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Genetic Factors Affect the Etiology, Clinical Characteristics and Outcome of Autoimmune Hepatitis

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Abstract

Autoimmune hepatitis (AIH) is characterized by chronic inflammation of the liver, hypergammaglobulinemia, serum autoantibodies, histologic evidence of interface hepatitis, and a favorable response to immunosuppressive treatment. Although the etiology of AIH remains undefined, human leukocyte antigen (HLA) class II alleles have been associated with disease onset for decades. AIH resistance and severity are presumably linked to HLA alleles as well. Individuals in different geographic regions worldwide may have varying susceptibility alleles that reflect indigenous triggering antigens. In this review, we describe the influence of HLA alleles and gene polymorphisms on AIH along with the results of genome-wide association studies on this disease.

Keywords: HLA, autoimmune hepatitis, primary biliary cirrhosis

Introduction

Autoimmune hepatitis (AIH) is characterized by chronic inflammation of the liver, hypergammaglobulinemia, serum autoantibodies, histologic evidence of interface hepatitis, and a favorable response to immunosuppressive treatment [1-3]. Two types of AIH have been identified to date based on serum autoantibody profiles: type 1 (AIH-1) that is positive for anti-nuclear and/or anti-smooth muscle antibodies and type 2 (AIH-2) defined by positivity for anti-liver kidney microsomal type 1 or anti-liver cytosol type 1 antibodies. Although the etiology of AIH is unknown, it is believed to be a multifactorial polygenic disease that is presumably caused by interactions among trigger and environmental factors in genetically susceptible individuals.

Human Leukocyte Antigen

Located in the major histocompatibility complex (MHC), the human leukocyte antigen (HLA) loci are the most genetically diverse loci in the human genome. The HLA genomic sequence was one of the first large regions to be fully deciphered [4] and has been found to contain approximately 260 genes over a span of roughly 4 Mb on chromosomal region 6p21.3 (Figure 1). The highly

polymorphic genes that encode the classical HLA class I and II alloantigens play important roles in the specificity determination of adaptive immune responses, susceptibility to autoimmune and infectious diseases, and transplantation outcome.

The IMGT/HLA database provides an online locus-specific database (LSDB) of the allelic sequences of HLA genes and nomenclature for the analysis of HLA systems. HLA antigen/allele designations are described in a recommended and standardized convention (http://hla.alleles.org), which starts with the HLA prefix denoting the HLA region, followed by a hyphen to separate the particular HLA locus from the HLA prefix. An asterisk (such as in *HLA-A** and *HLA-DRB1**) is a separator for the next set of digits. The ensuing one or more two-digit numbers are separated by colons (i.e., field separators). The first set of digits describes the allele family that corresponds to the serological antigen carried by the allotype (field 1). The second set of digits specifies one or more nucleotide substitutions that change the amino acid sequence of the encoded protein (i.e., non-synonymous substitution; field 2). The third set of digits distinguishes alleles that denote any synonymous mutations within the coding frame of the gene (field 3). The mutations outside of the coding region, such as

introns or 5’ or 3’ untranslated regions, are distinguished by the use of a fourth set of digits (field 4). A suffix may also be added to specify expression level or other non-genomic data by indicating A (‘Aberrant’ expression), C (present in the ‘Cytoplasm’ but not on the cell surface), L (‘Low’ cell surface expression), N (‘Null’ allele), Q (‘Questionable’ expression), or S (expressed as a soluble 'Secreted' molecule but not present on the cell surface).

HLA typing was initially carried out by serological analysis. However, following the introduction and evolution of the polymerase chain reaction (PCR), many variations of HLA typing methods, such as PCR-restriction fragment length polymorphism (PCR-RFLP), PCR-single strand conformation polymorphism (PCR-SSCP), PCR-sequence-specific oligonucleotides (PCR-SSO), and PCR-sequence-specific primers and sequence-based typing (PCR-SBT), have emerged. As most of the polymorphic sequence motif loci are localized in the second and third exons of HLA class I and in the second exon of HLA class II, the minimum requirements for HLA-DNA typing are complete sequencing of these areas of interest. The two methods that are currently predominant in HLA-DNA typing are PCR-SSO, such as the Luminex commercial methodology, and PCR–SBT by the Sanger method using a capillary auto-sequencing device. These

methods capture parts of sequence information in exons 2 and 3. Recently, high-throughput genotyping of HLA genes has been established using next generation sequencing (NGS) techniques [5] that can determine HLA allele sequences derived from a single DNA molecule with a high level of parallelism. HLA-DNA typing using the NGS platform provides numerous benefits, such as high-resolution genotyping at the 4-field level, a reduction in phase ambiguity, high through-put typing using barcodes, detection of null alleles, and cost effectiveness as compared with conventional methods. High-throughput genotyping of HLA genes in patients with autoimmune diseases is presently underway.

Associations of HLA with AIH Susceptibility

A genetic predisposition to AIH has been attributed to several MHC genes, especially those that code for HLAs. HLA serology was studied extensively in AIH patients from 1980 to the early 1990s (Table 1). In northern European populations, the A1-D8-DR3 haplotype was associated with susceptibility to AIH [6-8]. By excluding the DR3 antigen, DR4 was found to be a secondary antigen related to the disease [8] and was linked to AIH onset in Japan [9]. Since DR3 is scarce in

the Japanese general population, the susceptibility genes for AIH are presumably different from those in Caucasians.

Following the advent of HLA typing by PCR methods, a number of studies were published on culpable HLA alleles. In Mexican [10], Japanese [11, 12], and Korean [13] populations, AIH was associated with the DRB1*04:04* and DRB1:*04:05* alleles. In European populations, a link was reported between AIH and the DRB1**03:01* and DRB1**04:01* alleles [14, 15]. In Latin Americans, DRB1**13:01* was apparently correlated to AIH susceptibility [16-19]. Several investigations have also described protective alleles to AIH. For instance, DRB1**15:01* was related to prevention of disease onset in Japanese and Caucasian cohorts [12, 15]. Since the relative linkage disequilibrium value for HLA alleles is very high within populations, haplotype analysis is also important in the evaluation of HLA susceptibility and protection. In Japan [11, 12] and Korea [13], the HLA-DRB1**04:05*-DQB1**04:01* haplotype was associated with susceptibility to AIH (Table 2), while DRB1**15:01*-DQB1**06:02* conferred resistance to AIH in the Japanese [12]. DRB1**13:01*-DQB1**0603* was a risk haplotype in Latin America. In northern Europe and North America, three primary haplotypes have been associated with the disease: the frequencies of the

*DRB1*03:01-DQB1*02:01* and *DRB1*04:01-DQB1*03:02* haplotypes were significantly increased, and that of *DRB1*15:01-DQA1*01:02-DQB1*06:02* was significantly decreased, in patients with AIH as compared with disease-free individuals [15]. However, the mechanisms of an HLA association with autoimmune disease are not clearly elucidated and largely hypothetical. The most probable model is a breakdown in immunological tolerance to self-antigens presented by aberrant disease-associated HLA molecules. The properties of the peptide-binding groove of HLA molecules determine the targeting of particular autoantigens. As the amino acids that form the binding pockets are highly polymorphic, binding specificity can vary considerably among specific HLA alleles. The *DRB1* association with type 1 AIH may be explained by the amino acid motifs in the corresponding antigen-presenting grooves. In European and North American patients with AIH of this type, a model based on lysine at position 71 of the DRβ polypeptide has been proposed [20], and earlier studies also implicated a histidine residue at position 13 of the DRβ polypeptide as a critical determinant of disease susceptibility in Japan [21]. In a larger Japanese cohort, the incidence of valine-11, histidine-13, and serine-57 encoded by *DRB1*04:05* was significantly higher in AIH patients than in normal controls [12]. Moreover, a

valine/glycine dimorphism at position 86 of the DRβ polypeptide has been suggested in patients from Argentina and Brazil. The above studies indicate that multiple genetic associations with AIH exist among different populations.

Severity and Clinical Phenotype

Although susceptibility and resistance to AIH are strongly influenced by HLA alleles, these alleles can also act as modifiers of clinical phenotype [12, 14]. In Japan, the HLA DRB1*0405-DQB1*04:01 susceptibility haplotype was correlated with elevated serum IgG levels and anti-smooth muscle positivity, and the DRB1**15:01*-DQB1**06:02* protection haplotype was associated with the development of hepatocellular carcinoma. DRB1*08:03-DQB1*06:01, which is an important risk haplotype in primary biliary cirrhosis [22], was more frequent in patients who progressed to hepatic failure. In Caucasians with AIH, the presence of HLA-DRB1*04:01 was associated with decreased severity, a lower frequency of relapse, and presentation at an older age than in those with DRB1*03:01 [14]. A recent study from the Netherlands also uncovered that HLA-DRB1*0301/HLA-DRB1*04:01-positive patients had higher International Autoimmune Hepatitis Group (IAIHG) scores than did HLA-DRB1*03:01/DRB1*04:01-negative patients

[23]. While HLA-DRB1*03:01 was associated with higher IgG levels, DRB1*04:01 was linked to older presentation age and a female preponderance. Furthermore, DRB1*03:01-positive patients were more likely to receive immunosuppressive medication and liver transplantation.

The role of HLA in type 2 AIH is not well studied due to low disease prevalence, although published data have suggested associations with HLA-DRB1*07 and HLA-DQB1*02:01 [17, 24].

Serologic Phenotype

Antibodies to soluble liver antigen/liver pancreas (anti-SLA/LP) characterize patients with severe inflammatory activity and a propensity to relapse after corticosteroid withdrawal [25-28]. As they have been associated with *DRB1*03:01* [26, 27], antibodies to SLA/LP may also reflect pathogenic mechanisms prompted by *DRB1*03:01* or other genetic factors working in epistasis with this principal genetic driver. In Japan, none of 100 patients with type 1 AIH were positive for anti-SLA/LP (Umemura, unpublished data). Since *DRB1*03:01* is not commonly found in the Japanese, however, this AIH phenotype might only be present in European and American populations.

Non-HLA Associations in AIH

Although antigen presentation is a critical step in the immune response, numerous other stages exist that may be modulated by host genetic variation, such as the immediate aftermath of MHC-peptide-T-cell receptor interactions, at which time signaling by accessory molecules determines the ensuing course of events. One such accessory molecule, *cytotoxic lymphocyte antigen 4* (*CTLA-4*) is of particular interest. Switching from immune activation to immune memory occurs through the upregulation of CTLA-4 on CD25+ T cells. In North American and northern European patients, a polymorphism of the *CTLA-4* gene (+49A/G) was associated with an increased incidence of AIH [29, 30]. However, this relation has not been confirmed in studies from Japan or elsewhere [31-35].

Polymorphisms of the human *Fas* gene (*tumor necrosis factor-receptor superfamily* [*TNFRSF*] gene) have been associated with AIH onset in Japan [36]. In Caucasoid patients, an adenosine to guanine single nucleotide polymorphism in the *Fas* gene (*TNFRSF6*) was related to the early development of cirrhosis [37] as well.

A polymorphism in *tumor necrosis factor α* (*TNFA*2*) has been linked to highly inducible and elevated constitutive levels of TNF-α in the serum [38] and was shown to be more frequent in young Caucasian AIH patients who responded less favorably to corticosteroid therapy than patients without the polymorphism [39, 40]. Meanwhile, a case-control association study of 400 polymorphic microsatellite markers identified associations with chromosome 11 and 18 in the Japanese [41].

Finally, although genome-wide association studies have been conducted on primary biliary cirrhosis [42-45] and primary sclerosing cholangitis [46-48], no such reports on AIH appeared until 2014, when de Bore et al. performed the first multicenter genome-wide association study on type 1 AIH predisposition in Dutch and German patients [49]. They described significant associations with both HLA and non-HLA loci, including *SH2B3* (rs3184504, 12q24; $P = 7.7 \times 10^{-8}$) and *CARD10* (rs6000782, 22q13.1; $P = 3.0 \times 10^{-6}$). Importantly, the strong correlation between AIH and the HLA region was confirmed in this analysis; HLA DRB1*03:01 ($P = 5.3 \times 10^{-49}$) as well as HLA DRB1*04:01 ($P = 2.8 \times 10^{-18}$) were identified as prominent susceptibility genotypes.

Conclusions and Future Directions

The recent advancements of whole exome and genome sequencing have enabled the precise identification of numerous genes associated with susceptibility, resistance, disease severity, and outcome in AIH. Future genome-wide association studies are warranted both in Japan and abroad.

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