Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Rendu-Weber disease, is an autosomal dominant disorder characterized by multisystemic vascular dysplasia. HHT occurs with a wide geographic distribution among many ethnic and racial groups. It has an estimated prevalence of 1 in 40,000 [1]. However, this disorder is now considered to be more common than previously thought [1, 2]. Clinical manifestations include recurrent epistaxis, mucocutaneous telangiectasis, gastrointestinal hemorrhage, and pulmonary, cerebral, and hepatic arteriovenous malformation. The recognized manifestations of HHT are all due to abnormalities of vascular structure [2].

Linkage studies have shown at least two disease loci for HHT. The first, HHT1, is located on chromosome 9q34 and has been shown to be the endoglin gene [3, 4]. Endoglin is a transforming growth factor β (TGF-β) binding protein expressed predominantly by endothelial cells and placenta [5, 6]. The mutations in the endoglin gene were found to be protein truncation, suggesting a dominant-negative effect of binding protein function [7].

A second HHT locus (HHT2) has been mapped to chromosome 12q13 [8, 9]. The causative gene is the activin receptor-like kinase-1 (ALK-1) gene. ALK-1 is an endothelial cell type I receptor for the TGF-β superfamily of ligands. It has been shown to bind either activin or TGF-β in the presence of their respective type II receptors but does not bind ligand alone [10]. A recent study found ALK-1 in the TGF-β1 and -β3 receptor complexes associated with endoglin and TGF-β type II receptor, but not in activin receptor complexes containing endoglin [11].

A third rare variant of HHT has been reported in one large family with hepatic involvement as the major manifestation [12], with exclusion of linkage to both chromosome 9 and chromosome 12.
Case Report

This 67-year-old man had acute congestive heart failure and episodes of upper gastrointestinal bleeding. His family also had similar systemic lesions in these organs. Physical examination revealed a grade 3/6 systolic murmur over the apex and telangiectasia over the face and tongue. There were bruits over the right lower lung. Echocardiography revealed a dilated left atrium and ventricle. Panendoscopy showed gastric ulceration with active bleeding and a cherry red spot over the antrum. Computerized tomography (CT) scan and chest roentgenogram demonstrated a right lower lobe mass characteristic of an abnormal vascular structure (Fig. 1). Abdominal ultrasound demonstrated multiple dilated and tortuous tubular structures in the liver. Color Doppler flow mapping showed color flow signals in these structures and prominence of the hepatic artery with low-impedance flow based on the findings of spectral analysis and visible engorgement of the portal vein. Abdominal CT scan showed an ectatic vascular structure.

Members 03 and 04 of this family (Fig. 2) had episodes of upper gastrointestinal bleeding, and also had multiple dilated and tortuous tubular structures in the liver on color Doppler flow mapping. Members 07 and 08 (1 and 5 years old, respectively) were too young to manifest HHT symptoms.

Linkage analysis was performed with the ABI Prism Linkage Mapping Set (PE Applied Biosystems, Foster City, CA, USA). For HHT1, five polymorphic loci, ordered D9S287/D9S279/D9S290/D9S164/D9S158, which span chromosome 9q, were studied. For HHT2, five polymorphic loci, ordered D12S345/D12S85/D12S368/D12S83/D12S351, span chromosome 12q. The short tandem repeat polymorphisms were typed using the polymerase chain reaction (PCR) as described by the manufacturer. Electrophoresis and analysis were performed using the ABI Prism 377 DNA sequencer (PE Applied Biosystems). Data were analyzed using ABI Prism GeneScan Version 2.1 (PE Applied Biosystems).

The results of multipoint linkage analysis are shown in Fig. 2. The HHT1 locus is mapped between D9S290 and D9S158 [4]. As shown by chromosome 9q3 linkage data, recombination was found at loci D9S279, D9S164, and D9S158 in family member 04, and D9S290 was not linked with other loci in member 05. Moreover, clinical diagnostics showed that members 01, 03, and 04 were affected by HHT syndrome, but that 02 and 05 were not. One paternal allele was transmitted to all three children (03, 04, and 05). Therefore, HHT1 was excluded.

The HHT2 locus has been mapped between D12S347 and D12S368 [9]. Because D12S437 was not included in the mapping set used in this study, the nearest marker, D12S85, was selected. Thus, the D12S347 and HHT2 loci were located between D12S85 and D12S368. In the chromosome 12q13 linkage analysis (Fig. 2, HHT2), recombination was observed between D12S85 and D12S83 in members 04 and 05. Member 05 was normal; hence, his crossover occurred in the maternal allele between D12S85 and D12S368, and the paternal allele (thick line) was a normal allele. In this family, affected members 01, 03, and 04 had the same allele or partial (thick dotted line), suggesting that this family may be HHT2, despite the finding that member 04 had a crossover in the paternal allele between D12S85 and D12S368.

Amplification of the ALK-1 gene exons using PCR was carried out as previously described, with the same primer pairs [13]. PCR products were subjected to direct sequencing for mutation identification. Comparison of sequencing data with the GeneBank sequence revealed that this family had a one-base difference. The G-to-A substitution at 1,232 results

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**Fig. 1.** A) Chest roentgenogram from a lateral view shows a mass shadow (straight arrow) located between the heart and the posterior chest wall. B) Transverse abdominal sonogram through the right lobe of the liver shows multiple ectatic vascular structures. C) Computerized tomography scan of the chest reveals a well-enhanced mass representing arteriovenous malformation in the right hemithorax (straight arrow).
in an arginine-to-glutamine substitution at codon 411. This mutation in ALK-1 has been reported previously [9].

Discussion

Since HHT can be caused by mutations in more than one gene, linkage analyses were initially performed in this study to determine which gene was responsible for the disease. There have been several case reports of HHT in Asia, but only one has studied HHT1 mutation in this family for two young individuals, members 07 and 08 (Fig. 2). Since both carried the mutated ALK-1 gene, presymptomatic diagnosis could be performed.

In conclusion, we have established a systematic process for identification of the HHT mutation. The identification of mutations will facilitate studies to demonstrate the function and structure of ALK-1 in greater detail.

References