SHORT COMMUNICATION

How much do we know about genetic predisposition of hypersensitivity pneumonitis?

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INTRODUCTION

Hypersensitivity pneumonitis (HP) is an interstitial lung disease caused by iterative inhalation of various environmental agents. The clinical presentation is variable, acute HP commonly presents an inflammatory response, whereas the development and clinical consequences in chronic HP may be similar to IPF (idiopathic pulmonary fibrosis). The aim of this mini-review is to summarize the genetic variations and discovered to be important. Recently, the need to study miRNAs in ILD (interstitial lung disease) has been highlighted. The appropriate scientific literature was reviewed and analyzed.

Materials and method. The appropriate scientific literature was reviewed and analyzed.

Results. Studies have discovered relevant gene polymorphisms in HP, including polymorphisms in the major histocompatibility complex in the metalloproteinases genes. The length of the peripheral blood leukocyte telomere has been investigated and discovered to be important. Recently, the need to study miRNAs in ILD (interstitial lung disease) has been highlighted. Exposed HP developed only in some people and a genetic susceptibility significantly increases the risk. Further more current studies on large groups of patients are needed to learn more about the genetic predisposition and risk factors of HP.

Key words: hypersensitivity pneumonitis, MUC5B, TOLLIP, telomeropathy

GENETIC VARIATIONS

Diverse factors play crucial roles in the progression of the HP, especially genetic and environmental. The most common type of genetic variations are single nucleotide polymorphisms (SNPs). SNPs are the phenomenon of DNA sequence variation involving the change of a single nucleotide. SNPs can be used as biological markers of various diseases. Intensive research is being conducted on the relationship between gene polymorphisms and HP.

SNPs associated with IPF. Due to the development of pulmonary fibrosis in some HP patients, single nucleotide polymorphisms associated with IPF were investigated in patients with HP. In a study conducted by Ley et al. [5], two common SNPs characteristic of IPF were measured – MUC5B rs35705950 and TOLLIP rs5743890. It was discovered that, similar to IPF in HP patients, the frequency of the MUC5B minor alleles, but not the TOLLIP minor alleles, was significantly increased. The study also assessed the length of the peripheral blood leukocyte telomere. A shorter telomere length has been found to be associated with the range of fibrosis and reduced survival in a group of patients with HP [5]. Research on telomeres-related genes have been conducted, i.e. TERT (telomerase reverse transcriptase), TERC telomerase RNA component, DKC1 (dykerin 1), RTEL1 (regulator of telomere elongation helicase 1), PARN (poly[A]-specific ribonuclease), and TINF2 (TRF1 [telomere repeat binding factor 1]-interacting nuclear factor 2). The research found that HP patients with mutations in telomere-related genes had a worse clinical prognosis, such as shorter survival and faster progression (especially with TERT, RTEL1, and PARN genes). The study

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also suggested pathogenetic similarities between HP and IPF [6].

**Metalloproteinase SNPs.** Lung remodelling has been observed in patients with chronic HP and may be associated with excessive extracellular matrix (ECM) deposition. Therefore, studies of the polymorphism of metalloproteinase (MMPs) genes, the main task of which is the degradation of the extracellular matrix, were performed. Two polymorphisms were identified in the MMP1 (rs7125062) and MMP2 (rs11646643) genes that were associated with an increased risk of HP [7].

**Cytokine polymorphisms.** Kondoh et al. [8] studied polymorphisms of the genes for TNF-α, IL-10, TGF-β and IL-6. Thus far, no cytokine polymorphisms associated with hypersensitivity pneumonia have been found.

**HLA polymorphisms.** Association between human leukocyte antigen (HLA) polymorphisms and HP remains incomplete. Higher frequencies of the HLA-DR3 alleles (pigeon-breeder’s lung), the HLA-DQ3 alleles (Japanese summer-type HP) and HLA-A, HLA-B, and HLA-C loci antigens (farmer’s lung disease), were detected in HP. Also in HP patients were identified an increase in the frequency of HLA-DRB1*04:07, DRB1*04:05, DRB1*11:01, and DRB1*13:01 alleles [9, 10].

Aquino-Galvez et al. [11] conducted a study on transporters associated with antigen processing (TAP) genes which are located within the major histocompatibility complex (MHC) class II region. TAP are involved in the transport of peptides across the membrane of the endoplasmic reticulum for the formation of class I MHC molecules. They discovered that the frequencies of the alleles Gly-637 (GGC) and the genotypes Asp-637/Gly-637 and Pro-661/Pro-661 were increased in a group of Mexican patients with HP.

The limitation of these studies are the small groups of patients, and a lack of confirmation in other populations of patients. Nevertheless, these results emphasized the importance of research on the role of other MHC loci in this disease.

**MicroRNA.** Currently, research on the role of microRNAs is a rapidly developing field. The following miRNAs have been shown to be involved in lung homeostasis and development, i.e., miR-155, miR-26a, let-7, miR-29, miR15/miR-16, miR-223, miR-146a/b and the miR-17–92 cluster [12].

Based on a review of the PubMed database, studies on miRNA profiles have not yet been performed strictly in HP, although a study has been performed on the effect of miRNAs on the host’s immune response after fungal exposure. Croston et al. [13] reviewed this data. It was discovered that miR-21, miR-146, miR-132, miR-155, and the let-7 family members were involved in immune and inflammatory responses. It was also found that after fungal exposure, miRNAs presented the same profiles as in inflammation and allergy. In studies of exposure to Aspergillus fumigatus, Candida albicans, Cryptococcus neoformans, Paracoccidioides brasiliensis and Stachybotrys chartarum, responses of the following miRNAs were identified: miR-125a/b (macrophage polarization/activation), miR-132 ( toll-like receptor 2 – mediated signalling), miR-146a (TLR mediated signalling, alternative macrophage polarization), miR-29a/b (natural killer cell function, C-leptin signalling, inhibition of Th1 immune response). Interpretation of miRNA results is still difficult and requires further research in specific disease entities.

Table 1 shows a summary of the miRNAs functions, which could potentially play a role as biomarkers in the future.

### CONCLUSION

The review focused on attention on clinical genetics which has great potential and requires further research. Researchers are looking for genetic similarities in HP and IPF, especially in chronic forms of HP with fibrosis. Due to the complicated and not always fully discovered pathophysiological pathways in HP, especially complex disorders of the immune system, the interpretation of individual results of genetic polymorphisms creates difficulties.

### REFERENCES


<table>
<thead>
<tr>
<th>miRNA</th>
<th>Function</th>
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<tr>
<td>let-7 family (letal-7)</td>
<td>Control of innate immune responses to pathogenic agents, regulator of TLR mediated signalling. Involved in regulation of IL-13.</td>
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<tr>
<td>miR-17–92 cluster</td>
<td>Regulation of lung epithelial cell development</td>
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<tr>
<td>miR-21</td>
<td>Inhibition pro-fibrogenic activity of TGF-beta pathway in fibroblasts</td>
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<tr>
<td>miR-29</td>
<td>Regulation of natural killer cells function. Inhibition of Th1 immune responses. C-leptin signalling.</td>
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<td>miR-125</td>
<td>Regulation of macrophage polarisation. Increase macrophage activation.</td>
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<tr>
<td>miR-132</td>
<td>Regulation of TLR mediated signalling.</td>
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<tr>
<td>miR-146</td>
<td>Negative regulation of TLR mediated signalling. Induction of alternative macrophage activation.</td>
</tr>
<tr>
<td>miR-155</td>
<td>Regulation of TLR mediated signalling. Increase macrophage activation. Influence on Th2 immune response.</td>
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<tr>
<td>miR-200 family</td>
<td>Regulation of epithelial mesenchymal transition, action to maintain the epithelial phenotype by targeting the expression of the E-cadherin transcriptional repressors, ZEB1 and ZEB2</td>
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