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HLA Genes and its Associated Genetic Disorders

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ABSTRACT
The Human Leukocyte Antigen (HLA) system is a region of high degree of polymorphism which plays essentially central roles in immune recognition by regulating the presentation of antigens and also adaptive immune responses. Because of its broad genetic diversity, due to individuals likely suffering from autoimmune or infectious diseases, rather than having a normal immune response, it is an essential factor in present–day immunology and clinical medicine. This article gives an overview of the genomic structure of HLA complex Class I, II and III genes with a special focus on their biological function in immune regulation and furthermore the association of specific HLA alleles with the major autoimmune diseases, namely Spondyloarthritis, Behçet's disease, Celiac disease and rheumatoid arthritis, and the diagnostic and prognostic importance of these HLA alleles. The study also analyzes the HLA typing technologies development from classic serological methods to novel advanced molecular techniques such as polymerase chain reaction (PCR)–based techniques, Sanger sequencing and next–generation sequencing (NGS) that improves transplantation matching and overall accuracy of typing. The latest development in high–resolution sequencing and bioinformatics has enhanced the clinical utility of HLA analysis in precision medicine, immunotherapy and disease hazard assessment. By putting an emphasis on the overall importance of this topic in clinical practice and evolving technologies, it is possible to analyze HLA biology with more detail in personalized medicine and immunological research.

Keywords: Immune regulation; Autoimmune diseases; Spondyloarthritis; Behçet's disease; Celiac disease; Rheumatoid arthritis

INTRODUCTION
The Human Leukocyte Antigen (HLA) system is a crucial part of the human immune system and it is important for distinguishing self and foreign antigens. It is made up of a cluster of genes on the short arm of chromosome 6 (6p21.3) that contain genes for cell surface proteins that present antigens and recognize them in the immune system. The function of these proteins is to allow the immune system to recognize foreign substances, and to elicit the right immune response to fight infection and disease. There are three main groups of the HLA system: Class I, Class II and Class III. Class I molecules, such as HLA–A, HLA–B and HLA–C, are anchored to the cell surface and display the intracellular antigens to the cytotoxic T lymphocytes, helping the immune system to identify the virus–infected or abnormal cells. The class II molecules (HLA–DR, HLA–DQ, HLA–DP) are involved in the presentation of extracellular antigens to helper T cells and thus in coordinating adaptive immune responses. Class III genes are not directly associated with antigen presentation, but they do encode a number of proteins associated with immune regulation and inflammation, and are not found in Class I and Class II molecules. The HLA system not only serves as a defense against infectious agents but is also known to contribute to susceptibility to certain autoimmune and inflammatory conditions, such as ankylosing spondylitis, rheumatoid arthritis, celiac disease and type 1 diabetes. In the field of organ and hematopoietic stem cell transplantation, which are dependent on the compatibility of HLA molecules between donor and recipient, HLA genes have also played an important role and compatibility is crucial to reduce transplant rejection and enhance transplant outcome.[1–6,8,22]

The HLA system was originally discovered in the research of tissue transplants and immune rejection. These findings confirmed that much of the compatibility or translatability of a recipient depends upon the difference in

HLA genes between the donor and the recipient and resulted in the development of donor–recipient HLA type matching techniques. Over the last decades, molecular biological developments have significantly enhanced HLA typing techniques, thus improving the diagnosis of disease, enhancing the success of transplants and gaining insight into immune mediated diseases.[18,19]

The HLA system is still an important target for immunological studies due to its unique genetic polymorphism and wide clinical relevance. Its involvement in disease susceptibility, transplantation, cancer immunology, pharmacogenomics, and precision medicine continues to be a focus of study and a valuable tool for enhancing patient care and developing individualized therapeutic strategies.[4,7,8] The HLA genes are organized into a cluster.

Major histocompatibility complex (MHC)

The Major Histocompatibility Complex (MHC) is a large, gene–dense genomic region that contains genes for the production of glycoproteins present on the cell surface which mediate antigen presentation and immune recognition. A major function of these molecules in adaptive immunity is to display peptide antigens to T lymphocytes, thus helping the immune system distinguish between self and non–self. The MHC is highly conserved across vertebrate evolution, but is essential for host defence against pathogens.[1–4, 7, 24]

In humans the MHC is known as the Human Leukocyte Antigen (HLA) system. The MHC is called MHC in all vertebrates, but in humans, it is called HLA. The HLA complex is located on the short arm of chromosome 6 (6p21.3) and is one of the more gene dense and polymorphic areas of the human genome, covering ~ 3.6–4.0 Mb.[1–4, 8]

There are three major regions of the HLA complex: Class I, Class III and Class II. The Class I and Class II regions contain genes which code antigen–presenting molecules that present endogenous and exogenous antigens to T lymphocytes, while the Class III region contains genes involved in immune regulation, inflammation and complement activation. These regions work together to mediate innate and adaptive immune responses. The structure and the functions of each region are explained in the next sections.[1–6, 23]

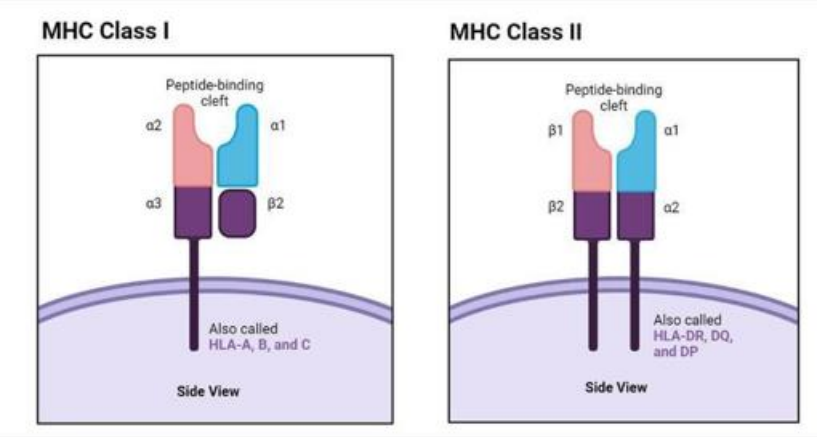

Figure 1: Adapted from Biocare Medical, Meet the Marker: HLA-DR.

HLA (Human Leukocyte Antigen) Genes classification.

One of the regions in our genome which shows diversity is the HLA system, which is the human version of the Major Histocompatibility Complex (MHC). The estimated size of the HLA genes is 3.6 Mb and they are situated on the short arm of chromosome 6 (6p21.3). It is made up of more than 200 genes that rely on the immune system. The genomic structure and biological functions of these genes are used to distinguish class I, class II, and class III HLA genes. [3,4,8]

HLA Class I Genes

The telomeric end of the MHC [I] contains the MHC's HLA Class I area, which is ~ 1.8 Mb in size. It has numerous other genes such as protein–coding genes (PCG), pseudogenes and non–programming genes. The Class I genes are divided into classical and non–classical genes.[3,4,8]

HLA–A, HLA–B, HLA–C are classical Class I genes that are expressed on almost all nucleated cells and are

highly polymorphic. These genes can present proteins to a part of the immune system, specifically CD8+ cytotoxic T lymphocytes, which can detect virus–infected or abnormal cells as "peptides" within the cell.[5,23]

The Class I non–classical genes (HLA–E, HLA–F and HAL–G) show less genetic variation and have more specific functions. HLA–E is involved in the regulation of NK cells activity and HLA–G is playing an important role in maintaining immune tolerance during pregnancy by protecting foetus from maternal immune response.[7] The Class I region also has a number of pseudogenes such as HLA–H and HLA–L, that are not functional and probably contribute to the evolution of the HLA family.[7]

HLA Class II Genes

The HLA Class II region spans approximately 0.7 Mb and contains several functional genes along with pseudogenes and gene candidates. These genes encode two distinct protein chains and that collectively make up the Class II molecule. HLA–DP, HLA–DQ and HLA– DR are all examples of classical Class II genes. Dendritic cells, macrophages, B lymphocytes and thymic epithelial cells are the primary sites where these genes are expressed. Their function is to deliver peptides from extracellular pathogens to CD4+ helper T lymphocytes, which initiate adaptive immune responses.' HLA–DM and HLA–DO, two non–classical Class II genes, they are also less polymorphic and are primarily responsible for controlling the loading of Class I molecules within intracellular compartments.[6]

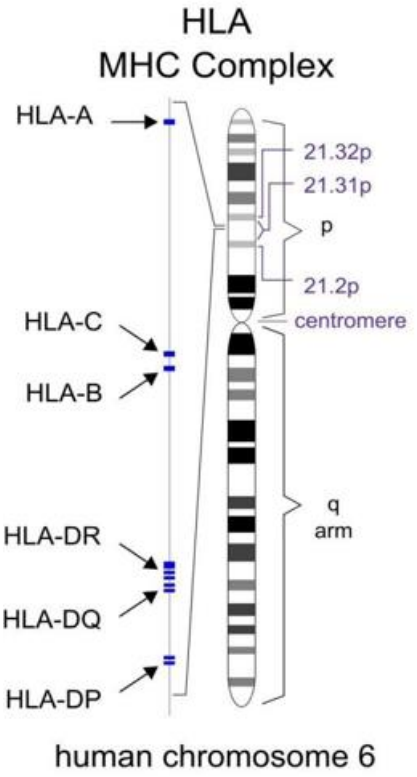

Figure 2: Adapted from Peakman M, Vergani D. Basic and Clinical Immunology.

HLA Class III Genes

The HLA Class III region spans about 0.9 Mb and is located halfway between the Class I and Class II regions. Class III genes do not encode antigen–presenting molecules, unlike Class I and Class II genes. Rather, they generate proteins involved in innate immunity, inflammation, and immune system control. Among the Class III genes are complement components (C2, C4A, C4B and CFB), inflammatory cytokines (TNF and LTB) and heat shock proteins (HSPA1A and HSPA1B). This region also contains several genes involved in cellular metabolism, protein synthesis, signal transduction and maintenance of normal physiology.[4,7]

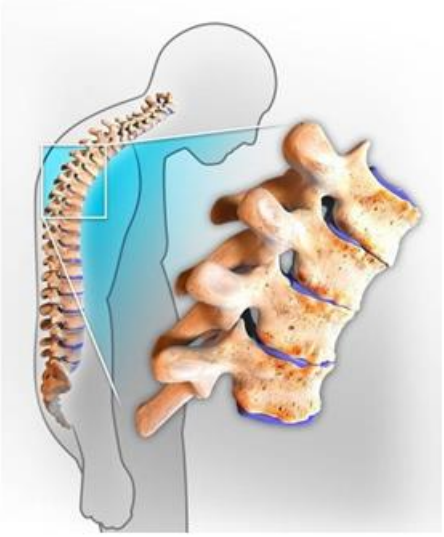

Figure 3: Arthritis-health.com (Veritas Health).

CLINICAL SIGNIFICANCE OF HLA

HLA in Autoimmune Diseases

MHC Class I: HLA–B27and Spondyloarthritis (SpA) The spondyloarthritis (SpA) group of clinical entities is a group of inflammatory diseases with characteristic axial and/or peripheral joint involvement, enthesitis, and often associated with inflammatory eye disease, particularly anterior uveitis. SpA is one of the most prevalent rheumatic diseases in the US with prevalence of 0.4–1.3%, which is similar to Europe and lower in African and Asian countries. It also poses a major burden both socially and economically due to work disability occurring in18.5– 21% of SpA patients. The common denominator of various entities of the SpA family is the frequent binding to MHC class I molecules, especially to HLA–B27, which has become significant in a routine diagnostic work–up in the past decades. HLA–B27 is a member of the MHC class I molecules. It is primarily the presenter of intracellular peptides to CD8–positive T lymphocytes. These "MHC class I" T cells can have a cytotoxic or regulatory function, which translates to tolerance if the peptides presented are "self", activation of cell–mediated immunity if "non–self" antigens are presented or a maladaptive autoimmune response if the "self" antigen is misrecognized. [9–16,25,26]

Clinical Relevance

Due to the strong association of the genetic marker HLA–B27 with spondyloarthritis (SpA), it is one of the most important genetic markers to be considered. In Caucasians with inflammatory back pain (IBP), it has 83 to 96% sensitivity, and 90 to 96% specificity for ankylosing spondylitis (AS). The Assessment of Spondyloarthritis International Society (ASAS) classification criteria and Amor criteria for SpA include a positive HLA–B27 test. There are current guidelines to test HLA–B27 in people who have a suspected diagnosis of SpA, but not for the general population. The positive result is only a sign of genetic susceptibility, and most people with the HLA–B27 gene have no disease. In our laboratory, analyzing 192 patient's blood samples, 38 were found HLA B27 positive, corresponding to 20 percent. The RADAR (Recognizing and Diagnosing Ankylosing Spondylitis Reliably) study demonstrated that referring patients with chronic back pain, who are younger than 45 years of age, who have inflammatory back pain and/or MRI imaging evidence of sacroiliitis, is effective to improve the diagnosis of axial SpA. It is particularly useful to use MRI findings in conjunction with HLA–B27 markers to detect early or non–radiographic axial SpA. HLA–B27 also gives a prognosis. In AS, the presence of HLA–B27 has been associated with earlier disease onset, increased disease activity, increased risk of peripheral joint involvement, increased severity of sacroiliitis and increased risk of requiring biological therapy. HLA–B27 patients tend to have a better response to treatment with TNF–α inhibitors. HLA–B27 is primarily associated with axial disease, enthesitis, dactylitis and symmetric sacroiliitis in psoriatic arthritis (PsA). There are haplotypes that have more severe clinical symptoms. There is a strong association between HLA–B27 and acute anterior uveitis and isolated HLA–B27–positive uveitis is a risk factor for the development of SpA. Similarly, in patients with reactive arthritis, the disease course tends to be more severe in HLA–B27–positive patients than in HLA–B27–negative patients. Interestingly, the HLA–B27 seems to be protective against a number of different

viruses such as HIV, Hepatitis C, influenza, Epstein–Barr virus, herpes simplex virus and hantavirus, yet it may make one more susceptible to malaria. There is also new evidence suggesting a possible link with persistent joint pain following infection with the Chikungunya virus. Genome–wide association studies (GWAS) have identified other susceptibility genes for SpA, including genes outside of the HLA locus, but these are not yet routinely used in clinical practice.[9–16,25,26]

MHC Class I: HLA–B51 and Adamantiades–Behçet's Disease (BD).

Behçet's disease (BD) is one of the vasculitides with variable vessels according to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, and is associated with inflammatory eye disease (uveitis), oral and genital ulcers. Like SpA, BD is also highly geographically distributed, with the Mediterranean and Asian populations being the most vulnerable, hence the nickname of "Silk Road disease". The prevalence of BD is 17–42/10,000 in Turkey, 2.1–420/100,000 in Asian and North African populations, and 0.3–7.5/100,000 in Western Europe and the United States. In patients with BD, the lesion is often accompanied by the presence of an MHC class I molecule named HLA–B51, particularly Turkish and Asian patients; the association in Caucasian patients is less strong. A recent meta–analysis showed that the prevalence of HLA–B51 in BD patients was between 50% and 72% versus a prevalence of 10–15% in healthy controls in high–risk populations.[27]

Other genetic and environmental factors are probably involved in the pathogenesis of BD to a further extent. Recently, a change of BD phenotype, namely a reduction of the frequency of HLA–B51 has been reported in Japanese patients.[28]

Clinical Relevance

Concerning the clinical significance, the HLA typing is not included in International Criteria for Behçet disease, but it can be done in a few medical laboratories. The sensitivity is an estimated 51% and the specificity is an estimated 71%. It is essential to know the limitations and the diagnostic value of a positive and negative result. It is not intended for diagnostic purposes, but for assisting the diagnosis. Screening of high–risk individuals is not recommended because most individuals who are HLA–B51 do not have BD. However, in the absence of HLA–B51, BD cannot be ruled out.[29]

HLA–B51 is potentially a useful marker, as the presence of HLA–B51 has been associated with an increased risk of genital ulcers and/or eye or skin involvement. HLA–B51 positivity is more common among male patients. Some subtypes may be associated with particular risk profiles—such as Turkish HLA–B51:03 patients having a greater risk of neurological involvement—and some with a decreased risk of papulopustular lesions, such as HLA–B51:09.[29]

Other alleles of BD susceptibility such as HLA–A03, A26, B15, 27 and 57 have a low specificity and are not at present clinically or diagnostically relevant.

MHC class II (HLA–DQ2/DQ8) and Celiac disease (CD)

Celiac disease (CD) is one of the most common organ–specific autoimmune diseases with a prevalence of 1% that primarily affects the small intestines following gluten exposure. It is well associated with both genetic and environmental factors, the latter being gluten exposure. The genetic factors are strongly associated with MHC class II alleles, HLA–DQ2 and DQ8. Non–MHC genes have also been implicated in GWAS.[17]

Clinical Relevance

Regarding the clinical and diagnostic relevance, the testing of DQ2/DQ8 has an excellent negative predictive value of 99%: a negative test virtually excludes CD, while a positive test merely indicates genetic susceptibility. An advantage of HLA testing is that a gluten–free diet is not necessary for optimal diagnostic conclusiveness in marked contrast to autoantibody testing and histology.

According to the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of celiac disease, testing of HLA–DQ2/DQ8 should be included in the diagnostic work–up of celiac disease in children. Small–bowel biopsy may not be necessary in the paediatric population in case of symptomatic patients with significantly elevated tTG (tissue Transglutaminase) and EMA (EndoMysial Antibodies) antibody titers and HLA–DQ2/DQ8 positivity. A similar straightforward approach has been suggested for all age groups with suspected CD. This so–called "four out of five rule" allows the diagnosis of

CD if four of the following five criteria are met: typical symptoms, significant elevation of CD antibodies, HLA–DQ2 or HLA–DQ8, typical biopsy result, response to gluten–free diet.[17]

US Guidelines do not recommend HLA–DQ2/8 testing in the routine diagnostic work–up of CD; however, it may be useful in selected clinical situations, such as a discrepancy between histologic and serologic results.

HLA testing may also be useful to exclude CD in high–risk individuals, such as first–degree relatives of CD patients, patients with autoimmune diabetes mellitus, selective IgA deficiency, Down syndrome, Turner syndrome, Williams syndrome, or autoimmune thyroiditis. Testing could also be considered in case of unexplained iron deficiency anaemia or early onset osteoporosis. With the help of HLA testing, the number of invasive diagnostic procedures may be reduced in this high–risk population.[17]

Figure 4: Celiac Disease adapted from BGAPC (2021).

MHC Class II: HLA–DRB1, Shared Epitope Hypothesis, and Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a common chronic systemic autoimmune disease, which primarily presents with a symmetrical polyarthritis and has a prevalence of 0.5–1% worldwide. Although the exact pathogenesis of RA remains unclear, its complex association with MHC class II molecules has been described. The contribution of HLA genes to susceptibility is estimated to account for 50% of risk.[17]

Remarkably, RA seems to be associated with such HLA–DRB1 alleles, which share sequences of five amino acids in position 70–74 of the antigen–binding groove of HLA–DR–β chains, as described by the shared epitope hypothesis. The shared epitopes (for example QKRAA, QRRAA, RKRAA, RRRAA) are present in 70–90% of Caucasian patients with seropositive RA in contrast to the prevalence of 20–30% in the general population and patients with seronegative RA. The highest relative risk of developing RA has been attributed to HLA–DRB1*0401 and 0404*, which can be detected in 50–61% and 27–37% of seropositive patients, respectively. DRB10404 may also be associated with seronegative RA. The latter population also exhibits *HLA–DRB1*0101.[17] The HLA–DRB1*0401/*0404 genotype is associated with elevated risk of disease, earlier onset, seropositivity, accelerated joint damage, and the presence of rheumatoid nodules.[17]

Ethnic differences have been reported; the prevalence of DRB1 in African–American patients is lower (25%). HLA–DRB1*0405* is the most frequent allele in Asian RA patients. HLA–*DRB1*1402 is associated with RA in Native American patients. A large European meta–analysis has shown that HLA–DRB1*13:01 provides protection against anti–citrullinated protein antibodies (ACPA)–positive disease but not against ACPA–negative RA.[17]

Homozygosity or compound heterozygosity for HLA–DRB1 alleles containing one of the shared epitope sequences is associated with increased risk of developing RA. Patients carrying two shared epitope–containing HLA–DRB1*04 alleles—especially homozygosity for HLA–DRB1*0401—have a higher risk of extraarticular manifestations including rheumatoid vasculitis.[17]

HLA TYPING TECHNIQUES

Serological Typing

Serological techniques were the first HLA typing technology to emerge in the 1950s. HLA was first described by

Jean Dausset in 1958, who observed the patterns of agglutination of leukocytes in the serum of repeatedly transfused patients. This leukocyte antigen was named "MAC" due to the naming of the volunteers who actually participated in the experiment. Furthermore, the presence of leukocytes antibody in the sera of multiparous women was confirmed, thus supporting the existence of the leukocyte antigen.[18]

The complement–dependent cytotoxicity (CDC) microassay was introduced by Terasaki and McClelland in the early 1960s, and has been the standard method of HLA typing for more than 25 years. Other techniques for histocompatibility testing have also been developed, including flow cytometry, immunoprecipitation/isoelectric focusing and cellular techniques like mixed lymphocyte reactivity; however, the CDC micro assay has been adopted by all as the most convenient method for HLA typing technology.[18]

Viable lymphocytes are first incubated with antisera against the HLA antigens in the CDC assay. When antigens are on the cells and antibodies are in the serum that match, the complement system is activated and the cell dies and takes a vital dye with it. After the addition of rabbit serum (which provides the complement), the results are obtained by counting the live cells.

Class I typing had already been carried out while class II typing had just started with cell separation technology. Confirmation of the discovery of HLA–D was obtained when a pair of HLA–A– and HLA–B– identical siblings had a mixed lymphocyte reaction, which was later renamed HLA–DR (DR for D–related).[19]

While HLA class I molecules are present on all nucleated cells, class II molecules are only expressed on professional antigen–presenting cells such as dendritic cells, B cells and monocytes. The separation of cells was necessary in class II typing because B cells are the cells that express class II antigens the most. HLA–DR specificity was first described at the 7th International Histocompatibility Testing Workshop in 1977 when the reaction pattern of B lymphocyte–reactive sera was analyzed. Since then, the HLA–DR and HLA–DQ typing of B lymphocytes have been made easier by cell separation.[18,19]

The CDC micro assay is complex and time consuming, and problems of cross–reactivity make interpretation difficult. In addition, there are also limited reagents available for serology that further limits its usefulness. Live cells and antisera, mainly from multiparous women or patients who have had repeated transfusion, are needed to perform this assay.[18]

Another drawback is the resolution. In 2011, a definition of the histocompatibility typing terms was published that defines the first field of the DNA typing nomenclature (A*01 or A*02) as low resolution. High resolution typing is used to detect the protein sequence of the antigen binding site and excludes the detection of alleles that do not code for the protein as a cell surface protein. High resolution refers to a second field precision of at least the second field and eliminates the ambiguities of polymorphisms of the exons 2 and 3 in the class I locus and exon 2 in the class II locus. Any difference cannot be detected by serological typing unless it is large enough to be recognized by means of antibody specificity. Moreover, HLA antisera can react with cross–reactions with minor amino acids variations, which could cause mistyping. An example of this is a study that found an error rate of 25% in HLA–B typing.[18]

Hence, serologic HLA typing is associated with bad results for transplantation. For these reasons, serological methods are quickly getting replaced with DNA based methods.[18,22]

PCR–Based Typing

DNA technology which is called human leukocytic antigen typing (HLA typing). In the early 1990s, DNA–based HLA typing technologies were introduced as a result of the development of PCR technology. This greatly enhanced the resolution of HLA typing at both class I and class II. At the same time, allelic sequence diversity (ASD) has become a topic of the fastest growing cases. The polymorphic regions are all in the peptide binding regions of the class I genes (exons 2 and 3) and the class II genes (exon 2) and are called the core exons and are the most commonly genotyped regions. Primers are generally used to amplify alleles at certain loci for DNA–based HLA typing. The amplified polymorphic sequences between the primer pairs are then detected by various methods such as oligonucleotide probes, sequencing reactions, restriction enzymes and sequence–specific primer binding. The most frequently used methods are sequence specific oligonucleotide (SSO) probe hybridization, sequence specific primers (SSP) and sequence–based typing (SBT).[20,21]

Sequencing–Based Typing

With the advent of the modern Sanger sequencing, more than 8000 alleles of both HLA class I and II have been identified (IMGT/HLA Database, Release 3). But, less than 10% of these alleles have been fully sequenced and only about 10% of these alleles are defined as common, well–documented (CWD) alleles. Over 40% of the alleles have been reported only once (as reported in the 16th IHWS HLA Rare Allele Workshop). It is only the peptide binding regions of HLA class I (exons 2 and 3) and class II (exon 2) that are routinely examined. Clinical studies have shown that matching these regions of the six major loci provides the best clinical outcomes (i.e., less rejection and least GvHD) in solid organ and haematopoietic stem cell transplantation.[20,21]

In ideal transplants, about 30% of recipients have adverse events within 5 years, however. It is not clear whether this is the result of genetic or non–genetic factors, and whether it reflects mismatches in regions not analysed using current methods—either other regions of HLA genes or other genes in other genomic regions.[22]

Furthermore, in some of those who have had typing, the ambiguous combinations of alleles will be demonstrated. These might be due to the ambiguities of cis–trans or to the effect of specific allele combinations being the same over the regions typically analyzed. One way to resolve the issue of genotyping ambiguity is to analyse additional exons or even entire genes. This is possible with the existing sequencing methods but is much costlier and time consuming. Furthermore, the amount of additional variation that is going to be detected is probably going to be a small fraction of what is now being detected and its value still has to be determined.[20,21]

NGS: Next–Generation Sequencing

Since the early 2010s, NGS has been recognized as a high–resolution HLA typing technology capable of resolving ambiguity. This technology encompasses methods such as Ion Torrent's semiconductor technology and Illumina's reversible terminator approach, both of which have become widely used in HLA typing. Various NGS platforms and methodologies have been investigated, including long–range PCR amplification, exome capture, and whole–genome sequencing. The introduction of massively parallel NGS platforms has enabled high–throughput, high–resolution HLA typing. Early research on NGS–based HLA typing technology primarily focused on demonstrating its efficiency, achieving high accuracy and low ambiguity. By integrating two suitable software programs, HLA genotyping accuracy reached 100%, with an ambiguity rate of only 0.8%. Another study demonstrated 100% concordance between NGS and Sanger sequencing results, along with a 93.5% reduction in ambiguity.[20,21]

NGS also aids in the identification of novel HLA alleles and the completion of partially sequenced alleles. The IPD–IMGT/HLA database serves as the primary repository for HLA allele sequences. As of September 2024, the IMGT/HLA database has cataloged over 40,000 HLA alleles, with the adoption of NGS technology significantly boosting the rate of new HLA allele discoveries due to its high–resolution capabilities.[8,20,21]

Despite its advantages, NGS technology, which relies on prior PCR amplification and short reads, faces several limitations when used for HLA typing. First, short tandem repeat regions such as HLA–DRC can disrupt accurate typing due to replication slippage mutations. Second, the 100–300 bp short reads are unable to span all genes completely, resulting in residual phasing ambiguity. Additionally, issues such as inappropriate primer binding can lead to allele dropout, and PCR amplification bias during gene enrichment before sequencing may cause allelic imbalance. Allelic dropout must be carefully considered when confirming homozygous results. Although the integration of bioinformatics with NGS technologies has improved HLA typing, long–read sequencing is necessary to address these limitations and further enhance HLA typing accuracy.[20,21]

CONCLUSION

The Human Leukocyte Antigen (HLA) system is the most genetically polymorphic and functionally significant part of the human genome and is the basis for antigen presentation and adaptive immune responses. The high polymorphism of the HLA genes enables the recognition of a broad range of pathogens, and at the same time, the genes play a role in susceptibility to autoimmune diseases, infectious diseases, cancer and side effects of drug treatment. Over the last few decades, a lot of work has been done that has demonstrated that HLA molecules are very important in determining compatibility for transplantation, have a role in predicting the risk of disease, and have a role in helping to guide clinical decisions.

The field of molecular diagnostics has revolutionized HLA typing from a serological to a more precise technology based on DNA science, including PCR–SSP, PCR–SSO, Sanger sequencing, and next generation

sequencing (NGS). This has dramatically improved the resolution of typing, reduced the ambiguity, enhanced matching of donors and recipients, improved outcomes after transplantation, and expanded personalized medicine use. Furthermore, recent studies have revealed that classical and non–classical HLA molecules are both implicated in tumor immune evasion and in the treatment of cancer by immunotherapy, thus extending beyond transplantation and autoimmune disease.

Despite these advances, many aspects of the biology of HLA remain unknown. Lots of recently discovered alleles will require further study including their functional importance, the mechanisms that underlie the HLA–associated disease susceptibility and the HLA genomics integration in precision medicine. Research in the future that combines high–resolution sequencing technologies, bioinformatics, and artificial intelligence is likely to give a deeper understanding of HLA diversity and its clinical consequences. Overall, continued research into the HLA system will further improve our understanding of immune regulation and enable the development of improved diagnostics, targeted therapies, and personalized treatment approaches, which will aid the advancement of immunology, transplantation, oncology, and precision medicine.

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