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Genetic Insights into Allergic Rhinitis: A Comprehensive Review

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ABSTRACT

Allergic rhinitis, a common upper respiratory condition, imposes significant healthcare costs worldwide each year due to its widespread occurrence. This condition has become a major global health concern. In recent years, there has been increasing interest in the study of allergic rhinitis, particularly about its rising prevalence and its association with other conditions such as asthma. This review focuses on single nucleotide polymorphisms (SNPs) associated with allergic rhinitis. It examines potential candidate genes associated with the condition and the SNP variants that may contribute to its development. The findings presented are based on research conducted globally, involving individuals diagnosed with allergic rhinitis. The results highlight several SNPs in different genes that are correlated with allergic rhinitis, with some potentially offering insights into the pathophysiology of the disease and paving the way for novel approaches to immunotherapy.

Keywords: Asthma, Allergic rhinitis, Nucleotide polymorphisms, Genetic findings

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Introduction

Allergic rhinitis (AR), often referred to as hay fever, is an inflammatory condition that affects the nasal mucosa [1]. Common symptoms include a runny nose, sneezing, itching, and nasal congestion [2]. The condition is marked by the infiltration of eosinophils, activation of cytokines, and increased mucus production. It is frequently found alongside other health issues such as nasal polyps, asthma, sinusitis, middle ear infections, and, in rare cases, lower respiratory tract infections [3-5].

As one of the most widespread conditions globally, allergic rhinitis affects about 25% to 40% of people worldwide [6-8]. Studies show its prevalence to be 38.5% in Asia, 23-30% in Europe, 12-30% in the United States, and 7.7% in Africa [9]. Evidence from family and twin studies suggests that allergic rhinitis has a heritability range of 33% to 75% [10].

The onset and progression of allergic rhinitis are influenced by a mix of genetic, epigenetic, and environmental factors [11-14]. This has led to extensive global research aimed at identifying genetic variations associated with the condition. Understanding these genetic changes could potentially lead to better prevention strategies and more effective treatment options for managing allergic rhinitis.

This review focuses on single nucleotide polymorphisms (SNPs) associated with allergic rhinitis. It examines potential candidate genes linked to the condition and the SNP variants that may contribute to its development.

Results and Discussion

This collection of studies delves into the genetic variations associated with allergic rhinitis by comparing the genomes of affected individuals with those of healthy participants. The focus of these investigations was on single nucleotide polymorphisms (SNPs) present in genes linked to the onset and progression of allergic rhinitis. In the

following discussion, we summarize the key outcomes from these studies to highlight new insights and practical findings emerging in the field.

Genetic variations associated with allergic rhinitis

SNPs are common genetic alterations that can result in differences in phenotypic traits among individuals. Depending on their location in a gene, whether in the promoter, exonic, or intronic regions, these variations can lead to changes in how much a gene is expressed, the type of amino acid coded for, or how the RNA transcript is processed. If these SNPs alter the function or expression of proteins, they are considered pathogenic polymorphisms, which may contribute to disease.

Role of chemokines and their receptors in allergic rhinitis

Chemokines and their corresponding receptors are essential in the recruitment of inflammatory cells to areas affected by allergic reactions, making them critical in the context of allergic rhinitis. The role of these molecules has been studied in various allergic conditions. One chemokine, RANTES, has been closely linked with allergic diseases. For example, Kim's research found that the A403 and G28 alleles of the RANTES gene promoter were significantly more prevalent in allergic rhinitis patients compared to healthy controls. Another study by Nakamura *et al.* [15] identified a strong association between the Ile64 polymorphism in the CCR2 gene and the C51 polymorphism in the CCR3 gene with allergic rhinitis in a Japanese cohort. This research further revealed that the haplotype Ile/780C/51C64 was notably more common in allergic rhinitis patients than in the healthy group.

Eosinophil peroxidase gene

The gene responsible for encoding eosinophil peroxidase (EPO) produces a cationic enzyme released by activated eosinophils. Eosinophils are critical in defending the body against parasitic infections and also play a significant role in allergic inflammation. A study conducted by Nakamura *et al*. [16] analyzed specific polymorphisms in the EPO gene, namely Arg 202 (660G) in exon 6 and Leu358 in exon 7. These genetic variants were found to be linked to the onset of allergic rhinitis in individuals from Japan. Another study by Hrdlickova and Izakovicova-Holla [17] revealed that the A/G3979 polymorphism showed a marked association with allergic rhinitis, influencing serum IgE levels.

Cytokines and their receptors

Cytokines are water-soluble proteins secreted by various immune cells, which facilitate immune responses by activating macrophages and transforming B lymphocytes into plasma cells. These molecules are crucial in the progression of allergic rhinitis. Research by Bottema *et al.* [18] identified the C-1111T polymorphism in the IL-13 gene as strongly associated with different types of rhinitis, particularly in atopic individuals. They also found that certain polymorphisms like Arg130Gln and G870A in the IL-13 gene correlated with asthma and elevated IgE levels. Similarly, a study by Chen *et al.* [19] found that the rs20541 variant in the IL-13 gene is a risk factor for allergic rhinitis in Asian populations. Additionally, research by Shazia *et al.* [20] in Pakistan suggested that the A-1512C polymorphism in IL-13 could contribute to the development of both asthma and allergic rhinitis. Further studies, such as those by Hu *et al.* [21], linked the rs7517847 variant of the IL-23R gene with an increased risk of allergic rhinitis. Another study by Micheal *et al.* [22] demonstrated a significant association of the TT genotype in rs2243250 and the GG genotype in rs2227284 with allergic rhinitis, while no significant correlation was found with rs2070874 polymorphism in the IL-4 gene.

MRPL4 and TNF-α genes

The MRPL4 gene, located near the intracellular adhesion molecule-1 (ICAM-1), plays an important role in cellular adhesion, particularly in the respiratory epithelium. Its proximity to the ICAM gene suggests it may be a potential risk factor for allergic rhinitis. Wei *et al.* [23] showed that individuals with the rs1799964 polymorphism in the MRPL4 gene had a higher frequency of allergic rhinitis associated with NF-α than healthy controls.

TNFSF4 and BLK genes

Recent research indicates that the TNFSF4 gene, involved in immune cell signaling, and the BLK gene, which regulates B and T cell functions, might collectively contribute to allergic rhinitis susceptibility. Shen *et al*. [24] explored various polymorphisms in these genes, including rs1234314 and rs1234315 in TNFSF4, as well as

rs13277113 and rs1600249 in BLK, in a Chinese population. Their findings suggested that the CC genotypes in rs1234314 and rs1234315, and the AA genotypes in rs1600249 and rs13277113, may offer protection against allergic rhinitis. In contrast, the AG genotype at rs13277113 was linked to an increased risk of the condition. The study further indicated that certain haplotypes, such as ACC (rs1234313, rs1234314, rs1234315) and GA (rs2254546, rs13277113), might lower the risk of developing allergic rhinitis, while other haplotypes, like GGT and AG, may provide protective effects.

TSLP and OX40L genetic variations

Thymic stromal lymphopoietin (TSLP) plays a critical role in initiating allergic responses, particularly within epithelial dendritic cells [25]. OX40L, part of the tumor necrosis factor receptor family, has been implicated in various autoimmune and inflammatory disorders [26]. Research by Soto-Quiros *et al.* [27] revealed that genetic variations in the TSLP and OX40L genes are closely linked to allergic rhinitis, demonstrating their strong association with both allergic symptoms and elevated IgE levels, notably in pediatric cases.

FOXP3 gene and immune regulation

The FOXP3 gene encodes a protein essential for immune system regulation, particularly in the function of T cells. Variations in this gene may result in immune dysfunction, contributing to the development of allergic diseases [27]. Hassannia *et al.* [28] found that the FOXP3-3279 polymorphism occurred more frequently in allergic rhinitis sufferers than in healthy controls, suggesting a potential role in the condition's development.

Leukotriene involvement in allergic inflammation

Leukotrienes are lipid mediators involved in inflammatory processes, such as smooth muscle contraction and cell migration, during allergic reactions [29-31]. In a study by Gülçin Eskandari *et al.* [32], the A-444C polymorphism of the leukotriene C4 synthetase gene was linked to a higher risk of allergic rhinitis in individuals from Turkey, with the AC genotype and C allele significantly increasing susceptibility.

GATA3 gene's role in Th2 responses

The GATA3 gene regulates the activity of Th2 cells, which are central to allergic immune responses. Research by Shirkani *et al*. [33] showed a marked association between the rs1269486 polymorphism in GATA3 and the increased prevalence of the GG genotype in allergic rhinitis patients, compared to the control group. Zhang *et al*. [34] also observed a higher frequency of the G allele of rs1269486 in patients, suggesting a potential link between this variant and allergic disease susceptibility.

TIM-1 gene and T cell differentiation

Located on chromosome 11, the TIM-1 gene is involved in T cell differentiation and plays a role in allergic conditions. Mou *et al.* [35] highlighted the association of the G > C416 and G > A1454 polymorphisms in the TIM-1 gene with greater susceptibility to allergic rhinitis, as well as elevated levels of IgE and IgA.

PTPN22 and CTLA-4 in immune regulation

The PTPN22 and CTLA-4 genes are key regulators of immune responses, with their variations linked to autoimmune diseases. In a study conducted by Song *et al.* [36] on Chinese children, the CC genotype and C allele of rs1310182 in PTPN22 were significantly more prevalent in allergic rhinitis patients than in controls. Additionally, the AA genotype of rs231725 was less common in the patient group.

Toll-like receptors and immune response

Toll-like receptors (TLRs) are essential for detecting pathogens and triggering immune responses. Nilsson *et al*. [37] studied the genetic variations in TLR7 (rs179008) and TLR8 (r12407992) genes in the Danish population and found that these polymorphisms were associated with an increased likelihood of developing allergic rhinitis.

FCRL3 and immune regulation in allergic rhinitis

FCRL3, a gene involved in immune regulation, has been shown to contribute to autoimmune diseases [38, 39]. Gu *et al.* [40] identified polymorphisms in FCRL3, including rs7528684, rs10489678, and rs7522061, as significant risk factors for allergic rhinitis in a Chinese population. The study also demonstrated that the AGT haplotype was notably more frequent in allergic rhinitis patients.

Histamine inactivation pathways in allergic rhinitis

Histamine is a central player in the allergic response, often released from mast cells and contributing to the typical symptoms of allergic rhinitis. Its inactivation involves two major enzymes: histamine N-methyltransferase (HNMT) and diamine oxidase (DAO). According to Qili's findings, variations in the HNMT and DAO genes can alter the function of these enzymes, leading to reduced histamine breakdown and potentially exacerbating allergic reactions. Meza-Velázquez *et al.* [41] investigated the effect of specific genetic variations (C314T and C2029G) in these genes on allergic rhinitis severity in children from Mexico. The study concluded that carriers of the mutated alleles were more prone to higher histamine levels in the serum, stronger allergic symptoms, and a greater likelihood of developing chronic allergic rhinitis.

Role of vitamin D metabolism in allergic rhinitis

Vitamin D influences immune function by regulating macrophages and reducing the production of Th2 cytokines, which are pivotal in the development of allergic conditions [42]. The enzyme encoded by the CYP2R1 gene, responsible for the conversion of vitamin D to its active form, plays a crucial role in this process. Tian *et al*. [43] examined the link between genetic variations in the vitamin D receptor (VDR) and CYP2R1 genes and the persistence of allergic rhinitis in a Chinese cohort. Their results indicated that the AA genotype of the CYP2R1 rs2060793 polymorphism increased the likelihood of persistent allergic rhinitis, especially in younger individuals (under 16 years). In addition, the AG and GG genotypes of the VDR rs731236 polymorphism were found to increase the risk of reduced allergic rhinitis persistence.

Conclusion

Allergic rhinitis, a common condition triggered by IgE reactions to allergens, often coexists with diseases like asthma [44]. The hallmark symptoms include sneezing, nasal congestion, itching in the eyes and nose, along with watery nasal discharge [45]. These symptoms can significantly disrupt daily activities, social interactions, and work or school commitments, reducing the overall quality of life. Both genetic factors and environmental exposures play pivotal roles in the onset of allergic rhinitis [46]. Research highlights that variations in several genes, such as those involved in interleukins, cytokines, leukotrienes, eosinophil peroxidase, MRPL4, TNF-α, histamine-N-methyltransferase, diamine oxidase, VDR, CYP2R1, Toll-like receptors, PTPN22, CTLA-4, FCRL3, TSLP, OX40L, FOXP3, GATA3, and TIM, contribute to the disease's development [21-46]. These genetic differences may also influence an individual's response to medications, emphasizing the need to consider genetic profiling for more personalized treatment approaches in managing allergic rhinitis and related conditions like asthma.

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