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Introductory Chapter: Concept of Human Leukocyte Antigen (HLA)

Batool Mutar Mahdi

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1. Introduction

The human leukocyte antigen (HLA) system is a cluster of gene complex encoding the major histocompatibility complex (MHC) proteins known as antigens located on the cell membrane of leukocytes in humans from which its name was derived. The functions of these cell surface proteins are many like responsible for the regulation of the immune system whether humoral or cellular in humans. It is the most important area in the vertebrate genome regarding infection and autoimmunity, and is essential in adaptive and innate immunity. The HLA gene complex is located on a 3-Mbp stretch within short arm of chromosome number 6p21. HLA genes are codominantly expressed and highly polymorphic, those have many different alleles that modify the adaptive immune system that helps body to distinguish the body's own protein from foreign invaders protein like virus, bacteria, or any other pathogens [1, 2].

1.1. Classification

The antigens of the HLA complex can be classified into three classes: class 1, class 2, and class 3.

1-MHC class I: There are three major and three minor MHC class I genes in HLA.

Major MHC class I:

- HLA-A
- HLA-B
- HLA-C

Minor MHC class I:

- HLA-E

- HLA-F

HLA-G β_2-microglobulin binds with major and minor gene subunits to produce a heterodimer.

2-MHC class II: There are three major and two minor MHC class II proteins encoded by the HLA.

Major MHC class II:

1. HLA-DP

- α-chain encoded by HLA-DPA1 locus

- β-chain encoded by HLA-DPB1 locus

2. HLA-DQ

- α-chain encoded by HLA-DQA1 locus

- β-chain encoded by HLA-DQB1 locus

3. HLA-DR

- α-chain encoded by HLA-DRA locus

- β-chains (only three possible per person),

They are encoded by HLA-DRB1, DRB3, DRB4, and DRB5 loci.

The genes of the class II combine to form heterodimeric (αβ) protein receptors that are typically expressed on the surface of antigen-presenting cells.

Minor MHC class II:

- DM

- DO

They are used in the internal processing of antigens, loading the antigenic peptides generated from pathogens onto the HLA molecules of antigen-presenting cell [3, 4].

A person's HLA complex is genetically inherited from their parents (50% from each parent), so you are more likely to have stronger matches with your siblings than with a random member of the population; however, each pair of siblings still only has a 25% chance of matching perfectly. The likelihood of having a perfect match with someone unrelated to you is approximately 1 in 100,000. Thus, the closer the match between two people like identical twins, the less likely the recipient's immune system will attack the donor's cells (**Figure 1**) [5].
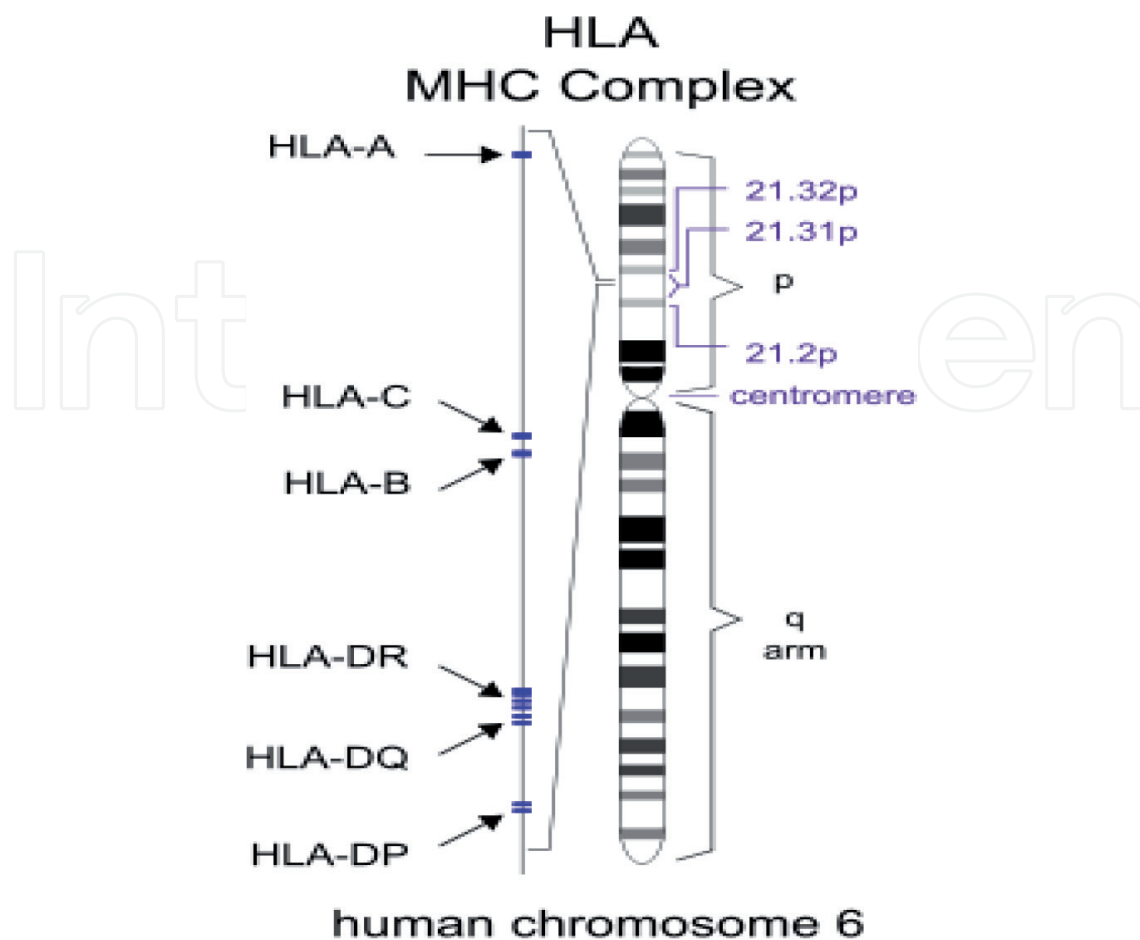
Figure 1. HLA complex is found on chromosome 6 in humans [5].

1.2. Structure

1.2.1. MHC class I

MHC class I molecule structure is consisting from two heterodimer polypeptide chains, α and β_2-microglobulin that linked together noncovalently by interaction of beta-2 microglobulin with α_3 domain of alpha chain. The alpha chain is encoded by many genes which are highly polymorphic, while beta-2 microglobulin subunit is not polymorphic and encoded by genes called beta-2 microglobulin gene. The other domain is α_3 domain which is plasma membrane that interacts with CD8 receptor of T-cytotoxic lymphocytes. This α_3-CD8 complex holds the MHC I molecule and the T-cell receptor (TCR) on the cell surface of the cytotoxic T cell binds its α_1-α_2 heterodimer and examines the foreign substance for antigenicity. The two domains, α_1 and α_2, fold to form a groove or basket for antigenic peptides to bind to it which consists of 8–10 amino acid in length (**Figure 2**) [6].

1.2.2. MHC class II

Class II molecules are also heterodimers in their structure, but consist of two homogenous peptides, an α and β polypeptide chain, both of which are encoded in the MHC. The alpha chain has two domes which are α_1 and α_2. Beta polypeptide chain has also two domains, β_1
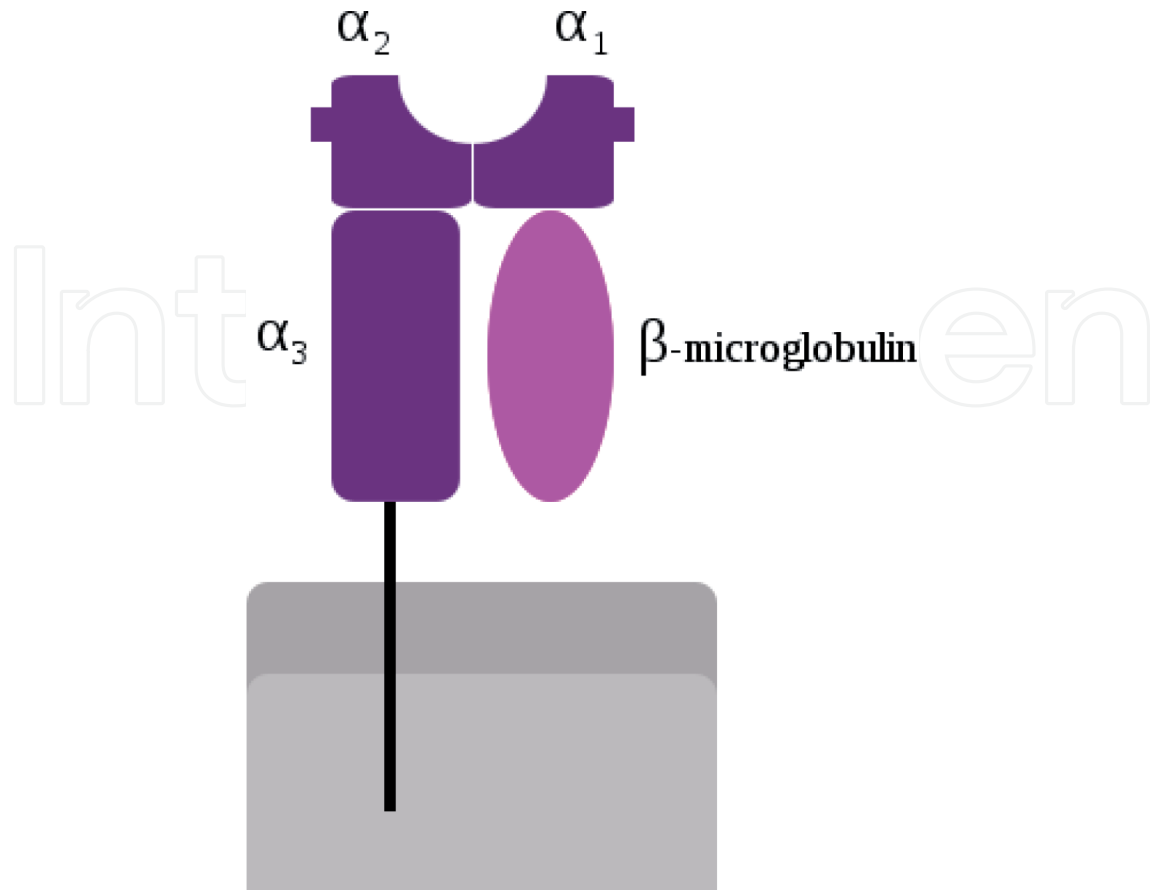
Figure 2. Structure of MHC class I.

and β_2. Every domain is encoded by a diverse exon gene, and other genes contain domains that encode different parts (leader sequences, transmembrane sequences, and cytoplasmic tail). The α_1 and β_1 regions of the chains form a membrane peptide binding domain, while the α_2 and β_2 regions form a membrane-proximal immunoglobulin-like domain. The groove or basket that binds the antigen or peptide is made up of two α-helix walls and β-sheet. Antigen-binding groove of MHC class II molecules is open at both ends and the groove on class I molecules is closed at each end resulting in antigens that bind to MHC class II molecules longer about 15–24 amino acid residues long. These domains are also highly polymorphic (**Figure 3**) [7].

1.3. Function

The major histocompatibility complex is a highly polymorphic region in the human genome located on short arm of chromosome number 6 about 200 genes in the region and is directly involved with the immune system. This is due to balancing selection acting on many genes with recombination in the MHC region [8]. These genes are in association with nonimmunologic genes like noncoding RNA genes, including expressed pseudogenes. MHC genes showed haplotype-specific linkage disequilibrium patterns contain the strongest cis- and trans-eQTLs/meQTLs in the genome and are called as a hot spot for disease associations.
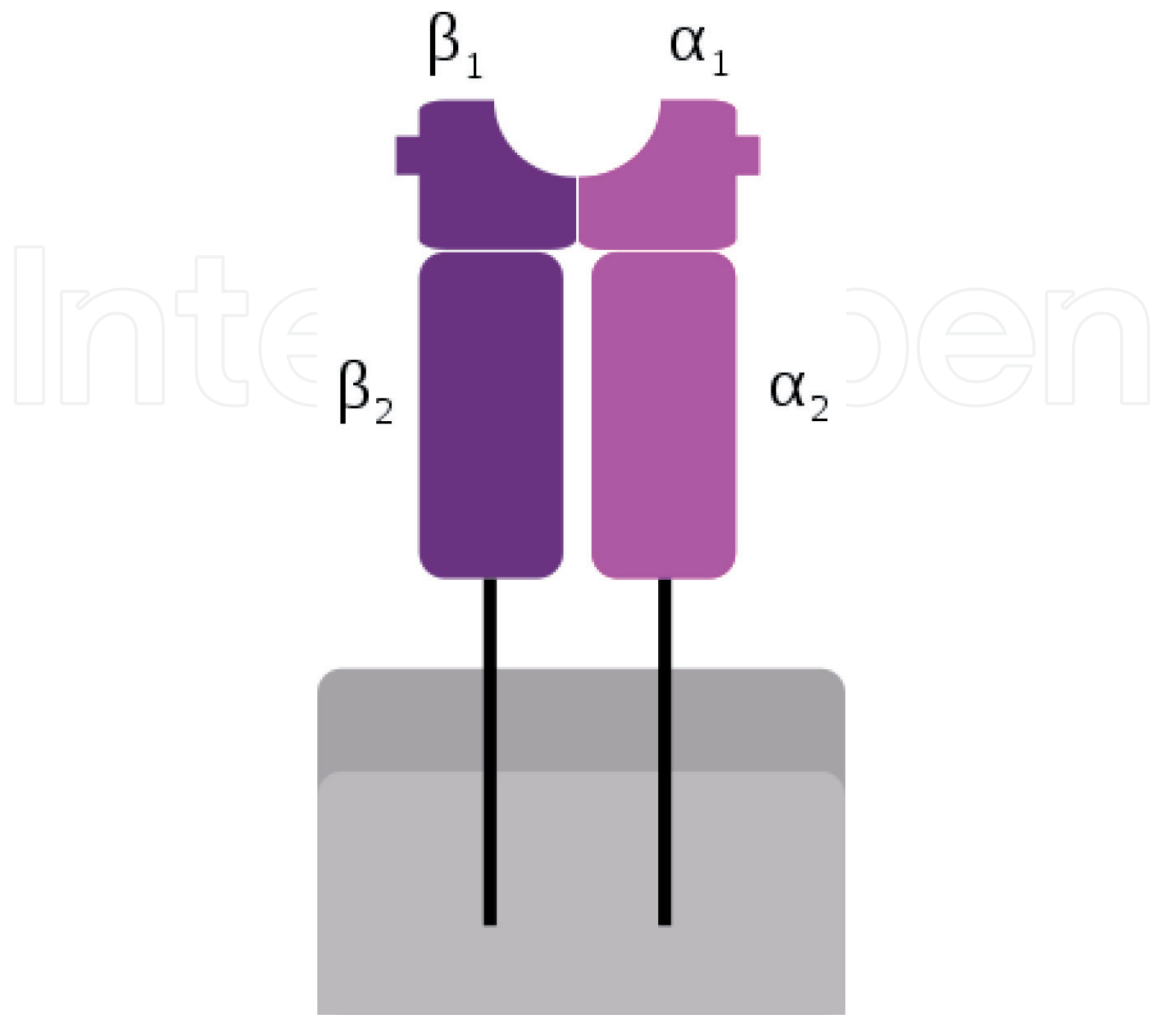
Figure 3. Structure of MHC class II.

The haplotype HLA-DR/DQ is structurally most variable and shows the highest number of disease associations. Dependence on a single reference sequence is not easy. Thus, analysis of GWAS for the MHC region is needed. One of the several issues with expected GWAS analysis is that it does not address this additional layer of polymorphisms unique to the MHC region [9]. Genome-wide association studies (GWAS) demonstrated that MHC is an important area for disease association, for example, autoimmune diseases [10, 11]. This very high-variety and broad-linkage disequilibrium leads to difficulty in assessing the one that leads to disease development and associations. Genome mapping can be sequence in addition to MHC haplotype and genome reference [12–14]. Many methods are defined but they are expensive [15–18]. Thus, many alleles of HLA had an association with cancer, infection with microorganisms in addition to its relation with transplant rejection.

1.4. Role of human leukocyte antigens (HLA) in transplantation

Human leukocyte antigens have an important role in graft rejection. One of the important squeal of mismatched graft is the development of donor-specific antibodies (DSA), which

causes antibody-mediated rejection, graft loss, and repeat transplantation in addition to tissue typing. These DSA are induced by foreign epitopes present on the leukocytes mismatched with HLA antigens of the donor [19]. The presence of pretransplant DSAs in deceased donor transplantations is a risk marker for graft loss, whereas nondonor-specific anti-HLA antibodies are not associated with a lower graft survival and sensitized patients with these antibodies directed against class I and II may be a risk marker for graft loss in the long term [20]. These antibodies develop through pregnancy, blood transfusions, or organ transplants. After viral infection or vaccination, antibodies produced may have the capacity to cross-react with HLA called heterologous immunity caused by T-cell alloreactivity or by bystander activation of dormant HLA-specific memory B cells [21].

1.5. Human leukocyte antigen and disease association

HLA had an important role in immunopathogenesis of many diseases. The strongest association is HLA-B27 and ankylosing spondylitis. There is a long list of diseases associated with HLA. Bullous pemphigoid is the most common autoimmune blistering disease and is due to IgG recognition of two hemidesmosomal antigens, that is, BP230 (BP antigen 1) and BP180 (BP antigen 2, collagen XVII). The role of HLA-DQB1*03:01 binding to the immunogenic portion of BP180 provides a potential mechanism by which exposure to neuronal collagen BP180 may lead to cutaneous disease. Patients who have allele HLA-DQB1*03:01 had an increased T-cell avidity to many epitopes like BP180-NC16a domain. Patients with Th1/Th2 imbalance, anergy is absent and T-cells are subsequently primed end in autoimmunity against the BP180-NC16a domain and disease development [22]. Type 1 diabetes patients are more liable to develop celiac disease because these two diseases are associated with DQB1 *02:01 and DQB1 *03:02 and the patients with coexisting T1 diabetes and celiac disease had an HLA profile more similar to T1D patients than CeD patients [23].

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References

[1] Trowsdale J. Genomic structure and function in the MHC. Trends in Genetics. 1993;**9**:117-122

[2] Horton R, Wilming L, Rand V, et al. Gene map of the extended human MHC. Nature Reviews. Genetics. 2004;**5**:889

[3]   Milner CM, Campbell RD. Genes, genes and more genes in the human major histocompatibility complex. BioEssays. 1992;**14**:565-571

[4]   Shiina T, Inoko H, Kulski JK. An update of the HLA genomic region, locus information and disease associations: 2004. Tissue Antigens. 2004;**64**:631

[5]   Rhodes DA, Trowsdale J. Genetics and molecular genetics of the MHC. Reviews in Immunogenetics. 1999;**1**:21-31

[6]   Toh H, Savoie CJ, Kamikawaji N, Muta S, Sasazuki T, Kuhara S. Changes at the floor of the peptide-binding groove induce a strong preference for proline at position 3 of the bound peptide: Molecular dynamics simulations of HLA-A*0217. Biopolymers. 2000;**54**:318-327

[7]   Jones EY, Fugger L, Strominger JL, Siebold C. MHC class II proteins and disease: A structural perspective. Nature Reviews. Immunology. 2006;**6**:271-282

[8]   DeGiorgio M, Lohmueller KE, Nielsen R. A model-based approach for identifying signatures of ancient balancing selection in genetic data. PLoS Genetics. 2014;**10**:e1004561

[9]   Kennedy AE, Ozbek U, Dorak MT. What has GWAS done for HLA and disease associations? International Journal of Immunogenetics. 2017;**44**:195-211

[10] Trowsdale J, Knight JC. Major histocompatibility complex genomics and human disease. Annual Review of Genomics and Human Genetics. 2013;**14**:301-323

[11] Zhou F, Cao H, Zuo X, Zhang T, Zhang X, Liu X, et al. Deep sequencing of the MHC region in the Chinese population contributes to studies of complex disease. Nature Genetics. 2016;**48**:740-746

[12] Horton R, Gibson R, Coggill P, Miretti M, Allcock RJ, Almeida J, et al. Variation analysis and gene annotation of eight MHC haplotypes: The MHC haplotype project. Immunogenetics. 2008;**60**:1-18

[13] Dilthey A, Cox C, Iqbal Z, Nelson MR, McVean G. Improved genome inference in the MHC using a population reference graph. Nature Genetics. 2015;**47**:682-688

[14] Dilthey AT, Gourraud PA, Mentzer AJ, Cereb N, Iqbal Z, McVean G. High-accuracy HLA type inference from whole-genome sequencing data using population reference graphs. PLoS Computational Biology. 2016;**12**:e1005151

[15] Chaisson MJ, Huddleston J, Dennis MY, Sudmant PH, Malig M, Hormozdiari F, et al. Resolving the complexity of the human genome using single-molecule sequencing. Nature. 2015;**517**:608-611

[16] English AC, Salerno WJ, Hampton OA, Gonzaga-Jauregui C, Ambreth S, Ritter DI, et al. Assessing structural variation in a personal genome—Towards a human reference diploid genome. BMC Genomics. 2015;**16**:286

[17] Selvaraj S, Schmitt AD, Dixon JR, Ren B. Complete haplotype phasing of the MHC and KIR loci with targeted Haplo Seq. BMC Genomics. 2015;**16**:900

[18] Maretty L, Jensen JM, Petersen B, Sibbesen JA, Liu S, Villesen P, et al. Sequencing and de novo assembly of 150 genomes from Denmark as a population reference. Nature. 2017;**548**(7665):87-91

[19] Kramer CSM, Roelen DL, Heidt S, Claas FHJ. Defining the immunogenicity and antigenicity of HLA epitopes is crucial for optimal epitope matching in clinical renal transplantation. HLA. 2017;**90**:5-16

[20] Michielsen LA, Wisse BW, Kamburova EG, et al. A paired kidney analysis on the impact of pre-transplant anti-HLA antibodies on graft survival. Nephrology, Dialysis, Transplantation. 25 Oct. 2018. DOI: 10.1093/ndt/gfy316. [Epub ahead of print]

[21] Heidt S, Feltkamp MC, Karahan GE, et al. No evidence for cross-reactivity of virus-specific antibodies with HLA alloantigens. Transplantation. 2018;**102**:1844-1849

[22] Amber KT, Zikry J, Hertl M. A multi-hit hypothesis of bullous pemphigoid and associated neurological disease: Is HLA-DQB1*03:01, a potential link between immune privileged antigen exposure and epitope spreading? HLA. 2017;**89**:127-134

[23] Viken MK, Flåm ST, Skrivarhaug T, Amundsen SS, et al. HLA class II alleles in Norwegian patients with coexisting type 1 diabetes and celiac disease. HLA. 2017;**89**:278-284