A genetic landscape of Pulmonary Fibrosis in Japanese population. -Preliminary Results-

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Several large-scale genetic studies on pulmonary fibrosis had been conducted in population of European descent and identified multiple causal genes, such as telomere related genes and pulmonary surfactant protein genes. The *MUC5B* "gain-of-function" promoter variant, rs35705950, which is common in Europeans with a minor allele frequency (MAF) of 10%, was also known to have a large effect size (OR: 4.8, 95%CI: 4.4-5.4) for pulmonary fibrosis and account for 5-10% of disease liability in Europeans. However, the transferability of the genetic findings of Eurocentric studies to non-Europeans is not guaranteed, especially for rare variants.

The present study is aimed to better understand the genetic architecture of pulmonary fibrosis in Japanese population. To do so, we performed whole-genome sequencing (WGS) of 51 familial pulmonary fibrosis (FPF) patients (44 unrelated probands) and 161 sporadic idiopathic pulmonary fibrosis (IPF) patients. We first tried to identify rare putative deleterious (p-del) variants in the candidate genes, namely, *ABCA3, DSP, NAF1, PARN, RTEL1, SFTPA2, SFTPA1, STN1, TERC, TERT, TINF2* in FPF individuals. We further aimed to replicate the associations of gene-based analysis and genome-wide association study (GWAS) of European descent. For association studies, we used 3,103 unrelated Japanese individuals with WGS from Japanese haplotype reference panel as controls.

Amongst 44 unrelated FPF, up to 16 individuals (36%, 95%CI: 24-51%) had at least one p-del variants in candidate genes; six individual had p-del variants in *RTEL1*, as well as four in *TERT*, three in *SFTPA2*, two in *PARN*, two in *DSP*, and one in *TERC*. Gene-based collapsing test by using rare p-del variants found the weak associations between *TERT* and sporadic IPF (p=0.01). The association with rs35705950 was also nominally replicated in Japanese FPF but not in sporadic IPF (OR: 51.8, 95%CI: 2.7-978, p=0.008 for FPF and OR 2.9, 95%CI: 0.4-22.5, p=0.31 for sporadic IPF, respectively).

Our results confirmed the enrichment of rare putative deleterious variants in candidate genes and replicated the associations with rs35705950 in Japanese FPF patients. A future nation-wide large-scale genetic study is warranted to identify population specific variants and genes associated with pulmonary fibrosis.