

# FIBROSES PULMONAIRES FAMILIALES

---

Pr Raphael Borie  
Service de Pneumologie A  
Hôpital Bichat  
DES de Pneumologie  
Décembre 2022

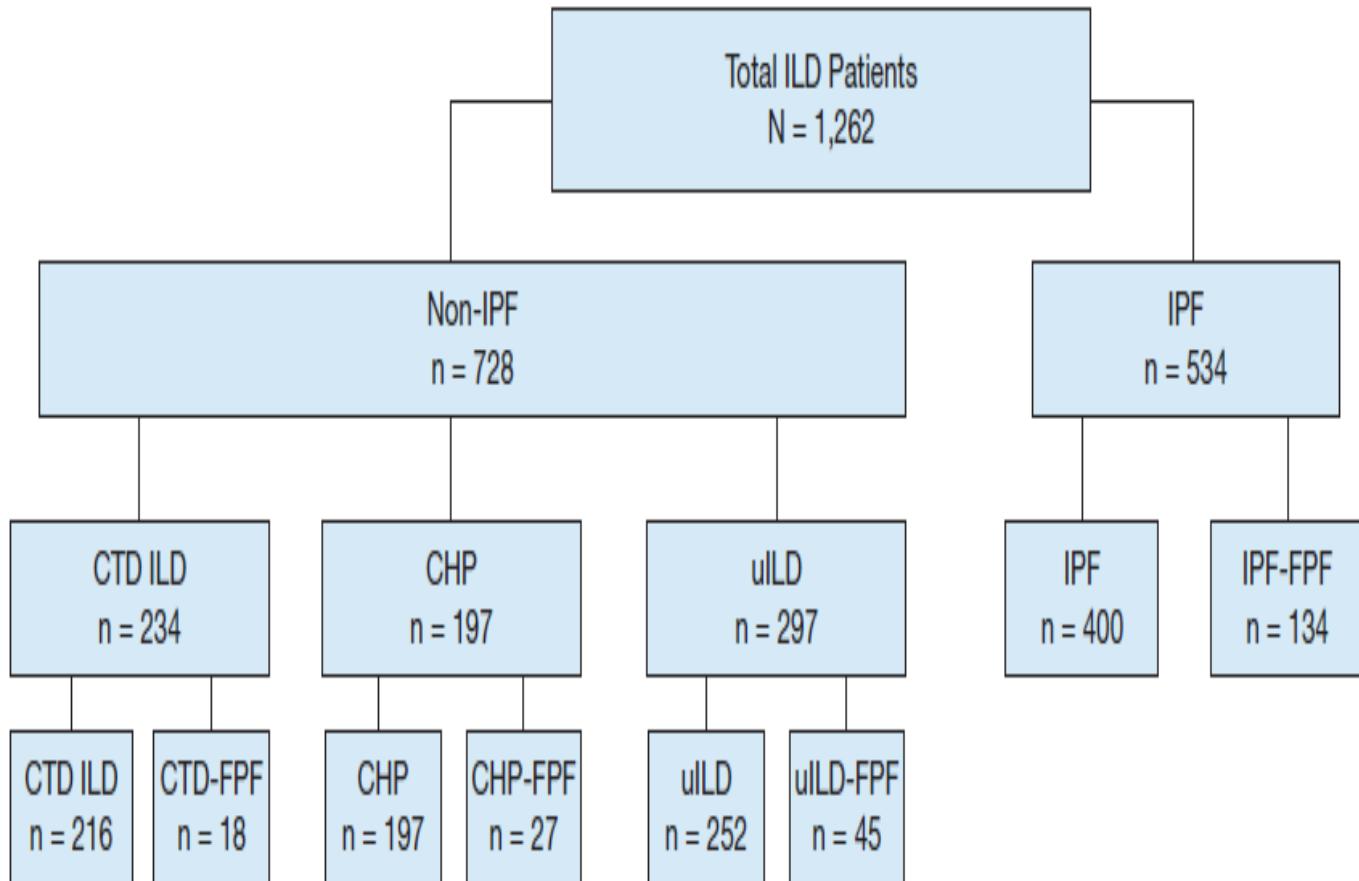
# Conflict of interest disclosure

I have the following real or perceived conflicts of interest that relate to this presentation:

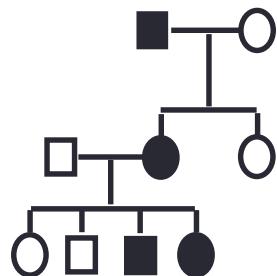
Affiliation / Financial interest	Commercial company
Grants/research support:	Boehringer Ingelheim/Roche
Honoraria or consultation fees:	Boehringer Ingelheim/Roche
Participation in a company sponsored bureau:	SANOFI
Stock shareholder:	
Spouse / partner:	
Other support / potential conflict of interest:	

# Fibrose Pulmonaire Familiale

- Définition consensuelle
  - Au moins 2 membres de la famille
  - 1 ou 2 degrés de parenté
  - Non limitée aux PID idiopathiques...
- Fréquence rapportée variable:
  - 8% dans la cohorte française COFI de FPI
  - 25% dans la FPI?
  - 12,5% PID non-FPI?
- Suggère une prédisposition génétique



# Hétérogénéité des fibroses pulmonaires familiales



	<i>Scanner</i>	<i>Histologique</i>
	Probable (n = 231)	Definite (n = 78)
IPF/UIP	181 (78.4)	67 (85.9)
NSIP	12 (5.2)	8 (10.3)
COP	0	2 (2.6)
Centrilobular nodules	1 (0.4)	0
Unclassified ILD	37 (16.0)	1 (1.3)

## Hétérogénéité dans 45% des familles

## UIP + inclassable (60%)

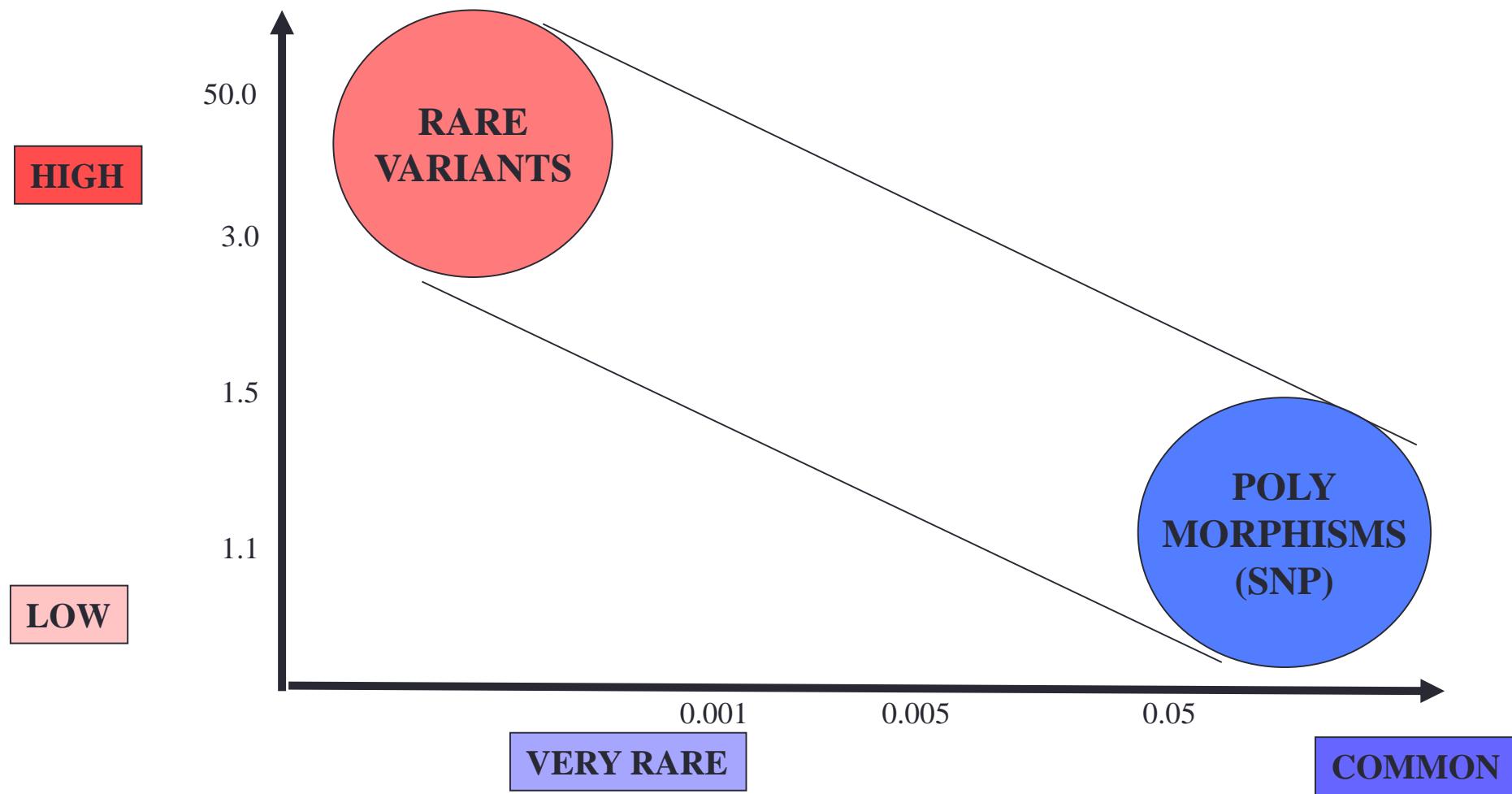
UIP + NSIP (30%)

## **UIP + COP (*très rare*)**

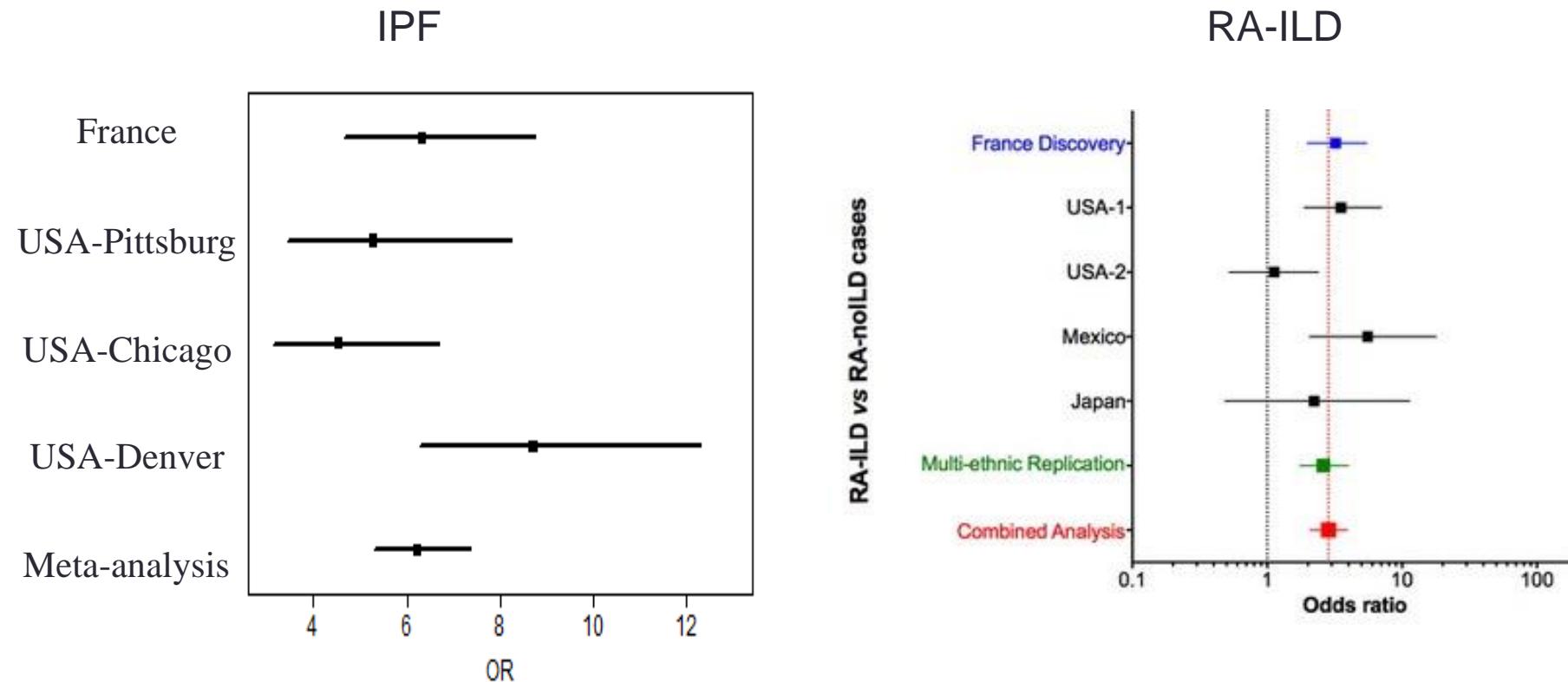
## **UIP + RB-ILD (*très rare*)**

# MENDELIAN DISEASE OR GENETIC RISK FACTOR

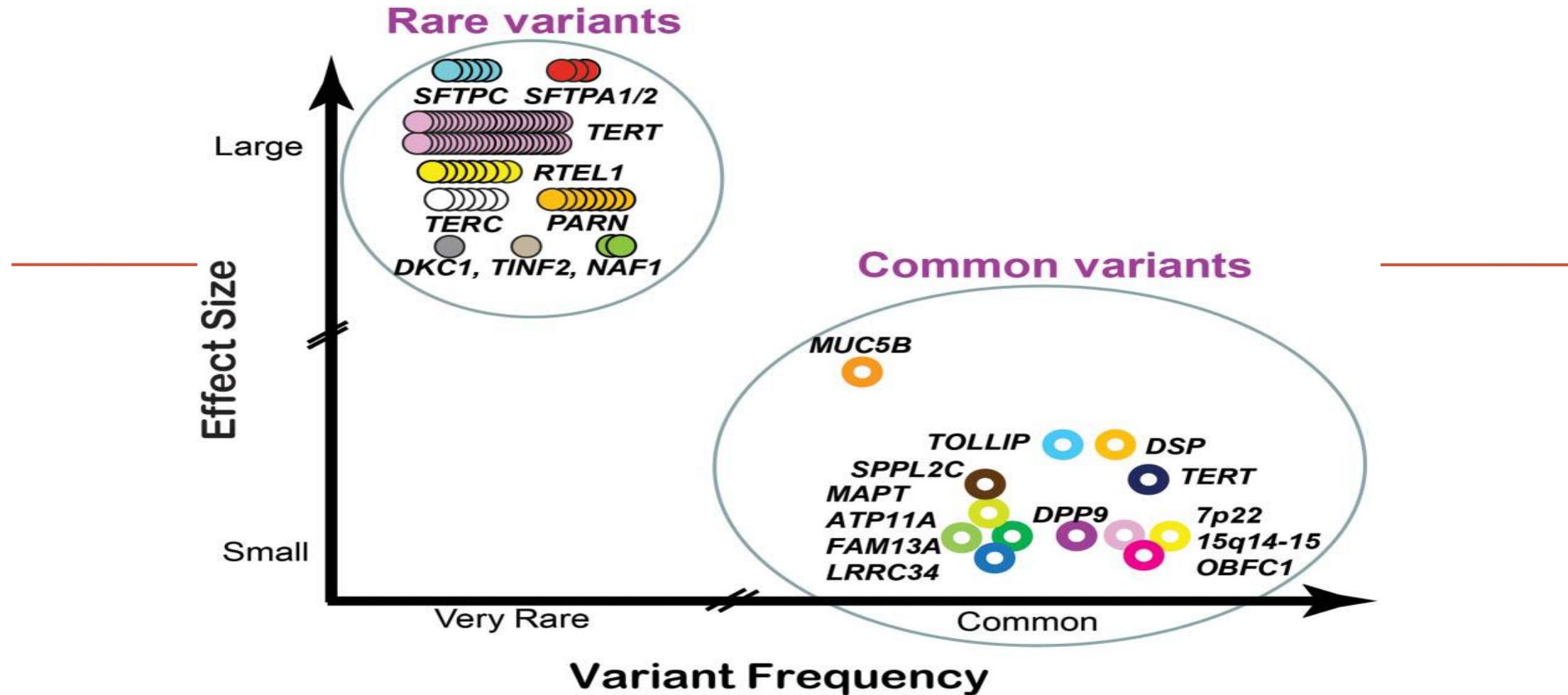
Power of the effect



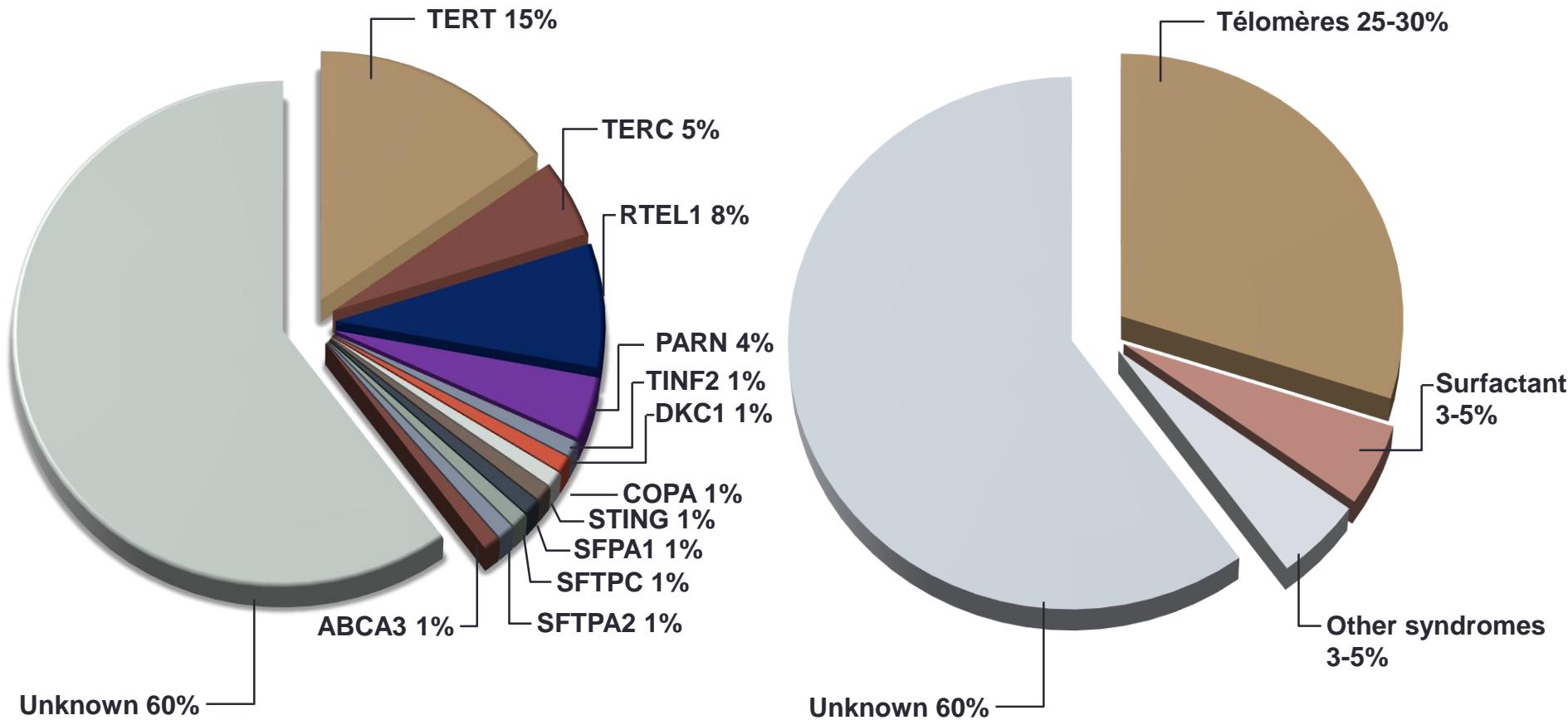
# *MUC5B* augmente le risque de FPI/PIC dans les populations caucasiennes



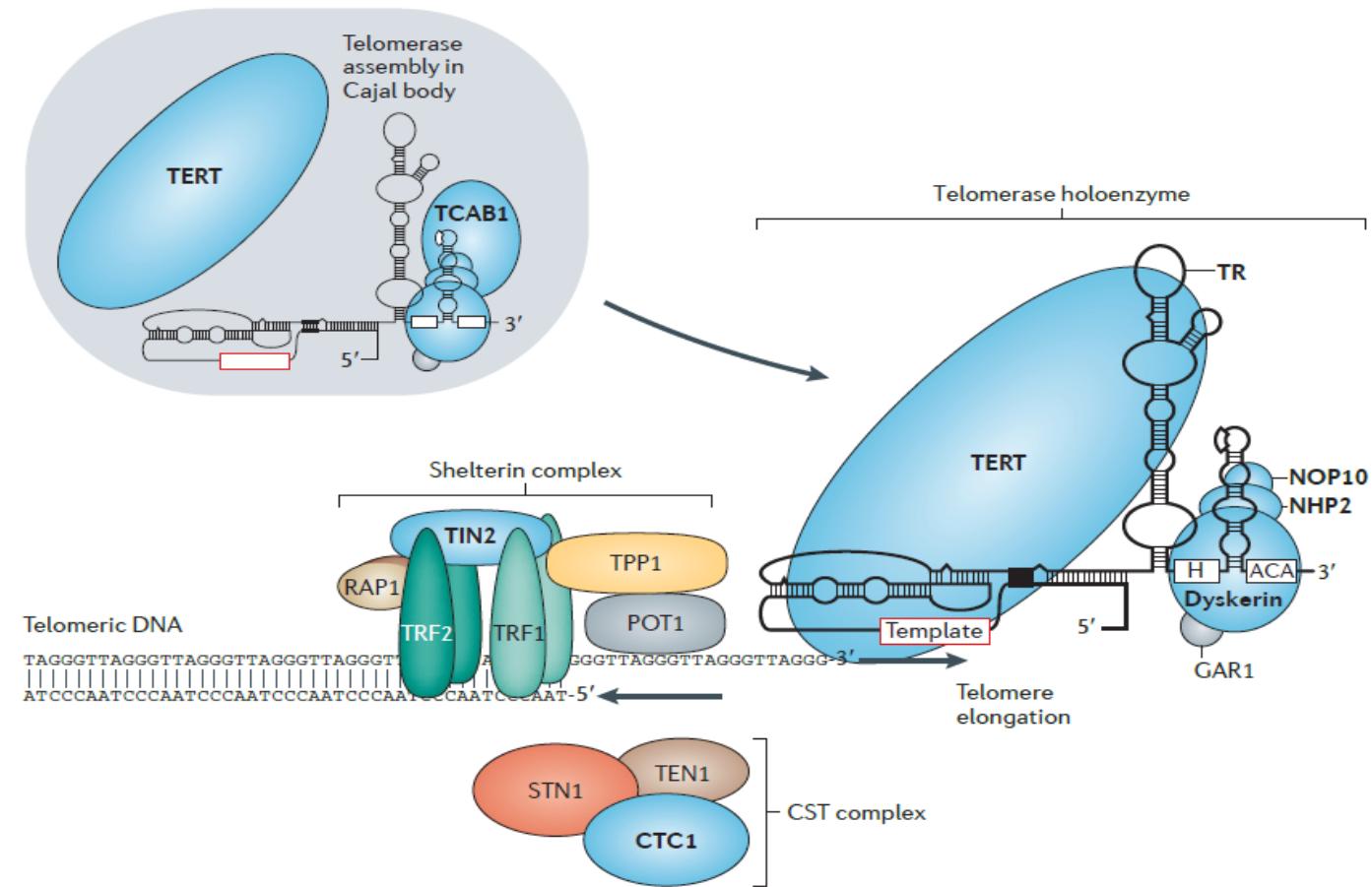
# Maladie mendélienne ou facteur de risque génétique?



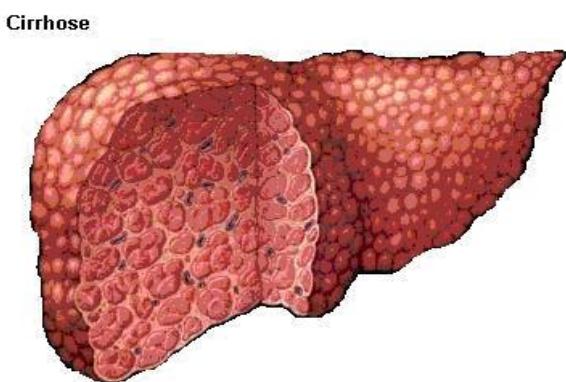
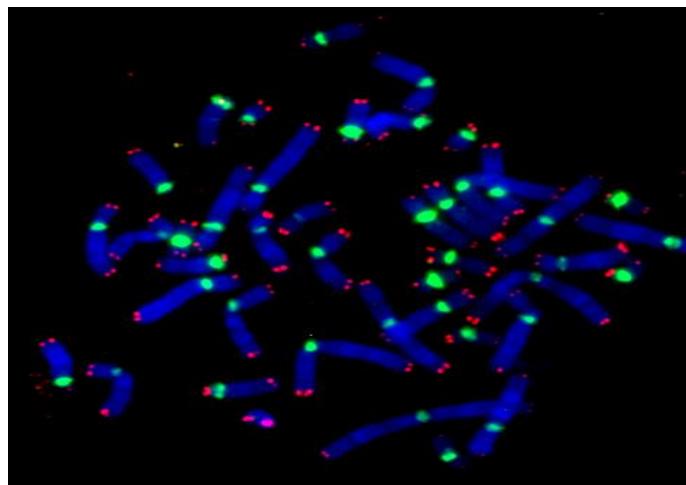
# De très nombreux genes...



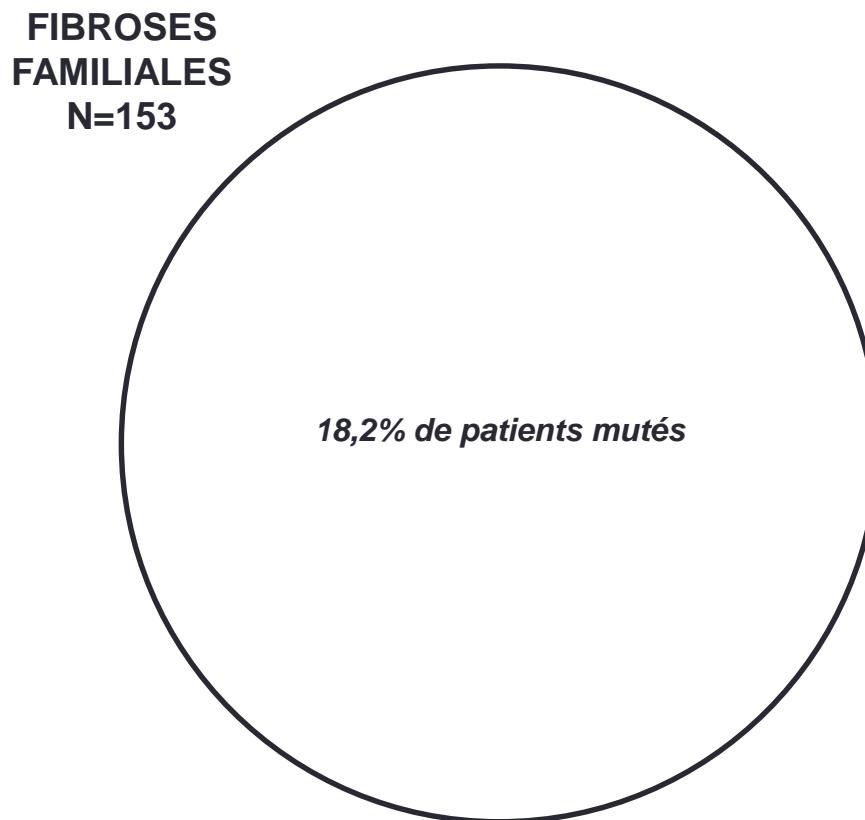
# Le complexe télomérase

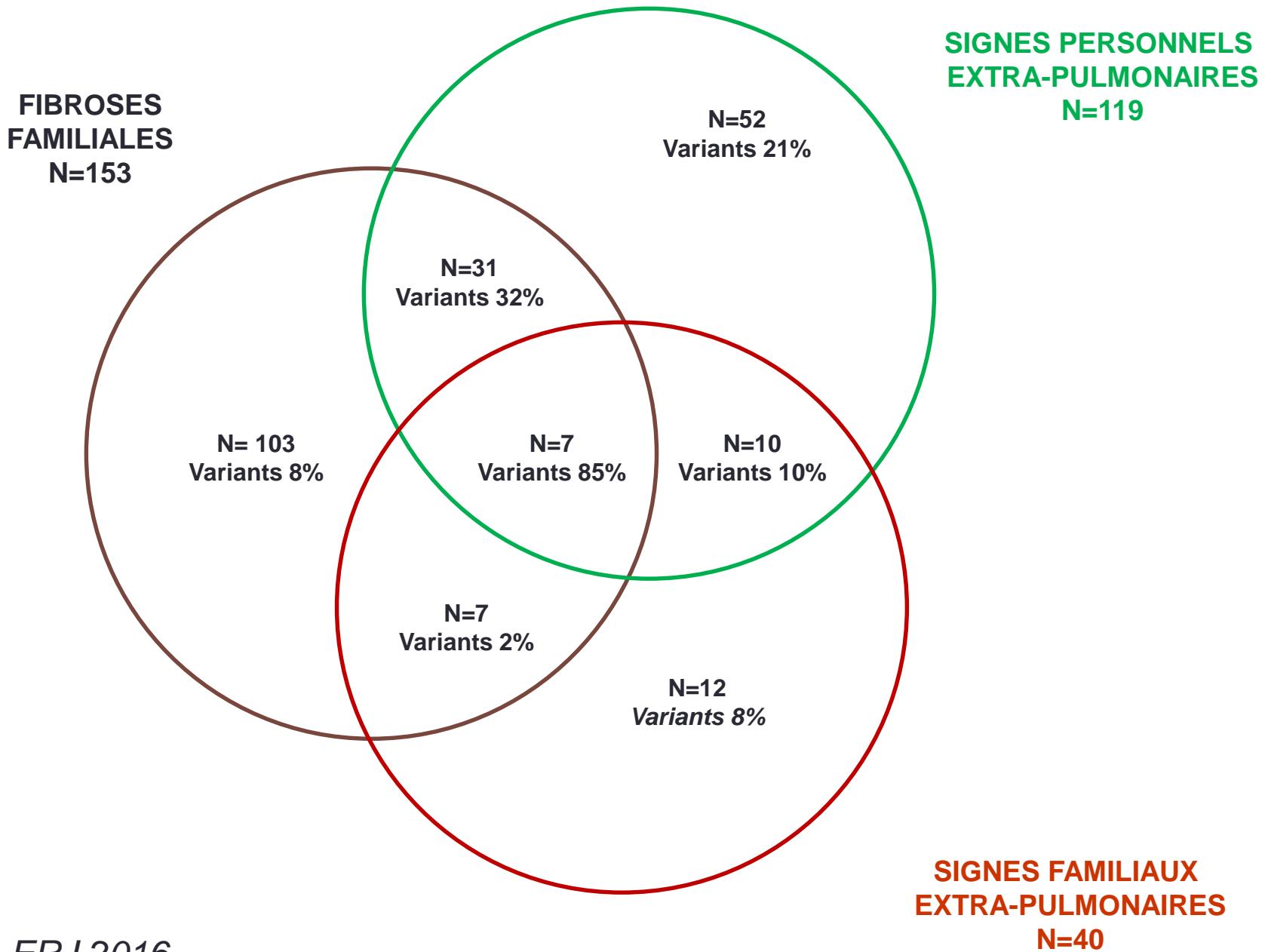


# Telomere related genes

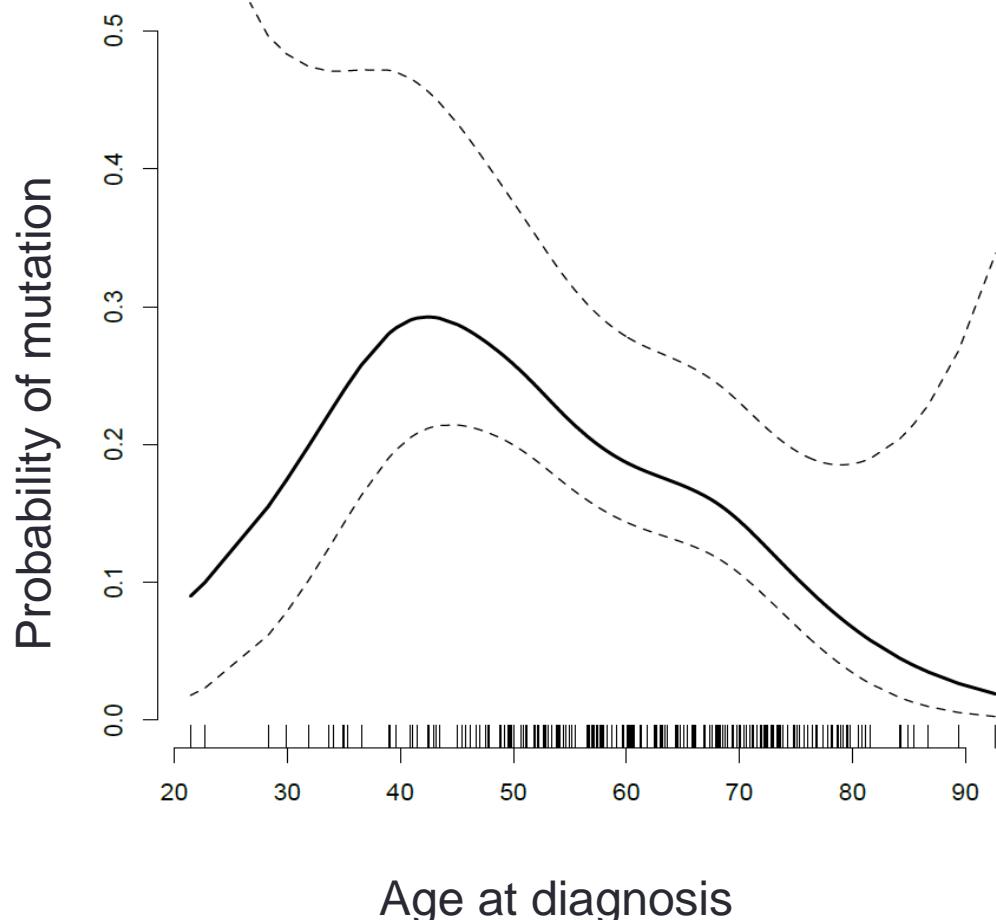


# Prévalence des mutations *TERT/TERC*





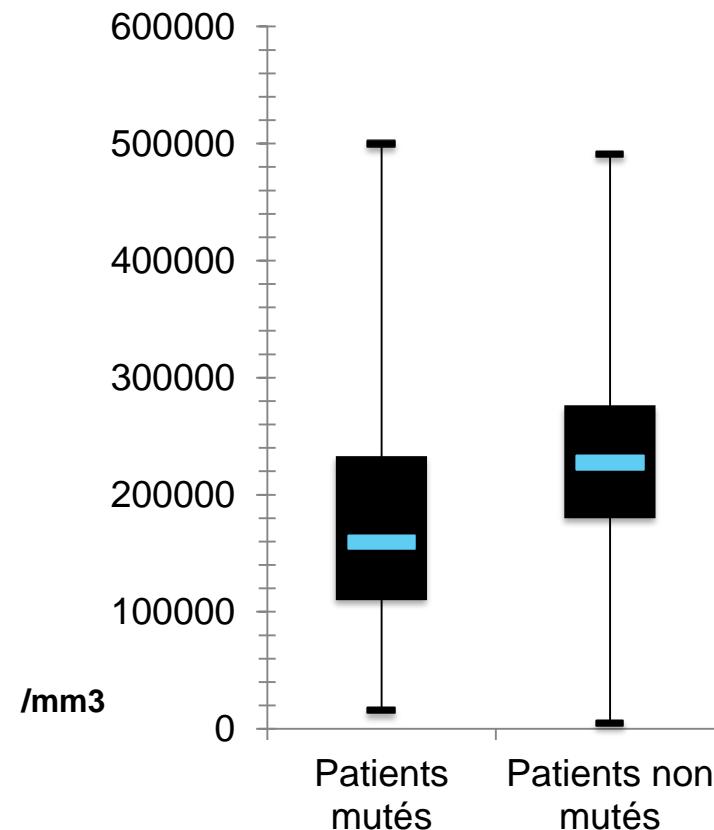
# Probabilité de mutation *TERT/TERC* en fonction de l'âge



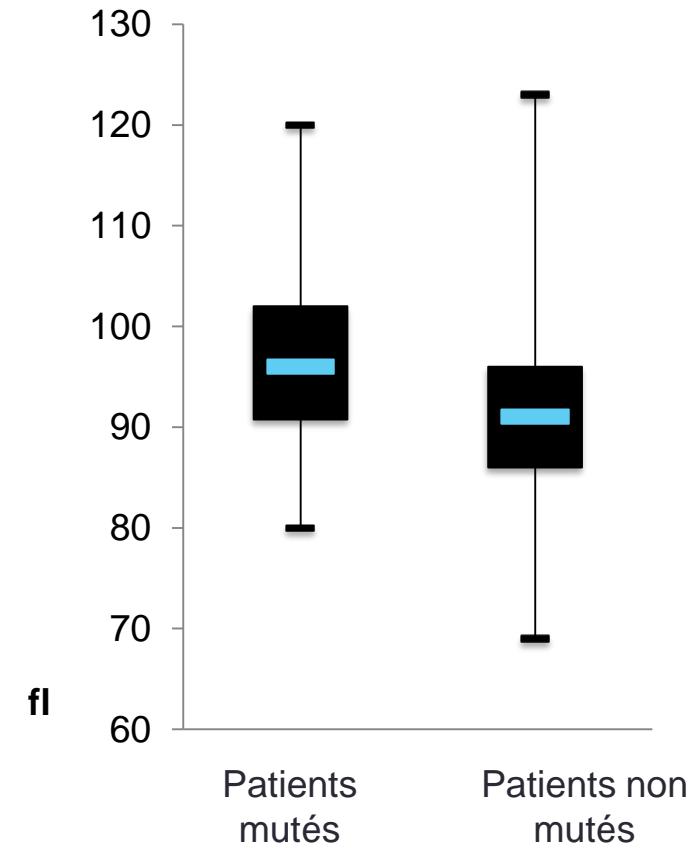
	Transplanted (n = 149)	Non-transplanted (n = 282)
Age at diagnosis (med)	60 (37-74)	70 (39-85)
Male (%)	112 (75%)	194 (67.7%)
Family history	17 (11.4%)	24 (8.5%)
Telomere gene rare variant(%)	36 (24.2%)	33 (11.7%)
TERT	9*	9
TERC	5**	2
RTEL1	12	14
PARN	9	6
NAF1	4	2
ACMG pathogenic or likely pathogenic	20 (13.4%)	11 (3.9%)
Telomere length <10 <sup>th</sup> %	32 (25.2%)	18 (6.8%)

# NFS au diagnostic des patients mutés *TERT/TERC*

Plaquettes

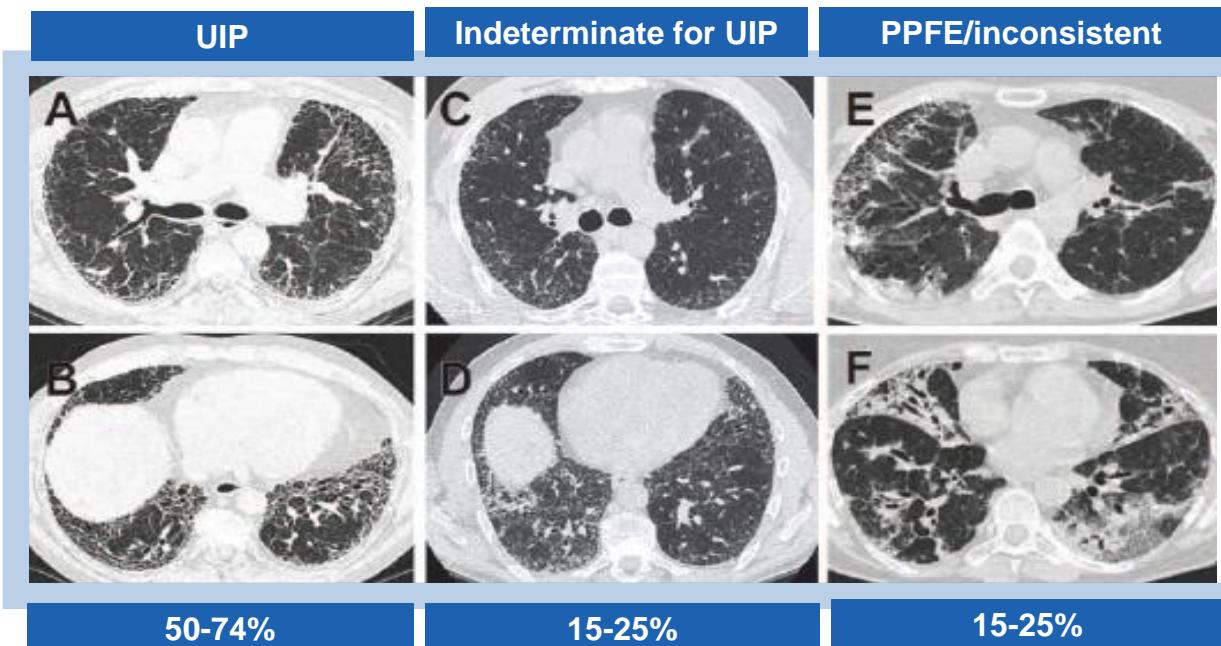


VGM

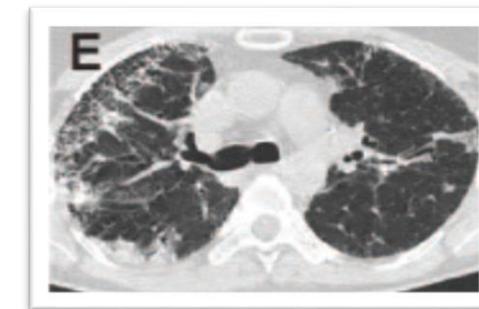


# Le scanner est-il un élément orientant du diagnostic?

Le plus souvent non



En cours d'évaluation



PPFE?



Emphysema Fibrosis

Exceptionnellement oui:  
Phénotypes extrêmes

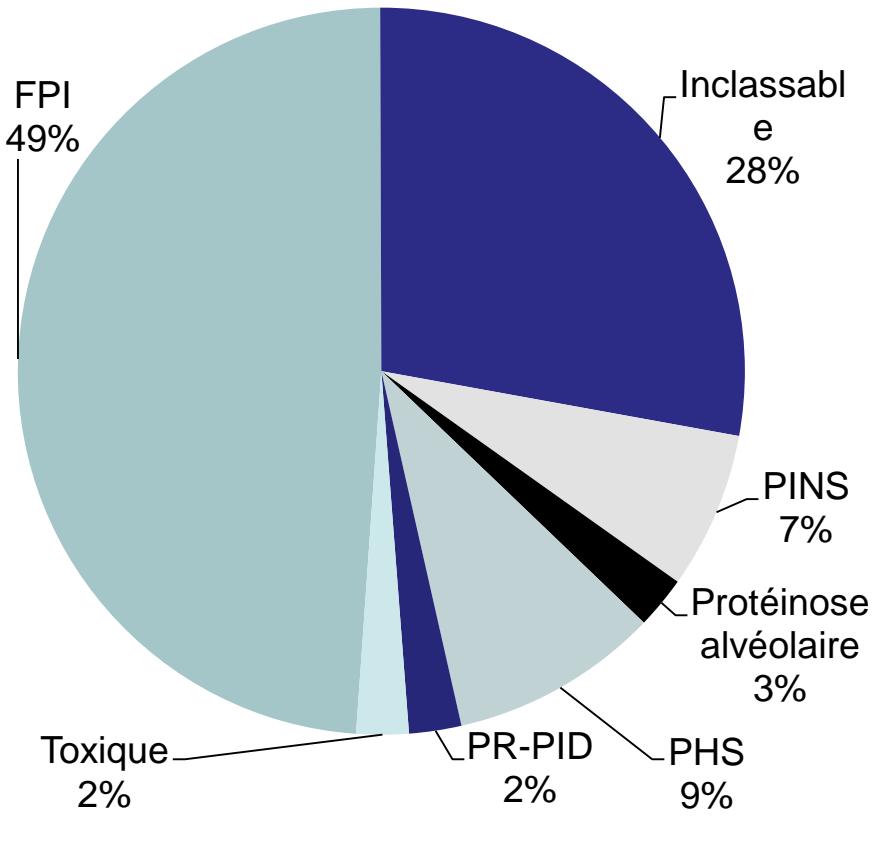


Syndrome  
Hepatopulmonary



Pneumocystose

# Diagnostic pulmonaire



Diagnostic	Nombre
<b>FPI</b>	<b>35 (45,5)</b>
PINS	3 (2,6)
DIP	1 (1,3)
PPFE	8 (10,4)
Inclassable	15 (19,5)
PHS	9 (11,7)
Connectivite-PID	2 (2,6)
IPAF	5 (6,5)

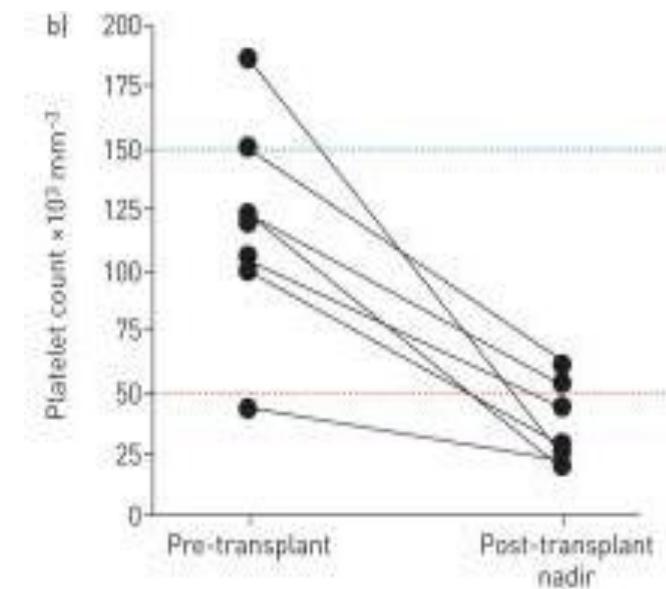
Borie, ERJ, 2016

Newton, ERJ, 2016

# GENES/ENVIRONNEMENT INTERACTION

Lung	N	Smoking	Lung toxic
Diaz de Leon	53	63%	71%
French cohort	43	52%	32%

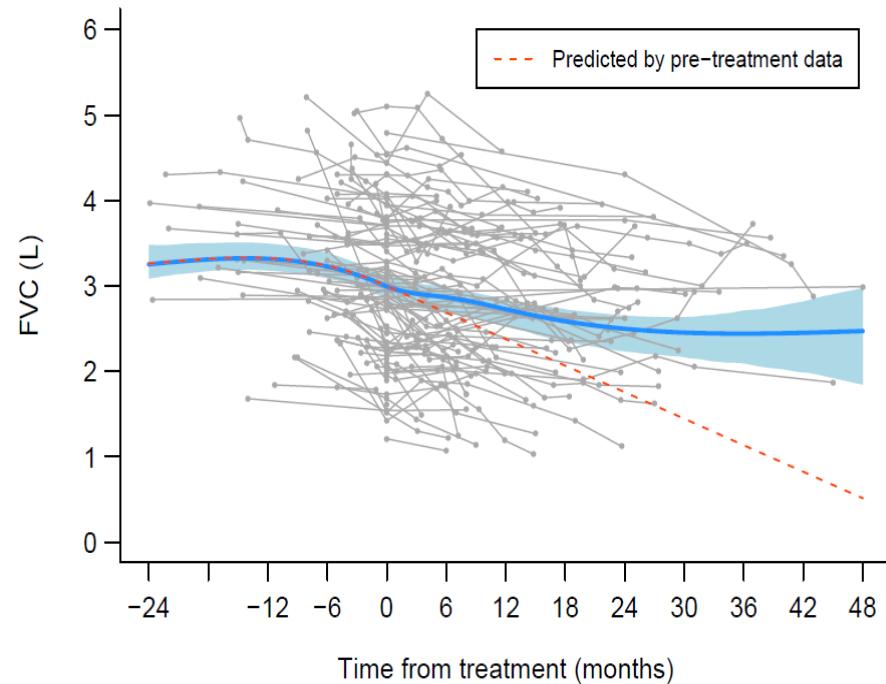
- Liver:
  - Increased risk death in patients with cirrhosis and TRG if alcohol or viral infection
- Blood
  - Hematological complications after lung transplantation and use of cytotoxic drugs



Diaz de Leon, P One, 2010; Calado, Hepatology, 2011;  
Silhan, ERJ, 2010; Borie, ERJ, 2016

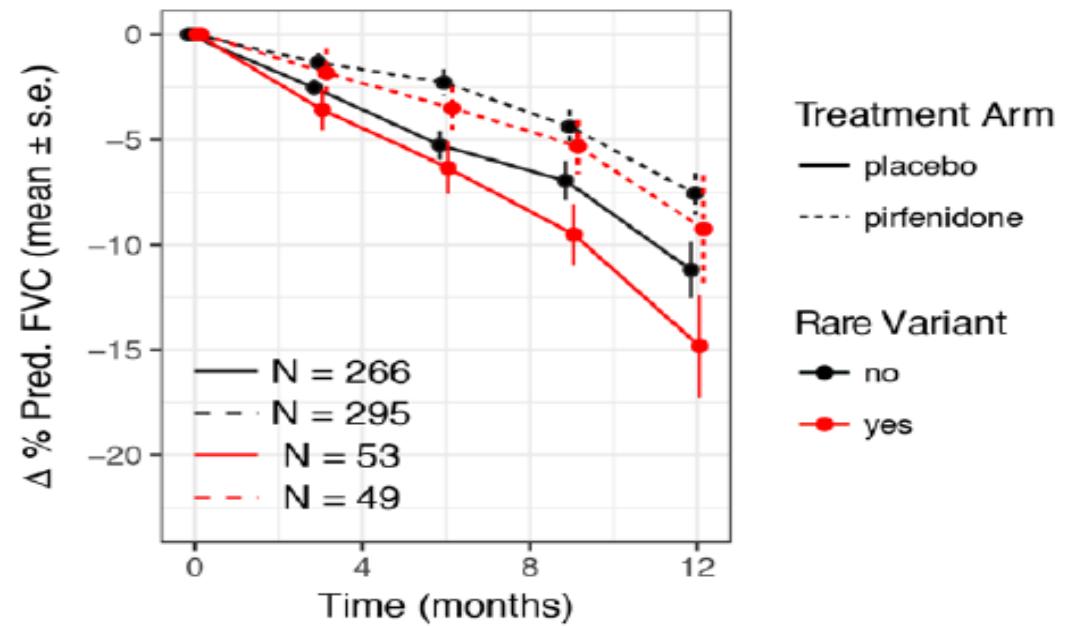
# Les traitements antifibrosant ne sont pas plus toxiques et ont probablement une efficacité comparable

Etude retrospective européenne  
nintedanib or pirfenidone



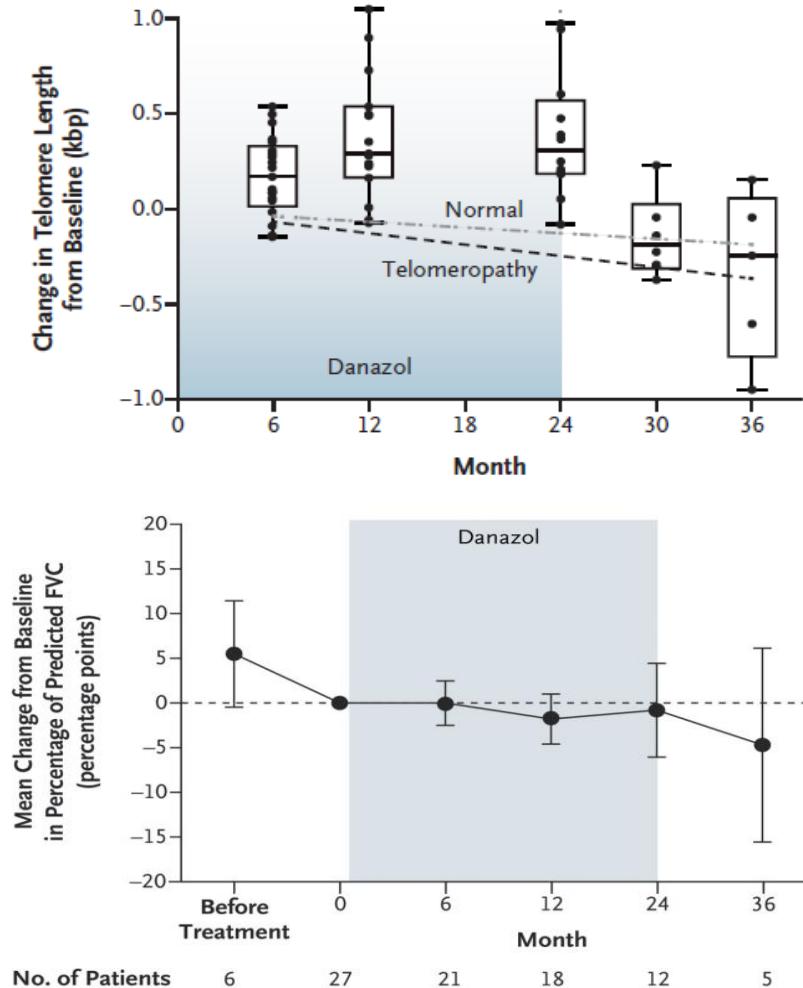
Justet, ERJ, 2020

Analyse post-hoc analysis des essais de phase 3  
pirfenidone



Dressen, Lanc Res Med, 2018

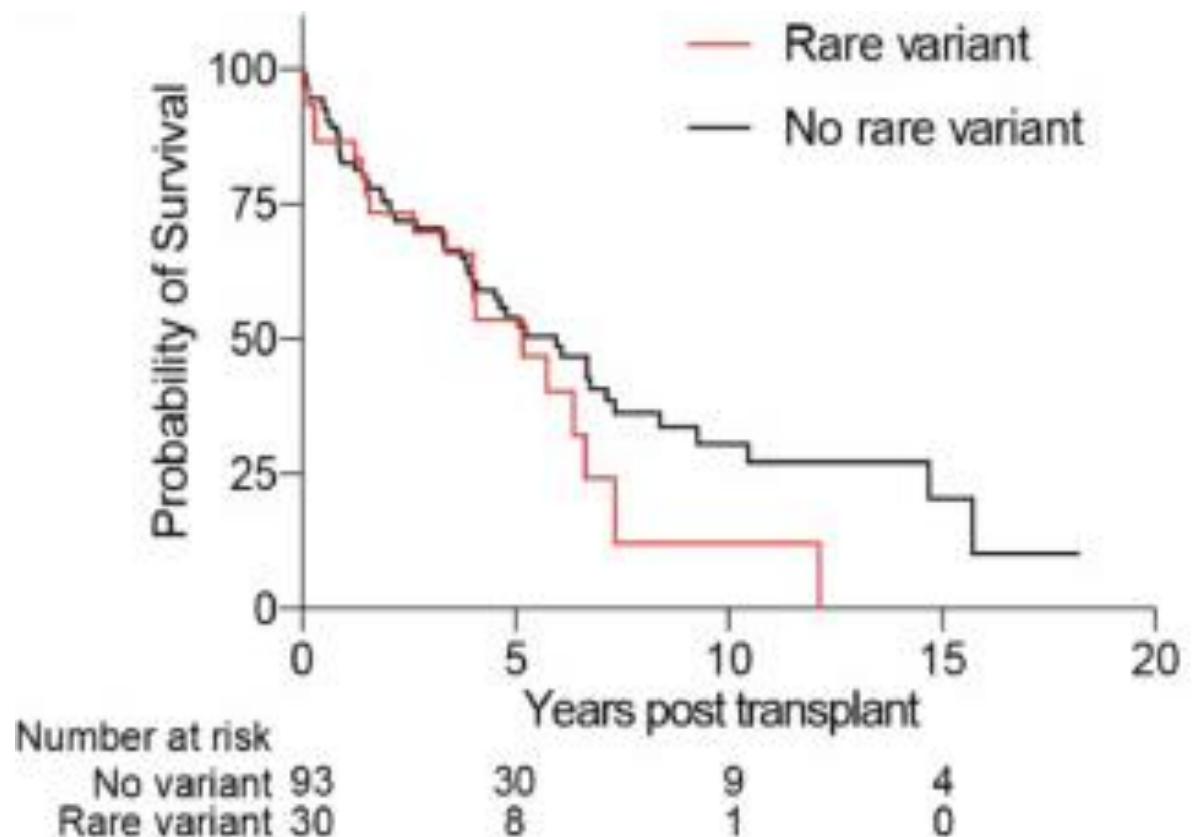
# Traitements ciblés: danazol, une lueur d'espérance?



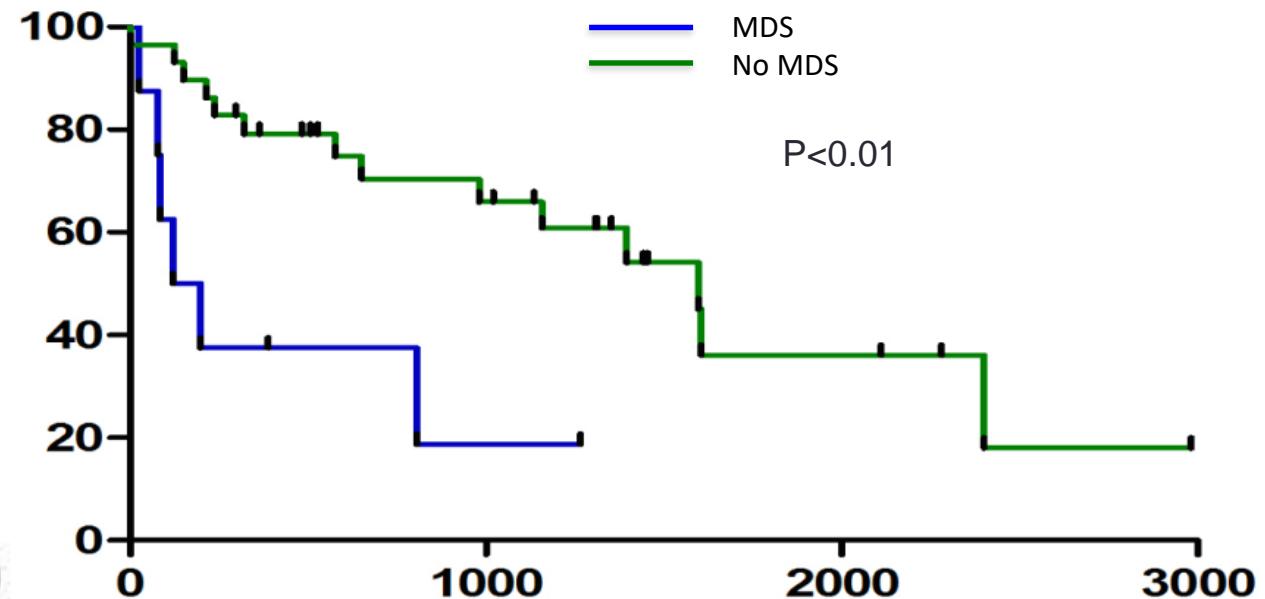
Phase 2:  
ANDROTELO study  
Inclusion

N	25
Age	62.5 y [36.5-80.5]
Men/women	16/9
FVC (L)	2.4 [1.4-9.1]
FVC (%)	69 [40-120]
DLCO (%)	44 [29-84]
TRG	
<i>TERT</i>	12
<i>TERC</i>	5
<i>PARN</i>	2
<i>RTEL1</i>	6

# Les Mutations des TRG ne modifient pas la survie après transplantation pulmonaire



Alder, *jhlt*, 2022



Phillips, *Am J Transplant*, 2022

# Genetic counselling for relatives?

## Lung

- One case stable for >20y
- Frequent asymptomatic ILD
  - Mean DLCO 77%
  - ILD on CT up to 70%

## Hematology

- Mean MCV  $97\mu\text{m}^3$
- Platelets 209 G/L

## Skin

- White hair before 30y/o in 40% of carriers

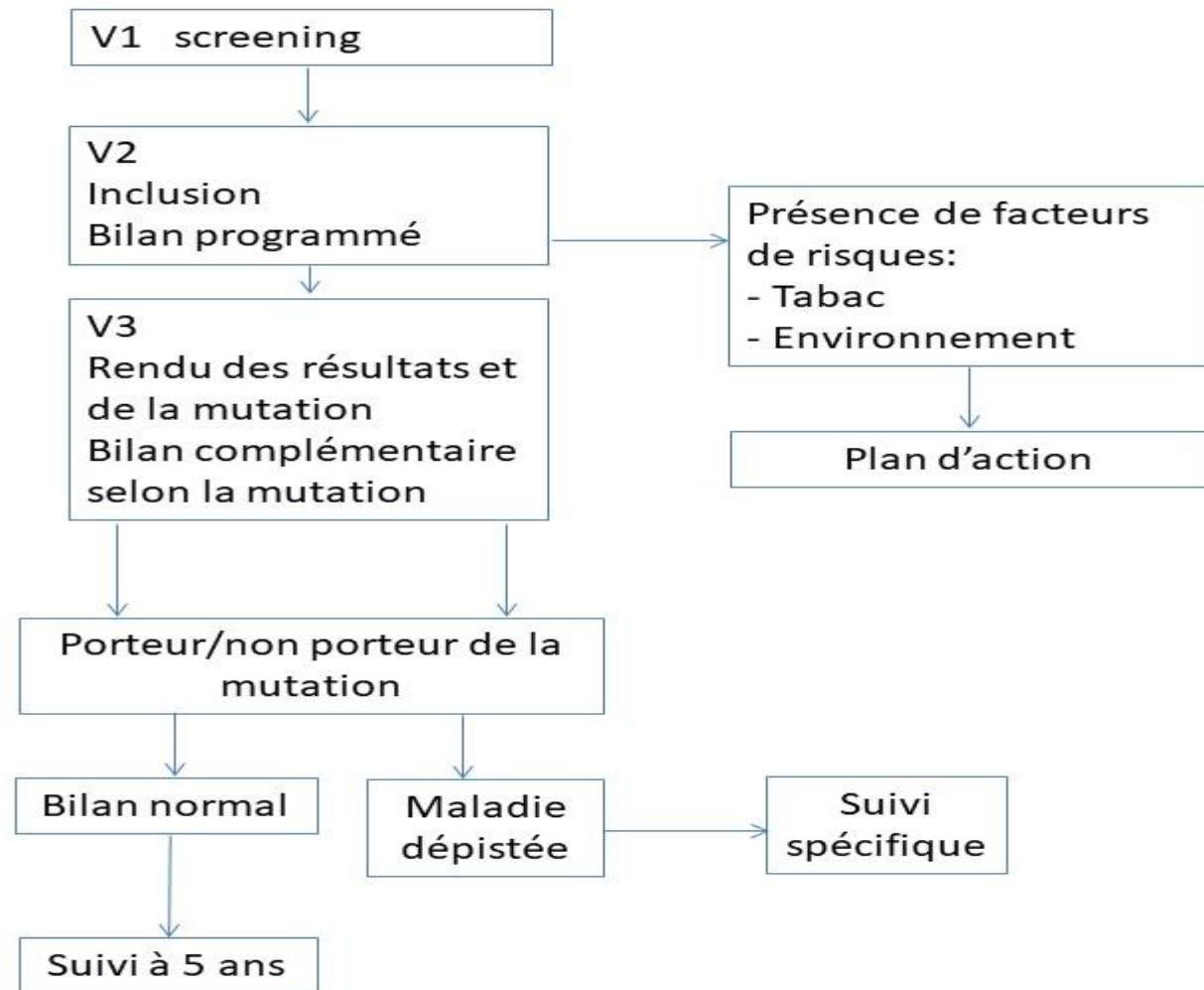
## Psychological support

COHORTE FIFA



# Diagramme de suivi des apparentés

- **RADICO-FIFA:**
- Examen clinique
- Bilan biologique
- EFR
- Echographie abdominale
- **Indication du TDM thoracique**
- - symptômes, examens cliniques anormaux, ou,
- - après 40 ans, ou,
- - dans les 10 ans avant l'âge de survenue de la PID chez le cas index

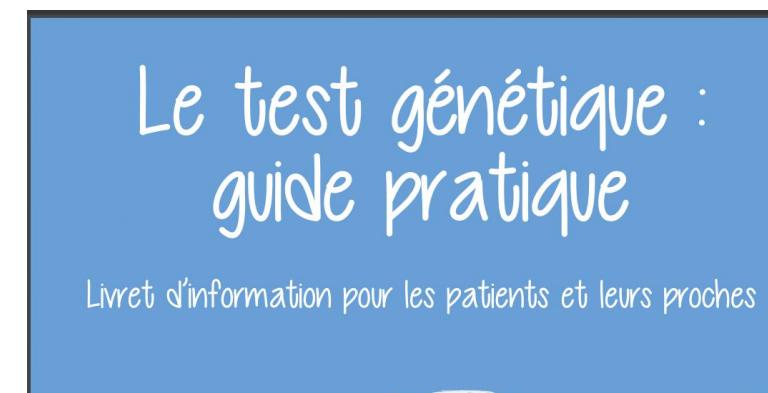


# Impact du conseil génétique

- Modification des expositions à risques?
- Impact psychologique?
  - 90 apparentés de fibrose pulmonaire familiale
    - 58% aucun regret
    - 33% ont de légères regrets
    - 9% ont des regrets modérés
- Des traitements préventifs?

# Des outils pour les patients et leurs familles

- PNDS (site HAS)
- Livrets (site respifil)



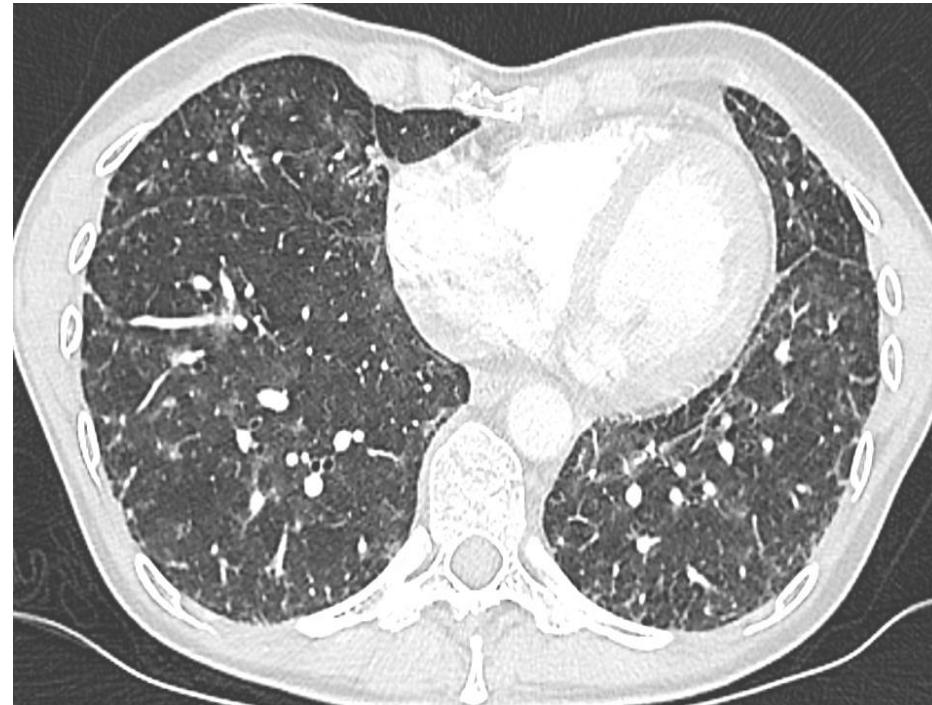
Pneumopathies interstitielles diffuses (PID)

Maladies du surfactant pulmonaire et transmission génétique

Centre de Référence  
des maladies pulmonaires rares  
(OrphaLung)

# Phénotypes pulmonaires variables

- Femme de 47 ans
- Fibrose pulmonaire connue depuis 6 mois
- Thrombopénie connue depuis 25 ans 130 G/L
- Aggravation respiratoire rapide

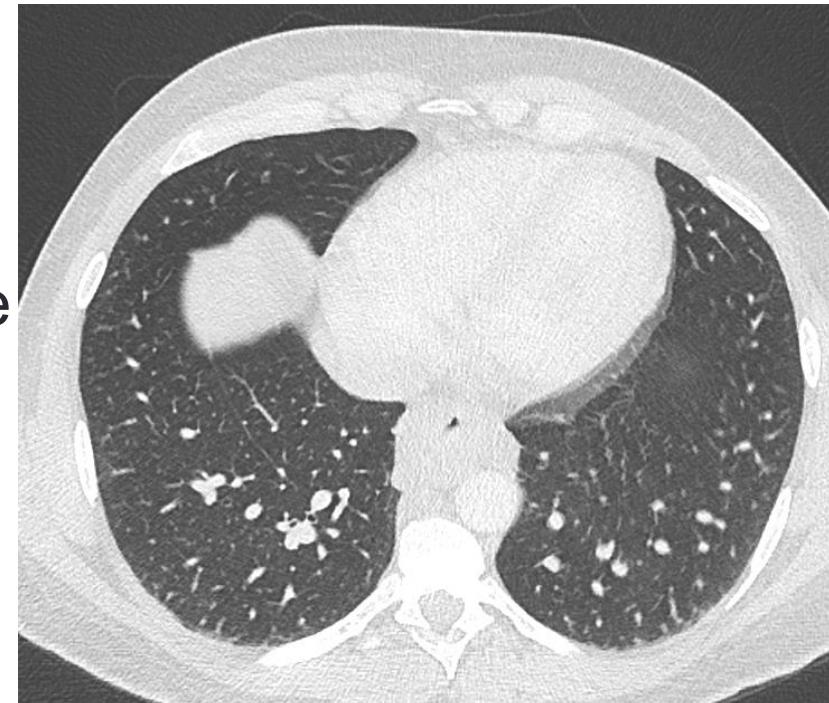


# Diagnostic et prise en charge?

- Indication à un diagnostic génétique?
- Exacerbation aigue?
- Prise en charge?
  - Corticoides
  - Endoxan
  - Inscription sur liste de transplantation?
- Oui
  - Mutation de *TERC*
- Pneumocystose au LBA
- Thrombopénie sous Bactrim
- Bilan pré greffe fait
- Stable sous nintedanib +danazol

# Uniquement des PID?

- Homme de 44 ans
- Non fumeur, exposé aux solvants
- Aplasie médullaire
- Cheveux blancs depuis l'âge de 18 ans
- Dyspnéique
  - Hypoxémique <65 mm Hg
- Père décédé de fibrose pulmonaire
- Scanner « PID »?



# Syndrome hépato-pulmonaire et mutation de *TERT*

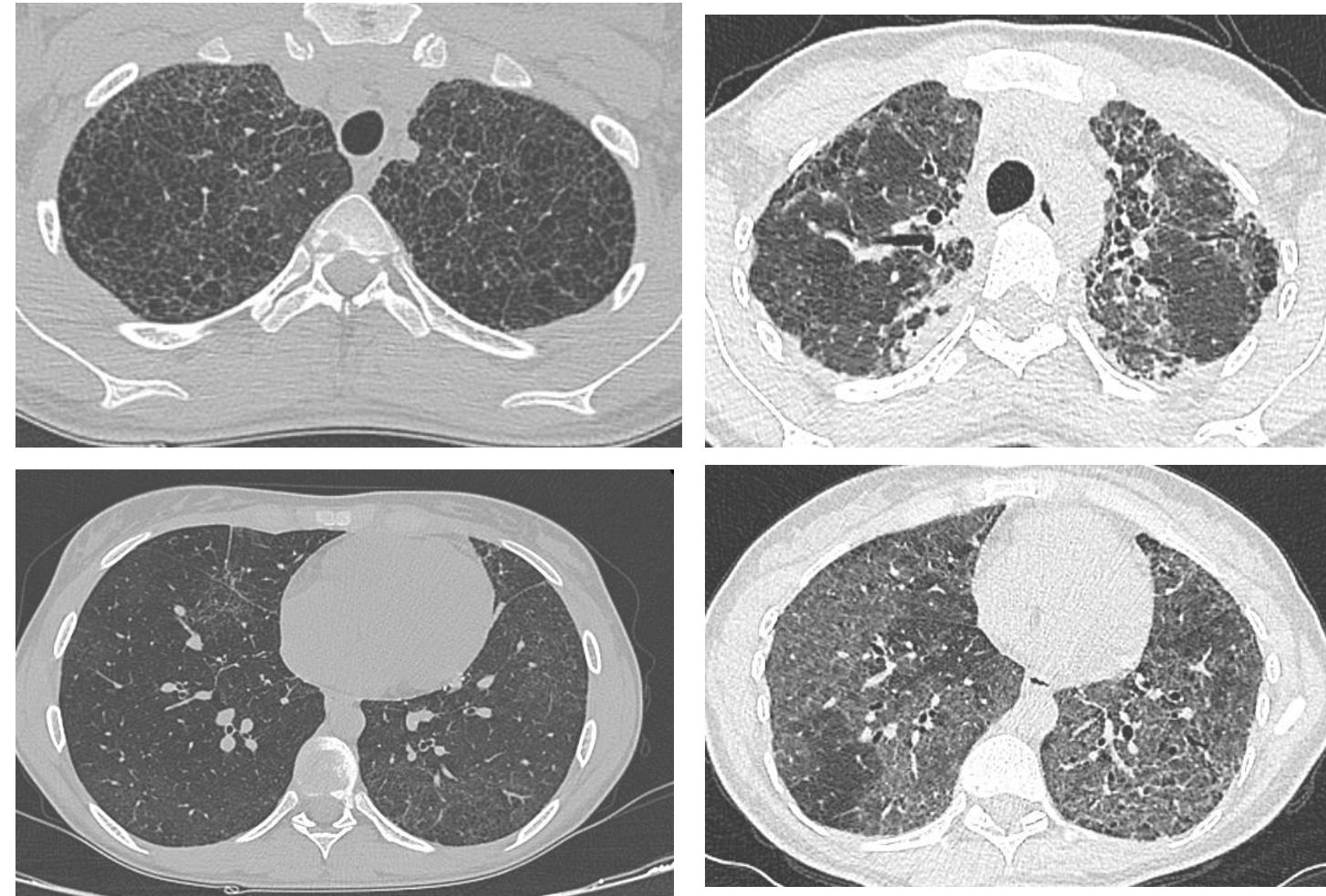
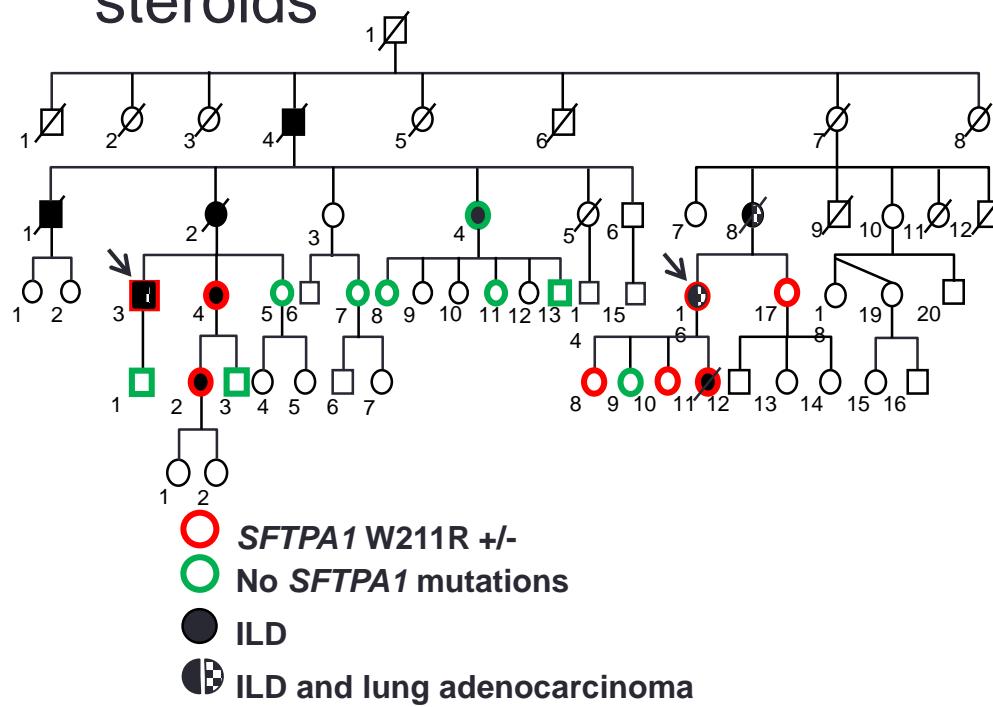


Gorgy, Chest 2015



# Surfactant mutations

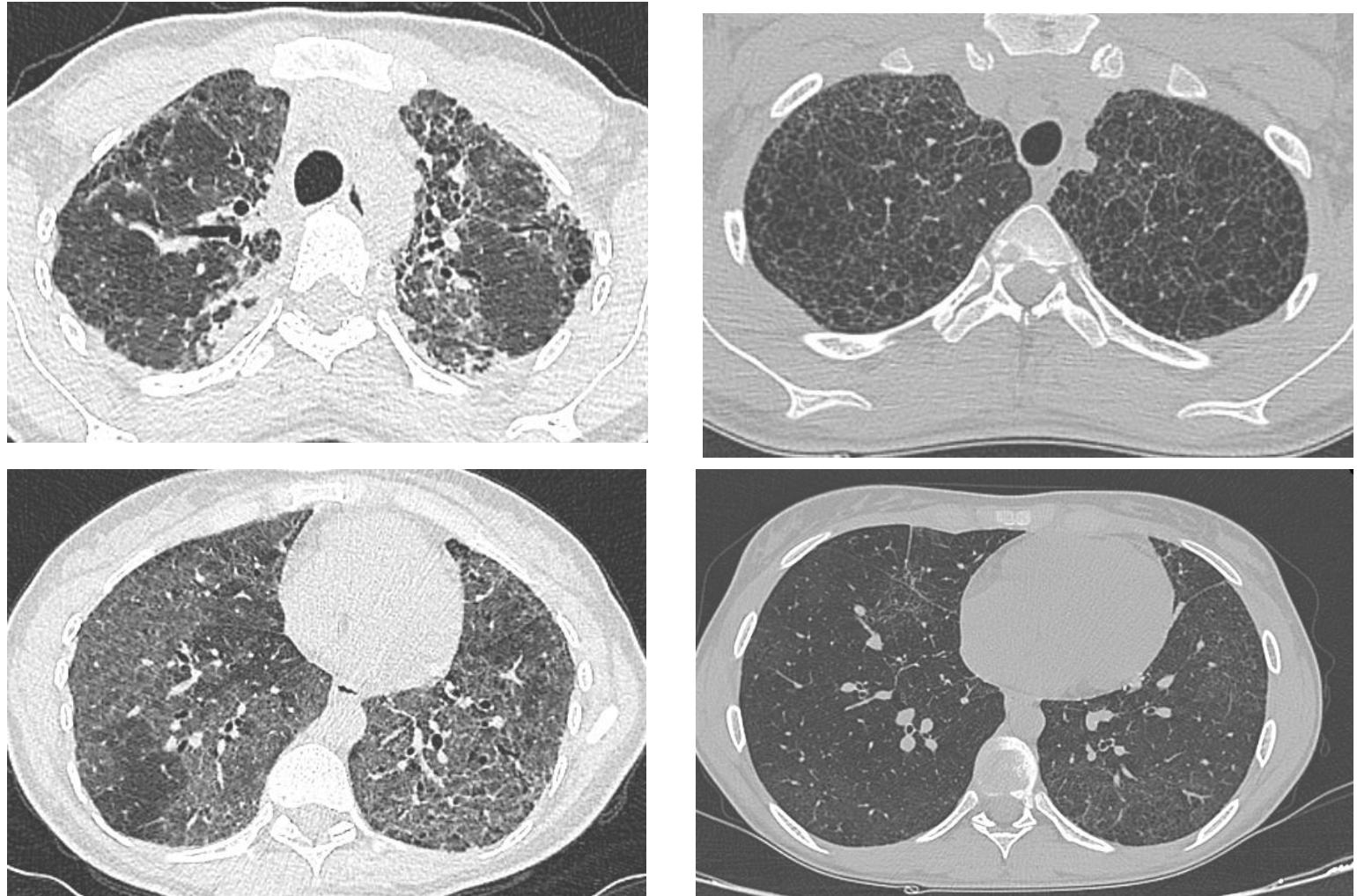
- Children or young adults
- HRCT : Lung cysts, Ground glass cancer
- Improvement possible with steroids

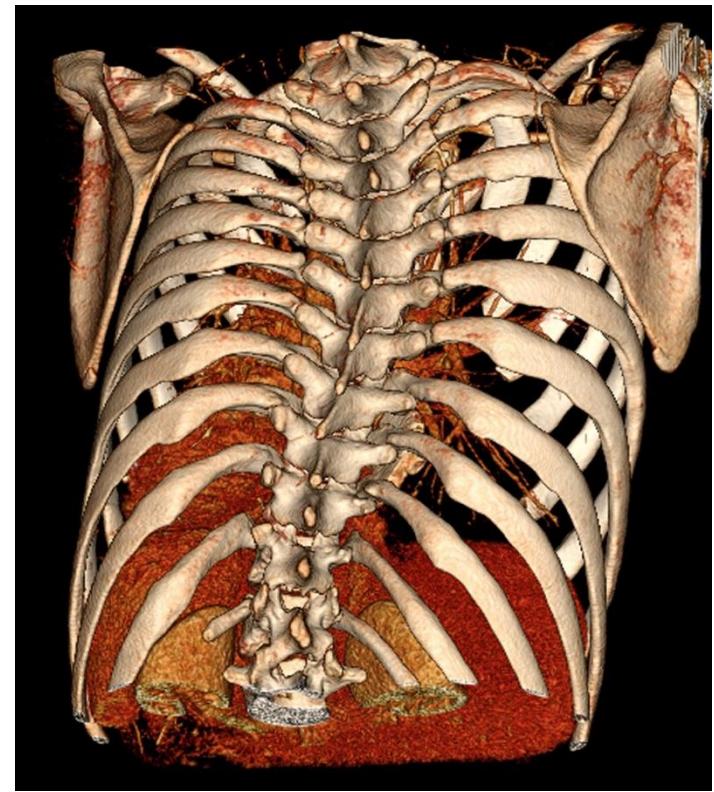
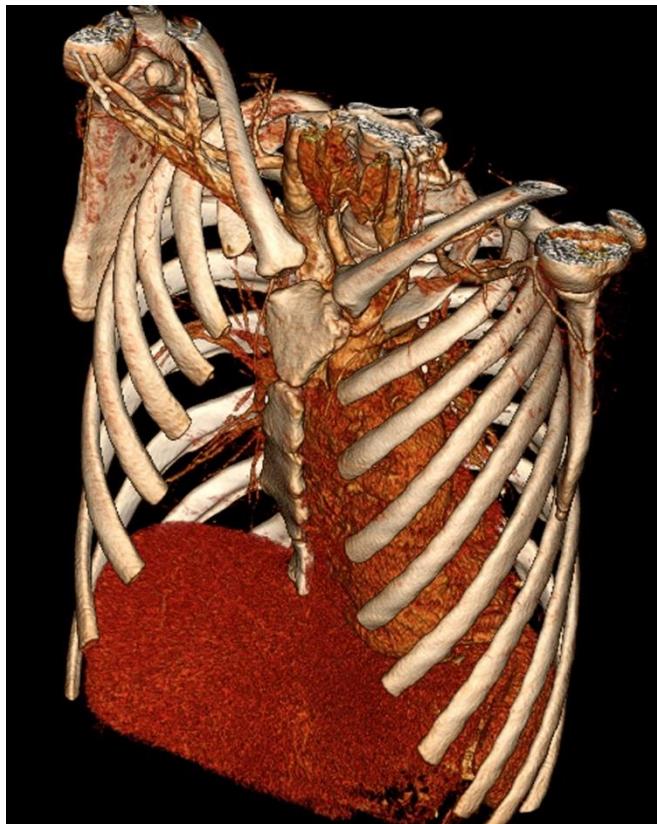
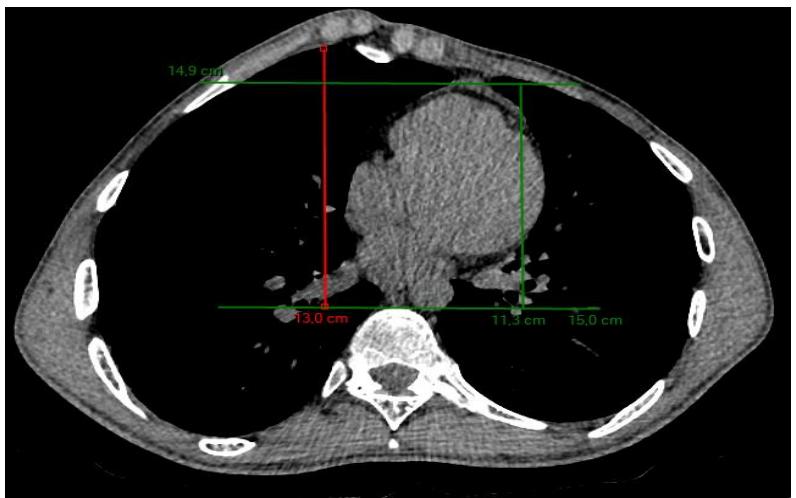
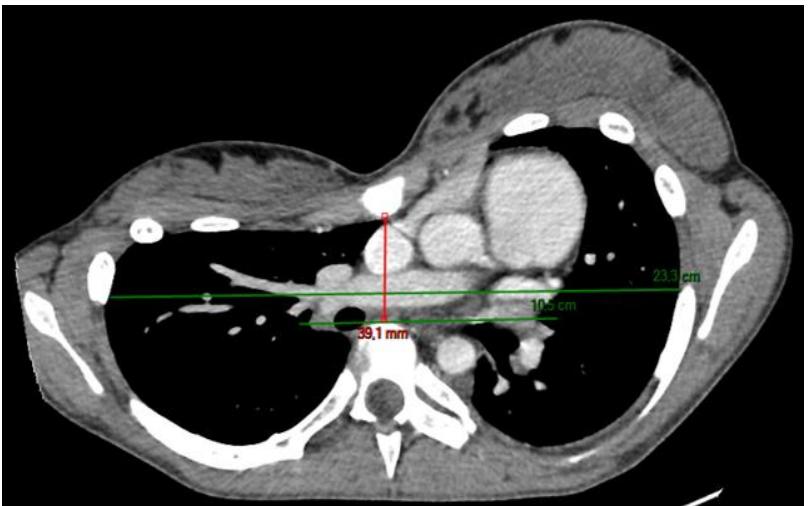


# Mutations SFTPC/ABCA3

## Scanner

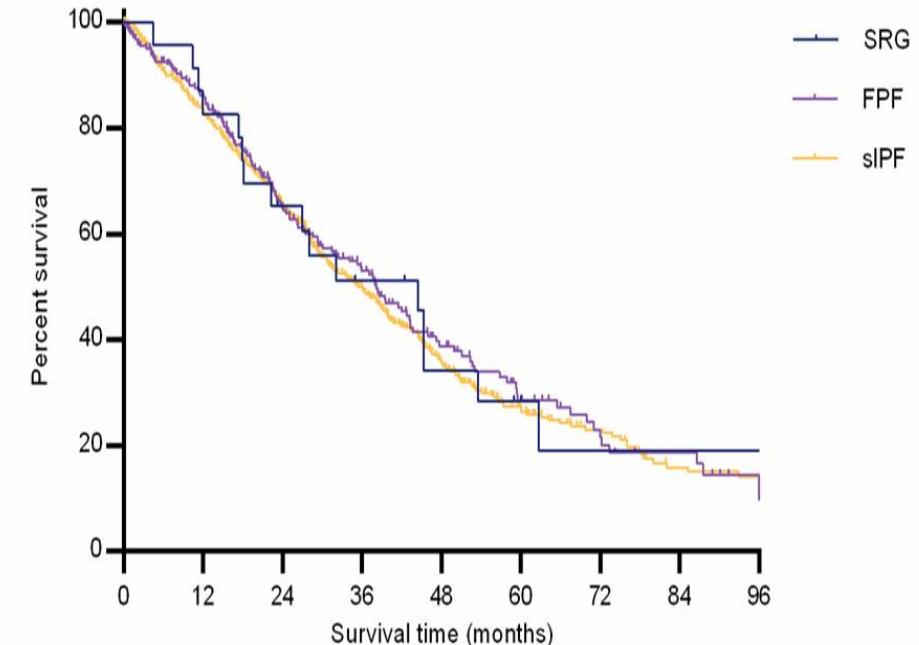
- Kystes pulmonaires (20%)
- Verre dépoli (100%)
- Prédominance possible dans les lobes supérieurs
- Epaississement septal
- Rayon de miel
- Déformation Thoracique:
  - Pectum excavatum
  - Pectum carinatum





# Traitemen<sup>t</sup> ?

- Chez l'adulte?
  - Utilisation pédiatrique
    - Stéroïdes jusqu'à 1/3 d'amélioration
    - Macrolides (azithromycine) jusqu'à 1/3 d'amélioration
    - Hydroxychloroquine
      - jusqu'à 50% d'amélioration retrospective,
      - un essai prospectif pédiatrique plutôt négatif
    - Transplantation pulmonaire possible sans récidive décrit
  - Rare cas rapportés, pas de contrôles, pas de cas adultes
  - Amélioration en rapport avec la croissance spontanée du poumon?
  - Ivacaftor ou ciclosporine hors AMM active sur certaines mutations *d'ABCA3 in vitro*
  - Prescription possible de nintedanib chez l'enfant



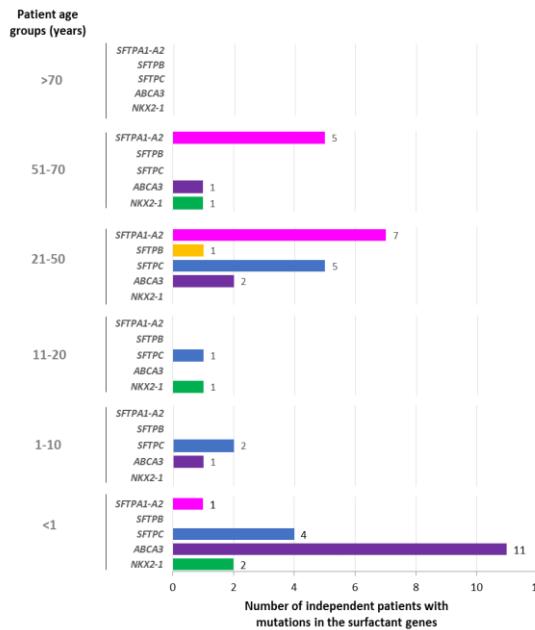
# Mutation du surfactant et cancer

Table 5: Univariable analysis

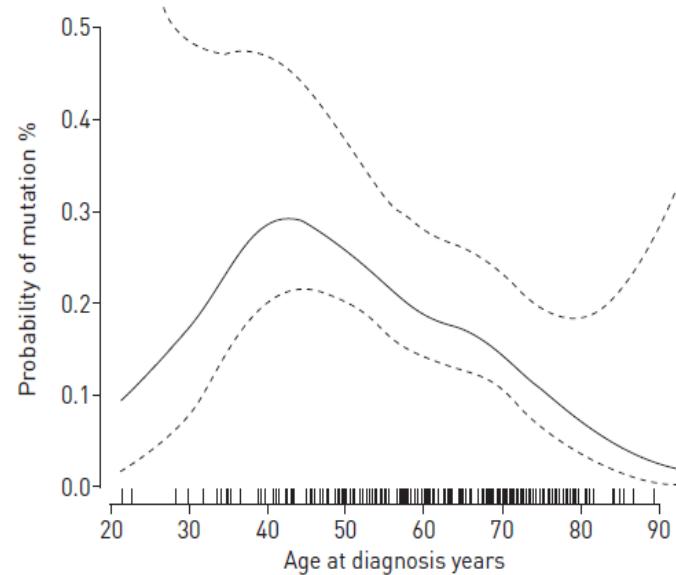
	No lung cancer	Lung cancer	p	OR	p
Patients	81	19			
Age at fibrosis diag.	35.7 [27.80, 47.80]	48.4 [43.7, 54.0]	0.004	1,04 [1,01-1,08]	0,01
Men	51.9% (n=42)	52.6% (n=10)	1.0	/	
Tobacco exposure	12.3% (n=10)	79% (n=15)	<0.001	19,9 [6,25-73,6]	<0,001
Professional exposure	6% (n=5)	5,3% (n=1)	0.48	/	
Fibrosis	80.2% (n=65)	89.5% (n=17)	0.54	2,09 [0,52-14,04]	0,35
Antifibrotic	4.9% (n=4)	21.1% (n=4)	0.026	/	
Surfactant related mutation			0.053		
<i>SFTPA1</i>	13.6% (n=11)	36.8% (n=7)		REF	
<i>SFTPA2</i>	28.4% (n=23)	36.8% (n=7)		0,48 [0,13-1,71]	0,25
<i>SFTPC</i>	27.2% (n=22)	15.8% (n=3)		0,21 [0,04-0,93]	0,049
<i>NKX2.1</i>	12.3% (n=10)	10.5% (n=2)		0,31 [0,04-1,68]	0,2
<i>ABCA3</i>	18.5% (n=15)	0%		NA	NA
Lung transplantation	28,4% (n=23)	21.1% (n=4)	0.7	/	
Death	19.8% (n=16)	63.2% (n=12)	0.001	/	

# Prevalence des mutations/age

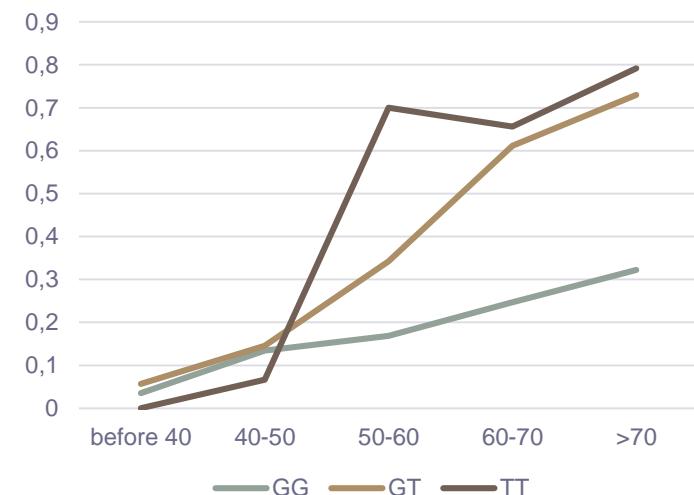
Nombre de mutation du surfactant dans la database de Trousseau



Probabilité de mutation TERT/TERC dans les fibroses pulmonaires familiales



Prevalence de PID selon le génotype *MUC5B* dans la cohorte de Denver fibroses pulmonaires familiales



Disease	Genes	Mode of inheritance	Age of presentation pulmonary symptoms	Non ILD pulmonary and Extra pulmonary phenotype	Frequency	Most frequent pattern	Implication for management/Therapy for pulmonary disease
Hermansky-Pudlak syndrome	HPS1	AR	30-40yo	-Albinism	Rare	Unclassifiable pulmonary fibrosis	Unknown:
	AP3B1 / HSP2	AR	2 – 15 y	- Spontaneous bleeding			Antifibrotic drugs?
	HPS4	AR				Lung transplantation may be considered	
Interferonopathy	STING1/TMEM173	AD	Infancy-young adult	Vasculopathy with onset in infancy, Auto-inflammatory features (SAVI)	Rare	Unclassifiable pulmonary fibrosis , Alveolar hemorrhage	Unknown:
	COPA	AD		Arthralgia, kidney disease			Antifibrotic drugs ?
	OAS1	AD		Fever, dermatitis, inflammatory bowel disease,	Ultrarare	Alveolar proteinosis	Jak inhibitor? Allogeneic stem cell transplantation?
Interferonopathy	ZNFX1	AR	Infancy, children	Viral infections, Inflammatory episodes, early-onset seizures, renal disease	Ultrarare	Unclassifiable pulmonary fibrosis	Jak inhibitor?
Aminoacyl-tRNA synthetases	MARS	AR	Infancy-young adult (Founder effect Reunion Island)	Anemia, hepatomegaly, feeding difficulties, failure to thrive and hypoalbuminemia	Rare	Pulmonary alveolar proteinosis, Pulmonary fibrosis	Methionine supplementation? Whole lung lavage?
	FARS1	AR	Infancy, childhood	Neurological findings, liver dysfunction, and connective tissue, muscular and vascular abnormalities.	Ultra rare	Interstitial lung disease with cholesterol pneumonitis	Unknown
GM-CSF receptor	CSF2RA	AR	Infancy, childhood, adults		Ultra rare	Alveolar proteinosis	Whole lung lavage? Autologous transplantation of genetically corrected macrophages? GM-CSF? Stem cell transplantation?
	CSF2RB	AR	Infancy, childhood, adults		Ultra rare	Alveolar proteinosis	Whole lung lavage? Stem cell transplantation?
Fibrosis, neurodegeneration, and cerebral angiomas (FINCA)	NHLRC2	AR	Infancy-young adult	Neurodegeneration and cerebral angiomas	Ultra rare	desquamative interstitial pneumonia; non-specific interstitial pneumonia	Unknown
Acid Sphingomyelinase Deficiency (ASMD, Niemann-Pick disease)	SMPD1	AR	Type A / 3yo	Hepatomegaly	Rare	Not Fibrosing Interstitial lung disease with ground glass opacities	Enzyme replacement therapy to be confirmed
			Type B : later onset	Splenomegaly Thrombocytopenia			
Niemann-Pick disease, Type C	NPC1, NPC2	AR	Type C	ILD, PAP, Hepato-splenomegaly	rare	Unclassifiable pulmonary fibrosis, Alveolar Proteinosis	Unknown
GATA2 deficiency	GATA2	AR	Adult	monoMac syndrome: moncytopenia, Mycobacterial infection	Rare	Unclassifiable pulmonary fibrosis, Alveolar Proteinosis	Stem cell transplantation
				Myelodysplastic syndrome			
Pulmonary alveolar microlithiasis	SLC34A2	AR	5-41 yo		Ultra rare	Not Fibrosing sandstorm-like	Lung transplantation may be considered
Poikiloderma lung fibrosis	FAM111B	AD	young	Hereditary Fibrosing Poikiloderma with Tendon Contractures, Myopathy, Exocrine pancreatic dysfunction, pancreatic cancer	Ultra rare	Unclassifiable pulmonary fibrosis	Unknown
Prolidase deficiency	PEPD	AR	young	Mental retardation, facial dysmorphism, dermatologic manifestations including ulcerations	Ultra rare	Unclassifiable pulmonary fibrosis	Unknown
Lysinuric protein intolerance	SLC7A7	AR	Infancy-young adult	metabolic: S: vomiting, diarrhea, failure to thrive, hepatomegaly, diffuse cirrhosis, low blood urea, hyperammonemia, and leukopenia	Ultra rare	Alveolar proteinosis	Specific diet
Mitochondrial respiratory chain complex deficiency : Fanconi renotubular syndrome 5	NDUFAF6	AR	2-40 yo	renotubular syndrome, interstitial renal fibrosis; pulmonary microlithiasis	Ultra rare	Unclassifiable pulmonary fibrosis	Unknown
Werner	WRN	AR	>10-yo	scleroderma-like skin changes, cataract, subcutaneous calcification, premature arteriosclerosis, diabetes mellitus, and premature aged facies	Ultra rare	Unclassifiable pulmonary fibrosis	Unknown

# Conclusion

---

- Il existe des polymorphismes à risque de PID
  - Intérêt diagnostic?
  - Intérêt thérapeutique?
- Il existe des maladies monogéniques responsables de PID

PNDS

ERS  
Taskforce

Groupe  
Américain

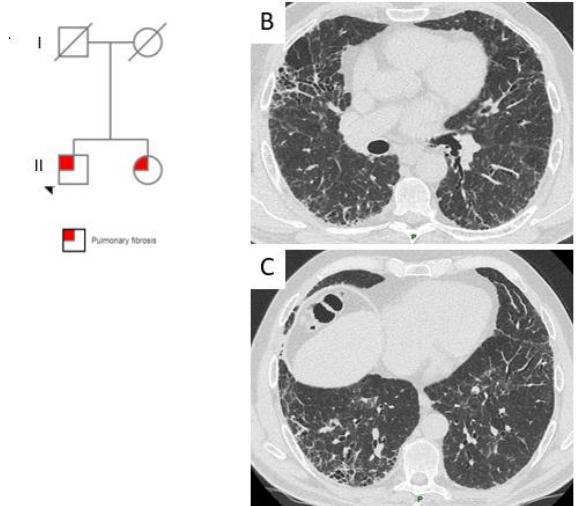
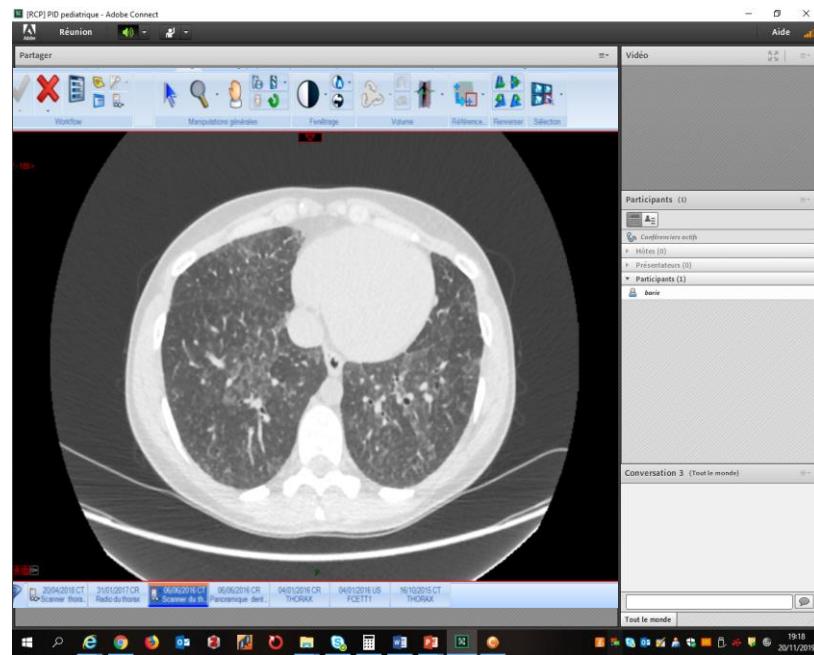
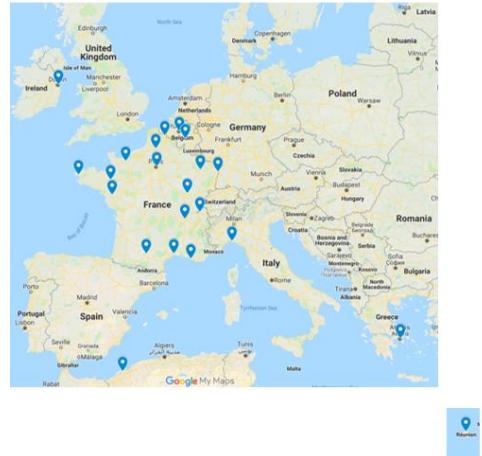
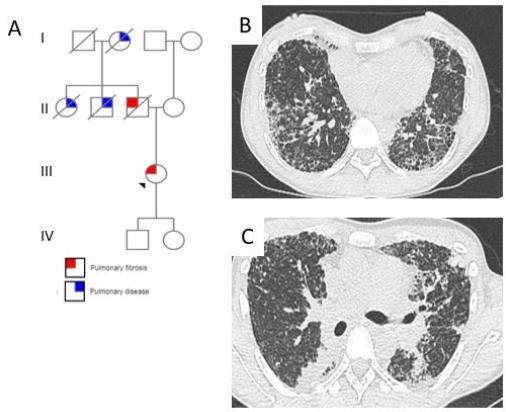
## INDICATIONS DE DIAGNOSTIC GENETIQUE:

Formes familiales de PID

Suspicion de téloméropathies (foie, poumon, peau, hémato)

PID idiopathique <50 ans

# GENETIC MDD



# Conclusion prise en charge

- Formes familiales de PID
- Suspicion de syndrome des télomères courts (foie, poumon, peau, hémato)
  - Séquençage NGS « telomeres »
    - Attention à l'utilisation de cytotoxiques (médicamenteux)
- PID idiopathique <50 ans
  - Mutation du surfactant
    - Traitement corticoides/macrolides/ plaquenil?