Explainable Deep Learning Frameworks for Predicting Transplant Compatibility from High-Resolution Immune Gene Haplotypes Derived from Long-Read Data

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Abstract

The accurate prediction of transplant compatibility remains a critical challenge in clinical medicine, particularly given the extreme polymorphism of human leukocyte antigen (HLA) genes and the increasing availability of long-read sequencing data that can resolve full-length haplotypes with unprecedented resolution. Deep learning models offer powerful capabilities for capturing complex, non-linear interactions among immune gene variants, yet their opaque nature raises significant concerns for clinical deployment where interpretability, trust, and regulatory compliance are paramount. This paper presents a comprehensive systems-level analysis of explainable deep learning frameworks designed to predict transplant outcomes from high-resolution immune gene haplotypes derived from long-read data. We examine the architectural trade-offs inherent in integrating long-read sequencing pipelines with deep neural networks, emphasizing the need for modular, scalable, and auditable system designs. The discussion encompasses model transparency techniques such as attention mechanisms, Shapley additive explanations, and concept-based interpretability methods, and evaluates their suitability for graft survival prediction, acute rejection risk stratification, and donor-recipient matching. Beyond technical considerations, we address governance, fairness, and policy implications, including data privacy for genomic information, algorithmic bias across ethnic populations, and the regulatory pathways required for clinical adoption. Cross-domain comparisons with analogous challenges in precision oncology and drug discovery are drawn to contextualize the infrastructure requirements and sustainability challenges of deploying such systems at scale. By synthesizing technical, ethical, and operational dimensions, we provide a forward-looking framework for building robust, equitable, and explainable AI

systems that can transform transplant medicine while upholding the highest standards of accountability and safety.

Keywords

explainable artificial intelligence, transplant compatibility, HLA typing, long-read sequencing, deep learning, clinical decision support, algorithmic fairness, governance.

1. Introduction

Solid organ and hematopoietic stem cell transplantation depend critically on the degree of immunological compatibility between donor and recipient, which is primarily determined by the highly polymorphic genes of the major histocompatibility complex, known in humans as the HLA system. The traditional approach to compatibility assessment relies on serological or low-resolution genotyping of a limited set of classical HLA loci, but increasing evidence demonstrates that high-resolution, allele-level matching across multiple loci significantly improves graft survival and reduces the incidence of graft-versus-host disease [1], [2]. The advent of long-read sequencing technologies, including single-molecule real-time and nanopore platforms, has enabled the routine generation of full-length phased haplotypes covering entire HLA genes and their regulatory regions, thereby capturing structural variants and rare alleles that are missed by short-read approaches [3], [4]. The resulting data are high-dimensional, sparse, and exhibit complex linkage disequilibrium patterns, making them well-suited for analysis by deep learning models that can automatically learn hierarchical representations. However, the clinical deployment of such models demands more than predictive accuracy; it requires interpretability at the level of individual predictions, robustness to distribution shifts in donor-recipient demography, and adherence to stringent regulatory standards for medical devices [5]. This paper adopts a systems engineering perspective to examine the design and deployment of explainable deep learning frameworks for transplant compatibility prediction. We focus on the structural trade-offs among model complexity, interpretability, and operational feasibility, and we situate the technical discussion within the broader contexts of infrastructure governance, data stewardship, and equity in organ allocation. By integrating insights from computational immunology, interpretable machine learning, and health policy, we aim to provide a roadmap for building AI systems that are both powerful and trustworthy in the high-stakes setting of transplantation.

2. Background and Motivation

The immunological matching process in transplantation involves the comparison of HLA alleles at multiple loci, typically HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1, with increasing attention to non-classical and minor histocompatibility antigens. The resolution of HLA typing has advanced from serological and low-resolution molecular methods to next-generation sequencing, and most recently to long-read sequencing that can span entire genes with single-nucleotide accuracy [6]. The IMGT/HLA database currently lists over 30,000 allele sequences, and the number continues to grow as population-specific variants are discovered [1]. Long-read data not only resolve phase ambiguities but also detect novel alleles, copy number variations, and structural rearrangements that influence immunogenicity [7]. Deep learning models trained on such data can capture epistatic interactions and non-additive effects that traditional logistic regression or linear risk scores cannot represent [8]. Promising results have been reported for predicting acute rejection, graft survival, and donor-specific antibody development using convolutional, recurrent, and graph neural networks. Nevertheless, the black-box nature of these models poses a fundamental barrier to clinical

acceptance. Clinicians and patients need to understand why a particular donor-recipient pair is assigned a certain risk score, which features drove the decision, and whether the model's reasoning aligns with established immunological knowledge. Moreover, regulatory bodies such as the U.S. Food and Drug Administration require that algorithms used in medical decision-making be validated for safety and effectiveness, which increasingly includes demands for transparency and the ability to audit model behavior across subpopulations [9]. The motivation for explainable deep learning frameworks in this domain is therefore twofold: to foster trust and adoption among medical practitioners, and to satisfy legal and ethical standards for algorithmic accountability in healthcare.

3. System Architecture and Framework Design

A production-grade system for predicting transplant compatibility from long-read HLA haplotypes must be designed as a modular pipeline that separates data acquisition, processing, inference, and explanation generation. At the input layer, raw sequencing reads from either whole-genome or targeted capture approaches are aligned to a reference graph that encompasses known HLA alleles and structural variations. The scalable framework described in [12] exemplifies the requirements for comprehensive typing of polymorphic immune genes from long-read data, including automated phasing, variant calling, and haplotype assembly. Following haplotype resolution, the data are encoded as fixed-length vectors or graph structures that preserve locus identities, allele frequencies, and linkage relationships. The deep learning model itself may adopt an architecture such as a transformer with self-attention layers, which can capture long-range dependencies across loci, or a graph neural network where nodes represent alleles and edges encode linkage disequilibrium or shared epitopes [10], [18]. The choice of architecture entails trade-offs: transformers are highly expressive and scalable to many loci but require large training datasets and substantial computational resources, while graph models can incorporate prior biological knowledge more naturally but may be harder to train for extremely rare alleles. The prediction output can be a continuous graft survival probability, a multi-class rejection grade, or a compatibility score. Surrounding the core model, an explanation generation module must be integrated without degrading inference latency or requiring extensive retraining. This module can employ post-hoc methods such as Shapley additive explanations (SHAP), which assign importance values to each allele or haplotypic feature, or attention-based interpretability that extracts learned weights from the transformer layers to highlight contributing genomic regions [7], [11]. Additionally, counterfactual explanation techniques can generate minimal changes to the input haplotype that would alter the prediction, providing clinically actionable insights such as which mismatched epitopes are most critical. The entire pipeline must be deployed on a scalable infrastructure, often using cloud-based or high-performance computing clusters, with data encryption and access controls to protect patient genomic information. Ensuring robustness requires rigorous testing for dataset shift, where the donor-recipient cohort may differ from the training population, and implementing continuous monitoring of model drift.

4. Explainability Mechanisms and Interpretability

Explainability in deep learning for transplant compatibility is not a monolithic requirement; it encompasses multiple levels of transparency that address different stakeholders. For the clinical user, local explanations that justify a single prediction are most valuable, as they allow the transplant surgeon or immunologist to verify that the model's reasoning is consistent with established immunogenicity principles [13]. SHAP values provide a principled way to decompose the prediction into additive contributions from each HLA allele, weighted by their

presence in the input haplotype, and have been successfully applied in other clinical prediction tasks. Attention-based explanations from transformer models are inherently local and can be visualized as heatmaps across the HLA region, though their faithfulness remains a subject of active research because attention weights do not always correlate with causal influence [6], [8]. A complementary approach is concept-based explainability, where the model is trained to predict both the outcome and intermediate biomedically meaningful concepts such as cross-reactive epitope groups, electrostatic mismatches, or functional distances at the peptide-binding groove. This constrains the model to learn representations that are interpretable by domain experts and facilitates debugging when predictions are counterintuitive. Global interpretability methods, such as feature importance rankings aggregated over a population, are useful for model validation and discovering novel risk factors. For instance, a global analysis might reveal that certain infrequent alleles at the HLA-DPB1 locus consistently drive high rejection risk, a finding that could inform future matching policies [14]. However, there is an inherent trade-off between fidelity and interpretability: simpler explanation methods like linear proxy models may be more interpretable but can oversimplify complex interactions, while more faithful methods like exhaustive SHAP are computationally expensive for high-dimensional genomic inputs. The choice of explanation technique must therefore be guided by the intended use case, the regulatory context, and the computational budget of the deployment environment. Moreover, any explanation method must be validated for robustness to adversarial perturbations, as genomic data can contain sequencing errors or allele calling uncertainties that could mislead both the model and its explanations.

5. Ethical, Governance, and Policy Implications

Deploying AI-based transplant compatibility systems raises profound ethical and governance challenges that extend beyond technical performance. The use of genomic data involves sensitive personal information with potential implications for donor and recipient privacy, discrimination, and familial inference. Data governance frameworks must ensure informed consent, anonymization, and strict access controls, particularly when data are shared across transplant centers for collaborative model training [15]. Fairness is a critical concern: HLA allele frequencies vary considerably among ethnic groups, and training data often overrepresent populations of European ancestry. Models trained on such data may systematically underestimate rejection risk for minority populations, exacerbating existing disparities in transplant outcomes [16]. The deep learning model itself may learn spurious correlations, such as associations with geographic ancestry that are not causally related to immunogenicity, leading to biased predictions. Explainability methods can help detect such biases by examining whether the model relies on ancestry-linked features rather than immunologically relevant alleles. Policy frameworks need to mandate that model performance is evaluated and reported across demographic subgroups, and that thresholds for high-risk predictions are calibrated to ensure equitable clinical action. Regulatory approval pathways, such as the FDA's premarket clearance for software as a medical device, require evidence of not only accuracy but also clinical utility and interpretability [9]. Furthermore, because transplant decisions involve scarcity of organs and life-or-death outcomes, any AI-assisted matching system must be subject to human oversight and appeal mechanisms. The governance model should also address the liability for erroneous predictions, particularly whether the institution, the algorithm developer, or the clinical user bears responsibility. These issues are not unique to transplantation—they parallel debates in criminal justice and

credit scoring—but the medical context heightens the stakes and demands robust procedural safeguards.

6. Case Illustrations and Cross-Domain Comparisons

To ground the architectural and policy discussions, it is instructive to consider concrete scenarios. In kidney transplantation, the risk of acute rejection is influenced by HLA-DR and HLA-DQ mismatches, but also by non-HLA factors such as donor-recipient age difference and cold ischemia time. An explainable deep learning model trained on long-read haplotypes could output a risk score and simultaneously highlight that a specific amino acid substitution at position 74 of HLA-DRB1 is the primary driver of the elevated risk, allowing the clinician to decide whether to proceed or request additional immunosuppression. In bone marrow transplantation, where donor-recipient matching is even more stringent due to the risk of graft-versus-host disease, the model might need to incorporate high-resolution typing at HLA-C and -DPB1, as well as killer immunoglobulin-like receptor (KIR) compatibility. Attention-based explanations can reveal how the model weighs each locus, providing insights that can refine donor selection guidelines. Cross-domain comparisons with precision oncology reveal analogous challenges: deep learning models that predict drug response from tumor genomic profiles require explainability to identify actionable mutations, and similar methods like SHAP and attention have been adopted. In drug discovery, graph neural networks that predict molecular properties are being augmented with concept-based explanations to ensure alignment with medicinal chemistry knowledge. The transplant domain, however, presents unique difficulties because the genome is germline rather than somatic, and the training data are extremely sparse for rare haplotypes. Infrastructure lessons can be drawn from large-scale genomics projects such as the UK Biobank, where federated learning and secure multi-party computation have been used to train models across multiple sites without sharing raw genomic data [17]. Such decentralized approaches could mitigate privacy concerns while enabling the construction of more diverse training sets.

7. Future Directions and Sustainability

The sustainability of explainable deep learning frameworks for transplant compatibility depends on several evolving factors. First, the cost of long-read sequencing is decreasing, but the computational overhead for full haplotyping and deep learning inference remains substantial. Energy-efficient hardware and model compression techniques, such as quantization and knowledge distillation, will be necessary to deploy these systems in resource-constrained transplant centers in low- and middle-income countries [19]. Second, the models must be continually updated as new alleles are discovered and as transplant practices evolve. This requires a continuous learning infrastructure that can incorporate new data without catastrophic forgetting and that can provide versioned explanations to maintain audit trails. Third, the explainability methods themselves need to advance. Current post-hoc methods often produce explanations that are not validated against causal mechanisms, and there is a pressing need for intrinsic interpretability, where the model architecture is designed from the ground up to be transparent. This might involve building "immunologically informed" neural networks that embed known epitope structures as hard constraints, thereby ensuring that the model's internal representations are inherently interpretable. Fourth, the governance of such systems must evolve with the technology, establishing standards for explanation fidelity, bias testing, and clinical validation that are accepted by professional societies and regulators. Finally, the integration of explainable AI into the clinical workflow

requires careful human-centered design: explanations must be presented in a visualization that clinicians can quickly understand and act upon, without causing information overload.

8. Conclusion

Explainable deep learning frameworks for predicting transplant compatibility from high-resolution immune gene haplotypes represent a convergence of advanced sequencing, machine learning, and clinical decision support. This paper has argued that the successful deployment of such systems hinges not only on predictive accuracy but on the careful balancing of architectural trade-offs, the thoughtful selection of explanation methods, and the proactive addressing of ethical, legal, and infrastructural challenges. Long-read sequencing provides the data richness needed to capture the full extent of HLA polymorphism, and deep learning models can exploit this richness to improve patient outcomes. However, without interpretability, these models cannot gain the trust of clinicians or meet regulatory requirements for medical devices. By embedding explainability into the entire pipeline—from data encoding to post-hoc analysis to governance—transplant centers can leverage the power of AI while maintaining accountability and safety. The path forward demands interdisciplinary collaboration among immunologists, computer scientists, ethicists, and policymakers to ensure that the technology serves all patients equitably and that the insights it generates are both scientifically rigorous and practically actionable.

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