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Huntington Disease

Synonym: Huntington Chorea

Nicholas S Caron, PhD,[1] Galen EB Wright, PhD,[1] and Michael R Hayden, MB, ChB, PhD, FRCP(C), FRSC[1]

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Summary

Clinical characteristics

Huntington disease (HD) is a progressive disorder of motor, cognitive, and psychiatric disturbances. The mean age of onset is 35 to 44 years, and the median survival time is 15 to 18 years after onset.

Diagnosis/testing

The diagnosis of HD rests on positive family history, characteristic clinical findings, and the detection of an expansion of 36 or more CAG trinucleotide repeats in *HTT*.

Management

Treatment of manifestations: Pharmacologic therapy including typical neuroleptics (haloperidol), atypical neuroleptics (olanzapine), benzodiazepines, or the monoamine-depleting agent tetrabenazine for choreic movements; anti-parkinsonian agents for hypokinesia and rigidity; psychotropic drugs or some types of anti-seizure medication for psychiatric disturbances (depression, psychotic symptoms, outbursts of aggression); valproic acid for myoclonic hyperkinesia. Supportive care with attention to nursing needs, dietary intake, special equipment, and eligibility for state and federal benefits.

Prevention of secondary complications: Attention to the usual potential complications in persons requiring long-term supportive care and to side effects associated with pharmacologic treatments.

Surveillance: Regular evaluations of the appearance and severity of chorea, rigidity, gait abnormalities, depression, behavioral changes, and cognitive decline; routine assessment of functional abilities using the Behavior Observation Scale Huntington (BOSH) and the Unified Huntington's Disease Rating Scale (UHDRS).

Agents/circumstances to avoid: L-dopa-containing compounds (may increase chorea), alcohol consumption, smoking.

Author Affiliation: 1 Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada; Email: ncaron@cmmt.ubc.ca; Email: gwright@cmmt.ubc.ca; Email: mrh@cmmt.ubc.ca.

Other: Children and adolescents with a parent with HD may benefit from referral to a local HD support group for educational materials and psychological support.

Genetic counseling

HD is inherited in an autosomal dominant manner. Offspring of an individual with a pathogenic variant have a 50% chance of inheriting the disease-causing allele. Predictive testing in asymptomatic adults at risk is available but requires careful thought (including pre- and post-test genetic counseling) as there is currently no cure for the disorder. However, asymptomatic individuals at risk may be eligible to participate in clinical trials. Predictive testing is not considered appropriate for asymptomatic at-risk individuals younger than age 18 years. Prenatal testing by molecular genetic testing and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Huntington disease (HD) **should be suspected** in individuals with any of the following:

- Progressive motor disability featuring chorea. Voluntary movement may also be affected.
- Mental disturbances including cognitive decline, changes in personality, and/or depression
- Family history consistent with autosomal dominant inheritance

Note: The appearance and sequence of motor, cognitive, and psychiatric disturbances can be variable in HD (see Clinical Description).

Establishing the Diagnosis

The diagnosis of HD **is established** in a proband with clinical signs and symptoms of HD by the identification of a heterozygous abnormal CAG trinucleotide repeat expansion in *HTT* by molecular genetic testing (see Table 1).

Note: Pathogenic $(CAG)_n$ repeat expansions in *HTT* **cannot currently be detected by clinical** sequence-based multigene panels, exome sequencing, or genome sequencing.

CAG repeat sizes

- **Normal.** 26 or fewer CAG repeats
- **Intermediate.** Range from 27 to 35 CAG repeats. An individual with an allele in this range is not at risk of developing symptoms of HD but, because of instability in the CAG tract, may be at risk of having a child with an allele in the HD-causing range [Semaka et al 2006]. Risk estimates for germline CAG expansion have been established [Semaka et al 2013a, Semaka & Hayden 2014].
- **Pathogenic HD-causing alleles.** 36 or more CAG repeats. Persons who have an HD-causing allele are considered at risk of developing HD in their lifetime. HD-causing alleles are further classified as:
  - **Reduced-penetrance HD-causing alleles.** Range from 36 to 39 CAG repeats. An individual with an allele in this range is at risk for HD but may not develop symptoms. Elderly asymptomatic individuals with CAG repeats in this range are common [Kay et al 2016].
  - **Full-penetrance HD-causing alleles.** 40 or more CAG repeats. Alleles of this size are associated with development of HD with increased certainty assuming a normal life span.

Molecular genetic testing relies on targeted **analysis to characterize the number of** *HTT* CAG repeats.

Table 1. Molecular Genetic Testing Used in Huntington Disease

Gene [1]	Method [2, 3]	Proportion of Probands with a Pathogenic Variant Detectable by Method
HTT	Targeted analysis for CAG trinucleotide expansions	100%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Table 6 for specific methods to characterize the number of CAG repeats in *HTT*.
3. Current clinical sequence-based multigene panels, exome sequencing, and genome sequencing cannot detect pathogenic repeat expansions in this gene.

Note: For comprehensive recommendations pertaining to predictive genetic testing for HD, see Genetic Counseling and MacLeod et al [2013].

Clinical Characteristics

Clinical Description

During the prodromal phase of Huntington disease (HD) individuals may have subtle changes in motor skills, cognition, and personality (see Figure 1) [Tabrizi et al 2013, Ross et al 2014, Liu et al 2015]. These subtle changes can occur as early as 15-20 years prior to the clinical onset of manifest HD.

Reilmann et al [2014] present guidelines for the diagnostic criteria of presymptomatic, prodromal, and manifest HD; see Table 2. This table can be used to place individuals into different diagnostic categories, which may have clinical management implications over time. For example, awareness of presymptomatic and prodromal HD may allow for preventive (rather than symptomatic) therapies. Note the clear differentiation of genetically confirmed HD in the classification system.

Table 2. Categories of Huntington Disease Diagnosis

HD Classification		HD Signs/Symptoms
Genetically Confirmed	NOT Genetically Confirmed	
Presymptomatic HD: HD, genetically confirmed, presymptomatic	**Clinically at risk for HD:** HD, not genetically confirmed, clinically at risk	• No clinical motor signs/symptoms (motor DCL = 0 or 1) • No cognitive signs/symptoms • May have changes in imaging, quantitative motor assessments, or other biomarkers • No symptomatic treatment indicated • Disease-modifying treatment when safe & available
Prodromal HD: HD, genetically confirmed, prodromal	**Clinically prodromal HD:** HD, not genetically confirmed, clinically prodromal	• Subtle motor signs (usually motor DCL = 2) AND/OR subtle cognitive signs or symptoms • Minor decline from individual premorbid level of function possibly detectable, but not required & not detectable on TFC • Apathy or depression or other behavioral changes judged related to HD may be present. • Usually changes in imaging & quantitative motor assessments • May/may not require symptomatic treatment (e.g., for depression) • Disease-modifying treatment appropriate

Table 2. continued from previous page.

HD Classification		HD Signs/Symptoms
Genetically Confirmed	NOT Genetically Confirmed	
Manifest HD: HD, genetically confirmed, manifest	**Clinically manifest HD:** HD, not genetically confirmed, clinically manifest [1]	• Presence of clinical motor &/or cognitive signs & symptoms that have an impact on life, with: ◦ Functional changes (e.g., ↓ TFC); ◦ Motor DCL = 3 or 4 (or motor DCL of 2 if cognitive changes significant AND evidence of progression) • Symptomatic & disease-modifying treatment appropriate

Adapted from Reilmann et al [2014]; used with permission
DCL = diagnostic confidence level (from the UHDRS rating scale); HD = Huntington disease; TFC = total functional capacity
1. Requires motor DCL = 4, plus cognitive changes

The mean age of onset for HD is approximately 45 years [Bates et al 2015]. About two thirds of affected individuals first present with neurologic manifestations; others present with psychiatric changes. In the early stages following diagnosis, manifestations include subtle changes in eye movements, coordination, minor involuntary movements, difficulty in mental planning, and often a depressed or irritable mood (see Table 3). Affected individuals are usually able to perform most of their ordinary activities and to continue working [Ross et al 2014, Bates et al 2015].

In approximately 25% of individuals with HD, the onset is delayed until after age 50 years, with some after age 70 years. These individuals have chorea, gait disturbances, and dysphagia, but a more prolonged and benign course than the typical individual.

In the next stage, chorea becomes more prominent, voluntary activity becomes increasingly difficult, and dysarthria and dysphagia worsen. Most individuals are forced to give up their employment and depend increasingly on others for help, although they are still able to maintain a considerable degree of personal independence. The impairment is usually considerable, sometimes with intermittent outbursts of aggressive behaviors and social disinhibition.

In late stages of HD, motor disability becomes severe and the individual is often totally dependent, mute, and incontinent. The median survival time after onset is 15 to 18 years (range: 5 to >25 years). The average age at death is 54 to 55 years [Bates et al 2015].

Table 3. Onset of Clinical Signs and Symptoms in HD

Clinical Signs in HD	
Early	• Clumsiness • Agitation • Irritability • Apathy • Anxiety • Disinhibition • Delusions • Hallucinations • Abnormal eye movements • Depression • Olfactory dysfunction

Table 3. continued from previous page.

Clinical Signs in HD	
Middle	• Dystonia • Involuntary movements • Trouble w/balance & walking • Chorea, twisting & writhing motions, jerks, staggering, swaying, disjointed gait (can seem like intoxication) • Trouble w/activities that require manual dexterity • Slow voluntary movements; difficulty initiating movement • Inability to control speed & force of movement • Slow reaction time • General weakness • Weight loss • Speech difficulties • Stubbornness
Late	• Rigidity • Bradykinesia (difficulty initiating & continuing movements) • Severe chorea (less common) • Significant weight loss • Inability to walk • Inability to speak • Swallowing difficulties; danger of choking • Inability to care for oneself

Abnormalities of movement. Disturbances of both involuntary and voluntary movements occur in individuals with HD. Chorea, an involuntary movement disorder consisting of nonrepetitive, nonperiodic jerking of limbs, face, or trunk, is the major sign of the disease. Chorea is present in more than 90% of individuals, and typically increases in severity during the first ten years. The choreic movements are continuously present during waking hours, cannot be suppressed voluntarily, and are worsened by stress.

With advancing disease duration, other involuntary movements such as bradykinesia, rigidity, and dystonia occur. Impairment in voluntary motor function is an early sign. Affected individuals and their families describe clumsiness in common daily activities. Motor speed, fine motor control, and gait are affected. Oculomotor disturbances occur early and worsen progressively. Difficulty in initiating ocular saccades, slow and hypometric saccades, and problems in gaze fixation may be seen in up to 75% of symptomatic individuals [Blekher et al 2006, Golding et al 2006]. Dysarthria occurs early and is common. Dysphagia occurs in the late stages. Hyperreflexia occurs early in 90% of individuals, while clonus and extensor plantar responses occur late and less frequently.

Abnormalities of cognition. A global and progressive decline in cognitive capabilities occurs in all individuals with HD. Cognitive changes include forgetfulness, slowness of thought processes, impaired visuospatial abilities, and impaired ability to manipulate acquired knowledge. Several studies have identified subtle but definite cognitive deficits prior to the onset of motor symptoms [Bourne et al 2006, Montoya et al 2006, Paulsen et al 2008, Tabrizi et al 2009, Rupp et al 2010]. The initial changes often involve loss of mental flexibility and impairment of executive functions such as mental planning and organization of sequential activities.

Memory deficits with greater impairment for retrieval of information occur early, but verbal cues, priming, and sufficient time may lead to partial or correct recall. Early in the disease the memory deficits in HD are usually much less severe than in Alzheimer disease.

The overall cognitive and behavioral syndrome in individuals with HD is more similar to frontotemporal dementia than to Alzheimer disease. Attention and concentration are involved early [Peinemann et al 2005], resulting in easy distractibility. Language functions are relatively preserved, but a diminished level of syntactic

complexity, cortical speech abnormalities, paraphasic errors, and word-finding difficulties are common in late stages.

Neuropsychologic testing reveals impaired visuospatial abilities, particularly in late stages of the disease. Lack of awareness, especially of one's own disabilities, is common [Ho et al 2006, Bates et al 2015].

Psychiatric disturbances. Individuals with HD develop significant personality changes, affective psychosis, or schizophrenic psychosis [Rosenblatt 2007]. Prior to onset of HD, they tend to score high on measures of depression, hostility, obsessive-compulsiveness, anxiety, and psychoticism [Duff et al 2007]. Unlike the progressive cognitive and motor disturbances, the psychiatric changes tend not to progress with disease severity [Epping et al 2016]. Behavioral disturbances such as intermittent explosiveness, apathy, aggression, alcohol abuse, sexual dysfunction and deviations, and increased appetite are frequent. Delusions, often paranoid, are common. Hallucinations are less common.

Depression and suicide risk. The incidence of depression in preclinical and symptomatic individuals is more than twice that in the general population [Paulsen et al 2005b, Marshall et al 2007]. The etiology of depression in HD is unclear; it may be a pathologic rather than a psychological consequence of having the disease [Slaughter et al 2001, Pouladi et al 2009]. Suicide and suicide ideation are common in persons with HD, but the incidence rate changes with disease course and predictive testing results [Larsson et al 2006, Robins Wahlin 2007, van Duijn et al 2018]. The critical periods for suicide risk were found to be just prior to receiving a diagnosis and later, when affected individuals experience a loss of independence [Baliko et al 2004, Paulsen et al 2005a, Eddy et al 2016].

Other. Persons with HD tend to have a lower body mass index than controls [Pratley et al 2000, Stoy & McKay 2000, Djoussé et al 2002, Robbins et al 2006], which may be related to altered metabolism [Duan et al 2014] and could represent a biomarker of clinical progression [van der Burg et al 2017]. Individuals with HD also demonstrate disturbed cholesterol metabolism [Valenza & Cattaneo 2006, Wang et al 2014]. It is also common for persons with HD to demonstrate increased appetite and energy expenditure [Pratley et al 2000, Trejo et al 2004, Gaba et al 2005].

Sleep and circadian rhythms are disrupted in individuals with HD [Goodman & Barker 2010, Morton 2013], possibly as a result of hypothalamic dysfunction [Petersén & Björkqvist 2006] and/or alterations in melatonin secretion [Kalliolia et al 2014]. Insomnia and daytime somnolence may also be present, although this is more commonly due to psychiatric changes, depression, or chorea [Videnovic et al 2009].

Neuropathology. The primary neuropathologic feature of HD is degeneration of neurons in the caudate and putamen as well as the cerebral cortex [Waldvogel et al 2015]. The preferential degeneration of enkephalin-containing, medium spiny neurons of the indirect pathway of movement control in the basal ganglia provides the neurobiologic basis for chorea [Galvan et al 2012]. The additional loss of substance P-containing medium spiny neurons of the direct pathway results in akinesia and dystonia [Galvan et al 2012]. There is also evidence for loss of neurons in the globus pallidus, subthalamic nucleus, thalamus, hypothalamus, substantia nigra, and hippocampus [Vonsattel et al 1985, Vonsattel & DiFiglia 1998, Heinsen et al 1999, Petersén et al 2005, Guo et al 2012, Domínguez et al 2013, Singh-Bains et al 2016]. Region-specific patterns of neuronal loss in the basal ganglia and cortex may underlie the most evident symptoms in affected individuals and could contribute to the phenotypic variability among individuals [Thu et al 2010, Hadzi et al 2012, Kim et al 2014, Waldvogel et al 2015, Mehrabi et al 2016]. Pathology is also observed in peripheral tissues [Björkqvist et al 2008, van der Burg et al 2009].

Intraneuronal inclusions containing huntingtin, the protein expressed from *HTT*, are also a prominent neuropathologic feature of the disease. However, the expression of the huntingtin protein and the pattern and timing of huntingtin-containing inclusions in the brain do not correlate with the selective degeneration of the

disease and are not believed to be primary determinants of pathology [Kuemmerle et al 1999, Michalik & Van Broeckhoven 2003, Arrasate et al 2004, Slow et al 2005, Slow et al 2006].

Neuroimaging. Imaging studies provide additional support for the clinical diagnosis of HD and are valuable tools for studying progression of the disease [Biglan et al 2009, Paulsen 2009, Tabrizi et al 2011, Tabrizi et al 2012, Tabrizi et al 2013]. In addition to significant striatal atrophy in symptomatic individuals, regional and whole-brain gray and white matter changes have been detected [Majid et al 2011, Tabrizi et al 2011, Tabrizi et al 2012, Tabrizi et al 2013]. Furthermore, MRI studies have revealed progressive gray and white matter atrophy many years prior to predicted disease onset [Tabrizi et al 2011, Tabrizi et al 2012, Tabrizi et al 2013]. Numerous studies in recent years have used neuroimaging to elucidate the clinical progression of HD, with the specific interest of using these objective measures in clinical trials for testing efficacy of experimental therapeutics [Tabrizi et al 2012, Tabrizi et al 2013].

Juvenile HD is defined by the onset of symptoms before age 20 years and accounts for 5%-10% of individuals with HD [Gonzalez-Alegre & Afifi 2006, Quarrell et al 2013]. The motor, cognitive, and psychiatric disturbances observed in adult HD are also observed in juvenile HD, but the clinical presentation of these disturbances is different. Severe mental deterioration, prominent motor and cerebellar symptoms, speech and language delay, and rapid decline are also characteristic of juvenile HD [Nance & Myers 2001, Gonzalez-Alegre & Afifi 2006, Squitieri et al 2006, Yoon et al 2006]. Epileptic seizures, unique to the youngest-onset group, are present in 30%-50% of those with onset of HD before age ten years [Gonzalez-Alegre & Afifi 2006].

In teenagers, symptoms are more similar to adult HD, in which chorea and severe behavioral disturbances are common initial manifestations [Nance & Myers 2001].

Intermediate alleles (IA). An individual with a CAG repeat in the 27-35 range is not believed to be at risk of developing HD but, because of instability in the CAG tract, may be at risk of having a child with an allele in the pathogenic CAG range [Semaka et al 2006, Kay et al 2018]. Limited data suggest that individuals with IAs may exhibit behavioral changes as well as motor and cognitive impairments, although more research is required in this regard [Killoran et al 2013, Cubo et al 2016].

Genotype-Phenotype Correlations

A significant inverse correlation exists between the number of CAG repeats and the age of onset of HD [Langbehn et al 2004, Langbehn et al 2010]. See Molecular Genetics.

- Individuals with adult onset of symptoms usually have an *HTT* allele with CAG repeats ranging from 36 to 55.
- Individuals with juvenile onset of symptoms usually have an *HTT* allele with CAG repeats greater than 60.
- Intermediate alleles (ranging from 27 to 35 CAG repeats) usually have not been associated with disease but are prone to CAG repeat instability [Semaka et al 2013b].

For data on the age-specific likelihood of onset by trinucleotide repeat size, see ubc.ca (pdf).

In addition to age at clinical onset, CAG repeat length has also been shown to predict age at death, but not the duration of the illness [Keum et al 2016].

The rate of deterioration of motor, cognitive, and functional measures increases with larger CAG repeat sizes [Aziz et al 2009, Chao et al 2017].

The progression of behavioral symptoms appears not to be related to repeat size [Ravina et al 2008].

Homozygotes for fully penetrant HD alleles appear to have a similar age of onset to heterozygotes, but may exhibit an accelerated rate of disease progression [Squitieri et al 2011, Lee et al 2012].

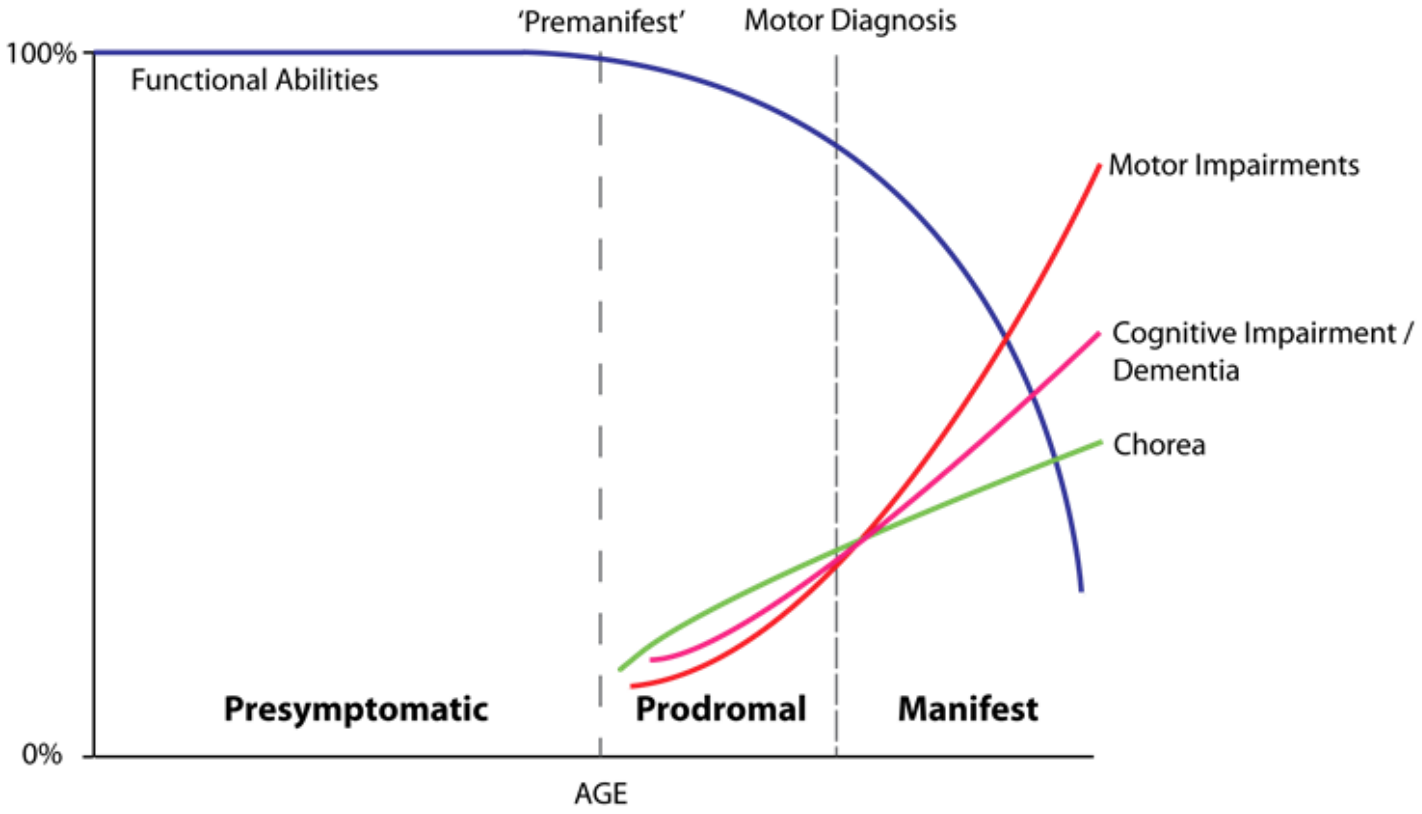

Figure 1. Natural history of Huntington disease (HD). Presymptomatic individuals are free from signs and symptoms of HD. During the prodromal phase, subtle signs and symptoms may be present prior to the diagnosis of HD, which is usually based on motor symptoms. During manifest HD, chorea may be one of the most prominent features, followed by a slow progression of motor and cognitive impairments.

Modified from Ross et al [2014]; reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Neurology

A significant negative correlation also exists between CAG size and *variability* of onset, in which more variability in the late age of onset is associated with smaller CAG sizes, suggesting that non-CAG modifiers may have a greater effect at lower CAG sizes than at larger CAG sizes [Langbehn et al 2004, Gusella & Macdonald 2009]. On average, the CAG repeat size accounts for up to 70% of the variability in age of onset, with an estimated 10%-20% of the residual variability being accounted for by heritable factors [Li et al 2006, Gusella & Macdonald 2009]. Many genes at other loci have been shown to account for small amounts of this heritable portion of the variability [GeM-HD Consortium 2015].

Significant progress has been made in recent years in the identification of these additional genomic modifiers, both at the *HTT* locus and throughout the genome.

- ***Cis*-acting factors.** The most common CAG repeat tract (>95% of alleles) has a CAA interruption in the penultimate repeat [(CAG)n-CAA-CAG]. Uninterrupted CAG repeats [(CAG)n] are associated with decreased age of onset in HD and increased somatic instability of the repeat [Ciosi et al 2019, GeM-HD Consortium 2019, Wright et al 2019] (GeM-HD 2019 full text). These findings suggest that uninterrupted CAG length is more predictive than polyglutamine length in estimating HD age of onset.
- ***Trans*-acting factors.** Genome-wide association studies have identified other candidate modifier genes for HD [GeM-HD Consortium 2015, Moss et al 2017]. These analyses have shown the important role of biologic pathways involved in DNA repair, mitochondrial fission, and oxidoreductase activity with regard to this phenotype, and have identified candidate modifier genes for future study (e.g., *FAN1*, *MLH1*, *MTMR10*, *MSH3*, and *RRM2B*).

Penetrance

Alleles with 36 to 39 CAG repeats are considered HD-causing alleles, but exhibit incomplete penetrance. Elderly asymptomatic individuals with CAG repeats in this range are common [Kay et al 2016].

Disease risk varies for the common [(CAG)n-CAA-CAG] interrupted repeat, observed in more than 95% of alleles, and the rare [(CAG)n] uninterrupted repeat, observed in about 1% of alleles [Ciosi et al 2019, GeM-HD Consortium 2019, Wright et al 2019] (GeM-HD 2019 full text):

- **36-39 repeats.** Approximately one third of symptomatic individuals have a pure [(CAG)n] repeat.
- **36 and 37 repeats.** The majority of symptomatic individuals have a pure [(CAG)n] repeat.

The loss of the CAA repeat has been termed the loss of interruption (LOI) variant [Wright et al 2019] and will be useful in modifying the probability of disease in individuals with 36-39 CAG repeats.

Alleles that contain more than 40 CAG repeats are completely penetrant. No asymptomatic elderly individuals with alleles of more than 40 CAG repeats have been reported.

Anticipation

Anticipation, the phenomenon in which increasing disease severity or decreasing age of onset is observed in successive generations, is known to occur in HD. Anticipation occurs far more commonly in paternal transmission of the mutated allele. The phenomenon of anticipation arises from instability of the CAG repeat during spermatogenesis [Semaka et al 2013a]. Large expansions (i.e., an increase in allele size of >7 CAG repeats) occur almost exclusively through paternal transmission. Most often children with juvenile-onset disease inherit the expanded allele from their fathers, although on occasion they inherit it from their mothers [Nahhas et al 2005].

Nomenclature

In the pre-molecular-genetic era, there were many different names for chorea, including St. Vitus's dance and Sydenham's chorea.

Juvenile HD, or childhood-onset HD, was previously called the Westphal variant of HD.

Individuals who do not yet show symptoms are in the **premanifest** phase of HD. Individuals who have been diagnosed with chorea and/or other validated signs of the disorder have **manifest** HD.

Prevalence

HD prevalence varies across world regions. Populations of European ancestry display an average prevalence of 9.71:100,000 [Rawlins et al 2016], but estimates as high as 17:100,000 have been reported [Fisher & Hayden 2014, Baig et al 2016]. In contrast, HD appears much less frequently in Japan, China, Korea, and Finland, as well as in indigenous African populations from South Africa, with estimated prevalence values ranging from 0.1:100,000 to 2:100,000 [Pringsheim et al 2012, Sipilä et al 2015, Xu & Wu 2015].

Individuals living in the Lake Maracaibo region of Venezuela are believed to have the highest prevalence of HD in the world [Wexler et al 2004].

The uneven distribution of HD is at least partially explained by the distribution of specific predisposing alleles and haplotypes in the general population of these ethnic groups [Warby et al 2009, Warby et al 2011, Kay et al 2018]. For example, a recent study of 15 diverse global populations demonstrated that the mean CAG size in a population, as well as intermediate allele frequency, correlates with HD prevalence and contributes to differences in disease prevalence across major ancestry groups [Kay et al 2018].

Reduced-penetrance *HTT* alleles (see Establishing the Diagnosis, **CAG repeat sizes**) have recently been shown to occur at a high frequency in the general population, with as many as one in 400 individuals having these alleles – although the penetrance rate was determined to be lower than previously reported (i.e., 0.2%-2% for 36-38 CAG alleles) [Kay et al 2016].

Genetically Related (Allelic) Disorders

Biallelic pathogenic missense variants in *HTT* are reported to cause the autosomal recessive neurodevelopmental disorder Lopes-Maciel-Rodan syndrome (LOMARS) (OMIM 617435). Individuals with LOMARS present in childhood with a Rett syndrome-like phenotype and intellectual disability.

Differential Diagnosis

Huntington disease (HD) falls into the differential diagnosis of chorea, dementia, and psychiatric disturbances. The differential diagnosis of several HD-like disorders is summarized here and reviewed elsewhere [Schneider et al 2007, Martino et al 2013]. The co-occurrence of Alzheimer disease and HD has also been reported [Davis et al 2014].

Noninherited conditions are associated with chorea, but most can be excluded easily in an individual with suspected HD based on associated findings and the course of illness. Causes of chorea include tardive dyskinesia, levodopa-induced dyskinesia, thyrotoxicosis, cerebrovascular disease, cerebral lupus, polycythemia, and group A beta-hemolytic *Streptococcus*.

Inherited conditions. See Table 4.

Table 4. Inherited Conditions to Consider in the Differential Diagnosis of Huntington Disease

Disorder	Gene(s)	MOI	Clinical Features of the Disorder	
			Overlapping w/HD	Distinguishing from HD
Frontotemporal dementia &/or amyotrophic lateral sclerosis	*C9orf72*	AD	• Movement disorders • Dementia • Psychiatric disturbances	• Myoclonus • Tremor • Torticollis
Huntington disease-like 1 (HDL1) (OMIM 603218) [1]	*PRNP*	AD	Range of clinical features that overlap w/HD	• Early onset • Slow progression
Huntington disease-like 2 (HDL2)	*JPH3*	AD	Clinically indistinguishable from HD	Prevalence highest among & perhaps exclusive to individuals of African descent
Chorea-acanthocytosis (ChAc)	*VPS13A*	AR	• Progressive movement disorder • Progressive cognitive & behavior changes	• Myopathy • ↑ serum CK • Acanthocytosis • Seizures common • Mean age of onset ~30 yrs
McLeod neuroacanthocytosis syndrome (MLS)	*XK*	XL	• Cognitive impairment • Psychiatric symptoms	• Acanthocytosis • Compensated hemolysis • McLeod blood group phenotype
Spinocerebellar ataxia type 17 (SCA17)	*TBP*	AD	• Chorea • Dementia • Psychiatric disturbances	Cerebellar ataxia is the prominent movement disorder.

Table 4. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features of the Disorder	
			Overlapping w/HD	Distinguishing from HD
Dentatorubral-pallidoluysian atrophy (DRPLA)	*ATN1*	AD	• Progressive movement disorders & dementia • Psychiatric disturbances	Ataxia & myoclonus are prominent movement disorders.
Benign hereditary chorea (OMIM 118700)	*NKX2-1*	AD	Chorea	• Nonprogressive chorea • Not assoc w/dementia
Hereditary cerebellar ataxia (See Hereditary Ataxia Overview.)	Many	AD AR XL	Movement disorder	Hereditary cerebellar ataxia assoc w/prominent cerebellar & long tract signs
Familial Creutzfeld-Jakob disease (fCJD) (See Genetic Prion Disease.)	*PRNP*	AD	• Typically late onset • Progressive dementia • Movement disorders • Behavior changes • Psychiatric symptoms	• fCJD progresses more rapidly. • Myoclonus is a prominent involuntary movement.
Early-onset familial Alzheimer disease	*APP* *PSEN1* *PSEN2*	AD	Dementia	No movement disorders
Familial frontotemporal dementia with parkinsonism-17	*MAPT*	AD	• Late onset • Progressive movement disorders, dementia, & behavior changes • Psychiatric disturbances	No chorea

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; MOI = mode of inheritance; XL = X-linked

1. HDL1 is caused by a specific pathogenic variant (8 extra octapeptide repeats) in the prion protein gene, *PRNP*, on chromosome 20p [Laplanche et al 1999, Moore et al 2001]. Similar pathogenic variants at this locus also result in other forms of prion disease such as familial Creutzfeldt-Jakob disease.

The diagnosis of HD in children is straightforward in a family with a history of HD. In simplex cases (an affected individual with no known family history of HD), ataxia-telangiectasia, pantothenate kinase-associated neurodegeneration (previously known as Hallervorden-Spatz syndrome), Lesch-Nyhan syndrome, Wilson disease, progressive myoclonic epilepsy [Gambardella et al 2001], and other metabolic diseases must be excluded.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Huntington disease (HD), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Physical examination
- Neurologic assessment
- Assessment of the full range of motor, cognitive, and psychiatric symptoms associated with HD. Among a range of clinical scoring systems that have been described, the Unified Huntington's Disease Rating Scale (UHDRS) provides a reliable and consistent assessment of the clinical features and progression of HD.
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Pharmacologic therapy is limited to symptomatic treatment [Mestre et al 2009, Killoran & Biglan 2014].

- Choreic movements can be partially suppressed by typical (haloperidol) and atypical (olanzapine) neuroleptics; benzodiazepines; or the monoamine-depleting agent tetrabenazine [de Tommaso et al 2005, Bonelli & Wenning 2006, Huntington Study Group 2006]. Tetrabenazine can be effective as an antichoreic drug; however, its use is associated with severe adverse effects including extrapyramidal symptoms. Deutetrabenazine, a deuterated analog of tetrabenazine, has been modified by deuterium atom substitutions at specific sites on the molecule to increase half-life and systemic exposure [Stamler et al 2013]. These properties allow for less frequent dosing with fewer adverse effects [Frank et al 2016, Reilmann 2016].
- Anti-parkinsonian agents may ameliorate hypokinesia and rigidity, but may increase chorea.
- Psychiatric disturbances such as depression, psychotic symptoms, and outbursts of aggression generally respond well to psychotropic drugs or some types of anti-seizure medication.
- Valproic acid has improved myoclonic hyperkinesia in Huntington disease [Saft et al 2006].

Supportive care with attention to nursing, diet, special equipment, and eligibility for state and federal benefits is much appreciated by individuals with HD and their families. Numerous social challenges beset individuals with HD and their families; practical help, emotional support, and counseling can provide relief [Williams et al 2009].

Prevention of Secondary Complications

Significant secondary complications of HD include the following:

- The complications typically observed with any individual requiring long-term supportive care
- The side effects associated with various pharmacologic treatments. Drug side effects are dependent on a variety of factors including the compound involved, the dosage, and the individual; with the medications typically used in HD, side effects may include depression, sedation, nausea, restlessness, headache, neutropenia, and tardive dyskinesia. For some individuals, the side effects of certain therapeutics may be worse than the symptoms; such individuals would benefit from being removed from the treatment, having the dose reduced, or being "rested" regularly from the treatment. Current medications used to treat chorea are particularly prone to significant side effects. Individuals with mild-to-moderate chorea may be better assisted with nonpharmacologic therapies such as movement training and speech therapy.
- Depression. Standard treatment is appropriate when indicated [Paulsen et al 2005b, Phillips et al 2008].

Surveillance

Regular evaluations should be made to address the appearance and severity of chorea, rigidity, gait abnormalities, depression, behavioral changes, and cognitive decline [Anderson & Marshall 2005, Skirton 2005].

The Behavior Observation Scale Huntington (BOSH) is a scale developed for the rapid and longitudinal assessment of functional abilities of persons with HD in a nursing home environment [Timman et al 2005]. For longitudinal studies, the Unified Huntington's Disease Rating Scale (UHDRS) is used [Huntington Study Group 1996, Siesling et al 1998, Youssov et al 2013]. The total functional capacity (TFC) scale is used to describe the progression of HD, the level of functioning, and requirements for additional caregiver aid.

Agents/Circumstances to Avoid

L-dopa-containing compounds may increase chorea.

Alcohol and smoking are discouraged.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

A wide range of potential therapeutics are under investigation in both animal models of HD and human clinical trials [Wild & Tabrizi 2014]. This diversity reflects the variety of cellular pathways known to be perturbed in HD [Bonelli et al 2004, Rego & de Almeida 2005, Borrell-Pagès et al 2006, Graham et al 2006, Bonelli & Hofmann 2007].

- Pharmacologic agents being investigated include inhibitors of: apoptosis, excitotoxicity, huntingtin aggregation, huntingtin proteolysis, huntingtin phosphorylation, inflammation, oxidative damage, phosphodiesterase activity, histone deacetylase, and transglutaminase activity; as well as compounds that modulate mitochondrial function, chaperone activity, transcription, and neurotrophic support.
- Therapeutics that have shown improvements in preclinical animal models of HD and have been advanced to clinical trials include minocycline, sodium butyrate, essential fatty acids, racemide, creatine, cystamine, riluzole, memantine, resveratrol, cannabis extract (THC and CBD), coenzyme Q_{10}, and a phosphodiesterase 10a inhibitor [Bender et al 2005, Puri et al 2005, Bonelli & Wenning 2006, Ondo et al 2007, Okamoto et al 2009, Huntington Study Group DOMINO Investigators 2010, Hersch et al 2017, McGarry et al 2017]. Notably, many of these therapeutic agents have failed to meet clinical endpoints and demonstrate efficacy in modifying clinical progression of HD. Experimental therapeutics including pridopidine, laquinimod, and a semaphorin-4D neutralizing antibody are still in clinical development.
- Gene-silencing approaches to target the cause of HD have been shown to be safe and efficacious in preclinical animal studies and are currently undergoing or on the verge of entering clinical trials. These include approaches using RNA interference (RNAi) or antisense oligonucleotides (ASOs) [Boudreau et al 2009, Pfister & Zamore 2009, Hu et al 2010, McBride et al 2011, Kordasiewicz et al 2012, Aronin & DiFiglia 2014, Dufour et al 2014, Stanek et al 2014, Pfister et al 2018]. These approaches either aim to silence all huntingtin expression in a nonselective manner [Boudreau et al 2009, McBride et al 2011, Kordasiewicz et al 2012] or are allele selective for only the mutated *HTT* allele [Gagnon et al 2010, Carroll et al 2011, Evers et al 2011, Skotte et al 2014, Southwell et al 2014, Datson et al 2017]. Allele selectivity can be achieved by targeting the expanded CAG tract [Gagnon et al 2010, Evers et al 2011, Datson et al 2017] or by targeting polymorphisms in linkage disequilibrium with the CAG expansion [Carroll et al 2011, Skotte et al 2014, Southwell et al 2014, Kay et al 2015, Southwell et al 2018]. Results from the first in-human Phase I/IIa clinical trial evaluating the *HTT* targeted ASO showed that IONIS-HTT_{Rx} (RG6042) was well tolerated at all doses tested and resulted in dose-dependent reductions of mHTT in cerebrospinal fluid (CSF) [Tabrizi et al 2019].
- Cell transplantation studies in HD have shown variable results with small numbers of individuals [Furtado et al 2005, Bachoud-Lévi et al 2006, Farrington et al 2006, Dunnett & Rosser 2007, Barker et al 2013]; however, additional larger studies are under way [Lopez et al 2014]. Moreover, the safety and efficacy of intravenously injected mesenchymal stem cells is currently being tested in a first-in-human clinical trial for individuals with HD (NCT02728115). Of concern, recent studies suggest that mutated huntingtin is capable of spreading into the allografted neural tissue [Cicchetti et al 2014].

Numerous human clinical trials are planned or under way for HD and are listed at huntingtonstudygroup.org. A number of drug trials have been completed and/or are ongoing.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Other

Biomarker studies, such as TRACK-HD, PREDICT-HD, and ENROLL-HD, have been conducted to identify early changes in disease progression using imaging, clinical scales, and physiologic measurements [Scahill et al 2012, Ross et al 2014]. Longitudinal studies of persons at risk for HD have also been performed [Huntington Study Group PHAROS Investigators 2006, Paulsen et al 2006, Tabrizi et al 2012].

A number of candidate molecular biomarkers of disease onset and clinical progression have been assessed in HD patient cohorts, yet only a few have been validated. Mutated huntingtin levels in CSF have been shown to correlate with disease stage in HD [Southwell et al 2015, Wild et al 2015] and potentially reflect levels of mHTT in the brain [Southwell et al 2015]. Therefore, mHTT levels in CSF may provide a reliable biomarker of clinical progression and may provide a proxy measurement for HTT suppression in the brain for *HTT*-targeted clinical trials. Moreover, levels of neurofilament light chain in blood and CSF have been shown to be a potential prognostic biomarker of disease onset and clinical progression as well as regional brain atrophy in individuals with HD [Byrne et al 2017, Johnson et al 2018].

Children and adolescents living with a parent affected with HD, sometimes in very deprived conditions, can have special challenges. Referral to a local HD support group for educational material and needed psychological support is helpful (see Resources).

Donepezil, a drug used to treat Alzheimer disease, has not improved motor or cognitive function in HD [Cubo et al 2006].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Huntington disease (HD) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with HD have an affected parent.
- The family history of some individuals diagnosed with HD may appear to be negative for one of the following reasons:
  - Failure to recognize the disorder in family members
  - Early death of the parent before the onset of symptoms
  - The presence of an intermediate allele (range: 27-35 CAG repeats) or an *HTT* allele with reduced penetrance (range: 36-39 CAG repeats) in an asymptomatic parent (See **Offspring of a proband**.)
  - Late onset of the disease in the affected parent
- Molecular genetic testing is recommended for the parents of a proband who appears to represent a simplex case (i.e., a single occurrence in a family).

Sibs of a proband. The risk to the sibs of a proband depends on the genetic status of the proband's parents:

- If a parent has an *HTT* allele with CAG length of 40 or greater, the risk to the sibs of inheriting a full-penetrance HD-causing allele is 50%.
- If a parent has an *HTT* allele with reduced penetrance (36-39 CAG repeats), the risk to the sibs of inheriting a pathogenic HD-causing allele (of either reduced or full penetrance) is 50% (see Anticipation).
- If a parent has an intermediate *HTT* allele (27-35 CAG repeats), the risk to the sibs of inheriting a CAG expansion greater than 35 repeats or a "new HD-causing allele" depends on a variety of factors, including the following (see also Anticipation):
    - **The CAG size of the allele.** Larger CAG sizes are more prone to expansion.

      CAG size-specific estimates for repeat instability in sperm have been reported to enable genetic counselors to provide more accurate risk assessment for persons who receive an intermediate allele predictive test result [Hendricks et al 2009, Semaka et al 2013a, Semaka & Hayden 2014]. While all intermediate CAG repeat sizes were shown to have the possibility of expansion, the probability of expansion increases dramatically with increasing CAG size; approximately 21% of 35 CAG alleles expanded into the disease-associated range. Evidence-based genetic counseling implications for intermediate allele predictive test results have been published by Semaka & Hayden [2014].
    - **The sex and age of the transmitting parent.** Paternally inherited intermediate alleles are more prone to CAG expansion than maternally inherited intermediate alleles; maternal expansions are extremely rare [Semaka et al 2015]. Expanded intermediate alleles are preferentially transmitted by males with advanced paternal age.
    - **The DNA sequence in *cis* configuration with the CAG expansion.** CAG tracts interrupted with CAA and CCG trinucleotides are more stable.

Offspring of a proband

- At conception, each child of an individual with HD as a result of heterozygosity for a CAG repeat expansion in *HTT* has a 50% chance of inheriting the HD-causing allele. Offspring who inherit a:
    - **Reduced-penetrance allele (36-39 CAG repeats)** are at risk for HD but may not develop symptoms (see Penetrance);
    - **Full-penetrance allele (40 or more CAG repeats)** are at risk of developing HD with increased certainty assuming a normal life span.
- Each child of an affected individual who is homozygous for CAG repeat expansion in *HTT* will inherit an HD-causing allele.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected or has a CAG expansion in *HTT*, the parent's family members are at risk.

Related Genetic Counseling Issues

Predictive testing (i.e., testing of asymptomatic at-risk individuals). Testing of asymptomatic adults at risk for HD is possible. Testing for the pathogenic variant in the absence of definite symptoms of the disease is predictive testing. Such testing is not useful in accurately predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. However, data reported by Langbehn et al [2004] and Langbehn et al [2010] concerning the likelihood that an individual with a particular size of CAG repeat will be affected by a specific age may be useful. Current diagnostic assays are only capable of measuring CAG length up to the penultimate CAA in the canonic sequence. In the presence of the loss of interruption variant (CAA to CAG), current diagnostic methods would underestimate CAG length by two CAG repeats. This does not affect the majority of individuals with HD [Wright et al 2019]. See **Supplementary Tables** at ubc.ca (pdf). When testing

at-risk individuals for HD, it is helpful to test for the CAG expansion in *HTT* in an affected family member to confirm that the disorder in the family is HD.

- At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Asymptomatic individuals at risk may also be eligible to participate in clinical trials. Others may have different motivations including simply the "need to know." Testing of asymptomatic at-risk adult family members usually involves pretest interviews in which the motives for requesting the test, the individual's knowledge of HD, the possible impact of positive and negative test results, and neurologic status are assessed. Those seeking testing should be counseled about problems they may encounter with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. Interestingly, a study has found that genetic testing does not increase the risk for discrimination; perceived genetic discrimination is more likely due to the family history of HD regardless of gene status, rather than due to the specific results of the HD genetic test [Bombard et al 2009]. Other issues to consider include implications for the at-risk status of other family members [Bombard et al 2012]. Depression and suicide ideation are issues to be addressed as part of the predictive testing program for HD [Robins Wahlin et al 2000, Robins Wahlin 2007]. Informed consent should be obtained and records kept confidential. Individuals with a mutated allele need arrangements for long-term follow up and evaluations.
- Short-term follow up of the participants in the Canadian Predictive Testing Program has revealed that predictive testing for HD may maintain or even improve the psychological well-being of at-risk individuals even though some had negative experiences. About 10% of the group who were determined to be at decreased risk had serious difficulties adapting to their new status. The major issue for these individuals is the realization that they are facing an unplanned future. Overall, the demand for testing of at-risk asymptomatic adults has been lower than expected in studies conducted before the availability of direct molecular genetic testing. Consistent with use of medical services and genetic testing in general, women are more likely than men to undergo predictive testing for HD [Taylor 2005, Baig et al 2016].
- In their study of psychological distress in the partners of asymptomatic individuals who had inherited an HD-causing allele, Decruyenaere et al [2005] found that partners have at least as much distress as the individuals found to have the HD-causing allele, yet their grief tends to be "disenfranchised" or not socially recognized.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of HD, it is appropriate to consider testing of symptomatic individuals regardless of age.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent has an HD-causing *HTT* allele (>35 CAG repeats) or an intermediate allele (27-35 repeats), nonmedical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

Prenatal Testing and Preimplantation Genetic Testing

For fetuses at 50% risk. If the presence of an HD-causing *HTT* allele has been confirmed in the affected parent or in an affected relative of the at-risk parent, prenatal testing for a pregnancy at increased risk is possible.

Preimplantation genetic testing (PGT) may be an option for families in which an HD-causing *HTT* allele has been identified in an affected family member. Existing PGT exclusion protocols allow for testing of the embryo for couples in an at-risk family who do not wish to undergo presymptomatic testing for the HD-causing allele themselves [Sermon et al 2002, Stern et al 2002, Moutou et al 2004, Jasper et al 2006]. Counseling and ethical issues affecting PGT for HD are discussed by Asscher & Koops [2010].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing when the testing is being considered for the purpose of pregnancy termination or for early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **European Huntington's Disease Network (EHDN)**
  Germany
  www.ehdn.org
- **HDBuzz**
  HDBuzz
- **Huntington Society of Canada**
  151 Frederick Street
  Suite 400
  Kitchener Ontario N2H 2M2
  Canada
  Phone: 800-998-7398 (toll-free); 519-749-7063
  Fax: 519-749-8965
  Email: info@huntingtonsociety.ca
  www.huntingtonsociety.ca
- **Huntington's Disease Africa**
  Phone: 254746734559
  Email: info@hd-africa.org
  www.hd-africa.org
- **Huntington's Disease Society of America (HDSA)**
  505 Eighth Avenue

Suite 902
New York NY 10018
Phone: 800-345-4372 (toll-free); 212-242-1968
Fax: 212-239-3430
Email: hdsainfo@hdsa.org
www.hdsa.org

- **International Huntington Association**
  Netherlands
  Email: svein@iha-huntington.org
  www.huntington-disease.org
- **La Société Huntington du Québec (Huntington Society of Quebec)**
  Montréal Quebec
  Canada
  Phone: 514-282-4272; 877-282-2444; 877-220-0226
  Fax: 514-937-0082
  Email: shq@huntingtonqc.org
  www.huntingtonqc.org
- **National Library of Medicine Genetics Home Reference**
  Huntington disease
- **Testing for Huntington Disease: Making an Informed Choice**
  Booklet providing information about Huntington disease and genetic testing
  University of Washington Medical Center
  Seattle WA
  Testing for Huntington Disease: Making an Informed Choice
- **Hereditary Disease Foundation**
  3960 Broadway
  6th Floor
  New York NY 10032
  Phone: 212-928-2121
  Fax: 212-928-2172
  Email: cures@hdfoundation.org
  www.hdfoundation.org
- **European Huntington's Disease Network (EHDN) Registry**
  Germany
  EHDN Registry
- **Huntington Study Group (HSG)**
  95 Allens Creek
  Building 1, Suite 132
  Rochester NY 14618
  Phone: 800-487-7671 (toll-free)
  Fax: 585-672-9912
  Email: info@hsglimited.org
  www.huntingtonstudygroup.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Huntington Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HTT	4p16.3	Huntingtin	HTT database	HTT	HTT

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Huntington Disease (View All in OMIM)

143100	HUNTINGTON DISEASE; HD
613004	HUNTINGTIN; HTT

Molecular Pathogenesis

HTT encodes the huntingtin protein. A CAG trinucleotide repeat expansion in exon one of *HTT* is translated into an uninterrupted stretch of glutamine residues in huntingtin. This polyglutamine expansion in huntingtin elicits toxic effects by dysregulating vital cellular processes, which ultimately leads to cell death.

Of note, huntingtin acts as a scaffold to facilitate several essential functions in the cell, including cytoskeletal dynamics, endocytosis, vesicular trafficking (BDNF), energy metabolism, protein turnover, and gene expression (transcription and RNA processing). In the presence of a CAG expansion, many of its roles are disrupted, likely contributing to the disease phenotype [Saudou & Humbert 2016].

Mechanism of disease causation. The primary mechanism is gain of function; however, many studies support loss of function.

Table 5. *HTT* Technical Considerations

Technical Issue	Comment [Reference]
Sequence of repeat	CAG; however, an interrupted repeat, [(CAG)n-CAA-CAG], is present on the majority of alleles [Wright et al 2019]; for clinical implications see Genotype-Phenotype Correlations.
Methods to detect expanded allele (see Table 6)	Conventional PCR, triplet-primed PCR (TP-PCR) [Jama et al 2013], and Southern blotting [Bean & Bayrak-Toydemir 2014] have been described.
Somatic instability	Alleles with an abnormal number of CAG repeats may display somatic instability of the repeat [Telenius et al 1994].
Germline instability	Although expansion & contraction of repeat length can occur w/maternal or paternal transmission, expansion occurs far more commonly in paternal transmission, w/large expansions (i.e., >7 CAG repeats) occurring almost exclusively through paternal transmission [Semaka et al 2013a]. Most individuals w/ juvenile-onset HD inherit the expanded allele from their fathers [Nahhas et al 2005].

Methods to characterize *HTT* CAG repeats. Due to the technical challenges of detecting and sizing *HTT* CAG trinucleotide repeat expansions, multiple methods may be needed to rule out or detect CAG repeat expansion (see Table 6). Most repeats may be detected by traditional PCR. However, detection of apparent homozygosity for a normal CAG repeat does not rule out the presence of a very large expanded CAG repeat. Thus, testing by

triplet-primed PCR (TP-PCR) or Southern blotting may be required. In addition, somatic and germline instability of expanded repeats must be considered.

Table 6. Methods to Characterize *HTT* CAG Repeats

Interpretation of CAG Repeat Number	Expected Results by Method		
	Conventional PCR	Triplet-Primed PCR [1]	Expanded Repeat Analysis [2]
Normal: ≤26	Detected [3]	See footnote 1.	Expansions can be detected, & repeat size can be approximated. [6]
Intermediate: 27-35	Detected [3, 4]	Expansions may be detected, but repeat size cannot be determined. [5]	
Pathogenic (reduced penetrance): 36-39	Detected [3, 4]		
Pathogenic (full penetrance): ≥40	Most alleles detected [3, 4]	Expansions detected, but repeat size cannot be determined. [5]	

1. The design of a triplet-primed PCR (TP-PCR) assay may include conventional PCR primers to size normal repeats and detect expanded repeats in a single assay. The TP-PCR assay itself does not determine repeat size, even alleles in the normal range.
2. Methods to detect and approximate the size of expanded repeats include long-range PCR sized by gel electrophoresis and Southern blotting. The upper limit of repeat size detected will vary by assay design, laboratory, sample, and/ or patient due to competition by the normal allele during amplification.
3. Detection of an apparently homozygous repeat does not rule out the presence of an expanded CAG repeat; thus, testing by TP-PCR or expanded repeat analysis is required to detect a repeat expansion.
4. PCR-based methods detect alleles up to about 115 CAG repeats [Potter et al 2004, Levin et al 2006]. Other methods may occasionally be useful to identify large CAG repeat tracts. The upper limit of repeat size detected will vary by assay design, laboratory, sample, and/or patient due to competition by the normal allele during amplification.
5. Repeats at the lower end of this range may not show the characteristic stutter pattern that indicates an expanded allele.
6. Southern blotting for the CAG repeat expansion has been described [Bean & Bayrak-Toydemir 2014].

Table 7. Notable *HTT* Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Repeat Range
NM_002111.8 NP_002102.4	c.52CAG[9_26]	p.Gln18[9_26]	Normal
	c.52CAG[27_35]	p.Gln18[27_35]	Intermediate
	c.52CAG[36_39]	p.Gln18[36_39]	Reduced penetrance
	c.52CAG[40_?]	p.Gln18[40_?]	Full penetrance

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Booklets available through the Huntington Society of Canada:

- Loss and Grief: Coping with the Death of a Loved One and with Other Losses Related to Huntington Disease
- A Physician's Guide to the Management of Huntington Disease (3rd edition)
- Caregiver's Handbook for Advanced Stages of Huntington Disease
- Juvenile Huntington Disease: A Resource for Families, Health Professionals and Caregivers

- Understanding Behaviour in Huntington Disease: A Guide for Professionals (3rd edition)
- Personal Perspectives on Genetic Testing for Huntington Disease
- Understanding Huntington Disease: A Resource for Families

Author History

Nicholas S Caron, PhD (2018-present)
Rona K Graham, PhD; University of Sherbrooke, Quebec (2007-2018)
Brendan Haigh, PhD; University of British Columbia (1998-2007)
Michael R Hayden, MB, ChB, PhD, FRCP(C), FRSC (1998-present)
Mahbubul Huq, PhD; University of British Columbia (1998-2007)
Simon C Warby, PhD; University of Montreal (2007-2018)
Galen EB Wright, PhD (2018-present)

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