

Atopy: A Concoction of Allergen Exposure and Interleukin Genes, Cannot be Ignored

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INTRODUCTION

Allergic diseases are of great health concern with a wide geographical distribution [1,2]. The disease is being considered as an epidemic in developed countries and has doubled in past 2 to 3 decades but, currently the incidence is increasing alarmingly both in developing and developed world. India is experiencing an increasing trend, which otherwise was considered as low endemic zones for such disorders [3]. The disease is multi etiological without a single factor being established as a causal agent. Therefore, etiology remains unclear rather than conclusive. Epidemiological research over the last years has helped to identify possible environmental factors associated with allergic diseases. Among the various risk factors like smoke in different forms, pollution, microbial infections, occupational exposures, diet, pesticide use etc have been associated with allergies. However, the worldwide variation in its incidence suggests a complex interplay of multiple environmental, socioeconomic, and cultural factors [4-7]. Further research regarding the role of various risk factors in modulating differences in allergic disease prevalence between migrant and native populations will enhance our understanding of the complex gene-environment interactions involved in the pathogenesis of allergic disorders.

The condition that result due to exposure of body to environmental substances is characterized by raised IgE levels- a feature of allergic diseases. It results due to immune reaction to a substance called an allergen, which is normally harmless [8,9]. Allergen-specific IgE- antibodies cause most allergic reactions. A number of atopy susceptibility interleukin genes have been identified which regulate the production of IgE [10,11]. Genome wide Association studies (GWAS) have identified strong linkage of different genes with atopy in different populations [12-14]. IL-13 and STAT6 genes have been found to be involved in the regulation of IgE synthesis and manifestation of allergic disorders [15-17]. A number of studies regarding the different polymorphic variants of inflammatory markers and allergic phenotypes are available [18-20]. Considering the hyperactive immune response in the form of increased levels of IgE and altered interleukins genetic variants as a common biochemical manifestation among allergic patients as reported

elsewhere [21-25]. With a suitable environmental settings for presence of huge variety of allergens, there is a general perception that visible particles in air such as fluffy seeds from poplars and blooms could result in increased incidence of allergies in Kashmir. But, with little or no information to support such observations, we intend to identify the patients having different types of allergic disorders and find out any possible correlation with certain gene variants of interleukins.

Since, in allergic disorders an increased level of IgE and mutations in different inflammatory genes like IL4, IL4 receptor alpha etc are a common biochemical manifestation as reported elsewhere with none of the studies available in study population, it has created the opportunity to develop novel clinical strategies for the management and treatment of these patients in study population. IL4 is involved in the regulation of IgE synthesis and manifestation of allergic disorders [26] through its binding capacity with IL4 receptor- a membrane receptor. IL4 gene (HGNC: 6014) is clustered in a 160 kb region on the long arm of chromosome 5, recruit eosinophils and mast cells and induce B-cells for IgE synthesis [27,28]. In addition, IL4 is also responsible for regulating differentiation of naive T cells into Th2 subtype. In response to allergen IL4 strongly influence bronchial hyperreactivity resulting in airway inflammation, mucus hypersecretion and airway remodelling [25]. The gene coding for IL4R β (IL4R; HGNC: 6015) is located at chromosome 16p12.1. Polymorphic variants of several IL4R, have been associated with different atopic phenotypes and increased production of IgE [20]. The IL4R I50V (+A148G; rs1805010) single nucleotide polymorphism (SNP) in the coding region at position 50 in the amino acid sequence have been shown to affect the strength of signaling through the receptor and may be able to regulate other genes down the pathway [29]. Another polymorphism IL4R Q576R (A1902G; rs1801275) consists of an A-to-G transition at nucleotide 1902, causing a change from glutamine (Q) to arginine (R) at codon 576 in the cytoplasmic domain of the IL4R has been associated with hyper-IgE syndrome, severe atopic dermatitis, and a phenotype of atopy [30,31]. It has been reported that B lymphocytes isolated from allergic patients bearing Q576R variation in IL4R gene have an enhanced CD23 (soluble form of low affinity IgE receptor) induction in response to IL-4 [30,31].

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Received: July 02, 2021; **Accepted:** July 16, 2021 ; **Published:** July 23, 2021

Citation: Mudassar S (2021) Atopy: A Concoction of Allergen Exposure and Interleukin Genes, Cannot be Ignored. J Allergy Ther. 12: 263.

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IL4 70bp VNTR polymorphism exists due to presence of variable number of tandem repeats (VNTRs) in intron 3 of IL4 gene [32]. It has been suggested that specific number of VNTR copies affect the transcriptional activity of the gene, thereby modifying the resulting immune response. The Rp1 allele (2 repeats) is more responsive to transcription, leading to IL4 over-expression, thereby altering the Th1/Th2 balance by upregulation of the Th2 immune response and downregulation of the Th1 immune response [33]. Individuals with different copy numbers of the repeat sequences differ in the number of potential protein binding sites, thereby altering the amount of cytokine production [32].

CONCLUSION

Different cytokines as modulating factors of the immune response and inflammatory reactions are involved in the pathogenesis of Atopy. It is an inflammatory disorder of upper airways and skin resulting from environmental and genetic factors individually as well as complex interactions between the two. With a suitable environment for housing a huge variety of allergens, Kashmir valley has a significant number of Atopic patients. There has been an increase in number of people seeking medical help for complaints ranging from seemingly mild symptoms such as watery and itchy eyes, cough and cold to serious asthmatic attacks. The discovery of these genetic alterations has created the opportunity to develop novel clinical strategies for the management and treatment of these patients. In this background, we intend to identify the patients having atopic disorders and elucidate the role of IL4 and IL4R gene variants alone as well as their combinational effect on atopic disorders in presence of different life style and environmental factors

CONFLICT OF INTEREST

The authors have declared that they have no conflict of interest.

FUNDING SOURCE

None

REFERENCES

1. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet*. 2006; 368(9537): 733-43.
2. Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: A systematic review of epidemiological studies. *PLoS One*. 2012; 7(7): e39803.
3. Szeffler SJ. Epidemiology of asthma in india. *Indian J Pediatr*. 2002; 69(4): 309-12.
4. Barr RG, Avilés-Santa L, Davis SM, Aldrich TK, Gonzalez F, Henderson AG, et al. Pulmonary disease and age at immigration among hispanics. Results from the hispanic community health study/study of latinos. *Am J Respir Crit Care Med*. 2016; 193(4): 386-95.
5. Cabieses B, Uphoff E, Pinart M, Antó JM, Wright J. A systematic review on the development of asthma and allergic diseases in relation to international immigration: the leading role of the environment confirmed. *PLoS One*. 2014; 9(8): e105347.
6. Eldeirawi K, McConnell R, Furner S, Freels S, Stayner L, Hernandez E, et al. Associations of doctor-diagnosed asthma with immigration status, age at immigration, and length of residence in the united states in a sample of mexican american school children in chicago. *J Asthma*. 2009; 46(8): 796-802.
7. Yao J, Sbihi H. Prevalence of non-food allergies among non-immigrants, long-time immigrants and recent immigrants in canada. *Can J Public Health*. 2016; 107(4-5): e461-e6.
8. Akdis CA. Allergy and hypersensitivity: mechanisms of allergic disease. *Curr Opin Immunol*. 2006; 18(6): 718-26.
9. Chatzi L, Alegakis A, Tzanakis N, Siafakas N, Kogevinas M, Lionis C. Association of allergic rhinitis with pesticide use among grape farmers in crete, greece. *Occup Environ Med*. 2007; 64(6): 417-21
10. Marsh DG, Hsu SH, Roebber M, Ehrlich-Kautzky E, Freidhoff LR, Meyers DA, et al. Hla-dw2: a genetic marker for human immune response to short ragweed pollen allergen ra5. I. Response resulting primarily from natural antigenic exposure. *J Exp Med*. 1982; 155(5): 1439-51.
11. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol*. 2008;8(3):183-92.
12. Hirota T, Takahashi A, Kubo M, Tsunoda T, Tomita K, Sakashita M, et al. Genome-wide association study identifies eight new susceptibility loci for atopic dermatitis in the japanese population. *Nat Genet*. 2012; 44(11): 1222-6.
13. Munir S, ber Rahman S, Rehman S, Saba N, Ahmad W, Nilsson S, et al. Association analysis of gwas and candidate gene loci in a pakistani population with psoriasis. *Molecular immunology*. 2015; 64(1): 190-4.
14. Weidinger S, Klopp N, Wagenpfeil S, Rummeler L, Schedel M, Kabesch M, et al. Association of a stat 6 haplotype with elevated serum ige levels in a population based cohort of white adults. *J Med Genet*. 2004; 41(9): 658-63.
15. Liu X, Beatty TH, Deindl P, Huang SK, Lau S, Sommerfeld C, et al. Associations between total serum ige levels and the 6 potentially functional variants within the genes il4, il13, and il4ra in german children: The german multicenter atopy study. *J Allergy Clin Immunol*. 2003; 112(2): 382-8.
16. Liu X, Nickel R, Beyer K, Wahn U, Ehrlich E, Freidhoff LR, et al. An il13 coding region variant is associated with a high total serum ige level and atopic dermatitis in the german multicenter atopy study (mas-90). *J Allergy Clin Immunol*. 2000; 106(1 Pt 1): 167-70.
17. Basehore MJ, Howard TD, Lange LA, Moore WC, Hawkins GA, Marshik PL, et al. A comprehensive evaluation of il4 variants in ethnically diverse populations: association of total serum ige levels and asthma in white subjects. *J Allergy Clin Immunol*. 2004; 114(1): 80-7.
18. Liu S, Li T, Liu J. Interleukin-4 rs2243250 polymorphism is associated with asthma among caucasians and related to atopic asthma. *Cytokine*. 2012; 59(2): 364-9.
19. Mitsuyasu H, Izuhara K, Mao X-Q, Gao P-S, Arinobu Y, Enomoto T, et al. Ile50val variant of il4r1 upregulates ige synthesis and associates with atopic asthma. *Nat Genet*. 1998; 19(2): 119.
20. Amirzargar AA, Movahedi M, Rezaei N, Moradi B, Dorkhosh S, Mahloji M, et al. Polymorphisms in il4 and il4ra confer susceptibility to asthma. *J Investig Allergol Clin Immunol*. 2009; 19(6): 433-8.
21. Arima K, Umeshita-Suyama R, Sakata Y, Akaiwa M, Mao XQ, Enomoto T, et al. Upregulation of il-13 concentration in vivo by the il13 variant associated with bronchial asthma. *J Allergy Clin Immunol*. 2002; 109(6): 980-7.
22. Barnes KC, Neely JD, Duffy DL, Freidhoff LR, Breazeale DR, Schou C, et al. Linkage of asthma and total serum ige concentration to markers on chromosome 12q: evidence from afro-caribbean and caucasian populations. *Genomics*. 1996; 37(1): 41-50.

23. Kabesch M, Tzotcheva I, Carr D, Hofler C, Weiland SK, Fritzsche C, et al. A complete screening of the *il4* gene: novel polymorphisms and their association with asthma and ige in childhood. *J Allergy Clin Immunol*. 2003; 112(5): 893-8.
24. Heinzmann A, Mao XQ, Akaiwa M, Kreomer RT, Gao PS, Ohshima K, et al. Genetic variants of *il-13* signalling and human asthma and atopy. *Hum Mol Genet*. 2000; 9(4): 549-59.
25. Li X, Ampleford EJ, Howard TD, Moore WC, Torgerson DG, Li H, et al. Genome-wide association studies of asthma indicate opposite immunopathogenesis direction from autoimmune diseases. *J Allergy Clin Immunol*. 2012; 130(4): 861-8.
26. Lee GR FP, Griffin TJ, Flavell RA. Regulation of the th2 cytokine locus by a locus control region. *Immunity*. 2003; 19(3): 145-53.
27. Lee GR, Fields PE, Griffin IV TJ, Flavell RAJI. Regulation of the th2 cytokine locus by a locus control region. *Immunity* 2003; 19(1): 145-53.
28. Risma KA, Wang N, Andrews RP, Cunningham CM, Ericksen MB, Bernstein JA, et al. V75R576 IL-4 Receptor β is Associated with Allergic Asthma and Enhanced IL-4 Receptor Function. *J Immunol* 2002; 169(3): 1604-10.
29. Isidoro-García M, Dávila I, Laffond E, Moreno E, Lorente F, González-Sarmiento RJC, et al. Interleukin-4 (*il4*) and interleukin-4 receptor (*il4ra*) polymorphisms in asthma: a case control study. *Clin Mol Allergy* 2005; 3(1): 1-7.
30. Hershey GKK, Friedrich MF, Esswein LA, Thomas ML, Chatila TAJNEJoM. The association of atopy with a gain-of-function mutation in the β subunit of the interleukin-4 receptor. *N Engl J Med* 1997; 337(24): 1720-5.
31. Birbian N, Singh J, Jindal SK, Sobti RCJC. High risk association of *il-4* vnttr polymorphism with asthma in a north indian population. *N Engl J Med*. 2014; 66(1): 87-94.
32. Vandenbroeck K, Martino G, Marrosu MG, Consiglio A, Zaffaroni M, Vaccargiu S, et al. Occurrence and clinical relevance of an interleukin-4 gene polymorphism in patients with multiple sclerosis. *J Neuroimmunol*. 1997; 76(1-2): 189-92.