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Title: Donor-Recipient Genomic Incompatibilities in Solid Organ Transplantation

Allograft failure is becoming an increasingly expensive public health problem. Approximately 20% of the US kidney transplant waiting list consists of candidates with failed grafts. Improvement of long-term allograft survival represents one of the major challenges for the transplant community. In this proposal, we hypothesize that unrecognized genomic incompatibilities beyond the traditional HLA and ABO loci contribute to the risk of rejection.

In our pilot study, we hypothesize that solid organ transplantation represents a unique situation in which homozygous gene-disrupting variants can incidentally predispose to allosensitization and rejection. We provide compelling preliminary data in support of this hypothesis. In a genetic study of nearly 3,000 kidney allograft recipients, we identified a common gene-disrupting deletion that conveyed a strong risk of acute rejection when present in a homozygous state (Columbia discovery study N=705, HR=1.79, $p=2 \times 10^{-4}$ followed by replication in three independent cohorts: N=2,149, HR=1.63, $p=2 \times 10^{-5}$). This association was near genome-wide significant in the combined meta-analysis (N=2,855, HR=1.66, $p=8.8 \times 10^{-8}$). The gene disrupted by this variant is abundantly expressed in renal tissue and represents an excellent candidate for a novel minor histocompatibility antigen.

Our promising preliminary results motivate a more comprehensive genome-wide survey of genomic incompatibilities in transplantation. As part of this study, we propose to: (1) expand the bio-bank of transplant patients followed at the New York Presbyterian Hospital (NYPH) / Columbia University Medical Center (CUMC); (2) provide further replication of the pilot associations and assess their relevance in the setting of non-renal organ transplantation; and (3) perform higher resolution genomic scans to identify novel rejection loci. The long-term objective of this effort is to develop a new model for risk stratification and optimal matching of donors and recipients based on personal genomic information.

The NYPH/CUMC has one of the largest solid organ transplant programs in the country. Systematic banking of DNA from transplant donors and recipients will build a unique and valuable resource for the NYPH transplant research community and will enable powerful genetic studies of end organ failure and transplant-related outcomes. Our preliminary data strongly suggest that one could improve transplantation outcomes by personalizing donor-recipient matching criteria. This strategy may be used to prevent the occurrence of rejection and reduce the need for immunosuppression. Therefore, this project has a potential to lead to a major paradigm shift in the approach of donor selection and organ allocation.