

A Case of Idiopathic Renal Hypouricemia with *SLC22A12* Gene Mutation Showing General Weakness and Incidental Renal Stone

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Idiopathic renal hypouricemia (iRHUC) is a rare hereditary disease caused by a defect in urate handling of renal tubules. Type 1 renal hypouricemia (RHUC1) is diagnosed with confirmation of a mutation in *SLC22A12* gene which encodes a renal urate-anion exchanger (URAT1). The majority of iRHUC patients are asymptomatic, especially during childhood, and thus many cases go undiagnosed or they are diagnosed late in older age with complications of hematuria, renal stones, or acute kidney injury (AKI). We report a case of a 7-year-old boy with subtle symptoms such as general weakness and dizziness and revealed hypouricemia and incidental nephrolithiasis. Homozygous mutations were detected in the *SLC22A12* (c.774G>A) by molecular analysis. The present case suggests that fractional excretion of uric acid (FEUA) screening could be better followed by the coincidental discovery of hypouricemia, to prevent conflicting complications of iRHUC, even with normal urine uric acid to creatinine ratio (U_{UA}/U_{Cr}), and sequential genetic analysis if needed.

Key words: Idiopathic renal hypouricemia, *SLC22A12* gene, Urate-anion exchanger, URAT1

Introduction

Idiopathic renal hypouricemia (iRHUC) is characterized by impaired uric acid transport, reabsorption insufficiency, or accelerated secretion of uric acid^{1,2}. There are two types of iRHUC according to two different genetic mutations. A Mutation of *SLC22A12* gene encoding a renal urate-anion exchanger (URAT1) causes iRHUC type 1 while a mutation of *SLC2A9* gene encoding a glucose and urate transporter (GLUT9) leads to iRHUC type 2³. Since symptoms of iRHUC are mostly mild or nonspecific, diagnosis is usually made after complications have developed⁴. Occasionally hematuria, nephrolithiasis, or exercise- or dehydration-induced acute kidney injury (AKI) could be initial symptoms^{5,6}. Symptomatic iRHUCs are known to be relatively more frequent in homozygous *SLC2A9* mutations than *SLC22A12* mutations. We present a case of a 7-year-old boy who was diagnosed iRHUC with *SLC22A12* mutations by hypouricemia and unexpected renal stone.

Case report

A 7-year-old boy visited the outpatient clinic due to persisting dizziness and general weakness from a few years ago. He was born out of normal vaginal delivery and his past medical history since birth was nonspecific except for an event of gross hematuria when he was 7-month-old. But urinalysis at the time showed no hematuria and the symptom never recurred. At his first visit, height was 132 cm (75th percentile), weight 26 kg (25–50th percentile), and BMI 14.9 kg/m² (10–25th percentile). His vital signs were normal. However, dizziness and general weakness had been aggravated nearly to syncope that the patient was frequently absent from school. Otherwise, there were no specific symptoms and physical examination also showed no abnormal findings including costovertebral angle tenderness. Laboratory findings were Hb of 11.9 g/dL (normal range; 11.0–16.0 g/dL), blood urea nitrogen of 14.7 mg/dL (5.0–18.0 mg/dL), creatinine of 0.53 mg/dL (0.22–0.59 mg/dL), and serum sodium of 137 mmol/L (134–143 mmol/L). The following parameters were within normal limits: renin, aldosterone, and thyroid function test. However, serum uric acid level was 0.85 mg/dL (normal range; 2.0–5.0 mg/dL), which is abnormally low. Repeated test of uric acid consistently showed low level (0.62 mg/dL). A sequential spot urine test revealed urine uric acid to creatinine ratio (U_{UA}/U_{Cr}) of 0.58 but fractional excretion of uric acid (FEUA) of 48.6% (normal range; <10%). Microscopic hematuria was not found on urinalysis. Kidney sonography showed parapelvic high echogenicity and a 4 mm-sized calyceal stone in the left kidney without hydronephrosis (Fig. 1). To identify the underlying cause of the hypouricemia, diagnostic

exome sequencing (DES) was performed by Green Cross Genome Corp. using Celeomics G-Mendeliome DES kit. Genomic DNA sequencing of the entire coding region of the *SLC22A12* was conducted using polymerase chain reaction and the amino acid 258 (tryptophan, TGG) was replaced with a stop codon (TGA) by mutation of G774A [W258X]. The patient was diagnosed a homozygous mutation in the *SLC22A12* gene, which is known to be a pathogenic variant of iRHUC (Fig. 2). Accordingly, a whole fa-

SLC22A12 NM_144585.4:c.774G>A (p.Trp258*)

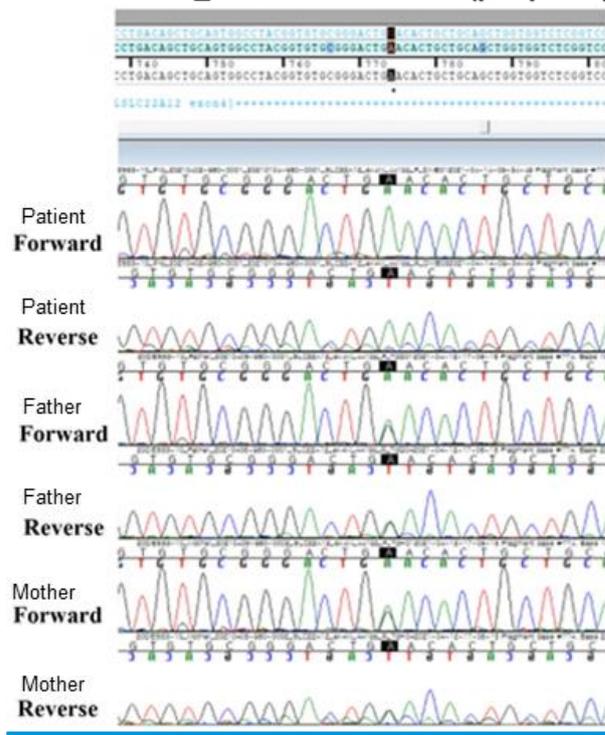


Fig. 2. Sequences around the c.774G>A (p.W258X) mutation of the patient and his parents. The black points indicates 774G>A.

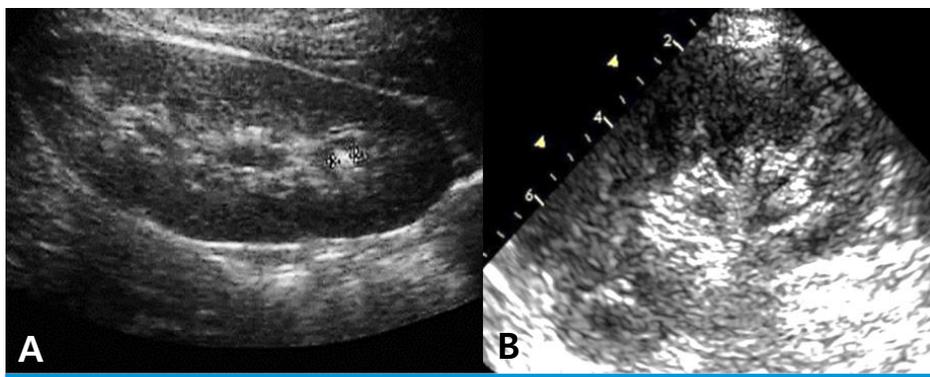


Fig. 1. The kidney sonography of patient shows a renal stone and high echogenicity. A, Calyceal stone* sized (4 mm in size) without hydronephrosis; B, increased echogenicity in parapelvic region.

mily including the patient's mother, father, and brother completed DES. The results revealed that his mother and father had heterozygous mutations of the *SLC22A12* gene, the amino acid 258 (TGG) replaced with TGA, while his brother had no mutation (Fig. 3). The patient's mother was the only one who had a clinical symptom nonspecific as fatigue. Laboratory findings of her showed low level of serum uric acid, 2.2 mg/dL (normal range 2.6–7.2 mg/dL), and high level of FEUA (18.6%). Serum uric acid levels of the patient's father and brother were 4.35 and 4.25 mg/dL, respectively. FEUA of them were 20.4% and 10.4%, each (Table 1). The patient was advised to avoid intense physical activity and dehydration. He has been on conservative management with potassium citrate for a month now and symptoms are similar so far. Also, he is on yearly follow-up, checking serum and urine uric acid level, and kidney sonography.

SLC22A12 NM_144585.4:c.774G>A (p.Trp258*)

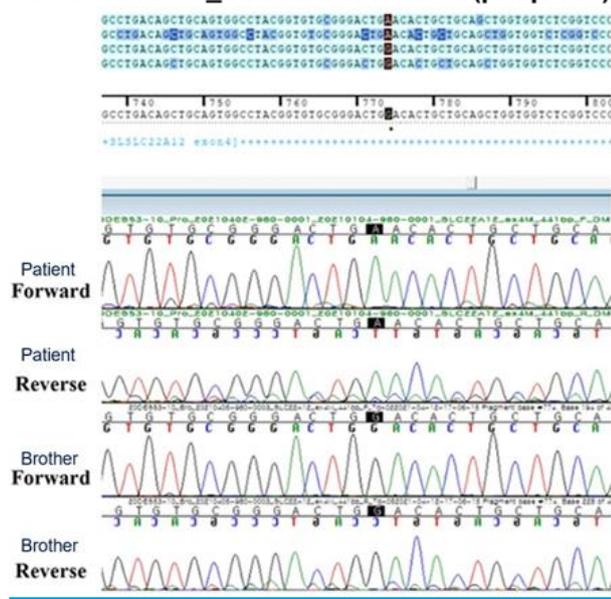


Fig. 3. Sequences around the c.774G>A (p.W258X) mutation of the patient and his brother. His brother had no mutation. The black points indicates 774G>A.

Discussion

Hypouricemia is caused by diminished uric acid production or increased uric acid clearance⁷. iRHUC, also known as familial hypouricemia, is an autosomal recessive disorder characterized by serum uric acid level lower than 2 mg/dL due to increased renal clearance with FEUA above 10%¹⁴. Genetic analysis of the mutations in *SLC22A12* and *SLC2A9* is a confirmative test. The impact of *SLC2A9* mutations on renal excretion of uric acid is reported exceeding that of *SLC22A12*¹⁷. Therefore, patients with mutations in *SLC22A12* tend to show relatively minor symptoms, while those with *SLC2A9* mutations represent severe symptoms such as hematuria, nephrolithiasis, or AKI. URAT1, encoded by *SLC22A12*, is located on the apical surface of the renal proximal tubule and it regulates urate homeostasis. Mutations on *SLC22A12* gene decrease the function of URAT1, which leads to renal hypouricemia type 1⁸⁻¹⁰. Most of iRHUC cases are caused by the mutation in the *SLC22A12*. About half are known to be homozygotes while the rest are compound heterozygotes and heterozygotes in order¹⁴. Of all reported mutations in *SLC22A12*, W258X mutation is a predominant genetic cause of iRHUC in Koreans and Japanese¹⁴.

In Korea, several cases of iRHUC caused by *SLC22A12* mutations, showing homozygous W258X, are reported (Table 2)¹⁹. Only one case, Cheong et al.¹⁴, out of four had no symptoms. One patient showing uricosuria was diag-

Table 1. The laboratory findings of the patients and his family

	Uric acid (mg/dL)		Creatinine (mg/dL)		U _{UA} /U _{Cr}	FEUA (%)
	Serum	Urine	Serum	Urine		
Patient	0.62	89.91	0.53	158.07	0.58	48.6
Mother	2.33	41.30	0.63	60.66	0.68	18.4
Father	4.35	72.64	0.98	80.15	0.90	20.4
Brother	4.25	95.06	0.71	152.16	0.62	10.4

U, urine; UA uric acid; Cr, creatinine; FEUA, fractional excretion of uric acid.

Table 2. Reported cases of idiopathic renal hypouricemia with *SCL22A12* mutations, homozygous W258X, in Korea

Reference	Sex/Age (y)	Serum UA (mg/dL)	Serum Cr (mg/dL)	U _{UA} /U _{Cr}	FEUA (%)	Complications
Cheong et al. 2005	M/7	0.4	0.6	0.30	45.1	Incidental hypouricemia
Lee et al. 2006	M/3	0.7	0.3	Not done	41.7	Orange-colored urine
Kim et al. 2011	M/25	2.0	4.3	0.3	66	EIAKI
Kim et al. 2015	M/24	0.5	1.6	Not done	23.95	EIAKI Urolithiasis

U, urine; UA, uric acid; Cr, creatinine; FEUA, fractional excretion of uric acid; EIAKI, exercise induced acute kidney injury.

nosed at a young age, and the rest cases were detected late after complications developed. Especially, Kim et al.¹⁹⁾ presented a case of familial renal hypouricemia with repetitive exercised-induced AKI. Repetitive complications including AKI might have been prevented if the first diagnosis of renal hypouricemia was made at a younger age and so that patients were given precautions. Unlike existing reports, in the current case, the patient was young, which could be referred to as a lower chance of exposure to intense physical activity, and without typical symptoms associated with complications. However, nonspecific symptoms such as severe general weakness and the past event of red urine which is now presumed to be uricosuria might have been related to the iRHUC. Even random urine test showed uric acid to creatinine ratio (U_{UA}/U_{Cr}) within normal range, FEUA turned out to be prominently high and the *SLC22A12* mutation was detected. Therefore, patients with an accidental finding of hypouricemia, regardless of U_{UA}/U_{Cr} value, should be cautiously evaluated using FEUA. Molecular analysis should also be considered sequentially if needed. In addition, as incidental renal stone coexisted in the patient, unexplained renal stones need close inspections since nephrolithiasis might occur in 10% of patients with *SLC22A12* mutations and in 40% of *SLC2A9* mutations¹³⁾. Since lab tests and genetic evaluations of the patient's grandparents were not performed, pedigree analysis was not able to be done further. Additional evaluation of his family members could have made the trait and heritability of the disease more clear.

Low level of uric acid, an effective antioxidant acting as a vasodilator, and anaerobic exercises triggering vasoconstriction have a negative synergistic effect on glomerular filtration rate¹¹⁾. Thus, sudden onset of AKI can occur a few hours or days after strenuous physical exercises and within the same context, episodes of acute gastroenteritis may cause AKI in patients with renal hypouricemia. Accordingly, in Japan, it is asserted that screening for iRHUC detection using serum uric acid should be done before strenuous physical education classes¹²⁾.

There has been a lack of attention for hypouricemia so far because it rarely shows symptoms or requires immediate treatment. Among *SLC22A12* mutations, the predominant cause of iRHUC, only few are confirmed with functional significance¹⁸⁾. However, the W258X mutation, which is

relatively common in Korea, tends to express symptoms compared to other subtypes of *SLC22A12* mutations. Therefore, most patients with iRHUC are at potential risks for AKI and nephrolithiasis. As the serum uric acid level shows the lowest level between 2.2 and 2.5 mg/dL at 2–3 months of age and increases with age²⁰⁾, children with uric acid level under 2.0 mg/dL should all be excluded from iRHUC.

In short, the current case reports a 7-year-old boy with nonspecific symptoms diagnosed iRHUC as early as before exposure to strenuous physical activities. Also, this report suggests that FEUA, with molecular analysis according to needs, should be done to all patients with hypouricemia to prevent delayed diagnosis and repetitive AKI which might occur.

Patient consent

This study was approved by the Institutional Review Board of Konyang University Hospital (IRB number 2021-03-033). Consent was obtained from the patient and his parents.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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References

- Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH, et al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. *Nature* 2002;417:447-52.
- Stiburkova B, Sebesta I, Ichida K, Nakamura M, Hulkova H, Krylov V, et al. Novel allelic variants and evidence for a prevalent mutation in URAT1 causing renal hypouricemia: Biochemical, genetics and functional analysis. *Eur J Hum Genet* 2013;21:1067-73.
- Vitart V, Rudan I, Hayward C, Gray NK, Floyd J, Palmer CN, et al. SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. *Nat Genet* 2008;40:437-42.
- Nishizaki N, Fujinaga S, Hirano D, Kanai H, Kaya H, Ohtomo Y, et al. Hereditary renal hypouricemia: a cause of calcium oxalate urolithiasis in a young female. *Clin Nephrol* 2012;77:161-3.
- Kamei K, Ogura M, Ishimori S, Kaito H, Iijima K, Ito S, et al. Acute kidney injury after acute gastroenteritis in an infant with hereditary hypouricemia. *Eur J Pediatr* 2014;173:247-9.
- Sebesta I, Stiburkova B, Bartl J, Ichida K, Hosoyamada M, Taylor J, et al. Diagnostic tests for primary renal hypouricemia. *Nucleosides Nucleotides Nucleic Acids* 2011; 30:1112-6.
- Ichida K, Hosoyamada M, Hisatome I, Enomoto A, Hikita M, Endou H, et al. Clinical and Molecular Analysis of Patients with Renal Hypouricemia in Japan-Influence of URAT1 Gene on Urinary Urate Excretion. *Am Soc Nephrol* 2004;15:164-73.
- Graessler J, Graessler A, Unger S, Kopprasch S. Association of the Human Urate Transporter 1 With Reduced Renal Uric Acid Excretion and Hyperuricemia in a German Caucasian Population. *American College of Rheumatology An* 2006;54:1.
- Atsushi K, Keiko I, Hideki W, Ken-ichi S, Akihiko Y. Analysis of Mutations in the Urate Transporter 1 (URAT1) Gene of Japanese Patients with Hypouricemia in Northern Japan and Review of the Literature. *Renal Failure* 2006;28:3.
- Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proc Natl Acad Sci USA* 1981;78:6858-62.
- Shimizu Y, Wakabayashi K, Totsuka A, Hayashi Y, Nitta S, Hara K, et al. Exercise-Induced Acute Kidney Injury in a Police Officer with Hereditary Renal Hypouricemia. *Case Rep Nephrol Dial* 2019;9: 92-101.
- Nakamura A, Niimi R, Yanagawa Y. Renal hypouricemia in school-aged children: screening of serum uric acid level before physical training. *Pediatr Nephrol* 2006;21:1898-900.
- Peris Vidal A, Marin Serra J, Lucas Sáez E, Ferrando Monleón S, Claverie-Martin F, Perdomo Ramírez A, et al. Hipouricemia renal hereditaria tipo 1 y 2 en tres niños españoles. Revisión de casos pediátricos publicados. *Nefrología* 2019;39:355-61.
- Cheong HI, Kang JH, Lee JH, Ha IS, Kim S, Komoda F, et al. Mutational analysis of idiopathic renal hypouricemia in Korea. *Pediatr Nephrol* 2005;20:886-90.
- Kim YH, Cho JT. A case of exercise-induced acute renal failure with G774A mutation in SCL22A12 causing renal hypouricemia. *J Korean Med Sci* 2011;26:1238-40.
- Han MH, Park SU, Kim DS, Shim JW, Shim JY, et al. A case of idiopathic renal hypouricemia. *Korean J Pediatr* 2007;50:489-92.
- Dinour D, Gray NK, Campbell S, Shu X, Sawyer L, Richardson W, Rechavi G, et al. Homozygous SLC2A9 mutations cause severe renal hypouricemia. *J Am Soc Nephrol* 2010;21:64-72.
- Iwai N, Mino Y, Hosoyamada M, Tago N, Kokubo Y, Endou H. A high prevalence of renal hypouricemia caused by inactive SLC22A12 in Japanese. *Kidney Int* 2004;66:935-44.
- Kim HO, Ihm CG, Jeong KH, Kang HJ, Kim JM, Lim HS, et al. A Case Report of Familial Renal Hypouricemia Confirmed by Genotyping of SLC22A12, and a Literature Review. *Electrolyte Blood Press* 2015;13:52-7.
- Stiburkova B, Bleyer AJ. Changes in serum urate and urate excretion with age. *Adv Chronic Kidney Dis* 2012;19:372-6.