Hereditary hemorrhagic telangiectasia

Genetics, pathogenesis, clinical manifestation and management

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Hereditary hemorrhagic telangiectasia (HHT), Morbus Osler or Osler-Weber-Rendu syndrome (OMIM 187300), is an autosomal dominant disorder characterized by epistaxis, telangiectasia, multi-systemic vascular dysplasia and clinical presentation of wide variation. The pathogenesis involves dilated post-capillary venules or telangiectases in the mucus membrane of various organs as well as larger arteriovenous malformations. Genetic heterogeneity of HHT is confirmed; 2 disease loci, ACVRL1 and ENG genes, have been identified and characterized. The 2 major types of the disease, HHT1 and HHT2, are attributed to mutations in the ENG and ACVRL1 genes. ENG and ACVRL1 genes code for proteins, namely endoglin and activin-receptor-like kinase 1 (ALK-1), which are members of the TGF-beta receptor family, are essential for maintaining vascular integrity. Another gene has been implicated in HHT; the HHT3 locus linked to chromosome 5. In the last 2 decades, the genetics, pathogenesis, clinical manifestations and management of HHT have been extensively researched. At this stage, it is deemed appropriate to review the wealth of information accumulated on the topic. Better understanding of the functions of endoglin, ALK-1, and other proteins involved in the pathogenesis of HHT should facilitate better management of patients with this disorder.

Saudi Med J 2007; Vol. 28 (1):11-21

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Interestingly, Stevenson described his own ailment in a philosophical statement: “All our lives long, we may have been about to break a blood vessel … and that has not prevented us from eating dinner, no, nor from putting money in the Saving Bank” from “The Sinking Ship”.15

**Epidemiology.** Hereditary hemorrhagic telangiectasia shows a wide geographic and ethnic spreading,16 as reflected by reports on patients of African,17 Algerian,18 Asian,19,20 and Arabic origin.21 The prevalence rate shows considerable regional variations with a figure of 1:1331 in the Netherlands Antilles,22 1:2,351 in eastern France,23 1:3,500 in the Danish island Funen,24 1:16,500 in Vermont, USA,25 and 1:39,216 in northern England.9 However, the average prevalence rate in Caucasians is estimated at 1:10,000.8

**The vascular malformation in hereditary hemorrhagic telangiectasia.** The vascular malformations in HHT consist of direct arteriovenous connections through thin-walled aneurysms, and range from small telangiectases to larger visceral arteriovenous malformations (AVM). In HHT, the arteriovenous fistulae are commonly formed in specific visceral organs such as liver, as well as in the lungs, and brain. However, the angioplasia can also happen in other organ system, as in the rare reported cases of renal arteriovenous malformations,26 conjunctival angioplasia,27 retinal angioplasia28 and calvarial, orbital and dural vascular anomalies.29 Weakness of the vessel wall can lead to multiple cerebral arteriovenous malformations,30,31 splenic vascular malformations, and portal hypertension.32 By light- and electron microscopy, Braverman et al33 have elegantly demonstrated that the development of a cutaneous telangiectasia is a progressive process. In the early stage, a focal dilatation develop to involve the whole dermis of a post-capillary venule. The dilatation expands towards an arteriole so that eventually the venule will form a direct arteriovenous fistula without the normal intermediary capillary net. The loss of the capillary-wall causes reduced pressure and flow of blood. In the order of frequency, the sites affected by telangiectasia are the mucocutaneous layers of the nose (prime site), gastrointestinal, pulmonary, cerebral, and urogenital vessels.

**Genetic heterogeneity.** **Genes involved in HHT.** Several studies have confirmed genetic heterogeneity of HHT. The first disease locus,10,34,35 is the endoglin-coding gene on chromosome 9q34.1 (ENG; OMIM 131195). Mutations of the ENG gene are associated with type 1 HHT.36 The second disease locus,37,38 is the activin receptor-like kinase coding gene on chromosome 12q13 (ACVRL1), activin-receptor-like kinase 1 [ALK-1]; OMIM 601284). Mutations of the ACVRL1 gene are associated with type 2 HHT.39 Evidence has recently been presented for existence of a third HHT locus (HHT3) which was mapped to chromosome 5.40 Furthermore, a rare form of HHT exists as an overlap syndrome with a juvenile polyposis disease. This rare form type of the disease was attributed to mutations in MADH4 (SMAD4) gene.41

**Hereditary hemorrhagic telangiectasia-1 is associated with ENG gene.** It has been shown that the first gene locus responsible for HHT (HHT1) was located on the long arm of chromosome 9 (9 q33-q34.1) and was initially called ORW1.10,34,35,42 The respective disease-causing gene was subsequently identified and named as ENG gene.43 Up to May 2006, a total of 218 presumably disease causing mutations and 21 polymorphisms of the ENG gene have been logged in the HHT mutation data base (http://www.macs.hw.ac.uk/hht). The ENG gene extends over 40 kbp and consists of 15 exons; exon 9 has 2 parts 9a and 9b43,44 (Figure 1). The coding segments vary in size from 39 to 258 bp and are interrupted by introns of different lengths (136 to 13267 bp). Endoglin consists of 658 amino acids and is a trans-membrane homo-dimer glycoprotein of 180k Da with disulphide bridges linking its 2 subunits.45 This protein comprises 3 domains; an extracellular, a transmembrane, and a cytoplasmic domain.46 Exons 2-12 of the ENG gene code for the extracellular, exon 13 for the trans-membrane, and exon 14 for the cytoplasmic domain.47,48 The human
endoglin contains an arginine-glycine-aspartate (RGD) tripeptide sequence that serves as a potential binding-site for cell adhesions, receptors and integrines.46 Endoglin is mostly expressed in vascular endothelial cells49 and in placental syncytiotrophoblasts.50,51

**Hereditary hemorrhagic telangiectasia-2 is associated with ACVRL1 gene.** The second locus for HHT could be located on chromosome 12 close to the centromere (12 q11-q14).37,38 This is the activin receptor-like kinase ACVRL1, or ALK1 gene. Mutations in this gene are held responsible for HHT type 2.52 Up to May 2005, 184 presumably disease causing mutations and 14 polymorphisms of the ACVRL1 gene have been logged in the HHT mutation data base (http://www.macs.hw.ac.uk/hht). The ACVRL1 gene extends over 14 kbp; its 10 exons comprise segments ranging from 61 to 276 bp, and are interrupted by introns of 203 bp to 2.8 kbp.39 Currently, the isolated mRNA transcripts of the gene differ in the size of the 5'-untranslated region (5'UTR). The first more frequent transcript starts in exon 2,53 whereas the second transcript is a splice variant that starts in exon 1.54 Exons 2 to 10 of the ACVRL1 gene code for a protein made of 503 amino acids that comprise a membrane receptor domain. Exon 3 and part of 4 code for the extracellular domain of the protein, the rest of exon 4 code for the transmembrane domain, exon 5 codes for the intracellular Gly-Ser domain, and exons 6 to 10 code for the intracellular kinase domain (Figure 2).39 The ALK-1 protein is mostly expressed in endothelial cells and smooth muscle vascular cells, especially in heavily vascularized tissues such as the lungs and the placenta.53,54 Hence, this resembles the expression pattern of endoglin. ACVRL1 mutations are associated with diverse effects, including the vascular dilatation characteristic of HHT and the occlusion of small pulmonary arteries that is typical of primary pulmonary hypertension (Figure 3).

**Hereditary hemorrhagic telangiectasia-3 is linked to a locus mapped to chromosome 5.** Since the known 2 loci were excluded in one family, at least one further locus for HHT had been postulated.55 Linkage analysis in this family, with pulmonary arteriovenous malformations as the prominent manifestation of the disease, provided strong evidence that the presumed HHT3 locus maps to chromosome 5.40

**Genetic heterogeneity underlines disease types.** Depending on the disease-causing gene, there are 2 main types of the disease: HHT1 and HHT2. Hence, genetic heterogeneity underlines a clinical heterogeneity. Even within the same family there could be great variations with respect to manifestation and severity of the disease.44 However, investigations for detection of disease-causing mutations have led to further illumination of the phenotype/genotype relationships of the disease. Presently the following correlations could be observed: 1) A generally milder phenotype is seen in HHT2 than in HHT1. Hereditary hemorrhagic telangiectasia-2 has a higher number of non-penetrant cases and later onset age of manifestations of the disease.52,56,57 2) Pulmonary arterio-venous malformations are significantly more frequent in HHT1 than in HHT2,44,56-59 and in HHT1, they are more often encountered in women compared to men.57 3) A predominance of ACVRL1 mutations has been described for HHT2 patients with primary pulmonary hypertension.50,61 Pulmonary arteriovenous malformations are encountered in HHT type 3.40 4) Cerebral arteriovenous malformations occur more often in HHT1.57 5) Hepatic arteriovenous malformations are more frequent in HHT2,57 and they are more frequent in women compared to men.57 6) Gastrointestinal bleedings are more severe in HHT1 than in HHT2.59 In a recently published review, Abdalla and Letarte present additional views on genetics and mechanisms of disease in HHT.62

**Pathogenesis.** Endoglin and ALK-1 exert their actions by being components of the transforming growth factor-beta (TGF-β) cytokine family. The TGF-β members assume several functions in different cell types; they modulate cell proliferation, migration, and differentiation, and they also regulate apoptosis, hematopoiesis and immunoreactions. As reparatory
cytokines, TGF-ß members stimulate healing of wounds and tissue repair following injury and infectious reactions, and they stimulate the synthesis of matrix proteins and angiogenesis.\textsuperscript{63,64} Identified human examples of these are 3 iso-forms of the TGF (TGF-ß1, TGF-ß2, and TGF-ß3), the bone morphogenetic proteins (BMP) and the activins. On the basis of their structure and sequence homology, endoglin and ALK-1 proteins are considered components of the TGF-ß family. The \textit{ACVRL1} gene codes for a type I receptor (ALK-1, TßR-I) with a serine-threonine kinase domain.\textsuperscript{53} Transfection studies in COS-1 cells have shown that the ALK-1 protein has the ability to bind TGF-ß1 or activin, in the presence of the TßR-II or the activin type II-receptor (Act R-II).\textsuperscript{65} However, the ALK-1 physiological ligand in vivo has not yet been identified.\textsuperscript{66} The current model of the receptor and the mechanism of signal transduction via TGF-ß have been elegantly postulated and described by Blobe et al.\textsuperscript{64} Recently, Pece-Barbara et al\textsuperscript{67} have obtained results suggesting that endoglin modulates TGF-ß1 signaling in endothelial cells by regulating surface TGF-ß receptors and suppressing Smad1 activation. Thus, an altered balance in TGF-ß receptors and downstream Smad pathways may underline defects in vascular development and homeostasis. Although the precise mechanism of vascular abnormalities observed in HHT patients remains to be resolved, it seems reasonable to assume that disturbed balance in Alk-1 and endoglin mediated TGF-ß1 pathways plays a major role in the development of endothelial cell dysfunction during angiogenesis. Evidence has been obtained for reduced endothelial secretion and plasma levels of TGF-ß1 in patients with HHT type 1. The lower endoglin expression in the endothelial cells may alter the regulation of TGF-ß via Smad-independent pathways.\textsuperscript{68} Furthermore, it has been shown that some of the HHT2-related mutations generate a dominant negative effect, while others give rise to a null phenotype via loss of protein expression or receptor activity. These data indicate that loss-of-function mutations in a single allele of the \textit{ACVRL1} locus are sufficient to contribute to defects in maintaining endothelial integrity.\textsuperscript{69} The new findings on the molecular mechanisms that take place in endothelial cells to regulate and switch between TGF-ß-induced biological responses were recently described in detail by Lebrin et al.\textsuperscript{70} Transforming growth factor-beta-ß has a peculiar characteristic of being both a stimulator and an inhibitor of angiogenesis in vitro and in vivo. A model has been proposed in which TGF-ß by binding to the TGF-ß type II receptor can activate 2 distinct type I receptors in endothelial cells, namely the endothelial-cell-restricted ALK-1 and the broadly expressed ALK-5, which have opposite effects on endothelial cells behavior. Activin-receptor-like kinase-1 via Smad 1/5 transcription factors stimulates endothelial cells proliferation and migration, whereas ALK-5 via Smad 2/3 inhibits endothelial cells proliferation and migration.\textsuperscript{70}

\begin{figure}[h]
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\caption{Relationship between diseases (squares) and mutated genes (boxes). Hereditary hemorrhagic telangiectasia (HHT) may be caused by mutations in endoglin (\textit{ENG}) on chromosome 9q, activin receptor-like kinase 1 (\textit{ACVRL1}) (ALK1) on chromosome 12q, or in one or more unknown gene(s) one of which was mapped to chromosome 5q. Mutations in the mothers against decapentaplegic, Drosophila, homolog of 4 (\textit{MADH4}) (also designated as \textit{SMAD4}) gene have been identified in patients with a juvenile polyposis/HHT overlap syndrome (JPHT). Pulmonary hypertension is mainly caused (broad arrow) by mutations in the \textit{BMPR2} gene on chromosome 2q and rarely caused (small arrow) by mutations in the \textit{ACVRL1} gene. Intracranial aneurysm and hemorrhage are associated with a polymorphism in the \textit{ENG} gene.}
\end{figure}
Experiments on knock-out mice. In ENG-knockout mice, the abnormal vascular and cardiologic developments at 10.5 to 11.5 day of embryogenesis lead to death.\textsuperscript{71,72} In the egg yolk-sac, immature vascular plexus that causes hemorrhage in embryonic tissue could be seen. In addition, disturbances of heart development could be observed.\textsuperscript{73} The egg yolk-sac localized vascular defect and the early embryo lethality could also be observed in mice in which coding genes for ALK-1,\textsuperscript{46} TGF-B1,\textsuperscript{74} TßR-II,\textsuperscript{75} or SMAD 5\textsuperscript{76,77} were functionally inactivated. The inactivation of TGF-B2\textsuperscript{78} or TGF-B3\textsuperscript{79} similarly led to prenatal death, whereby in TGF-B3 knockout mice abnormal dilated pulmonary veins with extensive intrapulmonary and pleural bleeding, showed a picture very reminiscent of the human HHT pulmonary malformations. In \textit{ACVRL1} knockout mice, the considerable vascular abnormalities showed characteristic fusions of the capillary plexus to form cavernous vessels in addition to the considerably dilated larger vessels.\textsuperscript{80}

By breeding of mice in which only one ENG allele was put out of function, it was possible to generate the first animal HHT model. Since a part of the heterozygote animals showed telangiectases in the ears, recurrent superficial bleeding eventually epistaxis, dysplastic-dilated vessels, cerebral and pulmonary or hepatic involvement, multi-organ manifestations of the human HHT clinical picture could thus be reproduced. In this respect, the 129/OLA strain of mice showed the disease manifestations significantly more frequent, so that the effect of the modified gene was identified.\textsuperscript{73}

Clinical manifestations. 1) Epistaxis. The most common early symptom of HHT is chronic epistaxis that results from vascular dysplasia of the nasal epithelium, a symptom observed in approximately 95% of all patients, whereby more than 90% of them will show the typical symptom before they reach the age of 21 (mean 12 years). Not uncommonly the frequent nasal bleeding leads to iron deficiency-anemia that in certain cases may require blood transfusions as a necessary treatment.\textsuperscript{81} In approximately 70% of patients diagnosed with HHT, the cutaneous and mucocutaneous telangiectases are not formed before the second to third decade of age,\textsuperscript{82} and the telangiectases increase in size and number with age.\textsuperscript{83} The telangiectases are mostly located in the nasal epithelium, face, lips, tongue, and gums, and these are the sites of profuse bleeding.\textsuperscript{83}

2) Pulmonary arteriovenous malformations. In more than 20% of patients with HHT, pulmonary arteriovenous malformations (PAVM) are formed, where direct connections between pulmonary-arterioles and pulmonary-venules exist.\textsuperscript{2} The formed fistulae are often singular but may be multiple and involve the whole basal lung tissue.\textsuperscript{84} The vessels with dysplasia tend to enlarge\textsuperscript{85} and rarely revert to normal size spontaneously.\textsuperscript{86} They can cause bleeding into the pleural cavity of a bronchiole and hence lead to life-threatening hemoptosis.\textsuperscript{87} The most common clinical symptoms and serious complications are due to the functional consequences of the right to left vascular shunts. Depending on the shunt-volumes, hypoxia, dyspneea and cyanosis can be caused. Larger arteriovenous fistulae increase the chance that an existing embolism will escape filters in the lung and reach the left side of circulation. This can lead to development of cerebral ischemia (transitional ischemic attack; ischemic insult) in one third of the patients with pulmonary fistulae,\textsuperscript{84} and septic brain abscess in 5-9% of the patients.\textsuperscript{87,88} Normally, the pulmonary malformations become clinically observable at the third or fourth decade of age.\textsuperscript{82} Hereditary hemorrhagic telangiectasia patients with silent AVMs are still at risk of hemorrhage and are more commonly prone to neurological complications due to embolism.

3) Central nervous system complications. Cerebrovascular malformations (CVM) have been reported in approximately 15% of asymptomatic patients with HHT2. However, since screening of asymptomatic patients is rarely undertaken, it is possible that the number could be even higher.\textsuperscript{3} Investigations using magnetic resonance imaging (MRI) in 184 patients showed incidence of CVM in 23% of them.\textsuperscript{7} A primary (CNS bleeding) neurological complication of HHT is formation of embolisms in the basement of the pulmonary arteriovenous fistulae. Secondary complications result from formation of vascular anomalies in the brain or the spinal cord, the intracerebral or subarachnoidal bleeding, leading to epileptic attacks, and paraplegia.\textsuperscript{50} Migraine is a further frequent neurological manifestation that is encountered in up to 50% of all patients.\textsuperscript{84} The extents to which undiscovered cerebral or pulmonary vascular malformations contribute to the development of the above mentioned manifestations is not yet clear.\textsuperscript{9} The initial symptoms of serious neurological complications\textsuperscript{84} are believed to cause the major portion of the estimated 10% mortality in HHT.\textsuperscript{41}

4) Gastrointestinal bleeding. Gastrointestinal bleeding in HHT does not normally begin before the fifth or sixth decade of life\textsuperscript{83} with a mean age of 55 years\textsuperscript{89} and is seen in 11-40% of patients with HHT2. By gastrointestinal endoscopy, the telangiectases have been observed to localize in the stomach or the duodenum, but they could also be seen in the small intestines and colon.\textsuperscript{3,89} In rare cases of HHT larger arteriovenous malformations or angioplastia could be seen by angiography.\textsuperscript{90} As with intensive epistaxis, the blood loss in the gastrointestinal tract can lead to serious iron-deficiency anemia that partly necessitates
therapeutic blood transfusions. Occasionally the acute bleeding could be life-threatening.5

5) Hepatic manifestation. Hepatic manifestations of HHT have been estimated to affect about 8-16% of the patients.6 In patients with HHT and symptomatic liver involvement, the clinical presentations include high-output heart failure, portal hypertension, and biliary disease. In some, but not all, HHT patients with portal hypertension, the cause could be attributed to shunts from the hepatic artery to the portal vein.7 The hepatic vascular malformation is mostly associated with fibrosis and/or atypical cirrhosis.8 Although the formed fibrosis leads to microscopically observable nodular changes, the lobular architecture remains intact, so that the changes are called ‘pseudocirrhosis’.9 The changes must be distinguished from the secondary hepatic lesions of post-transfusion hepatitis, hepatic insufficient circulation due to right-heart exhaustion, or transfusion hemosiderosis.10 If the hepatic arteriovenous malformations are so intensive that they lead to hemodynamic functional shunts, the patient may develop hyper-circulatory coronary-insufficiency.11 Venous shunts of the portal artery can cause portal hypertension with the expected complications like ascites or varices.12 There are some reports on the development of hepatic telangiectases and porto-systemic encephalopathy caused by the portal artery-shunts.13 Frequently, hepatomegaly associated with splenomegaly, and vascular malformations in the spleen have been observed.14 In the clinical chemistry, icteric cholangitis can be indicated by an elevation of serum gamma-glutamyl transferase and alkaline phosphatase15 thus proving a correlation between vascular malformations and the liver function parameters.16 Furthermore, in HHT patients reduced liver function has been observed that may lead to progressive hepatic failure in severe cases.17 In a recent study of our research group involving 19 German patients with HHT, 13 different disease-causing mutations could be detected in 14 of those patients. The genetic alterations comprised 8 missense, 4 deletions, one nonsense, and one potential splice mutation. Ten patients in this cohort showed hepatic manifestation, and in 7 of them there was a mutation in the ACVRL1 gene. One patient had a mutation in both the ACVRL1 gene and the ENG gene. The disease-causing mutation could not be detected in 2 patients with hepatic manifestations. Therefore, this result supports the notion that hepatic manifestation in HHT patients is associated with mutations in the ACVRL1 gene, but rarely with the ENG mutations.18 Similarly Argyriou et al19 provided further support for involvement of the ACVRL1 gene with hepatic manifestation in HHT patients; ACVRL1 mutations but no ENG mutations, were detected in all 6 liver transplanted patients and 2 who were scheduled for liver transplantation. These results are of potential prognostic value with respect to the need for liver transplantation in HHT patients with hepatic manifestation.

6) Homozygous lethality of HHT. Homozygosity for HHT has once been considered a lethal condition by Snyder and Doan100 who reported 2 affected parents having a stillborn offspring with extensive angiomatous malformations of the viscera. Six decades later the hypothesis of homozygous lethality has gained support by a study of an Arab family in which a novel ENG mutation (c.932T→C) was identified.101 Marriage between 2 affected first cousins carrying this c.932T→C mutation yielded one healthy, 4 affected siblings, and 2 miscarriages. Hence, Karabegovic et al102 deduced that the 2 deceased fetuses could have been homozygous for the mutant allele and died in utero at a time when endoglin was essential for the cardiovascular development. On the other hand, Muller et al18 had calculated a high probability of homozygosity (0.99975) for a live proband of a large multi-generation family who had severe but exceptionally unusual manifestations of the disease but no mutation analysis was performed in this patient. In a large Saudi Arabian family with HHT, the authors of this article have identified the ACVRL1 nonsense mutation Q490X as a disease-causing variant.102 In this family, a consanguineous marriage between spouses both having HHT and carried the Q490X mutation, resulted in 12 pregnancies: 3 ended in spontaneous abortions, 4 early neonatal deaths, and only 5 living offspring all of whom have HHT and are heterozygous for the Q490X mutation. Clinically, the reported causes of the spontaneous abortions were intrauterine growth retardation of the fetuses and severe internal organ malformations leading to hemorrhages. In the early neonatal death, reported causes included severe organ malformations, respiratory distress syndrome, and failure to thrive. It was deduced that the 7 deaths are mostly attributed to Q490X homozygosity, although the possibility that other inherited or acquired diseases might have caused some of the fetal and neonatal deaths in this highly consanguineous family can not be ruled out completely. The high number of spontaneous abortions (25%) and neonatal deaths (33%) and the absence of homozygosity in all living offspring support the view that homozygosity for HHT-causing mutations is lethal. This hypothesis gains further support from animal studies: ACVRL1 homozygous mouse embryos, which die at mid gestation, exhibit severe vascular abnormalities.66 Therefore, the findings of El-Harith et al103 are the first that directly corroborate the deduction of homozygous lethality in HHT patients.

Diagnosis of HHT. Initial diagnosis of HHT in an individual or a family should rely on the targeted physical examination and medical history as well as family history. Identification of a causative gene in
an affected individual can be helpful in clarifying the diagnosis in other at risk relatives (usually younger) in whom the diagnosis is less clear based on examination and history. Early diagnosis is important for appropriate management of HHT. According to the Curaçao criteria, the current clinical diagnosis of HHT requires that at least 3 out of 4 criteria should be fulfilled in order to confirm the diagnosis. When 2 criteria are fulfilled, the diagnosis can be rated as ‘suspected diagnosis’. When only one criterion is fulfilled the diagnosis is rated as ‘unlikely’. Thus, the relevant clinical criteria for HHT are: 1) Epistaxis: spontaneous and recurrent nose bleeds. 2) Telangiectases: multiple at characteristic sites (lips, oral cavity, fingers, nose). 3) Visceral lesions (AVMs; telangiectasia): gastrointestinal telangiectasia (with or without bleeding), pulmonary AVM, hepatic AVM, cerebral AVM, and spinal AVM. 4) Familial frequency: a first-degree relative with HHT. For children of affected individuals, the age-dependent penetrance should be taken into consideration (see clinical manifestations-epistaxis). Patients with HHT who are suspected of having pulmonary AVMs should initially be screened with contrast echocardiography followed by measurement of PaO₂ while breathing 100% oxygen; this seems to be the best screening procedure for identification of pulmonary AVMs. Screening with chest radiography and pulse oximetry was shown to be insufficient. Detection of cerebral AVMs MRI is currently the most sensitive non-invasive test, though it may miss detection of a significant proportion of AVMs. Gastrointestinal telangiectases, similar in size and appearance to mucocutaneous telangiectases, occur in the whole gastrointestinal tract but more common in the stomach and duodenum than in the colon. These telangiectases can be visualized by endoscopy, whereas gastrointestinal AVMs and aneurysms can be detected by angiography. Hepatic AVM, suspected by hepatomegaly, or abnormal liver function tests, can be visualized by angiography, computed tomography (CT scan), MIR or Doppler sonography.

**Clinical management of HHT.** All of the presently known therapeutic approaches are basically of the symptomatic rather than the curative type. When making a choice of therapy for HHT, a scrutinized balance between the benefits and risks for the patient must be taken into account. In the management of all HHT patients, it is advised to suspect presence of the most serious complications such as pulmonary AVMs brain abscess, or early onset stroke. Generally, epistaxis, gastrointestinal bleeding, and other visceral involvement should be managed symptomatically by appropriate specialists. All HHT patients should be screened for pulmonary AVMs, even when asymptomatic, and arrangements for treatment at experienced centers should be made. The currently variable different modalities of treatment for HHT are briefly reviewed here. 1) In the treatment of epistaxis, known to impair the health and/or quality of life, several therapeutic measures are available. These include emergency nasal packing, septal dermoplastic surgery, topical and oral administration of estrogen, vascular cauterization, and laser surgery. Cauterization is best avoided due to damage of nasal vascular re-growth. The only antihemorrhagic therapy supported by evidence is the use of female hormones, such as 50 µg ethinyl oestradiol and 1 mg norethisterone, in transfusion dependent patients. Repeated laser therapy may also be used. Surgery, in general, has limited success due to recurrence, but may still be useful in emergency control of hemorrhage for discrete lesions. Repetition of the treatment is mostly needed because disease recurrence, caused by development of collateral circulation, is often encountered. 2) Pulmonary AVM complications can be limited if the condition is diagnosed and treated with transcatheter embolotherapy. There are experienced centers that perform this procedure with high safety profiles, in earlier treatment of asymptomatic patients, and in clinical screening of high risk groups. 3) Since 50% of the arteriovenous malformations present asymptomatic, until they are excluded prophylactic antibiotic treatment is recommended prior to any surgical or dental intervention. In order to prevent the severe neurological complications, pulmonary arteriovenous fistulae from an arterial diameter of more than 3 mm should be ligated, whereby catheter-embolisation is a milder procedure relative to the surgical intervention. 4) In the treatment of cerebral vascular malformations, neurovascular surgery, neuroradiologic treatment, and application of therapeutic coils, are available for choice. In the treatment of gastrointestinal bleeding, most patients are managed with oral iron therapy, and, if necessary, blood transfusions. Severe iron-deficiency anemia, which may also be caused by nasal bleeding, can be treated by iron substitution or in the severe cases by blood transfusion. Iron supplementation by diet is sufficient for many HHT patients whereas others may require transfusions. Administration of estrogen-progesterone has proven to be effective, although the mechanism of action is not exactly known. It is possible that enhancement of the continuity of the vascular endothelium and the squamous membrane, leads to better membrane-defense against traumas. In certain cases, laser-surgery is also used as a treatment of the gastrointestinal bleeding. For treatment of the cardiac insufficiency, caused by existence of hepatic arteriovenous shunt, catheter-embolization of the affected hepatic arteries is one of the choices available. A further therapeutic variant is...
the surgical ligation of the affected vessels. However, the 2 techniques may entail severe complications. 7) In therapy-resistant cases with advanced hepatic insufficiency, the indication for liver transplantation should be considered.

In conclusions, although the first description of HHT, as an inherited bleeding disorder, was made more than a century ago, only in the last decade the concept of HHT as a group of clinically linked diseases rather than a single disorder became evident. At present, the 2 disease loci ENG and ACVRL1, have been identified and mutations in either of these genes can lead to HHT (Figure 3). In addition, evidence for one further locus for HHT with pulmonary involvement has been obtained. The pathogenesis of HHT and the role of the 2 hitherto identified genes have been relatively well illustrated: HHT is a Mendelian disorder caused by mutations in one of at least 3 different genes. However, the extent to which genetic modifier and epigenetic factors contribute to the manifestation of the disease warrants further molecular and animal model studies. As endoglin, ALK1, and a newly postulated disease modifier(s) will also belong to the same transforming (TGF-ß), it is very likely that the presumed genetic evidence for one further gene associated with pulmonary telangiectasis in the Afro-Carribean population of the Netherlands Antilles: a family screening. J Med Genet 2003; 116A: 324-328.

Acknowledgment. The support given by the Alexander von Humboldt Foundation (Germany) is hereby gratefully acknowledged.

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