

Effects of **BMPR2** Mutation and Pulmonary Arterial Hypertension



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Genetics 677
May 04, 2010

What is PAH?

Pulmonary arterial hypertension (PAH):

- Arteries of a lung  High blood pressure

Definition:

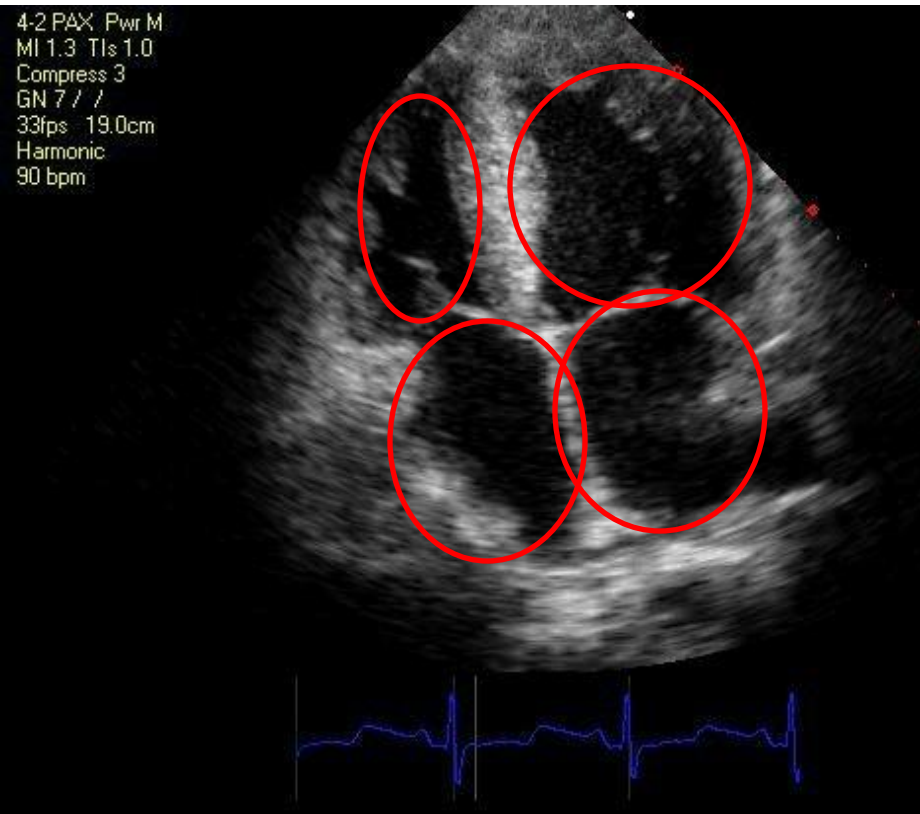
- A mean pulmonary arterial pressure (mPAP) **higher than 25 mmHg** (McLaughlin et al. 2009)

Causes:

- Primary cause is unclear
- Consequence of a primary cause:
Proliferation of endothelial cells (i.e. SMC)
(Farber & Loscalzo 2004)

Increased size of RV

WT



PAH

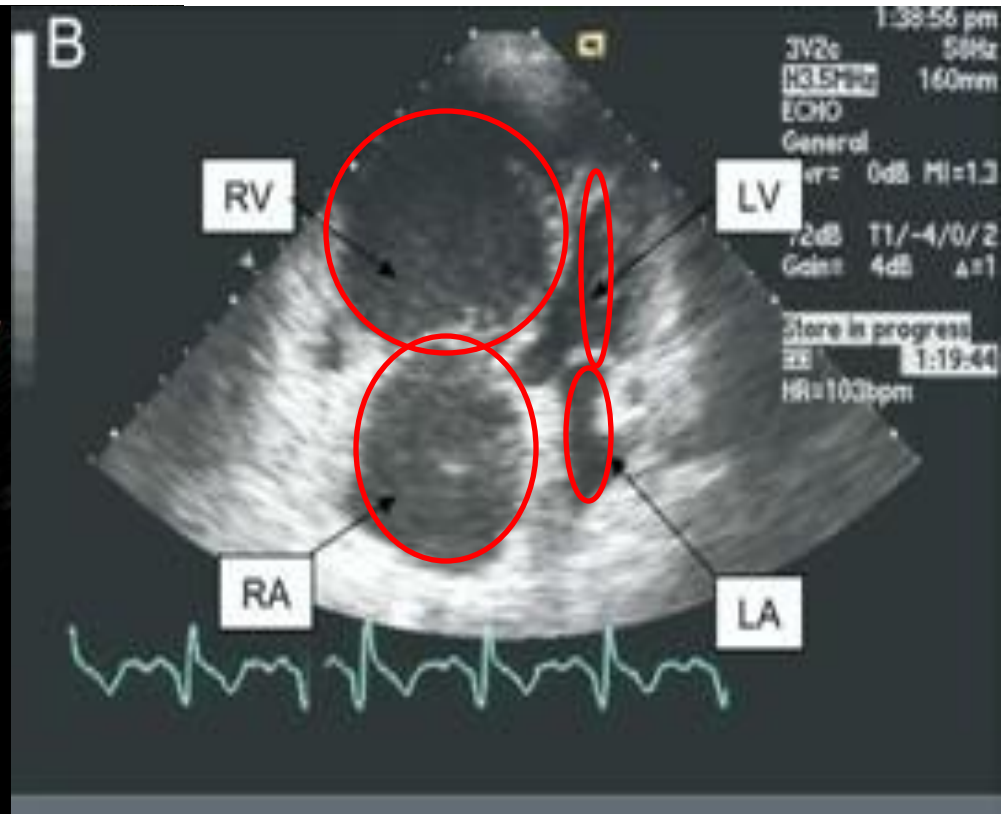
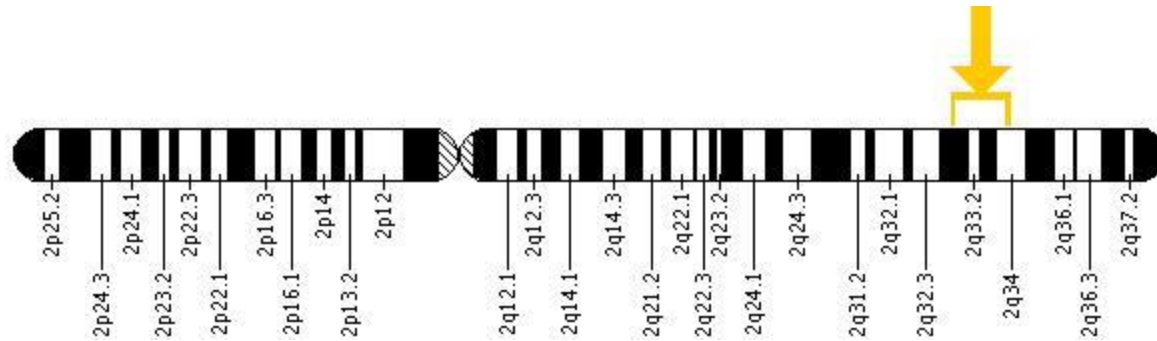


Image from [http://rst.gsfc.nasa.gov/Intro/apical four chamber view.jpg](http://rst.gsfc.nasa.gov/Intro/apical%20four%20chamber%20view.jpg)
Image retrieved from McLaughlin et al. (2009)

BMPR2 is associated with PAH

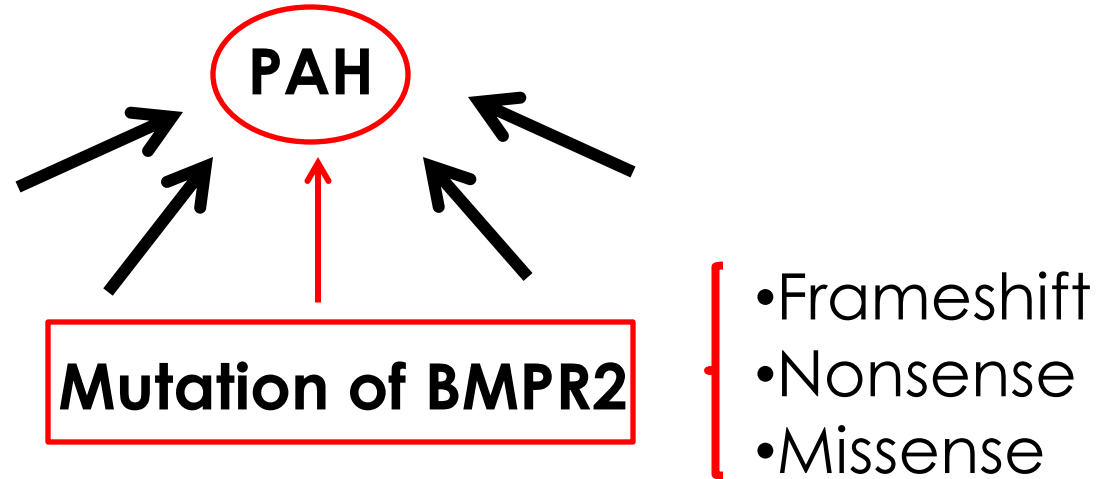


Full name: Bone morphogenetic protein receptor, type II

Location: the gene on Chromosome 2 q33-q34

General functions: regulate growth and differentiation of various cell types

PAH and BMPR2



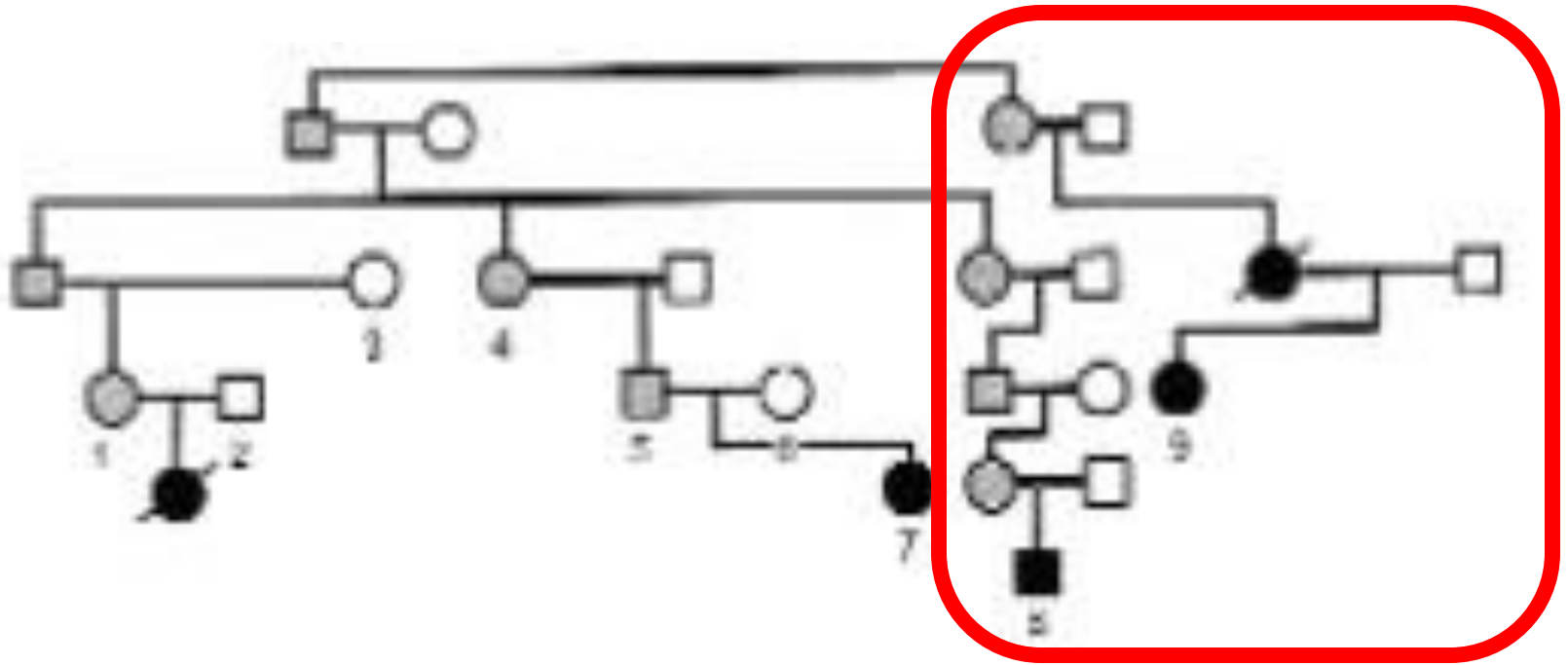
Mutation of BMPR2 is responsible for

- ~50% of Familial PAH cases (autosomal dominant)
- ~26% of Idiopathic PAH cases

Prevalence:

- 2-3 million cases per a year (IPAHA)
- 10% of these cases: Familial PAH (**penetrance: 20%**)

BMPR2 is autosomal dominant



Structural effects on PA

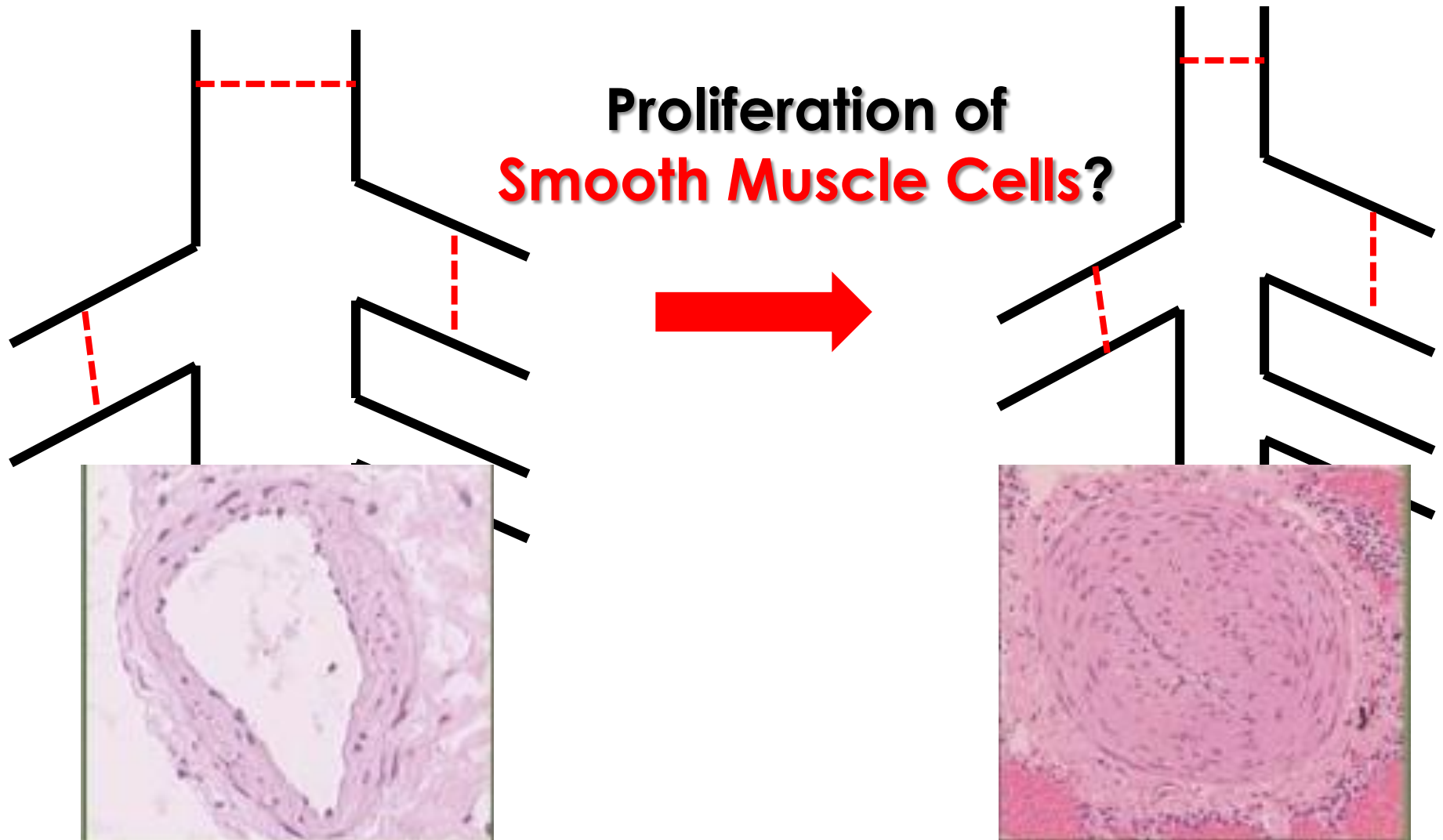
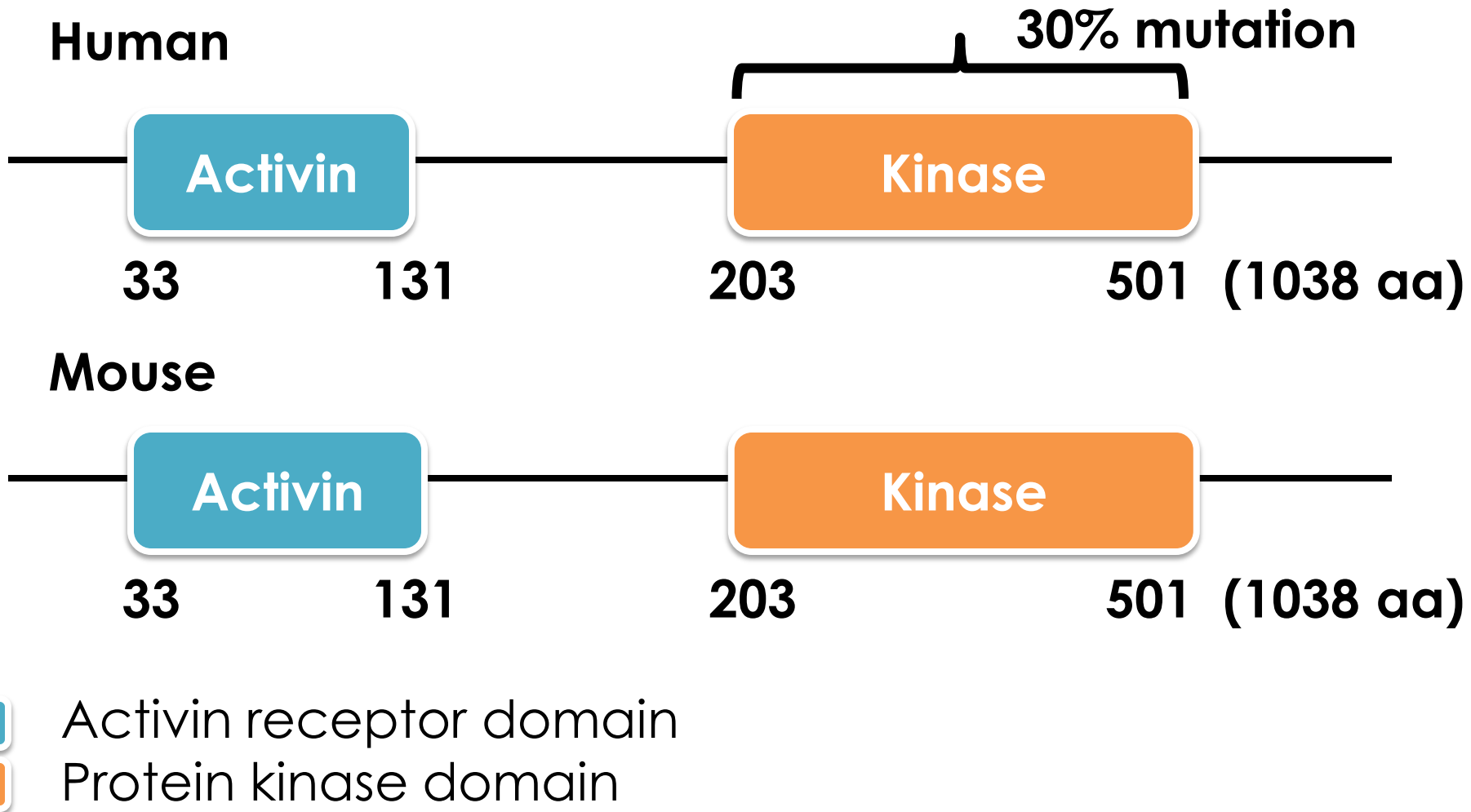


Image retrieved from McLaughlin et al. (2009)

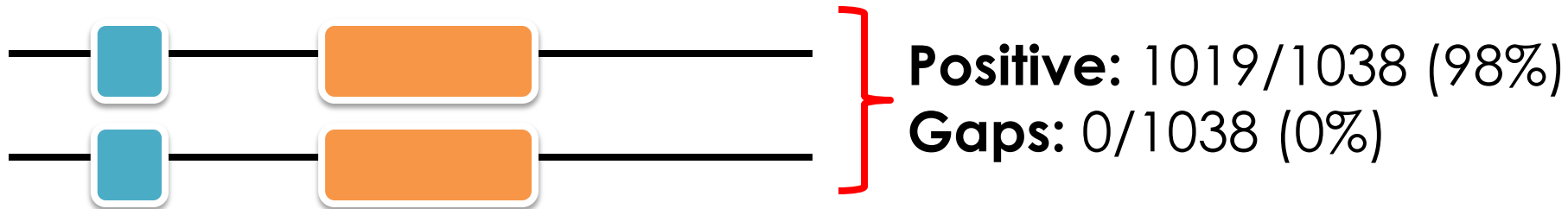
BMPR2 protein domains



BMPR2 is well conserved

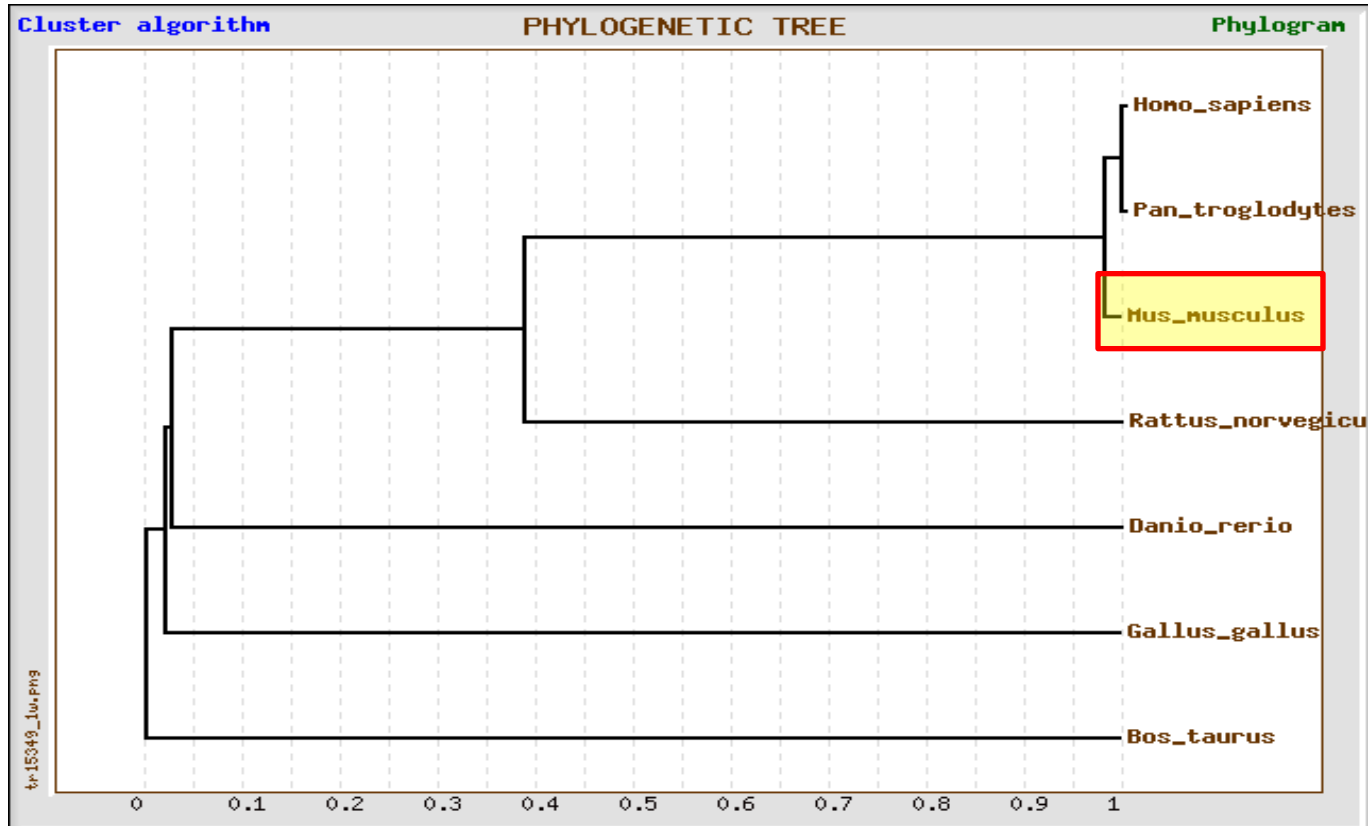
BMPR2 in Human and Mouse

Domain conservation



Mouse is closed to human

Phylogeny



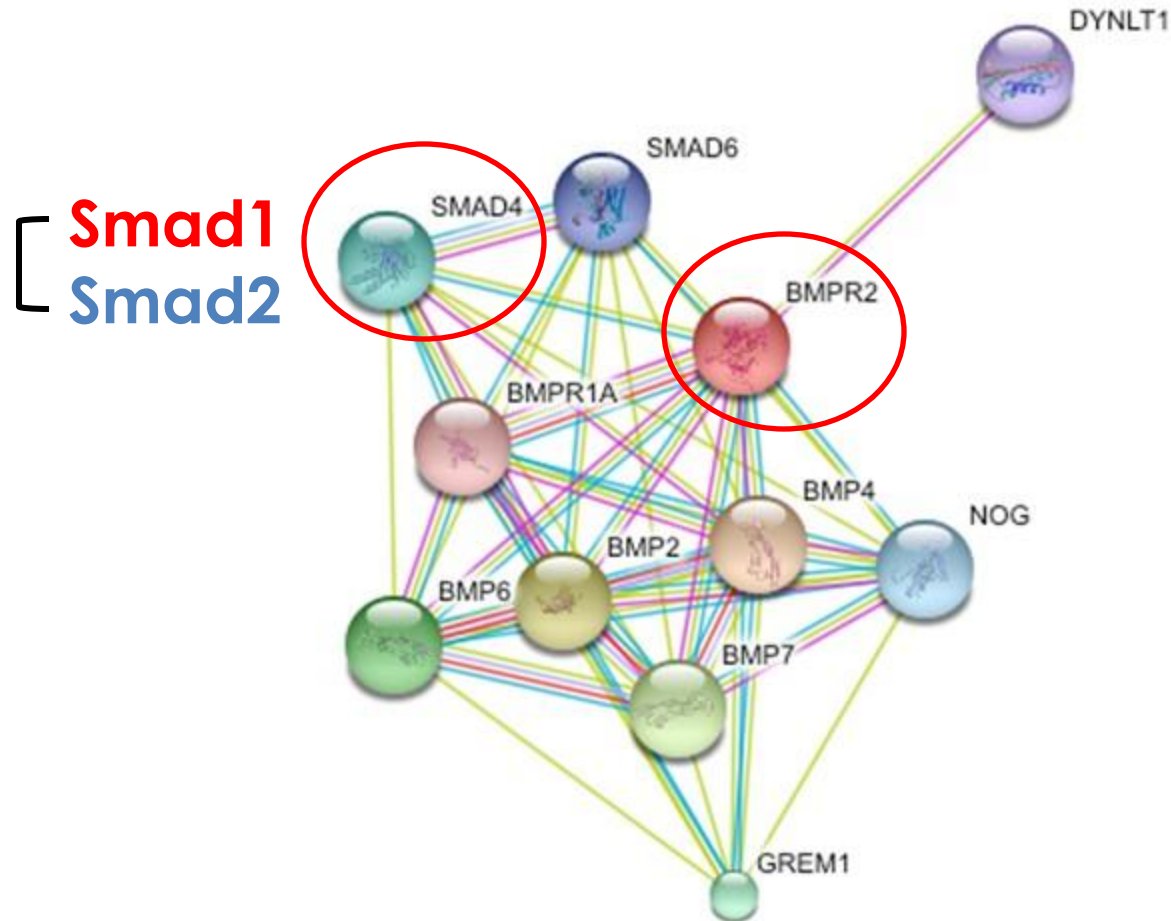
Mouse is a good test model

Mus musculus



- Great **similarity** with human BMPR2 protein
- **Easy** to handle
- **Cheap**
- **Many research** have been done with mouse

Protein interaction of BMPR2



WT vs. KO (BMPR2)

WT

BMPR2 KO

WT		BMPR2 KO	
BMPR2	BMPR1	BMPR2	BMPR1
Smad1	Smad2	Smad1	Smad2
TGF- β R1	TGF- β R2	TGF- β R1	TGF- β R2
Smad4	Smurf2	Smad4	Smurf2

Green: cultured SMC from **normal** mouse lung tissue

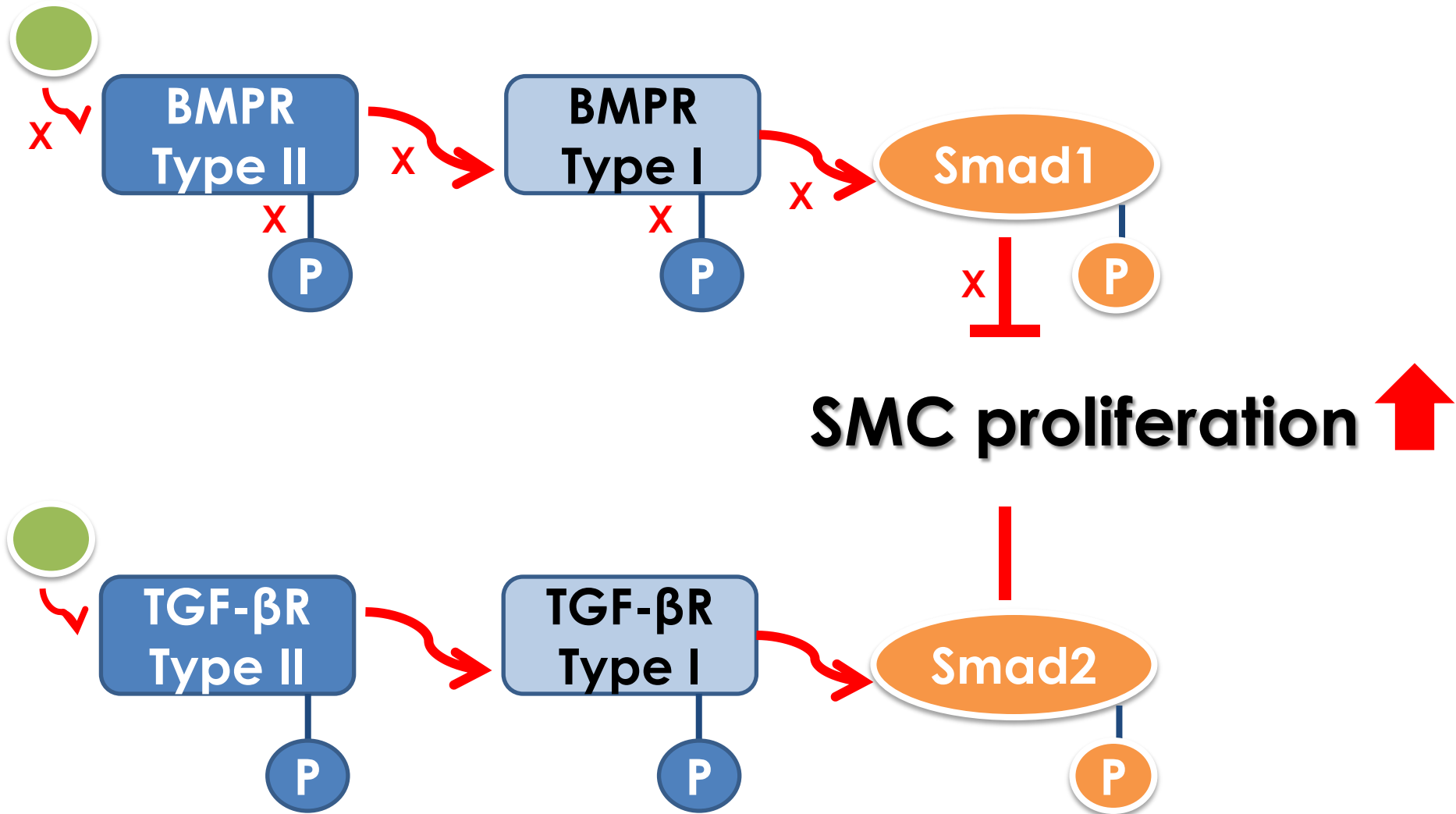
Red: cultured SMC from BMPR2 **knockout** mouse lung tissue

Hypothesis

Question of my study:

Does **phosphorylation of Smad** due to **BMPR2 mutation** play an important role in pathological pathway of PAH by **proliferating vascular smooth muscle cells (SMC)**?

Hypothesis



To test level of SMC

Main experiment:

To determine if **BMPR2 (mutation)** causes abnormal **SMC proliferation**

Group 1 (Control)

BMPR II (Normal)

Group 2

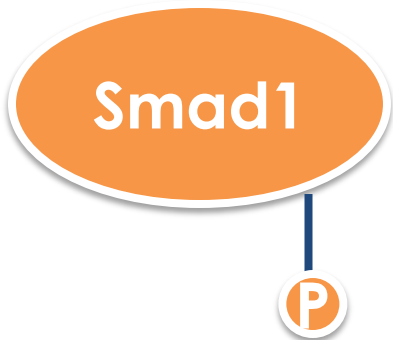
BMPR II (Mutation)

To test Smad signaling

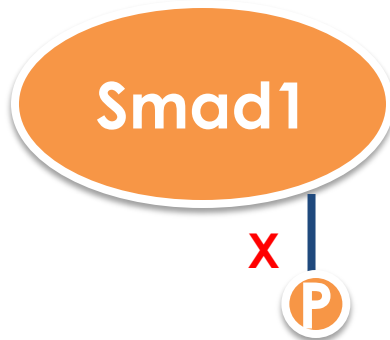
Following experiment:

To show **Smad** is involved with **SMC proliferation**

Control 1



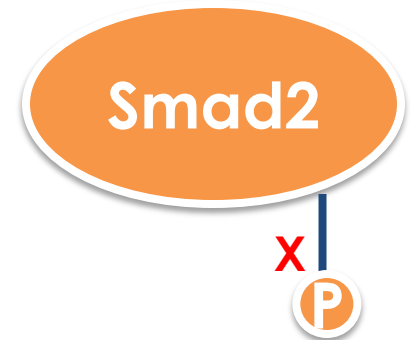
Experimental 1



Control 2

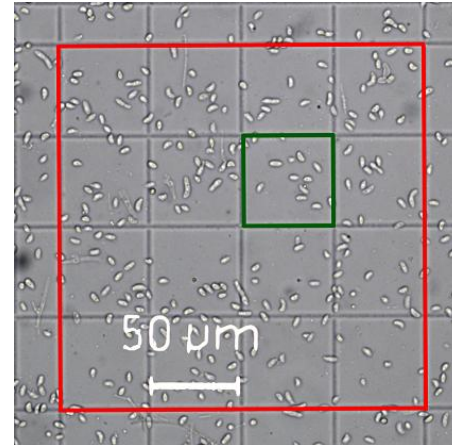


Experimental 2



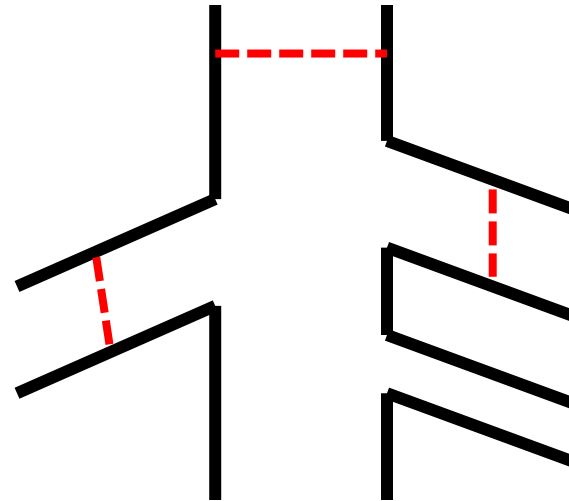
How to observe phenotype

1) To count number of SMC by using hemocytometer



2) To use isolated mouse lung quantification system

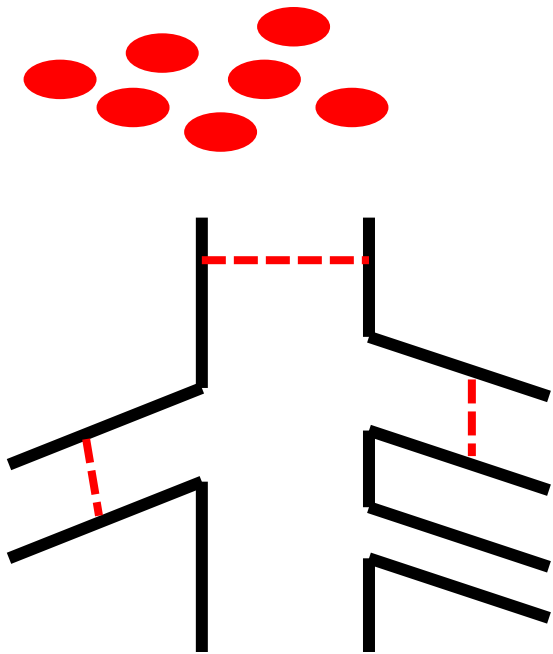
- to measure PA diameter
- to count # of arteries per a certain range of diameter



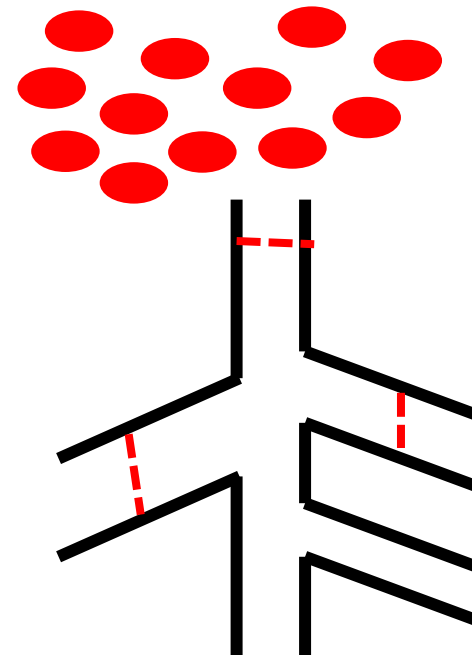
Expected results

Main experiment:

Group 1: BMPR2 (Normal)
(control)



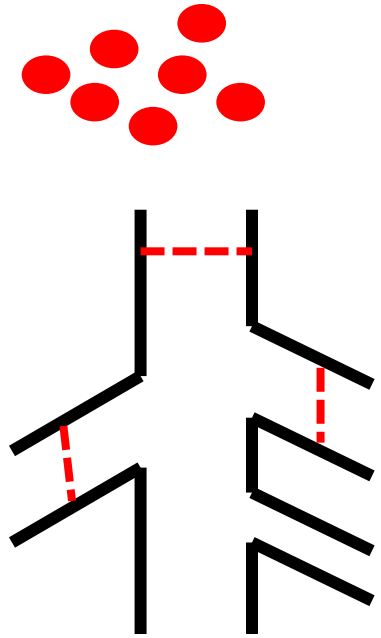
Group 2: BMPR2 (Mutation)



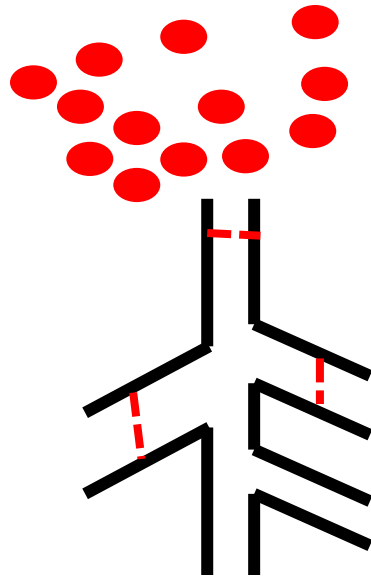
Continued

Following experiment:

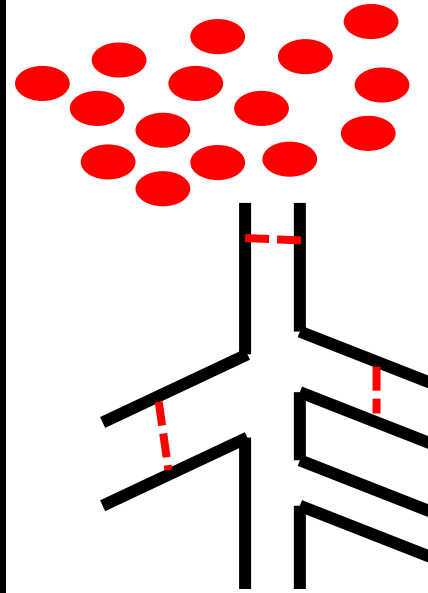
Control
(p-Smad1)



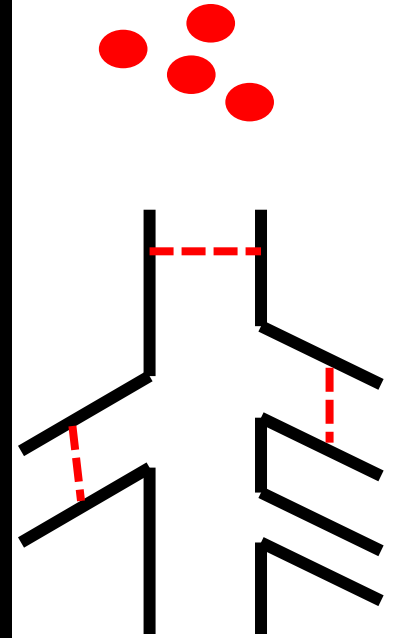
Exp 1
(de.p-Smad1)



Control
(p-Smad2)

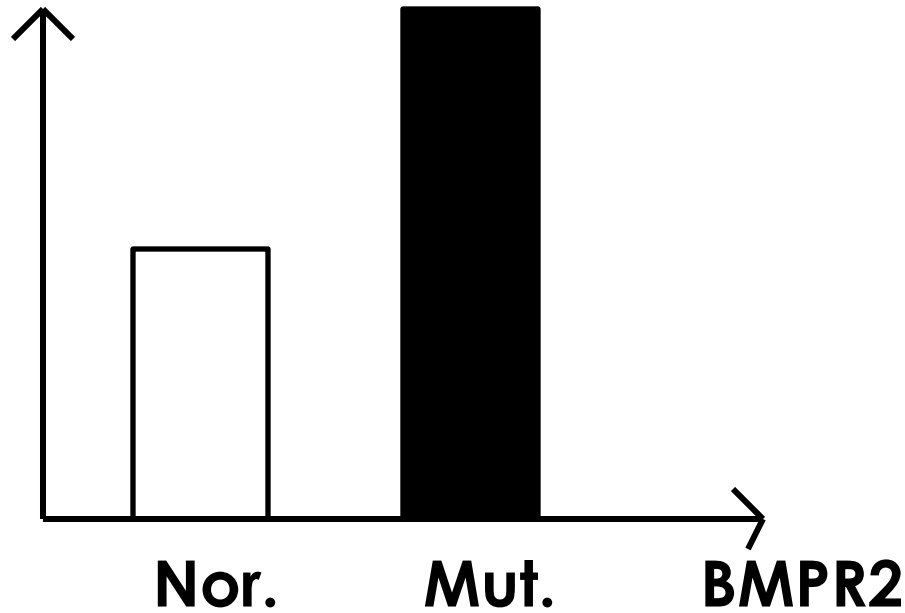


Exp 2
(de.p-Smad2)

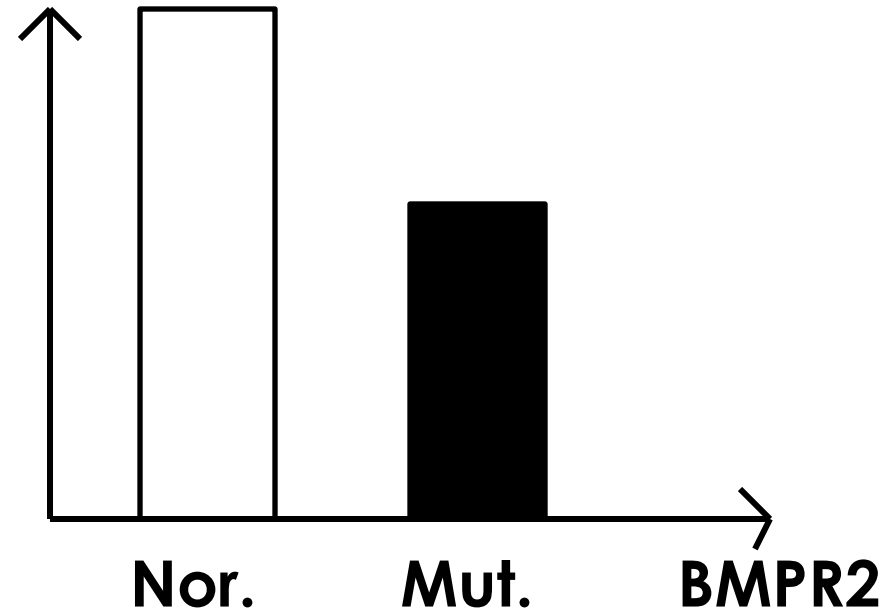


Summary

of SMC



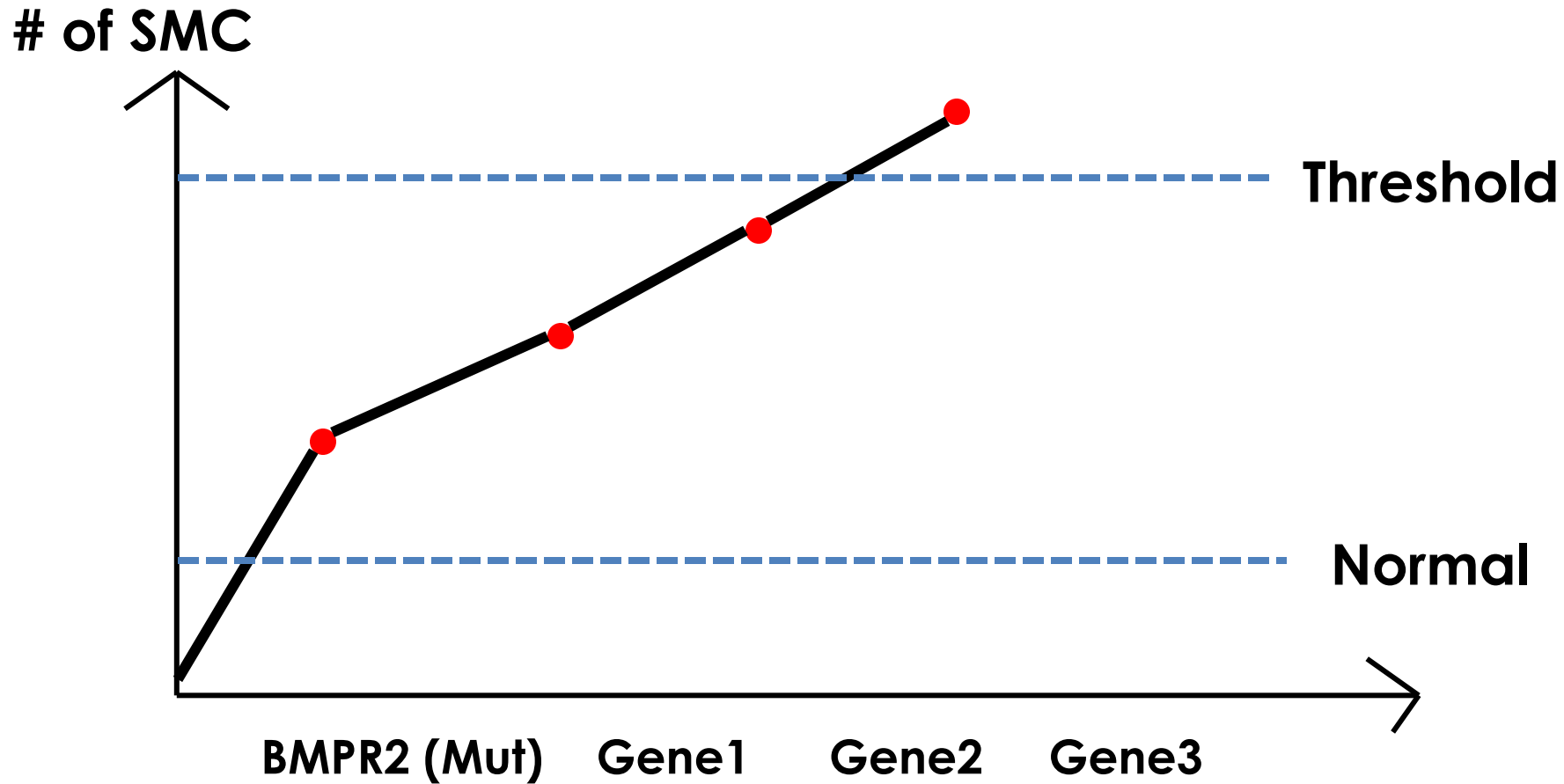
Diameter of PA



Future studies

- 1) Detail signaling pathway of BMPs & Smad**
- 2) Other proteins involve for regulating Smad signaling? Need to investigate which genes are involved with**
- 3) If other genes are involved, need to investigate how they are turned on or mutated in order to stimulate Smad2**

Future direction



Reference

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