GENEReviews

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Hereditary Hemorrhagic Telangiectasia

[*HHT, Osler-Weber-Rendu Disease. Includes: ACVRL1-Related Hereditary Hemorrhagic Telangiectasia, ENG-Related Hereditary Hemorrhagic Telangiectasia*]

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Summary

Disease characteristics. Hereditary hemorrhagic telangiectasia (HHT) is characterized by the presence of multiple arteriovenous malformations (AVMs) that lack intervening capillaries and result in direct connections between arteries and veins. Small AVMs (or telangiectases) close to the surface of skin and to mucous membranes often rupture and bleed after slight trauma. The most common clinical manifestation is spontaneous and recurrent nosebleeding beginning at approximately 12 years of age. About 25% of individuals with HHT have GI bleeding, which most commonly begins after age 40 years. Large AVMs often cause symptoms when they occur in the brain, lungs, or gastrointestinal tract; complications from bleeding or shunting may be sudden and catastrophic.

Diagnosis/testing. The diagnosis of HHT is based on family history and the presence of cutaneous or mucocutaneous telangiectases or large visceral AVMs. HHT is caused by a mutation in either *ENG*, the gene encoding endoglin or *ACVRL1*, the gene encoding the activin receptor. Molecular genetic testing of these genes detects mutations in 60-80% of individuals with HHT and is available on a clinical basis.

Management. Management includes surveillance for undiagnosed AVMs and treatment for identified complications such as nosebleeds, gastrointestinal bleeding, anemia, pulmonary AVMs, cerebral AVMs, and hepatic AVMs. Treatment of nosebleeds with humidification and nasal lubricants, laser ablation, septal dermoplasty, or estrogen-progesterone therapy can prevent anemia and allow individuals with HHT to pursue normal activities. Individuals with GI bleeding are treated with iron therapy to maintain hemoglobin concentration; endoscopic application of a heater probe, bicep, or laser; surgical removal of bleeding sites; and estrogen-progesterone therapy. Iron replacement and red blood cell transfusions are used to treat anemia. Pulmonary AVMs with feeding vessels that exceed 3.0 mm in diameter require occlusion. Cerebral AVMs greater than 1.0 cm in diameter are treated by surgery, embolotherapy, and/or stereotactic radiosurgery. The treatment of choice for hepatic AVMs is liver transplantation. Antibiotic prophylaxis is recommended for dental and invasive procedures. Surveillance includes annual evaluations for anemia and neurologic conditions and re-evaluation for pulmonary AVMs every one to two years during childhood and every five years thereafter.

Women with HHT considering pregnancy are screened and treated for pulmonary AVMs; if pulmonary AVMs are discovered during pregnancy, they are treated during the second trimester. Individuals should avoid vigorous nose blowing, cautery for nosebleeds, and anticoagulant and anti-inflammatory agents.

Genetic counseling. HHT is inherited in an autosomal dominant manner. Most individuals have an affected parent. Each child of a proband and the sibs of most probands have a 50% risk of inheriting the mutation. Prenatal testing is available.

Diagnosis

Clinical Diagnosis

The diagnosis of hereditary hemorrhagic telangiectasia (HHT) is based on the presence of arteriovenous malformations (AVMs), which may be cutaneous or mucocutaneous telangiectases or large visceral AVMs [Marchuk et al 1998].

The clinical diagnosis of HHT [Shovlin et al 2000] is considered:

- **Definite** when three or more findings are present,
- **Possible or suspected** when two findings are present, and
- **Unlikely** when fewer than two findings are present.

Findings:

- Nosebleeds (epistaxis): spontaneous and recurrent (night-time nosebleeds heighten the concern for HHT)
- Mucocutaneous telangiectases (small blanchable red spots that are focal dilatations of post-capillary venules or delicate, lacy red vessels composed of markedly dilated and convoluted venules): multiple, at characteristic sites, including lips, oral cavity, fingers, and nose
- Visceral arteriovenous malformation (AVM): an arteriovenous malformation lacks capillaries and consists of direct connections between arteries and veins. AVMs may be:
  - Pulmonary
  - Cerebral
  - Hepatic
  - Spinal
  - Gastrointestinal
- Family history: a first-degree relative in whom HHT has been diagnosed

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. Two genes are associated with classic hemorrhagic telangiectasia [Berg et al 1997]:

- *ENG*. Hereditary hemorrhagic telangiectasia type 1 (HHT1)

- *ACVRL1*. Hereditary hemorrhagic telangiectasia type 2 (HHT2)

The percentage of mutations in *ENG* and *ACVRL1* thus far reported are virtually equal (53% and 47% respectively) after founder effects are excluded [Bayrak-Toydemir et al 2004].

Other loci (HHT3). At least two kindreds appear to have mutations in a third as-yet-unknown gene [Wallace & Shovlin 2002; McDonald, unpublished data]. Cole et al (2005) reported a 5.4-cm disease gene interval on chromosome 5 based on linkage analysis in one pedigree.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Predictive testing
- Prenatal testing

Molecular genetic testing: Clinical methods

- **Sequence analysis/mutation scanning.** Sequence analysis of *ENG* and *ACVRL1* has identified mutations in 60-80% of individuals with HHT [Lesca et al 2004; Schulte et al 2005; J McDonald, unpublished data and personal communication]. Sequencing of the *ENG* and *ACVRL1* coding regions detects missense and nonsense mutations, small insertions and deletions, and splice site mutations. There are no common mutations, and sequence variants interpreted to be of uncertain significance are particularly common. The mutation detection rate using mutation scanning is unknown but presumed to be slightly lower than the mutation detection rate for sequence analysis.
- **Duplication/deletion analysis.** Several techniques including quantitative PCR, multiplex ligation-dependent probe amplification (MLPA), and southern blot analysis are used to identify deletions not detectable by sequence analysis. Some data suggest that use of these methods in addition to sequence analysis could increase the detection rate by up to 10% [Cymerman et al 2003].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in HHT

Gene	Test Methods	Mutations Detected	Mutation Detection Rate [1]	Test Availability
ENG	Sequence analysis	ENG sequence alterations	30-40%	Clinical Testing
	Duplication/deletion analysis	ENG deletions	Unknown	
ACVRL1	Sequence analysis	ACVRL1 sequence alterations	30-40%	Clinical Testing
	Duplication/deletion analysis	ACVRL1 deletions	Unknown	

1. In all individuals with HHT

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related Disorders

No other phenotypes are associated with mutations in *ENG* or *ACVRL1*.

Clinical Description

Natural History

HHT is characterized by the presence of multiple arteriovenous malformations (AVMs) that lack intervening capillaries and result in direct connections between arteries and veins. Small arteriovenous malformations are called telangiectases. Telangiectases present on the lips, fingers, nose, tongue, and gastrointestinal mucosa typically vary in size from pinpoint to pinhead. Because of their thin walls, narrow tortuous paths, and closeness to the surface of the skin or to a mucous membrane, these vessels can rupture and bleed after only slight trauma. Since the contractile elements in the vessel wall are lacking, given the abnormal arterial connection, the bleeding from telangiectases is frequently brisk and difficult to stop.

The term AVM usually refers to the "large" telangiectases, greater than one-half inch in diameter and sometimes up to three to six inches in diameter. AVMs occur most commonly in the brain, lung, or liver. In contrast to the smaller telangiectases, the complications of AVMs often result from the shunting of blood, thrombosis, or embolus rather than hemorrhage. Complications of solid organ AVMs may be catastrophic and may occur without prior warning.

In HHT, the most common manifestations are epistaxis (nosebleeds) and telangiectases. The nasal mucosa is fragile and minor insults from drying air and repeated minor abrasions result in frequent bleeding. Epistaxis is usually the earliest symptom with an average age of onset of about 12 years of age. As many as 95% of affected individuals eventually experience recurrent epistaxis, with one-third having onset by age ten years and 80-90% by age 21 years [AAssar et al 1991]. However, many do not have nosebleeds that are frequent or severe enough to cause anemia or to result in medical treatment or consultation. While a similar proportion of affected individuals eventually develops telangiectases of the face, oral cavity, or hands, the average age of onset is generally later, in the early 30s. Thirty percent of affected individuals report telangiectases first appearing prior to age 20 years and two-thirds before age 40 years [Berg et al 2003].

Telangiectases can also be found anywhere in the gastrointestinal (GI) system. Most commonly, the stomach and the proximal small intestine (duodenum) are involved. It is estimated that about one-quarter of all individuals with HHT have gastrointestinal bleeding [Reilly & Nostrant 1984, Proctor et al 2005]. Bleeding from GI telangiectases most commonly begins after age 40 years, is usually slow but persistent, and often becomes increasingly severe with age. No particular foods, activities, or medications have been identified as contributors to GI bleeding in individuals with HHT.

Epistaxis and/or GI bleeding can cause mild to severe anemia, sometimes requiring blood transfusion and/or iron replacement therapy.

In one study, pulmonary AVMs occurred in 33% of affected individuals and cerebral AVMs in 11% of affected individuals [Haitjema et al 1996]. Spinal AVMs appear to be significantly less common. The frequency of hepatic vascular abnormalities was shown to be 74% in one study that systematically imaged the liver of affected individuals using CT [Ianora et al 2004] and 41% in another study using ultrasound [Buscarini et al 2004]. However, only a small minority (8% in the study using CT) were symptomatic. Although data suggest that the incidence of visceral AVMs may vary between HHT types, with pulmonary and possibly cerebral AVMs being more common in HHT1 than in HHT2 [Berg et al 1996] and hepatic AVMs more common in HHT2 [Buscarini et al 1997, McDonald et al 2000], all of these lesions have been seen in individuals with both HHT types.

Although hemorrhage is often the presenting symptom of cerebral AVMs, most visceral AVMs present as a consequence of blood shunting through the abnormal vessel and bypassing the capillary bed. Shunting of air, thrombi, and bacteria through pulmonary AVMs, thus bypassing the filtering capabilities of the lungs, may cause transient ischemic attacks (TIAs), embolic stroke, and cerebral and other abscesses. Migraine headache, polycythemia, and hypoxemia with cyanosis and clubbing of the nails are other complications of pulmonary AVMs [Guttmacher et al 1995, Haitjema et al 1996, White et al 1996, Shovlin & LeTarte 1999, Kjeldsen et al 2000]. Hepatic AVMs can present as high-output heart failure, portal hypertension, or biliary disease [Garcia-Tsao et al 2000].

In one series, serious neurologic events including TIA, stroke, and brain abscess occurred in 30-40% of individuals with pulmonary AVMs who had feeding arteries 3.0 mm or greater in diameter [White 1996]. These neurologic complications may occur in individuals with isolated pulmonary AVMs and near-normal arterial oxygen tension. Pulmonary AVMs frequently enlarge with time [White 1996]. One study of 42 children with pulmonary AVMs demonstrated that children can have life-threatening complications from these lesions. More than half presented with exercise intolerance, cyanosis, or clubbing, and although the neurologic complications were less frequent than in adults, they had occurred in 19% prior to detection and treatment [Faughnan et al 2004].

Table 2. Age of Onset of Various Signs of HHT

Age	0-9 Years	1-19 Years	20-29 Years	30-39 Years	40-49 Years	50-59 Years	60+ Years
Nosebleed n=492 [1]	37%	33%	12%	7%	4%	2%	
Telangiectases n=406	10%	20%	20%	18%	11%	5%	2%
GI Bleed n=114	4%	7%	11%	25%	18%	21%	13%

1. Number of individuals reporting [Guttmacher, unpublished]

Pregnancy. Pregnant women with HHT and untreated pulmonary AVMs are also at high risk for lung hemorrhage. Women with treated pulmonary AVMs appear to be at no higher risk during pregnancy than those without pulmonary AVMs.

Primary pulmonary hypertension (PPT). Lung disease indistinguishable from primary pulmonary hypertension (PPT) has been reported in individuals who have HHT or an immediate family history of HHT. It is suspected that mutations in *ACVRL1* may lead to occlusion of the pulmonary arteries as well as vascular dilatation manifested as telangiectases and arteriovenous malformations. In one study, molecular analysis of 11 probands with PPT and HHT identified eight missense mutations in *ACVRL1* and two in *ENG* [Harrison et al 2003]. In another study, *ACVRL1* mutations were found in all (4/4) families with PPT and HHT [Abdalla et al 2004].

Genotype-Phenotype Correlations

Current data suggest that while no absolute genotype-phenotype correlations exist between clinical phenotypes and specific mutations or mutational types [Shovlin et al 1997], certain clinical manifestations, in particular pulmonary AVMs, may be more common in HHT1 than in HHT2. However, both types are clearly multisystem vascular dysplasias, with all but one of the above-mentioned manifestations described in individuals with each type [McDonald et al 2000, Kjeldsen et al 2001]. The exception is spinal AVMs, which to date have not been reported in an individual known to have HHT1.

Penetrance

HHT displays age-related penetrance with increased manifestations developing over a lifetime (see Table 2).

- Approximately 50% of diagnosed individuals report having nosebleeds by age ten years and 80-90% by age 21 years. As many as 95% eventually develop recurrent epistaxis.
- The percentage of individuals with telangiectases of the hands, face, and oral cavity is similar to the percentage with epistaxis, but the age of onset of telangiectases is generally five to thirty years later than for epistaxis [Plauchu et al 1989, Porteous et al 1992].
- Intracranial hemorrhage secondary to AVM has been reported as the presenting symptoms of HHT in infants and children with HHT [Morgan et al 2002].

Prevalence

HHT occurs with wide ethnic and geographic distribution.

A number of studies indicate that HHT is significantly more frequent than formerly thought, at least in the populations investigated. The prevalence of HHT in the French department of Ain is at least 1:2,351 [Plauchu & Bideau 1984], on the Danish island of Funen approximately 1:3,500 [Vase & Grove 1986], in the Leeward Islands 1:5155 [Jessurun et al 1993], in the state of Vermont in the US 1:11,000 [Guttmacher et al 1994; Guttmacher, unpublished data], and in northern England 1:39,216 [Porteous et al 1992].

The overall incidence of HHT in North America is estimated to be about 1:10,000 [Marchuk et al 1998]; however, it is likely that this represents an underestimation because of underdiagnosis of the condition.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Telangiectases and epistaxis are relatively common in otherwise healthy individuals. Recurrent epistaxis can be a sign of various bleeding diatheses, including von Willebrand disease.

Telangiectases occur in a number of conditions:

- Ataxia-telangiectasia, which is characterized by progressive cerebellar ataxia beginning between one and four years of age, oculomotor apraxia, frequent infections, choreoathetosis, telangiectases of the conjunctivae, immunodeficiency, and an increased risk for malignancy, particularly leukemia and lymphoma. Diagnosis relies upon clinical findings, including slurred speech, truncal ataxia, oculomotor apraxia, family history, and neuroimaging. Molecular genetic testing of the *ATM* gene is available.
- CREST syndrome
- Hereditary benign telangiectasia, which is characterized by widespread telangiectases, predominantly on the face, upper limbs, and upper trunk. The telangiectases are venular and associated with upper dermal atrophy. It should be suspected in persons without the history/family history of nosebleed or other bleeding, mucosal telangiectases, AVM, or characteristic pattern of telangiectasia distribution found in HHT.

- Pregnancy
- Chronic liver disease

Most individuals with a pulmonary AVM have HHT; those individuals who have pulmonary AVMs without HHT usually have isolated pulmonary AVMs.

Cerebral AVMs occur most frequently as an isolated finding, but may be a manifestation of HHT or another dominantly inherited vascular dysplasia such as capillary malformation-arteriovenous malformation (CM-AVM) caused by mutatations in *RASA1* [Eerola et al 2003]. Families have also been reported with autosomal dominant AVMs of the brain and no other features of HHT. The absence of a family history of recurrent nosebleed and presence of telangiectases specifically on the lips, face, and hands best distinguish HHT from other vascular dysplasias.

Mutations in *MADH4(SMAD4*) have been reported in families/individuals with a combined syndrome of juvenile polyposis syndrome and hereditary hemorrhagic telangiectasia [Gallione et al 2004].

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Medical history, with particular attention to epistaxis and other bleeding, anemia, or polycythemia, pulmonary disease, and neurologic symptoms
- Physical examination, including inspection for telangiectases, particularly on fingers, lips, tongue, oropharynx, cheeks, or conjunctiva, as well as listening for abdominal bruits
- Stool assessment for occult blood
- Complete blood count, with particular attention to anemia or polycythemia. If anemia is present, it is important to consider other causes of anemia, particularly when the anemia seems to be disproportionate to the amount of epistaxis. People with HHT may develop medical problems unrelated to HHT (such as ulcers or colon cancer) that can cause GI blood loss.
- Measurement of oxygen saturation via pulse oximetry
- Contrast echocardiography for detection of pulmonary AVM [Oxhoj et al 2000, Nanthakumar et al 2001]. When pulmonary shunting is suggested (or if dependable contrast echocardiography is not available), CT with 3-5mm cuts to define size of lesions(s) is the next step [Cottin et al 2004].
- If contrast echocardiogram is positive for pulmonary shunting but no pulmonary AVM is demonstrated by chest CT, a lifetime recommendation for prophylactic antibiotics with dental cleaning and other "dirty" procedures is advised because of the risks of abscess, particularly brain abscess, associated with right to left shunting. A chest CT should be repeated at about five-year intervals to see if smaller lesions have grown.

  Note: The risk associated with these lesions is not for subacute bacterial endocarditis (SBE).
- Any pulmonary AVM with a feeder artery greater than 3.0 mm detected by chest CT should be treated by transcatheter embolization.

- Head MRI (with and without gadolinium) to detect cerebral AVMs, performed as early as possible, preferably in the first year of life [Morgan et al 2002]. If no CAVMs are detected, MRI does not need to be repeated later in life.
- Consideration of ultrasound examination to look for evidence of hepatic AVM, especially if the individual has symptoms associated with hepatic vascular abnormalities.

Note: (1) Screening for hepatic AVMs in asymptomatic individuals is not common practice because hepatic AVMs are rarely symptomatic and, when they do become symptomatic, it is not sudden and catastrophic, as is seen with PAVMs and CAVMs. (2) Treatment options for HAVM are less satisfactory.

Treatment of Manifestations

Nosebleeds

- It is appropriate to consider intervention for nosebleeds in the case of anemia attributable to the nosebleeds or if an individual feels that the frequency or duration interferes significantly with normal activities.
- Humidification and the daily application of nasal lubricants by the individual may be helpful.
- Laser ablation may be the most effective intervention for control of mild to moderate nosebleeds [Parkin & Dixon 1981, Rebeiz et al 1991].
- Otolaryngologists adept at septal dermoplasty using split-thickness skin grafts have had good results in individuals with severe epistaxis [Saunders 1973, Fiorella et al 2005].
- A recent meta-analysis of studies of hormonal and anti-hormonal treatment concluded that estrogen-progesterone at doses used for oral contraception may eliminate bleeding in symptomatic HHT and is a reasonable initial option to consider for fertile women [Jameson & Cave 2004].

Gastrointestinal bleeding

- Treatment is unnecessary unless aggressive iron therapy has been ineffective in maintaining hemoglobin concentration in the normal range.
- Endoscopy, capsule endoscopy, mesenteric and celiac angiography, and radionuclide studies may be used to localize the source of bleeding and its type.
- Endoscopic application of a heater probe, bicap, or laser are the mainstays of local treatment.
- Small bowel bleeding sites and larger malformations can be removed surgically after they are identified by nuclear medicine studies [Gostout et al 1988].
- In some trials, hormonal treatment with estrogen-progesterone has decreased transfusion needs [van Cutsem et al 1990].

Anemia

- Treatment of anemia with iron replacement and red blood cell transfusion, if necessary, is appropriate.
- Persons with profound iron deficiency who are intolerant of or who do not respond to oral iron usually benefit from parenteral administration of iron.

Pulmonary AVMs

- Treatment is indicated for dyspnea, exercise intolerance, and hypoxemia, but is most important for prevention of the neurologic complications of brain abscess and stroke and lung hemorrhage, even in those who are asymptomatic in terms of pulmonary function [Moussouttas et al 2000]. Pulmonary AVMs with feeding vessels that exceed 3.0 mm in diameter require occlusion [Hughes & Allison 1990, Ference et al 1994, White 1996, Lee et al 1997]. Transcatheter embolotherapy (TCE) with detachable balloons and/or stainless steel coils is the treatment of choice. A follow-up chest CT in approximately one year is advised to assure that treated PAVM(s) have not reperfused.

Cerebral AVMs

- Cerebral AVMs greater than 1.0 cm in diameter are usually treated using neurovascular surgery, embolotherapy, and/or stereotactic radiosurgery [Fulbright et al 1998].

Hepatic AVMs

- Treatment of cardiac failure or liver failure secondary to hepatic AVMs is currently problematic. Embolization of hepatic AVMs, which is successful for treatment of pulmonary AVMs, has led to lethal hepatic infarctions [Odorico et al 1998].
- Liver transplantation is currently considered the treatment of choice for those (usually older) individuals whose symptoms necessitate treatment [Boillot et al 1999].

Note: Before proceeding with treatment for any visceral AVM, individuals and their doctors are encouraged to contact the nearest multidisciplinary HHT clinic, which can be located through the HHT Foundation International to assure that appropriate diagnostic and treatment plans are in place.

Prevention of Secondary Complications

To prevent brain abscess, antibiotic prophylaxis in accordance with American Heart Association guidelines is recommended for dental and invasive procedures and should be given to any affected individual who has an untreated pulmonary AVM or has not had a normal contrast echocardiogram to evaluate for evidence of pulmonary shunting [Christensen 1998].

Surveillance

The following protocol is recommended for follow-up of all individuals for whom the diagnosis of HHT is definite and for all individuals at risk for HHT based on family history:

- Annual evaluation by a health care provider familiar with HHT, including interval history for epistaxis or other bleeding, shortness of breath or decreased exercise tolerance, and headache or other neurologic symptoms
- Annual stool evaluation for occult blood
- Periodic hematocrit/hemoglobin determination with appropriate treatment for anemia
- Re-evaluation for pulmonary AVM at approximately five-year intervals. Contrast echocardiogram is used, if available, if the previous contrast echocardiogram did not reveal evidence of a pulmonary/right to left shunt; chest CT is used if the previous contrast echocardiogram revealed evidence of a pulmonary/right to left shunt.

Childhood

- Pulse oximetry in the supine and sitting positions to screen for pulmonary AVMs every one to two years during childhood. It may be of concern if the sitting value is even a few percentage points below that of the supine value. (Since most pulmonary AVMs are in the lower lobes, many individuals with pulmonary AVMs have higher oxygen saturation when lying than when sitting because of the effect of gravity.) Oxygen saturations below 97% should be followed up with contrast echocardiogram.
- At about age ten years, additional evaluation should be performed by contrast echocardiography, with a follow-up CT if positive.
- Individuals who have been treated for pulmonary AVMs need to be re-evaluated by chest CT approximately every five years because small pulmonary AVMs can increase in size over time.

Pregnancy

- Pregnant women with HHT and untreated pulmonary AVMs are at high risk for lung hemorrhage. Therefore, screening for and treatment of pulmonary AVMs should be performed before pregnancy.
- A pregnant woman who has not had a recent pulmonary evaluation should be evaluated as soon as pregnancy is recognized [Shovlin et al 1995].
- Women not discovered to have pulmonary AVMs until they are already pregnant should be treated during the second trimester.

Agents/Circumstances to Avoid

- Individuals with significant epistaxis are advised to avoid vigorous nose blowing, lifting of heavy objects, straining during bowel movements, and finger manipulation in the nose.
- Most otolaryngologists with experience treating individuals with HHT advise against electric and chemical cautery and transcatheter embolotherapy for treatment of recurrent nosebleeds in most situations.
- Anti-coagulants such as aspirin and nonsteroidal anti-inflammatory agents such as ibuprofen that interfere with normal clotting should be avoided unless required for treatment of other medical conditions.

Testing of Relatives at Risk

Individuals at risk should follow the same surveillance protocol as described above for affected individuals.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Hereditary hemorrhagic telangiectasia (HHT) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with HHT have an affected parent.
- A proband with HHT may have the disorder as the result of a *de novo* gene mutation; however, *de novo* mutations for HHT are rare.
- Recommendations for the evaluation of parents of a child who represents an apparent simplex case (i.e., a single occurrence in a family) include physical examination, documentation of medical history targeted at symptoms and manifestations of HHT, and molecular genetic testing if a mutation has been identified in the proband.

Sibs of a proband

- The risk to the sibs depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be lower. It should be noted, however, that although highly penetrant, the disease may not present until after age 40 years. Observable symptoms and manifestations can be subtle, even well into adulthood.
- No instances of germline mosaicism have been reported, although it remains a possibility.

Offspring of a proband. Each child of an individual with HHT has a 50% chance of inheriting the disease-causing mutation.

Other family members. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations include alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of prenatal testing is before pregnancy.

Testing of at-risk asymptomatic individuals during adulthood and childhood. Testing of at-risk asymptomatic individuals for HHT is available using the same techniques described in Molecular Genetic Testing. This testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. When testing at-risk individuals for HHT, an affected family member should be tested first to confirm (and identify) the molecular diagnosis in the family. Testing of asymptomatic at-risk family members usually involves pre-test consultation to discuss the possible impact of positive and negative test results. 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. Informed consent should be

procured and records kept confidential. Individuals with a positive test result need arrangements for long-term follow-up and evaluations.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated from either the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Hereditary Hemorrhagic Telangiectasia

Gene Symbol	Chromosomal Locus	Protein Name
ACVRL1	12q11-q14	Serine/threonine-protein kinase receptor R3
ENG	9q34.1	Endoglin

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Hereditary Hemorrhagic Telangiectasia

131195	ENDOGLIN; ENG
187300	TELANGIECTASIA, HEREDITARY HEMORRHAGIC, OF RENDU, OSLER, AND WEBER; HHT
600376	OSLER-RENDU-WEBER SYNDROME 2; ORW2
601284	ACTIVIN A RECEPTOR, TYPE II-LIKE KINASE 1; ACVRL1

Table C. Genomic Databases for Hereditary Hemorrhagic Telangiectasia

Gene Symbol	Locus Specific	Entrez Gene	HGMD
ACVRL1	ACVRL1	94 (MIM No. 601284)	ACVRL1
ENG	ENG	2022 (MIM No. 131195)	ENG

For a description of the genomic databases listed, click here.

ACVRL1

Normal allelic variants: *ACVRL1* contains ten exons and spans approximately 14 kb of genomic DNA.

Pathologic allelic variants: Current data suggest that mutations in *ACVRL1* are functionally null alleles [Berg et al 1997, Pece et al 1997, Gallione et al 1998]. No common disease-causing mutations or mutational "hot spots" have been identified. (For more information, see Genomic Databases table above.)

Normal gene product: Serine/threonine-protein kinase receptor R3 is a type I cell-surface receptor for the TGF- superfamily of ligands [Johnson et al 1996]. It is expressed predominantly on endothelial cells.

Abnormal gene product: Current data suggest that most disease-causing mutations in *ACVRL1* result in truncated, non-expressed proteins. HHT is assumed to be the result of haploinsufficiency.

ENG

Normal allelic variants: *ENG* contains 14 exons and spans approximately 40 kb of genomic DNA.

Pathologic allelic variants: Current data suggest that mutations in *ENG* are functionally null alleles [Berg et al 1997, Pece et al 1997, Gallione et al 1998]. No common disease-causing mutations or mutational "hot spots" have been identified. (For more information, see Genomic Databases table above.)

Normal gene product: Endoglin is a component of the transforming growth factor beta (TGF-beta) receptor complex [McAllister et al 1994]. It is expressed predominantly on endothelial cells.

Abnormal gene product: Current data suggest that most disease-causing mutations in *ENG* result in truncated, non-expressed proteins. HHT is assumed to be the result of haploinsufficiency.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

HHT Foundation International, Inc
PO Box 329
Monkton, MD 21111
Phone: 800-448-6389; 410-357-9932 Canada: 604-596-3418 Other
Fax: 410-357-9931 or 604-596-0138
Email: hhtinfo@hht.org
www.hht.org

National Library of Medicine Genetics Home Reference
Hereditary hemorrhagic telangiectasia

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Acknowledgments

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Revision History

- 22 November 2005 (me) Comprehensive update posted to live Web site
- 16 March 2004 (cd) Revision: sequence analysis
- 26 February 2004 (cd) Revision: quantitative PCR added as a test method
- 4 August 2003 (cd) Revisions
- 17 June 2003 (ca) Comprehensive update posted to live Web site
- 26 June 2000 (me) Review posted to live Web site
- January 2000 (jm) Original submission