Annals of Agricultural and Environmental Medicine 2022, Vol 29, No 2, 306–308
www.aaem.pl

SHORT COMMUNICATION

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

Justyna Błach[1,B-D], **Barbara Mackiewicz**[2,C,E-F]

[1] *Department of Clinical Immunology, Medical University, Lublin, Poland*
[2] *Department of Pneumonology, Oncology and Allergology, Medical University, Lublin, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Błach J, Mackiewicz B. How much do we know about genetic predisposition of hypersensitivity pneumonitis? Ann Agric Environ Med. 2022; 29(2): 306–308. doi: 10.26444/aaem/148049

Abstract

Introduction and Objective. 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 the study is to present the latest discoveries regarding the genetic predisposition of HP.
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.
Conclusion. Objective. 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

INTRODUCTION

Hypersensitivity pneumonitis (HP) is an interstitial lung disease (ILD) induced by the aspiration of a variety of antigens. The incidence of HP is difficult to estimate and depends on geographic conditions, local practices (agricultural and industrial), and host risk factors. The prevalence of HP in Europe ranges from 0.3 – 0.9 per 100,000 inhabitants [1]. More than 200 antigens which can cause HP have been identified. The clinical picture and progression of the disease vary depending on the type of antigen, exposure period and individual host factors. HP can be classified as acute, subacute or chronic. Typically, subacute and chronic forms develop after prolonged exposure to an antigen. Most antigens come from fungi, bacteria, animal and plant proteins, chemicals and metals [2]. Bird fancier's lung (BFL) is the most common form of HP worldwide, accounting for approximately 66 – 68% of all cases [3]. The essential pathogenic mechanisms manifest features of both type III and type IV hypersensitivity responses [4].

HP develops in only a small number of people exposed to the antigen. Some patients show acute symptoms of the disease, in others, the disease has a chronic manifestation and even fibrotic changes in the lungs occur; hence, it is important to identify which factors contribute to these differences. The aim of this mini-review is to summarize the genetic predisposition to HP, which may become biomarkers of this disease in the future.

Address for correspondence: Barbara Mackiewicz, Department of Pneumonology, Oncology and Allergology, Medical University, 20-954 Lublin, Poland
E-mail: b.mack@wp.pl

Received: 11.02.2022; accepted: 05.04.2022; *first published:*

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 (dyskerin 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

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 [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-125 a/b (macrophage polarization/activation), miR-132 (toll-like receptor 2 – mediated signalling), miR-146a (TLR mediated signalling, alternative macrophage activation), miR-29a/b (natural killer cell function, C-leptin signaling, inhibition of Th1 immune response). Interpretation of miRNA results is still difficult and requires further research in specific disease entities.

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

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

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

1. Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity pneumonitis: perspectives in diagnosis and management. Am J Respir Crit Care Med. 2017; 196: 680–689.
2. Pereira CA, Gimenez A, Kuranishi L, Storrer K. Chronic hypersensitivity pneumonitis. J Asthma Allergy. 2016; 9: 171–181. doi:10.2147/JAA.S81540
3. Chan AL, Juarez MM, Leslie KO, Ismail HA, Albertson TE. Bird fancier's lung: a state-of-the-art review. Clin Rev Allergy Immunol. 2012; 43(1–2): 69–83.
4. Johansson E, Boivin GP, Yadav JS. Early immunopathological events in acute model of mycobacterial hypersensitivity pneumonitis in mice. J Immunotoxicol. 2017; 14: 77–88.
5. Ley B, Newton CA, Arnould I, et al. The MUC5B promoter polymorphism and telomere length in patients with chronic hypersensitivity pneumonitis: an observational cohort-control study. Lancet Respir Med. 2017; 5(8): 639–647. doi:10.1016/S2213-2600(17)30216-3
6. Ley B, Torgerson DG, Oldham JM, et al. Rare protein-altering telomere-related gene variants in patients with chronic hypersensitivity pneumonitis. Am J Respir Crit Care Med. 2019; 200(9): 1154–1163. doi:10.1164/rccm.201902-0360OC
7. Santiago-Ruiz L, Buendía-Roldán I, Pérez-Rubio G, et al. MMP2 Polymorphism affects plasma matrix metalloproteinase (MMP)-2 levels, and correlates with the decline in lung function in hypersensitivity

pneumonitis positive to autoantibodies patients. Biomolecules. 2019; 9(10): 574. doi:10.3390/biom9100574
8. Kondoh K, Usui Y, Ohtani Y, Inase N, Miyake S, Yoshizawa Y. Proinflammatory and anti-inflammatory cytokine gene polymorphisms in hypersensitivity pneumonitis. J Med Dent Sci. 2006; 53(1): 75–83.
9. Furukawa H, Oka S, Shimada K, et al. Genetics of interstitial lung disease: vol de nuit (night flight). Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine 2015; 9(S1)1–7. doi: 10.4137/CCRPRPM.S23283
10. Falfan-Valencia R, Camarena A, Pineda CL. Genetic susceptibility to multicase hypersensitivity pneumonitis is associated with the TNF-238 GG genotype of the promoter region and HLA-DRB1*04 bearing HLA haplotypes. Respir Med. 2014; 108(1): 211–217.
11. Aquino-Galvez A, Camarena A, Montaño M, et al. Transporter associated with antigen processing (TAP) 1 gene polymorphisms in patients with hypersensitivity pneumonitis. Exp Mol Pathol. 2008; 84(2): 173–177. doi:10.1016/j.yexmp.2008.01.002
12. Kiszałkiewicz J, Piotrowski W, Brzezińska-Lasota E. Signaling pathways and their miRNA regulators involved in the etiopathology of idiopathic pulmonary fibrosis (IPF) and hypersensitivity pneumonitis (HP). Adv Respir Med. 2017; 85(3): 169–178. doi:10.5603/ARM.2017.0029
13. Croston TL, Lemons AR, Beezhold DH, Green BJ. MicroRNA regulation of host immune responses following fungal exposure. Front Immunol. 2018; 9:170. Published 2018 Feb 7. doi:10.3389/fimmu.2018.00170