



# Understand the allergic diseases biology using human populations by a transdisciplinary approach

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The deciphering of the complex mechanisms underlying multifactorial diseases, such as asthma and allergic diseases, is a major public health challenge, given the increased incidence of these diseases in the population. Over the past decades, there have been considerable efforts to characterize the genetic determinants of asthma and allergic diseases with the emergence of genome-wide association studies (GWASs). To date, the asthma susceptibility genes should be included in one of the fourth class of genes as defined by Vercelli [1]: A) genes associated with innate immunity and immunoregulation, B) genes associated with Th2-cell differentiation and effector function, C) genes expressed in epithelial cells and involved in mucosal immunity, and D) genes involved in lung function, airway remodelling, and asthma severity. The prevalence and severity of asthma differ in individuals with different ethnic origin and individuals exposed to different environments. These differences suggest the existence of specific genetic factors influencing the development and the expression of the disease in populations with different genetic background in addition to common genetic factors across populations. It also leads to the effort in integrating the environmental component considering gene by environment (e.g. viral infection and microbiome) interactions and epigenetics to solve a part of missing heritability in asthma. A cellular integration of the asthma genetics also benefits to the understanding of the disease pathogenesis. In time, the knowledge may allow prediction of the development of allergic diseases and may help to develop disease prevention actions and interventions at an individual level (personalized medicine).

GWAS have been successful in identifying novel susceptible genes associated with asthma and allergy-related phenotypes, and they have provided new insights into the biological mechanisms underlying these diseases. However, the characterization of the causal variants responsible for the association signals and their functional effects on disease remain to be further explored. The identification of causal variations in human diseases can greatly be facilitated by the study of population with special characteristics,

namely consanguineous or admixture populations. Moreover, characterization of population structures is an essential step before linkage disequilibrium mapping in GWASs. In this issue, Ortega and Meyers [2] discussed the basis of genetic diversity and population structures, and they illustrated how to take advantage of specific population structures, such as admixture populations, to facilitate gene discovery and to uncover new molecular mechanisms involved in asthma and allergic diseases in the context of modern human genetics.

In asthma, many genetic factors act primarily through complex mechanisms that involve interactions with other genes and environmental factors including viral exposure and microbiome and/or epigenetic mechanisms, so such genetic factors may be missed if they are examined independently (this concept refer to missing heritability). Consequently, disentangling asthma susceptibility will benefit from not only exploring heritable, but also environmental determinants and their interplay. In terms of environmental component, it is well recognized that the viral infection contributes, in childhood, to respiratory tract inflammation and epithelium cell modifications; therefore, viral exposure involves asthma exacerbations and contributes to asthma severity. Recently, several studies illustrate that the microbiome community of the airways of the asthmatic individuals significantly differs from the microbiome of the nonasthmatic nonallergic ones. Other studies report that particular gut microbiome communities are also associated with susceptibility to allergic diseases, including asthma. Several birth cohort studies on asthma are currently underway [e.g. the Canadian Healthy Infant

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**Curr Opin Allergy Clin Immunol** 2014, 14:379–380

DOI:10.1097/ACI.000000000000103

Longitudinal Development study (<http://www.canadianchildstudy.ca>) and the Cohort for Childhood Origin of Asthma and allergic diseases study]. These studies aim to document the contributions of genetics, epigenetics, and environmental factors in early life to allergic disease susceptibility. They help to decipher the natural history of allergic diseases and asthma and contribute to predict the risk for an individual to develop the disorder considering the interaction between genetic and environmental factors including, among others, microbiome and viral infections. A brief overview of these research fields provides the evidence that the microorganism composition is really important in the development and evolution of the allergic diseases, including asthma, at the individual level. In her review, Daley [3] examined the recent evidence regarding the impact of the interactions between viral and microbial exposures in early life with consideration of genetic susceptibility in asthma.

Asthma is principally known and defined as a Th2 disease with an allergic response involving Th2 cytokines (IL-4, IL-5, IL-13, etc.), immunoglobulin (Ig) G1 and IgE, and immune cells as lymphocytes, basophils, mast cells, neutrophils, eosinophils, monocytes, and macrophages. Allergic asthma begins with allergen presentation to naïve lymphocytes (Th0), which induces their differentiation into Th2 cells and then induces the production of IgE molecules by B lymphocytes. Only minutes after this, both mast cells and basophils are involved in the early phase. IgE binding at their high affinity IgE receptors leads to the secretion of pro-inflammatory factors as histamine, leukotrienes, cytokines, and also chemokines. These chemokines will recruit immune cell types involved in the late phase. Those are eosinophils and neutrophils. Neutrophils are mostly found in the airway tissue of individuals with severe asthma. As for the eosinophils, it is considered as a key cell in asthma. Once activated, they both induce a proinflammatory response through the secretion of IL-4, IL-5, IL-13, and other mediators. This brief description of allergic processes in asthma attributes the proinflammatory cytokine sources essentially to Th2 cells; however, recent advances in the effort for the understanding of the inflammatory responses – related to asthma or not – allow the discovery of a novel population of cells that can produce type-2 cytokines. This population of cells, named type-2 innate lymphoid cells (ILC2s), is able to produce sufficient amounts of

type-2 cytokines to cause allergy in mice models. Interestingly, the literature reports a GWAS in which polymorphisms in asthma genes related to the ILC2s' biological functions, including RAR-related orphan receptor alpha (RORA), *IL13*, interleukin 1 receptor-like 1 (*IL1RL1*), and *IL33*, were significantly associated [4]. This new evidence supports the idea that these cells are important in the asthma pathophysiology. In the present issue, Dr Barlow's review [5] depicts the roles of ILC2s in human complex traits with an inflammatory component, which allows appreciation of the complexity yet to be elucidated at the cellular and molecular levels. This review helps to fully understand this mechanism and illustrates also how these cells might offer an interesting target for the therapeutic avenue in future.

The outcomes of this genetic research are multiple. They can not only help in better understanding the biological processes underlying diseases but can also assist in disease prevention by identifying individuals at high risk for disease in whom targeted surveillance can be optimized. Ultimately, they can lead to the development of novel biomarkers, diagnostic tests, and molecularly targeted therapies. Thus, the emergence of personalized medicine is having a significant impact on the process of developing new diagnostic tools and therapeutics. However, the potential for translation of the research findings in medical applications raised several issues from an ethical, legal, and social point of view, and those will be discussed by Joly *et al.* [6] in their review.

### Acknowledgements

*None.*

### Conflicts of interest

*There are no conflicts of interest.*

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