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# Huntington Disease-Like 2

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## Summary

### Clinical characteristics

Huntington disease-like 2 (HDL2) typically presents in midlife with a relentless progressive triad of movement, emotional, and cognitive abnormalities which lead to death within ten to 20 years. HDL2 cannot be differentiated from Huntington disease clinically. Neurologic abnormalities include chorea, hypokinesia (rigidity, bradykinesia), dysarthria, and hyperreflexia in the later stages of the disease. There is a strong correlation between the duration of the disease and the progression of the motor and cognitive disorder.

### Diagnosis/testing

The diagnosis of HDL2 rests on positive family history, characteristic clinical findings, and the detection of an expansion of 40 or more CTG trinucleotide repeats in *JPH3*.

### Management

*Treatment of manifestations:* Treatment is symptomatic and is presumably similar to that for HD and other neurodegenerative disorders – although this must be considered speculative pending objective data. Pharmacologic agents that may suppress abnormal movements include tetrabenazine and its derivatives, low-dose neuroleptic agents such as fluphenazine and haloperidol. Antidepressants, antipsychotics, mood stabilizers (lithium, valproic acid, carbamazepine, and lamotrigine), and occasionally stimulants may improve psychiatric manifestations. Education about the course of disease and environmental interventions (regular schedules, use of lists to assist memory). Remove loose rugs and clutter from the individual's home and minimize or eliminate the need for stairs to help prevent falls and other injuries; driving may need to be curtailed or limited to prevent risk of accidents; food should be prepared in such a manner as to prevent choking.

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*Surveillance:* Monitor: nutrition and swallowing in order to implement feeding changes when necessary to minimize risk of aspiration; gait and use appropriate strategies or devices to minimize falls; driving to assure that affected individuals do not present a danger to themselves or others; mood and irritability, such that measures to decrease the risk of suicide, other behavioral abnormalities, and distress may be implemented.

*Agents/circumstances to avoid*: Any agents that increase ataxia should be used with caution; avoid polypharmacy, which may exacerbate delirium.

## Genetic counseling

HDL2 is inherited in an autosomal dominant manner. HDL2 resulting from a *de novo* pathogenic variant has not been reported but is theoretically possible. Offspring of an individual with HDL2 have a 50% chance of inheriting the HDL2-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. Predictive testing is not considered appropriate for asymptomatic at-risk individuals younger than age 18 years. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible once an HDL2-causing expansion has been identified in an affected family member.

# Diagnosis

## Suggestive Findings

Huntington disease-like 2 (HDL2) **should be suspected** in individuals – particularly of African descent or with African ancestry (even if distant) – who present with clinical features typical of Huntington disease (HD) but do not have a disease-causing CAG expansion (i.e., reduced-penetrance allele or full-penetrance allele) in *HTT*. A family history is suggestive, but a negative family history should not exclude the diagnosis as information about family members may be missing, or hidden to avoid possible stigmatization.

**Clinical features**

- Progressive motor disability featuring involuntary movements (especially chorea) and affecting voluntary movement (e.g., gait, speech, swallowing). Rigidity and bradykinesia may predominate in the later stages of the disease.
- Psychiatric disturbances including changes in personality and depression
- Progressive dementia
- Family history consistent with autosomal dominant inheritance. Note, however, that family history may be unavailable or inaccurate.

## Establishing the Diagnosis

The diagnosis of Huntington disease-like 2 **is established** in a proband with the above Suggestive Findings and a heterozygous expansion of a CTG trinucleotide repeat in *JPH3* identified by molecular genetic testing (see Table 1).

**Allele sizes**

- **Normal alleles.** Six to 28 CTG repeats [Holmes et al 2001]. The diagnosis can be excluded if neither allele has a repeat length greater than 28 CTG repeats.
- **Alleles of questionable significance.** 29 to 39 CTG repeats; the pathogenicity of alleles in this range is unknown. Repeats in this range could be either of the following:

- **Mutable normal alleles** that do not have a phenotypic effect in the individual but are unstable in vertical transmission

  Note: (1) A woman age 48 years with an atypical cerebellar disorder (rapid onset following hospitalization for out-of-control diabetes mellitus, little or no progression) had a *JPH3* CTG repeat length of 33 in one allele. Her son age 30 years had developed Cogan's syndrome, an autoimmune disease resulting in complete hearing loss, at age 25 years. He complained of tinnitus, occasional lapses of concentration, and difficulty with balance, all associated with the onset of Cogan's syndrome. Examination suggested possible cerebellar involvement. He had a CTG repeat length of 35, suggesting repeat length instability at this range. (2) An individual with molecularly diagnosed Huntington disease coincidentally also had a *JPH3* allele of 34 CTG repeats [Author, personal observation].

- **Reduced-penetrance alleles** that result in very late-onset disease and/or a different phenotype and/or no occurrence of clinical disease in a normal life span

- **Full-penetrance (disease-causing) alleles.** 40 CTG repeats or greater. In the presence of a clinical syndrome consistent with HDL2, an allele with 40 or more CTG repeats is considered diagnostic of HDL2.

  Notes: (1) Apparently unaffected individuals with repeat lengths in the pathogenic range may eventually develop the disease. One individual (in a family with a proband with clinically, neuropathologically, and molecularly defined HDL2) had an expanded allele of 44 CTG repeats without clear evidence of clinical HDL2 at age 65 years. It is possible that the effects of a mild stroke several years prior to examination masked signs of HDL2. (2) PCR-based assays, standard in genetic laboratories, are typically accurate to within ~±1 triplet, complicating interpretation of alleles of borderline length. (3) An allele with 39 CTG repeats has been reported in an individual with an HDL2 phenotype. (4) The longest repeat expansion detected to date is 60 CTG repeats.

**Molecular genetic testing** approaches include **targeted testing** for the CTG repeat length at the *JPH3* locus.

**Table 1.** Molecular Genetic Testing Used in Huntington Disease-Like 2

| Gene [1] | Method | Proportion of Probands with a Pathogenic Variant [2] Detectable by Method |
|---|---|---|
| *JPH3* | Targeted analysis [3] | 100% [4] |

*1.* See Table A. Genes and Databases for chromosome locus and protein.
*2.* See Molecular Genetics for information on allelic variants detected in this gene.
*3.* Detects CTG trinucleotide repeat number. PCR-based methods can detect expanded alleles including the largest reported allele of 60 CTG repeats [Anderson et al 2019a].
*4.* The test should detect nearly all expanded alleles [Holmes et al 2001, Krause et al 2015]. However, it is theoretically possible that expanded repeats may not be detected because of a polymorphism at the primer site or an unusually long repeat. It is recommended that retesting with an alternative primer pair should be attempted in the setting of strong clinical suspicion and apparent homozygosity of allele length, as a SNP may occasionally interfere with allele detection by PCR.

# Clinical Characteristics

## Clinical Description

Like Huntington disease (HD), Huntington disease-like 2 (HDL2) typically presents in midlife with a relentless progressive triad of movement, emotional, and cognitive abnormalities. However, unlike HD, HDL2 has been described exclusively in individuals with African ancestry. More than half of individuals with HDL2 have been reported from South Africa; most of the remaining individuals are from North and South America [Anderson et al 2017, Walker et al 2018].

The average age of onset is 41 years (SD=11.1), although the range has been reported to be wide (12-66 years) [Anderson et al 2017]. The length of the CTG expansion has an inverse correlation with age of onset. Death usually follows ten to 20 years after disease onset [Margolis et al 2001].

HDL2 has a broad clinical phenotype which is characterized by dementia, with chorea and oculomotor abnormalities as the initial motor symptoms. With longer disease duration, there is progression to a rigid and bradykinetic state with worsening dystonia. HDL2 is indistinguishable from HD in the clinical setting [Anderson et al 2019a].

Chorea is the most common movement abnormality, followed by rigidity, bradykinesia, dysarthria, and dystonia. Hyperreflexia is a late feature of the disease [Anderson et al 2017]. Oculomotor dysfunction, despite earlier reports [Margolis et al 2001, Walker et al 2003a, Anderson et al 2017], appears to be as common in HDL2 as in HD, and worsens with longer disease duration [Anderson et al 2019a]. As in HD, some patients present with a more rigid, dystonic form of the illness with relatively less chorea.

Dementia is a universal feature of HDL2 and is similar to the dementia profile seen in HD [Anderson et al 2017]. Depression, apathy, and irritability are the most common forms of psychiatric disturbance.

**Acanthocytosis** has been reported in four individuals with HDL2 [Walker et al 2002, Walker et al 2003b]. Subsequent reports have not found acanthocytes in individuals with HDL2. Furthermore, a blinded controlled study did not find acanthocytes in individuals with HDL2 [Anderson et al 2017]. Therefore, the presence of acanthocytes is unlikely to have clinical or pathogenic relevance in HDL2.

**Brain MRI** shows the typical features of HD: prominent atrophy of the caudate and cerebral cortex with sparing of the brain stem and cerebellum [Margolis et al 2001]. A comparison of brain volumes in individuals with HDL2 and HD using semiautomated MRI image analysis confirmed similar cortical and striatal volume loss with greater thalamic atrophy in individuals with HDL2 [Anderson et al 2019b].

**Neuropathology.** Neuronal loss is most prominent in the striatum and the cerebral cortex. Striatal loss appears limited to medium spiny neurons and occurs in a dorsal-to-ventral gradient as in HD. Intranuclear inclusions that stain with antibodies against polyglutamine, ubiquitin [Margolis et al 2001, Walker et al 2002], torsinA [Walker et al 2002], and TBP have been detected, predominantly in the cortex [Rudnicki et al 2008].

## Genotype-Phenotype Correlations

As in HD, longer CTG repeat length correlates with an earlier age of onset in HDL2 [Margolis et al 2004, Anderson et al 2017]. It is possible that longer repeat length (~≥50 CTG repeats) may be associated with a more aggressive course (less chorea; more dystonia, rigidity, and weight loss), observed primarily in the large index family [Margolis et al 2001], although alternative genetic or environmental factors may be relevant.

## Penetrance

For ethical reasons, only a few unaffected individuals from families with HDL2 have been tested; therefore, the penetrance is unknown, though as noted above, one individual with a repeat of 44 triplets did not have evidence of HDL2 at age 65, suggesting the possibility of reduced penetrance in some individuals.

## Anticipation

Limited evidence from the large index pedigree suggests that anticipation may occur [Margolis et al 2001]. An example of anticipation through paternal inheritance has been described [Greenstein et al 2007]. So far, no large changes in allele size have been detected in either maternal or paternal transmission. A difference of +3 repeats has been detected in a few sibships, but data are limited.

## Nomenclature

HDL2 is occasionally (and incorrectly) referred to as HD2.

## Prevalence

Although rare, HDL2 appears to be the most common HD phenocopy in populations with African ancestry. These include France [Mariani et al 2016], parts of the Americas [Margolis et al 2004, Walker et al 2018], and South Africa [Krause et al 2015]. Individuals with HDL2 share a common haplotype which originated in Africa [Krause et al 2015]. The highest number of affected individuals are from South Africa [Anderson et al 2017]. An analysis of blood samples from individuals with an HD-like phenotype referred for HD testing [Krause et al 2015] found that 15% of black South Africans and no white individuals were found to have HDL2, while 62% of whites and 36% of blacks were found to have HD. Therefore, for every two black individuals diagnosed with HD there was approximately one individual diagnosed with HDL2.

Outside of South Africa, HDL2 has been identified in as few as 1% of individuals with clinically or pathologically defined HD who do not have an *HTT* pathogenic variant [Rosenblatt et al 1998, Stevanin et al 2003, Margolis et al 2004]. In Brazil, where an estimated 44% of the population is of African descent, as many as 10% of individuals with an HD-like disorder may have HDL2 [Rodrigues et al 2011].

- Of 300 individuals referred to a large commercial diagnostic laboratory in the United States for HD testing who had tested negative for the HD-causing expansion, two were found to have the HDL2-causing expansion.
- The first case of HDL2 from Botswana was recently described in a male age 47 years [Ocampo et al 2018].
- Among 74 individuals (60 of French origin) with a variety of movement disorders with and without dementia, 36% of whom had an autosmal dominant inheritance pattern [Stevanin et al 2002], only one case of HDL2 was detected, in an individual from North Africa.
- Among 1600 individuals with movement disorders referred for genetic testing by neurologists in Germany and Austria who did not have an expanded HD allele (including 147 individuals with a family history of chorea), no HDL2 expansions were found [Bauer et al 2002].
- If the cases described above are narrowly defined, the frequency of HDL2 is much higher than indicated. For instance, of four individuals identified by Rosenblatt et al [1998] with HD-like autosomal dominant disorders, two ultimately proved to have HDL2.
- No cases of HDL2 have yet been detected in Japan, though only a small number of individuals have been tested.
- HDL2 has been detected in several pedigrees in the Caribbean.

# Genetically Related (Allelic) Disorders

CTG expansions within *JPH3* have not been associated with other phenotypes. Syndromes arising from deletions including *JPH3* have been identified [Authors, unpublished communication]; the relevance to HDL2 is uncertain.

# Differential Diagnosis

The differential diagnosis of Huntington disease-like 2 (HDL2) is the same as for Huntington disease (HD), and is based on the co-occurrence of: (1) movement abnormalities (chorea, dystonia, and/or parkinsonism) reflecting basal ganglia dysfunction, dementia, and psychiatric disturbances; and (2) autosomal dominant inheritance.

The most obvious diagnosis to exclude is HD itself. HD and other disorders to be considered are summarized in Table 2.

**Table 2.** Inherited Conditions to Consider in the Differential Diagnosis of Huntington Disease-Like 2 (HDL2)

| Differential Diagnosis Disorder | Gene(s) | MOI | Clinical Features of Differential Diagnosis Disorder | |
|---|---|---|---|---|
| | | | Overlapping w/HDL2 | Distinguishing from HDL2 |
| Huntington disease | *HTT* | AD | Clinically indistinguishable from HDL2 | Possibly greater thalamic volume than in HDL2 (unlikely to be diagnostically useful in single cases) |
| Neuroferritinopathy | *FTL* | AD | • Chorea<br>• Dystonia<br>• Parkinsonism | Dementia rare |
| Dentatorubral-pallidoluysian atrophy | *ATN1* | AD | • Progressive movement disorder & dementia<br>• Psychiatric disturbances | • Prominent ataxia & myoclonus<br>• More common in Japan |
| Chorea-acanthocytosis | *VPS13A* | AR | • Progressive movement disorder<br>• Progressive cognitive & behavior changes | • Myopathy<br>• ↑ serum CK<br>• Acanthocytosis<br>• Seizures common<br>• Mean onset age ~30 yrs |
| Benign hereditary chorea (OMIM 118700) | *NKX2-1* | AD | Chorea | • Usually childhood onset<br>• Chorea is non-progressive.<br>• No dementia |
| Spinocerebellar ataxia type 2 | *ATXN2* | AD | • Chorea<br>• Parkinsonism<br>• Dystonia<br>• Oculomotor dysfunction | Cerebellar ataxia is the prominent movement disorder. |
| Spinocerebellar ataxia type 3 | *ATXN3* | AD | Chorea (rare) | Cerebellar ataxia is the prominent movement disorder. |
| Spinocerebellar ataxia type 17 | *TBP* | AD | • Chorea<br>• Dementia<br>• Psychiatric disturbances | Cerebellar ataxia is typical but not uniformly present. |
| Familial Creutzfeld-Jakob disease (fCJD) (See Genetic Prion Disease.) | *PRNP* | AD | • Typically late onset<br>• Progressive dementia<br>• Movement disorders<br>• Behavior changes & psychiatric symptoms | • Progresses more rapidly than HDL2<br>• Prominent myoclonus |
| Wilson disease | *ATP7B* | AR | • Movement disorders<br>• Psychiatric disorders | • Liver disease<br>• Kayser-Fleischer rings<br>• Copper abnormalities<br>• Exclusion is essential since Wilson disease is treatable. |
| Neuronal ceroid-lipofuscinoses | >10 genes [1] | AR<br>AD | Movement disorder | Usually AR w/childhood onset, rarely AD w/adult onset |
| Pantothenate kinase-associated neurodegeneration | *PANK2* | AR | • Parkinsonism<br>• Dystonia<br>• Dementia | • Childhood onset w/early falls & visual disturbances<br>• MRI features |

*Table 2. continued from previous page.*

| Differential Diagnosis Disorder | Gene(s) | MOI | Clinical Features of Differential Diagnosis Disorder | |
|---|---|---|---|---|
| | | | Overlapping w/HDL2 | Distinguishing from HDL2 |
| Primary familial brain calcification (familial idiopathic basal ganglia calcification) | *PDGFB*<br>*PDGFRB*<br>*SLC20A2*<br>*XPR1* | AD | • Parkinsonism<br>• Chorea<br>• Dystonia | MRI features |
| Mitochondrial disorders (See Mitochondrial Disorders Overview.) | See footnote 2. | AR<br>AD<br>mt | • Chorea<br>• Cognitive impairment | • MRI necrosis<br>• Pyruvate/lactate abnormalities |
| McLeod neuroacanthocytosis syndrome | *XK* | XL | • Cognitive impairment<br>• Psychiatric symptoms<br>• Chorea | • Acanthocytosis, compensated hemolysis, & McLeod blood group phenotype<br>• Seizures<br>• Peripheral neuropathy<br>• Hyporeflexia<br>• Cardiomyopathy<br>• Hepatosplenomegaly |
| Parkinsonian conditions (See Parkinson Disease.) | See footnote 3. | AD<br>AR<br>XL [4] | • Parkinsonism<br>• Dystonia<br>• Family history | • Striatal atrophy early<br>• No chorea |
| Progressive supranuclear palsy; corticobasal ganglia degeneration; frontotemporal dementia w/parkinsonism-17 (See *MAPT*-Related Frontotemporal Dementia.) | *MAPT* | AD | • Late-onset<br>• Progressive movement disorders, dementia, & behavior changes<br>• Psychiatric disturbances | No chorea |
| Frontotemporal dementia &/or amyotrophic lateral sclerosis | *C9orf72* | AD | • Movement disorders<br>• Dementia<br>• Psychiatric disturbances | Myoclonus, tremor, torticollis |
| Huntington disease-like 1 (OMIM 603218) [5] | *PRNP* | AD | Range of clinical features that overlap w/HD | Early-onset, slowly progressive |
| Hereditary cerebellar ataxia (See Hereditary Ataxia Overview.) | Many | AD<br>AR<br>XL | Movement disorder | Hereditary cerebellar ataxia assoc w/ prominent cerebellar & long tract signs |
| Early-onset familial Alzheimer disease (See Alzheimer Disease Overview.) | *APP*<br>*PSEN1*<br>*PSEN2* | AD | Dementia | No movement abnormalities |

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; mt = mitochondrial; XL = X-linked

*1.* See Phenotypic Series: Ceroid lipofuscinoses for genes associated with this phenotype in OMIM.

*2.* Mitochondrial disorders may be caused by defects of nuclear DNA or mtDNA (see Mitochondrial Disorders Overview).

*3.* See Phenotypic Series: Parkinson disease to view genes associated with this phenotype in OMIM.

*4.* Mendelian (monogenic) forms of Parkinson disease are inherited in an autosomal dominant, autosomal recessive, or, rarely, X-linked manner. For mendelian forms of Parkinson disease, genetic counseling depends on the mode of inheritance. In contrast, most Parkinson disease is thought to be non-mendelian and to result from the effects of multiple genes as well as environmental risk factors.

*5.* HDL1 is caused by a specific pathogenic variant (8 extra octapeptide repeats) in the prion protein gene, *PRNP*, on chromosome 20p. Similar pathogenic variants at this locus also result in other forms of prion disease, such as familial Creutzfeldt-Jakob disease (see Genetic Prion Disease).

Nonfamilial disorders that may present like HDL2 include: tardive dyskinesia (common), Sydenham's chorea, systemic lupus erythematosus (SLE), neurosyphilis, hyperglycemia, acquired forms of Creutzfeld-Jakob disease, pregnancy, multisystem atrophy, and thyroid disease.

HDL2-like symptoms can also arise from drugs including: antipsychotics, anticonvulsants, oral contraceptives, lithium, and stimulants.

# Management

## Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Huntington disease-like 2 (HDL2), the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Neuroimaging studies to exclude other lesions, such as subdural hematomas secondary to falls, which may be contributing to signs or symptoms
- Standardized rating assessments to track progress, such as the Unified Huntington's Disease Rating Scale (UHDRS) or Quantitated Neurological Examination (QNE) for motor abnormalities and the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) for cognition
- Consultation with a clinical geneticist and/or genetic counselor

## Treatment of Manifestations

Treatment is symptomatic and based on the treatment for HD and other neurodegenerative disorders.

- Pharmacologic agents may suppress abnormal movements. The most common choices are tetrabenazine and its derivatives; consider also low-dose neuroleptic agents such as fluphenazine or haloperidol.
- Tremor in one individual was suppressed with clonazepam. However, clonazepam, levodopa/carbidopa, anticholinergics, and typical and atypical neuroleptics were not found helpful in treating the abnormal movements of other affected individuals.
- Based on experience with Huntington disease, antidepressants, antipsychotics, mood stabilizers (lithium, valproic acid, carbamazepine, and lamotrigine), electroconvulsive therapy, and occasionally stimulants may be effective in treating the psychiatric manifestations of HDL2.
- In the only report specifically related to HDL2, depression partially responded to sertraline in one individual and to nortriptyline in another individual [Walker et al 2003b].
- The affected individual, other family members, and care providers should be educated regarding the likely course of the disease. Assurance that cognitive decline, depression, apathy, and irritability are manifestations of the disease rather than the "fault" of the individual can decrease stress and guilt.
- Environmental interventions (establishing regular schedules, easing of expectations to maintain the family finances, encouraging the use of lists to assist with memory) may help.
- Implementation of safety precautions, particularly at home: removal of loose rugs and clutter, minimizing or elimination of the need for stairs, careful assessment of competency for driving. Food preparation may need to be altered to prevent choking.
- Planning for financial matters (e.g., assigning power of attorney)
- Families often need help in obtaining social services (see Resources).

## Surveillance

Nutrition and swallowing should be monitored. Feeding changes should be implemented when necessary to minimize the risk of aspiration.

Gait should be monitored, with consultation as needed from physical therapists to provide the most appropriate strategies or devices to minimize falls.

Driving safety should be monitored, with consideration of formal driving safety evaluations if safety is uncertain.

Monitor mood and irritability so that measures to decrease behavior abnormalities, distress, and the risk for suicide may be implemented.

## Agents/Circumstances to Avoid

Any agents that increase ataxia should be used with caution.

Individuals with HDL2, like others with neurodegenerative disorders, are vulnerable to delirium from medical illnesses and medicines, especially polypharmacy.

## Evaluation of Relatives at Risk

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

## Pregnancy Management

There is no specific information available about disease management during pregnancy. Prudence suggests close attention to prevention of falls and monitoring for swallowing difficulties. Medications should be reviewed to assess their safety during pregnancy. See MotherToBaby for further information on medication use during pregnancy.

## Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

# 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-like 2 (HDL2) is inherited in an autosomal dominant manner.

Note: HDL2 and Huntington disease cannot be clinically distinguished [Anderson et al 2019a], complicating genetic counseling in families in which a diagnosis has not been confirmed with molecular genetic testing (see Diagnosis); this distinction is critical for predictive testing and may be of relevance if treatments specific for Huntington disease emerge from ongoing clinical trials.

## Risk to Family Members

**Parents of a proband**

- Most individuals with HDL2 have an affected parent.
- *De novo* pathogenic variants have not been reported as a cause of HDL2, but information about repeat length transmission is lacking in most families. It is theoretically possible that a repeat expansion of a

mutable normal allele / reduced-penetrance allele into the affected range may occur, as it does in Huntington disease; however, such an event has not been documented to date.
- It is appropriate to offer molecular genetic testing to asymptomatic parents of a proband who appears to represent a simplex case (i.e., a single occurrence in a family). Note: Testing for the expansion in the absence of symptoms of the disease is predictive testing and genetic counseling, both before and after testing, is essential.
- Although most individuals diagnosed with HDL2 have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

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

- If a parent of the proband is affected and/or has a *JPH3* allele with 40 CTG repeats or greater, the risk to the sibs is 50%.

  Theoretically, an affected parent with a repeat length just at the disease threshold could transmit an expanded allele to one sib and an unexpanded allele to another sib; such a case has not yet been detected.
- If a parent has a high normal-length *JPH3* allele (i.e., close to 40 repeats), the risk of the offspring inheriting an HDL2-causing allele is currently uncertain, but would be greater than 0%. If one sib has inherited an expanded allele from a parent with a high normal-length allele, the risk would be predicted to be significant, though not yet quantifiable.
- A sib who inherits a *JPH3* reduced-penetrance allele may or may not develop symptoms of HDL2.

**Offspring of a proband**

- At conception, each child of an individual with HDL2 has a 50% chance of inheriting the HDL2-causing allele.
- Offspring who inherit a *JPH3* reduced-penetrance allele may or may not develop symptoms of HDL2.

**Other family members**

- The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected and/or heterozygous for an HDL2-causing expansion, the parent's other family members are at potential risk depending on their relatedness.
- Offspring of an asymptomatic individual heterozygous for an allele of fewer than 40 repeats may be at risk for HDL2 because of the potential for expansion during vertical transmission. This is probably more likely if the allele of the asymptomatic individual is close to 40 repeats in length.

## Related Genetic Counseling Issues

**Considerations in families with an apparent *de novo* expansion.** When neither parent has an HDL2-causing expansion (≥40 CTG triplets) or an allele of questionable significance (29-39 triplets), explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption may need to be explored, as the information could have implications for other potentially at-risk family members.

**Testing of at-risk asymptomatic adults (predictive testing).** Testing of asymptomatic adults at risk for HDL2 is possible. When testing at-risk individuals for HDL2, an affected family member should be tested first to confirm the molecular diagnosis of HDL2 in the family.

Whether an asymptomatic adult will develop HDL2 can be predicted by the presence of a repeat expansion at the HDL2 locus, although this prediction must be qualified by the fact that the correlation between repeat length and disease has been examined in relatively few individuals. In particular, the penetrance of repeat lengths near

the disease threshold and the association between age of onset and repeat length have not been well established. As additional persons with HDL2 are reported, the reliability of clinical predictions based on the length of the HDL2-causing expansion will increase.

At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Others may have different motivations including simply the "need to know." Testing of asymptomatic at-risk adult family members involves pre-test counseling in which the motives for requesting the test, the individual's knowledge of HDL2, the possible impact of positive and negative test results, and neurologic status are discussed. Those seeking testing should be counseled about possible problems that they may encounter with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members, and the limited information available about HDL2. Informed consent should be procured, and records kept confidential. Individuals with a positive test result need arrangements for long-term follow up and evaluations.

The best model for HDL2 predictive testing is Huntington disease predictive testing. Prudence suggests following the same genetic testing guidelines used for Huntington disease, including counseling prior to testing, a confidant to serve as a social support, and availability of counseling following the disclosure of genetic results.

**Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals 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. This recommendation may change if effective disease-modifying treatments are developed.
- 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 HDL2, it is appropriate to consider testing of symptomatic individuals regardless of age.

**Family planning**

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

**For fetuses at 50% risk.** If the presence of an HDL2-causing 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 and preimplantation genetic testing (PGT) are possible.

A PGT exclusion protocol may be an option for testing of the embryo of couples in an at-risk family who do not wish to undergo presymptomatic testing for the HDL2-causing allele themselves. While there is no known example of PGT applied to HDL2, the concepts and procedures would be nearly identical to those of HD.

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.*

- **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
- **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

- **National Library of Medicine Genetics Home Reference**
  Huntington disease

# 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-Like 2: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *JPH3* | 16q24.2 | Junctophilin-3 | JPH3 database | JPH3 | JPH3 |

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-Like 2 (View All in OMIM)

| | |
|---|---|
| 605268 | JUNCTOPHILIN 3; JPH3 |
| 606438 | HUNTINGTON DISEASE-LIKE 2; HDL2 |

## Molecular Pathogenesis

**Introduction.** HDL2 is caused by a CTG expansion on chromosome 16q24.2, which is located on the sense strand in exon 2A of *JPH3*. The primary *JPH3* transcript does not contain exon 2A with the repeat [Holmes et al 2001].

The junctophilin-3 protein, which is primarily expressed in the brain, appears to help establish the junctional complex between the cytoplasmic membrane and the endoplasmic reticulum (ER). This may serve to link voltage-gated calcium channels with calcium release channels in the ER [Nishi et al 2000, Takeshima et al 2000, Ito et al 2001]. Other possible functions of the protein have not been systematically investigated; however the closely related protein junctophilin-2 may function as a transcriptional regulator factor [Guo et al 2018].

A *JPH3* transcript containing exon 1 and exon 2A is also expressed. Because alternate splice acceptor sites occur between exon 1 and exon 2A in this transcript, the repeat may exist in three alternate reading frames, in which it could encode polyalanine or polyleucine, or fall in the 3' untranslated region.

The expression pattern and function of the exon 1 – exon 2A transcript variants are not known. This short transcript contains the plasma membrane recognition motif, but not the ER insertion domain, present in the full-length transcript.

In the antisense strand, the repeat consists of a CAG repeat predicted to encode a polyglutamine tract within a cryptic unnamed gene. The antisense gene does appear to be transcribed, though whether it is transcribed when the repeat is expanded, and whether the transcript is translated, remains unknown [Wilburn et al 2011, Seixas et al 2012].

**Mechanism of disease causation.** Although associated with CTG expansion, the molecular pathogenesis of HDL2 remains unknown. Available evidence suggests at least three non-mutually exclusive mechanisms:

- Loss of function by sequestration of *JPH3* RNA carrying the expanded repeat, with subsequent loss of protein expression [Seixas et al 2012]
- Gain of function from toxic properties of *JPH3* transcripts containing an expanded repeat [Rudnicki et al 2007]

- Toxic gain of function from the expression of protein containing an expanded polyamino acid tract from either sense or antisense strands [Wilburn et al 2011]

***JPH3*-specific laboratory technical considerations.** Laboratory testing is similar to that performed for other repeat expansion diseases. As such, unknown variations in sequence that affect PCR efficiency, or very long repeat lengths, could lead to a failure to detect a repeat expansion. Therefore, detection of a single allele should not automatically lead to the conclusion that an individual is homozygous for a repeat of that length; repeat length in other family members, or additional testing, may be necessary to prove that a long expansion is not present.

# Chapter Notes

## Author Notes

The laboratory of Dr Russell L Margolis at Johns Hopkins School of Medicine, which identified the first known family with HDL2 as well as the genetic cause, is actively investigating the phenotype and pathogenesis of HDL2 and welcomes questions regarding individuals possibly affected with HDL2. Contact Dr Margolis at rmargoli@jhmi.edu with questions or additional information about HDL2.

The Division of Human Genetics, at the National Health Laboratory Services and the School of Pathology, The University of the Witwatersrand is studying the detailed molecular genetics of the HDL2 locus and its association with clinical manifestations of HDL2. The laboratory will offer diagnostic testing for HDL2 for individuals from outside of South Africa. For further details, contact Professor Amanda Krause at amanda.krause@wits.ac.za. Clinical questions can also be directed to Dr David Anderson at the University of Witwatersand, david@neuro.joburg.

The authors would like to be informed of all newly diagnosed individuals with HDL2 to expand information about this rare disease.

## Revision History

- 27 June 2019 (sw) Comprehensive update posted live
- 26 April 2012 (me) Comprehensive update posted live
- 13 August 2009 (me) Comprehensive update posted live
- 10 March 2006 (me) Comprehensive update review posted live
- 30 January 2004 (me) Review posted live
- 15 September 2003 (rm) Original submission

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- Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 12-29-22.
- National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 12-29-22.

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