Case Report

폐동맥고혈압 동반 유전출혈모세혈관확장증

ACVRL1 Mutation에 의한 HHT type 2 및 PAH 증례

정정희 | 서울아산병원 호흡기내과 | 2026.5.27

PART I

Case 1

Patient Profile (2007)

Age/Sex

40Y, F

C.C/Onset

DOE (NYHA functional class I), 4YA

Past medical history

N/S

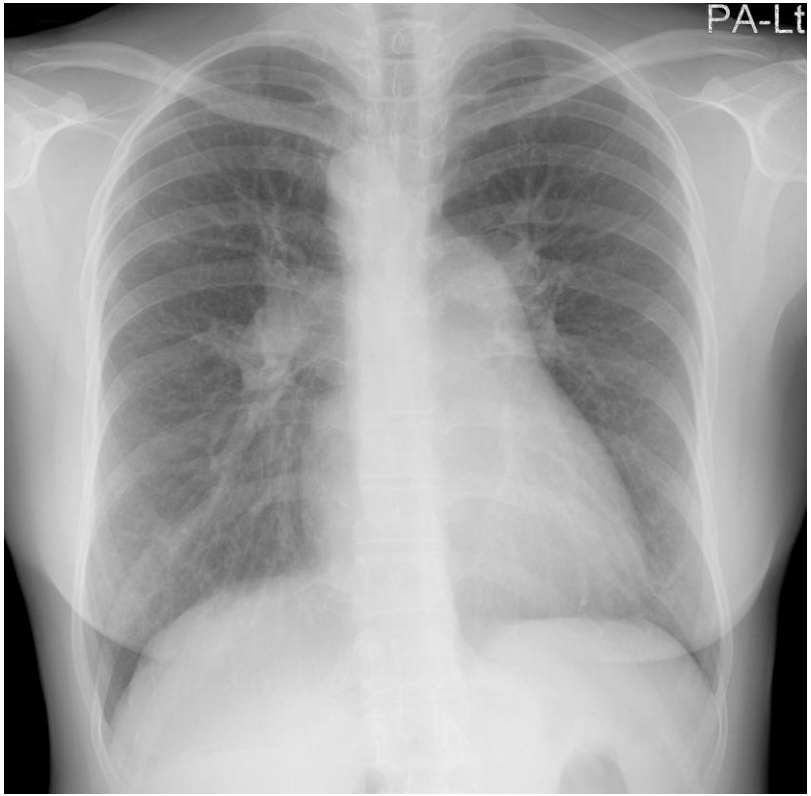
Family history

N/S

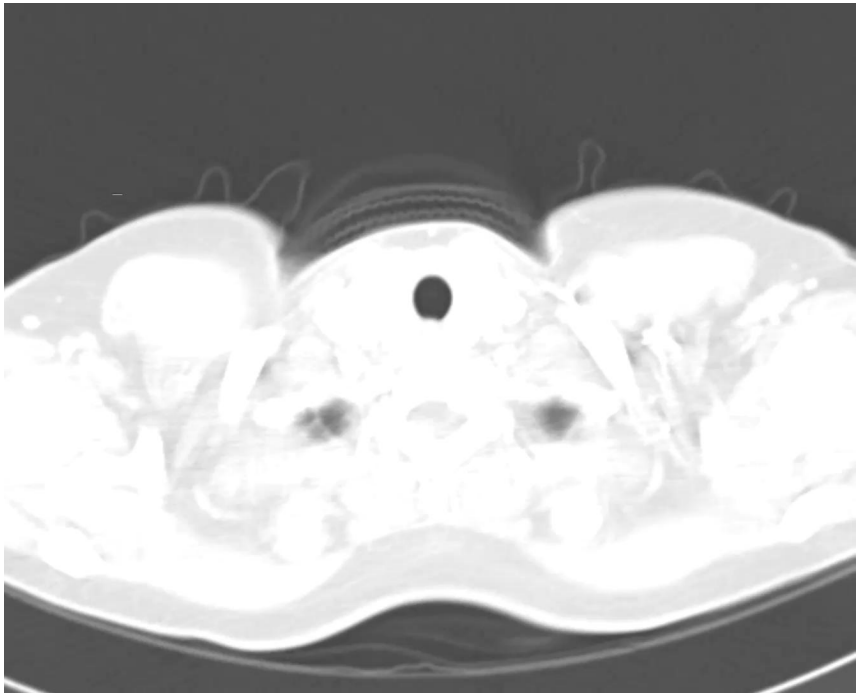
Vital Signs

Blood Pressure	**160/98 mmHg**
Heart Rate	**92 bpm**
Respiratory Rate	**24 /min**
Body Temperature	**37.1 ℃**

Initial Workup



Initial Chest X-ray



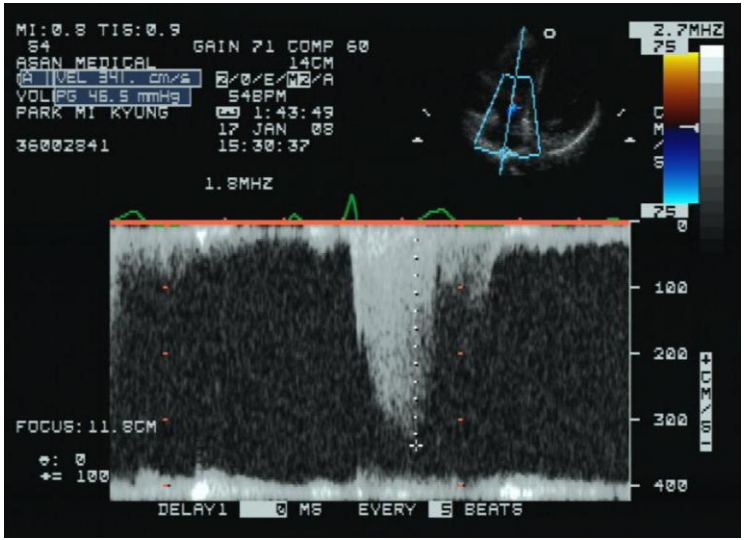
Initial Chest CT

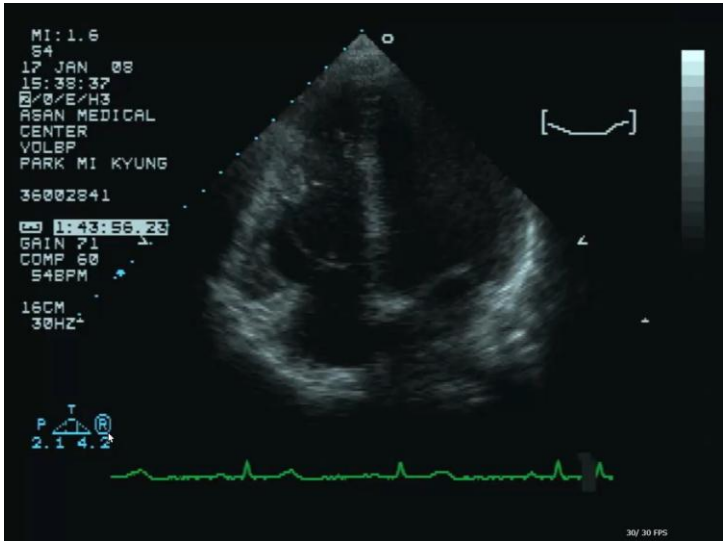
CBC, Chemistry

WBC (Qn)[ChemR-I],Blood	4.5
RBC (Qn)[ChemR-I],Blood	4.65
Hb (Qn)[ChemR-I],Blood	12.9
Hct (Qn)[ChemR-I],Blood	39.0
MCV (Qn)[ChemR-I],Blood	83.9
MCH (Qn)[ChemR-I],Blood	27.7
MCHC (Qn)[ChemR-I],Blood	33.1
RDW (Qn)[ChemR-I],Blood	16.1
Platelet (Qn)[ChemR-I],Blood	229

Total calcium (Qn)[ChemR-I],Blood	8.9
Phosphorus (Qn)[ChemR-I],Blood	3.8
Glucose (Qn)[ChemR-I],Blood	106
Creatinine (Qn)[ChemR-I],Blood	0.7
BUN (Qn)[ChemR-I],Blood	14
Uric acid (Qn)[ChemR-I],Blood	3.1
Total cholesterol (Qn)[ChemR-I],Blood	148
Total protein (Qn)[ChemR-I],Blood	7.4
Albumin (Qn)[ChemR-I],Blood	3.9
AST(SGOT) (Qn)[ChemR-I],Blood	20
ALT(SGPT) (Qn)[ChemR-I],Blood	15
Alkaline phosphatase (Qn)[ChemR-I],Blood	42
γ-GT (Qn)[ChemR-I],Blood	14
Total bilirubin (Qn)[ChemR-I],Blood	0.8
Sodium (Qn)[EM],Blood	141
Potassium (Qn)[EM],Blood	4.0
Chloride (Qn)[EM],Blood	107
Total CO2 (Qn)[ChemR-I],Blood	22.3
eGFR(MDRD) (Qn),Blood	≥90

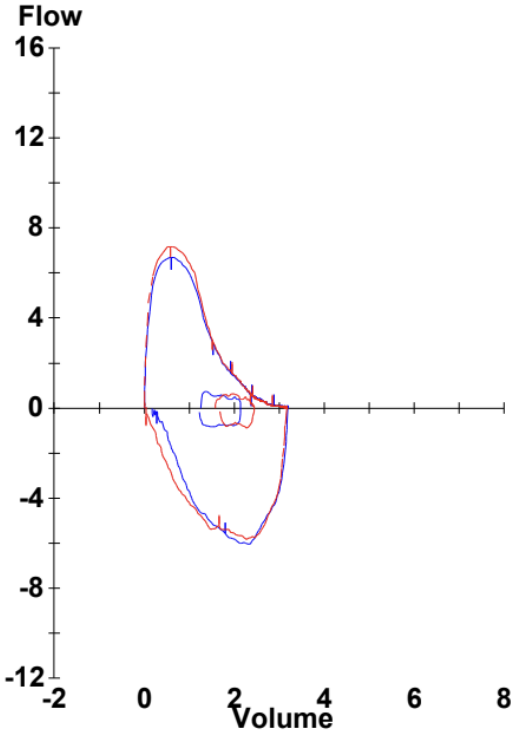
Transthoracic Echocardiography





TR V_{max} 3.4 m/s, PG 46 mmHg
Mild resting PH
Slightly decreased RV contractility
Normal LA/LV

Pulmonary Function Test



Spirometry

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
FVC	Liters	3.41	3.21	94	3.18	93	-1
FEV1	Liters	2.65	2.42	91	2.44	92	1
FEV1/FVC	%	77	75		77		
FEF25-75%	L/sec	3.10	1.92	62	2.09	67	9
IsoFEF25-75	L/sec	3.10	1.92	62	2.07	67	8
PEF	L/sec	6.08	6.68	110	7.16	118	7
FET100%	Sec		9.46		10.91		15
FVL ECode			000000		000000		
MVV	L/min	106					
f	BPM						

Right Heart Catheterization (2008)

RHC result

Parameter	2008
mPAP	35 mmHg
PAWP	23 mmHg
CO	6.8 L/min

⚠ Diagnostic Dilemma

1. PAWP 23 mmHg
   → post-capillary pattern
2. CT상 GGO + septal thickening
   → PVOD 배제 불가
3. Vasodilator 치료 보류,
   경과관찰

PART II

Clinical Progress

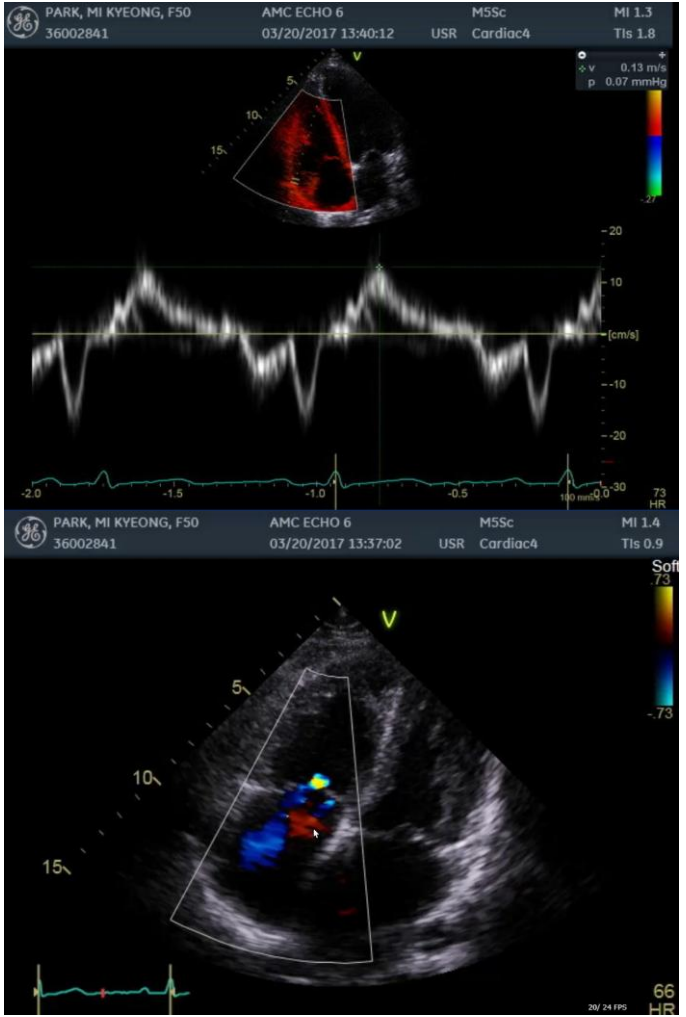
Re-workup (2018)

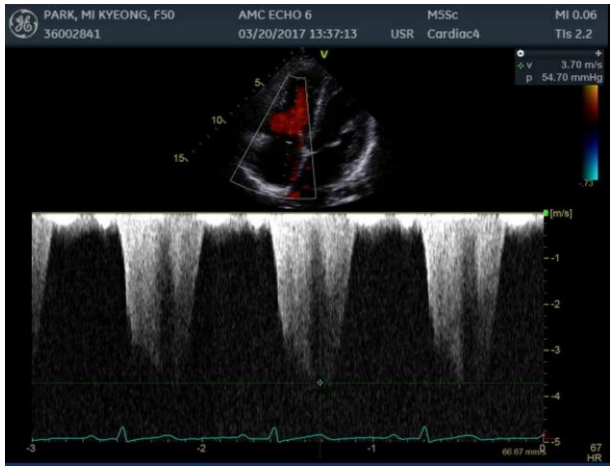
RHC results

Parameter	2008	2017
mRAP	—	6 mmHg
mPAP	35 mmHg	**39 mmHg**
PAWP	23 mmHg	**10 mmHg**
CO	6.8 L/min	6.0 L/min
PVR	—	**4.7 WU**
$S_{cv}O_2$	—	67%

TTE results

Parameter	2007	2017
TR V_{max}	3.4 m/s	**3.7 m/s**
PG	46 mmHg	**55 mmHg**
Resting PH	mild	**moderate**
RA/RV	Sl. decreased	Normal
LA/LV	Normal	Normal





Diagnosis of IPAH

1. Pre-capillary PAH, PVR 4.7WU
   → IPAH 기준 충족, PVOD 배제됨

2. Macitetan 치료 시작 (2017.05~)

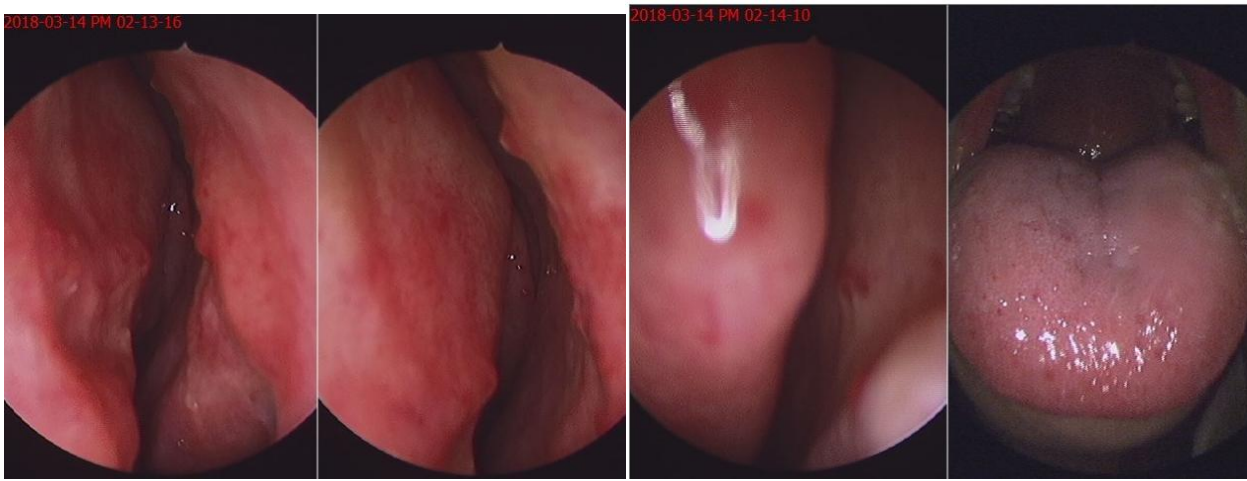
Development of New Symptom (2018)

C.C

Recurrent epistaxis

Vital sign

- BP 150/76 mmHg
- HR 87bpm
- RR 20/min
- BT 37.1°C



Nasal examination :
multiple telangiectatic lesions

CBC

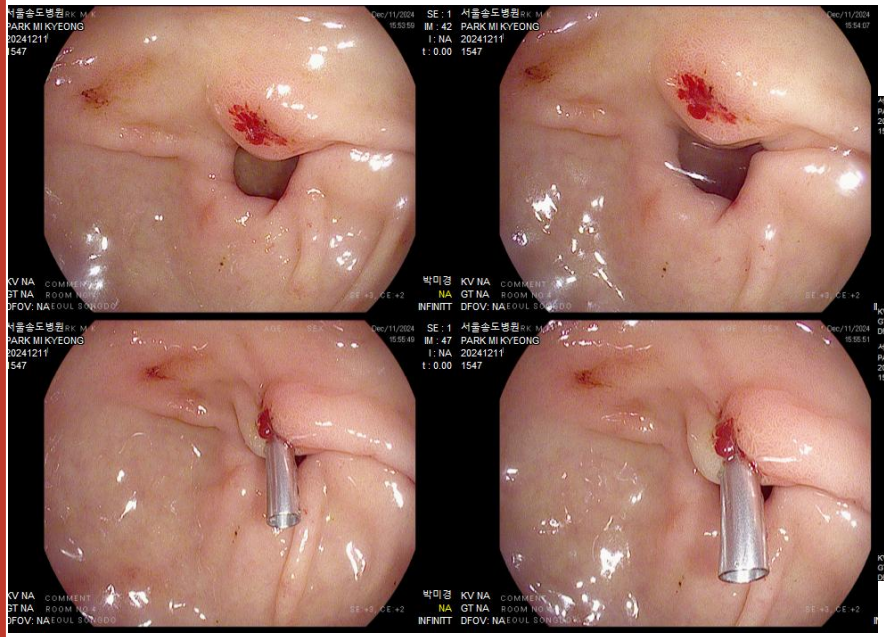
AC0089	WBC (Qn)[ChemR-I],Bl...	4.1		4	10	x10³/uL
AC0090	RBC (Qn)[ChemR-I],Bl...	3.65	▼	4	5.4	x10^...
AC0091	Hb (Qn)[ChemR-I],Blood	6.5	▼	12	16	g/dl
AC0092	Hct (Qn)[ChemR-I],Blood	24.0	▼	36	48	%
AC0157	MCV (Qn)[ChemR-I],B...	65.8	▼	80	100	fl
AC0158	MCH (Qn)[ChemR-I],B...	17.8	▼	26	32	pg
AC0159	MCHC (Qn)[ChemR-I],...	27.1	▼	32	36	%
AC0123	RDW (Qn)[ChemR-I],B...	22.6	▲	11.5	14.5	%
AC0093	Platelet (Qn)[ChemR-I...	254		150	350	x10³/uL

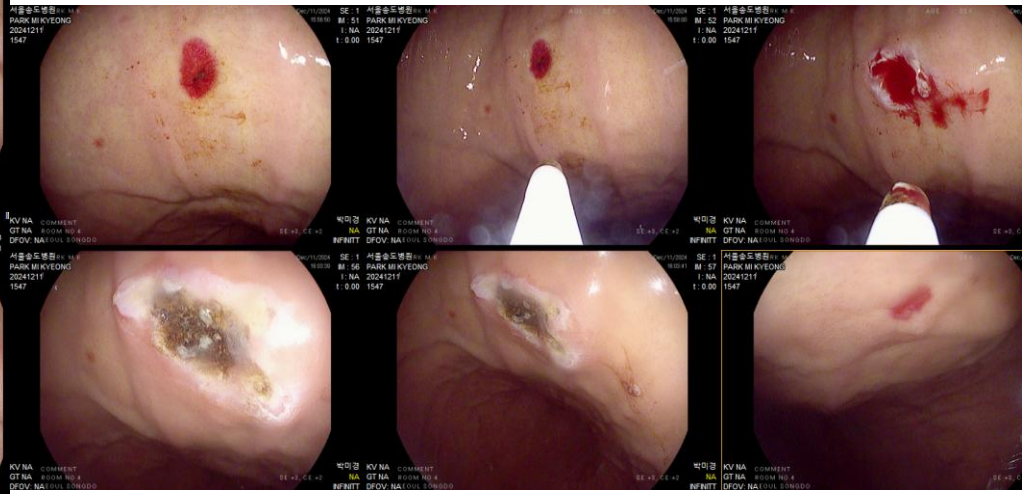
BC0018	Iron (Qn)[ChemR-I],Bl...	16	▼	50	130	ug/dL
BC0019	TIBC (Qn)[ChemR-I],Bl...	526	▲	280	400	ug/dL
BC0071	Ferritin (Qn),Blood	4.4	▼	10	290	ng/ml

Diagnosis of IDA

→ Started iron supplement

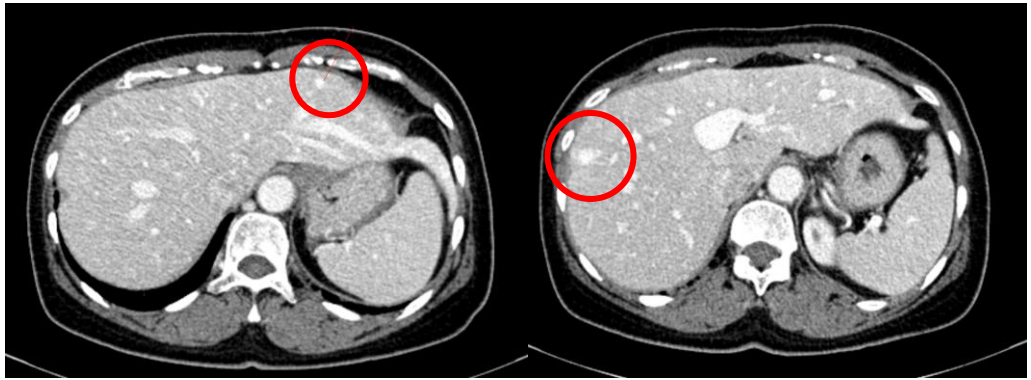
Outside EGD (2024)



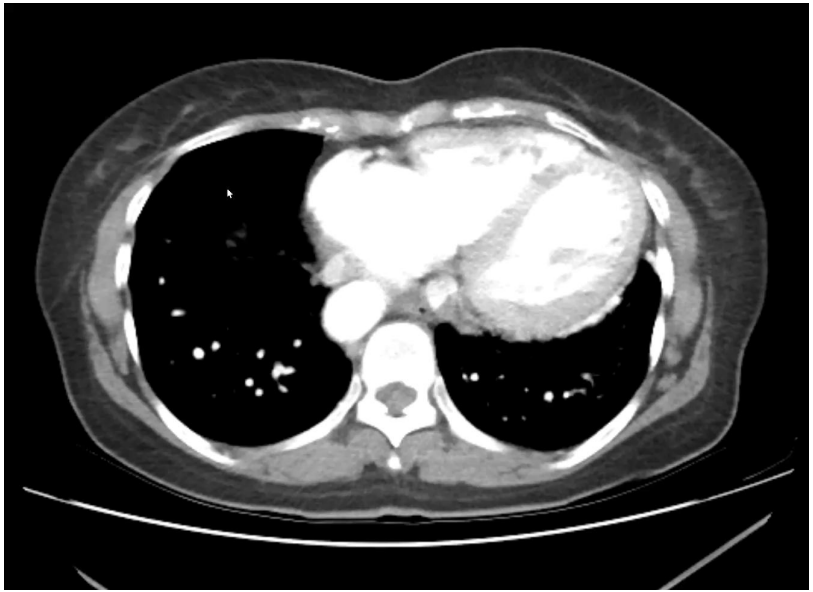


Multiple angiodysplasia in stomach, duodenum; erosion at antrum
→ s/p APC, endoscopic clipping (2024.12)

Hepatic Arterioportal Shunts (2025)



2025.5 Adrenal CT



2025.12 Liver dynamic CT

Curaçao's diagnostic criteria for Hereditary Hemorrhagic Telangiectasia (HHT, Rendu-Osler-Weber syndrome)

(Shovlin C.L. et al., . Am. J. Med. Genet. 91:66-67, 2000)

1. Epistaxis: spontaneous, recurrent nose bleeds

2. Telangiectases: multiple, at characteristic sites (lips, oral cavity, fingers, nose)

3. Visceral lesions such as gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformation (AVM), hepatic AVM, cerebral AVMs, spinal AVM

4. Family history: a first degree relative with HHT according to these criteria

Diagnosis of HHT
Definite: 3 criteria are present
Possible or suspected: 2 criteria are present
Unlikely: <2 criteria are present

Gene Mutation Tests (2025)

ACVRL1 gene mutation

검사명 : ACVRA1 gene mutaiton

진단명 : Hereditary Hemorrhagic Telangiectasia
유전자 : ACVRL1 on 12q13.13.
검사방법 : PCR-Sequencing
유전방식 : 상염색체우성유전
검체 : PB
OMIM Disease : #187300
OMIM Gene : *601284
GeneBank NT : NG_009549.1
GeneBank NM : NM_000020.3

[Result]
Heterozygous LP, c.920C>A (p.A307E) was detected in ACVRL1.

[Interpretation]
1. Hereditary Hemorrhagic Telangiectasia 2 (HHT2)는 ACVRL1 (activin A receptor, type II-like 1) 유전자의 돌연변이에 의합니다 (1).

2. ACVRL1 유전자의 돌연변이 여부를 확인하기 위하여, ACVRL1 유전자의 10개의 exon 및 exon-intron boundary에 대한 염기서열을 분석하였습니다.

3. 염기서열 분석 결과, 본 검사대상자는 ACVRL1 유전자의 exon7에서 c.920C>A (p.Ala307Glu) (p.A307E) 변이를 이형접합자로 보였습니다.

c.920C>A (p.A307E) (rs863223411)는 ClinVar에 병인 변이로 보고된 변이로, likely pathogenic (LP, PM1 PM2 PP3 PP5)으로 분석되는 돌연변이입니다 (2).

4. 본 검사대상자는 ACVRL1 유전자의 c.920C>A (p.A307E) 이형접합자 LP 돌연변이에 의한 HHT2 환자입니다.

5. 가족구성원에 대한 유전상담이 필요합니다.

ENG gene mutation

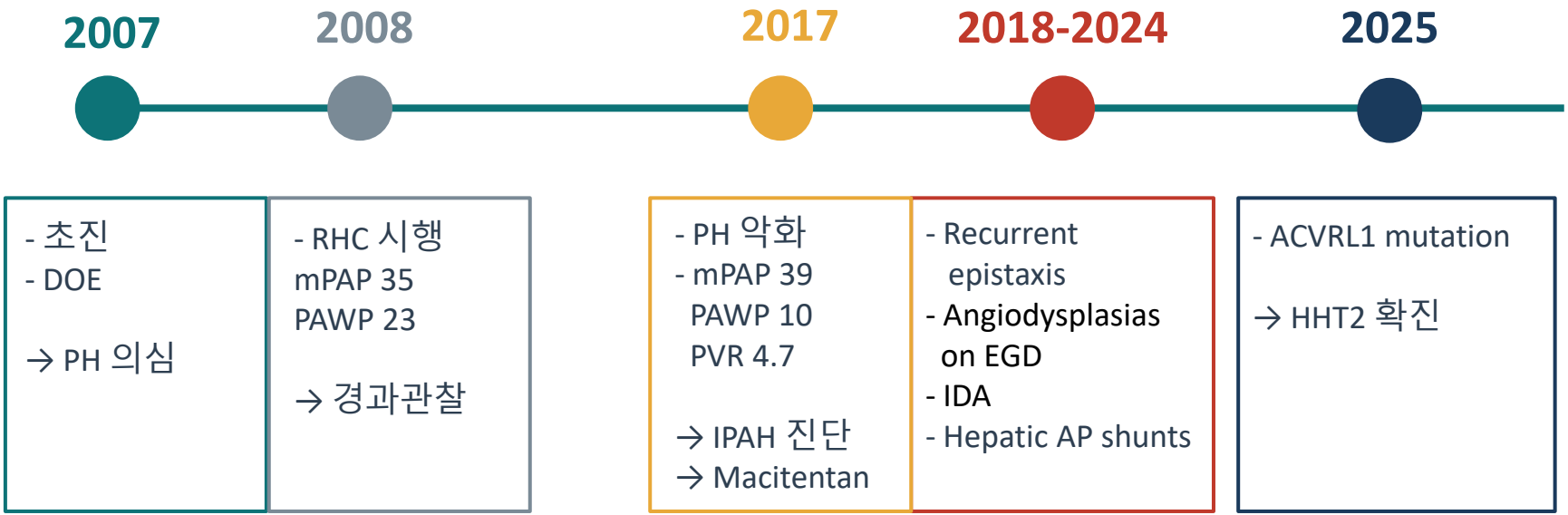
검사명 : ENG gene mutation

진단명 : Hereditary hemorrhagic telangiectasia
유전자 : ENG on 9q34.1
검사방법 : PCR-Sequencing
유전방식 : 상염색체우성유전
검체 : PB
OMIM Disease : #187300
OMIM Gene : *131195
GeneBank NT : NT_008470.20
GeneBank NM : NM_000118.3

[Result]
No mutation was detected in coding region of ENG gene.

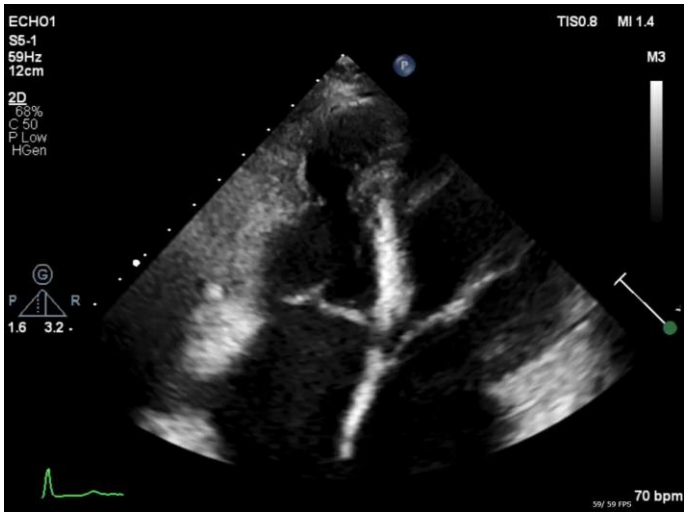
→ **Diagnosis of HHT type 2**

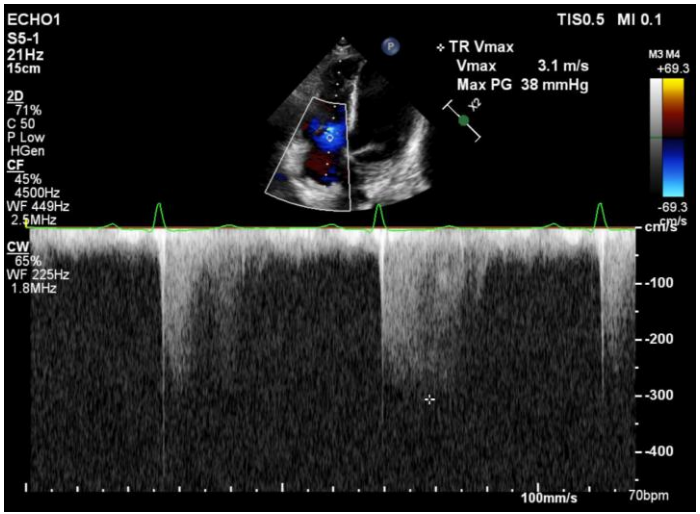
Summary of Clinical Timeline



Current Status (2026)

- Macitentan for 9 years, stable course without significant worsening
- ACVRL1 mutation → On family genetics consultation
- Last TTE (2026.3)
  - Enlarged RV with preserved contractility
  - mild PH (TR V_{max} 3.1m/sec, no IVC plethora)
  - LA enlargement, normal LV





PART I

Case 2

Patient Profile (2026.4)

Age/Sex

52Y, F

C.C/Onset

Epistaxis, 4YA

Past medical history

IPAH

Family history

N/S

Vital Signs

Blood Pressure	**104/62 mmHg**
Heart Rate	**60 bpm**
Respiratory Rate	**16 /min**
Body Temperature	**36.3 ℃**

Past history

1995 임신 중 hemoptysis 발생, IPAH 진단, Warfarin 복용

2005 f/up loss

2013.8 hemoptysis로 재내원

TTE 상 PH 악화되어 volibris 투약 → 6개월 후 f/up loss

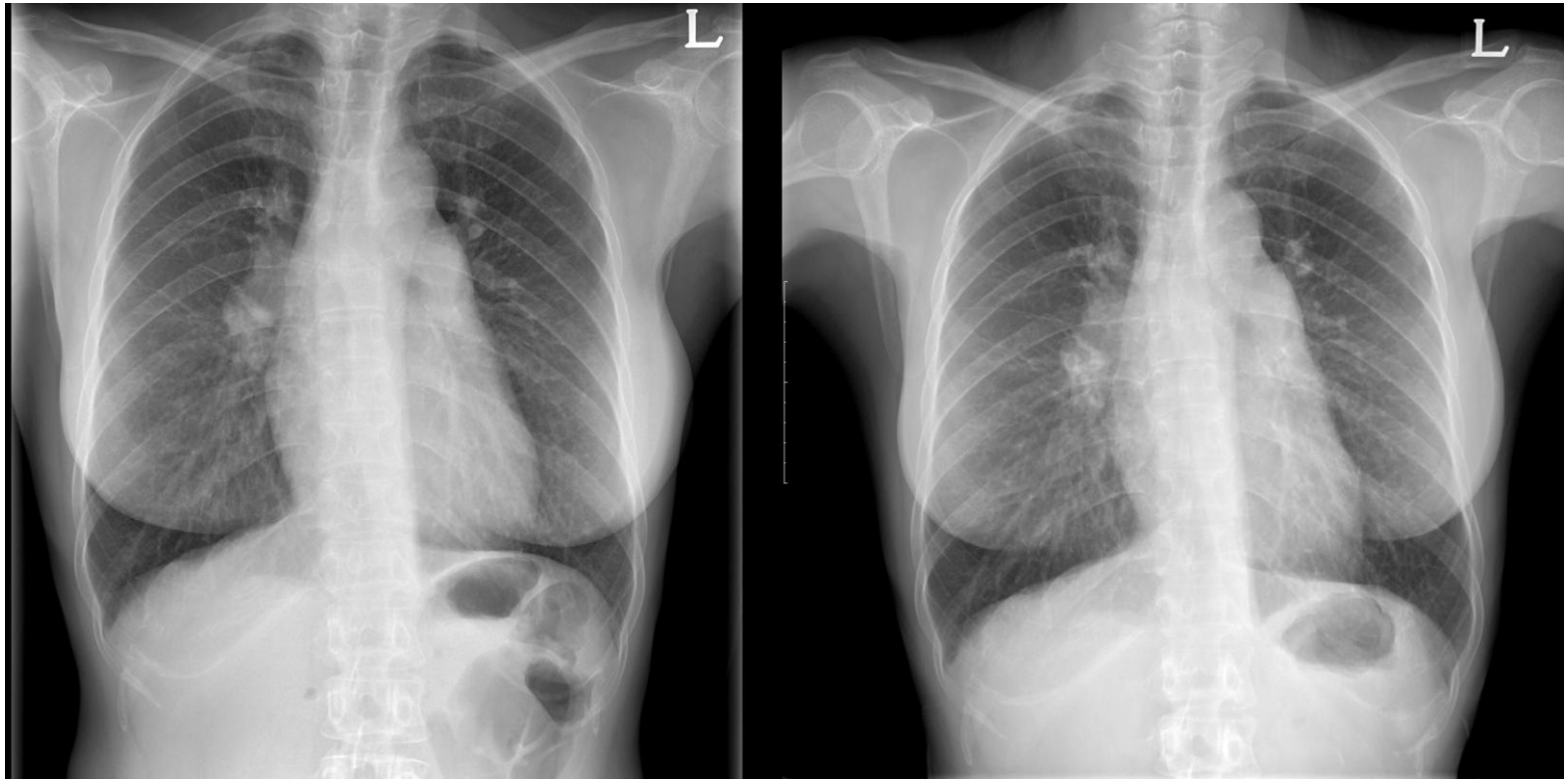
2018.5 치료 다시 원하여 내원, volibris 재투약 → 3개월 후 loss

2022.5 코피로 타원 응급실 방문.

다시 본원 추적 시작. Opsumit 투약 → 1개월 후 loss

2026.4 반복적인 코피로 재내원

Chest PA



2026.4

2022.5

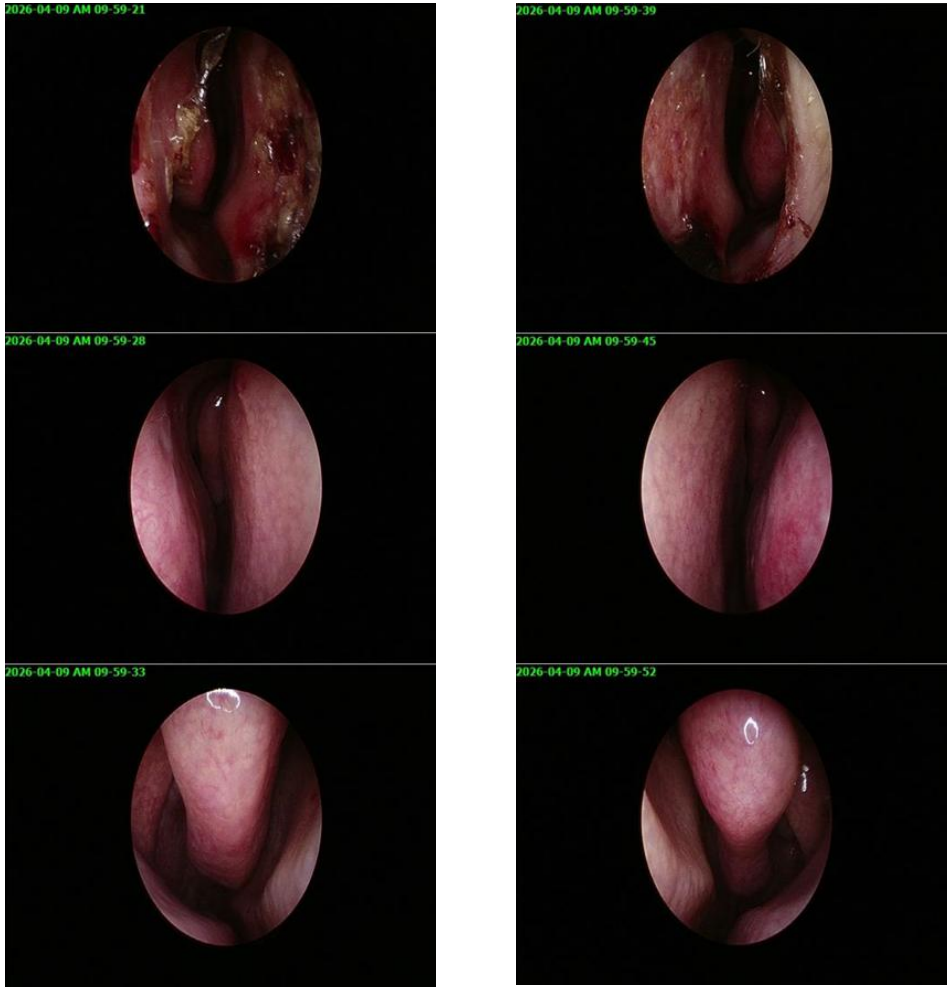
CBC, Chemistry

WBC (Qn)[ChemR-I],Blood	5.2
RBC (Qn)[ChemR-I],Blood	4.36
Hb (Qn)[ChemR-I],Blood	12.8
Hct (Qn)[ChemR-I],Blood	39.0
MCV (Qn)[ChemR-I],Blood	89.4
MCH (Qn)[ChemR-I],Blood	29.4
MCHC (Qn)[ChemR-I],Blood	32.8
RDW (Qn)[ChemR-I],Blood	13.2
Platelet (Qn)[ChemR-I],Blood	169

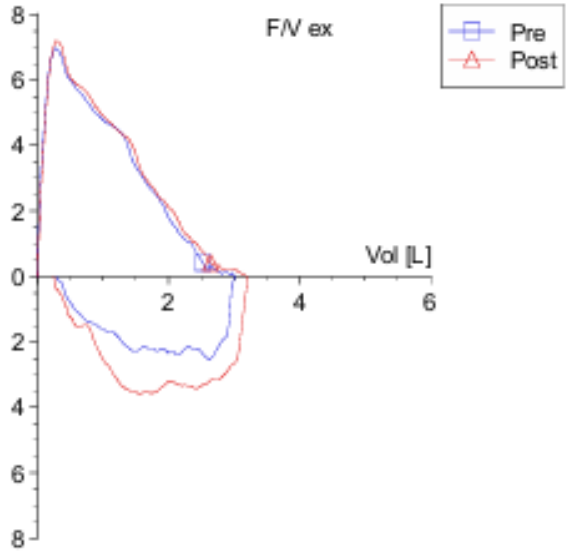
Total calcium (Qn)[ChemR-I],Blood	9.6
Phosphorus (Qn)[ChemR-I],Blood	2.8
Glucose (Qn)[ChemR-I],Blood	143
Creatinine (Qn)[ChemR-I],Blood	0.71
BUN (Qn)[ChemR-I],Blood	15
Uric acid (Qn)[ChemR-I],Blood	4.3
Total cholesterol (Qn)[ChemR-I],Blood	179
Total protein (Qn)[ChemR-I],Blood	7.0
Albumin (Qn)[ChemR-I],Blood	3.7
AST(SGOT) (Qn)[ChemR-I],Blood	28
ALT(SGPT) (Qn)[ChemR-I],Blood	14
Alkaline phosphatase (Qn)[ChemR-I],Blood	67
γ-GT (Qn)[ChemR-I],Blood	14
Total bilirubin (Qn)[ChemR-I],Blood	0.6
Sodium (Qn)[EM],Blood	139
Potassium (Qn)[EM],Blood	4.2
Chloride (Qn)[EM],Blood	106
Total CO2 (Qn)[ChemR-I],Blood	24.0
CRP (Qn),Blood	0.09
eGFR(CKD-EPI) (Qn),Blood	98
eGFR(MDRD) (Qn),Blood	≥60(86)

Nasal examination

No evidence of telangiectatic lesions



Pulmonary Function Test



Spirometry

	Ref	Pre	%Pre	Post	%Post	%Chg
FVC	3.31	2.98	90	3.18	96	6
FEV1	2.73	2.51	92	2.60	95	4
FEV1/FVC	81	84	104	82	101	-3
FEF25-75	2.75	2.78	101	2.67	97	-4
IsoFEF25-75		2.78		3.24		16
PEF	5.75	6.99	122	7.23	126	3
FET100		5.51		4.82		-13
E ATS05		201		201		0
MVV	97.96					
f						

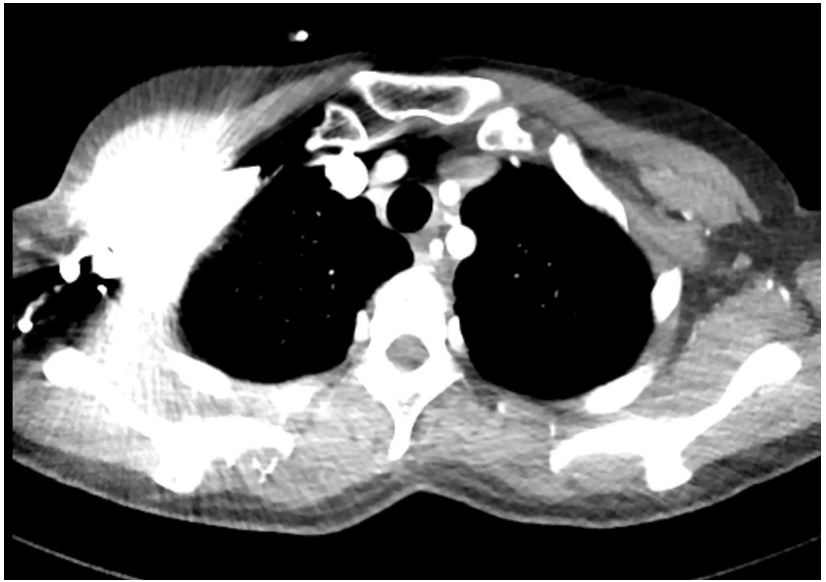
Diffusion

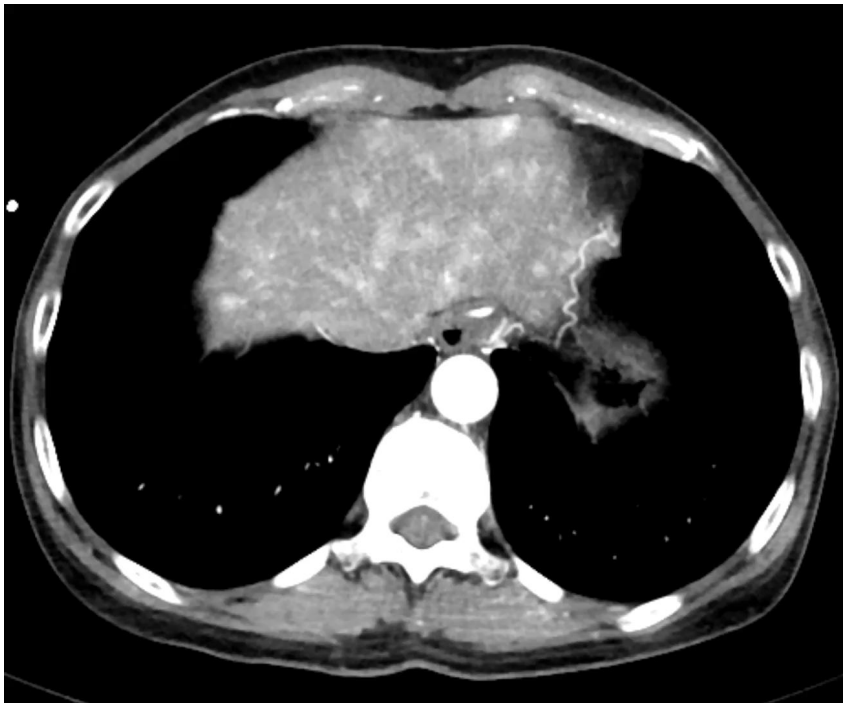
	Ref	Pre	%Pre	Post	%Post	%Chg
DLCO	20.0	13.4	67			
DL Adj	20.0	13.4	67			
DLCO/VA	4.52	2.61	58			
DL/VA Adj		2.61				
DLCO ECode		0				
VA	4.70	5.13	109			
IVC	3.31	2.93	88			
BHT		12.07				

Lung Volume

	Ref	Pre	%Pre	Post	%Post	%Chg
TLC	4.71	4.97	106			
VC	3.31	3.02	91			
IC	2.04	1.11	54			
FRC PL	2.61	3.86	148			
Vtg		4.07				
ERV	1.02	1.92	188			
RV	1.71	1.94	114			
RV/TLC	36.38	39.09	107			
L Vol ECode		1				

Chest CT, AP CT





Right Heart Catheterization

PA	MPA	Pressure	55	19	33
		saturation	77.5		
	RPA	Pressure	54	19	33
		saturation			
	LPA	Pressure			
		saturation			
	Lt. PAWP	Pressure			
		saturation			
	Rt. PAWP	Pressure	8	9	6
		saturation			

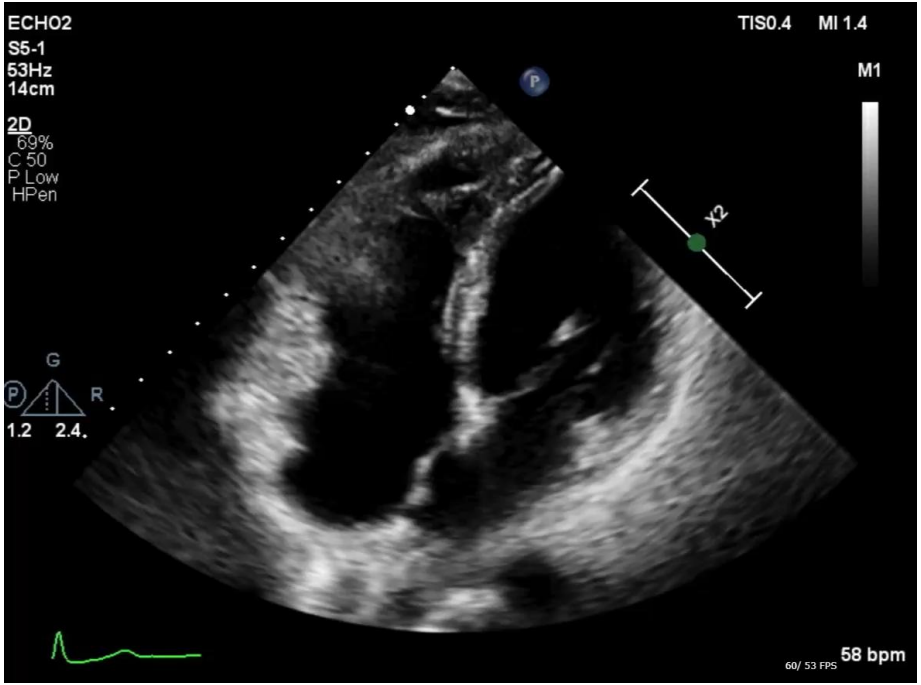
Resistance

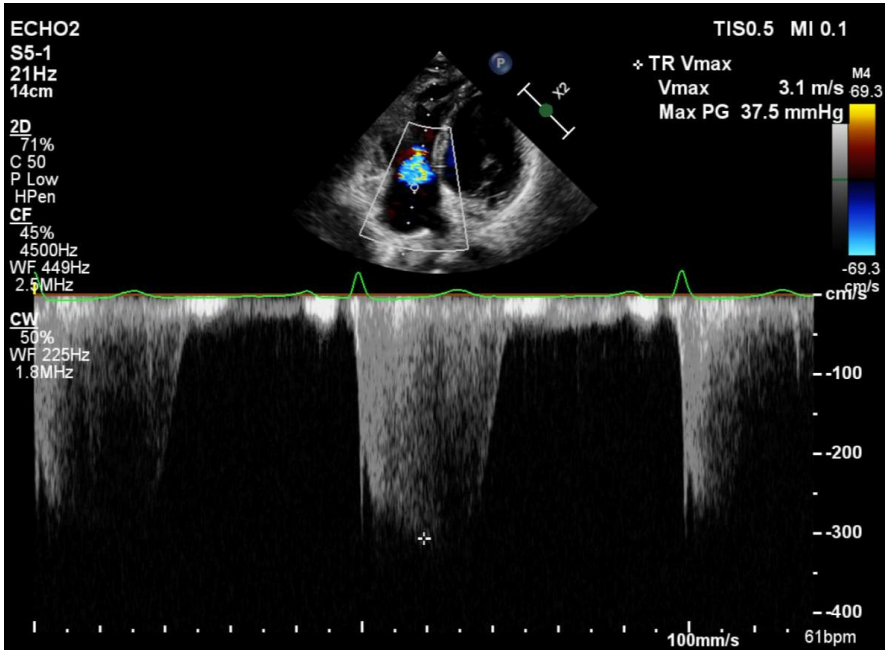
PVR(Wood units)(by indirect fick)	4.48
PVR(Wood units)(by thermodilution)	4.71
SVR(Wood units)	13.08
PVR index(Wood units)	6.96
SVR index(Wood units)	20.33
Rp / Rs	0.34

conclusion

- ☐ No evidence of pulmonary hypertension
- ■ Pre - capillary pulmonary hypertension
- ☐ Isolated post - capillary pulmonary hypertension
- ☐ Combined post - and pre - capillary pulmonary hypertension
- ☐ Exercise pulmonary hypertension
- ■ Other: vasoreactivit test result: negative

Transthoracic Echocardiography





Mild resting PH, mild TE (TR Vmax 3.1 m/sec)
Normal LV/RV

Gene Mutation Tests (2026)

ACVRL1 gene mutation

검사명 : ACVRA1 gene mutaiton

진단명 : Hereditary Hemorrhagic Telangiectasia
유전자 : ACVRL1 on 12q13.13.
검사방법 : PCR-Sequencing
유전방식 : 상염색체우성유전
검체 : PB
OMIM Disease : #187300
OMIM Gene : *601284
GeneBank NT : NG_009549.1
GeneBank NM : NM_000020.3

[Result]
Heterozygous LP, c.1120C>T (p.R374W) was detected in ACVRL1.

[Interpretation]
1. Hereditary Hemorrhagic Telangiectasia 2 (HHT2)는 상염색체 우성유전으로, ACVRL1 (activin A receptor, type II-like 1) 유전자의 돌연변이에 의합니다 (1).

2. ACVRL1 유전자의 돌연변이 여부를 확인하기 위하여, ACVRL1 유전자의 10개의 exon 및 exon-intron boundary에 대한 염기서열을 분석하였습니다.

3. 염기서열 분석 결과, 본 검사대상자는 ACVRL1 유전자의 exon8에서 c.1120T>C (p.Arg374Trp) (p.R374W) 변이를 이형접합자로 보았습니다.

c.1120C>T (p.R374W) (rs28936401)는 Berg JN 등이 HTT2 환자에서 처음 보고한 변이로, likely pathogenic (LP, PM1 PM2 PM5 PP3 PP5)으로 분석되는 돌연변이입니다 (2,3).

4. 본 검사대상자는 ACVRL1 유전자의 c.1120C>T (p.R374W) 이형접합자 돌연변이에 의한 HHT2 환자입니다.

5. 가족구성원에 대한 유전상담이 필요합니다.

ENG gene mutation

검사명 : ENG gene mutation

진단명 : Hereditary Hemorrhagic Telangiectasia
유전자 : ENG on 9q34.11
검사방법 : PCR-Sequencing
유전방식 : 상염색체우성유전
검체 : PB
OMIM Disease : #187300
OMIM Gene : *131195
GeneBank NT : NG_009551.1
GeneBank NM : NM_000118.3

[Result]
No mutation was detected in coding region of ENG gene.

[Interpretation]
1. Hereditary hemorrhagic telangiectasia 1 (HHT1, or Osler-Weber Rendu syndrome)은 상염색체 우성유전으로, ENG (endoglin) 유전자의 돌연변이에 의합니다 (1).

2. ENG 유전자의 돌연변이 여부를 확인하기 위하여, ENG 유전자의 14개 exon 및 exon-intron boundary에 대한 염기서열을 분석하였습니다.

3. 염기서열 분석 결과, 본 검사대상자는 ENG 유전자의 모든 exon 및 exon-intron boundary에서 병인 변이가 관찰되지 않았습니다.

4. 본 검사대상자는 ENG 유전자의 coding region 및 exon-intron boundary의 splicing junction에서의 점돌연변이는 없습니다.

5. 본 검사대상자는 ACVRL1 유전자의 c.1120C>T (p.R374W) 이형접합자 LP 돌연변이에 의한 HHT2 환자입니다.

→ Diagnosis of HHT type 2

평가(Assessment)

IPAH (1995); 2013 volibris 6개월, 2018 3개월, 2022 opsumit 1개월 투여

-> PAH associated with HHT2

PART III

Disease Review

HHT and PH

Hereditary Hemorrhagic Telangiectasia

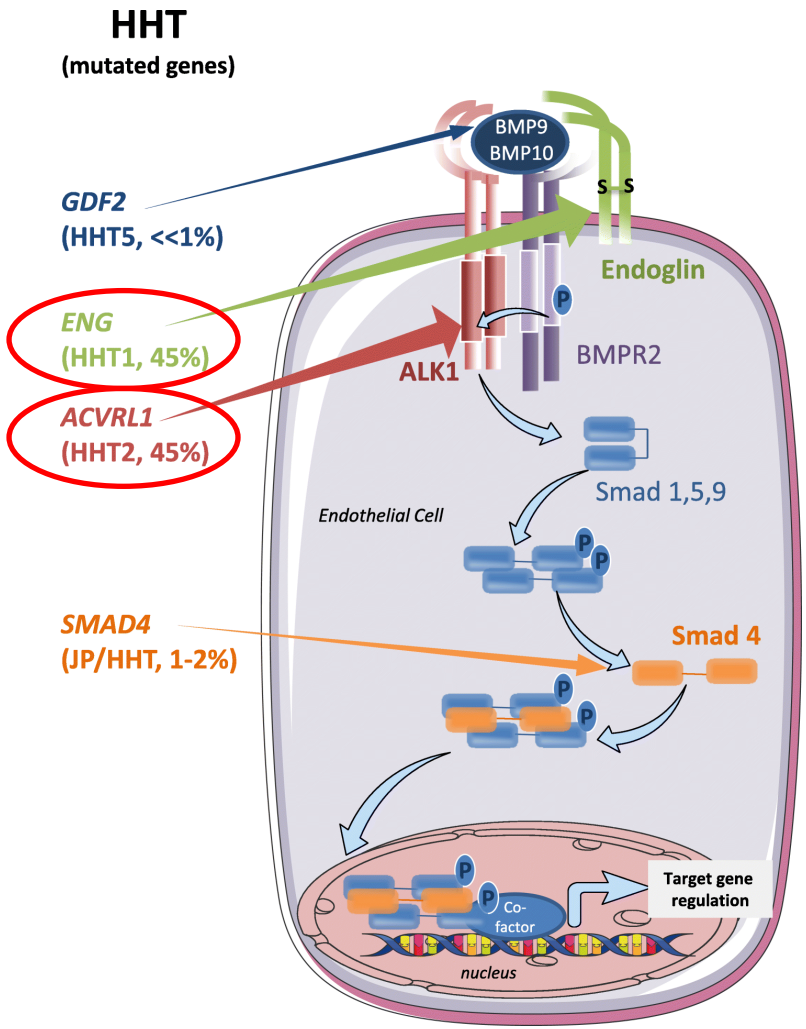
(Osler-Weber-Rendu Disease)

- Multisystemic vascular dysplasia
- Autosomal dominant
- 1/5000-8000 worldwide
- Pathogenic mutations
  - ENG (HHT1)
  - ACVRL1 (HH2)

  } -95% of all HHTs

  - SMAD4, GDF2 ...

Pathogenesis



Robert, F., Desroches-Castan, A., Bailly, S. *et al.* Future treatments for hereditary hemorrhagic telangiectasia. *Orphanet J Rare Dis* **15**, 4 (2020).

Diagnosis : Curaçao Diagnostic Criteria

Curaçao's diagnostic criteria for Hereditary Hemorrhagic Telangiectasia (HHT, Rendu-Osler-Weber syndrome)

(Shovlin C.L. et al., . Am. J. Med. Genet. 91:66-67, 2000)

1. Epistaxis: spontaneous, recurrent nose bleeds m/c, ~95%
2. Telangiectases: multiple, at characteristic sites (lips, oral cavity, fingers, nose) 70%
3. Visceral lesions such as gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformation (AVM), hepatic AVM, cerebral AVMs, spinal AVM
   15% ~ 45% 70%~ ~20%
4. Family history: a first degree relative with HHT according to these criteria

Diagnosis of HHT

Definite: 3 criteria are present

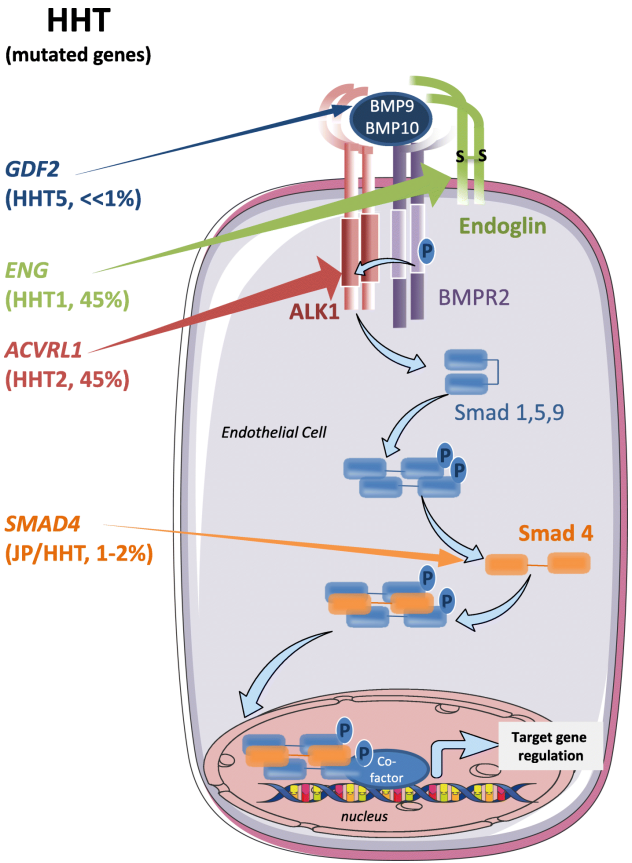
Possible or suspected: 2 criteria are present

Unlikely: <2 criteria are present

HHT1 vs HHT2

	HHT1	HHT2
Mutation	ENG	ACVRL1
Symptoms		
Epistaxis	++, Younger	+++, Older
Pulmonary AVM	50-70%	5-10%
Cerebral AVM	10%	1%
Hepatic AVM	40%	60%
GI bleedings	5%	15%
PH	+, post-capillary HOHF	++, post-capillary HOHF, PAH
Prognosis	Good	Good (sl. Better)

HHT1 vs HHT2



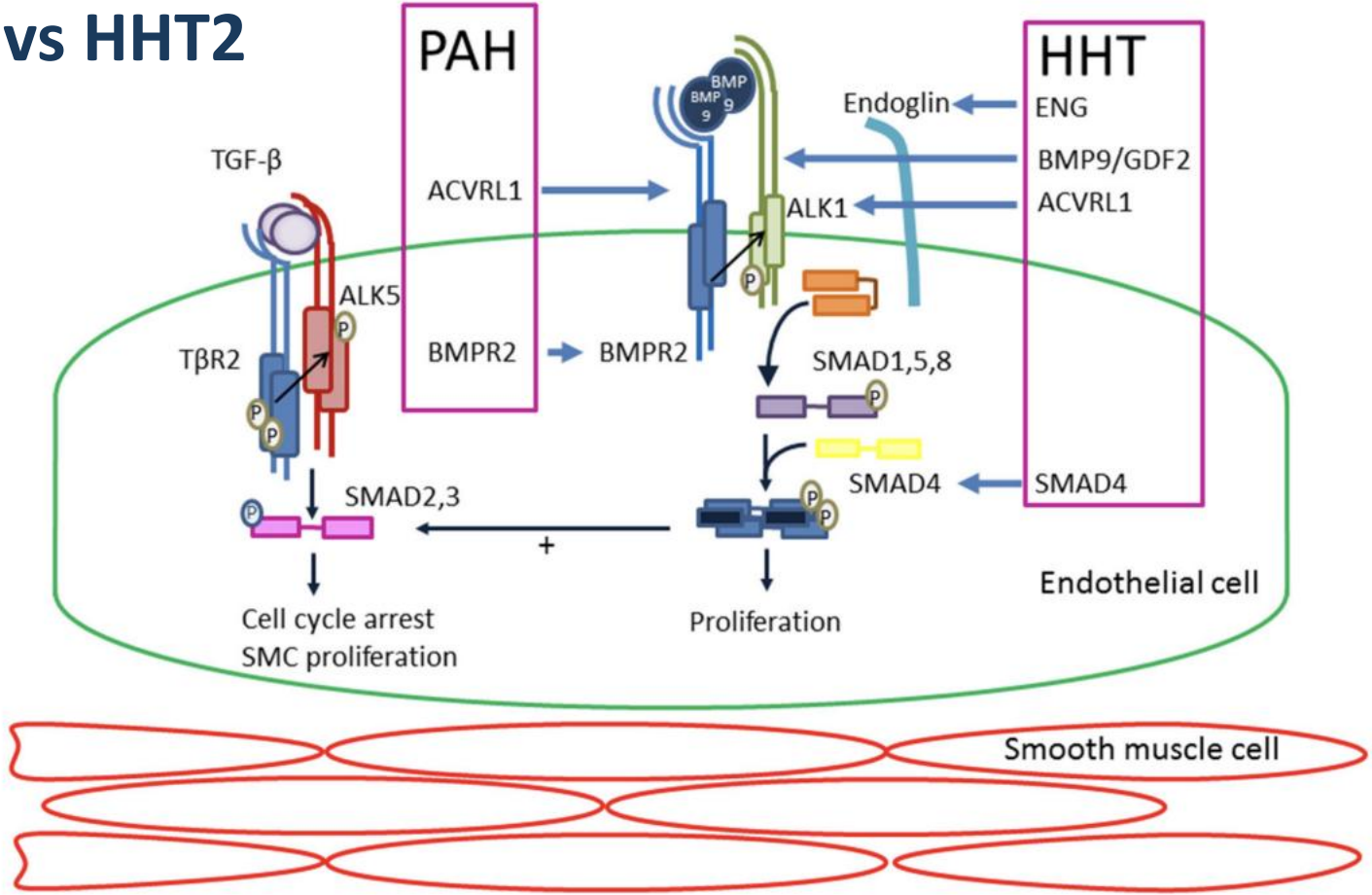
- ENG: co-receptor
  - 높은 혈류의 큰 혈관 내피세포에서 강하게 발현
  - Mutation → large AVMs (lung, cerebral)

- ACVRL1: key type I receptor
  - 소혈관, 모세혈관 내피세포에서 강하게 발현
  - Mutation → small vessels malformations

    → hepatic AVMs, small vessels occlusions

PAH

HHT1 vs HHT2



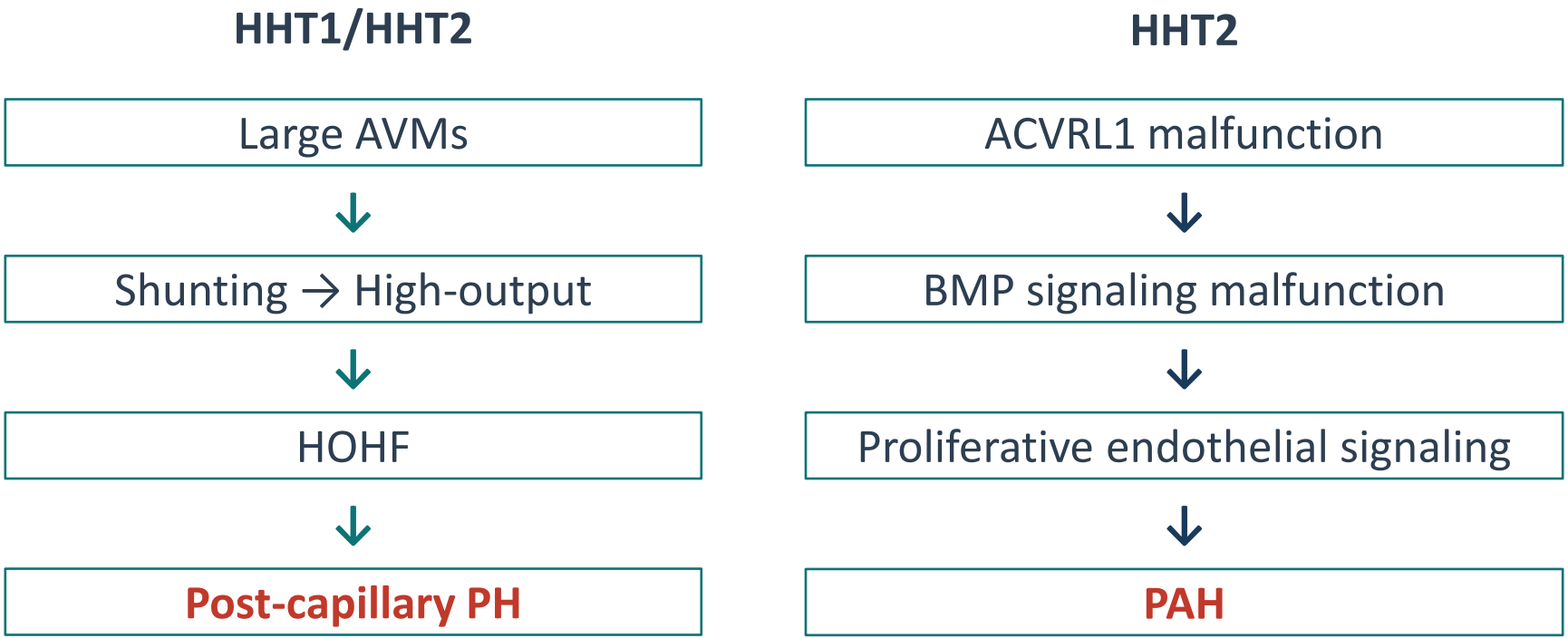
Vorselaars VMM, Hosman AE, Westermann CJJ, Snijder RJ, Mager JJ, Goumans MJ, Post MC. Pulmonary Arterial Hypertension and Hereditary Haemorrhagic Telangiectasia. Int J Mol Sci. 2018 Oct 17;19(10):3203.

PH in HHT

① **Post-capillary PH** *(more common)*
- Hepatic AVMs ± anemia → High-output heart failure (HOHF)
- Elevated PAWP, high cardiac output
- HHT2 > HHT1

② **Pulmonary Arterial Hypertension (PAH)** *(less common)*
- Pathogenic mutation of ACVRL1
  → obliterative vasculopathy of small pulmonary arteries
- Pre-capillary pattern: elevated PVR, normal PAWP
- Clinically indistinguishable from IPAH
- Only in HHT2

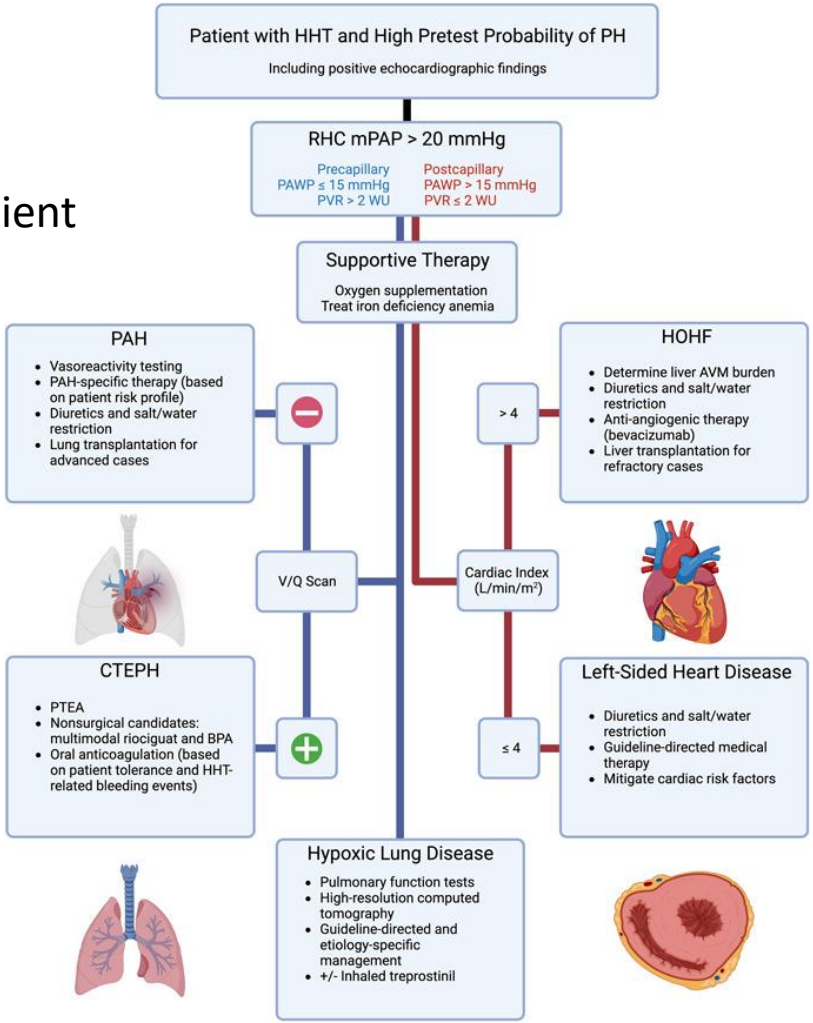
PH in HHT


HHT1/HHT2
Large AVMs
Shunting → High-output
HOHF
Post-capillary PH
HHT2
ACVRL1 malfunction
BMP signaling malfunction
Proliferative endothelial signaling
PAH

PH in HHT

- Multiple etiologies may coexist in a single patient
  → complete hemodynamic profiling (RHC) is encouraged

- Treatment should be individualized



Summary

- PAH can precede overt HHT manifestations by decades.
- ACVRL1 mutation with PAH is clinically indistinguishable from IPAH.
- PH in HHT has multiple etiologies.
- Early genetic diagnosis matters.

References

1. Robert, F., Desroches-Castan, A., Bailly, S. *et al.* Future treatments for hereditary hemorrhagic telangiectasia. *Orphanet J Rare Dis* **15**, 4 (2020).
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3. Mathavan A, Mathavan A, Reddy R, Jones K, Eagan C, Alnuaimat H, Ataya A. Pulmonary hypertension in hereditary hemorrhagic telangiectasia: A clinical review. Pulm Circ. 2023 Oct
4. Vorselaars VMM, Hosman AE, Westermann CJJ, Snijder RJ, Mager JJ, Goumans MJ, Post MC. Pulmonary Arterial Hypertension and Hereditary Haemorrhagic Telangiectasia. Int J Mol Sci. 2018 Oct 17;19(10):3203.
5. Tillet E, Bailly S. Emerging roles of BMP9 and BMP10 in hereditary hemorrhagic telangiectasia. Front Genet. 2015 Jan 8;5:456.

Thank you for your attention!