

Genetic Testing for Hereditary Hemorrhagic Telangiectasia

Barbara A. Bernhardt, MS, CGC

ABSTRACT

- **Objective:** To review the rationale and process of genetic testing for hereditary hemorrhagic telangiectasia (HHT) in families and to discuss resources available for facilitating testing.
- **Methods:** Review of the literature.
- **Results:** HHT can be diagnosed according to clinical diagnostic criteria including epistaxis, multiple telangiectases, visceral arteriovenous malformations and a family history of HHT. Early identification and treatment of HHT can reduce morbidity and mortality. In at-risk family members, the diagnosis can be made or excluded by genetic testing for the familial mutation in an HHT-associated gene if a mutation can be identified in an affected relative. Resources are available to address barriers to genetic testing for HHT. These resources can facilitate ordering of appropriate genetic tests by primary care providers and specialty physicians.
- **Conclusion:** Primary care providers can play a key role in educating patients about the availability of genetic testing and in facilitating access to genetic tests.

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder of vascular development occurring in at least 1 in 5000 individuals [1]. It was initially described as a hereditary disorder comprised of telangiectases and epistaxis by Rendu in 1896 [2]. Shortly after, Osler [3] and Weber [4] described additional families with similar findings, leading to the disease appellation of Osler-Weber Rendu syndrome. In 1909, Hanes renamed the condition hereditary hemorrhagic telangiectasia [5].

Signs and symptoms of HHT are caused by the presence of multiple arteriovenous malformations (AVMs) lacking intervening capillaries, resulting in direct connections between arteries and veins. Telangiectases are tiny AVMs which are thin-walled, close to the surface of the skin or mucosal membranes, and prone to bleeding. When telangiectases are present in the nasal mucosa, they

predispose to frequent and heavy nosebleeds, including nocturnal epistaxis. Nearly all individuals with HHT eventually develop telangiectases of the face, oral cavity, or hands. Telangiectases can be present throughout the gastrointestinal tract, but are most commonly associated with gastrointestinal (GI) bleeding in patients over age 50.

Larger AVMs occur most frequently in the brain, the lungs, or the liver. Cerebral AVMs are congenital and present in approximately 10% of affected individuals [6]. Pulmonary AVMs occur in up to 50% of affected individuals [7]. A pulmonary AVM can allow bacteria and blood clots in veins to travel directly to the arterial circulation without being filtered by lung capillaries. This can result in a transient ischemic attack (TIA), stroke or cerebral abscess if the brain is involved, or ischemic damage to an organ such as the kidney. Morbidity associated with pulmonary AVMs can be dramatically reduced by embolization of any pulmonary AVM that can be reached by a catheter, including those with a feeding artery as small as 2 mm [7,8].

Left untreated, HHT-associated AVMs in the lungs, brain, liver, and GI tract can lead to chronic anemia, hypoxemia, stroke, or brain abscess. Identification of the disorder and treatment of complications can reduce morbidity and mortality [9]. HHT, however, is under-recognized, and many affected individuals may not be diagnosed until a catastrophic complication has occurred [1]. Since nearly every person with HHT has an affected parent, identification of individuals at risk for HHT can be accomplished through the taking of a family history. Because most of the signs and symptoms of HHT are age-dependent, determining which at-risk children and young adults in a family have HHT and which do not is often difficult. Genetic testing in families can greatly simplify identification of those family members who need

From the University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

to be screened and followed for clinical involvement from HHT.

This article provides information about diagnosing HHT and reviews the rationale and process for genetic testing for HHT in families. In addition, barriers to genetic testing are discussed as well as practical information for physicians to address those barriers so they can adequately assist patients who might benefit from genetic testing for HHT.

DIAGNOSIS

A clinical diagnosis of HHT is based on the presence of well-defined diagnostic criteria [10]. The 4 criteria include:

- Epistaxis (spontaneous recurrent nosebleeds)
- Multiple telangiectases at characteristic sites (lips, oral cavity, fingers, nose)
- Visceral lesions (such as GI telangiectases or pulmonary, cerebral, hepatic, or spinal AVMs)
- Family history of a first-degree relative with HHT according to these criteria.

A diagnosis of HHT is considered to be definite if 3 or 4 of these criteria are present, possible if 2 are present, and unlikely if fewer than 2 criteria are present. The presence of characteristic visceral lesions, especially when there are multiple lesions, is especially suggestive of HHT [7,11,12].

A clinical diagnostic evaluation for HHT involves reviewing the medical history focusing on signs and symptoms consistent with HHT; obtaining a complete family history; and conducting a physical examination, especially focusing on the skin and mucosal membranes to look for the presence of telangiectases. The clinical evaluation should include a magnetic resonance imaging (MRI) study with and without contrast to screen for cerebral AVMs, and a transthoracic contrast echocardiogram to screen for pulmonary AVMs [1,6]. If the contrast echocardiogram is considered positive for a shunt at the level of the lungs by virtue of late right-to-left passage of contrast, a computed tomography (CT) scan of the thorax with and without contrast should be performed to confirm the presence of pulmonary AVMs [1,6].

HHT is inherited in an autosomal dominant manner with considerable variability within and between families. Each child and most siblings of an affected person will have a 50% risk of being affected. Individuals who are at

up to 50% risk need to be screened by history, physical examination, and various imaging modalities periodically until the diagnosis is either established or the patient is old enough to be reasonably sure that features will not develop. This age has not been established firmly, leading to uncertainty for both patients and their health care providers. The difficulty of excluding a diagnosis of HHT in someone who is at risk, especially in children, led to steps to make molecular testing for HHT available [13].

GENETICS AND GENETIC TESTING

Until very recently, the diagnosis of HHT could only be made on clinical grounds. In the past 20 years, new genetic technologies have led to improved understanding of the genetic basis of HHT and to diagnostic genetic testing. The 2 genes involved with the majority of cases of HHT, endoglin (*ENG*) and activin receptor-like kinase 1 (*ACVRL1*), were discovered in 1994 and 1996 [14–16]. Both genes are involved in the transforming growth factor-beta ($TGF\beta$) and bone morphogenetic protein (BMP) signaling pathway. Hundreds of distinct mutations in either of these genes, many seen in only a single family, may cause HHT. In addition to these 2 genes, mutations in the gene encoding SMAD-related protein 4 (*SMAD4*) cause a combined syndrome of juvenile polypos and HHT [17]. At least 2 other unidentified genes also appear to be associated with HHT [18,19].

Genetic testing for HHT can be somewhat complex because a mutation in one of several genes can cause HHT, not all disease-associated genes have been discovered, and most families have their own “private” HHT mutation. Despite the complexity, a number of clinical molecular diagnostic laboratories around the world, including 5 in the United States, provide testing for mutations in *ENG*, *ACVRL1*, and *SMAD4* by direct sequencing and assaying for deletions and duplications. For a person who meets clinical diagnostic criteria for HHT, genetic testing by first sequencing *ENG* and *ACVRL1*, followed by duplication and deletion testing of these 2 genes should detect a mutation in approximately 87% of those tested [20]. If testing of *ENG/ACVRL1* is negative, testing of *SMAD4* identifies a mutation in an additional 2% of cases diagnosed with HHT [21].

Genetic testing for HHT is done for several reasons. First, it may be useful in establishing a diagnosis of HHT in someone with possible HHT who does not warrant a diagnosis based on current clinical diagnostic criteria. However, in such circumstances (that is, when not testing

for a known familial mutation), genetic testing can never exclude a diagnosis of HHT because genetic testing only identifies a disease-associated mutation in about 89% of affected individuals. Using molecular techniques to diagnose HHT may be further complicated because genetic testing of *ENG/ACVRL1/SMAD4* may reveal a variant of uncertain significance such as a novel missense mutation which may or may not be causative of HHT.

Genetic testing is most frequently used to determine which asymptomatic at-risk family members are affected by HHT. Once HHT is diagnosed in a family, all relatives are considered to be at risk for having HHT. The diagnosis can be made clinically by evaluating for nosebleeds, telangiectases and visceral AVMs. Because the most easily identified manifestations of HHT, such as telangiectases and epistaxis, often do not appear until adolescence or later, it is particularly difficult to determine whether young at-risk individuals have inherited HHT from an affected parent. If genetic testing is not used, these children need to be screened for brain and pulmonary AVMs using procedures that will require sedation in young children. Moreover, some of the manifestations of HHT such as epistaxis and cutaneous telangiectases are common in the general population, complicating diagnosis. Because of these issues, genetic testing can be particularly helpful in determining which family members have HHT.

Because an HHT-causing mutation cannot be found in all families, predictive testing for at-risk asymptomatic family members requires prior identification of the disease-causing mutation in an affected person in the family. If genetic testing of the relative with HHT does not pick up a deleterious mutation, or if only a variant of uncertain significance is found, genetic testing of at-risk relatives will not yield useful information, and these relatives will need to be screened clinically as described above, and treated if warranted. If the family mutation is identified (which occur in about 89% of HHT families), asymptomatic relatives or those with only minor nosebleeds or a few telangiectases can be tested to determine if they are affected. For those relatives who do not carry the familial mutation, reassurance can be provided and no further HHT screening undertaken. This is an especially welcome result for young children who can be spared a brain MRI, contrast echocardiogram, and ongoing monitoring for signs of HHT. Relatives not carrying the familial mutation can also be reassured that they are not at increased risk for having affected children. Screen-

ing for complications of HHT can be directed only to those relatives who have inherited the familial disease-causing mutation. Screening for HHT in families by identifying the familial mutation and then using genetic testing to identify family members who do not need further work-up has been shown to be highly cost-effective when compared to performing clinical screening in all at-risk family members [22].

ADDRESSING BARRIERS TO GENETIC TESTING FOR HHT

Despite the clinical utility of genetic testing for HHT, genetic testing in families is infrequently performed [23]. Through online discussion groups involving people with HHT and their family members, a variety of barriers to genetic testing for HHT have been identified recently [23]. From the perspective of families with HHT, many people fail to understand the rationale for genetic testing or the benefits of early detection and treatment. Many believe that genetic testing is expensive and not covered by insurance. They report that primary care providers may not know how to order genetic testing for HHT, or understand enough about genetic testing to accurately interpret results. Access to HHT testing may be limited by distance from an HHT center or a genetics clinic. Many individuals in HHT families are reluctant to seek out genetic testing due to fear of insurance discrimination, denial of having HHT or being at risk, or feelings of guilt and stigma.

Fortunately, these barriers to genetic testing can be addressed. Patients can be reassured that the possibility of genetic discrimination in employment and health insurance is reduced with the passage of the federal Genetic Information Nondiscrimination Act of 2008 (GINA) [24]. GINA prohibits a health insurer or employer from discriminating against an individual based on that person's genetic risk for future disease. Genetic test results cannot be used by health insurers as a basis for determining eligibility or premiums, nor can they be used by employers as a basis for hiring, firing or other terms of employment. Nearly all states also have laws prohibiting various forms of discrimination based on genetic test results. Protections through GINA and various state laws should lessen the risk of the misuse of genetic information and encourage people to utilize potentially useful genetic testing. The benefits of genetic testing through determining whether an at-risk person is or is not affected by HHT likely greatly outweigh the very small risk of insurance discrimination.

Education about HHT, including information about genetic testing and the importance of early detection, is available through the Hereditary Hemorrhagic Telangiectasia Foundation International (www.hht.org). The HHT Foundation's website includes educational materials for both patients and providers which address the rationale for genetic testing, the clinical variability of HHT, and the importance of early detection and treatment. The website also contains information about protections against insurance discrimination through GINA. Directing patients to this website should both prepare patients for genetic testing and address some of the misperceptions and concerns that exist about testing.

The HHT Foundation has established HHT Centers of Excellence that provide comprehensive medical and counseling services as well as access to genetic testing for patients and families with HHT. There are now 15 centers in North America; contact information may be found on the HHT Foundation website.

For patients who are unable to travel to an HHT Center of Excellence, genetic testing can be ordered by primary care or specialty physicians. Although genetic testing is usually performed on a small sample of blood, several of the laboratories offering testing for HHT can perform the test on a sample of saliva. This can facilitate testing of children, people who fear blood draws, and people who don't have easy access to phlebotomy services.

Providers may initially find that ordering genetic testing is confusing, for example, whether to order full gene sequencing followed by deletion and duplication analysis (which would be ordered when testing the first person in the family with HHT in order to identify the familial mutation), or testing for a single mutation (which would be ordered when testing an at-risk person for the familial mutation). If primary care providers have questions about testing, they can call one of the labs that offer testing; these labs are listed on the website www.genetests.org. In addition, a comprehensive listing of all laboratories offering any type of genetic test is now available through the NIH's new Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr). All 5 laboratories offering genetic testing for HHT employ genetic counselors who can assist providers with test ordering, facilitate sample collection and shipping, and help with interpretation of results. Providers can also call one of the HHT Centers of Excellence and ask to speak with a genetic counselor about genetic testing. The testing labs also include information on their

websites that addresses many common questions about genetic testing.

If the family cannot travel to an HHT center and the provider is unable to order HHT genetic testing, genetic testing can often be obtained through a genetic counselor (who can be identified through the National Society of Genetic Counselors (www.nsgc.org) or through a genetics clinic (a list is available at www.geneclinics.org). In addition, genetic counseling and genetic testing are increasingly available through companies such as Informed DNA which offer telephone genetic counseling. Such services, in conjunction with genetic testing done on a sample of saliva mailed to a testing lab, can increase access to genetic testing services to people residing in rural or underserved areas.

Families can be reassured that although genetic testing, especially full gene sequencing, is expensive, it is usually covered by insurance, including Medicare and state medical assistance programs. The cost of genetic testing varies among laboratories and according to type of test. Testing to initially determine which mutation is present in a family through sequencing analysis of the *ENG* and *ACVRL1* genes can cost several thousand dollars, with additional charges if deletion or duplication testing is needed, or if testing of *SMAD-4* is performed. Once a mutation has been identified in the family, testing of other family members for that mutation currently costs only \$200 to \$300. Several of the laboratories performing genetic testing will assist patients and providers with obtaining verification of insurance coverage. Although a letter of medical necessity may sometimes be requested, genetic testing is generally covered as a regular laboratory test. Rarely, insurance policies will specifically exclude genetic testing. If a patient is capitated for laboratory services to a lab that does not offer particular genetic tests, an out-of-cap referral to one of the testing labs can generally be obtained.

CONCLUSION

Genetic testing is currently available for over 2000 genetic disorders such as HHT that are due to changes in single genes. For many of these disorders, genetic testing can facilitate diagnosis in both symptomatic and nonsymptomatic individuals who are at increased risk, and early diagnosis and disease management can reduce morbidity and mortality. Education of both patients and providers is needed so that the benefits of genetic testing can be realized.

Primary care providers can play a key role in educating patients about the availability of genetic testing, and in facilitating access to genetic tests. Resources are available to assist providers in ordering tests, and in interpreting results. With additional education and support for ordering genetic tests and interpreting results, primary care providers can help to ensure that patients who might benefit from genetic testing for autosomal dominant disorders with age-dependent manifestations have access to genetic testing.

Corresponding author: Barbara Bernhardt, MS, CGC, 3400 Spruce St., Penn Tower 1115, Philadelphia, PA 19104, Barbara.bernhardt@uphs.upenn.edu.

Funding/support: Grant 1-P50HG004487-01 from the National Human Genome Research Institute, National Institutes of Health.

Financial disclosures: None.

REFERENCES

1. Faughnan ME, Palda VA, Garcia-Tsao G, et al. International guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. *J Med Genet* 2009;48:73–87.
2. Rendu HJ. Épistaxis répétées chez un sujet porteur de petits angiomes cutanés et muqueux. *Gaz Hop* 1896;1322–33.
3. Osler W. On a family form of recurring epistaxis, associated with multiple telangiectases of the skin and mucous membranes. *Bull Johns Hopkins Hosp* 1901;12:333–7.
4. Weber FP. Multiple hereditary developmental angiomas (telangiectases) of the skin and mucous membranes associated with recurring haemorrhages. *Lancet* 1907;2:160–2.
5. Hanes FM. Multiple hereditary telangiectases causing hemorrhage (hereditary hemorrhagic telangiectasia). *Bull Johns Hopkins Hosp* 1909;20:63–73.
6. McDonald J, Bayrak-Toydemir P, Pyeritz RE. Hereditary hemorrhagic telangiectasia: An overview of diagnosis, management and pathogenesis. *Genet Med* 2011;13:607–16.
7. Trerotola SO, Pyeritz RE. PAVM embolization: an update. *AJR* 2010;195:837–45.
8. Cottin V, Dupuis-Girod S, Lesca G, Cordier JF. Pulmonary vascular manifestations of hereditary hemorrhagic telangiectasia (Rendu-Osler disease). *Respiration* 2007;74:361–78.
9. Sabba C, Pasculli G, Suppressa P, et al. Life expectancy in patients with hereditary haemorrhagic telangiectasia. *Q J Med* 2006;99:327–34.
10. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet* 2000;91:66–7.
11. Kjeldsen AD, Vase P, Green A. Hereditary hemorrhagic telangiectasia: a population-based study of prevalence and mortality in Danish patients. *J Intern Med* 1999;245:31–9.
12. Bharatha A, Faughnan ME, Kim H et al. Brain arteriovenous malformation multiplicity predicts the diagnosis of hereditary hemorrhagic telangiectasia. *Stroke* 2012;43:72–8.
13. Messner D, Pyeritz RE, Bernhardt BA. Comment on the impact of gene patents and licensing practices on access to genetic testing: Lessons from hereditary hemorrhagic telangiectasia. *Genet Med* 2010;12:746–8.
14. Arthur HM, Ure J, Smith AJ, et al. Endoglin, an ancillary TGFβ receptor, is required for extraembryonic angiogenesis and plays a key role in heart development. *Dev Biol* 2000;217:42–53.
15. Johnson DW, Berg JN, Baldwin MA, et al. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. *Nat Genet* 1996;13:189–95.
16. McAllister KA, Grogg KM, Johnson DW, et al. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. *Nat Genet* 1994;8:345–51.
17. Gallione CJ, Repetto GM, Legius E, et al. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). *Lancet* 2004;363:852–9.
18. Cole SG, Begbie ME, Wallace GM, Shovlin CL. A new locus for hereditary haemorrhagic telangiectasia (HHT3) maps to chromosome 5. *J Med Genet* 2005;42:577–82.
19. Bayrak-Toydemir P, McDonald J, Akarsu N, et al. A fourth locus for hereditary hemorrhagic telangiectasia maps to chromosome 7. *Am J Med Genet A* 2006;140:2155–62.
20. Richards-Yutz J, Grant K, Chao EC, et al. Update on molecular diagnosis of hereditary hemorrhagic telangiectasia. *Hum Genet*. 2010;128:61–77.
21. Gallione CJ, Richards JA, Letteboer TG, et al. SMAD4 mutations found in unselected HHT patients. *J Med Genet*. 2006;43:793–7.
22. Bernhardt BA, Zayac C, Trerotola SO, et al. Cost savings through molecular diagnosis for hereditary hemorrhagic telangiectasia. *Genet Med* 2012. In press.
23. Bernhardt BA, Zayac C, Pyeritz RE. Why is genetic screening for autosomal dominant disorders underutilized in families? The case of hereditary hemorrhagic telangiectasia (HHT). *Genet Med* 2011;13:812–20.
24. Hudson KL, Holohan MK, Collins FS. Keeping pace with the times—the Genetic Information Nondiscrimination Act of 2008. *N Engl J Med* 2008;358:2661–3.