, a GABA-mimetic drug. *Ann. Neurol.* **4**, 279–284.
Simpson S. A. and Johnston A. W. 1989 The prevalence and patterns of care of Huntington's chorea in Grampian. *Br. J. Psychiatry* **155**, 799–804.
Slow E. J., Graham R. K., Osmand A. P., Devon R. S., Lu G., Deng Y. *et al.* 2005 Absence of behavioral abnormalities and neurodegeneration *in vivo* despite widespread neuronal huntingtin inclusions. *Proc. Natl. Acad. Sci. USA* **102**, 11402–11407.
Smith R., Chung H., Rundquist S., Maat-Schieman M. L., Colgan L., Englund E. *et al.* 2006 Cholinergic neuronal defect without cell loss in Huntington's disease. *Hum. Mol. Genet.* **15**, 3119–3131.
Song W., Chen J., Petrilli A., Liot G., Klinglmayr E., Zhou Y. *et al.* 2011 Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity. *Nat. Med.* **17**, 377–382.
Spargo E., Everall I. P. and Lantos P. L. 1993 Neuronal loss in the hippocampus in Huntington's disease: a comparison with HIV infection. *J. Neurol. Neurosurg. Psychiatry*. **56**, 487–491.
Spires T. L. and Hannan A. J. 2007 Molecular mechanisms mediating pathological plasticity in Huntington's disease and Alzheimer's disease. *J. Neurochem.* **100**, 874–882.
Spokes E. G. 1980 Neurochemical alterations in Huntington's chorea: a study of post–mortem brain tissue. *Brain* **103**, 179–210.
Steffan J. S., Kazantsev A., Spasic-Boskovic O., Greenwald M., Zhu Y. Z., Gohler H. *et al*. 2000 The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription. *Proc. Natl. Acad. Sci. USA* **97**, 6763–6768.
Steffan J. S., Agrawal N., Pallos J., Rockabrand E., Trotman L. C., Slepko N. *et al.* 2004 SUMO modification of Huntingtin and Huntington's disease pathology. *Science* **304**, 100–104.
Steffan J. S. 2010 Does Huntingtin play a role in selective macroautophagy? *Cell Cycle* **9**, 3401–341.
Suhr S. T., Senut M. C., Whitelegge J. P., Faull K. F., Cuizon D. B. and Gage F. H. 2001 Identities of sequestered proteins in aggregates from cells with induced polyglutamine expression. *J. Cell Biol.* **153**, 283–294.
Tabrizi S. J., Scahill R. I., Owen G., Durr A., Leavitt B. R., Roos R. A. *et al.* 2013 Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol.* **12**, 637–649.
Tagawa K., Marubuchi S., Qi M. L., Enokido Y., Tamura T., Inagaki R. *et al*. 2007 The induction levels of heat shock protein 70 differentiate the vulnerabilities to mutant huntingtin among neuronal subtypes. *J. Neurosci*. **27**, 868–880.
Takano H. and Gusella J. F. 2002 The predominantly HEAT-like motif structure of huntingtin and its association and coincident nuclear entry with dorsal, an NF-kB/Rel/dorsal family transcription factor. *BMC Neurosci.* **3**, 15.
Thakur A. K., Jayaraman M., Mishra R., Thakur M., Chellgren V. M., Byeon I. J. *et al.* 2009 Polyglutamine disruption of the

huntingtin exon 1 N terminus triggers a complex aggregation mechanism. *Nat. Struct. Mol. Biol*. **16**, 380–389.

The Huntington's Disease Collaborative Research Group 1993 A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* **72**, 971–983.

Trushina E., Dyer R. B., Badger J. D. 2nd, Ure D., Eide L., Tran D. D. *et al.* 2004 Mutant huntingtin impairs axonal trafficking in mammalian neurons in vivo and in vitro. *Mol. Cell Biol.* **24**, 8195–8209.

Turjanski N., Weeks R., Dolan R., Harding A. E. and Brooks D. J. 1995 Striatal D_1 and D_2 receptor binding in patients with Huntington's disease and other choreas. A PET study. *Brain* **118**, 689–696.

Twelvetrees A. E., Yuen E. Y., Arancibia-Carcamo I. L., MacAskill A. F., Rostaing P., Lumb M. J. *et al.* 2010 Delivery of GABAARs to synapses is mediated by HAP1-KIF5 and disrupted by mutant huntingtin. *Neuron* **65**, 53–65.

Valor L. M. 2015 Transcription, epigenetics and ameliorative strategies in Huntington's Disease: a genome–wide perspective. *Mol. Neurobiol.* **51**, 406–423.

van Hagen M., Piebes D. G. E., de Leeuw W. C., Vuist I. M., van Roon-Mom W. M. C., Moerland P. D. *et al.* 2017 The dynamics of early-state transcriptional changes and aggregate formation in a Huntington's disease cell model. *BMC Genomics* **18**, 373.

Veldman M. B., Rios-Galdamez Y., Lu X. H., Gu X., Qin W., Li S. *et al.* 2015 The N17 domain mitigates nuclear toxicity in a novel zebrafish Huntington's disease model. *Mol. Neurodegener.* **10**, 67.

Verbessem P., Lemiere J., Eijnde B. O., Swinnen S., Vanhees L., Van Leemputte M. *et al.* 2003 Creatine supplementation in Huntington's disease: a placebo-controlled pilot trial. *Neurology* **61**, 925–930.

Verny C., Allain P., Prudean A., Malinge M. C., Gohier B., Scherer C. *et al.* 2007 Cognitive changes in asymptomatic carriers of the Huntington disease mutation gene. *Eur. J. Neurol*. **14**, 1344–1350.

Videnovic A., Leurgans S., Fan W., Jaglin J. and Shannon K. M. 2009 Daytime somnolence and nocturnal sleep disturbances in Huntington disease. *Parkinsonism Relat. Disord*. **15**, 471–474

Vonsattel J. P. and DiFiglia M. 1998 Huntington disease. *J. Neuropathol. Exp. Neurol.* **57**, 369–384.

Vonsattel J. P., Myers R. H., Stevens T. J., Ferrante R. J., Bird E. D. and Richardson E. P. Jr. 1985 Neuropathological classification of Huntington's disease. *J. Neuropathol. Exp. Neurol.* **44**, 559–577.

Walker F. O. 2007 Huntington's disease. *Lancet* **369**, 218–228.

Wexler N. S., Lorimer J., Porter J., Gomez F., Moskowitz C., Shackell E. *et al.* 2004 Venezuelan kind reds reveal that genetic and environmental factors modulate Huntington's disease age of onset. *Proc. Natl. Acad. Sci. USA* **101**, 3498–3503.

Wolf R. C., Vasic N., Schönfeldt-Lecuona C., Ecker D. and Landwehrmeyer G. B. 2009 Cortical dysfunction in patients with Huntington's disease during working memory performance. *Hum. Brain Mapp.* **30**, 327–329.

Wong Y. C. and Holzbaur E. L. 2014 The regulation of autophagosome dynamics by huntingtin and HAP1 is disrupted by expression of mutant huntingtin, leading to defective cargo degradation. *J. Neurosci.* **34**, 1293–1305.

Wright H. H., Still C. N. and Abramson R. K. 1981 Huntington's disease in black kindreds in South Carolina. *Arch. Neurol.* **38**, 412–414.

Xi W., Wang X., Laue T. M. and Denis C. L. 2016 Multiple discrete soluble aggregates influence polyglutamine toxicity in a Huntington's disease model system. *Sci. Rep*. **6**, 34916.

Yanai A., Huang K., Kang R., Singaraja R. R., Arstikaitis P., Gan L. *et al.* 2006 Palmitoylation of huntingtin by HIP14 is essential for its trafficking and function. *Nat. Neurosci.* **9**, 824–831.

Yang S. H., Cheng P. H., Banta H., Piotrowska-Nitsche K., Yang J. J., Cheng E. C. *et al.* 2008 Towards a transgenic model of Huntington's disease in a non-human primate. *Nature* **453**, 921–924.

Zakzanis K. K. 1998 The subcortical dementia of Huntington's disease. *J. Clin. Exp. Neuropsychol*. **20**, 565–578.

Zala D., Hinckelmann M. V. and Saudou F. 2013 Huntingtin's function in axonal transport is conserved in *Drosophila melanogaster*. *PLoS One* **8**, 3.

Zeitlin S., Liu J. P., Chapman D. L., Papaioannou V. E. and Efstratiadis A. 1995 Increased apoptosis and early embryonic lethality in mice nullizygous for the Huntington's disease gene homologue. *Nat. Genet.* **11**, 155–163.

Zuchner T. and Brundin P. 2008 Mutant huntingtin can paradoxically protect neurons from death. *Cell Death Differ.* **15**, 435–442.

Zühlke C., Riess O., Bockel B., Lange H. and Thies U. 1993 Mitotic stability and meiotic variability of the (CAG)n repeat in the Huntington disease gene. *Hum. Mol. Genet*. **2**, 2063–2067.