Linkage and Genetic Association in Severe Asthma

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KEYWORDS

• Asthma • Genetics • Severe • GWAS • Linkage • Genotype • Endotype
• Phenotype

KEY POINTS

- The pathogenesis of severe asthma is poorly understood, which leads to difficulty in management of the disease.
- Genetic variation has been associated with severe asthma in children and adults.
- Genetic association studies may lead to improved understanding of severe asthma pathophysiology and therapeutic treatments.

INTRODUCTION

Severe asthma is defined in the National Heart, Lung, and Blood Institute 2007 guidelines by the frequency of symptoms, β2-agonist use, limitations on daily activities, and exacerbations requiring systemic steroids.[1] The American Thoracic Society (ATS) defines severe asthma as "asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic CS) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy" (European Respiratory Society/ATS Guidelines on Definition, Evaluation, and Treatment of Severe Asthma). It is estimated that severe asthma occurs in approximately less than 10% of patients with asthma. However, the burden of severe asthma on health care use and expenditures and loss of school/work days are disproportionate compared with milder asthma types.

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Overall, severe asthma is poorly understood, although considerable work has been done in the area. The natural history and progression of the disease have not been clearly elucidated. Some patients tend to have severe symptoms in childhood that persist and may worsen in adulthood. Other patients may exhibit a milder disease phenotype in childhood and progress to a more severe phenotype in adulthood. It is also not well understood as to what the primary contributors or triggers are for development of the severe asthma phenotype. Potential triggers or contributors of severe asthma include environment exposures (eg, air pollution), virus exposure, hormonal changes, and comorbid conditions. As phenotypes of asthma related to underlying disease pathophysiology have been more readily recognized, specific pathophysiologic phenotypes have also been associated with severe asthma. Eosinophilic asthma has been described to exist in up to one-half of adult patients with severe asthma, whereby eosinophils persist in the airway despite high-dose inhaled and systemic steroid exposure.[2] Aspirin-induced asthma, characterized by nasal polyps, aspirin sensitivity, and asthma, is another phenotype that has been associated with severe asthma. Prevalence rates of aspirin-induced asthma among adults with severe asthma have been reported at approximately 14%.[3] Neutrophilic asthma has also been associated with severe asthma. Studies have demonstrated that patients with severe asthma often have a neutrophil predominance in their sputum. Neutrophilic asthma has been observed in patients experiencing an exacerbation and also associated with fatal asthma exacerbations.[4] A Pauci-inflammatory phenotype has also been described whereby typical inflammatory cells are not observed on bronchoscopy. Little is known about this possible phenotype, and some have suggested that the lack of inflammatory cells may be the result of corticosteroid treatment rather than a distinct phenotype.[5]

Genetic association studies may lead to better understanding of the severe asthma phenotype regarding biological pathways involved and may also lead to improved treatments. Severe asthma is likely multifactorial, which is the result of specific environmental exposures or triggers in a genetically susceptible host. For example, in some children with a specific genetic makeup, exposure to a specific virus during a specific time in physiologic development may lead to severe asthma. Furthermore, an adult with a specific genetic signature exposed to a certain cumulative environmental exposure may lead to the development of severe asthma. Genetic variation is also important to consider when discussing the variation in observed natural history of the disease and therapeutic response. The purpose of this review is to describe some of the potentially relevant genetic variants that have been associated with severe asthma, which may lead to better understanding of the disease phenotype and improved treatment in the future. Genome-wide association studies (GWAS) and candidate gene studies have been important in identifying potential variants and disease pathways to focus on in relation to severe asthma pathogenesis, clinical features, and potentially, treatment response in children and adults.

GENETIC VARIANTS ASSOCIATED WITH SEVERE ASTHMA

17q21 Region

Sequence variation on chromosome 17q21 was initially identified in relation to risk of early-onset childhood asthma and risk of asthma associated with tobacco smoke exposure within GWAS. Among 12 single-nucleotide polymorphisms (SNPs) identified in their analysis to be associated with asthma risk, 7 of them were located in the 17q21 region, indicating that this gene region is likely of importance in the disease.[6] One variant, rs7216389, located in the intronic region of *GSDMB*, has been associated