HHT AND BRAIN AVMS: GENETICS, PHENOTYPE AND NATURAL HISTORY

Marie E. Faughnan MD MSc

Toronto HHT Centre

St Michael's Hospital

University of Toronto

Montreal HHT Centre

Unviversite de Montreal

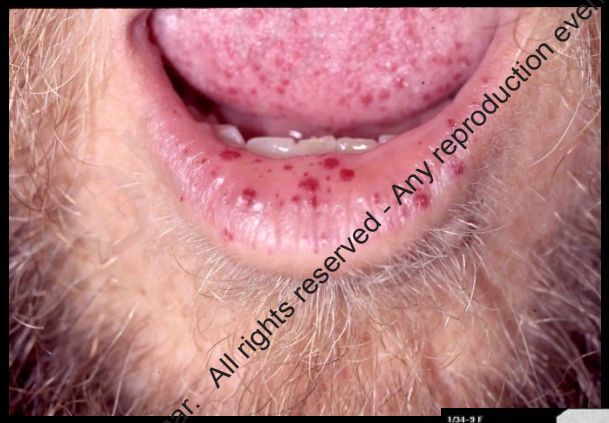
OUTLINE

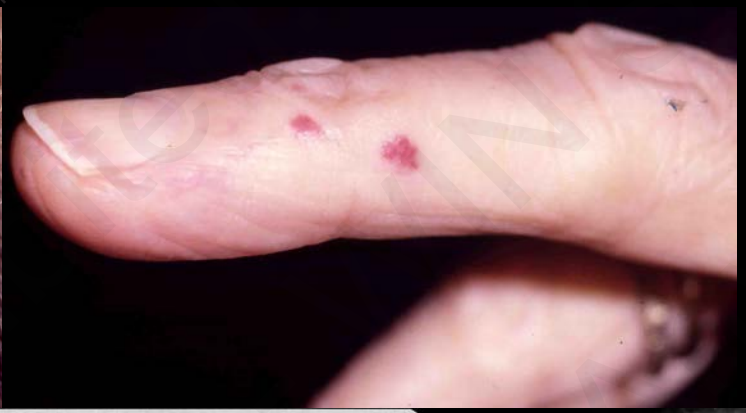
- Clinical overview of HHT
- Genetics of HHT
- Natural history of BAVMs in HHT
- Determinants of hemorrhage
- Imaging features of HHT
- Should we lump or split?
- Brain AVMs: an opportunity to diagnose HHT

MY PERSPECTIVE

- My background: pulmonary, clinical epidemiology
- My interests:
  - Hereditary Hemorrhagic Telangiectasia (HHT)
  - AVMs lungs, brain, etc.
  - Phenotype
  - Prevention…stop AVMs from bleeding
  - Cure…stop AVMs from forming?
- My priority: Best care for people with HHT

HEREDITARY HEMORRHAGIC TELANGIECTASIA

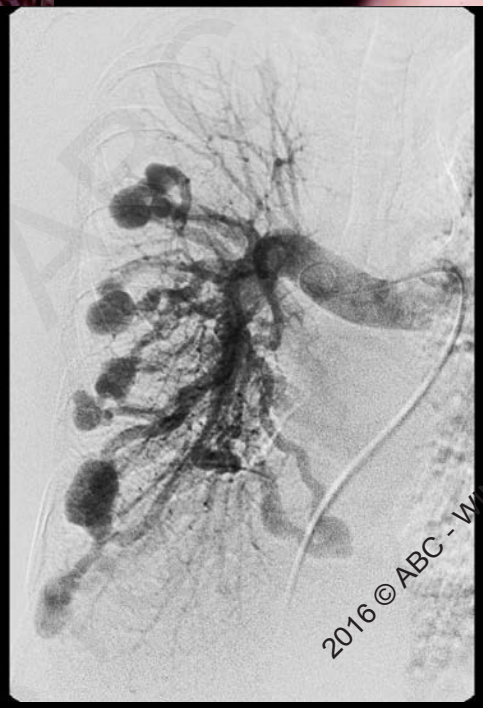


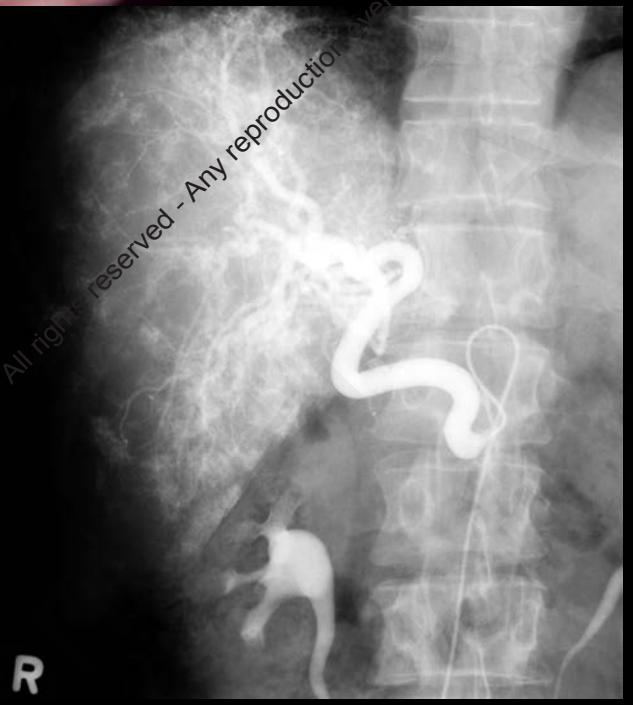


Autosomal dominant

Prevalence

1/8000





HHT AND ORGAN MANIFESTATIONS

• Epistaxis	90%
• Muco-cutaneous telangiectasia	90%
• Liver VMs	75%
• Pulmonary AVMs	40%
• GI bleeding	20%
• Brain VMs	10%
• Spinal AVMs	1%
• Pulmonary hypertension	1%

CLINICAL PRESENTATIONS IN HHT

- Chronic bleeding: nasal, GI, anemia
- Acute/massive hemorrhage: lung, brain, GI, nasal
- Complications from shunt/other:
  - Lung AVMs: stroke, brain abscess, hypoxemia
  - Liver VMs: heart failure, portal hypertension, biliary ischemia
  - Brain AVMs: seizure/rarely heart failure

CLINICAL PRESENTATION BY ORGAN IN HHT

Organ	Chronic low-grade bleeding	Acute massive hemorrhage	Complix from shunt/ other
Nose	+++	+	-
GI tract	+++	+	-
Liver	-	-	+++
Lung	+	++	+++
Brain	-	+++	+

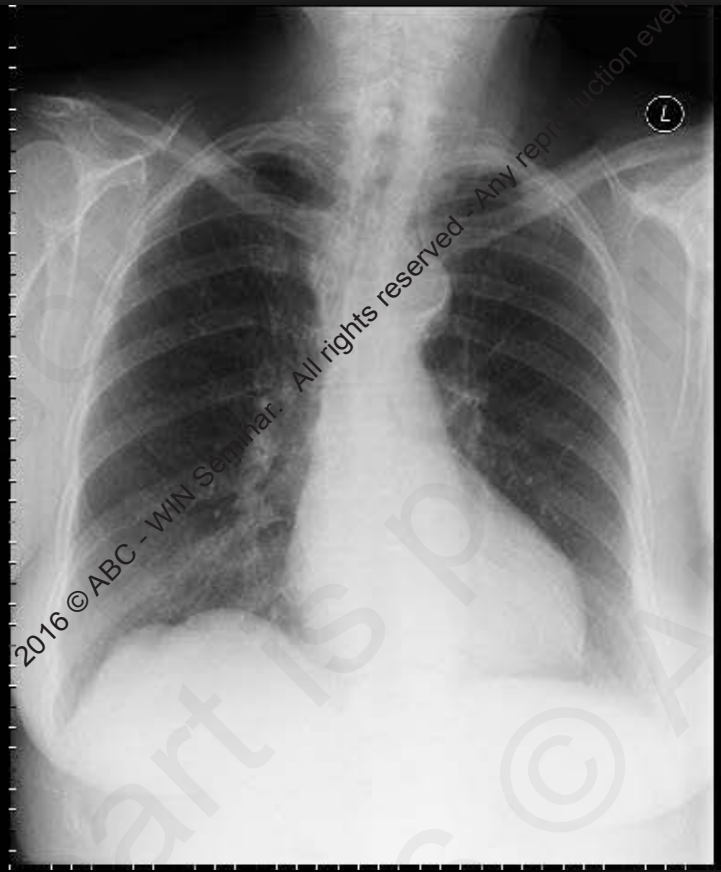
CLINICAL PRESENTATION BY ORGAN IN HHT

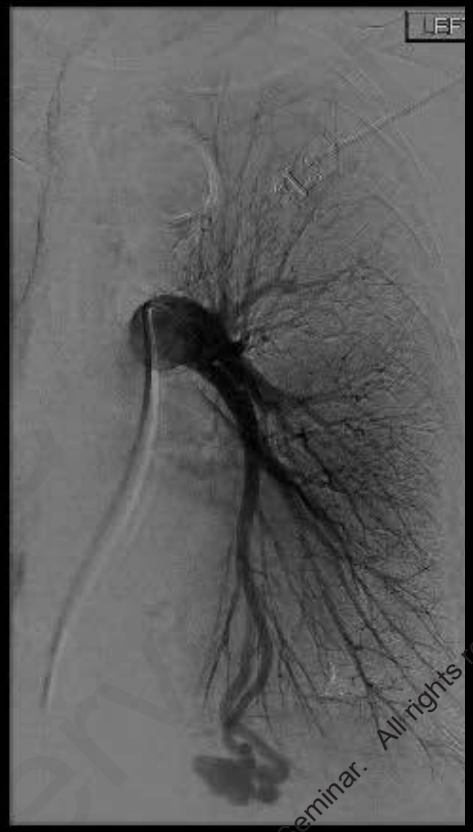
Organ	Chronic low-grade bleeding	Acute massive hemorrhage	Complix from shunt/ other
Nose	+++	+	-
GI tract	+++	+	-
Liver	-	-	+++
Lung	+	++	+++
Brain	-	+++	+

CLINICAL PRESENTATION BY ORGAN IN HHT

Organ	Chronic low-grade bleeding	Acute massive hemorrhage	Complix from shunt/ other
Nose	+++ ☐	+	-
GI tract	+++ ☐	+	-
Liver	-	-	+++ ☐
Lung	+	++ ☑	+++ ☑
Brain	-	+++ ☐	+

PULMONARY AVM: EMBOLOTHERAPY





SUMMARY OF PAVM APPROACH

People with PAVMs are at risk of life threatening complications, yet effective treatment is available.

- Screen HHT patients for PAVMs
- Treat PAVMs preventatively with transcatheter embolotherapy
- Follow people with PAVMs long-term

CLINICAL PRESENTATION BY ORGAN IN HHT

Organ	Chronic low-grade bleeding	Acute massive hemorrhage	Complix from shunt
Nose	+++ ☐		
GI tract	+++ ☐		
Liver	-	-	+++ ☐
Lung	+	++ ☑	+++ ☑
Brain	-	+++ ☐	+

Anti-angiogenic therapies?

CHALLENGE OF TREATING BRAIN VMS IN HHT

- Lack information about risk of ICH:
  - What is the risk?
  - What are determinants of risk
  - Patient and lesion specific risk assessment
- Lack information about treatment outcomes in HHT
  - Risks/benefits
  - What are the determinants?

RISK OF ICH IN HHT: SINGLE CENTRE STUDIES

Estimates of risk of ICH from brain AVMs in HHT

• 1.4-2%/year	N=ND	Easey et al 2003
• 0.4-0.7%/year	N=24	Willemse et al 2000
• 1.3%/year	N=12	Yang et al. Neurosurg 2015

- Has led some to conclude that HHT brain AVMs have a “more benign course”
- Need larger number, multicenter, imaging to estimate risk and determinants of it.

TREATMENT OPTIONS FOR BRAIN VMS

- Surgical resection
- Embolisation
- Gamma-knife radiosurgery
- Combined modalities

- Should we be investigating anti-angiogenic therapy? Anti-inflammatory? Other medical therapies?

WHY IS THE HHT PERSPECTIVE INTERESTING?

- High risk group for brain VMs
- Opportunity to observe natural history
- Opportunity to understand development of AVMs
- Understanding the pathophysiology may help us understand why other AVMs develop…what went wrong? How can we stop/prevent AVMs?
- Are there medical approaches to treat AVMs?

HHT CLINICAL DIAGNOSIS

Curaçao criteria:

- Epistaxis (recurrent, spontaneous)
- Telangiectasia (typical, location)
- Visceral AVMs
- Family History

Definite: At least 3 criteria

Shovlin CL et al. AJMG 2000

HHT GENETICS

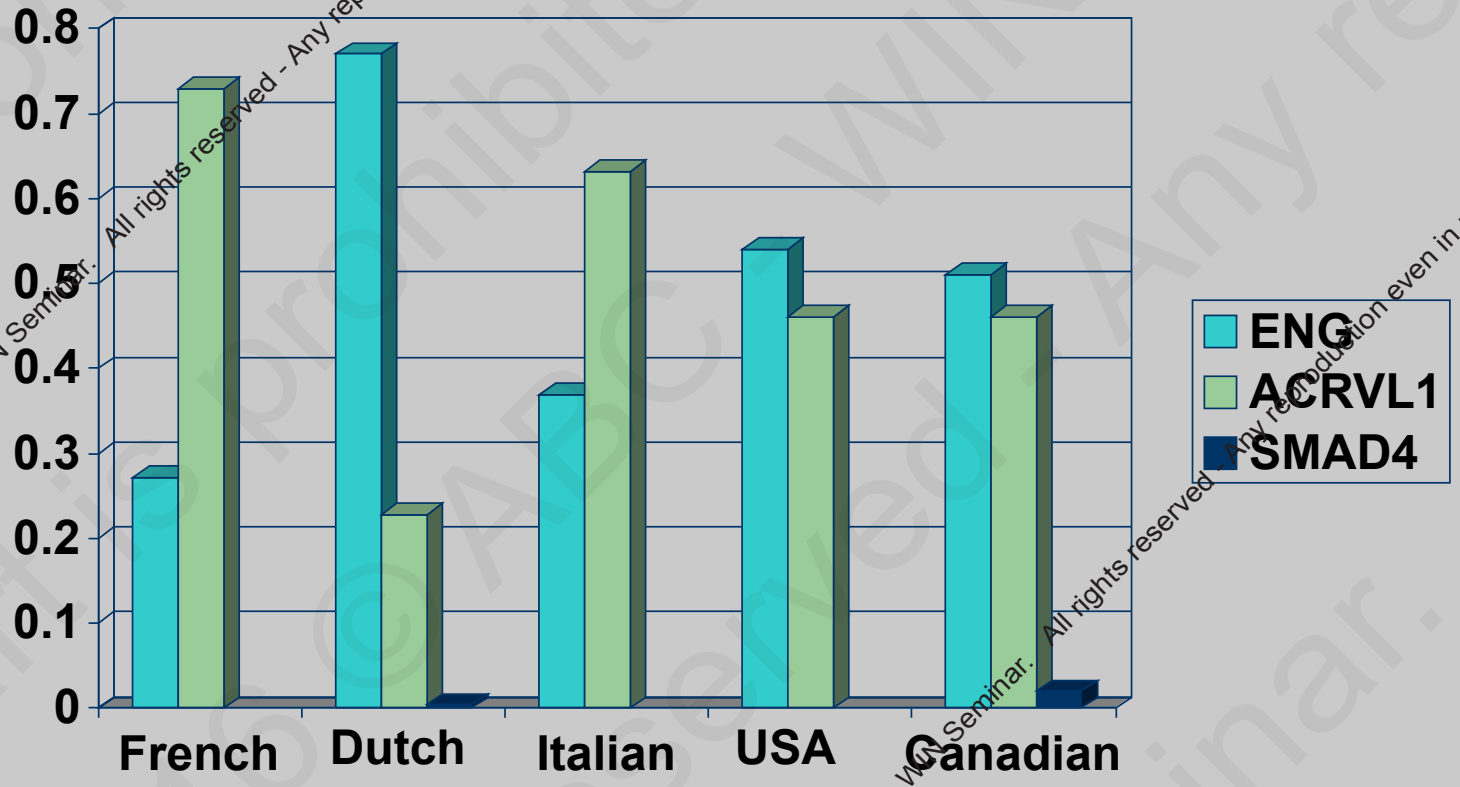
- HHT-1: Endoglin
- HHT-2: ALK1 or ACVRL1
- JP-HT: SMAD4
- ?BMP9 ?RASA1 ?BMPR2
- Most families have a private mutation
- All types mutations
- Mutations distributed throughout genes

HHT GENETIC DIAGNOSIS

- 80% HHT families have mutation in Endoglin or ALK1
- 3% SMAD4 mutation, JP overlap
- Rarely other genes presently

- Indication for genetic testing: to confirm or rule out disease in asymptomatic at-risk patient

Genotype varies around the world



Genotype Phenotype Correlations

Clinical Manifestation	ENG (N=93)	ACVRL1 (N=250)
Mean Age (years, SD)	44 (18)	52 (16) *
Epistaxis	90 (96.8%)	223 (89.2%) *
Telangiectasia	91 (97.8%)	233 (93.2%)
CAVM	2/22 (9.1%)	2/50 (4%)
PAVM	27/50 (54%)	19/149 (12.8%) *
GI Bleeding	6 (6.5%)	41 (16.4%)*
Symp. Liver VM	0 (0%)	19 (7.6%)*

*P<0.05

Lesca, G., et al. Genet Med, 2007. 9(1): p. 14-22.

Genotype Phenotype Correlations

Clinical Manifestation	ENG (N=735)	ACVRL1 (N=216)
Mean Age (years, SD)	44.8 (17.2)	46.2(16.6)
CAVM	38/260 (14.6%)	1/76 (1.3%) *
PAVM	167/343 (48.7%)	6 /114 (5.3%) *
GI Telangiectasia	56/78 (71.8%)	19/29 (65.5%)
Liver VM	11/144 (7.6%)	13/32 (40.6%)*

*P<0.05

0.4% SMAD4

Letteboer, T.G., et al. J Med Genet, 2006. 43(4): p. 371-7.

*P<0.05

Early Canadian Results

	ENG (N=255)	*ACRVL1* (N=229)
Age (years)	48.6 (16.8, 5-89)	48.1 (18.5, 5-84)
Gender (%Female)	149/254 (58.7%)	130/227 (57.3%)
Anemia (Hb<100)	7/177 (4.0%)	14/160 (8.8%)
Epistaxis	226/251(90.0%)	202/218 (92.7%)
Telangiectasia	232/250 (92.8%)	204/215 (94.9%)
CAVM	25/208 (12.0%)	10/177 (5.6%)*
PAVM	158/242 (65.3%)	37/209 (17.7%)*
GI Bleeding	45/223 (20.2%)	43/184 (23.4%)
Symptomatic Liver VM	7/227 (3.1%)	12/189 (6.3%)

*p<0.05

Edwards et al. 2012

HHT GENES AND BRAIN VMS

Country	Endoglin	ALK1	Author
France	9.1% (93)	4.0% (250)	G Lesca 2007
Netherlands	14.6% (735)*	1.3% (216)	T Letteboer 2006
Italy	20.9% (45)*	0.0% (77)	C. Sabba 2007
USA	16.4% (61)*	2.0% (50)	P Bayrak-Toydemir 2006
Canada	12.0% (255)*	5.6% (229)	C Edwards 2011

15% (9-21) 3% (0-6)

*p<0.05

Determinants of ICH in HHT BAVMs

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics

Brain Arteriovenous Malformations Associated With Hereditary Hemorrhagic Telangiectasia: Gene–Phenotype Correlations

Takeo Nishida,[1,2] Marie E. Faughnan,[2,3,4,5]* Timo Krings,[2,6] Murali Chakinala,[2,7] James R. Gossage,[2,8] William L. Young,[2,9,10,11] Helen Kim,[2,9,12,13] Tony Pourmohamad,[9] Katharine J. Henderson,[1,2] Stacy D. Schrum,[2,7] Melissa James,[2,8] Nancy Quinnine,[2,9] Aditya Bharatha,[14] Karel G. terBrugge,[2,6] and Robert I. White Jr[1,2]

[1]Yale HHT Center, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut

[2]Brain Vascular Malformation Consortium, Rare Disease Clinical Research Network**

[3]Division of Respirology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

[4]Toronto HHT Program, Division of Respirology, Department of Medicine, St. Michael's Hospital, Toronto, Ontario, Canada

Gene-Phenotype Correlations

Retrospective review of brain AVM cases from:

- Toronto HHT Centre
- Yale HHT Center
- Brain Vascular Malformation Consortium (BVMC): early recruitment

Gene-Phenotype Correlations

TABLE I. Demographic and Clinical Characteristics of 171 Patients With HHT and BAVM

Characteristics	
Gender (N = 171)	
Male (#, %)	69 (40%)
Genotype (N = 109)	
ENG mutation (#, %)	75 (69%)
ACVRL1 mutation (#, %)	18 (17%)
SMAD4 mutation (#, %)	2 (2%)
No mutation identified (#, %)	14 (13%)
Age at first BAVM Diagnosis (mean years, SD) (N = 165)	29 ± 18
History of ICH (#, %) (N = 152)	41 (27%)
Age at ICH (mean years, SD) (N = 39)	26 ± 18
History of seizure (#, %) (N = 164)	28 (17%)
Multiple BAVMs (#, %) (N = 170)	39 (23%)
Number of BAVMs (mean, SD) (N = 170)	1.5 ± 1.3
History of other HHT manifestations	
Epistaxis (#, %) (N = 169)	132 (78%)
Pulmonary AVM (#, %) (N = 166)	101 (61%)
HHT-related GI bleeding (#, %) (N = 166)	13 (8%)
Symptomatic liver AVM (#, %) (N = 161)	5 (3%)

HHT, hemorrhagic hereditary telangiectasia; BAVM, brain arteriovenous malformation, SD, standard deviation; ICH, intracranial hemorrhage, AVM, arteriovenous malformation, GI, gastrointestinal.

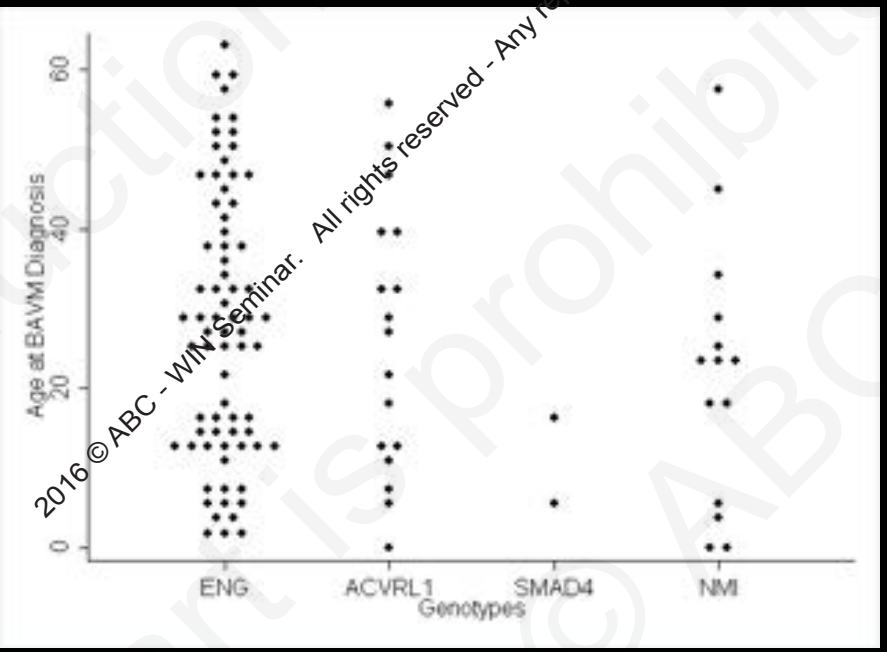
HHT BAVM G-P paper: 171 patients

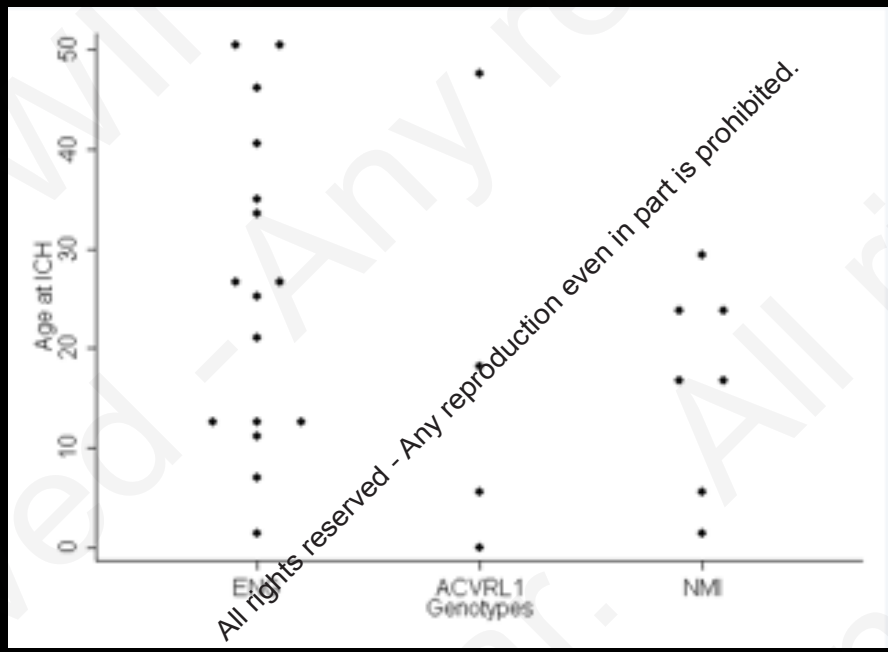
Female (#, %)	102 (60%)
ENG mutation (#, %)	75 (69%)
ACVRL1 mutation (#, %)	18 (17%)
SMAD4 mutation (#, %)	2 (2%)
No mutation identified (#, %)	14 (13%)
Age at BAVM Diagnosis (mean years, SD)	29 ± 18
History of ICH (#, %) (N=152)	41 (27%)
Age at ICH (mean years, SD) (N=39)	26 ± 18
History of Seizure (#, %) (N=164)	28 (17%)
Multiple BAVMs (#, %) (N=170)	39 (23%)
Number of BAVMs (mean, SD) (N=170)	1.5 ± 1.3

HHT BAVM G-P paper: 171 patients

	ENG N=75	*ACVRL1* N=18
Male (#, %)	30 (40%)	4 (22%)
Age of BAVM Dx (mean yrs, SD)	28 ± 17	26 ± 17
Hx of ICH (#, %)	16 (24%)	4 (27%)
Age at ICH (mean years, SD)	26 ± 16	18 ± 21
Multiple BAVMs (#, %)	21 (28%)	3 (17%)
Number of BAVMs (mean, SD)	1.5 ± 0.8	1.2 ± 0.5
Hx of Seizure (#, %)	9 (12%)	1 (6%)

HHT BAVM G-P paper: 171 patients





Gene-Phenotype Correlations

- Limited by sample size, clinical care data

- No evidence to date that HHT gene mutated determines severity or timing of clinical presentation
- No evidence to date that BAVM screening decisions should be based on gene or age

Determine risk factors for hemorrhage in HHT BAVM patients

Brief Report

Hemorrhage Rates From Brain Arteriovenous Malformation in Patients With Hereditary Hemorrhagic Telangiectasia

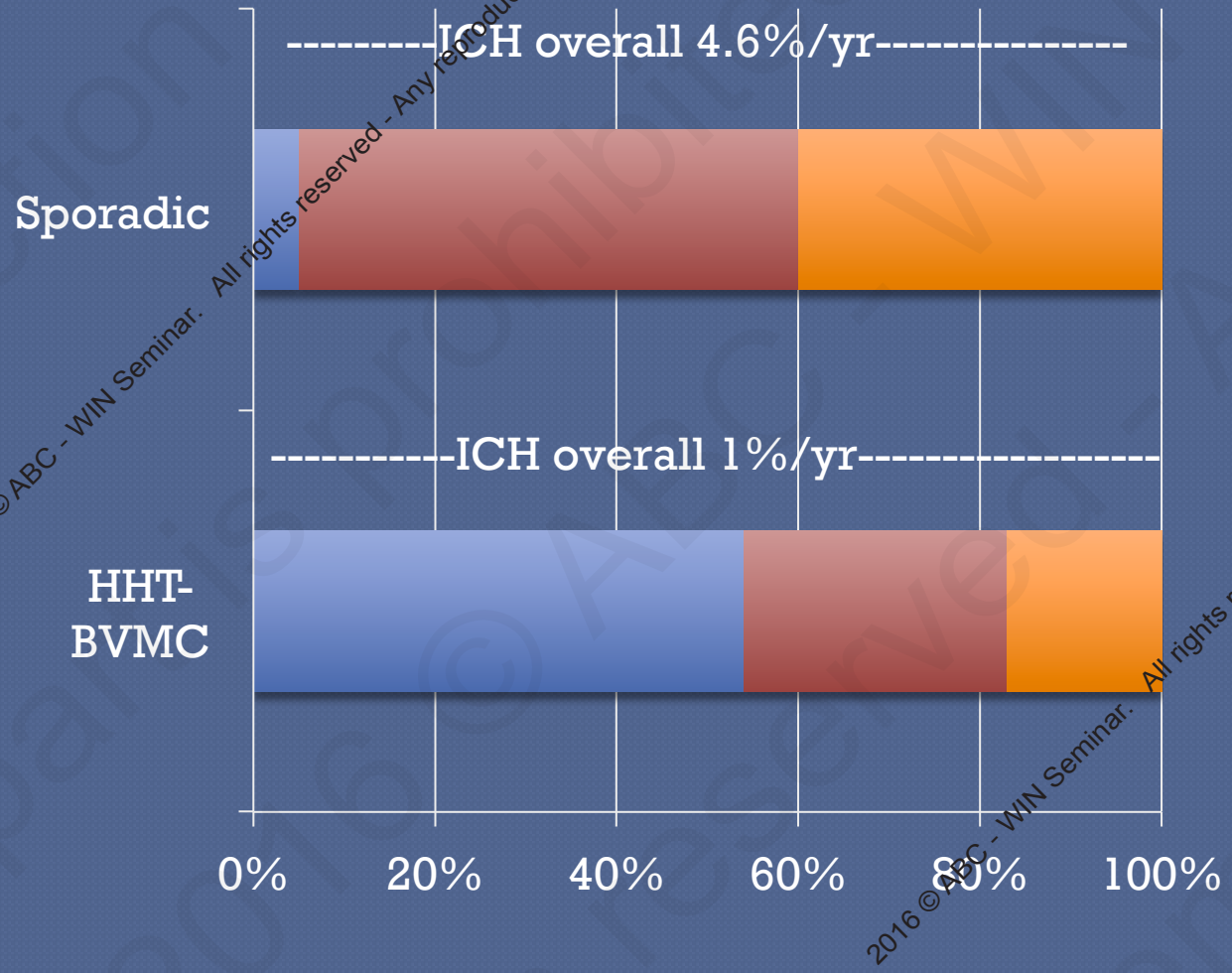
Helen Kim, PhD; Jeffrey Nelson, MS; Timo Krings, MD, PhD; Karel G. terBrugge, MD; Charles E. McCulloch, PhD; Michael T. Lawton, MD; William L. Young, MD†; Marie E. Faughnan, MD, MSc; the Brain Vascular Malformation Consortium (BVMC) HHT Investigator Group

Background and Purpose—Hereditary hemorrhagic telangiectasia (HHT) is a systemic disease characterized by mucocutaneous telangiectasias, epistaxis, and arteriovenous malformations (AVMs). Intracranial hemorrhage (ICH) rates in this population are not well described. We report ICH rates and characteristics in HHT patients with brain AVMs (HHT-BAVMs).

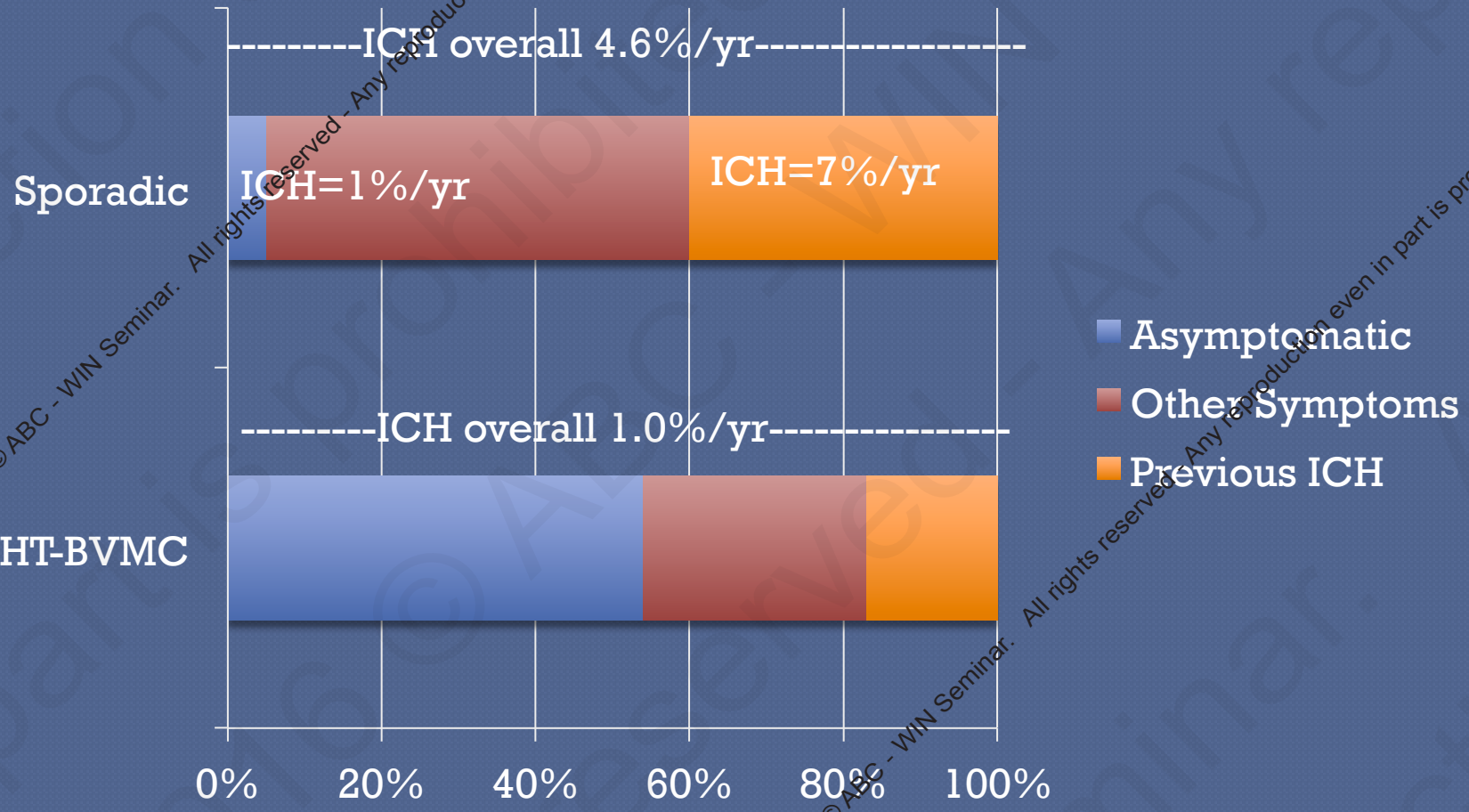
Methods—We studied the first 153 HHT-BAVM patients with follow-up data enrolled in the Brain Vascular Malformation Consortium HHT Project. We estimated ICH rates after BAVM diagnosis.

Results—The majority of patients were women (58%) and whites (98%). The mean age at BAVM diagnosis was 31±19 years (range, 0–70), with 61% of cases diagnosed on asymptomatic screening. Overall, 14% presented with ICH; among

brain AVM series:



Typical brain AVM series: screening bias



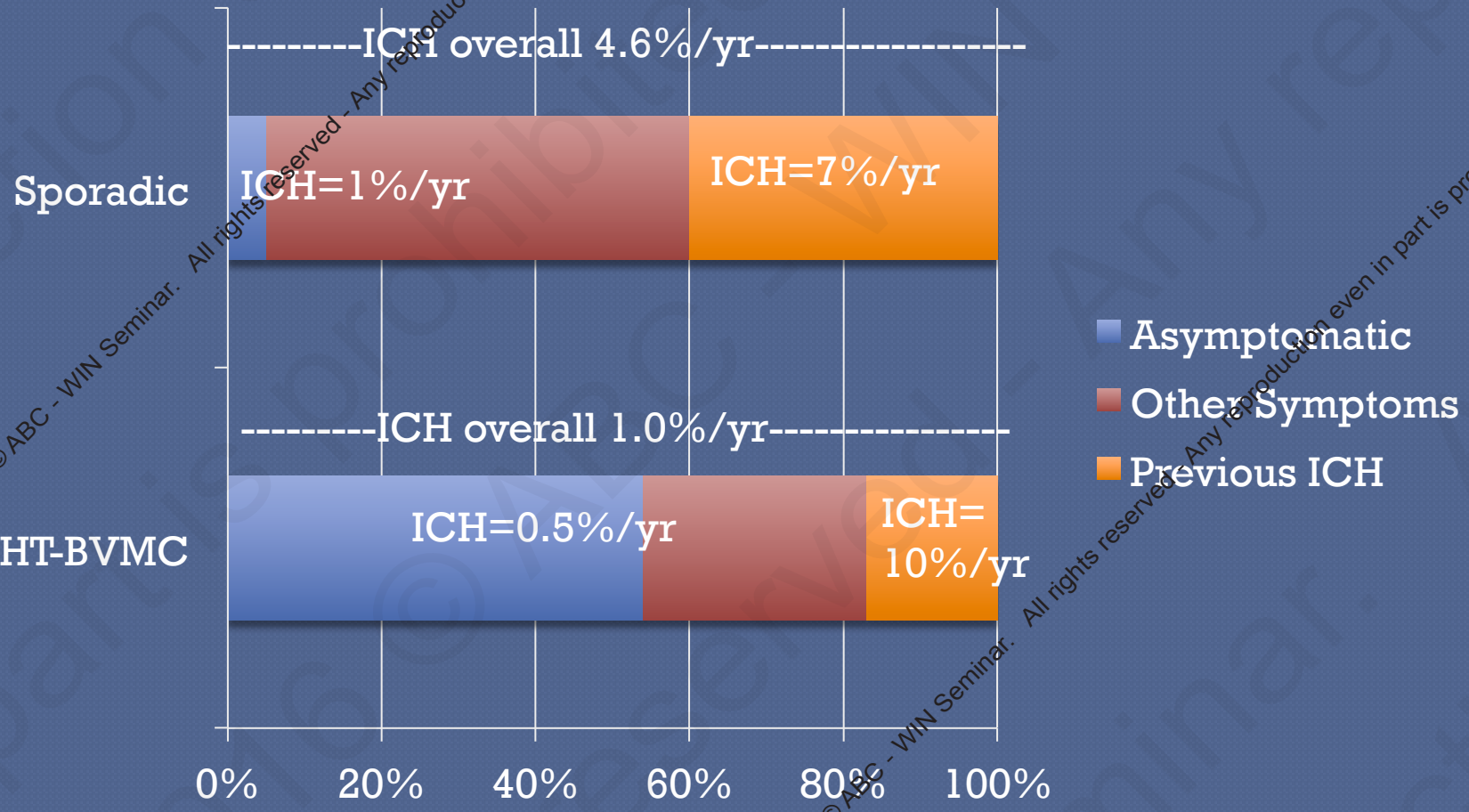
ICH in HHT

ICH rate: 1.04% per year (95% CI: 0.42 – 2.44%)

ICH-free survival differed significantly by ICH presentation (P=0.003)

Ruptured cases had a higher ICH rate (10.07%, 95% CI: 3.25 – 31.21%) than unruptured cases (0.43%, 95% CI: 0.11 – 1.73%).

Typical brain AVM series: screening bias



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Determine risk factors for hemorrhage in HHT BAVM patients

ORIGINAL RESEARCH
BRAIN

Neurovascular Manifestations in Hereditary Hemorrhagic Telangiectasia: Imaging Features and Genotype-Phenotype Correlations

T. Krings, H. Kim, S. Power, J. Nelson, M.E. Faughnan, W.L. Young, K.G. ter Brugge, and the Brain Vascular Malformation Consortium HHT Investigator Group

ABSTRACT

BACKGROUND AND PURPOSE: Hereditary hemorrhagic telangiectasia is an autosomal dominant disease that presents in 10%–20% of patients with various brain vascular malformations. We aimed to report the radiologic features (phenotype) and the genotype-phenotype correlations of brain vascular malformations in hereditary hemorrhagic telangiectasia.

MATERIALS AND METHODS: Demographic, clinical, genotypic, and imaging information of 75 patients with hereditary hemorrhagic telangiectasia with brain arteriovenous malformations enrolled in the Brain Vascular Malformation Consortium from 2010 to 2012 were reviewed.

Imaging Features in HHT

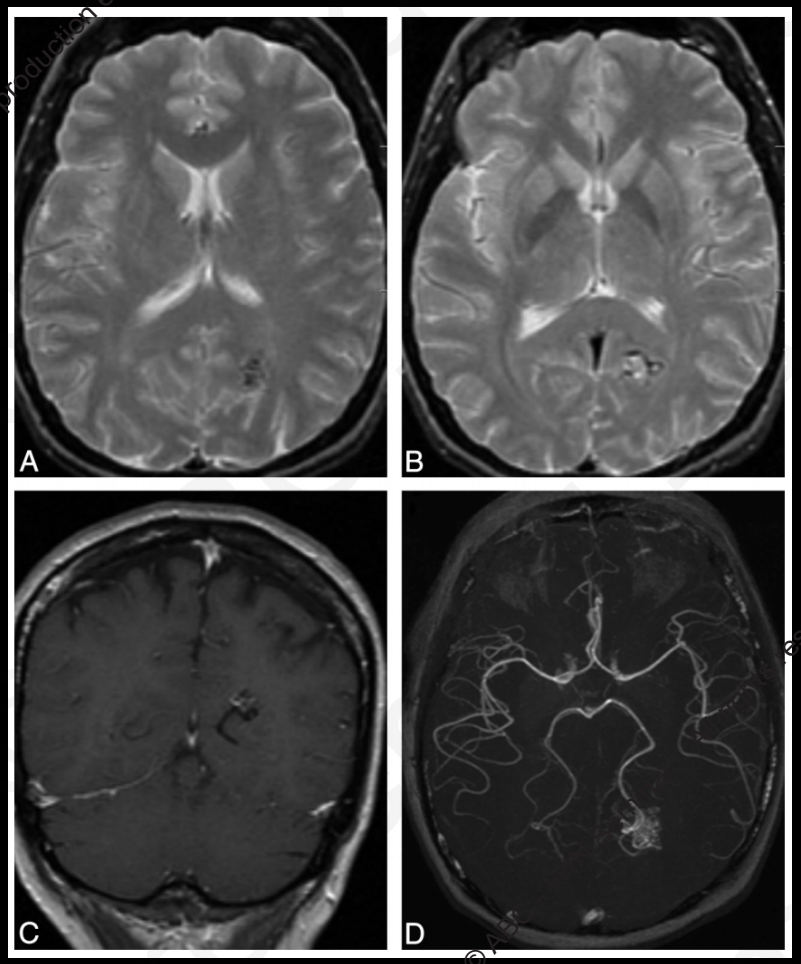
- Patients recruited to BVMC
  - Brain vascular malformation
  - Imaging available for review
  - Clinical history data

Imaging Features in HHT

Table 1: Overview of 75 subjects with HHT and brain vascular malformations

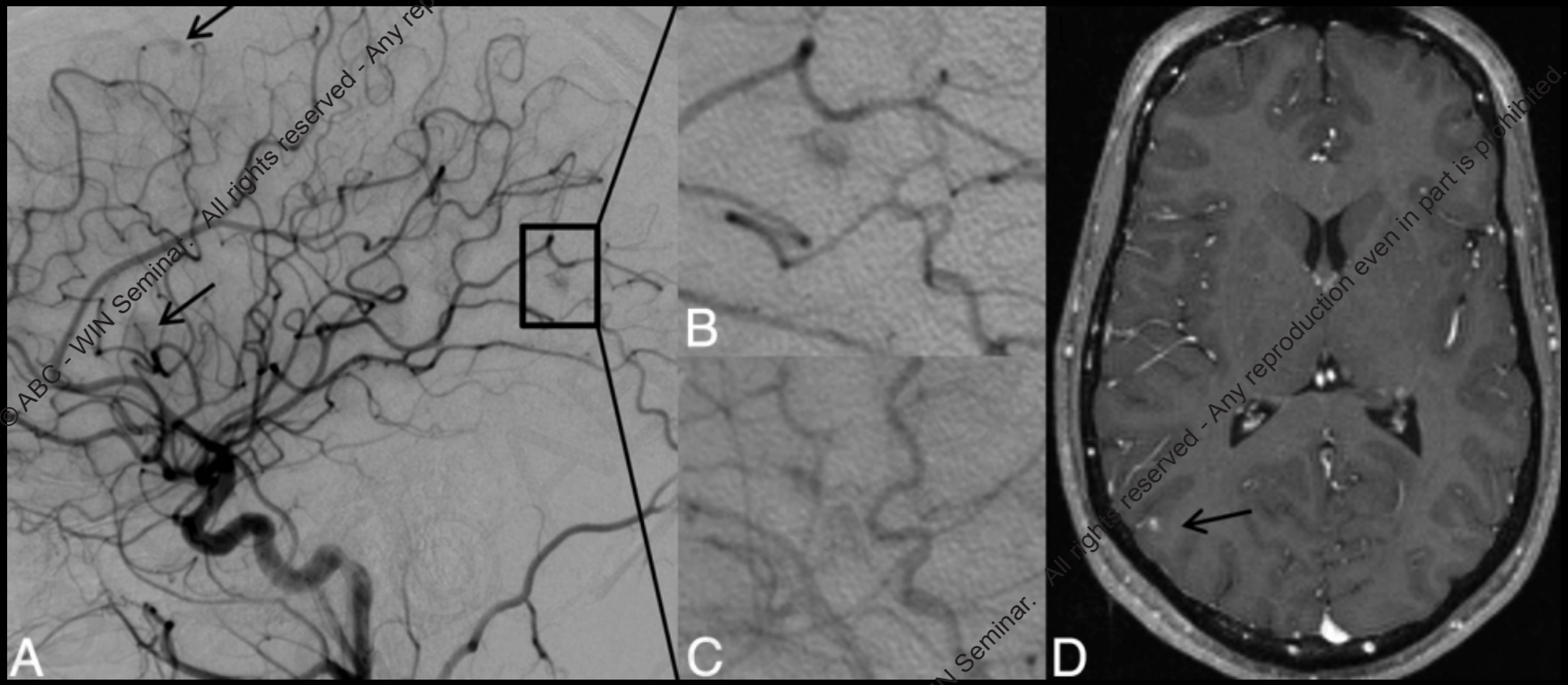
Characteristic	Summary[a]
Demographics	
Female sex	41/75 (55%)
Age at enrollment (yr) ($n = 75$)	36.6 ± 19.9
Age at brain malformation diagnosis (yr) ($n = 68$)	30.1 ± 19.7
HHT-related symptoms	
Epistaxis	66/73 (90%)
Anemia	20/72 (28%)
GI bleeding	5/67 (7%)
Pulmonary AVM	45/69 (65%)
Liver VM	4/66 (6%)
HHT-causing mutation	
ALK1	13/45 (29%)
Endoglin	27/45 (60%)
SMAD4	1/45 (2%)
All test findings negative	4/45 (9%)

Arteriovenous Malformation



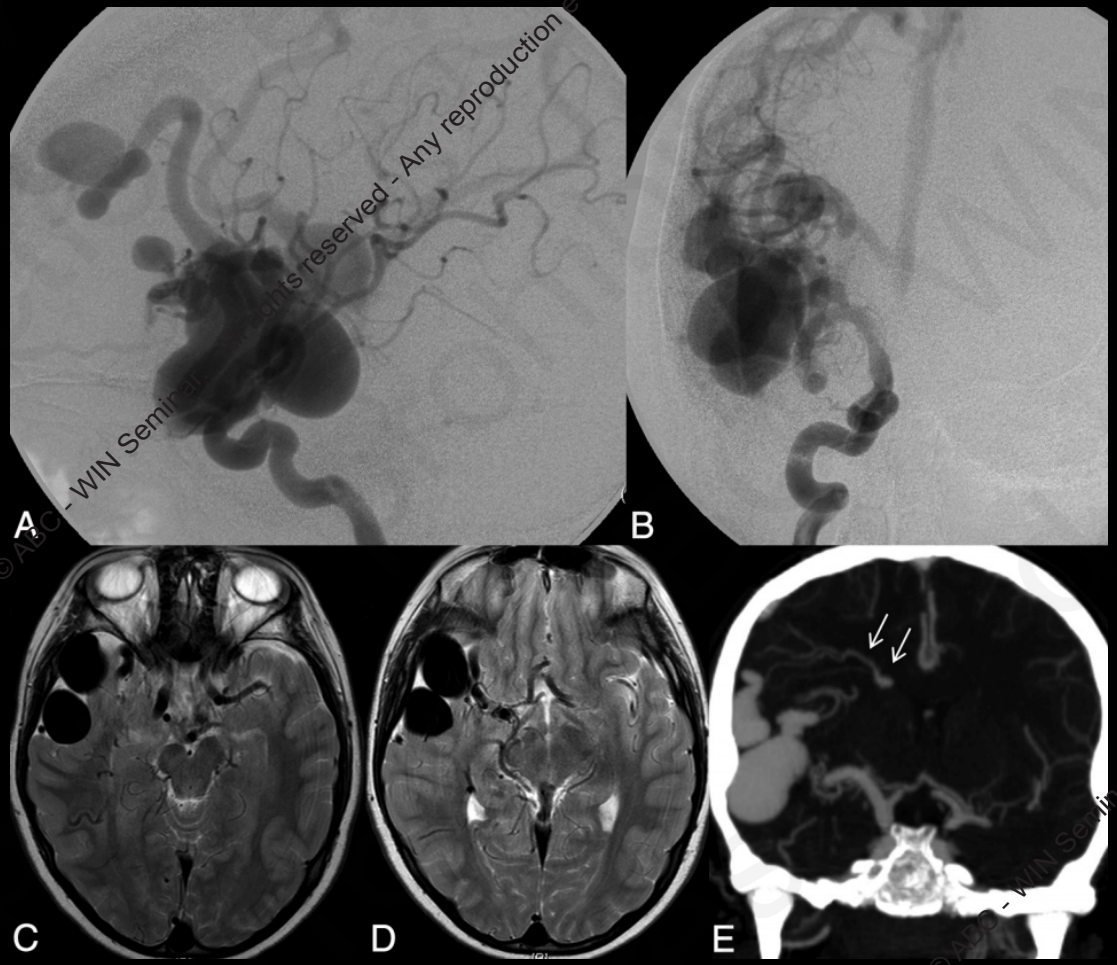
presence of a shunt with early filling of a vein through a dilated network of abnormal vessels

Capillary Malformation



no shunt was visible on angiography and no dilated feeding arteries or veins were identified; just a blush of abnormal vessels was seen in the capillary phase

Arteriovenous Fistula



absence of an intervening nidus between the feeding artery and draining vein in the presence of a shunt

Imaging Features

Largest series with detailed BAVM phenotype in HHT

- 76 patients, 125 brain VMs
- 61% capillary VMs
- 43% AVMs
- 11% AVFs (significantly younger)
- 44% multiple

➔Lesion type not associated with HHT gene mutation, sex

BAVM phenotype

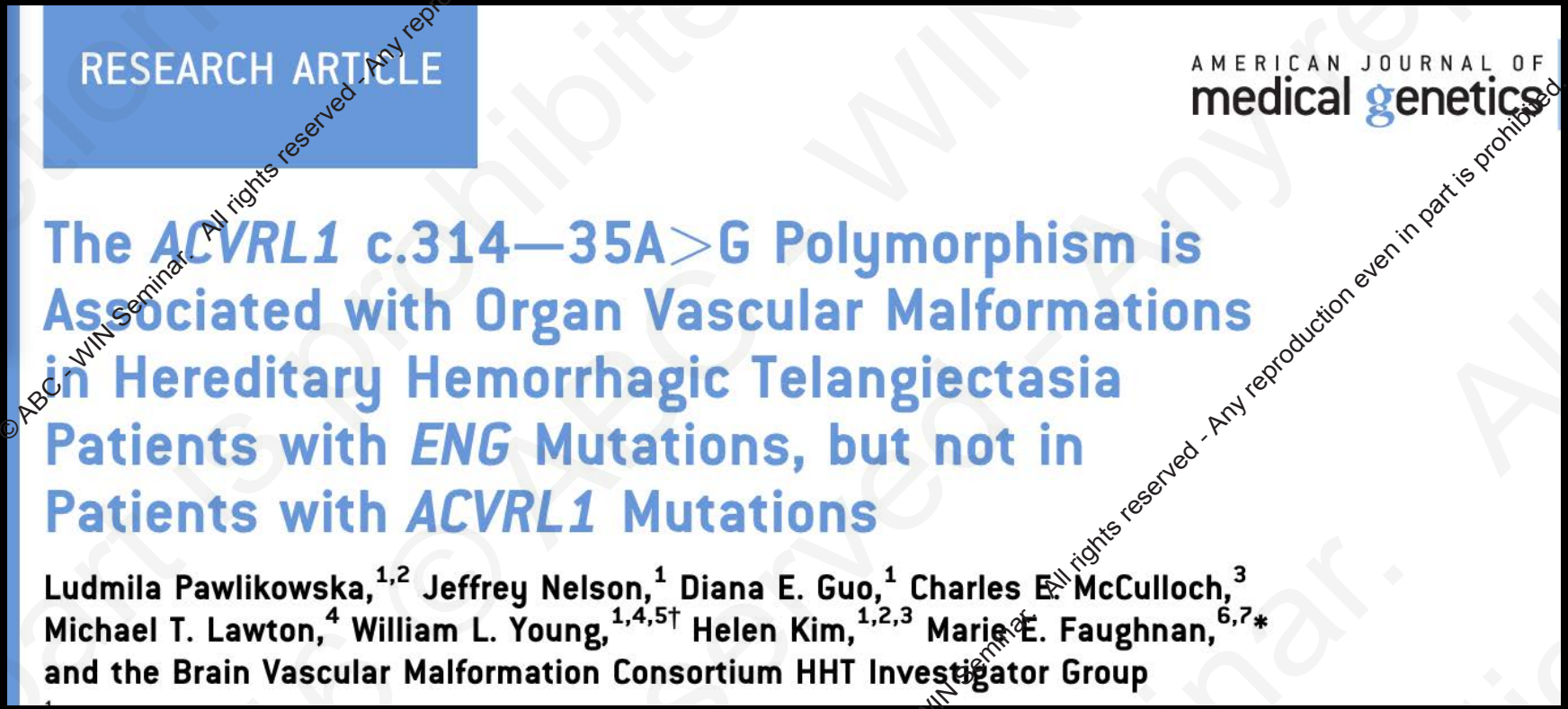
- Very group of lesions from sporadics
- The high proportion of capillary VMs…are these lower risk and driving the overall ICH rate down?
- Is lesion type a determinant of ICH in HHT? Size? Location? Venous drainage?

…can we separate high and low risk lesions?

Determinants of ICH

- Hemorrhagic presentation = determinant
- Angiographic features =?determinants
- Genes as determinants?
  - HHT gene mutation…no evidence yet
  - Genetic modifiers

Use of genotype as potential marker for increased ICH risk.



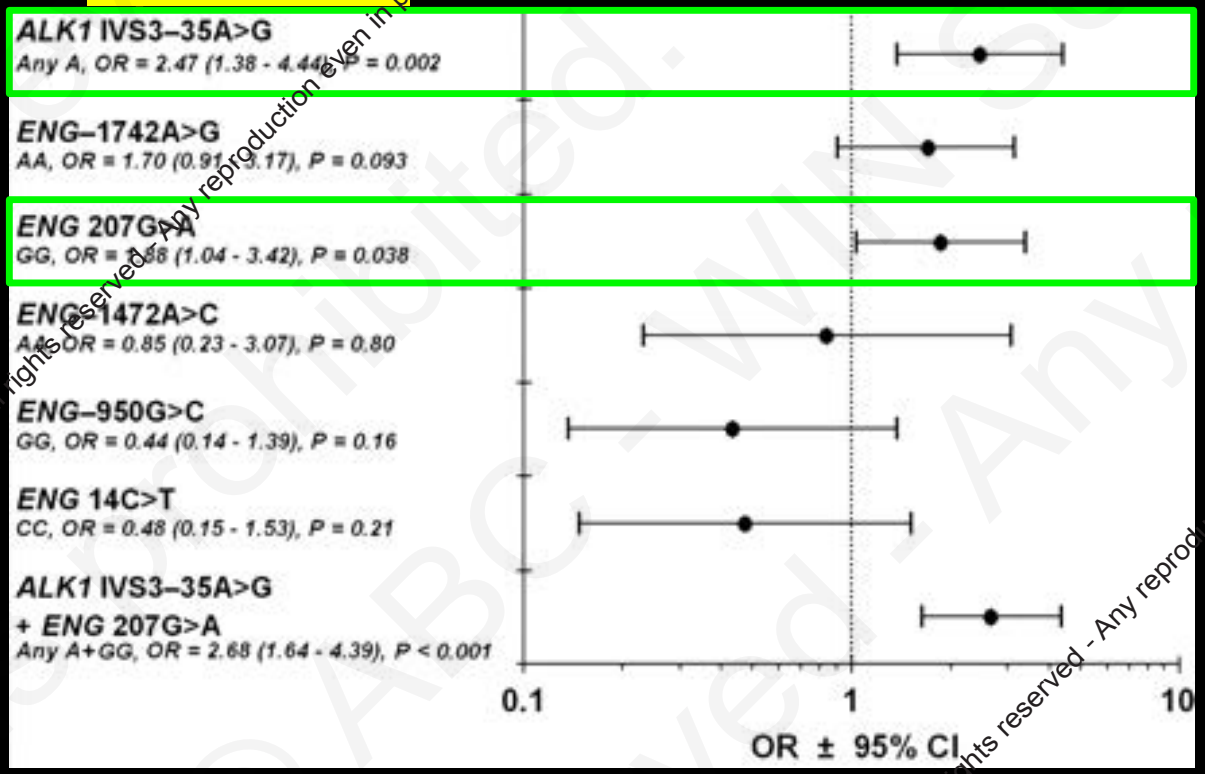
RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics

The *ACVRL1* c.314—35A>G Polymorphism is Associated with Organ Vascular Malformations in Hereditary Hemorrhagic Telangiectasia Patients with *ENG* Mutations, but not in Patients with *ACVRL1* Mutations

Ludmila Pawlikowska,[1,2] Jeffrey Nelson,[1] Diana E. Guo,[1] Charles E. McCulloch,[3] Michael T. Lawton,[4] William L. Young,[1,4,5†] Helen Kim,[1,2,3] Marie E. Faughnan,[6,7*] and the Brain Vascular Malformation Consortium HHT Investigator Group

ALK1 and *ENG* polymorphisms associated with sporadic BAVM: candidate SNPs



- Association of sporadic brain AVM with common polymorphisms in HHT genes ALK1 and ENG, *Pawlikowska et al Stroke 2005*
- *ALK1 IVS3-35A>G replication: Simon et al J Neurosurg 2006*

Association of *ALK1* IVS3-35A>G with AVM in HHT patients with *ENG* mutations

		All Subjects				*ALK1* Mutation				*ENG* Mutation			
Outcome	SNP	n	OR	95% CI	p	n	OR	95% CI	p	n	OR	95% CI	p
AVM	ALK1 IVS3-35A>G	689	1.34	0.87, 2.07	0.178	181	0.79	0.38, 1.63	0.520	209	**2.66**	**1.15, 6.13**	**0.022**
AVM	ENG 207G>A	689	1.10	0.70, 1.72	0.682	181	1.29	0.57, 2.93	0.537	209	0.41	0.12, 1.40	0.155
BAVM	ALK1 IVS3-35A>G	716	1.11	0.68, 1.80	0.675	189	1.03	0.33, 3.16	0.960	211	0.74	0.36, 1.52	0.411
BAVM	ENG 207G>A	716	1.19	0.73, 1.93	0.482	189	3.09	0.63, 15.1	0.163	211	0.62	0.29, 1.32	0.215
PAVM	ALK1 IVS3-35A>G	690	1.48	0.90, 2.22	0.062	183	0.57	0.25, 1.33	0.192	208	**2.45**	**1.18, 5.06**	**0.016**
PAVM	ENG 207G>A	690	1.29	0.86, 1.93	0.220	183	0.91	0.36, 2.27	0.835	208	1.80	0.86, 3.77	0.122
LAVM	ALK1 IVS3-35A>G	677	1.46	0.85, 2.50	0.170	182	1.57	0.65, 3.81	0.320	203	**n/a***	**3.10, ∞***	**0.001***
LAVM	ENG 207G>A	677	1.05	0.62, 1.79	0.856	182	1.17	0.44, 3.10	0.758	203	0.55	0.16, 1.85	0.332

- Association with risk genotypes for sporadic BAVM (adjusted for age, gender, family clustering)
- *all 21/21 LAVM + had risk genotypes

- *Pawlikowska et al, Am J Med Genetics A, 2015 in press*

GENETIC MODIFIERS IN HHT

These results suggest:

Common polymorphisms in HHT genes other than the mutated gene modulate phenotype severity of HHT disease, specifically presence of organ VMs.

Ongoing and Future: Testing other genetic modifiers identified for sporadic BAVM, ICH and for PAVM in HHT.

CONCLUSION AND OPINION ☺

Not all brain VMs in HHT have the same natural history.

Task: In order to move forward with patient care decisions about brain VMs in people with HHT, we need to continue to dissect the factors associated with hemorrhage, from genetic modifiers to imaging features, so that we can adequately estimate the risk for an individual patient…

How: Continued collaboration, multicentre, large numbers, long follow-up.

UNDERDIAGNOSIS IN HHT

- Many families/people with HHT have not been diagnosed: approximately 2/3 undiagnosed in US
- Large time delays to diagnosis:
  - 30 years from first symptoms
  - 15 years from first ENT consult
- Diagnosis allows for family screening and treatment

How can the neuroradiologist help?

Grosse et al. Gen Med 2014
Latino G et al. OJRD 2014
Pierucci P. et al, OJRD 2012

BAVM MULTIPLICITY AND HHT

Table 2. Univariate Analysis of Risk Factors for Predicting HHT in Patients With bAVM

Variable	No.	OR	95% CI	*P*
Age, decade	1937	0.77	0.65–0.91	0.002
Gender, male	1989	0.65	0.38–1.12	0.122
Hemorrhagic presentation	1989	0.58	0.32–1.04	0.068
Symptomatic Presentation	1985	0.54	0.30–0.96	0.035
Multiple bAVM	1989	82.74	39.53–173.19	<0.001
Angiography	1983	1.37	0.66–2.83	0.380

Bharatha A et al. Stroke 2011

MULTIPLICITY= OPPORTUNITY FOR DIAGNOSIS

The presence of multiple brain AVMs is highly predictive of HHT…

"This is HHT until proven otherwise"

THANK YOU!

- The organizing committee
- HHT patients everywhere
- Colleagues and Collaborators
- Mentors