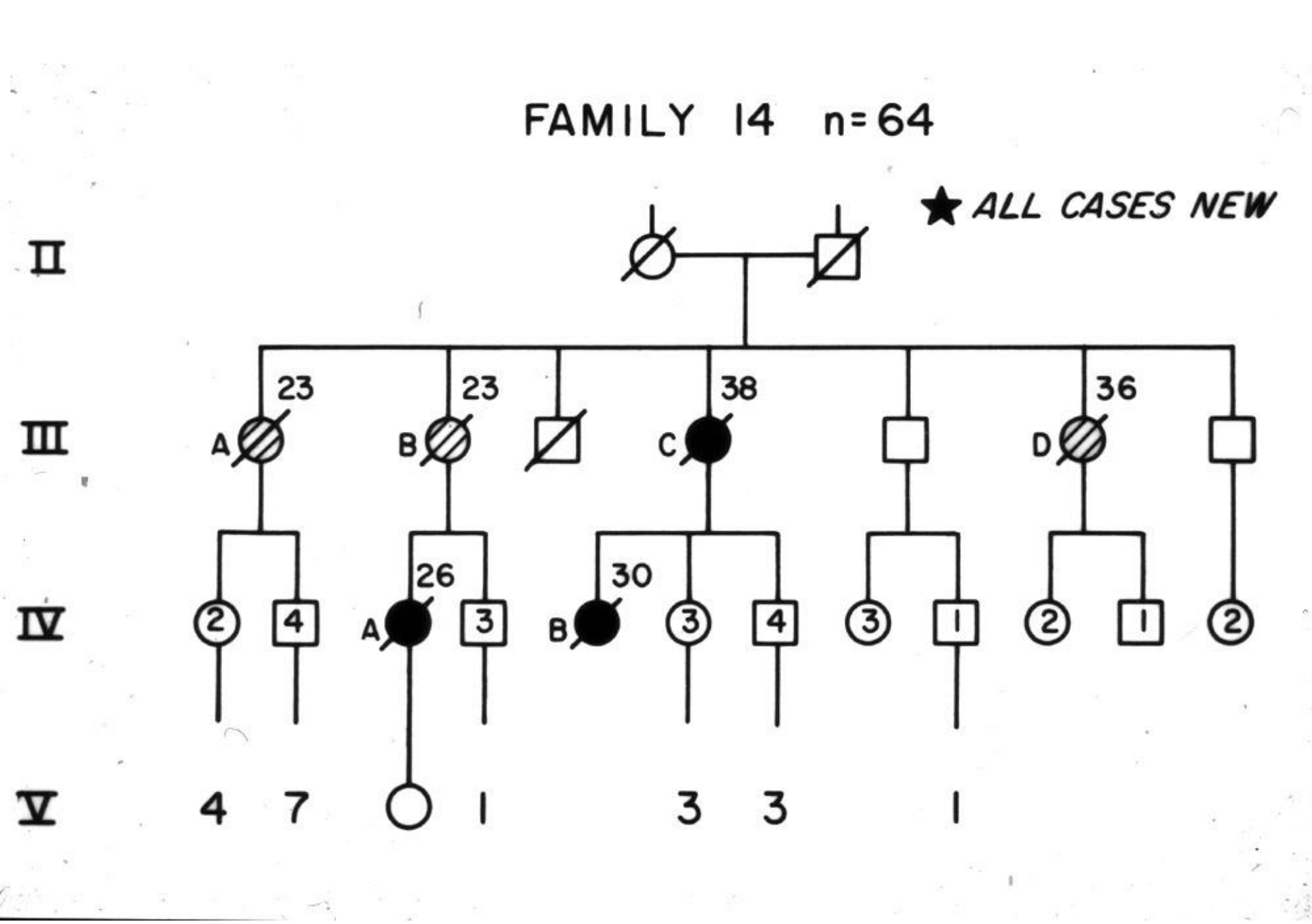
1980: Should We Get Involved in The Genetics of PH ?
The Grass Looks Greener, but…….

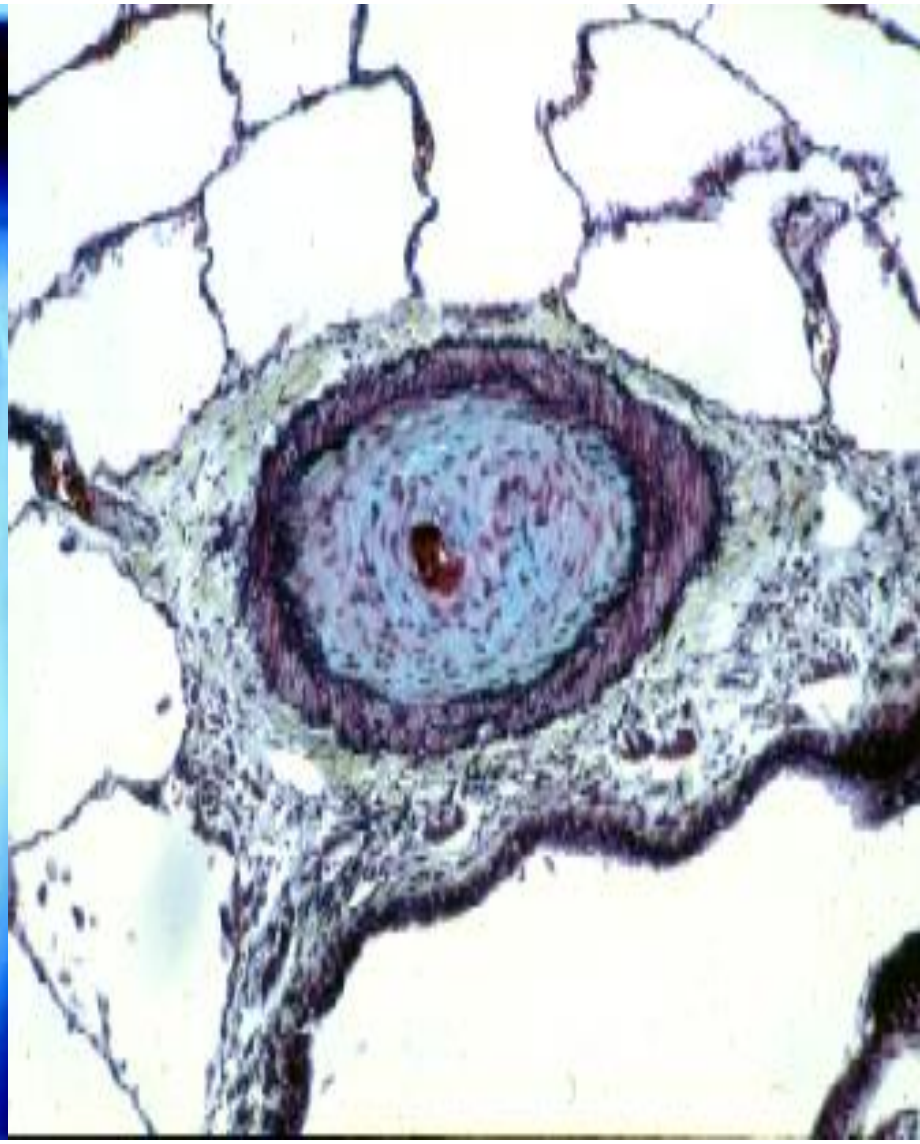
What is New in the Genetic/Genomic Basis of PAH

1. Genetic causes are common. Odd presentations.
2. BMPR2 downregulation is integral to IPAH as well as HPAH
3. Caveolin 1 is a new family mutation
4. No other highly prevalent mutations, rather rarer ones
5. Whole exome, genome and next gen sequencing .
6. Pre-implantation detection of BMPR2 mutations
7. Genetic anticipation is not a feature of BMPR2 HPAH.
8. Risk of disease in BMPR2 mutation carriers has changed.
9. BMPR2 + patients are younger, less vasoreactivity, do worse
10. microRNA and siRNA research may give leads to therapy

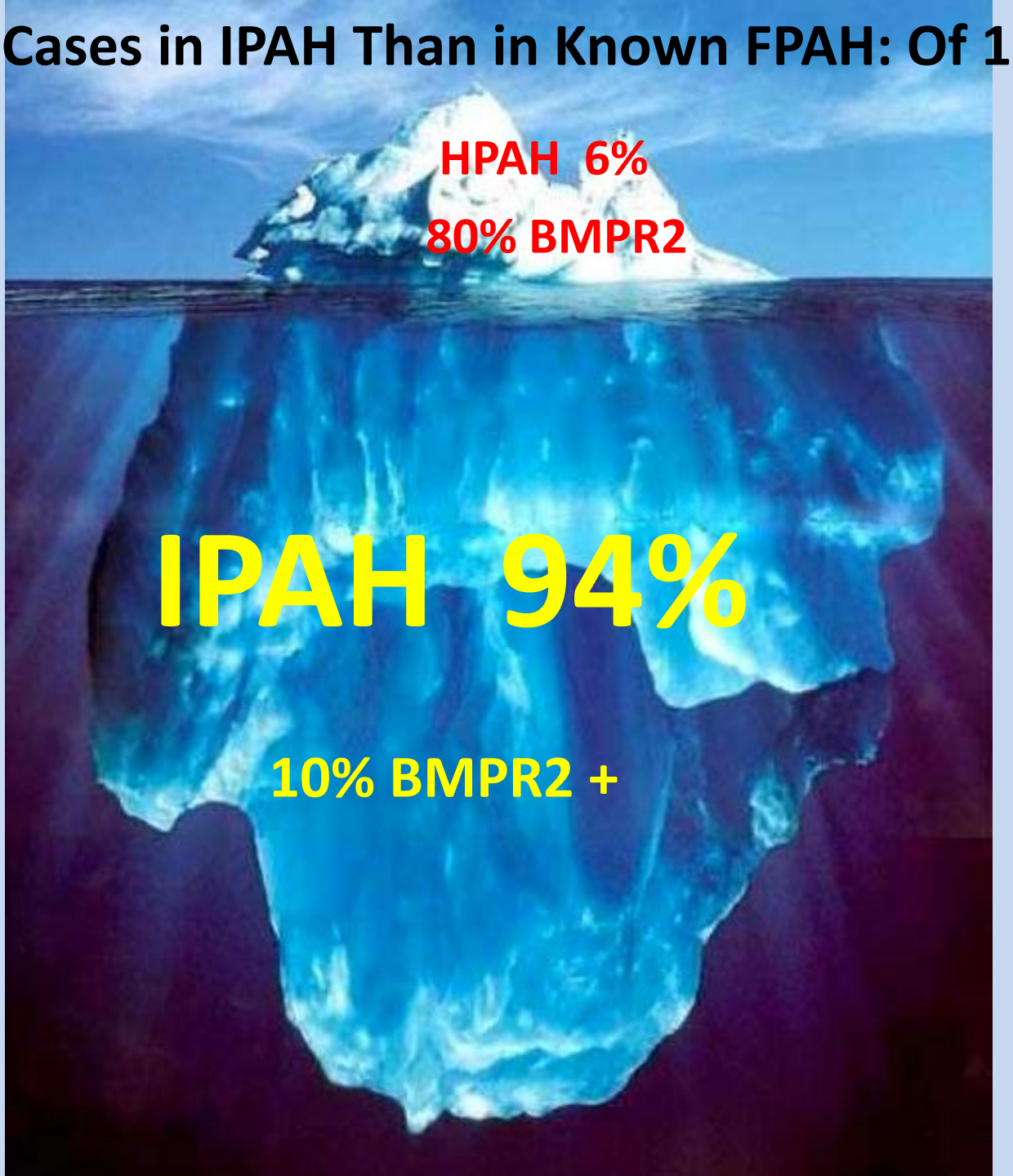
FAMILY 14 n=64



HPAH or IPAH : Phenotype is Similar



More Genetic Cases in IPAH Than in Known FPAH: Of 100 Cases



Why Progress in BMPR2 Has Been Slow

- No specific downstream product to measure function. SMADs are ubiquitous. Multiple pathways.
- Immunohistochemistry and immunoassays have been very difficult to develop. Can't measure receptor.
- The mutational state is heterozygotic with decreased function. Hard to quantify.
- Multiple ligands cross over with other TGFb receptors: BMP 2-7-9.
- Multiple inhibitors: noggin, DAN, cerebrus
- Can't determine the effector cell.

BMPR2 mutations in PAH

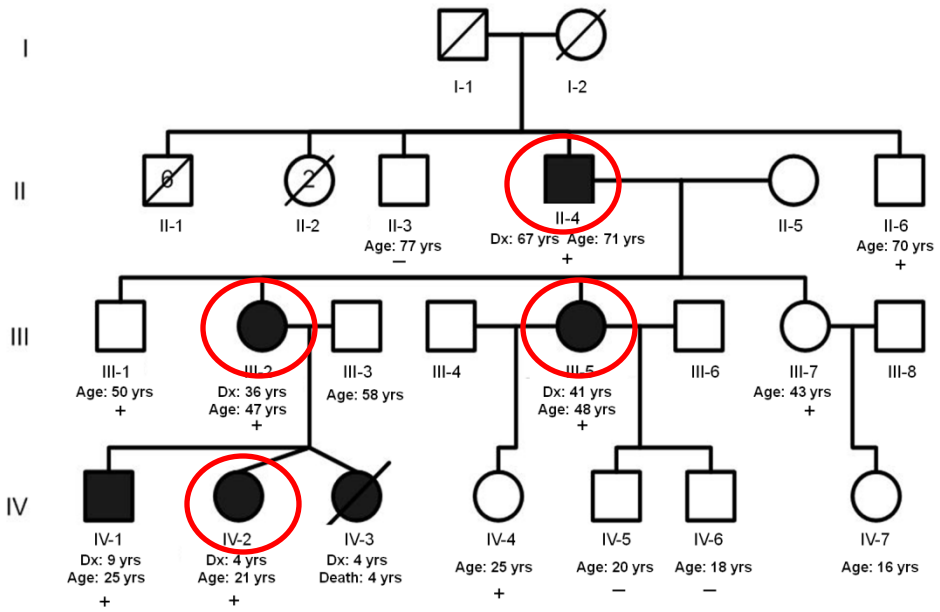
- **Population prevalence: unknown but <u>very</u> rare**

Familial PAH (FPAH)	≥ 80%
Idiopathic PAH (IPAH)	10-40%
Congenital heart disease	6%
Scleroderma	Not detected
HIV	Not detected
Hemolytic disease	Not reported

BMPR2 & other genes associated with PAH

- Transforming Growth Factor β (TGFβ) Pathway
  - Receptors
    - BMPR2 **
    - ALK1
    - endoglin
  - Downstream signaling
    - SMAD proteins

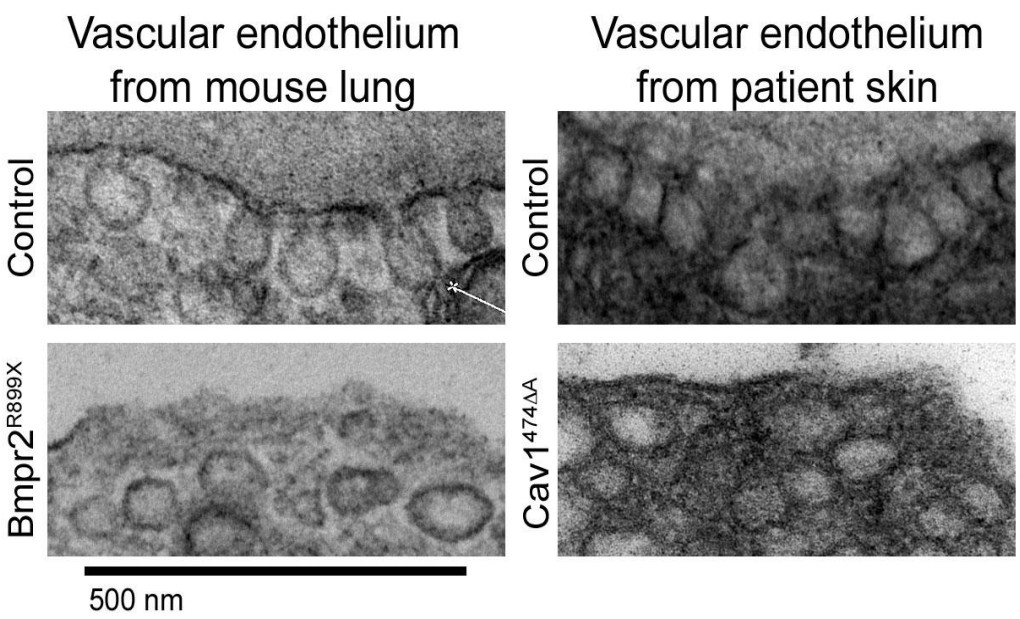
Whole Exome Sequencing for Rare Variants



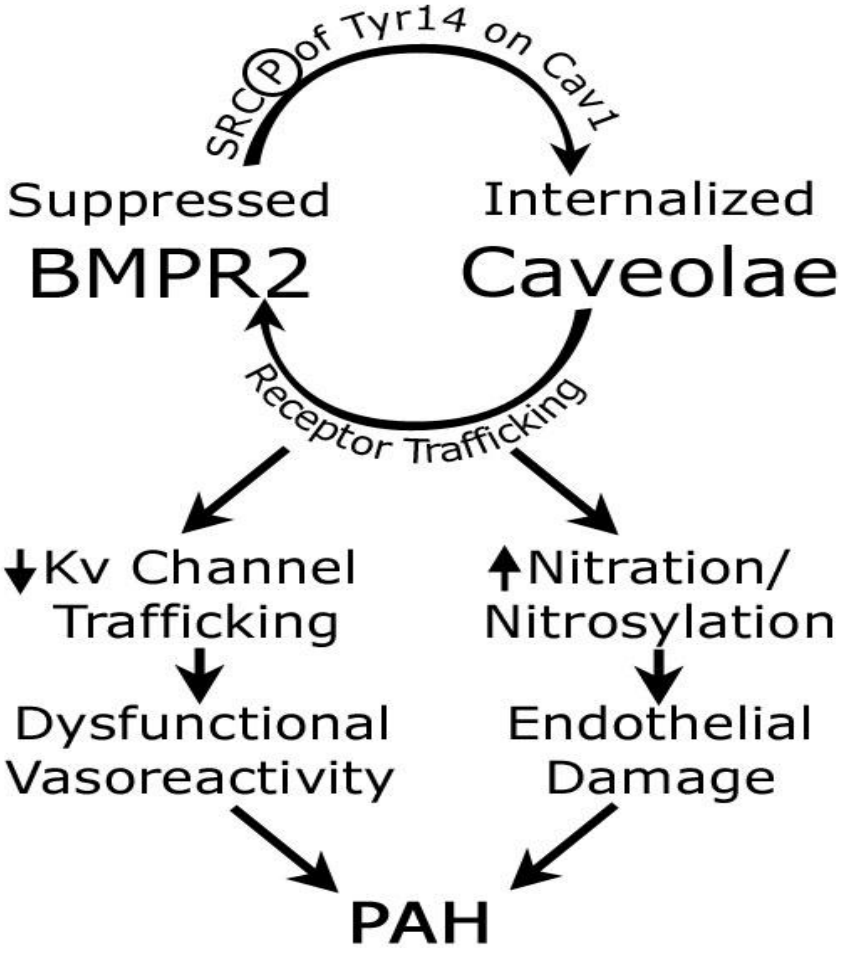
- 52 shared novel variants
- 16 coding region & predict detrimental
  - 11 confirmed by Sanger
- Test 5th patient in family
- 3 genes with non-synonymous mutations in coding regions
- SNAP, SIFT, Polyphen
  - 1 of 3 predicted to be deleterious (*CAV1*)

Austin, Ma et al *Circ Genetics,* in press

CAV1: mechanism relevant?

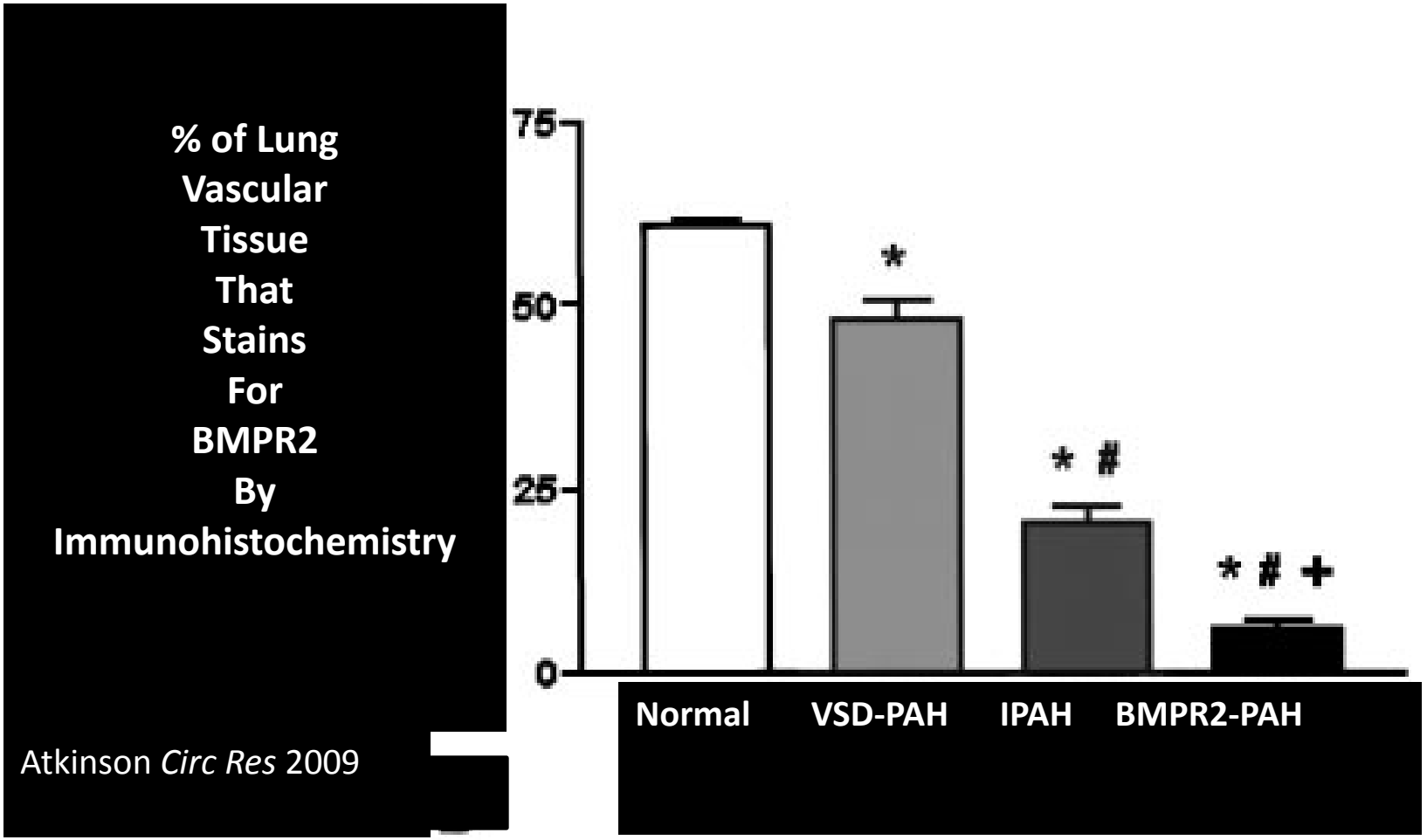


Uniform Hypothesis

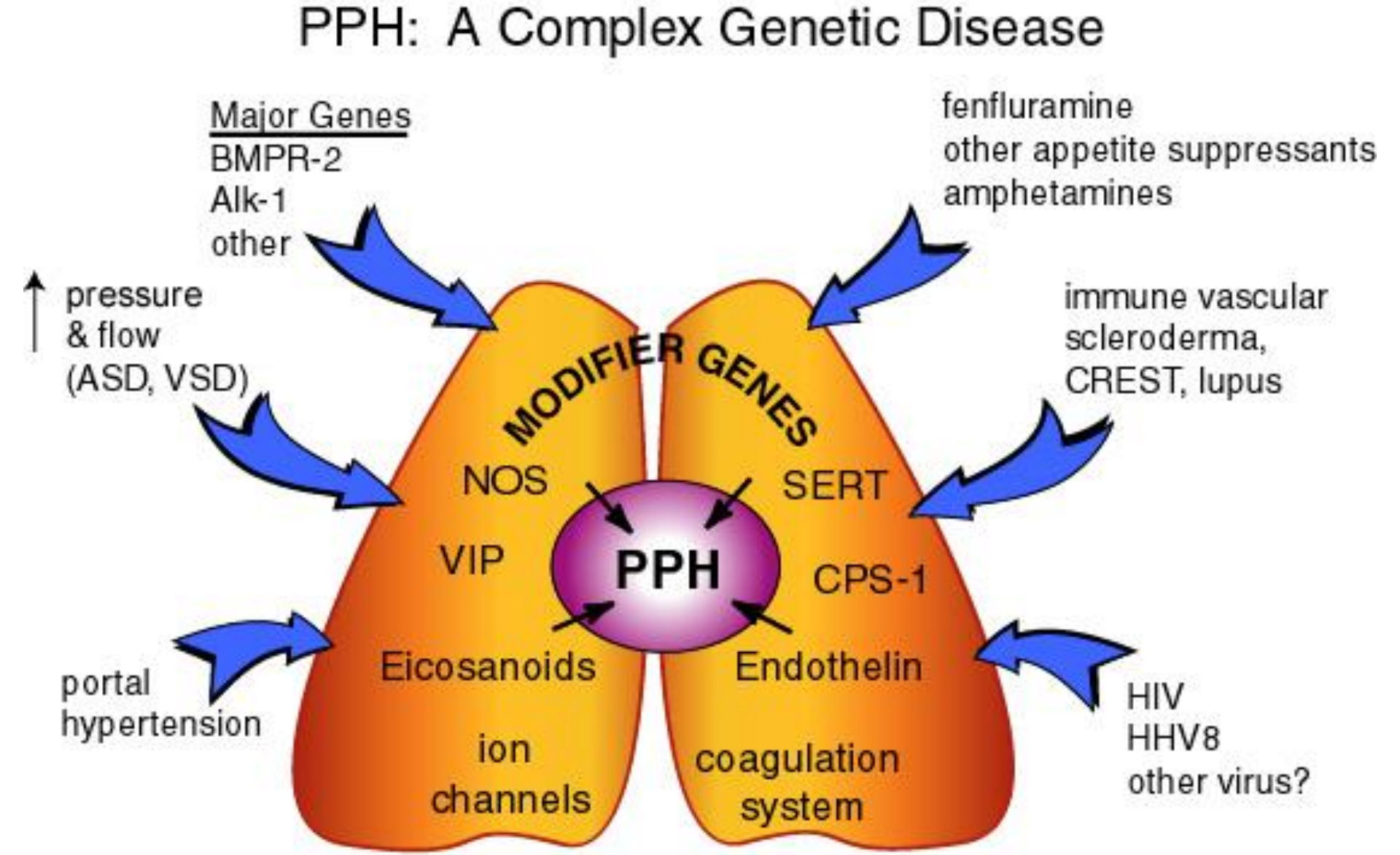


Austin, Loyd, Lane, Kenworthy, West; *unpublished*

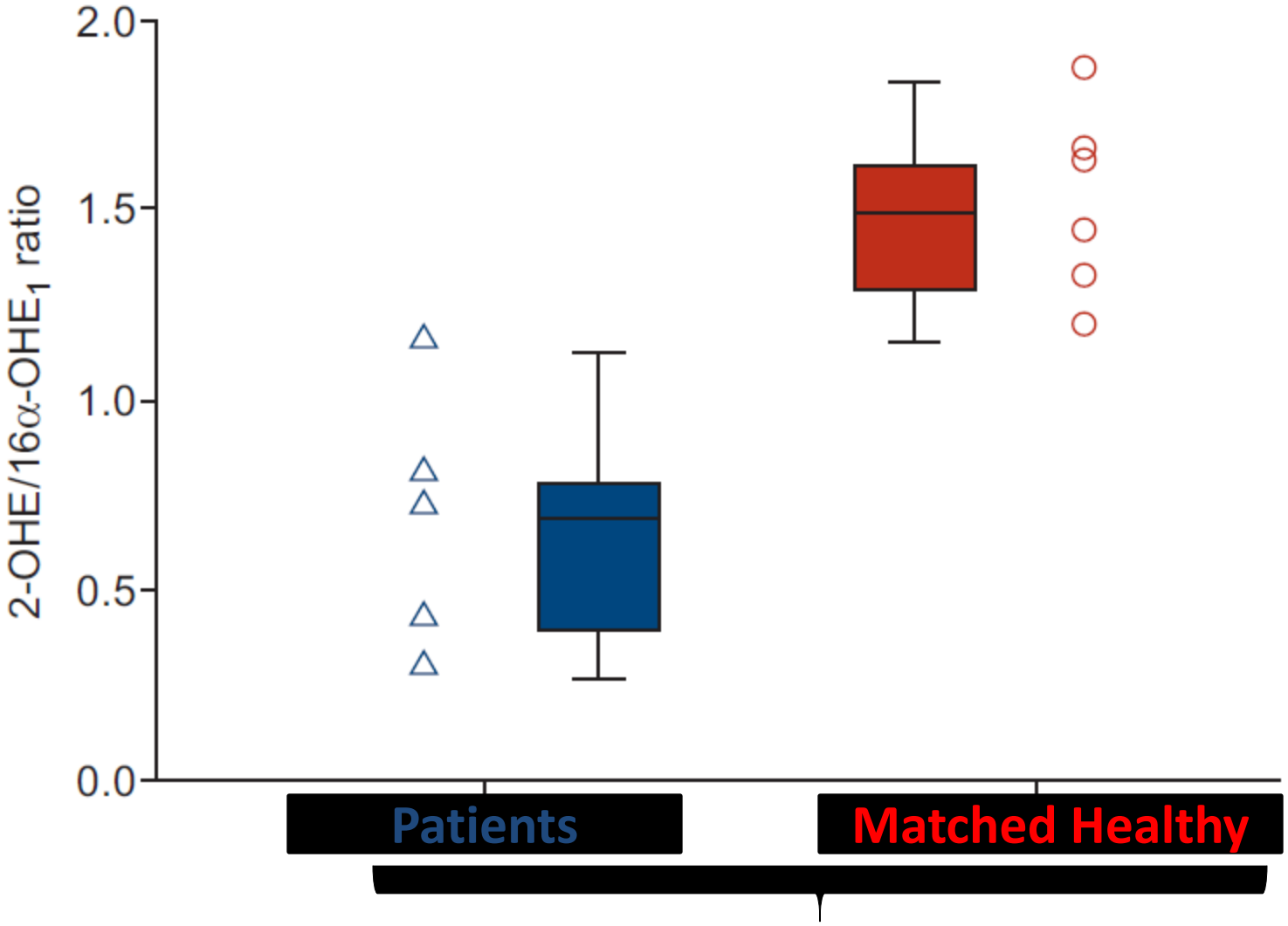
BMPR2 protein reduced in multiple forms of PAH



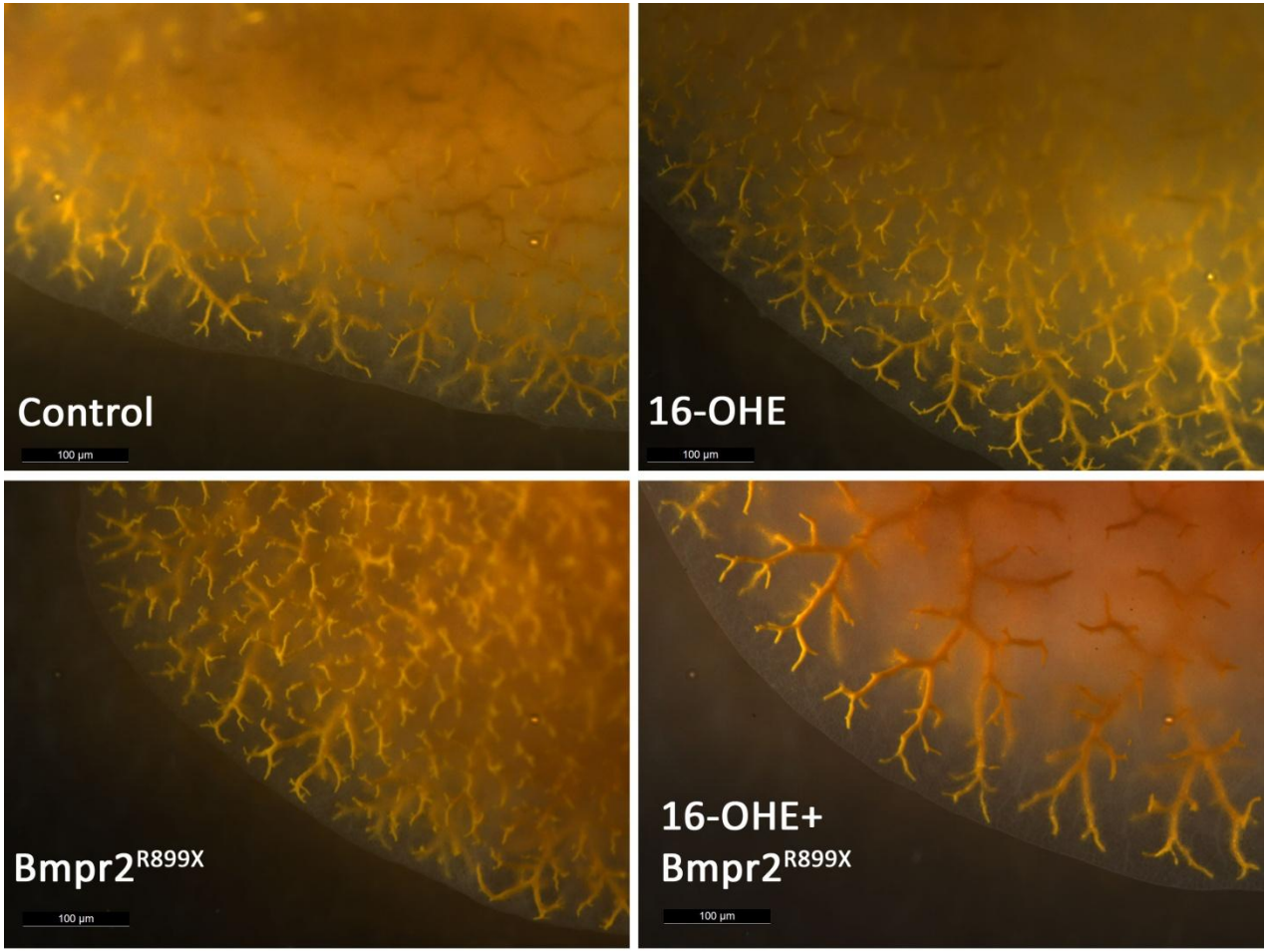
Atkinson *Circ Res* 2009



Maybe insights from next gen sequencing

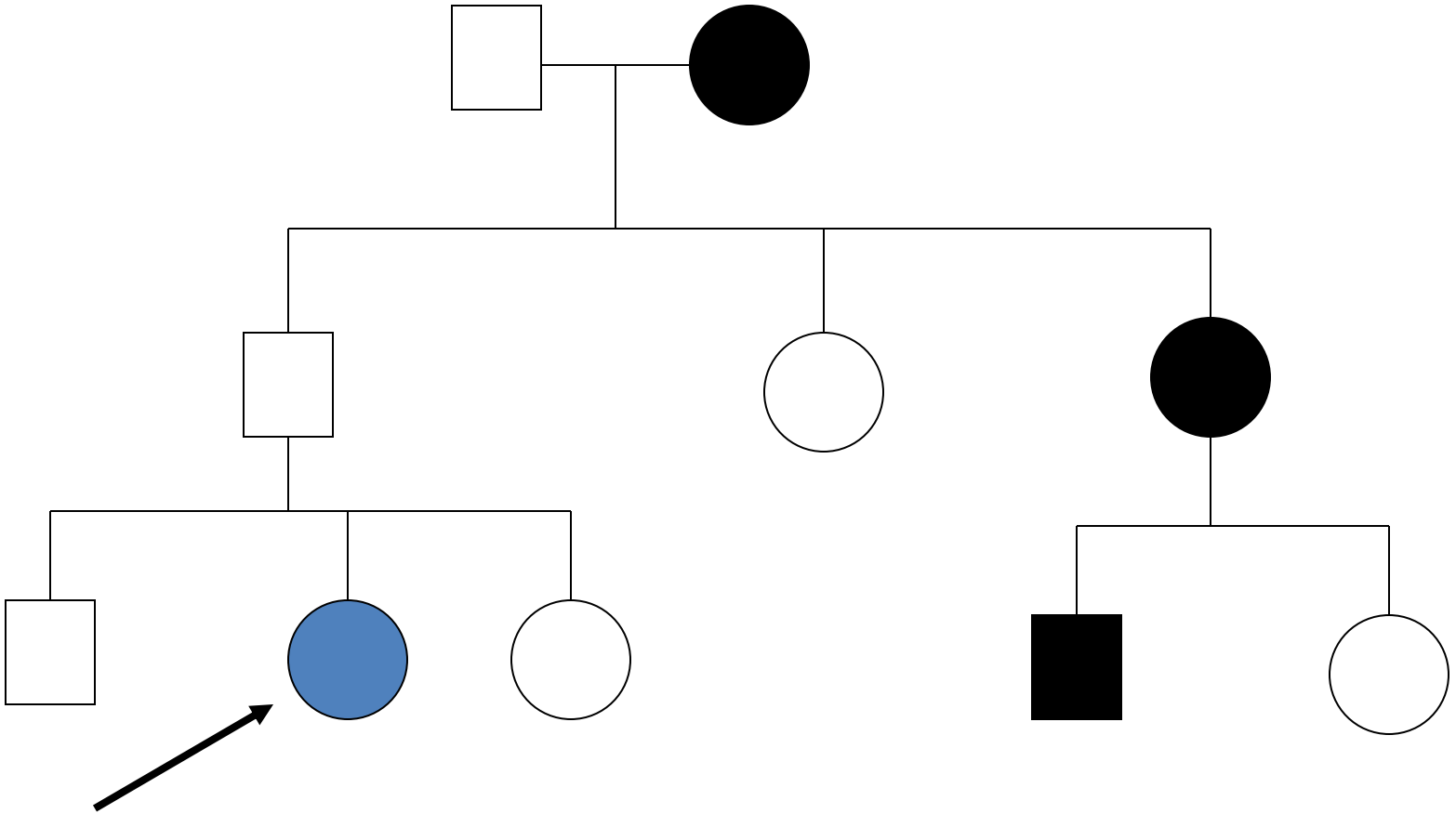

2-OHE/16α-OHE1 ratio
2.0
1.5
1.0
0.5
0.0
Patients
Matched Healthy
All BMPR2 Mutation Carriers

16-estrogens accelerate progression of PAH in Bmpr2^{R899X} mice of both genders



Courtesy of James West & Anna Hemnes

INFORMED CONSENT AND IMPLICATIONS OF GENETIC TESTING



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

Nelly Frydman Julie Steffann Barbara Girerd René Frydman Arnold Munnich Gérald Simonneau Marc Humbert

Service de Pneumologie, Hôpital Bicêtre, 78 rue du Général Leclerc, 94270 Le Kremlin Bicêtre, France.

"An unaffected embryo was implanted, leading to a successful pregnancy and the birth of a healthy child who was not carrying the deleterious*BMPR2* mutation."

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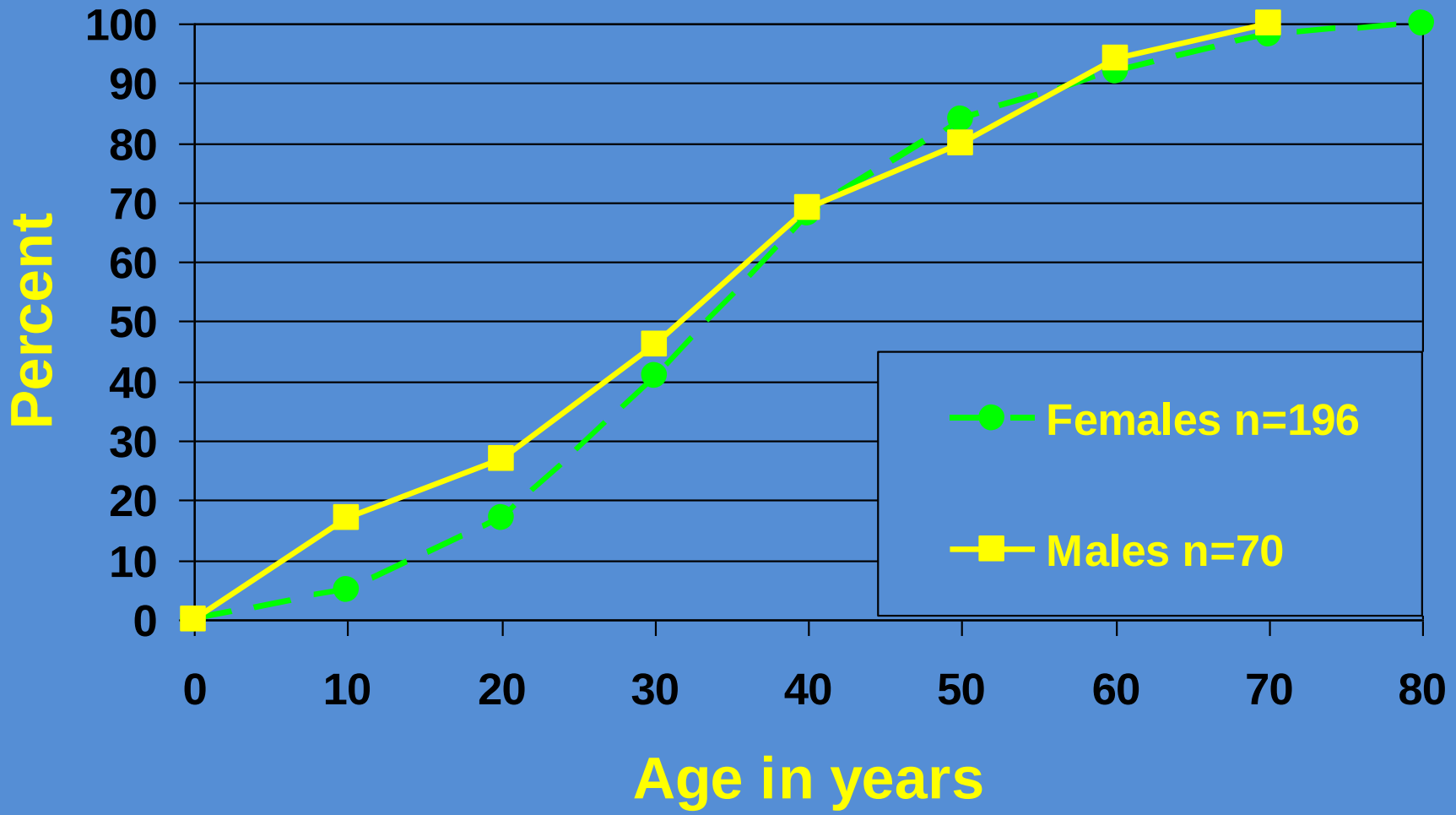
Cumulative Mortality HPAH



Apparent Genetic Anticipation in HPAH

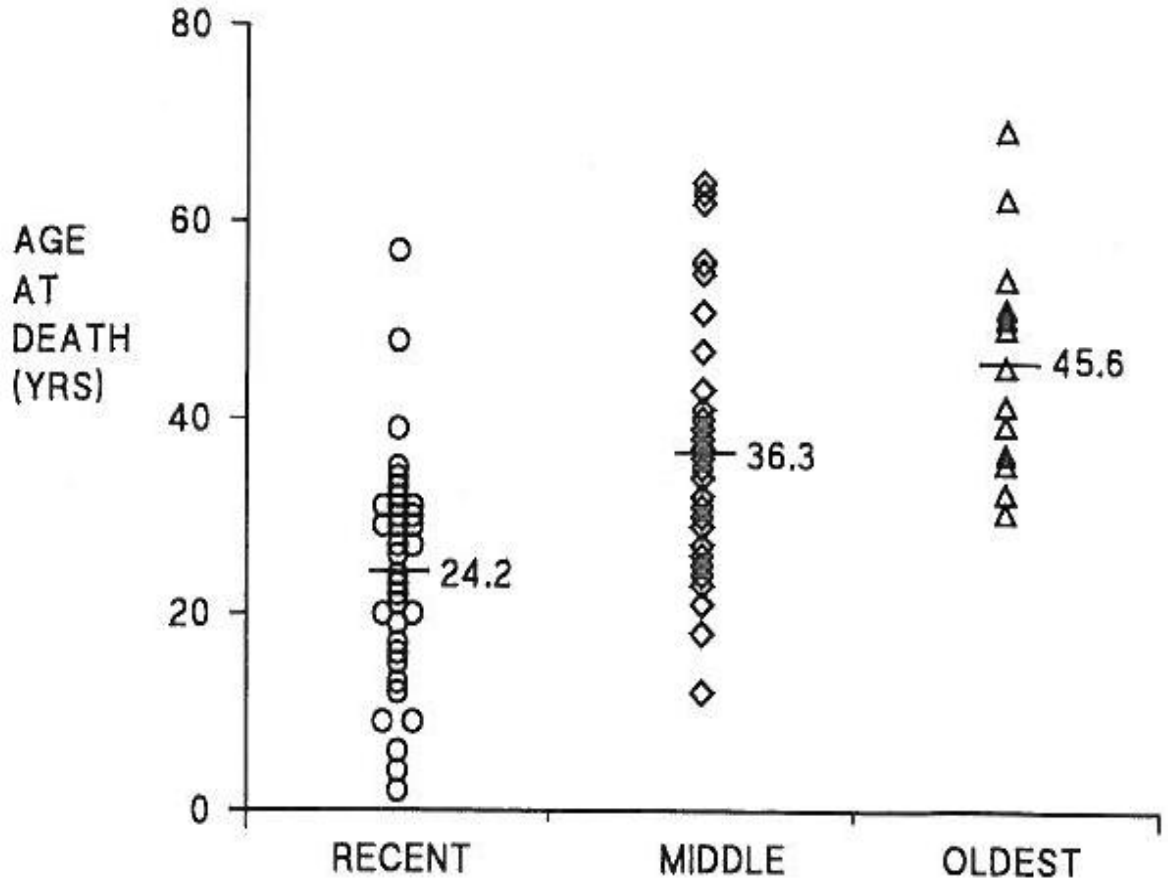
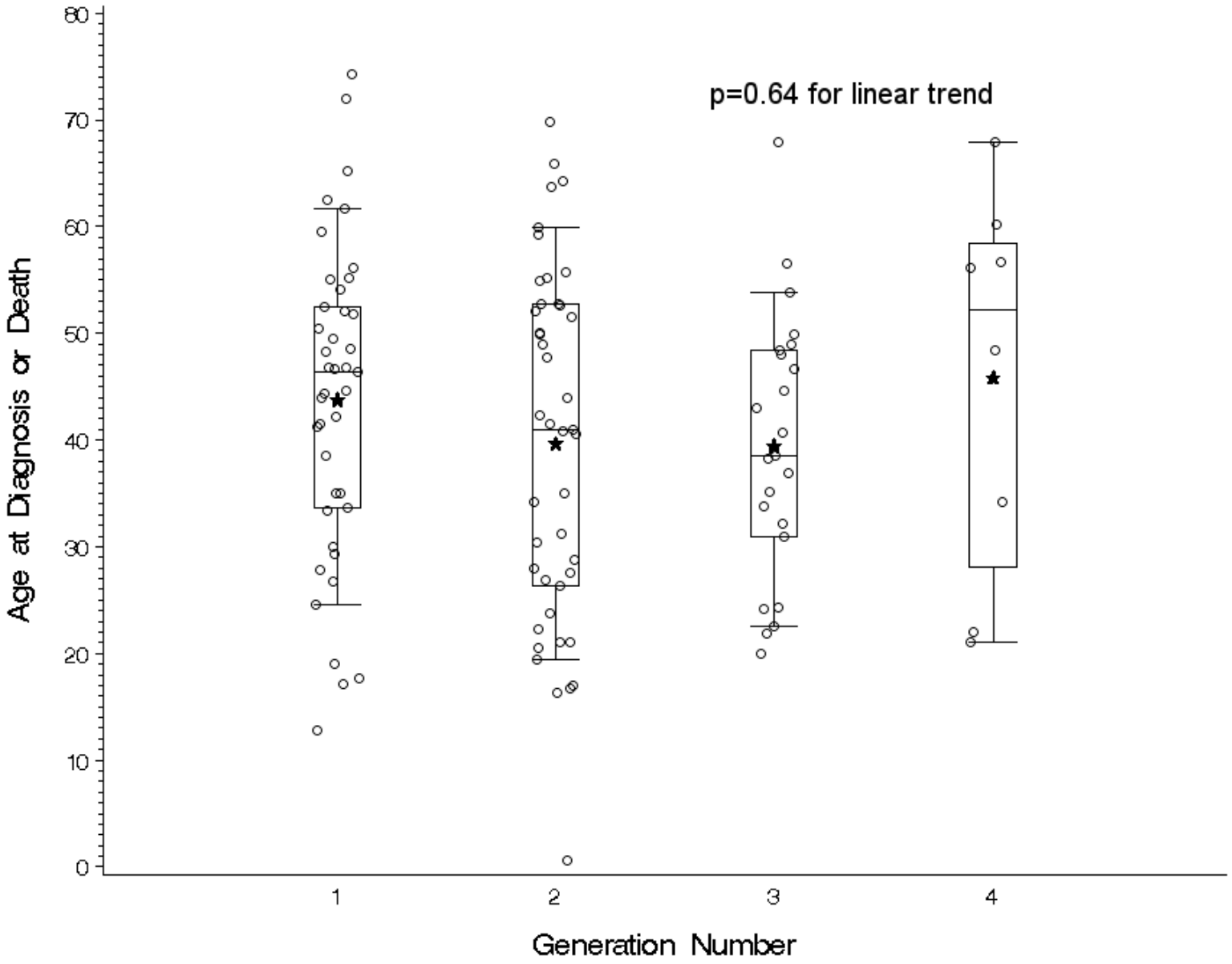


Figure 4. Age at death versus generation in familial primary pulmonary hypertension. The mean age at death was significantly different for each generation, $p < 0.05$.

Genetic Anticipation Disappears When Generations of Sibships Have Been Observed for 57 Years

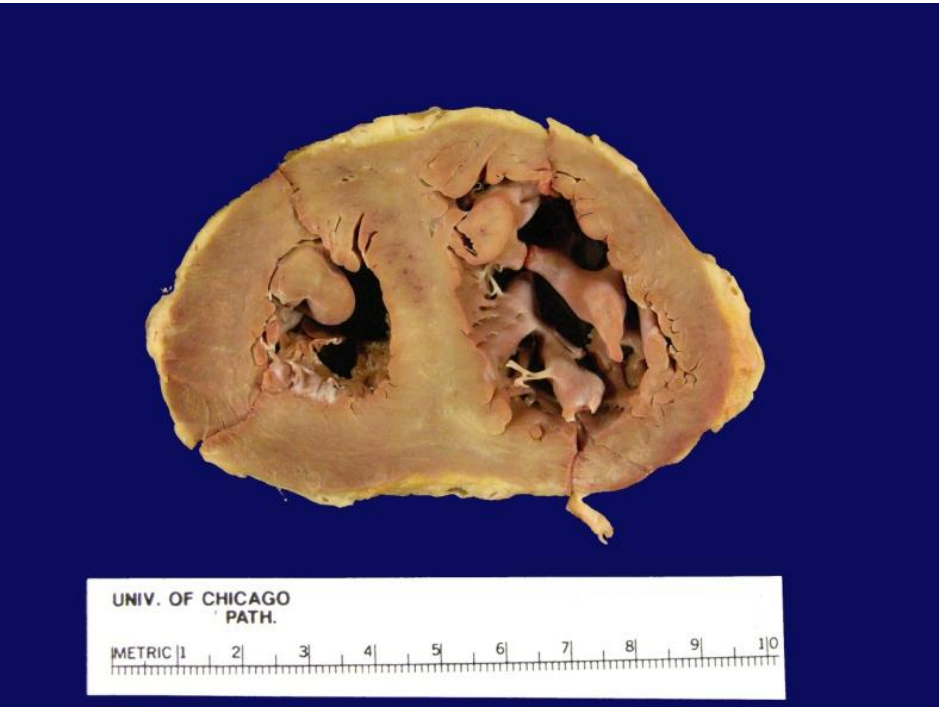


To Assess Penetrance from Vanderbilt Registry

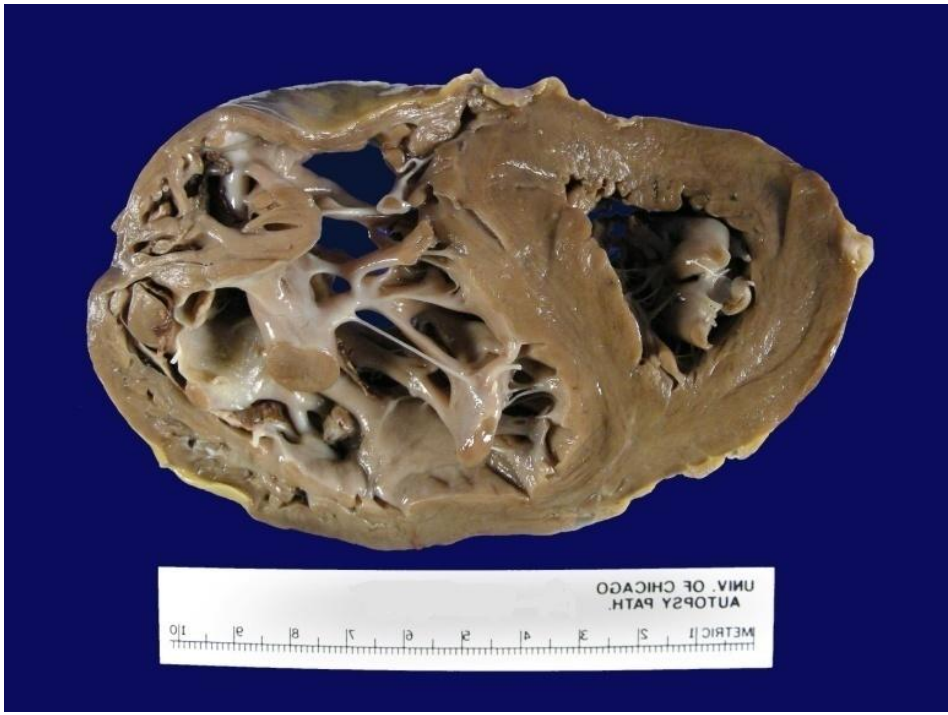
1683 total siblings at risk from affected sibships born <1955
842 (50%) would be predicted to have the BMPR2 mutation = 842
Of these 842 siblings, 232 were affected with clinical PAH
Of these 842 siblings the number of males and female was equal.

Female:Male ratio of affecteds = 3:1
Overall Penetrance 232/842 = 27%
Females 177/421 = 42% penetrance
Males 59/421 = 14% penetrance

Right Ventricular Response to Chronic Severe Pulmonary Hypertension



This patient

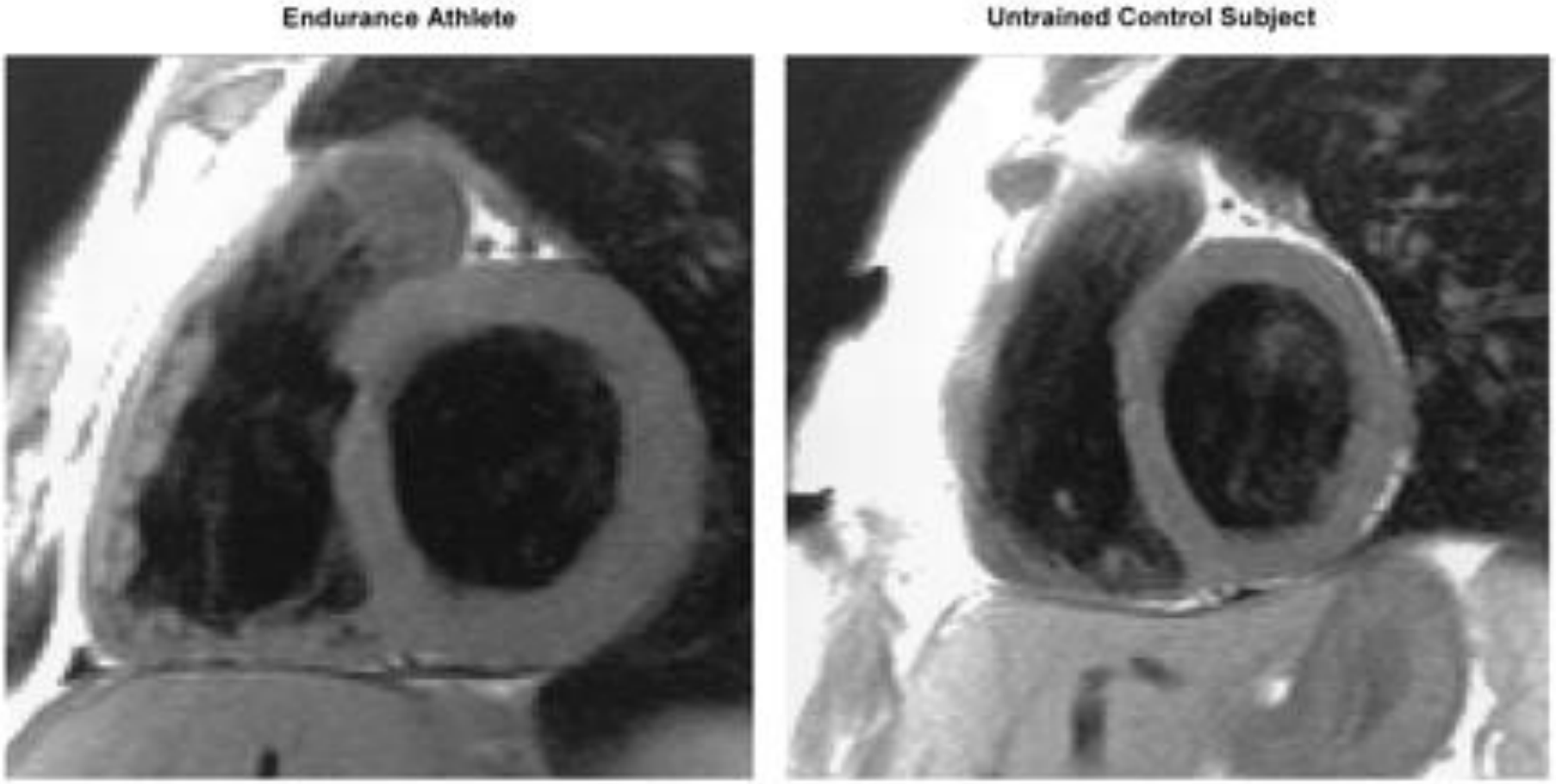


Other patient with PAH who died with RV failure

BACK to the RV: Is Hypertrophy Good?

Hypertrophy Is Good in Health and Disease to a Point

(aortic stenosis, hypertension, ASD , athletes heart)



Genes and Ventricular Stress: Research Approaches

“…….round up the usual suspects”

Where Are We Going in Genomic PAH?
The Goal is to Discover Treatments and Prevention

Next Gen sequencing, will reveal **genetic/genomic relationships**

Genetic studies of IPAH will be informative in IPAH and HPAH

Connecting the dots in BMPR2 signaling should reveal **treatment sites**

Micro RNA is exciting

Genetic testing, counselling and **genetic therapy** will emerge

Application of these **techniques to the RV** will be essential

Genetic/Genomic Progress in PAH Since 2008

Disclaimer:

I have abundant conflicts of interest, but none that I get paid for.

C’est un honte, je le sais

The Journey Against PH

"Life is short, the art long."

Hippocrates c.460 - 357 BC

"If you don't know where you are going, you will wind up somewhere else.“ (yogi berra)

"We make war that we may live in peace.”

Aristotle 384 - 322 BC