HLA and Disease Associations

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Preface

The human leukocyte antigen (HLA) or tissue types are the products of a rapidly developing field of knowledge within the last 20 years. In the early stages of the research many investigators suspected the existence of a complex series of transplantation antigens, but it was widely believed that these antigens would not be well-defined even in this century. Yet in the last two decades as many as 124 different HLA antigens determined by at least 7 very closely linked genes located on the short arm of chromosome 6 have been identified and subsequently agreed upon by an international nomenclature committee.[1] Extensive international collaboration fueled by the potential clinical application of these antigens to clinical transplantation has advanced the field rapidly. There were nine international histocompatibility workshops held during this period. Although identification of HLA antigens was of primary clinical importance in transplantation and of great basic interest in human genetics and anthropology,[2] a rather unexpected bonus has been the determination that HLA antigens are associated with disease susceptibility to a greater extent than any other known genetic marker in man.

In the past, many genetic polymorphisms have been suspected to be associated with diseases. The most extensively studied markers are blood groups, enzymes, and serum proteins. A comprehensive account of published studies, totalling approximately 1,000, of these markers is available in a book by Mourant et al.[3] Aside from the extensive nature of these studies, one is struck by the data showing only very weak association of diseases with these markers. The relative risk in all of these reports has been less than 2. One of the most thoroughly investigated associations is that of carcinoma of the stomach with blood group A. Analysis of the data on 53,155 patients shows a relative risk of 1.22 indicating that a type A person is only 1.22 times more likely to develop stomach cancer than those who are not type A.[3]

In contrast, the association between HLA-B27 and ankylosing spondylitis has a relative risk of 69. There are many diseases in which relative risk value is greater than 2. Thus, the available data on HLA associations with diseases have far surpassed all the existing knowledge in this field. What is more remarkable is that HLA and disease associations were developed principally in the last 10 years during which approximately 4,000 articles have been published. This burst of activity occurred throughout the world in many different centers, as witnessed by the diverse sources of the bibliography. In many of these diseases the genetic

component had long been suspected but now for the first time it has become possible to actually find the genetic inheritance through a well-defined marker.

It was rather surprising that the strength of the association of HLA-B27 with ankylosing spondylitis, first described by our laboratory in 1973[4] and by Brewerton et al.[5] which had been the primary stimulus for the study of other diseases has, in fact, not been exceeded by the many other diseases that have been subsequently found to be associated with the HLA antigens. Thus among more than 530 diseases that have been studied in 4,000 publications, relative risk that is higher than that for ankylosing spondylitis has not been noted. To a certain extent this might be considered to have been somewhat of a disappointment because many of us had expected more diseases to have such a high association. In addition, some diseases that "theoretically" should have been associated with HLA have not yielded the expected association. Instead a rather obscure disease, ankylosing spondylitis, continues to be the disease with the strongest association.

Despite these disappointments, from the research work of the past 12 years, the actual degree of HLA association with various diseases is gradually becoming clear. Although a given single study may have overstated certain associations, there has now been time enough for their confirmation in many different laboratories and thus a more accurate picture of the degree of association is slowly emerging. In this book we have tried to stay close to the data published by the various authors and have refrained from too many interpretations. An attempt has been made for comprehensive coverage, even in instances where we have had suspicions that the data may not have been completely correct. Associations that are true tend to be validated by subsequent studies in other laboratories and those that are spurious are not confirmed in later reports. Important studies on important diseases tend to be followed up whereas findings that are too suspect tend not to be reinvestigated by others. Thus, we leave the reader to draw his conclusions from the comprehensive data presented in this book.

One of the highlights in the study of HLA and disease was an international symposium held in Paris in 1976.[6] This volume presents many of the associations known up to that time, together with ideas on the mechanisms responsible for these associations. Reviews of the literature have been published by Braun in 1979[7] and by Ryder et al.[8] The present book is meant to be a comprehensive account in which all the articles published on HLA and diseases that we are aware of are included. Many of the studies demonstrating associations with the new HLA-DR locus antigens have been undertaken since the publication of the aforementioned reviews.

We hope that this book will serve as a reference for all those who may wish to initiate studies in this interesting area. We also hope that our colleagues will not be too harsh with us for not offering a study involving a resynthesis or strong interpretation of the literature. Our hope has been to make it easy for the reader to arrive at his own conclusions for each of the disease categories.

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Contents

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Charles A. Pollock has worked on this project from the beginning when we started the computerized database and literature search. The original programs to analyze the population frequency data stored in the Data General computer was written by him. He continued to provide his enthusiastic support even after accepting a new position outside the university. Various changes and modifications to upgrade this program were made by Yong Cho, Ron Oblea, and Nori Sasaki.

In the later stages of this project it became necessary to utilize the flexibility and the convenience of a wordprocessor and also a letter-quality printer. In the laboratory these facilities were available only on the microcomputers and hence a new set of programs for these computers were written by Kevin Hanson, David Kandasamy, and Dennis Aoki. The final manuscript was produced by these programs.

Dr. Pawel Kaszubowski translated many of the papers without an English abstract and also helped in the interpretation of the clinical data in these reports. Dr. Sarina Cats has kindly read the entire manuscript and provided valuable comments.

The manuscript was typed by Pam Kaisaki and the editorial assistance was provided by Rita Loew.