

A Retrospective Analysis of Genetic Factors Correlated with Graft Function After Liver, Kidney, or Pancreas Transplantation

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Mission:

The University of Washington Transplant Services aims to improve expertise through innovative research and continuous education in order to give patients with organ failure an opportunity to pursue a higher quality of life. Research in this field will ultimately facilitate better clinical care for liver, kidney, or pancreas transplant patients, improving their quality of life and reducing morbidity and mortality of solid organ transplantation.

Hypothesis of Research Project:

Differences in genetic factors may partially account for interindividual differences in graft function assessments, organ rejection, efficacy of the transplant procedure, efficacy/toxicity of immunosuppressant drug therapy or other adjuvant drug therapies, susceptibility to disease, disease development, and re-occurrence of disease. Interindividual differences have become apparent as patients with comparable disease history receive identical drug therapies and treatment regimens, yet experience various complications and less than optimal transplant outcomes.

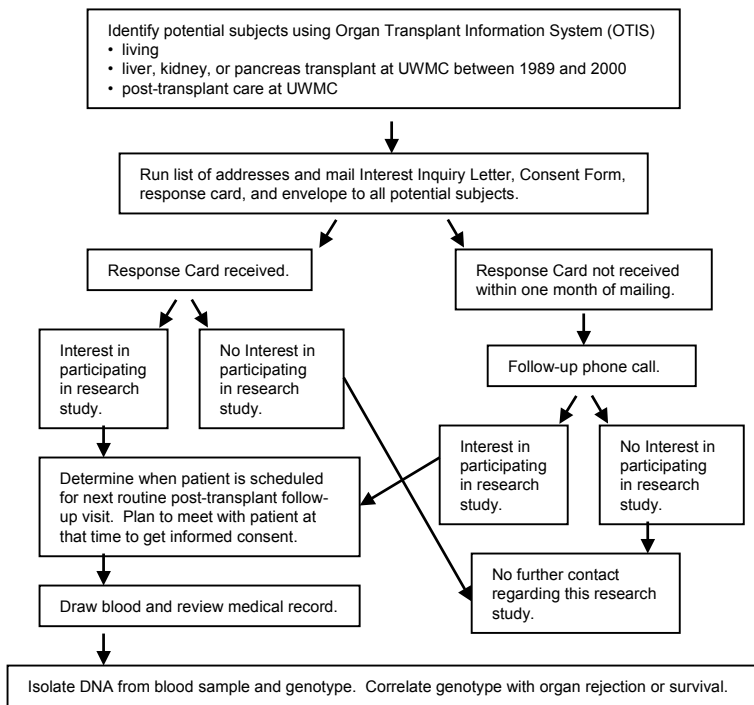
Background of Practicum Project:

Since 1989, transplant surgeons at UWMC have been routinely collecting blood and clinical outcome data from liver, kidney, and pancreas transplant patients. The resulting information was evaluated and studied to monitor and improve patient outcome and graft survival. However, recent literature and relevant research suggests that genetic factors may be partially responsible for interindividual differences in graft function assessments and immunosuppressive drug metabolism among liver, kidney, or pancreas transplant patients. In order to be in compliance with all components of research involving this patient population, the investigators were required to submit a Human Subjects Review Committee Application prior to re-contacting these transplant patients for participation in genetic research.

Goal of Practicum Project:

Complete Human Subject Review Committee Application for research project entitled "A retrospective analysis of genetic factors correlated with graft function after liver, kidney, or pancreas transplantation."

Method for Investigation:



Genes to be investigated:

CYP3A4
CYP3A5
Multi-drug resistance gene (MDR1)
Tumor necrosis factor-alpha (TNF α)
Interleukin-2 (IL-2) receptor

Interleukin-12 (IL-12)
T-cell signal transduction peptides
Human leukocytic antigens (HLA)
Miscellaneous cytokines

Function:

drug metabolizing enzyme
drug metabolizing enzyme
transporter involved in elimination of drugs
cytokine involved in inflammatory process
stimulate activation and proliferation of CD4+ cells
enhance T cell proliferation/responses
stimulate expression of T cell growth factors
present peptides to CD8+/CD4+ T cells
signal between cells

Pharmacogenetics:

The goals of pharmacogenomics are to elucidate the genetic differences in drug disposition, to provide a stronger scientific basis for selecting the optimal immunosuppressive drug therapy and dosages for each patient, and to reduce drug-caused morbidity and mortality. Basic research into the molecular basis of drug action and genetic determinants of drug response should greatly improve clinical practice, in that pharmacogenomic information will guide the clinical use of many medications. From the patient perspective, pharmacogenomics should increase the chance that a prescribed drug will alleviate disease and reduce the incidence of adverse drug reactions.

Patient Demographics:

- Primarily from Washington, Oregon, Idaho, Alaska, and Montana.
- >18years old.
- Approximately equal numbers of males and females.
- Primarily Caucasian population.

Type of transplant	# of transplants (1989-2000)	Approx. survival rate
Liver	614	83%
Kidney	619	90%
Pancreas	239	94%

Outcome and Applications of Project :

Approval of Human Subjects Review Committee Application #01-0444-A 01 entitled "A retrospective analysis of genetic factors correlated with graft function after liver, kidney, or pancreas transplantation."

In the future, clinicians may use information gained from studies such as this in decisions regarding type(s) and dosing of immunosuppressant agents to provide the best possible outcome for an individual patient with a specific genetic makeup. The consent form and Human Subjects Review Committee Application will serve as a template for clinical research at UWMC involving genetic variability.

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