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性腎不全を合併した腎性低尿酸血症の一例. ***第40回日本腎臓学会西部学術大会***, 広島, 2010.10.8-2010.10.9.

H. 知的所有権の取得状況

1. 特許取得

特許（出願中）：発明の名称：尿酸トランスポーター，並びに，尿酸輸送関連疾患素因及び炎症関連疾患素因の評価方法及び評価キット，検査体及び薬． 特許出願中，発明者：松尾洋孝，高田龍平，鈴木洋史，池淵祐樹，伊藤晃成，市田公美，中村好宏，四ノ宮成祥.

2. 実用新案登録

該当無し

研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍・総説

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
松尾洋孝, 四ノ宮成祥	腎性低尿酸血症の遺伝学	寺内康夫, 伊藤裕, 石橋俊	Annual Review 糖尿病・代謝・内分泌	中外医学社	東京	2012	145-154
市田公美	尿酸代謝における最近のトピックス-尿酸代謝の新たな展開-Glucose transporter family member SLC2A9と血清尿酸値	細谷龍男, 上田孝典, 藤森新, 山中寿, 山本徹也	高尿酸血症と痛風	メディカルレビュー	大阪	2012	109-114 (Vol.19)
市田公美	低尿酸血症		痛風と核酸代謝	日本痛風・核酸代謝学会	福井	2011	159-168 (Vol.35)
市田公美	腎性低尿酸血症		腎臓	日本腎臓財団	東京	2011	10-15 (Vol.34)
市田公美	腎における尿酸トランスポーター		日本医師会雑誌	日本医師会	東京	2011	316 (Vol.140)
市田公美	尿細管疾患の臨床遺伝性低尿酸血症		日本腎臓学会誌	日本腎臓学会	東京	2011	142-145 (Vol.53)
市田公美	尿酸トランスポーター	寺内康夫, 伊藤裕, 石橋俊	Annual Review 糖尿病・代謝・内分泌	中外医学社	東京	2011	468-474 (Vol.33)
市田公美	キサンチン尿症		日本臨床別冊・腎臓症候群	日本臨牀社	大阪	2011	365-368
市田公美	腎性低尿酸血症（特発性、続発性）		日本臨床別冊・腎臓症候群	日本臨牀社	大阪	2011	842-845
千葉俊周, 松尾洋孝, 中山昌喜, 市田公美, 四ノ宮成祥	遺伝性腎性低尿酸血症	遠藤文夫	日本臨床	日本臨床社	大阪	2012	807-811
千葉俊周, 松尾洋孝, 市田公美, 四ノ宮成祥	テーマ:A.診断 8.低尿酸血症の頻度，原因，分類を教えてください	細谷龍男	腎と透析	東京医学社	東京	2012	301-304

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松尾洋孝, 市田公美, 高田龍平, 中山昌喜, 四ノ宮成祥	尿酸動態の支配要因 としての尿酸 トランスポーター	金井好克	細胞工学	学研 メディカ ル 秀潤社	東京	2012	553-557
市田公美	尿酸トランスポータ ー研究の進歩		THE BONE	メディカ ルレビュ ー	大阪	2012	331-333 (Vol.26)
市田公美	尿酸代謝異常症の 最前線		Bio Clinica	北隆館	東京	2012	124-129 (Vol.27)
市田公美	キサンチン酸化酵素 と臓器障害		Heart View	メディカ ルレビュ ー	大阪	2013	154-159 (Vol.17)
市田公美	低尿酸血症の臨床的 取り扱い		Medicina	医学書院	東京	2012	1355-135 7(Vol.49)
市田公美	健康診断で血清尿酸 値の低い人がいます。 何か不都合はありま すか？	細谷龍男, 上田孝典, 藤森新, 山中寿, 山本徹也	高尿酸血症と 痛風	メディカ ルレビュ ー	大阪	2012	78-80 (Vol.20)
市田公美	尿酸トランスポータ ー異常症(GLUT9)		小児内科	東京 医学社	東京	2012	1693-169 6(Vol.44)
市田公美	健診で尿酸値の低い 人がいます。その対応 を教えてください		腎と透析	東京 医学社	東京	2012	305-308 (Vol.73)
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PATHOGENIC GLUT9 MUTATIONS CAUSING RENAL HYPOURICEMIA TYPE 2 (RHUC2)

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□ *Renal hypouricemia (MIM 220150) is an inherited disorder characterized by low serum uric acid levels and has severe complications such as exercise-induced acute renal failure and urolithiasis. We have previously reported that URAT1/SLC22A12 encodes a renal urate-anion exchanger and that its mutations cause renal hypouricemia type 1 (RHUC1). With the large health-examination database of the Japan Maritime Self-Defense Force, we found two missense mutations (R198C and R380W) of GLUT9/SLC2A9 in hypouricemia patients. R198C and R380W occur in highly conserved amino acid motifs in the "sugar transport proteins signatures" that are observed in GLUT family transporters. The corresponding mutations in GLUT1 (R153C and R333W) are known to cause GLUT1 deficiency syndrome because arginine residues in this motif are reportedly important as the determinants of the membrane topology of human GLUT1. Therefore, on the basis of membrane topology, the same may be true of GLUT9. GLUT9 mutants showed markedly reduced urate transport in oocyte expression studies, which would be the result of the loss of positive charges in those conserved amino acid motifs. Together with previous reports on GLUT9 localization, our findings suggest that these GLUT9 mutations cause renal hypouricemia type 2 (RHUC2) by their decreased urate reabsorption on both sides of the renal proximal tubule cells. However, a previously reported GLUT9 mutation, P412R, was unlikely to be pathogenic. These findings also enable us*

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to propose a physiological model of the renal urate reabsorption via GLUT9 and URAT1 and can lead to a promising therapeutic target for gout and related cardiovascular diseases.

Keywords Renal hypouricemia; *GLUT9/SLC2A9*; *GLUT1/SLC2A1*; gout/hyperuricemia; urate reabsorption transporter

INTRODUCTION

Renal hypouricemia is a common inherited disorder that is characterized by low serum uric acid (urate) levels and impaired renal urate transport; it is typically associated with severe complications such as exercise-induced acute renal failure and nephrolithiasis.[1,2] We have previously reported that a causative gene for renal hypouricemia is *URAT1/SLC22A12*.[3] However, the existence of renal hypouricemic patients without *URAT1* mutations[4,5] implies the presence of another urate transporter. Recent genome-wide association studies have revealed that the most significant single-nucleotide polymorphisms (SNPs) are associated with urate concentrations map within *GLUT9/SLC2A9*.[6–8] Therefore, we decided to search an actual human health examination database to genetically identify and investigate human hypouricemia patients with GLUT9 deficiency.

MATERIALS AND METHODS

Clinicogenetic Analysis of Hypouricemia with *GLUT9* Mutations

We used a large human database in our approach, and finally succeeded in identifying the *GLUT9* gene as the novel causative gene for renal hypouricemia. To collect a sufficient number of hypouricemia cases, we used the health examination database for about 50,000 Japan Maritime Self-Defense Force (JMSDF) personnel. We selected 21,260 personnel data sets in which serum urate data were available. Among them, 200 persons showed serum urate levels of $\leq$3.0 mg/dl (178 μM) (0.94%). 50 JMSDF persons who gave written consent and an additional 20 outpatients with hypouricemia (70 hypouricemic cases in sum) participated in this clinicogenetic study. First, we excluded the *URAT1* W258X mutation, the most frequent mutation in Japanese hypouricemia patients. After 47 cases having the *URAT1* W258X mutation were excluded, the remaining 23 hypouricemic cases were analyzed to find mutations in *GLUT9*.

Mutation Analysis and Functional Analysis of GLUT9

For the *GLUT9* sequence determination, we used primers described by Li et al. with slight modifications.[8] Some primer sequences were newly selected according to the genomic structure of the human *GLUT9*. High molecular

weight genomic DNA was extracted from peripheral whole blood cells[9] and was amplified by PCR. The PCR products were sequenced in both directions using a 3130xl Genetic Analyzer (Applied Biosystems). Functional analysis of GLUT9 mutants was performed using the *Xenopus* oocyte expression system, as described elsewhere.[3]

RESULTS

GLUT9 Mutations in Patients with Renal Hypouricemia

The human *GLUT9* gene contains 14 exons (1 noncoding and 13 coding) and is located on chromosome 4p15.3-p16. The alternative splicing of the *GLUT9* gene results in two main transcripts: GLUT9 isoform 1 (long isoform, GLUT9L) and isoform 2 (short isoform, GLUT9S). Two heterozygous missense mutations were identified in the patients with renal hypouricemia. Both are missense mutations from the basic amino acid arginine to neutral amino acids. GLUT9L mutations were R380W and R198C, and GLUT9S mutations were R351W and R169C, which correspond to R380W and R198C in GLUT9L.

Urate Transport Activity in Oocytes

High urate transport activities were observed in oocytes that express each wild-type GLUT9 isoform. In contrast, urate transport activity in oocytes was markedly reduced (4.6%–10.8%) both in GLUT9L mutants (R198C and R380W) (Figure 1A) and in GLUT9S mutants (R169C and R351W) (Figure 1B). The P412R mutation[10] is unlikely to be a pathogenic mutation for renal hypouricemia because neither the P412R mutation in GLUT9L nor the P383R mutation in GLUT9S, which corresponds to P412R in GLUT9L, reduced their urate transport activities at all (Figure 1). The results from the GLUT9L mutants (Figure 1A) are quite similar to those from the GLUT9S mutants (Figure 1B), suggesting the reproducibility and reliability of the results.

Amino Acid Conservation in GLUT Family Transporters

GLUT9 mutations (R198C and R380W) are observed at the well-known conserved motif (D/E-x(2)-G-R-R/K) and another conserved motif (Y-x(2)-E-x(6)-R-G) that is 100% conserved in all GLUT family transporters. These motifs are a part of the consensus patterns 1/2 that are demonstrated in the PROSITE database (http://au.expasy.org/prosite/) as "sugar transport proteins signatures 1/2." The mutation sites in GLUT9 would be key residues in these consensus patterns.

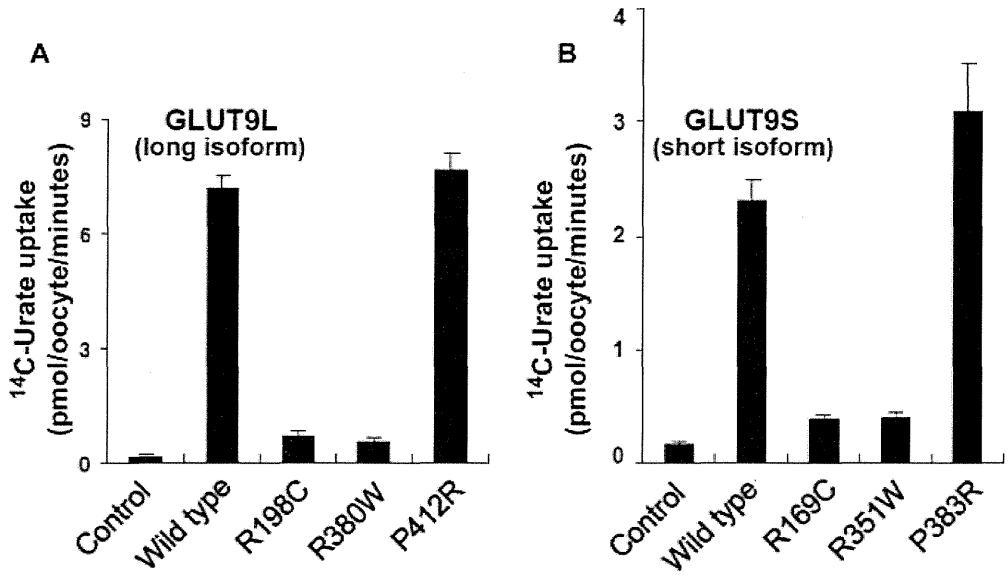

FIGURE 1 Urate transport activity via wild-type and mutant GLUT9 expressed in oocytes. Urate transport activity in oocytes was markedly reduced both (A) in GLUT9L mutants (R380W and R198C) and (B) in GLUT9S mutants (R351W and R169C, which correspond to R380W and R198C in GLUT9L). These figures also show that a P412R mutation in the *GLUT9* gene had less effect on the transport function.

DISCUSSION

Physiological Importance of GLUT9 in Human Urate Transport

The urate metabolism in humans is quite different from that in mice due to the lack of uricase.[11] Therefore, it is of great significance to identify the nonfunctional mutations in human *GLUT9* using the large human database. In MDCK cells, GLUT9L and GLUT9S show basolateral and apical localization, respectively.[12] Since nonfunctional mutations of either GLUT9L or GLUT9S dramatically reduced the urate transport activity in our in vitro studies (Figure 1), renal hypouricemia caused by these mutations may be ascribed to the decreased urate reabsorption on both sides of the renal proximal tubules, where GLUT9 expresses.[13] Based on our findings, we propose a physiological model in which GLUT9 mediates renal urate reabsorption. These findings are also supported by Dinour et al., who reported on severe renal hypouricemia patients with GLUT9 homozygous mutations.[14]

GLUT9 Mutations and Perturbation of Membrane Topology

Interestingly, these *GLUT9* mutations (R198C and R380W) correspond to the *GLUT1* pathogenic mutations (R153C and R333W), which cause GLUT1 deficiency syndrome.[15] Sato and Mueckler reported that the loss of positive charges of GLUT1 result in the perturbation of the membrane topology and aberrant "flipping" of the corresponding cytoplasmic loop into the exogenous compartment.[16] This showed that the positive charge

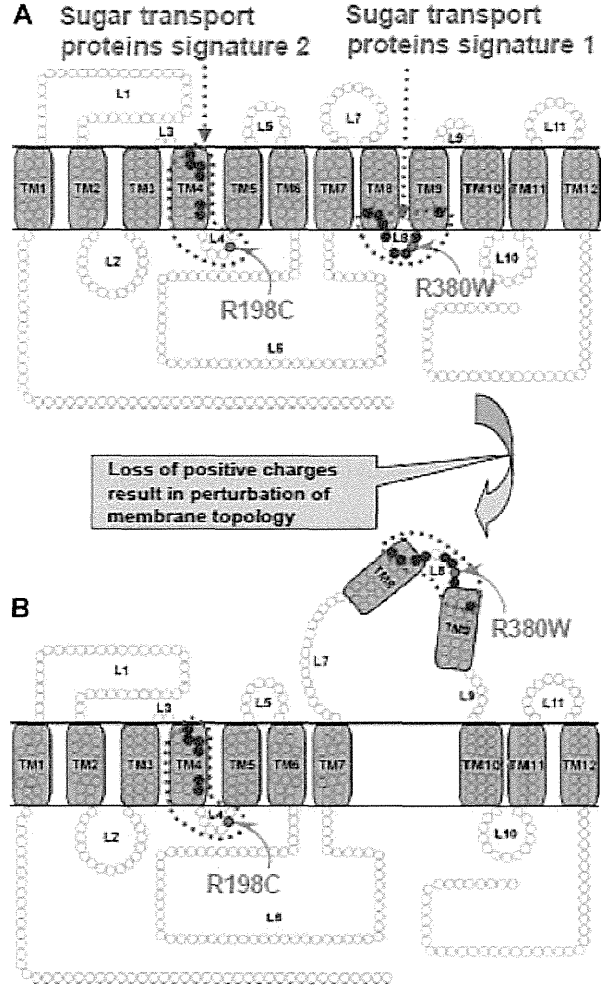

FIGURE 2 Pathogenic GLUT9 mutations causing renal hypouricemia type 2 and possible mechanisms. Both mutations are at equivalent positions within the cytoplasmic loops, which causes a loss of positive charge and results in diminished urate transport function via GLUT9.

of arginine residues in this conserved motif plays a critical role in forming cytoplasmic anchor points that are involved in the membrane topology of human GLUT1. The marked reduction of the urate transport activity in mutated GLUT9 may be ascribed to the loss of cytoplasmic anchor points and the local perturbation of the membrane topology (Figure 2).

GLUT9: Promising Therapeutic Target for Gout/Hyperuricemia

Taken together, we have identified *GLUT9* as a causative gene for renal hypouricemia type 2 (RHUC2) and demonstrated that human GLUT9 physiologically regulates serum urate levels in vivo. Since another urate reabsorption transporter, URAT1, is known to be a therapeutic target of a uricosuric agent benzbromarone, our results suggest that a urate reabsorption transporter GLUT9 can also be a promising therapeutic target for hyperuricemia and gout.

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Significant association of serum uric acid levels with *SLC2A9* rs11722228 among a Japanese population

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ABSTRACT

Genome-wide association studies identified that *SLC2A9* (*GLUT9*) gene polymorphisms were associated with serum uric acid (SUA) levels. Among the Japanese, a C/T polymorphism in intron 8 (rs11722228) was reported to be highly significant, though the function and strength of association were unknown. This study aimed to confirm the association, estimating the means of SUA according to the genotype, as well as OR of the genotype. Subjects were 5024 health checkup examinees (3413 males and 1611 females) aged 35 to 69 years with creatinine <2.0 mg/dL. Since *SLC22A12* 258X allele and *ABCG2* 126X allele are known to influence SUA levels strongly, the subjects with *SLC22A12 258WW* and *ABCG2 126QQ* (3082 males and 1453 females, in total 4535 subjects) were selected. The genotype frequency of *SLC2A9* rs11722228 was 2184 for *CC*, 1947 for *CT*, and 404 for *TT*, being in Hardy–Weinberg equilibrium (p = 0.312). Mean SUA was 6.10 mg/dL for *CC*, 6.25 mg/dL for *CT*, and 6.45 mg/dL for *TT* among males (p = 1.5E-6), and 4.34 mg/dL, 4.59 mg/dL, and 4.87 mg/dL among females (p = 4.6E-11), respectively. Males with SUA less than 5.0 mg/dL were 14.7% for *CC*, 10.6% for *CT*, and 7.8% for *TT* (p = 2.3E-4), and females with SUA less than 4.0 mg/dL were 34.1%, 25.5%, and 15.4% (p = 3.7E-6), respectively. This study was the first report to estimate the impact of *SLC2A9* rs11722228 on SUA levels. Since the allele frequency of rs11722228 is similar among different ethnic groups, the impact remains to be examined in other ethnic groups.

1. Introduction

Serum uric acid (SUA) levels are partly regulated by genetic traits. *ATP-binding cassette subfamily G member 2* (*ABCG2*) gene in chromosome 4q22, coding a uric acid transporter, has a functional polymorphism, Q126X (rs72552713), which was reported to reduce transportation activity, resulting in hyperuricemia [1–3]. Uric acid transporter 1 (URAT1) encoded by *SLC22A12* in chromosome 11q13 is a uric acid anion exchanger, which reabsorbs uric acid in renal tubules [4,5]. *SLC22A12* W258X polymorphism with the reduced function causes renal hypouricemia [6–8]. Glucose transporter 9 (GLUT9) encoded by *SLC2A9* in chromosome 4p16-15.3 is also the molecule to reabsorb uric acid in kidney. The rare mutations of *SLC2A9* were found in hypouricemia patients; R380W and R198C in Japanese [9], L75R in an Israeli-Arab family, exon 7 deletion in Ashkenazi-Jewish [10], and Ile118HisfsX27 (g.27073insC at exon 3, causing Ile118His and stop codon at position 27) in a Czech family [11].

A genome-wide association study (GWAS) on SUA for 28,141 participants of European descent demonstrated the associations with nine genes including *SLC22A12*, *SLC2A9*, and *ABCG2*[12]. The polymorphism of *SLC2A9* selected in the GWAS was rs734553, whose minor allele frequency was reported to be 0.011 in a Japanese population (HapMap-JPT, ss80703). Another GWAS for 1017 African American detected four polymorphisms (rs3775948, rs7663032, rs6856398, and rs6449213) of *SLC2A9* associated with SUA [13]. For 14,700 Japanese, a GWAS identified the associations with *SLC22A12*, *SLC2A9*, and *ABCG2*[14]. In the Japanese GWAS, a C/T polymorphism in intron 8 of *SLC2A9* (rs11722228) was identified as a highly significant polymorphism (p = 7.1E-24).

In this study, we aimed to confirm the association with rs11722228, and further to examine the strength of the association in terms of odds ratio (OR), after eliminating the effects of *SLC22A12*

Abbreviations: ABCG2, ATP-binding cassette subfamily G member 2; bp, base pairs; CI, confidence interval; GLUT9, glucose transporter 9; GWAS, genome-wide association study; OR, odds ratio; PCR-CTPP, polymerase chain reaction with confronting two-pair primers; SUA, serum uric acid; URAT1, uric acid transporter 1.

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