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Late Reoccurrence of Collapsing FSGS After Transplantation of a Living-Related Kidney Bearing APOL 1 Risk Variants Without Disease Evident in Donor Supports the Second Hit Hypothesis

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Recent studies indicate that living kidney donors have higher rate of end-stage renal disease (ESRD) over their lifetime after donation compared with well-matched controls, with a much higher risk in African Americans (AA).¹⁻³ Over the past decade, our understanding of the genetic underpinnings of chronic kidney disease (CKD) in the AA population has been enhanced by the discovery of common variants G1 and G2 in the apolipoprotein L1 gene (APOL1) that are associated both with higher rates of CKD and faster progression to ESRD.⁴ The G1 allele consists of missense variants in linkage disequilibrium, Ser342Gly and Ile384Met, and the G2 allele is a 2-amino acid deletion, delAsn388/Tyr389. 13% of the AA population carries 2 risk alleles (G1/G1, G1/G2, or G2/G2) and the inheritance of 2 risk alleles increases risk of hypertension-associated renal disease 7- to 10-fold and the risk of focal segmental glomerulosclerosis (FSGS) 10- to 17-fold. These risk alleles also appear to adversely affect renal allograft outcomes with deceased donor kidneys carrying 2 risk

alleles having an approximately twofold increased risk of graft failure, whereas recipient genotype has no impact.⁵⁻⁷

We report a patient with FSGS and a strong family history of ESRD who received a kidney from a sibling. He developed abrupt and severe nephrotic syndrome with collapsing FSGS 10 years posttransplant unresponsive to plasmapheresis that rapidly progressed to ESRD. Although both recipient and donor carry 2 APOL 1 risk variants, the donor remains free of hypertension or proteinuria.

The Recipient

The recipient (III-2, Figure 1) is an AA male who at age 40 years developed FSGS unresponsive to steroids and progressing to ESRD within a year of diagnosis. In early 2005 at age 44 years, he underwent living donor transplant from his half-brother on his mother's side. The patient was not sensitized and received daclizumab for induction, and maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and prednisone, which was discontinued early in the posttransplant period due to mood swings. Both the donor and recipient were cytomegalovirus IgG positive. Graft function was immediate and until late 2015, he maintained a creatinine in the range of 1.0 to 1.3 mg/dL. In his most recent routine follow-up approximately 1 year before developing nephrotic range proteinuria, his urine protein-to-creatinine ratio was 0.9 mg and serum creatinine was 1.3 mg/dL. He had no history of acute rejection episodes or microscopic hematuria after transplantation.

He presented to the transplant clinic in 2015 with a 2-week history of increasing lower extremity edema and decreasing urine output. Except for a self-limiting diarrheal illness approximately 3 months earlier, the review of systems was negative.

On examination, he was hypertensive and with bilateral pitting edema. Laboratory testing at the time of his clinic visit revealed a serum creatinine of 2.8 mg/dL, serum albumin of 2.7 mg/dL, and a random urine protein-to-creatinine ratio of 12. Renal allograft biopsy showed several glomeruli with features of the collapsing variant of focal segmental glomerulosclerosis. C4d staining was negative (Figure 2). Further serum/plasma testing for human immunodeficiency virus, antinuclear antibody, perinuclear anti-neutrophil cytoplasmic antibodies and cytoplasmic antineutrophil cytoplasmic antibodies, hepatitis B and C antibodies, and

Received 26 January 2017. Revision requested 3 May 2017.

Accepted 5 May 2017.

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R.K., C.T., R.S. participated in the writing of the article. R.K., C.T., R.S., P.R., D.K. participated in the performance of the research. R.K., C.T., R.S. participated in data analysis.

The authors declare no funding or conflicts of interest.

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ISSN: 2373-8731

Transplantation Direct 2017;3: e185; doi: 10.1097/TXD.0000000000000697
 Published online 3 July, 2017.

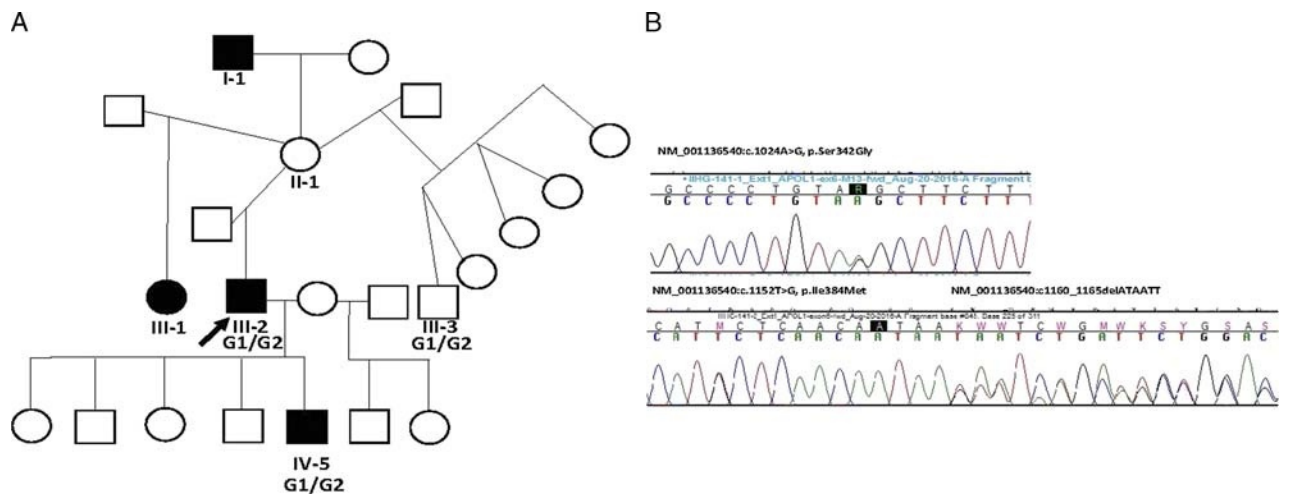


FIGURE 1. Pedigree chart and chromatogram. A, Pedigree chart. III-3 is living donor to III-2. III-1, III-2, and IV-5 have been transplanted. III-2, III-3 and IV-5 are compound heterozygous for the ApoL1 G/G2 allele. Cause of ESRD in I-1 is not known. B, Chromatogram shows heterozygous G1 and G2 alleles.

parvovirus B19 and cytomegalovirus by polymerase chain reaction were negative.

Genetic screening was performed with KidneySeq, a targeted renal multigene panel, to evaluate for genetic causes of kidney disease.⁸ Testing revealed that the patient is compound heterozygous for APOL1 risk alleles: G1 (c.1024A > G, p.Ser342Gly and c.1152T > G, p.Ile384Met) and G2 (c.1160_1165delATAATT). Patient was treated with 10 sessions of plasmapheresis, 1 dose of rituximab (375 mg/m²) and prednisone 20 mg daily with no clinical or laboratory response, and progressed to ESRD 8 weeks after the initial diagnosis. He is currently waitlisted for another kidney transplant.

The Donor

The donor (III-3, Figure 1) is his healthy half-brother, who was approved for kidney donation at age 43 years after a standard donor work-up. He had no history of hypertension

or proteinuria, and normal renal imaging. His serum creatinine was 1.4 mg/dL, CKD-EPI GFR was 85.3 mL/min per 1.73 m² and his adjusted measured creatinine clearance was 113 mL/min per 1.73 m².

His last known creatinine after nephrectomy was 1.8 mg/dL in late 2005. At the time of diagnosis of collapsing glomerulopathy in his brother (recipient), the donor serum creatinine was 1.7 mg/dL, CKD-EPI GFR was 52.2 mL/min per 1.73 m², and blood pressure was 115/69 mm Hg. Urinalysis was negative for protein or blood, random urine protein-to-creatinine ratio was 0.1 mg. Focused genetic testing revealed that the donor is also a compound heterozygote for the APOL1 G1 and G2 risk alleles.

Family History

Although detailed family history was not originally available, it was subsequently learnt that the recipient's son (IV-5, Figure 1), his half-sister (III-1) via his mother and his

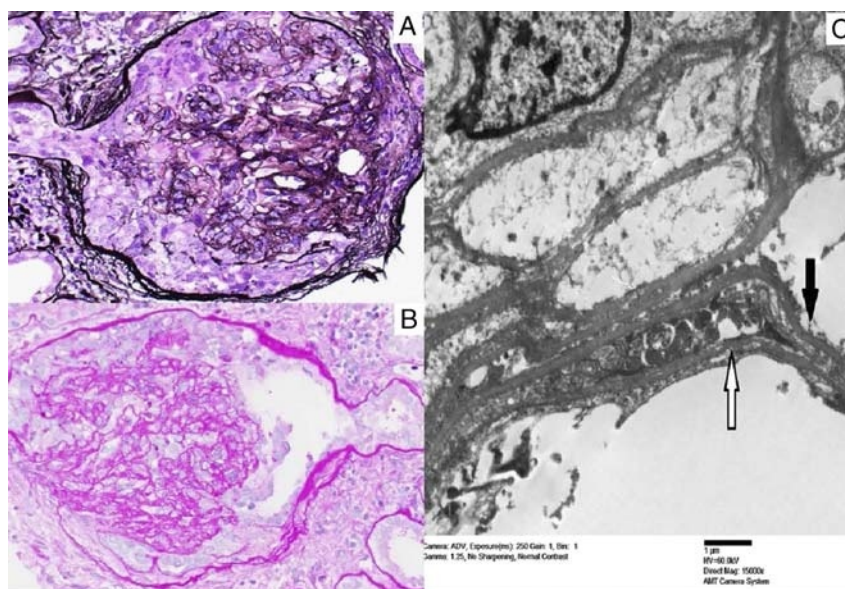


FIGURE 2. Transplant renal biopsy (III-2) showing collapsing FSGS. A, JMS stain, 400× (B) PAS stain, 400×, Collapsing FSGS with collapsed capillary tuft, protein droplets, podocyte hyperplasia. C, Electron micrograph: Transplant glomerulopathy with double layering of glomerular basement membrane (white arrow) and severe foot process effacement (black arrow).

maternal grandfather had also progressed to ESRD. The recipient's son presented at age 21 years with uremic symptoms, and carries the G1 and G2 risk alleles. The recipient's half-sister presented at age 33 years with nephrotic syndrome and a renal biopsy demonstrated membranous nephropathy.

DISCUSSION

In 2005, we did not know the relationship between APOL1 variants and the increased incidence of CKD in AA. We only recently learned that both the donor (who is well) and the recipient (who has lost his allograft from recurrent FSGS), as well as one of the recipient's children (who also underwent a kidney transplant) are compound heterozygous for the APOL1 variants. As most people with 2 risk variants remain well, albeit with a higher risk of CKD, it is likely that a second event, possibly another genetic risk variant or an environmental trigger, is required for onset and/or progression of kidney disease. Interestingly, a potential "second hit" in the recipient was the brief episode of diarrhea 3 months before the development of clinical symptoms of recurrent FSGS. We can only hypothesize this mechanism because the patient was not worked up for the diarrhea illness at the time he was symptomatic; therefore, it is not clear that the diarrhea was of infectious etiology, a mechanism proposed of the "second hit" associated to FSGS. Despite the presence of 2 risk variants and the reduction in eGFR that comes from donation, the donor has remained well, although he remains at higher risk for ESRD estimated at 1 in 104 over 15 years for African American men compared with 1 in 294 for white men.¹ Due to the absence of proteinuria, hematuria, hypertension, or progressive decline in renal function (donor creatinine several months after nephrectomy was 1.8 and 1.7 mg/dL 10 years later), we did not biopsy the donor at the time of the diagnosis of recurrent disease in the recipient. Furthermore, we confirmed with genetic testing his predisposition to FSGS. The absence of a diagnostic biopsy of the donor is a limitation of our case because we do not have histologic confirmation that the donor is not affected by the disease. In principle, larger than expected decline in renal function or new onset proteinuria/hematuria should warrant thorough investigation by the transplant centers.

There are 2 published cases of living donor transplants between siblings with APOL1 risk variants. In the first, of identical twin's compound heterozygous for the G1 and G2 alleles, the recipient developed FSGS progressing to ESRD at 5 and donor developing proteinuria 7 years postdonation.⁹ The second, of HLA identical siblings, reported that the recipient developed proteinuria from FSGS 5 years posttransplant, and the donor presented with hypertensive emergency, massive proteinuria, and advanced stage 5 CKD.¹⁰ Our case report is different: unlike the other 2 sibling pairs where both donor and recipient developed severe progressive CKD, in the case of our sibling pair, the donor remains well 10 years after transplantation. This likely relates to the fact that the other 2 pairs are genetically more alike with 1 set being monozygotic twins and the other sharing several alleles from both parents including the HLA loci, whereas our pair shares just 1 parent, supporting the notion that additional genetic loci or an environmental assault is necessary for the development of disease in the recipient or the donor with 2 APOL1 risk alleles.

The emerging evidence that recipients of APOL1 risk bearing kidneys have a higher risk of graft failure imposes new challenges on the transplant community. Just recently, Julian et al¹¹ studied the contribution of the APOL1 variants to a revised Kidney Donor Risk Index equation in a study with more than 600 deceased AA donors and demonstrated that replacing donor race with APOL1 genotype better defines risk associated with kidneys transplanted from these donors. The issue of the increased risk of ESRD in AA living donors with APOL1 risk variants is more complicated. We already acknowledge that AA donors have a substantially higher lifetime risk of ESRD compared with their white counterparts even without donation, with a twofold higher risk attributable to donation.^{1,2} If APOL1 genotyping will further refine this risk, then APOL1 genotyping should be offered to all AA donors and be used to counsel rather than affirm or exclude donors, although this is controversial.¹²⁻¹⁶

In summary, we report the late and abrupt onset of collapsing FSGS with rapid progression to ESRD 10 years after the transplantation of a donor kidney with 2 APOL1 risk alleles. The donor sibling remains well despite the at-risk genotype. More research needs to be conducted on the impact of APOL1 and other risk variants on the development of CKD in both recipients and living donors.

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