Book Review

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The Hereditary Basis of Allergic Disease. Edited by S. T. Holgate and J. W. Holloway. Basel: Birkauser Verlag, 2002. Pp. 198. $142.

Recent years have seen an exponential growth in knowledge of the DNA sequence of the human genome. Simultaneously, high-throughput technologies for analysis of the genome and genetic variation have been developed, allowing the extraction of an amount of genetic information many magnitudes greater than was possible just a few years ago. This has led to a dramatic increase in the number of studies aimed at understanding the genetic background of complex diseases, followed by an enormous number of reports from such studies. This increase can be expected to accelerate even further in the coming years. For allergy, as for other complex diseases, both linkage and association studies have put forth mostly ambiguous conclusions—interesting results often followed by a lack of replication by other research groups. On this background, *The Hereditary Basis of Allergic Diseases* is a daring enterprise to attempt to cover the subject. The reader who seeks an extensive review of linkage and association results will be disappointed; on the other hand, few unambiguous conclusions about allergy have been reached so far, and such a text would likely be outdated fairly rapidly. This problem is, to a large extent, avoided by the editors, S. T. Holgate and J. W. Holloway, in their focusing the main parts of the book not only on possible genetic etiological factors but also on mechanistic issues.

In the first of 11 chapters, Tarja Laitinen gives an inspired introduction to the heredity of allergy and asthma that covers disease-specific subjects, such as twin and family studies and modes of inheritance, followed by a more general section on disease models of complex diseases, strategic issues, and the role of selection in mapping attempts. A major conclusion of this chapter is that the heritability of asthma is on the order of 60%–80%. Despite considerable efforts, no clear conclusions can be drawn from linkage and association studies, suggesting that, at the population level, dozens of different loci are involved in the development of asthma and that significant locus heterogeneity exists between families.

In the second chapter, genome scans for asthma are described. Only four genome scans are described in detail. Because no clear conclusions can be drawn and because, since the book's publication, genome scans with more significant results have been reported and will continue to be reported, this chapter soon will be mainly of historical interest. In this chapter, as in the remaining chapters, impressive *P* values are reported, which might lead the unexperienced reader to false conclusions. A discussion of genomewide significance, here or elsewhere in the book, would have been appropriate.

In the third chapter, the role of founder populations in mapping complex disease genes is discussed. The chapter is mainly a very short description (five pages long) of the author's (Carole Ober's) studies in the Hutterites.

The next seven chapters discuss the role of different functional candidate genes or gene families in allergic diseases or, rather, in asthma. As in the rest of the book, there is little or no discussion of other clinical allergy phenotypes, like allergic rhinitis or atopic dermatitis. Maybe a more appropriate title for the book would have been "The Hereditary Basis of Asthma."

The importance of immune regulatory responses is covered in N. Hizawa's chapter on genetic regulation of specific IgE responsiveness and in A. H. Mansur's chapter on genetic variation at the HLA and TCR loci and on the development of allergy and asthma. These two chapters contain very detailed discussions and >200 references. In the chapter by N. Hizawa, there is some discussion of candidate regions suggested by a genome scan in which the maximal NPL scores were between 2.23 and 1.28. First, it should have been emphasized that NPL scores are not the same as common LOD scores, and, second, it should have been stressed that the *P* values obtained are far from reaching genomewide significance and are very likely false-positive observations owing to chance.

In chapter 6, chromosomal region 11q13, one of the first candidate regions to be identified by linkage to atopy, is discussed. Again, initial positive findings are followed by a few supportive studies but also by several negative reports. Interestingly, some of the studies indicate maternal inheritance of disease susceptibility. One obvious functional candidate gene located in this region, namely, the gene encoding the β subunit of the high-affinity IgE receptor, has attracted special interest. Several studies report association between polymorphisms of this gene and measures of atopy, but, again, several studies fail to reproduce these findings.

In the next chapters, a series of functional candidate genes are discussed, including genes for IL-13, IL-13 receptors, IL-9, and the IL-9 receptor; genes for nitric oxide syntases; and genes involved in regulation of leukotriene production and activity. In these chapters, the main focus is on asthma—to some extent on disease etiology but to a larger extent on pathophysiological mechanisms. Especially in the chapter on leukotrienes, the important subject of genetically determined treatment response is discussed. In this chapter alone, 140 references are listed.

In the final short chapter, genes affecting asthma severity and the extent to which these genes may or may not differ from genes of etiological importance are discussed. Only a

limited number of studies of disease severity have been performed; therefore, only a few genes are discussed, including genes for IL-4 and its receptor, the β_2-adrenergic receptor, and for α_1-antitrypsin.

The reader who seeks a detailed review of genetic epidemiological methods and of results of studies on allergic diseases should seek this information elsewhere. On the other hand, the book gives a thorough description of a number of functional candidate genes that might be involved in the etiology of these diseases and that are surely important for the pathophysiology. In that respect, most of the chapters are very informative, and the list of references is extensive (700 total). It should be borne in mind, however, that it is still impossible to predict the extent to which genetic susceptibility to allergy and asthma will be explained by variation in obvious functional candidate genes. A few of the recent highly publicized studies on allergy-susceptibility genes have identified genes that nobody would have suspected, like ADAM33 (chromosome 20), PHF11 (chromosome 13), DPP10 (chromosome 2), and GPRA (chromosome 7), but it is important to stress that, currently, it is not clear to what extent these genes explain part of the genetic susceptibility to allergic diseases.

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