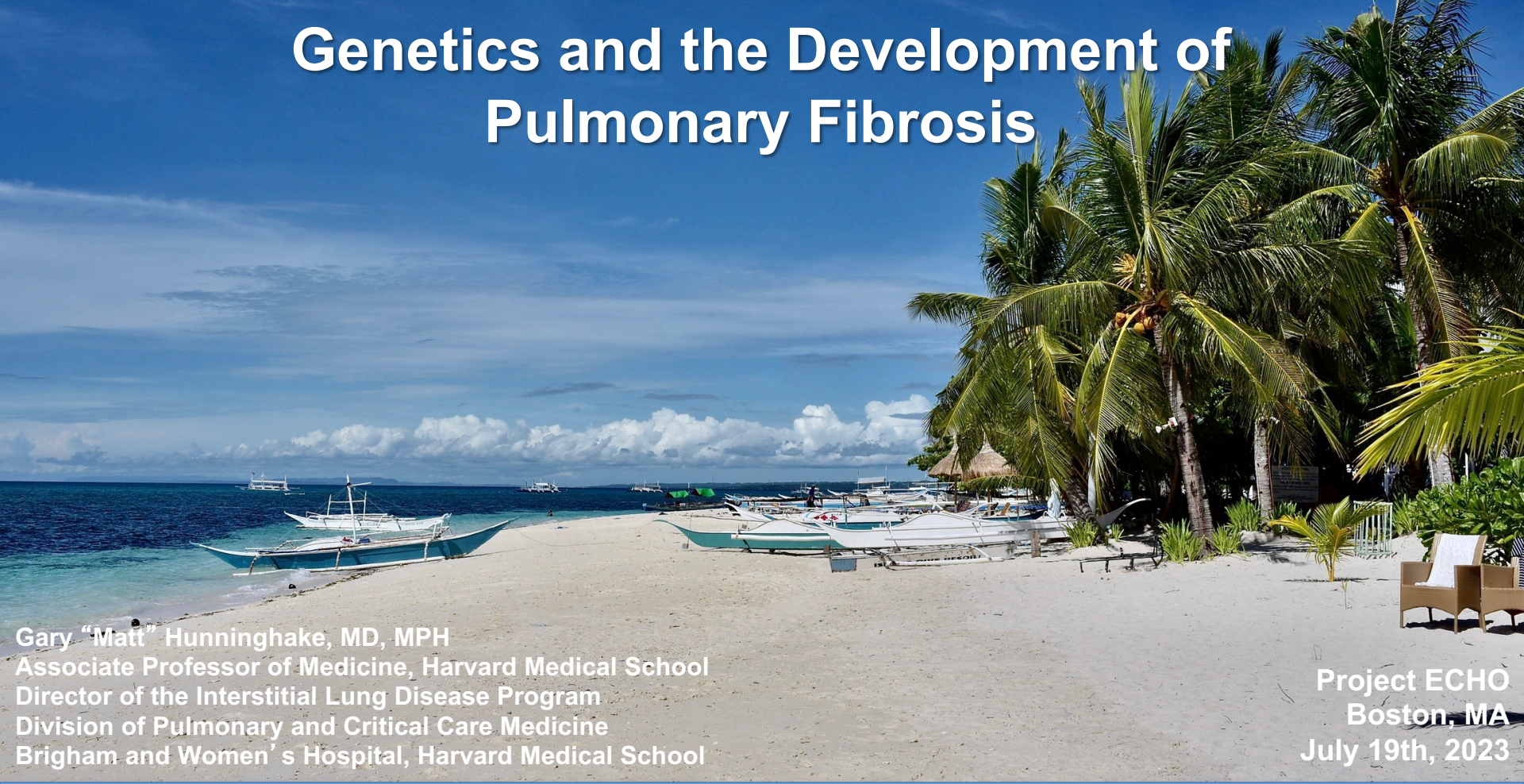
Genetics and the Development of Pulmonary Fibrosis



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Division of Pulmonary and Critical Care Medicine
Brigham and Women's Hospital, Harvard Medical School

Project ECHO
Boston, MA
July 19th, 2023

Disclosures

- **Relevant financial relationships with a commercial interest:**

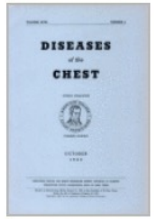
  I have performed consulting work for Boehringer-Ingelheim and the Gerson Lehrman Group.

Pulmonary Fibrosis in Families

ELSEVIER

Diseases of the Chest

Volume 18, Issue 4, October 1950, Pages 330-344



Idiopathic Pulmonary Fibrosis; Its Occurrence in Identical Twin Sisters

J. WINTHROP PEABODY M.D., F.C.C.P. [a], J. WINTHROP PEABODY JR. M.D. [a],
E.W. HAYES M.D., F.C.C.P. [b], E.W. HAYES JR. M.D. [b]

Dis. Chest. 1950; 18: 330–344.

IPF is a heritable disease

- Heritability of IPF – estimated 32%
  (based on common and rare variants)

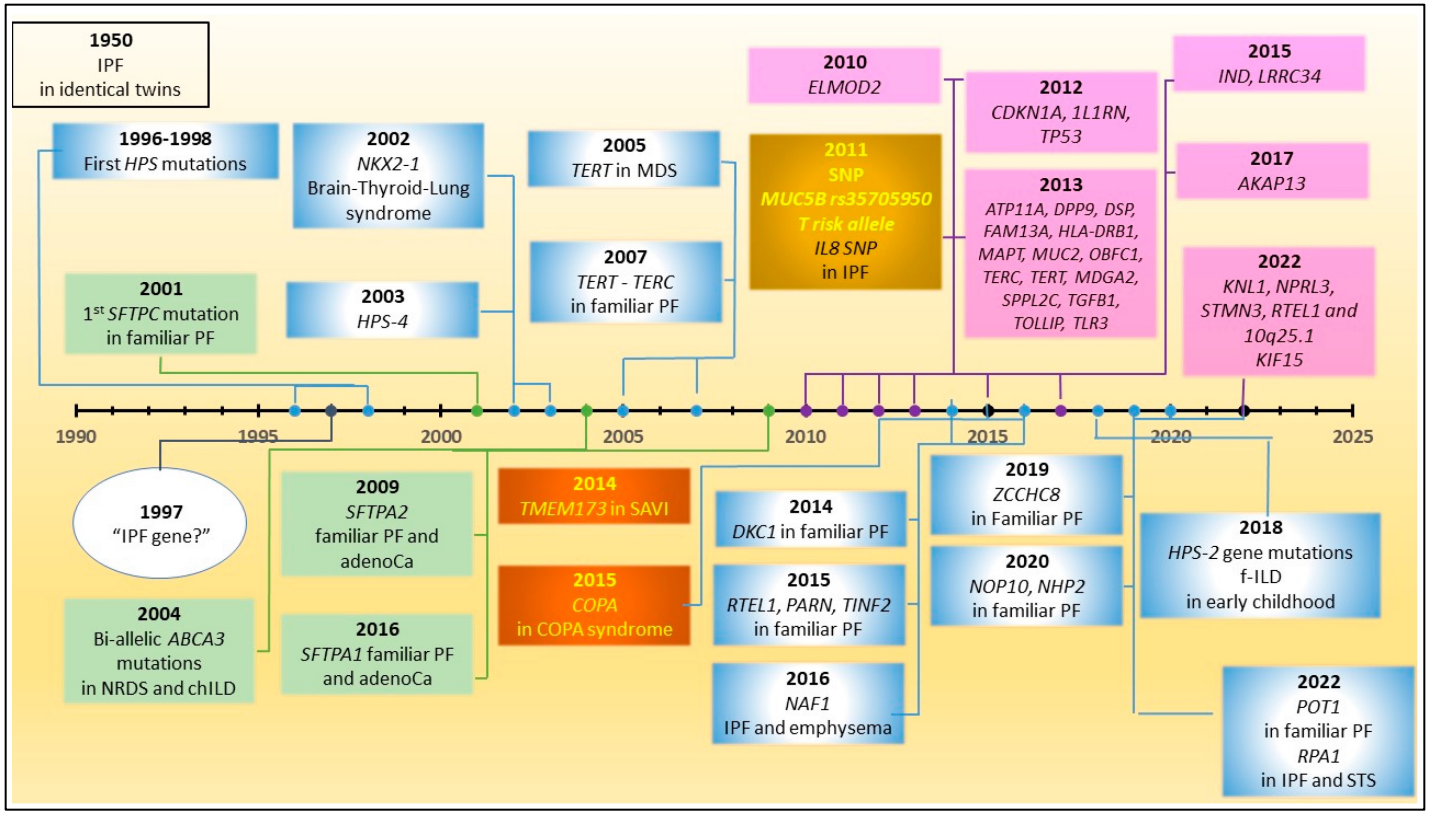
Am J Respir Crit Care Med. 2023; 207(9): 1194–1202.

Familial Pulmonary Fibrosis

- Estimates of genetic risk in families
  - Rare variants explain ~15-23% of risk
  - Estimates from whole genome sequencing in 569 FPF kindreds

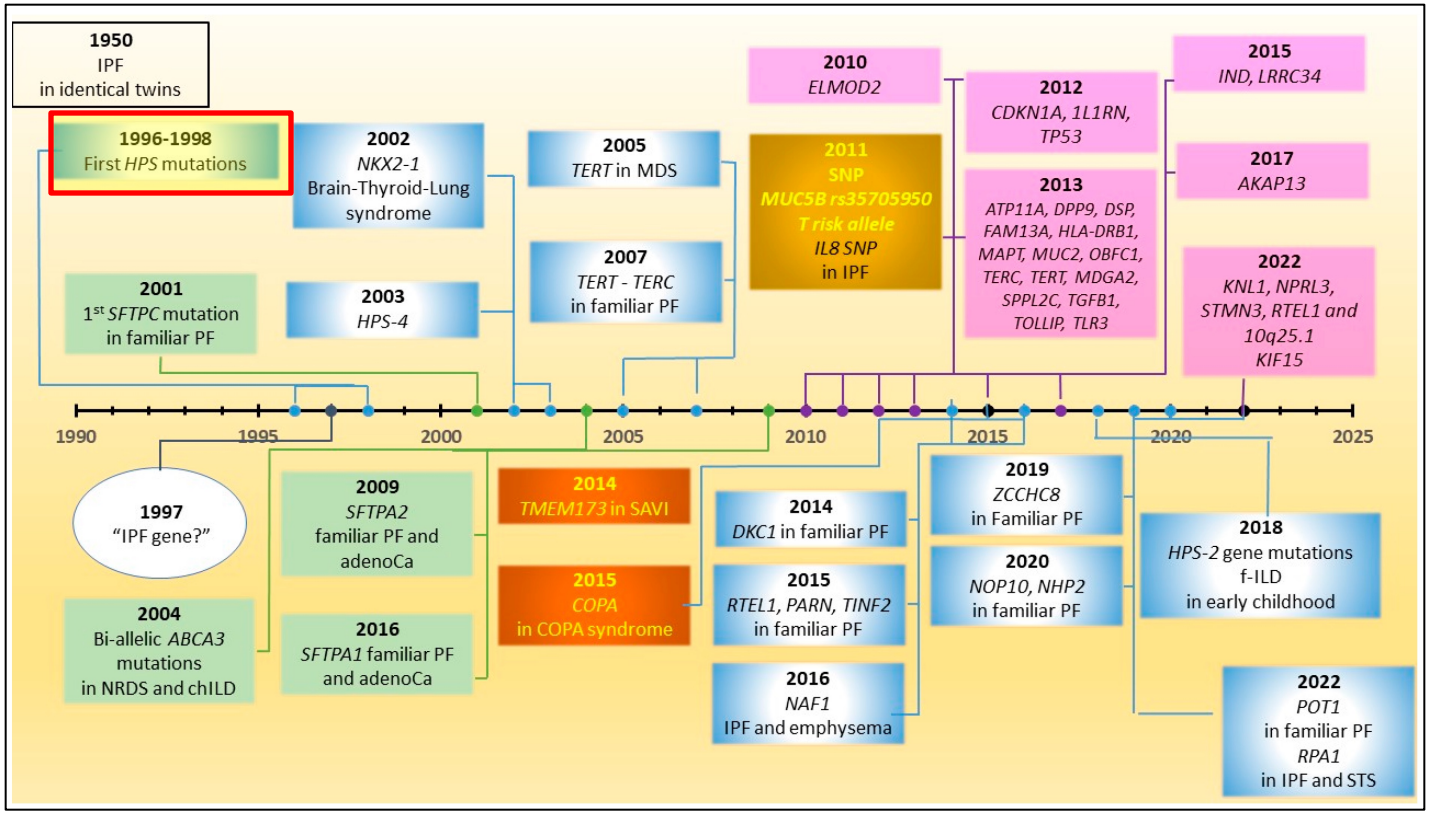
Am J Respir Crit Care Med. 2023; 207(10): 1345–1357.

Pulmonary Fibrosis in Families



Diagnostics **2022**, *12*(12), 2928.

Pulmonary Fibrosis in Families



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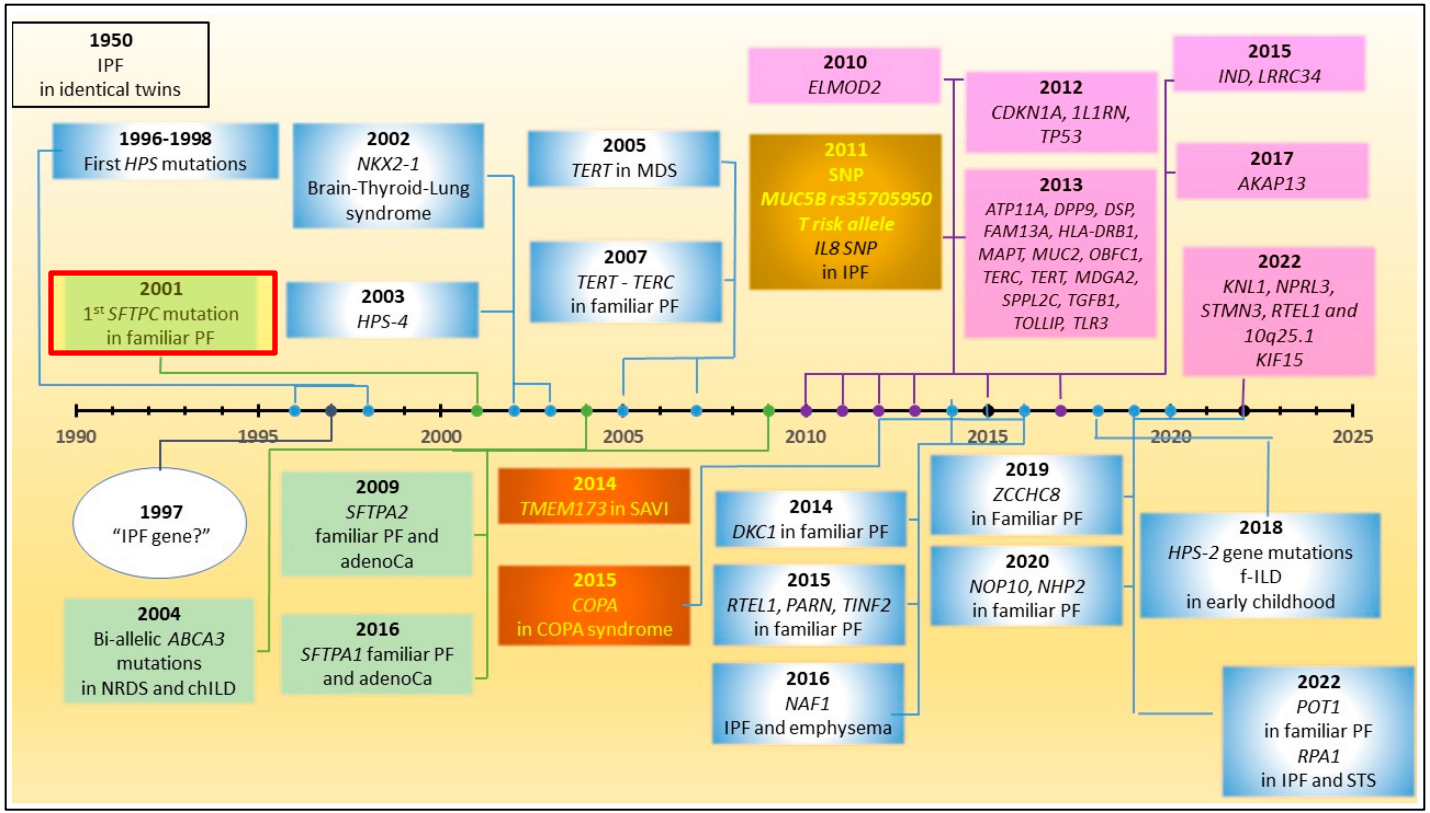

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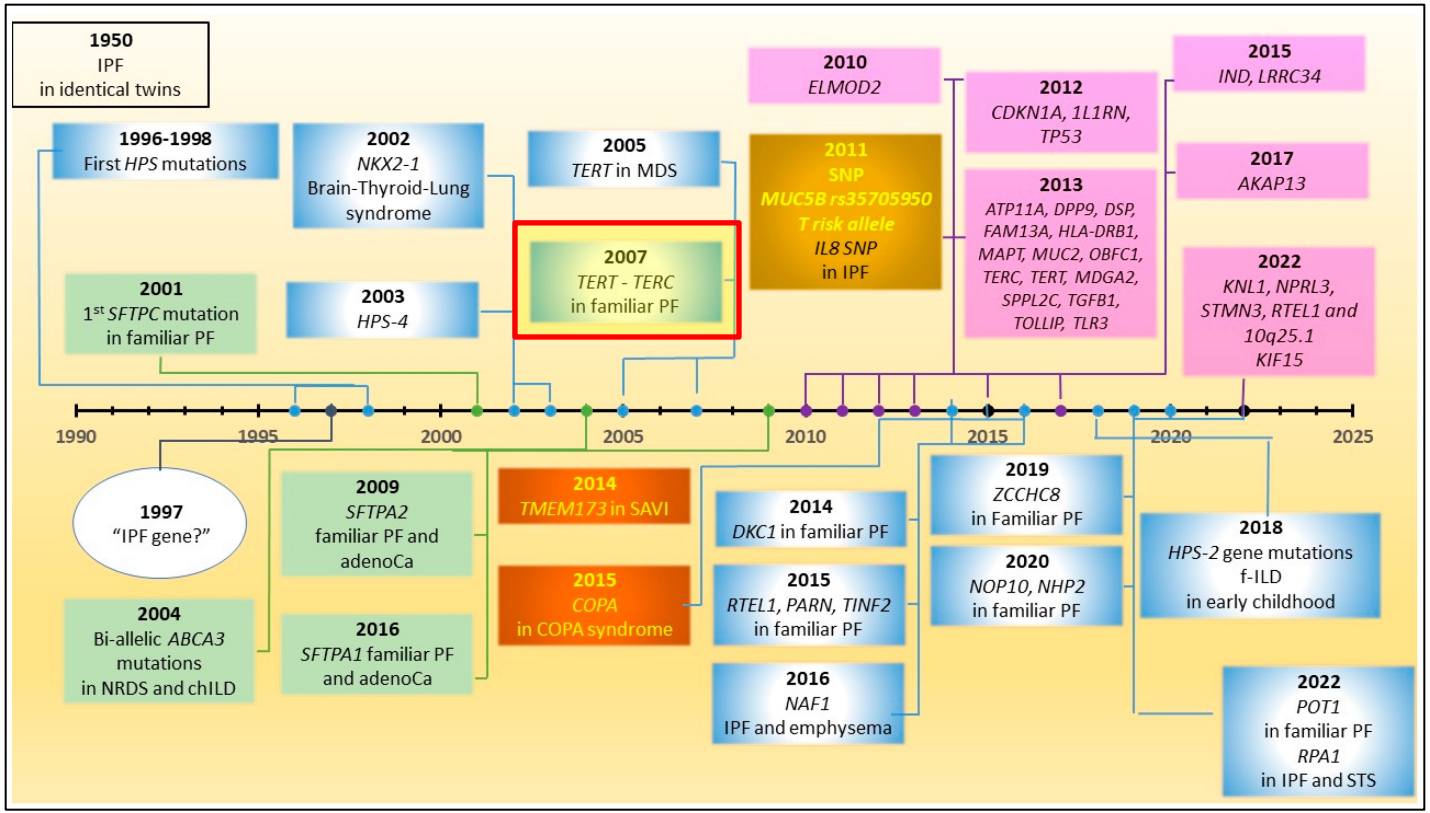
Pulmonary Fibrosis in Families



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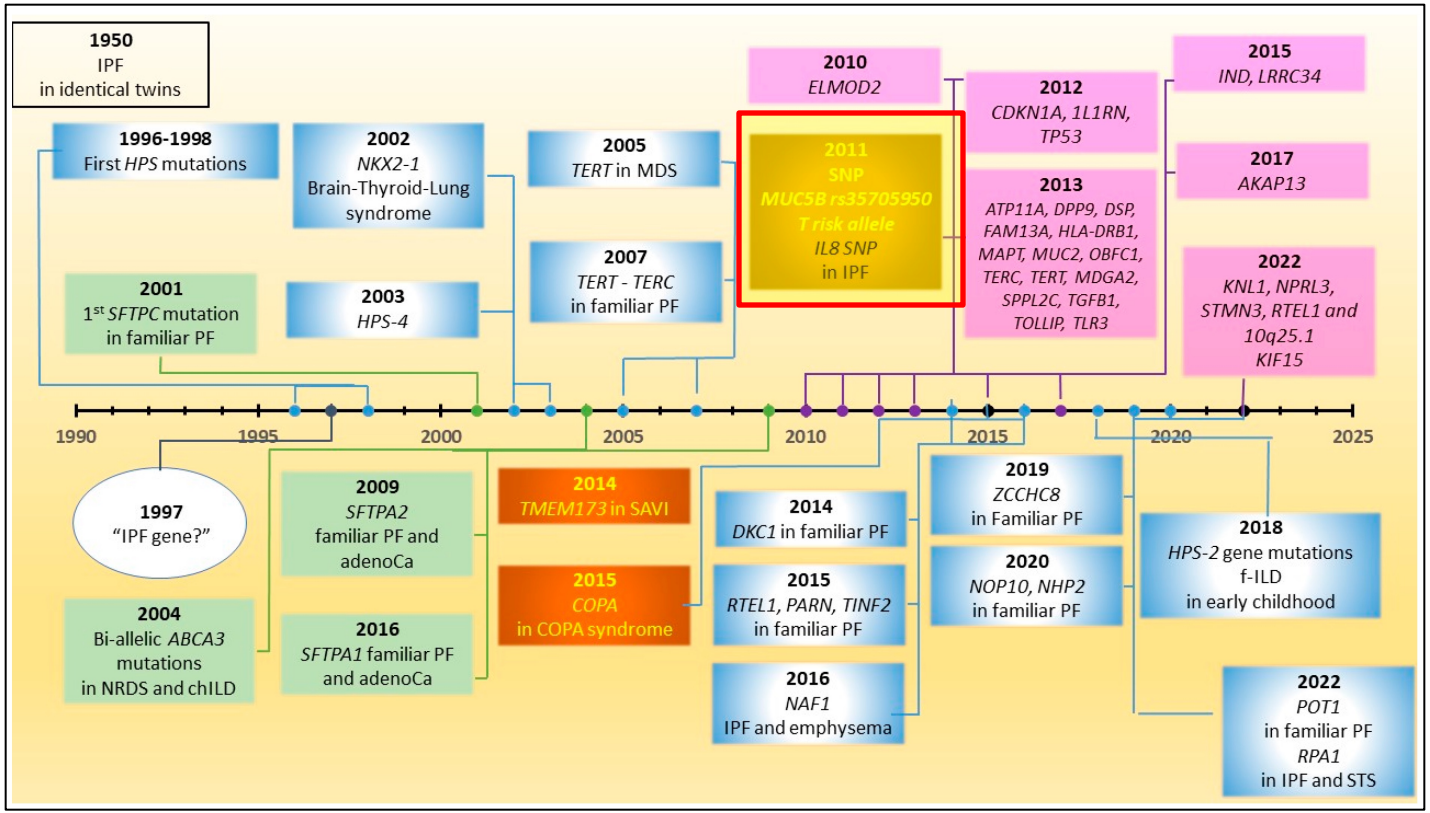

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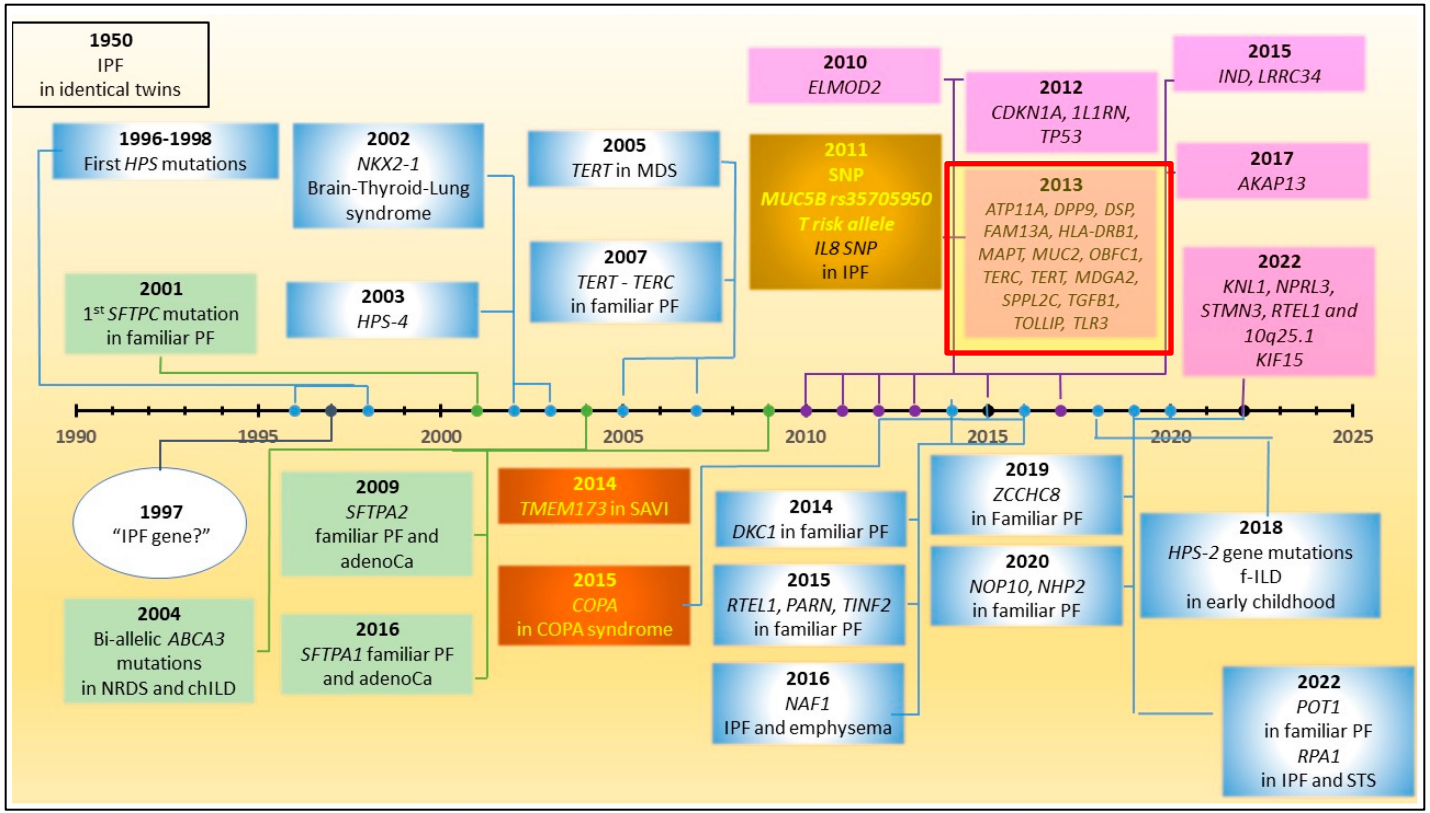
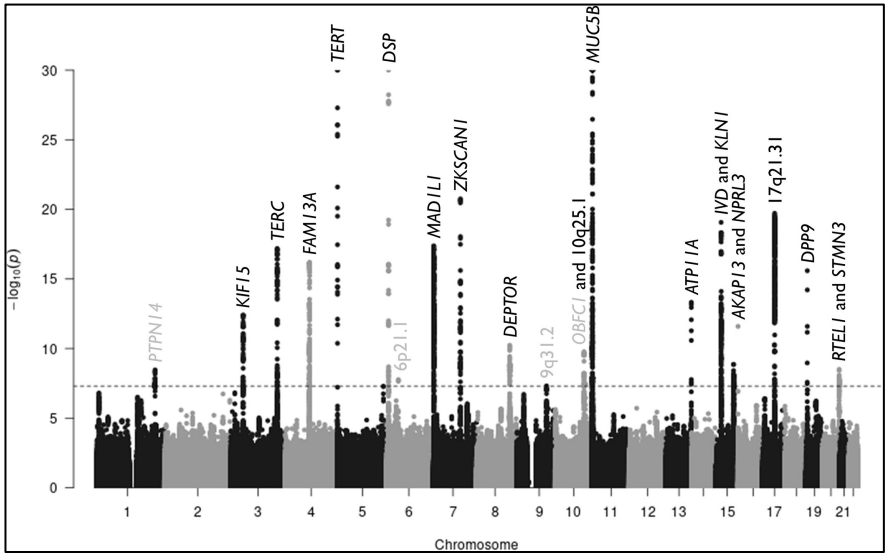
Pulmonary Fibrosis in Families



Diagnostics **2022**, *12*(12), 2928.

Genetics of IPF

- Common genetic variation explains a substantial portion of the disease
  - ~23-25 common variants associated with IPF
  - Some debate (estimates from 8-18% in the general population)



Thorax. 2022; 77(8):829-33.

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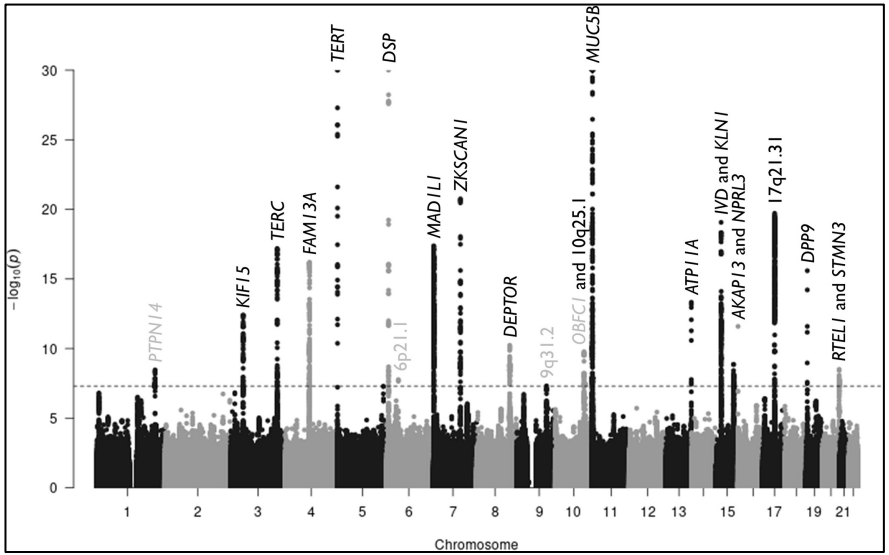
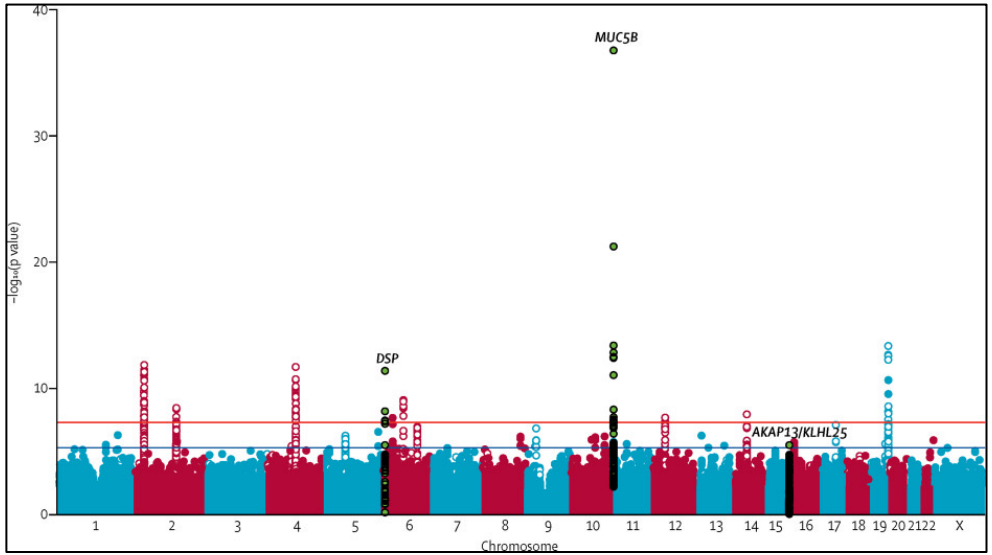




Thorax. 2022; 77(8):829-33.
Lancet Respir Med. 2017; 5(11): 869-880.

Genetics of IPF

Common variants associated with IPF	**Gene Function**	**Gene**	**Risk Allele(s)**
	Airway mucin production	*MUC5B*	rs35705950
		MUC2	rs7934606
	Cell-cell adhesion	*DSP*	rs2076295
		DPP9	rs12610495
	Toll-like receptor signaling	*TOLLIP*	rs111521887, rs5743894 rs2743890
		TLR3	rs3775291 (L412F)
		ATP11A	rs1278769
	Cytokine/growth factor signaling	*IL1RN*	VNTR*2 haplotype block
		IL8	rs4073, rs2227307
		IL4	rs2243250
		TGFB1	rs1800470
	Telomere maintenance	*TERT*	rs2736100
		OBFC1	rs11191865
	Cell cycle regulation	*KIF15*	rs78238620
		MAD1L1	rs12699415
		CDKN1A	rs2395655
		TP53	rs12951053, rs12602273

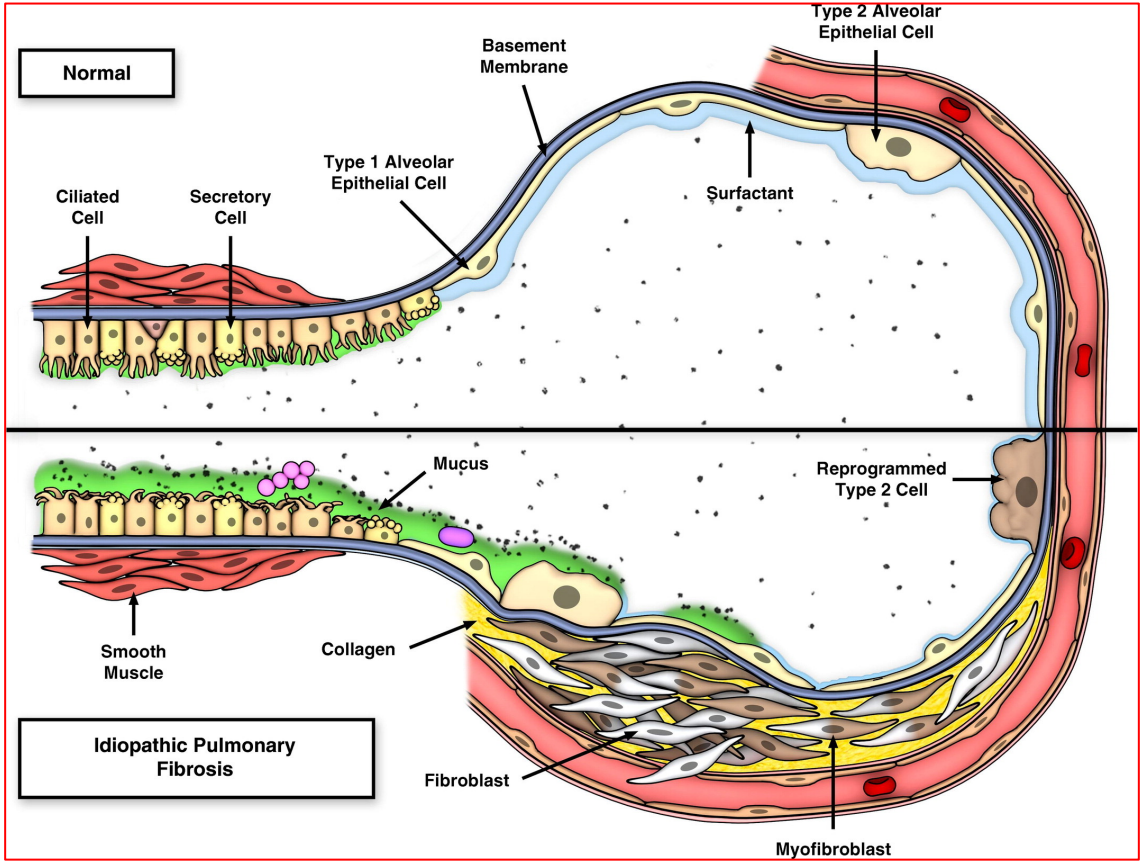
J Inflamm Res. 2020; 13: 1305-1318.

Genetics of IPF

Rare variants associated with IPF	**Gene Function**	**Gene**	**Mutation(s)**
	Surfactant production/secretion	*SFTPA1*	T622C, W211R
		SFTPA2	G231V, F198S
		SFTPC	I73T, M71V, multiple others
		ABCA3	S1261G, R288K
	Telomere maintenance	*TERT*	L55Q, R901W, T1110M, multiple others
		TERC	98G>A, 37A>G, multiple others
		TINF2	K280E, R282H, R282S
		DKC1	T405A, multiple others
		RTEL1	R213W, T49M, F964L
		PARN	A383V, multiple others

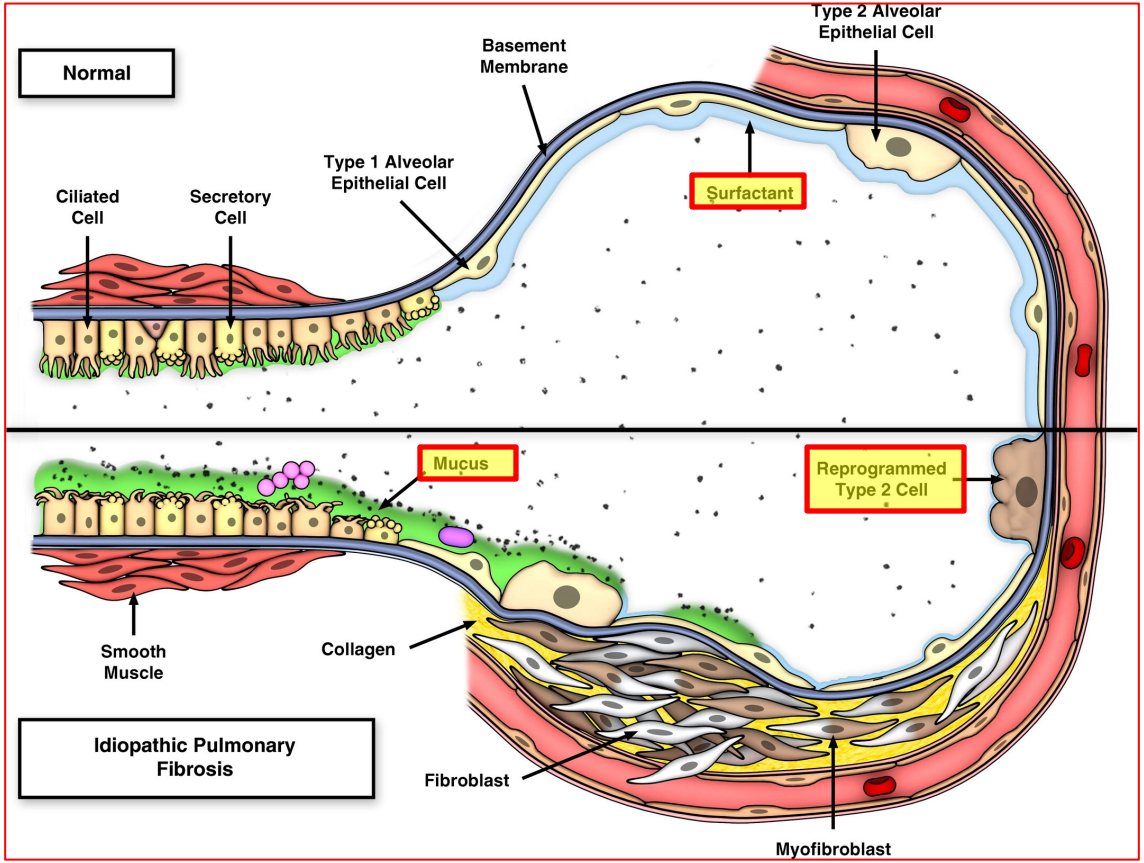
J Inflamm Res. 2020; 13: 1305-1318.

Genetics of IPF



AnnalsATS. 2018; 15(3): s192-s197

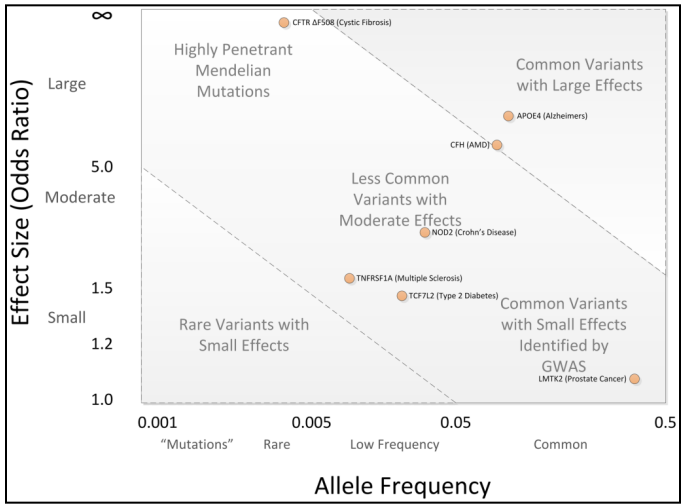
Genetics of IPF



AnnalsATS. 2018; 15(3): s192-s197

Genetics of IPF

- Common genetic variation may explain a substantial portion of the disease
  - *MUC5B* promoter variant (rs35705950)
  - The minor allele of rs35705950 is present in ~20% of European CEPH [Centre d'etude du polymorphisme humain] trios in HapMap.
  - resulted in a substantial increase in the odds for disease (the minor allele of rs35705950 confirmed a >6-fold increase in the odds for sporadic IPF).



PLoS Comput Biol. 2012; 8(12):e1002822.
N Engl J Med. 2011; 364(16): 1503-12.
AJRCCM. 2014; 189(7): 770-8.

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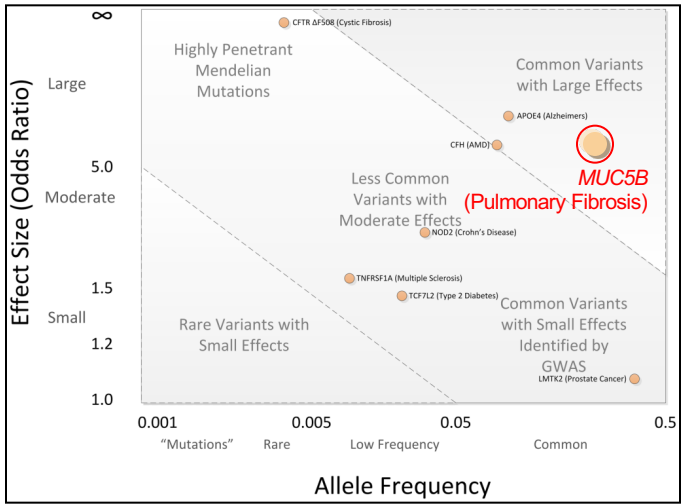

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Genetics of Pulmonary Fibrosis

- Substantial overlap in the genetic variants predicting both sporadic and familial pulmonary fibrosis (including the *MUC5B* risk allele).

Am J Respir Crit Care Med. 2023; 207(9): 1194–1202.

Genetics of Pulmonary Fibrosis

- Substantial overlap in the genetic variants predicting both sporadic and familial pulmonary fibrosis (including the *MUC5B* risk allele).
- Substantial overlap in the genetic variants predicting IPF and fibrotic hypersensitivity pneumonitis (including the *MUC5B* risk allele).

Am J Respir Crit Care Med. 2023; 207(9): 1194–1202.
Thorax. 2022; 77(5): 508-510.

Genetics of Pulmonary Fibrosis

- Substantial overlap in the genetic variants predicting both sporadic and familial pulmonary fibrosis (including the *MUC5B* risk allele).
- Substantial overlap in the genetic variants predicting IPF and fibrotic hypersensitivity pneumonitis (including the *MUC5B* risk allele).
- The *MUC5B* risk allele is associated with rheumatoid arthritis associated interstitial lung disease.

Am J Respir Crit Care Med. 2023; 207(9): 1194–1202.
Thorax. 2022; 77(5): 508-510.
NEJM. 2018; 379(23): 2209-2219.

What are interstitial lung abnormalities (ILA)?

- Sets of chest CT imaging features suggestive of an underlying interstitial lung disease in a person without a clinical diagnosis.

Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society

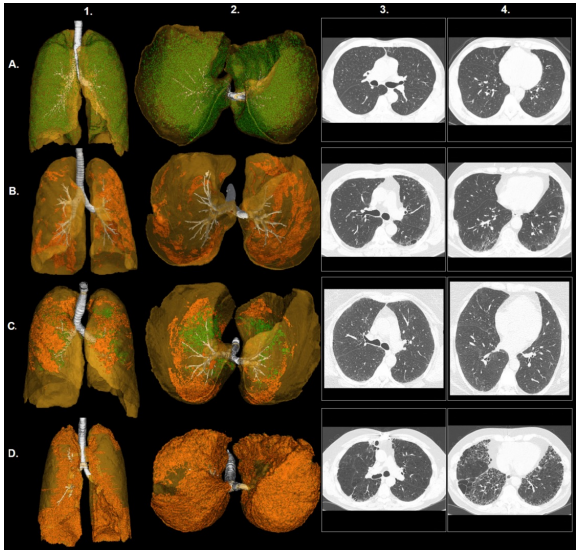
Hiroto Hatabu*, Gary M Hunninghake, Luca Richeldi, Kevin K Brown, Athol U Wells, Martine Remy-Jardin, Johny Verschakelen, Andrew G Nicholson, Mary B Beasley, David C Christiani, Raúl San José Estépar, Joon Beom Seo, Takeshi Johkoh, Nicola Sverzellati, Christopher J Ryerson, R Graham Barr, Jin Mo Goo, John H M Austin, Charles A Powell, Kyung Soo Lee, Yoshikazu Inoue, David A Lynch†

Lancet Respir Med 2020; 8: 726–37

*Chair and †co-chair of the Fleischner Society Writing Committee for Position Paper on interstitial lung abnormalities

Department of Radiology (Prof H Hatabu MD, R San José Estépar PhD), and Department of Pulmonary and Critical Care Medicine (G M Hunninghake MD), Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; Unità Operativa Complessa di

The term interstitial lung abnormalities refers to specific CT findings that are potentially compatible with interstitial lung disease in patients without clinical suspicion of the disease. Interstitial lung abnormalities are increasingly recognised as a common feature on CT of the lung in older individuals, occurring in 4–9% of smokers and 2–7% of non-smokers. Identification of interstitial lung abnormalities will increase with implementation of lung cancer screening, along with increased use of CT for other diagnostic purposes. These abnormalities are associated with radiological progression, increased mortality, and the risk of complications from medical interventions, such as chemotherapy and surgery. Management requires distinguishing interstitial lung abnormalities that represent clinically significant interstitial lung disease from those that are subclinical. In particular, it is important to identify the subpleural fibrotic subtype, which is more likely to progress and to be associated with mortality. This multidisciplinary Position Paper by the Fleischner Society addresses important issues regarding interstitial lung abnormalities, including standardisation of the definition and terminology; predisposing risk factors; clinical outcomes; options for initial evaluation, monitoring, and management; the role of quantitative evaluation; and future research needs.



Lancet Respir Med 2020; 8(7): 726-37.
N Engl J Med. 2011; 364(10): 897-906.

Genetics of ILA

Research participants with ILA in the general population are more likely to have >1 copy of the minor allele of *MUC5B* promoter genotype (rs35705950)

	Number of Participants	Logistic Regression			
		Baseline		Adjusted	
ILA Definition		Odds Ratio, 95% CI	P - value	Odds Ratio, 95% CI	P - value
ILA	(177 cases vs. 1370 controls)	2.3 (1.6-3.1)	<0.001	2.8 (2.0-3.9)	<0.001
Definite Fibrosis	(47 cases vs. 1370 controls)	3.0 (1.8-5.0)	<0.001	6.3 (3.1-12.7)	<0.001

N Engl J Med. 2013; 368(23):2192-200.

Genetics and ILA

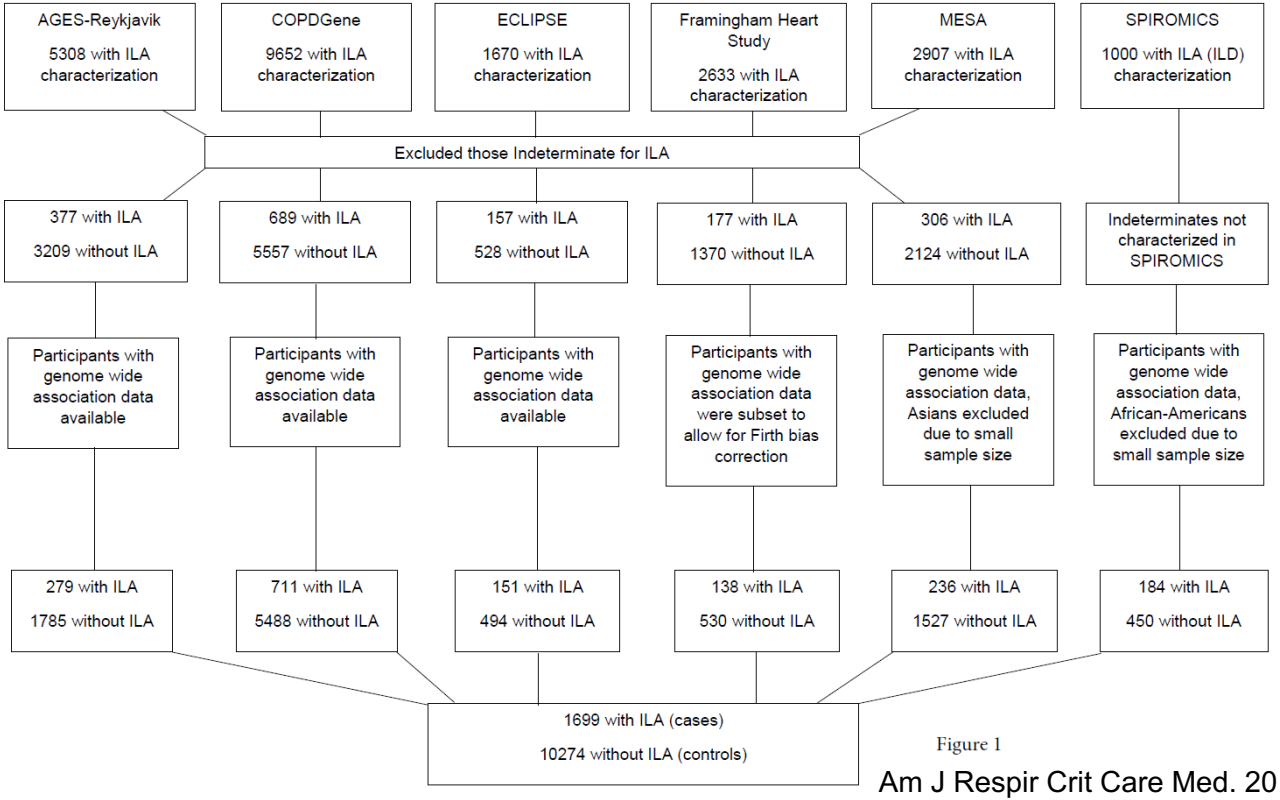


Figure 1

Brian Hobbs

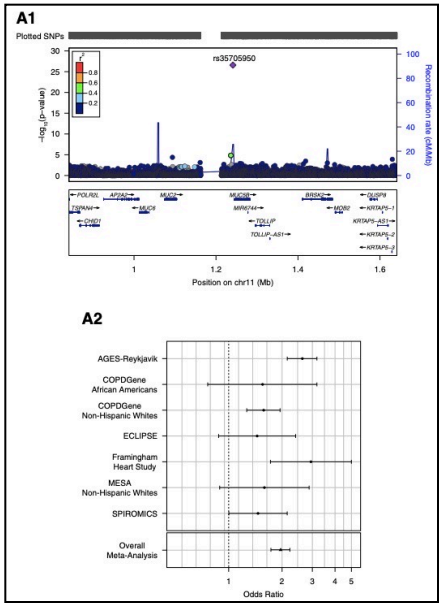
Rachel Putman

Am J Respir Crit Care Med. 2019; 200(11): 1402-1413.

Genetics and ILA

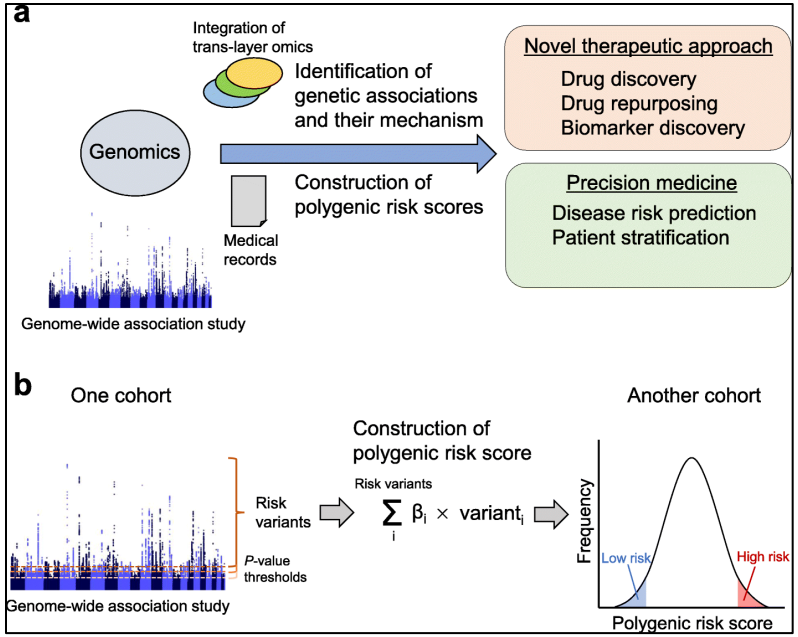
- GWA study suggests there is a substantial genetic overlap between ILA and IPF there are also important differences.

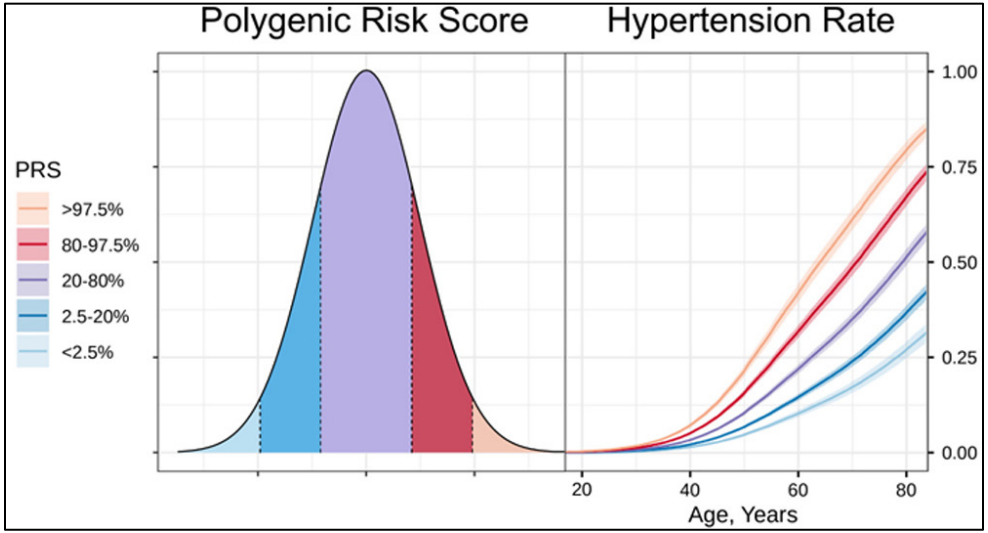
Chromosome/ Location	rs number	Nearest Gene	Studies	IPF Odds Ratio (95% CI)	ILA vs No ILA		Subpleural ILA vs No ILA	
					Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
4q22.1	rs2609255	FAM13A	Fingerlin, NG, 2013	1.4 (1.3, 1.6)	1.18 (1.07, 1.3)	0.0005	1.2 (1.1, 1.4)	$3x10^{-4}$
6p24.3	rs2076295	DSP	Fingerlin, NG, 2013 Allen, LRM, 2017	1.4 (1.3, 1.6)	1.14 (1.05, 1.2)	0.001	1.2 (1.08, 1.3)	$3x10^{-4}$
11p15.5	rs35705950	MUC5B	Fingerlin, NG, 2013	2.4 (2.1, 2.8)	2.0 (1.7, 2.2)	$3x10^{-27}$	2.2 (1.9, 2.5)	$1.7x10^{-29}$
15q15.1	rs2034650	IVD	Fingerlin, NG, 2013	1.3 (1.2, 1.4)	1.08 (0.99, 1.17)	0.07	1.15 (1.05, 1.3)	$3x10^{-3}$
19p13.3	rs12610495	DPP9	Fingerlin, NG, 2013	1.3 (1.2, 1.4)	1.14 (1.02, 1.3)	0.01	1.2 (1.1, 1.4)	$2x10^{-4}$



Am J Respir Crit Care Med. 2019; 200(11): 1402-1413.

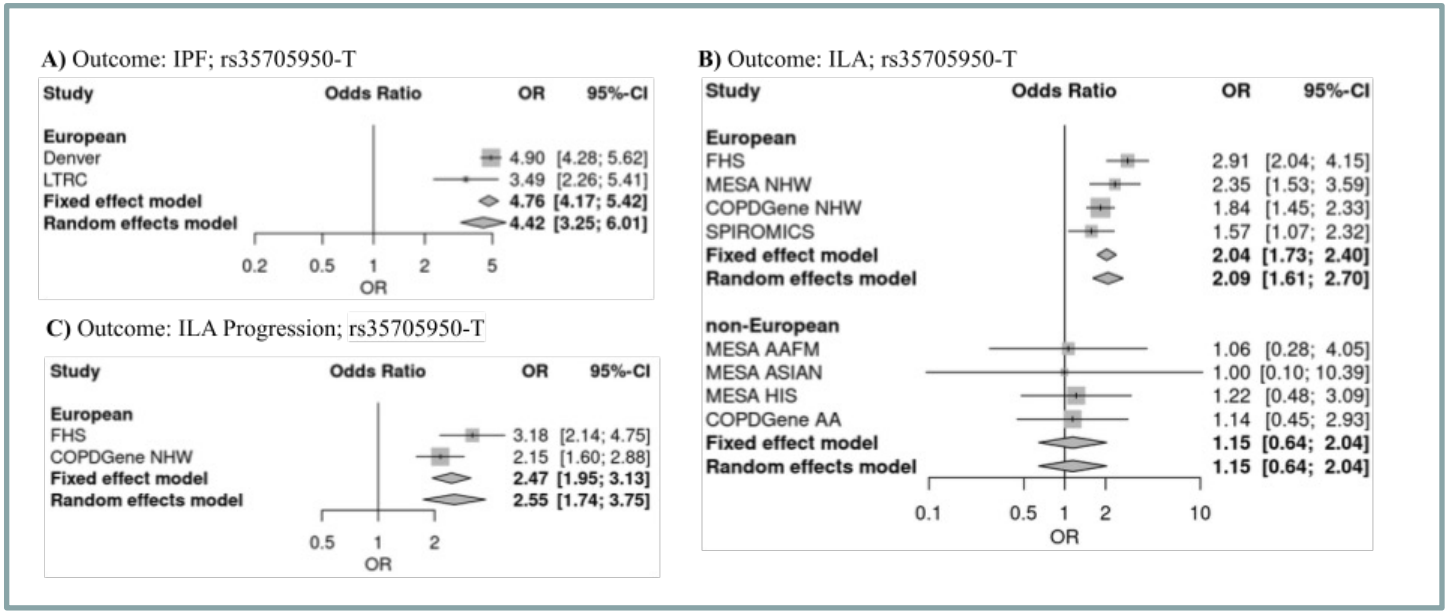
Concept of Polygenic Risk





Hypertension. 2021;77:1119–1127.
Inflamm Regen. 2021 Jun 17;41(1):18.

Polygenic Risk of IPF and ILA



Matt Moll

Anna Peljto

John Kim

Polygenic Risk of IPF and ILA

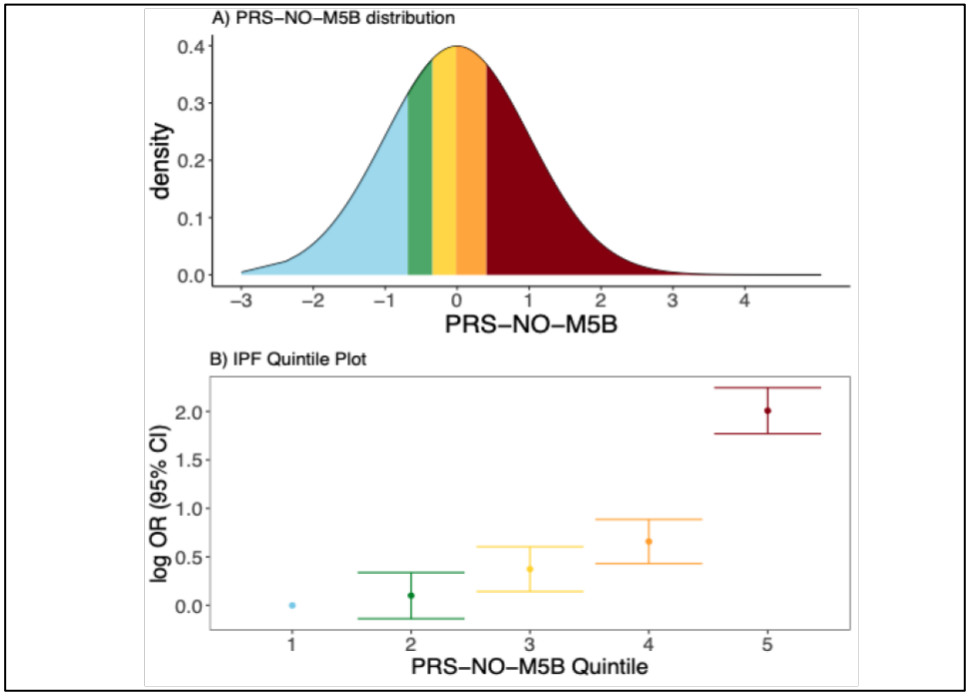
- Created PRS excluding the *MUC5B* genomic region (using a stacked clumping and thresholding method – LASSO)
- This no-*MUC5B* PRS included >60K variants

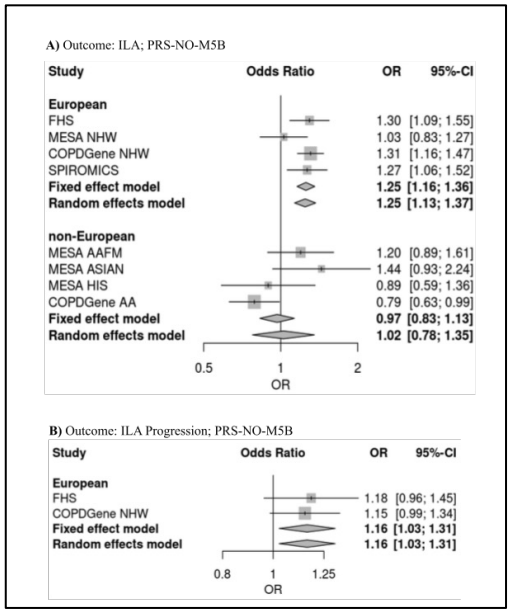
Matt Moll

Anna Peljto

John Kim

Polygenic Risk of IPF and ILA





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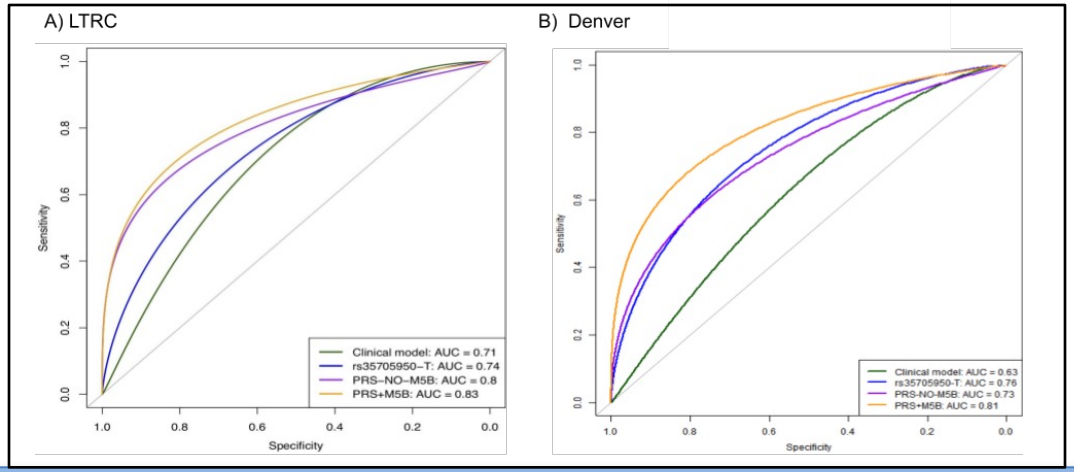
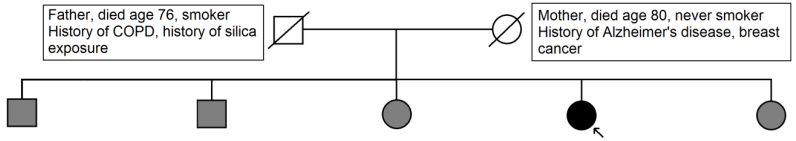
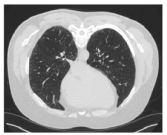
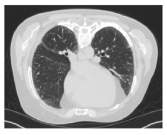
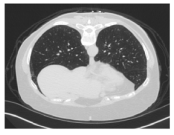
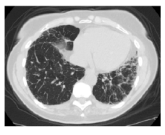
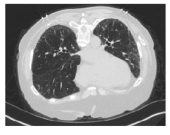
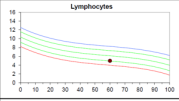
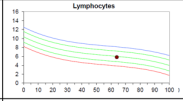
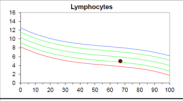
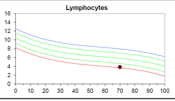
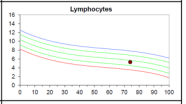
Polygenic Risk of IPF and ILA

- There is a substantial portion of the genetic risk to develop IPF that is explained by common genetic variants outside of the *MUC5B*.
- Combined with MUC5B the no-*MUC5B* PRS is associated with an increased ability to predict the risk for IPF (AUC 0.81-0.82).
- Both MUC5B and the no-MUC5B PRS are associated with ILA and ILA progression.
- These perform less well in other racial/ethnic groups



Clinical Genetics and Screening for Pulmonary Fibrosis



Age	Age = 60	Age = 64	Age = 67	Age = 70	Age = 74
History of Smoking	Never Smoker	Former Smoker	Never Smoker	Never Smoker	Never Smoker
Diagnosis	ILD	ILD	ILA	IPF	ILD
Pulmonary Function Tests	FVC = 4.98L 109% TLC = 6.52L 96% DLCO = 25.57 90%	FVC = 4.10L 83% TLC = 5.70L 77% DLCO = 18.65 62%	FVC = 3.18L 121% TLC = 4.68L 101% DLCO = 18.49 92%	FVC = 1.82L 70% TLC = 3.07L 66% DLCO = 12.00 61%	FVC = 2.75L 95% TLC = 4.21L 80% DLCO = 12.52 59%
Chest CT image					
Lymphocyte Telomere Lengths					
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