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IMMUNOGENOMICS IN PRECISION MEDICINE: LINKING GENETIC VARIABILITY TO DISEASE SUSCEPTIBILITY AND THERAPEUTIC RESPONSE

Dr Vyshak T V[1], Rajesh Chandra Verma[2], S Subthra devi M. D[3], Dr.D.Kasthuri Santira Kumari[4], Dr. Sanghamitra Jena*[5]

[1]Post Graduate Student, Kalinga Institute of Dental Sciences, Bhubaneshwar, Odisha, Department of Orthodontics and Dentofacial Orthopaedics, Email ID: vyshaktv54@gmail.com, City Pincode : Bhubaneshwar(Odisha), 75102
[2]Assistant Professor, Chemistry, Chemistry and Health sciences, Agra College, Agra (Dr. B.R. Ambedkar University, Agra) Pin 282010, India, Email ID: jcb.rajesh@gmail.com
[3]Tutor, Department of microbiology, Government medical College and Hospital, Affiliated to Dr.M.G.R Medical university,Namakkal, Tamilnadu , India. Email: drsubamani1978@gmail.com.
[4]Assistant Professor, Advanced Zoology and Biotechnology, Jayaraj Annapackiam College for Women(Autonomous), Periyakulam, E-mail id : kasthuriharrison@gmail.com, Orcid ID: 0009-0007-2880-1378
[5*]Professor, Kalinga Institute of Dental Sciences, Bhubaneshwar, Odisha, Department of Orthodontics and Dentofacial Orthopaedics, Email ID: sanghamitra.jena@kids.ac.in, City Pincode : Bhubaneshwar(Odisha), 751024

ABSTRACT

Immunogenomics has become an important part of precision medicine, as it helps to understand the effect of genetic variation on immune function, disease susceptibility and therapeutic response. This review covers the genetic structure of immune system genes, especially human leukocyte antigen, killer-cell immunoglobulin-like receptor, cytokine, complement and T-cell and B-cell receptor genes. It outlines the role of polymorphisms, structural variation, epigenetics and population-level evolutionary pressures in immune recognition and clinical outcomes. The review further examines the relationship between immune associated genetic polymorphisms and autoimmune diseases, infectious diseases, cancer as well as allergic or atopic diseases. The clinical relevance of immunogenomics in the fields of pharmacogenomics, immune checkpoint inhibitor response, vaccine responsiveness, and transplant compatibility are highlighted. Examples of established applications include HLA guided prevention of severe drug hypersensitivity, prediction of response to immunotherapy and enhanced donor–recipient matching. Next generation sequencing, high resolution HLA typing, single-cell immunogenomics, immune-receptor sequencing, multi-omics techniques, and AI and machine learning are also factored. Although significant advances have been made, the translation of clinical research is limited by polygenic complexity, lack of uniformity in analyses, population heterogeneity, cost, privacy issues and unequal access to genomic technologies. Further progress will demand for more heterogeneous cohorts, defined procedures, functional assays, transparent algorithms and robust integration of genomic, immunological and clinical data. Immunogenomics, thus, has a lot of potential in better predicting risk of disease, choosing treatment, monitoring treatment, and in the personalization of healthcare.

KEYWORDS: Immunogenomics; precision medicine; genetic variability; therapeutic response; immune-related diseases

1. INTRODUCTION

Precision medicine has redefined the current landscape of health care by moving away from broad treatments to treatments that fit the patient's unique biological, genetic, environmental and clinical profile. In the past decade, through progress in genomic sequencing, computation, electronic health records and artificial intelligence, it has become possible to increasingly identify molecular differences between individuals that impact their susceptibility to disease, progression, prognosis, and response to treatment. In this changing landscape, immunogenomics has become a particularly significant component of the immune system, as the immune system is regulated by highly heterogeneous and integrated sets of genes. Genetic, immunological and clinical data can be combined to facilitate accurate disease classification, better risk stratification and personalised therapeutic management. This is further reinforced by the use of artificial intelligence, which allows for the analysis of large and complex datasets of both genomic variants and immune responses as well as medical history and treatment outcomes (Chen et al., 2025).

An immunogenomics can be considered generally as the study of the effects of genomic variation on the development, regulation and functional activity of the immune system. It explores genes and genomic regions related to the immune system such as human leukocyte antigen and major histocompatibility complex loci, killer-cell immunoglobulin-like receptors, cytokine genes, complement genes, and T-cell and B-cell receptor repertoires. Of these, HLA genes are particularly significant as they control antigen presentation and interactions between cells of the immune system and foreign or self-derived peptides. Mutations in these HLA class I genes can affect immune recognition and lead to differences in susceptibility to infections, autoimmunity and other immune responses related to disease (Debebe et al., 2020).

Genetic variation in the immune pathways is clinically important as it means that people can react differently to the same infectious disease, vaccine, drug or immunotherapeutic therapy. These variations are caused by polymorphisms, gene–

gene interactions, epigenetics, environmental exposures, past infections, ageing and other host factors. Genomic information can be used to understand variability of vaccine-induced immunity and to develop vaccines for specific populations or individuals, examples of which are vaccinomics and personalized vaccinology (Poland et al., 2018). This is especially important in situations where standard vaccination fails to generate an equal antibody response, cellular immunity, or long-term immunity. There are both genetic and non-genetic factors that affect the immune response after vaccination. Genetic background of the host may impact antigen recognition, cytokine signalling, activation of innate immunity, antibody production, and development of immunological memory.

Concurrently, immune protection may be affected by age, sex, nutritional status, microbiome composition, maternal antibodies, comorbidities, and vaccine-related factors in terms of magnitude and duration (Zimmermann & Curtis, 2019). Knowing these interactions is crucial in immunogenomics as it establishes a link between genetic heterogeneity and immune phenotypes and outcomes. While immunogenomics is potentially important, there are significant challenges of population representation and equity in immunogenomic research. The availability of genomic databases and large-scale association studies has been biased towards European populations, reducing the applicability of estimates of genetic risk and predictive models to other populations. This deviation can lower the precision of polygenetic risk scores, recommendations for pharmacogenomics, HLA associations and prediction of immune response in underrepresented groups. Thus, greater ancestral diversity is needed to maximize the potential of immunogenomic discoveries for precision medicine in ways that do not increase the health disparities between groups (Popejoy & Fullerton, 2016).

This review focuses on the role of immunogenomics in precision medicine, and explores the relationship between genetic variability and disease susceptibility and therapeutic responses. It aims to explain the genetics of the immune system, examine immune system genome variation and its linkage with autoimmune, infectious, malignant and allergic diseases, and examine the role of immunogenomics in pharmacogenomics, immunotherapy, vaccination and transplantation. Additionally, enabling technologies, clinical translation, limitations of population diversity, ethical issues, and future research priorities are all taken into account during the review. It includes key immune related gene families, disease associated variants, markers of treatment response, new analytical platforms, and the opportunities and challenges of harnessing immunogenomic information for personalised healthcare.

2. Genetic Architecture of the Immune System

The genetic structure of immune system is very complex, polymorphic and functionally linked. Contains genes related with antigen presentation, recognition by immune cells, cytokines signalling, receptor diversification, complement activation and inflammatory regulation. Polymorphisms of these genes underlie differences in immune responses, disease susceptibility and treatment at the individual and population level. Some of the most important regions of the genome include genes within the human leukocyte antigen (HLA) complex, killer-cell immunoglobulin-like receptor (KIR) genes, cytokine-related genes, T-cell receptor (TCR) genes, and B-cell receptor (BCR) genes, as well as complement-system genes. Figure 1 depicts the main immune-cell lineages and their respective genetic markers, highlighting the influence of genomic variation on immune-cell differentiation, receptor expression, and immune function (Roederer et al., 2015).

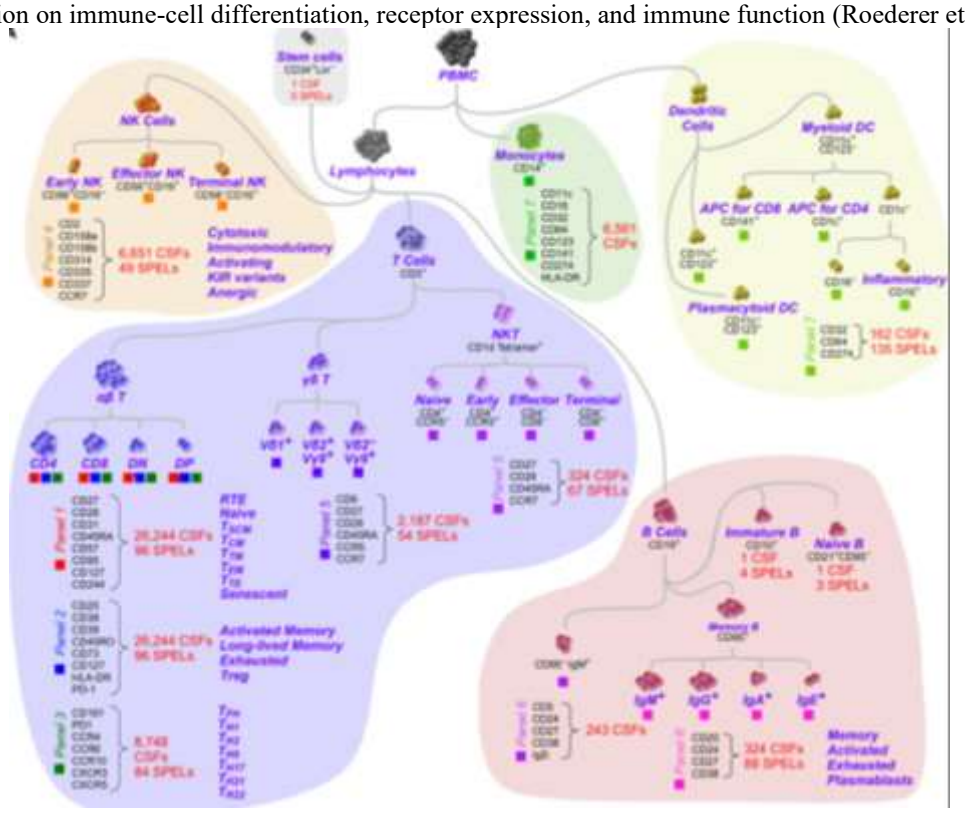

Figure 1. Genetic architecture and immunogenomic regulation of immune-cell populations (Roederer et al., 2015)

2.1 Immune-Related Gene Families

One of the most polymorphic regions of the human genome is the human leukocyte antigen system, which is part of the major histocompatibility complex on chromosome 6. HLA class I molecules start displaying intracellular peptides to the CD8+ T cells, while the HLA class II molecules primarily display extracellular peptides to the CD4+ T cells. Peptide

binding properties can affect immune recognition, clearance of pathogens, self-tolerance and immune-mediated disease development. The disease associated variants of the HLA have different immunological interactions, not a single uniform biological pathway (Debebe et al., 2020). Killer-cell immunoglobulin-like receptors are predominantly expressed on natural killer cells and some subsets of T cells. Their interaction with HLA class I ligands controls activation vs. inhibition of immune signals.

The KIR genes are arranged in two different centromeric and telomeric haplotypes which have high inter-individual and inter-population variation. Specific activation and inhibitor KIR genes could influence susceptibility to infectious, autoimmune, inflammatory, reproductive and malignant diseases (Elagab et al., 2025). In addition, there are other gene families that are important for immunity, such as cytokine genes and cytokine receptors, complement genes, and T-cell receptor and B-cell receptor. Polymorphism of inflammatory cytokines could affect the magnitude and duration of inflammatory reaction, and complement-gene variation may affect pathogen recognition, clearance of immune complexes and tissue damage. TCR and BCR loci to make highly diverse receptor repertoires that are able to bind to a wide array of antigens are subjected to somatic recombination. The table (Table 1) summarizes major immune-related gene families along with their biological functions and main types of genetic polymorphisms and their potential association with disease susceptibility and therapeutic response.

Table 1. Major immune-related gene families and their immunogenomic significance

Gene family or genomic region	Major biological function	Important forms of variation	Clinical or disease relevance	Supporting references
Human leukocyte antigen/major histocompatibility complex	Presents intracellular and extracellular peptides to T cells and regulates immune recognition	Allelic polymorphisms, amino acid substitutions, haplotypes, and structural variation	Autoimmune disease, infectious-disease susceptibility, drug hypersensitivity, immunotherapy response, and transplantation	(Debebe et al., 2020); (Zhao et al., 2020)
Killer-cell immunoglobulin-like receptors	Regulate activating and inhibitory signals in natural killer cells through interactions with HLA class I ligands	Gene-content variation, activating and inhibitory receptor combinations, and centromeric/telomeric haplotypes	Infectious disease, autoimmunity, inflammatory disorders, reproductive outcomes, and malignancy	(Elagab et al., 2025); (Kuśnierczyk , 2013)
Cytokine and cytokine-receptor genes	Control immune-cell communication, inflammation, differentiation, and immune activation	Single-nucleotide polymorphisms and regulatory variants	Variation in inflammatory intensity, immune-mediated disease, vaccine response, and infection severity	(Dieter et al., 2022)
T-cell receptor and B-cell receptor loci	Generate antigen-specific adaptive immune repertoires through somatic recombination	V(D)J recombination, clonal expansion, and repertoire diversity	Infection control, vaccine-induced immunity, autoimmunity, and tumour recognition	(Franco et al., 2013)
Complement-system genes	Support pathogen recognition, immune-complex clearance, inflammation, and tissue defence	Single-nucleotide variants, copy-number variation, and functional mutations	Infection susceptibility, inflammatory injury, and immune-mediated disease	(Vasconcelos et al., 2021)
Polygenic immune-regulatory loci	Coordinate multiple immune pathways and influence cumulative inherited risk	Numerous common low-effect variants	Autoimmune risk, cancer response, immune-related adverse events, and population-level susceptibility	(Chen et al., 2024); (Khan et al., 2020

2.2 Polymorphism and Genetic Diversity

The diversity of the immune system is generated by single-nucleotide polymorphisms, copy-number variations, insertions, deletions, structural variants, and immune-systems gene content variations. Individual differences in antigen presentation exist because of the diversity of the amino acid sequences of the HLA alleles. Likewise, the regions containing KIR genes also differ with respect to the number and type of genes present. This diversity leads to the formation of distinct activating and inhibitory receptor profiles and heterogeneity in natural killer-cell function (Kuśnierczyk, 2013). The structural diversity of immune genes can be advantageous to the population level: greater diversity of pathogens that can be recognized. The same diversity can, however, make one more susceptible to autoimmunity, allergy, graft rejection or inappropriate inflammatory response. Immune-related polymorphisms are thus a compromise between successful host defence and the potential for immune-mediated tissue injury.

2.3 Epigenetic Regulation of Immune-Gene Expression

Epigenetic mechanisms such as DNA methylation, modification of the histone proteins, chromatin remodelling and non-coding RNA activity also regulate immune responses. These mechanisms regulate the expression of immune genes, and modify the activity of the genes without any change in the DNA sequence of the genes themselves. Epigenetic regulation plays a critical role in immune-cell differentiation, activation, exhaustion, and memory. Immune-cell epigenetic profiles can be altered by environmental exposures, infection, nutrition, ageing, medications and chronic inflammation. Therefore, people with the same genetic variants could have different immune phenotypes. Epigenetic mechanisms then link environmental and physiological factors to genomic variation passed down from generation to generation.

2.4 Population-Level Variation and Evolutionary Pressures

Immune-related genes differ significantly among populations due to the effects of past pathogens, migration, genetic drift, natural selection, and reproductive pressures. The diversity of HLA and KIR genes demonstrates that host populations can have multiple strategies for immunity to survive variable infectious challenges. The frequencies of KIR genes and haplotypes vary across geographic regions, which is due to evolutionary histories and disease pressures in different populations (Elagab et al., 2025). Natural selection may maintain variants that confer resistance against specific diseases, even if they result in an autoimmune or inflammatory disease. The remarkable genetic polymorphism of KIR and their HLA ligands illustrates the evolutionary significance of having highly flexible immune-recognition systems (Kuśnierczyk, 2013). To interpret genetic associations and create accurate immunogenomic applications that work across a variety of ancestral groups, one needs to understand the population-level variation.

3. Genetic Variability and Disease Susceptibility

Individual differences in susceptibility and severity, progression and clinical outcome of disease, are highly influenced by genetic variability within immune related genes. Changes in HLA, KIR, cytokine and other genes that regulate immune responses can impact antigen presentation, immune-cell activation, inflammatory signalling and self-tolerance. These effects are most pronounced in autoimmune diseases, infectious diseases, cancer and immune-mediated allergic diseases.

3.1 Autoimmune Diseases

Autoimmune diseases are a consequence of loss of immune tolerance and the targeting of self-antigens. The genes coding for HLA molecules are among the most important genetic contributors since they dictate the binding properties of peptides presented to T cells. There are known associations of specific HLA alleles with specific PILDs, but the strength and direction of the association depends on the disease type and population (Mack, 2022). HLA-related susceptibility has also been found in autoimmune neurological disorders where the disease is associated with autoantibodies. Some HLA class II variants could facilitate the presentation of neuronal or neuromuscular antigens and consequently enhance the autoreactive T-cell and B-cell responses (Muñiz-Castrillo et al., 2020).

The exact example of how close the amino acid is to the HLA molecule can alter disease risks is clearly illustrated with type 1 diabetes. The binding properties of peptides to the molecules of the HLA-DQ complex are shaped by certain residues that may account for a considerable part of the genetic risk linked to the high risk DQ2 and DQ8 haplotypes (Zhao et al., 2020). Other amino acid associations within the HLA-DQ and HLA-DR molecules also illustrate that a combination of variants can lead to an autoimmune risk not the individual alleles (Hu et al., 2015). Antigen-presentation pathways also play a role in the pathogenesis of several organ systems in HLA class II-mediated autoimmune diseases (Panhuber et al., 2022). In addition to the genes of the HLA complex, the polymorphisms of the KIR genes can also affect susceptibility to autoimmunity by modulating activation of natural killer cells and their relationship with HLA ligands. There are reports of associations with inflammatory bowel disease, but this is not found in all ethnic groups or study designs (Fathollahi et al., 2018).

3.2 Infectious Disease Susceptibility

The immune-genetic variation affects the recognition of pathogens, the control of viral replication and the regulation of inflammatory responses. The expression of KIR gene profiles may influence the susceptibility to HIV-1 infection, through modulation of the activity of natural killer cells and the ability to recognize virus-infected cells (Zwolińska et al., 2016). The variations in HLA have been extensively studied in the context of the susceptibility to, severity and mortality from COVID-19. Peptide-binding capacities could differ between the two, which influences the effectiveness of SARS-CoV-2 antigen presentation to cytotoxic T cells (Hoseinnezhad et al., 2024).

Some HLA types have been suggested as potential risk factors and others as protective factors, but some of the results have been inconsistent between populations (Migliorini et al., 2021). More broad genetic polymorphisms across inflammatory and immune pathways may also be responsible for severe COVID-19 outcomes (Dieter et al., 2022). People with a relatively small repertoire of HLA class I viral-peptide binding may be at greater risk of developing more severe disease from SARS-CoV-2 due to their ability to present fewer peptides (Basir et al., 2022). Population-specific HLA associations also suggest that the origin and frequency of alleles should also be taken into account when interpreting infectious disease risk (Fakhkhari et al., 2023). Thus, host genomic variation can explain inter-individual variation in viral entry, activation of immune responses, regulation of cytokines, and clinical progression (Vasconcelos et al., 2021).

3.3 Cancer Risk and Immune Surveillance Genes

Genetic mutations that lead to immune system defects, a lack of immune recognition of the tumour, and defects of the tumour microenvironment are partly responsible for cancer susceptibility. Germline genetic modification has the ability to regulate immune-cell infiltration, antigen presentation, cytokine activity and interactions between malignant and immune cells. These inherited variations could affect cancer risk as well as the way immunotherapy is working on the tumor (Pagadala et al., 2023).

3.4 Allergic and Atopic Conditions and Polygenic Risk

Multiple low effect variants are typically involved in allergic and immune-mediated diseases, not one single gene. Polygenic risk scores are able to aggregate many immune related variants to measure inherited susceptibility and to uncover common pathways between autoimmune, allergic and malignant diseases. Patients with exceptional responses to cancer treatment may have distinct polygenetic profiles related to autoimmunity, indicating a relationship between inherited immune activity and cancer therapy responses (Chen et al., 2024).

Biological effects of immune checkpoint blockade may also be affected by polygenetic susceptibility to autoimmunity of the skin. The results of such studies illustrate the potential of inherited immunologic dysregulations to influence treatment-related immunologic responses and susceptibility to disease (Khan et al., 2020). Figure 2 illustrates the role that changes in genes that regulate the immune system (HLA, KIR, cytokines and others) play in autoimmune disease, infectious disease, susceptibility to cancer and allergic or atopic disease. Table 2 summarizes the main genetic factors and the biological mechanisms underlying autoimmune, infectious, malignant and immune diseases, as well as their clinical relevance.

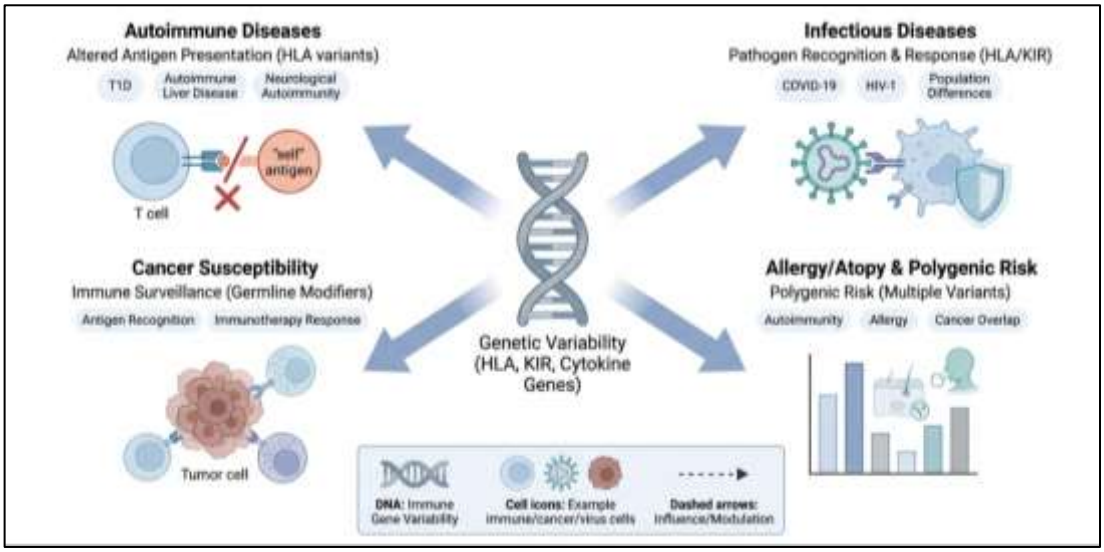

Figure 2. Impact of genetic variability in immune genes on disease susceptibility

Table 2. Immunogenomic associations with major disease categories

Disease category	Principal immunogenomic factors	Proposed biological mechanism	Main clinical significance	Supporting references
Autoimmune liver diseases	Specific HLA alleles and haplotypes	Altered presentation of self-derived hepatic antigens and loss of immune tolerance	Disease susceptibility, classification, and population-specific risk estimation	(Mack, 2022)
Autoimmune neurological diseases	HLA class II variants	Presentation of neuronal or neuromuscular self-antigens and autoantibody-associated immune activation	Identification of genetic susceptibility and disease-specific immune pathways	(Muñiz-Castrillo et al., 2020)
Type 1 diabetes	HLA-DQ and HLA-DR amino acid residues and haplotypes	Changes in peptide-binding properties and presentation of pancreatic self-antigens	Improved understanding of inherited risk and HLA-mediated autoimmunity	(Zhao et al., 2020); (Hu et al., 2015)
IgG4-related autoimmunity	HLA class II variants	Promotion of autoreactive T-cell and B-cell responses	Identification of genetic susceptibility across IgG4-mediated disorders	(Panhuber et al., 2022)
Inflammatory bowel disease	KIR gene profiles and KIR–HLA interactions	Altered natural killer-cell activation and inflammatory regulation	Population-dependent susceptibility assessment	(Fathollahi et al., 2018)
HIV-1 infection	KIR gene variation	Differences in natural killer-cell recognition and elimination of infected cells	Variation in infection susceptibility and host antiviral defence	(Zwolińska et al., 2016)
COVID-19	HLA alleles, peptide-binding capacity, and immune-pathway polymorphisms	Variation in viral-peptide presentation, inflammatory regulation, and antiviral T-cell activation	Differences in susceptibility, severity, progression, and mortality	(Hoseinnezhad et al., 2024); (Basir et al., 2022)

Cancer	Germline variants influencing antigen presentation and the tumour immune microenvironment	Altered immune-cell infiltration, tumour surveillance, and tumour-antigen recognition	Cancer susceptibility and variation in response to immunotherapy	(Pagadala et al., 2023)
Allergic and immune-mediated conditions	Polygenic immune-risk profiles	Combined effects of multiple low-effect immune-regulatory variants	Risk stratification and identification of shared immune pathways	(Chen et al., 2024)

4. Immunogenomics and Therapeutic Response

Immunogenomics is a tool for precision medicine, in that inherited and acquired genetic factors can be identified that affect drug safety, effectiveness of immunotherapies, vaccine responses, and transplant outcomes. Changes in HLA and other immune-related genes may affect antigen presentation, activation of the immune system, susceptibility to hypersensitivity, treatment response and immune-mediated toxicity.

4.1 Pharmacogenomics of Immune-Related Drug Reactions

One of the most well-established clinical applications of immunogenomics is the use of HLA-guided pharmacogenomics. The HLA-B57:01 allele is strongly associated with abacavir hypersensitivity and pre-treatment genetic testing is likely to significantly decrease the risk of severe immune-mediated reactions (Martin et al, 2012). Systematic evaluation also confirms that HLA-B57:01 testing prior to abacavir use is a sufficiently good predictor (Sousa-Pinto et al., 2015). The mechanism is based on the alteration of the peptide repertoire presented by the major histocompatibility complex molecules by the drugs, which triggers the drug-specific T-cell responses (Ostrov et al., 2012). Adverse reactions to anticonvulsants is also affected by HLA variation. However, screening for HLA-B15:02 and HLA-A31:01 is recommended prior to treatment with carbamazepine or oxcarbazepine in relevant populations due to their association with severe cutaneous reactions (Phillips et al., 2018). HLA-B15:21 has also been associated with Stevens–Johnson syndrome (SJS) that is carbamazepine-induced, especially in Southeast Asian population (Jaruthamsophon et al., 2017). HLA-based toxicity prediction is highly clinically relevant, as HLA-A32:01 was strongly associated with vancomycin-induced drug reaction with eosinophilia and systemic symptoms (Konvinse et al., 2019).

4.2 Predicting Response to Immunotherapies

The clinical responses to ICI are highly variable, and ICI represent a paradigm shift in cancer treatment. With the advent of recent advancements, several biomarkers have been adopted to foretell treatment advantage, including programmed death-ligand expression, microsatellite instability, immune-cell infiltration, tumour mutational burden, and HLA diversity (Wang & Chan, 2025). Checkpoint blockade response is a result of interaction between tumour's genomics, antigen presentation and the tumour microenvironment (Havel et al. 2019). The genomic changes within immune pathways have been linked to the response to therapy in clear-cell renal-cell carcinoma (Miao et al., 2018).

TMB can serve as a prognostic marker for the potential to generate immunogenic neoantigens, but its predictive value varies amongst tumour types and therapeutic contexts (Sha et al., 2020). Therefore, the use of a combination of the genomic, cellular, and circulating biomarkers may yield more predictive accuracy than any individual biomarker (Bindal et al., 2021). The diversity of tumour-derived peptides presented to T cells is determined by inherited HLA class I genotype, which may drive checkpoint-inhibitor response (Chowell et al., 2018). Germline immunogenetic variation can also contribute to the establishment of personalised biomarker approaches in the field of immuno-oncology (Kirchhoff & Ferguson, 2019).

4.3 Vaccine Response Variability and Genetic Determinants

These genetic variations are responsible for antibody production, cellular immunity and vaccine persistence. Personalized vaccinology uses genomic and immunological data to improve the design and delivery of vaccines (Poland et al., 2018). The antibody response to vaccines can be modified by host polymorphisms with effects on antigen presentation, cytokines and innate immunity (Linnik & Egli, 2016). Gene-expression patterns that are linked to influenza-vaccine responsiveness have been identified through integrative genomic analyses (Franco et al., 2013). Other factors that impact vaccine outcomes include age, sex, health status, microbiome composition, prior exposure to vaccine components, and environmental factors (Zimmermann & Curtis, 2019). Immune response variations to BNT162b2 mRNA vaccine have been linked to HLA variation (Esposito et al., 2024). Adverse-event mechanisms and immune-mediated molecular effects are, however, very speculative and should be interpreted with caution and further validated (Bellavite et al., 2023).

4.4 Transplant Immunogenetics and Immune-Related Toxicity

Although there have been advances in transplantation techniques, HLA compatibility has continued to play a pivotal role in transplantation as mismatched epitopes can trigger the production of donor specific antibodies and rejection of grafts (Tambur & Claas, 2015). Epitope-based matching might yield a more accurate evaluation of compatibility than traditional antigen-level matching (Duquesnoy, 2016). However, there is a balance between immunological risk, donor availability, and waiting time that needs to be maintained when doing HLA matching (Zachary & Leffell, 2016). To avoid kidney-transplant rejection, the immunological monitoring, selection of compatible donors, and personalized immunosuppression are all deployed (Malhotra & Jethwani, 2023). HLA-DQ mismatching is especially significant as it is often linked to DSA and chronic graft damage (Tambur et al., 2021). Collectively, these results highlight the potential of immunogenomic biomarkers for better treatment selection, toxicity avoidance and post-transplant monitoring. Immunogenomics can be used to inform personalized treatment decisions, as illustrated in Figure 3 in the following ways: prediction of drug hypersensitivity, prediction of immunotherapy response, prediction of vaccine variability, and prediction of transplant

compatibility. Table 3 lists the major immunogenomic markers and their uses in drug screening for safety, immunotherapy selection, customization of vaccines, transplantation, and precision medicine with the help of artificial intelligence.

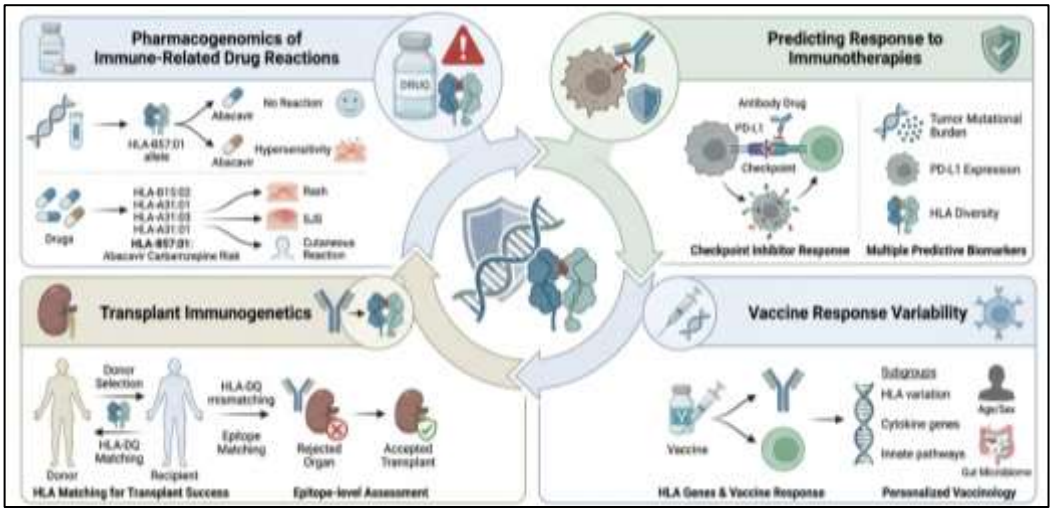

Figure 3. Immunogenomics and therapeutic response in precision medicine

Table 3. Clinical applications of immunogenomics in therapeutic decision-making

Clinical area	Immunogenomic biomarker or approach	Application	Expected clinical benefit	Supporting references
Abacavir pharmacogenomics	HLA-B*57:01 screening	Genetic testing before abacavir treatment	Prevention of abacavir hypersensitivity reactions	(Martin et al., 2012); (Sousa-Pinto et al., 2015)
Carbamazepine and oxcarbazepine safety	HLA-B15:02, HLA-A31:01, and HLA-B*15:21	Pre-treatment risk assessment in genetically susceptible populations	Reduced incidence of Stevens–Johnson syndrome and severe cutaneous reactions	(Phillips et al., 2018); (Jaruthamsophon et al., 2017)
Vancomycin safety	HLA-A*32:01	Identification of patients at increased risk of drug reaction with eosinophilia and systemic symptoms	Safer antibiotic selection and early monitoring	(Konvinse et al., 2019)
Immune checkpoint inhibition	HLA class I genotype, tumour mutational burden, microsatellite instability, and immune biomarkers	Prediction of treatment response and patient stratification	Improved selection of patients likely to benefit from immunotherapy	(Chowell et al., 2018); (Sha et al., 2020)
Personalized vaccination	HLA variation, host polymorphisms, gene-expression profiles, and immune-response signatures	Prediction of antibody and cellular immune responses	Improved vaccine design, dosing, and population-specific vaccination strategies	(Poland et al., 2018); (Linnik & Egli, 2016)
mRNA vaccine response	HLA variants	Assessment of variability in immune response to BNT162b2 vaccination	Identification of factors influencing vaccine responsiveness	(Esposito et al., 2024)
Solid-organ transplantation	HLA compatibility, HLA-DQ matching, and epitope-based matching	Donor–recipient selection and post-transplant monitoring	Reduced donor-specific antibody formation, rejection, and long-term graft injury	(Tambur & Claas, 2015); (Tambur et al., 2021)
Artificial intelligence-supported precision medicine	Integration of genomic, immunological, and electronic health-record data	Biomarker discovery, risk prediction, and clinical decision	More accurate patient classification and individualized therapeutic planning	(Chen et al., 2025)

		support		

5. Technologies, Clinical Translation, and Challenges

Technologies are essential for generating, combining, and analyzing vast quantities of genomic and immunological data, which are necessary to the development of immunogenomics. The molecular, cellular, and population characterization of immune variation has been greatly enhanced by high-throughput sequencing, single-cell analysis, immune-receptor profiling, multi-omics platforms, and artificial intelligence. Yet for clinical success, it must be analytical valid, be easily interpreted, be representative, be ethically managed and be accessible.

5.1 Enabling Technologies

The identification of immune related genetic variants like HLA alleles, single nucleotide polymorphisms, structural variants and rare mutations has greatly enhanced by next generation sequencing. High resolution HLA typing can be applied in fields of transplantation, pharmacogenomics, infectious diseases and immunotherapy to give detailed information about antigen-presentation capacity and compatibility. Single-cell immunogenomics provides a way to study gene expression and genomic variation in single immune cells simultaneously. This can be used to detect cellular heterogeneity, rare immune-cell subpopulations, and elucidate the role of specific subsets of lymphocytes or myeloid cells in disease progression and response to therapy. Sequencing of T-cell receptor and B-cell receptor provides additional insights into the evaluation of immune cell clonality, antigen-specific expansion, immune memory, and effects of therapy on adaptive immunity. Multi-omics approaches integrate genomic, transcriptomic, epigenomic, proteomic and metabolomic data to provide a more holistic view of immune function. These intricate datasets can be combined with electronic health records, lab results, imaging data, and treatment records using artificial intelligence and machine-learning techniques. This integration can enhance disease classification, biomarker discovery, patient stratification, and prediction of therapeutic outcomes (Chen et al., 2025).

5.2 Clinical Implementation and Translation

Immunogenomic results must be translated into clinical practices that can be translated into practical tests and practical recommendations. Current uses include the potential selection of drugs based on HLA, prediction of severe hypersensitivity reactions, donor/recipient matching, predicting vaccine responses, predicting disease risk, and identifying patients most likely to respond to immunotherapy. Biomarkers need to be analytically accurate, clinically valid and clinically useful before implementation. Standardized laboratory procedures, quality-control systems, validated computational pipelines and interpretation criteria are crucial. Immunogenomic data can be combined with patient-specific factors and treatment protocols in clinical decision-support systems, which can help healthcare providers. However, human oversight is still required since algorithmic predictions could be impacted by incompleteness of records, population bias, and variability in interpretation of the variants.

5.3 Challenges and Limitations

Immunogenomic traits are often polygenetic and are also regulated by exposure to the environment, age, infection, co-morbidity, and epigenetic control. So, the genetic variation seen in different people accounts for only a small fraction of the risk for disease or response to treatment. The comparability of studies is also hampered by study design, sequencing platforms, outcome definitions and population structure. One of the significant challenges is that certain ancestral groups are not adequately represented in genomic studies. Results based mainly in European populations do not necessarily apply to populations with different allele frequencies, linkage, and environmental factors. The imbalance can undermine the accuracy of genetic-risk models, and may exacerbate the health disparities that already exist (Popejoy & Fullerton, 2016). Other issues are the high costs of testing, lack of facilities and equipment, demands for data storage, concerns about privacy, informed consent, genetic discrimination, and questions of who owns the genomic information and how it can be repurposed. These challenges are especially significant in areas where there is a lack of specialist knowledge and sequencing resources.

5.4 Future Directions

Future immunogenomic studies should take into consideration larger multi-ancestry cohorts, harmonized protocols, functional validation of identified variants, longitudinal monitoring. Single-cell technology, spatial profiling, immune-receptor sequencing and AI could be combined to boost knowledge of dynamic immune responses. Clinical systems of the future should also leverage genomic and immunological data along with the everyday health data collected to enable real-time, personalized decision making (Chen et al., 2025). When it comes to equitable implementation, affordable testing, transparent algorithms, a diversity of reference databases, reinforced data governance and professional training will be essential. Immunogenomics can overcome these scientific, ethical and infrastructural challenges to move beyond association research and to dependable and accessible precision healthcare.

6. CONCLUSION

The understanding of the role of genetic variation in immune function, disease susceptibility, and therapeutic response has made immunogenomics an important aspect of precision medicine. The differences in genes related to the specificity of antigen presentation, activation of immune cells, maintenance of self-tolerance, and recognition of pathogens and inflammatory response are seen in the HLA, KIR, cytokine-related genes, and other genes involved in regulation. These differences in genetics result in differences in auto-immune diseases, infectious diseases, cancer susceptibility, allergic and other immune-mediated diseases at the individual and population levels. Immunogenomics is most relevant to clinical applications in the fields of pharmacogenomics, immunotherapies, vaccinations, and transplantation. Severe drug hypersensitivity reactions can be prevented by HLA-guided testing and genomic and immune biomarkers can aid in patient selection for immune checkpoint inhibitors. Immunogenomic profiling can also enhance the ability to predict human responses to vaccines, donor/recipient matching, surveillance of grafts and personalized immunosuppressive therapy. The

next generation sequencing, high resolution HLA typing, single-cell analysis, sequencing of T- and B-cell receptors, multi-omics and now AI have pushed the ability to investigate complex immune-genetic interactions to new levels. Polygenic complexity, varying analytical approaches, unclear variant interpretation, expensive implementation, data-privacy issues, and under-representation of diverse populations, however, limit clinical translation. However, future advances will depend on the large multi-ancestry cohorts, the use of standardized laboratory and computational protocols, longitudinal studies, functional validation, and the integration of genomic data with clinical records. The need for ethical governance, affordable testing, transparent algorithms and equal access should also continue to be paramount. In conclusion, immunogenomics holds significant promise for revolutionizing disease-risk classification, drug safety selection and monitoring, as well as personalized medicine.

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