Familial Pulmonary Fibrosis

Effrosyni D. Manali[1], Likurgos Kolilekas[2], Caroline Kannengiesser[3], Raphael Borie[4], Paschalina Giouleka[1], Ioannis Tomos[1], Konstantinos Kagouridis[1], Anna Karakatsani[1], Demosthenes Bouros[5], Bruno Crestani[4], Spyros A. Papiris[1]

[1]2nd Pneumonology Medicine Department, "Attikon" University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
[2]7th Department of Pneumonology and Asthma Center, "Sotiria" Chest Diseases Hospital, Greece
[3]APHP Service de Génétique, Hôpital Bichat, Paris, France, Université Paris Diderot, Sorbonne Paris Cité, Paris, France
[4]APHP, Hôpital Bichat, Service de Pneumologie A, DHU FIRE Centre de Competence des Maladies Pulmonaires Rares, Paris, France, Université Paris Diderot, Sorbonne Paris Cité, Paris, France
[5]1st Department of Pneumonology, "Sotiria" Chest Diseases Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

Corespondence:
Effrosyni D. Manali, Assistant Professor of Medicine, 2nd Pneumonology Medicine Department, "Attikon" University Hospital, 1 Rimini Street, 12462, Haidari, Greece,
Tel.: +302105831184, E-mail: fmanali@otenet.gr

Most cases of idiopathic pulmonary fibrosis are sporadic, that is they occur in individuals with no family history with the disorder. Familial pulmonary fibrosis is defined by the presence of at least two cases of pulmonary fibrosis in the same family[1,2]. In that case the presence of multiple pulmonary fibrosis cases in a family may regard idiopathic pulmonary fibrosis alone, or idiopathic pulmonary fibrosis in association with pulmonary fibrosis of known etiology such as pulmonary fibrosis related to autoimmune rheumatic disease and chronic hypersensitivity pneumonitis or idiopathic pulmonary fibrosis and other idiopathic interstitial pneumonias such as desquamative interstitial pneumonia or pleuroparenchymal fibroelastosis[3-5].

We now know that 2-20% of the idiopathic pulmonary fibrosis patients have a family history consistent with familial pulmonary fibrosis[1] and a detailed family history for each patient with idiopathic pulmonary fibrosis is deemed necessary in quest of such traits in a family pedigree. The type of inheritance for the majority of patients is autosomal dominant with vertical transmission from generation to generation[6,7]. The last 15 years there has been great progress in the discovery of genes related to the development of familial pulmonary fibrosis. Some of these gene variants are very common and strongly related to the disease however they have a very modest size effect separately (polygenic inheritance), whereas other variants are quite rare but have a very high size effect for the development of the disease (monogenic inheritance)[8-10]. The most representative gene variants related to familial pulmonary fibrosis are those related to the telomerase complex, to the surfactant proteins and finally to the mucin 5B[9,11] (Table 1).

The discovery of genes related to monogenic pulmonary fibrosis provided new clues on the pathogenesis of idiopathic pulmonary fibrosis both sporadic and familial[12].

The first identified mutation was in *SFTPC* gene, the gene encoding surfactant protein C in a family with a mother with desquamative interstitial pneumonia since childhood and her baby girlwith non-specific interstitial pneumonitis[4]. The studies that followed discovered further mutations in genes encoding surfactant proteins C, A2 and A1 (*SFTPC, SFTPA2, SFTPA1*) as well as ATP binding cassette family A, member 3 transporter (*ABCA3*)[13-18]. The above mentioned surfactant proteins are exclusively expressed in alveolar epithelial cells (AEC) type II and have a cardinal role in lung alveolar structure maintenance and function whereas *ABCA3* transporter is responsible for transporting SP-B and SP-C towards the cell membrane in lamellar bodies[1,12]. The effect of these genetic mutations in the pathogenesis

TABLE 1. Genetic variants in familial pulmonary fibrosis validated through at least one independent cohort (table modified from reference 11)

Gene	Protein	Function	Inheritance
SFTPA1	SP-A1	Surfactant	monogenic
SFTPA2	SP-A2	Surfactant	monogenic
SFTPC	SP-C	Surfactant	monogenic
ABCA3	ABCA3	Surfactant	monogenic
TERT	TERT	Telomere	monogenic
TERC	TR	Telomere	monogenic
RTEL1	RTEL1	Telomere	monogenic
DKC1	DKC1	Telomere	monogenic
TINF2	TIN2	Telomere	monogenic
MUC5B	MUC5B	Mucin	polygenic

SFTPA1, SFTPA2, SFTPC: genes encoding proteins A1, A2 and C of surfactant, *ABCA3*: ATP binding cassette family A, member 3 transporter, *TERT:* reverse transcriptase of telomerase, *TERC:* RNA component of telomerase, *RTEL1*: human regulator of telomere elongation helicase 1, *DKC1*: dyskerin, *TINF2: TERF-1* interacting nuclear factor 2, *MUC5B:* mucin 5B.

of pulmonary fibrosis are shown to be related so far to pathways implicating cellular senescence, endoplasmic reticulum stress, the unfolded protein response and the DNA-damage response as well dysregulation of numerous immune responses[12,19,20].

The discovery of surfactant protein mutations was followed by the identification of the telomerase complex mutations[21,22]. This time pulmonary fibrosis was examined as part of a rare multisystem disorder affecting mostly children called "dyskeratosis congenita" (DC) characterized by dystrophic nails, patchy skin hyperpigmentation and oral leukoplakia[23]. A subset of these patients develops severe bone marrow failure syndromes, liver disease and/or pulmonary fibrosis[23]. Mutations in the genes encoding the telomerase complex were first described in DC and then in FPF patients[24]. Telomerase is a multimeric ribonucleoprotein enzyme that catalyzes the addition of repetitive DNA sequence to telomeres, specialized structures at the end of linear chromosomes and thus protecting chromosomes from genetic material loss during mitoses. Telomerase complex includes a variety of active parts such as dyskerin (*DKC1*), telomerase reverse transcriptase (*TERT*) and the telomerase RNA component (*TERC*)[1,25]. Mutations in these genes as well as in a number of other telomere-associated genes are implicated in FPF[21,22,26-30] (Table 1). Possible mechanisms through which telomerase mutations increase the risk for the development of pulmonary fibrosis include mainly functional deficits in telomere maintenance (short telomere length) linked to epithelial cell senescence and impaired response to epithelial injury as well as non-telomeric effects related to lung injury response and fibrotic remodeling[12,31-36].

The group of rare genetic variants with a high size effect for FPF described so far was enriched by the discovery in 2011 of a common genetic variant that increases the risk for IPF six to eight times: a common single nucleotide polymorphism (SNP) (rs35705950) in the promoter of the gene encoding for mucin 5B (*MUC5B*)[37]. This finding was validated in further studies[38]. Interestingly this polymorphism seems to be related only to idiopathic forms of pulmonary fibrosis and not to those related to sarcoidosis or scleroderma disease[39]. Mucin 5B is among the two major gel forming proteins in human airway secretions. In IPF patients it is found increasingly expressed in the distal small airways and in the cells covering the honeycomb cysts[37,40]. Its role in the pathogenesis of IPF seems to be related to injury, barrier function, innate immunity and impaired repair in the distal airway epithelium as well as to dysregulated inflammation and macrophage mediated responses in the lungs[12,40,41].

Familial and sporadic pulmonary fibrosis may be clinically and histopathologically indistinguishable. However meticulous studying of familial pulmonary fibrosis patients reveals many differentiating and original aspects concerning epidemiology, risk factors, radiographic and histopathologic presentation, natural history, extrapulmonary manifestations and outcome that warrant special consideration[1]. Based on the literature, the number of family members with FPF affected in a family ranges from a minimum of 2 and overpasses sometimes 6 to 7[42]. Familial pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis [OR=6.1 (95% CI 2.3-15.9)] whereas it increases significantly the risk of death from pulmonary fibrosis in first and second degree relatives (RR=4.7 and 1.92 respectively)[43,44]. In these family cohorts, male smoker patients seem to be more frequently affected[6]. Both smoking and environmental exposures such as asbestos, welding, carpentry and sandblasting are significantly related to the development of the disease in FPF patients[25]. From another study comparing 77 FPF patients with 50 sporadic ones it becomes obvious that although symptoms of disease at diagnosis such as dyspnea and cough are indistinguishable, the age both at symptom onset and at diagnosis is younger for the

FPF patients (57.97 years vs 63.85 and 61.43 vs 66.58 respectively)[45]. In both FPF and sporadic cases diffusing capacity of the lung for carbon monoxide (DL_{CO}) is found to be the most sensitive parameter to disclose impairment[45]. In asymptomatic patients pulmonary function tests including DL_{CO} may be normal and lung auscultation in combination with high resolution computerized tomography of the chest (HRCT) may reveal abnormal findings[46] (Figure 1). In symptomatic FPF patients, HRCT of the chest findings are often atypical with reticulation either alone or in combination with ground glass opacities representing the most common findings (82%) whereas honeycombing lesions are encountered in less than 35% of cases[47] (Figure 2). The distribution of the lesions may be more diffuse compared to the subpleural predominance of typical sporadic cases or even predominate in the upper lobes. Cystic lesions, micronodules and lymph node enlargement are also described[47]. More than half of patients are considered to have unclassifiable disease necessitating histopathological documentation. Among radiographically unclassifiable cases, many patients are histopathologically diagnosed as usual interstitial pneumonia disease whereas a significant number will still remain unclassifiable[47].

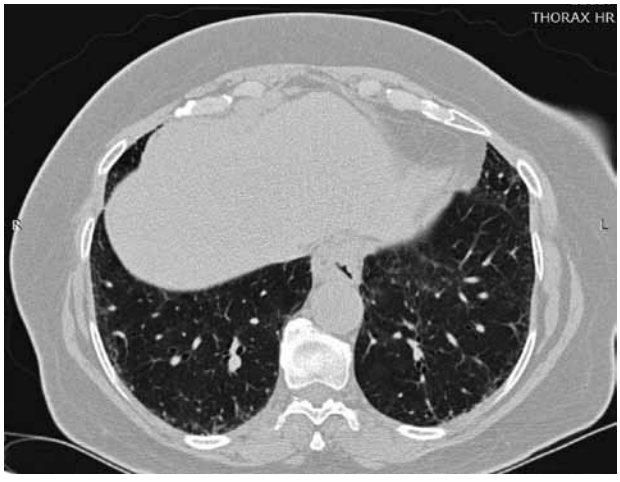

FIGURE 1. High resolution tomography of the chest of a 64 year old non-smoker female. The patient had a family history positive for a father with liver cirrhosis, two sisters and one brother with idiopathic pulmonary fibrosis and a brother and nephew with leukemia. Although asymptomatic, clinical examination revealed velcro sounds at lung bases; the screening test with HRCT of the chest demonstrated minimal changes of interstitial lung disease with subpleural distribution. Results of genetic testing are pending

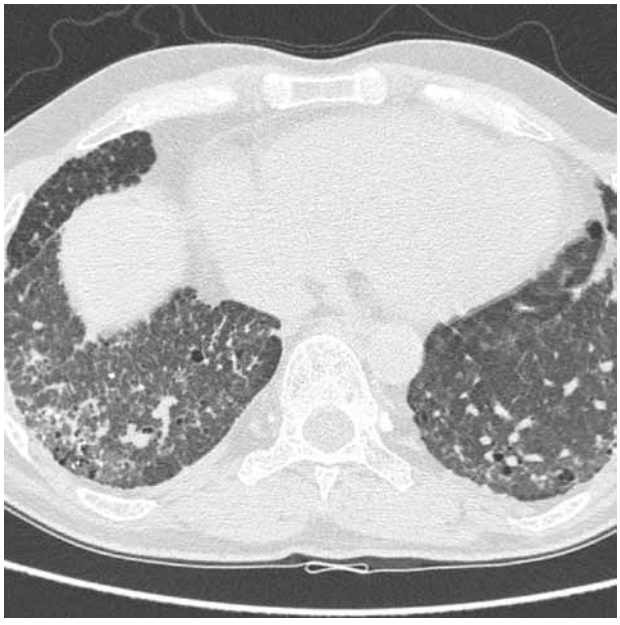

FIGURE 2. High resolution tomography of the chest of a 46 year old male non-smoker patient demonstrating reticulation, ground glass opacities and traction bronchiectasis at the bases of the lungs. Open lung biopsy was performed at the age of 42 and the histopathologic findings were compatible with usual interstitial pneumonia pattern. The patient had two first degree relatives with interstitial lung disease, one with idiopathic pulmonary fibrosis and one with pulmonary fibrosis related to rheumatoid arthritis. Genetic testing revealed *TERC* mutation.

As we already described, many pulmonary fibrosis cases with a heritable component were initially reported in the background of dyskeratosis congenita syndrome, highlighting the fact that patients with telomerase complex mutations may also have extrapulmonary manifestations such as liver and/or bone marrow disease. There is evidence showing that patients with FPF but without any DC findings may also develop themselves or their family members bone marrow failure syndromes such as myelodysplasia and aplastic anemia or/and liver disease such as liver cirrhosis[48-51]. The risk of associated extrapulmonary manifestations is difficult to estimate[1]. Risk factors such as viral infections, toxic medication and alcohol may enhance presentation and should be avoided. Hematologic disease's risk increase from generation to generation, a phenomenon called anticipation, due to short telomere inheritance[1].

Another fact that we should take into consideration in FPF patients especially those with mutations of the telomerase complex is their fragility when they are re-

ferred for lung transplantation. Two studies from centers of excellence one in the USA and the other in France have clearly shown that these patients have a shorter transplant free survival time and that they are very vulnerable when exposed to post transplantation immunosuppressive regimens, often developing bone marrow failure syndromes and succumbing prematurely due to hematologic, infective and renal failure complications. These observations justify specific genetic, hematologic and hepatology consultation before lung transplantation in pulmonary fibrosis patients as well as selected adjustment of the post-transplantation regimens for those patients at increased risk[52,53]. Indeed a study performed in a context of pre-transplant evaluation for lung transplantation for patients with short telomere disease demonstrated that subclinical bone marrow and liver abnormalities are found in patients with pulmonary fibrosis and short telomeres even without clinically significant signs in peripheral blood counts and liver function tests[54].

In general, patients with telomerase complex mutations have poorer survival compared to sporadic disease patients irrespective of lung transplantation[25]. On the contrary, the MUC5B promoter polymorphism is associated with increased survival in both sporadic and familial pulmonary fibrosis patients[55,56]. Concerning FPF patients with surfactant protein and *ABCA3* mutations, outcome ranges from asymptomatic disease to death. Phenotypic manifestations vary from severe respiratory failure at a very young age to only lung fibrosis, combined pulmonary fibrosis and emphysema or lung fibrosis and cancer in adults[16,57-59].

Investigating familial pulmonary fibrosis patients makes also scientists wonder whether early identification of the disease through screening of FPF families could positively influence its natural history which remains dismal besides new treatments and whether the genetic profile of each patient could bring in the future some kind of useful information regarding treatments and the response to them. For the time being what we know is that early screening of asymptomatic patients from FPF families may reveal interstitial lung disease changes in almost 14-25% of them[46,60]. Very recently, an exhaustive work-up with questionnaires, blood examination, chest HRCT, and bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy was undertaken in 75 asymptomatic subjects at risk for familial interstitial pneumonia. The authors found that there was evidence of lung parenchymal remodeling and epithelial dysfunction in these subjects and that only longitudinal follow-up will explain its significance in the pathogenesis of pulmonary fibrosis[60].

Even more recently, National Institute of Health scientists published their observations concerning the treatment of patients with telomere disease, mostly bone marrow failure and/or pulmonary fibrosis with a synthetic androgen, danazol. Initial results were encouraging since telomere elongation was achieved with stabilization mainly of hematologic disease in certain patients[61].

In the future we may have the opportunity to incorporate genetic signatures into therapeutic decisions for our patients by more accurately comprehending pathogenesis, severity, risk of progression and response to treatment[2,62,63].

At present, what we mostly need is the wise utilization of all this new genetic information concerning FPF patients[64]. Genetic diagnostic and counselling should be performed after written informed consent in a framework of a multidisciplinary expert team that includes a geneticist and should apply in patients with a history of FPF, in patients with signs of short telomere syndrome, in young patients as well as to those referred for lung transplantation. Screening family members of affected individuals could prove meaningful in the future as well as counseling of avoidance of any exposure including smoking that could harm sensitive organs such as the lung, bone marrow and liver in the next generations[1].

The progress that has supervened in genetics in IPF the last few years, has allowed new insights for sporadic and familial pulmonary fibrosis patients. Hopefully, next guidelines for diagnosis and treatment of idiopathic pulmonary fibrosis will appreciate and organize the accumulated new knowledge and will dedicate some lines to genetic diagnostic, counselling and management of familial pulmonary fibrosis patients as well.

ACKNOWLEDGEMENTS

The authors would like to greatly thank the following colleagues for their precious collaboration concerning familial pulmonary fibrosis patients in Greece: V. Tzilas, E. Bouros, A. Xifteri, M. Gaggadi, A. Charitou, Aik. Markopoulou, E. Fouka, H. Papanikolaou, Chr. Bazaka, I. Korbila, G. Papadaki, P. Lyberopoulos, S. Laparidou, Z. Sardelis, E. Markozannes, M. Kasiola, T. Tsiligiannis, P. Steiropoulos, P. Bakakos, S. Loukides.

REFERENCES

1. Borie R, Kannengiesser C, Nathan N, et al. Familial pulmonary fibrosis. Rev Mal Respir 2015; 32:413-34
2. Spagnolo P, Grunewald J, du Bois RM. Genetic determinants of pulmonary fibrosis: evolving concepts. Lancet Respir Med 2014; 2:416-28
3. Okamoto T, Miyazaki Y, Tomita M, et al. A familial history of pulmonary fibrosis in patients with chronic hypersensitivity pneumonitis. Respiration 2013; 85:384-90
4. Nogee LM, Dunbar AE III, Wert SE, et al. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med 2001; 344:573-9
5. Watanabe K. Pleuroparenchymal Fibroelastosis: its clinical characteristics. Curr Respir Med Rev 2013; 9:229-37
6. Steele MP, Speer MC, Loyd JE, et al. Clinical and pathologic features of familial interstitial pneumonia. Am J Respir Crit Care Med 2005; 172:1146-52
7. Hodgson U, Laitinen T, Tukiainen P. Nationwide prevalence of sporadic and familial idiopathic pulmonary fibrosis: evidence of founder effect among multiplex families in Finland. Thorax 2002; 57:338-42
8. Mathai SK, Schwartz DA, Wang LA. Genetic susceptibility and pulmonary fibrosis. Curr Opin Pulm Med 2014; 20:429-35
9. Kropski JA, Blackwell TS, Loyd JE. The genetic basis of idiopathic pulmonary fibrosis. Eur Respir J 2015; 45:1717-27
10. Antonarakis SE, Chakravarti A, Cohen JC, et al. Mendelian disorders and multifactorial traits: the bog divide or one for all? Nat Rev Genet 2010; 11:380-4
11. Chu SG, El-Chemaly S, Rosas IO. Genetics and Idiopathic Interstitial Pneumonias. Semin Respir Crit Care Med 2016; 37:321-30
12. Kropski JA, Lawson WE, Young LR, et al. Genetic studies provide clues on the pathogenesis of idiopathic pulmonary fibrosis. Dis Mod Mech 2013; 6:9-17
13. Thomas AQ, Lane K, Philipps J III, et al. Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. Am J Respir Crit Care Med 2002; 165:1322-8
14. Wang Y, Kuan PJ, Xing C, et al. Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer. Am J Hum Genet 2009; 84:52-9
15. Van Moorsel CHM, van Oosterhout FM, Barlo NP, et al. Surfactant protein C mutations are the basis of a significant portion of adult familial pulmonary fibrosis in a Dutch cohort. Am J Respir Crit Care Med 2010; 182:1419-25
16. Nathan N, Giraud V, Picard C, et al. Germline *SFTPA1* mutation in familial idiopathic interstitial pneumonia and lung cancer. Hum Mol Genet 2016; 25:1457-67
17. Bullard JE, Wert SE, Whitsett JA, et al. *ABCA3* mutations associated with pediatric interstitial lung disease. Am J Respir Crit Care Med 2005; 172:1026-31
18. Bullard JE, Nogee LM. Heterozygocity for ABCA3 mutations modifies the severity of lung disease associated with a surfactant protein C gene (SFTPC) mutation. Pediatr Res 2007; 62:176-9
19. Garmany TH, Moxley MA, White FV, et al. Surfactant composition and function in patients with ABCA3 mutations. Pediatr Res 2006; 59:801-5
20. Mulugeta S, Nureki SI, Beers MF. Lost after translation: insights from pulmonary surfactant for understanding the role of alveolar epithelial dysfunction and cellular quality control in fibrotic lung disease. Am J Physiol Lung Cell Mol Physiol 2015; 309:L507-25
21. Armanios MY, Chen JJ, Cogan JD, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med 2007; 356:1317-26
22. Tsakiri KD, Cronkhite JT, Kuan PJ et al. Adult-onset pulmonary fibrosis caused by mutations in telomerase. Proc Natl AcadSci USA 2007; 104:7552-7
23. Calado RT, Young NS. Telomere diseases. N Engl J Med 2009; 361:2353-65
24. Vulliamy T, Marrone A, Goldman F, et al. The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenital. Nature 2001; 413:432-5
25. Diaz de Leon A, Cronkhite JT, Katzenstein ALA, et al. Telomere lengths, pulmonary fibrosis and telomerase mutations. PLoS one 2010; 5:e10680
26. Alder JK, Parry EM, Yegnasubramanian S, et al. Telomere phenotypes in females with heterogyzous mutations in the *dyskeratosis congenital 1* gene. Hum Mutat 2013; 34:1481-5
27. Fukuhara A, Tanino Y, Ishii T et al. Pulmonary fibrosis in dyskeratosis congenital with TINF2 gene mutation. Eur Respir J 2013; 42:1757-9
28. Stuart BD, Choi J, Zaidi S, et al. Exome sequencing links mutations in PARN and RTEL1 with familial pulmonary fibrosis and telomere shortening. Nat Genet 2015; 47:512-7
29. Kannengiesser C, Borie R, Ménard C, et al. Heterozygous RTEL1 mutations are associated with familial pulmonary fibrosis. Eur Respir J 2015; 46:474-85
30. Cogan JD, Kropski JA, Zhao M, et al. Rare variants in RTEL1 are associated with familial interstitial pneumonia. Am J Respir Crit Care Med 2015; 191:646-55
31. Armanios MY, Blackburn EH. The telomere syndromes. Nat Rev Genet 2012; 13:693-704
32. Armanios MY. Telomeres and age-related disease: how telomere biology informs clinical paradigms. J Clin Invest 2013; 123:996-1002
33. Batista LF, Pech MF, Zhong FL, et al. Telomere shortening and loss of self-renewal in dyskeratosis congenital induced pluripotent stem cells. Nature 2011; 474:399-402
34. Hoffmeyer K, Raggioli A, Rudloff S, et al. Wnt/beta-catenin signaling regulates telomerase in stem cells and cancer cells. Science 2012; 336:1549-54
35. Cronkhite JK, Xing C, Raghu G, et al. Telomere shortening in familial and sporadic pulmonary fibrosis. Am J Respir Crit Care Med 2008; 178:729-37
36. Alder JK, Barkauskas CE, Limjunyawong N, et al. Telomere dysfunction causes alveolar stem cell failure. Proc Natl Acad Sci USA 2015; 112:5099-104
37. Seibold MA, Wise AL, Speer MC, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med 2011; 364:1503-12

38. Peljto AL, Selman M, Kim DS, et al. The MUC5B promoter polymorphism is associated with idiopathic pulmonary fibrosis in a Mexican Cohort but is rare among Asian ancestries. Chest 2015; 147:460-4
39. Borie R, Crestani B, Dieudé P, et al. The MUC5B variant is associated with idiopathic pulmonary fibrosis but not with systemic sclerosis interstitial lung disease in the European Caucasian population. PloS one 2013; 8:e70621
40. Yang IV, Fingerlin TE, Evans CM, et al. MUC5B and idiopathic pulmonary fibrosis. Ann Am Thorac Soc 2015; 12:S193-9
41. Roy MG, Livragni-Butrico A, Fletcher AA, et al. MUC5B is required for airway defense. Nature 2014; 505:412-6
42. Lee HL, Ruy J, Wittmer MH, et al. Familial idiopathic pulmonary fibrosis. Clinical features and outcome. Chest 2005; 127:2034-41
43. Garcia-Sancho C, Buendia-Roldán I, Fernández-Plata MR, et al. Familial Pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis. Res Med 2011; 105:1902-7
44. Scholand MB, Coon H, Wollf R, et al. Use of genealogical database demonstrates heritability of pulmonary fibrosis. Lung 2013; 191:475-81
45. Fernandez BA, Fox G, Bhatia R, et al. A Newfoundland cohort of familial and sporadic idiopathic pulmonary fibrosis patients: clinical and genetic features. Res Res 2012;13:64
46. Rosas IO, Pen P, Avila NA, et al. Early interstitial lung disease in familial pulmonary fibrosis. Am J Respir Crit Care Med 2007; 176: 698-705
47. Lee HY, Seo JB, Steele M, et al. High resolution CT scan findings in familial interstitial pneumonia do not conform to those of idiopathic interstitial pneumonia. Chest 2012; 142:1577-83
48. Calado RT, Brucho J, Mehta P, et al. Constitutional telomerase mutations are genetic risk factors for cirrhosis. Hepatology 2011; 53:1600-7
49. Calado RT, Regal JA, Kleiner DE, et al. A spectrum of severe familial liver disorders associate with telomerase mutations. Plos ONE 2009; 4:E7926
50. Towsley DM, Dimitriu B, Young NS. Bone marrow failure and telomeropathies. Blood 2014; 124:2775-83
51. Yamaguchi H, Calado RT, Ly H, et al. Mutations in TERT, the gene for telomerase reverse transcriptase in aplastic anemia. N Engl J Med 2005; 352:1413-24
52. Silhan LL, Shah PD, Chambers DC, et al. Lung transplantation in telomerase mutation carriers with pulmonary fibrosis. Eur Respir J 2014; 44:178-87
53. Borie R, Kannengiesser C, Hirchi S, et al. Severe hematologic complications after lung transplantation in patients with telomerase complex mutations. J Heart Lung Transpl 2015; 34:538-46
54. George G, Rosas IO, Cui Y, et al. Short telomeres, telomeropathy and subclinical extrapulmonary organ damage in patients with interstitial lung disease. Chest 2015; 147:1549-57
55. Peljto A, Zhang Y, Fingerlin TE, et al. Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. JAMA 2013; 309:2232-9
56. Van der Vis JJ, Snetselaar R, Kazemier KM, et al. Effect of MUC5B promoter polymorphism on disease predisposition and survival in idiopathic interstitial pneumonias. Respirology 2016; 21:712-7
57. Wambach JA, Casey AM, Fishman MP, et al. Genotype-phenotype correlations for infants and children with ABCA3 deficiency. Am J Respir Crit Care Med 2014; 189:1538-43
58. Epaud R, Delestrain C, Louha M, et al. Combined pulmonary fibrosis and emphysema syndrome associated with ABCA3 mutations. Eur Respir J 2014; 43:635-8
59. Cottin V, Reix P, Khouatra C, et al. Combined pulmonary fibrosis and emphysema syndrome associated with familial SFTPC mutation. Thorax 2011; 66:918-9
60. Kropski JA, Pritchett JM, Zoz DF, et al. Extensive phenotyping of individuals at risk for familial interstitial pneumonia reveals clues to the pathogenesis of interstitial lung disease. Am J Respir Crit Care Med 2015; 191:417-26
61. Townsley DM, Dumitriu B, Liu D, et al. Danazol treatment for telomere diseases. N Engl J Med 2016; 374:1922-31
62. Putman RK, Rosas IO, Hunninghake GM. Genetics and early detection in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2014; 189:770-8
63. Mathai SK, Yang IV, Schwartz MI, et al. Incorporating genetics into the identification and treatment of Idiopathic pulmonary fibrosis. BMC Med 2015; 24;13:191
64. Marian AJ. Challenges in medical applications of whole exome/genome sequencing discoveries. Trends Cardiovasc Med 2012; 22:219-23