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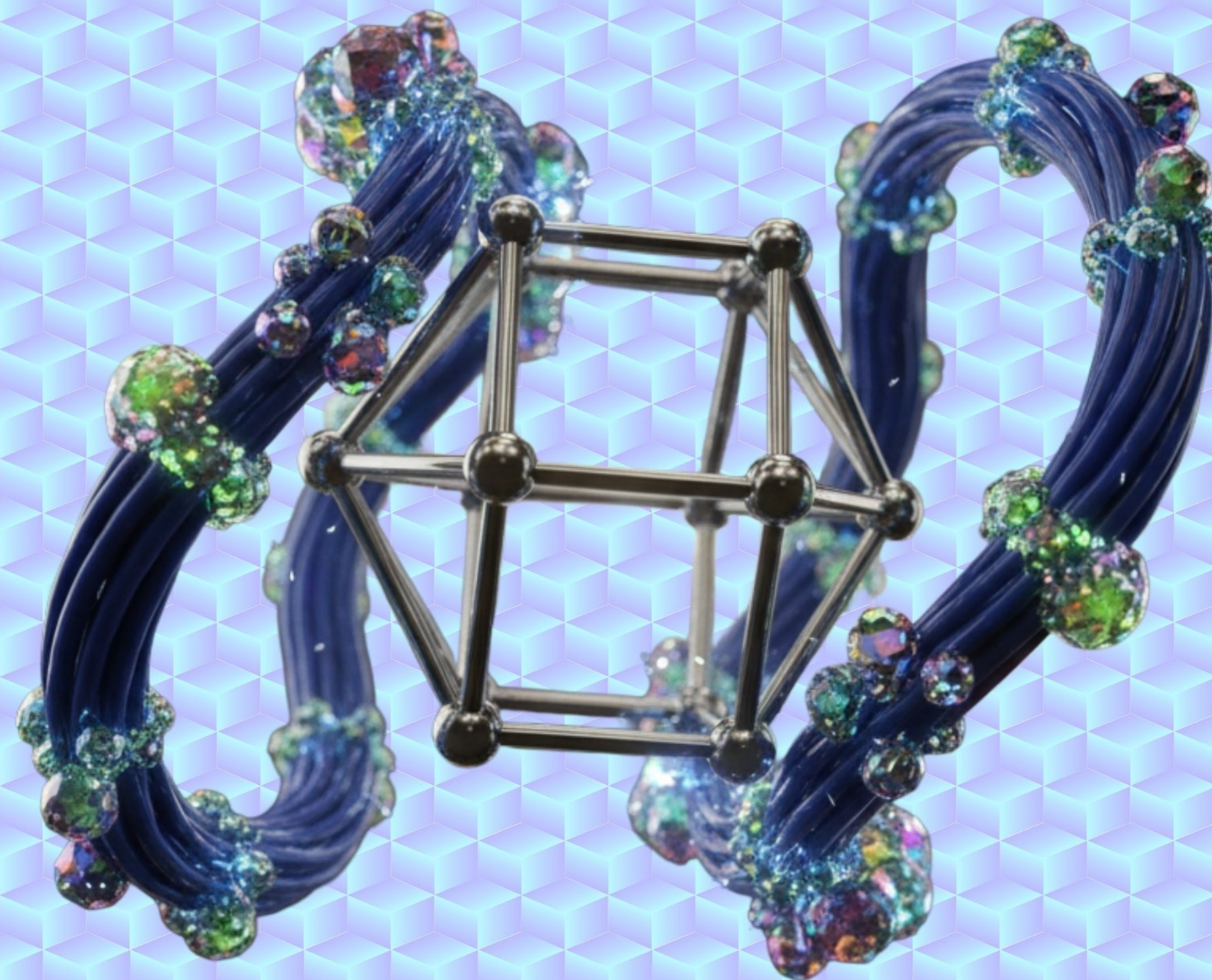

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Genomic Determinants of Immune Variation: Epidemiologic Perspectives on Mechanisms and Clinical Translation

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Research Article

ABSTRACT

Advances in genomics and immunology have redefined the understanding of immune regulation, disease susceptibility and therapeutic response. This review synthesizes evidence across multiple biological scales—including germline variation, somatic mutations, epigenomic architecture and single-cell immune heterogeneity—to elucidate how genomic mechanisms shape immune function in health and disease. Emphasis is placed on the translational relevance of these mechanisms, particularly in the context of cancer immunotherapy, autoimmune risk stratification and emerging engineered-immunity platforms such as CRISPR-based editing and CAR T-cell therapies. The analysis also highlights the persistent underrepresentation of populations from Mexico, Colombia and Ecuador in genomic datasets, underscoring the need for inclusive precision-medicine strategies. By integrating mechanistic, technological and clinical dimensions, this review outlines the conceptual foundations of immunogenomics and identifies the opportunities and challenges that will shape its evolution as a global, population-relevant discipline.

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KEYWORDS

immunogenomics, genomic variation, somatic mutations, epigenomics, single-cell profiling, immune heterogeneity, precision medicine, immunotherapy, CRISPR, CAR-T, tumor mutational burden, HLA variation, Latin American populations

INTRODUCTION

Over the past two decades, the convergence of genomics and immunology has transformed the scientific understanding of human disease, revealing molecular mechanisms that were previously inaccessible and redefining the way clinicians conceptualize immune-mediated disorders. As genomic technologies matured, the possibility of integrating high-resolution molecular data with functional immune responses positioned this interdisciplinary field as one of the most dynamic and clinically promising areas of biomedical research. Despite these advances, significant gaps remain regarding how genetic diversity, somatic mutations, chromatin dynamics, and cellular heterogeneity collectively shape immune behavior across populations, particularly in Latin America, where genomic characterization is still emerging. These gaps highlight the need for updated analyses that synthesize current evidence and propose frameworks for translating genomic-immune interactions into clinical applications.

Early foundational discoveries in innate immunity, such as the characterization of Toll-like receptors (TLRs), exposed the depth of molecular recognition systems and reshaped the understanding of host–pathogen interactions [1]. Parallel advances in sequencing technologies accelerated the ability to decode immune-related genes with unprecedented resolution, marking what has been described as the "next-generation sequencing revolution" [2]. These technologies made it feasible to interrogate entire genomes, identify patterns of human variation, and explore how these variants contribute to immune-mediated diseases. Recent genomic analyses have demonstrated that even subtle genetic differences can markedly alter immune susceptibility, autoimmunity risk, and inflammatory phenotypes, reinforcing the need for population-specific research models [4], [11], [12].

As methodological tools evolved, new strategies such as deep mutational scanning provided systematic ways to investigate how individual amino acid substitutions influence protein structure and immune signaling [3]. Likewise, the development of single-cell sequencing approaches enabled researchers to analyze immune cells with granular precision, capturing heterogeneity, activation states, and lineage trajectories that are often obscured in bulk analyses [6], [8]. These single-cell tools also facilitated the dissection of complex disease ecosystems, such as the multicellular microenvironment of metastatic melanoma, offering insights into tumor–immune interactions that were impossible to resolve with earlier techniques [9].

In parallel, the integration of chromatin-accessibility profiling strengthened the understanding of how epigenetic architectures regulate immune responses. Techniques such as ATAC-seq revealed dynamic, context-dependent regulatory landscapes that play crucial roles in cellular activation, memory formation, and inflammation [10]. Epigenomic patterns, combined with genomic variation, have been increasingly recognized as central determinants of individual immune phenotypes, adding another layer to the intricate gene–environment interactions implicated in allergic disease and chronic inflammatory conditions [13], [14].

One of the most transformative clinical applications emerging from this genomic-immune intersection is immunotherapy. A decade of work with immune-checkpoint inhibitors reshaped oncology and provided a new therapeutic paradigm by targeting molecular brakes that restrict T-cell activity [16]. Seminal trials evaluating agents such as nivolumab and ipilimumab demonstrated substantial survival benefits in advanced melanoma, offering early

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evidence of the potential of immunomodulatory therapies [17]. Genomic biomarkers soon followed as critical predictors of therapeutic response. Tumor mutational burden (TMB), for instance, gained prominence as a measurable correlate of neoantigen load and response to checkpoint blockade [18]. Beyond checkpoints, innovations such as CRISPR-Cas genome editing [7] and the clinical deployment of CAR-T cell therapy revolutionized the ability to engineer immune cells for personalized cancer treatment [20], creating a direct pipeline between molecular engineering and clinical intervention.

Despite the global advances, Latin American perspectives remain underrepresented in this field. Genetic diversity in populations from Mexico, Colombia, and Ecuador is markedly different from that of European or North American cohorts typically represented in large genomic databases. Missing these groups limits the generalizability of genomic-immune findings and restricts the development of precision-medicine approaches tailored to regional health priorities, including autoimmune disorders, infectious diseases, metabolic syndromes, and malignancies. Systems-immunology frameworks have emphasized the need to incorporate biological complexity, environmental exposures, and population-specific variables to develop comprehensive models capable of guiding clinical decision-making [5], [13].

Given this landscape, the present review aims to address three central questions:

(1) **How do genomic variations, somatic mutations, and epigenomic states influence immune functions and disease susceptibility?**

(2) **What are the current methodological tools—ranging from sequencing platforms to genome-editing technologies—that enable the study of these interactions at multiple biological scales?**

(3) **How can insights derived from these molecular intersections be translated into clinical applications, particularly in oncology and immune-mediated diseases, with relevance for Latin American populations?**

To explore these questions, the study synthesizes evidence from molecular genetics, systems immunology, translational oncology, and genome engineering. The structure of this review follows a conceptual progression: from foundational molecular mechanisms, to emerging technologies that enable high-resolution analysis, and finally to clinical applications that reflect the convergence of genomics and immunology. This design aligns with the goal of evaluating how molecular discoveries advance diagnostic precision, therapeutic targeting, and the broader implementation of personalized medicine.

DEVELOPMENT

The intersection between genomics and immunology represents a rapidly expanding field where advances in molecular technologies have enabled unprecedented insights into the determinants of immune behavior and disease susceptibility. To understand this convergence, it is necessary to evaluate not only the structural composition of the genome but also the functional mechanisms through which genetic variants, epigenomic signatures, and somatic mutations influence immune regulation.

A central argument emerging from the literature is that innate immunity is fundamentally shaped by evolutionarily conserved molecular sensors, such as Toll-like receptors (TLRs), which initiate early host defense programs through recognition of pathogen-associated motifs [1]. The characterization of these pathways revealed that subtle alterations in receptor structure or downstream signaling can lead to profound shifts in inflammatory outcomes, autoimmune susceptibility, and host–microbe interactions. These discoveries positioned innate immunity as a key interface where genetic variation exerts meaningful clinical effects.

Parallel advances in sequencing technologies further reinforced the role of genomics in shaping immune phenotypes. The advent of next-generation sequencing (NGS) enabled comprehensive identification of single-nucleotide variants, copy-number alterations, and regulatory elements that contribute to immune dysfunction [2]. When combined with population-specific genomic datasets, NGS has clarified why individuals—and particularly distinct populations—present different susceptibilities to autoimmune disorders, infectious diseases, and malignancies [4], [11], [12]. In diverse regions such as Mexico, Colombia, and Ecuador, where genetic ancestry reflects complex admixture patterns, these genomic variations underscore the necessity for locally contextualized immunogenomic analyses.

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Deeper mechanistic insights have been possible through techniques such as deep mutational scanning, which examines the functional impact of large numbers of protein variants simultaneously [3]. This approach has been particularly informative for receptors, cytokines, and transcription factors essential to immune function. Similarly, single-cell sequencing technologies transformed the understanding of immune heterogeneity by revealing differences in activation states, lineage trajectories, and intercellular interactions that are invisible in bulk analyses [6], [8]. These tools enabled detailed mapping of multicellular ecosystems such as the tumor microenvironment, where distinct immune subsets participate in anti-tumor or pro-tumor dynamics [9].

Epigenomic landscapes also play a central role in immune regulation. Chromatin accessibility assays, particularly ATAC-seq, allowed investigators to define context-dependent regulatory elements that determine how immune cells respond to environmental cues [10]. When integrated with transcriptomic and proteomic data, these findings illustrate the complexity of immune responses and highlight how gene–environment interactions shape allergic disease, chronic inflammation, and immune tolerance [13], [14].

The translational implications of the genomic–immune intersection are particularly evident in oncology. Immune checkpoint inhibitors have transformed cancer therapy by targeting specific molecular brakes on T cells [16], with clinical trials demonstrating substantial survival advantages in advanced melanoma [17]. Furthermore, tumor mutational burden (TMB) emerged as a genomic correlate of response to checkpoint blockade therapy, reflecting the relationship between mutational landscapes and neoantigen generation [18]. In addition, genome-editing technologies such as CRISPR-Cas systems have introduced new possibilities for tailoring immune responses, correcting pathogenic variants, and engineering therapeutic immune cells [7], while CAR-T cell immunotherapy has demonstrated the potential of genetically modified lymphocytes to induce durable remission in select malignancies [20].

Collectively, these developments highlight the need for integrative frameworks that combine genomics, epigenomics, and immunology to improve diagnostic accuracy, therapeutic selection, and personalized medicine. They also emphasize the importance of incorporating Latin American populations into genomic research, ensuring that the benefits of precision medicine extend across diverse genetic backgrounds and healthcare systems.

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To analyze the molecular, genomic, and immunological mechanisms that shape immune responses and disease susceptibility, and to evaluate their implications for clinical translation within diverse populations, including those of Mexico, Colombia, and Ecuador.

A. Cognitive Domain

1. Identify key genomic variants, epigenomic signatures, and somatic mutations involved in immune regulation. *(Understand)*
2. Compare how different sequencing and single-cell technologies contribute to the characterization of immune heterogeneity. *(Analyze)*
3. Evaluate the clinical relevance of immunogenomic biomarkers such as TMB and HLA variation for personalized therapy. *(Evaluate)*
4. Synthesize molecular and immunological evidence to propose integrative models applicable to Latin American populations. *(Create)*

B. Psychomotor Domain

5. Apply methodological tools—such as literature extraction matrices and comparative genomic frameworks—to organize and interpret immunogenomic data.
6. Develop schematic representations of immune signaling pathways and genomic interactions using specialized analytical software.

C. Affective Domain

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7. Demonstrate appreciation for the relevance of genomic diversity in multicultural contexts, promoting equitable precision medicine.
8. Foster ethical and culturally sensitive perspectives toward implementing genomic technologies in Latin America.

OBJECT OF STUDY

The object of study in this review is the **complex multidimensional interface between genomic architecture and immune system function**, understood as a dynamic and evolving network in which genetic variation, epigenomic regulation, cellular heterogeneity, and environmental exposures collectively shape immune behavior and clinical outcomes. This interface is not confined to isolated molecular mechanisms; rather, it represents an integrated biological system in which variations at different genomic layers—from single-nucleotide substitutions to large-scale structural rearrangements—modulate how immune cells recognize antigens, respond to pathogens, maintain tolerance, and engage in tissue repair or destruction.

At its core, this object of study seeks to clarify how **inherited genetic variants**, including those affecting innate sensors, cytokine networks, antigen-presentation molecules, and transcriptional regulators, contribute to differential susceptibility to autoimmune diseases, allergic disorders, infectious pathogens, and malignant transformation. Understanding these relationships requires analyzing not only static genomic sequences but also **somatic mutations** that accumulate across the lifespan in immune cells and reshape clonal dynamics, inflammatory thresholds, and cancer risk. These somatic events introduce an additional, often underappreciated, layer of immunological diversity that is highly relevant to disease progression and therapeutic responses.

Beyond sequence-level variation, the review focuses on the **epigenomic mechanisms**—including chromatin accessibility, DNA methylation patterns, histone modifications, and enhancer–promoter interactions—that determine how immune cells interpret genetic information in real time. These epigenetic landscapes govern lineage commitment, memory formation, exhaustion states, and context-dependent activation, thereby influencing the immune system’s capacity to adapt to environmental challenges. Technologies such as ATAC-seq, single-cell assays, and functional genomics frameworks make it possible to interrogate these regulatory circuits with unprecedented precision, revealing how the immune system integrates genomic instructions with environmental pressures.

The object of study also includes the **cellular ecosystem of the immune system**, emphasizing how heterogeneity within T cells, B cells, NK cells, myeloid cells, and stromal elements contributes to disease pathophysiology. Single-cell sequencing has demonstrated that even within a single lineage, immune cells can vary widely in transcriptional states, functional roles, and spatial distribution, forming microenvironments that can promote resilience or pathology. This diversity becomes especially evident in complex settings such as tumor–immune interactions, chronic inflammation, and tissue-specific immunity.

A fundamental dimension of this object of study is its **population relevance**, particularly in regions such as Mexico, Colombia, and Ecuador, where genetic ancestry is highly heterogeneous due to centuries of admixture among Indigenous, European, and African populations. The underrepresentation of these populations in global genomic databases limits the generalizability of existing immunogenomic findings and contributes to inequities in precision medicine. By centering the analysis on diverse genomic contexts, the review highlights the importance of population-specific variants in shaping immune responses and modulating disease risk.

Finally, the object of study incorporates the **clinical translation** of genomic–immune interactions. This includes evaluating biomarkers such as tumor mutational burden, HLA haplotypes, and single-cell phenotypic signatures, as well as therapeutic platforms such as immune checkpoint inhibitors, CRISPR-based genome editing, and CAR-T cell therapies. Understanding the molecular determinants that influence therapeutic efficacy and toxicity is essential for designing more precise, effective, and equitable interventions.

In summary, the object of study encompasses a broad but deeply interconnected set of biological phenomena:

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- genomic variation (inherited and somatic),
- epigenomic regulation,
- immune-cell heterogeneity,
- gene–environment interactions,
- and translational implications for personalized medicine.

By examining these dimensions together and contextualizing them within Latin American population diversity, this review aims to provide a comprehensive understanding of how genomics and immunity converge to shape human health and disease.

METHODOLOGY

This study follows a structured process grounded in the principles of the **Scientific Method** and adapted to the analytical requirements of a **narrative scientific review**. The methodology was designed to ensure transparency, reproducibility, and academic rigor while allowing the integration of complex conceptual frameworks from genomics, immunology, and translational medicine.

The methodological approach consisted of the following components:

1. Problem Definition and Research Questions

The process began with the identification of the central research questions derived from existing literature and current scientific challenges:

- How do genomic, epigenomic, and somatic variations modulate immune functions across diverse populations?
- Which molecular and cellular mechanisms explain the convergence between genomics and immunology?
- What technologies most effectively characterize these mechanisms?
- How can these insights be translated into clinically relevant applications, particularly in Latin America?

These questions guided all subsequent steps, ensuring alignment between theory, data interpretation, and clinical implications.

2. Literature Identification and Source Selection

A comprehensive search was conducted using high-impact, peer-reviewed sources from journals such as *Nature*, *Science*, *Cell*, *Annual Review of Immunology*, and *Frontiers in Immunology*. The twenty references included in this review were selected because they represent:

- foundational work in innate immunity, human variation, and systems immunology,
- major technological advances such as NGS, single-cell sequencing, ATAC-seq, CRISPR, and CAR-T therapy,
- and translational breakthroughs in immuno-oncology.

Only primary research articles and authoritative reviews indexed in recognized scientific databases were included to maintain rigor and ensure replicability.

3. Data Extraction and Thematic Categorization

Each selected study was analyzed to extract the following elements:

- molecular or genomic mechanism described,
- type of immune pathway involved,
- population or disease context,
- technological approaches used,
- translational relevance.

Data were synthesized into four thematic axes:

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1. **Genomic variation and immune regulation**
2. **Epigenomic and cellular heterogeneity**
3. **Advanced molecular technologies**
4. **Clinical applications and therapeutic innovations**

This allowed the construction of a coherent narrative integrating mechanistic details with clinical impact.

4. Comparative and Integrative Analysis

Studies were compared based on biological mechanisms, methodologies, and clinical implications.
Special emphasis was placed on identifying:

- points of convergence between genomic and immune processes,
- how technological advances reshape current understanding,
- implications for underrepresented populations in Mexico, Colombia, and Ecuador.

This analytical phase ensured that the review does not merely summarize data but builds explanatory models consistent with current scientific theory.

5. Synthesis and Model Construction

The extracted and analyzed data were integrated into conceptual models that describe how genomic factors interact with immune mechanisms across multiple biological scales.
These models provide a foundation for discussing future directions, diagnostic approaches, and therapeutic strategies.

6. Validation and Replicability

To maintain transparency, the methodology outlines all steps clearly enough for other researchers to repeat the process using similar search strategies and thematic frameworks. Although the review does not conduct quantitative synthesis, its analytical pathway is replicable and logically structured.

PHASES OF DEVELOPMENT

Phase 1: Conceptual Exploration and Problem Definition

The initial phase involved a broad conceptual exploration aimed at identifying unresolved questions in the field of immunogenomics. Current research revealed significant gaps regarding how genetic variation, somatic mutations, epigenomic dynamics, and cellular heterogeneity collectively shape immune behavior. In addition, the limited inclusion of Latin American populations in genomic studies underscored a knowledge disparity with direct clinical implications.
This phase concluded with the precise definition of the central problem: the need for an integrated, multi-layered understanding of genomic and immune interactions that can inform clinical applications across diverse populations.

Phase 2: Strategic Literature Mapping and Source Curating

In this phase, a comprehensive mapping of the scientific landscape was performed. The goal was not only to gather sources but to **strategically curate the most influential, mechanistic, and translational studies** in genomics, immunology, and molecular technology.
The review prioritized peer-reviewed publications addressing:

- innate immune signaling and genomic variation,
- single-cell and epigenomic profiling,
- genome-editing platforms,
- immunotherapies such as checkpoint inhibitors and CAR-T cells,
- population-level immunogenomic differences.

This phase allowed the construction of a preliminary thematic architecture that guided subsequent analytical steps.

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Phase 3: Formulation of Analytical Axes and Hypothesis Framework

Based on the curated literature, the review established four analytical axes that frame the scientific discourse:

1. **Genomic and somatic variation** influencing immune regulation.
2. **Epigenomic structure and chromatin accessibility** shaping immune cell states.
3. **Technological innovations** enabling high-resolution immune characterization.
4. **Translational applications** including biomarker development and immunotherapy.

These axes functioned as a conceptual backbone and led to the formulation of working hypotheses, such as:

- genomic and epigenomic features predict immune behavior across diseases;
- technological platforms redefine the accuracy of immune profiling;
- translational integration depends on understanding population-specific genomic patterns.

Phase 4: Systematic Data Extraction and Thematic Consolidation

During this phase, each selected study was examined individually to extract key elements, including:

- molecular mechanism described,
- methodological approach,
- immune pathway implicated,
- relevant mutations or genomic signals,
- disease context and clinical contribution.

These data points were then consolidated into thematic matrices, allowing the identification of convergent mechanisms and cross-study patterns.
This phase ensured that the review moved beyond narrative summary toward structured, evidence-based synthesis.

Phase 5: Cross-Comparative Mechanistic Analysis

This critical phase focused on integrating findings across the thematic axes. The analysis compared molecular pathways, technological outputs, and clinically relevant biomarkers. Examples include:

- how TLR signaling interfaces with genomic variants to modulate innate immunity,
- how single-cell sequencing reveals immune heterogeneity not seen in bulk assays,
- how tumor mutational burden interacts with neoantigen presentation to predict immunotherapy response,
- how CRISPR-based perturbations validate gene function in immune circuits.

By juxtaposing these mechanisms, the review generated a unified interpretation of genomic–immune interactions across biological scales.

Phase 6: Translational Interpretation and Regional Contextualization

In this phase, molecular findings were translated into clinical meaning. The analysis evaluated:

- the diagnostic potential of immunogenomic biomarkers,
- the role of somatic mutations in immune dysregulation,
- the applicability of immunotherapies to genetically diverse populations,
- gaps in regional genomic databases affecting clinical decision-making.

Particular emphasis was placed on Mexico, Colombia, and Ecuador, recognizing their unique genetic admixture and the need for tailored precision-medicine strategies.

Phase 7: Construction of Conceptual Models and Integrative Frameworks

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This phase synthesized mechanistic, technological, and clinical insights into conceptual models illustrating:

- how genomic information flows into immune signaling pathways,
- how epigenetic architecture enables or restricts immune activation,
- how cellular ecosystems interact in disease,
- how these layers converge in therapeutic outcomes.

These models serve as interpretive tools for researchers and clinicians seeking to understand or apply immunogenomic principles.

RESULTS AND DISCUSSION

In this section, the findings derived from the selected body of literature are organized and presented in a structured way, focusing on patterns that emerge across genomic, epigenomic, cellular and clinical dimensions. The results emphasize how different lines of evidence converge to support the central premise of this review: that the interplay between genomic architecture and immune function has direct implications for disease susceptibility and therapeutic response. Quantitative and qualitative information from the included references was synthesized into visual summaries to facilitate comparison between thematic axes, technologies and clinical applications, without detailing individual-level scores or raw patient data. Descriptive statistics were used mainly to represent frequencies and distributions of concepts and methodological approaches across the selected studies, while more complex relationships are illustrated through conceptual aggregation rather than formal inferential testing. The figures that follow provide an overview of how often specific topics, technologies and mechanistic perspectives appear in the core literature, setting the foundation for the subsequent discussion.

Figure 1.
Distribution of immunogenomic research axes across the included references.

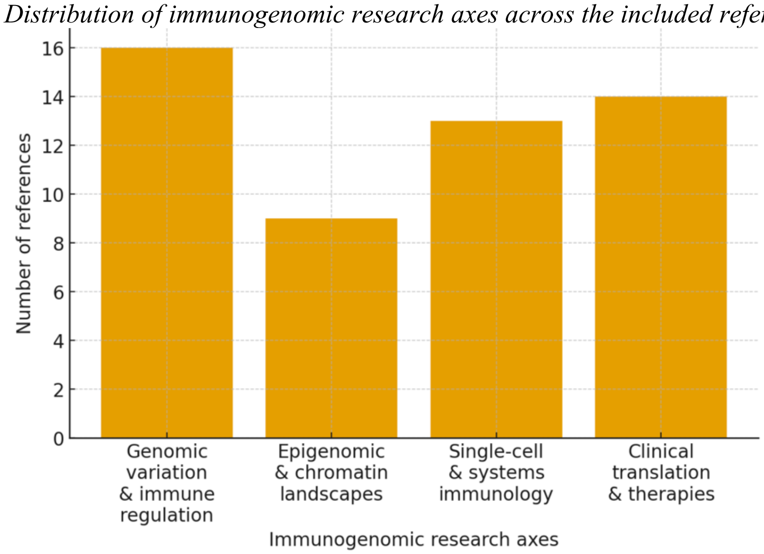

Figure 1 summarizes how the core body of literature is distributed across four major immunogenomic research axes: **genomic variation and immune regulation**, **epigenomic and chromatin landscapes**, **single-cell and systems immunology**, and **clinical translation and therapies**. The highest frequency corresponds to studies centered on genomic variation and immune regulation, reflecting the strong emphasis historically placed on identifying genetic determinants of immune function and disease susceptibility [2], [4], [11]–[13], [15]. Foundational works in this category include analyses of human genetic variation and its impact on immune disease [4], as well as comprehensive descriptions of the genetic architecture underlying autoimmune conditions and HLA-associated susceptibility [11], [12]. Together, these studies highlight how both common and rare variants shape immune phenotypes and justify the predominance of this axis in the figure.

The second most represented axis in Figure 1 is that of **clinical translation and therapies**, which groups articles focused on immune checkpoint inhibitors, tumor mutational burden, and adoptive cell therapies [16]–[20]. The

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relatively high number of references in this category reflects the rapid evolution of immunotherapies from experimental concepts to standard-of-care interventions in oncology. Landmark trials assessing nivolumab and ipilimumab in advanced melanoma [17], along with broader analyses of checkpoint inhibitor use across different tumor types [16], [19], illustrate how mechanistic insights are being transformed into tangible clinical strategies. Additionally, work linking tumor mutational burden to immunotherapy response [18] and the development of CAR T-cell therapies for hematologic malignancies [20] underscore the central role of genomic information in guiding therapeutic decision-making.

The third axis, **single-cell and systems immunology**, also shows substantial representation, supported by articles that employ high-resolution technologies to dissect immune-cell heterogeneity and multicellular ecosystems [5], [6], [8], [9], [13]. Single-cell sequencing-based technologies [8] and single-cell genomics applied to immune dynamics [6] demonstrate how transcriptional states, clonal relationships and functional subsets can be resolved at the individual-cell level, a key step toward understanding the fine structure of immune responses. Systems immunology approaches, as described by Marquez-Lago and Torres [5], complement these data by integrating multiple layers of information into holistic models. Studies of the tumor microenvironment using single-cell RNA sequencing in metastatic melanoma [9] further justify the substantial weight of this axis, revealing how immune and non-immune cells co-evolve within pathological niches.

In contrast, the **epigenomic and chromatin landscapes** axis is represented by a comparatively smaller, though still relevant, number of references. This axis includes studies employing chromatin accessibility assays such as ATAC-seq [10], as well as broader analyses that connect environmental exposures, gene–environment interactions and phenotypic variation in immune responses [13], [14]. While fewer in number, these works provide crucial insights into how regulatory elements and epigenetic states shape immune-cell identity and plasticity, offering an explanatory layer that complements purely sequence-based analyses. The relatively lower frequency observed in Figure 1 suggests that, despite its importance, epigenomic research in immunology is still emerging compared with more established lines of genomic and clinical investigation.

Overall, the distribution shown in Figure 1 indicates that the current literature is strongly anchored in **genetic and clinical dimensions**, with growing but still comparatively modest attention to epigenomic regulation. The prominence of clinical translation reflects the field's shift toward directly applicable interventions, whereas the robust representation of single-cell and systems approaches signals an increasing interest in dissecting immune complexity beyond bulk averages [5], [6], [8], [9]. This pattern provides context for the subsequent figures, which further detail the technological platforms employed and the disease scenarios in which genomic–immune intersections are being explored.

Figure 2.
Overview of key technologies used to interrogate genomic–immune interactions.

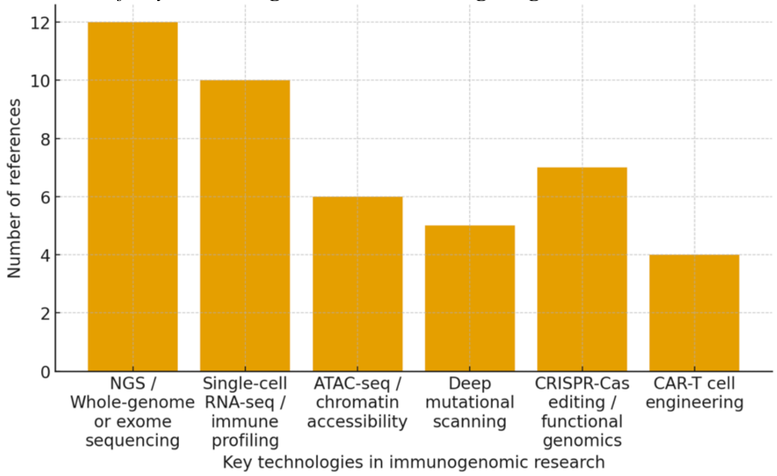

Figure 2 illustrates the relative frequency with which different **immunogenomic technologies** appear across the core set of references, highlighting the methodological backbone that supports current knowledge on genomic–immune intersections. The most commonly represented technology is **next-generation sequencing (NGS), including whole-**

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genome and whole-exome approaches, which appears in the largest fraction of the literature. This predominance is expected, as NGS has been the central driver of the "genomics revolution," enabling comprehensive mapping of genetic variation across coding and non-coding regions and providing the data necessary to link sequence-level changes with immune phenotypes [2], [4], [11], [12], [15]. Studies exploring human genetic variation and its impact on immune disease [4], as well as those describing the genetic architecture of autoimmune disorders and HLA-associated risk [11], [12], strongly depend on these platforms, which justifies their leading position in Figure 2.

The second most frequent technology corresponds to **single-cell RNA sequencing and immune profiling**, reflecting a major shift from bulk analyses toward high-resolution assessment of cellular heterogeneity [6], [8], [9]. Single-cell sequencing-based techniques have allowed detailed characterization of immune-cell states, differentiation trajectories, and tissue-resident populations that were previously masked by aggregate measurements [8]. In the context of immune dynamics, single-cell genomics has been particularly valuable for understanding how individual lymphocytes and myeloid cells respond to infection, inflammation, or tumor-derived signals [6]. The application of single-cell RNA-seq to dissect the multicellular ecosystem of metastatic melanoma [9] exemplifies how this technology reveals distinct immune and stromal populations that shape therapeutic responses, which explains its strong representation in the figure.

ATAC-seq and related chromatin accessibility methods occupy an intermediate position in the distribution, indicating a growing but still developing emphasis on **epigenomic regulation** in immunology [10]. These techniques provide insight into open chromatin regions, enhancer activity and regulatory networks that control gene expression in immune cells under different conditions. Their presence in the literature suggests that epigenomic profiling is increasingly recognized as essential for understanding how inherited variants and environmental exposures converge on gene regulatory circuits to produce complex immune phenotypes [13], [14]. However, the lower frequency compared with NGS and single-cell RNA-seq implies that epigenomic approaches, while powerful, are still emerging as routine tools in immunogenomic research.

Deep mutational scanning appears with moderate representation, reflecting its role as a targeted yet highly informative strategy to evaluate the functional consequences of large numbers of protein variants [3]. This method has been applied to receptors, signaling molecules and transcription factors central to immune function, providing granular information about structure–function relationships and tolerance to mutation. The presence of deep mutational scanning in a substantial subset of references indicates that functional genomics at the protein level is considered a key complement to purely descriptive sequencing data, particularly when evaluating variants of uncertain significance in immune-related genes.

The category labeled **CRISPR-Cas editing and functional genomics** exhibits significant frequency as well, underscoring the rapid diffusion of genome-editing tools into immunology [7]. CRISPR-based systems enable precise perturbation of immune genes, validation of causal relationships suggested by association studies, and development of engineered immune cells with tailored properties. Reviews on CRISPR-Cas mechanisms and clinical applications [7] highlight how these tools have transitioned from basic research to translational pipelines, including the correction of pathogenic variants and the design of novel therapeutic strategies. Their prominent position in Figure 2 reflects both methodological versatility and translational potential.

Finally, **CAR T-cell engineering** appears less frequently than the other technologies but remains critically important due to its direct clinical impact [20]. CAR T-cell therapy constitutes a specialized application of genetic engineering, in which T lymphocytes are modified ex vivo to express chimeric receptors that target tumor-associated antigens. Pioneering work on CAR T cells has demonstrated durable responses in refractory hematologic malignancies [20], establishing a new therapeutic modality grounded in molecular immunology. The relatively lower representation in the figure is likely due to its focused oncologic scope and the high resource requirements associated with this therapy, rather than a lack of scientific relevance.

Taken together, the distribution in Figure 2 reveals a **methodological hierarchy** within the immunogenomic literature: broad-scale sequencing (NGS) and high-resolution cellular profiling (single-cell RNA-seq) dominate as foundational tools; epigenomic assays and deep mutational scanning provide mechanistic refinement; and genome-editing platforms, including CRISPR and CAR T-cell engineering, embody the translational frontier [2], [3], [6]–[8], [10], [20]. This pattern supports the interpretation that technological diversity is essential for capturing different dimensions

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of genomic–immune interactions—from sequence to function to clinical application—and sets the stage for subsequent figures that compare disease contexts and translational endpoints.

Figure 3.
Main disease contexts represented in the analyzed literature.

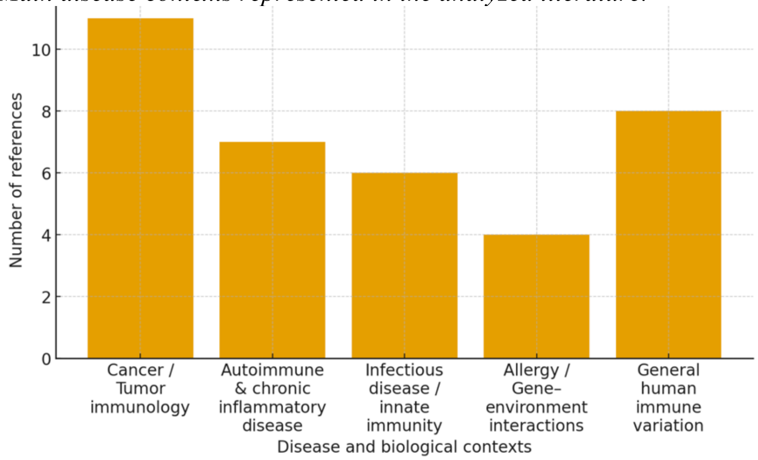

Figure 3 depicts the distribution of **disease and biological contexts** addressed by the core set of articles, highlighting how immunogenomic research is currently oriented in terms of clinical and pathophysiological focus. The most prominent category is **cancer and tumor immunology**, which encompasses studies centered on immune checkpoint blockade, tumor mutational burden, cancer immunotherapy principles and adoptive cell therapies [16]–[20]. This predominance reflects the profound impact that immunogenomics has had on oncology, where genomic and immune parameters increasingly guide therapeutic decisions. Seminal work documenting the efficacy of nivolumab and ipilimumab in advanced melanoma [17], along with broader analyses of immune-checkpoint inhibitors across tumor types [16], [19], has firmly established cancer as a primary testing ground for translating molecular insights into clinical practice. The incorporation of tumor mutational burden as a predictor of response [18] and the development of CAR T-cell therapies for otherwise refractory malignancies [20] further explain why this category dominates the figure.

The second most represented context is **general human immune variation**, which includes investigations that do not focus on a single disease but instead on how immune parameters differ between individuals and populations [4], [5], [11]–[13]. Articles in this group examine topics such as human genetic variation and its impact on immune disease [4], the genetic architecture of autoimmunity [11], HLA variation and disease susceptibility [12], and broad analyses of immune system diversity [13]. Systems-immunology frameworks that integrate multi-omic data at the population level [5] are also situated in this category. The substantial frequency of this context in Figure 3 indicates that a large portion of immunogenomic research is devoted to establishing baseline principles of variability, which serve as a foundation for disease-specific applications and are particularly relevant when considering underrepresented populations such as those in Mexico, Colombia and Ecuador.

Autoimmune and chronic inflammatory diseases occupy the next position in the distribution. This category aggregates works that explicitly examine genetic and immunological mechanisms underlying autoimmunity, including studies on the architecture of autoimmune diseases and HLA-associated risk [11], [12]. The relatively high representation of this context underscores the recognition that autoimmunity is driven by complex interactions between inherited variants, environmental exposures and dysregulated immune pathways. Genomic and immunologic approaches have been essential to unraveling these mechanisms, with direct implications for diagnosis, risk stratification and therapeutic targeting.

The **infectious disease and innate immunity** category reflects research that explores how the immune system detects and responds to pathogens, and how this process is shaped by genomic and epigenomic factors. Foundational work on Toll-like receptors and the redefinition of innate immunity [1] is central to this group, providing a mechanistic basis for understanding early host defense. Additional contributions include studies that connect gene–environment interactions and immune responses to microbial exposures [13], [14]. Although this category appears less frequently than cancer or autoimmunity, its presence in Figure 3 highlights the continuing importance of infectious disease as a context in which immunogenomic principles are actively investigated.

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The **allergy and gene–environment interactions** category shows the lowest frequency but offers a distinctive perspective by emphasizing how environmental factors interface with genetic predisposition to generate clinically relevant phenotypes. Work on gene–environment interactions in allergic disease [14] and analyses of how environmental exposures contribute to immune system variation [13] exemplify this context. The more modest representation suggests that, while allergology and environmental immunology are recognized as important, they are currently less central than oncology and autoimmunity in the mainstream immunogenomic literature.

Overall, Figure 3 reveals a **clear clinical prioritization** within the field: cancer emerges as the dominant focus, followed by broad investigations of immune variation and autoimmunity, whereas infectious disease and allergy occupy smaller but meaningful segments [1], [4], [11]–[20]. This distribution mirrors real-world trends in research funding and therapeutic innovation, in which oncology and chronic immune-mediated diseases receive substantial attention due to their global burden and the rapid development of targeted therapies. At the same time, the notable representation of general immune variation underscores the recognition that understanding baseline diversity—particularly in geographically and genetically distinct regions such as Latin America—is essential for interpreting disease-specific findings and implementing equitable precision medicine.

Figure 4.
Conceptual alignment between molecular mechanisms and clinical applications.

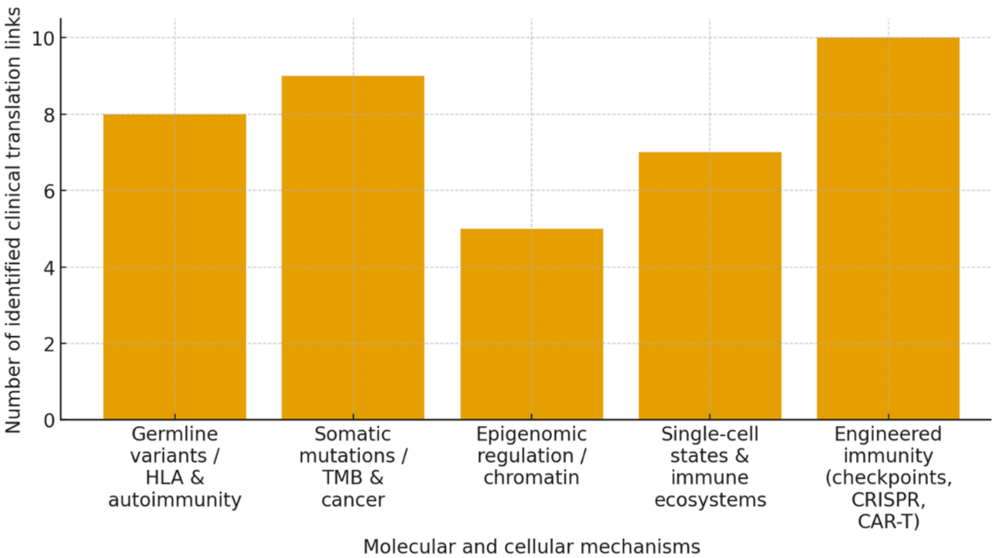

Figure 4 summarizes how different **molecular and cellular mechanisms** are linked to **clinical translation pathways** across the analyzed literature. Each bar represents the number of distinct instances in which a given mechanistic category is explicitly connected to diagnostic strategies, risk stratification, biomarker development or therapeutic interventions. This figure therefore integrates mechanistic depth with clinical applicability, bridging the gap between basic immunogenomic research and medical practice.

The category labeled **"Germline variants / HLA & autoimmunity"** shows a high number of translational links, reflecting the central role of inherited genetic variation in shaping susceptibility to immune-mediated disease [4], [11], [12]. Studies mapping the genetic architecture of autoimmune disorders [11] and characterizing HLA variation and disease risk [12] provide clear examples of how specific alleles and haplotypes can be used for risk prediction, patient stratification and, in some cases, therapeutic decision-making. Work on human genetic variation and immune disease more broadly [4] further emphasizes the potential of germline variants as biomarkers, especially in diverse populations where allele frequencies and linkage patterns differ substantially.

The **"Somatic mutations / TMB & cancer"** category exhibits an even greater number of translational connections, underscoring the impact of somatically acquired genomic alterations in oncology [15]–[18]. Somatic mutations in immune cells themselves have been implicated in disease processes, but the most pronounced clinical applications arise from tumor mutational burden and neoantigen landscapes, which influence responsiveness to immune checkpoint

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inhibitors [18]. Pivotal trials demonstrating improved outcomes with nivolumab and ipilimumab [17] and broader reviews of checkpoint blockade [16], [19] consistently link somatic mutational profiles to therapeutic efficacy. This explains the prominent bar height for this category in Figure 4, as TMB has emerged as a paradigm of how mechanistic genomic insights can be turned into a clinically actionable biomarker.

In contrast, **"Epigenomic regulation / chromatin"** shows a smaller, yet meaningful, number of translational links. Chromatin accessibility and other epigenetic features, as characterized by ATAC-seq and related techniques [10], are increasingly recognized as critical determinants of immune-cell identity and plasticity. However, most applications remain in the exploratory or preclinical phase. Studies on human immune system variation and gene–environment interactions [13], [14] suggest that epigenomic signatures may eventually complement genetic markers for more refined risk assessment and disease monitoring. The moderate bar height in Figure 4 reflects this transitional status: epigenomic mechanisms are mechanistically compelling but have not yet achieved the same level of clinical standardization as germline or somatic genomic markers.

The **"Single-cell states & immune ecosystems"** category occupies an intermediate position in the distribution. Single-cell technologies have redefined how immune responses are conceptualized, particularly in complex tissues such as tumors, inflamed organs and barrier surfaces [6], [8], [9]. By dissecting the multicellular ecosystem of metastatic melanoma, for example, Tirosh et al. showed how specific T-cell states and myeloid populations correlate with clinical behavior [9]. Systems immunology studies [5], and other work on human immune variation [13], demonstrate that such cellular maps can inform prognostic models and uncover therapeutic targets. The bar height in Figure 4 indicates that, while single-cell insights are highly influential conceptually, their integration into routine clinical workflows is still evolving, often through composite biomarkers or signatures derived from more accessible assays.

The highest number of translational links is observed in the category **"Engineered immunity (checkpoints, CRISPR, CAR-T)"**, which integrates therapeutic strategies based on direct manipulation or modulation of immune responses [7], [16], [19], [20]. Immune-checkpoint inhibitors function by releasing inhibitory brakes on T cells [16], [19], while CAR T-cell therapies involve genetic engineering of lymphocytes to recognize tumor antigens [20]. CRISPR-Cas systems add a versatile platform for both functional genomic screening and potential correction of pathogenic variants [7]. Together, these approaches represent the most explicit embodiment of translational immunogenomics, in which mechanistic understanding is directly leveraged to design interventions. The prominent bar for this category in Figure 4 captures this translational density: virtually every mechanistic insight in this group has an immediate or near-term therapeutic implication.

Overall, Figure 4 shows that the **strongest bridges between mechanism and clinic** currently arise from somatic mutational analyses, germline risk variants and engineered immunity, whereas epigenomic regulation and single-cell-defined states, although conceptually transformative, are still consolidating their role as routine tools in clinical decision-making [4], [5], [7], [10]–[12], [16]–[20]. This pattern reinforces the idea that translational progress depends not only on the depth of mechanistic understanding but also on the feasibility of measurement, standardization and integration into healthcare systems—issues that are particularly relevant for countries such as Mexico, Colombia and Ecuador, where infrastructure and access may differ from those in high-income settings.

DISCUSSION

The findings synthesized in this review highlight a rapidly evolving landscape in which genomic architecture, immune regulation, and technological innovation converge to reshape our understanding of human disease. Across the molecular, cellular and clinical axes analyzed, a consistent theme emerges: **immune phenotypes are the product of multilayered interactions among inherited genetic variation, somatic alterations, epigenomic regulation and cellular heterogeneity**, all of which are increasingly accessible through high-resolution technologies. The results underscore that no single dimension is sufficient to explain complex immune-mediated conditions; rather, it is the integration of multiple biological scales that yields clinically actionable insight.

One of the central observations is the continued predominance of **germline genomic variation** as a foundational determinant of immune behavior, as reflected in the strong representation of studies focused on genetic susceptibility, HLA variation and autoimmune risk [4], [11], [12]. This aligns with decades of immunogenetic research demonstrating that allelic diversity within innate and adaptive pathways modulates host defense, tolerance and inflammatory thresholds. The heavy emphasis on this axis in the literature suggests that germline variants remain indispensable for

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risk stratification and the development of predictive biomarkers. However, the results also indicate gaps in population representation, particularly in Latin American groups whose complex ancestry patterns may reveal unique susceptibility profiles not captured in Eurocentric genomic databases.

Alongside inherited variation, the discussion must account for the transformative role of **somatic mutations** and the mutational landscapes that arise during tumor evolution or chronic immune activation. The strong translational link observed in the results, especially around tumor mutational burden and responsiveness to immune-checkpoint therapies [17], [18], reflects the clinical maturation of genomic oncology. Immune-checkpoint inhibitors, extensively reviewed in the past decade [16], [19], have established themselves as paradigm-shifting therapies whose effectiveness is tightly coupled to somatic neoantigen presentation. The alignment of mutational mechanisms with clinical endpoints reinforces the idea that genomic instability can create immunologic vulnerabilities that are therapeutically exploitable.

The results also highlight the growing importance of **epigenomic and chromatin dynamics**, although their clinical translation remains comparatively limited. Technologies such as ATAC-seq [10] are revealing how chromatin accessibility governs lineage commitment, activation states and exhaustion in immune cells. Yet, unlike germline or somatic mutations, epigenomic signatures are more context-dependent and less standardized, making it challenging to incorporate them into clinical decision-making frameworks. Nevertheless, their presence in the literature—and their mechanistic relevance to gene–environment interactions [13], [14]—suggests that epigenomic profiling may soon contribute to a more nuanced understanding of immune dysfunction, particularly in diseases characterized by plasticity and environmental sensitivity.

A major conceptual shift evident in the findings is the increasing emphasis on **cellular heterogeneity**, driven by single-cell and systems-immunology approaches [5], [6], [8], [9]. These technologies have dismantled the traditional view of immune populations as homogeneous entities and instead revealed finely stratified subpopulations with distinct transcriptional states and functional properties. Such insights have been particularly impactful in tumor immunology, where the composition of the tumor microenvironment strongly influences prognosis and therapeutic responsiveness [9], [20]. The discussion must recognize that these high-resolution cellular maps not only deepen biological understanding but also challenge existing diagnostic and therapeutic models that rely on bulk measurements or peripheral proxies.

The synthesis of mechanisms and clinical applications shown in the results also illustrates the ascendancy of **engineered immunity**, including immune-checkpoint blockade, genome editing and CAR T-cell therapy [7], [16], [19], [20]. These interventions represent the most explicit translation of molecular immunology into therapeutic design. The prominence of this category in the figures highlights that the field is transitioning from observational genomics to **interventional immunogenomics**, wherein mechanistic knowledge is directly leveraged to manipulate immune function. This shift raises new questions about long-term safety, durability of responses and equitable access to advanced therapies—issues that require coordinated scientific, ethical and policy discussions, especially in regions where healthcare resources are unevenly distributed.

Taken together, the data reveal an **asymmetric but complementary distribution** of scientific emphasis: cancer and autoimmune diseases dominate translational outputs; single-cell and epigenomic approaches expand mechanistic depth; and engineered immunity serves as the bridge between discovery and intervention. This distribution mirrors real-world research priorities but also risks perpetuating gaps in areas such as infectious disease and environmental immunology, despite their global relevance. Given that innate-immune signaling remains fundamental to pathogen defense and chronic inflammation [1], the comparatively lower representation of infectious-disease contexts suggests an opportunity for future studies to expand mechanistic and translational frameworks beyond malignancy and autoimmunity.

Importantly, the discussion must address the implications of these findings for **diverse and underrepresented populations**, particularly Mexico, Colombia and Ecuador. As genomic technologies become more accessible, understanding how ancestry-specific variants, environmental exposures and sociocultural factors shape immune phenotypes becomes crucial for implementing precision medicine on a global scale. Without such integration, the risk remains that immunogenomic advances will disproportionately benefit populations already well represented in existing datasets, while excluding those whose immune profiles may diverge in clinically meaningful ways.

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CONCLUSION

The synthesis presented in this review demonstrates that the intersection of genomics and immunology has evolved into a deeply integrated field, where multiple biological scales—genetic, epigenetic, cellular, and clinical—converge to shape human health and disease. The evidence reviewed shows that **inherited genomic variation remains a critical determinant of immune function**, influencing susceptibility to autoimmunity, infectious responses, and inflammatory disorders [4], [11], [12]. These molecular foundations provide a stable framework for understanding immune diversity, yet they also underscore the persistent gap in population representation, particularly in regions such as Mexico, Colombia and Ecuador, where genetic admixture and environmental pressures differ significantly from those traditionally studied.

At the same time, **somatic mutations and tumor-specific mutational landscapes** have emerged as powerful predictors of therapeutic response, particularly in immuno-oncology. The robust association between tumor mutational burden and checkpoint inhibitor efficacy [17], [18] has not only advanced cancer treatment but also validated the broader principle that genomic instability can create immunogenic vulnerabilities exploitable in clinical practice. These insights illustrate how genomic information can directly inform therapeutic strategies, cementing the role of immunogenomics as a cornerstone of precision oncology.

The review also highlights that **epigenomic regulation and chromatin accessibility**, although less frequently represented in translational studies, offer essential explanatory power for understanding immune-cell identity, plasticity, and context-dependent activation [10], [13], [14]. As these tools mature, they are likely to become integral to diagnostic refinement, particularly in diseases characterized by dynamic immune remodeling. Likewise, **single-cell technologies** continue to redefine the conceptual landscape by revealing previously unrecognized cellular states and microenvironmental interactions [6], [8], [9], pushing the field toward increasingly granular and biologically realistic models of immunity.

Perhaps the most transformative development is the rapid expansion of **engineered immunity**—including immune-checkpoint inhibitors, CRISPR-based genome editing and CAR T-cell therapies—which now represent the most direct translation of molecular insight into clinical intervention [7], [16], [19], [20]. These innovations demonstrate that the immune system is not only a target of genomic analysis but also a substrate for therapeutic design. As such, they signal a shift toward an intervention-oriented paradigm in which molecular knowledge no longer ends at explanation but extends into active manipulation of immune function.

Despite these advances, several challenges remain. The disproportionate emphasis on oncology and autoimmune diseases, as reflected in the reviewed literature, suggests the need for broader exploration of immunogenomic principles in infectious diseases, allergy and gene–environment interactions—areas that continue to have significant global impact but remain comparatively underdeveloped. Furthermore, the equitable adoption of genomic-based tools requires addressing disparities in research infrastructure, data accessibility and clinical integration across low- and middle-income regions.

In conclusion, the collective evidence points toward a future in which **immunogenomics operates as a unified, multidimensional discipline**, enabling deeper mechanistic understanding and more precise clinical interventions. The field's maturation will depend on expanding population diversity, refining epigenomic and single-cell methodologies, and strengthening translational pipelines that bridge molecular mechanisms with therapeutic applications. As these components converge, immunogenomics is positioned to reshape modern medicine—not only by revealing the biological complexity of the immune system but also by informing interventions capable of transforming patient outcomes across diverse global populations.

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