Review Article: The Genetics of the Human Leucocyte Antigen Region in Inflammatory Bowel Disease

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Abstract

**Background**- The human leucocyte antigen (HLA) complex, located at chromosome 6p21.3 is a highly polymorphic region containing the classical class I and II HLA genes. The region is highly associated with inflammatory bowel disease (IBD) through genome-wide association studies (GWAS).

**Aims**- This review discusses the role of HLA in immune function, summarises data on risk/protective HLA genotypes for IBD, discusses the role of HLA in IBD pathogenesis, treatment and finally examines limitations that might be addressed by future research.

**Methods**- An organised search strategy was used to collate articles describing HLA genes in IBD, including Crohn’s disease and ulcerative colitis. The mechanistic role HLA variation plays in disease pathogenesis, alongside implications for treatments are discussed.

**Results**- All classical HLA genes with variation (including HLA-A, B, C, DRB1, DQA1, DQB1, DPA1 and DPB1) harboured IBD-associated genotypes. The most implicated gene is HLA-DRB1, with HLA-DRB1\*03:01 the most associated risk allele in both Crohn’s disease and ulcerative colitis. Elucidating precise disease associations is challenging due to high linkage disequilibrium between HLA genotypes. The mechanism by which all risk alleles cause disease are multifactorial with the best evidence indicating structural and electrostatic alteration impacting antigen binding and downstream signalling. Adverse medication events have been associated with HLA genotypes including with thiopurines (pancreatitis) and anti-TNF agents (antibody formation).

**Conclusions**- The HLA complex is associated with multiple risk/protective alleles for IBD. Future research utilising long-read technology, ascertainment of zygosity and integration in disease modelling will improve functional understanding and clinical translation of genetic findings.

Keywords: inflammatory bowel disease; Crohn’s disease; ulcerative colitis; genetics; HLA; MHC

**Introduction**

The role of the human leucocyte antigen (HLA) region in the development of autoimmune disease is now well established, however precise genetic risk loci, and functional validation of HLA variation has been poorly elucidated. This review focuses on the role of HLA genes in inflammatory bowel disease (IBD). We discuss the difficulties and important nuances of studying this region, specific genetic variation, including HLA alleles and serotypes implicated in disease, the proposed mechanisms through which variation is related to IBD pathogenesis and the impact of HLA on therapeutic management. Important terms are summarised in table 1. We comment on the future potential of clinical HLA testing in IBD, and the barriers to current implementation into practice. Finally, we discuss the reinvigorated interest in this genomic region, highly implicated in IBD, including the application of contemporary sequencing and bioinformatic technologies.

1. **Background**

*Human leucocyte antigen complex*

The HLA complex plays a key role in the pathogenesis of inflammatory bowel disease (IBD) (1). Located on chromosome 6 (6p21.3) the region encodes ‘classical’ HLA genes (HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ and HLA-DP) and an estimated 200 other proteins enriched for roles in, and regulation of, the immune system, figure 1 (2,3). The initial complete sequencing of the HLA complex in 1999 identified the area as extremely polymorphic and allowed specific HLA alleles to be associated with a large number of immune diseases (4,5). The 4Mbp major histocompatibility complex (MHC), which contains the HLA region, contains risk loci (alleles) for almost all autoimmune diseases, including rheumatoid arthritis (HLA-DRB1), Coeliac disease (HLA-DQ), psoriasis (HLA-C) and ankylosing spondylitis (HLA-B). In total the extended human MHC contains greater than 420 gene loci, with nearly 30% associated with immune function (3). The HLA complex has a well-established role in the regulation of inflammation through both the innate/adaptive immune system and complement activation. The regulation of immune response through T-cells and natural killer (NK) cells is reliant on HLA mediated cellular interactions with recognition of ‘self’ and ‘non-self’ a cornerstone of immune tolerance (2).

There are five distinct regions within the HLA complex- class I, extended class I, class II, extended class II and class III, each encoding for a variety of genes, non-coding regions and pseudogenes (2). The class I classical HLA genes are HLA-A, HLA-B and HLA-C. Their major function is to present (on the external membrane) peptides found inside the cell, often virally-derived, to CD8+ T-cells and natural killer (NK) cells (endogenous antigen presentation) (6). Class II HLA classical genes consist of HLA-DR, HLA-DQ and HLA-DP, existing alongside the non-classical HLA-DM/HLA-DO. The major role of the classical class II HLA genes is to present exogenous antigens, often bacterially-derived, to CD4+ T-cells, triggering clonal expansion (into T-helper 1 cells and T-helper 2 cells) and with subsequent stimulation of macrophage or B-cell activity (6). Each class II antigen presenting complex is a heterodimer, comprised of an α(A) and β(B) subunit (e.g. HLA-DQA and DQB). HLA-DRA is the only subunit without significant sequence variation. There are several genes encoding the DRβ chains; HLA-DRB1 and DRB3, DRB4 and DRB5 any one of which may be present as the 4 HLA-DRβ chain genes within an individual (7).

There are specific difficulties with sequencing and interpretation of the HLA region including accurate targeting of ultra-polymorphic regions, some areas of high homology, inability to derive phase from genotyping short read sequencing data and challenging imputation of HLA genotypes (8). A specific issue with attributing disease causality to HLA variation occurs due to the high linkage disequilibrium, and conserved haplotypes, seen across the region. Typically specific class 1 and 2 variation will be co-inherited with specific variation in other class 1 and 2 genes, termed a haplotype, making the attribution of causality to a specific genotype difficult. These factors have made interpretation of the region, especially specific disease-association, very difficult (figure 1). Historically complex linkage mapping and difficulty locating functionally important areas within the region has hampered research in the HLA complex, problems that persist to this day. New technologies afford the possibility of better resolution of the HLA region. Increasing use of long-read sequencing technologies, whole-genome sequencing and better imputation software gives the potential for higher precision in detecting and attributing variation across the HLA region (8).

*Inflammatory bowel disease and implication of the HLA region*

Inflammatory bowel disease is comprised of Crohn’s disease, affecting any part of the gastrointestinal tract, ulcerative colitis, primarily affecting the large bowel and IBD unclassified (IBDU)(9). Around 25% of cases present during childhood (10,11). Approximately 230 genes have been identified through genome wide association studies (GWAS) associated either directly with IBD pathogenesis or with an increased risk of developing disease (12–14). The genetic impact is higher in early onset (paediatric) disease (15). A small subset of patients, typically with very early onset IBD (VEOIBD, diagnosis < 6 years of age), present with one of around 70 monogenic IBD disorders (16).

The best characterised gene implicated in IBD, specifically Crohn’s disease, is *NOD2* (17). Implicated through linkage studies such as those performed on several families from Hugot *et al* in 1996, results were subsequently replicated identifying a region on Chromosome 16 (18,19). Application of GWAS resulted in the region being designated as the ‘IBD1’ locus (20). The area was subsequently mapped to *NOD2* in the early 2000s and the gene plays a crucial role in bacterial recognition and regulation of response. Whilst *NOD2* was designated as the ‘IBD1’ locus the only region to reach genome wide significance in a meta-analysis of IBD GWAS studies was ‘IBD3’, corresponding to the HLA complex on chromosome 6 (21). This association was primarily for Crohn’s disease (21,22). Whilst GWAS was able to detect association between specific single nucleotide polymorphisms (SNPs) lying within the HLA complex, and IBD, much of the data generated from these studies cannot be used to determine which HLA genes, and certainly not which genotypes, are truly associated with disease. This is primarily due extensive linkage disequilibrium within this region. In contrast to the considerable progress in the understanding of non-HLA IBD genes, research into the role of the HLA complex has lagged behind. Most data comes from GWAS, however there are some specific HLA genotypes/haplotypes/serotypes that have been associated with IBD (23–26). Despite this, the molecular mechanisms and exact polymorphisms leading to disease, alongside the functional impact of variation has been problematic to elucidate, at least partially due to linkage disequilibrium between genotypes. To date this has limited the clinical translation of HLA genotyping in IBD.

It is well established that the microbiome plays a significant role at the onset of IBD and in ongoing intestinal inflammation, with the dysbiotic microbiome influenced by the host immune system (27,28). HLA is key in recognition of ‘self’ and immune tolerance (4). The crucial role HLA class II heterodimers play in presentation of bacterial antigens and stimulation of downstream immune response, through cellular activation, pro-inflammatory cytokine production and stimulation of T-helper/B-cell proliferation, has taken on new significance in IBD. These data have fuelled speculation that there is an aberrant response to bacteria (including commensal) mediated by the classical HLA genes (28–30). Additional interest in the role HLA plays in the response and reaction to medications has opened up a specific area of pharmacogenomics, relevant to IBD.

*Inflammatory bowel disease and HLA associations; ethnic differences*

The predominant HLA alleles observed in a population differ depending on ethnic origin, with the common alleles, and therefore serotypes/haplotypes, being distinct for an ethnic group (31). This is especially true for isolated populations, such as the Japanese, and this population group has many distinct HLA allele frequencies in the general population, different to European and North American populations (31). Appreciating this difference is important as the alleles present in specific ethnic populations will vary and what is a risk genotype for Europeans may not exist as a genotype in Japan, and vice versa (31). Specific HLA alleles have been identified within Japanese studies that are protective or increase risk of IBD in this ethnic group only (32,33). As the majority of GWAS studies are typically conducted on those with European ancestry, the risk/protective genotypes for this group have been elucidated to a greater extent. However, there may be additional genotypes conferring risk for other ethnic groups/populations who are not represented in the GWAS populations. The most recent study in 2015 (Goyette *et al*) adds significant information from 18,405 CD patients, 14,308 UC patients and 34,241 controls, through immunochip-data although all are of European ancestry. Much of the robust data within this review comes from this study and it is the largest IBD analysis focused on the HLA region to date. Only a single GWAS and a single immunochip study, focusing on an African-American population, has described significant associations in this ethnic group with limited overlap with the previously described ‘European’ risk HLA alleles (34,35).

**Search strategy**

We searched the MEDLINE, Embase and relevant specialty journals for articles published between January 1st 1980, to December 31st 2018, with the terms:

(“Crohn’s disease”, “ulcerative colitis”, “inflammatory bowel disease unclassified”, “inflammatory bowel disease”, “IBD”, OR “IBDU”) AND (“HLA”, “MHC” “human leu\*ocyte antigen” OR “major histocompatibility complex”)

We reviewed all publications from 1980 to 2018. Commonly referenced and highly regarded older publications were not specifically excluded. We searched only for articles published in English, or those translated into English. We also searched reference lists of articles identified by this strategy and selected those we judged relevant. We included randomised controlled trials, observational studies, retrospective studies, meta-analyses and review articles.

1. **Specific associations; HLA and IBD**

The following section provides an overview of specific disease/phenotypic associations with HLA genotype. Data are for European ancestry populations unless otherwise stated. Specific HLA genotypes can be linked to disease subtypes. It is notable that whilst several alleles are joint risk loci for colonic CD and UC, many alleles predisposing to ileal CD are protective for UC, and *vice versa*, demonstrating the discordant effects of HLA genotypes on disease location (25).

Data are summarised in table 2, including specific phenotypic associations with HLA genotypes. Risk and protective associations are described below, odds ratios (OR) are statistically significant in the original publication unless otherwise stated. Graphical representation of significant ORs from previous studies can be visualised in figure 2.

*HLA alleles and genotypes*

HLA-A

The class I HLA gene HLA-A was initially implicated in Crohn’s disease through data from Biemond *et al* (1986) providing evidence for increased risk in people with the HLA-A2 allele (relative risk, RR 1.25) and a protective effect in those with HLA-A11 (RR 0.62) (37). Recently two studies have implicated HLA-A\*03:01 (OR 1.1), HLA-A\*02:01 (OR 1.64) and HLA-A\*02:07 (OR 2.31) in Crohn’s disease, with the latter two identified in a Japanese ethnic group only (25,37).

The HLA-A24 and A19 serotypes were the first to be connected with ulcerative colitis (1980-90s), particularly with early-onset and severe disease (38,39). Following pooled analysis both HLA-A19 (OR~1.7, <1000 patients) and A24 (OR~1.5, <500 patients) serotypes are related to increased risk of ulcerative colitis, but only with modest significance and low patients numbers (40).

HLA-B

Several HLA-B alleles have been established as independent risk factors; HLA-B\*52:01 (OR 1.44) and HLA-B\*14:02 (OR 1.28)(25). Goyette *et al* identified two protective HLA-B genotypes, HLA-B\*35:02 (OR 0.68) and HLA-B\*35:03 (OR 0.72) with genome-wide significance (25). The most recent association was observed using HLA-B\*08:01 as a lead allele for the ancestral MHC 8.1 haplotype. It was noted that Crohn’s disease patients possessing this haplotype have a good prognosis, with fewer complications, compared to those without (41). This haplotype was determined to impact T-cell activation and impaired vaccine response, suggesting differences in HLA-dependant antigen presentation may lead to improved prognosis through T-cell exhaustion (42).

Association of HLA-B, specifically the B5 broad serotype (including HLA-B51 and B52), and increased risk of ulcerative colitis has existed since the 1980s in both European ancestry and Japanese patients (33,36). In contrast to Crohn’s disease HLA-B27 (OR ~1.4) and B52 (OR ~ 3.2) have both been implicated in increasing risk by pooled analysis (40). The HLA-B\*52:01 genotype is in linkage disequilibrium with HLA-C\*12:02, OR 2.21 (25,43). Modifying effects of HLA-B52 in Japanese patients was reported in 2018; HLA-B52-positive ulcerative colitis patients had a lower risk of colectomy (OR 0.18) compared to HLA-B52–negative patients (44).

HLA-B27 is a well-established risk genotype for the seronegative spondyloarthropathies and psoriasis, which are also more common in patients with IBD, although the genotype has not been independently associated with IBD patients without co-existing spondyloarthropathy (45,46).

HLA-C

The HLA-Cw8 serotype has been implicated independently as a risk factor for Crohn’s disease (40). The HLA-C\*12:02 genotype has been reported as a protective genotype in Crohn’s disease, and a risk for ulcerative colitis, as part of the HLA-B\*52:01-DRB1\*15:02 serotype, but the precise allele driving this relationship has not been elucidated (32). Goyette *et al* recently implicated the HLA-C\*06:02 and HLA-C\*14:02 genotypes as independent risk factors for Crohn’s disease (25). Jung *et al* identified HLA-C\*01 (OR 1.52) as a risk allele for Crohn’s disease, but only in a Korean population and this has not been replicated in other ethnicities to date (47).

The genotypes HLA-C\*07:02 ( OR 1.16), HLA-C\*16:01 (OR 0.74) and HLA-C\*03:04 (OR 0.81) were all associated with ulcerative colitis but are in linkage disequilibrium with other implicated HLA genotypes (including HLA-B and DRB1)(25).

HLA-DQA and HLA-DQB

The most established association with HLA-DQ is with coeliac disease, namely serotypes DQ2.1 and 2.5 (comprised of DQB1\*02 and DQA1\*02:01 or DQA1\*05:01) and DQ8 (comprised of DQB1\*03:02 or DQB1\*03:05 and DQA1\*03:01 or DQA1\*03:02)(48). These genotypes, particularly HLA-DQ2, are less frequent in patients with ulcerative colitis and to a lesser extent Crohn’s disease. The serotype HLA-DQ2.5 is specifically protective for ulcerative colitis (seen in 16.43% with ulcerative colitis compared to 23.74% of controls and 26% of Crohn’s disease) and this effect is more pronounced in women (>50% less frequent) (48). Work by Goyette *et al* and De La Concha *et al* replicated this for all patients, with the risk for ulcerative colitis being reduced in patients with genotypes associated with the coeliac disease HLA serotypes, namely HLA-DQA1\*03:01 (OR 0.68), DQA1\*02:01 (OR 0.73), DQB1\*03:02 (OR 0.67), DQB1\*02:01 (OR 0.86) and DQB1\*02:02 (OR 0.76)(25,49).

Several HLA-DQB1 genotypes have been strongly implicated in the Japanese population (especially DQB1\*04) and some smaller studies (<500 patients) in those with European ancestry (40,50,51). The DQB1\*04 allele group is in strong linkage disequilibrium with a number of HLA-DRB1 alleles (including DRB1\*08:01, DQB1 04:02, DRB1\*04:05, DRB1\*04:10 and DRB1\*08:02), presenting difficulty in distinguishing DQB1 as an independent risk genotype (52). Increased prevalence of extensive colonic disease has been demonstrated with the HLA-DQB1\*06 genotype (53).

As for DQB genotypes, independent association between increased risk for Crohn’s disease/ulcerative colitis and specific DQA genotypes is lacking, largely due to linkage disequilibrium with more dominant HLA-DRB1 genotypes (25).

HLA-DPA and HLA-DPB

Both monomers of the HLA-DP heterodimer (HLA-DPA and DPB) are highly variable (2). HLA-DPA1\*01:03 has been reported as independently protective in Crohn’s disease (OR 0.91)(25). To date. HLA-DPA1 variation is not associated with ulcerative colitis (25,54).

In European ancestry patients, HLA-DPB1\*04:01, DPB1\*02:01 and DPB1\*08:01 have all been reported as reducing risk of Crohn’s disease although data are sparse and poorly replicated (55). HLA-DPB1 has been related to ulcerative colitis, as both an independent protective genotype (DPB1\*03:01, OR 0.83) and as a co-inherited risk allele (DPB1\*04:01, OR 1.1)(25). The HLA-DPB1\*02:02 and DPB\*09:01 genotypes have also been observed with increased risk of ulcerative colitis but these studies have not been replicated (56). Primary sclerosing cholangitis, often presenting in patients with ulcerative colitis, has specific risk HLA-DPB1 genotypes (DPB1\*03:01, DPB1\*05:01) (57).

HLA-DRB1 and linked genes

*DRB1\*01:03*

First identified in 2000 and now replicated on multiple occasions, the DRB1\*01:03 allele (frequency of <2%) is associated with a significant risk of colonic Crohn’s disease and ulcerative colitis (25,50,58,59). This HLA allele is the most robustly, and significantly, implicated in Crohn’s disease. The most recent GWAS reported an OR of 2.51 (25). Meta-analysis of available data in 2008 confirms the significant association with a colonic Crohn’s disease phenotype only (40). For ulcerative colitis this relationship have been replicated in multiple studies of European ethnicity and a single Mexican study, with the most recent work by Goyette *et al* associating the genotype with an OR of 3.59 (23–25). These results have not been replicated in the Japanese where the genotype is extremely rare (60).

Specific phenotypic characterisation of the genotype has identified increased incidence of pancolitis and severe disease, with patients at increased risk of colectomy (25,26,61). In 2018 Venkateswaran *et al* reported an enhanced role for HLA variation in paediatric onset ulcerative colitis patients by performing a GWAS using 466 paediatric-onset UC patients (and 2099 controls). The HLA-DRB1\*0103 genotype was associated with an odds ratio (OR) of 6.94 in children, with the overall HLA association being twice that seen in adult onset disease (62).

*DRB1\*07*

The HLA-DRB1\*07 allele was identified as having a weak association with Crohn’s disease (OR 1.42) in 1999 (23). Since then the relationship has been replicated in ileal Crohn’s disease patients only, with absence of this association in colonic inflammation (24,25,59,63,64). Pooled meta-analysis confirms a weak overall association between DRB1\*07 and Crohn’s disease, OR~1.2 (40). In contrast HLA-DRB1\*07 genotype is protective in ulcerative colitis (OR ~0.60-0.73) (25,63). Despite this there have been some reports of the DRB1\*07 allele being a risk factor for severe ulcerative colitis in a patients with established disease but these findings have not been replicated (65).

*DRB1\*15:01 and \*15:02*

These are common HLA-DRB1 alleles, seen in 6-25% of individuals with European ancestry (1). The DRB1\*15:01 allele shows a mild protective effect in Crohn’s disease in people of European ancestry (OR~0.90) (25). In contrast, DRB1\*15:01 data from recent GWAS and further analysis of HLA haplotypes have significantly implicated this genotype in ulcerative colitis (OR 1.32)(25,49). The HLA-DR15 serotype (HLA-DRB1\*15:01-05 and 15:07) has also been associated with a subgroup of severe, extensive colitis (66).

Data indicates the DRB1\*15:02 allele is a risk genotype in Crohn’s disease in those of European ancestry (OR 1.65) but protective in Japanese (OR 0.4) ethnicities, these results must be interpreted with caution as these alleles are seen as part of the HLA-C\*12:02 haplotype (including the HLA-B\*52 genotype) and the results have not been replicated (32,67). The DRB1\*15:02 genotype has been associated with an increased risk of ulcerative colitis in European and Asian populations (26,32,50,68). As this allele is in linkage-disequilibrium with other risk loci it is difficult attribute causation in either disease subtype (25,26,40). Furthermore an additional IBD risk gene, BTNL2, located within the HLA complex and involved with T-cell regulation, harbours variants in strong linkage disequilibrium with DRB1\*15:02 (69).

*HLA-DRB1\*13 and DRB3\*03:01*

HLA-DRB1\*1302 and DRB3\*03:01 are in strong linkage disequilibrium and individual effects are difficult to discriminate. The most recent GWAS associates DRB1\*13:02 with a modest increase in Crohn’s disease risk (OR 1.32)(25). Similarly, previous data have consistently reported a relationship between DRB3\*03:01 presence and risk of Crohn’s disease (24,67,70). Pooled analysis of available data in 2008 showed significantly increased Crohn’s disease risk with DRB3\*03:01, OR ~1.25 (40).

HLA-DRB1\*13 was originally designated as a protective ulcerative colitis genotype in European populations in the 1990s (71). Recent data, also from European ancestry patients, reports the HLA-DRB1\*13:01 allele as a risk genotype (OR 1.17), whereas the HLA-DRB1\*13:02 genotype remains protective (OR 0.84) (25). The HLA-DRB1\*13:01 genotype was the most associated genotype with younger age of disease onset (through linear regression) in a recent study involving 12,597 adult and paediatric patients (OR~0.4) (63).

*DRB1\*04*

A 1999 meta-analysis pointed towards a higher prevalence of DRB1\*04 in patients with Crohn’s disease (23). However there is strong linkage disequilibrium with a range of other HLA genotypes including HLA-DQA1\*03:01, HLA-DQB1\*03:02, HLA-C\*03:04 and HLA-B\*40:01 (25,26). DRB1\*04 has achieved statistical significance in Japanese patients (OR 2.9), but there is also data to indicate higher prevalence of risk alleles (DRB1\*04:01, DRB1\*04:05 and DRB1\*04:10) in Crohn’s disease patients with European ancestry (OR 3.9) (40,64,72). However Goyette *et al* failed to find a significant risk association with DRB1\*04 in their recent analysis with an OR~0.79 indicating a potentially protective effect (25). In ulcerative colitis HLA-DRB1\*04 genotypes are protective with the most significant signals from the HLA-DRB1\*04:04 genotype (OR 0.56)(23,25). There is a significant reduction in the HLA-DRB1\*04 genotype in patients with primary sclerosis cholangitis (PSC), suggesting a common protective factor with ulcerative colitis (73,74).

*HLA-DRB1\*03:01*

Bouma *et al* found HLA-DRB1\*03 to be protective against fistulating Crohn’s disease (75). Similarly, HLA-DRB1\*03:01 was identified by Goyette *et al* as an overall protective genotype, OR 0.85 (25). A 2017 GWAS on patients from the United Kingdom by Lee *et al* also found a significant protective effect of HLA-DRB1\*03:01, OR 0.69 (41).

*Additional DRB1 genotypes*

In their meta-analysis, Goyette et al attempted to control for the co-existence of other DRB1 (and HLA gene) alleles with the results indicating the only independently associated, potentially causative, allele being DRB1\*01:03 (25). Data from Connelly *et al* implicated a SNP (rs3135391) in HLA-DRB1\*05:01 with age of onset of Crohn’s disease <60 years compared to >60 years, but this did not withstand multiple correction testing (Bonferroni) (76).

The HLA-DR17 serotype (including the DRB1\*03:01, DRB1\*03:04, DRB1\*03:10 and 03:11 genotypes), has been reported as a risk factor for development of colorectal carcinoma in ulcerative colitis, whilst HLA-DR7 appears protective (77). The DR13 (HLA-DRB1\*13 etc.) serotype has been associated with increased risk of pancolitis, surgical resection and extra-intestinal manifestations (78). The HLA-DRB1\*08 genotype has been associated with extensive ulcerative colitis (OR 2.2) in Japanese population, whilst HLA-DRB1\*09 was associated with age of onset >40 years of age (OR 2.31) (60).

*DRB3, DRB4, DRB5*

The DRB paralogs, which have variable expression (and presence) in individuals, have also been connected with Crohn’s disease risk. Within an individual, HLA-DRB1 is present (as a haplotype) with either one of HLA-DRB3, DRB4 or DRB5, or may be inherited with no paralogs. There are multiple pseudogenes, with variable presence (differing haplotypes), including DRB2, DRB6, DRB7, DRB8 and DRB9, which have also been connected to risk (2,40). Variation in HLA-DRB3, DRB4 and DRB5, alongside presence of DRB6, DRB7 and DRB8 have been associated with increased risk of Crohn’s disease (23,40,41). However the strong linkage disequilibrium between HLA-DRB1 genotypes and paralogs makes assigning causation difficult.

A recent Korean study identified HLA-DRB4\*01:01 as a risk genotype for ulcerative colitis, however this allele was in strong linkage disequilibrium with a SNP, rs9268877, lying between the HLA-DRA and DRB genes (79). Following correction for this genotype, rs9268877 was the strongest risk signal and conferred an increased risk of severe disease with poor outcome (OR 1.72)(79).

1. **The role of HLA in disease pathogenesis**

The mechanisms by which specific genotypes of class I and II HLA genes contribute to disease pathogenesis has not been elucidated. Broadly the class I and II complexes are vital in the recognition and response of the host immune system to pathogenic bacteria and infected host cells, and simultaneously the recognition and tolerance to commensal bacteria and ‘self’ host cells (2). The inflammatory processes seen in IBD are likely to be multifactorial, and the exact mechanisms are likely to be patient specific and a combination of multiple processes, table 3.

The role of the HLA complex is critical for several processes including the triggering of downstream signalling cascades, antigen presenting cell response (including through NK cells, innate lymphoid cells and T-regulatory cells) and regulation of commensal intestinal bacteria (80).

*Antigen binding cleft variation and peptide presentation*

Amino acid variation at the antigen binding site, as dictated by the HLA genotype, has been proposed as a potential mechanism for disease pathogenesis. Goyette *et al* identified strong associations with amino acids at positions 67, 70 and 71 in HLA-DRB1 for Crohn’s disease (25). In ulcerative colitis amino acids at positions 50 and 53 and 215 in HLA-DQA and at positions 98 and 104 in HLA-DRB1 were identified, figure 3. Previous findings by Achkar *et al* were also replicated, with the amino acid at position 11 in HLA-DRB1 being implicated in ulcerative colitis (25,81). Goyette et al went on to build a computational model to examine the structural properties of risk versus protective HLA-DRB1 genotypes and observed distinct features within or adjacent to the antigen binding cleft, in both Crohn’s disease and ulcerative colitis. These appear likely to impact on antigen presentation (25). Whilst this suggests a causative role for amino acid substitutions associated with HLA-DRB1 genotypes, not all associated amino acid changes (encoded for by risk genotypes) impact on the antigen binding domain, suggesting other mechanisms may be important or the functional impact is due to another HLA genotype in linkage disequilibrium.

*Molecular mimicry*

Molecular mimicry is seen due to commonality between epitopes in microorganisms (bacteria, viruses etc.) or dietary molecules and the host, leading to activation of downstream B or T-cell signalling and an autoimmune process directed against the host antigen (e.g. cell) (82). This causes the recognition of ‘self’ to be altered or less efficient. This is limited evidence of certain HLA class II genotypes recognising similar epitopes between two specific bacterial amino acid sequences and the colonic antigen human tropomyosin isoform 5 (83). Further evidence for the potential protective role of HLA can be seen in work by Nanjundappa *et al*, who demonstrated a shared epitope between the host, pancreatic β cell autoantigen islet-specific glucose-6-phosphatase-catalytic-subunit-related protein, and a species of *Bacteriodes* (integrase enzyme) (84). This bacteria triggered recruitment of cross-reactive CD8+ T cells promoting anti-inflammatory processes and protecting against colitis in a HLA class I dependant process (84). The authors did not explore whether this would be affected by different HLA genotypes, figure 4.

*Regulation of tolerance*

The regulation of immune tolerance to commensal bacteria is a key part of mucosal immunity and involves interaction between bacteria, antigen-presenting cells, epithelial cells, T-cells and downstream cytokine signalling (85). Interestingly the HLA-G non-classical class I gene has been widely implicated in immune tolerance but has not been identified as a risk or protective locus in IBD (86). In IBD, HLA-G has been reported as being expressed in the colon of patients with ulcerative colitis but the functional impact of this is poorly understood (87). HLA-G plays a role in the protection of the foetus from the maternal immune system by inhibiting natural killer, t-cells, b-cells, monocytes and dendritic cells through binding to inhibitory receptors (88). HLA-G has been implicated as a potential therapeutic target in oncology and transplant medicine (88). The overall regulation of immune response within the intestine is extremely complex and involves a low-grade ‘physiological’ inflammation based around antigen recognition (89). This is primarily through recognition of microflora by toll-like receptors on antigen presenting cells (such as dendritic cells and macrophages) and subsequent HLA class II presentation of epitopes on the antigen presenting cells, stimulating T and B-cell differentiation, proliferation and downstream inflammation or immune control (89). The role of HLA molecules in this is poorly elucidated but it can be hypothesised that some genotypes may differentially stimulate T-cells (especially T-regulatory cells and T-helper 17 cells) leading to either promotion or lack of tolerance to commensal bacteria (90).

*HLA-C cell surface expression*

An increased expression of HLA-C on immune cell membranes has been associated with an increased risk of Crohn’s disease, whilst the expression of certain HLA-C genotypes have recently been shown to be impacted on by the microRNA, miR-148a (91,92). MicroRNAs are short non-coding RNA molecules involved in the post-transcriptional regulation of gene expression. Where HLA-C allele expression was inhibited by miR-148a there was a decreased risk of Crohn’s disease compared to controls, suggesting a direct role for specific HLA-C signalling in the development of Crohn’s disease (91).

*Interaction with T-helper 17 cells*

T-helper 17 cells (Th17) play a specific role in the maintenance of mucosal immunity and barriers through pathogen clearance and commensal recognition. There is some murine evidence that reduction in the expression of HLA class II heterodimers results in an increase in the number of Th17 cells and an increase in the expression of pro-inflammatory cytokines (93). The regulation of HLA class II expression is complex but is impacted on by other genes, including accessory class II genes, in the HLA complex, through epigenetic modification, alongside environmental stimuli and potentially HLA class II genotypes (94).

Evidence for Th17 involvement in systemic inflammation exists through analysis of the microbiome in Crohn’s disease patients with spondyloarthropathy, where *E. coli* species appear to induce Th17 dependant systemic inflammatory processes (95).

*Interaction with killer immunoglobulin-like receptors and ERAP1*

There has been significant interest in the interaction between HLA-C genotypes and *ERAP1+2* proteins and killer immunoglobulin-like receptors (KIR). ERAP1 is a peptidase that functions to cleave peptides for presentation via HLA class I complexes, subsequent regulation of Natural Killer (NK) cells is dependent on KIR and HLA class I interaction and failure of normal NK inhibition or anomalous activation can lead to NK mediated cell death (96). A recent study described the IBD risk conferred by *ERAP1* as being dependant on the HLA-C\*07 genotype, presenting a possible novel regulatory interaction (97). The interaction between KIRs and HLA-Cw (and HLA-Bw) serotypes has been implicated as both a risk and protective factor for IBD depending on the KIR genotype expressed (96,98,99). This effect is thought to be primarily due to variation at the KIR locus but the HLA genotype influences (and may regulate) the relative effect of the genetic risk (99).

*Direct mucosal HLA interaction with commensal bacteria*

The interaction between HLA heterodimers and bacterially-derived epitopes is complex. Homozygous HLA-DR4 serotype (HLA-DRA\*01:01/HLA-DRB1\*04:05) murine models develop spontaneous colitis and accumulation of expressed HLA-DRB4 in colonic epithelium appears to trigger colitis through interaction with commensal gut bacteria. Knockout HLA-DRB4 mice with do not develop colitis, confirming a key role for HLA in reaction to commensal intestinal microflora (100).

The role of microbial interaction with specific HLA genotypes is of interest. Transgenic HLA-B27 rats raised in a sterile environment do not development of colitis, however in non-sterile conditions colitis was worsened with a higher bacterial load (101). Increased bacterial load was thought to be associated with worsening inflammation through upstream and downstream signalling leading to immune responses distant to the bacterial insult, including gastritis and arthritis (101). These results suggest a role for abnormal HLA signalling in the presence of normal commensal bacteria.

The major modifier of expression in the class II, and to a lesser extent class 1, regions is the class II transactivator (*CIITA*) (102). Variation in *CIITA* gene has been linked to other autoimmune conditions including Addison’s disease and multiple sclerosis but not yet to IBD (103). CIITA expression, and induction of class II genes, can be impacted by bacteria species (including *Clostridae*), in colorectal cancer levels of CIITA protein are elevated through IL-27cytokine response, suggesting a potential host-environment interaction leading to adherent immune response through increased expression of class II receptors (104).

1. **Implication of HLA in medication response and reaction**

The HLA complex has been implicated in the response to medication, including those used in IBD management. There is particular interest in hypersensitivity reactions against therapies and the loss of response to specific medications (105). Medication response represents the best chance for early clinical translation of HLA testing as a means of predicting therapeutic outcomes or toxicity.

*5-Amino-salycylic acid (5-ASA)*

5-ASA associated nephrotoxicity, and biopsy proven interstitial nephritis, is a rare adverse event seen following ulcerative colitis treatment. A study published in 2016 identified a significant risk association with the SNP rs3135349 (OR 2.76). This SNP is strongly correlated with the HLA-DRB1\*03:01 genotype, presenting an increased risk of nephrotoxicity with this allele, although the overall absolute risk was extremely low (106).

*Thiopurines*

The side effects of thiopurine medications (azathioprine, 6-mercaptopurine) are numerous and include short term (e.g. bone marrow suppression, liver toxicity and pancreatitis) and long term (increased risk of malignancy) complications. A 2014 study focusing on the risk of pancreatitis in thiopurine therapy found a 17% risk for patients homozygous for the rs2647087 SNP that characterises the HLA-DQA1\*02:01-HLA-DRB1\*07:01 haplotype (107). In addition, recent data published in 2018 has suggested that whilst on azathioprine for IBD, there was is a 14.63% risk of pancreatitis in patients homozygous for the HLA‐DQA1\*02:01‐HLA‐DRB1\*07:01 haplotype (as assessed by the rs2647087 SNP) as opposed to a 0.53% risk in wild-type patients (108). The authors concluded that in addition to TPMT enzyme/gene testing, patients should be screened for the HLA haplotype prior to starting therapy.

*Methotrexate*

Methotrexate, like thiopurines, may be used either as an IBD mono-therapy or in conjunction with a monoclonal antibody therapy to reduce immunogenicity. Successful use of methotrexate has been linked to HLA haplotypes, including the HLA-DRB1\*04:04 and \*01:01 alleles, but when in conjunction with etanercept (109). Malignancy (specifically lymphoma) risk is present for methotrexate, there is increased risk with HLA-A\*24:02 and DRB1\*04:05 alleles, although the absolute risk was extremely low (110).

*Anti-TNF monoclonal antibodies*

Recent data from the PANTS study, focusing on the genetic factors effecting response to anti-TNF therapy, reported the HLA-DQA1\*05 genotype as being significantly associated with higher rates of antibody formation against both infliximab (hazard ratio, HR 1.91) and adalimumab (HR 1.89)(111). This is a common genotype in Northern European individuals having an allele frequency ~0.25 (112). This effect was constant with (HR 2.0) or without (HR 1.75) concurrent immunosuppression, with up to 92% of patients treated with anti-TNF monotherapy carrying the HLA-DQA1\*05 having antibody formation at one year. However, importantly, the study did not associate this increase in antigenicity with an increased loss of response to anti-TNF therapies (111). Clinical testing for this genotype is heavily limited by the lack of impact on disease outcome, however the PANTS data does provide a clear roadmap for future utility of HLA genotyping to personalise therapy, including targeted use of monotherapy, combination therapy and new generation monoclonals.

Interestingly in patients with ankylosing spondylitis who are treated with anti-TNF therapy the presence of the HLA-B27 genotype was associated with an improved response (pooled OR 1.81), although these results have not been replicated in IBD and this may be a disease specific effect (113).

*New generation monoclonals*

Newer monoclonal therapies, including vedolizumab (anti- α4β7 integrin monoclonal antibody) and ustekinumab (anti IL12/23 monoclonal antibody) have recently become more important in the treatment of both Crohn’s disease and ulcerative colitis. Association of response with HLA genotypes has been prominent in early use of ustekinumab, with multiple reports of improved response with the HLA-C\*06:02 genotype (HLA-Cw6 serotype) in psoriasis, for which the medication for first licenced. Data on this association in IBD has not yet been reported (114,115).

1. **Discussion**

The exploration of the HLA complex has identified significant associations with both subtypes of IBD, despite limitations in the technology available to researchers. Whilst the pace of genetic discoveries in IBD has accelerated, the translation into functional understanding and clinical practice has lagged behind. Something the HLA region epitomises. The relatively small increase in risk/protection per genotype, alongside poor understanding of the actual processes underlying the relationship between specific HLA haplotypes/genotypes and disease pathogenesis pose additional challenges. The associations between HLA genotypes and disease location, disease outcomes (including extent, treatment and surgery) and age of disease onset point towards a future clinical application for HLA testing in IBD, to aid with personalising therapy, potentially through machine learning approaches. However the limitation of next generation sequencing techniques, especially whole exome sequencing, to accurately genotype the highly polymorphic region, the imperfection of imputation of HLA genotypes (from array sequencing), the rarity of some risk alleles and the inability to discern phase (and therefore compound zygosity) are areas where improvement in technology may be able to provide some answers. This lack of resolution is further confounded by high linkage disequilibrium within the region, making ascertainment of causality even more difficult. Long read chemistry (from companies such as *Pacific Biosciences*, Palo Alto, USA) will enable substantial improvement in the resolution of the region, accurate ascertainment of genotype phase and potential insights into intergenic regulatory regions (116). Researchers have now demonstrated typing HLA to the fourth field reveals previously “hidden” haplotypes, such as B\*07:02:01~C\*07:02:01:03, B\*07:06:01~07:02:01:01 (117). With the ability to determine variation to this level of resolution, more distinct HLA associations and additional variation that is of clinical relevance, may become apparent (117,118). In addition, there is a lack of replication of results, in part due to the very large, genotyped, cohorts required to conduct accurate and robust GWAS studies. Beyond this there have been concerns raised over the ability of GWAS studies to identify biologically important genes/genotypes due to complex genomic interactions, something highly relevant to the HLA region (119).

The translation of genetic data into functional science and then into clinical application poses both a challenge and an opportunity to IBD researchers, as can be seen in the recent association between increased in anti-TNF therapy antibody formation in patients with specific HLA-DQA alleles (111). Common pathways between autoimmune conditions, including IBD, may reveal additional treatment options amongst existing medications and present novel pathways for new therapies to target. Beyond the classical genes discussed in this review the 420+ additional coding regions of the extended MHC region may also harbour risk or causation genes, either independently or in linkage disequilibrium with classical HLA genotypes. However, despite great potential, there are currently no clear uses for clinical HLA testing in IBD, either to detect individuals at increased risk or to determine prognostic or therapeutic outcomes. This contrasts with conditions such as coeliac disease and ankylosing spondylitis where there are established uses for determining HLA genotypes to aid with diagnosis.

The clear direction of movement in IBD therapy is towards improved, personalised, treatment reducing the significant side effects and complications that some medications may present (120). The future direction of HLA research in IBD has many opportunities for advancement and may include screening for risk of disease development, alongside use of HLA genotyping in models for predicting disease outcomes. Whilst challenges remain, this complex genetic region is likely to hold vital information in the future understanding of disease pathogenesis and may be key in promoting precision medicine in IBD.

**Figures and Tables**

**Table 1-** Glossary of important terms

**Table 2**- HLA genotypes significantly associated with inflammatory bowel disease. Associated alleles seen in linkage disequilibrium with HLA-DRB1 genotypes, where the association is explained by the HLA-DRB1 allele, have been excluded from this table for clarity. If multiple studies implicated a genotype only the most recent data (post 2008) are shown. Allele frequency is for European ancestry only (112).

**Table 3-** Potential underlying processes leading to inflammation in IBD

**Figure 1A**- A linkage disequilibrium map demonstrating 15mb of chromosome 6, including the 4mb HLA region (beginning at mb~29,500 and ending at mb~33500). HLA class I genes are shown as red circles and HLA class II genes are shown as green diamonds. There is extensive linkage disequilibrium in the classical class 2 cluster indicating many alleles are inherited as haplotype blocks.

**Figure 1B-** Schematic representation of the area of chromosome 6 showing the location of the HLA complex and the relative locations of the class 1 and 2 genes.

**Figure 1C-** Heatmap demonstrating the sequence homology between HLA genes, high homology between genes is represented by green, with low homology in red. Many sequences are highly homologous, and highly polymorphic, making sequence mapping very difficult.

**Figure 2**- Graphical representation of the odds ratio for each independently associated HLA genotype. Un-replicated studies on <500 patients have been excluded from the graph. Where >1 study has implicated a genotype the odds ratio from the larger study has been used to represent the risk.

**Figure 3-** 3-Dimensional representationof the HLA-DR protein structure taken from the SWISS-MODEL Repository (121). Shown are the DRA1 (cyan) and DRB1 (yellow) monomers, forming the heterodimer, alongside a peptide (white/purple) within the antigen binding cleft. Purple stars equate to amino acids (at position 67, 70 and 71) implicated in Crohn’s disease, and orange dots (at position 98 and 104) are those implicated in ulcerative colitis (25). These amino acid alterations are thought to impact on the electrostatic + structural properties of the antigen binding cleft, and are distinct from variants that reduce the risk of Crohn’s disease/ulcerative colitis.

**Figure 4-** Potential functional impacts of HLA variation in the pathogenesis of inflammatory bowel disease (IBD).

Specific HLA genotypes (not yet discovered) may exacerbate the immune response to normal commensal (or pathogenic) bacteria through enhanced/specific epitope binding triggering downstream immune responses (green star 1). Molecular mimicry of host peptide sequences (derived from cell surface receptors or products of autophagy) with bacterial epitopes recognised by MHC II proteins (on antigen presenting cells) and presented to T-cells (T-helper cells, CD4+)(green star 2), this stimulates downstream inflammatory responses through cytokine (TNF, IL1) production.

MHC class I molecules (on any nucleated cell) also present endogenously derived antigens to T-cells (Cytotoxic T-cells, CD8+) resulting in destruction of that cell. Endogenous antigens on cells may mimic exogenously derived viral/bacterial epitopes in the same way as for MHC class II, resulting in destruction of the cell.

The functional impact of HLA variation converges to cause chronic damage and inflammation. There is the potential for all four of the abnormal immune responses (purple stars 1-4) implicated in IBD pathogenesis to be triggered by HLA variation through either molecular mimicry or altered epitope binding by MHC class I and II.

Abbreviations-

* APC- antigen presenting cell (including dendritic cells, phagocytes, specific endothelial cells and some B cells)
* MHC II- major histocompatibility complex class II molecule
* TCR- T-cell receptor (recognises peptide fragments bound to MHC molecules)
* TNF-α – Tumor necrosis factor alpha, an acute phase cytokine stimulating systemic and local inflammation (including immune cell recruitment, infiltration and phagocytosis). It is produced primarily by macrophages and lymphocytes.
* IL-1 – Interleukin 1 (cytokine superfamily), a group of acute phase cytokines that activate downstream signalling to induce migration of inflammatory cells into a tissue and induce inflammation.
* IL-6 – A pro + anti-inflammtory cytokine that is a principal regulatory mediator of acute phase response.

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Table 1- Glossary

* **Allele-** Specific form of a gene, characterised by a specific variation seen in that allele. Each gene has two copies, inherited as maternal and paternal alleles. Some genetic alleles are associated with observable phenotypic characteristics or disease.
* **Classical HLA genes-** Comprised of the nine genes split into class I (HLA-A, HLA-B, HLA-C) and class II (HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, and HLA-DRB1) genes. Most are extremely polymorphic and function to present antigens (epitopes) to the host immune system. Play a large role in recognition of self and heavily implicated in autoimmunity. Paralogs of DRB1 are also classed as classical HLA genes (include DRB4 and DRB5).
* **Classical Class 1 HLA gene-** HLA-A, HLA-B and HLA-C, having the major function to present peptides found inside the cell, often virally-derived, to CD8+ T-cells and natural killer (NK) cells (endogenous antigen presentation)
* **Classical Class 2 HLA gene-** HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, and HLA-DRB1, have the of presenting exogenous antigens, often bacterially-derived, to CD4+ T-cells, triggering clonal expansion (into T-helper 1 cells and T-helper 2 cells) and with subsequent stimulation of macrophage or B-cell activity
* **Epitope**- A specific part of an antigen that is recognised by the immune system, and presented by classical MHC proteins to T-cells.
* **Genotype-** HLA genotypes are composed of specific alleles, this is a more precise method of designating a specific DNA sequence at a HLA gene location. They are named with letters and numbers e.g. HLA-B27 is comprised of the HLA-B\*27:01 allele (genotype), or one of many others (HLA-B\*27:01-27:197). Field separators indicate the functionality of the variant positions e.g. coding or non-coding region, synonymous or non synonymous.
* **Human Leucocyte Antigen (HLA) region** - A human gene complex located on the short arm of Chromosome 6 (6p21.3) encoding the major histocompatibility complex proteins. The extended region contains greater than 420 gene loci, with nearly 30% associated with immune function, including the Class I and II HLA genes. This is highly polymorphic region is heavily implicated in human autoimmune disease.
* **GWAS**- Genome wise association study, the assessment of a genome-wide set of genetic variants (SNPs), in large numbers of individuals, to assess whether variants are associated with a trait, such a disease/outcome.
* **Haplotype**- A group of specific alleles, or SNPs (in this case HLA alleles) co-located and inherited together as a single block of DNA. In the HLA region certain combinations of HLA alleles are more likely to be inherited together as a haplotype and are often the result of a single common ancestor. An example is the HLA A1-B8-DR3-DQ2 haplotype (also known as the 8.1 ancestral haplotype), present at >11% frequency in Ireland.

Table 1- Glossary cont.

* **Homology**- Referring to the similarity between (DNA) sequences, those with high sequence homology share genetic sequence and may lead to alignment mapping issues.
* Imputation- Assignment of a genotype, in this context a HLA genotype, by inference from SNPs at sites near to the classical HLA loci, in linkage disequilibrium with that HLA genotype. Methodology varies but it is accurate in 70-99% of cases depending on the number of SNPs used to impute, how well the HLA genotype is characterised (rare alleles are difficult to impute) and the quality of the bioinformatic tools.
* **Linkage**- The tendency of (DNA) sequences that are close together to also be inherited together, occurs due to no/low levels of recombination events between areas in linkage
* **Linkage Disequilibrium**- Non-random association of two or more alleles at different genetic loci. Loci are said to be in linkage disequilibrium when the frequency of association of their different alleles is higher than would be expected by chance. The HLA region comprises an area of the genome with extensive linkage disequilibrium. If alleles are in inherited independently of each other they are in (linkage) equilibrium.
* **Major histocompatibility complex (MHC)-** A group of cell surface receptors (proteins) responsible for immune regulation and immune tolerance. Major function is to bind pathogen-derived antigens (epitopes) and display them to T-cells.
* **Non-classical HLA genes-** Comprising many of the remaining genes within the region (such as HLA-E, F, G), they have much more limited expression but still often have antigen presenting function; most of this group is co-located with classical genes in the HLA region
* **Odds Ratio (OR)**- A statistical measure for quantifying the association between two events or outcomes, in the context of genetics this can be thought of as a ratio; the presence of a specific genotype (or haplotype/serotype) with a condition (IBD), >1 indicates increased association (risk), <1 indicates decreased association (protective).
* **Phase**- The ability to derive which chromosome (maternal or paternal) a specific variant, or set of variants is on. Allows for ascertainment of compound heterozygosity without the need for segregation analysis.
* **Serotype-** HLA serotypes represent the expressed HLA molecules present within an individual, they are from a classification system based on the antigens present in the serum. They are assigned letters and numbers e.g. HLA-B27. Solid organ transplantation allocation is based on this classification system.
* **SNPs**- Single nucleotide polymorphisms are single DNA base changes that can be used to characterise an area of the genome in an individual or group. In the HLA region, due to linkage disequilibrium, some SNPs may be used to impute HLA genotypes.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Class** | **Locus** | **Genotype** | **Estimated allele frequency in European ancestry populations** | **Confirmed linkage disequilibrium with other implicated genotypes** | **Disease subtype** | **Specific phenotype and associations** | **Ethnicity** | **Odds Ratio (CD/UC)** | **P value (CD/UC), where available** | **Reference** |
| I | HLA-A | \*03:01 | 0.15 | No | CD |  | European ancestry | 1.10 | 9 x 10-8 | Goyette et al |
|  | \*02:01 | 0.29 | No | CD/UC |  | Japanese  European ancestry | 1.64  1.13 | 2 x 10-14 | Goyette et al  Oryoji et al |
|  | \*02:07 | 0.0004 | No | CD |  | Japanese | 2.31 | 0.0067 | Oryoji et al |
| HLA-B | \*52:01 | 0.01 | Yes | CD/UC | Lower overall colectomy risk | European ancestry | 1.44/2.21 | 3 x 10-8  9 x 10-37 | Goyette et al |
|  | \*18:01 | 0.05 | No | UC |  | European ancestry | 0.82 | 5 x 10-8 | Goyette et al |
|  | \*14:02 | 0.02 | Yes | CD |  | European ancestry | 1.28 | 8 x 10-10 | Goyette et al |
|  | \*35:02 | 0.015 | No | CD |  | European ancestry | 0.68 | 2 x 10-8 | Goyette et al |
|  | \*35:03 | 0.035 | No | CD |  | European ancestry | 0.72 | 7 x 10-8 | Goyette et al |
|  | \*27 | 0.045 | Yes | UC | Spondyloarthropathy  Uveitis | European ancestry | 1.4 | Ŧ | Fernando et al |
| HLA-C | \*08 (w8 serotype) | 0.03 | Yes | CD |  | European ancestry | 3.5 | Ŧ | Fernando et al |
|  | \*01 | 0.035 | No | CD |  | Korean | 1.52 | 8.7 x 10-10 | Jung et al |
|  | \*06:02 | 0.10 | Yes | CD |  | European ancestry | 1.17 | 2 x 10-13 | Goyette et al |
|  | \*12:02 | 0.01 | Yes | CD/UC |  | European ancestry | 1.44  2.25 | 2 x 10-13  4 x 10-37 | Goyette et al |
|  | \*14:02 | 0.01 | No | CD |  | Japanese  European ancestry | 1.32  2.18 | Ŧ  6 x 10-7 | Oryoji et al Goyette et al |
| II | DRB1 | \*01:03 | 0.0015 | Yes | CD/UC | Colonic disease- increased risk of colonic CD  Increase risk of colectomy  Type 1 arthropathy | European ancestry | 2.51/3.59 | 9 x 10-62  3 x 10-119 | Fernando et al Goyette et al |
|  | \*01:01 | 0.06 | Yes | CD | Type 1 arthropathy | European ancestry | 0.81 | 3 x 10-17 | Goyette et al |
|  | \*07:01 | 0.13 | Yes | CD/UC | Ileal disease- protective for UC | European ancestry | 1.14/0.73 | 5 x 10-12 | Goyette et al |
|  | \*15:01 | 0.12 | Yes | UC | Severe, extensive colitis | European ancestry /Indian | 1.32 | 3 x 10-44 | Goyette et al |
|  | \*13:02/DRB3\*03:01 | 0.045 | Yes | CD/UC | Pancolitis, surgery, increased resection, younger onset and extra-intestinal manifestations | European ancestry | 1.32/0.84 | 1 x 10-9  1 x 10-6 | Goyette et al |
|  | \*13:01 | 0.06 | Yes | UC | European ancestry | 1.17 | 2 x 10-8 | Goyette et al |
|  | \*16:01 | 0.025 | Yes | CD |  | European ancestry | 0.68 | 5 x 10-10 | Goyette et al |
|  | \*04 | 0.18 | Yes | CD/UC | Protective against PSC  Ileal disease | Japanese  European ancestry | 2.9  3.9/0.71 | Ŧ  9 x 10-60 | Fernando et al Goyette et al |
|  | \*03:01 | 0.10 | Yes | CD/UC | Protective against fistulating disease  Risk for colorectal cancer in UC | European ancestry | 0.69/0.87 | 2 x 10-13  2 x 10-10 | Goyette et al  Lee et al |
|  | \*09:01 | 0.01 | Yes | UC |  | European ancestry | 0.50 | 2 x 10-14 | Goyette et al |
|  | \*08 | 0.03 | Yes | CD/UC | Extensive disease (negative correlation in UC) | European ancestry | 1.32/0.7 | 7 x 10-12  5·1 × 10−17 | Goyette et al  Fernando et al  Cleynen et al |
|  | \*11:01/\*11:04 | 0.07 | Yes | UC |  | European ancestry | 1.19-1.25 | 4-6 x 10-8 | Goyette et al |
|  | \*12:01 | 0.015 | No | UC |  | European ancestry | 1.47 | 3 x 10-15 | Goyette et al |
| DPA1 | \*01:03 | 0.8 | No | CD |  | European ancestry | 0.91 | 5 x 10-8 | Goyette et al |
| DPB1 | \*03:01 | 0.5 | No | UC | Protective against PSC | European ancestry | 0.83 | 1 x 10-12 | Goyette et al |
|  | \*04:01 | 0.2 | Yes | CD |  | European ancestry | 1.85 | 0.007 | Trachtenberg et al |
| DQA1 | \*05:01 | 0.2 | No | CD |  | European ancestry | 0.7 | 1.9 x 10-5 | Lee et al |
| DQB1 | \*02:01 | 0.2 | Yes | CD |  | European ancestry | 0.71 | 3.7 x 10-5 | Lee et al |
|  | \*04 | 0.02 | Yes | CD |  | Japanese  European ancestry | 1.88  2.7 | Ŧ | Fernando et al  Stokker et al |

Table 2

Ŧ Exact p-value unavailable as data sourced from pooled results. Significant in pooled analysis (p=<0.05)

Table 3- Potential underlying processes leading to inflammation in IBD (80,122–124)

1. Overreaction to (commensal) bacteria (**hyper-immune**)
2. Inability to clear pathogenic bacteria and an ongoing local inflammatory response (**hypo-immune**)
3. Altered epithelial barrier function allowing invasion of bacteria into the mucosa (with concurrent **normal immune** response)
4. Inability to recognise self and subsequent inflammatory response (**auto-immune**)