Unravelling the genetics of pulmonary hypertension

Pr David Montani

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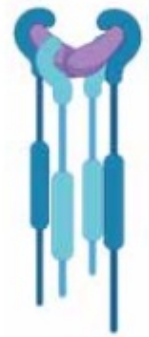
Conflicts of interest

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, Boerhinger, Ferrer, GSK, Janssen, Pfizer, MSD, Acceleron
Honoraria or consultation fees:	Actelion, Bayer, Boerhinger, 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

HISTORY OF GENETIC DISCOVERY IN HERITABLE PAH

PAH predisposing genes



BMP/TGF-β family	Channels	Transcription factors	Other
ACVRL1 (ALK1)[#]	*ATP13A3* (ATPase 13A3)	*EIF2AK4* (GCN2)[¶]	*KDR* (VEGFR2)
BMPR2 (BMPR2)	*KCNK3* (TASK1)	*SOX17* (SOX17)[+]	*TET2* (TET2)
ENG (endoglin)[#]	*ABCC8* (MRP8)	*TBX4* (TBX4)[+]	*GGCX* (GGCX)
GDF2 (BMP9)			
SMAD9 (SMAD8)			
CAV1 (caveolin-1)			

HISTORY OF GENETIC DISCOVERY IN HERITABLE PAH

Gene	Pulmonary hypertension phenotypic association	Putative molecular mechanism	Inheritance pattern
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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
CAV1	Heritable and idiopathic PAH Lipodystrophy	Gain of function; dominant negative	Autosomal dominant
TBX4	Heritable and idiopathic PAH Small patella syndrome (ischiopatellar dysplasia) Parenchymal lung disease Bronchopulmonary dysplasia Persistent pulmonary hypertension of the neonate	Unknown	Autosomal dominant
EIF2AK4	Pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis	Loss of function	Autosomal recessive
KDR	Heritable and idiopathic PAH	Loss of function	Autosomal dominant
ENG		Unknown	Autosomal dominant
ACVRL1	Heritable and idiopathic PAH; hereditary haemorrhagic telangiectasia	Haploinsufficiency	Autosomal dominant
GDF2		Haploinsufficiency	Autosomal dominant

Autosomal dominant transmission

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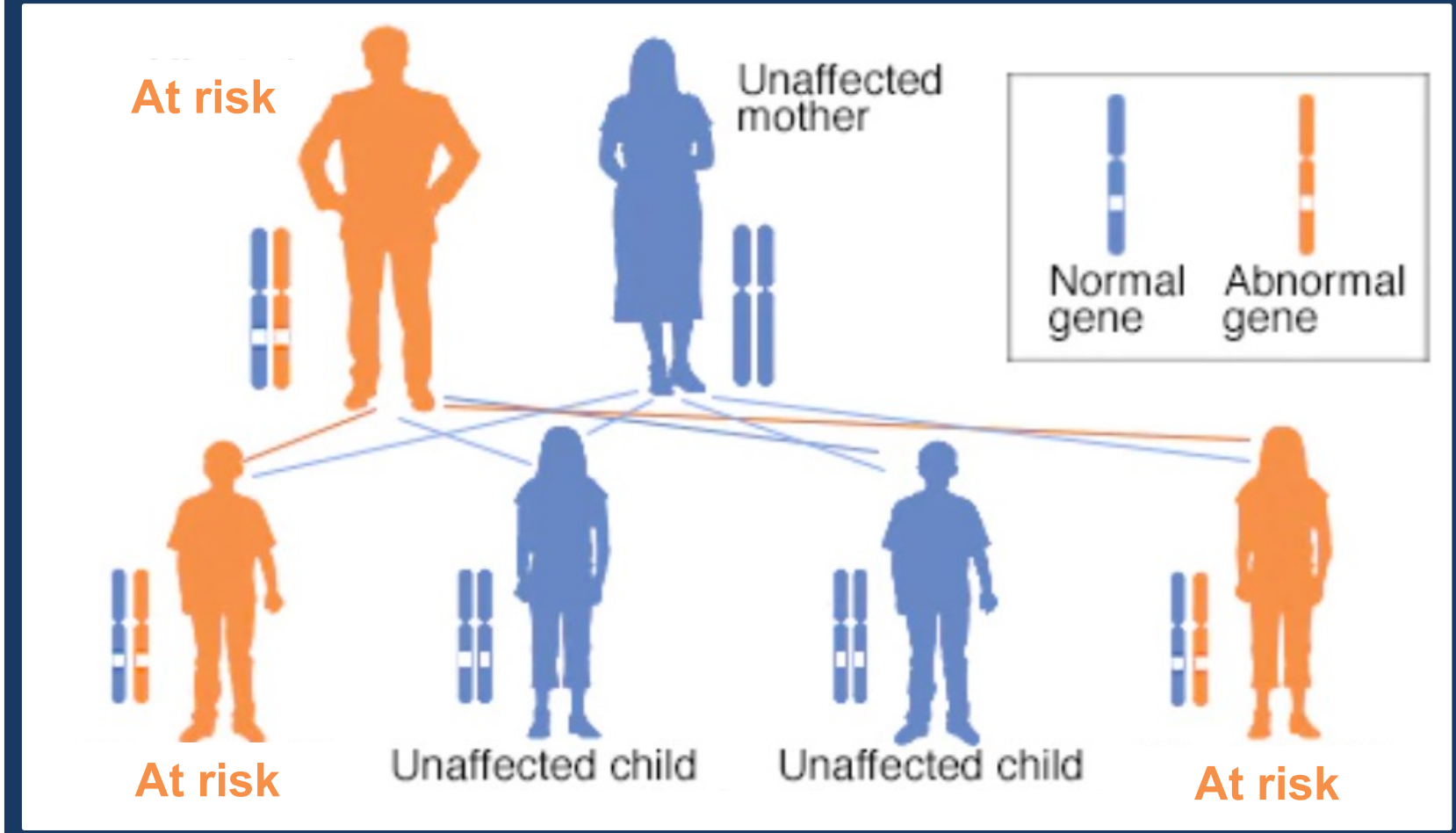
Autosomal dominant transmission



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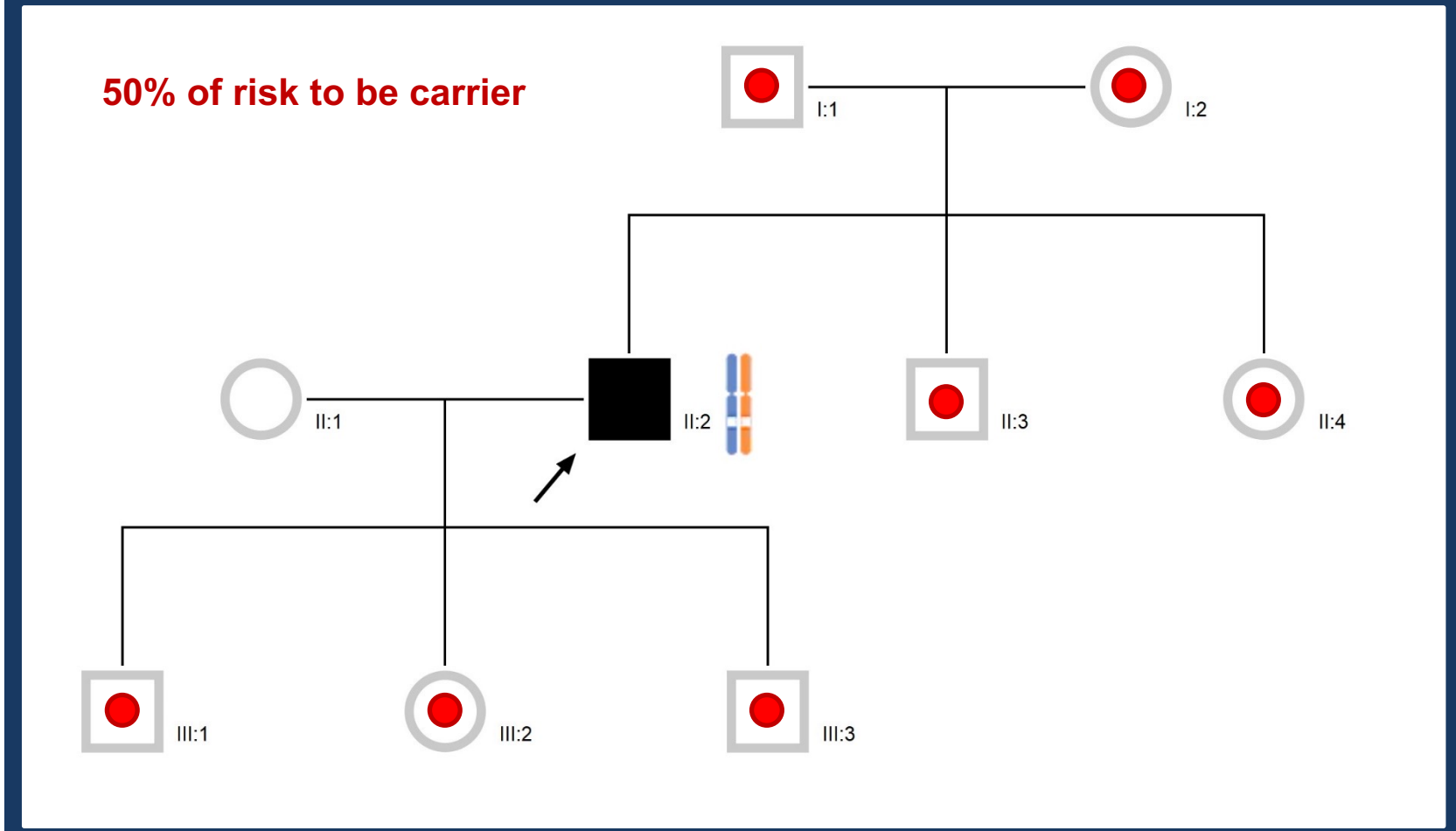

HISTORY OF GENETIC DISCOVERY IN HERITABLE PAH & PVOD

PAH predisposing genes: BMPR2

BMPR2

BMP/TGF-β family

ACVRL1 (ALK1)#
BMPR2 (BMPR2)
ENG (endoglin)#
GDF2 (BMP9)
SMAD9 (SMAD8)
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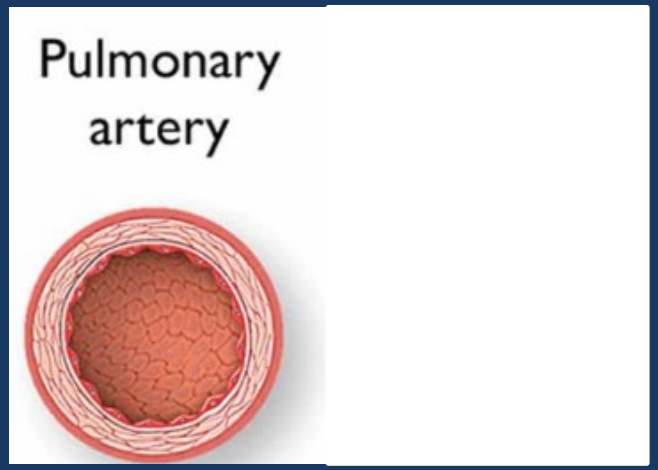
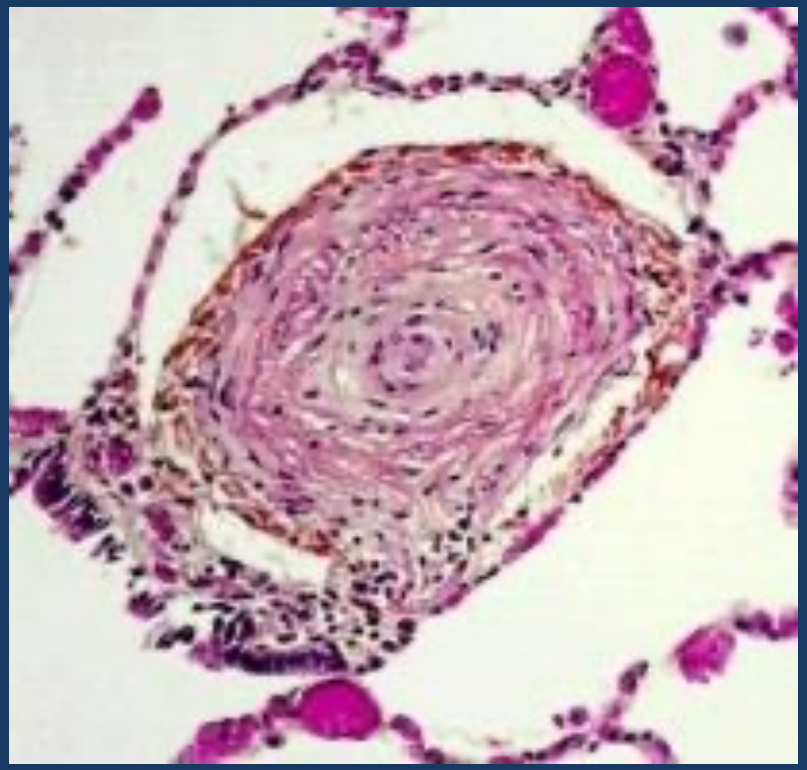
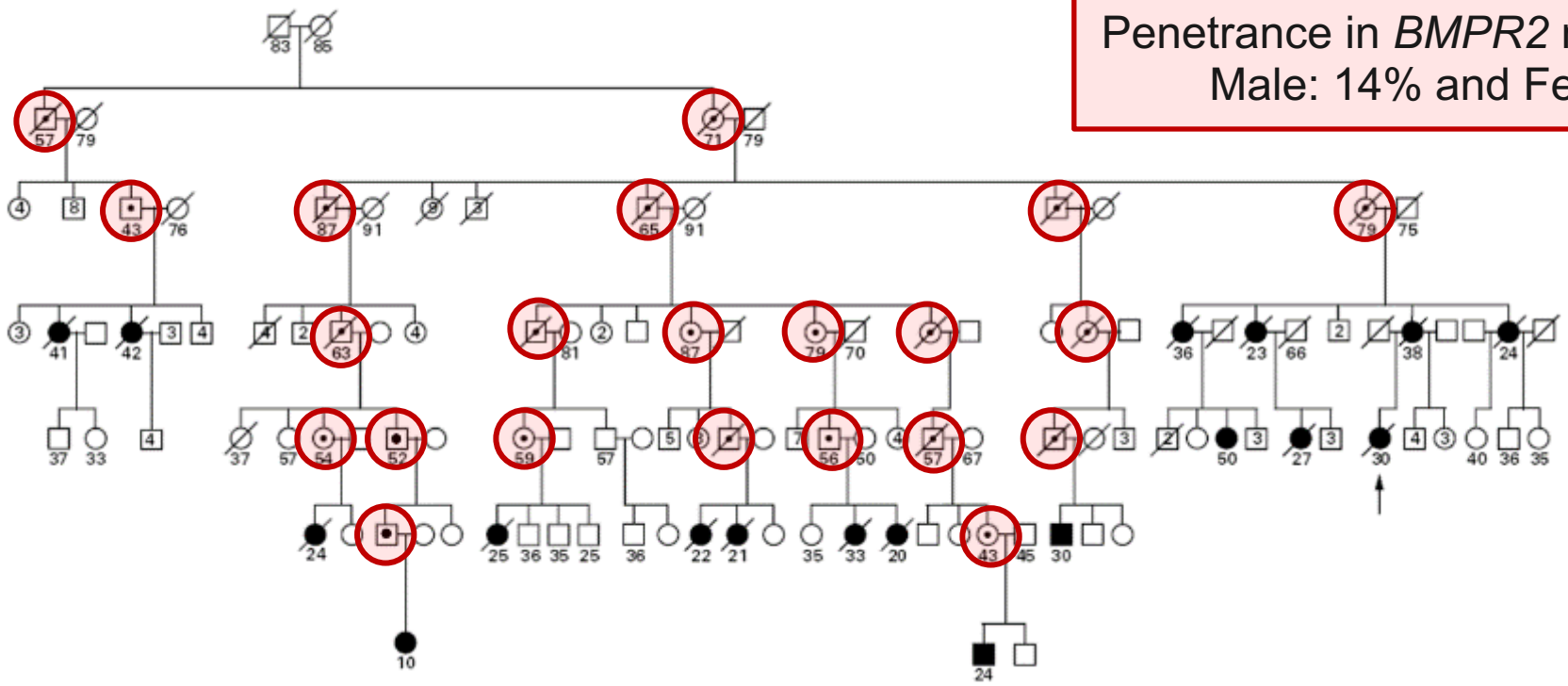




Genetic transmission of *BMPR2* mutation

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

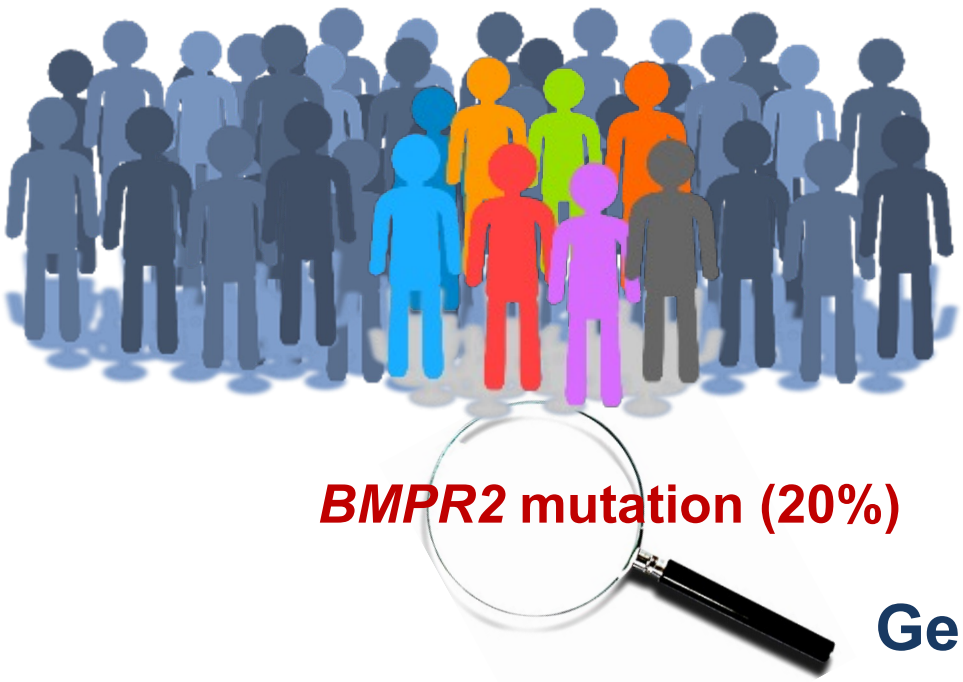


Penetrance in *BMPR2* mutation carriers
Male: 14% and Female: 42%

Larkin, *Am J Crit Care Med* 2012

PAH associated with *BMPR2* mutation

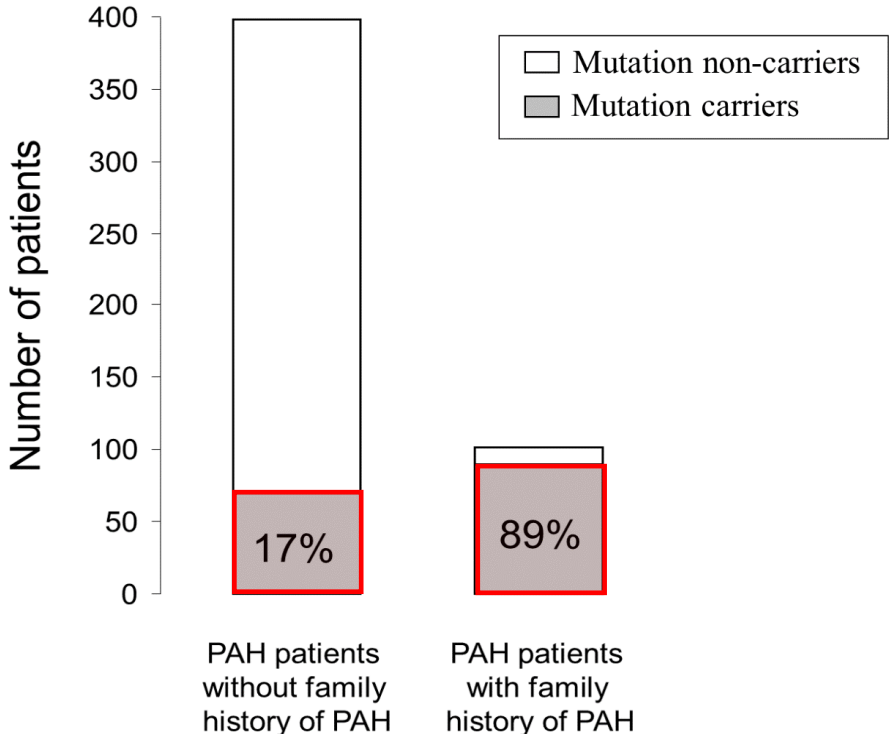
Sporadic or familial PAH patients



***BMPR2* mutation (20%)**

Genetic testing

Genetic Counseling in the French Referral Centre for PH



Girerd B, *Eur Respir J* 2016

PH and developmental genes

HISTORY OF GENETIC DISCOVERY IN HERITABLE PAH & PVOD

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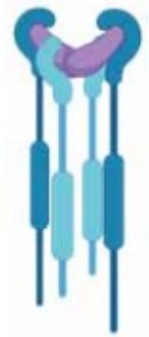

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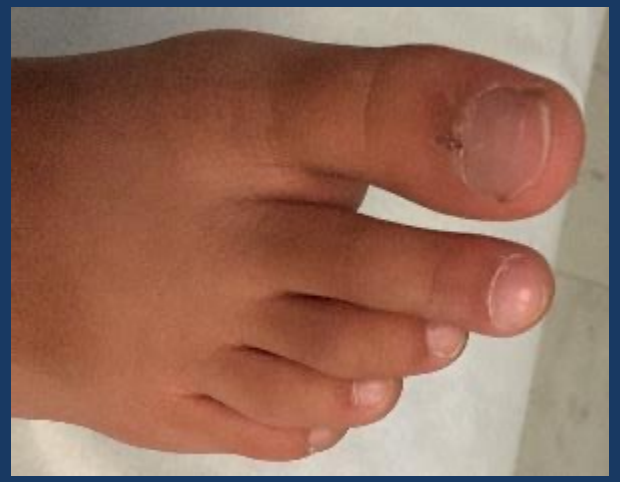
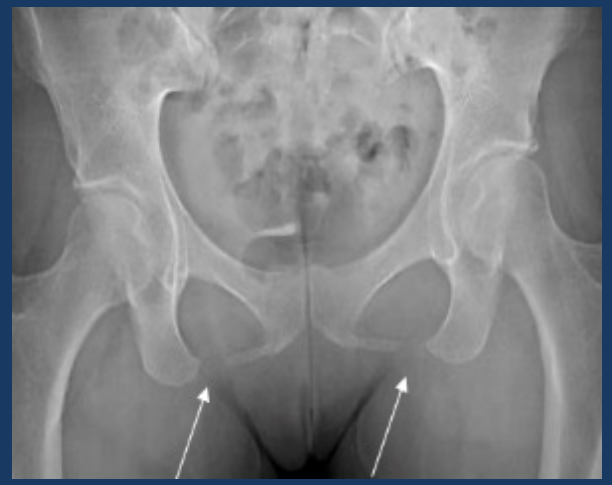
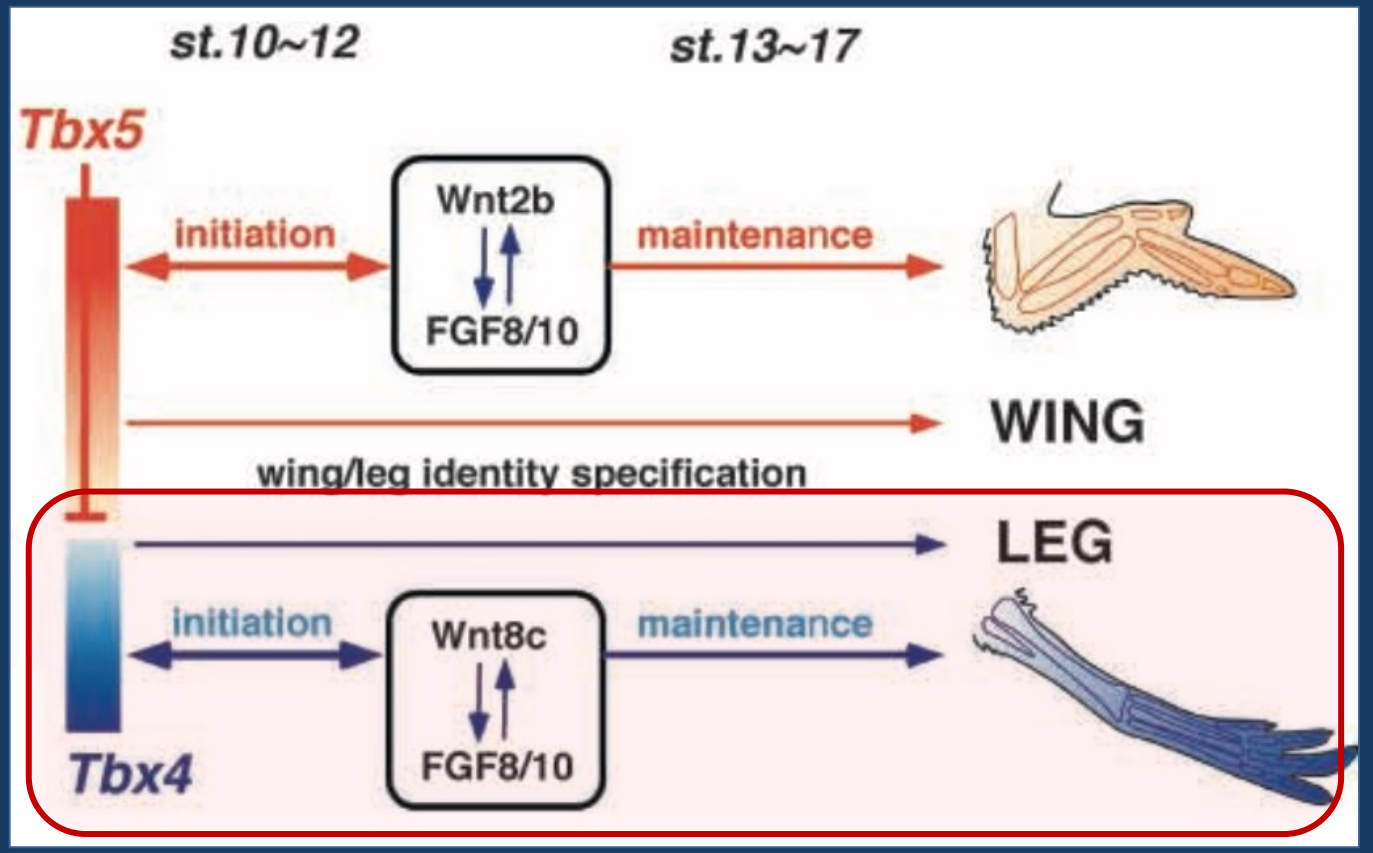
SMAD9 (SMAD8)			
CAV1 (caveolin-1)			

TBX4 MUTATIONS IN PAH : Small Patella Syndrome

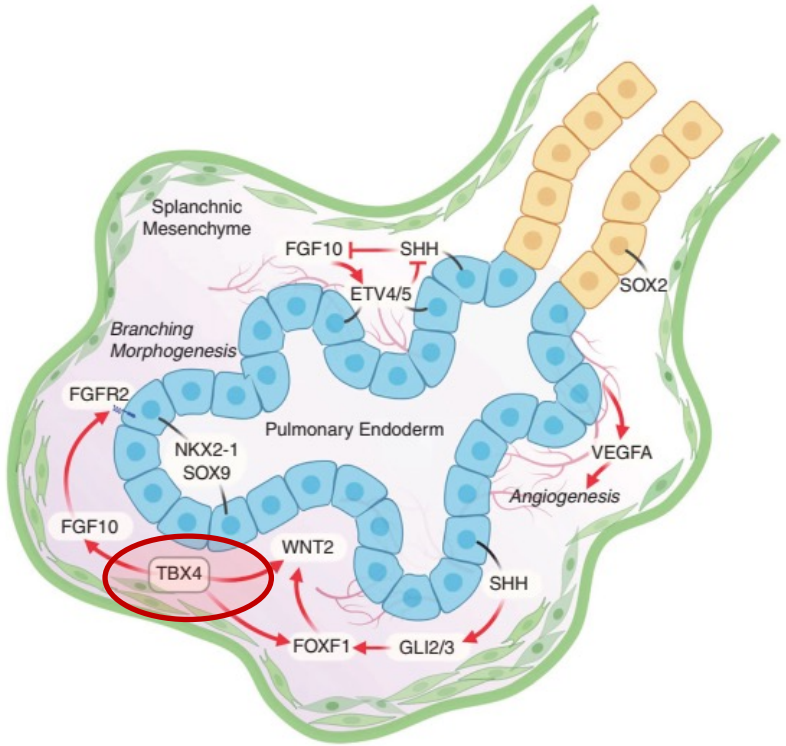






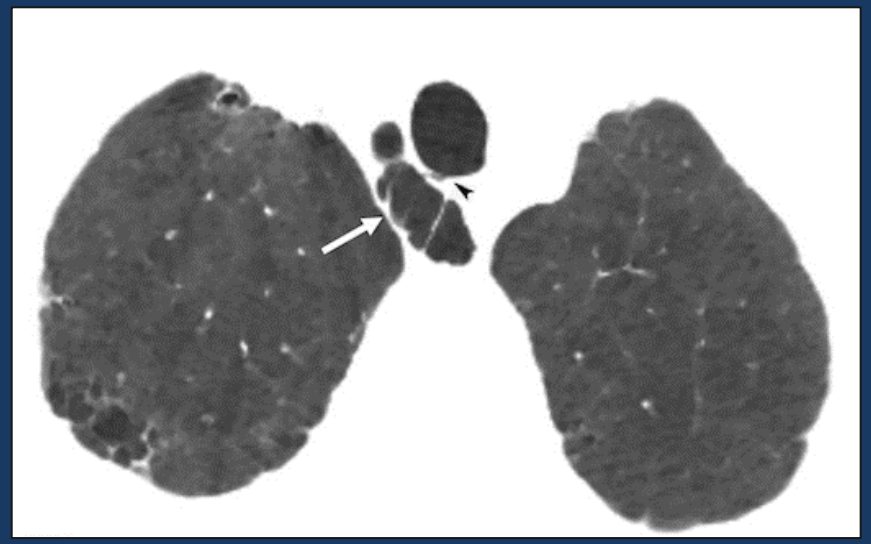
Major variation of phenotypic expression
usually mild or asymptomatic

TBX4 MUTATIONS IN PAH

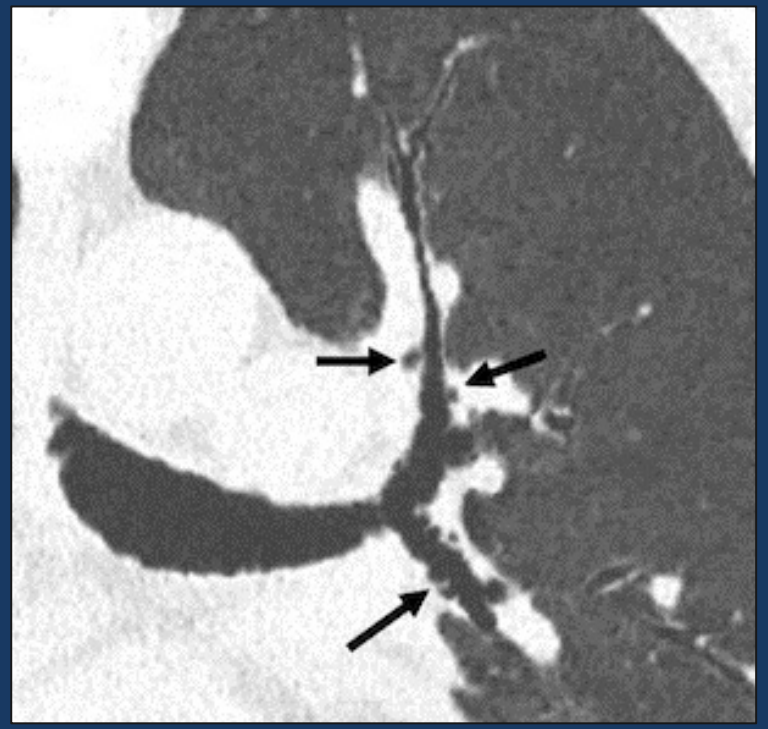


Lung branching & Pulmonary development

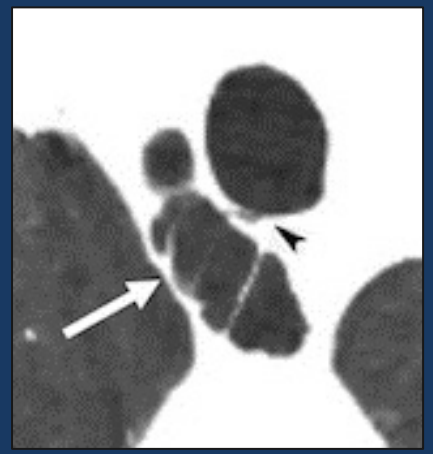
Emphysema



Peri-bronchial cysts

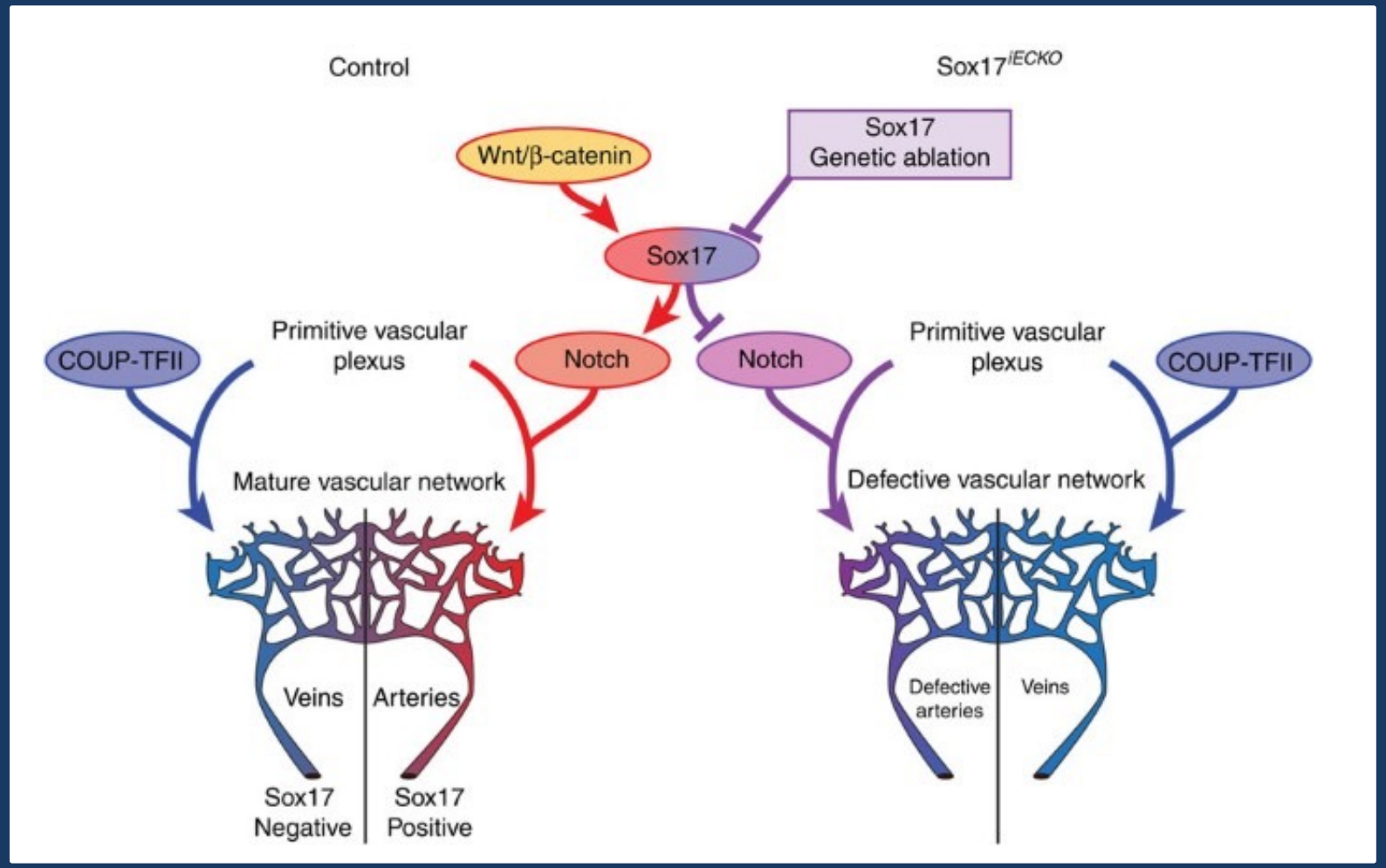


Tracheal diverticula



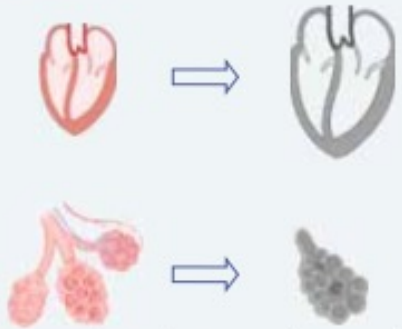
Karolak, *Am J Respir Crit care Med* 2023
Thoré P, *Eur Respir J* 2020

DEVELOPMENTAL GENE in PAH: *SOX17*



SOX17 *in vivo* models

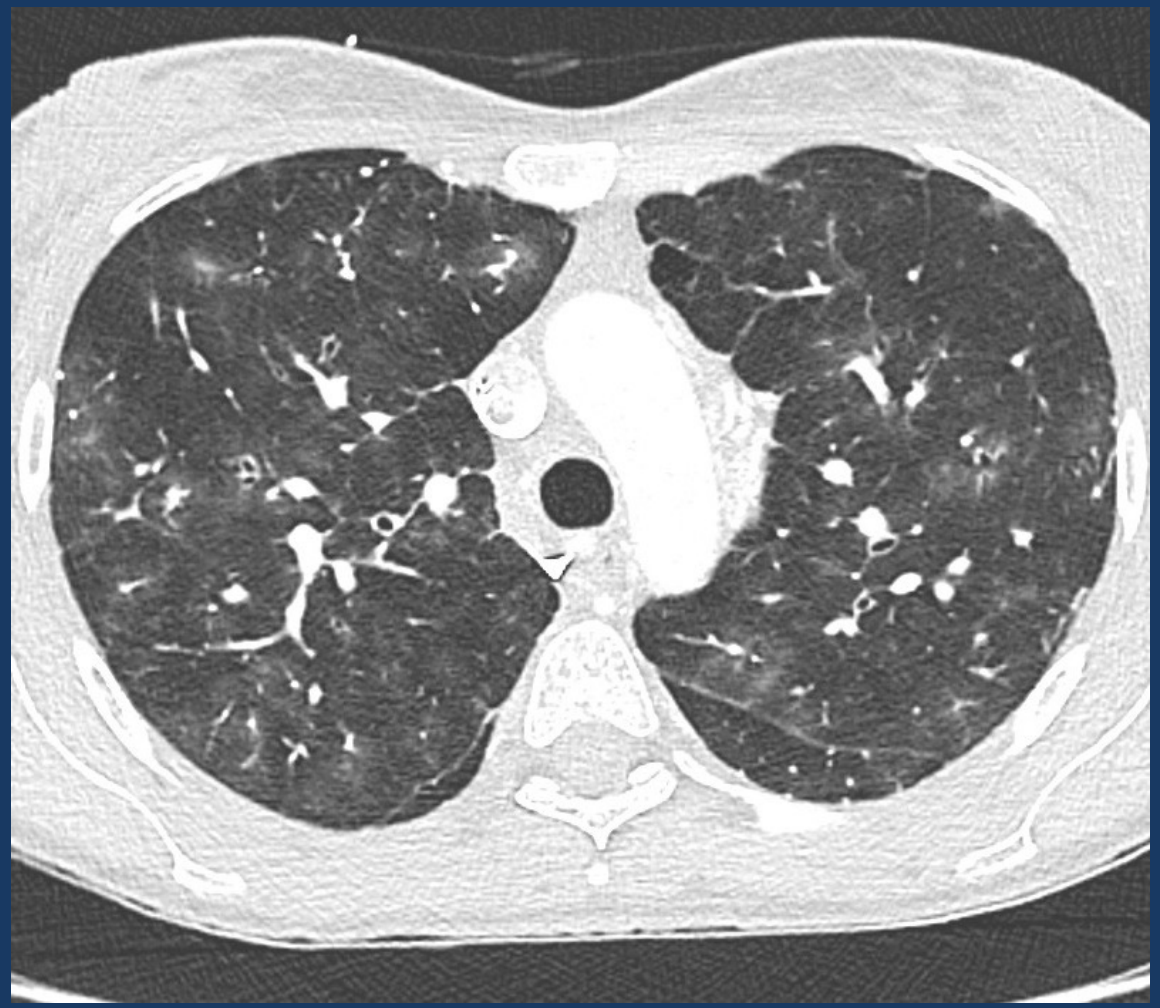
KOs and expression reduction

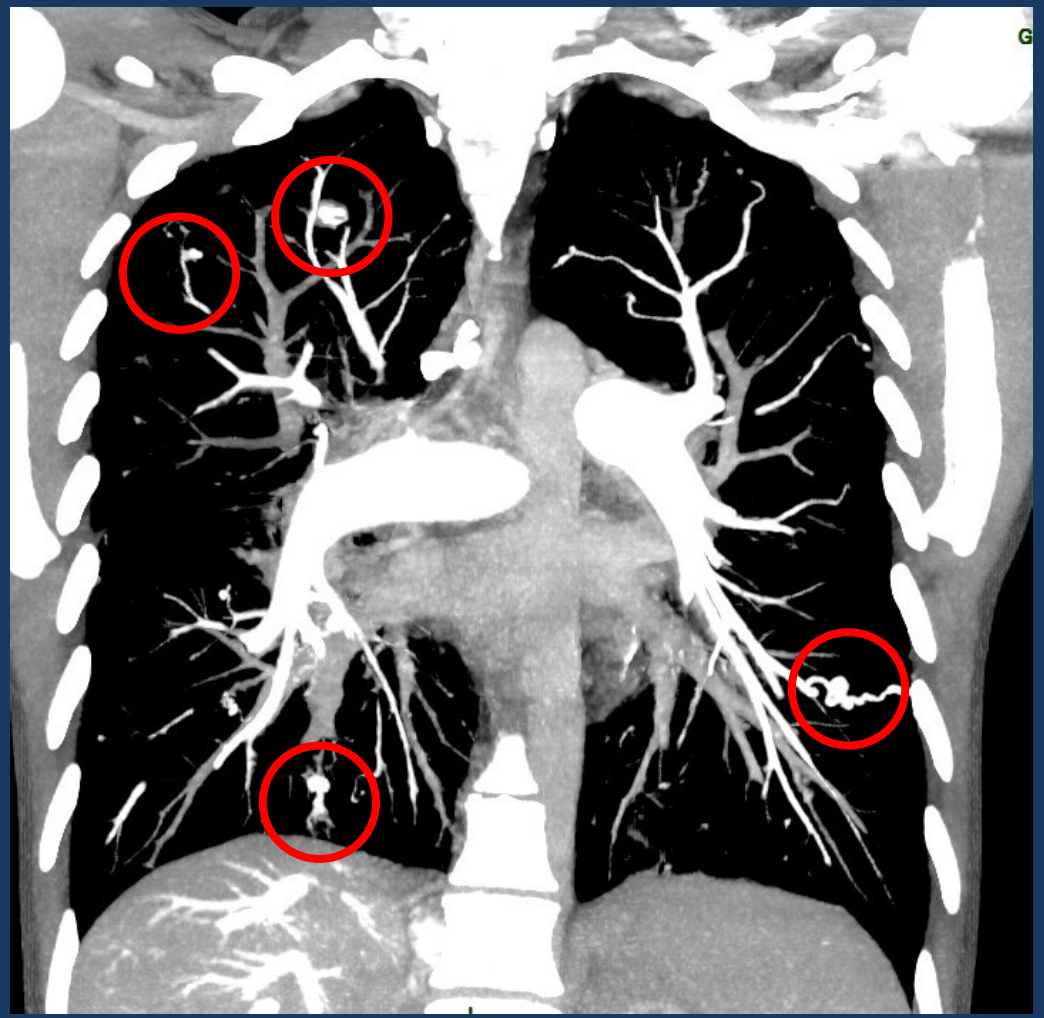


Varices and enlarged arteries
Biventricular hypertrophy
Alveolar simplification
Cardiac enlargement
Decreased pulmonary blood flow
Neonatal lethality

Wu, *Eur Respir J* 2021

DEVELOPMENTAL GENE in PAH: *SOX17*

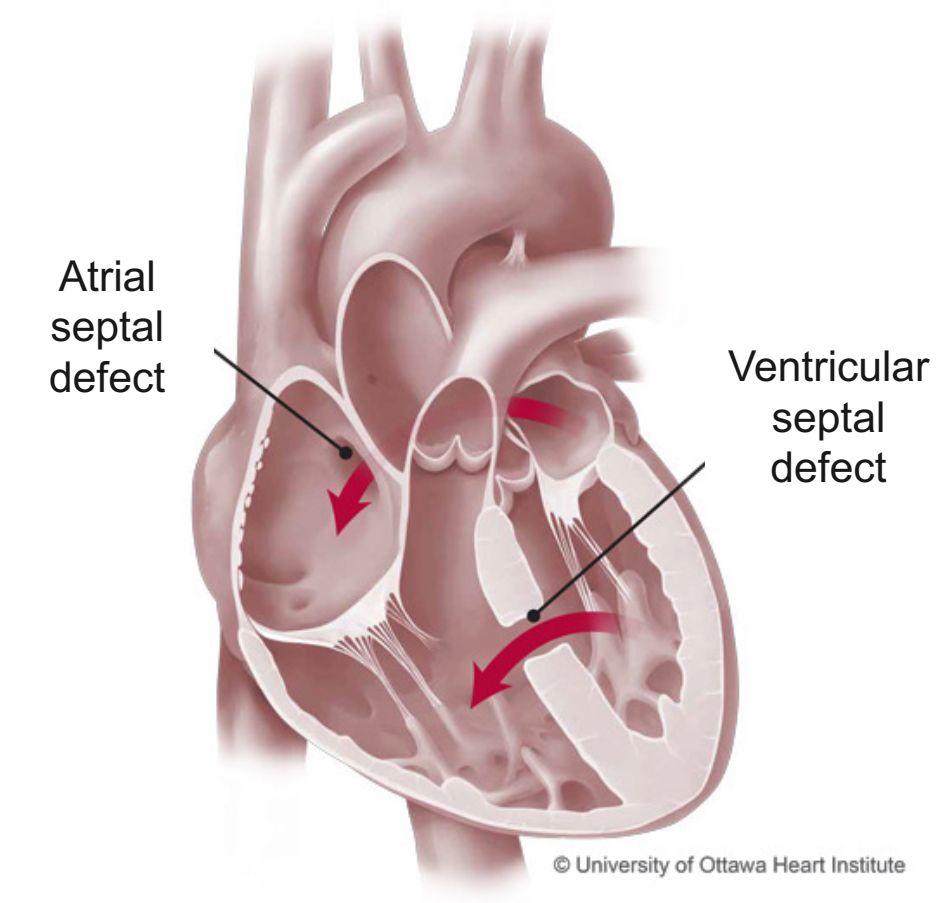


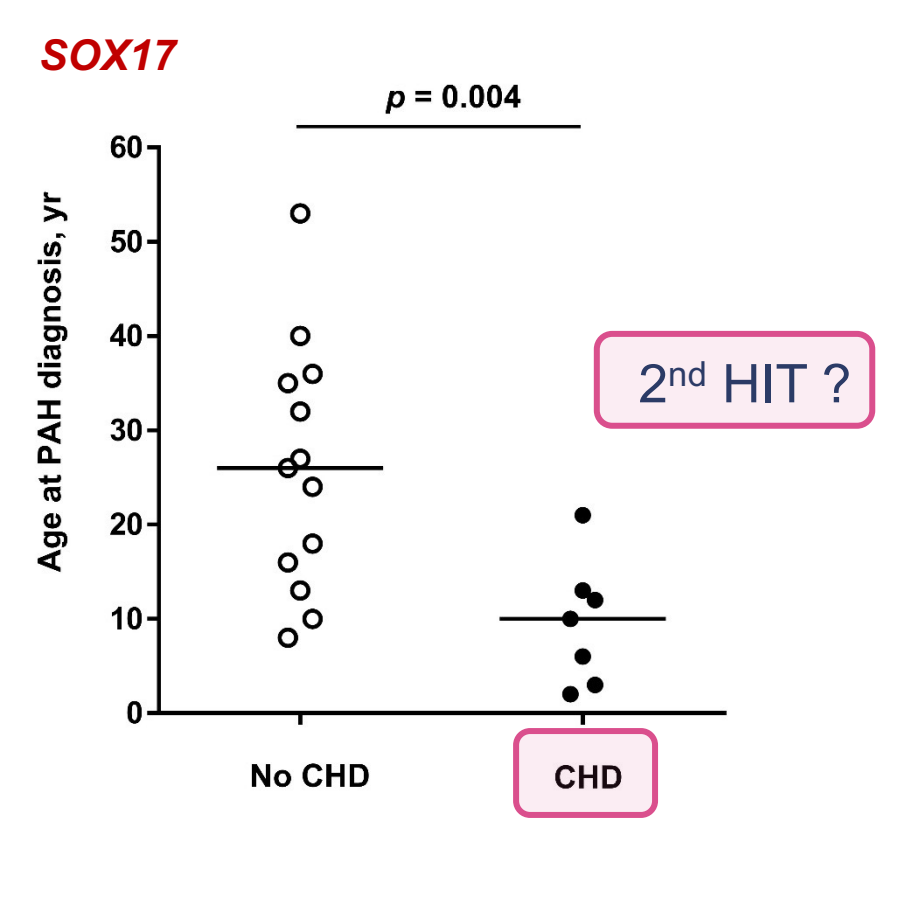


Montani, *Eur Respir J 2022*

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

- Frequent congenital heart diseases ++++





Genetic testing and counseling

Genetic counselling : Example of French PH network

- **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)

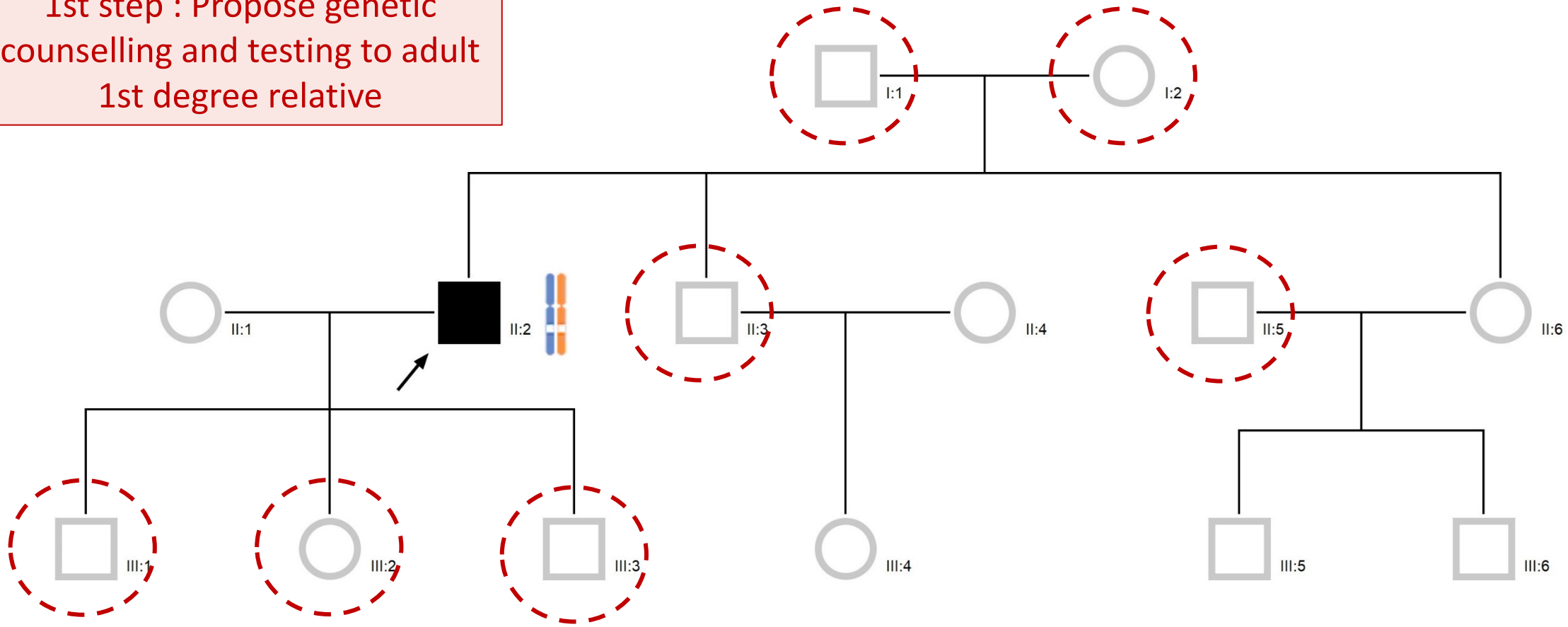
- **Next Generation Sequencing (NGS)**

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

- Whole **GENOME sequencing program**

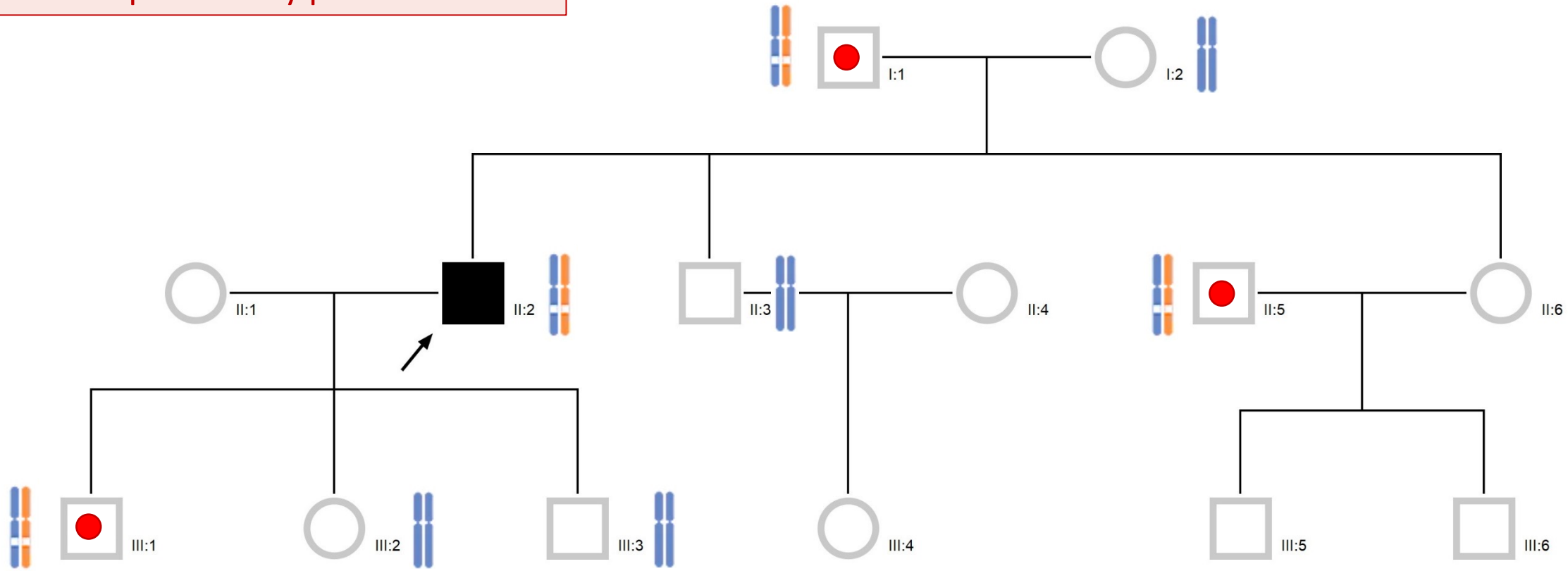
Genetic counselling

1st step : Propose genetic counselling and testing to adult 1st degree relative



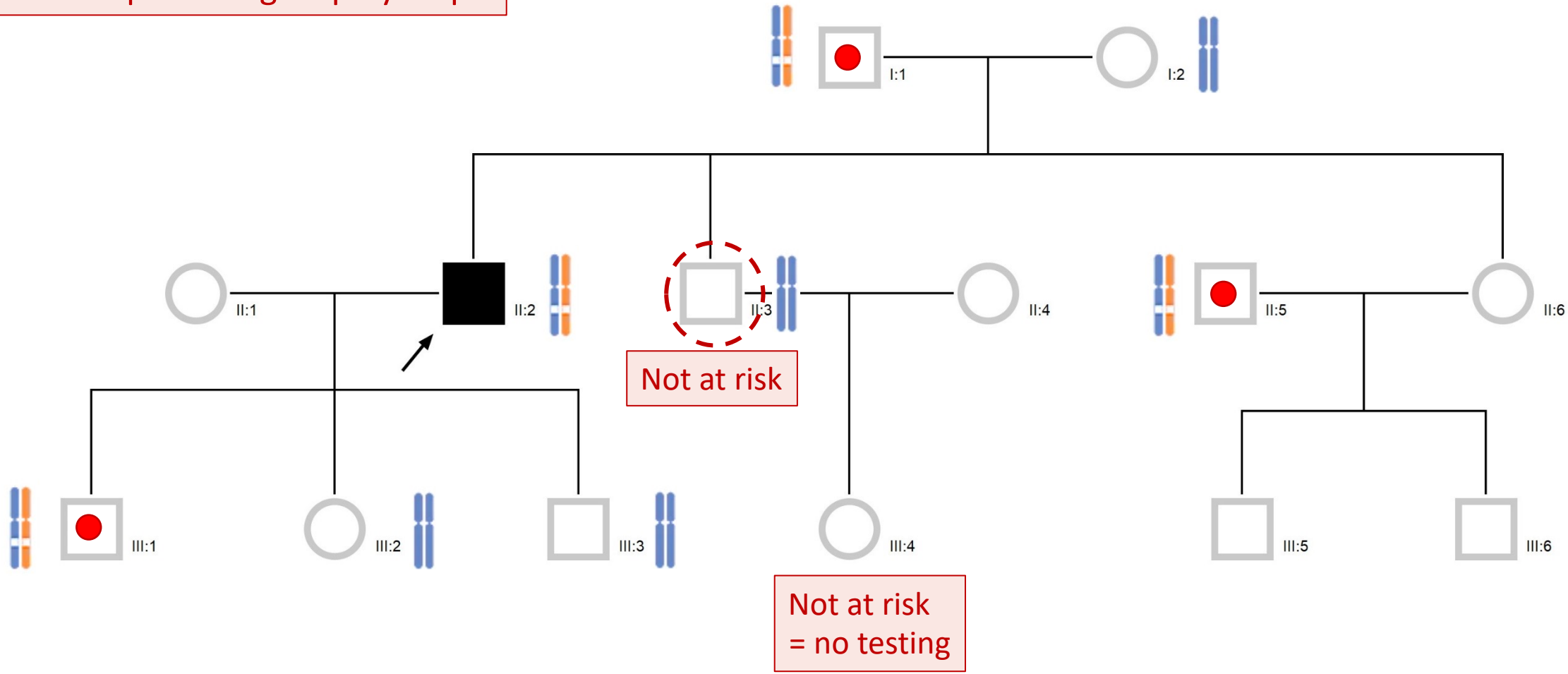
Genetic counselling

2nd step : identifiy patients at risk



Genetic counselling

3rd step : testing step by step



Genetic counselling

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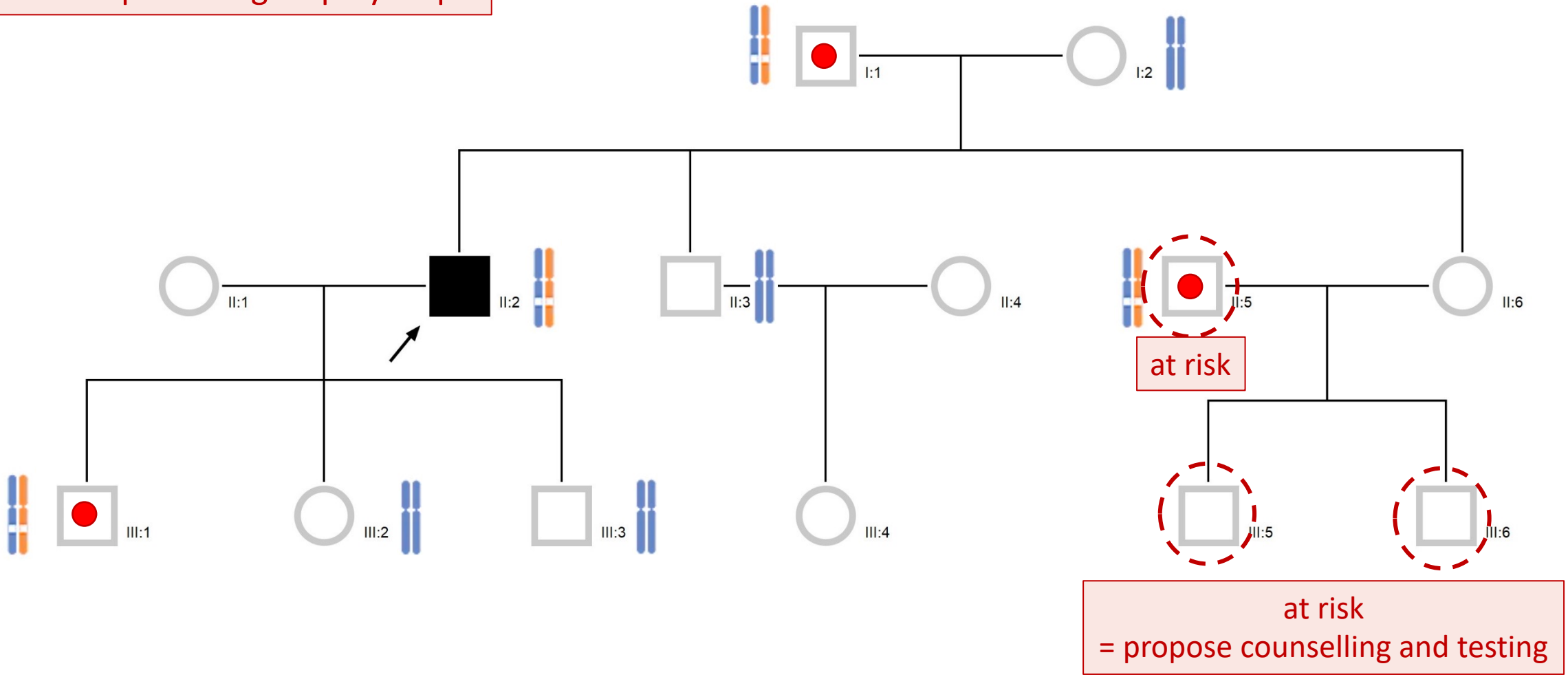

Conseil génétique des apparentés *BMPR2*

PAH patients

***BMPR2* mutation (20%)**

Genetic testing

Genetic counseling

Asymptomatic 1st degree relatives

Adults only

50% of *BMPR2* mutation

?

PAH

DELPHI-2 Study

Asymptomatic *BMPR2* mutation carriers (adults)

Every 12 months or symptoms

Visit
- . NYHA
- . NT-pro BNP
- . ECG
- . Chest Rx

Functional tests
- . 6MWT
- . CPET
- . PFTs, DLco

Echocardio
- . TRJ
- . TAPSE
- . RV, RA

Biobank
- . Plasma
- . serum

Dyspnea or unexplained syncopa

or

Decrease in VO_2 max > 20 %

or

TRJ > 2.8 m/s

EARLY DIAGNOSIS +++

Right Heart Cath
Rest / exercise

Confirmed PAH

Management according to ERS / ESC guidelines

Montani, *Eur Respir J* 2021

Conseil génétique des apparentés *BMPR2*

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Genetic testing

Genetic counseling

Asymptomatic 1st degree relatives

Children ?

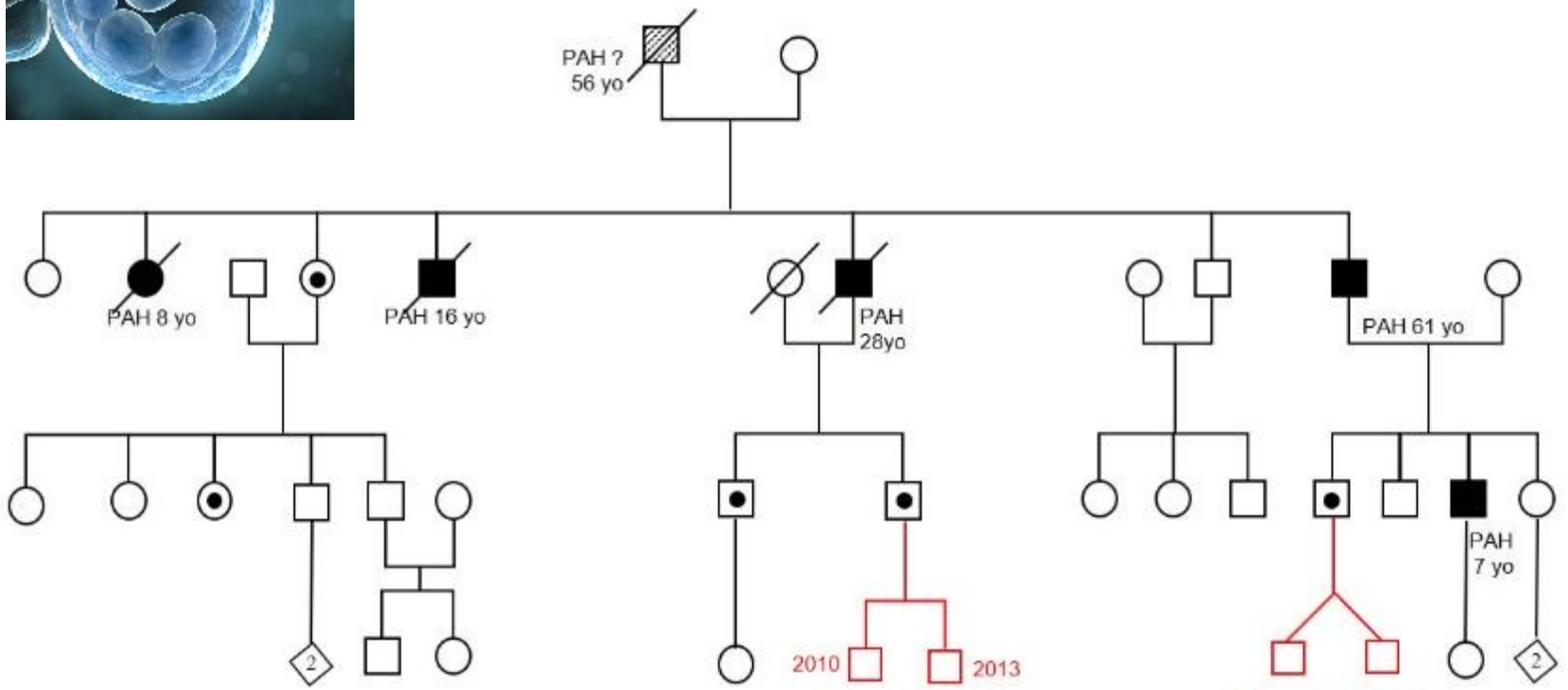
50% of *BMPR2* mutation

Depends of national ethical laws

In France : genetic testing not possible in asymptomatic children = absence of preventive treatment

Pre-implantation genetic diagnosis

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



Unravelling the genetics of pulmonary hypertension

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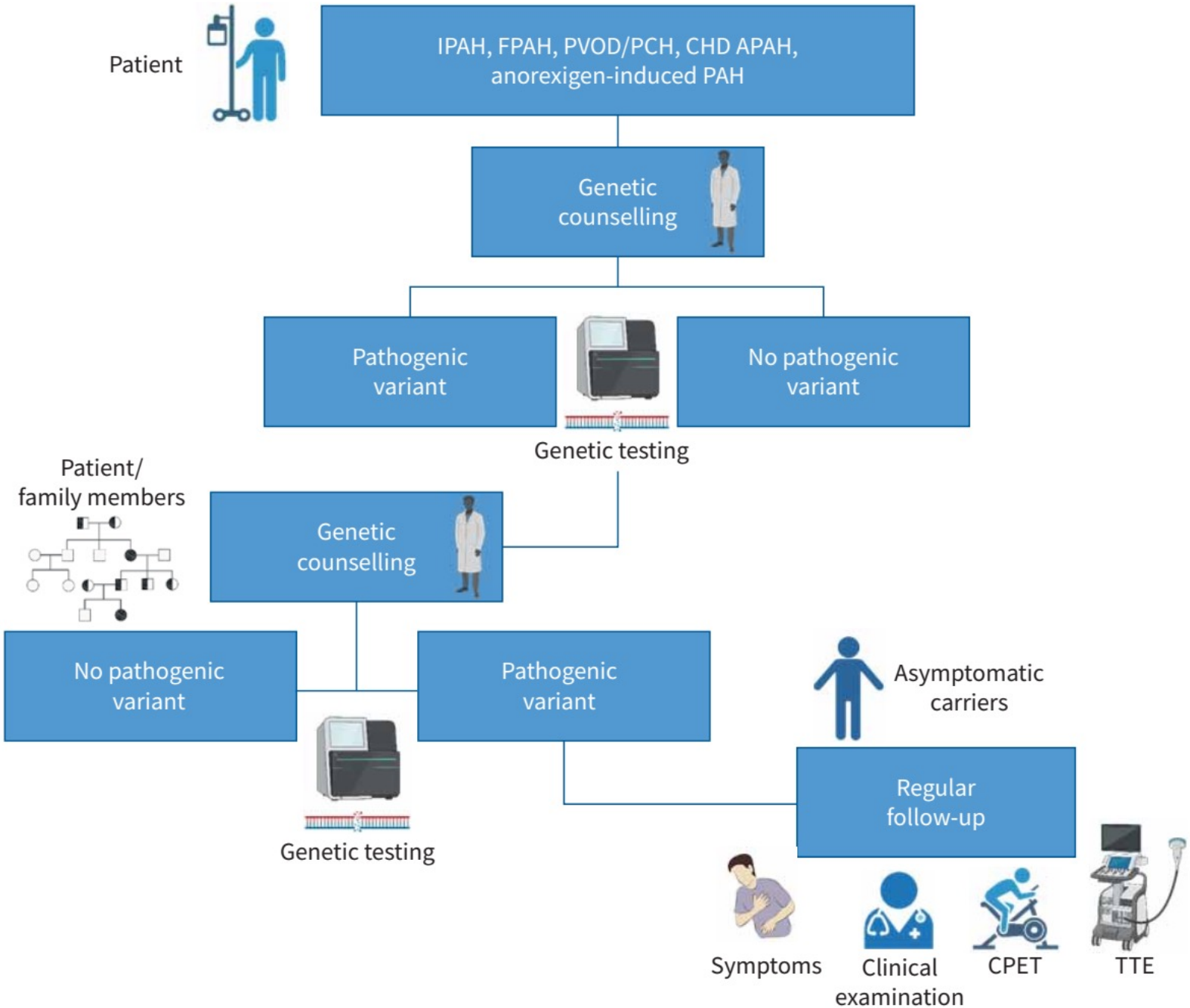
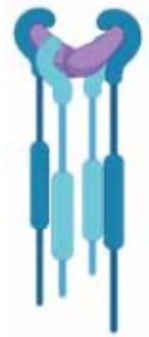

Patient
IPAH, FPAH, PVOD/PCH, CHD APAH, anorexigen-induced PAH
Genetic counselling
Pathogenic variant
No pathogenic variant
Genetic testing
Patient/ family members
Genetic counselling
No pathogenic variant
Pathogenic variant
Genetic testing
Asymptomatic carriers
Regular follow-up
Symptoms
Clinical examination
CPET
TTE

HISTORY OF GENETIC DISCOVERY IN HERITABLE PAH & PVOD

PAH predisposing genes



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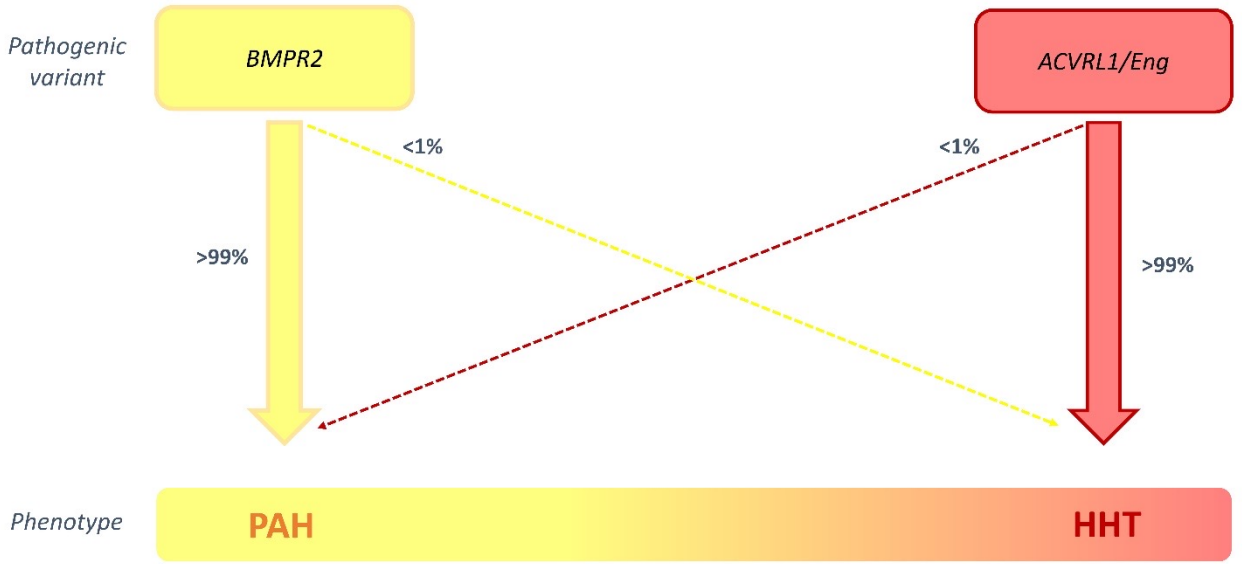
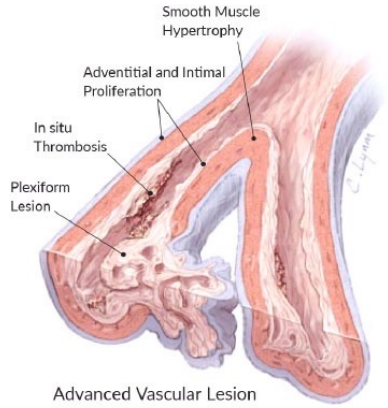
SMAD9 (SMAD8)			
CAV1 (caveolin-1)			

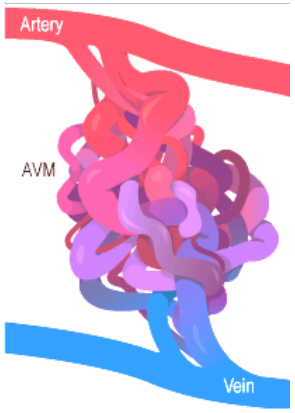
Genetics of signalling pathway in PAH

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

BMPRII/TGFβ Pathway







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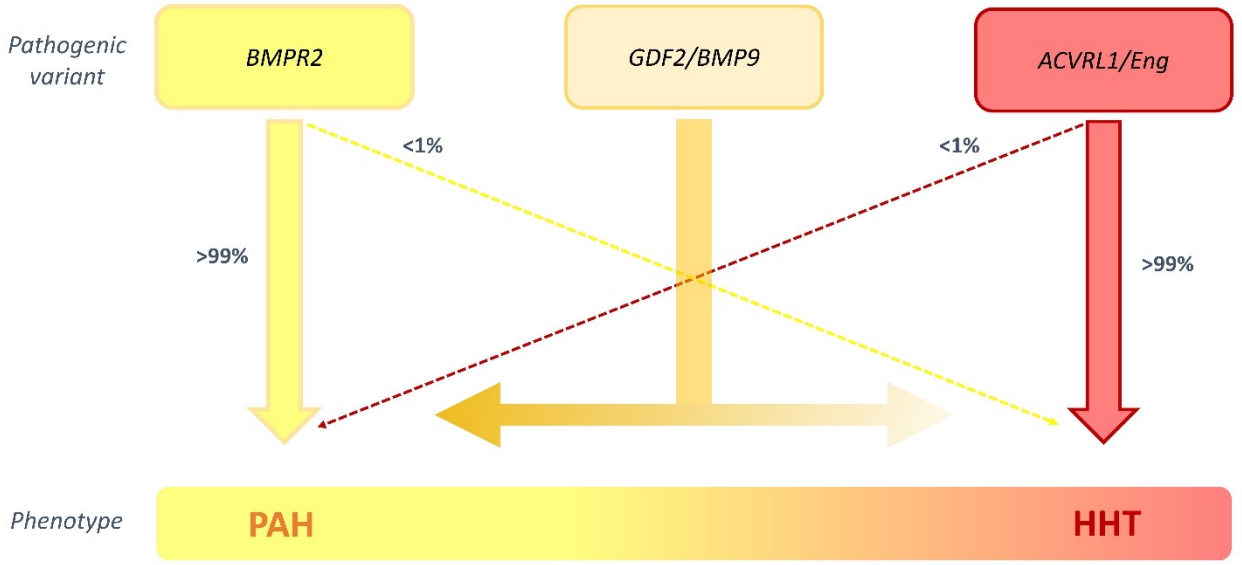
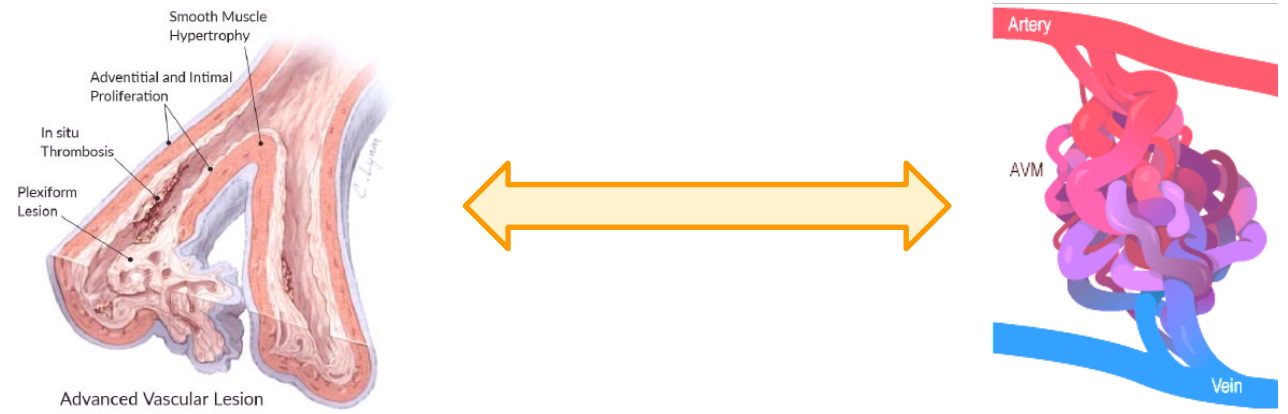
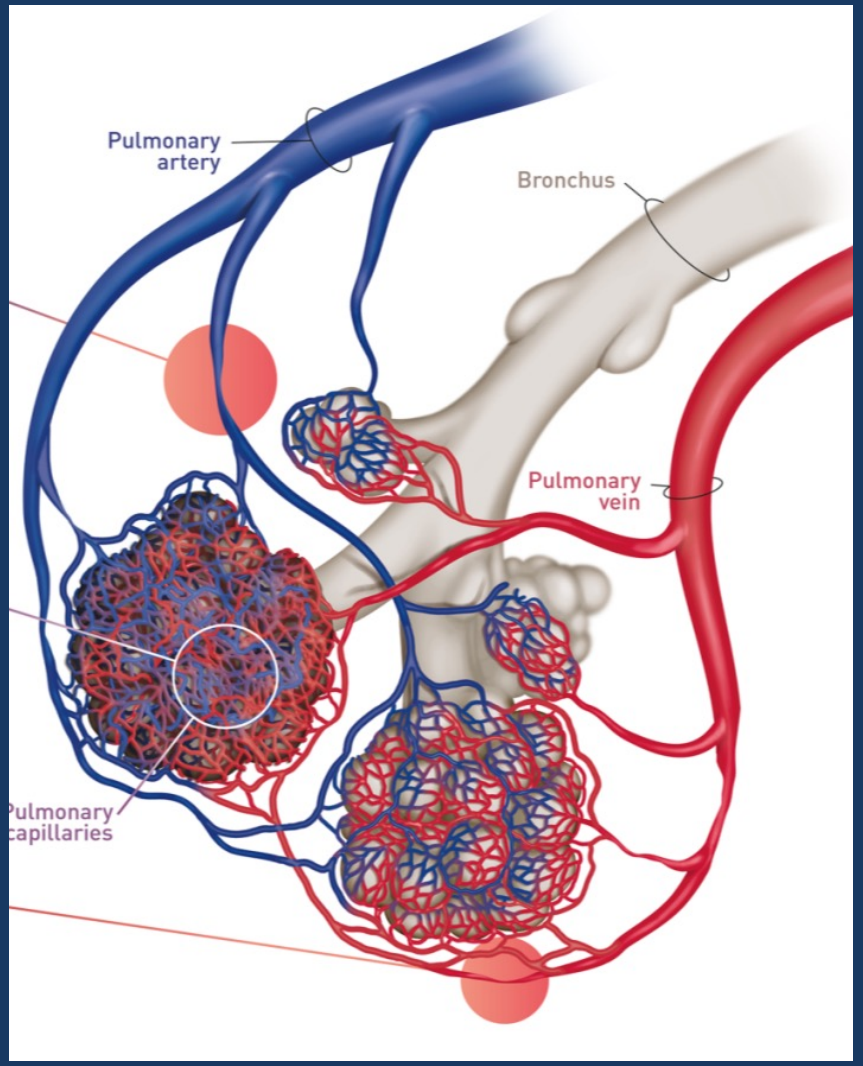
BMPRII/TGFβ Pathway

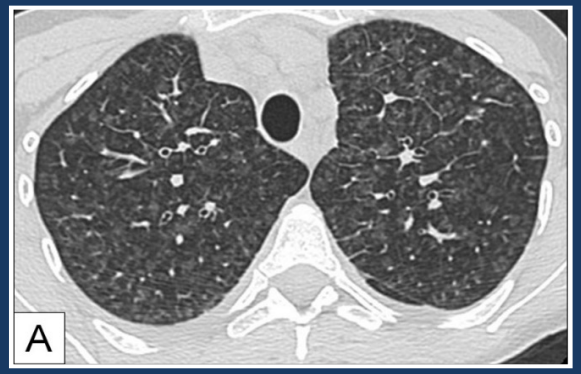


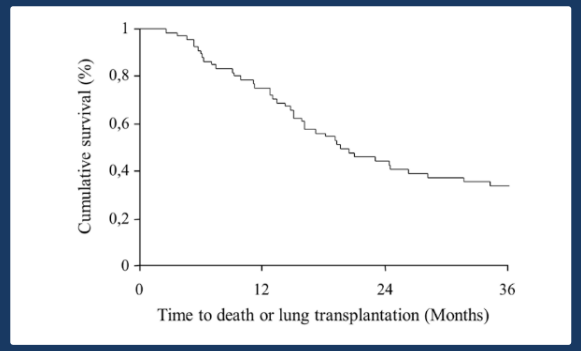


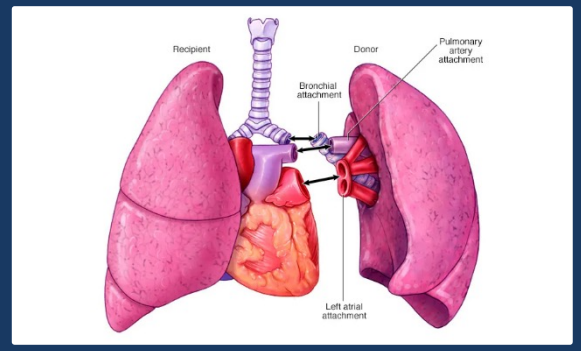
Pulmonary veno-occlusive disease

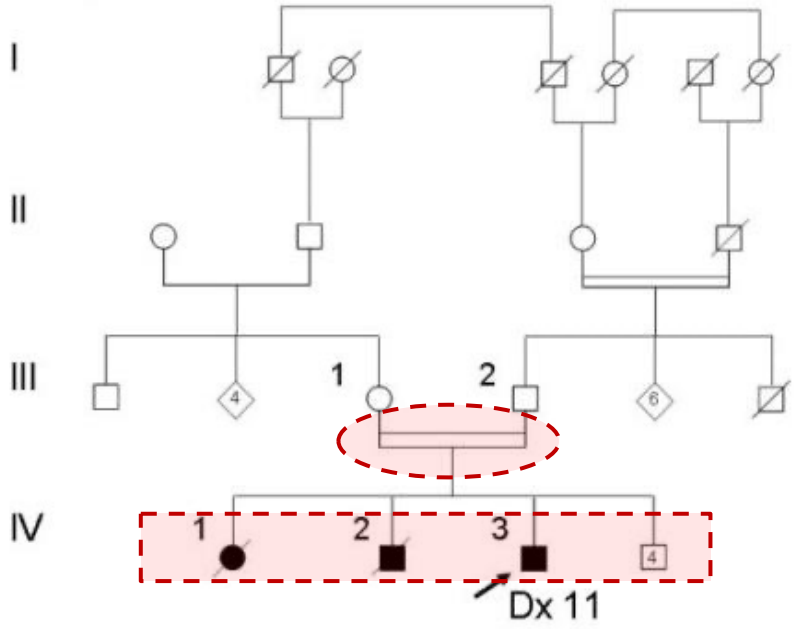
PULMONARY VENO-OCCLUSIVE DISEASE











Autosomal recessive transmission

Biallelic mutations in ***EIF2AK4* gene**

Montani D et al. *Eur Respir J* 2016

Eyries, *Nature Genet* 2014

HISTORY OF GENETIC DISCOVERY IN HERITABLE PVOD

Gene	Pulmonary hypertension phenotypic association	Putative molecular mechanism	Inheritance pattern
BMPR2	Heritable and idiopathic PAH	Haploinsufficiency	Autosomal dominant
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
CAV1	Heritable and idiopathic PAH Lipodystrophy	Gain of function; dominant negative	Autosomal dominant
TBX4	Heritable and idiopathic PAH Small patella syndrome (ischiopatellar dysplasia) Parenchymal lung disease Bronchopulmonary dysplasia Persistent pulmonary hypertension of the neonate	Unknown	Autosomal dominant
EIF2AK4	Pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis	Loss of function	Autosomal recessive
KDR	Heritable and idiopathic PAH	Loss of function	Autosomal dominant
ENG		Unknown	Autosomal dominant
ACVRL1	Heritable and idiopathic PAH; hereditary haemorrhagic telangiectasia	Haploinsufficiency	Autosomal dominant
GDF2		Haploinsufficiency	Autosomal dominant

Autosomal recessive transmission