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The Hereditary Basis of Allergic Diseases

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Preface

Allergic diseases are complex and involve a range of environmental factors interacting with a susceptible genotype. The familial clustering of diseases, such as asthma and hay fever, have been recognised for over two centuries, but the basis for this has had to await the molecular biological revolution. Estimates of the contribution that genetic factors make to asthma susceptibility range from 35–70%. For the majority of allergic diseases, segregation analysis has not identified a consistent Mendelian pattern of inheritance, which, when combined with multiple phenotypes and environmental interactions, has made identifying candidate genes especially difficult and, at times, controversial. Part of the difficulty has been lack of agreement over phenotype definitions, reduced power of studies to predict linkage and association, and, importantly, lack of true heterogeneity between populations.

Despite these difficulties, the last decade has witnessed enormous progress in this field. *The Hereditary Basis of Allergic Diseases* brings together scholarly reviews of the emergent and promising genetic factors influencing susceptibility to and progression of allergic diseases such as asthma. There are important, up-to-date contributions on the understanding of the heritable basis of atopy and asthma phenotypes (Tarja Laitinen), and these have been used to undertake genome-wide searches to identify linkage to specific chromosomal regions (Mathias Wjst). The importance of immune regulatory responses is highlighted by focused contributions on genetic regulation of specific immunoglobulin E (IgE) responses and the importance of human leucocyte antigen (HLA) and T-cell receptor variation and altered signalling through FcεR1 receptors.

The recognition that allergic disorders result from an imbalance between Th1 and Th2 cytokines in favour of the latter provides the basis for further key chapters. This includes chapters on interleukin (IL)-13 polymorphism (Tineke Van der Pouw-Kraan and colleagues) and a contribution from Roy Levitt and colleagues on the role of polymorphism in the IL-9/IL-9R system in asthma. The target tissue in which an allergic disease expresses itself is also subject to genetic influences. Thus, genetic factors influencing asthma severity and bronchial hyper-responsiveness are well covered by Peter Paré and colleagues.

It is not possible to refer to allergic disease without considering the role of individual mediators. The leukotriene pathway is especially relevant to asthma, and the recent identification of polymorphism in some of the synthetic enzymes has not only helped sub-phenotype asthma, e.g., aspirin-intolerant asthma and the A–444C polymorphism of the LTC_4 synthase promoter, but, as pointed out by Ian Sayers and Tony Sampson, also provides a basis for drug variation in therapeutic responses. A mediator that has attracted much recent interest in asthma and rhinitis is nitric oxide. The recent identification of genetic variants in the nitric oxide synthase enzymes, as described by Drs Grasemann and Drazen, is of considerable interest.

The ongoing research into genetic factors behind the development and pathogenesis of atopy and allergic disease, as exemplified by the studies described in this book, will in due course provide us with a greater understanding of the fundamental mechanisms of these disorders. Study of these genetic factors in large longitudinal cohorts with extensive environmental information will allow the identification of both the environmental factors that in susceptible individuals trigger allergic disease and the periods of life in which this occurs, potentially leading to prevention of disease by environmental modification. Identification of genetic variants that predispose to allergic disease will result in several outcomes. First, the greater understanding of the susceptibility factors for the disease will allow development of specific new drugs both to relieve and prevent symptoms. In addition, different genetic variants may also influence the response to therapy. The identification of individuals with altered response to current drug therapies will allow optimisation of current therapeutic measures. Second, the identification of susceptibility factors for allergic disease will allow early identification of susceptible individuals, thus allowing them to be targeted at an early age for both therapy and environmental intervention such as avoidance of allergen exposure. Thus, genetic screening in early life may become a practical and cost-effective option in preventing allergic disease.

Overall, this book provides a comprehensive approach to advancing the understanding of the genetic factors influencing allergy. With the unravelling of the code of the human genome, the identification of the 27,000 or so genes, of which almost 60% are still with unknown function, will provide an ample challenge for the future. As scientists embark on further mining this extraordinary set of data, it is rewarding that already good progress is being made in uncovering genes involved in a disease area that touches almost everyone at some time in their lives. We are extremely grateful for all the time and effort that the authors have put into their chapters, which, as a consequence, led to a state-of-the-art publication in this field.

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