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Relationship between HLA Typing and Different Diseases in IRAQ

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Abstract

Human leukocyte antigen system is the major histocompatibility complex in humans, which includes several hundreds of genes located in a highly polymorphic region of chromosome 6 that encode for proteins critical for the immune system. HLA Class I antigens (A, B and C) transport and present peptides produced by degradation of proteins inside the cell like viral antigens, to CD8+ T cells, in addition to that the HLA Class I, carry also foreign or not-self antigens. Under normal conditions, these T –cell CD 8+ cells recognize but do not destroy those cells with the right "self"Ag, unless they also carry a non-self antigen. Under pathological conditions, like in certain autoimmune diseases T cells can destroy cells carrying self-antigens, causing autoimmune diseases. The role of HLA Class II antigens (DRB1, DRB3,4,5, DQA1/DQB1, DPB1) is to present the peptides from processed proteins that are produced outside the cell, derived from bacteria and protozoa, to helper T-cells CD4+ to stimulate their multiplication. These helper T cells then stimulate B-cells to produce antibodies against the foreign antigens. HLA and disease associations have been widely studied across the populations worldwide and are found to be important in prediction of disease susceptibility, resistance or protective and of evolutionary maintenance of genetic diversity. Here, in this review, we have collected HLA association data on some autoimmune diseases, infectious diseases, cancers, and other diseases with unknown etiology in Iraq and attempt to summarize some remarkable HLA alleles related with specific diseases.

Keywords: HLA; Disease association; Iraq

Introduction

There is a strong association between some diseases and HLA (human leukocyte antigen) [1]. These diseases are chronic and debilitating and many of them their treatments are available but are inadequate [2]. Therefore, this could help in the greater understanding of the disease mechanisms, pathogenesis and the development of new therapeutic agents [3]. The major histocompatibility complex (MHC), also known in humans as the human leukocyte antigen (HLA) region, encompasses 7.6 Mb on chromosome 6 p21 and is the most gene dense region within the human genome encoding 252 expressed loci [4]. The genetic system of MHC contains more than 70 known genes on the short arm of chromosome 6 and spans about 4 million base pairs of DNA. The high resolution typing of class I and class II MHC genes and the identification of other genes in the region have increased the definition of the genetic basis of immune responses and diseases of unknown etiology such as the autoimmune diseases [5]. Many individuals who have certain HLA allele increased vulnerability to certain diseases [6]. However, the association between HLA type and most infectious diseases is not very clear because of the multiplicity of factors that can affect their outcome. Nevertheless, in some cases such a relation is obvious, a situation that may be helpful in establishing either the resistance or susceptibility to certain infectious diseases and even a prognosis of the disease progression HLA types found in tropical countries tend to differ a lot from those in temperate parts of the world, thus people susceptibility to disease differ because the viruses found there are different. Some Africans have developed HLA that give them resistance to malaria. The European arrived in the Americas, bringing with them new viruses on the continent, the biggest part of the Native American population of the North America was wiped out as they did not have the right antigens to fight off even the common cold. Some HLA types are known to attack the body own cells causing autoimmune diseases.

The HLA System and Genetic Disease

The human leukocyte antigen (HLA) system comprises closely linked genes controlling highly polymorphic proteins involved in the presentation of peptides to the T-cell receptor [7]. HLA-DR is a MHC class II cell surface receptor encoded by the human leukocyte antigen complex on chromosome 6 region 6p21.31. The complex of HLA-DR and its ligand, a peptide of 9 amino acids in length or longer, constitutes a ligand for the T-cell receptor (TCR). HLA-DR is also closely linked to HLA-DQ and this linkage often makes it difficult to resolve the more causative factor in disease. HLA-DR molecules are upregulated in response to signalling. In the instance of an infection, the peptide is bound into a DR molecule and presented to T-cell receptors found on T-helper cells. Some diseases had an association with MHC-class I alleles while other diseases had an association with MHC-class II alleles. In addition to that other diseases had an association with HLA linked genes TNF genes [8]. Exogenous peripheral antigens are internalized via antigen presenting cells (APC) and are degraded into 13-18 amino acid residue peptides, preferentially bound by HLA class II molecules, in the increasingly acidic compartments of the endocytic pathway. HLA class II molecules are synthesized in the rough endoplasmic reticulum (RER) where they associate with the invariant chain (Ii) to prevent endogenous peptide binding. The HLA class II molecule is then routed to the endocytic pathway, where Ii is degraded, leaving a short fragment of the Ii class II-associated invariant chain peptide (CLIP) bound, which is then exchanged for peptide [9]. The HLA class II peptide complex is then transported to the cell surface for recognition by CD4+ Th cells, which determine whether an immune response is mounted. If an immune response is mounted CD4+ Th cells activate naive B cells to produce antibodies, or in the case of self-antigens autoantibodies, and aid in macrophage recruitment. Activated autoreactive CD4+ Th cells against a variety of exogenous autoantigens, including pancreatic

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beta cells, thyroid components and myelin, have been detected in TID, GD and MS respectively, suggesting a role in disease susceptibility [10].

HLA class I molecules could also be associated with diseases due to their role in inhibiting NK cell activity. NK cell cytotoxic activity is controlled by a balance between activating and inhibitory receptors on their surface [11]. Activation signals are blocked by inhibitory signals produced through interaction of killer immunoglobulin-like receptors (KIR) with a variety of HLA class I molecules loaded with peptide [12]. If HLA class I expression is normal then NK cell mediated destruction is inhibited. KIR/HLA-C interactions can be altered by peptide loading and presentation by HLA-C [13], which could suggest that interaction seen in Graves' disease (GD) and multiple sclerosis (MS) of the associated HLA-C molecules with a given auto antigen could be affecting KIR binding and that this interaction between KIRs and HLA-C could play a role in autoimmune onset [14]. Variation in the interaction of other molecules that bind to HLA class I and monitor HLA class I expression, including leukocyte Ig-like receptors (LIRs), members of the Ly49 family (Ly49) and the CD94/NKG2 family of receptors, could also provide another mechanism by which HLA class I could lead to diseases or autoimmune diseases [15].

Diseases linked to HLA specificities

Diseases linked to specific HLA alleles differ according to race of populations [16]. Therefore it is important to study HLA association with diseases in different racial groups [17]. Studies using this new information have made obvious the fact that there are significant correlations between certain HLA types and specific diseases. Consequently, HLA typing is becoming a tool to screen susceptibility to certain autoimmune diseases, as a factor affecting the prognosis of certain diseases like cancer, autoimmune and infectious diseases. Here, we would talk about the different HLA – typing and disease association like: Addison's disease–B8, DR3, Dw3; ankylosing spondylitis–B27; Behçet's disease–B5; Buerger's disease–B12; celiac disease–gluten-sensitive enteropathy-B8, Dw3; chronic active hepatitis–DR3; de Quervain thyroiditis–Bw35; dermatitis herpetiformis–Dw3; Goodpasture syndrome–DR2; mesangio proliferative glomerulonephritis–DR4; Graves' disease–B8 in whites, Bw35 and Dw12 in Japanese, Bw46 in Chinese; hemochromatosis–A3, B7, B14; IDDM–B8. B15, DRw3, DRw4; IgA nephropathy–B35; juvenile rheumatoid arthritis–B27, DR5, DR8; late onset adrenal hyperplasia with hirsutism–Aw33/B14; myasthenia gravis–A1, A3, B8, Dw3, DR3; psoriasis–Cw6; psoriatic arthritis–B27; Reiter syndrome–B27; rheumatoid arthritis–DR4; Salmonella arthritis–B27; Sjögren syndrome–DR3, B8; lupus erythematosus–DR2, DR3; Takayasu's disease–B52; Yersinia arthritis–B27 etc.

The association of HLA haplotypes with specific diseases is determined by calculating Relative risk Patients and Absolute risk Patients. This study will shed a light on different diseases and its association with HLA typing in Iraq.

Grave's disease: It is an autoimmune disease characterized by auto antibodies against thyroid gland. It may occur in genetically susceptible individuals in same family. The HLA alleles associated with GD in Iraqi Arab Muslims patients are (A19, B35, B40) [18].

Ankylosing spondylitis (AS):It is a chronic inflammatory disease affecting sacroiliac joint with gibbous formation ending in bumbo spine. HLA-B27 is strongly associated with AS in (97%) of the patients. In Iraq, there is a strong association between Ankylosing spondylitis and (HLA-B27) [19].

Coeliac disease: This autoimmune disorder of the small intestine is triggered by gluten proteins that occur in genetically predisposed people. The condition causes chronic diarrhea, fatigue and other problems, with the only effective therapy being a gluten-free diet. In Iraq, the dominant HLA associated with celiac disease is HLA- B8 and B12 [20].

Insulin dependent Diabetes Mellitus: It is an autoimmune disease destructing beta cell of the pancreas. A disease strongly linked to HLA genes, the most common allele in Iraqi patients with IDDM are (HLA-A1, B8, B22, B40, B44, DR3, DR4) [21] and in non Insulin dependent Diabetes Mellitus are (HLA-A24, B8, B15, DR3, DR4, DQ2, DQ3) [22].

Psoriasis: It is a dermatological disease has an association with HLA typing. HLA-A1, B13, Cw7, DR7genes have been identified as playing important roles in the pathogenesis and that the presence of any of these two genes increases the risk of contracting the disease 5-6-fold [23].

Behcet's syndrome: It is a systematic diseases characterized by vasculitis, oral and genital ulceration with ocular involvements. The HLA-B51 (B5) allele is known to be associated with BD in Iraqi patients [24].

Rheumatoid arthritis: RA is a complex inflammation occurs within the joint causing erosion and destruction of articular components. RA is triggered by environmental and genetic factors .Presence of these HLA- B5, DR3, DR4 types increases the risk factor of contracting the disease in Iraqi population [25].

Cancer: Like in the case of autoimmune diseases, there are clear associations between some cancer's resistance or susceptibility and the classic HLA profile of an individual. In Iraqi patients with colorectal carcinoma showed an association with HLA-A2, A28, B39, DR7 [26]. HLA typing have shown that alleles HLA-A*03010101-07, 09-11N, 13-16 allele are associated with the presence of breast cancer in Iraqi patients [27].

Inflammatory bowel disease(IBD): Inflammatory bowel disease (IBD) is a group of disorders defined by the presence of chronic gastrointestinal inflammation not due to a specific disease-producing organism. Two clinical forms of the disease exist—ulcerative colitis and Crohn's disease—which have a number of different clinical and pathological features.HLA-A9, B41 and DR8 showed an association with this disease [28]. There is a strong association between IBD and HLA-G [29].

From Table 1 there is some differences in HLA typing between Iraqi and not Iraqi populations , this may be due to racial, religions, environmental factors contribute in the developing this diseases.

Therefore, from the result of this study, one can predict the occurrence of these diseases in the different ethnic Iraqi groups. The expression of non-classic HLA Class I (HLA-G) is under epigenetic control, i.e. when the DNA is methylated the expression of HLA-G is suppressed [28]. There is evidence that HLA-G produce by many types of cancer cells. This situation suggests that HLA-G may play some role in tumor cells evading immune surveillance by inducing tolerance of the immune system. In addition to the cell-associated HLA-G, there is a secreted, circulating form, sHLA-G that may suppress the immune regulation of cancer cells [29]. The production of HLA-G can be a good indicator for the clinical prognosis of different cancers. As a rule, HLA-G is always associated with malignant tumor cells and it never has

Name of diseases	HLA alleles in Iraqi patients	References	HLA alleles in Non-Iraqi patients	References
Grave's disease	A19, B35, B40	[18]	B8 in whites, Bw35 and Dw12 in Japanese, Bw46 in Chinese	[17]
Ankylosing spondylitis	B27	[19]	B27	[17]
Coeliac disease	B8 , B12	[20]	B8, Dw3	[17]
Insulin dependent Diabetes Mellitus	A1, B8, B22, B40, B44, DR3, DR4	[21]	B8, B15, DRw3, DRw4	[17]
Insulin non dependent Diabetes Mellitus	A24, B8, B15, DR3, DR4, DQ2,DQ3	[22]	-	-
Psoriasis	A1, B13, Cw7, DR7	[23]	Cw6	[17]
Behcet's syndrome	B5	[24]	B5	[17]
Rheumatoid arthritis	B5, DR3, DR4	[25]	DR4	[17]
Colorectal carcinoma	A2, A28, B39, DR7	[26]	-	-
Breast carcinoma	A*03010101-07, 09-11N,	[27]	-	-
Inflammatory bowel disease(IBD):	A9 , B41, DR8	[28]	-	-

Table 1: Relation between HLA alleles and different diseases in Iraqi and non-Iraqi patients.

been found in normal cells. Thus, HLA-G appears to be a promising biomarker to predict the clinical progression of different cancers.

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