GENETICA DELL'IPF E CLINICA: ESISTE DAVVERO UNA RICADUTA CLINICA?

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Thorax (1964), **19**, 515.

Familial interstitial pulmonary fibrosis

E. W. HUGHES

From Tehidy Hospital, Camborne, Cornwall

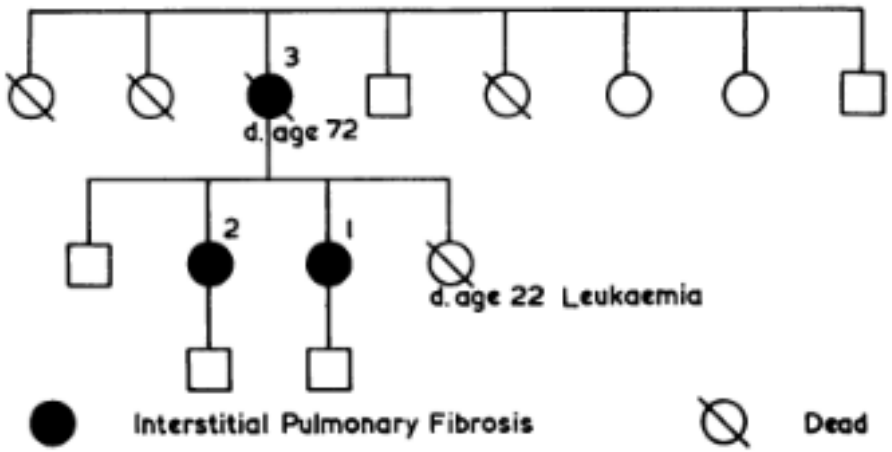
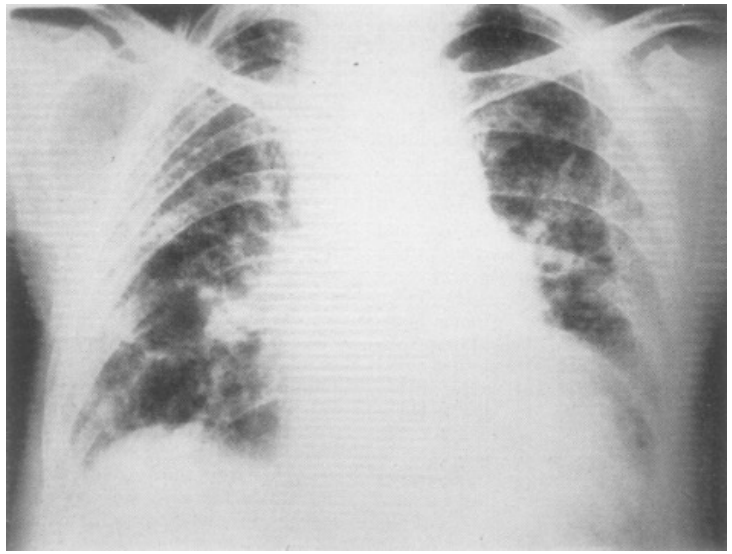
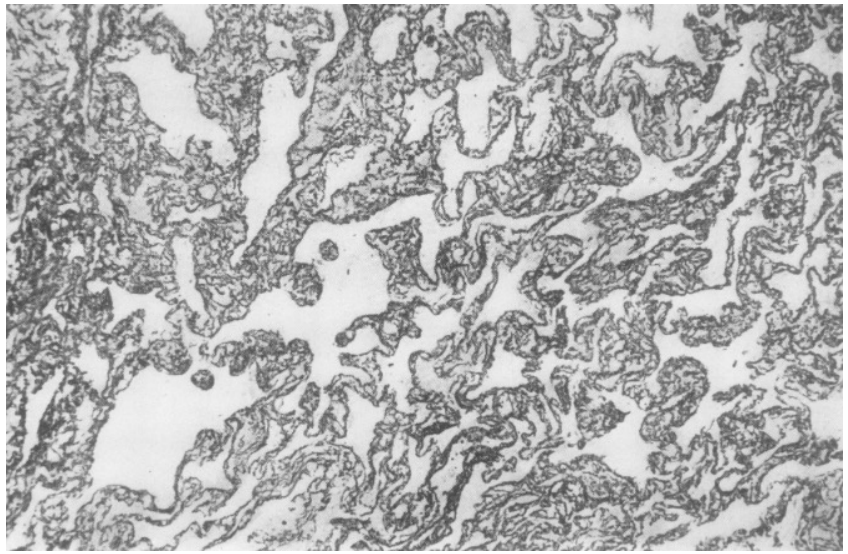
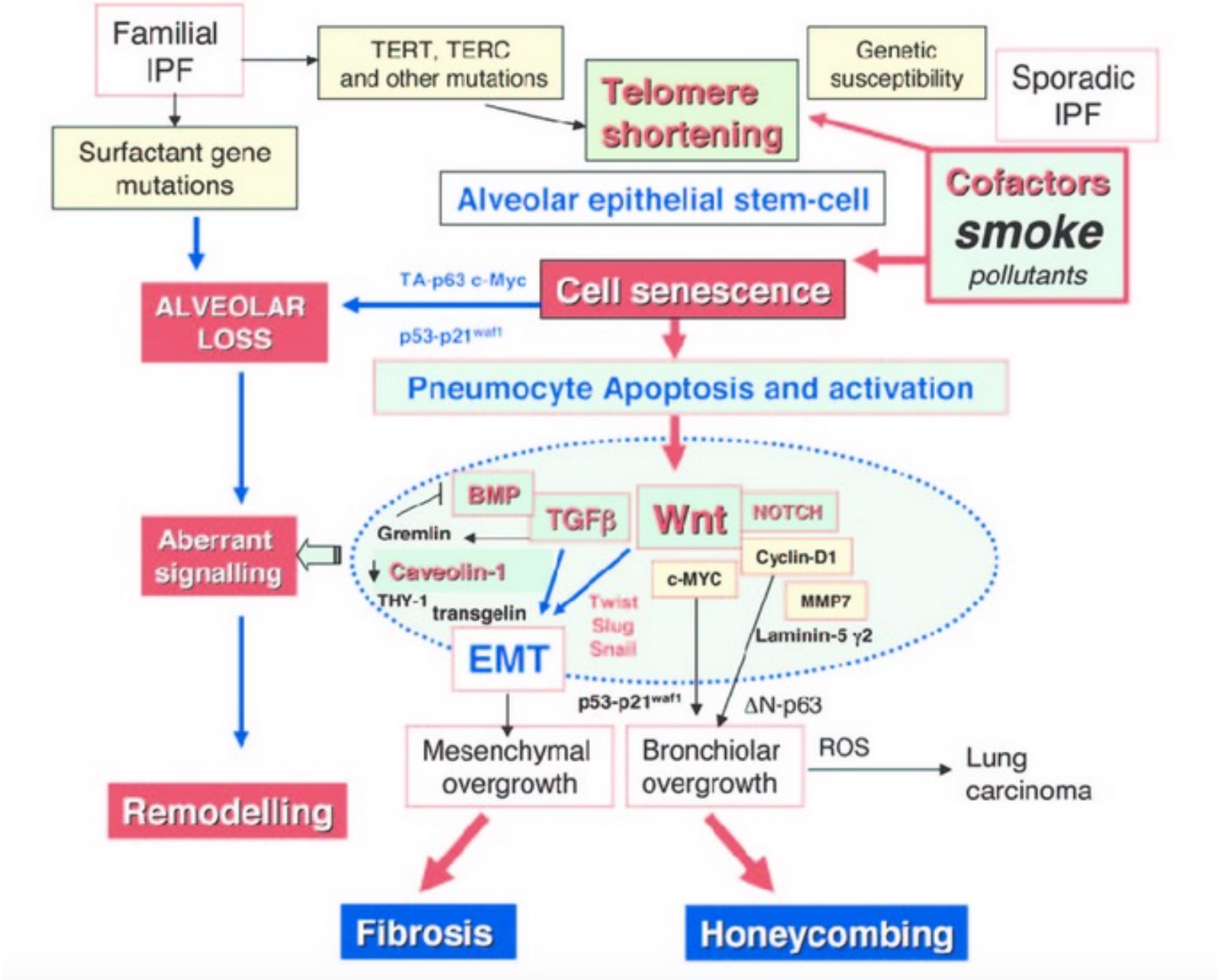


FIG. 10. *Pedigree of family.*







Chilosi M, Doglioni C, Murer B, Poletti V. Sarcoidosis Vasc Diffuse Lung Dis. 2010; Chilosi M, Poletti V, Rossi A. Respir Res. 2012

Familial pulmonary fibrosis

- Complex disease (genetic and environmental factors)
- **Family history of pulmonary fibrosis is the strongest risk factor for IPF.**
- **Familial IPF** = two or more members of a family

- **10% of idiopathic interstitial pneumonias**
- **19% of lung transplant referrals**
- Diagnosis relies on detailed patient-clinician discussions
- Mean age at diagnosis: 55 years

Ref. Spagnolo P. Lecture

Borie R, J Bras Pneumol. 2019

García-Sancho C, Respir Med. 2011

FEATURES AND OUTCOME OF FAMILIAL IDIOPATHIC PULMONARY FIBROSIS

Table 3. Comparison of pulmonary function tests (PFTs) at diagnosis between familial and sporadic groups.

Pulmonary Function Tests at Diagnosis					
LFTs	F-IPF patients with abnormal findings (FVC<80%p, TLCO<80%p, DLCO<80%p, SpO2<90%), N (%)	Mean +/- SD	Non F-IPF patients with abnormal findings, N (%)	Mean +/- SD	P
FVC,% p	12 (40%)	84,20 ± 20,37	65 (52,85%)	78,14 ± 17,29	0,099
TLC,% p	18 (64,3%)	72,64 ± 18,97	62 (78,48%)	70,99 ± 12,36	0,601
DLCO,% p	21 (72,4%)	51,09 ± 18,05	104 (95,41%)	51,51 ± 15,13	0,901
SpO2,%					
at rest	8 (30,8%)	95,85 ± 2,62	0	95,31 ± 1,83	0,25
on exercise	16 (61,5%)	90,54 ± 5,29	43 (55,12%)	88,95 ± 4,43	0,14

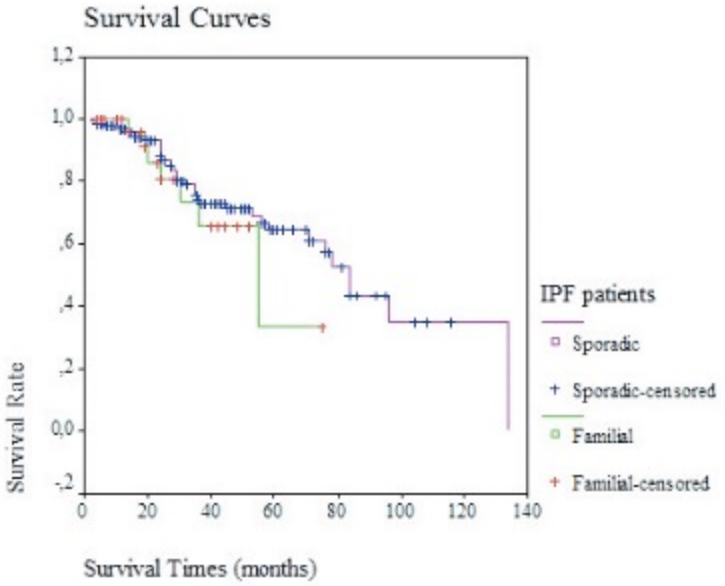
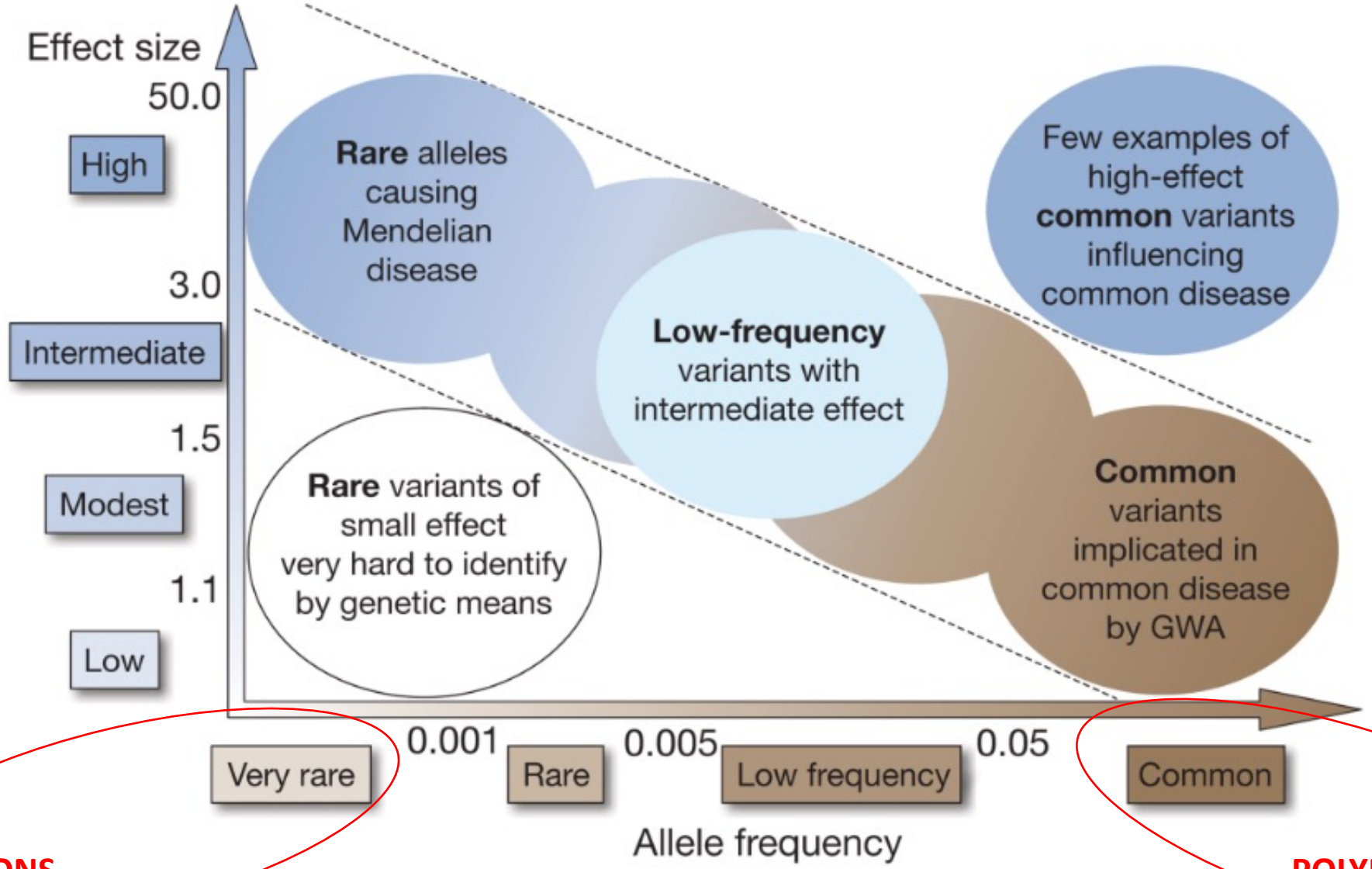


Table 2. Age at onset of pair of relatives from different generations with familial IPF.

	First generation (f-IPF)	Second generation (f-IPF)	Significance of difference (p)
Age at diagnosis (years)	74,2	57,8	0,001

Ravaglia C, Sarcoidosis Vasc Diffuse Lung Dis. 2014

GENETIC VARIANTS



HIGH EFFECT

SMALL EFFECT

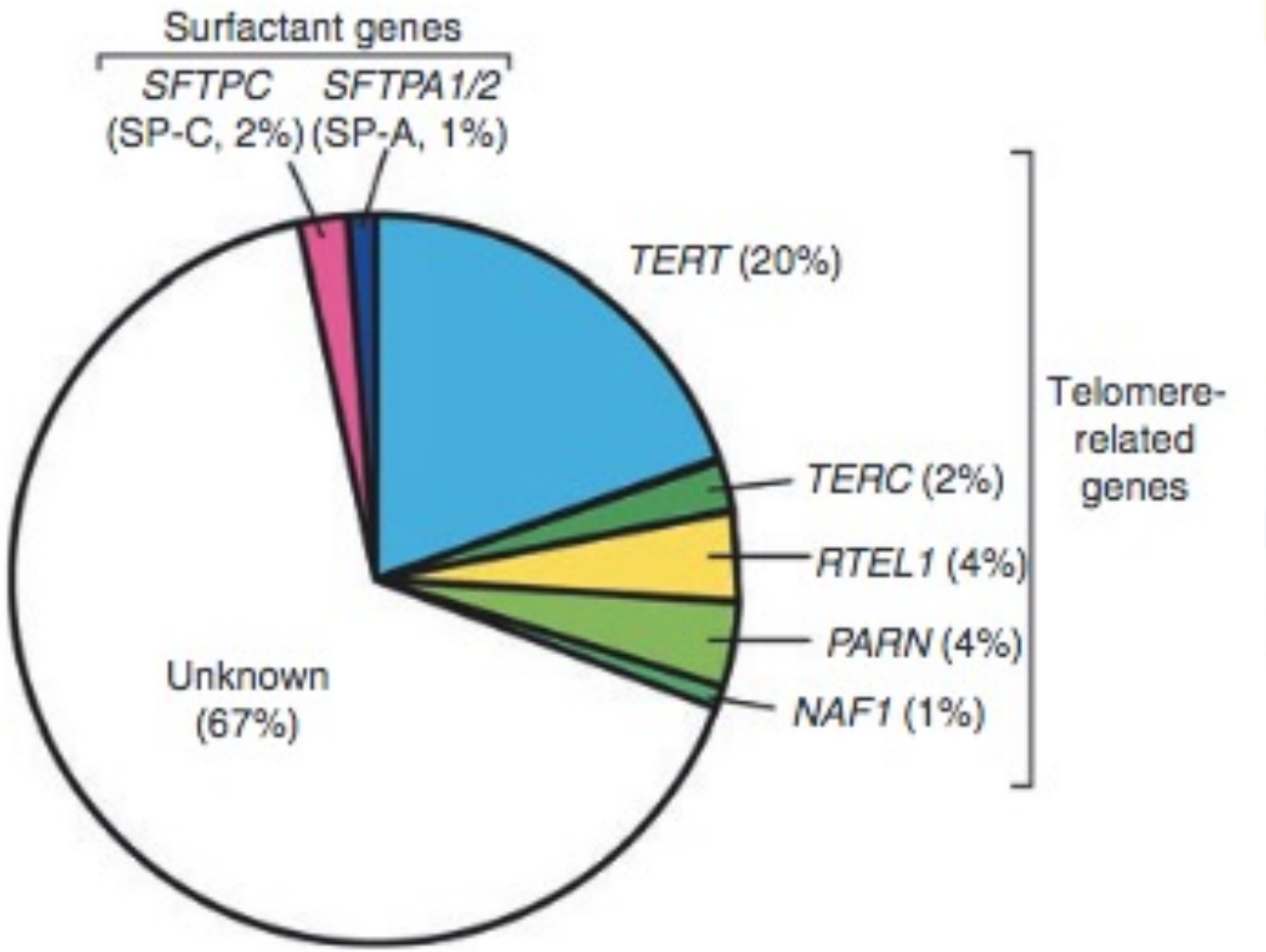
MUTATIONS

POLYMORPHISMS

Manolio TA, Nature. 2009

GENETIC VARIANTS

FAMILIAL FORMS



Percentage of variants in different genes found in FPF probands. Only variants that are considered pathogenic or likely pathogenic were included; none were found in DKC1, TINF2, or SFTPA1. Rare variants were not included if the family analysis demonstrated a lack of co-segregation of the variant and fibrotic ILD or if there was no indication that the variant led to a deleterious effect on protein function. Overall, ~30% of probands have pathogenic variants in telomere-related genes, and ~3% of probands have pathogenic variants in surfactant-related genes.

Adams, T.N., Garcia, C.K. (2019). Genetics of Pulmonary Fibrosis. In: Meyer, K., Nathan, S. (eds) Idiopathic Pulmonary Fibrosis. Respiratory Medicine. Humana Press, 2018

Rare variants associated with IPF

Alveolar instability

-SFTPC; Component of surfactant

Pathological consequences of mutation: altered trafficking and disrupted proteostasis; increased endoplasmic reticulum stress

-SFTPA2; Modulation of immune and adaptive immunity

Pathological consequences of mutation Increased endoplasmic reticulum stress

-ABCA3; Transport of liquids across plasma membrane

Pathological consequences of mutation Retention of lipids in the endoplasmic reticulum , endoplasmic reticulum stress and apoptotic signaling

Ref. Spagnolo P. Lecture

Cell senescence / impaired response to epithelial injury

-TERT: enzyme of telomerase complex;

Pathological consequence of mutation: telomere shortening

-**TERC: template of telomerase complex;**

Pathological consequence of mutation: telomere shortening

-**DKC1: stabilization of the template of the telomerase complex**

Pathological consequence of mutation: telomere shortening

-**TINF2: telomere maintenance**
Pathological consequence of mutation: telomere shortening

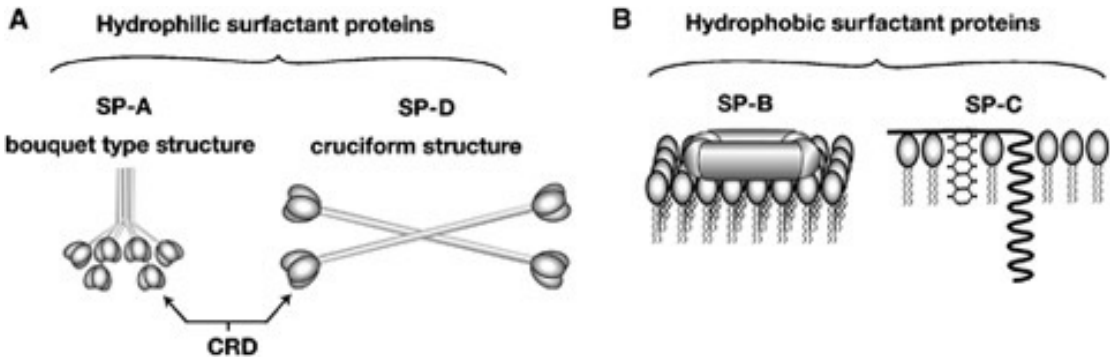
-**RTEL1: DNA helicase**

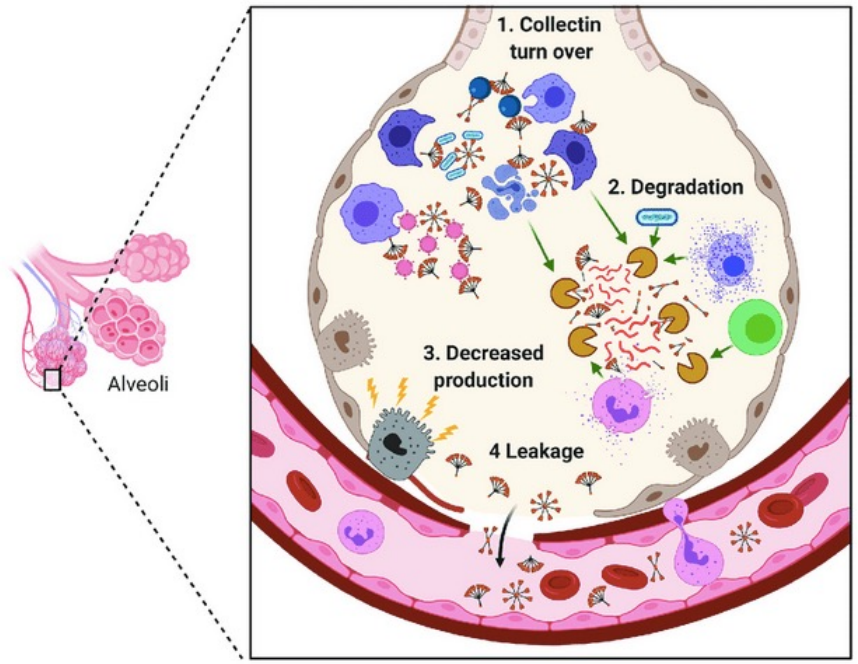
Pathological consequence of mutation: telomere shortening

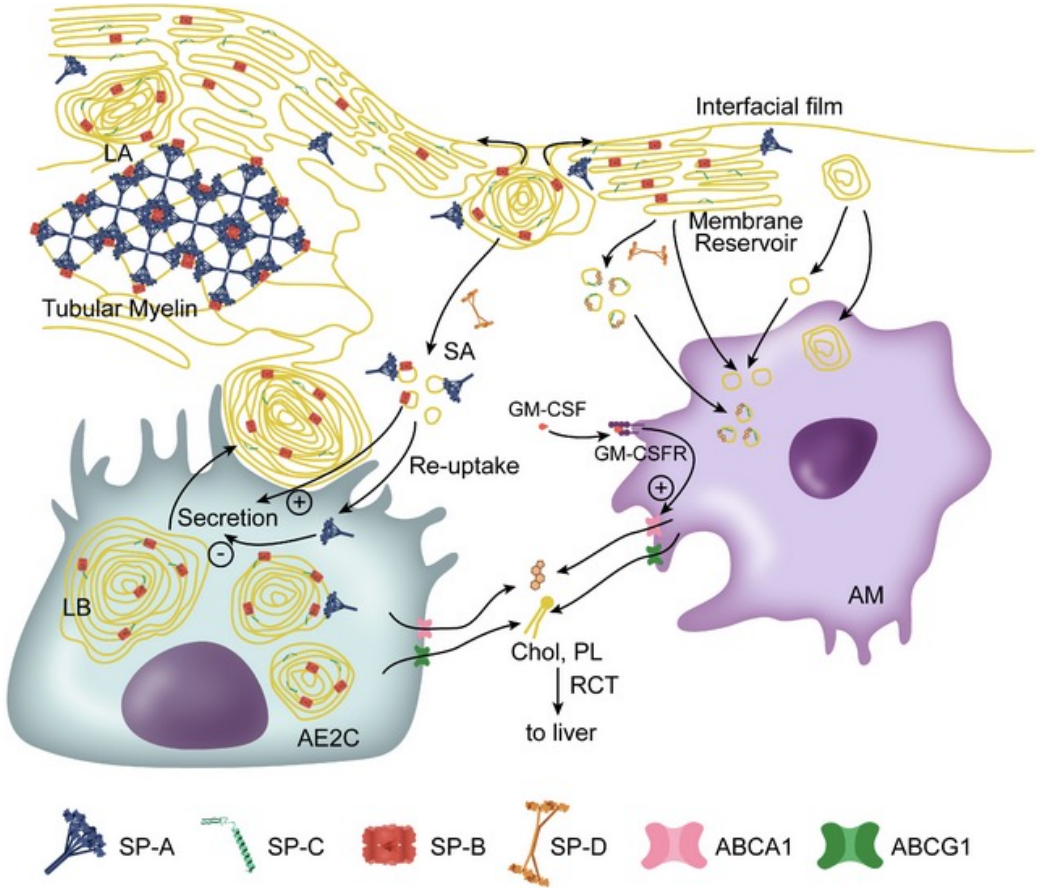
-**PARN: mRNA stability**

Pathological consequence of mutation: telomere shortening

Rare Variants in Surfactant Metabolism Genes







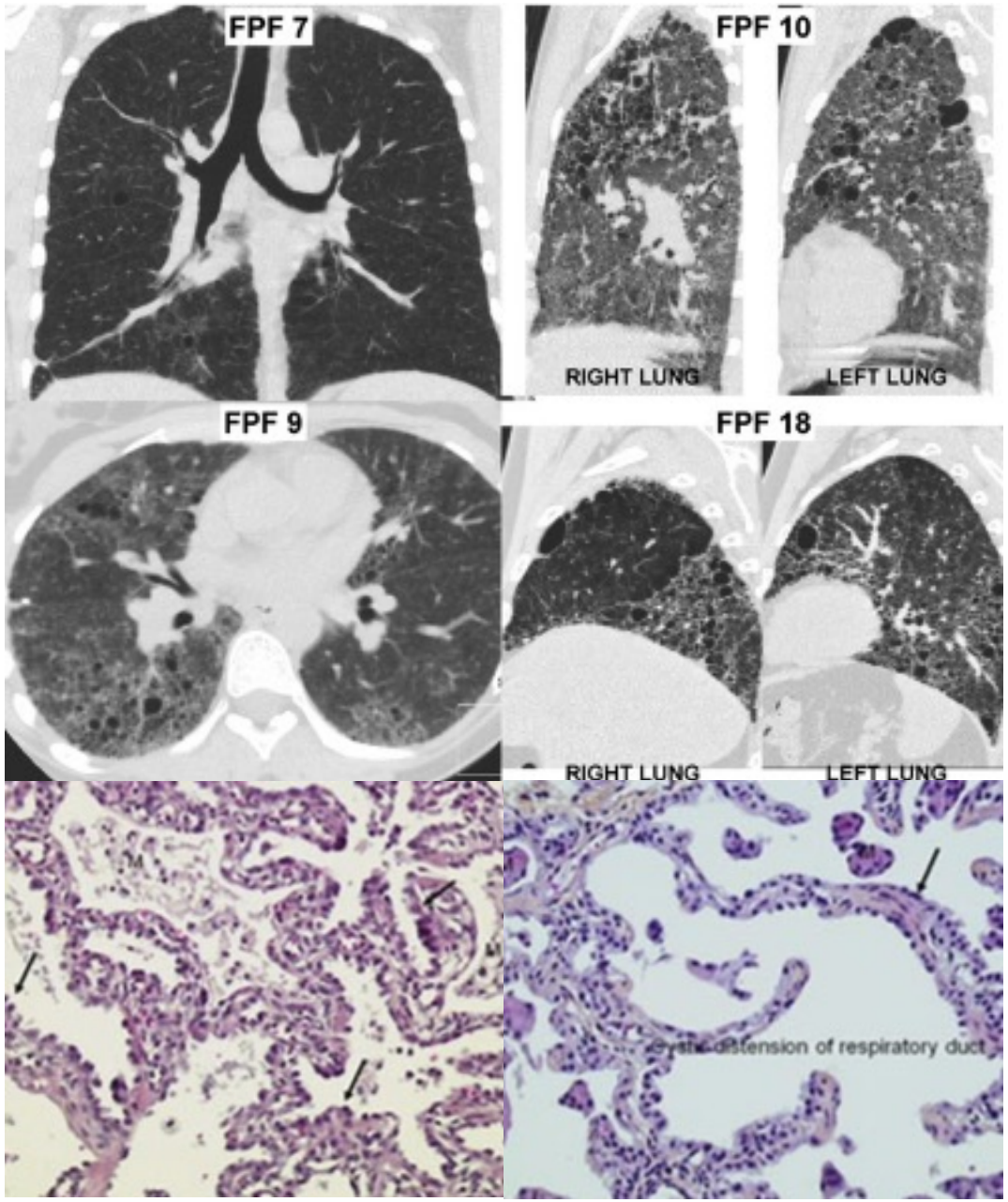
Watson A, Front Immunol. 2021

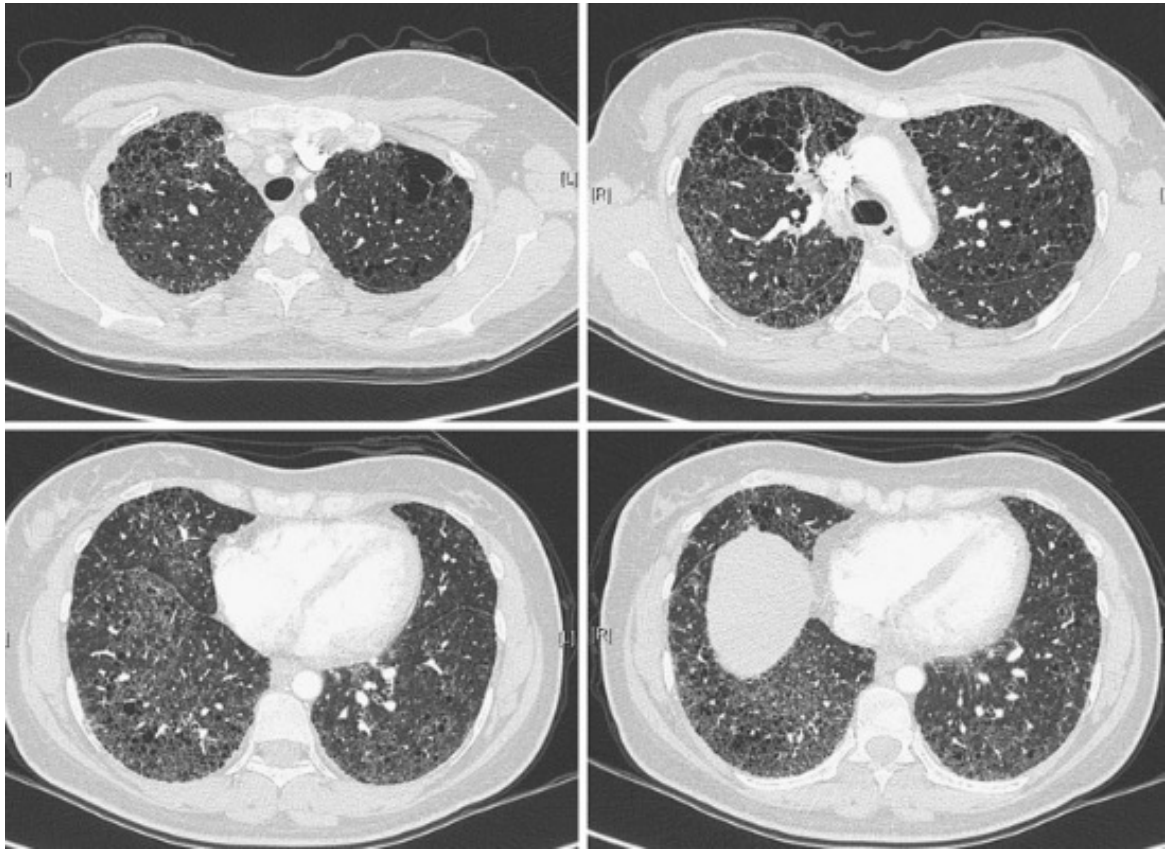
Cañadas O, Int J Mol Sci 2020

Rare Variants in Surfactant Metabolism Genes

SP-B deficiency (autosomal recessive)	Neonatal respiratory failure	
Bi-allelic ABCA3 mutations	Severe neonatal disease or ILD in infancy or childhood	Adult ILD case reports
SFTP-A1 and SFTP-A2 (heterozygous variants) Dicreased secretion of mature SP-a		Pulmonary fibrosis and lung adenocarcinoma
SFTP-C mutations **(autosomal dominant)** **> 40 different mutations** **protein misfolding, toxic gain of function of the misfolded protein or alterations in autophagic vacuole maturation.** **Incomplete penetrance ➔ phenotypic heterogeneity**	**Neonatal respiratory distress**	**Adult onset is common** **Up to 25% of FPF**

Nogee LMJ Clin Invest 1994; Andersen C, Am J Perinatol. 2000; Flamein F, Hum Mol Genet. 2012; Nogee LM, N Engl J Med. 2001; Thomas AQ, Am J Respir Crit Care Med. 2002; Mulugeta S, Am J Respir Cell Mol Biol. 2005; Hawkins A, Am J Physiol Lung Cell Mol Physiol. 2015; Wang Y, Am J Hum Genet. 2009; Nathan N, Hum Mol Genet. 2016; van Moorsel CH, Am J Respir Crit Care Med. 2015

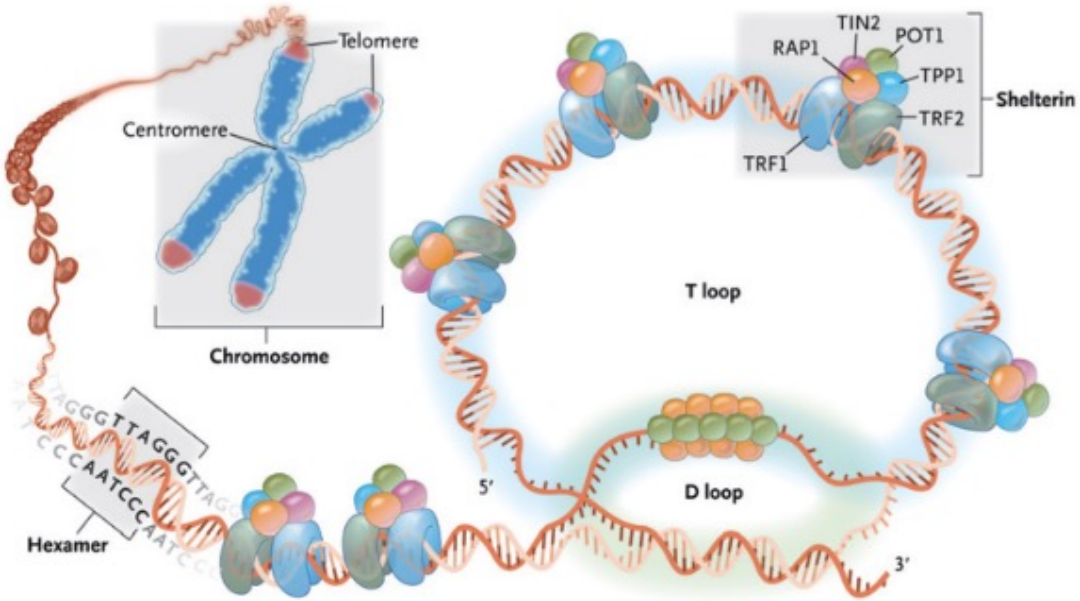




-HRCT: diffuse GGOs, septal thickening, upper lobe predominant sub-pleural cysts
-Histologic patterns: UIP, NSIP, OP, and DIP

van Moorsel CH, Am J Respir Crit Care Med. 2010; Mechri M, Pediatr Pulmonol. 2010 ; Cottin V, Thorax. 2011

The overall length of the telomere is influenced by its starting length, the cellular activity of telomerase, the number of cell divisions, and the environment.



Expression of telomerase prevents senescence of stem cells or those with increased replicative potential

Calado RT, N Engl J Med. 2009

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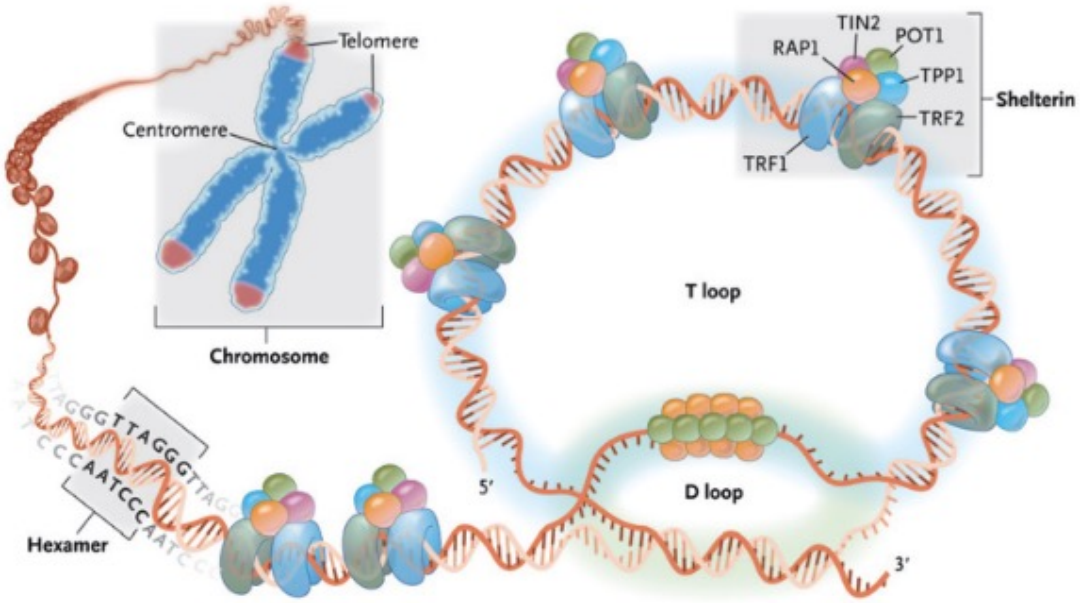

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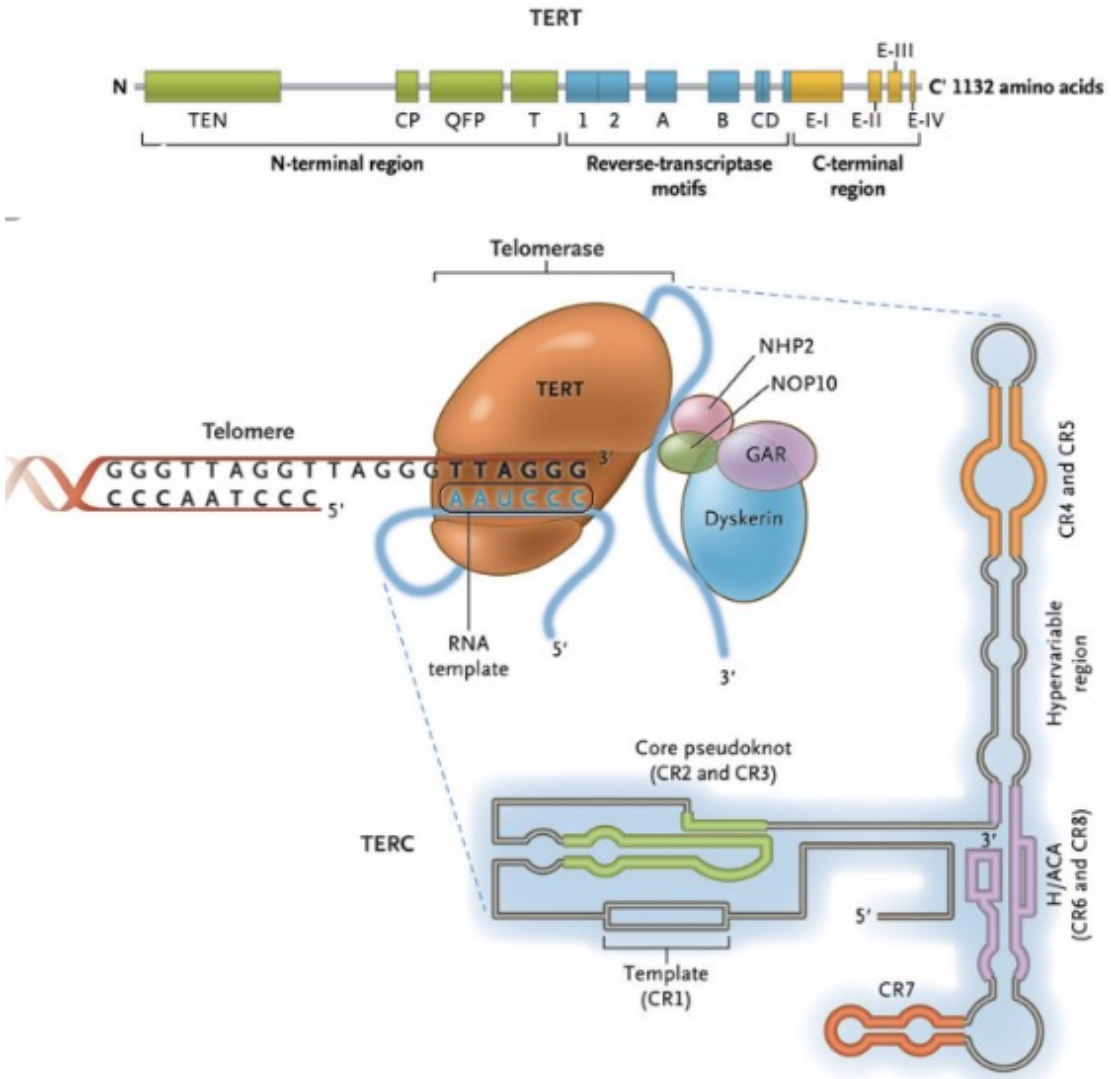


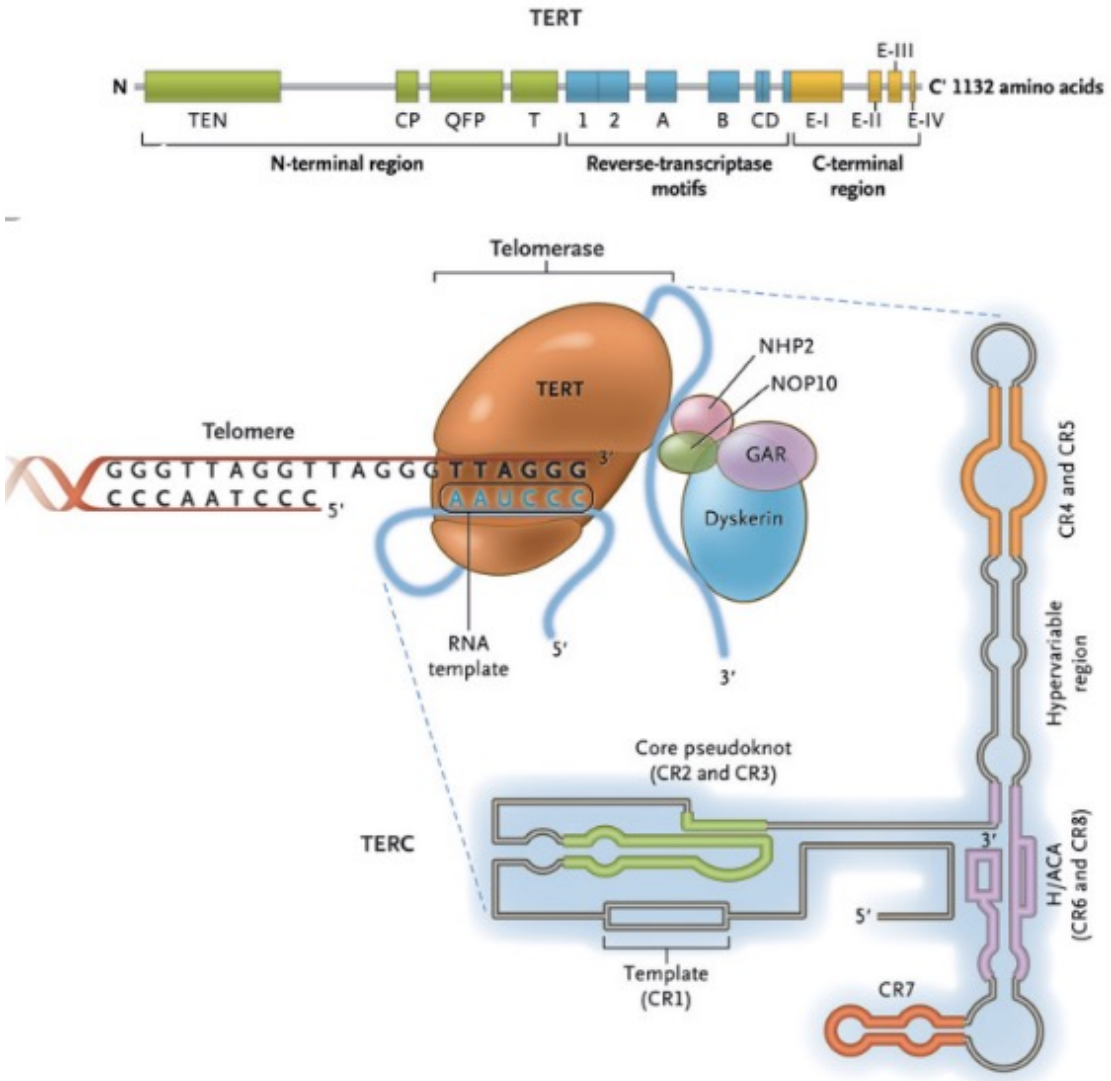
Calado RT, N Engl J Med. 2009

Most rare variants in telomere-related genes:

1) **TERT**
2) **TERC**
3) **RTEL1**
4) **PARN**

*Fewer cases are linked to **NAF1 , DKC1 , and TINF2**

Telomerase is encoded by **TERT**
RNA template is encoded by **TERC**
RTEL1 encodes the regulator of telomere length
PARN encodes for a polyadenylation-specific RNase which allows TERC to serve as the template for the telomere repetitive sequence
NAF1 loads dyskerin core complexes onto TERC



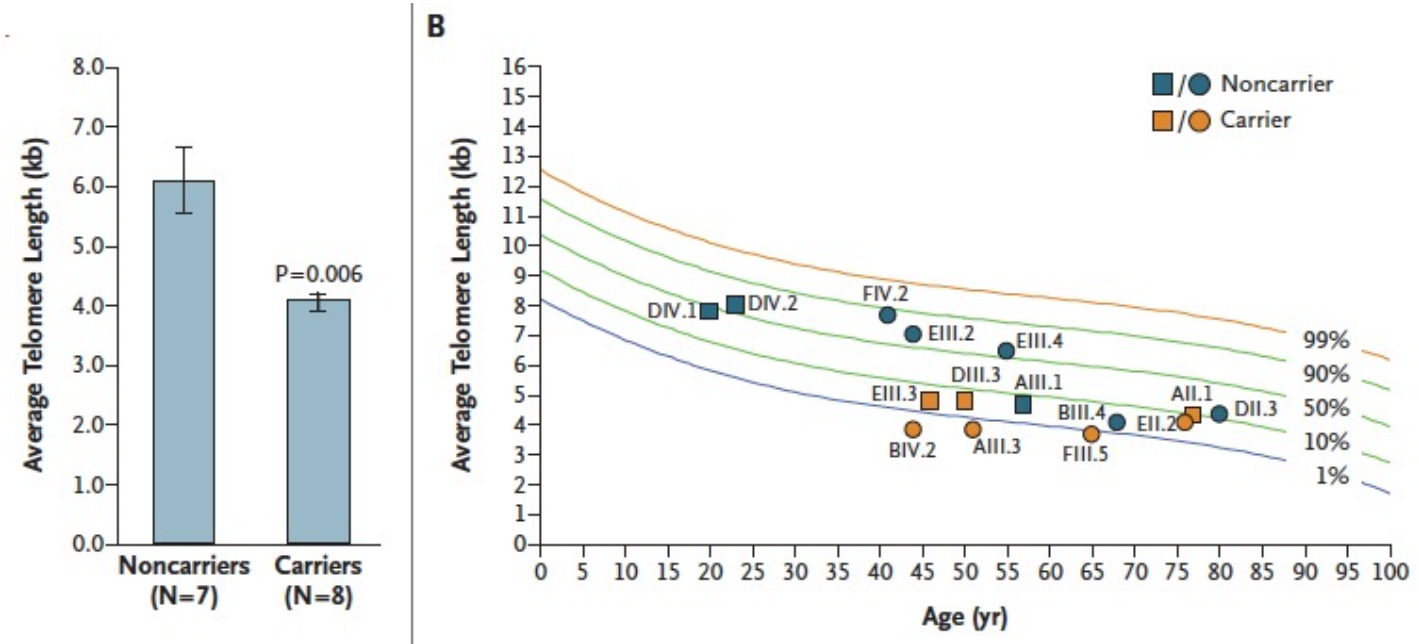
Calado RT, N Engl J Med. 2009

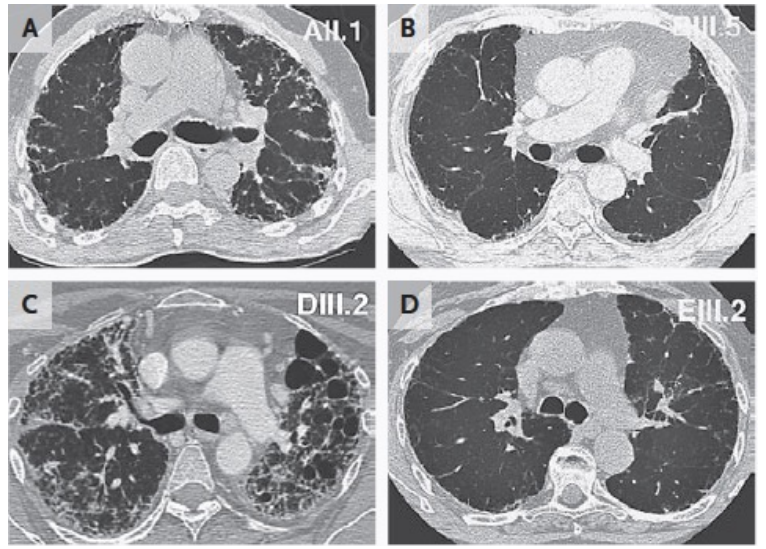
Telomerase Mutations in Families with Idiopathic Pulmonary Fibrosis

Table 1. Mutations in Telomerase and Associated Clinical Features of the Six Probands.*

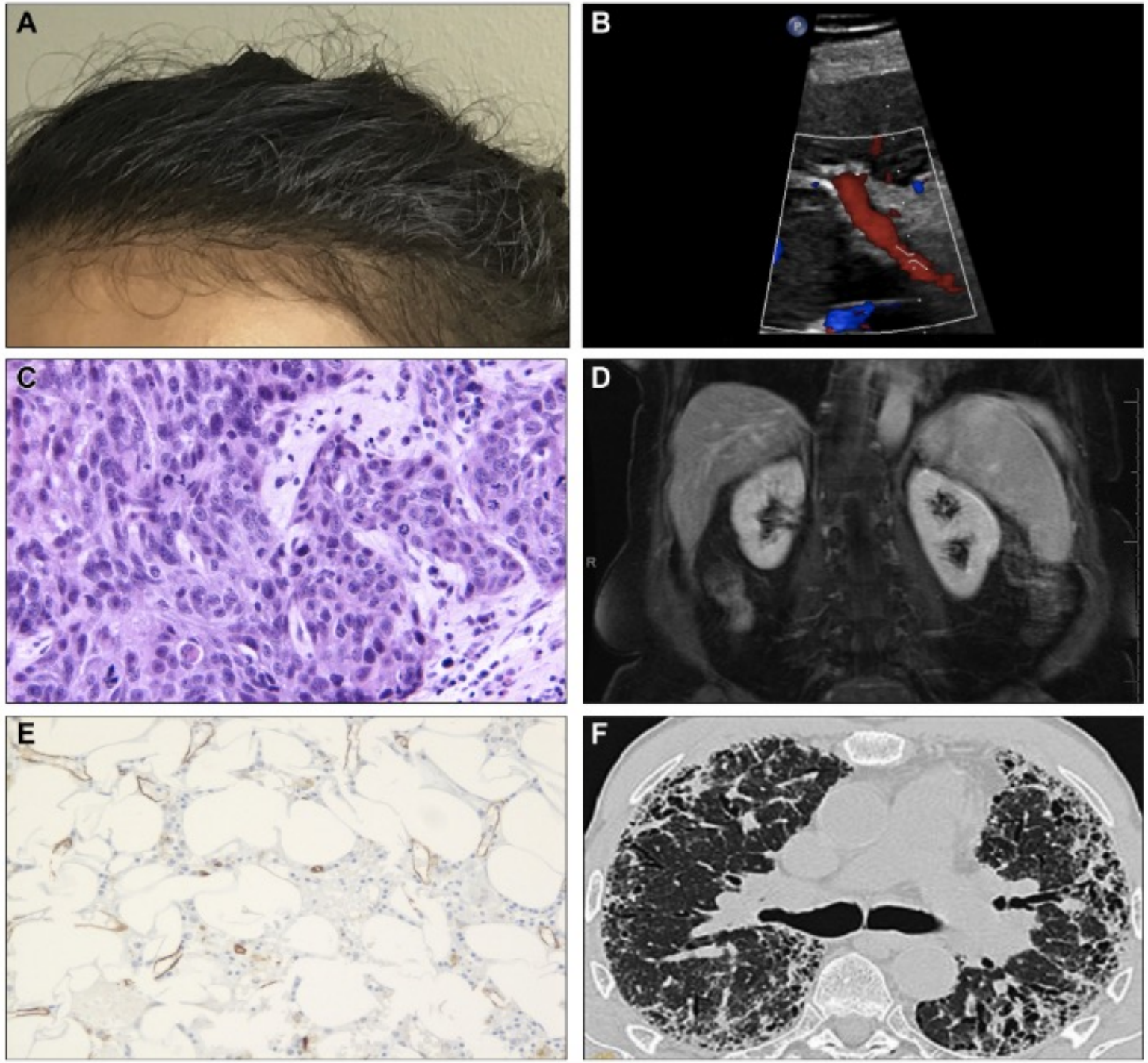
Proband No.	Mutation	Sex	Age		Presenting Symptom	Smoking History	Pulmonary Function			Findings on Lung Biopsy	Complete Blood Count		
			At Onset	At Time of Study			TLC	FVC	DLCO		WBC	Hgb	Platelet
			yr				*liters (% of predicted value)*				*per mm³*	*g/dl*	*per mm³*
AII.1	*hTERT* CTG→CAG Leu55Gln	M	77	81	Dyspnea	None	4.45 (68)	3.02 (68)	14.2 (76)	Usual interstitial pneumonia	5,500	14.0	206,000
BIII.5	*hTERT* IVS1+1 G→A	M	58	67†	Cough	None	3.17 (44)	2.10 (44)	12.5 (49)	Usual interstitial pneumonia	8,800	14.1	282,000
CII.7	*hTERT* codon 112 del C	M	58	61	Dyspnea	30 pack-years	5.28 (69)	3.55 (66)	12.8 (47)	Usual interstitial pneumonia	8,800	16.2	201,000
DIII.2	*hTERT* IVS9-2 A→C	F	48	49†	Dyspnea	32 pack-years	NA	1.31 (43)	NA	Idiopathic interstitial pneumonia	10,800	13.8	235,000
EII.2	*hTERT* ACG→ATG Thr1110Met	F	68	76	Dyspnea	None	3.25 (68)	1.69 (47)	12.5 (54)	Usual interstitial pneumonia	9,500	15.5	317,000
FIII.5	*hTR* 98 G→A	F	60	66†	Dyspnea	None	2.48 (51)	1.2 (45)	7.07 (32)	Usual interstitial pneumonia	6,800	12.8	218,000

73 families
6 mutations
Short telomere





Armanios MY. NEJM 2007



Adegunsoye A, Chest. 2019

Genetic associations with sporadic pulmonary fibrosis

Gene Variants	Gene Function	Phenotype
IL1RN	Inhibits pro-inflammatory effect of IL-1aand IL-1b	IPF
IL8	Pro-inflammatory cytokine	IPF
FAM13A	Affects signal transduction	IPF
TLR3	Recognition of pathogens and activation of innate immunity	IPF
TERT	Telomerase complex enzyme that maintains telomere length	IPF, CPFE
HLA-DRB1	Major histocompatibility complex, critical to immune system	IPF, cHP, CTD-ILD
DSP	Cell adhesion, integrity, and mechano-transduction	IPF
OBFC1	Stimulates DNA polymerase-alpha-primase activity	IPF
MUC2	Mucin production	IPF
TOLLIP	TLR-mediated immune responses, TGF-b signaling pathway	IPF
ATP11A	Phospholipid translocation	IPF

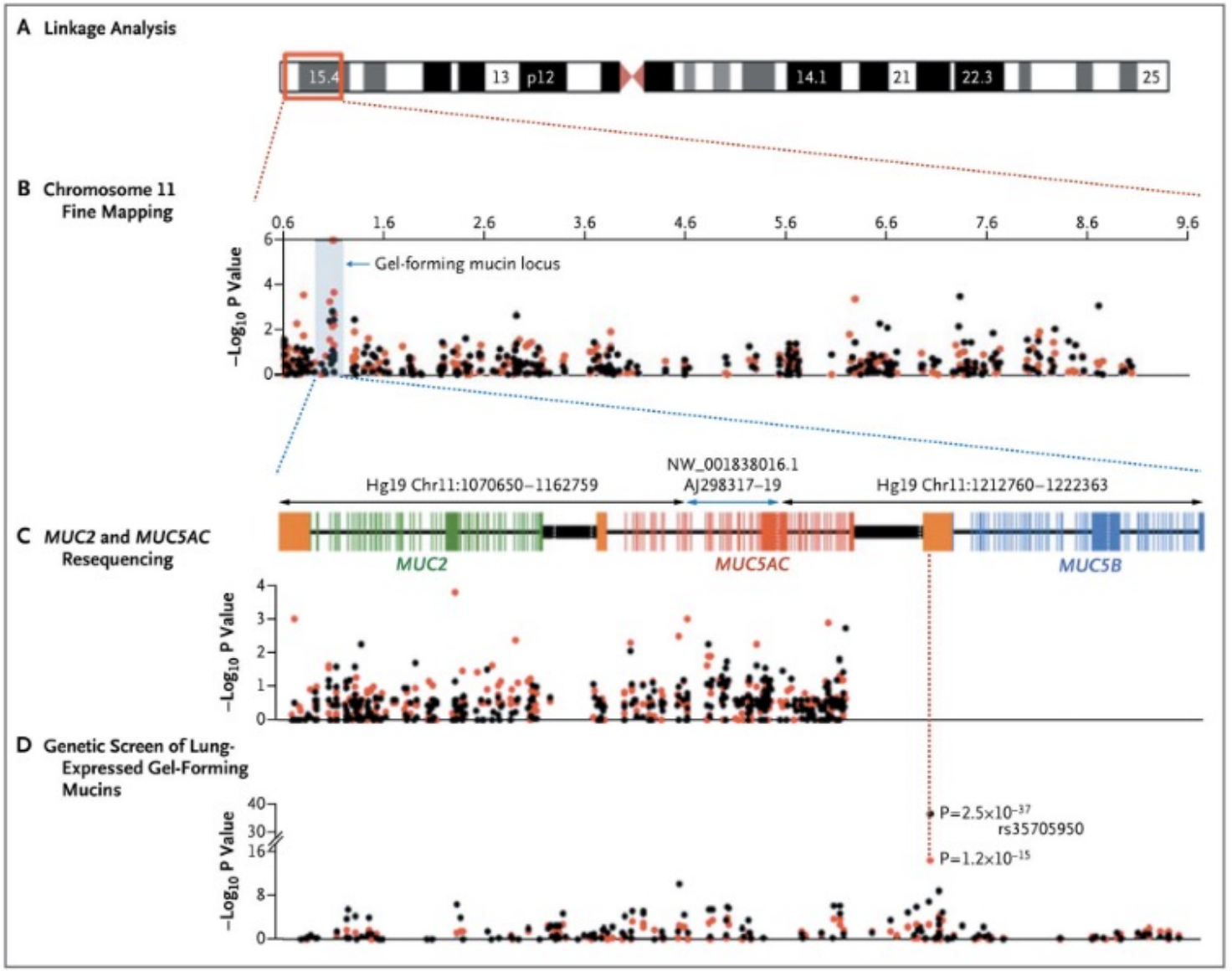
Adegunsoye A, Chest 2019; 155: 1026

Genetic associations with sporadic pulmonary fibrosis

Gene Variants	Gene Function	Phenotype
MDGA2	Cell-cell interaction	IPF
MAPT	Promotes microtubule assembly and stability	IPF
SPPL2C	Protein cleavage	IPF
TP53	Production of tumor suppressor protein p53	IPF
CDKN1A	Critical in cell cycle and response to DNA damage	IPF
IVD	Isovaleryl-CoA dehydrogenase mitochondrial matrix enzyme	IPF
LRRC34	Leucine-rich repeat protein for pluripotent stem cells	IPF
AKAP13	Regulates activation of profibrotic signaling pathways	IPF
TGFB1	Controls proliferation and differentiation of diverse cell types	IPF
DPP9	Cell adhesion, integrity, and mechano-transduction	IPF
MUC5B	Airway mucus properties, muco-ciliary transport, airway defense	IPF, cHP, AR-ILD

Adegunsoye A, Chest 2019; 155: 1026

A Common MUC5B Promoter Polymorphism and PulmonaryFibrosis



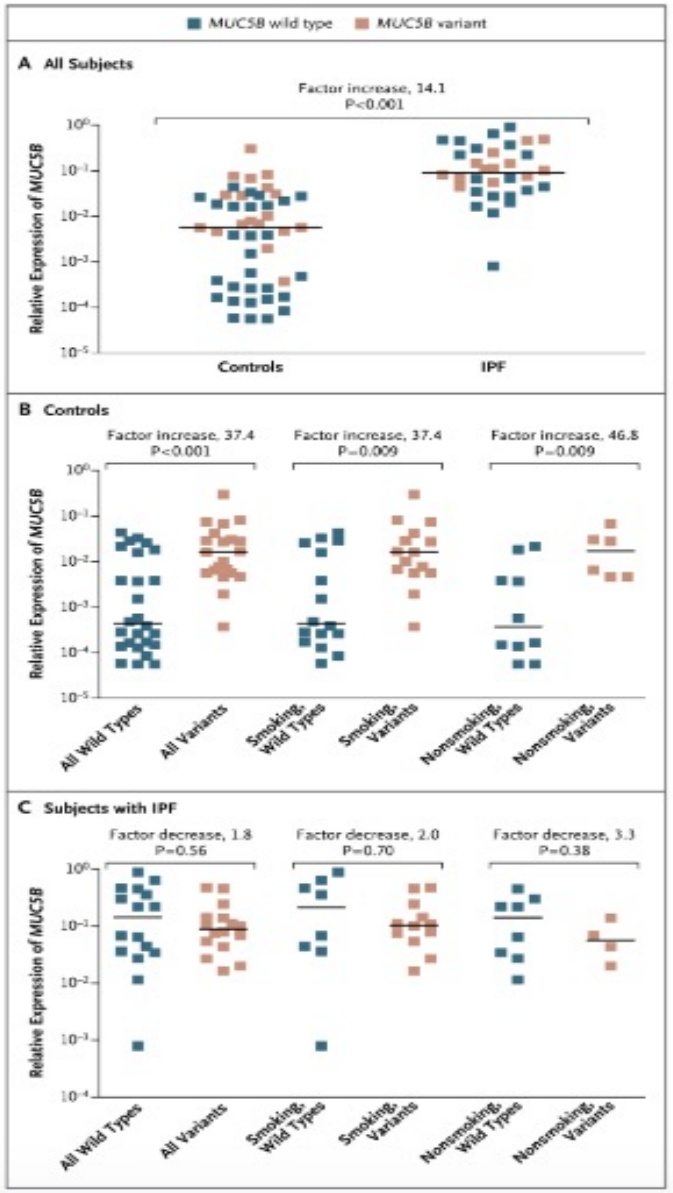
MUC5B (rs35705950):
-34% of familial IP
-38% of IPF
-9% of controls

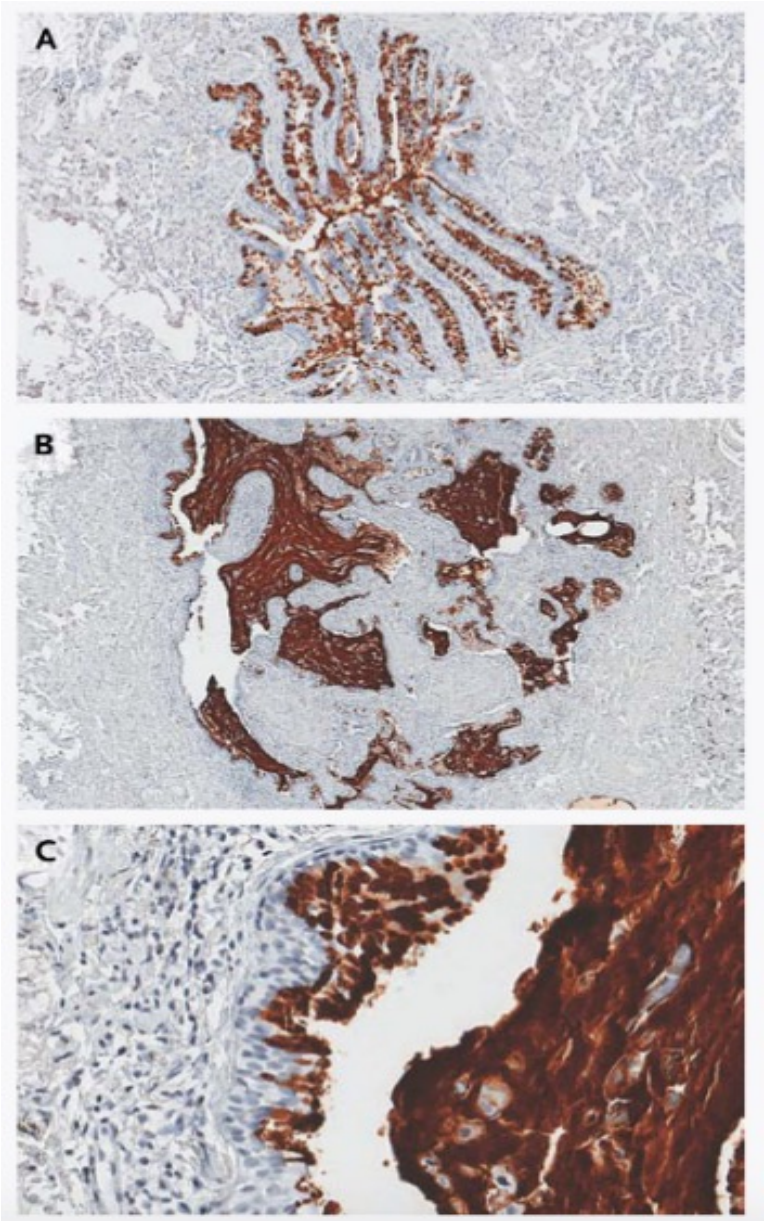
Odds ratios for disease (familial IP):
-heterozygous subjects 6.8
-homozygous subjects 20.8

Odds ratios for disease (IPF):
-heterozygous subjects 9.0
-homozygous subjects 21.8

Seibold MA, N Engl J Med. 2011

A Common MUC5B Promoter Polymorphism and PulmonaryFibrosis





-MUC5B expression in the lung
-14.1 times in IPF P<0.001
-rs35705950 variant allele
-MUC5B protein expressed in lesions of IPF

Seibold MA, N Engl J Med. 2011

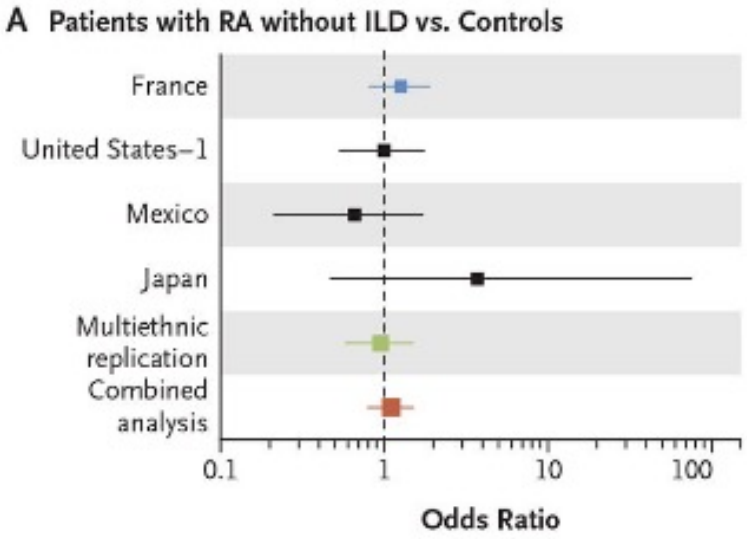
MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease

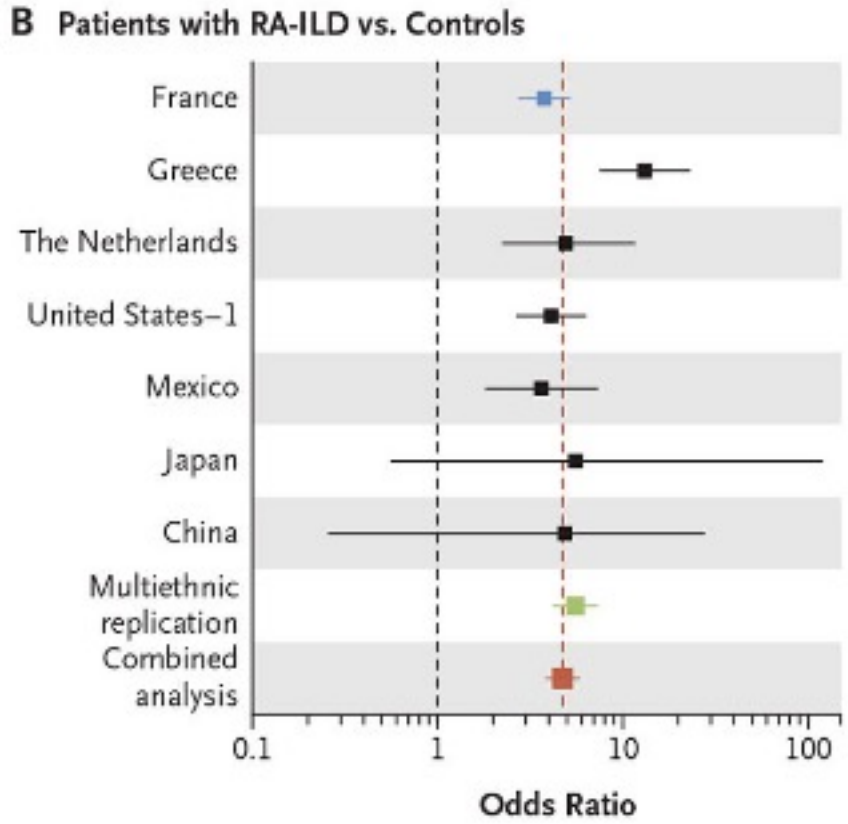
Table 2. Genotypic Association of *MUC5B* rs35705950 Single-Nucleotide Polymorphism in Patients with RA, with and without ILD, and Unaffected Controls.*

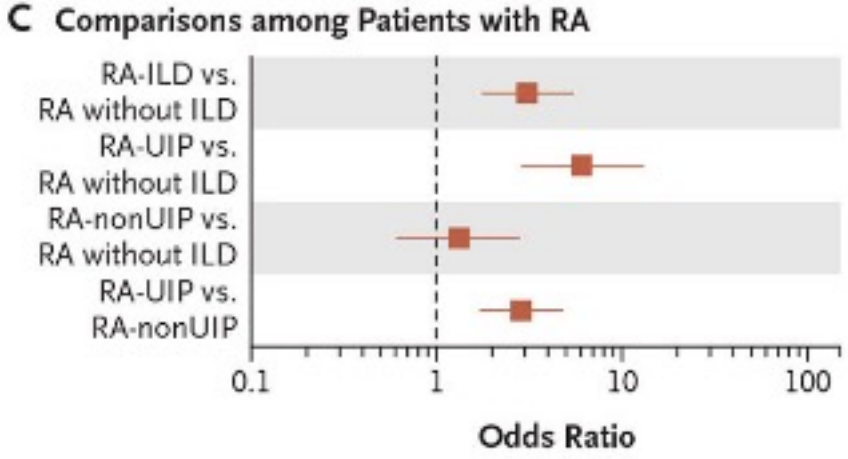
Variable	France†	Greece	The Netherlands	United States–1	United States–2	Mexico	Japan	China	Multiethnic Replication Sample	Combined Analysis
No. of persons										
Controls	1229	1795	249	500	—	347	315	1013	4219	5448
RA without ILD	105	—	—	68	72	69	300	—	509	614
RA-ILD	118	56	40	99	48	55	182	22	502	620
Minor allele frequency of *MUC5B* rs35705950 — %										
Controls	10.9	3.8	9.0	10.7	—	5.3	0.2	0.8	—	—
RA without ILD	12.9	—	—	11.0	12.5	3.6	0.5	—	—	—
RA-ILD	32.6	26.8	30.0	28.8	13.5	16.4	1.1	2.3	—	—
Genotypic association test										
RA without ILD vs. controls										
Crude odds ratio for RA without ILD (95% CI)	1.2 (0.8–1.8)	—	—	1.0 (0.6–1.8)	—	0.7 (0.2–1.6)	3.2 (0.4–64.3)	—	1.0 (0.6–1.5)	1.1 (0.8–1.5)
Crude P value	0.40	—	—	0.91	—	0.42	0.32	—	0.90	0.60
Adjusted odds ratio for RA without ILD (95% CI)‡	1.3 (0.8–1.9)	—	—	1.0 (0.5–1.7)	—	0.7 (0.2–1.7)	3.7 (0.5–75.1)	—	1.0 (0.6–1.5)	1.1 (0.8–1.5)
Adjusted P value‡	0.28	—	—	0.99	—	0.42	0.26	—	0.83	0.54
RA-ILD vs. controls										
Crude odds ratio for RA-ILD (95% CI)	3.8 (2.8–5.2)	13.2 (7.6–22.9)	5.6 (2.9–11.2)	4.1 (2.7–6.3)	—	3.4 (1.8–6.2)	7.1 (1.0–138.6)	3.0 (0.2–15.6)	5.5 (4.2–7.2)	4.7 (3.8–5.8)
Crude P value	3.8×10^{-17}	2.2×10^{-20}	5.0×10^{-7}	5.8×10^{-11}	—	1.1×10^{-4}	0.08	0.30	3.9×10^{-35}	1.3×10^{-49}
Adjusted odds ratio for RA-ILD (95% CI)‡	3.8 (2.8–5.2)	13.2 (7.6–23.0)	4.9 (2.2–11.5)	4.1 (2.7–6.3)	—	3.6 (1.8–7.3)	5.5 (0.6–119.1)	4.9 (0.3–27.5)	5.5 (4.2–7.3)	4.7 (3.9–5.8)
Adjusted P value‡	9.7×10^{-17}	6.2×10^{-20}	1.2×10^{-4}	5.6×10^{-11}	—	2.2×10^{-4}	0.16	0.14	4.7×10^{-35}	1.3×10^{-49}
RA-ILD vs. RA without ILD										
Crude odds ratio for RA-ILD (95% CI)	3.8 (2.2–6.8)	—	—	5.4 (2.6–11.7)	1.1 (0.5–2.5)	5.7 (2.1–18.6)	2.2 (0.5–11.4)	—	3.1 (2.0–5.0)	3.4 (2.4–4.8)
Crude P value	5.9×10^{-6}	—	—	7.9×10^{-6}	0.80	0.002	0.30	—	5.3×10^{-7}	1.6×10^{-11}
Adjusted odds ratio for RA-ILD (95% CI)§	3.1 (1.6–6.3)	—	—	NA	NA	3.8 (1.2–13.3)	3.1 (0.3–28.0)	—	2.9 (1.1–8.4)	3.1 (1.8–5.4)
Adjusted P value§	9.4×10^{-4}	—	—	NA	NA	0.03	0.30	—	0.04	7.4×10^{-5}

Juge PA, N Engl J Med. 2018

MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease

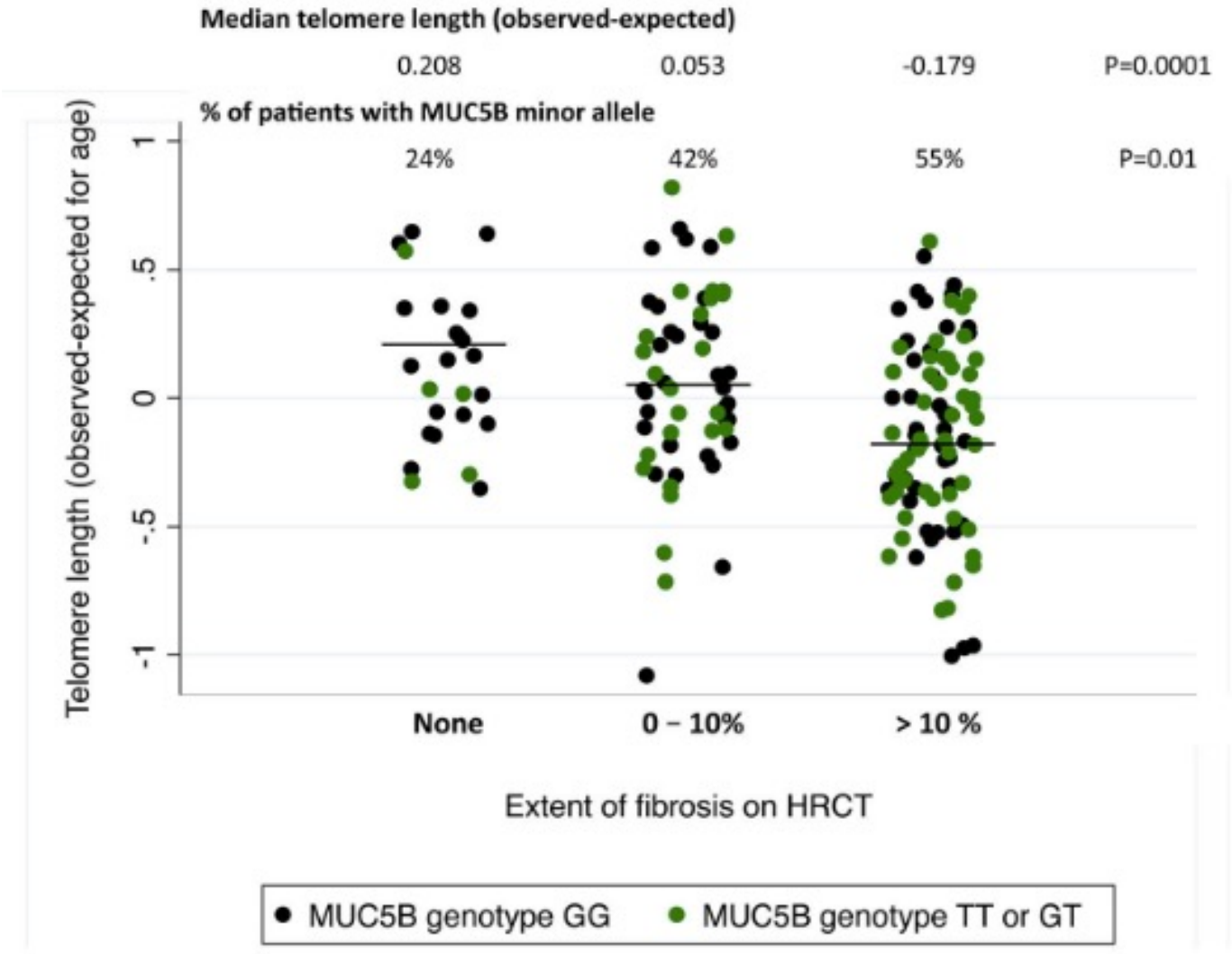






Juge PA, N Engl J Med. 2018

The MUC5B promoter polymorphism and telomere length in patients with chronic hypersensitivity pneumonitis

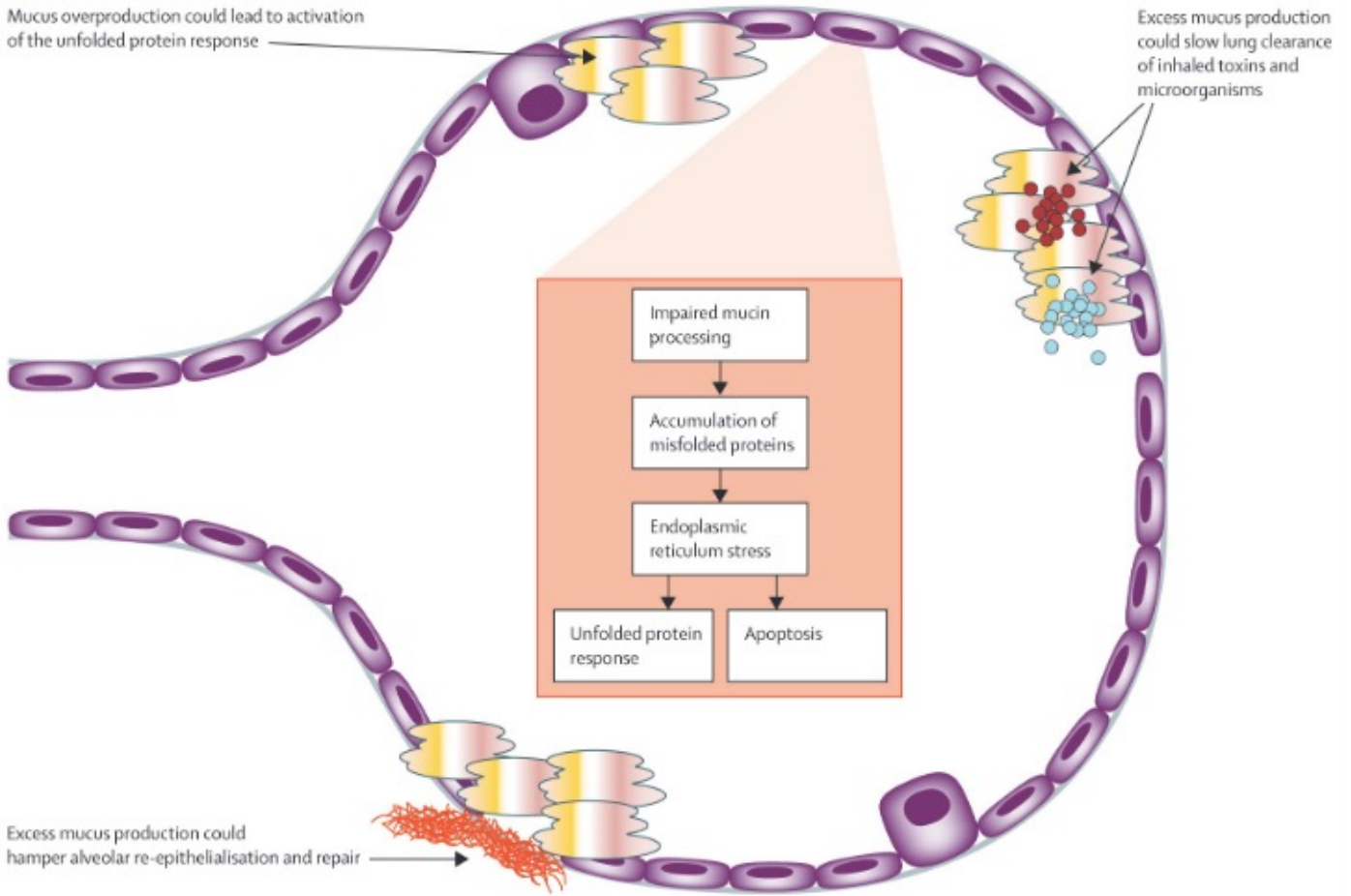


-2 independent cohorts (UCSF, UTSW)
-chronic HP
-MUC5B rs35705950
-TOLLIP rs5743890
-PBL telomere length

-MUC5B increased in cHP
-MUC5B and shorter telomere length associated with extent of fibrosis on CT

Ley B, Lancet Respir Med. 2017

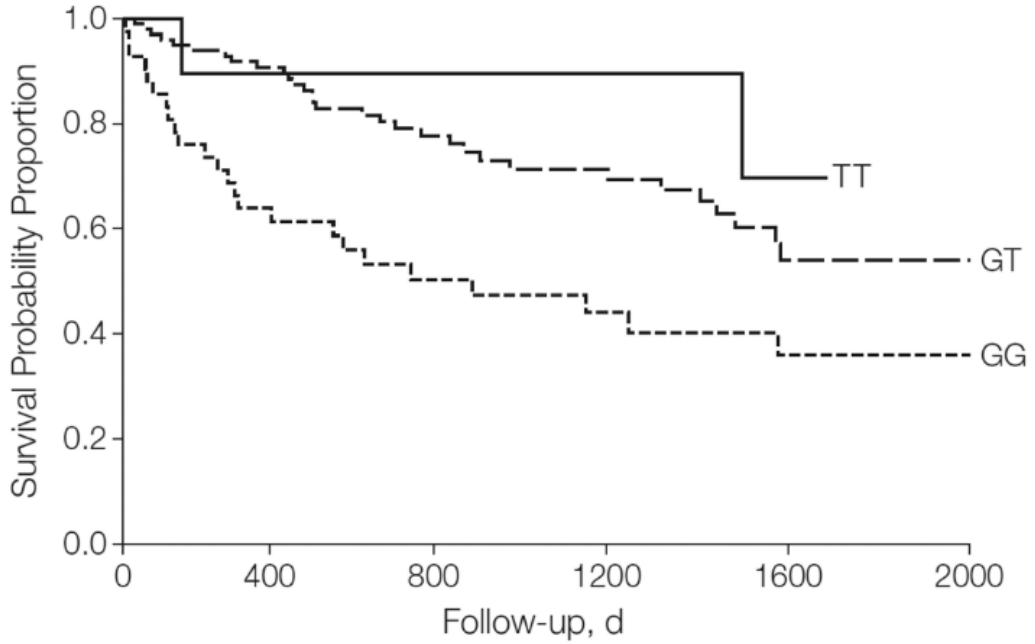
Genetic determinants of pulmonary fibrosis: evolving concepts



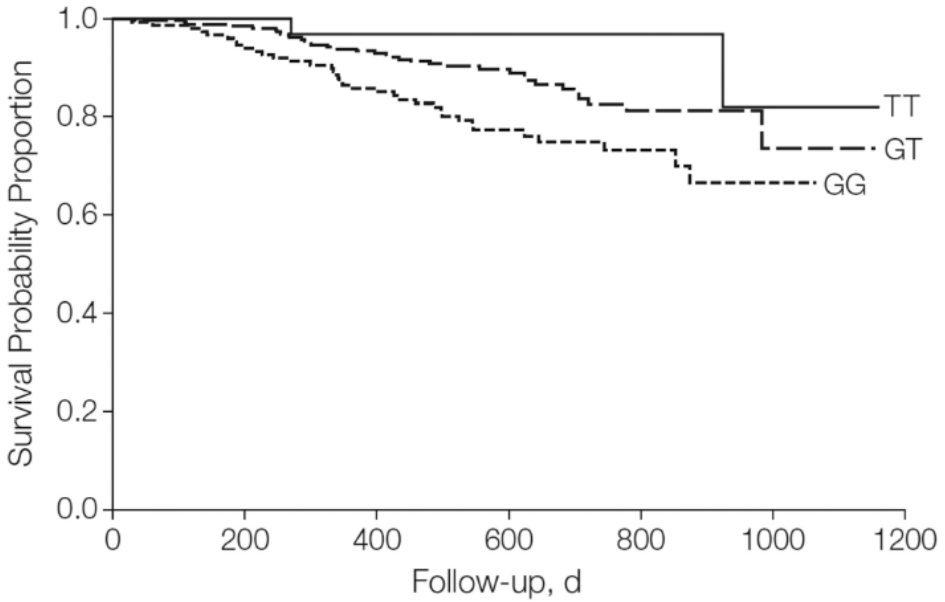
Proposed mechanisms through which abnormal MUC5B might contribute to the development of pulmonary fi brosis

Spagnolo P, Lancet Respir Med. 2014

Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis



No. at risk					
TT	7	4	4	1	0
GT	78	47	35	15	1
GG	24	16	10	7	1



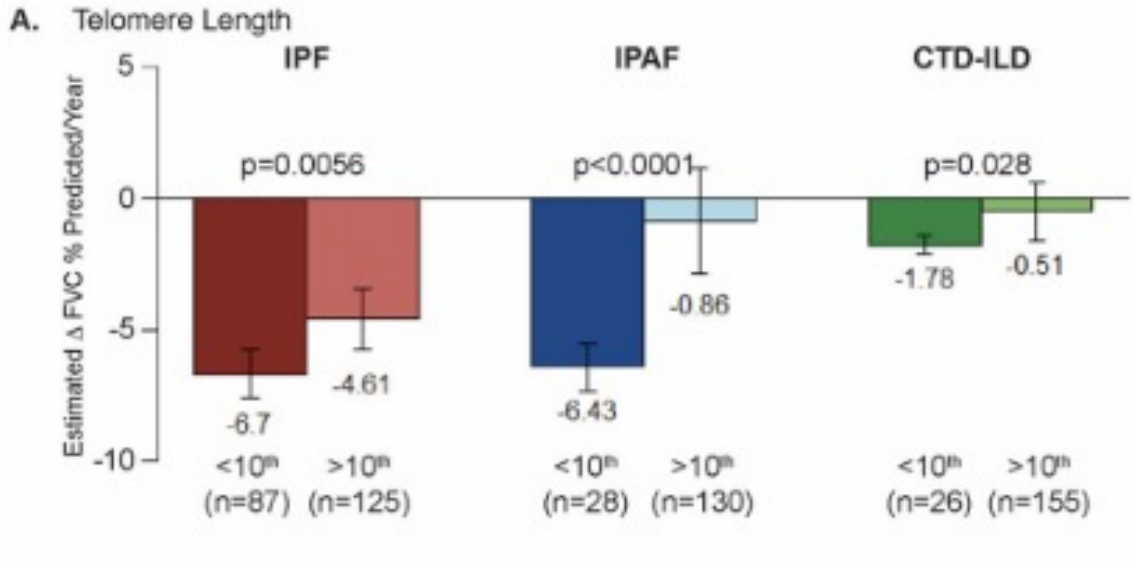
No. at risk						
TT	31	26	21	11	3	0
GT	255	224	122	55	8	0
GG	140	115	67	36	5	0

Peljto AL, JAMA. 2013

Telomere length and genetic variant associations with interstitial lung disease progression and survival

	IPF (N=384)		IPAF (N=199)		CTD-ILD (N=194)	
	HR (95% CI)*	p-value	HR (95% CI)*	p-value	HR (95% CI)*	p-value
Telomere Length, <10th percentile	2.00 (1.50–2.69)	**<0.0001** †	2.63 (1.47–4.69)	**0.0011** †	1.53 (0.74–3.18)	0.25
MUC5B rs35705950, TT/GT	0.45 (0.34–0.61)	**<0.0001** †	1.62 (0.98–2.68)	0.060	1.97 (1.00–3.86)	0.049

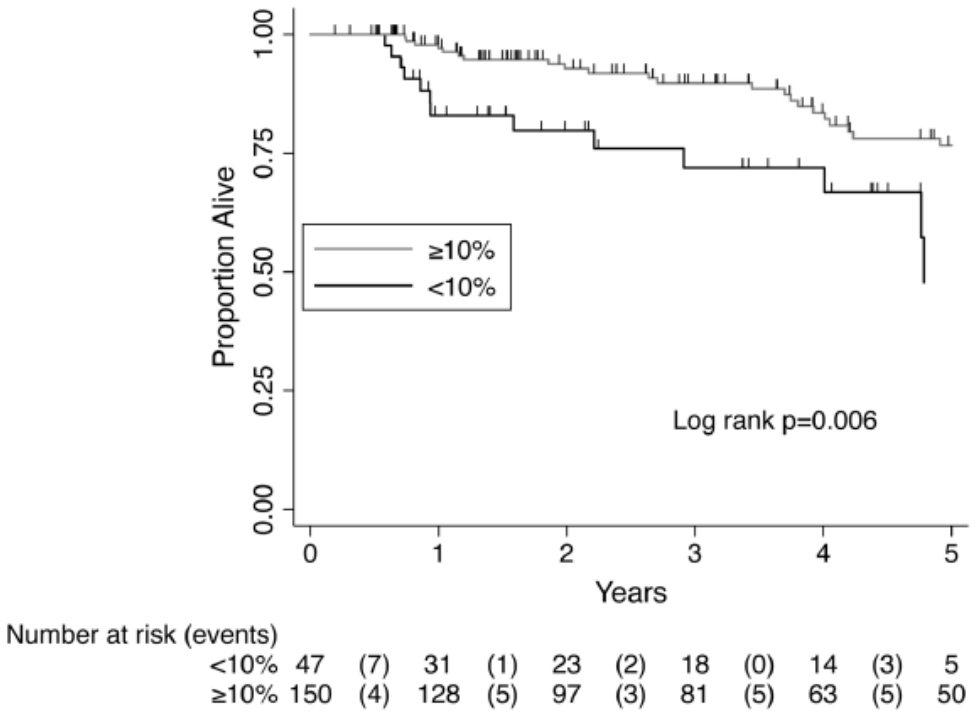
Estimated change of FVC % predicted/ year for patients with IPF, IPAF and CTD-ILD stratified by an age-adjusted blood leukocyte telomere length less than or greater than 10th percentile

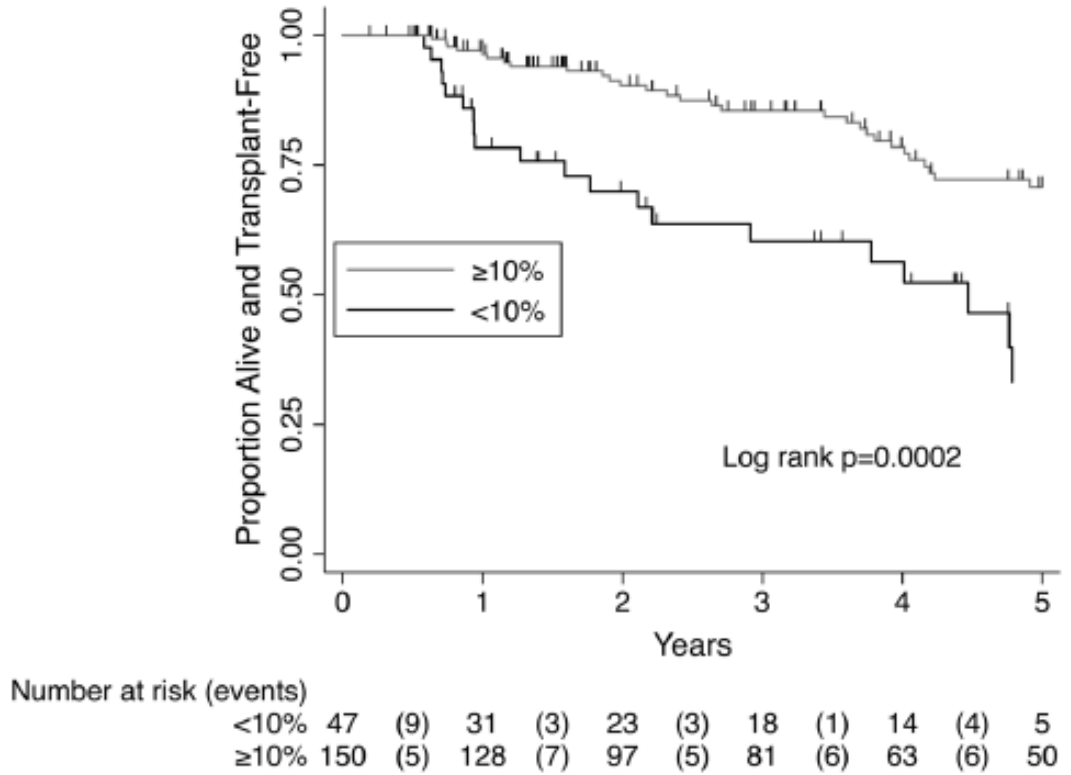


Independent associations of telomere length and the MUC5B rs35705950 single-nucleotide polymorphism for transplant-free survival in patients with Idiopathic Pulmonary Fibrosis (IPF), Interstitial Pneumonia with Autoimmune Features (IPAF), and Connective Tissue Disease-associated Interstitial Lung Disease (CTD-ILD)

Newton CA, Eur Respir J. 2019

The MUC5B promoter polymorphism and telomere length in patients with chronic hypersensitivity pneumonitis

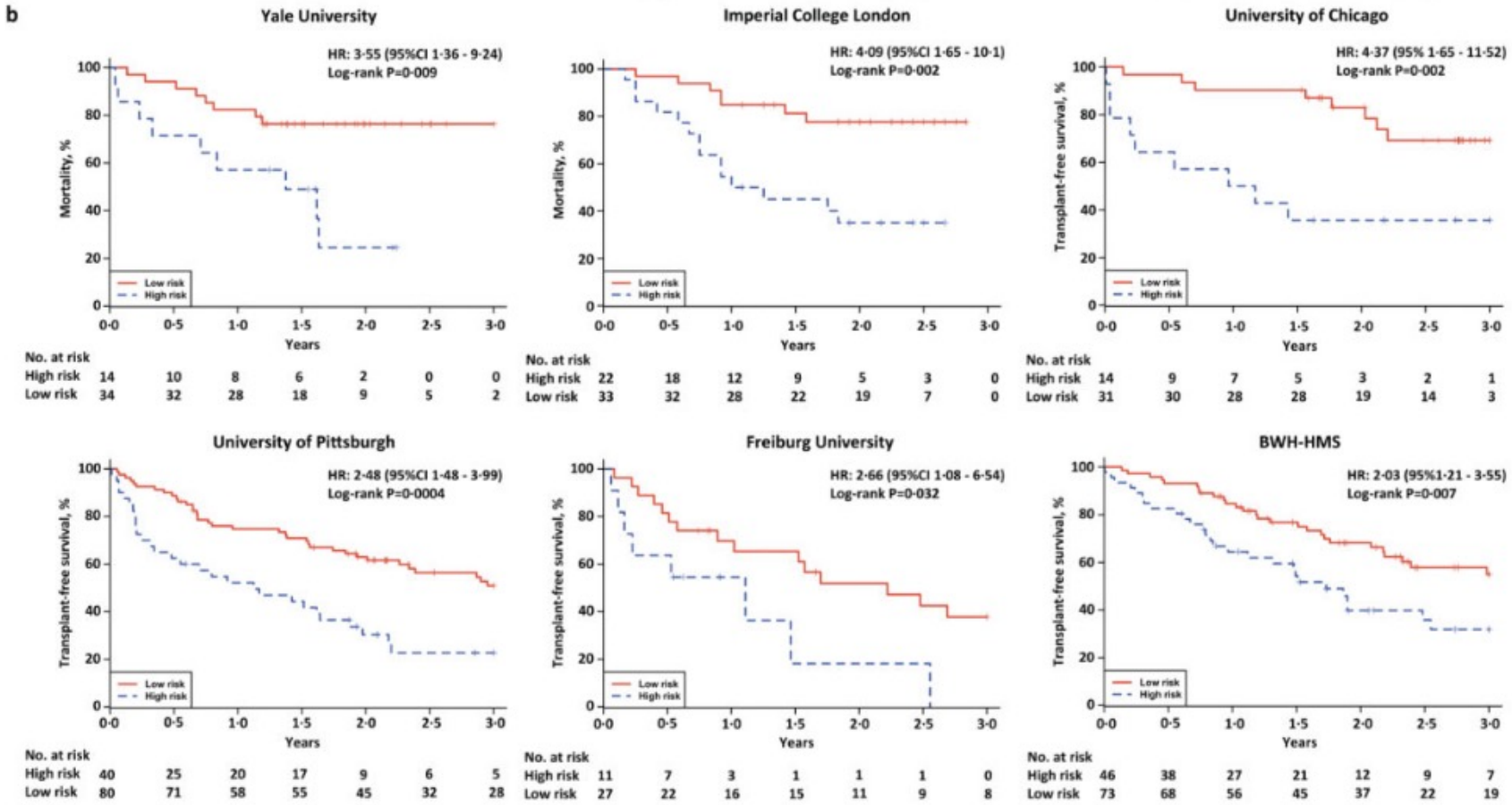




Survival (A) and transplant–free survival (B) in the combined cohort of patients with chronic hypersensitivity pneumonitis with peripheral blood leukocyte telomere less than or greater than the 10th percentile for age

Ley B, Lancet Respir Med. 2017

Validation of a 52-gene risk profile for outcome prediction in patients with idiopathic pulmonary fibrosis: an international, multi-centre, cohort study



Mortality and Transplant-free survival (TFS) differs between high vs low risk profiles based on the 52-gene signature in each independent cohort.

Herazo-Maya JD, Lancet Respir Med. 2017

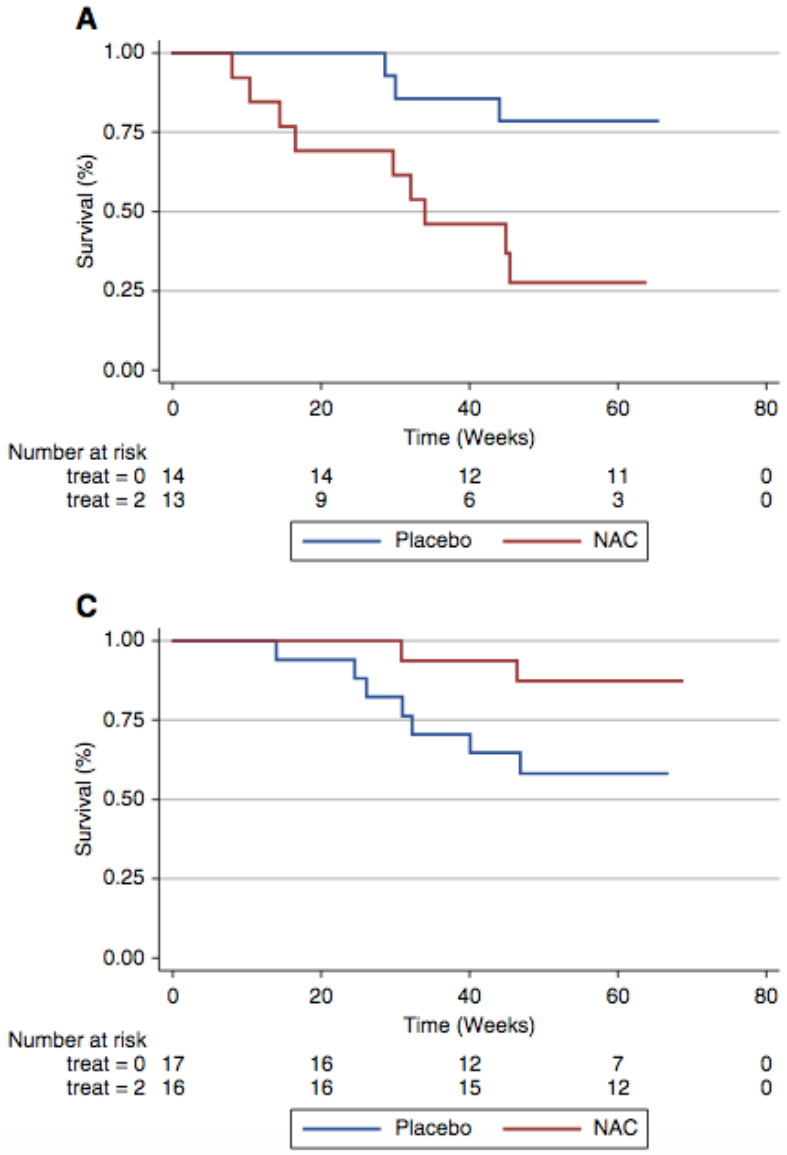
Peripheral Blood Mononuclear Cell Gene Expression Profiles Predict Poor Outcome in Idiopathic Pulmonary Fibrosis

Gene	Gene symbol	Cox score
Phospholipase B domain containing 1	*PLBD1*	3.32
Tyrosylprotein sulfotransferase 1	*TPST1*	3.25
Chromosome 19 open reading frame 59 (mast cell–expressed membrane protein 1)	*C19orf59 (MCEMP1)*	3.13
Interleukin-1 receptor, type II	*IL1R2*	3.05
Haptoglobin	*HP*	2.91
FMS-related tyrosine kinase 3	*FLT3*	2.90
S100 calcium-binding protein A12	*S100A12*	2.89
Lymphocyte-specific protein tyrosine kinase	*LCK*	−2.50
Calcium/calmodulin-dependent protein kinase II8	*CAMK2D*	−2.50
Nucleoporin 43 kD	*NUP43*	−2.51
SLAM family member 7	*SLAMF7*	−2.52
Leucine-rich repeat containing 39	*LRRC39*	−2.52
Inducible T cell costimulator	*ICOS*	−2.53
CD47 molecule	*CD47*	−2.54
Limb bud and heart development	*LBH*	−2.55
SH2 domain containing 1A	*SH2D1A*	−2.55
CCR4-NOT transcription complex, subunit 6–like	*CNOT6L*	−2.56
Methyltransferase-like 8	*METTL8*	−2.56
V-ets erythroblastosis virus E26 oncogene homolog 1	*ETS1*	−2.58
Chromosome 2 open reading frame 27A	*C2orf27A*	−2.60
Purinergic receptor P2Y, G protein–coupled, 10	*P2RY10*	−2.60
T cell receptor–associated transmembrane adaptor 1	*TRAT1*	−2.61
Butyrophilin, subfamily 3, member A1	*BTN3A1*	−2.62
La ribonucleoprotein domain family, member 4	*LARP4*	−2.63
Tandem C2 domains, nuclear	*TC2N*	−2.63
G protein–coupled receptor 183	*GPR183*	−2.65
MORC family CW-type zinc finger 4	*MORC4*	−2.67
Signal transducer and activator of transcription 4	*STAT4*	−2.67
Lysophosphatidic acid receptor 6	*LPAR6*	−2.67
Chromosome 7 open reading frame 58 (cadherin- like and PC-esterase domain containing 1)	*C7orf58 (CPED1)*	−2.68
Dedicator of cytokinesis 10	*DOCK10*	−2.69
Rho GTPase-activating protein 5	*ARHGAP5*	−2.71
Major histocompatibility complex, class II, DPα1	*HLA-DPA1*	−2.72
Baculoviral IAP repeat containing 3	*BIRC3*	−2.73
G protein–coupled receptor 174	*GPR174*	−2.73

Gene	Gene symbol	Cox score
CD28 molecule	*CD28*	−2.73
Utrophin	*UTRN*	−2.76
CD2 molecule	*CD2*	−2.76
Major histocompatibility complex, class II, DPβ1	*HLA-DPB1*	−2.77
ADP-ribosylation factor–like 4C	*ARL4C*	−2.78
Butyrophilin, subfamily 3, member A3	*BTN3A3*	−2.79
Chemokine (C-X-C motif) receptor 6	*CXCR6*	−2.81
Dynein cytoplasmic 2 light intermediate chain 1	*DYNC2LI1*	−2.84
Butyrophilin, subfamily 3, member A2	*BTN3A2*	−2.84
IL-2–inducible T cell kinase	*ITK*	−2.85
Small nucleolar RNA host gene 1	*SNHG1*	−2.94
CD96 molecule	*CD96*	−3.03
Guanylate binding protein 4	*GBP4*	−3.03
Sphingosine-1-phosphate receptor 1	*S1PR1*	−3.06
Nucleosome assembly protein 1–like 2	*NAP1L2*	−3.10
Kruppel-like factor 12	*KLF12*	−3.15
Interleukin-7 receptor	*IL7R*	−3.48

Herazo-Maya JD, Sci Transl Med. 2013

TOLLIP, MUC5B, and the Response to N-Acetylcysteine among Individuals with Idiopathic Pulmonary Fibrosis



PANTHER Cohort

Composite endpoint-free survival between N-acetylcysteine (NAC) and placebo groups after stratification by rs3750920 (TOLLIP) genotype.

A) CC genotype: NAC therapy is associated with worse survival
B) CT genotype: survival is similar between groups
C) TT genotype: NAC therapy is associated with improved survival

Oldham JM, Am J Respir Crit Care Med. 2015

Clinical implications

- Genomic factors impact development and prognosis of pulmonary fibrosis
- Increasing interest in assessing their clinical implications for individuals at risk.
- Need for improved understanding of the underlying patho-biologic pathways
- There are no standardized guidelines that address when to perform genetic testing
- Need to individualize genetic testing based on the specific situation

When to Suspect FPF?

-A detailed family history

-First, second, and more distantly related family members (incomplete penetrance)

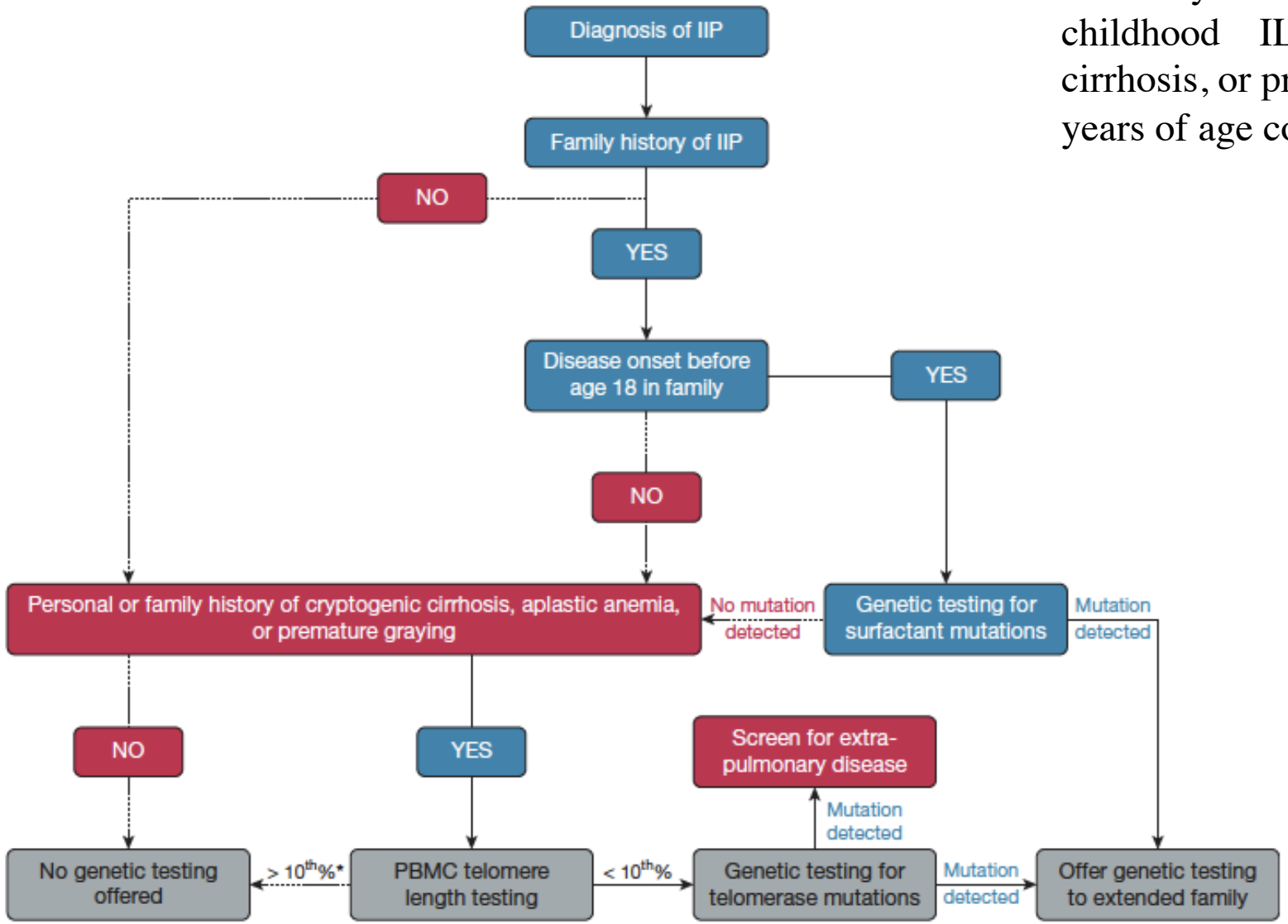
-Personal or family history of bone marrow failure, liver disease (short telomere)

-Personal or family history of early graying of hair (short telomere)

-Genetic anticipation = earlier age of onset in subsequent generations (short telomere)

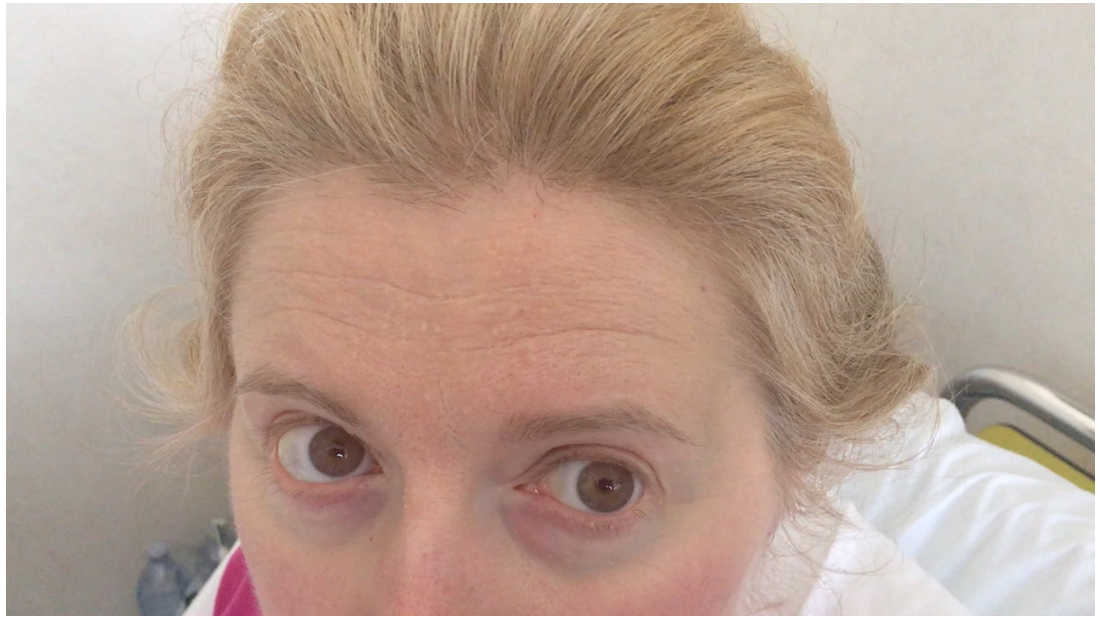
DOI:10.1007/978-3-319-99975-3_8

A family history of neonatal respiratory distress, childhood ILD, aplastic anemia, cryptogenic cirrhosis, or premature graying before 25
years of age could be indicative of short telomeres



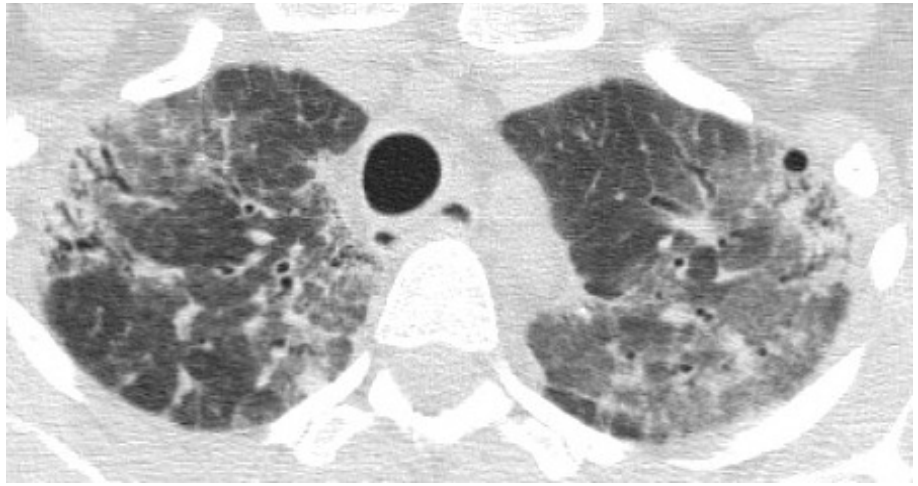
Adegunsoye A, Chest. 2019

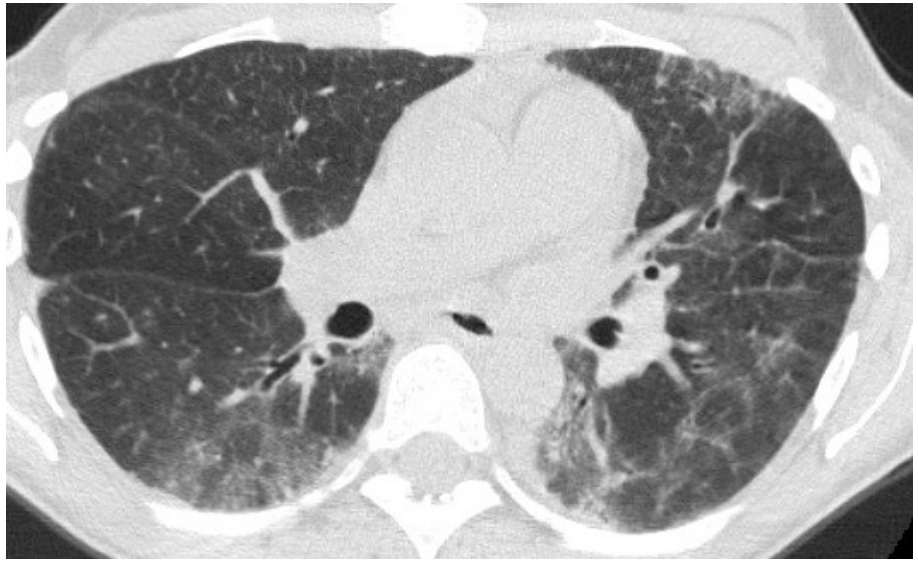
Specific gene polymorphisms may be targeted when chorea and hypothyroidism (NFKX2-1) or Oculo-cutaneous albinism is present (HPS): Hermanski Pudlak



Video – nistagmo + albinismo

HRCT torace





Clinical Testing for FPF

-Clinical evaluation of all first-degree relatives of FPF patients

(baseline PFTs and HRCT for family members > 40 years)

- If the patient is asymptomatic: no additional testing is recommended.

-Avoidance of fibrogenic exposures and regular exercise.

- If cough or exertional dyspnea: serial PFTs instead of serial CT chest scans

-There are no clear guidelines regarding the frequency of testing.

DOI:10.1007/978-3-319-99975-3_8

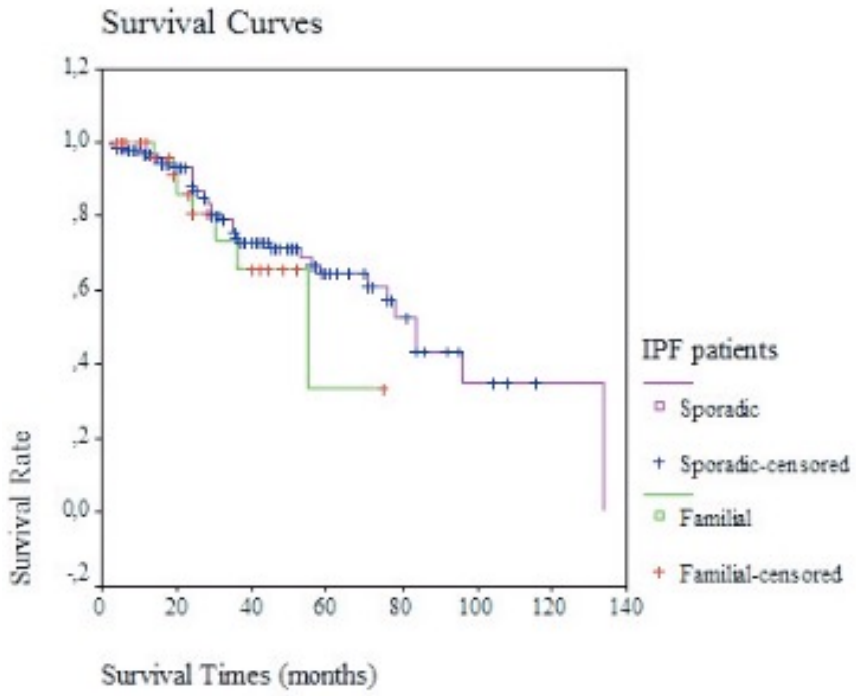
FEATURES AND OUTCOME OF FAMILIAL IDIOPATHIC PULMONARY FIBROSIS

Table 3. Comparison of pulmonary function tests (PFTs) at diagnosis between familial and sporadic groups.

Pulmonary Function Tests at Diagnosis					
LFTs	F-IPF patients with abnormal findings (FVC<80%p, TLCO<80%p, DLCO<80%p, SpO2<90%), N (%)	Mean +/- SD	Non F-IPF patients with abnormal findings, N (%)	Mean +/- SD	P
FVC,% p	12 (40%)	84,20 ± 20,37	65 (52,85%)	78,14 ± 17,29	0,099
TLC,% p	18 (64,3%)	72,64 ± 18,97	62 (78,48%)	70,99 ± 12,36	0,601
DLCO,% p	21 (72,4%)	51,09 ± 18,05	104 (95,41%)	51,51 ± 15,13	0,901
SpO2,%					
at rest	8 (30,8%)	95,85 ± 2,62	0	95,31 ± 1,83	0,25
on exercise	16 (61,5%)	90,54 ± 5,29	43 (55,12%)	88,95 ± 4,43	0,14

Table 2. Age at onset of pair of relatives from different generations with familial IPF.

	First generation (f-IPF)	Second generation (f-IPF)	Significance of difference (p)
Age at diagnosis (years)	74,2	57,8	0,001



Ravaglia C, Sarcoidosis Vasc Diffuse Lung Dis. 2014

Genetic Testing for FPF

Implications regarding prognosis or diagnostic workup.

A syndrome may explain divergent phenotypes in patients or family members.

Test family members when a pathogenic variant is identified in the index case

Genetic counselor (discuss risks, benefits, and costs)

Potential discrimination (transplant, life insurance, etc.)

Patient should understand what results are possible

- pathogenic variant
- likely pathogenic variant
- VUS (= variant uncertain significance) * confusion/frustration?*

DOI:10.1007/978-3-319-99975-3_8

Genetic Testing for FPF

Genetic testing not recommended

-low pretest probability

-the information provided would not change clinical management for the patient or family member.

-common SNPs (e.g. MUC5B or TOLLIP SNPs)

Avoid smoking, minimize environmental fibrogenic exposures, and avoid medications associated with pulmonary fibrosis

Telomere-related mutation carriers: counseled for bone marrow and liver disease

DOI:10.1007/978-3-319-99975-3_8

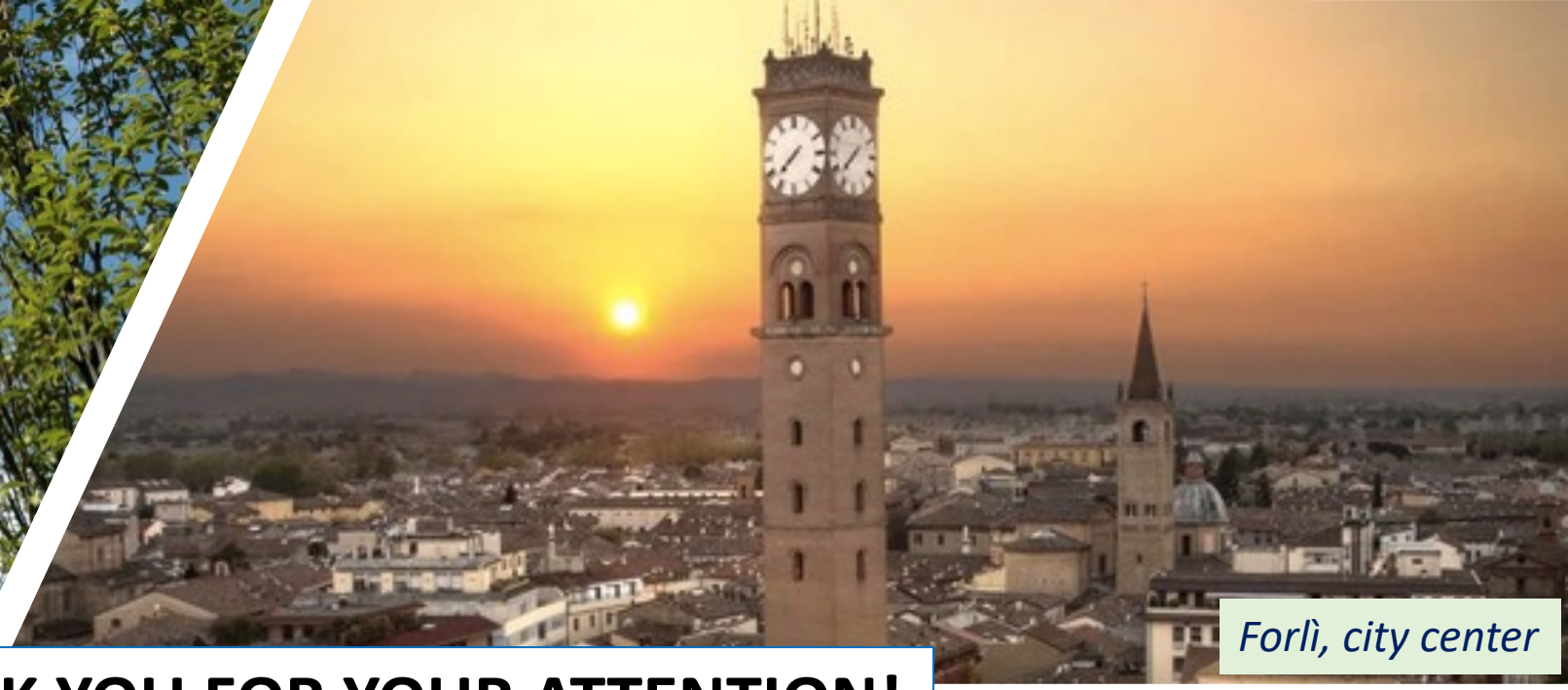
Conclusion

- Genetic factors may impact
  - Development of (idiopathic) pulmonary fibrosis
  - Outcome of (idiopathic) pulmonary fibrosis
  - Response to treatment of (idiopathic) pulmonary fibrosis

- There are no clear guidelines regarding the frequency of testing.

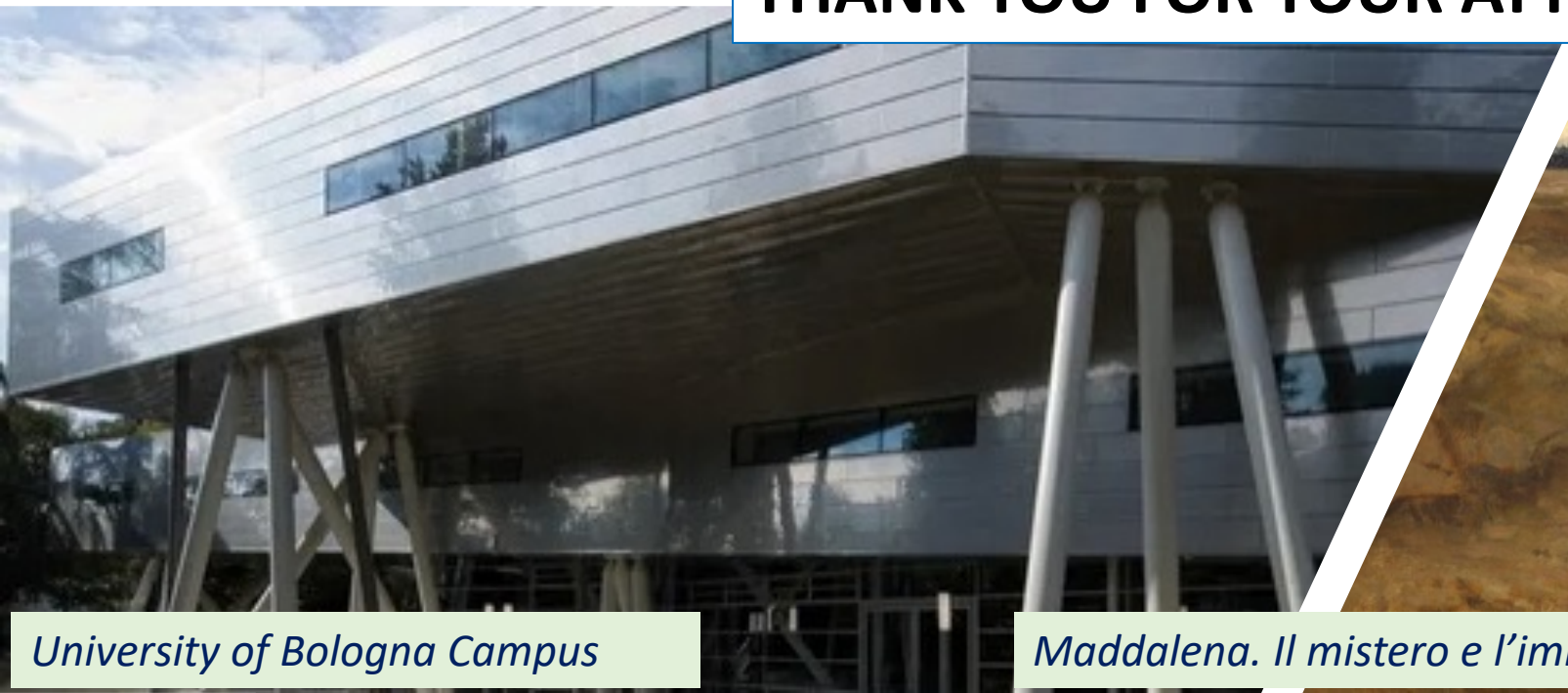
- Clinical studies could be designed stratifying patients for genetic background (outcome and response to treatment may be variable)

GB Morgagni Hospital, Forlì Italy



Forlì, city center

THANK YOU FOR YOUR ATTENTION!



University of Bologna Campus

Maddalena. Il mistero e l'immagine. Dal 27 marzo al 10 luglio 2022. Forlì