

# Genetic in PAH

## *Genotype-Phenotype Relationship*

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# Conflicts of interest

I have the following real or perceived conflicts of interest outside the topic of this presentation:

Affiliation / Financial interest	Commercial company
Grants/research support:	Actelion, Bayer, Boehringer, Ferrer, GSK, Janssen, Pfizer, MSD, Acceleron
Honoraria or consultation fees:	Actelion, Bayer, Boehringer, Chiesi, Ferrer, GSK, Janssen, Pfizer, MSD, Acceleron
Participation in a company sponsored bureau:	None
Stock shareholder:	None
Spouse / partner:	None
Other support / potential conflict of interest:	None



# Consensus statement

TEXTES OFFICIELS

## Conseil génétique et dépistage de l'hypertension artérielle pulmonaire – consensus du Consortium international pour les études génétiques dans l'HTAP – version française<sup>☆</sup>



*Genetic counselling and testing in pulmonary arterial hypertension – A consensus statement on behalf of the International Consortium for Genetic Studies in PAH – French version*

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W.K. Chung<sup>g</sup>, S. Gräf<sup>h,i,j</sup>, E. Grünig<sup>c,d</sup>, M. Humbert<sup>a,b</sup>,  
R. Quarck<sup>f</sup>, J.A. Tenorio-Castano<sup>k,l,m</sup>, F. Soubrier<sup>n</sup>,  
R.C. Trembath<sup>o</sup>, N.W. Morrell<sup>h,i</sup>,  
for the PAH-ICON associated with the PVRI<sup>2</sup>



# Pulmonary arterial hypertension

*Predisposing genes*



# FAMILIAL PULMONARY HYPERTENSION

1<sup>st</sup> familial cases of PAH reported in 1954 by Dresdale DT

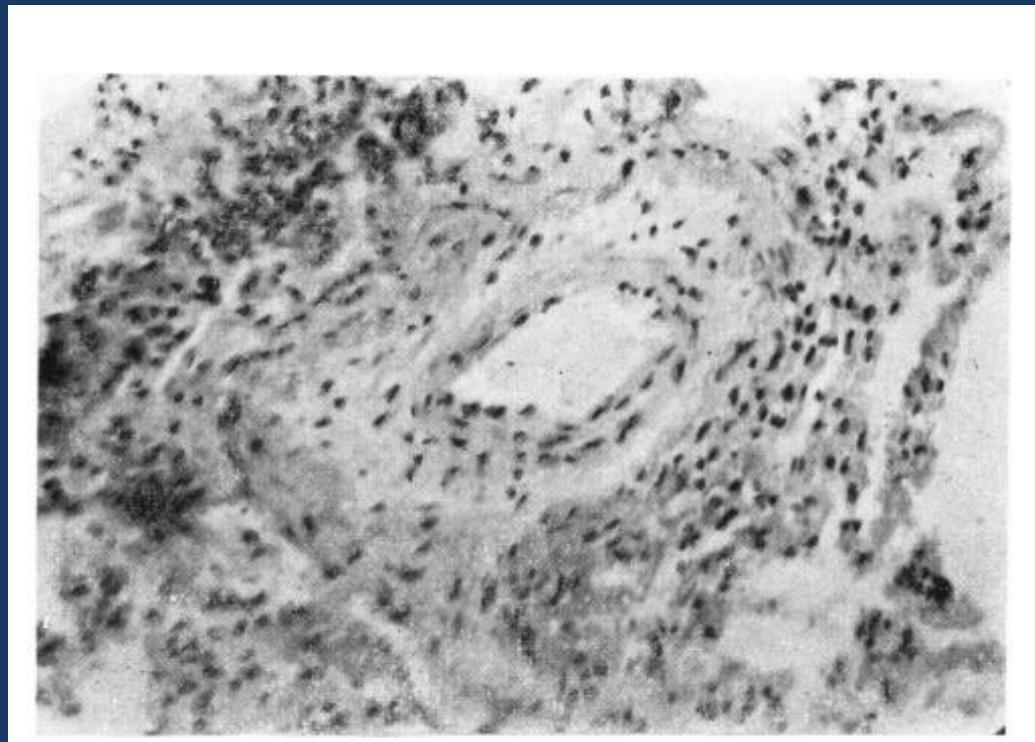
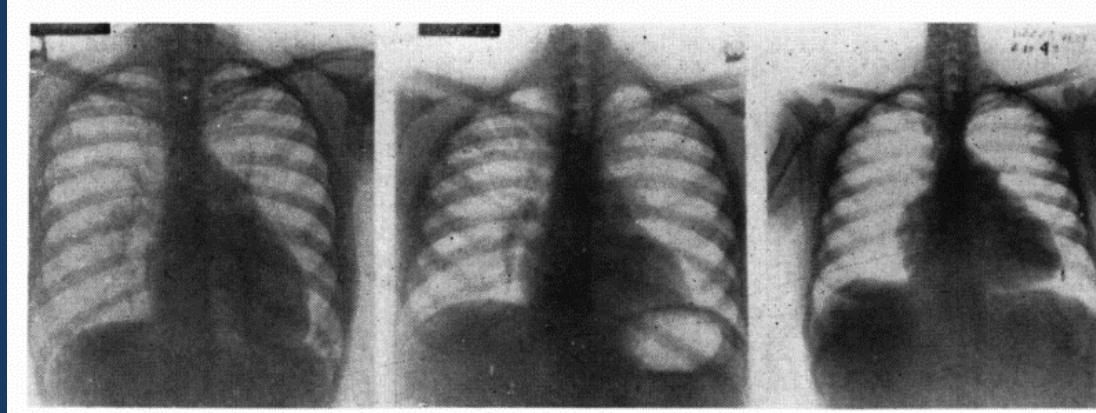
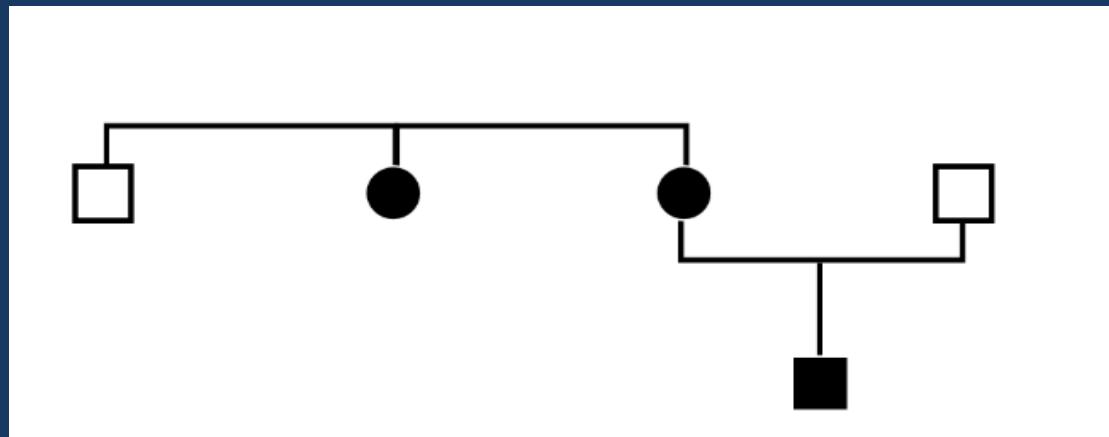


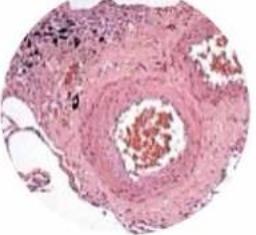
Fig.1—Marked intimal sclerosis of a small intrapulmonary artery is noted; X 500.



# CLASSIFICATION – ESC/ERS Guidelines 2022

1

Pulmonary arterial hypertension (PAH)



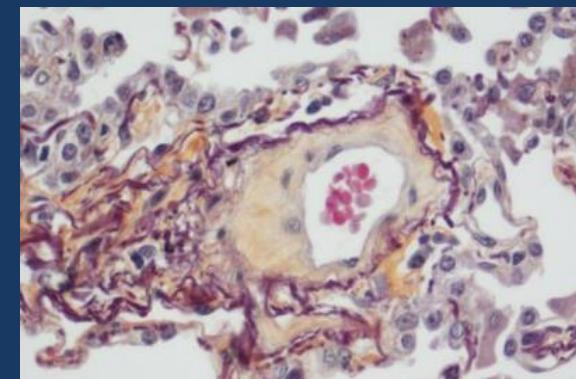
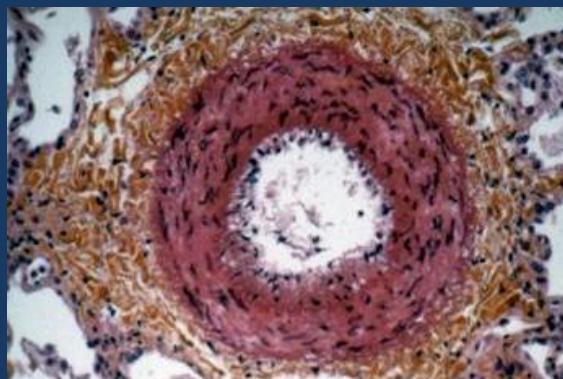
- Idiopathic/heritable
- Associated conditions

PREVALENCE

Rare



- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.5.1 Connective tissue disease
  - 1.5.2 HIV infection
  - 1.5.3 Portal hypertension
  - 1.5.4 Congenital heart disease
  - 1.5.5 Schistosomiasis
- 1.5 PAH long-term responders to CCB
- 1.6 PAH with overt signs of venous/capillaries (PVOD/PCH) involvement
- 1.7 Persistent PH of the Newborn syndrome



# HISTORY OF GENETIC DISCOVERY IN HERITABLE PAH & PVOD

Gene	Pulmonary hypertension phenotypic association	Putative molecular mechanism	Inheritance pattern	Potential distinguishing clinical and examination features
BMPR2	Heritable and idiopathic PAH	Haploinsufficiency	Autosomal dominant	No specific or diagnostic clinical features described
ATP13A3		Unknown	Autosomal dominant	
AQP1		Unknown	Autosomal dominant	
ABCC8		Haploinsufficiency	Autosomal dominant	
KCNK3		Haploinsufficiency	Autosomal dominant	
SMAD9		Haploinsufficiency	Autosomal dominant	
Sox17	Heritable and idiopathic PAH Congenital heart disease	Unknown	Autosomal dominant	No specific or diagnostic clinical features described
CAV1	Heritable and idiopathic PAH Lipodystrophy	Gain of function; dominant negative	Autosomal dominant	Deficiency of subcutaneous adipose tissue
TBX4	Heritable and idiopathic PAH Small patella syndrome (ischioPATellar dysplasia) Parenchymal lung disease Bronchopulmonary dysplasia Persistent pulmonary hypertension of the neonate	Unknown	Autosomal dominant	Patellar aplasia Skeletal abnormalities, in particular pelvis, knees, and feet
EIF2AK4	Pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis	Loss of function	Autosomal recessive	Distal phalangeal clubbing
KDR	Heritable and idiopathic PAH	Loss of function	Autosomal dominant	No specific or diagnostic clinical features described
ENG		Unknown	Autosomal dominant	Telangiectasia
ACVRL1	Heritable and idiopathic PAH; hereditary haemorrhagic telangiectasia	Haploinsufficiency	Autosomal dominant	Abnormal blood vessel formation
GDF2		Haploinsufficiency	Autosomal dominant	Visceral arteriovenous malformations Bleeding diathesis

High level of evidence
<b>BMPR2</b>
<b>ACVRL1 (ALK1)</b>
<b>ENG</b>
<b>SMAD9</b>
<b>CAV1</b>
<b>GDF2 (BMP9)</b>
<b>KCNK3, ABCC8</b>
<b>TBX4, KDR</b>
<b>SOX17</b>
<b>EIF2AK4 (PVOD)</b>



**BMPRII/TGF $\beta$  Pathway**

**CHANNELOPATHY**

**DEVELOPMENT**

**GCN2**



# Pulmonary arterial hypertension

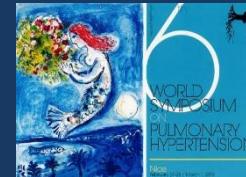
*Genotype/Phenotype relationship*



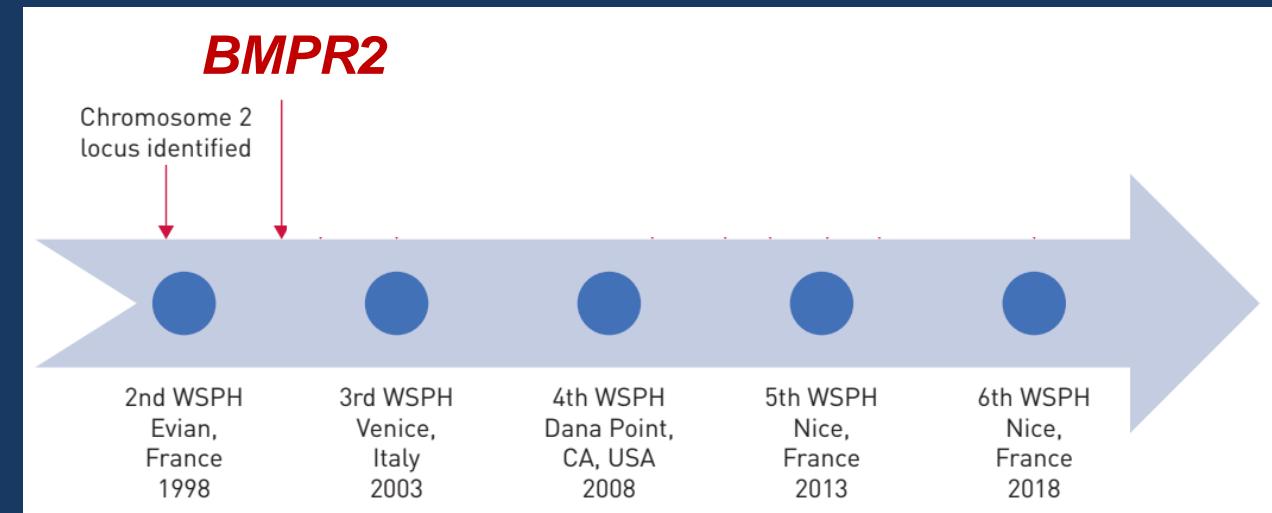
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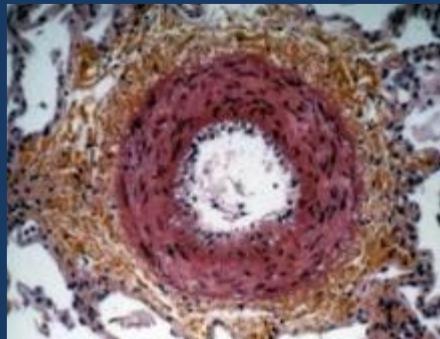
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- 1.3 Drugs and toxins induced
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- 1.7 Persistent PH of the Newborn syndrome**



## TASKFORCE 2: Genetics & Genomics

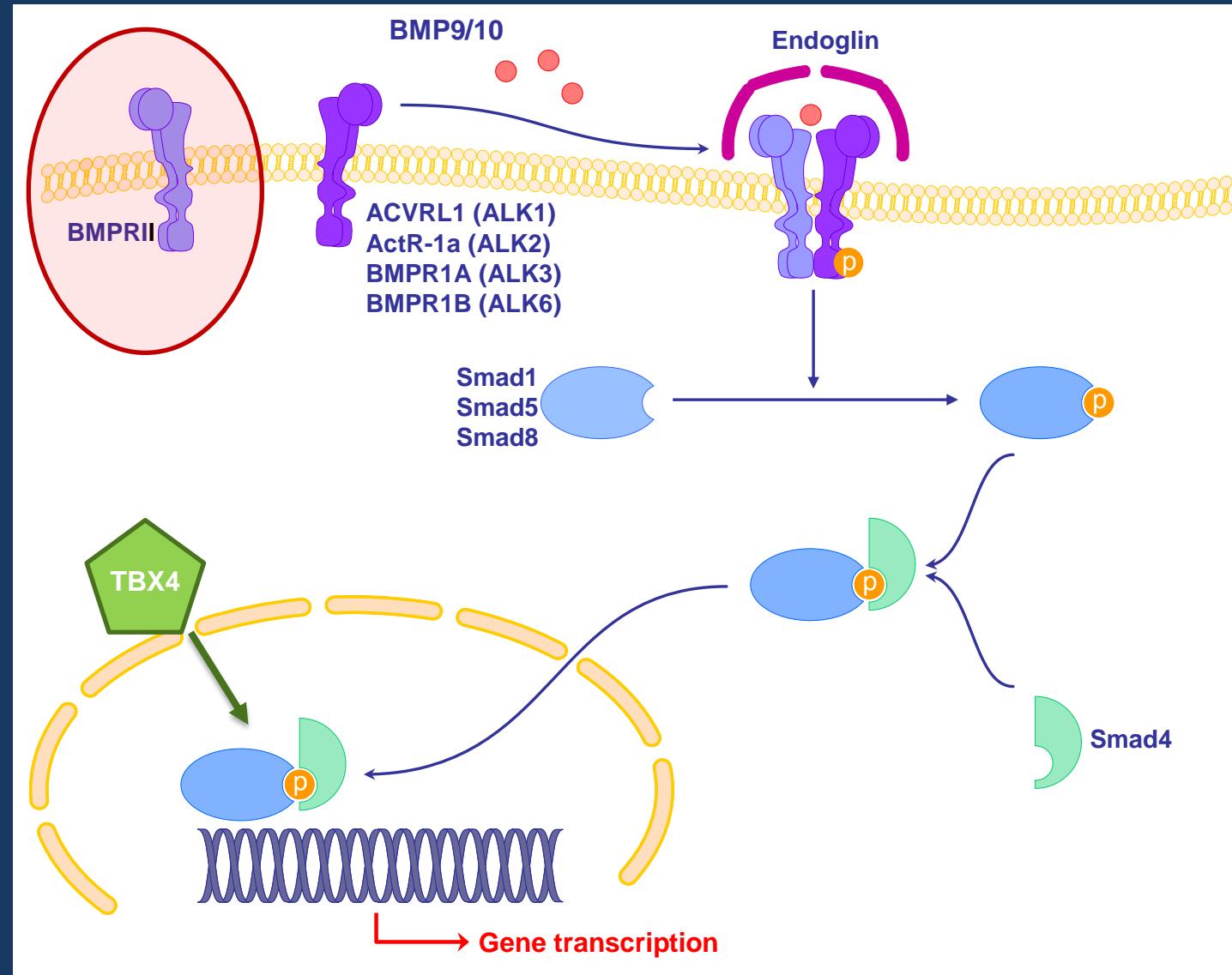


# BMPRII SIGNALLING PATHWAY IN PAH

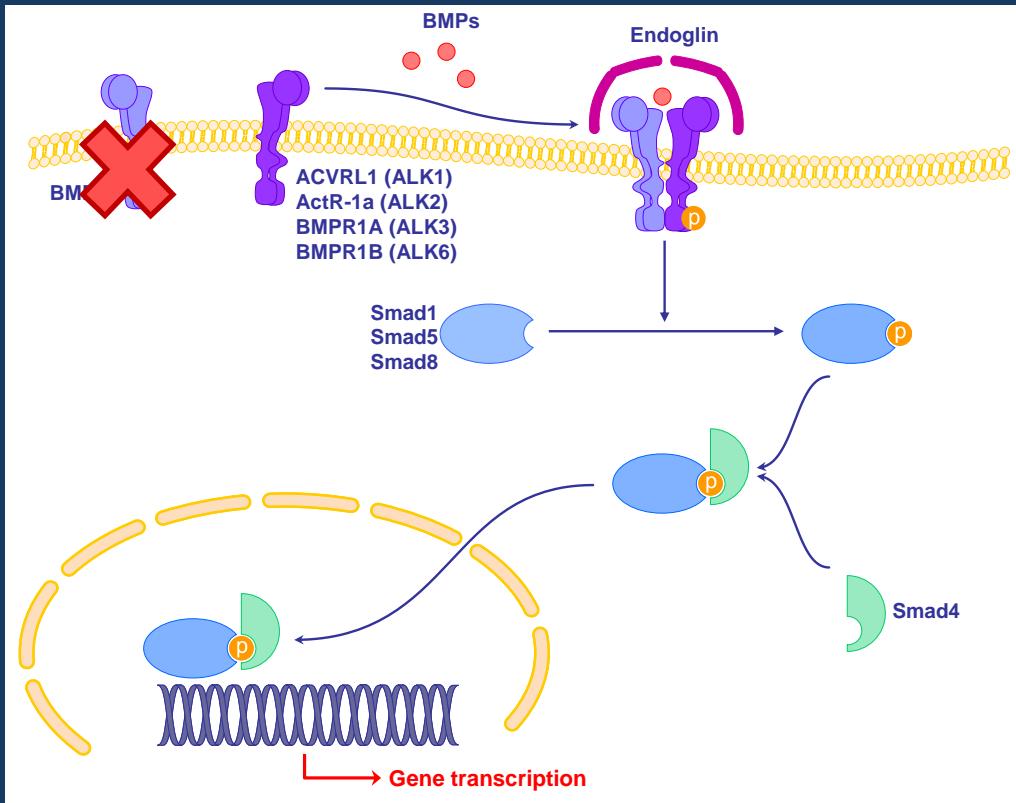


1997: locus on chromosome 2

2000: identification of *BMPR2* mutations

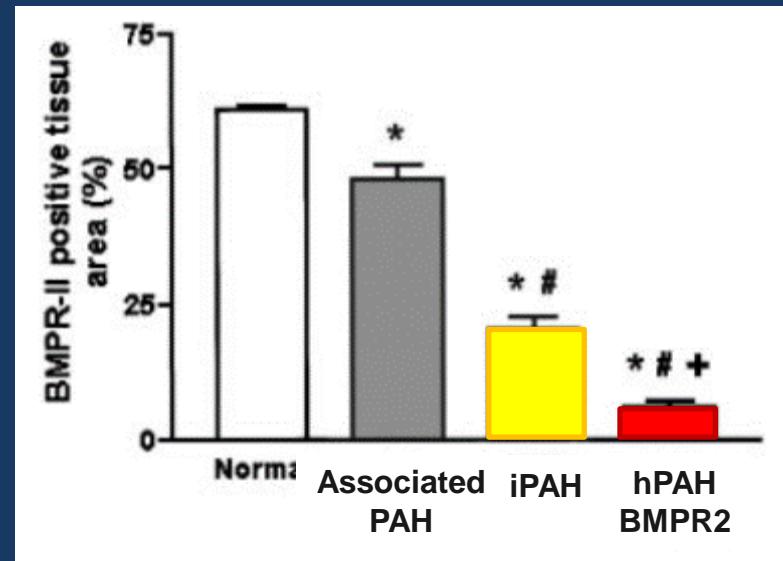


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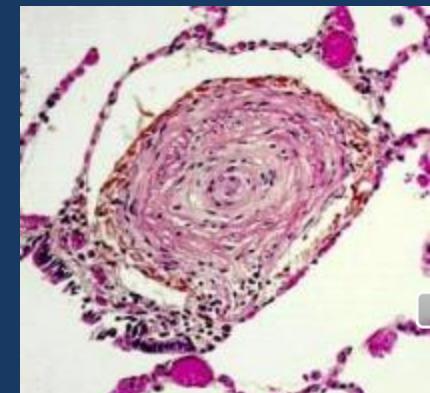
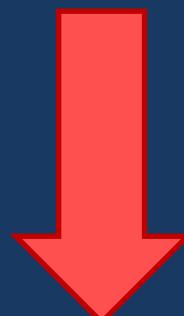
1. Promotes regeneration of small arteries
2. Induces apoptosis of cells that occlude the vessel
3. Maintains elastic fibers
4. Blocks inflammation
5. Preserves mitochondria, repairs damaged DNA

BMPR-II expression



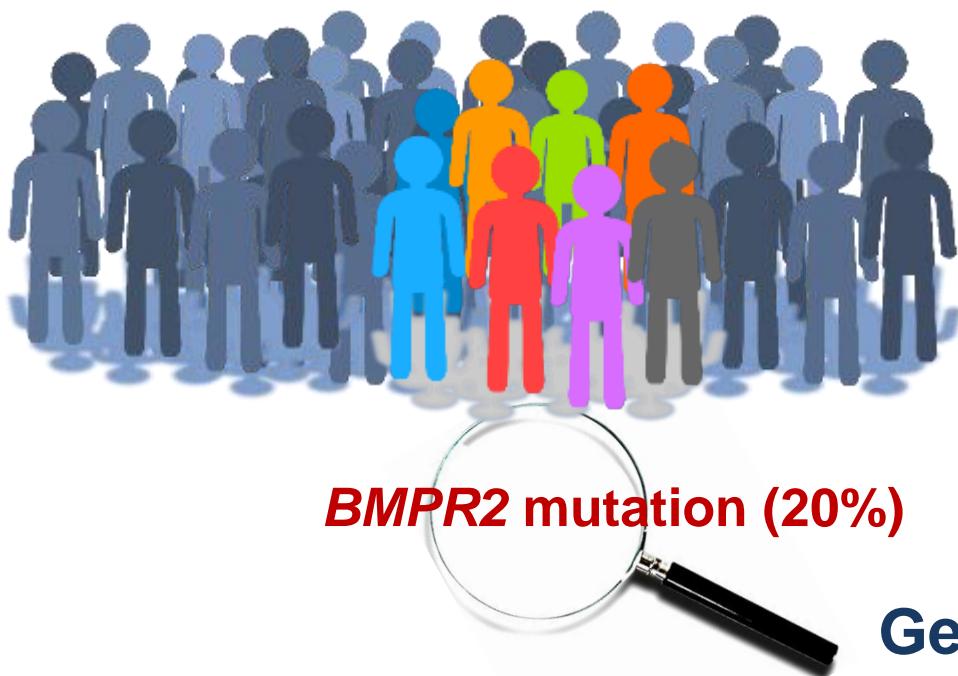
Atkinson, *Circulation* 2002

BMPRII

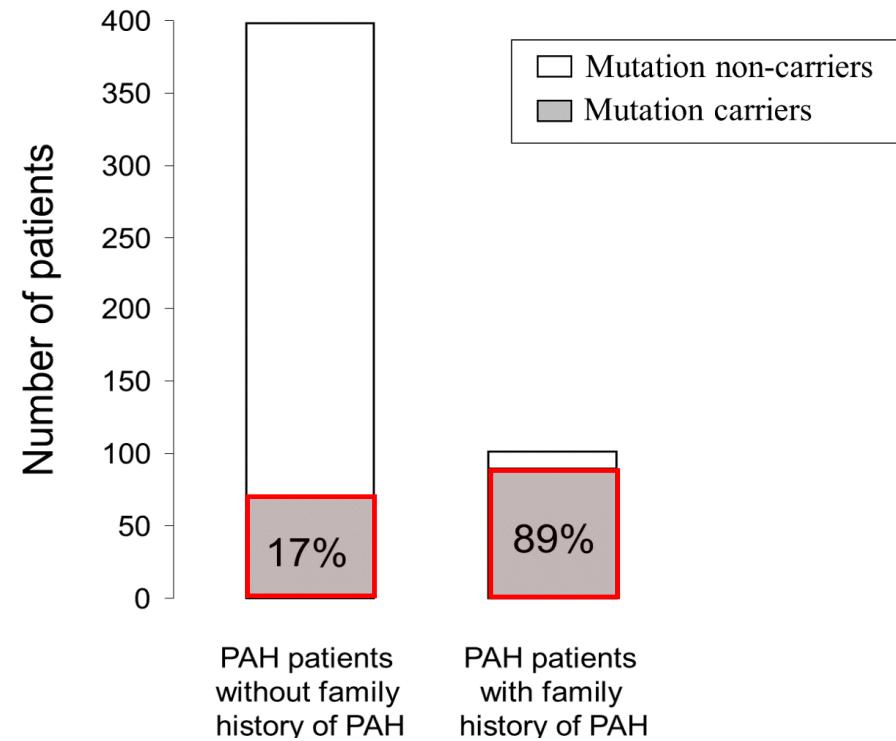


# PAH associated with *BMPR2* mutation

## Sporadic or familial PAH patients

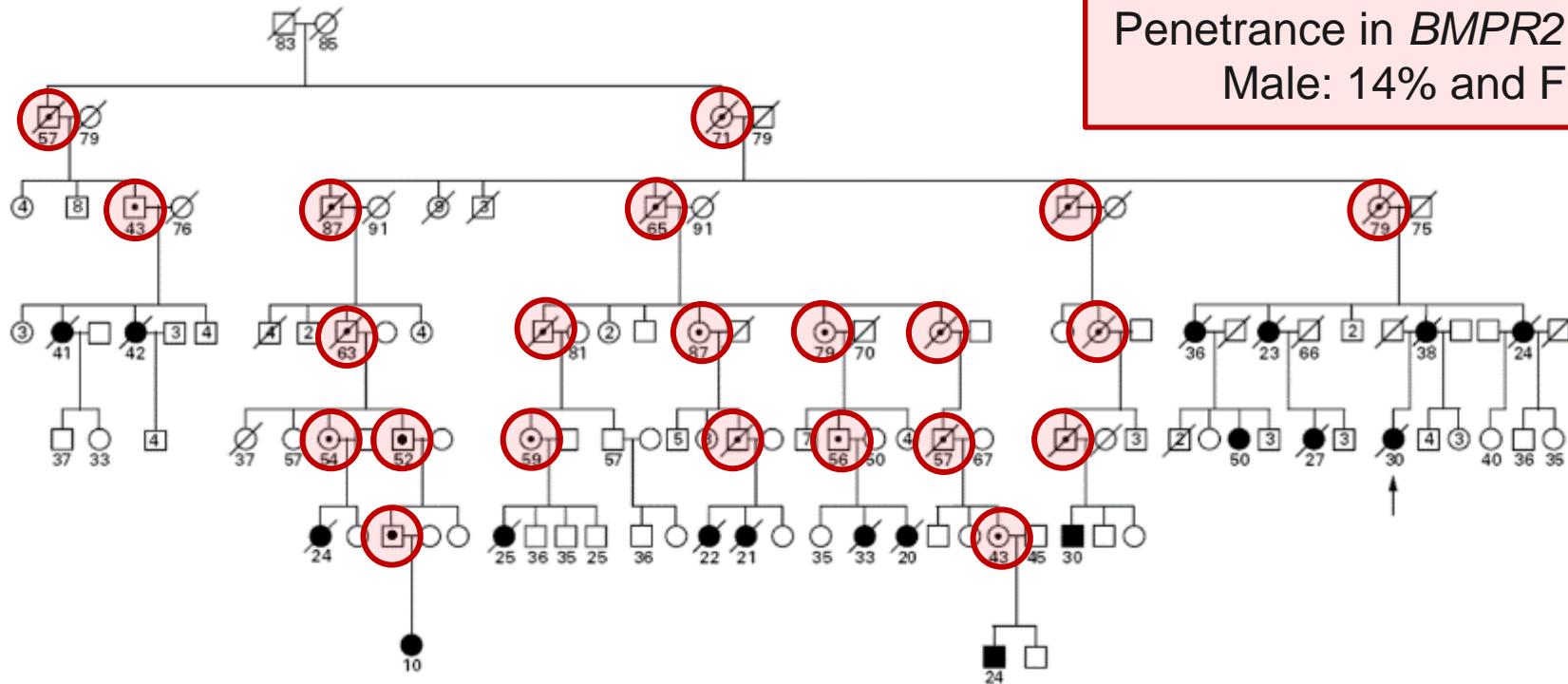


## Genetic Counseling in the French Referral Centre for PH



# Genetic transmission of *BMPR2* mutation

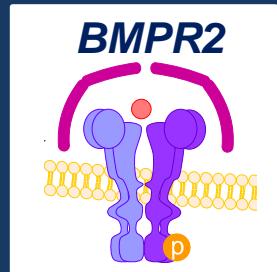
- *BMPR2* mutation (such as all PAH predisposing genes) are characterized by :
    - autosomal dominant trait
    - female predominance
    - incomplete penetrance



Penetrance in *BMPR2* mutation carriers  
Male: 14% and Female: 42%



# BMPR2 mutation carriers present with more severe disease



French study in 2008 <sup>1</sup>

Confirmation from 9 cohorts reporting 1624 patients <sup>2</sup>

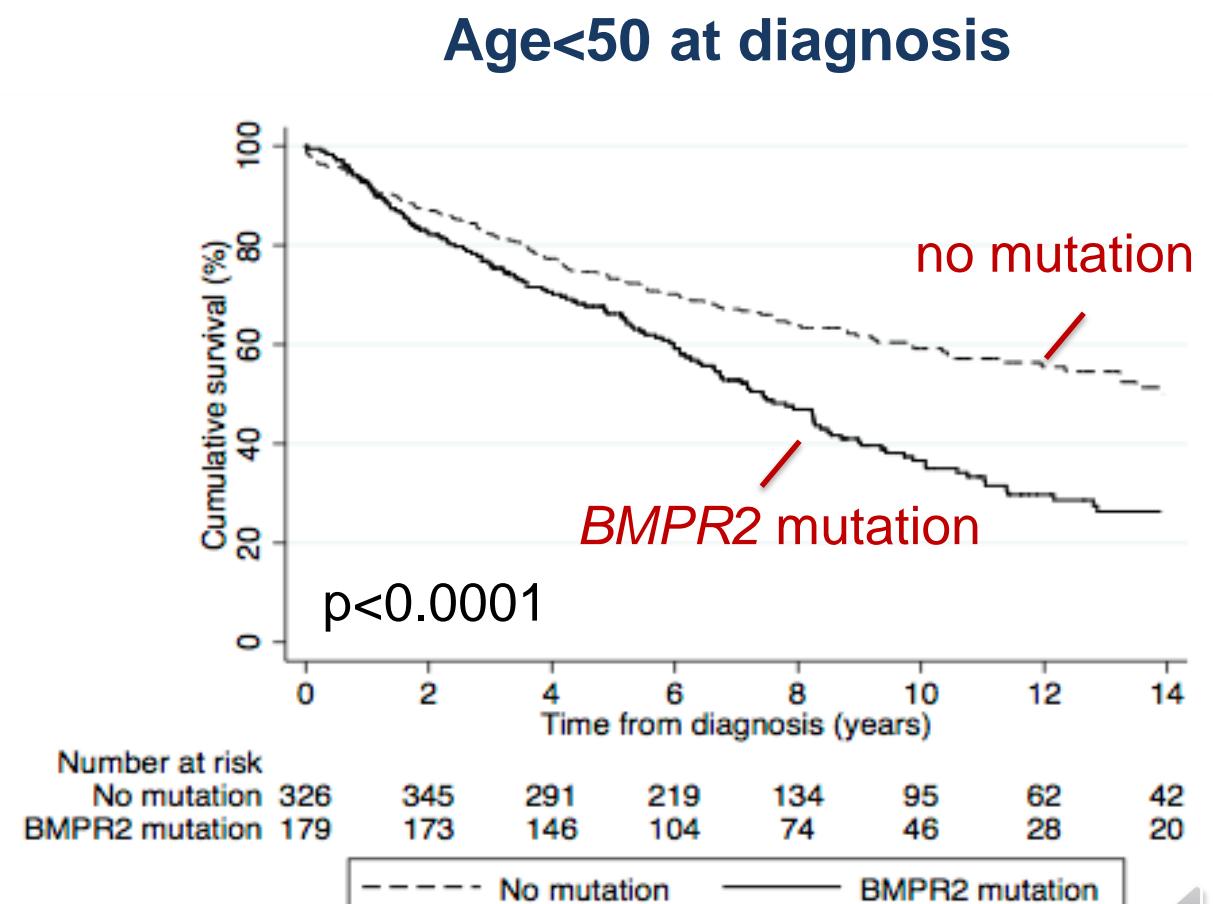
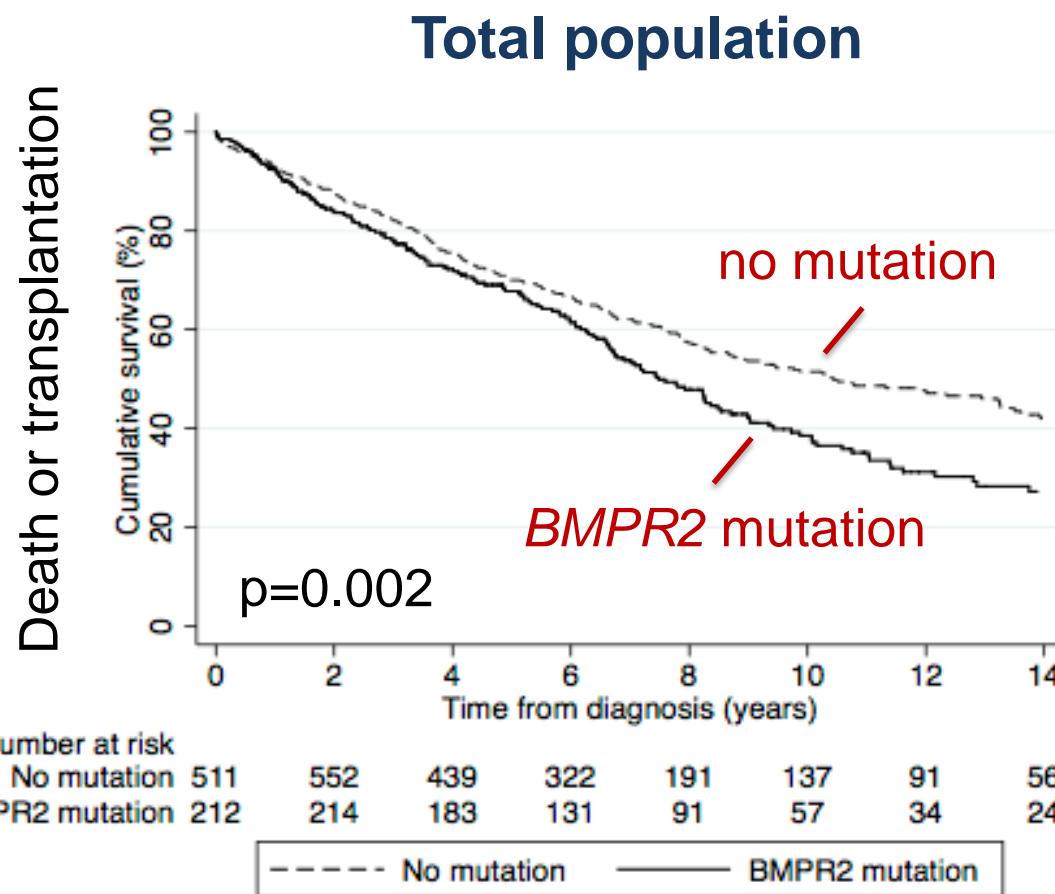
Paris, Giessen, Shanghai, Beijing, Bologna, Nashville, Salt Lake City, Heidelberg, New York, Japan

	BMPR2 mutation status		
	Non-carriers (N=1102)	Carriers (N=448)	p value
Age at diagnosis (N=1447), years	42.0 (17.8)	35.4 (14.8)	<0.0001
Male sex	302/1097 (28%)	138/448 (31%)	0.20
6-min walk distance (N=1072), m	374 (128)	388 (113)	0.088
NYHA functional class			0.38
I-II	313/1031 (30%)	110/394 (28%)	
III	647/1031 (63%)	249/394 (63%)	
IV	72/1031 (7%)	35/394 (9%)	
Mean pulmonary artery pressure (N=1503), mm Hg	56.4 (15.3)	60.5 (13.8)	<0.0001
Pulmonary vascular resistance (N=1300), Wood units	12.9 (8.3)	16.6 (8.3)	<0.0001
Cardiac index (N=1358), L/min per m <sup>2</sup>	2.51 (0.92)	2.11 (0.69)	<0.0001
Vasodilator responder	147/907 (16%)	10/380 (3%)	<0.0001

<sup>1</sup> Sztrymf, AJRCCM 2008  
<sup>2</sup> Evans et al, Lancet Respir Med 2016

# BMPR2 mutation carriers present with more severe disease

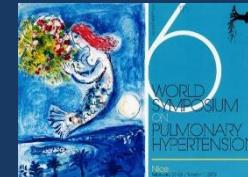
## Time to Death or Transplantation



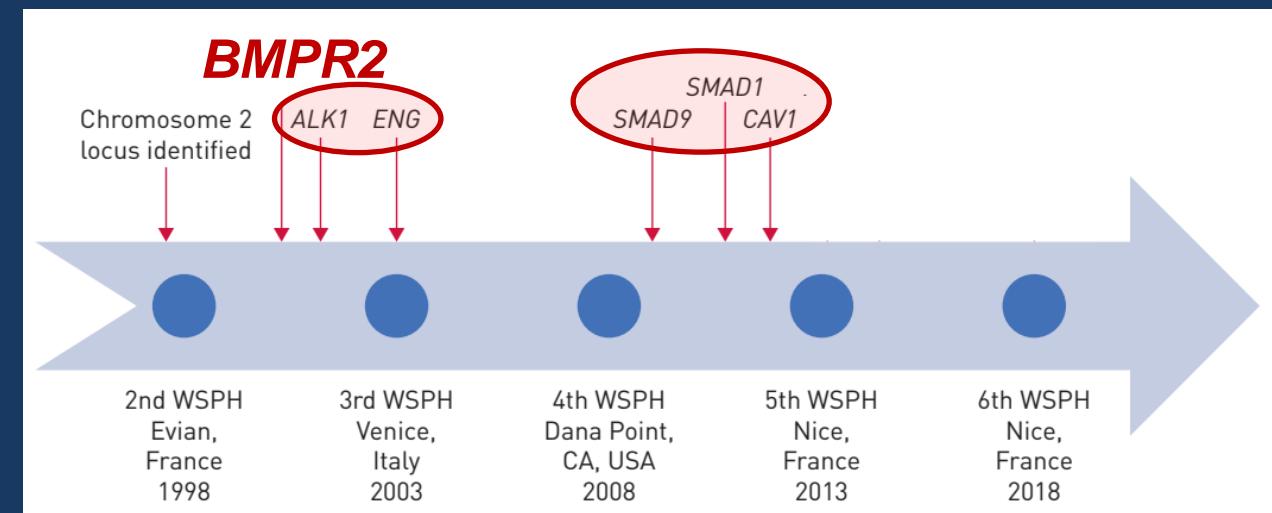
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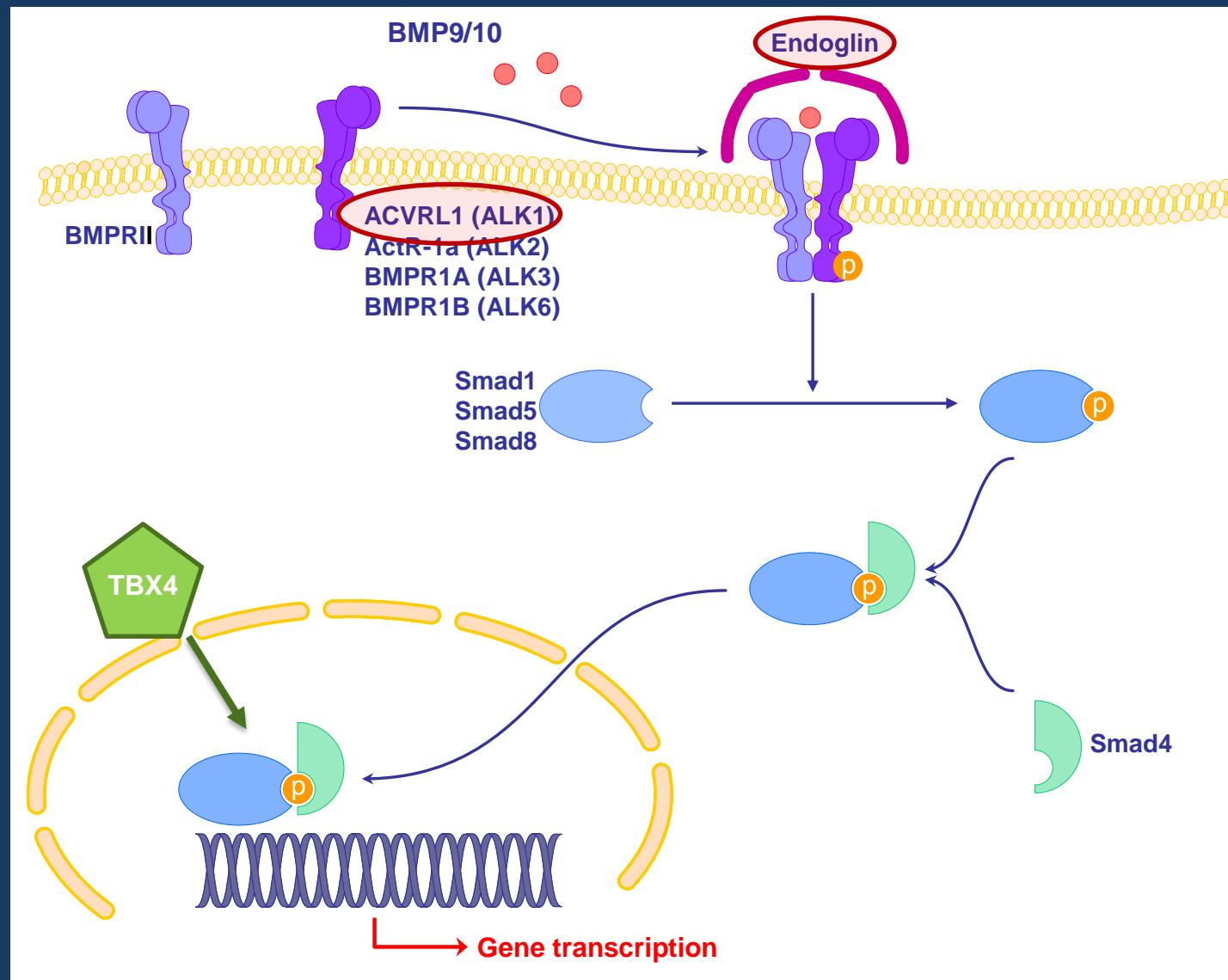
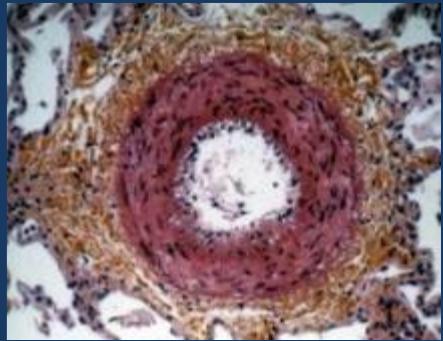
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## TASKFORCE 2: Genetics & Genomics

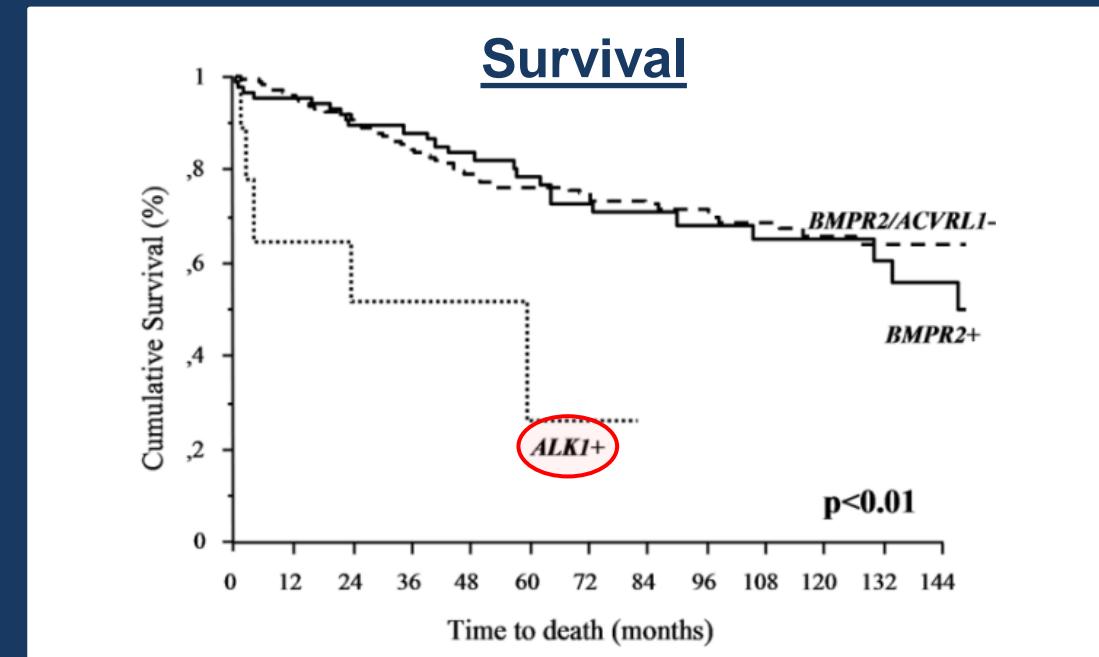


# PREDISPOSING GENES IN PAH : ACVRL1 & Endoglin



# ACVRL1(ALK1): predisposing gene for HHT but also PAH

	<i>ALK1</i> mutation carriers n=32	<i>BMPR2</i> mutation carriers n=93
Gender, female/male (ratio)	25 / 7 (3.6)	60 / 33 (1.8)
Age at diagnosis, yrs (mean±SD)	$21.8 \pm 16.7$ †	$35.7 \pm 14.9$ *
Six-minute walk test distance, m	$407 \pm 99$	$346 \pm 100$
mPAP, mmHg	$60 \pm 17$	$63 \pm 13$ *
CI, L/min/m <sup>2</sup>	$3.04 \pm 1.33$ †	$2.11 \pm 0.64$ *
PVRi, UW.m <sup>2</sup>	$19.0 \pm 10.0$	$23.8 \pm 12.8$ *
Acute vasodilator responders, %	0/23	1/91



PAH is usually associated with signs of **Heredity Hemorrhagic Telangiectasia (HHT)** in patients or in their family.

Female predominance ≠ HHT



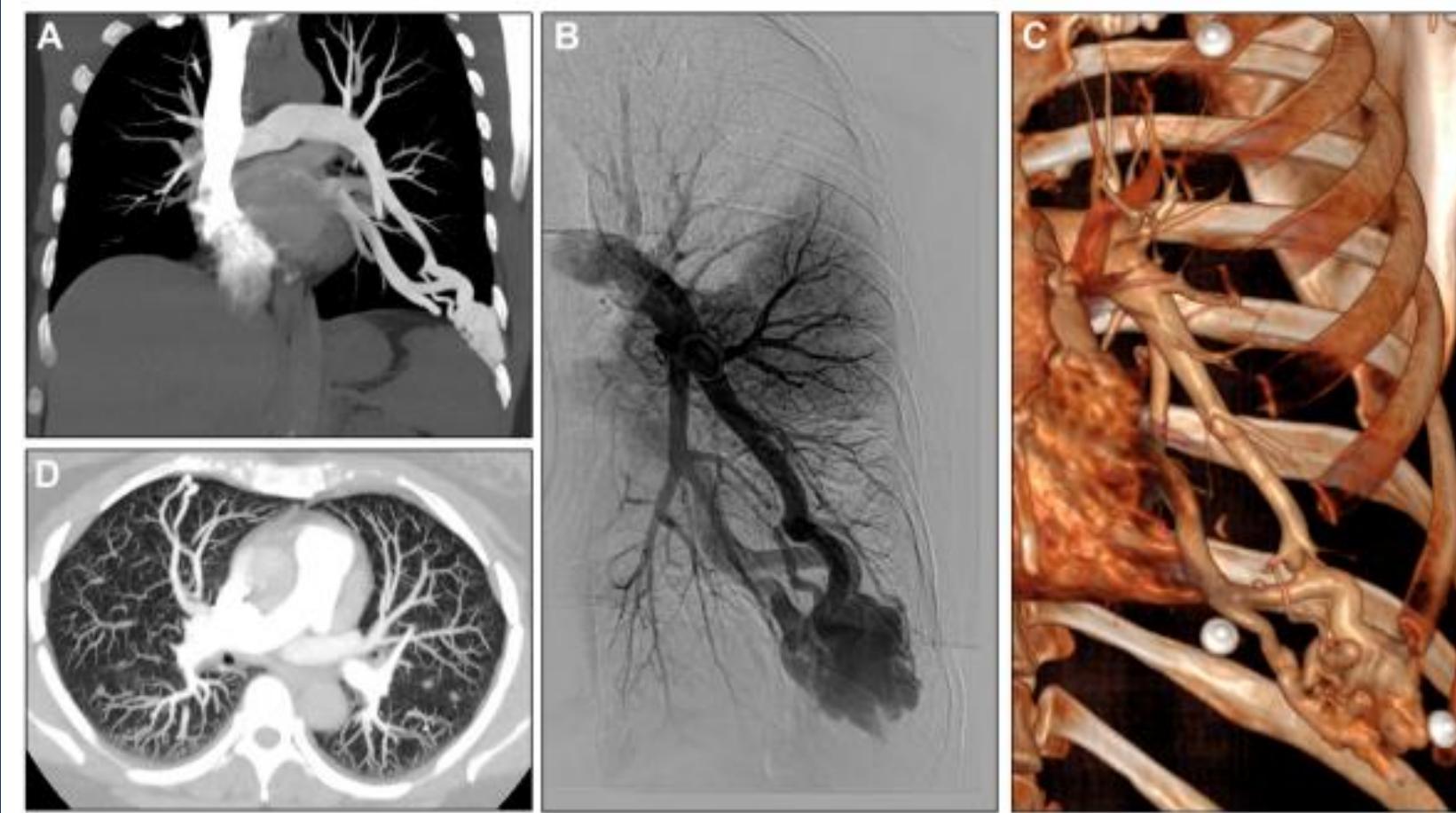
PAH may be the 1st symptom of HHT



# **BMPR2 variants: distinct phenotype**



## Isolated Pulmonary Arteriovenous Malformations Associated With *BMPR2* Pathogenic Variants



# Genetics of signalling pathway in PAH

High level of evidence

**BMPR2**

**ACVRL1 (ALK1)**

**ENG**

**SMAD9**

**CAV1**

**GDF2 (BMP9)**

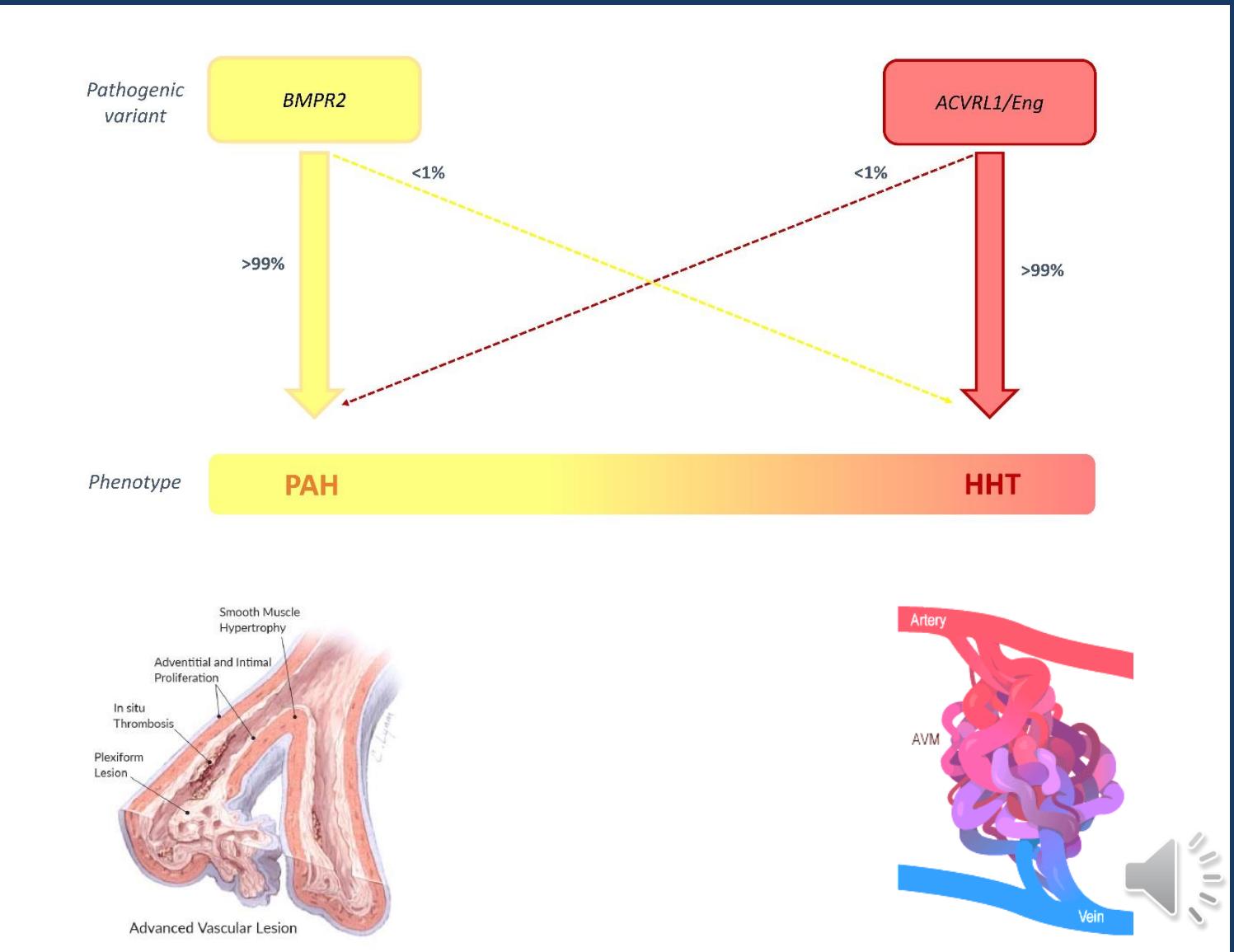
**KCNK3, ABCC8**

**TBX4, KDR**

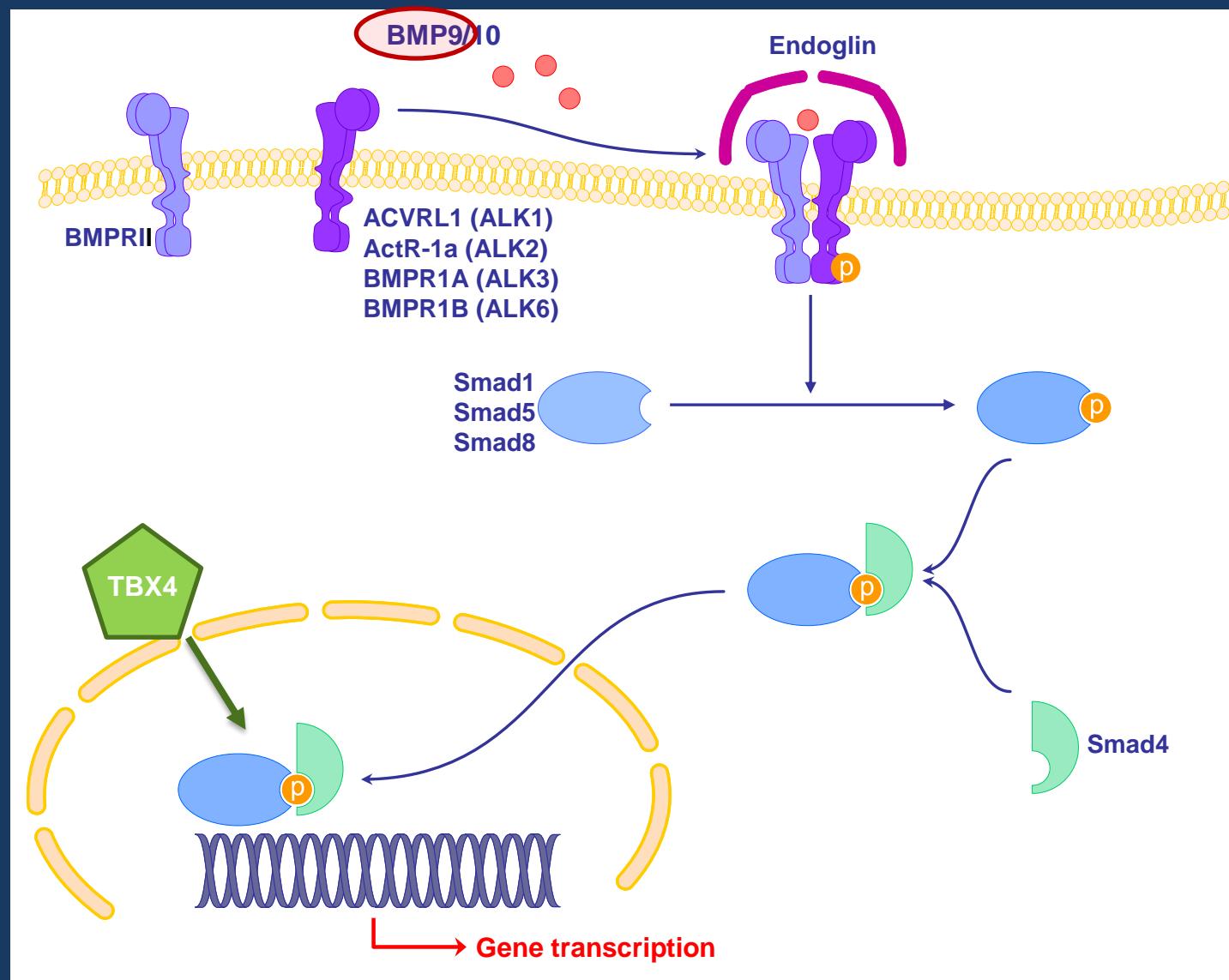
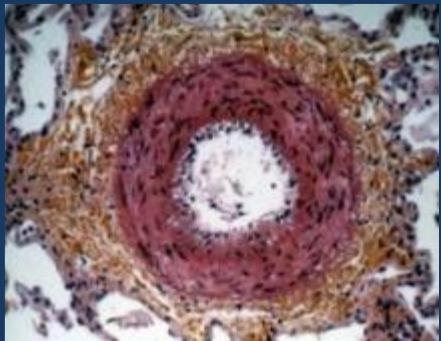
**SOX17**

**EIF2AK4 (PVOD)**

BMPRII/TGF $\beta$  Pathway



# GDF2 mutations (BMP9)



# Genetics of signalling pathway in PAH

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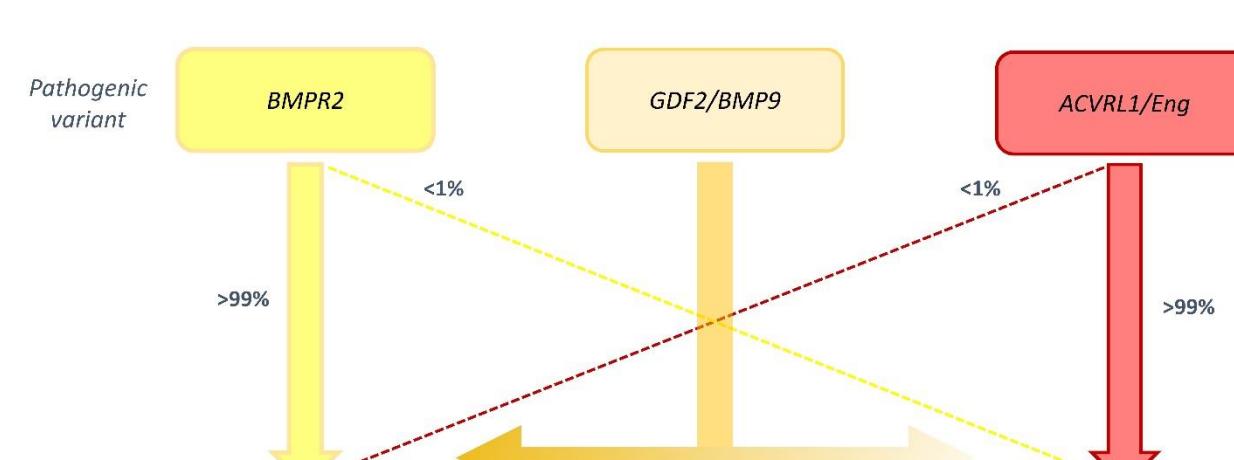
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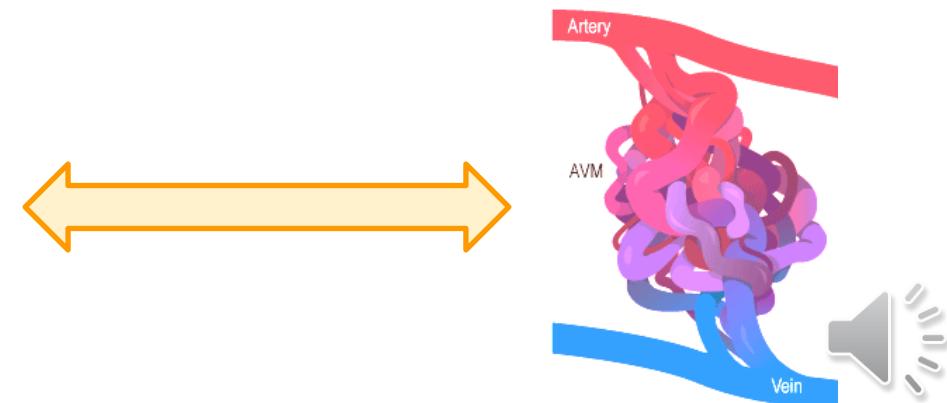
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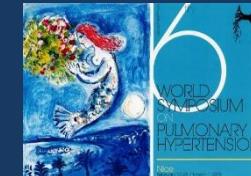
Phenotype



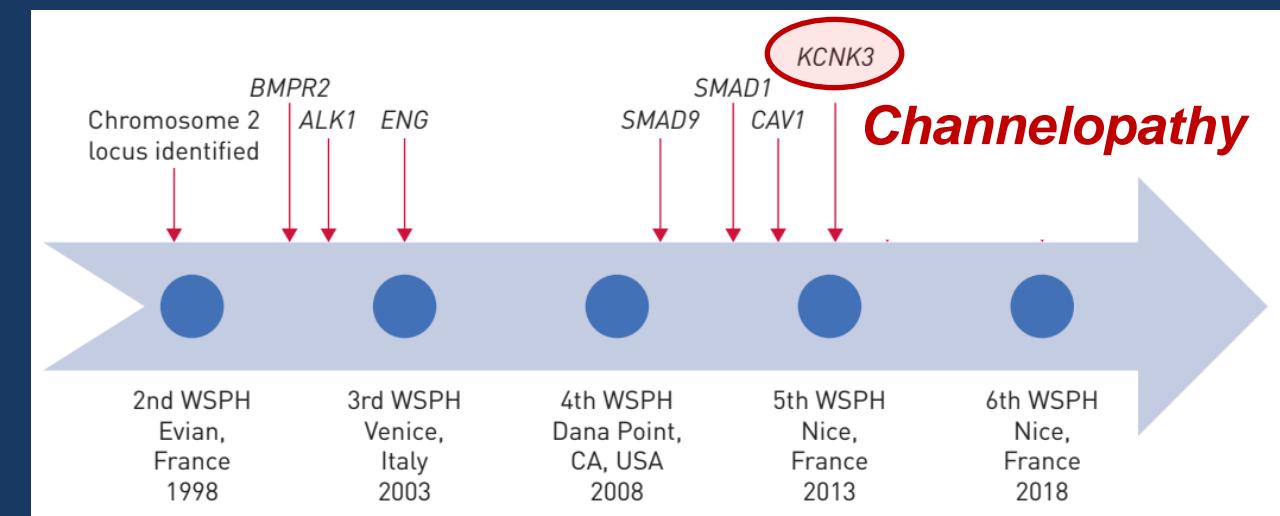
# PREDISPOSING GENES IN PAH : KCNK3

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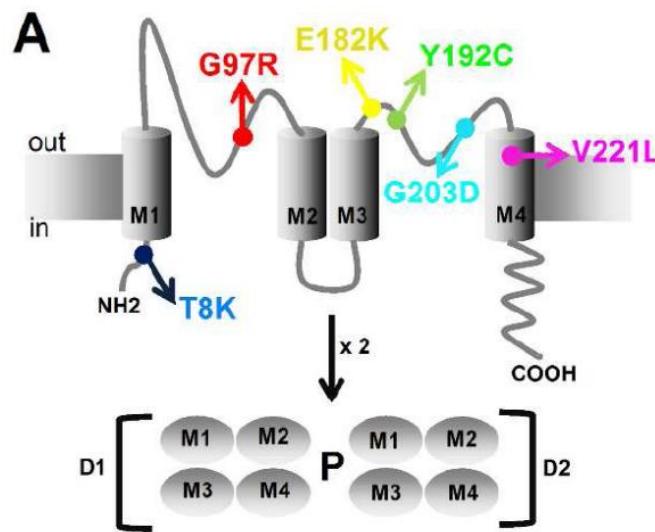
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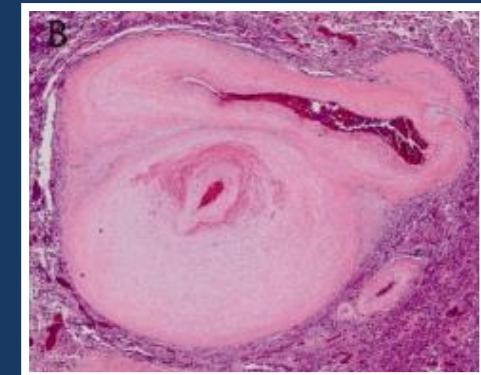
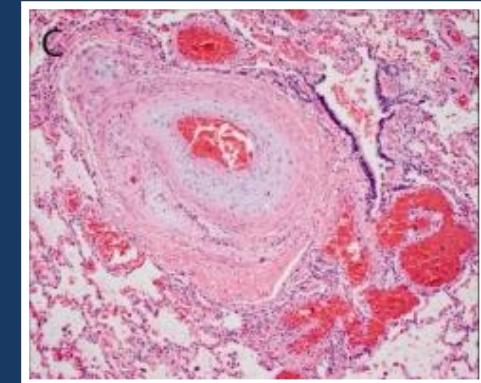
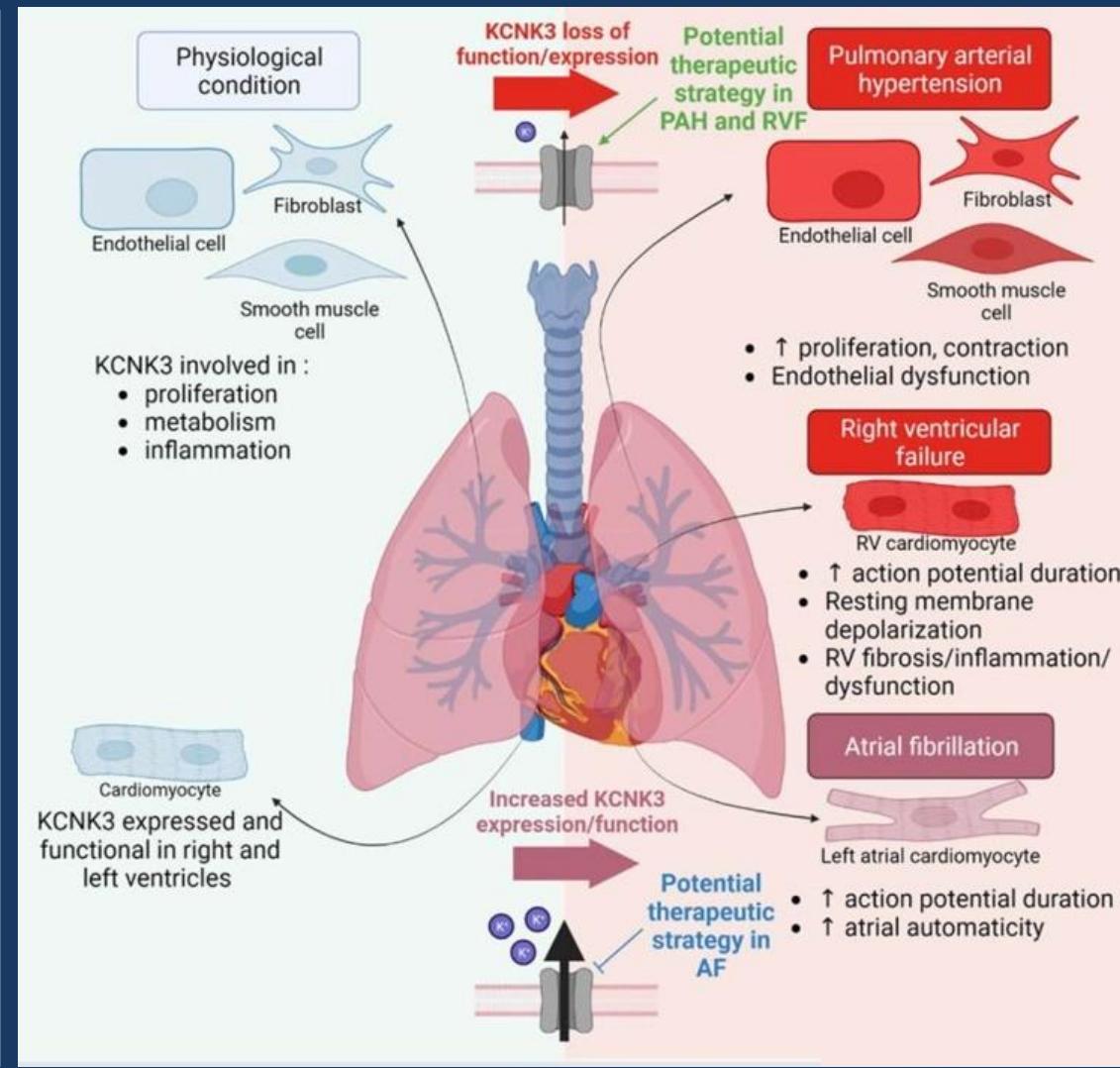
# PREDISPOSING GENES IN PAH : KCNK3

The NEW ENGLAND JOURNAL of MEDICINE

## A Novel Channelopathy in Pulmonary Arterial Hypertension



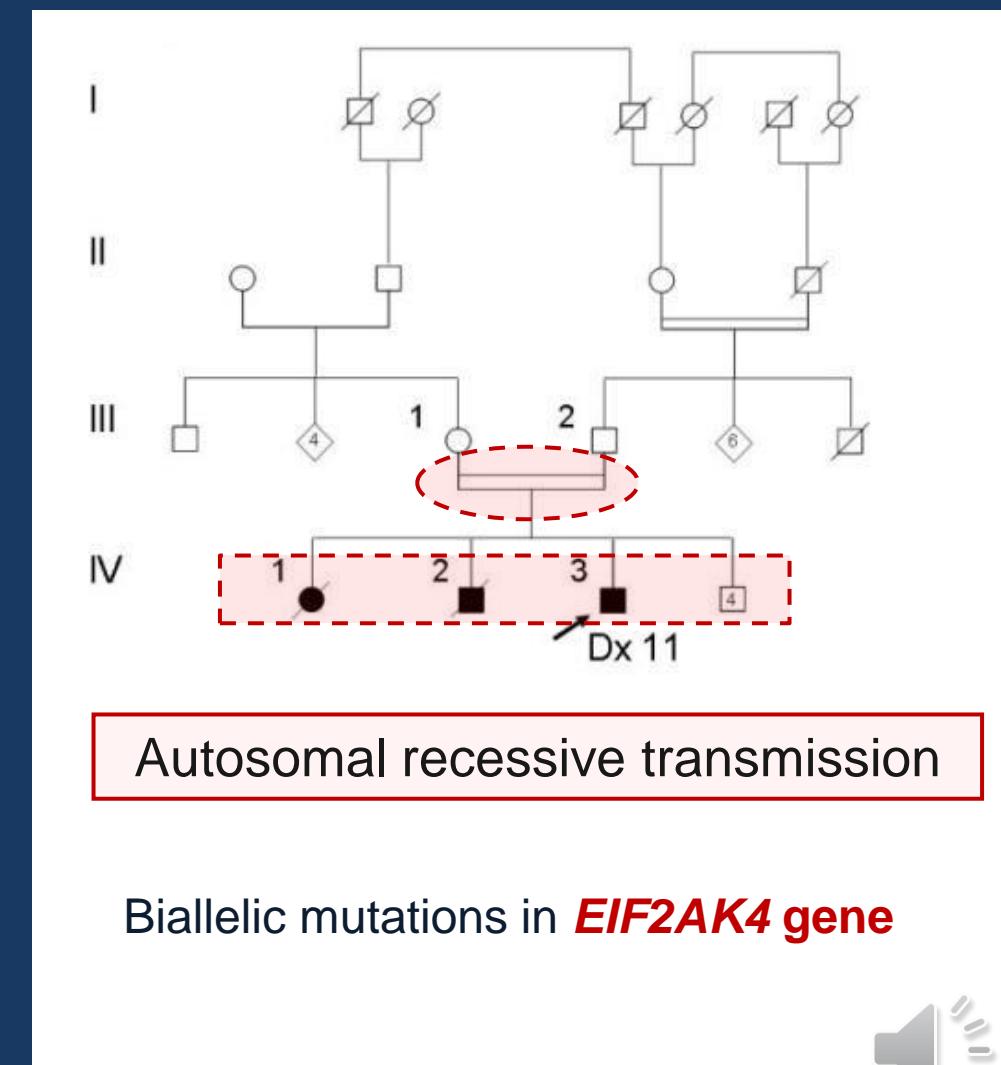
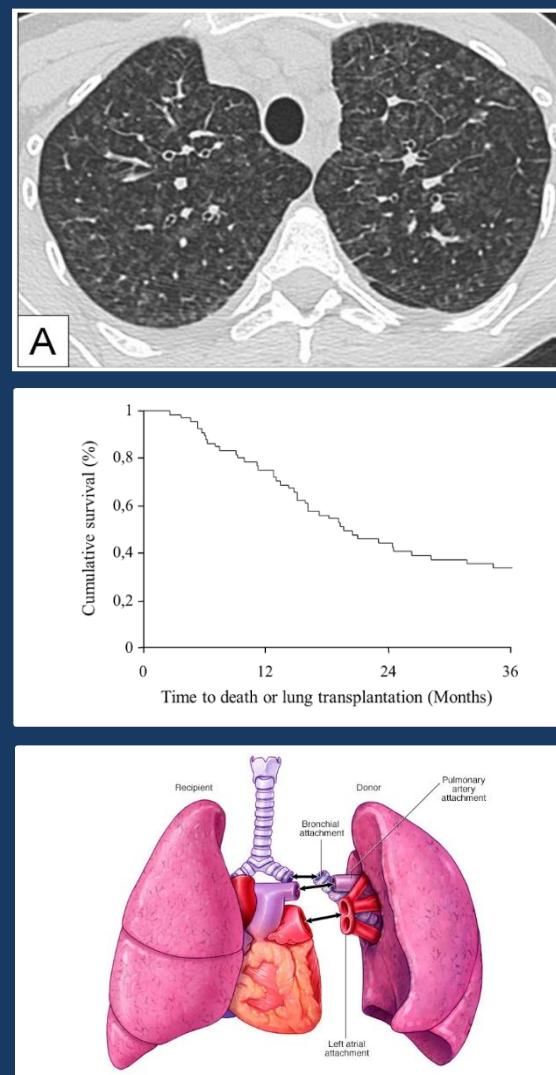
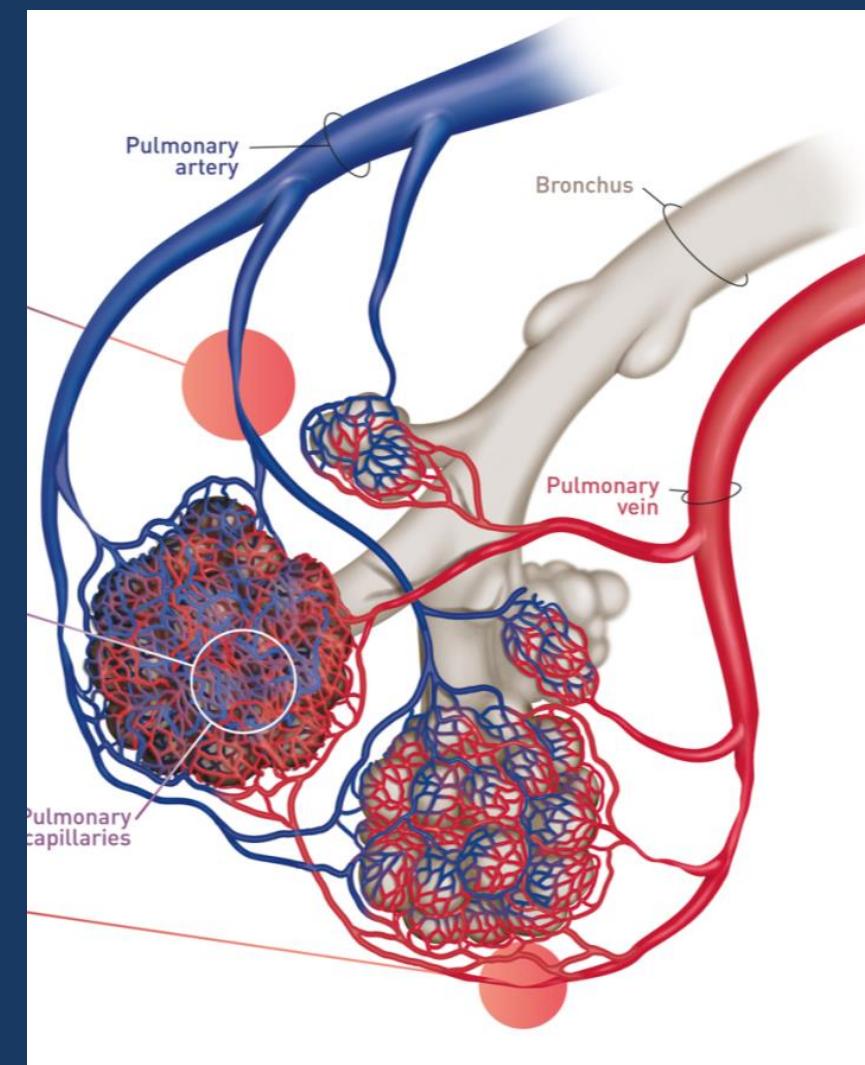
Potassium channel KCNK3:  
Control the resting membrane potential  
in many cell types (**PA-SMCs**)



# Pulmonary veno-occlusive disease



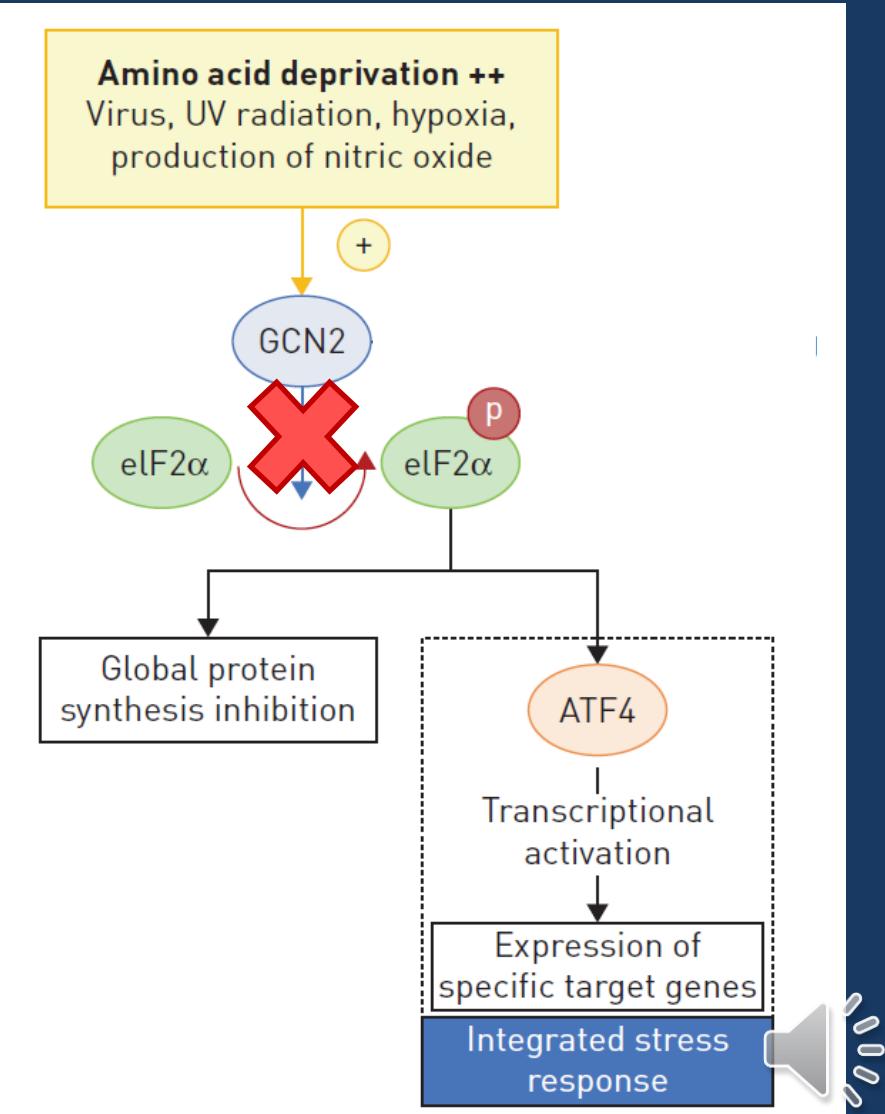
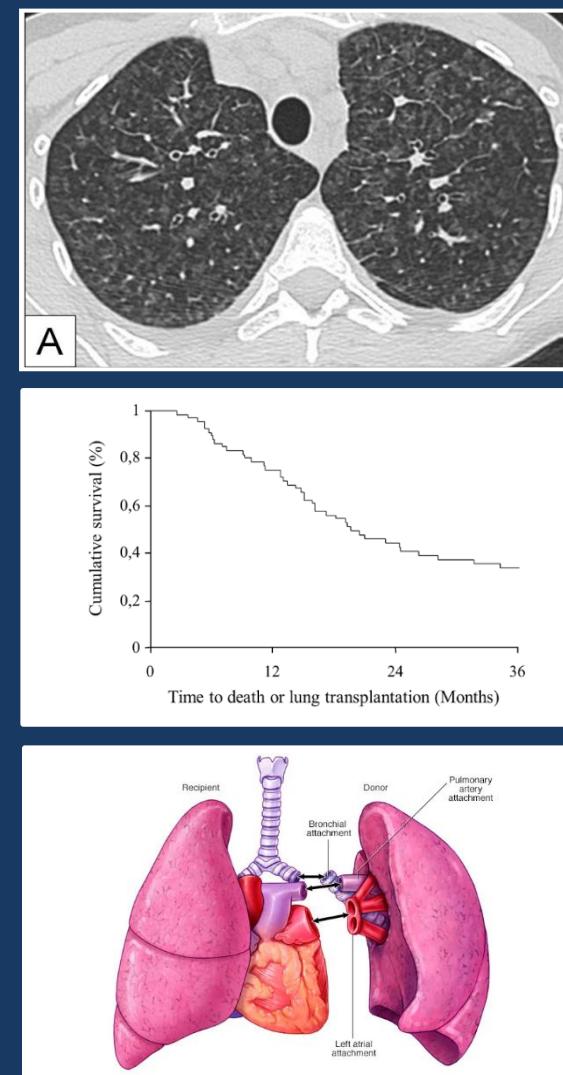
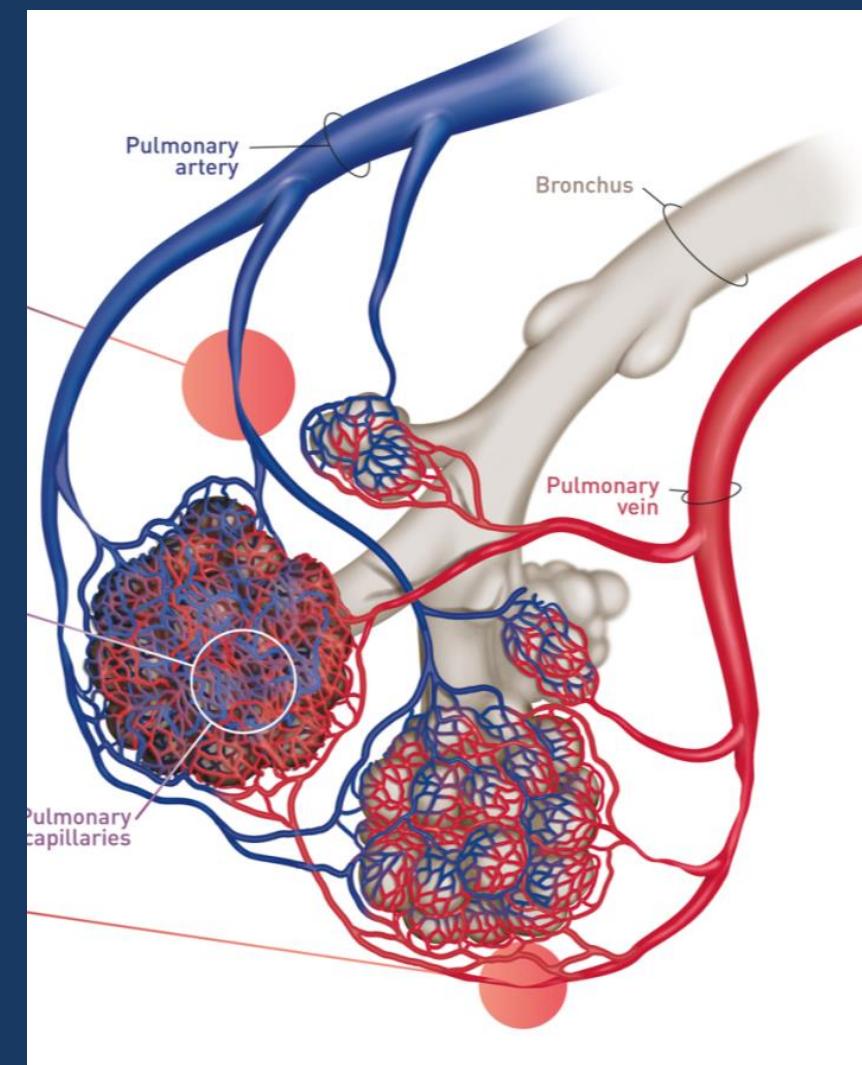
# PULMONARY VENO-OCCLUSIVE DISEASE



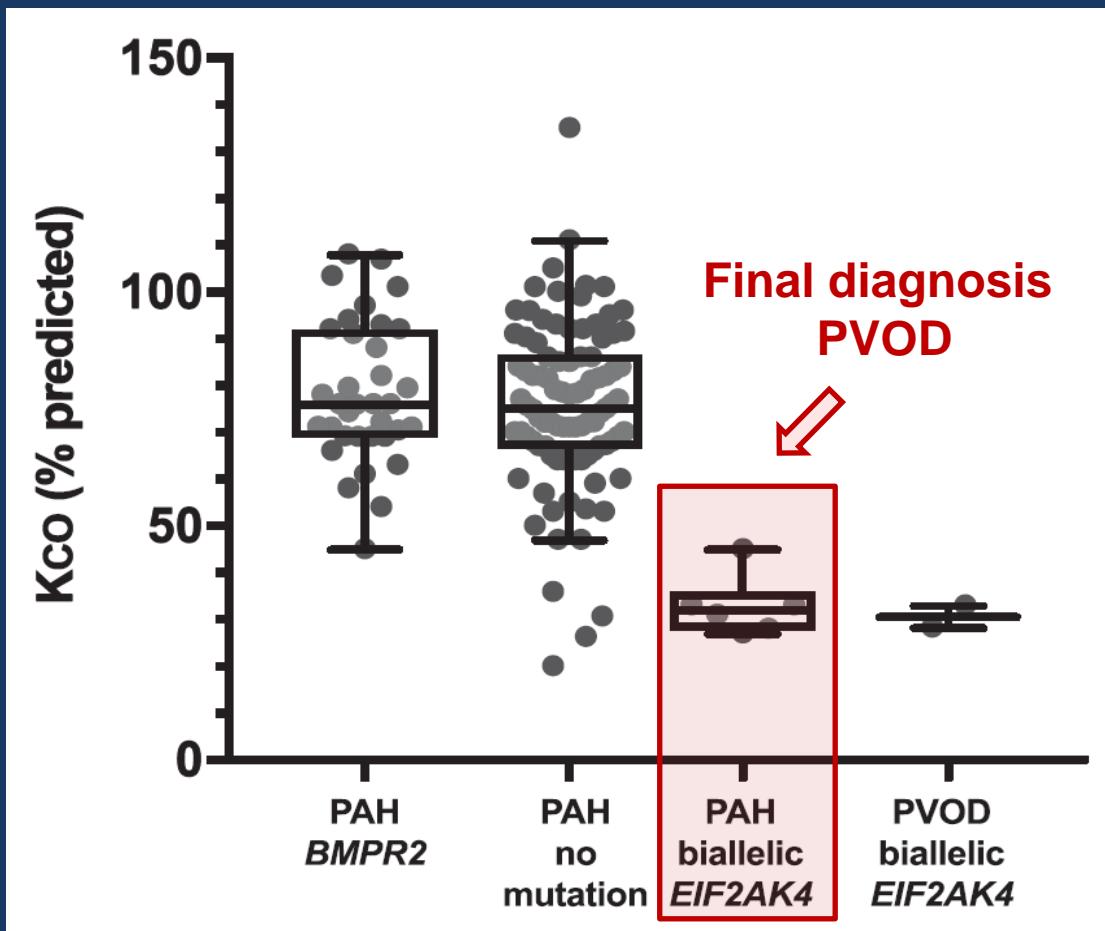
Biallelic mutations in **EIF2AK4** gene



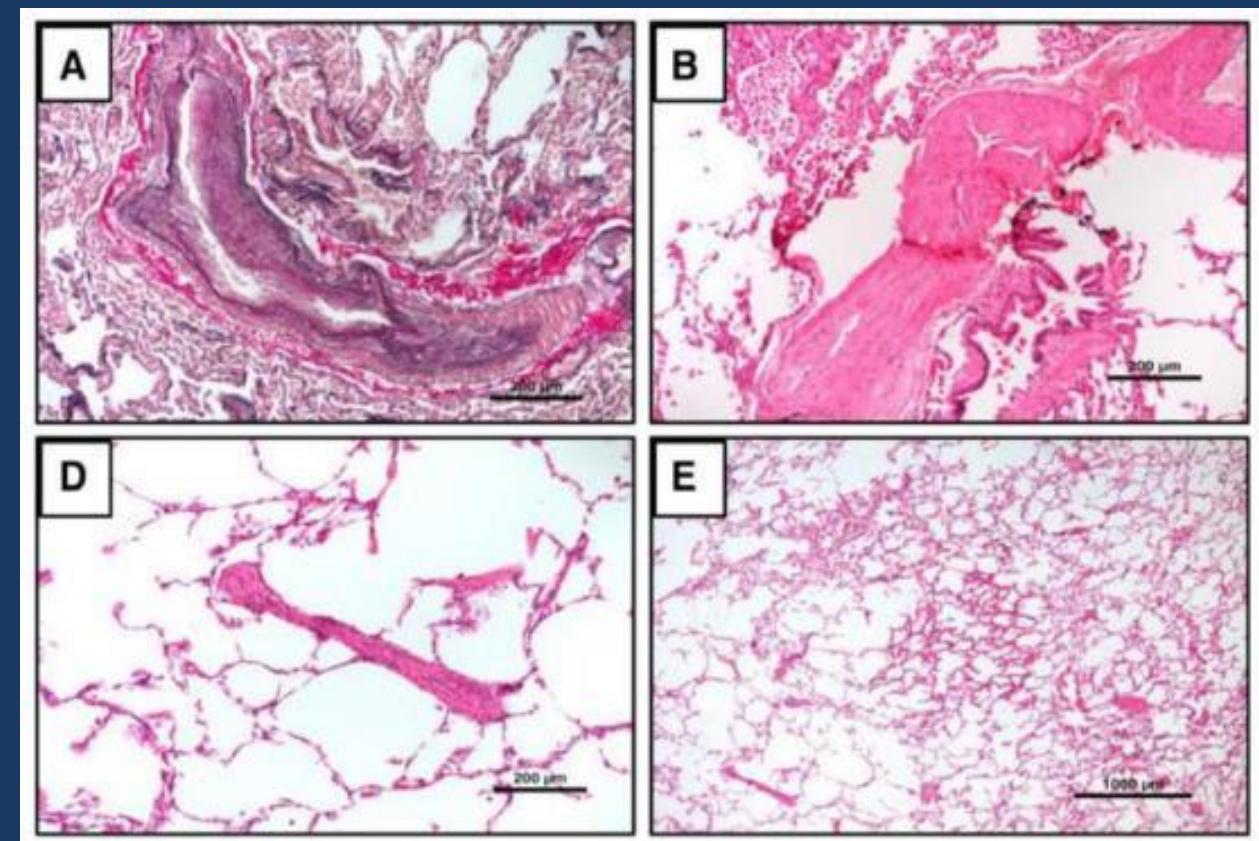
# PULMONARY VENO-OCCLUSIVE DISEASE



# GENETIC TESTING CAN CORRECT CLINICAL DIAGNOSIS



Histological analysis confirmed PVOD



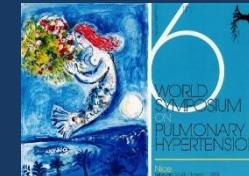
# PH and developmental genes



# PREDISPOSING GENES IN PAH : Developmental Genes

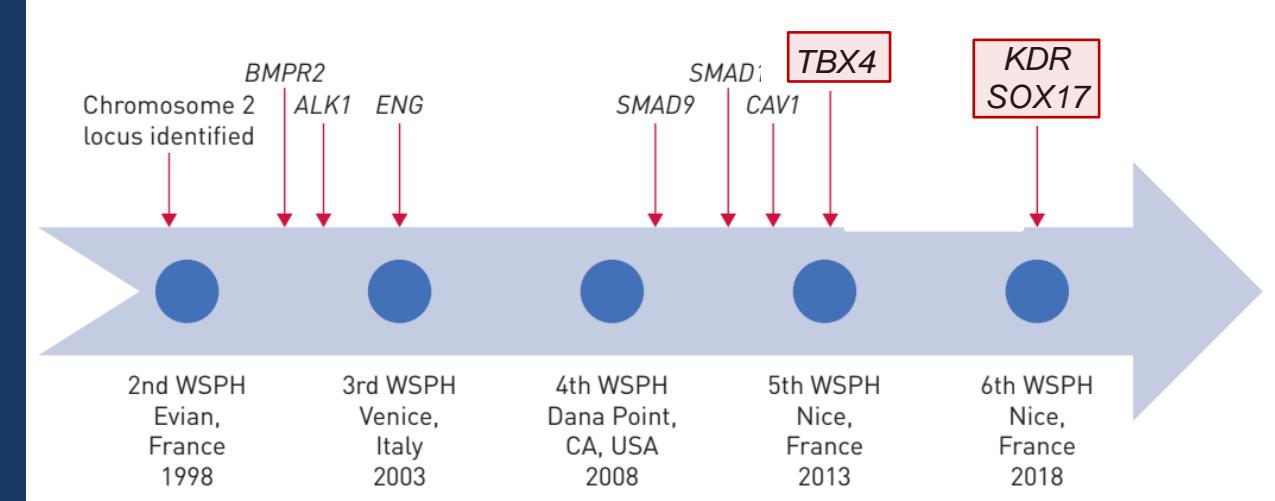
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## TASKFORCE 2: Genetics & Genomics

### Development



# **TBX4 MUTATIONS IN PAH : Small Patella Syndrome**



- Knee: patellar aplasia or hypoplasia
- irregular ossification of the ischiopubic junctions
- foot anomalies :      wide gap between the 1<sup>st</sup> and 2<sup>nd</sup> toes  
                              short 4<sup>th</sup> and 5<sup>th</sup> toes  
                              pes planus

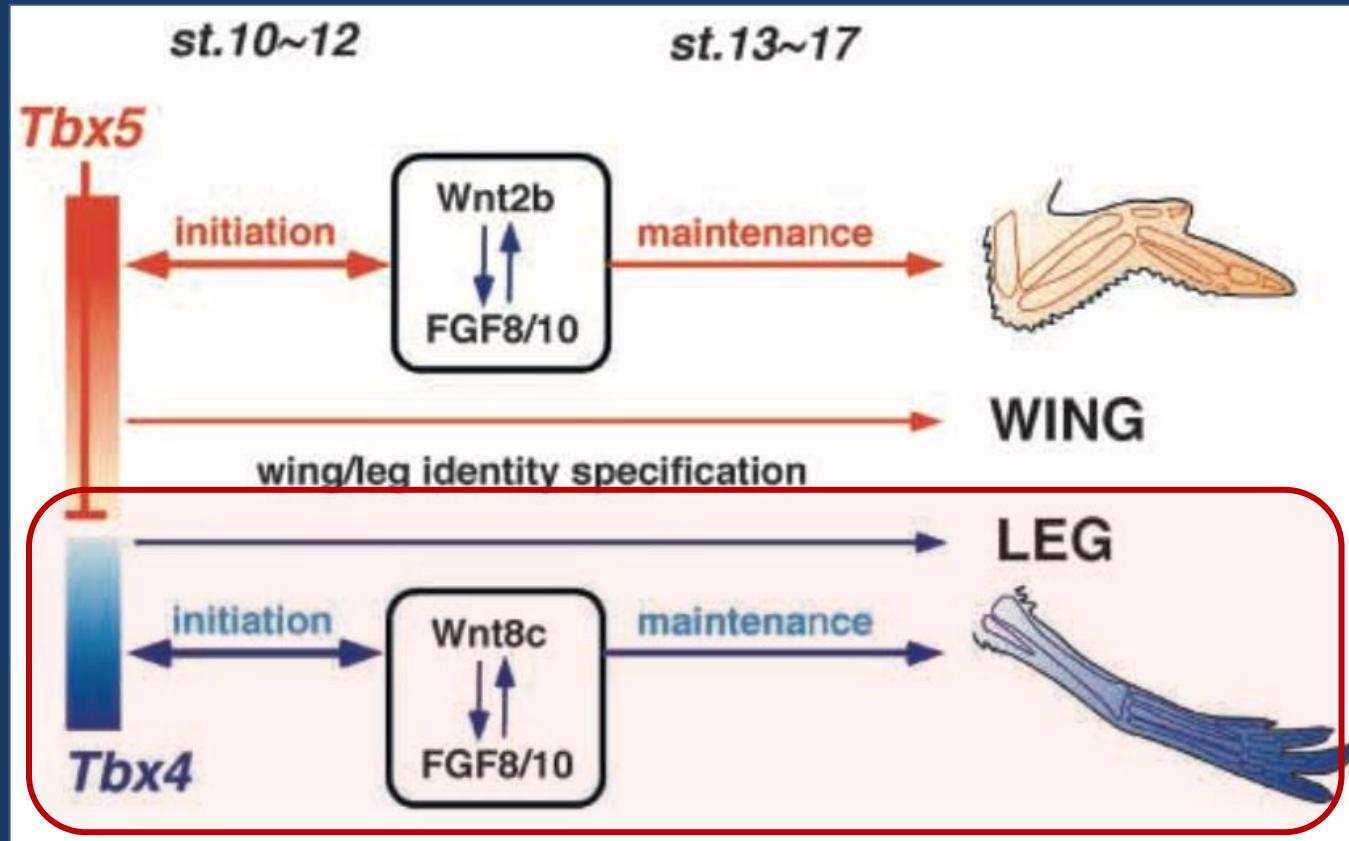


Sometimes include in the 17q23 microdeletion syndrome  
(*TBX4 / TBX2*)

⇒ Craniofacial anomalies, hear loss, congenital heart disease



# TBX4 MUTATIONS IN PAH : Small Patella Syndrome



Major variation of phenotypic expression  
usually mild or asymptomatic



# **TBX4 MUTATIONS IN PAH**

## **Phenotype characterisation of *TBX4* mutation and deletion carriers with neonatal and paediatric pulmonary hypertension**

Csaba Galambos <sup>1,19</sup>, Mary P. Mullen<sup>2,19</sup>, Joseph T. Shieh<sup>3</sup>, Nicolaus Schwerk<sup>4</sup>, Matthew J. Kielt<sup>5</sup>, Nicola Ullmann<sup>6</sup>, Renata Boldrini<sup>7</sup>, Irena Stucin-Gantar<sup>8</sup>, Cristina Haass<sup>9</sup>, Manish Bansal<sup>10</sup>, Pankaj B. Agrawal<sup>11</sup>, Joyce Johnson<sup>12</sup>, Donatella Peca<sup>7</sup>, Cecilia Surace<sup>7</sup>, Renato Cutrera <sup>6</sup>, Michael W. Pauciulo<sup>13</sup>, William C. Nichols<sup>13</sup>, Matthias Griesse<sup>14</sup>, Dunbar Ivy<sup>15</sup>, Steven H. Abman<sup>16</sup>, Eric D. Austin<sup>5</sup> and Olivier Danhaive<sup>17,18</sup>

Galambos, *Eur Respir J* 2019

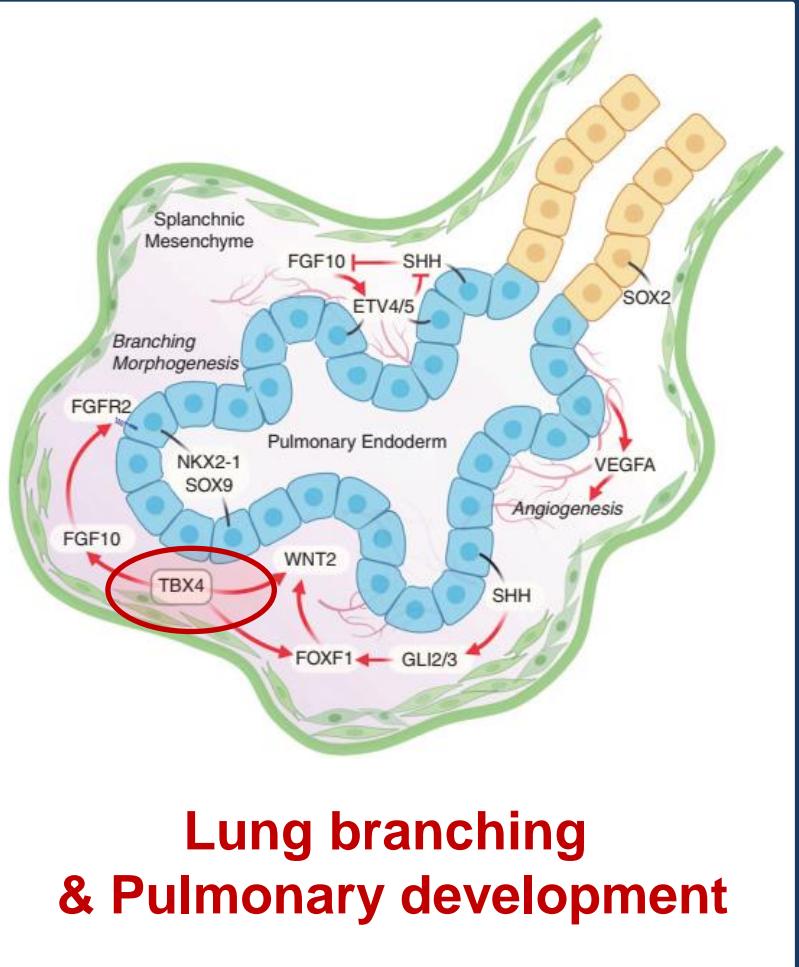
## **Phenotype and outcome of pulmonary arterial hypertension patients carrying a *TBX4* mutation**

Pierre Thoré <sup>1,2,3,16</sup>, Barbara Girerd<sup>1,4,5,16</sup>, Xavier Jais<sup>1,4,5</sup>, Laurent Savale <sup>1,4,5</sup>, Maria-Rosa Ghigna <sup>5,6</sup>, Mélanie Eyries<sup>7</sup>, Marilyne Levy<sup>8</sup>, Caroline Ovaert<sup>9</sup>, Amélie Servettaz <sup>10</sup>, Anne Guillaumot<sup>2</sup>, Claire Dauphin<sup>11</sup>, Céline Chabanne<sup>12</sup>, Emmanuel Boiffard<sup>13</sup>, Vincent Cottin <sup>14</sup>, Frédéric Perros<sup>1,4,5</sup>, Gérald Simonneau<sup>1,4,5</sup>, Olivier Sitbon <sup>1,4,5</sup>, Florent Soubrier <sup>6</sup>, Damien Bonnet<sup>8</sup>, Martine Remy-Jardin<sup>15</sup>, Ari Chaouat <sup>2,3</sup>, Marc Humbert <sup>1,4,5</sup> and David Montani <sup>1,4,5</sup>

Thoré P, *Eur Respir J* 2020



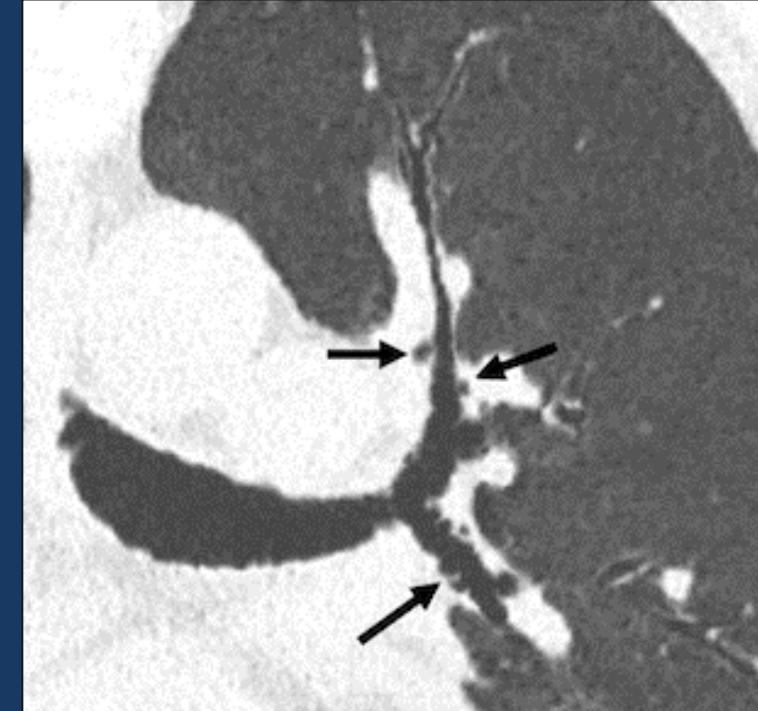
# TBX4 MUTATIONS IN PAH



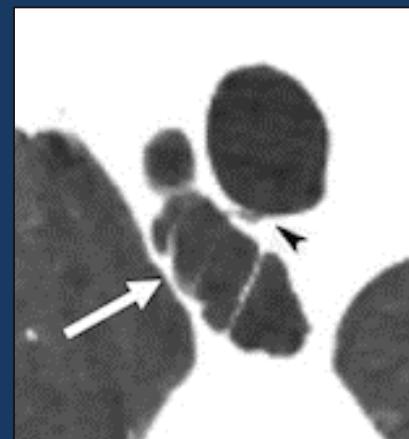
Emphysema



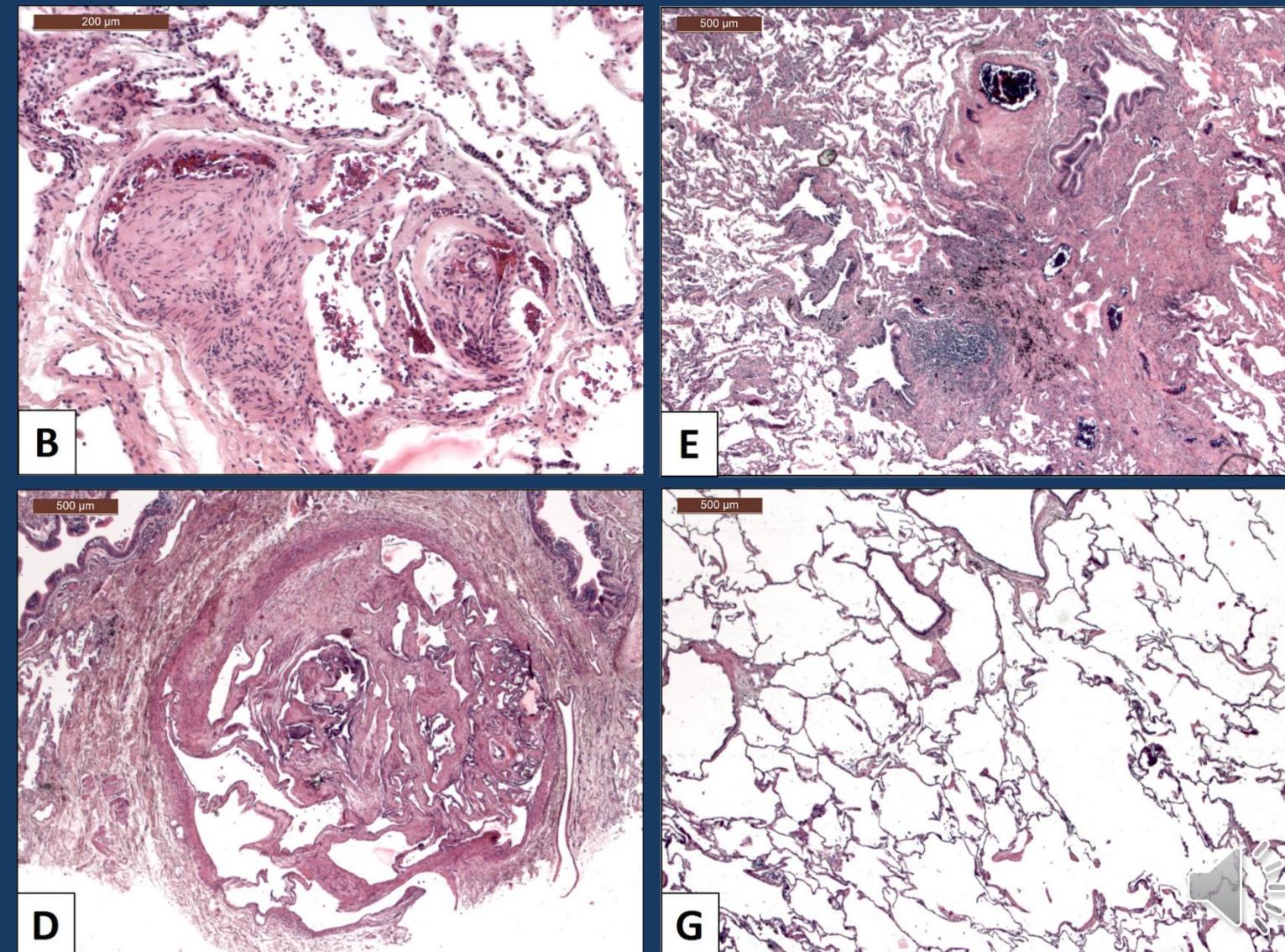
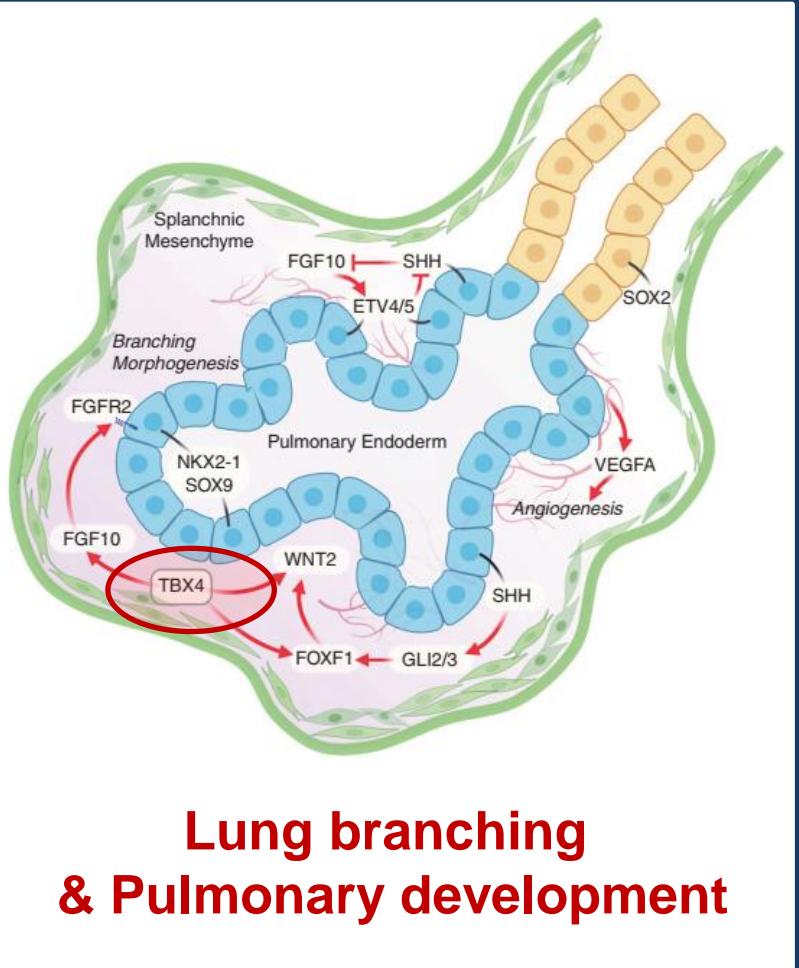
Peri-bronchial cysts



Tracheal diverticula



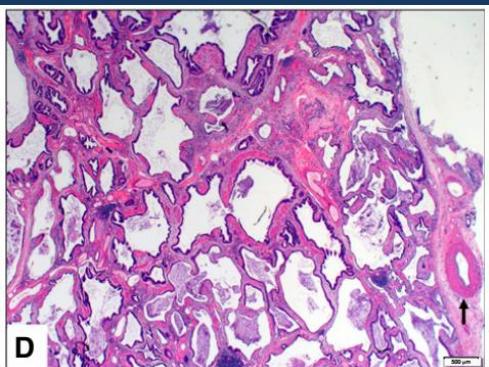
# TBX4 MUTATIONS IN PAH



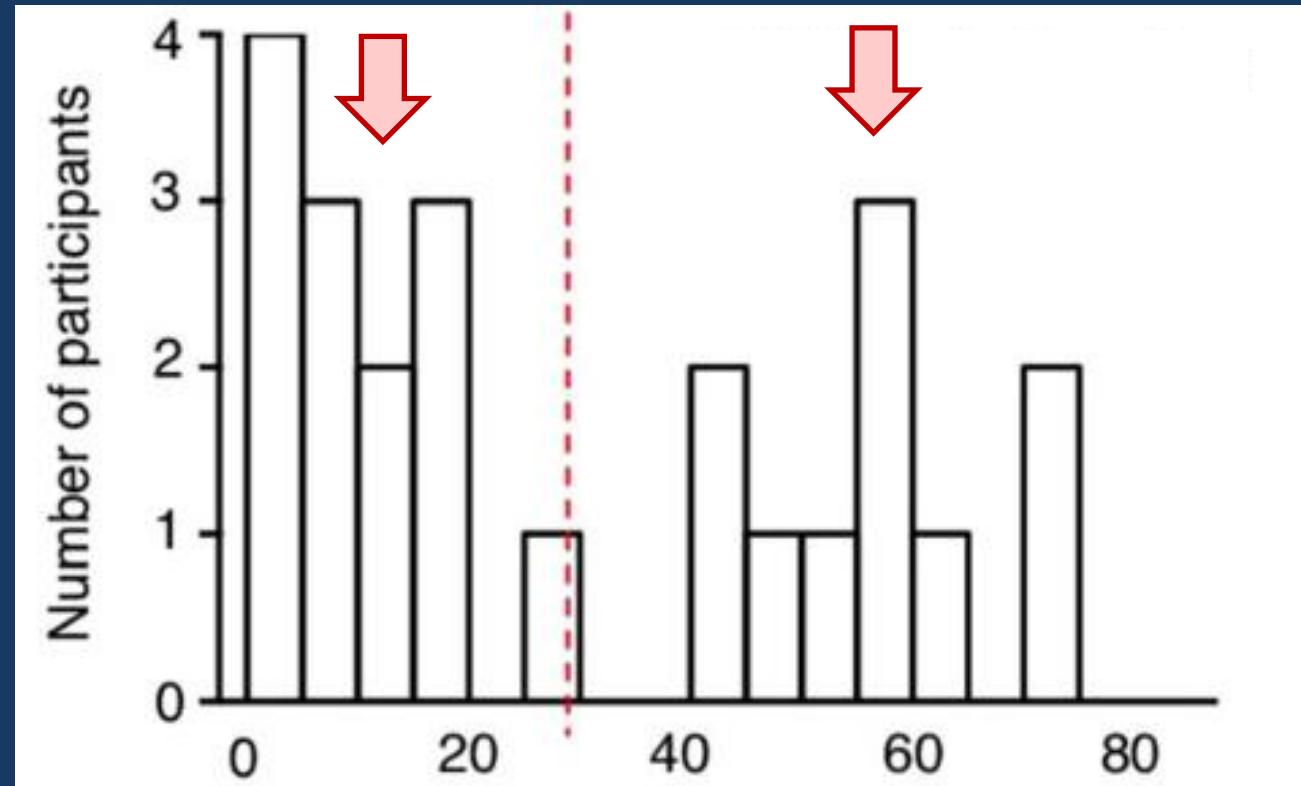
# TBX4 MUTATIONS IN PAH : Small Patella Syndrome

Severe lung developmental disorders and moderate vascular involvement

≈ PH group 3  
developmental disorders

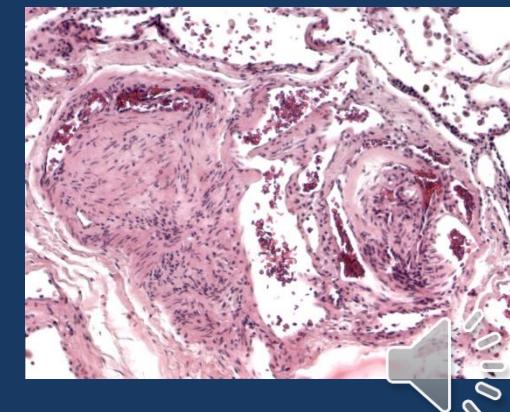


Age distribution at diagnosis of PAH

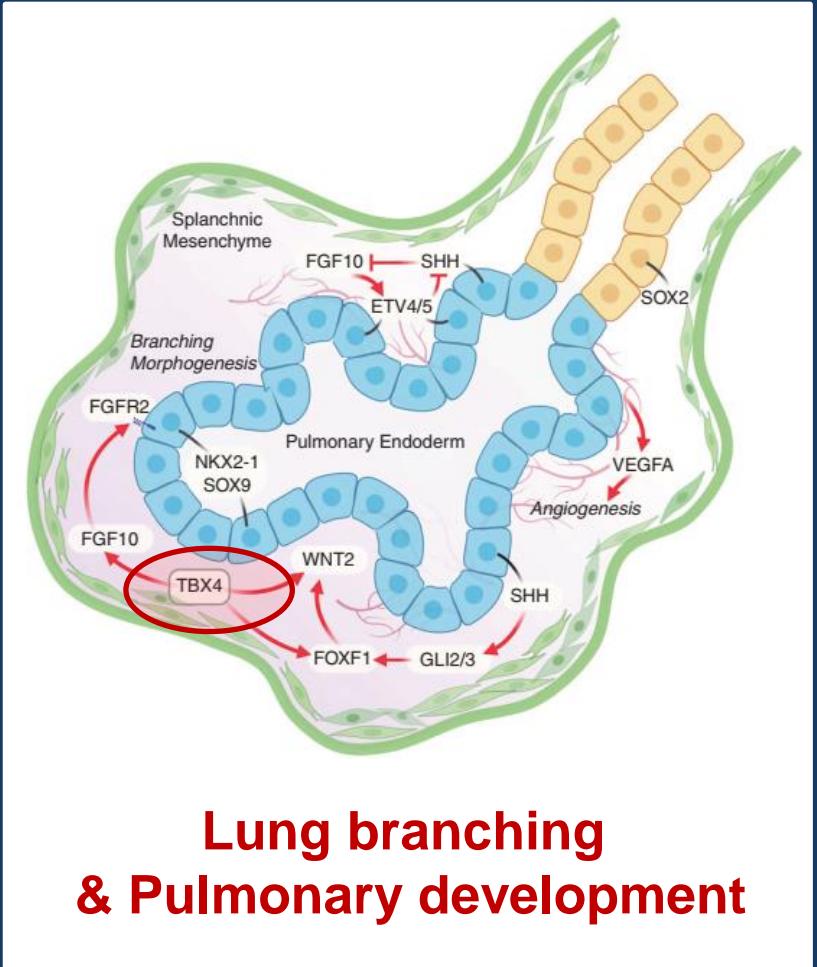


Mild or absence of lung developmental disorders and severe PH

≈ PAH group 1



# TBX4 MUTATIONS IN PAH : Small Patella Syndrome



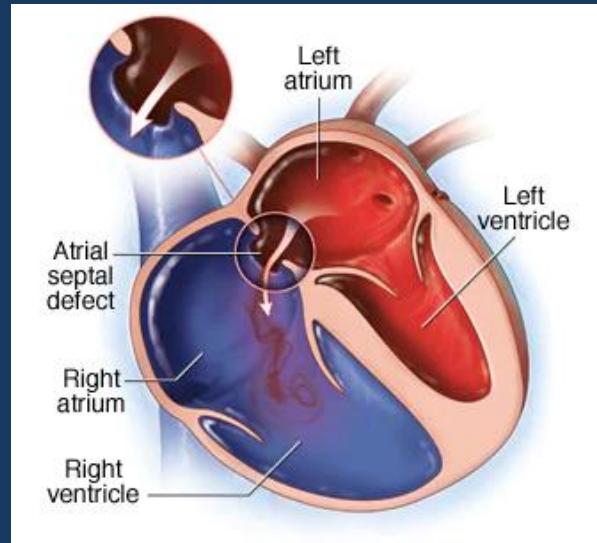
Severe PH  
&  
Non-specific  
chronic respiratory  
diseases

severe  
PH group 3 ?

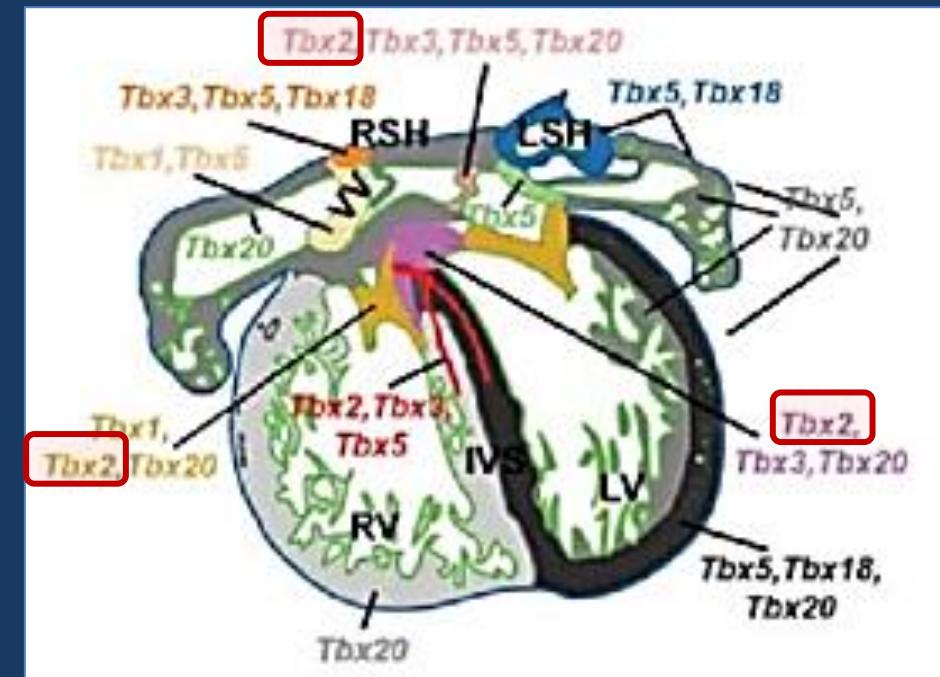


# *Small Patella syndrome: Congenital heart disease*

10-15% Congenital heart diseases  
ASD, patent ductus arteriosus



Several T-box involved in heart development

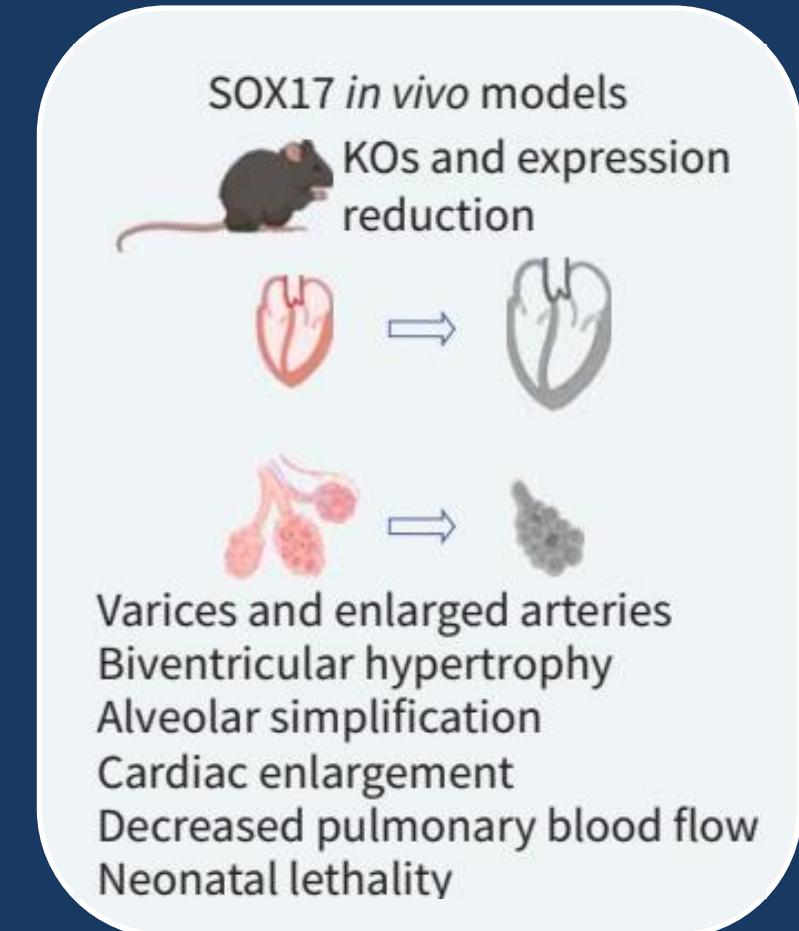
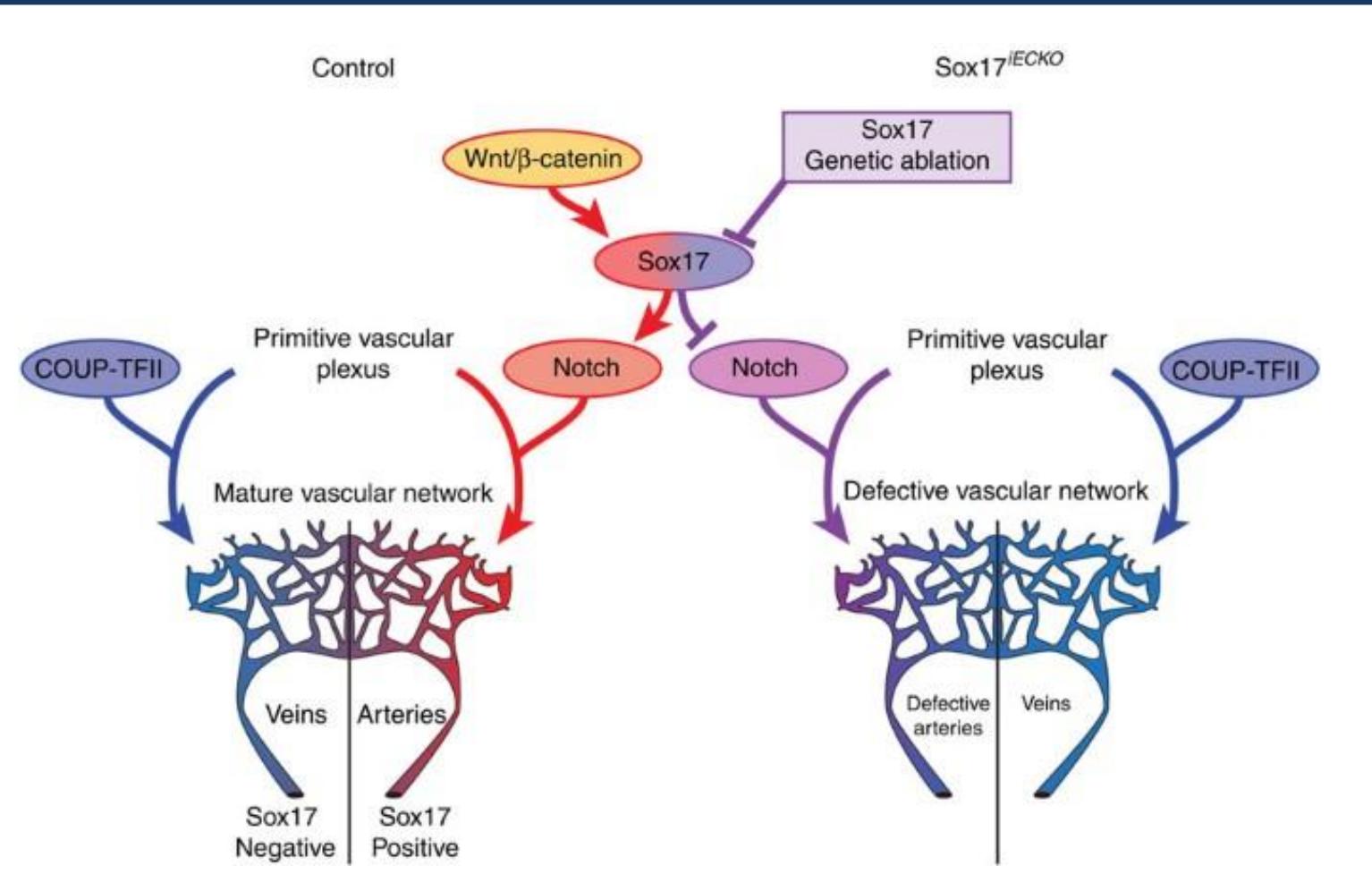


≈ PAH group 1  
Congenital heart disease

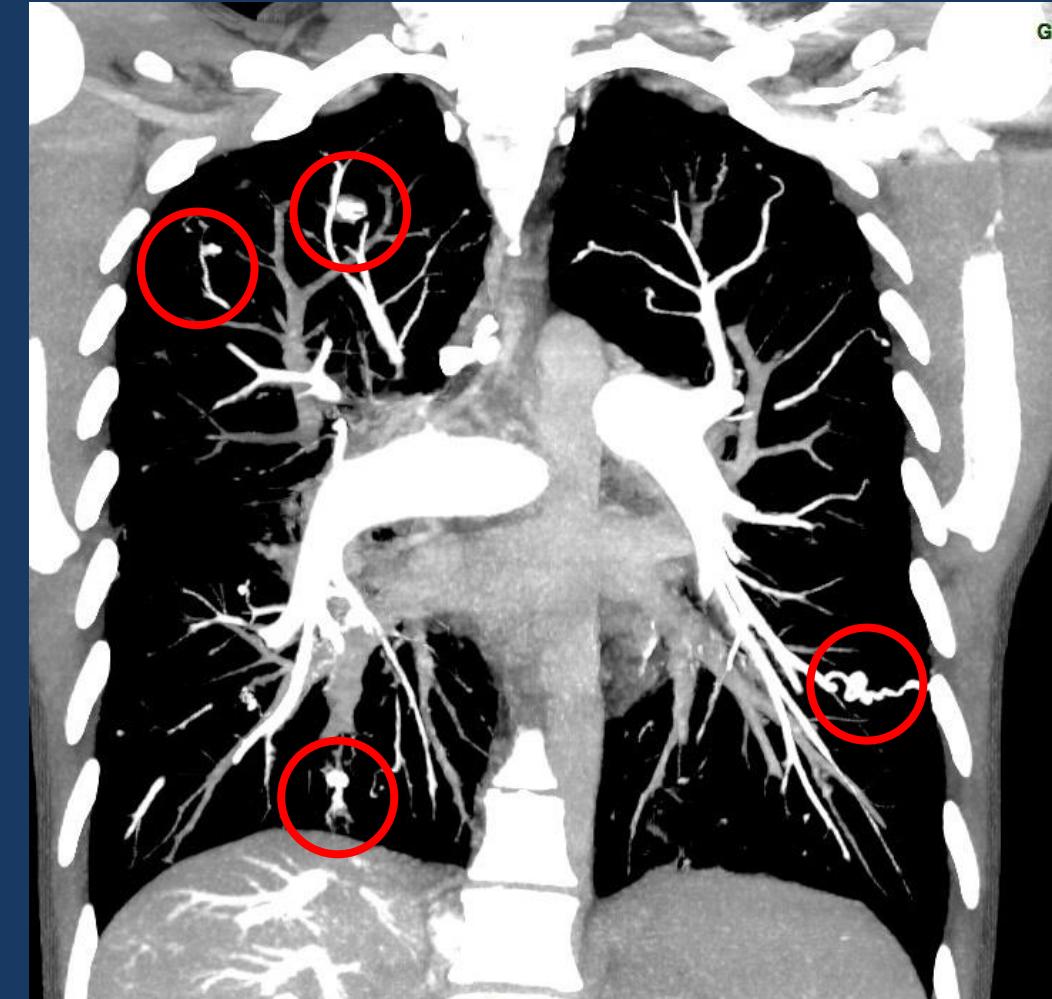
17q23 microdeletion syndrome  
(TBX4 and TBX2)



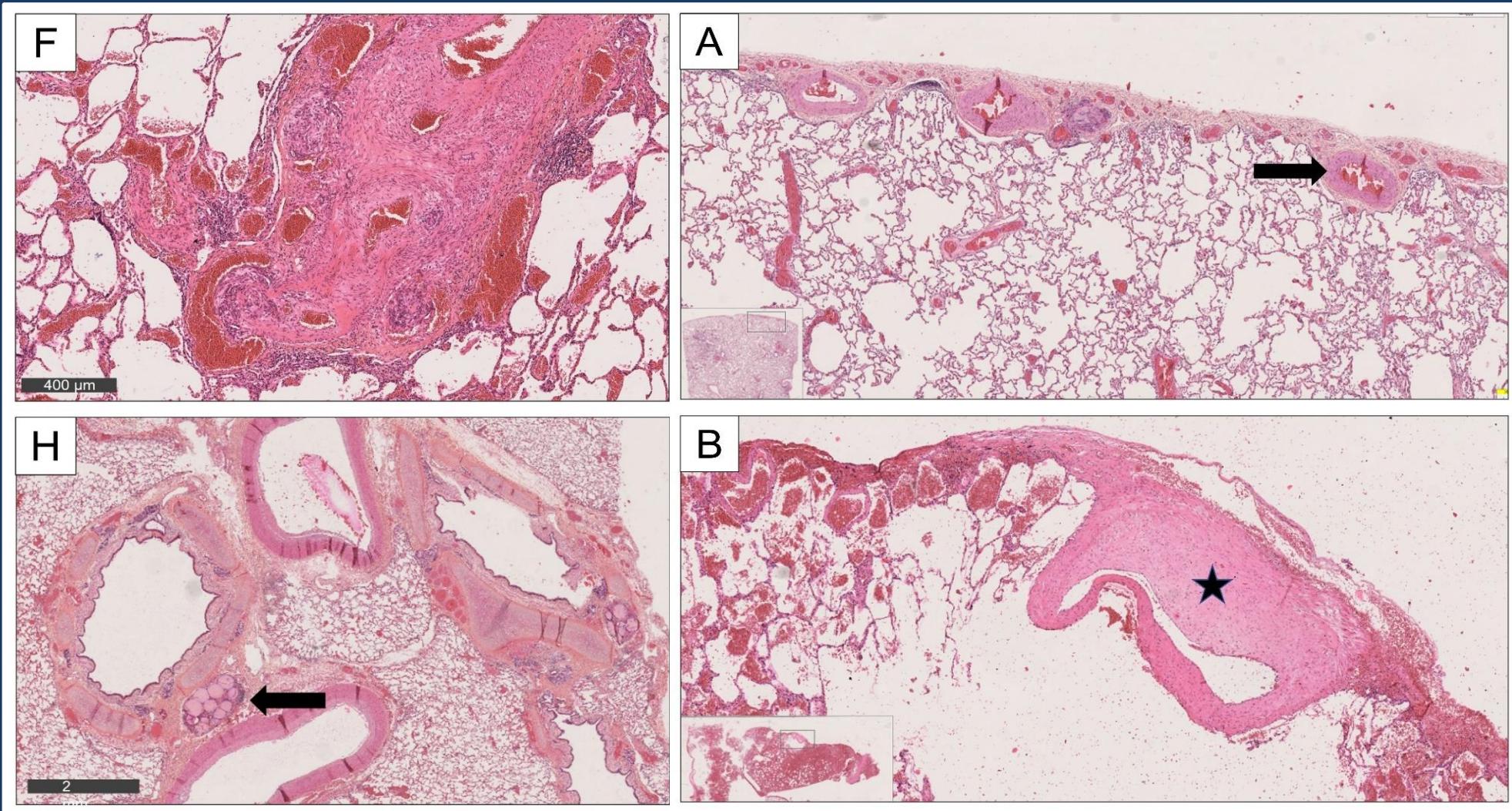
# DEVELOPMENTAL GENE in PAH: SOX17



# DEVELOPMENTAL GENE in PAH: SOX17

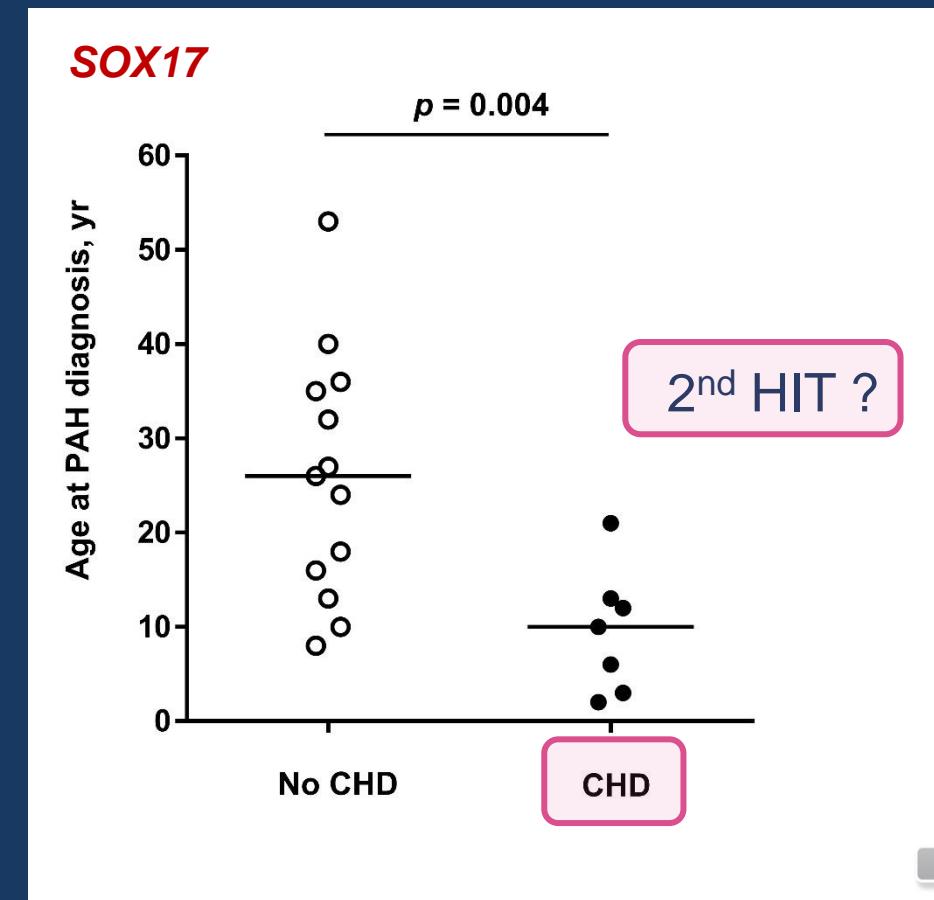
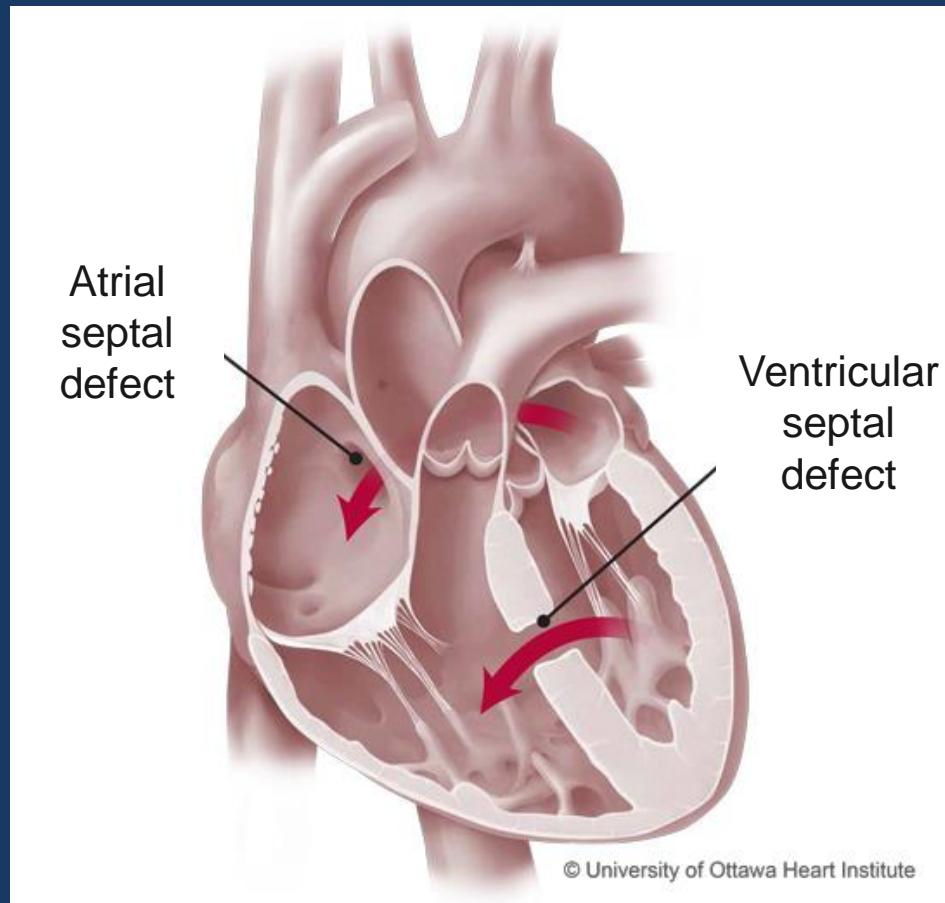


# DEVELOPMENTAL GENE in PAH: SOX17



# DEVELOPMENTAL GENE in PAH: *TBX4*, *KDR*, *SOX17*

- Frequent congenital heart diseases +++



# Depistage HTAP



# Conseil génétique de l'HTAP en France

## ➤ Strategy of genetic counselling

All PAH patients      considered to be idiopathic  
with a family history of PAH  
with anorexigen exposure

All PAH associated with CHD

All PVOD patients

} underwent genetic counseling and were offered genetic screening (no cost)

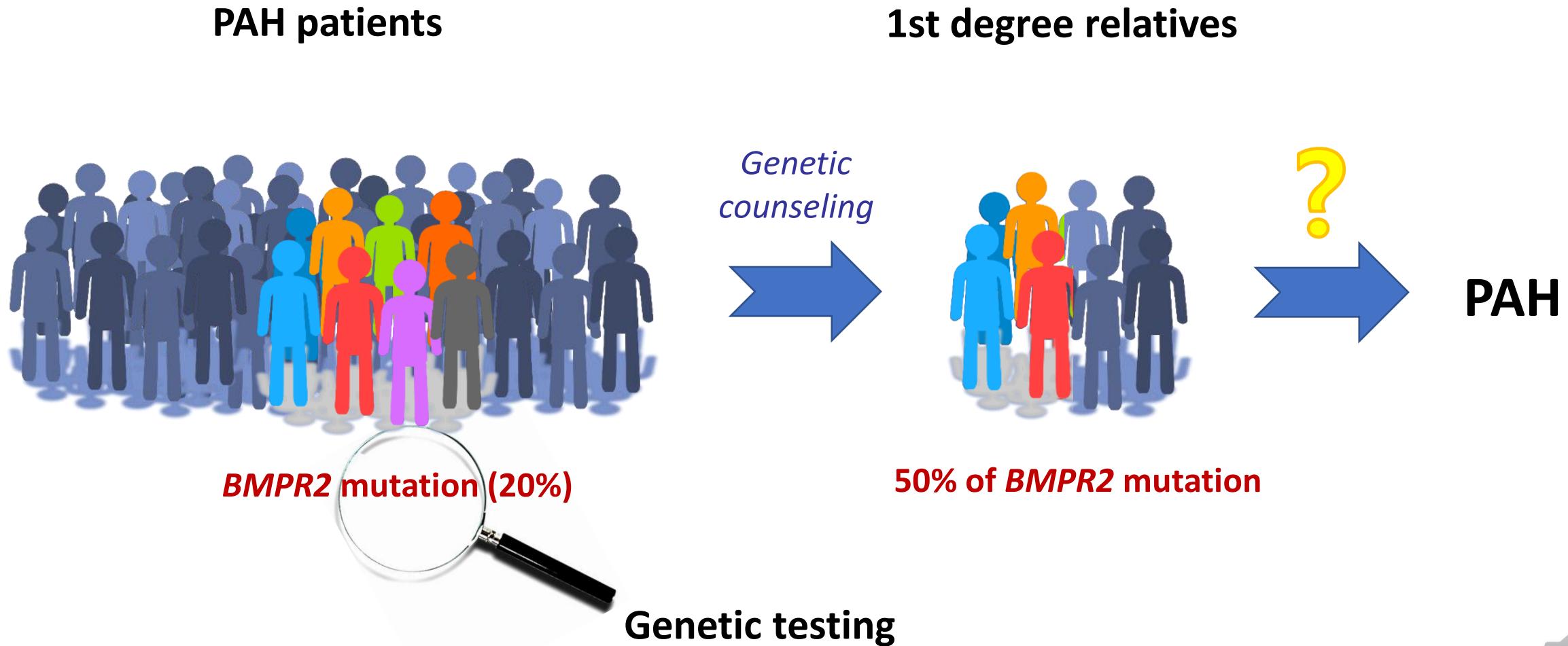
## ➤ Next Generation Sequencing (NGS)

*BMPR2, ACVRL1, ENG, CAV1, KCNK3, SMAD9, TBX4, SMAD4, GDF2, EIF2AK4....*

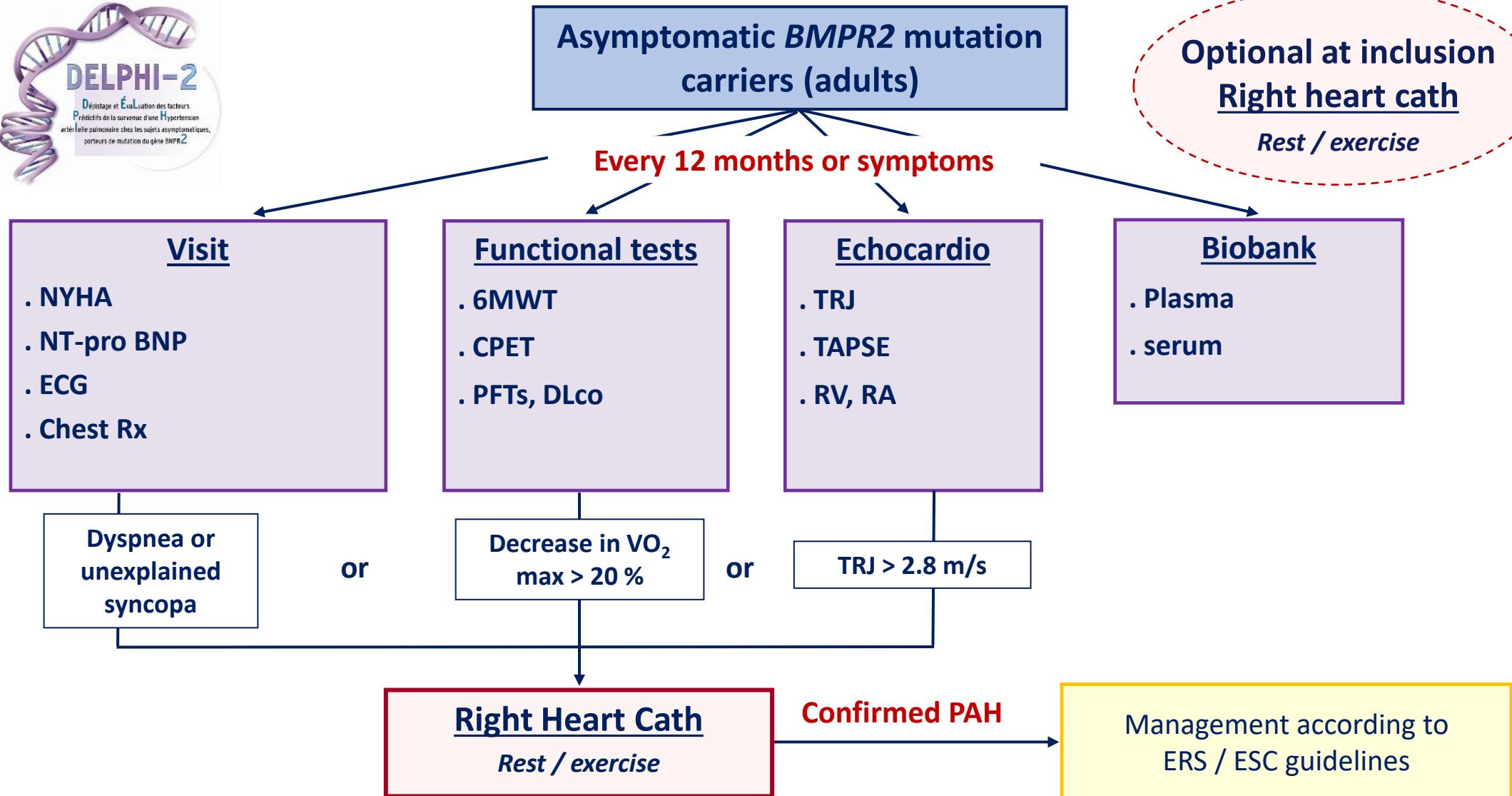
## ➤ Whole GENOME sequencing program



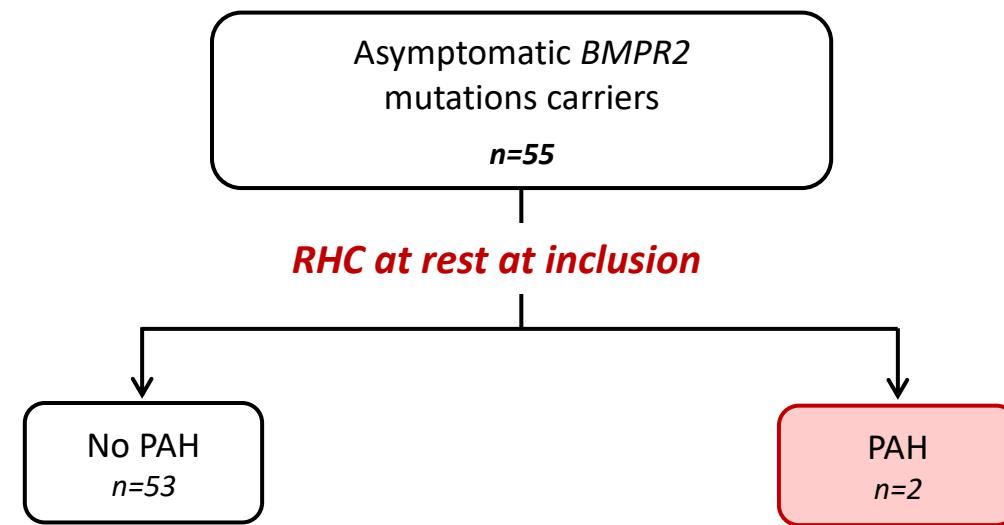
# Conseil génétique des apparentés *BMPR2*



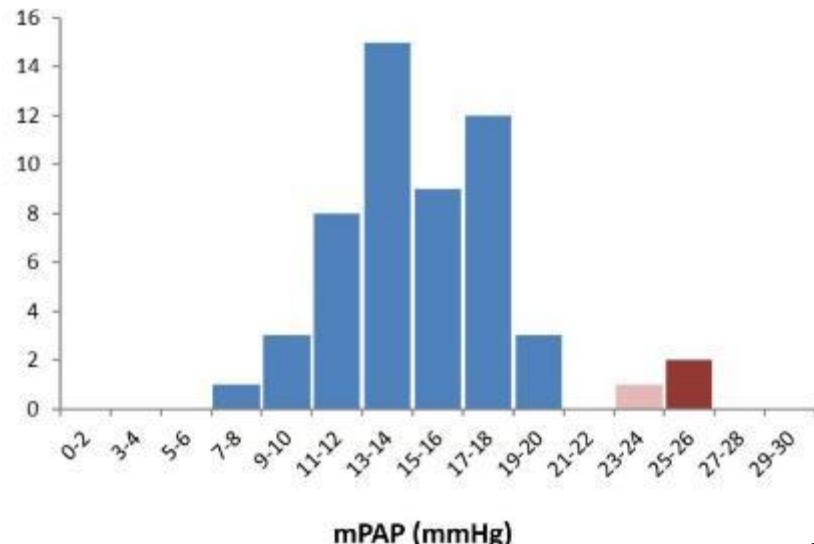
# DELPHI-2 Study



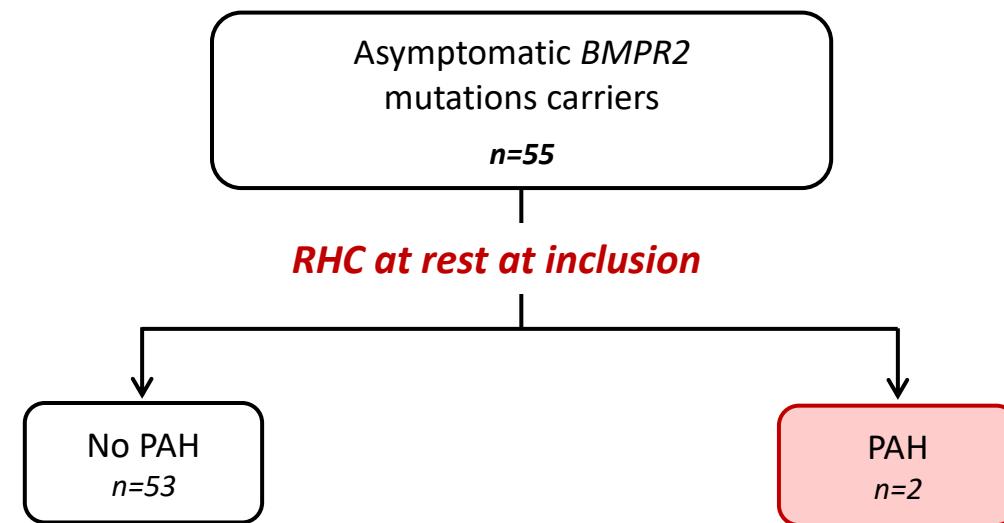
# DELPHI-2 Study



## Distribution mPAP



# DELPHI-2 Study



## Non-invasive tools for screening

*Blinded from RHC*

- Echocardiography
- ECG
- CPET (probability score)
- Pulmonary function tests
- NT-proBNP

- Echocardiography and NT-proBNP failed to screen asymptomatic PAH patients
- ECG, CPET, PFTs (DLco) may be useful



# DELPHI-2 Study

**Exercise PH :**  
early marker of pulmonary vascular remodeling ?

Asymptomatic *BMPR2*  
mutations carriers  
*n=55*

**RHC at rest at inclusion**



No PAH  
*n=53*

PAH  
*n=2*

**RHC at exercise** (*n=52*)

**RHC at exercise**

No PH at exercise  
*n=39*

PH at exercise \*  
*n=12 (23%)*

\* defined as *mPAP ≥ 30 mmHg and TPR > 3 WU*

**Long-term extension study**

247 visits, 3-5 years follow-up

PAH *n=1*  
after 6 years

= 2.5%

PAH *n=2*  
after 6 years

= 17%



# DELPHI-2 Study

## Long-term extension study

247 visits  
3 to 5 years additional period

**9.1% of asymptomatic *BMPR2* carriers developed PAH during follow-up**

**Incidence of PAH : 2.25 % /yr**

3.4% in female and 1% in male

	DELPHI-2 study		Long-term extension study		
<b>Age, years</b>	25.5	78.1	49.9	46.8	72.5
<b>Gender, M/F</b>	F	F	F	M	F
<b>NYHA</b>	I	I	II	II	I/II
<b>mPAP, mmHg</b>	25	26	43	50	29
<b>Cardiac index, L.min<sup>-1</sup>.m<sup>2</sup></b>	4.38	2.80	2.31	2.36	1.94
<b>PVR, WU</b>	2.5	4.4	9.2	9.2	7.3
<b>TRV, m/s</b>	2	2.65	4.2	4.4	3.3
<b>NT-proBNP / BNP</b>	normal	normal	increased	increased	normal



# DELPHI-2 Study

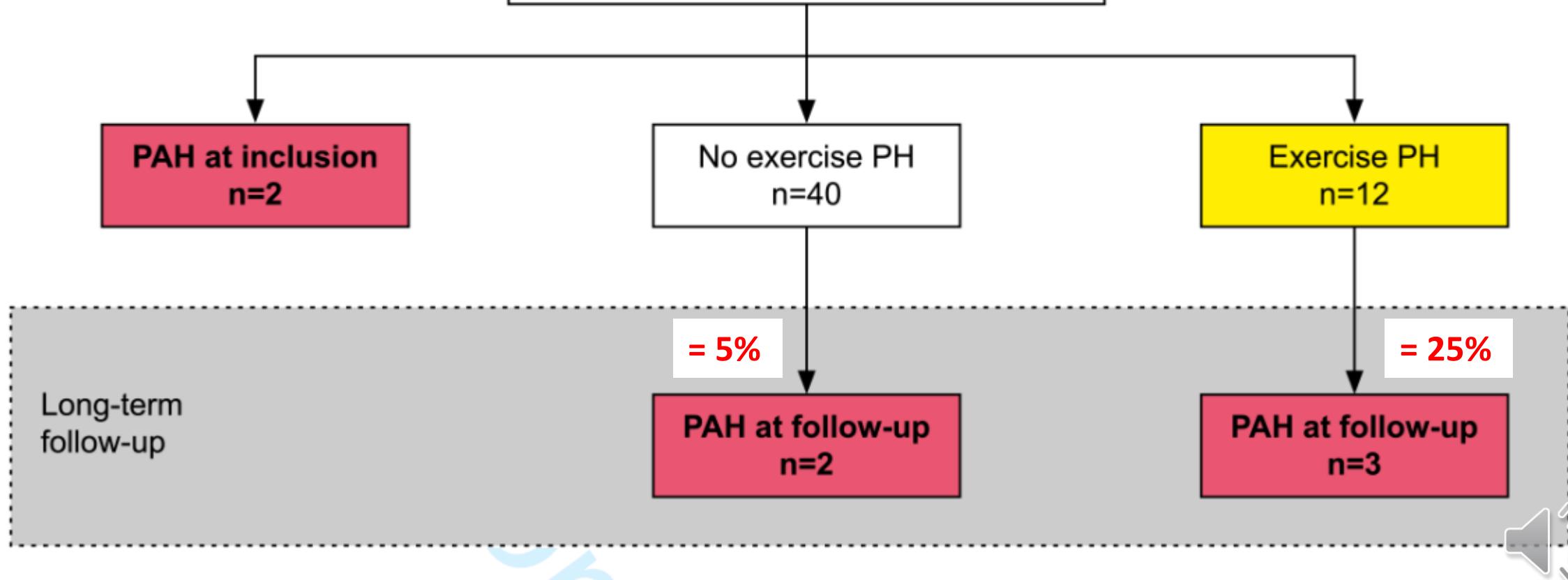
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
<b>Delay between diagnosis and assessment, months</b>	101	99	35	36	35
<b>PAH therapies</b>	ERA + PDE5i	iPDE5	ERA + PDE5i	ERA + PDE5i	ERA + PDE5i
<b>REVEAL 2.0 Score</b>					
Score at last follow-up	4 (low risk)	4 (low risk)	5 (low risk)	2 (low risk)	3 (low risk)
<b>ESC/ERS Guidelines</b>					
<b>Signs of right heart failure</b>	No	No	No	No	No
<b>Progression of symptoms</b>	No	No	No	No	No
<b>Syncope</b>	No	No	No	No	No
<b>NYHA functional class</b>	II	I	II	I	II
<b>6MWD, m</b>	587	358	454	490	533
<b>NT-proBNP, ng/mL</b>	96	234	66	92	113
<b>Echocardiography : RA area</b>	< 18	< 18	-	< 18	< 18
<b>PE</b>	No	No		No	No
<b>RHC RAP, mmHg</b>	6	7	5	4	11
<b>Cl, L.min<sup>-1</sup>.m<sup>2</sup></b>	2.57	2.56	2.83	2.42	2.68
<b>SvO<sub>2</sub>, %</b>	71	68	73	71	71



# DELPHI-2 Study

**Exercise PH :**  
early marker of pulmonary  
vascular remodeling ?

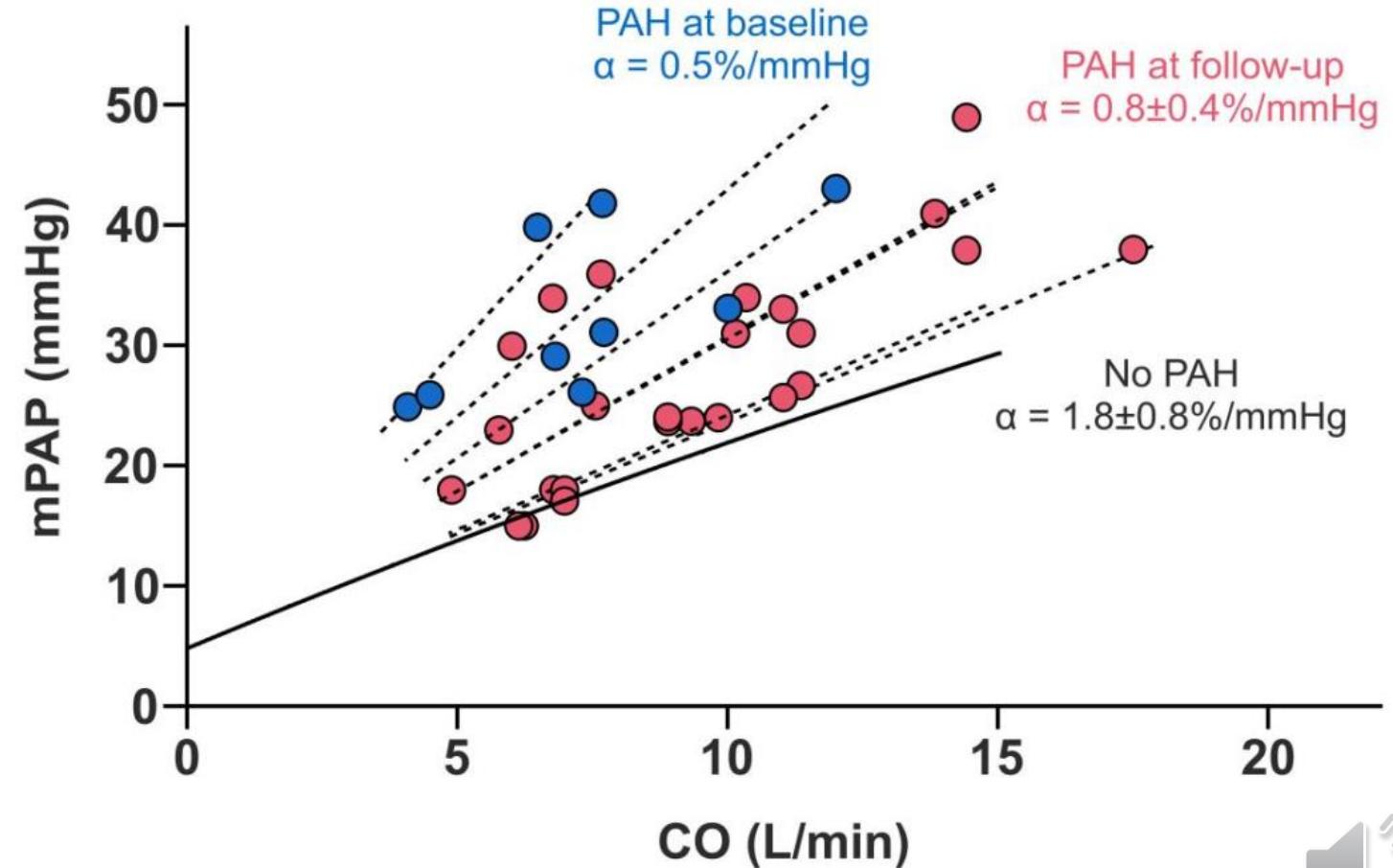
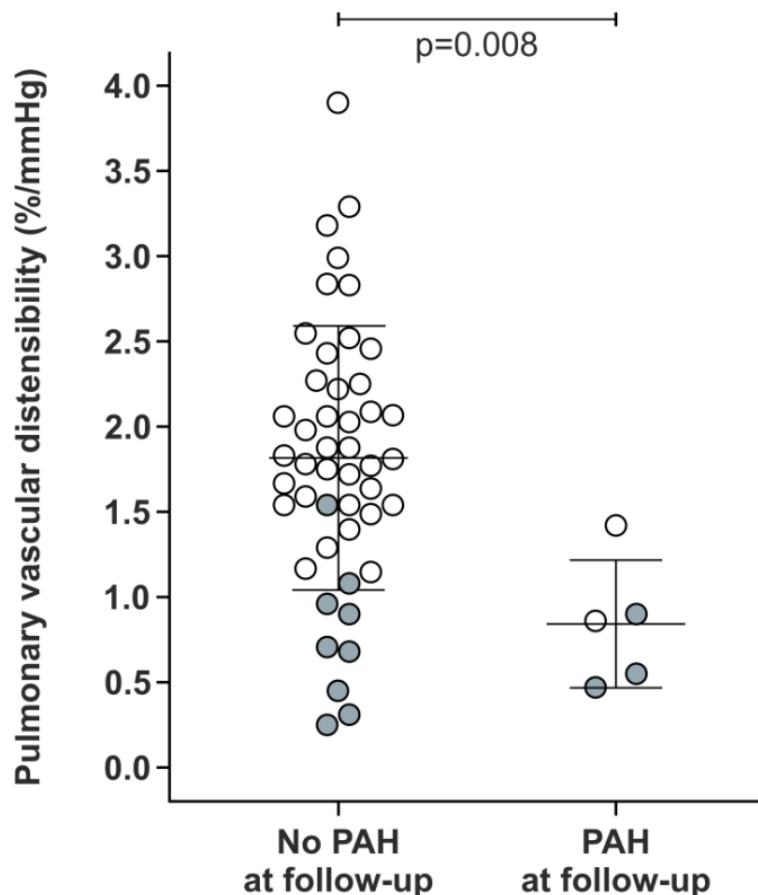
Asymptomatic *BMPR2* mutation carriers  
undergoing RHC at rest and exercise  
n=54



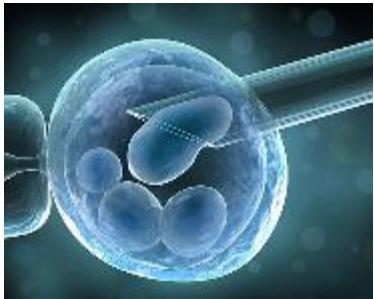
# DELPHI-2 Study

## Pulmonary vascular distensibility

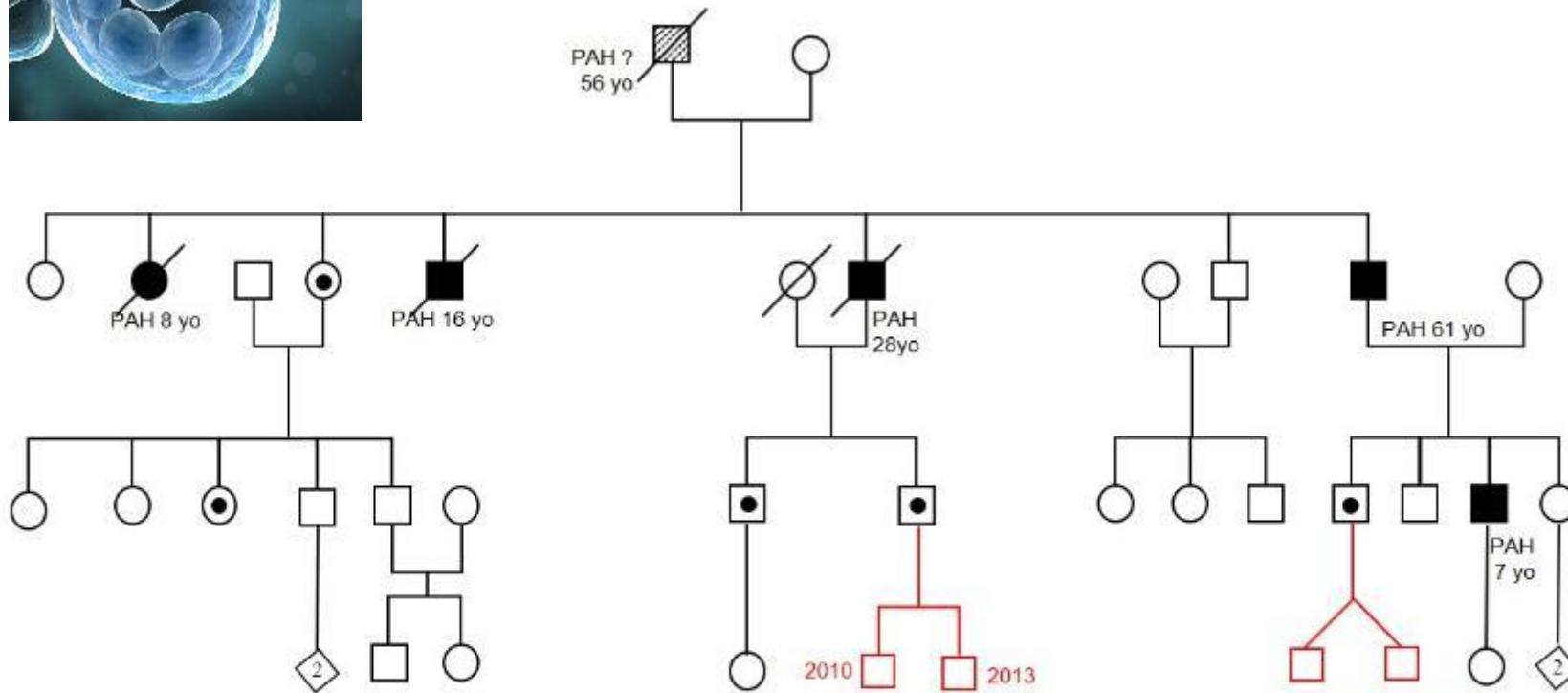
$$mPAP = [(1 + \alpha * mPAWP)^5 + 5\alpha R_0 CO]^{1/5} - 1$$



# CONSEIL GENETIQUE DANS L'HTAP



Pre-implantation genetic diagnosis in pulmonary arterial hypertension due to *BMPR2* mutation



# Conclusions



# CONCLUSIONS

## 2022 ESC/ERS Clinical classification of PH

### GROUP 1 Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
  - 1.2 Heritable<sup>a</sup>
  - 1.3 Associated with drugs and toxins<sup>a</sup>
  - 1.4 Associated with:
    - 1.4.1 Connective tissue disease
    - 1.4.2 HIV infection
    - 1.4.3 Portal hypertension
    - 1.4.4 Congenital heart disease
    - 1.4.5 Schistosomiasis
  - 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
  - 1.6 Persistent PH of the newborn

### GROUP 2 PH associated with left heart disease

- 2.1 Heart failure:
  - 2.1.1 with preserved ejection fraction
  - 2.1.2 with reduced or mildly reduced ejection fraction<sup>b</sup>
- 2.2 Valvular heart disease
- 2.3 Congenital/acquired cardiovascular conditions leading to post-ca

TBX4,  
KDR, SOX17

### GROUP 3 PH associated with lung diseases and/or hypoxia

- 3.1 Obstructive lung disease or emphysema
- 3.2 Restrictive lung disease
- 3.3 Lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoventilation syndromes
- 3.5 Hypoxia without lung disease (e.g. high altitude)
- 3.6 Developmental lung disorders

### GROUP 4 PH associated with pulmonary artery obstructions

- 4.1 Chronic thrombo-embolic PH
- 4.2 Other pulmonary artery obstructions<sup>c</sup>

### GROUP 5 PH with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders<sup>d</sup>
- 5.2 Systemic disorders<sup>e</sup>
- 5.3 Metabolic disorders<sup>f</sup>
- 5.4 Chronic renal failure with or without haemodialysis
- 5.5 Pulmonary tumour thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis



# Stratégie du conseil génétique en France



## CONSEIL GENETIQUE

Toutes les HTAP et MVO familiales et « idiopathiques »  
HTAP associée à cardiopathie congénitale

Proposition de test génétique  
*Sans coût financier pour le patient*

### PANEL NGS (Pitié-Salpêtrière)

> 20 gènes de prédisposition testés

+

#### HTAP héritable

> 95% des formes familiales  
> 15% des HTAP sporadiques

-



#### HTAP sans cause génétique identifiée



### Conseil génétique ( $\pm$ test) des apparentés du 1<sup>er</sup> degré

*obligation légale*



# Genetic in PAH

## *Genotype-Phenotype Relationship*

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University Paris-Saclay

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