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HTRA1 Disorder

Synonym: CARASIL (*C*erebral *A*utosomal *R*ecessive *A*rteriopathy with *S*ubcortical *I*nfarcts and *L*eukoencephalopathy)

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Summary

Clinical characteristics

HTRA1 disorder is a phenotypic spectrum in which some individuals have few to no symptoms and others manifest with the more severe CARASIL (*c*erebral *a*utosomal *r*ecessive *a*rteriopathy with *s*ubcortical *i*nfarcts and *l*eukoencephalopathy) phenotype. Those who have a heterozygous *HTRA1* pathogenic variant may have mild neurologic findings (sometimes identified only on neuroimaging) or mild-to-moderate neurologic signs and symptoms of CARASIL. In this chapter, the term "classic CARASIL" refers to the more severe phenotype associated with biallelic pathogenic variants, and "*HTRA1* cerebral small vessel disease" (*HTRA1*-CSVD) refers to the milder phenotype associated with a heterozygous *HTRA1* pathogenic variant.

- Classic CARASIL is characterized by early-onset changes in the deep white matter of the brain observed on MRI, and associated neurologic findings. The most frequent initial symptom is gait disturbance from spasticity beginning between ages 20 and 40 years. Forty-four percent of affected individuals have stroke-like episodes before age 40 years. Mood changes (apathy and irritability), pseudobulbar palsy, and cognitive dysfunction begin between ages 20 and 50 years. The disease progresses slowly following the onset of neurologic symptoms. Scalp alopecia and acute mid- to lower-back pain (lumbago) before age 30 years are characteristic.
- The most frequent initial symptom in individuals with *HTRA1*-CSVD is slowly progressive gait disturbance after age 40 years, which may be followed by the development of mood changes and cognitive dysfunction. A majority of affected individuals have a stroke-like episode after age 40 years. Spondylosis and alopecia are seen in a minority of individuals with *HTRA1*-CSVD.

Diagnosis/testing

The diagnosis of *HTRA1* disorder is established in a proband by identification of either a heterozygous or biallelic pathogenic variant(s) in *HTRA1* on molecular genetic testing.

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Management

Treatment of manifestations: Consideration of anti-platelet therapy and anti-hypertensive therapy for those with cerebral microbleeds; physical therapy, walking aids, and home adaptations for those with gait disturbance; consideration of medication (baclofen or tizanidine) for spasticity; wig or hairpiece for those with alopecia; standard treatment for spinal spondylosis and mood disorder; supportive care including emotional support and counseling for affected individuals and their families.

Surveillance: Follow-up intervals are based on the severity and type of symptoms and the needs of the individuals and their caregivers.

Agents/circumstances to avoid: Smoking and a high-salt diet, which may hasten the progression of arteriosclerosis.

Genetic counseling

HTRA1 disorder caused by biallelic pathogenic variants (i.e., the classic CARASIL phenotype) is inherited in an autosomal recessive manner. *HTRA1* disorder caused by heterozygous pathogenic variants is inherited in an autosomal dominant manner.

- *Autosomal recessive inheritance*. At conception, each sib of an affected individual has a 25% chance of inheriting both *HTRA1* pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither pathogenic variant and not being at risk for *HTRA1* disorder.
- *Autosomal dominant inheritance*. Each sib of an affected individual has a 50% risk of inheriting the pathogenic variant from their affected parent.

Once the *HTRA1* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *HTRA1* disorder are possible.

GeneReview Scope

HTRA1 Disorder: Included Phenotypes
• Classic CARASIL • *HTRA1* cerebral small vessel disease (*HTRA1*-CSVD)

For synonym s and outdated names see Nomenclature.

Diagnosis

Clinical diagnostic criteria for *HTRA1* disorder, including the classic CARASIL phenotype ("classic CARASIL"), have not been published.

Suggestive Findings

HTRA1 disorder **should be suspected** in individuals with the following clinical, neuroimaging, and family history findings.

Clinical features. Individuals **presenting before age 55 years** with the following:

- Slowly progressive dementia
- Mood changes, such as apathy and irritability
- Slowly progressive gait disturbance with spasticity in the lower extremities [Fukutake & Hirayama 1995, Fukutake 2011, Nozaki et al 2014]

Note: Those with a heterozygous *HTRA1* pathogenic variant (*HTRA1* cerebral small vessel disease) may present with these features after age 55 years.

Additional young adult-onset findings in those with biallelic pathogenic variants in *HTRA1* (classic CARASIL):

- Spondylosis deformans. Acute mid- to lower-back pain (lumbago) associated with spondylosis and disk degeneration with osteophyte formation in the lumbar spine
- Alopecia. Typically seen before age 30 years

  Note: Alopecia is variable; affected individuals with biallelic *HTRA1* pathogenic variants without alopecia have been reported [Nishimoto et al 2011, Nozaki et al 2014].

Neuroimaging. Extended white matter lesions and external capsule lesions:

- Early-onset leukoaraiosis (changes in deep white matter in the brain, observed on MRI or CT). Leukoaraiosis may precede neurologic symptoms [Fukutake 2011, Nozaki et al 2015].
- Brain MRI resembling that of CADASIL (*c*erebral *a*utosomal *d*ominant *a*rteriopathy with *s*ubcortical *i*nfarcts and *l*eukoencephalopathy). Findings in symptomatic individuals may include the following [Fukutake 2011, Nozaki et al 2015]:
  - Symmetrically distributed white matter hyperintensities located in the periventricular and deep white matter

    Note: White matter changes may precede the onset of neurologic symptoms, including gait disturbance, mood change, and cognitive decline.
  - T_2-weighted signal abnormalities in the white matter of the anterior part of the temporal lobe, cerebellum, brain stem, and middle cerebellar peduncle (arc sign), and in the external capsule
  - Relative preservation of U-fibers
  - Lacunar infarcts (linearly arranged groups of rounded and circumscribed lesions with signal intensity identical to that of cerebrospinal fluid) in the basal ganglia and subcortical white matter
  - Microbleeds in the cerebral cortex, basal ganglia, brain stem, and cerebellum

    Note: It is not clear if the white matter changes in the anterior temporal poles and external capsule, which are characteristic signs in CADASIL, are also observed in early stages of CARASIL.

Family history is consistent with:

- Autosomal recessive inheritance in those with classic CARASIL;
- Autosomal dominant inheritance for those with a heterozygous *HTRA1* pathogenic variant (*HTRA1*-CSVD).

Note: Absence of a known family history of *HTRA1* disorder does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *HTRA1* disorder **is established** in a proband by identification of either a heterozygous pathogenic (or likely pathogenic) variant or biallelic pathogenic (or likely pathogenic) variants in *HTRA1* on molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is

understood to include likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing or genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *HTRA1* disorder is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of CARASIL has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and imaging findings suggest the diagnosis of classic CARASIL, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *HTRA1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Given the mechanism of disease causation (see Molecular Genetics), it is unclear whether exon or whole-gene deletions/duplications cause this phenotype.
- **A cerebral small vessel disease multigene panel** that includes *HTRA1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of CARASIL or *HTRA1* disorder is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *HTRA1* Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
HTRA1	Sequence analysis [3]	Estimated >95% [4]
	Gene-targeted deletion/ duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Hara et al [2009]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

HTRA1 disorder is a phenotypic spectrum in which some individuals have few to no symptoms and others manifest with the more severe classic CARASIL (*c*erebral *a*utosomal *r*ecessive *a*rteriopathy with *s*ubcortical *i*nfarcts and *l*eukoencephalopathy) phenotype. Those who have a heterozygous *HTRA1* pathogenic variant may have mild neurologic findings (sometimes identified only on neuroimaging) or mild-to-moderate neurologic signs and symptoms of CARASIL [Verdura et al 2015, Nozaki et al 2016].

HTRA1 Disorder Caused by Biallelic *HTRA1* Pathogenic Variants (Classic CARASIL)

Neurologic symptoms begin between ages 20 and 50 years.

- The most frequent initial symptom is slowly progressive gait disturbance from spasticity and pyramidal signs in the lower extremities beginning between ages 20 and 40 years.
- Mood change (depression and irritability) and cognitive dysfunction begin between ages 20 and 50 years.
- Pseudobulbar palsy also begins between ages 30 and 50 years.
- Forty-four percent of affected individuals have a stroke-like episode (e.g., hemiparesis or hemisensory impairment) before age 40 years.
- The disease progresses slowly following the onset of neurologic symptoms. In the advanced stage, emotional incontinence, abulia, and akinetic mutism develop.

Spondylosis (disk degeneration with osteophyte formation), which typically follows acute lower- and mid-back pain (lumbago), results in lower-limb pain beginning between ages ten and 30 years. Severe spondylosis deformans with osteoporosis in the cervical and lumbar spine [Nozaki et al 2015] and deformity and formation of osseous specula in the knee joints [Yanagawa et al 2002] may be appreciated on plain radiographs.

Alopecia is frequently (not always) seen before age 30 years.

- Scalp alopecia is diffuse, not confined to the frontal or parietal regions.
- There is no obvious body hair loss.

Pathology. From the autopsy findings, arteriosclerosis associated with intimal thickening and dense collagen fibers, loss of vascular smooth muscle cells, and hyaline degeneration of the media have been observed in

cerebral small arteries. These pathologic findings resemble those observed in persons with non-hereditary ischemic cerebral small vessel disease [Okeda et al 2004, Oide et al 2008, Ito et al 2016]. However, multilayering and splitting of elastic laminae may be specific for CARASIL. These changes are predominant in cerebral small arteries; therefore, skin biopsy is not useful for diagnosis.

Note: Granular osmiophilic material within the vascular media close to smooth muscle cells, a pathologic hallmark for CADASIL, is never observed in CARASIL.

HTRA1 Disorder Caused by a Heterozygous Pathogenic Variant (*HTRA1* Cerebral Small Vessel Disease)

Neurologic symptoms typically begin after age 40 years [Nozaki et al 2016] and include the following:

- Slowly progressive gait disturbance (the most frequent initial symptom)
- Mood change (depression and irritability) and cognitive dysfunction
- A stroke-like episode (e.g., hemiparesis or hemisensory impairment) in 63% of affected individuals
- Slow progression of the disease following the onset of neurologic symptoms

Spondylosis and alopecia are rarer findings.

- Spondylosis deformans is seen in about 36% of affected individuals.
- Alopecia is seen in about 20% of affected individuals.

Pathology. Small vessels in the central nervous system have shown intimal proliferation, splitting of the internal elastic lamina, and degeneration of smooth muscle cells in the tunica media. The features resemble those of individuals with classic CARASIL [Nozaki et al 2016, Ito et al 2018].

Genotype-Phenotype Correlations

No strong genotype-phenotype correlations for *HTRA1* have been identified in classic CARASIL [Hara et al 2009, Favaretto et al 2019].

Those who have a heterozygous *HTRA1* missense variant that either leads to defective trimerization or is located in the LD or L3 domain may have a more severe phenotype than those who have a heterozygous *HTRA1* loss-of-function variant [Nozaki et al 2016, Uemura et al 2019].

Nomenclature

Other names for *HTRA1* disorder include the following:

- CARASIL, for those who have biallelic *HTRA1* pathogenic variants
- Familial young adult-onset arteriosclerotic leukoencephalopathy with alopecia and lumbago without arterial hypertension
- Nemoto disease
- Maeda syndrome
- CADASIL2 (*c*erebral *a*rteriopathy, *a*utosomal *d*ominant, with *s*ubcortical *i*nfarcts and *l*eukoencephalopathy, type 2; OMIM 616779)

Prevalence

HTRA1 disorder has been reported in individuals from Asia, Europe, and North America. However, no founder haplotype has been identified; thus, the authors suspect that the disease will be found more widely.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *HTRA1*.

Differential Diagnosis

Other inherited disorders that cause leukoaraiosis in adulthood are summarized in Table 2. They can be distinguished from *HTRA1* disorder by clinical signs, MRI findings, and appropriate laboratory investigations.

Note: Classic CARASIL should be considered in any young person who has alopecia in conjunction with multiple white matter lesions on MRI.

Table 2. Inherited Disorders with Adult-Onset Leukoaraiosis to Consider in the Differential Diagnosis of *HTRA1* Disorder

Gene(s)	Disorder	MOI	Clinical Description
COL4A1, *COL4A2*	*COL4A1*- & *COL4A2*-related small vessel disease (See *COL4A1*-Related Disorders.)	AD	• Intracranial aneurysm • Renal abnormalities (hematuria, cystic kidney) • Muscle cramps • Retinal arteriolar tortuosity (retinal hemorrhages)
CTSA	CARASAL	AD	Therapy-resistant hypertension [1]
GLA	Fabry disease	XL	• Periodic severe pain in extremities • Angiokeratoma • Renal insufficiency • Hypohidrosis • Left ventricular hypertrophy • Corneal opacities
ITM2B	Familial British dementia (OMIM 176500)	AD	Ataxia, spasticity
NOTCH3	CADASIL [2, 3]	AD	Isolated T_2-weighted hyperintensities involving temporal poles on brain MRI
TREX1	HERNS (OMIM 192315)	AD	• Contrast-enhancing lesion mimicking tumor on brain MRI • Retinal artery abnormalities (macular capillary dropout, tortuous telangiectasia) • Progressive visual loss • Raynaud phenomenon • Migraine • Proteinuria & hematuria

AD = autosomal dominant; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASAL = cathepsin A-related arteriopathy with strokes and leukoencephalopathy; HERNS = hereditary endotheliopathy with retinopathy, nephropathy, and stroke; MOI = mode of inheritance; XL = X-linked

1. Bugiani et al [2016]

2. Chabriat et al [2009]

3. Recommended laboratory investigations: skin biopsy evaluation for NOTCH3 protein expression and electron microscopy for granular osmiophilic material

Other. The clinical characteristics and MRI abnormalities in the following conditions may also resemble those of CARASIL:

- Small vessel diseases (e.g., familial SVD, Portuguese-French type [Verreault et al [2006]])
- Swedish hereditary multi-infarct dementia [Low et al 2007]

- Sporadic small vessel diseases including Binswanger disease and primary angiitis of the nervous system (Binswanger disease can be distinguished from CARASIL by the presence of hypertension.)

Management

Consensus clinical management guidelines for *HTRA1* disorder, including classic CARASIL, have not been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *HTRA1* disorder, the evaluations summarized in Table (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *HTRA1* Disorder

System/Concern	Evaluation	Comment
Neurologic	Neurologic evaluation	Incl scales to evaluate severity of gait disturbance & pseudobulbar palsy
	T_2*-weighted gradient echo imaging	To evaluate for cerebral microbleeds
Psychiatric	Neuropsychiatric evaluation	To screen for anxiety, mood disturbance, & cognitive dysfunction
Gastrointestinal	Consider feeding &/or swallowing study.	If there is concern for pseudobulbar palsy
Skeletal	Consider MRI of spine.	To evaluate for degenerative changes in lumbar or cervical spine
Dermatologic	Assessment for scalp alopecia	
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	Incl genetic counseling
	Family supports/resources	

Treatment of Manifestations

Supportive care in the form of practical help, emotional support, and counseling are appropriate for affected individuals and their families.

Table 4. Treatment of Manifestations in Individuals with *HTRA1* Disorder

Manifestation/Concern	Treatment	Considerations/Other
Cerebral microbleeds	Anti-platelet therapy & anti-hypertension therapy may be considered.	There is no evidence for their effectiveness.
Gait disturbance	Physical therapy to ameliorate coordination difficulties, especially w/walking	
	Crutches (less often canes) & walkers	To prevent falls
	Home adaptations incl grab bars for bathtub or shower chairs, raised toilet seats, & ramps to accommodate motorized chairs, as needed	
	Medication (e.g., baclofen, tizanidine)	May be considered for those w/spasticity
Mood disorder	Standard treatment per psychiatrist	Personality changes may necessitate antipsychotic medication.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Pseudobulbar palsy	Speech-language therapy	Communication devices such as writing pads & computer-based devices may also be of benefit.
	Video esophagrams can identify consistency of food least likely to trigger aspiration.	Weighted eating utensils & dressing hooks help maintain a sense of independence.
Spinal spondylosis	Standard treatment per orthopedist	For those w/neurologic deficits due to spinal compression
Alopecia	Wig or hairpiece	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment for need of home nursing

Surveillance

The interval at which a person with *HTRA1* disorder is followed depends on the severity and type of symptoms and the needs of the affected individual and caregivers.

Agents/Circumstances to Avoid

Smoking and a high-salt diet, which may hasten the progression of arteriosclerosis, should be avoided.

Evaluation of Relatives at Risk

It has been speculated that hypertension or smoking may influence the age of onset and frequency of stroke episodes in individuals with *HTRA1* disorder; smoking may result in earlier disease onset [Singhal et al 2004], and smoking or hypertension may increase the frequency of stroke episodes in individuals with the classic CADASIL phenotype [Adib-Samii et al 2010]. Therefore, it is appropriate to test the older and younger sibs of a proband for presence of the *HTRA1* pathogenic variant(s) in the family in order to identify early in adulthood (ideally at age ≥18 years) those who would benefit from initiation of treatment and preventive measures such as oral administration of anti-hypertensive drugs and abstinence from smoking.

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to 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

HTRA1 disorder caused by biallelic pathogenic variants (classic CARASIL) is inherited in an autosomal recessive manner.

HTRA1 disorder caused by a heterozygous pathogenic variant (*HTRA1*-CSVD) is inherited in an autosomal dominant manner.

Autosomal Recessive Inheritance

Risk to Family Members

Parents of a proband

- The parents of an individual with biallelic *HTRA1* pathogenic variants are obligate heterozygotes (i.e., presumed to be heterozygous for one *HTRA1* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *HTRA1* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- It is not clear whether individuals who are heterozygous for an *HTRA1* pathogenic variant associated with classic CARASIL are asymptomatic. Some reports suggest a mild phenotype in heterozygous individuals [Mendioroz et al 2010, Chen et al 2013, Bianchi et al 2014, Uemura et al 2019]. However, it is difficult to distinguish their symptoms from small vessel disease in the elderly; further study is necessary to clarify this issue.

Sibs of a proband

- If both parents are known to be heterozygous for an *HTRA1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting both *HTRA1* pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither pathogenic variant and not being at risk for *HTRA1* disorder.
- It is not clear whether carriers (heterozygotes) are asymptomatic (see **Parents of a proband**).

Offspring of a proband. The offspring of an individual with biallelic pathogenic variants are obligate heterozygotes for one *HTRA1* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for one *HTRA1* pathogenic variant.

Heterozygote Detection

Molecular genetic testing for at-risk family members requires prior identification of the *HTRA1* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with autosomal dominant *HTRA1* disorder have an affected parent.
- Because simplex cases (i.e., a single occurrence in a family) have not been evaluated sufficiently to determine if a pathogenic variant occurred *de novo*, the proportion of *HTRA1* disorder caused by a *de novo* pathogenic variant is unknown. (To date, *de novo* pathogenic variants have not been reported in *HTRA1* disorder.)

- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of a proband inheriting a pathogenic variant from a parent with germline mosaicism have been reported.
- The family history of some individuals diagnosed with *HTRA1* disorder 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. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

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 is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known *HTRA1* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *HTRA1* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for *HTRA1* disorder because of the possibility of age-related penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant *HTRA1* disorder has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *HTRA1* pathogenic variant, other members of the parent's family may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *HTRA1* pathogenic variant(s) have been identified in an affected family member.
- Potential consequences of such testing including (but not limited to) socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result – as well as the capabilities and limitations of predictive testing – should be discussed in the context of formal genetic counseling prior to testing.

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.
- 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 *HTRA1* disorder, it is appropriate to consider testing symptomatic individuals regardless of age.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, 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, are heterozygous, or are at risk of being affected or of being heterozygous.

Prenatal Testing and Preimplantation Genetic Testing

Once the *HTRA1* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for *HTRA1* disorder are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. 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.

- **National Library of Medicine Genetics Home Reference**
  Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy
- **American Stroke Association**
  National Center
  7272 Greenville Avenue
  Dallas TX 75231
  Phone: 800-AHA-USA-1; 800-242-8721
  www.stroke.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. HTRA1 Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

HTRA1	10q26.13	Serine protease HTRA1	HTRA1 database	HTRA1	HTRA1

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 HTRA1 Disorder (View All in OMIM)

600142	CEREBRAL ARTERIOPATHY, AUTOSOMAL RECESSIVE, WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY; CARASIL
602194	HTRA SERINE PEPTIDASE 1; HTRA1
616779	CEREBRAL ARTERIOPATHY, AUTOSOMAL DOMINANT, WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY, TYPE 2; CADASIL2

Molecular Pathogenesis

Introduction. HTRA1 belongs to the HTRA protein family, the members of which have dual roles as chaperones and serine proteases [Clausen et al 2002]. They serve as stress sensors for unfolded proteins and repress transforming growth factor-beta (TGF-β) family signaling [Clausen et al 2002, Oka et al 2004]. HTRA1 proteins exist as trimers, thus allowing communication between adjacent subunits to regulate protease activity [Truebestein et al 2011].

In vitro functional expression studies with *HTRA1* known pathogenic variants showed a loss of protease activity and consequent inability to repress TGF-β family signaling [Hara et al 2009]. Additionally, the mutated HTRA1 proteins of some pathogenic variants show a dominant-negative effect by interfering with communication between adjacent subunits [Nozaki et al 2016, Uemura et al 2019].

Mechanism of disease causation. Loss of function. Some pathogenic variants have a dominant-negative effect [Hara et al 2009, Nozaki et al 2016, Uemura et al 2019].

Chapter Notes

Revision History

- 7 November 2019 (ma) Comprehensive update posted live
- 11 September 2014 (me) Comprehensive update posted live
- 17 February 2011 (cd) Revision: prenatal testing available clinically
- 27 April 2010 (me) Review posted live
- 5 January 2010 (oo) Original submission

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