Original Article

Donor-derived hypouricemia in irrelevant recipients caused by kidney transplantation

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Background: Hereditary renal hypouricemia (HRH) is a genetically heterogenetic disease. Patients with HRH are almost asymptomatic; but some may experience exercise-induced acute kidney injury (EAKI) and nephrolithiasis which may bring concerns regarding the risk-benefit ratio as marginal kidney donors. This study examined the pathogenic mutations of hypouricemia in two recipients after receiving kidney transplantation, providing preliminary evidence for the mechanism of hypouricemia.

Methods: Two participants underwent detailed biochemical examinations. DNA and RNA were extracted from transplant specimens for sequencing. The whole-genome sequencing and polymerase chain reaction (PCR) amplification were performed to confirm the pathogenic genes. Functional effects of mutant proteins were verified by bioinformatics analysis. RNA-sequencing (RNA-seq) was used to study the transcriptome of hypouricemia.

Results: Both of the recipients had the low serum uric acid (UA) (45–65 μmol/l), high fraction excretion of UA (44% and 75%) and an increase in the UA clearance (35.9 and 73.3 mL/min) with a functioning graft. The sequencing analyses revealed 7 kinds of potential mutational genes in this case, two novel mutations p.R89H and p.L181V in SLC22A12 gene which were revealed by bioinformatics could be pathogenic in nature.

Conclusions: Two novel mutations of SLC22A12 were identified. Preliminary functional analysis revealed a potential deleterious effect of these mutations in the grafts derived from the donor and sequencing analysis expand the molecular mechanisms of renal hypouricemia.

Keywords: Hereditary renal hypouricemia (HRH); single nucleotide polymorphism (SNP); kidney transplantation; SLC22A12

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Introduction

Hereditary renal hypouricemia (HRH) is a hereditary and heterogenetic disorder characterized by defective tubular uric acid (UA) transport, reabsorption insufficiency, and/or increased renal urate clearance resulting from the loss-of-function mutations in UA transport genes (1). HRH patients are mostly asymptomatic but 10% of the patients are susceptible to exercise-induced acute renal failure (EIARF) and/or nephrolithiasis, while 20% of them are afflicted by hypercalciuria, which can lead to nephrocalcinosis in the distal tubules (2-4). Currently, two biochemical parameters are in use to diagnose HRH: (I) serum UA concentration less than 2 mg/dL (equivalent to 119 μmol/L), and (II) more than 10% fractional excretion of UA (5,6). In Japan, the rate of HRH incidence is reportedly about 2.54% among hospitalized patients and 0.12–0.72% in the general population (7-9).

The first successful genetically matched kidney transplantation for HRH was reported in 2006 (10). In 2016, a kidney transplant recipient patients with HRH reported a rare case of nephrocalcinosis in the distal tubules three months after transplant surgery (4). Other than these sporadic reports, there is a dearth of scientific data on the transmission of renal hypouricemia in irrelevant donor-recipient transplantation.

Over the past decade, genome-wide association studies and case reports have shown an increase in the number of genetic variants that influence serum UA concentrations, such as SLC2A9, SLC22A12, SLC17A3, and ABCG2 (11,12). Single nucleotide polymorphisms (SNPs) in regulatory regions (rSNPs) modulate levels of gene expression in an allele-specific manner; however, there is lack of such studies in kidney transplantation research. Further, majority of published studies on hypouricemia includes case report or case series, which lack essential statistical analysis and comparison with healthy controls. Herein, we present two unrelated recipients who had no history of hypouricemia before renal transplantation but experienced sudden and unexpected hypouricemia after receiving transplants from a donor of different genetic background. We performed a DNA sequencing analysis in one healthy control and two kidney transplant recipients and followed up for 3.5 years after their surgery. Our results showed differential gene expression profile between healthy individuals and HRH patients and indicated possible pathogenic pathways associated with disease onset and progression.

Methods

Biochemical and ultrasound evaluation

To evaluate the factors associated with hypouricemia, we checked parameters such as blood biochemistry and urine routine for the UA metabolism, renal tubular acidosis and urine electrolytes, and the liver was examined by ultrasound.

Tissue samples

Two of the three transplant specimens were collected at the time of transplantation and preserved at the hospital, while the other transplant specimen was collected in recipient 1 followed up for 3.5 years after transplantation surgery. Renal biopsy tissue was obtained from a live healthy renal transplant-recipient and the sample was used as the healthy control (*Figure 1A*). The study details were explained to all the participants, and a signed informed consent was obtained after their agreement. Extraction of DNA was performed using the Axyprep™ Blood Genomic DNA Miniprep Kit (Axyprep, USA) following the manufacturer's recommendations. DNA was eluted in approximately 100 μL of buffer AE. DNA integrity was checked on 1% agarose gel and purity were checked using the NanoPhotometer® spectrophotometer (IMPLEN, CA, USA). DNA was quantified using Qubit® DNA Assay Kit in Qubit® 2.0 Flurometer (Life Technologies, CA, USA).

Library preparation and sequencing

A total of 700 ng DNA from each sample was used as the input material for the DNA library preparations. Sequencing libraries were generated using NEB Next® Ultra DNA Library Prep Kit for Illumina® (NEB, USA) following manufacturer's recommendations and index codes were added to attribute sequences to each sample. The NEB Next Adaptor with hairpin loop structure were ligated to 3' adenylated DNA fragments to prepare for hybridization and electrophoresis was carried out to select DNA fragments of specified length. Subsequently, 3 μL USER Enzyme (NEB, USA) was used with size-selected DNA at 37 ℃ for 15 min and 95 ℃ 5 min before carrying out polymerase chain reaction (PCR). PCR was performed with Phusion High-Fidelity DNA polymerase, Universal PCR primers, and Index (X) Primer to enrich final adaptor modified fragmented sample. Finally, the library fragments were purified using AMPure XP system (Beckman Coulter, Beverly, USA). The clustering of the index-coded samples

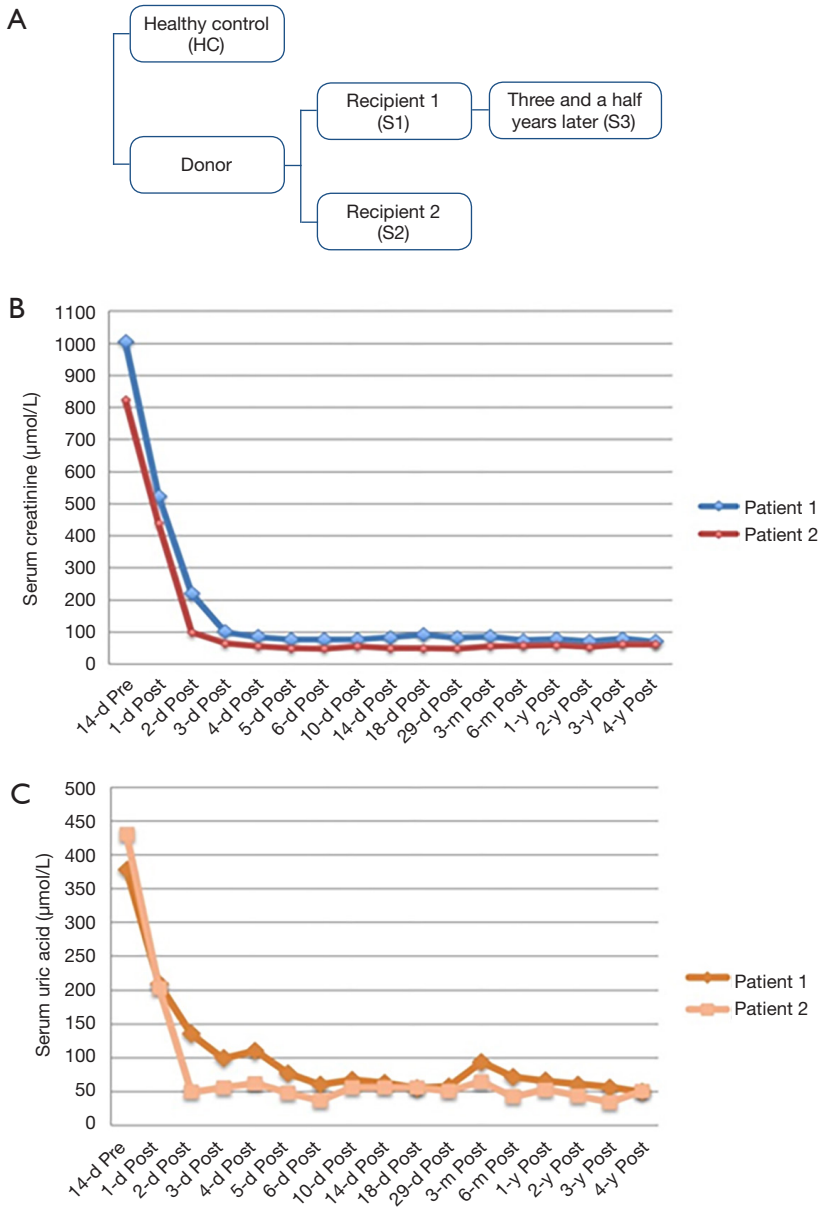

Figure 1 Clinical data of the patients. (A) We collected the implants transplanted into the two recipients immediately (S1 and S2) and followed for three and a half years post-transplantation (S3) and a healthy control (HC). Variation of serum creatinine (B) and uric acid (C) within years of follow-up in the two recipients.

was performed on a cBot Cluster Generation System using HiSeq 2500 PE Cluster Kit (Illumina) according to the manufacturer's instructions. After cluster generation, the library preparations were sequenced on an Illumina Hiseq 2500 platform.

PCR amplification and sequence analysis

The genomic DNA was isolated from the transplant samples obtained from the recipients and live donors using the AxyprepTM Blood Genomic DNA Miniprep Kit (Axyprep, USA). Seven pairs of oligonucleotide

Table 1 Laboratory data on admission

Biochemical date	Recipient 1	Recipient 2
Gender	Male	Female
Age (years)	41	37
Complete blood cell count		
WBC (×10^9/L)	7.6	6.3
Hemoglobin (g/dL)	118	83
Hematocrit (%)	35.7	26.7
Platelets (×10^9/L)	145	128
Serum chemistries		
Total protein (g/L)	87.6	–
Albumin (g/L)	50.7	45
BUN (mg/dL)	17.1	17.6
Cr (μmol/L)	1004	823
Uric acid (μmol/L)	378	431
Sodium (mmol/L)	137	132
Potassium (mmol/L)	4.97	3.7
Chloride (mmol/L)	97	89
Calcium (mmol/L)	2.75	2.5
Phosphorus (mmol/L)	2.29	1.6
Urinalysis		
pH	5.5	8.5
Specific gravity	1.014	1.008
Protein	++	++
Occult blood	+++	+++
WBC sediment (/HPF)	1–3	0–2

primers were generated to amplify the different regions obtained from DNA sequencing and were sequenced directly. A total of 80 ng of genomic DNA was amplified in 20 μL reaction volume containing 10 μL Premix Taq (TaKaRa) and 0.8 μM primers. Amplification products were purified on 1.5% agarose gel using 0.5× TBE buffer and Wizard SV gel and Gel/PCR DNA Fragments Extraction Kit (Promega, USA). DNA sequencing was performed with an automated DNA sequencer (Applied Biosystems 3730-Avant Genetic Analyzer; Applied Biosystems, USA).

RNA isolation and cDNA library construction

Total RNA was extracted from implants of two kidney transplant recipient using Trizol reagent (Invitrogen, USA), and RNase-free DNase I (TaKaRa, Japan) following the manufacturer's protocol. One was the healthy control and the other was recipient1 after three and a half years post-transplantation. A total of 1.5 μg of RNA per sample was used as input material for RNA sample reparations. The differentially expressed genes were detected using an Affymetrix Mouse Genome 430 2.0 microarray (Thermo Fisher Scientific). The experimental procedures for microarray were performed at the Hangzhou Tianke Corporation (Hangzhou, China). The clustering of the index-coded samples was performed on a cBot Cluster Generation System using the TruSeq SR Cluster Kit v3-cBot-HS (Illumina) according to the manufacturer's instructions. After the cluster generation, the library preparations were sequenced on an Illumina HiSeq 2500 platform.

Results

Clinical and biochemical investigations

On September 2012, a 41-year-old male (recipient 1) and a 37-year-old female (recipient 2) with end-stage renal disease caused by chronic kidney disease (CKD) received renal transplantation from a deceased donor who had died from craniocerebral injury. On admission, they had a serum creatinine of 1,004 and 823 μmol/L (*Table 1*). Recipient 1 had a gradually increased serum creatinine (S-Cr) level beginning in 2000 diagnosed as IgA nephritis and started on hemodialysis at the age of 34 years. Serum creatinine level gradually increased in recipient 2 for 8 years and she began hemodialysis at the age of 35 years. The donor was a 30-year-old male (serum creatinine: 79 μmol/L) with no significant past medical history (*Figure 1A*). Within the first week of transplant, the serum creatinine levels decreased to 76 and 49 μmol/L respectively (*Figure 1B*). In addition, their physical examination, laboratory examination and grafts biopsy at zero time were uneventful and they were released from the hospital after great recovery. Both of them received triple immunosuppressive therapy consisting of cortico-steroids, mycophenolate mofetil, and tacrolimus. Since then, the two recipients have reported fluctuating low serum UA levels (patient 1: 55–65 μmol/L, normal serum creatinine: 70–80 μmol/L; patient 2: 45–55 μmol/L, normal

serum creatinine 60–70 µmol/L) (*Figure 1C*). We confirmed a well-functioning kidney graft (serum creatinine 82 µmol/L, eGFR 102 mL/min and serum creatinine 60 µmol/L, eGFR 109 mL/min respectively) with no proteinuria or haematuria after three years the transplantation except for the high fraction excretion of UA (FEUA) of 44% and 75% (normal <10%) and UA clearance of 35.9 and 73.3 mL/min (normal 7.3–14.7 mL/min). We reviewed the results of pre-operative laboratory examinations of donor and found that the donor had a very low serum UA of 48 µmol/L. Our findings suggested that the low serum UA in two recipients could be associated with HRH, and therefore, molecular genetic analysis was performed to confirm the same.

UA transporter genes analysis

PCR followed by DNA sequence analysis revealed 7 types of mutations. Probands were heterozygous for the unpublished missense mutation p.Q141K(c.C421A) in exon 5 and p.Q126X(c.C376T) in exon 4 in the ABCG2 and heterozygous for the unidentified missense mutation p.R89H(c.G266A) and p.L181V(c.C541G) in exon 1 in the *SLC22A12* gene. Variants p.R89H and p.L181V are novel and have not yet been identified in *SLC22A12* gene. Moreover, the nature of these mutations appears pathogenic as per the PolyPhen software (http://genetics.bwh.harvard.edu/pph2/) indicates that substitutions in SLC22A12 were probably damaging (score of 0.809; sensitivity 0.84; specificity 0.93 and score of 0.996; sensitivity 0.55; specificity 0.98, respectively).

Other variations, one homozygous exon variant (p.R294H) and one heterozygous exon variant (p.A100T) have been previously reported (*Figure 2*, *Table 2*).

Gene expression analysis by RNA-sequencing (RNA-seq)

To study the effect of mutations on the gene expression, we analyzed the transcriptomes of the transplant tissues by RNA-seq (*Table S1*). Analysis of the RNA-seq data revealed that a total of 57 genes were differentially regulated among the hypouricemia patients and the healthy controls (fold change >2, P value <0.05). Out of 57 gene, 21 were upregulated, while 36 genes were down regulated. We used unsupervised clustering hierarchy (*Figure 3A*) and the details of the differentially expressed genes are given in *Table 3*. KEGG pathway analysis revealed that the differentially expressed genes were played roles in hematopoietic cell lineage, T cell receptor signaling pathway, cancer related pathways, MAPK signaling pathway, and other important regulatory processes (*Figure 3B*).

Relationship between gene mutation and expression levels

We tried to elucidate the relationship between SNPs, gene expression, and phenotypes together. Mutation analysis findings point towards epithelial growth factor (EGF) receptor (EGFR), IL-7 receptor (IL7R) and growth hormone receptor (GHR) which could implicate the important role in transcriptional regulation through cancer related pathways, MAPK signaling pathway, regulation of actin cytoskeleton cytokine-cytokine receptor interaction, hematopoietic cell lineage, and Jak-STAT signaling pathway to exert their influence on the phenotypes (*Table 3*).

Discussion

HRH, is defined arbitrarily as serum UA concentration less than 119 µmol/L and increased fractional excretion of uric acid (FEUA) and/or uric acid clearance (CUA), with exclusion of other diseases that present hypouricemia as a symptom (13). Loss-of-function mutations in the SLC22A12 gene coding the UA transporter 1 (URAT1) and SLC2A9 gene coding the glucose transporter (GLUT9) caused type 1 (RHUC1) and 2 (RHUC2), respectively. Most renal hypouricemia is caused by mutations in the *SLC22A12* gene. The high incidence of RHUC1 has been reported in the Asia region and Roma ethnicity. The allele frequency of c.774G>A (p.W258X) and c.269G>A (p.R90H) were 2.37% and 0.40 % in SLC22A12 among Japanese and Koreans (14,15). Frequencies of the c.1245_1253del and c.1400C>T variants were present in the Roma population at 1.87% and 5.56%, respectively (16,17).Several GWAS have indicated a substantial association between urate concentration and SNPs at 10 genetic loci including transporter-coding genes such as SLC2A9 (GLUT9), ABCG2 (BCRP), SLC17A1 (NPT1), SLC17A3 (NPT4), SLC17A4 (provisionally named as NPT5), SLC22A11 (OAT4), SLC22A12 (URAT1), and SLC16A9 (MCT9) as well as urate transport related scaffolding protein PDZK1 (18). However, Hurba *et al*. (19) reported the non-synonymous allelic variants on of GLUT9 were not related to urate uptake activity. But several studies reported clear function impact of GLUT9 variants in patients with renal hypouricemia 2 (20-22). For example, Dinour *et al*. (23) reported that homozygous mutations of GLUT9 cause a total defect of UA absorption and are associated with a high incidence of renal calculus and EIAKI and nephrolithiasis. Previously, a successful

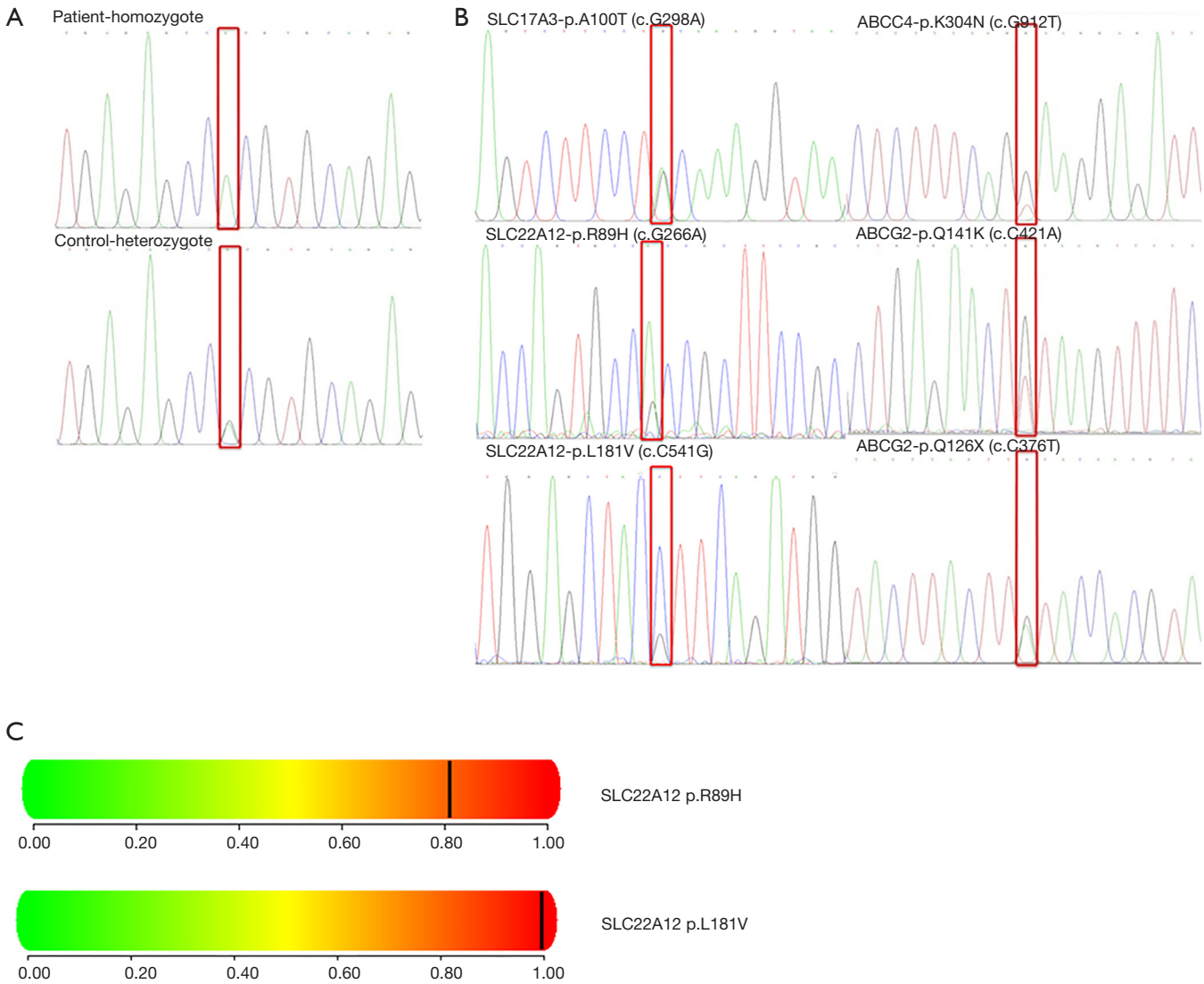

Figure 2 Mutations found in implants (S1, S2, S3) with hereditary hypouricemia. (A) The homozygous mutation of SLC2A9-p.R294H (c.G881A) discovered in the implants (S1, S2, S3) and the healthy control had happened to find the heterozygous mutation as well; (B) the other mutations discovered in this study; (C) SLC22A12 p.R89H mutation is predicted to be possibly damaging with a score of 0.809 (sensitivity: 0.84; specificity: 0.93); p.L181V mutation is predicted to be probably damaging with a score of 0.996 (sensitivity: 0.55; specificity: 0.98).

living-related kidney transplant has been reported in HRH. Both the donor and the recipient had the same disorder of urate metabolism and were homozygous for G774A before kidney transplantation (10). Another rare case reported nephrocalcinosis in the distal tubules caused by HRH in a living-donor renal transplantation. Genetic analysis revealed a heterozygous nonsense mutation of C889T in exon 5 of the urate transporter 1 (*URAT1*) gene in both, the donor and the recipient (4). In this study, we present a rather rare case of donor-derived HRH. To the best of our knowledge, this is the first report to show that unrelated recipients can acquire unexpected hypouricemia after kidney transplantation from the same donor with a different genetic background.

DNA analysis was performed on the tissue before being transplanted into the two recipients. The cases and a control

Table 2 Sequence variations of coding regions in candidate genes between the implants transplanted into the two recipients immediately (S1 and S2) and followed for three and a half years post-transplantation (S3) and a healthy control (HC)

Chr	Exon	SNP	Nucleotide change	Amino acid change	HC	S1	S2	S3	Gene	Previously reported
4	7	C>T	c.G881A	p.R294H	Heter	Homo	Homo	Homo	SLC2A9	Yes
4	5	G>T	c.C421A	p.Q141K	None	Heter	Heter	Heter	ABCG2	No
4	4	G>A	c.C376T	p.Q126X	None	Heter	Heter	Heter	ABCG2	No
6	3	C>T	c.G298A	p.A100T	None	Heter	Heter	Heter	SLC17A3	Yes
11	1	G>A	c.G266A	p.R89H	None	Heter	Heter	Heter	SLC22A12	No
11	1	C>G	c.C541G	p.L181V	None	Heter	Heter	Heter	SLC22A12	No
13	8	C>A	c.G912T	p.K304N	None	Heter	Heter	Heter	ABCC4	No

SNP, single nucleotide polymorphism.

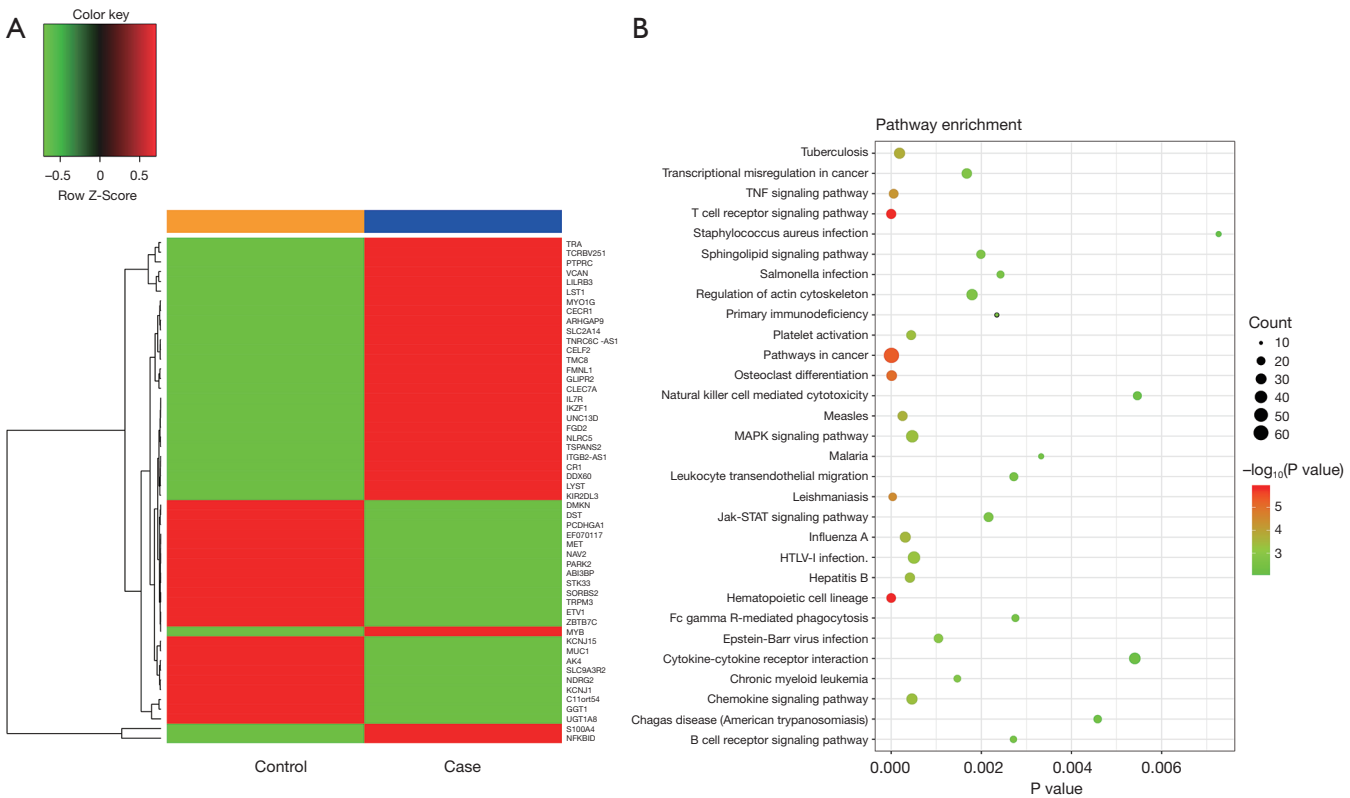

Figure 3 Screening for differentially expressed genes in hypouricemia. (A) The clustering of differential genes in heatmap. The color in the heatmap represents the log 2-fold change of expression values. Text on the right of heatmap indicates the enriched gene ontology terms for each cluster of genes; (B) top 30 pathways from Kyoto Encyclopedia of Genes and Genomes enrichment analysis. The x-axis represents KEGG enrichment scores and the y-axis represents pathway terms. The colors of circle indicate P values and the size of circle indicates the numbers of differential RNAs. The circle with redder and larger indicating that the enrichment of the pathway is higher and differential RNAs number is larger in the pathway.

Table 3 Other SNP sites found in transplants and possible pathways

Gene	SNP ID	Chr	Risk allele	Possible pathway
EGFR	rs62452902	7	A	Pathways in cancer
				MAPK signaling pathway
				Regulation of actin cytoskeleton
				Cytokine-cytokine receptor interaction
IL7R	rs10058453	5	T	Hematopoietic cell lineage
				Jak-STAT signaling pathway
				Cytokine-cytokine receptor interaction
GHR	rs4146624	5	A	Jak-STAT signaling pathway
				Cytokine-cytokine receptor interaction

SNP, single nucleotide polymorphism; GHR, growth hormone receptor.

were followed for 3.5 years post-transplantation. Our results showed that the mutated genes in the grafts of the donor remained unchanged after transplantation in a different un-URH environment up to the follow-up duration of 3.5 years. Many non-pathogenic single point mutations identified in the present study have been reported earlier and included the homozygous missense mutation, p.R294H in SLC2A9 in exon 7 (24) and a heterozygous sequence variant, p.A100T in SLC17A3 in exon 3 (25). We could not confirm the nosogenetic mutations from the family of the deceased donor. Therefore, the effect of previously unreported mutations on the hypouricemia remains unknown and needs to be answered in future. Genetic variants have been associated with many human diseases. However, about 88% of the GWAS-nominated SNPs are in intronic or intergenic regions suggesting that the noncoding regions of the genome can contribute to the disease risk, and may be involved in gene regulation. However, the underlying mechanism by remains unclear (26). SNPs can modulate the gene expression through a change in chromatic structure to distance a gene from its enhancers and by altering the copy number (27). Within each susceptibility locus, candidate risk genes have been prioritized based largely on bioinformatic evaluations of the relationships among genes, the presence of coding SNPs, or the gene expression-genotype correlations (28-30). Regulatory and coding variants often modify the functional impact of each other that can be detected by the sequencing data. Characterizing these mutual effects might help us understand functional mechanisms behind genetic associations to human phenotypes (31). For example mutational signatures related to liver carcinogenesis revealed frequently mutated coding and noncoding regions, such as long intergenic noncoding RNA genes (NEAT1 and MALAT1), promoters, CTCF-binding sites, and regulatory regions (32). Biswajit *et al.* unveiled rs2279590 at *PTK2B–CLU* locus, a risk factor previously associated with Alzheimer's disease, to have an enhancer effect on two nearby genes coding for protein tyrosine kinase 2 beta (*PTK2B*) and epoxide hydrolase-2 (*EPHX2*) (33). Based on these results, we speculate that defects in DNA sequences could probably affect tubule function through differential RNA expression. DNA mutation analysis have identified three risk loci that increase renal hypouricemia risk: (I) SNP (rs62452902) at EGFR locus, (II) SNP (rs10058453) at IL7R locus, (III) SNP (rs4146624) at GHR. We performed enrichment analysis from the data of the differentially expressed genes and identified that pathways related to cancers, MAPK signaling, regulation of actin cytoskeleton, cytokine-cytokine receptor interaction, hematopoietic cell lineage, and Jak-STAT signaling were significantly altered in hypouricemia transplant tissue, indicating that these pathway may be involved in the disease. EGF risk alleles may upregulate pathways related to cancer, MAPK signaling, alter actin cytoskeleton, and cytokine-cytokine receptor interactions to promote elevated blood UA by impacting UA metabolism and inhibiting UA excretion. Though our study presents interesting findings, its limitations include small number of cases and therefore requirement of further work to validate this work.

Conclusions

We report a renal transplantation case of donor-derived

hypouricemia caused by mutations in the transplant tissue of donor with HRH. Seven kinds of potent mutations were discovered in this case, including two novel mutations which could be pathogenic in nature. However, further studies are needed to prove the role of these mutations in HRH pathogenicity.

Acknowledgments

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study details were explained to all the participants, and a signed informed consent was obtained after their agreement.

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Supplementary

Table S1 The value of differentially expressed genes in hypouricemia

Gene symbol	Value control	Value renal hypouricemia	log2 (fold change)	P value	Biological process
AK4	80.8162	0.391208	–7.69057	0.043357	ATP metabolic process
PTPRC	3.75744	767.974	7.67517	0.015972	Immunoglobulin biosynthetic process
CR1	1.03823	38.5892	5.21599	0.043357	Complement receptor mediated signaling pathway
S100A4	43.3991	3757.78	6.43607	0.027141	Epithelial to mesenchymal transition
MUC1	137.403	1.12964	–6.92641	0.007747	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest
LYST	2.09134	44.666	4.41668	0.018538	T cell mediated immunity
CELF2	1.17293	89.9344	6.26068	0.007747	RNA processing
TSPAN32	1.03685	50.396	5.60303	0.035989	Negative regulation of cell proliferation
NAV2	6.79902	0.032998	–7.68679	0.018538	Regulation of systemic arterial blood pressure by baroreceptor feedback
C11orf54	243.97	5.42007	–5.49225	0.048447	Metabolic process
STK33	3.86033	0.047077	–6.35757	0.044526	Protein autophosphorylation
KCNJ1	53.6641	0.363949	–7.20408	0.027141	Kidney development
SLC2A14	1.40047	136.596	6.60786	0.028838	Multicellular organismal development
CLEC7A	1.14152	181.946	7.31641	0.035989	Pattern recognition receptor signaling pathway
ARHGAP9	2.00949	141.798	6.14087	0.007747	Small gtpase mediated signal transduction
TRA	18.6176	679.856	5.19049	0.007747	–
NDRG2	63.7139	3.18928	–4.32031	0.043357	Negative regulation of cytokine production
SLC9A3R2	75.0647	1.82555	–5.36173	0.007747	Protein complex assembly
NLRC5	3.88494	53.4241	3.78153	0.007747	Positive regulation of type I interferon-mediated signaling pathway
FMNL1	4.68808	223.525	5.5753	0.012214	Cortical actin cytoskeleton organization
TMC8	2.19739	97.797	5.47592	0.035989	Regulation of cell growth
UNC13D	1.64857	58.1647	5.14086	0.021719	Positive regulation of exocytosis
TNRC6C-AS1	8.19721	87.8446	3.42175	0.032078	–
ZBTB7C	0.851521	0.090405	–3.23557	0.027141	Immune response
KIR2DL3	0.344843	25.4095	6.20328	0.007747	–
DMKN	22.4149	0.978012	–4.51846	0.041821	–
NFKBID	62.2206	2800.48	5.49214	0.034038	Inflammatory response
LILRB3	2.73845	526.051	7.5857	0.007747	Adaptive immune response
UGT1A8	427.903	0.162788	–11.3601	0.007747	Negative regulation of steroid metabolic process
KCNJ15	140.173	5.13269	-4.77135	0.030624	Potassium ion transport
ITGB2-AS1	1.46492	40.9133	4.80368	0.034038	–
GGT1	205.465	13.256	–3.95418	0.041821	Regulation of immune system process
CECR1	5.01392	151.328	4.9156	0.040912	Adenosine catabolic process
ABI3BP	5.27652	0.01453	–8.50441	0.04645	Positive regulation of cell-substrate adhesion
DDX60	3.1429	36.694	3.54538	0.032078	Positive regulation of MDA-5 signaling pathway
SORBS2	12.1655	0.050895	–7.90105	0.043357	Cell growth involved in cardiac muscle cell development
IL7R	0.829966	59.2623	6.15792	0.044526	Regulation of DNA recombination
VCAN	1.18801	573.609	8.91537	0.007747	Skeletal system development
PCDHGA1	32.3432	2.55042	–3.66466	0.037849	Homophilic cell adhesion via plasma membrane adhesion molecules
LST1	5.50722	464.119	6.39703	0.007747	Negative regulation of lymphocyte proliferation
FGD2	2.79516	65.8158	4.55743	0.012214	Regulation of small gtpase mediated signal transduction
MYB	0.035818	1.13568	4.9867	0.007747	G1/S transition of mitotic cell cycle
DST	21.8556	1.26056	–4.11586	0.028838	Maintenance of cell polarity
PARK2	6.04009	0.042097	–7.1647	0.007747	Positive regulation of mitochondrial fusion
IKZF1	0.646565	58.6186	6.50242	0.040912	Lymphocyte differentiation
EF070117	8.70526	0.170523	–5.67385	0.007747	–
MET	8.68294	0.047729	–7.50719	0.027141	Negative regulation of hydrogen peroxide-mediated programmed cell death
TCRBV2S1	19.5629	635.724	5.02221	0.007747	–
ETV1	1.52424	0.054565	–4.80398	0.043357	Positive regulation of transcription from RNA polymerase II promoter
MYO1G	1.31113	157.821	6.91133	0.041821	Fc-gamma receptor signaling pathway involved in phagocytosis
GLIPR2	2.81901	205.933	6.19084	0.044526	Positive regulation of epithelial to mesenchymal transition
TRPM3	12.1687	0.009194	–10.3702	0.037849	Sensory perception of temperature stimulus