The relationship between IL-4 polymorphisms and asthma: a systematic review

A relação entre polimorfismos de IL-4 e asma: uma revisão sistemática

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ABSTRACT

Asthma is a chronic and heterogeneous disease of the airways that begins in childhood and persists, in many cases, into adulthood. The disease is the result of environmental, epigenetic and genetic interactions. This work aims to review the polymorphisms described in the literature in the IL-4 gene associated with susceptibility or protection to the development of asthma. This is a systematic literature review, carried out in PubMed, MEDLINE and Science Direct databases in the time frame from 2000 to July 2021, revealing the following key points: IL-4, Polymorphisms and Asthma. The search resulted in 29 articles, all in English. Despite some divergent studies, the SNP rs2243250, which was the most studied in populations from different countries, was also the one that found the most correlations of susceptibility with the disease. It is concluded that although there is controversial data on IL-4 SNPs related to the disease, the association of pangenomic studies has brought a list of genes and their variations associated with the risk of developing asthma, such as the rs2243250 SNP that was well related in populations of several countries analyzed.

Keywords. Polymorphisms, Interleukin-4, Asthma.

RESUMO

A asma é uma doença crônica e heterogênea das vias aéreas que tem início na infância e persiste em muitos casos até a vida adulta. A doença é resultado de interações ambientais, epigenéticas e genéticas. Este trabalho tem como objetivo revisar sobre os polimorfismos descritos na literatura no gene IL-4 associados à susceptibilidade ou proteção ao desenvolvimento da asma. Trata-se de uma revisão sistemática da literatura, feita nos bancos de dados PubMed, MEDLINE e Science Direct no corte temporal de 2000 a julho de 2021, ressaltando os seguintes pontos-chave: IL-4, Polimorfismos e Asma. A pesquisa resultou em 29 artigos, sendo em sua totalidade em língua inglesa. Apesar de alguns estudos divergentes, o SNP rs2243250, que foi o mais estudado em populações de diversos países, também foi o que mais encontrou correlações de susceptibilidade com a doença. Conclui-se que, apesar de haver dados controversos sobre os SNPs de IL-4 relacionados à doença, a associação dos estudos pangenômicos tem trazido uma lista de genes e variações deles associados com o risco de desenvolver a asma, como o SNP rs2243250 que foi bem relacionado em populações de vários países analisados.

Palavras-chave. Polimorfismos, Interleucina-4, Asma.

INTRODUCTION

According to The Global Initiative for Asthma (GINA), asthma can be defined as a multifactorial chronic inflammatory disease that affects the lower airways with hyperresponsiveness[1]. Asthma is one of the most frequent chronic inflammatory diseases in developed countries. It is estimated that it affects more than 300 million people globally and that causes great socioeconomic damage to countries in the health-disease binomial[2]. Pulmonary function measures, such as the percentage value of forced expiratory volume in one second (FEV1), which reflects the characteristics of lung capacity, are decisive for classifying severe asthma[3].

Antigens are normally introduced into the respiratory tract by inhalation and by diffusion into the mucosa, sensitizing B lymphocytes that produce allergen-specific immunoglobulin (Ig) E, IgE specifically binds to its high-affinity receptor on the mast cell membrane[4]. When exposed to the same allergen again, mast cells degranulate, resulting in the rapid release of chemical compounds such as histamine, leukotrienes, prostaglandins and other pro-inflammatory mediators[5]. These molecules play a central role in the immunopathogenesis of asthma, producing a cascade of events that act as a trigger for a greater inflammatory response, largely responsible for airway hyperresponsiveness and reversible airflow obstruction, generating the main asthma symptoms that include wheezing, coughing, and dyspnea[5].

Asthma is linked to atopic phenotypes and is typically caused by a type 1 hypersensitivity reaction, which results in a T helper (Th) 2 lymphocyte response, mediated by inflammatory cells, with increased production of cytokines such as interleukins (IL) 4, IL-5 and IL-13 and IgE antibodies[6]. High serum total IgE levels are a clinical condition associated with asthma and atopy in western communities[7] and were related to a range of genetic and environmental risk factors[8].

Dendritic cells (DCs) are the main antigen-presenting cells (APCs) that act as pattern recognition receptors (PRRs), which are ideal for the main contact between the immune system and external allergens. During the primary response, dendritic cells originating from the bone marrow are attracted by inflammatory chemokines, such as macrophage inflammatory protein -3α (MIP-3α) to the tissues. Costimulatory molecules on the surface of APCs, in particular, the B7.2/CD28 interaction participates in primary and secondary allergic sensitization and can lead to *naive* T cell proliferation, which is also mediated by binding between the T cell-specific receptor (TCR) and the APC MHC-II complex, thus undergoing differentiation into Th2. Dendritic cells have the ability to produce CC chemokine ligand 22 (CCL22) and CCL17 which are chemotactic for Th2 cells[9].

IL-4 is related to the recruitment of polymorphonuclear cells, for example, basophils and eosinophils. IgE produced in asthmatic airways binds to high-affinity receptors for IgE (FcεRI) on mast cells and basophils, preparing them for their activation by antigen. In this sense, immediate hypersensitivity is generated when there is cross-linking of a multivalent antigen to the IgE molecules previously bound to the FcεRI receptor, which is present in these cells, activating them. IL-4 also upregulates the endothelial expression of vascular adhesion molecule 1 (VCAM-1) on the endothelium. The interaction of VCAM-1 with the very late activating antigen 4 (VLA-4) promotes the recruitment of eosinophils. IL-4 also induces chemotaxis and fibroblast activation and, together with IL-3, promotes the growth of human basophils and eosinophils. Eosinophils are activated by IL-5, generated by the Th2 subpopulation. Mast cells, basophils, and eosinophils also produce IL-4[10].

It also exerts effects on monocytes and macrophages. It increases the surface expression of class II Histocompatibility Complex (MHC class II) molecules and the antigen-presenting capacity of macrophages

but inhibits macrophage colony formation and tumor necrosis factor (TNF) cytokine release, IL-1, IL-12, interferon-alpha (IFN-α), IL-8 and macrophage inflammatory protein-1 alpha (MIP-1α). Along with other cytokines, such as granulocyte colony-stimulating factor (G-CSF) and IL-6, IL-4 can promote the growth of mast cells and myeloid and erythroid progenitors. IL-4 has inhibitory effects such as suppression of metalloproteinase biosynthesis in human alveolar macrophages, inhibition of inducible nitric oxide synthase (NOS) expression in human epithelial cells, and reduction of CCL5 and IL-8 expression in human airway smooth muscle cells. With the rapid activation of macrophages, there is the production of reactive oxygen species (ROS)[11].

The main activity of IL-4 is to profile the Th2 immune response. The differentiation of Th2 cells from *naive* CD4 T cells is typically dependent on the presence of IL-4 in the local cytokine environment, as it requires transcription factors such as GATA3 and STAT6, which prepare Th2 cells for cytokine secretion. Binding of the IL-4 receptor (IL-4R) induces JAK1/3-mediated phosphorylation and signal transducer and activator of transcription-6 (STAT6) dimerization. pSTAT6 dimers then translocate to the nucleus and induce GATA3 expression[12].

Thus, following genetic predisposition, *naive* T lymphocytes from asthmatic individuals undergo differentiation into Th2 after exposure to allergens. Elevated frequencies of Th2 cells in the airways release specific cytokines that control the rebound of allergic inflammation, including IL-4[13]. In addition, IL-4 is very important in driving the differentiation of helper T lymphocyte precursors into Th2 response cells[14].

IL-4 is a lymphokine that acts as a growth factor (CSF) that induces the Th2 response while inhibiting the Th1 response, further increasing the expression of low-affinity IgE receptors (FcεRII) in non-activated B cells and macrophages. The cited cytokine also plays a role in the activation of B cells by increasing the expression of MHC class II molecules, as well as increasing the expression of CD23, CD40 and the alpha chain of the IL-2 receptor (IL-2RA)[15].

The Th2 subpopulation response synthesizes cytokines that, in turn, promote B lymphocyte differentiation. B lymphocytes differentiate into antibody-secreting cells (plasmocytes) resulting in the expression of IgE messenger RNAs (short and long) and generating the synthesis of specific IgE proteins for specific allergens. In activated B cells, IL-4 mainly promotes the production of IgE (by switching immunoglobulin class) and IgG1, and its effect is antagonized by IFN-γ[16].

The process of IgE secretion by B cells induced by T lymphocytes was called the two-signal model. The first signal is related to the production of IL-4 and IL-13. These interleukins share the IL-4 receptor α chain (IL-4Rα) as these cytokines bind to receptors on B cells. Once combined, translocation to the STAT6 nucleus stimulates transcription of the Cε gene locus containing the coding sequences (exons) for the heavy chain and IgE constant regions. The second occurs by contact by the interaction between a transmembrane protein called CD40 Ligand (CD40L or CD15) expressed on the surface of activated helper T lymphocytes and the CD40 receptor, a co-stimulating molecule of B lymphocytes[17].

The mutual action between the two molecules triggers genetic reorganization (recombination of loss of transformation), bringing all elements of the heavy chain back into function. The result is the complete multi-exon genetic coding of the heavy chain. The combination of these two signals determines a class switch for IgE cell and B cell proliferation. Complementary interactions between other pairs of ligands and receptors (between B7-2/CD28 and B7-2/CTLA-4 and between a L ß2 integrin and intercellular adhesion molecule-1 (ICAM-1) may add to or modulate the activation of B cells dependent on T cells after the binding of CD40 to its ligand. These functional capabilities of the cytokine make it extremely important for the immunopathogenesis of allergic asthma[18].

The highlighted cytokine may play a role in both defending and exacerbating the inflammatory process of asthma. Elevated IL-4 levels are related to monocyte polarization to M2-type macrophages, increased Th17 and Th2 cell counts, NLRP3 inflammasome activation, impaired IgA expression and B-cell autophagy[19–23]. The human IL-4 gene (OMIM#: 147780) is found on the long arm of chromosome 5 (5q31.1), is nearly 10 kilobases (kb) in length, and has 4 exons and 3 introns[24].

The joint participation of cells (such as eosinophils, mast cells, fibroblasts, macrophages/monocytes and neutrophils), cytokines such as IL-4, IL-5, IL-8, IL-6, IL-9, IL-10, IL-13, TGF-β, INF-γ, TNF-α, adhesion molecules (ICAM-1, VCAM-1, CD18 and CD11) and other elements of inflammation in asthma provide the basis for genes that could be studied. Immunogenetic studies are important because they make it possible to associate, among other objectives, genetic polymorphisms with the development of the disease and with interpersonal variability in the response to therapy. It is estimated that more than 80% of the variability in therapeutic response has a genetic basis[25].

Single nucleotide polymorphisms (SNPs) are the most common type of variation in the human genome and they are primarily equivalent to the nitrogenous bases Adenine (A), Thymine (T), Cytosine (C) and Guanine (G)[26]. They can affect coding regions (exons) or non-coding regions (introns). SNPs in exons are subdivided into synonyms and non-synonyms. Synonymous or silent SNPs are the types that do not affect protein structure, as they do not produce changes in amino acid sequences. On the other hand, non-synonymous SNPs can generate amino acid substitutions, affecting the function of the encoded protein or generating stop codons. Insertions and deletions can cause functional gene changes depending on whether they preserve or break the reading frame. Consequently, polymorphic variants of the IL-4 gene are of great interest for assessment of sensitivity or protection against asthma[27].

In this context, the following research problem arises: which IL-4 SNPs are associated with asthma susceptibility or protection?

MATERIAL AND METHODS

This is a systematic literature review, which aims to theoretically and conceptually describe the correlations between IL-4 gene polymorphisms and the development of asthma published in the literature.

The study followed the formation stages: 1) Elaboration of the research question and problem; 2) Stipulation of inclusion and exclusion criteria; 3) Choice of the sample; 4) Analysis of the articles; 5) Interpretation, discussion, and presentation of the review[28].

For the elaboration of the research question, the PICO strategy was used, related to the anagram: population; intervention; comparison; and outcome, as this generates greater integration of results and resolution of the highlighted problem[29].

Thus, the following question was raised: which SNPs exist in the IL-4 gene that are proven to cause susceptibility or protection to the development of asthma? Following the questions: Patient: patients with asthma / Intervention – evaluate IL-4 SNPs for each population studied and asthma / Comparison – IL-4 and asthma SNPs / Outcome – identification of which IL-4 SNPs are associated with susceptibility or protection to asthma.

In this way, the research question was asked, through which the following keywords were selected as a search strategy: "IL-4" and "Polymorphisms" and "Asthma", with the Boolean operator "AND". The search took place in the following databases: US National Library of Medicine National Institutes of Health (PubMed), Cochrane Collaboration and Medical Literature Analysis and Retrieval System Online (MEDLINE) and Science Direct.

As inclusion criteria, available articles, complete in the original categories in Portuguese, English and Spanish, of the types cross-sectional studies, case series, case-control, cohort studies, comparative studies, experimental studies (randomized clinical trials, field trials, community trials) and *in vitro* and *in vivo* trials from 2000 to July 2021. This period was used in order to seek to extend the research to more data. The exclusion criteria were articles published before the year 2000, articles that were duplicated, only the abstract available, letters to the editor, and articles with topics not relevant to the research question. In this way, we arrived at the final sample, characterized by all the steps, including and excluding them.

The data selection step for the search visualization was performed by consensus of two investigators (MJAS and EOLM) independently. To classify the studies, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE system) was used, which is a system created to identify the degree of evidence and the strength of health recommendations[30]. The Excel software was used to organize and sort the titles and abstracts and the GRADE pro GDT software to classify the articles in the system.

The data retrieved from the articles for data extraction and synthesis were based on the collection and evaluation of the following: author, year, title, methodology, study population, country and results. The accepted SNPs were from both the introns and exons of the highlighted gene. The PRISMA flowchart, based on the PRISMA protocol, was used to present the steps followed for the present study[31].

RESULTS

A total of 155 studies were listed in the search for articles in the databases. After excluding 10 duplicate studies, in addition to 10 letters to the editor, and 20 studies with only the abstract available, 86 studies irrelevant to the topic were removed based on title, abstract and body text (**Figure**). The final sample consisted of 29 articles (**Table**).
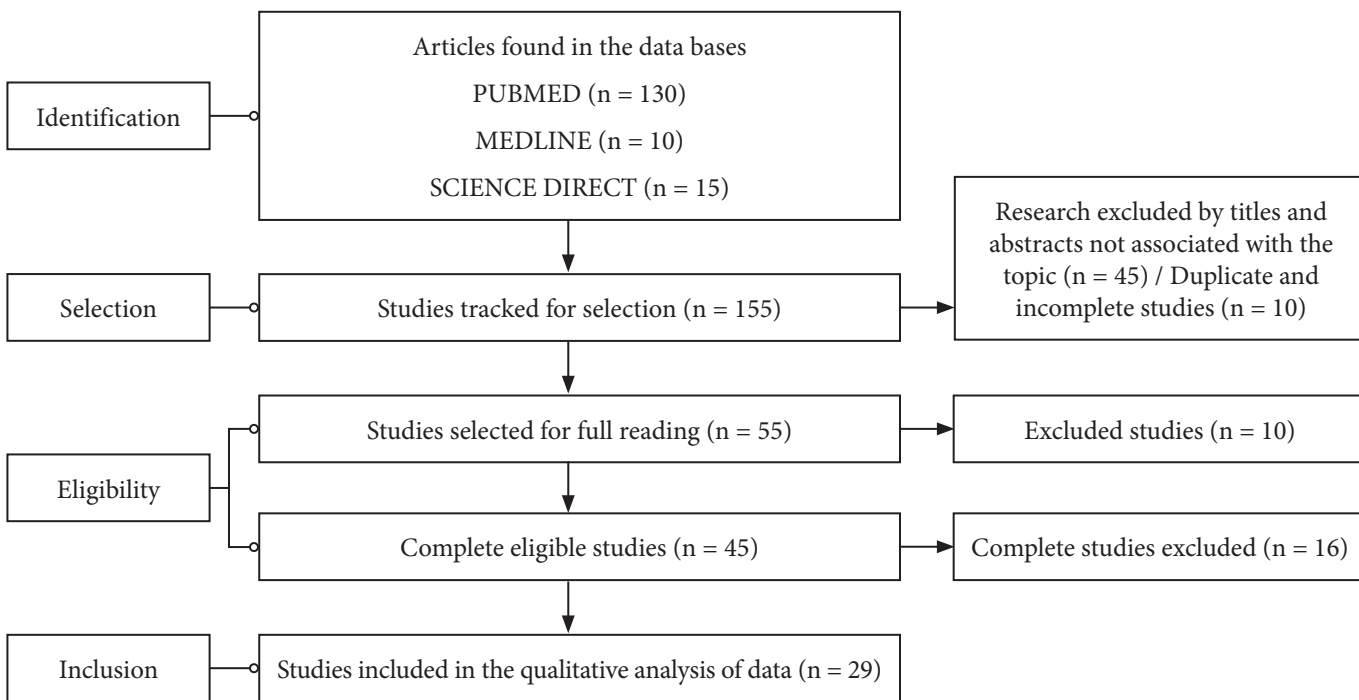
Figure. Flowchart of procedures for identification, selection, eligibility and inclusion of articles for analysis. Belem, PA, Brazil

Table. Characteristics of the studies included in the systematic review

Manuscript	Year of publication	Database	Methodology/ Population Size	Country	SNP	Results
Single nucleotide and copy-number variants in IL-4 and IL-13 are not associated with asthma susceptibility or inflammatory markers: a case-control study in a Mexican-mestizo population[32].	2020	PUBMED	Case-control/ 486 individuals	Mexico	rs2070874.	There were no statistically significant relationships.
Maternal genetic variants of IL-4/IL-13 pathway genes on IgE with "Western or Eastern Environments/ Lifestyles"[33].	2014	PUBMED	Cohort study/ 1208 individuals	Finland and Russia	rs2243250; rs2070874; rs2227284.	For SNP rs2243250, in C>T, the mutant allele: increased serum IgE and susceptibility to asthma. For SNP rs2070874, in C>T, the mutant allele: increased serum IgE and susceptibility to asthma. For SNP rs2227284, in G>T, the mutant allele: serum IgE elevation and susceptibility to asthma.
Polymorphisms of the IL-12B, IL-1B, and TNFA genes and susceptibility to asthma[34].	2013	PUBMED	Case-control/ 376 individuals	Spain	rs2243248; rs2243250; rs2070874.	For all analyzed SNPs, no associations were possible.
Relationship between polymorphisms in IL-4 and asthma in Japanese women: the Kyushu Okinawa Maternal and Child Health Study[35].	2013	PUBMED	Case-control/ 1370 individuals	Japan	rs2243250; rs2070874; rs2227284; rs2243290.	For SNP rs2243290, in C>A, the mutant allele: asthma susceptibility. For the other SNPs, no associations were possible.
Interleukin-4 (IL-4) and Interleukin-4 receptor (IL-4Rα) polymorphisms in asthma: a case control study[36].	2005	PUBMED	Case-control/ 212 individuals	Spain	rs2070874.	In C>T, the mutant allele: asthma risk.
Association of a 4-locus gene model including IL-13, IL-4, FCER1B, and ADRB2 with the asthma predictive index and atopy in Chinese Han Children[37].	2018	PUBMED	Case-control/ 385 children	China	rs2243250.	In C>T, the mutant allele: susceptibility to asthma and atopy.

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Manuscript	Year of publication	Database	Methodology/ Population Size	Country	SNP	Results
Genetic polymorphisms and asthma: findings from a case-control study in the Madeira island population[38].	2014	MEDLINE	Case-control/ 282 individuals	Portugal	rs2243250; RP2.	For SNP rs2243250, in C>T, the mutant allele: about 2-fold increased risk of developing moderate asthma and 4-fold increased risk for severe asthma. For the RP2 SNP, genotypes 253183/183183: 2-fold increased risk of moderate asthma and about 3-fold increased risk for severe asthma.
Immunological parameters and gene polymorphisms (C-590T IL-4, C-597A IL-10) in severe bronchial asthma in children from the Krasnoyarsk region, West Siberia[39].	2013	PUBMED	Case-control/ 150 children	Russia	rs2243250.	In C>T, the mutant allele: increased serum IL-4 level and association with uncontrolled atopic bronchial asthma.
A preliminary study on the association of single nucleotide polymorphisms of interleukin 4 (IL-4), IL-13, IL-4 receptor alpha (IL-4Rα) & Toll-like receptor 4 (TLR4) genes with asthma in Indian adults[40].	2015	PUBMED	Case-control/ 150 individuals	India	rs2243250; rs2070874.	For SNP rs2243250, in C>T, the mutant allele: asthma susceptibility. For SNP rs2070874, in C>T, the mutant allele: asthma risk.
The association between the IL-4, ADRβ2 and ADAM 33 gene polymorphisms and asthma in the Taiwanese population[41].	2012	PUBMED	Case-control/ 591 individuals	Taiwan	rs2243250.	In C>T, the mutant allele: asthma risk.
Unifying candidate gene and GWAS Approaches in Asthma[42].	2010	PUBMED	Cohort study/ 1361 individuals	Germany	rs2243250; rs2070874; rs2243248.	For SNP rs2243250, in C>T, the mutant allele: asthma risk. For SNP rs2070874, in C>T, the mutant allele: asthma susceptibility. For SNP rs2243248, in T>G, the mutant allele: asthma susceptibility. No significant associations were possible
Expression of asthma susceptibility genes in bronchial epithelial cells and bronchial alveolar lavage in the Severe Asthma Research Program (SARP) cohort[43].	2016	PUBMED	Cohort study/ 201 individuals	United States	rs2243248.	For SNP rs2243250, in C>T, the mutant allele: asthma risk. For SNP rs2070874, in C>T, the mutant allele: asthma susceptibility. For SNP rs2243248, in T>G, the mutant allele: asthma susceptibility. No significant associations were possible.

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Variation in conserved non-coding sequences on chromosome 5q and susceptibility to asthma and atopy[44].	2005	PUBMED	Case-control/ 30 individuals	United States	rs2243250.	In C>T, the mutant allele: asthma risk.
The -590C/TIL4 single-nucleotide polymorphism as a genetic factor of atopic allergy[45].	2010	PUBMED	Case-control/ 204 individuals	Philippines	rs2243250.	In C>T, the mutant allele: risk of asthma *per se* and atopic allergy.
Single nucleotide polymorphisms predisposing to asthma in children of Mauritian Indian and Chinese Han ethnicity[46].	2014	PUBMED	Case-control/ 766 individuals	India and China	rs2243250.	No correlations were possible.
Association of TGF-beta1, IL-4 and IL-13 gene polymerphisms with asthma in a Chinese population[47].	2011	PUBMED	Case-control/ 307 individuals	China	rs2070874.	No significant associations were possible.
Single-nucleotide polymorphisms in genes predisposing to asthma in children of Chinese Han nationality[48].	2009	PUBMED	Case-control/ 384 individuals	China	rs2243250.	No correlations were possible.
Ethnicity-specific gene-gene interaction between IL-13 and IL-4Rα among African Americans with asthma[49].	2007	PUBMED	Case-control/ 352 individuals	United States	rs2243250; rs2070874; rs2243251; rs2243290.	No correlations were possible between any of the aforementioned SNPs and asthma.
Gene-gene and gene-environment interactions on cord blood total IgE in Chinese Han children[50].	2021	PUBMED	Cohort study/ 989 individuals	China	rs2243250.	For SNP rs2243250, in C>T, the mutant allele: asthma susceptibility. Gene-environment interaction in elevated umbilical cord IgE levels was found between the cited SNP and maternal atopy.

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Manuscript	Year of publication	Database	Methodology/ Population Size	Country	SNP	Results
Sequencing the IL-4 locus in African Americans implicates rare noncoding variants in asthma susceptibility[51].	2009	PUBMED	Cohort study/ 142 individuals	United States	rs10080170; rs10065221; rs10058157; rs2243242; rs2243247; rs2243248; rs2243249; rs2243250; rs2070874; rs2243251; rs2243252; rs734244; rs2243253; rs11479198; rs2243258; rs2243259; rs2227284; rs2243260; rs2243261; rs2227282; rs2243263; rs2243264; rs2243265; rs2243266; rs2243267; rs2243268; rs9282745; rs9282746; rs2243269; rs2243270; rs2243271; rs2243272; rs2243273; rs2243274; rs2243275; rs2243276; rs2243277; rs2243278; rs2243281; rs2243285; rs2243286; rs2243287; rs2243288; rs2243289; rs2243290.	For SNP rs2243249, in T>C, the mutant allele: asthma susceptibility. For SNP rs2243252, in T>C, the mutant allele: asthma susceptibility. For SNP rs2243258, in C>T, the mutant allele: risk of asthma. For SNP rs2243259, in C>T, the mutant allele: asthma risk. For SNP rs2243260, in A>T, the mutant allele: asthma susceptibility. For SNP rs2243264, in A>G, the mutant allele: risk of asthma. For SNP rs2243265, in C>A, the mutant allele: asthma susceptibility. For SNP rs9282745, in T>A, the variant allele: asthma risk. For SNP rs9282746, in G>A, the variant allele: asthma susceptibility. For SNP rs2243271, in G>A, the variant allele: asthma risk. For SNP rs2243272, in G>T, the mutant allele: asthma susceptibility (the mutation being only found in asthmatic patients). For SNP rs2243273, in C>T, the mutant allele: asthma susceptibility. For SNP rs2243275, in T>C, the mutant allele: asthma risk. For SNP rs2243276, in T>C, the variant allele: asthma susceptibility. For the rs2243277 SNP, in C>T, the mutant allele: asthma susceptibility (the mutation being only found in asthmatic patients). For the rs2243278 SNP, the mutation (deletion) in the wild-type ACTAAAGACACGCAGGCCGAGTC allele generated susceptibility to asthma. For SNP rs2243281, in T>C, the mutant allele: asthma risk. For SNP rs2243286, in C>T, the mutant allele: risk of asthma *per se*. For SNP rs2243287, in G>C, the variant allele: associated with asthma. For the other SNPs, no significant associations were possible.

Manuscript	Year of publication	Database	Methodology/ Population Size	Country	SNP	Results
Identification of IL-13 C1923T as a single nucleotide polymorphism for asthma in children from Mauritius[52].	2015	PUBMED	Case-control/ 382 individuals	Mauricio Islands	rs2243250.	No significant associations were possible.
TNF-alpha, IL-4Rα and IL-4 polymorphisms in mild to severe asthma from Italian Caucasians[53].	2013	PUBMED	Case-control/ 181 individuals	Italy	rs2243250; rs2243248; rs2070874.	For SNP rs2243250, in C>T, the mutant allele: asthma risk (severe and moderate). For the other SNPs, no significant associations were possible.
Differences in candidate gene association between European ancestry and African American asthmatic children[54].	2011	PUBMED	Comparative study/ 1845 children	United States	rs2243250; rs2243282; rs2243274; rs2243268; rs2243263; rs2243248; rs2243283.	For SNP rs2243250, in C>T, the mutant allele: asthma susceptibility. For SNP rs2243274, in G>A, the variant allele: asthma risk. For SNP rs2243263, in G>C, the mutant allele: asthma susceptibility. For SNP rs2243248, in T>G, the mutant allele: asthma risk. For SNP rs2243283, in C>G, the variant allele: asthma risk. For the other SNPs, no significant associations were possible. For SNP rs2243250, in C>T, the wild-type allele: asthma susceptibility. The T (mutant) allele and the TT genotype: atopic bronchial asthma. Carriers of the C allele (wild): reduced risk of asthma. Furthermore, the TT genotype was found to be related to higher serum concentrations of IgE and IL-4 compared to the CT and CC genotypes. No significant associations were possible.
Genotyping of IL-4 -590 (C>T) gene in Iraqi asthma patients[55].	2017	PUBMED	Case-control/ 73 individuals	Iraq	rs2243250.	For SNP rs2243250, in C>T, the mutant allele: asthma susceptibility. For SNP rs2243274, in G>A, the variant allele: risk asthma risk. For SNP rs2243263, in G>C, the mutant allele: asthma susceptibility. For SNP rs2243248, in T>G, the mutant allele: asthma risk. For SNP rs2243283, in C>G, the variant allele: asthma risk. For the other SNPs, no significant associations were possible. For SNP rs2243250, in C>T, the wild-type allele: asthma susceptibility. The T (mutant) allele and the TT genotype: atopic bronchial asthma. Carriers of the C allele (wild): reduced risk of asthma. Furthermore, the TT genotype was found to be related to higher serum concentrations of IgE and IL-4 compared to the CT and CC genotypes. No significant associations were possible.

Manuscript	Year of publication	Database	Methodology/ Population Size	Country	SNP	Results
Analysis of polymorphisms in T(H)2-associated genes in Russian patients with atopic bronchial asthma[56].	2012	PUBMED	Case-control/ 396 individuals	Russia	rs2070874.	For SNP rs2243250, in C>T, the mutant allele: asthma susceptibility. For SNP rs2243274, in G>A, the variant allele: asthma risk. For SNP rs2243263, in G>C, the mutant allele: asthma susceptibility. For SNP rs2243248, in T>G, the mutant allele: asthma risk. For SNP rs2243283, in C>G, the variant allele: asthma risk. For the other SNPs, no significant associations were possible. For SNP rs2243250, in C>T, the wild-type allele: asthma susceptibility. The T (mutant) allele and the TT genotype: atopic bronchial asthma. Carriers of the C allele (wild): reduced risk of asthma. Furthermore, the TT genotype was found to be related to higher serum concentrations of IgE and IL-4 compared to the CT and CC genotypes. No significant associations were possible.
IL-4 receptor α polymorphisms may be a susceptible factor for work-related respiratory symptoms in Bakery workers[57].	2013	PUBMED	Cohort study/ 373 individuals	South Korea	rs2243248.	For SNP rs2243250, in C>T, the mutant allele: asthma susceptibility. For SNP rs2243274, in G>A, the variant allele: asthma risk. For SNP rs2243263, in G>C, the mutant allele: asthma susceptibility. For SNP rs2243248, in T>G, the mutant allele: asthma risk. For SNP rs2243283, in C>G, the variant allele: asthma risk. For the other SNPs, no significant associations were possible. For SNP rs2243250, in C>T, the wild-type allele: asthma susceptibility. The T (mutant) allele and the TT genotype: atopic bronchial asthma. Carriers of the C allele (wild): reduced risk of asthma. Furthermore, the TT genotype was found to be related to higher serum concentrations of IgE and IL-4 compared to the CT and CC genotypes. No significant associations were possible.
IL-4 gene polymorphisms and their association with atopic asthma and allergic rhinitis in Pakistani patients[58].	2013	PUBMED	Cohort study/ 334 individuals	Pakistan	rs2243250; rs2227284; rs2070874.	For SNP rs2243250, C>T, the mutant allele: susceptibility to asthma and allergic rhinitis. For SNP rs2227284, in T>G, the variant allele: susceptibility to asthma and allergic rhinitis. For SNP rs2070874, no significant association was possible.

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Manuscript	Year of publication	Database	Methodology/ Population Size	Country	SNP	Results
Polymorphisms in the interleukin-4 and interleukin-4 receptor alpha chain genes confer susceptibility to asthma and atopy in a Caucasian population[59].	2003	PUBMED	Case-control/ 525 individuals	England	rs2243250; rs2070874.	For rs2243250, in C>T, the mutant allele: asthma susceptibility. For rs2070874, in C>T, the variant allele: asthma risk.
An ADAM33 polymorphism associates with progression of preschool wheeze into childhood asthma: a prospective case-control study with replication in a birth cohort study[60].	2015	PUBMED	Case-control/ 198 individuals	Netherlands	rs2070874; rs2243250.	For SNP rs2070874, in C>T, the variant allele: asthma susceptibility. For SNP rs2243250, in C>T, the mutant allele: asthma susceptibility.

DISCUSSION

The immune response to innocuous antigens generated in the presence of Th2-type cytokines, such as IL-4, is associated with the development of asthma. IL-4 reverses the immune response to anti-inflammatory effects, inhibits the pro-inflammatory functions of macrophages and regulates the secretion of pro-inflammatory cytokines. IL-4 initiates critical immediate allergic reactions by triggering IgE-mediated mast cell activation. IL-4 plays a key role in directing *naive* T cells to Th2 differentiation and in exacerbating allergic inflammation by inducing the expression of VCAM-1, which recruits leukocytes and ensures their survival. Through its role in the proliferation of bronchial fibroblasts, myofibroblasts, and airway smooth muscle, this cytokine induces the airway remodeling found in asthma[13].

Thus, the manifestation of asthma may be related to the presence/absence of polymorphisms, such as SNPs, in the IL-4 gene, in addition to other genetic, epigenetic and environmental factors, considering it to be a multifactorial disease. Variations in the regulatory sequences of genes can determine risks for the disease, causing different levels of expression, leading to an exacerbated immune and inflammatory response[24].

Different studies that looked for an association between single nucleotide polymorphisms (SNPs) of genes (as in the case of this study) and asthma (as well as in other diseases) had divergent results between different populations. According to some researchers, the fact may come from the "*genetic background*" of the individuals studied so far[61]. The "*genetic background*" corresponds to the individual's genetic identity, which can change over the years and with exposure to environmental factors[62-64].

In this case, 29 studies published in the literature investigating the association between IL-4 SNPs and asthma were reported and analyzed, with the majority of studies corresponding to China and the United States, both with equal contributory shares of 5 studies (17.24% each).

The IL-4 SNPs associated with asthma in the surveys found were: rs2243250, rs2070874, rs2227284, rs2243290, RP2, rs2243248, rs2243249, rs2243252, rs2243258, rs2243259, rs2243260, rs2243264, rs2243265, rs9282745, rs9282746, rs2243271, rs2243272, rs2243273, rs2243275, rs2243276, rs2243277, rs2243278, rs2243281, rs2243286, rs2243287, rs2243274, rs2243263, rs2243283.

The SNP that was most analyzed in the number of studies (22 studies, 75.86%) associating IL-4 with asthma in different populations was rs2243250, with the T allele, a mutant highlighted by susceptibility in 15 studies (51.72%): Finnish and Russian[33,39]; Chinese[37,50]; Portuguese[38]; Indian[40]; Taiwanese[41]; German[42]; North-american[44,54]; Filipinos[45]; Italian[53]; Pakistani[58]; British[59]; and Dutch population[60]. In an Iraqi population, the C, wild allele conferred greater susceptibility to asthma[55]. In 6 studies (20.69%) no significant associations were possible between the cited SNP and the disease in: Spanish[34]; Japanese[35]; Indian and Chinese[46]; Chinese[48]; North-american population[51]; Mauritius population[52].

The rs2243250 SNP is an upstream variant (5') of the promoter region of the gene found at residue position 589. With regard to the change that occurred in the gene in relation to the function of IL-4, there is an effect of transcriptional addition, with an increase in the binding affinity of transcription factors, leading to overexpression of IL-4 mRNA, generating a phenotype susceptible to asthma and reducing the levels of pro-inflammatory cytokines, increasing the production of IgE and the induction of overexpression of IgE receptors in airway mast cells, resulting in increased recruitment of eosinophils[50,65,66].

The only SNP reported in one study (3.45%) as protective for the disease was the C (wild) allele at rs2070874 from a Russian population[56]. The rs2070874 SNP is an upstream variant (5') of the promoter

region of the gene found at residue position 33. Its role in IL-4 function corresponds to the influence on mRNA stability, as well as the transcriptional efficiency of IL-4, considering that the 5' UTR (5 *prime untranslated region*) can involve many cis-acting elements[56,65,67].

No associations between SNP and disease were found for any population: rs22432484 in a Spanish population[34]; rs10080170, rs10065221, rs10058157, rs2243242, rs2243247, rs2243248, rs2243250, rs2070874, rs2243251, rs734244, rs2243253, rs11479198, rs2227284, rs2243261, rs2227282, rs2243263, rs2243266, rs2243267, rs2243268, rs2243269, rs2243270, rs2243274, rs2243277, rs2243278, rs2243281, rs2243285, rs2243286, rs2243287, rs2243288, rs2243289, rs2243290 in a North-american population[51].

The development of new therapeutic, interventional and preventive strategies through SNPs can be a differential for patients with a disease due to genetic mutation, since they act as genetic biomarkers for susceptible individuals and, thus, enable the implementation of precision medicine principles. In clinical practice, that is, better targeting of pharmaceutical resources based on individual characteristics. In this sense, the focus on SNPs, such as rs2243250, in the IL-4 promoter region, which affects its level of expression, may be of great interest in interventional methodologies for patients, for example, in gene therapy guided to this gene or even through anti-IL-4 drugs for asthmatics. In addition to the fact that the identification of polymorphisms in genes involved in the response pathway of inflammatory mediators, such as IL-4, can still lead to a great impasse, since multiple genes can be involved in the pathogenesis of the same disease[68].

IL-4 is one of the most studied genes for asthma, because, among other things, it causes a change in the isotype of B cells for the synthesis of IgE in the presence of an allergen[69]. Current studies indicate an inconsistent benefit in asthmatic subjects when targeting IL-4 or the IL-4 α receptor (which blocks both IL-4 and IL-13 pathways) in murine and human studies[70,71]. In contrast, Tachdjian et al, demonstrated an important role for the immunoreceptor tyrosine-based inhibitory motif (ITIM) in the cytoplasmic tail of the IL-4 α receptor in contributing to airway inflammation and airway responsiveness[72]. Thus, there are mixed results regarding the feasibility of targeting therapy for the IL-4 gene.

The limitations of the present study come up against: a) the definition of asthma adopted to frame the data and studies analyzed; b) association of gene-gene interaction of IL-4 SNPs with other genes with asthma; c) association of gene-environment interaction between IL-4 SNPs and environmental factors; d) the SNPs used for assessment in this review meet the requirement to be referenced in the National Center for Biotechnology Information (NCBI); e) for the inclusion of studies, research with the IL-4 α receptor gene, which has a great impact on the IL-4 gene, was not considered because they are different genes and SNPs; f) heterogeneity of SNPs acting as a possible bias in characteristics such as ethnicities and different ages of populations due to the phenomenon of genetic background.

CONCLUSION

To date, there are many divergent results and data on the association of SNPs and asthma. The rs2243250 SNP, which was the most studied in populations from different countries, was also the most correlated with the disease. It is considered that the pathophysiology and phenotypes of the disease need to be better related to SNPs through broader epidemiological studies of the case-control type, cohort studies, ecological studies, comparative studies, cross-sectional studies, case studies, case series and clinical trials

with subjects from different continents. It is expected that the data generated in this can be the basis for further research and it is believed that the combination of bioinformatics modeling, functional validation and integrative omics technologies (corresponding to metabolomics, genomics and proteomics) through polymorphism studies will make the clinical study of the disease more focused on a panoramic map of different individual outcomes.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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