



# Comprehensive integration of genetic and environmental determinants to increase knowledge of the allergic diseases

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The prevalence of allergic diseases such as asthma, allergic rhinitis and atopic dermatitis has been rising steadily over the last few decades and reached pandemic proportions in industrialized countries. The WHO estimates that 235 million people currently suffer from asthma and that this common chronic disease is the cause of 1 in every 250 deaths in the world [1]. Asthma is often associated with other allergic diseases, as allergic rhinitis. Thus, asthma and allergic rhinitis are common comorbidities: 75% of asthmatics develop rhinitis and 40% of patients with rhinitis suffer from asthma. Although asthma and rhinitis are strongly correlated and have some common physiopathological pathways including the allergic response, they also differ in many respects such as target organs, nature of the allergens (size). This leads us to assume the existence of both common and specific determinants (genetic and environmental) for rhinitis and asthma. Boulay *et al.* (pp. 000–000) describe recent developments on the complex relationship between asthma and rhinitis, stressing the importance of rhinitis management on asthma development and control.

There have been considerable efforts to characterize the genetic determinants of asthma and atopic dermatitis, including candidate gene studies, genome-wide linkage screens, followed by positional cloning studies and more recently genome-wide association studies, but genetic studies conducted for rhinitis were rarer [2]. Indeed, the genetic component of asthma and allergy-related phenotypes is substantial with estimates of heritability ranging from 35 to 95% in twin and pedigree studies [2]. Recent years have seen considerable progress in unraveling the contribution of the genetic determinants of the susceptibility to the development of asthma as well as the severity of the disease. Although these studies have been successful in identifying novel loci, these genetic factors explain only a small part of the genetic component of asthma and

the exact nature of the causal genetic variants is yet to be discovered. One of the reasons to explain what is called the missing heritability is that many genetic factors act primarily through complex mechanisms that involve interactions with an environmental factor or more complex pathways involving multiple genes and exposures.

The increase in allergic disease prevalence observed over the past decades cannot only be attributed to the changes in the diagnosis and the study of symptoms over time; this has led to extensive research regarding environmental determinants, deleterious or protective that could have changed during that time period [3]. Epidemiologic studies have highlighted many associations between environmental exposures and subsequent risk for asthma and allergy. Deleterious factors (i.e. active/passive smoking, occupational exposure, indoor domestic allergens, diet and outdoor air pollutants) and protective factors (mainly farm animals and related products) have been identified. Moreover, these studies have established that the period and the intensity of exposure in the life cycle are essential parameters in determining risk, and more particularly have emphasized the importance of early life period. Among the environmental factors found associated with asthma, two are the

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subject of reviews in this issue by Carlsten and Melén (pp. 000–000) and Wlasiuk and Vercelli (pp. 000–000), one conferring risk (air pollution) and another having a protective effect.

Adverse health effects from air pollutant are important. It is well known that, in patients with asthma, acute exposure to traffic-related air pollution is associated with adverse respiratory effects such as increased respiratory symptoms or hospitalizations. A causative link between chronic exposure to air pollutant and asthma incidence is increasingly evident, but the same relation between pollutant exposure and allergy is still questionable as stated by Carlsten and Melén (pp. 000–000) in their review. Both extrinsic (e.g. climate condition, coexposure to other factors like allergens, diet and microbiome) and intrinsic (e.g. age) factors can explain the variability in responses to pollutant exposure. But there is growing evidence that key factors in determining individual response to air pollution exposure are due to genetic and epigenetic changes between individuals. Assessing chronic exposure to air pollution at the individual level remains a real challenge. Thus, more research is needed to better characterize the long-term effect of air pollution on asthma and allergy, and to improve our understanding whereby air pollution influences respiratory health.

Epidemiological studies have shown that children who live in farms are less likely to develop allergic diseases and asthma than those who do not live in the same environment. Recent advances in the comprehension of farming lifestyle protective effect is discussed very elegantly and balanced in a review provided by Wlasiuk and Vercelli (pp. 000–000). In particular, they point to the central role played by microbial diversity in protective effects of traditional dairy farm on the risk of asthma development and in a lesser extent on allergy. Moreover, one interesting finding of recent works conducted in this field is the identification of three exposures that account for all the protective farm effect on asthma but not to atopy. These discrepancy results are in favor of distinct mechanisms mediating protection from asthma and atopy. Such hypothesis was also suggested at the genetic level by the large GABRIEL (a multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community) consortium-based genome-wide association study results [4] in which there was minimum overlap (only interleukin-13 gene) between the most significant single nucleotide polymorphisms (SNPs) associated with asthma and the most significant SNPs associated with total serum immunoglobulin E (IgE), suggesting that asthma

and IgE-mediated pathways may be largely genetically distinct.

However, the mechanisms by which environmental factors act and more particularly interact with genetic determinants to affect disease susceptibility are still unknown. Most cases of asthma of both childhood and adulthood onset are now considered to originate in early life and to belong to a group of complex diseases that are programmable by specific early life exposures (*in utero* or early childhood). How exposure in early life can change one's susceptibility to asthma is not well understood. Epigenetic modifications are amongst the factors that are likely to have an important role in modulating such disease risk.

Understanding these mechanisms is a formidable challenge. Genetic studies of mice are offering clues into the biology underlying these phenotypes and the link between genetic and environmental factors. Indeed, new genomic and proteomic data from ongoing studies conducted on various asthma populations should promote the development of new animal models of asthma and allergy that mirror more closely the inflammatory or non-inflammatory environments identified from the human studies. The principal mice models developed for the investigation of allergic airway diseases and for the assessment of the role of selected genes in the physiopathology of these diseases are described by Blanchet *et al.* (pp. 000–000). They also provide an illustration on how these tools can lend insights into lung inflammation response and their utility for the development and the assessment of potential new therapies.

Further research is needed to clarify the importance of the factors influencing asthma and allergic disease development and to elucidate the mechanisms through which each of these factors modifies the risk for asthma and allergy. Multivariate analysis with the integration of multiple 'omics' datasets (genomic, transcriptomic, proteomic and epigenetics) and environmental factor effects can lead to better define the molecular nature of asthma, especially allergic asthma, and the characterization of allergic disease subphenotypes. Taken together, the reviews of this series give an update on new developments and future perspectives in asthma and allergy.

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**Conflicts of interest**

*There are no conflicts of interest.*

**REFERENCES**

1. WHO. WHO Fact sheet N°307, May 2011: Asthma. <http://www.who.int/mediacentre/factsheets/fs307/en/index.html> [Accessed 4 July 2012].
2. Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. *Immunol Rev* 2011; 242:10–30.
3. Ober C, Vercelli D. Gene-environment interactions in human disease: nuisance or opportunity? *Trends Genet* 2011; 27:107–115.
4. Moffatt MF, Gut IG, Demenais F, *et al.*, GABRIEL Consortium. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010; 363:1211–1221.