Human leukocyte antigens in inflammatory bowel disease

Francisco Rodríguez-Moranta* and Jordi Guardiola

Inflammatory Bowel Diseases Unit, Gastroenterology Department, IDIBELL, Hospital Universitario Bellvitge, Hospitalet del Llobregat, Barcelona, Spain

Abstract

Major histocompatibility complex MHC proteins are encoded by highly polymorphic genes called human leukocyte antigens (HLA). These proteins play an important role in cell-mediated adaptive immune responses and their main function is to discriminate between host antigens and foreign antigens, as well as being involved in other regulatory functions of the immune system. Almost all autoimmune diseases (including inflammatory bowel disease) have been linked to the HLA complex. Associations between HLA genotypes and the risk of developing inflammatory bowel disease, the location of the disease, the extent, severity, the risk of surgery, the age of onset of the disease, and the coexistence of extraintestinal manifestations have been described. In addition, a link between adverse drug effects and certain risk alleles has been described, including the risk of immunogenicity to biological agents with potential utility in clinical practice.

Key words: Major histocompatibility complex. Human leukocyte antigens. Inflammatory bowel diseases. Crohn. Ulcerative colitis.

Introduction

The major histocompatibility complex (MHC) contains more than 420 genetic loci. This group of genes is found on the short arm of chromosome 6 (6p21.31)¹. It includes more than 250 genes, and it is one of the areas with the highest gene density.

MHC proteins are encoded by highly polymorphic genes which are known as human leukocyte antigens or (HLA) or. This region encodes MHC “classic” HLA genes and more than 200 proteins. These proteins play an important role in cell-mediated adaptive immune responses. They present peptides at the cell surface to CD8+ and CD4+T cells and their main function is to discriminate between host antigens and foreign antigens, as well as being involved in other regulatory functions of the immune system².

HLA is divided into Class I antigens, Class II antigens, and Class III antigens according to distribution and function. The heavy chain of MHC Class I, which corresponds

to Classical Class I antigens, is the expression of three genes called HLA-A, HLA-B, and HLA-C. The α and β chains of MHC Class II, which are also called Classical Class II antigens, are the expression of three pairs of genes. These genes include HLA-DP, HLA-DQ, and HLA-DR. Finally, Class III antigens contain genes necessary for the synthesis of proteins with immune function. These are HLA-F, E, H, X, DN, DO, and DM; and others including the complement system³.

Relationship between HLA and autoimmune diseases

The HLA complex performs functions in the regulation of inflammation through the innate and adaptive immune system. The regulation of the immune response depends on cellular interactions mediated by the HLA complex with recognition of self and foreign as a cornerstone of immune tolerance. Virtually all immune-related diseases have been linked to the HLA complex.

Correspondence:

Francisco Rodríguez Moranta

E-mail: frmoranta@bellvitgehospital.cat

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Patients with aplastic anemia present loss of the short arm of chromosome 6 in 13% of cases (0.09% in the healthy population)⁴. Furthermore, HLA-DRB3 * 01:01 is key to immune response in fetal and neonatal alloimmune thrombocytopenia⁵. This disease is caused by antibodies directed against the human platelet antigen 1a. The HLA-DRB3 * 01:01 allele has a dose-dependent effect on anti-HPA-1a levels.

Behçet's disease is more common in carriers of the HLA-B15 genotype. In these, symptoms appear earlier and may be associated with neurological and gastrointestinal manifestations⁶.

HLA-DR2 is closely related with multiple sclerosis⁷. This relationship is so close that it has motivated the development of trials of targeted immunotherapy against the DR2 antigen.

Celiac disease is limited to HLA-DQ haplotypes, psoriasis to HLA-C, and ankylosing spondylitis to HLA-B. The presence of the HLA-B27 allele is not essential for the development of spondyloarthropathy, but it is strongly associated with its development. HLA-B27 is present in up to 90% of patients with ankylosing spondylitis, and in up to 40-80% in uveitis patients and, less frequently, in psoriatic arthritis, and inflammatory bowel disease patients (IBD)⁷.

Rheumatoid arthritis is associated with HLA-DRB1⁸. Furthermore, HLA DRB1 * 15:01 may have an inducing effect with adult Still's disease (AOSD), while DRB1 * 09:01 has a protective effect⁹. In addition, a strong relationship between HLA-DRB1 * 11 and systemic juvenile idiopathic arthritis has been identified¹⁰. In this sense, it is interesting to note that both adult Still's disease and juvenile idiopathic arthritis are caused by abnormalities in the innate immune system and share clinical characteristics and HLA profile.

Sjögren's syndrome and sarcoidosis are related to the HLA DR3 gene. Graft-versus-host disease has been associated with the presence of donor antibodies against HLA Class II antigens¹¹.

IBD is no exception. There is a close relationship in both Crohn's disease and ulcerative colitis and the different polymorphisms of the HLA complex. The Genome-wide association study GWAS platforms have made it possible to establish associations between specific single nucleotide polymorphisms within the HLA complex and IBD. However, the molecular mechanisms and specific polymorphisms that lead to the development of IBD, as well as the functional impact of its variants, are complex due to the linkage disequilibrium between these genotypes. That is to say that they have a recombination frequency < 50%, since the loci involved are on the same chromosome, which makes it impossible to transfer them

to the progeny in a random way. At present, this is limiting the clinical translation of the HLA genotype in IBD¹².

HLA complex in the pathogenesis of IBD

The inflammatory processes observed in IBD are multifactorial. An exaggerated reaction to commensal bacteria, the inability to eliminate pathogenic bacteria, the alteration of the epithelial barrier, and the inability to discriminate between host and foreign antigens have all been suggested as mechanisms that lead to IBD. Classes I and II complexes are essential for the discrimination between host and foreign antigens and play a crucial role in the response of the host's immune system to bacterial pathogens. Several mechanisms have been proposed as possible mechanisms¹²:

The regulation of the intestinal immune response is very complex and implies a low intensity physiological inflammatory state. This is based on the recognition of the antigen (diet and microbiota) by Toll-like receptors in antigen-presenting cells (dendritic cells and macrophages) and the subsequent presentation of HLA Class II epitopes in antigen-presenting cells, stimulating the differentiation of T and B cells. Certain genotypes may stimulate regulatory T cells and h17 T cells leading to the promotion of or lack of tolerance to commensal bacteria.

The amino acids arranged at the antigen-binding site (peptide-binding cleft zone) are conditioned by the HLA genotype. A change of amino acids in the cleft zone will modify its structural properties. Several variants have been identified that increase or reduce the risk of CD and UC¹² (Fig. 1).

Experimental studies have observed that a reduction in the expression of HLA Class II heterodimers in intestinal epithelial cells increases the number of Th17 cells and increases the expression of pro-inflammatory cytokines.

The expression of HLA-C in the membrane of immune cells has been associated with a higher probability of developing CD. In contrast, the inhibition of its expression mediated by miR-148a micro-RNA has been associated with a lower risk of CD¹².

Endoplasmic reticulum aminopeptidase 1 (ERAP1) is a peptidase that slices peptides for presentation through HLA Class I complexes. An increased risk of ERAP1-related IBD dependent on the HLA-C * 0796 genotype has been observed¹².

Experimental studies have shown that homozygosity for HLA-DR4 (HLADRA * 01:01/HLA-DRB1 * 04:05) induces colitis spontaneously. The accumulation of HLA-DRB4 expressed in the colon epithelium appears to trigger colitis through interaction with intestinal commensal bacteria. Interestingly, CIITA (MHC Class II

Figure 1. MHC I and MHC II structure.

transactivator) knockout mice do not express HLA-DRB4 and, in this case, do not develop colitis. This experiment confirms the relationship between HLA and the reaction against intestinal commensal bacteria¹³.

Some epitopes from diet and from microorganisms (viruses and bacteria) show similarities to host cells. This could cause the activation of B or T cell signaling and lead to an autoimmune process directed against the host antigen¹².

Risk of developing IBD related to HLA

It is critical to understand that HLA-related studies from one population cannot be extrapolated to another population. This is due to significant variations in the frequency of haplotypes of the HLA complex between different ethnic groups. This is more important when we consider isolated groups. Thus, a risk genotype for a Caucasian is not necessarily risky for an Asian.

Highlighting this aspect is essential because most studies have been carried out in a Caucasian population. The largest study and the one that has provided the most information to date¹⁴ is of European descent and therefore should only be considered for this ethnic group. This study included 32,713 patients with IBD and 34,241

controls. The limited African-American studies available have observed certain similarities with the HLA risk alleles identified in the Caucasian population¹⁵.

Studies of the HLA complex using GWAS have identified multiple associations with IBD. However, in general this translates into a small impact on clinical practice because most of these associations have a small effect (protective factor or risk factor). In any case, at present we have a large amount of information corresponding to populations of European descent. Numerous specific HLA genotypes related to CD and UC have been reported, as well as their different location, severity, and association with extraintestinal manifestations.

Associations between HLA genotypes and the location of the disease have been described, along with the extent, severity, risk of surgery, age of onset of the disease, and the coexistence of extraintestinal manifestations. Interestingly, there are risk alleles common to CD and UC with a colonic location while, in contrast, some alleles that predispose to ileal CD are protective factors for the development of UC. These data are summarized in [tables 1 and 2](#). At present, this information cannot be transferred to the clinical practice. However, it is a field with great potential for personalizing the treatment of patients with IBD in the future¹⁴.

Table 1. Risk Genotypes in Crohn's Disease (Adapted from Ashton, 2019)⁶

Class	Locus	Genotype	Ethnicity	OR	Phenotype
Class I	HLA - A	*03:01	Caucasian	1.10 (1.07-1.15)	Lower risk of colectomy
		*02:01	Japanese	1.64 (1.10-2.44)	
		*02:07	Japanese	2.31 (1.10-2.44)	
	HLA - B	*52:01	Caucasian	1.44 (1.27-1.64)	
		*14:02	Caucasian	1.28 (1.18-1.38)	
		*35:02	Caucasian	0.68 (0.59-0.78)	
		*35:03	Caucasian	0.72 (0.64-0.81)	
	HLA - C	*08	Caucasian	3.5 (2.14-5.52)	
		*01	Korean	1.52 (1.21-1.93)	
		*06:02	Caucasian	1.17 (1.13-1.23)	
		*12:02	Caucasian	1.44 (1.27-1.65)	
		*14:02	Japanese	1.32 (1.27-1.65)	
Class II	DRB1	*01:03	Caucasian	2.51 (2.25-2.80)	Colon involvement Ileum involvement Surgery, early onset, extraintestinal manifest Lower risk of Sclerosing cholangitis Extensive diseases Lower risk of fistulizing diseases
		*07:01	Caucasian	1.14 (1.10-1.18)	
		*13:02	Caucasian	1.20 (1.13-1.28)	
		*04	Japanese	2.9	
		*08	Caucasian	1.32 (1.22-1.43)	
		*16:01	Caucasian	0.68 (0.61-0.77)	
		*03:01	Caucasian	0.85 (0.82-0.89)	
		*01:01	Caucasian	0.81 (0.77-0.85)	
	DPA1	*01:03	Caucasian	0.91 (0.88-0.94)	Risk of immunogenicity (anti-TNF) Lower risk of sclerosing cholangitis
	DPB1	*04:01	Caucasian	1.10 (1.07-1.13)	
	DQA1	*05:01	Caucasian	0.70 (0.60-0.83)	
	DQB1	*02:01	Caucasian	0.86 (0.88-0.94)	
		*04	Caucasian	1.88-2.7	

Table 2. Risk Genotypes in Ulcerative colitis (Adapted from Ashton, Alim Pharmacol Ther, 2019)⁶

Class	Locus	Genotype	Ethnicity	OR	Phenotype
Class I	HLA - A	*02:01	Caucasian	1.13 (1.09-1.16)	Lower risk of colectomy Spondyloarthropathy
	HLA - B	*52:01	Caucasian	2.21 (1.96-2.50)	
		*27	Caucasian	1.40 (1.13-1.90)	
		*18:01	Caucasian	0.82 (0.77-0.88)	
	HLA - C	*12:02	Caucasian	2.25 (1.11-1.21)	
Class II	DRB1 DPB1	*01:03	Caucasian	3.59 (3.22-4.00)	Risk of colectomy Severe UC, extensive UC
		*15:01	Caucasian	1.32 (1.27-1.37)	
		*13:01	Caucasian/Indio	1.17 (1.11-1.24)	
		*11:01	Caucasian	1.19 (1.12-1.27)	Lower risk of sclerosing cholangitis
		*11:04	Caucasian	1.25 (1.15-1.35)	
		*12:01	Caucasian	1.47 (1.34-1.62)	
		*04	Caucasian	0.71 (0.68-0.74)	Risk of colorectal cancer
		*13:02	Caucasian	0.84 (0.78-0.90)	
		*03:01	Caucasian	0.87 (0.83-0.90)	
		*07:01	Caucasian	0.73 (0.70-0.76)	Lower risk of extensive colitis
		*08	Caucasian	0.70 (0.64-0.76)	
		*09:01	Caucasian	0.50 (0.42-0.59)	
		*03:01	Caucasian	0.83 (0.79-0.87)	Lower risk of sclerosing cholangitis

HLA as a marker of good prognosis¹²

CD patients who carry the HLA-B * 08: 01 haplotype have a lower risk of complications related to the depletion of CD8 T cells. In addition, UC patients with the

HLA-B52 haplotype have a lower risk of colectomy (odds ratios [OR] 0.18). Likewise, HLA-DPB1 * 03: 01 and HLA-DRB1 * 04 haplotypes are associated with a lower risk of developing primary sclerosing cholangitis. Finally, the

HLA-DR7 genotype could be a protective factor for the development of colorectal cancer associated with UC.

HLA as a marker of poor prognosis¹²

Early-onset UC has been associated with the HLA-A24 and A19 serotypes. These serotypes have also been associated with severe forms of UC. On the other hand, the most consistent association with early-onset UC is related to the HLA-DRB1 * 13: 01 genotype. The HLA-DRB1 * 01:03 genotype was associated with pediatric-onset IBD with an OR of 6.93 compared to the population without IBD. This association was twice that observed in IBD that started in adulthood. In contrast, HLA-DRB1 * 09 was associated with an age of onset of more than 40 years (OR 2.31).

Likewise, the DRB1 * 01: 03 genotype is the allele that has shown the highest risk of CD. Its frequency in the population is < 2% and it is associated with a significant risk of UC and colonic CD. In addition, it has been associated with the CD phenotype with exclusive involvement of the colon, an increased risk of severe disease and the need for colectomy. HLA-DR15 serotype (HLADRB1 * 15: 01-05 and 15:07) has been implicated in a subgroup of extensive and severe UC. The HLA-DRB1 * 08 genotype has been observed in extensive UC (OR 2.2), in this case, exclusively in the Japanese population. DRB1 * 07 is a risk factor for severe UC.

The DR13 serotype has been associated with an increased risk of pancolitis and the need for colectomy. Extensive colonic disease has also been described with the HLA-DQB1 * 06 genotype.

The HLA-DR17 serotype has been described as a risk factor for the development of colorectal carcinoma in UC.

The DR13 serotype has also been associated with the appearance of extraintestinal manifestations. HLA-B27 is a well-established risk genotype for the development of seronegative spondyloarthropathies, psoriasis, and IBD. However, HLA-B27 has not been independently associated with the development of IBD without the coexistence of spondyloarthropathy.

Risk of side effects of non-biological drugs

Treatment options for IBD have improved in recent years. However, the drugs used in the treatment of IBD have a relatively high risk of adverse events. Therefore, there is a particular interest in being able to predict their toxicity. GWAS analyses have identified some genotypes of the HLA complex that could be useful in clinical practice.

Sulfasalazine-induced agranulocytosis occurs in 1/2400 patients during the 1st month of treatment and in 1/700 during the 2nd and 3rd months after onset. A study of 36 patients who developed agranulocytosis and 5170 controls, identified that carriers of the HLA-B * 08: 01 and HLA-A * 31: 01 haplotypes had a higher risk of developing this complication. The NNT to avoid one case was 1500¹⁶.

One of the side effects of mesalazine is its nephrotoxicity. Mesalazine-induced interstitial nephritis is a serious and unpredictable complication. A multicenter case-control study included 151 patients with toxicity attributed to mesalazine and 4109 healthy controls. The mean time to the development of renal dysfunction was 3 years. A significant risk association with the single nucleotide polymorphisms (SNP) rs3135349 was identified (OR 2.76). This SNP is strongly related to the HLA-DRB1 * 03: 01 genotype. A three-fold increase in the risk of tubulointerstitial nephritis was calculated in carriers of this SNP¹⁷. However, it is a rare serious adverse event, so in absolute terms the risk is also very low and, therefore, not easily transferable to clinical practice¹⁷.

The genetic risk associated with the use of thiopurines was evaluated in a multicenter case-control study. One hundred and seventy-two cases of thiopurine-associated pancreatitis and 2035 controls were included in the study. Carriers of the SNP rs2647087 were more likely to experience this adverse event (OR 2.59). HLA region mapping identified this association with the HLA-DQA1 * 02: 01 - HLA-DRB1 * 07: 01 haplotype. The overall population risk of developing pancreatitis after taking thiopurines was 4%. In contrast, carriers heterozygous and homozygous for rs2647087 had a risk of pancreatitis of 9% and 17%¹⁸. Likewise, these findings were confirmed by a recent study that obtained a risk of pancreatitis of 14.63% and 0.53, respectively, in carriers and non-carriers of this SNP. Given that 8% of the population is homozygous, the NNT to avoid a case of pancreatitis is 76¹⁹.

Finally, a recent study suggests an increased risk of lymphoproliferative diseases in methotrexate-treated patients carrying the HLA-A * 24: 02 and DRB1 * 04: 05 alleles. However, the absolute risk is so low that it does not allow us to make recommendations in this regard²⁰.

In summary, although some findings are interesting, the use of the analysis of the different HLA haplotypes for the evaluation of the risk of adverse events of these drugs does not currently seem realistic.

Figure 2. Therapeutic algorithm based on HLA DQA1 * 05.

Risk of developing immunogenicity against anti-tumor necrosis factor (TNF)

There is evidence that suggests an innate risk of developing immunogenicity. A cohort of 187 patients treated with infliximab and then switched to adalimumab was evaluated for the presence of anti-infliximab (ATI) and anti-adalimumab antibodies (AAA). Patients who produced antibodies to the first anti-TNF were 11 times more likely to develop antibodies to a second anti-TNF²¹. Another study carried out in 634 patients with hidradenitis suppurativa and rheumatoid arthritis identified HLA genotypes associated with a lower risk of immunogenicity against adalimumab. Different HLA alleles have been described as associated with a greater or lesser risk of developing AAA. HLA-DRB1 * 01, HLA-DRB1 * 07, and HLA-DQB1 * 05 alleles have been associated with a lower probability of AAA, with OR of 0.25 95% CI (0.073-0.927), 0.28 95% CI (0.078-1.004), and 0.4 95% CI (0.186-0.862), respectively. In contrast, HLA-DRB1 * 03 and HLA-DRB * 011 alleles are associated with a lower probability of AAA formation (OR of 2.52 95% CI [1.37-4.63] and 2.64 95% CI [1.240-4.045], respectively)²².

Key research in this context is the UK PANTS cohort study. This prospective study included 1240 patients with CD undergoing treatment with infliximab or adalimumab. Variants associated with the development of ATI or AAA

were investigated from a GWAS analysis using a drug-tolerant assay. At 12 months, 44% of patients developed anti-drug antibodies. The risk was higher for infliximab than for adalimumab and higher in monotherapy than in combination therapy with immunosuppressants. Carriers of the HLA-DQA1 * 05 allele were found to have twice the risk of developing immunogenicity (HR 1.90) regardless of anti-TNF or immunosuppressive treatment. The patients with the highest risk were carriers of the unfavorable haplotype in infliximab monotherapy (92% cumulative probability at 12 months). In contrast, those with the lowest risk were those without the unfavorable haplotype treated with adalimumab in combo therapy (10% at 12 months)²³. Interestingly, this risk may vary depending on the haplotype class. HLA-DQA1 * 05: 01 and its extended haplotype are significantly associated with immunogenicity against infliximab, but not against adalimumab. In contrast, HLA-DQA1 * 05: 05 and its extended haplotype are significantly associated with the development of AAA and less strongly with ATI²⁴.

The European ABIRISK consortium conducted a multicenter prospective study in 560 patients with different immune-mediated diseases, including IBD, who were being treated with anti-TNF, interferon beta 1a, interferon-beta-1b, rituximab, or tocilizumab. In a multivariate Cox regression model, the HLA-DQA1 * 05 allele was identified as a risk factor for immunogenicity (HR = 3.9

[1.923-5.976], $p < 0.0001$ for homozygotes). In contrast, the use of immunosuppressants and antibiotics was associated with a lower risk of anti-drug antibodies²⁵.

These findings are especially interesting because 40% of the European population is a carrier of HLA-DQA1 * 05, although for the same reason, these observations cannot be extrapolated to other ethnic groups. In addition, it is important to note that the mechanism that explains these findings functionally have not yet been established and studies are therefore needed to analyze the functional association between HLA alleles and ADA formation.

Prediction of secondary loss of response to anti-TNF based on HLA

HLA-B27 carriers with ankylosing spondylitis have a better response to infliximab, although the mechanism and whether this only applies to rheumatologic disease are unknown²⁶. A study carried out in our setting sequenced the entire genome of 41 patients with CD without previous anti-TNF treatment in search of variants related to response to treatment. Two homozygous mutations were identified in HLA-B (variant rs41563412) and HLA-DRB1 (variant rs1071752) associated with non-response and remission, respectively, at week 14²⁷.

Regarding secondary loss of response, the PANTS cohort determined that carriers of the HLA-DQA1 * 05 genotype had a greater probability of developing immunogenicity, especially in monotherapy. One of the main mechanisms of loss of response to anti-TNF is related to its consumption by anti-drug antibodies. A recent retrospective cohort study evaluated 262 IBD patients exposed to infliximab. Forty percent were carriers of the HLA-DQA1 * 05 haplotype. Carriers of this variant had a higher risk of secondary loss of response to infliximab (HR = 2.34) and treatment interruption (HR = 2.27) but not an increased risk of adverse events²⁸. Similar results were obtained by our group in a cohort of 64 IBD patients with a primary response to infliximab. The presence of the HLA-DQA1 * 05 haplotype was independently associated with a higher probability of secondary loss of response (HR 3.5)²⁹. These results were replicated in a cohort of 54 patients treated with adalimumab. Regardless of body mass index, smoking, or immunosuppressive treatment, an unfavorable haplotype was associated with a greater probability of secondary loss of response (HR 2.75) and loss of drug (HR 4)³⁰.

Use of HLA-DQA1 * 05 in clinical practice

Pending targeted RCTs, it seems prudent to recommend that patients with the HLA-DQA1 * 05 haplotype use combined treatment with immunosuppressants (especially with infliximab) and, in case of contraindications for combined use, consider using strategies that improve the persistence of the drug³¹ (e.g., proactive pharmacokinetic monitoring) or the use of an alternative target (Fig. 2).

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Conflicts of interest

J. Guardiola has served as a speaker for Abbvie, Takeda, MSD, General Electric, Kern Pharma, and Pfizer, and has received Investigator Research Grants from MSD, General Electric, and Kern Pharma.

F. Rodríguez-Moranta has served as a speaker for Abbvie, Takeda, Jansen, Pfizer and MSD.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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