Review Article

Gene polymorphisms in asthma: a narrative review

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Background and Objective: Asthma is a heterogeneous disease caused by interactions between genetic and environmental factors. Genome-wide association studies (GWAS) have revealed that genetic variation plays a crucial role in the occurrence and development of asthma. The objective is to systematically review the existing literature on the association between gene polymorphisms and asthma to better understand the relationship between genetic factors and the occurrence and development of asthma.

Methods: We used keywords "asthma" and "gene polymorphism" with their combinations to search for relevant literature published from 2000 to 2021 in the PubMed database and the foreign medical literature retrieval service (FMRS). All articles included in the review are English. Then, we summarized the information pertaining to the genetic factors related to asthma susceptibility.

Key Content and Findings: This study summarized the information on 10 gene variants related to the risk of asthma published over the past 20 years, which will assist in further understanding the role of genetic variants in the risk of asthma.

Conclusion: Dozens of candidate genes have been identified that were associated with asthma risk. Asthmatics existed specific gene variation performed different response to therapy. Personalized therapy based on genotypic profiling would be an important direction in the future. However, it remains a great challenge for us to explore the relationship between gene polymorphisms and pathophysiological mechanism of asthma.

Keywords: Asthma; gene polymorphism; single nucleotide polymorphism; genome-wide association study

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Introduction

Bronchial asthma (hereafter referred to as asthma) is a heterogeneous disease caused by complex interactions between a variety of genes and environmental factors. Previous study (1) has confirmed that various environmental risk factors such as allergens, smoking, air pollution, and microbial exposures are significantly associated with the risk of asthma. However, we knew little about the impact of genetic variation on asthma development. The depth studies on families and twins (2) revealed that genetic variation also plays a crucial role in the pathogenesis of asthma. Moreover, Thomsen *et al.* (3) found that although the prevalence of asthma due to environmental factors has increased dramatically, the estimated value of heritability has also increased over time. This phenomenon may occur because environmental factors increase the penetrance of asthma-susceptible genotypes, with the effects driven through gene-environment interactions (GEIs). Therefore, the genetic studies of asthma may help us identify the

Table 1 The search strategy summary

Items	Specification
Date of Search (specified to date, month and year)	2020-03-01 to 2021-09-01
Databases and other sources searched	PubMed and FMRS
Search terms used (including MeSH and free text search terms and filters)	"asthma", "gene polymorphism"
Timeframe	2000-04-01 to 2021-08-01
Inclusion and exclusion criteria (study type, language restrictions etc.)	The study collected the relevant meta-analyses and GWASs published in English, excluded candidate gene association studies and articles before 2000
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Fei Shi and Yu Zhang collected and assembled the data. Finally, all authors reached an agreement on the manuscript
Any additional considerations, if applicable	None

individuals within population susceptible to environmental exposures, and provide novel insights into interindividual variable responses to medications of asthma.

In recent years, due to the development of next-generation sequencing technology, genome-wide association studies (GWASs) have become a novel approach to identify associations between genotypes and phenotypes. GWASs, candidate gene association studies, and genome-wide linkage analyses have become the three primary methods for studying complex disease-susceptibility genes. The first GWAS of childhood asthma identified an asthma-related variant, rs7216389, in the 17q21 region, which not only increased the risk of developing asthma in children but was also involved in the regulation of the ORMDL3 gene expression (4). Until now, researchers have identified more than 100 candidate genes associated with asthma using these research techniques (5). However, many results of previous researches based on candidate gene association studies are contradictory, lack of reproducibility, and hard to make a reliable conclusion. Herein, we summarize the data of multiple candidate genes related to asthma that have been discovered in recent years based on meta-analyses and GWASs, which may be more reliable for the effect of genetic polymorphism on asthma. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2170/rc).

Method

We used the keywords "asthma" and "gene polymorphism" to search for literature related to genetic polymorphisms in asthma published over the past 20 years in the PubMed database and the foreign medical literature retrieval service (FMRS). The references cited in relevant articles were also reviewed to obtain more information. Finally, the information on genetic factors related to asthma susceptibility was summarized. *Table 1* describes the study sequence and details.

Discussion

Vitamin D receptor (VDR) gene

Vitamin D deficiency is strongly associated with decreased lung function and worsening symptoms in asthma patients (6). In addition, vitamin D combined with VDR could function its potent immunomodulatory power, thereby regulate the airway inflammation (7). Increasing evidence indicates that there is an association between childhood asthma and VDR gene polymorphisms. There are four common restriction fragment length polymorphisms (RFLPs) in the VDR gene: BsmI (rs1544410), ApaI (rs7975232), FokI (rs2228570), and TaqI (rs731236) (8). BsmI, ApaI, and TaqI are located at the 3' end of the VDR gene and participate in the regulation of gene expression by regulating the stability and expression of mRNA (9), while FokI can lead to different protein sizes (10). A meta-analysis (11) revealed the following: (I) the ApaI polymorphism was significantly associated with an increased risk of childhood asthma in Asians; (II) there may be a correlation between the FokI polymorphism and pediatric asthma in Caucasian populations; and (III) the BsmI polymorphism has a minimal effect on susceptibility to childhood asthma, and the TaqI polymorphism is not significantly correlated with the risk of childhood asthma.

Previous study (12) had shown that FokI polymorphisms could result in the synthesis of shorter VDR protein, which was associated with asthma exacerbation and out of control. Moreover, the VDR FokI T allele was significantly associated with steroid resistance in asthmatics, and exogenous administration of vitamin D may elevate the response to corticosteroids in these asthmatic patients with FokI genetic variation (13).

Interleukin-13 (IL-13) gene

High T-helper 2 (Th2)-type asthma is an endotype of bronchial asthma. It is characterized by increased levels of Th2-type inflammation in the respiratory tract, including elevated Th2 cytokine (e.g., IL-4, IL-5, and IL-13) expression and eosinophilia, and is often accompanied by atopy. In particular, IL-13 seems to be a marker cytokine of this endotype. In a mouse model, IL-13 was shown to be the main mediator of allergic airway disease development (14). Moreover, IL-13 signaling in airway epithelial cells is critical for the development of airway hyperresponsiveness (15). The IL-13 gene is located at 5q31-q33, which is a region that is often associated with asthma, serum total IgE levels, airway reactivity, and other asthma phenotypes (16).

Single nucleotide polymorphisms (SNPs) of IL-13 may be involved in the regulation of serum total IgE (17) and eosinophilic inflammation intensity (18). Nie *et al.* found that the IL-13 –1112C/T (rs1800925) polymorphism was associated with an increased risk of asthma in Caucasians and that the IL-13 +2044A/G (rs20541) polymorphism was significantly associated with the risk of asthma in Asians and Caucasians (19). Another meta-analysis (20) examining the relationship between these two polymorphisms and asthma susceptibility on different continents and between various races revealed that the IL-13 +2044A/G (rs20541) polymorphism was significantly associated with asthma risk in Europeans, Asians, and Caucasians, which was consistent with previously reported results. The IL-13 –1112C/T (rs1800925) polymorphism was also found to be associated with asthma in Europeans and Asians, and the IL-13 +1923C/T polymorphism was significantly associated with an increased risk of asthma. A previous subgroup analysis of race indicated that the alleles and genotypes of this variant were associated with asthma in Asians and Caucasians (21).

IL-17 gene

IL-17 is a proinflammatory cytokine secreted by Th17 cells (22), and the IL-17 gene is located on chromosome 6p12 (23). This family includes six members (IL-17A–IL-17F), of which IL-17A and IL-17F have the greatest homology and may be heterodimers. Studies have shown that IL-17 may enhance the recruitment ability of neutrophils at sites of airway inflammation (24) and promote airway remodeling (25), leading to the occurrence and development of asthma. Therefore, the IL-17 gene is a potential candidate gene for asthma susceptibility.

Study (26) has reported several asthma-related SNPs of the IL-17 gene. The IL-17A rs2275913 (–197G>A) polymorphism has been shown to reduce the risk of post-bronchiolitis asthma at 11–13 years of age, but not in earlier life. IL-17F rs1889570 (C/T), IL-17A rs4711998 (A/G), and IL-17A rs3819024 (A/G) may be potential risk factors for asthma susceptibility (27). The IL17A-737C/T gene polymorphism prevents asthma in allele models, dominant models, and heterozygous models. The effect of the IL17A-737C/T gene polymorphism is also significant in Asians and children based on stratification by race and age (28).

Toll-like receptor (TLR) genes

TLRs are an important family of pattern recognition receptors in the innate immune system. TLRs regulate the immune system by controlling the secretion of cytokines and the production of soluble factors in the local dendritic cell network (29), thereby playing a key role in host defense against microorganisms. Additionally, TLRs participate in allergic reactions by identifying microorganisms or endogenous molecules in the environment and airborne allergens (30).

TLRs are associated with the pathogenesis of allergic diseases such as asthma. A previous meta-analysis reported that the TLR2 rs4696480 polymorphism is significantly associated with asthma susceptibility and that the TLR2 rs4696480 polymorphism is a risk factor for asthma (31). These findings are important for the early diagnosis and prevention of asthma, as well as for the development of treatment strategies for this chronic inflammatory disease. The results of another meta-analysis indicate that rs3804099 in TLR2 and rs4986791 in TLR4 are significantly associated with the risk of asthma (32,33). Tizaoui *et al.* (34) found that the TLR9-1237 polymorphism was weakly correlated with the risk of asthma in a codominant model, while an analysis using an allele comparison model indicated that the major TLR9-1237 T alleles were often important protective factors.

Human leukocyte antigen (HLA)-DRB1 gene

The HLA gene is located in the 6p21 region and is a gene cluster encoding the major histocompatibility complex (MHC). HLA genes play important roles in the immune system and other basic molecular and cellular processes (35). Among them, the HLA-DRB1 gene may affect asthma by regulating the Th1/Th2 balance. A previous study (36) demonstrated that the HLA-DRB1 allele is associated with asthma. The results showed that DRB1*03 was positively correlated and DRB1*15 is negatively correlated with the risk of asthma, but no correlation was found for other HLA-DRB1 alleles. A subanalysis indicated that DRB1*03, DRB1*04, DRB1*09, and DRB1*15 are associated with childhood asthma, DRB1*03 and DRB1*15 are associated with asthma in Caucasians, and DRB1*07 and DRB1*14 are associated with asthma in Asians (36). Vince *et al.* (37) showed that the HLA-DRB1*09:01 allele is associated with elevated tIgE levels in asthma patients.

β2-adrenergic receptor (β2-AR) gene

β2 receptor agonists are commonly used asthma treatment drugs. These drugs bind to β2-AR of airway smooth muscle cells, resulting in specific G protein activation and the subsequent production of cyclic adenosine monophosphate (cAMP), thereby resulting in bronchiectasis and a decrease in wheezing symptoms (38). β2-AR is highly expressed in lung tissues and plays an important role in the regulation of lung function. This gene is located on chromosome 5q31-q32. Four missense mutations (Arg16Gly, Gln27Glu, Val34Met, and Thr1641I1) and the Arg19Cys polymorphism in the 5'-end leader of the mRNA have been identified as potentially clinically relevant genes (39). Studies (40) has shown that the duration of intensive care unit (ICU) hospitalization and that of nebulized inhalation of β2 receptor agonist therapy in children with severe asthma with the Arg16Gly polymorphism Gly/Gly genotype were significantly shorter than those without this genotype, indicating that this gene polymorphism may affect the responsiveness to treatment in these patients. In a multi-center study (41), asthma patients with Arg/Arg homozygous genotypes received inhaled corticosteroids (ICSs) or long-acting β_2 agonists, and their hyperresponsiveness status did not change, suggesting good treatment responses in patients with the Gly/Gly genotype.

In contrast, patients with the Arg/Arg genotype have a poor response to treatment. A meta-analysis by Liang *et al.* (42) indicated that β2-AR gene polymorphisms were not associated with the risk of asthma in the overall population. However, in an ethnic stratification analysis, the Arg16Gly polymorphism was associated with an increased risk of asthma in the South American population, and the Gln27Glu polymorphism showed a significant protective effect in the North American population. In addition, in an age-stratified analysis, the Gln27Glu polymorphism showed a protective effect in a recessive mode in children and a protective effect in a dominant mode in adults. Furthermore, a recent study (43) showed that the Gln27Glu (rs1042714) polymorphism has a protective association with asthma in the general population and child subgroups.

Interferon-γ (IFN-γ) gene

IFN-γ is an important Th1 cytokine that can stimulate both immune and structural cells (e.g., macrophages and epithelial cells) to release chemokines, leading to the recruitment and infiltration of inflammatory cells, thereby amplifying immune responses. IFN-γ also has an inhibitory effect on Th2 cell differentiation. In asthma patients, the synthesis of IFN-γ by T cells is reduced, which is related to asthma severity (44). IFN-γ mediates the inhibitory effect of allergen-specific Th1 cells on allergen-specific Th2 cells (such as eosinophilia, goblet cell hyperplasia, and bronchial hyperresponsiveness) (45). The IFN-γ gene is located on chromosome 12 and has multiple polymorphisms, of which +874A/T is the most widely studied. +874A/T exerts a functional effect on the transcription of IFN-γ, potentially leading to a decrease in the production of IFN-γ (46). In recent years, an increasing number of studies have shown that the +874T/A polymorphism is a potential risk factor for asthma. Nie *et al.* (47) found that there was a significant association between the +874A/T polymorphism and asthma susceptibility. Subgroup analysis by ethnicity also revealed a significant association among Caucasians and Asians.

A disintegrin and metalloproteinase 33 (ADAM33) gene

The ADAM33 gene is located on the short arm of chromosome 20p13. ADAM protein plays an important role in cell fusion, cell signal transduction, cell adhesion, and proteolysis (48). In addition, increased mRNA and protein levels of ADAM33 have been observed in bronchial biopsies or bronchoalveolar lavage fluid from asthma patients, and the mRNA and protein levels of ADAM33 are associated

with asthma severity (49). This suggests that the ADAM33 gene may be associated with the pathogenesis of asthma. The ADAM33 F+1 homozygous mutant genotype (AA) and ST+4 heterozygous and homozygous mutant genotypes (AC and CC) and mutant alleles of both polymorphisms are significantly associated with the risk and severity of moderate to severe asthma (50). Another study showed that the ADAM33 F+1 polymorphism was associated with asthma risk in the general population and Caucasian children, the T2 polymorphism was associated with asthma risk in Asian children, and the T1 polymorphism was significantly and consistently associated with asthma risk in Caucasian and Chinese children, suggesting that the ADAM33 T1 polymorphism may be a potential predictor of asthma susceptibility in Asian children (51). Moreover, a previous meta-analysis indicated that the ADAM33 S2 polymorphism is associated with asthma susceptibility in Europeans and that the ADAM33 ST+4 polymorphism is associated with asthma in Asians and adults. A recent meta-analysis showed that the ADAM33 T2, Q1, and F+1 polymorphisms are associated with asthma susceptibility in Asian populations (52). Therefore, there is a correlation between various ethnic groups and different ADAM33 gene polymorphisms.

Cluster of differentiation 14 (CD14) gene

CD14 is an important component of the lipopolysaccharide (LPS) receptor that is expressed on the cell surface of monocytes, macrophages, and neutrophils. It can activate innate immune system pathways, neutralize bacterial endotoxins, and form a coreceptor with TLR4 (53). CD14 presents LPS to the TLR-MD2 complex to promote immune activation (54) and induce the secretion of cytokines such as IL-12 and IL-18, thereby promoting Th1 differentiation. In addition, IL-12 can inhibit the development of specific Th2 cells, thereby improving airway inflammation in allergic asthma (55). Therefore, functional defects in CD14 may affect Th2 differentiation and IgE-mediated allergic diseases. Available evidence has shown that CD14 gene polymorphisms are associated with asthma/allergy (56). A recent meta-analysis study found that the (-159 C/T) SNP in the CD14 promoter is associated with asthma and may reduce the risk of asthma susceptibility in adults (56). In addition, the TT genotype is associated with higher levels of soluble CD14 (sCD14), suggesting that the T allele has a protective effect in this disease (57).

Cadherin-related family member 3 (CDHR3)

Human rhinovirus (HRV) is the main cause of acute asthma attacks. Rhinoviruses are divided into three categories (A, B, and C) in the family of small RNA viruses. Numerous studies have found that HRV-C infection is more strongly associated with acute exacerbations of severe asthma compared to HRV-A and HRV-B (58,59). CDHR3, a protein expressed in ciliated airway epithelial cells (60), is a receptor for HRV-C (61). Accordingly, CDHR3 was necessary for HRV-C infection in respiratory tract, which has special clinical significance and could lead to asthma acute exacerbations. The potential mechanism for CDHR3 affecting asthma exacerbation may be a change in barrier function of airway ciliated cell resulting in greater penetration of virus or other toxins in the airway (62). A GWAS found that an SNP, rs6967330, was associated with wheezing diseases and hospitalization in children with asthma (63). Moreover, the rs6967330 polymorphism may increase the risk of severe acute onset of asthma in children by increasing the level of HRV-C infection and protein surface localization (62). Another study involving the Japanese population found that the CDHR3 rs6967330 polymorphism is an important susceptibility factor for early-onset severe adult asthma and that genetic susceptibility and atopy of early respiratory tract viral infection together promote the occurrence of asthma (64).

Summary

To date, more than one hundred of candidate genes have been identified to be associated with the risks of asthma. However, we only described 10 gene variants which are more common in the asthmatic researches. Although, the results of multiple original researches of the same gene are often contradictory, meta-analysis facilitates the aggregation of data from multiple comparable studies to expand the sample size and use specialized statistical methods to obtain more robust results. With the development of molecular biology techniques, an increasing number of genes related to asthma susceptibility have been identified. To now, there are no drugs targeting specific gene polymorphism for asthma. However, a study demonstrated that asthmatic existed specific IL-4 receptor α gene variation performed better response to pitrakinra (an IL-4/IL-13 pathway antagonist) therapy (65). It means that asthma personalized therapy based on genotypic profiling especially for severe asthma would be an important direction in the future.

Meanwhile, our understanding of asthma genetics still faces substantial challenges. Multiple environmental factors affect the onset of asthma, and more work needs to be done to clarify the interactions between environmental factors and genetic factors in asthma. In the future, it is necessary to carry out more individual genetic association studies with larger sample sizes, as well as in-depth analyses of more associations between gene polymorphisms and population characteristics, intrinsic phenotypes of asthma, and individual differences in drug responses.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2170/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2170/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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