European Respiratory Society Statement on

Familial Pulmonary Fibrosis

Supplementary materials

Telomere length analysis methods

Quantitative polymerase chain reaction (Q-PCR)

The QPCR determination of telomere lengths was first described by Cawton et al, 2002 [1]. It consists of measuring telomere signal (T) normalized to a reference single-gene copy signal (S). The measure provides a T/S ratio [2].

Advantages: easily available, cheap, fast, from extracted DNA, low amount of DNA needed (50 ng), easy to apply to large populations

Disadvantages: amplification step (PCR), poor reproducibility, intra-assay variation >10%, no information on the "shortest telomere" [3].

Terminal restriction fragment analysis

It consists of measuring TL with a TTAGGG-labelled probe by a southern blot. It measures the intensity of a telomere smear and thus provides average TL.

Advantages: reproducible, applicable to several tissues, quantitative, No amplification step

Disadvantages: long, difficult to apply to large populations, large amount of DNA required (3 µg), difficulty to detect very short telomeres, results may vary based on the restriction enzymes used.

Single TElomere Length Analysis (STELA)

Single TElomere Length Analysis or STELA consists of the application of single molecule PCR to generate highly accurate telomere mesures from a small amount of starting material. STELA takes advantage of the fact that telomeres end with a single stranded 3' G-rich overhang, used as a template that allows ligating an oligonucleotide linker to the 5' end of the telomere. A linker-specific primer is then used in with a primer specific for a unique subtelomeric sequence and generates a

single amplicon for each telomere. The main drawback is that not all chromosome ends have suitable sequence for the design of unique chromosome arm primers, and thus STELA is usually restricted to well characterized ends; XpYp, 2p, 11q, 12q and 17p. To minimize PCR artifacts, sub-visible amplification is conducted, and STELA products are resolved by agarose gel electrophoresis, Southern blotted and probed with the specific subtelomeric sequence.

Advantage: requires very few cells (>50), does not require specific material, powerful in research for relative and absolute TL measure, applicable to several tissues

Disadvantages: requires high expertise, not standardized at this point, not validated for clinical purposes.

(Q-FISH and) Flow-FISH

Interphase quantitative fluorescence in situ hybridization (Q-FISH) consists of determining telomere fluorescent intensity after hybridization with a fluorescent peptide nucleic acid telomeric repeat. The technique may be applied to metaphase, but only on proliferating cells.

Flow-FISH is a similar method where fluorescence is measured by fluorescent-accelerated cell signal (FACS) [4]. Flow FISH now offers an extensive quantitative reference data related to telomere length currently available and is the first of the telomere length methods to have been validated for clinical diagnostic purposes. Flow-FISH is feasible on nucleated cells, which means that the material (DNA) is readily available. Flow-FISH is currently the most reliable and easily applicable method to measure telomere length.

Advantages: reproducible, several samples handled at the same time, possible to implement in clinical practice

Disadvantages: requires expertise, necessity of a control population curve, not applicable in patients with blood involvement of telomere syndrome, requires living cells (blood) (<48h)

Perspectives in TL techniques

New techniques are currently developed.

- Luminex assay
- WGS for TL measurement

Comparison of TL measure

Although several reviews [5, 6] on TL measurement methods exist, only few teams directly compared those methods on a similar population [7–9]. Some data exist on direct comparison between TL measure by Q-PCR and Flow-FISH: all studies demonstrate that Flow-FISH is more reliable, reproducible and yields the best sensitivity and specificity.

Supplementary Figure PRISMA flow diagram of literature selection.

Methods for the Literature search:

Databases: PubMed; Embase.com

Limits: publication date: no

Language: no

Study types: no

Age: no

Exclude animal studies and conference abstracts

Search: 15 september 2020.

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(("Pulmonary Fibrosis"[Mesh] OR "Pulmonary Fibros*"[tiab] OR "Lung Fibros*"[tiab] OR "Hamman-Rich Syndrome"[tiab] OR "familial interstitial pneumoni*"[tiab] OR "Cryptogenic Organizing Pneumonia*"[tiab] OR "Lung Diseases, Interstitial"[Mesh:NoExp] OR "Alveolitis, Extrinsic Allergic"[Mesh:NoExp] OR "Idiopathic Interstitial Pneumonias"[Mesh:NoExp] OR "idiopathic Interstitial Pneumoni*"[tiab] OR (("interstitial lung disease*"[tiab] OR "ILD"[ti] OR "ILDs"[ti]) NOT ("adult"[mesh] NOT ("infant"[mesh] OR "child"[mesh] OR "adolescent"[mesh]))) OR "hypersensitivity pneumoni*"[tiab]) AND ("Genes"[Mesh:NoExp] OR "Gene"[tiab] OR "Genes"[tiab] OR "Genetics"[Mesh:NoExp] OR "Human Genetics"[Mesh:NoExp] OR "Genetics, Medical"[Mesh] OR "Genetic*"[tiab] OR "Mutation"[Mesh:NoExp] OR "mutation*"[tiab] OR "Mucin-5B"[Mesh] OR "Mucin-5B"[tiab] OR "MUC5B"[tiab] OR "rs35705950"[tiab] OR "Telomerase"[Mesh] OR "telomerase*"[tiab] OR "STELA"[tiab] OR "Telomere*"[tiab] OR "familial*"[tiab] OR "hereditary"[tiab] OR "inheritance*"[tiab] OR "Anticipation, Genetic"[Mesh] OR "Penetrance"[Mesh] OR "penetrance*"[tiab] OR "SFTPA1"[tiab] OR "SFTPA2"[tiab] OR "Surfactant Metabolism Dysfunction, Pulmonary, 1" [Supplementary Concept] OR "SFTPB"[tiab] OR "Surfactant Metabolism Dysfunction, Pulmonary, 2" [Supplementary Concept] OR "SFTPC"[tiab] OR "Surfactant Metabolism Dysfunction, Pulmonary, 3" [Supplementary Concept] OR "ABCA3"[tiab] OR "AP3B1"[tiab] OR "NKX2-1"[tiab] OR "COPA"[tiab] OR "Surfactant Metabolism Dysfunction, Pulmonary, 4" [Supplementary Concept] OR "CSF2RA"[tiab] OR "CSF2RB"[tiab] OR "FARSB"[tiab] OR "FLNA"[tiab] OR "GATA2"[tiab] OR

"SLC7A7"[tiab] OR "MARS"[tiab] OR "STAT3"[tiab] OR "STING"[tiab] OR "TBX4"[tiab] OR "Hermanski-Pudlak Syndrome"[Mesh] OR "Hermanski-Pudlak"[tiab])) OR (("Pulmonary Surfactant-Associated Proteins/deficiency"[Mesh] OR ("surfactant"[tiab] AND "protein*"[tiab] AND "deficienc*"[tiab])) AND ("Lung Diseases"[Mesh:NoExp] OR "Respiration Disorders"[Mesh:NoExp] OR "Respiratory Distress Syndrome, Newborn"[Mesh] OR "respiratory failure"[tiab] OR "respiratory distress"[tiab])) NOT ("animals"[Mesh] NOT "humans"[mesh])

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(('lung fibrosis'/de OR 'Pulmonary Fibros*':ti,ab,kw OR 'Lung Fibros*':ti,ab,kw OR 'Hamman-Rich Syndrome':ti,ab,kw OR 'familial interstitial pneumoni*':ti,ab,kw OR 'Cryptogenic Organizing Pneumonia*':ti,ab,kw OR 'interstitial lung disease'/de OR 'allergic pneumonitis'/de OR 'interstitial pneumonia'/de OR 'idiopathic Interstitial Pneumoni*':ti,ab,kw OR (('interstitial lung disease*':ti,ab,kw OR 'ILD':ti OR 'ILDs':ti) NOT ('adult'/exp NOT 'juvenile'/exp)) OR 'hypersensitivity pneumoni*':ti,ab,kw) AND ('gene'/de OR 'Gene':ti,ab,kw OR 'Genes':ti,ab,kw OR 'genetics'/de OR 'human genetics'/exp OR 'Genetic*':ti,ab,kw OR 'mutation'/de OR 'mutation*':ti,ab,kw OR 'mucin 5B'/de OR 'Mucin-5B':ti,ab,kw OR 'MUC5B':ti,ab,kw OR 'rs35705950':ti,ab,kw OR 'telomerase'/de OR 'telomerase*':ti,ab,kw OR 'STELA':ti,ab,kw OR 'Telomere*':ti,ab,kw OR 'familial*':ti,ab,kw OR 'hereditary':ti,ab,kw OR 'inheritance*':ti,ab,kw OR 'genetic susceptibility'/de OR 'penetrance'/de OR 'penetrance*':ti,ab,kw OR 'SFTPA1':ti,ab,kw OR 'SFTPA2':ti,ab,kw OR 'SFTPB':ti,ab,kw OR 'SFTPC':ti,ab,kw OR 'ABCA3':ti,ab,kw OR 'AP3B1':ti,ab,kw OR 'NKX2-1':ti,ab,kw OR 'COPA':ti,ab,kw OR 'CSF2RA':ti,ab,kw OR 'CSF2RB':ti,ab,kw OR 'FARSB':ti,ab,kw OR 'FLNA':ti,ab,kw OR 'GATA2':ti,ab,kw OR 'SLC7A7':ti,ab,kw OR 'MARS':ti,ab,kw OR 'STAT3':ti,ab,kw OR 'STING':ti,ab,kw OR 'TBX4':ti,ab,kw OR 'ocular albinism'/exp OR 'Hermanski-Pudlak':ti,ab,kw)) OR ((('surfactant associated protein'/de OR 'surfactant':ti,ab,kw) AND 'protein*':ti,ab,kw AND 'deficienc*':ti,ab,kw) AND ('lung disease'/de OR 'breathing disorder'/de OR 'neonatal respiratory distress syndrome'/de OR 'respiratory failure':ti,ab,kw OR 'respiratory distress':ti,ab,kw)) NOT 'conference abstract'/it NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)

Table S1 Other genes associated with ILD

Disease	Genes	Mode of inheritance	Age of presentation pulmonary symptoms	Non ILD pulmonary and Extra pulmonary phenotype	Fre-quency	Most frequent pattern	Implication for management/ Therapy for pulmonary disease	References
Hermansky–Pudlak syndrome	*HPS1*	AR	30-40yo 2 – 15 y	-Albinism - Spontaneous bleeding	rare	Unclassifiable pulmonary fibrosis	Unknown: Antifibrotic drugs? Lung transplantation may be considered	[10, 11]
	AP3B1 / HSP2	AR						
	HPS4	AR						
Interferonopathy	*STING1/TMEM173*	AD	Infancy-young adult	Vasculopathy with onset in infancy, Auto-inflammatory features (SAVI)	rare	Unclassifiable pulmonary fibrosis , Alveolar hemorrhage	Unknown: Antifibrotic drugs ? Jak inhibitor?	[12, 13]
	COPA	AD		Arthralgia, kidney disease				[14]
	OAS1	AD		Fever, dermatitis, inflammatory bowel disease,	Ultrarare	Alveolar proteinosis	Allogeneic stem cell transplantation?	[15–17]
Interferonopathy	*ZNFX1*	AR	Infancy, children	Viral infections, Inflammatory episodes, early-onset seizures, renal disease	Ultrarare	Unclassifiable pulmonary fibrosis	Jak inhibitor?	[18]

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?	[19, 20]
	FARS1	AR	Infancy, childhood	Neurological findings, liver dysfunction, and connective tissue, muscular and vascular abnormalities.	Ultra rare	Interstitial lung disease with cholesterol pneumonitis	Unknown	[21]
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?	[22]
	CSF2RB	AR	Infancy, childhood, adults		Ultra rare	Alveolar proteinosis	Whole lung lavage? Stem cell transplantation?	[23]
Fibrosis, neurodegeneration, and cerebral angiomatosis (FINCA)	*NHLRC2*	AR	Infancy-young adult	Neurodegeneration and cerebral angiomatosis	Ulta rare	desquamative interstitial pneumonia; nonspecific interstitial pneumonia	Unknown	[24]

Acid Sphingomyelinase Deficiency (ASMD, Niemann–Pick disease)	*SMPD1*	AR	Type A / 3yo Type B : later onset	Hepatomegaly Splenomegaly Thrombocytopenia	rare	Not Fibrosing Interstitial lung disease with ground glass opacities	Enzyme replacement therapy to be confirmed	[25, 26]
Niemann–Pick disease, Type C	*NPC1, NPC2*	AR	Type C	ILD, PAP, Hepato-splenomegaly	rare	Unclassifiable pulmonary fibrosis, Alveolar Proteinosis	Unknown	[27]
GATA2 deficiency	*GATA2*	AR	Adult	monoMac syndrome: monocytopenia, Mycobacterial infection Myelodysplastic syndrome	Rare	Unclassifiable pulmonary fibrosis, Alveolar Proteinosis	Stem cell transplantation	[28, 29]
Pulmonary alveolar microlithiasis	*SLC34A2*	AR	5-41 yo		Ultra rare	Not Fibrosing sandstorm-like	Lung transplantation may be considered	[30]
Poikilodermia lung fibrosis	*FAM111B*	AD	young	Hereditary Fibrosing Poikiloderma with Tendon Contractures, Myopathy, Exocrine pancreatic dysfunction,	Ultra rare	Unclassifiable pulmonary fibrosis	Unknown	[31, 32]

				pancreatic cancer				
Prolidase deficiency	*PEPD*	AR	young	Mental retardation, facial dysmorphism, dermatologic manifestations including ulcerations	Ultra rare	Unclassifiable pulmonary fibrosis	Unknown	[33, 34]
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	[35, 36]
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	[37]
Werner	*WRN*	AR	>10-yo 55 yo	scleroderma-like skin changes, cataract, subcutaneous calcification, premature arteriosclerosis,	Ultra rare	Unclassifiable pulmonary fibrosis	Unknown	[38, 39]

				diabetes mellitus, and premature aged facies				
Calcium pathway?	*S100A13/* *S100A3*	AR (Founder effect Saudi Arabia)	Young : 12-15yo		Ultra rare	Unclassifiable pulmonary fibrosis	Unknown	[40]

Table S2 Result of the survey for Familial Pulmonary Fibrosis (FPFFPF) definition

How should we call it? *	n=13
Familial interstitial pneumonia	3 (21.3%)
Familial pulmonary fibrosis	3 (32.3%)
Familial ILD	10 (76.9%)
What does the definition of FPF require?*	n=13
At least 2 members	13 (100%)
At least 3 members	0 (0%)
At least 4 members	0 (0%)
Only 1 patient with ILD and a pathogenic mutation that causes ILD	9 (69.2%)
What degree of relationship still define FPF?*	n=13
1st degree (siblings, parents, Children)	11 (84.6%)
2nd degree (siblings, aunts/uncles grandparents, grandchildren, nephew/niece (children of your sibs), half-sibs)	12 (92.3%)
3rd degree (cousin,…)	3 (23.1%)
4th degree	1 (7.7%)
What kind of ILD should be included in the definition of FPF? *	n=13
ILD must be idiopathic	3 (23.1%)
ILD must be chronic	4 (30.8%)
ILD must be fibrotic	2 (15.4%)
ILD must be progressive	1 (7.7%)
None of them is required	7 (53.8%)
For instance, do you include the following? *	n=12
Acute Organizing Pneumonia	7 (58.3%)
Chronic Organizing Pneumonia	10 (83.3%)
Acute Hypersensitivity Pneumonitis	6 (50%)
Chronic Hypersensitivity Pneumonitis	11 (91.7%)
Non fibrotic Interstitial Lung abnormalities (ILA)	5 (41.7%)
Fibrotic Interstitial Lung abnormalities (ILA)	8 (66.7%)
Sarcoidosis	8 (66.7%)
Lymphangioleiomyomatosis	1 (8.3%)
Langherans cell Histiocytosis	1 (8.3%)
Autoimmune Pulmonary alveolar Proteinosis	3 (25%)
Non-sarcoidosis granulomatosis	3 (25%)
Birt Hogg Dube	1 (8.3%)
Do you support the following definition of familial ILD : occurrence of 2 or more first or second degree related family members with fibrotic ILD	N=13
Yes	13 (100%)
No	0 (0%)
How should we call it?*	N=14
Monogenic	5 (35.7%)
Genetic	4 (28.6%)
Heritable	4 (28.6%)
Predisposition to	2 (14.2%)
Familial	1 (7.1%)

Do you include any polymorphisms in your diagnostic workup?	N=13
Yes	1 (7.7%)
No	12 (92.3%)

Table S3 Result of the survey for the screening of asymptomatic relatives

Should we offer a screening for asymptomatic relatives?	N=14
Yes	10 (71.4%)
No	4 (28.6%)
Who should be evaluated?*	N=14
All relatives of FPF	9 (64.3%)
Only if a mutation is evidenced in the proband	3 (21.4%)
Only relatives carriers of the know mutation	2 (14.3%)
Should we do a Pulmonary CT scan?	N=14
Yes	14 (100%)
No	0
When should we do a Pulmonary CT scan?*	N=14
In case of symptoms	10 (71.4%)
In case of auscultation abnormalities	10 (71.4%)
IN every relatives	
>18	3 (21.4%)
>40	7 (50%)
>50	10 (71.4%)
>60	0 (0%)
10 years before the proband ILD onset	6 (42.9%)
Should we offer other pulmonary evaluation?*	N=13
Pulmonary function test	12 (92.3%)
Pulmonary echocardiography	1 (7.7%)
Should we offer other test in TRG relatives?*	N=14
Complete blood count	13 (92.9%)
Hepatic enzyme	12 (85.7%)
Hepatic echocardiography	4 (28.6%)
Telomere length analysis	4 (28.6%)
How often should we offer this screening?	N=13
Only once	1 (7.7%)
Every Year	3 (23.1%)
Every 2 years	2 (15.4%)
Every 3 years	1 (7.7%)
Every 4 years	1 (7.7%)
Every 5 years	5 (38.5%)

For marked questions (*) respondents could choose more than one choice.

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