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Review

Unravelling the Genetic Tapestry of Immunity: A Comprehensive Review of Immunogenetics

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Abstract

The overlap of immunology and genetics has become immunogenetics, an exciting new field that promises to reveal previously inaccessible details of interactions between genetic variation and immune reactions, disease development and resolution, drug efficacy and tolerance. As global health is increasingly influenced by immune-mediated disorders and it spans autoimmune disease, cancer, and new emerging infectious risks, precision, population-specific interventions have never been more urgent. This review brings together fundamental immunogenetics and translational research under one umbrella, discussing the contributions of HLA polymorphism, the diversity of antibody/T-cell receptor, cytokine networks, and immune checkpoint regulation in the development of antigen recognition and immune tolerance. We explain disruptive technologies, such as next-generation sequencing, CRISPR-Cas9, and integrative multi-omics, that are redefining the field of diagnostics and therapeutics. Certain persistent issues cannot be ignored, e.g., equal utilization of genetic information amongst human genetic variations, ethical management of genetic information, and biomarker validation are equally evaluated. We propose the future directions using systems biology, consortia of global genomics, and predictive modelling made possible through AI as the basis of next-generation precision medicine, with the next factor of precision medicine being immunogenetics.

Keywords

Immunogenetics, HLA polymorphism, Immune tolerance, Next-generation sequencing (NGS), CRISPR-Cas9, Multiomics, Precision medicine

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1. Introduction

Immunogenetics, a field with over half a century of foundational discoveries linking genetic variation to immune function, has become an imperative field as immunology and genetics combine to decipher the mechanisms of inherited and acquired genetic variations that determine the immune process [1]. Early research on human leukocyte antigen (HLA) polymorphisms and the major histocompatibility complex (MHC) demonstrated that genetic factors significantly alter each person's immune system's ability to identify and respond to antigens. Building on this basis, modern molecular profiling techniques have increased our comprehension of the ways in which immunoglobulin repertoires, T-cell receptor diversity, and cytokine gene variants affect immunological responsiveness and illness outcomes [2]. Such disparities contribute to an understanding of why people are dissimilar in regard to infectious diseases, susceptibility to developing autoimmune conditions, their capacity to identify and excise tumors, and their reaction to transplants. Precision medicine is still an evolving standard in most healthcare systems, immunogenetics has emerged as a strategic approach whereby diagnostics and therapeutics can be adjusted to the individual genetic and immunological phenotype of a given patient [3].

Advances in technology, like next-generation sequencing to high-resolution immune repertoire mapping, CRISPR-Cas9 to provide precise editing capabilities, integrative multi-omics efforts, and beyond, are making it possible to understand more about immune regulation and dysregulation at scale and magnitude never before accomplished [4].

In addition to expanding our knowledge of disease pathophysiology, these technical advancements are starting to influence the creation of novel vaccines, targeted immunotherapies, and transplantation techniques that induce tolerance. The quick advancements being achieved highlight the revolutionary potential of immunogenetics, even though these precision-guided methods are still mostly in the early phases of translation. However, the field still faces several obstacles, such as a lack of worldwide representation, moral dilemmas, and the difficulty of incorporating genetic results into standard medical procedures.

There are still issues with transferring the findings to other populations around the world that are not well represented in genomic databases. There are serious ethical concerns about how genetic data are collected, shared, and utilized, and the proper governance of such practices is needed to avoid abuse and unfairness. Moreover, the multifaceted, dynamic nature of the regulation of immunity is a product of genetic and environmental influences, which requires favouring systems-level, integrative strategies [5].

This review summarizes the underpinning principles, important genetic factors of immunity, and their clinical utility in key disease settings. It also points to interdisciplinary and technological innovations that have to be leveraged to overcome existing limitations. Defining both the existing and emerging state of affairs, we will place immunogenetics as a critical force behind the next-generation precision healthcare enabled by increased equity.

2. Foundations of Immunogenetics

The fundamental principles of immunogenetics practice focus on the role of genetic variability in the development of immune responses and the establishment of disease predisposition. The key to this notion is a genetic polymorphism (especially in the wide-ranging human leukocyte antigen (HLA) system). The remarkable polymorphisms of the HLA molecules allow the immune system to have the ability to recognize numerous different antigens, but also facilitate its individual variations in the immune responses [6]. The antigen presentation can also affect the autoimmune pathogenesis, as that is been demonstrated by certain alleles strongly linked to specific diseases, HLA-B*27 with ankylosing spondylitis and HLA-DR3/DR4 with type 1 diabetes. In addition to polymorphisms, critical modulation of immune gene expression occurs through the means of gene regulation mechanisms. The temporal and spatial regulation of the expression of immune-related genes is mediated by transcription factors like NF- κ B and STATs as well as epigenetic regulatory factors, including DNA methylation and acetylation of histone [7]. Moreover, non-coding RNAs such as microRNAs and long non-coding RNAs are important post-transcriptional regulators. Immune tolerance can be interfered with by dysfunctions in these systems and lead to the development of such diseases as systemic lupus erythematosus (SLE), in which there is a global hypomethylation of DNA that supports the activation of autoreactive lymphocytes. Gene-gene interaction (e.g., epistasis) further complicates the situation by affecting immune phenotypes in a greater way than that of a single gene [8]. An archetypical example includes the encounter of killer-cell immunoglobulin-like receptors (KIRs) on natural killer (NK) cells with their HLA class I ligands. This interaction dictates the licensing and responsiveness of NK cells and can affect the likelihood of viral infections, tumor surveillance, and the outcome of hematopoietic stem cell transplantation (HSCT). Heritability estimates of multi-trait experiments (e.g., twin studies, genome-wide association studies (GWAS) show that most immune traits, e.g., vaccine responsiveness, or autoimmune predisposition, are highly genetic [9]. In the meantime, somatic mechanisms, including V(D)J recombination and somatic hypermutation, are of critical importance to the generation of the diversity of B-cell receptors (BCRs) and T-cell receptors (TCRs). These mechanisms are genetically programmed, though not inherited, and could be interfered with under primary immunodeficiency disorders [10].

The above principles together emphasize the genetic nature of the high variability and specificity of the immune system. Learning about these basic mechanisms is critical to understanding immune variation at health and disease and for developing and harnessing personalized immunological interventions.

Immunoglobulin genes for antibody formation, T-cell receptor genes for antigen recognition, cytokine gene polymorphisms involved in signalling pathways, and MHC molecules for antigen presentation are the basic elements of immunogenetics [11], as illustrated in Figure 1.

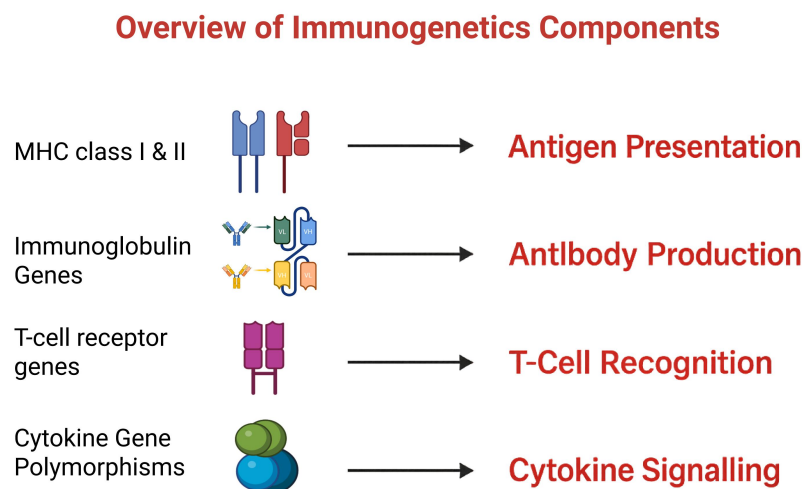


Figure 1. The major histocompatibility complex (MHC) antigen presentation pathways.

Figure 1 illustrates an overview of MHC Class I and Class II antigen presentation by drawing. MHC Class I molecules display endogenously derived peptides to CD8⁺ cytotoxic T lymphocytes, whereas MHC Class II poses exogenous-originated peptides to CD4⁺ helper T lymphocytes. Polymorphisms of MHC genes are so high and affect peptide binding specificity and responsiveness to the immune system.

The HLA (major histocompatibility complex or MHC) is the most polymorphic region human genome. HLA class I (HLA-A, -B, -C) encoding of the chromosome 6p21 presents endogenous antigens to CD8⁺ T cells, whereas the class II (HLA-DR, -DQ, -DP) expressed by antigen-presenting cells activates CD4⁺ T cells. This polymorphism broadens the antigen presentation capacity across populations, with significant clinical implications [12]. Specifically, HLA-B 57:01 prevents the faster progression of HIV, whereas HLA-B 35 advances the disease. HLA mismatches cause the rejection of grafts during transplantation, and HLA-DQ2/8 are risk factors of celiac disease. Immunoglobulin (Ig) genes, consisting of heavy (IGH), kappa (IGK), and lambda (IGL) chains, are arranged in an order in which they are recombined through V(D)J by RAG1/2 enzymes [13]. Diversity at junctions, combinatorial pairing, somatic hypermutation, and class-switch recombination provide more than 10¹¹ specificities of antibodies. Dysfunction in the recombination process leads to severe combined immunodeficiencies (SCID), and the role of autoreactive clones lies in the development of autoimmune disease. On the same note, T-cell receptor (TCR) diversity arises through somatic recombination of variable (V), diversity (D), and joining (J) gene segments, producing an estimated 10¹⁵-10²⁰ unique receptor sequences. Two major classes of TCRs are alpha and beta, in a fashion called alpha-beta or hookups, and gamma-delta, known as gamma-delta receptors. There are central tolerance mechanisms of deletion of self-reactive TCRs, and their failures result in autoimmunity [14].

Immune responses are significantly modulated by polymorphisms in cytokine genes. The alteration in TNF-alpha (e.g., -308G>A), IL-10 (-1082G/A), and IL-6 (-174G>C) changes its levels of expression, which has implications in controlling inflammation and the severity of the disease. FOXP3 Transcription factors are involved in the regulation of regulatory T cell development, with defects in this protein leading to IPEX syndrome, and GATA3 plays a role in Th2 differentiation in allergic responses. The entirety of these genetic elements makes up the blueprint of immune functions, diversity, and susceptibility to disease [15].

2.1 Immunogenetics in Disease Pathogenesis

2.1.1 Autoimmune Diseases

Acquired Immunodeficiency Syndrome (AIDs) is complicated by the interaction between individual and environment which causes loss of tolerance to self-immunity and destruction of body tissue caused by the immune system. Immunogenetics has been very important in providing key details on the role played by certain genetic variations in terms of risk, development and treatment of the numerous autoimmune disorders. A very strong genetic predisposing factor exclusive to rheumatoid arthritis (RA) is contained within the HLA-DRB1 gene. Some alleles promote the special point, which is called the shared epitope, a typical amino acid sequence especially created to augment the exposure of arthritogenic peptides on autoreactive CD4⁺ T cells [16]. It is the process that triggers and perpetuates chronic synovial

inflammation. Furthermore, pathogenesis in the disease is contributed by non-HLA genes. Recent genome-wide association studies (GWAS) and cross-disease meta-analyses have shown that multiple non-HLA loci account for a significant amount of autoimmune disease heritability. Variants in TNFAIP3 (A20), IRF5, CTLA4, and TYK2 highlight the roles of NF- κ B regulation, interferon signalling, and T-cell co-stimulation in sustaining inflammation in rheumatoid arthritis, in addition to PTPN22 and STAT4 [17]. These loci, albeit having small effect sizes, converge on immunological pathways that are similarly involved in type 1 diabetes, systemic lupus erythematosus, and multiple sclerosis. According to meta-analytic research, such pleiotropic loci identify a common genetic architecture among autoimmune illnesses, linking dysregulated cytokine signalling, deficient immunological checkpoints, and abnormal cell activation to disease start and progression. The combination of fine-mapping, expression quantitative trait loci (eQTL) analysis, and single-cell transcriptomics is helping to refine these relationships and discover functionally significant variations with translational potential [18].

PTPN22 is a lymphoid-specific phosphatase gene linked to a failure to regulate T-cell receptor signalling, retaining T-cell activation. Mutations in STAT4 stimulate hyperactive Th1 and Th17 responses, which are the key factors of RA-related inflammation. The interaction between gene and environment also adjusts the risk of disease. The example of such a combined effect is the synergy between smoking and HLA-DRB1 shared epitope alleles, raising the risk of developing anti-citrullinated protein antibody (ACPA) positive RA, possibly due to elevated protein citrullination and presentation of neoantigens [19].

A similar HLA linkage is also present in the case of type 1 diabetes (T1D). Heterozygous individuals with HLA-DR3 and DR4 have a very high risk of the disease because they have an efficient presentation of pancreatic islet autoantigens [20]. Other hereditary factors are insulin gene polymorphisms, which influence thymic insulin and central tolerance, and CTLA4, which is an important checkpoint of T-cell inhibition. A breakdown of these pathways aids in immune-mediated damage of the pancreatic β -cells [21].

Multiple Sclerosis (MS) also shows significant genetic types with the HLA-DRB1-15:01 being the most remarkable because it harbors the presentation of the central nervous system (CNS) myelin-derived peptides to the autoreactive T cells [22]. Additional risk-related genes include IL7R and TYK2 and are also associated with T-cell development, cytokine signalling, and effector function. These polymorphisms in combination tend to bias immune responses to autoimmunity in the CNS.

In addition to the germline contribution, different disease pathogenesis is linked to epigenetic dysregulation. As an example, hypomethylation of a broad panoply of DNA sequences in CD4⁺ T cells triggers erroneous expression patterns of immune genes in systemic lupus erythematosus (SLE) and elicits autoreactivity. These epigenetic changes can be worsened by environmental triggers, including exposure to UV light or viral infections, to cause disease flares [23]. All in all, the studies provided support the view that immunogenetic variations in the HLA and non-HLA genes, gene environment interaction, and epigenetic changes interact to result in immune regulatory defects, which eventually lead to the onset of autoimmune diseases.

2.1.2 Infectious Diseases

Host genetic variability significantly determines the result of infectious diseases in terms of susceptibility, the course of the disease and the effectiveness of immune responses. Immunogenetics shows the influence of particular alleles and variants of certain genes in the host-pathogen interface, which has provided very important information regarding innate and adaptive immune responses [24]. As shown in Figure 2, genetic variants such as CCR5- Δ 32, TLR/IFNG polymorphisms, and HLA-B53 illustrate how host factors modulate susceptibility or resistance to major infectious diseases.

Human immunodeficiency virus (HIV) infection is one of the diseases that possess genetic variants in human hosts that influence susceptibility and disease development. Among the best-known ones is the CCR5-gene deletion mutation that is a 32-base pair deletion in the gene encoding the CCR5 chemokine receptor. This receptor is a co-receptor of the virus. Invasion of the CD4⁺ T cells by HIV. Homozygous carriers of CCR5- Δ 32 are severely resistant to HIV-1 infection, whereas the heterozygotes progress more slowly [25]. In addition, some alleles of HLA class I, especially HLA-B57 and HLA-B27, are linked with better control of the viruses. One proposed mechanism suggests that these alleles preferentially present conserved HIV epitopes to T cytotoxic lymphocytes (CTLs), leading to more effective antiviral immune responses, although this remains under active investigation [26]. In the instance of tuberculosis (TB), which is a disease caused by the *Mycobacterium tuberculosis*, the genetic susceptibility is associated with several (multiple) loci. HLA-DR2 allelic variations determine the outcome of antigen presentation and the activation of T-helper cells. Toll-like receptors (TLR2 and TLR4) have polymorphisms that change the recognition of pathogens and subsequent signalling and influence the innate immune reaction [27]. Additionally, the impairment in the interferon-gamma (IFN- γ) and interleukin-12 (IL-12) axis, which is essential in the stimulation of macrophage and formation of granuloma, leads to the inability to control *Mycobacteria*. Mendelian susceptibility to mycobacterial disease (MSMD) is a rare feature that can be caused by a rare mutation in IL12RB1 or IFNGR1/2, again representing a clear requirement of cytokine signalling in TB protection [28].

Gene Susceptibility to Infectious Diseases

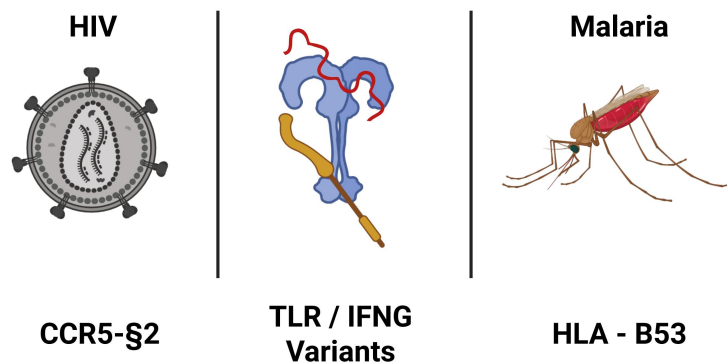


Figure 2. Genetic susceptibility to infectious disease.

Figure 2 summarizes the primary host genetic variables that influence infectious illness outcomes. The CCR5-Δ32 mutation resists HIV infection, while variations in TLR and IFNG genes impact immunological recognition and tuberculosis susceptibility. HLA-B53 is related to improved protection against malaria. These examples demonstrate how immunogenetic variability regulates pathogen entrance, immunological activation, and disease development.[29].

In the context of malaria, host genetic adaptations have evolved under strong selective pressure exerted by *Plasmodium* species. The SCT (HbAS) protects the *Plasmodium falciparum* because the mechanism promotes the elimination of infected red cells by increasing phagocytosis and reforming the red blood cell physiology. Similarly, Duffy antigen negativity prevalent in people of West African origin provides immunity against *Plasmodium vivax* by inhibiting the ability of the parasite to invade red blood cells because *P. vivax* uses the Duffy antigen as a binding site. Moreover, HLA-B*53, which is common in the West African population, is linked to higher responses of cytotoxic T-cells against liver-stage malaria antigens, which contribute to productive parasite clearance by the pre-erythrocytic form [30].

The importance of host immunogenetic diversity in infectious disease outcomes has been further emphasized by recent research during the COVID-19 pandemic. Differences in susceptibility and illness severity in SARS-CoV-2 infection have been linked to variations in genes encoding innate immune system components, such as TLR7 and OAS1 [31]. For instance, TLR7 loss-of-function mutations affect type I interferon responses, making individuals—especially men—more vulnerable to severe symptoms. Similarly, it has been shown that HLA polymorphisms influence vaccine response and viral clearance by affecting the strength and range of T-cell responses against SARS-CoV-2. Beyond COVID-19, genetic factors like HLA-DP and HLA-DQ alleles influence immune regulation in response to Hepatitis B virus (HBV) infection, impacting whether a person recovers or develops chronic hepatitis. These findings highlight the potential of precision medicine approaches in vaccine development and antiviral therapies, as well as the clinical importance of immunogenetic diversity [32].

Such evidence demonstrates how genetic selection can take place at the level of pathogen drivers of immune landscapes in human populations. The comprehension of these genetic factors, besides the study of the pathogenesis of infectious diseases, contributes to the design of vaccines and the creation of specific cures.

2.1.3 Cancer

Immunogenetics is central to regulating immune surveillance, tumor recognition and immune evasion and therefore cancer susceptibility, progression and therapeutic success. Immunity may recognize and destroy the cancerous cells by presenting antigens and cytotoxic attacks but cancer can develop to avoid this immune monitoring [33].

Relatively speaking, the downregulation or loss of HLA class I molecules is the crucial immune evasion tactic because it interferes with antigen presentation to cytotoxic T lymphocytes (CTLs). This enables the tumor cells to become invisible to the immune attack by T cells. At the same time, cancers might use immune checkpoints, including pathways of PD-1/PD-L1 and CTLA-4 to inhibit anti-tumor immunity [34]. Functional exhaustion and immune tolerance occur through the upregulation of PD-L1 on the tumor cells that bind on PD-1 receptors on T-reg cells. The mutation of JAK/STAT pathway, especially among JAK1/2, is also a possible contribution by interfering with the interferon signalling system and the immune response mechanism against cancer cells [35]. Similarly, genetic differences in immunosuppressive cytokines e.g. IL-10 and TGF- pool can affect tumor-promoting microenvironment quenching the infiltration and response of immune cells.

The role of diagnostic immunogenetic predictors has transformed the face of cancer treatment especially with regards to immune checkpoint inhibitor treatment. How to evaluate the tumor mutational burden (TMB) and microsatellite instability-high (MSI-H) status which has become the most essential parameters of immunotherapy response [36].

Because of defects in the mismatch repair of DNA bases, MSI-H tumors have numerous neoantigens and they are more visible to the immune cells and respond well to the inhibitory therapies of PD-1 [37].

Zygosity and diversity of the HLA also appear as a possible indicator of immune responsiveness. Increased HLA class I heterozygosity leads to a better breadth of antigen presentation, thereby having a higher probability of recognizing a neoantigen and resulting T cell response [38]. Also, killer-cell immunoglobulin-like receptor (KIRs) and HLA ligands are important in regulating the availability of natural killer (NK) cell action in innate tumor surveillance. NK cell-mediated cytotoxicity of tumor cells may be enhanced by specific KIR-HLA combinations. Within the context of hematological malignancies, i.e., acute myeloid leukemia (AML), KIR-HLA mismatch in the graft-versus-host direction when hematopoietic stem cell transplantation (HSCT) is performed has been linked to the presence of more promising graft-versus-tumor (GvT) effects, less frequent relapse and no increased rates of graft-versus-host disease (GvHD) [39]. The immunogenetic map of cancer not only plays a pivotal role in cancer risk identification, but also plans individually targeted immunotherapy, such as the block of checkpoints, the NK cells-based immunotherapies and cancer vaccines.

Recent studies have shown that polymorphisms in immune-related genes significantly influence the tumor immunological microenvironment and patient prognosis. Single-nucleotide polymorphisms (SNPs) in genes encoding immune checkpoint molecules, including CTLA4, LAG3, and PDCD1 (PD-1), have been associated with alterations in immune tolerance and protein expression across various cancers such as colorectal, lung, and melanoma [40]. The concept of "immunogenetic biomarkers" is increasingly being explored to guide precision immunotherapy, as these genetic differences can affect the efficacy and toxicity of immune checkpoint inhibitors. Some HLA genotypes are also linked to immune-related adverse events (irAEs), indicating that immune tolerance to self-tissues shares genetic influences with tumor recognition [41]. Additionally, tumor neoantigen immunogenomics is reshaping cancer vaccination strategies. The identification of tumor-specific neoantigens presented by HLA molecules and targeted by cytotoxic T cells has opened new paths for personalized vaccines. Tumors with high mutational loads, like melanoma and non-small-cell lung cancer, tend to provoke stronger immune responses due to their abundance of neoantigens. Currently, immunogenetic profiling enables the prediction of neoepitope-HLA binding, facilitating the development of personalized mRNA vaccines and adoptive T-cell therapies aimed at these neoepitopes. By forecasting treatment response, reducing resistance, and improving long-lasting tumor elimination, the combination of immunogenetics, next-generation sequencing, and artificial intelligence holds the potential to completely transform cancer immunotherapy [42].

2.2 Transplantation

Immunogenetics of transplantation is very important in determining the acceptance of the gadgets, immune tolerance, and complications after transplant. The human leukocyte antigen (HLA) system is among the most important immunogenetic factors as it translates the proteins that play an important role in antigen presentation and immune recognition. In hematopoietic stem cell transplantation (HSCT), donor-recipient HLA matching has become a key to successful transplantation: 77 percent of the transplants using matched cellular products survived up to 5 years after transplantation and compared with transplantation into the immune-incompetent mouse, there was significantly reduced graft-versus-host effects. Solid organ transplants also rely on effective donor-recipient HLA matching to receive the best possible outcomes, especially in kidney transplantation [43]. With solid organ transplantation, there is only a slight mismatch at HLA where T-cell-mediated alloreactivity can cause acute or chronic graft rejection. HSCT HLA mismatches, notably at HLA-A, HLA-B, HLA-C, and HLA-DRB1 loci are associated with potentially devastating graft-versus-host disease (GVHD) with donor T cells directing their attack on recipient tissues. Nevertheless, the mismatch to a certain extent may be exploited in malignancy diseases to augment graft-versus-leukaemia (GvL) effects and minimize the chances of relapse [44].

In addition to the classical HLA molecules, there are also minor histocompatibility antigens (mHAg), which are a result of polymorphic peptides on HLA molecules, thus serving the same purpose as their classical HLA counterparts: to induce alloimmune responses. Imbalance in mHAg, even in HLA-matched transplants, may cause immune responses such as GVHD and graft rejection [45]. The presence of donor-specific antibodies (DSAs), especially those targeting mismatched HLA antigens, is closely associated with antibody-mediated rejection (AMR) and poor graft outcomes. Therefore, comprehensive pre-transplant screening for DSAs and careful donor-recipient matching remain crucial components of immunogenetic compatibility assessment [46].

The killer-cell immunoglobulin-like receptor (KIR)/HLA-I interplay represents a critical tier of natural immune control during a transplant because killing by Natural Killer (NK) cells depends on the expression of killer-cell immunoglobulin-like receptors (KIR). In the haploidentical HSCT, the KIR-HLA mismatch is useful. Given the absence of recipient HLA ligands and, therefore, the lack of inhibitory signals by donor NK cells, their activation results in potent graft-versus-leukemia (GvL) effect without developing GVHD. This alloreactivity of NK cells has been utilized in enhancing the response of the high-risk leukemias [47].

In addition, post-transplant care has been largely influenced by a section of medicine known as pharmacogenetics which is the science behind the influence of genetic variations on drug metabolism. An outstanding one is the CYP3A5, which is a factor gene encoding the most important enzyme, a tacrolimus, which is a common calcineurin inhibitor. Patients

who express CYP3A5 (patients possessing one or more CYP3A5 -1 allele) have a faster breakdown rate of tacrolimus more, and thus need to be given a higher dosage to reach therapeutic concentrations. On the contrary, non-expressers (CYP3A5 3/3 genotype) need less doses to prevent toxicity. Individualized dosing of tacrolimus, which is dependent upon CYP3A5 genotype, is an effective example of personally chosen immunogenetics medicine [48].

The overall application of HLA compatibility, KIR-HLA interactions, DSA profiling and pharmacogenetics can provide more insightful, patient-specific transplantation, that will help to achieve maximum graft success with limited immunological issues.

Table 1 represents an overview of the main genetic variants, related immune elements, and clinical meaning of these in the context of autoimmune, infectious, and cancer-related diseases. Evidence is based on the existing literature and presents the examples of the way genetic polymorphisms contribute to the susceptibility, progression of certain diseases, and response to treatments.

Table 1. Chosen immunogenetic correlations of big diseases.

Disease Category	Example Condition	Key Genetic Variant(s)	Immune Component Affected	Clinical Impact	References
Autoimmune	Rheumatoid Arthritis	HLA-DRB1 (shared epitope), PTPN22	T-cell activation, cytokine regulation	Increased risk, severity, and therapy response variability	[49]
Autoimmune	Type 1 Diabetes	HLA-DR3, HLA-DR4, INS, CTLA4	Antigen presentation, T-cell regulation	Beta-cell destruction, early-onset disease	[50]
Infectious	HIV	CCR5-Δ32, HLA-B*57	Viral entry, CTL-mediated clearance	Resistance to infection, slower disease progression	[51]
Infectious	Tuberculosis	HLA-DR2, TLR2/4, IFNG, IL12B	Antigen presentation, macrophage activation	Increased susceptibility or protection	[52]
Infectious	Malaria	HbS (sickle cell trait), HLA-B53	Erythrocyte structure, CTL activity	Reduced severity, protection against infection	[53]
Cancer	Colorectal Cancer (MSI-H)	MMR gene defects, HLA diversity	Neoantigen presentation	High immunotherapy response rates	[54]
Cancer	Leukemia	KIR-HLA interactions	NK cell-mediated cytotoxicity	Enhanced graft-versus-leukemia effect in HSCT	[55]

2.3 Technological Advances in Immunogenetics

Immunogenetics is currently undergoing a revolution driven by the rapid development of genomics, facilitating an understanding as never before of both the complexity of immune control and the processes of disease pathology, as well as the opportunity to target and treat disease and it is depicted in Figure 3. Of these, next-generation sequencing (NGS) is one of the breakthrough technologies, with high throughput, high-resolution information, which is fundamental to research and clinical applications. Its evolution into long-read and single-molecule sequencing platforms continues to improve resolution and accuracy. HLA typing using NGS has greatly overcome the shortcomings of serological and low-resolution molecular typing methods and has opened the possibility of allele-level resolution required by transplant matching, identification of disease associations, and vaccine design [56]. This high res. typing helps in the discovery of rare and novel HLA alleles, improves the donor-recipient compatibility screening, and minimizes the development of adverse effects, such as graft rejection and GVHD. Simultaneously, T-cell receptor (TCR) and B-cell receptor (BCR) immune repertoire sequencing creates rich snapshots of the adaptive immune system. Such profiles are used to monitor clonal expansions, tumor-infiltrating lymphocytes (TILs), vaccine responses and to screen minimal residual disease (MRD) of haematological malignancies [57].

Single-cell RNA sequencing (scRNA-seq) is the next step; it will permit the resolution of immune cell diversity of a complex immune ecosystem, such as the tumor microenvironment or the diseased organ. It aids in the detection of rare immune cell types, deciphers the states of complete cells, and molecules of crosstalk in a dynamic disease that would include infections, cancer, and autoimmunity.

Longitudinal NGS allows the researcher to follow the dynamics of immune clones in time, showing the level of immune responses over time during infection, therapy, or disease progression. This is specifically useful in immuno-oncology, where the way the duration and breadth of T-cell responses are understood might help in treating it successfully along with response to resistance. CRISPR-Cas9 genome editing is driving functional immunogenetics into the therapeutic domain. With it being capable of manipulating immune-relevant genes with precision, CRISPR not only allows one to explore the functions of these genes (e.g., FOXP3 in regulatory T cells), but also demonstrates a benefit in the creation of new therapies as well. An example is the knockout of the PD-1 receptor in CAR-T cells, which resulted in longer persistence and cytotoxicity by avoiding T-cell exhaustion as mediated by tumor cells [58]. Figure 3 shows genetic

variations such as HLA polymorphisms, cytokine gene variants, and immune checkpoint gene alterations both promote the pathogenesis of autoimmune diseases and infectious diseases, cancers, and transplant rejection.

Recent advances in CRISPR/Cas9 and single-cell multi-omics have enabled direct clinical application. CRISPR-edited CAR-T cells targeting PD-1 and TRAC loci have shown promising results in clinical trials, while gene-edited hematopoietic stem cells have resulted in functional cures for β -thalassemia and sickle cell disease. These progressions demonstrate how immunogenetic insights are already being used for targeted, patient-specific therapies [59].

Immunogenetics in Disease Pathogenesis

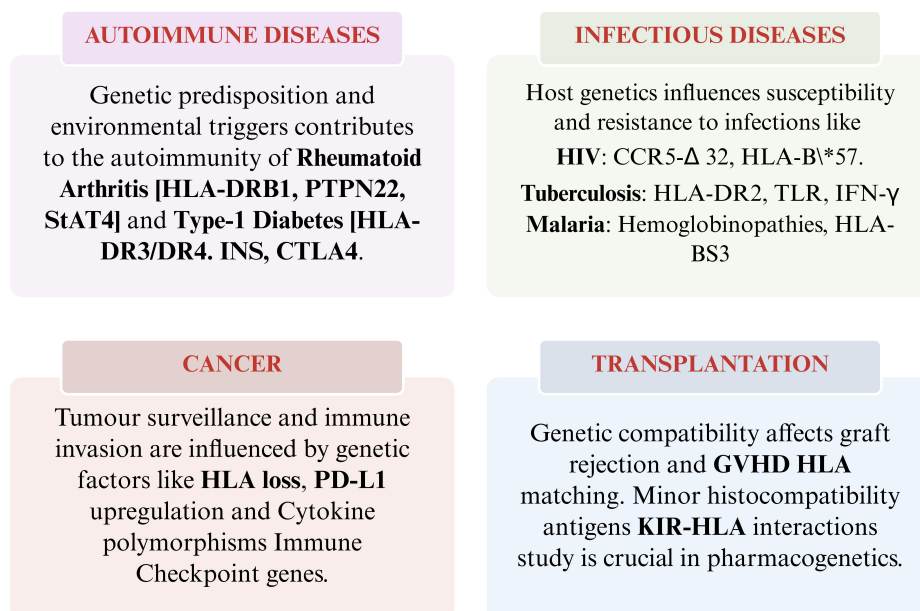


Figure 3. Immunogenetics of disease pathogenesis.

Along with these technologies in laboratories, a dense network of bioinformatics tools and databases has developed. Immunogenetic sequence information is curated in sites like IMGT (International ImmunoGeneTics Information System) and programs such as NetMHC can predict HLA-peptide binding, an essential part of epitope discovery to develop vaccines and therapies. These resources allow researchers to combine multi-omic data (such as genomics, transcriptomics, proteomics, and epigenomics) to build comprehensive models of immune regulation--and bring precision immunology and precision oncology [60].

To conclude, the meeting of the cutting-edge technologies of sequencing, gene editing and computational immunology not only increased our knowledge about immune genetics but became a powerful aid in personalized solutions to diagnostics, prognostics and treatments across a wide range of diseases.

2.4 Ethical and Translational Challenges in Immunogenetics

Although the field of immunogenetics promises incredible changes in the field of healthcare, it itself poses a wide range of ethical, social, and translational issues that should be resolved to facilitate the responsible and satisfying utilization of it. Among the ethical issues the topic of genetic privacy/ data security can be put forward as one of the major. The sensitive data that is usually disclosed through the immunogenetic testing is not only to the individual though but also to the biological relatives and the issue concerning informed consent, the ownership of the data and its possible abuse also arises. Genetic discrimination, with regard to employment, insurance, or access to healthcare, is a very tangible and pressing concern, especially in jurisdictions with weak protective laws in force [61].

Genomic testing is a scenario with further complications involving informed consent. The patient might not be mature enough to understand the repercussions of immunogenetic findings alongside accidental carrying out of such findings or inconclusive findings that carry gray meaning. In addition, complication of discussing risks on basis of probabilistic genetic markers particularly risky results are not affected by environmental exposures necessitate subtle and culturally sensitive counselling [62]. The next challenge is that the majority of genomic research databases are Eurocentric. Any lack of biomarker generalizability to multiple ethnic groups is due to the underrepresentation of non-European populations. For example, Polygenic Risk Scores (PRS) for heart disease, breast cancer, and diabetes, developed from European datasets, often perform poorly in African, South Asian, and East Asian populations [63]. Similarly, risk alleles like those in FGFR2 and MAP3K1, identified in Europeans, show weaker or no association in African and Asian

women. This highlights the impact of Eurocentrism in global health and underscores how such disparities hinder the development of equitable diagnostics and treatments [64].

There are also translational barriers that hamper clinical utility of immunogenetic findings. Laboratory standardization of assays has not reached a standard throughout facilities and there is not a solid understanding of clinical interpretation system of genetic results. Moreover, the predictive value of particular genetic variations is a problem complicated by gene-environment interactions, as well as polygenic effects. These aspects result in the difficulty in the risk assessment making it inconsistent and unpredictable, making it difficult to deal with patients and making clinical decisions. There is also an issue of access and affordability of personalized immunogenetic therapies since their promise. Complex genomic diagnostics and precision treatment (e.g., CAR-T cell treatments or neoantigen vaccines) are in most cases prohibitively costly and mostly restricted to high-capacity settings. This produces a disparate world in access to precision medicine, and no doubt contributes to the already present health inequalities.

In order to deal with such issues, the accent on inclusive research programs is increasing. Other initiatives like H3Africa (Human Heredity and Health in Africa) and All of Us (USA) are designed to balance out genomic data, so that disadvantaged populations reap the rewards of the immunogenetic research. The programs promote community participation, morality in government and capacity development in genomic sciences [65].

In a nutshell, the ethical and translational issues of immunogenetics require a multidisciplinary intervention- one that will combine bioethics, public policy, clinical practice and community involvement. The key to realizing the potential of immunogenetics into effective population health lies in ensuring justice, inclusion, and transparency to all people and populations.

2.5 Future Directions in Immunogenetics

Immunogenetics carries the future that involves precision medicine, technological advancement, and inclusivity of the world. As our knowledge about the interactions between the immune and genes grows, new horizons are becoming apparent in terms of both diagnostics, therapeutics, and the prevention of diseases as depicted in Figure 4.

Immunogenetics can be considered as an "immunogenetic continuum of immune responsiveness" that theoretically connects infection, autoimmunity, cancer, and transplantation via shared genetic and molecular processes. Individuals' positions on this continuum are determined by variations in HLA molecules, cytokine genes, and immune checkpoint pathways, which range from insufficient immune activation in infections to hyperactivation in autoimmunity, with cancer and transplantation representing intermediate states of immune tolerance and evasion. This integrative approach redefines immunogenetics as a systems-level science of immunological balance, capable of predicting both protective and pathogenic responses across situations.

Furthermore, cross-disease immunogenetic connections are developing as a key study area. Certain HLA alleles and cytokine polymorphisms linked to autoimmune illnesses, for example, influence cancer immunotherapy toxicity, whereas chronic infection-induced immune fatigue is linked to tumor immune evasion. Exploring these overlaps can reveal conserved immune signals that can be used to discover biomarkers and build therapies for various diseases. Integrating these similar pathways with improvements in multi-omics and artificial intelligence (AI) will allow for a more unified, predictive understanding of immune regulation, bridging molecular biology and therapeutic application.

The most significant direction is the creation of HLA-based vaccines and cytokine polymorphism-based treatments. Vaccinology is at the cusp of a paradigm shift whereby personal HLA data sets will enter into the calculations on epitope design, to provide vaccines better efficacy and longevity. Individual vaccines against viral infections and cancer may make use of neoepitope mapping using high-resolution HLA typing as an example. In the same manner, cytokine gene polymorphisms (e.g., IL-6, IL-10, or TNF- α) could direct candidate dosage and immunomodulatory treatment on the basis of a specific genetic immune profile in the patient. Immunotherapies are likely to become routinely genetically stratified. Immune checkpoint blockade therapy or CAR-T cell treatment can be selected among patients with certain polymorphisms in the genes of immune checkpoints (e.g., PDCD1, CTLA4) or other regulators of the tumor microenvironment and increase the response rates and safety. Combining multi-omics technologies will take the center stage in the future of immunogenetics. OMICs integration (i.e. the combination of genomics, transcriptomics, proteomics and epigenomics) will enable researchers to create a detailed picture of immune regulatory networks. Not only it will help find new biomarkers and drug targets but also allow tracking the immune response in patients in real-time when disease progresses or during treatment. This is an already rich landscape, which will further be enriched by the integration of metabolomics and microbiomics to elucidate the interactions between host immunity, host metabolism, and its microbial community [66].

Research on global populations will be essential to address the existing Eurocentric bias and to identify the evolutionary adaptations that shape immune responses. Understanding population-specific mutations, such as malaria resistance alleles like HbAS or G6PD deficiency, could lead to region-specific interventions [67]. The emergence of programs like H3Africa and the development of South-South alliances will also be crucial in collecting immunogenetic diversity and promoting equity in precision medicine. Such population-level insights are also highly relevant to transplantation, where genetic diversity and immune tolerance are closely intertwined. Future transplantation tools will focus on tolerance induction. Strategies like gene-edited regulatory T cells (Tregs), chimeric antigen receptor (CAR)-Tregs, and

costimulatory blockade therapies (e.g., CTLA4-Ig, CD40/CD154 antagonists) aim to reduce the clinical requirements for long-term immunosuppression while preserving graft function. These approaches could significantly improve outcomes, especially in small-mismatched or high-risk transplant recipients [68].

Lastly, AI and machine learning could come to enhance the importance of immunogenetics. Multi-omic data can be combined through AI algorithms to help predict the risk of a particular infection, autoimmunity, cancer, transplant rejection, or unmask latent patterns of immune responses and determine predictive biomarkers. The predictive modelling will improve clinical decision support systems, make better choices of patients to be treated, and decrease adverse consequences in immunotherapies. Overall, immunogenetics is expected to grow exponentially in the future under the banner of precision, personalization, and inclusivity. With the evolving maturity of technologies and the continually growing dataset, immunogenetics will be one of the pillars of 21st-century medicine that will allow proactive, patient-centered, and predictive care [69].

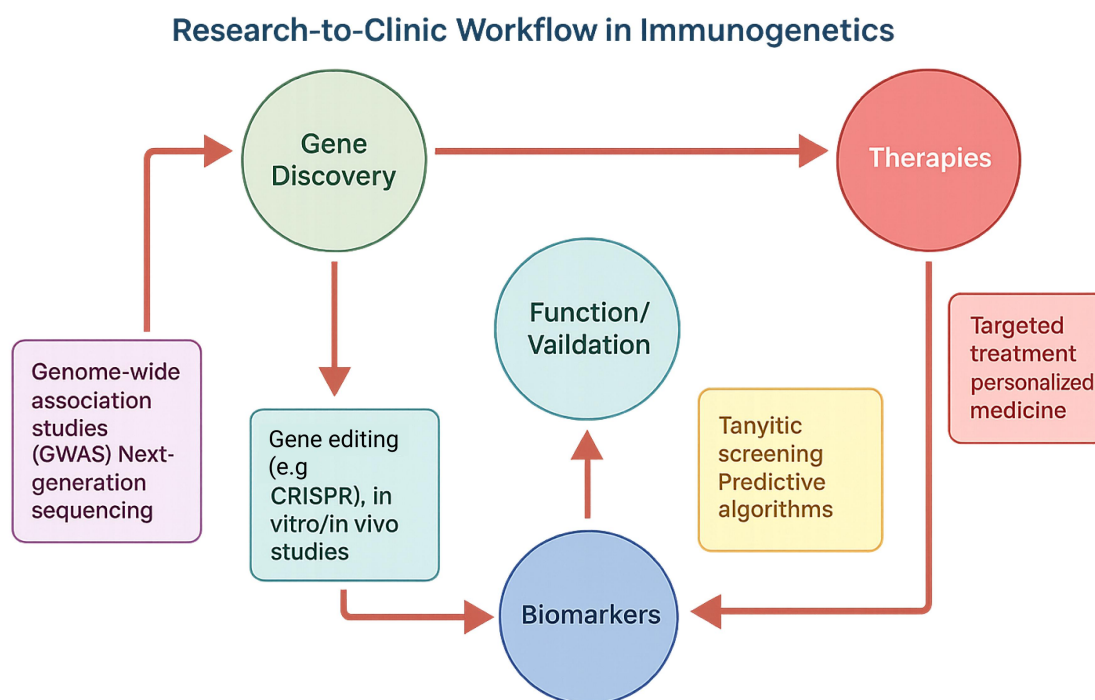


Figure 4. Immunogenetics research-to-clinic workflow.

3. Conclusion

Immunogenetics has fundamentally altered our understanding of how genetic diversity influences immunological responses, disease susceptibility, and therapeutic results. Previously a descriptive science, it now serves as the foundation for precision medicine by combining genetic profiling, CRISPR-based editing, and cellular engineering. Recent clinical successes, including CRISPR-edited Exa-cel therapy for sickle cell disease and β -thalassemia, CAR-T and TCR-engineered cell therapies for haematologic cancers, and personalized mRNA neoantigen vaccines in melanoma, show that immunogenetic discoveries are translating into tangible, patient-specific treatments. However, there are still issues with maintaining ethical standards in genomic medicine, resolving gene-environment complexity, assuring data diversity, and harmonizing assays. Immunogenetics has the potential to further develop individualized, patient-centered care and reshape the future of contemporary medicine by promoting international cooperation and fair access.

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Conflict of Interest

The authors declare no conflict of interest

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