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Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.

Hereditary Hemorrhagic Telangiectasia

Synonyms: HHT, Osler-Weber-Rendu Disease

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Initial Posting: June 26, 2000; Last Update: November 24, 2021.

Estimated reading time: 37 minutes

Summary

Clinical 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. The most common clinical manifestation is spontaneous and recurrent nosebleeds (epistaxis) beginning on average at age 12 years. Telangiectases (small AVMs) are characteristically found on the lips, tongue, buccal and gastrointestinal (GI) mucosa, face, and fingers. The appearance of telangiectases is generally later than epistaxis but may be during childhood. Large AVMs occur most often in the lungs, liver, or brain; complications from bleeding or shunting may be sudden and catastrophic. A minority of individuals with HHT have GI bleeding, which is rarely seen before age 50 years.

Diagnosis/testing. The diagnosis of HHT is established in a proband with **three or more** of the following clinical features:

- Epistaxis
- Mucocutaneous telangiectases in characteristic locations
- Visceral AVMs
- A first-degree relative diagnosed with HHT on the basis of the preceding criteria

Identification of a heterozygous pathogenic variant in *ACVRL1*, *ENG*, or *SMAD4* establishes the diagnosis if clinical features are inconclusive.

Management. *Treatment of manifestations:* Nosebleeds are treated with humidification, topical moisturizing therapy, hemostatic products, antifibrinolytic therapy, ablation therapy, systemic antiangiogenic agents, septodermoplasty, and nasal closure as needed. GI bleeding and anemia is treated with iron replacement therapy and (if needed) blood transfusions and antiangiogenic agents. Pulmonary AVMs with a feeding vessel 1-2 mm or greater in diameter typically require occlusion for stroke prevention. When pulmonary shunting is present, use antibiotic prophylaxis for dental and non-sterile invasive procedures, taking care to prevent air bubbles from being introduced in intravenous lines. This may include an air filter when available and compatible with the medication being administered. Treatment of pulmonary artery hypertension as per cardiologist, pulmonologist, and other relevant specialists. Symptomatic hepatic AVMs are managed medically; liver transplantation is recommended for individuals who do not respond to medical therapy and who develop high-output heart failure. Cerebral AVMs are treated as indicated by size, location, or symptoms: by surgery, embolotherapy, and/or stereotactic radiosurgery. Gastrointestinal polyps are treated according to guidelines for juvenile polyposis syndrome.

Surveillance: Annual evaluation by a health care provider familiar with HHT for signs and symptoms of complications; annual hematocrit, hemoglobin, and ferritin; evaluation for pulmonary AVMs every five years with transthoracic contrast echocardiography (TCE) in adults, TCE or chest radiograph with pulse oximetry in children; brain MRI with and without contrast using sequences that detect blood products in infancy and again after puberty for cerebral AVMs; colonoscopy at age 15 years and repeated every three years if no polyps are found, or annually with esophagogastroduodenoscopy if colonic polyps are identified in those with *SMAD4*-HHT.

Agents/circumstances to avoid: Vigorous nose blowing; lifting heavy objects; straining during bowel movements; finger manipulation in the nose; anticoagulant and anti-inflammatory agents (including aspirin) in individuals with significant nose or GI bleeding; scuba diving unless TCE within the last five years was negative for evidence of a right-to-left shunt; liver biopsy.

Evaluation of relatives at risk: Molecular genetic testing is offered to at-risk family members if the germline pathogenic variant has been identified in the family. If the pathogenic variant in the family is not known, at-risk family members should be evaluated for signs and symptoms of HHT, and screening should be offered to at-risk family members if the diagnosis cannot be ruled out.

Pregnancy management: Women with HHT considering pregnancy are screened and treated for pulmonary and cerebral AVMs; sizable pulmonary AVMs discovered during pregnancy are treated during the second trimester. Iron replacement is preferred for anemia, but transfusion of packed red blood cells may be necessary for symptomatic anemia despite aggressive iron replacement therapy.

Genetic counseling. HHT is inherited in an autosomal dominant manner with considerable intrafamilial variability. Most individuals have an affected parent. Each child of a proband and the sibs of most probands are at a 50% risk of inheriting the pathogenic variant. Prenatal testing is possible for a pregnancy at increased risk if the pathogenic variant in the family is known.

Diagnosis

According to published consensus clinical diagnostic criteria, the diagnosis of HHT is considered "definite" in an individual with **three or more** of the following suggestive findings. The diagnosis of HHT is considered "possible or suspected" in an individual with **two** of the following suggestive findings [Shovlin et al 2000, Faughnan et al 2020].

Suggestive Findings

Hereditary hemorrhagic telangiectasia (HHT) **should be considered** in an individual with any of the following features:

- **Spontaneous and recurrent nosebleeds (epistaxis).** Night-time nosebleeds heighten the concern for HHT.
- **Multiple telangiectases at characteristic sites.** 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. Transillumination of the digits is helpful for detecting vascular lesions not evident on the skin [Mohler et al 2009].
- **Visceral arteriovenous malformation (AVM).** Typically pulmonary, cerebral, hepatic, spinal, gastrointestinal, or pancreatic. AVMs outside these locations are uncommon and not suggestive of HHT.

- **Family history.** A first-degree relative in whom HHT has been diagnosed according to these criteria. Note: Any family history of the above clinical features is suggestive of HHT, but only a first-degree relative with a diagnosis of HHT based on Curaçao criteria fulfills this diagnostic criterion.

Establishing the Diagnosis

The clinical diagnosis of HHT can be **established** in a proband using criteria referred to as the Curaçao criteria, which require **three or more** of the above suggestive findings [Shovlin et al 2000, Faughnan et al 2020], or the molecular diagnosis can be established in a proband with suggestive findings and a heterozygous pathogenic variant in one of the genes listed in Table 1 identified by molecular genetic testing.

Note: (1) The application of clinical diagnostic criteria to children at risk for HHT can fail to identify affected children. Signs and symptoms of HHT generally develop during childhood and adolescence; epistaxis, telangiectases, and symptoms of visceral AVMs are frequently absent in affected children [Gonzalez et al 2018, Gonzalez et al 2019] (see Evaluation of Relatives at Risk). (2) The vascular malformations of HHT occur in characteristic locations. Telangiectases and AVMs in locations other than those listed above as characteristic should not be considered suggestive of HHT.

Molecular genetic testing approaches can include a combination of **concurrent gene or serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. 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 HHT has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Concurrent gene or serial single-gene testing can be considered. Sequence analysis of *ACVRL1* and *ENG* can be performed first. Deletion/duplication analysis of *ACVRL1* and *ENG* can be done next if no pathogenic variant is found.

- Sequence analysis of *SMAD4* should be considered first in any person with HHT and intestinal polyps. *SMAD4* sequence analysis should also be considered in symptomatic individuals in whom no pathogenic variant is identified through sequence analysis and deletion/duplication analysis of *ACVRL1* and *ENG*.
- Sequence analysis of *GDF2*, *RASA1*, and *EPHB4* (see Differential Diagnosis) could be considered for symptomatic individuals in whom no pathogenic variant is identified in *ACVRL1, ENG*, or *SMAD4*, particularly if dermal telangiectases appear larger than pinhead-pinpoint size, are not limited to the hands, mouth, and face, are haloed, and/or are considered innumerable (see Capillary Malformation-Arteriovenous Malformation Syndrome).

An HHT multigene panel that includes *ACVRL1*, *ENG*, *SMAD4*, and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included and the sensitivity of multigene panels 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*; thus, clinicians need to determine which multigene panel 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. (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

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **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 Hereditary Hemorrhagic Telangiectasia

Gene [1, 2]	Proportion of HHT Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
ACVRL1	52% [6]	90% [7]	10% [7]
ENG	44% [6]	90% [7]	10% [7]
SMAD4	1% [6]	>99% [7]	1 reported [8]
Unknown	~3% [6, 9]	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in these genes.
4. 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.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include 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. McDonald et al [2020]
7. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
8. To date, one large deletion has been reported in an individual with juvenile polyposis and HHT [Wain et al 2014].
9. Linkage analysis in one pedigree suggests a 5.4-cm disease gene interval on chromosome 5 (HHT3) [Cole et al 2005]. Linkage analysis in another pedigree suggests a disease gene in a 7-Mb region on the short arm of chromosome 7 (7p14) (HHT4) [Bayrak-Toydemir et al 2006a]. Rare pedigrees are not linked to any of these loci, suggesting additional heterogeneity.

Clinical Characteristics

Clinical Description

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 are called telangiectases. The term AVM usually refers to the "large" telangiectases, greater than a few millimeters in diameter and sometimes up to several centimeters in diameter. The most common feature that brings individuals with HHT to medical attention are epistaxis (nosebleeds).

Table 2.

Hereditary Hemorrhagic Telangiectasia: Frequency of Select Features

Feature	% of Persons with Feature [1]	Comment
Epistaxis	~95%	
Telangiectases	~95%	Primarily on the lips, tongue, buccal, nasal & GI mucosa, face, & fingers
Anemia	50%	
Pulmonary AVMs	30%-50%	
Hepatic AVMs	~40%-70%	<10% are symptomatic.
Cerebral AVMs	~10%	
Pulmonary hypertension	~1%-5%	

AVMs = arteriovenous malformations; GI = gastrointestinal

1. Features of HHT are age-related.

Epistaxis (Nosebleeds)

Minor insults to the nasal mucosa (e.g., drying air) result in recurrent bleeding of nasal telangiectases. Epistaxis has an average age of onset of approximately 12 years [Aassar et al 1991]; 33% have onset by age ten years, approximately 80% by age 20 years, and 90% before age 30 years [Berg et al 2003]. However, many do not have nosebleeds that are frequent or severe enough to cause anemia or to result in medical treatment or consultation.

Telangiectases

Telangiectases associated with HHT are found primarily on the lips, tongue, face, fingers, buccal and gastrointestinal (GI) mucosa, and nasal mucosa. The average age of onset for non-nasal telangiectases is generally later than epistaxis but may be during childhood; 30% of affected individuals report telangiectases first appearing before age 20 years and two thirds before age 40 years [Berg et al 2003]. They typically appear as pinpoint to pinhead-size lesions, but in older individuals are occasionally larger, raised lesions with multiple draining venules. Of note, the oral and cutaneous telangiectases associated with HHT are rarely numerous or innumerable at a given location [Wooderchak-Donahue et al 2019]. It is typical, even in adulthood, for an affected individual to have only ten to 20 telangiectases on careful examination [McDonald, unpublished data].

Telangiectases are distinguished from petechiae and angiomata by their ability to blanch with pressure, and then immediately but often slowly refill. Because of their thin walls, narrow tortuous paths, and proximity to the surface of the skin or to a mucous membrane, telangiectases can rupture and bleed after only slight trauma. Since the contractile elements in the vessel wall are lacking, given the abnormal arterial connection, bleeding from telangiectases is frequently

brisk and difficult to stop. Telangiectases of the skin are significantly less likely to bleed than those of the nasal mucosa.

Telangiectases are common in adulthood throughout the GI mucosa, but the stomach and proximal small intestine (duodenum) are most commonly involved. Approximately one quarter of all individuals with HHT eventually have bleeding from GI telangiectases; GI bleeding is rare before age 50 years [Plauchu et al 1989, Kjeldsen & Kjeldsen 2000]. It presents most often as iron deficiency anemia, rather than acute GI hemorrhage; but GI bleeding is a less common cause of iron deficiency in individuals with HHT than underappreciated epistaxis. No particular foods, activities, or medications have been identified as contributors to GI bleeding in individuals with HHT.

Anemia

Epistaxis, or less commonly GI bleeding, can cause mild-to-severe anemia, often requiring iron replacement therapy or (rarely) blood transfusion [Kasthuri et al 2017]. In older adults, GI bleeding may become a contributor to anemia and iron deficiency.

Arteriovenous Malformations (AVMs)

AVMs occur most commonly in the lungs, liver, and brain. While hemorrhage is often the presenting symptom of cerebral AVMs, most lung and liver AVMs present as a consequence of blood shunting through the abnormal vessel and bypassing the capillary bed.

Pulmonary AVMs occur in approximately 50% of affected individuals and create high-flow right-to-left shunts [Dupuis-Girod et al 2017]. Pulmonary AVMs present with a wide variety of clinical manifestations including dyspnea or hypoxemia; but even in asymptomatic individuals they pose a significant risk of serious complications including stroke, transient ischemic attacks, and brain abscess or other abscesses when air, thrombi, or bacteria shunt through the AVM, bypassing the filtering capabilities of the lungs. Less commonly, individuals with pulmonary AVMs present with hemoptysis or intrapulmonary hemorrhage. Pulmonary AVMs are most frequently congenital but can enlarge with time. Migraine headache and polycythemia are additional complications of pulmonary AVMs [Circo & Gossage 2014, Meier et al 2018].

The frequency of **hepatic** vascular abnormalities was 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 examination [Buscarini et al 2004a]. However, only a small minority were symptomatic (8% in those imaged by liver CT). Hepatic AVMs most often present as high-output heart failure, portal hypertension, or biliary disease [Garcia-Tsao 2007, Buscarini et al 2018]. Hepatic focal nodular hyperplasia is also associated with the shunting effects of blood through these high-flow vascular lesions [Buscarini et al 2004b, Brenard et al 2010].

Cerebral AVMs are typically present at birth, occurring in approximately 10% of individuals with HHT [Brinjikji et al 2017].

Spinal AVMs appear to be significantly less common but may present with paralysis.

Vascular lesions in the pancreas are found in 18% of individuals with HHT but rarely result in clinical issues [Welle et al 2019].

Pulmonary Hypertension

Pulmonary hypertension is another pulmonary vascular manifestation of HHT, although much less common than pulmonary AVMs. Pulmonary hypertension can either result from systemic arteriovenous shunting in the liver leading to increased cardiac output, or be clinically and

histologically indistinguishable from idiopathic pulmonary arterial hypertension [Lyle et al 2016, Revuz et al 2017, Vorselaars et al 2017] (see Pulmonary Arterial Hypertension).

Phenotype Correlations by Gene

Pulmonary and cerebral AVMs are more common in individuals with *ENG* pathogenic variants, and hepatic AVMs are more common in individuals with *ACVRL1* pathogenic variants. However, pathogenic variants in both *ENG* and *ACVRL1* cause multisystem vascular dysplasias, with most manifestations associated with both [Kjeldsen et al 2005, Bayrak-Toydemir et al 2006b, Letteboer et al 2006, Lesca et al 2007].

Pulmonary hypertension in the absence of severe vascular shunting, a rare HHT manifestation, has occurred most commonly in individuals with pathogenic variants in *ACVRL1,* but has also been reported in individuals with pathogenic variants in *ENG* [Soubrier et al 2013].

Pathogenic variants in *SMAD4* have been reported in families with a combined syndrome of juvenile polyposis syndrome (JPS) and HHT [Gallione et al 2004], as well as in families reported to have JPS or HHT only. A recent study found that the majority of families with an *SMAD4* pathogenic variant who presented with JPS only were found to have features of HHT when specifically reexamined for such manifestations [O'Malley et al 2012].

Genotype-Phenotype Correlations

Data suggest that no absolute genotype-phenotype correlations exist between clinical phenotypes and specific pathogenic variants [McDonald et al 2015].

Penetrance

Penetrance is approximately 95% by late adulthood.

Nomenclature

The original description of the syndrome was made by Sutton in 1864. However, Osler in the US, Parkes Weber in the UK, and Rendu in France are typically given credit; hence the eponymous Osler-Weber-Rendu syndrome (or Rendu-Osler-Weber in articles in the French literature). The designation "hereditary hemorrhagic telangiectasia" was suggested in 1912 by one of Osler's residents.

The gene now identified as *ACVRL1* is referred to in many publications as *ALK1*. Note: Other genes were also previously named *ALK1*.

Prevalence

The incidence of HHT in North America is estimated at 1:10,000 [Marchuk et al 1998]; however, this is likely an underestimate [Guttmacher et al 2013]. For example, when a proband is diagnosed, it is not unusual to identify multiple relatives in the family who have not been diagnosed with HHT but have experienced epistaxis, embolic stroke, and/or other manifestation(s) of HHT.

HHT occurs with wide ethnic and geographic distribution. The condition is especially prevalent in the Netherland Antilles because of a founder effect.

Genetically Related (Allelic) Disorders

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

Allelic disorders associated with pathogenic variants in *ACVRL1* and *SMAD4* are summarized in Table 3.

Table 3.

Allelic Disorders

Gene	Disorder	Comment / Reference
ACVRL1	Pulmonary arterial hypertension	See Heritable Pulmonary Arterial Hypertension Overview.
SMAD4	Juvenile polyposis syndrome/HHT syndrome	The proportion of persons w/a pathogenic variant in *SMAD4* who manifest HHT only is unknown, but all pathogenic variants in *SMAD4* most likely put persons & families at risk for manifestations of both JPS & HHT. [1]
	Juvenile polyposis syndrome	Reports to date suggesting that most persons w/*SMAD4* pathogenic variants have JPS only are likely attributable to variable expressivity, age-related penetrance of HHT, & clinical eval that did not focus on manifestations of HHT. [2]
	Myhre syndrome	Connective tissue disorder w/multisystem involvement, progressive & proliferative fibrosis that may occur spontaneously or following trauma or surgery, mild-to-moderate ID, & in some cases autistic-like behaviors. (Note: Whereas Myhre syndrome is caused by heterozygous gain-of-function pathogenic variants, JPS & HHT are caused by heterozygous loss-of-function pathogenic variants.)

HHT = hereditary hemorrhagic telangiectasia; ID = intellectual disability; JPS = juvenile polyposis syndrome

1. Gallione et al [2010]
2. O'Malley et al [2012]

Differential Diagnosis

Telangiectases and epistaxis can also be seen in otherwise healthy individuals.

Recurrent epistaxis can be a sign of various bleeding diatheses, including von Willebrand disease (see Table 4).

Telangiectases occur in a number of conditions:

- Hereditary disorders of known genetic cause (see Table 4).
- Hereditary disorders of unknown genetic cause:
  - CRST (*c*alcinosis, *R*aynaud phenomenon, *s*clerodactyly, *t*elangiectasia) syndrome (OMIM 181750)
  - Hereditary benign telangiectasia (OMIM 187260). 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 a history or family history of nosebleed or other bleeding and no mucosal telangiectases, AVMs, or characteristic pattern of telangiectasia distribution found in hereditary hemorrhagic telangiectasia (HHT).
- Pregnancy

- Chronic liver disease (However, the telangiectases are almost always of the "spider" class and occur on the face and chest and around the umbilicus.)

Additionally, adults can develop one or a couple of cutaneous telangiectases with age. These often raise concern, especially when the person also has multiple cherry angiomata, which are quite frequent in older individuals and are unrelated to HHT.

Arteriovenous malformations (AVMs) occur in other vascular dysplasia syndromes (see Table 4). The presence of telangiectases specifically on the lips, oral cavity, and hands (particularly fingers) best distinguish other vascular dysplasias from HHT.

- **Pulmonary AVMs.** The majority of individuals (≥70%) with a pulmonary AVM have HHT [Majumdar & McWilliams 2020]. A significant minority of isolated pulmonary AVMs represent sporadic events.
- **Cerebral AVMs** occur most frequently as an isolated finding but may be a manifestation of HHT or another dominantly inherited vascular dysplasia. Families have also been reported with autosomal dominant AVMs of the brain and no other features of HHT. However, the presence of multiple cerebral AVMs is highly suggestive of HHT [Bharatha et al 2012].

Table 4.

Hereditary Disorders of Known Genetic Cause in the Differential Diagnosis of Hereditary Hemorrhagic Telangiectasia

Gene(s)	Disorder / Phenotype	MOI	Key Shared Feature(s)	Comment
ATM	Ataxia-telangiectasia	AR	Telangiectases	Characterized by progressive cerebellar ataxia beginning at age 1-4 yrs, oculomotor apraxia, frequent infections, choreoathetosis, telangiectases of the conjunctivae, immunodeficiency, & ↑ risk for malignancy, esp leukemia & lymphoma
BMPR2	*BMPR2*-related disorder	AD	Pulmonary AVMs, PAH	PAH is the common presentation. 1 person reported w/signs of HHT (epistaxis, bilateral pulmonary AVMs) & PAH [Rigelsky et al 2008]; 2 others reported w/pulmonary AVMs & PAH only [Handa et al 2014, Soon et al 2014]
RASA1 *EPHB4*	Capillary malformation-arteriovenous malformation syndrome	AD	Cerebral AVMs, telangiectases, epistaxis	• Characterized by multiple, small (1-2 cm in diameter) capillary malformations mostly on face & limbs • May be assoc w/cerebral & spinal AVMs &/or arteriovenous fistulas [1] • Telangiectases reported primarily in those w/*EPHB4*-related CM-AVM syndrome; typically on lips, perioral

Gene(s)	Disorder / Phenotype	MOI	Key Shared Feature(s)	Comment
				region, trunk, & arms/legs & usually "numerous" or "innumerable" in a location where they occur & surrounded by a white halo. Except for lips as a commonly affected area, findings differ from HHT. [2] • Cutaneous telangiectases are less frequently reported in *RASA1*-related CM-AVM syndrome, but 3 persons had telangiectases in locations characteristic of HHT; 2 also had epistaxis, 1 had pulmonary AVM & 2 had liver vascular malformations typical for HHT [Hernandez et al 2015, El Hajjam et al 2021].
GDF2	*GDF2*-related vascular-anomaly syndrome	AD	Cerebral AVMs, telangiectases, epistaxis, PAH	• PAH is most common feature reported to date [Gräf et al 2018, Hodgson et al 2020]. • In a small number of persons,1 or 2 of the following: pulmonary AVM, cerebral AVM, & GI AVM; epistaxis; telangiectases • Neither epistaxis nor characteristic cutaneous telangiectases are consistent features. Telangiectases when reported are atypical for HHT in location (face excluding lips) & appearance (linear or spidery versus punctate). [3] • Several persons w/features overlapping w/HHT reported [4]
VWF	von Willebrand disease	AD AR	Recurrent epistaxis	Other bleeding diatheses can also be considered.

AD = autosomal dominant; AR = autosomal recessive; AVM = arteriovenous malformation; CM-AVM = capillary malformation-arteriovenous malformation syndrome; GI = gastrointestinal; MOI = mode of inheritance; PAH = pulmonary arterial hypertension

1. Fast-flow vascular anomalies that typically arise in the skin, muscle, bone, spine, and brain
2. Wooderchak-Donahue et al [2019]
3. It is uncertain whether *GDF2*-related vascular-anomaly syndrome will ultimately be considered a type of HHT versus a rarer overlapping, but distinct, disorder. However, cases described to date, w/reports of four individuals w/PAVM & two individuals w/CAVM, suggest that medical management similar to that

recommended for individuals w/*ACVRL1*- or *ENG*-related HHT is indicated [Liu et al 2020, Topiwala et al 2020, Farhan et al 2021, Hodgson et al 2021].

4. A *GDF2* variant of uncertain significance was identified in one individual with clinical criteria of HHT [Hernandez et al 2015] and multiple individuals with features similar to HHT [Wooderchak-Donahue et al 2013, Liu et al 2020, Topiwala et al 2020, Farhan et al 2021, Hodgson et al 2021].

Management

Guidelines for management of hereditary hemorrhagic telangiectasia (HHT) have been published [Faughnan et al 2011, Faughnan et al 2020]. They should be considered supplementary to those recommended by an expert in clinical management of HHT.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with HHT, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended [Faughnan et al 2011, Hosman et al 2017, Faughnan et al 2020].

Table 5.

Recommended Evaluations Following Initial Diagnosis in Individuals with Hereditary Hemorrhagic Telangiectasia

System/Concern	Evaluation	Comment
Epistaxis / Other bleeding / Anemia	• Assess for history of epistaxis & GI bleeding. • Physical exam for telangiectases	Also consider other causes of anemia if disproportionate to the amt of epistaxis; medical problems unrelated to HHT (e.g., ulcers, colon cancer) can cause GI blood loss.
	Complete blood count to assess for anemia &/or polycythemia	Polycythemia raises suspicion for pulmonary AVMs.
	Ferritin level to assess for iron deficiency	
AVMs	Assess for history of heart, lung &/or liver diseases & neurologic symptoms.	• Heart failure secondary to liver AVMs • TIA, stroke, dyspnea, migraines, hemoptysis secondary to pulmonary AVMs
Pulmonary AVMs / Pulmonary arterial hypertension	In those diagnosed in **adulthood**: TCE w/agitated saline contrast for detection of pulmonary shunting/AVMs, w/measurement of pulmonary artery systolic pressure	When pulmonary shunting is suggested by TCE: CT angiography w/cuts ≤3 mm to define size & location of lesions(s)
	In those diagnosed in childhood: • TCE w/agitated saline contrast **OR**	Most serious complications of pulmonary AVM during childhood have occurred in hypoxemic children.

System/Concern	Evaluation	Comment
	• Chest radiograph w/pulse oximetry; if chest radiograph is abnormal or oxygen saturation is <96%, proceed w/TCE w/agitated saline contrast.	
Hepatic AVMs	Options in adults: • Clinical screening (e.g., history & physical exam) • Doppler ultrasound (best option when local expertise is available) • Multiphase contrast CT • Contrast abdominal MRI	There is no consensus regarding imaging for hepatic AVMs in asymptomatic persons because: • Hepatic AVMs are not usually symptomatic & when they do become symptomatic, it is not sudden & catastrophic • Treatment options for hepatic AVMs are less satisfactory than those for pulmonary or cerebral AVMs.
Cerebral AVMs	Head MRI (w/& w/o contrast using sequences that detect blood products) to assess for AVMs	• As early as possible, preferably in 1st yr of life • In all persons at diagnosis (incl adults)
***SMAD4*-HHT**	See Juvenile Polyposis Syndrome, Evaluations Following Initial Diagnosis for additional recommendations.	Colonoscopy at age 15 yrs; rpt every 3 yrs if no polyps found, or annually w/EGD if colonic polyps are identified [Faughnan et al 2020].
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of HHT in order to facilitate medical & personal decision making

AVMs = arteriovenous malformations; EGD = esophagogastroduodenoscopy; GI = gastrointestinal; HHT = hereditary hemorrhagic telangiectasia; MOI = mode of inheritance; TCE = transthoracic contrast echocardiography; TIA = transient ischemic attack

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 6.

Treatment of Manifestations in Individuals with Hereditary Hemorrhagic Telangiectasia

Manifestation/ Concern	Treatment	Considerations/Other
Nosebleeds (epistaxis)	• Humidification • 2x-daily topical moisturizing therapy • Hemostatic products (e.g., gauze, sponge, powder products)	Consider additional treatments if epistaxis is causing anemia or interfering w/normal activities.
	• Antifibrinolytic therapy (oral tranexamic acid) • Ablation therapies (e.g., laser treatment, radiofrequency ablation, electrosurgery, sclerotherapy)	Consider if epistaxis does not respond to topical moisturizing therapies.
	• System antiangiogenic agents (e.g., intravenous bevacizumab) • Septodermoplasty & nasal closure	Consider if epistaxis does not respond to topical moisturizing therapies, tranexamic acid, &/or ablative therapies [Faughnan et al 2020]. Surgical treatment for severe epistaxis in persons w/HHT should be performed by surgeons who regularly treat people w/HHT [Richer et al 2012].
GI bleeding	• EGD is 1st-line diagnostic approach for suspected bleeding [Faughnan et al 2020]. • Consider capsule endoscopy if EGD does not identify the source of suspected GI bleeding to help localize the source of bleeding [Grève et al 2010].	Endoscopic argon plasma coagulation may be administered concurrent w/initial EGD, but should be used sparingly during endoscopy & rpt sessions avoided [Faughnan et al 2020].
	In those w/mild GI bleeding (i.e., anemia controlled w/iron replacement): consider oral antifibrinolytics (e.g., tranexamic acid).	Treatment is typically unnecessary unless iron therapy has been ineffective in maintaining a normal hemoglobin level.
	In those w/GI bleeding that requires intravenous iron therapy or blood transfusions: consider systemic antiangiogenic agents (intravenous bevacizumab) [Faughnan et al 2020].	

Manifestation/ Concern	Treatment	Considerations/Other
Anemia	• Oral iron therapy • IV iron in those intolerant or unresponsive to oral iron therapy • Red blood cell transfusion only in those w/: hemodynamic instability/shock, comorbidities that require a higher hemoglobin target, need to ↑ the hemoglobin acutely (e.g., prior to surgery or pregnancy), or inability to maintain adequate hemoglobin despite frequent iron infusions	
Pulmonary AVMs	Transcatheter embolotherapy is the treatment of choice: • Consider occlusion for any pulmonary AVM w/a feeding vessel >1-2 mm in diameter [Trerotola & Pyeritz 2010]. • Treatment is indicated for dyspnea, exercise intolerance, & hypoxemia, but is most important for prevention of lung hemorrhage & neurologic complications of brain abscess & stroke, even in those w/normal pulmonary function & oxygen saturation.	• See Footnote 1. • Occasionally, a small lesion cannot be reached by transcatheter embolotherapy because of its location or the size of the feeding vessel.
	Chest CT &/or contrast echocardiography after embolization of pulmonary AVMs because of reported recanalization & development or growth of untreated pulmonary AVMs [Cottin et al 2007].	Usually, follow-up CT 6-12 mos post occlusion; then, if no recanalized or new pulmonary AVMs are noted, follow-up CT every 5 yrs [Trerotola & Pyeritz 2010, Faughnan et al 2011].
Cerebral abscess / Air embolism	If contrast echocardiography shows pulmonary shunting (even if no pulmonary AVM is identified on chest CT): • Prophylactic antibiotics in accordance w/the American Heart Association protocol for dental cleaning & other	Note: The risk assoc w/these lesions is not for subacute bacterial endocarditis.

Manifestation/ Concern	Treatment	Considerations/Other
	procedures w/risk of bacteremia is advised because of the risk of abscess (esp brain abscess) assoc w/right-to-left shunting [Dupuis-Girod et al 2017]. • Caution not to introduce air bubbles (to incl air filter if available) is recommended w/IV lines. • Avoid scuba diving in those w/evidence of pulmonary AVMs.	
Pulmonary artery hypertension	Treatment per cardiologist, pulmonologist, & other relevant specialists	
Hepatic AVMs	• Most w/symptomatic hepatic AVMs can be managed w/intensive medical therapy [Buscarini et al 2011]. • Consider intravenous bevacizumab for those w/symptomatic high-output cardiac failure due to hepatic AVMs who have failed to respond to first-line management [Faughnan et al 2020].	• See Footnote 1. • Treatment of symptomatic hepatic AVMs is currently problematic. Embolization of hepatic AVMs (successful for treatment of pulmonary AVMs) has led to lethal hepatic infarctions.
	Referral for consideration of liver transplantation for those w/symptomatic hepatic AVMs causing refractory high-output heart failure, biliary ischemia, or complicated portal hypertension [Faughnan et al 2020]	• Liver transplantation has been standard treatment for those (usually older) persons whose symptoms of hepatic failure do not respond to medical management [Iyer et al 2019]. • Liver biopsy should be avoided in persons w/HHT [Buscarini et al 2006].
Cerebral AVMs	Cerebral AVMs are typically treated using neurovascular surgery, embolotherapy, &/or stereotactic radiosurgery depending on size, location, & symptoms.	See Footnote 1.

Manifestation/ Concern	Treatment	Considerations/Other
Intestinal polyps assoc w/*SMAD4*-HHT	See Juvenile Polyposis Syndrome, Treatment of Manifestations.	

AVMs = arteriovenous malformations; EGD = esophagogastroduodenoscopy; GI = gastrointestinal; HHT = hereditary hemorrhagic telangiectasia; IV = intravenous

1. Before proceeding with treatment for any visceral AVM, patients and their doctors are encouraged to contact the nearest multidisciplinary HHT clinic, which can be located through the support group Cure HHT, to assure that appropriate diagnostic and treatment plans are in place [Faughnan et al 2011].

Surveillance

The following surveillance is recommended for all individuals with an established diagnosis of HHT and for all individuals at risk for HHT based on family history in whom HHT has not been ruled out by molecular diagnosis [Faughnan et al 2020].

Table 7.

Recommended Surveillance for Individuals with Hereditary Hemorrhagic Telangiectasia

System/Concern	Evaluation	Frequency
General	Eval by health care provider familiar w/HHT, incl interval history for epistaxis, other bleeding, shortness of breath, ↓ exercise tolerance, headache, & other neurologic symptoms	Annually
Anemia	• Hematocrit/hemoglobin • Ferritin	
Pulmonary AVM	• In **adults**: TCE w/agitated saline contrast if previous TCE did not reveal evidence of a significant right-to-left shunt • In **children**: TCE w/agitated saline contrast OR chest radiograph w/pulse oximetry	• In those w/o previous pulmonary AVM: every 5 yrs • In those w/pulmonary AVM: frequency per vascular specialist
Cerebral AVM	Brain MRI (w/& w/o contrast using sequences that detect blood products)	Rpt after puberty if initial brain MRI was done in childhood, as development or evolution of cerebral AVMs in 1st 2 decades of life has been reported [Hetts et al 2014].
***SMAD4*-HHT**	See Juvenile Polyposis Syndrome, Surveillance for additional	Colonoscopy at age 15 yrs; rpt every 3 yrs if no polyps found or

System/Concern	Evaluation	Frequency
	recommendations.	annually w/EGD if colonic polyps are identified [Faughnan et al 2020].

AVM = arteriovenous malformation; EGD = esophagogastroduodenoscopy; HHT = hereditary hemorrhagic telangiectasia; TCE = transthoracic contrast echocardiography

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. Some individuals with HHT experience increased epistaxis after drinking alcohol.

Anticoagulants including 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. However, HHT is not an absolute contraindication for anticoagulation (prophylactic or therapeutic) or antiplatelet therapy. It is recommended that individuals with HHT receive these therapies when there is an indication, with consideration of their individualized bleeding risks [Faughnan et al 2020]. Two case series demonstrated that anticoagulation or antiplatelet therapy is well tolerated by most individuals with HHT [Edwards et al 2012, Devlin et al 2013].

When anticoagulation is pursued, unfractionated heparin, low-molecular-weight heparin, and vitamin K antagonists are preferred over direct-acting oral anticoagulants, which are less well tolerated in individuals with HHT [Shovlin et al 2019]. In individuals with atrial fibrillation, if anticoagulation is not tolerated, alternate approaches can be considered, such as left atrial appendage closure [Vorselaars et al 2015]. Avoiding the use of dual antiplatelet therapy and/or combination of antiplatelet and anticoagulation is recommended when possible.

Scuba diving should be avoided unless contrast echocardiography performed within the last five years was negative for evidence of a right-to-left shunt.

Liver biopsy should be avoided in individuals with HHT [Buscarini et al 2006].

Evaluation of Relatives at Risk

It is recommended to evaluate at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from surveillance and prompt initiation of treatment to reduce morbidity and mortality.

If the pathogenic variant in the family is known, evaluate with molecular genetic testing.

If the familial pathogenic variant is not known and the diagnosis of HHT cannot been ruled out by molecular testing, at-risk family members should follow the same protocol as is recommended for individuals in whom the diagnosis of HHT is established (see Surveillance).

- Individuals older than age 40 years should have a targeted medical history and clinical examination for features of HHT. The absence of mild but recurrent epistaxis and subtle telangiectases in characteristic locations on careful examination is reassuring.
- In individuals age 40 years and younger, targeted medical history and clinical examination for features of HHT in addition to an evaluation for brain and pulmonary AVMs should be done initially, as features of HHT may not be identified by medical history and clinical examination in younger individuals.

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

Pregnancy Management

Pregnant women with HHT and untreated pulmonary AVMs are at increased risk for complications related to hemorrhage or embolic events. Women with treated pulmonary AVMs appear to be at no higher risk during pregnancy than those without pulmonary AVMs. For this reason, published management guidelines recommend that pregnant women with HHT who have not been recently screened and/or treated for pulmonary AVM should be managed as follows:

- In asymptomatic women, initial screening for pulmonary AVMs should be performed using either transthoracic contrast echocardiography with agitated saline contrast or low-dose noncontrast chest CT, depending on local expertise. Chest CT, when performed, should be done early in the second trimester.
- In women with symptoms suggestive of pulmonary AVM, diagnostic testing should be performed using low-dose noncontrast chest CT. This testing can be performed at any gestational age, as clinically indicated.
- Pulmonary AVMs should be treated starting in the second trimester unless otherwise clinically indicated.

An unenhanced brain MRI is recommended in pregnant women with symptoms suggestive of cerebral AVM. Women who are asymptomatic do not require routine screening for cerebral AVMs during pregnancy.

Iron replacement is preferred for anemia, but transfusion of packed red blood cells may be necessary for symptomatic anemia refractory to aggressive iron replacement therapy.

Expert consensus is to not withhold an epidural because of a diagnosis of HHT, and that screening for spinal vascular malformations is not required. Two case series showed no evidence of hemorrhagic complications from epidural or spinal anesthesia [Shovlin et al 2008, de Gussem et al 2014, Faughnan et al 2020].

Therapies Under Investigation

Newer therapies designed to interfere with the development of abnormal vascular connections are being investigated; while numerous case reports and small uncontrolled series indicate promise, results from controlled trials are needed [Flieger et al 2006, Mitchell et al 2008, Bose et al 2009, Davidson et al 2010, Lebrin et al 2010, Brinkerhoff et al 2011, Fodstad et al 2011, Suppressa et al 2011, Dupuis-Girod et al 2012].

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.

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

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 rarely have the disorder as the result of *de novo* pathogenic variant or mosaicism [McDonald et al 2015].
- If the proband appears to be the only affected family member (i.e., a simplex case), and:
    - The HHT-causing pathogenic variant has been identified in the proband, molecular genetic testing is recommended for the parents of the proband to confirm their genetic status, allow reliable recurrence risk counseling, and determine if a parent should undergo clinical examination for features of HHT.
    - The HHT-causing pathogenic variant has not been identified in the proband, recommendations for the evaluation of parents of the proband include physical examination and documentation of medical history targeted at symptoms and manifestations of HHT.

      Note: If the familial pathogenic variant is not known and, consequently, HHT cannot been ruled out by molecular testing, at-risk family members should follow the same protocol as is recommended for individuals in whom the diagnosis of HHT is definite (see Surveillance).
- If the proband has a known *ACVRL1*, *ENG*, or *SMAD4* pathogenic variant that cannot be detected in leukocyte DNA of either parent, and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with HHT may appear to be negative because of failure to recognize the disorder in affected family members, reduced penetrance, 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 the HHT-causing pathogenic variant has been identified in the proband and molecular genetic testing has established that neither parent is heterozygous for the familial pathogenic variant.

Sibs of a proband. The risk to the sibs 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 HHT-causing pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the proband has a known HHT-causing 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 are clinically unaffected but their genetic status is unknown, sibs should be considered at risk for HHT and, if the familial pathogenic variant is known, offered molecular genetic testing. If the familial pathogenic variant is not known, sibs should follow the same protocol as is recommended for individuals in whom the diagnosis of HHT is definite (see Surveillance). Although HHT is highly penetrant, a heterozygous parent may not have manifestations of the disorder until after age 40 years and observable symptoms and manifestations can be subtle, even well into adulthood.

Offspring of a proband. Each child of an individual with HHT 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 is affected or has an HHT-causing pathogenic variant, his or her family members are at risk.

Related Genetic Counseling Issues

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

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.

Testing of at-risk asymptomatic individuals. Consideration of molecular genetic testing of young, at-risk family members is appropriate for guiding medical management (see Surveillance). Molecular genetic testing can be used with certainty to clarify the genetic status of at-risk family members when a clinically diagnosed relative has undergone molecular genetic testing and is found to have a pathogenic variant in an HHT-related gene.

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 regarding possible problems that they may encounter with respect 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 identified to have a pathogenic variant in one of the three HHT-related genes need long-term follow up and evaluations.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, 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 genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the HHT-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing 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.

- **Cure HHT**
  PO Box 329
  Monkton MD 21111
  Phone: 410-357-9932
  Fax: 410-357-0655
  Email: hhtinfo@curehht.org
  www.curehht.org
- **MedlinePlus**
  Hereditary hemorrhagic telangiectasia

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.

Hereditary Hemorrhagic Telangiectasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ACVRL1	12q13.13	Activin receptor type-1-like	HHT Mutation Database (ACVRL1) ACVRL1 database	ACVRL1	ACVRL1
ENG	9q34.11	Endoglin	HHT Mutation Database (ENG) ENG database	ENG	ENG
SMAD4	18q21.2	Mothers against decapentaplegic homolog 4	SMAD4 database	SMAD4	SMAD4

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 Hereditary Hemorrhagic Telangiectasia (View All in OMIM)

131195	ENDOGLIN; ENG
175050	JUVENILE POLYPOSIS/HEREDITARY HEMORRHAGIC TELANGIECTASIA SYNDROME; JPHT
187300	TELANGIECTASIA, HEREDITARY HEMORRHAGIC, TYPE 1; HHT1

600376	TELANGIECTASIA, HEREDITARY HEMORRHAGIC, TYPE 2; HHT2
600993	SMAD FAMILY MEMBER 4; SMAD4
601101	none found
601284	ACTIVIN A RECEPTOR, TYPE II-LIKE 1; ACVRL1
610655	TELANGIECTASIA, HEREDITARY HEMORRHAGIC, TYPE 4; HHT4

Molecular Pathogenesis

Currently, all known genetic defects that cause HHT are in genes that encode proteins within the transforming growth factor beta (TGF-β) signaling pathway.

- *ACVRL1* encodes serine/threonine-protein kinase receptor R3, a type I cell-surface receptor for the TGF-superfamily of ligands. It is expressed predominantly on endothelial cells [Abdalla & Letarte 2006].
- *ENG* encodes endoglin, a component of the transforming growth factor beta (TGF-beta) receptor complex. It is expressed predominantly on endothelial cells.
- *SMAD4* encodes a 552-amino acid protein that functions as an intracellular signaling molecule in the TGF-beta/BMP pathway.

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

David Stevenson, MD is a practicing medical geneticist at Stanford University and helps direct the Stanford HHT Center of Excellence.
www.stanfordchildrens.org/en/service/genetics/vascular-anomaly-genetic-clinic.

Jamie McDonald MS, CGC, Associate Professor, Emeritus, Department of Pathology at the University of Utah was the Co-Director of the University of Utah HHT Center of Excellence from 2009-2021; and its co-founder and genetic counselor since 1996.

Jamie has many publications related to HHT, including invited review articles and original research focused particularly on the clinical and molecular diagnosis of HHT. She has served on the Cure HHT Global Research and Medical Advisory Board for many years. She co-chaired the Clinical and Molecular Diagnosis Group at the International HHT Guidelines Conference, which led to publication of the initial consensus guidelines for diagnosis and management in 2011. She was an invited member of the international conference which led to the publication in 2021 of the second consensus guidelines for the diagnosis and management of HHT.
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Acknowledgments

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Revision History

- 24 November 2021 (sw) Comprehensive update posted live
- 2 February 2017 (sw) Comprehensive update posted live
- 24 July 2014 (me) Comprehensive update posted live
- 5 January 2012 (me) Comprehensive update posted live
- 19 May 2009 (me) Comprehensive update posted live
- 22 November 2005 (me) Comprehensive update posted live
- 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 live
- 26 June 2000 (me) Review posted live
- January 2000 (jm) Original submission

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