Genetics of Allergic Diseases

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KEYWORDS

• Allergic disease • Genetics • Single nucleotide polymorphism
• Genome-wide association study • Next-generation sequencing • Epigenetics
• Transcriptome

KEY POINTS

- Nearly 100 asthma genes/loci in addition to multiple genes/loci for atopic dermatitis, allergic rhinitis, and immunoglobulin E have been identified by genome-wide association studies.
- Next-generation sequencing strategies are increasingly being used to hone in on the causal variants associated with allergic diseases.
- A goal of the genetics of allergic disease is to better match individualized treatments to specific genotypes to improve therapeutic outcomes and minimize adverse effects.

INTRODUCTION

Coca and Cooke were the first to describe asthma, atopic dermatitis (AD), allergic rhinitis (AR), food allergy, and urticaria as "phenomena of hypersensitiveness" at the annual meeting of the American Association of Immunologists in 1922.[1] Just prior to and following this discourse, there was considerable focus on the relative influence of the environment versus hereditary factors on allergic diseases, with family-based twin and migration studies providing the earliest and most compelling evidence for genetic contributions.[2–6] Studies on the prevalence of allergic traits in relation to family history demonstrated incremental increases in risk of developing asthma, AR, or AD with the presence of at least 1 parent with allergic disease, and greater than 3 times the risk if allergic disease occurred in more than 1 first-degree relative.[7] To date, and despite the dramatic technological advances that have led to the identification of hundreds of genetic variants in genes associated

Disclosure Statement: The authors have nothing to disclose.
K.C. Barnes was supported in part by the Mary Beryl Patch Turnbull Scholar Program; R.A. Ortiz was supported by NHLBI Diversity Supplement 3R01HL104608-02S1.
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Immunol Allergy Clin N Am 35 (2015) 19–44
http://dx.doi.org/10.1016/j.iac.2014.09.014 **immunology.theclinics.com**
0889-8561/15/$ – see front matter

with asthma, AD remains one of the most reliable tools for prognosis of allergic disease.

Approaches for disentangling the genetic basis for the allergic diseases have evolved as technological tools for the field of molecular genetics have progressed. With the introduction of the polymerase chain reaction (PCR) in the 1980s, DNA fragments in the human genome could be amplified and then studied for variable fragment lengths of repeats, or genetic fingerprinting. With a catalog of microsatellite markers spanning the human genome, genome-wide linkage studies emerged as a robust approach for identifying genetic hot spots associated with complex traits. Nearly a dozen genome-wide linkage screens were performed on asthma and its associated phenotypes,[8–18] for which multiple chromosomal regions provided significant evidence for linkage. From several of these family-based linkage genome-wide screens, 6 novel asthma genes were identified by positional cloning.[18–23] Similarly, multiple linkage studies were performed for AD[24] and AR.[25–29] It was frequently observed that loci overlapped across associated traits; for example, Daniels and colleagues[8] observed overlapping linkage peaks with quantitative traits associated with asthma including total serum IgE, skin test index, and eosinophil counts, as well as atopy as a qualitative trait. Alternatively, the multiethnic *Collaborative Study on the Genetics of Asthma* reported linkage peaks that were specific to different racial and ethnic groups.[9]

With the publication of initial efforts in sequencing the human genome,[30,31] the opportunity to genotype markers directly in genes of interest was greatly expanded as polymorphisms were identified in the approximately 20,000 to 25,000 genes across the 3 billion chemical base pairs that make up human DNA. Relying upon one of the simplest of these polymorphisms, single nucleotide polymorphisms (SNPs), and relatively simple structural variants, such as insertions/deletions and repeats, this advancement allowed researchers to expand genetic studies beyond linkage toward the genetic association study design. For asthma alone, literally hundreds of candidate genes have been elucidated, and summarized elsewhere,[32–35] representing the relative success of this approach.

THE GENOME-WIDE ASSOCIATION STUDIES ERA

Following completion of the Human Genome Project, the International HapMap Project[36–38] cataloged genomes representing 4 biogeographical groups (whites from the United States with northern and western European ancestry; Yorubans from Ibadan, Nigeria [YRI]; Han Chinese from Beijing, China [CHB]; and Japanese from Tokyo, Japan [JPT]) to advance the development of new analytical methods and investigating patterns of genetic variation. Simultaneously, the technological capacity to rapidly (and cheaply) genotype more than 1 million common (>5%) SNPs on thousands of DNA samples from patients phenotyped for various complex clinical traits took the spotlight, and the GWAS era took off. The content of commercially available GWAS chips grew exponentially with expansion of the human genome catalog through the Thousand Genomes Project (TGP),[39] and the capacity for discovery of genetic associations has likewise increased with the development of SNP genotype imputation methodologies,[40,41] whereby genotyped content from the chip can be combined with the more than 35 million sequenced variants cataloged in the TGP. In the span of only 7 years, over 1924 publications and 13,403 SNPs associated with various complex and quantitative traits[42,43] have been generated by GWAS (**Fig. 1**A).

GWAS have been widely employed in the field of allergic disease. Although the precise number of GWAS are difficult to determine, approximately 40 asthma, 3 atopy,