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A Novel Homozygous *SLC2A9* Mutation Associated with Renal-Induced Hypouricemia

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Key Words
Hypouricemia · Glucose transporter 9 · *SLC2A9* · Acute kidney injury

Abstract
Background: Hereditary renal hypouricemia (RHUC) is a genetically heterogenous disorder characterized by defective uric acid (UA) reabsorption resulting in hypouricemia and increased fractional excretion of UA; acute kidney injury (AKI) and nephrolithiasis are recognized complications. Type 1 (RHUC1) is caused by mutations in the *SLC22A12* gene, whereas RHUC2 is caused by mutations in the *SLC2A9* gene. Patient ethnicity is diverse but only few Caucasian families with an *SLC2A9* mutation have been reported. ***Methods:*** The current report describes the clinical history, biochemical and molecular genetics findings of a native Austrian family with RHUC2. The propositus presented with 2 episodes of exercise-induced AKI and exhibited profound hypouricemia. Mutational screening of the *SLC22A12* and *SLC2A9* genes was performed. ***Results:*** The molecular analyses revealed the homozygous c.512G>A transition that leads to the p.Arg171His missense substitution in *SLC2A9*, confirming the diagnosis of RHUC2. Segregation study of the causal mutation revealed that the mother and elder sister were heterozygous carriers, whereas the younger sister was found to be homozygous. ***Conclusion:*** We report the identification of a novel mutation in *SLC2A9* as the cause of RHUC2 in a native Austrian family. We show that glucose transporter 9 mutations cause severe hypouricemia in homozygous individuals and confirm the high risk of AKI in male individuals harbouring these mutations. In our literature review, we provide an overview of the putative underlying pathophysiology, potential renal complications, findings on kidney biopsy as well as potential long-time renal sequelae.

Introduction

Hereditary renal hypouricemia (RHUC) is a genetically heterogenous disorder caused by recessive mutations in genes encoding distinct urate transporters in the proximal renal tubule. The resultant defective urate reabsorption causes increased urate clearance with very low serum uric acid (UA) levels (<2 mg/dl) [1]. While affected individuals frequently remain asymptomatic, a predisposition for nephrolithiasis and acute kidney injury (AKI), often following exercise, has been recognized.

Mutations in 2 genes account for virtually all reported cases, with notable exceptions [2, 3]. In a majority of patients, the defect is caused by loss-of function mutations in the *SLC22A12* gene that codes for the urate transporter URAT1 (RHUC1). In addition, familial hypouricemia

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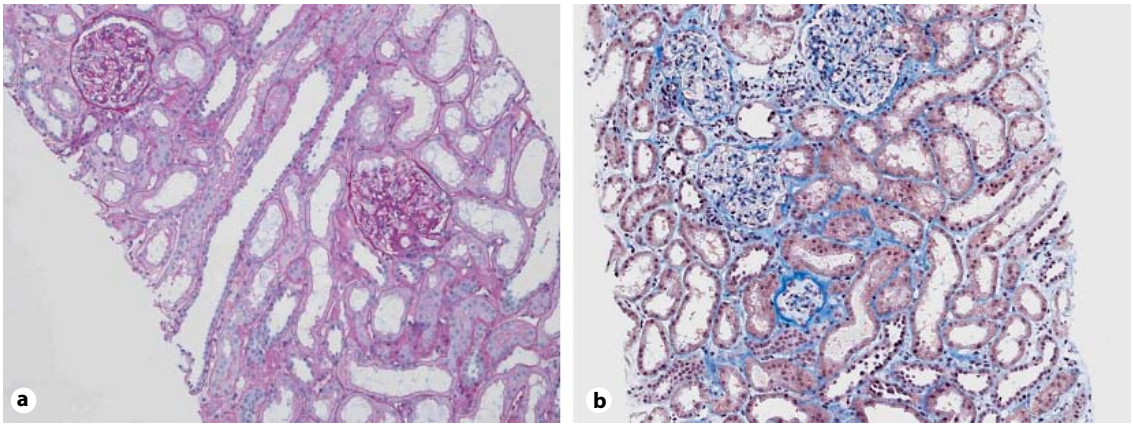

Fig. 1. Renal biopsy showing mild signs of acute tubular injury with tubular ectasia with flattening of epithelia cells (focal interstitial oedema) with very few scattered interstitial inflammatory cells, no casts or precipitations within tubuli (and no glomerular lesions): **a** periodic acid-Schiff; **b** trichrome acidic fuchsin orange-G.

has also been described in patients harbouring homozygous or compound heterozygous mutations in the *SLC2A9* gene, which encodes another key player in UA homeostasis, glucose transporter 9 (GLUT9; RHUC2). Patient ethnicity is diverse and includes Japanese, Chinese, Arab, Ashkenazi-Jewish, Anglo-Saxon, Greek, and Czech; to date, only few Caucasian families with a GLUT9 mutation have been reported [4–7].

We describe a young native Austrian man who experienced 2 episodes of exercise-induced AKI, exhibited profound hypouricemia with markedly increased fractional excretion (FE) of UA and was found to be homozygous for a novel missense mutation in *SLC2A9*. While the mother and elder sister tested heterozygous for the mutation, the younger sister carried the mutation in homozygosity and displayed extremely low serum UA levels; however, she has not experienced any episodes of AKI.

Case Report

A previously well 16-year-old Caucasian male was admitted because of sudden onset of bilateral loin pain, nausea and vomiting. There was no history of nephrolithiasis and family history was unremarkable. He was on no regular medications and did not smoke or use illicit drugs. The previous day, he had engaged in 20 min of barbell-training. On admission, the patient was euvolemic, afebrile; blood pressure was 144/82 mm Hg and pulse rate 96 beats per minute. Apart from mild abdominal tenderness, physical examination was unremarkable.

Pertinent laboratory results were as follows: serum creatinine 2.1 mg/dl, creatine kinase (CK) 1,503 U/l, lactate dehydrogenase 250 U/l; full blood count was normal. Urinalysis showed trace of protein (+) but no cells, casts, haemoglobin or myoglobin; urinary pH was 6. Serologic data (anti-nuclear antibody, hepatitis B and C, human immunodeficiency virus and complement) were all normal. Toxicology screen was negative. A renal ultrasound showed normal-sized kidneys with no evidence of obstruction. Within 3 days, serum creatinine peaked at 4.4 mg/dl, while CK normalized. UA, which was not done initially, was 1.1 mg/dl at that time. A kidney biopsy was performed and showed only subtle signs of acute tubular injury without intratubular UA precipitation (fig. 1a, b). Renal function recovered spontaneously and profound hypouricemia (0.2 mg/dl at discharge) became evident. Blood results from a previous admission 3 years earlier showed normal serum creatinine (0.8 mg/dl) but UA of 0.1 mg/dl. No secondary causes of low UA were evident. FE-UA was very high (126%, normal range 7–12%) in the acute phase.

In view of the marked hypouricemia and high FE-UA, a diagnosis of RHUC was suspected, which led us to perform mutational screening of the *SLC22A12* and *SLC2A9* genes, as previously described [8]. The molecular analyses revealed the homozygous c.512G>A transition (seq. ref.: NM_020041.2) that leads to the p.Arg171His missense substitution (GLUT9L, seq.ref.: NP_064425.2) in *SLC2A9*, thus confirming the diagnosis of the RHUC type 2 (fig. 2). Interestingly, the Arg171 residue has been previously reported by Dinour et al. [9] to be substituted by a Cys residue in 3 siblings, born of consanguineous Israeli-Arab parents, with RHUC2 and without complications. In vitro functional expression studies showed that the p.Arg171Cys mutant protein had significantly reduced UA transport activity (16% of control values). Furthermore, homology modelling indicated that the mutation occurred in the inner channel that expels UA from the cytoplasmic to extracellular regions [9].

The serum UA levels were screened in other family members and were 2.7 mg/dl (mother), 2.7 mg/dl (elder sister) and 0.1 mg/dl (younger sister); FE-UA was 22, 14.2 and >150%, respectively. The father could not be contacted. Segregation study of the causal mutation, performed for all available relatives, revealed that the mother and elder sister were heterozygous carriers (fig. 2), whereas the younger sister was found to be homozy-

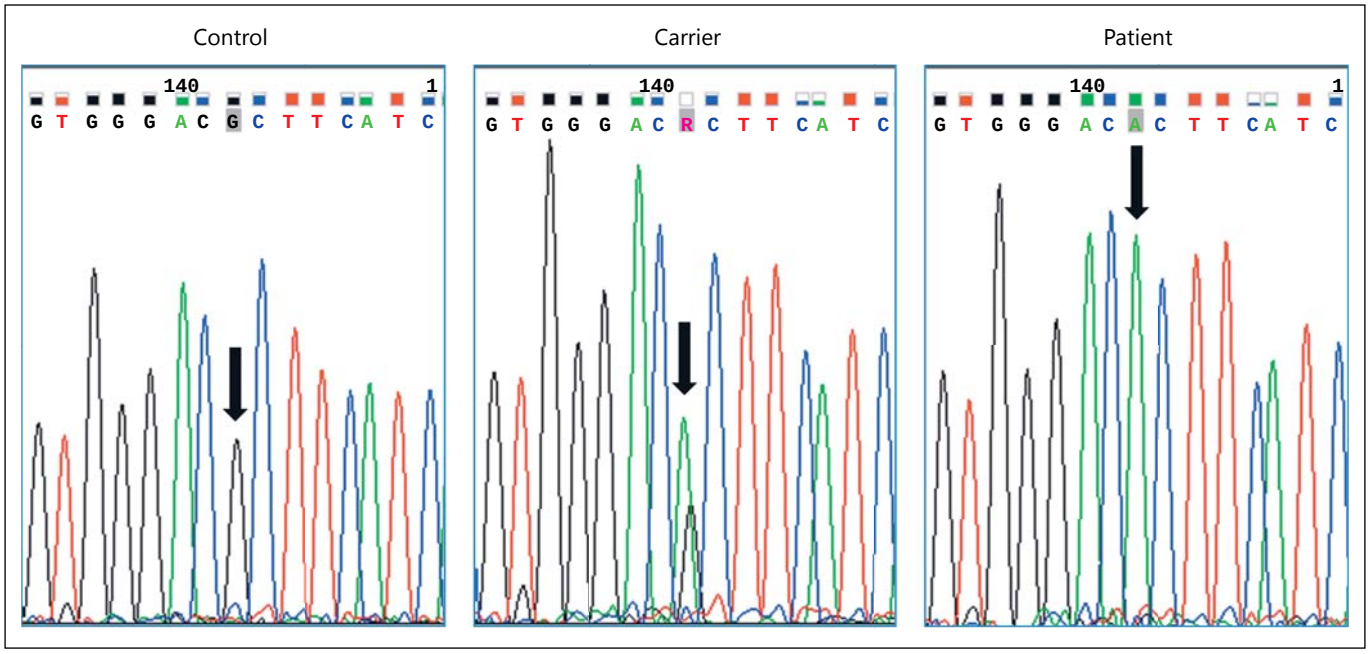

Fig. 2. Molecular characterization. Sequence chromatogram showing the position of the novel c.512G>A transition (NM_020041.2, GLUT9L) that corresponds to c.425G>A (NM_00100290.1, GLUT9S), leading to the p.Arg171His missense mutation (NP_064425.2, GLUT9L) and to p.Arg142His (NP_001001290.1, GLUT9S). The mutation was found in homozygosity in the index patient and his younger sister and in heterozygosity in his mother and elder sister; the father was not available for genetic testing. Mutations are annotated according to HGVS nomenclature (http://www.hgvs.org/mutnomen).

gous, in agreement with her very low UA levels. However, despite an active lifestyle, at the age of 24, she remained asymptomatic until this date.

In contrast, and 9 months after his initial presentation, the index patient was readmitted with abdominal pain and myalgia of the upper arms. The previous day, he had moved furniture for several hours. At presentation, only 1 day after the onset of symptoms, his serum creatinine was 3.9 mg/dl. Again, no structural abnormalities were detected on renal ultrasound. Urinary dipstick showed protein (quantified at 0.8 g at that time) but no haemoglobinuria; urinary pH was 6. No UA crystals were found under urine microscopy. Kidney function and proteinuria normalized spontaneously. On follow-up, UA remained between 0.1 and 0.2 mg/dl and FE-UA was calculated repeatedly >150%. By avoidance of strenuous exercise no further episode of exercise-induced AKI has occurred to date.

The presence of a novel mutation in homozygosity is suggestive of consanguinity, though the family pedigree could not be defined with certainty.

Discussion

In humans, urate is the end product in purine metabolism and it exerts important oxidative defence. Its serum concentration is governed by hepatic production and predominantly renal removal. Urate is filtered freely by the glomerulus and is almost completely reabsorbed in the proximal tubule; consequently, the kidney plays a dominant role in maintaining serum urate levels [1].

Hypouricemia is arbitrarily defined as a serum urate concentration of <2 mg/dl. While it can result from decreased UA production, it is usually due to renal urate wasting [4]. Following Erley's description in 1989 of a young Turkish man who experienced exercise-induced AKI requiring transient dialysis and was later found to be profoundly hypouricemic, it became evident that RHUC constitutes not just a mere biochemical curiosity [10]. The ensuing years saw an increasing number of reports of RHUC patients presenting with acute kidney failure [11]. However, the underlying molecular defect remained obscure until Enomoto et al. [12] reported the identification of the first kidney specific urate transporter URAT1 *(SLC22A12)* in 2002. Inactivating mutations in this gene have been subsequently found in individuals with idiopathic RHUC and >100 patients have been described, the majority being Japanese [13]. However, the existence of RHUC patients without URAT1 mutations implied the presence of additional major urate regulators [1].

In 2007, GLUT9 (encoded by *SLC2A9*) was identified as another high capacity urate transporter [14]. GLUT

proteins are encoded by the SLC2 genes and mediate the transport of monosaccharides and other small carbon compounds across cell membranes. To date, 14 GLUT proteins have been identified, but GLUT9 represents the only member of this family whose substrate is urate. Its 2 variants – long (GLUT9L) and short (GLUT9S) – act in tandem with URAT1 in renal reabsorption of UA [15]. While urate uptake from the tubular lumen into the cell is mediated by URAT1 and by apical GLUT9S, GLUT9L is the only major urate efflux transporter at the basolateral membrane. Hence, loss of function of GLUT9 precludes UA reabsorption by all of the apical transporters through complete inhibition of UA efflux from the cell [9].

Shortly thereafter, mutations in *SLC2A9* were described in hypouricemic patients, rendering *SLC2A9* another causative gene linked to RHUC [16]. When compared to patients with URAT1 mutations, individuals harbouring homozygous GLUT9 mutations exhibit more pronounced hypouricemia with FE-UA often >150%, and appear to be more vulnerable for exercise-induced AKI and nephrolithiasis [13, 16]. Subjects with heterozygous GLUT9 mutations show a wider spectrum of serum UA levels, ranging from 2.0 to 4.5 mg/dl, whereas FE-UA values range from 3.2 to 21.7% in one study from Israel [16]; these authors concluded that haploinsufficiency results in mild hypouricemia. The recent report of a 54-year-old Czech woman with a novel heterozygous missense mutation in the *SLC2A9* gene, exhibiting low serum UA levels (1.16–1.78 mg/dl) and FE-UA of 17.7%, is in line with this observation; functional study of the identified mutation showed a significant decrease in urate uptake [7]. We have previously summarized the molecular and clinical features of all RHUC2 patients reported until 2014 [8], and only a few new cases were published in the meanwhile [6, 7, 17, 18].

Several mechanisms have been proposed to explain the pathophysiology of AKI in RHUC. Although Erley's description demonstrated urate nephropathy as the histological correlate of acute renal failure, further reports did not substantiate this finding [19]; indeed, a majority of renal biopsies has shown acute tubular injury without intratubular UA precipitation [20]. However, luminal microcrystals will not be inevitably evident on histology. As discussed in our previous report, the UA precipitation hypothesis proposes that prolonged or severe exercise can be associated with an elevation in UA production and urinary excretion [8]. If this condition is associated with hypovolemia, increased urine concentration and low urine pH, it favours the precipitation and crystallization of UA. Notably, a recent paper on 'heat stress nephropathy' discusses the potential detrimental effects of cyclic, exercise-induced uricosuria in the pathogenesis of Mesoamerican nephropathy. The authors show that high concentrations of noncrystalline UA per se, potentiated by volume depletion and urinary acidification in the course of exercise, cause renal tubular injury [21]. This concept could also apply to RHUC patients.

While the precise mechanism for kidney injury remains elusive, the role of UA as an antioxidant has increasingly garnered attention. Murakami et al. [22] were the first to suggest that oxygen-free radicals produced during exercise lead to renal tissue damage. Total serum UA and the amount mobilized into the tubular cells are very small in RHUC patients, resulting in insufficient antioxidant action in the renal cortex. As oxidative stress increases during exercise, renovascular spasm may ensue and reperfusion after exercise mimics ischemia-reperfusion injury [23]. The histological finding of interlobular artery intimal thickening in a normotensive RHUC2 patient, attributed to repeated vasoconstriction, renders further support to this pathophysiological concept, which is also backed by CT findings showing patchy wedge-shaped enhancement in renal parenchyma [18, 24]. Interestingly, evidence for a more systemic oxidant imbalance at presentation with AKI accumulates: 3 cases of posterior reversible encephalopathy syndrome have been recently reported in RHUC1 and RHUC2 patients, and one Japanese RHUC1 individual exhibited reversible T-wave inversion on ECG; together, these reports are suggestive of cerebral and coronary artery constriction, respectively [19, 24–26]. That being said, other disorders associated with hypouricemia, such as hereditary xanthinuria, are not usually associated with AKI. Moreover, RHUC patients can remain asymptomatic throughout their life, as exemplified by an 84-year-old subject with a homozygous *SLC2A9* mutation [9]. We have previously speculated that additional genetic risk factors, for instance, sequence variations in other urate transporters, and various environmental triggers, may contribute to the development of complications [8]. Lastly, expression of URAT1 and GLUT9 is not confined to the kidney: while URAT1 is expressed by vascular smooth muscle cells, GLUT9 is also found in the brain [25, 27]. We hypothesize that this systemic distribution might account for the non-renal complications of RHUC.

The presentation follows a remarkably stereotypical pattern. After various forms of exercise (occasionally trivial activities such as house cleaning) [20], loin pain, nausea and vomiting develop. The short time lag between exercise and symptom onset in the presentation is notewor-

thy and in keeping with reversible vasoconstriction rather than urate nephropathy. While moderate CK elevation is commonly found, frank rhabdomyolysis is unusual.

The marked male preponderance for exercise-related AKI, with a male:female ratio of 8:1 in one study, has been noted before and is found consistently in the literature [8, 11, 21]. Gender-related differences in oxidative stress, attributed to estradiol, might account for this phenomenon [23].

Previous laboratory examinations, when available, may assist in RHUC diagnosis. While complex urine examination was commonly performed in patients with hypouricemia before the characterization of the major urate transporters, suggestive biochemistry and family history should prompt early molecular analysis of the 2 known causative genes, as illustrated by our reports.

Patients should be counselled to avoid strenuous exercise and ensure adequate fluid intake after exercise. Rather counterintuitively, allopurinol, a potent inhibitor of xanthine oxidase, may have a role in preventing recurrent episodes [3]. While this basically fits with the 'cyclic uricosuria'-hypothesis, (high-dose) allopurinol has also been shown to improve endothelial function by reducing vascular oxidative stress, perhaps unrelated to its effect on UA [28]. In the metabolism of xanthine to UA, free radicals are generated; it is conceivable, therefore, that allopurinol exerts its effect as a powerful antioxidant.

Although some patients require interim dialysis, the short-term prognosis of RHUC appears to be favourable. However, recurrence of AKI has been described and there is evidence that repeated kidney injury can cause chronic structural alterations [18, 20]; end-stage renal disease in RHUC patients has been reported [29]. Furthermore, a recent large cross-sectional population-based study from Japan demonstrated that men with hypouricemia face a higher risk of reduced kidney function [30].

As stipulated by Stiburkova et al. [13], lack of awareness of RHUC likely allows cases to go undetected. Indeed, patients have been subjected to repeat renal biopsies when hypouricemia was not noticed at first presentation [17].

To summarize, we report the identification of a novel mutation in *SLC2A9* as the cause of RHUC2 in a native Austrian family. In analogy with previous reports, we show that GLUT9 mutations cause severe hypouricemia in homozygous individuals and confirm the high risk of AKI in male individuals harbouring these mutations.

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Disclosure Statement

The authors declare that there is no conflict of interests.

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