Review Article

Gene Susceptibility in Iranian Asthmatic Patients: A Narrative Review

Alizadeh-Navaei R, Rafiei A, Hedayatizadeh-Omran A, Mohammadzadeh I[1], Arabi M[2]

Molecular and Cell Biology Research Center, Mazandaran University of Medical Sciences, [1]Department of Community Medicine, Mazandaran University of Medical Sciences, Sari, [2]Non Communicable Pediatric Research Center, Babol University of Medical Sciences, Babol, Iran

Address for correspondence:
Dr. Alireza Rafiei,
Molecular and Cell Biology Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
E-mail: rafiei1710@gmail.com

Abstract

As environmental factors are important in the development of asthma, genetic factors could have a critical role in the expression of the disease. Hence, we carried out a systematic review to assess the susceptible genes for asthma in Iranian population. We conducted a literature search by using the electronic database PubMed, Biological Abstracts Web of Science, Current Contents Connect, Cinahl, ScienceDirect, Scopus, IranMedex, and Scientific Information Database to identify articles that evaluated the association between genetic variants and the risk of asthma in Iranian population (until April 30, 2012). The search terms were used include: Asthma and gene in combination with Iran for international database. The following criteria were used for selecting literatures in this review: The study should evaluate the association between gene polymorphism and risk of asthma in Iranian population, and the study should be a case-control design with normal subject as ac control group that published in a journal. Finally, 14 case-control studies were extracted from local and international database. In this study, we reviewed 38 polymorphisms in 19 genes. Polymorphism in *interleukin*-13 (*IL*-13), *IL*-10, *IL*-1, *IL*-2, *IL*-12, *E-Selectin*, *S*128*R* and *Exon* 9 *Vitamin D Receptor* were susceptible for asthma and polymorphism in *chemokine receptor* 5, *transforming growth factor-a* (*TGF-a*), *Intron* 8 of the *Vitamin D Receptor*, *angiotensin-converting enzyme* gene, *IL*-6 and *interferon-c* were not susceptible for asthma in Iranian population. Polymorphism in *IL*-4, *tumor necrosis factor-α* and *TGF-b* had inconsistent findings. This systematic review indicated that three polymorphisms (*IL*-13, *IL*-10, and *IL*-1) are associated with risk of asthma in Iranian population.

Keywords: Allergic asthma, Gene susceptibility, Polymorphism

Introduction

Asthma is one of the most common chronic respiratory diseases and the prevalence of this disease has increased during the last decades.[1-3] The prevalence of asthma symptoms in Iran is higher than that estimated in the international reports, a systematic review and meta-analysis from Iran show that the lowest prevalence of asthma symptoms was 2.7% in Kerman and the highest was 35.4% in Tehran. Overall prevalence of asthma symptoms at a national level was estimated as 13.14% (95% confidence interval: 9.97–16.30%).[4] It is well established that asthma is a complex disease and both genetic and environmental factors is responsible for beginning and progress of this disease.[5,6] Many studies regarding associations between genetic variants and asthma risk have been published and many genes were proposed as asthma susceptible genes.[7-10] Many genes were suggested as asthma risk factors for Iranian population; however, many of the studies have contradictory results. Hence, we carried out a systematic review to assess the susceptible genes for asthma in Iranian population.

Access this article online	
Quick Response Code:	**Website:** www.amhsr.org
	DOI: *****

Materials and Methods

We conducted a literature search by using the electronic database PubMed, Biological Abstracts Web of Science, Current Contents Connect, Cinahl, ScienceDirect, Scopus as international database and IranMedex and Scientific

Information Database (SID) as local database to identify articles that evaluated the association between genetic variants and the risk of asthma in Iranian population (until April 30, 2012). The search terms were used as follows: Asthma (in meSH) in combination with Iran for PubMed; asthma in combination with gene and Iran in topic field for Biological Abstracts Web of Science, Current Contents Connect; asthma in combination with gene and Iran in all field for Cinahl; asthma in title filed in combination with gene and Iran in all field for ScienceDirect; asthma in title filed in combination with gene in "Title-Abstract-Keyword" field and Iran in affiliation field for Scopus; asthma in combination with gene in simple search for IranMedex and SID. The following criteria were used for selecting literatures in this review: the study should evaluate the association between gene polymorphism (no expression) and risk of asthma in Iranian population, the study should be a case-control design with normal subject as ac control group that published in a journal, and there was Hardy-Weinberg equilibrium in related polymorphism. Two independent authors checked all potentially relevant studies and reached a consensus on all items. Additional data were requested from authors. The following data were collected from each study: First author, year of publication, ages, genotype frequencies in cases and controls. The genotypic distribution (no allelic distribution) was considered for susceptibility between case and control.

Results

Finally, 14 case-control studies were extracted from local and international database in our search [Table 1]. Study population in one study was children and in other studies was adult. In this study, we reviewed 38 polymorphisms in 19 genes. One thousand one hundred and eighty-four patients in case group (asthmatic patients) and 1650 subjects in control group were studied. There were polymorphisms that was susceptible for asthma and other was nonsusceptible for asthma and a few polymorphism was susceptible in some studies and nonsusceptible in other studies.

Susceptible polymorphism

Polymorphism in *interleukin*-13 (*IL*-13), *IL*-10 and *IL*-1 in several studies and *IL*-2, *IL*-12, *E-Selectin, S*128*R* and *Exon* 9 *Vitamin D Receptor* in different study had effect on the occurrence of allergic asthma and theirs proportion in asthmatic patient in comparison with control group.

Nonsusceptible polymorphism

There was significant relation between *CCR*5, *transforming growth factor-a* (*TGF-a*), *Intron* 8 *of the Vitamin D Receptor*, *angiotensin-converting enzyme* gene, *IL*-6 and *interferon-c* (*IFN-c*) polymorphism in different study and *IL*-16 and *IFN-y* polymorphism in two different studies with allergic asthma in comparison with control group.

Inconsistent polymorphism

Polymorphism in *IL*-4 was frequent polymorphism that studied in different studies and some study reported an association between asthma and this polymorphism in comparison with control but in another studies there was not significant difference. Polymorphism in *tumor necrosis factor*-α (*TNF*-α) in three different studies and *TGF-b* in two different studies had inconsistent findings for this relation.

Discussion

Asthma is a complex polygenetic disease with a clear genetic predisposition.[25] The aim of this review was to combine results from studies on this relation to produce more precise results. The current study is to disclose the roles of genetic variants and their associations with risk of asthma in Iranian population. In this study, we finally identified 38 polymorphisms in 19 genes in Iranian population. Among them, three polymorphisms (*IL*-13, *IL*-10 and *IL*-1 in more than one study) were statistically associated with increased risk of asthma. *IL*-13 and *IL*-10 genes are mainly involved either in Th2 cell differentiation and immunoregulatory, respectively.[26] *IL*-13 is a T-helper type 2 cytokine. Animal models have implicated *IL*-13 as a critical cytokine in the development of asthma. *In vitro IL*-13 exerts important effects on both structural and inflammatory cells within the airway and has the capacity to drive the clinical features of airways disease. In asthma, this view is strongly supported by associations with *IL*-13 genetic polymorphisms and increased messenger RNA and protein expression in blood, sputum and bronchial submucosa. In particular, *IL*-13 up-regulation is associated with severe disease.[27] Zhang *et al*. reported that *IL*-13 is an important gene which is associated with asthma.[28] Rosenwasser and Borish reported that *IL*-10 promoter polymorphism is a potential molecular mechanism for dysregulation of these cytokine genes in asthma.[29]

Result show that two polymorphisms (*IL*-16 and *IFN-y* in more than one study) were not significant relation with asthma. *IL*-16 is an immunomodulatory cytokine whose expression is increased in the bronchial mucosa, bronchoalveolar lavage fluid and induced sputum of asthmatic patients. It has been suggested that *IL*-16 has a regulatory role in the pathophysiology of asthma. A single-nucleotide polymorphism has been described in the promoter region of the gene and it has been hypothesized that this polymorphism may be associated with altered levels of *IL*-16 expression, and account for the increased levels of *IL*-16 seen in the asthmatic airway. Similar to our result in Australian population it is not associated with asthma.[30] In similar to our result, were not associated with the susceptibility and disease severity of bronchiolitis as well as *IFN-gamma* in Chinese population.[31] However, in Taiwan children there was strong association between *IFN-gamma* polymorphisms and risk of asthma.[32]

Table 1: The distribution of polymorphism related to asthma in Iranian population

Study	Population	Number case/control	Significant polymorphism	Nonsignificant polymorphism
Amirzargar *et al.*[11]	Children	59/139	*IL*-4–590 *IL*-4–33 *IL*-4–1098 *IL*-4*RA*+1902	
Kamali-Sarvestani *et al.*[12]	Adult	203/113	*IL*-4–589	*TNF-α* –308
Hosseini-Farahabadi *et al.*[13]	Adult	30/50	*IL*-4–590 *IL*-13 *R*130*Q*	*IL*-16–295*T*
Nadi *et al.*[14]	Adult	172/173	*E-Selectin S*128R	
Tavakkol Afshari *et al.*[15]	Adult	20/20	*IL*-4 *IL*-13	
Kazemi Arababadi *et al.*[16]	Adult	100/100	*Exon* 9 *of the Vitamin D receptor*	*Intron* 8 *of the Vitamin D receptor*
Movahedi *et al.*[17]	-	60/140	*IL*-10–1082 *IL*-10–819 *IL*-10–592 *IL*-12–1188 *TGF-β–codon* 25 *IL*-2–330	
Abdi-Rad *et al.*[18]	Adult	62/212		*ACE* gene
Mahdaviani *et al.*[19]	Adult	60/140	*TNF-α* –308 *TNF-α* –238 *IL*-1*α TC*–889 *IL*-1 *β TC*–511 *IL*-1*RA TC Mspa-I* 11100	
Daneshmandi *et al.*[20]	Adult	81/124		*IL*-6 *G*–174*C* *TNF-α G*–308A *TGF-β T*869*C* *IL*-4 *C*–590*T* IFN-*c T*874A
Hosseini-Farahabadi *et al.*[21]	Adult	30/50	*IL*-4–590*C*>*T* *Coding region of IL*-13	*IL*-16 –295*T*>*C*
Abdi-Rad *et al.*[22]	Adult	64/109		IFN-*γ* +874 *IL*-4 –590
Daneshmandi *et al.*[23]	Adult	81/80		*IL*-4 *C*–589*T* IFN-*γ A*+874*T*
Abousaidi *et al.*[24]	Adult	162/200		*CCR*5

ACE: Angiotensin-converting enzyme, TNF-α: Tumor necrosis factor alpha, IL: Interleukin, TGF-β: Transforming growth factor-beta, IFN: Interferon

Result show that two polymorphisms (*IL*-4 and *TNF-α* in more than one study) had inconsistent result and needs to additional study such as individual or meta-analysis about *IL*-4.

There were some limitations in this review. First, only published articles in the selected electronic databases were included in this study, it may be possible that some unpublished studies, were not included in this study. Second, there were heterogeneity results and different position for polymorphism in these studies. To our knowledge, this is the first genetic systematic review to date conducted in Iranian descent for asthma.

In conclusion, this systematic review indicated that three polymorphisms (*IL*-13, *IL*-10 and *IL*-1) are associated with risk of asthma in Iranian population. Asthma is a complex inflammatory disease of multifactorial origin, and is influenced by both environmental and genetic factors and there were geographic variations on asthma prevalence, the disparities in asthma prevalence among the world's geographic locations are more likely to be associated with genetic differences.[33]

References

1. Morales-Suarez-Varela M, Llopis-González A, Gimeno-Clemente N, Jiménez-López MC, García-Marcos Álvarez L. International study of asthma and allergy in childhood phase III (ISAAC III): The role of non-response in Valencia. Iran J Allergy Asthma Immunol 2010;9:175-80.
2. Ghaffari J, Aarabi M. The prevalence of pediatric asthma in the Islamic republic of Iran: A systematic review and meta-analysis. J Pediatr Rev 2013;1:2-11.
3. Mohammadzadeh I, Ghafari J, Savadkoohi RB, Tamaddoni A, Esmaeili-Dooki MR, Alizadeh-Navaei R. The Prevalence of asthma, allergic rhinitis and eczema in North of Iran. Iran J Pediatr 2008;18:117-22.
4. Entezari A, Mehrabi Y, Varesvazirian M, Pourpak Z, Moin M. A systematic review of recent asthma symptom surveys in Iranian children. Chron Respir Dis 2009;6:109-14.
5. Zhang Y, Zhang J, Huang J, Li X, He C, Tian C, *et al*. Polymorphisms in the transforming growth factor-beta1

gene and the risk of asthma: A meta-analysis. Respirology 2010;15:643-50.

6. Denham S, Koppelman GH, Blakey J, Wjst M, Ferreira MA, Hall IP, *et al*. Meta-analysis of genome-wide linkage studies of asthma and related traits. Respir Res 2008;9:38.
7. Weiss ST, Raby BA, Rogers A. Asthma genetics and genomics 2009. Curr Opin Genet Dev 2009;19:279-82.
8. Pinto LA, Depner M, Klopp N, Illig T, Vogelberg C, von Mutius E, *et al*. MMP-9 gene variants increase the risk for non-atopic asthma in children. Respir Res 2010;11:23.
9. Litonjua AA, Tantisira KG, Lake S, Lazarus R, Richter BG, Gabriel S, *et al*. Polymorphisms in signal transducer and activator of transcription 3 and lung function in asthma. Respir Res 2005;6:52.
10. Bossé Y, Lemire M, Poon AH, Daley D, He JQ, Sandford A, *et al*. Asthma and genes encoding components of the vitamin D pathway. Respir Res 2009;10:98.
11. Amirzargar AA, Movahedi M, Rezaei N, Moradi B, Dorkhosh S, Mahloji M, *et al*. Polymorphisms in IL4 and iLARA confer susceptibility to asthma. J Investig Allergol Clin Immunol 2009;19:433-8.
12. Kamali-Sarvestani E, Ghayomi MA, Nekoee A. Association of TNF-alpha -308 G/A and IL-4 -589 C/T gene promoter polymorphisms with asthma susceptibility in the south of Iran. J Investig Allergol Clin Immunol 2007;17:361-6.
13. Hosseini-Farahabadi S, Tavakkol-Afshari J, Rafatpanah H, Farid Hosseini R, Khaje Daluei M. Association between the polymorphisms of IL-4 gene promoter (-590C and gt; T), IL-13 coding region (R130Q) and IL-16 gene promoter (-295T and gt; C) and allergic asthma. Iran J Allergy Asthma Immunol 2007;6:9-14.
14. Nadi E, Hajilooi M, Zeraati F, Ansari M, Tavana S, Hashemi SH, *et al*. E-selectin S128R polymorphism leads to severe asthma. Iran J Allergy Asthma Immunol 2007;6:49-57.
15. Tavakkol Afshari J, Farid Hosseini R, Hosseini Farahabadi S, Heydarian F, Boskabady MH, Khoshnavaz R, *et al*. Association of the expression of IL-4 and IL-13 genes, IL-4 and IgE serum levels with allergic asthma. Iran J Allergy Asthma Immunol 2007;6:67-72.
16. Kazemi Arababadi M, Abousaidi H, Hassanshahi G, Pourfathollah AA, Daneshmandi S, Akbarpour V, *et al*. Polymorphisms within Exon 9, But Not Intron 8, of the Vitamin D receptor gene are associated with asthma. Iran J Basic Med Sci 2011;14:225-30.
17. Movahedi M, Mahdaviani SA, Rezaei N, Moradi B, Dorkhosh S, Amirzargar AA. IL-10, TGF-beta, IL-2, IL-12, and IFN-gamma cytokine gene polymorphisms in asthma. J Asthma 2008;45:790-4.
18. Rad IA, Bagheri M, Rahimi-Rad MH. Deletion allele of the ACE gene is not a risk factor for asthma predisposition. Pneumologia 2011;60:208-12.
19. Mahdaviani SA, Rezaei N, Moradi B, Dorkhosh S, Amirzargar AA, Movahedi M. Proinflammatory cytokine gene polymorphisms among Iranian patients with asthma. J Clin Immunol 2009;29:57-62.
20. Daneshmandi S, Pourfathollah AA, Pourpak Z, Heidarnazhad H, Kalvanagh PA. Cytokine gene polymorphism and asthma susceptibility, progress and control level. Mol Biol Rep 2012;39:1845-53.
21. Hosseini-Farahabadi S, Tavakkol-Afshari J, Rafatpanah H, Farid Hosseini R, Khaje Daluei M. Association between the polymorphisms of IL-4 gene promoter (-590C and gt; T), IL-13 coding region (R130Q) and IL-16 gene promoter (-295T and gt; C) and allergic asthma. Iran J Allergy Asthma Immunol 2007;6:9-14.
22. Abdi-Rad I, Bagheri M, Rahimi-Rad MH, Moradi Z. IFN-γ +874 and IL-4-590 polymorphisms and asthma susceptibility in North West of Iran. Tanaffos 2010;9:22-7.
23. Daneshmandi S, Pourfathollah AA, Pourpak Z, Heidarnazhad H. Relation of Interleukine-4 (C-589T) and Interferon-gamma (A+874T) allele polymorphism with asthma. J Zanjan Univ Med Sci 2008;16:75-83.
24. Abousaidi H, Vazirinejad R, Arababadi MK, Rafatpanah H, Pourfathollah AA, Derakhshan R, *et al*. Lack of association between chemokine receptor 5 (CCR5) d32 mutation and pathogenesis of asthma in Iranian patients. South Med J 2011;104:422-5.
25. Le Souëf PN. Gene-environmental interaction in the development of atopic asthma: New developments. Curr Opin Allergy Clin Immunol 2009;9:123-7.
26. Meng JF, Rosenwasser LJ. Unraveling the genetic basis of asthma and allergic diseases. Allergy Asthma Immunol Res 2010;2:215-27.
27. Brightling CE, Saha S, Hollins F. Interleukin-13: prospects for new treatments. Clin Exp Allergy 2010;40:42-9.
28. Zhang J, Paré PD, Sandford AJ. Recent advances in asthma genetics. Respir Res 2008;9:4.
29. Rosenwasser LJ, Borish L. Genetics of atopy and asthma: the rationale behind promoter-based candidate gene studies (IL-4 and IL-10). Am J Respir Crit Care Med 1997;156:S152-5.
30. Akesson LS, Duffy DL, Phelps SC, Thompson PJ, Kedda MA. A polymorphism in the promoter region of the human interleukin-16 gene is not associated with asthma or atopy in an Australian population. Clin Exp Allergy 2005;35:327-31.
31. Dong L, Huang ZY, Chen XF, Zhou XC, Li JY, Lin J. Association of INF-gamma/A+874T gene polymorphisms with respiratory syncytial virus bronchiolitis. Zhongguo Dang Dai Er Ke Za Zhi 2009;11:21-4.
32. Jie Y, Isa ZM, Jie X, Ju ZL, Ismail NH. Urban vs. rural factors that affect adult asthma. Rev Environ Contam Toxicol 2013;226:33-63.

How to cite this article: ????

Source of Support: Nil. **Conflict of Interest:** None declared.