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SLC2A9—a fructose transporter identified as a novel uric acid transporter*

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Key findings

SLC2A9 was recently cloned and identified as a member of the *SLC2A* gene family of hexose facilitative transporters, where its main physiological role was assumed to be in the transport of glucose and fructose. However, new findings have unearthed a novel role for SLC2A9 (also known as GLUT9) as a modulator of uric acid levels. Specifically, after conducting genome-wide scans, Doring *et al*. and Vitart *et al*. have identified several noncoding genetic variants of *SLC2A9* that were strongly associated with a decrease in serum uric acid concentrations and an increase in fractional excretion of uric acid. Accordingly, the variants were also associated with a decreased risk of gout, suggesting a protective role for the minor alleles. Interestingly, in both of the studies, gender-specific effects were more pronounced in women than in men. Doring *et al*. estimated the additive effect to be −0.45 mg/dl per copy of the minor allele in women and −0.25 mg/dl in men. Overall, genetic variants of *SLC2A9* are potentially responsible for 1.2–6.0% of the variance in serum uric acid concentrations. Of importance is the functional determination that SLC2A9 is a strong urate transporter, implicating it as a key player in the renal excretion of uric acid that could greatly impact clinical practices.

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*References of Articles:

[1]Doring A, Gieger C, Mehta D *et al*. SLC2A9 influences uric acid concentrations with pronounced sex-specific effects. *Nat Genet* 2008; 40: 430–436.

[2]Vitart V, Rudan I, Hayward C *et al*. SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. *Nat Genet* 2008; 40: 437–442.

Brief review

Unlike most mammals, humans cannot regulate uric acid levels very effectively, largely because of the mutational loss of uricase (urate oxidase) that degrades uric acid to allantoin. A major consequence of the lack of this hepatic enzyme is a relatively unique susceptibility of humans to develop hyperuricemia in response to diet, such as from purine-rich meats, seafood and beer. In addition, fructose, which is present in table sugar or sucrose, the sweetener high fructose corn syrup and fruits, can raise uric acid levels due to the unique ability of this sugar to cause intracellular ATP depletion and adenine nucleotide turnover.

While diet is likely a key factor in modulating uric acid levels in the population, genetic mechanisms are also known to be important regulators of uric acid concentrations which is considered to be strongly heritable, ranging from 25 to 73% [1,2]. Some rare genetic causes of hyperuricemia include those associated with the *de novo* purine synthesis pathway, such as complete or partial deficiency in hypoxanthine–guanine phosphoribosyltransferase and increased phosphoribosylpyrophosphate synthetase (PRPP). More recently, the disease, familial juvenile hyperuricemic nephropathy (FJHN), was found to be due to mutation in uromodulin (Tamm Horsfall protein). Although elevated uric acid can be caused by the increased breakdown of endogenous and exogenous purines, impairments of the renal excretion of uric acid is the main cause of ∼90% of all hyperuricemia incidents; thus, it is more clinically significant [3,4]. Renal transport of uric acid is governed by a complex system of transporters in the proximal tubule (Figure 1) [4,5]. Several genetic polymorphisms in the apical transporter, URAT1, have already been linked with hyperuricemia [6,7]. In addition, mutational loss of URAT1 can cause the rare syndrome of hypouricemia with exercise-induced acute renal failure [8].

Recently, genome-wide studies have been conducted to identify new genes involved in uric acid homeostasis. Several loci associated with hyperuricemia have been identified, including in chromosome 4q25 observed in Taiwanese aborigines [4], in chromosomes 2, 8 and 15 in the Framingham Heart Study [2] and in chromosome 6q22–23 in

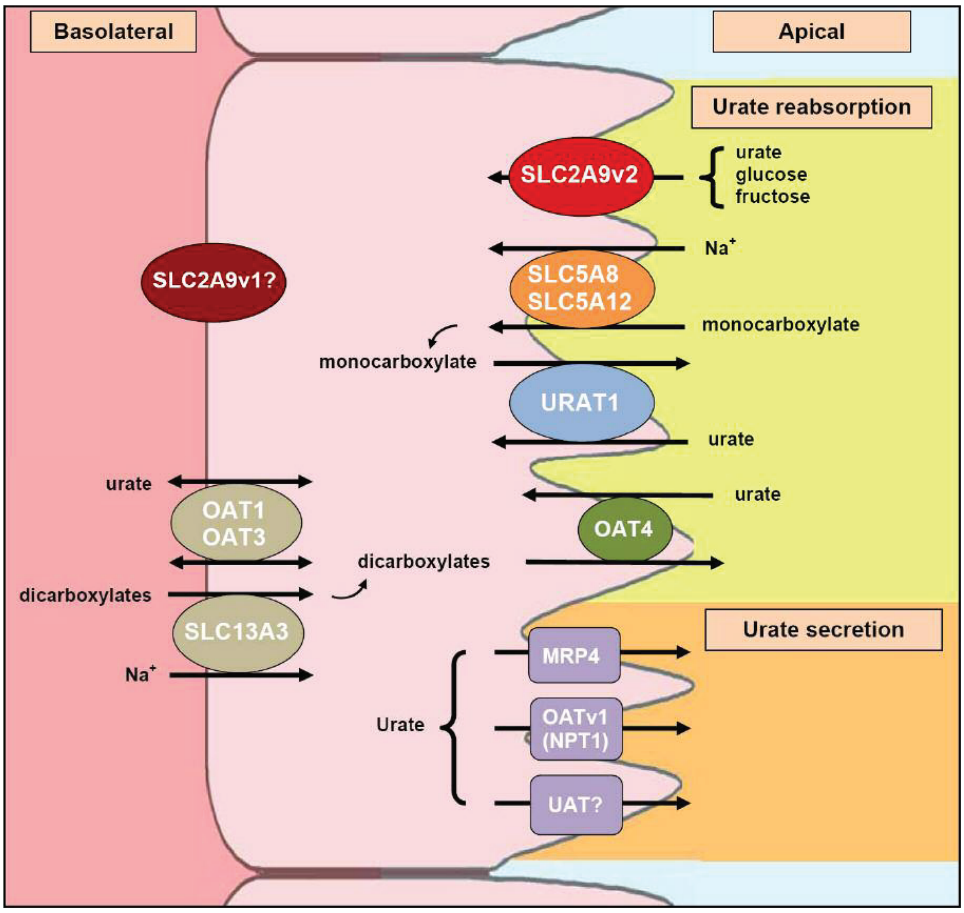

Fig. 1. Urate transport in the proximal tubule. Several transporters have recently been identified as potential molecular components in the renal transport of urate [4,5]. URAT1, a urate-anion exchanger, and OAT4, an organic anion-dicarboxylate exchanger, are mediators of urate reabsorption. URAT1 is considered to be a key player in uric acid homeostasis and has been estimated to be responsible for 50% of urate reabsorption. Its activity, however, is driven by sodium-anion transporters, potentially by SLC5A8 and SLC5A12, which provide the main source of anions needed for URAT1 function. For urate secretion into the lumen, a urate transporter/channel (UAT), a voltage-driven organic anion transporter (OATv1 or NPT1) and an ATP-binding cassette transporter (MRP4) are potential efflux candidates. Although very little is known about the basolateral transport of urate, two anion-dicarboxylate transporters, OAT1 and OAT3, have been shown to have the ability to transport urate, but the direction of the urate transport still needs to be characterized. Furthermore, their activity may be coupled with SLC13A3 that drives the intake of Na^+ and dicarboxylates. In addition to all these transporters, SLC2A9 has been discovered to be a candidate protein in the excretion of urate and may play a dominant role in urate reabsorption [12]. The short isoform, SLC2A9v2, localizes exclusively to the apical membrane and has been shown to transport urate. The role of the long isoform, SLC2A9v1, on the uric acid transport remains to be elucidated.

Mexican Americans [1]. However, one of the most striking associations was localized to *SLC2A9* on chromosome 4p15.3–16. After conducting genome-wide scans by utilizing chips consisting of 300K–500K single nucleotide polymorphisms (SNPs), genetic variants of *SLC2A9* were strongly associated with reduced levels of serum uric acid in Caucasian cohorts from Italy [9,10], the UK [11], Croatia [12], the United States [10], Germany and Austria [13]. The strongest associations were mapped to noncoding SNPs located near the 5′ of the gene and within introns 3–7, but further studies are needed to elucidate their impact on the protein's function. Interestingly, *SLC2A9* polymorphisms (rs6855911, rs7442295, rs6449213, rs12510549, rs737267 and rs1014290) were shown to have gender-specific effects on uric acid concentrations, resulting in a greater reduction in women (−0.352 to −0.880 mg/dl) than in men (−0.128 to −0.428 mg/dl) (Table 1). Consequently, genetic variants of *SLC2A9* are potentially responsible for 5.3–6.0% of the variance in serum uric acid concentrations in women and 1.2–1.7% in men.

How do alterations in *SLC2A9* alter serum uric acid levels? Recent studies suggest that one mechanism may be by modulating renal excretion of uric acid. There are two common variants of SLC2A9 (GLUT9): a long isoform (SL2A9v1) and a short isoform (SLC2A9v2) [14]. From *in vitro* studies, it was shown that the long isoform trafficked predominantly to the basolateral membrane of proximal tubule epithelial cells while the short isoform was exclusively localized to the apical membrane. Utilizing *Xenopus laevis* oocytes, SLC2A9v2 was shown to have a high capacity for the urate transport [12]. Polymorphisms of *SLC2A9* were also shown to be associated with the increased

Table 1. *SLC2A9* SNPs showing gender-specific effects on serum uric acid concentrations

SNP	Region	Minor allele (% in Caucasians)	Reduction of serum uric acid per copy of minor allele (mg/dl)	
			Men	Women
rs12510549	5′	C (27)	−0.428 [10] −0.229 [13]	−0.352 [10] −0.416 [13]
rs1014290	Intron 3	C (31)	−0.36 [12]	−0.76 [12]
rs6449213	Intron 4	C (24)	−0.384 [10] −0.165 [13] −0.36 [12]	−0.492 [10] −0.481 [13] −0.88 [12]
rs7442295	Intron 6	G (25)	−0.366 [10] −0.202 [13] −0.297 [9]	−0.503 [10] −0.503 [13] −0.383 [9]
rs6855911	Intron 7	G (31)	−0.411 [10] −0.128 [13] −0.289 [9]	−0.479 [10] −0.472 [13] −0.359 [9]
rs737267	Intron 7	T (31)	−0.38 [12]	−0.88 [12]

Six single nucleotide polymorphisms (SNPs) of *SLC2A9* have been reported from various genome-wide association studies to cause gender-specific differences in serum uric acid levels. All six mutations were located in noncoding regions of the gene: five polymorphisms were in intronic regions and one polymorphism was located 5′ of the *SLC2A9* gene sequence. Mutations in the gene caused a greater additive effect in women than in men. For women with one copy of the minor allele, the effect size ranged from −0.359 to −0.88 mg/dl. For men, the effect size ranged from −0.128 to −0.428 mg/dl. If an individual has two copies of the minor allele, the reduction in serum uric acid levels would generally double. The frequencies of these mutations are relatively common, affecting ∼24–31% of the Caucasian population.

fractional excretion of uric acid, suggesting that these polymorphisms may effectively modulate uric acid excretion.

Discussion

There is a growing interest in understanding the genetic determinants of urate homeostasis due to the concern that elevated serum uric acid concentrations may be a risk factor for several common disorders, including gout, hypertension [15], metabolic syndrome [16,17], cardiovascular disease [18], type 2 diabetes mellitus [19], diabetic nephropathy [20] and kidney disease [21,22]. The discovery of SLC2A9, along with other proteins involved in the urate transport, may greatly impact our understanding of uric acid homeostasis. Clinically, new insights in this field can enhance the utilization of current medications and can generate novel genetic therapeutic targets for the control of uric acid concentrations. For instance, with the discovery of URAT1, the assumed action of pyrazine carboxylic acid (PZA) as an inhibitor of urate secretion has been debunked. Instead, PZA has been shown increase urate reabsorption by stimulating URAT1 activity, thus invalidating the four-component model of the renal urate transport [4].

Since fructose itself results in uric acid generation, the observation that SLC2A9, a fructose transporter, can also function as a urate transporter raises the interesting possibility that this transporter may ‘fine tune’ the movement of uric acid in and out of the cell in response to fructose. For example, a polymorphism of *SLCA29* could lead to a relatively higher concentration of uric acid within the cell in response to fructose. The importance of this potential function could be significant given recent studies suggesting that fructose-induced hyperuricemia may have a critical role in mediating the metabolic syndrome [23] and by studies suggesting that intracellular uric acid levels may largely mediate many of the pro-inflammatory effects of uric acid in various cell types [24]. Besides being expressed in a variety of other sites, such as the liver, placenta, brain, lung and leukocytes, SLC2A9 is also expressed in chrondrocytes [12,14,25]. Can SLC2A9 be responsible for the buildup of urate in gouty arthritis?

Combined with its strong activity as a urate transporter and the strong associations between genetic variants of *SLC2A9* and serum uric acid concentrations, SLC2A9 is an important modulator of uric acid levels. Interestingly, it was the minor alleles of the genetic variants of *SLC2A9* that was associated with reduced levels of serum uric acid levels. Assuming that the mutations impair the function of the protein, SLC2A9 is then implicated as an essential player in inducing hyperuricemia in humans. Thus, individuals with the mutations are protected and less likely to develop gout and potentially other disorders. Furthermore, SLC2A9 may be important to the underlining differences in uric acid concentrations reported between women and men.

Take home message

Serum uric acid levels and renal uric acid excretion have been found to be modulated by genetic polymorphisms in *SLC2A9*, a fructose transporter, which can influence the risk for gout by affecting renal urate reabsorption.

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Conflict of interest statement. None declared.

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