A Comprehensive Review of Asthma: Genetic, Environmental and Multifactorial Influences

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Abstract:
Asthma is a chronic inflammatory disease characterized by airway obstructiveness, bronchial hyperresponsiveness, and recurring respiratory symptoms. It affects more than 260 million people worldwide and varies in severity across individuals and populations (World Health Organization, WHO, 2023). This review examines whether genetics, environmental factors, and gene-environment interaction cause asthma. Studies estimate heritability between 35-70% (Ober and Yao, 2011). Susceptibility loci, mainly the 17q21 region (Moffatt et al.,2007) interact with environmental triggers such as tobacco, pollution, and allergens (Papi et al., 2008). The evidence supports asthma as a multifactorial disease contributed to by susceptibility and environmental interactions.

Introduction:

Asthma is a chronic respiratory disease marked by airway inflammation, reversible airflow limitation, and bronchial hyperresponsiveness (Busse & Lemanske et al.,2001). It commonly causes wheezing, shortness of breath, chest tightness, and cough, though symptoms and severity varies. While asthma often begins in childhood, it may continue into adulthood or develop later in life. This variability reflects the fact that asthma is not a single uniform condition, but a complex disorder with different underlying biological and clinical patterns.

Over the past several decades, asthma prevalence has increased globally, pointing to the influence of environmental changes acting alongside genetic susceptibility (Asher et al., 2020). Factors such as air pollution, allergens, tobacco smoke, respiratory infections, and urban living may all contribute to disease risk, especially in individuals who are already genetically predisposed. Examining asthma through this broader lens helps explain its complexity and supports a more complete understanding of its development and progression.

Epidemiology of Asthma:

Asthma is one of the most common chronic respiratory diseases worldwide, affecting more than 260 million people worldwide. The increased prevalence in recent years is a reflection of the influence of environmental and lifestyle factors. Asthma commonly begins in childhood and is one of the chronic diseases in children. Asthma prevalence varies across geographic regions. Higher diagnosed rates are typically reported in industrialized countries, while underdiagnosis remains a concern in lower-income settings (WHO, 2023). Urban populations generally experience a greater burden of asthma compared to rural populations, likely due to increased exposure to air pollution, indoor and outdoor allergens, and differences in lifestyle.

However, pollution alone does not fully explain the global distribution of asthma. Differences in genetic susceptibility, dietary patterns, early-life microbial exposures, access to healthcare, environmental factors and infrastructure, and variations in diagnostic practices all contribute to the observed regional disparities.

Genetic Contributions:
Estimates from the twin studies show that heritability estimates (passed down from generation to generation through genes) are between 35 to 70% (Ober and Yao, 2011). Genes such as ORMDL3 and GSDMB have strong association with childhood onset asthma(Moffatt et al., 2007) and genes such as IL4, IL5, IL13, IL33, ST2, ADAM33,and HLA-DRB1 regulate immune signaling and airway remodeling(Cookson et al., 2017)

Table 1: Genetic Factors Associated with Asthma

Gene	Chromosome	Biological Role	Association
ORMDL3	17q21	Sphingolipid regulation	Childhood asthma risk
GSDMB	17q21	Epithelial cell function	Airway inflammation
IL4	5q31	IgE class switching	Allergic asthma
IL5	5q31	Eosinophil survival	Eosinophilic asthma
IL13	5q31	Mucus production	Airway hyperresponsiveness
IL33	9p24	Alarmin cytokine	Type 2 inflammation
ADAM33	20p13	Airway remodeling	Chronic airflow limitation
HLA-DRB1	6p21	Antigen presentation	Immune regulation

Immunological Mechanisms:
Type 2 inflammation by Th2 and ILC2s (Hammad and Lambrecht et al, 2015) drives asthma. IL-33(epithelial injury) activates ILC2 and dendritic cells. IL4, IL-5 and IL-13 support the maturation of eosinophils and play a key role in the increase in mucus production (Fahy et al., 2015). Persistent inflammation leads to changes in airways such as subepithelial fibrosis and smooth muscle hypertrophy (Wenzel et al., 2012).

Environmental Risk Factors:
Environmental exposures play an important role in the development of exacerbation of asthma. The main effects are airway inflammation and immune regulation. Particulate matter, Ozone, tobacco smoke, and nitrogen dioxide have been shown to determine asthma pathogenesis (Papi et al., 2018). The key mechanisms are oxidative stress and epithelial irritation. All the

environmental pollutants and the mechanisms (increased airway responsiveness, immune dysregulation, etc.) explain the asthma onset and severity.

Table 2: Environmental Mechanisms in Asthma Development

Factor	Source	Mechanism	Outcome
PM2.5	Traffic/Industry	Oxidative stress	Airway inflammation
NO2	Vehicle emissions	Epithelial irritation	Hyperresponsiveness
Ozone	Atmospheric reactions	Reactive oxygen species	Exacerbation
Tobacco Smoke	Smoking	Chronic inflammation	Increased severity
RSV/HRV	Viral infections	Immune priming	Childhood asthma risk
Allergens	Dust/mold/pets	IgE activation	Allergic asthma

Gene- Environment Interactions:

Understanding the gene-environment interaction is central to explaining phenotypic variability observed in any respiratory and inflammatory disease. Individuals' exposure to similar environmental factors often has different clinical outcomes, which suggests that genetic susceptibility changes the biological response to external triggers.

The GSTM1 null genotype has been associated with decreased antioxidant capacity. GSTM1 is known to play an important role in reactive oxygen species, and deletion of this gene may impair cellular defense mechanisms and vulnerability to oxidative stress by environmental exposures(Zhu et al., 2018).

In addition to the genetic variability, epigenetic regulation plays another important role in how environmental factors shape the expression of disease. DNA Methylation and acetylation change patterns of gene transcription without interfering DNA sequence. Genetic changes

induced by environmental factors contribute to alterations in immune function, which influences both disease susceptibility and severity (Holgate et al., 2012)
Thus, genetic predisposition and epigenetic modulation explain the differences in an individual's phenotype and the complex interplay between biology and environment.

Discussion:
It is essential to ascertain whether asthma is primarily the result of genetic predisposition, environmental factors, or a combination of both. This understanding can facilitate the identification of diverse treatment modalities and provide insights into the underlying causative factors of the condition. Such knowledge is critical for developing effective strategies to manage asthma and mitigate its impact on affected individuals. The convergence of epidemiological, genetic, and immunological evidence supports asthma as heterogeneous, multifactorial disease. Precision medicine interventions targeting IL-5 and IL-4 receptor alpha emphasize the significance of Type 2 inflammatory pathways (Bleecker et al.,2006)

Conclusion:
Together with findings from epidemiological, genetic, and immunological research emphasize that asthma is a complex multifactorial disease rather than a single disease. This paper concludes that asthma appears to arise through interactions between inherited susceptibility and environmental influences. Progress in molecular immunology and advances in targeted environmental health will be critical for deepening one’s understanding of asthma and helping advancement into more targeted, effective treatment strategies.

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