Genomic collision may explain why many kidney transplants fail

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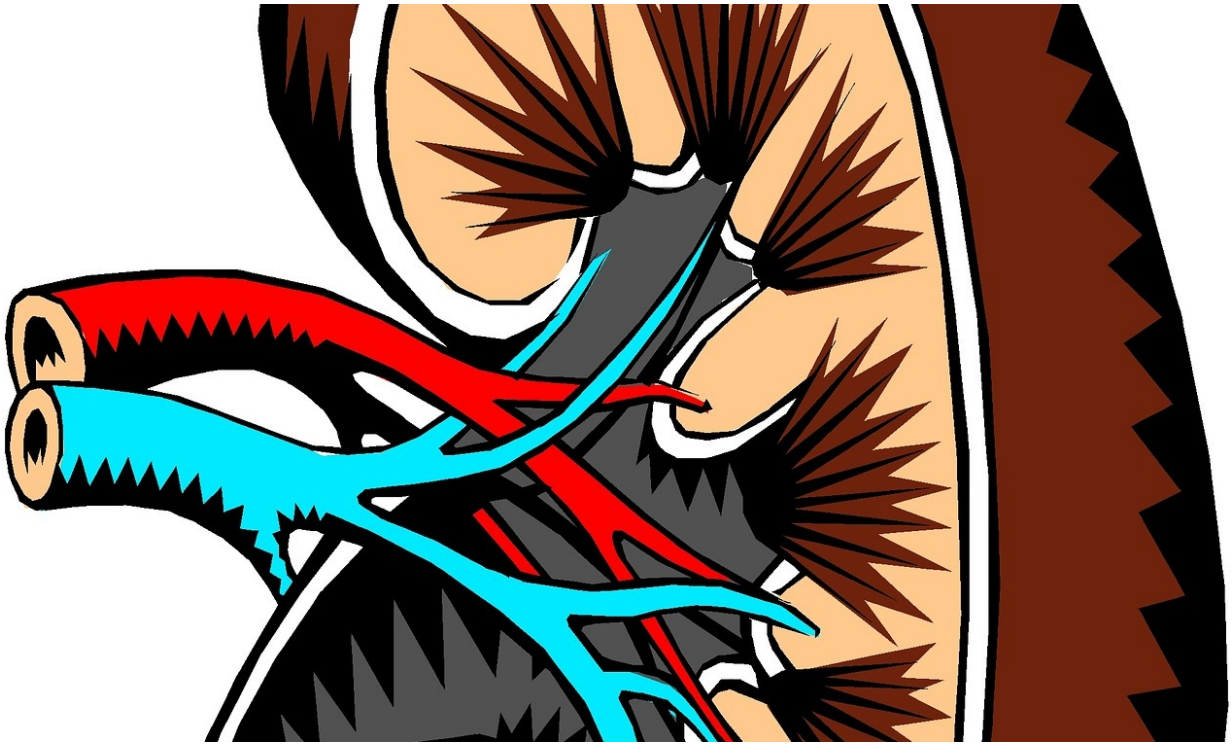

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A genomic collision could explain why many kidney transplants fail, even when donors and recipients are thought to be well-matched, according to a new study from researchers at Columbia University Vagelos College of Physicians and Surgeons. This genomic collision is a genetic incompatibility between kidney donor and recipient, causing the

recipient to mount an immune attack against the donor protein.

The findings, published online today in the *New England Journal of Medicine*, could lead to more precise matching between donors and patients, and reduce kidney transplant failures. The same genomic collision may also potentially occur in heart, liver, and lung transplants.

A Different Possible Mechanism for Kidney Rejection

A successful organ transplant depends in large part on assuring genetic compatibility between donor and recipient. This is done by matching the donor and recipient's human leukocyte antigens (HLAs)—cell surface proteins that help the immune system determine which cells are foreign—as closely as possible. But HLA mismatches can only explain only about two-thirds of transplants that fail for immunological reasons. "The rest of those failures are probably due to less common antigens, or so-called minor histocompatibility antigens. However, the identity of most of these antigens and how they lead to rejection is largely not known," says co-senior author Krzysztof Kiryluk, MD, the Herbert Irving Assistant Professor of Medicine at Columbia University Vagelos College of Physicians of Surgeons.

The researchers hypothesized that a person whose genome carries a kidney gene with a deleted section might be especially sensitive to organs from a donor whose genome carries the full-sized gene. "The recipient would then be exposed to a protein their immune system would sense as foreign," says Kiryluk.

To test their hypothesis, they screened 705 kidney recipients transplanted at Columbia University Irving Medical Center for deletions in 50 kidney genes that were present as full-sized versions in the donor.

The deletions associated with rejection were then confirmed in an additional 2,004 donor-recipient pairs from three international transplant cohorts.

What the Study Found

The study found that kidney recipients with two copies of a deletion near a gene called LIMS1 had a significantly higher risk of rejection when the donor kidney had at least one full-sized version of the same gene. The risk of rejection was 63 percent higher among the donor-recipient pairs with this genomic collision, compared to those without this mismatch. "To put this into perspective, the risk of rejection from LIMS1 mismatch is roughly three times as high as the risk due to a single allele mismatch in the HLA," Dr. Kiryluk says.

Kidney transplant recipients with two copies of the deletion who developed rejection had detectable levels of anti-LIMS1 antibodies in their blood—further evidence that this genomic collision contributes to rejection.

"The exact mechanism by which this deletion exerts its effects is unknown," says Kiryluk. "It's likely that it reduces the amount of LIMS1 protein produced, since we find that individuals with two copies of the deletion have lower levels of LIMS1 gene transcript in their kidneys. When these individuals are exposed to a high level of LIMS1 protein in a newly transplanted organ, their immune system is more likely to recognize the LIMS1 antigen as foreign, resulting in rejection."

Transplanted organs commonly experience a significant period of low oxygenation, which appears to compound the genomic collision. In cells that produce LIMS1, the researchers found that low oxygen levels increase LIMS1 production on the cell surface, which may increase the risk of an immune attack.

1 in 7 Transplants in Some Populations May Be Affected

LIMS1 mismatches would be expected to occur in approximately 12 to 15 percent of transplants from unrelated donors among persons of European and African ancestry, but it would be very rare among persons of East Asian ancestry because the deletion is very rare in these populations.

"LIMS1 mismatches could be avoided by pre-transplant genetic screening," Kiryluk says. "But first we need to validate our findings in larger studies."

The findings may apply to other types of organ transplants since LIMS1 is also expressed in the lung, heart, and liver. Similarly, other genetic incompatibilities may also be contributing to rejection of these organs.

"This project illustrates how genetic analysis is empowering clinical care by enabling better matching and the antibody test potentially presents a noninvasive method for screening for organ rejection in individuals with an existing transplant," says co-senior author Ali G. Gharavi, MD, professor of medicine at Columbia University Vagelos College of Physicians and Surgeons.

The LIMS1 gene has gone previously undetected in earlier searches, partly due to the limited sample size of previous studies, Kiryluk says. "We estimate that a traditional genome-wide association study would need to analyze a minimum of 13,000 kidney recipients to find this gene," he adds. "The genomic collision approach provides a new method to find additional mismatches in a smaller number of donor-recipient pairs. And coupled with new methods of antibody detection, is likely to propel future discoveries in this area."

The study is titled, "Genomic Mismatch at LIMS1 Locus and Kidney-Allograft Rejection."

Provided by Columbia University Irving Medical Center