The Role of Human Leukocyte Antigen (HLA) Complex in IBD: Crohn’s Disease and Ulcerative Colitis


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Abstract

The human leukocyte antigen complex on chromosome 6 is the most extensively studied genetic region in inflammatory bowel disease (IBD). Consistent evidence of linkage to IBD3 (6p21.1-23), an area which encompasses the HLA complex, has been demonstrated for both Crohn’s disease and ulcerative colitis. However, despite these efforts the HLA susceptibility genes for IBD remain elusive and unclear, a possible consequence of strong linkage disequilibrium, extensive polymorphism, high gene density across this region and different allele frequencies in several populations around the world.

This article confirms the role of HLA complex genes in Crohn’s disease and ulcerative colitis susceptibility, and principally the HLA-DRB1 locus.

Keywords: HLA, Crohn disease, ulcerative colitis, inflammatory bowel disease

1 INTRODUCTION

Since the first report of an HLA association with inflammatory bowel disease (IBD) in 1972 [Gleeson et al., 1972], more than 100 studies have been published
investigating the role of HLA genes in determining susceptibility and phenotype of IBD. Early data derived from both association and linkage analyses were inconsistent, reflecting the difficulties of inadequate sample size, low resolution typing methods, poor statistical analysis and a failure to test disease heterogeneity. Genome-wide scans have shown consistent evidence of linkage to IBD3 (6p21.1-23), an area which encompasses the HLA complex. This has been demonstrated in several independent studies of both Crohn’s disease (CD) and ulcerative colitis (UC) [Ma et al., 1999; Dechairo et al., 2001]. The importance of this area was further highlighted by a meta-analysis of 10 published genome wide scans [van Heel et al., 2004]. Notably in this study, IBD3 was the only locus that met genome-wide significance, and provided stronger evidence of linkage than 16p13.1-16q12.2 (IBD1), the locus that contains the susceptibility gene CARD15. Although it is difficult to estimate the importance of this region in determining overall genetic susceptibility, calculations derived from studies of HLA allele sharing within families suggest that this region contributes between 10-33% of the total genetic risk of CD and 64-100% of that of UC [Ahmad et al., 2006].

Interest in the HLA complex in IBD has traditionally focused on association with the classical class II HLA alleles, but recent insights into the biological function of other genes encoded within this region have led investigators to a more diverse exploration of this region. Our aim was to study the relationship between allele frequencies of HLA class I and class II alleles with IBD development, particularly in CD and UC patients.

2 PATIENTS AND METHODS

2.1 SUBJECTS

Peripheral blood was obtained from unrelated healthy Murcians, all of them Caucasoid, from Murcia Region, in the Southeast of Spain [Lucas et al., 2008] and patients with IBD, including CD and UC pathologies. All subjects gave their informed consent prior to their inclusion in this study to the collection and storage of blood, isolation of DNA, and determination of gene polymorphisms. Indeed, the study was approved by the local medical committee.

2.2 HLA CLASS I AND CLASS II GENOTYPING

Genomic DNA was extracted from peripheral blood lymphocytes with the Maxwell16 extractor (Promega, WI), as reported [Muro et al., 2008]. For HLA typing, a two-step strategy, low- or intermediate resolution typing by polymerase chain reaction using sequence-specific oligonucleotide probes (PCR-SSOP) followed by allelic specific typing by PCR-SSP (sequence specific primers). HLA-A and B genotyping was performed using PCR-SSO for the exons 2, 3 and HLA-DR for the exon 2 of HLA genes by using luminex technology (OneLambda,
Amplification and detection were carried out according to the manufacturer’s instructions. These alleles were assigned on the basis of SSOP hybridization patterns predicted from known HLA alleles.

2.3 STATISTICAL ANALYSIS

Allele and haplotype frequencies were calculated by using Arlequin population genetic software (Genetics and Biometry Laboratory, University of Geneva, Geneva, Switzerland, as previously published [Lucas et al., 2008].

3 RESULTS AND DISCUSSION

The allele frequencies of HLA class I loci, HLA-A and HLA-B in CD and UC patients were not different to those observed in control subjects, although we found an increased allele frequency of A*03 allele in CD with respect to UC patients. Haplotype frequencies of HLA class I and II (HLA-A,-B and –DRB1) in CD and UC patients were also not different to those observed in controls. However, in the HLA-DRB1 locus, we found increased allele frequencies of DRB1*13, DRB1*01 and DRB1*0103 alleles, and a decreased allele frequency of DRB1*15 in CD patients with respect to UC patients and control subjects. These data are in concordance with other previous studies suggesting that amongst British patients with isolated colonic CD, DRB1*0103 is associated with the development of severe disease as defined by the requirement for infliximab or colectomy [Ahmad et al., 2006, Silverberg et al., 2003] and positive association of CD with DRB3*0301 and DRB1*13 [Ahmad et al., 2002; Stokkers et al., 1999]. Indeed, DRB1*15 was negatively associated with CD which explains the earlier negative association reported with the serological antigen DR2 highlighted in the 1999 meta-analysis [Stokkers et al., 1999]. This allele appears to confer protection against all subgroups of CD, in all ethnic groups including Japanese. However, HLA-DRB1*07 frequency allele, associated in unselected patients with CD in other studies [Ahmad et al., 2006; Newman et al. and Fernandez et al., 2004], was not different in our CD and UC patients, and controls. Additionally, an increased frequency in HLA-DRB1*04 allele in CD was not found in our patients in a different manner to other reported studies [Matake et al., 1992; Nakajima et al., 1995; Yoshitake et al. and Stokkers et al., 1999].

On the other hand, in our UC patients, allele frequencies of DRB1*15 were strongly increased with respect to CD patients and control subjects. However, the frequency of the DRB1*04 allele was decreased in UC patients with respect to CD patients and control subjects.

In this sense, our data are agreed with other reports showing that HLA-DRB1*15 is associated with UC in European [Ahmad et al., 2003], North American [Trachtenberg et al., 2000], Japanese [Futami et al., 1995] and Korean [Myung et al., 2002] populations. In parallel, HLA-DRB1*04 allele was also negatively
associated with UC in Northern Europeans and Japanese populations, in contrast to the positive association in CD, as reported [Ahmad et al., 1999].

As a possible explanation of these data in IBD, cross reactivity (known as "molecular mimicry") may exist between the peptides derived from bacterial luminal flora and from self antigens present in the gut. This may lead to the generation of auto reactive T cells which contribute to disease pathogenesis through either stimulation or inhibition of the immune system. This mechanism is supported by identification of murine MHC-restricted CD4+ T cells reactive to enteric bacterial antigens that are able to induce colitis by adoptive transfer [Ahmad et al., 2006].

4 CONCLUSIONS

This article confirms the role of HLA complex genes in CD and UC susceptibility and protection, and principally the HLA-DRB1 locus.

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References


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