Evolutionary and Population-Aware AI Models for Characterizing Global Diversity of Polymorphic Immune Genes Across Human Populations

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Abstract

Polymorphic immune genes, particularly the human leukocyte antigen system, exhibit extraordinary diversity across global human populations, shaped by millions of years of evolutionary pressure from pathogens, environmental factors, and demographic history. This diversity underpins critical differences in disease susceptibility, vaccine response, and transplantation compatibility, yet existing computational approaches for characterizing these genes are largely built on datasets dominated by individuals of European ancestry and fail to incorporate population structure or evolutionary dynamics. This paper presents a system-level examination of evolutionary and population-aware artificial intelligence models designed to characterize global diversity of polymorphic immune genes across human populations. We propose that such models must integrate principles from population genetics, evolutionary biology, and scalable machine learning architectures to produce robust, generalizable, and equitable typings. The discussion focuses on structural trade-offs in model design, data governance frameworks, computational infrastructure requirements, deployment strategies across diverse settings, sustainability of large-scale inference pipelines, fairness considerations in training and validation, and the policy implications for global genomic equity. We illustrate how explicit encoding of demographic histories and selective sweeps into model representations can reduce bias while improving predictive accuracy for underrepresented populations. The paper further examines the challenges of harmonizing heterogeneous long-read and short-read sequencing data across thousands of samples, the necessity of privacy-preserving architectures for sensitive genetic information, and the broader socio-technical infrastructure needed to support continuous learning from emerging population-level data. A case illustration based on the scalable framework for comprehensive typing from long-read data is used to contextualize these architectural decisions. The paper concludes by outlining a roadmap for future research that aligns technological development with ethical imperatives and global health priorities.

Keywords

evolutionary artificial intelligence, population genomics, immune gene diversity, large-scale systems, data governance, algorithmic fairness, genomic infrastructure.

1. Introduction

The immune system is the most genetically variable component of the human genome, and its polymorphic genes, especially those within the major histocompatibility complex, have been shaped by a long history of coevolution with pathogens, population migrations, and natural selection [1,2]. This variation is not merely a biological curiosity; it directly affects clinical outcomes ranging from autoimmune disease risk to the success of organ transplantation and the efficacy of vaccines across different ethnic groups [3,4]. Despite the profound medical and evolutionary significance of this diversity, the computational tools used to characterize immune gene variation are often trained and validated on datasets that are geographically and ancestrally narrow, leading to systematic errors and reduced accuracy when applied to non-European populations [5,6]. The challenge is compounded by the extreme polymorphism of these regions, which include multigene families with high sequence similarity, structural variation, and rapid evolution, making traditional alignment-based methods brittle and resource-intensive.

Recent advances in artificial intelligence, particularly deep learning and representation learning, have opened new possibilities for capturing complex patterns in genomic data that are not easily captured by linear models [7,8]. However, applying these techniques to immune gene diversity demands more than simply scaling up existing architectures. It requires a fundamental rethinking of how models incorporate population structure, evolutionary history, and selective constraints as explicit components of the learning process. Without such awareness, AI models risk memorizing population-specific biases and failing to generalize across the full spectrum of human genetic diversity [9,10]. This paper addresses this gap by offering a system-level analysis of evolutionary and population-aware AI frameworks designed to characterize polymorphic immune genes globally. We examine the architectural choices, data governance challenges, deployment trade-offs, and fairness implications that arise when such systems are built and operated at scale. The analysis is informed by recent developments in long-read sequencing technologies, which provide the resolution necessary to resolve complex immune loci but also introduce new computational and infrastructural burdens [11].

2. The Biological and Evolutionary Context of Immune Gene Polymorphism

Polymorphic immune genes, particularly those encoding HLA class I and class II molecules, are among the most diverse regions of the human genome, with over thirty thousand known alleles catalogued to date [12]. This diversity is maintained by balancing selection, which favors rare alleles that confer protection against novel pathogens, and by frequency-dependent selection, which prevents any single allele from dominating a population [3]. Additionally, demographic events such as bottlenecks, founder effects, and admixture have produced distinct allelic frequency distributions across geographic regions, creating a mosaic of population-specific haplotypes that remain poorly characterized in many parts of the world [1,2]. The functional implications of this diversity are profound: certain alleles are strongly associated with autoimmune disorders, while others provide robust protection against infectious diseases such as HIV, malaria, and tuberculosis [4]. Understanding this variation at a global scale is therefore not only a matter of basic evolutionary biology but also a prerequisite for equitable precision medicine.

Traditional computational methods for typing immune genes, such as sequence alignment to reference databases and imputation from genotyping arrays, were developed when sequencing costs were high and diversity data were scarce. These methods assume that the reference genome and its associated allele catalog are broadly representative, which is increasingly known to be false [5,6]. For example, populations in sub-Saharan Africa and Oceania carry many alleles that are absent from major reference databases, leading to high rates of failed or erroneous typing when standard pipelines are applied. Moreover, the structural complexity of immune gene regions, which include duplications, deletions, and inversions, is poorly captured by short-read sequencing, and long-read technologies are only now beginning to provide the contiguous assemblies needed for accurate characterization [11]. This biological and technical complexity demands computational models that are not only accurate but also capable of adapting to new diversity as it is discovered, a requirement that aligns naturally with AI approaches that support continual learning and representation updating.

3. Evolutionary and Population-Aware AI Model Architecture

Designing AI models that genuinely capture global immune gene diversity requires moving beyond generic sequence classification architectures toward frameworks that embed population structure and evolutionary dynamics into the model itself. At the core of such an architecture is the idea that allele frequencies, haplotype phase, and linkage disequilibrium patterns are not noise to be removed but signals that contain information about demographic history and selective pressures [1,2]. A population-aware model might include an explicit encodings of population ancestry, perhaps inferred from principal components or admixture coefficients, as input features or as conditioning variables in a generative framework. Alternatively, hierarchical Bayesian methods can model the allele distribution in each population as a mixture of latent components that capture shared and lineage-specific variation [8]. The key architectural trade-off here is between flexibility and computational tractability: fully nonparametric approaches can capture complex population structures but are difficult to scale to thousands of populations and millions of sequences, while simpler linear mixtures risk oversmoothing rare but clinically important variants.

Another critical design choice concerns the representation of the immune gene sequence itself. Traditional one-hot encodings or k-mer frequency vectors ignore the spatial structure of B-cell and T-cell epitopes, which determine functional immune recognition [7]. More recent approaches use convolutional neural networks or attention-based transformers to learn position-specific determinants of binding and presentation, but these models require large, well-labeled training datasets that are heavily biased toward common alleles [5,6]. For rare or population-specific alleles, transfer learning from related species or synthetic data generation based on evolutionary models could provide a remedy, though such approaches introduce additional uncertainties about the validity of extrapolation [8]. A population-aware architecture might therefore include a modular design where a core sequence encoder is shared across all populations, while population-specific adapter layers or fine-tuning modules learn local deviations from the global norm. This modularity supports sustainability by allowing the base model to be updated as new global data become available, while preserving specialized knowledge for each group.

4. Data Infrastructure and Governance for Global Immune Gene Datasets

The operationalization of population-aware immune gene AI models depends critically on the availability of diverse, high-quality, and well-annotated datasets. Long-read sequencing technologies, which can span entire immune gene regions with a single contiguous read, are

rapidly becoming the gold standard for comprehensive typing, but their adoption is uneven across the globe due to cost, infrastructure, and logistical barriers [11]. Building a truly global data infrastructure will require coordinated efforts across sequencing centers, consortia, and national biobanks, each of which operates under different regulatory and ethical frameworks [9,10]. Data governance must address questions of consent, data sovereignty, benefit sharing, and privacy, particularly when working with indigenous populations or historically marginalized communities whose genetic data have been used without adequate protections. The FAIR principles—findability, accessibility, interoperability, and reusability—provide a starting point, but they must be adapted to the specific sensitivities of immune genetic information, which can be used to infer disease risk and ancestry with high precision [13].

Infrastructure for such a system must also support continuous integration of new data as sequencing becomes cheaper and more widespread. This requires building data pipelines that can automate quality control, harmonize allele nomenclature across different reference databases, and update model parameters without requiring full retraining on the entire dataset. Cloud-based architectures with containerized workflows and orchestrated microservices are well-suited to this task, but they introduce concerns about vendor lock-in, data locality, and latency for researchers in low-resource settings [14]. Federated learning offers a promising alternative, allowing models to be trained across multiple sites without centralizing sensitive sequence data, though it requires careful management of statistical heterogeneity across populations and may reduce model accuracy for rare variants if not carefully tuned [9]. The tension between global model accuracy and local data sovereignty is one of the central governance challenges for this field.

5. Deployment, Scalability, and Sustainability

Deploying population-aware AI models for immune gene typing at a global scale presents engineering challenges that go beyond conventional machine learning systems. The inference pipelines must handle terabytes of long-read or short-read data from diverse platforms, each with different error profiles and base-calling algorithms [11]. Real-time clinical applications, such as rapid HLA typing for transplant matching, impose latency constraints that are difficult to reconcile with computationally expensive deep learning models. One potential solution is to use a tiered architecture where a lightweight classifier performs initial typing on high-confidence regions, and a more complex model refines results for ambiguous or low-coverage loci. This trade-off between speed and accuracy must be evaluated not only in terms of mean performance but also in terms of fairness across populations: if the lightweight model is tuned on common alleles, it may systematically misclassify rare variants, worsening healthcare disparities [15].

Sustainability is another crucial dimension. Training large transformer-based models on genomic data consumes substantial energy, and the carbon footprint of such systems can be significant if deployed across multiple geographic regions with high computational demands [16]. Furthermore, the models must be adapted to local computing environments, which may range from cloud clusters with GPU accelerators to edge devices with limited memory and processing power. A sustainable deployment strategy would involve model compression techniques such as quantization, knowledge distillation, and pruning, applied with careful attention to any resulting loss of accuracy for underrepresented populations. Additionally, the system should incorporate monitoring and alerting mechanisms to detect concept drift when new population data challenge previously learned patterns, triggering retraining cycles that are scheduled to minimize disruption and cost.

6. Robustness, Fairness, and Ethical Considerations

Fairness in immune gene AI models is not simply a matter of statistical parity across populations; it requires that the model performs equally well in predicting clinically relevant outcomes for all groups, even when the data available for some groups are sparse [9,10]. Bias can enter at multiple points: in the training data, which may sample certain populations more extensively; in the label assignment, where reference databases may systematically miss population-specific alleles; and in the evaluation metrics, which may prioritize overall accuracy over subgroup performance. A population-aware model must therefore include explicit fairness constraints, such as group-conditional performance bounds, and must be evaluated using diverse validation sets that reflect true global diversity rather than convenience sampling [17]. This is particularly important for immune genes, where misclassification can lead to erroneous genetic counseling, incompatible transplants, or ineffective vaccine design.

Robustness to distributional shifts is another critical requirement. When a model trained on one set of populations is applied to a new, unseen population, its predictions may degrade unpredictably if the evolutionary processes that shape allele frequencies in that population are not captured in the training data [2,6]. Techniques from domain adaptation and causal inference, such as invariant risk minimization, can help learn representations that are stable across populations, but these methods require auxiliary information about the underlying causal structure, which is often unknown. A more practical approach is to maintain a living model that continuously integrates new data and updates its population-specific parameters, supported by a governance framework that incentivizes data-sharing and ensures that contributions from historically underrepresented groups are recognized and rewarded [15].

7. Policy Implications and Global Governance

The deployment of population-aware AI for immune gene characterization raises significant policy questions concerning data sovereignty, intellectual property, and equitable access to the benefits of genomic research. Many high-throughput sequencing datasets originate from well-funded consortia in high-income countries, while the populations with the greatest genetic diversity—in Africa, Asia, and the Pacific Islands—remain understudied [1,4]. Without deliberate policy interventions, AI models will continue to reflect the biases of their training data, reinforcing existing disparities in medical knowledge and healthcare delivery. International frameworks such as the Global Alliance for Genomics and Health provide principles for responsible data sharing, but they lack enforcement mechanisms and are often not aligned with national regulations on genetic data [13]. Policymakers must therefore engage with researchers and communities to establish binding agreements that ensure that models trained on global data do not disproportionately benefit any single region or corporation.

Additionally, the computational infrastructure needed to support these models may create dependencies on cloud providers and proprietary software, raising concerns about digital sovereignty for low- and middle-income countries. Investments in open-source toolkits, interoperable formats, and portable model formats can help mitigate this risk, but they require sustained funding and community support [14]. A governance model that treats immune gene variation as a global public good, with shared responsibility for data generation, model validation, and ethical oversight, is essential for the long-term success of this endeavor. Without such a framework, the technological promise of population-aware AI will remain unevenly distributed, and the full picture of human immune diversity will remain incomplete.

8. Conclusion

Polymorphic immune genes represent one of the most fascinating and clinically important frontiers of human genetic diversity, yet they remain inadequately captured by current computational methods. This paper has argued that evolutionary and population-aware artificial intelligence models offer a path forward, but only if they are designed, deployed, and governed with explicit attention to the structural trade-offs, infrastructural challenges, and ethical imperatives that characterize large-scale genomic systems. We have examined how model architecture must encode demographic history and selective dynamics, how data governance must balance openness with sovereignty, how deployment must reconcile speed with accuracy and sustainability, and how fairness must be measured and enforced across diverse populations. The evolution of these systems will require not only technical innovation but also sustained interdisciplinary collaboration among computer scientists, population geneticists, immunologists, ethicists, and policymakers. By embedding population awareness at every layer of the system, we can move toward a future where the diversity of the human immune system is not a source of bias but a resource for more precise and equitable health interventions.

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