

# 14 Huntington's Disease

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## **Introduction**

Huntington's disease (HD) is an inherited neurodegenerative disorder of the basal ganglia. It has a prevalence of around 5-10 per 100,000 worldwide (2.5–10 in the UK), although there are suggestions that epidemiological studies to date may have substantially underestimated the numbers and that the prevalence is likely to be at least double that of previous estimates.<sup>1</sup> It generally starts in mid-life and progresses relentlessly to dependence and death over a period of 15-30 years. However, the range of ages at onset is broad, with cases described from infancy to old age. It comprises progressive motor, cognitive, and psychiatric symptoms and, by the middle stages of the disease, all three modalities will be present to varying degrees. However, subtle cognitive and behavioural symptoms may be present for many years before disease onset is recognised clinically, and a longitudinal study of people with pre-symptomatic HD demonstrated the presence of structural MRI changes in the striatum at least 20 years before predicted onset.<sup>2</sup> Additionally, it is now recognised that HD is associated with some neurological symptoms outwith the striatum as well as some symptoms that may be non-neurological in origin.

## **Genetics**

HD is caused by a single gene mutation, which was identified in 1993 as being a CAG repeat expansion in exon 1 of a gene now known as *huntingtin* on chromosome 4.<sup>3</sup> The normal version of the Huntington gene is expressed widely in both neural and non-neural tissues. The gene product is known as huntingtin (from the association of the mutated form with HD), but its function in normal cells is still incompletely understood. The normal gene contains a repeat of the nucleotides CAG, encoding a polyglutamine ('polyQ') stretch at the N terminus end of the associated protein, which is typically 6-20 repeats in length. By contrast, repeat lengths of more than 39 are associated with HD, and the majority of these patients have repeat lengths in the range of 40-50,<sup>3</sup> although much longer repeat length can occur and are often associated with juvenile-onset HD. HD is an autosomal dominant condition and appears to have 100% penetrance for repeat numbers above 39. Alleles between 36 and 39 have a more variable penetrance and studies are ongoing to determine the precise consequence of this repeat range on disease onset.

There is an inverse relationship between repeat length and disease onset on a population basis, with longer repeat lengths being associated with earlier-onset disease. Patients with early onset-disease tend to have more rigidity and dystonia and less in the way of chorea. This is particularly true of juvenile (the Westphal variant) of HD. However, there is no clear and absolute separation of early and adult onset disease clinically. Moreover, the relationship between repeat length and age of onset is not precise enough to allow prediction of onset on an individual basis.<sup>4</sup> Indeed, although the presence of the expanded CAG repeat sequence in the Huntingtin gene is the absolute determinant as to whether an individual develops HD, calculations predict that it only accounts for around 50% of the influence over the age at which the condition develops. The other 50% is likely to be influenced by other genes and perhaps also by environmental factors. A genome-wide association (GWA) analysis to identify loci harbouring genetic variations that alter the age at neurological onset of HD was undertaken and identified two independent loci on chromosome 15 that accelerate or delay onset by 6.1 years and 1.4 years, respectively, and a chromosome 8 locus that hastens onset by 1.6 years<sup>5</sup>. These findings are being explored further, in particular, for a role in DNA handling and repair mechanisms, which may relate to the CAG instability discussed below<sup>6</sup>.

Another feature of CAG repeat mutations is their instability. This has been confirmed in HD in two contexts. First, there is evidence that transmission of the gene through the paternal line leads to germ line instability, such that the repeat length tends to be greater when it is passed down the paternal line.<sup>8</sup> This leads to the phenomenon of anticipation and is reflected in the fact that the majority of juvenile

HD is passed through the paternal line. Secondly, somatic CAG instability has been reported and appears to be particularly pronounced in the striatum, the brain region most affected in HD, such that post-mitotic striatal neurons acquire substantially longer repeat lengths over time<sup>9,10</sup> This is intriguing, as it offers a potential explanation for the relative anatomical specificity seen in HD, although the precise role of this phenomenon in the pathogenesis has yet to be established. Post-mitotic CAG expansion also links to the finding of variation in DNA repair genes described above, as mismatch and base-excision repair have been shown to be important in the somatic expansion of repeated sequences in mouse models of HD and other trinucleotide repeat disorders<sup>7</sup>.

### **Practicalities of predictive and diagnostic gene testing**

In the UK predictive testing, i.e. genetic testing of asymptomatic individuals is generally undertaken over the age of eighteen and through the Medical Genetics services. A similar practice is followed in many European countries. Experience has demonstrated the need for at-risk individuals to be adequately prepared for the result and to properly explore whether they really want to know their gene status through counselling sessions administered by trained physicians and/or genetic counsellors. There are also issues of confidentiality and information distribution to family members that needs to be considered. Guidelines have been drawn up by the UK predictive consortium.<sup>11</sup> Diagnostic testing is performed in the context of a patient with symptoms and signs that would be compatible with a diagnosis of HD, and which would require further investigation even if the HD gene test were to be negative. The test must be performed with the appropriate written consent and can be undertaken on a person under 18 in special circumstances, with permission of their parents or guardian. It is important to be aware that the specific CAG length has limited value for predicting age of onset, as discussed above.

### ***Pathology***

At the macroscopic level, post-mortem studies reveal that the lateral ventricles become enlarged as the striatum degenerates, and this can be frequently detected in MR imaging during life.<sup>12</sup> The two main nuclei of the neostriatum (the caudate and the putamen) show progressive shrinkage and atrophy as the disease progresses, although of the two the caudate nucleus is affected earlier and to a greater extent than the putamen. The progression of shrinkage has been categorised into a series of stages, graded from 0 to 4.<sup>13</sup> This system is very widely used for descriptive neuropathological staging of the disease. At the microscopic level the predominant cell loss is of the 'medium spiny' population of neurones, which constitute the major class of projection neuron in the striatum, and which use the inhibitory amino acid GABA as their primary neurotransmitter. By contrast, the interneurons of the striatum are strikingly less affected by the disease. Although the striatum undoubtedly bears the burden of the pathology, other areas of brain, including selected areas of cortex, may be involved even before overt symptoms occur<sup>14,15</sup>. In the advanced stages widespread cortical atrophy is common-place.<sup>16</sup>

The exact cellular processes by which the mutant huntingtin protein, with its expanded polyglutamine tail, produces disease are not yet fully understood. It seems that the mutation confers a toxic gain of function, rather than producing substantial disruption of the functions of the normal protein. Some (but by no means all) of these toxic effects have been identified in the years following identification of the gene. However, it is clear that there is a pressing need for a clearer, more detailed understanding of the cellular and molecular pathogenesis, as well as a clearer understanding of the functions of the normal protein in order to design specific interventions to interfere with the disease process and slow disease progression.<sup>17-21</sup> A characteristic microscopic feature of HD are the intracellular inclusions, which have been observed in both HD transgenic animals and in post-mortem human brains.<sup>22,23</sup> However, even the relationship between these inclusions and disease state (whether the inclusions are part of the process of cell dysfunction and death, simply an associated epiphenomenon, or even neuroprotective), is as yet unclear.<sup>24</sup>

### ***Clinical Features***

There has been much work over the last 15 years to better characterise the neurological and neuropsychiatric features of the disease. The most obvious and well-known motor feature of the disease is the choreiform movement. These are involuntary "purposeless" movements affecting the

limbs, trunk, head, face, and bucco-oro-lingual regions. They may be the first noticeable feature of the condition, at which stage it may be difficult to differentiate them from fidgeting. However, chorea may be subtle or absent altogether. Indeed, absence of choreiform movements is common in Juvenile HD, but they may also be absent or minimal in adult-onset disease.

Although choreiform movements can be one of the more striking features of HD, unless they are marked they often cause less disability than one would imagine. In the early stages patients themselves may be unaware of the movements even when relatives are acutely aware of them,<sup>25</sup> and successful reduction of chorea by medication is often disappointing in terms of restoring function. The reason for this is almost certainly that other co-existing motor abnormalities are responsible for as much, if not more, disability.<sup>26</sup> These include rigidity, bradykinesia, postural instability, apraxia, and dystonia. Bradykinesia and rigidity frequently co-exist with the chorea and in the absence of chorea they can lead to confusion and an erroneous diagnosis of Parkinson's disease. Dystonia may occur at any stage of the disease but is particularly prominent in more advanced patients in whom generalised dystonia may be a major management issue.

Balance is frequently affected early in HD, although patients usually remain ambulatory until the moderate to later stages. Movement of the eyes is often abnormal early on and progresses so that voluntary pursuit and saccadic eye movements may be virtually absent in advanced disease. Speech is often indistinct, even in the early to moderate stages, and may be associated with involuntary vocalisations (including fragments of speech, grunts, clicks and even shouts). It deteriorates progressively, becoming more effortful and difficult to understand, until the late stages during which most patients have very limited spontaneous vocalisation, are often unintelligible, and may be mute. Although the speech disturbance in HD has been thought of as representative of dysarthria, there is increasing evidence that language is also affected in HD.<sup>27-29</sup> There is usually an accompanying dysphagia, manifest early on by choking and coughing on food and liquids, but progressing to marked difficulty swallowing, vomiting, and risk of aspiration, possibly leading to a requirement for PEG feeding.

The cognitive deficits in HD are characterised by a dysexecutive syndrome, impaired attention and reduced psychomotor speed.<sup>30,31</sup> Although the motor symptoms may be the most apparent to the observer, the psychiatric and cognitive aspects of the disease often contribute more to the misery and family stress associated with HD.

The common psychiatric manifestations of HD include depression and anxiety, irritability, rage attacks, apathy, disinhibition perseveration and obsessive compulsive symptoms.<sup>32</sup> The apathy, irritability and perseveration appear to be "core" features that are present early on, or possibly in the prodromal phase, and tend to worsen as the condition progresses. Drug and alcohol addition are also common and add to the management problems. The psychiatric manifestations are unpredictable in their appearance, and it can be difficult to know (even in retrospect) whether a bout of depression is 'reactive' or related specifically to the neurodegenerative process. The psychiatric and cognitive aspects of this condition contribute to the association of HD with socioeconomic decline and family break-up.

A number of other troublesome symptoms frequently complicate the course of HD,<sup>33</sup> many of which may have their origin in hypothalamic, endocrine and metabolic abnormalities. As yet these symptoms have been relatively under-explored and are incompletely understood. Weight loss is a prominent (although not universal) symptom, especially in advanced disease.<sup>31</sup> The cause remains unclear, although it may be multifactorial, including metabolic disturbance, anorexia, dysphagia, and the presence of involuntary movements.<sup>34,35</sup> There is also a recognised association of sleep disturbance, which may be due to disruption of circadian circuits.<sup>36</sup> Interestingly, there is recent evidence that imposing a sleep-wake cycle in transgenic HD mice can improve their cognitive function.<sup>37,38</sup>

The onset and duration of the pre-symptomatic phase is notoriously difficult to estimate clinically and there is evidence that subtle cognitive decline may precede the clear onset of motor symptoms by a number of years.<sup>39</sup> There is great interest in identifying biomarkers for onset and disease progression, both for clinical management and for increasing the accuracy and power of clinical trials

in early and pre-symptomatic individuals. Two large multicentre studies set out to discover biomarkers of disease onset: PREDICT-HD,<sup>40</sup> coordinated from the University of Iowa, USA, and the TRACK-HD study, supported by the European Huntington's disease Network and coordinated from the National Institute for Neurology, UCL.<sup>41,42</sup>

## ***Management***

The following is not intended to be exhaustive, but to act as a brief guide to the more common management needs. There are currently no disease-modifying treatments available for HD, although there is a coordinated international effort to identify such treatments (see below). However, until such therapies are available, treatment is centred around symptom management and support<sup>43</sup>. It is important that family members/friends are involved in the management plans for a number of reasons: First, the loss of insight, poor motivation, intellectual decline, and behavioural disturbance associated with HD can make it difficult to obtain an accurate picture of the patient's disease status and social circumstances; secondly, the same factors can impede the patient's ability to co-operate with the management plan; and finally, HD has a massive impact on family life and so both the patient and the carers need information and support. This is important if quality of life is to be maximised. In the UK, HD is increasingly managed in specialist (often multidisciplinary) clinics, although there are not yet sufficient clinics to provide full geographical coverage. Some information about the location of HD clinics can be found on the EHDN website ([www.euro-hd.net](http://www.euro-hd.net)). Help and advice can be obtained from the Huntington's Disease Association (HDA), which also provides regional HD advisors in many areas ([www.hda.org.uk](http://www.hda.org.uk)).

An important starting point for the management of HD is to recognise that, although chorea is often the most striking aspect of the disease, it may be the symptom least in need of treatment. Mild chorea may be much more troubling to relatives than to the patient who is often not fully aware of the presence of chorea, and reduction of chorea may have no impact on the patient's function<sup>22</sup>. More severe chorea may have a functional impact and may also be tiring and uncomfortable for patients. The best-known antichoreic medication is tetrabenazine, a VMAT-inhibitor that promotes the early metabolic degradation of dopamine. The principle drawbacks for its use in HD are depression (15%) and parkinsonism. 12.5mg tds is often sufficient to reduce the level of chorea without inducing undue drowsiness or parkinsonism. Some of the newer anti-psychotic medications, such as olanzapine and quetiapine, have gained prominence as the first line choices amongst HD experts in the UK, as anecdotally they appear to be as effective as tetrabenazine but possibly associated with fewer adverse effects. However, it is important to emphasise that to date there is very little in the way of an evidence base for any of these symptomatic therapies for HD. Unfortunately, many of the more disabling motor complications, such as dystonia, bradykinesia, and dysarthria, are much less amenable to treatment in HD. Pharmacological approaches to dystonia rarely appear to produce any sustained benefit, and although L-dopa may produce transient improvement in some patients with marked parkinsonian symptoms, the effect tends not to be sustained.

Some of the psychiatric symptoms such as depression and anxiety appear to be responsive, at least in part, to a range of medications used in conventional psychiatric practice, although other symptoms, such as the irritability, have proven to be more difficult to treat. There is anecdotal evidence that a number of drugs may reduce irritability levels. Citalopram or sertraline are currently favoured in the UK for this purpose, although again there is little in the way of an evidence base. Sadly, there is no treatment strategy for the cognitive impairment as yet<sup>43,44</sup>.

Non-pharmacological approaches are important, for example speech therapy input to assess and advise on the swallowing deficit, dietetic advice on nutrition, OT assessment of the home for mobility and care aids, and support from social services. There is increasing recognition of the potential of physiotherapy and exercise<sup>45</sup> and international guidelines for physiotherapy strategies specifically for HD are available (<http://www.ehdn.org/clinical-guidelines/>).

## ***Future Treatments***

The international effort to understand more about HD has been fuelled both by a desire to find a treatment for this unpleasant destructive condition that frequently affects young people, and by

recognition that HD provides a good model of neurodegeneration that is amenable to study and may inform on how to treat neurodegeneration more generally. There has been a great deal of progress over the past 10 years, partly due to coordinated activity such as the European HD network ([www.euro-hd.net](http://www.euro-hd.net)) and its sister organisation the Huntington's Study Group (HSG) in the USA ([www.huntington-study-group.org](http://www.huntington-study-group.org)). The emphasis has been on systematic longitudinal collection of clinical, biological and genetic data in large cohorts of patients, ranging from gene positive asymptomatic to severely affected individuals. These collections were generated by the Registry-HD project<sup>46</sup>, and more recently Enroll-HD (<https://www.enroll-hd.org/>). The purpose is to gain a thorough understanding of the condition, which is a pre-requisite to the development of targeted new therapies, and to facilitate well-conducted clinical trials. An example of where such large collective efforts have started to bear fruit is the genome-wide association analysis discussed under "gene mutation" above. This study drew on DNA samples and high quality matched clinical data, that would not have been available in the

The growth in understanding of the various molecular, cellular, and system pathways underlying the deficits in HD is at last leading to rational strategies that may eventually lead to more satisfactory symptomatic treatments and to disease-modifying therapies (reviewed in<sup>47</sup>). Several approaches that are already on a translational pathway include potential disease modifying agents such as HDAC inhibitors; and non-pharmacological therapies such as delivery of growth factors, deep brain stimulation<sup>48</sup>, motor and cognitive training therapies and cell replacement therapies (neural transplantation)<sup>49</sup>. Huntingtin lowering strategies, in particular, are currently generating interest and optimism. They are based on evidence that lowering huntingtin protein (both mutant and wild-type together) in mouse models of HD can improve neurological deficits, presumably by reducing the dose of toxic mutant huntingtin protein that cells are exposed to. This can be achieved through various methods, including some that are aiming to selectively lower the mutant protein, leaving the wild-type protein at normal levels. The first to take the initial steps to clinical translation is an antisense oligonucleotide (ASO) developed by Ionis pharmaceuticals<sup>50</sup>. The ASO does not cross the blood-brain-barrier and was therefore delivered intrathecally in a small safety and feasibility trial in centres in the UK, Germany and Canada. A top line preliminary result was reported in December 2017, stating that the ASO produced dose-dependent lowering of CSF huntingtin, (<http://ir.ionispharma.com/news-releases/news-release-details/ionis-pharmaceuticals-licenses-ionis-htt-rx-partner-following>; <https://en.hdbuzz.net/249>). It is unlikely that this small study will have sufficient power to demonstrate clinical efficacy, but it does provide the impetus for a follow-on study, currently under consideration by Roche who have bought the licence for this therapeutic.

A more "bottom up" approach to the development of novel therapies is the systematic screening of known drugs for potential activity in HD, using a cascade of biological screening tools moving from test-tube, to culture models, to animal studies. The development of induced pluripotent stem (IPS) cell technology may have a significant impact on this sort of approach by greatly increasing the availability of cell culture systems carrying the human huntingtin mutation. The ability to direct such cells to a medium spiny phenotype will be important for such drug discovery work and will be critical for reparative strategies such as neural transplantation.<sup>51</sup>

## ***Summary***

HD is a devastating neurodegenerative condition for which there is currently no disease-modifying treatment. A number of potential treatment strategies are being explored, but understanding the molecular and cellular events underlying the neurodegeneration in HD will be crucial for the development of truly rationale treatments for the future. It is envisaged that advances made in the treatment of HD will also lend insight into and provide benefits for other currently untreatable neurodegenerative diseases.

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