

The Asian side of asthma and allergy

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Current Opinion in Allergy and Clinical Immunology 2008, 8:384–390

Purpose of review

There is wide variation in the global epidemiology of allergic diseases, and the prevalence rates of asthma and allergy differ significantly among different Asian populations. The diversity of environment and ethnic background in Asia provide excellent opportunities for research into the environmental and genetic determinants of asthma and allergies. This review summarizes important lessons learnt from research findings from Asia on asthma and allergy.

Recent findings

Recent epidemiologic studies revealed wide variation and increasing prevalence of asthma and allergy in many Asian countries. Comparative studies of population of the same ethnic background living in different environments revealed important environmental risk factors for asthma. Ambient air pollution plays an important role in the morbidity of patients with asthma but does not seem to affect the prevalence of asthma. There were many genetic association studies for allergic diseases from Asia. These studies identified novel gene targets, such as CD40, DCNP1 and PTGS2, for asthma and allergen sensitization whereas many others replicated the genetic associations on known candidate genes for asthma and atopic dermatitis.

Summary

Epidemiologic and genetic researches in Asia advance our knowledge on the disease prevalence, healthcare burden and pathogenesis of asthma and allergy.

Keywords

Asia, asthma, atopic dermatitis, epidemiology, genetics

Curr Opin Allergy Clin Immunol 8:384–390
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1528-4050

Introduction

Asthma is one the most common chronic diseases worldwide, and there is wide variation in the global epidemiology of allergic diseases [1]. Allergies have been found to be relatively more common in western countries, but the prevalence and public awareness of these diseases are highly variable across Asia. The wide variations in the genetic background, lifestyle and environmental exposures among Asian countries offer attractive research opportunities to identify the risk and protective factors for these allergic diseases. The pathogenesis of allergies involves complex interactions between many susceptibility genes and a wide variety of environmental factors. Published data strongly suggests wide and ethnic-specific disparity in the genetic epidemiology of these susceptibility genes [2]. Researches on the genetics of asthma and atopic dermatitis in the Asian population would help us to better understand the implications of findings generated from published genetic association studies. With the rapid improvement and the changing environmental exposures, the prevalence of allergic diseases has been increasing steadily over the past two decades. Clear

understanding of the important factors and how these factors interact with the underlying genetic determinants for asthma may provide insights on how to develop primary preventive strategies against the development of asthma and related allergic disorders. The purpose of this review is to highlight the important lessons learnt from studies from Asian countries and to evaluate how these studies contribute to the understanding of the pathogenesis of asthma and allergies.

Epidemiology and risk factors of asthma and allergies

Many epidemiologic studies from many Asian countries have documented increasing prevalence of asthma and allergies (Table 1). In many Asian countries, the prevalence of asthma has increased by three to four times over the past 20 years [1,3–12]. However, most of the data were collected in a nonstandardized fashion using different types of written questionnaires without proper validation. In the last decade, many Asian countries have participated in the International Study of Asthma and Allergies in childhood (ISAAC) using standardized and

Table 1 Asthma prevalence and trends in Asian countries

Region	Year of study	Age group (years)	Asthma or wheeze ever (%)
Beijing	1995	13–14	6.9
	2001	13–14	6.3
Hong Kong	1989	8–10	7.4–7.7
	1992	12–16	6.6
	1995	13–14	11
	2002	13–14	10.2
Indonesia	1981	7–15	2.3
	1998	13–14	1.6
	1998	6–7	6.6
Malaysia	1990	7–12	8.7
	1995	7–12	10.3
	2001	6–7	8.3*
Philippines	1991	<15	3.9
	1998	13–14	17.9
Singapore	1987	6–12	13.7
	1996	6–7	20.7
	1996	13–14	18.5
	2001	13–14	27.4
Taiwan	1974	7–15	1.3
	1985	7–15	5.1
	1998	13–14	5.4 [†]
	2001	13–14	7.0 [†]
	2005	6–8	7
Thailand	1987	6–12	4.3
	1998	6–7	9.5
	1998	13–14	13.5 [†]
	2002	13–14	13.9 [†]

* Prevalence of wheeze ever.

[†] Prevalence of wheeze in past year. Modified from [1,3–13].

validated instrument [1,3,9,13]. The results of the ISAAC Phase I clearly demonstrated wide variation of the prevalence of asthma in the region. Interestingly, those centers that have participated in both Phase I and Phase 3 ISAAC did not reveal a dramatic increase in the prevalence of asthma such as the results from Hong Kong [14].

The more intriguing fact is that populations with a similar genetic background from different environments were found to have very different asthma prevalence rates. For example, the ISAAC Phase I results revealed that the prevalence of wheeze in the past 12 months among 13–14 year old Chinese schoolchildren from Hong Kong was 10%, whereas the average rate in mainland China was only 3.3% [9]. Given the similar genetic background among the various Chinese populations, environmental factors are likely to be important in explaining the observed differences. Several populations of Chinese schoolchildren had participated in the ISAAC Phase II study, the results again showed that children from Hong Kong has a prevalence rate of wheeze and skin prick sensitization almost double compared with those children from Beijing and Guangzhou. Furthermore, among the individuals recruited from Hong Kong, those born and raised in Hong Kong had a much higher rate of asthma and related allergic symptoms such as eczema and allergic rhinitis compared with those born in China with subsequent migration to Hong Kong [14]. This clearly indi-

cated that exposure to the environment in mainland China might provide protection against subsequent development of asthma and allergies. Indeed, detailed analyses of the Phase II results revealed that several environmental factors and dietary differences could explain the difference in prevalence of asthma among the three groups of children [13]. These factors included the use of foam pillow, the use of cotton quilt, the use of gas as cooking fuel, exposure to house dampness, consumption of fruits and raw vegetables. Multivariate logistic regression showed that living in mainland no longer has a protective effect against the development of asthma once these six factors were corrected in the models. These factors, or unmeasured factors associated with these, may be responsible for the higher prevalence of asthma in children from Hong Kong.

In addition to cross-sectional studies, birth cohorts offer a reliable source of prospective data that delineate the risk and protective factors for atopic disorders. The Osaka Maternal and Child Health Study which started recruiting subjects in November 2001 investigated the physical and mental health of Japanese pregnant women and the development of common childhood diseases in their newborns. The researchers studied the relationship between formaldehyde exposure and the prevalence of allergic disorders in 998 pregnant women [15[•]]. Formaldehyde levels at least 47 ppb were associated with an increased prevalence of eczema but not asthma or allergic rhinitis, and this finding was found mainly in women with a negative familial allergic history. This Study Group also investigated intake of fish or n-3 polyunsaturated fatty acids in their pregnant women [16[•]]. Allergic rhinitis was less common among those with higher intake of eicosapentaenoic and docosahexaenoic acids. There was also a trend for individuals with high intake of n-6 polyunsaturated fatty acids to have less allergic rhinitis. Newborns of these pregnant women were followed during infancy, during which data on perinatal environmental factors were prospectively collected. When infants were assessed by questionnaire at 2–9 months old, a high house dust mite allergen level from maternal bedclothes and mold in the kitchen during pregnancy were associated with an increased risk of atopic eczema. On the contrary, frequent vacuuming practices during pregnancy and giving the infant a bath or shower at least once a day were protective against the development of eczema [17[•]]. About one quarter of the individuals had ever wheezed by age 3 years, but only 4.3% were diagnosed to have asthma. Neither exclusive breastfeeding for at least 4 months nor partial breastfeeding for at least 6 months were associated with the risks of wheeze or asthma in Japanese infants [18^{••}].

Another group from Fukuoka conducted a cross-sectional study of over 23 000 Japanese schoolchildren. They

investigated the association between the early feeding pattern and the prevalence of current allergic disorders as diagnosed according to the International Study of Asthma and Allergies in Childhood (ISAAC) criteria [19[•]]. The prevalence rates of wheeze, asthma, eczema and allergic rhinoconjunctivitis in preceding 12 months were 10.7, 7.6, 6.8 and 7.7%, respectively. Children who were breastfed after birth had a higher prevalence of atopic dermatitis, particularly among children without a parental allergic history. In addition, this study observed a positive dose-response relationship between breastfeeding duration and the prevalence of the disease. On the contrary, early feeding practice was not associated with wheeze or allergic rhinoconjunctivitis. In the same study, they analyzed the effects of environmental tobacco smoke (ETS) exposure at home on the prevalence of allergic disorders [20[•]]. Current heavy ETS exposure and at least seven pack-years of smoking in the household were associated with an increased prevalence of wheeze and asthma, especially in children with a positive parental allergic history. Such association was not observed for eczema or allergic rhinoconjunctivitis. Published data suggested that Bacillus Calmette-Guérin (BCG) vaccination might protect against allergic disorders. These investigators thus collected data on BCG vaccination and tuberculin tests from school records [21[•]]. In addition, BCG vaccination in infants was not related to the prevalence of allergic disorders, positive tuberculin reactivity in the first grade was independently associated with 20–23% lower prevalence of wheeze, asthma and eczema.

Genetically predisposed individuals typically undergo an 'atopy march' during early childhood, but there is no data on the prevalence and risk factors for atopic disorders among Asian preschool children. Using the ISAAC methodology, we conducted a population study on 3089 children aged 2–6 years old from 14 nurseries and kindergartens in Hong Kong [22^{••}]. The prevalence of 'ever' and 'current' wheeze were 16.7 and 9.3%, respectively. Consistent with our earlier report for older Chinese children [13], the use of foam pillow and gas as cooking fuel in infancy were significant risk factors for current wheeze in these young Chinese children. We also found that current wheeze was less common in children born in mainland China as compared with those born and raised in Hong Kong. These results clearly indicated the importance of early environmental exposure and the subsequent development of asthma and allergies and the critical period appears to be in the first 3 years of life.

Two independent groups published secular trends of asthma and allergies in the Asian population. Using the ISAAC questionnaire, Trakultivakorn *et al.* [23[•]] conducted Phase III study in primary and secondary schoolchildren from Bangkok and Chiang Mai in

Thailand. When compared with Phase I data, there was an increase in the prevalence of current asthma, rhinitis, rhinoconjunctivitis and flexural eczema in the younger individuals. The prevalence of rhinitis and rhinoconjunctivitis increased in the older age group, but asthma prevalence was either unchanged (for Bangkok) or lower (for Chiang Mai) in these children. Using National Health Insurance (NHI) data from 1996 to 2002, Yeh *et al.* [24^{••}] reported the average incidence rates of hospitalization for Taiwanese children (<18 years) and adults to be 105.0 and 116.7 per 100 000 individuals, respectively. The figure for children increased by 6.5% annually but remained static for adults during this period. On the contrary, adults were hospitalized for longer and readmitted more frequently when compared with children.

Effects of air pollution on respiratory health

Ko *et al.* [25[•]] conducted a retrospective ecological study on the effects of ambient air pollutants on the hospitalization rates for asthma in Hong Kong. They retrieved data on emergency asthma-related hospital admissions to 15 major hospitals and indices of important air pollutants between January 2000 and December 2005 in Hong Kong. Among 69 716 admissions during this period, they observed significant associations between asthma-related hospitalizations and levels of NO₂, O₃, PM₁₀ and PM_{2.5}. In a multipollutant model, O₃ was associated with increased admissions for asthma. In another study, Bell *et al.* [26^{••}] investigated the relationship between cause-specific hospitalizations and sandstorms and air pollution in Taipei between 1995 and 2002. They found that the risk of ischemic heart disease admissions was associated with a number of sandstorm indices, and hospital admissions for this disease were 16–21% higher on sandstorm days compared with other days. Asthma admissions increased 4.5% per 28 µg/m³ increase in PM₁₀ levels and 7.6% per 10 ppb increase in O₃. Improvement in air quality most likely will reduce the morbidity in individuals with preexisting asthma. However, the prevalence of asthma is highest in Hong Kong school children among the various Chinese populations who have taken part in the ISAAC study. Many cities in mainland China have far higher levels of environmental pollution and yet the prevalence of asthma is much lower than that in Hong Kong.

Genetics of asthma among Asian populations

There have been many Asian studies in the field of genetic research of allergic diseases. Table 2 [25[•], 27[•], 28^{••}, 29[•], 30[•], 31–35, 36^{••}, 37^{••}, 38[•], 39[•], 40[•], 41[•], 42^{••}, 43] summarizes the important asthma genetic studies from the region. Similar to many other genetic studies in Caucasians, most research studies aimed at evaluation

Table 2 Recent genetic studies of asthma and allergies in Asia

Research groups	Ethnic groups	Genes evaluated	References
Mainland China, Taiwan, Hong Kong	Chinese	TIM-1, PTGS2, Mbl2, PTGDR, PTPRD	[27 [•] ,28 ^{••} ,29 [•] ,30 [•] ,31–35]
South Korea	Korean	SD40, IL-27, PTGER3, DCNP1, IL-13, TNFA	[36 ^{••} ,37 ^{••} ,38 [•] ,39 [•] ,40 ^{••} ,41 [•]]
Japan	Japanese	ORMDL3, INPP4A, DP receptor	[42 ^{••} ,43]
Singapore	Chinese Malay, Indian	IL-4 receptor	[25 [•]]

of the genes related to the immune system as well as various cytokines and chemokines. Recently, we have studied the role of several candidate genes in the Chinese populations including the IL-13 gene, the CTLA4 gene, Mannose-binding lectin gene, and the prostaglandin-endoperoxidase synthase 2 genes in the pathogenesis of asthma and allergies (Table 2). Other Asian research groups have also investigated the roles of other possible candidate genes. In view of the importance of CD40 in cell-mediated and humoral immunity, Park [36^{••}] investigated the genetic associations between single-nucleotide polymorphisms (SNPs) of CD40 and asthma and serum total IgE levels in Koreans. None of the seven studied SNPs was associated with asthma, but total IgE levels were associated with the G-580A and C-1T among the asthmatic patients. The SNP at position -1 also regulated CD40 expression on B cells.

Two other Korean groups published their findings on genetic associations for immune targets of asthma. IL-27 acts as a versatile cytokine in the early regulation of the initiation of type-1 T-helper (Th1) and suppression of Th2 immunity. Chae *et al.* [37^{••}] reported that asthma was associated with A-964G of *IL-27* p28. Because dendritic cells are crucial antigen-presenting cells in the lung, Kim *et al.* [38[•]] studied the associations between asthma and SNPs of the gene encoding dendritic cells-specific DCNP1. This case-control study revealed significant association between the T allele of C-1289T in *DCNP1* promoter and low mite-specific IgE among Korean asthmatic patients. Liu *et al.* [27[•]] genotyped two promoter polymorphisms, G-416C and G-1454A, from the gene encoding T cell immunoglobulin and mucin domain-1 (*TIM1*) in 409 Han Chinese patients with asthma and 305 healthy controls. They detected significant association between asthma susceptibility and G-416C, and that this SNP altered the transcriptional activity of *TIM1*.

In a recent genome-wide association study (GWA), Mofatt *et al.* [44^{••}] identified highly significant association between asthma and SNPs on chromosome 17q21.1 locus in children recruited from many Caucasian countries. Specifically, the association was the strongest for genetic variants of *ORMDL3*. Hirota *et al.* [42^{••}] published the first replication study in Japanese children. They studied the SNP rs7216389, being the strongest signal from the

above GWA, in 545 children with atopic asthma and 738 healthy individuals. Atopic asthma was significantly associated with the T allele of rs7216389. In addition, they showed that the *ORMDL3* expression was potentially induced by polyinosine–polycytidylic acid in normal human lung fibroblasts. This last finding suggests that *ORMDL3* may play a role in viral respiratory infections.

Two studies from Asia published results on genetic targets of prostaglandin metabolism for asthma. As cyclooxygenase-2 plays essential roles in inflammation, we studied the effects of four tagging SNPs of the gene encoding prostaglandin-endoperoxide synthase 2 (*PTGS2*) on asthma in Chinese children [28^{••}]. *PTGS2*.8473 showed significant association with asthma and atopy, with carriers of the C allele having a 1.5-fold risk of developing asthma when compared with those homozygous for the T allele. This SNP also correlated with forced expiratory volume in 1 s and peak expiratory flow rate. Park *et al.* [36^{••},39[•]] investigated 19 SNPs in the genes encoding prostaglandin E2 receptor subtypes EP1-4 (*Ptger1-4*) in 480 Korean asthmatics and 140 controls. They found that T1388C of *Ptger3* was associated with asthma, and the four-locus haplotype C-C-A-A in *Ptger3* was protective against moderate-to-severe asthma in this population.

In contrast to these positive genetic associations, several groups published important negative studies on known asthma candidate genes. The first of these was done on the prostanoid DP receptor gene (*PTGDR*), the individual SNPs and haplotype of which was initially shown to be associated with asthma in Caucasian children [43]. Subsequent to this report, investigators published negative findings for any genetic association between asthma traits and *PTGDR* in the Latinos [45]. In the last year, Li *et al.* [29[•]] studied the same three SNPs as in the original article in 336 Han Chinese patients with asthma and 264 controls. Unlike the results observed in American and European populations, neither these SNPs nor their haplotypes was associated with asthma susceptibility. In addition, the frequencies for both high-transcriptional-efficiency haplotype (C-C-C) and low-transcriptional-efficiency haplotype (T-C-T) were much lower than the published results. Our group joined them by reporting recently that *PTGDR* was not associated with any asthma or atopy traits in 676 southern Chinese children in Hong Kong [30[•]]. These results highlight the importance of replication studies, especially in ethnically

diverse populations in supporting or disproving any initial genetic association study.

Microbial exposure and activation of innate immunity are increasingly recognized to be important in modulating the development of asthma and allergy [46,47]. Mannose-binding lectin (MBL) is one of the key molecules in complement activation pathways that are associated with the defense against many infectious diseases. Wang *et al.* [48•] studied three SNPs in the gene encoding this molecule (*mb12*) in 579 Japanese asthmatic adults and 232 controls. They could not find any significant difference between asthmatics and controls in *mb12* genotype distribution. This negative study echoed our earlier report on three *mb12* genotypes for asthma and serum IgE levels in Hong Kong Chinese children [34]. Although individual genotypes and *mb12* haplotypes altered serum MBL levels, these genetic markers were not related to the susceptibility to develop asthma or atopy.

More than a dozen major asthma candidate genes have been published, and these genes also interacted with each other to confer this susceptibility to asthma [35,49]. Several Asian groups studied this epigenetic interaction. TNF- α is a pivotal proinflammatory cytokine increased in asthmatic airways. The TNF- α gene family was associated with asthma and bronchial hyperresponsiveness (BHR), and recently published clinical trials showed that therapies targeted against TNF- α might be useful treatment for severe asthma. In addition, TNF- α production might be modulated by CD14-expressing cells. Hong and coworkers [40••] determined the genotypes at G-308A of *TNFA* and T-159C of *CD14* in 799 Korean asthmatic children and 153 controls. Although these SNPs were individually not associated with asthma risk, the degree of BHR was significantly higher in asthmatic children with the risk allele A of *TNFA*. They also observed that the risk alleles for the above two SNPs interacted synergistically to determine BHR. The same group also investigated the epigenetic interaction between the above SNP of *TNFA* and G2044A of *IL13* in Korean children [41•]. Similarly, they detected significant interactions between these SNPs and the risks of asthma and BHR.

Most genetic association studies published to date focused on the risks of asthma and atopy traits. However, it was recognized from the Childhood Asthma Management Program that lung function declined in about one-quarter of children with mild-to-moderate asthma [50]. There has not been any genetic study for this longitudinal change in lung function. Our group analyzed the effects of a panel of eight SNPs in six asthma candidate genes in relation to changes in spirometric

variables in Chinese asthmatic children [51••]. Annual FEV₁ change was associated with C1570T of signal transducer and activator of transcription 6 gene (*STAT6*). We also observed epigenetic interactions between SNPs at *IL13*, *ADRB2* and *STAT6* for FVC changes.

Under the hygiene hypothesis, heightened Th2 immunity due to lack of microbial exposure may predispose individuals to asthma and atopy. Moller *et al.* [52••] hypothesized that genetic variants in *STAT6*, an important signaling molecule in Th2-specific pathway, would also influence parasitic worm infections. These investigators studied nine SNPs for *STAT6* in a rural Chinese population and an urban United Kingdom population, and assessed serum IgE levels and severity of *Ascaris* infection in these individuals. Consistent with the hygiene hypothesis, individuals with low IgE/high worm burden suffered from a reduced risk of allergies and those with high worm burden had a lower expected risk of asthma. They also observed for the first time that *STAT6* haplotypes were associated with serum IgE levels, allergy and worm burden.

Conclusion

In conclusion, this review identifies many exciting researches in the field of epidemiology of asthma as well as genetics of asthma and related allergic diseases. Half of the world population lives in Asia. The current prevalence of asthma in Asia is still relatively low. However, one percent increase in the prevalence of asthma in China will result in four million more asthmatic children and this number is approximately equal to the population in the whole of New Zealand. The prevalence of asthma is likely to increase in the next two decades. Such increase will result in a significant burden on the society. In contrast to the relatively homogenous and developed western societies, the environment in Asia is very diverse and there are tremendous variations in terms of the genetic background of the Asian population. In particular, we have populations with similar genetic background living in different environments with drastically different prevalence of asthma like what we have found in Chinese children. Furthermore, the environment in Asia is undergoing rapid urbanization and westernization. Careful comparative studies and meticulous documentation of these changes will shine light on the roles of various environmental factors which may be important in the pathogenesis of asthma and allergies. Future research should expand the international collaborative efforts to identify risk and protective factors for allergies through the study of rural–urban environments in Asia, and to design therapeutic interventions for asthma and related atopic diseases that are targeted against some of the novel gene targets.

Acknowledgement

The authors' research relevant to this article has been supported by Research Grants Council of the Hong Kong Special Administrative Region (CUHK 4165/02M and 4512/06M); and Research Committee Group Research Scheme 2007/2008 (no. 3110034) and Direct Grant for Research of The Chinese University of Hong Kong.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 489–490).

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