# Genetic and Epigenetic Components of Aspirin-Exacerbated Respiratory Disease

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**KEYWORDS**

• Cysteinyl leukotriene • Eosinophil • Biomarker • Epigenetics • Polymorphism
• AERD

**KEY POINTS**

- Aspirin-exacerbated respiratory disease (AERD) severity and its clinical phenotypes are characterized by genetic variation within pathways for arachidonic acid metabolism, inflammation, and immune responses.
- Epigenetic effects, including DNA methylation and histone protein modification, contribute to regulation of many genes that contribute to inflammatory states in AERD.
- The development of noninvasive, predictive clinical tests using data from genetic, epigenetic, pharmacogenetic, and biomarker studies will improve precision medicine efforts for AERD and asthma treatment.

## INTRODUCTION

Aspirin intolerance is a severe and rare asthmatic endotype, with prevalence rates of 10% in the adult asthmatic population and up to 25% in patients with severe, persistent asthma.[1–4] Consistent with the classification of asthma as a set of individual subtypes of diseases of varying symptoms and severity, AERD is distinguished from other types of severe asthma primarily by its clinical characteristics. The clinical features of AERD include airway obstruction, increased exacerbations, chronic rhinosinusitis, the presence of nasal polyps (NPs), eosinophilia, increased need for systemic glucocorticoids and poor response to asthma controller medication, and an increase in urinary leukotrienes (LTs), both in comparison to aspirin-tolerant asthma (ATA) and after aspirin challenge and symptom exacerbations.[5,6] Due to the discovery

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that increased production of LTs is a characteristic of AERD, the LT and prostaglandin (PG) production pathways were among the first to be investigated, and the subsequent identification of polymorphisms in LT-related genes in affected patients suggested a pivotal role for genetic variation in the development of AERD.[6–8] As a result, variation in patient genetics has received considerable focus as a potential determinant of AERD pathogenesis.

The observation that severely asthmatic subjects responded favorably to antileukotriene asthma medications contributed further evidence toward a mechanistic role for LTs, while also providing an opportunity for clinicians to more appropriately tailor treatment to a specific patient group.[7,9–12] Subsequent genetic studies revealed considerable evidence for genetic variation in AERD pathophysiology across multiple biological pathways[7,13] as well as variation in interindividual treatment responses to multiple asthma drug classes, including leukotriene modifiers and inhibitors.[14] The exact mechanisms by which LT synthesis becomes dysregulated in AERD, however, are still unknown. Due to corresponding alteration of immune molecules (eg, type 2 helper T cell [$T_H2$] cytokines), PGs (eg, $PGE_2$), and other inflammatory biomarkers (eg, interleukin [IL]-5, periostin, immunoglobulin (Ig) E, apolipoprotein A1, and others), multiple interacting pathways and mechanisms likely also contribute. Evidence that AERD has a heritable basis is minimal, and only two studies reported that 1% to 6% of individuals with AERD had an affected family member.[4,15] The adult onset of AERD, combined with the low genetic penetrance and inconsistent replication of results from genetic associations, point toward involvement of environmental exposures and epigenetic factors in its progression. Achieving a better understanding of the genetic and epigenetic determinants of heterogeneity of AERD through genome-wide and epigenome-wide interrogation is, therefore, anticipated to improve strategies to develop more precisely tailored therapeutic agents, treatment regimens, and potentially cures for the disease.

## UPDATE ON THE GENETICS OF ASPIRIN-EXACERBATED RESPIRATORY DISEASE

The quest to discover determinants of AERD (and its unique clinical features) has yielded a rapidly increasing number of candidate gene and genetic association studies. These studies reveal mechanistic insights into the molecular pathways for aspirin hypersensitivity, including arachidonic acid metabolism and cysteinyl leukotriene (CysLT) production, inflammatory cascades initiated by eosinophils, mast cells, platelets, airway epithelial cells, and others. For reference, this article summarizes the major results from these studies in **Table 1**. Findings from many of these studies are conflicting, however, and a majority of reported associations lack replication. This section provides a comprehensive update of the status of genetic investigations of aspirin-sensitive asthma and AERD, highlighting major discoveries published within the past several years. In addition to discussing genetics association studies of AERD risk, recent findings are presented from investigations of genetic markers associated with two predominant AERD clinical features—nasal polyposis[2] and eosiniophilia.[6]

### *Genetic Markers Associated with Disease Status and Clinical Features of Aspirin-Exacerbated Respiratory Disease*

#### *Aspirin-exacerbated respiratory disease susceptibility*

Previous studies have yielded a substantial number of genes and genetic markers associated with AERD affection status and/or clinical phenotypes (summarized in **Table 1**). This section discusses recent discoveries with compelling evidence for a role in AERD pathogenesis.