



HHT FOUNDATION INTERNATIONAL

www.hht.org

*“Learn more
about...”*



*Hereditary
Hemorrhagic
Telangiectasia.’’*

(Osler-Weber-Rendu Syndrome)



HEREDITARY HEMORRHAGIC TELANGIECTASIA OVERVIEW



Introduction

Hereditary Hemorrhagic Telangiectasia (HHT) is a genetic disorder of the blood vessels, which affects about one in 5,000 people. It affects males and females from all racial and ethnic groups.

The disorder is also sometimes referred to as *Osler-Weber-Rendu (OWR)* after several doctors who studied HHT 100 years ago. In 1896 Dr. Rendu first described HHT as a hereditary disorder involving nosebleeds and characteristic red spots that was distinctly different from hemophilia. Before Dr. Rendu's work, doctors did not understand that individuals with what we now call HHT have abnormalities of their blood vessels, not a clotting problem in the blood itself. Drs. Weber and Osler reported on additional features of HHT in the early 1900s. *One hundred years later*, HHT is still often misdiagnosed in affected individuals and many doctors do not understand all of its manifestations.

What is HHT?

Most blood vessels in the body of someone with HHT are normal. However, a small percentage of the blood vessels in a person with HHT have a specific type of abnormality.

A person with HHT has a tendency to form blood vessels that lack the capillaries between an artery and vein. This means that arterial blood under high pressure flows directly into a vein without first having to squeeze through the very small capillaries. This place where an artery is connected directly to a vein tends to be a fragile site that can rupture and result in bleeding.

We usually call a blood vessel that is abnormal in this way a **telangiectasia** (tel-AN-jee-eck-TAZE-ee-ya) if it involves small blood vessels. We tend to call it an arteriovenous malformation (AVM) if it involves larger blood vessels. So, an AVM might be thought of as a big telangiectasia. The basic abnormality in the blood vessel is the same. Telangiectases tend to occur at the surface of the body such as the skin and the mucous membrane that lines the nose. AVMs tend to occur in the internal organs of the body.

The telangiectases and AVMs of HHT occur primarily in the nose, mouth and skin of the face and hands, as well as the lining of the stomach and intestines (GI tract), lungs, brain and liver. It is not currently known why they tend to occur in certain parts of the body and not others.

How does HHT affect a person?

Its location in the body determines what problem(s) a telangiectasia or AVM might cause. In most locations, and at any size, a telangiectasia or AVM has a greater tendency to rupture and bleed than a normal blood vessel. In the nose, skin, GI tract (stomach and intestines), and brain the primary problem they can cause is bleeding. AVMs in the lungs or liver are less likely to rupture and bleed, but can cause other problems that are less obvious to doctors and patients who lack an in depth understanding of HHT.

No one with HHT has all of the signs and symptoms listed below. One of the characteristics of HHT is its extreme variability even within a family. A parent may have horrible nosebleeds, but no AVM in an internal organ. Yet, their child may have a nosebleed only rarely but AVMs in one or more internal organs. We also cannot predict how likely someone is to have one of the hidden, internal AVMs based on how many nosebleeds or skin telangiectases they have.

Telangiectases in the **nose**, along with the nosebleeds they cause, are the most common sign of HHT. About **95%** of people with HHT have recurring nosebleeds by the time they reach middle age. The average age at which nosebleeds begin is 12, but they can begin as early as infancy,



Although there is not yet a way to prevent the telangiectases or AVMs from occurring, most can be treated once they occur.

or as late as adulthood. The nosebleeds can be as infrequent as a couple a year or can occur daily. When a nosebleed occurs it can last only seconds or, occasionally, hours. The amount of blood lost may be one or two drops, or enough to require a blood transfusion.

Telangiectases in the **skin** of the hands, face and mouth are also found in about **95%** of all people with HHT. These often do not become apparent until the 30s or 40s, however. They appear as small red to purplish spots or distinct areas of delicate, lacy red vessels. In some individuals with HHT they become quite prominent by late adulthood; in others they are more subtle. These telangiectases on the skin and in the mouth can bleed also, but they are less likely to than those in the nose. Both telangiectases of the skin and nosebleeds have a tendency to become more numerous with increasing age.

About **25%** of those with HHT will develop **GI bleeding**. Again, it can range from mild to severe. Telangiectasies can be found anywhere in the gastrointestinal system, including the esophagus (swallowing tube), the stomach, the small intestines, and the colon (large intestines), but most commonly, the stomach and the beginning of the small intestines are involved. They look similar to telangiectases on the skin. Telangiectases in the GI tract do not cause pain or discomfort. Symptoms of GI bleeding are black or bloody stools and/or anemia. Anemia (low blood count) in turn can cause fatigue, shortness of breath, chest pain or lightheaded feelings.

Approximately **30%** of people with HHT have one or more AVMs in the **lungs** (pulmonary AVM or PAVM). AVMs in the lung have a risk to rupture, particularly during pregnancy in women when blood pressure and blood volume tend to increase. This can be life threatening. However, there are addi-

tional concerns about untreated lung AVMs. The capillaries between an artery and vein in the lung have functions in addition to slowing down the blood in an artery before it enters the vein. These capillaries also act as a filter for impurities (clots, bacteria, air bubbles) in the blood before the blood circulates to the brain. Someone with a lung AVM above a certain size is thus at significant risk for stroke (what happens when a clot goes to the brain) or brain abscess (a brain infection that can result from bacteria getting to the brain). Stroke and brain abscess can be life threatening or disabling. Fortunately, lung AVMs are usually easily treatable.

Brain AVMs are found in about **15%** of people with HHT and can also be successfully treated in most cases. They can be life threatening or disabling if they bleed. Since they often do not cause warning symptoms prior to bleeding, we recommend screening for them in all people with HHT.

Spinal AVMs are more rare and can also be removed. They can cause pain in the back over the spine, or loss of feeling or function in an arm or leg.

Liver AVMs can also occur, but their frequency in HHT is not well known. They are unlikely to rupture, and most are not currently treated. Large AVMs in the liver sometimes cause heart and liver failure, usually later in life. Heart failure can occur if the heart has been overworked for years, pumping extra blood through the low resistance pathway of an AVM (in this context an AVM is sometimes called a Shunt), as well as through all the normal vessels of the body.

What Causes HHT?

An abnormal gene on either chromosome 9 or 12 causes HHT. The gene on chromosome

9 is called endoglin and the gene on chromosome 12 is called activin-like kinase 1 (ALK-1). Any particular individual or family will have only one of these two abnormal genes. Normally, these genes tell the body to produce a substance that is involved in the formation of blood vessels. Because of an abnormality in one of these genes, individuals with HHT make less of one of these substances. This in turn can interfere with normal formation of a blood vessel.

The abnormal gene is usually inherited from one parent who has HHT. HHT is a “dominant” disorder, meaning it only takes one abnormal copy of the gene, from only one parent, to cause the disorder. Each child of a parent with an HHT gene has a 50% chance of inheriting this abnormal gene. If a given child does not inherit the HHT gene from his or her parent, he/she has no chance to pass the HHT gene to their children or grandchildren. The gene does not skip generations! However, sometimes it can appear that it has skipped, because it is possible for an individual with the HHT gene to either have symptoms that are either so mild that they have not been recognized, or have been recognized but simply not been attributed to HHT. Very rarely in HHT, a genetic accident (new mutation) occurs in a sperm or egg cell of an unaffected parent and causes HHT in the child. But in most cases, the abnormal HHT gene has been in the family for generations.

Can HHT be Treated?

Yes. Although there is not yet a way to prevent the telangiectases or AVMs from occurring, most can be treated once they occur. They should be treated if they are either causing a significant problem (as in the case of frequent nosebleeds) or if they have a high risk to cause a problem (such as a stroke from a lung AVM). The current recommended treat-

ment for a telangiectasia or AVM depends on both its size and location in the body.

Bleeding from telangiectases in the nose sometimes responds satisfactorily to some everyday practical treatments implemented at home. Humidification of the air and lubrication of the lining of the nose help keep the mucous membrane of the nose moist and can reduce nosebleeds. If everyday, home treatments do not result in a satisfactory reduction in nosebleeds, the first treatment that should usually be considered is **laser therapy**. Laser coagulation therapy is preferable to electric and chemical cautery primarily because, if done carefully by someone with expertise, it has much less risk to damage the inside of the nose. Most patients who undergo laser therapy see significant improvement for a period of time, but it often needs to be repeated.

Septal dermoplasty is another treatment option for nosebleeds, but is usually only considered when laser therapy has repeatedly failed to help. Septal dermoplasty replaces the thin lining of the nose (called the mucous membrane) with a thicker graft of skin. When performed by an ENT (Ears, Nose, and Throat) physician knowledgeable and experienced with the Saunderson's method, it can significantly reduce the frequency and severity of nosebleeds. It is a more drastic treatment than laser in that it permanently removes the natural lining of the nose and replaces it with skin. Daily care and attention to the nose is required after septal dermoplasty to keep the nose moist and clean. Some studies or small series have shown hormonal therapy to be helpful in some patients for whom the local therapies (i.e. home moisturizing care and laser therapy) have not been successful.

Embolization (blocking off an artery) can be used to halt severe nosebleeds that have been unresponsive to other treatments, but is usually only effective for 6-8 weeks. Other arteries enlarge and cause recurrence. This therapy for the nose should thus be used only on an emergency basis and then only as a temporary measure.

Telangiectases of the **skin** can also be treated with laser therapy if they bleed to an extent that is bothersome or are a cosmetic concern. Lesions of the skin are usually best treated by a dermatologist who has expertise in the use of lasers.

What is the Impact of HHT on Pregnancy?

You are probably aware that HHT affects members of your family in different ways, even though everyone with HHT in any one particular family will have the same basic genetic defect. This suggests that factors in addition to the mutated gene contribute to how HHT develops in any one individual.

Female hormones are known to affect the way in which abnormal HHT vessels bleed. In some women, nosebleeds vary through the menstrual cycle and menopause. More recently, we have also realized that being female influences whether abnormal HHT vessels will develop or grow in the lungs. HHT affects the same number of women as men, but on average, of 100 individuals with pulmonary arteriovenous malformations (PAVMs) due to HHT, 62 will be women and only 38 will be men. Although it is not clear why women are more prone to PAVMs, one reason may be the process of pregnancy, and it is important for you, your family and your doctors to be aware of information that is now available from studies on a large series of UK families (161 pregnancies), and other sources.

The majority of pregnancies are safe for the mother with HHT and for the baby.

The Mother: Most pregnancies result in no serious HHT-related complications for the mother. New skin telangiectases may be detected, but some women actually report an improvement in nosebleeds, for example. However, serious complications have occurred in mothers who had involvement of the blood vessels in their lungs. In our reported series of 161 pregnancies, most of the complications occurred in the 23 pregnancies in women with PAVMs. Two pregnancies were complicated by life-threatening bleeding from untreated PAVMs in the mother (a risk highlighted in another report from the Yale group). In six more pregnancies, PAVMs developed or enlarged during pregnancy, sometimes revealed by a sudden drop in the mother's blood oxygen level after the birth of the baby. Three further pregnancies were complicated by strokes related to the presence of a PAVM.

The eleven women who had these pregnancy-related complications belong to eight different HHT families. There appears to be nothing special about these families as in all except one other female members with HHT have had successful, uncomplicated pregnancies. In four of these families, the genetic mutation is in the endoglin gene on chromosome 9 (all four mutations were different); the gene mutated in the other four families is not yet known.

The Baby: Two published reports have now shown that the miscarriage rate is comparable in HHT and non-HHT pregnancies. Obviously, one-half of the babies born to an HHT mother (or father) may go on to develop HHT, but there is no evidence for additional abnormalities developing more commonly than in non-HHT pregnancies. It is important to realize that even if PAVMs have caused a very low blood oxygen level in the mother, the baby can still develop at a normal rate, although premature births were common amongst the women in our series with the lowest oxygen levels.

Why Does Pregnancy Cause These Changes in PAVMs?

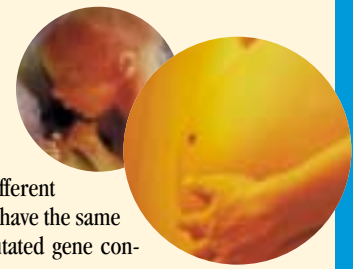
The reason for changes in PAVMs during pregnancy appears to be related to the 60% increase in circulating blood during pregnancy, which is normal and essential for the development of the baby. This means fragile blood vessels (including PAVMs) are more prone to burst. In addition, the body copes with this extra blood by making many of the mother's blood vessels dilate, and these do not always return to their pre-pregnancy size. In women with HHT, this process may provoke the enlargement of previously undetectable PAVMs. It is not known if these PAVMs would have gone on to enlarge later in life, in the absence of pregnancy.

I have HHT and Plan To Have Children. What Should I Do?

The first message is "DON'T PANIC!" Women with HHT have been having children for centuries, and most have entirely normal pregnancies. The important step is to check if you have PAVMs, if possible before pregnancy. You and your doctor should check with the HHT Foundation or the HHT Center/Clinic closest to you to determine exactly how your lungs should be "screened" for PAVM. PAVMs do tend to run in families, so this screening is particularly important if someone else in your family has PAVMs. However, there is always the first case in a family (about 5% of the Hammersmith PAVM cases were women of child-bearing age or less who had no definite family history of PAVMs), so at the moment, we recommend PAVM screening for everyone with HHT. During pregnancy, if there is any bleeding from the lungs (coughing up blood), you need urgent review by doctors who can diagnose and treat PAVMs. Embolization is possible even in the later stages of pregnancy.

REFERENCES:

- Shovlin CL, Winstock AR, Peters AM, Jackson JE and Hughes JMB (1995) *Medical Complications of pregnancy in HHT*. *Quart J Med* 88, 879-887.
Ferenc BA, Shannon TM, White RI, Zawin M, and Burdge CM, (1994). *Life threatening pulmonary hemorrhage with PAVMs and HHT*. *Chest* 106, 1387-1392.
Shovlin CL, Letarte M. "Hereditary Haemorrhagic Telangiectasia and Pulmonary Arteriovenous Malformations: Issues in Clinical Management and Review of Pathogenic Mechanisms" *THORAX*, August 1999, Vol 54, No. 8, pp 714-729.
Gershon AS, Faughnan ME, Chon KS, Pugash RA, Clark JA, Bohan MJ, Henderson KJ, Hyland RH, White RI Jr. *Transcatheter embolotherapy of maternal pulmonary arteriovenous malformations during pregnancy*. *Chest* 2001 Feb; 119(2): 470-7.





Treatment for Symptomatic Liver Involvement in HHT

Symptomatic liver involvement in HHT is rarer than lung or brain involvement, but does occur. If anyone in your HHT family has been diagnosed with liver disease, they should seek a second opinion at an HHT Treatment Center. **It is vitally important that the following procedures SHOULD NOT BE DONE without seeking such a second opinion:**

- LIVER EMBOLIZATION (blocking the hepatic artery with particles);
- LIVER BIOPSY (sampling the liver tissue with small needle and pathology);
- ERCP (endoscopic retrograde cholangiopancreatography—which is passing a tube through the mouth into stomach, duodenum, and biliary ducts).

Invasive study or treatment of the rare patient with symptomatic liver disease due to HHT can make a patient much worse.

Similarly, screening for liver disease as is done for lung and brain involvement is not recommended at this time. To our knowledge, no sudden events leading to serious disability, such as are known to occur with lung and brain involvement and HHT, occur with liver involvement from HHT.

Bleeding from the **stomach or intestines** is generally treated only if it causes anemia (low blood count). Iron replacement therapy is the first line of defense. Iron is usually given orally, but can be given intravenously (IV) if oral iron is not adequate. If iron therapy does not control the anemia, transfusion and endoscopic treatments using a heater probe, bipolar or laser are options. Hormonal treatment has also been helpful in some people.

Lung and brain AVMs should be treated **before** they cause symptoms or problems in most cases. This is why testing or screening for them is recommended in all individuals with HHT, regardless of their specific symptoms. **Lung AVMs** can almost always be treated completely and permanently using an outpatient procedure called embolization. An Interventional Radiologist inserts a small tube (catheter) in a large vein in the groin. The tube is then passed through the blood vessels system to the AVM in the lung. A balloon or coil is placed in the artery leading to the malformation to permanently remove it from the lung's circulation. The procedure usually takes 1-2 hours and requires only a few hours of recuperation. **Brain AVMs** are treated in different ways depending on the size, structure and location in the brain of the abnormal blood vessel. Surgery, embolization and stereotactic radiosurgery can all be used, separately or in combination, to successfully treat brain AVMs.

Liver AVMs are currently treated only if a patient shows signs of liver or heart failure as a result of their liver AVM. Embolization, so successful for the treatment of pulmonary AVMs, has led to severe complications when performed in the liver. Decisions regarding treatment of liver AVM are made on a case by case basis and should be managed by a physician very familiar with the liver manifestations of HHT.

Recommended Screening for Manifestations of HHT

There are several tests that everyone who is known or suspected to have HHT should have. Since lung and brain AVMs can cause serious damage without warning, and they can be treated, testing is strongly suggested for these malformations. This is referred to as screening, meaning the abnormality is looked for prior to its causing a problem.

To screen for **brain AVMs** an MRI with and without gadolinium is recommended. It is currently thought that this only needs to be done once early in life. If no AVM is detected it does not need to be repeated and it is considered that the individual will not need to worry about complications from a brain AVM in their lifetime.

Screening for **lung AVMs** is dependent on the age of the individual, and to a lesser degree, their symptoms. A contrast echocardiogram (echo bubble) is usually recommended to screen for lung AVM in adults. It is a very sensitive test (meaning it will miss very few lung AVM), but everyone with a “positive” or “abnormal” echo bubble test does not have a lung AVM large enough to require treatment by embolization. To determine who requires treatment by an embolization procedure, a chest CT scan, with no contrast and 5 mm cuts, is usually done to follow-up on abnormal echo bubble tests. Lung AVMs larger than a certain size require embolization. For smaller ones only prophylactic antibiotic with dental work and other non-sterile invasive procedures are recommended. If a pregnant woman has not had recent evaluation for lung AVM, it is imperative as soon as pregnancy is recognized. Preferably, individuals with HHT will have had screening for lung AVMs by the time of their early teens.

Lung and brain AVMs are the only problems associated with HHT for which we recommend pre-symptomatic, preventive screening. Most insurance companies will pay for the recommended screening tests if a brief explanation of the association between HHT and AVMs in these internal organs is provided. *Until lung AVMs are excluded by this testing, a person known or suspected to have HHT should follow the American Heart Association guidelines (see your dentist) for taking antibiotics before all dental cleaning or work.* This is to prevent brain abscess, which occurs when bacteria in the mouth enter the bloodstream during dental work or cleaning.

Other than in the brain and lungs, HHT can be treated only as the symptoms warrant. With this in mind, a yearly evaluation by a physician familiar with the wide spectrum of symptoms associated with HHT is recommended, along with an annual check of hematocrit/hemoglobin.



Based on the fact that some children did have complications from PAVMs, we currently advocate screening for all children of a parent with HHT.

Should your Child be Screened for Lung AVM?

During the last twenty years, we have learned a great deal about pulmonary (lung) arteriovenous malformations (PAVMs) in adults. We know that they frequently cause neurological complications, such as stroke or brain abscess. Dr. Robert I. White, Jr. of the Yale University School of Medicine has shown that treatment of PAVMs is safe and effective. For this reason, we now recommend screening for PAVMs in all adults, so that they can be treated and the neurological complications prevented.

However, it is less clear what constitutes appropriate screening and treatment of PAVMs in children. Until recently, only single cases had been reported in the medical literature. Most of the children reported to have PAVMs in the medical literature did not undergo any form of therapy or underwent surgical removal of the PAVM. For this reason, we reviewed the information on the 28 children who have been diagnosed with PAVMs at the Yale Vascular Malformation Clinic and at the Canadian HHT Center in Toronto since 1997. As of 2002, we have treated 40 children with PAVMs, but follow-up is incomplete at this writing.

From reviewing these children's cases, we noticed several things. First, the children were diagnosed at a variety of ages. Second, neurological complications occurred in very few children. The ones that did have neurological complications had very low oxygen levels in

the blood. Most of the other children felt short of breath when exercising. Twenty-six of these children were treated with embolization, just as adults currently are. Embolization is a little more complicated in children, since many need general anesthesia. Despite this, children had no more complications from embolization than adults do. They tolerated the embolization very well.

However, approximately a third of the children needed re-embolization of some of their PAVMs. When blood flow returns through a PAVM after it has been embolized, this is called re-perfusion. Children seem to have more re-perfusion after embolization than adults. This may be due to the fact that they are growing and thus their blood vessels are growing too. This means that children need to be followed closely after embolization, to make sure that their PAVMs, in fact, remain blocked.

So what should we do about Screening Children?

Based on the fact that some children did have complications from PAVMs, we currently advocate screening for all children of a parent with HHT. If a child is complaining of shortness of breath when exercising, or is having a hard time keeping up in sports, they should have definitive testing for PAVM by echo bubble. If the echo bubble is abnormal, then the child should be evaluated in one of the HHT Centers. If a child is not experiencing shortness of breath, then....?

Dental Care and HHT



Since the most common route for entry of bacteria into the blood stream is from the gingivae (gums), it is very important to inform your dentist that you have HHT before any dental work including **dental cleaning**. If pulmonary arteriovenous malformations are present, the bacteria once in the bloodstream can pass through them and may lodge in the brain and cause a **brain abscess**. A brain abscess is an extremely serious medical emergency and could be life threatening. If you have HHT and have not been specifically screened for lung AVMs, to prevent a brain abscess **antibiotics must be taken prior to any dental procedure**. It is *essential* that patients with HHT receive antibiotics using the American Heart Association Guidelines before dental cleaning or dental work of any kind.

You should also discuss with your dentist and dental hygienist any home care procedure or device that has been recommended, such as oral irrigation or any procedure that could introduce bacteria into the bloodstream.

After you have been to an HHT Center and confirmed you do not have lung AVMs, you will not require antibiotics. If you do have lung AVMs, even if they have been treated, you will always need to take antibiotics before dental work. If you have not been screened for lung AVMs, simply take your dentist's choice of antibiotics 1 hour before dental work.

Also, there are medications that should not be routinely prescribed for HHT patients. Dental professionals should be aware of these. Any anti-inflammatory agent such as Advil, Motrin, Naprosyn, Aleve, and Aspirin should generally not be taken by individuals with HHT because these medications can increase bleeding. Many times these medications are prescribed following dental procedures.

We recommend that your dentist work with your physician if your dentist is unfamiliar with HHT. If your primary physician is not familiar with HHT, you must provide for his/her education. Give them the HHT Foundation number or website address as a first step. Together, they can ensure that you receive the care you need.

Consult with your dentist about the AMERICAN HEART ASSOCIATION recommended standard prophylactic regimen for dental, oral, or upper respiratory tract procedures in all adult patients who are at risk.

REFERENCES:

- Guttmacher AE, Marchuk DA, White RI: "Current Concepts: Hereditary Hemorrhagic Telangiectasia" the New England Journal of Medicine, Volume 333, Number 14, pp. 918-924. October 3, 1995.
- Showlin CL, Letarte M: "Hereditary Haemorrhagic Telangiectasia and Pulmonary Arteriovenous Malformations: Issues in Clinical Management and Review of Pathogenic Mechanisms". THORAX, Vol 54, No. 8, pp 714-729, August 1999.
- Christensen GJ: "Nosebleeds May Mean Something Much More Serious: An Introduction to HHT", Journal of the American Dental Association, Vol. 129, May 1998, pp 635-637



HHT FOUNDATION INTERNATIONAL, INC.

(Osler-Weber-Rendu Syndrome)

Centers of Excellence for the Treatment of HHT

YALE UNIVERSITY SCHOOL OF MEDICINE

Department of Diagnostic Radiology
P.O. Box 208042
333 Cedar St., Room 5039 LMP
New Haven, CT 06520
USA

Contact: *Cinda for Kate Henderson &
Dr. Robert White*
203-737-5395
<http://www.hhtavm.org>

UNIVERSITY OF UTAH MEDICAL CENTER

50 North Medical Dr.
HHT Clinic/1A71 SOM
Salt Lake City, UT 84132
USA

Contact: *Jamie McDonald &
Dr. Frank Miller*
866-292-4448
www.uuhsc.utah.edu/rad/hht/html

OREGON HEALTH & SCIENCE UNIVERSITY

Pulmonary & Critical Care Medicine
3181 S.W. Sam Jackson Park Rd.,
UHN-67
Portland, OR 97239
USA

Contact: *Dr. Mark Chesnutt*
TEL: 888-222-6478 ext 7644
or 503-494-7644
<http://www.ohsu.edu/hht>

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

660 South Euclid Ave.
St. Louis, MO 63110-1093
USA

Contact: *Chris Fubler,
Dr. Daniel Goodenberger &
Dr. Andy White* (Pediatrics)
314-362-8065
<http://hht.im.wustl.edu>

UNIVERSITY OF CALIFORNIA at SAN DIEGO

UCSD Medical Center
200 West Arbor Dr. 8756
San Diego, CA 92103
USA

Contact: *Julie Fisher, Eric Rosenthal
& Dr. Frank Miller*
888-770-0296
www.medicine.ucsd.edu/radiology
www.ucsd.vascularomain.com

UNIVERSITY OF PENNSYLVANIA

Division of Medical Genetics,
538 Maloney
3400 Spruce St.
Philadelphia, PA 19104-4283
USA

Contact: *Olga for Lisa Kessler &
Dr. Reed Pyeritz*
215-662-4740
www.uphs.upenn.edu/penngen

MAYO CLINIC HHT CENTER

Division of Pulmonary &
Critical Care Medicine
200 First Street S.W.
Rochester, MN 55905
USA

Contact: *Dr. Karen Swanson &
Dr. Michael J. Krowka*
507-266-0416
www.mayo.edu

MEDICAL COLLEGE OF GEORGIA HHT CENTER

Division of Pulmonary Medicine
1120 15th St. BBR 5513
Augusta, GA 30912-3135
USA

Contact: *Jody Kenny*
706-721-0470

TORONTO HHT NETWORK

St. Michael's Hospital
30 Bond St., Office 2 Bond,
Room 027
Toronto, ON M5B 1W8
CANADA

Adult HHT & Pulmonary AVM Center
Contact: *Dr. Marie Faughnan*
416-864-5516

HHT Genetics Team
Contact: *Ms. Shelley Kennedy*,
Genetics Counselor
416-813-6389
www.hhttoronto.com

HHT ENGLAND

Hammersmith Hospital
London, England

Contact: 44-208-383-3269

You can also contact the
Telangiectasia Self-Help Group
(TSHG) at www.telangiectasia.co.uk

NATIONAL HHT CENTRE IRELAND

Mercy University Hospital
Grenville Place
Cork, IRELAND

Contact: *Margaret Murphy &
Dr. Adrian Brady*
353-21-2305040
Margaret@hht.ie

HHT GERMANY

Univ. HNO-Klinik
D-66421 Homburg
Saar, 49 GERMANY

Contact: *Dr. Urban W. Geisthoff*
TEL: 49-0-6841-162-2900
FAX: 49-0-6841-162-2997
EMAIL:
hnougei@uniklinik-saarland.de
or
Urban.Geisthoff@uniklinik-saarland.de

You can also contact Morbus-Osler-Selbsthilfe e. V. (the HHT Self-Help Group for German-speaking countries) at www.mobus-osler.de

HHT THE NETHERLANDS

St. Antonius Ziekenhuis
Koekoekslaan 1
3435 CM Nieuwegein,
THE NETHERLANDS

Contact: *Dr. Hans Jurgen Mager*
31-30-609-9111

HHT DENMARK

Svendborg Hospital
Svendborg, DENMARK

Contact: *Dr. Anette Kjeldsen*
045-6320-2120 or 045-6320-2127

HHT ITALY

University of Bari
Dipartimento di Medicina Interna e
Medicina Pubblica
Universita Policlinico
Piazza G. Cesare, Bari 70124 ITALY

Contact: *Professor Carlo Sabba, M.D.*
TEL/FAX: 39-080-5478708

Gastroenterologia ed Endoscopia
Digestiva
Ospedale Maggiori
Via Maccaie 1
Crema, 26103 ITALY

Genetica Medica
Universita di Pavia
Via Forlanini 14
Pavia, 27100 ITALY

HHT Clinical Team
Dr. Elisabetta Buscarini
TEL: 0039-0373-280422/280726
(secretary)
FAX: 0039-0373-280654
ebuscarini@rim.it

HHT Genetics Team
Contact: *Professor Cesare Danesino*
TEL: 0039-0382-507737
FAX: 0039-0382-525030
cidi@unipv.it

HHT CENTER JAPAN

Akita University School of
Health Services
Department of Physical Therapy
1-1-1 Hondo, Akita, 010-8543 JAPAN

Contact: *Dr. Takanobu Shioiwa*
81-18-884-6110 or 81-18-884-6531

HHT CENTER SPAIN

Hospital Sierrallana
(Servicio Cantabro de Salud)
Servicio de Medicina Interna
Barrio Ganzo s/n
39300 Torrelavega (Cantabria)
SPAIN

Contact: *Dr. Roberto Zarrabeitia
Dr. Perez del Molino*
TEL: 942-847400
FAX: 942-847501



IS THERE A DIAGNOSTIC TEST FOR HHT?



Genetic testing for HHT became available in late 2003. It is very complex family (as opposed to individual) based testing that should be explained and ordered by an HHT Center or genetics professional (a Medical Geneticist or a Genetic Counselor). There are no more than one or two genetics laboratories in any one country which perform HHT testing.

The first step for a particular family interested in genetic testing for HHT is to schedule an appointment with an HHT Center or genetics professional. At this appointment the family history of HHT will be confirmed, a multi-generation pedigree (family history) will be constructed, and the genetic testing process, possible results and their significance will be explained. “False negative”, “false positive”, and uncertain test results are all possible. A detailed “Consent Form” specific to HHT testing is signed by both the patient and the medical professional who provides this genetic counseling.



Next, an initial blood sample is drawn from a family member who has been determined with certainty to have HHT (based on published diagnostic criteria) and is sent to an appropriate genetics laboratory. An HHT Center or genetics professional has the expertise to decide which family member should be tested first.

Additional family members should only be tested if and when a clear cut HHT causing genetic alteration (mutation) is first detected in this clearly clinically affected family member. If additional family members then desire testing, the HHT Center or genetics professional can advise the family regarding the recommended order and process for testing.

What Research is Being Done on HHT?

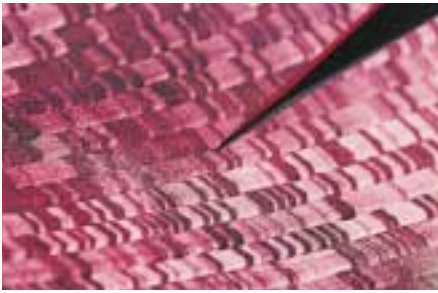
In the mid-1990s scientists discovered which two genes are responsible for most HHT. There may be one or more other genes that can cause HHT, but if so they are quite rare. Currently, scientists are trying to understand better exactly how it is that the abnormal gene can interfere with normal blood vessel formation. Research is also being done that may eventually lead to the ability to truly “cure” genetic disorders by either fixing the abnormal gene or by replacing the substance in the body that the abnormal gene is not producing. In the meantime, physicians at Universities around the world are working to develop better treatments and therapies for the manifestations and symptoms of HHT. Great advancements have been made in the last two decades in the treatment and management of HHT. Advancement in treatment will continue to be made as long as there are symptoms to treat.

How Can I get More Information and Help?

The HHT Foundation International, with its mission of patient/doctor education and support for research, provides multiple sources of information about HHT. A patient/family conference is held each year to which medical and scientific experts on HHT come to talk and participate. A newsletter is published three times yearly which provides ongoing, up-to-date information. Both are benefits of membership. By becoming a member you also support the important future work of this organization committed to the appropriate care and eventual cure for HHT. The HHT Foundation International can also refer you to a clinic/center that specializes in the diagnosis, management and treatment of HHT. There are currently eight in the U.S., one in Canada, and several others around the world.



HHT GENETIC/DNA TESTING



Genetic/DNA Fact Sheet

Clinical genetic testing is now available for families who are affected by HHT. Development of clinical genetic testing for HHT has been a long-standing priority of the HHT Foundation and we are grateful for the efforts of the many people who have made this possible.

Many families affected by HHT are excited about the availability of genetic testing, and they are anxious to have the testing done as soon as possible. We believe that it is important for everyone to have accurate information so that testing is done properly. The information below is meant to answer some of the questions that will be asked about genetic testing for HHT. We hope this material will be useful for individuals and families affected by HHT, and for their health care providers.



The material in this section was prepared by Eric Rosenthal, a genetic counselor with the HHT Center at the University of California San Diego, and Katherine Henderson, a genetic counselor at the HHT Center at Yale University. We are interested in your feedback concerning how useful you found this material and ways in which it can be improved. Please contact us with comments and suggestions at etrosenthal@ucsd.edu or kjh@diagnad.med.yale.edu.

Specific questions about your own genetic testing should be addressed to an HHT Center where you have already been a patient, or expect to be a patient in the future.

What is Genetic Testing for HHT?

HHT is caused by a change (mutations) in one of two different genes—endoglin and ALK-1. The endoglin gene is on chromosome 9 and the ALK-1 gene is on chromosome 12. Some people may have HHT as a result of a mutation in another gene that has not yet been discovered—we will discuss that more below.

Every person has two copies of both the endoglin gene and the ALK-1 gene. One copy is inherited from our father and the other copy from our mother. A person who inherits a damaged copy of either of these genes, from either of their parents, will have inherited HHT. Each child of a person with HHT has a 50:50 (50%) chance of inheriting the condition because there is an equal chance that the affected parent will pass on their normal or their damaged version of the gene. Which version of the gene gets passed on to each child is a random event, like flipping a coin.

Genetic testing for HHT consists of analysis of the endoglin and ALK-1 genes in the laboratory. The goal of this analysis is to find the exact change in the gene that is responsible for HHT in a family. This process begins with carefully analyzing both the endoglin and ALK-1 genes in their entirety. Once a mutation has been found in any family member who has a diagnosis of HHT, other family members can be tested to see if they also have the mutated version of the gene. This will allow us to say for sure which other family members have inherited HHT.

Why is Genetic Testing Useful? If I Already Know That I Have HHT, Why Should I Have Genetic Testing?

If a person already knows that they have HHT, because they meet the clinical diagnostic criteria, genetic testing can confirm the diagnosis. (The clinical diagnostic criteria are listed at the end of this section.) It is possible that as we learn more about the genetics of HHT we might be even be able to predict the kinds of health problems a person is likely to have based on the exact mutation found in the endoglin or ALK-1 gene.



The HHT Foundation strongly encourages individuals and families to arrange genetic testing through health care providers who understand all of the complexities and limitations of genetic testing for HHT.

The other reason why genetic testing is useful for someone who already has been diagnosed with HHT is because it will help other members of their family, especially young children. Young children and young adults with HHT often do not have visible symptoms of HHT, but they are still at risk for complications from lung AVMs and brain AVMs. The diagnosis of HHT can also be difficult to make in adults. In the past, we have recommended certain screening tests for all of the children and many of the relatives of an affected person. This screening is expensive, inconvenient, and uncomfortable, but it has been necessary because there was no way to reliably tell if they had HHT based on the presence of symptoms such as nosebleeds or telangiectases. In families where an endoglin or ALK-1 mutation has already been identified in a family member who clearly has HHT, testing other family members for this known mutation will allow us to identify which children and other family members really need these screening tests.

How Is Genetic Testing Done?

Genetic testing is done on a blood sample. A few teaspoons of blood are collected and shipped to one of the laboratories performing genetic testing for HHT. All of the laboratories require that the person being tested sign a consent form indicating that they understand the purpose of the test, the risks and benefits of testing, the limitations of the testing, and plans for the disposal or future use of any DNA left over after the testing is complete. Depending on the laboratory, results will be sent to the physician ordering the test within 4 to 8 weeks.

What's The Best Way To Arrange Genetic Testing For Myself And My Family?

The first person to be tested in a family should always be someone who has a clear and definite clinical diagnosis of HHT. Genetic testing for the first person in a family will consist of analyzing both the endoglin and ALK-1 genes in their entirety. This testing will be relatively expensive, because both genes have to be screened carefully to find mistakes. After a mutation is found in one family member, it is easy, and relatively inexpensive, to test other family members to see who else has inherited the mutated version of the gene.

Unfortunately, we know that there will be some HHT families in which the laboratories will not be able to find the responsible gene change in endoglin or ALK-1. If genetic testing is not able to identify a mutation in the endoglin or ALK-1 gene in a family member who clearly has HHT, it will not be useful to test other family members.

The HHT Foundation strongly encourages individuals and families to arrange genetic testing through health care providers who understand all of the complexities and limitations of genetic testing for HHT. This can be done by working with one of the HHT Centers or with a genetics clinic. Contact information for HHT Centers can be found at the HHT Foundation website (www.hht.org). If it is too difficult for you to travel to one of the HHT Centers, you can ask for a referral to a local genetics specialist. Genetics clinics can be found through the website of the National Society of Genetic Counselors (www.nsgc.org).

What Are The Possible Results From Genetic Testing?

As we said earlier, the first person tested from any family will be tested by methods that examine the complete sequence of both the endoglin and ALK-1 genes. There are 3 possible results from this analysis:

- **Positive for a “deleterious”** (disease causing) mutation. This result means that the laboratory found an error in either endoglin or ALK-1, and that the error is one that will definitely prevent the endoglin or ALK-1 gene from working properly. This result means that the laboratory has found the cause of HHT in that person. Other family members can now find out if they have HHT by having testing to see if they share the mutation
- **Negative for any sequence variation.** This result means that the laboratory is not able to find any changes in the endoglin or ALK-1 gene that could explain the person’s diagnosis of HHT. Genetic testing will not be useful for determining which other family members have HHT.
- **Sequence variant of uncertain significance.** The laboratory may find a change in the endoglin or ALK-1 gene for which it is not possible to predict whether or not it causes HHT. These kinds of gene variations are found in all genes and they may be common in the endoglin and ALK-1 genes. In most cases, a sequence variant of uncertain significance will not be useful for making decisions about which family members need screening.

For a person being tested to see if they have inherited a mutation already identified in another family member, there are 2 possible test results:

- **Positive for the family mutation.** This person has inherited the gene change known to cause HHT in their family. This person has HHT.
- **Negative for the family mutation.** This person has not inherited the gene change known to cause HHT in their family. This person almost certainly does not have HHT. The only exception is when there is reason to believe that there has been intermarriage between 2 different families that are both affected by HHT.

How Could Genetic Testing Fail To Find The Mutation That Causes HHT In Someone Who Clearly Has The Condition?

As we mentioned earlier, there will be cases where genetic testing will fail to identify a mutation in either the endoglin or ALK-1 gene. There are a few possible explanations why this could occur:

- The person who was tested does not really have HHT. Some people who have symptoms of HHT may have a different disease. Physicians who are not familiar with HHT may order testing for patients who do not actually have the condition. This is one reason why the HHT Foundation believes it is best if genetic testing is done only after someone has been evaluated by a physician who is experienced with HHT.
- The person has HHT as a result of a mutation in endoglin or ALK-1 that cannot be detected by the laboratory. For most genetic conditions for which testing is already available, there are mutations that cannot be detected. How often this occurs depends on the exact techniques used by the laboratories conducting the testing. Scientists often disagree on which methods are best, and cost is often a factor. One thing is certain—no method is guaranteed to find all possible mutations that can affect the function of a gene.

- The person has HHT because of a mutation in a gene other than endoglin or ALK-1. Endoglin and ALK-1 are probably responsible for most cases of HHT, but it is likely that there are other genes that have not yet been found. Researchers will certainly be very interested in working with families that have many individuals diagnosed with HHT, but where no mutation has been found.

We know from past experience with other genetic conditions that the success rate for finding mutations in clinical testing can be anywhere from 30% to 95%. At this time, it is very hard to predict how often genetic testing will be successful in finding mutations in people with HHT. The HHT Foundation believes it is very important to keep track of the results from clinical testing, and we are encouraging the laboratories offering testing to gather and share this information (without revealing any details about individual patients). The HHT Foundation also hopes that the various research groups working on the genetics of HHT will be interested in additional testing and research with families where mutations are not found in endoglin or ALK-1.

If A Physician Is Not Sure Whether Or Not A Patient Has HHT, Can They Use Genetic Testing To Decide?

Only if a mutation in endoglin or ALK-1 has already been found in one of the person's relatives. As discussed above, there are people who have HHT who will not have a detectable mutation in either the endoglin or ALK-1 gene. No one knows for sure how often this will happen until we have more experience with clinical genetic testing for this condition. This means that genetic testing will not be a reliable way to determine whether or not someone has HHT unless we have already found the responsible genetic change in another family member.

There will be cases where a person has some signs of HHT, but their physician is not able

to give them the diagnosis for certain. In cases like this, a positive test might allow us to say for sure that someone does have the condition, but a negative test will not rule it out.

What Happens If My Family Is One Of Those Where It Is Not Possible To Find A Mutation In The ENDOGLIN Or ALK-1 Gene?

Children and others from families without detectable mutations will still have to be screened for lung and brain AVM's, because we will not be able to use genetic testing to tell whether or not they have HHT.

It is possible that researchers will be interested in working with those families in which it is not possible to find a mutation in endoglin or ALK-1. This could be done using additional methods to find gene mutations or by trying to find new HHT genes. The HHT Foundation and the network of HHT Centers of Excellence will try to help interested families identify opportunities for research participation.

How Much Will Genetic Testing Cost And Will My Health Insurance Pay For Genetic Testing For HHT?

The cost of testing will vary between laboratories. Testing the first person from a family with comprehensive analysis of both ALK-1 and endoglin is likely to be somewhat expensive. Once a mutation has been identified in a family member who has HHT, testing for other family members will probably cost a few hundred dollars per person.

Insurance coverage of genetic testing will depend on the insurance company and individual circumstances. You will have to contact your insurance provider to ask if the cost of genetic testing is covered and to find out how to obtain necessary authorizations. HHT centers and genetics clinics may be able to help with these pre-authorizations, because they have genetic counselors and physicians who have experience with the insurance issues involved in genetic testing.

Diagnostic Criteria For HHT

The established diagnostic criteria for HHT are:

- Nosebleeds (epistaxis), which are spontaneous and recurrent (may be mild or severe)
- Telangiectases on the skin or mucous membranes (mucocutaneous). Telangiectases are small red spots that blanch under pressure, located at characteristic sites, including the lips, oral cavity, fingers, and nose.
- Visceral arteriovenous malformations (AVMs), consisting of direct connections between arteries and veins. They may be located in the lungs, brain, liver, spinal cord, or GI tract.

- A first-degree relative (brother, sister, parent or child) with HHT, based on these diagnostic criteria.

A diagnosis of HHT is considered definite when 3 or more of these features are present, *possible* or *suspected* when 2 findings are present, and unlikely with fewer than 2 findings.



LABORATORIES OFFERING HHT GENETIC TESTING IN NORTH AMERICA

A physician or genetic counselor must order all laboratory tests. The laboratories have requested that each patient contact their HHT Center Physician, Medical Geneticist or Genetic Counselor.

University of Pennsylvania: Genetic Diagnostic Laboratory

Department of Genetics
415 Curie Blvd.
Philadelphia, PA. 19104-6145

Contact: *Ms. Lynn Godmilow, MSW, Certified Genetic Counselor*

<http://www.med.upenn.edu/genetics/core-facs/gdl>

Testing Available From: November 3, 2003

ARUP Laboratories

500 Chipeta Way
Salt Lake City, UT 84108-1221

Contact: *Ms. Jamie McDonald, Certified Genetic Counselor*

<http://www.aruplab.com>

Testing Available From: January 20, 2004

HHT Solutions

Toronto Western Hospital
399 Bathurst Street
Ste. EW6-520
Toronto, Ontario M5T 2S8
CANADA

Contact: *Jeanne McKay*

<http://www.hhtsolutions.org>

Testing Available From: November 3, 2003

RESOURCES

HHT Foundation International, Inc.

P.O.Box 329
Monkton, MD 21111
Phone: (800) 448-6389 or (410) 357-9932
Fax: (410) 357-9931
Email: hhtinfo@hht.org
Website: <http://www.hht.org>

National Society of Genetic Counselors (NSGC)

233 Canterbury Drive
Wallingford, PA 19086-6617
Phone: (610) 872-7608
Fax: (610) 872-1192
Email: nsgc@aol.com
Website: <http://www.nsgc.org>

To find a genetic counselor in your local area, use the "Find a Counselor" link

GENEReviews

<http://www.genetests.org/>

To find information on HHT, follow the links to GENEReviews and search for HHT. This site also has useful general information about genetics and genetic testing if you follow the link to "Educational Materials".

OMIM

<http://www.ncbi.nlm.nih.gov/entrez/dispmim.cgi?id=187300>

OMIM provides fairly technical descriptions of genetic conditions. This material is appropriate for health professionals.

Genetic Alliance Resources:

http://www.geneticalliance.org/genetics_resources.html

The Genetic Alliance is an umbrella organization for people with genetic conditions. Look here for information about specific conditions and general information about genetics and social issues, such as insurance and employment discrimination. The Genetic Alliance also has excellent information about participation in research.

NHGRI

<http://www.nhgri.nih.gov/>

The National Human Genome Resource Institute is a part of the National Institutes of Health (NIH). NHGRI has educational material about genetics, genetic testing, and issues pertaining to insurance and employment discrimination.



HHT AT A GLANCE FOR HEALTH CARE PROVIDERS



- ▶ Hereditary Hemorrhagic Telangiectasia (AKA Osler-Weber-Rendu) is a multi-system vascular dysplasia.
- ▶ It is uncommon, but not rare. Approximately 1/2 million people worldwide have HHT.
- ▶ Telangiectases and arteriovenous malformations (AVMs) are the characteristic lesions.
- ▶ HHT has extremely variable expression in terms of both location of lesions and severity of symptoms.
- ▶ It is frequently misdiagnosed in affected individuals.
- ▶ The most commonly affected organs are the nose, lungs, GI tract and brain—in that order.
- ▶ HHT is an autosomal dominant genetic disorder.
- ▶ Denovo mutations are rare. A detailed family history shows most cases to be familial.
- ▶ HHT is heterogenic. Defects in two separate genes are known to cause HHT.
- ▶ 90-95% of individuals with HHT will develop epistaxis by adulthood, but severity varies from infrequent and minor to daily and severe.
- ▶ 90-95% develop at least a few telangiectasia on the skin of the face and/or hands by middle age, but they can be pin point size.
- ▶ 20% develop significant gastric or intestinal bleeding, but not usually before the decade of the 50s.
- ▶ 30% have pulmonary arteriovenous malformation (AVM).
- ▶ 10-15% have at least one cerebral AVM.
- ▶ An unknown percentage have hepatic AVM.
- ▶ The severity of epistaxis or telangiectases of the skin does not correlate with the likelihood to have internal (i.e. cerebral or pulmonary) AVMs.
- ▶ Severity and symptomology varies tremendously, even between close relatives.
- ▶ Untreated pulmonary AVMs are a common cause of ischemic stroke and brain abscess in HHT families.
- ▶ Untreated cerebral AVMs are a common cause of hemorrhagic stroke in HHT families.
- ▶ Treatments are available for all manifestations of HHT and have evolved significantly in the last decade.

***For further information,
please contact:***

HHT FOUNDATION
INTERNATIONAL INC.
P.O. BOX 329
MONKTON, MD 21111 U.S.A
U.S.A. Telephone: 1-800-HHT-NETW
1-410-357-9932 (other countries)
In Canada: 604-596-3418
Fax: 1-410-357-9931
Website: <http://www.hht.org>
Email: hhtinfo@hht.org

HHT FOUNDATION KEY PROGRESS MILESTONES

	ORGANIZATIONAL DEVELOPMENT	MEDICAL RESEARCH	GENETIC RESEARCH
2004	<ul style="list-style-type: none"> ▶ 17th HHT CENTER ESTABLISHED IN SPAIN 		
2003	<ul style="list-style-type: none"> ▶ \$1 MILLION RESEARCH FUND RAISED ON THE WAY TO \$10 MILLION RESEARCH ENDOWMENT ▶ \$200,000 GRANT AWARDED BY THE ARGOSY FOUNDATION ▶ MAYO CLINIC HHT CENTER ESTABLISHED ▶ MEDICAL COLLEGE OF GEORGIA HHT CENTER ESTABLISHED 		<ul style="list-style-type: none"> ▶ HHT 2 MOUSE MODEL DEVELOPED ▶ SECURED RELEASE TO PUBLIC DOMAIN OF HHT GENE PATENTS ▶ CLINICAL DNA BLOOD TEST DEVELOPED UNDER BUDGET AHEAD OF SCHEDULE!
2002	<ul style="list-style-type: none"> ▶ CAPITAL RESEARCH FUNDRAISING DRIVE INITIATED ▶ SAN DIEGO HHT CENTER ESTABLISHED ▶ UNIVERSITY OF PENNSYLVANIA HHT CENTER ESTABLISHED 	<ul style="list-style-type: none"> ▶ INCIDENCE OF BRAIN HEMORRHAGE IN CHILDREN PUBLISHED 	
2001	<ul style="list-style-type: none"> ▶ 12 WORLDWIDE HHT TREATMENT CENTERS 		
2000		<ul style="list-style-type: none"> ▶ HHT DIAGNOSTIC CRITERIA PUBLISHED 	
1999	<ul style="list-style-type: none"> ▶ FOUNDATION BOARD STRENGTHENED AND STRATEGIC PLAN DEVELOPED 		<ul style="list-style-type: none"> ▶ HHT 1 MOUSE MODEL DEVELOPED
1998	<ul style="list-style-type: none"> ▶ WASHINGTON UNIVERSITY HHT CENTER ESTABLISHED ▶ OREGON HEALTH & SCIENCE UNIVERSITY HHT CENTER ESTABLISHED 	<ul style="list-style-type: none"> ▶ CAVM BRAIN MRI CRITERIA PUBLISHED 	

HHT FOUNDATION KEY PROGRESS MILESTONES

	ORGANIZATIONAL DEVELOPMENT	MEDICAL RESEARCH	GENETIC RESEARCH
1997		<ul style="list-style-type: none"> ▶ CONSENSUS REACHED FOR HHT DIAGNOSTIC CRITERIA 	
1996	<ul style="list-style-type: none"> ▶ UNIVERSITY OF UTAH HHT CENTER ESTABLISHED ▶ UNIVERSITY OF TORONTO HHT CENTER ESTABLISHED 		<ul style="list-style-type: none"> ▶ ALK-1 GENE (CHROMOSOME 12) IDENTIFIED, HHT 2
1995		<ul style="list-style-type: none"> ▶ HHT REVIEW ARTICLE PUBLISHED — <i>New England Journal of Medicine</i> 	
1994		<ul style="list-style-type: none"> ▶ BRAIN AND LUNG TREATMENT AND OUTCOMES PUBLISHED 	<ul style="list-style-type: none"> ▶ ENDOGLIN GENE (CHROMOSOME 9) IDENTIFIED, HHT 1
1992	<ul style="list-style-type: none"> ▶ SCIENTIFIC AND MEDICAL ADVISORY BOARD FORMED 	<ul style="list-style-type: none"> ▶ BEGAN TO STANDARDIZE DIAGNOSIS AND TREATMENT 	<ul style="list-style-type: none"> ▶ BEGAN SEARCH FOR HHT GENE(S)
1991	<ul style="list-style-type: none"> ▶ FIRST HHT CENTER ESTABLISHED AT YALE UNIVERSITY 		



The HHT Foundation International Needs You!

RESEARCH PRIORITIES

**DNA Clinical
Test**

Blood Vessels

Children

**Nose/GI
Bleeding**

CAVM

Liver AVM

If not us, who?
JOIN US!

Please join us in our efforts to cure HHT.

We invite you to become a member of our Foundation or, if you are already one of our valued members, to renew your membership.

Two Children are Born Each Day with HHT!

We are the only voluntary organization dedicating our time to all affected HHT families to find a cure for this disorder.

We Work Daily On Your Behalf!

It is through your vital support and membership that we have been able to:

- Make the Clinical DNA Test a Reality: Ahead of Schedule and Under Budget
- Provide Support for Hands-On Physician Training in HHT Treatment
- Raise an initial \$1 million for research (in an 18-month time period) as the first step to our \$10 million endowment goal
- Obtain a \$200,000 Grant in 2003 from the Argosy Foundation for Research and Physician Training

Furthermore, your individual contributions make possible our on-going programs such as:

- Family Outreach Support Services and Conferences
- Coordination of Patient Care with the HHT Treatment Centers
- Physician Education on HHT
- The HHT Foundation Website and Newsletters—both of which communicate crucial information on HHT to patients and physicians all over the globe
- HHT Research to Improve Quality of Life and Find a Cure

Program support is enhanced by Foundation and Agency Grants that are awarded ONLY WHEN SOLID MEMBER SUPPORT AND A ROBUST MEMBERSHIP ARE DEMONSTRATED! That is why YOUR membership is so crucial to our continued success.

Please take time to become a member or renew your membership at the highest level of financial support you are able. **(We are a 501(c)(3) non-profit organization and your contribution is entirely tax deductible.)**

HHT Foundation International Membership Form



CAPITAL RESEARCH CAMPAIGN CONTRIBUTION:

CORNERSTONES: \$6 million

FOUNDERS: \$100,000 over Two
Years (Limited to 100)

BENEFACTORS:

Gold: \$50,000-\$99,999

Amount: _____

Silver: \$25,000-\$49,999

Amount: _____

Bronze: \$10,000-\$24,999

Amount: _____

Grand: \$5,000-\$9,999

Amount: _____

Major: \$2,500-\$4,999

Amount: _____

Benefactor: \$1,000-\$2,499

Amount: _____

Sponsor: \$500-\$999

Amount: _____

Patron: \$250-\$499

Amount: _____

Associates: \$100-\$249

Amount: _____

Friends: \$1-\$99

Amount: _____

Please make my above marked
capital research campaign
contribution in honor of / in
memory of (circle one)

I would like to include
the HHT Foundation
International in my
estate planning

Date: _____

Name: _____

Address: _____

City: _____

State: _____ ZIP: _____ Country: _____

Phone: _____ E-mail: _____

Birthdate: _____

How did you find us?

- Internet
 HHT Center at

 Conference
 Relative
 Physician
 Other: _____

MEMBERSHIP:

Check one: NEW MEMBER MEMBERSHIP RENEWAL

Membership Level:

- \$45 – DONOR \$250 – PATRON
 \$50 – FRIEND \$500 – BENEFACTOR
 \$75 – SUPPORTER \$1000 – PRESIDENT'S CLUB
 \$100 – SPONSOR \$5000 – DOCTOR'S CIRCLE (in honor of Dr. _____)
 OTHER: _____

GIFTS and DONATIONS:

- I would like to donate \$ _____ to the HHT Foundation in support of HHT research.
 I would like to make a donation in honor of / in memory of (circle one) _____.
 I would like to sponsor a gift membership for the following:

Recipient: _____

Address: _____

City: _____ State: _____ ZIP: _____ Country: _____

Phone: _____ E-mail: _____

PAYMENT SUMMARY

Membership: \$ _____

General Donation: \$ _____

Gift Membership: \$ _____

Capital Research

Campaign: \$ _____

TOTAL: \$ _____

METHOD OF PAYMENT:

- Check or Money Order (Please make all checks or money orders
payable in **U.S. dollars** to the *HHT Foundation International, Inc.*)
 Credit Card
Check one: VISA Mastercard Amex Discover
 YES! Please charge my credit card annually to renew my membership.

Name as it appears on card: _____

Account Number: _____ Exp. Date: _____

All information is strictly confidential!

Make your tax-deductible membership payment or donation to the
HHT Foundation International, a 501(c)(3) non-profit public corporation.

P.O. Box 329 • Monkton, Maryland 21111 USA • Phone (U.S.): **800-448-6389** or
(International) **410-357-9932** • Fax: **410-357-9931** • Internet: **http://www.hht.org**



HHT FOUNDATION INTERNATIONAL
P.O. Box 329
Monkton, Maryland 21111 USA

First Class
Presort
U.S. Postage
PAID
Permit No. 1608
Baltimore, MD



Hereditary Hemorrhagic Telangiectasia Foundation International *(Osler-Weber-Rendu Syndrome)*

MISSION:

EDUCATION AND SUPPORT — Medical Professionals and Families

RESEARCH — Focus on HHT: Basic and Clinical Research
Collaboration with Worldwide HHT Treatment Centers

ADVOCACY — Medical Privacy Protections
Freedom from Genetic Discrimination