Genetics of Asthma Susceptibility and Severity

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KEYWORDS

• Asthma • Genetics • Susceptibility • Severity • Personalized medicine • Therapy • Lung function

KEY POINTS

- Genes and environmental exposures interact to influence risk of asthma susceptibility and severity.
- Two large meta-analyses of asthma susceptibility identified 4 chromosomal regions that were associated with asthma in individuals of different ethnic backgrounds: loci in the ORMDL3 region of 17q21, IL1RL/IL18R on chromosome 2q, TSLP on 5q22, and IL33 on chromosome 9p24.
- Genome-wide screens for asthma susceptibility in Asian populations identified genetic variants in the major histocompatibility complex gene region (human leukocyte antigen region) on chromosome 6p21 associated with asthma risk; this locus has been a significant predictor of asthma susceptibility in several genetic studies.
- Genes that are associated with asthma subphenotypes, such as lung function, biomarkers levels, and asthma therapeutic responses, can provide insight into mechanisms of asthma severity progression.
- A joint model of risk variants in lung function genes identified in the general population were highly associated with lower lung function and increased severity in asthma populations.
- A pharmacogenetic genome-wide screen identified 2 correlated genetic variants in the GLCCI1 gene related to response to inhaled glucocorticoids.
- Future genetic studies for asthma susceptibility and severity will incorporate exome or whole-genome sequencing in comprehensively phenotyped asthmatics, which will contribute to personalized asthma therapy.

INTRODUCTION

Asthma is a heterogeneous disease with a complex cause. The interaction of genes and environmental exposures influences the development of asthma and determines the expression or progression of the disease (**Fig. 1**).[1] An overall aim of genetic studies in a complex disease such as asthma is to identify a group of genetic variants that will predict risk for development (susceptibility) or progression (severity) of asthma. Genetic factors related to asthma susceptibility and severity are not limited to a single gene but are caused by several gene variants that each contribute to the risk architecture.

There has been major progress in determining the genetic factors that are associated with asthma susceptibility, using genome-wide association study

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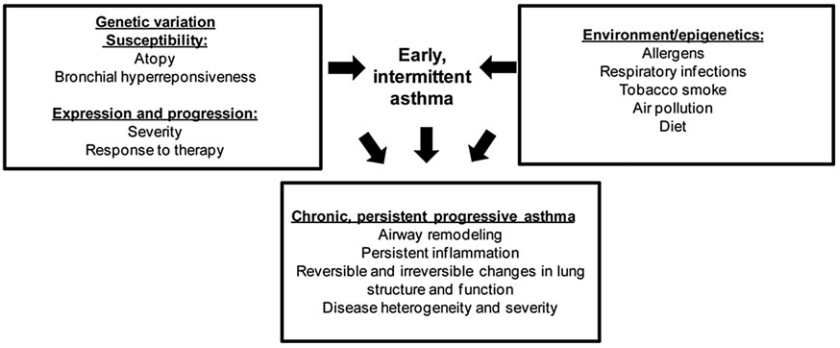

Fig. 1. Gene-environment interactions in asthma susceptibility and severity.

(GWAS) approaches.[2–11] GWAS genes such as interleukin (IL) 13, IL33, its receptor IL1 receptorlike 1 isoform 1 (IL1RL1), and thymic stromal lymphopoietin (TSLP) have been linked to asthma and several other allergic phenotypes, suggesting dysregulation of shared inflammatory pathways. In addition, the major histocompatibility complex (MHC) region, which was one of the first asthma susceptibility loci identified,[12] seems to contribute to asthma and allergen sensitization.[2] Regulatory T cell signaling may also play a role in asthma, because the SMAD family member 3 (SMAD3) gene, which encodes a transcriptional modulator related to transforming growth factor β, has also been identified in several genome-wide screens for asthma. Several of these susceptibility genes and their biologic pathways have been replicated in some, but often not all, asthma populations, suggesting that there may be heterogeneity in the genetic risk in populations of different ethnic backgrounds.[7,13] Results from major GWAS studies of asthma are reviewed in this article and are summarized in **Table 1**.

Many of the large genome-wide screens that have identified genes important to asthma susceptibility were based on a clinical diagnosis of asthma rather than more comprehensive phenotypes that would also evaluate the mechanisms of disease progression and severity. Current studies are now using more extensive characterization to investigate the progression of asthma. Thus, asthma severity may be related to specific subphenotypes, some of which are discussed in this article and summarized in **Table 2**: (1) genes related to pulmonary function; (2) biomarkers related to asthma progression and risk of exacerbations; (3) pharmacogenetic interactions in which an individual may have reduced responsiveness, or be resistant, to a specific asthma

Table1
Significant asthma susceptibility GWAS variants from meta-analyses or replicated studies

Gene(s)	Chromosomal Region	Ethnic Background(s)	References
ORMDL3/GSDML	17q21	All	Moffatt et al,[3,8] 2010, 2007; Torgersen et al,[11] 2011
IL1RL1/IL18R1	2q11	All	Moffatt et al,[3] 2010; Torgerson et al,[11] 2011
TSLP	5q22	All	Moffatt et al,[3] 2010; Torgerson et al,[11] 2011; Hirota et al,[30] 2011
IL33	9p24	All	Moffatt et al,[3] 2010; Torgerson et al,[11] 2011
SMAD3	15q23	European	Moffatt et al,[3] 2010
RORA	15q22	European	Moffatt et al,[3] 2010
HLA-DQ/DR	6p21	All	Moffatt et al,[3] 2010; Li et al,[2] 2010; Hirota et al,[30] 2011; Noguchi et al,[31] 2011
IL13	5q31	European	Moffatt et al,[3] 2010; Li et al,[2] 2010
PYHIN1	1q23	African	Torgerson et al,[11] 2011