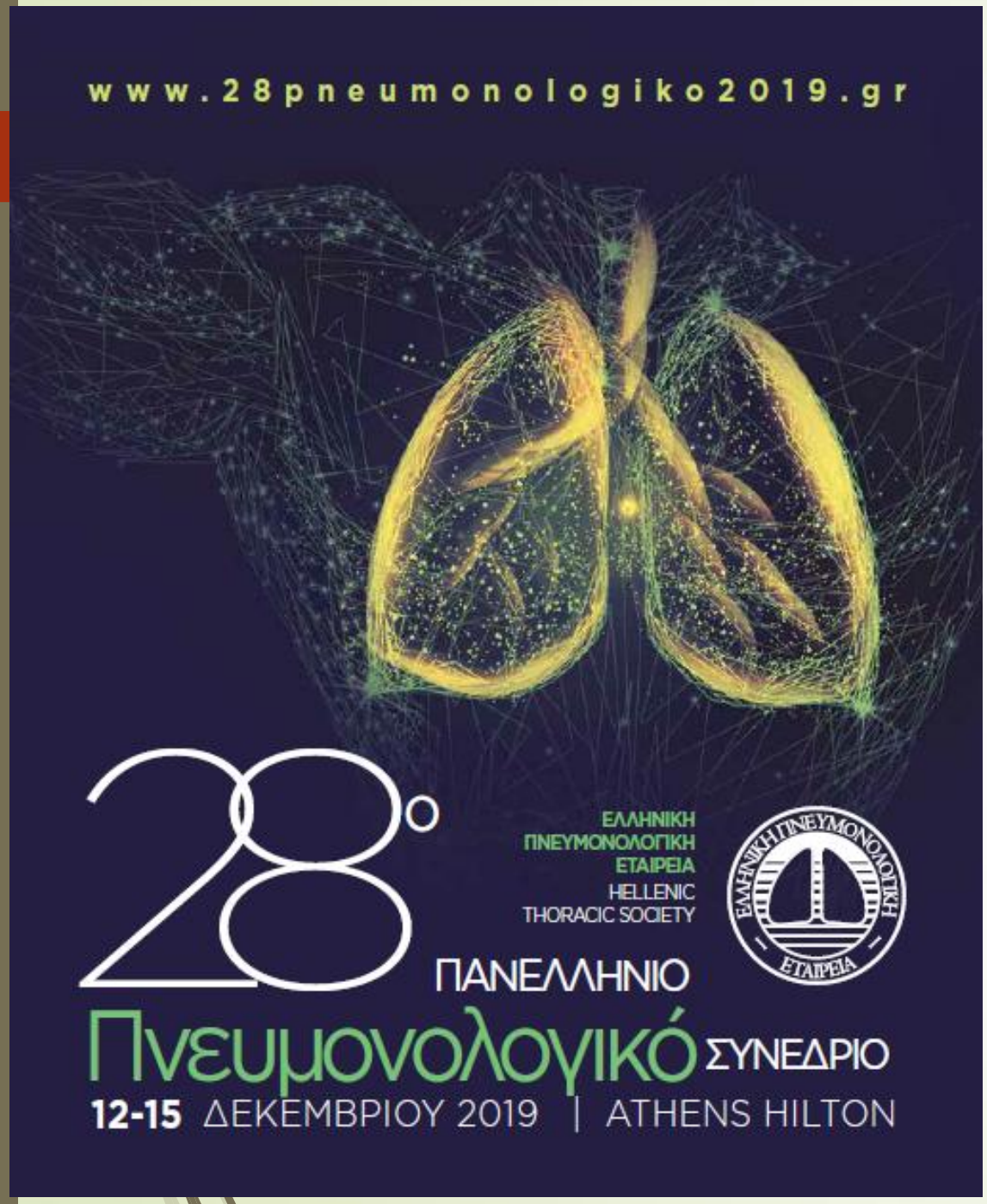


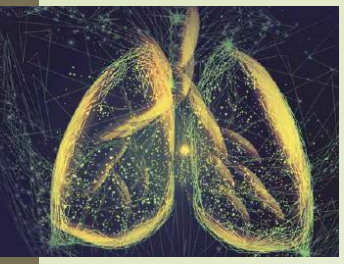
National and Kapodistrian UNIVERSITY OF ATHENS

ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ATTIKON

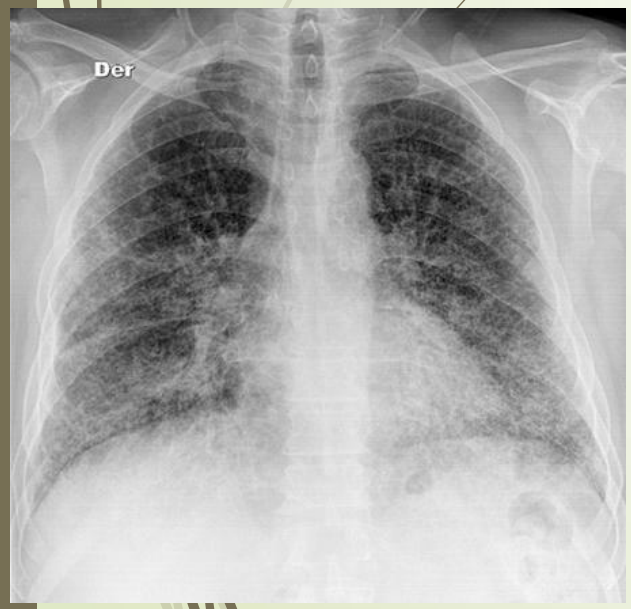
09:00-10:30	**Στρογγυλή Τράπεζα** **Ιδιοπαθής πνευμονική ίνωση και άλλες χρόνιες προοδευτικά εξελισσόμενες ινοποιές διάμεσες πνευμονοπάθειες** **Προεδρείο:** *Κ. Μαρκοπούλου - Β. Πολυχρονόπουλος* Παθογένεση IPF: Νέες υποθέσεις *Α. Τζουβελέκης* Άλλες χρόνιες προοδευτικά εξελισσόμενες ινοποιές διάμεσες πνευμονοπάθειες *Κ. Αντωνίου* Γενετική προδιάθεση *Ε. Μάναλη* Υπάρχουσες και αναδυόμενες θεραπείες στην IPF *Ζ. Δανιήλ*

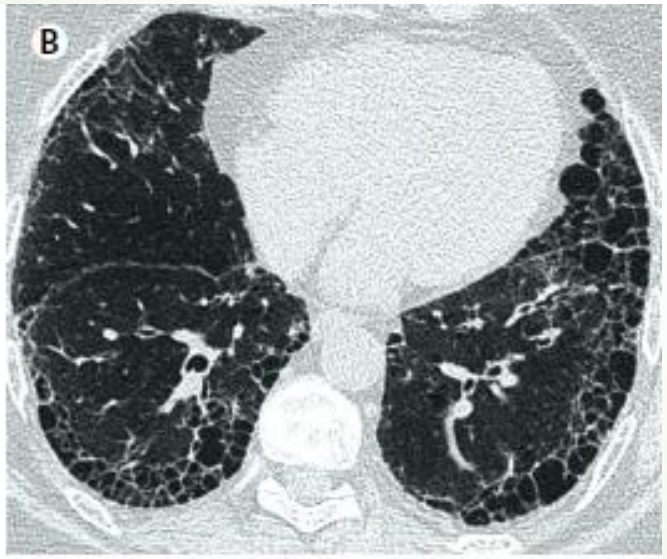
Πνευμονική ίνωση στα παιδιά?

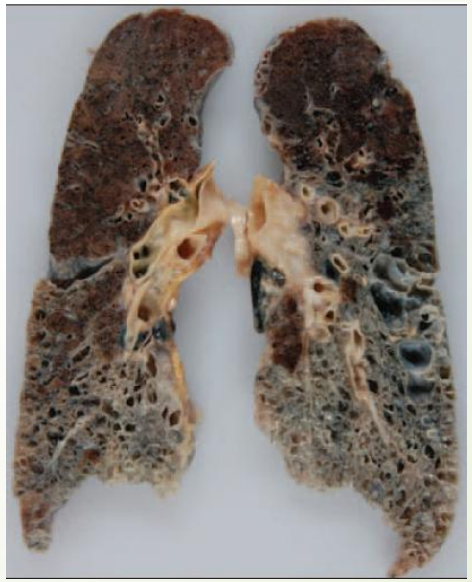
Ευφροσύνη Δ. Μάναλη
Επίκουρη Καθηγήτρια
Β' Πανεπιστημιακή Πνευμονολογική Κλινική
Γενικό Πανεπιστημιακό Νοσοκομείο Αθηνών «Αττικόν»
Ιατρική Σχολή , Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

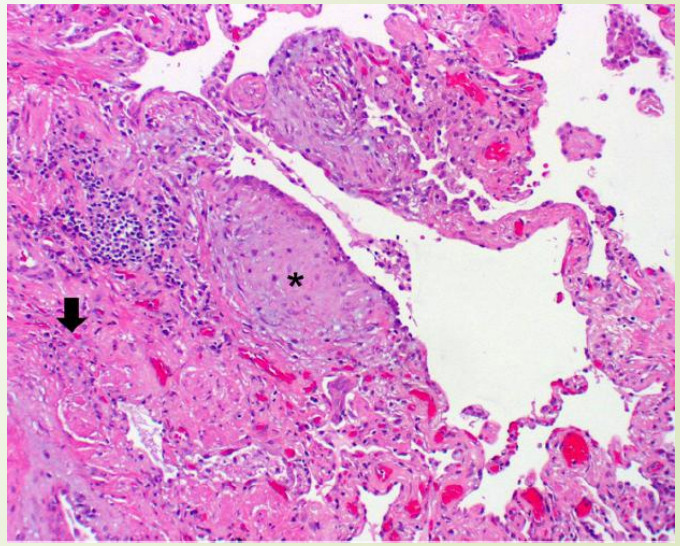


In adults
the most frequent and severe form of pulmonary fibrosis (PF)
is idiopathic PF (IPF)
diagnosed on a usual interstitial pneumonia (UIP) pattern

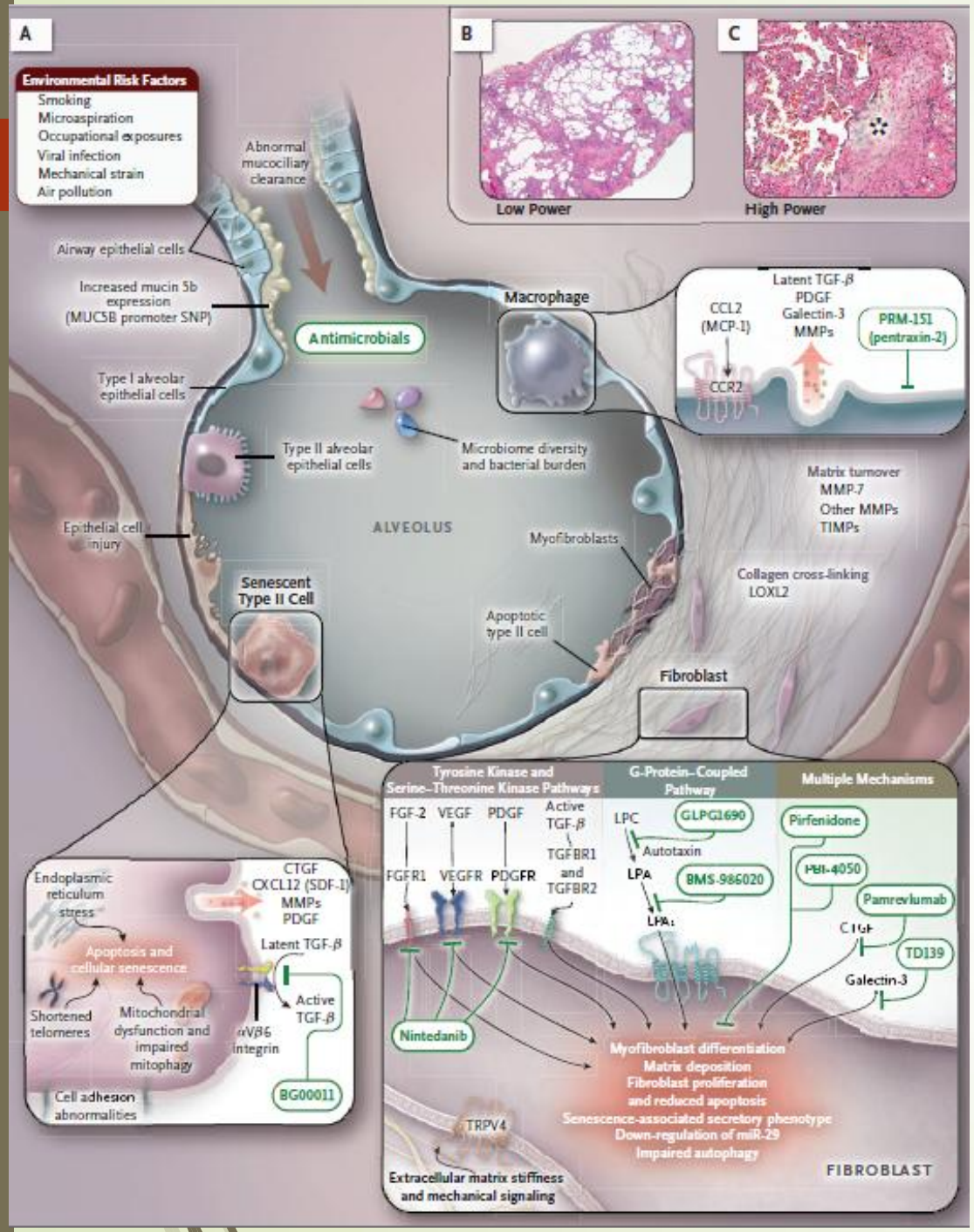


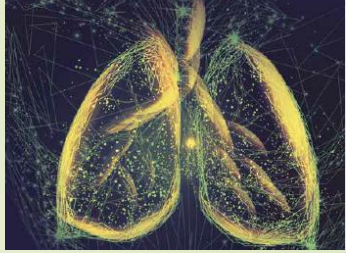






Am J Respir Crit Care Med 2011; Vol 183: 788–824

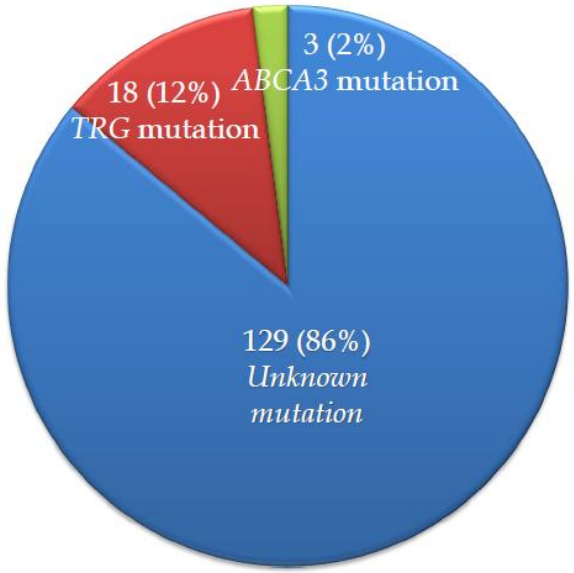


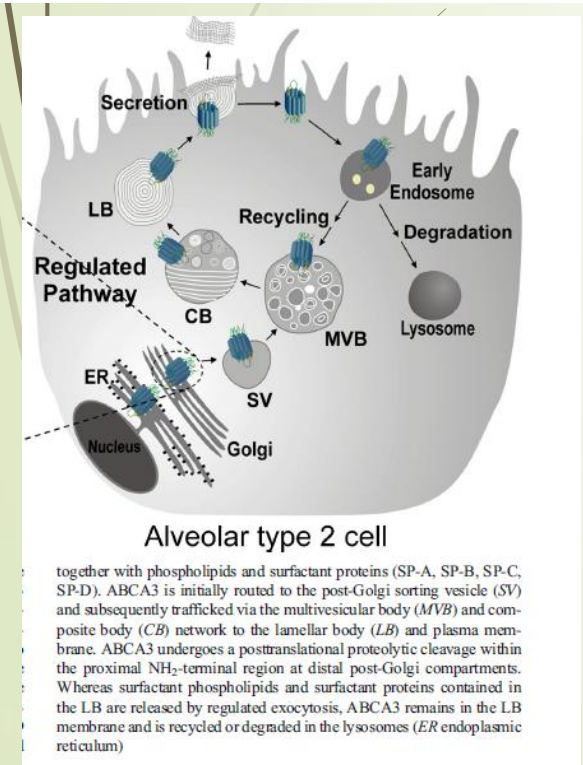


Maladaptive repair process

- ✓ Environmental risk factors
- ✓ Ageing
- ✓ Microbiome
- ✓ Genetic risk factors

Lederer DJ, Martinez FJ. N Engl J Med 2018; 378: 1811-1823
Richeldi L, et al. Lancet 2017; 389:10082





Alveolar type 2 cell

together with phospholipids and surfactant proteins (SP-A, SP-B, SP-C, SP-D). ABCA3 is initially routed to the post-Golgi sorting vesicle (*SV*) and subsequently trafficked via the multivesicular body (*MVB*) and composite body (*CB*) network to the lamellar body (*LB*) and plasma membrane. ABCA3 undergoes a posttranslational proteolytic cleavage within the proximal NH_2-terminal region at distal post-Golgi compartments. Whereas surfactant phospholipids and surfactant proteins contained in the LB are released by regulated exocytosis, ABCA3 remains in the LB membrane and is recycled or degraded in the lysosomes (*ER* endoplasmic reticulum)

TABLE 1 Main genes with rare variants associated with pulmonary fibrosis

Function	Gene	Transmission	Age of onset of pulmonary manifestation	Associated signs
Telomerase	*TERT-TERC*	AD	Adults, average 55 years	Telomeropathy; combined pulmonary fibrosis and emphysema
	TINF2	AD	Children, rare adults <50 years	Telomeropathy [31]
	DKC1	X	Children, rare adults <50 years	Telomeropathy [120]
Helicase	*RTEL1*	AD	Adults 35–60 years	Telomeropathy
RNA regulation	*PARN*	AD	Adults 47–81 years	Pulmonary granulomatosis; telomeropathy [33]
	NAF1	AD	Adults 45–60 years	Telomeropathy [5]
Surfactant	*SFTPA1-SFTPA2*	AD	From newborn to 72 years	Lung cancer [90, 121]
	SFTPB	AR	Newborn	[122]
	SFTPC	AD	Children, rare adults <50 years	Combined pulmonary fibrosis and emphysema [123]
	ABCA3	AR	Children, rare adults <50 years	Combined pulmonary fibrosis and emphysema [83]
	NFKX2-1 (TITF1)	AD	Children, rare adults <50 years	Chorea, hypothyroidism [93]
Tumour suppressor	*NF1*	AD	Adults	Type 1 neurofibromatosis [124]
Lysosome	*HPS-1 to HPS-8/AP-3B1*	AR	Adults	Hermansky–Pudlak syndrome [125]
Stimulation of interferon synthesis	*TMEM173*	AD	Children, rare adults <50 years	Recurrent fever; alopecia; skin rash; antinuclear antibodies; vasculitis [95, 100]
Endoplasmic reticulum stress	*COPA*	AD	Children, rare adults <25 years	Arthritis, antinuclear antibodies and ANCA [8]
Unknown	*FAM111B*	AD	7–30 years	Myopathy, poikiloderma [6]
Mitochondria	*NDUFAF6*	AR	19–50 years	Acadian variant of Fanconi syndrome [126]
Zinc finger transcription factors	*GATA2*	AD	4–76 years	Alveolar proteinosis; myeloid disease; monoMAC syndrome [10]

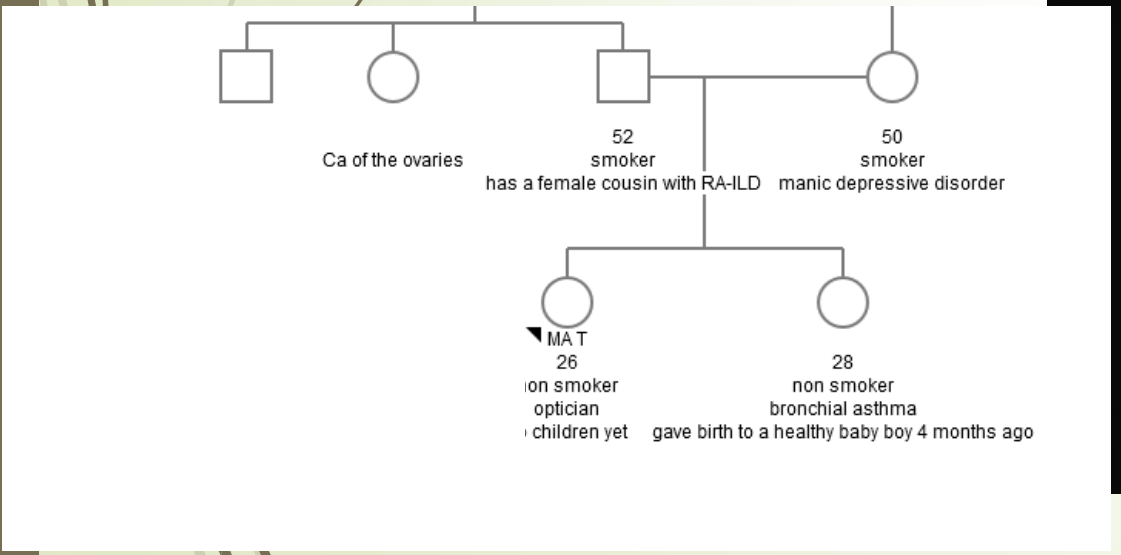
AD: autosomal dominant; X: X-linked; AR: autosomal recessive; ANCA: anti-neutrophil cytoplasmic antibodies.

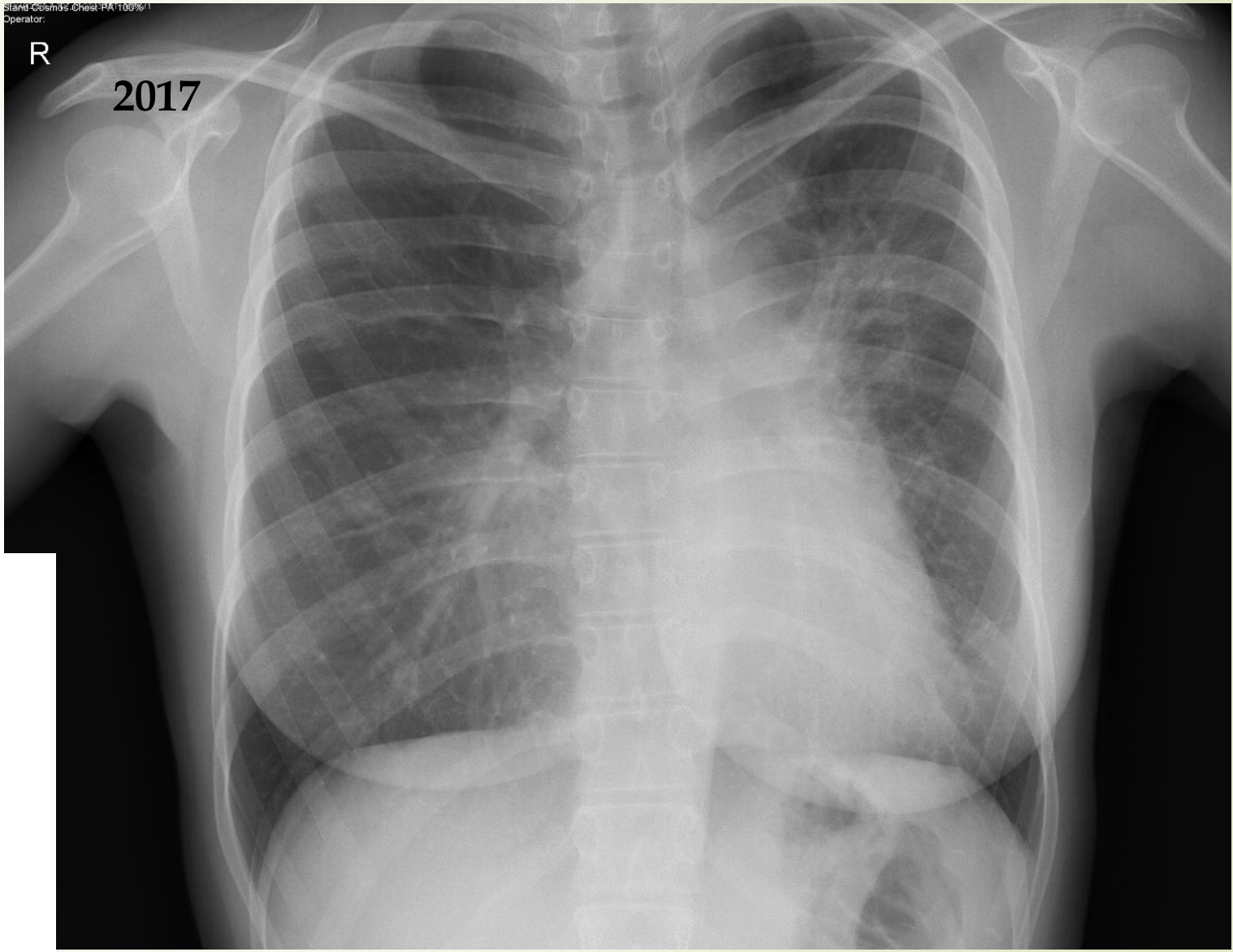
ABCA3

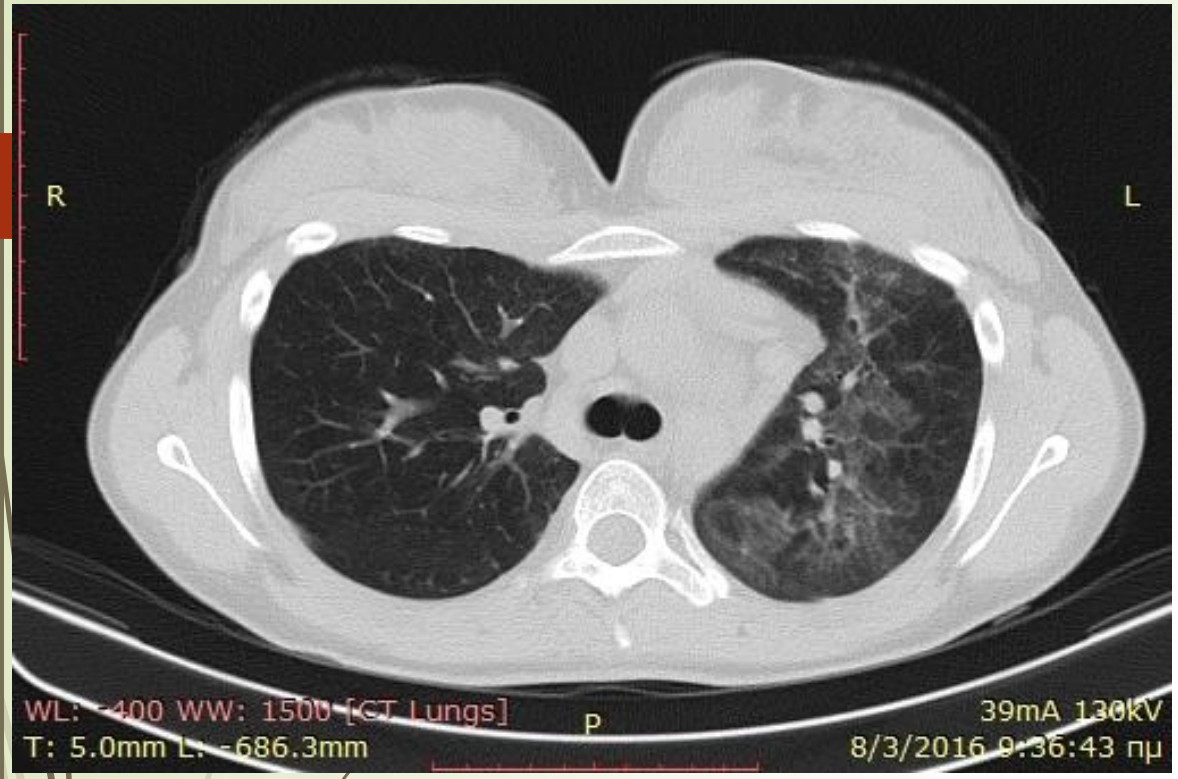
Borie R, Kannengiesser C, et al. Eur Respir Rev 2017; 26: 160122

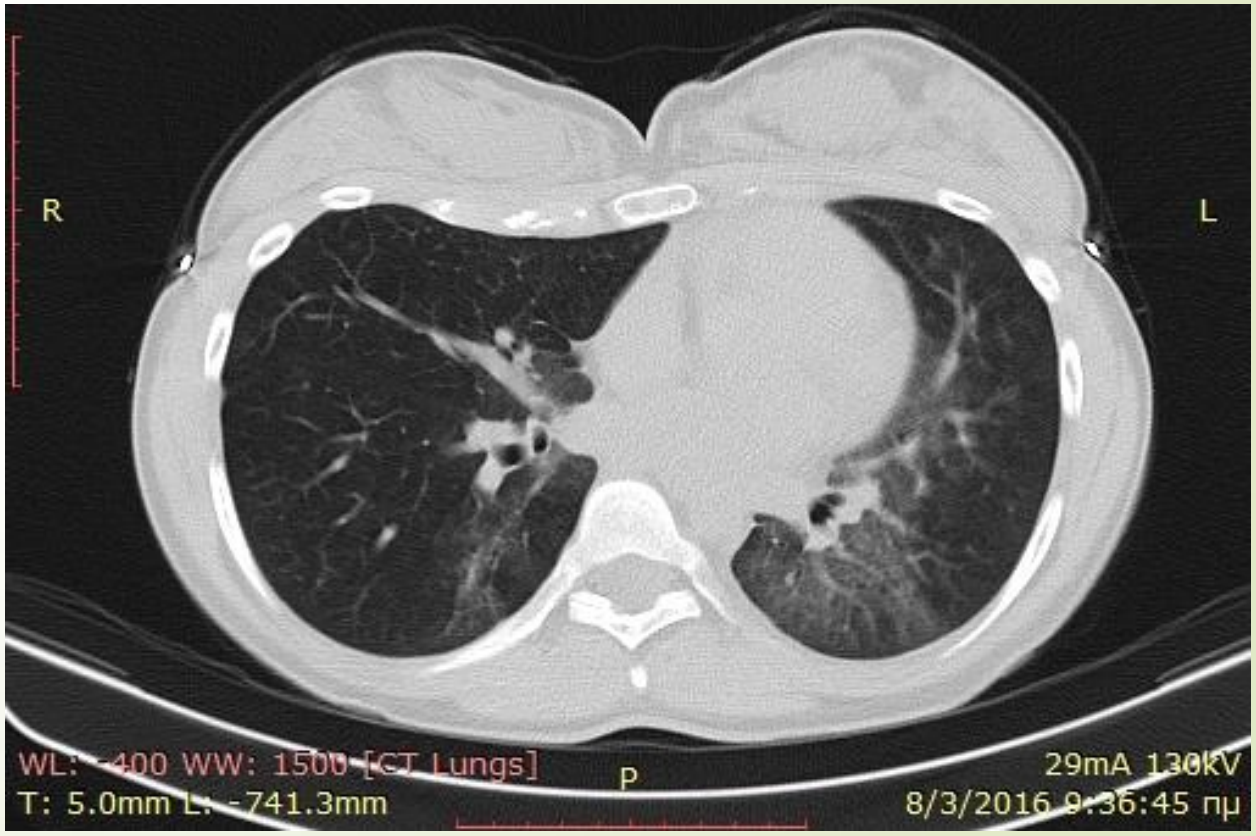
Patient # 1

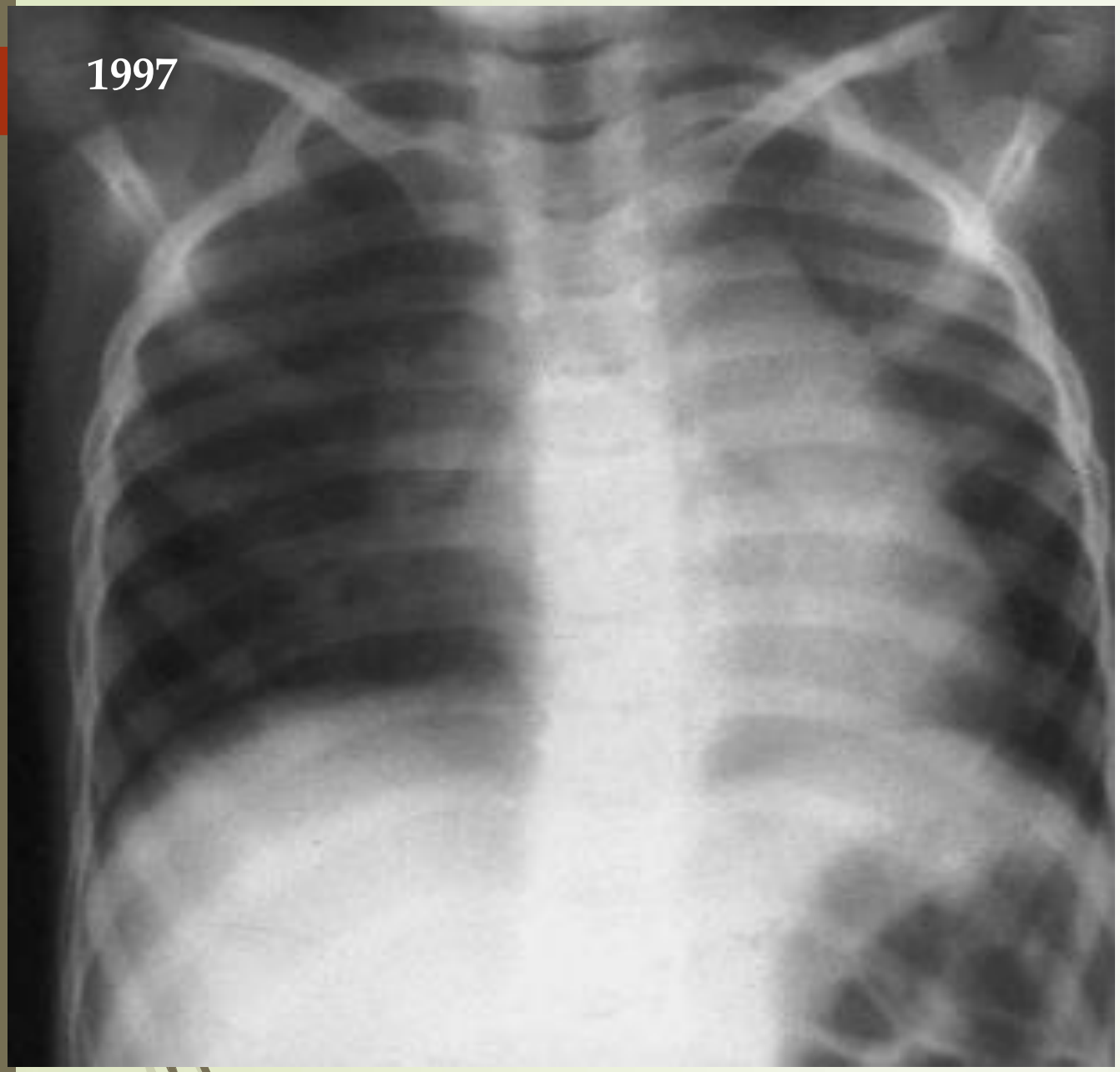
Female, non-smoker, 26 years old
ILD since the age of 5.5 years old
Finger clubbing
FEV1=60%, FVC=64%, Tf=83%,
TLC=55%, DLCO=35.5%






R
L
WL: -400 WW: 1500 [CT Lungs]
T: 5.0mm L: -686.3mm
P
39mA 130kV
8/3/2016 9:36:43 πμ


R
L
WL: -400 WW: 1500 [CT Lungs]
T: 5.0mm L: -741.3mm
P
29mA 130kV
8/3/2016 9:36:45 πμ



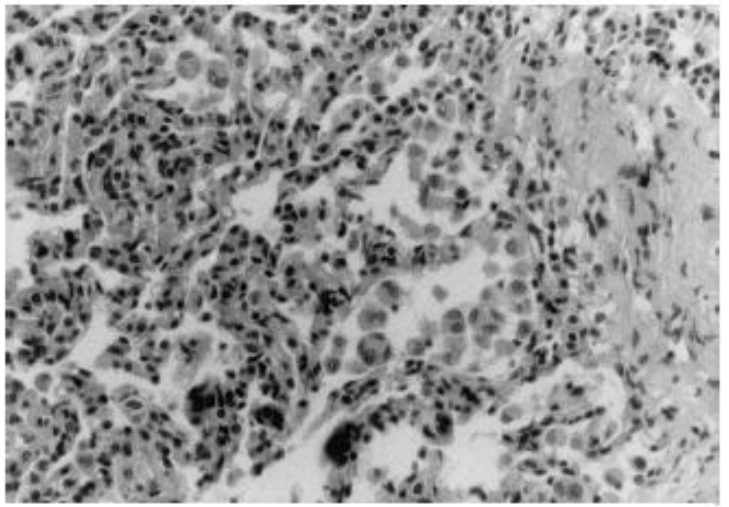


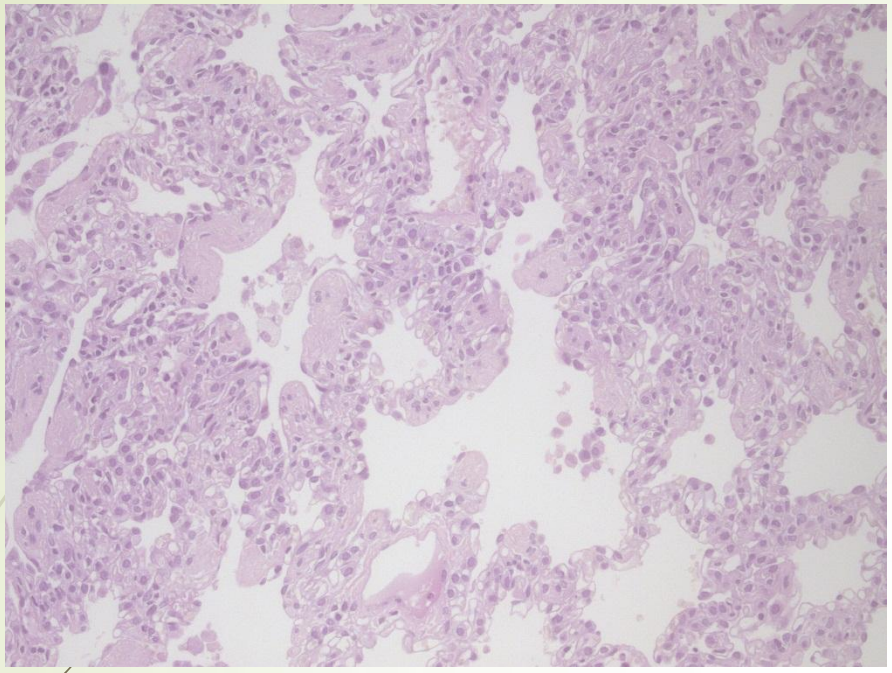
FIG. 2. Lung biopsy of patient 1 showing a diffuse interstitial infiltrate with histiocytes. Original magnification 25× hematoxylin and eosin (HE).

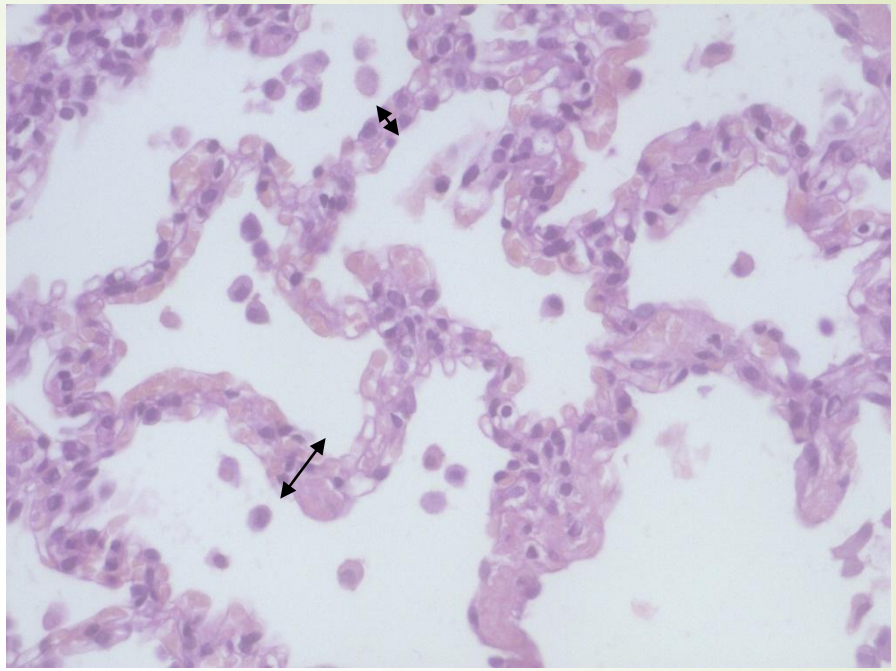
Cellular interstitial pneumonia

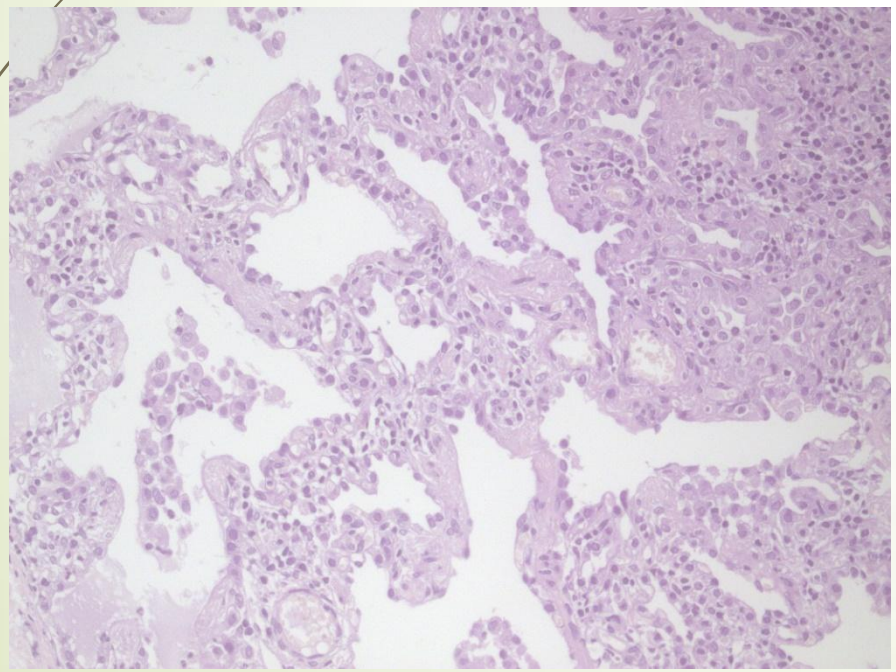
????

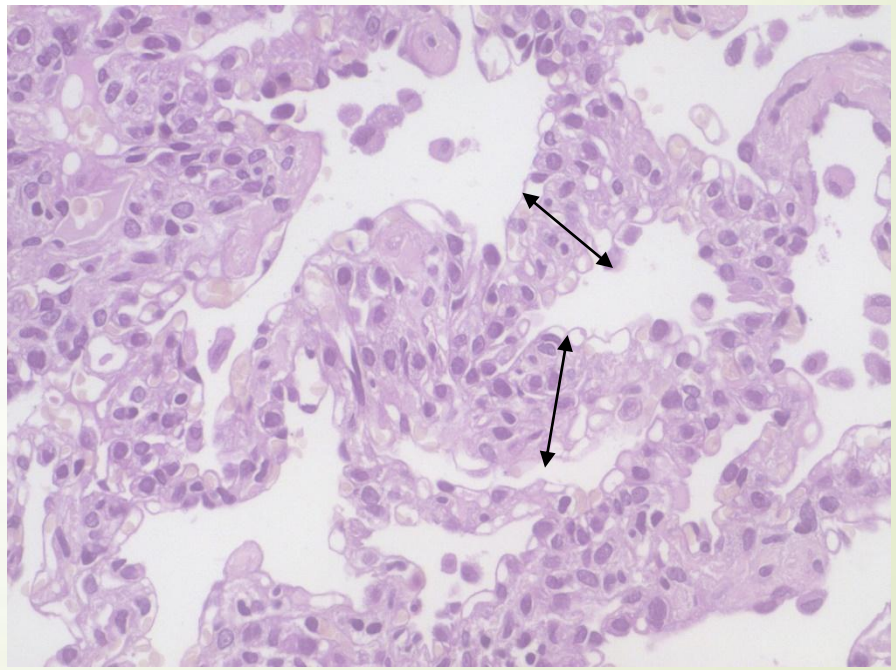
Nikolaidou P, et al. Pediatr Asthma , Allergy, Immunol 2003; 16: 45-51

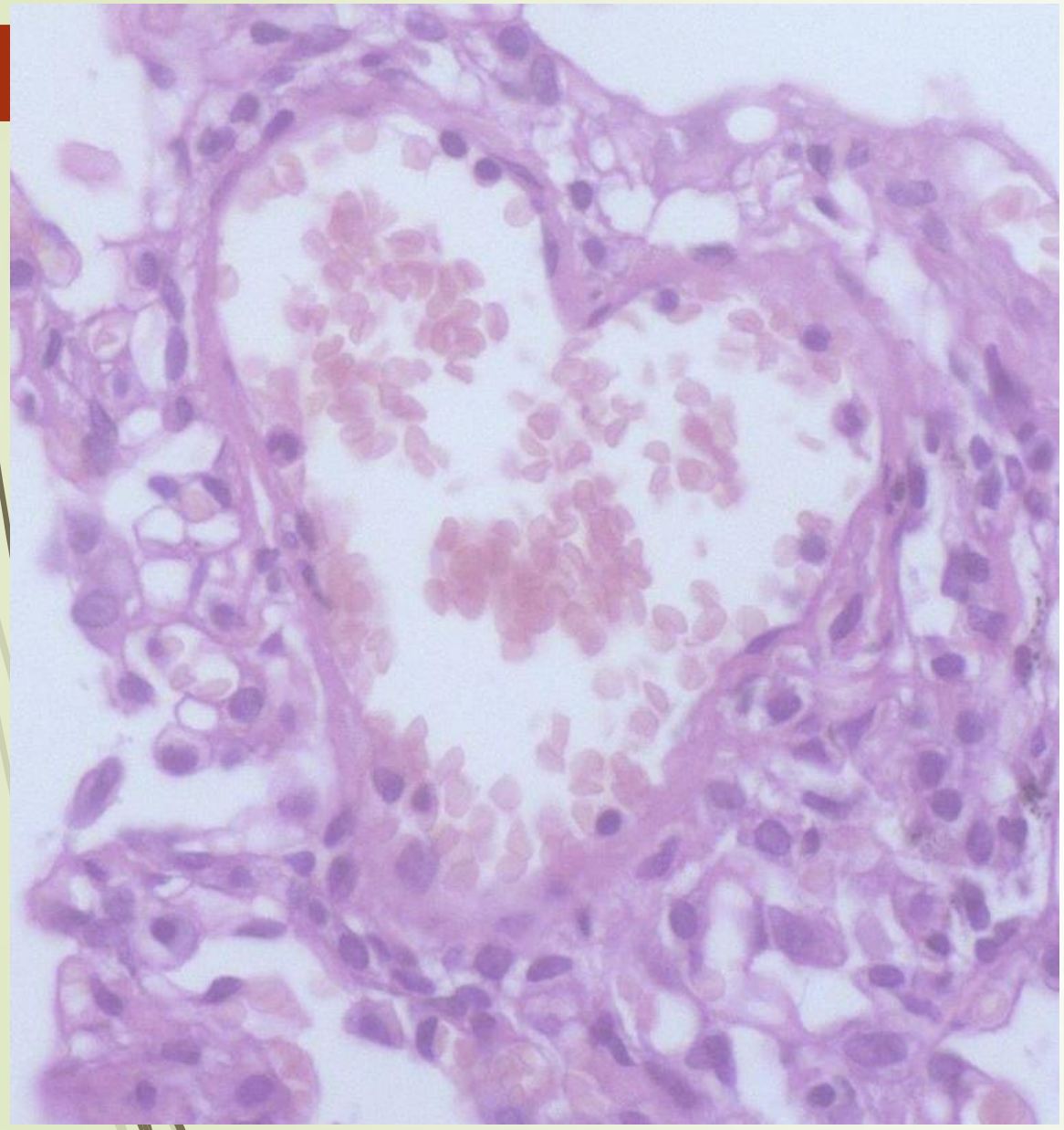
At the age of
6 years old







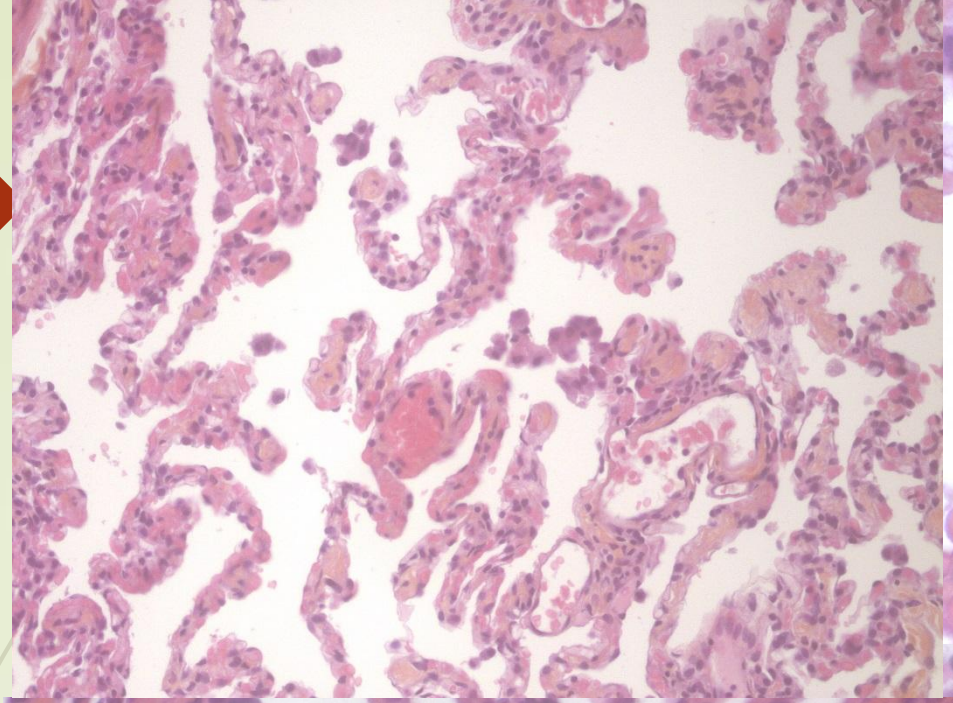


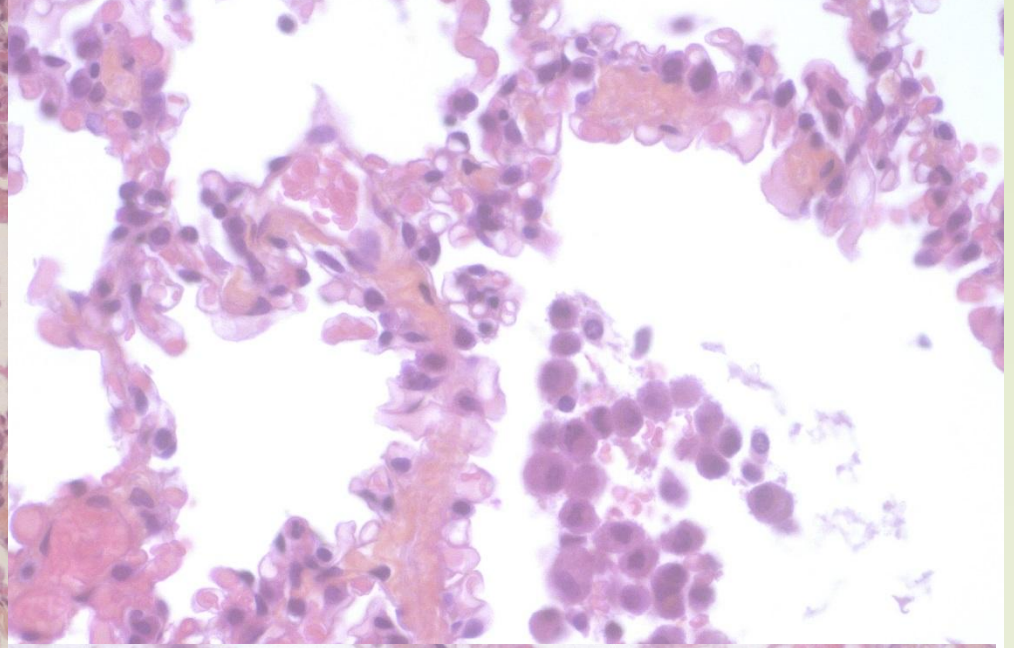


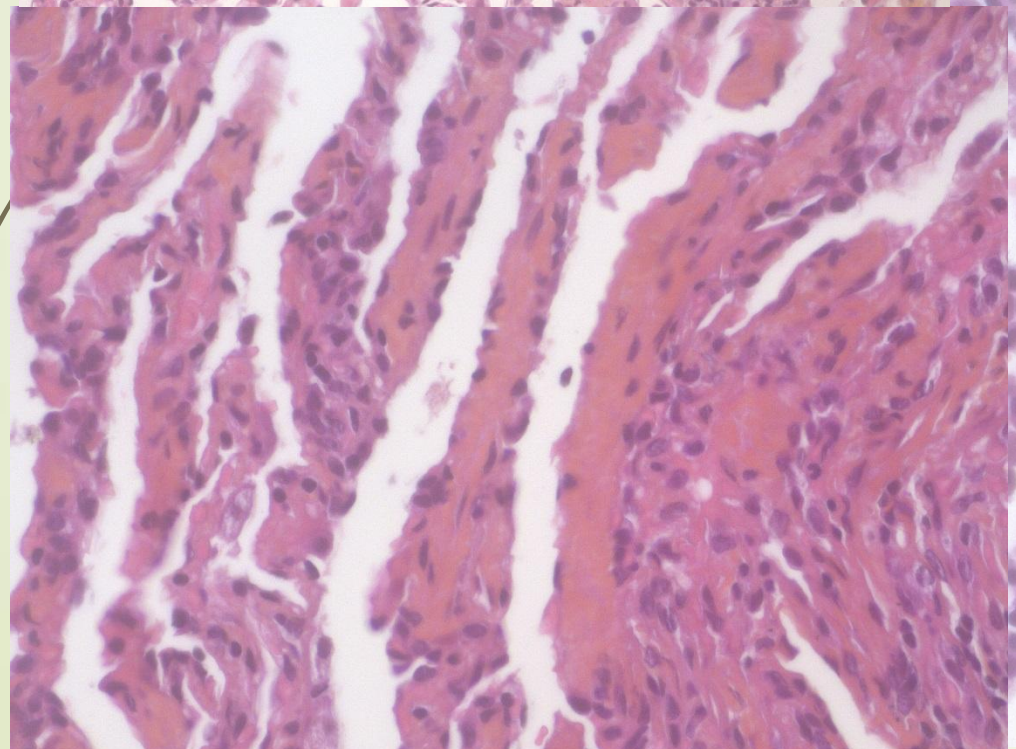
DIP and NSIP pattern without PAP and no major pneumocytes hyperplasia and very -very focal septal fibrosis

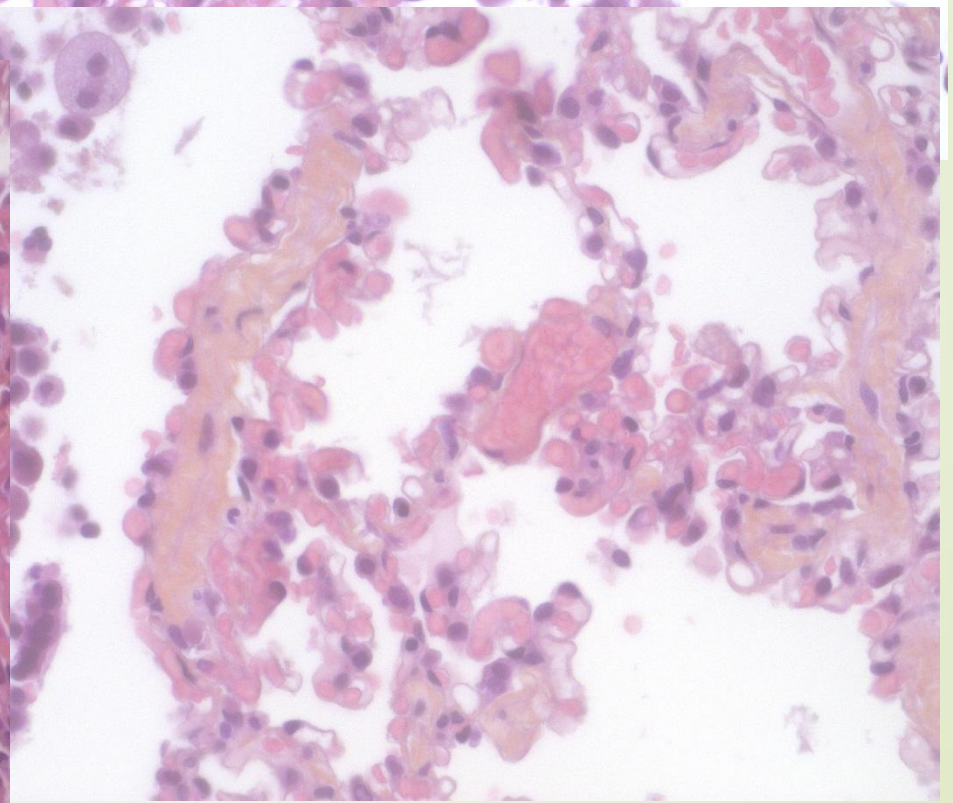
Courtesy of Professeur Aurore Coulomb-L'Hermine

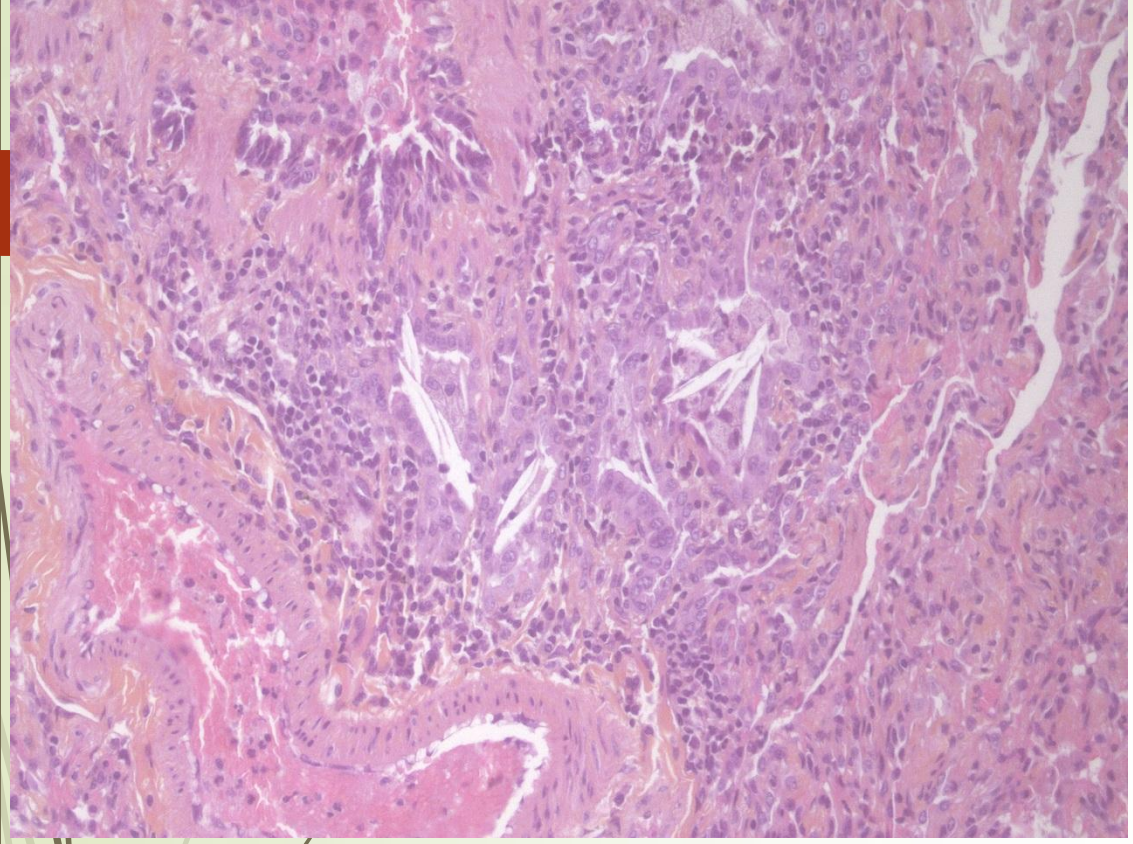
At the age
of
26 years old

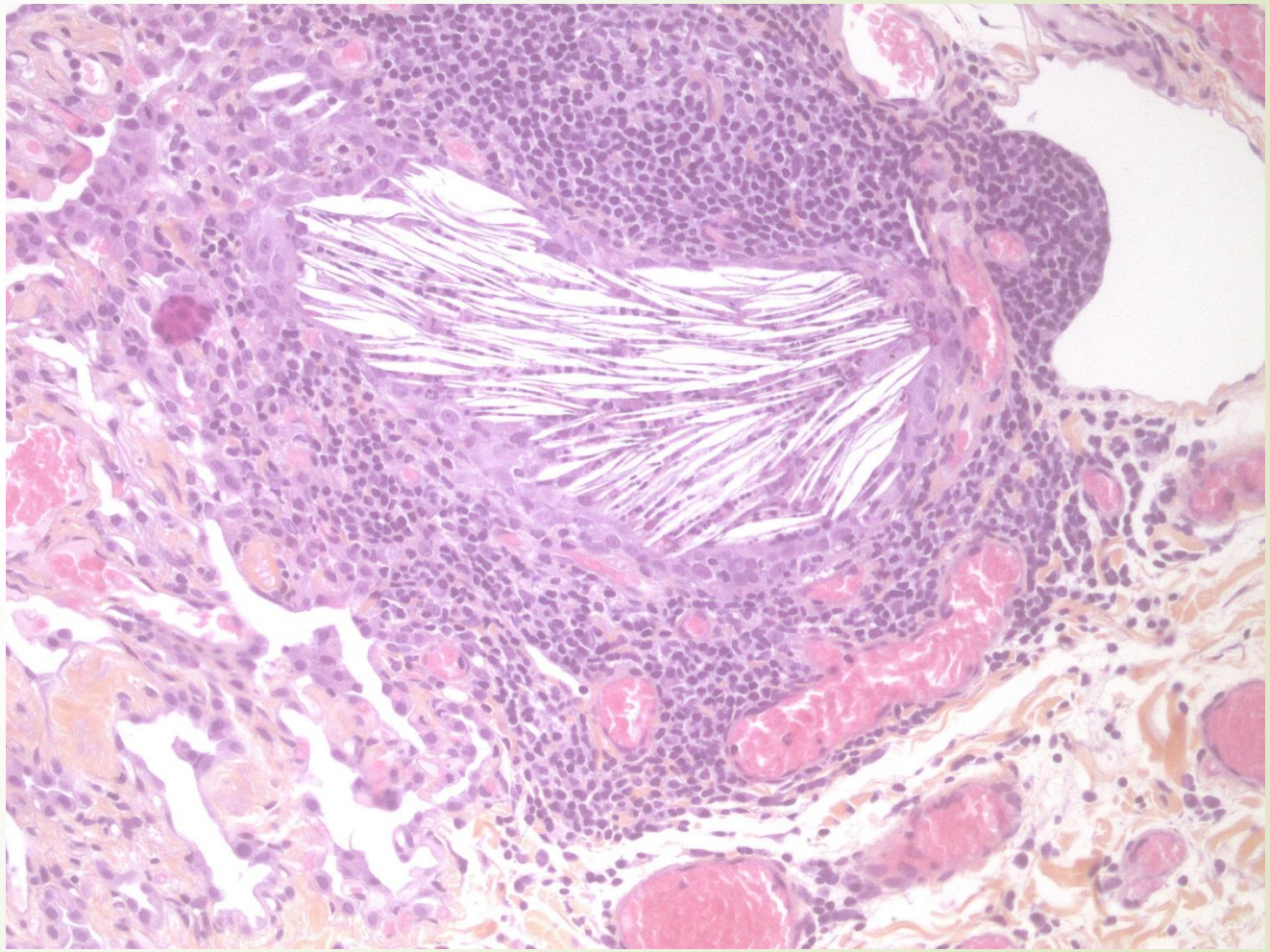












A similar pattern of NSIP with less DIP but with still focal fibrosis in the center of septa and persistence of the capillary bed

Courtesy of Professeur Aurore Coulomb L'Hermine

Hôpitaux Universitaires Est Parisien
• Saint-Antoine • Rothschild
• Trousseau La Roche-Guyon • Tenon

AP-HP - Hôpitaux Universitaires Est Parisien
Pôle de Biologie Médicale et Pathologie - Dr Vaubourdolle
Département de génétique médicale - Pr Siffroi
Hôpital d'enfants Armand Trousseau
U.F. de Génétique Moléculaire
Bâtiment Ketty Schwartz
26 avenue du Docteur Arnold Netter
75571 PARIS Cedex 12

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Responsable d'U.F. : **Pr. Serge Amselem**
Secrétariat: + 33 (0)1 44 73 52 95
Fax : + 33 (0)1 44 73 52 19
courriel : secret.genetiquemoleculaire@aphp.fr

Dr. Irina Giurgea +33 (0)1 44 73 52 45
Dr. Marie Legendre + 33 (0)1 44 73 52 21
Dr. Grégory Jouvion +33 (0)1 44 73 52 84
courriel : prenom.nom@aphp.fr

Docteur Effrosyni MANALI
ATTICON UNIVERSITY HOSPITAL
Department Pulmonary Medicine
HAIDARI
12462 ATHENE (Grèce)

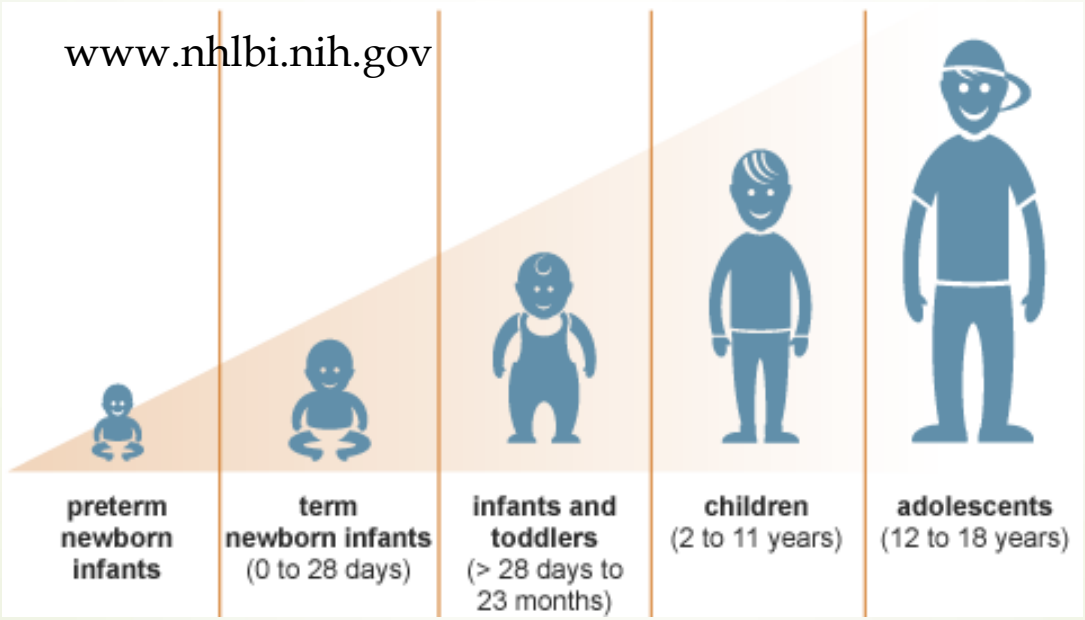
Résultat :

Variations pathogènes (classe 5) ou probablement pathogènes (classe 4) :

Gène (isoforme)	Mode de transmission	Statut	Exon	Nomenclature ADNc	Nomenclature protéique	Classe
ABCA3 (NM_001089)	Autosomique récessif	Hétérozygote	21	c.2890G>A	p.(Gly964Ser)	4 : Probablement pathogène
ABCA3 (NM_001089)	Autosomique récessif	Hétérozygote	29	c.4444C>T	p.(Arg1482Trp)	4 : Probablement pathogène

Date : 23/11/2017 11:04:14

In children pulmonary fibrosis (PF) is a very rare condition, which has been sparsely described in specific forms of children interstitial lung disease (chILD)



Nathan N, et al. Pulmonary Fibrosis in Children. J Clin Med. 2019 Aug 26;8(9). pii: E1312.

ChILD has a reported incidence of 1 to 4 per millions of children and covers heterogeneous disorders in the immunocompetent host

European Management Platform for Childhood Interstitial Lung Diseases

E-Rare

cost

ORIGINAL ARTICLE

International management platform for children's interstitial lung disease (chILD-EU)

Matthias Griese,[1] Elias Seidl,[1] Meike Hengst,[1] Simone Reu,[2] Hans Rock,[3] Gisela Anthony,[3] Nural Kiper,[4] Nagehan Emiralioğlu,[4] Deborah Snijders,[5] Lutz Goldbeck,[6] Reiner Leidl,[7] Julia Ley-Zaporozhan,[8] Ingrid Krüger-Stollfuss,[8] Birgit Kammer,[8] Traudl Wesselak,[1] Claudia Eismann,[1] Andrea Schams,[1] Doerthe Neuner,[1] Morag MacLean,[9] Andrew G Nicholson,[10] McCann Lauren,[11] Annick Clement,[12] Ralph Epaud,[12] Jacques de Blic,[12] Michael Ashworth,[13] Paul Aurora,[13] Alistair Calder,[13] Martin Wetzke,[14] Matthias Kappler,[1] Steve Cunningham,[9] Nicolaus Schwerk,[14] Andy Bush,[10,11] and the other chILD-EU collaborators

Thorax. 2018 Mar;73(3):231-239.

Table 3 Distribution of 346 subjects in the disease categories and subcategories of the chILD-EU register after peer review

Category	Subcategory/Diagnosis	Total	Percentage
A1—DPLD-diffuse developmental disorders		9	2.6%
	Alveolar capillary dysplasia with misalignment pulmonary vein	7	
	Congenital alveolar dysplasia	2	
A2—DPLD-growth abnormalities deficient alveolarisation		22	6.4%
	Related to preterm birth	11	
	Related to chromosomal disorders	8	
	Others	3	
A3—DPLD-infant conditions of undefined aetiology		64	18.5%
	Chronic tachypnoea of infancy (usual or aberrant)	30	
	Neuroendocrine cell hyperplasia of infancy	27	
	Pulmonary interstitial glycogenosis	5	
	Others	2	
A4—DPLD-related to alveolar surfactant region		77	22.3%
	ABCA3 mutations	18	
	SFTPC mutation	10	
	NKX2.1 mutations	3	
	NSIP	19	
	Pulmonary alveolar proteinosis	9	
	Others	18	
Ax—DPLD-unclear RDS in the mature neonate		5	1.4%
Ay—DPLD-unclear RDS in the almost (30–36 weeks) mature neonate		9	2.6%
B1—DPLD-related to systemic disease processes		54	15.6%
	Sarcoidosis	12	
	Idiopathic pulmonary haemosiderosis	6	
	Storage diseases	4	
	Immune-mediated/collagen vascular disorders	4	
	Familial dysautonomia	3	
	Filamin A mutation	3	
	Langerhans cell histiocytosis	3	
	GPA—Granulomatosis with polyangiitis (Wegener)	3	
	Others	16	
B2—DPLD-in the presumed immune intact host, related to exposures (infectious/non-infectious)		46	13.3%
	Infectious/postinfectious processes	17	
	BO	14	
	Exogen allergic alveolitis/hypersensitivity pneumonitis	7	
	Others	8	
B3—DPLD-in the immunocompromised host or transplanted		15	4.3%
	NSIP	4	
	BO	3	
	Related to transplantation and rejection	3	
	Others	5	
B4—DPLD-related to lung vessels structural processes		16	4.6%
	Pulmonary haemorrhage	8	
	Pulmonary hypertension	5	
	Others	3	
B5—DPLD-related to reactive lymphoid lesions		4	1.2%
	Lymphocytic interstitial pneumonia	3	
	Others	1	
Bx—DPLD-unclear RDS in the NON-neonate		1	0.3%
By—DPLD-unclear NON-neonate		5	1.4%
Bz—DPLD		1	0.3%
C1—localised, congenital gross structural abnormalities of the lungs		6	1.7%
C2—localised, acquired gross structural abnormalities of the lungs		0	0%
D—Airway disorders		12	3.5%
	Chronic bronchitis	7	
	Others	5	

Cases of chronic tachypnoea of infancy (usual or aberrant) had no biopsy and were defined as described previously;[16] cases were only labelled 'Neuroendocrine cell hyperplasia of infancy' if there was proof by biopsy and concordant clinical symptoms. Details on the classification system and definitions used are given in the supplement of Griese *et al*.[12]
BO, bronchiolitis obliterans; DPLD, diffuse parenchymal lung diseases; NSIP, non-specific interstitial pneumonitis; RDS, respiratory distress syndrome.

needed, genetic advice is also taken. After discussion, the lead clinician summarises the diagnosis, categorises the case and concludes the peer review. An automatic message informs the site physician about the result and further recommendations.

Results from peer reviewing by multidisciplinary review teams

Of the 575 patients included into the register for observation, 190 patients had insufficient data precluding the start of the peer review. In 385 patients, peer review requests were accepted, 39 could not be finalised due to information for which the reviewers

None of the classifications identified PF as a distinct chILD entity, and contrarily to adult PF, no PF diagnosis criteria have been proposed in children

Evaluation of inter-observer variation for computed tomography identification of childhood interstitial lung disease

Joseph Jacob[1,2], Catherine M. Owens[3], Alan S. Brody[4], Thomas Semple[5], Tom A. Watson[3], Alistair Calder[3], Pilar Garcia-Peña[6], Paolo Toma[7], Anand Devaraj[5], Henry Walton[8], Antonio Moreno-Galdó[9], Paul Aurora[10], Alexandra Rice[11], Timothy J. Vece[12], Steve Cunningham[13], Andre Altmann[2], Athol U. Wells[14], Andrew G. Nicholson[11] and Andrew Bush[15]

ERJ Open Res. 2019 Jul 29;5(3). pii: 00100-2019.

TABLE 1 Assignations of first-choice individual childhood interstitial lung disease (chILD) group or diagnosis in children under 2 years of age (n=35) and over 2 years of age (n=49) by 10 observers

chILD category	chILD group/diagnosis	Numbers of first-choice assignations	
		<2 years	>2 years
chILD groups	Normal	3	18
	Airways disease[#]	77	170
	Interstitial pneumonia	126	200
	Developmental/undefined aetiology disorders[¶]	99	48
	Unclassifiable	4	13
	Bronchopulmonary dysplasia	29	10
	Other	12	31
chILD Diagnoses	Exudative bronchiolitis	4	2
	Constrictive obliterative bronchiolitis	10	48
	Infection	48	86
	Chronic pneumonitis of infancy	47	12
	Pulmonary alveolar proteinosis	53	24
	Desquamative interstitial pneumonia	8	13
	Nonspecific interstitial pneumonia (cellular)	16	34
	Diffuse alveolar damage	3	8
	Fibrotic nonspecific interstitial pneumonia	1	47
	Organising pneumonia	0	30
	Diffuse alveolar haemorrhage	1	11
	Alveolar microlithiasis	0	3
	Sarcoidosis	0	6
	Langerhans cell histiocytosis	1	12
	Lung growth abnormality/chronic disease of prematurity	83	12
	Pulmonary interstitial glycogenosis	11	0
	Neuroendocrine cell hyperplasia of infancy	30	15
	Lymphoid interstitial pneumonia	1	23
	Diffuse lymphoid hyperplasia	1	2
	Lymphomatoid granulomatosis	1	4
	Follicular bronchiolitis	0	6
	Bronchus-associated lymphoid tissue	0	1
	Primary pulmonary arterial hypertension	1	4
	PVOD/PCH	3	5
	Thromboembolic disease	1	3
	Lymphangiomatosis	1	1
	Lymphangiectasia (primary and secondary)	7	7
	Secondary vasculopathies (*e.g.* due to cardiac disease)	6	2
	Primary and secondary pulmonary vasculitis	1	14
	Neoplasms	0	9
	Alternate diagnosis	11	24

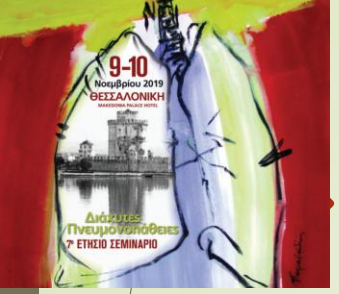
PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis. [#]: airways disease included infection and obliterative and exudative bronchiolitis; [¶]: developmental/undefined aetiology disorders included growth disorders such as alveolar hypoplasia, neuroendocrine cell hyperplasia of infancy and pulmonary interstitial glycogenosis.

Making chILD diagnoses on CT is difficult, even amongst sub-specialists

TABLE 2 Fleiss kappa values for observer agreement for first choice group assignation in the 84 study cases. Sub-analyses are shown for patients under 2 years of age (n=35) and over 2 years of age (n=49)

Patient groups	Observer groups	All cases	Airways disease[#]	Interstitial pneumonia	Developmental/undefined[¶]
All patients	All observers	0.30 (0.28–0.32)	0.37 (0.34–0.41)	0.36 (0.33–0.40)	0.18 (0.15–0.21)
	Senior radiologists	0.35 (0.27–0.42)	0.46 (0.34–0.58)	0.44 (0.31–0.56)	0.16 (0.04–0.29)
	Senior pulmonologists	0.28 (0.23–0.33)	0.34 (0.25–0.42)	0.36 (0.27–0.45)	0.21 (0.12–0.29)
	Junior radiologists	0.31 (0.23–0.38)	0.45 (0.33–0.57)	0.39 (0.27–0.51)	0.07 (−0.06–0.19)
Patients <2 years of age	All observers	0.22 (0.19–0.25)	0.28 (0.23–0.33)	0.30 (0.25–0.35)	0.14 (0.09–0.19)
	Senior radiologists	0.36 (0.24–0.48)	0.61 (0.42–0.80)	0.46 (0.26–0.65)	0.15 (−0.05–0.34)
	Senior pulmonologists	0.18 (0.10–0.26)	0.24 (0.11–0.38)	0.26 (0.12–0.39)	0.16 (0.02–0.29)
	Junior radiologists	0.13 (0.01–0.24)	0.35 (0.16–0.54)	0.19 (−0.00–0.38)	−0.05 (−0.24–0.14)
Patients >2 years of age	All observers	0.33 (0.31–0.36)	0.40 (0.36–0.45)	0.40 (0.36–0.44)	0.11 (0.07–0.15)
	Senior radiologists	0.31 (0.21–0.41)	0.36 (0.20–0.53)	0.42 (0.26–0.58)	0.12 (−0.04–0.29)
	Senior pulmonologists	0.32 (0.25–0.40)	0.36 (0.24–0.47)	0.43 (0.32–0.55)	0.09 (−0.02–0.21)
	Junior radiologists	0.42 (0.32–0.53)	0.52 (0.36–0.68)	0.48 (0.32–0.64)	0.09 (−0.07–0.25)

[#]: airways disease included infection and obliterative and exudative bronchiolitis; [¶]: developmental/undefined aetiology disorders included growth disorders such as alveolar hypoplasia, neuroendocrine cell hyperplasia of infancy and pulmonary interstitial glycogenosis.



PF reports in pediatric population

Diffuse Lung Disease in Young Children

Application of a Novel Classification Scheme

Gail H. Deutsch[1*], Lisa R. Young[2*], Robin R. Deterding[3], Leland L. Fan[4], Sharon D. Dell[5], Judy A. Bean[6], Alan S. Brody[7], Lawrence M. Nogee[8], Bruce C. Trapnell[9], Claire Langston[10], and the Pathology Cooperative Group: Eric A. Albright[11], Frederic B. Askin[12], Peter Baker[11], Pauline M. Chou[13], Carlyne M. Cool[14], Susan C. Coventry[15], Ernest Cutz[16], Mary M. Davis[17], Megan K. Dishop[10], Csaba Galambos[18], Kathleen Patterson[19], William D. Travis[20], Susan E. Wert[9], and Frances V. White[21]; on behalf of the ChILD Research Co-operative[†]

Am J Respir Crit Care Med Vol 176. pp 1120–1128, 2007

TABLE 2. AGE AT BIOPSY AND OUTCOME BY CATEGORY

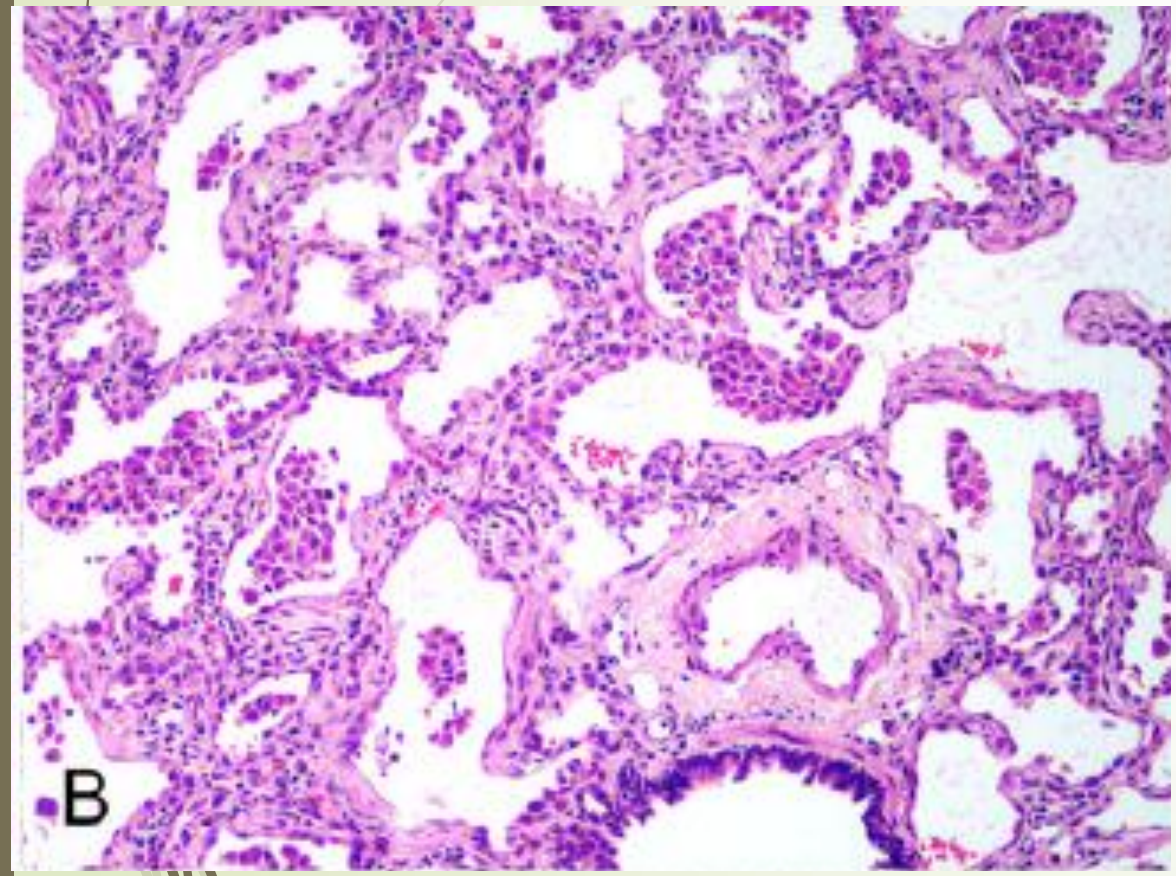
Category	Age at Biopsy, mo Mean ± SEM (*range*)	% Mortality	Age at Death, mo Mean ± SEM (*range*)	Age at Follow-up of Survivors, mo Mean ± SEM (*range*)
Diffuse developmental disorders	0.7 ± 0.2 (0.3–1.2)	100%	0.7 ± 0.1 (0.3–1.2)	n/a
Lung growth abnormalities	5.35 ± 0.8 (0.3–22)	34%	9.5 ± 2.7 (0.3–31)	25.3 ± 3.1 (3–64)
Pulmonary interstitial glycogenosis	1.3 ± 0.4 (0.3–3.0)	0%	n/a	20.3 ± 6.1 (2–43)
Neuroendocrine cell hyperplasia of infancy	13.9 ± 1.7 (2.7-24)*	0%	n/a	37.9 ± 5.3 (15–71)
Surfactant dysfunction (all)	5.8 ± 1.6 (0.2–22)	41.2%	1.9 ± 0.6 (0.4–4.5)	36.9 ± 7.9 (10–73)
SP-C mutations	8.9 ± 3.0 (2.0 –22)	0%	n/a	36.8 ± 8.4 (10–61)
ABCA-3 mutations	1.3 ± 0.5 (0.2 –3.0)[†]	100%	1.9 ± 0.7 (0.4–4.5)	n/a
Disorders of the normal host	13.1 ± 1.7 (1.2–24)	5%	15.0	39.7 ± 4.8 (11–72)
Disorders resulting from systemic disease processes	10.5 ± 3.6 (1–22)	20%	1.4	23.5 ± 3.8 (16–33)
Disorders of the immunocompromised host	11.6 ± 1.3 (1.5–24)	30.8%	12.4 ± 2.9 (2.5–28)	36.1 ± 3.3 (10–61)
Disorders masquerading as ILD	7.3 ± 2.3 (0.2–24)	28.6%	11.0 ± 5.0 (6–16)	17.8 ± 5.5 (7–33)

Definition of abbreviations: ILD = interstitial lung disease; NEHI = neuroendocrine cell hyperplasia of infancy; SP-C = surfactant protein C.

* $P < 0.05$ for NEHI versus other disorders of infancy.

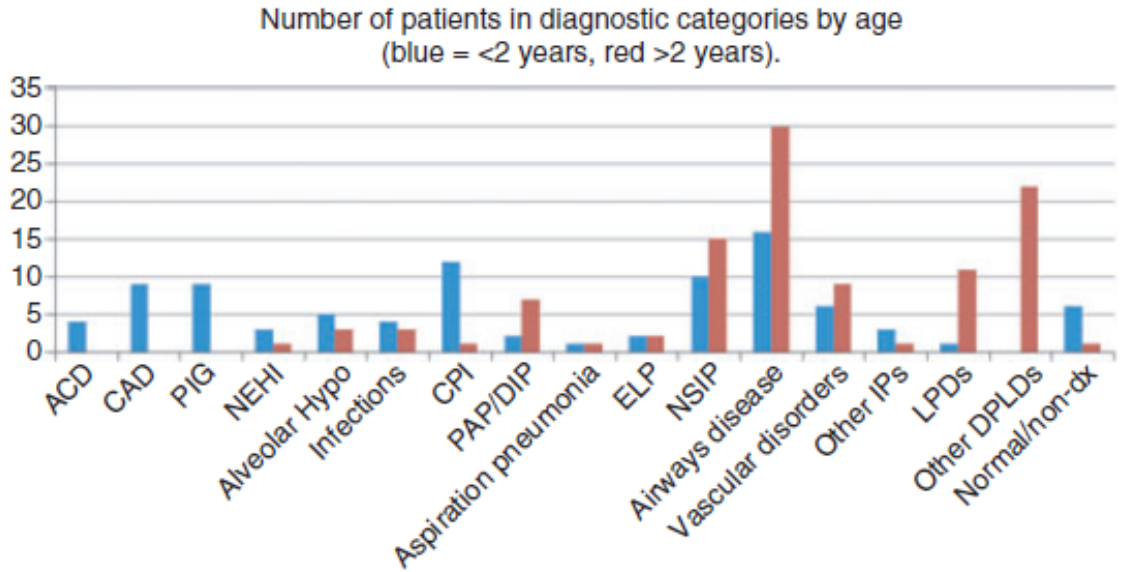
† $P < 0.01$ for ABCA-3 versus SP-C.

Deutsch et al. observed only one patient with PF out of a population of 99 pediatric patients with chILD.



- ✓ 22-months-old patient
- ✓ surfactant disorder due to *SFTPC* mutation
- ✓ non-specific interstitial pneumonia (NSIP) pattern, together with PAS-positive staining consistent with PAP

In 2013, Rice and al. reviewed the lung biopsies of 211 patients with various forms of chILD and confirmed the rarity of PF in children



2% of chILD < 2 years old and 7% aged 2-18 years

NSIP was the most prevalent histologic pattern,
but most pediatric patients harbour coexisting histologic patterns of ILD
within the same sample such as
alveolar proteinosis, desquamative interstitial pneumonia (DIP) or follicular bronchiolitis.

Histopathology 2013; 63:743-755

Journal of
Clinical Medicine

Review

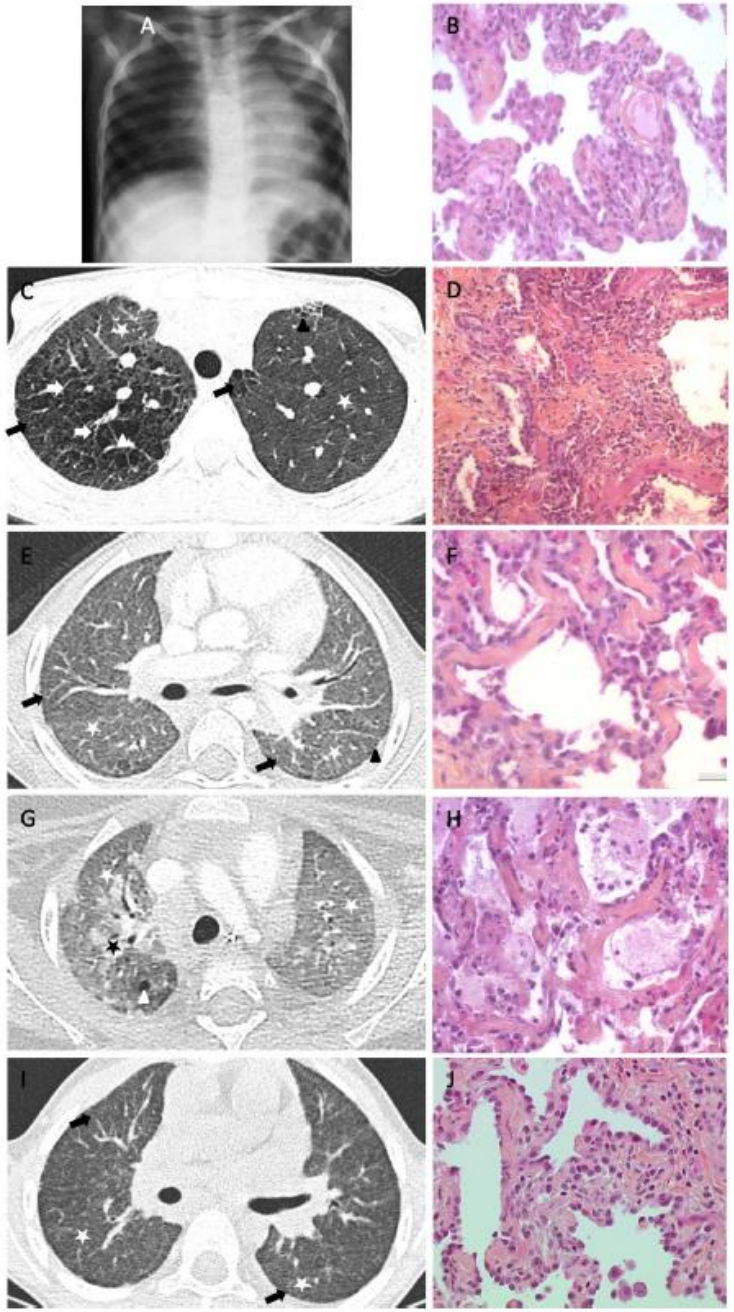
Pulmonary Fibrosis in Children

Nadia Nathan [1,2,*], Chiara Sileo [3], Guillaume Thouvenin [1], Laura Berdah [1], Céline Delestrain [1], Effrosyne Manali [4], Spyros Papiris [4], Pierre-Louis Léger [5], Hubert Ducou le Pointe [3], Aurore Coulomb l'Hermine [6] and Annick Clement [1,2]

Table 1. Suspected cases of pulmonary fibrosis (PF) in the children's interstitial lung disease (chILD) cohort of Armand Trousseau Hospital.

chILD Condition	Number of Patients	Number of Patients with Available Lung Samples	Number of Cases with Suspected PF
Surfactant disorders	17	5	2
Autoinflammatory and systemic disorders	6	6	1
Developmental disorders	8	8	0
Others	88	25	7
Total	**119**	**44**	**10**

J Clin Med. 2019 Aug 26;8(9). pii: E1312.



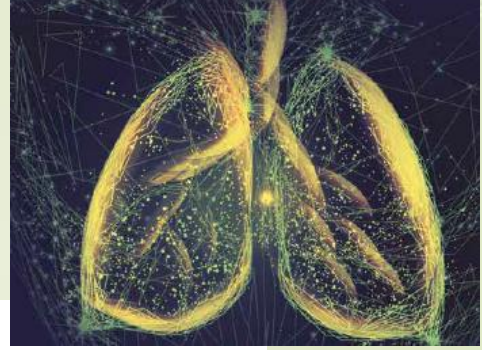


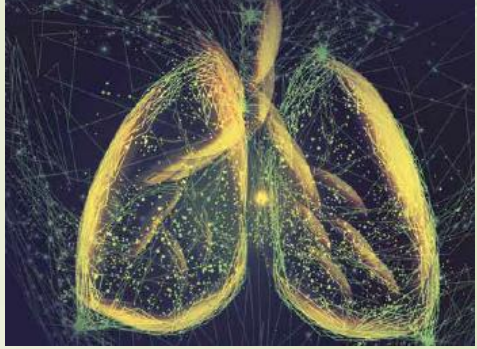
Table 2. Clinical data and outcomes of five patients of the Trousseau Hospital chILD cohort with lung fibrosis.

Patient Number	Clinical Presentation	Treatment	Outcome
1 [14,15]	6-year-old girl, *ABCA3*-related disease	HCQ, azithromycin	Diffuse fibrosing ILD at age 26
2 [16]	8-year-old boy, TMEM173-related disease	Corticosteroid pulses, oral corticosteroids, ruxolitinib at age 13.	Lung transplantation at age 14, died at age 16 after second lung transplantation
3	3-year-old boy, undefined chILD	Corticosteroids	Died at age 3 from respiratory failure
4	2-year-old girl, undefined chILD	Corticosteroid pulses, oral corticosteroids, azithromycin, immunosuppressive drugs	Died at age 2 from respiratory failure
5	2-year-old girl, undefined chILD	Corticosteroid pulses, oral corticosteroids, azithromycin	Asymptomatic at age 8

Abbreviations: chILD, children interstitial lung disease; HCQ, hydroxychloroquine.

- **No parenchymal distortion, diffuse thickening of the alveolar walls, hyperplasic AECs and moderate inflammatory cell recruitment**

- **moderate alveolar proteinosis: intra-alveolar deposit with giant cells and liproproteic material**

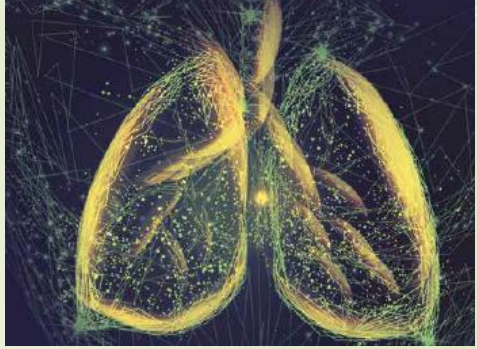


- It seems that adult radiologic and histologic lung fibrosis patterns partially fail to precisely describe pediatric PF lesions

and that UIP, the most common aspect of idiopathic PF (IPF) in adults is exceptionally or never observed in childhood

- A critical question is

whether the natural history of a children PF can evolve towards IPF

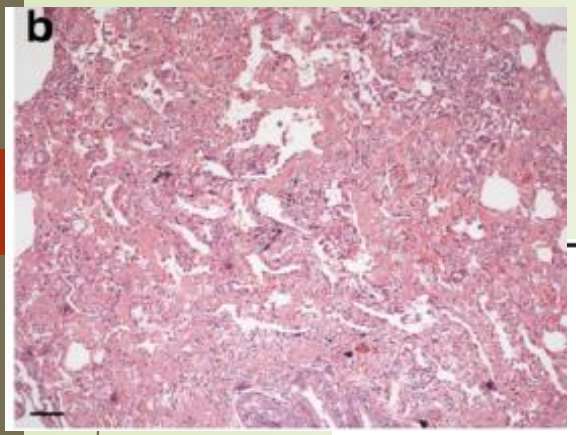


Two distinct situations may exist:

1. **Onset in infancy/childhood that rarely reach adulthood (cellular NSIP pattern→ fibrotic NSIP pattern)**

2. **Adult-onset diseases (fibrotic NSIP pattern or UIP pattern or CPFE pattern)**

A large kindred of pulmonary fibrosis associated with a novel ABCA3 gene variant



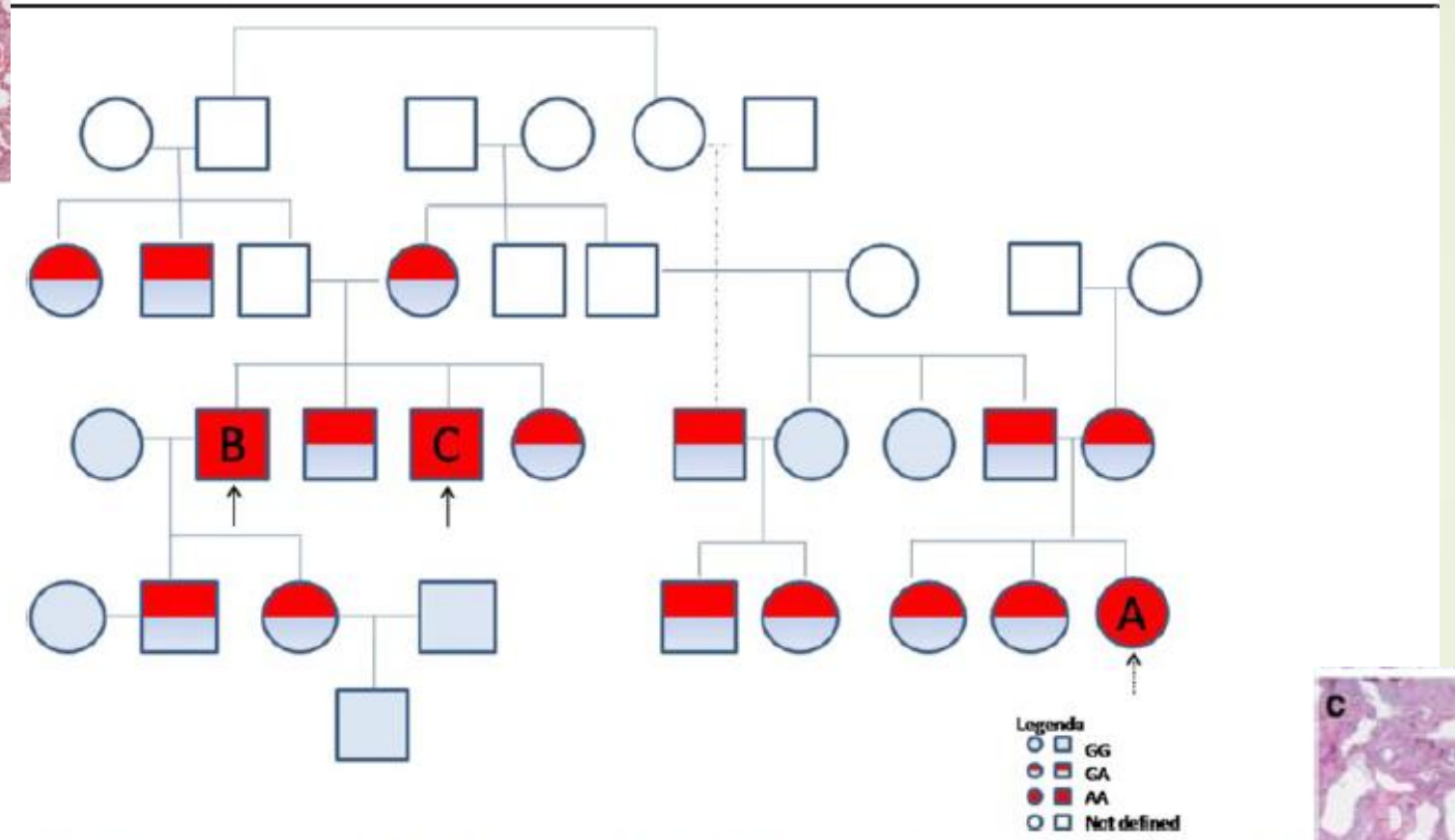
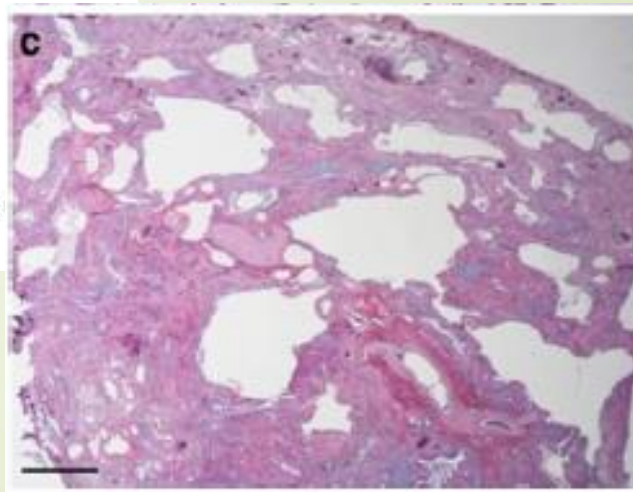


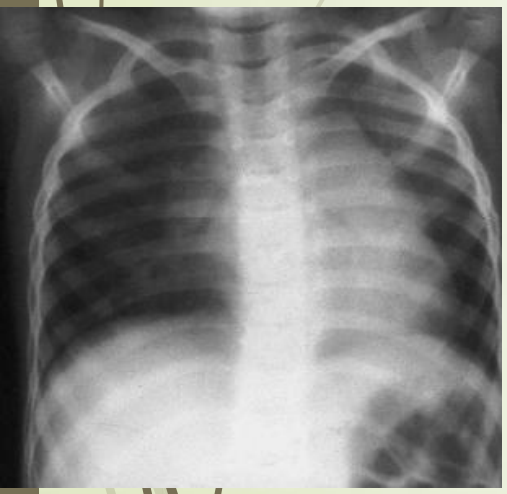
Figure 5 Family tree. The family genetic screening by the Taqman assay resulted in the identification of two other paternal members arrows), who were homozygous for the same ABCA3 Gly964Asp mutation. The proband is indicated by the dashed arrow.

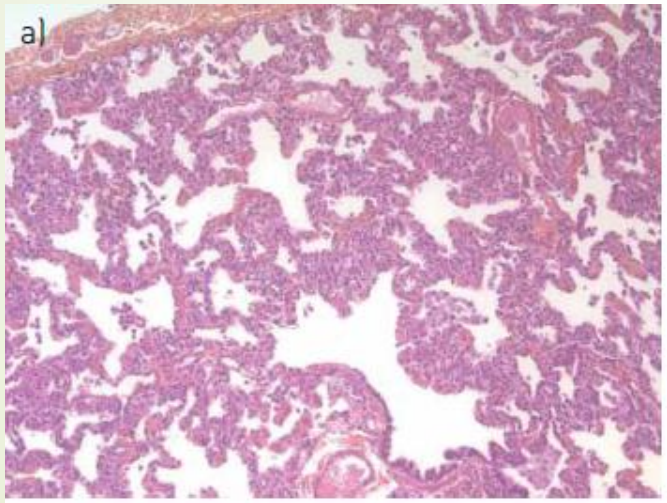


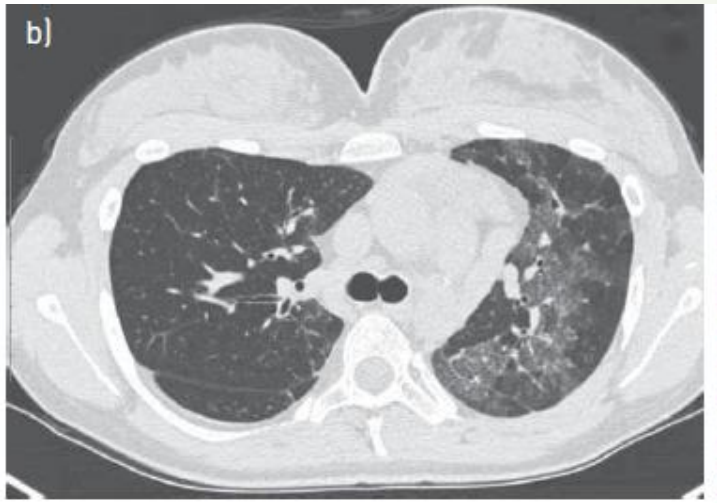
Campo *et al. Respiratory Research* 2014, **15**:43
http://respiratory-research.com/content/15/1/43

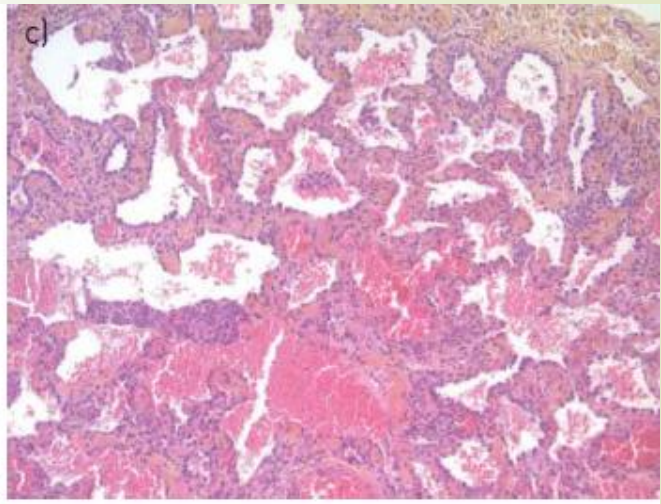
Bi-allelic missense *ABCA3* mutations in a patient with childhood ILD who reached adulthood

Effrosyni D. Manali[1,10], Marie Legendre[2,10], Nadia Nathan[3], Caroline Kannengiesser[4], Aurore Coulomb-L'Hermine[5], Theofanis Tsiligiannis[6], Pericles Tomos[7], Matthias Griese[8], Raphael Borie[9], Annick Clement[3], Serge Amselem[2], Bruno Crestani[4,9,10] and Spyros A. Papiris[1,10]









5.5 years old

26 years old

ERJ Open Res 2019; 5: 00066-2019

Résultat :

Variations pathogènes (classe 5) ou probablement pathogènes (classe 4) :

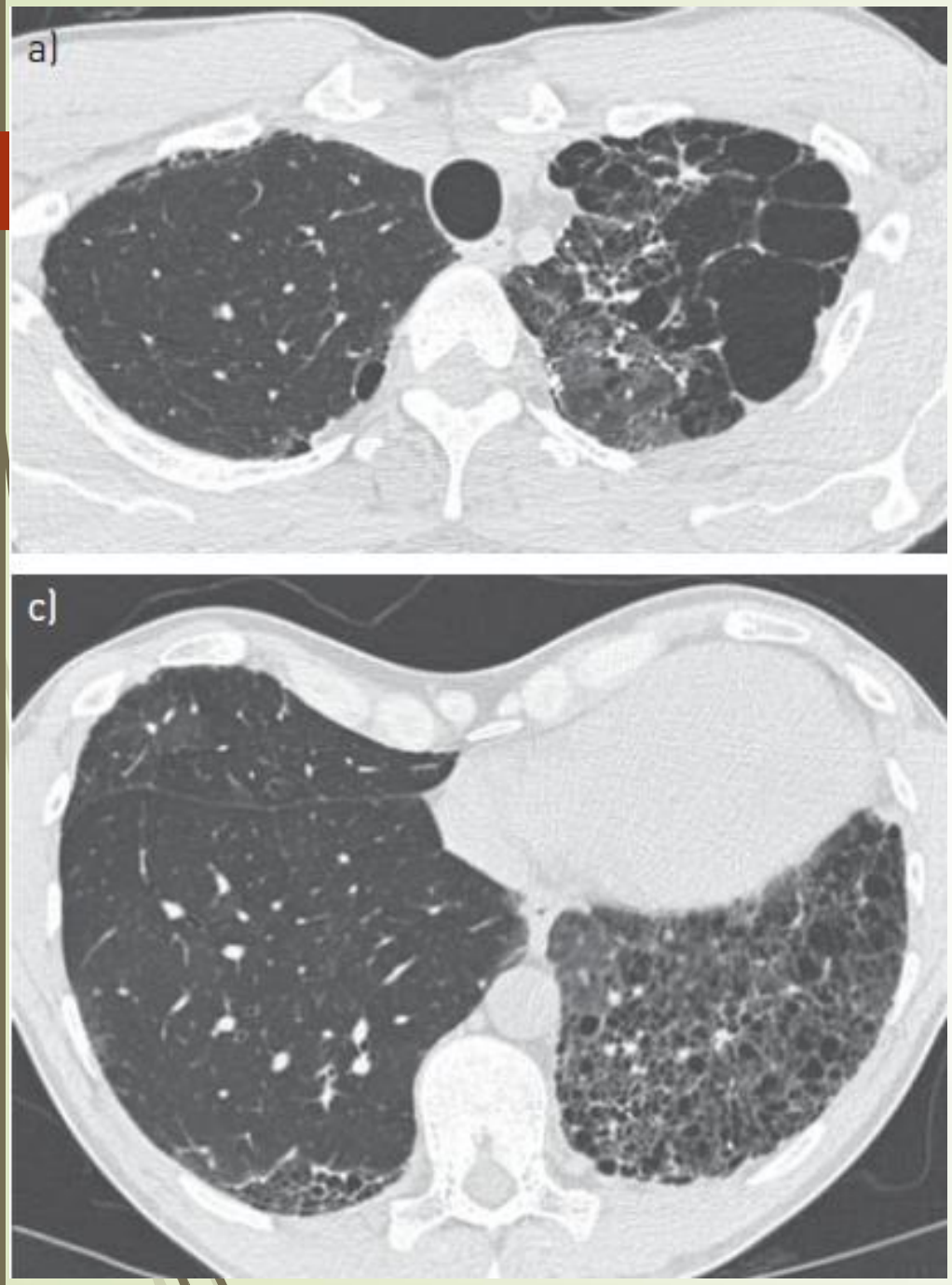
Gène (isoforme)	Mode de transmission	Statut	Exon	Nomenclature ADNc	Nomenclature protéique	Classe
ABCA3 (NM_001089)	Autosomique récessif	Hétérozygote	21	c.2890G>A	p.(Gly964Ser)	4 : Probablement pathogène
ABCA3 (NM_001089)	Autosomique récessif	Hétérozygote	29	c.4444C>T	p.(Arg1482Trp)	4 : Probablement pathogène

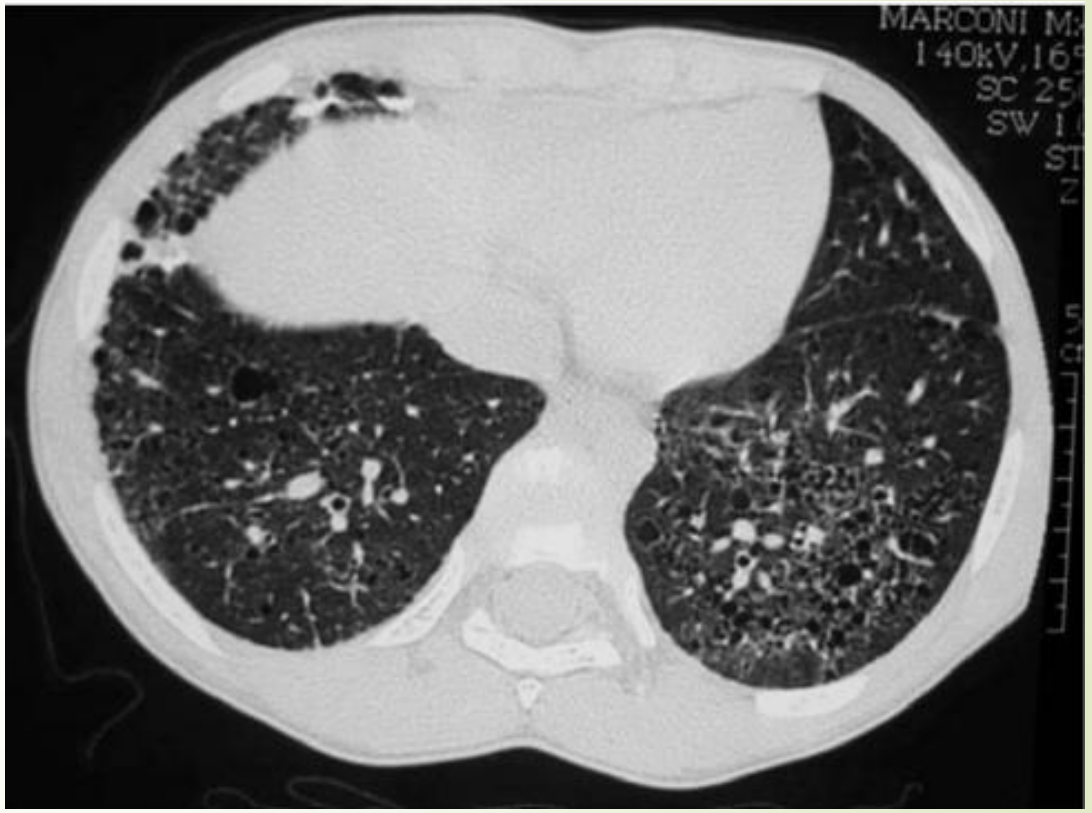
Date : 23/11/2017 11:04:14

1/2

To conclude, this study reports a chILD patient with bi-allelic missense *ABCA3* mutations who survived from childhood to adulthood. Non-progression to end-stage fibrosis was proven by a second biopsy 20 years later. Molecular diagnosis was made in adulthood and appropriate genetic counselling was provided accordingly. Genetic mechanisms should always be examined in specialised referral centres in adult patients with childhood onset ILD.

2. Adult-onset diseases
fibrotic NSIP or UIP or CPFE pattern

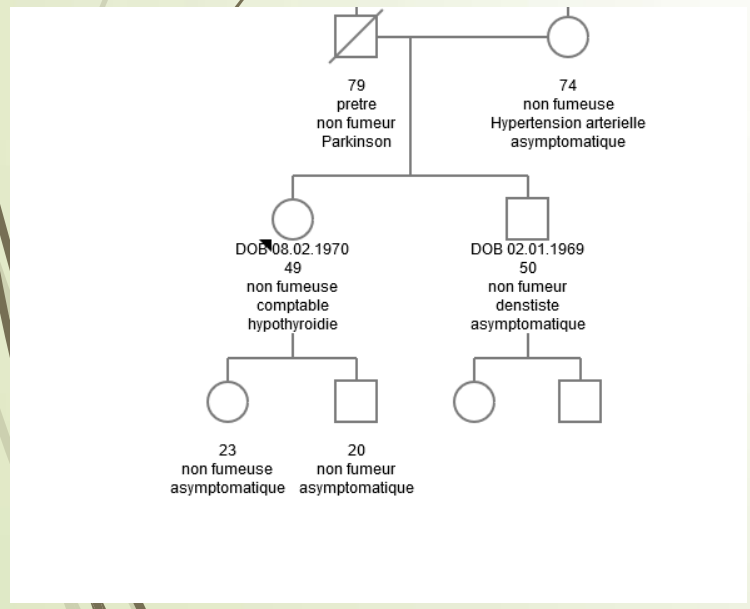


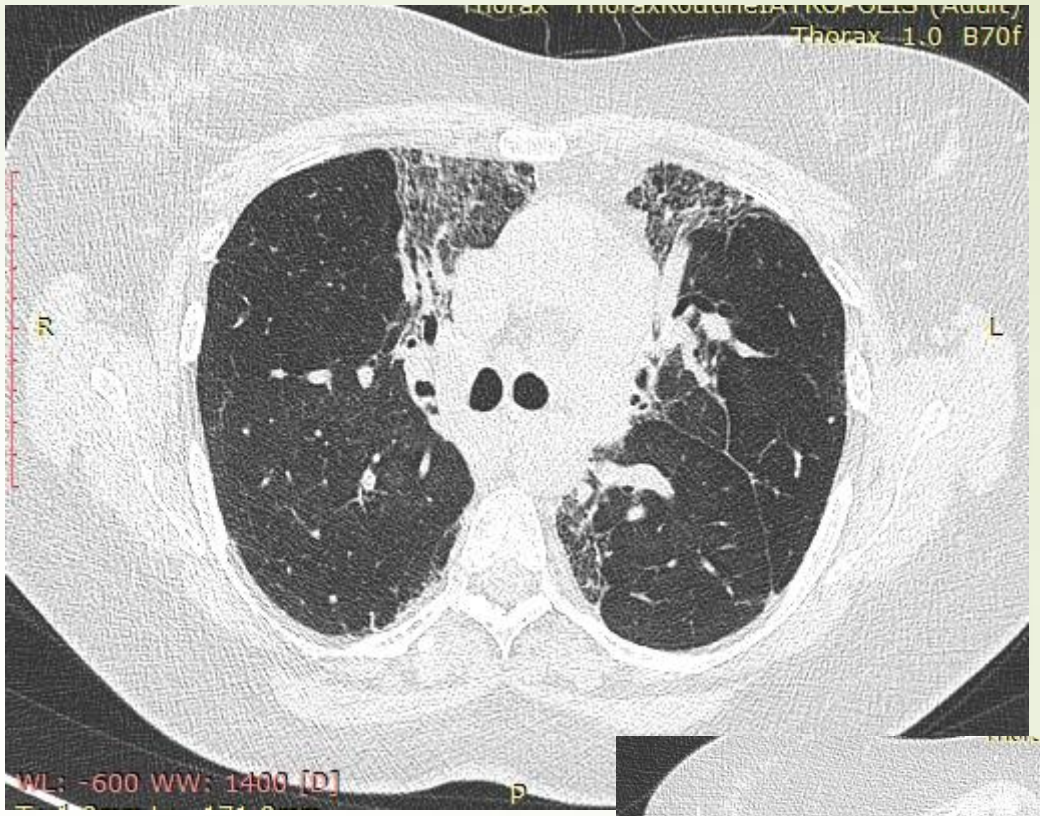


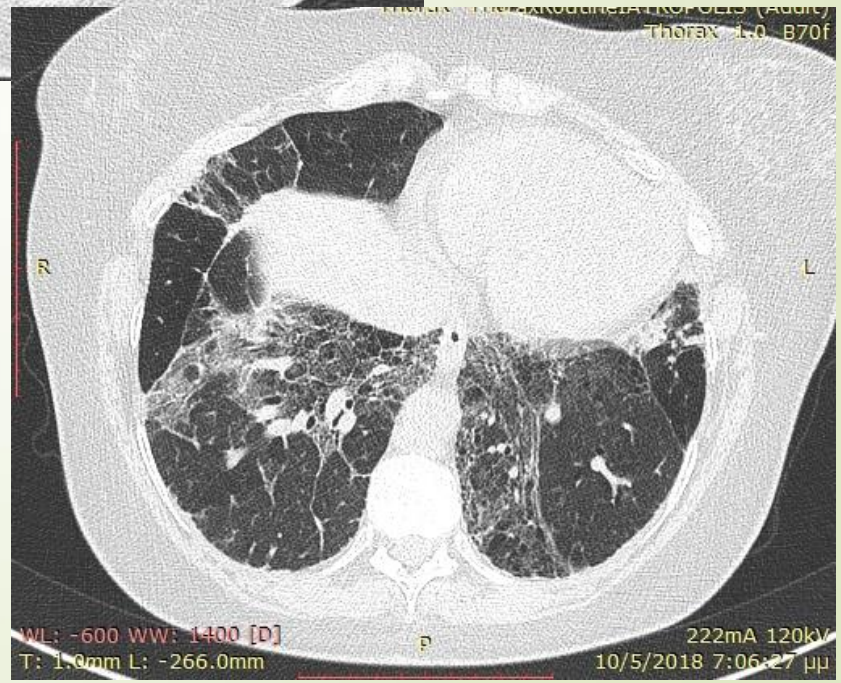
Epaud R, et al. Eur Respir J 2013, Borie R, et al. RMR 2014

Patient # 2

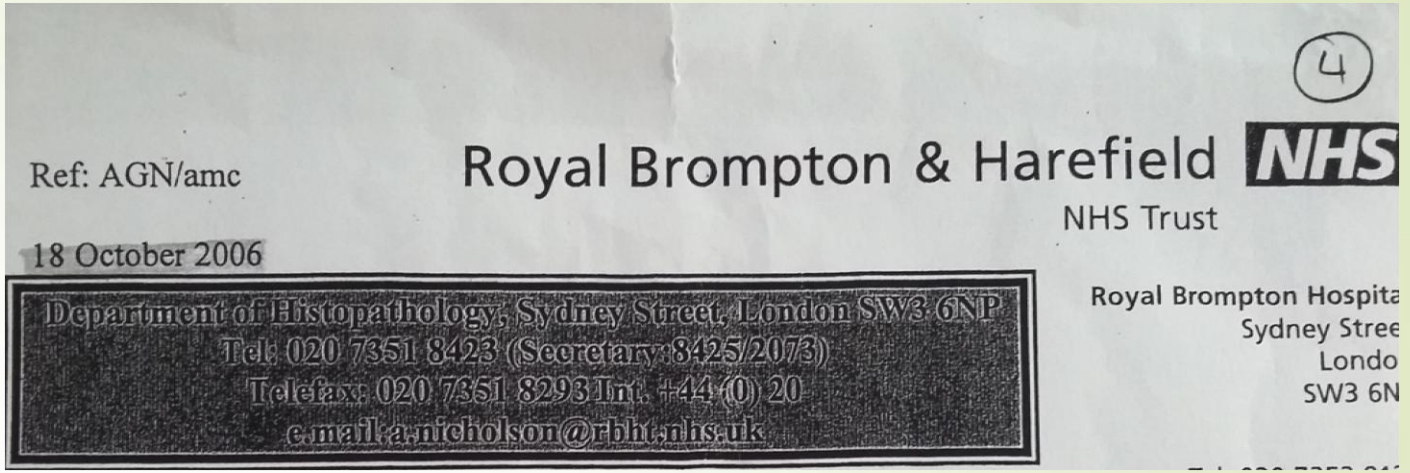
Female, non-smoker, 49 years old
ILD since the age of 30 years old
Finger clubbing
24h/d oxygen therapy
FEV1=38%, FVC=44%, Tf=73%,
TLC=67%, DLCO=36%







Courtesy of Professor Stylianos Loukides



(4)

Ref: AGN/amc

Royal Brompton & Harefield NHS

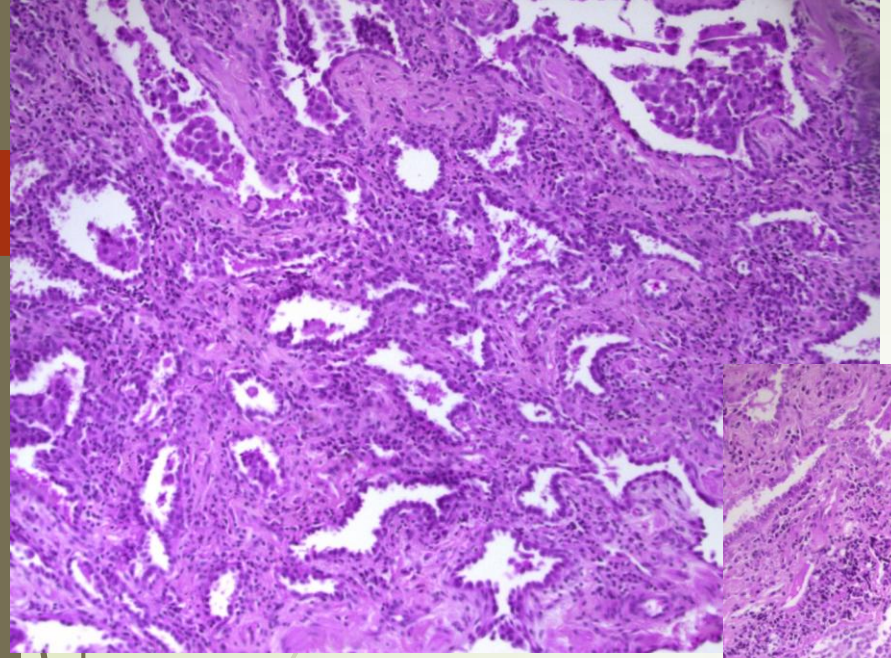
NHS Trust

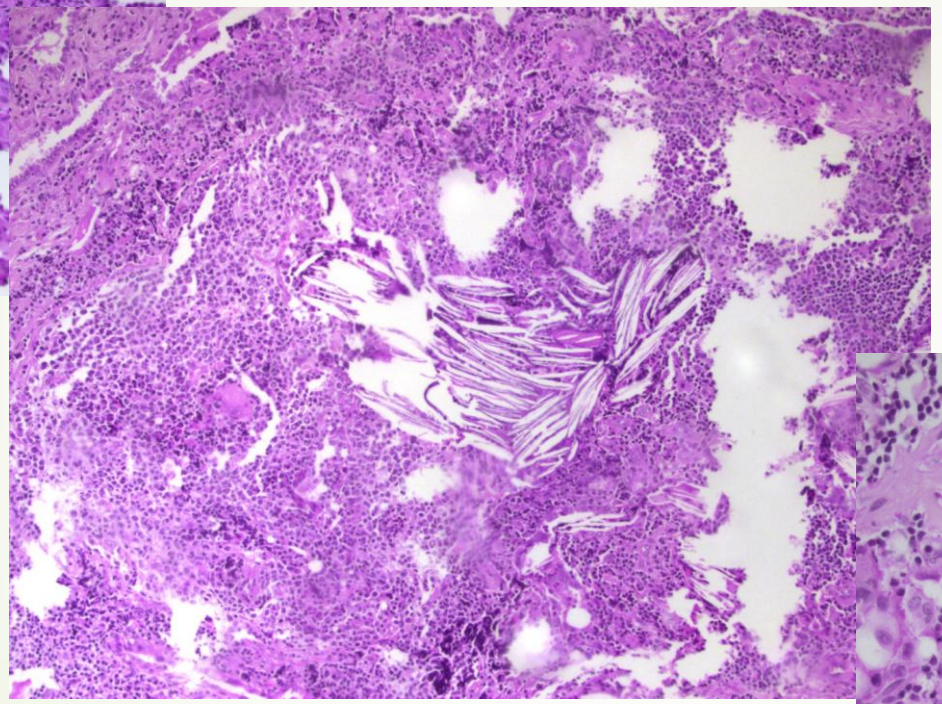
18 October 2006

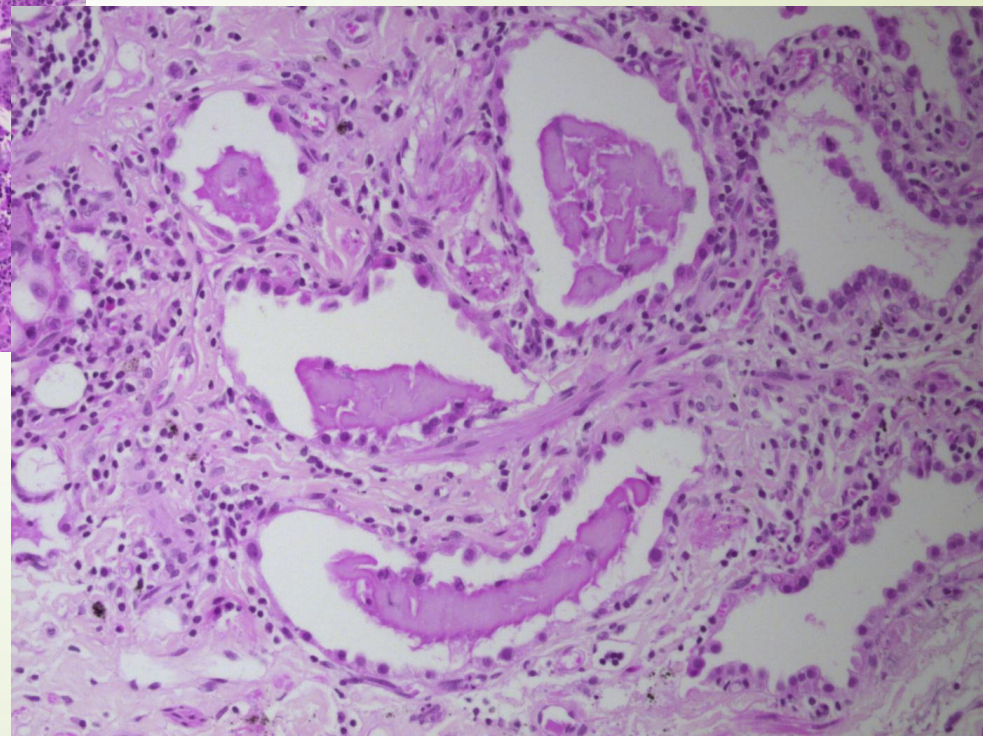
Department of Histopathology, Sydney Street, London SW3 6NP
Tel: 020 7351 8423 (Secretary 8425/2073)
Telefax: 020 7351 8293 Int. +44 (0) 20
e.mail a.nicholson@rbht.nhs.uk

Royal Brompton Hospita
Sydney Stree
Londo
SW3 6N

I would classify this as a fibrotic non-specific interstitial pneumonia, noting a quite marked inflammatory component. There is some loss of architecture but no classic honeycombing in this sample. In terms of a histologic pattern of fibrotic NSIP, there are numerous clinical associations but I can see no features that point towards extrinsic allergic alveolitis in this case or the changes being related to a history of smoking, neither does the biopsy look particularly like a case of idiopathic pulmonary fibrosis given the extent of chronic inflammation in the interstitium. There is no increase in eosinophils to suggest a drug reaction. Ultimately, none of the above can be absolutely excluded as the underlying clinicopathologic diagnosis on histology alone, but I wonder if this lady is someone who has true idiopathic NSIP and/or may subsequently present with systemic evidence of a collagen vascular disease.







Courtesy of Professeur Aurore Coulomb L'Hermine

Hôpitaux Universitaires Est Parisien
• Saint-Antoine • Rothschild
• Trousseau La Roche-Guyon • Tenon

AP-HP - Hôpitaux Universitaires Est Parisien
Pôle de Biologie Médicale et Pathologie - Dr Vaubourdolle
Département de génétique médicale - Pr Siffroi
Hôpital d'enfants Armand Trousseau
U.F. de Génétique Moléculaire
Bâtiment Ketty Schwartz
26 avenue du Docteur Arnold Netter
75571 PARIS Cedex 12

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Responsable d'U.F. : **Pr. Serge Amselem**
Secrétariat: + 33 (0)1 44 73 52 95
Fax : + 33 (0)1 44 73 52 19
courriel : secret.genetiquemoleculaire@aphp.fr

Dr. Irina Giurgea +33 (0)1 44 73 52 45
Dr. Marie Legendre + 33 (0)1 44 73 52 21
Dr. Grégory Jouvion +33 (0)1 44 73 52 84
courriel : prenom.nom@aphp.fr

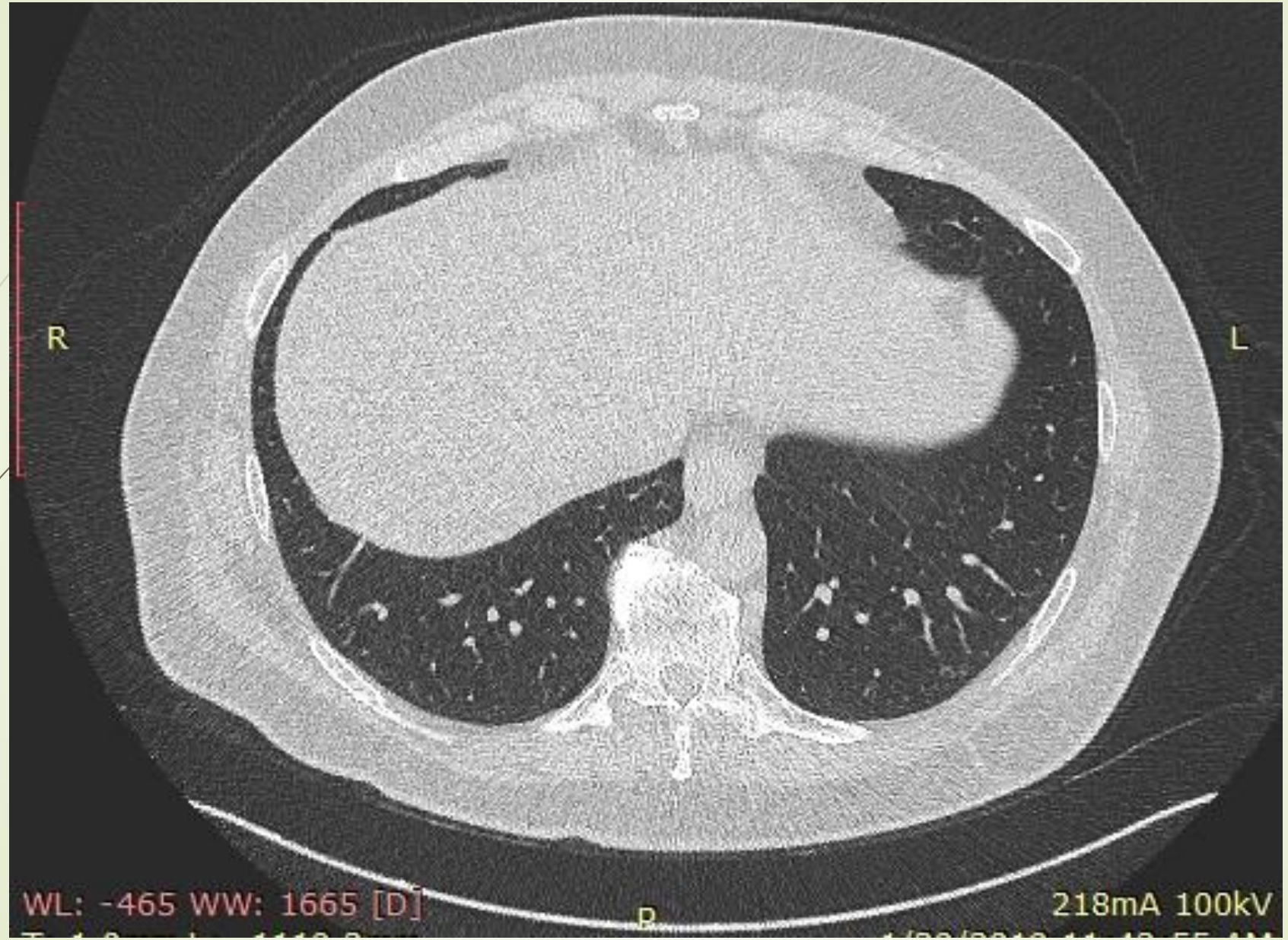
Docteur Effrosyni MANALI
ATTICON UNIVERSITY HOSPITAL
Department Pulmonary Medicine
HAIDARI
12462 ATHENE (Grèce)

Résultat :

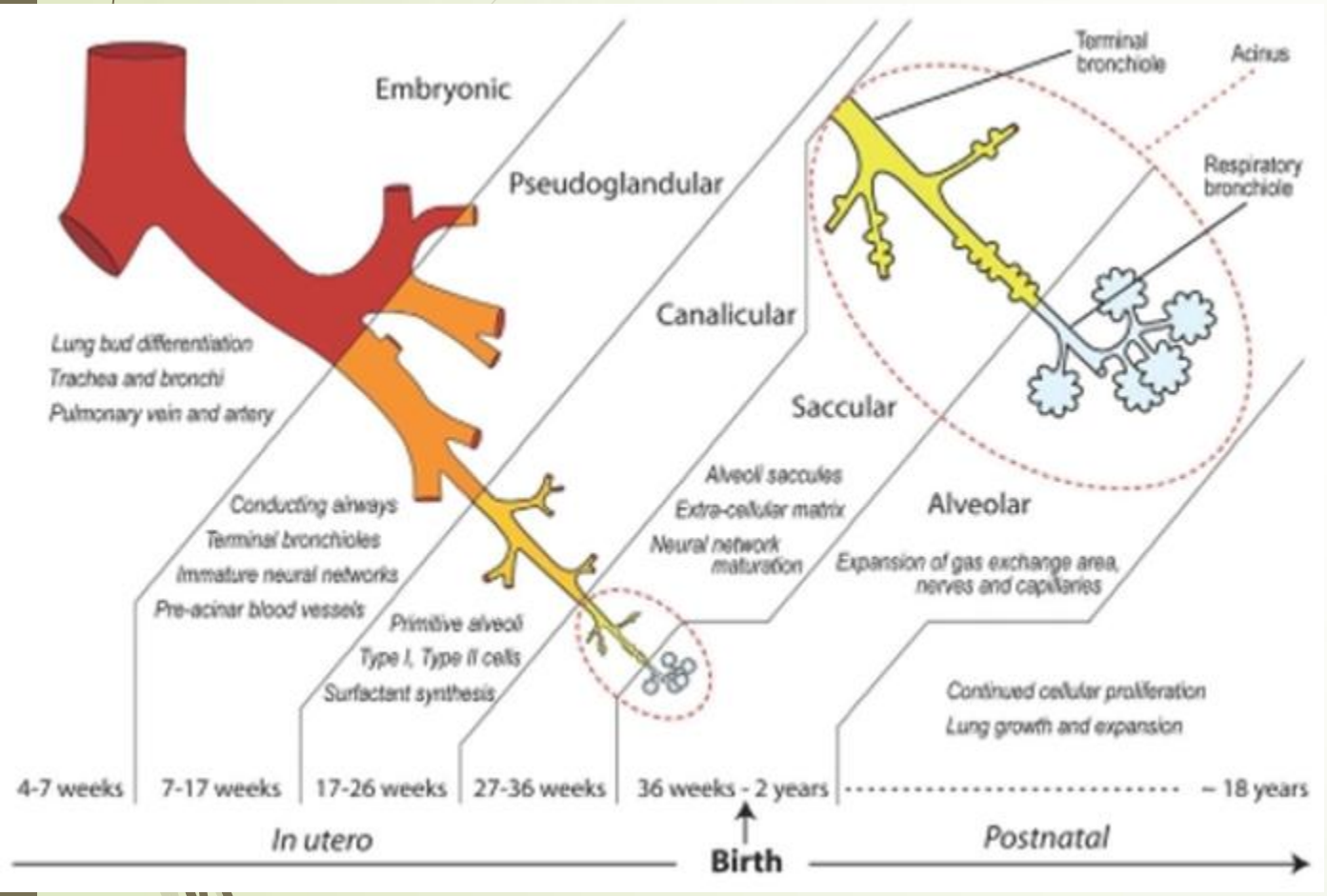
Variations pathogènes (classe 5) ou probablement pathogènes (classe 4) :

Gène (isoforme)	Mode de transmission	Statut	Exon	Nomenclature ADNc	Nomenclature protéique	Classe
ABCA3 (NM_001089)	Autosomique récessif	Hétérozygote	Exon 05	c.127C>T	p.(Arg43Cys)	4 : Probablement pathogène
ABCA3 (NM_001089)	Autosomique récessif	Hétérozygote	Exon 21	c.3004G>A	p.? ou p.(Gly1002Ser)	4 : Probablement pathogène

Potential functional studies regarding those missense variations…


R
L
WL: -465 WW: 1665 [D]
P
218mA 100kV

Pathophysiology



The pathophysiologic fibrosing process may be different occurring on a lung in development and growth versus on a grown-up, mature, and moreover senescent lung tissue

J Clin Med. 2019 Aug 26;8(9). pii: E1312.

Expression of fibroblast growth factors and their receptors during full-thickness skin wound healing in young and aged mice

Akiko Komi-Kuramochi[1], Mitsuko Kawano[1,2], Yuko Oda[1], Masahiro Asada[1], Masashi Suzuki[1], Junko Oki[1] and Toru Imamura[1]

[1]Signaling Molecules Research Laboratory, National Institute of Advanced Industrial Science and Technology (AIST), Higashi, Tsukuba 305-8566, Ibaraki, Japan

[2]University of Tsukuba, Tennodai, Tsukuba, Ibaraki 305-8572, Japan

(Requests for offprints should be addressed to T Imamura, National Institute of Advanced Industrial Science and Technology (AIST), Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki 305-8566, Japan; Email: imamura-toru@aist.go.jp)

The capacity for scarless repair is lost with age

Journal of Endocrinology 2005; 186: 273-289

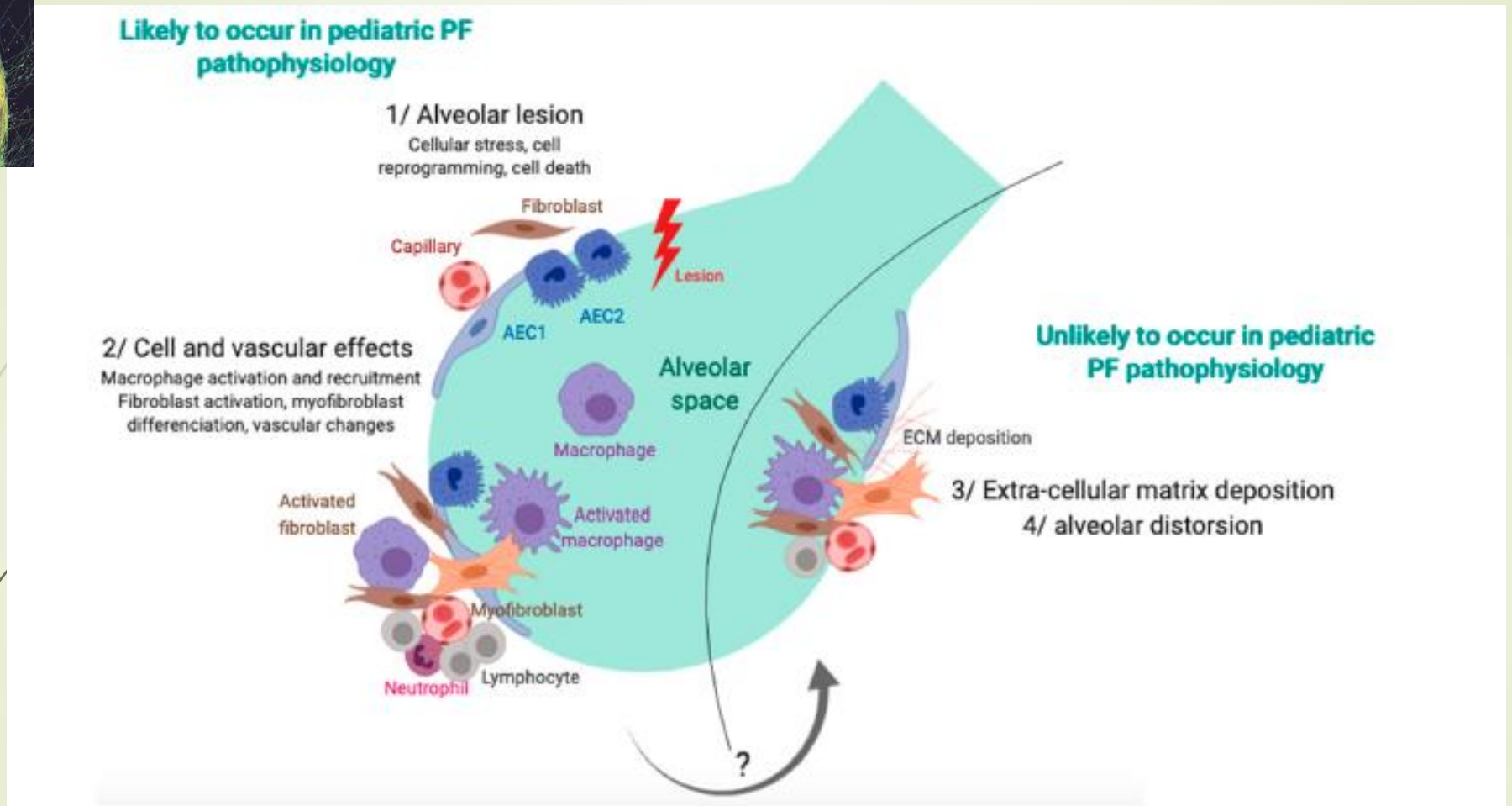
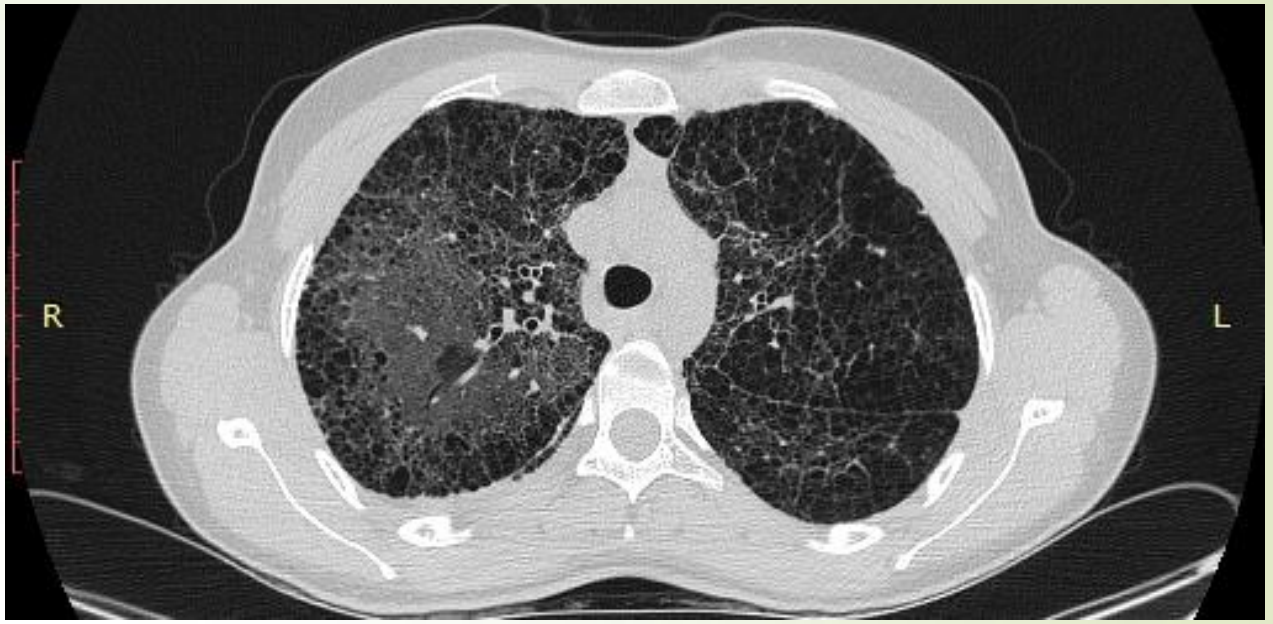


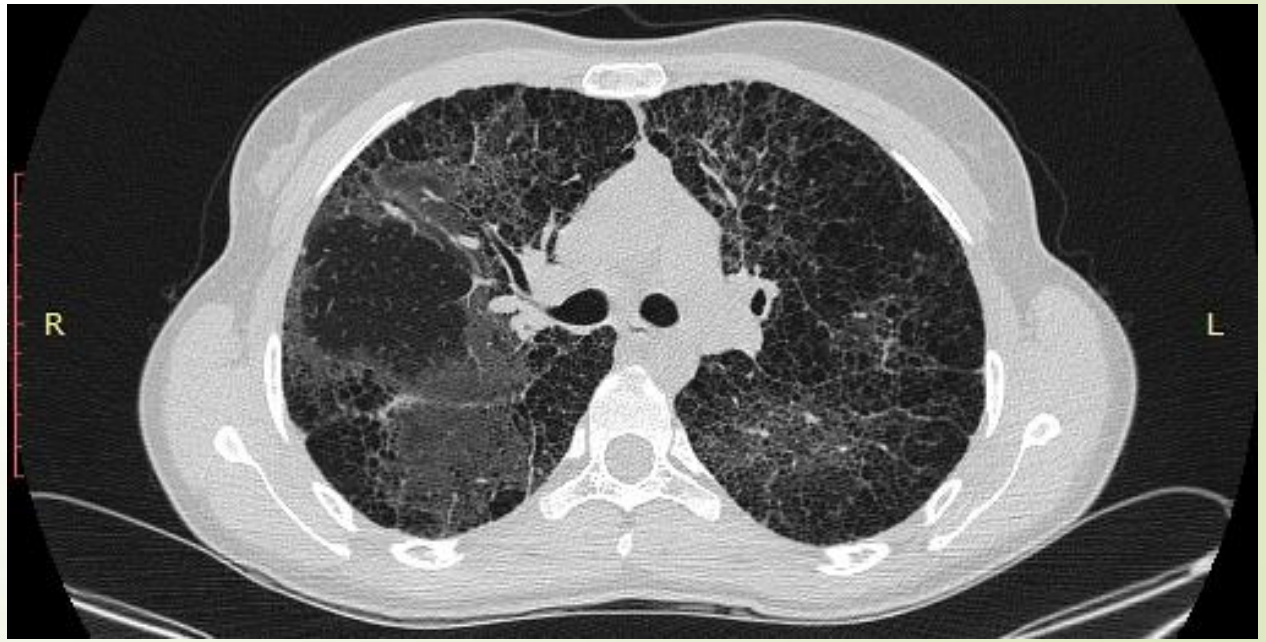
Figure 2. Potential pathophysiology pathway of pulmonary fibrosis in children. Repeated alveolar lesions' effects on AECs and alveolar macrophages are likely to be observed in children and adult pulmonary fibrosis, leading to a cellular NSIP pattern. The chance of an evolution toward an adult PF pattern with more fibroblastic activation and extracellular matrix deposition remains unknown.

J Clin Med. 2019 Aug 26;8(9). pii: E1312.

Patient # 3

Female, non-smoker,
22 years old student
ILD since ……..??
Finger clubbing
FVC=77%,
TLC=66%, DLCO=31.3%





Courtesy of Professor Anna Karakatsani

Hôpitaux Universitaires Est Parisien
Saint-Antoine • Rothschild
Trousseau La Roche-Guyon • Tenon

AP-HP - Hôpitaux Universitaires Est Parisien
Pôle de Biologie Médicale et Pathologie - Dr Vaubourdolle
Département de génétique médicale - Pr Siffroi
Hôpital d'enfants Armand Trousseau
U.F. de Génétique Moléculaire
Bâtiment Ketty Schwartz
26 avenue du Docteur Arnold Netter
75571 PARIS Cedex 12

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Responsable d'U.F. : **Pr. Serge Amselem**
Secrétariat: + 33 (0)1 44 73 52 95
Fax : + 33 (0)1 44 73 52 19
courriel : secret.genetiquemoleculaire@aphp.fr

Dr. Irina Giurgea +33 (0)1 44 73 52 45
Dr. Marie Legendre + 33 (0)1 44 73 52 21
Dr. Grégory Jouvion +33 (0)1 44 73 52 84
courriel : prenom.nom@aphp.fr

Docteur Effrosyni MANALI
ATTICON UNIVERSITY HOSPITAL
Department Pulmonary Medicine
HAIDARI
12462 ATHENE (Grèce)

Variations pathogènes (classe 5) ou probablement pathogènes (classe 4) :

Gène (isoforme)	Mode de transmission	Statut	Exon	Nomenclature ADNc	Nomenclature protéique	Classe
ABCA3 (NM_001089)	Autosomique récessif	Hétérozygote	Exon 06	c.347T>C	p.(Phe116Cys)	4 : Probablement pathogène
ABCA3 (NM_001089)	Autosomique récessif	Hétérozygote	Exon 08	c.838C>T	p.(Arg280Cys)	5 : Pathogène

Treatment in Pediatric PF (poor to moderate response)

Steroids?

Hydroxychloroquine?

Macrolides?

Combination therapy?

Lung transplantation

Antifibrotics?

Kroner C, et al. Thorax 2017; 72: 213-220

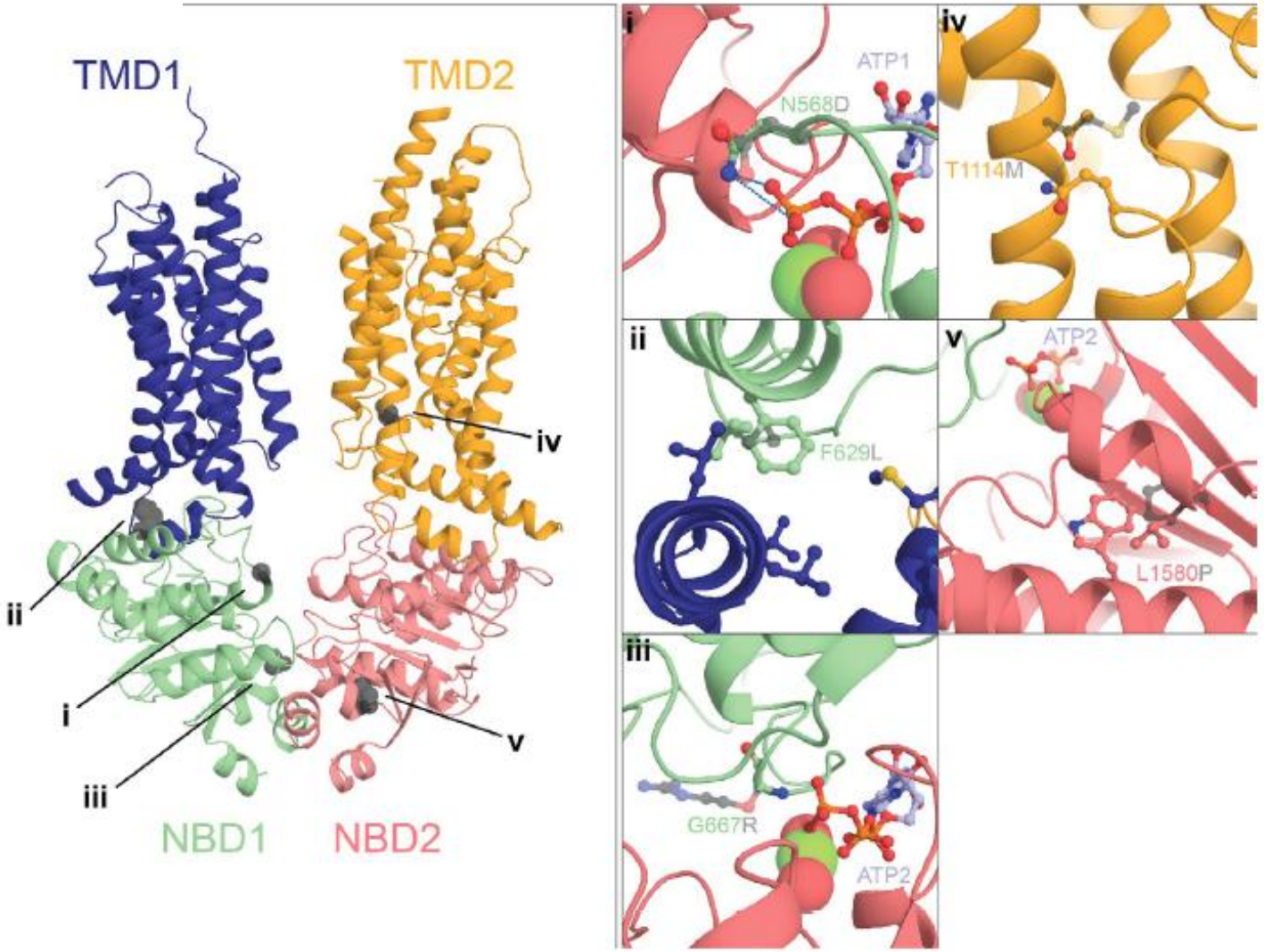
ORIGINAL ARTICLE

WILEY

Potentiation of ABCA3 lipid transport function by ivacaftor and genistein

Susanna Kinting[1,2] | Yang Li[1] | Maria Forstner[1,2] | Florent Delhommel[3,4] | Michael Sattler[3,4] | Matthias Griese[1,2]

J Cell Mol Med 2019



Outcome of PF in Childhood is globally poor but…

Table 2. Clinical data and outcomes of five patients of the Trousseau Hospital chILD cohort with lung fibrosis.

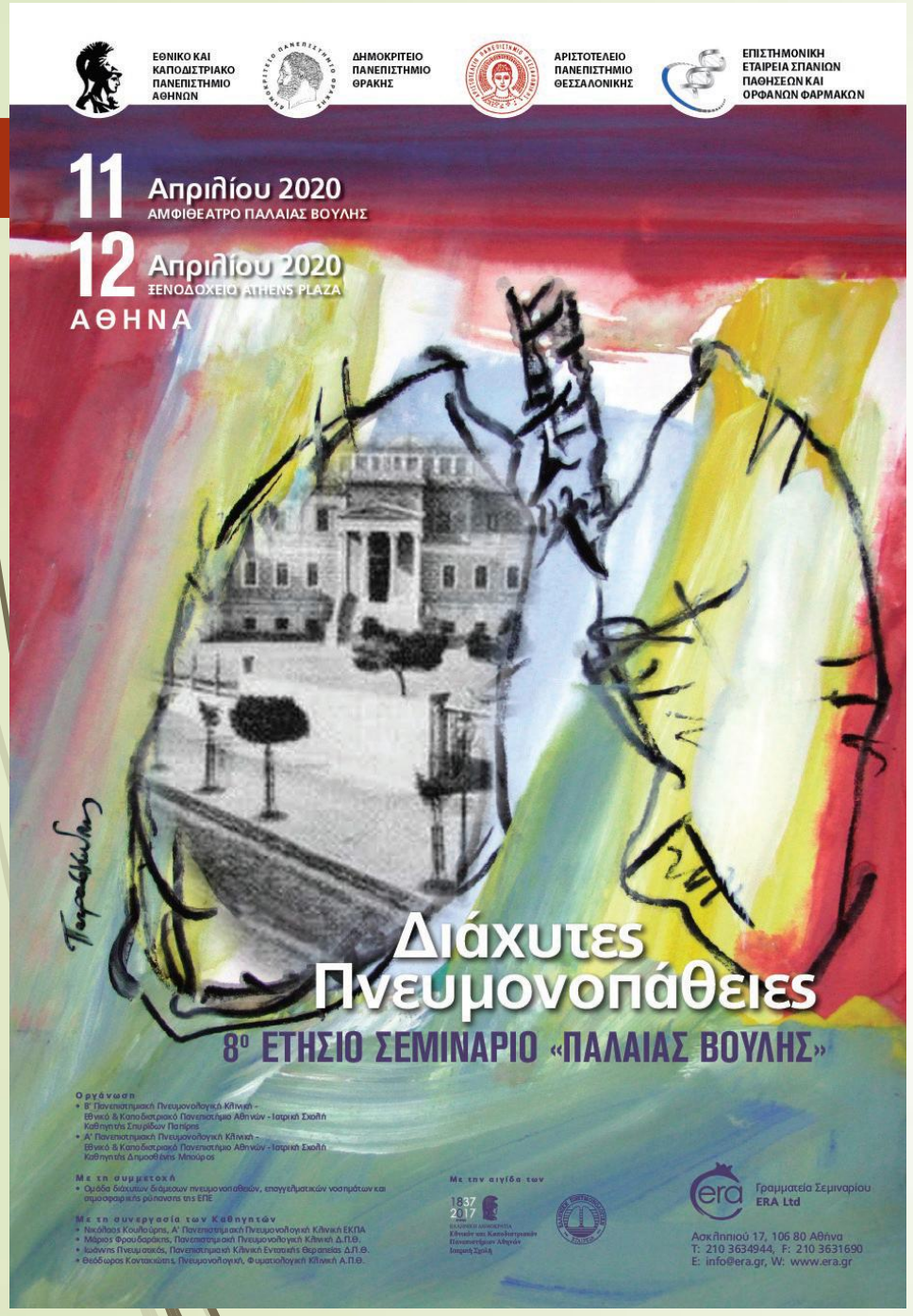
Patient Number	Clinical Presentation	Treatment	Outcome
1 [14,15]	6-year-old girl, *ABCA3*-related disease	HCQ, azithromycin	Diffuse fibrosing ILD at age 26
2 [16]	8-year-old boy, TMEM173-related disease	Corticosteroid pulses, oral corticosteroids, ruxolitinib at age 13.	Lung transplantation at age 14, died at age 16 after second lung transplantation
3	3-year-old boy, undefined chILD	Corticosteroids	Died at age 3 from respiratory failure
4	2-year-old girl, undefined chILD	Corticosteroid pulses, oral corticosteroids, azithromycin, immunosuppressive drugs	Died at age 2 from respiratory failure
5	2-year-old girl, undefined chILD	Corticosteroid pulses, oral corticosteroids, azithromycin	Asymptomatic at age 8

Abbreviations: chILD, children interstitial lung disease; HCQ, hydroxychloroquine.

The term "pulmonary fibrosis"
may have a different meaning in children than in adults
with more cellular recruitment, less collagen deposition
and less parenchymal destruction

Pneumologists will have to prepare for these young patients as they transfer into adult medicine

Nathan N, et al. J Clin Med. 2019 Aug 26;8(9). pii: E1312.
Griese M. Eur Respir Rev 2018; 27: 170100



Σας ευχαριστώ πολύ
Καλές Γιορτές