Asthma heterogeneity: the increasing genetic evidence

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Increasing evidences for genetic factors underlying asthma phenotypic heterogeneity

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Asthma, the most prevalent chronic respiratory disease worldwide, results from a complex interplay between genetic, environmental and behavioral risk factors. The genetic component of asthma is substantial but the asthma loci, identified so far, explain only a part of the genetic risk. Although it is well admitted that asthma is a heterogeneous disorder, constituted by overlapping separate syndromes,[1,2] to which extent this phenotypic heterogeneity reflects differences in risk factors and molecular mechanisms is still poorly characterized. In the *Lancet Respiratory Medicine*, Pividori M and colleagues report intriguing novel insights into the genetics of asthma by age at disease onset.[3]

Age at asthma onset is key discriminating criteria in identifying asthma phenotypes.[1] Childhood and adult-onset asthma differ with respect to many aspects, including individual characteristics (e.g. gender, more females with adult-onset asthma), asthma prognosis (worse prognosis for adult-onset asthma), response to treatments (e.g. poorer response to corticosteroid therapy in adult-onset asthma), clinical features (e.g. adult-onset asthma is less allergic), and previous studies identified differences in genetic risk factors (e.g. the 17q21 genetic loci being specifically associated with childhood-onset asthma).[4] Using the large UK Biobank data, including 9,433 cases with childhood-onset asthma (onset before 12 years of age), 21,564 cases with adult-onset asthma (onset between 25 and 66 years of age) and 318,237 controls, Pividori M and colleagues made an important step forward in our understanding of the genetic contribution and architecture of childhood and adult-onset asthma. First, this is the first large scale genetic study providing evidences for a greater genetic component in early-onset as compared to late-onset asthma, resulting from both a higher number of genetic loci and stronger effects size of risk alleles identified in childhood-onset asthma than in adult-onset asthma. The authors quantified this difference, by estimating that the SNP-based heritability was about three times higher for childhood *vs*. adult-onset asthma. Secondly, combined with gene expression data and tissue enrichment analysis, the study revealed shared immune mechanisms, consistently with results from a large meta-analysis of worldwide asthma GWAS,[5] but also distinct mechanisms, with dysregulated allergy and epithelial barrier function genes in early-onset asthma whereas genes identified in late-onset asthma were preferentially expressed in lung. Thirdly, the study identified 28 new genetic loci, including the first adult-onset asthma specific association located in the 2q22.3 region.

The authors should be commended for the sophisticated analysis conducted to provide biological meaningful interpretation to the genetic loci identified, as well as the sensitivity analysis conducted to address the robustness of the findings to the specificity of the childhood and adult-onset asthma definition. Nevertheless, no study is entirely perfect and this study has weaknesses, many of which have been properly acknowledged by the authors. A further limitation relates to the fact that age at asthma onset is only one dimension of the disease heterogeneity. Indeed, both childhood-onset asthma and, certainly in a greater extent, adult-onset asthma bring together separate syndromes (including obesity-related asthma, occupational asthma, neutrophilic asthma, peri-menstrual asthma, severe and mild asthma,…). The intriguing observation of nearly 2·5-times more adult-onset than childhood-onset cases in the UK Biobank data might partly be related to a recall bias of remittent early-onset asthma (part of the subjects with mild childhood-onset asthma that remits could have been included in controls), which would lead to a more homogeneous moderate-to-severe/persistent asthma among childhood compared to adult-onset asthma. Under the reasonable hypothesis that different asthma phenotypes partly reflect different endotypes and etiologies, as recently illustrated by a genome-wide association study for moderate-to-severe asthma,[6] considering a highly heterogeneous phenotype likely leads to a "dilution effect" of the risk factors. Therefore, the possible stronger phenotypic heterogeneity among adult-onset *vs*. childhood asthma could have partly biased the results, by contributing to show a greater genetic contribution in childhood *vs.* adult-onset asthma.

An additional limitation that is shared with many previous genetic studies, relates to the fact that the environment was not considered although it is admitted that asthma results from the interplay of genetic and environmental factors (gene-by-environment interactions). On the one hand, environmental factors may modulate the effect of the asthma susceptibility genetic variants. This was well illustrated for the 17q12-q21 genetic variants, found associated to early-onset asthma, and for which stronger magnitude of genetic variant effects were found in individuals exposed to environmental tobacco smoke and to viral infection in early-life.[4,7,8] On the other hand, some genetic variants may confer risk only in the presence of specific environmental exposure, and would be detectable only if gene-by-environment interaction is sought.[9] There is a need to include environment in genetic studies, with environmental factors address accurately, i.e. accounting for the windows of exposure as susceptibility to environmental factors/stimuli may vary according to time of exposure.

If “big is beautiful” is the general rule in genetic epidemiology, Pividori M and colleagues further demonstrated that efforts in phenotypic characterization, i.e. accounting for the disease heterogeneity, is an important step forward to unravel the genetic architecture of asthma. The novel genetic loci identified by the present study need to be replicated in independent cohorts, including different ethnic population, and further investigated using information from additional omic layers (i.e. epigenomics, transcriptomics). Such approaches should help better understanding of the etiology and physiopathology of asthma, which in turn might lead to the development of targeted treatment and prevention strategies to stop the asthma epidemic.

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