American Journal of Medicine and Medical Sciences 2023, 13(12): 1987-1992
DOI: 10.5923/j.ajmms.20231312.36

Deciphering the Genetic Puzzle of Asthma: Insights into Genetic Contributions to Disease Pathogenesis and Treatment Strategies

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Abstract Asthma, characterized by airway inflammation, immune response dysregulation, and bronchial hyperresponsiveness, is influenced significantly by genetic predispositions. The authors highlight the role of genome-wide association studies (GWAS) in identifying over 100 genes related to asthma. These genes primarily involve immune system functioning and lung physiology, offering insights into the disease's multifactorial nature. Focusing on specific gene polymorphisms, the article discusses variations in cytokines like IL-4, IL-13, and IL-17A, which are integral to asthma's pathogenesis. Variants in the IL-4 gene, for instance, are linked to increased asthma risk and influence disease phenotype, while IL-13 polymorphisms are associated with susceptibility and severity. The IL-17A gene's role in promoting airway inflammation and responsiveness is also explored. Additionally, the study examines immune regulation genes, such as CD-14, a cell surface receptor, and its controversial role in asthma. This highlights the complexity and ongoing debates in understanding the genetic dimensions of asthma. The article concludes by emphasizing the importance of genetic research in asthma. It suggests that unraveling the genetic basis of asthma can lead to personalized treatment strategies, potentially revolutionizing asthma management and offering hope for improved patient outcomes. This research underscores the potential for significant advancements in asthma therapy, pivoting towards a more tailored approach based on individual genetic profiles.

Keywords Asthma genetics, GWAS, Bronchial hyperresponsiveness, Treatment, Inflammatory response

1. Introduction

Asthma, a complex and serious respiratory disease, impacts millions globally, drawing significant attention from the scientific and medical communities [26]. Characterized by high morbidity, preventable mortality, and considerable societal costs, asthma represents a critical public health concern [3]. The disease manifests physiologically through extensive airway narrowing, leading to clinical symptoms such as episodic dyspnea, cough, and wheezing, often triggered by physical exertion or exposure to various airway irritants [7,12]. Environmental factors like allergens and pollution are well-recognized asthma triggers. However, groundbreaking research in genetics has unveiled a pivotal genetic component in the disease's onset and management.

Genetic predispositions in asthma substantially increase the disease's likelihood, acting as significant risk factors and shedding light on why certain individuals are more susceptible than others. Asthma's multifactorial nature, influenced by a complex interplay of genetic variations, has been illuminated through extensive genetic studies. These studies have identified numerous candidate genes associated with asthma susceptibility, particularly those involved in the immune response, airway remodeling, and inflammatory processes [33]. Understanding the functions of these genes is crucial in unraveling the intricate mechanisms of asthma pathogenesis.

This study aims to delve deeper into asthma from a genetic perspective, scrutinizing the role of genes in the disease's development and progression. It seeks to not only elucidate the genetic foundations of asthma but also to explore how these genetic factors interact with environmental triggers. Additionally, this research intends to examine the potential for personalized medical approaches in asthma treatment, leveraging genetic insights to tailor interventions to individual genetic profiles. Through this comprehensive approach, the study aspires to contribute to the advancement of asthma management, enhancing our capability to predict, prevent, and treat this complex disease more effectively.

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Received: Nov. 21, 2023; Accepted: Dec. 13, 2023; Published: Dec. 23, 2023
Published online at http://journal.sapub.org/ajmms

2. Materials and Methods

This study employed a comprehensive literature search to gather data on the genetic aspects of asthma. Databases such as PubMed, Scopus, Web of Science, and Google Scholar were utilized. Keywords used for the search included "asthma," "genetics," "genetic factors in asthma," "GWAS and asthma," "cytokine polymorphisms," and "immune response in asthma." The search was limited to articles published in English from January 2000 to December 2022.

Articles were selected based on their relevance to asthma genetics. Inclusion criteria encompassed original research articles, systematic reviews, and meta-analyses focusing on the genetic factors of asthma, GWAS studies related to asthma, and studies exploring immune response and cytokine polymorphisms in asthma. Exclusion criteria were articles not in English, non-peer-reviewed articles, and studies not primarily focused on asthma genetics.

Two reviewers independently extracted data from the selected articles, focusing on study objectives, methodologies, key findings related to asthma genetics, and the roles of specific genes and polymorphisms. Discrepancies between reviewers were resolved through discussion and consensus.

The quality of the selected articles was assessed using standardized checklists appropriate for each study type, such as the Newcastle-Ottawa Scale for observational studies and the PRISMA guidelines for systematic reviews and meta-analyses.

The information was synthesized thematically, focusing on common themes such as genetic predispositions to asthma, roles of specific genes and polymorphisms, and the interplay between genetic and environmental factors in asthma pathogenesis.

3. Genetic Factors Contributing to the Development of Asthma

Asthma, a multifaceted condition with a myriad of contributing factors, has been the subject of extensive genetic research. Despite significant advances in identifying genes associated with asthma, the precise extent of heritability remains elusive. Twin studies offer a robust methodology to estimate heritability by examining correlations in asthma phenotypes between monozygotic (MZ) and dizygotic (DZ) twins. These studies explore the genetic underpinnings of asthma, where certain mutations affect lung function and immune responses, significantly increasing morbidity risk [31]. However, the absence of these genetic markers does not necessarily reduce asthma incidence, underscoring the influence of environmental factors and lifestyle choices [35].

Twin studies serve as critical tools in dissecting the myriad factors contributing to asthma. By comparing MZ and DZ twins, researchers can discern the degree to which genetic, as opposed to environmental factors, contribute to asthma. The similarity between twin pairs is instrumental in estimating heritability—the proportion of phenotypic variability attributable to genetics versus environmental factors. These estimates, typically derived with high reliability, suggest a substantial genetic component in asthma pathogenesis [28,32,34]. Positional cloning and candidate gene studies have been employed to identify asthma-related gene variants [14].

Concordance rates in twin studies further elucidate asthma's heritability. For MZ twins, rates range from 0.08 to 0.66, and for DZ twins, from 0.05 to 0.45 [34]. Studies in the USA and Finland indicate similar concordance rates for MZ twins raised apart and together, implying minimal impact of shared environments in asthma development [9]. These findings collectively indicate that asthma is highly heritable, with genetic factors accounting for approximately 60-80% of its manifestation.

Recent advancements, particularly genome-wide association studies (GWAS), have significantly contributed to understanding asthma's genetic basis. GWAS enable comprehensive examination of asthma-related single nucleotide polymorphisms (SNPs) across the entire genome, identifying over 100 genes, many associated with immune and lung responses [18,23]. This body of research suggests that asthma is not a singular disease but a complex interplay of biological pathways and gene interactions.

In summary, while genetic studies provide insights into the interaction of asthmatic genes with environmental and other factors, the analysis of twin and family pedigrees remains pivotal. Genetics are a crucial component in understanding asthma pathogenesis, reinforcing the disease's complexity and multifactorial nature.

4. Asthma-Related Genes

Genes Involved in Immune Response and Inflammation: Asthma, a heterogeneous disease, is influenced by a combination of genetic and environmental factors. Central to asthma are dysregulation of immune responses and chronic airway inflammation. Genetic studies have significantly enhanced our understanding of these underlying mechanisms in asthma. It has been discovered that predisposition to asthma is linked to various genetic factors, notably genes involved in immune response and inflammation. For instance, recent research shows that genetic polymorphisms of cytokines like IL-4, IL-13, and IL-17A influence asthma's pathogenesis. IL-4, a cytokine crucial for immune response regulation, has several genetic polymorphisms. Studies have identified a significant association between the IL-4 -590C/T polymorphism and increased asthma risk in certain populations [43]. Additionally, IL-4 gene variants are known to influence the disease's phenotype, impacting factors such as age of onset, atopic status, and treatment response [2]. Understanding IL-4 gene polymorphisms may aid in developing personalized asthma treatments. Another key cytokine gene polymorphism is IL-13, closely related to IL-4 and also significant in asthma pathogenesis. IL-13 gene polymorphisms have been studied extensively in relation to

asthma susceptibility and severity. Specific IL-13 gene variants are linked to an increased asthma risk. The rs20541 polymorphism, for example, is significantly associated with asthma risk in dominant, allelic, and heterozygous models in Caucasians, while SNP rs1800925 is associated with asthma risk in various genetic models in general, Asian, and European populations [24]. IL-13 gene polymorphisms also affect asthma phenotypes, influencing IgE levels, airway hyperresponsiveness, and lung function [13]. Furthermore, polymorphisms in genes encoding IL-17 and IL-17A, which contribute to asthma susceptibility through effects on Th2-mediated inflammation and airway hyperresponsiveness, are particularly interesting [38]. IL-17, a pro-inflammatory cytokine produced mainly by Th17 cells, is involved in neutrophil recruitment and activation, stimulation of Th2 inflammation, and induction of airway remodeling [39]. Studies have reported significant associations between specific IL-17 and IL-17A polymorphisms and increased asthma risk. For instance, rs2275913 is linked to higher asthma risk, while rs8193036 might be associated with protective effects [17,35]. Some polymorphisms are also connected with more severe asthma symptoms, increased airway inflammation, and decreased corticosteroid treatment response [12]. Hence, studying cytokine genes may, in the future, enable the development of unique treatments for personalized strategies. Given asthma's complexity, involving numerous genes, studying cytokines at the genome level will allow for a tailored approach for each asthma patient.

Role of Genes Associated with Immune Regulation: In addition to genes involved in immune response and inflammation, genes that regulate the immune system also play a role. One such gene is CD-14, a glycosylphosphatidylinositol-anchored cell surface receptor that acts as a coreceptor for pathogen-associated molecular patterns (PAMPs) on bacterial cell walls. CD14 is mainly expressed by monocytes, macrophages, and dendritic cells. CD-14 has garnered interest as it is located on chromosome 5q31, a region identified in several whole-genome studies as containing variations relevant to asthma. Recent studies have also found CD14 in non-immune cells, including lung epithelial cells, indicating its role in localized immune responses [20]. The exact relationship between CD-14 genes and asthma remains a topic of debate, with studies yielding mixed conclusions. Research by Zhao et al. [44] and Lee et al. [10] suggest CD-14's involvement in asthma by regulating immune cells, while Zhang et al. [43] dispute its role in the disease. However, numerous studies have shown CD14 activation in asthma patients' airways, positively correlating with disease severity. Higher levels of soluble CD14 in serum have also been observed in asthma patients, suggesting CD14's role in initiating the inflammatory response [21,27,45]. Research into this area continues to evolve.

Recent advancements in the field of asthma genetics and immune response regulation have been groundbreaking, providing new insights and potential therapeutic targets. One of the most significant developments is the use of genome-wide association studies (GWAS). GWAS have identified numerous novel genetic variants associated with asthma, far beyond the previously known IL-4, IL-13, and IL-17A gene polymorphisms. These studies have expanded our understanding of the genetic landscape of asthma, revealing complex interactions between multiple genes and environmental factors. For instance, recent GWAS have uncovered new loci associated with asthma that are involved in epithelial cell biology and mucosal immune function, highlighting the role of airway epithelium in asthma pathogenesis [46].

Another breakthrough has been in the field of epigenetics, particularly the study of DNA methylation patterns in asthma. Epigenetic modifications can be influenced by environmental factors and are thought to play a crucial role in asthma development and severity. Researchers have begun to explore how these epigenetic changes, such as DNA methylation, affect gene expression in asthma and how they can be targeted for treatment [47].

Advances in biotechnology, such as CRISPR-Cas9 gene editing, have opened new avenues for asthma research. This technology allows for precise modifications of specific genes, providing a powerful tool for dissecting the functional roles of asthma-associated genetic variants. CRISPR-Cas9 has the potential not only to enhance our understanding of asthma pathogenesis but also to pave the way for novel gene-based therapies [48].

In the realm of immune regulation, recent studies have focused on understanding the role of regulatory T cells (Tregs) in asthma. Tregs are crucial for maintaining immune tolerance and preventing excessive inflammatory responses. Research has shown that dysfunction in Tregs can contribute to the development and exacerbation of asthma, suggesting that therapies targeting Treg function could be beneficial for asthma patients [49].

Furthermore, the advancements in single-cell RNA sequencing have allowed researchers to study the cellular heterogeneity within the asthmatic airways at an unprecedented resolution. This technology has enabled the identification of distinct cell types and states involved in asthma, providing a more detailed understanding of the disease's cellular mechanisms and identifying potential new targets for therapy [50].

Collectively, these advancements are not only enhancing our understanding of the complex genetic and immunological underpinnings of asthma but also opening new doors for the development of more effective and personalized treatments for asthma patients.

5. Conclusions

The study underlines asthma's status as a complex and heterogeneous disease, significantly influenced by genetic factors. It brings to light the multifactorial essence of asthma, where genetic predispositions are key contributors to individual variations in disease susceptibility, severity, and response to treatment. This recognition of asthma's genetic complexity is fundamental for advancing our comprehension

and management of the disease.

Through detailed analysis, the research identifies numerous genes involved in critical biological processes such as inflammation, immune response, airway remodeling, and bronchial hyperresponsiveness. These findings are instrumental in enhancing our understanding of the pathophysiological mechanisms of asthma and underscore the potential of targeted genetic therapies in future medical interventions.

The document emphasizes the pivotal role of GWAS in revealing a multitude of genetic variants that increase the risk of asthma. This has significantly expanded the horizon of asthma genetics, uncovering new genetic associations and contributing profoundly to the contemporary understanding of the disease.

The study acknowledges the intricate interplay between genetic predispositions and environmental influences in asthma. This highlights the necessity for a holistic approach in both research and clinical practice, integrating genetic insights with environmental considerations for a comprehensive understanding and effective management of asthma.

The research points towards the exciting potential of personalized medicine in asthma treatment, driven by a deeper understanding of genetic influences. It suggests the future possibility of tailoring treatment strategies to individual genetic profiles, heralding a new era of personalized care in asthma management.

Finally, the study emphasizes the need for ongoing research to fully unravel the complex genetic underpinnings of asthma. This continuous pursuit of knowledge is crucial for future breakthroughs in asthma treatment and management, with the ultimate goal of improving the lives of those affected by this chronic condition.

In summary, the document provides a comprehensive overview of the genetic factors influencing asthma, highlighting the importance of continued research in this field. These insights are vital for the future of asthma management, opening avenues for more personalized and effective treatment strategies.

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