An update on Huntington's disease: from the gene to the clinic

Samuel D. Kim[a,b] and Victor S.C. Fung[a,b]

Purpose of review
This review highlights the recent advances in Huntington's disease, with a particular focus on development of disease biomarkers for use in therapeutic trials in the premotor phase of the disease, as well as the growing literature regarding pathophysiological mechanisms and their relevance to potential therapeutic targets.

Recent findings
There have been continued advances in the development of disease biomarkers, and promising neuroprotection trials are beginning to emerge in the premotor stage of Huntington's disease. Deeper understanding of the pathophysiological mechanisms is being translated into potential therapeutic strategies.

Summary
The premotor stage of Huntington's disease provides an ideal time to trial disease-modifying therapy, but reliable biomarkers are required for monitoring disease progression, and this remains an area of intense research. Our understanding of the underlying pathophysiological mechanisms continues to expand, and a number of promising therapeutic strategies are emerging, including strategies to silence mutant huntingtin expression.

Keywords
biomarker, Huntington's disease, neurodegeneration, premanifest Huntington's disease, prodromal Huntington's disease

INTRODUCTION

Huntington's disease is an autosomal dominant disorder characterized by the key features of progressive movement disorder, cognitive impairment and neuropsychiatric disturbance and is caused by a CAG repeat expansion in exon 1 of the huntingtin (HTT) gene [1]. Of all the neurodegenerative disorders, it possibly holds the most promise in search of a disease-modifying therapy because of the fact that Huntington's disease is caused by a single gene mutation as opposed to other neurodegenerative disorders in which the precise cause and pathogenetic mechanisms are less well understood. However, to date, proven neuroprotective strategies remain elusive although there has been a rapid progress in the understanding of the pathogenetic mechanisms and development of novel therapeutic strategies. Part of the problem has been that most of the trials to date have attempted intervening at a time when the degenerative process is already far advanced and hence when it would be difficult even for the most effective therapy to demonstrate any benefit. In view of this, research efforts are being directed at the premotor stage of Huntington's disease when it should be more amenable to treatment, and development of biomarkers has become of paramount importance in order to provide a reliable measure of disease progression for use in neuroprotection trials.

PRODROMAL HUNTINGTON'S DISEASE OR PREMOTOR HUNTINGTON'S DISEASE

Subtle but measurable abnormalities in motor, cognitive and behavioural function are present before a

[a]Movement Disorders Unit, Department of Neurology, Westmead Hospital and [b]Sydney Medical School-Western, University of Sydney, Sydney, Australia

Correspondence to Associate Professor Victor S.C. Fung, PhD, FRACP, Movement Disorders Unit, Department of Neurology, Westmead Hospital and Sydney Medical School, Westmead, Sydney, NSW 2145, Australia. Tel: +61 2 9845 6793; fax: +61 2 9635 6684; e-mail: vscfung@ozemail.com.au

clinical diagnosis of Huntington's disease. A number of terms have been used to describe this phase in which Huntington's disease gene carriers do not yet exhibit significant motor signs to meet the diagnostic criteria for Huntington's disease , and terms such as premanifest, prediagnostic, presymptomatic, preclinical and prodromal phase have been used [2], but the authors suggest that this creates some ambiguity and we propose using the term premotor phase instead on the basis of the fact that a diagnosis of Huntington's disease depends on the presence of unequivocal motor signs of Huntington's disease in an individual with a positive genetic test or family history of Huntington's disease [2,3].

BIOMARKERS

It is necessary to identify biomarkers that will reliably detect subtle changes of disease progression in order to be able to accurately assess the effectiveness of disease-modifying therapies. Several biomarkers, including cognitive and behavioural, clinical, neuro-imaging and neurophysiological measures, have been investigated in the premotor phase. Two excellent recent review papers discuss the current state of play in biomarker development and future directions and readers are encouraged to refer to these [4▪▪,5▪].

Cognitive and behavioural

It has been shown that cognitive changes can be detected even 15 years before the diagnosis of Huntington's disease with the degree of cognitive impairment being greater in those individuals estimated to be closer to diagnosis [6]. A recent study examining the cognitive domains that predict time to diagnosis in Huntington's disease demonstrated that composite indices may be more sensitive to the worsening of cognitive functioning than single variables, and only motor planning or speed and sensory-perceptual processing predicted time to diagnosis [7]. Another study from the same group demonstrated that the strongest global effect was found for the Symbol Digit Modalities Test, a measure of visual scanning, working memory, fine motor speed and concentration, in line with previous reports and suggests that this might be a suitable outcome measure in neuroprotective agent trials [8▪]. The next challenge is to determine the relationship between cognitive trajectories and neuropathological changes measured by neuroimaging.

Motor

Mean reaction time has been shown to be prolonged in premotor Huntington's disease although ballistic movements did not significantly differ when compared with controls, suggesting difficulty in modifying a sustained motor programme [9]. An analysis of the neurobiologic predictors of Huntington's disease PREDICT-HD dataset has shown that the total motor score of Unified Huntington's Disease Rating Scale can detect statistically and substantively significant change in the premotor period [10].

Imaging

Degenerative changes in the basal ganglia involving the caudate nucleus and putamen are already observable well before (15–20 years) the appearance of motor manifestations of Huntington's disease [8▪,11].

TRACK-HD, a prospective observational biomarker study, demonstrated decline in overall and regional brain volumes over 24 months in both the premotor and early Huntington's disease patients, but there was only limited decline in cognitive, quantitative motor or oculomotor measures in the premotor group [12] although in a subset of the premotor patients who were classed as progressors, brain imaging changes exhibited a substantial association with clinical disease progression [12]. The extension of this study to 36 months demonstrated significantly increased rates of decline in the premotor group [13▪▪]. A voxel-based morphometry study on a subset of patients from TRACK-HD has demonstrated an association between striatal loss and impairment in quantitative motor and oculomotor measures in patients with premotor and early Huntington's disease [14].

A study has demonstrated that prefrontal cortex white matter diffusivity is significantly different between the premotor and normal control groups, with a gradient in the magnitude of the difference based on baseline disease progression. Additionally, there was significant correlation between mean fractional anisotropy and radial diffusivity and Trail Making Test B, which has a documented ability to detect cognitive deficits in premotor Huntington's disease patients, suggesting that mean radial diffusivity in regions of the right lateral prefrontal cortex could serve as a reliable biomarker to monitor disease progression in the premotor Huntington's disease stage in future longitudinal studies [15].

Recently, functional brain network has been shown to correlate with progression of premotor Huntington's disease using computational analysis of fluorodeoxyglucose PET, with changes beginning approximately 20 years before phenoconversion [5∎,16∎]. Additionally, blood flow abnormalities have been detected in premotor Huntington's disease by measuring arteriolar cerebral blood volume with ultra-high field (7T) MRI [5∎,17]. However, unlike structural imaging measures such as striatal atrophy which have been shown to be a robust biomarker that progress over the entire course of the disease, the aforementioned techniques have not yet been validated longitudinally [4∎∎].

Neurophysiology: transcranial magnetic stimulation

Huntington's disease results in significant motor impairments, and thus neurophysiological assessment of the central nervous system could potentially provide insights into the disease pathophysiology and development of useful biomarkers but to date studies with transcranial magnetic stimulation, including paired-pulse stimulation, which provide information about the corticomotorneuronal function, have produced mixed results partly because of differences in techniques used and small numbers of patients [18]. There have not yet been any large-scale longitudinal studies mapping the trajectory of cortical function.

CLINICAL FEATURES

Prevalence of Huntington's disease is highest amongst the whites and reportedly affects approximately five to seven per 100 000 individuals, but the rates are much lower in Asian and African populations [19–21]. The mean age of onset is approximately 40 years, but approximately 25% of patients are diagnosed after the age of 50 with some even being diagnosed in late life, with the range extending from infancy to the ninth decade [22,23]. CAG repeat length accounts for approximately 70% of the variability in age of onset [24], suggesting that there are other genetic and environmental modifying factors [25]. It is likely that the proportion of patients with late onset will become more common because of an increasingly ageing population in the western world. There is considerable heterogeneity amongst patients in terms of relative prominence of individual symptoms, but in general, age of onset broadly determines phenotypes such that late onset patients manifest with predominantly motor features and juvenile onset patients whilst also presenting with motor features, typically display dystonia and parkinsonism [19,26–28].

In a study of premotor participants who were followed as part of the neurobiologic predictors of Huntington's disease study, almost 50% of the patients were unaware of their motor signs despite the fact that they had developed unequivocal motor signs fulfilling the criteria for definite motor Huntington's disease [29∎].

There have been no other significant developments in the area of clinical features since the last review on this topic in *Current Opinion in Neurology* by Ha and Fung (2012) [30], and the readers are encouraged to refer to that review.

PATHOGENESIS

Huntington's disease pathophysiology is complex and likely arises predominantly from gain of toxic function from an abnormal conformation of mutant HTT [31,32], but there appears to be some contribution from loss of function of endogenous HTT protein [33]. Mutant HTT has been implicated in the disruption of multiple cellular processes, including protein clearance, protein–protein interaction, mitochondrial function, axonal trafficking, N-methyl-D-aspartate (NMDA) receptor activation, gene transcription and post-translational modification and more recently peripheral immune dysregulation.

Brain-derived neurotrophic factor

Wild-type HTT promotes the gene transcription of brain-derived neurotrophic factor (BDNF), a neurotrophin which has prosurvival effects and is involved in cortical–striatal synaptic transmission, synaptic plasticity and synaptic growth [34]. In Huntington's disease, BDNF gene transcription and axonal transport of proteins have been shown to result in selective neurodegeneration and neuronal dysfunction [35], and indeed overexpression of BDNF has been shown

to improve motor function, attenuate brain atrophy and/or extend survival in Huntington's disease mice [36,37]. BDNF acts via two receptors, the tropomyosin-related kinase B (TrkB) tyrosine receptor and p75 neurotrophin receptor, and a study has demonstrated that pharmacological activation of TrkB improves motor function, attenuates brain atrophy and extends survival in a Huntington's disease mouse model, providing proof of concept for the therapeutic potential of small-molecule TrkB agonists [37].

Transcriptional dysregulation

Transcriptional dysregulation occurs early in Huntington's disease, well before the onset of symptoms [38]. Histone deacetylase 4 (HDAC4) represses transcription of genes and plays a role in neuronal cell death. In Huntington's disease mouse models, it associates with mutant HTT *in vivo* in a polyglutamine-length-dependent manner and colocalizes with cytoplasmic inclusions in the brains and HDAC4 depletion has been shown to inhibit cytoplasmic aggregate formation and restore synaptic function. Furthermore, knockdown of HDAC4 partially restores motor coordination and other neurological phenotypes and extends lifespan [39■].

A recent study has reported a major depletion of cystathionine γ-lyase, the biosynthetic enzyme for cysteine, in Huntington's disease tissues, which reverses with supplementation with cysteine in intact mouse models of Huntington's disease. It has been demonstrated that the defect occurs at the transcriptional level and is likely caused by influences of mutant HTT on a transcriptional activator for cystathionine γ-lyase, specificity protein 1 [40].

Mitochondrial

There are several lines of evidence implicating mitochondrial dysfunction in Huntington's disease, including the following: first, impaired peroxisome proliferator-activated receptor gamma coactivator 1-alpha-mediated gene expression through its interaction with mutant HTT resulting in aberrant mitochondrial biogenesis [41]; second, altered gene expression levels of mitochondrial structural genes leading to mitochondrial fragmentation and abnormal mitochondrial dynamics [42]; third, interaction of mitochondrial protein dynamin-related protein-1 with the mutant HTT resulting in defective anterograde transport of mitochondria and selective synaptic degeneration [43], with restoration of mitochondrial fission and mitochondria transport and improved phenotype in mice by reducing dynamin-related protein-1 activity [43] and fourth,

impaired mitochondrial trafficking leading to disruption of mitochondrial maintenance and delivery of mitochondria to sites where there is high energy demand such as synapses [44].

Excitotoxicity

Glutamatergic excitotoxicity through aberrant NMDA receptor activity is postulated to play a role in striatal neuronal death [45]. Supportive evidence comes from studies in which animals injected with NMDA receptor agonists develop histological and behavioural changes reminiscent of Huntington's disease [46].

Accumulation and clearance of mutant huntingtin

Mutant HTT is pathogenic and its accumulation contributes to cell toxicity and reduced viability in Huntington's disease. Two major protein degradation pathways, namely ubiquitin–proteasome system and autophagy–lysosome pathway, are impaired because of toxic effect of the mutant HTT and abnormal interaction between the mutant HTT and autophagic vesicles, respectively [46]. It has been shown that symptoms of Huntington's disease can be ameliorated by blockade of mutant HTT expression [47]. Ubiquilin proteins involved in facilitation of protein disposal through the proteasome and lysosomal degradation pathways are diminished in Huntington's disease, and it has been demonstrated that ubiquilin-1 overexpression dramatically increases lifespan and delays formation of HTT inclusions, although it does not improve motor deficits [48■].

A recent study has demonstrated that aberrant splicing of exon 1 HTT mRNA results in short polyadenylated mRNA that is translated into an exon 1 HTT protein, which has been consistently shown to be pathogenic in Huntington's disease mouse models. This has an implication for current RNA-targeted therapeutic strategies as many of these approaches designed to lower the level of HTT do not lower the exon 1 HTT [49].

Post-translational modification

Several post-translational modifications occur in Huntington's disease, many of which are enzyme mediated, providing an attractive potential therapeutic option [38,50]. Mutant HTT has been shown to impair ubiquitination, leading to proteosomal dysfunction and accumulation of mutant HTT [38]. Phosphorylation of HTT has been shown to facilitate degradation and clearance of the protein,

and this process may be disrupted by mutant HTT, leading to reduced clearance [51]. Further research has shown that ganglioside GM1 induces phosphorylation of mutant HTT and restores normal motor behaviour in Huntington's disease mice [52]. Loss of Huntingtin-interacting protein 14 and Huntingtin-interacting protein 14-like, major palmitoyl acyltransferases for HTT, has been shown to result in neuropathological and motor features of Huntington's disease in mice [53,54,55■].

Peripheral immune system dysfunction

HTT is expressed in immune cells and both central and peripheral immune system abnormalities have been shown in patients with Huntington's disease [56]. There is correlation between elevated levels of plasma cytokine and chemokine and disease progression [57], and a number of recent studies have demonstrated the influence of peripheral immune system on Huntington's disease neuropathology. Specifically, in mouse models of Huntington's disease, transplantation of wild-type bone marrow partially reduces elevated plasma cytokine levels, increases synaptogenesis and rescues their motor deficits [58], whereas administration of a kynurenine 3-mono-oxygenase inhibitor decreases microglial activation, prevents synaptic loss and extends lifespan [59]. Huntington's disease peripheral blood mononuclear cells are the likely source of excessive inflammatory cytokines as a direct effect of mutant HTT on the nuclear factor kappa-light-chain-enhancer of activated B cells pathway, and lowering of HTT expression has been shown to improve the nuclear factor kappa-light-chain-enhancer of activated B cells pathway dysregulation with reversal of cytokine production and transcriptional changes [60■].

SYMPTOMATIC TREATMENT OR MANAGEMENT

There have been no significant developments in symptomatic treatment of Huntington's disease since the last review in this journal [30].

Disease-modifying therapy

High-dose coenzyme Q10 up to 2400 mg per day is currently being trialled in 600 participants with early Huntington's disease and is expected to be completed by 2017 [61]. This will confirm or refute the trend to improvement in functional decline that was observed with coenzyme Q10 600 mg per day [62]. Creatine Safety, Tolerability and Efficacy in Huntington's Disease, a multicentre, randomized, double-blind, placebo-controlled study of up to 40 g per day of creatine in 650 early-stage Huntington's disease patients, is currently recruiting patients and is estimated to be completed in 2016 [63].

PRECREST (Creatine Safety and Tolerability in Premanifest HD) trial, a phase II trial of creatine in at-risk Huntington's disease, demonstrated the feasibility of clinical trials in the premotor phase when the participants are unaffected by Huntington's disease [64■■]. Notably, this study introduced methods to recruit both premotor (genetically tested) and at-risk (untested) individuals while managing to preserve patient confidentiality, thus overcoming the difficulty in studying Huntington's disease at its earliest phase by avoiding the requirement to include only the tested given that only approximately 20% of eligible at-risk individuals choose to undergo testing [65].

Research in disease-modifying therapy is being directed at strategies against pathogenetic mechanisms as discussed in the section on pathogenesis, but an attractive option is blocking the mutant HTT given that Huntington's disease is a single gene disorder.

Strategies to silencing mutant huntingtin expression include use of antisense oligonucleotides (ASOs) and RNA interference (duplex RNAs) that target HTT mRNA [38,66]. Other emerging strategies aim to block the protein product using small synthetic peptides or antibodies that recognize mutant huntingtin. It has been demonstrated in Huntington's disease mouse models that inhibition of HTT expression by ASO and RNA interference alleviates symptoms and prolong survival [67–69], with transient infusion into the cerebrospinal fluid of symptomatic Huntington's disease mouse model resulting in a sustained reversal of phenotype that persists longer than the HTT knockdown [70]. Furthermore, promising results have been shown with ASOs infused directly into the lateral ventricles of mouse models of Huntington's disease. However, these approaches have not been examined in any clinical trials to date and considerable research is still required to resolve issues such as off-target effects, lack of effective delivery systems, overcoming immunologic defences and unknown effects of knocking down mutant and wild-type HTT alleles in the same cell [5■,71].

Recently, phosphodiesterase 10A (PDE10A), an enzyme that is highly enriched in striatal medium spiny neurons, has been proposed as a therapeutic target based on the observation that PDE10A inhibition significantly improved behavioural and neuropathologic abnormalities in transgenic mice [72]. However, there have been conflicting reports of PDE10A levels in

Huntington's disease striatum, including a PET study in Huntington's disease patients using a novel PET ligand (^{18}F-JNJ42259152) which reported that PDE10A level is already depleted in striatum, suggesting that pharmacological inhibition of PDE10A activity will not be clinically beneficial although it is still possible that the PDE10A depletion is a compensatory response rather than a direct pathogenic effect of mutant HTT [73■].

CONCLUSION

There have been many failed neuroprotective therapy trials in Huntington's disease, and still there is no proven disease-modifying therapy and a paucity of effective symptomatic therapies in Huntington's disease despite the fact that it has been over 20 years since the discovery of the Huntington's disease gene. However, Huntington's disease research continues to make progress in furthering our understanding of pathogenesis, which should translate into development of novel neuroprotective strategies. In addition, the ushering in of the era of drug trials in premotor Huntington's disease gives us ample hope that the Holy Grail of disease-modifying therapy is drawing near.

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Conflicts of interest

There are no conflicts of interest.

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