Reviewer’s report

Title: Incorporating genetics into the identification and treatment of Idiopathic Pulmonary Fibrosis

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Reviewer: Ivan O. Rosas

Reviewer’s report:

The manuscript titled “Incorporating genetics into the identification and treatment of Idiopathic Pulmonary Fibrosis” by Mathai et al., has two main sections, the first is a summary of prior work in the field, and the latter a discussion of the implications of these findings for patient care. The manuscript is written by experts in the field and the perspective provided in the latter part of the manuscript will be of interest to readers.

With this said the former part of the paper is poorly written and will require substantial editing. For example, in page 6 multiple sequential grammatical errors become very distracting: …Patients with these variants had profound shortening of telomeres in peripheral blood mononuclear cells (PBMCs), though the mechanism by which loss of PARN affects telomere length is unknown. These newly described rare variants further point to telomere length as important in the pathogenesis of IPF; …The previous studies focused on …; The authors determined utilizing a genome-wide linkage analysis follow by sequencing …

I have provided additional comments, unfortunately the grammatical errors are so frequent that they become distracting, please carefully edit the first section of the manuscript.

Comments:

1. Consider using throughout the manuscript standard nomenclature for IPF- not sporadic IPF, familial interstitial pneumonia- not familial IPF; there are multiple iterations in the manuscript
2. Background section, as the authors know the statement “fibroblastic foci, a structure unique to IPF” is inaccurate please correct accordingly
3. Background, the statement “Initial investigations distinguished between familial and sporadic forms of IPF, though there is increasing evidence that genetic risk factors play a significant role in both forms of the disease”, is vague and somewhat unrelated to the rest of the paragraph, rephrase or remove.
4. Page 5, Dyskeratosis Congenita, not congenital, please correct.
5. Page 5, Dyskeratosis Congenita 1, not dyskeratoticis, please correct.
6. Page 7, what is the message for the reader with the following statement: MUC5B has also been found in honeycomb cysts, one of the hallmark pathologic findings of IPF.
7. Page 7, I read this paragraph several times and unclear how the quoted frequencies justify the conclusions of gene by environment interactions, please be more precise: the frequency of the risk allele is 9.1% in the general non-Hispanic white population that comprised the control group, which implies interplay between genetic risk and environmental exposure in the development of IPF.

8. Page 8, “The association of the MUC5B promoter polymorphism appears to be specific to pulmonary fibrosis.” In cohorts with systemic sclerosis and interstitial lung disease, asbestosis, sarcoidosis ... be precise, pulmonary fibrosis encompasses all the non-IIP conditions listed; are you referring to idiopathic pulmonary fibrosis.

9. Page 8, Please reference the following statement: Interestingly, the MUC5B polymorphism is not present in African populations.

10. Page 9, please clarify, what you mean by “fibrotic IIP”; the idiopathic interstitial pneumonias are by definition a group of fibrotic disorders.

11. Page 9, “These common variants associated with fibrotic IIP suggest that host defense (MUC5B, ATP11A), cell-cell adhesion (DSP and DPP9), and DNA repair (TERT, TERC, and OBFC1) may be important in disease pathogenesis”; do you mean that the ontology of the genes in which the common variants are found suggest that these biological functions are relevant to the pathogenesis of IPF? Please edit.

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.