Chapter 6

Defining Molecular Endotypes in Severe Asthma Through Genomic and Proteomic Data Integration

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ABSTRACT

Severe asthma is a complex disease that remains uncontrolled in many individuals despite optimized therapy. This chapter offers a comprehensive overview of the epidemiological and clinical burden of severe asthma, emphasizing the limitations of conventional phenotypic classifications. It highlights the transition toward molecular endotyping, where subtypes are defined by distinct biological pathways. Key findings from recent genomic, transcriptomic, and proteomic research are presented, identifying susceptibility loci and protein biomarkers linked to clinically relevant endotypes. Integrative case studies, such as those from the U-BIOPRED consortium, demonstrate how multi-omics approaches reveal eosinophilic and neutrophilic endotypes with specific immune and microbial signatures. The chapter also discusses data integration strategies, including consensus clustering and network fusion, as well as practical implications for biomarker discovery, personalized therapeutics, and future directions in precision asthma medicine.

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INTRODUCTION

Asthma is a common chronic respiratory disease marked by episodes of wheezing, breathlessness, chest tightness, and coughing, due to airway inflammation and hyperresponsiveness. Severe asthma – affecting approximately 3–10% of all asthma patients – remains a major clinical problem (Song et al., 2019). Severe asthma persists uncontrolled despite maximal therapy (high-dose inhaled corticosteroids and long-acting β2-agonists) or requires such intensive treatment to maintain control (Lommatzsch & Virchow, 2014). Patients with severe asthma experience frequent exacerbations, hospitalizations, and marked quality-of-life impairment, imposing a substantial individual and societal burden (Lee et al., 2022). Globally, hundreds of millions of people live with asthma and nearly half a million deaths were attributed to asthma in 2017 (Global burden of 369 diseases and injuries in 204 countries and territories, 2020). Economic costs are high; for example, asthma-related healthcare costs in the United States exceed $80 billion annually. Severe asthma is highly heterogeneous in its clinical presentation and pathophysiology (Perez & Coutinho, 2021).

Historically, clinicians distinguished broad categories like “intrinsic” (non-allergic) versus “extrinsic” (allergic) asthma, or onset in childhood vs. adulthood (Trivedi & Denton, 2019). Decades ago, these distinctions had heuristic value (e.g. allergen avoidance in atopic asthma), but they have largely been abandoned because they do not consistently reflect underlying biology (Cipriani et al., 2017). Modern cluster analyses have revealed multiple overlapping clinical phenotypes: for instance, groups defined by early-onset atopic asthma, late-onset eosinophilic asthma, obesity-associated asthma, and neutrophilic asthma (Haldar et al., 2008). However, these observable phenotypes, while useful for some treatment decisions (e.g. checking FeNO and sputum eosinophils in eosinophilic asthma), do not elucidate the molecular drivers of disease (Porpodis et al., 2022). Indeed, many features (age, sex, obesity, comorbidities) co-segregate in complex ways, and phenotypes often overlap. There is growing recognition that classification by phenotype alone has reached its limits in guiding therapy or understanding pathogenesis. To address this complexity, the concept of endotypes has emerged. An endotype is a disease subtype defined by a distinct pathophysiological mechanism (Ray et al., 2022). In asthma, a key axis is type-2 (T2) inflammation vs. non–type-2 (T2-low) inflammation. For example, an “eosinophilic, Th2-driven” endotype is characterized by IL-4/IL-5/IL-13 cytokine signaling, elevated IgE and eosinophils, and responsiveness to corticosteroids or anti-IL5 therapy (Maspero et al., 2022). By contrast, “neutrophilic” or Th17-driven endotypes involve other cytokines (IL-17, IL-6, IL-1β) and may not respond to steroid therapy. Identifying endotypes is clinically valuable because it aligns patients with targeted treatments (Fouka et al., 2025). For instance, patients with a T2-high endotype benefit from biologics like anti-IL-5 or anti-IL-4Rα, which dramatically

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