Living donation: What's truly behind rapid APOL1 kidney decline?

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> Living kidney donation offers a lifeline to patients with end-stage renal disease, but the long-term health of the donor remains a critical consideration. While generally safe, the procedure carries a small but definite risk of accelerated kidney function decline for the donor. The question has always been: who is truly at risk?
> New understanding of genetic predispositions, specifically the APOL1 gene, now points to a clearer answer. This genetic marker, common in individuals of recent African ancestry, appears to significantly influence post-donation renal outcomes, demanding a re-evaluation of current donor screening protocols.

KEY TAKEAWAYS

- The Pivot: APOL1 genotype, particularly two risk alleles, is a critical predictor of accelerated kidney function decline in living kidney donors.
- The Data: Donors with two APOL1 risk alleles experienced a significantly greater eGFR decline, approximately 3 to 5 mL/min/1.73 m2 per year, compared to those with zero or one allele.
- The Action: Genotyping for APOL1 risk alleles should be considered a standard part of the pre-donation workup for all potential living kidney donors, especially those of African ancestry.

Living kidney donation has long been considered a safe procedure, with extensive follow-up studies demonstrating excellent long-term outcomes for most donors. However, a subset of donors experiences a more rapid decline in kidney function, sometimes progressing to end-stage renal disease. Identifying these individuals pre-emptively has been a persistent challenge for transplant centres globally. The focus has traditionally been on clinical factors like hypertension, diabetes, and proteinuria, but these do not fully explain the observed variability in outcomes.
A significant body of research now points to genetic factors, specifically variants in the Apolipoprotein L1 (APOL1) gene, as a key determinant. APOL1 risk alleles, G1 and G2, are highly prevalent in populations of recent African ancestry, a consequence of their protective effect against African trypanosomiasis (sleeping sickness). But this evolutionary advantage comes at a cost, as these same alleles are strongly associated with various forms of non-diabetic kidney disease, including focal segmental glomerulosclerosis (FSGS) and hypertension-attributed nephropathy. The question for transplant nephrologists became whether these risk alleles also predispose otherwise healthy donors to adverse outcomes after nephrectomy.

The genetic link to renal decline

Studies have consistently shown that individuals carrying two APOL1 risk alleles (G1/G1, G2/G2, or G1/G2 genotypes) face a substantially higher risk of developing kidney disease. This risk is amplified when a single kidney is removed, as

the remaining kidney must shoulder the entire filtration burden. The mechanism is thought to involve increased cellular toxicity and inflammation within the podocytes, the specialised cells in the glomerulus essential for kidney filtration. When one kidney is removed, the remaining kidney undergoes compensatory hypertrophy and hyperfiltration, which may exacerbate the underlying genetic susceptibility in those with high-risk APOL1 genotypes.

Multiple cohort studies, including large registries, have examined the association between APOL1 genotype and post-donation kidney function. These analyses consistently report that living kidney donors with two APOL1 risk alleles experience a greater reduction in estimated glomerular filtration rate (eGFR) over time compared to donors with zero or one risk allele. For instance, some data indicate an average annual eGFR decline that is approximately 3 to 5 mL/min/1.73 m2 per year greater in two-risk-allele carriers. This accelerated decline is not trivial; it can push individuals closer to the threshold for chronic kidney disease (CKD) stages 3 or 4 much sooner than their counterparts without the high-risk genotype.

The impact extends beyond just eGFR decline. While progression to end-stage renal disease (ESRD) after donation is rare for all donors (typically less than 0.5% at 10 years), the relative risk for two-risk-allele carriers is significantly elevated. One meta-analysis reported a hazard ratio for ESRD of ~8 to 10 for donors with two APOL1 risk alleles compared to those with zero or one allele. This translates to a small absolute risk, but a substantial relative increase for the individual donor. The implications for informed consent are clear: potential donors need to understand their personal genetic risk.

Refining donor selection

The clinical implications of these findings are profound for donor selection. Current guidelines for living kidney donation typically exclude individuals with pre-existing kidney disease, uncontrolled hypertension, or significant proteinuria. However, these criteria do not account for genetic predispositions that may manifest only after the stress of nephrectomy. Integrating APOL1 genotyping into the pre-donation evaluation process, particularly for individuals of African ancestry, could identify those at higher risk who might otherwise be deemed suitable based on traditional criteria.

But the implementation of APOL1 genotyping is not without its complexities. Ethical considerations surrounding genetic testing, potential discrimination, and the psychological impact of identifying a genetic risk for kidney disease in an otherwise healthy individual must be carefully navigated. Furthermore, the precise threshold of risk that warrants exclusion from donation remains a subject of ongoing debate. Some centres have adopted a policy of not accepting donors with two APOL1 risk alleles, while others engage in extensive counselling and shared decision-making, acknowledging the donor's autonomy. The Oxford Handbook of Nephrology and Hypertension offers practical guidance on managing complex cases in renal medicine.

The open-label nature of many of these studies is an obvious caveat, as is the retrospective design of some larger cohort analyses. Prospective, randomised trials on APOL1 genotyping and donor outcomes are not feasible for ethical reasons, meaning reliance on observational data will continue. Still, the consistency of the association across diverse cohorts strengthens the evidence. The long-term follow-up required to fully understand the trajectory of kidney function in these donors is also a challenge, as many studies have limited follow-up periods, often less than 10 years. The progression to ESRD can take decades, and longer-term data would provide a more complete picture of lifetime risk.

The data does not suggest that all individuals with two APOL1 risk alleles will develop ESRD after donation, but it does indicate a significantly higher probability of accelerated decline. This information empowers both the potential donor and the transplant team to make more informed decisions. The next step involves developing standardised guidelines

for APOL1 testing and counselling, ensuring equitable access to this information and avoiding perpetuating health disparities.

CLINICAL IMPLICATIONS

The evidence on APOL1 risk alleles and post-donation kidney function is now too compelling to ignore. For clinicians involved in living kidney donation, particularly nephrologists and transplant surgeons, this means a necessary shift in pre-operative risk assessment. Relying solely on traditional clinical markers is no longer sufficient when a clear genetic predisposition exists.

Implementing APOL1 genotyping as a routine part of the donor workup, especially for individuals of African ancestry, is a pragmatic step. This is not about exclusion, but about truly informed consent. A potential donor needs to understand their individual risk profile, however small the absolute risk of ESRD may be, before making a life-altering decision.

The broader implications extend to health equity. Given the higher prevalence of APOL1 risk alleles in populations of African descent, careful and culturally sensitive counselling is paramount. We must ensure that genetic information is used to empower individuals, not to create new barriers to donation or exacerbate existing health disparities. The goal remains to maximise safe donation while protecting donor health.

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