Land of hope and dreams

Selection of life science and translational medicine literature

by Marco Confalonieri

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic disease of the lungs that increases in prevalence with advanced age. The prognosis of the disease remains poor, similar to lung cancer, and the development of novel specific treatments for IPF has been limited because etiology and many aspects of its pathogenesis are still unclear. To better define the familiar cases, encoding for 5 to 20% of the IPF patients, there has been recently an explosion of genetic studies, as a key to better define the pathways involved and to contribute to the interpretation of pathogenesis mechanisms, as in other complex diseases. In the brief period from April to June 2013 three different important paper on IPF's genetics were quite simultaneously published in major journals. They used inkage analysis and candidate gene approaches to identify genes implied in familial and non-familial IPF. Initially, mutations in gene encoding surfactant proteins C and A2 (SFTPC and SFTPA2 respectively), telomerase reverse transcriptase (TERT), and telomerase RNA component (TERC) were discovered in familial IPF. Furthermore, a strong association with a single-nucleotide polymorphism (SNP), rs35705950 located 3 kb upstream of MUC5B, was associated with high odds ratio for IPF (9.0 for heterozygotes and 21.8 for homozygotes). MUC5B is known as a gene that produces a protein in mucus. These loci and others with as yet less clear attributions to particular genes have been recently identified in a genome wide association study published this year by Hunninghake and co-workers in the New England Journal of Medicine (1). Hunninghake et al. (1) reported rs35705950 in a general population sample from the Framingham Heart Study showing interstitial lung abnormalities on chest computed tomography (CT) and reduced lung volumes. About one quarter of subjects with abnormal CT and reduced volumes fulfilled criteria for diagnosis of IPF, and the odds ratio of having each copy of the minor rs35705950 allele were increased by a factor of 6.3.

Another genome-wide association study by Fingerlin et al. (2) published this spring on Nature Genetics identified multiple susceptibility loci for pulmonary fibrosis. Researchers from more than 20 institutions, led by National Jewish Health and the University of Colorado (2), confirmed the risk associated with specific genetic variants at region 11p15 of MUC5B, and a strong evidence for the role of telomeres (variants of TERT and TERC genes). The researchers (2) also identified three genes associated with connections that hold adjoining cells together, known as cell-cell adhesion. Impaired cell-cell adhesion can lead to lost tissue integrity. These findings support the researchers' belief that pulmonary fibrosis may be influenced by different genes in different people. Careful genotyping could identify different forms of the disease, allowing for more effective, individualized therapy.

Finally, Noth et al. (3) recently reported on The Lancet Respiratory Medicine the results of a genome-wide association study of more than 1,500 patients with IPF finding multiple association with the disease. Moreover, one variant in a gene called TOLLIP (toll interacting protein) was linked to an increased risk of death. That variant resulted in decreased expression of TOLLIP in the lungs of IPF patients. Because TOLLIP plays a role in regulating immunity to certain stimuli, this finding suggests that an abnormal immune response, possibly to infectious agents or even environmental injuries, may be central to the disease. Noth et al. (3) also confirmed the already reported independent association between the p-terminus of chromosome 11 (SNIP of MUC5B transcription start site) and IPF, suggesting that among patients with IPF, a common risk polymorphism in MUC5B is associated with better prognosis.

In conclusion, all these novel contributions to the genetics of IPF have highlighted the importance of genetic variants loci always linked with the response to external injuries, either viruses or other environmental factors. Genome-wide association studies continues to be the method of choice for identification of common genetic variants associated with complex diseases, but other more specific studies are needed to better understand the relationships between IPF-related genetic variants and environmental factors.

1) MUC5B promoter polymorphism and interstitial lung abnormalities

Hunninghake GM, Hatabu H, Okajima Y, Gao W, Dupuis J, Latourelle JC, Nishino M, Araki T, Zazueta OE, Kurugol S, Ross JC, San José Estépar R, Murphy E, Steele MP, Loyd JE, Schwarz MI, Fingerlin TE, Rosas IO, Washko GR, O'Connor GT, Schwartz DA

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Abstract

Background. A common promoter polymorphism (rs35705950) in MUC5B, the gene encoding mucin 5B, is associated with idiopathic pulmonary fibrosis. It is not known whether this polymorphism is associated with interstitial lung disease in the general population.

Methods. We performed a blinded assessment of interstitial lung abnormalities detected in 2633 participants in the Framingham Heart Study by means of volumetric chest computed tomography (CT). We evaluated the relationship between the abnormalities and the genotype at the rs35705950 locus.

Results. Of the 2633 chest CT scans that were evaluated, interstitial lung abnormalities were present in 177 (7%). Participants with such abnormalities were more likely to have shortness of breath and chronic cough and reduced measures of total lung and diffusion capacity, as compared with participants without

such abnormalities. After adjustment for covariates, for each copy of the minor rs35705950 allele, the odds of interstitial lung abnormalities were 2.8 times greater (95% confidence interval [CI], 2.0 to 3.9; P<0.001), and the odds of definite CT evidence of pulmonary fibrosis were 6.3 times greater (95% CI, 3.1 to 12.7; P<0.001). Although the evidence of an association between the MUC5B genotype and interstitial lung abnormalities was greater among participants who were older than 50 years of age, a history of cigarette smoking did not appear to influence the association.

Conclusions. The MUC5B promoter polymorphism was found to be associated with interstitial lung disease in the general population. Although this association was more apparent in older persons, it did not appear to be influenced by cigarette smoking.

2) Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis

Fingerlin TE, Murphy E, Zhang W, Peljto AL, Brown KK, Steele MP, Loyd JE, Cosgrove GP, Lynch D, Groshong S, Collard HR, Wolters PJ, Bradford ZW, Kossen K, Seiwert SD, du Bois RM, Garcia CK, Devine MS, Gudmundsson G, Isaksson HJ, Kaminski N, Zhang Y, Gibson KF, Lancaster LH, Cogan JD

Nature Genetics 2013;45:613-620

Abstract

We performed a genome-wide association study of non-Hispanic, white individuals with fibrotic idiopathic interstitial pneumonias (IIPs; n = 1,616) and controls (n = 4,683), with follow-up replication analyses in 876 cases and 1,890 controls. We confirmed association with TERT at 5p15, MUC5B at 11p15 and the 3q26 region near TERC, and we identified seven newly associated loci (Pmeta = 2.4×10^{-8} to 1.1×10^{-19}), including FAM13A (4q22), DSP (6p24), OBFC1 (10q24), ATP11A (13q34), DPP9 (19p13) and chromosomal regions 7q22 and 15q14-15. Our results suggest that genes involved in host defense, cell-cell adhesion and DNA repair contribute to risk of fibrotic IIPs.

3) Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study

Noth I, Zhang Y, Ma SF, Flores C, Barber M, Huang Y, Broderick SM, Wade MS, Hysi P, Scuirba J, Richards TJ, Juan-Guardela BM, Vij R, Han MK, Martinez FJ, Kossen K, Seiwert SD, Christie JD, Nicolae D, Kaminski N, Garcia JGN

Lancet Respir Med 2013;1:309-17

Abstract

Background Idiopathic Pulmonary Fibrosis (IPF) is a devastating disease that probably involves several genetic loci. Several rare genetic variants and one common single nucleotide polymorphism (SNP) of MUC5B have been associated with the disease. Our aim was to identify additional common variants associated with susceptibility and ultimately mortality in IPF.

Methods First, we did a three-stage genome-wide association study (GWAS): stage one was a discovery GWAS; and stages two and three were independent case-control studies. DNA samples from European-American patients with IPF meeting standard criteria were obtained from several US centres for each stage. Data for European-American control individuals for stage one were gathered from the database of genotypes and phenotypes; additional control individuals were recruited at the University of Pittsburgh to increase the number. For controls in stages two and three, we gathered data for additional sex-matched European-American control individuals who had been recruited in another study. DNA samples from patients and from control individuals were genotyped to identify SNPs associated with IPF. SNPs identified in stage one were carried forward to stage two, and those that achieved genome-wide significance (p<5 × 10-8) in a meta-analysis were carried forward to stage three. Three case series with follow-up data were selected from stages one and two of the GWAS using samples with follow-up data. Mortality analyses were done in these case series to assess the SNPs associated with IPF that had achieved genome-wide significance in the meta- analysis of stages one and two. Finally, we obtained gene-expression profiling data for lungs of patients with IPF from the Lung Genomics Research Consortium and analyzed correlation with SNP genotypes.

Findings in stage one of the GWAS (542 patients with IPF, 542 control individuals matched one-by-one to cases by genetic ancestry estimates), we identified 20 loci. Six SNPs reached genome-wide significance in stage two (544 patients, 687 control individuals): three TOLLIP SNPs (rs111521887, rs5743894, rs5743890) and one MUC5B SNP (rs35705950) at 11p15.5; one MDGA2 SNP (rs7144383) at 14q21.3; and one SPPL2C SNP (rs17690703) at 17q21.31. Stage three (324 patients, 702 control individuals) confirmed the associations for all these SNPs, except for rs7144383. Linkage disequilibrium between the MUC5B SNP (rs35705950) and TOLLIP SNPs (rs111521887 [r2=0·07], rs5743894 [r2=0·16], and rs5743890 [r2=0·01]) was low. 683 patients from the GWAS were included in the mortality analysis. Individuals who developed IPF despite having the protective TOLLIP minor allele of rs5743890 carried an increased mortality risk (meta-analysis with fixed-effect model: hazard ratio 1·72 [95% CI 1·24-2·38]; p=0·0012). TOLLIP expression was decreased by 20% in individuals carrying the minor allele of rs5743890 (p=0·097), 40% in those with the minor allele of rs111521887 (p=3·0×10-4), and 50% in those with the minor allele of rs5743894 (p=2·93×10-5) compared with homozygous carriers of common alleles for these SNPs.

Interpretation Novel variants in TOLLIP and SPPL2C are associated with IPF susceptibility. One novel variant of TOLLIP, rs5743890, is also associated with mortality. These associations and the reduced expression of TOLLIP in patients with IPF who carry TOLLIP SNPs emphasize the importance of this gene in the disease.