Donor-Derived Hereditary Renal Hypouricemia

To the Editor: Renal hypouricemia (RHUC) results from disease causing variations in urate transporter genes, notably *URAT1/SLC22A12* and *GLUT9/SLC2A9*, impairing tubular uric acid transport.[1] Although mostly asymptomatic, 10% of patients are susceptible to exercise-induced acute kidney injury and/or nephrolithiasis.[2] Diagnosis relies on 2 biochemical parameters, serum uric acid (SUA) <2 mg/dl and fractional excretion of uric acid (FeUA) >10%. We report the first case of donor-derived RHUC due to a single nucleotide change in *SLC2A9* gene in a kidney transplant recipient.

A 29-year-old Indian male with advanced kidney disease due to chronic glomerulonephritis presented seeking kidney transplantation. During evaluation for donation, his mother exhibited severe hypouricemia (SUA of 0.3 mg/dl) with high FeUA (95%), suggesting RHUC. She was born of nonconsanguineous marriage and had no history of exercise-induced acute kidney injury or nephrolithiasis (Supplementary Figure S1).

Clinical exome sequencing in the donor revealed compound heterozygous variant in *SLC2A9* gene associated with RHUC 2, with R380W classified as pathogenic and I335N classified as variant of uncertain significance (Supplementary Figure S1 and Supplementary Table S1). *In silico* prediction tools indicate that the I335N variant is probably deleterious due to its conservation across different species. No pathogenic or likely pathogenic mutation attributable to the etiology of end-stage kidney disease or RHUC was detected in the recipient. However, the variant of uncertain significance (VUS) is inherited from the mother.

After detailed counseling, kidney transplantation proceeded uneventfully. The patient was discharged with nadir creatinine of 0.8 mg/dl with advice to avoid strenuous physical activity and dehydration. Posttransplant, the recipient exhibited persistently low SUA (0.6 mg/dl) and high FeUA (38%). Both the donor and the recipient have normal renal function at 3 months posttransplant with no clinical manifestations of RHUC.

Few successful kidney transplants from donors having RHUC 1 (URAT1 mutation) have been documented mostly from Japanese population[3–5] (Table 1). Most of the recipients developed hypouricemia posttransplant with high FeUA levels; however, none had exercise-induced acute kidney injury or nephrolithiasis.

The R380W pathogenic variant, previously reported in heterozygous state in symptomatic individuals, typically maintains SUA between 1 to 3 mg/dl.[S1,S2] Further studies at functional and molecular levels are warranted to elucidate combined effect of the 2 variants, which may have resulted in unusually low SUA levels in our patient.

In conclusion, RHUC 1 or 2 should be suspected in hypouricemic patients with high FeUA. Prospective recipients from affected donors should be informed of potential risks. Although sporadic reports exist, more research is needed on the implications of RHUC in transplantation.

PATIENT CONSENT

We have obtained detailed informed consent from the patient and donor.

Table 1. Previous cases of donor-derived RHUC

Author, yr of publication	Serum uric acid (mg/dl)	FeUA	Donor mutated Gene	Variant details	Outcome
Tsuji *et al.*[3], 2020	2.5	20.8%	*SLC22A12*	c.269G > A (p.Arg90His) in heterozygous state	2 yr posttransplant, creatinine is normal, serum uric acid 3.8mg/dl, FeUA 12.4%. No exercise induced AKI or urolithiasis
Lisha Teng *et al.*[4], 2020	0.8	NA	*SLC22A12*	c.266G>A; (p.Arg89His) and c.541C>G; (p.Leu181Val) in compound heterozygous state	2 recipients – patient 1 maintains Cr 0.9 mg/dl, uric acid 1.1 mg/dl, FeUA 44% patient 2 Cr 0.9 mg/dl, Cr 0.8, FeUA 75%
Takamasa Miyauchi *et al.*[5], 2021	0.6	59.7%	*SCL22A12*	A homozygous variant resulting in Tyr258* (variant details not mentioned)	No exercise induced AKI At 9 mo, Cr 0.95, serum UA is 1 mg/dl and FEUA is 55%
Index case	0.3	95%	*SLC2A9*	c.1004T>A; (p.Ile335Asn) and c.1138C>T; (p.Arg380Trp) in compound heterozygous state	At 3 mo posttransplant, serum uric acid is 0.6 mg/dl and FeUA is 38%, no EI-AKI or urolithiasis Donor Cr 0.8 mg/dl and SUA is 0.4 mg/dl

AKI, acute kidney injury; Cr, creatinine; EI, exercise-induced; FeUA, fractional excretion of uric acid; RHUC, renal hypouricemia; SUA, serum uric acid; UA, uric acid.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

Figure S1. Pedigree chart.

Table S1. Whole exome sequencing report of donor and patient.

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