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Team aims to revolutionize understanding of how gene variants affect organ transplant outcomes

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Nearly 30,000 organ transplants are performed in the United States every year. They routinely extend lives, but the success of these procedures continues to be limited by problems that arise when the recipient's immune system rejects their new organ and other complications. Now, a large international team of transplant surgeons and scientists, co-led by researchers from the Perelman School of Medicine at the University of Pennsylvania, has come together to investigate the genetic factors behind transplant successes and failures. The project, involving more than three dozen research institutions around the world, is called the International Genetics & Translational Research in Transplantation Network (iGeneTRAiN). Their efforts are detailed in a pair of papers published today in *Genome Medicine* and in the journal *Transplantation*.

"The genetic datasets we've put together in this project are by far the largest ever assembled in transplant genomics," said Brendan J. Keating, DPhil, an assistant professor of Transplant Surgery at Penn Medicine. "We want to revolutionize our understanding of how genetic variants affect transplant outcomes, and use those findings to improve these outcomes in the future."

While large-scale studies used to link gene variants to other common diseases - such as Type 2 diabetes and certain forms of breast cancer - have been around for years, so far there are only few such studies

0specifically aimed at organ transplants. Moreover, the genome-wide transplantation studies that have been performed to date have only examined a few hundred individuals.

The consortium has grown rapidly in scale since its inception in 2012 and its participating institutions, whose separate studies around the globe - ongoing and completed - have already generated genomics and outcome data for over 32,000 organ donors and recipients. The iGeneTRAiN projects are initially focused on kidney, liver, heart and lung transplant outcomes, with three ultimate goals:

- Discovery of genetic variants that lead or contribute to rejection and other complications of transplantations;
- Expansion of biomarkers found in urine and blood samples that may predict rejection weeks or months before patients show symptoms;
- Individualized patient treatments.

Initial studies by iGeneTRAiN collaborators are primarily looking for links between gene variants and five common outcomes: survival of the transplanted organ, acute organ rejection, side-effects caused in part by immunosuppressive drugs (including new-onset diabetes after transplant and increased cholesterol and blood pressure), adverse events due to chronic immunosuppressive therapy such as infections and malignancies, and delayed function of the transplanted organ.

Scientists have known for decades that a particular set of proteins, the human leukocyte antigen (HLA) complex, provides a signature that identifies to the immune system the body's cells as belonging to oneself. A transplant recipient's immune cells are liable to attack donor cells that don't have the same HLA signature. Finding donors whose HLA genes make a good match with recipients' is therefore a standard procedure for most transplants.

Studies have shown, though, that rejection of transplanted organs can occur even when HLA genes appear well-matched between donor and recipient, which points to the existence of additional transplant-relevant genes in other parts of the human genome. These other genes are now known to include those encoding so-called killer-cell immunoglobulin-like receptors (KIR) on "natural killer" immune cells, which are well established to interact with HLA molecules and for which some studies suggest impact outcomes of a grafted organ. Genes that influence the body's metabolism of immunosuppressive drugs are also now recognized as likely factors in transplant complications. Further study into the role of KIRs and all other regions across the entire genome are a major goal of the consortium's efforts.

"We strongly suspect that there are many undiscovered genomic incompatibilities that underpin organ rejection," said Abraham Shaked, MD, PhD, the Eldrige L. Eliason Professor of Surgery, and Director of the Penn Transplant Institute. "Transplant outcomes such as acute rejection are likely to be influenced by multiple genetic factors in the donor and recipient, and in order to obtain the statistical power to detect all those factors we need very large datasets that can be appropriately combined."

A broad aim of iGeneTRAiN has been to generate and harmonize these very large existing genetic datasets across all available studies and examine the same questions, in the same ways, but with much larger statistical power to discover the genetic incompatibilities.

Keating and colleagues, in the paper published in *Genome Medicine* have described their specialized genetic array comprising tests for nearly 780,000 genetic variants across each of the human genomes analyzed, which has been used on the majority of the transplant recipient and donors in the iGeneTRAiN studies.

"We expect to gain many new insights into the biology of transplant rejection, tolerance and side-effects of immunosuppression drugs," Keating said. "That should enable us to better understand how donors and recipients genomes interact, to treat and monitor patients more effectively after their transplants, and ultimately to develop better drug dosing to prevent transplant complications and failures."

More information: Keating B, Shaked A, et al. Design and Implementation of the International Genetics & Translational Research in Transplantation Network (iGeneTRAiN). *Transplantation* 2015; In Press.

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