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Renal hypouricemia as the cause of exercise-induced acute kidney injury

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Hypouricemia is defined as a serum uric acid (UA) concentration of ≤2 mg/dL [1]. Renal hypouricemia (RHUC) is characterized by a decreased serum UA level (≤2 mg/dL) and increased fractional excretion of UA (FE_{UA} of >10%) caused by a mutation in the *SLC22A12* gene (encoding uric acid transporter 1 [URAT1]) or the *SLC2A9* gene (encoding glucose transporter member 9 [GLUT9]) [2,3]. These mutations lead to the production of URAT1 or GLUT9 protein with a reduced ability to reabsorb urate into the bloodstream. Although RHUC is usually asymptomatic, its relevance to exercise-induced acute kidney injury (EIAKI) and urolithiasis has been reported [1,4]. Here, we present two cases of type 1 RHUC caused by compound heterozygous mutations of the *SLC22A12* gene on exon 4 and exon 9 and by a homozygous mutation of the *SLC22A12* gene on exon 4, respectively, which presented distinct clinical courses.

Case 1

A 51-year-old man visited our outpatient clinic and reported pain upon exercise. According to his medical records, he had a history of myalgia, pain in both flanks, and progressive oliguria that had occurred one week after vigorous exercise nine years prior. He was taking anti-hypertensive drugs and statins and had no family history of kidney disease. On examination, his vital signs were stable, and he was apparently healthy. However, laboratory tests revealed acute kidney injury (AKI; serum creatinine, 9.2 mg/dL) (Table 1). The serum UA level was 6.1 mg/dL despite AKI. Renal ultrasound revealed normal kidney size and echogenicity but detected a 1.2-cm renal calyceal stone. The patient received intravenous normal saline for one week without dialysis. After 3 months, his renal function had fully recovered. However, his serum UA level was markedly below normal (0.8 mg/dL), and his FE_{UA} was 57.4% (Table 1). Genetic testing using next-generation sequencing identified compound heterozygous mutations of *SLC22A12* (a nonsense mutation of c.774G>A [p.W258X] on exon 4 and a missense mutation of c.269G>A [p.R90H] on exon 9) (Fig. 1A). Because the patient has the potential to experience repeat AKI, we recommended he avoid strenuous exercise and nephrotoxic drugs.

Case 2

A 37-year-old woman visited our outpatient clinic after

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Table 1. Laboratory findings

	Reference	Case 1			Case 2
		Admission	Outpatient (3 mo)	Outpatient (9 yr)	Outpatient
Urinalysis					
pH	4.8–7.5	5.0	6.0	6.0	6.0
Protein	Negative	Negative	Negative	Negative	Negative
Occult blood	Negative	Negative	Negative	Negative	Negative
Complete blood cell count					
Hemoglobin (g/dL)	13.0–18.0	14.3	16.0	16.0	12.6
Hematocrit (%)	40.0–54.0	39.9	46.0	47.0	38.8
Platelets ($\times 10^9$/L)	150–450	200	245	255	333
White blood cells ($\times 10^9$/L)	4.0–10.0	6.8	8.4	6.5	7.4
Eosinophils (%)	0–5	0.6		4.5	6.0
Serum					
Urea nitrogen (mg/dL)	7.0–20.0	79.5	13.5	13.0	10.3
Creatinine (mg/dL)	0.6–1.2	9.2	0.9	0.8	0.7
Uric acid (mg/dL)	2.6–7.2	6.1	0.8	0.6	0.5
Sodium (mmol/L)	136–146	140.0	141.0	140.0	139.0
Potassium (mmol/L)	3.5–5.1	5.1	4.3	4.9	4.3
Chloride (mmol/L)	98–106	105.0	105.0	104.0	101.0
Lactate dehydrogenase (U/L)	250–450	525.0		189.0	224.0
Creatine kinase (U/L)	26–200	222.0		147.0	140.0
Serum protein (g/dL)	6.6–8.3	7.0	7.2	7.0	7.8
C-reactive protein (mg/dL)	0.01–0.47	0.48		0.08	0.06
Calcium (mg/dL)	8.0–10.0	8.9		9.7	9.6
Phosphorous (mg/dL)	2.6–4.5	5.9		3.5	4.3
HCO_3^- (mmol/L)	21–28	16.8		25.1	29.3
Renal function					
eGFR (mL/min/1.73 m^2)	MDRD equation	6		107	93
FE_{Na} (%)		2.3			
FE_{UA} (%)		49.9		57.4	65.0

eGFR, estimated glomerular filtration rate; FENa, fractional excretion of sodium; FEUA, fractional excretion of uric acid; MDRD, Modification of Diet in Renal Disease.

hypouricemia was incidentally found during a medical checkup. She denied any history of AKI or urolithiasis. She had no family history of kidney disease, but her father also had hypouricemia. Her serum UA level was 0.5 mg/dL, and her FE_{UA} was 65% (Table 1). Genetic testing revealed a homozygous mutation of *SLC22A12* on exon 4, c.774G>A (p.W258X) (Fig. 1B). We explained her diagnosis and the risk for AKI after heavy exercise. Regular monitoring of renal function and serum UA level was recommended.

This report emphasizes the importance of genetic testing and sex differences in patients with suspected RHUC. The pathogenic mechanism of EIAKI in RHUC is not completely understood. Hosoyamada [5] have suggested that high intratubular UA concentration activates the sympathetic nervous system, resulting in afferent arteriolar constriction and AKI. Miyamoto et al. [6] have proposed that RHUC patients have an abnormal salvage pathway of purines, which are unable to resynthesize adenosine triphosphatase during anaerobic exercise and are vulnerable to stress-induced hypoxia. Such defects might be the cause of EIAKI in patients with RHUC.

In the present report, case 1 presented with EIAKI, whereas case 2 did not. In general, autosomal recessive diseases are caused by abnormalities in both alleles. In contrast, unlike case 2, case 1 experienced severe EIAKI even with only one allele anomaly. It has been well-documented

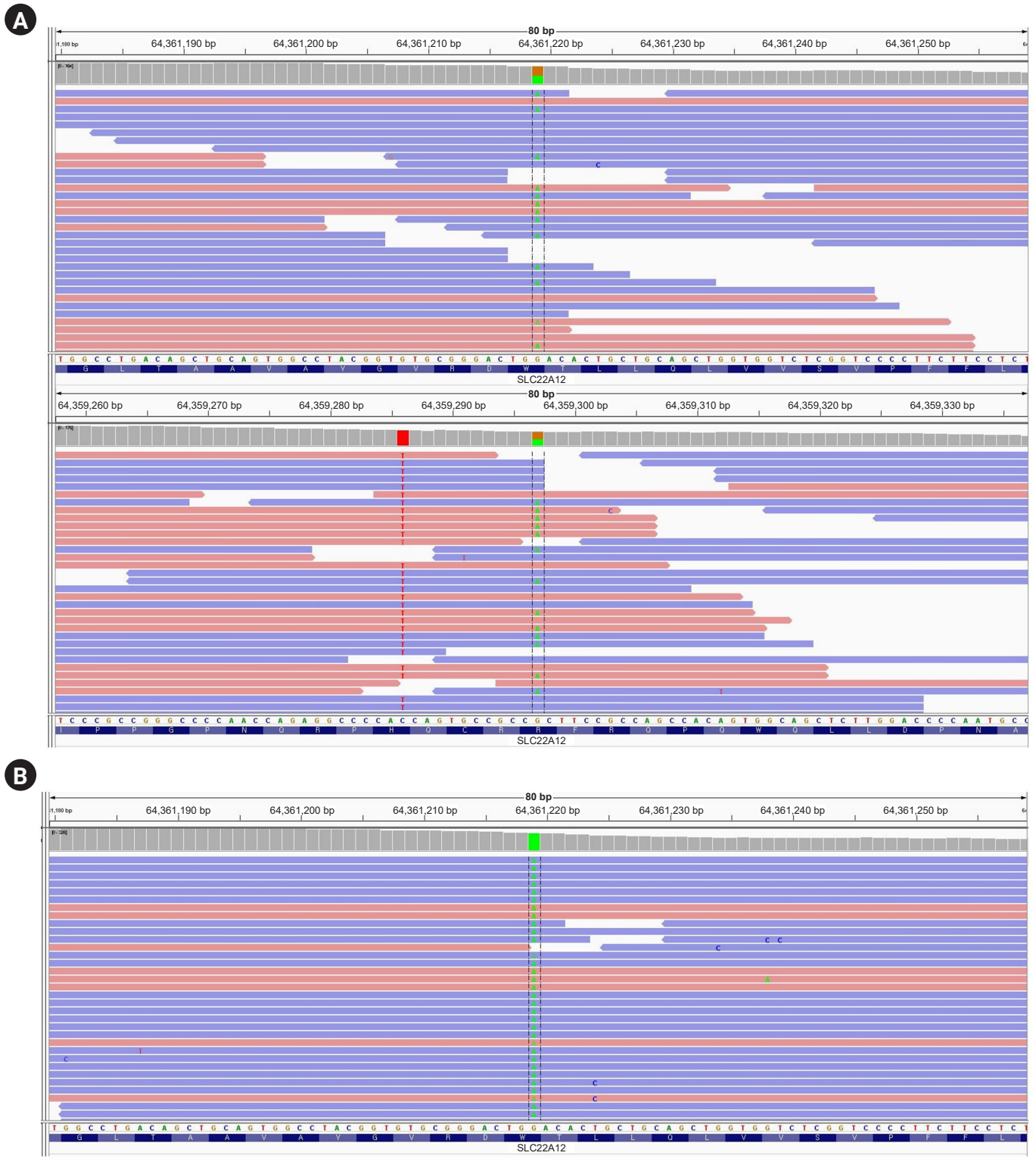

Figure 1. Next-generation sequencing results as viewed in the Integrative Genome Viewer. (A) Compound heterozygous mutations of the *SLC22A12* gene in case 1; c.774G>A (p.W258X) on exon 4 and c.269G>A (p.R90H) on exon 9. (B) A homozygous mutation of the *SLC22A12* gene in case 2; c.774G>A (p.W258X) on exon 4.

that patients with multiple mutations develop more severe clinical genetic cardiovascular diseases [7]. In contrast, it has not been determined whether the presence of multiple gene mutations of *SCL22A12* in RHUC (as in case 1) causes more severe clinical manifestations than homozygous gene mutations of *SCL22A12* (as in case 2). Consistent with genetic cardiovascular disorders, compound heterozygous mutations of the *SCL22A12* are more prone to AKI than one homozygous mutation of the *SCL22A12* gene, as was seen in our cases. It is not known whether the development of EIAKI in patients with RHUC is sex-dependent. RHUC exhibits autosomal recessive inheritance, but EIAKI has predominantly been reported in men. Although a typically lower exercise intensity is one reason for the low incidence of AKI in women [1], sex hormone differences may play a major role in the pathogenesis. Estrogen exerts protective effects against inflammation and mitochondrial dysfunction in AKI. Furthermore, females are more tolerant to renal ischemic reperfusion injury than males due to their depressing renal sympathetic tone [8]. These differences may at least partially explain the clinical differences observed in our cases.

In conclusion, we suggest that compound heterozygous gene mutations of the *SCL22A12* gene have an additive effect on the development of EIAKI, and sex differences may also be a major determinant in disease progression. It is important to identify patients with RHUC who would benefit most from earlier treatment by considering both their genetic analysis and sex.

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors' contributions

Conceptualization, Data curation: Haeun Lee, DK
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Writing–review & editing: DK, Hanbi Lee, JY, MK, CWP
All authors read and approved the final manuscript.

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