KEY POINTS

• The common autoimmune liver diseases (type 1 autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis) do not exhibit simple Mendelian inheritance attributable to a single gene locus.

• These autoimmune diseases are “genetically complex”, arising from the interaction of both environmental factors and one or more host genes.

• The alleles that are permissive for autoimmunity are common in the “healthy” population and by themselves are neither necessary nor sufficient for disease to occur.

• Most of the evidence for a genetic component in the pathogenesis of autoimmune liver disease is based on case–control (association) studies. Informative (multi-plex) families are rare, and conventional linkage data are not available.

• The most consistent data we have suggest strong links with the major histocompatibility complex (MHC) on chromosome 6p21.3. Possible links with other susceptibility alleles on a number of chromosomes are more speculative.

• Genetic effects on both disease susceptibility/resistance (i.e., disease risk) and disease progression (i.e., phenotype) have been documented. Identification of the latter provides the necessary background for a better understanding of the disease pathogenesis. Identification of the latter alleles may be more immediately useful in developing predictive indices for disease prognosis.

• Overlap syndromes and comparison with other autoimmune diseases indicate that there may be shared (common) disease susceptibility alleles acting as non-(disease)-specific promoters of autoimmunity. These findings indicate the activation of common pathways in the pathogenesis of autoimmunity and the processes underlying tolerance breakdown.

• Current knowledge of the genetics of autoimmune liver disease is incomplete, but the Human Genome Project has identified an astounding degree of polymorphism in our genes; 5 yr on, we still face a major challenge in integrating the “new genetics” into medical practice.

• The key issues for future investigators will be: defining the genetic mechanisms whereby self-tolerance is broken; defining the genetic mechanisms that determine the rate of disease progression; and identifying genetic markers to predict both progression and malignancy.

• The same HLA genes and haplotypes that are important in autoimmune liver diseases are also implicated in susceptibility and resistance to infectious liver disease, opening a new avenue for future investigations.

INTRODUCTION

Autoimmune liver diseases are not classical Mendelian autosomal or sex-linked genetic traits. However, there is considerable evidence that our genes play a significant role in determining individual susceptibility to (and progression of) these diseases. In the absence of a “simple” pattern of inheritance, attributable to a single gene locus, autoimmune liver diseases are classified as “genetically complex.” Variation at a gene locus gives rise to a number of alleles. When alleles are rare within a population (less than 1%), they are referred to as mutations. When alleles are common, they are referred to as polymorphisms. To the geneticist, “complex traits” are those in which one or more genes (alleles) acting alone or in concert increase or reduce the risk of a disease or syndrome (1). In Mendelian diseases, the permissive alleles are rare in the normal population (i.e., mutations), whereas in complex diseases, the permissive alleles are common (i.e., polymorphisms). Furthermore, it appears that alleles that are permissive for autoimmunity are not themselves abnormal and may be present in a large proportion of the “healthy” population. This finding suggests that inheritance of a specific allele or group of alleles is neither necessary nor sufficient for disease genesis but will simply increase (or reduce) the likelihood (risk) of disease.

Investigations of the genetic basis of complex disease hold three promises: (1) they will aid disease diagnosis, especially for near-Mendelian diseases; (2) they will identify alleles that
may inform disease management and therapy (in this respect pharmacogenetics is particularly important); and (3) they will identify alleles that inform the debate on disease pathogenesis. In the context of autoimmune liver diseases, the third promise is one that is most likely to bear fruit and here immunogenetics is the key.

Immunogenetics is concerned with the genes that regulate the immune response. Investigators in the mid-20th century, driven by clinical need, discovered complex systems in both mice and humans that govern the outcome of transplanted tissues: the major histocompatibility complexes (MHCs). For a considerable time it was thought that MHC genes were the only immune response (IR) genes. However, following completion of the human genome mapping project, we now know that nearly all human genes are polymorphic, and therefore any gene expressed in lymphoid tissue has the capacity to influence the immune response and thus (in the context of this chapter) disease risk. In the post-genome mapping era, understanding the role of host genes in autoimmune disease presents a major challenge. Approximately 11,000 of the 33,000 human genes may be expressed in lymphoid tissues, and there are more than 10.4 million variations in the genome (2). The most widespread of these are single-nucleotide polymorphisms (SNPs), which account for 90% of the human genetic polymorphisms. A comprehensive database of human genomic variations, dbSNPs, can be found at: http://www.ncbi.nlm.nih.gov/SNP/ (2).

INVESTIGATING COMPLEX DISEASE GENETICS

As the terminology implies, identifying disease-promoting mutations and polymorphisms (DPMs and DPPs) in “complex” diseases is not as simple as it may be for most Mendelian diseases. Classical approaches such as linkage analysis require multiplex families or sibling pairs and are most effective in near-Mendelian complex traits, in which there are few susceptibility loci and high levels of penetrance (1). Association analysis is the method of choice for diseases in which penetrance is low, onset is late, and/or families are rare (1,3–5). Almost all the work in autoimmune liver disease has been through association studies, a choice dictated by the relative paucity of multiplex families for study (5). Consequently, there are no linkage data from either genome scanning or large-scale family studies for any of the three diseases discussed here.

In association studies, two different genetic effects can be identified. Possession of an allele may increase or reduce the risk of disease (i.e., render an individual susceptible to or confer protection from the disease), or possession of an allele may determine the clinical phenotype, for example, disease severity or progression. These two effects are not exclusive, and one susceptibility allele may modify the effect of another.

The key to success with association analysis is adequate numbers (6). Thus the statistical power of any study to identify DPMs and DPPs is directly proportional to the number of patients and controls studied and the number of different candidate alleles assessed. Other common errors in association studies include use of poorly matched controls, analysis of multiple subgroups, and over-interpretation of the data (5–8). Association studies must be designed to include large, well-established patient series and appropriate controls. Calculations of statistical power should be performed prior to any study to determine the necessary sample size, and ideally all findings should be replicated in a second series prior to publication (5–8).

Two other factors that have a strong influence on our understanding of the genetics of complex diseases in general are strong publication bias in favor of significant probability values (making non-significant data difficult, or even impossible, to publish) and “case ascertainment bias,” which can arise when association studies are performed (as they most frequently are) at national and regional referral centers (5,6). Referral centers often see a higher proportion of “unusual” cases (most often a higher proportion of severe cases), and the case load at such centers rarely reflects the total disease population. Consequently, alleles may be falsely identified as “susceptibility alleles,” when their true role is in determining the disease phenotype. A recent example of this phenomenon was the identification of DRB1*0801 as a determinant of disease progression (severity) in primary biliary cirrhosis (9), which is discussed below.

WHERE TO LOOK: SELECTION OF CANDIDATE GENES

Gene loci for investigation are usually selected on the basis of either a known or potential functional role in disease pathogenesis or prior knowledge of linkage to or associations with other (similar) autoimmune diseases. As stated above, there are no linkage data for the three diseases discussed here, and knowledge of disease pathogenesis is patchy. Therefore, the latter criterion is the most frequently applied in the selection of candidate genes. The justification for this approach is based on the understanding that autoimmune diseases share common immune response pathways and often have similar genetic associations (10). It is reasonable to assume that only a proportion of the DPPs identified in any disease will be disease specific and that the remainder (even the majority), although no less important, may be nonspecific promoters of autoimmunity (10).

In autoimmunity, most studies have concentrated on polymorphism in the genes that control the adaptive immune response, centered on the role of T and B cells and the maintenance of immune homeostasis (tolerance to self). However, there is a growing interest in role of genes involved in innate immunity and the interaction with bacterial pathogens. This new interest in innate immunity has been fuelled by a number of factors. First, with the completion of the Human Genome Project, we have a much better knowledge about non-MHC IR genes in general. Second, recent studies in inflammatory bowel disease have been very successful in identifying major susceptibility loci outside the MHC (11). All of these genes (CARD15, CARD4, and CARD8) are important determinants.