Huntington disease

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Abstract | Huntington disease is devastating to patients and their families — with autosomal dominant inheritance, onset typically in the prime of adult life, progressive course, and a combination of motor, cognitive and behavioural features. The disease is caused by an expanded CAG trinucleotide repeat (of variable length) in *HTT*, the gene that encodes the protein huntingtin. In mutation carriers, huntingtin is produced with abnormally long polyglutamine sequences that confer toxic gains of function and predispose the protein to fragmentation, resulting in neuronal dysfunction and death. In this Primer, we review the epidemiology of Huntington disease, noting that prevalence is higher than previously thought, geographically variable and increasing. We describe the relationship between CAG repeat length and clinical phenotype, as well as the concept of genetic modifiers of the disease. We discuss normal huntingtin protein function, evidence for differential toxicity of mutant huntingtin variants, theories of huntingtin aggregation and the many different mechanisms of Huntington disease pathogenesis. We describe the genetic and clinical diagnosis of the condition, its clinical assessment and the multidisciplinary management of symptoms, given the absence of effective disease-modifying therapies. We review past and present clinical trials and therapeutic strategies under investigation, including impending trials of targeted huntingtin-lowering drugs and the progress in development of biomarkers that will support the next generation of trials. For an illustrated summary of this Primer, visit: http://go.nature.com/hPMENh

First described in detail by George Huntington in 1872 (REF. 1), Huntington disease is the most common monogenic neurological disorder in the developed world[2–4]. Owing to its autosomal dominant inheritance, typical onset in the prime of adult life, progressive course, and a combination of motor, cognitive and behavioural features, the condition is devastating to patients and their families.

Huntington disease is caused by an expanded CAG trinucleotide repeat in *HTT*[5], which identifies the pathogenetic agent — a mutant form of the multifunctional protein huntingtin. Mutant huntingtin contains an abnormally long polyglutamine (polyQ) sequence that corresponds to the CAG genetic expansion; the protein exhibits toxic properties that cause dysfunction and death of neurons. Medium spiny neurons of the striatum are particularly vulnerable to mutant huntingtin-induced harm, but Huntington disease is increasingly recognized as a disease of the whole brain and body. Its known genetic cause permits predictive and diagnostic genetic testing for the disease.

After a variable 'premanifest' period, a prodromal phase characterized by subtle motor, cognitive and behavioural changes, often precedes a formal clinical diagnosis of motor onset by up to 15 years (FIG. 1). Once signs and symptoms begin, they progress inexorably over the course of the illness, which — with the exception of those patients with late-onset disease, who may die of other causes — is uniformly fatal, with a median survival from motor onset of 18 years[6].

As no treatments can forestall or slow Huntington disease, the clinical care of patients focuses on expert assessment and the multidisciplinary management of symptoms, through medical and non-medical means, to maximize function and quality of life. Although incurable, Huntington disease is not untreatable.

Intensive study has provided substantial insights into the pathobiology of Huntington disease and has generated a multitude of rational targets for therapeutic development. Clinical trials are now planned or underway for novel agents designed with Huntington disease in mind — most notably, gene silencing or huntingtin-lowering agents aimed at diminishing production of the mutant protein. These trials will be supported by an array of biomarkers developed and qualified through systematic clinical testing. Moreover, the genetic certainty of Huntington disease enables it to be used as a model for studying shared mechanisms and therapeutic development across neurodegenerative diseases. In this Primer, we move

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from epidemiology to the genetics of Huntington disease and mechanisms of the pathobiology of mutant huntingtin, before discussing clinical features, challenges in management and, finally, the current status of biomarker research, therapeutic development and clinical trials that aim to improve the outlook for families affected by Huntington disease.

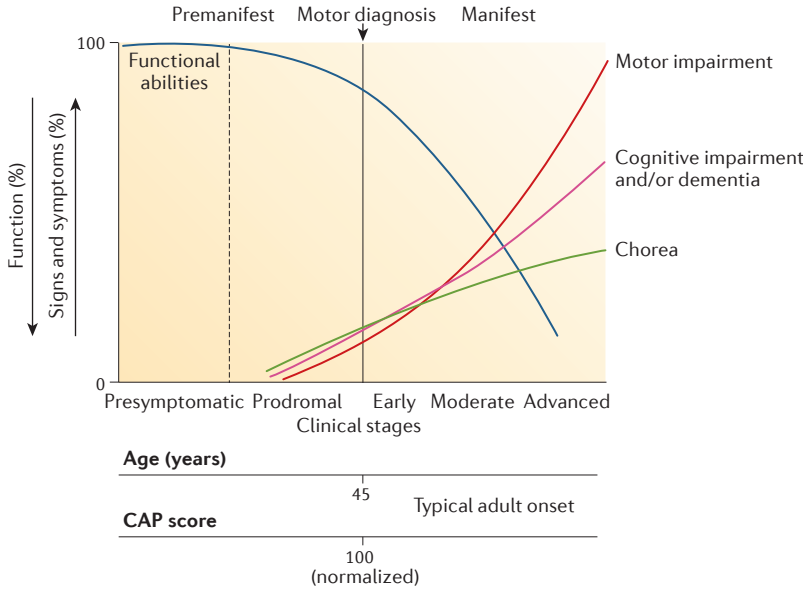

Figure 1 | **Natural history of clinical Huntington disease.** The normalized CAG age product (CAP) score enables progression of many individuals with different CAG expansion lengths to be plotted on the same graph. Mean disease onset is at CAP score ~100 (typically ~45 years of age), but there is substantial interindividual variability. Without normalization, the CAP score at onset exceeds 400. The period before diagnosable signs and symptoms of Huntington disease occur is termed 'premanifest'. During the 'presymptomatic' period, no signs or symptoms are present. In 'prodromal' Huntington disease, subtle signs and symptoms are present. Manifest Huntington disease is characterized by slow progression of motor and cognitive difficulties, and chorea is often prominent early but plateaus or even decreases later. Fine motor impairments (incoordination, bradykinesia and rigidity) progress more steadily. Figure adapted from REF. 6, Nature Publishing Group.

Epidemiology

Genetic confirmation of the CAG repeat expansion is the hallmark of modern epidemiological measures of Huntington disease. Accurate prevalence estimates depend on comprehensive genetic testing coupled with neurological evaluation of disease onset. Prevalence studies incorporating both genetic and clinical diagnostic standards show that 10.6–13.7 individuals per 100,000, or 1 in 7,300, are affected in Western populations[2–4].

Prevalence studies benefiting from genetic (molecular) diagnostics report higher rates of the disease than those using clinical measures alone[7]. Longitudinal analyses show a consistent increase in the prevalence of Huntington disease over the past two decades, coinciding with wider availability of the genetic test[4,8]. As family history was once a defining criterion of diagnosis, pre-molecular prevalence estimates were likely to have excluded sporadic or *de novo* cases that are now genetically proven to represent at least 5–8% of diagnosed patients[9,10]. In particular, the genetic test has enabled ascertainment of late-onset Huntington disease in the elderly population, for which family history is often lacking and neurological diagnosis can be more challenging owing to the higher rates of dementia and other neurodegenerative disorders in this population[7,10,11]. Ageing populations and longer patient survival can also contribute to increasing prevalence in addition to improved case ascertainment. The incidence of Huntington disease is estimated to be 4.7–6.9 new cases per million per year in Western populations, but whether incidence is increasing in parallel with point prevalence[9,10], which also represents increases over pre-molecular studies[12], is unclear.

Huntington disease is endemic to all populations but occurs at much higher frequencies among individuals of European ancestry. In Japan, Hong Kong and Taiwan, Huntington disease is diagnosed in only 1–7 individuals per million, approximately one-tenth as frequently as in Europe and North America[7]. In South Africa, black people also present with lower rates than white and mixed-ancestry subpopulations[13]. These differences are ancestry-specific, as shown in British Columbia, Canada, where Huntington disease is much more common among those of European descent (17.2 cases per 100,000) than in the ethnically diverse remainder of the population (2.1 cases per 100,000)[2]. Epidemiological data from other populations in Africa and Asia are limited to case studies or local clinical reviews — the overall prevalence or incidence of Huntington disease worldwide remains unclear. Several 'pockets' of high prevalence have been documented — most notably, the Maracaibo region of Venezuela, where hundreds of related patients have been traced to a single ancestor[14].

Ancestry-specific prevalence rates of Huntington disease are thought to result from genetic differences at the *HTT* locus. Average CAG repeat lengths are longer in populations with a high prevalence of the disease, from 18.4–18.7 repeats in people of European descent, to only 17.5–17.7 in East Asian and 16.9–17.4 in African populations[7] (FIG. 2). Underlying this genetic bias towards longer CAG repeats are specific haplotypes of high CAG

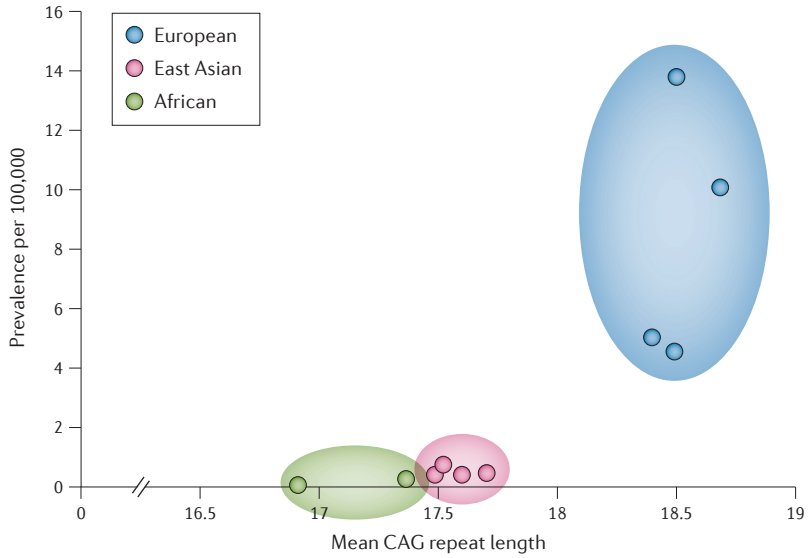

Figure 2 | **Ethnic differences in the prevalence of Huntington disease correlate with average CAG repeat length in each population.** Longer CAG repeats in individuals of European descent are thought to result in higher rates of CAG repeat expansion and *de novo HTT* mutation[7].

length found only in populations of European descent. Disease-causing alleles (≥36 CAG repeats) and intermediate alleles (27–35 CAG repeats) that lead to *de novo* Huntington disease are found preferentially on these haplotypes, which suggests repeated CAG expansion events in specific chromosomes[15,16]. Germline instability of intermediate alleles increases with CAG repeat length, indicating that longer CAG repeats in the general population might be linked to a higher CAG expansion rate and higher prevalence of Huntington disease[17–19]. By contrast, in populations with low prevalence, expanded CAG repeats are rare and occur on a mix of local haplotypes, suggesting a lower *de novo* mutation rate[20,21].

Mechanisms/pathophysiology

Genetics and genetic modifiers

HTT is located at chromosome 4p16.3 and encodes the protein huntingtin[5], the normal function of which is not wholly understood. Included in huntingtin is a polyQ segment of variable length near the amino terminus. The length of the CAG trinucleotide repeat that encodes this segment can be determined in any individual — normal, at risk or clinically diagnosed with Huntington disease — by a simple polymerase chain amplification assay with specific flanking oligonucleotide primers[5]. The repeat is polymorphic in the normal population in the range of 6–35 units; when expanded to ≥40 units, the mutation is highly penetrant, which triggers a disease process that inexorably leads to the onset of diagnostic motor signs. Repeats of 36–39 CAG units show reduced penetrance, as some individuals with these CAG lengths have Huntington disease, whereas others live a normal lifespan without being clinically diagnosed. The CAG repeat shows instability through meiotic transmission that is first notable in the intermediate CAG repeat range (27–35 units); this instability increases in frequency with increasing CAG length[22]. The repeat typically increases or decreases in length by one to a few CAGs, with increases predominating; an increase of much larger magnitude occurs rarely, but almost always involves transmission from a father, implying a particular predisposition to CAG repeat instability during spermatogenesis in some males[22]. Extensive genotype–phenotype studies in Huntington disease populations have set criteria for the mechanism that triggers pathogenesis[23] and have indicated that pathogenesis can be modified[24]. Accordingly, a treatment based on the pathogenetic process active in the human disease, although not currently available, should be possible to achieve.

The length of the CAG repeat in *HTT* determines whether an individual will develop Huntington disease; it is also the primary determinant of the rate of pathogenesis leading to the characteristic motor signs that underlie the clinical diagnosis[25–30]. Importantly, with respect to these motor signs, the timing of onset is determined by the allele with the longer CAG repeat in a completely dominant manner; the second *HTT* allele, regardless of its length (normal or otherwise), does not alter the rate of the process that leads to a clinical diagnosis[27]. The precise nature of the pathogenetic trigger that conforms to these genetically defined criteria (CAG length dependence and allele dose independence) is not known, but the demonstration that the length of the CAG repeat, even in the normal range, correlates with measures in some cellular assays (for example, cellular energy charge (ATP:ADP ratio[31]) or cellular adhesion[32] assays) suggests that it might involve a gain of function that acts through augmentation or dysregulation of one or more normal functions of huntingtin. In any event, molecular and functional consequences of the CAG expansion are detectable in cultured cells from human mutation carriers[31–33] and up to 15 years before clinical onset of Huntington disease in those individuals themselves[34].

In the typical CAG size range associated with mid-life adult onset of disease (40–55 CAGs), the length of the repeat accounts for ~56% of the variation observed in the age at motor onset[24]. Much of the remaining variation (estimated at 38–56%) can be attributed to functional genetic differences elsewhere in the genome of affected individuals that modify the rate of pathogenesis. Although several genes — including *ADORA2A*, *ATG7*, *CNR1*, *GRIK2*, *GRIN2A*, *GRIN2B*, *HAP1*, *PPARGC1A*, *MAP2K6*, *MAP3K5*, *NPY*, *NPY2R*, *OGG1*, *PEX7*, *TP53* and *UCHL1* — have been proposed as genetic modifiers of Huntington disease, none has yet withstood stringent statistical analysis[24]. However, genome-wide unbiased searches using the tools of modern genetics are underway and are expected to yield bona fide human genetic modifiers — naturally occurring functional variations that alter the course of Huntington disease in humans and that might provide clues to pathways or processes pre-validated as therapeutic targets capable of delaying disease onset.

Huntingtin structure and function

Huntingtin protein with a normal polyQ repeat length of 23 glutamines (Q_{23}) contains a total of 3,144 amino

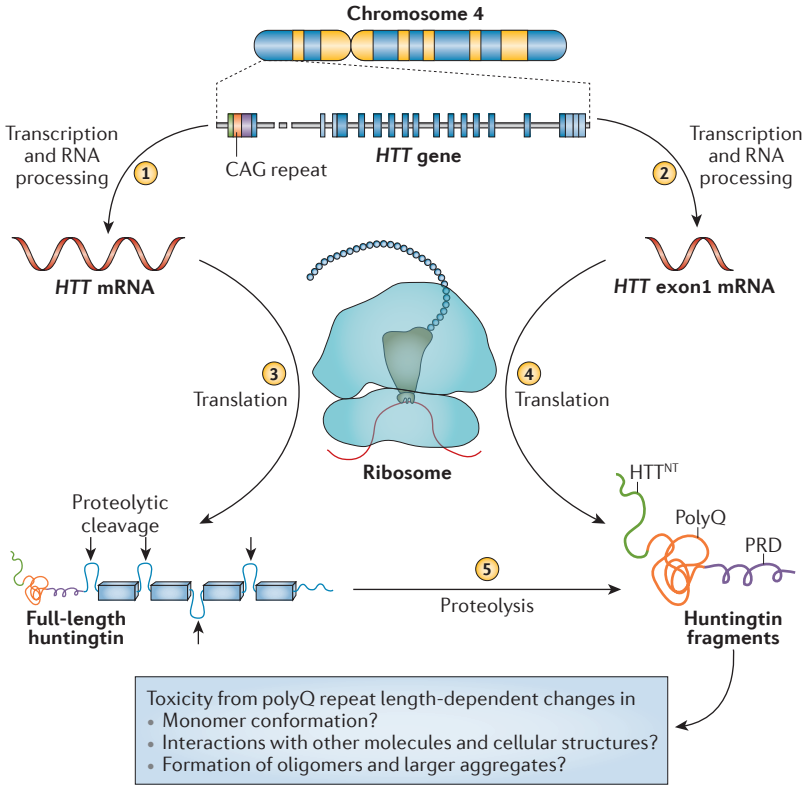

Figure 3 | **Huntingtin structure and transformations.** Expression of *HTT* generates an initial RNA transcript that is normally processed into an mRNA encoding the full-length huntingtin protein (label 1), but it can also be aberrantly processed into an mRNA encoding only exon1 if the gene contains an expanded CAG repeat (label 2). Translation generates either the full-length huntingtin protein (label 3) or the HTT exon1 protein (label 4). The HTT exon1 fragment consists of the 17-amino-acid mixed sequence HTT^{NT}, the polyglutamine (polyQ) sequence encoded by the CAG repeat and a proline-rich domain (PRD). The full-length huntingtin protein consists of this exon1 sequence followed by a series of ordered (boxes) and disordered (loops) protein segments. Proteolytic cleavage (label 5; cleavage sites indicated by arrows) mediated by recognition sequences located in the disordered segments generates a series of products, including HTT exon1-like fragments. Such fragments containing expanded polyQ segments have important roles in triggering Huntington disease by molecular mechanisms that are yet to be elucidated.

acids with a molecular weight of 348 kDa. Huntingtin is expressed throughout the body but at varying levels depending on cell type. Forms of the protein can be found in the nucleus and cytoplasm, and huntingtin can shuttle between these compartments. The normal functions of huntingtin are still being defined. Some broad biological functions of the normal protein have been uncovered, including its critical role in the development of the nervous system, its ability to influence brain-derived neurotrophic factor (BDNF) production and transport, and its role in cell adhesion[35]. At the same time, the specific biochemical functions of the protein in these processes, as well as the structural basis of these biochemical functions, remain largely unknown. Loss or modulation of normal huntingtin function in response to polyQ repeat expansion might also have a role in Huntington disease[35]. However, as Huntington disease is primarily a toxic gain-of-function disease, the new activities of huntingtin brought on by polyQ repeat expansion must somehow be linked to alterations in the protein structure, and much research has focused on identifying the critical conformational changes.

Huntingtin is linearly organized as a series of ordered domains interspersed with intrinsically disordered segments; further folding might occur as a result of interactions between folded domains. The known ordered domains are clusters of α-helical HEAT (Huntingtin, elongation factor 3, protein phosphatise 2A and TOR1) repeats[36] that are also found in several other proteins, in which they are binding motifs for macromolecules. There is considerable uncertainty about the exact number and location of the HEAT repeats and their roles in binding to the very large number of huntingtin interaction partners that have been described[37]. Separating the clusters of HEAT repeats are expanses of disordered structure, the only known functions of which are as regions for post-translational modifications (PTMs) such as proteolytic cleavage, phosphorylation and glycosylation[35,37]. The large number of PTM sites concentrated in the disordered segments of the protein represents the potential for highly complex and interactive pathways of regulation of protein activity, downregulation and targeting to cellular structures and compartments.

Proteolytic fragmentation has been shown to be a particularly prevalent PTM, and a variety of N-terminal fragments (derived from cleavage by caspases, calpains and other endoproteases at structurally accessible sites) have been described and their possible roles in toxicity explored[35,37]. Particularly important among these is an N-terminal fragment of about 100 amino acids, which for convenience has been termed HTT exon1, as it is encoded by the first exon of *HTT* (FIG. 3). HTT exon1 and related fragments, which can be generated in several ways (see below), consist of three sequence-defined, disordered domains: an N-terminal segment of 17 amino acids, known as HTT^{NT} or N17, that is likely to be rapidly shaved to 16 residues in the cell by enzymatic removal of the initiator methionine[38]; a CAG repeat-encoded polyQ segment of variable length; and a proline-rich domain (PRD) of 51 amino acids. HTT^{NT} has many roles, including membrane targeting[39], binding to chaperones[40], nuclear export[41] and other trafficking[42], as well as providing a site of potential regulatory PTMs[37,43] and the structural basis of oligomer formation[44,45]. Although the HTT^{NT} peptide is disordered in the monomeric state[45], it can take on an α-helical structure when it binds to membranes[46] or self-associates[44]. PolyQ sequences in monomeric peptides such as HTT exon1 tend to favour a condensed, disordered state[37]. Whether the polyQ repeat has any important function within normal huntingtin remains unclear[37,47]. Finally, the HTT exon1 PRD is a target for binding to some interaction partners such as certain WW domain-containing proteins[48]. The PRD in monomeric HTT exon1 is likely to exist in fluctuating segments of disorder and polyproline type II helix, a conformation that is known to be a good binding motif[37].

The nature of the alternative HTT exon1 conformations triggered by polyQ expansion that are responsible for development of Huntington disease continues to be debated. Given the general resistance of polyQ sequences

of all repeat lengths to adopt specific conformations, how a specific toxic conformation might be favoured within the expanded polyQ of monomeric HTT exon1 is unclear[37,47]. More-complex conformational effects in monomeric HTT exon1 linked to polyQ repeat length are formally possible but challenging to establish[37,49]. By contrast, the widely reported ability of HTT exon1 to readily form a variety of aggregated structures presents an array of plausible candidates that might mediate toxicity (see below)[37]. This aggregation links Huntington disease to other neurodegenerative diseases that feature a protein aggregation component, including Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis and spongiform encephalopathies.

Cells[50], model organisms[51] and patients[52] expressing expanded polyQ versions of huntingtin or its fragments can generate massive huntingtin-rich inclusions, which are so large that they can be visualized by light microscopy. Such aggregated inclusions can be multiple micrometres in diameter and can contain >100,000,000 molecules of huntingtin-related peptides[37]. With the advent of super-resolution fluorescence microscopy, it has become possible to identify aggregates that are smaller than inclusions, such as small clusters of amyloid fibrils, in cells with fluorescently labelled HTT exon1 (REF. 53). This type of aggregate might contain up to 100,000 individual huntingtin fragments[37]. Anything smaller is too small to see in microscopic real-time studies of huntingtin flux in the cell. However, using non-real-time methodologies, such small HTT exon1 aggregates[37] that exhibit a range of morphologies and sizes have been visualized *in vitro*[54] and *in vivo*[55,56]. The dependence of aggregation on the length of the polyQ segment has been consistently observed in a variety of molecular and environmental settings[57–59]. Indeed, this dependence is a robust correlate to the dependence of disease risk on CAG repeat length — a correlation that might be attributable to a mechanistic role for aggregates in the disease. Emerging evidence suggests facile formation of small oligomers composed of 4–15 HTT exon1 monomers[37,44,60] that are primarily driven by self-association of the HTT^{NT} N termini into α-helical clusters[44]. These initial aggregates can grow into non-β-oligomers[44] that contain hundreds of huntingtin fragments. These fragments can rearrange at a rate that increases as polyQ repeat length increases into nuclei for formation of β-sheet-rich polyQ amyloid fibrils[44] that individually contain several thousand fragments[37]. Such polyQ amyloid fibrils are quite stable and, along with the amyloid clusters and inclusions, represent the end point of HTT exon1 self-association *in vitro*; that is, once the process is initiated, the system tends to a fibrillar end. The situation is more complex in living cells constantly producing new huntingtin[56,60].

The initiation of amyloid growth requires nucleation, which involves the formation of a structure that is capable of efficient elongation into fibrils. In polyQ sequences without complex flanking sequences, nucleation is relatively unfavourable but is enhanced as polyQ repeat length increases[61]. However, nucleation of polyQ amyloid is greatly facilitated within HTT exon1 non-β-oligomers, whereby the attached polyQ chains are brought together at high local concentration and in the correct orientation required for nucleus formation[44,45]. The requirement for nucleation can also be completely bypassed by the introduction of preformed amyloid fibrils into the system[58] ('seeding') (FIG. 3).

Pathobiology of Huntington disease

A considerable body of data indicates that huntingtin fragmentation is a key early step in the pathogenetic mechanism of Huntington disease. Fragments can be detected in all full-length huntingtin mouse models of the disease, as well as in all brain regions of a young presymptomatic mouse model prior to detection of aggregates[55]; they have also been isolated from human post-mortem brains[62]. The relative concentration of huntingtin fragments between cell types depends partly on the level of *HTT* expression; its higher expression in neurons than in glial cells[63] is likely to contribute to the predominant neuronal pathology. The smallest huntingtin fragment is generated through an aberrant splicing event that leads to the production of an HTT exon1 protein[64]. Other fragments correspond to those generated through cleavage by caspases, calpains and other proteases that have been studied extensively[65]. Huntingtin (full-length and fragments) is post-translationally modified at multiple sites, and these processes can be influenced by the expanded polyQ segment and can, in turn, affect its toxicity. Some evidence supports the fact that the polyQ segment affects PTMs through alteration of the structural properties of huntingtin and its cleavage[65]. The likelihood that protein fragments accumulate to the concentration threshold required to initiate the cell-autonomous pathogenetic process will, therefore, depend on the expression level of the huntingtin protein, the extent to which the mis-splicing event occurs, specific protease activities and the presence of pathway-modifying PTMs.

The physical state of the huntingtin fragments responsible for cytotoxicity in Huntington disease — development of which is expected to exhibit dependence both on time and on polyQ repeat length — remains to be defined. Early suggestions[66] that polyQ expansion enables monomeric huntingtin fragments to adopt a toxic conformation that is not accessible to fragments with normal polyQ lengths have not held up to scrutiny[67,47]. Reliably detecting a polyQ repeat length-dependent conformational change in such a dynamic and flexible molecule is challenging *in vitro* and *in silico,* and even more so *in vivo*. On the one hand, it is not clear how a minute repeat length increase in the disordered polyQ sequence might so markedly shift conformational dynamics. On the other hand, in the aggregation model, the nucleation requirement might provide an explanation for the substantial increases in disease risk and age of onset in response to very small increases in repeat length[61,47]. As the polyQ repeat length and concentration increase, the time delay to nucleation of amyloid formation decreases[57]. The likelihood of a cell succumbing to the cell-autonomous effects of mutant huntingtin will depend on whether the huntingtin protein, or more

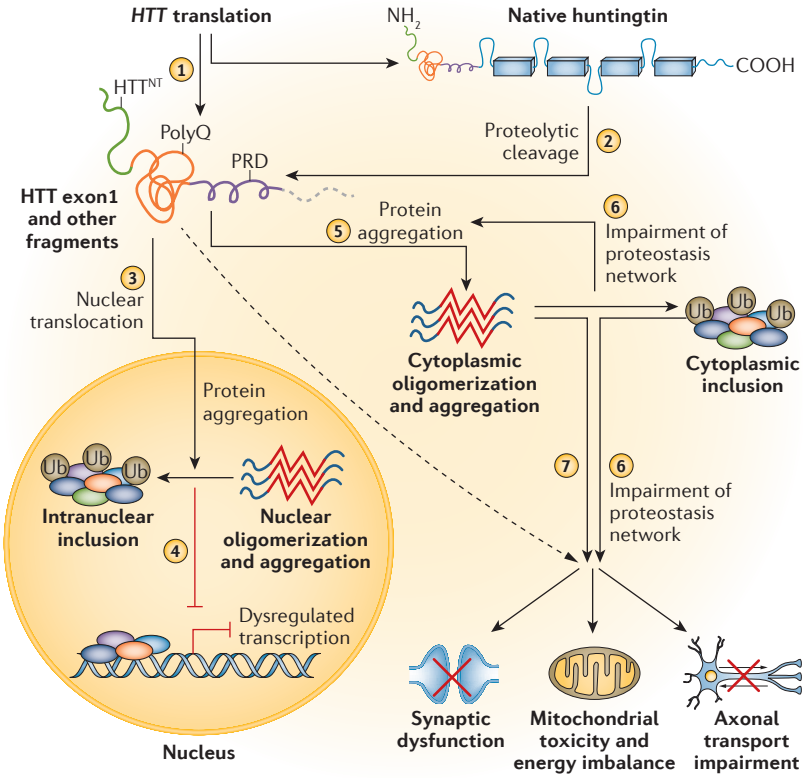

Figure 4 | **Pathogenetic cellular mechanisms in Huntington disease.** (1) *HTT* is translated to produce the full-length huntingtin protein as well as an amino-terminal HTT exon1 fragment (the result of aberrant splicing). The length of the polyglutamine (polyQ) tract in these proteins depends on the extent of somatic instability. (2) Full-length native huntingtin is cleaved through proteolysis to generate additional protein fragments. (3) Protein fragments enter the nucleus. (4) Fragments are retained in the nucleus through self-association, oligomerization and aggregation — leading to the formation of inclusions, a process that causes transcriptional dysregulation through the sequestration of other proteins and through other incompletely defined mechanisms. (5) Huntingtin fragments oligomerize and aggregate in the cytoplasm. (6) The aggregation of huntingtin is exacerbated through the disease-related impairment of the proteostasis network, which also leads to global cellular impairments. (7) The aberrant forms of huntingtin result in additional global cellular impairments, including synaptic dysfunction, mitochondrial toxicity and a decreased rate of axonal transport. PRD, proline-rich domain; Ub, ubiquitin.

likely a fragment thereof, reaches the concentration threshold needed to trigger these pathological events. Several factors could influence this initiation, including the level of expression of mutant huntingtin, whether the cell is in mitotic arrest, the size of the CAG repeat expansion, the extent to which aberrant splicing occurs, the production of huntingtin fragments through proteolysis, PTMs, the seeding of aggregation through the prion-like spread of aggregates from one cell to another and the competency of the proteostasis network within the cell. Other cells might become affected in a non-cell-autonomous process through dysfunctional activities, such as alterations in synaptic transmission that lead to network imbalance[68].

The concentration threshold required for the self-aggregation of huntingtin molecules decreases with the increasing length of the polyQ tract and, consistent with this process, more areas of the brain are affected in juvenile patients with Huntington disease (diagnosed at <20 years in age) who carry longer CAG repeat expansions than those with the adult-onset form of the disease. Highly expanded CAG repeats are also present in certain brain regions of individuals with adult-onset disease owing to CAG expansion through somatic instability[69]. Investigation of somatic expansion in mouse models of Huntington disease has shown that somatic expansion occurs in postmitotic neurons[70], depends on a functional mismatch repair system[71–73] and acts as a disease modifier[74,75]. The extent to which somatic expansion influences the onset and progression of the human disease is not known, but factors influencing it are likely to also act as disease modifiers in affected patients[76].

Several reports have provided evidence that large huntingtin-containing inclusions are not correlated with cytotoxicity[77] and might even be protective[50]. However, as discussed above, many aggregated precursors to inclusions are present, including individual amyloid fibrils, that are too small to be visualized by light microscopy and that were therefore undetectable in many of these studies. Although tracking the various oligomeric and aggregated forms of huntingtin that are below the size of an inclusion in either mouse models or patients *in vivo* is not possible, the observation of inclusions in a specific cell type provides evidence that self-association has progressed through a series of smaller aggregated species to an amyloid fibril end point. Inclusions form in a wide range of peripheral tissues in mouse models that carry highly expanded CAG repeats[78]. These inclusions occur predominantly in cells that have entered mitotic arrest, which suggests that cell division acts to delay the pathogenetic process.

The acceleration of aggregation through seeding suggests the possibility of a prion-like mechanism of cell-to-cell transmission[79]. *In vitro*, mammalian cells efficiently take up small amyloid fibrils of polyQ proteins[80] that can then recruit endogenous polyQ-containing proteins such as HTT exon1 into growing aggregates[81] and kill cells[80]. Recent reports suggest that the spread of aggregates from one cell to another might occur in Huntington disease[82,83]. Seeding also facilitates the recruitment of other polyQ proteins into huntingtin fibrils, which might provide a mechanism of polyQ toxicity through sequestration and depletion[84].

The chronic expression of mutant huntingtin leads to the collapse of the proteostasis network, which maintains the integrity of the proteome through molecular chaperones and protein clearance machineries[85] (FIG. 4). The levels of basal chaperones decrease with disease progression[86], endoplasmic reticulum stress occurs through multiple pathways[87], and the ubiquitin–proteasome system[88] and autophagy[89] might become compromised. However, some balance can be restored, as increasing protein folding capacity has been shown to alleviate disease-related phenotypes in multiple models[86]. The ability to rapidly respond to stress is important for all organisms to protect against environmental insults, but in Huntington disease the ability to induce the major stress response pathway — the heat shock response — becomes severely compromised with disease progression[90], which would be expected to further exacerbate pathogenesis.

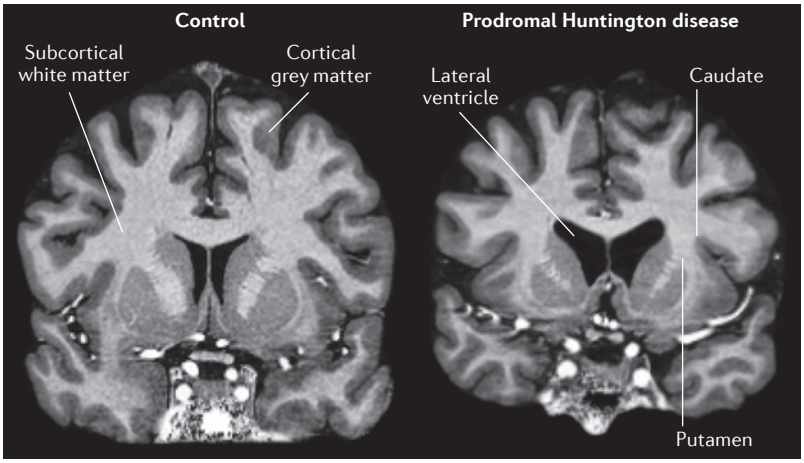

Figure 5 | **Atrophy in prodromal Huntington disease shown using 7T MRI.** Bilateral atrophy of the caudate and putamen, and a concomitant increase in size of the fluid-filled lateral ventricle, is observed in the gene carrier compared with the control. This prodromal participant has only subtle signs and symptoms that are insufficient for diagnosing manifest Huntington disease. There are also subtle changes in the cortical grey matter and overall atrophy of subcortical white matter.

Once the cytotoxic forms of huntingtin are generated, their aberrant behaviour can cause dysfunction in many downstream cellular processes[65] — including transcription and intracellular signalling[65,91], intracellular transport[92], the secretory pathway[87], endocytic recycling[77], mitochondrial impairment[92,93], synaptic dysfunction[94] and immunity[95] — leading to an extremely complex pathogenicity. Cellular dysfunction that arises from the intrinsic effects of mutant huntingtin results in network imbalance. For example, excitotoxicity arising from altered neuronal circuitry[68] and non-cell-autonomous dysfunction[96] contribute to the neurological and non-neurological symptoms of Huntington disease (FIG. 4).

Diagnosis, screening and prevention

Huntington disease is diagnosed on the basis of clinical evaluation, family history (if available) and, in most cases, genetic testing for the presence of the CAG expansion in *HTT*. The triad of symptoms that characterize the condition are motor dysfunction (most typically chorea), cognitive impairment (for example, problems with attention and emotion recognition) and neuropsychiatric features (such as apathy and blunted affect). Neuroimaging and other tests can support the diagnosis, primarily by ruling out other conditions, and are typically not necessary, especially if there is a characteristic presentation of an individual with a known family history and a positive genetic test. However, an MRI or CT scan showing symmetrical striatal atrophy (and often, to a lesser degree, atrophy in other subcortical regions, cerebral cortical grey matter and subcortical white matter) in the absence of other substantial changes is strongly suggestive of a diagnosis of Huntington disease, and changes might be detectible even prior to 'motor onset' (FIG. 5).

Diagnosis of motor onset of 'manifest Huntington disease' is currently made in someone at risk, or tested genetically positive for the CAG expansion, on the basis of the unified Huntington's disease rating scale (UHDRS)[97] motor examination; the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder yields a diagnostic confidence score of 4, which corresponds to 99% confidence that signs are attributable to Huntington disease[6,98]. A UHDRS total motor score (TMS) of approximately 15 in an adult — with characteristic findings of delayed and slow saccades, dysdiadochokinesis, chorea and difficulty with tandem walk — is usually strongly supportive of the diagnosis. The diagnosis can be made with greater confidence in individuals with relatively low scores (for example, <20) when the patient has been followed up longitudinally (for example, for several years) and clearly has progressive motor changes.

The definition of Huntington disease is evolving, and cognitive factors are increasingly being taken into account. Cognitive function test scores can support the diagnosis; however, owing to the wide range of baseline cognitive abilities, clear evidence of a change from baseline in an individual provides the strongest support. Recently, a more extensive series of diagnostic classifications has been proposed, which take into account results of recent natural history and neuroimaging studies (see below). In 2014, Reilmann *et al.*[98] proposed more-formal definitions of the following terms: premanifest (consisting of a presymptomatic period), followed by a prodromal phase and manifest Huntington disease (FIG. 1).

The differential diagnosis of Huntington disease is broad and includes autosomal dominant genetic conditions, such as Huntington disease-like 2 (HDL2) and dentatorubral-pallidoluysian atrophy, as well as spinocerebellar ataxia (types 2, 3, 12 and 17), neuroacanthocytosis[99] and brain–thyroid–lung syndrome[100]. In some cases, *C9orf72* expansions can cause an Huntington-like presentation, although careful examination of the phenotype is likely to demonstrate differences[99,101]. Some non-progressive extrapyramidal disorders, such as benign hereditary chorea and Sydenham chorea, are also included in the differential diagnosis. Juvenile Huntington disease is more difficult to diagnose because there is often little chorea. Occasionally, patients with juvenile-onset disease can be diagnosed even though their parents are seemingly unaffected because of striking anticipation. For example, a father in his 30s with a CAG repeat length of 45 might remain premanifest but, through expansion of the unstable CAG repeat, his child might have a repeat length of 50–60 units and have manifest juvenile-onset disease.

Genetic testing for Huntington disease

Genetic testing can be diagnostic or predictive depending on the circumstances. If a patient has features typical of Huntington disease, the most useful confirmatory diagnostic test is CAG-repeat testing[102]. A positive result has many implications for the patient and family, so it is usually best to give information about the disease beforehand so that they are prepared. When presenting the results of a positive test, the patient should come in with a spouse, supportive friend or family member. The delivery of a diagnosis can be a substantial emotional event

for the patient and represents a critical time for educating the family further about Huntington disease and its genetic implications for family members and family planning. If confirmatory genetic testing is negative, the patient is likely to need referral to a movement disorders expert to detect other possible causes of their symptoms.

International guidelines regarding predictive and prenatal testing for this fatal neurodegenerative disorder were written in 1994, shortly after the discovery of the *HTT* genetic defect[103] and updated in 2013 (REF. 104). The salient features of the earlier predictive testing guidelines include genetic counselling, a psychological assessment, a neurological examination, time for the patient to reconsider the decision to test and results to be given in person in the context of post-test support. The discussion should also include the fact that children under 18 years of age are not genetically tested unless they are symptomatic, as well as insurance and potential genetic discrimination issues. Current considerations include: genetic counselling via telemedicine[105]; performing a baseline neurological exam after, rather than before, genetic testing in some individuals; results given by a local family doctor after counselling at a Huntington disease centre; and involvement of specialists who can provide information on reproductive options[106]. The availability and uptake of prenatal and pre-implantation genetic diagnosis and testing vary considerably in different countries; the issue of uptake rates has now been discussed in detail[107,108]. Counselling implications for individuals with intermediate alleles have also been reported[109].

Natural history

The age of motor onset of Huntington disease is strongly dependent on the length of the CAG repeat expansion within *HTT*[110], with longer expansions causing earlier onset. The mean age of onset is about 45 years but can rarely occur in early childhood or late life. Longer CAG repeat expansions also cause more-rapid progression[29,111,112]. The index age × (CAG – *L*) is a good predictor of the extent of clinical progression during life and brain pathology post-mortem[6]; age refers to the current age of the individual, CAG is the repeat length, and *L* is a constant near the threshold of CAG repeat expansions for disease[113,114]. The CAG age product (CAP) score therefore provides an approximate measure of the length and severity of the patient's exposure to the effects of mutant huntingtin and is useful for conveying longitudinal data from cohorts of patients with a range of ages and CAG repeat lengths.

Several longitudinal observational studies of Huntington disease have shown that signs and symptoms begin many years before motor onset can be confidently diagnosed, and that brain changes can be detected at least 10–15 years before motor onset and progress gradually. These studies include the COHORT study, which followed up individuals with manifest and premanifest Huntington disease[115]; the PREDICT-HD[116] study, which is a large multicentre study with >800 patients with premanifest Huntington disease and 200 controls who were followed up for 10 years using clinical, neuropsychological and imaging measures; and TRACK-HD, which included 120 premanifest patients stratified by time to predicted onset, 120 early-stage patients and 120 matched controls, and involved extensive annual assessments with imaging and clinical measures[112]. Additionally, REGISTRY is the largest multicentre clinical study to date, with >13,000 participants from 16 countries, but does not have an imaging component. A longitudinal study at Johns Hopkins University has followed up patients and families clinically for >30 years and includes neuropsychology and imaging data. Finally, in some individuals, data have been gathered through the late stages of the disease to autopsy and neuropathological assessments[117].

Diagnosis of Huntington disease has traditionally been based on motor signs and symptoms. Motor signs can be specified and quantified reliably by neurological exam, and motor findings are fairly sensitive and specific because, for most individuals without previous neurological difficulties, the baseline UHDRS total motor score should be close to zero, or at least low and stable. However, there has been increasing appreciation of the importance of cognitive and emotional features of Huntington disease in causing functional disability, and thus the importance of including these features in diagnosis. Changes in cognition are especially important but sometimes difficult to document, as baseline cognitive abilities vary widely. Emotional features might be important in some individuals but are difficult to incorporate into diagnosis because many non-Huntington disease-related factors influence emotion. These issues are discussed in more detail elsewhere[98].

Motor disorder. Motor disorder in Huntington disease can be conceptualized as having two major components. The first component is involuntary movement disorder; chorea is common in adult patients but not in juvenile patients, and it usually begins early in the course of the disease. The second component consists of impairment of voluntary movements and includes incoordination and bradykinesia. The impairment is most prominent in early-onset disease (which is related to long CAG expansions), especially juvenile Huntington disease, and also supervenes in the late stages of the more common adult-onset disease. By contrast, chorea usually plateaus and often decreases in late stages of the disease, when parkinsonism, dystonia and rigidity dominate. Voluntary motor impairment progresses more steadily than chorea[111] and predicts functional disability better than chorea does[29].

The motor features of Huntington disease can be assessed using the UHDRS TMS[97,118], which has ratings for items that include eye movements, speech, chorea, dystonia, rapid alternating movements, bradykinesia and gait. Quantification of some features of the motor disorder can be achieved with force-transducer-based measures, as in the quantitative motor (Q-Motor) battery used in the TRACK-HD study[119,120]. Q-Motor assessments can have less variability than the UHDRS TMS and, accordingly, should be less susceptible to placebo effects in clinical trials.

Box 1 | **The Huntington disease health-care team**

- Neurologist: diagnosis and management
- Psychiatrist: diagnosis and management
- Genetics specialist: genetic counselling and genetic testing (including diagnostic, predictive or premanifest, prenatal or pre-implantation testing)
- Neuropsychologist: cognitive assessment and counselling
- Psychologist: psychological assessment; counselling and support (for patient and family)
- Physiotherapist: gait evaluation; exercise programme; assistive equipment
- Occupational therapist: home safety and adaptive equipment
- Speech pathologist: speech and communication assessment; dysphagia assessment and counselling
- Nutritional therapist: nutritional assessment and counselling
- Social worker: disability counselling; financial- and life-planning counselling; evaluation of in-home services or out-of-home placement; interface with criminal justice and government programmes
- Nurse or case manager: case management and family support
- Research team: engage patient and family in research
- Primary care provider: attend to other aspects of general health
- Dentist: ensure appropriate dental care
- Lay organization representatives: liaise with family and provide support
- Long-term care organization representatives: skilled care of patients in late stages of the disease

Cognitive disorder. Cognitive difficulty, similar to subtle motor problems, can occur years before diagnosable motor onset of Huntington disease[121]. Like motor impairment, cognitive decline progresses gradually. The features of cognitive disability in Huntington disease are similar to disorders associated with striatal–subcortical brain pathology (for example, vascular dementia and Parkinson disease) but are dissimilar to Alzheimer disease[122–124]. Notable in patients with Huntington disease are problems of attention, mental flexibility, planning and emotion recognition, along with cognitive slowing[121,125]. Learning and retrieval of new information are decreased but, different from Alzheimer disease, rapid forgetting is not as pronounced. Language in Huntington disease is relatively preserved even late in the course, although speech can be disrupted[123]. Cognitive losses often lie at the intersection between cognitive and psychiatric domains, and include problems with initiation, lack of awareness of deficits and disinhibition[126]. Thus, patients with Huntington disease can have social disengagement, decreased participation in conversation and slowed mentation, often accompanied by lack of awareness of deficits and by impulsivity[127].

In the TRACK-HD study, 10 of 12 cognitive outcomes showed evidence of deterioration in early Huntington disease[112,128,129]. Of these, the symbol digit modalities test (which measures visual attention and psychomotor speed), the circle tracing test (which measures visuomotor and spatial integration and transformation) and the Stroop word-reading test (which measures psychomotor speed within the spoken context) showed the most pronounced results for patients compared with controls. By contrast, in relatively late premanifest Huntington disease, a sample of 117 participants showed little evidence of detectable deterioration over 2 years. Many of the tests most affected in TRACK-HD have a substantial motor or psychomotor component, highlighting the close relationship between motor and cognitive features of Huntington disease, both of which depend on cortical–basal ganglia circuits.

Neuropsychiatric features. The neuropsychiatric features of Huntington disease are not as consistent as the motor or cognitive features, but they can cause substantial disability, be prominent early in the course of the disease and even occur as initial features. Depression is very common, and some depressive symptoms are reported by up to 50% of patients at some point during the course of the illness[130]. Major depression in Huntington disease is clinically similar to depression in individuals without the disease, and management is also similar[131]. Irritability is frequent and can be a feature[132]. Apathy is common and often disabling, especially in later stages of the disease, and is progressive[132]. Notably, the TRACK-HD study showed that apathy is a feature in individuals with premanifest Huntington disease[112]. Neuropsychiatric symptoms sometimes described as 'executive function' or 'frontal lobe' problems are significantly associated with functional decline in the early-stage disease. Less common, although clinically important, are more-severe psychiatric problems such as delusional depression or a schizophrenia-like psychosis. These conditions might require acute management that includes in-patient psychiatric treatment.

Management

In the absence of an effective disease-modifying therapy, the current management of Huntington disease is centred on treating symptoms. Ideal management of patients includes a team of health-care providers (BOX 1) who can attend to its wide-ranging impact on the individual and family[133]. Indeed, guidelines for management by the speech pathologist, physiotherapist, nutritional therapist, occupational therapist and dentist were reported by the European Huntington Disease Network Standards of Care group[134]. The key role of the nurse in the management of the patient and families has also been discussed[135].

The only drug specifically licensed by the US Food and Drug Administration (FDA) for use in patients with Huntington disease is the synaptic vesicular amine transporter inhibitor tetrabenazine, which was approved in 2008 for the treatment of chorea[136]. Studies are underway to investigate other potential treatments for chorea in patients with Huntington disease, including pallidal deep-brain stimulation[137,138] and a deuterated tetrabenazine molecule[137–140]. Indeed, several reviews have emphasized the weak evidence supporting any other pharmacological intervention in the management of Huntington disease[141,142]. In an effort to reduce therapeutic nihilism in the absence of proven treatments, a series of algorithms for the treatment of chorea, irritability and obsessive–compulsive behaviours were reported in 2011 by an international group based on surveys of Huntington disease experts[143–145]. Until better evidence

accrues, the clinician must adopt the attitude that treatments providing benefit to patients without Huntington disease who have neuropsychiatric symptoms should also be expected to help people with Huntington disease who have the same symptoms. Clinicians should proceed thoughtfully to optimize the patient's quality of life with available medications and supportive therapies.

For the 10% of affected individuals with juvenile-onset Huntington disease, special attention for a variety of reasons is pertinent. These patients often come from a family with a simultaneously affected father, present with severe behavioural issues before motor symptoms (which complicate the diagnosis) and can be experiencing seizures, rigidity and developmental behavioural challenges that require specialized care that is not always available even in specialized clinics[146,147]. The late stages of Huntington disease should not be neglected either. Affected individuals can spend 5–10 years in residential care[148,149]. There are specialized care facilities in some, but not most, areas of the world. Programmes to support individuals with late-stage Huntington disease have been described and, as the disease progresses and symptoms evolve, the ongoing need for each medication should be re-evaluated at intervals[135,150]. Hospice care can be appropriate in the terminal stages.

Current clinical trials

Clinical trials for Huntington disease have increased moderately over time, whereas the average number of participants has increased exponentially. From 1990 to 2004, 15 clinical trials were reported, with an average of 23 participants. From 2005 to 2014, 22 clinical trials reported results, and the average sample size was 139 participants. However, the overwhelming majority of studies to date have not demonstrated efficacy. A 2006 evidence-based review reported that, of the 20 level-I studies included, no clear treatment recommendation of clinical relevance could be made[151]. Similarly, a 2011 systematic review concluded that there is "weak evidence to support most of the treatment decisions in [Huntington disease]" (REF. 141).

Fuelled by the large unmet need, the FDA approval of tetrabenazine for the treatment of chorea in Huntington disease, continued scientific advances and increased interest in drugs for orphan conditions[152,153], interest in drug development is currently at its highest level ever. Ongoing and recently completed clinical trials are examining symptomatic treatments as well as treatments aimed at modifying the underlying pathogenesis of the disease (TABLE 1). The trials are diverse in their funding source (including academic institutions, government sources and industry), duration (from days to years) and stage of development (from Phase I to Phase IV). Some investigational therapies are aimed primarily at particular symptoms, such as motor disorders (cysteamine, deuterated tetrabenazine and pridopidine) and cognition (PBT2)[154–156]. Furthermore, many novel mechanisms are under investigation. For example, owing to the impairment of and decrease in levels of the transcription factor cAMP response element-binding protein (CREB) in Huntington disease, current drug trials are targeting phosphodiesterases that can increase CREB activation[157]. Other interventions, such as delayed-release cysteamine bitartrate, are being studied as potential disease-modifying and symptomatic treatments in patients[158].

Others experimental treatments, including coenzyme Q_{10} and creatine, are aimed at improving overall function for people with the disease. However, the trials of these compounds (2CARE and CREST-E studies) were the largest ever conducted in Huntington disease but were closed prematurely owing to futility[159,160]. The 2CARE study evaluated coenzyme Q_{10} (2,400 mg per day) in 609 individuals for a planned duration of 5 years. The CREST-E study evaluated creatine (up to 40 g per day) in 553 individuals for a planned duration of 3 years. Overall function for participants within the 2CARE and CREST-E studies was assessed on the basis of Total Functional Capacity. Their premature termination argues that more-sensitive markers of disease progression are needed to identify potential signs of efficacy (or the lack thereof) earlier and to minimize the risk and cost of large-scale studies of agents that lack efficacy.

Quality of life

The impact of Huntington disease on health-related quality of life (QOL) extends over the life of an individual and begins long before the diagnosis (FIG. 6). The assessment of QOL is challenging in this disease for three reasons: the lifelong influence of the disease on QOL; unawareness, denial and progression of dementia in affected individuals; and the absence, until recently, of disease-specific QOL tools.

The impact of Huntington disease often begins with the family-disrupting development of the disease in a parent, followed by the child's gradual awareness of his or her own genetic risk. In one study, more than 50% of 74 adults at risk had experienced adverse childhood events related to Huntington disease, including conflicts with family members and negative interactions with friends, parents and others; challenges in the performances of household tasks; and financial and health stresses[161]. To study these experiences, Dreissnack *et al.*[162] developed HD-Teen Inventory, which qualitatively assesses issues and concerns common in teenagers — including changes in personal and family relationships, genetic risk, information about the disease and emotional support. Similar concerns in adults were shown to affect social activities, career, marriage and reproductive decisions[163]. Unawareness, denial of symptoms, and the progression of dementia also complicate the measurement of QOL in symptomatic individuals. To address these difficulties, studies are ongoing to determine how and when to use caregiver or other proxy reports regarding QOL in addition to, or instead of, patient reports, and whether these are equivalent to the reports from the affected individual[164,165]. Indeed, clinical trials in Huntington disease increasingly include caregiver assessments of QOL as well as self-reported patient outcomes.

Subtle changes in cognition and mood begin years before the motor symptoms manifest[112,116], and Huntington disease-specific QOL tools that account for this feature are under development[164–167]. Some work has shown that QOL

Table 1 | **Status of recent and current clinical trials in Huntington disease***

Sponsor	Study name and/or identifier‡	Study agent	Target symptom	Design	Trial length	Status
Phase IV						
New York Medical College	NCT01834911	Tetrabenazine	Motor	Prospective case–control study comparing Stroop visual interference scores in individuals who are already taking tetrabenazine	6 hours	Currently enrolling
Phase II/III						
Raptor Pharmaceuticals	CYST-HD; NCT02101957	Cysteamine bitartrate delayed-release capsules	Motor	Double-blind, placebo-controlled study followed by an open-label extension study looking at total motor scores	36 months	Study ongoing; preliminary results released
Phase III						
US National Institute of Neurological Disorders and Stroke	2CARE; NCT00608881	Coenzyme Q_{10}	Function	Randomized double-blind study examining effect on slowing the worsening of symptoms	5 years	Study concluded for futility
US National Center for Complementary and Alternative Medicine	CREST-E; NCT00712426	High-dose creatine	Function	Randomized double-blind study examining effect on slowing progressive functional decline	3 years	Study concluded for futility
Auspex Pharmaceuticals	FIRST-HD; NCT01795859	SD-809 extended release	Motor	Randomized double-blind study examining effect on chorea; to be followed by an open-label, long-term safety study	12 weeks	Enrollment completed; study completed
Auspex Pharmaceuticals	ARC-HD; NCT01897896	SD-809 extended release	Motor	Open-label, long-term safety study testing safety and efficacy	58 weeks	The study is ongoing, but not recruiting participants
Assistance Publique – Hôpitaux de Paris	NEUROHD; NCT00632645	Olanzapine, tetrabenazine and tiapride	Behaviour	Randomized controlled trial comparing three neuroleptics and testing safety and efficacy	1 year	Currently enrolling
Phase II						
Charité University	ETON-Study; NCT01357681	Epigallocatechin gallate	Cognition	Randomized double-blind study testing efficacy in changing cognitive function and tolerability	1 year	Enrollment completed; study ongoing
Charité University	Action-HD; NCT01914965	Bupropion	Behaviour	Randomized double-blind study testing efficacy in changing apathy and tolerability	10 weeks	Enrollment completed; final study data collection completed
Ipsen	NCT02231580	BN82451B	Motor	Dose escalation, proof-of-concept study investigating safety, tolerability, pharmacokinetics and pharmacodynamics	28 days	Currently enrolling
Omeros Corporation	NCT02074410	OMS643762	Motor; cognition; behaviour	Randomized, double-blind, placebo-controlled, sequential cohort study to evaluate safety and efficacy	28 days	Clinical trial currently suspended§
Prana Biotechnology	REACH2HD; NCT01590888	PBT2	Cognition	Randomized, double-blind safety and tolerability study	6 months	Study completed; top-line results released
Pfizer	NCT01806896	PF-0254920	Motor	Randomized controlled trial evaluating safety, tolerability and brain cortico–striatal function	28 days	Completed
Pfizer	NCT02197130	PF-0254920	Motor	Randomized, double-blind, placebo-controlled proof-of-concept study of the efficacy and safety	26 weeks	Currently recruiting

Table 1 (Cont.) | **Status of recent and current clinical trials in Huntington disease***

Sponsor	Study name and/or identifier‡	Study agent	Target symptom	Design	Trial length	Status
Teva Pharmaceutical Industries	PRIDE-HD; NCT02006472	Pridopidine	Motor	Randomized, double-blind, placebo-controlled study of safety and efficacy	26 weeks	Currently enrolling
Teva Pharmaceutical Industries	OPEN-HART; NCT01306929	Pridopidine	Motor	Open-label, single-group assignment study assessing long-term safety	2 years	Enrollment completed; study ongoing
Teva Pharmaceutical Industries	Legato-HD; NCT02215616	Laquinimod	Motor	Randomized, double-blind, placebo-controlled, parallel-group study evaluating efficacy and safety	12 months	Currently enrolling

*As of November 2014. ‡See ClinicalTrials.gov. §This trial was suspended owing to an observation from a study in rats; the observation occurred in several of the rats receiving the study's maximum dose of OMS824, a dose that resulted in drug-free plasma concentrations that were several times higher than those measured in patients. The potential relevance of this animal study finding to humans, if any, is unknown. However, on the basis of communication with the US Food and Drug Administration (FDA), Omeros has suspended the clinical trial[256].

is affected by neuropsychiatric symptoms and executive dysfunction in gene-positive premanifest individuals[168]; depression and reduced functional capacity are also common in diagnosed individuals[169] and are determined by measurement of psychological function, social interaction and motor function[166]. Family members of patients frequently express concerns about emotional, social, physical, cognitive and end-of-life issues[170]. However, in the late stages of the disease, motor symptoms[171,172] and cognitive and functional — but (surprisingly) not psychiatric — features[172] predict placement into long-term care. Thus, disease-specific QOL tools for these patients must cover the whole spectrum: behavioural, cognitive, functional and motor domains.

With respect to patients receiving palliative care in the late stages of the disease, the following domains were identified by a panel of experts as being relevant: autonomy; dignity; meaningful social interaction; communication; comfort; safety and order; spirituality; enjoyment, entertainment, and well-being; nutrition; and functional competence[135]. However, no studies have evaluated the effects of interventions to these areas on QOL. Researchers in the Netherlands, a country where physician-assisted suicide (euthanasia) is legal, have emphasized the importance of a discussion between the patient and physician about end-of-life plans, including suicide, to the patient's autonomy and well-being[173].

Overall, the impact of Huntington disease on QOL in affected families changes over the lifetime of the affected individuals. Psychosocial issues dominate early in the life of an at-risk individual, and cognitive and behavioural issues during the prodromal and early symptomatic stages of the disease. In late-stage patients, reduced motor and functional capacity predominate. How to assess or improve QOL in the terminal stages of the disease remains an open question.

Outlook

Key outstanding questions in the pathobiology of Huntington disease centre on determining the structure and nature of toxic huntingtin species, their immediate cellular target or targets, and mechanisms of toxicity. Further study is needed, especially in humans, on the generation of the various huntingtin fragments and the extent to which each contributes to pathogenesis. Critical experiments need to be designed to address the extent to which prion-like aggregate propagation contributes to disease progression.

The most pressing unmet need in Huntington disease is for a therapeutic that shows evidence of disease modification — slowing, preventing or even reversing the disease in mutation carriers. Despite a multitude of therapeutic targets, few are well-validated and therapeutic successes in model systems have failed to translate to patients, partly because of the difficulty of studying the pathobiology in living humans. One mystery that will perhaps only be answered by clinical trials is the extent to which modulating the non-central nervous system pathology of Huntington disease, by agents acting peripherally, might be capable of modifying the course of the disease as animal studies have suggested[174]. If we were to reach the ultimate goal of preventing the disease in premanifest mutation carriers, we will need an array of effective and well-characterized biomarkers to give early indications that drugs are achieving the desired biological effects in people showing no overt signs of the disease.

Biomarkers

Biomarkers provide important information on drug effects (pharmacodynamics), the presence (trait) of disease or the severity (state) of disease. Genetic testing provides an excellent trait biomarker for Huntington disease[5,113]. Prevention of disease is the ultimate goal of trials in premanifest Huntington disease but, in the absence of clinical symptoms, it is difficult to determine whether a given intervention alters disease onset. Clinical, cognitive, neuroimaging and biochemical biomarkers are currently being investigated for their potential in clinical use and for their value in the development of future treatments for patients (TABLE 2). These biomarkers might eventually be used in combination to provide the optimal measure of onset and progression at different disease stages.

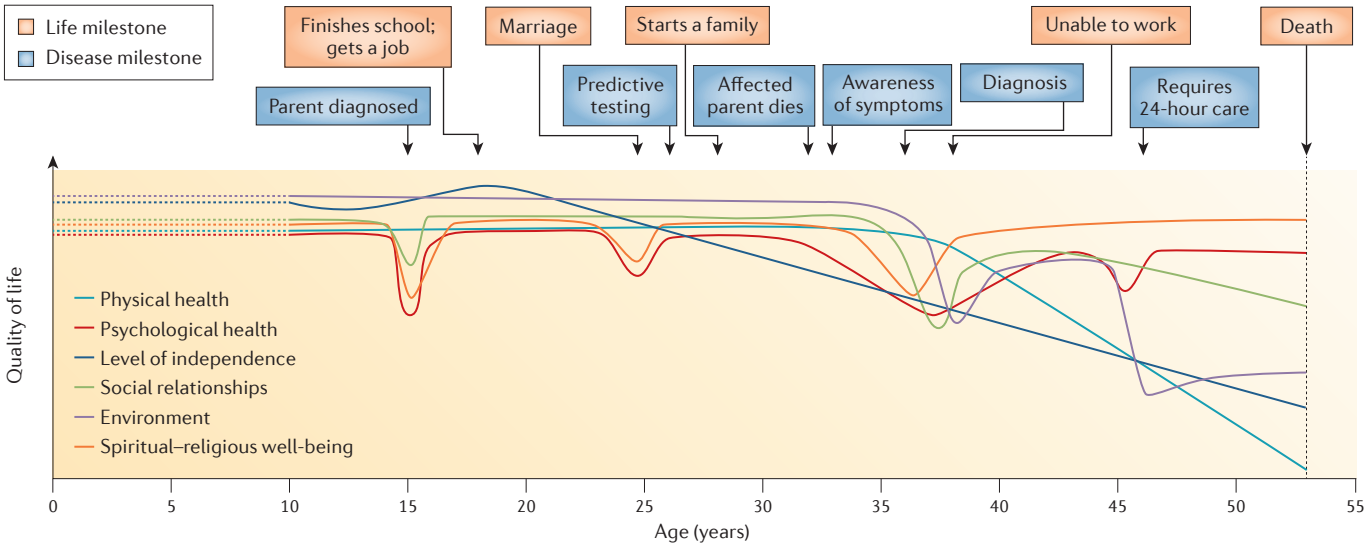

Figure 6 | **The impact of various life events and disease milestones on different domains of quality of life in a hypothetical person with Huntington disease.** The impact of the disease on an individual's quality of life begins long before the person has any symptoms of the disease. Quality-of-life domains are differentially affected by these events and milestones.

Cognitive and motor measures. Commonly used clinical rating scales such as the UHDRS might be insensitive to subtle changes over short periods of time, are subjective, susceptible to bias and are affected by inter-rater and intra-rater variability[118]. However, quantitative cognitive end points are emerging, such as the Huntington disease cognitive assessment battery (HD-CAB), which shows great potential for use in clinical trials in Huntington disease[175]. Unfortunately, many cognitive measures have substantial limitations owing to floor and ceiling effects and to confounding by the levels of education and moods of the patients. Accordingly, these measures might not be sensitive to subtle changes in cognitive function over time and might not respond to potential treatments. Quantitative motor assessments — such as finger tapping, grip force variability and tongue force measures — might counter such confounders and are currently being evaluated in Huntington disease drug trials[120].

Biosampling. Aside from these metrics, biomarker identification and quantification from various samples have yielded a number of candidates in Huntington disease, although none has yet been validated for therapeutic studies. The majority of published studies have examined the serum or plasma of patients, probably owing to the wide range of established analytical techniques available and the ease with which large volumes of samples can be obtained. Other components of blood such as erythrocytes, platelets or leukocytes are also potential sources of peripheral Huntington disease biomarkers[176,177]. Research in urine and saliva samples has been limited, despite the ease of obtaining these types of samples.

Recent attention has focused on samples derived from the central nervous system, specifically cerebrospinal fluid (CSF). The use of CSF for Huntington disease research is of great appeal because of its high concentration of brain-specific proteins[178]. Additionally, CSF studies have sparked a renewed interest in immune system dysfunction in Huntington disease[179]; elevated levels of cytokines (interleukin-6 (IL-6), IL-8 and clusterin) in CSF were found to correlate with disease progression[180,181]. However, sampling techniques, type of sample collected and analytic techniques vary widely between studies — often making comparisons difficult[182]. Furthermore, the relatively invasive lumbar puncture procedures required for CSF sample collection presents challenges in a wider clinical setting.

Electrophysiological measures. Electrophysiological measures such as electroencephalography have also been assessed in Huntington disease[183]. Alterations in visual[184], motor[185] and somatosensory[186]-related potentials have been reported, but small sample sizes and the variations in protocols make it difficult to draw conclusions about the usefulness of these potential biomarkers.

Pharmacodynamic biomarkers. Pharmacodynamic biomarkers for specific treatments are also a pressing need in Huntington disease research but will require validation for each drug. For example, *HTT*-silencing therapeutics are of great interest and are in development. Measurement of huntingtin levels in CSF might be a potential pharmacodynamic biomarker for these novel treatments. Indeed, the development of highly sensitive techniques to quantify low concentrations of mutant huntingtin in biofluids offers great hope for measuring the specific effects of these novel therapies. However, large-scale human studies are still needed to establish the utility of these types of clinical assays for use in clinical trials[177,187,188].

Longitudinal observational studies, including PREDICT-HD[34] and TRACK-HD[129,189], have identified

Table 2 | **Overview of potential biomarkers in Huntington disease**

Biomarker	Measure	Change	Ref.
Clinical			
Speeded tap interval	Q-motor	Increased	120
Grip force	Q-motor	Increased variability	120
HD-CAB	Cognitive	Increased score	175
Imaging			
Caudate volume	MRI	Decreased	129
Fractional anisotropy	Diffusion imaging	Decreased	257
Mean diffusivity		Increased	
Thalamic FDG activity	PET	Increased	193
Putaminal *N*-acetyleaspartate	MRS	Decreased	192
Putaminal myoinositol		Increased	
Electrophysiological			
Cortical activity	EEG	Decreased α-signal	183
Biochemical			
Neurofilament	CSF	Increased levels	258
Clusterin	Plasma	Increased levels	180
	CSF	Increased levels	
24-hydroxycholesterol	Plasma	Decreased levels	259
Pharmacodynamic			
Mutant huntingtin levels	CSF	Treatment response	187

CSF, cerebrospinal fluid; EEG, electroencephalography; FDG, fluorodeoxyglucose; HD-CAB, Huntington disease cognitive assessment battery; MRS, magnetic resonance spectroscopy; PET, positron-emission tomography.

a large number of potentially useful biomarkers that are currently being assessed in the context of ongoing investigational drug trials[6]. Predicting how a specific treatment will affect a given biomarker is difficult; thus, it is reasonable to assess multiple biomarkers in these studies. Furthermore, different combinations of biomarkers might be required to assess all the aspects of the disease that a drug targets. Along these lines, different biomarkers could be more useful at different points in the course of the disease, with some biomarkers correlating best with particular clinical features.

To date, only a few novel biomarkers have been assessed in drug studies in Huntington disease. Reported serum biomarkers, such as 8-hydroxy-2′-deoxyguanosine (8OHdG[190], a DNA oxidation product) or BDNF[191], have been evaluated in a few drug studies. However, these measures have not been validated; 8OHdG has specifically failed rigorous replication attempts[182]. Identification of reliable pharmacodynamic and state biomarkers will advance Huntington disease therapeutic development. Rigorous and blinded evaluation, including independent validation and assessment, of potential candidate biomarkers must be pursued to ensure that the potential benefits of biomarker development for Huntington disease is fully realized.

Neuroimaging. Imaging enables the visualization of the macroscopic neuropathological effects underlying Huntington disease, providing invaluable insights into the natural history of the disease[6]. However, a key focus now is the development and validation of imaging measures as biomarkers for use in clinical trials. Structural MRI shows considerable promise in this respect. For example, TRACK-HD[128,189] has identified progressive white matter atrophy across the spectrum of disease (FIG. 7). Measures such as caudate atrophy are robust across different scanners and are sensitive to disease effects, giving rise to large effect sizes that suggest sample sizes typical in clinical trials[129]. Altered metabolite patterns that are indicative of reduced neuronal health can be demonstrated using magnetic resonance spectroscopy[192], and this technique could be used to show a dynamic response to therapeutic intervention. Positron emission tomography (PET) imaging can highlight altered metabolic patterns[193,194]; a small open-label study recently demonstrated increased metabolic activity in response to pridopidine treatment[195]. In addition, PET imaging of microglial activation shows promise as a biomarker in the premanifest stages of the disease[196]. Many of these imaging modalities are currently being implemented as exploratory end points in ongoing clinical trials.

Future work is likely to focus on imaging techniques that provide additional information on the range of downstream effects of the presence of mutant huntingtin. For example, loss of connectivity within brain networks is increasingly recognized to occur many years before symptom onset and plays a key part in subsequent functional decline as cortico–striatal communication is compromised[197]; diffusion imaging coupled with advanced image analysis tools such as graph theory[198] are being implemented to provide detailed mapping of this changing connectivity. Brain activity can be interrogated using both task and resting-state functional MRI, and a growing number of PET tracers are available to highlight specific metabolic processes *in vivo*, such as depletion of dopamine receptors[199]. The relationship between imaging readouts and functional performance in Huntington disease is yet to be established, but future intervention studies are likely to provide insights.

Future clinical trials

Future clinical trials in Huntington disease will use broader objective measures of the disease, including quantitative motor assessments, biochemical biomarkers and imaging[112,200]. In addition, movement disorders with clear external manifestations that can be measured in response to treatment will see the implementation of innovative techniques, such as wearable sensors. These objective measures will initially be used to supplement subjective clinician-rated scales, but their applications and impact on movement disorder research are likely to expand over time[97,201].

Furthermore, future clinical trials aimed at modifying the underlying pathogenesis will increasingly rely on biological measures of disease activity to determine whether their action in humans mirrors that in animal studies. Future trials in Huntington disease will also

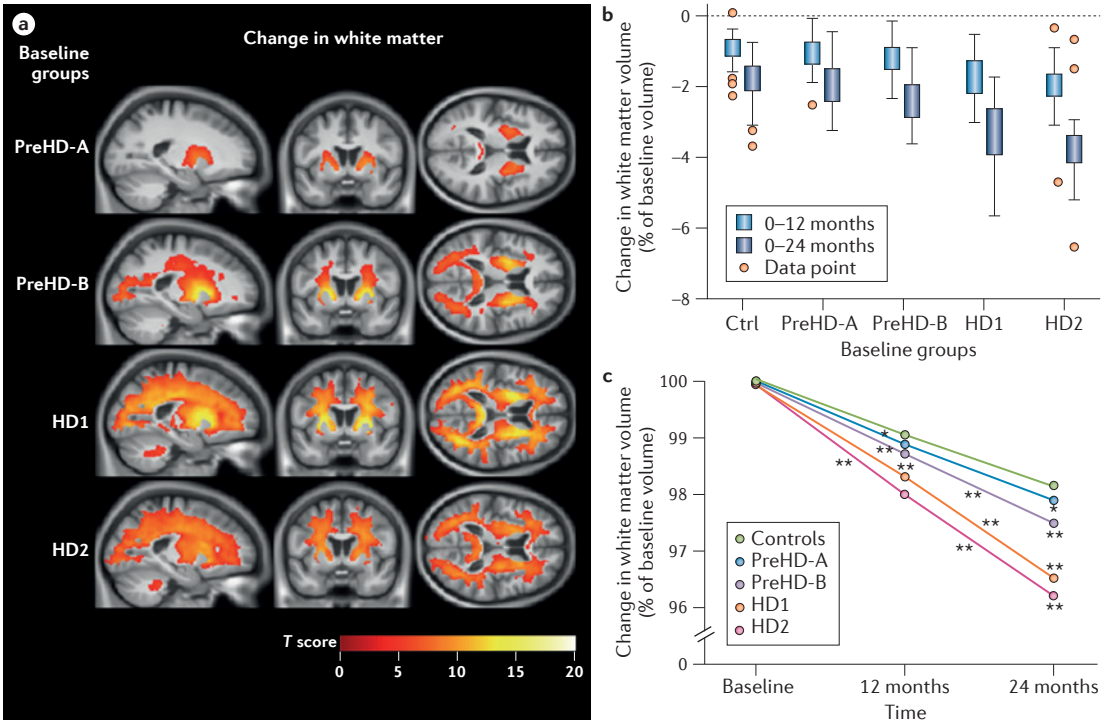

Figure 7 | **White matter atrophy across the spectrum of Huntington disease. a** | Statistical parametric maps, based on data from the TRACK-HD study, show regions with significant longitudinal change in white matter over 24 months relative to controls. Results were adjusted for age, sex, study site and scan interval, and are corrected for multiple comparisons with family-wise error at the $P < 0.05$ level. **b** | Boxplots show changes in white matter volume over 0–12 months and 0–24 months. **c** | The corresponding longitudinal plots show mean values at baseline, 12 months and 24 months. Significant change differences relative to controls over 0–12, 12–24 and 0–24 months are indicated; $*P < 0.05$, and $**P < 0.001$. Ctrl, control; PreHD-A, premanifest A (>10 years from predicted disease onset); PreHD-B, premanifest B (<10 years from predicted disease onset); HD1, stage 1 Huntington disease; HD2, Stage 2 Huntington disease. Reprinted from *Lancet Neurol.*, **11**, Tabrizi, S. J. *et al.*, Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK HD study: analysis of 24 month observational data., 42–53, Copyright (2012), with permission from Elsevier.

increasingly investigate intervention before the clear manifestation of symptoms. Because of its near-complete penetrance, evidence of its pathogenesis before symptom onset and potentially new regulatory framework for prodromal disorders, future trials will evaluate treatments in individuals who carry the expanded allele but do not yet have clear symptoms of the disease[189,202]. At least two previous trials in this population have demonstrated the feasibility of this approach[203,204].

The next decade will almost certainly witness more trials, increasingly aimed at the underlying pathogenesis[205,206]. With better means of assessing the efficacy of treatments (as has occurred in multiple sclerosis), screening and detection of potential efficacy will be easier and more informative. Huntington disease stands poised to become an increasingly treatable condition.

Experimental disease-modifying therapeutics. Our ever-increasing understanding of how mutant huntingtin causes neuronal dysfunction and death has produced a multitude of rational therapeutic targets (FIG. 8). Reducing production of mutant huntingtin ought to prevent its adverse effects. Indeed, 'designer' oligonucleotide-based therapeutics are being developed that bind to *HTT* mRNA selectively and target it for degradation by cellular mechanisms. When the agent is a short interfering RNA (siRNA) or microRNA, the *HTT* mRNA is degraded by cytoplasmic RNA-induced silencing complex (RISC) — a process known as RNA interference (RNAi). Alternatively, a single-stranded modified DNA molecule or antisense oligonucleotide (ASO) can be used to direct the transcript for degradation by nuclear ribonuclease H.

These methods now have a secure pedigree of preclinical success and have produced phenotypic reversal in multiple model systems[207–210]. However, delivery is a challenge: all such agents require direct administration to the central nervous system — intrathecally into the lumbar CSF for ASOs; and intraparenchymally or intraventricularly, encoded by a viral vector or infused under pressure, for RNAi. Two clinical trials have demonstrated safety and some efficacy signals for ASO-based drugs in familial amyotrophic lateral sclerosis[211] and spinal muscular atrophy[212]; the first clinical trial of an ASO therapeutic in Huntington disease is planned[213].

The first huntingtin-lowering drugs bind to both wild-type and mutant *HTT* mRNA, but allele-selective drugs are also under development. By targeting

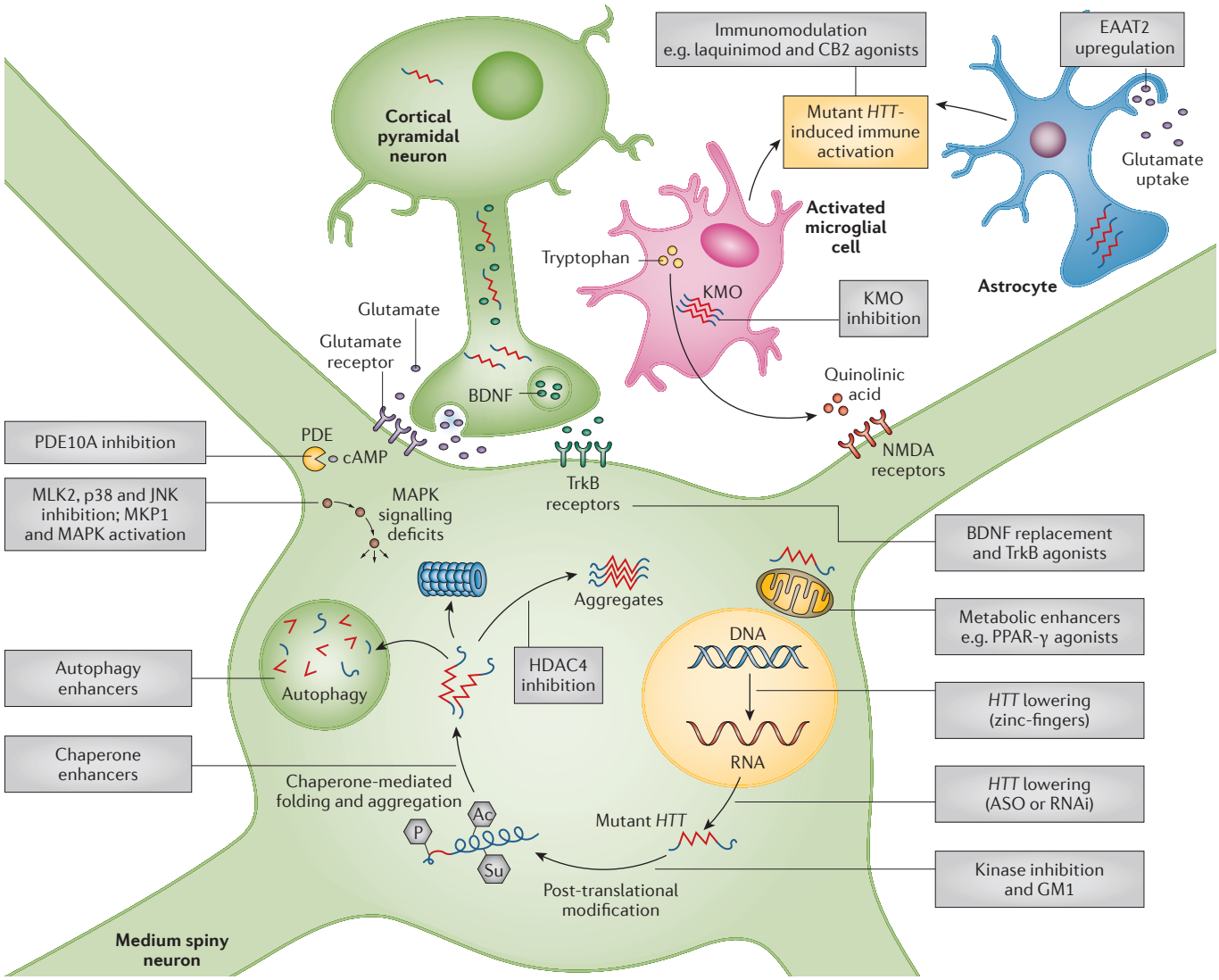

Figure 8 | **Current priority preclinical therapeutic targets under investigation for Huntington disease.** Several targets have been identified for potential exploitation in therapy, with strategies that include *HTT* lowering and immunomodulation[255]. Ac, acetyl group; ASO, antisense oligonucleotide; BDNF, brain-derived neurotrophic factor; CB2, cannabinoid receptor 2; EAAT2, excitatory amino acid transporter 2; GM1, monosialotetrahexosylganglioside; HDAC4, histone deacetylase 4; JNK, c-Jun N-terminal kinase (MAPK8, MAPK9 and MAPK10); KMO, kynurenine 3-monooxygenase; MAPK, mitogen-activated protein kinase; NMDA, *N*-methyl-D-aspartate; P, phosphate group; p38, mitogen-activated protein kinase (MAPK11, MAPK12, MAPK13 and MAPK14); PDE, phosphodiesterase; PPAR-γ, peroxisome proliferator-activated receptor-γ; RNAi, RNA interference; Su, sumoyl group; TrkB, tyrosine receptor kinase B. Figure adapted from REF. 6, Nature Publishing Group.

heterozygous single-nucleotide polymorphisms (SNPs) on the allele bearing the CAG expansion, these agents aim to avoid the theoretical risk of lowering wild-type huntingtin[214]. However, as each drug could only target a SNP found in a proportion of individuals, multiple agents would be needed to treat the majority of patients.

Zinc-finger therapeutics aim to achieve transcriptional repression of mutant *HTT* only and also to avoid possible toxicity from its mRNA. Necessitating viral delivery, these drugs face the same delivery challenges as RNA-based huntingtin-lowering drugs but have shown early promise in rodent models[215,216].

Some therapeutic approaches aim to reduce the toxicity of mutant huntingtin. Small-molecule kinase inhibitors might enhance PTMs, such as phosphorylation at serine residues 13, 16 and 421, which would encourage less-harmful forms or intracellular locations[217–219]. Such 'virtuous phosphorylation' has been suggested to underlie the striking phenotypic reversal seen in mouse models after intraventricular infusion of the ganglioside GM1, a member of a family of large membrane-associated organic molecules found abundantly in the central nervous system[220].

Therapeutic successes have also been reported from upregulating chaperone protein HSJ1a in transgenic

mice expressing human mutant HTT exon1 (REF. 221) and direct application of a recombinant chaperone moiety ApiCCT1 *in vitro*[222]. Several agents that enhance macroautophagy have been shown to enhance huntingtin clearance and improve phenotypes in model systems[223,224]. Selisistat, an inhibitor of the deacetylase sirtuin 1 (also known as NAD-dependent protein deacetylase sirtuin 1), produced beneficial effects in cell, fly and rodent Huntington disease models[225] and was recently shown to be safe and tolerable in patients[226].

Inhibition of histone deacetylases (HDACs) aims to prevent mutant huntingtin-induced transcriptional dysregulation. *HDAC4* knockdown produces potent phenotypic amelioration[227–230] but surprisingly does so through effects on cytoplasmic mutant huntingtin aggregation rather than transcriptional dysregulation[227]. This finding has prompted a reappraisal of previous success in mice with suberoylanilide hydroxamic acid, a nonselective HDAC inhibitor[231].

The phosphodiesterase PDE10A is a major modulator of striatal synaptic biology, regulating cAMP and cGMP signalling, synaptic plasticity and the response to cortical stimulation[232,233]. Treating model Huntington disease mice with a PDE10A inhibitor lessened motor deficits, striatal atrophy and neurotrophin depletion[234]. Two clinical trials of PDE10A inhibition are now underway[139,235].

Depletion of neurotrophins, especially BDNF, is a prominent feature of Huntington disease and a high-priority therapeutic target. However, direct or virally mediated delivery of neurotrophins is possible but challenging[236–238]. Agonism of the BDNF tyrosine receptor kinase B (TrkB) is appealing, but initial reports of successes[239,240] have not been replicated[241]; agonism by monoclonal antibodies is under investigation[241]. A clinical trial of cysteamine, which possibly acts through increasing BDNF levels, showed a suggestion of benefit in a subgroup analysis[158].

Many tractable aspects of glial function have been implicated in Huntington disease. Among the most promising are inhibition of kynurenine 3-monooxygenase (KMO), which determines the balance of excitotoxic and neuroprotective tryptophan metabolites produced by microglia[242] and has been implicated by numerous studies in model systems and by clinical trials[243,244]. The KMO inhibitor JM6 proved successful in a mouse model of the disease[174], and other KMO inhibitors are progressing towards clinical trials[245].

Modulation of the innate immune system, which is hyperactive in Huntington disease[181,246], is now a focus for therapeutics research. The first trial of an immunomodulatory agent, laquinimod, is beginning soon[247].

Finally, the mitogen-activated protein kinase (MAPK) signalling pathway is deranged in Huntington disease and presents numerous potential therapeutic targets, including activation of the dual-specificity protein phosphatase MKP1 (also known as DUSP1) and extracellular signal-regulated kinases or inhibition of MLK2 (also known as MAP3K10), c-Jun N-terminal kinases (MAPK8, MAPK9 and MAPK10) and p38 (MAPK11, MAPK12, MAPK13 and MAPK14)[248–253]. However, the complex intersecting pathways and their role in Huntington disease remain poorly understood. The same is true of the complex metabolic derangements in Huntington disease, for which extensive therapeutic trials have failed to yield clear success[254].

In this Primer, we have described the genetic and clinical diagnosis of Huntington disease, as well as the multidisciplinary management of symptoms. Although there are currently no effective disease-modifying therapies, past and present clinical trials have been carried out, and therapeutic strategies are under investigation. Importantly, there are impending trials of targeted huntingtin-lowering drugs, and the progress in development of biomarkers will support the next generation of trials.

1. Huntington, G. On chorea. *Med. Surg. Rep.* **26**, 320–321 (1872).
2. Fisher, E. R. & Hayden, M. R. Multisource ascertainment of Huntington disease in Canada: prevalence and population at risk. *Mov. Disord.* **29**, 105–114 (2014).
This study is the most recent and comprehensive ascertainment of patients with Huntington disease across a large, defined service area. It shows the combined use of genetic test results and clinical records to estimate the minimum and maximum prevalence of Huntington disease in a predominantly Caucasian population.
3. Morrison, P. J., Harding-Lester, S. & Bradley, A. Uptake of Huntington disease predictive testing in a complete population. *Clin. Genet.* **80**, 281–286 (2011).
4. Evans, S. J. W. *et al.* Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. *J. Neurol. Neurosurg. Psychiatry* **84**, 1156–1160 (2013).
5. The Huntington's Disease Collaborative Research Group A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. *Cell* **72**, 971–983 (1993).
This paper describes the identification and fundamental characteristics of the *HTT* genetic defect: a polymorphic CAG trinucleotide repeat in the coding sequence of huntingtin that is expanded beyond its normal size and that is unstable through intergenerational transmission.
6. Ross, C. A. *et al.* Huntington disease: natural history, biomarkers and prospects for therapeutics. *Nat. Rev. Neurol.* **10**, 204–216 (2014).
This review summarizes the current status of biomarker research in Huntington disease and places this process in the context of novel therapeutics in development and an improved understanding of the natural history of Huntington disease.
7. Kay, C., Fisher, E. R. & Hayden, M. R. in *Huntington's Disease* 4th edn Ch.7 (eds Bates, G. P., Tabrizi, S. J. & Jones, L.) (Oxford Univ. Press, 2014).
8. Morrison, P. J. Prevalence estimates of Huntington disease in Caucasian populations are gross underestimates. *Mov. Disord.* **27**, 1707–1709 (2012).
9. Almqvist, E. W., Elterman, D. S., MacLeod, P. M. & Hayden, M. R. 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 (2001).
10. Ramos-Arroyo, M. A., Moreno, S. & Valiente, A. Incidence and mutation rates of Huntington's disease in Spain: experience of 9 years of direct genetic testing. *J. Neurol. Neurosurg. Psychiatry* **76**, 337–342 (2005).
11. Koutsis, G., Karadima, G., Kladi, A. & Panas, M. Late-onset Huntington's disease: diagnostic and prognostic considerations. *Parkinsonism Relat. Disord.* **20**, 726–730 (2014).
12. Pringsheim, T. *et al.* The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. *Mov. Disord.* **27**, 1083–1091 (2012).
13. Hayden, M. R., MacGregor, J. M. & Beighton, P. H. The prevalence of Huntington's chorea in South Africa. *South Afr. Med. J.* **58**, 193–196 (1980).
14. Wexler, N. S. *et al.* Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. *Proc. Natl Acad. Sci. USA* **101**, 3498–3503 (2004).
15. Squitieri, F. *et al.* DNA haplotype analysis of Huntington disease reveals clues to the origins and mechanisms of CAG expansion and reasons for geographic variations of prevalence. *Hum. Mol. Genet.* **3**, 2103–2114 (1994).
This paper was the first to link specific haplotypes of the CAG expansion to high normal CAG repeat lengths in populations in which Huntington disease is more frequent, illuminating a genetic basis for variable prevalence of the disease.
16. Warby, S. C. *et al.* CAG expansion in the Huntington disease gene is associated with a specific and targetable predisposing haplogroup. *Am. J. Hum. Genet.* **84**, 351–366 (2009).
17. Costa, M. C. *et al.* The CAG repeat at the Huntington disease gene in the Portuguese population: insights into its dynamics and to the origin of the mutation. *J. Hum. Genet.* **51**, 189–195 (2006).
18. Semaka, A. *et al.* CAG size-specific risk estimates for intermediate allele repeat instability in Huntington disease. *J. Med. Genet.* **50**, 696–703 (2013).
19. Semaka, A. *et al.* High frequency of intermediate alleles on Huntington disease-associated haplotypes in British Columbia's general population. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **162**, 864–871 (2013).

20. Warby, S. C. *et al.* HTT haplotypes contribute to differences in Huntington disease prevalence between Europe and East Asia. *Eur. J. Hum. Genet.* **19**, 561–566 (2011).
21. Baine, F. K. *et al.* Huntington disease in the South African population occurs on diverse and ethnically distinct genetic haplotypes. *Eur. J. Hum. Genet.* **21**, 1120–1127 (2013).
22. Wheeler, V. C. *et al.* Factors associated with HD CAG repeat instability in Huntington disease. *J. Med. Genet.* **44**, 695–701 (2007).
23. Gusella, J. F. & Macdonald, M. Genetic criteria for Huntington's disease pathogenesis. *Brain Res. Bull.* **72**, 78–82 (2007).
This review summarizes the evidence that the disease process can be modified by other genetic factors prior to actual disease onset, suggesting a strategy to identify potential targets for therapeutic intervention from mutation carriers.
24. Gusella, J. F., MacDonald, M. E. & Lee, J. M. Genetic modifiers of Huntington's disease. *Mov. Disord.* **29**, 1359–1365 (2014).
25. Andrew, S. E. *et al.* The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. *Nat. Genet.* **4**, 398–403 (1993).
26. Duyao, M. *et al.* Trinucleotide repeat length instability and age of onset in Huntington's disease. *Nat. Genet.* **4**, 387–392 (1993).
27. Lee, J. M. *et al.* CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion. *Neurology* **78**, 690–695 (2012).
This paper establishes that the *HTT* mutation leads to motor onset in a completely dominant manner such that the length of the expanded CAG repeat both represents the trigger of Huntington disease pathogenesis and determines its rate, with no contribution of the normal-length CAG repeat in 'heterozygotes' or of a second expanded allele in 'homozygotes'.
28. Snell, R. G. *et al.* Relationship between trinucleotide repeat expansion and phenotypic variation in Huntington's disease. *Nat. Genet.* **4**, 393–397 (1993).
29. Rosenblatt, A. *et al.* Age, CAG repeat length, and clinical progression in Huntington disease. *Mov. Disord.* **27**, 272–276 (2012).
30. Aylward, E. *et al.* Association between age and striatal volume stratified by CAG repeat length in prodromal Huntington disease. *PLoS Curr.* **3**, RRN1235 (2011).
31. Seong, I. S. *et al.* HD CAG repeat implicates a dominant property of huntingtin in mitochondrial energy metabolism. *Hum. Mol. Genet.* **14**, 2871–2880 (2005).
32. Reis, S. A. *et al.* Striatal neurons expressing full-length mutant huntingtin exhibit decreased N-cadherin and altered neuritogenesis. *Hum. Mol. Genet.* **20**, 2344–2355 (2011).
33. HD iPSC Consortium. Induced pluripotent stem cells from patients with Huntington's disease show CAG-repeat-expansion-associated phenotypes. *Cell Stem Cell* **11**, 264–278 (2012).
34. Paulsen, J. S. *et al.* Detection of Huntington's disease decades before diagnosis: the Predict-HD study. *J. Neurol. Neurosurg. Psychiatry* **79**, 874–880 (2008).
35. Zuccato, C. & Cattaneo, E. in *Huntington's Disease* (eds Bates, G. P., Tabrizi, S. J. & Jones, L.) 243–273 (Oxford Univ. Press, 2014).
This recent review chapter summarizes current knowledge about the molecular evolution, post-translational modification, distribution and normal functions of the huntingtin protein.
36. Andrade, M. A. & Bork, P. HEAT repeats in the Huntington's disease protein [letter]. *Nat. Genet.* **11**, 115–116 (1995).
37. Wetzel, R. & Mishra, R. in *Huntington's Disease* (eds Bates, G. P., Tabrizi, S. J. & Jones, L.) 274–322 (Oxford Univ. Press, 2014).
This recent review chapter summarizes current knowledge about the structure of the huntingtin protein and its important exon 1 fragment, and how expanded polyQ versions of huntingtin fragments form aberrant molecular species that might be responsible for triggering Huntington disease.
38. Aiken, C. T. *et al.* Phosphorylation of threonine 3: implications for huntingtin aggregation and neurotoxicity. *J. Biol. Chem.* **284**, 29427–29436 (2009).
39. Atwal, R. S. *et al.* Huntingtin has a membrane association signal that can modulate huntingtin aggregation, nuclear entry and toxicity. *Hum. Mol. Genet.* **16**, 2600–2615 (2007).
40. Tam, S. *et al.* The chaperonin TRiC blocks a huntingtin sequence element that promotes the conformational switch to aggregation. *Nat. Struct. Mol. Biol.* **16**, 1279–1285 (2009).
41. Cornett, J. *et al.* Polyglutamine expansion of huntingtin impairs its nuclear export. *Nat. Genet.* **37**, 198–204 (2005).
42. Rockabrand, E. *et al.* The first 17 amino acids of huntingtin modulate its sub-cellular localization, aggregation and effects on calcium homeostasis. *Hum. Mol. Genet.* **16**, 61–77 (2007).
43. Steffan, J. S. *et al.* SUMO modification of huntingtin and Huntington's disease pathology. *Science* **304**, 100–104 (2004).
44. Jayaraman, M. *et al.* Slow amyloid nucleation via α-helix-rich oligomeric intermediates in short polyglutamine-containing huntingtin fragments. *J. Mol. Biol.* **415**, 881–999 (2012).
45. Thakur, A. K. *et al.* Polyglutamine disruption of the huntingtin exon 1 N terminus triggers a complex aggregation mechanism. *Nat. Struct. Mol. Biol.* **16**, 380–389 (2009).
46. Michalek, M., Salnikov, E. S., Werten, S. & Bechinger, B. Membrane interactions of the amphipathic amino terminus of huntingtin. *Biochemistry* **52**, 847–858 (2013).
47. Wetzel, R. Physical chemistry of polyglutamine: intriguing tales of a monotonous sequence. *J. Mol. Biol.* **421**, 466–490 (2012).
48. Faber, P. W. *et al.* Huntingtin interacts with a family of WW domain proteins. *Hum. Mol. Genet.* **7**, 1463–1474 (1998).
49. Caron, N. S., Desmond, C. R., Xia, J. & Truant, R. Polyglutamine domain flexibility mediates the proximity between flanking sequences in huntingtin. *Proc. Natl Acad. Sci. USA* **110**, 14610–14615 (2013).
50. Arrasate, M., Mitra, S., Schweitzer, E. S., Segal, M. R. & Finkbeiner, S. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. *Nature* **431**, 805–810 (2004).
51. Davies, S. W. *et al.* Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. *Cell* **90**, 537–548 (1997).
52. DiFIGlia, M. *et al.* Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. *Science* **277**, 1990–1993 (1997).
53. Sahl, S. J., Weiss, L. E., Duim, W. C., Frydman, J. & Moerner, W. E. Cellular inclusion bodies of mutant huntingtin exon 1 obscure small fibrillar aggregate species. *Sci. Rep.* **2**, 895 (2012).
54. Poirier, M. A. *et al.* Huntingtin spheroids and protofibrils as precursors in polyglutamine fibrilization. *J. Biol. Chem.* **277**, 41032–41037 (2002).
55. Landles, C. *et al.* Proteolysis of mutant huntingtin produces an exon 1 fragment that accumulates as an aggregated protein in neuronal nuclei in Huntington disease. *J. Biol. Chem.* **285**, 8808–8823 (2010).
56. Marcellin, D. *et al.* Fragments of HdhQ150 mutant huntingtin form a soluble oligomer pool that declines with aggregate deposition upon aging. *PLoS ONE* **7**, e44457 (2012).
57. Scherzinger, E. *et al.* Self-assembly of polyglutamine-containing huntingtin fragments into amyloid-like fibrils: implications for Huntington disease pathology. *Proc. Natl Acad. Sci. USA* **96**, 4604–4609 (1999).
58. Chen, S., Berthelier, V., Yang, W. & Wetzel, R. Polyglutamine aggregation behavior *in vitro* supports a recruitment mechanism of cytotoxicity. *J. Mol. Biol.* **311**, 173–182 (2001).
59. Morley, J. F., Brignull, H. R., Weyers, J. J. & Morimoto, R. I. The threshold for polyglutamine-expansion protein aggregation and cellular toxicity is dynamic and influenced by aging in *Caenorhabditis elegans*. *Proc. Natl Acad. Sci. USA* **99**, 10417–10422 (2002).
60. Ossato, G. *et al.* A two-step path to inclusion formation of huntingtin peptides revealed by number and brightness analysis. *Biophys. J.* **98**, 3078–3085 (2010).
61. Chen, S., Ferrone, F. A. & Wetzel, R. Huntington's disease age-of-onset linked to polyglutamine aggregation nucleation. *Proc. Natl Acad. Sci. USA* **99**, 11884–11889 (2002).
62. Lunkes, A. *et al.* Proteases acting on mutant huntingtin generate cleaved products that differentially build up cytoplasmic and nuclear inclusions. *Mol. Cell* **10**, 259–269 (2002).
63. Landwehrmeyer, G. B. *et al.* Huntington's disease gene: regional and cellular expression in brain of normal and affected individuals. *Ann. Neurol.* **37**, 218–230 (1995).
64. Sathasivam, K. *et al.* Aberrant splicing of HTT generates the pathogenic exon 1 protein in Huntington disease. *Proc. Natl Acad. Sci. USA* **110**, 2366–2370 (2013).
65. Hughes, A. & Jones, L. in *Huntington's Disease* (eds Bates, G. P., Tabrizi, S. J. & Jones, L.) 323–369 (Oxford Univ. Press, 2014).
66. Trottier, Y. *et al.* Polyglutamine expansion as a pathological epitope in Huntington's disease and four dominant cerebellar ataxias. *Nature* **378**, 403–406 (1995).
67. Klein, F. A. C. *et al.* Linear and extended: a common polyglutamine conformation recognized by the three antibodies MW1, 1C2 and 3B5H10. *Hum. Mol. Genet.* **22**, 4215–4223 (2013).
68. Levine, M. S., Wang, E. A., Chen, J. Y., Cepeda, C. & Andre, V. M. in *Huntington's Disease* (eds Bates, G. P., Tabrizi, S. J. & Jones, L.) 218–242 (Oxford Univ. Press, 2014).
69. Kennedy, L. *et al.* Dramatic tissue-specific mutation length increases are an early molecular event in Huntington disease pathogenesis. *Hum. Mol. Genet.* **12**, 3359–3367 (2003).
70. Gonitel, R. *et al.* DNA instability in postmitotic neurons. *Proc. Natl Acad. Sci. USA* **105**, 3467–3472 (2008).
71. Manley, K., Shirley, T. L., Flaherty, L. & Messer, A. Msh2 deficiency prevents *in vivo* somatic instability of the CAG repeat in Huntington disease transgenic mice. *Nat. Genet.* **23**, 471–473 (1999).
This was the first paper to show that ablation of the mismatch repair system prevents somatic instability in mouse models of Huntington disease, which prompted many further studies.
72. Tome, S. *et al. MSH3* polymorphisms and protein levels affect CAG repeat instability in Huntington's disease mice. *PLoS Genet.* **9**, e1003280 (2013).
73. Pinto, R. M. *et al.* Mismatch repair genes Mlh1 and Mlh3 modify CAG instability in Huntington's disease mice: genome-wide and candidate approaches. *PLoS Genet.* **9**, e1003930 (2013).
74. Kovalenko, M. *et al.* Msh2 acts in medium-spiny striatal neurons as an enhancer of CAG instability and mutant huntingtin phenotypes in Huntington's disease knock-in mice. *PLoS ONE* **7**, e44273 (2012).
75. Wheeler, V. C. *et al.* Mismatch repair gene *Msh2* modifies the timing of early disease in Hdh(Q111) striatum. *Hum. Mol. Genet.* **12**, 273–281 (2003).
76. Swami, M. *et al.* Somatic expansion of the Huntington's disease CAG repeat in the brain is associated with an earlier age of disease onset. *Hum. Mol. Genet.* **18**, 3039–3047 (2009).
77. Kim, M. *et al.* Mutant huntingtin expression in clonal striatal cells: dissociation of inclusion formation and neuronal survival by caspase inhibition. *J. Neurosci.* **19**, 964–973 (1999).
78. Moffitt, H., McPhail, G. D., Woodman, B., Hobbs, C. & Bates, G. P. Formation of polyglutamine inclusions in a wide range of non-CNS tissues in the HdhQ150 knock-in mouse model of Huntington's disease. *PLoS ONE* **4**, e8025 (2009).
79. Frost, B. & Diamond, M. I. Prion-like mechanisms in neurodegenerative diseases. *Nat. Rev. Neurosci.* **11**, 155–159 (2010).
80. Yang, W., Dunlap, J. R., Andrews, R. B. & Wetzel, R. Aggregated polyglutamine peptides delivered to nuclei are toxic to mammalian cells. *Hum. Mol. Genet.* **11**, 2905–2917 (2002).
81. Ren, P. H. *et al.* Cytoplasmic penetration and persistent infection of mammalian cells by polyglutamine aggregates. *Nat. Cell Biol.* **11**, 219–225 (2009).
82. Cicchetti, F. *et al.* Mutant huntingtin is present in neuronal grafts in Huntington disease patients. *Ann. Neurol.* **76**, 31–42 (2014).
83. Pecho-Vrieseling, E. *et al.* Transneuronal propagation of mutant huntingtin contributes to non-cell autonomous pathology in neurons. *Nat. Neurosci.* **17**, 1064–1072 (2014).
84. Kazantsev, A., Preisinger, E., Dranovsky, A., Goldgaber, D. & Housman, D. Insoluble detergent-resistant aggregates form between pathological and nonpathological lengths of polyglutamine in mammalian cells. *Proc. Natl Acad. Sci. USA* **96**, 11404–11409 (1999).

85. Balch, W. E., Morimoto, R. I., Dillin, A. & Kelly, J. W. Adapting proteostasis for disease intervention. *Science* **319**, 916–919 (2008).
86. Labbadia, J. & Morimoto, R. I. Huntington's disease: underlying molecular mechanisms and emerging concepts. *Trends Biochem. Sci.* **38**, 378–385 (2013).
87. Vidal, R., Caballero, B., Couve, A. & Hetz, C. Converging pathways in the occurrence of endoplasmic reticulum (ER) stress in Huntington's disease. *Curr. Mol. Med.* **11**, 1–12 (2011).
88. Ortega, Z. & Lucas, J. J. Ubiquitin-proteasome system involvement in Huntington's disease. *Front. Mol. Neurosci.* **7**, 77 (2014).
89. Martin, D. D. O., Ladha, S., Ehrnhoefer, D. E. & Hayden, M. R. Autophagy in Huntington disease and huntingtin in autophagy. *Trends Neurosci.* **38**, 26–35 (2014).
90. Labbadia, J. *et al.* Altered chromatin architecture underlies progressive impairment of the heat shock response in mouse models of Huntington disease. *J. Clin. Invest.* **121**, 3306–3319 (2011).
91. Seredenina, T. & Luthi-Carter, R. What have we learned from gene expression profiles in Huntington's disease? *Neurobiol. Dis.* **45**, 83–98 (2012).
92. Reddy, P. H. & Shirendeb, U. P. Mutant huntingtin, abnormal mitochondrial dynamics, defective axonal transport of mitochondria, and selective synaptic degeneration in Huntington's disease. *Biochim. Biophys. Acta* **1822**, 101–110 (2012).
93. Johri, A., Chandra, A. & Beal, M. F. PGC-1α, mitochondrial dysfunction, and Huntington's disease. *Free Radic. Biol. Med.* **62**, 37–46 (2013).
94. Nithianantharajah, J. & Hannan, A. J. Dysregulation of synaptic proteins, dendritic spine abnormalities and pathological plasticity of synapses as experience-dependent mediators of cognitive and psychiatric symptoms in Huntington's disease. *Neuroscience* **251**, 66–74 (2013).
95. Ellrichmann, G., Reick, C., Saft, C. & Linker, R. A. The role of the immune system in Huntington's disease. *Clin. Dev. Immunol.* **2013**, 541259 (2013).
96. Wang, N. *et al.* Neuronal targets for reducing mutant huntingtin expression to ameliorate disease in a mouse model of Huntington disease. *Nat. Med.* **20**, 536–541 (2014).
97. Huntington Study Group Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group. *Mov. Disord.* **11**, 136–142 (1996).
98. Reilmann, R., Leavitt, B. R. & Ross, C. A. Diagnostic criteria for Huntington's disease based on natural history. *Mov. Disord.* **29**, 1335–1341 (2014).
99. Cardoso, F. Differential diagnosis of Huntington disease: what the clinician should know. *Neurodegener. Dis. Manag.* **4**, 67–72 (2014).
100. Williamson, S., Kirkpatrick, M., Greene, S. & Goudie, D. A novel mutation of *NKX2-1* affecting 2 generations with hypothyroidism and choreoathetosis: part of the spectrum of brain-thyroid-lung syndrome. *J. Child Neurol.* **29**, 666–669 (2014).
101. Hensman Moss, D. J. *et al.* C9orf72 expansions are the most common genetic cause of Huntington disease phenocopies. *Neurology* **82**, 292–299 (2014).
102. Craufurd, D. *et al.* Diagnostic genetic testing for Huntington's disease. *Pract. Neurol.* **15**, 80–84 (2015).
103. International Huntington Association (IHA) and the World Federation of Neurology (WFN) Research Group on Huntington's Chorea Guidelines for the molecular genetics predictive test in Huntington's disease. *Neurology* **44**, 1533–1536 (1994).
104. MacLeod, R. *et al.* Experiences of predictive testing in young people at risk of Huntington's disease, familial cardiomyopathy or hereditary breast and ovarian cancer. *Eur. J. Hum. Genet.* **22**, 396–401 (2014).
105. Hawkins, A. K., Creighton, S., Ho, A., McManus, B. & Hayden, M. R. Providing predictive testing for Huntington disease via telehealth: results of a pilot study in British Columbia, Canada. *Clin. Genet.* **84**, 60–64 (2013).
106. De Die-Smulders, C. E. M., de Wert, G. M. W. R., Liebaers, I., Tibben, A. & Evers-Kiebooms, G. Reproductive options for prospective parents in families with Huntington's disease: clinical, psychological and ethical reflections. *Hum. Reprod. Update* **19**, 304–315 (2013).
107. Schulman, J. D. & Stern, H. J. Low utilization of prenatal and preimplantation genetic diagnosis in Huntington disease — risk discounting in preventive genetics. *Clin. Genet.* http://dx.doi.org/10.1111/cge.12523 (2014).
108. Van Rij, M. C. *et al.* The uptake and outcome of prenatal and pre-implantation genetic diagnosis for Huntington's disease in the Netherlands (1998–2008). *Clin. Genet.* **85**, 87–95 (2014).
109. Semaka, A. & Hayden, M. R. Evidence-based genetic counselling implications for Huntington disease intermediate allele predictive test results. *Clin. Genet.* **85**, 303–311 (2014).
110. Langbehn, D. R., Hayden, M. R. & Paulsen, J. S. CAG-repeat length and the age of onset in Huntington disease (HD): a review and validation study of statistical approaches. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.* **153B**, 397–408 (2010).
111. Rosenblatt, A. *et al.* The association of CAG repeat length with clinical progression in Huntington disease. *Neurology* **66**, 1016–1020 (2006).
112. Tabrizi, S. J. *et al.* 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 (2013).
This paper showed the additional power of a range of biomarkers, beyond that of age and CAG, for predicting conversion to manifest disease and subsequent clinical progression.
113. Penney, J. B., Vonsattel, J. P., MacDonald, M. E., Gusella, J. F. & Myers, R. H. CAG repeat number governs the development rate of pathology in Huntington's disease. *Ann. Neurol.* **41**, 689–692 (1997).
114. Warner, J. H. & Hayden, M. A new model for age-at-onset in Huntington's disease. *Found. Huntington' Dis. Ther. Conference* (2012).
115. Dorsey, E. R. *et al.* Natural history of Huntington disease. *JAMA Neurol.* **70**, 1520–1530 (2013).
116. Paulsen, J. S. *et al.* Clinical and biomarker changes in premanifest Huntington disease show trial feasibility: a decade of the PREDICT-HD study. *Front. Aging Neurosci.* **6**, 78 (2014).
117. Rosenblatt, A. *et al.* Predictors of neuropathological severity in 100 patients with Huntington's disease. *Ann. Neurol.* **54**, 488–493 (2003).
118. Hogarth, P. *et al.* Interrater agreement in the assessment of motor manifestations of Huntington's disease. *Mov. Disord.* **20**, 293–297 (2005).
119. Reilmann, R. *et al.* Grasping premanifest Huntington's disease — shaping new endpoints for new trials. *Mov. Disord.* **25**, 2858–2862 (2010).
120. Reilmann, R. *et al.* Q-motor – Quantitative motor assessments: Potential novel endpoints for clinical trials in pre-manifest and symptomatic Huntington's disease – 36 months longitudinal results from the multicenter TRACK-HD study. *Basal Ganglia* **3**, 67–68 (2013).
121. Stout, J. C. *et al.* Neurocognitive signs in prodromal Huntington disease. *Neuropsychology* **25**, 1–14 (2011).
122. Peavy, G. M. *et al.* Cognitive and functional decline in Huntington's disease: dementia criteria revisited. *Mov. Disord.* **25**, 1163–1169 (2010).
123. Aretouli, E. & Brandt, J. Episodic memory in dementia: Characteristics of new learning that differentiate Alzheimer's, Huntington's, and Parkinson's diseases. *Arch. Clin. Neuropsychol.* **25**, 396–409 (2010).
124. Folstein, S. E., Jensen, B., Leigh, R. J. & Folstein, M. F. The measurement of abnormal movement: methods developed for Huntington's disease. *Neurobehav. Toxicol. Teratol.* **5**, 605–609 (1983).
125. Stout, J. C. *et al.* Evaluation of longitudinal 12 and 24 month cognitive outcomes in premanifest and early Huntington's disease. *J. Neurol. Neurosurg. Psychiatry* **83**, 687–694 (2012).
126. Duff, K. *et al.* "Frontal" behaviors before the diagnosis of Huntington's disease and their relationship to markers of disease progression: evidence of early lack of awareness. *J. Neuropsychiatry Clin. Neurosci.* **22**, 196–207 (2010).
127. Papoutsi, M., Labuschagne, I., Tabrizi, S. J. & Stout, J. C. The cognitive burden in Huntington's disease: pathology, phenotype, and mechanisms of compensation. *Mov. Disord.* **29**, 673–683 (2014).
128. Tabrizi, S. J. *et al.* Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurol.* **10**, 31–42 (2011).
129. Tabrizi, S. J. *et al.* Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. *Lancet Neurol.* **11**, 42–53 (2012).
This paper defined a battery of potential outcome measures with utility for clinical trials in early Huntington disease.
130. Thompson, J. C. *et al.* Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. *J. Neuropsychiatry Clin. Neurosci.* **24**, 53–60 (2012).
131. Killoran, A. & Biglan, K. M. Current therapeutic options for Huntington's disease: Good clinical practice versus evidence-based approaches? *Mov. Disord.* **29**, 1404–1413 (2014).
132. Van Duijn, E. *et al.* Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). *J. Neurol. Neurosurg. Psychiatry* **85**, 1411–1418 (2014).
133. Nance, M. A. Comprehensive care in Huntington's disease: a physician's perspective. *Brain Res. Bull.* **72**, 175–178 (2007).
134. Simpson, S. A. & Rae, D. A standard of care for Huntington's disease: who, what and why. *Neurodegener. Dis. Manag.* **2**, 1–5 (2012).
135. Klager, J., Duckett, A., Sandler, S. & Moskowitz, C. Huntington's disease: a caring approach to the end of life. *Care Manag. J.* **9**, 75–81 (2008).
136. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. *Neurology* **66**, 366–372 (2006).
137. Jankovic, J. & Roos, R. A. C. Chorea associated with Huntington's disease: to treat or not to treat? *Mov. Disord.* **29**, 1414–1418 (2014).
138. Gonzalez, V. *et al.* Deep brain stimulation for Huntington's disease: long-term results of a prospective open-label study. *J. Neurosurg.* **121**, 114–122 (2014).
139. Study evaluating the safety, tolerability and brain function of 2 doses of PF-02545920 in subjects with early Huntington's disease [online], https://www.clinicaltrials.gov/ct2/show/NCT01806896 (2014).
140. First time use of SD-809 in Huntington disease (first-HD) [online], https://clinicaltrials.gov/ct2/show/NCT01795859 (2013).
141. Mestre, T. A. & Ferreira, J. J. An evidence-based approach in the treatment of Huntington's disease. *Parkinsonism Relat. Disord.* **18**, 316–320 (2012).
142. Bonelli, R. M. & Hofmann, P. A systematic review of the treatment studies in Huntington's disease since 1990. *Expert Opin. Pharmacother.* **8**, 141–153 (2007).
This is a systematic review of clinical pharamcological trials in Huntington disease through the mid-2000s.
143. Burgunder, J.-M. *et al.* An international survey-based algorithm for the pharmacologic treatment of chorea in Huntington's disease. *PLoS Curr.* **3**, RRN1260 (2011).
144. Groves, M. *et al.* An international survey-based algorithm for the pharmacologic treatment of irritability in Huntington's disease. *PLoS Curr.* **3**, RRN1259 (2011).
145. Anderson, K. *et al.* An international survey-based algorithm for the pharmacologic treatment of obsessive-compulsive behaviors in Huntington's disease. *PLoS Curr.* **3**, RRN1261 (2011).
146. Ribaï, P. *et al.* Psychiatric and cognitive difficulties as indicators of juvenile huntington disease onset in 29 patients. *Arch. Neurol.* **64**, 813–819 (2007).
147. Quarrell, O. W. J. *et al.* Managing juvenile Huntington's disease. *Neurodegener. Dis. Manag.* **3**, 267–276 (2013).
This is a summary of the current approaches to the management of juvenile-onset Huntington disease, emphasizing areas in which the management differs from that of adult-onset disease.
148. Dellefield, M. E. & Ferrini, R. Promoting Excellence in End-of-Life Care: lessons learned from a cohort of nursing home residents with advanced Huntington disease. *J. Neurosci. Nurs.* **43**, 186–192 (2011).
149. Nance, M. A. & Sanders, G. Characteristics of individuals with Huntington disease in long-term care. *Mov. Disord.* **11**, 542–548 (1996).
150. Moskowitz, C. B. & Marder, K. Palliative care for people with late-stage Huntington's disease. *Neurol. Clin.* **19**, 849–865 (2001).
151. Bonelli, R. M. & Wenning, G. K. Pharmacological management of Huntington's disease: an evidence-based review. *Curr. Pharm. Des.* **12**, 2701–2720 (2006).
This comprehensive review critically examines the evidence for a wide range of pharmaceutical agents for Huntington disease and finds little evidence for any treatment recommendation.
152. Braun, M. M., Farag-El-Massah, S., Xu, K. & Coté, T. R. Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. *Nat. Rev. Drug Discov.* **9**, 519–522 (2010).

153. Woodcock, J. The future of orphan drug development. *Clin. Pharmacol. Ther.* **92**, 146–148 (2012).
154. Huntington Study Group HART Investigators. A randomized, double-blind, placebo-controlled trial of pridopidine in Huntington's disease. *Mov. Disord.* **28**, 1407–1415 (2013).
155. De Yebenes, J. G. *et al.* Pridopidine for the treatment of motor function in patients with Huntington's disease (MermaiHD): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet. Neurol.* **10**, 1049–1057 (2011).
156. Huntington Study Group Reach2HD Investigators. Safety, tolerability, and efficacy of PBT2 in Huntington's disease: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* **14**, 39–47 (2015).
157. Leuti, A. *et al.* Phosphodiesterase 10A (PDE10A) localization in the R6/2 mouse model of Huntington's disease. *Neurobiol. Dis.* **52**, 104–116 (2013).
158. Raptor Pharmaceuticals. Raptor announces clinical results with rp103 in Huntington's disease Phase 2/3 trial [online], http://ir.raptorpharma.com/releasedetail.cfm?releaseid=826962 (2014).
159. Coenzyme Q10 in Huntington disease. *Huntingdon Study Group* [online], http://www.huntington-study-group.org/CurrentHSGClinicalTrials/2CARE/tabid/95/Default.aspx (2014).
160. Announcement of CREST-E early study group. *Huntingdon Study Group* [online], http://www.huntington-study-group.org/CurrentHSGClinicalTrials/CRESTE/tabid/105/Default.aspx (2014).
161. Van der Meer, L. B., van Duijn, E., Wolterbeek, R. & Tibben, A. Adverse childhood experiences of persons at risk for Huntington's disease or *BRCA1/2* hereditary breast/ovarian cancer. *Clin. Genet.* **81**, 18–23 (2012).
162. Driessnack, M., Williams, J. K., Barnette, J. J., Sparbel, K. J. & Paulsen, J. S. Development of the HD-Teen Inventory. *Clin. Nurs. Res.* **21**, 213–223 (2012).
163. Quaid, K. A. *et al.* Living at risk: concealing risk and preserving hope in Huntington disease. *J. Genet. Couns.* **17**, 117–128 (2008).
This paper includes pieces of patient experiences, which emphasizes the importance of qualitative experience in our understanding of quality of life in Huntington disease.
164. Hocaoglu, M. B., Gaffan, E. A. & Ho, A. K. The Huntington's disease health-related quality of life questionnaire (HDQoL): a disease-specific measure of health-related quality of life. *Clin. Genet.* **81**, 117–122 (2012).
165. Hocaoglu, M. B., Gaffan, E. A. & Ho, A. K. Health-related quality of life in Huntington's disease patients: a comparison of proxy assessment and patient self-rating using the disease-specific Huntington's disease health-related quality of life questionnaire (HDQoL). *J. Neurol.* **259**, 1793–1800 (2012).
166. Clay, E. *et al.* Validation of the first quality-of-life measurement for patients with Huntington's disease: the Huntington Quality of Life Instrument. *Int. Clin. Psychopharmacol.* **27**, 208–214 (2012).
167. Carlozzi, N. E. *et al.* HD-PRO-TRIAD™ validation: a patient-reported instrument for the symptom triad of Huntington's disease. *Tremor Other Hyperkinet. Mov.* **4**, 223 (2014).
168. Read, J. *et al.* Quality of life in Huntington's disease: a comparative study investigating the impact for those with pre-manifest and early manifest disease, and their partners. *J. Huntingtons. Dis.* **2**, 159–175 (2013).
169. Ho, A. K., Gilbert, A. S., Mason, S. L., Goodman, A. O. & Barker, R. A. Health-related quality of life in Huntington's disease: Which factors matter most? *Mov. Disord.* **24**, 574–578 (2009).
170. Carlozzi, N. E. & Tulsky, D. S. Identification of health-related quality of life (HRQOL) issues relevant to individuals with Huntington disease. *J. Health Psychol.* **18**, 212–225 (2013).
This is an initial report from one of the groups working to develop a Huntington disease-specific tool for measuring quality of life.
171. Wheelock, V. L. *et al.* Predictors of nursing home placement in Huntington disease. *Neurology* **60**, 998–1001 (2003).
172. Rosenblatt, A., Kumar, B. V., Margolis, R. L., Welsh, C. S. & Ross, C. A. Factors contributing to institutionalization in patients with Huntington's disease. *Mov. Disord.* **26**, 1711–1716 (2011).
173. Booij, S. J., Tibben, A., Engberts, D. P., Marinus, J. & Roos, R. A. C. Thinking about the end of life: a common issue for patients with Huntington's disease. *J. Neurol.* **261**, 2184–2191 (2014).
174. Zwilling, D. *et al.* Kynurenine 3-monooxygenase inhibition in blood ameliorates neurodegeneration. *Cell* **145**, 863–874 (2011).
JM6, a drug acting peripherally to produce inhibition of KMO in the central nervous system, extended survival in a Huntington disease model mouse. In addition to supporting KMO inhibition as a target, this study raises the prospect of developing therapies that do not cross the blood–brain barrier but that can produce benefits in the central nervous system nonetheless.
175. Stout, J. C. *et al.* HD-CAB: a cognitive assessment battery for clinical trials in Huntington's disease 1,2,3. *Mov. Disord.* **29**, 1281–1288 (2014).
This paper examines a large number of quantitative cognitive tests and develops a concise battery of cognitive assessments that are specifically designed for use as a clinical trial end point in Huntington disease therapeutic trials.
176. Weir, D. W., Sturrock, A. & Leavitt, B. R. Development of biomarkers for Huntington's disease. *Lancet Neurol.* **10**, 573–590 (2011).
177. Weiss, A. *et al.* Mutant huntingtin fragmentation in immune cells tracks Huntington's disease progression. *J. Clin. Invest.* **122**, 3731–3736 (2012).
178. Fang, Q. *et al.* Brain-specific proteins decline in the cerebrospinal fluid of humans with Huntington disease. *Mol. Cell. Proteom.* **8**, 451–466 (2009).
179. Wild, E., Björkqvist, M. & Tabrizi, S. J. Immune markers for Huntington's disease? *Expert Rev. Neurother.* **8**, 1779–1781 (2008).
180. Dalrymple, A. *et al.* Proteomic profiling of plasma in Huntington's disease reveals neuroinflammatory activation and biomarker candidates. *J. Proteome Res.* **6**, 2833–2840 (2007).
181. Björkqvist, M. *et al.* A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. *J. Exp. Med.* **205**, 1869–1877 (2008).
182. Borowsky, B. *et al.* 8OHdG is not a biomarker for Huntington disease state or progression. *Neurology* **80**, 1934–1941 (2013).
This paper resolves an outstanding issue in the field and shows unequivocally that 8OHdG is not a clinically useful biomarker in Huntington disease. It also establishes an important series of recommendations that should be considered for future biomarker validation studies.
183. Nguyen, L., Bradshaw, J. L., Stout, J. C., Croft, R. J. & Georgiou-Karistianis, N. Electrophysiological measures as potential biomarkers in Huntington's disease: review and future directions. *Brain Res. Rev.* **64**, 177–194 (2010).
184. Beste, C., Saft, C., Andrich, J., Gold, R. & Falkenstein, M. Stimulus-response compatibility in Huntington's disease: a cognitive-neurophysiological analysis. *J. Neurophysiol.* **99**, 1213–1223 (2008).
185. Beste, C. *et al.* Alterations in voluntary movement execution in Huntington's disease are related to the dominant motor system: evidence from event-related potentials. *Exp. Neurol.* **216**, 148–157 (2009).
186. Beniczky, S. *et al.* Somatosensory evoked potentials correlate with genetics in Huntington's disease. *Neuroreport* **13**, 2295–2298 (2002).
187. Weiss, A. *et al.* Single-step detection of mutant huntingtin in animal and human tissues: a bioassay for Huntington's disease. *Anal. Biochem.* **395**, 8–15 (2009).
188. Moscovitch-Lopatin, M. *et al.* Optimization of an HTRF assay for the detection of soluble mutant Huntingtin in Human Buffy Coats: A Potential Biomarker in Blood for Huntington disease. *PLoS Curr.* **2**, RRN1205 (2010).
189. Tabrizi, S. J. *et al.* Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *Lancet. Neurol.* **8**, 791–801 (2009).
190. Hersch, S. M. *et al.* Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG. *Neurology* **66**, 250–252 (2006).
191. Squitieri, F. *et al.* Riluzole protects Huntington disease patients from brain glucose hypometabolism and grey matter volume loss and increases production of neurotrophins. *Eur. J. Nucl. Med. Mol. Imag.* **36**, 1113–1120 (2009).
192. Sturrock, A. *et al.* Magnetic resonance spectroscopy biomarkers in premanifest and early Huntington disease. *Neurology* **75**, 1702–1710 (2010).
193. Eidelberg, D. & Surmeier, D. J. Brain networks in Huntington disease. *J. Clin. Invest.* **121**, 484–492 (2011).
This is a detailed review of techniques for identifying disease-related alterations in metabolic activity and their potential use in clinical trials.
194. Tang, C. C. *et al.* Metabolic network as a progression biomarker of premanifest Huntington's disease. *J. Clin. Invest.* **123**, 4076–4088 (2013).
195. Esmaeilzadeh, M., Kullingsjö, J., Ullman, H., Varrone, A. & Tedroff, J. Regional cerebral glucose metabolism after pridopidine (ACR16) treatment in patients with Huntington disease. *Clin. Neuropharmacol.* **34**, 95–100 (2011).
196. Tai, Y. F. *et al.* Microglial activation in presymptomatic Huntington's disease gene carriers. *Brain* **130**, 1759–1766 (2007).
197. Poudel, G. R. *et al.* White matter connectivity reflects clinical and cognitive status in Huntington's disease. *Neurobiol. Dis.* **65**, 180–187 (2014).
198. Bullmore, E. & Sporns, O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat. Rev. Neurosci.* **10**, 186–198 (2009).
199. Pavese, N. *et al.* Cortical dopamine dysfunction in symptomatic and premanifest Huntington's disease gene carriers. *Neurobiol. Dis.* **37**, 356–361 (2010).
200. Sampaio, C., Borowsky, B. & Reilmann, R. Clinical trials in Huntington's disease: interventions in early clinical development and newer methodological approaches. *Mov. Disord.* **29**, 1419–1428 (2014).
201. Reilmann, R., Bohlen, S., Kirsten, F., Ringelstein, E. B. & Lange, H. W. Assessment of involuntary choreatic movements in Huntington's disease — toward objective and quantitative measures. *Mov. Disord.* **26**, 2267–2273 (2011).
This study provides evidence for the use of in-clinic quantitative motor assessments that are now increasingly used as an objective measure in Huntington disease clinical trials.
202. Kozauer, N. & Katz, R. Regulatory innovation and drug development for early-stage Alzheimer's disease. *N. Engl. J. Med.* **368**, 1169–1171 (2013).
203. Rosas, H. D. *et al.* PRECREST: a Phase II prevention and biomarker trial of creatine in at-risk Huntington disease. *Neurology* **82**, 850–857 (2014).
204. Chandra, A., Johri, A. & Beal, M. F. Prospects for neuroprotective therapies in prodromal Huntington's disease. *Mov. Disord.* **29**, 285–293 (2014).
205. Gusella, J. F. *et al.* A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* **306**, 234–238 (1983).
206. Olding-Smee, L. Biomedical philanthropy: The money tree. *Nature* **447**, 251–251 (2007).
207. Harper, S. Q. *et al.* RNA interference improves motor and neuropathological abnormalities in a Huntington's disease mouse model. *Proc. Natl Acad. Sci. USA* **102**, 5820–5825 (2005).
208. Carroll, J. B. *et al.* Potent and selective antisense oligonucleotides targeting single-nucleotide polymorphisms in the Huntington disease gene / allele-specific silencing of mutant huntingtin. *Mol. Ther.* **19**, 2178–2185 (2011).
209. Stanek, L. M. *et al.* Silencing mutant huntingtin by AAV-mediated RNAi ameliorates disease manifestations in the YAC128 mouse model of Huntington's disease. *Hum. Gene Ther.* **25**, 461–474 (2014).
210. Kordasiewicz, H. B. *et al.* Sustained therapeutic reversal of Huntington's disease by transient repression of huntingtin synthesis. *Neuron* **74**, 1031–1044 (2012).
This is an important demonstration that huntingtin lowering, achieved through an antisense oligonucleotide drug of the kind entering clinical trials in the near future, produces reversal of Huntington disease manifestations in model rodents that outlasts the presence of the compound, supporting the notion of a 'huntingtin holiday' — a brief or minor repression of HTT synthesis that enables significant recovery through cellular repair mechanisms.
211. Miller, T. M. *et al.* An antisense oligonucleotide against SOD1 delivered intrathecally for patients with SOD1 familial amyotrophic lateral sclerosis: a phase 1, randomised, first-in-man study. *Lancet Neurol* **12**, 435–442 (2013).
212. Isis Pharmaceuticals reports data from ISIS-SMN Rx Phase 2 studies in infants and children with spinal muscular atrophy. *ISIS Pharmaceuticals* [online], http://ir.isispharm.com/phoenix.zhtml?c=222170&p=irol-newsArticle&ID=1976144 (2014).

213. Tabrizi, S. J. Huntingtin lowering as a treatment for Huntington's disease. *European Huntington's Disease Network Plenary Meeting* (2014).
214. Dragatsis, I., Levine, M. S. & Zeitlin, S. Inactivation of *Hdh* in the brain and testis results in progressive neurodegeneration and sterility in mice. *Nat. Genet.* **26**, 300–306 (2000).
215. Garriga-Canut, M. *et al.* Synthetic zinc finger repressors reduce mutant huntingtin expression in the brain of R6/2 mice. *Proc. Natl Acad. Sci.* **109**, E3136–E3145 (2012).
216. Zeitler, S. B.*et al.* Allele-specific repression of mutant Huntingtin expression by engineered zinc finger transcriptional repressors as a potential therapy for Huntington's disease. *Society for Neuroscience Annual Meeting* [online], http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=036f4722-3981-4c95-a391-6d5e2d3a2433&cKey=612cd78d-04f2-42de-9d00-49f3591b9536&mKey=8d2a5bec-4825-4cd6-9439-b42bb151d1cf (2013).
217. Gu, X. *et al.* Serines 13 and 16 are critical determinants of full-length human mutant huntingtin induced disease pathogenesis in HD mice. *Neuron* **64**, 828–840 (2009).
218. Atwal, R. S. *et al.* Kinase inhibitors modulate huntingtin cell localization and toxicity. *Nat. Chem. Biol.* **7**, 453–460 (2011).
219. Zala, D. *et al.* Phosphorylation of mutant huntingtin at S421 restores anterograde and retrograde transport in neurons. *Hum. Mol. Genet.* **17**, 3837–3846 (2008).
220. Di Pardo, A. *et al.* Ganglioside GM1 induces phosphorylation of mutant huntingtin and restores normal motor behavior in Huntington disease mice. *Proc. Natl Acad. Sci.* **109**, 3528–3533 (2012).
221. Labbadia, J. *et al.* Suppression of protein aggregation by chaperone modification of high molecular weight complexes. *Brain* **135**, 1180–1196 (2012).
222. Sontag, E. M. *et al.* Exogenous delivery of chaperonin subunit fragment ApiCCT1 modulates mutant Huntingtin cellular phenotypes. *Proc. Natl Acad. Sci. USA* **110**, 3077–3082 (2013).
223. Ravikumar, B. *et al.* Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nat. Genet.* **36**, 585–595 (2004).
224. Renna, M., Jimenez-Sanchez, M., Sarkar, S. & Rubinsztein, D. C. Chemical inducers of autophagy that enhance the clearance of mutant proteins in neurodegenerative diseases. *J. Biol. Chem.* **285**, 11061–11067 (2010).
225. Smith, M. R. *et al.* A potent and selective Sirtuin 1 inhibitor alleviates pathology in multiple animal and cell models of Huntington's disease. *Hum. Mol. Genet.* **23**, 2995–3007 (2014).
226. Reilmann, R. *et al.* Safety and tolerability of selisistat for the treatment of Huntington's disease: results from a randomized, double-blind, placebo-controlled Phase II trial (S47.004). *Neurology* **82**, S47.004 (2014).
227. Mielcarek, M. *et al.* HDAC4 reduction: a novel therapeutic strategy to target cytoplasmic huntingtin and ameliorate neurodegeneration. *PLoS Biol.* **11**, e1001717 (2013).
228. Moumné, L., Campbell, K., Howland, D., Ouyang, Y. & Bates, G. P. Genetic knock-down of *HDAC3* does not modify disease-related phenotypes in a mouse model of Huntington's disease. *PLoS ONE* **7**, e31080 (2012).
229. Bobrowska, A., Paganetti, P., Matthias, P. & Bates, G. P. *Hdac6* knock-out increases tubulin acetylation but does not modify disease progression in the R6/2 mouse model of Huntington's disease. *PLoS ONE* **6**, e20696 (2011).
230. Benn, C. L. *et al.* Genetic knock-down of *HDAC7* does not ameliorate disease pathogenesis in the R6/2 mouse model of Huntington's disease. *PLoS ONE* **4**, e5747 (2009).
231. Hockly, E. *et al.* Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. *Proc. Natl Acad. Sci. USA* **100**, 2041–2046 (2003).
232. Threlfell, S., Sammut, S., Menniti, F. S., Schmidt, C. J. & West, A. R. Inhibition of phosphodiesterase 10a increases the responsiveness of striatal projection neurons to cortical stimulation. *J. Pharmacol. Exp. Ther.* **328**, 785–795 (2009).
233. Threlfell, S. & West, A. R. Modulation of striatal neuron activity by cyclic nucleotide signalling and phosphodiesterase inhibition. *Basal Ganglia* **3**, 137–146 (2013).
234. Giampà, C. *et al.* Inhibition of the striatal specific phosphodiesterase PDE10A ameliorates striatal and cortical pathology in R6/2 mouse model of Huntington disease. *PLoS ONE* **5**, e13417 (2010).
235. Safety and efficacy of OMS643762 in subjects with *Huntington's* disease. [online], https://clinicaltrials.gov/ct2/show/NCT02074410 (2014).
236. Kells, A. P. *et al.* AAV-mediated gene delivery of *BDNF* or *GDNF* is neuroprotective in a model of Huntington disease. *Mol. Ther.* **9**, 682–688 (2004).
237. Pineda, J. R. *et al.* Neuroprotection by GDNF-secreting stem cells in a Huntington's disease model: optical neuroimage tracking of brain-grafted cells. *Gene Ther.* **14**, 118–128 (2006).
238. Marks Jr., W. J. *et al.* Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial. *Lancet Neurol.* **9**, 1164–1172 (2010).
239. Jiang, M. *et al.* Small-molecule TrkB receptor agonists improve motor function and extend survival in a mouse model of Huntington's disease. *Hum. Mol. Genet.* **22**, 2462–2470 (2013).
240. Simmons, D. A. *et al.* A small molecule TrkB ligand reduces motor impairment and neuropathology in R6/2 and BACHD mouse models of Huntington's disease. *J. Neurosci.* **33**, 18712–18727 (2013).
241. Todd, D. *et al.* A monoclonal antibody TrkB receptor agonist as a potential therapeutic for Huntington's disease. *PLoS ONE* **9**, e87923 (2014).
242. Vecsei, L., Szalardy, L., Fulop, F. & Toldi, J. Kynurenines in the CNS: recent advances and new questions. *Nat. Rev. Drug Discov.* **12**, 64–82 (2013).
243. Giorgini, F., Guidetti, P., Nguyen, Q., Bennett, S. C. & Muchowski, P. J. A genomic screen in yeast implicates kynurenine 3-monooxygenase as a therapeutic target for Huntington disease. *Nat. Genet.* **37**, 526–531 (2005).
244. Campesan, S. *et al.* The kynurenine pathway modulates neurodegeneration in a *Drosophila* model of Huntington's disease. *Curr. Biol.* **21**, 961–966 (2011).
245. Mrzljak, L. Development of kynurenine monooxygenase (K. M. O.) inhibitor C. H.D. I.-340246 for the treatment of Huntington's disease: a progress update. *CHDI Foundation 7th Annual HD Therapeutics Conference* (2013).
246. Träger, U. *et al.* HTT-lowering reverses Huntington's disease immune dysfunction caused by NFκB pathway dysregulation. *Brain* **137**, 819–833 (2014).
247. A clinical study in subjects with Huntington's disease to assess the efficacy and safety of three oral doses of laquinimod. [online], https://clinicaltrials.gov/ct2/show/NCT02215616 (2014).
248. Gianfriddo, M., Melani, A., Turchi, D., Giovannini, M. G. & Pedata, F. Adenosine and glutamate extracellular concentrations and mitogen-activated protein kinases in the striatum of Huntington transgenic mice. Selective antagonism of adenosine A2A receptors reduces transmitter outflow. *Neurobiol. Dis.* **17**, 77–88 (2004).
249. Liu, Y. F. Expression of polyglutamine-expanded huntingtin activates the SEK1–JNK pathway and induces apoptosis in a hippocampal neuronal cell line. *J. Biol. Chem.* **273**, 28873–28877 (1998).
250. Apostol, B. L. *et al.* Mutant huntingtin alters MAPK signaling pathways in PC12 and striatal cells: ERK1/2 protects against mutant huntingtin-associated toxicity. *Hum. Mol. Genet.* **15**, 273–285 (2006).
251. Ferrante, R. J. *et al.* Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice. *J. Neurosci.* **23**, 9418–9427 (2003).
252. Taylor, D. M. *et al.* MAP kinase phosphatase 1 (MKP-1/DUSP1) is neuroprotective in Huntington's disease via additive effects of JNK and p38 inhibition. *J. Neurosci.* **33**, 2313–2325 (2013).
253. Apostol, B. L. *et al.* CEP-1347 reduces mutant huntingtin-associated neurotoxicity and restores BDNF levels in R6/2 mice. *Mol. Cell. Neurosci.* **39**, 8–20 (2008).
254. Mrzljak, L. & Munoz-Sanjuan, I. Therapeutic strategies for Huntington's disease. *Curr. Top. Behav. Neurosci.* http://dx.doi.org/10.1007/7854_2013_250 (2013).
255. Wild, E. J. & Tabrizi, S. J. Targets for future clinical trials in Huntington's disease: what's in the pipeline? *Mov. Disord.* **29**, 1434–1445 (2014).
256. Omeros provides update on PDE10 inhibitor program. *PRNewswire* [online], http://www.prnewswire.com/news-releases/omeros-provides-update-on-pde10-inhibitor-program-322137646.html (2014)
257. Hobbs, N. Z. *et al.* Evaluation of multi-modal, multi-site neuroimaging measures in Huntington's disease: baseline results from the PADDINGTON study. *NeuroImage. Clin.* **2**, 204–211 (2012).
258. Constantinescu, R., Zetterberg, H., Holmberg, B. & Rosengren, L. Levels of brain related proteins in cerebrospinal fluid: an aid in the differential diagnosis of parkinsonian disorders. *Parkinsonism Relat. Disord.* **15**, 205–212 (2009).
259. Leoni, V. *et al.* Plasma 24S-hydroxycholesterol and caudate MRI in pre-manifest and early Huntington's disease. *Brain* **131**, 2851–2859 (2008).

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Author contributions

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Competing interests statement

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