Integrating Genomic and Epigenetic Data to Enhance Pediatric Liver and Kidney Transplant Outcomes

Study Rationale

Pediatric organ transplantation poses significant challenges due to varying responses to treatment and the genetic factors influencing outcomes. The rarity of cases limits available genomic data, but integrating data from six European TransplantChild ERN hospitals could contribute to addressing these challenges. The study focuses on liver and kidney transplants, with liver diseases often lacking diagnostic biomarkers and kidney disorders presenting highly heterogeneous phenotypes and genotypes. These complexities complicate early diagnosis and personalized treatment. This study aims to refine diagnostic precision, explore novel therapeutic strategies, and improve outcomes for pediatric transplant patients.

Extent and Evaluation of Current Knowledge

Pediatric transplantation requires lifelong immunosuppression (IS), presenting unique challenges due to children's metabolic and immune immaturity. Current IS regimens have reduced rejection and mortality but demand tailored approaches to minimize risks like infections, toxicity, and cancer. Genetic factors influencing rejection, allograft failure, and IS complications remain underexplored. This study integrates clinical and genomic data, focusing on:

- Genetic traits linked to primary disease.
- Pharmacogenetics of IS drugs.
- Immune-mediated rejection mechanisms and inflammatory responses.
- Host-pathogen interactions in infections.
- Long-term metabolic, endocrine, and developmental complications.

Epigenetics, particularly DNA methylation, offers potential biomarkers for immune responses, graft injury, and fibrosis, enabling personalized care and improved outcomes.

Objectives of the Study

The study aims to demonstrate the added value of integrating real-world data with genomic markers to predict adverse outcomes in pediatric liver and kidney transplant patients. A pilot study of 200 genomes and methylomes (retrospective and prospective) will analyze genomic and epigenomic determinants to achieve the following goals:

1. Comprehensive analysis of immune response determinants, pharmacogenomic profiles, and genetic markers for organ rejection.
2. Identification of susceptibility to infections using SNP markers for common and rare pathogens.
3. Refinement of genetic determinants and postzygotic variants related to diseases necessitating transplantation.

Primary Objectives

1. Identify new genes/genomic regions associated with liver and kidney transplantation and develop improved polygenic risk scores (PRS) using next-generation sequencing and machine learning.
2. Discover biomarkers for immunosuppressant drug toxicity, adverse reactions, and other outcomes, and estimate population-level pharmacogenetic (PGX) risks.
3. Apply episignature analysis to detect clusters of patients with similar CpG markers, identifying novel methylDNA signatures linked to diseases, genes, or variants currently unknown in transplanted children.

Secondary Objective

Integrate genomic data into the Beyond 1 Million Genomes project (B1MG) to support broader research efforts.

Study Design

The clinical study involves two cohorts of pediatric patients with renal or liver transplants from ERN-TransplantChild reference centers. Key steps include:

1. Informed Consent and Recruitment

Patients/families will provide consent for genomic and methylomic analyses.

2. Data Collection and Follow-Up

Clinical data, including adverse outcomes such as infections, rejection episodes, diabetes, and hypertension, will be collected before inclusion and during a 3-year follow-up.

3. Genomic and Methylomic Analysis

Genetic and methylation markers predicting outcomes like infections and rejection will be identified. Episignatures derived from DNA methylation patterns will serve diagnostic purposes.

4. Control Groups

Data from international databases and internal controls (800+ samples) will be used for comparison.

Data integration and mining will link phenotypes to diagnoses and outcomes.

Figure 1. Diagram illustrating the Clinical Study Design, highlighting key steps: informed consent, data collection, genomic and methylomic analysis, and comparison with control groups.

Study Procedures

Part A: Whole Genome Sequencing (WGS) and B-PRS calculation

WGS

1. Objective: Perform WGS on 200 samples to identify genetic variations predicting adverse outcomes.
2. Process:
    - Sample Preparation: Extract DNA from blood, prepare libraries, and sequence genomes using NGS platforms.
    - Data Analysis: Align sequences, conduct variant calling for SNPs, InDels, Structural Variants (SVs), and Copy Number Variants (CNVs), and perform functional annotation.
    - Quality Control: Ensure coverage depth, genotype quality, and resolve discrepancies through SNP arrays.
3. Platforms: Data processing will utilize VarSeq©, ensuring efficient analysis and storage.

Bayesian Polygenic Risk Score (B-PRS) Development

This innovative approach incorporates rare variants and models gene-gene/environment interactions through advanced machine

learning.

1. Features:
    - Rare variant inclusion.
    - Improved population stratification using Support Vector Machines (SVMs) and PCA.
    - Epistatic interactions modeled via deep learning.
    - Pleiotropy addressed through multivariate approaches.
2. Validation: Test models across genomic layers and phenotypes, integrating clinical data to enhance predictive accuracy.

Part B: Methylomes and Episignatures

Refinement of Episignatures

1. Objective: Enhance episignature accuracy for liver and kidney transplant patients by improving specificity, sensitivity, and robustness.
2. Methodology:
    - Recruit and analyze at least 200 clinically characterized patients.
    - Implement federated learning strategies to refine training sets without compromising patient data privacy.
    - Establish a selection committee to define inclusion/exclusion criteria, ensuring a diverse and relevant patient cohort.

Discovery and Validation of New Epigenetic Markers

1. Objective: Identify and validate novel disease-specific methylation markers.
2. Approach:
    - Assemble large cohorts with detailed clinical and molecular profiles.
    - Explore previously undetected epigenetic signatures linked to diseases or variants.
    - Validate new episignatures for diagnostic utility in pediatric transplants.

The activity will be aimed at improving the effectiveness of the episignature in liver and kidney transplanted patients.

Anticipated Impact

This study represents a significant advancement in pediatric transplant medicine. By integrating genomic, epigenomic and clinical data, it addresses gaps in diagnostic precision and personalized care. The findings will contribute to developing improved polygenic risk scores, refining episignatures, and paving the way for precision diagnostics and therapeutic strategies. The approach will enhance long-term outcomes and quality of life for children and families navigating the complexities of transplantation.

Top 5 Key Points

1. Collaborative approach for pediatric transplants

Integrating genomic and clinical data from six European TransplantChild ERN hospitals addresses the scarcity of data and diverse responses in pediatric liver and kidney transplants.

2. Focus on Genomics and Epigenetics

Utilizing Whole Genome Sequencing (WGS) and DNA methylation analysis (episignatures) to identify markers for organ rejection, infection susceptibility, and disease-specific traits.

3. Innovative risk assessment with B-PRS

Development of Bayesian Polygenic Risk Scores, incorporating rare variants and machine learning, to improve predictive accuracy for adverse outcomes in transplant patients.

4. Refinement of episignatures

Enhancing diagnostic specificity and sensitivity by analyzing at least 200 patients, leveraging federated learning to ensure secure data refinement without compromising privacy.

5. Impact on personalized medicine

Establishing precision diagnostics and therapeutic strategies to improve long-term outcomes and quality of life for pediatric transplant patients and their families.

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