Huntington's disease

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Huntington's disease is an autosomal-dominant, progressive neurodegenerative disorder with a distinct phenotype, including chorea and dystonia, incoordination, cognitive decline, and behavioural difficulties. Typically, onset of symptoms is in middle-age after affected individuals have had children, but the disorder can manifest at any time between infancy and senescence. The mutant protein in Huntington's disease—huntingtin—results from an expanded CAG repeat leading to a polyglutamine strand of variable length at the N-terminus. Evidence suggests that this tail confers a toxic gain of function. The precise pathophysiological mechanisms of Huntington's disease are poorly understood, but research in transgenic animal models of the disorder is providing insight into causative factors and potential treatments.

The hereditary nature of chorea was noted in the 19th century by several doctors,[1–4] but George Huntington's vivid description led to the eponymous designation of the disorder as Huntington's disease.[5] Over the next few decades, the worldwide distribution of the disorder and its juvenile form were recorded. The discovery of the causal *HD* gene (table 1) has stimulated research, and work is now focusing on molecular mechanisms of disease.

See Online for webmovie

Year	Event	Publications (n)*
1374	Epidemic dancing mania described	..
1500	Paracelsus suggests CNS origin for chorea	..
1686	Thomas Sydenham describes post-infectious chorea	..
1832	John Elliotson identifies inherited form of chorea[1]	..
1872	George Huntington characterises Huntington's disease[5]	..
1953	DNA structure elucidated	5
1955	Huntington's disease described in Lake Maracaibo region of Venezuela	13
1967	World Federation of Neurology meeting on Huntington's disease	38
1976	First animal model (kainic acid) of Huntington's disease described[6]	100
1983	Gene marker for Huntington's disease discovered	138
1993	HD gene identified;[7] Huntington study group formed for clinical trials	172
1996	Transgenic mouse developed[8]	242
2000	Drugs screened for effectiveness in transgenic animal models	344

*Approximate number of publications on Huntington's disease cited for that year in the Current List of Medical Literature (before 1966) and in PubMed (1967 onwards).

Table 1: **History of Huntington's disease**

Search strategy and selection criteria

I searched Pub Med from 1965-2005 for the term "Huntington's Disease" cross referenced with the terms "apoptosis", "axonal transport", "mitochondria", "animal model", "proteosome", "transcription", "juvenile", "suicide", "neurotransmitters", "age of onset", "identical twins", "neurodegeneration", and "imaging". I translated all non-English language publications that resulted from this search strategy. I mainly selected articles from the past five years, but did not exclude commonly referenced and highly regarded older publications. I also searched the reference lists of articles identified by this search strategy and selected those that I judged relevant. Several review articles and book chapters were included because they provide comprehensive overviews beyond the scope of this Seminar. The reference list was further modified during the peer-review process based on comments from the reviewers.

Clinical findings in Huntington's disease

Individuals with Huntington's disease can become symptomatic at any time between the ages of 1 and 80 years; before then, they are are healthy and have no detectable clinical abnormalities.[9] This healthy period merges imperceptibly with a prediagnostic phase, when patients show subtle changes of personality, cognition, and motor control. Both the healthy and prediagnostic stages are sometimes called presymptomatic, but in fact the prediagnostic phase is associated with findings, even though patients can be unaware of them.[10] Diagnosis takes place when findings become sufficiently developed and specific.[11] In the prediagnostic phase, individuals might become irritable or disinhibited and unreliable at work; multitasking becomes difficult and forgetfulness and anxiety mount. Family members note restlessness or fidgeting, sometimes keeping their partners awake at night.[4] Eventually, this stage merges with the diagnostic phase (see webmovie), during which time affected individuals show distinct chorea, incoordination, motor impersistence, and slowed saccadic eye movements.[12,13]

Cognitive dysfunction in Huntington's disease, often spares long-term memory but impairs executive functions, such as organising, planning, checking, or adapting alternatives, and delays the acquisition of new motor skills.[4,14] These features worsen over time; speech deteriorates faster than comprehension. Unlike cognition, psychiatric and behavioural symptoms arise with some frequency but do not show stepwise progression with disease severity. Depression is typical and suicide is estimated to be about five to ten times that of the general population (about 5–10%).[14–17] Manic and psychotic symptoms can develop.[4]

Suicidal ideation is a frequent finding in patients with Huntington's disease. In a cross-sectional study, about 9% of asymptomatic at-risk individuals contemplated suicide at least occasionally,[11] perhaps a result of being raised by an affected parent and awareness of the disease. In the prediagnostic phase, the proportion rose to 22%, but in patients who had been recently diagnosed, suicidal ideation was lower. The frequency increased again in later stages of the illness.[11] The correlation of suicidal ideation with suicide has not been studied in people with Huntington's disease, but suicide attempts are not

uncommon. In one study, researchers estimated that more than 25% of patients attempt suicide at some point in their illness.[18] Individuals without children might be at amplified risk,[19,20] and for these people access to suicidal means (ie, drugs or weapons) should be restricted. The presence of affective symptoms, specific suicidal plans, or actions that increase isolation (eg, divorce, giving away pets) warrants similar precautions.[20]

Although useful for diagnosis, chorea (figure 1) is a poor marker of disease severity.[21,22] Patients with early-onset Huntington's disease might not develop chorea, or it might arise only transiently during their illness. Most individuals have chorea that initially progresses but then, with later onset of dystonia and rigidity, it becomes less prominent.[21,22]

Another finding in Huntington's disease that contributes to patients' overactivity is motor impersistence—the inability to maintain a voluntary muscle contraction at a constant level (figure 2).[23] This difficulty leads to changes in position and sometimes compensatory repositioning. Incapacity to apply steady pressure during handshake is characteristic of Huntington's disease and is called milkmaid's grip. Motor impersistence is independent of chorea and is linearly progressive, making it a possible surrogate marker of disease severity.[7]

Fine motor skills, such as finger-tapping rhythm and rate, are useful for establishing an early diagnosis of Huntington's disease: gross motor coordination skills, including gait and postural maintenance, deteriorate later in the disorder's course. Such changes, unlike chorea, directly impair function, a finding that is, in part, indicated by the modern preference for the terminology Huntington's disease rather than Huntington's chorea.

As motor and cognitive deficits become severe, patients eventually die, usually from complications of falls, inanition, dysphagia, or aspiration. Typical latency from diagnosis to death is 20 years.[4]

Huntington's disease in juveniles (onset before age 20 years and as early as 2 years) and some adults can present with rigidity without signs of chorea.[2,24,25] Such individuals can be misdiagnosed with Parkinson's disease, catatonia, or schizophrenia. Slowed saccadic eye movements are usually prominent in these patients—jerking of the head to look to the side is characteristic. Seizures are fairly typical in young patients and cerebellar dysfunction can arise.[24,25] A decline in motor milestones or school performance is sometimes an early finding in children with Huntington's disease.

Differential diagnosis

Diagnosis of Huntington's disease is straightforward in patients with typical symptoms and a family history. However, dentatorubropallidoluysian atrophy,[26] Huntington's disease-like 2 (frequent in black Americans and South Africans),[27] and a few other familial disorders[28,29] are phenotypically indistinguishable from the disorder. Furthermore, about 8% of patients do not have a known affected family member.[30,31] Neuroacanthocytosis can also mimic Huntington's disease,[32] but areflexia, raised creatine kinase, and the presence of acanthocytes are distinctive. Huntington's disease should not be confused with tardive dyskinesia, chorea gravidarum, hyperthyroid chorea, vascular hemichorea, the sometimes unilateral post-infectious (Sydenham's) chorea, and chorea associated with antibodies against phospholipids. By comparison with Huntington's disease, these disorders have a different time course, are not familial, and do not have motor impersistence, impaired saccades, and cognitive decline as characteristics. In young people, Huntington's disease can be confused with hepatolenticular degeneration and subacute sclerosing panencephalitis.

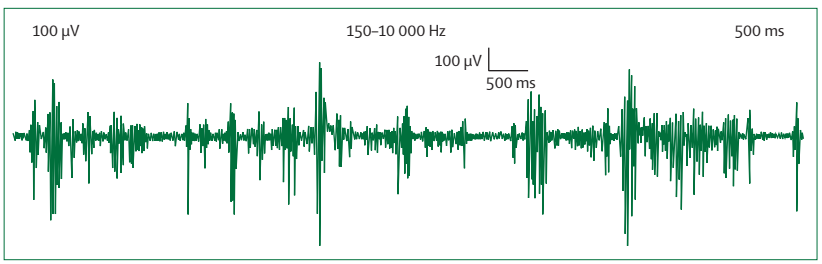


Figure 1: **EMG recording of chorea in patient with stage I Huntington's disease**
Recording is made with standard belly tendon using surface disc electrodes placed over the first dorsal interosseus muscle. Note the irregular pattern of discharges, with variable amplitude, duration, and rise times of every EMG burst. Healthy individuals at rest show no EMG activity.

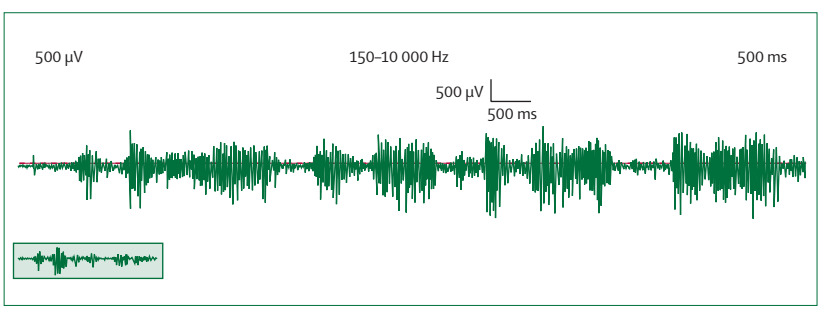


Figure 2: **EMG recording of motor impersistence**
The patient is instructed to maximally abduct the second digit against resistance and to maintain it. Note that motor activity fades repeatedly. The parenthetical inclusion is a copy of the first 400 ms of resting chorea shown in figure 1, adjusted for the different amplitude settings, for comparison. Note that choreiform bursts intermittently exceed the EMG activity from maximum volitional effort. Healthy individuals show consistent EMG amplitude during this task.

Neuropathology

Neuropathological changes in Huntington's disease are strikingly selective, with prominent cell loss and atrophy in the caudate and putamen.[33–35] Striatal medium spiny neurons are the most vulnerable. Those that contain enkephalin and that project to the external globus pallidum are more involved than neurons that contain substance P and project to the internal globus pallidum.[33,34] Interneurons are generally spared. These findings accord with the hypothesis that chorea dominates early in the course of Huntington's disease because of preferential involvement of the indirect

pathway of basal ganglia-thalamocortical circuitry.[11] Other brain areas greatly affected in people with Huntington's disease include the substantia nigra, cortical layers 3, 5, and 6, the CA1 region of the hippocampus,[36] the angular gyrus in the parietal lobe,[37,38] Purkinje cells of the cerebellum,[39] lateral tuberal nuclei of the hypothalamus,[40,41] and the centromedial-parafascicular complex of the thalamus.[42]

In early symptomatic stages of Huntington's disease, the brain could be free of neurodegeneration.[43–45] However, evidence of neuronal dysfunction is abundant, even in asymptomatic individuals. Cortical neurons show decreased staining of nerve fibres, neurofilaments, tubulin, and microtubule-associated protein 2 and diminished complexin 2 concentrations.[46,47] These elements are associated with synaptic function, cytoskeletal integrity, and axonal transport and suggest an important role for cortical dysfunction in the pathogenesis of the disorder.

One of the pathological characteristics of Huntington's disease is the appearance of nuclear and cytoplasmic inclusions that contain mutant huntingtin and polyglutamine.[48] Although indicative of pathological polyglutamine processing, and apparent in affected individuals long before symptom onset,[43] mounting evidence suggests that these inclusions are not predictors of cellular dysfunction or disease activity, which instead seem to be mediated by intermediate stages of polyglutamine aggregates.[49] In some transgenic mouse models of Huntington's disease, inclusions arise only after symptoms begin.[50] Cells that have inclusions seem to survive longer than those without,[51] and little correlation is seen between the various cellular and animal models of the disorder and human Huntington's disease, in terms of the appearance of inclusions in histopathological specimens and the onset of dysfunction or neurological symptoms.[43,50–54] A compound that enhances aggregate formation might actually lessen neuronal pathological findings.[55]

Imaging

Routine MRI and CT in moderate-to-severe Huntington's disease show a loss of striatal volume and increased size of the frontal horns of the lateral ventricles,[56] but scans are usually unhelpful for diagnosis of early disorder. Data from PET and functional MRI studies have shown that changes take place in affected brains before symptom onset,[57–59] and some MRI techniques can precisely measure cortex and striatum.[60,61] In fact, with these techniques, caudate atrophy becomes apparent as early as 11 years before the estimated onset of the disease and putaminal atrophy as early as 9 years.[61] In presymptomatic individuals carrying the *HD* gene who show no evidence of progression by clinical or neuropsychological tests over 2 years, tensor-based magnetic resonance morphometry shows progressive loss of striatal volume.[62]

Clinical genetics

The gene for Huntington's disease (*HD*) is located on the short arm of chromosome four and is associated with an expanded trinucleotide repeat. Normal alleles at this site contain CAG repeats, but when these repeats reach 41 or more the disease is fully penetrant.[34,63,64] Incomplete penetrance happens with 36–40 repeats, and 35 or less are not associated with the disorder. The number of CAG repeats accounts for about 60% of the variation in age of onset, with the remainder represented by modifying genes and environment.[65–71]

Trinucleotide CAG repeats that exceed 28 show instability on replication, which grows with increasing size of the repeat; most instability leads to expansion (73%), but contraction can also take place (23%).[67–69] Instability is also greater in spermatogenesis than oogenesis, in that large expansions of CAG repeats on replication happen almost exclusively in males.[72–74] These findings account for the occurrence of anticipation, in which the age of onset of Huntington's disease becomes earlier in successive generations, and the likelihood of paternal inheritance in children with juvenile onset symptoms. Similarly, new-onset cases of Huntington's disease with a negative family history typically arise because of expansion of an allele in the borderline or normal range (28–35 CAG repeats), most usually on the paternal side.[75]

Somatic instability of CAG repeats also happens in Huntington's disease. Although fairly minor, somatic mosaicism with expansion has been noted in the striatum in human beings and in animal models of the disease,[76–79] and this finding could contribute to selective vulnerability. Mosaicism in lymphocytes might rarely complicate genetic testing.[75]

Identical twins with Huntington's disease typically have an age of onset within several years of each other, but in some cases they show different clinical phenotypes.[76,77] Homozygous cases of the disorder show no substantial differences in age of onset,[78] but the rate of progression can be enhanced.[79]

Genetic testing and diagnosis of Huntington's disease

Despite early surveys that suggested a high amount of interest, fewer than 5% of individuals at risk for Huntington's disease choose to actually pursue predictive genetic testing.[80] Those who undergo testing generally do so to assist in making career and family choices; others elect not to test because of the absence of effective treatment. Predictive testing for the disorder is not without risk. Suicide can follow a positive result,[81,82] and people who are misinformed about the nature of Huntington's disease might seek testing inappropriately. Current protocols are designed to exclude testing for children or those with suicidal ideation, inform patients of the implications of test results for relatives (ie, identical twins), identify sources of subsequent support, and

protext confidentiality.[83–85] Genetic discrimination against individuals with Huntington's disease has been reported but, at least for now, has been rare.[86] Few centres are sympathetic with requests from doctors for help if recommended testing protocols have been ignored.[83–85]

For individuals who undergo pretest counselling, evidence suggests that the overall experience with the process is positive. Although anxiety and stress increase immediately after being given a positive test result, these symptoms return to baseline. Overall, at 2 years, distress is lower and well-being higher irrespective of the outcome of the test.[82] People who receive a negative result can sometimes have stress, known as survivor guilt,[84,87] and subsequent counselling can be of value. Prenatal testing is requested substantially less frequently than predictive presymptomatic testing, a finding attributed to denial, resistance to abortion (an option not needed for preimplantation genetic testing),[88] and concern about fetal risks.[89,90] Parents who opt not to test express hope that treatment will become available for affected offspring.

A positive genetic test is cost effective and provides confirmation for patients who have developed signs and symptoms consistent with Huntington's disease irrespective of family history. Negative test results could lead to diagnosis of a syndrome that resembles Huntingdon's disease. At-risk individuals who have survived to advanced age without developing signs or symptoms sometimes undergo exclusionary testing to allay fears that their children or grandchildren might have inherited the disorder. Experience with genetic testing in Huntington's disease has served as a model for testing protocols for other late-onset disorders and points out the challenges and opportunities of genome technology.[91]

Epidemiology and genetic fitness

Huntington's disease shows a stable prevalence in most populations of white people of about 5–7 affected individuals per 100 000. Exceptions can be seen in areas where the population can be traced back to a few founders, such as Tasmania[92] and the area around Lake Maracaibo[21] in Venezuela. In Japan, prevalence of the disorder is 0·5 per 100 000, about 10% of that recorded elsewhere, and the rate is much lower in most of Asia.[93] African populations show a similarly reduced prevalence,[2,4,94,95] although in areas where much intermarriage with white people takes place the frequency is higher.[2,4,94]

Currently, the higher incidence of Huntington's disease in white populations compared with African or Asian people relates to the higher frequency of huntingtin alleles with 28–35 CAG repeats in white individuals.[34,94] In people with dentatorubropallidoluysian atrophy, which is frequent in Asia, expanded alleles for the causal gene (*ATN1*) are much more typical in Asian populations.[34,93,94]

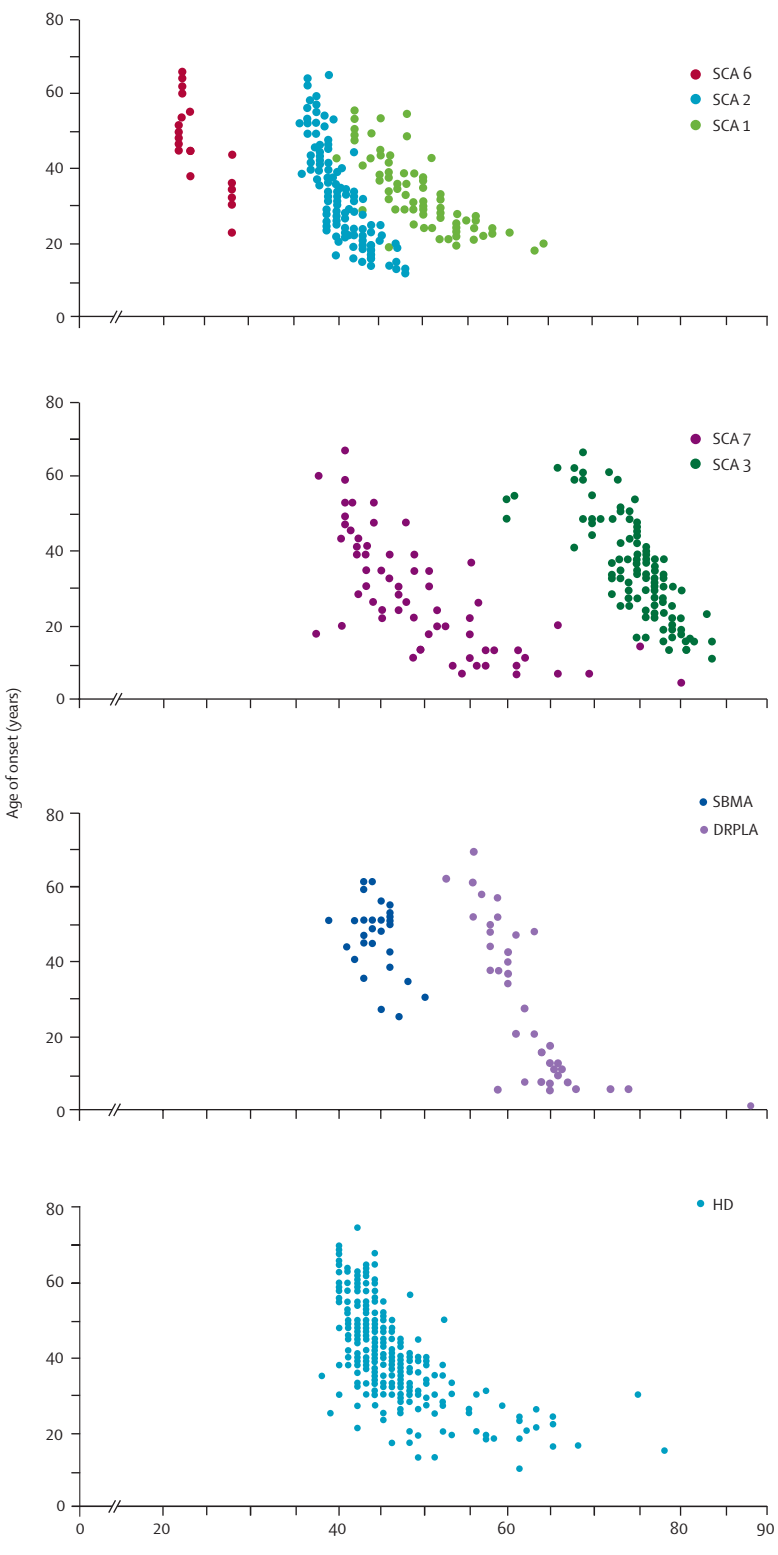
Why do population differences in huntingtin alleles persist? What is the genetic fitness of Huntington's disease? Findings have shown no consistent increase or decrease in the number of children of affected individuals.[4,94] Furthermore, the *HD* gene does not seem to confer any promising health benefits other than a possible lower incidence of cancer,[96] perhaps related to an upregulation of *TP53* in Huntington's disease.[97] No data suggest that expanded huntingtin alleles protect against epidemic infectious disease.

Huntingtin and pathogenesis of Huntington's disease

Huntingtin is expressed in all human and mammalian cells, with the highest concentrations in the brain and testes; moderate amounts are present in the liver, heart, and lungs.[98] Recognisable orthologs of the protein are present in many species, including zebrafish, drosophila, and slime moulds.[99,100] The role of the wild-type protein is, as yet, poorly understood, as is the underlying pathogenesis of Huntington's disease.

One mechanism by which an autosomal-dominant disorder such as Huntington's disease could cause illness is by haploinsufficiency,[101] in which the genetic defect leads to inadequate production of a protein needed for vital cell function. This idea seems unlikely[34,99] because terminal deletion or physical disruption of the *HD* gene in man[101,102] does not cause Huntington's disease. Furthermore, one copy of the *HD* gene does not cause a disease phenotype in mice. Whereas homozygous absence of the *HD* gene is associated with embryonic lethality in animals, people homozygous for the *HD* gene have typical development.[34,79,99]

Findings suggest that the mutant *HD* gene confers a toxic gain of function. A persuasive line of evidence for this idea comes from nine other known human genetic disorders with expanded (and expressed) polyglutamine repeats: spinocerebellar ataxia types 1, 2, 3, 6, 7, 12, and 17; dentatorubropallidoluysian atrophy; and spinobulbar muscular atrophy.[103–113] For none of these disorders is there evidence to suggest an important role for haploinsufficiency. In spinobulbar muscular atrophy, complete deletion of the androgen receptor is not associated with neuromuscular disease.[34,104,105] All nine diseases show neuronal inclusions containing aggregates of polyglutamines and all have a pattern of selective neurodegeneration. One of the most striking features of these disorders is the robust inverse correlation between age of onset and number of polyglutamine repeats (figure 3). Results suggest that the length of the polyglutamine repeat indicates disease severity irrespective of the gene affected, with the longest repeat lengths associated with the most disabling early-onset (juvenile) forms of these disorders. Although difficult to confirm, some data also suggest that the rate of progression might be faster with longer CAG repeats, particularly for individuals with juvenile-onset disease.[114–116]



The most convincing evidence for a gain of function in Huntington's disease is the structural biology of polyglutamine strands. In-vitro evidence suggests that polyglutamines will begin to aggregate, initially by forming dimers, trimers, and oligomers. This process needs a specific concentration of protein and a minimum of 37 consecutive glutamine residues, follows a period of variable abeyance and proceeds faster with higher numbers of glutamine repeats. These findings might account for both delayed onset of disease and the close correlation with polyglutamine length.[117] The rate of aggregation increases with the number of glutamine residues, which accords with evidence showing that length of expansion is associated with early age of onset. Huntington's disease arises only in patients with 36 repeats or more, corresponding to 38 glutamine residues (a normal huntingtin sequence after the poly-CAG tract contains CAA and CAG, which both code for glutamine).[99] Individuals with 36–40 CAG repeats (38–42 residues) show variable penetrance with respect to the Huntington's disease phenotype, with fewer people having symptoms with 36 repeats and only rare cases showing no symptoms at 40 repeats.[34,94] Other CAG-repeat disorders have closely related, but somewhat different, repeat ranges (figure 3) associated with age of onset, but it is noteworthy that only in Huntington's disease is the polyglutamine strand at the N-terminus of the expressed protein. Other characteristics of the expressed proteins in these disorders probably affect aggregation.

The mechanism whereby polyglutamine aggregation leads to selective neuronal dysfunction in Huntington's disease and eventually neurodegeneration has not yet been elucidated, but several key processes have been identified. The first steps seem to involve proteolysis and aggregation, as outlined above. Mutant huntingtin is at higher risk of proteolysis than wild-type protein and its truncation facilitates aggregation.[99,118–121] The polyglutamine strand in the mutant protein occupies only a small proportion of its length,[25] and a shorter protein could reduce steric interference. Evidence suggests that aggregates of truncated huntingtin are toxic and likely to translocate to the nucleus.[49,118–121]

Prolonged mutant huntingtin production and aggregate formation are believed to eventually overcome the ability of cells to degrade them, via either proteasomes or autophagic vacuolisation,[6,34,103] leading to an increased load of unmanageable aggregate proteins. Aggregates also interfere with normal proteins by recruiting some of them into their matrix. Such proteins include those that usually interact with wild-type huntingtin,[34,103,122] suggesting that perhaps truncated and aggregated mutant huntingtin retains active binding sites. Through

Figure 3: **Composite graphs plotting age of onset against number of CAG repeats in eight human polyglutamine disorders**[97,101–107]
Note the tight inverse correlation and the clustering of number of repeats for every genetic disorder. SCA=spinocerebellar ataxia. SBMA=spiobulbar muscular atrophy. DPPLA=dentatorubropallidoluysian atrophy. HD=Huntington's disease.

these and possibly other mechanisms, mutant huntingtin affects several nuclear and cytoplasmic proteins that regulate transcription,[8,34,103] apoptosis,[34,103,123] mitochondrial function,[34,103,124] tumour suppression,[97] vesicular and neurotransmitter release,[46,47,125] and axonal transport.[126] Through the many mechanisms described above, mutant huntingtin might not only have a toxic gain of function but also exert a dominant negative effect, in which it interferes with the typical function of wild-type huntingtin.[52,127,128]

Another step in the pathogenesis of Huntington's disease might entail cell-cell interactions. Mutant huntingtin might cause harm to a neuron, by disrupting the function of nearby neurons or glia that provide important support to that neuron. For example, in a transgenic mouse model of Huntington's disease, interference of mutant huntingtin with the axonal transport and vesicular release of brain-derived neurotrophic factor in corticostriatal neurons seems to contribute to intrinsic dysfunction of striatal neurons.[52,109,110]

Animal models of Huntington's disease

The earliest animal models of Huntington's disease were developed in the 1970s on the basis of selective vulnerability of striatal neurons to excitotoxic aminoacids.[129] These neurons have many glutamate receptors because corticostriatal pathways use this excitatory aminoacid as a primary neurotransmitter. Striatal neurons have also proven to be selectively vulnerable to 3-nitroproprionic acid, a mitochondrial toxin, suggesting that Huntington's disease might affect energy metabolism in neurons.[130]

Transgenic animal models of Huntington's disease were first created in mice[131] and subsequently in *Drosophila* spp and *Caenorhabditis* elegans.[132,133] The fly and mouse models consistently show neuronal polyglutamine inclusions and indicate that pathology is dependent on polyglutamine length, is late onset, progressive, motor, and degenerative, with neuronal dysfunction followed by neuronal death.[133] Similar animal models of other inherited polyglutamine disorders have been developed.[103,132,133]

Although post-mortem human brain tissue from end-stage Huntington's disease patients is available, animal models are invaluable because they provide material for histopathological and biological studies in the earliest stages of disease pathogenesis and for assessment of cell-cell interactions.[52] The transgenic animal models also allow insertion of modifying genes and blinded drug treatment trials.[99,132,133] For example, in a transgenic mouse model in which expression of mutant huntingtin protein with 94 polyglutamines could be switched off, not only was the clinical syndrome reversed but also

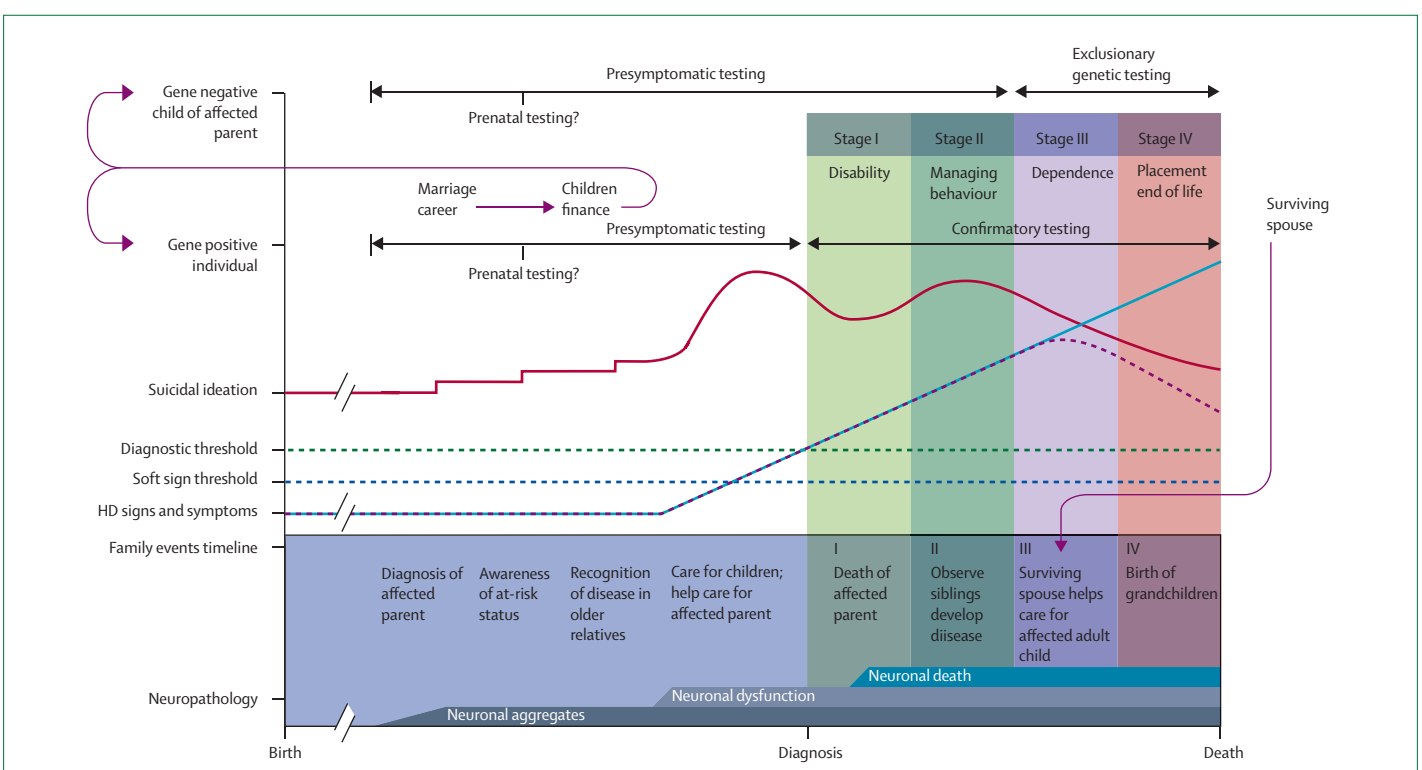


Figure 4: **Life cycle in Huntington's disease**
This figure depicts the sequential evolution of events and ultimately recurrent nature of Huntington's disease from the perspective of a child born to an affected parent. The family events timeline shows events that might occur in different sequences for different individuals; irrespective of timing, such events can have clinically significant implications.

***Panel:* Behavioural difficulties and symptoms in patients with Huntington's disease**[10,14]

Apathy or lack of initiative
Dysphoria
Irritability
Agitation or anxiety
Poor self-care
Poor judgment
Inflexibility

Frequent symptoms (20–50% of patients)
Disinhibition
Depressed mood
Euphoria
Aggression

Infrequent symptoms (5–12%)
Delusions
Compulsions

Rare symptoms (<5%)
Hypersexuality
Hallucinations

Drugs with reported benefit	Interventions with reported benefit	No benefits noted
Lithium	Stem cell transplants	Rofecoxib
Creatine	Environment enrichment	Dichloroacetate
Trehalose	Intrabodies	Aspirin
Paroxetine		Asialoerythropoietin
Clioquinol		S-PBN
Mercaptamine		
Sirolimus		
Remacemide		
Minocycline		
Phenylbutyrate		
Thioetic acid		
Gabapentin-lactam		

Table 2: **Potential treatments for Huntington's disease tested in transgenic animal models**

Drugs with reported symptomatic benefit (chorea only)	Drugs in clinical trials	No protective benefit recorded
Amantadine	Creatine	Baclofen
Remacemide	Riluzole	Vitamin E
Levetiracetam	Ethyl eicasapentaenoic acid	Lamotrigine
Tetrabenazine	Mercaptamine	Remacemide
	Minocycline	
	Phenylbutyrate	
	Coenzyme Q 10	
	OPC-14117 (Otsuka Pharmaceuticals, Tokushima, Japan)	
	Tauroursodeoxychalic acid	

Table 3: **Potential treatments for Huntington's disease tested in human trials**

pathological inclusions were resolved.[134] Work done in transgenic animal models might not always be applicable to human Huntington's disease because of species differences and variations in huntingtin gene length, promoters, and mechanisms of expression.[99,132] Nonetheless, the ability to test drugs in an animal that has a lifespan of days or months provides a useful model for screening compounds that would need years of testing in patients.

Symptomatic treatment of Huntington's disease

Diagnosis of Huntington's disease usually happens when patients seek medical advice with respect to difficulties with work. In such situations, a diagnosis might be partly welcome because it helps to establish disability. People who are doubtful about having Huntington's disease, however, could benefit from a delay in diagnosis until a follow-up visit, when laboratory confirmation is available and they are supported by a family member. The visit at which a diagnosis of Huntington's disease is made is especially important clinically. Family members might recall it in particular detail, so providing accurate information about genetics and sources of support is vital. Making the experience as positive as possible—by dispelling myths and identifying strategies for good family experiences—establishes a professional bond that can be helpful later should difficulties arise.

Like other chronic diseases, managing patients with Huntington's disease requires a proper appreciation of the limitations of medical management. Despite research advances in the past 20 years, medical treatment has made little progress. The survival of affected individuals in the Lake Maracaibo region of Venezuela, where medical technology is largely unavailable, is similar to that of populations with ready access to treatments.[14] Antichoreic drugs such as tetrabenezine[135] or neuroleptics offer patients with severe chorea a respite from their constant involuntary movements. However, declining function might not be an indication for increasing these drugs because they can cause bradykinesia, rigidity, and depression or sedation. Affective disorders in Huntington's disease are amenable to psychiatric treatment, so prompt intervention is advisable.

Counselling can be helpful for patients, their spouses, and individuals at risk for Huntington's disease. Even though only a few patients take advantage of predictive or prenatal testing, frank discussions can help them deal with the complex issues of family, financial, and career planning (figure 4). Support groups are invaluable sources of information and insight that can help patients and families through the recurring difficulties of Huntington's disease.

Behavioural aspects of Huntington's disease can be especially troublesome. In the doctor's office, patients and family members sometimes belabour the cosmetically distracting motor symptoms of the disorder, such as

dystonia or chorea, and might need direct questioning to describe treatable affective disorders or disruptive symptoms such as irritability or compulsions. Poor hygiene, impaired judgment, impulsiveness, and aggression can happen as well (panel).[136,137] Sometimes, acknowledging the difficulties faced by families and caregivers is all that can be done.

Patients with Huntington's disease love to eat, yet weight loss is typical in these individuals.[138] Discussion of food preferences is an enjoyable part of seeing such patients in the clinic. However, as their disease progresses, feeding becomes increasingly difficult, with dysarthria, dysphagia, and difficulty getting food into the mouth. Smaller bites, use of thickening agents, and reminders not to eat quickly may be of benefit.[139]

Experimental treatments

Currently, several drugs for Huntington's disease are in clinical trials to slow the progression of the disease; a few agents have shown promise in work done in animal models.[140,141] The most intriguing research to date has been with coenzyme Q10, which has shown effectiveness in transgenic animal models of Huntington's disease and a possibility of improvement in a human trial.[142] This substance is believed to work by enhancing mitochondrial function in Huntington's disease. A long-term clinical trial of high doses of coenzyme Q10 in patients with Huntington's disease has received federal funding and will begin soon.

However, for completion, standard clinical trials of drugs such as coenzyme Q10 take several years and entail many patients. One way to speed up assessment of promising treatments is with futility studies.[143] This type of study design—by prudent use of historical controls and predetermination of what constitutes a desirable magnitude of effect—can be used as an intermediate step to screen compounds for definitive trials. Such studies are especially useful when risks of long-term side-effects from treatment are possible or when funding and suitable volunteers are in limited supply. This type of study is currently being used to test minocycline, a drug with unique anti-inflammatory and antiapoptotic effects, in Huntington's disease. Tables 2 and 3 list other potential drugs.

The development of surrogate markers of Huntington's disease for clinical trials might also be a promising way to assess new treatments quickly and safely. Use of disease markers to monitor progression of cancer or HIV has accelerated the pace of drug discovery for these disorders. Current interest in Huntington's disease has focused on imaging biomarkers,[61] but the potential for serological markers is also of interest.[144–146] A promising study has shown that Huntington's disease transgenic mice without caspase 6 do not develop symptoms. Therefore, treatment of Huntington's disease in humans by interfering with the catabolism of mutant huntingtin by this enzyme could be possible.[147]

Future work

The best therapeutic option for Huntington's disease could entail starting treatment in the asymptomatic phase of the disorder. Currently, in several observational studies of at-risk individuals, the feasibility of using the onset of the clinical Huntington's disease phenotype or other biomarkers of disease (such as changes on imaging studies) is being investigated as a potential endpoint for future clinical trials.[148] Successes in animal models, identification of possible surrogate markers, progress in symptomatic treatment,[149] and design of efficient study designs all provide tangible reasons for optimism in the Huntington's disease community. With adequate funding for continued research, the discovery of meaningful treatment seems imminent.

Conflict of interest statement

I declare I have no conflict of interest.

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