Editorial



# Unraveling the genetic architecture of asthma

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Asthma is a complex disease resulting from the interaction of numerous exogenous and endogenous factors, with the important contribution of several environmental exposures and the individual's genetic composition (1). Indeed, the latter has been estimated to account for 30–90% of the total disease variation (2) as the combination of small effects of numerous genetic variants (3).

The great efforts of the genetic research of asthma in the last three decades have resulted in the identification of numerous promising loci (4,5). Shi *et al.* elegantly summarized the main contributions to this field in a recent publication in *Annals of Translational Medicine*, with the main focus on the genetic loci most commonly evidenced as candidates for asthma in the last 20 years (6). These include genes encoding for proteins with functions directly or indirectly related to the pathophysiology of asthma such as the immune response (*TLR2*, *TLR4*, *TLR9*, *CD14*, *HLA-DRB1*, *IFN-γ*), including inflammation-related processes (*IL-13*, *IL-17*); vitamin D metabolism (*VDR*); response to viral infections (*CDHR3*); cell-cell and cell-matrix interactions (*ADAM33*); and the activation of adenylate cyclase (*ADRB2*) (6). The effect alleles of genetic variants located at these genes have been associated with both protective and risk consequences on asthma-related traits in different populations, evidencing the broad functions of genes encoded at these loci (6). Interestingly, this selection of candidate genes is in line with recurrent recent evidence of the key implication of immune processes in the genetic architecture of asthma (7,8).

The article by Shi *et al.* reflects the approach followed in many asthma genetics studies to date, generally marked by the investigation of a handful number of genetic factors through hypothesis-driven strategies (5). Candidate-gene association studies have allowed the confirmation of the implication in molecular or cellular mechanisms underlying asthma of loci with previous functional or clinical evidence. Nonetheless, numerous limitations have been linked to this method, including the incapacity to reveal novel molecular markers without suspected causal implications in the disease pathophysiology (4,5). This was aimed to be solved by the development of genome-wide association study (GWAS) approaches, which have had the leading role in the genetic investigations of asthma in the last fifteen years (5), revealing the association of approximately 40 genomic regions with asthma susceptibility up to the present time (4).

Shi *et al.* aimed to summarize the main findings obtained using GWAS or meta-analysis approaches but, an overrepresentation of systematic reviews combining the association effects from candidate-gene association studies can be perceived (6). Thus, several important contributions of GWAS to the asthma field (4,5,9) have been missed. These include the identification of genes at the 17q12-21 chromosome region, despite being briefly introduced by the authors. This region was linked to asthma for the first time by Moffatt and colleagues in 2007 (10). Since then, it has been widely and strongly associated with the risk to develop childhood asthma in different populations (7), as well as other related traits to a lesser extent (e.g., response to treatment with inhaled corticosteroids (ICS), allergic sensitization, and lung function) (5,11). These pieces of

evidence make 17q12-21 the most promising central genetic marker of childhood asthma revealed until now (7).

GWASs have substantially increased the statistical power for the identification of novel genetic markers of asthma compared to previous methods (5,7). However, their highly demanding technical requirements and the limitations inherent to the study design of the investigations conducted until now have strongly hampered the promising potential of this strategy for the identification of functionally relevant genetic variants (12). Indeed, the genetic factors associated with asthma to date only explain a limited proportion of the heritability estimated for asthma, remaining the genetic picture of this disease incomplete (7). This fact represents a substantial constraint for the translation of the loci identified into the clinical management of asthma as markers for the prediction of disease onset, progression, and treatment response (13). For the same reason, no large improvements in the pharmacological therapy of this disease using the findings of genetic studies have been applied yet, as pointed out by Shi *et al.* Nevertheless, this has been suggested as the direction that should be followed in the future for the management of this disease (6).

Even though the authors of this article focused on the current catalog of identified loci for disease susceptibility, the need for the assessment of different asthma phenotypes beyond the overall disease risk was suggested (6). Indeed, a deeper investigation of these together with specific traits, such as the presence of airway eosinophil inflammation, treatment response, or disease severity, could be a very promising alternative to counteract the frequent limitation related to the reduced statistical power (12,14). This would facilitate the detection of large association effects in small sample-sized and homogenous extreme phenotype groups (7) that might contribute to gathering the individual pieces to construct the complete picture of mechanisms underlying asthma.

On the other hand, Shi and colleagues highlighted the fact that further research on gene-environment interactions (GxE) in asthma is required (6). This approach has certainly been evidenced to be very powerful, providing an additional point of view for disentangling the molecular mechanisms underlying asthma that might be missed without exploring the effect of environmental factors. Nevertheless, traditional GxE methods seem not to be sufficient, and several methodological improvements should be applied (1). These could be summarized by adopting a broader perspective of all the elements assessed, including a complete set of environmental exposures, the exploration of a larger proportion of the genome, the combination of association effects of genetic variants in the form of polygenic risk scores (PRS), and the consideration of the association with the individual genetic ancestry, among others (1). In addition, analyses of other omics layers such as epigenetics and transcriptomics in conjunction with environmental exposures would yield further insights into GxE effects (15).

These pieces of evidence demonstrate the need for the field of asthma genetics to be moved forward. Thus, gathering efforts to overcome the current limitations and continuing to take advantage of the utilities of GWAS approaches on imputed data should be the path to follow in parallel to less explored strategies that allow deeper coverage of the genome, as highlighted by many authors (9,12). In this sense, whole-genome sequencing (WGS) seems to be the optimal strategy (9). Although its usage in asthma research remains behind other fields (e.g., the investigation of rare diseases and cancer) (16,17), partially explained by the still high costs of next-generation sequencing (NGS) (18,19), it is expected to substantially grow in the next years (20). This should be added to the combination of information from several omics layers, a strategy firmly proposed as very promising for the identification of molecular markers of asthma but still scarcely applied in this field (5,21).

In summary, the publication by Shi *et al.* evidences once again the need for continued efforts in the investigation of genetic factors of asthma. The future of asthma research should be characterized by the application of the improvements widely proposed on the currently available genomic methods together with synchronized movements towards NGS-based strategies. Furthermore, the exploration of the genetic determinants of specific asthma phenotypes, interactions with environmental factors, and the combination with other sources of biological information should have a principal role. This might help us to define a new era of management of asthma characterized by personalized approaches of care with precision, which nowadays still seems on the verge of utopia.

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