Untangling 11p15.5 for Chronic Hypersensitivity Pneumonitis

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Hypersensitivity pneumonitis (HP) covers a range of diseases for which inhalation of an antigen leads to an inflammatory allergic reaction in the lungs. There are >300 forms of HP that reflect the range of antigens that cause this allergic response. This includes HP that is induced by animal proteins (eg, pigeon fancier’s lung), plant proteins (eg, wood fiber alveolitis), fungi (eg, farmer’s lung), bacteria/mycobacteria (eg, hot tub lung), and inorganic particles (eg, chemical worker’s lung).1,2

In many individuals, there is an acute response to the antigen that leads to coughing or shortness of breath after exposure. Treatment involves antiinflammatory steroids and avoidance of the relevant antigen, which generally leads to symptoms to resolve in a short period of time.3 In a small number of people, prolonged exposure to the antigen can lead to permanent lung scarring (pulmonary fibrosis), which leads to reduced lung function and can eventually be fatal. The reason that some individuals experience this severe form of HP, which is known as chronic HP (CHP), is not understood completely.

The most common form of pulmonary fibrosis is idiopathic pulmonary fibrosis (IPF). Although both CHP and IPF share similar clinical characteristics, there are some differences between the diseases. First, in IPF, rather than an aberrant inflammatory response to an allergen that leads to scarring of the lungs, there is an aberrant wound repair response to alveolar damage that leads to the fibrosis. Second, the individuals who are affected by the diseases can differ. Although CHP is more common in elderly individuals, it can present in younger individuals, whereas IPF is rare in individuals under the age of 50 years. IPF is also seen most commonly in individuals of European ancestry, whereas CHP is seen world-wide particularly in South Asian cohorts.1 However, there appears there could be a shared underlying genetic basis between the two diseases. Genome-wide association studies have identified a number of regions that are associated with IPF risk; many of these studies also show an association with CHP risk,4 though the way genes are expressed may be distinct between the two diseases.5

A single variant (rs35705950) in the promoter region of the MUC5B gene, which is located at the 11p15.5 region, shows the largest effect on IPF disease risk.6 It is believed that this variant leads to increased mucus production that impairs host defense resulting in lung damage. The frequency of the IPF risk allele (T) varies dramatically across populations. In European general populations, the frequency of the T allele is approximately 11% (and approximately 30% to 35% in European IPF cases) compared with an allele frequency of approximately 1% in East Asian general populations and 0% in many African populations.7 Three variants in the TOLLIP gene (rs111521887, rs5743894, and rs5743890), which are located about 15 kb downstream of the MUC5B gene, have been reported to be associated with IPF; however, there is inconclusive evidence as to whether these associations are independent of the nearby rs35705950 association.3,8 These variants also follow a similar geographic pattern of being uncommon in non-European populations.7 Given its role as a negative regulator of innate immunity, the TOLLIP gene is a biologically plausible candidate for CHP risk.

Generally, variants associated with IPF risk show little association with IPF disease progression. Both rs35705950 (MUC5B) and rs5743890 (TOLLIP) have been reported to show a possible weak association with improved survival after an IPF diagnosis. However, it is not possible to rule out that this association being caused by an index event bias (a bias that occurs in case-only
studies that leads to factors associated with risk to show a paradoxical association with improved survival.\textsuperscript{1,5} It is not clear whether the IPF risk variants are associated with CHP progression.

In this issue of CHEST, Katayanagi et al\textsuperscript{10} investigated the effect of TOLLIP variants on the progression of CHP (measured by changes in FVC) with the use of two Japanese cohorts that totaled 101 CHP cases. Because the three previously reported TOLLIP variants that are associated with IPF were monomorphic in the samples used, the authors focused on two variants (rs3750920 and rs5743899) that are known to have a functional impact on TOLLIP transcription levels.\textsuperscript{11,12}

Neither of these variants had an allele frequency significantly different to a reference Japanese population, meaning that there is no evidence these variants were associated with CHP risk. However, those with the GG genotype at rs5743899 showed a more rapid decline in FVC compared with those with either the AA or AG genotype in both of the cohorts that were studied. Functional follow-up analyses suggest that those patients with the GG genotype had lower expression levels of TOLLIP and that the decreasing FVC may be due to increased proinflammatory signaling (with increased Smad2 and IkB phosphorylation and proinflammatory cytokine levels) in individuals with the GG genotype.

There are some limitations of this analysis. The sample size of the analysis is relatively small, which means that there is power to investigate only candidate variants. Further larger analyses are needed to confirm these results and to study all variants in the region because we cannot exclude the possibility that a variant in linkage disequilibrium rs5743899 is driving this association. More research is also needed to establish how these genetic variations interact with the different exposures that can cause HP. Most individuals in this study were exposed to avian antigens, which may mean these results are not generalizable to forms of CHP caused by different antigens.

However, there are some key strengths to the study. Full functional follow-up analyses have identified potential biologic pathways that lead to increased fibrosis. Furthermore, a benefit of using a Japanese population is the low frequency of the MUC5B promoter polymorphism rs35705950_\textsuperscript{T}. This means the results presented here, hopefully, will describe the effects of TOLLIP independent of the MUC5B variant.

The role of the 11p15.5 region and different forms of interstitial lung disease remains unclear, but studies such as this will help us understand the similarities and differences between these diseases, which helps inform treatment options and gives hope that we can develop effective interventions that target the processes that are specific to each form of the disease.

References