

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

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 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

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.

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, dentatorubropallidolusian 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

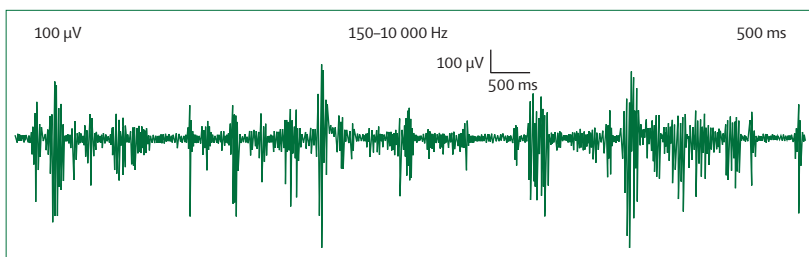


Figure 1: EMG recording of chorea in patient with stage I Huntington's disease

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.

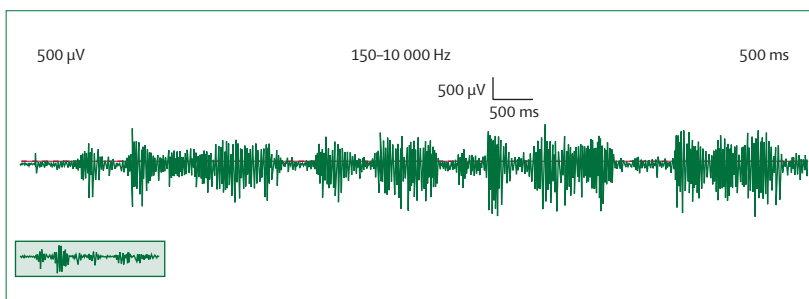


Figure 2: EMG recording of motor impersistence

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.

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.

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

protect 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 Huntington'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 Tasmania⁹² and the area around Lake Maracaibo²¹ 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 dentatorubropallidolusian atrophy, which is frequent in Asia, expanded alleles for the causal gene (*ATN1*) are much more typical in Asian populations.^{34,93,94}

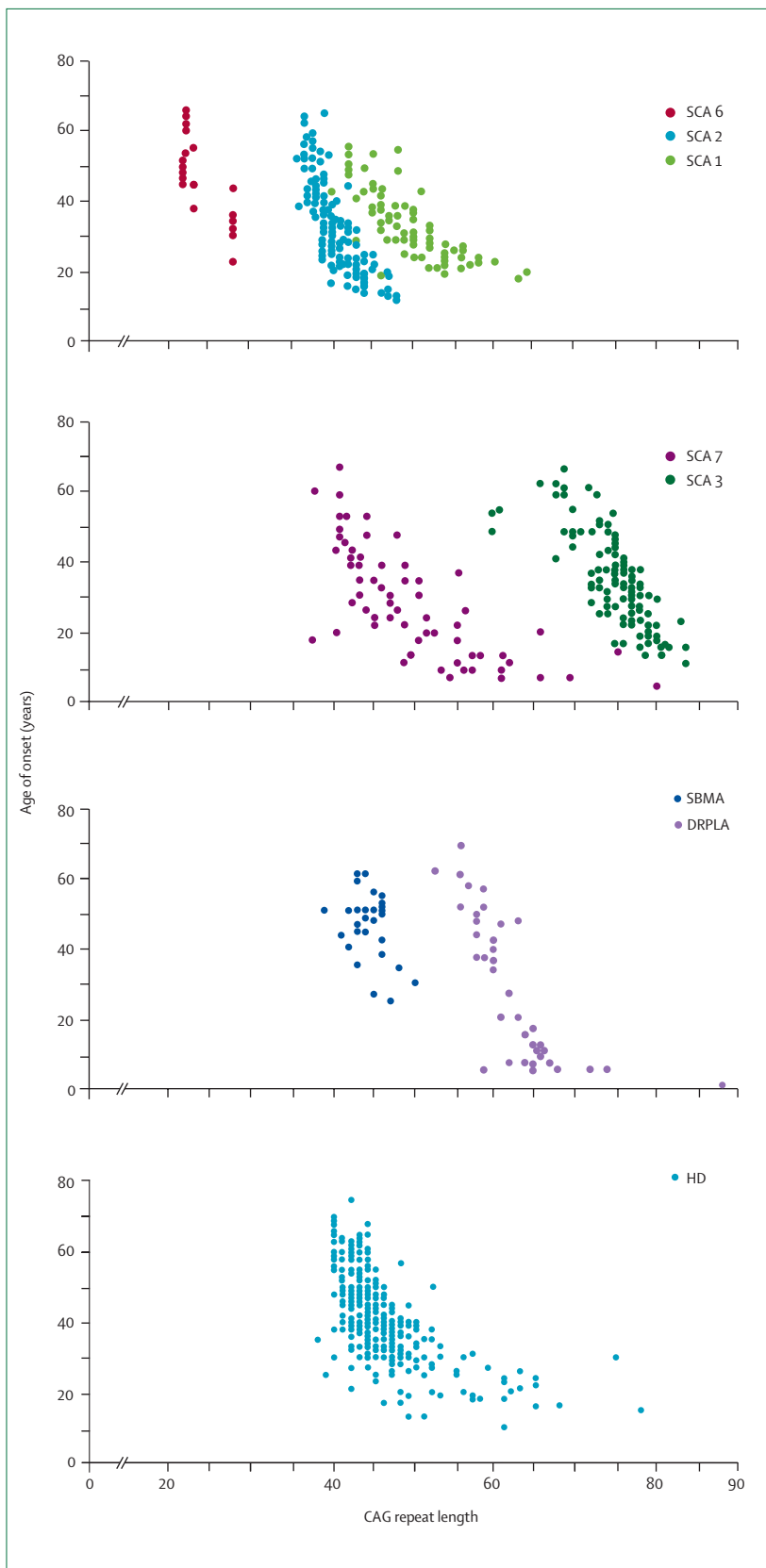
Why do population differences in huntingtin alleles persist? What is the genetic fitness of Huntington's disease? Findings have shown no consistent increase or decrease in the number of children of affected individuals.^{4,94} Furthermore, the *HD* gene does not seem to confer any promising health benefits 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; dentatorubropallidolusian 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.¹⁷ 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=spino-bulbar muscular atrophy. DRPLA=dentatorubropallidolysian 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-nitropropionic 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 mice¹³¹ 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

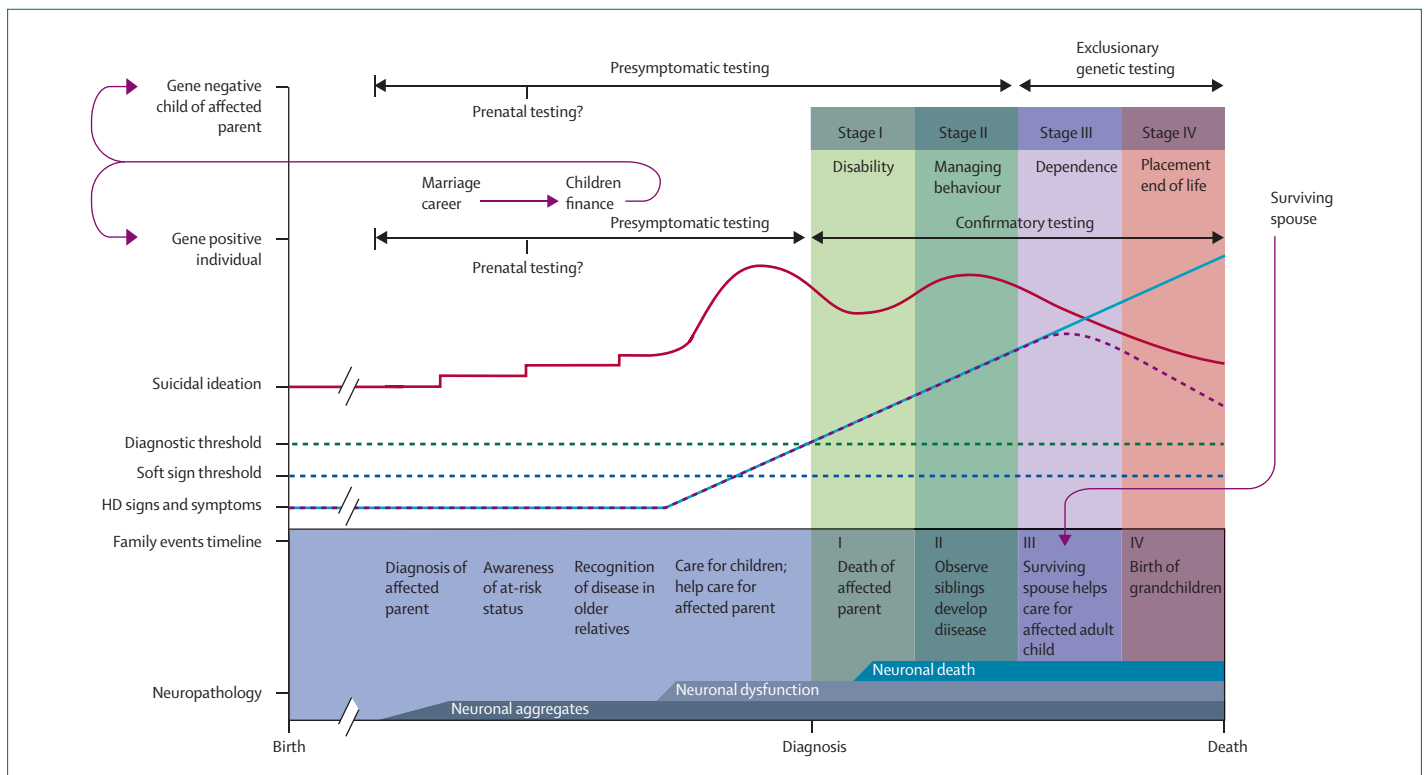


Figure 4: Life cycle in Huntington's disease

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

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 tetrabenzine¹³⁵ 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

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		
Thioctic 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
Tetrabenzine	Mercaptamine	Remacemide
	Minocycline	
	Phenylbutyrate	
	Coenzyme Q 10	
	OPC-14117 (Otsuka Pharmaceuticals, Tokushima, Japan)	
	Tauroursodeoxycholic acid	

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

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.

References

- 1 Elliottson J. Clinical lecture. *Lancet* 1832; **1**: 161–67.
- 2 Hayden MR. Huntington's chorea. New York: Springer, 1981.
- 3 Harper P. Huntington's disease: a historical background. In: Bates G, Harper P, Jones L, eds. Huntington's disease. New York: Oxford University Press, 2002: 3–27.
- 4 Folstein S. Huntington's disease: a disorder of families. Maryland: The Johns Hopkins University Press, 1989.
- 5 Huntington G. On chorea. *Med Surg Rep* 1872; **26**: 317–21.
- 6 Rangone H, Humbert S, Saudou F. Huntington's disease: how does huntingtin, an anti-apoptotic protein, become toxic? *Pathol Biol* 2004; **52**: 338–42.
- 7 Reilmann R, Kirsten F, Quinn L, Henningsen H, Marder K, Gordon AM. Objective assessment of progression in Huntington's disease: a 3-year follow-up study. *Neurology* 2001; **57**: 920–24.
- 8 Cha JH. Transcriptional dysregulation in Huntington's disease. *Trends Neurosci* 2000; **23**: 387–92.
- 9 Myers RH. Huntington's disease genetics. *NeuroRx* 2004; **1**: 255–62.
- 10 Snowden JS, Craufurd D, Griffiths HL, Neary D. Awareness of involuntary movements in Huntington disease. *Arch Neurol* 1998; **55**: 801–05.
- 11 Paulsen JS, Hoth KF, Nehl C, Stierman L. Critical periods of suicide risk in Huntington's disease. *Am J Psychiatry* 2005; **162**: 725–31.
- 12 Watts R, Koller W. Movement disorders: neurologic principles and practice. New York: McGraw-Hill, 1997.
- 13 Weiner W, Lang A. Movement disorders: a comprehensive survey. New York: Futura Publishing Company, 1989.
- 14 Craufurd D, Snowden J. Neuropsychological and neuropsychiatric aspects of Huntington's disease. In: Bates G, Harper P, Jones L, eds. Huntington's disease. New York: Oxford University Press, 2002: 62–94.
- 15 Baliko L, Csala B, Czopf J. Suicide in Hungarian Huntington's disease patients. *Neuroepidemiology* 2004; **23**: 258–60.
- 16 Di Maio L, Squitieri F, Napolitano G, Campanella G, Trofatter JA, Conneally PM. Suicide risk in Huntington's disease. *J Med Genet* 1993; **30**: 293–95.
- 17 Robins Wahlin TB, Backman L, Lundin A, Haegermark A, Winblad B, Anvret M. High suicidal ideation in persons testing for Huntington's disease. *Acta Neurol Scand* 2000; **102**: 150–61.
- 18 Farrer LA. Suicide and attempted suicide in Huntington disease: implications for preclinical testing of persons at risk. *Am J Med Genet* 1986; **24**: 305–11.
- 19 Muller DJ, Barkow K, Kovalenko S, et al. Suicide attempts in schizophrenia and affective disorders with relation to some specific demographical and clinical characteristics. *Eur Psychiatry* 2005; **20**: 65–69.
- 20 Maris RW. Suicide. *Lancet* 2002; **360**: 319–26.
- 21 Young AB, Shoulson I, Penney JB, et al. Huntington's disease in Venezuela: neurologic features and functional decline. *Neurology* 1986; **36**: 244–49.

- 22 Mahant N, McCusker EA, Byth K, Graham S. Huntington's disease: clinical correlates of disability and progression. *Neurology* 2003; **61**: 1085–92.
- 23 Gordon AM, Quinn L, Reilmann R, Marder K. Coordination of prehensile forces during precision grip in Huntington's disease. *Exp Neurol* 2000; **163**: 136–48.
- 24 Kremer B. Clinical neurology of Huntington's disease. In: Bates G, Harper P, Jones L, eds. Huntington's disease. New York: Oxford University Press, 2002: 3–27.
- 25 The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993; **72**: 971–83.
- 26 Nakano T, Iwabuchi K, Yagishita S, Amano N, Akagi M, Yamamoto Y. [An autopsy case of dentatorubropallidolysian atrophy (DRPLA) clinically diagnosed as Huntington's chorea] *No To Skinkei* 1985; **37**: 767–74.
- 27 Margolis RL, Holmes SE, Rosenblatt A, et al. Huntington's disease-like 2 (HDL2) in North America and Japan. *Ann Neurol* 2004; **56**: 670–74.
- 28 Toyoshima Y, Yamada M, Onodera O, et al. SCA17 homozygote showing Huntington's disease-like phenotype. *Ann Neurol* 2004; **55**: 281–86.
- 29 Kambouris M, Bohlega S, Al-Tahan A, Meyer BF. Localization of the gene for a novel autosomal recessive neurodegenerative Huntington-like disorder to 4p15.3. *Am J Hum Genet* 2000; **66**: 445–52.
- 30 Almqvist EW, Elterman DS, MacLeod PM, Hayden MR. High incidence rate and absent family histories in one quarter of patients newly diagnosed with Huntington disease in British Columbia. *Clin Genet* 2001; **60**: 198–205.
- 31 Siesling S, Vegter-van de Vlis M, Losekoot M, et al. Family history and DNA analysis in patients with suspected Huntington's disease. *J Neurol Neurosurg Psychiatry* 2000; **69**: 54–59.
- 32 Danek A, Walker RH. Neuroanthocytosis. *Curr Opin Neurol* 2005; **18**: 386–92.
- 33 Gutekunst C, Norflus F, Hersch S. The neuropathology of Huntington's disease. In: Bates G, Harper P, Jones L, eds. Huntington's disease. New York: Oxford University Press, 2002: 251–75.
- 34 Rubinsztein DC. Molecular biology of Huntington's disease (HD) and HD-like disorders. In: Pulst S, ed. Genetics of movement disorders. California: Academic Press, 2003: 365–77.
- 35 Vonsattel JP, DiFiglia M. Huntington disease. *J Neuropathol Exp Neurol* 1998; **57**: 369–84.
- 36 Spargo E, Everall IP, Lantos PL. Neuronal loss in the hippocampus in Huntington's disease: a comparison with HIV infection. *J Neurol Neurosurg Psychiatry* 1993; **56**: 487–91.
- 37 Macdonald V, Halliday G. Pyramidal cell loss in motor cortices in Huntington's disease. *Neurobiol Dis* 2002; **10**: 378–86.
- 38 Macdonald V, Halliday GM, Trent RJ, McCusker EA. Significant loss of pyramidal neurons in the angular gyrus of patients with Huntington's disease. *Neuropathol Appl Neurobiol* 1997; **23**: 492–95.
- 39 Jeste DV, Barban L, Parisi J. Reduced Purkinje cell density in Huntington's disease. *Exp Neurol* 1984; **85**: 78–86.
- 40 Kremer HP. The hypothalamic lateral tuberal nucleus: normal anatomy and changes in neurological diseases. *Prog Brain Res* 1992; **93**: 249–61.
- 41 Kremer HP, Roos RA, Dingjan GM, Bots GT, Bruyn GW, Hofman MA. The hypothalamic lateral tuberal nucleus and the characteristics of neuronal loss in Huntington's disease. *Neurosci Lett* 1991; **132**: 101–04.
- 42 Heinsen H, Rub U, Bauer M, et al. Nerve cell loss in the thalamic mediodorsal nucleus in Huntington's disease. *Acta Neuropathol (Berl)* 1999; **97**: 613–22.
- 43 Gomez-Tortosa E, MacDonald ME, Friends JC, et al. Quantitative neuropathological changes in presymptomatic Huntington's disease. *Ann Neurol* 2001; **49**: 29–34.
- 44 Mizuno H, Shibayama H, Tanaka F, et al. An autopsy case with clinically and molecular genetically diagnosed Huntington's disease with only minimal non-specific neuropathological findings. *Clin Neuropathol* 2000; **19**: 94–103.
- 45 Myers RH, Vonsattel JP, Paskevich PA, et al. Decreased neuronal and increased oligodendroglial densities in Huntington's disease caudate nucleus. *J Neuropathol Exp Neurol* 1991; **50**: 729–42.
- 46 DiProspero NA, Chen EY, Charles V, Plomann M, Kordower JH. Early changes in Huntington's disease patient brains involve alterations in cytoskeletal and synaptic elements. *J Neurocytol* 2004; **33**: 517–33.
- 47 Modregger J, DiProspero NA, Charles V, Tagle DA, Plomann M. PACSIN 1 interacts with huntingtin and is absent from synaptic varicosities in presymptomatic Huntington's disease brains. *Hum Mol Genet* 2002; **11**: 2547–58.
- 48 Davies SW, Turmaine M, Cozens BA, et al. Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. *Cell* 1997; **90**: 537–48.
- 49 Mukai H, Isagawa T, Goyama E, et al. Formation of morphologically similar globular aggregates from diverse aggregation-prone proteins in mammalian cells. *Proc Natl Acad Sci USA* 2005; **102**: 10887–92.
- 50 Menalled LB, Sison JD, Dragatsis I, Zeitlin S, Chesselet MF. Time course of early motor and neuropathological anomalies in a knock-in mouse model of Huntington's disease with 140 CAG repeats. *J Comp Neurol* 2003; **465**: 11–26.
- 51 Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. *Nature* 2004; **431**: 805–10.
- 52 Zuccato C, Liber D, Ramos C, et al. Progressive loss of BDNF in a mouse model of Huntington's disease and rescue by BDNF delivery. *Pharmacol Res* 2005; **52**: 133–39.
- 53 Van Raamsdonk JM, Pearson J, Slow EJ, Hossain SM, Leavitt BR, Hayden MR. Cognitive dysfunction precedes neuropathology and motor abnormalities in the YAC128 mouse model of Huntington's disease. *J Neurosci* 2005; **25**: 4169–80.
- 54 Kaytor MD, Wilkinson KD, Warren ST. Modulating huntingtin half-life alters polyglutamine-dependent aggregate formation and cell toxicity. *J Neurochem* 2004; **89**: 961–73.
- 55 Bodner RA, Outeiro TF, Altmann S, et al. Pharmacological promotion of inclusion formation: a therapeutic approach for Huntington's and Parkinson's diseases. *Proc Natl Acad Sci USA* 2006; **103**: 4246–51.
- 56 Stober T, Wussow W, Schimrigk K. Bicaudate diameter: the most specific and simple CT parameter in the diagnosis of Huntington's disease. *Neuroradiology* 1984; **26**: 25–28.
- 57 Kunig G, Leenders KL, Sanchez-Pernaute R, et al. Benzodiazepine receptor binding in Huntington's disease: [11C]flumazenil uptake measured using positron emission tomography. *Ann Neurol* 2000; **47**: 644–48.
- 58 Lawrence AD, Weeks RA, Brooks DJ, et al. The relationship between striatal dopamine receptor binding and cognitive performance in Huntington's disease. *Brain* 1998; **121**: 1343–55.
- 59 Paulsen JS, Zimbleman JL, Hinton SC, et al. fMRI biomarker of early neuronal dysfunction in presymptomatic Huntington's disease. *AJNR Am J Neuroradiol* 2004; **25**: 1715–21.
- 60 Rosas HD, Koroshetz WJ, Chen YI, et al. Evidence for more widespread cerebral pathology in early HD: an MRI-based morphometric analysis. *Neurology* 2003; **60**: 1615–20.
- 61 Aylward EH, Sparks BF, Field KM, et al. Onset and rate of striatal atrophy in preclinical Huntington disease. *Neurology* 2004; **63**: 66–72.
- 62 Kipps CM, Duggins AJ, Mahant N, Gomes L, Ashburner J, McCusker EA. Progression of structural neuropathology in preclinical Huntington's disease: a tensor based morphometry study. *J Neurol Neurosurg Psychiatry* 2005; **76**: 650–55.
- 63 Rubinsztein DC, Leggo J, Coles R, et al. Phenotypic characterization of individuals with 30–40 CAG repeats in the Huntington disease (HD) gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36–39 repeats. *Am J Hum Genet* 1996; **59**: 16–22.
- 64 McNeil SM, Novelletto A, Srinidhi J, et al. Reduced penetrance of the Huntington's disease mutation. *Hum Mol Genet* 1997; **6**: 775–79.
- 65 Wexler NS, Lorimer J, Porter J, et al. Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. *Proc Natl Acad Sci USA* 2004; **101**: 3498–503.
- 66 Rosenblatt A, Brinkman RR, Liang KY, et al. Familial influence on age of onset among siblings with Huntington's disease. *Am J Med Genet* 2001; **105**: 399–403.
- 67 Chattopadhyay B, Baksi K, Mukhopadhyay S, Bhattacharyya NP. Modulation of age at onset of Huntington's disease patients by variations in TP53 and human caspase activated DNase (hCAD) genes. *Neurosci Lett* 2005; **374**: 81–86.

- 68 Djousse L, Knowlton B, Hayden MR, et al. Evidence for a modifier of onset age in Huntington disease linked to the HD gene in 4p16. *Neurogenetics* 2004; **5**: 109–14.
- 69 MacDonald ME, Vonsattel JP, Shrinidhi J, et al. Evidence for the GluR6 gene associated with younger onset of Huntington's disease. *Neurology* 1999; **53**: 1330–32.
- 70 Kehoe P, Krawczak M, Harper PS, Owen MJ, Jones AL. Age of onset in Huntington disease: sex specific influence of apolipoprotein E genotype and normal CAG repeat length. *J Med Genet* 1999; **36**: 108–11.
- 71 Chattopadhyay B, Ghosh S, Gangopadhyay PK, et al. Modulation of age onset in Huntington's disease and spinocerebellar ataxia type 2 patients originated from eastern India. *Neurosci Lett* 2003; **345**: 93–96.
- 72 Kremer B, Almqvist E, Theilmann J, et al. Sex-dependent mechanisms for expansions and contractions of the CAG repeat on affected Huntington disease chromosomes. *Am J Hum Genet* 1995; **57**: 343–50.
- 73 Ranen NG, Stine OC, Abbott MH, et al. Anticipation and instability of IT-15 (CAG)_n repeats in parent-offspring pairs with Huntington disease. *Am J Hum Genet* 1995; **57**: 593–602.
- 74 Trottier Y, Biancalana V, Mandel JL. Instability of CAG repeats in Huntington's disease: relation to parental transmission and age of onset. *J Med Genet* 1994; **31**: 377–82.
- 75 Harper PS. The epidemiology of Huntington's disease. In: Bates G, Harper P, Jones L, eds. *Huntington's disease*. New York: Oxford University Press, 2002: 159–97.
- 76 Georgiou N, Bradshaw JL, Chiu E, Tudor A, O'Gorman L, Phillips JG. Differential clinical and motor control function in a pair of monozygotic twins with Huntington's disease. *Mov Disord* 1999; **14**: 320–25.
- 77 Anca MH, Gazit E, Lowenthal R, Ostrovsky O, Frydman M, Giladi N. Different phenotypic expression in monozygotic twins with Huntington disease. *Am J Med Genet* 2004; **124**: 89–91.
- 78 Wexler NS, Young AB, Tanzi RE, et al. Homozygotes for Huntington's disease. *Nature* 1987; **326**: 194–97.
- 79 Squitieri F, Gellera C, Cannella M, et al. Homozygosity for CAG mutation in Huntington's disease is associated with a more severe clinical course. *Brain* 2003; **126**: 946–55.
- 80 Laccone F, Engel U, Holinski-Feder E, et al. DNA analysis of Huntington's disease: five years experience in Germany, Australia, and Switzerland. *Neurology* 1999; **53**: 801–06.
- 81 Almqvist EW, Bloch M, Brinkman R, Craufurd D, Hayden MR. A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after predictive testing for Huntington's disease. *Am J Hum Genet* 1999; **64**: 1293–304.
- 82 Almqvist EW, Brinkman RR, Wiggins S, Hayden MR. Psychological consequences and predictors of adverse events in the first 5 years after predictive testing for Huntington's disease. *Clin Genet* 2003; **64**: 300–09.
- 83 Tibben A, Vegter-vd Vlis M, vd Niermeijer MF, et al. Testing for Huntington's disease with support for all parties. *Lancet* 1990; **335**: 553.
- 84 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* 1994; **44**: 1533–36.
- 85 Tibben A. Genetic counseling and presymptomatic testing. In: Bates G, Harper P, Jones L, eds. *Huntington's disease*. New York: Oxford University Press, 2002: 198–250.
- 86 Harper PS, Gevers S, de Wert G, Creighton S, Bombard Y, Hayden MR. Genetic testing and Huntington's disease: issues of employment. *Lancet Neurol* 2004; **3**: 249–52.
- 87 Huggins M, Bloch M, Wiggins S, et al. Predictive testing for Huntington disease in Canada: adverse effects and unexpected results in those receiving a decreased risk. *Am J Med Genet* 1992; **42**: 508–15.
- 88 Moutou C, Gardes N, Viville S. New tools for preimplantation genetic diagnosis of Huntington's disease and their clinical applications. *Eur J Hum Genet* 2004; **12**: 1007–14.
- 89 Evers-Kiebooms G, Nys K, Harper P, et al. Predictive DNA-testing for Huntington's disease and reproductive decision making: a European collaborative study. *Eur J Hum Genet* 2002; **10**: 167–76.
- 90 Post SG. Huntington's disease: prenatal screening for late onset disease. *J Med Ethics* 1992; **18**: 75–78.
- 91 Hayden MR. Predictive testing for Huntington's disease: a universal model? *Lancet Neurol* 2003; **2**: 141–42.
- 92 Pridmore SA. The large Huntington's disease family of Tasmania. *Med J Aust* 1990; **153**: 593–95.
- 93 Takano H, Cancel G, Ikeuchi T, et al. Close associations between prevalences of dominantly inherited spinocerebellar ataxias with CAG-repeat expansions and frequencies of large normal CAG alleles in Japanese and Caucasian populations. *Am J Hum Genet* 1998; **63**: 1060–66.
- 94 Harper PS, Jones L. Huntington's disease: genetic and molecular studies. In: Bates G, Harper P, Jones L, eds. *Huntington's disease*. New York: Oxford University Press, 2002: 113–58.
- 95 Wright HH, Still CN, Abramson RK. Huntington's disease in black kindreds in South Carolina. *Arch Neurol* 1981; **38**: 412–14.
- 96 Sorensen SA, Fenfer K, Olsen JH. Significantly lower incidence of cancer among patients with Huntington's disease: an apoptotic effect of an expanded polyglutamine tract? *Cancer* 1999; **86**: 1342–46.
- 97 Bae BI, Xu H, Igarashi S, et al. P53 mediates cellular dysfunction and behavioral abnormalities in Huntington's disease. *Neuron* 2005; **47**: 29–41.
- 98 DiFiglia M, Sapp E, Chase K, et al. Huntingtin is a cytoplasmic protein association with vesicles in human and rat brain neurons. *Neuron* 1995; **14**: 1075–81.
- 99 Jones L. The cell biology of Huntington's disease. In: Bates G, Harper P, Jones L, eds. *Huntington's disease*. New York: Oxford University Press, 2002: 348–62.
- 100 Chicurel M. Innovation and standardization: accelerating the search for Huntington's disease therapies—Albert Parvin Foundation Workshop. http://www.hdfoundation.org/news/Jan2005-WS-rpt_FINAL.htm (accessed Aug 1, 2005).
- 101 Ambrose CM, Duyao MP, Barnes G, et al. Structure and expression of the Huntington's disease gene: evidence against simple inactivation due to expanded CAG repeat. *Somat Cell Mol Genet* 1994; **20**: 27–38.
- 102 Pulst S. *Genetics of movement disorders*. California: Academic Press, 2003.
- 103 Bates GP, Benn C. The polyglutamine diseases. In: Bates G, Harper P, Jones L, eds. *Huntington's disease*. New York: Oxford University Press, 2002: 429–74.
- 104 Piccioni F, Simeoni S, Andriola I, et al. Polyglutamine tract expansion of the androgen receptor in a motoneuronal model of spinal and bulbar muscular atrophy. *Brain Res Bull* 2001; **56**: 215–20.
- 105 Margolis RI, Ross CA. Expansion explosion: new clues to pathogenesis of repeat expansion neurodegenerative diseases. *Trends Mol Med* 2001; **7**: 479–82.
- 106 Stevanin S, Durr A, Brice A. Clinical and molecular advances in autosomal dominant cerebellar ataxias: from genotype to phenotype and physiopathology. *Eur J Hum Genet* 2000; **8**: 4–18.
- 107 Geschwind DH, Perlman S, Figueroa KP, et al. The prevalence and wide clinical spectrum of the spinocerebellar ataxia type 2 trinucleotide repeat in patients with autosomal dominant cerebellar ataxia. *Am J Hum Genet* 1997; **60**: 842–50.
- 108 Geschwind DH, Perlman S, Figueroa KP, et al. Spinocerebellar ataxia type 6: frequency of the mutation and genotype-phenotype correlations. *Neurology* 1997; **49**: 1247–51.
- 109 Pulst SM, Nechiporuk A, Nechiporuk T, et al. Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. *Nat Genetics* 1996; **14**: 237–38.
- 110 Komure O, Sano A, Nishino N, et al. DNA analysis in hereditary dentatorubral-pallidolusian atrophy: correlation between CAG repeat length and phenotypic variation and the molecular basis of anticipation. *Neurology* 1995; **45**: 143–49.
- 111 Mariotti C, Castellotti B, Pareyson D, et al. Phenotypic manifestations associated with CAG-repeat expansion in the androgen receptor gene in male patients and heterozygous females: a clinical and molecular study of 30 families. *Neuromuscul Disord* 2000; **10**: 391–97.
- 112 Andrew SE, Goldberg YP, Kremer B, et al. The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. *Nat Genet* 1993; **4**: 398–403.
- 113 O'Hearn E, Holmes SE, Calvert PC, et al. SCA-12: tremor with cerebellar and cortical atrophy is associated with a CAG repeat expansion. *Neurology* 2001; **56**: 299–303.
- 114 Mahant N, McCusker EA, Byth K, Graham S. Huntington's disease: clinical correlates of disability and progression. *Neurology* 2003; **61**: 1085–92.

- 115 Squitieri F, Cannella M, Simonelli M. CAG mutation effect on rate of progression in Huntington's disease. *Neurol Sci* 2002; **23** (suppl 2): S107–08.
- 116 Foroud T, Gray J, Ivashina J, Conneally PM. Differences in duration of Huntington's disease based on age at onset. *J Neurol Neurosurg Psychiatry* 1999; **66**: 52–56.
- 117 Wanker E, Droge A. Structural biology of Huntington's disease. In: Bates G, Harper P, Jones L, eds. Huntington's disease. New York: Oxford University Press, 2002: 327–47.
- 118 Saudou F, Finkbeiner S, Devys D, Greenberg ME. Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. *Cell* 1998; **95**: 55–56.
- 119 Peter MF, Nucifora FC Jr, Kushi J, et al. Nuclear targeting of mutant Huntingtin increases toxicity. *Mol Cell Neurosci* 1999; **14**: 121–81.
- 120 Wellington CL, Leavitt BR, Hayden MR. Huntington disease: new insights on the role of huntingtin cleavage. *J Neural Transm Suppl* 2000; **58**: 1–17.
- 121 Lunkes A, Mandel JL. A cellular model that recapitulates major pathogenic steps of Huntington's disease. *Hum Mol Genet* 1998; **7**: 1355–61.
- 122 Mills IG, Gaughan L, Robson C, et al. Huntingtin interacting protein 1 modulates the transcriptional activity of nuclear hormone receptors. *J Cell Biol* 2005; **170**: 191–200.
- 123 Hickey MA, Chesselet MF. Apoptosis in Huntington's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; **27**: 256–65.
- 124 Panov AV, Burke JR, Strittmatter WJ, Greenamyre JT. In vitro effects of polyglutamine tracts on Ca²⁺-dependent depolarization of rat and human mitochondria: relevance to Huntington's disease. *Arch Biochem Biophys* 2003; **410**: 1–6.
- 125 Freeman W, Morton AJ. Regional and progressive changes in brain expression of complexin H in a mouse transgenic for the Huntington's disease mutation. *Brain Res Bull* 2004; **63**: 45–55.
- 126 Charrin BC, Saudou F, Humbert S. Axonal transport failure in neurodegenerative disorders: the case of Huntington's disease. *Pathol Biol* 2005; **53**: 189–92.
- 127 Gauthier LR, Charrin BC, Borrell-Pages M, et al. Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. *Cell* 2004; **118**: 127–38.
- 128 Busch A, Engemann S, Lurz R, et al. Mutant huntingtin promotes the fibrillogenesis of wild-type huntingtin: a potential mechanism for loss of huntingtin function in Huntington's disease. *J Biol Chem* 2003; **278**: 41452–61.
- 129 Coyle JT, Schwarcz R. Lesion of striatal neurons with kainic acid provides a model for Huntington's chorea. *Nature* 1976; **263**: 244–46.
- 130 Beal MF, Brouillet E, Jenkins B, Henshaw R, Rosen B, Hyman BT. Age-dependent striatal excitotoxic lesions produced by the endogenous mitochondrial inhibitor malonate. *J Neurochem* 1993; **61**: 1147–50.
- 131 Mangiarini L, Sathasivam K, Seller M, et al. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. *Cell* 1996; **87**: 496–506.
- 132 Bates GP, Murphy K. Mouse models of Huntington's disease. In: Bates G, Harper P, Jones L, eds. Huntington's disease. New York: Oxford University Press, 2002: 387–428.
- 133 Marsh JL, Pallos J, Thompson LM. Fly models of Huntington's disease. *Hum Mol Genet* 2003; **12** (Spec No 2): R187–93.
- 134 Yamamoto A, Lucas JJ, Hen R. Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. *Cell* 2000; **101**: 57–66.
- 135 Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. *Neurology* 2006; **66**: 366–72.
- 136 Thompson JC, Snowden JS, Craufurd D, Neary D. Behavior in Huntington's disease: dissociating cognition-based and mood-based changes. *J Neuropsychiatry Clin Neurosci* 2002; **14**: 37–43.
- 137 Paulsen JS, Ready RI, Hamilton JM, et al. Neuropsychiatric aspects of Huntington's disease. *J Neurol Neurosurg Psychiatry* 2001; **71**: 310–14.
- 138 Djousse L, Knowlton B, Cupples LA, et al. Weight loss in early stage of Huntington's disease. *Neurology* 2002; **59**: 1325–30.
- 139 Hunt VP, Walker FO. Dysphagia in Huntington's disease. *J Neurosci Nurs* 1989; **21**: 92–95.
- 140 Gardian G, Browne SE, Choi DK, et al. Neuroprotective effects of phenylbutyrate in the N171-82Q transgenic mouse model of Huntington's disease. *J Biol Chem* 2005; **280**: 556–63.
- 141 Huntington Project. SET-HD updates: Sept 28, 2006: <http://www.huntingtonproject.org/SETHD/SETHDCompoundReviews/tabid/48/Default.aspx>. (accessed Sept 28, 2006).
- 142 Huntington Study Group. A randomized, placebo-controlled trial of coenzyme Q₁₀ and remacemide in Huntington's disease. *Neurology* 2001; **57**: 397–404.
- 143 Tilley BC, Palesch YY, Kiebertz K, et al. Optimizing the ongoing search for new treatments for Parkinson disease: using futility designs. *Neurology* 2006; **66**: 628–33.
- 144 Borovecki F, Lovrecic L, Zhou J, et al. Genome-wide expression profiling of human blood reveals biomarkers for Huntington's disease. *Proc Natl Acad Sci USA* 2005; **102**: 11023–28.
- 145 Strand AD, Aragaki AK, Shaw D, et al. Gene expression in Huntington's disease skeletal muscle: a potential biomarker. *Hum Mol Genet* 2005; **14**: 1863–76.
- 146 Hersch SM, Gevorkian S, Marder K, et al. Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH²dG. *Neurology* 2006; **66**: 250–52.
- 147 Graham RK, Deng Y, Slow EJ, et al. Cleavage at the caspase-6 site is required for neuronal dysfunction and degeneration due to mutant huntingtin. *Cell* 2006; **125**: 1179–91.
- 148 Huntington Study Group. Clinical trials and research studies in progress. <http://www.huntington-studygroup.org/CLINICAL%20TRIALS%20in%20PROGRESS.html> (accessed March 19, 2006).
- 149 Higgins DS. Huntington's disease. *Curr Treat Options Neurol* 2006; **8**: 236–44.