Editorial



# Contributions of candidate-gene associations studies and genome-wide association studies (GWAS) to identification of genetic variations associated with asthma

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The paper "*Gene polymorphisms in asthma*: *a narrative review*" by Shi *et al.* (1) aims 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.

Dozens of candidate genes have been identified and were associated with asthma risk. Gene variations may influence both asthma development and the response to therapies as well. Personalized medicine based on genotyping may be an important direction in the future. However, it remains a challenge for clinicians to explore the relationship between gene polymorphisms and the pathophysiological mechanism of asthma.

Bronchial asthma is a complex and not well understood disease, but it is known that genetics and environmental factors contribute to the development of different asthma phenotypes (2). Over the last few years, studies using new powerful genetic tools have been performed and published, and the knowledge and complexity of genetic factors for asthma development has increased. Furthermore, according to Thomsen *et al.* the prevalence of asthma from 1994 to 2003 has also significantly increased among adolescent twins (3). Therefore, the hypothesis brought by the study suggests that the increase of asthma prevalence may be caused by environmental factors increasing the penetration of asthma-susceptibility genotypes (1,3). This hypothesis helps to improve the knowledge of asthma etiology and, therefore, genetic studies could benefit the screening and diagnosis of individuals with high susceptibility considering also environmental exposure. It will also increase the perception of interindividual variations in the response to asthma interventions (1). As the use of next-generation sequencing is increasing, also genome-wide association studies (GWAS) contributed to identify variation associated with disease risk (1,3).

More than one hundred candidate genes have been associated with the risks of asthma. We can use the asthma genetic studies to provide insights into interindividual differences in responses to medications.

In recent years, GWAS, candidate gene association studies and genome-wide linkage analyses were responsible for studying asthma-susceptibility genes. The first GWAS of childhood asthma identified an asthma-related variant, rs7216389. This variation located within intron 1 of GSDML/GSDMB strongly influences the expression of the nearby gene ORM1-like protein 3 (ORMDL3; MIM 610075) through chromatin remodeling. ORMDL3 is a ubiquitously expressed transmembrane protein participating in signaling and facilitation of endoplasmic reticulum-mediated inflammatory responses. Since a relationship between rs7216389 and childhood asthma was first reported, the association has been replicated by several independent studies and the variant underscores ~17% of asthma in European populations (4). In the sense of the variety of genes identified to be associated with the risks of asthma, there are still no drugs targeting specific gene polymorphism for asthma. Yet, a personalized medicine

study demonstrated that a specific gene variation receptor (IL-4α) performed better in response to pitrakinra (and IL-4/IL3 pathway antagonist) therapy. So, personalized therapy is an important way to improve diagnosis and treatment in the future.

In conclusion, a large number of genes related to asthma susceptibility have been identified, and asthmatics performed different responses to therapy depending on their specific gene variation (1). Thus, an important direction in the future would be asthma personalized treatment centers focusing on the genotypic pattern shown by those individuals, especially for severe asthma. On the other hand, as our understanding of asthma genetics still needs to be improved, it is essential to implement genetic association studies with large sample sizes, as well as in-depth analyses of associations between gene polymorphisms and population characteristics, intrinsic phenotypes of asthma, and individual differences in drug responses.

Asthma is a disease caused by complex interactions between a variety of genes and environmental factors. Regardless of the increasing development of molecular biology techniques and identification of genes related to susceptibility, currently there are no drugs targeting specific gene polymorphism for this respiratory disease. Hence, further projects need to be done to clarify and to expand the understanding of these multifactorial interactions in asthma's development and treatment.

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