

Title: Familial Pulmonary Fibrosis *GeneReview* – Evidence for further locus heterogeneity

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Evidence for Further Locus Heterogeneity

No other genes are definitely known to be associated with FPF; however, the following observations suggest possible roles for other genes in FPF causation.

- In a cohort from Mexico, pathogenic variants in the genes encoding surfactant protein A1 (*SFTPA1*) and surfactant protein B (*SFTPB*) have been shown to be associated with IPF in nonsmokers and smokers, respectively [Selman et al 2003].
- Normal allelic variants of the genes encoding various cytokines (IL-1RA, TNF-alpha, and IL-6) have been reported to be associated with the development of IPF [Whyte et al 2000, Pantelidis et al 2001]. An additional study showed significant association of IPF with *TNF* [Riha et al 2004].
- Normal allelic variants of various candidate genes for IIP include *TGFB1*, *FN1*, *IGF1*, complement receptor-1 (*CR1*), *IFNG*, HLA genotypes, *SERPINA1*, *TP53*, and *ACE*. Replication of these studies is warranted to evaluate the significance of these findings [Schwartz 2008].
- *ELMOD2* was identified as a candidate gene for FPF in a genomic screen of six multiplex families from southeastern Finland [Hodgson et al 2006].
- MUC5B promoter SNP G>T (rs35705950) was reported by Seibold et al (2011) to be present at a minor allele frequency of 34% in FPF cases, 38% in sporadic IPF cases and 9% in controls with genotype frequency estimates of 50-60% in FPF and IPF. The authors further showed that odds ratios for disease amongst heterozygotes and homozygotes ranged from 6.8-9.0 and 20.8-21.8 for FPF and sporadic IPF respectively. These findings have been replicated in 6 independent study populations. Moreover, Hunninghake et al [2013] found that the MUC5B promoter variant could be used to identify early interstitial lung disease among individuals older than 50 years of age. MUC5B expression was increased by 14.1 times in the lungs of patients with IPF vs. controls, and was increased by 37.4 times in unaffected subjects with at least one copy of the SNP compared to wild type subjects. In a follow up study (Peljto et al), an association between the MUC5B promoter SNP and increased survival was shown for heterozygotes and homozygotes compared to wild-type subjects which could be used as a prognostic tool for clinicians.
- A large GWAS study made up of individuals (N=1616) with fibrotic IIPs (inclusive of FPF) confirmed the association with *TERT*, *MUC5B* and a region near *TERC* and then reported seven new loci with strong associations (*FAM13A* at 4q22,

DSP at 6p24, *OBFC1* at 10q24, *ATP11A* at 13q34, *DPP9* at 19p13, and regions 7q22 and 15q14-15) [Fingerlin et al 2013].

- A novel missense mutation in telomerase pathway gene dyskerin (*DKC1*) was reported by Kropski et al [2014] in one kindred where two brothers were affected with FPF. In addition to FPF, the brothers presented clinically with features of hyperpigmented skin rashes, macrocytosis and nail changes, of which have been described in families with X-linked inherited Dyskeratosis Congenita, a known telomere disorder. The novel mutation was also associated with profoundly shortened telomeres in both peripheral blood and lung tissue of the brothers.
- Cogan et al [2015] discovered heterozygous rare variants in the gene encoding for regulator of telomere elongation helicase (*RTEL1*) in the in 9 unrelated kindreds (4.7%) with FPF that segregated with disease. The rare variants were associated with severe telomere shortening and increased T-circle formation in peripheral blood mononuclear cells. *RTEL1* is a gene involved with telomere replication and stability.

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