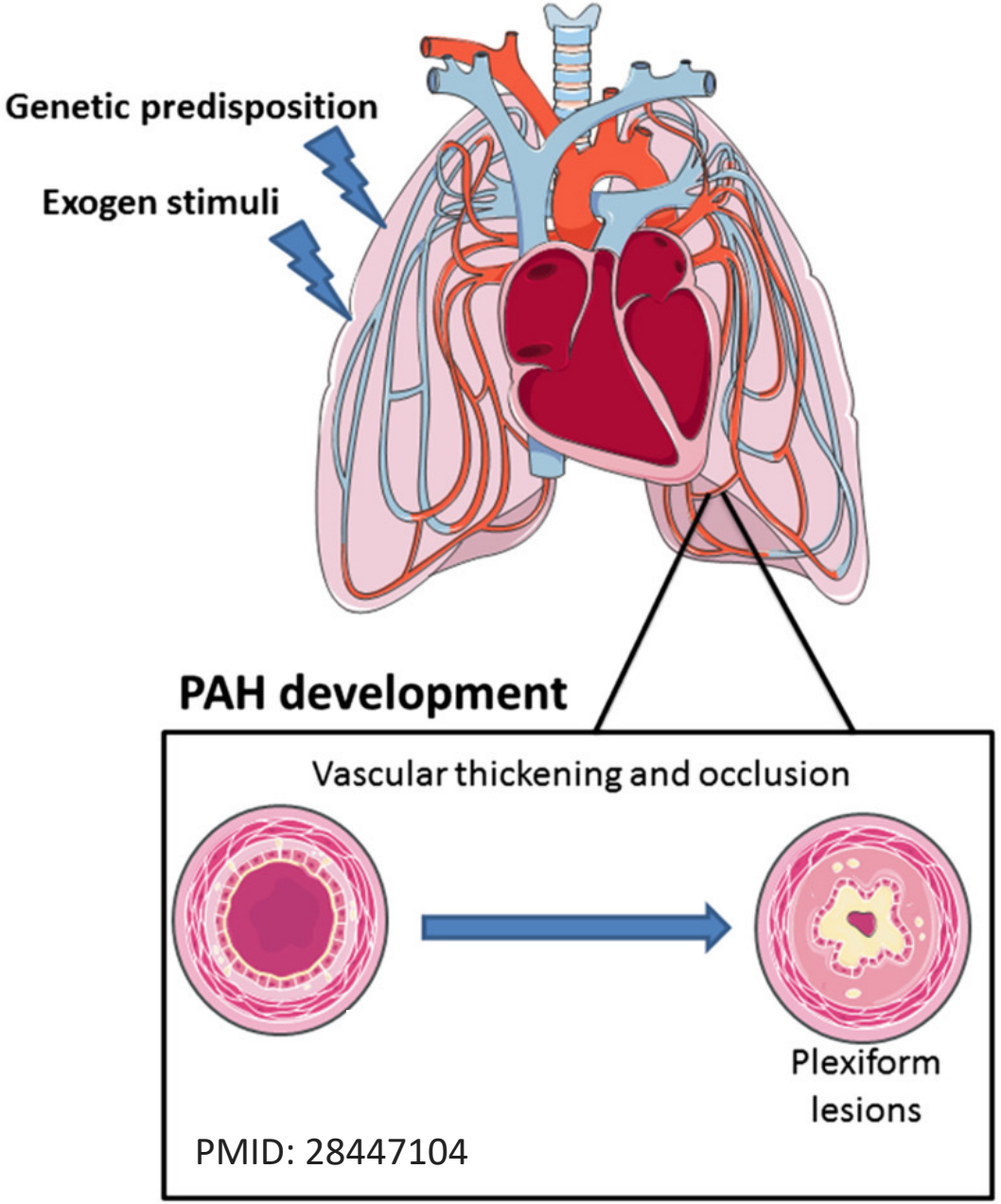
Unravelling the genetics of pulmonary hypertension

Matina Prapa, MD, PhD

Consultant in Clinical Genetics

St George's Hospital & Royal Brompton Hospital

London, UK



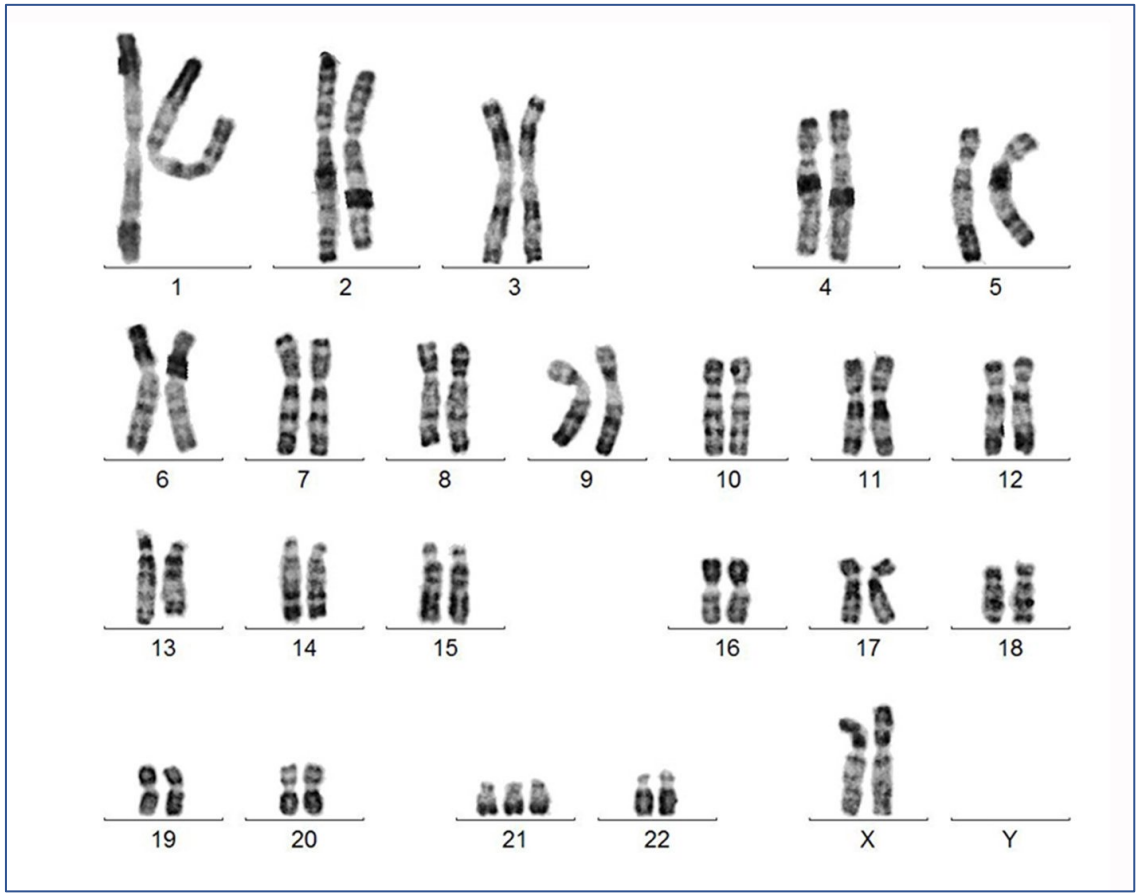
1.PAH

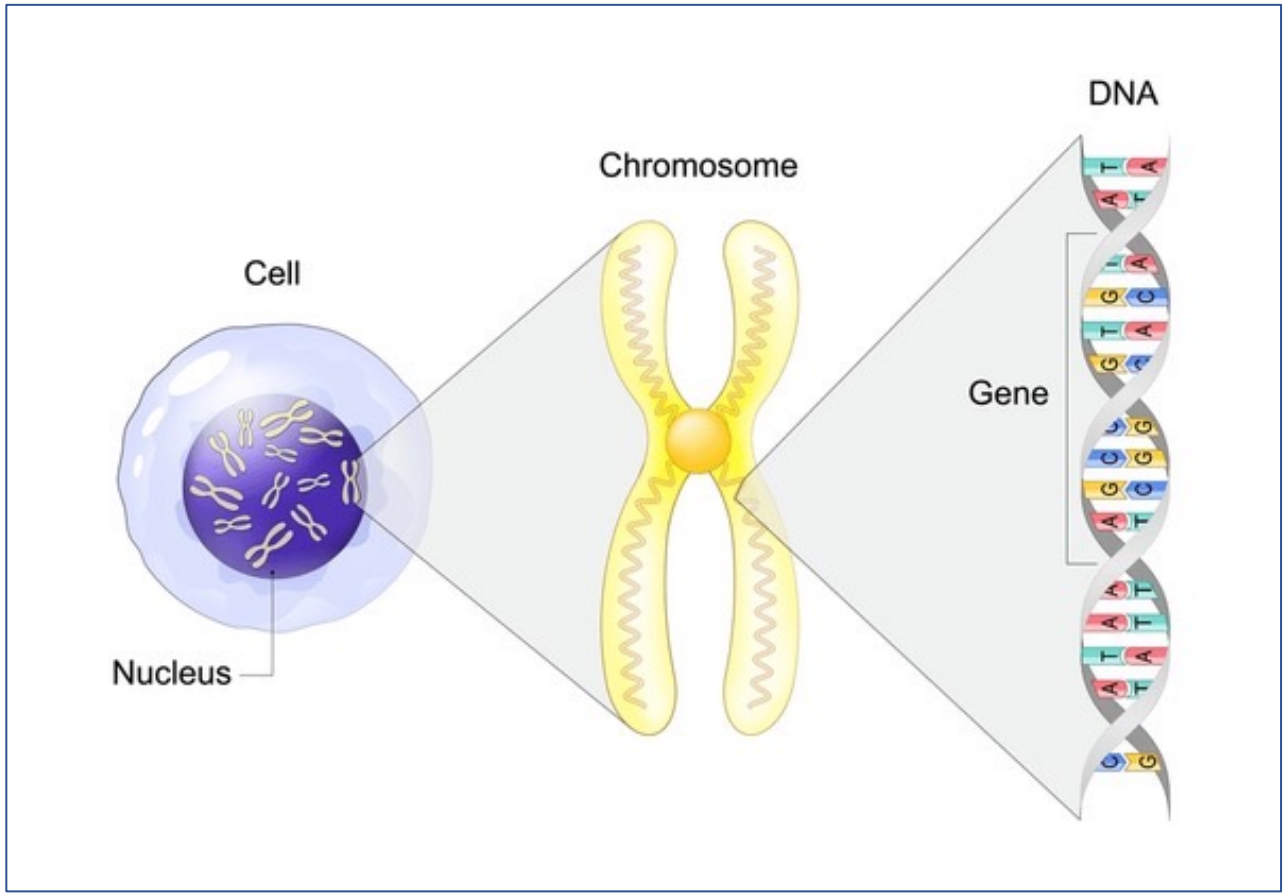
1.1 Idiopathic PAH
1.2 Heritable
1.3 Associated with drugs and toxins
1.4 Associated with CTD, CHD, etc.
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent pulmonary hypertension of the newborn syndrome

2. PH due to left heart disease	3. PH due to lung disease and/or hypoxia
4. PH associated with pulmonary artery obstructions	5. PH with unclear and/or multifactorial mechanisms

Simonneau et al, *JACC* 2013

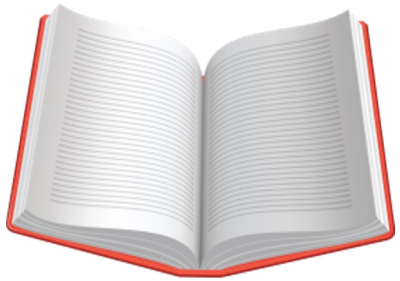
Introduction to genetics





Types of genetic tests

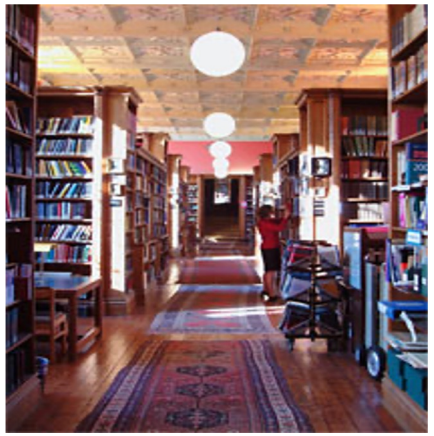
Single gene testing



Screen for “spelling mistakes” in the DNA code:
The car was red.
The car was rdd.

Gene panel

Whole exome sequencing

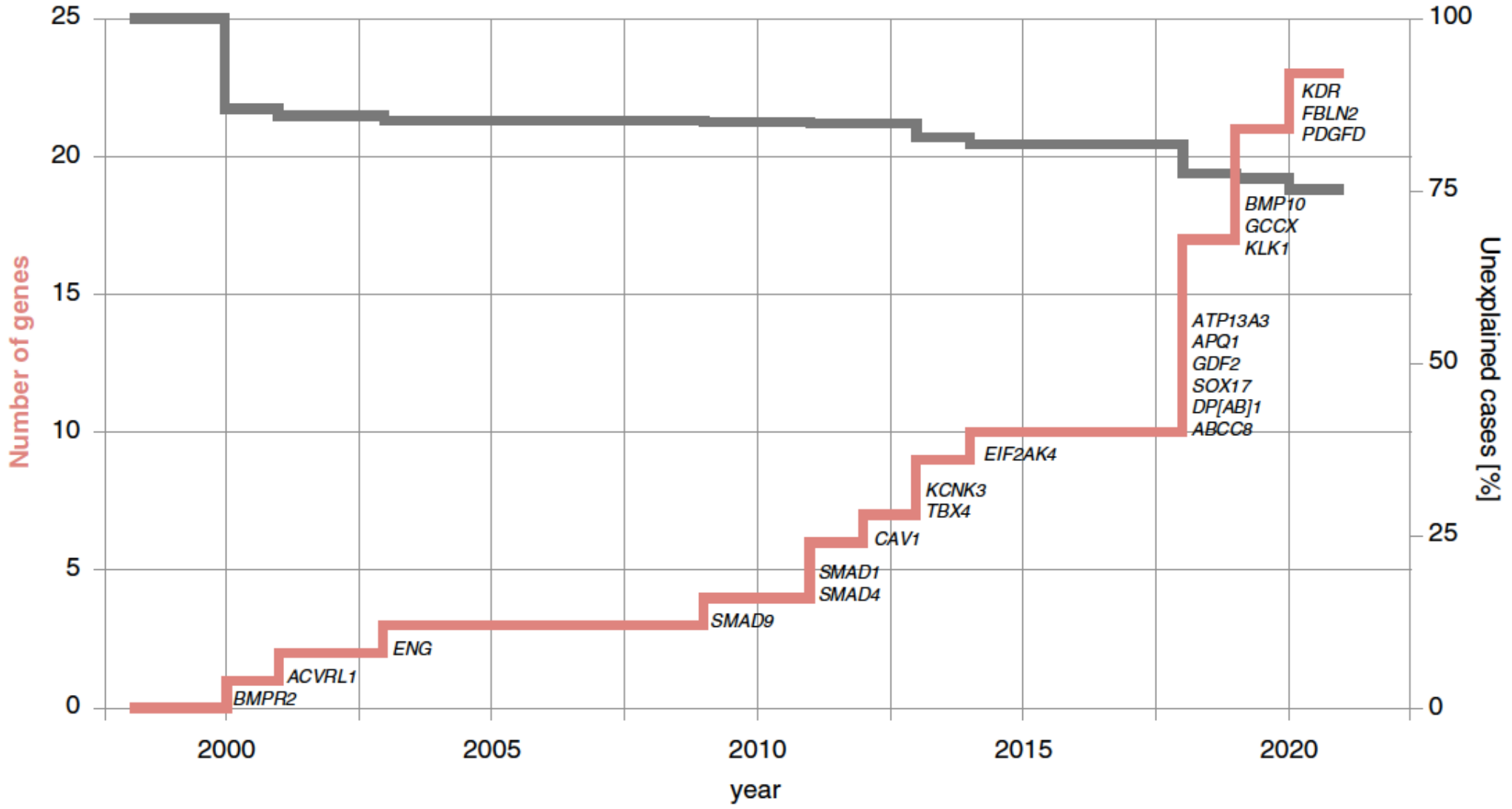


Look for errors in the most important chapters in the book

Whole genome sequencing

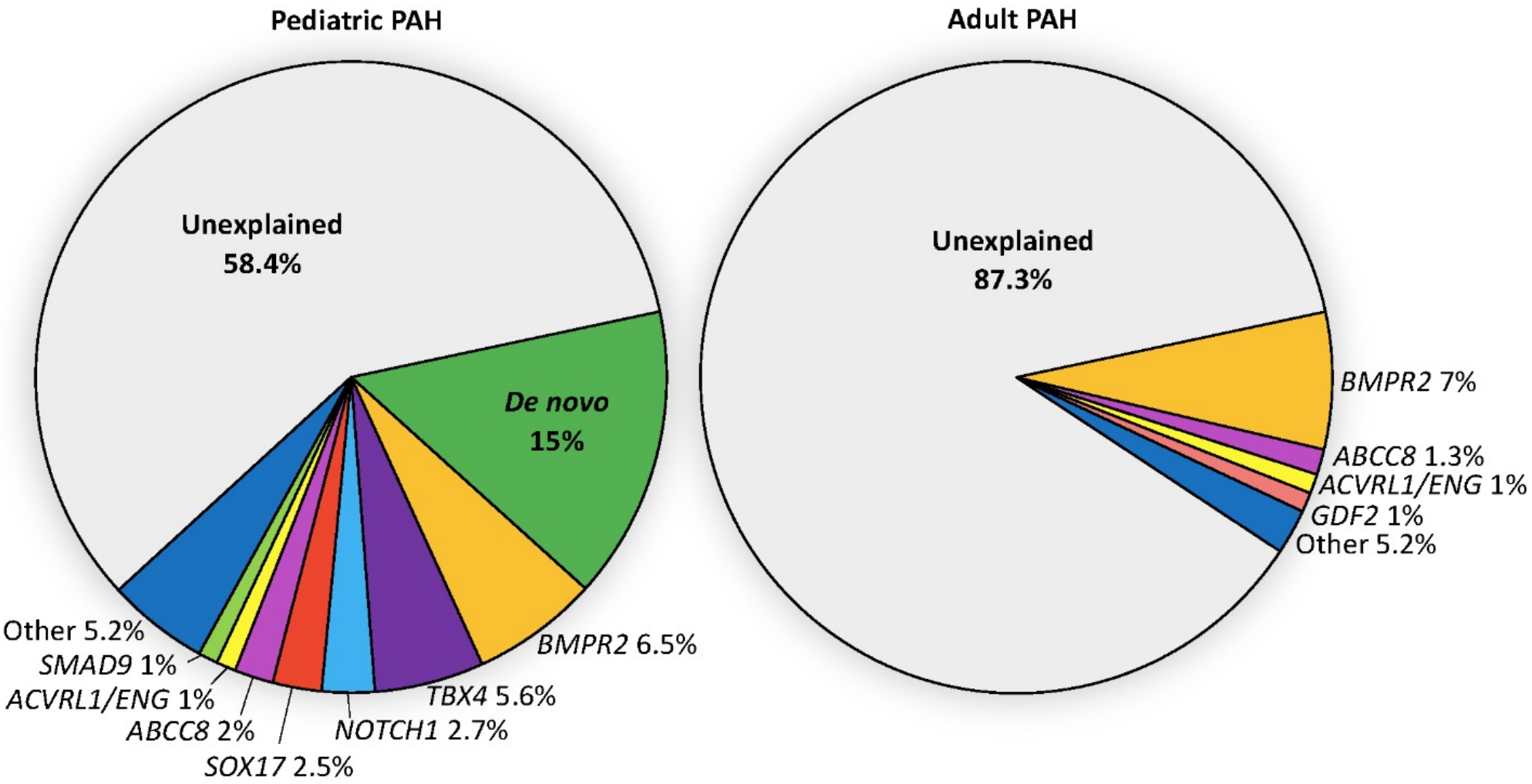
Look for errors in every single word in the book

Gene discovery in pulmonary arterial hypertension (PAH)



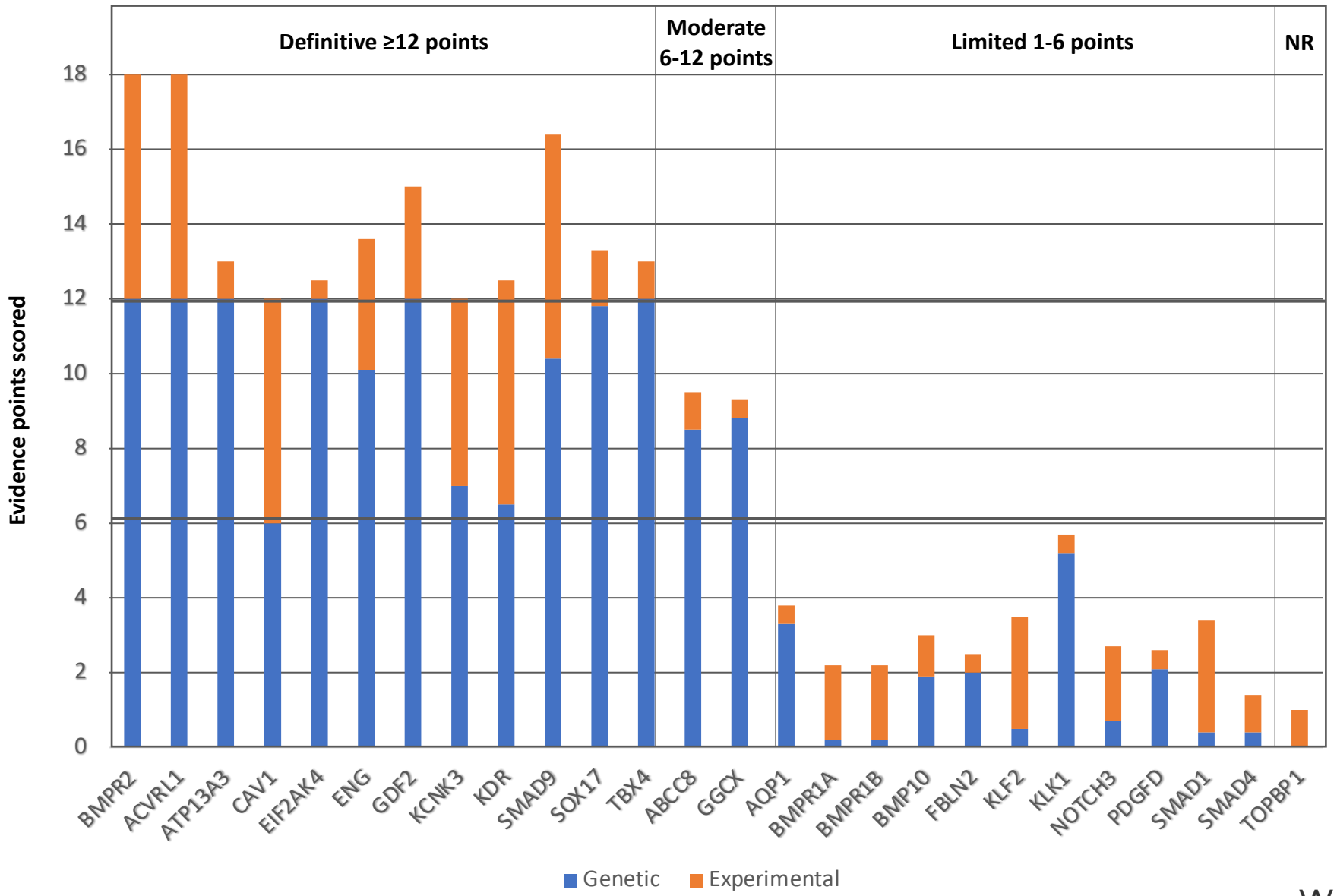
Swietlik EM, Prapa M, et al. *Genes* 2020

Likelihood of identifying a genetic cause



CL Welch & WK Chung Genes 2020

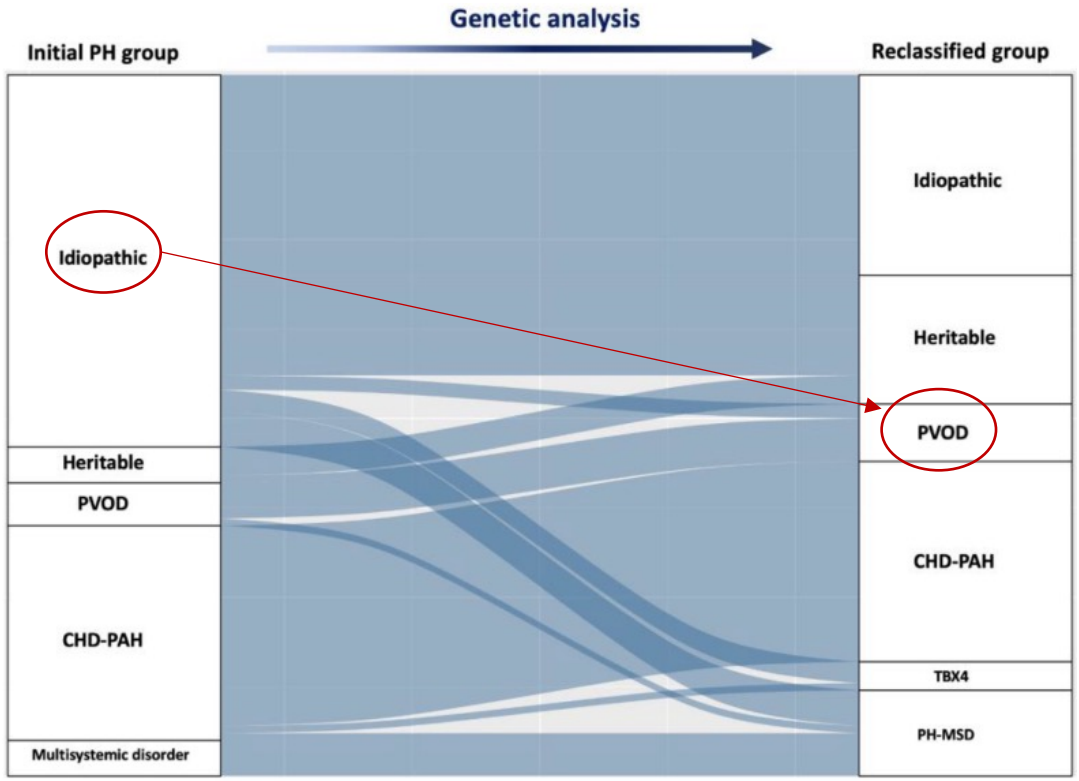
Which genes should be examined?



Welch et al. Genet Med. 2023

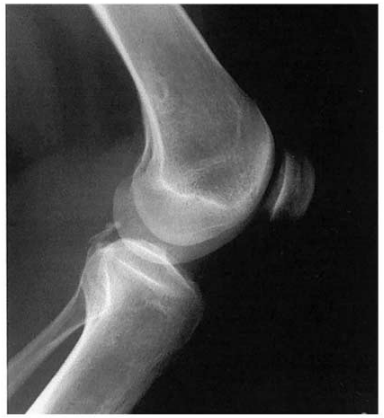
Benefits of genetic testing

PH classification

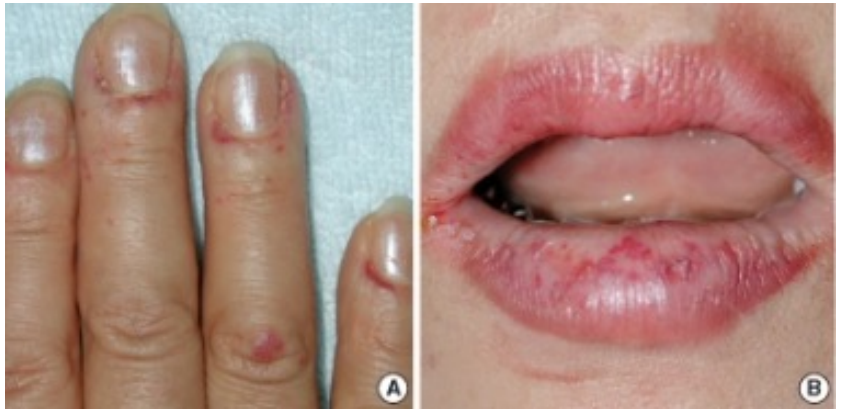


Cruz-Utrilla A et al. Int J Mol Sci. 2022

Accurate diagnosis/other features



TBX4



ACVRL1, ENG

Family screening

1 in 2 risk to next generation

1 in 3 carriers develop disease
(more likely in females)

Example of genetic test report (1)

Classification	Gene	Transcript	DNA Variant	Protein Variant	Genomic Location (hg38)	Zygosity
Pathogenic	*BMPR2*	NM_001204	c.683del	p.(Ala228ValfsTer2)	chr2:202518883	heterozygous

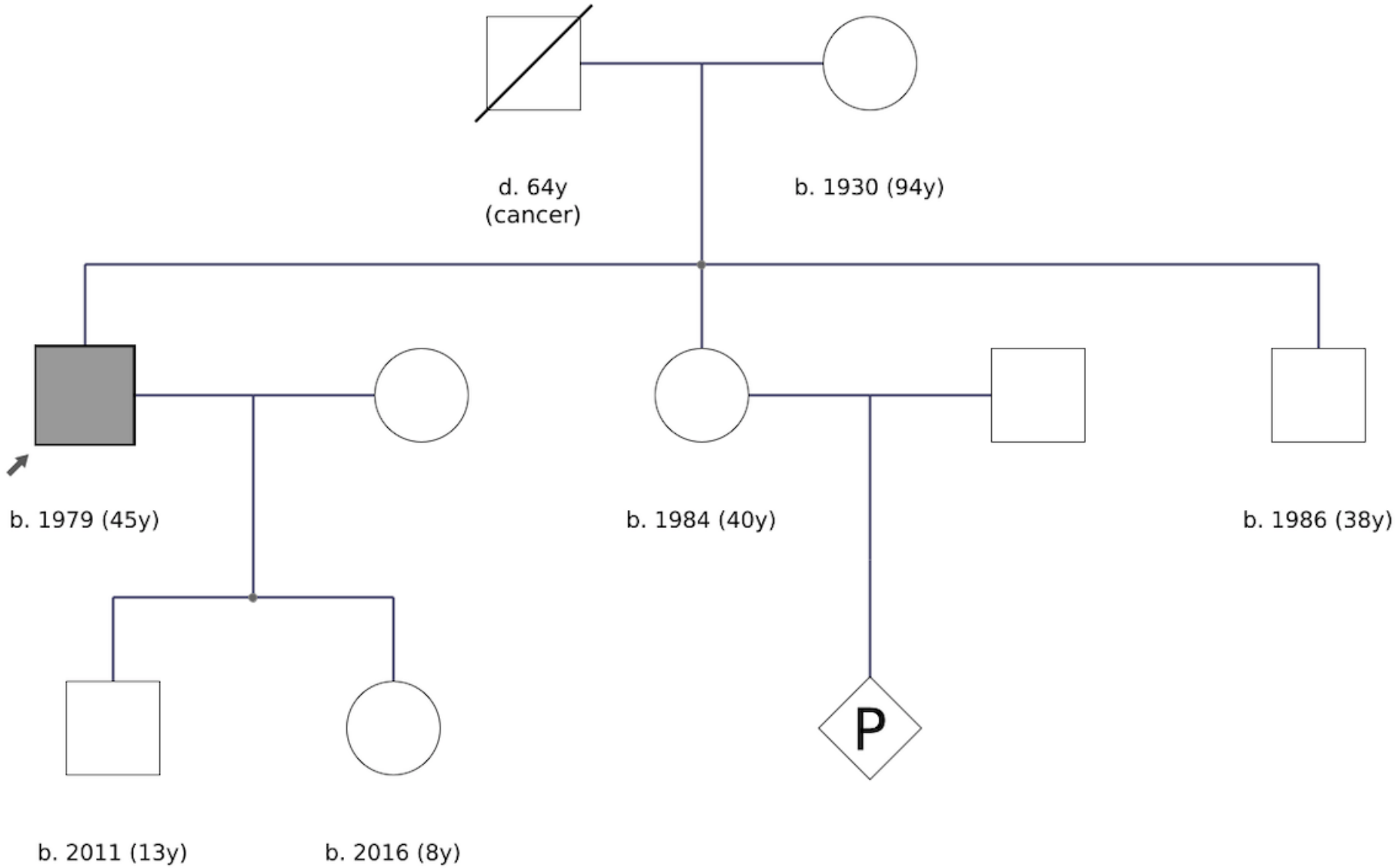
”Missing letter” in position 683

ACVRL1:NM_000020	100.00%	*BMPR2*:NM_001204	100.00%	*AQP1*:NM_198098	100.00%	*ATP13A3*:NM_024524	100.00%	*BMP10*:NM_014482	100.00%
CAV1:NM_001753	100.00%	*EIF2AK4*:NM_001013703	100.00%	*ENG*:NM_001114753	100.00%	*GDF2*:NM_016204	100.00%	*KCNK3*:NM_002246	100.00%
KDR:NM_002253.3	100.00%	*SARS2*:NM_001145901	100.00%	*SMAD9*:NM_001127217	100.00%	*SOX17*:NM_022454	100.00%	*TBX4*:NM_001321120	100.00%

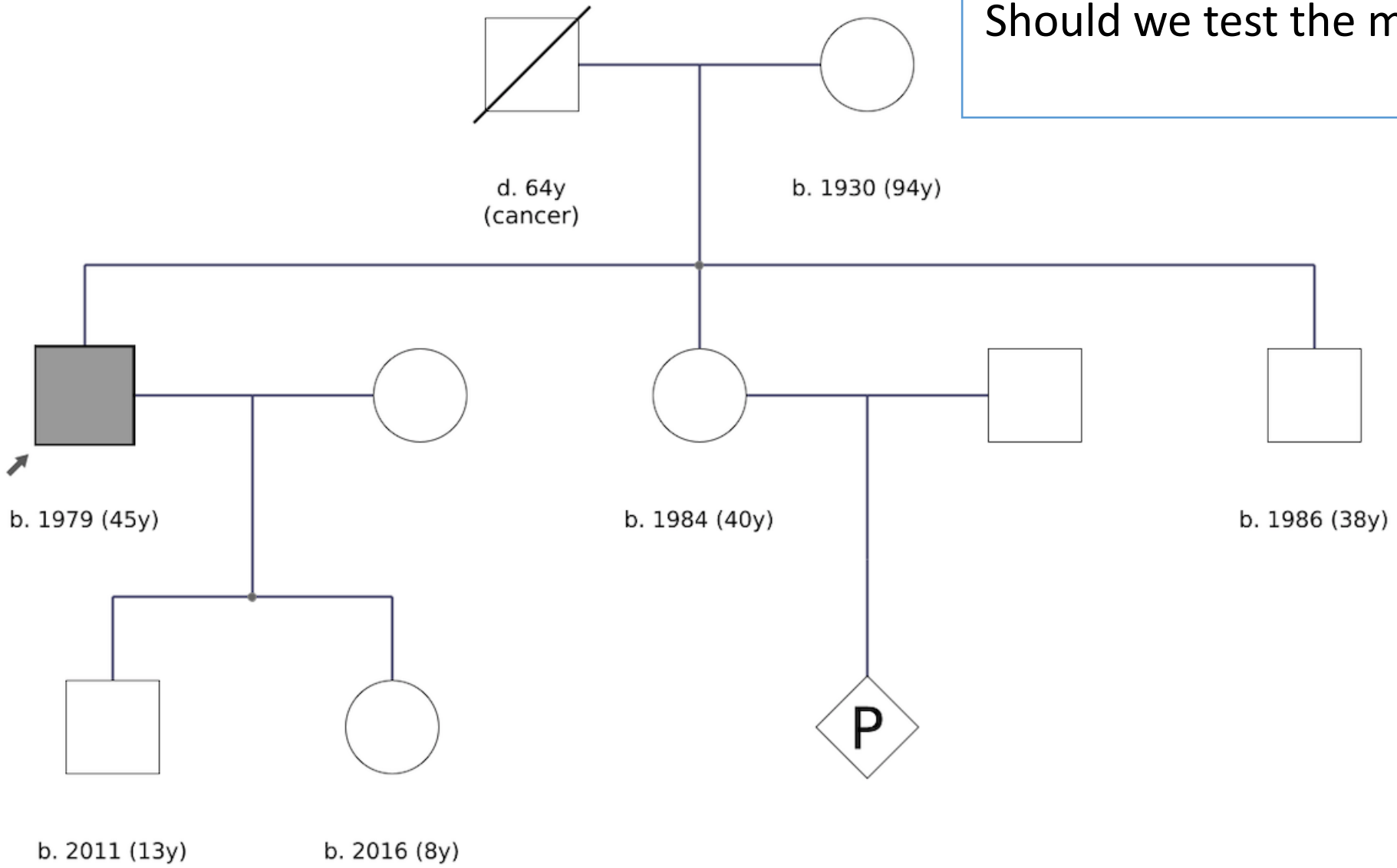
List of genes that were tested;
% means how well we could “read” them

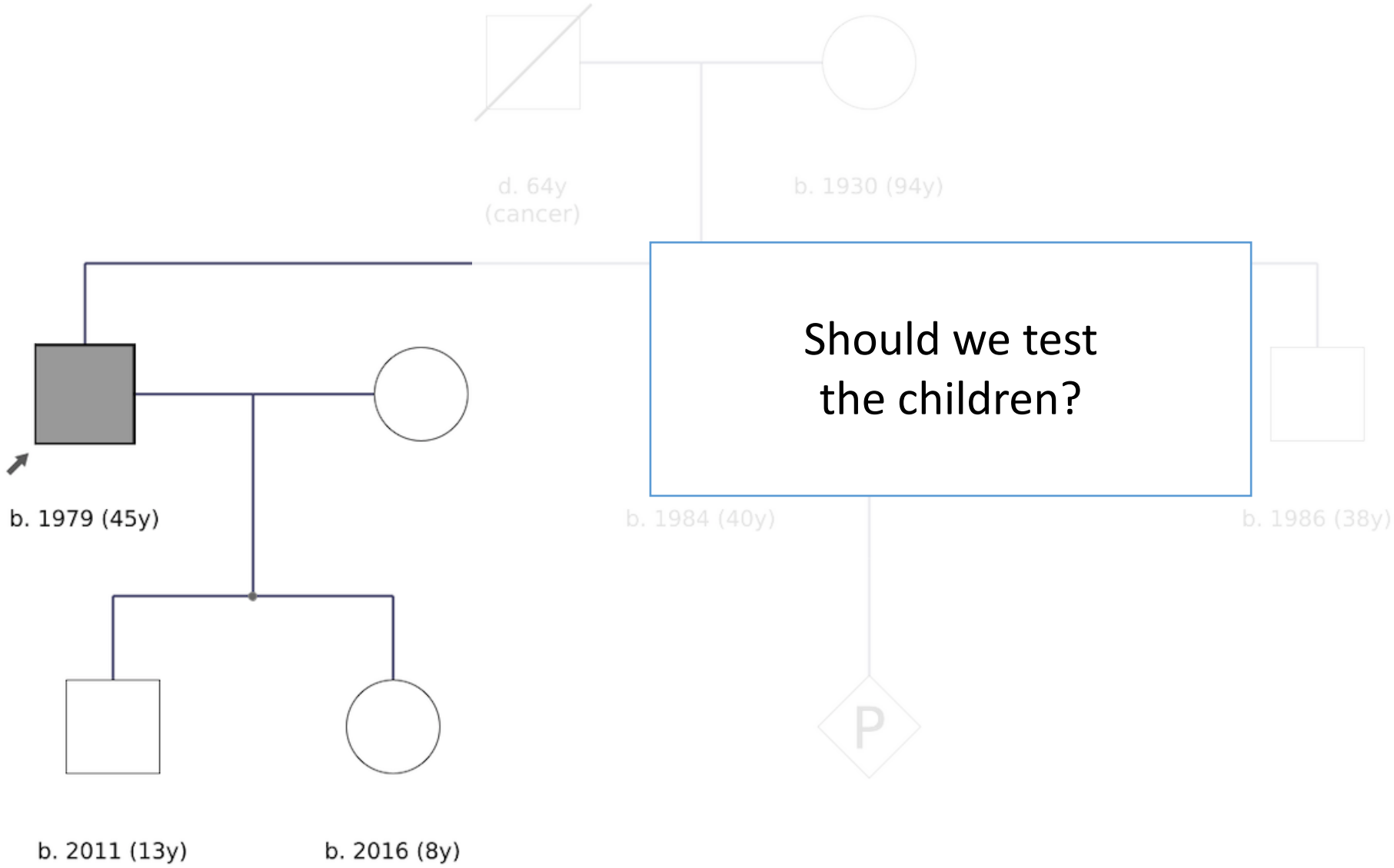
This result confirms [redacted] clinical diagnosis of PAH and has implications for other family members, who may wish to consider genetic testing.

Predictive testing of at-risk family members is available following referral to a Clinical Genetics service.


d. 64y
(cancer)
b. 1930 (94y)
b. 1979 (45y)
b. 1984 (40y)
b. 1986 (38y)
P
b. 2011 (13y)
b. 2016 (8y)

Should we test the mother?

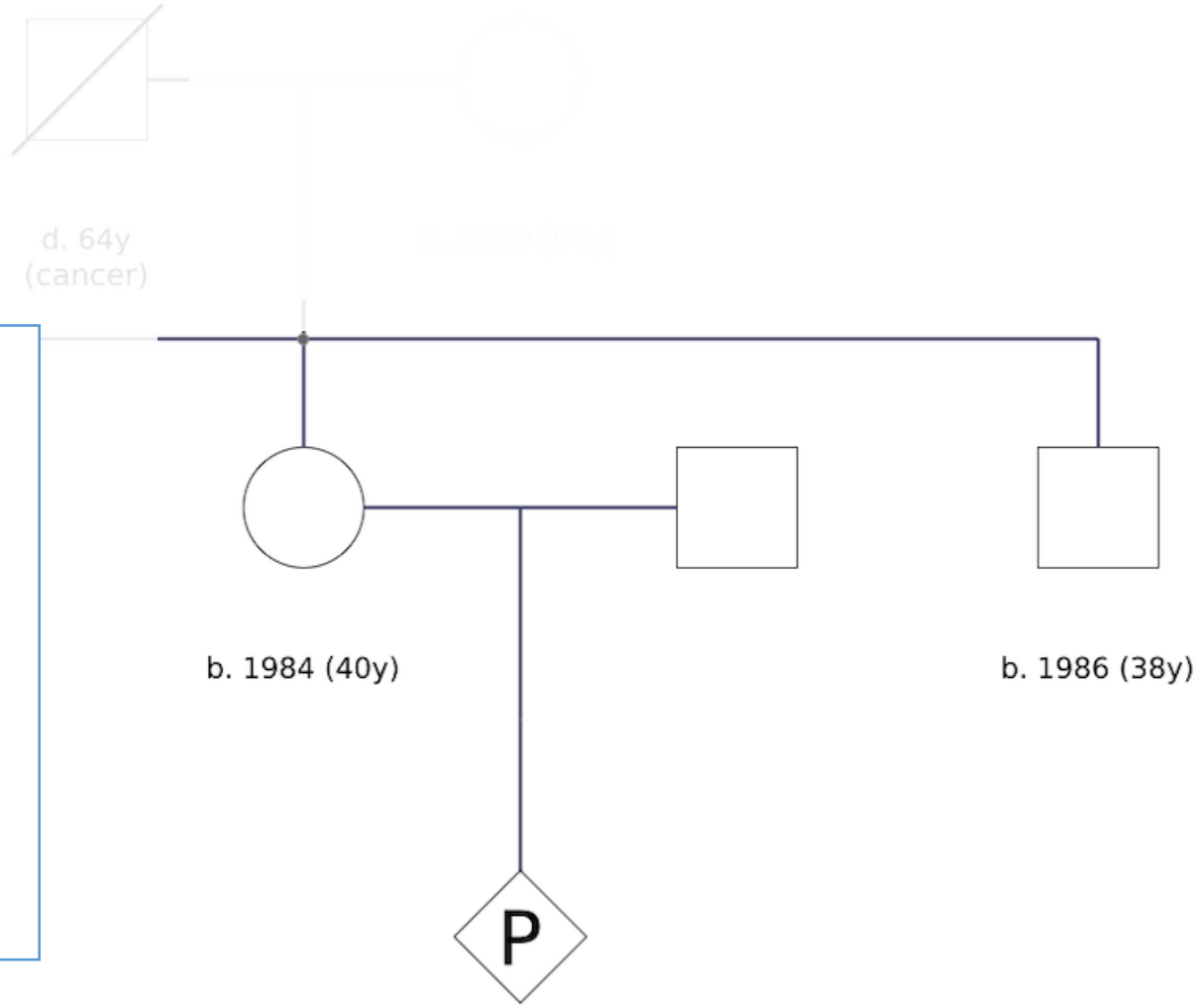




Should we test the children?

How to manage the sister's pregnancy?

Does this result inform the brother's future family planning?



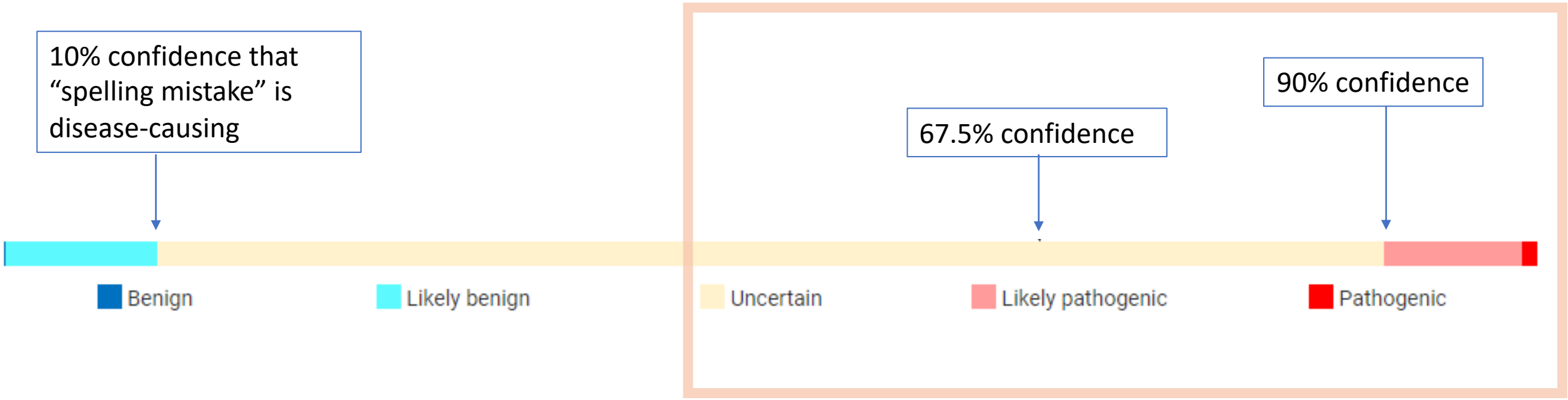
Example of genetic test report (2)

Classification	Gene	Transcript	DNA Variant	Protein Variant	Genomic Location (hg38)	Zygosity
VUS	*SMAD9*	NM_001127217	c.166G>C	p.(Glu56Gln)	chr13:36879524	heterozygous

”Spelling mistake” in position 166:
Letter G instead of C

In the absence of any further evidence the significance of this variant is uncertain and therefore we cannot confirm [redacted] PH is caused by a pathogenic variant in any of the genes analysed. If possible, segregation analysis of further affected family members is recommended; this may provide more information about the pathogenicity of this variant. Predictive testing of unaffected family members is currently not appropriate. Referral of these individuals to a Clinical Genetics service should be considered.

Variant classification



Examples of used evidence:
Has this gene alteration been seen before in affected/unaffected individuals?
Do computational models predict a damaging effect to the function of the gene?

Any questions?