Current perspectives

Resolving the etiology of atopic disorders by using genetic analysis of racial ancestry

Jayanta Gupta, MD, PhD,[a] Elisabet Johansson, PhD,[a] Jonathan A. Bernstein, MD,[b] Ranajit Chakraborty, PhD,[c] Gurjit K. Khurana Hershey, MD, PhD,[a] Marc E. Rothenberg, MD, PhD,[d] and Tesfaye B. Mersha, PhD[a] *Cincinnati, Ohio, and Fort Worth, Tex*

Atopic dermatitis (AD), food allergy, allergic rhinitis, and asthma are common atopic disorders of complex etiology. The frequently observed atopic march from early AD to asthma, allergic rhinitis, or both later in life and the extensive comorbidity of atopic disorders suggest common causal mechanisms in addition to distinct ones. Indeed, both disease-specific and shared genomic regions exist for atopic disorders. Their prevalence also varies among races; for example, AD and asthma have a higher prevalence in African Americans when compared with European Americans. Whether this disparity stems from true genetic or race-specific environmental risk factors or both is unknown. Thus far, the majority of the genetic studies on atopic diseases have used populations of European ancestry, limiting their generalizability. Large-cohort initiatives and new analytic methods, such as admixture mapping, are currently being used to address this knowledge gap. Here we discuss the unique and shared genetic risk factors for atopic disorders in the context of ancestry variations and the promise of high-throughput "-omics"–based systems biology approach in providing greater insight to deconstruct their genetic and nongenetic etiologies. Future research will also focus on deep phenotyping and genotyping of diverse racial ancestry, gene-environment, and gene-gene interactions. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Atopic march, food allergy, atopic dermatitis, allergic rhinitis, asthma, racial ancestry, admixture mapping, phenotyping, gene-environment interaction, -omics*

The development of atopic disorders often follows an age-dependent pattern that starts early in life and progresses (marches) from one tissue to another in the same patient, a phenomenon referred to as the atopic march (Fig 1).[1-3] The International Study of Asthma and Allergies in Children, which examined the global prevalence of atopic dermatitis (AD), food allergy (FA), allergic rhinitis (AR), and asthma, found that the prevalence of these disorders differed among races.[4,5] Delineating genetic and environmental risk factors that relate more specifically to certain atopic disorders and ancestry than to other factors provides valuable information to address the following questions: Are atopic disorders genetically inherited and/or interrelated? Do all atopic disorders share the same loci, or are there unique genetic loci associated with each atopic disorder? Are there ancestry differences in the risk of atopic disorders, and what are their potential sources? Is an individual ancestry or race a good predictor of atopic disorders?

In this review we discuss the genetics of atopic disorders, racial ancestry risk differences, the role of gene-environment interactions, and recent evidence of shared and unique causes of atopic disorders. Because the world is becoming highly multiethnic and racially admixed and thus genetically diverse, patients who self-identify as a particular race can have widely varying genetic ancestry.[6-8] Thus we discuss the admixture mapping (AM) approach from the vantage point of disentangling ancestry-specific risk loci.

Enormous progress has been made on developing high-throughput genotyping technology, but focus on devising high-throughput methods to standardize phenotyping is still in its infancy. Our review emphasizes the need for high-throughput methodologies for constructing causative models that will help resolve the underlying clinical and ancestral complex architecture of atopic disorders to yield greater insights. These approaches have the potential to target atopic phenotypes with interventions relevant to specific disorders and ancestry groups. In addition, we provide an overview of the complex components of atopic disorders, as well as future research strategies.

ATOPIC DISORDERS AND RACE

It has long been recognized that there are differences among racial and ethnic groups in the prevalence and severity of atopic disorders,[9-12] and these differences are believed to have both

From the Divisions of [a]Asthma Research and [d]Allergy and Immunology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati; [b]the Division of Immunology/Allergy Section, Department of Internal Medicine, University of Cincinnati, Cincinnati; and [c]the Center for Computational Genomics, Institute of Applied Genetics, Department of Molecular and Medical Genetics, University of North Texas Health Science Center, Fort Worth.

Supported by National Institutes of Health grants K01 HL103165, U19 AI066738, U19 AI070235, R01 DK076893, R01 HL132344, and R37 A1045898 and the Diversity and Health Disparities Award of the Cincinnati Children's Research Foundation.

Disclosure of potential conflict of interest: J. A. Bernstein is a PI and consultant for Genentech, Novartis, Boehringer Ingleheim, Astra Zeneca, GSK, TEVA, Shire, and CSL Behring; has NIAID funding; is a speaker for Shire, Genetech/Novartis, Greer and Baxalta; and is Editor-in-Chief of the *Journal of Asthma*. G. K. Khurana Hershey and T. B. Mersha have received grants from the National Institutes of Health. M. E. Rothenberg has consultant arrangements with Receptos, Celsus Therapeutics, Genentech/Roche, NKT Therapeutics; is an inventor for patents submitted and owned by Cincinnati Children's Health Medical Center; has received royalties from Teva Pharmaceuticals; has stock/stock options with Immune Pharmaceuticals, Receptos, Celsus Therapeutics, and NKT Therapeutics; and is a speaker for Merck. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 10, 2015; revised February 9, 2016; accepted for publication February 25, 2016.

Corresponding author: Tesfaye B. Mersha, PhD, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229-3039. E-mail: tesfaye.mersha@cchmc.org.

0091-6749/$36.00

© 2016 American Academy of Allergy, Asthma & Immunology

http://dx.doi.org/10.1016/j.jaci.2016.02.045

Abbreviations used
AD: Atopic dermatitis
AM: Admixture mapping
AR: Allergic rhinitis
eQTL: Expression quantitative trait loci
ETS: Environmental tobacco smoke
FA: Food allergy
GWAS: Genome-wide association study
LABA: Long-acting β_2-agonist
LD: Linkage disequilibrium
miRNA: MicroRNA

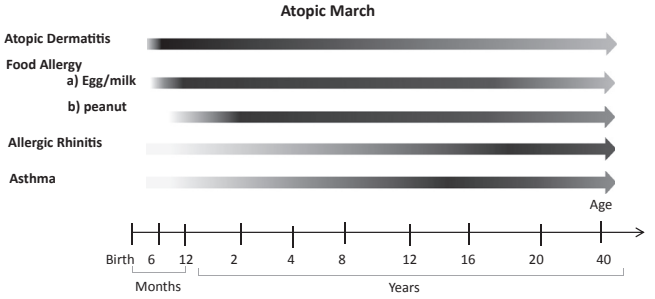

FIG 1. Schematic diagram illustrating age-dependent progression (ie, atopic march) of atopic disorders. FA and AD peak in the first years of life and decrease after that time. Asthma and AR increase over time as sensitization develops further. Food sensitization can be used as an early indicator for identifying children at risk for subsequent allergic disease who might benefit from early intervention.

environmental and genetic components.[13-15] However, it is notable that there are racial and ethnic minority populations in the United States that are underrepresented in cohort studies and clinical trials and that the vast majority of genome-wide association studies (GWASs) of atopic disorders conducted thus far have used populations of European ancestry.

Genomic studies often do not translate well from one race to another because of ancestral variation. Different populations have different linkage disequilibrium (LD) structures (otherwise known as haploblock structures), allele frequencies, and effect sizes,[16] and thus single nucleotide polymorphism (SNP) associations can be population specific.[17] As a consequence, our current knowledge might be skewed toward the European ancestry–based etiology of atopic disorders, and important genetic and environmental clues to population differences might have been missed. This is because most of the risk alleles and index variants are derived by using commercial genotyping arrays ascertained from populations of European ancestry. This drawback biases the generalization of the results of these studies to other ancestral populations because not all atopic disorder loci found in Europeans are transferable to all populations. Identification of causal variants through transancestry fine mapping and sequencing in different populations will help us understand the genetic contribution to the disparity in atopic disorder prevalence. In particular, the differential and lower level of LD in patients of African ancestry will likely greatly improve the fine mapping of causal variants using transancestry meta-analysis efforts.

In addition, many of the diagnostic tools used for atopic diseases, such as pulmonary function tests, are developed mainly for patients of European ancestry. However, marked differences in lung function and allergic sensitization between children of different racial backgrounds exist, even when known confounders, including socioeconomic status, are taken into account.[18-20] For example, spirometric assessments of FEV_1 and forced vital capacity are known to be reduced by 14% in subjects of African ancestry compared with those of European ancestry.[21-24] The use of race-specific reference equations can help minimize such differences and improve accuracy.[20,25]

Differences in racial ancestry can have implications for clinical practice; an example is the use of long-acting β_2-agonists (LABAs) in patients with asthma. Although combining corticosteroid treatment with a LABA can lead to better asthma control for most patients, a small proportion of patients, including African Americans, appear to be at increased risk for harmful effects and even fatal outcomes from the use of LABAs.[26] The reason for this observed difference is still controversial. Some studies have suggested that genetic differences in the β_2-adrenergic receptors and their interaction with race might be responsible.[27,28] Several studies have shown that African American asthmatic patients have an increased likelihood of treatment failures and overall differential response to treatment that can be caused by genetic variants specific to their ancestry.[29,30] However, race is a crude proxy to genetic ancestry and falls short of explaining the variation in response to medication.[6]

Investigators trying to address the knowledge gaps in our understanding of the racial aspects of atopic disease are faced with several challenges. Assembling minority cohorts large enough to power the detection of genetic associations can be difficult and requires very active outreach, especially to racial/ethnic groups that might be underserved by the health care system. Another approach is to increase power by using newer statistical methods, such as AM. In conventional association studies the high degree of recent genetic admixture in many racial minorities in the United States can lead to population stratification–ancestry differences between cases and control subjects. It is well recognized that racial minorities in the United States, including African-American and Latinos, have a lower socioeconomic status, which is often associated with environmental factors, such as diet, presence of allergens, and pollution exposure.[15] These factors can have a direct effect on the development of allergic disorders and need to be carefully adjusted for in statistical analyses.[31]

Different ancestral populations have different proportions of rare genetic variants, and it has been shown that populations of African ancestry have up to 3 times as many rare variants as populations of European and Asian origin.[32] Although rare variants are believed to be enriched for functionality,[33,34] they present a challenge in association studies because of the large sample sizes needed for their detection.[35,36] Transancestry studies have been invaluable in deconstructing the genetic architecture of complex diseases, such as asthma. They provide an opportunity to replicate signals in independent populations and for meta-analyses to boost statistical power. For example, African genome analysis enables prioritizing candidate variants in follow-up and fine-mapping functional variants because of the unique short-range LD in African ancestry. The use of a population with short-range LD will result in the greatest localization success rate in distinguishing the causal SNP from its neighbors.[37-39] The recent completion of whole-genome sequencing data from

Download English Version:

https://daneshyari.com/en/article/5646770

Download Persian Version:

https://daneshyari.com/article/5646770

Daneshyari.com