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Role of HLA typing on Crohn's disease pathogenesis

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A B S T R A C T

Crohn's disease (CD) is the main type of chronic inflammatory bowel disease of unknown etiology. Evidence from family and twin studies suggests that genetics plays a significant role in predisposing an individual to develop Crohn's disease. A susceptibility locus for Crohn's disease has been mapped 3 to chromosome 16: a frameshift variant and two missense variants of NOD2, encoding a member of the Apaf-1/Ced-4 superfamily of apoptosis regulators which is expressed in hematopoietic compartment cells and intestinal epithelial cells as well as in paneth cells, where NOD2 may play an important role in the pathogenesis of Crohn disease in the gastrointestinal system. This leads to alteration the structure of either the leucine-rich repeat domain of the protein or the adjacent region. NOD2 activates nuclear factor NF-kB; this activating function is regulated by the carboxy-terminal leucine-rich repeat domain, which has two functions, first an inhibitory role and also acts as an intracellular receptor for components of microbial pathogens. Thus, NOD2 gene product confers susceptibility to Crohn's disease by altering the recognition of these components and/or by over-activating NF-kB in intestinal epithelial cells as well as in paneth cells. Further confirmation of a genetic predisposition comes from studies of the association between the human leukocyte antigen (HLA) system and CD. The immunogenetic predisposition may be considered an important requirement for the development of CD, as several alleles of human major histocompatibility complex had an association with CD. Although it is difficult to estimate the importance of this region in determining overall genetic susceptibility in a population, studies of HLA allele sharing within families suggest that this region contributes between 10% and 33% of the total genetic risk of Crohn's disease.

1. Introduction

Crohn's disease (CD) has been known since 1932, when Crohn et al. reported fourteen cases of terminal ileitis [1]. Crohn's disease is a relapsing inflammatory disease that mainly affects the gastrointestinal tract from mouth to anus. It involves any part of the gastrointestinal tract most commonly the terminal ileum or the perianal region in a non-continuous fashion [2]. The microscopic features of Crohn's disease include thickened submucosa, transmural inflammation, fissuring ulceration and non — caseating granulomas. CD frequently presents with abdominal pain and fever, and it sometimes may lead to life-threatening complications [3]. CD affects about 500,000 persons in North America and its prevalence in Asia ranges from 3.6 to 7.7 per 100,000 people [4,5]. It can occur at any age and usually between 15 and 30 years of age [6]. Initial symptoms of CD can be more subtle because of 'patchy' nature of

the gastrointestinal disease and superficial involvement of affected tissues [7].

2. Pathogenesis

The precise causes of Crohn's Disease are not well understood. It is a multifactorial disease including hereditary, genetics, and/or environmental factors inaddition to diet and stress may aggravate Crohn's Disease [8].

2.1. Gastrointestinal pathogens

The gastrointestinal tract (GIT) contains harmless bacteria, many of which aid in digestion. The immune system usually attacks and kills foreign invaders, such as bacteria, viruses, fungi, and other microorganisms. Under normal circumstances, the harmless bacteria in the intestines are protected from such an attack. In people with CD, these bacteria are mistaken for harmful invaders and the immune system mounts a response. Cells travel out of the blood to

the intestines and produce inflammation by production of IL-8, MCP-1, and ENA-78 by endothelial cells, LPMNC, and epithelial cells could establish a chemotactic gradient capable of influencing the increased migration of monocytes/macrophages, granulocytes, and lymphocytes from the blood stream through the endothelium into both the mucosa and submucosa. The ability of chemokines to induce chemotaxis, leukocyte activation, granule exocytosis, increased production of metalloenzymes, and up-regulation of respiratory burst activity indicates that there may be a variety of different mechanisms by which chemokines could markedly increase chronic inflammation and chronic intestinal tissue damage [9]. However, the inflammation does not subside, leading to chronic inflammation, ulceration, thickening of the intestinal wall, and eventually causing patient symptoms [10]. Thus, biodiversity of the microflora remains high in patients with CD [11]. Other bacteria like adherent-invasive *E. coli* which is a pathogenic group of *E. coli* able to adhere to and invade intestinal epithelial cells had long polar fimbriae as a key factor for it to target Peyer's patches [12]. Enterobacteria were also observed in GIT of CD patients [13].

2.2. Enviroment

The environment in which you live also appears to play a role in progression the disease. Crohn's is more common in developed countries rather than developing countries, in urban rather than rural areas, and in northern rather than southern climates of the world. The disease is most common among people of eastern European backgrounds, including Jews of European descent. The increasing trends observed in Asia still account for a low prevalence of the disease [14].

2.3. Genetic mutation

Genetic factor is important factor in developing disease. Crohn's tends to run in families, so if you're relative have the disease or your family members have a disease, this will increased chance of developing Crohn's. Studies have shown that 5%–20% of affected individuals have a first − degree relative with one of the diseases [15]. A susceptibility locus for Crohn's disease has been mapped to chromosome 16. Entry of bacteria into host cells is a significant virulence mechanism. Through peptidoglycan recognition, the nucleotide-binding oligomerization domain (NOD) proteins NOD1 and NOD2 enable detection of intracellular bacteria and promote their clearance through initiation of a pro-inflammatory transcriptional programme and other host defense pathways, including autophagy.NOD1 which is expressed in a wide range of hematopoietic and non-hematopoietic cells, the expression of NOD2 is restricted to hematopoietic compartment cells and intestinal epithelial cells as well as in paneth cells, where NOD2 may play an important role in the pathogenesis of Crohn disease in the GI system. Also, the role of NOD2 in CD mainly depends on changes in the interaction of mutant NOD2 with peptidoglycan, which leads to perturbation of protective inflammatory response and subsequent compensatory chronic inflammation [16]. The genetic analysis includes frameshift variant and two missense variants of *NOD2*, encoding a member of the Apaf-1/Ced-4 superfamily of apoptosis regulators. NOD2 activates nuclear factor NF-kB; this activating function is regulated by the carboxy-terminal leucine-rich repeat domain, which has an inhibitory role and also acts as an intracellular receptor for components of microbial pathogens. These observations suggest that the *NOD2* gene product confers susceptibility to Crohn's disease by altering the recognition of these components and/or by over-activating NF-kB [17]. The insertion mutation in the *NOD2* gene confers an increased susceptibility to Crohn's disease [18]. NOD1 and NOD2 and have elucidated the

signaling pathways that are triggered downstream of NOD activation. *In vivo*, NOD1 and NOD2 have complex roles, both during bacterial infection and at homeostasis. The association of alleles that encode constitutively active or constitutively inactive forms of NOD2 with different diseases highlights this complexity and indicates that a balanced level of NOD signaling is crucial for the maintenance of immune homeostasis [19]. Thus, Carrying two NOD2/CARD15 mutations predicts youthful onset, ileal disease involvement, and development of *stricturing* or non-perianal *fistulizing* complications while Smoking and early onset independently influence ileal site and time to surgery [20].

2.4. Human leukocyte antigens

Human leukocyte antigen (HLA) located on chromosome 6p21.3 and encodes genes for the major histocompatibility complex (MHC). HLA region contains multiple genes with wide range of immunological function encodes proteins on surface of leukocytes with critical role in immunity, including antigen processing and presentation to T helper cell, and self-recognition by immune cells, as ligands receptors, cytokines production, transduction signaling factors, heat shock proteins, and transcription factors regulators [21].

2.4.1. Role and importance of HLA class I and II in disease mechanisms

HLA class I molecules present on the surface of most somatic cells and present endogenous antigens like viruses and intracellular bacteria, for recognition by the immune cells. This process involves degradation of Ags into short 8−16 amino acid peptides, optimal for HLA class I binding groove. These are subsequently transported into the rough endoplasmic reticuluim where they bind HLA class I molecules combined with beta2 microglobulin and being transported to the cell surface [22]. HLA class I presented antigen is then recognized by CD8+ T cells and become effecter T lymphocytes and natural killer (NK) cells. These cells are producing cytokines, lymphokines and chemokines, which aid in the enrollment of other cells to the site of inflammation that have a cytolytic activity ending cell destruction [23].

Several hypotheses have been suggested to clarify how variation in HLA class I genes could trigger Crohn's disease. HLA class I molecules play a role in presenting virus or bacteria that present in the intestine (endogenous antigens) that triggers for disease development through molecular mimicry that activate autoreactive T cells and acting as superantigens that stimulate large number of T cells [24]. In addition to that alteration HLA class I and II expression, potentially leading to greater antigen presentation to CD8+ and CD4+ T cells, with certain alleles more prone to disease [25]. HLA class I molecules could play an important role due to their role in inhibiting NK cell activity by controlling the balance between activating and inhibitory receptors on their surface [26].

2.4.2. Role of HLA typing in screening, treatment and prognosis of disease

HLA typing is an important genetic method plays an important role in Crohn's disease. Epigenetic changes in the DNA of patients with Crohn's disease may provide important insight into how the disease develops depending on interactions between genetics and environmental factors (such as diet and gut bacteria). Ultimately, these findings could contribute to screening people with Crohn's and developing new treatments to fight the illness and detect the prognosis. Adams et al., 2014 [27] identified 65 individual CpG sites (where cytosine (C) lies next to guanine (G) in the DNA sequence) with methylation alterations that had epigenome-wide significance. In addition, they found 19 differently methylated regions

displaying unidirectional methylation change. Researchers also found a highly significant enrichment of methylation changes around this genome-wide association study, particularly the HLA region and MIR21. There was a significant differences in DNA methylation in CD, defining the disease-associated epigenome. There ia an association between GWAS loci, with compelling evidence implicating MIR21 and the HLA region. The detection of phenotype-determining genes as opposed to disease susceptibility genes requires precise phenotypic characterization of patients and large sample size. Peripheral arthropathies in CD are well recognized and are classified with the HLA-B*27-related spondyloarthropathies by the European Spondyloarthropathy. However, previous HLA studies in CD have only shown this association with axial disease rather than peripheral arthropathy. Type 1 arthropathy was associated with HLA-DRB1*0103 (DR103; a rare subtype of DR1) in 33% and associated with extraintestinal manifestations (arthropathy, erythema nodosum, uveitis), B*35 in 30%, and B*27 in 26%. In contrast, type 2 was associated with HLA-B*44 in 62%. These data suggest that the clinical classification into type 1 and type 2 arthropathies describes immunogenetically distinct entities and establish that in polygenic disorders [28]. This implies that genes of the HLA region have an important role in determining the clinical course of the articular disease in CD. Type 2 arthropathy is not associated with HLA-B*27 and its immunogenetic characteristics suggest an etiology different from the other seronegative spondyloarthropathies. It has been suggested that HLAB*44, which is associated with type 2 arthropathy, may form part of an extended haplotype with DR4 in rheumatoid arthritis (particularly in association with Felty's syndrome) [29]. Therefore, the association with DRB1*0103 is particularly strong in patients with extensive or severe disease of CD. In addition to the interest in using biomarkers to predict CD susceptibility, there is also considerable interest in using molecular and serological markers to assist in the discrimination of Crohn's disease from ulcerative colitis. Indeed the shared association of DRB1*0103 and B*52 with ulcerative colitis and colonic Crohn's disease suggests the presence of at least one shared HLA susceptibility factor, providing a hint to the potential molecular basis for the definition of colonic inflammation. The apparent differential effect of HLA-DRB1*0401, which is a susceptibility allele in Crohn's disease and a protective allele in ulcerative colitis is interesting [30]. Thus, HLA genotype is likely to be most useful in the prediction of disease course in patients with an established diagnosis of Crohn's disease or ulcerative colitis.

2.4.3. HLA and CD association

Several studies showed the importance of the association of HLA alleles with CD. HLA typing is also differ according to race and religion [31], in Japanese population –East Asia-the studies found that a positive association of HLA-DR4 and DQ4 with Crohn's disease, allelic analysis showed that DRB1*0405, DRB1*0410, DQA1*03, DQB1*0401, and DQB1* 0402 are positively associated and DRB1*1501, DRB1*1302, and DQB1*0602 negatively associated with Crohn's disease. However, according to Arimura's et al., 2014 meta-analysis of Japanese IBD genetics [18], HLA-DRB1*0405 is confirmed to have a positive association with Crohn's disease whereas DRB1*1502 is confirmed to have a negative association with Crohn's disease. Other loci reported previously were not confirmed by the meta-analysis. DP genes analysis showed no significant association with Crohn's disease. Haplotype analysis showed positive associations with DRB1*0405-DQA1*03-DQB1*0401, DRB1*0410-DQA1*03-DQB1*0402, and DRB1*0802-DQA1*03-DQB1*0402 haplotypes and negative associations with DRB1*1501-DQA1*0102-DQB1*0602 and DRB1*1302-DQA1*0102-DQB1*0604 haplotypes. Thus, HLA-linked disease susceptibility gene is primarily associated with DQB1*04, in which leucine at the

56th position is a unique amino acid, and the disease resistance allele is suggested to be DQA1*0102 [32]. HLA class II genes are candidates for a role in genetic susceptibility to CD, because their products play a central role in the presentation of the antigens and immune response. Multiple studies have reported associations between HLA-DR or -DQ phenotypes and Crohn's disease, but much of the data are still controversial. Crohn's disease had a positive association with DR7, DRB3*0301, and DQ4 and a negative association with DR2 and DR3 [33]. Peripheral arthropathies in CD is well recognized and are classified with the HLA-B*27-related spondyloarthropathies by the European Spondyloarthropathy Study Group. However, HLA studies in CD have only shown this association with axial disease rather than peripheral arthropathy. Type 1 arthropathy was associated with HLA-DRB1*0103 in 33%, B*35 in 30% and B*27 in 26%. In contrast, type 2 was associated with HLA-B*44 in 62%. Similar significant associations to type 1 arthropathy were found in reactive arthritis, except that the HLA-B*27 association was significantly stronger and an association was found with DRB1*0101 in 43%. IBD-AS was associated only with HLA-B*27 and DRB1*0101 [34].Published studies on the association between HLA class II genes and CD contradictory perhaps because of the limited size, method used, clinical course of diseased patients selected and ethnic heterogeneity of the populations studied. French population demonstrated an increase in DQB1*0501 allele frequency and a decrease in DQB1*0602/0603 allele frequencies. DRB1 analysis showed associations with three allelic variations: an increase in the frequencies of DRB1*01 and DRB1*07 alleles and a decrease in that of the DRB1*03 allele. The alleles DRB1*01 and DRB1*07 are associated with susceptibility to Crohn's disease development. The strong negative association between the DRB1*03 allele and Crohn's disease suggests that the HLA-DRB1*03 allele mediates resistance and protective to Crohn's disease [35]. Crohn's disease appears indifferent forms that it has been hypothesized CD might be a syndrome rather than a disease, with different pathogenic mechanisms leading to the various clinical presentations and phenotypes. The course of the disease will also be effected by HLA alleles like the close association between HLA-DR5 in those CD with the ileocecal type, and the -Bw51 and small intestine type [36]. A Caucasian Dutch CD patients with fistulising (peri-anal fistulas) showed a striking decrease in the frequency of the DRB1*03 allele when compared with a panel of 2400 healthy controls (3% vs 25%). The DRB1*03 allele is in strong linkage disequilibrium with a polymorphism at position −308 in the promoter region of the gene encoding TNFα (TNFA-308*2). Thus, patient selection with specific clinical presentation may largely determine the outcome of genetic association studies in CD. This suggests recombination between the DRB1 and TNFA loci in this group of patients may help to define the biological basis of fistula formation in CD patients [37]. CD with extra-intestinal manifestation had an association with DRB1*0103. CD with symmetrical arthritis is associated with HLA-B*44 [38]. Uveitis has also been associated with DRB1*0103 and HLA-B*27, and erythema nodosum with the TNF promoter SNP TNF-1031C [39]. Religion is also important in HLA typing, Akolkar et al., 2000 [40] demonstrated that 132 CD patients, of which 82 were Ashkenazi Jewish, were HLA-typed using both serologic and DNA molecular methods. Ethnically matched controls were similarly typed. No association with DR1 or DR13 was observed in the Jewish CD population. Furthermore, a significant negative association with DR7 and DQ2 was observed in the Jewish population.

The association of Crohn's disease with HLA typing in some different countries can be summarized in following tables: (Tables 1 and 2).

Linkage disequilibrium and haplotype frequency is also important in CD, Okada Y et al. [47] have demonstrated that a particular HLA haplotype, HLA- B*5201-Cw*1202- DRB1*1502, has a

Table 1
Some HLA class I positively associated with Crohn's disease in some different countries.

No.	Country and study population	HLA class I associated with development of CD	Association with disease course	Positive vs. negative association	Reference
1-	United Kingdome	B 27	+	+	Rashid T and Ebringer A 2011 [41]
2-	Japan	B27	+	+	Kobashigawa et al., 2014 [42]
3-	Germany	B27	+	+	Purrmann et al., 1988 [43]
		B44			
2-	Caucasoid	A2	+	+	Biemond et al.,1986 [44]
3-	Israeli Jewish	DR1	−	−	Delpre et al., 1980 [45]
		DR13			Akolkar et al., 2000 [40]
		DR7			
		DQ2			

Table 2
Some HLA class II positively associated with Crohn's disease in some different countries.

No.	Country and study population	HLA class II associated with development of CD	Association with disease course	Positive vs. negative association	Reference
1-	Japan	DR4 and DQ4	+	+	Nakajima et al., 1995 [33]
		DRB1*0405, DRB1*0410, DQA1*03, DQB1*0401, DQB1*0402			Arimura's et al., 2014 [18]
2-	Meta analysis	DR7, DRB3*0301, DQ4	+	+	Stokkers et al., 1999 [33]
3-	France	DRB1*01, DRB1*07, DQB1*0501	+	+	Danzé et al., 1996 [35]
4-	Germany	DRB1*07	+	+	Reinshagen et al., 1996 [46]

protective effect on CD in Japanese population. The specific pathogens recognized by this haplotype will promote the inappropriate proliferation and differentiation of naïve T helper cells and induce the Th1/Th2/Treg imbalance in the intestinal immune response. This imbalance will contribute to the opposite directions of the susceptibility to CD. Contrary to these results, this haplotype did not have such effect on European population which is due to ethnic differences. Other haplotype which is B21- *Cw8* conferred the greatest risk for CD [48]. Other study showed the association of CD with SNP rs1799964; 21 loci outside the HLA region had more significance [49].

The other part of class I MHC is non-classical (HLA-E, −F and G) genes. The expression of non-classical MHC I molecules is altered in CD like selective absence of CD1d in Crohn's disease. Expression of HLA-G was absent in CD and can be used for diagnostic purposes to distinguish between CD and UC in cases of indeterminate colitis [50]. The 14-bp deletion polymorphism in the HLA-G gene was associated with ileocecal resection in Crohn's disease. In CD patients with ileocecal resection, the frequency of the Del+/Del + genotype was 47.0% compared with 27.3% in patients without ileocecal resection, The frequency of the Del + allele was significantly increased in CD patients with in relation to those patients without ileocecal resection (69.7 versus 52.7%).Thus, the HLA-G play important role in the course of CD [51].

The human MHC class I chain-related genes (MICA and MICB) are located within the HLA class I region of chromosome 6. MICA/MICB organization, expression and products differ from classical HLA class I genes. There is seven MIC loci (MICA−MICG), of which only MICA and MICB encode transcripts, while MICC, MICD, MICE, MICF, and MICG are pseudogenes. MICA gene is located 47 kb centromeric to HLAB in the MHC class I region [52]. Genetic study found that MICA*010 and HLA-B*1501 in English patients with fistulous CD [53]. MICA and MICB bind to an activating receptor natural killer group 2D (NKG2D) which is expressed on NK cells, T helper cells and macrophages and the interactions between these two receptors may stimulate cell cytotoxicity and providing co-stimulation for NK and T cell activation.

The last class in MHC is Class III, the proteins produces by this class are TNF, alpha and beta and heat shock proteins. HSP70 and HLA-DR up-regulation was present in professional (dendritic cell) and nonprofessional antigen presenting cells (fibroblast). This implies a role for HSP70 in antigen processing and/or presentation with APC activation, which is essential for the initiation and modulation of the immune response and inflammation [54]. TNF play an important role as pro-inflammatory cytokine with elevated serum and tissue levels in patients with CD [55].

Genetic predisposition to Crohn's Disease may be associated with response to therapy or may serve as a factor for design more effective personalized therapy. About 70 loci are associated with susceptibility to Crohn's disease development, particularly in pathways of innate immunity, autophagy, and pathogen recognition. A multilocus approach using autophagy-related genes provides insight into CD phenotype−genotype associations and genetic markers for predicting therapeutic responses [56]. Single nucleotide polymorphisms (SNPs) in TNF receptor superfamily (TNFRSF) 1A and 1B, and Fas ligand (FASLG) genes, have been associated with responsiveness to infliximab (IFX) in treatment Crohn's disease. The TNFRSF1B polymorphisms may contribute to predict efficacy of infliximab. Moreover, FASLG and TNFRSF1B polymorphisms may confer genetic susceptibility to severe infusion reactions during treatment of CD [57]. Crohn's disease (CD) has been related to nucleotide-binding oligomerisation domain containing 2 (NOD2) and ATG16L1 gene variants and those patients require a more aggressive therapy with anti-tumour necrosis factor to reduce the extent of inflammation and the risk of relapse [58].

3. Conclusions

Crohn's disease are associated with specific HLA class I and II phenotypes and susceptibility to Crohn's disease may relate to specific allotypes on the human major histocompatibility complex. Further analysis of these phenotypes and subgroup analysis may elucidate how these alleles contribute to screening, susceptibility and treatment CD. Finally, identification of Crohn's disease as a

syndrome of overlapping phenotypes that involves variable influences of genetic and environmental factors.

Conflict of interest

There is no conflict of interest.

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Ethical approval

Yes.

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