Review Article

Genetic Findings in Allergic Rhinitis: A Review

Felicia Manole[1,2], Gabriel Mihai Mekeres[1,2*], Lavinia Davidescu[3]

[1]Department of Surgical, Faculty of Medicine and Pharmacy, University of Oradea, 410087 Oradea, Romania. [2]County Clinical Emergency Hospital of Oradea, 410087 Oradea, Romania. [3]Department of Pneumology, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania.

Abstract

Allergic rhinitis is one of the most common diseases of the upper respiratory system, which imposes a high cost on countries every year due to its high prevalence. This disease is a global health problem. In recent years, due to the increase in prevalence and clinical importance of allergic rhinitis in other diseases, such as asthma, the study of this disease has received much attention. In this article, single nucleotide polymorphisms involved in allergic rhinitis have been studied in particular. In this study, the possible candidate genes related to allergic rhinitis in people with this disease and the single nucleotide polymorphism variants related to the said disease were investigated. The data collected in this study was the result of studies conducted in different parts of the world. The population studied in the articles are people with allergic rhinitis. The results have shown the association of several single nucleotide polymorphisms in different genes with allergic rhinitis, some of which may be useful in understanding the pathophysiology and finding new methods for immunotherapy of allergic rhinitis.

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

Introduction

Allergic rhinitis (AR), also known as hay fever, is an inflammatory disease of the nasal mucosa [1]. Runny nose, itching, sneezing, and nasal congestion are the most common clinical symptoms [2], and the penetration of europhilia, cytokine responses, and mucus secretion are among the characteristics of allergic rhinitis. Therefore, the coexistence of this disease with other diseases such as asthma, sinusitis, nasal polyps, middle ear inflammation, and rarely lower respiratory tract infection has been reported [3-5].

Allergic rhinitis is one of the most common diseases worldwide, so almost a quarter to 40% of the world's population is affected by this disease [6-8]. Previous studies show that the current prevalence of allergic rhinitis is 38.5% in Asia, 30-23% in Europe, 12-30% in the United States, and 7.7% in Africa [9]. Based on family and twin studies, it has been shown that allergic rhinitis has a heritability rate of 33-75% [10].

The complex interaction of genetics, epigenetics, and environmental factors plays an important role in the occurrence and development of allergic rhinitis [11-14]. Therefore, many studies have been conducted around the world to find genetic changes effective in the occurrence of allergic rhinitis; perhaps by identifying these changes, necessary preventions, and appropriate therapeutic interventions should be adopted.

Results and Discussion

In the studies conducted, people with allergic rhinitis and the genetic changes observed in the genome of these patients compared to healthy people have been investigated. In all reviewed articles, single nucleotide polymorphisms in candidate genes related to the occurrence and progression of allergic rhinitis were investigated. In the following, we discuss the findings of these studies so that we can access new and practical findings in this field from the results of these researchers' studies.

Polymorphic Changes in Allergic Rhinitis

Single nucleotide polymorphisms (SNPs) are among the most common changes in the genome that cause phenotypic differences between individuals. SNPs, by being located in the promoter, exonic, or intron region of a gene, can cause changes in gene expression level, coded amino acid type, and primary transcript splicing, respectively. In general, when SNPs cause changes in the function or expression of the

Address for correspondence: Gabriel Mihai Mekeres, Department of Surgical, Faculty of Medicine and Pharmacy, University of Oradea, 410087 Oradea, Romania.
mekeres_gabriel@yahoo.com

How to cite this article: Manole F, Mekeres GM, Davidescu L. Genetic Findings in Allergic Rhinitis: A Review. Arch Pharm Pract. 2023;14(1):99-103. https://doi.org/10.51847/qzRdommmTg

protein product, they are known as pathogenic polymorphisms [14].

Chemokines and Chemokine Receptors

Chemokines and their receptors are necessary for the chemical movement of various inflammatory cells to the site of inflammation; therefore, their relationship was investigated in general in allergic processes and especially in allergic rhinitis. RANTES is one of the chemokines whose relationship with allergic diseases has been extensively studied. In the study of Kim [14], it was shown that the polymorphic alleles A403 and G28 of the RANTES gene promoter are significantly higher in allergic rhinitis patients than in the healthy group. Nakamura *et al*. [15] showed that Ile64 polymorphism in the CCR2 gene and C51 polymorphism in the CCR3 gene were significantly associated with allergic rhinitis in the Japanese population. This study also showed a high frequency of Ile/780C/51C64 haplotype in allergic rhinitis patients compared to the control group.

Eosinophil Peroxidase

The eosinophil peroxidase (EPO) gene encodes a cationic protein that is released from activated eosinophils. Eosinophil granulocytes play an important role in protecting organisms against parasites. They are also proposed as cells that are effective in allergic inflammation. Nakamura *et al*. [16] conducted a study on eosinophil peroxidase gene polymorphisms, the results of which indicated the effect of polymorphisms Arg 202 (660G) in exon 6 and Leu358 in exon 7 of the EPO gene in causing allergic rhinitis in the Japanese population. Hrdlickova and Izakovicova-Holla [17] investigated gene polymorphisms, and finally, only polymorphism A/G3979 had a significant association with allergic rhinitis, and levels showed IgE serum.

Interleukins and Interleukin Receptors

Cytokines are a group of water-soluble protein molecules that are secreted from various cells of the immune system and can activate macrophages, convert B lymphocytes into plasma cells, and induce the production of different classes of antibodies. Studies have confirmed the important role of this factor in the development of allergic rhinitis. Bottema *et al*. [18] stated in a study that C-1111T of the IL-13 gene polymorphisms are significantly related to rhinitis types and atopic genotypes, Arg130Gln and G870A of the IL13 gene polymorphisms are significantly related to asthma and IgE serum level. Chen *et al*. [19] showed the association of rs20541 of the IL-13 gene polymorphism with the risk of allergic rhinitis in the Asian population. Shazia *et al*. [20], during a study they conducted in Pakistan, finally proposed the A-1512C polymorphism of the 13-IL gene as a risk factor for asthma and allergic rhinitis. Hu *et al*. [21] showed the association of rs7517847 of the IL-23R gene polymorphism with allergic rhinitis. The significant association of rs2243250 polymorphic TT genotype and rs2227284 polymorphic GG genotype and non-association of rs2070874 polymorphic genotype on IL4 gene was proposed by Micheal *et al*. [22].

MRPL4 / TNF-α

Intracellular adhesion molecule type 1 gene is expressed in the respiratory epithelium and plays an important role in ocular sensitivities. The MRPL4 gene is located near 1-ICAM and at position p13.219 on the chromosome, and for this reason, it may be considered a risk factor for the occurrence of AR. Wei *et al*. [23] reported that the frequency of rs1799964 of the MRPL4 gene polymorphisms is significantly higher in people with NF-α allergic rhinitis than in healthy people.

TNFSF4/ BLK

Recent studies indicate that the interaction between the type 4 tumor necrosis factor receptor gene and the B lymphocyte kinase gene can synergistically determine the direction of B and T cells. Shen *et al*. [24] studied rs1234314 and rs1234315 polymorphisms of the TNFSF4 gene and rs13277113 and rs1600249 polymorphisms of the BLK gene as effective biomarkers in allergic rhinitis susceptibility in the Chinese population. The results showed that the CC genotype (rs1234314 (r1234315) and the AA (rs1600249, 113277113) genotype have a protective effect against allergic rhinitis. At the same time, the AG (rs13277113) genotype was proposed as a risk factor in the occurrence of AR. It was also stated that the ACC haplotype in rs1234313 rs1234314 rs1234315 and GA in rs2254546 rs13277113 significantly reduce the risk of AR while GGT and AG haplotypes show a protective effect against AR.

TSLP/ OX40L

Cytokine thymus-dependent stromal lymphoprotein (TSLP) is a key molecule in epithelial dendritic cells that causes allergic inflammation [25]. OX40L is related to the family of tumor necrosis factor receptors. Studies have shown that X40-0X40 interactions play an important role in the development of several inflammatory and autoimmune diseases [26]. Hence, Soto-Quiros *et al*. [27] studied polymorphisms of TSLP and OX40L genes about allergic rhinitis and stated that polymorphisms in TSLP OX40 genes were significantly associated with AR and related phenotypes and also showed that polymorphic T allele rs1837253 in TSLP gene is strongly related to rhinitis and allergic genotypes and clinical symptoms of allergic rhinitis and it was also stated that TSLP and OX40L gene polymorphisms are strongly associated with total IgE levels in children.

FOXP3

The gene coding for FOXP3 protein, which is also known as scruffin, is involved in the response of the body's immune system. Genetic variations in the FOXP3 gene may be associated with dysfunction of T cells [27]. Hassannia *et al*. [28] investigated the frequency of the FOXP3-3279 polymorphism and showed that the haplotypes formed by the

A 3279 allele are significantly higher in allergic rhinitis patients than in the control group.

Leukotrienes

Leukotrienes (LT) are active lipid mediators that have been reported to mediate chemical movement cell activation and smooth muscle contraction during allergic inflammation [29-31]. Gülçin Eskandari *et al*. [32] investigated the frequency of A-444C leukotriene C4 synthetase gene polymorphism in allergic rhinitis patients in Turkey, and the results showed that the AC genotype and the C allele of this SNP increase the risk of allergic rhinitis.

GATA3 Transcription Factor

GATA3 transcription factor is the most important effective factor in increasing Th2 function. In the study of Shirkani *et al*. [33], a significant association was observed between the rs1269486 polymorphism of the GATA3 gene and the high frequency of the GG genotype, and the G allele of this SNP was obtained in the patient group compared to the healthy group. The results obtained from Zhang *et al*. [34] also showed the high frequency of the G allele of rs1269486 polymorphism and the low frequency of the A allele of rs2229360 polymorphism of the GATA3 gene in the group of patients.

TIM (T Cell Immunoglobulin and Mucin Domain)

The TIM-1 gene is located at position q31-335 on the chromosome and is involved in the differentiation of T cells and allergic diseases. Mou *et al*. [35] stated that G>C416 and G>A1454 polymorphisms of the TIM-1 gene are associated with susceptibility to allergic rhinitis and IgE and IgA levels.

PTPN22/ CTLA-4

Studies have shown that protein tyrosine phosphatase and related protein or cytotoxic T lymphocytes are associated with several immune-related diseases. In a study conducted by Song *et al*. [36] among Chinese children, it has been shown that the prevalence of CC genotype and C allele of rs1310182 polymorphism in the group of allergic rhinitis patients is higher than that of PTPN22 gene in the control group, and they also stated that AA genotype and allele A polymorphism of rs231725 is significantly reduced in the patient group.

Toll-like Receptor

The importance of Toll receptor proteins in host protection and initiation of innate and adaptive immune responses has been reported. Nilsson *et al*. [37] showed that the genetic variations of rs179008 in the TLR7 gene and r12407992 in the TLRS gene are effective in the risk and incidence of allergic rhinitis in the Danish population.

FCRL3

FCRL3 (Fc receptor-like gene) is a new immune regulatory gene whose role in autoimmune diseases has been reported [38, 39]. Gu *et al*. [40] introduced rs7528684, rs10489678, and rs7522061 polymorphisms as a strong risk factor, and polymorphism of r945635 was introduced as a weak risk factor for allergic rhinitis disease in the Chinese population. Based on this study, it was shown that the haplotype of strong risk SNPs (AGT) showed significantly high frequency in allergic rhinitis patients.

Histamine-N-Methyl Transferase/Diamine Oxidase

Histamine is one of the key inflammatory mediators that are activated and secreted by mast cells and mast cells and cause the symptoms of allergic rhinitis. Histamine is broken down through two main metabolic pathways involving the enzymes histamine N-methyltransferase (HNMT) and diamine oxidase (DAO). The results of Qili's research showed that the nucleotide changes of HNMT and DAO genes could change their enzyme activity; therefore, a variety of genetic variants that reduce the activity of these enzymes can reduce the ability of these enzymes to inactivate histamine and contribute to the development and chronicity of allergic inflammation. Meza-Velázquez *et al*. [41] have studied the association of C314T and C2029G polymorphisms in HNMT and DAO genes, respectively, by examining the severity of allergic rhinitis in a group of Mexican children. The results showed that patients who have mutated alleles of any of the SNPs are at a higher risk of allergic rhinitis, increased serum histamine levels, and more severe symptoms.

VDR/ CYP2R1

Previous research results have shown that vitamin D activates macrophages and reduces the production of cytokines by Th2. Th2 cytokines are necessary for the initiation and progression of allergic reactions; therefore, it is thought that the metabolic pathway of vitamin D is involved in the development of allergic diseases [42]. CYP2R1 encodes the enzyme hydroxylase (vitamin D 25-hydroxylase), which is effective in absorbing vitamin D. Tian *et al*. [43] found the association of polymorphisms in vitamin D receptor and cytochrome P450 2R1 (cytochrome P450 2R1 = vitamin D 25-hydroxylase) with mite persistent allergic rhinitis in investigated the Chinese population. This study stated that the AA genotype of the CYP2R1 gene polymorphism rs2060793 increased the risk of PER in the subgroup under 16 years of age. The AG and AG/GG genotypes of the VDR gene polymorphism rs731236 gene increased the risk of PER reduction.

Conclusion

Allergic rhinitis is a highly prevalent disease caused by IgE reactions after exposure to allergens. This disease is often associated with other diseases, such as asthma [44]. This disease's main symptoms are sneezing, congestion, itchy eyes and nose, and runny nose and eyes [45]. Therefore, this disease can affect the patient's quality of life, and daily activities affect social relationships, work, and school. Evidence shows that genetic predisposition and environmental factors are the main causes of this disease [46]. The results obtained from several studies indicate that single

nucleotide polymorphisms in several coding genes, including interleukins and their receptors, cytokines and their receptors, leukotrienes, eosinophil peroxidase, MRPL4 TNF-α, histamine-N-methyltransferase, diamine oxidase, VDR, CYP2R1, Toll-like receptor, PTPN22, CTLA-4, FCRL3, TSLP, OX40L, FOXP3, GATA3, and TIM [21-46]. The different genetic make-up of people can also cause differences in people's response to a particular drug. Therefore, different genetic variants and their effect on the response to drug treatments in allergic diseases such as asthma and allergic rhinitis are very important to adopt the most suitable treatment based on the genetic make-up of people.

ACKNOWLEDGMENTS: None
CONFLICT OF INTEREST: None
FINANCIAL SUPPORT: None
ETHICS STATEMENT: None

References

1. Bousquet J, Anto JM, Bachert C, Baiardini I, BosnicAnticevich S, Canonica GW, et al. Allergic rhinitis. Nat Rev Dis Primers. 2020;6(1):1-7.
2. Zheng R, Wu X, Huang X, Chen Y, Yang Q, Li Y, et al. Gene expression pattern of Treg and TCR Vγ subfamily T cells before and after specific immunotherapy in allergic rhinitis. J Transl Med. 2014;12(1):24.
3. Khaltaev N, Bousquet J. Allergic Rhinitis and its Impact on Asthma Update (ARIA 2008) The Perspective from Spain. J Investig Allergol Clin Immunol. 2008;18(5):327-34.
4. Ajwa N, Alhuwayji ZA, Masiri HM, Alhaddad NM, Tawfik L, Allaf AM, et al. Prevalence of dental defects among pediatric patients with cerebral palsy: a systematic review. Ann Dent Spec. 2022;10(4):84-90.
5. Alhammad IM, Aseri AM, Alqahtani SA, Alshaebi MF, Alqahtani SA, Alzahrani RA, et al. A review on updates in management and Treatment of Psoriasis. Arch Pharm Pract. 2021;12(1):74-8.
6. Rabin R, Vieths S. Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis_Regulation and Standardization of AIT extracts. Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis. 2015:219-21.
7. Mardi K. Diagnostic pitfalls in minimal deviation adenocarcinoma of the uterine cervix: Review and update. Clin Cancer Investig J. 2021;10(6):269-74.
8. Akdis CA, Hellings PW, Agache I. Global atlas of allergic rhinitis and chronic rhinosinusitis. EAACI; 2015.
9. Yang D, Yuan Y, Zhang S, Zhao K, Li F, Ren H, et al. Association between IL-13 Gene rs20541 Polymorphism and Glioma Susceptibility: A Meta-Analysis. Oncol Res Treat. 2018;41(1-2):14-21.
10. Harb H, Renz H. Update on epigenetics in allergic disease. J Allergy Clin Immunol. 2015;135(1):15-24.
11. Passali D, Cingi C, Staffa P, Passali F, Muluk NB, Bellussi ML. The International Study of the Allergic Rhinitis Survey: Outcomes from 4 geographical regions. Asia Pac Allergy. 2018;8(1):1-8.
12. Aljebrin YJ, Rashed AA, Alahmed MA, Alsamadani JH, Mahamat FM, Alrsheedi AS, et al. Literature Review: The Efficacy of Glucocorticoids in IgA Nephropathy Patients. Entomol Appl Sci Lett. 2021;8(2):85-90.
13. Meng Y, Wang C, Zhang L. Recent developments and highlights in allergic rhinitis. Allergy. 2019;74(12):2320-8.
14. Kim JJ, Lee JH, Jang CH, Kim YS, Chae SC, Chung HT, et al. Chemokine RANTES promoter polymorphisms in allergic rhinitis. Laryngoscope. 2004;114(4):666-9.
15. Nakamura H, Higashikawa F, Nobukuni Y, Miyagawa K, Endo T, Imai T, et al. Genotypes and haplotypes of CCR2 and CCR3 genes in Japanese cedar pollinosis. Int Arch Allergy Immunol. 2007;142(4):329-34.
16. Nakamura H, Miyagawa K, Ogino K, Endo T, Imai T, Ozasa K, et al. High contribution contrast between the genes of eosinophil peroxidase and IL-4 receptor α-chain in Japanese cedar pollinosis. J Allergy Clin Immunol. 2003;112(6):1127-31.
17. Hrdlickova B, Izakovicova-Holla L. Association of single nucleotide polymorphisms in the eosinophil peroxidase gene with allergic rhinitis in the Czech population. Int Arch Allergy Immunol. 2009;150(2):184-91.
18. Bottema RW, Nolte IM, Howard TD, Koppelman GH, Dubois AE, De Meer G, et al. Interleukin 13 and interleukin 4 receptor-α polymorphisms in rhinitis and asthma. Int Arch Allergy Immunol. 2010;153(3):259-67.
19. Chen ML, Zhao H, Huang QP, Xie ZF. Single nucleotide polymorphisms of IL-13 and CD14 genes in allergic rhinitis: a meta-analysis. Eur Arch Oto-RhinoLaryngol. 2018;275:1491-500.
20. Shazia M, Kanza M, Mehwish I, Irum S, Farida A, Asifa A. IL-13 gene polymorphisms and their association with atopic asthma and rhinitis in Pakistani patients. Iran J Allergy Asthma Immunol. 2013:391-6.
21. Hu D, Hu G, Zhu J, Shen Y, Kang H, Hong S. Association between polymorphisms of the IL-23R gene and allergic rhinitis in a Chinese Han population. PloS One. 2013;8(5):e63858.
22. Micheal S, Minhas K, Ishaque M, Ahmed F, Ahmed A. IL4 gene polymorphisms and their association with atopic asthma and allergic rhinitis in Pakistani patients. J Investig Allergol Clin Immunol. 2013;23(2):107-11.
23. Wei X, Zhang Y, Fu Z, Zhang L. The association between polymorphisms in the MRPL4 and TNF-α genes and susceptibility to allergic rhinitis. PloS one. 2013;8(3):e57981.
24. Shen Y, Liu Y, Wang XQ, Ke X, Kang HY, Hong SL. Association between TNFSF4 and BLK gene polymorphisms and susceptibility to allergic rhinitis. Mol Med Rep. 2017;16(3):3224-32.
25. Wang YH, Liu YJ. Thymic stromal lymphopoietin, OX40ligand, and interleukin-25 in allergic responses. Clin Experiment Allergy. 2009;39(6):798-806.
26. Croft M, So T, Duan W, Soroosh P. The significance of OX40 and OX40L to T-cell biology and immune disease. Immunol Rev. 2009;229(1):173-91.
27. Soto-Quiros M, Avila L, Hunninghake G, Weiss S, Celedon J. Polymorphisms in TSLP and TSLP-related Genes Are Associated with Allergic Rhinitis. J Allergy Clin Immunol. 2010;125(2):AB235.
28. Hassannia H, Abediankenari S, Ghaffari J. FOXP3 and TGF-β gene polymorphisms in allergic rhinitis. Iran J Immunol. 2011;8(4):218-25.
29. Duroudier N, Tulah A, Sayers I. Leukotriene pathway genetics and pharmacogenetics in allergy. Allergy. 2009;64(6):823-39.
30. Sadhu P, Kumari M, Rathod F, Shah N, Patel S. A Review on Poly(amidoamine) Dendrimers: Properties, Synthesis, and Characterization Prospects. Arch Pharm Pract. 2022;13(4):1-6.
31. Nasr AM, Ahmed YA, Gafar AA, Ahmed SA, Meshref ET, Ahamed EA, et al. Prevalence and Risk Factors of Choriocarcinoma in Saudi Arabia: A Systematic Review. Clin Cancer Investig J. 2022;11(6):4-8.
32. Gülçin Eskandari H, Ünal M, Görüroğlu Öztürk Ö, Vayisoğlu Y, Muşlu N. Leukotriene C4 synthase A-444C gene polymorphism in patients with allergic rhinitis. Otolaryngol—Head Neck Surg. 2006;134(6):997-1000.
33. Shirkani A, Mansouri A, Abbaszadegan MR, Faridhosseini R, Azad FJ, Gholamin M. GATA3 Gene Polymorphisms Associated with Allergic Rhinitis in an Iranian Population. Rep Biochem Mol Biol. 2017;5(2):97.
34. Zhang L, Zhang L, Wang X, Han D, Duan H, Zhao Y. Association of single nucleotide polymorphisms in GATA with allergic rhinitis. Acta oto-laryngol. 2009;129(2):190-4.
35. Mou Z, Shi J, Tan Y, Xu R, Zhao Z, Xu G, et al. Association between TIM-1 gene polymorphisms and allergic rhinitis in a Han Chinese population. J Investig Allergol Clin Immunol. 2010;20(1):3-8.
36. Song SH, Wang XQ, Shen Y, Hong SL, Ke X. Association between PTPN22/CTLA-4 gene polymorphism and allergic rhinitis with asthma in children. Iran J Allergy Asthma Immunol. 2016;15(5):413-9.

37. Nilsson D, Andiappan AK, Halldén C, De Yun W, Säll T, Tim CF, et al. Toll-like receptor gene polymorphisms are associated with allergic rhinitis: a case-control study. BMC Med Genet. 2012;13(1):66.
38. Kouhkan A, Pourpak Z, Moin M, Dorosty AR, Alizadeh RS, Teimorian S, et al. A study of malnutrition in Iranian patients with primary antibody deficiency. Iran J Allergy Asthma Immunol. 2004:189-96.
39. Safaralizadeh R, Minuchehr Z, Soheili Z, Moin M, Pourpak Z, Kardar G, et al. Phylogenetic analyses of human alpha subunit of FCepsilonRI with other species. InALLERGY 2009 Jan 1 (Vol. 64, pp. 268-268). COMMERCE PLACE, 350 MAIN ST, MALDEN 02148, MA USA: WILEY-BLACKWELL PUBLISHING, INC.
40. Gu Z, Hong SL, Ke X, Shen Y, Wang XQ, Hu D, et al. FCRL3 gene polymorphisms confer autoimmunity risk for allergic rhinitis in a Chinese Han population. PloS one. 2015;10(1):e0116419.
41. Meza-Velázquez R, López-Márquez F, Espinosa-Padilla S, Rivera-Guillen M, Gutíerrez-Díaz N, Pérez-Armendáriz L, et al. Association between two polymorphisms of histamine-metabolizing enzymes and the severity of allergic rhinitis in a group of Mexican children. Allergol Immunopathol. 2016;44(5):433-8.
42. Zhang L, Zhang S, He C, Wang X. VDR Gene Polymorphisms and Allergic Diseases: Evidence from a Meta-analysis. Immunol Investig. 2020;49(1-2):166-77.
43. Tian HQ, Chen XY, Lu Y, Lu WM, Wang ML, Zhao HL, et al. Association of VDR and CYP2R1 polymorphisms with mite-sensitized persistent allergic rhinitis in a Chinese population. PloS one. 2015;10(7):e0133162.
44. Tohidinik HR, Mallah N, Takkouche B. History of allergic rhinitis and risk of asthma; a systematic review and meta-analysis. World Allergy Organ J. 2019;12(10):100069.
45. Kakaje A, Alhalabi MM, Alyousbashi A, Hamid A, Hosam Aldeen O. Allergic Rhinitis and Its Epidemiological Distribution in Syria: A High Prevalence and Additional Risks in War Time. BioMed Res Int. 2020:27;2020.
46. Li Y, Rui X, Ma B, Jiang F, Chen J. Early-life environmental factors, IFN-γ methylation patterns, and childhood allergic rhinitis. Int Arch Allergy Immunol. 2019;178(4):323-32.