

ORIGINAL ARTICLE

Hereditary hemorrhagic telangiectasia in Japanese patients

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To describe clinical presentations of hereditary hemorrhagic telangiectasia (HHT) patients in Japan. There were 80 patients (40 men and 40 women, age 2–78, mean 39.4 years old), who were either genetically verified or genetically not identifiable but clinically definite HHT patients. Clinical presentations of these HHT patients were analyzed retrospectively. Radiological examinations, which included at least brain magnetic resonance imaging and lung computed tomography, were performed when indicated. Seventy-eight patients had either *endoglin* (*ENG*) or *activin A receptor type II-like 1* (*ACVRL1*) mutation. They were 53 HHT1 patients with *ENG* mutation in 27 families and 25 HHT2 patients with *ACVRL1* mutation in 17 families. Two other female patients were clinically definite HHT, but genetic mutation could not be identified. Nosebleeds were noted in 53/53 (100%) HHT1 and 24/25 (96%) HHT2 patients. Telangiectases were observed in 34/53 (64%) HHT1 and 18/25 (72%) HHT2 patients. Pulmonary arteriovenous malformations (AVMs) were noted in 33/52 HHT1 (63%) and 5/25 HHT2 patients (20%). Brain AVMs were detected in 12/51 HHT1 (24%) and 1/25 HHT2 (4%) patients. Hepatic AVMs were noted in 7/29 (24%) HHT1 and 16/20 (80%) HHT2 patients. The number of HHT1 patients was roughly twice as many as that of HHT2 patients in Japan. Pulmonary and brain AVMs were predominantly observed in HHT1 while hepatic AVMs were detected in HHT2. It seemed that ethnicity and regionality had minimal roles in the clinical presentation of HHT.

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Keywords: genotype; hereditary hemorrhagic telangiectasia; Japanese; phenotype

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu–Osler–Weber disease, is inherited in the autosomal dominant manner, and its incidence is reported as approximately 1 in 5000–8000.^{1,2} HHT produces a variety of vascular lesions in many organs, including skin and mucosa, gastrointestinal (GI) tract, lung, liver, brain and spinal cord.^{3,4} Among them, pulmonary and brain arteriovenous malformations (AVMs) are the main sources of substantial morbidity and mortality. Clinical diagnosis of HHT is usually based on the Curaçao criteria.⁵ Two gene mutations; that is, mutations of *endoglin* (*ENG*) at chromosome 9q34.1^{6–8} and *activin A receptor type II-like 1* (*ACVRL1*) at chromosome 12q31,^{9,10} are known to produce HHT1 and HHT2, respectively. These two genes encode for receptors, which are involved in the transforming growth factor-beta signaling pathway. They are predominantly expressed on the surface of endothelial cells, and are involved in angiogenesis. In addition to *ENG* and *ACVRL1* gene, mutation of SMAD family member 4 (*SMAD4*) gene is reported to be related to a combined syndrome of HHT and juvenile polyposis.¹¹ Genotype–phenotype correlations have been reported mostly from North America and Europe.^{12,13}

Although HHT in Japanese patients had been reported as a case report or case series, there has been no large series so far.^{1,14} The purpose of this study is to describe the clinical presentations

of HHT patients in Japan. This is the largest Japanese series of genetically verified HHT patients and their clinical analyses. Contrary to the previous reports, nearly all patients in this series underwent reliable examinations of the pulmonary and brain AVMs.

MATERIALS AND METHODS

There were 80 patients (40 men and 40 women, age 2–78, mean 39.3 years old, s.d. 20.9 years), who were genetically verified or genetically not identifiable but clinically definite HHT patients. They were among 100 patients with suspected HHT or their family members who were referred to the HHT Center in Osaka City General Hospital, between September 2010 and April 2013 and were screened for HHT. Clinical presentations of 80 HHT patients were reviewed retrospectively. These patients were all Japanese, and mostly lived in the western part of Japan. Clinical evaluation included medical, personal and familial history and physical examinations. Radiological examination was performed when indicated. Genetic analysis was approved by the institutional review board of the National Cerebral and Cardiovascular Center, Osaka, Japan and written informed consent was obtained from each patient or from parents of patients younger than 18 years old.

Clinical diagnosis of HHT was based on the Curaçao criteria,⁵ which are as follows: (1) spontaneous recurrent nosebleeds; (2) mucocutaneous telangiectasia at the characteristic sites (lips, tongue, fingertips and so on); (3) visceral AVMs in lung, liver, brain or spinal cord; and (4) affected patients in the first-degree relative according to these criteria. When the patients have

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more than three criteria, they are classified as 'definite' HHT patients, and when two criteria were met, they were 'probable' HHT patients. When one or no criterion was present, they were classified as 'unlikely' HHT patients. According to these criteria, 80 HHT patients were categorized as 69 definite, 10 probable and 1 unlikely HHT patients (Figure 1).

Mutation analyses were performed at National Cerebral and Cardiovascular Center by sequencing both *ENG* and *ACVRL1* genes first. In cases in which mutations of *ENG* or *ACVRL1* genes were not found, mutation of these genes were further examined with multiple ligation probe amplification method. In cases in which these two methods failed to find mutation in patients with clinical diagnosis of 'definite' or 'probable' HHT, *SMAD4* gene was additionally analyzed. The patients with clinical diagnosis of 'unlikely' HHT, only *ENG* and *ACVRL1* genes were analyzed. The patient with definite clinical diagnosis of HHT, in whom *ENG*, *ACVRL1* and *SMAD4* mutations were not found, was considered to have a yet unknown gene mutation, and categorized as the patients with not identifiable mutation. Eighty HHT patients among 100 screened patients and their family members were categorized as *ENG*, *ACVRL1*, *SMAD4*, not identifiable mutation and non-HHT groups (Figure 1).

Principally, all patients in whom genetic mutation was identified and/or clinical diagnosis was either definite or probable HHT, underwent at least lung computed tomography (CT) and brain magnetic resonance (MR) imaging without contrast material. Thus, radiological examination was not performed in clinically 'unlikely' patients without gene mutation. Exception was two pediatric patients (3- and 6-year-old girls) in the HHT family, who were asymptomatic, and scheduled to undergo radiological examinations in the near future. Diagnosis of pulmonary AVM was established by lung CT in all patients except for one pregnant patient, who was diagnosed by transthoracic echocardiography with agitated saline. CT examination of the lung was usually performed with 16 or 64 multi-detector CT scanners with a slice thickness of <3 mm without a contrast material, but some patients underwent additional contrast enhanced study combined for hepatic examination. MR examination of the brain included at least T1-weighted, T2-weighted and fluid-attenuated inversion recovery axial images without contrast material as well as three-dimensional time-of-flight MR angiography with 1.5 or 3.0 Tesla MR scanners. The other examinations including contrast enhanced CT for the hepatic AVMs in 49 patients, which were performed in dynamic CT protocol in the selected cases (scanning in the early, intermediate and late phases) to detect the hemodynamics of hepatic AVMs. Endoscopic examination for GI tracts were limited and performed only for 19 patients. Examination for spinal AVM was least performed, with sagittal and axial MR imaging and/or contrast enhanced CT in 11 patients.

Statistic analyses were performed using the R statistic package (version 3.0.0: The R Foundation for Statistical Computing, <http://www.R-project.org>). The characteristics of the patients and results of the radiological examinations between HHT1 and HHT2 were compared using Fisher's exact test. Intergroup difference of the age was compared using Welch two sample *t*-test. Statistically, *P*-value < 0.05 was considered to be significant.

RESULTS

Demographic and clinical characteristics of 80 patients are shown in Table 1. Among the 100 patients and their family members screened for HHT, either *ENG* or *ACVRL1* gene mutation was found in 78 patients in 44 families. Two female patients (20- and 52-year-old women) with a diagnosis of definite HHT did not have gene mutation of *ENG*, *ACVRL1* or *SMAD4*. *ENG* mutation was found in 53 patients (HHT1 patients: M/F = 29/24, age 2–78, mean 35.1, s.d. ± 20.1 years old) in 27 families and *ACVRL1* mutation was found in 25 patients (HHT2 patients: M/F = 11/14, age 8–77, mean 48.6, s.d. ± 20.0 years old) in 17 families. In the remaining 20 patients with a clinical diagnosis of unlikely HHT, *ENG* or *ACVRL1* gene mutation was not found. All of the latter patients were family members of the genetically verified HHT patients. All patients with a clinical diagnosis of 'definite' or 'probable' HHT had gene mutation. However, among 21 patients with a clinical diagnosis of 'unlikely' HHT, one patient had *ACVRL1* mutation (1/100 patient, 1%, false negative by the Curaçao criteria) while the remaining 20 patients had no gene mutation (Figure 1).

The correlation between genetic results and clinical diagnosis is shown in Table 2. Genetically proved 78 patients (53 HHT1 and 25 HHT2 patients) were categorized by the Curaçao criteria as follows: 53 HHT1 patients being categorized as 47 definite, 6 probable and 0 unlikely; and 25 HHT2 patients as 20 definite, 4 probable and

Table 1 Demographic and clinical characteristics of 80 HHT patients in Japan

<i>Gender</i> (N = 80)	
Male	40 (50%)
Female	40 (50%)
<i>Age</i> (N = 80)	
	39.3 (s.d. ± 20.9)
<i>Genotype</i> (N = 80)	
<i>Endoglin</i>	53 (66%)
<i>ACVRL1</i>	25 (31%)
<i>SMAD4</i>	0 (0%)
Not identifiable mutation	2 (3%)
<i>Curaçao criteria</i> (N = 80)	
Definite	69 (86%)
Probable	10 (13%)
Unlikely	1 (1%)
<i>Clinical presentation</i>	
Nose bleeds (N = 80)	79 (99%)
Telangiectasia (N = 80)	53 (66%)
Pulmonary AVM (N = 79)	40 (51%)
Brain AVM (N = 78)	13 (17%)
Hepatic AVM (N = 51)	24 (47%)
Spinal AVM (N = 11)	1 (9%)
GI tract lesions (N = 20)	13 (65%)
Family history (N = 80)	75 (94%)

Abbreviations: ACVRL1, activin A receptor type II-like 1; AVM, arteriovenous malformation; GI, gastrointestinal; HHT, hereditary hemorrhagic telangiectasia.

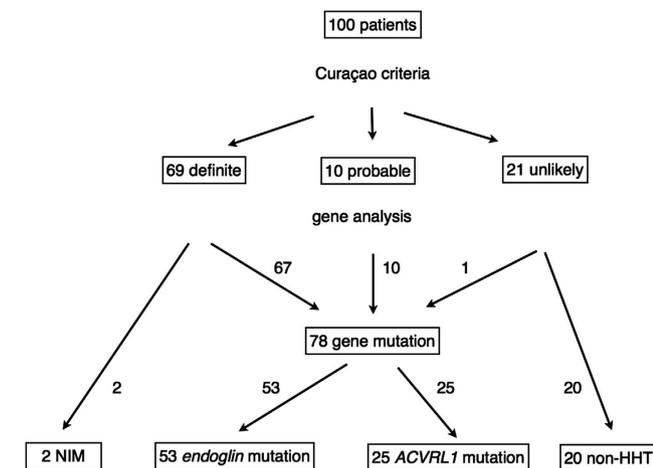


Figure 1 Stratification of the 100 screened patients and their family members by the Curaçao criteria and gene analysis. Eighty HHT patients; that is, 53 patients with endoglin mutation, 25 patients with *ACVRL1* mutation and 2 patients without identifiable mutation, are further examined clinically and radiologically. *ACVRL1*, *activin A receptor type II-like 1*; HHT, hereditary hemorrhagic telangiectasia; NIM, not identifiable mutation.

Table 2 Characteristics of HHT1 and HHT2 of 78 Japanese patients

	HHT1	HHT2	P-value
Number of patients (N=78)	53	25	
Male	29 (55%)	11 (44%)	0.47
Age	35.1 (s.d. ± 20.1)	48.6 (s.d. ± 20.0)	<0.01
<i>Curação criteria (N = 78)</i>			
Definite	47	20	
Probable	6	4	
Unlikely	0	1	
<i>Clinical presentation</i>			
Nose bleeds (N=78)	53/53 (100%)	24/25 (96%)	0.32
Telangiectasia (N=78)	34/53 (64%)	18/25 (72%)	0.61
Pulmonary AVM (N=77)	33/52 (63%)	5/25 (20%)	<0.01
Brain AVM (N=76)	12/51 (24%)	1/25 (4%)	<0.05
Hepatic AVM (N=49)	7/29 (24%)	16/20 (80%)	<0.01
Spinal AVM (N=11)	1/8 (12%)	0/3 (0%)	1
GI tract lesions (N=19)	6/8 (75%)	6/11 (55%)	0.63
Family history (N=78)	49/53 (92%)	24/25 (96%)	1

Abbreviations: ACVRL1, activin A receptor type II-like 1; AVM, arteriovenous malformation; GI, gastrointestinal; HHT, hereditary hemorrhagic telangiectasia.

1 unlikely. One patient, who had *ACVRL1* gene mutation and was clinically 'unlikely' HHT, was a 23-year-old man, who had no nose bleed, no telangiectasia or no visceral AVMs including lung, brain, liver and spinal cord. He was a member of a large HHT2 family.

Number of types of *END* mutation was 7 missense mutations in 10 patients, 5 nonsense mutations in 8 patients, 5 frame shift mutations in 9 patients, 3 multi-exon deletions in 10 patients and 7 splicing mutations in 16 patients. Two unrelated families (family no. 10 and 11) had the same splicing mutation. Number of types of *AVRL1* mutation was 9 missense mutations in 15 patients, 4 nonsense mutations in 4 patients, 2 frame shift mutations in 3 patients and 2 splicing mutations in 3 patients. Two unrelated families (family no. 35 and 36) had the same missense mutations and the other two unrelated families (family no. 43 and 44) also had the same nonsense mutations. The frequencies of any types of mutations were not significantly different between HHT1 and HHT2 ($P > 0.05$). Gene mutations and their types are listed in Tables 3a, 3b and 4.

Recurrent nose bleeds were observed in 79/80 (M/F = 39/40, 99%) HHT patients; that is, 53/53 (M/F = 29/24, 100%) HHT1 and 24/25 (M/F = 10/14, 96%) HHT2 patients. Difference between HHT1 and HHT2 was not significant, $P = 0.32$. Telangiectases at the characteristic sites were observed in 53/80 (M/F = 24/29, 66%) HHT patients; that is, 34/53 (M/F = 17/17, 64%) HHT1 and 18/25 (M/F = 7/11, 72%) HHT2 patients. Difference between HHT1 and HHT2 was not significant, $P = 0.62$.

Pulmonary AVMs were noted in 40/79 (M/F = 21/19, 51%) patients; that is, 33/52 HHT1 (M/F = 18/15, 63%) and 5/25 HHT2 patients (M/F = 3/2, 20%). Difference between HHT1 and HHT2 was significant, $P < 0.01$. Multiple pulmonary AVMs were observed in 28 HHT1 patients and 3 HHT2 patients. Brain AVMs were detected in 13/78 (M/F = 8/5, 17%) patients; that is, 12/51 HHT1 (M/F = 8/4, 24%) and 1/25 HHT2 (M/F = 0/1, 4%) patients. Difference between HHT1 and HHT2 was significant, $P < 0.05$. Multiple brain AVMs were detected in 10 HHT1 patients and 1 HHT2 patient. Hepatic AVMs were noted in 24/51 (M/F = 8/16, 47%) HHT patients; that is, 7/29 (M/F = 3/4, 24%) HHT1 and 16/20 (M/F = 5/11, 80%) HHT2 patients. Difference between HHT1 and HHT2 was significant,

Table 3a Mutation list of *endoglin*

Family no.	cDNA	Protein	Type of mutation	References
1	c.97C>T	p.Gln33Ter	Nonsense	This paper
2	c.219G>A	IVS2 ds G-A -1	Splicing	Gedge <i>et al.</i> ²²
3	c.319delC	p.Leu107Cys fs	Frame shift	This paper
4	c.360 + 1G>A	IVS3 ds G-A + 1	Splicing	Pece <i>et al.</i> ²³
5	c.360 + 1G>C	IVS3 ds G-C + 1	Splicing	Dakeishi <i>et al.</i> ¹
6	c.461_2insG	p.Ile156Hisfs	Frame shift	This paper
7	c.497A>C	p.Gln166Pro	Missense	This paper
8	c.524-1G>C	IVS4 as G-C -1	Splicing	This paper
9	c.685delG	p.Ala229Profs	Frame shift	This paper
10	c.816 + 2T>A	IVS6 ds T-A + 2	Splicing	Lenato <i>et al.</i> ²⁴
11	c.816 + 2T>A	IVS6 ds T-A + 2	Splicing	Lenato <i>et al.</i> ²⁴
12	c.991G>A	p.Gly331Ser	Missense	Letteboer <i>et al.</i> ²⁰
13	c.1087T>A	p.Cys363Ser	Missense	Bossler <i>et al.</i> ²⁵
14	c.1103T>C	p.Met368Thr	Missense	Brakensiek <i>et al.</i> ²⁶
15	c.1109T>C	p.Leu370Pro	Missense	McDonald <i>et al.</i> ²⁷
16	c.1134G>A	IVS8 ds G-A -1	Splicing	Letteboer <i>et al.</i> ²⁰
17	c.1169G>A	p.Trp390Ter	nonsense	Fontalba <i>et al.</i> ²⁸
18	c.1235G>A	p.Cys412Tyr	Missense	Lesca <i>et al.</i> ²⁹
19	c.1306C>T	p.Gln436Ter	Nonsense	Lenato <i>et al.</i> ²⁴
20	c.1411C>T	p.Gln471Ter	Nonsense	This paper
21	c.1513G>T	p.Glu505Ter	Nonsense	Lenato <i>et al.</i> ²⁴
22	c.1517T>C	p.Leu506Pro	Missense	This paper
23	c.1672_1684del13bp	p.Gly558fs	Frame shift	Paquet <i>et al.</i> ³⁰
24	c.1687delG	p.Glu563Lysfs	Frame shift	This paper
25	Exons 13–14 del		Multi-exon deletion	This paper
26	Exons 3–14 del		Multi-exon deletion	Richards-Yutz <i>et al.</i> ³¹
27	Exons 3–8 del		Multi-exon deletion	McDonald <i>et al.</i> ²⁷

Abbreviations: ACVRL1, activin A receptor type II-like 1; cDNA, complementary DNA.

$P < 0.01$. Thus, pulmonary and brain AVMs were significantly more frequent in HHT1 than in HHT2, and hepatic AVMs were significantly more frequent in HHT2 than in HHT1.

Spinal AVM was detected only in 1/8 HHT1 symptomatic male patient (13%) while no spinal AVM was detected in 3 HHT2 patients. GI tract lesions were detected in 6/8 (M/F = 4/2, 75%) HHT1 and 6/11 (M/F = 3/3, 55%) HHT2 patients.

Transient ischemic attack and/or cerebral infarction were observed in 9/51 (18%) HHT1 patients and 0/25 (0%) HHT2 patient. Brain abscess was observed in 1/51 (2%) HHT1 and 1/25 (4%) HHT2 patients. All patients with transient ischemic attack, cerebral infarction and/or brain abscess had pulmonary AVMs.

Positive family history, which means affected patient(s) in the first-degree relative, was observed in 75/80 (94%) HHT patients; that is, 49/53 (92%) HHT1 and 24/25 (96%) HHT2 patients. Difference between HHT1 and HHT2 was not significant, $P = 1$. Thus, 4/53 (8%) HHT1 patients and 1/25 (4%) HHT2 patient had no family history. One HHT1 21-year-old female patient was proved to have *de novo* mutation of *ENG*, which her parents did not have.

Table 3b Mutation list of ACVRL1

Family no.	Family		Type of mutation		References
	cDNA	Protein	mutation		
28	c.95T>A	p.Val32Glu	Missense		This paper
29	c.270C>G	p.Cys90Trp	Missense		This paper
30	c.430C>T	p.Arg144Ter	Nonsense		Abdalla <i>et al.</i> ³²
31	c.480_486dup CAGTCTC	p.Ile163Gln fs	Frame shift		This paper
32	c.505C>T	p.Gln169Ter	Nonsense		This paper
33	c.525 + 1G>C	IVS4 ds G-C + 1	Splicing		This paper
34	c.598C>G	p.Arg200Gly	Missense		This paper
35	c.614T>G	p.Val205Gly	Missense		This paper
36	c.614T>G	p.Val205Gly	Missense		This paper
37	c.772 + 4_5insAA	IVS6 ds insAA + 4_5	Splicing		This paper
38	c.839A>G	p.His280Arg	Missense		Richards-Yutz <i>et al.</i> ³¹
39	c.969_970insA	p.Pro324Thr fs	Frame shift		This paper
40	c.982C>T	p.His328Tyr	Missense		This paper
41	c.1132C>T	p.Pro378Ser	Missense		Richards-Yutz <i>et al.</i> ³¹
42	c.1271C>T	p.Pro424Leu	Missense		Letteboer <i>et al.</i> ²⁰
43	c.1435C>T	p.Arg479Ter	Nonsense		Lesca <i>et al.</i> ²⁹
44	c.1435C>T	p.Arg479Ter	Nonsense		Lesca <i>et al.</i> ²⁹

Abbreviations: ACVRL1, activin A receptor type II-like 1; cDNA, complementary DNA.

Table 4 Types of gene mutations in HHT1 and HHT2

Types of mutation	HHT1		HHT2		Total		P-value
	Fm (pt)	% (Fm)	Fm (pt)	% (Fm)	Fm (pt)	% (Fm)	
Nonsense	5 (8)	18.5	4 (4)	23.5	9 (12)	20.5	0.48
Missense	7 (10)	25.9	9 (15)	52.9	16 (25)	36.4	0.07
Frame shift	5 (9)	18.5	2 (3)	11.8	7 (12)	15.9	0.44
Deletion	3 (10)	11.1	0 (0)	0	3 (10)	6.8	0.22
Splicing	7 (16)	25.9	2 (3)	11.8	9 (19)	20.5	0.23
Total	27 (53)	100	17 (25)	100	44 (78)	100	

Abbreviations: Fm, families; HHT, hereditary hemorrhagic telangiectasia; pt, patients.

DISCUSSION

HHT presents clinically a variety of symptoms including recurrent nose bleeds, telangiectasia of the mucocutaneous lesions including GI tract, pulmonary, hepatic, brain and spinal AVMs.^{3–5} Among them, pulmonary and brain AVMs are considered as the main causes of substantial morbidity and death. In our series of 80 HHT patients, nose bleeds was observed in 99%, telangiectasia in 66%, pulmonary AVM in 51%, brain AVM in 17% and positive family history in 94%. It is reported that at least 30% of HHT patients have pulmonary AVMs and 10% have brain AVMs.¹⁵ Higher detection rate of pulmonary and brain AVMs than the previous studies was due to thorough study with thin-slice CT for the lung and MR examination of the brain principally for all the patients.

Two well-known genetic loci, *ENG* and *ACVRL1*, are known to produce HHT1^{6–8} and HHT2,⁹ respectively. Although intra- and inter-familial variations in manifestation of HHT were well known, clinical manifestation of HHT1 and HHT2 is different. In our series, pulmonary AVMs were revealed in 63% of HHT1 and 20% of HHT2

patients, with significant difference of $P < 0.01$. Brain AVMs were noted in 24% of HHT1 patients and in 4% of HHT2 patients, with significant difference of $P < 0.05$. Hepatic AVMs were noted in 24% of HHT1 and in 80% of HHT2 patients, also with significant difference of $P < 0.01$. It is reported that HHT1 due to *ENG* mutation is more prone to pulmonary^{8,12,13,16} and brain AVMs^{12,13} while HHT2 due to *ACVRL1* mutation is less frequent to have pulmonary AVM,⁹ and is prone to have hepatic AVMs.^{12,13} This was proved by our study.

The ratio of *ENG* and *ACVRL1* mutation varies considerably from one country to another. *ENG/ACVRL1* mutation ratio of 119 French patients was 0.51 (40/79 patients) and that of 343 French and Northern Italian patients was 0.37 (93/250 patients) with *ACVRL1* mutation prevalence.^{13,17} This ratio of German patients was 0.89 (16/18 patients or families)¹⁸ and that of Canadian 31 families was 0.72 (13/18 families).¹⁹ Contrary to these reports, it was 1.22 in 111 patients in Utah, USA,¹² 1.31 in 97 mostly Dutch patients²⁰ and 2.0 in 21 Danish families (14/7 families)²¹ with *ENG* mutation prevalence. Our results of 78 patients or 44 families were 2.12 or 1.59, respectively. They were similar to the results in Dutch and Denmark. Although the reason of different *ENG/ACVRL1* mutation ratio remained to be confirmed, possible explanations include (1) recurrent mutations of *ENG* or *ACVRL1* in the given country (area), (2) random variation due to small sample size and selection bias and (3) early presentation of *ENG* mutation, of which phenotype is more severe than *ACVRL1* mutation.¹⁷

Although most of the patients in this series presented typical symptoms of HHT, some patients with a clinical diagnosis of probable or unlikely HHT did not show such symptoms. For the latter, only genetic analysis provides an accurate diagnosis. Children with HHT usually do not present symptoms until puberty when they commonly start to present nose bleeds. Later onset of symptoms of HHT2 is reported in comparison with HHT1.¹⁶ This is the case with our series that the mean age of HHT2 is 48.6 years old while that of HHT1 is 35.1 years old ($P < 0.01$). Although the Curaçao criteria remains to be clinically useful, especially patients with symptoms, 'unlikely' diagnosis for HHT by the Curaçao criteria cannot deny the diagnosis of HHT. Thus, definite diagnosis of HHT should rely on gene analysis and this supports the importance of gene analysis. For example, except for positive family history, a 23-year-old male patient had no symptoms, including nasal bleeding and telangiectasia, but *ACVRL1* mutation was discovered since all HHT family members underwent gene analysis. It is known that 9% of HHT2 patients over 60 years did not experience nose bleeds.¹³ This shows that genetic analysis is indicated to deny gene mutation definitely among family members of HHT. With the result of genetic analysis, genetic consultation can be provided, and even without clinical symptoms, close clinical follow-up will be planned.

In conclusions, this report is, the largest HHT series in Japan. The number of the HHT1 patients was roughly twice as many as that of HHT2 patients in our series. Prevalence of cerebral and pulmonary AVMs was higher than that reported previously. Brain and pulmonary AVMs were predominantly observed in HHT1 while hepatic AVMs were noted in HHT2. It seemed that ethnicity had a minimal role in the clinical presentation of HHT.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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