Inflammatory bowel disease: Ulcerative Colitis and Crohn's disease

Crohn's disease (CD) and ulcerative colitis (UC) are related inflammatory diseases of the gastrointestinal tract commonly known as inflammatory bowel diseases (IBD, MIM 266600). These diseases show a peak incidence in early adulthood and affect approximately 1-2 individuals per thousand. Clinically, CD is characterized by a discontinuous transmural inflammation affecting any portion of the gastrointestinal tract, but most commonly the terminal ileum; while UC is characterized by inflammation of the colonic mucosa, extending to a variable extent, from the rectum to the proximal colon.

Several independent genome-wide scans in both CD and UC have shown evidence of linkage to the MHC (also known as the IBD3 locus) [1-7]. A recent meta-analysis of genome-wide linkage data has confirmed the importance of this region in IBD [8]. Interestingly, it has been suggested that this region may exert a greater effect in susceptibility to UC rather than CD. Specifically, based on estimates of empirical risk and monozygotic twin concordance rate, the genetic contribution of the IBD3 region to disease has been estimated as 60-100% for UC and closer to 10% for CD [9].

Over the past 35 years, over 100 association studies have investigated the role of the MHC in determining IBD susceptibility and clinical expression. These early studies focused on the classical HLA genes, particularly the HLA-DR alleles. The role of TNF promoter polymorphisms in IBD susceptibility has been the focus of recent interest given the successful use of the TNF-alpha antagonist, infliximab, in the treatment of active IBD. Initial studies of the MHC in IBD have shown inconsistent associations and suffered from a lack of
power due to small sample size and investigation of a limited number of loci. To gain further insight into the role of the class I genes HLA-A and HLA-B, Biemond et al. [10] undertook a meta-analysis of 12 CD and 14 UC association studies published between 1972 and 1982. This study confirmed the presence of predisposing and protective alleles in the class I region, including the risk alleles HLA-A2 and HLA-B18 for CD and HLA-B27, HLA-B35 and HLA-B5 for UC. Similarly, Stokkers et al [11] undertook a meta-analysis of 19 UC and 17 CD studies published between 1980 and 1998 for the class II genes, HLA-DR and -DQ in IBD. This study confirmed the presence of several predisposing and protective alleles in the class II region, including the risk alleles HLA-DR7, HLA-DQ4 and HLA-DRB3*0301 for CD and HLA-DR9, HLA-DRB1*1502 and HLA-DRB1*0103 for UC. Subsequent studies have provided supporting evidence for some, but not all of these observations, as well as further describing the association of specific HLA-DRB1 alleles with clinical sub-phenotypes.

HLA-DRB1*1502 and HLA-DRB1*0103 have shown consistent association with UC [11-18]. HLA-DR2 and its sub-specificity HLA-DR15, both of which encompass HLA-DRB1*1502, also predispose to UC [11] most likely as a result of the latter association. HLA-DRB1*1502 predisposes to disease in different populations including Japanese UC cohorts where the allele is highly prevalent (20-25%) [13,15,17,18], and European populations where it is rare (less than 1%) [19]. The class I allele HLA-B*52 [14,18], found in LD with DRB1*1502, has also shown association with disease. It is presently unclear where the primary association lies given the long range conservation of this haplotype. HLA-DRB1*0103 represents the most reproducible association
observed to date in UC [11,12,14,20-23]. In recent studies, this allele has been associated with a more aggressive disease phenotype, a shorter mean time to surgery, as well as the presence of extra-intestinal manifestations [14,20,21]. Microsatellite polymorphisms of the class I-related gene, *MICA*, have also been investigated in IBD patients, and non-replicated associations were observed for 3 different alleles *MICA*007, *MICA5.1* and *MICA6* with UC in Caucasian, Chinese and Japanese populations respectively [18,24,25]. The *MICA*007 allele was in LD with *HLA-B27*, while the *MICA6* association in Japanese UC was found to be secondary to *HLA-B52* [18,24]. Finally, investigation of the class III locus in UC has largely centered on the role of *TNF* promoter polymorphisms (as discussed above). So far the results of these studies have not proven to be conclusive.

The current pooled analysis includes 37 UC and 40 CD studies, of which 9 UC and 11 CD studies are common to the previously published study by Stokkers et al [11].

The main association signals (7 out of 13) shown for UC in our pooled analysis arise from *HLA-DRB1*0103 and *HLA-DRB1*1502 haplotypes and substantiate the current literature base (Figure 2). The greatest OR in the dataset are observed with the individual alleles *HLA-DRB1*0103 (OR 4.6), encompassed within the *HLA-DR1* specificity (OR 1.4), *HLA-DRB1*1502 (OR 3.2) and *HLA-B52* (OR 3.3) which is in LD with *HLA-DRB1*1502. The broad specificities, *HLA-DR2* and *HLA-DR15* also show association. Our results also demonstrate a weak predisposing effect of the microsatellite allele *MICA5.1* in UC. Other novel associations are demonstrated for *HLA-DR5* (and its sub-
specificities HLA-DR11 and -DR12, HLA-A19 and HLA-A24 (in LD with DRB1*1502 and other alleles including HLA-DRB1*0405).

In contrast to UC, four separate HLA-DRB alleles show reproducible association with CD: HLA-DRB1*07, HLA-DRB1*0103, HLA-DRB1*04 and HLA-DRB3*0301 [11]. The most consistently replicated association between the MHC and CD is that with HLA-DRB1*07 [11,26-28]; specifically, HLA-DRB1*0701 is associated with ileal disease [26-28]. DRB1*0103 is associated with susceptibility to CD as well as UC [11,12,26-29] and shows sub-phenotype specificity to colonic CD [26-28]. However, the low prevalence of DRB1*0103 (less than 2% in Europeans) restricts its usefulness in predicting clinical outcome. Several studies have reported weak association of HLA-DRB1*04 [11,13,27,30,31] with CD. In particular, the subtypes HLA-DRB1*0405 and HLA-DRB1*0410 and their linked HLA-DQ alleles, DQB1*0401 and DQB1*0402 respectively, are associated with CD predominantly in patients of Japanese origin. A small number of studies have reported association of HLA-DRB3*0301 with CD [11,26]. However, the HLA-DRB3 locus has not been subject to a thorough investigation in CD since it is present in less than 50% of European and white North American populations due to haplotype-specific expression. Disease association is further confounded by the predisposing HLA-DRB1*1302 and HLA-Cw*0802 alleles which are in tight LD with HLA-DRB3*0301 [26]. The majority of studies examining polymorphisms in the TNF promoter have yielded contradictory results, with only the TNF-857 promoter polymorphism showing replicated association with susceptibility to CD [32-36].
The current pooled analysis includes 37 UC and 40 CD studies, of which 9 UC and 11 CD studies are common to the previously published study by Stokkers et al [11].

Fourteen of the 22 significant association signals in CD map to haplotypes previously shown to predispose to disease, specifically \textit{HLA-DRB1*0103}, \textit{HLA-DR4}, \textit{HLA-DR7} and \textit{HLA-DRB3*0301} (Figure 2). The strongest association is observed with \textit{HLA-DRB1*0410} (OR 3.9). The \textit{HLA-DR4} specificity encompasses \textit{HLA-DRB1*0410} and \textit{HLA-DRB1*0405}, all of which demonstrate association with susceptibility to CD. Similarly, \textit{HLA-DQB1*0401} and \textit{HLA-DQB1*0402}, subtypes of \textit{HLA-DQB1*04} and found in LD with \textit{HLA-DRB1*0405} and \textit{HLA-DRB1*0410} respectively, also show significant association with CD. As described in previous studies, the association signal at \textit{HLA-DRB1*0410} in our pooled analysis largely derives from Japanese patients: of all CD study cases bearing \textit{HLA-DRB1*0410} in this pooled analysis 60% were of Japanese origin, while CD patients of Japanese origin represent only 18% of the overall CD sample base. The \textit{HLA-DRB3*0301} linked alleles, \textit{HLA-Cw8}, \textit{HLA-DRB1*1302} (together with \textit{HLA-DQB1*0604} found in LD with 1302), show association in this study, however we find no association specifically with \textit{HLA-DRB3*0301} as the relevant studies did not fulfill our inclusion criteria. We demonstrate a robust signal with \textit{HLA-DRB1*0103} allele, previously associated with colonic CD. \textit{HLA-DRB1*07} reported to be weakly associated with CD, also shows a weak signal in our study with narrow CI. We also confirm previously reported association signals with \textit{HLA-B18} and \textit{HLA-B21} class I alleles, and identify novel associations to
HLA-DR6 (encompassing HLA-DRB1*1401), HLA-DR8 (including HLA-DRB1*0802 and *0803), and HLA-DR10 class II subtypes in CD (OR~1.5).

We confirm previous reports of association of the TNF promoter polymorphism, TNF-857T with CD in Japanese populations and further show association with TNF-1031C and TNF-863A again in Japanese cohorts; all three SNPs show modest association with OR from 1.3 to 1.5. In contrast, case-control and family-based studies in Caucasian CD show association with the common TNF-857C allele suggesting that the polymorphism itself is not causal but shows association secondary to LD [32,34,35].

In summary, the current pooled analysis confirms the previously reported MHC associations in IBD, but also identifies several novel potentially predisposing alleles. The shared association of DRB1*0103 with UC and colonic CD supports the notion of a common molecular basis for the colonic IBD phenotype. It has been suggested that the MHC plays a stronger role in susceptibility to UC rather than CD, however, given the large number of relatively low risk variants in CD, it is possible that the overall effect of MHC risk in CD is quite sizeable, albeit genetically heterogeneous.

REFERENCES


