

## Exploration of the Genetic Epidemiology of Asthma: A Review, with a Focus on Prevalence in Children and Adolescents in the Caribbean

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### ABSTRACT

*Asthma is a chronic disease caused by the inflammation of the main air passages of the lungs. This paper outlines a review of the published literature on asthma. While a few studies show a trend of rising asthma cases in the Caribbean region, even fewer have explored the genetic epidemiological factors of asthma. This is a literature review that seeks to sum the body of knowledge on the epidemiology of asthma. Specifically, the major objective of the literature review is to provide a unified information base on the current state of factors involved in the genetic epidemiology of asthma. The review is a simple, yet detailed summary of the literature sources and their methodology and findings on the genetic epidemiology of asthma. Further, it seeks to direct this effort to the Caribbean region. The paper then reviews a summarized and synthesized collection of the body of previous research. Of specific interest are peer-reviewed sources that have been published in recent times. The paper provides more recent insight and recapitulates on the previous research, while tracing the intellectual progress on the debate. Where possible, reviewing and discussing the results of the previous literature, this review singles out the gaps and potential future research directions for studying the genetic epidemiology of asthma. Overall, we hope to contribute to a more synthesized knowledge and improved understanding of the previous literature and future potential direction of genetic and epidemiological asthma research.*

**Keywords:** Adolescents, asthma, Caribbean, epidemiology, genetic

## Exploración de la Epidemiología Genética del Asma: Una Revisión, con un Enfoque sobre la Prevalencia en Niños y Adolescentes en el Caribe

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### RESUMEN

*El asma es una enfermedad crónica causada por la inflamación de las vías respiratorias principales de los pulmones. Este trabajo realiza una revisión de la literatura publicada sobre el asma. Si bien son pocos los estudios que muestran una tendencia al aumento de los casos de asma en la región del Caribe, menos aún son los que han explorado los factores genéticos y epidemiológicos del asma. Esta revisión de la literatura busca resumir el conjunto de conocimientos existentes sobre la epidemiología del asma. En concreto, el principal objetivo de la revisión es proporcionar una base de información unificada sobre el estado actual de los factores involucrados en la epidemiología genética del asma. La revisión es un resumen simple pero detallado de las fuentes de literatura y su metodología, así como de los hallazgos en relación con la epidemiología genética del asma. Además, el trabajo dirige su empeño a la región del Caribe, y realiza una recopilación resumida y sintetizada del conjunto de investigaciones*

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*anteriores. De especial interés son las fuentes arbitradas por colegas especializados, publicadas en los últimos tiempos. El trabajo ofrece una visión más reciente, y recapitula investigaciones anteriores, a la vez que sigue el progreso intelectual en el debate. Donde es posible, mediante la revisión y discusión de los resultados de la literatura anterior, esta revisión señala las lagunas en los conocimientos, así como las potenciales direcciones de las investigaciones futuras del estudio de la epidemiología genética del asma. En general, esperamos contribuir a un conocimiento más sintetizado, y lograr una mejor comprensión, tanto de la literatura anterior como de la potencial dirección futura de la investigación genética y epidemiológica del asma.*

**Palabras claves:** Adolescentes, asma, Caribe, epidemiología, genética

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## INTRODUCTION

Asthma is a complex disease caused by inflammation in the acute phase which, over time, leads to chronic airway changes as a result of remodelling. Initially, asthma was thought of as abnormal constriction of the smooth muscle cells in the bronchioles, however, this is now seen as an oversimplification of what is a much more intricate process. During the acute phase, inflammatory cells lining the airways release mediators such as cytokines, which act to recruit a variety of cells including mast cells, eosinophils and neutrophils. This leads to shedding of epithelial cells and mucus production that occludes the airways. This inflammation may also be present in the absence of clinical symptoms and is thought to contribute to increased responsiveness of the airways to particular triggers. Over time, this chronic inflammation of the main air passages leads to hypertrophy and hyperplasia of smooth muscle cells as well as impairment of mucus clearance, making it difficult for continuous air flow through the lungs (1). Asthma exacerbations can range from mild to severe and acute to chronic, each having its own set of clinical findings (2). Common symptoms include wheezing, dyspnoea, congestion with phlegm, sore throat and persistent cough, which generally respond to short-acting beta agonists. However, in more severe exacerbations, tachypnoea and unresponsiveness to bronchodilators can lead to fatigue of respiratory muscles and acute respiratory failure. Asthma prevalence is global, and is common to both developed and developing countries (3, 4). According to the American Lung Association, while prevalence of asthma has increased, mortality and hospital admissions and discharges have steadily decreased. This is most likely due to better understanding of asthma pathophysiology and improved treatment protocols (5). Yet, in the United States of America (USA), prevalence is not uniformly distributed across ethnic and racial groups. Puerto Ricans and Blacks comprise nearly one-third of childhood asthma patients; these groups seem to be representative of the populations in which asthma prevalence in children continues to rise. In addition, asthma is a growing condition in the Caribbean and prevalence in most islands is unknown, and potential inter-island variation has not as of yet been determined (6). Prevalence studies are

starting to be conducted worldwide including many of the islands across the Caribbean. In one cross-sectional community-based survey in Jamaica, nearly 20% of children between two and seven years self-reported wheeze and 16.7% were diagnosed with asthma symptoms. Asthma and allergies were high and risk factors for Jamaican children included chest infections in patients less than one year of age, family history and the presence of pets (3).

Although the study applied a strong internationally recognized data collection instrument – the International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire – the data on the prevalence of both asthma and allergies were on a subjective platform of individual responses that may have been overestimated (7, 8). Many causes of asthma have been identified including allergens, irritants, psychosocial issues and environmental conditions (9–12). Additionally, genetics plays a role in asthma development in children. Studies identified nearly 200 genes that are likely associated with asthma, but most studies have focussed on European and Asian groups while little attention has been paid to Latino and Caribbean ethnic groups. This concise review concentrates on genetic epidemiology studies focussing on these groups.

## METHODS

A PubMed search was conducted, focussing primarily on studies conducted within the time period 1994–2013. Key word phrases used during the search included, but were not limited to: genetic epidemiology of asthma, asthma in the Caribbean, asthma in Caribbean children, genetics and asthma.

## RESULTS

Recent studies appear to suggest that a combination of concomitant genetic and environmental risk factors generally constitute the highest risk for an individual to develop asthma (12). It has been observed that asthma is one of the most serious allergic diseases and the most common child and adolescent disease in developed countries (13). The list of candidate genes in asthma appears to be endless. This has inspired scientists to find a true correlation between

susceptibility genes, their locations and possible correlations with asthma in specific populations. Different genes may be involved in the pathogenesis of asthma, explaining the possibility of different outcomes amongst affected individuals (14, 15). The complexity of the immunological network involved in the demonstration of the complete linkage of genes and asthma remain a barrier in understanding the aetiology, pathophysiology and management of asthma (16).

Candidate genes and their association with asthma have been demonstrated in large populations in various areas, derived from large numbers of single nucleotide polymorphisms (SNPs). The literature is rich in examples of studies of European and Indian populations of candidate genes and SNPs and their association with asthma. In one study, a susceptibility gene for asthma found on chromosome 20p13, and identified by positional cloning, is a member of the A-Disintegrin and Metalloprotease protein family coded 33 (ADAM 33). ADAM33 is a highly studied polymorphic gene (17), whose functions relate to the activation, proteolysis, adhesion, fusion and intracellular signalling. It is strongly linked with asthma, and has been studied in families. Indeed, more studies have demonstrated an influence of ADAM33 in early lung function and epithelial-mesenchymal dysfunction in children, revealing that its presence predisposes children to asthma (10, 18, 19). Polymorphisms in ADAM33 lead to faster reduction in expiratory volume (20).

Previous studies have also demonstrated the association of polymorphism in the promoter of interleukin-4 (IL-4) – a cytokine secreted by the T2 helper cells – with asthma and modification of disease severity (20). Another candidate gene for asthma, implicated in the disease pathophysiology of certain populations, is interferon gamma (IFN- $\gamma$ ). In spite of the isolation of this gene and demonstration of its possible link with asthma, the literature has not been rooted on specific populations (21).

In a cross-sectional study of leather tannery workers from Pakistan, a gene,  $\beta$ -chain of the high-affinity receptor for IgE (Fc $\epsilon$ RI $\beta$ ) located on the surfaces of Langerhan's cells, mast cells, basophils and eosinophils, mediated immediate reactions of the binding of allergen to the receptor-bound IgE. As a consequence, Fc $\epsilon$ RI $\beta$  mediates asthma by activating inflammatory cells (14, 16, 22). Further studies in the Indian population confirmed that a promoter-dependent mechanism mediates Fc $\epsilon$ RI $\beta$ 's pathway, leading to asthma (23). In a study of gene association in Italian families with allergic asthma, a hierarchical genotyping design was used to isolate G-protein-coupled receptor for asthma [GPRA] (24). Data obtained from the literature give the impression of the genes' involvement in the atopy and asthma pathogenesis (25, 26). This contrasts from earlier studies, one of which found that neither the prevalence of asthma nor the atopic status of the asthmatic relatives was influenced by the proband asthmatic status and concluded that atopy and asthma are likely independently inherited (27). In that early study, asthma prevalence of first-degree related children was found

to be significantly higher than in relatives of control children, with a more pronounced difference for relatives of atopic probands, and atopic asthma was more common than non-atopic asthma among the relatives of the asthmatics (27). In addition, atopic asthma was more common than non-atopic asthma among the relatives of asthmatics, regardless of the atopic status of the proband (27).

Other common candidate genes in asthma, isolated from North Indian populations, are interleukin-10 (IL-10), an anti-inflammatory cytokine, and interleukin-21 (IL-21), which regulates IgE production (28, 29). More segregation analyses demonstrated high heritability of IgE levels in asthma. Further studies showed a clear relationship between atopy and bronchial hyper-responsiveness (30–32).

Another study, characterizing over 317 000 SNPs from 994 different asthmatics with childhood onset vs 1243 non-asthmatics, revealed multiple markers on chromosome 17p21 to be significantly and reproducibly associated with childhood onset asthma, and found that SNPs were strongly associated *in cis* with transcript levels of ORMDL3 [a member of a gene family encoding transmembrane proteins anchored in the endoplasmic reticulum] (33). The authors stated that the results indicated that genetic variants regulating ORMDL3 expression are determinants of childhood asthma susceptibility (33).

According to another study, segregation analyses were conducted with and without residual family effects in 3369 individuals from 906 nuclear families enrolled, without selection, in a longitudinal respiratory study, with and without the covariate (34). In this study, the hypothesis of a single two-allele locus for asthma was rejected (34). In addition, this study determined that either a polygenic/multifactorial mode of inheritance alone, or an oligogenic model (with some evidence of recessive component present in the population with the high frequency of 0.67), depending on residual familial effect assessment method, was compatible with their study data (34).

A recent study focussed on single nucleotide polymorphisms on specific genes associated with asthma and whether these genes were specific to Latino ethnic groups, specifically Puerto Ricans and Mexicans (35). This study came to several interesting conclusions. The first being that there are common variants that alone contribute small risk but together with other common variants have an additive effect on the risk of developing asthma (35). Furthermore, there are rarer variants specific to population groups, most likely arising after they diverged from larger populations that contribute a much more significant risk (35). This is then confounded in certain Latino and Caribbean groups due to mixing of many ethnic groups over the last few centuries (35). There were genes identified in this study that confer risk across ethnic Latino groups in addition to genes specific for certain subgroups, likely accounting for differences in prevalence between subgroups of Latinos (35).

## DISCUSSION

There are multiple methodological caveats in most studies on genetics and asthma, due to heterogeneity of susceptibility genes, suggesting possible change of methodology in future studies on genes and asthma. More than 100 genes in particular chromosomes have been linked with asthma. The associations between susceptibility genes and asthma have varied strengths in various global regions. In practically all of the reviewed gene-asthma association studies in this literature review, the populations are either from Europe or from the Asian sub-continent. Limited studies, so far, have focussed on Latino and Caribbean ethnic groups. Hispanics, whose genetic perspectives carry the components of indigenous American, European and African populations, comprise the largest minority population in the USA (36). However, Puerto Ricans account for the highest prevalence of childhood asthma cases, indicating population-specific genetic variants conferring this risk.

Many cross-sectional studies have confirmed increases in the incidence and prevalence of asthma over the past two to three decades, but much remains unknown as to the fundamental immunologic, genetic and environmental mechanisms underlying the development of this condition and its increased expression, especially in the developed world (24). It is likely that detailed studies of epigenetics will eventually untangle the inconsistencies among the many conflicting study outcomes. The Caribbean region has long been plagued with asthma as a common public health problem (37). The high number of patients attending the asthma management centres and the rate at which these numbers are exponentially rising is alarming. Despite asthma being a common regional health problem in the Caribbean, where prevalence is high and seems to be increasing (37), little has been done to determine its prevalence and whether the disease varies among different islands. Furthermore, unsatisfactory information has been given about the potential environmental and genetic factors that constitute the spread of this disease in the Caribbean. For example, one study investigated the prevalence of asthma, comparing two Caribbean islands (Trinidad and Tobago), in addition to comparing other regions (6). While geographically these two islands are only separated by 32 km, the ethnic composition of both islands is vastly different. The population of Tobago is predominantly of African origin, while Trinidad is multi-ethnic with a large ethnic Indian population. Additionally, Trinidad is one of the most industrialized of all the islands in the Caribbean, while the economy of Tobago relies mainly on fishing and tourism. Given these differences in industrialization *vs* alternate forms of economy reliance between these two countries, it is possible and potentially inferred that environmental factors may be involved in the exacerbation of asthma triggers and the resultant differences in the prevalence of this condition in these regions. This may be true and contributory to differences in other countries as well, given similar contributing environmental factors.

Using the ISAAC, that same study investigated 5000 adolescents in the two islands of Trinidad and Tobago, and their study revealed that severe asthma occurred more frequently in students from Tobago (6). A quarter of the respondents in the survey from the two islands reported wheezing, and night cough was the commonest reported symptom, occurring in over 35% of respondents (6). It was found that although self-reported wheeze is common in the Trinidad and Tobago adolescents, there is variation between the two territories, with high school students in the less industrialized Tobago reporting more severe asthma symptoms as well as exercise-induced wheeze (6). Economic parameters and access to healthcare were thought to be potential explanations for the reported results; however, these are similar between the two islands; thus, differences in ethnicity were cited as potential explanations for the findings (6). These results were surprising to the surveyors because the prevalence of asthma has been found to be higher in industrialized and developed countries, and in city centres (38), with an overall increase in the prevalence of asthma in centres worldwide (7). Another study found that, regarding asthma symptoms prevalent in subjects in California, patients of African descent had a four-fold higher rate of hospital admission for asthma, even when controlling for economic differences (39). In another study, the ISAAC questionnaire was repeated in 193 404 children aged six to seven years from 66 centres in 37 countries, and 304 679 children aged 13–14 years from 106 centres in 56 countries, chosen from a random sample of schools in a defined geographical area at least five years after Phase One. It was found that there was a worldwide rise in prevalence of symptoms in many centres, which was concerning, yet reassuring that there were no increases in prevalence for centres with high existing prevalence in the older age groups (7).

## CONCLUSION

To more accurately understand the gene-asthma association, more studies are advised in the areas of gene-gene and gene-environment interactions, as well as comparing and contrasting findings with specific focus on the roles of these genes. These interactions appear to be complex with no rigid implication of various genes on specific site locations on chromosomes, their specific function, how they contribute to development of asthma, or their possible association with isolated populations outside of the traditional research regions of Asia and Europe. Presently, genome-wide association studies are either unclear or incomplete. For instance, while IL-4 and ADAM33 genes were shown in these studies to be associated with asthma, many gene variants of these two proteins are not associated with asthma (32, 40).

Collaboration between researchers on the pathophysiology, epidemiology and genetics of asthma is essential for further understanding of the genetic-asthma association as well as potential improvement in genetic screening and management of asthma based on the findings. Finally, it

bears repeating that asthma is a potentially debilitating and serious disease, especially for the children and adolescent patients that are affected, which is increasingly important to note as studies have found the prevalence of asthma is increasing in city centres across the world (7). The fact that asthma aggregates in families and combines the dimensions of genes and environment to produce complicated multifactorial outcomes is clear. Thus, further research is needed to elucidate the precise mechanisms whereby families acquire such a chronic and at times potentially lethal disease.

#### AUTHORS' NOTE

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