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.

Materials and Methods

We conducted a literature search by using the electronic database PubMed, Biological Abstracts Web of Science, Current Contents Connect, Cinhail, 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 a 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, S128R 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-a 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
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, S128R 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 CCR5, transforming growth factor-α (TGF-α), 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-γ 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 polygenic disease with a clear genetic predisposition. 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-γ 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Number case/control</th>
<th>Significant polymorphism</th>
<th>Nonsignificant polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amirzargar et al.[11]</td>
<td>Children</td>
<td>59/139</td>
<td>IL-4–590, IL-4–33, IL-4–1098, IL-4RA+1902</td>
<td></td>
</tr>
<tr>
<td>Kamali-Sarvestani et al.[12]</td>
<td>Adult</td>
<td>203/113</td>
<td>IL-4–589</td>
<td>TNF-α –308</td>
</tr>
<tr>
<td>Hosseini-Farahabadi et al.[13]</td>
<td>Adult</td>
<td>30/50</td>
<td>IL-4–590, IL-13 RT30Q</td>
<td>IL-16–295T</td>
</tr>
<tr>
<td>Nadi et al.[14]</td>
<td>Adult</td>
<td>172/173</td>
<td>E-Selectin S12BR</td>
<td></td>
</tr>
<tr>
<td>Tavakkol Afshari et al.[15]</td>
<td>Adult</td>
<td>20/20</td>
<td>IL-4</td>
<td></td>
</tr>
<tr>
<td>Kazemi Arababadi et al.[16]</td>
<td>Adult</td>
<td>100/100</td>
<td>Exon 9 of the Vitamin D receptor</td>
<td>Intron 8 of the Vitamin D receptor</td>
</tr>
<tr>
<td>Movahedi et al.[17]</td>
<td>-</td>
<td>60/140</td>
<td>IL-10–1082, IL-10–819, IL-10–592, IL-12–1188, TGF-β–codon 25, IL-2–330</td>
<td>ACE gene</td>
</tr>
<tr>
<td>Abdi-Rad et al.[18]</td>
<td>Adult</td>
<td>62/212</td>
<td>TNF-α –308, TNF-α –238, IL-1α TC–889, IL-1 β TC–511, IL-1RA TC Mspa-I 11100</td>
<td></td>
</tr>
<tr>
<td>Daneshmandi et al.[20]</td>
<td>Adult</td>
<td>81/124</td>
<td>IL-4–590C&gt;T Coding region of IL-13</td>
<td>IL-16 –295T&gt;C</td>
</tr>
<tr>
<td>Hosseini-Farahabadi et al.[21]</td>
<td>Adult</td>
<td>30/50</td>
<td>IFN-γ +874, IL-4 –590</td>
<td></td>
</tr>
<tr>
<td>Abdi-Rad et al.[22]</td>
<td>Adult</td>
<td>64/109</td>
<td>IFN-γ A–874T</td>
<td></td>
</tr>
<tr>
<td>Daneshmandi et al.[23]</td>
<td>Adult</td>
<td>81/80</td>
<td>IL-4 C–589T</td>
<td></td>
</tr>
<tr>
<td>Abousaidi et al.[24]</td>
<td>Adult</td>
<td>162/200</td>
<td>CCR5</td>
<td></td>
</tr>
</tbody>
</table>

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


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