HLA and Gastrointestinal Disorders

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Introduction

The association of histocompatibility leukocyte antigens (HLA) and disease has generated a great deal of interest and activity. Recently, the biological functions of the HLA antigens have been discovered to be closely associated with the basic immune reactions. It is now possible to classify heterogenous syndromes into distinct HLA dependent disease entities, e.g. insulin-dependent diabetes mellitus which has a strong HLA association as opposed to non-insulin dependent diabetes mellitus which does not have HLA association. Such classifications are expected to lead to a better understanding of the pathophysiology of disease processes. Products of HLA genes are also intimately involved in immune reactions, which explains the association of diseases with a strong immunological background, e.g., autoimmune diseases. Finally, certain strong associations and in some cases genetic linkage with HLA antigens are proving useful as diagnostic and prognostic markers for individuals at risk.

Keywords: Histocompatibility antigen, gastrointestinal disorders, liver diseases.

The human HLA system consists of a cluster of genes situated on the short arm of the sixth chromosome. Three classes of genes are recognised, of which class I and class II genes control classical MHC products. Class III genes lie sandwiched between class I and class II gene clusters and code for complement components C4, C2, Bf, and the enzyme 21-hydroxylase (Fig).

HLA and Disease Association

The association of diseases with genetic markers may be investigated by (a) population studies in which the frequency of a marker in an adequate sample of cases is compared with its frequency in a control group, or (b) multiple case family studies in which the co-inheritance of the genetic marker with the disease is investigated. The results of population studies are usually expressed as relative risk (RR) values, which indicate the increased risk that a particular individual inheriting the genetic marker has of developing the disease, compared to one who does not inherit the marker. RR is calculated as follows:

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\text{No of Ag}^+\text{ve cases} : \text{No of Ag}^-\text{ve controls} \\
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Many hypotheses have been put forward to explain the association of diseases with HLA antigens. The association is not merely fortuitous considering the very strong association seen with some diseases, e.g., HLA B27 in 95% of cases of ankylosing spondylitis (AS). One hypothesis is of "molecular mimicry" in which the close structural resemblance between an HLA antigen and a disease causing organism may help the organism to evade the host immune system by masquerading as "self". Such a mechanism has been postulated for the HLA B27-AS association where the strong cross reactivity between the B27 antigen and certain Escherichia coli strains has been demonstrated.

A second hypothesis suggests that an HLA antigen itself acts as a receptor for a foreign antigen, thus making individuals bearing the antigen susceptible to the disease. However, recent knowledge of the lymphocyte receptors for antigen makes this possibility unlikely. A third hypothesis is based on the strong linkage disequilibrium between HLA genes and class II antigens which results in an apparent association between disease and a class II antigen.

HLA and the Gut

Duodenal ulcer: The occurrence of DU is three times more common in first degree relatives of patients compared to the general population. The RR for developing DU has been reported as 1.3 for those with blood group O, 1.5 for non-secretors and 2.5 for those who have the O group and are non-secretors. HLA studies have revealed different results in different ethnic
groups. Among white Caucasians significant deviations of HLA B5, B12, Bw35 and B14 have been reported. B5 and Bw35 are strongly cross-reactive antigens, lending further significance to this deviation. However, the HLA frequencies in American blacks showed significant deviation and studies on Asian Indians from South Africa\(^6\) showed a significant decrease rather than an increase in B5 and elevated B40. A limited study for the association of HLA antigens and the acid secretory status by pepsinogen test showed a weak association between high secretors and HLA A1 and normal said secretors and Bw35. Although suggestive evidence has been presented, a study of families with multiple cases of endoscopically proved DU may help to settle the issue.

Coeliac disease or gluten sensitive enteropathy is one of the very early diseases reported to have a clear-cut HLA association. Although the initially reported association was with HLA B38, Dw3 was later found to be the primary association. Subsequently, DR3 and DR7 were found to be significantly increased in these patients,\(^7,8\) but not among Ashkenazi Jews.\(^9\) An elevated frequency of B8 and B12 was reported in 40 Israeli children with GSE.\(^9\) The disease has been infrequently reported in India and no HLA studies are available.

Family studies in GSE have revealed an increased frequency of HLA A1, B8 but this was not an absolute association. The 8th International Workshop study\(^4\) compared haplotypes of 15 affected and 15 normal French families and found that B8-Cw7-DR3 was the most frequent haplotype. In exhaustive study, Falchuk et al\(^10\) reported 35 families with 13 of 53 sibs being HLA identical with patients, and only one of these had GSE. The frequency of GSE among members bearing the B8 carrying haplotype was very low. The two possible models for the disease are (1) two separate susceptibility genes, either DR3 and DR7 or genes in close linkage with them; (2) one susceptibility gene in close linkage disequilibrium with both DR3 and 7. In all reported studies there is a small percentage of patients, ranging from \(1.5-13.6\%\), lacking DR3 and DR7. In a recent multicentric report\(^11\) all cases with GSE and DR3, DR7 negativity had DR4 antigen, indicating a 100\% association of this disease with HLA. These data await confirmation.

Immunological mechanisms have been implicated to explain the abnormal sensitivity of the small bowel mucosa to gluten. Leukocyte migration inhibition (LMI) using gluten as the test antigen has been reported to be greater in normal B8 positive as compared to B8 negative individuals.\(^12\) However, LMI with gluten was comparable in both B8 positive and negative patients. Genetically determined factors related to HLA appear to control the immune responses to gluten, resulting in GSE.

Tropical sprue: In spite of the common occurrence in certain tropical populations, studies on the genetic aetiology are lacking. Our own study on 26 cases of endemic tropical sprue revealed an increased frequency of B8 with an RR of 2.9.\(^7\) No etiological factor, analogous to gluten in GSE, has been found in this condition. However, similar immunological processes may play a role in tropical sprue and a study of these factors and their relationship to B8 needs further exploration.

Non-specific inflammatory bowel disease: Although ulcerative colitis and Crohn's disease are not classic genetic disorders, 15-40\% of patients show multiple familial occurrences with some overlap of the two conditions in 25\% of affected families.\(^13\) A number of studies on HLA antigen frequencies in random cases of Crohn's disease failed to reveal any significant association. A recent report from Vienna\(^14\) on a small group of 27 Crohn's cases showed an increase in B12, a finding which needs confirmation by other studies. The above study revealed a high degree of association with a particular haplotype. A recent report\(^15\) of an interesting family with 5 affected sibs also suggested a close linkage between HLA and Crohn's disease.

Crohn's disease is a relatively uncommon entity in our country. The other component of IBD—idiopathic ulcerative colitis (IUC)—is however not infrequently encountered. The frequency of HLA antigens in ulcerative colitis has been investigated by many workers. No consistent findings have been reported in Caucasian patients. In Japanese patients, HLA B5 has been found to be elevated along with a decrease in frequency of Bw35 and Aw30 and 31. More recently DR2 has been reported to be very strongly associated with Japanese IUC (70\% of 40 patients vs 31\% of 51 controls) with a high frequency of DR2-B5 haplotype.\(^16\) In Jewish patients,\(^17\) however, Bw35 is significantly elevated along with increase in A2, B40 and Aw24. There is some indication that Aw24-positive patients have a more severe disease. Our own investigation\(^18\) of 52 North Indian IUC patients and 120 controls showed decreased frequency of A11 with an increased frequency of A29 in patients.

Gut malignancies: A single study of HLA antigens in cancer of the oesophagus in South African blacks found no significant association.\(^19\) A study of HLA typing in 21 cases with immunoproliferative small intestinal disease, 10 with and 11 without \(\alpha\)-chain disease, showed an increase in frequency of Aw19 and B12.\(^20\) One large pedigree of "cancer family syndrome", which is believed to have autosomal dominant inheritance, had 10 cases with adenocarcinoma of the colon.\(^21\) Sixty-six members were HLA typed and a significant HLA association with the inherited adenocarcinoma was observed.

Pernicious anaemia: A number of studies conducted on this disease have reported a significant association with DR2, with RR ranging from 2.0\(^\text{b}\) to 5.93.\(^22\) A significant negative correlation has been found with DR3 antigen. Thus, it seems to be an organ specific autoimmune disease associated with DR2 and not with DR3.

HLA and the Liver

Hepatitis B carriers: Since a relationship has been established between chronic carriers of hepatitis B...
surface antigen (HBsAg) and hepatocellular carcinoma (HCC). Interest has centred on the fact that only some individuals infected with hepatitis B virus (HBV) become chronic carriers. Studies on 144 dialysis and transplant recipients showed 22 transiently positive and 33 persistently positive patients; 2635 was increased in both groups, but 2615 was elevated in the transiently positive and 2617 in the persistently positive. A second study found increase of 2615 in 24 asymptomatic HBsAg carriers (RR 5.8) and not in 54 carriers with hepatitis. A recent report found A28 B15 haplotype to be associated with carrier state. The constant finding of increased B15 in these three studies is interesting. A study from Singapore of 114 Chinese patients with HCC showed that HLA B15 was significantly high among 27 alpha fetoprotein negative patients (RR 4.6); B5 was associated with HBsAg-ve cases and B17 with anti-HBs-ve cases. A significant HLA association was found among 182 blacks with HCC and no evidence to indicate that the chronic HBsAg carrier state had a genetic basis. A highly significant elevation of B12 has been reported in 52 unrelated Greek patients of HCC (RR 3.2), but this study neither investigated the HBV status of the patients nor correlated HCC prevalence with alcohol ingestion. It is, therefore, difficult to comment on the observation. What is interesting is that HLA B15 and antigens strongly correlate with it—B5 and B17—have been repeatedly found to correlate with chronic carrier state for HBV, and with the phenomenon of progression to HCC. These studies need to be repeated in larger groups, especially in this country where the HBsAg carrier state is reported to be fairly high. Close follow-up of cases to study the progression to chronic disease in the context of the HLA genotype would be very fruitful.

Chronic active hepatitis: This term encompasses a heterogeneous group of diseases with a common clinical and histological picture but different etiological factors. The increase in the frequency of A1, B8 and DR3 reported in the autoantibody positive group of CAH was confirmed in Caucasians in the 8th International Histocompatibility Workshop study on CAH. The study of the immunoglobulin allelic markers (Gm system) in 52 patients of autoimmune CAH together with HLA demonstrated that Gm type (a2b2) was found in 19/40 patients who had B8 but none of the B8 positive controls. The RR for Gm (a2b2) and B8 was 15, suggesting that an additional gene linked to the Ig allelic system increases risk for the disease. Using an in vitro cytotoxicity system, the lymphocyte cytotoxicity for liver cells was found to be more in A1, B8, DR3 -ve patients. A1, B8 and DR3 antigens are in strong linkage disequilibrium in Caucasians and appear to be a marker for auto-aggression, appearing in a number of diseases with autoimmune etiopathogenesis, such as Graves, myasthenia gravis, autoimmune thyroiditis, etc. The increased cytotoxicity of A1, B8, DR3 positive lymphocytes adds support to this observation. No studies on Indian patients with CAH are available.

Alcohol liver disease: Associations between different HLA antigens and alcoholic liver disease have been reported, but a majority of studies have been conducted in Caucasians. The criteria for selection of patients have been variable and in many instances inadequate. Since the numbers in many of the series were very small, Eddleston and Davie did a combined analysis of 7 series and found a small increase of Aw32, B8, B13, B27, B40 and B37. The impression from a number of studies of an association between B8 and alcoholic liver damage was not adequately substantiated in this combined analysis. A prospective analysis was undertaken to further probe this point. Seventy-six cirrhosis were interviewed for lifetime alcohol consumption and their HLA-B8 typing was done. The duration of regular drinking of more than 40 g daily was significantly shorter in B8 positive cirrhotics and was more significant in B8 positive females. This study indicates that B8 positive individuals may be more prone to the fibrosis and cirrhosis following alcohol damage. In a study of 29 among Jewish patients with cryoprotective cirrhosis, no B8 association was found. More recent report from Australia has found a highly significant increase (47.4 vs 26.1%) in DR3 in 57 patients with alcoholic cirrhosis and an increase in DR5 in 43 patients with alcoholic CAH. It was suggested that the progression to the two conditions is controlled by different mechanisms. Larger groups of patients with adequate controls consisting of individuals consuming equal quantity of alcohol but with no evidence of liver damage need to be studied in order to give the final answer about the role of genetic factors in alcohol induced liver damage.

Primary biliary cirrhosis: Like chronic active hepatitis, PBC has been reported to have an association with A1, B8, and DR3, with an RR of 7-6 for DR3, suggesting an autoimmune etiology. This finding has not been substantiated in other studies.

Miscellaneous

Idiopathic haemochromatosis: This disease is controlled by an HLA-linked recessive allele and its association is with HLA A3 primarily and secondarily with B14. Of 7 cases with sideroblastic anaemia, 5 were found to have A3, as against 25-5% of controls (RR 7-3). Further, haemochromatosis and abnormal iron metabolism were found in several members of two large families with idiopathic refractory sideroblastic anaemia (IRSA). These authors therefore concluded that patients with IRSA carry a single allele for haemochromatosis, which is responsible for iron overload.

References:


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