



The genetics of asthma and allergic diseases: pieces of the puzzle are starting to come together

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Allergic asthma, a prevalent chronic allergic disorder of the respiratory system, afflicts patients of all ages, causes significant morbidity and mortality and consequently, generates substantial costs in industrialized countries. Although its pathogenesis remains largely undefined, we know that genetic and environmental factors play an important role. In recent years, we have seen considerable progress in the unraveling of the genetic contribution to the susceptibility of developing asthma and disease severity. Genome-wide association studies (GWAS) have been successful in identifying loci associated with asthma, eczema and related phenotypes as illustrated in this issue by Lockett and Holloway [1] and Marenholz *et al.* [2]. However, as for many complex diseases or phenotypes, the genetic variants identified by GWAS confer relatively small increases in risk and explain only partially the genetic component of these multifactorial traits. Thus, many other genes remain to be identified and verified for their biological relevance in diseases.

The detection of genes involved in complex diseases and the biological interpretation of GWAS findings can be facilitated with gene expression data. In his review, Bossé [3] discussed the strengths and weaknesses of many expression quantitatively trait locus (eQTL) mapping studies conducted until recently for asthma and asthma-related traits and described the recent findings of eQTL studies performed in relevant asthma cell type and tissues.

In addition to identifying genetic association with diseases at the genome level, GWAS have also been successful in generating new hypotheses regarding disease pathogenesis. More particularly, GWAS have shown that genes with pleiotropic effects are more frequent than anticipated. In other words, there are more genes associated with multiple diseases than previously expected. The identification of these pleiotropic genes implies that there are master regulators of biological processes. In this issue Marenholz *et al.* [2] described new findings regarding common pathways involved in the development of eczema and other immune-related traits, including asthma, allergy, and coeliac disease. Moreover, as stated by the authors, the

identification of shared genetic factors between eczema, asthma and allergic rhinitis should aid in resolving the complex biological mechanisms underlying the atopic march. For that purpose, studying simultaneously some diseases and/or some quantitative traits, which may share common genetic determinants, can help to identify and to characterize genes with pleiotropic effects.

To date, most of the GWAS analyses have focused on detecting associations at the single nucleotide polymorphism level and highlighting those associations, which reached a stringent genome-wide statistically significant level. As illustrated by Lockett and Holloway [1], the efforts now are to move toward the application of new strategies and analytical methods for mining the large amount of interesting findings that failed to reach genome-wide significance. These methods integrate gene–gene ($G \times G$), gene–environment ($G \times E$), and gene–pathway interactions in order to improve power to detect genetic variants with small marginal effects.

In the identification of novel genetic variants associated with complex diseases, one needs to consider a large variety of genetic variations (from rare to common variants) and use different statistical approaches. For example, GWAS focus on common variants, but are not useful in identifying rare variants involved in complex diseases. In the past 2 years, the advances in next-generation sequencing (NGS) technologies have intensified the search for rare variants involved in causing complex traits. The availability of such data has led to the development of specialized association tests and methodologies which have been reviewed by Burkett and Greenwood [4]. However,

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as explained by the authors, no one approach seems to outperform the others given the wide range of possible disease models and more methodological developments are necessary.

Another aspect to consider in the search for genetic determinants is the effort to translate the 'omics' findings to biological relevance. To date, the ability to integrate genetic/epigenetic and cellular findings has been extremely useful in understanding disease pathogenesis. In the field of asthma, genetic and cellular studies conducted in the last decades have highlighted the role and importance of epithelial cells in asthma pathogenesis as the majority of associated genes identified in GWASs are related to epithelial cell functions as reviewed in this issue by Anne Tsicopoulos [5].

The importance of the bronchial epithelium response to environmental factor exposure is recognized to be aberrant in the context of asthma and is related to asthma progression and exacerbations. Therefore, the chronic or continual environmental insults lead to tissue alteration or airway remodeling. Furthermore, functional studies indicated that epithelial cells produced cytokines such as interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin which may activate a subset of cells called antigen-independent innate lymphoid, which can produce, in response to allergens, Th2 cytokines and subsequently contribute to asthma pathogenesis.

Furthermore, the recent discoveries in epigenetics suggest a strong relationship between epithelial genes identified through GWAS and environmental exposures. The bronchial epithelium is well recognised as the first line in immune responses. It secretes cytokines which are important in the recruitment and activation of other innate immune cells including eosinophils, basophils and lymphocytes. These cells are coordinated and orchestrated in the inflammatory and remodelling processes specific to asthma, as illustrated schematically in a review by Nadif *et al.* [6] (see also Lin *et al.* [7]). Intriguingly, all these genetic and epigenetic observations point to a central cell type: the epithelial cells. Marenholz *et al.* [2] illustrated in their review the importance of these 'epithelium genes', the epithelium being the first barrier or contact between genetic determinants and environment.

With the development of NGS technologies that are generating extensive amount of data, we will have access to various types of genome-wide data that include not only DNA variation (genomics), but also genetic variants in regulatory regions (regulome), gene expression (transcriptomics), regulation of gene expression (epigenomics), and protein modification (proteomics). In the next decades, the combination of diverse 'omics' data sources will face the challenge on the development of study design that will optimize the translational value of the data (including pleiotropy) without compromising the importance of fine-phenotyping. In this context, extensive methodological works are needed in order to handle such complex and large-scale data, and the large variety of genetic variations, complex mechanisms (e.g. gene–gene and gene–environment interactions and pleiotropy), and integration of various 'omics' data.

Taken together, the investigation of genetics and epigenetics of asthma and allergic diseases at the cellular level allows a better understanding of disease pathogenesis. The asthma puzzle is beginning to see its genetic and epigenetic pieces coming together to show a complete picture of the disease.

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Conflicts of interest

There are no conflicts of interest.

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