

Review Article

Human Leukocyte and Platelet Antigens in Transplantation and Transfusion Medicine: Precision Immunology, Molecular Advances, Clinical Applications, and Future Perspectives

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Abstract

Human leukocyte antigens (HLAs) and human platelet antigens (HPAs) are highly polymorphic immunogenetic systems essential for immune recognition, transplantation, and transfusion medicine. Their genetic diversity influences donor–recipient compatibility, alloimmune responses, graft survival, and transfusion outcomes. This review examines their molecular genetics, biological functions, population diversity, clinical significance, emerging technologies, challenges, and research priorities. A narrative review of peer-reviewed literature, international guidelines, consensus statements, registry reports, and authoritative databases was conducted, critically synthesizing evidence on immunogenetics, transplantation, transfusion medicine, molecular diagnostics, artificial intelligence, and precision medicine. Advances in high-resolution typing, next-generation sequencing, long-read sequencing, multi-omics, and artificial intelligence have improved compatibility assessment, donor selection, alloantibody detection, and clinical decision-making, supporting better outcomes in solid organ and hematopoietic stem cell transplantation. Molecular characterization has also enhanced the diagnosis and management of platelet transfusion refractoriness, fetal and neonatal alloimmune thrombocytopenia, and other alloimmune disorders. Emerging computational approaches and genome editing offer further opportunities for personalized care and therapeutic innovation. Integrating genomic technologies, molecular diagnostics, and computational biology can advance precision immunogenetic medicine. Addressing donor shortages, population underrepresentation, ethical concerns, and implementation costs through interdisciplinary research and international collaboration is essential for improving transplantation outcomes, transfusion safety, and equitable healthcare.

1. Introduction

Human leukocyte antigens (HLAs) and human platelet antigens (HPAs) are highly polymorphic immunogenetic systems essential for immune recognition, transplantation, transfusion safety, and precision immunology [1]. Their genetic diversity influences donor–recipient compatibility, alloimmunization, and individualized therapeutic decisions [2]. The discovery of HLA and identification of the human

major histocompatibility complex on chromosome 6 established the genetic foundation of histocompatibility and transplantation matching [3, 4]. Advances in molecular typing and next-generation sequencing (NGS), alongside expansion of the IPD IMGT/HLA database, have improved allelic resolution and revealed extensive HLA diversity [5, 6]. HPAs arise predominantly from single nucleotide polymorphisms affecting platelet membrane glycoproteins [7]. Despite their comparatively lower polymorphism, antigen incompatibility contributes to fetal and neonatal alloimmune thrombocytopenia (FNAIT), post-transfusion purpura, and platelet transfusion refractoriness. Molecular genotyping and improved antibody detection have strengthened diagnosis and transfusion support [8, 9]. HLA compatibility predicts graft acceptance, antibody-mediated rejection, donor-specific antibody formation, and long-term survival following solid organ transplantation [10]. High-resolution matching also reduces complications in hematopoietic stem cell transplantation [11]. HLA alloimmunization and HPA antibodies remain important causes of platelet transfusion refractoriness and immune-mediated platelet destruction [12–14]. Emerging technologies, including long-read sequencing, artificial intelligence (AI), machine learning, and multi-omics, enable detailed characterization of immunogenetic variation and improved prediction of alloimmune responses [15, 16]. Integrating genomics, transcriptomics, proteomics, and computational analytics supports individualized diagnosis, donor selection, immunosuppression, and transfusion strategies [4, 16, 17]. However, underrepresentation of African populations in immunogenetic databases, high sequencing costs, inadequate infrastructure, and ethical concerns limit implementation [17–19]. International collaboration, population-specific registries, standardized methods, and equitable diagnostic access are essential [19–21]. This review examines HLA and HPA biology, clinical applications, technological advances, research gaps, and emerging therapeutic strategies.

2. The HLA Molecular Structure, Biological Functions, and Clinical Significance

The human leukocyte antigen (HLA) system constitutes the major histocompatibility complex (MHC), a highly polymorphic genomic region located on chromosome 6p21.3 that regulates antigen presentation, immune responses, inflammation, and host defense [16, 22]. Its classical loci include HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, and HLA-DP, whose extensive diversity influences immune protection and donor–recipient compatibility [5]. The HLA region comprises three classes. Class I molecules present intracellular peptides to CD8⁺ cytotoxic T lymphocytes, facilitating the elimination of infected and malignant cells. Class II molecules present extracellular peptides to CD4⁺ helper T lymphocytes, stimulating cytokine production, B-cell maturation, and antibody responses. Class III genes encode complement components and inflammatory mediators [23–25]. HLA molecules are central to transplantation immunology because recipient immune cells recognize donor HLA molecules, potentially triggering T-cell activation, donor-specific antibody formation, and graft rejection [26, 27]. Molecular assessments incorporating amino acid polymorphisms, epitope mismatches, and eplet disparities can improve predictions of antibody-mediated rejection and graft survival beyond conventional antigen-level matching [2, 28, 29]. HLA polymorphisms also influence susceptibility to autoimmune diseases, infectious diseases, vaccine responses, cancer immunotherapy, and adverse drug reactions [16, 30]. Population diversity further complicates compatibility assessment. African populations exhibit particularly extensive HLA polymorphism, while migration, genetic drift, and population bottlenecks contribute to differences in allele distributions worldwide [29, 31]. Underrepresentation of diverse populations in international donor registries reduces access to compatible donors, emphasizing the need for inclusive recruitment and population-specific databases [19, 32]. Advances in next-generation sequencing, long-read sequencing, computational immunogenetics, artificial intelligence, and machine learning enable higher-resolution typing and improved prediction of compatibility and transplant outcomes [16, 33, 34]. Integrating these technologies into clinical practice supports precision immunology, individualized donor selection, and therapeutic decision-making across transplantation, transfusion medicine, and personalized healthcare [5, 17, 21].

3. HPAs: Molecular Structure, Biological Functions and Clinical Significance

Human platelet antigens (HPAs) are genetically determined polymorphic epitopes on platelet membrane glycoproteins that influence hemostasis, immune recognition, and transfusion compatibility [35]. Primarily arising from single nucleotide polymorphisms, these antigens can trigger alloimmune responses following pregnancy or transfusion [3]. Despite their lower diversity than human leukocyte antigens (HLAs), HPA incompatibility causes fetal and neonatal alloimmune thrombocytopenia (FNAIT), platelet transfusion refractoriness (PTR), and post-transfusion purpura (PTP) [9]. More than forty HPA systems have been recognized, including HPA-1, HPA-2, HPA-3, HPA-4, HPA-5, and HPA-15, which account for many clinically significant platelet alloantibodies [34, 36]. These antigens occur on glycoproteins responsible for platelet adhesion and aggregation, including integrin α IIb β 3, glycoprotein Ib/IX/V, glycoprotein Ia/IIa, and CD109 [37, 38]. Their genetic variation influences alloimmunization risk and donor compatibility across populations [39]. During pregnancy, maternal exposure to paternally inherited fetal HPAs can stimulate IgG alloantibody production. These antibodies cross the placenta, destroy fetal platelets, and potentially cause severe thrombocytopenia, intracranial hemorrhage, neurological damage, or death [34]. Diagnosis and management involve maternal antibody screening, fetal genotyping, intravenous immunoglobulin, and compatible platelet transfusions when indicated [34]. In transfusion medicine, HPA and HLA alloantibodies contribute to PTR, particularly among repeatedly transfused patients. When HLA-compatible transfusions fail, HPA antibody testing, genotyping, crossmatching, and antigen-compatible donor selection can improve transfusion outcomes [13, 40, 41]. Molecular diagnostic advances, including polymerase chain reaction, real-time PCR, and next-generation sequencing, enable accurate HPA genotyping, rare-variant detection, and improved donor registry development [42]. Integrating these technologies with computational immunogenetics supports precision transfusion medicine [4]. However, underrepresentation of African and other populations in HPA databases necessitates multicentre genomic studies and internationally harmonized registries [9].

4. The HLA and HPA in Stem Cell Transplantation

Human leukocyte antigen (HLA) compatibility is fundamental to transplantation medicine, influencing donor selection, graft acceptance, rejection, and long-term survival. Advances in high-resolution HLA typing, donor-specific antibody (DSA) assessment, and molecular mismatch analysis have improved compatibility assessment and personalized transplantation [12]. Despite immunosuppressive advances, HLA incompatibility remains an important cause of allograft injury [2, 43]. In solid organ transplantation, particularly kidney transplantation, HLA matching reduces rejection risks and improves graft survival. Donor HLA recognition activates T lymphocytes, B cells, and complement

pathways, potentially causing cellular rejection, antibody-mediated rejection, and chronic graft dysfunction [12, 44, 45]. High-resolution typing and eplet-based mismatch assessment improve prediction of DSA development and graft outcomes [28, 46]. Pre-existing or newly developed DSAs can damage graft endothelial cells, promoting inflammation and antibody-mediated rejection. Luminox-based assays support antibody detection and immunological risk assessment [47, 48]. Human platelet antigens (HPAs) have a complementary role in transplantation, principally through platelet immunology and transfusion support rather than conventional organ compatibility matching. HPA incompatibility may trigger alloantibody formation, platelet destruction, and platelet transfusion refractoriness in transplant recipients requiring repeated platelet support. HPA typing and compatible platelet selection can therefore help manage immune-mediated thrombocytopenia and improve transfusion support during transplantation. However, HLA remains the principal immunogenetic determinant of conventional graft compatibility. In hematopoietic stem cell transplantation (HSCT), high-resolution matching of HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DPB1 helps reduce graft rejection, graft-versus-host disease (GVHD), and transplant-related mortality [6]. Donor T cells can attack recipient tissues, although they may also eliminate malignant cells through the graft-versus-leukemia effect. Balancing GVHD prevention with antitumor immunity remains essential [6, 49, 50].

5. HLAs and HPAs in Transfusion Practice

Human leukocyte antigens (HLAs) and human platelet antigens (HPAs) are important determinants of transfusion compatibility, particularly in patients requiring repeated platelet transfusions. Although HLA incompatibility is the predominant cause of immune-mediated platelet transfusion failure, HPA alloimmunization also contributes to adverse transfusion outcomes [47]. Advances in immunogenetics and molecular diagnostics have improved antibody detection, donor selection, and individualized transfusion support [9, 15, 35]. Platelet transfusions are essential for patients with hematological malignancies, bone marrow failure, major hemorrhage, and treatment-related thrombocytopenia [51]. However, repeated exposure to donor platelets may stimulate HLA and HPA antibody production, accelerating platelet clearance and reducing transfusion effectiveness, particularly among repeatedly transfused patients and previously sensitized individuals [46, 52]. Platelet transfusion refractoriness (PTR) is characterized by inadequate platelet count increments following transfusion. Although infection, bleeding, and disseminated intravascular coagulation are important non-immune causes, immune-mediated PTR commonly involves antibodies against HLA class I antigens and, less frequently, HPAs. Assessment includes corrected count increments, antibody testing, platelet crossmatching, and immunogenetic evaluation to guide compatible donor selection [32, 53]. HPAs are particularly significant in fetal and neonatal alloimmune thrombocytopenia (FNAIT), which occurs when maternal IgG antibodies target fetal platelets expressing inherited paternal antigens. Severe cases may cause intracranial hemorrhage and perinatal complications. Maternal antibody screening, HPA genotyping, antenatal intravenous immunoglobulin, and compatible platelet transfusions support management [17, 34, 54, 55]. Post-transfusion purpura is another potentially severe complication involving platelet-specific alloantibodies, requiring prompt diagnosis and treatment, commonly with intravenous immunoglobulin [56–58]. Molecular techniques, including PCR and next-generation sequencing, enable accurate HPA genotyping and identification of compatible donors [59, 60]. Integrating HLA and HPA testing can strengthen transfusion safety and individualized platelet support [4, 34].

6. Molecular Typing Technologies and Advances in Immunogenetics

Accurate characterization of human leukocyte antigen (HLA) and human platelet antigen (HPA) polymorphisms is fundamental to transplantation and transfusion medicine [61]. Molecular technologies have advanced from conventional serological methods to high-resolution sequencing, improving donor matching, alloimmune risk prediction, and individualized clinical management [4, 5, 16, 42]. Long-read sequencing, including single-molecule real-time and nanopore technologies, enables comprehensive HLA haplotype characterization, accurate phasing, and detection of structural variants, enhancing compatibility assessment [15, 60]. Similarly, PCR-based assays, digital PCR, and next-generation sequencing improve HPA genotyping, supporting diagnosis of fetal and neonatal alloimmune thrombocytopenia, platelet transfusion refractoriness, and post-transfusion purpura, alongside selection of compatible platelet donors [9, 62]. International databases, including IPD-IMGT/HLA and standardized HPA classifications maintained by the International Society of Blood Transfusion, facilitate allele identification, consistent nomenclature, and harmonization of laboratory practices [5, 63]. Despite these advances, implementation remains constrained by sequencing costs, limited infrastructure, shortages of trained personnel, and inadequate bioinformatics capacity. Underrepresentation of African and other diverse populations in reference databases also threatens equitable donor matching and diagnostic accuracy [64]. International collaboration, investment in genomic infrastructure, inclusive population databases, and affordable sequencing technologies are essential for expanding equitable precision immunogenetics globally [18, 19].

7. Artificial Intelligence and Computational Immunogenetics

Artificial intelligence (AI) and computational immunogenetics are transforming transplantation and transfusion medicine by enabling rapid genomic analysis, compatibility prediction, and personalized clinical decisions [65–67]. Machine learning integrates HLA genotypes, HPA profiles, donor-specific antibodies, and clinical variables to improve donor selection and predict rejection, graft-versus-host disease, platelet transfusion refractoriness, and graft survival [11, 67]. These approaches support individualized immunosuppressive management and precision immunology. AI-assisted bioinformatics also automates allele assignment, variant classification, quality control, and HLA haplotype reconstruction from next-generation sequencing data. These applications improve analytical efficiency, reduce human error, and enhance reproducibility in histocompatibility laboratories [68]. Continued integration of AI with advanced sequencing technologies is expected to strengthen routine clinical immunogenetics and optimize transplantation and transfusion outcomes [15, 69].

8. Global Population Genetics of Human Leukocyte Antigens and Human Platelet Antigens

The polymorphism of human leukocyte antigens (HLAs) and human platelet antigens (HPAs) reflects human evolution, migration, natural selection, and environmental adaptation [64]. These immunogenetic systems influence transplantation, transfusion medicine, infectious disease susceptibility, and precision medicine. Geographic variations in allele frequencies and haplotypes affect donor availability,

compatibility, and alloimmune risk [70]. HLA is the most polymorphic region of the human genome, with substantial allele variation across populations. Balancing selection driven by infectious diseases has enhanced immune protection but complicates unrelated donor matching [66, 70]. African populations exhibit particularly high HLA diversity, including greater allelic richness and rare variants, yet individuals of African ancestry often face reduced access to optimally matched donors. Expanding African donor recruitment and genomic databases is therefore essential [71, 72]. HPA polymorphisms also vary geographically, influencing fetal and neonatal alloimmune thrombocytopenia (FNAIT), platelet transfusion refractoriness (PTR), and post-transfusion purpura (PTP). HPA-1a incompatibility predominates in European FNAIT cases, whereas HPA-4 and HPA-5 may be more important in Asian and certain African populations [9, 73]. HPA-1a antibodies are also clinically important in pregnancy-associated platelet alloimmunization [74]. Equitable transplantation and transfusion require representative donor registries, standardized molecular typing, and international collaboration [64, 75, 76]. Investment, research capacity, and accessible genomic resources are crucial for addressing population data gaps and advancing precision immunology worldwide [77].

9. Precision Immunology and Personalized Medicine

Precision immunology integrates immunogenetics, genomics, molecular diagnostics, bioinformatics, artificial intelligence (AI), and clinical medicine to provide individualized healthcare based on patients' immunological profiles [78]. Advances in high-resolution molecular typing, next-generation sequencing (NGS), and computational immunogenetics enable detailed characterization of HLA and HPA polymorphisms, improving donor matching and immunological risk assessment [33, 79]. These approaches help predict donor-specific antibody (DSA) formation and personalize transplantation strategies [29]. Precision transplantation also incorporates individualized immunosuppression and post-transplant monitoring. Molecular mismatch analysis, DSA surveillance, circulating biomarkers, and donor-derived cell-free DNA facilitate earlier graft injury detection and risk-adapted treatment, potentially improving graft survival [80, 81]. Immunosuppressive therapy can consequently be tailored to patients' molecular and immunological risk profiles rather than standardized protocols [82]. Future developments integrating AI, digital pathology, wearable biosensors, and global immunogenetic databases may improve personalized prediction of disease susceptibility, donor compatibility, treatment response, and clinical outcomes, advancing equitable precision transplantation and transfusion medicine worldwide [80, 83].

10. Current Challenges and Research Gaps

HLA molecular complexity, novel alleles, structural variants, and rare haplotypes complicate donor matching and clinical interpretation [61, 84, 85]. Uncertainties regarding rare alleles and eplet mismatches necessitate further functional studies to improve compatibility prediction [29, 86]. Implementation is hindered by the high costs of sequencing, bioinformatics infrastructure, expertise, and quality assurance, particularly in low- and middle-income countries [87]. Despite advances in international standardization, variability persists in laboratory protocols, compatibility algorithms, and antibody testing. Harmonized standards and reporting guidelines remain essential [88, 89]. Integrating multi-omics technologies into clinical practice also requires further validation [90]. Large multicenter prospective studies involving diverse populations, standardized analytical methods, and long-term follow-up are needed to establish their clinical utility [88, 91, 92]. Addressing these gaps through investment, collaboration, and equitable genomic research will advance precision immunology globally.

11. Future Perspectives

The integration of immunogenetics, molecular diagnostics, artificial intelligence (AI), and precision medicine is transforming transplantation and transfusion medicine [10, 93]. Future precision immunology platforms will predict immune responses, optimize donor selection, personalize immunosuppressive therapy, and improve clinical outcomes [91, 94]. Molecular compatibility profiling, including allele-level typing, mismatch analysis, and peptide-binding prediction, may improve prediction of donor-specific antibodies and rejection while reducing unnecessary immunosuppression [79]. Integrating genomics, transcriptomics, proteomics, metabolomics, epigenomics, and single-cell sequencing will enhance biomarker discovery and prediction of rejection, alloimmunization, and treatment responses [88, 95, 96]. CRISPR-Cas technologies may enable engineered donor cells, universal donor platelets, and hypoimmunogenic cellular therapies, potentially reducing dependence on extensive donor matching [65, 97]. Digital health, wearable biosensors, and computational immune models may facilitate early complication detection and personalized therapeutic predictions [98–100]. Equitable progress requires diverse immunogenetic databases, affordable sequencing, and stronger genomic research infrastructure, particularly in underrepresented African populations [101, 102]. Ultimately, interdisciplinary collaboration will help integrate these innovations into safer, more effective, and equitable clinical care worldwide [88, 94].

12. Conclusion

Human leukocyte and platelet antigens remain fundamental to transplantation, transfusion safety, and precision immunology. Advances in molecular typing, next-generation sequencing, artificial intelligence, and computational biology are transforming compatibility assessment, donor selection, rejection prediction, and personalized treatment. These innovations improve graft survival, strengthen platelet transfusion management, and support individualized clinical decisions. However, limited genomic representation, technological inequalities, complex immunogenetic variation, and ethical concerns continue to hinder equitable implementation. Addressing these challenges requires international collaboration, representative donor registries, standardized diagnostic approaches, and investment in genomic infrastructure. Ultimately, integrating immunogenetics with precision medicine will advance safer, more effective, and equitable transplantation and transfusion care worldwide.

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